Editorials

Allergen avoidance

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With allergic diseases that have a seasonal or episodic nature, the causal role of the allergen is often obvious. Thus ragweed pollen in the fall causes symptoms in allergic individuals and moving to the west coast or preventing entry of pollen into the home can decrease symptoms. Similarly, yellow jacket venom can cause anaphylaxis, and avoiding stings is universally recognized as an effective method of preventing these reactions. By contrast, with most indoor allergens and also those fungi that have a long season, naturally occurring changes in exposure over the year are not sufficient to provide evidence about causality. For these allergens and for dust mites in particular, studies on avoidance have provided important evidence about the role of allergens in disease.[1-4] There are 2 main forms of avoidance studies, those in which the patient is moved to a different (ie, allergen-free) environment and those in which measures designed to decrease exposure are taken in the patient's home.

The studies in sanatoria or hospital rooms have been almost uniformly successful and have provided evidence about the levels of mite exposure (generally <0.5 μg of Der p 1/g of dust) that will result in significant symptom improvement.[2,4-6] The second type of study must always be judged by 2 criteria: (1) Did the measures taken decrease exposure, and (2) did the change in exposure result in a significant clinical improvement? In evaluating the published clinical studies on mite avoidance as a treatment for asthma, only a minority have achieved a prolonged decrease in allergen levels.[3,7] However, each of those studies reported improvement in asthma symptoms (Table I).[3,8-11] From the successful trials, several conclusions about avoidance are possible: first, that effective avoidance is primarily based on physical rather than chemical measures; second, that effective avoidance requires a full regimen in the bedroom; third, that avoidance is only relevant to subjects who are specifically allergic; and finally, that avoidance studies can have a large placebo or Hawthorne effect because patients often change their behavior when they are enrolled in studies of this kind.[7]

Given the importance of controlled trials of mite allergen avoidance both to understanding the role of allergen exposure in disease and in designing treatment, it is very disturbing when the *New England Journal of Medicine* publishes 2 articles that are interpreted as showing that mattress covers are not an effective measure for treating allergic rhinitis or asthma.[13,14] The studies were striking because they enrolled large numbers of patients, they were continued for a year, and they used mattress covers that were almost certainly effective at preventing live mites or mite allergens from leaving the mattress. Because of their possible impact on treatment, these articles have already received considerable comment.[15-17] Using the criteria proposed above, neither study would be considered successful because there was not a major decrease in allergen compared with that seen in the control population. In addition, there are specific problems with each that make it difficult to reach conclusions in relation to clinical practice.

Terreehorst et al,[13,18] from the Netherlands, reported a controlled trial of mattress covers in the treatment of allergic rhinitis. There are 2 major problems with this study. First, many of the patients did not present with allergic rhinitis but were initially enrolled in the study as patients with asthma or atopic dermatitis. In keeping with this, the geometric mean total serum IgE level of 230 IU/mL is surprisingly high for an unselected group of patients with allergic rhinitis. Thus the conclusions of the study might only be relevant to highly allergic patients. The other major problem is that the intervention was restricted to covers, and both groups were advised to "wash and clean the bedding weekly at 60°C, to clean the house and to heat and ventilate regularly. . . ." Thus the difference in mattress covers was expected to make a difference against a background of house and bedding cleaning in both the active and placebo groups. Previous authors have always concluded that individual parts of an avoidance protocol cannot be evaluated separately.[1,7] Tovey et al,[16] in Sydney, have demonstrated that changes measured in dust samples obtained from the mattress surface might not be reflected in directly measured inhaled allergen.[19] Thus although the authors reported a modest but significant decrease in allergens on the mattress, their intervention probably did not have a significant effect on inhaled allergen levels. The problems with testing one intervention (ie, avoidance) while allowing other medications have recently been pointed out by Chowdhury.[15] However, more serious problems arise from testing one part of an avoidance regimen while carrying out the rest of the protocol.

While recognizing that there are major problems with this study on "allergic rhinitis," it is important to realize

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TABLE I. Controlled trials of allergen avoidance achieving a prolonged decrease in mite allergen levels

Study	Duration	Avoidance	N	Decrease in mite allergen	Primary outcome(s)
Murray and Ferguson (1983)[9]	1 y	Physical barriers	10/10	++	BHR*
Carswell et al (1996)[12]	6 mo	Physical barriers and Acarosan§	24/25	+	PEFR,† BHR
Ehnert et al (1992)[3]	1 y	Physical barriers and tannic acid	8/16	++	BHR*
Van der Heide et al (1997)[10]	1 y	Physical measures	15/15/15	++	BHR‡
Walshaw and Evans (1986)[8]	1 y	Physical barriers	22/20	++	PEFR/BHR*
Htut et al (2001)[11]	12 mo	Heat treatment	10/10/10	++	BHR‡

BHR, Bronchial hyperreactivity; *PEFR*, peak expiratory flow rate.
*Highly significant improvement.
†Improvement but not significant.
‡Significant improvement.
§Benzyl benzoate powder.

that there is very little objective evidence about the effect of allergen avoidance on perennial allergic rhinitis. Indeed, it has always been a mystery how the allergic rhinitis guidelines conclude that the use of mite avoidance measures for perennial rhinitis is "evidence based."[20]

The report by Woodcock et al[14] investigates the use of "allergen impermeable bed covers as a single intervention" in a primary-care setting. Their results add to the already sufficient evidence that single measures, applied without either establishing specific sensitivity or providing education about avoidance, are not effective in the treatment of asthma. However, the most striking feature of the study was how little decrease in allergen was achieved given previous reports from the same group about the efficacy of mattress covers.[21] They record a modest decrease in allergen levels at 6 months and no significant effect at 12 months. This was in part because they only tested dust from a minority of the homes, and the allergen assays were only carried out on reservoir dust samples from the mattresses. However, the results strongly suggest that the measures taken did not achieve a sustained decrease in inhaled allergen.

In a recent review by several members of the group in The Netherlands, they recognize that their studies focus on the effect of covers alone because such studies can be blinded. However, they fail to recognize how much the interpretation is obstructed because of extensive use of avoidance measures, including polished floors and hot washing of bedding by the placebo group.[22] An excellent example is the study from 2002, in which there was, in addition, a significant dropout of patients in the placebo group because of asthma instability.[23]

The studies being discussed here are on secondary avoidance to investigate whether decreasing exposure can reduce symptoms in patients with established disease.

It has also been proposed that avoidance can be used to prevent sensitization of individuals with negative skin test results or even from birth (ie, primary avoidance).[24-27] Before considering the evidence, it is important to recognize that exposure is necessary for sensitization. Children raised in a community without dust mite allergen (eg, northern Sweden or Los Alamos, NM) do not become allergic to dust mites. Similarly, children raised with minimal or no exposure to cockroach allergens (eg, suburban areas of New Zealand, Delaware, or Sweden) do not become allergic to cockroaches. For many years, primary avoidance studies were designed on the assumption that exposure needed to occur in the subject's home and that not having a cat would protect children from sensitization to cat. For domestic cats, it is now clear that the major allergen, Fel d 1, which is carried on dander particles, spreads throughout the community. Thus significant quantities of Fel d 1 can be found in floor dust from schools, public buildings, and homes without a cat.[28-30] Furthermore, it is now clear that airborne Fel d 1 can be detected in the air of homes without a cat.[31,32] Thus avoiding having a cat is not an effective measure to prevent sensitization to cats and indeed might have the opposite effect.[33-35] In a recent study in New Zealand, those families who chose not to own a cat because of a family history of allergy had a higher prevalence of cat sensitization than comparable families who had a cat (Erwin et al—unpublished data, 2004).

For dust mite, there is very little evidence for passive transfer of allergen, and thus the presence of mite allergen in a dust sample is generally taken as evidence that mites are growing locally. On the other hand, children are not raised in a single house, and the question is not only how much allergen it takes but also how long it takes to become sensitized. Clearly some pollens with a relatively short season, such as Chinese elm or maple, can induce sensitization and disease. Are 2 weeks spent with a relative or 3 afternoons a week in daycare sufficient to sensitize to dust mites? This, however, would only be relevant in an area in which granny's house or the daycare center is likely to have high concentrations of dust mite. To return to our previous examples, if you live in Los Alamos and grandma lives in Santa Fe, the child will not be exposed to dust mites in either place. By contrast, attempts to prevent sensitization to dust mites in Sydney, Vancouver, Manchester, or Atlanta might be stymied by the presence of mite allergen in homes other than the child's own home. Obviously, a similar effect could occur with cat, except that exposure to cat allergen is ubiquitous, and therefore it would be impossible to assess the effect of a transient exposure to high levels. Despite these problems, some primary avoidance studies have been effective. For example, Nishioka et al,[36] in

Tokyo, showed that aggressive mite avoidance measures in the bedroom can decrease mite sensitization among children with atopic dermatitis.

As with many therapeutic strategies, allergen avoidance in the treatment of allergic disease can be seen as a cup that is half full or half empty. The recent epidemiologic evidence argues strongly against cat avoidance as a viable method of decreasing sensitization. Increasingly, the evidence suggests that mite avoidance also fails as a primary measure, perhaps because of short periods of exposure in other homes. On the other hand, decreasing exposure to dust mite allergens is an effective part of the treatment of asthma, rhinitis, and atopic dermatitis.[1-11,37] The meta-analysis published in 1998 originally tried to interpret the published results on mite avoidance and asthma as negative.[38] However, that result depended on including a large number of studies that had no effect on allergen exposure. When the analysis was revised, those studies that used physical measures resulted in significant clinical improvement ($P < .02$).[39] The 2 recent studies simply reinforce the fact that effective avoidance requires both education and a comprehensive protocol.[7,13,14] The implied argument of many commentaries is that allergen avoidance is too expensive or too difficult. These arguments underestimate the intelligence of most patients, who realize that decreasing exposure is the logical treatment for a disease that is caused by exposure and do not like taking medicines on a regular basis. There are very few medicines that are truly without side effects. Recent evidence about adrenal suppression of children receiving high-dose inhaled steroids or the fact that long-acting β_2-agonists can increase the incidence of severe attacks of asthma has done nothing to reassure patients about the safety of taking inhaled medicines chronically. Many physicians fail to appreciate the resistance of parents and children to using medicines to control a disease.

Over the last 10 years, there has been a successful movement to establish guidelines for the management of many chronic diseases, including asthma.[20,40,41] The guidelines focus on "evidence-based" treatments, and it might be worth considering the meaning of that term. To be considered evidence based requires a large, double-blind, placebo-controlled trial. Inevitably, almost all of these studies are designed and sponsored by a pharmaceutical company. This results in strict rules about the design of the studies, the enrollment criteria, and above all the treatments that are allowed in parallel or in the control group. Clearly, companies are unlikely to invest in testing another company's drug, a drug that is off patent, or a physical procedure, such as allergen avoidance. Sponsored studies generally would not allow patients outside the criteria, for example patients with atopic dermatitis in a rhinitis study. Equally, these studies are very careful to restrict the concomitant use of other treatments that could confuse the result. As has recently been pointed out, the effect size recorded in some studies that are considered to be evidence based is not very large.[15] Reading through controlled trials of either allergen avoidance or immunotherapy, there are some consistent themes: the studies are difficult to blind, the numbers enrolled are generally modest, and in many cases other treatments have been allowed.[42] In some of the successful studies on allergen avoidance, a significant result has been recorded despite small numbers because the effect size was so large (Table I).[3,7] The 2 recent studies focused on achieving blinding of the investigators and the subjects at the cost of not achieving a real difference in exposure.[13,14]

Taken together, it is clear that recent studies should not change our conclusions. Allergen avoidance remains a cornerstone of treatment of allergic patients who present with rhinitis, asthma, or atopic dermatitis. Successful treatment requires defining specific sensitivity (skin tests or serum IgE antibodies), education, and an overall plan to reduce exposure in the home.[7] Success will always depend on the involvement of the patient, the relevance of other allergens, and exposure outside the patient's home. In a world in which a large proportion of the population is taking tablets or inhalers every day, we should take full advantage of a treatment strategy that can be maintained easily without side effects, improve symptoms consistently, decrease bronchial hyperreactivity, and decrease reliance on drug treatment.

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