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A M E R I C A N C O L L E G E O F
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Hidden Allergic Factors in the Etiology of Asthma*

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Increasing evidence from case control surveys, population studies and allergen avoidance studies suggests inhalant allergy plays an important role in the etiology of asthma. Recent studies in hospital emergency rooms have compared the prevalence of serum IgE antibodies to common allergens (mite, cat, cockroach, rye grass and ragweed pollen) in patients admitted with acute asthma attacks and in unselected age-matched control subjects. These studies, carried out in central Virginia and northern California, showed a highly increased prevalence of IgE antibodies to inhaled allergens among asthmatic patients, and suggest that the development of allergen specific IgE antibody responses is a major risk factor for emergency room admission with asthma. Presentation at the emergency room appeared to be related to patients' exposure to specific allergens: in central Virginia, in the fall, dust mite was the

predominant allergy, whereas in northern California, in May-June, most asthmatic patients (>90 percent) were allergic to rye grass. New immunoassay technology, based on the use of monoclonal antibodies, has been developed to measure the quantities of "indoor" allergens (mite, cat, cockroach) in asthmatic patients' houses. It is now possible to propose tentative levels of mite allergens which should be considered both as a risk for IgE antibody sensitization (2µg allergen/g dust) and as a risk for acute asthma attacks (10µg allergen/g dust). Future management of asthma will require analysis of indoor allergens and the development of efficient allergen avoidance procedures. Further research is necessary to investigate the relationship between airborne allergen levels, particle size and the precipitation of asthma attacks and also to investigate immunologic mechanisms which may cause bronchial hyperreactivity.

Although an association between inhalant allergy and asthma has been recognized for over 50 years, in many cases it has been difficult to demonstrate cause and effect. This is because in part some asthmatic patients are nonallergic, and even in allergic patients many other factors are known to trigger asthma attacks, including viral infections, chemical exposure and non-specific irritants. Also, patients are often not aware of a direct association between exposure to a specific allergen (dust mite) and the development of respiratory symptoms. As a result, the role of allergy is often "hidden" from the patient and many physicians regard allergic reactions as factors likely to exacerbate asthma, rather than a primary cause. Some authoritative texts suggest that <10 percent of acute or severe asthma in adults is attributable to allergen exposure,^{1,2} even though population surveys and studies of outpatient clinics report a high prevalence of immediate hypersensitivity in patients with asthma. Over the past 10-20 years, there have been major advances in immunochemistry of allergens which have made it easier to define patients' sensitivities and to identify the relevant indoor allergens which may cause asthma attacks. This has facilitated epidemiologic studies which suggest that inhalant allergy is a major risk factor for acute asthma attacks. In addition, it is now possible to establish levels of indoor and outdoor environmental

allergen exposure which should also be considered as risk factors for the exacerbation of allergic respiratory disease.

EVIDENCE FOR AN ETIOLOGIC ROLE FOR INHALANT ALLERGY IN ASTHMA

It is well known that bronchial provocation with nebulized allergen can cause acute airway obstruction in appropriately sensitized individuals and there are several examples where environmental exposure to specific allergens can cause immediate asthma attacks (perhaps the most common example being cat allergen). However, several other lines of evidence suggest that inhalant allergy plays a role in the etiology of a much larger number of asthma cases.

Studies in Europe, North America and Japan have shown that many asthmatic patients (in some studies >80 percent) show immediate hypersensitivity to common allergens (dust mites, pollens, animal danders, etc) as demonstrated by skin tests, bronchial challenge and measurements of serum IgE antibodies (ab).³⁻⁵ The problem with these studies is that the prevalence of inhalant allergy in the general population is high (10-30 percent) and there are always a significant number of asymptomatic individuals with allergen-specific IgE. Nonetheless, several population surveys have demonstrated that the prevalence of IgE ab is significantly higher among asthmatic patients than control populations^{3,6-8} and some studies have shown skin test reactivity is correlated with increased bronchial reactivity.⁹

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Marked improvements in symptoms and reduction in bronchial hyperreactivity have been demonstrated in patients living for prolonged periods in allergen-free conditions. These studies have involved patients living in convalescent sanatoria at high altitudes^{10,11} and also keeping patients in carefully controlled air filtered hospital rooms.¹² It is important to note that in these studies it took between four months to one year for bronchial reactivity to return to near normal values. Clinical improvement following allergen avoidance has also been demonstrated following rigorous avoidance and cleaning regimens in the houses of patients with asthma.^{13,14} The important feature of those studies is that the avoidance techniques used must be rigorous enough to produce genuine reductions in allergen (dust mite) levels. Studies where reductions in allergen levels have not been demonstrated have usually not been effective.^{15,16}

Some patients develop asthma following occupational exposure to inhaled allergens, but are otherwise symptom free. Typical examples would be asthma in laboratory workers sensitized to rat urine allergens¹⁷ and in lumber workers sensitized to western red cedar.¹⁸ In these situations, asthma can develop within minutes of exposure to allergens, and in many cases, patients have easily detectable serum IgE ab.¹⁹

Finally, there are very interesting studies performed on natives of Papua New Guinea by Dowse, Turner and Woolcock²⁰ which suggest that the introduction of an allergen (in this case dust mite) into the environment has been associated with a dramatic increase in the prevalence of asthma. Asthma in the South Fore region of the Eastern Highlands of Papua New Guinea was virtually an unknown disease 20 years ago, but today this area has one of the highest prevalence rates for asthma in the world (7.3 percent). Because of Western influence, there have been several changes in lifestyle in the South Fore in recent years; however, the introduction of dust mites on cotton blankets used for bedding appears to be most strongly associated with the increased prevalence of asthma. Skin tests positive to mite allergen were demonstrated in 90 percent of asthmatic patients and the mean mite numbers found in blanket dust were very high (1300 mites/g dust).

EMERGENCY ROOM STUDIES

Clearly, much of the evidence described above is circumstantial, but emphasizes the strong association between asthma and inhalant allergy. We have re-examined the role of allergens in asthma by studying the prevalence of inhalant allergy in unselected asthmatic patients and control subjects presenting to the emergency room (ER). There are over 2 million ER admissions for asthma in the US each year and these acute attacks are responsible for much of the mortality

and most of the morbidity of the disease.²¹ Emergency room admissions for asthma are increasing and in some urban and inner city areas the ER is the primary source of treatment, particularly for indigent patients. Presentation in the ER is based solely on the patients' assessment of their symptoms and involves no prior investigation of the etiology of the disease. This "random" presentation of the patients is an advantage for epidemiologic studies. We studied the prevalence of serum IgE ab to five common inhalant allergens (dust mites, cat, cockroach, grass pollen and ragweed pollen) in 102 randomly selected patients with acute airway obstruction and 118 controls, presenting to the ER at the University of Virginia Hospital, Charlottesville.²² The IgE ab were measured quantitatively using the radioallergosorbent test (RAST) and the results were analyzed by age and also for seasonal and socioeconomic differences. Among patients between 16-30 years of age, the prevalence of IgE ab to one or more of the allergens was significantly higher in asthmatics (~75 percent) than controls (~15 percent) ($p < 0.001$). Similar but smaller differences in the prevalence of IgE ab were also observed in the 31-50 age group, but in patients over 50, there was no significant difference in IgE ab prevalence between asthmatic patients and control subjects. These results show that for patients <50 years old, the presence of IgE ab to inhalant allergens is a major risk factor for acute asthma attacks (odds ratio 9.7, $p < 0.001$). Most asthmatic patients had high levels of IgE ab to mite, cat or cockroach and a smaller number had IgE ab to pollens. IgE ab to cat was only a risk factor among white patients, whereas IgE ab to cockroach was only a risk factor among black patients. These racial differences were highly significant (χ^2 7.6, $p < 0.001$) and appeared to correlate with socioeconomic and housing conditions. Seasonal effects of allergen exposure were also significant: patients with dominant IgE ab to dust mite were more likely to present in Aug-Dec (when mite allergen levels in Charlottesville are high), whereas patients with dominant IgE ab to pollens presented mostly in Mar-July (χ^2 8.8, $p < 0.001$).

A striking relationship between pollen allergen exposure and ER asthma admissions has been demonstrated in studies carried out by Reid and colleagues²³ at Travis Air Force Base in Northern California. Each year in May-June this area has intense rye grass pollination which is accompanied by a well documented, "epidemic" in ER admissions for asthma. Admissions for asthma routinely rise by 20-fold and correlate with the rise in pollen counts. Approximately 40 percent of the total yearly ER visits at Travis AFB occur during this two to three week period in the spring. In May-June 1986, we studied the prevalence of allergen specific IgE ab in 59 asthmatic patients and 59 control subjects presenting to the ER at Travis

AFB.²⁴ Ninety two percent (54/59) of asthmatic patients had highly elevated levels of IgE ab to rye grass pollen (>200 RAST units/ml) as compared to 8/59 controls ($\chi^2 = 22$, $p < 0.001$). Thus, at Travis AFB the presence of IgE ab to grass pollen was significantly associated with ER admissions for asthma. In contrast to the Charlottesville ER studies, the prevalence of IgE ab to cat and cockroach in asthmatic patients was not increased relative to control subjects; however, there was a small but statistically significant difference in the prevalence of IgE ab to dust mite ($\chi^2 = 4.4$, $p = 0.034$). In both studies, the prevalence of IgE ab in ER controls was similar to that observed in the general population, *ie*, ~15 percent.

Both the Charlottesville and Travis ER studies involved "adult" patients: >15 years of age. The presence of allergen specific IgE ab was only a risk factor for ER admission in patients <50 years old. Most patients aged over 50 presented with partially reversible airway obstruction and it is presumed that they have underlying fixed obstruction. In these patients, asthma was usually attributable to chronic tobacco abuse. Asthma is one of the most common causes of ER admission in children and we²⁵ have recently shown a very high prevalence of inhalant allergy in a study of pediatric ER asthma cases carried out in collaboration with Dr. Thomas Smith (Emory University) at Grady Memorial Hospital, Atlanta. In that study, the prevalence of allergy among asthmatic patients was 80 percent, as opposed to 32 percent in control subjects, and dust mite, cockroach and grass pollen were the most common allergies (44 percent of patients had dominant IgE ab to dust mite).

Although the ER studies clearly demonstrate a high prevalence of inhalant allergy in patients admitted with asthma, they do not prove that these acute asthma attacks were provoked by allergen exposure or caused by an IgE-mediated mechanism. The interpretation of these results is that IgE ab is a risk factor and that individuals with elevated IgE ab are significantly more likely to present to the ER with asthma. Our working hypothesis is that in allergic individuals, prolonged allergen exposure causes inflammatory events in the lung (which could be IgE-mediated) and the subsequent development of bronchial hyperreactivity. Once patients develop bronchial hyperreactivity, acute asthma attacks may be triggered by a variety of nonspecific stimuli as well as inhalant allergens. This view is in keeping with the work of Cockcroft, Hargreave and colleagues, described in this issue (see page 178). The results of the ER studies suggest that patients admitted to the ER with asthma should be evaluated for inhalant allergy and that management should include allergen-specific avoidance procedures. The RAST test is a reliable method for measuring serum IgE ab to inhalant allergens and could be

routinely applied in ER situations. The five allergens used in our studies in Charlottesville were chosen on the basis of skin testing results, which indicated that they were the most common environmental allergens in our area. Sensitization may differ in other geographic areas and IgE ab to other allergens; tree pollens, fungi and dog dander may also need to be considered as potential risk factors. We have recently reviewed avoidance procedures for dust mites, including treatment of bedding, carpets, clothing and furniture, the use of acaricides and control of humidity.⁵ We have seen dramatic improvements in mite-sensitive patients with asthma and/or atopic dermatitis when avoidance procedures are vigorously applied over long periods (weeks to months). While these procedures may also benefit patients sensitive to other indoor allergens (cockroach, molds and fungi), more work needs to be on the quantities and distribution of those allergens in houses before systematic avoidance regimens can be developed.

ASSESSMENT OF ENVIRONMENTAL ALLERGEN EXPOSURE

The development of both IgE ab responses and symptoms is clearly related to allergen exposure; however, until recently, there have been considerable technical problems in measuring environmental allergens. Pollen counts have been used as a measure of pollen allergen exposure and "high" pollen counts (>300 ragweed pollen grains/m³) are used to predict the severity of symptom days in grass or ragweed sensitive patients with hayfever and/or asthma. There is no comparable assessment of indoor allergen exposure; however, several methods are now available for measuring allergens, such as dust mite and cat, in the houses of asthmatic patients. Three methods are used for assessment of mite allergen exposure: mite counts, guanine assay and specific immunoassays for the major allergens. Mite counts are important for studies on mite species distribution and biology, but are time consuming and require technical skills in mite isolation and taxonomy, which makes them unsuitable for routine use. Mite counts may also underestimate mite *allergen* levels because the major (group 1) allergens are produced in mite feces.²⁵ Bischoff, Pauli and colleagues have developed a chemical test for mites based on the detection of guanine. In house dust, mites are the major producer of guanine and this simple "dipstick" test appears to show a reasonable correlation with mite allergen levels. However, assessments of mite allergen exposure based on guanine cannot be directly compared with levels of other dust allergens, such as cat and cockroach. This type of comparison can only be made using quantitative assays for individual allergens. Over the past ten years, advances in allergen immunochemistry have resulted

in the purification and characterization of the major allergens from dust mites (group 1 and group 2 allergens)⁵ and cat (*Fel d I*),^{27,28} and sensitive and specific immunoassays for these allergens have been developed. They first used polyclonal rabbit antibodies in either radioimmunoassay or immunodiffusion based tests (rocket electrophoresis), but are increasingly becoming monoclonal antibody based. Monoclonal antibodies have defined specificity, can readily be produced in large quantities and can be used in sensitive, radioimmunoassay or enzyme immunoassay (ELISA) tests, which do not require purified allergen. These tests are ideal for epidemiologic studies involving large numbers of samples and are also potentially simple enough for routine tests in hospitals or doctors offices (see ref 29 for review). The principle of the monoclonal assays is as follows: plastic microtiter wells coated with monoclonal antibody are incubated with the test sample (house dust extract), and the bound allergen is detected using a second biotinylated or enzyme labelled antibody, directed against a different antigenic site on the allergen molecule. The assays are quantitated using a reference preparation of known allergen concentration to form a control curve. We have developed monoclonal based assays for the group 1 and group 2 allergens from dust mites (*Der p I* and *Der f I*, *Der p II* and *Der f II*) and also for cat allergen, *Fel d I*, and used these assays to quantitate allergen levels in samples of house dust and in allergen extracts used for diagnosis and treatment.^{5,28-31} The assays are extremely sensitive (ng range) and are technically straightforward to the extent that the most labor intensive step in measuring allergen levels in house dust is now processing (sieving and extracting) the dust samples!

ALLERGEN LEVELS AS RISK FACTORS FOR DISEASE

Several studies have compared the quantities of inhalant allergens in the dust and airborne in asthmatic patients' houses.³²⁻³⁴ High levels (up to 25 μ g/g dust) of mite allergens, *Der p I* and *Der f I*, have been found in house dust samples from several areas of the US, including Charlottesville, Seattle, Atlanta and Baltimore³⁵⁻³⁹ and similar high levels of cat allergen, *Fel d I*, have also been reported.^{24,28,38-41} Studies on seasonal variation in mite allergen exposure in Charlottesville showed that mite counts peaked in July and August, but then fell rapidly, whereas mite group I allergen levels remained high (>10 μ g/g dust) from August-January before falling in March-April.³⁵ Thus, although there may be seasonal variation in mite numbers, mite allergens can persist for prolonged periods during the year. In houses with cats, *Fel d I* levels remained high throughout the year and showed no evidence of seasonal variation.²⁸ Clinical observations during this year-round study suggested that mite

group I allergen levels of >10 μ g/g dust were associated with exacerbation of respiratory symptoms in asthmatic patients and that those levels should be regarded as the indoor equivalent of a high pollen count.³⁵ Analysis of dust samples from the Travis ER study showed that very few houses contained >10 μ g/g mite allergen, but that the indoor *pollen* allergen levels were very high and often exceeded 50 μ g/g. At Travis AFB, the rise in pollen count was matched by high pollen allergen levels in house dust, thus reinforcing the view that both specific IgE ab responses and relevant allergen exposure are risk factors for acute asthma.

The availability of quantitative techniques for measuring indoor allergens now means that it is possible to tentatively propose levels of allergen exposure which should be regarded as risk factors for the development of respiratory symptoms in appropriately sensitized individuals. At a recent meeting on dust mite allergy sponsored by the World Health Organization and the International Association of Allergy and Clinical Immunology, provisional guidelines for the interpretation of mite allergen levels were proposed, based on published studies from several parts of the world.⁴² These proposals were that group I allergen levels of 2 μ g/g dust (roughly equivalent 100 mites/g or 0.6 mg guanine/g) should be considered a risk for developing IgE ab responses and asthma, and that levels of >10 μ g/g should be regarded as a level at which most asthmatic patients will experience symptoms and are a significant risk for acute attacks. Further clinical studies will obviously be needed to verify these values and to establish the quantitative or percentage of reduction in allergen levels that is necessary to produce symptomatic improvement. It will also be important to establish whether the predicted values for mite allergens also apply to other indoor allergens, particularly cat and cockroach.

Our results suggest that in the future the management of allergic asthma will require analysis of indoor allergen levels in patients' houses and immunologic monitoring of allergen avoidance regimens. While assays for mite and cat allergens are established, assays for cockroach, molds and fungi, and possibly other animal allergens will need to be developed, because these are important allergens in other geographic areas. The combined use of these *in vitro* assays should lead to significant new developments in clinical management and in better understanding of the role of inhalant allergens in both the acute and chronic symptoms of asthma.

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