

Epidemiology of emergency room asthma in northern California: Association with IgE antibody to ryegrass pollen

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To examine the relationship between allergy and acute attacks of asthma, we have examined adult patients with acute asthma presenting during a defined pollen season. Sera from 59 patients presenting with acute asthma to the David Grant Medical Center emergency room at Travis Air Force Base during the spring "epidemic" of asthma were assayed for IgE antibody (Ab) to five allergens (mite, cat, cockroach, ryegrass pollen, and ragweed) with RAST. Control sera were obtained from 34 patients without asthma and 25 employees. The results demonstrate that 92% of the patients with asthma had >200 units of IgE Ab to ryegrass pollen (~20 ng of IgE Ab per milliliter) compared to 14% of the control subjects ($\chi^2 = 69$; $p < 0.0001$; odds ratio = 69). Some of the grass pollen-allergic patients also had increased levels of IgE Ab to ragweed, but only 25% had >200 units. In contrast, there was no significant difference between subjects with asthma and control subjects in the prevalence of IgE Ab to the three indoor allergens (mite, cockroach, and cat). Twelve percent of the patients with asthma compared to 5% of the control subjects had >200 units of IgE Ab to one of these three ($\chi^2 = 0.98$; $p > 0.1$; odds ratio = 2.5). Dust samples from the homes of 15 of the patients with asthma demonstrated very high levels of grass pollen (13/15 houses with >10 μg of allergen per gram of dust), low levels of mite (13/15 homes with <2 μg of allergen per gram of dust), and no detectable cockroach allergen. These results demonstrate that the development of IgE Ab to an inhalant allergen (i.e., grass pollen) increased the patients' odds of developing acute asthma during a period of increased exposure. (J ALLERGY CLIN IMMUNOL 1988;82:224-30.)

There are many case-control studies on clinic patients and population surveys that demonstrate that there is a high prevalence of allergy among patients with asthma.^{1,6} In some outpatient clinics, inhalant allergy is actively investigated as a possible etiology in all cases of reversible airway disease. By contrast, recognized medical authorities suggest that only 10%

Abbreviations used

DGMC: David Grant Medical Center
TAFB: Travis Air Force Base
Ab: Antibody
ER: Emergency room

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Supported by National Institutes of Health Grant No. A120565. Presented in part at the Forty-third Annual Meeting of the American Academy of Allergy and Immunology in Washington, D.C., February 1987.

Received for publication Aug. 18, 1987.

Accepted for publication Jan. 20, 1988.

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***Recipient of Public Health Service National Research Service Award A107255.

of acute or severe asthma in adults is related to allergy.^{7, 8} In keeping with this view, routine care of acute asthma in ERs rarely involves investigation of etiology beyond excluding acute respiratory infection. A recent study on 102 adults with acute asthma treated in the ER of the University of Virginia demonstrated that up to 70% of the patients younger than 50 years of age had significant elevations of IgE Ab to one of five common inhalant allergens (dust mite [*Dermaphagoides farinae*], cockroach, cat dander, grass pollen, and ragweed pollen). The results demonstrated that a high level of IgE Abs to one of the "indoor" allergens was a major risk factor for acute attacks of

asthma.⁹ To examine further the relationship between allergy and asthma, we have examined adult patients with acute asthma presenting during a defined pollen season in a different part of the country.

During the spring of each year, the inland areas of northern California experience an intense ryegrass pollination that is accompanied by a sharp rise in both peak pollen counts and patient encounters for asthma and rhinitis. The DPMC ER located at TAFB serves both the military and civilian population in this area and routinely records a twentyfold increase in patient visits for asthma coincident with the rise in pollen counts.¹⁰ Selected patients observed during this spring "epidemic" have been found to have immediate hypersensitivity to ryegrass pollen and have been successfully treated with immunotherapy.¹⁰ However, no study has examined a random population with asthma presenting during this period and compared the prevalence of IgE Abs in these patients to their prevalence in a control population.

We present in this article a case-control study on 59 patients with acute asthma and 59 control subjects who were assessed for IgE Ab to the same five allergens. The objective of this case-control study was to quantitate the risk of IgE Ab to ryegrass pollen as a risk factor for acute attacks of asthma during a ryegrass-pollen season.

MATERIAL AND METHODS

Pollen counts were recorded from a gravity collector located on the roof of the DPMC and compared to those measured by a rotorod located on the roof of Fairfield Community Hospital located 5 miles from TAFB. The results from the two centers were very similar, and results from the cascade impactor were recorded in counts per square centimeter.

Fifty-nine patients presenting within 2 weeks of the peak pollen count were randomly entered into the study. The patients were diagnosed by history and physical examination, and peak flow measurements were made with a mini-Wright peak flow meter (Armstrong Medical Industries Inc., Northbrook, Ill.). The average peak expiratory flow pretreatment was 203 ± 97 , and posttreatment was 395 ± 99 L/min. All 59 of the patients with asthma demonstrated a $\geq 25\%$ increase in peak flow after treatment.

Sera were obtained from patients with asthma, from 34 age-matched patients presenting to the ER during the same time period with any diagnosis other than asthma or rhinitis, and also from 25 age-matched employees. All subjects filled out a brief questionnaire concerning their home environment and their history of allergy, asthma, and rhinitis.

Serum assays for IgE Abs

Sera were analyzed for presence of IgE Ab to five inhalant allergens (dust mite [*D. farinae*], cat dander, cockroach,

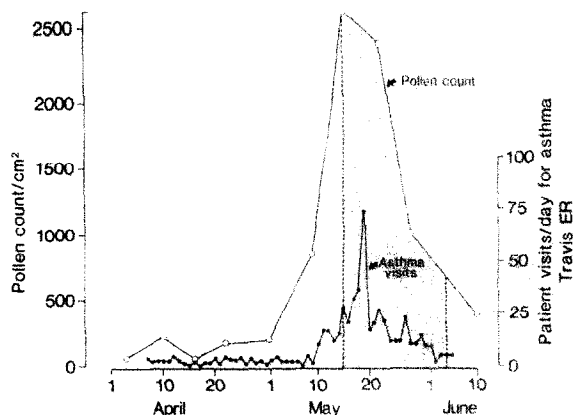


FIG. 1. Ryegrass-pollen counts and patient visits for asthma at TAFB during the spring of 1986. Pollen counts recorded from a gravity collector located on the roof of the allergy clinic at TAFB and expressed in counts per square centimeter (○—○). Total patient visits for asthma recorded daily (●—●). Shaded area indicates the study period.

ryegrass pollen, and short ragweed pollen) with RAST, as previously described.¹¹⁻¹³ Results were quantitated by reference to a single control curve with *D. farinae* disks and a mite-allergic serum pool (UVA 85) that had been substandardized against the National Institute of Biological Standards and Control *D. farinae* reference serum (82/528) and contains 1000 RAST units of IgE Ab to *D. farinae*. All sera were assayed at two dilutions, 1:2 and 1:10, and results in units were extrapolated from the control curve (each RAST unit is ~ 0.1 ng of IgE). In each assay, five positive and five negative control sera were run. *Cladosporium* and cottonwood disks were obtained from Pharmacia (Piscataway, N.J.), and sera from 30 patients with asthma were screened for presence of IgE Ab to these two aeroallergens.

House dust samples and allergen assays

Dust samples were obtained from four locations in 15 homes of the patients with asthma within 2 weeks of the patients' ER visit. Samples were obtained from a 1 m² area of the living room carpet, the bedroom carpet, the bedding and/or from the surface of the living room furniture. The sampled areas were vacuumed for 2 minutes each with a specially adapted vacuum cleaner (Douglas hand vacuum, Douglas Products, Walnut Ridge, Ark.). Dust samples were assayed for levels of mite, cat, ryegrass, and cockroach allergen.

Dust samples were first sieved, and 100 mg of dust was extracted with 2 ml of buffered saline. The extracts were stored at -30° C. The dust mite allergens (*Der f* I and *Der p* I) and cat allergen (*Fel d* I) were measured with a two-site monoclonal antibody radioimmunoassay, as described previously, and the results were expressed as micrograms per gram of dust.¹⁴ Ryegrass-pollen allergen was measured by two-site radioimmunoassay with rabbit antisera to *Lol p* I as capturing Ab, followed by human IgE Ab

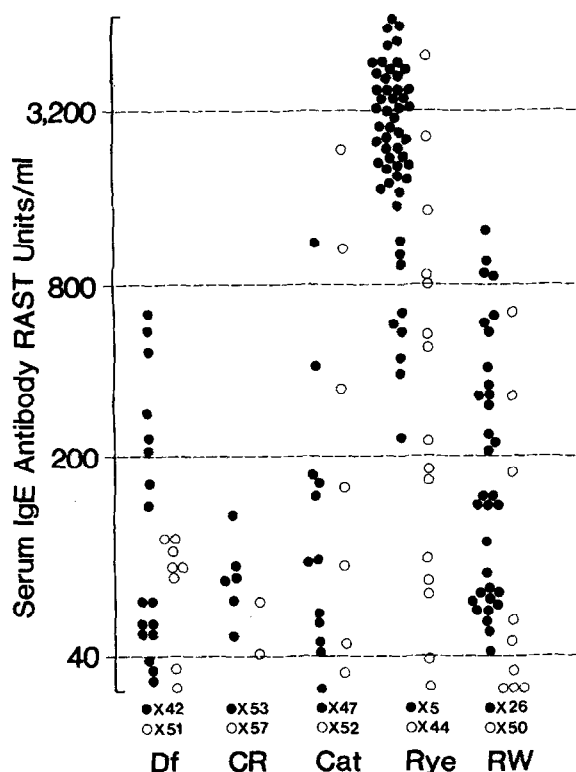


FIG. 2. Levels of serum IgE Ab in patients with asthma (●) and control subjects (○) to five inhalant allergens (dust mite [*D. farinae*], cat, cockroach, ryegrass, and ragweed pollens). Results expressed in RAST units with each unit ~ 0.1 ng of IgE. Levels >40 are positive, >200 are elevated, >800 are highly elevated. Values not depicted on graph (i.e., ● X 42 and ○ X 51 for Df) had no measurable IgE Ab to the specific allergen.

(serum from a patient who was highly allergic to grass pollen), and ^{125}I -labeled anti-IgE to detect bound grass-pollen allergen. This assay has been described in detail previously¹⁵ and results are expressed as units of ryegrass-pollen allergen. However, comparison of the binding curves with purified *Lol p I* (provided by Dr. David Marsh, Johns Hopkins University) suggested that 1 unit of ryegrass contained ~ 0.1 ng of *Lol p I*, and the results are presented here in micrograms of *Lol p I* per gram of dust. Cockroach allergen was measured with RAST inhibition, with mixed cockroach allergen on cellulose disks, with tenfold less allergen than was used to measure IgE Ab to increase sensitivity (i.e., 100 μl of 1/200 dilution of a 10 mg/ml solution added to each disk).

In March 1987, 8 months after the completion of the initial phase of the study and before the 1987 pollen season, the patients with asthma were recontacted by telephone and questioned concerning their symptoms since the 1986 pollen season and their ongoing medication needs. Ten of the homes that had been visited in 1986 were visited to obtain dust samples again in March 1987, and the second dust samples were assayed for ryegrass pollen and mite antigens.

Statistics

Results for IgE Ab in sera were compared with the chi-square test. The odds ratios or relative odds that define the odds of a disease occurring in exposed individuals relative to the odds of disease occurring in unexposed individuals were calculated as described by Schlesselman.¹⁶

RESULTS

In 1986, the ryegrass-pollen count in Fairfield County, California, peaked at >2000 counts per square centimeter during the week of May 19 to 26. During this same week, 205 patients visited the ER at the DGMC complaining of shortness of breath and were treated for acute asthma (Fig. 1). This accounted for $>40\%$ of the 496 total visits to this ER for asthma during the year from July 1985 through June 1986.

There was a highly significant increased prevalence of elevated serum IgE Ab to ryegrass pollen among patients with asthma; 54/59 patients with asthma had >200 RAST units of IgE Ab compared to 8/59 control subjects ($\chi^2 = 69$; $p < 0.0001$; odds ratio = 69) (Fig. 2). Similarly, 48/59 patients with asthma versus 4/59 control subjects had >800 RAST units of IgE to ryegrass pollen ($\chi^2 = 60$; $p < 0.0001$) (Table IA). All eight of the control patients with elevated levels of IgE Ab to ryegrass pollen reported symptoms of rhinitis and/or conjunctivitis during the study period. Similarly, most of the patients with asthma were aware of symptoms of seasonal hay fever. The composition of the control population was analyzed for three different variables: whether they were patients or employees, their age, and length of stay at TAFB. When the control subjects were matched to the patients with asthma for all three variables, the differences between the groups remained highly significant ($\chi^2 = 38$; $p < 0.0001$; data not presented).

Patients with asthma also had an increased prevalence of IgE Ab to ragweed with 15/59 patients with asthma versus 2/59 control subjects having >200 RAST units. All 17 of the individuals with elevated levels of IgE Ab to ragweed pollen also had elevated levels of IgE Ab to ryegrass pollen. There was no significant difference between patients with asthma and control subjects in prevalence of IgE Ab to the indoor allergens (dust mite, cockroach, and cat). Seven patients with asthma and three control subjects had >200 RAST units per milliliter of IgE to one of these three allergens ($\chi^2 = 0.98$; $p > 0.1$; odds ratio = 2.5) (Table IB).

During the 4-week period surrounding their peak, the grass-pollen counts rose from 184 counts per square centimeter in early May and fell to 200 counts per square centimeter by the second week of June. During this same period, several other aeroallergens,

TABLE IA. Prevalence of IgE Ab to ryegrass pollen*: Study at TAFB

Max RAST†	Ryegrass				X ²	p Value
	Asthma		Control			
	No.	%	No.	%		
>800	48	81	5	8	60	<0.0001
>200	54	92	8	14	69‡	<0.0001
>40	54	92	13	22	55	<0.001
<40	5	8	46	78		

Max = maximum.

*IgE Ab to ryegrass-pollen allergen measured in serum of 59 randomly selected patients with asthma treated in the Travis Air Force Base emergency room and 59 age-matched randomly selected control subjects.

†IgE levels expressed in RAST units. Each unit is ~0.1 ng of IgE.

‡When employees are excluded from the control group, $\chi^2 = 38$; $p < 0.0001$.

TABLE IB. Prevalence of IgE Ab to the indoor allergens*: Study at TAFB

Max RAST†	Ryegrass				X ²	p Value
	Asthma		Control			
	No.	%	No.	%		
>800	1	2	2	3	0.34	>0.1
>200	7	12	3	5	0.98‡	>0.1
>40	22	37	12	20	4.1	>0.1
<40	37	63	47	80		

*IgE antibody to one of the indoor allergens (dust mite, cat, or cockroach) measured in the serum of 59 randomly selected patients with asthma treated in the Travis Air Force Base emergency room and 59 age-matched randomly selected control subjects.

†IgE levels expressed in RAST units. Each unit is ~0.1 ng of IgE.

‡When the dust mite data were analyzed independently, a small but statistically significant difference was found in the prevalence of IgE antibody to *Der f I* between patients with asthma and control subjects (6/59 versus 0/59; $\chi^2 = 4.4$; $p = 0.034$).

including the pollens of juniper, cottonwood, eucalyptus, cedar cypress, and ragweed, and also a variety of fungal spores, were recorded at TAFB. The only significant increases involved cottonwood (240 counts per square centimeter, May 19), juniper (326 counts per square centimeter, May 28), and *Cladosporium* (129 counts per square centimeter, May 5). Assaying sera of 30 patients for IgE Ab to cottonwood pollen and *Cladosporium* revealed no positive results.

The high pollen counts recorded locally indicated that all subjects were exposed to high levels of pollen allergen outside the home. To examine exposure to pollen and other allergens in patients' homes, 41 dust samples from 15 homes were assayed for levels of dust mite, cat, cockroach, and ryegrass allergen (Table II). On average, the levels of grass-pollen allergen were tenfold to 100-fold higher than values previously obtained inside homes during peak pollen season in central Virginia.¹⁵ In 13/15 houses, at

least one sample had >10 $\mu\text{g/gm}$ of grass allergen, and 15/15 houses had at least one sample with >2 $\mu\text{g/gm}$. Only two dust samples had levels of mite allergen >2 $\mu\text{g/gm}$ of dust. The remaining 13 homes had levels of mite allergen less than the levels that have been associated with exacerbations of atopic disease in allergic individuals.¹⁵ All 13 samples taken from the four homes with cats had levels of the cat allergen *Fel d I* >10 $\mu\text{g/gm}$ of dust, whereas only 4/28 samples from three of the 11 homes without cats had similar elevations. Patients living in the four homes with elevated levels of cat allergen had negative serum assays for IgE Ab to cat. None of the dust samples contained detectable cockroach allergen, as measured by RAST inhibition.

In March 1987, 24 of the 59 patients originally enrolled in the study were contacted and questioned concerning their asthma history since May 1986. None of the 24 patients interviewed reported symptoms dur-

TABLE II. Allergen levels in dust from the houses of patients admitted to the TAFB emergency room with asthma, May 1986

Allergen concentration $\mu\text{g/gm}$ of dust	No. of houses with a given allergen concentration							
	May 1986*					March 1987†		
	Dust mite		Cat		Grass	Dust mite		Grass
	<i>Der f I</i>	<i>Der p I</i>	(cat + ve) <i>Fel d I</i>	(cat - ve) <i>Fel d I</i>	<i>Lol p I</i>	<i>Der f I</i>	<i>Der p I</i>	<i>Lol p I</i>
>50	0	0	3	1	5	0	0	0
11-50	0	3	1	2	8	0	0	0
2-10	2	0	0	4	2	2	1	3
<2	13	12	0	4	0	8	9	7

*Forty-one samples were obtained from 15 houses; the values demonstrate the highest levels found in any dust sample for each house.

†Ten samples from 10 houses.

‡Values assume that 1 Food and Drug Administration unit of *Fel d I* equals 4 μg and 1 unit of grass allergen equals 0.1 ng of *Lol p I*. Values for mite allergens are obtained from extracts substandardized against the International Union of Immunological Societies standard National Institute of Biological Standards and Control 82/518.

ing March 1987, and only 4/24 had continued with medical therapy after June 1986. All four patients who had required continuing medical therapy had been controlled on a theophylline preparation alone. Dust samples were obtained in March 1987 from 10 of the 15 homes originally sampled, and these were assayed for mite and ryegrass allergen. All 10 homes had levels of both allergens that were $<10 \mu\text{g/gm}$ of dust. Seven of the 10 homes had $<2 \mu\text{g}$ of ryegrass-pollen allergen compared to 0/15 homes with $<2 \mu\text{g}$ of ryegrass allergen per gram of dust in May 1986. In the three homes with levels of ryegrass allergen $>2 \mu\text{g/gm}$ of dust in March 1987, this level nevertheless represented an 80% to 98% decrease in allergen level from their initial sampling in May 1986. Eight of 10 homes sampled in March 1987 had $<2 \mu\text{g}$ of mite allergen per gram of house dust compared to 13 of 15 houses with similar levels in May 1986.

DISCUSSION

Previous work has suggested that there is a much higher prevalence of asthma associated with allergy among adults between 18 and 50 years of age than the 10% that is reported in standard medical texts.^{7,8} The patients evaluated in a year-round study in Virginia were often unaware of the association between inhalant allergens and their asthma, presumably because their acute attacks were triggered by nonallergic factors and not by direct exposure to an allergen. However, correlations found between mite-sensitive patients presenting with an acute flare of asthma during the months of peak mite-allergen levels and pollen-

sensitive patients requiring ER treatment most often during the months surrounding the peak pollen counts suggested that the acute symptoms in the allergic patients were related to exposure.

The yearly asthma "epidemic" at TAFB is an ideal situation to investigate further the association between the development of immediate hypersensitivity, continued exposure to a relevant allergen, and presentation with acute attacks of asthma. It has previously been reported that many of the patients with asthma presenting during the pollen season demonstrated immediate hypersensitivity to ryegrass pollen and could benefit from immunotherapy with this allergen.¹⁰ The present study demonstrates a clear difference between patients with asthma and control subjects in the prevalence of IgE Ab to ryegrass pollen. Furthermore, patients with asthma presenting during the peak pollen count did not differ significantly from control patients in the prevalence of IgE to cat, cockroach, and mite allergens. These allergens are common in other parts of the country but, with the exception of cat allergen found in homes with cats, were not found in significant quantities in the homes we sampled in the TAFB area during May.

Previous studies have suggested that levels of mite allergen $>10 \mu\text{g/gm}$ of dust are associated with exacerbations of allergic disease and levels from 2 to 10 $\mu\text{g/gm}$ of dust increase an atopic individual's chance of developing allergic symptoms.¹⁵ In examining the environment of the patients with asthma at TAFB, it is clear that pollen allergen is not only airborne outdoors during May but also gains entry into patients'

homes, and high levels were found in carpeting, bedding, and upholstered furniture. During May, the outdoor temperature averages $\sim 70^{\circ}$ F and falls to $\sim 55^{\circ}$ F at night with a relative humidity of $\sim 40\%$. The low levels of mite allergen are consistent with the low humidity in these houses.^{17, 18} Homes are ventilated primarily through window opening, and pollen entry through these open windows is often accelerated by the use of window fans, resulting in indoor pollen levels of >50 $\mu\text{g/gm}$ of dust. These levels decrease to "normal" outside the pollen season. Our results do not allow us to analyze what proportion of pollen exposure occurred indoors; however, most patients spent far more time indoors than outdoors, and it appears possible that "indoor" pollen could make a significant contribution to pollen exposure.

The results of this study support the view that atopic individuals who have developed IgE Ab to an environmental allergen are at increased risk for developing acute attacks of asthma during periods of continued exposure. Although the data suggest very strongly that, at TAFB, the patients presented to the ER because of exposure to pollen, the results do not explain why they presented on a particular day. It is possible that presentation is related to airborne-pollen quantity; however, it is also possible that the timing was triggered by one of the many nonspecific factors known to exacerbate asthma. Some of these atopic individuals may have developed increased bronchial hyperreactivity as a result of repeated exposure to pollen.^{19, 20} In general, the patients were not aware of having inhaled pollen on any particular occasion, but they did associate their asthma with the period of the year when they experienced rhinitis/conjunctivitis symptoms. After their ER admission, these patients were treated aggressively with bronchodilators and local and systemic steroids, if these were needed. Approximately 80% of the patients interviewed 8 months after the study period had had no further exacerbations of disease.

The implications of our findings for the therapy of asthma are numerous. To the health care personnel serving this patient population, our findings present a good case for prophylactic treatment of asthma in sensitized individuals. Patients can be educated about local pollen counts during the spring and can attempt to reduce the introduction of pollen into their home, as local pollen counts rise. Reliable patients can be supplied with starter supplies of bronchodilators and local or oral corticosteroids to take at the onset of coughing or shortness of breath. Patients who respond poorly to medical therapy or who have contraindications to asthma medications can be treated with

immunotherapy, which is successful in preventing not only rhinitis/conjunctivitis symptoms but also flares of asthma.¹⁰

Our findings reinforce our previous work concerning the role of other inhalant allergens in adult asthma. Clearly, in certain circumstances, allergy plays a role in $>10\%$ of cases of acute asthma and, in the population reported here, can be associated with $\geq 90\%$ of the cases presenting during the pollen season. Although the level of airborne pollen is much higher in northern California than in the rest of the country, other allergens may be just as significant in specific locations at different times of the year. *Alternaria* and *Cladosporium* spore counts can rise to very high levels during local growing seasons in the central plains areas of the United States. Similarly, in the southeast and on the gulf coast, many houses develop very high levels of mite allergen during the late summer and fall.^{15, 21} Once it is recognized that an individual patient with asthma is allergic to an allergen, it is logical to advise the patient to reduce exposure. This is true both for the indoor allergens and also for pollens. It remains to be demonstrated that closing houses and using air conditioning will reduce the risk of asthma in pollen-allergic patients. However, we have already found that individual houses in which air-conditioning is used have lower levels of grass-pollen allergen (unpublished data).

The rise in asthma morbidity and mortality that was observed in the United States in the past several years²² suggests greater effort is needed in investigating the etiology of adult asthma. At present there is very little data on the role that allergens play in asthma mortality. However, the evidence that inhalant allergens play a major role in acute attacks of asthma suggests that they may also play a role in the increased mortality. Although it is still unclear what percentage of cases of asthma can be attributed to allergy, it appears to be at least 50% in adults younger than 50 years of age. In order to reduce asthma morbidity and mortality, we believe these specific IgE Ab responses should be identified and that patients should be educated to the adverse effects of continued exposure to these allergens in the same manner that patients with coronary vascular disease are warned of the effects of continued tobacco abuse or untreated hypertension.

Although it is not possible to predict which of the sensitive patients will develop acute asthma, it is rational to attempt to reduce this risk. In the present study the clinical course of the patients demonstrates that reduced exposure (outside of the pollen season) reduces their symptoms and the risk of acute attacks. Allergen avoidance has already been dem-

onstrated to be effective in the treatment of mite-allergic asthma.²³⁻²⁵ The implication is that specific sensitivity should be identified in patients with acute or chronic asthma and should be used as a basis for advice on allergen avoidance.

We thank Dr. Edward E. Philpot and Dr. J. D. Sprenger for allowing us to study patients under their care, TSgt J. Michael Kwasnicki and Martha Brown for their excellent technical assistance, and the physicians and staff of the DGM C ER for their cooperation with our study.

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