

Association of Asthma with Serum IgE and Skin Test Reactivity to Allergens Among Children Living at High Altitude

Tickling the Dragon's Breath

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Asthma in children and young adults is strongly associated with immediate hypersensitivity to indoor allergens, notably those derived from the house dust mite. In addition, outdoor air pollution is considered to aggravate existing asthma. We investigated the prevalence of asthma and the pattern of allergen sensitization in a mite-free environment with low levels of outdoor air pollution. A total of 567 children aged between 12 and 14 attending Los Alamos Middle School, NM (altitude 7,200 feet) were screened using a respiratory questionnaire; 120 children (53 control children) underwent allergen skin testing and serum IgE measurement, and their bronchial reactivity to histamine was measured. Dust was collected from 111 homes and the level of indoor mite and cat allergen measured. The prevalence of respiratory symptoms was high (13%), and from the detailed testing it was estimated that 6.3% of the children had asthma (defined as symptomatic bronchial reactivity). Children with asthma had elevated IgE, 367 (179 to 755) versus 38 (23 to 61), and predominant sensitization to cat, 68 versus 20% ($p < 0.001$). A high number of households (77%) had a pet cat or dog. The concentration of mite allergen was very low (mean $0.18 \mu\text{g Der p I/g}$ sieved house dust), whereas that of cat allergen was high in homes with a cat ($80.8 \mu\text{g Fel d I/g}$) but also in homes with no cat ($3.2 \mu\text{g Fel d I/g}$). The results show that in a mite-free environment with low levels of outdoor air pollution, asthma was still a major cause of morbidity among schoolchildren. Asthma was strongly associated with elevated IgE and sensitization to other indoor allergens, notably those derived from cat. **Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TAE. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med* 1995;151:1388-92.**

There is a growing body of evidence to suggest that in genetically predisposed individuals, a causal relationship exists between exposure to indoor allergens and the development of asthma (1). In many areas of the world, allergens derived from the house dust mite are of prime importance (2-4). Indeed, it has been proposed that changes in houses that have led to increased mite growth have been an important factor in progressive increases in the prevalence of asthma. The mite content of house dust decreases with increasing elevation in temperate climates. Charpin and colleagues reported reduced levels of dust mite allergen, a lower

prevalence of sensitization, and a lower prevalence of asthma among schoolchildren living in Briançon (elevation 4,350 feet) in the French Alps (5). However, in these and other areas with limited mite exposure, such as in Scandinavia, asthma is not unknown (6, 7). Neither is the morbidity caused by asthma limited in North America to areas with the highest mite exposure (8). This has been interpreted as suggesting that additional allergens are of importance or that non-IgE-mediated mechanisms may contribute to the development of asthma in children. Growing public concern has focused attention on the role of outdoor air pollution in aggravating respiratory illness (9). However, it is unclear whether outdoor air pollution has a primary role in the initiation of asthma (10, 11). We investigated a population of North American schoolchildren living at high altitude in Los Alamos, New Mexico (elevation 7,200 feet). The location of this research community was originally chosen to be remote from both industrial and city areas. Our aims were to report the prevalence of asthma and to reexamine the association between asthma and allergen sensitization in a house dust mite-free, low air pollution environment.

METHODS

Los Alamos, New Mexico (population around 12,000) is one of the highest

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Experiments were carried out in Los Alamos, New Mexico, to determine the critical mass of plutonium by incremental increases, described by R. Feynman as "tickling the dragon's tail." (Feynman, R., and R. Leighton. 1986. Surely You're Joking Mr. Feynman! Adventures of a Curious Character. Unwin.)

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stable communities in North America. A large, predominantly white (of mainly European ancestry) population lives at an altitude of 7,200 feet. This isolated scientific community consists of a research complex, residential areas, the Middle School (elevation 7,200 feet), and the dormitory suburb of White Rock (elevation 6,400 feet). We have undertaken a study of respiratory symptoms in a general population of children aged between 12 and 14. All children attending seventh and eighth grades at Los Alamos Middle School were eligible for enrollment. Ethical permission was obtained from the Human Investigation Committee of the University of Virginia and from the Los Alamos Medical Center. In addition, permission for the study was obtained from the Board of Governors of the Los Alamos Middle School.

A respiratory questionnaire, based on Woolcock's modified American Thoracic Society questionnaire for children, was administered as part of a science class (12). A similar questionnaire was mailed to the parents of each child at the same time as permission was sought to include the child in the study. The school study period was 1 wk in March 1992. Parents who did not respond to the first mailing were sent an additional questionnaire 1 month later. The questionnaire inquired into respiratory symptoms, the current use of medications for asthma, their past and current smoking habits, and the presence of household pets. The parents' questionnaire asked additional questions about the child's respiratory symptoms, whether a physician diagnosis of asthma had ever been made, medications used, emergency room attendances, hospital admissions, period of residence in Los Alamos, and parental smoking. Of the 600 children enrolled in the school, information was obtained on 95% (567, including 285 boys). A total of 525 student questionnaires were completed and 520 parental questionnaires were returned.

On the basis of the questionnaire responses, the children were divided into two groups: those who had respiratory symptoms and/or treatment for asthma and those who did not. If there was a discrepancy between parental and student responses, the parental responses were used. Those with no respiratory problems were randomized and invited to attend for the second phase of the study. In addition, those with respiratory problems were stratified according to severity and sequentially invited to attend, commencing with the most severe. An equal number of symptomatic and control children were invited to participate in the second phase of the study, undertaken at the Los Alamos Medical Center. A total of 120 children (54 control children) underwent skin prick testing and venipuncture, and their bronchial responsiveness to histamine was assessed. Skin reactivity to extracts of the house dust mites (*Dermatophagoides farinae*

and *Dermatophagoides pteronyssinus*), cockroach, cat dander, and pollens (grass mix, ragweed mix, mountain cedar, Russian thistle, common sagebrush, grama grass, and a tree mix) (Miles, Spokane, WA) was assessed using a lancet technique (13). The wheal diameter was measured after 15 min, and the responses were compared to a negative (diluent) and a positive (histamine, 1 mg/ml) control. A positive reaction was recorded if the mean diameter of the skin wheal was ≥ 4 mm larger than the negative control. Blood was obtained from 108 children and total IgE was measured. The children were considered atopic if they showed a positive skin wheal to one or more allergen.

A DeVilbiss hand-held nebulizer (DeVilbiss Health Care, Somerset, PA) was used to assess bronchial responsiveness to inhaled histamine in the children according to the technique of Yan and colleagues (14). After saline challenge, increasing doses of histamine were administered and followed 1 min later by measurements of forced expiratory volume in one second with a Vitalograph spirometer (Vitalograph Inc., Lenexa, KS). The histamine dose was progressively doubled until the forced expiratory volume in one second decreased to 80% of the value after saline challenge. Children were considered hyperresponsive if this occurred at or before the maximal cumulative dose of 7.8 μ mol histamine. The output of the nebulizers was calibrated in Los Alamos. Medications were withheld before testing. In this age group, the test has been shown to be repeatable within one doubling dilution of histamine (12). Children whose initial forced expiratory volume was below 80% of that predicted for their height underwent a bronchodilator test and were considered to show bronchial responsiveness if their forced expiratory volume improved by 20% from baseline following two puffs (400 μ g) of albuterol. The children were considered to have asthma if they reported wheezing in the previous year and showed bronchial responsiveness to 7.8 μ mol or less of histamine.

Dust was collected by a standard procedure from the mattress, bedroom floor, livingroom floor, and kitchen floor during September 1992 (15). The dust was sieved and weighed, and after aqueous extraction the content of *Der p* 1, *Der f* 1, and *Fel d* 1 allergens were measured using two-site monoclonal antibody enzyme-linked immunoassays (16, 17). These allergens are those derived from the house dust mites (*D. pteronyssinus* and *D. farinae*) and cat, respectively. In keeping with the recommendations of an international workshop, the results were expressed as micrograms allergen per gram sieved dust (μ g/g) (18). The limit of detection of *Der p* 1 and *Der f* 1 was 0.1 μ g/g.

The level of ambient ozone, nitrogen dioxide, sulfur dioxide, and particulate matter (PM₁₀) during the study period was obtained from routine

TABLE 1
PREVALENCE OF REPORTED RESPIRATORY DISORDERS

	Phase 1			Phase 2	
	Total		Born in Los Alamos† (%)*	Respiratory Symptoms	Control Subjects
	%*	Boys:Girls			
Student self-assessment	n = 525		n = 255	n = 67	n = 53
Asthma ever	17.4	53:39	16.8	53	2
Asthma last year	13.2	40:30	12.8	44	1
Wheeze last year	19.2	51:50	19.1	34	8
Current medications for asthma	13.6	40:32	14.0	48	1
Parental assessment	n = 520		n = 255	n = 67	n = 53
Wheeze last year	17.8	50:42	15.7	53	0
Physician diagnosis asthma ever	17.6	52:40	15.3	56	0
Resident smoker	11.9	32:30	11.0	8	6
Medications for asthma ever	19.0	58:41	17.6	60	0
ER attendance for asthma ever	6.5	25:9	6.3	27	0
Hospital admission asthma ever	2.9	12:3	2.0	11	0

* Percentage of completed questions.

† Children born and raised in Los Alamos.

measurements made by a monitoring station of the Environment Department of the State of New Mexico sited at Los Alamos. Ozone, nitrogen dioxide, and sulfur dioxide measurements were made hourly; PM₁₀ measurements were made weekly. Comparisons between clinical groups were made by nonparametric methods. Contingency tables were analyzed by the chi-square method. Odds ratios were calculated as the ratio of exposure to nonexposure among the children with asthma.

RESULTS

Reported Prevalence of Respiratory Symptoms

The reported prevalence of respiratory symptoms was high, judged by both the student and parental surveys (Table 1). Of all children, 13% reported that they had an episode of asthma in the last year and 14% were currently on medication for asthma. This prevalence was confirmed by the parental questionnaires. In addition, the parents reported that 18% of the children had been given a physician diagnosis of asthma at some time in their lives. A total of 99 children had taken medications for asthma, which included 90 children who had used β_2 agonist inhalers. The prevalence of respiratory symptoms was not significantly lower among children born and raised in Los Alamos. In particular, the prevalence of wheeze in the last year (19.1%) and current medications for asthma (14%) was exactly the same in this group. The reported prevalence of smoking was low: 62 children lived in a house with a smoker; 106 children (58 boys) admitted to having smoked at some time; and 9 children had smoked more than 10 cigarettes in the previous week.

Prevalence of Asthma

A total of 120 children were studied in Phase 2 (Table 1). They consisted of a group with reported respiratory problems and a control group. The first group contained the majority of asthmatic children requiring regular treatment. Bronchial responsiveness to histamine (BHR) was seen almost exclusively in this group, although only a third of the children reacted to ≤ 7.8 μmol hista-

mine (Table 2). Only 16 children responded to ≤ 3.8 and 8 to ≤ 1 μmol histamine. The prevalence of BHR among the children with respiratory symptoms was 33%, and 23 children met the definition of asthma. The extrapolated prevalence of asthma in the whole population was 6.3%, assuming that of the 467 unstudied children with parental reports, among the 39 with reported wheeze in the last year, there was a similar proportion of children with histamine bronchial hyperreactivity as in the 53 studied. If a more stringent threshold of bronchial hyperresponsiveness was used (provocative concentration of histamine producing a 20% fall in FEV₁ ≤ 3.8 μmol), the extrapolated prevalence fell to 5.3%.

Outdoor Air Pollution and Indoor Allergen Concentration

The levels of outdoor pollution in Los Alamos were low. The monthly mean (and maximum) levels of ozone was 0.051 (0.078) ppm, and no value exceeded the U.S. Environmental Protection Agency ambient air quality standard of 0.12 ppm. The mean (and maximum) levels of other pollutants were also very low: for nitrogen dioxide, 0.003 (0.008) ppm, sulfur dioxide, 0.001 (0.001) ppm, and particulate matter, PM₁₀, 8 (21) $\mu\text{g}/\text{m}^3$. House dust samples were collected from the homes of 111 children. The level of mite allergens was very low, bordering on the level of detection of the assay. The geometric mean value of *Der p 1* and *Der f 1* was 0.18 and 0.13 $\mu\text{g}/\text{g}$, respectively. In only five samples was the value greater than 2 μg per gram sieved dust, and four of these samples came from a household relocated from the East Coast 9 mo previously. Overall, a large number of households had a pet cat or dog: 189 (37%) reported a cat and 315 (61%) homes a dog. Indeed, 392 (77%) households contained either a cat or dog. Of the homes from which dust was collected, 50 (45%) contained a cat. The mean concentration of cat allergen in homes with and without a cat was 80.8 (53.2 to 122.8) and 3.2 (2.3 to 4.4) $\mu\text{g}/\text{g}$ of *Fel d 1* (95% confidence interval), respectively. Cat allergen was detectable in all houses, and high concentrations were found in some homes without a cat (Figure 1).

Allergen Sensitization

The prevalence of atopy was very high in symptomatic and control children, 73 and 64%, respectively (Table 2). The prevalence of sensitization to pollens was especially high in both groups. By contrast, more of the asthmatic children were sensitized to indoor allergens, and the mean total IgE was higher among the asth-

TABLE 2
ALLERGEN SENSITIZATION AND BRONCHIAL
HYPERRESPONSIVENESS OF CHILDREN STUDIED IN PHASE 2

	Children with Respiratory Symptoms n = 67 (35 boys)	Control Children n = 53 (25 boys)
Atopic*	49 (28 boys)	34 (15 boys)
Sensitized to*		
Cat	26	7
<i>D. pteronyssinus</i>	18 [§]	5
<i>D. farinae</i>	14	6
Cockroach	17 [§]	5
Mountain cedar	29	17
Russian thistle	24	14
Common sagebrush	20 [§]	7
Ragweed	15 [†]	5
Grass grass	25	16
Grass mix	31	26
Tree mix	15	6
BHR†	22 [†]	1
Mean IgE, IU/ml	99	48
95% confidence interval	60–162	28–80

* A skin wheal ≥ 4 mm on allergen skin prick testing.

† Bronchial hyperresponsiveness to ≤ 7.8 μmol $\dagger$ histamine (see METHODS).

‡ p < 0.05 compared with control children.

§ p < 0.025 compared with control children.

† p < 0.001 compared with control children.

|| p < 0.005 compared with control children.

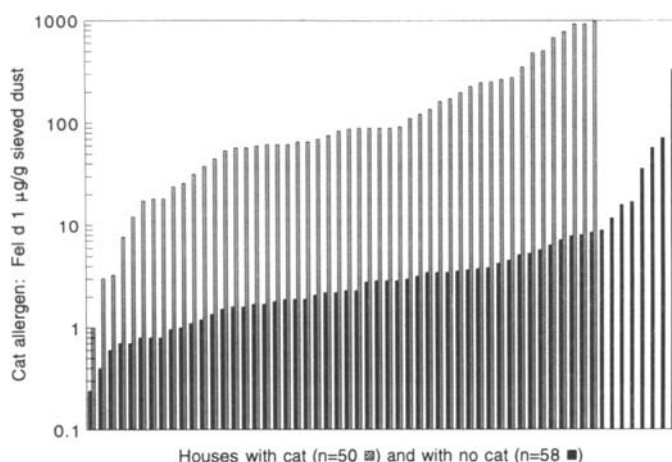


Figure 1. The ranked concentration of cat allergen (*Fel d 1*, $\mu\text{g}/\text{g}$ sieved dust) in homes sampled with (n = 50, hatched bars) and without (n = 58, solid bars) a cat.

matic children. The relationship between allergen sensitization, lifetime residence, atopy, and asthma was further analyzed in three groups of children: those born and raised in Los Alamos, those who demonstrated bronchial hyperreactivity to histamine, and those with asthma (Table 3). Among the lifetime residents of Los Alamos, the striking difference was that fewer were sensitized to house dust mites ($p < 0.025$). Among the 23 children who demonstrated bronchial hyperreactivity to histamine, cat and cockroach sensitization was more prevalent ($p < 0.001$ and $p < 0.025$, respectively). The levels of serum IgE were highest in this group. In the group with asthma, 16 of 19 (84%) were sensitized to either cat, mite, or cockroach compared with 37 (36%) of the remaining 101 children studied ($p < 0.001$).

In this virtually mite-free environment, the presence of bronchial hyperreactivity to histamine or asthma was not associated with sensitization to the house dust mite. In contrast, exposure to cat allergen was common and cat sensitization was strongly associated with asthma. Indeed, 10 of the 16 children with asthma whose houses were visited were both cat sensitized and exposed to $> 10 \mu\text{g}$ cat allergen/g dust compared with 19 of 90 of those without asthma ($p < 0.001$). The odds ratio (95% confidence interval) for a child who was both cat sensitized and exposed to cat allergen having asthma was 6.2 (2.2 to 17.6).

DISCUSSION

In this population-based study of children living at high altitude, respiratory symptoms were very common. Of all children, 13% reported having an episode of asthma in the previous year and 18% had a diagnosis of asthma or had used medications for asthma. However, the severity of asthma judged by emergency room (ER) attendance, hospital admittance, and objective measurements of nonspecific hyperresponsiveness to histamine was low. Indeed, the majority of children who reported having current wheeze failed to demonstrate any responsiveness to histamine. Depending on the criteria used to define asthma, the point prevalence

ranged from 13.2% (based on questionnaire responses) to 6.3% (based on the subset of children studied who had symptomatic bronchial hyperresponsiveness). Extrapolating prevalence from studies of an incomplete group selected sequentially according to the severity of symptoms may be insecure. This latter prevalence could be an overestimation because the children with the most persistent symptoms were invited to participate first. Ideally the entire population would have been tested, but this was impractical. Indeed, provocative testing in general populations of schoolchildren is an area of research that before this study was rarely undertaken in North America. Over half of the self-reported "asthmatic" population and an equal number of control children were studied. Many workers have commented that an accurate measure of asthma prevalence remains elusive. The use of objective measurements of bronchial responsiveness to histamine has been advocated; although a considerable number of children wheeze but do not show histamine bronchial responsiveness, and a few children do not wheeze but show histamine bronchial responsiveness (19). Despite these limitations, Woolcock and colleagues proposed that asthma can be defined as symptomatic bronchial hyperresponsiveness (20). This definition provides a practical epidemiologic tool that enables comparisons to be made of populations living in different environments. Published reports of general populations of children living at sea level studied using the same methodology have shown the prevalence of asthma to be 7.2% in New Zealand (19) and 9.6% in coastal Australia (12).

Although the prevalence of asthma in our study was lower than that reported from Australasia, it is clear that asthma was still very common in Los Alamos. Indeed, there were clearly children born and raised in this town who had asthma. The persistence of asthma in this community cannot be explained by air pollution, by passive tobacco smoke, or by mite allergen exposure. The ambient levels of air pollution were low. The prevalence of smoking in this community was low, and there was no significant association between active or passive smoking and respiratory symptoms. The concentration of house dust mite allergens found in the homes was extremely low, and sensitization to the house dust mite was unusual among children born in Los Alamos. Survival of the house dust mite is critically dependent on relative humidity, which at this altitude, even during the "moistest" month of September, is too low for mite growth (21). The concentration of house dust mite allergens was well below the thresholds suggested for the development of sensitization or asthma (18, 22). However, the relationship between total serum IgE and asthma was very similar to that reported for lowlander populations (23, 24). Indeed, it was recently reported that the level of IgE correlated with the presence of bronchial responsiveness to histamine in a general population study of schoolchildren (25). In our population there is no need to invoke novel mechanisms to explain the development of asthma, which again appeared to be associated with the presence of immediate hypersensitivity. However, the pattern of sensitization reflected exposure to local allergens. Sensitization to the house dust mite was unusual among children born in Los Alamos. Sensitization to pollens was very common, as has been found in other high-altitude populations (5), but pollen sensitization was not associated with asthma (5, 24). In contrast, the strongest associated risk factor for the presence of asthma was cat sensitization. A large number of households had a cat, and these remained indoors during the night for fear of coyotes. High levels of cat allergen were also found in some homes without a cat, as has been previously reported, suggesting that exposure to this allergen was very common in this community. Studies undertaken at sea level have consistently found that the majority of asthmatic children are strongly sensitized to house dust mite (1). Recent studies of chil-

TABLE 3
ALLERGEN SENSITIZATION OF SUBGROUPS OF
CHILDREN STUDIED IN PHASE 2

	Total	Born in Los Alamos*	BHR†	Asthmatics‡
n =	120	60	23	19
Atopic	84	41	19	17††
IgE, IU/ml	73	66	407	367
95% CI	51–105	40–108	210–790	179–755
Sensitized to				
Cat	33	14	15**	13**
<i>D. Pteronyssinus</i>	23	6§	7	6
<i>D. farinae</i>	20	4§†	5	4
Cockroach	22	10	8	7
Mountain cedar	46	22	12	9
Russian thistle	38	18	11	9
Common sagebrush	27	10	8	6
Ragweed	20	9	6	4
Grass grass	41	19	9	8
Grass mix	57	28	11	8
Tree mix	21	8	6	4

* Children born and raised in Los Alamos: 9 children with BHR and 6 asthmatic children were born in Los Alamos.

† Bronchial hyperresponsiveness to $\leq 7.8 \mu\text{mol}$ histamine (see METHODS).

‡ The presence of BHR and parental reported wheeze in last year (20).

§ Significantly lower.

|| $p < 0.025$ compared with the remainder of the studied children.

†† $p < 0.005$ compared with the remainder of the studied children.

** $p < 0.001$ compared with the remainder of the studied children.

††† $p < 0.05$ compared with the remainder of the studied children.

dren and young adults attending the ER for exacerbations of asthma in Atlanta, GA, Wilmington, DE, and Poole, England revealed that the majority were sensitized to mite, cat, or cockroach and exposed to the relevant allergen (26–28). A number of families in the present study had moved to Los Alamos because of the perception that their children's asthma might improve with "mountain air." Indeed, a number of children reported that since their arrival they had not wheezed; however, they had not lost their sensitization to the house dust mite.

Among these children living at high altitude, the prevalence of symptoms and treatment was very high. The results demonstrate that among children living with high levels of exposure to cat antigen, this protein can become an important cause of sensitization and asthma (29). Recent results from our laboratory show that dog allergen exposure and sensitization to dog allergens judged by serum assays was also strongly associated with asthma among this population (30). Increasing evidence suggests that identification of relevant allergens and their avoidance are an important advance in the treatment of asthma (31, 32). The results confirm that low levels of allergen exposure, such as for the dust mite in Los Alamos, are not associated with sensitization or bronchial hyperreactivity. The study of this unique population has provided further insights into the pivotal role of indoor allergen exposure in asthma. Despite low levels of house dust mite sensitization among children born and raised in Los Alamos, there was a strong association between asthma, elevated levels of IgE, and sensitization to other domestic allergens, notably those derived from the cat.

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