

Airway responsiveness in atopic dermatitis

Alan F. Barker, MD,* Carol A. Hirshman, MD,** Ray D'Silva, BS,* and
Jon M. Hanifin, MD*** Portland, Ore.

Twelve of 123 patients with atopic dermatitis (AD) were screened by questionnaire and spirometry for the absence of smoking, hay fever, and respiratory disorders. Seven of these 12 patients had a positive methacholine challenge test. None of eight patients with another skin disorder, psoriasis, screened in a similar fashion, had a positive methacholine challenge. We conclude that hyperresponsive airways are a frequent finding in patients with AD and that similar mechanisms may account for the cutaneous physiologic and pharmacologic abnormalities that have been observed in AD. (J ALLERGY CLIN IMMUNOL) 1991;87:780-3.)

Most patients with AD have symptoms of allergic rhinitis or asthma at some point in their lives, but a proportion of patients, estimated at approximately 21%, never have clinical evidence of allergic respiratory disease.¹ We questioned whether this latter category of patients might have subclinical evidence of hyperreactive airways.

If atopy and nonspecific airway hyperresponsiveness are two separate and distinct disorders that only occasionally coexist in man, then patients who are atopic but with no history of respiratory disease should have a low prevalence of airway hyperresponsiveness similar to that found in a normal population. Atopy, as defined by prick testing, has been positively associated with bronchial hyperresponsiveness.^{2,3} Fish and Norman⁴ reported that patients with hay fever and patients with asthma react to the prostanoid mediator, prostaglandin F₂, but that only patients with asthma respond to methacholine, suggesting differing mediators in those two groups. Pulmonary challenge studies involving patients with allergic rhinitis^{5,6} and AD⁷ have been inconclusive. In an attempt to clarify this relationship, we compared airway responses to methacholine in patients with atopic AD and nonatopic (psoriasis) skin disorders, but with no history of allergic respiratory disease.

Abbreviations used

OHSU: Oregon Health Sciences University

AD: Atopic dermatitis

METHODS

Subjects with AD or psoriasis were recruited from the dermatology clinics at the Oregon Health Sciences University. The patients with AD all manifested typical features and satisfied standard diagnostic criteria.⁸ From a group of 123 adult patients, 12 satisfied requirements for the absence of smoking, chronic respiratory disease (asthma, chronic bronchitis, and emphysema), seasonal or chronic rhinitis, or acute respiratory infection in the previous 6 weeks. None of the 12 had been a cigarette smoker. Each of these patients was an adult (age range, 22 to 74 years) with childhood onset of chronically recurring, pruritic dermatitis affecting antecubital and popliteal flexures. Skin testing and serum IgE levels were not obtained, although two of the patients had previously been skin tested and demonstrated positive responses and five other patients had previous IgE determinations that ranged from 10 to 6900 ng/ml. Disease severity ranged from mild localized dermatitis to extensive and severe. We chose, as a control group, patients with psoriasis, an inflammatory cutaneous disorder, no known associated pulmonary pathology, nor parasympathetic hyperresponsiveness. Among a population of 43 patients with typical plaque-type psoriasis, eight satisfied the above-listed requirements for absence of respiratory disease. After initial clinical screening, standardized respiratory questionnaires were administered in the pulmonary function laboratory to further eliminate persons with histories of cough and wheezing.⁹ Patients taking systemic glucocorticosteroids, bronchodilators, or methotrexate were excluded. The studies were performed at the same time of morning after or overnight fast.

Spirometry was performed with a Stead-Wells spirometer (maximodular lung analyzer, Warren E. Collins, Inc., Brain-

From the Departments of *Internal Medicine, **Anesthesiology, and ***Dermatology, Oregon Health Services University, Portland, Ore.

Supported by Public Health Service Grants AI 15557, AI 18615, HL 25831, and Biomedical Research Support Grant funds.

Received for publication Oct. 24, 1989.

Revised Nov. 27, 1990.

Accepted for publication Nov. 27, 1990.

Reprint requests: Alan F. Barker, MD, Pulmonary & Critical Care, 3181 SW Sam Jackson Park Rd., Portland, OR 97201.

1/1/27070

TABLE I. Methacholine challenge

Age (yr)	Sex	Baseline FEV ₁ (% predicted)	Methacholine challenge (breath units if positive)
Atopic subjects			
35	F	98	90
45	M	98	42
22	F	111	90
36	M	102	15
38	M	98	15
28	F	94	15
29	M	108	40
26	F	119	—
39	M	116	—
31	M	138	—
31	F	98	—
74	F	124	—
Subjects with psoriasis			
23	F	109	0
57	F	117	0
28	F	122	0
35	F	107	0
54	F	105	0
45	M	99	0
46	M	99	0
52	M	102	0

tree, Mass.). The spirogram with the largest FEV₁ of at least three trials was used as a baseline. Bronchial inhalational challenge was performed with methacholine because of its reproducibility in repeated studies, short duration of action, safety in administration, and absence of long-term or permanent side effects.¹⁰⁻¹² After inhalation of five breaths of normal saline (diluent control), five breaths of methacholine of increasing concentrations (1, 2, 5, 10, and 25 mg/ml) were administered every 10 minutes by No. 646 nebulizer (DeVilbiss Co., Somerset, Pa.) attached to a dosimeter (Table I). Spirometry was repeated three times 1 to 3 minutes after each five-breath dose. If the FEV₁ fell $\geq 20\%$ at any concentration, the test was stopped, and isoproterenol aerosol was administered to reverse spirometric abnormalities. A test was considered positive if the fall in the FEV₁ was $\geq 20\%$ below baseline at any concentration up to a maximum of 215 cumulative breath units. (Breath units at any level are measured by the product of the concentration times the number of breaths at that level.) A negative test occurred if the patient received 215 breath units and the FEV₁ remained $>80\%$ of baseline. The provocative dose was recorded as the breath-unit dose at which the fall in the FEV₁ was $\geq 20\%$. All studies were approved by the Committee for Human Research at Oregon Health Sciences University. The results were analyzed by Fisher's exact probability test.

RESULTS

One hundred twenty-three patients with AD were screened. One hundred eleven patients were elimi-

nated because of the presence of smoking, a respiratory disease, or systemic medication. Patients with psoriasis were evaluated in a similar fashion. The atopic patients included six male and six female patients with a mean age of 37. The control patients with psoriasis included five female and three male patients with a mean age of 42.5 years. Baseline spirometry, including FVC, FEV₁, and FEV₁/FVC, was normal with values $>90\%$ of predicted in all patients. The methacholine results for the patients are presented in Table I. Seven of 12 patients with AD responded with $>20\%$ fall in FEV₁, whereas none of the eight patients with psoriasis reacted. All reactors did so at concentrations of methacholine of 10 mg/ml or less. The number of reactors from the group with AD was significant at the level of $p < 0.01$ as compared to the group with psoriasis.

We noted no clear correlation between disease severity and methacholine reactivity. There was a trend to more severe skin disease in the methacholine-positive group, but two of those seven patients had very mild disease and total numbers were too small to ascertain a statistical correlation.

DISCUSSION

In performing this study, we attempted to determine whether patients with typical AD but no history of

respiratory disease have latent airway hyperreactivity that might predispose to later development of asthma. The answer appears to be that at least some of these patients do have this predisposition, as reflected by airway responsiveness to methacholine. Because the patients were selected from a university medical center and because of the small number of subjects who satisfied the very stringent respiratory disease exclusion criteria for this study, it is not possible to make firm conclusions about the prevalence of reactive airways among the general population of patients with AD. We have demonstrated a significantly increased frequency of methacholine reactivity in this small group, as compared to a similarly selected group of patients with psoriasis or to the normal, nonatopic population. Longitudinal studies would be needed to assess future development of asthma in either the methacholine-positive or negative populations or the appearance of methacholine sensitivity in the methacholine-negative patients.

The epidemiologic relationship between asthma and AD is difficult to assess. The onset of respiratory disease is generally much later than AD, making age an important factor in population surveys. Another complicating factor is the frequently observed alternation in the course of the two conditions, Brocq's "alternance morbide,"¹¹ whereby approximately half the patients with AD and asthma have considerable or complete resolution of one set of symptoms when the other condition is flaring. We might anticipate that even more children would demonstrate hyperreactivity. In spite of these obstacles to case finding, an increased association between AD and asthma appears probable. A latent predisposition to asthma in AD, as reflected by pulmonary function testing, was suggested by Lutz and Korting.¹³ They tested for bronchodilation by epinephrine inhalation and recorded an improvement in minute ventilation in 15 of 25 young adults (average age, 25 years) with AD.¹³

We demonstrated a 55% prevalence of methacholine hyperreactivity in patients with AD who were screened by two clinical histories and spirometry for the absence of respiratory disorders. None of the eight control patients with psoriasis screened by the same questionnaires and spirometry reacted to the methacholine challenge. It is unknown but unlikely that patients with psoriasis have diminished reactivity to methacholine. Masuda et al.⁷ demonstrated a heightened sensitivity to cholinergic (acetylcholine) inhalation in patients with AD, but no concurrent control subjects were studied. The 71% prevalence of positive acetylcholine challenge in these patients may reflect differences in testing or, more likely, their lower threshold for test positivity (10% fall in FEV₁).⁷ Price

et al.¹⁴ reported that 29 of 41 children with eczema had exercise-induced bronchospasm, but 23 of those 29 patients had histories of wheezing. We screened 123 patients (older than 18 years) to find only 12 atopic patients with AD with no history of respiratory disease.

Most, if not all, patients with asthma have a positive methacholine challenge at 215 breath units or less, whereas normal individuals respond at much larger doses, if at all.^{6, 15} In children and young adults, the upper limit of responsiveness is somewhere between 100 and 200 breath units.¹⁶

Hyperresponsiveness to a variety of stimuli, including parasympathetic agents, is characteristic of patients with atopic disease. In patients with asthma, this relates to the airways, and in patients with AD, the skin is abnormally reactive. In patients with asthma, the manifestation is bronchospasm, and in patients with AD, it is a lowered itch threshold and abnormal vascular and sweat gland responses to pharmacologic agents.¹⁷ Abnormal cutaneous responses have also been observed in asthma.¹⁸

REFERENCES

1. Rajka G. Essential aspects of atopic dermatitis. Berlin: Springer-Verlag, 1989:36.
2. Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26-9.
3. Cookson WOCM, Musk AW, Ryan G. Associations between asthma history, atopy, and nonspecific bronchial responsiveness in young adults. *Clin Allergy* 1986;16:425-32.
4. Fish JE, Norman PS. Responsiveness to prostaglandin F₂ in atopic and nonatopic subjects. *Chest* 1985;87(suppl):206-7.
5. Bryant DH, Burns MW. The relationship between bronchial histamine reactivity and atopic status. *Clin Allergy* 1976;6:373-81.
6. Townley R, Bewtra A, Nair N, Brodkey FD, Watt GD, Burke KM. Methacholine inhalation challenge studies. *J ALLERGY CLIN IMMUNOL* 1979;64:569-74.
7. Masuda T, Naito A, Kinoshita M, et al. Acetylcholine inhalation test in atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1967;40:193-201.
8. Hanifin JM, Lobitz WC Jr. Newer concepts of atopic dermatitis. *Arch Dermatol* 1977;113:663-70.
9. Ferris BG. Epidemiology standardization project. *Am Rev Respir Dis* 1978;118(Pt 2):11-47.
10. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. *ATS News* 1980;6:11-9.
11. Ryan G, Dolovich MB, Roberts RS, et al. Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis* 1981;123:195-9.
12. Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;33:705-10.
13. Lutz E, Korting GW. Zur lungenfunktion des endogenen ekzematikers. *Archiv Fur Klin Exp Dermatol* 1958;205:597-604.
14. Price JF, Cogswell JJ, Joseph MC, Cochrane GM. Exercise-

- induced bronchoconstriction, skin sensitivity, and serum IgE in children with eczema. *Arch Dis Child* 1976;51:912-7.
15. Malo J, Pineau L, Cartier A, Martin RR. Reference values of the provocative concentrations of methacholine that cause 6% and 20% changes in forced expiratory volume in one second in a normal population. *Am Rev Respir Dis* 1983;128:8-11.
16. Hopp RJ, Bewtra AK, Nair NM, Townley RG. Specificity and sensitivity of methacholine inhalation challenge in normal and asthmatic children. *J ALLERGY CLIN IMMUNOL* 1984;74:154-8.
17. Hanifin JM. Pharmacophysiology of atopic dermatitis. *Clin Rev Allergy* 1986;4:43-65.
18. Agosti JM, Sprenger JD, Lum LG, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988;319:1623-8.

Source of the aeroallergen of soybean dust: A low molecular mass glycopeptide from the soybean tela

**Mark C. Swanson, BA,* James T. C. Li, MD,*
Patricia E. Wentz-Murtha, BA,* Walter L. Trudeau, BA,**
Enrique Fernandez-Caldas, PhD,** Alice Greife, PhD,***
Maria A. J. Rodrigo, MD,**** Ferran Morell, MD,**** and
Charles E. Reed, MD* Rochester, Minn.; Tampa, Fla.; and Barcelona, Spain**

Airborne soybean allergens in the dust generated during the unloading of soybeans in the harbor caused asthma epidemics in Barcelona, Spain. The major allergen causing the epidemics was a glycopeptide <14 kd molecular mass abundant in soybean dust. This allergen occurs in all parts of the soybean plant at all stages of growth, but the telae (hulls) and pods are by far the richest source. Small amounts of a similar cross-reacting allergen are found in some other grain dusts. The botanical function and significance of this soybean plant component is not known nor is the potential for airborne dispersion of this allergen at other grain-handling sites. (J ALLERGY CLIN IMMUNOL 1991;87:783-8.)

Dust discharged into the air in the harbor during soybean unloading has been identified as the cause of the epidemics of asthma in Barcelona, Spain.¹⁻³ We previously reported that soybean telae (hulls) col-

Abbreviations used

SDS-PAGE: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
PBS: Phosphate-buffered saline
MM: Molecular mass

From the *Allergic Diseases Research Laboratory, Mayo Clinic, Rochester, Minn.; **Division of Allergy and Immunology, University of South Florida, Tampa, Fla.; ***National Institute for Occupational Safety and Health, Cincinnati, Ohio; and ****Servicios de Bioquímica y Pneumología Hospital Vall d'Hebron, Barcelona, Spain.

Supported by National Institute of Allergy and Infectious Diseases Grant No. AI 21255, Mayo Clinic and Foundation, Minnesota Lung Association, and, in part, by Fondo de investigaciones Sanitarias Grant FISS 89/0924.

Received for publication Aug. 13, 1990.

Revised Nov. 27, 1990.

Accepted for publication Nov. 28, 1990.

Reprint requests: Charles E. Reed, MD, Department of Internal Medicine, Division of Allergic Diseases, Mayo Clinic, Rochester, MN 55905.

1/1/27072

lected in Barcelona from beans shipped both from the United States and Brazil were rich in an allergen that is a glycopeptide with a low MM of about 14 kd.³ Only trace amounts of the allergen were found in cleaned soybeans or soybean flakes. Furthermore, asthma from soybean dust has been reported in only a few isolated cases in farmers or workers in soybean-processing plants in the United States. Therefore, we considered the possibility that the allergen developed during the sea voyage from Toledo, Ohio, or São Paulo, Brazil, where the beans were loaded, per-