

Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients

One hundred thirteen patients with severe atopic dermatitis were evaluated for food hypersensitivity with double-blind placebo-controlled oral food challenges. Sixty-three (56%) children experienced 101 positive food challenges; skin symptoms developed in 85 (84%) challenges, gastrointestinal symptoms in 53 (52%), and respiratory symptoms in 32 (32%). Egg, peanut, and milk accounted for 72% of the hypersensitivity reactions induced. History and laboratory data were of marginal value in predicting which patients were likely to have food allergy. When patients were given appropriate restrictive diets based on oral food challenge results, approximately 40% of the 40 patients re-evaluated lost their hypersensitivity after 1 or 2 years, and most showed significant improvement in their clinical course compared with patients in whom no food allergy was documented. These studies demonstrate that food hypersensitivity plays a pathogenic role in some children with atopic dermatitis and that appropriate diagnosis and exclusionary diets can lead to significant improvement in their skin symptoms. (J PEDIATR 1985;107:669-675)

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ATOPIC DERMATITIS is a condition primarily of early childhood, characterized by an erythematous, papulovesicular, intensely pruritic rash.¹ Scratching frequently leads to excoriations, bleeding, oozing and crusting, secondary infection, and eventually to a lichenified dermatitis. This disorder is believed to account for 1% of all office visits to pediatricians² and to affect 1.1% to 4.3% of the pediatric population.^{3,4} The pathogenesis of atopic dermatitis is unknown. Histologic sections of eczematoid skin demonstrate a mononuclear round cell infiltrate,⁵ a histopathologic finding unlike that found in most other atopic conditions. However, several factors suggest a role for IgE-mediated hypersensitivity in the pathogenesis of atopic dermatitis: (1) approximately two thirds of children have positive family histories for atopic disease⁶; (2) 50%

to 80% of children with atopic dermatitis develop allergic rhinitis or asthma^{7,8}; (3) serum IgE concentrations are elevated in about 80% of children with atopic dermatitis⁹; and (4) most children have positive immediate skin tests and radioallergosorbent tests (RAST) to various dietary and environmental allergens.^{10,11} In addition, immediate reactions mediated by IgE may be followed by late-phase reactions, characterized by a mixed cellular infiltrate (eosinophils, lymphocytes, basophils, and neutrophils) at 6 to 8 hours, and thereafter by a mononuclear round cell

RAST Radioallergosorbent test

infiltrate indistinguishable from that seen in eczematous skin.^{12,13}

In 1936, Engman et al.¹⁴ suggested that ingestion of food might provoke severe pruritus, which would result in scratching and rubbing. The consequent trauma would lead to typical eczematous lesions. Engman described a wheat-sensitive child with atopic dermatitis who was hospitalized and fed a wheat-free diet until skin symptoms cleared. Wheat was then reintroduced into the diet, resulting in intense pruritus, scratching, and the development of typical eczematous changes on the side of his body not protected by an occlusive dressing. Although Engman's

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Table I. Results of prick skin tests to food antigens in 113 patients with atopic dermatitis

Antigen	Number positive	Antigen	Number positive	Antigen	Number positive
Egg	55	Pork	32	Green bean	7
Peanut	49	Beef	18	Corn	7
Milk	26	Potato	7	Chocolate	4
Wheat	15	Pea	19	Rye	8
Soy	34	Shrimp	18	Oats	7
Fish	29	Rice	8	Strawberry	1
Chicken	19	Tomato	5	Total	368 (16%)

Each patient was tested with a battery of 20 food antigens. In addition to the above 368 positive reactions, there were 1892 (84%) negative skin test reactions.

article and many other anecdotal reports have implicated food hypersensitivity in the pathogenesis of atopic dermatitis, the topic remains highly controversial. Estimates on the prevalence of food hypersensitivity in children with atopic dermatitis range from 0% to 25%.¹⁵ Recently a link between immediate food hypersensitivity and cutaneous symptoms in some children with atopic dermatitis was provided when 14 of 26 children were found to develop cutaneous erythema and pruritus shortly after the ingestion of food antigen administered in a double-blind placebo-controlled food challenge.¹⁶ The purpose of this report is to expand our previous observations and to assess the therapeutic outcome in a limited number of patients.

METHODS

Subjects. One hundred thirteen patients referred for evaluation of severe atopic dermatitis were enrolled in the study. All subjects fulfilled the criteria of Hanifin and Lobitz¹⁷ for the diagnosis of atopic dermatitis. Most patients had a history of eczema dating back to infancy, and in all the condition was uncontrolled with regimens of topical lubricating creams, topical steroids, and antihistamines. Virtually all patients had undergone various elimination diets without notable success. About 75% of patients had used systemic steroids to control cutaneous symptoms on at least one occasion. Informed consent was obtained for each subject. All studies were approved by the Duke University Internal Review Board.

Procedures. Prior to admission of the subjects to the Duke University Clinical Research Center, medical histories and previous skin test or RAST results were reviewed. On the basis of this review, parents were instructed to eliminate totally up to six suspected food allergens from the child's diet for a period of 1 to 2 weeks before admission. Diet information sheets were mailed in advance to assist parents in identifying all sources of particular food antigens. Patients were required to discontinue antihistamines for 5 to 7 days before admission, and beta agonists 12 hours before admission. Most patients were using low to

intermediate strength topical steroids, but none was receiving systemic corticosteroids.

Skin tests. Shortly after admission, all patients underwent skin testing with a battery of 20 different food antigens, as previously described.¹⁶ In some cases, up to 10 extra food antigens were used to assess potential hypersensitivity. Standard glycerinated extracts (1-20 weight/volume; Greer Laboratories, Lenoir, N.C.) were applied by the prick technique; mean diameters of erythema and wheal reactions were recorded. Wheal reactions 3 mm greater than the negative control were considered positive.¹⁸

Food challenges. Double-blind placebo-controlled food challenges were performed as previously described.¹⁶ Briefly, up to 8 gm dehydrated food was administered in opaque capsules or juice over 1 hour. Two challenges were performed each day, one at 8 AM and one at 12:30 PM. One of the two daily challenges consisted of a suspected food, and the other of a placebo (sucrose or corn starch). The sequence of challenges was determined by Clinical Research Center dieticians using a computerized randomization scheme, so that patients, parents, nursing staff and investigators were unaware of the contents of the challenges. If no symptoms developed, the code was broken and the patients were given the food openly before discharge, to confirm the negative result of the blinded challenge.

Symptom score. All reactions were scored as to type, time of onset, severity, and duration; we used a standardized scoring sheet previously described.¹⁶

RESULTS

Sixty-three males and 50 females were enrolled in the study. Subjects ranged in age from 4 months to 24.5 years (median 6 years); 98 (87%) had elevated serum IgE concentrations (median 4100 IU/ml, range 8.4 to 45,000 IU/ml). Family history was positive for atopic disorders in 106 (94%) patients. In addition to atopic dermatitis, 57 (50%) children had both allergic rhinitis and asthma, whereas 27 (24%) patients had only allergic rhinitis and six

(5%) had asthma. Ninety-three (82%) children had at least one positive skin reaction to the standard battery of 20 food antigens administered at the time of admission (Table I). A total of 370 double-blind placebo-controlled food challenges were performed; 101 were interpreted as positive in 63 (56%) patients. In two instances, negative blinded food challenges were followed by reactions to the open feeding (false negative, two of 269, or 0.7%). One child, age 5 years, developed cutaneous gastrointestinal, nasal, and respiratory symptoms approximately 15 minutes after openly ingesting a standard portion of peas; a second child, age 4 years, developed cutaneous, nasal, and respiratory symptoms after consuming approximately 100 ml milk. The second child was rechallenged in blinded and open tests, and again reacted only to the open challenge. One placebo challenge was interpreted as positive (false positive, one of 340, or 0.2%). Sixteen challenges were not performed because of convincing histories of a prior major anaphylactic reaction requiring emergency medical therapy. In each case, patients had a strongly positive prick skin test to the food in question: peanut, nine patients; egg, three; fish, three; and potato, one. No patient in this study experienced a major anaphylactic reaction in response to the food challenge, although several subjects required orally administered diphenhydramine for severe pruritus, and two required subcutaneous administration of epinephrine for respiratory symptoms.

Blinded food challenges (Table II). Initial onset of symptoms occurred within 2 hours of ingesting the food antigen in all cases. A recurrence of cutaneous pruritus 6 to 8 hours later was seen in several patients, but late reactions were not seen without preceding immediate symptoms. Skin symptoms consisting of a diffuse erythematous macular or morbilliform rash and pruritus were seen in 84% of positive challenges; isolated cutaneous reactions, however, were seen in only 34% of positive reactions. Patient scratching frequently produced superficial excoriations and, occasionally, bleeding. Urticarial lesions were rarely seen (four patients), and generally consisted of only two or three lesions. Although patient histories rarely suggested adverse gastrointestinal symptoms secondary to food hypersensitivity, about half of the positive food challenges induced abdominal complaints. Nausea, abdominal pain, or both, plus emesis, diarrhea, or both, occurred in 53 (52%) instances. Respiratory symptoms, including stridor, wheezing, severe nasal congestion, or sneezing, developed in 32% of the positive challenges. Although respiratory tract reactions occurred only in individuals with allergic rhinitis or asthma, patient histories had not implicated food antigens as a potential cause of respiratory symptoms. As recently reported, most patients with atopic dermatitis experiencing positive food

Table II. Symptoms induced by food challenge in 63 patients with atopic dermatitis

	<i>n</i>	%
Positive food challenges	101	
Cutaneous symptoms		
Total	85	84
Skin symptoms only	34	34
GI symptoms		
Total	53	52
Abdominal symptoms only	10	10
Respiratory symptoms (nasal symptoms or wheezing)		
Total	32	32

Table III. Foods inducing positive challenges in 63 of 113 patients with atopic dermatitis

<i>Antigen</i>	<i>n</i>	%
Egg	44 (3)	42
Peanut	20 (9)	19
Milk	11	11
Soy	5	5
Wheat	5	5
Fish	4 (3)	4
Chicken	3	3
Pork	2	2
Beef	2	2
Potato	2 (1)	2
Other	6	6
Total	104	100

Number based on positive history in parenthesis.

challenges were found to have elevated plasma histamine concentrations.¹⁹

Despite the large variety of food antigens consumed in the typical American diet, six foods accounted for more than 85% of the positive responses (Table III). Egg accounted for nearly half of the reactions seen. Although most children tended to have positive prick skin test reactions to several food antigens (mean 4.3, range 0 to 11), most of those who experienced a positive oral food challenge did so to only one food (36 of 63, or 57%). Twenty (32%) children reacted to two food antigens, six (9.5%) to three antigens, and one (1.5%) child reacted to four food antigens. Only one child had a positive oral challenge to two foods within the same botanical family, and no child reacted to two different foods from the same animal species (e.g., milk and beef). However, skin test (or RAST) results frequently were positive to several foods within a botanical family or animal species.

Natural history. As a group, children found to be allergic to a food by double-blind challenge tended to be slightly younger (median age 4.7 years vs 7.7 years) and

Table IV. Results of food challenges in 31 children retested to 40 allergens 1 to 2 years after initial positive challenge and subsequent restricted diet

Antigen	Total	Positive		Negative	
		n	%	n	%
Egg	20	14	70	6	30
Milk	7	3	43	4	57
Wheat	4	3	75	1	25
Soy	3	1	33	2	67
Peanut	1	1	100	0	0
Other	5	1	20	4	80
Total	40	23	58	17	42

have more positive prick skin test reactions to food antigens (mean 4.5 vs 1.7) than children without food hypersensitivity. However, there was no significant difference between the two groups in median initial serum IgE concentrations, number of children with at least one positive skin test reaction to food antigens, symptoms of asthma or allergic rhinitis, or a positive family history for atopy. Patients with normal serum IgE concentrations had an equally high rate of food hypersensitivity as did those children with elevated serum IgE values (10 of 15 patients, or 67%, vs 53 of 98 patients, or 54%). Thirty-one children experiencing 40 positive oral food challenges underwent repeat double-blind placebo-controlled food challenges 1 to 2 years after the initial challenge. In the interval, all children were given a diet that strictly eliminated the offending food antigen. Of the 40 repeat food challenges, 23 (58%) were again positive (Table IV); peanut, wheat, and egg hypersensitivity were more likely to persist than sensitivity to the other allergens. Patients experiencing a negative reaction to rechallenge were fed the food openly under observation, and then were allowed to add the previously restricted food to their diet. No recurrence of allergic symptoms or worsening of eczema has been observed. Skin test reactivity to the food in question remained unchanged in all patients who lost their clinical hypersensitivity, as previously reported.²⁰ However, unlike the findings reported by Bock,²⁰ there was no difference in the development of food antigen tolerance between children older or younger than 3 years. The median age of children who lost their hypersensitivity was 7.4 years; this was not significantly different from that of children with persistent hypersensitivity (median age 5.3 years, $P = 0.4$).

The clinical courses of the first 27 children, who had been enrolled in the study for approximately 3 years, were reviewed. Group 1 consisted of 13 children in whom a food identified as causing clinical symptoms had been elimi-

nated from the diet; group 2 consisted of 14 children in whom no offending food was identified or eliminated (two children were found to be allergic to a food but failed to comply with the diet). A crude scoring system was devised (0 to +++) based on the patient's skin symptoms, medication requirements, physician visits, and days absent from school. Each patient was assigned a score from 0 (no change in the course of patient's disease after entering the study) to ++++ (patient's skin essentially clear with little or no therapy). In addition, serum IgE concentrations at the time patients entered the study were compared with values at the time of review for both groups, because serum IgE concentrations have been reported to correlate roughly with disease activity in atopic dermatitis.²¹ Group 1 fared much better clinically than did group 2 (Table V). In addition, serum IgE concentrations decreased significantly in group 1 over 2 to 3 years (median prestudy 11,000 IU/ml, poststudy 4700 IU/ml, $P < 0.05$), whereas they increased significantly in group 2 over that same period (median prestudy 3950 IU/ml, poststudy 7900 IU/ml, $P < 0.05$). Both patients with food hypersensitivity who did not comply with their restricted diets failed to show any significant improvement in clinical course, and both experienced significant elevations in serum IgE concentrations. Although in no way conclusive, these data do suggest that the elimination of foods provoking clinically documented hypersensitivity responses will favorably affect the course of atopic dermatitis.

DISCUSSION

The cause of atopic dermatitis has remained elusive, but increasing evidence suggests a pathogenic role for IgE-mediated hypersensitivity mechanisms. Several physiologic and immunologic abnormalities of the skin have been described^{22, 23}: increased sweating, decreased sebum production, abnormal vascular responses such as white dermographism, frequent colonization of the skin with *Staphylococcus aureus*, and increased susceptibility of the skin to viral infections. However, the link between these abnormalities and the underlying pathogenic mechanism is not apparent, and treatment remains largely symptomatic.

The concept that food hypersensitivity may exacerbate skin symptoms in patients with atopic dermatitis is not new; several reports have implicated food hypersensitivity in its pathogenesis.²⁴⁻²⁹ However, the uncontrolled nature of these studies has left most physicians unconvinced about the role of specific food antigens. In a well-controlled study of 81 hospitalized children younger than 5 years with atopic dermatitis, Hammar³⁰ was able to provoke skin symptoms in 15 after the second or third daily administration of 100 gm milk or cereal. The significance of these

Table V. Changes in clinical course and serum IgE concentrations after 3 years

Group 1 Food hypersensitive patients with restricted diet				Group 2 Food nonsensitive patients with unrestricted diet			
Patient	Clinical change	Initial IgE (IU/ml)	Subsequent IgE (IU/ml)	Patient	Clinical change	Initial IgE (IU/ml)	Subsequent IgE (IU/ml)
1	++++	26,000	3,150	1	0	5,600	12,500
2	++++	45,000	4,700	2	+++	1,700	2,700
3	+++	4,200	6,200	3	+	2,610	13,000
4	++	4,600	3,100	4*	±	8,300	16,600
5	+++	52,000	22,000	5*	±	18,000	52,000
6	++++	3,800	3,800	6	++	1,550	3,000
7	+++	1,040	2,950	7	++	970	5,200
8	++++	1,800	1,530	8	±	4,100	19,000
9	+++	11,000	8,400	9	±	3,600	19,000
10	++++	12,000	10,600	10	+++	7,800	3,700
11	+++	22,000	11,000	11	++	6,100	8,400
12	++	27,000	10,500	12	++	3,800	3,500
13	++++	2,200	3,200	13	++	14,000	7,400
				14	+++	2,900	920

0, No change; +, slight improvement; ++, moderate improvement; +++, marked improvement; +++++, skin essentially clear.

*Food sensitive, noncompliant.

findings has been questioned because 11 of 15 children had lost their sensitivity when rechallenged in the same manner 18 months later.³¹ Bock et al.³² noted exacerbations of skin symptoms in three of four patients with atopic dermatitis who underwent double-blind food challenges. In our study, 63 (56%) of 113 children referred for evaluation of severe, intractable atopic dermatitis were found to develop skin symptoms within 2 hours of ingesting the offending food antigen in double-blind placebo-controlled challenges. Prior to the initiation of challenges, eczematoid lesions were cleared with an aggressive regimen of soaking baths, lubricating creams, low-strength topical steroids, oral antibiotics and diet restriction. The development of skin symptoms was generally heralded by pruritus, and consisted of an erythematous macular or morbilliform rash over more than 5% of the body surface. A previous study showed that these clinical changes were associated with increases in plasma histamine concentration.¹⁹ The mechanisms involved in the cutaneous changes resulting from food allergen ingestion remain speculative. Engman et al.¹⁴ initially suggested that the frequent ingestion of a food allergen led to cutaneous pruritus. Trauma, secondary to scratching, then resulted in typical eczematous skin lesions. More recent evidence suggests that other mediators released during IgE hypersensitivity responses, such as mast cell-derived prostaglandins and leukotrienes or eosinophil "major basic protein," may also contribute to the skin changes seen.³³

In our series of patients, parental history of suspected food allergy was of little value in predicting who would have a positive response to the food challenges. Only in the children requiring prior emergency therapy after allergen exposure (i.e., those children not challenged in the study) was history helpful. Bock and May³⁴ also found history quite unreliable in their series of patients with primarily respiratory allergy. However, both series evaluated patients with severe chronic disease who had been seen (and possibly biased) by several physicians before enrollment. Therefore, acquisition of history in the primary setting (i.e., before multiple referrals) may be more productive.

Various historic and laboratory factors were assessed for their value in predicting food hypersensitivity in patients with atopic dermatitis. Children with food hypersensitivity tended to be slightly younger and to have more positive prick skin test reactions than did patients without demonstrable food allergy. However, these factors were of little predictive value in individual cases. Furthermore, no other historical or laboratory features were of any predictive significance. Consequently, it would appear that clinical findings and routine laboratory studies are of little value in predicting which children will have food hypersensitivity. A child (especially younger than 7 years) with atopic dermatitis unresponsive to routine therapy (lubricating creams, topical steroids, antihistamines, and occasional short bursts of systemic steroids) appears to have greater

than a 50% chance of having food hypersensitivity. Such children should therefore undergo appropriate evaluation, as discussed below.

In the past, and even more recently,³⁵ some investigators have suggested that children with atopic dermatitis are allergic to a wide variety of food antigens. These statements generally were based on results of skin tests or RAST tests, clinical impressions, or uncontrolled dietary exclusion and challenge studies. Although many of our patients had many (mean 4.3) positive prick skin test reactions to food antigens, 90% of the children who experienced a positive oral food challenge did so to only one or two foods. In addition, three foods (egg, peanut, and milk) accounted for nearly 75% of the documented hypersensitivity reactions.

Based on data from this study, the practice of empirically avoiding all foods in a botanical family or from the same animal species when one is suspected of causing an allergic reaction appears unwarranted. Many children had positive prick skin test reactions to several members of a botanical family (e.g., legume-peanut, soybean, green bean, pea), but only one child reacted to two members of the bean family: (pea-bean and navy bean). Clinical hypersensitivity appears to be very specific to individual food antigens, whereas skin test sensitivity (as demonstrated by positive prick skin test results) will reflect some common antigens among members of a botanical family. For example, no child sensitive to peanut reacted to any other member of the legume family tested. Similarly, no child allergic to eggs reacted to chicken, or vice versa. Therefore, identification of specific food allergens contributing to patient symptoms should eliminate the potentially hazardous^{31, 36} and poorly accepted^{37, 38} practice of instituting broadly restrictive diets.

The most appropriate means of diagnosing food hypersensitivity in patients with atopic dermatitis remains the topic of considerable debate. As reported previously,³⁹ prick skin testing is an excellent means of excluding immediate food hypersensitivity. Positive results, on the other hand, are useful only for limiting the number of food antigens requiring evaluation with more definitive studies. A positive skin test reaction (properly performed) merely indicates the presence of antigen-specific IgE bound to cutaneous mast cells (i.e., immunologic sensitization). The clinical significance of the positive skin test reaction can only be ascertained by other diagnostic means. Diet manipulation and elimination at home are inadequate diagnostic modalities in patients with atopic dermatitis. Virtually all patients in our study had participated previously in various diet exclusionary programs without success. In the home setting, compliance with specified diets is often inadequate, and environmental variables (e.g., heat,

inhalant allergen exposure, stress) and parent bias are uncontrolled. Blinded challenges at home eliminate parental bias but fail to control environmental variables and are potentially dangerous.⁴⁰ Double-blind placebo-controlled food challenges conducted in a hospital or clinic provide a highly accurate, reproducible means of diagnosing immediate food hypersensitivity. The most common food allergens are readily available in dried form from local supermarkets and camping outlets. In addition, dehydrated foods packaged in opaque capsules recently have become commercially available. In a controlled setting, food challenges performed in a systematic fashion, as described here or by Bock and May,³⁴ are safe. However, the potential for major anaphylactic reactions should never be disregarded, and appropriate equipment to treat major reactions should be available.

The double-blind placebo-controlled food challenge provides a scientifically acceptable means of diagnosing adverse food reactions and should be considered standard for clinical investigations. However, such challenges may be impractical for general clinical use. The use of an open or single-blind challenge in a clinic setting, after a brief period of allergen avoidance, may be acceptable in many cases. The major disadvantage of the open and single-blind challenge is the increased incidence of false positive results, primarily because of observer and parent bias. Exclusion diets based on these results, therefore, may be excessively restrictive. However, if a child is diagnosed as allergic to one major food (e.g., egg, milk, wheat, or soy) or fewer than four minor foods (e.g., beef, chicken, peanut, fish, potato, peas), the diet would not be excessively restrictive, and results of such challenges would be acceptable. Results implicating more than one major food or more than a total of four foods should be considered suspect, and double-blind placebo-controlled food challenges performed. Once food hypersensitivity is appropriately diagnosed, the assistance of a dietician is often helpful to ensure complete antigen avoidance and a nutritionally balanced diet.

In some children, food hypersensitivity does play a pathogenic role in atopic dermatitis. This hypersensitivity to food is generally limited to one or two antigens and may be lost after several years. Consequently, appropriate elimination diets should not pose the nutritional hazard or difficulties with compliance frequently anticipated. Children appropriately diagnosed and given restricted diets can be expected to show significant improvement in their clinical course. Symptomatic improvement is quickly apparent, within 1 or 2 months, but is variable from patient to patient. Some children experience virtually complete resolution of skin symptoms, but other factors (e.g., temperature extremes; stress; contact with house dust

mite, animal danders, and possibly pollen allergens; and unknown factors) continue to provoke flare-ups in many patients in whom food hypersensitivity can be documented.

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