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Placebo-controlled double-blind food challenge in asthma

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*To determine the prevalence of food allergy as a cause of exacerbation of asthma, we studied 300 consecutive patients with asthma (7 months to 80 years of age) who attended a respiratory clinic. Each patient was screened for possible food allergy by means of a questionnaire and by skin prick tests with the six food allergens most common in our area. Patients with either a suggestive history and/or a positive prick test and/or RAST underwent double-blind food challenge with lyophilized food in capsules or food mixed in a broth to disguise its taste. Pulmonary function tests and symptoms were followed for 8 hours after each challenge. Of the 300 patients screened, only 25 had either a history or skin prick tests or RAST responses suggestive of food allergy. Twenty patients had interpretable food challenges. In these 20 patients, food challenge caused asthma in six and caused other symptoms (atopic dermatitis and gastrointestinal symptoms) in five. On rechallenge after pretreatment with disodium cromoglycate (300 mg 30 minutes before the food challenge), the asthmatic response was blocked in four of five subjects. The patients with asthma with food allergy were generally young, had a current or past history of atopic dermatitis, and high total serum IgE levels. Our findings confirm that food allergy can elicit asthma, but its incidence is low, even in the population attending a specialty clinic. Food elimination diets should not be prescribed for all patients reporting an adverse reaction to foods or having a positive skin prick test and/or RAST with food allergens. In patients with asthma caused by food allergy, disodium cromoglycate may be used to complement elimination diets. (*J ALLERGY CLIN IMMUNOL* 78:1139-46, 1986.)*

Food allergy is now accepted as one of the causes of AD,^{1,2} of AU,³⁻⁵ of reactions of the GIT, and of

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Abbreviations used

- AU: Acute urticaria
AD: Atopic dermatitis
DBFC: Double-blind food challenge
GIT: Gastrointestinal tract
PD₂₀: Provocative dose eliciting a 20% fall in FEV₁
PRIST: Paper radioallergosorbent test

acute systemic anaphylaxis.^{6,7} Its role in asthma appears to be less clear.⁸ Some investigators^{9,10} estimate that it is a frequent cause of asthma in children or adults, whereas other investigators believe it is unimportant.^{11,12}

The diagnosis of food allergy is difficult because the allergen extracts currently available are not standardized, and their stabilities are usually poorly determined. For allergen extracts that are rapidly degraded like those of fruits and legumes,^{13,14} skin tests may be falsely negative in food-allergic patients. Conversely, some extracts may contain irritative substances, causing false positive skin tests.^{4,15,16} The titration of food-specific IgE is available only for certain foods, and, in contrast, with better characterized inhalant allergens, the sensitivity of the test is not yet known for most unpurified food allergens.^{6,17} Moreover, as in inhalant allergen sensitivity, the presence of food IgE in serum does not always correlate with a food allergy. For these reasons DBFC appears to be the best method used for diagnosing a food allergy.^{3,4,15,18,19}

In order to assess the prevalence of food allergy in asthma, we studied 300 patients with asthma, ranging in age from 7 months to 80 years, and who attended consecutively the Clinic of Respiratory Diseases of Montpellier. When suspicion of food allergy was raised either by the response to a questionnaire or to skin tests and/or specific IgE, the patients had a DBFC with the relevant allergen(s). Moreover, since oral cromoglycate has been demonstrated to block symptoms during food challenge,^{20,21} many of the patients who had a positive response to DBFC underwent a second food challenge after pretreatment with cromoglycate.

MATERIAL AND METHODS

Patients

Three hundred patients, ranging in age from 7 months to 80 years (mean $\pm$ SD 28.2 ± 21.6 years) were studied. Asthma was diagnosed according to the criteria of the American Thoracic Society,²² and we tried to eliminate as much as possible reversible airway obstruction caused by bronchial infections or patients with chronic bronchitis. None of these patients was suffering from pulmonary emphysema or from cardiovascular disorders. All patients more than the age of 6 years were able to perform an FVC maneuver. When airway obstruction was found according to predictive values,²³ the reversibility was examined after inhalation of 200 μ g of salbutamol, and only patients with reversible airway obstruction were studied further. When pulmonary function was within normal limits, a carbacholine inhalation test²⁴ was done, and all patients had a positive test, responding to doses <1000 μ g.

AD was defined according to the criteria of Hanifin and Lobitz.²⁵ Absolute features included pruritus, typical mor-

phology and distribution such as flexural lichenification in adults and facial and extensor involvement in childhood and infancy, and a tendency toward chronic or chronically relapsing dermatitis. Moreover, patients often presented a white dermographism and four or more of the following features: xerosis/ichthyosis/hyperlinear palms, pityriasis alba, keratosis pilaris, facial palor/infraorbital darkening, Dennie-Morgan infraorbital fold, keratoconus, tendency toward nonspecific hand dermatitis, or tendency toward repeated cutaneous infections.

Allergen extracts

Allergen extracts were obtained from the Laboratoires des Stallergenes (Fresnes, France). Many inhalant extracts were standardized. Most inhalant allergens found in the Mediterranean area were tested, including mites, animal danders, molds, and pollens. All extracts were used diluted in 50% glycerol (1/10 or 1/20 w/v for nonstandardized extracts). Glycerinated food extracts (1/20 w/v) were also used. They were not standardized except for wheat flour. All were prepared according to the proposals of the International Committee on Standardization of the International Union of Immunological Societies. Shelf life was assessed for most inhalant allergens but not for food allergens; they were therefore discarded 6 months after their preparation.

Skin tests

Skin tests were performed by means of the modified prick test according to the method of Pepys.²⁶ Tests were done in parallel with three positive control solutions (histamine hydrochloride, 1 and 10 mg/ml, and codeine phosphate, 9%) and one negative control solution (50% glycerol used as a diluent). None of the patients was under treatment that might modify skin tests.²⁷ Skin tests were considered to be positive when the wheal induced by the allergen extract was at least 50% of that induced by the codeine phosphate positive control solution.

Total serum IgE

Total serum IgE was measured by the Phadebas PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the package insert.

Serum-specific IgE

Serum specific IgE was measured by the classic Phadebas RAST (Pharmacia Diagnostics AB) according to the procedure described in the package insert. RAST discs were purchased from Pharmacia Diagnostics. RAST tests were done according to the results of skin tests. When the titer of total serum IgE was >1000 ku/L the sera were diluted to avoid nonspecific binding to the RAST discs.²⁸

Placebo-controlled DBFC

Food challenges were performed in a manner similar to that reported by Bock et al.,¹⁹ May,²⁹ and Sampson and Albergo¹⁷ with slight modifications. The food suspected as causing symptoms was eliminated from the diet for a minimum of 2 weeks before testing. The selection of foods for administration was based either on a positive skin test and

TABLE I. Food allergens tested

<i>Wheat flour*</i>	Banana	Artichoke
<i>corn</i>	Cherry	Beet
Maize	Apple	Carrot
Lamb	Lemon	Celery root
Pork	Orange	Spinach
Veal	Raspberry	Onion
Beef	Strawberry	Garlic
Chicken	Peach	Potato
	Pear	Tomato
<i>Mixed fish</i>	Apricot	Green peas
Codfish	Peanut	<i>Whole egg</i>
Sardine	<i>Mixed nuts</i>	Ovalbumin
	Walnut	Chocolate
Shrimp	<i>Milk</i>	Hops
Crab	Cheese	Mustard
Lobster	Gruyère cheese	Saccharomyces cerevisiae
Muscle		Saccharomyces minor
		Mustard

The strength of these extracts was 1/20 w/v. *Italicized extracts* are those tested in every patient of the study.

*All extracts tested were not standardized except wheat flour.

RAST or on a strongly positive history despite negative skin test and/or RAST.

Patients were instructed to stop antihistamines, oral cromoglycate, and ketotifen a week before the DBFC; β_2 -agonists, theophylline, and inhaled cromoglycate were stopped 12 hours before the procedure. No patient had received systemic steroids within 1 month before admission to the study, as suggested by Sampson and Alberg.¹⁷

When it was possible, foods were administered in the form of lyophilized powder placed in size 0 tartrazine-free opaque capsules. When lyophilized solid foods were not available or when foods were administered as liquids, they were mixed in a broth or a juice to hide the taste. A member of the staff randomized all challenges so that investigators and patients were unaware of the content of any challenge.

Although no patient tested had a history of anaphylactic reaction, allergen doses were increased slowly (100 mg, 1 gm, and 10 gm) during a period of 90 minutes to avoid a possible anaphylactic reaction, as suggested by Bernstein et al.³

All patients were admitted to the day hospital for DBFC and were serially monitored for 8 hours after the challenge. FVC and FEV₁ were measured on a Collins water spirometer (Gould Godart, Baillenville, France) before the challenge and every 30 minutes thereafter. The challenge was only started when the basal FEV₁ was within 20% of predicted values. FEV₁ and maximal midexpiratory flow rate were studied. The patients were also followed clinically by a physician who noticed the eventual symptoms of asthma, urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, pruritus, atopic dermatitis, and anaphylaxis (blood pressure and pulse rate). When such symptoms occurred or a decrease in PD₂₀ FEV₁ was observed, the patient was kept in the hospital and was monitored for 12 to 24 hours according to the course and severity of the symptoms. If any

symptoms were believed to be secondary to the challenge, this was interrupted.

On day 1, the patient randomly received either the placebo or the food between 8 and 9 A.M. The patient was monitored for 8 hours after the last dose. When there was no objective abnormality as previously described and/or FEV₁ was unchanged, the test was considered to be negative, and the patient was rechallenged with the crossover capsules the next day. When the test was found positive according to the defined criteria, the crossover test was performed 1 week later.

In patients who had a positive DBFC, treatment with increasing doses of cromoglycate was administered in order to achieve a total daily dose of 600 mg (children less than 10 years) to 900 mg by increasing slowly the doses from 300 mg daily to the maintenance dose. Then the patient was rechallenged with the food as previously indicated, 30 minutes after the ingestion of 300 mg of cromoglycate. The patients were monitored as indicated.

Protocol

A detailed history of allergic diseases investigating particularly the possible symptoms of food allergy and intolerance (AD, AU, angioedema, acute anaphylaxis, GIT involvement) was obtained from each patient. All patients had skin prick tests with inhalant allergens and with extracts of six foods (wheat, corn, whole egg, cow's milk, fish, and nuts). Extracts of crustacea and peanut were not selected because these foods are infrequent sensitizers in our area. When there was a history of food intolerance or symptoms suggesting a food intolerance, skin prick tests were performed for all food allergens listed in Table I. All patients had a titration of their serum total IgE.

When a food skin test was positive, the titration of specific IgE was performed when the RAST was available, and

TABLE II. Patients with positive double-blind food challenges

Patient No.	History		Age	IgE (Ku/L)	Positive prick test	Positive RAST	Inhalant allergy	Food challenge
	Symptoms	AFR						
1	A, R, AD, GIT	Yes	4	239	0	Egg	Po, molds	Egg: GIT, A*
2	A, R, AD	No	8	872	Wheat	Wheat, corn	Mi, molds	Wheat: A Corn: A
3	A, R, AD	No	5	147	Egg	0	0	Egg: GIT, A*
4	A, AD, AU	No	32	2426	Egg, milk, corn	Egg, milk, corn	Mi, molds, Po, Dand	Egg: AD
5	A, R	No	14	544	Wheat, corn	Wheat	Mi, molds, Po, Dand	Wheat: A
6	A, AD, GIT	Yes	10	1321	Egg, corn	Egg	Mi, molds, Po, Dand	Egg: AD
7	A, AD	Yes	17	1010	0	Egg, milk	Dand	Milk: neg Egg: AD Coca-Cola: AD
8	A, R	No	8	1076	Milk, fish	Milk, fish	0	Milk: GIT Fish: neg
9	A, AD	No	26	8452	Fish	Fish	Po, molds, Mi, Dand	Fish: AD
10	A, AD	Yes	11	1502	Milk, egg	Milk, egg, fish	Po, molds, Mi	Egg: A Milk: ND Fish: ND
11	A, AD	No	5	3408	Milk, egg, fish	Milk, egg	Po, Mi	Egg: A, AD Milk: ND Fish: ND

AFR = history of adverse food reaction reported by the patient; A = asthma; Mi = mites; Po = pollens; Dand = animal danders; ND = food challenge not performed; neg = negative response to food challenge.

*Asthma attack during the food challenge; the ventilatory parameters were not available because the patients were too young to perform the test.

the complete skin test screening of food allergens was done. In case of a positive skin test to one or several foods, a DBFC was performed. When there was a history of food intolerance without positive skin tests, a RAST screen (fish, walnut, milk, egg, shrimp, wheat, and corn) was performed, and DBFC was performed in case of positivity (two patients). Patients claiming to be intolerant to a given food were also challenged orally as previously indicated. The diagnosis of inhalant allergy was based on a suggestive history, the presence of positive prick tests, and RAST.

RESULTS

Among the 300 patients with asthma tested, 25 had criteria suggesting a food allergy. Two patients were only selected on the basis of a suggestive history of adverse food reaction (patients 1 and 7 of the positive DBFC group). Some patients had both a suggestive history of adverse food reaction and a positive prick test to foods (patients 6 and 9 of the positive DBFC group and patients 3, 7, and 9 of the negative DBFC group). Other patients had no direct history of adverse food reactions, although most had atopic dermatitis and/or GIT symptoms. Three patients did not have

DBFC because two patients had an FEV₁ that did not make it possible to perform safely a food challenge (45% and 51% from predicted values), and one patient refused to have a DBFC. Thus, only 22 patients had a DBFC, but in two occasions it was not possible to make a clear-cut conclusion as to whether or not the challenge was positive. Therefore, these two patients were also excluded from the study.

Patients with a positive food challenge

Of the 20 patients identified as having a possible food allergy, 11 had a positive DBFC (Table II), but none experienced a systemic anaphylactic reaction. All patients reacted to the highest dose. Asthma was observed in six patients (2%). Two patients could not be tested by means of pulmonary function tests because they were too young to cooperate (Nos. 1 and 3). The asthmatic symptoms or the fall in FEV₁ started between 90 and 120 minutes after the last food challenge, and the peak of the asthmatic reaction was observed after 2 to 4 hours. The effect of oral cromoglycate on the response to food challenge was

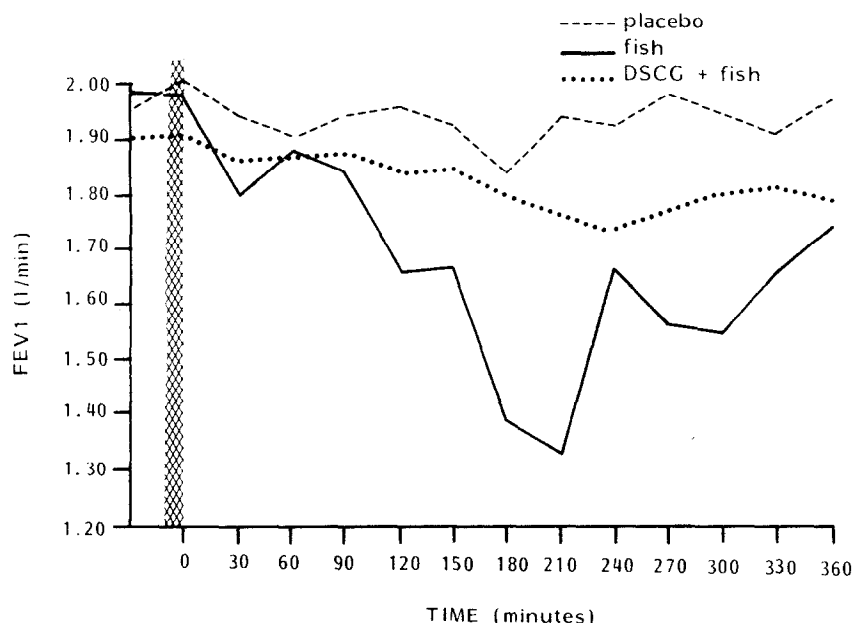


FIG. 1. Double-blind food challenge with fish that elicited a positive response in a patient with asthma. The decrease in FEV₁ was blocked by a pretreatment with disodium cromoglycate.

TABLE III. Characteristics of subjects with asthma

Groups of patients	Positive food challenge	Negative food challenge	Pollen allergy	Perennial allergy	Nonallergic subjects
No. of subjects	11	9	102	74	102
Age (yr)	4 to 32 (a)	5 to 67	4 to 70 (b)	3 to 70 (c)	1 to 80
M ± SD	12.5 ± 9.1	16.2 ± 18.3	25.7 ± 16.8	34.3 ± 21.6	
Sex (% M)	45.4	88.8	64.8	45.1	54.8
Nonasthmatic symptoms (%)					
Current AD	45.4 (d)	11.1	21.1 (e)	10.8 (f)	5.3
Previous AD	36.4	44.1	7.0	6.8	2.5
AU	9.0	11.1	15.4	15.7	13.4
GIT symptoms	36.3	22.2	28.2	23.5	22.1
Age of occurrence of asthma (yr)	1 to 25 (g)	1 to 51	1 to 49 (h)	1 to 56 (i)	1 to 80
M ± SD	6.5 ± 9.4	8.5 ± 15	16.4 ± 14.3	15.1 ± 14.3	24.1 ± 20.1
Inhalant allergy (%)	81.8	100			
Total serum IgE (ku/L)	147 to 8452 (j)	1010 to 4888 (k)	30 to 3874 (l)	32 to 6790 (m)	0 to 669
M ± SD	1908 ± 2370	2236 ± 1517	605 ± 694	698 ± 1082	84 ± 145

(a/b): $p < 0.01$; (a/c): $p < 0.01$; (g/h): $p < 0.05$; (g/i): $p < 0.05$; (j/l): $p < 0.01$; (j/m): $p < 0.01$; (k/m): $p < 0.01$ (Student's *t* test); d/e: $p < 0.001$; d/f: $p < 0.001$ (chi-square test).

tested in five of these patients (Nos. 1, 2, 5, 10, and 11); asthmatic symptoms and the fall in FEV₁ were completely blocked in four patients (Nos. 1, 2, 10, and 11) (Fig. 1), whereas the response was unaltered in one patient. Cutaneous symptoms consisting of pruritus and/or rash followed by a recurrence or an aggravation of AD, as described by Sampson,¹ were observed in five patients, and GIT symptoms consisting of nausea, abdominal pain, and diarrhea

were observed in three patients. There was no case of AU.

Foods that elicited a positive challenge included egg (seven patients), wheat (two), corn (one), fish (two), milk (one) and Coca-Cola beverage (one patient). Most patients were also sensitive to many inhalant allergens. These patients differed from those who did not present a food allergy (Table III) in that they were younger ($p < 0.01$), had a higher ($p < 0.01$) per-

TABLE IV. Patients with negative double-blind food challenges

Patient No.	History		Age	IgE (Ku/L)	Positive skin tests	Positive RAST	Inhalant allergy	Food challenge
	Symptoms	AFR						
1	A, R	No	11	2228	Wheat, corn, fish	Wheat, corn	Mi, Po, Dand	Corn: neg Wheat: neg
2	A	No	8	1674	Wheat, corn	Wheat, corn, egg, milk	Mi, Po, molds	Wheat: neg Corn: neg
3	A, R, AD, GIT	Yes	11	4888	Wheat, corn	Wheat, corn	Mi, molds, Po, Dand	Wheat: neg Corn: neg
4	A, R	No	67	4362	Egg, corn	Egg, corn	Po, Mi	Egg: neg Corn: neg
5	A, R	No	10	2142	Egg, wheat	Egg, wheat	Po, molds, Mi, Dand	Egg: neg Wheat: neg
6	A, AD	No	9	3211	Egg, milk	Egg	Mi	Egg: neg
7	A, AD, GIT	Yes	5	1000	Fish, egg, chocolate	Egg, fish	Mi, Po	Egg: neg Fish: neg
8	A, AD	No	26	1222	Corn, wheat, egg	Corn, wheat, egg	Mi, molds, Po, Dand	Corn: neg Wheat: neg Egg: neg
9	A, AD, GIT	Yes	12	1622	Fish, egg	Egg	Mi, molds, Po, Dand	Egg: neg Fish: neg

AFR = history of adverse food reaction reported by the patient; A = asthma; R = rhinitis; Po = pollens; Mi = mites; Dand = animal danders; neg = negative response to food challenge.

centage of AD, and had a higher mean total serum IgE level ($p < 0.01$).

Patients with a negative food challenge

Nine patients with history or skin tests suggesting food allergy had negative response to DBFC (Table IV). They were indistinguishable from patients who had a positive challenge by means of age, total serum IgE, and presence of inhalant allergy. They presented a nonsignificantly lower percentage of current AD. Foods incriminated included wheat (five patients), corn (five), egg (five), and fish (two) patients.

Correlation of skin tests, RAST, and food challenges

Thirty-five DBFC were carried out. Thirty-nine percent of these challenges were positive. DBFC were positive in 32% of patients who had positive prick tests. In two occasions, food challenges were performed in patients who had a negative prick test to egg. Challenge was positive in one occasion (patients 1 and 7).

DISCUSSION

Asthma induced by a food allergy was demonstrated to exist in the present study, but its prevalence in the population attending a specialty clinic was rather low, 2% of test patients (eventually 2.5% of the subjects

with asthma since one fifth of the patients could not be tested). Most cases presented herein were observed in children. Patients who had a positive oral challenge often presented current or past histories of AD, but many of them did not recognize the adverse food reaction before they had a DBFC. Mean total serum IgE level was very high in patients with a positive DBFC. Moreover, it appears that food can elicit cutaneous symptoms without asthma in many subjects. Oral cromoglycate is able to block respiratory symptoms during food challenges.

The selection of patients was based on a history of possible reactions to foods and skin tests and/or RAST. Skin tests were performed by the prick technique that may be less sensitive than intradermal tests but represents the most widely used technique.^{3, 4, 17, 18} Patients that may be more prone to develop a food-allergic reaction had skin tests with a complete battery of food allergens, whereas the other patients were tested only with the six foods most commonly diagnosed as a cause of allergy in our area. In our experience with food allergy, we observed that nuts, peanuts, meats, and crustacea were rarely involved. Patients of this study were only found skin test positive to a few foods, i.e., wheat, corn, egg, milk, and fish. Food extracts prepared from vegetables and fruits are usually of rather poor quality, and we may have excluded some patients allergic to these

foods.^{13, 14} However, since in our area *Compositae* and *Betulacea* pollens are rare,³⁰ apple, walnut, and celery sensitivities^{13, 31, 32} are not commonly reported.

Oral challenges were performed double-blind with a placebo in a similar manner to that proposed by several investigators^{3, 17, 19, 29} but adapted for asthma, since this was the aim of the study. Thus, most patients were serially followed by means of pulmonary function tests, and usual requirements for bronchial challenges with antigen were fulfilled.^{21, 33}

As indicated previously, only a fraction of patients who have skin and circulating IgE antibodies to foods develop symptoms when they are challenged with the offending food. As others have reported,^{3, 17, 29} we observed that only about one third of food challenges was positive. This may be due either to the fact (1) that the doses administered during the challenge were not sufficient, and/or (2) that a positive skin prick test and RAST do not necessarily mean that the patient is clinically allergic, and/or (3) that some patients outgrew their food sensitivities.^{34, 35}

In the present study, most patients with a DBFC were both allergic to food and inhalant allergens, and the prevalence of food allergy was low. By contrast, in a Scandinavian study,³⁶ the percentage of subjects with asthma reporting a reaction to different foods was much higher than in the present study, but these reactions included aspirin intolerance. The diagnosis of food intolerance was not based on food challenges, and most patients were also allergic to birch pollen, which is known to be cross-reactive with some food allergens.^{13, 31} Thus, food allergy in asthma appears to be a minor cause, and this study does not support the concept that many subjects with so-called "intrinsic" asthma are in fact allergic to foods.⁹ However, food allergy should not go unrecognized, since some rare patients with asthma greatly benefit from a diet,³⁷ and some patients without any history of adverse food reaction have a true food allergy.

Most patients who developed a reaction during DBFC were children and adolescents, and although asthma induced by food allergy was observed in adults,^{3, 6-9, 37} it appears to be less common than in children. Subjects with asthma who are allergic to foods present some particular features. More frequently they have AD and have a significantly higher mean value of total serum IgE. The meaning of this high IgE level is not known but has already been reported.³⁸ It may be related to the presence of AD in these patients because it was demonstrated that subjects with asthma with AD have a significantly higher IgE level.³⁹ Alternatively, food allergy may occur in patients who are "high IgE responders" and more prone to develop a sensitization toward many aller-

gens, including foods. According to this study, it appears that children with asthma with current or past history of AD and/or elevated total serum IgE level should be carefully assessed for a possible food allergy.

Egg was the most frequent offending food antigen in this study as it was in others.^{5, 17} Fish and wheat ranked in second order, but milk was only found to be responsible for a positive DBFC in one case. Moreover, Coca-Cola beverage elicited symptoms of AD in one patient, but the allergic origin of this reaction was not proved. Many patients had a negative response to DBFC with corn or wheat, whereas they had a positive skin test and RAST. All were allergic to grass pollens. Thus, corn and wheat IgE detected in patients with a negative response to DBFC may in fact be cross-reactive with grass-pollen IgE.⁴⁰

The presence of a positive skin test or RAST to a given food should not lead to an elimination diet because only 6/20 patients had asthma when they were challenged orally, although a positive DBFC should lead to an elimination diet. Oral cromoglycate was found to prevent asthma in 4/5 patients who underwent a food challenge after a pretreatment with this drug and may therefore be an adjunctive treatment to elimination diets.

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