

Jerome Glaser Lectureship

The role of food allergy and mediator release in atopic dermatitis*

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Unlike most dermatoses, AD has no primary skin lesion but is identified by a constellation of symptoms.¹ It is an inflammatory skin disorder characterized by extreme pruritus, chronically relapsing course, and typical distribution. The rash is generally an erythematous, papulovesicular eruption, which progresses to a scaly, lichenified rash over time.² Besnier³ was credited with first describing AD in 1892. He drew attention to the association of allergy with AD. Wise and Sulzberger⁴ further emphasized this relationship and coined the term "atopic dermatitis" by which the disorder is generally known today.

For reasons unknown, the distribution of the skin rash in AD changes as a child grows older.⁵ In infancy, the rash involves primarily the face and extensor surfaces of the arms and legs. As the child grows older, the rash tends to involve the neck and flexural creases of the arms and legs, and later in the teenage years, it has a strong predisposition to the hands and feet. The appearance of the skin rash differs significantly, depending on whether one views it in its more acute

Abbreviations used

AD:	Atopic dermatitis
DBPCFC:	Double-blind, placebo-controlled food challenge
FC:	Food challenge
LCAR:	Late-phase cutaneous allergic reaction
PG:	Prostaglandin
LT:	Leukotriene
PAF:	Platelet-activating factor
MBP:	Major basic protein
HRF:	Histamine-releasing factor
SBHR:	Spontaneous basophil histamine release
LC:	Langerhans' cell
desArg:	Amino acid arginine removed

or chronic stages. Consequently, there has been considerable discrepancies in the literature regarding the diagnostic features of AD. However, the recent criteria proposed by Hanifin and Rajka¹ appear to be universally accepted and should minimize this source of confusion.

The etiology of AD remains unknown. Several immunologic and physiologic abnormalities have been noted,^{6, 7} but the underlying defect has not been established. Abnormalities of both humoral and cellular immunity have been described in patients with AD: (1) elevated serum IgE concentration in approximately 80% of patients,⁸ (2) defective delayed-type skin responsiveness to various antigens and increased susceptibility to various viral infections of the skin,^{9, 10} (3) variably decreased lymphocyte response to mitogens, recall antigens, and alloantigens in vitro,¹¹ (4) defective generation of cytotoxic T-lymphocyte response in vitro,¹² and (5) variably decreased phagocytic capacity and chemotaxis and neutrophils and monocytes.¹³

Although an allergic pathogenesis has been suggested since Besnier's initial descriptions of AD, there is considerable debate over the role of IgE in this disorder. Several clinical observations have suggested a central role for an IgE-mediated mechanism: the

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*This article represents the presentation presented at the first Jerome Glaser Lectureship at the Forty-third Annual Meeting of the American Academy of Allergy and Immunology. Dr. Glaser was a pioneer and strong advocate of the subspecialty of pediatric allergy and had a great interest in atopic dermatitis, food hypersensitivity, and the prophylaxis of these disorders. It was a distinct honor reviewing the pathogenic role of food hypersensitivity in atopic dermatitis in a forum honoring such a highly regarded, clinically astute, productive pediatric allergist.

Data were managed and analyzed with CLINFO.

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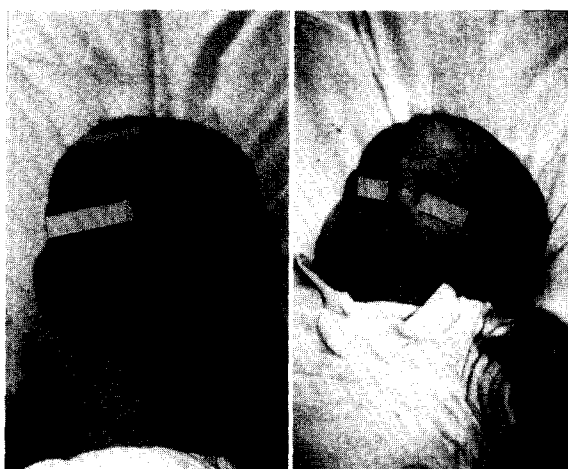


FIG. 1. Exclusively breast-fed infant whose symptoms of infantile AD cleared when his mother started receiving an egg-restricted diet. Patient is observed here before and 4 hours after the reintroduction of egg into his mother's diet. Symptoms appeared about 20 minutes after breast feeding.

high rate of personal^{14, 15} and family history of other atopic disorders,¹⁶ the presence of elevated serum IgE concentrations and positive skin tests to a variety of allergens in 80% of patients,^{17, 18} and the numerous studies correlating clinical flares with exposure to various foods and inhalants.¹⁷ Since at least 20% of patients with AD do not share these features, the significance of IgE in the pathogenesis of AD has been doubted. In addition, the histology of an eczematous lesion is more indicative of a type IV cell-mediated response.¹⁹ Although the dermal pathology varies with the temporal nature of the clinical lesion,²⁰ both the acute and chronic phases are characterized by a lymphocytic infiltrate. In the acute phase, there is slight psoriasiform hyperplasia of the epidermis, spongiosis secondary to intercellular edema, and ballooning of the keratinocytes secondary to intracellular edema. Normal numbers of mast cells are observed with no obvious increase in basophils or eosinophils. In the chronic lesions, there is moderate to marked hyperplasia of the epidermis with elongation of the rete ridges and prominent hyperkeratosis. Varying degrees of intercellular edema are present, but vesicle formation is not observed unless there is a superimposed acute exacerbation. The numbers of mast cells and LCs are significantly increased in chronic lesions. Interestingly, frequent exposure to an allergen, dust mite, has been demonstrated to lead to increased numbers of mast cells in the skin of patients with AD and with dust mite sensitivity.²¹ Rarely are eosinophils observed. Capillary number is often increased, and capillary walls may be thickened. Demyelination and

fibrosis of cutaneous nerves are observed at all levels of the dermis.

The role of IgE in the pathogenesis of AD is controversial, but perhaps even more controversial is the potential role of IgE-mediated food hypersensitivity in pathogenesis. In view of the obvious discrepancies in the literature, studies were undertaken to address this issue.²²⁻²⁴ To date, 160 patients with AD have been evaluated with DBPCFC. Patients enrolled in the study fulfilled the criteria of Hanifin and Rajka¹ for the diagnosis of AD. Subjects ranged in age from 3 months to 24 years, with a median age of 5.3 years. All patients were studied on a Clinical Research Unit (RR-30 and RR-00052) for control of environmental variables and diet. Patients were often treated for several days with an intensive topical regimen to clear cutaneous erythema and pruritus. Selection of foods for DBPCFC was based on skin test and RAST results and/or a strongly suggestive history of food hypersensitivity. The order of the oral FCs was established by a computerized randomization scheme. Up to 10 gm of dehydrated food was administered during 1 hour in opaque capsules or camouflaged in juice. Two challenges were conducted each day, one containing a food antigen and one containing a placebo. All reactions occurred within 3 hours of initiating the challenge. Many patients experiencing "immediate" skin symptoms developed pruritus and, less frequently, a macular, pruritic rash in reaction sites 6 to 8 hours after the initial response. Although pruritus associated with the immediate reaction was severe and generally short-lived (less than 2 hours), pruritus associated with the later response was less intense but longer lasting (often 4 to 6 hours). No isolated late reactions were observed.

A total of 514 DBPCFCs were conducted in the initial evaluation of these children with AD. DBPCFCs were not conducted in 25 instances because history revealed a "convincing" account of a major anaphylactic reaction. History was considered "convincing" when a patient experienced severe respiratory compromise (laryngeal edema and/or wheezing) and/or hypotension within minutes of ingesting an isolated food and required emergency care by a physician. In each case, patients had a strongly positive prick skin test to the food in question: peanut, 16; egg, 4; fish, 4; and potato, 1. No patient experienced a severe anaphylactic reaction associated with the challenge, although three patients were administered subcutaneous epinephrine for wheezing.

As frequently stressed by Glaser,²⁵ several investigators have confirmed that infants can react to food antigens transmitted in their mothers' breast milk.²⁶⁻³⁰ Six infants (aged 2.5 to 6 months) who developed

classic infantile eczema, while they were being exclusively breast-fed, have been observed in this study. All babies had a positive prick skin test to egg and normal serum IgE concentrations. Each of the infants demonstrated complete clearing of their skin while their mother maintained an egg-free diet. Four of these infants underwent an indirect FC (mothers were fed egg) on the Clinical Research Unit. An eczematous rash developed in each infant 4 to 36 hours after the mother had egg reintroduced into her diet (Fig. 1). One infant not challenged developed severe wheezing requiring an emergency room visit 6 hours after his mother ate two eggs. Three of these children subsequently have undergone DBPCFC, two, 1 year after the indirect challenge, and one child on two successive years after the indirect challenge. All children remain sensitive to egg but have had virtually no difficulty while they maintained an egg-elimination diet.

A total of 334 DBPCFCs were interpreted as negative, and 180 were positive. All patients experiencing a negative challenge were fed the food openly before discharge to confirm results of the DBPCFC. Three children, two, aged 4 years, and one child, aged 2 years, developed cutaneous reactions only after ingesting milk openly. One child, aged 5 years, developed respiratory, gastrointestinal, and cutaneous symptoms on two separate occasions (1 year apart) after openly ingesting a normal portion of peas. Cutaneous reactions developed in 143 instances (79%) and consisted of a pruritic, erythematous, macular, or morbilliform rash. Symptoms confined exclusively to the skin occurred in only 29% of the reactions. Urticarial lesions were rarely observed and generally consisted of only two or three lesions. Gastrointestinal symptoms were observed in 43% of the reactions, even though a history of gastrointestinal symptoms, other than poor appetite, was rarely elicited from the patients. The gastrointestinal symptoms observed consisted of nausea, abdominal pain, or both, plus vomiting, diarrhea, or both. Interestingly, appetite generally improved in these patients once the specific food allergen was eliminated from their diet. Respiratory symptoms involving primarily the upper respiratory tract were observed in 28% of the positive DBPCFCs. Respiratory symptoms included nasal congestion, rhinorrhea, sneezing, stridor, and/or wheezing.

IgE-mediated reactions may involve both an "immediate" and "late-phase" component.³¹⁻³³ The former is characterized by the release of mast cell mediators, especially histamine, in response to antigen challenge and is most frequently appreciated in the skin as a wheal-and-flare response. Since patients with AD reacting to FCs generally developed an erythematous morbilliform rash, it was important to establish that

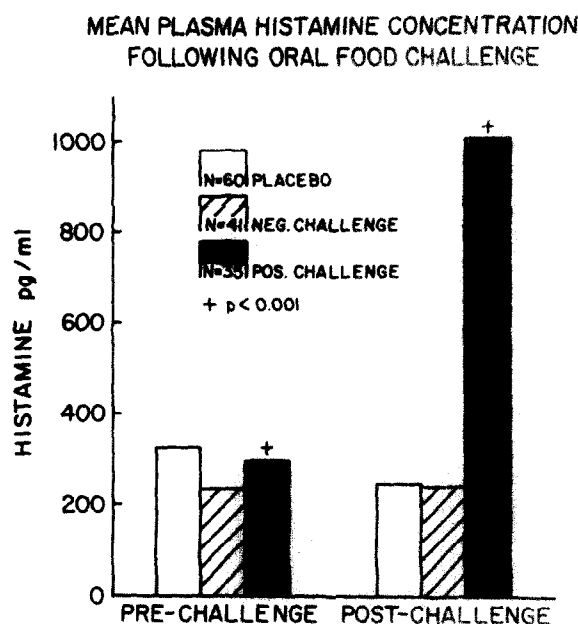


FIG. 2. Change in plasma histamine concentrations associated with DBPCFCs (adapted from reference 23).

this was due to an IgE-mediated mechanism. As illustrated in Fig. 2, patients experiencing symptoms after oral FC were found to have a significant rise in plasma histamine, whereas patients experiencing no symptoms to a food antigen or to a placebo had no change in plasma histamine. Since many of these patients had no respiratory or gastrointestinal symptoms and since histamine is so rapidly catabolized, it is most likely that the rise in plasma histamine reflected activation of mast cells or basophils proximate to the site of sampling (i.e., in the skin).

To determine whether basophils had been activated during the challenge, venous samples have been obtained before challenge, immediately after challenge, and 30 minutes after the development of the first objective symptoms.³⁴ Samples were evaluated for basophil number, total histamine content of the leukocyte preparation, and unstimulated ("spontaneous") histamine release in vitro. There was no difference in basophil number, total histamine content, or unstimulated histamine release at any time point. This would suggest that basophils were not contributing significantly to the changes in plasma histamine observed.

Several investigators have demonstrated the presence of circulating food antigen-antibody complexes after oral FC.³⁵⁻³⁷ To rule out the possibility that mast cell degranulation was secondary to complement activation, C3a desArg and C5a desArg were quantitated before DBPCFC, and immediately, 15 minutes, and 30 minutes after the development of objective symptoms with very sensitive radioimmunoassays.

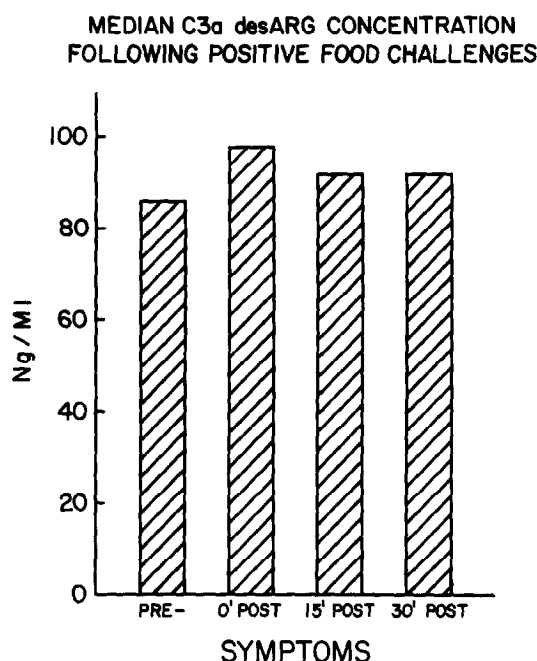


FIG. 3. Median Plasma C3a desArg concentrations in 18 patients experiencing objective clinical symptoms after DBPCFCs.

Measurement of the anaphylatoxins, C3a and C5a, are very sensitive indicators of complement activation.³⁸ There was no significant change in plasma C3a desArg concentrations, illustrated in Fig. 3, after positive DBPCFCs in 18 patients. C5a desArg was undetectable in all samples examined. Therefore, it is extremely unlikely that changes in plasma histamine after positive food challenges were secondary to complement-induced anaphylactoid reactions.

Results of the DBPCFC indicate that IgE-mediated food hypersensitivity readily produces a pruritic, erythematous rash in some children with AD.²²⁻²⁴ Patients scratch vigorously, often excoriating themselves, for 1 to 2 hours after the brief allergen exposure. The question is whether such a limited reaction could lead to the chronically pruritic, eczematous skin changes observed in AD. Several lines of evidence suggest that it could.

In reality, patients receive several exposures each day to allergens, such as egg, milk, soy, and wheat, which are consumed in some form at virtually every meal or snack. These allergens are consumed with other foods, such as fats, which may alter absorption rates.³⁹ Symptoms that appeared distinct when foods are ingested in isolation on an empty stomach, during the DBPCFC, may be less pronounced, blending into each other and appearing more constant. Consequently, frequent scratching, which has been demonstrated to be necessary for the development of

lichenification,⁴⁰ leads to the typical skin changes of AD.

Perhaps more central to the pathogenesis of AD is the role of the "late-phase" of IgE-mediated hypersensitivity. Dolovich et al.³¹ were first to describe the LCAR in humans nearly 15 years ago. Since then, several groups have contributed to our knowledge of this reaction. More than 50 years ago, Brunner and Walzer⁴¹ and Wilson and Walzer⁴² unequivocally demonstrated that ingested food antigens cross the gastrointestinal barrier and come in contact with skin mast cells within minutes to 2 hours of ingestion. Although experimental LCARs use allergens injected into the skin instead of those introduced via the circulation, they probably serve as a useful model for the mechanisms involved in cutaneous reactions secondary to food hypersensitivity.

Studies by Kaliner and other investigators⁴³⁻⁴⁵ in the rat model, Zweiman, Atkins, and other investigators⁴⁶⁻⁴⁸ with the use of denuded skin blisters in man, and additional investigators⁴⁹⁻⁵² have demonstrated that within minutes of encountering an allergen, cutaneous mast cells become activated and release histamine (and other mediators) into local tissue. This results in pruritus, vasodilation (observed as erythema), and capillary "leakiness" (observed as edema). Approximately 2 to 4 hours later, neutrophils and eosinophils infiltrate the area. In the rat model, a high-molecular-weight component present in the mast cell granule appears responsible for this infiltration.⁵³ In man, both neutrophil and eosinophil chemotactic factors have been identified after mast cell activation,^{54,55} but the exact source of these mediators is not established. One possible source for the neutrophil chemotactic factor is in local capillary endothelial cells. Farber et al.⁵⁶ recently demonstrated the rapid generation of a lipid neutrophil chemoattractant from cultured endothelial cells in the presence of histamine. Once this is present, neutrophils could contribute to the skin pathology by releasing various proinflammatory mediators, for example, PGDs, LTB₄, PAF, and toxic oxygen radicals. In man, eosinophils also are prominent in the infiltrate and may release a variety of mediators, which could contribute to the pathogenesis,^{57,58} as discussed below. During the ensuing 24 to 48 hours, monocytes and lymphocytes infiltrate the area, presenting a histologic picture indistinguishable from a type IV cell-mediated response.

Eosinophils are infrequently observed in histologic sections of skin biopsy specimens from eczematous lesions,¹⁹ casting doubt on the role of a late-phase mechanism in AD. However, in a study with Leiferman et al.,⁵⁹ biopsy specimens from patients with AD were evaluated for the presence of eosinophil MBP,

a cytolytic protein secreted almost exclusively by eosinophils. MBP is known to damage skin epithelial cells⁶⁰ and to promote further mast cell histamine release.⁶¹ With an antibody specific for MBP and an indirect fluorescein-staining technique, specimens from 18 patients were examined. MBP was distributed in a fibrillar pattern in the superficial dermis of all specimens obtained from eczematous skin lesions.⁵⁹ Dispersed granules were observed in 12 specimens. MBP was not found in biopsy specimens from uninvolved skin sites in these same patients, indicating that this eosinophil product was the result of specific deposition and not nonspecific sequestration via the circulation. Evaluation of biopsy specimens from other skin disorders, including contact dermatitis, did not reveal similar deposition of MBP. More recently, two food-allergic patients, who had experienced clearing of their skin lesions after maintaining appropriate food allergen-restricted diets, underwent repeat DBPCFCs in a subsequent study. Both patients developed a pruritic morbilliform skin rash within 30 to 60 minutes. Skin biopsy specimens obtained from involved sites 4 and 14 hours later revealed an infiltration of eosinophils and MBP deposition. The dermal infiltrate contained more eosinophils and less prominent MBP deposition than was observed with the chronic lesions. These findings support the theory that food allergen-induced mast cell activation may trigger both an "immediate" and "late-phase" response in the skin. Furthermore, it suggests that the typical mononuclear round cell infiltrate found in AD skin lesions may result from an IgE-mediated mechanism.

Previously, eosinophil-associated enzymes were believed to neutralize many mediators of anaphylaxis, including histamine, slow-reacting substances of anaphylaxis, and PAF.⁶² Recent data cast doubt on this dampening effect of eosinophils in anaphylaxis.⁵⁷ Besides MBP, eosinophils may release several other mediators that could contribute to the eczematous changes observed in skin biopsy specimens, for example, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase.⁵⁷ MBP is toxic to many cell types and can cause histamine release from mast cells. Eosinophil-derived neurotoxin, a powerful neurotoxin, may account for the demyelination of nerves in the dermal layer observed in eczematous skin. Eosinophil cationic protein, also a potent neurotoxin, has been demonstrated to inhibit lymphocyte proliferation and could contribute to the cutaneous anergy observed in patients with AD. Eosinophils also produce LTC₄ and PAF, which may contribute to the inflammatory process. The exact role of eosinophils in the pathogenesis of LCARs and eczematous skin lesions remains to be established. How-

ever, the ability of corticosteroids to block LCARs and bring about clearing of skin lesions in AD may be due to their ability to block eosinophil- and neutrophil-promoted inflammation.

Early studies demonstrated increased histamine content in affected skin of patients with AD.^{63,64} More recently, analyses of suction blister fluids raised over involved skin have demonstrated elevated LTB₄ compared to blister fluid from noninvolved skin and skin from normal donors.⁶⁵ Studies in children with AD and food hypersensitivity comparing suction blister fluid from normal appearing skin with normal donor skin revealed no significant difference in blister fluid histamine concentration (unpublished observation). The presence of elevated levels of histamine in skin lesions suggested more persistent mast cell activation and prompted a search for other factors that could provoke histamine release. One possibility is an HRF, first described by Theuson et al.^{66,67} Since this initial description, several investigators have identified HRFs from several different sources, including lymphocytes,^{68,69} lung macrophages,⁷⁰ platelets,⁷¹ blister fluid,⁷² and nasal lavage fluid⁷³ obtained during late-phase reactions in the skin and nose, respectively. These factors probably activate mast cells and basophils by binding to surface-bound IgE molecules.⁷² These factors may be responsible for allergic reactions that appear too late and are too prolonged to be accounted for by the classic IgE-mediated reaction.

In recent studies,³⁴ patients with AD and food hypersensitivity were found to have high SBHR from peripheral blood basophils *in vitro* (mean 34% versus 2.6%; $p < 0.001$), a property first observed in food-allergic individuals by May.^{74,75} In contrast, patients who had experienced good clearing of their skin lesions while they were being maintained with the appropriate food allergen-avoidance diet for at least 1 year were found to have significantly lower SBHR (4.9%). In addition, peripheral blood mononuclear cells from food-allergic individuals were found to produce an HRF that would activate basophils from other food-sensitive individuals, but not food-nonsensitive subjects. HRF was synthesized *in vitro*, even in mononuclear cells that had not been exposed to food allergen for several months. Studies are now underway to establish kinetics of production and dose-response effects of HRF generated from various patients. Circulating food antigens may lead to HRF production *in vivo*, which then could activate or lower the "threshold" of activation for mast cells and could account for the increased basophil "releasability" observed in some patients with AD⁷⁶ and the high SBHR observed in food-sensitive subjects *in vitro*.

Since low-affinity Fc ϵ receptors have been found on B cells, T cells, monocytes, macrophages,^{77,78} eo-

TABLE I. Results of prick skin tests to a standard battery of glycerinated food extracts in 160 children with AD

Food	Patients positive
Egg	89
Peanut	81
Fish	45
Soy	45
Pork	44
Shrimp	41
Milk	39
Beef	31
Pea	30
Chicken	27
Wheat	24
Rice	14
Rye	14
Potato	12
Corn	12
Oats	9
Green beans	7
Tomato	7
Chocolate	5
Strawberry	1
Total	575

sinophils,⁷⁹ and platelets,^{80, 81} it is possible that IgE may affect a number of immunologic responses through "nonmast cell" IgE-mediated mechanisms. Although Fc E receptors on lymphocytes appear to be involved in regulation of IgE synthesis, Fc E receptors on monocytes, macrophages,⁸² and eosinophils are directly involved in the killing of IgE-coated targets and release of various mediators. Human monocytes stimulated *in vitro* with aggregated IgE released LTC₄, LTB₄, and PGE₂,⁸³ all of which can contribute to the inflammatory response. Similarly, platelets coated with antigen-specific IgE have been activated *in vitro* by the addition of relevant antigen.⁸⁴

Recently Bruynzeel-Koomen et al.⁸⁵ demonstrated that IgE molecules are bound exclusively to epidermal LCs in patients with AD. LCs are similar to macrophages in that they serve as an antigen-presenting cell and synthesize various mediators, especially PGD₂.⁸⁶ The increased number of LCs in eczematous skin lesions and the frequent improvement in patients with AD exposed to ultraviolet light (which selectively destroys LCs) suggest a central role for LCs in the pathogenesis of AD. The unique presence of Fc E receptors on LCs of patients with AD suggests another mechanism by which allergens could contribute to patho-

TABLE II. Foods eliciting hypersensitivity reactions in children with AD

Food	No. of patients	% Of reactions
Egg	78 (4)	38%
Peanut	48 (16)	24%
Milk	22	11%
Fish	15 (4)	7%
Soy	10	5%
Wheat	8	4%
Chicken	4	2%
Pork	2	1%
Beef	2	1%
Potato	3 (1)	1.2%
Others	12	5.8%
Total	204	100%

Diagnosis made by DBPCFC or by acquisition of "convincing" history of a severe reaction after an isolated ingestion of a food indicated by number in parentheses.

genic skin changes. It is therefore evident that food antigens may interact with several different cells capable of releasing a variety of inflammatory mediators.

Interestingly, the target organ responses observed varied with the antigen being administered in the DBPCFC. Of 32 children reacting to two different foods, 19 experienced different target organ responses for each food antigen, and 13 children experienced similar responses to both foods. Of six children reacting to three foods by DBPCFC, none experienced similar symptoms to all foods. Ten patients receiving the same food antigen on two occasions within a several-day to 2-month period, all experienced virtually identical symptoms on both occasions. This would suggest that different foods can elicit different target organ responses.

The best method for diagnosing food hypersensitivity in children with AD remains controversial. Information generated in these studies strongly implicate an IgE-mediated mechanism in food hypersensitivity, but routine diagnostic procedures were not specific. Historical information and elimination diets were rarely helpful. Similarly, laboratory data were of limited value. In a previous study, results of prick skin tests, RAST, and DBPCFC were compared.⁸⁷ It was concluded that a positive prick skin test (or RAST) should be considered as a suggestive indicator of immediate food hypersensitivity requiring confirmation with a more definitive study, such as the blinded oral food challenge. A negative prick skin test, however, virtually excludes immediate food hypersensitivity in

TABLE III. Food antigen-specific antibodies in egg-allergic children rechallenged after receiving an egg-free diet for 1 year

	1st Challenge	Rechallenge
Egg rechallenge positive group (N = 20) (median/range)		
Serum IgE (IU/ml)	4200 32-52,000	5200 46-15,000
Oval spec IgE (ng/ml)	132.5 3.2-14,000	77.7 1.7-12,000
IgA (μ g/ml)	297.5 29-2877	211.5 29-4017
IgG (μ g/ml)	42.5 4.0-556	27.9 2.5-50.6
Egg rechallenge negative group (N = 8)		
Serum IgE (IU/ml)	1720 8-19,600	3950 40-10,000
Oval spec IgE (ng/ml)	58.9 1.9-469	32.8 2.3-278
IgA (μ g/ml)	415.5 15-1,323	300.5 146-939
IgG (μ g/ml)	46.1 5.5-297	12.5 0.6-74.4

Oval spec = ovalbumin-specific.

AD, unless it is presented with a very convincing history to the contrary.

Many studies have suggested that children with AD are sensitive to a large number of food antigens.⁸⁸ Of 20 possible food allergens tested (Table I), children in this study had positive prick skin tests to an average of 3.2, range 0 to 8. However, there was about one third as many positive FCs as positive prick skin tests. Indeed, most children (78%) reacted to only one or two foods by DBPCFC, 43 children (44%) were sensitive to only one food, 33 (34%), to two foods, 19 (19%), to three foods, and three children were sensitive to four or more different foods. Six food antigens (egg, peanut, milk, wheat, fish, or soy) accounted for about 90% of the positive clinical responses (Table II).

Clinical reactivity to a food appears to be highly specific. Although results of skin tests (and RASTs) commonly demonstrate cross-reactivity among members of a botanical family or animal species, there was only one case of intrabotanical cross-reactivity and no evidence of intraspecies cross-reactivity, as determined by DBPCFC. Consequently, the practice of avoiding all foods within a botanical family, when one member is suspected of provoking allergic symptoms, appears to be unwarranted.

Therapy of IgE-mediated food hypersensitivity is straightforward. Strict avoidance of the offending food allergen is the only proven therapy. Contrary

to many studies, a recent double-blind, placebo-controlled crossover trial of oral cromolyn in 10 patients with AD and with challenge-proven food hypersensitivity demonstrated no benefit from this preparation.⁸⁹ Other therapeutic modalities proposed, such as rotational diets, immunotherapy, and sublingual and subcutaneous neutralization, have never been demonstrated to be efficacious in controlled trials.

In food-sensitive children, loss of clinical sensitivity frequently develops over time so that restrictive diets can be stopped. Approximately 1 year after initiating appropriate elimination diets, 67 children with food hypersensitivity were rechallenged to 102 antigens. Forty-one children retained sensitivity to all the food antigens previously eliciting symptoms, three lost sensitivity to some food antigens, and 23 children lost their sensitivity to all antigens previously eliciting positive clinical responses. Twenty-one children who retained their food sensitivity underwent another repeat challenge 1 to 2 years later. Only three of these children lost their clinical reactivity. Overall, the 67 children studied developed clinical tolerance to about one third of the foods previously provoking an allergic response.

The reason clinically apparent food sensitivity is lost remains an enigma. In an earlier study,⁹⁰ 28 children with AD and egg hypersensitivity were rechallenged after maintaining an egg-free diet for 1 year.

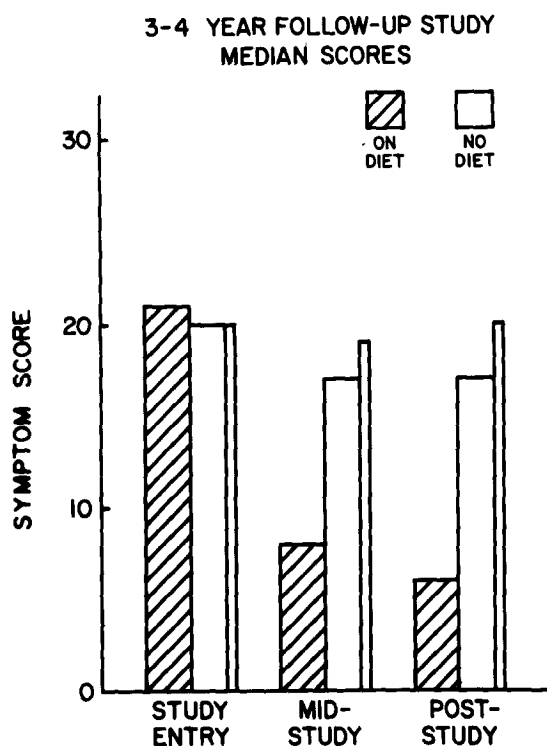


FIG. 4. Median clinical symptom scores in 34 patients with AD followed prospectively for 3 to 4 years (see text).

Repeat skin testing before the second challenge revealed no apparent loss of sensitivity. Twenty children again experienced a positive FC. Eight patients developed no symptoms during the challenge and were able to eat normal quantities of the food with no apparent adverse effect. Ovalbumin-specific antibodies were quantitated in both groups at the time of the first and second challenge. Both groups experienced a statistically insignificant decrease in ovalbumin-specific IgE, IgA, and IgG antibodies after 1 year of egg avoidance (Table III). In addition, there was no significant difference in ovalbumin antibodies between the two groups at either time period. Therefore, loss of clinically apparent hypersensitivity did not appear to be directly related to the quantity of ovalbumin-specific antibody of the isotypes tested.

If IgE-mediated food hypersensitivity plays a significant pathogenic role in AD, the clinical course of patients appropriately diagnosed and maintained with a relevant antigen-free diet should improve relative to untreated patients. The clinical course of 34 children with AD who have been followed for 3 to 4 years is depicted in Fig. 4.²⁴ One group consisted of 17 children with food hypersensitivity who were maintained with appropriate elimination diets (on diet). The other group was comprised of 12 children in whom no food hypersensitivity could be detected by DBPCFC and

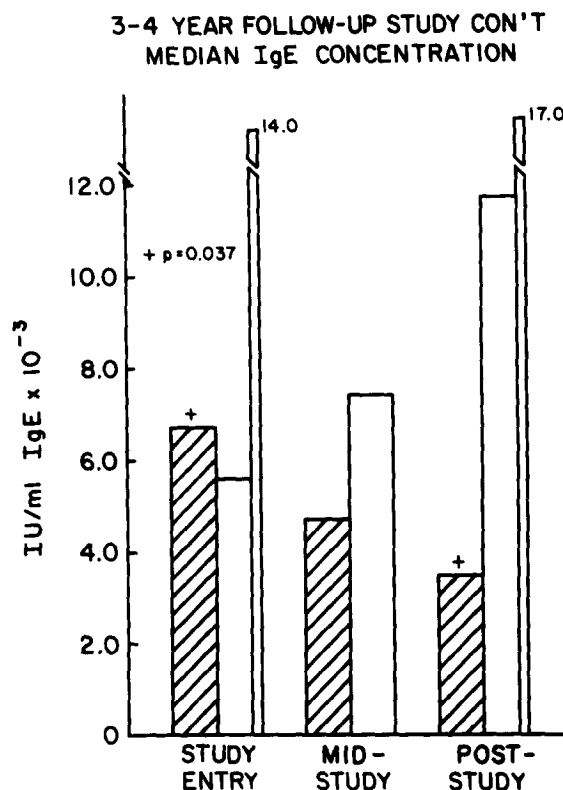


FIG. 5. Median total serum IgE concentration in 34 patients with AD followed prospectively for 3 to 4 years (see text).

five children who were food sensitive but who failed to comply with the diet (no diet). AD symptoms were scored at 6-month intervals with a standardized symptom score sheet. The scoring scale ranged from 0 (no symptoms) to 30 (severe symptoms). Factors considered in generating the score included the extent of the rash (0 to 6), course (0 to 3), intensity of daytime symptoms (0 to 6), intensity of nighttime symptoms (0 to 6), use of antihistamines (0 to 3), use of antibiotics or steroids (0 to 3), and days missed from school or parent days missed from work because of AD (0 to 3). There was no significant difference between the two groups in symptom scores or serum IgE concentrations at the initiation of the study. As illustrated in Fig. 4, the group receiving an elimination diet (on diet) demonstrated a highly significant improvement in clinical scores by midstudy ($p < 0.001$) with further slight improvement by the end of the study period. The group that failed to comply with the diet (no diet) demonstrated slight improvement in clinical scores by midstudy ($p < 0.05$), but no further improvement through the remainder of the study. The initial slight improvement was probably due to the institution of more intensive skin care, since improvement occurred early and did not change over the course of the study.

The clinical symptom scores of the "on diet" group were significantly better than the scores of the "no diet" group at midstudy and at the end of the study period ($p < 0.001$). Similarly (Fig. 5), the "on diet" group experienced a significant decrease in total IgE during the course of the study (midstudy, $p = 0.045$; after the study, $p = 0.037$), whereas the "no diet" group experienced an increase in total serum IgE values. The five noncompliant patients with food hypersensitivity in the "no diet" group demonstrated no significant improvement in the clinical course, and all experienced an increase in total serum IgE concentration during the course of the study. These data demonstrate that appropriate diagnosis and elimination of foods provoking hypersensitivity responses can favorably affect the course of AD.

In many of his lectures, Dr. Glaser²⁵ stressed his belief that symptoms of allergy, and AD in particular, could be prevented by modifying an infant's diet. Although considerable controversy remains on this topic, the weight of the evidence would appear to confirm Dr. Glaser's impression. In one study by Kajosaari and Saarinen,⁹¹ exclusive breast feeding was found to reduce the number of infants developing food hypersensitivity in the first year of life. However, further follow-up suggested that breast feeding may simply postpone the development of food allergy in those predisposed infants not developing clinical hypersensitivity in the first year.⁹² Since breast feeding provides many other benefits to the developing infant, even postponing food allergy until after the neonatal period in itself is sufficient reason to advocate this practice.

Studies reviewed here suggest a significant role for IgE-mediated food hypersensitivity in the pathogenesis of AD in some patients. In addition, the possible role of IgE-mediated reactions to inhalant allergens (ragweed, *Alternaria*, and dust mites) in the pathogenesis of AD in some patients is suggested by early studies of Tuft et al.,⁹³ Tuft and Heck,⁹⁴ and recent studies by Mitchell et al.²¹ Studies more than 50 years ago clearly demonstrated that foreign antigens readily cross the respiratory⁹⁵ and gastrointestinal^{41,42} barriers and are rapidly distributed to the skin. Once breaching the outer barrier of these bodies, these allergens could trigger a variety of cell types possessing Fc E receptors. Unraveling the complexities of the IgE-mediated response and the effects of the vast number of mediators released by activated cells must await further research.

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