

# Food Hypersensitivity as a Pathogenic Factor in Atopic Dermatitis

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## ABSTRACT

*The role of food hypersensitivity in the pathogenesis of atopic dermatitis has been debated for years. One-hundred thirty-two children with severe atopic dermatitis were evaluated for food hypersensitivity using double-blind placebo-controlled oral food challenges. Fifty-nine percent of the children experienced at least one immediate hypersensitivity response. Definitive diagnosis of food allergy and initiation of an appropriate elimination diet resulted in significant clinical improvement in the majority of patients with atopic dermatitis and food hypersensitivity.*

The French physician, Besnier, is credited with the first description of atopic dermatitis, initially called "prurigo diathesique," in 1892<sup>1</sup>. Besnier emphasized the chronically recurring course, association with asthma and hayfever, and familial tendency of this disorder. Later Wise and Sulzberger<sup>2</sup> further emphasized the relationship between asthma, allergic rhinitis and

atopic eczema by coining the term "atopic dermatitis," by which the disorder is generally known today. Atopic dermatitis (AD) is an extremely pruritic, erythematous, papulovesicular eruption often beginning in early infancy and progressing to a scaly, lichenified rash over time<sup>3</sup>. The distribution of the dermatitis varies with age<sup>4</sup>. In early infancy, it involves primarily the cheeks and extensor surfaces of the arms and legs. In the young child, flexor surfaces are more commonly involved, and in the teenage patient and young adult, hand and foot eczema are more prevalent. The incidence of AD is estimated at between 1.1 and 4.5% of the pediatric population<sup>5,6</sup>. A recent survey revealed that AD accounted for 1% of pediatric office visits in North America<sup>7</sup>.

The investigation of AD has been hampered by discrepancies in diagnostic criteria, which have resulted in large numbers of contradictory studies. In the last several years, a classification system has been proposed for the diagnosis of AD, which should eliminate the confusion and inexactness of earlier clinical reports. The criteria proposed emphasize the extremely pruritic nature of the rash and its typical morphology, distribution, and tendency toward a chronic or relapsing course<sup>8,9</sup>.

The etiology of atopic dermatitis is unknown. The role of allergy (and food allergy in particular) in the pathogenesis of AD has been debated for years. Several factors suggest a role for an IgE-mediated mechanism in this disorder: 1) a positive family history of atopic disease in two-thirds of eczema patients<sup>10</sup>, 2) the serum IgE concentration is elevated in 80 to 90% of children<sup>11</sup>, 3) positive immediate skin tests and RAST's to various dietary and environmental allergens are found in ap-

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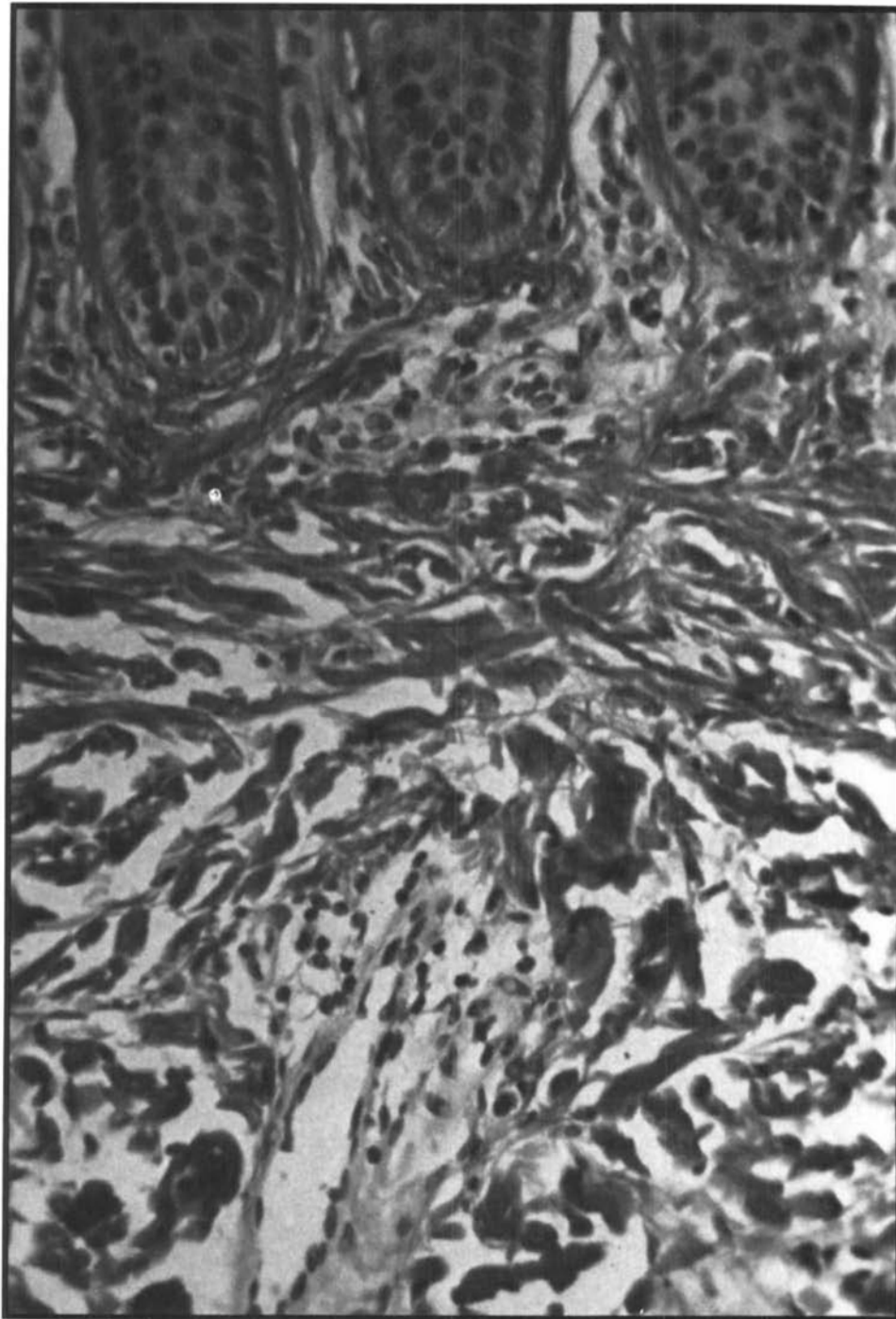


**Figure 1a.** High power view (X400) of the epidermal-dermal junction from an eczematous lesion in a patient with AD. Fig. 1a is the hematoxylin and eosin preparation and Fig. 1B is the adjacent section stained with a fluorescein-labeled anti-MBP antibody. The immunofluorescent pattern suggests MBP adherence to elastic fibers at the dermal-epidermal junction (Photographs courtesy of Dr. K. Leiferman Dept. Dermatology, Mayo Clinic).

proximately 80% of children<sup>12,13</sup>, and 4) 50 to 80% of children with atopic dermatitis go on to develop other atopic disorders such as allergic rhinitis and asthma<sup>14,15</sup>.

However, many investigators have discounted the possible role of Type I, or IgE-mediated reactions on the basis of the histology of the skin lesions. Spongiosis with

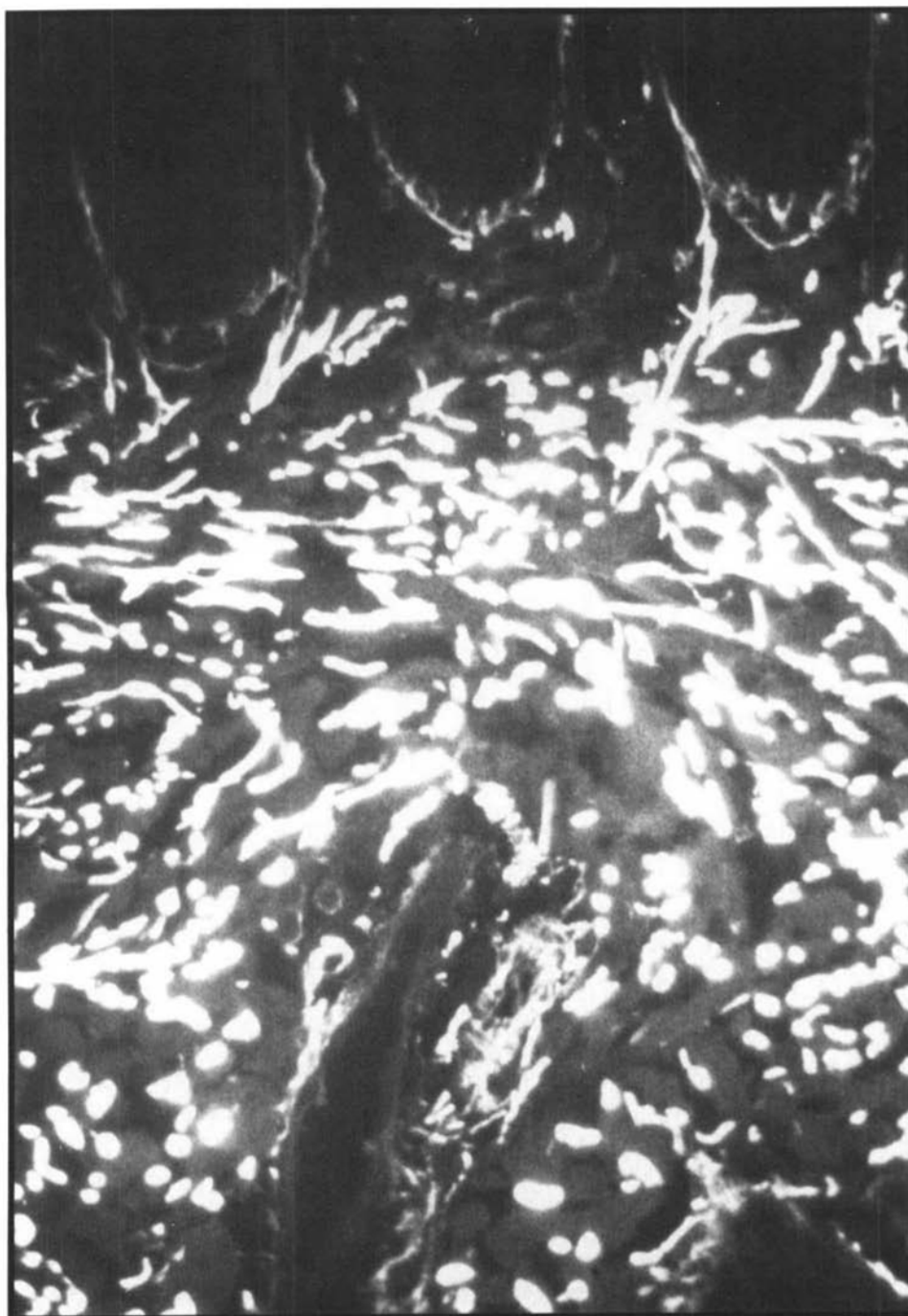


*Figure 1b. continued*

inter- and intra-cellular edema, marked hyperplasia of the epidermis, and mononuclear round cell infiltrates, especially at the dermal-epidermal junction are characteristic of skin biopsy specimens obtained from patients with atopic dermatitis. In particular, the presence of a mononuclear round cell infiltrate has prompted

many investigators to propose a classic Type IV, or cell-mediated immune reaction as the main cause of the eczematous lesion<sup>16</sup>.

Recent developments in our understanding of the "late-phase" response following mast cell activation may help resolve the apparent paradox between the

strong clinical association of eczema with IgE-mediated diseases and the atypical and histologic appearance. In those patients with food hypersensitivity, the "immediate-phase" following ingestion of allergen leads to release of histamine<sup>17</sup> (and probably other preformed mediators) resulting in cutaneous pruritus, subsequent scratching and excoriation, as suggested by the classic experiment of Engman<sup>18</sup>. During the early phase of mast cell degranulation, neutrophil and eosinophil chemotactic factors are generated and neutrophils and eosinophils are attracted to the area. As proposed by Gleich and his co-workers, eosinophils release major basic protein (MBP), an arginine-rich cytolytic protein known to damage skin epithelial cells<sup>19</sup> and to lead to further mast cell histamine release<sup>20</sup>. In collaboration with Drs. Leiferman, Gleich, and their co-workers at the Mayo Clinic<sup>21</sup>, it was found that skin biopsies from involved areas of AD patients' skin contained large quantities of MBP in the superficial dermis (Fig. 1). Biopsies from uninvolved areas of skin revealed virtually no MBP in the dermal layer. The exact role of this cytolytic protein in the development of eczematous skin lesions remains unclear. Several hours to days following mast cell degranulation, infiltration of neutrophils and eosinophils, and the release of MBP, mononuclear round cells migrate to and persist in the area of the initial IgE-mediated reaction; this histologic picture is virtually indistinguishable from that seen in skin specimens from AD lesions<sup>22</sup>.

Over the past three years, we have had the opportunity to evaluate 132 patients with AD for the presence of food hypersensitivity using double-blind placebo-controlled oral food challenges. The median age of the study subjects was 5.8 years with a range of four months to 24 years. Eighty-six percent of these patients had elevated serum IgE concentrations with a median of 3,750 IU/ml and a range of 8.4 to 52,000 IU/ml (Duke Pediatric Immunology Laboratory normal range for IgE: 5–621 IU/ml). Ninety-five percent of these children had positive family histories for atopic disease and nearly half, 63 patients, had both allergic rhinitis and asthma. Allergic rhinitis alone was present in 34 (26%), asthma alone in seven (5%), and neither allergic rhinitis nor asthma in 28 (21%). All patients enrolled in the study fulfilled the criteria of Hanifin and Lobitz<sup>8</sup> for the diagnosis of atopic dermatitis. Patient histories and previous allergy tests were reviewed prior to admission to the Clinical Research Center (RR-30). Selection of foods for challenge was based upon positive skin tests and/or strong histories of possible food hypersensitivity. Foods selected for the challenge protocol were excluded from the patient's diet for 10–14 days prior to admission. In addition, all antihistamines were discontinued for one week prior to the admission date.

Following admission, prick skin testing to a battery of 20–30 foods was performed to confirm previous results. Prior to initiating food challenges, a heparin-lock was inserted for atraumatic serial blood sampling and for providing an open line in case of anaphylactic reactions. The double-blind placebo-controlled food challenges were performed in a manner similar to that described by May and Bock<sup>23</sup>. Two challenges were performed each day, one containing placebo and one containing the test food. The order of all challenges was determined by the Clinical Research Unit dietician using a randomization scheme on the Center's computer (CLINFO). Only the dietician was aware of the contents of the challenge. Up to eight grams of dehydrated, powdered food was administered in opaque capsules or in 100 cc of juice over a one hour period. The initial dose was generally less than 500 mg and was increased in a step-wise fashion at ten to 15 minute intervals until a reaction occurred or the entire eight grams was consumed. Each challenge was evaluated and scored using a previously published symptom sheet. If a patient had a negative challenge, he was fed the food openly prior to the time of discharge to ensure the accuracy of the blinded challenge and assure the patient and parent that the food could be consumed without difficulty. In over 450 food challenges performed, there have been two instances of negative blinded food challenges followed by reactions to the open feeding. One child, age five years, developed cutaneous gastrointestinal, nasal, and respiratory symptoms approximately 15 minutes after openly ingesting a standard portion of peas. A second child, age four, developed cutaneous nasal and respiratory symptoms after consuming approximately 100 cc of milk.

As shown in Table I, there were 461 positive skin tests in the 132 children studied. Skin tests were considered positive if the wheal was 3 mm greater than the negative control. Egg, peanut, milk, wheat, soy, and fish accounted for the majority of the positive skin tests. Interestingly, tomato, corn, chocolate, and strawberry, foods frequently cited as exacerbating atopic dermatitis, rarely induced a positive immediate skin test.

Four-hundred fifty-eight double-blind placebo-controlled food challenges have been carried-out in this group of children with atopic dermatitis. Nineteen 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 12, 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 oral diphenhydramine for severe pruritis and two required subcutaneous epinephrine

Table I

## Results of prick skin tests to food antigens in 132 study patients

| Reagent | Number Positive | Reagent | Number Positive | Reagent    | Number Positive |
|---------|-----------------|---------|-----------------|------------|-----------------|
| egg     | 67              | pork    | 39              | gr. bean   | 7               |
| peanut  | 61              | beef    | 26              | corn       | 10              |
| milk    | 31              | potato  | 10              | chocolate  | 6               |
| wheat   | 18              | pea     | 22              | rye        | 10              |
| soy     | 42              | shrimp  | 27              | oats       | 8               |
| fish    | 38              | rice    | 11              | strawberry | 1               |
| chicken | 21              | tomato  | 6               |            |                 |
|         |                 |         |                 | total      | 461             |

Table II

## Symptoms Induced by Food Challenge in 132 Patients with Atopic Dermatitis

|                                                                |           |
|----------------------------------------------------------------|-----------|
| Positive food challenges:                                      | 139       |
| Cutaneous symptoms—total                                       | 118 (85%) |
| Skin symptoms only                                             | 39 (28%)  |
| GI symptoms—total                                              | 80 (57%)  |
| GI symptoms only                                               | 13 (9%)   |
| Respiratory symptoms—total<br>(nasal symptoms and/or wheezing) | 50 (36%)  |
| Negative food challenges                                       | 319       |

for respiratory symptoms. As shown in Table II, 319 of the double-blind challenges were interpreted as negative.

Of the 139 positive food challenges, 118 (85%) involved cutaneous symptoms. Skin changes consisted of a pruritic, erythematous, macular or morbilliform rash which involved greater than 5% of the total body surface. Only 28% of reactions were confined to the skin alone. Patients' scratching frequently produced superficial excoriations and occasionally bleeding. Urticarial lesions were rarely seen and generally consisted of only two or three lesions.

Surprisingly, 57% of the positive challenges involved gastrointestinal symptoms. Virtually none of the patients studied had reported gastrointestinal symptoms during the review of medical history. The gastrointestinal symptoms seen consisted of nausea, abdominal pain or both, plus emesis, diarrhea or both.

Respiratory symptoms involving primarily the upper respiratory tract were seen in 50 (36%) of the positive

food challenges. Respiratory symptoms included nasal congestion, rhinorrhea, sneezing, stridor, and/or wheezing.

As reported previously, most patients with atopic dermatitis experiencing positive food challenges were found to have a rise in their plasma histamine<sup>24</sup>. No such rise was seen in negative or placebo challenges. All reactions occurred within two hours of the oral challenge, often within ten–15 minutes of initiating the study. No "delayed" responses have been seen, and systematic attempts to document such reactions have been unsuccessful to date. No "behavioral" changes have occurred in the absence of typical allergic symptoms.

Several reports have suggested that children with atopic dermatitis are allergic to a wide variety of foods. Although most children in this study tended to have positive prick skin tests to several food antigens (mean 3.5; range zero to 11), most children (86%) reacted to only one or two foods. Thirty-eight children (49%) reacted to only one antigen, 29 (37%) reacted to two antigens, ten (13%) reacted to three antigens, and only one child reacted to four different foods.

Table III lists the foods eliciting positive challenges in the children studied. Compared to the number of positive prick skin tests, there were only about one-third as many positive food challenges. Six antigens, egg, peanut, milk, wheat, fish and soy accounted for nearly 90% of the positive clinical reactions. Although results of skin tests commonly demonstrate cross-reactivity among members of a botanical family or animal species, there was no evidence of intra-botanical or intra-species cross-reactivity as determined by the blinded oral food challenge. Consequently, the practice of avoiding all foods within a botanical family when one member is suspected of provoking allergic symptoms appears to be unnecessary. Elimination of this practice should im-

Table III

## Foods Inducing Positive Challenges

|          |         |       |         |       |      |
|----------|---------|-------|---------|-------|------|
| Egg      | 78 (3)  | 49%   | Chicken | 4     | 3.5% |
| Peanut   | 25 (12) | 16%   | Pork    | 2     | 1.5% |
| Milk     | 15      | 9%    | Beef    | 2     | 1.5% |
| Wheat    | 10      | 6%    | Potato  | 3 (1) | 2.0% |
| Fish     | 7 (3)   | 4.5%  | Others  | 6     | 4.0% |
| Soy      | 6       | 4%    | Total   | 158   | 100  |
| Subtotal | 141     | 89.5% |         |       |      |

( )—number based on "convincing" positive history

Table IV

## Comparison of Patients with Normal and Elevated Serum IgE Concentrations

|                                                    | Total Group<br>(132) | Normal IgE<br>(19) | Elevated IgE<br>(113) |
|----------------------------------------------------|----------------------|--------------------|-----------------------|
| Patient's Median Age (yr.)                         | 5.79                 | 1.6                | 6.34                  |
| Patients with at least one pos. skin test          | 112 (85%)            | 15 (79%)           | 97 (86%)              |
| Average no. of positive skin tests                 | 3.5                  | 2.5                | 3.7                   |
| Patients with at least one positive food challenge | 78 (59%)             | 12 (63%)           | 66 (58%)              |
| Atopic symptoms:                                   |                      |                    |                       |
| rhinitis (AR)                                      | 97 (73%)             | 9 (47%)            | 88 (78%)              |
| asthma (A)                                         | 70 (53%)             | 5 (26%)            | 65 (58%)              |
| both AR and A                                      | 63 (48%)             | 5 (26%)            | 58 (51%)              |

prove patient compliance and reduce the likelihood of implementing nutritionally deficient diets.

The best method for diagnosing food hypersensitivity in children with AD remains controversial. Historical information and elimination diets have rarely been helpful<sup>17,25</sup>. Similarly, laboratory data is of limited value. Although most children with atopic dermatitis have elevated serum IgE concentrations, a child with a normal serum IgE concentration is no less likely to have food hypersensitivity than his counterpart with an elevated serum IgE value. As shown in Table IV, children with normal serum IgE concentrations tend to be slightly younger, have fewer positive skin tests and less frequent concomitant allergic rhinitis and/or asthma than children with elevated serum IgE levels. There was no difference in the percentage experiencing positive food challenges. A review of several historical and laboratory parameters in children with AD (Table V) revealed that food sensitive children tended to be slightly younger and have more positive prick skin tests to foods than children without food hypersensitivity.

In a previous study comparing results of prick skin tests, RAST's, and double-blind placebo-controlled

Table V

## Comparison of Patients With and Without Food Hypersensitivity

|                                 | Food Sensitive<br>(78) | Food Tolerant<br>(54) |
|---------------------------------|------------------------|-----------------------|
| Median age (yr.)                | 4.3                    | 7.6                   |
| Average no. positive skin tests | 4.8                    | 1.6                   |
| Median IgE (IU/ml)              | 3650                   | 3950                  |
| Pos. family history             | 75 (96%)               | 50 (93%)              |
| Atopic symptoms:                |                        |                       |
| asthma (A)                      | 40 (51%)               | 31 (62%)              |
| rhinitis (AR)                   | 57 (73%)               | 40 (74%)              |
| both AR and A                   | 37 (47%)               | 26 (48%)              |

food challenges, it was concluded that the prick skin test alone was an excellent means for excluding potential food allergens but was of little value in identifying clinically relevant allergens.<sup>26</sup> In addition, there appeared to be no advantage of the RAST alone or in combination with prick skin testing over prick skin test-

ing alone in the evaluation of food hypersensitivity in children with AD. Consequently, a positive skin test should be considered as a suggestive indicator of immediate hypersensitivity necessitating a more definitive study, such as the double-blind placebo-controlled food challenge. Overall, a negative prick skin test virtually excludes immediate food hypersensitivity, although a few patients with skin test wheals less than three mm have reacted to an oral food challenge (especially egg and milk).

Therapy of food hypersensitivity is straight-forward. Strict avoidance of the offending food allergen is the only proven therapy. As reviewed by Dr. Dorothy Sogn at a conference on food hypersensitivity,<sup>27</sup> over 25 studies evaluating the effects of oral cromolyn sodium have been published in the world's literature. General study design and disease definition were frequently inadequate and results of these studies were conflicting. A recently completed double-blind placebo-controlled cross-over trial of oral cromolyn sodium in ten patients with proven food hypersensitivity demonstrated no benefit from this preparation.<sup>25</sup> Other methods proposed such as rotational diets, immunotherapy, sublingual neutralization, and subcutaneous neutralization have never proven to be of any benefit in controlled trials.

In the past year, 40 children with documented food hypersensitivity have been rechallenged to 47 antigens. Twenty-three children retained sensitivity to all the food antigens previously eliciting symptoms. Three retained sensitivity to one food while losing it to another, and 14 children lost their sensitivity to all antigens previously eliciting positive clinical responses. As seen in Table VI, loss of food sensitivity was antigen dependent. Patients allergic to peanut, wheat, and egg were less likely to lose their sensitivity than children allergic to other food antigens. Overall, the 40 children appeared to develop tolerance one year after initiating an appropriate elimination diet to 45% of the food antigens previously provoking allergic responses.

Table VII depicts the clinical courses of the first 27 children who had been enrolled in the study for approximately three years. Group one consisted of 13 children in whom a food was identified as causing clinical symptoms and had been eliminated from the diet; Group two consisted of 12 children in whom no offending food was identified and/or eliminated and two children who were found allergic to a food but failed to comply with the diet. A scoring system based on the patient's skin symptoms, medication requirements, physician visits, and days absent from school was devised. Each patient was assigned a score from zero (no change in the course of the patient's disease after entering the study) to four plus (patient's skin essentially clear with little or no therapy). In addition, the initial

**Table VI**

**Food Challenges Repeated After 1-2 Years  
of Restricted Diet**

| Antigen | Total | Positive | Negative |
|---------|-------|----------|----------|
| egg     | 25    | 17 (68%) | 8 (32%)  |
| milk    | 7     | 3 (43%)  | 4 (57%)  |
| wheat   | 4     | 3 (75%)  | 1 (25%)  |
| soy     | 3     | 1 (33%)  | 2 (67%)  |
| peanut  | 1*    | 1 (100%) | 0 (0%)   |
| others  | 7     | 1 (20%)  | 6 (80%)  |
| total   | 47    | 26 (55%) | 21 (45%) |

\* 4 accidental ingestions all resulted in clinical symptoms.

serum IgE concentration at the time the patient entered the study and the percentage change over the course of the study are indicated. Total serum IgE concentrations were evaluated because they have been reported to correlate roughly with disease activity in AD. As may be seen from Table VII, Group one fared much better clinically than Group two. In addition, serum IgE concentrations decreased significantly in Group one over two to three years (median pre-study 11,000 IU/ml, post study 4,700 IU/ml;  $p < .05$ ) whereas they increased significantly in Group two over the same time period (median pre-study 950 IU/ml, post-study 7,900 IU/ml;  $p < .05$ ). Both patients with food hypersensitivity who failed to comply with their restricted diets showed no significant improvement in their clinical courses and both experienced significant rises in their serum IgE concentration. These data suggest that the elimination of food provoking clinically documented hypersensitivity responses will favorably affect the course of atopic dermatitis.

A large number of conflicting studies have appeared in the literature evaluating the beneficial effect of breastfeeding on the prevention of atopic dermatitis and food hypersensitivity disorders. Many of these studies suffer from being retrospective and/or failing to carefully monitor maternal diet and supplemental feeding. A particularly well-done study was reported by Saarinen and her colleagues from Finland.<sup>31</sup> These investigators prospectively studied 135 infants of atopic parents presenting at a well baby center. The study group (Group one) consisted of 70 babies who were exclusively breastfed for the first six months of life. The control group (Group two) consisted of 65 infants who had "hypoallergenic" solid foods introduced at three months of age. From six to 12 months of age, both groups were allowed to have similar diets. When the groups were

Table VII

The First 27 Children Enrolled in AD/Food Hypersensitivity Study. Changes in Their Clinical Course and Serum IgE Concentration After 3 Years are Compared (See Text).

| Group I<br>Food Hypersensitive Patients on Restricted Diet |                 |                                      | Group II<br>Food Nonsensitive Patients on Unrestricted Diet |                 |                                      |
|------------------------------------------------------------|-----------------|--------------------------------------|-------------------------------------------------------------|-----------------|--------------------------------------|
| Patient                                                    | Clinical Change | Percentage Change in Total Serum IgE | Patient                                                     | Clinical Change | Percentage Change in Total Serum IgE |
| 1                                                          | ++++            | -88%                                 | 1                                                           | 0               | +123%                                |
| 2                                                          | ++++            | -90%                                 | 2                                                           | +++             | +58%                                 |
| 3                                                          | +++             | +48%                                 | 3                                                           | +               | +398%                                |
| 4                                                          | ++              | -33%                                 | 4*                                                          | ±               | +100%                                |
| 5                                                          | +++             | -58%                                 | 5*                                                          | ±               | +189%                                |
| 6                                                          | ++++            | 0%                                   | 6                                                           | ++              | +94%                                 |
| 7                                                          | +++             | +100%                                | 7                                                           | ++              | +436%                                |
| 8                                                          | ++++            | -15%                                 | 8                                                           | ±               | +363%                                |
| 9                                                          | +++             | -24%                                 | 9                                                           | ±               | +428%                                |
| 10                                                         | ++++            | -12%                                 | 10                                                          | +++             | -53%                                 |
| 11                                                         | +++             | -50%                                 | 11                                                          | ++              | +38%                                 |
| 12                                                         | ++              | -61%                                 | 12                                                          | ++              | -8%                                  |
| 13                                                         | ++++            | +45%                                 | 13                                                          | ++              | -47%                                 |
|                                                            |                 |                                      | 14                                                          | +++             | -68%                                 |

0—no change

+—slight improvement

++—moderate improvement

+++—marked improvement

++++—skin essentially clear

\* Food sensitive, non-compliant

examined at one year of age, Group one was found to have significantly less eczema than Group two (14% versus 35%) and a significantly lower prevalence of food allergy (7% versus 37%). On the basis of these results, the authors recommended exclusive breastfeeding for the first six months of life and the late introduction of solid foods as a prophylactic measure for food allergy and atopic eczema in infants who are at risk for atopy. Interestingly, the influence of early or late introduction of solid foods seem to be nonspecific in that the hypoallergenic foods given initially (such as potatoes and carrots), were not the ones later responsible for food hypersensitivity responses. Commonly implicated foods in food hypersensitivity reactions (eggs, milk, peanut, fish) were most often responsible for symptoms. Since food antigens may be transmitted in maternal breast milk, careful monitoring of mothers' diets in breastfeeding infants at risk for atopic disorders is recommended. For example, moderate consumption of major allergens such as peanut, milk, and eggs would be rec-

ommended for mothers of infants predisposed to atopic disease.

In summary, 132 patients with severe atopic dermatitis have been evaluated for food hypersensitivity using the double-blind placebo-controlled oral food challenge. Fifty-nine percent of these children experienced positive food challenges involving reactions of the skin, gastrointestinal, and respiratory tracts. Egg, peanut, and milk accounted for 74% of the hypersensitivity reactions induced. History and laboratory data were generally of marginal value in predicting which patients were likely to have food allergy. When patients were placed on appropriate diets based on oral food challenge results, approximately 45% of the 47 cases re-evaluated lost their hypersensitivity after one to two years, and most patients showed significant improvement in their clinical course compared to 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 following definite diagnosis,

exclusionary diets can lead to significant improvement in their skin symptoms.

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