

ECZEMA AND FOOD HYPERSENSITIVITY

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Prior to Columbus' voyage to the New World, an Italian physician, Paolo Bagellardo, wrote the first known scientific discussion of eczema in a pediatric textbook, *Libellus de Aegretudinibus Infantium*. The chapter on skin outlined recommendations for lubricating the skin and preventing scratching in children with this skin disorder. In the early 1600s, Helmont noted the association between a pruritic skin rash and asthma, and about 250 years later von Hebra described the flexural distribution of a chronic itchy skin disease.³⁴ However, it was the French physician, Besnier, who provided the first comprehensive description of atopic dermatitis in the late 1800s.⁶ He emphasized the hereditary nature of the disorder, its chronic course, and its association with hay fever and asthma. Wise and Sulzberger⁹² coined the term *atopic dermatitis*, further emphasizing the relationship between atopic eczema, asthma, and hayfever. The incidence of atopic dermatitis has been increasing over the past 40 years and now is estimated to affect between 12% and 15% of the pediatric population.³⁵

Atopic dermatitis [AD] is one form of eczema, which generally begins in early infancy and is characterized by extreme pruritus, chronically relapsing course, and distinctive distribution. AD is typically the first manifestation of a child prone to develop atopic disease, with 50% of all AD developing in the first year of life and 80% by 5 years of age. Approximately 80% of children with AD develop asthma or allergic rhinitis, with many losing their AD with the onset of respiratory allergy. The acute rash of AD is typically an erythematous, papulovesicular eruption, frequently with weeping and crusting that is more commonly

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seen in early life. It typically progresses to a subacute form marked by erythema and scaling papules, and especially in older patients, to a chronic form characterized by thickened, lichenified skin and fibrous papules.⁹ The distribution of the rash varies with age,³⁸ involving the cheeks and extensor surfaces of the arms and legs in infancy, the flexor surfaces in the young child, and flexor surfaces, hands, and feet in the teenage patient and young adult. AD is identified by a constellation of symptoms. The diagnostic criteria proposed by Hanifin and Rajka³⁶ are an accepted standard for diagnosing AD, and the SCORAD Index,²⁴ adapted by the European Task Force on Atopic Dermatitis provides a standardized method for gauging severity.

The pathogenic role of allergy in AD has been debated since Besnier's original description; however, recent studies delineating the immunopathogenic role of IgE-bearing antigen-presenting cells [APCs; e.g., Langerhans' cells and other dendritic cells] in establishing the Th2 lymphocytic response and of the IgE-mediated late-phase response in provoking cutaneous inflammation are compelling. Acute skin lesions of AD are described as spongiotic, with epidermal hyperplasia and ballooning of the keratinocytes secondary to intracellular edema. Mast cell and basophil numbers are normal, and eosinophils are rare.⁸³ In chronic skin lesions, the epidermis has moderate to marked hyperplasia, with elongation of the rete ridges and prominent hyperkeratosis. Spongiosis is variable and the number of mast cells and Langerhans' cells are significantly increased. Eosinophils are sparse. Demyelination and fibrosis of cutaneous nerves are observed at all levels of the dermis, and capillary numbers are often increased.

IMMUNOPATHOLOGY OF ATOPIC DERMATITIS

Approximately 85% of patients with AD have elevated serum IgE levels, and about 85% of these have evidence of specific IgE antibodies to food and inhalant allergens.⁶⁸ The role of allergen-specific IgE antibodies in the pathogenesis of AD involves a number of cell types. Receptors for IgE antibodies have been identified on B cells, T cells, monocytes, macrophages, dendritic cells, eosinophils, and platelets.^{16, 49, 79} Langerhans' cells, "professional" APCs in the skin, are increased in atopic dermatitis lesions, possess allergen-specific IgE antibodies on their surface,¹² and promote Th2 responses to allergens.^{59, 60} The pattern of cytokine expression found in lymphocytes infiltrating skin lesions in AD has been studied using *in situ* hybridization and has been found to reflect an allergic milieu. Infiltrating T lymphocytes in acute AD lesions express predominantly the Th2 cytokines, interleukin-(IL)-4, IL-5, and IL-13 whereas T cells in chronic lesions express predominantly IL-5 and IL-13.^{31, 32} This expression is in contrast to classic type IV cellular responses, such as PPD or rhus dermatitis (poison ivy) where cells express primarily mRNA for interferon (IFN) and IL-2, but not IL-4 and IL-5.⁸⁴

The Th2 profile of cytokines promotes chronic allergic inflammation

by upregulating adhesion molecules on vascular endothelial cells (e.g., VCAM-1, E-selectin, and ICAM-1),⁸⁸ upregulating high affinity receptors for IgE antibodies on Langerhans' cells and other APCs recruiting eosinophils and other inflammatory cells to the site, and promoting local synthesis of IgE antibodies. Recent studies demonstrated that adhesion molecules are not expressed in the skin of nonatopic individuals, are expressed in normal appearing skin of AD patients, and are markedly upregulated in lesional skin or following epicutaneous application of allergen in sensitized, AD patients.²¹ Other studies showed an absence of expression of MHC class II antigens on keratinocytes in AD, a sign of IFN- γ stimulation as seen in typical delayed-type cell-mediated reactions.³ The high-affinity receptors for IgE on Langerhans' cells, through bound IgE antibodies, play a special role as "nontraditional" receptors on these APCs.⁷ These IgE-bearing Langerhans' cells are 100- to 1000-fold more efficient at presenting allergen to T cells (primarily Th2 cells) and activating T-cell proliferation.^{59, 60}

Although evidence at the cellular and molecular level strongly suggests an allergic component to AD, identification of relevant allergens has been problematic. A number of lines of evidence support the role of food allergy in these immunopathogenic responses (Table 1). Patients with AD generally have elevated levels of total⁴⁶ and food-protein specific IgE antibodies.³⁹ Blinded oral food challenges in food-allergic AD patients lead to sharp increases in plasma histamine concentrations,⁷³ activation of plasma eosinophils,⁸¹ and elaboration of eosinophil products.⁵⁶ In addition, AD patients with IgE-mediated milk-induced skin symptoms possess allergen-specific, cutaneous lymphocyte antigen (CLA)-bearing T cells in their circulation, which are not present in patients with milk-induced gastrointestinal disease¹ or asthma (Fig. 1). Food-antigen-specific⁸⁷ (and aeroallergen-specific⁸⁶) T cells have been cloned from active skin lesions and normal skin of patients with AD. Food-antigen-specific T cells have been routinely identified from periph-

Table 1. FOOD ALLERGY AND ATOPIC DERMATITIS IN CHILDREN

Clinical Associations

Double-blind, placebo-controlled oral challenges result in symptoms
Appropriate food elimination ameliorates symptoms
"Prevention" diets reduce prevalence or severity

Pathophysiologic Associations

Elevated food-specific IgE antibodies
Positive food challenges associated with acute elevation in plasma histamine
Positive food challenges associated with activation of eosinophils
CLA +, milk-reactive T cells demonstrated in milk-allergic patients
Food-reactive T cells cloned from active skin lesions
Langerhans' cells bear high-affinity IgE receptors
Increased spontaneous basophil histamine release in patients ingesting causal foods
Increased histamine releasing factors in children consuming allergenic food
Eosinophil products found in lesions

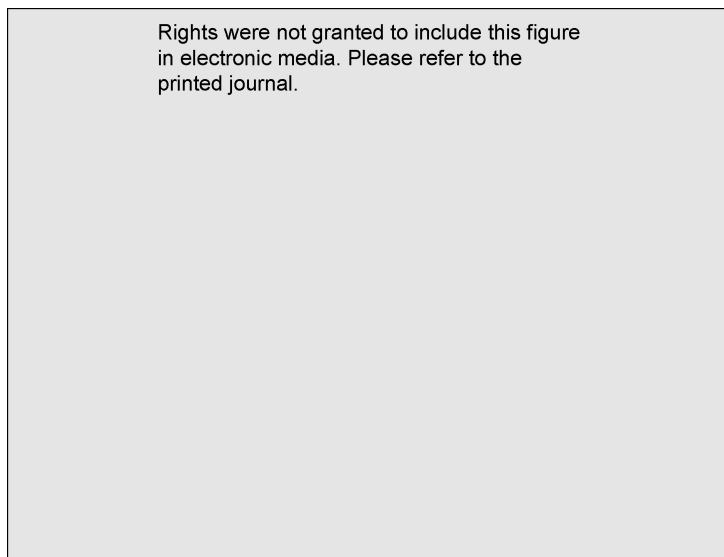


Figure 1. Milk-allergic patients with AD have significantly increased lymphocytes bearing the CLA in vitro compared with patients with gastrointestinal milk allergy and normal controls. There is no similar increase in CLA + cells for an irrelevant antigen. *Candida albicans*. Eczema (open bars). Allergic eosinophilic gastroenteritis (AEG) (shaded bars). Normal (solid bars). * = $P < 0.05$. (From Abernathy-Carver K, Sampson HA, Picker L, et al: Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 95:913, 1995; with permission.)

eral blood in subjects with relevant food-protein-induced AD.^{1, 64, 90} Some workers have suggested that specific food-induced, late-onset (increased rash developing at least 2 hours after oral challenge) eczematous lesions are correlated with in vitro lymphocyte proliferative responses to the implicated food.⁵⁴ Other workers have demonstrated, however, an increased lymphocyte proliferative response to relevant food proteins in patients with immediate reactions and nonatopic controls,⁶⁴ and the utility of this test as a diagnostic modality is marginal because there is considerable overlap in individual proliferative responses.⁴⁰

Mechanisms involving IgE molecules, other than direct IgE allergen activation of cutaneous mast cells, also may be involved in the inflammation of eczematous skin. Children with AD and food hypersensitivity who were chronically ingesting foods to which they were allergic were found to have high "spontaneous" basophil histamine release (SBHR) from peripheral blood basophils in vitro compared with patients with AD without food allergy or to normal controls (mean: $35.1 \pm 3.9\%$ versus $1.8 \pm 0.2\%$ versus $2.3 \pm 0.2\%$, $P < 0.001$).⁷² When the food-allergic children were placed on an appropriate elimination diet for at least 1 year, they experienced good clearing of their eczema and a significant fall in SBHR ($38.0 \pm 9.6\%$ to $4.3 \pm 2.1\%$, $P < 0.01$). Peripheral

blood mononuclear cells from food-allergic patients with high SBHR were found to elaborate cytokines termed *histamine releasing factors* (HRFs) that could activate basophils from food-sensitive but not food-insensitive children. It has been established that several isoforms of IgE are secreted,⁵⁸ and some investigators have postulated that HRFs interact specifically with some isoforms of IgE. Passive sensitization experiments using basophils from nonatopic control donors and IgE from food-allergic patients revealed that these basophils could be rendered sensitive to HRF.⁷² Passive transfer of IgE from nonallergic individuals to these same basophils did not render the basophils sensitive to HRF.

Although eosinophils do not appear prominent in histologic sections of AD lesions, they have been shown to play a major role in the pathogenesis of this disorder. Immunohistochemical staining of AD patient skin has revealed the presence of eosinophil major basic protein (MBP) and eosinophil-derived neurotoxin (EDN) in active eczematous lesions. MBP is a cytolytic protein secreted almost exclusively by eosinophils that can damage skin epithelial cells²⁸ and promote mast cell degranulation.⁶³ Biopsies of eczematous skin lesions from patients with AD were found to have extensive extracellular MBP deposition in a fibrillar pattern in the superficial dermis⁵⁶ and not in uninvolved skin sites in these same patients. Similar studies in patients with contact dermatitis (rhus dermatitis) revealed no dermal deposition of MBP. These studies provide further evidence of an IgE/Th2-induced cutaneous reaction, with eosinophil degranulation and dermal deposition of MBP. Infiltrating lymphocytes are capable of releasing a variety of interleukins that may promote mast cell proliferation (IL-3), cell surface expression of Fc receptors and IgE synthesis (IL-4), and eosinophil proliferation (IL-5).

EARLY STUDIES OF FOOD HYPERSENSITIVITY AND ATOPIC DERMATITIS

By the beginning of this century, physicians were claiming that reactions to food proteins could provoke eczematous skin rashes. Schloss was among the first to provide evidence that food allergy could play a pathogenic role in atopic dermatitis.⁷⁷ He reported several cases of patients who experienced improvement in their eczematous skin lesions after avoiding specific foods. Shortly thereafter, Talbot⁸² and then Blackfan⁸ each described a series of patients who were found to have positive skin tests to certain foods and who experienced clearing of their skin when suspected foods were removed from their diets. Since that time, a number of reports have appeared in the literature implicating food allergy in the pathogenesis of AD.^{27, 65} After performing unblinded food challenges in eczema patients, however, other investigators discounted these findings,⁴¹ and a recent review suggested that allergy had no role in AD.³⁰

Many physicians are unaware of the rapidity with which food

allergens penetrate the mucosal defenses and reach the skin. In a classic series of experiments, Walzer et al^{11, 91} unequivocally demonstrated that ingested food antigens readily penetrate the gastrointestinal barrier and are transported in the circulation to mast cells in the skin. To demonstrate this phenomenon, 65 normal adults were passively sensitized by intracutaneous injection of serum from a patient with severe fish allergy and serum from a normal donor.¹¹ The following day these volunteers were fed fish, and within 90 minutes, 61 out of 65 developed a wheal and flare reaction at the sensitized site but not at the control site. Similar results were found in a series of experiments conducted in 66 normal children with serum from an egg-allergic subject.⁹¹ Walzer also studied the absorption of food antigens from various locations along the gastrointestinal tract and other sites, such as the nose, eye, and urinary bladder.⁸⁹ He concluded that "the absorption of unaltered protein into the circulation is a normal, physiologic phenomenon occurring in nonatopic as well as atopic individuals, at all ages, and with many allergens."⁸⁹ In addition, he demonstrated that the intravenous injection of the equivalent of 1/44,000 of one peanut kernel was sufficient to induce wheal and flare at a skin site passively sensitized with serum from a peanut-allergic patient.

In 1936, Engman et al²³ described a study on a child with AD in whom the ingestion of a wheat cracker was reported to produce intense itching in the child. To evaluate this and demonstrate the role of trauma (scratching and rubbing) in the development of eczema, they admitted the patient to the hospital when his skin was clear and bandaged his left arm and leg in a thick crinoline bandage. The child was fed two wheat crackers, and within 2 hours he developed pruritus and scratching. The following morning, the child had typical eczematous lesions on the open skin, but under the bandages the skin appeared clear. Engman reportedly repeated this experiment in several other children. Taken together, these studies conducted over 60 years ago clearly showed that ingested food allergens were readily accessible to cutaneous mast cells and the "skin-associated lymphoid tissue," and that in the sensitized host, they could produce intense pruritus, scratching, and rubbing, which led to typical eczematous lesions. In the late 1970s, Hammar reported a study in which eczematous skin lesions were induced in 15 of 81 hospitalized children less than 5 years of age after 2 to 3 days of ingesting 100 mL of milk daily.³³ Subsequently the significance of Hammar's findings were questioned because the milk challenges were not "blinded," and when milk challenges were repeated 18 months later, only 4 of the 15 children reacting had recurrence of skin symptoms.²⁰ Today, however, we know that at least 50% of these milk-allergic children would be expected to lose their sensitivity in this period of time.⁴²

CLINICAL STUDIES OF FOOD HYPERSENSITIVITY AND ATOPIC DERMATITIS

In the past two decades, a number of approaches have been taken to address the relevance of food allergy in AD. The weight of the

evidence supports a pathogenic role for food hypersensitivity in a subset of children and adolescents with AD. Appropriate studies in adult patients are inadequate to draw any conclusions, but most investigators agree that food hypersensitivity plays a very minor role, if any, in adult AD. To establish the causative association between food hypersensitivity and AD, clinical studies have been performed to address the three tenets of Koch's postulates: removal of the causative agent leads to resolution of the disorder; introduction of the causative agent provokes the disorder; and avoidance of the causative agent prevents the disorder. As with other chronic, atopic disorders (e.g., asthma), a variety of factors can trigger eczematous lesions [wheezing in the case of asthma] making such studies very difficult to control adequately and subject to skepticism.

The therapeutic effect of removing foods to which children with AD are allergic has been addressed in a number of studies. Atherton et al² reported that two thirds of children with AD between the ages of 2 and 8 years showed marked improvement during a double-blind cross-over trial of egg and milk exclusion. The trial was conducted over a 12-week period in the patients' homes. Unfortunately, 45% of the patients enrolled in this study dropped out or were excluded from analysis, environmental factors and other triggers of AD were not controlled for, and a significant order effect was found, all raising some question about the authors' conclusions. Utilizing a similar trial design, Neild et al⁶² were able to demonstrate improvement in some patients during the milk and egg exclusion phase, but overall no statistically significant difference was seen in 40 patients completing the cross-over trial. Juto et al⁵⁰ reported that 7 of 20 infants with eczema healed, and 12 of 20 improved on a highly restricted elimination diet. In addition, nonblinded milk challenges reportedly resulted in increased itching and rash in the 12 infants. Hill et al³⁷ treated eight children with severe AD with an amino acid-derived formula for 2 weeks followed by the addition of two vegetables and two fruits for 3 months. All patients experienced improvement in their eczema while on the diet and relapsed within weeks of discontinuing the diet. While supporting a role for food reactivity in the exacerbation of AD, these studies failed to control for other trigger factors, placebo effect, or observer bias. A double-blind study in 23 adults retained in the hospital while on an antigen-free diet failed to show any significant difference between the antigen-free and placebo groups.⁶¹ However, the study groups were too small to conclude "no significant difference" (type II statistical error), and some adults with markedly elevated serum IgE concentrations appeared to respond to the antigen-free diet.

In a prospective follow-up study of 34 patients with AD, 17 children with food allergy, who were diagnosed with food allergy by double-blind placebo-controlled oral food challenges and placed on an appropriate allergen elimination diet, experienced a marked improvement in their eczematous rash at 1 to 2 years and 3 to 4 years follow-up. These children showed significantly greater improvement than 12 similar AD patients who did not have food allergy and 5 children with food allergy

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Figure 2. Patients with food-allergic AD placed on an appropriate food allergen elimination diet (*open bars*) experienced significant improvement in their eczema over 3–4 y of follow-up compared with patients with AD without food allergy (*shaded bars*) and patients with food-allergic AD who did not maintain their food allergen elimination diet (*solid bars*). $n = 17, 12, \text{ and } 5$, respectively. (From Sampson HA: Immunologically mediated reactions to foods: IgE in eczema. *Annals of Allergy* 59:71, 1987; with permission.)

and AD who did not adhere to their diet (Fig. 2).⁶⁹ Lever et al³⁷ carried out a prospective, blinded, randomized controlled trial of egg elimination in young children with atopic dermatitis. Children presenting to a dermatology clinic with AD and a positive RAST to egg (majority under age 2 years) were enrolled. At the close of the study, egg allergy was confirmed by oral challenge and 55 egg-allergic children were ultimately identified. A physician blinded to the dietary instructions evaluated the children. There was a significant decrease in both area affected (19.6% to 10.9%, $P = 0.02$) and symptom scores (33.9 to 24.0, $P = 0.04$) in the children avoiding egg compared with the controls' (percent involved 21.9% to 18.9%; $P = \text{not significant [ns]}$) symptom score (36.7 to 33.5; $P = \text{not significant [ns]}$). Further studies utilizing blinded-diet protocols are in progress.

Several investigators have attempted to provoke eczematous skin changes by challenging patients with AD and suspected food allergy. In their studies of children primarily with suspected food hypersensitivity and respiratory allergy, May and Bock¹⁰ reported that four of seven children with a history of eczematous reactions to foods developed skin rashes within 2 hours of administration of a double-blind, placebo-controlled, oral food challenge (DBPCFC) Using a similar challenge protocol, the authors have systematically studied over 500 patients referred for evaluation of severe atopic dermatitis. Burks et al¹³ also employed the

DBPCFC to study 165 children with mild to severe AD, who presented to a university allergy and dermatology clinic. As seen in other controlled oral challenge studies, positive DBPCFCs resulted in cutaneous, respiratory, and gastrointestinal symptoms. Sixty percent of the patients with AD had a positive prick skin test to at least one of seven foods tested (milk, egg, peanut, soy, wheat, codfish, cashew). A total of 266 DBPCFCs were carried out, and 64 patients (38.7% percent of the total group with AD) were found to be food-allergic. There was no correlation between the likelihood of having a positive food challenge and the severity of the AD.

In a 15-year period, the authors and their colleagues evaluated 470 patients with AD for evidence of food hypersensitivity utilizing DBPCFCs.^{48, 66, 70, 74} Subjects ranged in age from 3 months to 24 years with a median age of 4.1 years. The median clinical score for the group was 15 (range 0 to 30) at the time of their first admission to the Clinical Research Unit, based upon a standard clinical scoring system.⁷⁰ Family history was positive for atopic disease in 91% of subjects. One hundred fifty-seven patients (39%) had allergic rhinitis and asthma at the time of their initial evaluation, whereas only 94 patients (20%) had neither allergic rhinitis nor asthma. Serum IgE concentrations were elevated in 376 patients (80%), with a median IgE level of 3410 IU/mL and a range of 1.5 to 45,000 IU/mL.

Any patient with chronic, severe eczema fulfilling the criteria of Hanifin and Rajka³⁶ for the diagnosis of AD was eligible for the study, regardless of whether clinical history or previous allergy tests suggested a diagnosis of food hypersensitivity. All patients were admitted to the Clinical Research Unit to provide a stable, low allergen environment. Foods administered during DBPCFCs were selected on the basis of skin test (and RAST) results or a strongly suggestive history of food hypersensitivity. Foods selected for the challenge protocol were excluded from the patient's diet for 7 to 10 days prior to admission. In addition, the following medications were withheld: oral corticosteroids for at least 1 month prior to admission, antihistamines for at least 7 to 10 days, and inhaled and oral beta adrenergic drugs for 8 hours prior to the challenge. Inhaled cromolyn sodium and oral theophylline were not discontinued.

The initial 220 patients were skin tested to a battery of 20 food extracts (Greer Laboratories, Lenoir, NC) on the day of admission to confirm previous results, standardize skin test data, and determine which foods would be used in the DBPCFC. While on the Clinical Research Unit, patients were treated with an aggressive topical regimen consisting of two to three soaking baths (or wet wraps) per day followed by the application of a lubricating cream to the entire body and topical corticosteroid (1% hydrocortisone cream for the face and 0.025% – 0.1% triamcinolone ointment for the trunk and extremities) to active eczematous areas. Anti-staphylococcal antibiotics were generally administered, and chloral hydrate was used for sedation. Utilizing this regimen, erythema and pruritus could generally be controlled in 3 to 4 days. Once a stable baseline was achieved, an intravenous line was placed prior to

initiating challenges in order to provide an open line in case of a major anaphylactic reaction and to provide access for atraumatic, serial blood sampling.

During a 1-week admission, three to four DBPCFCs were conducted.⁶⁷ The Clinical Research Unit Dietitian determined the order of all challenges using a randomization scheme on the Unit's computer. Only the dietitian was aware of the contents of individual challenges until the code was broken at the end of the study week. Two challenges were performed each day, one containing the test food antigen and one containing placebo. Over a 60 to 90 minute period, up to 10 g of dehydrated powdered food was administered in opaque capsules (14 to 18 "00" capsules depending upon the food antigen), in 100 to 150 mL of liquid [fruit juice, infant formula, Vivonex or Neocate), or in a pureed food (baby food, rice cereal, etc). Challenges in the past several years all have been camouflaged in juices or pureed foods. The initial challenge dose was generally 100 mg to 500 mg and was increased in a step-wise fashion at 15-minute intervals until the entire 10 g was consumed or a reaction occurred. Each challenge was evaluated and scored using a previously published symptom score sheet.⁷⁰ All negative DBPCFCs were confirmed by feeding the food openly to the patient prior to the time of discharge to ensure the accuracy of the blinded challenge and to assure the patient (and parent) that the food can be ingested safely. In the initial 1000 food challenges performed, there were five reactions during the open feeding following negative DBPCFCs [$<1\%$ false-negative results]. Three children, two age 4 years and one age 2 years, developed symptoms after drinking milk. One child developed cutaneous, nasal, and respiratory symptoms after consuming approximately 100 mL of milk, one child developed cutaneous symptoms and periorcular edema after ingesting about 80 mL, and the third child developed cutaneous, upper respiratory, and gastrointestinal symptoms after ingesting about 10 mL of milk. The fourth child, age 5 years, developed cutaneous, gastrointestinal, nasal, and respiratory symptoms after eating a standard portion of peas. The fifth child, age 3 years, developed scattered urticaria following the ingestion of one teaspoon of peanut butter.

In the initial evaluation of 470 children with AD, a total of 1776 DBPCFC have been conducted (Table 2). DBPCFCs were not conducted in 193 instances because clinical history indicated a convincing account

Table 2. RESULTS OF FOOD CHALLENGES IN 470 PATIENTS WITH AD

Total number of challenges	1776
Negative challenges	1062
Positive (by convincing history, usually peanut)	193
Positive challenges	714
Cutaneous symptoms	529 (74%)
Isolated cutaneous	195 (27%)
Gastrointestinal symptoms	358 (50%)
Respiratory symptoms	322 (45%)

of a major anaphylactic reaction (mostly to peanuts and nuts). History was considered convincing when a patient experienced severe respiratory symptoms (laryngeal edema or wheezing) or hypotension within minutes of ingesting an isolated food and required emergency care by a physician. In each case when the challenge was not performed, the patients had a markedly positive prick skin test to the food in question. No patient experienced a severe anaphylactic reaction during DBPCFC, although about one half the patients required oral diphenhydramine for severe pruritus, and several patients required subcutaneous epinephrine for respiratory symptoms. Of the 1776 DBPCFCs performed, 714 were positive and 1062 were interpreted as negative. Cutaneous reactions developed in 529 cases (74%) and consisted of a pruritic, erythematous, macular or morbilliform rash primarily in previous predilection sites. Symptoms confined exclusively to the skin occurred in only 30% of the reactions. Typical urticarial lesions were rarely seen and generally consisted of only a few lesions. Intense pruritus and scratching frequently resulted in superficial excoriations and occasionally bleeding. Gastrointestinal symptoms were seen in 358 of the reactions (50%) even though history rarely revealed previous gastrointestinal symptoms in the patients. The gastrointestinal symptoms seen consisted of nausea, abdominal pain, or both, plus vomiting, diarrhea, or both. Respiratory symptoms most frequently involved the upper respiratory tract and were seen in 322 of the positive DBPCFC (45%). Respiratory symptoms included nasal congestion, rhinorrhea, sneezing, tightness of the throat, hoarseness or wheezing.

Initial symptoms secondary to the blinded food challenges typically developed between 5 minutes and 2 hours of starting the challenge. Symptoms associated with the immediate response were generally abrupt in onset, marked, and lasted 1 to 2 hours. Several patients experienced a second episode of increased cutaneous pruritus and transient morbilliform rash 6 to 10 hours after the initial positive challenge. Symptoms associated with this late response were less prominent than the immediate symptoms and tended to last for several hours. Only one child developed an isolated delayed reaction. This reaction consisted of a pruritic, erythematous rash developing approximately 4 hours after the child ingested an egg challenge. In our studies, most patients (80%) reacted to only one to three foods, even though many reports have suggested that children with AD are sensitive to a large number of foods. Most children in this study had positive prick skin tests to several foods [mean: 3.5; range: 0–10], but only about one third of positive skin tests correlated with clinical reactions during food challenges: 169 children (36%) reacted to only one food, 122 (26%) reacted to two foods, 85 (18%) reacted to three foods, 47 children (10%) reacted to four foods, and 47 patients (10%) reacted to five or more different foods. Five foods [egg, peanut, milk, wheat, and soy] accounted for about 80% of the positive clinical responses (Table 3).

Allergic reactions to foods were very specific. Although patients frequently had positive skin tests [and RASTs] to several members of a

Table 3. FOODS RESPONSIBLE FOR 80% OF POSITIVE CHALLENGES IN 470 PATIENTS WITH ATOPIC DERMATITIS

Food	Positive Challenge	Positive History	Total	%
Egg	178	35	213	57
Milk	96	47	143	38
Peanut	28	82	110	29
Soy	55	4	59	16
Wheat	43	0	43	11

botanical family or animal species, indicating immunologic cross-reactivity, the frequency of patients experiencing symptomatic intra-botanical or intra-species cross-reactivity is variable (Table 4). Legume cross-reactivity was evaluated in 69 children with AD utilizing prick skin tests, in vitro measurements of specific IgE antibodies (immunodot blot) and Western blot analysis.^{4, 5} Extensive immunologic cross-reactivity was demonstrated in skin prick tests, RASTs, and immunoblots in most patients; however, only 2 patients were symptomatic to more than one legume when challenged orally. Both patients had a history of severe allergic reactions to peanut and experienced mild reactions to a soy challenge, and both outgrew their reactivity to soy within 2 years. Similar studies with cereal grains showed significant IgE antibody cross-reactivity between grains (wheat, barley, rye, oat) and grass pollens but clinical cross-reactivity among the grains in only about 20% of patients.⁴⁷ Although intra-species immunologic cross-reactivity is common, approximately 5% of egg-allergic children reacted to chicken, and about 10% of milk-allergic children reacted to beef. Consequently, the practice of avoiding all foods within a botanical family when one member is suspected of provoking allergic symptoms appears to be unwarranted. Interestingly, 90% of children allergic to cow's milk react to goat's milk,¹⁵ and approximately 40% of children reacting to beef also react to lamb.

As noted previously, patients experiencing positive DBPCFCs were found to develop a pruritic, morbilliform rash instead of the classical urticarial lesion. To demonstrate that the ingestion of food antigens led to IgE-mediated reactions, markers of mast cell activation were sought.

Table 4. CLINICAL CROSS-REACTIVITY

Primary Allergy	Associated Allergy	Percentage
Peanut	Other legumes	3%–5%
Cereal grains	Other grains	~20%
Egg	Chicken	~5%
Cow's milk	Goat's milk	90%
Cow's milk	Beef	10%
Beef	Lamb	40%

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Figure 3. Patients' mean plasma histamine levels before and after DBPCFCs. Thirty-five (open bars) challenges were considered clinically positive, and 101 were considered negative. Of the negative DBPCFCs, 41 (shaded bars) were negative to food allergens, and 60 (solid bars) were negative to placebo. * = $P < 0.05$. (Figure adapted from data published in Sampson HA, Jolie PL: Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 311:372, 1984; with permission.)

Thirty-three patients undergoing DBPCFCs were monitored for changes in circulating plasma histamine.⁷³ Histamine concentrations were evaluated prior to initiating the challenge and following the ingestion of the test antigen. Patients experiencing clinical symptoms following the blinded challenge developed a rise in their plasma histamine (mean: 296 ± 80 pg/mL to 1055 ± 356 pg/mL; $P < 0.001$). As shown in Figure 3, subjects ingesting placebo or a food that did not provoke clinical symptoms had no demonstrable rise in their plasma histamine concentration. Basophils were evaluated to determine if they were activated during the food challenge and were responsible for the rise in plasma histamine. Samples were obtained prior to the challenge, immediately following and 30 minutes following the development of the first objective symptoms and evaluated for basophil number and total histamine content of the leukocyte preparation.⁷² There was no difference in basophil number or total histamine content of the basophils at any time point. This indicated that circulating basophils contributed little to the challenge-induced rise in plasma histamine.

Studies utilizing the DBPCFC clearly demonstrate an immediate, IgE-mediated food hypersensitivity reaction in a subset of children with AD. Such distinct reactions are rarely seen under normal circumstances because foods are generally not ingested following prolonged periods of food allergen avoidance and then taken in isolation on an empty stomach. Chronic ingestion of a food allergen results in a downregulation of the immediate response.⁸⁰ The second onset of pruritus and rash in some children following DBPCFC is suggestive of a late-phase component of

an IgE-mediated response. Two food-allergic patients who had experienced clearing of their eczema after maintaining an appropriate food allergen avoidance diet were rechallenged to establish that the ingestion of an allergen during a DBPCFC could induce a late-phase response.⁷¹ Both patients developed a pruritic morbilliform skin rash within 30 to 60 minutes that cleared within 60 minutes. Skin biopsies obtained from the involved sites 4 and 14 hours later revealed an infiltration of eosinophils and deposition of MBP. The dermal infiltrates contained more eosinophils and less prominent MBP deposition than observed in chronic lesions. In three food-allergic patients who had experienced clearing of their eczema after maintaining an appropriate food allergen avoidance diet, the density profiles of circulating eosinophils changed from normodense (nonactivated) to hypodense (activated) following a positive food challenge (unpublished data). Suomalainen et al⁸¹ reported a rise in plasma eosinophil cationic protein (ECP) levels in milk-allergic children experiencing skin symptoms following a milk challenge but not in children experiencing only gastrointestinal symptoms. These studies indicated that food allergen ingestion in sensitized patients leads to activation of circulating eosinophils, which may infiltrate the skin of patients with AD.

Children with AD and newly diagnosed food hypersensitivity were found to have high spontaneous basophil histamine release (SBHR) from peripheral blood basophils, *in vitro*, compared with patients with AD and no food allergy and normal controls (mean: 35.1% + 3.9% versus 1.8% + 0.2% versus 2.3% + 0.2%, $P < 0.001$).⁷² When these food-allergic patients were placed on appropriate elimination diets for at least 1 year, good clearing of their eczema was seen and a significant fall in SBHR was noted. Unstimulated peripheral blood mononuclear cells from food-allergic subjects with high SBHR produced a histamine-releasing factor *in vitro*, which could activate basophils from other food-sensitive individuals but not food nonsensitive subjects. When food-allergic patients were maintained on an appropriate food allergen-free diet for 9 to 12 months, mononuclear cells no longer generated HRF. It was postulated that ingestion of food allergens leads to histamine-releasing factor production *in vivo*, which can activate or lower the threshold of activation, of mast cells, and other IgE-bearing cells. The loss of spontaneously generated histamine-releasing factor was found to correlate directly with the loss of cutaneous hyperreactivity (increased pruritus caused by a variety of minor stimuli such as heat, stress, or irritants) and inversely with the improvement in the patients' skin.

A number of investigators have evaluated the effect of excluding dietary allergens on the development of AD in young infants. In the 1930s Grulee and Sanford were first to report a decrease in the incidence of AD in breastfed infants.²⁹ Since that time there have been numerous conflicting reports about the relative benefit of breast feeding infants to prevent or delay the onset of atopic disease.^{17, 55, 85} The potential benefit of breastfeeding is complicated by transmission of food antigens in maternal breast milk.^{43, 44} We evaluated six exclusively breastfed infants

(age 2.5 to 6 months) who developed classic infantile AD. Each infant had a positive prick skin test to egg and experienced complete clearing of eczematous lesions when their mothers totally eliminated egg-containing foods from their diet. Four of the six infants were challenged on a clinical research unit by first feeding their mothers eggs and then having their mothers breastfeed. All infants developed an eczematous rash 4 to 36 hours after their mothers ingested eggs. This evidence and findings from other studies support the practice of placing selected mothers on allergen-avoidance diets while breastfeeding. Several investigators have evaluated the effect of eliminating certain foods from the maternal diet during lactation.^{18, 42, 93} In two series, infants from families who were atopic whose mothers eliminated eggs, cow's milk, and fish from their diets during lactation (prophylaxis group) had significantly less AD and food allergy at 18 months compared with infants whose mothers' diets were unrestricted. At 4 years, the prophylaxis group had less AD, but there was no difference in food allergy or respiratory allergy (Fig. 4).⁷⁸

In a prospective, randomized allergy prevention trial, Zeiger et al compared the benefits of maternal and infant food allergen avoidance on the prevention of allergic disease in infants at high risk for allergic disease.⁹⁴⁻⁹⁶ Breastfeeding was encouraged in both prophylaxis and control groups. In the prophylaxis group, mothers eliminated egg, milk, and peanut from their diets, a casein hydrolysate formula was utilized for supplementation or weaning, and solid foods were delayed until 6 months. In the control group, mothers' diets were unrestricted, infants received cow milk formula for supplementation or weaning, and the

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Figure 4. Infants from families who were atopic whose mothers eliminated eggs, cow's milk, and fish during lactation (*open bars*) compared with similar infants whose mothers had no dietary restrictions during lactation (*shaded bars*). AR = allergic rhinitis; FH = food allergy. (From Sigurs N, Hattevig G, Kjellman B: Maternal avoidance of eggs, cow's milk, and fish during lactation: Effect on allergic manifestation, skin prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics* 89:735, 1992; with permission.)

American Academy of Pediatrics recommendations for infant feeding were followed (peanuts, nuts, and fish are not recommended in the first 2 years). The prevalence of food allergy, cow milk sensitization, and AD were reduced significantly in the prophylaxis group during the first 2 years compared with the control group, but the period prevalence of AD was no longer significantly different beyond 3 years; however, the cumulative prevalence of food allergy and AD remained lower in the prophylaxis group at ages 4 and 7 years compared with that of the control group. Zeiger concluded that maternal and infant food allergen avoidance reduces food allergy and AD in high-risk infants during the first few years of life but failed to modify other allergic disease beyond 2 years of age.⁹⁴

In a prospective nonrandomized study of 1265 unselected neonates, the effect of solid food introduction was evaluated over a 10-year period.^{25, 26} A significant linear relationship was found between the number of solid foods introduced into the diet by 4 months of age and subsequent AD. There was a threefold increase in recurrent eczema at 10 years of age in infants receiving four or more solid foods compared with infants receiving no solid foods prior to 4 months of age. No relationship was noted between asthma and the introduction of solid foods. A prospective, nonrandomized study comparing breast-fed infants receiving their first solid foods at 3 months or 6 months of age revealed reduced AD and food allergy at 1 year of age in the group avoiding solids for the 6-month period⁵²; however, further follow-up at 5 years revealed no significant difference.⁵¹ Because neither series randomized patients, these studies must be considered suggestive until an appropriate randomized trial confirms the benefit of delaying solid food introduction.

Because most studies to date are plagued with design issues, and results are inconclusive, it is difficult to make firm recommendations regarding prevention strategies for food allergy and AD. In families at high risk for atopic disorders, however, it would seem prudent to avoid exposing young infants to food allergens that provoke lifelong sensitization (e.g., peanuts, nuts, fish, or shellfish) for the first 2 to 3 years of life. In highly motivated "high-risk" families, avoidance of cow's milk for the first year and egg for the first 2 years may prevent some AD and food allergy. Mothers of high-risk infants might also be prudent to avoid peanuts, nuts, fish, and shellfish while breastfeeding and perhaps even during the third trimester of pregnancy because these foods do not generally comprise a major part of the diet. Whether it is beneficial for all lactating mothers in high-risk families to avoid milk and eggs remains an open question.

DIAGNOSIS OF FOOD HYPERSENSITIVITY IN PATIENTS WITH ATOPIC DERMATITIS

The double-blind placebo controlled oral food challenge remains the gold standard for diagnosing food hypersensitivity in chronic atopic

disorders, such as AD. In the typical office practice, however, a careful history and evidence of food antigen-specific IgE antibodies (prick skin tests, RASTs) may indicate foods that can be eliminated for a 2- to 3-week dietary trial. Symptoms may be recorded in a diary during the trial period. If unequivocal improvement is documented, foods believed to be least likely to be responsible for reactions (e.g., foods other than egg, peanut, milk, soy, and wheat) are added back to the diet; however, any food suspected of causing a severe anaphylactic reaction should *never* be administered at home because of the potential for inducing anaphylactic shock.¹⁹ If a clear deterioration in the patient's AD occurs when a food is added back, it should be removed from the diet. If cause and effect can be established, the patient should remain on the avoidance diet unless it requires elimination of more than one major food (egg, milk, soy, or wheat) or two or more minor foods (all others). If severe symptoms persist on the elimination diet and food allergy is still in question, a brief trial (1 to 2 weeks) of an extensively restricted diet may be implemented. If the dietary elimination results are equivocal, or several foods are implicated, blinded oral food challenges should be performed once the patient's skin has been sufficiently cleared (may require hospitalization) to interpret challenge outcome. Multiple dietary restrictions are rarely necessary.

A recent study compared the results of DBPCFCs in 196 children and adolescents with AD to the concentrations of food-specific IgE antibodies determined with the Pharmacia CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden) (reported in kU/L).⁷⁶ As shown in Table 5, levels of food-specific IgE indicating the positive (PPV) and negative (NPV) predictive values for the test were calculated based on the outcome of the challenges. For egg, milk, peanut, and codfish allergies, diagnostic levels were derived above which clinical reactivity was highly likely (greater than 95% PPV). Therefore, patients with concentrations of food-specific IgE above these values are very likely to react following ingestion of the specific food, and no further evaluation would be required. An oral challenge would be needed to confirm symptomatic allergy in children with levels of food-specific IgE falling below the 90%

Table 5. POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF FOOD-SPECIFIC IgE CONCENTRATIONS (kU/L) FOR PREDICTING REACTIONS UPON ORAL CHALLENGE*

	> 95% PPV	> 90% PPV	> 95% NPV	> 90% NPV
Egg	6	2	—	0.6
Milk	32	23	0.8	1.0
Peanut	15	9	Best NPV = 85% at < 0.35 kU/L	
Fish	20	9.5		
Soy	Best PPV = 50% at 65 kU/L		2	5
Wheat	Best PPV = 75% at 100 kU/L		5	79

*There was no relationship between IgE level and severity.

PPV = positive predictive value; NPV = negative predictive value.

or 95% PPV because many of these patients would still react to the food in question.

MANAGEMENT OF FOOD HYPERSENSITIVITY IN PATIENTS WITH ATOPIC DERMATITIS

Once food hypersensitivity is diagnosed, therapy consists of placing the patient on a diet completely eliminating all forms of the offending food allergen. Instructing the patient and family to read food labels to avoid hidden sources of the suspect food and to avoid potential sources of allergen contamination is critical.⁵³ Hidden food sources may be found as follows:

- **MILK:** Artificial butter flavor, butter, butter fat, buttermilk, casein, caseinates (sodium, calcium, etc.), cheese, cream, cottage cheese, curds, custard, Half & Half, hydrolysates (casein, milk, whey), lactalbumin, lactose, milk (derivatives, protein, solids, malted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized protein concentrate), yogurt. MAY be contained in brown sugar flavoring, natural flavoring, chocholate, caramel flavoring, high protein flour, margarine, Simplese.
- **EGG:** Albumin, egg (white, yolk, dried, powdered, solids), egg substitute, eggnog, globulin, livetin, lysozyme, mayonnaise, meringue, ovalbumin, ovomucin, ovomucoid, Simplese.
- **WHEAT:** Bread crumbs, bran, cereal extract, cracker meal, enriched flour, farina, gluten, graham flour, high gluten flour, high protein flour, malt, vital gluten, wheat bran, wheat germ, wheat gluten, wheat starch, whole wheat flour, spelt. MAY be contained in gelatinized starch, hydrolyzed vegetable protein, modified food starch, modified starch, natural flavoring, soy sauce, starch, vegetable gum, vegetable starch.
- **SOY:** Hydrolyzed vegetable protein, miso, shoyu sauce, soy (flour, grits, nuts, milk, sprouts), soybean (granules, curd), soy protein (concentrate, isolate), soy sauce, textured vegetable protein (TVP), tofu. MAY be contained in hydrolyzed plant protein, hydrolyzed soy protein, hydrolyzed vegetable protein, natural flavoring, vegetable broth, vegetable gum, vegetable starch.
- **PEANUT:** Cold pressed peanut oil, ground nuts, mixed nuts, Nu-Nuts artificial nuts, peanut, peanut butter, peanut flour. MAY be contained in African, Chinese, Thai, and other ethnic dishes, baked goods (pastries, cookies, and so forth), candy, chili, chocholate candy, egg rolls, hydrolyzed plant protein, hydrolyzed vegetable protein, marzipan, nougat.

A major reason that dietary management fails in food-allergic patients is because of inadequate patient instruction by the treating

physician. Helpful information may be obtained from the Food Allergy Network (800-929-4040), a lay organization based in Fairfax, VA. Antihistamines and corticosteroids may modify the symptoms of food hypersensitivity after an accidental ingestion, but they have no prophylactic role in the treatment of food allergy. Although prevention of food allergen-induced symptoms with oral cromolyn has been advocated by some investigators, a controlled, blinded trial of oral cromolyn in patients with challenge-proven food hypersensitivity demonstrated no benefit.¹⁴ Treatment of food hypersensitivity with oral desensitization, immunotherapy, and rotational diets also have not been proven effective in controlled trials.

NATURAL HISTORY OF FOOD HYPERSENSITIVITY IN ATOPIC DERMATITIS

Approximately one third of children with AD and food allergy will lose (or outgrow) their clinical reactivity to food over 1 to 3 years.⁷⁵ Three factors appear to be important in determining the probability of patients losing their clinical reactivity: the food to which the patient is allergic (i.e., patients allergic to peanuts, nuts, fish, and shellfish are not likely to lose their clinical reactivity, whereas those allergic to soy, wheat, milk, and egg are much more likely to develop clinical tolerance); the level of specific IgE antibody to a particular food (i.e., the higher the level of food antigen-specific IgE, the less likely that clinical tolerance will develop in the subsequent few years),⁴⁵ and the degree to which the patient adheres to the elimination diet (i.e., patients ingesting small amounts of allergen or having frequent accidental ingestions are less likely to develop clinical tolerance). Prick skin test results do not correlate with loss of clinical reactivity and may remain positive for many years after the food has been re-introduced into the diet. It is recommended that patients be re-challenged at set intervals (e.g., egg: every 2–3 years; milk, soy, and wheat: every 1–2 years; foods other than peanut, nuts, fish, and shellfish: every 1–2 years) to determine whether their food allergy persists. To date, no patients have experienced a recurrence of allergic symptoms or worsening of eczema once food hypersensitivity was lost.

Despite years of debate and some persistent dissenting voices, it is now apparent that food hypersensitivity plays a significant pathogenic role in up to 40% of children with moderate to severe AD.²² The significance of food allergy in adults with AD remains to be established. The continued study of this subset of AD patients with food-induced inflammation should provide an excellent human model to study the IgE-mediated hypersensitivity reaction.

References

1. Abernathy-Carver K, Sampson HA, Picker L, et al: Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 95:913, 1995

2. Atherton DJ, Soothill JF, Sewell M, et al: A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1:401, 1978
3. Barker J, MacDonald D: Epidermal class II human lymphocyte antigen expression in atopic dermatitis: A comparison with experimental allergic contact dermatitis. *J Am Acad Dermatol* 16:1175, 1987
4. Bernhisel-Broadbent J, Sampson HA: Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol* 83:435, 1989
5. Bernhisel-Broadbent J, Taylor S, Sampson HA: Cross-allergenicity in the legume botanical family in children with food hypersensitivity. II. Laboratory correlates. *J Allergy Clin Immunol* 84:701, 1989
6. Besnier E: Premiere note et observations preliminaires pour servir d'introduction a l'etude des pruripos diathesiques. *Ann de Dermatol Syphil* 23:634, 1892
7. Bieber T, Kraft S, Jugend M, et al: New insights in the structure and biology of the high affinity receptor for IgE (Fc epsilon RI) on human epidermal Langerhans' cells. *J Dermatol Sci* 13:71, 1996
8. Blackfan KD: A consideration of certain aspects of protein hypersensitiveness in children. *Am J Med Sci* 160:341, 1920
9. Blaylock WK: Atopic dermatitis: Diagnosis and pathobiology. *J Allergy Clin Immunol* 57:62, 1976
10. Bock S, Lee W, Remigio L, et al: Studies of hypersensitivity reactions to food in infants and children. *J Allergy Clin Immunol* 62:3327, 1978
11. Brunner M, Walzer M: Absorption of undigested proteins in human beings: The absorption of unaltered fish protein in adults. *Arch Intern Med* 42:173, 1928
12. Bruynzeel-Koomen C, Van Wicker DF, Toonstra J, and et al: The presence of IgE molecules on epidermal Langerhans' cells in patients with atopic dermatitis. *Arch Dermatol Res* 297:205, 1986
13. Burks AW, James JM, Hiegel A, et al: Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 132:132, 1998
14. Burks AW, Sampson HA: Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. *J Allergy Clin Immunol* 81:417, 1988
15. Businco L: Allergic reactions to goat's milk in cow's milk allergic children. *Allergologie* 18:412, 1995
16. Capron M, Capron A, Joseph M: IgE receptros on phagocytic cells and immune response to Schistosoma infection. *Monograph Allergy* 18:33, 1983
17. Chandra R, Puri S, Cheema PS: Predictive value of cord blood IgE in the development of atopic disease and role of breast-feeding in its prevention. *Clin Allergy* 15:517, 1985
18. Chandra R, Shakuntla P, Hamed A: Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 299:228, 1989
19. David TJ: Anaphylactic shock during elimination diets for severe atopic dermatitis. *Arch Dis Child* 59:983, 1984
20. David TJ, Waddington E, Stanton RHJ: Nutritional hazards of elimination diets in children with atopic dermatitis. *Arch Dis Child* 59:323, 1984
21. de Vries IJ, Langeveld-Wildshut EG, van Reijssen F: Adhesion molecule expression on skin endothelia in atopic dermatitis: Effects of TNF- α and IL-4. *J Allergy Clin Immunol* 102:461, 1998
22. Eigenmann PA, Sicherer SH, Borkowski TA, et al: Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 101:E8, 1998
23. Engman WF, Weiss RS, Engman MF: Eczema and environment. *Med Clin North Am* 20:651, 1936
24. European Task Force on Atopic Dermatitis: Severity scoring of atopic dermatitis: The SCORAD index. *Dermatology* 186:23, 1993
25. Fergusson D, Horwood L, Shannon F: Asthma and infant diet. *Arch Dis Child* 58:48, 1983
26. Fergusson DM, Horwood LJ, Shannon FT: Early solid feeding and recurrent eczema: A 10-year longitudinal study. *Pediatrics* 86:541, 1990

27. Flood JM, Perry DJ: Role of food allergy in eczematoid dermatitis. *Archives of Dermatology and Syphilology* 55:493, 1947
28. Gleich G, Frigas E, Loegering DA, et al: Cytotoxic properties of eosinophilic major basic protein. *J Immunol* 123:2925, 1979
29. Grulee CG, Sanford HN: The influence of breast feeding and artificial feeding in infantile eczema. *J Pediatr* 9:223, 1936
30. Halbert AR, Weston WL, Morelli JG: Atopic dermatitis: Is it an allergic disease? *J Am Acad Dermatol* 33:1008, 1995
31. Hamid Q, Boguniewicz M, Leung DYM: Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 94:870, 1994
32. Hamid Q, Naseer T, Minshall EM, et al: In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 98:225, 1996
33. Hammar H: Provocation with cow's milk and cereals in atopic dermatitis. *Acta Derm Venerol (Stockh)* 7:159, 1977
34. Hanifin JM: Atopic dermatitis. In Middleton E, Reed CE, Ellis EF, (eds): *Allergy: Principles and Practice*. St. Louis, Mosby, 1993, p 1581
35. Hanifin JM: Epidemiology of atopic dermatitis. *Monogr Allergy* 21:116, 1987
36. Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 92:44, 1980
37. Hill DJ, Lynch BC: Elemental diet in the management of severe eczema in childhood. *Clin Allergy* 12:313, 1982
38. Hill LW, Sulzberger MB: Evaluation of atopic dermatitis. *Archives of Dermatology and Syphilology* 32:451, 1935
39. Hoffman DR: Food allergy in children: RAST studies with milk and egg. *Advances in the Diagnosis of Allergy: RAST. Conference Proceeding*, 1975
40. Hoffman KM, Ho DG, Sampson HA: Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of cow's milk allergy. *J Allergy Clin Immunol* 99:360, 1997
41. Holt LE: Conference on infantile eczema. Some challenge studies with foods. *J Pediatr* 66:235, 1965
42. Host A: Cow's milk protein allergy and intolerance in infancy. *Pediatr Allergy Immunol* 5:5, 1994
43. Husby S, Jensenius J, Svehag S: Passage of undegraded dietary antigen into the blood of healthy adults. Quantification, estimation of size distribution and relation of uptake to levels of specific antibodies. *Scand J Immunol* 22:83, 1985
44. Jakobsson I, Lindberg T, Benediktsson B, et al: Dietary bovine β -lactoglobulin is transferred to human milk. *Acta Paediatr Scand* 74:342, 1985
45. James JM, Sampson HA: Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 121:371, 1992
46. Johnson E, Irons J, Patterson R, et al: Serum IgE concentration in atopic dermatitis. *J Allergy Clin Immunol* 59:94, 1974
47. Jones SM, Magnolfi CF, Cooke SK, et al: Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *J Allergy Clin Immunol* 96:341, 1995
48. Jones SM, Sampson HA: The role of allergens in atopic dermatitis. In Leung DYM (ed): *Atopic Dermatitis: From Pathogenesis to Treatment*. Georgetown, Texas, R.G. Landes Company, 1996, p. 41
49. Joseph M, Capron A, Ameisen J-C: The receptors for IgE on blood platelets. *Eur J Immunol* 16:306, 1986
50. Juto P, Engberg S, Winberg J: Treatment of infantile atopic dermatitis with a strict elimination diet. *Clin Allergy* 8:493, 1978
51. Kajosaari M: Atopy prophylaxis in high-risk infants: Prospective 5-year follow-up study of children with 6 months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol* 310:453, 1991
52. Kajosaari M, Saarinen UM: Prophylaxis of atopic disease by six months; total solid food elimination. *Arch Paediatr Scand* 72:411, 1983
53. Koerner CB, Sampson HA: Diets and nutrition. In Metcalfe DD, Sampson HA, Simon

- RA (eds): *Adverse Reactions to Foods and Food Additives*. Oxford, Blackwell Scientific, 1996, p 461
54. Kondo N, Fukutomi O, Agata H, et al: Proliferative responses of lymphocytes to food antigens are useful for detection of allergens in nonimmediate types of food allergy. *J Investig Allergol Clin Immunol* 7:122, 1997
55. Kramer MS, Moroz B: Do breast-feeding and delayed introduction of solid food protect against subsequent atopic dermatitis? *J Pediatr* 98:546, 1981
56. Leiferman K, Ackerman S, Sampson H, et al: Dermal deposition of eosinophil-granule major basic protein in atopic dermatitis. Comparison with onchocerciasis. *N Engl J Med* 313:282, 1985
57. Lever R, MacDonald C, Waugh P, et al: Randomized controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 9:13, 1998
58. Lyczak JB, Zhang K, Saxon A, et al: Expression of novel secreted isoforms of human immunoglobulin E proteins. *J Biol Chem* 271:3428, 1996
59. Mudde G, Bheekha R, Bruijnzeel-Koomen C: Consequences of IgE/CD23-mediated antigen presentation in allergy. *Immunol Today* 16:380, 1995
60. Mudde G, van Reijssen F, Boland G, et al: Allergen presentation by epidermal Langerhans' cells from patients with atopic dermatitis is mediated by IgE. *Immunol* 69:335, 1990
61. Munkvad M, Danielsen L, Hoj L, et al: Antigen-free diet in adult patients with atopic dermatitis. *Acta Dermatol* 64:524, 1984
62. Neild VS, Marsden RA, Bailes JA, et al: Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 114:117, 1986
63. O'Donnell MC, Ackerman S, Gleich G, et al: Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. *J Exp Med* 157:1981, 1983
64. Reekers R, Beyer K, Niggemann B, et al: The role of circulating food antigen-specific lymphocytes in food allergic children with atopic dermatitis. *Br J Dermatol* 135:935, 1996
65. Rowe A, Rowe AH: Atopic dermatitis in infants and children. *J Pediatr* 39:80, 1951
66. Sampson HA: Atopic dermatitis [review]. *Ann Allergy* 69:469, 1992
67. Sampson H: Diagnosing food allergy. In Spector S (ed): *Provocation Testing in Clinical Practice*. New York, Marcel Dekker, 1995, p 623
68. Sampson HA: Food sensitivity and the pathogenesis of atopic dermatitis. *J R Soc Med* 90:3, 1997
69. Sampson HA: Immunologically mediated reactions to foods: IgE in eczema. *Ann Allergy* 59:71, 1987
70. Sampson HA: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 71:473, 1983
71. Sampson HA: The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 81:635, 1988
72. Sampson HA, Broadbent KR, Bernhisel-Broadbent J: Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 321:228, 1989
73. Sampson HA, Jolie PL: Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 311:372, 1984
74. Sampson HA, McCaskill CC: Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. *J Pediatr* 107:669, 1985
75. Sampson HA, Scanlon SM: Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 115:23, 1989
76. Sampson H, Ho D: Relationship between food-specific IgE concentration and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 100:444, 1997
77. Schloss OM: Allergy to common foods. *Trans Am Pediatr Soc* 27:62, 1915
78. Sigurs N, Hattevig G, Kjellman B: Maternal avoidance of eggs, cow's milk, and fish during lactation: Effect on allergic manifestation, skin prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics* 89:735, 1992

79. Spiegelberg H: Structure and function of Fc receptors for IgE on lymphocytes, monocytes and macrophages. *Adv Immunol* 35:61, 1984
80. Strobel S, Ferguson A: Immune response to fed protein antigens in mice. 3. Systemic tolerance or priming is related to age at which antigen is first encountered. *Pediatr Res* 18:588, 1984
81. Suomalainen H, Soppi E, Isolauri E: Evidence for eosinophil activation in cow's milk allergy. *Pediatr Allergy Immunol* 5:27, 1994
82. Talbot FB: Eczema in childhood. *Med Clin North Am* 1:985, 1918
83. Tong AKF, Mihm MC: The pathology of atopic dermatitis. *Clin Rev Allergy* 4:27, 1986
84. Tsicopoulos A, Hamid Q, Varney V, et al: Preferential messenger RNA expression of Th-1-type cells (IFN- γ , IL-2) in classical delayed-type (tuberculin) hypersensitivity reactions in human skin. *J Immunol* 148:2058, 1992
85. Van Asperen P, Kemp AS, Mellis CM: Relationship of diet in the development of atopy in infancy. *Clin Allergy* 14:525, 1984
86. van Reijssen F, Bruynzeel-Koomen C, Kalthoff FS, and et al: Skin-derived aeroallergen-specific T-cell clones of the Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 90:184, 1992
87. van Reijssen F, Feliuss A, Wauters AK, et al: T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 101:207, 1998
88. Wakita H, Sakamoto T, Tokura Y, et al: E-selectin and vascular cell adhesion molecule-1 as critical adhesion molecules for infiltration of T lymphocytes and eosinophils in atopic dermatitis. *J Cutan Pathol* 21:33, 1994
89. Walzer M: Absorption of allergens. *J Allergy* 13:554, 1942
90. Werfel T, Ahlers G, Schmidt P, et al: Detection of a kappa-casein-specific lymphocyte response in milk-responsive atopic dermatitis. *Clin Exp Allergy* 26:1380, 1996
91. Wilson SI, Walzer M: Absorption of undigested proteins in human beings. IV. Absorption of unaltered egg protein in infants. *Am J Dis Child* 50:49, 1935
92. Wise F, Sulzberger MB: Editorial remarks. In Wise F, Sulzberger MB (eds): *Yearbook of Dermatology and Syphilology*. Chicago, Yearbook Medical Publishers, 1933, p 31
93. Zeiger RS: Development and prevention of allergic disease in childhood. In Middleton E, Reed C, Ellis E, et al (ed): *Allergy: Principles and Practice*. St. Louis, Mosby, 1993, p 1137
94. Zeiger R, Heller S: The development and prediction of atopy in high-risk children: Follow-up at seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 95:1179, 1995
95. Zeiger R, Heller S, Mellon M, et al: Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. *J Allergy Clin Immunol* 84:72, 1989
96. Zeiger R, Heller S, Mellon M, et al: Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: A prospective randomized study of food allergen avoidance. *Pediatr Allergy Immunol* 3:110, 1992

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