

Epidemiology of food allergy

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H. A. Sampson

Johns Hopkins University School of Medicine,
Baltimore, Maryland, USA

H. A. Sampson, Pediatric Allergy & Immunology,
Johns Hopkins Hospital, CMSC-1102,
600 N. Wolfe Street,
Baltimore, MD 21287-3923, USA.

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Epidemiologic research is concerned with the frequency of illness and health-related phenomena in the general population. The utility and comparability of epidemiologic studies obviously depend upon an acceptance of strict criteria for diagnosing a specific disorder. Well-designed epidemiologic studies can provide the physician with a variety of information useful for his/her clinical practice: prevalence rates, changing attack rates, possible pathogenic factors, the course and natural history, and potential prophylactic measures to avoid development of various disorders.

Although a form of adverse food reaction was recognized nearly 4,500 years ago by the Chinese emperor, Shen Nung, it was not until 75 years ago that the first scientific evidence was presented attempting to explain these disorders. Prausnitz & Kustner demonstrated that a serum-borne factor (later proven to be IgE) was capable of transferring Kustner's fish allergy to his non-allergic collaborator, Prausnitz (1). Shortly after ingesting fish, Prausnitz developed a wheal and flare at the site where Kustner's serum had been injected 24 h earlier. In 1950, Loveless established the unreliability of patients' historical reports of food allergy and advocated the use of blinded, placebo-controlled food trials for diagnosing food allergy (2). Twenty-five years later May (3) demonstrated the utility of double-blind placebo-controlled oral food challenges (DBPCFC) for diagnosing food allergy, the procedure now considered the "gold standard" for diagnosing food allergic disorders. Utilizing more stringent criteria of diagnosis and study design, epidemiologic studies in the past two decades have begun to delineate the diversity, prevalence and natural history of food allergic disorders.

Definitions

Recently the European Academy of Allergy and Clinical Immunology proposed standardized definitions for food reactions based solely on mechanism (4). An adverse food reaction refers to any aberrant reaction following the ingestion of a food or food additive. Adverse food reactions are divided into toxic and non-toxic food reactions. Toxic reactions will occur in everyone provided a sufficient dose is ingested. Non-toxic reactions depend on individual susceptibility and may be the result of immune mechanisms (Allergy or hypersensitivity) or non-immune mechanisms (intolerances). Type I, IgE-mediated food allergies have been most clearly delineated, but non-IgE-mediated immune reactions are clearly responsible for a variety of food allergic disorders. Food intolerances may be due to pharmacologic properties of the food (e.g. theobromine in chocolate, tyramine in aged cheeses), or traits of the host such as metabolic disorders (e.g. lactase deficiency) or idiosyncratic responses.

Prevalence

The general public "perceive" adverse reactions to foods and food additives as a major health problem. Approximately one-third of American households were found to alter their eating practices because a member of the family was believed to suffer from food allergies (5) and approximately 20% of 7,500 households surveyed in the United Kingdom reported a food intolerance (6). In the latter survey, 19.4% of subjects reporting adverse reactions had their symptoms confirmed by DBPCFC, suggesting an overall prevalence of adverse food reactions of

Table 1. Food hypersensitivity disorders

Gastrointestinal	<i>IgE-mediated</i>
	Oral allergy syndrome (oral & perioral pruritus & angioedema, throat tightness) Gastrointestinal anaphylaxis (nausea, cramping, emesis, diarrhea) Allergic eosinophilic gastroenteritis (subset) Infantile colic (~15% of infants with colic)
	<i>Non-IgE-mediated</i>
	Food-induced enterocolitis (1-3 h post-ingestion: emesis, diarrhea, failure to thrive, and rarely hypotension) Food-induced proctocolitis (2-12 h post ingestion: blood in stools) Allergic eosinophilic gastroenteritis (post-prandial nausea, emesis, weight loss) Food-induced enteropathy ("celiac-like"; nausea, malabsorption, steatorrhea, weight loss) Celiac disease
Cutaneous	<i>IgE-mediated</i>
	Acute (common) and chronic (rare) urticaria Atopic dermatitis (pruritic morbilliform rash ==> eczematous lesion)
	<i>Non-IgE-mediated</i>
	Dermatitis herpetiformis Contact hypersensitivity Contact irritation (especially with acidic fruits and vegetables)
Respiratory	<i>IgE-mediated</i>
	Rhinoconjunctivitis Laryngeal edema Asthma (both acute wheezing and increased bronchial hyperreactivity)
	<i>Non-IgE-mediated</i>
	Heiner's syndrome (rare form of pulmonary hemosiderosis)
Other - mechanism unknown	
	Migraine (rare) Arthritis (rare subset)

1.4% to 1.8%. A recent Dutch study found that 10% of a randomly selected adult population reported adverse food reactions, but following DBPCFCs it was concluded that about 2% of the adult Dutch population are affected by adverse food reactions (7). Patients frequently suspect adverse reactions to food additives. In a second population survey in the United Kingdom, 7.4% of the population sampled claimed to have reacted to a food additive, but challenges revealed that the true prevalence was between 0.01% and 0.23% (8).

Adverse reactions to foods are more common in young children, and in part may relate to the feeding practices of the population studied. In a prospective study of 480 newborns followed in an American general pediatric practice for 3 years, parents reported adverse food reactions in 28% of the infants, but reactions were confirmed by oral challenge in only about one-third of suspected cases, or 8% of the total group (9). Interestingly, parents reported reactions to fruits and fruit juices in 75 infants [16%], and complaints were confirmed in 56 [12%] by open challenges. Overall there were 60 positive challenges consisting of skin rashes and/or diarrhea,

and were attributed to orange juice in 14 children [23%], tomato juice in 14 [23%], apple in 7 [12%], grape in 4 [7%], and other fruit juices in the remaining 21 reactions [35%]. Cow milk allergy has been studied most extensively. A survey of 1,759 Danish infants found that the prevalence of cow milk allergy was greatest in the first year, affecting 2.2% of infants (10). Similarly, a study of 1,386 Dutch infants found 2.8% of infants affected by cow milk allergy (11). Overall, it appears that about 2.5% of infants experience cow milk allergy in the first years of life (9-12) but that nearly 85% of sensitive infants lose their reactivity by 3 years of age (13). Adverse reactions to food additives also appear to be more common in children. In a study of 4,274 Danish schoolchildren, 6.6% were reported to have adverse reactions to food additives, but results of DBPCFC in a cohort of subjects suggested an overall prevalence of 1% to 2% (14).

Atopic individuals appear to have a higher prevalence of food allergy. In children with mild to moderate atopic dermatitis attending a university dermatology/allergy clinic, about one-third were found to have skin symptoms provoked during DBPCFCs

Fig 1. ALLERGY PREVENTION WITH MATERNAL DIET DURING LACTATION - 4 Years

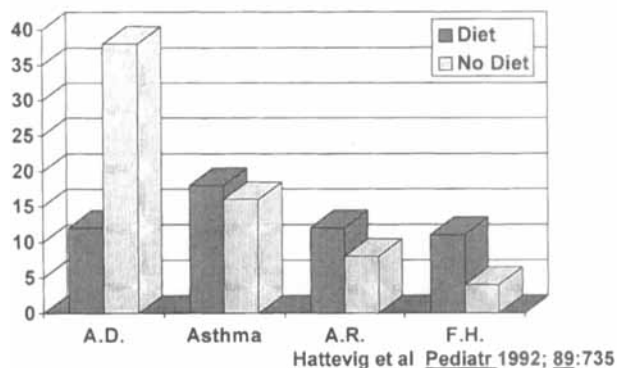


Fig. 1. Comparison of maternal food allergen elimination during lactation; four-year follow-up (66).

(15). The more severe the atopic eczema in young children, the more likely they are to have food allergy (16). Two studies of asthmatic children attending pulmonary clinics revealed that 6% to 8% of the children had food-induced wheezing (17, 18). Virtually all the children with food-induced asthma had atopic dermatitis or a history of atopic dermatitis. In another study, children with food allergy prior to 4 years of age were found to be nearly twice as likely to develop allergic rhinitis and asthma by age 7 years compared to children without food allergy (19). Interestingly, infants with egg allergy or evidence of IgE antibody to egg protein have a markedly increased risk of developing asthma compared to infants with no evidence of IgE sensitization (19, 20). Infants with non-IgE-mediated gastrointestinal allergy are not at increased risk for atopic disease.

While clinicians working with food allergic patients often recognize a familial pattern of inheritance, no formal studies have been conducted in food allergic patients. In a review of approximately 220 families of children referred for evaluation of atopic dermatitis or food allergies, two or more children with food allergies were seen in 20 families, indicating multiple food allergic family members in at least 10% of families. Interestingly, 18 sibling pairs were found to be allergic to the same food(s); 13/20 to egg, 12/20 to milk, 7/20 to peanut and 3/20 to soy. However, large-scale epidemiologic studies must be performed in order to confirm this observation and establish the potential mode of inheritance. Nevertheless, food allergy in young children should probably be considered one component of an "allergic quadrad;" i.e. food allergy, atopic dermatitis, asthma, and allergic rhinitis, since food allergy in young infants is frequently a harbinger of future atopy.

Fig 2. ALLERGY PREVENTION IN "HIGH" RISK INFANTS

Halken et al *Allergy* 1992; 47:545.

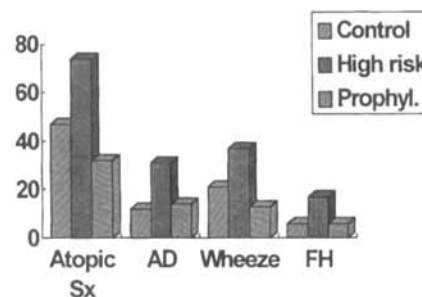


Fig. 2. The effect of an allergy prevention program on the incidence of atopic disease in "high-risk" infants (72).

Development of food allergy

The timing of exposure and type of foods introduced into an infant's diet appears to play a role in determining the development of specific food hypersensitivities. For example, a lower incidence of cow milk allergy at one year was reported in infants who were started on cow milk after 6 months of age compared to those introduced to cow milk at an earlier age (21). Infants and young children in the United States have been exposed to peanut products earlier in life over the past 30 years, and the prevalence of peanut allergy appears to be increasing. A prospective study examining the efficacy of food allergen avoidance in preventing atopic disease in infants at "high risk" for atopy found that, of 185 control infants, 80% were exposed to peanut products by their first birthday and 100% by their second birthday (22). Follow-up at 7 years of age revealed that about 7% of "high-risk" children had positive skin tests to peanut, and 4% were felt to be reactive based on history and/or oral food challenges (19). In a review of 115 children with moderate to severe atopic dermatitis referred to the author between 1981 and 1985 for evaluation, 44% were found to have evidence of IgE antibodies (i.e., positive prick skin tests) to peanut and 16% had either a positive DBPCFC or convincing history of peanut-induced anaphylaxis. In a similar group of 155 children referred between 1991 and 1995, 68% had evidence of IgE antibodies to peanut and 31% had either a positive challenge or convincing history of peanut induced anaphylaxis; over a 50% increase in sensitivity and nearly a 100% increase in reactivity to peanut in 10 years. A recent survey of 4 year olds on the Isle of Wight in the United Kingdom found that 1.1% of 4-year-olds were sensitized to

peanut, i.e. had positive prick skin tests, and about one half of them had overt manifestations of peanut allergy (23). These findings are particularly alarming because of the ubiquitous nature of peanut proteins in the American food supply, the apparent "lifelong" sensitivity to this protein, and the apparent greater severity of allergic reactions that peanuts and nuts elicit compared to many other foods. Today peanuts are believed to be one of the leading causes of food-allergic reactions in the U.S. (24, 25) and together with tree nuts, probably the leading cause of fatal and near-fatal food-induced anaphylaxis (26–29).

Food allergens

Foods are comprised of proteins, carbohydrates and lipids, although it is the protein portion which is believed to comprise the major allergenic component. In general, the major food allergens which have been identified are water-soluble glycoproteins which have molecular weights ranging from 5 to 60 kDa and are stable to treatment with heat, acid, and proteases (30). However, other physicochemical properties which account for their unique allergenicity are poorly understood. A limited number of foods account for the vast majority of food allergic reactions. About 90% of all challenge-documented allergic reactions in the pediatric population are due to egg, milk, peanut, soy, wheat and fish, with the majority of the remaining reactions secondary to tree nuts and shellfish.

Clinical symptoms

Although man is endowed with a number of physiologic and immunologic barriers to prevent the absorption of foreign food proteins, it has been clearly documented that food antigens penetrate the normal gastrointestinal tract (1, 31, 32). In normal individuals, immunologic tolerance develops, although T cell responses *in vitro* can be demonstrated and low concentrations of IgG, IgM, and IgA food-specific antibodies are commonly found in the serum (33). In general, food antibody levels will be greater the younger an infant is when a food antigen is introduced into the diet (34). In the genetically predisposed host, a breakdown in the development of oral tolerance may occur resulting in a variety of hypersensitivity responses to an ingested food antigen. Table 1 lists adverse food reactions which are believed to be the result of abnormal immunologic responses.

Anaphylactic reactions have long been the most feared complication of food allergy. The exact prevalence of food-induced anaphylaxis is unknown, but a recent survey suggested that food allergy is the most common cause of severe anaphylaxis treated

in US emergency departments, occurring twice as frequently as insect sting-induced anaphylaxis (28). In 6 fatal and 6 near-fatal food-induced anaphylactic reactions in children, common risk factors were found to include the following: all patients had asthma (although generally well controlled); all patients were unaware that they were ingesting the food allergen; all patients had experienced previous allergic reactions to the incriminated food; and all patients had immediate symptoms with about half experiencing a quiescent period prior to a major respiratory collapse (27).

The incidence of food-dependent, exercise-induced anaphylaxis appears to be increasing, possibly due to the increased popularity of exercising in the past decade. These reactions may follow the ingestion of specific foods and rarely may follow the ingestion of any food (35, 36). Anaphylaxis will occur when a patient exercises within 2–4 hours of ingesting a food, but otherwise the patient can ingest the food without any apparent reaction and can exercise without any apparent reaction as long as the specific food has not been ingested within the past several hours.

Natural history

The prevalence of food allergy is greatest in the first year of life, affecting about 4–5% of young infants (9), and then falling to about 2% by the end of the first decade as children "outgrow" their sensitivity. In a prospective study of milk hypersensitivity in infants followed through the first 3 years of life (10), about one-half of the children were found to "lose" their clinical reactivity by 1 year of age, 70% by 2 years, and 85% of infants by their third birthday (13). All children found to have negative prick skin tests to milk at 1 year of age lost their milk sensitivity by 3 years of age, whereas 25% of those with positive skin tests at one year remained milk allergic at their third birthday. Infants with evidence of IgE antibodies to cow milk were also found to be at increased for developing other food sensitivities (10, 37).

Although children less than 3 years of age appear more likely to "outgrow" their IgE-mediated food allergy (38, 39), older children will lose their reactivity if the responsible food allergen can be identified and completely eliminated from the diet (38, 40). In prospective studies, approximately one-third of children lost their clinical reactivity after 1 to 2 years of allergen avoidance (40–42). Results of prick skin tests and radioallergosorbent tests remained positive for many years and did not predict when children lost their clinical reactivity. A high ratio of food allergen-specific IgE/IgG has been demonstrated to show an association with the in-

creased likelihood of "outgrowing" egg and milk allergic reactions (43, 44). The severity of the initial allergic reactions do not necessarily correlate with the likelihood of "losing" clinical reactivity (38, 40), but the degree of compliance with the allergen avoidance diet (40, 45) and the food allergen responsible for the reaction did affect outcome (40, 46). Patients allergic to peanuts, nuts, fish, or shellfish rarely lose clinical reactivity, and therefore frequent re-challenges to determine the status of their "reactivity" are not usually warranted.

Most non-IgE mediated gastrointestinal food hypersensitivities in infants are "outgrown" in the first few years of life. However, food-induced enterocolitis and allergic eosinophilic gastroenteritis in older children may persist for long periods of time. Long-term follow-up studies on these disorders are lacking. Celiac disease is a lifelong sensitivity, and gluten-containing cereals must be avoided for life. The continued ingestion of gluten-containing products, even in the absence of significant symptoms, significantly increases the risk of gastrointestinal malignancy and lymphoma in these patients (47).

Prevention of food hypersensitivity

Since Grulee's & Sanford's early report that exclusive breastfeeding reduced atopic dermatitis sevenfold compared to cow milk in a large cohort of infants (48), the effectiveness of breastfeeding and various measures to prevent food allergy and atopy have been debated. Theoretically an infant may be exposed to food allergens passed through the placenta in prenatal life, from dietary allergens passed in maternal breast milk, from formula feedings, in solid foods, and possibly in airborne droplets (49). Prenatal sensitization with antigen-specific IgE in cord blood has been reported, but is felt to be relatively rare (13, 50, 51).

Falsh-Magnusson et al (51, 52) reported no differences in sensitization to food nor the development of atopic disease at 6 or 18 months in infants whose mothers had been restricted of egg and milk during the third trimester of pregnancy compared to infants of mothers taking a normal diet throughout pregnancy. Furthermore, no differences were detected in atopic prone infants whose mothers were randomized to diets either high or low in egg and milk (53). These studies suggested that food sensitization *in utero* is an uncommon event. However, recent studies by Warner et al suggested that lymphocytes are programmed *in utero* for allergen sensitization (54), and that small amounts of food allergens in breast milk are necessary to promote the development of tolerance (55). The latter finding is in distinct contrast to a number of previous studies evaluating measures to prevent the development of atopy, as discussed below.

Exclusive breastfeeding has been promoted as a means of preventing food allergy and atopic disease, but considerable controversy remains regarding the effectiveness of this practice. Human breast milk is the optimal nutritional source for newborns, providing both protection against foreign antigen exposure and promotion of gut integrity (56). Several factors are felt to account for the protective effect of breast milk: minimal concentrations of foreign proteins, s-IgA antibodies which provide passive protection against foreign proteins and pathogens, passive transfer of soluble (e.g. lactoferrin, lysozymes, cytokines, superoxides) and cellular (e.g. macrophages, neutrophils, lymphocytes) antimicrobial factors, and growth factors which promote earlier maturation of the gut barrier and the infant's immune response (57). In a retrospective study of atopic-prone infants who were exclusively breast-fed, an association was reported between low levels of cow milk-specific s-IgA in maternal milk and reactivity to cow milk (58). However, this was not confirmed in a later prospective study (56).

In a prospective study of 446 unselected preterm neonates, the protective effect of human breast milk was compared to the use of a preterm formula (59). When infants from atopic families were compared, 16% of the infants receiving banked human breast milk developed atopic dermatitis at 18 months compared to 41% of infants receiving formula. In a prospective study of 1,726 Danish infants, infants exclusively breastfed for at least one month had significantly less cow milk allergy/intolerance than infants never breastfed or breastfed for less than one month; 1.7% vs 4.1% (60). In contrast to these studies, 18% of infants fed cow milk formula in the first few days of life prior to initiating breastfeeding developed atopic disease compared to 33% infants who were exclusively breastfed, suggesting a role for antigen feeding in tolerance induction (61). However, Schmitz et al were unable to reproduce these findings in a prospective study in which cow milk or a partially hydrolyzed whey formula were given prior to breastfeeding (62).

Several studies have been conducted evaluating the effect of eliminating highly allergenic foods from the maternal diet during lactation, since food proteins have been demonstrated in maternal breast milk (13, 57, 63). In two studies, infants from atopic families whose mothers excluded egg, milk and fish from their diets during lactation (prophylaxis group) had significantly less atopic dermatitis and food allergy at 18 months of age compared to infants whose mothers' diets were unrestricted (64, 65). As seen in Fig. 1, the prophylactic group had less atopic dermatitis at 4 years of age, but there was no difference in food allergy, asthma or allergic rhinitis (66). In this study, patients were not truly randomized, but assigned to groups by hospital.

In a prospective, randomized trial of allergy prevention measures, Zeiger et al evaluated the benefits of excluding major allergens from the maternal and infant diets on the prevention of allergic disease in infants from highly atopic families (19, 22, 67). Breastfeeding was encouraged in both prophylaxis and control groups, but in the prophylaxis group ($n = 103$), the mothers were restricted of egg, cow milk and peanut during the third trimester of pregnancy and while breastfeeding. In addition, a casein hydrolysate formula was utilized for supplementation or weaning, and solid food introduction was delayed in the infant. The control infants ($n = 185$) received cow milk formula for supplementation and followed the American Academy of Pediatrics recommendations for infant feeding (peanuts, nuts and fish are not recommended in the first 2 years) (19). While the cumulative prevalence of food allergy remained lower in the prophylaxis group at 4 (22) and 7 (67) years of follow-up, the period prevalence of food allergy, cow milk sensitization, and atopic dermatitis in the prophylaxis group were reduced significantly during the first two years compared to the control group, but were no longer significantly different beyond 2 years of age. No effect was seen on respiratory allergy. These investigators concluded that maternal and infant food allergen avoidance compared to standard feeding practices failed to modify allergic disease after 2 years of age, and that the benefits of food allergy preventative measures are of limited duration because of the frequent remission of food allergy in early childhood (19). In a similar prospective, randomized trial of maternal and infant food allergen avoidance in infants at high risk for atopic disease, delayed introduction of solid foods, and dust mite avoidance, infants in the prophylactic group were found to have fourfold less asthma and eczema at 1 year (68), and significantly less eczema at 2 years (69). In the prophylactic group, infants received breast milk (mothers' diets restricted of egg, milk, nuts and fish) and/or a soy hydrolysate, delayed introduction of solid foods (i.e. cow milk and soy until 9 months, eggs until 11 months), and use of acaricides and bed encasings. The control group were encouraged to breastfeed but no maternal or infant restrictions were imposed. A more recent study in atopy-prone newborns compared the effects of excluding egg, milk, fish, and nuts from the diets of lactating mothers to unrestricted maternal diet (69–71). Halken et al compared 105 “high-risk” infants who were exclusively breastfed and/or received a hypoallergenic formula combined with the avoidance of solid foods for the first 6 months of life with a similar group of 54 infants seen in a previous year and a control group (72). All mothers had unrestricted diets. Avoidance of tobacco smoke, furred pets, and dust-collecting materials in the bed-

room was recommended for the prevention group. As shown in Fig. 2, the prevention group had significantly less atopic symptoms, atopic dermatitis, wheezing and food allergy than the “high-risk” control group, but was similar to the unselected control group. Fifteen selected infants were included in the prophylactic group and compared to 30 matched infants in the control group; both groups were evaluated at 3, 6, 12, and 18 months. At 6, 12, and 18 months there was significantly more eczema and tendency to increased numbers of positive prick skin tests to foods in the prophylactic group. Lymphocyte proliferative responses to casein, β -lactoglobulin, and ovalbumin were similar in cord blood lymphocytes but had fallen significantly at 6 months in infants of the non-dieting mothers, whereas proliferative responses remained high and unchanged in the infants of mothers on dietary restriction. These authors concluded that small amounts of food antigens in the breast milk may be necessary to induce tolerance to various food antigens. Since infants were not randomized and numbers are small, further studies will be necessary to resolve these conflicting conclusions.

In a prospective, non-randomized study of 1,265 unselected neonates, the effect of solid food introduction was evaluated over a 10-year period (73, 74). A significant linear relationship was found between the number of solid foods introduced into the diet by 4 months of age and subsequent atopic dermatitis, with a three-fold increase in recurrent eczema at 10-years of age in infants receiving 4 or more solid foods compared to infants receiving no solid foods prior to 4 months of age. No relationship was noted between asthma and the introduction of solid foods. Another prospective *non*-randomized study comparing breastfed infants who first received solid foods at 3 months or 6 months of age, revealed reduced atopic dermatitis and food allergy at 1 year of age in the group avoiding solids for the 6-month period (75), but no significant difference in these parameters at 5 years (76). Since neither of these series were randomized, these studies must be considered suggestive until an appropriate randomized trial confirms the benefit of delaying solid food introduction.

Conclusion

Current epidemiologic data indicate that food allergy is most prevalent in young infants, but continues to affect about 1%–2% of the general population. It also suggests that the prevalence of food allergy is greater in atopic individuals and appears to be increasing, presumably because of changes in feeding patterns. Based on published studies to date, there is insufficient evidence to make firm recommendations regarding prophylactic measure to prevent

food allergies and atopic disease. However, it would seem prudent to avoid exposing young infants at high risk for atopic disorders to food allergens which provoke "lifelong" sensitization (e.g. peanuts, nuts, fish, shellfish) for the first 2–3 years of life. Mothers of high-risk infants probably should avoid peanuts, nuts, fish and shellfish while breastfeeding. Whether avoidance of these foods during pregnancy would be beneficial needs to be re-examined, especially since these foods do not generally comprise a major part of the diet. The utility of lactating mothers avoiding milk and eggs remains an open question. Epidemiologic studies have provided a much clearer picture of the diversity and importance of food allergy, but further studies will be necessary to determine what measures can be taken to reverse the trend of increasing prevalence.

References

1. PRAUSNITZ C, KUSTNER H. Studies on supersensitivity. *Centrabl Bakteriell* 1921; 86: 160–9.
2. LOVELESS MH. Milk allergy: a survey of its incidence; experiments with a masked ingestion test. *J Allergy* 1950; 21: 489–99.
3. MAY CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. *J Allergy Clin Immunol* 1976; 58: 500–15.
4. BRUIJNZEEL-KOOMEN C, ORTOLANI C, et al. Adverse reactions to food. Position paper. *Allergy* 1995; 50: 623–35.
5. SLOAN AE, POWERS ME. A perspective on popular perceptions of adverse reactions to foods. *J Allergy Clin Immunol* 1986; 78: 127–33.
6. YOUNG E, STONEHAM MD, PETRUCKEVITCH A, BARTON J, RONA R. A population study of food intolerance. *Lancet* 1994; 343: 1127–30.
7. NIESTIJL JANSEN JJ, KARDINAAL AFM, HUIJBERS GH, et al. Prevalence of food allergy and intolerance in the adult Dutch population. *J Allergy Clin Immunol* 1994; 93: 446–56.
8. YOUNG E, PATEL S, STONEHAM MD, RONA R, WILKINSON JD. The prevalence of reactions to food additives in a survey population. *J R Coll Physicians Lond* 1987; 21: 241–71.
9. BOCK SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987; 79: 683–8.
10. HØST A, HALKEN S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990; 45: 587–96.
11. SCHRANDER JJP, VAN DEN BOGART JPH, FORGET PP, SCHRANDER-STUMPEL CTRM, KUIJTEN RH, KESTER ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993; 152: 640–4.
12. HIDE DW, GUYER BM. Cow milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983; 37: 285–7.
13. HØST A. Cow's milk protein allergy and intolerance in infancy. *Pediatr Allergy Immunol* 1994; 5: 5–36.
14. FUGLSANG G, MADSEN C, SAVAL P, ØSTERBALLE O. Prevalence of intolerance to food additives among Danish school children. *Pediatr Allergy Immunol* 1993; 4: 123–9.
15. BURKS AW, MALLORY SB, WILLIAMS LW, SHIRRELL MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113: 447–51.
16. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 1992; 128: 187–92.
17. NOVEMBRE E, DE MARTINO M, VIERUCCI A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988; 81: 1059–65.
18. OEHLING A, CAGNANI CEB. Food allergy and child asthma. *Allergol Immunopathol* 1980; 8: 7–14.
19. 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* 1995; 95: 1179–90.
20. HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Clinical symptoms and IgE responses to common food proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987; 17: 571–8.
21. HALPERN SR, SELLARS W, JOHNSON R, ANDERSON D, SAPERSTEIN S, REISCH J. Development of childhood allergy in infants fed breast, soy, or cow milk. *J Allergy Clin Immunol* 1973; 51: 139–51.
22. ZEIGER R, HELLER S, MELLON M, FORSYTHE A, O'CONNOR R, HAMBURGER R. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989; 84: 72–89.
23. TARIQ S, STEVENS M, MATTHEWS S, RIDOUT S, TWISLTON R, HIDE D. Cohort study of peanut and tree nut sensitization by age of four years. *BM J* 1996; 313: 514–7.
24. SAMPSON HA, METCALFE DD. Food allergies. *JAMA* 1992; 268: 2840–4.
25. BOCK SA, ATKINS FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990; 117: 561–7.
26. YUNGINGER JW, SWEENEY KG, STURNER WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988; 260: 1450–2.
27. SAMPSON HA, MENDELSON LM, ROSEN JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380–4.
28. YOCUM MW, KHAN DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994; 69: 16–23.
29. BOCK S. The incidence of severe adverse reactions to food in Colorado. *J Allergy Clin Immunol* 1992; 90: (4)683–5.
30. SAMPSON HA. Adverse reactions to foods. In: MIDDLETON EJ, REED CE, ELLIS EF, ADKINSON NFJ, YUNGINGER JW, BUSSE WW, editors. *Allergy. Principles and practice*. St. Louis: Mosby, 1993: 1661–86.
31. WALZER M. Studies in absorption of undigested proteins in human beings. 1. A simple direct method of studying the absorption of undigested protein. *J Immunol* 1927; 14: 143–74.
32. WALZER M. Studies in absorption of undigested proteins in human beings. 1. A simple direct method of studying the absorption of undigested protein. *J Immunol* 1994; 14: 143–74.
33. JOHANSSON S, DANNAEUS A, LILJA G. The relevance of anti-food antibodies for the diagnosis of food allergy. *Ann Allergy* 1984; 53: 665–72.
34. SAVILAHTI E, SALMENPERÄ L, TAINIO V, HALME H, PERHEENTUPA J, SIIMES M. Prolonged exclusive breast-feeding results in low serum concentration of immunoglobulin G, A, and M. *Acta Paediatr Scand* 1987; 76: 1–6.
35. KIDD J, COHEN S, SOSMAN A, FINK J. Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; 71: 407–11.

36. DOHI M, SUKO M, SUGIYAMA H, et al. Food-dependent exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol* 1991; 87: 34–40.
37. HILL DJ, BANNISTER DG, HOSKING CS, KEMP AS. Cow milk allergy within the spectrum of atopic disorders. *Clin Exp Allergy* 1994; 24: 1137–43.
38. BOCK SA. The natural history of food sensitivity. *J Allergy Clin Immunol* 1982; 69: 173–7.
39. HILL DJ, FIRER MA, BALL G, HOSKING CS. Recovery from milk allergy in early childhood: antibody study. *J Pediatr* 1989; 114: 761–6.
40. SAMPSON HA, SCANLON SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989; 115: 23–27.
41. HILL DJ, FIRER MA, SHELTON MJ, HOSKING CS. Manifestations of milk allergy in infancy: clinical and immunological findings. *J Pediatr* 1986; 109: 270–6.
42. BUSINCO L, BENINCORI N, CANTANI A, et al. Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study. *Ann Allergy* 1985; 55: 844–7.
43. DANNAEUS A, INGANÄS M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody level to milk, egg and fish. *Clin Allergy* 1981; 11: 533–9.
44. JAMES JM, SAMPSON HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 1992; 121: 371–7.
45. PASTORELLO E, STOCCHI L, PRAVETONNI V, et al. Role of the food elimination diet in adults with food allergy. *J Allergy Clin Immunol* 1989; 84: 475–83.
46. BOCK SA, ATKINS FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83: 900–4.
47. HOLMES G, PRIOR P, LANE M, et al. Malignancy in coeliac disease – effect of a gluten-free diet. *Gut* 1989; 30: 333–8.
48. GRULEE CG, SANFORD HN. The influence of breast feeding and artificial feeding in infantile eczema. *J Pediatr* 1936; 9: 223–5.
49. ZEIGER R. Prevention of food allergy in infancy. *Ann Allergy* 1990; 65: 430–41.
50. BUSINCO L, MARCHETTI F, PELLIGRINI G, BERLINI R. Predictive value of cord blood IgE levels in "at-risk" newborn babies and influence of type of feeding. *Clin Allergy* 1983; 13: 503–8.
51. FÄLTH-MAGNUSSON K. Dietary restrictions during pregnancy. In: DE WECK A, SAMPSON H, editors. *Intestinal immunology and food allergy*. New York: Raven Press, 1995: 191–201.
52. FÄLTH-MAGNUSSON K, KJELLMAN N-IM. Development of atopic disease in babies whose mothers were receiving exclusion diets during pregnancy – a randomized study. *J Allergy Clin Immunol* 1987; 80: 868–75.
53. LILJA G, DANNAEUS A, FÄLTH-MAGNUSSON K, GRAFF-LONNEVIG, V, JOHANSSON S, KJELLMAN N-IM. Immune response of the atopic woman and fetus: effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy* 1988; 18: 131–42.
54. WARNER J, MILES E, JONES A, QUINT D, COLWELL B, WARNER J. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic disease? *Clin Exp Allergy* 1994; 24: 423–30.
55. POLLARD C, BEVIN S, LITTLE S, HOURIHANE J, WARNER J, DEAN T. Influence of maternal diet during lactation upon allergic manifestation in infants – tolerisation or sensitisation? *J Allergy Clin Immunol* 1996; 97: 240 (abstract).
56. ZEIGER R. Breast-feeding and dietary avoidance. In: DE WECK A, SAMPSON H, eds. *Intestinal immunology and food allergy*. New York: Raven Press, 1995: 203–22.
57. ZEIGER RS. Development and prevention of allergic disease in childhood. In: MIDDLETON E, REED C, ELLIS E, ADKINSON N, YUNGINGER J, BUSSE W, editors. *Allergy: principles and practice*. St. Louis: Mosby, 1993: 1137–71.
58. MACHTINGER S, MOSS R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986; 77: 341–7.
59. LUCAS A, BROOKE O, MORLEY R, COLE T, BAMFORD M. Early diet of preterm infants and development of allergic or atopic disease: randomized prospective study. *BMJ* 1990; 300: 837–40.
60. HØST A, HUSBY S, ØSTERBALLE O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988; 77: 663–70.
61. LINDFORS A, ENOCKSSON E. Development of atopic disease after early administration of cow milk formula. *Allergy* 1988; 43: 11–16.
62. SCHMITZ J, DIGEON B, CHASTANG C, et al. Effects of brief early exposure to partially hydrolyzed and whole cow milk proteins. *J Pediatr* 1992; 121: S85–S89.
63. 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* 1985; 22: 83–92.
64. HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B, KJELLMAN N-IM. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989; 19: 27–32.
65. CHANDRA R, SHAKUNTALA P, HAMED A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 1989; 299: 228–30.
66. 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* 1992; 89: 735–9.
67. ZEIGER R, HELLER S, MELLON M, HALSEY J, HAMBURGER R, SAMPSON H. 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* 1992; 3: 110–27.
68. ARSHAD S, MATTHEWS S, GANT C, HIDE D. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992; 339: 1493–7.
69. HIDE D, MATTHEWS S, MATTHEWS L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994; 93: 842–6.
70. STROBER W, EHRHARDT R. Regulation of IgA B cell development. In: OGRA P, ed. *Handbook of mucosal immunology*. San Diego: Academic Press, 1994: 159–76.
71. ANDREW D, BERLIN C, HONDA S, et al. Distinct but overlapping epitopes are involved in alpha-4 beta-7-mediated adhesion to vascular cell adhesion molecule-1, mucosal addressin-1, fibronectin, and lymphocyte aggregation. *J Immunol* 1994; 153: 3847–61.
72. HALKEN S, HØST A, ØSTERBALLE O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 "high-risk" infants. *Allergy* 1992; 47: 545–53.

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73. FERGUSON D, HORWOOD L, SHANNON F. Asthma and infant diet. *Arch Dis Child* 1983; 58: 48–51.
74. FERGUSON DM, HORWOOD LJ, SHANNON FT. Early solid feeding and recurrent eczema: a 10-year longitudinal study. *Pediatrics* 1990; 86: 541–6.
75. KAJOSAARI M, SAARINEN UM. Prophylaxis of atopic disease by six months; total solid food elimination. *Arch Paediatr Scand* 1983; 72: 411–4.
76. KAJOSAARI M. Atopy prophylaxis in high-risk infants: prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol* 1991; 310: 453–8.