

ALLERGIC DISEASE PREVENTION AND RISK FACTOR IDENTIFICATION

Mary V. Lasley, MD

There is a widespread impression that the incidence of allergic diseases (asthma, allergic rhinitis, and eczema) has increased in the past 15 to 20 years.^{9,30} Although asthma is the most serious of these atopic diseases, the impact on quality of life of patients with allergic rhinitis is significant. Despite major advances in asthma management, morbidity and mortality from asthma continue to increase.^{13,14} It has been estimated that 4% to 6% of children have food allergies, 8% to 10% have asthma, and 15% to 25% have allergic rhinitis (Fig. 1).

Genetic predisposition and environmental exposure are important factors in the development of allergic disease. Many parents seek advice from their primary care physician or allergist on ways to prevent allergies in their children. Although genetic engineering holds promise for the future, current recommendations are based on reduction of allergen exposure to prevent sensitization.

PREDICTING ALLERGY IN INFANTS

Many studies have been performed to identify children who may be at risk for developing allergic disease. Ideally, the identification method should predict atopy at birth so that methods to reduce sensitization can

From the Department of Pediatrics, University of Washington School of Medicine; Children's Hospital and Medical Center; and Northwest Asthma and Allergy Center, Seattle, Washington

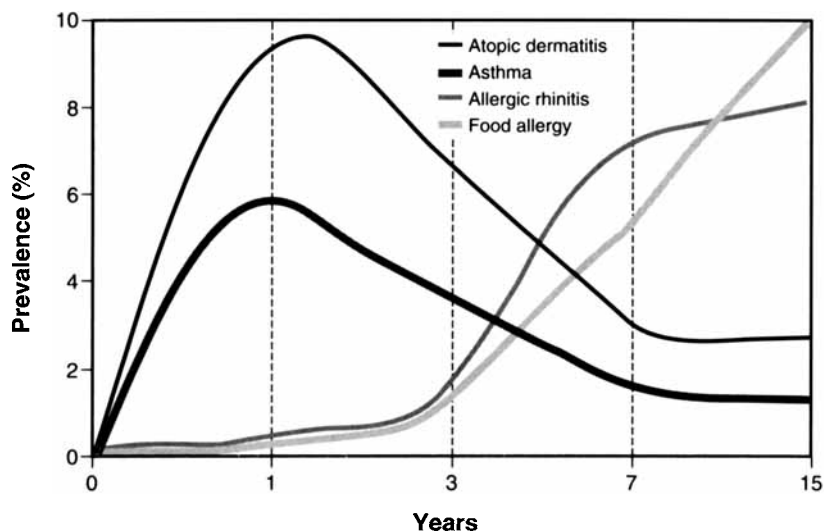


Figure 1. Relative prevalence of allergic disease. (From Food hypersensitivity reactions [slide show]. Current Views in Allergy and Immunology 21, January 1993; with permission.)

be implemented. Many immunological markers have been examined, including umbilical cord total IgE levels,^{8, 32, 35} serum IgE levels in infancy,⁴⁰ serum-specific IgE levels,^{11, 40} blood eosinophilia in infancy,⁷ serum eosinophil cationic protein in infancy,³⁷ and serum gamma-interferon/interleukin-4 ratios.^{6, 65}

Many of these markers are helpful as research tools. As early as 11 weeks, IgE production has been detected in fetal liver and lungs.⁴⁷ The clinical relevance is unknown. Similarly, specific IgE to parasites has been observed prenatally, whereas an IgE response to common food or inhalant allergens does not develop during fetal life.⁶⁸

A prospective study followed nearly 1700 children from birth through the age of 11 years.³⁵ The best predictors for development of an atopic disease were an elevated umbilical cord IgE level and a positive family history. In this group of children, 76% developed allergic disease. For children with only a history of elevated umbilical cord IgE level, 58% subsequently developed allergic disease, although 38% of the children with only a family history developed allergies. A more recent study followed 129 newborns through the age of 18 months for subsequent allergy development.⁵³ The sensitivity of using cord blood IgE levels and eosinophil counts ranged from 25% to 79%, with a specificity ranging from 40% to 74%. If infants had a combination of dry skin, a history of two or more atopic family members, and an elevated umbilical cord IgE level, the chance of developing allergy was 89%. Umbilical cord IgE levels greater than 1.0 IU/mL appear to correlate well with the atopic diathesis⁸; however, analysis of umbilical cord IgE level can be con-

founded by contamination with maternal blood or inaccurate laboratory technique.⁵⁴

It appears that in most clinical settings, a family history of atopy is most predictive in identifying high-risk infants. Umbilical cord IgE level is reserved for research studies. The predictive value of family history is highest if allergy is found in either parents or siblings and less predictive if extended family members are affected.

THE ROLE OF GENETICS

Epidemiological, family, and twin studies provide evidence that genetic factors are involved in the propensity for atopy. For example, if one parent has allergies, the risk is 25% to 40% that the child has some atopic disease; if both parents have allergies, the risk increases to 50% to 70%.²² Nevertheless, as demonstrated in other studies, genetic factors are not the only factors responsible for developing allergies. A large twin study examined the concordance rates for allergic diseases in almost 7000 twin pairs.⁴¹ As expected, the rates for asthma, allergic rhinitis, and eczema were higher for monozygotic twins compared with dizygotic twins; however, even the concordance rates in monozygotic twins ranged from 15% to 21%, suggesting that other factors are contributory.

Recently, several cytokines with the potential to influence IgE production have been identified; these cytokines are encoded on chromosome 5q.^{43, 55} In the future, it may become possible to target genetic markers not only to identify atopic individuals but also to intervene.

SEASON OF BIRTH

The season of birth and its effect on allergy development have been investigated. A recently published study found increased prevalence of IgE antibody to food and dander in children born from September through February.⁵¹ Pollen sensitization was least common for children born in the spring.

Children born in the months prior to the pollen season may develop pollen sensitivity and allergic rhinitis more frequently than children born during the pollen season,⁷⁰ although this is not always consistent.⁵⁹

FAMILY SIZE

Large family size appears to have a preventive effect against allergic sensitization. An inverse relationship has been described between the number of older siblings and the incidence of hay fever.⁵⁶ A recent retrospective survey of more than 11,000 Italian men aged 18 to 24 years also found an inverse relationship between prevalence of atopy and number of siblings.⁴⁵ The prevalence of atopy was 25% in those men

without siblings compared with 9% in the men with five or more siblings. The theory contends that infections acquired early in infancy or during childhood might prevent development of atopy later in life. The shift from Th2 lymphocytes to Th1 lymphocytes occurs with infections.⁶¹ Therefore, children born into large families would be exposed to more illnesses and less likely to become allergic.

INFANT IMMUNIZATIONS

Researchers have attempted to link some component of infant immunization as a risk factor for the development of asthma in childhood. The published reports are inconsistent, however. In one study, more than 1200 New Zealand children were followed.³³ Only 23 children had not received immunizations for diphtheria/pertussis and polio at the ages of 3 and 5 months, respectively, and for measles/mumps/rubella at the age of 12 to 15 months. Prior to the age of 10 years, these 23 children had no documented episodes of asthma, supposedly supporting an inverse relationship between immunization and allergic disease. An important limitation of this study was the size of the nonvaccinated group. Another study suggested that pertussis vaccination increased the risk of asthma, whereas a randomized trial of two types of acellular pertussis vaccine, whole-cell pertussis vaccine, and no vaccine showed no difference in wheezing or rhinitis symptoms at 2 years of age.^{50, 52}

The risk factors that have been discussed thus far cannot be easily altered, and the likelihood of manipulation of these factors to prevent atopic sensitization is small. An area that has received much interest because of the more realistic likelihood of making modifications is diet.

ROLE OF DIET

The effect of diet has been evaluated with regard to maternal diet during pregnancy, maternal diet during lactation, breast-feeding, infant formulas, and solid food introduction. Each of these areas is discussed below.

Two prospective, randomized, controlled studies compared third trimester pregnancy maternal diets. One of the studies followed 197 high-risk atopic infants and altered the maternal diet during the third trimester so that eggs and cow's milk were excluded.¹⁸⁻²⁰ No effect on food-specific or total serum IgE was found in the offspring up to the age of 5 years. The other study randomized 171 pregnant women with a history of respiratory allergy symptoms into two groups.^{39, 40} One group ingested small amounts of eggs and cow's milk during the third trimester, and the other group ingested eggs and dairy products daily. Again, the maternal avoidance diet failed to show any effect on infant atopy or IgE levels. The conclusion of these studies is that third trimester maternal allergen avoidance diets fail to alter the clinical development of

allergic disease in high-risk infants. Maternal dietary avoidance regimens during pregnancy should not be recommended as a way to prevent allergies.

Human breast milk is considered the optimum nutrition for infants. The benefits of breast-feeding include nutritional, immunological, psychological, and intestinal factors. It is unclear if breast milk modifies the development of food allergies and other atopic disease, as there are design limitations in studies which preclude definitive conclusions.

One of the first studies to report that breast-feeding could prevent allergic disease was reported in 1936.²³ In a cohort of nearly 20,000 infants, exclusive breast-feeding reduced the incidence of atopic dermatitis sevenfold compared with that in children who drank cow's milk exclusively.

Recently, a Finnish group studied human breast milk as a prophylaxis against atopic disease.⁵⁷ They studied 150 infants up to the age of 17 years. The children were categorized by the length of time breast-fed: less than 1 month, 1 to 6 months, and greater than 6 months. Overall, the prevalence rates for atopy were 65%, 36%, and 42%, respectively. Atopic eczema was least prevalent at the ages of 1 and 3 years in the group of children breast-fed longer than 6 months. A 20-year follow-up study showed similar results. Long-term prognosis of childhood asthma was better in children breast-fed longer than 2 months as compared with those breast-fed less than 1 week⁴; however, the conclusions of these studies must be moderated, as the study design failed to randomize groups.

One prospective randomized study compared the development of allergy in a group of preterm infants fed either human milk or cow's milk.⁴² For the neonates at high risk because of family history, those fed cow's milk showed an increased risk of eczema at the age of 18 months.

If breast-feeding is best, what, if any, is the role of avoidance diets in lactating mothers? Bovine milk antigens,^{1, 11, 12, 31, 34, 64} egg ovalbumin,^{11, 12, 34} and gliadin⁶⁶ have been detected in human milk 2 to 6 hours after maternal consumption of milk, egg, and wheat. Small amounts of protein from food ingested by the mother can pass through her milk and potentially lead to allergic sensitization. Recognition of this potential led to two prospective controlled studies of maternal avoidance diets during lactation. First, the effect of maternal avoidance of eggs, cow's milk, and fish during the first 3 months of lactation was studied.^{25-27, 62} The infants' diet consisted of human breast milk or Nutramigen (Mead-Johnson, Evansville, IN) until they were 6 months of age, with cow's milk introduced after they reached 6 months of age and eggs and fish introduced after they reached 9 months of age. The infants were followed from birth until the age of 10 years. Although the incidence and severity of atopic dermatitis were less in the first 6 months of life in infants with a history of atopy, a reduction in eczema was not seen in these children at the age of 18 months or 10 years. There were no differences in skin test results or other manifestations of atopy.

In the other prospective randomized study, cow's milk, eggs, peanuts, soy, and fish were eliminated during the entire lactation period,

and the infants were followed until they were 18 months of age.¹⁶ Only 22% of the infants whose mothers were on the restricted diet had eczema compared with 48% of the infants whose mothers were not restricting their diet. Maternal avoidance diets during lactation appear to have a preventive effect on atopic dermatitis, especially in the first 1 to 2 years of life.

Other studies have examined the role of infant formula and the development of allergies. Randomized prospective studies of atopic-prone infants fail to show a reduction in atopy when soy formula is substituted for cow's milk.^{15, 36} Soy formula does not appear to be hypoallergenic; therefore, soy milk should not be used for the purpose of milk allergy prophylaxis.

Available protein hydrolysate formulas may be substituted for purposes of allergy prevention. Both Nutramigen and Alimentum (Ross, Abbott Laboratories, Columbus, OH) are casein hydrolysates and have been defined by the American Academy of Pediatrics as hypoallergenic.⁵⁷ The safety and hypoallergenicity of Nutramigen have been documented during more than 50 years of commercial use in milk protein allergic infants and children⁷¹; however, allergic reactions have rarely been reported.^{8, 38} Therefore, the introduction of casein hydrolysate formulas should occur under the supervision of physicians knowledgeable about food allergies and experienced in treating anaphylaxis. On the other hand, Good Start (Carnation, Nestlé USA, Inc., Glendale, CA), a partial whey hydrolysate formula, has been shown to frequently induce allergic reactions in infants with cow's milk protein allergy.¹⁰ For infants at high risk for developing allergies, protein hydrolysate formulas may be used in an attempt to prevent food allergy. High-risk infants fed either protein hydrolysate formula or cow's milk formula from birth in non-breast-fed infants or as a supplement in breast-fed infants revealed a lower incidence of cow's milk allergy and serum-specific milk IgE at 1 year of age.⁷⁴

Diet manipulation by delaying introduction of solid foods has been practiced for years. It has been suggested that early introduction of solid foods may increase the risk of an infant developing an allergy. In an uncontrolled prospective study, more than 1200 neonates were followed for 10 years for development of atopy.²¹ The children exposed to solid foods during the first 4 months of life had a threefold increase in eczema compared with those children not exposed to early solid food feeding practices. This relationship was evident at the age of 2 years and appeared to continue until the age of 10 years.

A randomized, controlled, prospective study of combined maternal and infant allergen avoidance was conducted in nearly 300 children.^{72, 74} More than half were available for follow-up at the age of 7 years. The treatment group consisted of mothers who avoided cow's milk, peanuts, and eggs during the last trimester of pregnancy and lactation and infants who avoided cow's milk until they reached the age of 1 year, eggs until they reached the age of 2 years, and peanuts and fish until they reached the age of 3 years. Casein hydrolysate supplementation was used prior to the age of 1 year. The control group consisted of maternal/infant

pairs without specific elimination diets. A significant reduction in food allergy and milk sensitization was found in infants before the age of 2 years, but these differences subsequently disappeared. By the age of 7 years, there were no differences between the two groups in terms of food allergy, atopic dermatitis, allergic rhinitis, or asthma.

A group from the Isle of Wight added dust mite avoidance strategies to the maternal and infant food allergen avoidance protocol.^{1, 28, 29} This prospective, randomized, controlled study found that infants in the avoidance group had a significant reduction in eczema and asthma at 1 year of age. By the ages of 2 and 4 years, the reduction in asthma was not statistically significant, but a reduction in eczema was still evident. The control children also had more positive skin prick tests to dietary and environmental allergens than the children in the prophylactic group at the ages of 2 and 4 years.

ENVIRONMENTAL EXPOSURES

Environmental exposures to tobacco smoke and indoor allergens have been implicated in allergic sensitization. The association of maternal smoking with higher rates of asthma and onset of asthma at an earlier age is well described.^{17, 24, 44, 69} More than 1000 infants were followed prospectively through their first year for development of atopy.² Maternal smoking was the single most important risk factor for the development of asthma. In those infants of smoking mothers, the prevalence rate of asthma was 17.8% compared with 7.8% for infants of nonsmoking mothers.

A recent study found that maternal smoking during pregnancy and lactation was associated with an increased risk of atopic eczema.⁶⁰ A questionnaire was completed by the parents of over 600 preschool-aged children which asked them to recall maternal smoking history during pregnancy and lactation. Fifty-two percent of children whose mothers had smoked during pregnancy and lactation manifested atopic dermatitis in contrast to 35% of children of nonsmoking mothers. In another study, children with atopic eczema whose mothers smoked were more likely to develop asthma.⁴⁹

Early exposure to indoor allergens as a potential risk factor has also been assessed. The relationship between exposure to house dust mite allergen and the development of infant sensitization and asthma was evaluated in nearly 70 high-risk children followed to the age of 11 years.⁶³ Children who were exposed to high levels of dust mites ($>10 \mu\text{g Der p I}$ per gram of dust) as infants were more likely to develop dust mite sensitivity and asthma than those not exposed to these levels.

Further studies have investigated this relationship. In one study 1314 newborns were followed prospectively for their first 36 months of life.⁶⁷ Dust mite and cat allergen levels in the home were measured at intervals. The early induction of sensitization to indoor allergens during infancy and early childhood correlated with dust mite or cat allergen

exposure. Another study prospectively investigated the relationship between exposure to cats, dogs, and house dust mites and sensitivity at 5 years of age in 86 high-risk children.⁴⁸ Investigators discovered that sensitization to indoor allergens may occur at lower house dust allergen levels than previously suggested. The majority of the children sensitized to cat dander were exposed to less than 1 µg of cat allergen per gram of dust, whereas previous studies suggest *Fel d* I levels greater than 8 µg/g of dust as a critical sensitization level. Dog allergen levels as low as 1.5 µg/g of dust were associated with sensitivity.

CONCLUSIONS

Atopy is a genetically inherited trait whose expression is dependent on exposure. Although genetic engineering holds promise for absolute prevention in the future, our current approach must rely on reductions in allergen exposure.

A family history of allergy should be elicited, preferably at the prenatal visit. Realistically, most families take precautionary steps after already having one severely affected child in hopes of preventing allergic disease in siblings. In allergy-prone families, breast-feeding should be encouraged, especially for the first 6 to 12 months of life and possibly with a restricted maternal diet excluding peanuts, tree nuts, and fish. These foods are relatively easy to avoid and may lead to a lifelong sensitivity as compared with milk, egg, and soy allergies, which are typically outgrown. In infants not fed human breast milk, protein hydrolysate formulas such as Nutramigen and Alimentum should be considered rather than cow's milk, goat's milk, or soy formula. The introduction of solid foods should be delayed until the child is 4 to 6 months of age. Each food should be introduced individually so that parents can identify and eliminate those foods that cause a reaction. It may be best to avoid eggs through the age of 2 years and peanuts, tree nuts, and fish through the age of 3 years. Dust mite and pet dander avoidance measures may help to reduce the occurrence of subsequent atopic development. Finally, it is imperative that children not be exposed to secondhand tobacco smoke prenatally or during childhood. Although it is not possible to prevent allergies completely in young children, these preventive strategies may help to reduce or delay the occurrence of atopic disorders.

References

1. Arshad SH, Hide DW: Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 90:235-241, 1992
2. Arshad SH, Matthews S, Gant C, et al: Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 339:1493-1497, 1992
3. Axelsson I, Jakobsson I, Lindberg T, et al: Bovine β-lactoglobulin in human milk. *Acta Paediatr Scand* 75:702-707, 1986
4. Blair H: Natural history of childhood asthma. *Arch Dis Child* 52:613-619, 1977

5. Bock SA: Probable allergic reaction to casein hydrolysate formula [letter]. *J Allergy Clin Immunol* 84:272, 1989
6. Borres MP, Einarsson R, Björkstén B: Serum levels of interleukin-4, soluble CD23 and IFN γ in relation to the development of allergic disease during the first 18 months of life. *Clin Exp Allergy* 25:543-548, 1995
7. Borres MP, Odelram H, Irander K, et al: Peripheral blood eosinophilia in infants at 3 months of age is associated with subsequent development of atopic disease in early childhood. *J Allergy Clin Immunol* 95:694-698, 1995
8. Bousquet J, Menardo JL, Viala JL, et al: Predictive value of cord serum IgE determination in the development of 'early-onset' atopy. *Ann Allergy* 51:291-295, 1983
9. Burney PGJ, Bousquet J, Blumenthal M, et al: Evidence for an increase in atopic disease and possible causes. *Clin Exp Allergy* 23:484-492, 1993
10. Businco L, Cantani A, Longhi A, et al: Anaphylactic reactions to cow's milk whey protein hydrolysate (Alfa-Re, Nestle) in infants with cow's milk allergy. *Ann Allergy* 62:333-335, 1989
11. Cant A, Marsden RA, Kilshaw PJ: Egg and cow's milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk. *BMJ* 291:932-935, 1985
12. Cavagni G, Paganelli R, Caffarelli C, et al: Passage of food antigens into circulation of breast-fed infants with atopic dermatitis. *Ann Allergy* 61:361-365, 1988
13. Centers for Disease Control and Prevention: Asthma-United States, 1989-1992. *MMWR* 43:952-955, 1995
14. Centers for Disease Control and Prevention: Asthma mortality and hospitalization among children and young adults-United States, 1990-1993. *MMWR* 45:350-353, 1996
15. Chandra RK, Singa G, Shridhara B: Effect of feeding whey hydrolysate, soy, and conventional cow's milk formulas on incidence of atopic disease in high risk infants. *Ann Allergy* 63:102-106, 1989
16. Chandra RK, Puri S, Hamed A: Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 299:228-230, 1989
17. Dekker C, Dales R, Bartlett S, et al: Childhood asthma and indoor environment. *Chest* 100:922-926, 1991
18. Faith-Magnusson K, Kjellman N-IM: Allergy prevention by maternal elimination diet during pregnancy: A 5 year follow-up of a randomized study. *J Allergy Clin Immunol* 89:709-713, 1992
19. Faith-Magnusson K, Kjellman N-IM: Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy: A randomized study. *J Allergy Clin Immunol* 80:868-875, 1987
20. Faith-Magnusson K, Kjellman N-IM, Magnusson KE: Antibodies IgG, IgA, and IgM to food antigens during the first 18 months of life in relation to feeding and development of atopic disease. *J Allergy Clin Immunol* 81:743-749, 1988
21. Fergusson DM, Horwood J, Shannon FT: Early solid feeding and recurrent childhood eczema: A 10-year longitudinal study. *Pediatrics* 86:541-546, 1990
22. Gerrard JW, Ko CG, Vickers P, et al: The familial incidence of allergic disease. *Ann Allergy* 36:10-15, 1976
23. Grulee CG, Sanford HN: The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 9:223-225, 1936
24. Halken S, Høst A, Nilsson L, et al: Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 50:97-105, 1995
25. Hattevig G, Sigurs N, Kjellman B: Maternal food antigen avoidance during lactation and allergy during the first 10 years of age [abstract]. *J Allergy Clin Immunol* 97(Part 3):241, 1996
26. Hattevig G, Kjellman B, Sigurs N, et al: Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 19:27-32, 1989
27. Hattevig G, Kjellman B, Sigurs N, et al: The effect of maternal avoidance of eggs, cow's milk, and fish during lactation on the development of IgE, IgG, and IgA antibodies in infants. *J Allergy Clin Immunol* 85:108-115, 1990

28. Hide DW, Matthews S, Tariq S, et al: Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 51:89-93, 1996
29. Hide DW, Matthews S, Matthews L, et al: Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 93:842-846, 1994
30. Hopper JL, Jenkins MA, Carlin JB, et al: Increase in the self-reported prevalence of asthma and hay fever in adults over the last generation: A matched parent offspring study. *Aust J Public Health* 19:120-124, 1995
31. Jakobsson I, Lindberg T, Benediktsson B, et al: Dietary bovine β -lactoglobulin is transferred to human milk. *Acta Paediatr Scand* 74:342-345, 1985
32. Johnson CC, Ownby D, Peterson EL: Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy* 26:624-629, 1996
33. Kemp T, Pearce N, Fitzharris P, et al: Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 8:678-680, 1997
34. Kilshaw PJ, Cant AJ: The passage of maternal dietary proteins in human breast milk. *Int Arch Allergy Appl Immunol* 75:8-15, 1984
35. Kjellman N-IM, Croner S: Cord blood IgE determination for allergy prediction: A follow-up to seven years of age in 1651 children. *Ann Allergy* 53:167-171, 1984
36. Kjellman N-IM, Johansson SGO: Soy versus cow's milk in infants with a biparental history of atopic disease: Development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin Allergy* 9:347-358, 1979
37. Koller DY, Wojnarowski C, Herkner KR, et al: High levels of eosinophil cationic protein in wheezing infants predict the development of asthma. *J Allergy Clin Immunol* 99:752-756, 1997
38. Lifschütz CH, Hawkins HK, Guerra C, et al: Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. *J Pediatr Gastroenterol Nutr* 7:141-144, 1988
39. Lilja G, Dannaus A, Foucard T, et al: Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age: In-vivo results. *Clin Exp Allergy* 19:473-479, 1989
40. Lilja G, Dannaus A, Foucard T, et al: Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants. *Clin Exp Allergy* 21:195-202, 1991
41. Lubs M-LE: Empiric risks for genetic counseling in families with allergy. *J Pediatr* 80:26-31, 1972
42. Lucas A, Brooke OG, Morley R, et al: Early diet of preterm infants and development of allergic or atopic disease: Randomised prospective study. *BMJ* 300:837-840, 1990
43. Marsh DG, Neely JD, Breazeale BG, et al: Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 264:1152-1156, 1994
44. Martinez FD, Cline M, Burrows B: Increased incidence of asthma in children of smoking mothers. *Pediatrics* 89:21-26, 1992
45. Matricardi PM, Franzinelli F, Franco A, et al: Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 101:439-444, 1998
46. Michel FB, Bousquet J, Greiller P, et al: Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic disease in infancy. *J Allergy Clin Immunol* 65:422-430, 1980
47. Miller DL, Hirvonen T, Gitlin D: Synthesis of IgE by the human conceptus. *J Allergy Clin Immunol* 52:182-188, 1973
48. Munir AKM, Kjellman N-IM, Björkstén B: Exposure to indoor allergens in early infancy and sensitization. *J Allergy Clin Immunol* 100:177-181, 1997
49. Murray A, Morrison B: It is children with atopic dermatitis who develop asthma more frequently if the mother smokes. *J Allergy Clin Immunol* 86:732-739, 1990
50. Nilsson L, Kjellman N-IM, Storsaeter J, et al: Lack of association between pertussis vaccination and symptoms of asthma and allergy [letter]. *JAMA* 275:760, 1996
51. Nilsson L, Björkstén B, Hattveig G, et al: Season of birth as predictor of atopic manifestations. *Arch Dis Child* 76:341-344, 1997
52. Odent MR, Culpin EE, Kimmel T: Pertussis vaccination and asthma: Is there a link [letter]? *JAMA* 272:592-593, 1994

53. Olderam H, Björkstén B, Leander E, et al: Predictors of atopy in newborn babies. *Allergy* 50:585-592, 1995
54. Ownby DR: Clinical significance of IgE. In Middleton E, Jr, Reed CE, Ellis EF, et al (eds): *Allergy Principles and Practice*, ed 4. St Louis, Mosby, 1993, pp 1059-1076
55. Postma DS, Bleeker ER, Amelung PJ, et al: Genetic susceptibility to asthma-bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 333:894-900, 1995
56. Räsänen M, Laitinen T, Kaprio J, et al: Hay fever, asthma, and number of older siblings: A twin study. *Clin Exp Allergy* 27:515-518, 1997
57. Saarinen UM, Kajosaari M: Breastfeeding as prophylaxis against atopic disease: Prospective follow-up study until 17 years old. *Lancet* 346:1065-1069, 1995
58. Sampson HA, Bernhisel-Broadbent J, Yang E, et al: Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 118:520-525, 1991
59. Schäfer T, Przybilla B, Ring J, et al: Manifestation of atopy is not related to patient's month of birth. *Allergy* 48:291-294, 1993
60. Schäfer T, Dirschedl P, Kunz B, et al: Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring. *J Am Acad Dermatol* 36:550-556, 1997
61. Shirakawa T, Enomoto T, Shimazu S, et al: The inverse association between tuberculin responses and atopic disorder. *Science* 275:77-79, 1997
62. Sigurs N, Hattevig G, Kjellman B: Maternal avoidance of eggs, cow's milk, and fish during lactation: Effect on allergic manifestations, skin prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics* 89:735-739, 1992
63. Sporik R, Holgate ST, Platts-Mills TAE, et al: Exposure to house-dust mite allergen (*Der p 1*) and the development of asthma in childhood. *N Engl J Med* 323:502-507, 1990
64. Stuart CA, Twiselton R, Nicholas MK, et al: Passage of cows' milk protein in breast milk. *Clin Allergy* 14:533-535, 1984
65. Tang M, Kemp A, Varigos G: IL-4 and interferon-gamma production in children with atopic disease. *Clin Exp Immunol* 92:120-124, 1993
66. Troncone R, Scarcella A, Donatiello A, et al: Passage of gliadin into human breast milk. *Acta Paediatr Scand* 76:453-456, 1987
67. Wahn U, Lau S, Bergmann R, et al: Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 99:763-769, 1997
68. Weil GJ, Hussain R, Kumaraswani V, et al: Prenatal allergic sensitization to helminth antigens in offspring of parasite-infected mothers. *J Clin Invest* 71:1124-1129, 1983
69. Weitzman M, Gortmaker S, Klein-Walker D, et al: Maternal smoking and childhood asthma. *Pediatrics* 85:505-511, 1990
70. Wjst M, Dold S, Reitmeir P, et al: Month of birth and allergic disease at the age of 10. *Clin Exp Allergy* 22:1026-1031, 1992
71. Zeiger RS: Prevention of food allergy and atopic disease. *J R Soc Med* 90(Suppl 30):21-33, 1997
72. Zeiger RS, Heller S: Development of nasal basophilic cells and nasal eosinophils from age 4 months through 4 years in children of atopic parents. *J Allergy Clin Immunol* 91:723-734, 1993
73. Zeiger RS, Heller S: The development and prediction of atopy in high-risk children: Follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 95:1179-1190, 1995

Address reprint requests to

Mary V. Lasley, MD
Northwest Asthma and Allergy Center
4540 Sand Point Way NE, Suite 200
Seattle, WA 98105