

The epidemiology of the atopic child: Who is at risk for what?

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In the past few decades, a number of epidemiologic studies have identified risk factors for the development of allergic disease. Although both maternal and paternal history of allergy are associated with an increased risk of atopy, maternal history of asthma confers the greater risk for childhood asthma, which suggests that environmental factors such as the in utero immunologic environment may confer additional susceptibility. Cytokine profiles at birth may also indicate a predisposition to allergic disease in later childhood. Specifically, low interferon- γ appears to be associated with an increased risk for later development of allergic symptoms and atopic disease. Allergen exposure may also increase the risk of atopic consequences, but the outcome is highly dependent on dose of the allergen, timing of exposure, and, most interestingly, the nature of the allergen in question. Endotoxin exposure during infancy has been associated with increased wheezing during the first years of life, but several studies indicate that early exposure may confer some protection against allergy later in life. Clearly, all these factors should be evaluated in identifying the appropriate prevention measures and treatment for the child who is at risk for allergic disease. (*J Allergy Clin Immunol* 2004;113:S2-7.)

Key words: Allergen, atopic disease, asthma, endotoxin, IL-4, IFN- γ

Researchers have made great strides during the last few years in identifying characteristics of children who are at risk for developing serious atopic disease. It has long been known that both genetic and environmental factors can influence risk for atopy. More recently, research investigating these relationships in greater detail has identified risks that may suggest underlying mechanisms for this increased susceptibility to allergic disease. For example, the finding that maternal history of asthma confers greater risk for asthma in the child directs attention to the early life environment that the mother and infant share.¹ Furthermore, it has been observed that the relationship among environmental factors such as allergen and endotoxin exposure to allergic manifestations may vary with age, being protective in some contexts and adverse in others. The emerging understanding of factors related to allergic disease is important in assessing an individual child's risk for atopy, and identifying appropriate interventions.

Abbreviations used

Bla g 1 or 2: Cockroach allergen
Der p1: House-dust mite allergen
IFN- γ : Interferon- γ
IL: Interleukin
PBMC: Peripheral blood mononuclear cell
T_H2: T-helper 2 cytokines

NATURAL HISTORY OF ALLERGIC DISEASE

Allergic disease may manifest at different stages of childhood as eczema, allergic rhinitis, wheeze, or asthma,² and the prevalence of each condition varies with age. Eczema and wheeze are the most commonly diagnosed atopic conditions in children under the age of 2 years. Asthma becomes more common with increasing age, as does response to skin prick tests (atopy). In fact, a majority of children older than 11 years are atopic.

A second point about allergic disease in childhood is that these conditions are interrelated. For example, the presence of eczema in infancy is associated with greater risk for developing atopic diseases such as asthma later in life. This relation was assessed as part of our Tucson Children's Respiratory Study, a longitudinal investigation of risk factors for asthma among 1246 children enrolled at birth. Eighteen percent of children who had persistent wheezing at age 6 had eczema before 2 years of age, compared with only 7% of children who never wheezed up to this age ($P < .001$).³ Similarly, 57% of those with eczema responded to one or more skin prick tests by 6 years of age, compared with 36% of children who did not have a history of eczema ($P < .001$). These findings suggest that eczema may be an early manifestation of additional atopic diseases later in childhood.

POTENTIAL PRENATAL INFLUENCES ON ATOPIC OUTCOMES

Familial history plays a strong role in the development of atopic disease. However, one of the intriguing things about the role of asthma in the parents is that asthma in the mother confers greater risk for asthma in the child, relative to paternal asthma. Litonjua et al conducted a cross-sectional study examining the relative influence of maternal and paternal asthma on childhood development of asthma in the siblings of those enrolled in the Home Allergen Study.¹ A total of 306 children, 1 to 24 years old, from 217 families with a history of asthma or allergies were evaluated in the study. Having either an asthmatic mother or asthmatic father was associated with a higher risk for asthma among the child. However, of par-

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TABLE. Joint effects of parental conditions and children's age on children's asthma risk factor¹

Parental asthma	Children's age	OR (95% CI)
Neither parent has asthma	<5 y	1.0
Maternal asthma	<5 y	5.0 (1.7-14.9)
	≥5 y	4.6 (1.1-19.0)
Paternal asthma	<5 y	1.6 (0.5-5.9)
	≥5 y	4.1 (1.0-16.0)

ticular interest was the fact that maternal asthma was a greater predictor of childhood asthma than was paternal asthma, with an odds ratio of 4.1 (95% CI, 1.7-10.1) compared with an odds ratio of 2.7 for paternal asthma (95% CI, 1.0-7.2).¹ When the relation was assessed by age (Table), maternal asthma was a greater predictor for asthma in children younger than 5 years (odds ratios of 5.0 vs 1.6 for paternal asthma), but the same effect was not seen in children 5 years of age and older (maternal OR, 4.6 vs paternal OR, 4.1).¹

These findings suggest that there may be preferential transmission of atopic disease through the mother. It has been speculated that one possible mechanism for the enhanced effect of maternal allergy is the transplacental transfer of antigens, maternal antibodies, or maternally derived cytokines. Some studies have shown a relation between maternal exposure to allergens in pregnancy and response at birth of cord blood mononuclear cell to stimulation with that allergen, suggesting that in utero exposure to allergens may influence the capability of the infant to respond immunologically to allergen exposure.^{4,5}

The immune response of infants predisposed towards atopy may be further influenced by the fact that pregnancy is, by nature, a T_H2-skewed environment.⁶ When coupled with the hereditary aspect of atopy, this environment may predispose some infants to a T_H2-biased response at birth.⁶ For example, the peripheral blood mononuclear cells (PBMCs) from infants born into families with a familial history of atopy have a reduced capacity to produce the T_H1 cytokine interferon (IFN)- γ when compared with infants from nonatopic families.^{7,8} But the relations are certainly more complex than suggested by the T_H1-T_H2 paradigm. For example, in the ongoing Tucson Infant Immune Study, umbilical cord blood mononuclear cell cytokine production was assessed for relation with maternal asthma status. Infants born to mothers with a history of asthma had significantly lower levels of *both* interleukin (IL)-4 and IFN- γ (0.435 μ g/mL and 162 μ g/mL, respectively) compared with mothers with no history of asthma (0.62 μ g/mL and 577 μ g/mL, respectively; $P < .05$).

Finally, maternal exposure to infection during pregnancy may also play a role in the development of atopic disease in childhood. A cohort study of 24,690 children younger than 10 years investigated the link between prenatal infection and the risk of childhood asthma, eczema, and hay fever.⁹ Maternal incidence of infection was assessed by the number of antibiotic courses received during pregnancy.⁹ The researchers found that exposure

to antibiotics prenatally is associated with a dose-related increase in the risk of atopic disease.⁹ Odds for asthma associated with two or more courses of antibiotics were 1.68 (95% CI, 1.51-1.87). Additional research is required to determine whether this association is linked to the infection, maternal immune response to the infection, or the antibiotics themselves.

CYTOKINE PROFILES IN INFANCY AND RISK FOR ATOPIC DISEASE

There have been numerous studies linking cytokine profiles at birth to future development of allergic disorders.^{7,10} Because low levels of IFN- γ have been found in adults with allergic disease, decreased IFN- γ is considered by some as a marker for atopic disease. To investigate the relation of early cytokine production to later allergy, cord blood IFN- γ was assessed in 35 newborns who were then followed for one year.⁷ Results showed that infants who either exhibited symptoms of atopic disease or had a positive skin test at one year of age produced significantly less IFN- γ at birth compared with nonatopic infants (Fig 1).⁷ However, it is worth noting that there is a substantial spread of IFN- γ levels for both those with and without manifestations of allergy, indicating that factors other than cytokine profiles at birth influence risk for allergy.

To determine if a skewed T_H2 environment at birth conferred a greater risk for later development of allergies, Prescott et al assessed PBMC proliferative response and cytokine responses to specific allergens and tetanus toxoid every 6 months from birth to 2 years of age.¹⁰ At the end of the study, there were 13 low-risk, nonatopic children and 18 atopic children with physician-diagnosed allergic disease.¹⁰ Both atopic and nonatopic children showed similar proliferative responses after birth. However, nonatopic infants exhibited a gradual decrease up to 18 months of age in IL-4 mRNA response to house-dust mites, whereas no similar decrease was observed for atopic infants.¹⁰ Furthermore, nonatopic children had a marked increase in IFN- γ by 6 months of age, which was significantly greater than that seen in the atopic group.¹⁰

As part of the Tucson Children's Respiratory Study, the link between IFN- γ and IL-2 production by PBMCs during infancy and both parental history of atopy and the development of atopy later in childhood was assessed.¹¹ Infant production of IFN- γ and IL-2 at 9 months of age was inversely related to parental skin test reactivity to seven local allergens.¹¹ When the children in the study underwent skin testing at 6 years of age, an inverse relation was also seen between positive skin test response and IFN- γ and IL-2 production at 9 months (Fig 2).¹¹ These findings suggest that the ability to produce T_H1-type cytokines such as IFN- γ in early life may predict a child's susceptibility to later atopic disease.

ALLERGEN EXPOSURE IN EARLY LIFE

One of the predominant theories explaining the increase in allergic disease worldwide has been that early

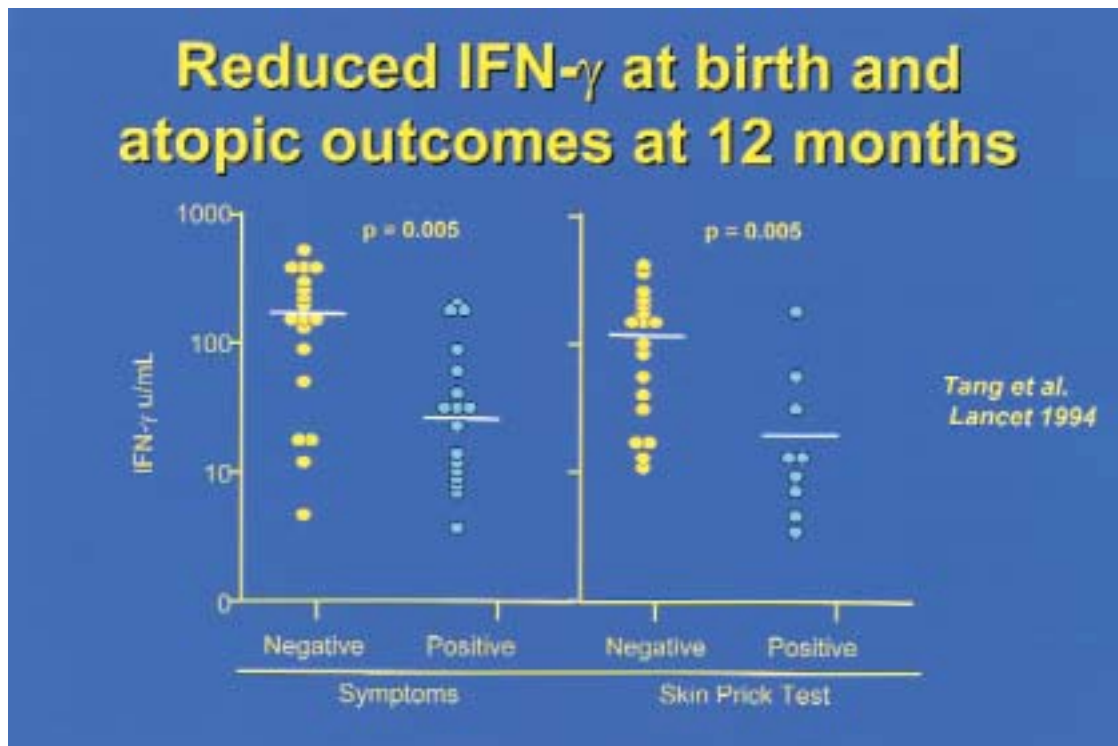


FIG 1. Infants who either exhibited symptoms of allergic disease or who had positive skin tests produced significantly less IFN- γ at birth compared with nonatopic infants. Reprinted with permission from Tang et al. Lancet 1994;334:983-5.

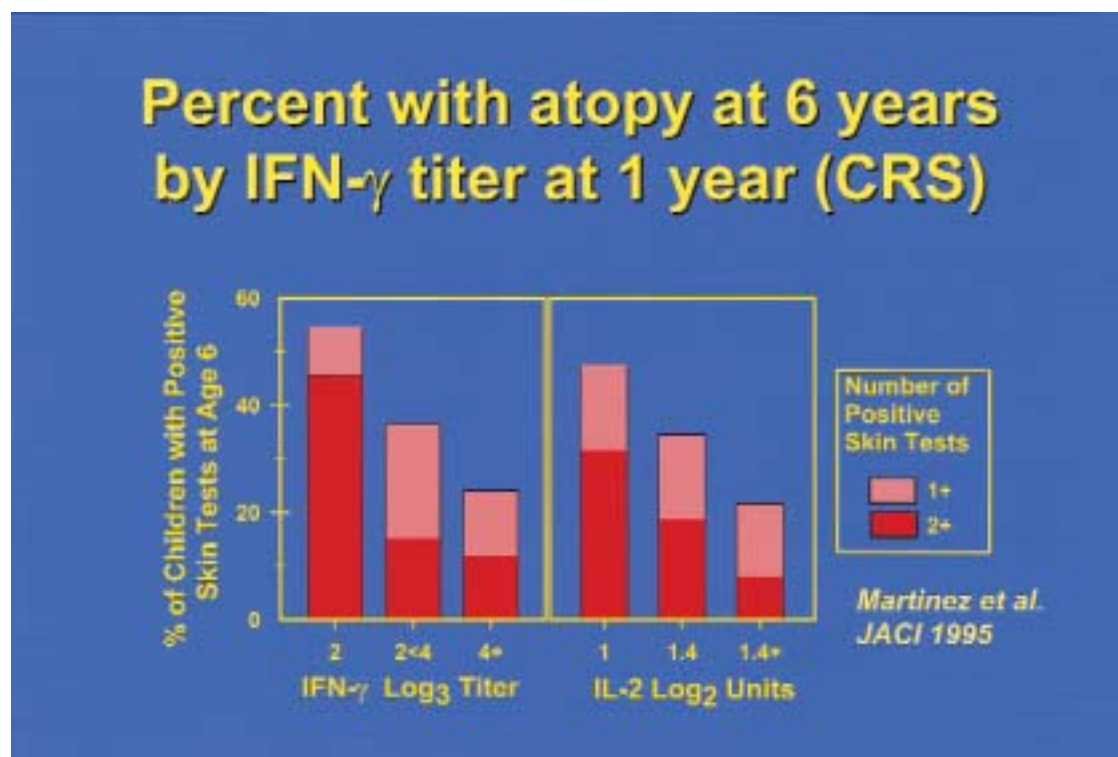


FIG 2. The percentage of children with positive skin tests at age 6 years was inversely correlated to IFN- γ and IL-2 production at 9 months. Adapted with permission from Martinez et al. J Allergy Clin Immunol 1995;96:652-60.

exposure to allergens has changed, which has in turn altered risk for acquisition of atopic disease, particularly asthma.¹²⁻¹⁵ A great deal of research has been conducted regarding this question, with contradictory results depending on the dose of the allergen, the timing of exposure, and characteristics of the specific allergen, as well as susceptibility of the child.

One of the seminal early works in this area concerned the relationship between exposure to house-dust mite allergen (Der p1) and the development of atopic sensitization and asthma in a cohort of children with a family history of atopy.¹² There was a trend toward a dose-response between exposure to Der p1 and degree of sensitization at one year of age.¹² There was also a significant association between sensitization to Der p1 at 11 years of age and asthma by 11 years of age.¹² Most of the children with asthma at 11 years of age had been exposed to more than 10 µg/g of dust during infancy (16 of 17 children).¹² The relative risk of developing asthma by 11 years of age in children who had been sensitized to Der p1 was 5.3 (95% CI, 2.3-12.6).¹² However, it should be pointed out that in a separate study with the same group of children, the investigators showed that the risk for developing asthma was 14.6 (95% CI, 3.9-54) in children who were sensitized to any allergen.¹⁶ This suggests that the association between allergen exposure and risk of allergic disease has more to do with general capacity to mount an allergic response, rather than to levels of exposure to any specific allergen.

Other studies have investigated the relation of allergen exposure to frequent wheeze in early life, which is often one of the early manifestations of asthma.¹³ Although wheeze in the first year of life is usually predicted by factors such as maternal smoking, low birth weight, prematurity, and lower respiratory disease, researchers have hypothesized that environmental factors, particularly exposure to aero-allergens, further augment the risk.¹³ To test this hypothesis, Gold et al prospectively studied a birth cohort of 499 children with asthmatic/allergic parents in the Home Allergen Study.¹³ In a multivariate analysis that adjusted for maternal asthma, dogs in the home, maternal smoking, lower respiratory infection, and low birth weight, Bla g 1 or 2 (cockroach) allergen level in the family room was a significant predictor of having two or more wheezing episodes in the first year of life.¹³ After further adjustments for socioeconomic factors such as income and race, only levels of Bla g 1 or 2 remained a significant predictor for recurrent wheeze.¹³ The relative risk of wheeze in children exposed to at least 0.05 µg of Bla g 1 or 2 was 1.63 (95% CI, 1.05-2.55).¹³ Although these findings suggest that cockroach exposure may increase risk for later asthma, longer follow-up indicates that the risk may change with age. The 226 siblings of subjects in the previous study were assessed for wheeze for a longer interval. In this group, the risk for frequent wheeze associated with Bla g 1 or 2 exposure in the home was no longer significant after 4 years.¹⁵ These findings indicate that a critical variable in the investigation of the relations of allergen exposure to allergic symptoms is the age of the child at the assessment of the allergic outcome.

Effect of family pets on atopy development

The effect of family pets, such as dogs and cats, on the development of atopic disease has been similarly controversial. In their follow-up of siblings to subjects in the Home Allergen Study, Litonjua et al also investigated the independent effects of early life exposure to cats and dogs on the development of wheezing.¹⁴ Having a dog in the home was associated with a reduced risk for frequent wheeze (OR, 0.12; 95% CI, 0.01-0.97), although paradoxically endotoxin exposure (which is elevated in the presence of dogs) was associated with an increased risk of frequent wheeze (OR, 2.57; CI, 1.00-6.62). Of particular interest, however, was the finding that the risk of wheeze associated with endotoxin exposure decreased with further follow-up until it became nonsignificant.

The relation between dog exposure and wheezing was also investigated as part of the Tucson Children's Respiratory Study.¹⁷ Children were followed from birth through 13 years of age, and the time to onset of frequent wheeze was assessed. Children living in households with one or more dogs at birth were significantly less likely to develop frequent wheeze compared with children living in households without dogs.¹⁷ Furthermore, when the dog was removed from the home, the apparent protective effect was reduced.

Some of the studies of the relation between exposure to Fel d 1 (cat) allergen and/or cats themselves to the development of wheezing have also suggested a potential protective effect. As part of the Home Allergen Study, Celedón et al showed that in children who did not have a maternal history of asthma, exposure to Fel d 1 concentrations of at least 8 µg/g at the age of 2 to 3 months was associated with a reduced risk of wheezing between the ages of 1 and 5 years.¹⁸ In children with a maternal history of asthma, similar exposures were associated with an increased risk of wheezing by 3 years of age, and the risk associated with cat exposure became greater with increasing duration of follow-up.¹⁸ Because most of the children in the study continued to be exposed to Fel d 1 beyond infancy, it is possible that the repeated exposure to the allergen in combination with maternal history played a more significant role in increasing the risk of atopy, compared with early sensitization to the allergen.¹⁸

MICROBIAL EXPOSURE IN EARLY LIFE

Like allergen exposure, early exposure to microbes and their products has been shown to alter the risk for development of allergic disorders.^{14,19-21} In contrast to the studies of the effects of allergen exposure, which sometimes show an increased risk of atopy, evidence suggests that early microbial exposure and/or infection may actually confer protection against later development of allergic disorders.

Although maternal exposure to infections during pregnancy may increase a child's risk of developing atopy later in life, there is some evidence to suggest that infections in infancy may actually confer protection against

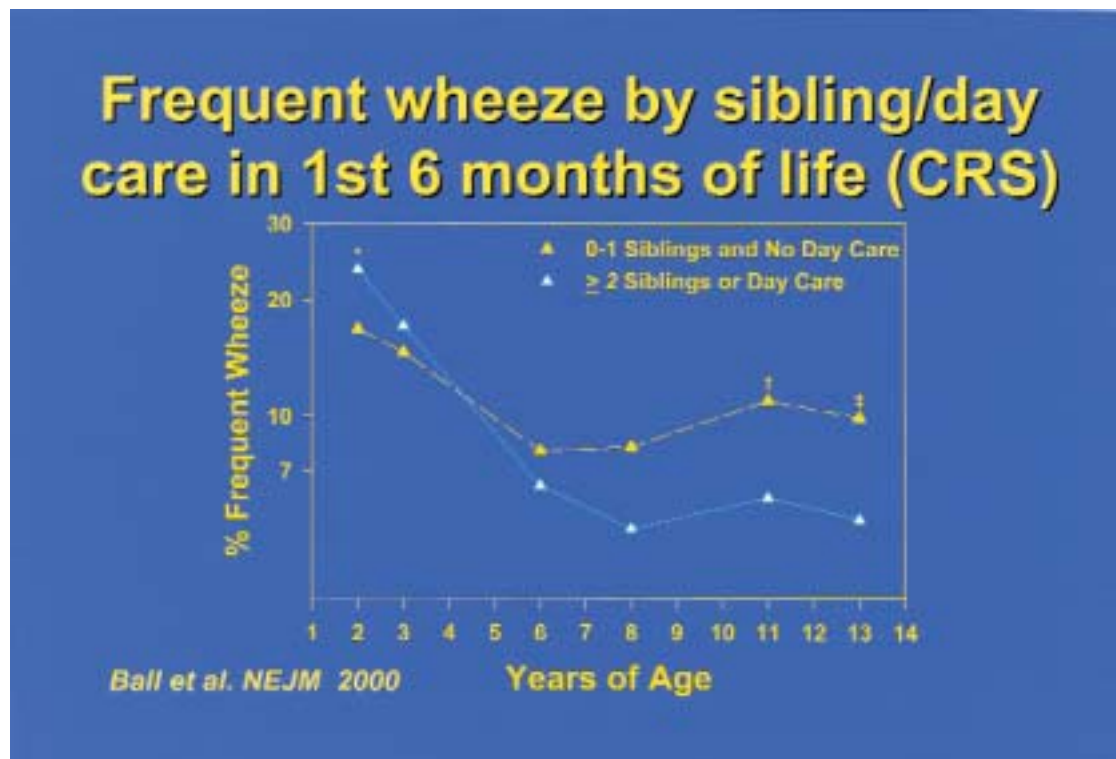


FIG 3. Children with two or more older siblings or who were in large group daycare as infants were more likely to have recurrent wheezing at 2 years of age. However, their risk of recurrent wheezing was significantly decreased beginning at 11 years of age. Adapted with permission from Ball et al. *N Engl J Med* 2000;343:538-43.

the development of asthma later in life. To study this effect, the Tucson Children's Respiratory Study looked at the relationship between asthma in children 6 to 13 years of age and exposure to other children either through other siblings in the home or large group daycare.²⁰ In theory, the greater the exposure to other children, the greater likelihood of exposure to infection. As anticipated, children with older siblings or who were in daycare as infants were more likely to have recurrent wheezing at 2 years of age. However, these children were less likely to have wheezing from 6 to 13 years of age.²⁰ Both the presence of siblings and attendance at daycare during infancy decreased the risk of asthma later in childhood (Fig 3).²⁰ In the case of siblings at home, the relative risk was 0.8 for each additional older sibling (95% CI, 0.7-1.0); in the case of daycare attendance, it was 0.4 (95% CI, 0.2-1.0).²⁰ Therefore, whereas possible increased exposure to infection due to multiple siblings or daycare attendance was initially associated with an increase in wheeze, it appeared to offer protection against later wheezing.²⁰ It is important to note that in addition to showing lower rates of wheeze, children who were exposed to more children in infancy than others also had lower total serum immunoglobulin E levels and a smaller percentage were atopic at age 6.

A cross-sectional survey looked at the effect the farm environment in early life had on the development of wheeze, asthma, and general atopy by 6 to 13 years.¹⁹

The prevalence of asthma was significantly lower among children exposed to stables and farm (ie, unpasteurized) milk during the first year of life, compared with children not exposed to either stables or farm milk in infancy (1% vs 12%, respectively; $P < .05$).¹⁹ A similar pattern was seen in episodes of wheezing, with only 3% of children exposed to both stables and farm milk having more than one wheezing episode in the past year, compared with 15% of children not exposed to either ($P < .05$).¹⁹

The substance proposed as underlying these links between airway disease and exposure to pets and farm animals is endotoxin.²² Endotoxin (or lipopolysaccharide, a component of the cell wall of gram-negative bacteria) stimulates maturation of antigen presenting cells,²³ resulting in production of IL-12, which promotes differentiation of T_H1 -type cells and production of IFN- γ .²⁴ Several studies have shown that house-dust endotoxin exposure in the first years of life increases the incidence of wheezing in infants with a familial history of allergy. In one study, 226 children younger than 5 years were followed for 4 years.¹⁴ Initially, high levels of house-dust endotoxin was associated with an increased risk of recurrent wheeze.¹⁴ However, by the end of the study, the risk had decreased dramatically, with a trend toward being protective. This is consistent with the finding from another study that showed that infants who were atopic had been raised in homes that contained lower levels of house-dust endotoxin compared with homes of nonsensi-

tized infants.²¹ It has also been shown that levels of endotoxin in dust from the mattress are inversely associated to the occurrence of hay fever, atopic asthma, and atopic sensitization.²⁵ In addition, high levels of house dust endotoxin are associated with higher levels of IFN- γ producing CD4 T-cells.^{14,21} Therefore, chronic endotoxin exposure during infancy may provide the stimulus toward enhanced production of T_H1-type cytokines, and thus may provide protection against allergen sensitization later in life.²¹

CONCLUSIONS

Numerous factors need to be considered when determining a profile for risk of the development of atopic disease in childhood. A maternal history of asthma confers greater risk for childhood asthma than does paternal asthma during the early years of life; although the mechanism is not known, an inherited predisposition to allergy may be further augmented by some aspect of the in utero immunologic milieu. There also appear to be alterations in the cytokine profile in cord blood at birth, particularly reductions in IFN- γ production, that may signal a susceptibility to allergic disease in later childhood. Although an infant's allergen exposure may increase the risk of atopic consequences, the outcome is highly dependent on the dose received, timing of exposure, and susceptibility of the child. Endotoxin exposure early in life is associated with an increase of recurrent wheezing during the first years of life, but it appears to confer protection from allergy later in life. Although each of these factors needs to be considered when evaluating the at-risk child, assessing factors individually only offers a single piece of the puzzle. Rather, evaluating each factor in the context of all the others should provide a more comprehensive picture that can assist in the determination of appropriate therapy.

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