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The current paradigm of allergy pathogenesis is that allergy develops in individuals with a genetic predisposition only after they are exposed to allergens (Fig. 1). This hypothesis implies that factors in the environment can determine the initiation of allergic sensitization and can potentially influence the clinical manifestations and severity of disease. Because the prevalence of atopic diseases such as allergic rhinitis, asthma, atopic dermatitis, and food allergy have increased worldwide in the past several decades, and there is no mechanism for changes in population genetics over this short period of time, changes in the human environment are most likely responsible for these trends. From this line of reasoning, it follows that if the factors responsible for the increasing prevalence can be identified, then there would be an opportunity to develop strategies to reverse these trends. It also would be helpful to identify infants who are at risk for developing allergy, so that preventive strategies could be used most effectively.

In this article, studies to determine the contributions of genetics and the environment to the development of allergic diseases in childhood are explored. In addition, progress in identifying risk factors for allergy and preventive therapies for those children at risk are also addressed.

THE DEVELOPMENT OF ALLERGY IN CHILDREN

Genetic Factors

Atpy, or the genetic predisposition to produce antigen-specific IgE after exposure to an allergen, is a common component of atopic diseases, such as

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asthma, allergic rhinitis, food allergy, and atopic dermatitis. In addition, pathogenic factors common to allergic disorders include acute and chronic inflammation involving mast cells, basophils, allergen-specific T cells, and activated eosinophils. Many of the genes for the cytokines and receptors that regulate allergic inflammation are clustered on a short segment of chromosome 5q, and linkage of total serum IgE levels to these genes has been demonstrated in some kindreds. In contrast, production of IgE specific for many of the common pollen and pet allergens has been linked to certain human leukocyte antigen (HLA) Class II molecules located on chromosome 6. These data indicate that the inheritance of allergic disorders is multifactorial. Furthermore, there appear to be additional factors that influence whether a person born into an atopic family will develop allergic rhinitis, asthma, atopic dermatitis, or some combination of these disorders. For example, Dold et al found that families that included one parent with atopic dermatitis were more likely to have a child with atopic dermatitis (odds ratio [OR] 3.4) than were families with one parent with either asthma (OR 1.5) or allergic rhinitis (OR 1.4). Similar trends were observed when inheritance of asthma or atopic dermatitis was examined, and these findings suggest that there are specific genetic or environmental factors that influence which organ system(s) are affected by allergy. In support of this concept, genes within chromosome 5q and elsewhere have been linked to the development of bronchial hyperresponsiveness, a key feature of asthma.

**Cytokine Abnormalities Associated with Allergy and Asthma**

The atopic trait can be defined in a number of ways: total serum IgE antibody levels, allergen-specific antibody levels using skin tests or radio-
allergosorbent tests (RAST), and most recently, by a characteristic pattern of cytokine secretion, the T helper 2 (Th-2)-like response, noted in both rodent and human studies. In this regard, the Th-1 or Th-2 paradigm of lymphocyte cytokine elaboration has received considerable attention as a marker associated with atopy and as a contributor to the pathogenesis of acute and chronic allergic inflammation.

Based on original work in rodents, lymphocyte cytokine elaboration has been divided by many groups into a Th-1 (interleukin [IL]-2, interferon [IFN]-γ, IL-12), Th-2 (IL-4, IL-5, IL-13), and most recently, a Tc-2 pattern of response. Although this paradigm has received criticism for its simplicity in terms of the overall immune cytokine network, many groups have considered it as a useful starting point in unraveling the pathogenesis of allergic inflammation. The Th-2 pattern of response has been found in tissue samples obtained at sites of allergic or parasitic inflammation, whereas the Th-1 response has been more associated with delayed hypersensitivity and response to virus infections. The Th-1 and Th-2 profiles of response appear to be reciprocally regulated.

From data obtained using specific mRNA or absolute levels (IFN-γ, IL-4, IL-5) or ratios (IL-4/IFN-γ) of Th-1 and Th-2 cytokines in various biologic tissues and fluids, it has been proposed that an imbalance, or immunologic deviation, favoring a Th-2 cytokine profile is associated with allergic disorders. Various investigators have noted that this Th-2 polarization is established during infancy and early childhood; indeed, some have noted that diminished IFN-γ production can be demonstrable in cord blood of infants at high risk of developing allergic disease based on parental histories of atopy. Perhaps most importantly, infants with this type of IFN-γ profile have a significantly increased risk of going on to develop atopic diseases including both eczema and asthma.

With a particular profile of Th-1 or Th-2 cytokines appearing to be characteristic of atopy, recent work has focused on how this response may be regulated, and perhaps dysfunctional, in atopic or asthmatic patients. Because IFN-γ production appears to be abnormal in a number of studies, regulation of this cytokine has been evaluated. Two cytokines, IL-12 and IL-18 (IFN-γ inducing factor), are potent stimulators of IFN-γ production. Interestingly, cord blood mononuclear cells have been noted to produce less IL-12 mRNA and protein compared with adult cells, but IFN-γ production in response to IL-12 was similar. Therefore, alterations in IFN-γ production in the developing infant and child may be a reflection, at least in part, in cytokine regulation of its production. Furthermore, it has been noted that atopic asthmatic patients have a deficient IL-12 response when whole blood cultures are stimulated with a strain of Staphylococcus aureus. Taken together, these findings suggest that the observed decreases in IFN-γ production in atopic patients may be related to abnormalities in positive regulatory signals, such as IL-12.

Natural History of Allergen Sensitization

The natural history of allergic diseases provide clues as to the relationship between exposure to allergens and sensitization. Food allergies tend to occur early in life, and together with atopic dermatitis, tend to be the earliest manifestation of allergy. Sensitization to respiratory allergens rarely occurs before 2
years of age, and positive skin tests for indoor allergens such as house dust mite and cat proteins usually precede the development of pollen allergy by several years. This temporal sequence suggests that prolonged contact of high concentrations of allergens with mucosal surfaces provides optimal conditions for allergen sensitization to occur, and this observation has been substantiated in animal models of allergy.

Not surprisingly, patterns of allergen sensitization reflect the geographical or social climate in which the child is raised. For example, peanut allergy is common in the United States but is relatively rare in Scandinavia where per capita peanut consumption is low. The prevalence of fish allergy in children from these two different locations, following patterns of consumption, is reversed. In addition, geographic and climatic conditions are major determinants of the pattern of respiratory allergies. House dust mite allergy is common in humid coastal areas but does not occur in desert climates, where sensitization to Alternaria species is common. In contrast, cockroach allergy is common in inner city areas. Despite obvious differences in the patterns of allergen exposure, the overall prevalence of allergic rhinitis and asthma in coastal and desert regions are similar.

Asthma in children is strongly linked to the development of respiratory allergy. It is estimated that up to 90% of children with asthma have respiratory allergies, especially to indoor allergens such as house dust mite, Alternaria species, cockroach, or cat. In addition, there is a strong correlation between the number of positive skin tests in children and the severity of asthma.

With the recognition that allergy is often a continuum that begins in early infancy, a number of studies have been conducted to determine whether environmental exposures in infancy, or even in utero, can influence the risk of developing allergic diseases and asthma. These studies are discussed in the following sections.

Prenatal Influences

Cytokines in the Uterine Environment

The uterus provides a unique immunologic environment that must foster growth of the developing fetus while protecting it from being rejected by maternal allogeneic T-cell responses. Cytokines generated in the uterus are likely to play a major role in this protective effect. For example, it has been demonstrated in the rodent that IL-4, IL-5, and IL-10 are all produced in the uterus or amnion during pregnancy; similar patterns of cytokine secretion have now been reported in human placental tissue. These cytokines may serve to regulate maternal immune responses that would otherwise be deleterious. For example, IL-4 and IL-5 are Th-2-like cytokines that could downregulate maternal IFN-γ and tumor necrosis factor-alpha (TNF-α), cytokines that could potentiate cytotoxic responses. IL-10, which downregulates both Th-1 and Th-2 cytokine secretion from a variety of cell types, may be even more important for the induction of immune tolerance.

The intrauterine cytokine milieu, which may protect the fetus from cytotoxic immune responses, is likely to also have effects on development of the fetal immune system. High levels of Th-2-like cytokines and IL-10 could reduce secretion of IFN-γ and other Th-1 cytokines from the fetus, as well as the maternal immune system. These activities could have the net effect of biasing the neonatal immune response towards the production of Th-2-like cytokines.
that could promote allergy. This concept is supported by studies of cytokine production from neonatal T cells, which have generally been found to produce relatively low levels of IFN-γ and overproduce Th-2-like cytokines. In addition, if maternal allergy causes a further deviation of the placental immune response towards Th-2-like cytokines, this effect could explain why the risk of developing allergic disease in childhood is more closely related to maternal allergy than to paternal allergy.

**Maternal Diet**

There is experimental evidence to support the concept that allergen sensitization can occur in utero. First, several cases have been reported in which young infants have developed allergic reactions upon their first ingestion of a specific food protein. Considering that IgE does not cross the placenta, one potential explanation for this phenomenon is that sensitization in utero via traces of antigenic proteins that circulate in the maternal circulation cross the placenta and sensitize fetal lymphocytes. To test this hypothesis, several studies have been conducted to detect neonatal allergen sensitization. In support of this, Warner et al demonstrated allergen-specific proliferative responses in cord blood lymphocytes. Although the latter findings suggest that fetal lymphocytes can be activated by allergenic proteins in the maternal circulation, positive responses do not necessarily indicate allergy, and these activated lymphocytes could just as well be cells involved in tolerance. In older children, positive lymphocyte responses to allergens can be found in both allergic and nonallergic individuals and have not been found to be useful discriminators of allergy. Additional research is needed to clarify the significance and predictive value of lymphocyte responses in newborns.

Finally, several clinical studies have tested the hypothesis that modifying the maternal diet during pregnancy could reduce the risk for subsequent allergy in the baby. Although this hypothesis is attractive, two large prospective, randomized, and controlled studies to examine the effect of third trimester hypoallergenic diets have had disappointing results. Both studies excluded egg and cow milk proteins from the maternal diet, and follow-up evaluations of the children up to age 5 years showed no effect on the incidence of cord blood IgE, skin test results, or the incidence of atopic diseases. Studies to evaluate restricting the postnatal diet of children and breast-feeding mothers have been more successful and are discussed later.

**Maternal Cigarette Smoking**

The effects of cigarette smoking on the fetal pulmonary development are multiple. Smoking causes lower birth weights and corresponding reductions in lung size, and small lung size has been identified as a risk factor for wheezing lower respiratory illnesses in infancy. In addition to decreasing lung size, in utero exposure to tobacco smoke has been shown to reduce newborn lung function. To measure this effect, techniques have been developed to measure pulmonary function during resting tidal breathing in babies and infants at a very early age. The outcome variable that has been used most often to study the effects of tobacco on infant pulmonary function is the time to peak tidal expiratory flow as a proportion of the total expiratory time ($T_{PEF}/T_e$); this index measures slowing of expiration by the combination of glottic narrowing and diaphragmatic tone and is reduced in adults with obstructive airway disease. Using these techniques, mild airway obstruction has been detected in infants
born to smoking mothers within 3 days of birth, strongly suggesting that smoking causes reduced pulmonary function in the developing fetus. This concept is further supported by a study of Hoo et al., who evaluated pulmonary function prior to discharge in 108 preterm infants, 40 of whom were born to mothers who smoked during pregnancy. In this study, decreased T
\[\text{T}_{\text{PEF}}\] was associated with exposure to tobacco smoke in utero, but not birth weight or length, and this relationship persisted in the multivariate analysis. Together, these studies provide compelling evidence that maternal cigarette smoking can harm developing lungs both before and after birth, and these effects are likely to contribute to increasing the risk of developing wheezing with viral infections and chronic asthma.

Postnatal Environmental Factors

Diet

The incidence of food allergy is highest in the first few years of life, and because allergic reactions to most foods fade over time, the prevalence of food allergy begins to decrease after 3 years of age. These demographics suggest that prevention of food allergy is attainable if diets are modified to exclude highly allergenic foods during the first few years of life. Furthermore, because food allergy is followed in many cases by the appearance of respiratory allergy and asthma, it is conceivable that preventing food allergy might interrupt this progression.

There have been numerous studies of the effects of dietary restrictions on the prevention of allergic diseases, but the findings of many of these studies are limited by inadequate controls, length of follow-up, or sample size. Two large well-designed studies have examined the effects of combined maternal and infant dietary restrictions, and have instructive findings. Chandra et al. prospectively followed 109 infants with allergic siblings. The mother's diet was restricted (no milk, egg, fish, beef, and peanut) during the third trimester of pregnancy and lactation, and infants were either exclusively breast-fed for 5 to 6 months or ate an unrestricted diet. At the 1-year follow-up visit, the group of children with the restricted diet tended to have a lower prevalence of eczema, and if eczema was present, its severity was significantly reduced.

In a larger prospective study by Zeiger and Heller, children of atopic parents were randomly assigned into an intervention (n = 103) or control (n = 185) group and completed a 2-year evaluation; results have been published for follow-up after 7 years for most of the study subjects. The intervention consisted of maternal avoidance of milk, egg, and wheat, with limited soy and wheat intake during lactation and breast-feeding. In addition, infants in the intervention group were breast-fed or given a casein hydrolysate formula until 12 months of age. Solid foods were introduced starting at age 6 months, but egg protein was withheld until 24 months of age or older, and peanut and fish were started after 36 months of age. Children in the intervention group had less atopic dermatitis and food allergy at 1 year of age (Fig. 2), and allergy to cow's milk was reduced through 2 years of age. By age 7, there were no group-specific differences in the period prevalence of eczema and food allergy. Because of effects before the age of 2 years, the cumulative prevalence of food allergy remained lower at age 7, suggesting that the interventions did more than just delay the onset of food allergy and actually prevented some cases. Notably,
changes in the infant diet did not reduce the incidence of allergic rhinitis and asthma by the age of 7 years.

Together, these studies indicate that a hypoallergenic diet during lactation and infancy can reduce the prevalence of atopic dermatitis and food allergy in the first year or two of life. Considering the fact that other studies have shown that restricting the maternal diet during pregnancy is not helpful, it is clear that the beneficial effects seen in the studies by Chandra and Zeiger were caused by modifications in the postnatal diet. Although these results are promising, the practical significance of these findings is tempered by the fact that these effects were not of long duration, and the subsequent incidence of respiratory allergy
was not affected. The ability to modulate immune responses with infant formula containing nucleotides has recently been of interest; however, its potential ability to influence the development of allergic diseases in infancy and early childhood has yet to be evaluated.

Whether or not breast-feeding can prevent childhood allergy has been debated since the 1930s, when Grulee and Sanford reported that breast-fed infants were at lower risk for developing asthma compared with infants that were fed cow’s milk. Although the numerous studies in the interim have so far failed to resolve this issue, several points are clear. First, because of multiple beneficial effects on growth, development, and the immune system, breast milk is the ideal infant diet and should be advocated regardless of the allergic history of the family. Second, food proteins consumed by the mother can be detected in breast milk, and this low level (nanogram quantities) of food protein is sufficient to cause allergen sensitization and to induce allergic symptoms in a subset of allergy-prone infants. Excluding highly allergenic foods such as cow’s milk and egg from maternal diet during lactation can reduce the infant’s risk of food allergy and eczema and provides a preventive strategy for highly allergic families.

**Exposure to Inhaled Allergens**

Several epidemiologic studies have demonstrated that season of birth influences the subsequent development of respiratory allergy: children born in the spring are at increased risk for developing birch and grass allergy, whereas those born during ragweed season have an increased risk of ragweed allergy. These observations suggest that there may be a period during the first few months of life in which the immune system is particularly susceptible to developing Th-2-like T-cell responses to certain inhaled allergenic proteins. This concept is especially intriguing when one considers the temporal sequence of this process: The early exposure to allergenic proteins initiates a process that is not clinically evident for several years because pollen allergy is rarely diagnosed until children have reached school age. These findings, along with data derived from experimental models of sensitization in animals, suggest that early exposure to inhaled proteins initiate allergen-specific T-cell responses, but additional elements in the immune system, such as dendritic cells or other antigen-presenting cells, must mature before allergy to these proteins can develop. Alternately, the initial allergen-specific T-cell responses may require repeated restimulation, and the intermittent nature of pollen exposure could explain why hay fever takes longer to develop compared with allergy to either foods or perennial inhalants.

Allergy and allergen exposure are closely associated with asthma in children. Observations from the United States and many other locations worldwide documented a close epidemiologic association between allergy to house dust mite and asthma. Furthermore, environmental controls to limit exposure to house dust mite proteins were found to reduce asthma disease activity in carefully controlled studies. Finally, Sporik et al conducted a large prospective study in which dust mite protein levels were measured in a large cohort of homes in the United Kingdom. In this study, the degree of exposure to house dust mite protein during infancy was to an earlier onset of symptoms in children with asthma. Together, these studies provide evidence of a close epidemiologic relationship between house dust mite exposure and childhood asthma and imply a cause and effect relationship, suggesting that if house dust mite exposure could be controlled or eliminated, there would be less asthma. Enthusiasm for this approach has been tempered, however, by subsequent studies that
demonstrated comparable or greater prevalences of allergic rhinitis and asthma in humid environments, where dust mites flourish, and in desert or inner city environments, where exposure to house dust mite protein is reduced or absent.26, 77, 84

**Indoor and Outdoor Air Pollution**

The data linking asthma and allergic rhinitis with exposure to indoor allergens and air pollutants are convincing. The most significant pollutant of indoor air is tobacco smoke, and active or passive exposure to smoke is associated with an increased incidence of many respiratory disorders, including asthma and allergic rhinitis.10, 55, 105, 108

The effect of outdoor air pollution and asthma and allergies is more controversial. Epidemiologic evidence linking increased rates of allergy and asthma to the inner city environment, and even the proximity of the home to major highways, suggests that air pollution enhances allergic sensitization.13, 68 In addition to these findings, there is now experimental evidence that diesel particles, and perhaps other pollutants as well, act as adjuvants to enhance production of Th-2-like cytokines and IgE production in cell culture and in the human in vivo.13, 68 Contrary to these findings, however, is a large study conducted in Germany shortly after reunification.97 German schoolchildren who presumably have a very similar genetic background but live in two different environments were evaluated for allergic sensitization and respiratory diseases. One group of children resided in Munich in the former West Germany, whereas the other group was from Halle, a city in the former East Germany with high levels of air pollution because of the burning of high-sulfur in home furnaces to provide heat. Although the total incidence of respiratory disease was greatest in the group from Halle, asthma and skin test positivity were nearly three times higher in the Munich schoolchildren. This study, like others, indicates that there are factors associated with the Western lifestyle that increase the risk for developing asthma and allergy. Furthermore, pollution did not seem to be associated with greater asthma or allergy. Clearly, air pollution is a complex entity, and it seems likely that individual pollutants may have divergent effects on the risk for developing allergy. Additional information is needed to determine the effects of specific pollutants or combinations of pollutants on rates of allergen sensitization.

**Infectious Diseases**

There is now evidence that viral infections in early childhood may also act on the immune system to modify the subsequent risk of allergen sensitization or asthma.76 For example, several studies have shown that the odds of allergen sensitization are inversely related to the number of older siblings in the family, which presumably determines the frequency of exposures to infectious diseases in early childhood.86, 87, 96 In addition, data from Africa indicate that measles infection in early childhood reduces the risk of allergen sensitization.80 Some bacterial infections may have similar effects: Japanese schoolchildren who develop a strong positive tuberculin skin test after Calmette-Guérin bacillus (BCG) vaccination, possibly signifying exposure to tuberculosis, also have reduced rates of allergy and asthma.81 Vaccination with either BCG or measles virus, however, is not associated with a reduced risk of atopy.1, 81

In contrast to the implications of these studies, data indicate that severe infections with respiratory syncytial virus (RSV) may enhance allergen sensitiza-
tion and the risk of developing asthma. Although not all studies have found RSV infections to increase the risk of allergy, these findings suggest that the effects of infections on the subsequent risk of developing allergies or asthma may depend on which pathogen infects the host early in immune development.

In infants, infection with RSV has received much attention because of its predilection to produce a pattern of symptoms termed bronchiolitis, which parallels many of the characteristics of childhood and adult asthma. RSV causes about 70% of these episodes, and it is estimated that, by 1 year of age, 50% to 65% of children will have been infected with this virus. Children 3 to 6 months of age are most prone to develop lower respiratory tract symptoms, suggesting that a developmental component (e.g., lung or immunologic maturation) may be involved as well.

The relationship between RSV infections during the first year of life and the subsequent development of the asthmatic phenotype has been the subject of much interest as well as controversy. Variations in reporting longitudinal outcomes (e.g., recurrent wheezing, measurements of airway hyperresponsiveness, diagnosis of asthma) appear to be influenced mostly by the criteria used to define bronchiolitis. These criteria include the type of virus producing the symptoms (in addition to RSV, viruses that may contribute to the development of bronchiolitis in this age group could be the parainfluenza virus, coronavirus, influenza virus, and rhinovirus), the age at the time of infection, the nature and severity of symptoms required for inclusion, and finally, the characteristics of both the study population (community versus hospital based) and the study design (retrospective versus prospective).

A number of long-term prospective studies of children admitted to a hospital with documented RSV-induced bronchiolitis have shown that about 75% will experience wheezing in the first 2 years after the initial illness, more than 50% will still wheeze 3 years later, and approximately 40% continue to wheeze after 5 years. Although some groups have found that those children most likely to have persistent wheezing were children born to atopic parents, others have not. Although some have found that personal atopy is not more prevalent in symptomatic children after bronchiolitis, others have found that documented RSV bronchiolitis significantly increases a child’s chances (32% versus 9% in controls) of subsequently developing IgE antibody or lymphocyte proliferative responses to both food and aeroallergens.

RSV infections may interact with immunoinflammatory mechanisms involved in immediate hypersensitivity responses in a number of ways. First, it has been suggested that viruses capable of infecting lower airway epithelium may lead to enhanced absorption of aeroallergens across the airway wall predisposing to subsequent sensitization. Second, RSV-specific IgE antibody formation may lead to mast cell mediator release within the airway, resulting in the development of bronchospasm and the ingress of eosinophils. Third, similar to various allergenic proteins, the processing of RSV antigens and their subsequent presentation to lymphocyte subpopulations may provide a unique mechanism of interaction to promote a Th-2–like response in a predisposed host.

RSV belongs to the family Paramyxoviridae, the genera Pneumovirus, and can be differentiated into two serologic subgroups, A and B. It has 10 genes, with 12 potential gene products. The G (attachment) and F (fusion) proteins are the major surface glycoproteins against which neutralizing antibody is directed. Interestingly, in both murine and human in vitro experiments, it has been noted that the G protein elicits a predominant Th-2 response, whereas the F protein produces a predominant Th-1 response. In mice, to test the activities of
T cells recognizing individual RSV proteins in vivo, virus-specific T-cell lines have been produced using recombinant vaccinia viruses that express either the G or F proteins. Following passive transfer of these cell lines to naive recipients and subsequent intranasal inoculation with RSV virus, mice receiving G-specific cells have more severe illnesses characterized by lung hemorrhage, pulmonary neutrophil recruitment, and intense pulmonary eosinophilia. These experiments are of interest based on the adverse clinical response noted in many infants who received a formalin-inactivated RSV vaccine and subsequently became infected with RSV.

These intriguing observations regarding RSV and its influence on Th-1 or Th-2 responses have recently been expanded. Roman et al evaluated 15 hospitalized infants (1–15 months) with an acute lower respiratory tract infection caused by RSV. Compared with control infants, the infected children had a suppression of their IFN-γ production and, although IL-4 production was also decreased, the IL-4/IFN-γ ratio was significantly increased. Renzi et al prospectively followed 26 infants hospitalized with bronchiolitis by obtaining blood samples at the time of illness and 5 months later. Compared with age-matched control infants, infected patients had an increased percentage of CD4+, CD25+, and CD23+ lymphocytes at the 5-month follow-up. Plasma IL-4 levels, although initially not different from control patients, increased significantly in the infected children 5 months later. Blood lymphocytes, obtained during the time of bronchiolitis, produced less IFN-γ in response to IL-2 in children who went on to develop a pattern of recurrent wheezing. Finally, peripheral blood lymphocytes from infants who had persistent wheezing produced more IL-4 in response to Dermatophagoides farinae antigen. Unfortunately, the pattern of cytokine response these infants had prior to infection was not evaluated, again begging the question as to which of the observed results may be cause and which may be effect.

Thus, current observations in this area do not provide sufficient information to deduce causality and leave a number of important questions unanswered. Does cytokine dysregulation influence the immunologic response to RSV leading to more severe disease (i.e., bronchiolitis)? Does RSV infection promote the development of cytokine dysregulation, thereby increasing the risk of developing atopic disorders? Do imprinted patterns of cytokine secretion and RSV infections interact at a critical time point to establish a particular wheezing phenotype with future infections or exposures? Additional prospective studies are needed to determine whether childhood infections can cause lasting effects on the immune system to modulate the subsequent risk of allergy and asthma. Alternatively, there may be immune factors, perhaps genetically determined, that regulate both the immune response to infections and the risk of developing allergies or asthma.

PREDICTING ALLERGIC DISEASES IN CHILDREN

If atopy is indeed a major risk factor for the development of asthma, the ability to measure some marker associated with the atopic trait would be beneficial, particularly if asthma has its roots in infancy and interventions aimed at primary prevention can be made a reality. Clearly, family history of allergy increases the risk of subsequent allergic diseases in children, and this has been demonstrated in several long-term prospective studies conducted in the United States and in Europe. For example, Croner and Kjellman conducted a large prospective study in which 1,654 Swedish children were evaluated at birth and followed until the age of 11 years. The cumulative incidence of atopic diseases was 27% in the group as a whole, but this increased to 43% in children
with at least one "obviously atopic" parent (positive response to questions regarding atopic dermatitis, urticaria, food allergy, asthma, or allergic rhinoconjunctivitis). In this study, there was no difference in the prevalence of atopic diseases in children of atopic mothers or fathers, although some studies have found that maternal allergy has a greater effect on cord blood IgE levels and the development of asthma.

Many studies have investigated the utility of measuring cord blood IgE as a predictor of allergy in neonates with a positive family history. It has been documented in a number of studies that children with elevated cord blood IgE are at increased risk of developing atopic diseases. Finding other markers of atopy, such as increased eosinophils or basophils in nasal secretions, positive skin prick tests to egg protein, or atopic skin changes in infancy is also an indicator of increased risk for the subsequent development of asthma, allergic rhinitis, or other atopic disorders. Unfortunately, many or most children who eventually develop allergic diseases do not have identifiable atopic markers in infancy, and the low sensitivity of these tests makes them unsuitable for screening purposes.

A common clinical problem in evaluating infants with wheezing illnesses is to determine which children will go on to develop chronic asthma, and total IgE levels have also been evaluated in this regard. Martinez et al reported that elevated levels of IgE antibody at 9 to 12 months of age, but not in cord blood, are associated with an increased risk of recurrent wheezing that persists beyond 3 years of age. Although this finding suggests that total IgE levels could be useful as a prognosticator in infants with virus-associated wheezing, other indicators that do not require sampling of blood may be just as useful. For example, a history of infantile eczema or a maternal history of atopy have about the same prognostic significance value as an increase in total IgE, and unfortunately, combining these indicators does not increase the predictive value of these measurements.

Levels of eosinophil cationic protein (ECP) in blood or nasal secretions have been evaluated as predictors of children at risk for additional episodes of wheezing. ECP levels are increased in the serum and nasal secretions of infants with bronchiolitis, and in children with symptoms of acute asthma. Infants with elevated ECP during acute wheezing illnesses in infancy are at increased risk for developing additional episodes of wheezing in short-term follow-up. For example, Koller et al obtained serum for ECP determinations on 33 infants with no previous history of allergic disease and found that median ECP levels were four times higher in those infants who went on to develop recurrent wheezing in the following year. Additional studies are needed to evaluate whether increased ECP is associated with persistent asthma and whether this will be useful as a screening tool.

Finally, abnormalities in the pattern of cytokine responses have been noted in infants at risk for developing allergy and asthma. Low IFN-γ production has been noted in cord blood cells from infants born to allergic parents and also is a risk factor for development of eczema and positive prick skin tests to allergens at 1 year of age. In addition, low IFN-γ and IL-2 production from peripheral blood mononuclear cells at 9 months of age are associated with an increased risk of developing allergen-specific IgE but not increased total serum IgE at 6 years of age. These results have led to the hypothesis that cytokine dysregulation, and IFN-γ deficiency in particular, may play a critical role in the pathogenesis of allergic diseases. So far, however, the techniques required to measure these factors are confined to research laboratories, and large-scale epidemiologic studies will be required to elucidate the value of these tests in clinical practice.
As is alluded to throughout this article, there are large gaps in the current understanding of the pathogenesis of allergic diseases in children that have hindered the development of truly effective preventive strategies. Despite these shortcomings, there are sufficient data to support certain environmental modifications that are likely to reduce the risk of subsequent allergy and asthma.

First, raising children in a smoke-free environment, beginning in utero, is likely to be the single most important intervention to reduce the rate of both allergic and nonallergic respiratory disorders in children. There are a growing number of options to support smoking cessation in parents and parents-to-be, and several excellent reviews of medical and supportive strategies to stop smoking have recently been published.61, 51

Second, modifying the diets of infants from allergic families, and lactating mothers, should be considered. Changes in the prenatal diet do not affect the risk for allergy and are unnecessary. Sensible dietary modifications for babies include breast-feeding, delaying the introduction of solid foods until 6 months of age, and withholding highly allergenic foods such as cow’s milk, egg, and peanut for 2 to 3 years. Several formulas in which the protein source has been hydrolyzed to reduce antigenicity are listed in Table 1. These formulas may be used in a preventive fashion if the mother decides not to breast-feed89 or as alternatives to cow’s milk or soy-based formulas after cessation of breast-feeding. Changing from breastmilk to a hypoallergenic formula seems to have little additional value, however, for infants who are breast-fed for longer than 6 months.86 Hypoallergenic formulas have the disadvantages of being more costly than standard infant formulas and have a strong taste that some infants find unpalatable, especially if the infant was initially fed breastmilk. In infants older than 6 months of age, alternatives to hypoallergenic formulas include vitamin D and calcium-fortified rice milk or orange juice, and these beverages are available in many health food stores and supermarkets.

Finally, reducing the exposure to environmental allergens can reduce symptoms in patients who already have respiratory allergies, and although the data are as yet incomplete, there are early indications that they could prevent or delay the onset of respiratory allergy or asthma. For example, Hide et al have conducted a study in which 120 infants were prospectively enrolled to determine the effects of combined dietary and environmental interventions on the development of atopic disorders.61 31 In the active group, infants and lactating mothers were prescribed hypoallergenic diets, and house dust mite protein levels were controlled with acaricides and mattress covers. In addition to having significantly less atopic dermatitis at 1, 2, and 4 years of age, the prophylactic group had less asthma at 1 year of age and fewer children with positive skin tests at age 4 years. These results need to be independently confirmed but suggest that limiting exposure to inhalant and dietary allergens may have additive effects in the prevention of childhood allergies. Sensible guidelines for limiting exposure to indoor respiratory allergens (that were designed for patients with existing asthma) have been proposed by the National Heart Lung and Blood Institute62 and can be considered for preventive therapy. These guidelines follow:

- Animal danders: Do not allow furred pets in the home.
- House dust mite
  Essential: Encase mattresses and pillows in allergen-impermeable covers and wash sheets and blankets in hot (≥130°C) water every 7–14 days.
  Desirable: Reduce indoor humidity <50%, remove carpets from the
| Table 1. INFANT FORMULAS WITH REDUCED ANTIGENICITY |
|---------------------------------------------------|
| **Nutramigen**               | **Pregestamil**             | **Good Start**               | **Alimentum**               | **Neocate**                     |
| Manufacturer                  | Mead Johnson (Princeton, NJ) | Mead Johnson                 | Nestle/Carnation (Glendale, CA) | Ross Products/Abbott Laboratories (Abbott Park, IL) | Scientific Hospital Supplies (Gaithersburg, MD) |
| Protein source                | Casein hydrolysate          | Casein hydrolysate           | Partial whey hydrolysate      | Casein hydrolysate              | Amino acids                     |
| Recommended for milk-         | Yes*                        | Yes*                         | No                             | Yes*                            | Yes                             |
| allergenic patients           |                             |                               |                                |                                 |                                 |
| Recommended for               | Yes                         | Yes                           | ?                             | Yes                             | Yes                             |
| prevention of food allergy/AD |                             |                               |                                |                                 |                                 |
| Comments                      | Fat source: medium          | Commonly causes               |                                | Amino acids are often           |
|                               | chain triglycerides         | allergic symptoms in         |                                | tolerated by babies who         |
|                               |                             | children with cow            |                                | have adverse reactions          |
|                               |                             | milk allergy                 |                                | to hydrolyzed milk              |
|                               |                             |                               |                                | protein                         |

*Allergic reactions to extensively hydrolyzed milk protein based formulas are rare but have been reported.
bedroom and from concrete floors, and avoid sitting on upholstered furniture.

- Cockroaches: Use poison bait or traps to control; do not leave food or garbage exposed.
- Indoor mold: Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to <50%.

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Address reprint requests to
James E. Gern, MD
University of Wisconsin Hospital
H4/438 CSC
600 Highland Avenue
Madison, WI 52792-4108
e-mail gern@medicine.wisc.edu