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Immunocompetence and Allergy

Stephen J. McGeady, MD

ABSTRACT. Developed nations are experiencing a marked increase in prevalence of the familial allergic diseases including asthma, allergic rhinitis, atopic dermatitis, and allergic gastroenteropathy, which are often called atopic diseases. No satisfactory explanation for this epidemic is known, but it has been proposed that some facets of modern life tend to bias immune responses away from the Th1 cellular immune responses that protect against many infections and toward Th2 responses that favor atopy. There are 2 hypotheses to explain why this epidemic is occurring now. Hypothesis 1 suggests that nutritional patterns have changed or that we are exposed to environmental toxicants that were not previously present. Hypothesis 2 holds that some aspects of modern lifestyles in affluent nations have minimized exposure to infectious agents or to their by-products, such as endotoxin. This feature of contemporary lifestyle, it is suggested, has favored the development of Th2 immune responses to environmental allergens and the development of the attendant atopic diseases. This latter theory has been designated the "hygiene hypothesis." Although there is evidence both for and against both hypotheses, evidence for hypothesis 2 is stronger and more convincing. *Pediatrics* 2004;113:1107-1113; *atopy, asthma, Th1 cells, Th2 cells, hygiene hypothesis.*

ABBREVIATIONS. Ig, immunoglobulin; IL, interleukin; IFN- γ , interferon- γ ; TNF- β , tumor necrosis factor- β ; MAS, Multicenter Allergy Study;

The term "allergy" refers to any clinical event that is caused by immune mechanisms and is harmful to the host.¹ Although allergic reactions have been classified into 4 types,² it is type 1 allergic reactions that are caused by immunoglobulin (Ig) E antibody and lead to the release of chemical mediators that are by far the most common and of greatest clinical concern. Whereas some IgE-mediated conditions, such as anaphylaxis, occur sporadically in the population, the IgE-related diseases that run in families and are encountered most often include allergic rhinitis, atopic dermatitis, allergic asthma, and gastrointestinal allergies. These are referred to as "atopic" diseases.¹ They afflict >20% of the population in the United States,³ and their prev-

alence is rising at an alarming rate in developed nations.⁴⁻⁶ There is no completely satisfactory explanation for this increased prevalence, but the enormous cost of these diseases in terms of human suffering and their economic impact has led to extensive research. This has extended from investigation of the basic immune mechanisms leading to atopy to epidemiologic studies that have considered the prevalence of atopy over time and by geographic distribution. Although a great deal has been learned about atopic diseases, the full explanation of the "epidemic of atopy" remains elusive.

IMMUNOLOGY OF ATOPY

In 1986, it was discovered that when naïve helper (CD4⁺) T cells are stimulated, they may develop into 2 distinct populations depending on the nature of the stimulus (see Fig 1); these populations are defined by the types of cytokines produced. One population of CD4⁺ cells, designated Th1, produces interleukin (IL)-2, interferon- γ (IFN- γ) and tumor necrosis factor- β (TNF- β). A second population, called Th2, produces IL-4, IL-5, IL-6, and IL-13.^{7,8} The cytokines produced persist over time, indicating that the cells are lineage committed once they have acquired these defining properties. The cytokines in the microenvironment at the time of stimulation of the naïve helper T cells determine which pathway of development the cell will follow. If the naïve T cells are exposed to IFN- γ , then they develop into Th1 cells, whereas if IL-4 is prevalent, then they become Th2 cells. Thus, if either IFN- γ or IL-4 is abundant when a CD4⁺ helper cell is activated, then the T cells will be guided into the Th1 or Th2 pathway, respectively, and the other pathway will be inhibited. Subsequent studies have identified a third population, designated Th0, which produces cytokines of both types, although the relevance of this population is unclear.⁹ It has been shown that human antibody-producing cells exposed to IL-4 and IL-13 will produce IgE antibody, and this effect plus that IL-5 promotes eosinophilic inflammation indicates that atopy is a Th2-dependent process.¹⁰ Our current attempts to understand the development of atopy are aimed at determining what causes naïve CD4⁺ T cells, which have the potential to enter either the Th1 or the Th2 pathway, to become persistently "deviated" toward Th2 in atopic individuals.¹¹ It is known that all infants are normally born with a bias toward Th2 responses to newly encountered antigens and transiently produce IgE antibody. This is possibly because the Th2 mode avoids rejection of the pregnancy.¹² In most infants, however, this tendency to

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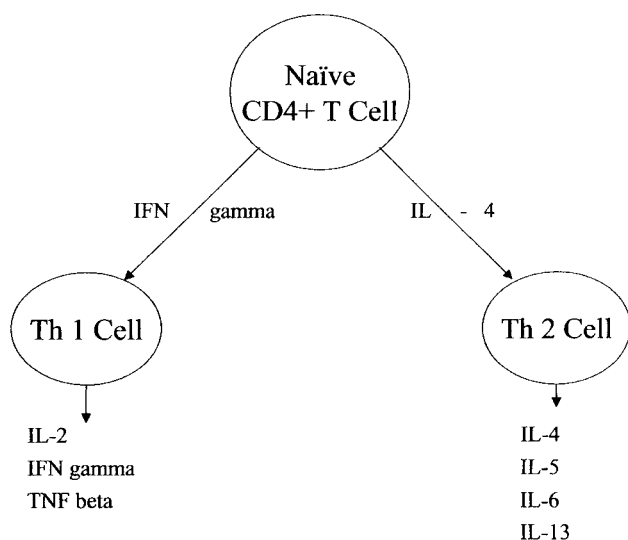


Fig 1. T helper cell differentiation.

produce IgE antibody is lost early in life, possibly as a result of the appearance of IFN- γ . In infants who are destined to develop into atopic individuals, however, there is less IFN- γ produced and the Th2 bias persists, and these children continue to produce IgE antibody in excessive quantities to commonly encountered substances such as foods and environmental allergens.¹³

HEREDITY AND ATOPY

The definition of atopy, as noted above, includes the familial nature of atopic diseases, so there is no question of the role of genetic factors in the development of atopy. It has become clear that atopic diseases are "complex" diseases in which multiple major and minor genes interact, some of which are immune-response genes and some are IgE-regulating genes^{14,15}; both types may themselves be modulated by nongenetic factors such as the level and frequency of allergen exposure.¹⁶⁻¹⁸ The ultimate phenotype of atopy versus nonatopy or in the specific atopic disease developed is likely to reflect this highly complicated and variable system. Although the role of genetics in the development of atopic disease is undisputed, it is not able to explain the "epidemic of atopy" that is observed today. Why has allergic rhinitis, which was virtually unknown 200 years ago in Europe and North America,¹⁹ progressed to where it now afflicts >20% of the population in industrial nations?²³ During the past 2 decades, 2 general hypotheses have been generated to explain the increase of atopy and of asthma in childhood:

1. New risk factors that were not present in the past have become relevant. These might reflect changes in nutrition or environmental exposure.
2. Abandonment of the more traditional lifestyle of the past has led to the loss of factors that protect against atopy.¹⁶

Critical Times of Vulnerability for Atopic Sensitization

Before considering the possible influences proposed in these hypotheses, it is helpful to consider

the development of allergy as a function of the child's age. Investigators have sought explanation for the current "epidemic of atopy" in events of the first years of life.^{16,18} As noted, a bias toward Th2 immune responses is present at birth in all infants but is soon replaced by a balanced Th1/Th2 response pattern in nonatopic infants. Although the specific influences that cause retention of the Th2 response in atopic infants are not known with certainty,^{13,20} there is evidence that compartmentalization into Th1 or Th2 of long-lived memory T cells that recognize allergen occurs before the age of 5 years.^{13,21} Studies of birth dates show that birth during or shortly before a pollen season is associated with increased pollen allergy later in life, suggesting a critical role for early exposure.^{22,23} Epidemiologic studies of former East and West German populations show that lifestyle differences in the first year of life influence the development of atopy in populations that are genetically similar.²⁴ In the recent Multicenter Allergy Study (MAS) of German children, it was found that some early childhood viral infections may actually protect against development of asthma²⁵ or atopy.²⁶ Only those infections contracted during the first year of life exerted such an effect, however. Finally, antibodies of the IgG and IgE classes to house dust mite were shown to be present in the second and third years of life in children of 1 atopic parent, suggesting that early sensitization is expressed soon after it occurs.²⁷ These findings in aggregate suggest that initial sensitization or events that modulate asthma or atopy occur very early in life. Little is known about whether the vulnerability persists or wanes over time, but interventions to prevent the development of atopy, such as maternal dietary avoidance during pregnancy or dietary interventions for the child during early infancy, have been attempted. The majority of studies seem to indicate that the benefits of such interventions are at best marginal and that later development of asthma will not be prevented, suggesting that the potential for sensitization persists and may only be delayed by early avoidance measures.¹⁶ Cytokine production profiles reflecting the Th1 and Th2 cell balance in atopic and nonatopic children become similar at 4 to 5 years of age, suggesting that the earlier years, when Th2 responses may dominate in the atopic child, may be critical for atopic sensitization.^{13,28} There is, however, evidence showing that high allergen concentration may cause atopic sensitization in school-aged children,²⁹ indicating that the period of vulnerability to being sensitized may extend beyond infancy. In addition, many atopic adult health care workers became sensitized to allergens associated with natural rubber latex in the 1980s and early 1990s, indicating that the capacity to develop allergy is retained well beyond the early years.³⁰

HYPOTHESIS 1 FOR THE INCREASE OF ATOPY

The hypothesis that new factors previously not present may be relevant in causing the observed increase in prevalence of atopy has been explored in terms of nutrition and environmental exposure.

Nutrition

Breast milk is seen as the food least likely to elicit allergies in the "at-risk" infant. In reality, however, despite the many proven advantages of breastfeeding, its ability to prevent allergies is highly controversial.¹⁸ In a review of 14 published prospective studies of the anti-allergic potential of breast milk, nursing was found to be beneficial in 8 studies but was either of no benefit or made allergies worse in 6.³¹ A recent longitudinal study found that breastfeeding for 4 months or longer led to lower IgE levels in children at ages 6 and 11 years. This effect was seen, however, only when the mother herself had low IgE levels. In mothers with high IgE levels, nursing for 4 months or longer was associated with increased IgE at those ages.³² It must be concluded that the anti-allergic effect of breastfeeding is complicated and presently unproved.

Nutritional interventions have consisted of avoidance of highly allergenic foods during pregnancy, during lactation, or in early infancy. These dietary manipulations have generally shown transient effects and have failed to prevent asthma and atopy in later childhood.^{33,34} One interesting theory holds that changes in the diet in more affluent industrialized nations influence the bacterial flora of the gut and fail to redirect the Th2 responses seen in atopic infants toward a more balanced Th1/Th2 response seen in nonatopic infants.^{35,36}

Environment

Environmental toxicants have been scrutinized closely in relation to the increase of atopy because many contemporary toxicants were scarce or nonexistent in the past. In considering the impact of environmental toxicants, asthma and atopic sensitization are best thought of separately because wheezing in young children is thought to be heterogeneous, and distinct subtypes may result in wheezing early in life. In more than half of children, wheezing illnesses in the first 3 years of life have been associated with diminished airway function at birth, and wheezing in these children often disappears by age 6 years. Such children are nonatopic but may develop a wheezing response as a result of an irritant rather than an immune response to the toxicant. A significant minority of children with early wheezing, however, are atopic and are more likely to have persistent asthma.³⁷

Environmental pollution has been divided into type I, consisting of sulfur dioxide and large dust particles, which is prevalent in Eastern European nations, and type II, characterized by nitrogen oxides, ozone, tobacco smoke, and diesel exhaust, which is found in industrialized Western nations with many motor vehicles.³⁸ In the past decade, some epidemiologic studies have compared the prevalence of asthma and atopic sensitization in populations that live in the highly polluted Eastern nations with those in the supposedly cleaner West. Paradoxically, the populations that live in the West have shown a higher prevalence of both asthma and atopy.^{39–42} An explanation of this finding may lie in

the observation that type II pollutants are able to promote asthma and atopic diseases.^{43,44} Some type II pollutants, such as ozone, may cause wheezing symptoms by acting as primary irritants, but others, such as diesel exhaust particles, seem to function as immunologic adjuvants that shift the balance of T helper cells toward the allergic Th2 pathway.^{45–48} Additional evidence that type II pollutants may have this effect is the finding of higher rates of atopic sensitization and asthma prevalence in inner cities of the United States, where such pollution is greater.^{41,49,50} Of the substances associated with type II pollution, the role of environmental tobacco smoke in the early years of life has been examined most closely, and there is evidence that, even in utero, exposure to smoke can contribute to both atopic sensitization and asthma.^{51–53} In addition to promoting overall atopic sensitization, exposure to smoke in utero seemed to lower the age of subsequent allergen sensitization in the large MAS in Germany.⁵² Postnatal exposure to maternal smoking has also been reported to increase the relative risk of developing asthma in children,^{53,54} and there is evidence that exposure early in life to a mother who smoked may increase the odds of having asthma or wheezing in adolescence and adult life.⁵⁵ Other studies, however, have failed to confirm the role of environmental pollutants, including tobacco smoke. In Munich, high traffic volume increased respiratory symptoms but failed to increase allergic sensitization, asthma, or bronchial hyperreactivity.⁵⁶ A similar assessment in Dresden failed to show association between pollution levels and atopy or bronchial hyperreactivity,⁵⁷ and a large British investigation concluded that air pollution was completely unassociated with atopy.⁵⁸ Some surveys evaluating the effects of environmental tobacco smoke have likewise come to contradictory conclusions, including the study referenced above, which actually noted a decrease in atopy among individuals whose mothers smoked while pregnant.⁵⁸ Other investigators have also found a decrease in atopic sensitization⁵⁹ or no association⁶⁰ in children whose mothers smoke during their early years. Despite these conflicting findings on the association of smoking with asthma and atopy, there is almost unanimous agreement that tobacco smoke is associated with increased risk of lower respiratory tract illness in infancy and childhood, including bronchitis, pneumonia, and significant reduction in pulmonary function.^{51,61} It is also widely accepted that environmental tobacco smoke causes more asthmatic episodes and increased severity in children with previously diagnosed asthma.^{16,61} Thus, whether pollutants, including tobacco smoke, cause atopy and asthma either alone or in concert with allergens or merely increase morbidity by functioning as irritants remains uncertain.

HYPOTHESIS 2 FOR THE INCREASE OF ATOPY

This hypothesis suggests that fewer people live the more traditional agrarian lifestyle of the past and that aspects of that life provided protection against the development of atopy. Support for this phenomenon is found in lifestyle surveys documenting a

higher prevalence of asthma and atopy in highly industrialized Western nations compared with less developed former Soviet bloc nations.^{24,35,36} Some of these investigations compare populations that are genetically similar, making lifestyle-associated factors particularly suspect in causing the observed differences. Insight into the specific aspects of the traditional lifestyle that contribute to decreased asthma and atopy has come from evaluation of children who live on farms in Western nations.^{62,63} Comparing farm-residing children with non-farm-residing children from the same region has shown a significantly lower prevalence of atopy in the farm-residing children. These results were confirmed in a large multinational project involving subjects who lived in Germany, Austria, and Switzerland.^{64,65} Using multiple regression analysis, this study identified contact with livestock or poultry as the feature of farm life that most protected against the development of asthma, hay fever, and symptoms of allergic rhinitis. The effect was most prominently seen, however, when contact with farm animals occurred during pregnancy or early in life. The mechanism by which protection is conferred is not known, but it has been noted that farm-residing children are exposed to significantly higher levels of bacterial endotoxin.⁶⁶ Bacterial endotoxins are potent stimulators of IL-12 production, which in turn elicits IFN- γ and evokes a Th1 response from naïve helper T cells.^{33,66} This sequence of events may explain a diminished tendency for Th2 responses and thus a lower prevalence of atopy. Additional support for a beneficial role of endotoxin may be found in a recent prospective survey that found that children from homes with 2 or more dogs or cats, a known source of endotoxin, during their first year of life have a decrease in the risk of atopic sensitization to several allergens at age 6 to 7 years.⁶⁷ Although atopy may be less important in causing wheezing associated with irritant pollutants, it is clearly associated with some childhood asthma; thus, decreased atopic sensitization may explain the lower prevalence of asthma in children from farms.

A number of investigators have examined the role of infection in the development of asthma and atopic disease. In affluent Western nations, families are smaller, antibiotics are used liberally, immunizations are routinely given to young children, and obvious sources of infection are avoided. It has recently been recognized, however, that there is a possible protective role for some viral infections against the development of asthma,²⁵ atopic sensitization,⁶⁸ and elevated IgE levels.⁶⁹ The protective effect of viral infections seemed limited to those that occur very early in life, which is a finding consistent with the study of children in child care cited above.²⁶ Attendance at child care was found to be associated with a decrease in allergies at school age, detected by questionnaire and skin test, but the effect was seen only when the child began child care at <12 months of age. Other researchers have reported a decrease in atopic sensitization in children from large sibships, suggesting that multiple early exposures to viral infections may decrease atopic sensitization.^{58,59,69,70} An often-cited study examined the effect of myco-

bacteria on allergic symptoms, IgE levels, and Th2 cytokine production in Japanese children who were given bacille Calmette-Guérin immunization. It was found that a positive tuberculin test at ages 6 and 12 years was inversely correlated with asthma, atopic characteristics, and levels of Th2 cytokines.⁷¹ Others, however, have failed to find a beneficial role of measles⁷² or of bacille Calmette-Guérin immunization⁷³ in preventing asthma or atopic disease. Nonetheless, the evidence supporting an anti-allergic effect by at least some infections is considerable. The theory that infectious diseases have become so few in affluent Western societies that their Th1-promoting effect has been lost has become known as the "hygiene hypothesis" and is often proposed as an explanation for the rapidly increasing prevalence of atopic diseases in these societies.⁷⁴ On balance, the evidence that lifestyle changes have led to conditions that favor the development of atopy and asthma (hypothesis 2) seems more convincing than evidence for environmental toxicants promoting these conditions (hypothesis 1), but the influences of modern lifestyle are likely to be complex, and the hypotheses are not mutually exclusive.³⁸

Allergen Effect on the Increase of Atopy

There is abundant evidence that exposure to high levels of allergens in early life is a major contributor to the development of atopy. Because atopic sensitization is strongly associated with persistent wheezing in children,^{37,52} it would be very helpful to determine whether critical levels of allergen exposure exist below which sensitization does not occur. It has been found that sensitization to specific allergens reflects the mean level of allergen found in homes. In many communities, house dust mite is the principal allergen, but where house dust mites are rare, such as in dry climates or high altitudes, the principal allergens are emanations from dogs and cats.⁷⁵ In the inner cities of the United States, low-income people who live in heavily infested houses are most often sensitized to allergens derived from German cockroaches.⁷⁶ Because of these differences, attempts to define a sensitizing dose of an allergen are complicated and are made more so by the different properties of allergens. The principal allergens of house dust mites (designated Der pI for one species of mite and Der fI for another) and German cockroaches (Bla gI) are found on weighty particles that are best quantified in house dust because they settle quickly, and the quantity thus is expressed as micrograms of allergen per gram of house dust. In contrast, the emanations of house pets are airborne in 5 μ m or smaller particles, and their level of exposure might best be measured by air-sampling techniques. Epidemiologic surveys of pet allergens to date, however, have reported the animal allergens in micrograms per gram of house dust,¹⁷ and it is not known how well this method reflects the exposure level.

House dust mite has been the allergen most often measured to determine the sensitizing dose, and data from a number of studies have suggested critical doses. It was found in 1 survey that a level of exposure of <2 μ g Der pI per gram of house dust should

be recommended for primary prevention of sensitization in children.²⁹ In another report, the prevalence of dust mite sensitization increased from 4.3% in homes where the average dust mite allergen was found to be 1 $\mu\text{g/g}$ of dust to >25% where dust mite allergen exceeded 20 $\mu\text{g/g}$.⁷⁷ In a study that prospectively evaluated 67 children in the United Kingdom, a trend toward correlation between dust mite allergen level in the home and atopic sensitization was found. No child with exposure to <2 μg of Der pI per gram of dust became sensitized, whereas of those who were exposed to >10 $\mu\text{g/g}$ of dust, 50% were sensitized.⁷⁸ In the German MAS, the investigators noted that family background exerted a strong effect modification on sensitization. They found that in children with a family history of atopy, a mite allergen concentration below 0.75 $\mu\text{g/g}$ of house dust resulted in a 3% sensitization rate. In children with no family history of atopy, an exposure level of 25 $\mu\text{g/g}$ was needed to produce a 3% sensitization rate. These researchers concluded that no general exposure threshold for any allergen could be proposed, because children with genetic risk could respond to very low exposure levels.⁷⁹ Exposure thresholds have been proposed for other allergens, including cockroach, for which a level of <2 U/g of dust was suggested as safe,⁷⁶ but the same qualification regarding genetic risk would apply. The importance of allergen exposure in the development of atopy and asthma is emphasized by a recently published meta analysis evaluating all environmental factors suspected of being responsible for the increased prevalence of these conditions. After comparing the strength of all effects, the authors concluded, on the basis of the literature, that indoor allergen exposure has the strongest effect on the manifestation of asthma.⁸⁰

EXTRAPOLATION OF ANIMAL DATA TO INFANTS AND CHILDREN

A great deal of information derived from experimental animals contributes to understanding the immunology of atopic disease. The paradigm of Th1/Th2 divergence of helper T cells is based on studies in murine species⁹ and has been shown to be applicable to humans as well. This model may ultimately provide the immunologic explanation for the "epidemic of allergy."¹³ The positive contributions of animal research must be viewed along with their limitations. Some observations in animals may not be applicable to humans. An example of failure to apply might be the observation of the effect of diesel particles enhancing IgE antibody production in experimental animals.^{46,47} As noted above, the evidence that this occurs in humans is at best conflicting.^{57,58} Data from animal studies can be useful but must be viewed critically for its applicability.

POLICY AND RESEARCH IMPLICATIONS

Much has been learned about the development of atopy, but a central question remains unanswered: Why is the prevalence of atopy rising rapidly in developed nations? Although many of the findings summarized in this discussion provide fascinating

data and lead to interesting new theories, almost all are countered by studies that present opposing data, and the debates continue. At a time in history when science and technology are at an unprecedented level of sophistication, experimental design has been greatly refined, powerful information technology is available, the power of intergroup collaboration has been appreciated, more robust statistical methods have been developed, and research funding through the National Institutes of Health and other agencies has risen by an order of magnitude in a short time, these conflicting findings are now resolvable. Some key questions that remain unresolved include the following:

1. Why are there conflicting data on the effect of environmental pollution and living standard on atopy and asthma? Populations in Eastern Europe, which is relatively poor and polluted, have less atopy and asthma, whereas in the United States, indigent people in the polluted inner cities have more atopy and asthma.
2. What is the relationship between atopy and asthma? Although it is clear that the conditions are closely related, we see evidence that some environmental conditions lead to an increase in asthma but not in atopic sensitization. Conversely, high allergen concentrations contribute to an increase in atopic sensitization but not necessarily in asthma. It seems that the conditions are separate. Although it is widely recognized that wheezing is a heterogeneous condition, the relationship to atopy needs better delineation.
3. Does exposure to passive tobacco smoke aggravate asthma and/or promote atopic sensitization? Does it protect against such sensitization, or is there no effect on these conditions at all? Large, well-conducted studies support each of these positions. Because tobacco smoke is 1 variable that public education campaigns might modify, it is important to know its impact.

There are many other questions that would be important to explore, but these seem fundamental.

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