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Mechanisms and advances in allergic diseases

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There have been many attempts to explain the increases in the incidence of allergic diseases, including hay fever and allergic asthma, that have been documented worldwide in recent decades. Epidemiologic studies offer rich opportunities to uncover sometimes unexpected correlations between lifestyle, environmental exposures, temporal development of the immune system, and genetics. Examples include the differing prevalence of atopy, bronchial hyperresponsiveness, and asthma in East and West Germany around the time of reunification, which suggests that a "western" lifestyle presents a greater risk for the development of allergic responses than the more traditionally suspected factor of outdoor air pollutant levels. Other epidemiologic studies suggest how infections may interface with an atopic patterning: Evidence from natural measles exposure and nonwheeze-inducing lower respiratory tract infections in young children implicate early childhood viral infections as protective against the development of atopy and airway allergic sensitivity, although in later life viral airway infections exacerbate asthma symptoms. These studies and others involving the scrutiny of lymphocyte subtypes in atopic individuals, notably T_{H1} and T_{H2} cells, are helping to formulate a theory of interdependence between the early development of the immune system, allergen exposure, and the diverse community of airway cells whose secretory products generate the final physiologic response pattern. (*J Allergy Clin Immunol* 2000;105:S593-8.)

Key words: Allergy, asthma, atopy, cytokines, hay fever, measles, T lymphocytes

The past few decades have seen numerous studies that reported a rise in the incidence of allergic conditions around the world. Reports from Europe, Australia,

Abbreviations used

APC: Antigen-presenting cell
95% CI: 95% Confidence interval

Africa, and North America appear to have uncovered meaningful changes in the epidemiology of allergic diseases, including hay fever and allergic asthma, and do not merely represent methodologic artifact. In the United States, the number of people with asthma has more than doubled since 1980,¹ and many European countries discovered similar trends, particularly among children, in the late 1980s or early 1990s.² An increasingly modernized lifestyle has been suggested to underlie this trend, as urban populations grow and inhabitants are subjected to air pollution from vehicle exhaust and shift to confined and crowded living conditions, which in some cases provide excellent microclimates for house-dust mite or indoor mold proliferation. In spite of several proposed explanations and data to support some of them, unexpected correlations have arisen to indicate that no simple answers will suffice; rather, this is a multifaceted health problem that we are only just beginning to understand.

A diversity of experimental, population, and clinical studies are revealing glimpses of what undoubtedly is a remarkably complex interplay between environment, immune and inflammatory cells, their products, and their relative chronologic importance in the establishment of an allergy-prone or allergy-resistant phenotype. A great deal of interest has been generated recently about how early development of the immune system, in particular, might result in an allergic phenotype.

LIVING CONDITIONS AND ASTHMA: LESSONS FROM GERMANY

Population studies from around the world have included some unique situations for gaining insight into the

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TABLE I. Prevalence of respiratory and allergic diseases in West and East Germany

Doctor-diagnosed condition	% Prevalence		P value
	West Germany (n = 5030)	East Germany (n = 2623)	
Asthma ever	9.3	7.2	<.05
Current asthma	5.9	3.9	<.0005
Bronchitis	15.9	33.7	<.0005
Hay fever	8.6	2.7	<.0005

Adapted with permission from von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann H-H. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64. Official Journal of The American Thoracic Society. Copyright American Lung Association.

TABLE II. Changes in prevalence of sensitivity to specific allergens in children from Leipzig, East Germany, before and after reunification

Antigen	% Prevalence (n)		P value
	1991-1992 (n = 1303)	1995-1996 (n = 1624)	
Mite	4.6 (60)	8.1 (131)	.0002
Cat	3.3 (43)	3.1 (50)	.7
Dog	2.8 (37)	2.6 (42)	.7
Grass pollen	9.1 (118)	11.5 (187)	.03
Birch pollen	8.4 (109)	14.2 (231)	<.0001
Hazel pollen	3.8 (50)	6.7 (108)	.0008
At least 1 pollen	14.3 (186)	21.5 (349)	<.0001
At least 1 allergen	19.3 (252)	26.7 (434)	<.0001
More than 1 allergen	8.2 (107)	11.8 (191)	.002

Adapted from von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862-6. Copyright by The Lancet Ltd, 1998.

relationship between environment and the immune system. Several investigators have taken advantage of the recent reunification of East and West Germany, which, in 1990, brought together genetically similar populations that previously had divergent living conditions and cultural practices. An initial surprise in studies of these 2 regions was that East German populations had a lower prevalence of atopic diseases compared with their Western counterparts before reunification.³⁻⁵ Because of a more conspicuously poor outdoor air quality, it had been expected that the East German cities would have had a more irritating environment that would have been evocative of allergic responses. Some studies have sampled an adult population; other studies have focused on children, in the hopes of learning something about ontogeny of allergic illnesses.

Among adults sampled from 1 West German and 1 East German city (Hamburg and Erfurt, respectively), a higher prevalence of atopic sensitization to common allergens, of methacholine-induced bronchial hyperresponsiveness, and of elevated IgE levels to specific allergens, typified the western population.³ In addition, compared with individuals in the eastern sector, lung function

was poorer with spirometry testing, and natural exposure to allergens in atopic individuals produced more symptoms. It was concluded that exposure to higher levels of particulates and sulfur dioxide in the air of Erfurt, because of widespread coal burning for home heating and power plants, was in fact less of a risk to pulmonary function than the living conditions associated with a western lifestyle.³ Possible, but untested "western" risk factors included exposure to automobile exhaust and indoor heating and ventilation systems. Also proposed were increased exposure to indoor allergens (house-dust mite, pet dander) within the contained environment of modern housing, a smaller family size, and relatively higher socioeconomic status.^{3,5}

Among children, a large database of about 5000 children in West Germany (Munich) and 2600 children in East Germany (Leipzig) compared the incidence of atopy, hay fever, and current asthma shortly after reunification.⁴ The incidences of all 3 conditions were significantly higher in Munich (Table I), contrary to the expectation that higher pollution rates to which children would have been exposed in the east would correlate with higher allergic airway disease. Why atopic sensitization was 2.5 to 3 times higher in Munich could not be explained easily.

Cross-sectional surveys of children taken in 1 East German city (Leipzig) shortly after reunification (1991-1992) and 4 years later (1995-1996) show a dramatic increase in the prevalence of atopy by skin-prick test to common aeroallergens (Table II). The overall sensitization rate increased significantly ($P < .0001$) from 19.3% to 26.7% during that period. In addition, the incidence of doctor-diagnosed hay fever increased significantly ($P < .0001$) from 2.3% to 5.1%. This suggested that a change to westernized living may underlie the increase in allergic airway disease. However, the incidence of asthma and bronchial hyperresponsiveness did not change. Because children in this study would have been at least 3 years of age when their living conditions changed, this disparity between the trend in allergy and in asthma suggested to the authors that environmental exposures in early life determine the development of childhood asthma, whereas atopic sensitization and hay fever can develop from exposures beyond infancy.⁵

These studies pose intriguing questions regarding the relationships between lifestyle, environmental exposures, genetics, and airway allergic disease. They are consistent with the concept that early-life exposures can set the stage for future disease, but the story is far from simple. For example, the Leipzig data do not support the well-accepted relationship between allergen sensitization and asthma risk, because the significant increase in sensitization over the 4 years between data collection was not paralleled with an increase in asthma. But the considerably higher rates of atopic sensitization in Munich, West Germany, were so related to asthma occurrence that accounting for atopy in individuals removed any influence of location on asthma incidence.⁴ An explanation for these apparent discrepancies may be found in the time required for conditions to arise once

TABLE III. Relation of IgE levels and atopy at the age of 6 years to wheezing and nonwheezing lower respiratory tract infection history up to the age of 3 years

Table available in print only.

exposures have increased, but there likely are additional and unidentified factors. Furthermore, it should be pointed out that, in spite of seeking populations with high genetic similarity, there remained in these studies a strong association between atopy and family history, such that the difference in sensitization rates between Hamburg and Erfurt were no longer significant when this was taken into account.³

NATURAL DISEASE EXPOSURE AND ATOPY

Another intriguing facet in the discussion of underlying causes for increased asthma incidence is a potential role for early-childhood respiratory illness. This remains a controversial topic that more recently has begun to draw from biochemical evaluations of cytokine production both before and concurrent with established disease. The role of viral infections in particular has been debated,⁶⁻⁸ and, again, population studies have some intriguing findings to offer.

In Guinea-Bissau, West Africa, an evaluation of 262 young adults for atopy and for whom reliable histories could be obtained with regard to childhood (0-6 years of age) measles found a negative correlation between having contracted measles and being atopic.⁹ Atopy was defined in these individuals, aged 14 to 21 years, by skin-prick response to 1 or more of 7 allergens (*Der-matophagoides pteronyssinus*, *D farinae*, southern grass mix, aspergillus, cat, dog, and cockroach mix). Odds ratios for atopy were calculated with respect to measles infection; and after adjustment for breast-feeding, mother's schooling, number of siblings, and other factors, a significant ($P = .01$) relative risk of 0.36 (95% confidence interval [CI], 0.17-0.78) was found. This implies that there is a protective benefit from naturally acquired measles infection. In the same study, other factors associated with a decreased risk of atopy were breast-feeding for longer than 12 months (odds ratio, 0.47; 95% CI, 0.12-1.9) and the presence of pigs in the living space (odds ratio, 0.67; 95% CI, 0.32-1.4). Mother's schooling of greater than 4 years was associated with higher risk of atopy (odds ratio, 1.9; 95% CI, 0.82-4.6).

Another study of approximately 900 children in Tucson, Ariz, found a reduced incidence of atopy and lower serum IgE levels in children who had experienced a non-wheeze-inducing viral airway infection early in life.¹⁰ IgE levels were obtained at birth (in cord blood), at 9 months, and at 6 years of age and evaluated for relationship to having had a wheeze- or nonwheeze-inducing lower respiratory tract illness and to atopy by skin wheal reaction at age 6 years. Significant correlations were revealed between IgE levels, atopy, and a history of having a wheeze-inducing infection within the first 3 years of life (Table III). Specifically, those children who had experienced an infection without wheeze had reduced IgE levels and skin test reactivity at 9 months and 6 years, compared with children who had either no infection or 1 with an associated wheeze. The reduced IgE levels were encountered in individuals with nonwheeze infections only after, and not before, that infection. Moreover, production of IFN- γ , a cytokine released by monocytes and subsets of lymphocytes in reaction to viral infections, was higher in the nonwheezing group at 9 months (inconclusive at birth). Children who had experienced a wheezing infection did not have any indication of predisposition toward allergy-induced bronchial hyperresponsiveness based on their IgE levels, which were within a normal range at all 3 sampling times. The relationships found among these variables suggested that a lower airway infection before the age of 3 years, as long as it did not include wheeze, was protective against the development of atopy and that IFN- γ may be protective. The specific pathogens involved in the infections were not assessed.

These studies suggest that natural infection by certain common childhood illnesses may be protective against the development of an allergic susceptibility. The time of exposure to airway pathogens may be of great importance, as may be the precise pathogen involved. In later life or in individuals with established airway hyperresponsiveness, airway infection can exacerbate the condition. In a small group of patients ($n = 8$ patients) with a history of ragweed-induced airway sensitivity but no cur-

rently active clinical manifestations of asthma, experimental infection with rhinovirus-16 increased bronchial responsiveness to histamine, methacholine, and antigen.¹¹ Further, concomitant infection resulted in a late-phase reaction to airway challenge in 5 patients, only 1 of whom previously had a history of a late-phase response. Plasma histamine was significantly elevated in this group compared with those patients who continued to exhibit only an immediate-phase response. This study concluded that infection, at least with rhinovirus-16, induced resident or recruited airway mast cells (or basophils) to release greater quantities of mediators, which then provoked airways with an already established, but quiescent, allergic disposition.

An indication that viral infection may enhance airway sensitivity is a community study of 108 older children (9-11 years of age) in Southampton, England, who were followed for 13 months for incidence of wheezing and of upper respiratory infections.¹² The study documented the presence of a viral cause for the infections in more than 80% of children who had concomitant wheezing episodes; two thirds of those episodes were rhinoviral infections. An attractive hypothesis to explain these associations is that inflammatory cells already implicated in asthma (antigen-presenting cells [APCs], mast cells, eosinophils, basophils, lymphocytes) are induced to release cytokines by viral infections, and these trigger or exacerbate airway hyperresponsiveness.

CELLULAR MECHANISMS OF EARLY IMMUNE SYSTEM DIFFERENTIATION

Thus whereas viral infections are associated in later life with worsening of asthma symptoms, early life exposures may somehow influence the likelihood of the development of airway hyperresponsiveness or even atopy. This effect may be protective or provocative. How this may come about, however, remains conjecture, but it has been suggested that IFN- γ may have a regulating influence on the early modeling of immune response patterns. A possible mechanism is through the inhibitory effects of IFN- γ on the activity and possibly the differentiation of a subset of helper T lymphocytes (T_H cells) associated with airway inflammatory symptoms.⁷ Thus stimulation of IFN- γ would dampen the activity of such cells and perhaps even prevent the original establishment as a colony of memory cells after first allergen exposure. Conversely, if the respiratory infection enhances T_{H2} activity (ie, generation of IL-4 or -5), the tendency toward asthma is favored.

Murine models of allergy and, increasingly, biochemical data from humans have generated the concept that, in very early life, undifferentiated T_H cells (T_{H0}) can be directed toward either a T_{H1} or a T_{H2} phenotype with differing patterns of cytokine secretion; these cells perhaps also may switch between the 2 phenotypes under certain conditions of their surrounding environment. The pattern of cytokines that each phenotype elaborates, which includes a variety of interleukins and other intercellular

mediators, is distinct. In general, T_{H1} secretory products (particularly IL-2 and IFN- γ) are associated with pathogen-defeating immune responses, whereas T_{H2} products (notably IL-4 and IL-5) enhance allergic responses. Direct evidence in humans for this T_H -cell polarity is found in the highly skewed cytokine production profile of peripheral blood mononuclear cells obtained from pollen-sensitive subjects; the production of IL-4 was substantially higher and the production of IFN- γ was substantially lower than in nonatopic control subjects.¹³

The details of what takes place in a naive immune system to direct it toward an allergy-prone (T_{H2} -dominated) state are, as yet, poorly understood but appear to have a basis in genetic predisposition and cellular responses to environmental exposures. Most fundamental is an established genetic propensity for atopy, but the overlay of early environmental exposures may be crucial to the actual development of the manifestations. It has been suggested that fetal exposures in the form of placental transfer of common aeroallergens or foods constitute the first, and a variable, environmental influence on a developing immune system.⁷ Such exposures stimulate fetal elevations in IL-4 levels and a transitory IgE antibody response, as well as an IgG response. These responses are believed to emanate from actions of naive (but allergen-specific) T_{H0} (precursor) cells capable of both IL-2 and IL-4 synthesis.⁷ Factors that determine the further differentiation of these cells into T_{H1} or T_{H2} clones that will be responsive to that same allergen are unknown.

Interestingly, subsequent repeated exposure to allergens through the gastric mucosa appears to cause the deletion of T-cell clones that recognize the allergens, resulting in a loss of immune response with maturation; conversely, repeated airway mucosa exposures induce progressively higher T_{H1} - or T_{H2} -mediated responses.¹⁴ Further, allergen-specific memory T cells appear to be produced in comparable frequencies by both atopic and nonatopic adults, so that atopy does not depend on the presence of an allergen-specific T-cell clone. Rather, it is the cytokine profile of those memory cells (hence, their designation as T_{H1} or T_{H2} cells) that is believed responsible for the 2 divergent reactions to subsequent allergen exposure.⁷

The key question, with regard to the development of an atopic disposition, then becomes: How does a primary immune response by naive T cells develop into an atopic or nonatopic (T_{H1} - or T_{H2} -dominated) pattern? This is a question of great interest that is far from answered. Genetically determined levels of IFN- γ may play a role, because lower levels may establish a milieu permissive for T_{H2} cells. Pertinent to this is the observation that levels of IFN- γ in cord blood are lower in children who go on to experience the development of an atopic constitution than in those who do not.^{15,16} In addition, children at high risk of atopy (by genetic background) have peripheral T cells with a lower capacity for IFN- γ synthesis.

The manner in which allergens are processed by APCs of a naive system also may be important.⁷ For example, a slow postnatal development of dendritic cells in the nasal mucosa may lead to poor immune processing and differentiation.¹⁷ In rodent experimental systems, APCs present allergens to CD8⁺ T cells that produce high levels of IFN- γ . Because this cytokine is inhibitory to the emergence and action of the T_{H2} phenotype, sluggish APC activity may reduce a needed allergen-processing activity in the airways that would minimize T_{H2} emergence.¹⁸

Additional studies have led to the postulate that there is a "window" during early development during which time allergic sensitization occurs and sets the pattern of atopic response in some individuals.⁷ The likelihood of sensitization, as opposed to benign response to allergen exposure during this time, is hypothesized to depend on the lymphocytic and cytokine milieu of the individual at that time, which is seen to be a plastic internal environment capable of switching or being induced by environmental factors to switch, between a physiologic condition supportive of either a benign response to potential allergens or an atopic response. It is further suggested that the naive immune system is skewed toward a T_{H2} phenotype, but, with normal exposures to environmental allergens, it becomes T_{H1} dominated in nonatopic individuals. Those who develop allergen sensitivities are seen to have a dysfunction in this early T_{H1}-enhancing shift.

A final comment should be directed toward the changing perspective on the role of diverse cells in the asthmatic response. Whereas much attention originally was placed on mast cells and their secretions as instigators of airway inflammation and on eosinophil influx as a major component of late-phase airway reactions, several other less-recognized airway cellular constituents are emerging as integral players in the inflammatory/immune process. That lymphocytes are integral to the process is clear, not just from the foregoing discussion but also as evidenced by a correlation in the abundance of several subsets in the plasma of patients with asthma while they are undergoing acute attacks.¹⁹ Compared with those in normal control subjects, 3 subsets of T cells and an indicator of their activation (by the presence of IL-2 surface receptors) are significantly elevated ($P < .05$) in plasma during such an attack, and their numbers return to pre-event levels when symptoms resolve. Resident airway cells, notably epithelial cells and fibroblasts, also clearly are implicated in airway inflammation. For example, bronchial epithelial cells produce RANTES, a chemoattractant for eosinophils that appears also to induce their transendothelial migration and to stimulate their release of eosinophil cationic protein.²⁰

Lung fibroblasts also produce RANTES and another eosinophil chemoattractant, eotaxin, and do so in a manner that may be under complex control by T_{H1} and T_{H2} cytokines.²¹ These are just a few examples of an abundant new generation of biochemical data that hopefully will answer more questions about the ontogeny and persistence of airway allergic responses that they will generate.

SUMMARY

The changing epidemiologic patterns of airway allergic diseases have motivated a search for common themes and cellular or biochemical explanations. Clearly, there is an interplay between lifestyle, early-childhood and even fetal allergen exposures, and genetically determined cellular properties that will need to be unraveled over the next several years to find a satisfactory answer. Nevertheless, progress is being made in understanding the cellular mechanisms that underlie an atopic propensity. Continued progress in this direction promises to deepen our appreciation for the complexity of the immune system and its interface with environment. Ideally, we will reach a level of understanding that allows the manipulation of disease-generating cellular patterning so that the epidemic in asthma can be vanquished.

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