Internal and External Environmental Influences in Allergic Diseases

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Allergy defines the hypersensitivity reactions caused by allergen-specific immunoglobulin E binding to mast cells, being cross-linked by subsequent allergen exposure, and releasing mediators of immediate hypersensitivity that initiate inflammatory cascades. Allergic diseases have both genetic and environmental components. Growing concern about allergic disease comes from the observed increase in incidence and prevalence and association with the development of asthma. This risk appears to be compounded by Western lifestyle, including indoor environment, diet, air pollution, and psychological stress. With increasing understanding of these mechanisms, new and improved modes of therapy are being developed to manage and possibly prevent allergic sensitization.

Allergy describes a series of immune-based reactions occurring as a result of the induction of allergen-specific immunoglobulin E (IgE) that binds to mast cells via high-affinity Fcε receptors. Subsequent reexposure of the individual to the inciting allergen causes a cross-linking of the mast cell–bound IgE with activation and release of mast cell contents such as histamine, leukotrienes, and tryptase. These mediators create the signs and symptoms of allergic airway disease that typically begin within 1 hour of allergen exposure. Six to 24 hours later, a second round of symptoms (called late-phase reactions) develops from the recruited inflammatory cells in the airway resulting in major congestion, itching, and drainage.

Allergic diseases are common clinical problems. Up to 30% of the general population suffers from various forms of this malady during a normal life span. Physician visits occur more commonly for allergic problems than any other single category except cardiovascular. Up to 70% of all asthma cases involve IgE-mediated reactions as major pathogenic mechanisms.

An estimated 40 million Americans (nearly 25% of the population) have allergic diseases. Allergic rhinitis (AR), still considered by many to be a trivial condition that has no significant morbidity or mortality, has an extremely large socioeconomic impact in the world today, particularly in industrialized nations. Allergic rhinitis, asthma, and contact dermatitis (or eczema) are among the 15 most common diagnoses made by physicians. Estimates of the annual medical costs associated with AR are $3.4 billion ($2.3 billion in medications and $1.1 billion in physician billings). These figures do not include an estimated 20 million lost school days and 3.5 million lost workdays each year, resulting in $154 million in direct wages lost because of seasonal nasal allergies.

Additionally, it is conservatively estimated that there are up to 28 million days of decreased productivity (in school and work) from either the symptoms of the illness or the side effects of medications used to treat it. Moreover, increased symptoms of AR have been linked to depression and anxiety disorders. Also, effects of AR on cognition and learning are well documented. Children with suboptimally treated AR have documented learning deficiencies.

Overview of an Allergic Reaction Normal Immunity

In the normal host, presentation of antigen for a specific protective immune response elicits a complex series of events that results in a mixed cellular and humoral protective response, the intensity and nature of which depends on the specific inciting antigen. In general, extracellular pathogens (ie, bacteria) incite primarily a humoral response while intracellular pathogens (ie, virus, fungi, mycobacteria, etc) elicit a cell-mediated response. The central control of the cellular versus humoral response to an antigenic challenge appears to be via production of specific cytokine milieu.

A central source of these cytokines comes from CD4+ helper T (Th) cell subpopulations, often referred to as Th1 and Th2 cells. Human Th1 cells secrete a specific cytokine profile including interferon-γ (IFN-γ) and tumor necrosis factor β (TNF-β). These cytokines are important helper factors in the generation of cellular immune responses. Additionally, IFN-γ in particular has an antagonistic activity against Th2 cytokines. Interleukin-12 (IL-12), produced primarily by activated macrophages, plays a central role in inducing IFN-γ production.

In contrast, Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13, which are involved in isotype switching of B cells as well as proliferation and differentiation into antibody-secreting plasma cells. In particular, IL-4 and IL-13 are involved in the isotype switch from IgM to IgE.
the antibody responsible for classic allergy and implicated in the pathophysiology of allergic asthma. Interleukin-4 and IL-10 are also regulatory cytokines, antagonizing the activities of Th1 cytokines. Thus, the nature, intensity, and duration of a specific immune response depend on the delicate balance between Th1 and Th2 numbers or activities (or both).

It is now commonly understood that an allergic reaction involves the production of allergen-specific IgE, which binds to mast cells and, on subsequent cross-linking by allergen reexposure, causes mast cell degranulation with release of preformed mediators such as histamine. Depending on the target organs affected, signs and symptoms of the specific allergic condition ensue. Yet, it is less well appreciated that the immunologic basis for local syndromes such as AR and asthma actually results from a systemic dysregulation of immunity.

An allergic reaction occurs when the IgE-mast cell-eosinophil mechanism is directed against an otherwise harmless antigenic stimulus such as pollen, mold, insect and animal proteins, collectively referred to as allergens. In the genetically susceptible host, allergen-specific IgE is formed after initial exposure of naive T and B cells. The allergen-specific IgE binds to mast cells typically located at mucosal surfaces and around blood vessels (perivascular). Subsequent exposure of the host to the specific allergen allows for a crosslinking of the mast cell–bound IgE, resulting in mast cell activation and degranulation.

**Gene–Environmental Interactions in Allergic Diseases**

Identifying the genes involved in a complex disease is a significant biomedical challenge. In the case of allergy and asthma, genotype and environmental factors both participate in development of disease that results in the atopic phenotype. The interaction between these two risk factors is complex and variable among distinct populations.

- **Genetic Component of Atopy—Clinical**

  Population studies have demonstrated that risk for allergic disease is inherited, most likely in polygenic fashion. In families in which one parent has atopic disease, at least 30% of the children will also be allergic; if both parents are atopic, at least 50% of the children will have similar, if not worse, allergies (suggesting a dominantly inherited condition). Yet, the familial clustering could also reflect shared environmental exposures and does not firmly prove a genetic basis for the disease. This gene-environmental interaction is supported by atopy and asthma studies among monozygotic twins raised in different environments having differences in concordance of disease.

  Unlike diseases for which one culprit gene with complete penetrance has been identified, there exist probably at least 50 genes that influence susceptibility to allergy or asthma phenotypes (Table). This suggests a relatively small effect of individual genes. Rather, the net clinical phenotypic expression of allergy or asthma occurs through complex interactions with other genes and environmental risk factors.

  Multiple genome-wide surveys have been conducted on asthma and related atopic diseases. They have focused on various phenotypic manifestations of atopic disease, such as elevated IgE levels, bronchial hyperresponsiveness, asthma, allergic sensitization, and eosinophilia. The most consistent data show evidence for linkage to chromosome 6p and chromosome 12q. The areas on chromosome 6 are close to the major histocompatibility complex, or human leukocyte antigen region, which has long been known to be associated with atopic phenotypes. Several other studies have implicated up to 20 other regions in allergy and asthma susceptibility.

- **Environmental Factors That Have an Impact on Allergy and Asthma—**It is clear that environment plays a role in the susceptibility to the development of allergic sensitization (Figure 1). Several environmental factors have been intensively studied for their impact on allergy and asthma sensitization. Epidemiologic studies have shown increased incidence and severity of allergic diseases, especially rhinitis and asthma in urban areas, especially the inner city. The basis for this finding is likely multifactorial, because poor air quality from environmental pollution, indoor allergen exposure, and high stress lifestyles have all been associated with increased risk for AR or asthma (or both).

  External environmental influences are largely related to air quality. One of

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**Table**

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**Figure 1. Environmental factors that influence development of allergic sensitization.**

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**Checklist**

- **External Factors**
  - Allergens
    - Pollens
    - Mold spores
    - Pollutants
    - Ozone
    - Diesel exhaust particles
  - Internal Factors
    - Dust mites
    - Cockroach
    - Animal danders
    - Mold spores
the proposed reasons for increased incidence of asthma in urban areas is air pollution. There is a clear association between ozone levels, nitrogen dioxide and sulfur dioxide air particulates (especially diesel exhaust), and allergic and asthmatic mechanisms. The proposed mechanism for the association between pollution and allergy and asthma relates to the ability of these pollutants to augment allergen-specific IgE production, as well as alter the normal Th1/Th2 ratio toward a predominant Th2 profile.

The immune-modulating effect of diesel exhaust particles on allergy and asthma is widely recognized. They have been shown to act as an adjuvant during the sensitization phase of allergen response, and they exacerbate symptoms in patients who are already sensitized. In atopic, ragweed-sensitive patients, exposure to diesel exhaust particles plus ragweed allergen increases both total IgE and ragweed-specific IgE levels in nasal lavage fluid. In fact, the combination of diesel exhaust particles and allergen produces an even greater rise in ragweed-specific IgE than the allergen alone, suggesting magnification of a recall antigen response in patients who are already sensitized. Not only do diesel exhaust particles influence allergen-specific IgE production, but they also appear to skew cytokine release toward a Th2 pattern. Diesel exhaust particles can even promote primary allergic sensitization to a neoallergen.

Endotoxin and Allergic Sensitization: The Hygiene Hypothesis—Although many external environmental influences are associated with increased susceptibility to allergy and asthma, other more internal environmental factors such as various infections, group care settings, and farm homes all appear to have a potentially protective effect on allergy and asthma susceptibility. The hygiene hypothesis has been advanced to explain the increasing incidence of allergy and asthma in Western society. According to this theory, Western lifestyle habits, including overly clean environments, dietary changes, extensive use of antimicrobials, widespread vaccinations, and indoor air-quality problems all contribute to the “proallergic” environmental influence.

Endotoxin (lipopolysaccharide [LPS]) and allergen often occur together in indoor air. After inhalation into the airways, both can cause inflammation; however, they appear to influence the immune balance through different pathways. Endotoxin stimulates innate immune elements (monocytes, macrophages, natural killer cells), whereas allergens stimulate adaptive immunity (T cells, B cells). Recent studies suggest that exposure of infants at high genetic risk for the development of allergy and asthma to endotoxin during infancy may protect against atopy and asthma by promoting enhanced Th1 response and tolerance to allergens. This concept is supported by studies that show rural children in farm homes have a lower incidence of atopy and asthma while having a significantly higher LPS exposure in the home when compared with urban children.

Role of Stress in Allergy and Asthma

A common clinical observation is the often adverse relationship between stress and disease. Indeed, various sources have estimated that up to 75% of all visits to physicians’ offices are stress-related. This estimate appears to be particularly true in relation to immune-based dysfunctions. Although such dysfunctions have been thought of primarily as immunosuppressive, recent data have suggested immunoregulatory dysfunctions may play a more central role. Thus, because of an inappropriate rather than deficient immune response, otherwise healthy individuals may, at times of significant stress, have one or a combination of the following: increased incidence, severity, and duration of multiple distinct conditions.

Psychological stress has known adverse effects on existing allergic and asthmatic diseases. There is also an association between higher rates of allergic disorders and depressive symptoms, as well as anxiety disorders. First, depression predisposes individuals to allergic disorders through endocrine and immune dysregulation. Depression and stress can augment humoral immunity at the expense of cell-mediated immunity, thus providing a clear mechanism through which stress and depression favor the production of IgE. The immunologic changes associated with depressive disorders, particularly the shift from Th1 to Th2, promote allergic responses

Hypercortisolism is associated with depression. In this context, it is noteworthy that glucocorticoids enhance Th2 activity, and thus amplify IL-4 and IgE antibody synthesis. Indeed, pharmacologic as well as physiologic levels of glucocorticoids can simultaneously increase production of IL-4 and suppress IL-2 in vivo; these data help explain why patients with allergy may actually show increases in IgE when treated with glucocorticoids.

Catecholamines also influence allergic and asthmatic diseases. Norepinephrine acts through β-adrenoceptors to inhibit IL-2, interferon (IFN-γ), and IL-12, while stimulating production of IL-6 and IL-10. Norepinephrine also enhances IL-4–stimulated IgE production. Mast cells have a close anatomic relation with nerve fibers that release norepinephrine, among other substances. Moreover, catecholamine production from sympathetic nerve terminals and the adrenal medulla.

Although there are relatively few studies to date, current evidence supports modulation of allergic responses by mood and psychological stressors. For example, atopic dermatitis is a chronic inflammatory skin disease that affects 10% to 15% of the population. One study demonstrated significant positive correlations between a number of Minnesota Multiphasic Personality Inventory distress-related scales and enhanced skin reactivity in response to allergens. Similarly, Sugarman et al found that psychiatric patients had higher levels of IgE to specific allergens than control subjects; the highest levels were recorded in depressed patients, with lower levels in schizophrenic and alcoholic patients. Older literature also suggested that allergic skin disorders were substantially reduced by administration of antianxiety medications.

A recent study provides excellent evidence that stress can enhance allergic inflammatory responses. Sputum
Diagnosis of Allergic Sensitivity

Allergic disease is diagnosed primarily by history of specific exposures coupled with characteristic clinical findings confirmed by appropriate laboratory tests that demonstrate the presence of allergen-specific IgE (Figure 2). Pertinent history includes the presence of indoor pets, symptoms that worsen in the spring or fall pollen seasons (or both), or after exposure to dusty or moldy areas, and possible development of comorbidities after the rhinitis symptoms begin, including skin and lower airway symptoms such as itching, rash, coughing, dyspnea, or wheezing, occurring singly or in combination.

Therapy for Allergic Diseases

A comprehensive treatment plan typically involves a combination of allergen avoidance or controlled exposure coupled with appropriate pharmacotherapy. When indicated, allergen immunotherapy can be most useful.

Allergen Avoidance—Perhaps the most fundamental of therapeutic principles is to avoid exposure to allergens that provoke immediate hypersensitivity reactions. For example, if a patient becomes ill with lip and tongue swelling, wheezing, and diarrhea after eating shell fish, it is wise for that individual to avoid that food in the future. The same holds true for indoor pets to which a patient is sensitive. There is simply no cat or dog shot that works as well as getting Fido or Fluffy out of the house. Many allergens cannot be avoided completely, such as allergens contained in dust and mold, as well as grass and weed pollens. In these cases, minimizing exposure can have a positive therapeutic benefit.

Drug Therapy—The classes of drugs available are used to either counteract the effects of most cell mediators on target cell receptors or decrease the release of mediators from mast cells. Specific details and drug treatment strategies are the main subjects of the accompanying article in this supplement.

Checklist

- **History**
  - Seasonality of symptoms
  - Specific exposures
  - Recurrence of symptoms
  - Family history

- **Physical Examination**
  - Facial examination
  - Conjunctival pallor
  - Denne’s lines
  - Turbinate swelling/pallor
  - Nasal crease
  - Oropharyngeal cobblestoning
  - Absence of lymphadenopathy

- **Skin Examination**
  - Eczema
  - Urticaria

- **Chest Examination**
  - Prolonged expiration
  - Wheezing

- **Laboratory Examination**
  - Allergy skin test
  - In vitro allergen-specific IgE
  - ImmunoCAP
  - Radioallergosorbent test (RAST)

Figure 2. Diagnosis of allergic sensitivity.

Physical findings include periorbital darkening (often called *allergic shiners*), nasal congestion from swollen turbinates, nonexudative oropharyngeal cobblestoning, and sometimes expiratory wheezing. The suspicion of allergic sensitivity is confirmed with either allergy skin testing or in vitro methods such as radioallergosorbent (RAST) or the more sensitive ImmunoCAP assay.

Although asthma is a complex, multifactoral syndrome, patients with allergic asthma are worsened clinically when exposed to allergens to which they are sensitive. Further, AIT has been shown to alter the Th1-Th2 cytokine imbalance known to be associated with allergic mechanisms in patients with AR. This same imbalance has been shown to be involved with the immunopathophysiology of asthma as well. Allergen immunotherapy can have a direct effect on eosinophils and mast cells, diminishing their responsiveness and activities in allergic diseases. Additionally, because airway remodeling appears to be a consequence of the chronic airway inflammation characteristic of allergic asthma, AIT may well prevent or even alter established inflammatory airway changes. Finally, as it is appreciated that AR is a risk factor for the development of asthma in both children and adults, aggressive management with AIT...
might actually prevent the development of asthma, at least in selected populations.\textsuperscript{75}

**Comment**

Allergic diseases are common maladies of Western society that have significant impact on health care in terms of socioeconomic costs, morbidity and, in the case of asthma, mortality. Environmental influences, both internal and external, are thought to have the most impact on the increasing prevalence of allergic diseases. Proper diagnosis is critical to initiate appropriate therapy.

New approaches to therapy will include attention to environmental control of exposure, stress management, and earlier intervention to alter and readjust immune imbalances so characteristic of these clinical conditions.

**Acknowledgment**

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