ALLERGY AND ALLERGIC DISEASES

First of Two Parts

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Allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic ill health. These diseases are increasing in prevalence, and they add considerably to the burden of health care costs. In Sweden, for example, the number of children with allergic rhinitis, asthma, or eczema roughly doubled over a 12-year period, and in the United States the annual cost of treating asthma is about $6 billion.

The term “allergy” was introduced in 1906 by von Pirquet, who recognized that in both protective immunity and hypersensitivity reactions, antigens had induced changes in reactivity. With the passage of time the word has become corrupted and is now frequently used synonymously with IgE-mediated allergic disease. It was von Pirquet’s intent that the term should apply to the “uncommitted” biologic response, which may lead either to immunity (a beneficial effect) or allergic disease (a harmful effect).

The term “atopy” (from the Greek atopos, meaning out of place) is often used to describe IgE-mediated diseases. Persons with atopy have a hereditary predisposition to produce IgE antibodies against common environmental allergens and have one or more atopic diseases (i.e., allergic rhinitis, asthma, and atopic eczema). Some allergic diseases, such as contact dermatitis and hypersensitivity pneumonitis, develop through IgE-independent mechanisms and in this sense can be considered nonatopic allergic conditions. This article reviews the basis of atopic allergy, the diseases with which it is associated, and approaches to treatment.

ATOPY AND TYPE 2 HELPER T CELLS

All of us inhale aeroallergens derived from pollen, house-dust mites, and cat dander. In general, adults and children without atopy mount a low-grade immunologic response; they produce allergen-specific IgG1 and IgG4 antibodies, and in vitro their T cells respond to the allergen with a moderate degree of proliferation and the production of interferon-γ by type 1 helper T (Th1) cells. Persons with atopy, by contrast, have an exaggerated response characterized by the production of allergen-specific IgE antibodies; they have elevated serum levels of IgE antibodies and positive reactions to extracts of common aeroallergens on skin-prick tests. T cells from their blood respond to allergens in vitro by inducing cytokines produced by type 2 helper T (Th2) cells (i.e., interleukin-4, 5, and 13), rather than cytokines produced by Th1 cells (interferon-γ and interleukin-2). There are many exceptions to this rule, but the immunopathological hallmark of allergic disease is the infiltration of affected tissue by Th2 cells.

In utero, T cells of the fetus are primed by common environmental allergens that cross the placenta. As a result, the immune response of virtually all newborn infants is dominated by Th2 cells. It has been proposed that during subsequent development the normal (i.e., nonatopic) infant’s immune system shifts in favor of a Th1-mediated response to inhaled allergens (a process termed “immune deviation”), whereas in the potentially atopic infant there is a further increase in Th2 cells that were primed in utero. Microbes are probably the chief stimuli of protective Th1-mediated immunity. Macrophages that engulf microbes secrete interleukin-12, which induces Th1 cells and natural killer cells to produce interferon-γ, thereby shifting the immune system into an “allergy-protective” Th1-mediated response. Other factors may also influence whether Th1 or Th2 cells dominate the response, including the amount of allergen, the duration of exposure to the allergen, and the avidity of allergen-specific interactions between T cells and antigen-presenting cells (Fig. 1).

RISING INCIDENCE OF ALLERGIC DISEASE

The marked increase in the prevalence of atopic disease in Western Europe, the United States, and Australasia during recent years indicates the importance of environmental influences. An informative example is the change in the incidence of seasonal allergic rhinitis and asthma after the reunification of Germany. These disorders were less common in East Germany than West Germany before reunification, whereas since reunification, the prevalence of atopy and hay fever, but not asthma, has increased among children who spent their early childhood in East Ger-
This phenomenon raises the possibility that a Western lifestyle accounts for the increases in prevalence. Perhaps in Western countries the developing immune system is deprived of the microbial antigens that stimulate Th1 cells, because the environment is relatively clean and the use of antibiotics for minor illnesses in early life is widespread.17

The results of epidemiologic studies support this theory. Evidence that the bacteria that colonize the gastrointestinal tract prevent atopic sensitization was found in studies of one-year-old infants in countries with a low prevalence of atopy (Estonia) and a high prevalence (Sweden). Lactobacilli and eubacteria predominated in Estonian infants, whereas clostridia were more frequent in Swedish infants.18 When studied one year later, the children with atopy were colonized less often by lactobacilli and had higher levels of aerobic bacteria (such as coliforms and Staphylococcus aureus) than children without atopy.19 Moreover, atopy and allergic asthma were less frequent in populations exposed to Helicobacter pylori, Toxoplasma gondii, and hepatitis A virus. By producing an environment rich in interleukin-12, these microbes could drive a Th1-mediated response. This mechanism may explain why in Europe and Africa, farming or living in a rural community, which increases the likelihood of exposure to bacteria found in barns, protects against atopic disease.20

Other factors that may favor the Th2 phenotype in infants include diet and being born when pollen counts are high.21 Furthermore, atopic allergic diseases are less common in younger children who have three or more older siblings and among children who have had measles or hepatitis A — another indication that repeated immune stimulation may protect against atopic allergy.22 This view is supported by the study by Ball et al., who provided evidence that exposure of young children to older children at home or to other children at day-care centers protected against the development of asthma and frequent wheezing in childhood.23

This “hygiene” hypothesis is not easily reconciled...
with the increased prevalence among poor blacks in
the United States of atopic asthma associated with
sensitization to cockroaches and house-dust mites.\textsuperscript{25,26}
However, we need more data on the rates of infec-
tion by foodborne and orofecal microbes in inner
cities in the United States: the compounding effect
of gut flora that does not protect against atopy and
heavy exposure to allergens may explain this paradox.

The development of specific allergic diseases may
be related to alterations in the target organ. For ex-
ample, the cofactors required for an asthma attack
may include respiratory virus infections and exposure
to allergens, tobacco smoke, and air pollutants.\textsuperscript{27}
These factors, alone or in combination, may alter immuno-
regulatory mechanisms at mucosal surfaces in ways
that promote a Th2-mediated allergic inflammatory
response (Fig. 2).

**ALLERGENS**

Many allergens are soluble proteins that function
in their natural state as enzymes, by, for example, in-
ducing proteolysis. Allergenic properties may be re-
lated to the enzymatic activity (e.g., increased muco-
sal permeability) and to aerodynamic properties, which
in turn depend on the size of the particle. The major
allergens of Western developed countries are Der p 1
and Der p 2, from the house-dust mite (\textit{Dermatoph-
agogus pteronyssinus}); Fel d 1, from the cat (\textit{Felis do-
metricus}); several tree allergens, including Bet v 1 from
the birch tree (\textit{Betula verrucosa}); and many grasses,
such as Phl p 1 and Phl p 5 from timothy (\textit{Phleum
pratense}). The ragweed allergens Amb a 1, 2, 3, 5,
and 6 from short ragweed (\textit{Ambrosia artemisifolia})
and Amb t 5 from giant ragweed (\textit{Ambrosia trifida})
are important seasonal allergens in North America.
Allergies to Hev b 1 through 7 from latex, the milky
sap harvested from the rubber tree (\textit{Hevea brasiliensis}),
and Ara h 1, 2, and 3, which are highly allergenic pea-
nut proteins, are increasingly important problems.\textsuperscript{28}

**GENETICS**

Atopic allergic diseases are familial and have a ge-
netic basis. The difficulties of conducting genetic stud-
ies of allergy are due in part to the multiple markers
for atopy and allergic diseases. For instance, atopy
(manifested by positive skin-prick tests and elevated
serum IgE levels) and asthma (manifested by airway
hyperresponsiveness) are not always inherited togeth-

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**Figure 2. Factors Influencing the Development of Atopy and Allergic Inflammation Mediated by Th2 Cells (Atopic Allergic Disease).**

The induction of atopy is dependent on interactions between genes and the environment. The induction of atopic allergic disease may require further interactions between defects in the target organ and various environmental triggers. \textit{FceRI-}\textit{b} denotes the gene for the \textit{b} chain of the high-affinity receptor for IgE.
er. Techniques used to identify genes that are relevant to allergy and asthma include the candidate-gene approach, which depends on the identification of polymorphisms in a known gene, and positional cloning, which links the inheritance of a specific chromosomal region with the inheritance of a disease. Such studies have linked several loci to atopy, but the clinical relevance of these findings is unclear. Examples are the associations between an allele of the HLA-DR locus and reactivity to the ragweed allergen Ra 5 and the linkage of atopy to a polymorphism of the gene for the β chain of the high-affinity receptor for IgE (FcεRI-β) and to the interleukin-4 family of cytokine genes on chromosome 5. By contrast, certain alleles of the tumor necrosis factor gene complex, although linked to asthma, are independent of serum IgE levels and other measures of atopy.

Polymorphisms of the FcεRI-β gene appear to be associated with equal frequency to severe atopy, asthma, and eczema. Also, positional cloning indicates that chromosomal 2q, 5q, 6q, 12q, and 13q contain loci linked to both asthma and atopy. Polymorphisms in the gene encoding the high-affinity receptor for bacterial lipopolysaccharide (CD14) have been linked to total serum IgE levels and may help explain the association between childhood infections and the development of atopy.

Several of the genes and genetic regions that have been linked to atopy and asthma have also been implicated in rheumatoid arthritis (chromosome 2) and inflammatory bowel disease (chromosomes 2 and 12). There has been recent interest in loci with pharmacologic relevance. Polymorphisms within the promoter region of the 5-lipoxygenase gene and in the β-adrenergic receptor gene may regulate the response to inhibitors of 5-lipoxygenase or β-adrenergic agonists, respectively. These findings raise the possibility that genotyping will become useful in planning therapy for asthma and other allergic diseases.

IgE AND ITS RECEPTORS

Acute allergic reactions result from the release of preformed granule-associated mediators, membrane-derived lipids, cytokines, and chemokines when an allergen interacts with IgE that is bound to mast cells or basophils by the α chain of the high-affinity IgE receptor (FcεRI-α). This receptor also occurs on antigen-presenting cells, where it can facilitate the IgE-dependent trapping and presentation of allergen to T cells. Eosinophils also possess FcεRI-α, but in these cells it is almost entirely intracellular; after being released by degranulation of the eosinophil, it may help regulate local levels of IgE.

The most important inducers of the production of IgE are interleukin-4 and interleukin-13. These cytokines initiate transcription of the gene for the epsilon class of the constant region (Cε) of the immunoglobulin heavy chain. The production of IgE also requires two transcription factors, nuclear factor κB and STAT-6; the former pathway involves the co-stimulatory molecules CD40 and the CD40 ligand (CD154), and the latter is activated when interleukin-4 binds to the high-affinity α chain of the interleukin-4 receptor.

Allergens, including the products of some infectious microorganisms (e.g., Aspergillus fumigatus) and helminthic parasites, evoke Th2-mediated responses that are characterized by high serum levels of IgE, whereas other bacterial antigens (such as those associated with Listeria monocytogenes and Mycobacterium tuberculosis) elicit a Th1-mediated response that is dominated by cellular immunity (the appearance of cytotoxic T cells and delayed hypersensitivity). In this latter class of organisms, the DNA contains repeating sequences of cytosine and guanosine nucleosides called CpG repeats. These CpG repeats can bind to receptors on antigen-presenting cells and trigger the release of interleukin-12. This cytokine, which is produced almost exclusively by antigen-presenting cells, drives and maintains the Th1-mediated response. Furthermore, the interferon-γ produced by activated Th1 cells and interleukin-18, produced by macrophages, join forces to suppress the production of IgE antibodies. Therefore, at least theoretically, interferon-γ, interleukin-12, and interleukin-18, either alone or in combination, have therapeutic potential for inhibiting the synthesis of IgE. Furthermore (as discussed below), CpG repeats may redirect allergens to produce a Th1-mediated, rather than a Th2-mediated, immune response.

The physiologic relevance of the low-affinity IgE receptor (CD23) remains speculative. It may be involved in antigen trapping and presentation, thereby augmenting the production of interleukin-4 or interleukin-13. It can, however, override the positive effects of antigen presentation by combining with excess IgE and antigen under conditions in which high levels of interleukin-4 have caused the up-regulation of this type of receptor.

ALLERGIC INFLAMMATION

In a person with atopy, exposure of the skin, nose, or airway to a single dose of allergen produces a cutaneous wheal-and-flare reaction, sneezing and runny nose, or wheezing within minutes. Depending on the amount of the allergen, these immediate hypersensitivity reactions are followed by a late-phase reaction, which reaches a peak six to nine hours after exposure to the allergen and then slowly resolves. In the skin, late-phase reactions are characterized by an edematous, red, and slightly indurated swelling; in the nose, by sustained blockage; and in the lung, by further wheezing.

Immediate hypersensitivity is the basis of acute allergic reactions. It is caused by molecules released by mast cells when an allergen interacts with membrane-
bound IgE. The complex of allergen, IgE, and FcεRI on the surface of the mast cell triggers a noncyto-
toxic, energy-dependent release of preformed, granule-
associated histamine and tryptase and the membrane-
derived lipid mediators leukotrienes, prostaglandins,
and platelet-activating factor. These mast-cell medi-
ators have a critical role in anaphylaxis, rhinoconjunc-
tivitis, and urticaria. The role of histamine in chronic
asthma and eczema is probably minimal, however, as
shown by the relative ineffectiveness of histamine an-
tagonts in controlling these conditions.

Mast cells produce the three cysteinyl leukotrienes
C₄, D₄, and E₄, which cause the contraction of smooth
muscles, vasodilatation, increased vascular permeabil-
ity, and the hypersecretion of mucus when they bind
to specific receptors.⁴³

Eosinophils, macrophages, and monocytes are also
major sources of cysteinyl leukotrienes. Mast cells also
contain tryptase, a four-chain neutral protease that
activates the protease-activated receptors on endothe-
lial and epithelial cells. The activation of these recep-
tors initiates a cascade of events, including the up-regu-
lation of adhesion molecules that selectively attract
eosinophils and basophils.⁴⁷

In the cutaneous late-phase reaction, eosinophils
and neutrophils accumulate, and then CD4⁺ T cells
and basophils infiltrate the site.⁴⁴ Late-phase asth-
matic⁴⁵ and nasal¹⁰ reactions have a similar pattern of
cellular infiltration, although basophils are not prom-
inent in the lower airways.⁴⁶

Depending on the target organ, late-phase reactions
can be provoked by the activation of mast cells or T cells. In the skin of atopic subjects and normal sub-
jects, cross-linking of mast-cell–bound IgE with an
antibody against IgE provokes both immediate hyper-
sensitivity and late-phase reactions.⁴⁷ Late-phase reac-
tions can be induced in patients with atopic asthma in
the absence of immediate hypersensitivity involving
mast cells. These reactions were induced in patients
with asthma who were allergic to cats by an intrader-
mal injection of peptides derived from a cat allergen.⁴⁸

The fact that these late-phase reactions were independ-
ent of IgE and were major-histocompatibility-com-
plex (MHC)–restricted indicates that the activation
of T cells alone is sufficient to initiate airway narrow-
ing in patients with allergic asthma.

Antigen-presenting cells are critical in initiating
and controlling allergic inflammation. Dendritic cells
and cutaneous Langerhans’ cells are particularly im-
portant in asthma and atopic eczema, respectively.
They present antigen to CD4⁺ Th2 cells in an MHC
class II–restricted fashion. Overproduction of the
granulocyte–macrophage colony-stimulating factor in
the airway mucosa of patients with asthma enhances
antigen presentation and increases the local accumu-
lation of macrophages.¹² Alveolar macrophages ob-
tained from patients with asthma by bronchoalveolar
lavage present allergen to CD4⁺ T cells and stimulate
the production of Th2-type cytokines,⁴⁹ whereas al-
veolar macrophages from control subjects do not.

Th2-type cytokines such as interleukin-4, 5, 9,
and 13 influence a wide range of events associated
with chronic allergic inflammation. Interleukin-4 and
interleukin-13 stimulate the production of IgE and
vascular-cell adhesion molecule 1; interleukin-5 and in-
terleukin-9 are involved in the development of eo-
sinophils; interleukin-4 and interleukin-9 promote
the development of mast cells; interleukin-9 and inter-
leukin-13 help promote airway hyperresponsiveness⁵⁰;
and interleukin-4, interleukin-9, and interleukin-13

### Table 1. The Role of Cytokines Produced by Th2 Cells in Chronic Allergic Inflammation.

<table>
<thead>
<tr>
<th>Event</th>
<th>Th2-Type Cytokines Involved</th>
<th>Other Factors Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of IgE</td>
<td>Interleukin-4, interleukin-9, and interleukin-13</td>
<td>Interferon-γ, interleukin-12, and interleukin-18</td>
</tr>
<tr>
<td>Development and accumulation of eosinophils and basophils</td>
<td>Interleukin-4, interleukin-5, interleukin-9, and interleukin-13</td>
<td>Interleukin-3, granulocyte–macrophage colony-stimulating factor, eotaxin-1, eotaxin-2, eotaxin-3, RANTES, monocyte chemotactic protein 3, monocyte chemotactic protein 4, and vascular-cell adhesion molecule 1</td>
</tr>
<tr>
<td>Development of mast cells</td>
<td>Interleukin-4, interleukin-9, and interleukin-13</td>
<td>Interleukin-3 and stem-cell factor</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Interleukin-9 and interleukin-13</td>
<td>Interleukin-11 and growth factors involved in remodeling</td>
</tr>
<tr>
<td>Overproduction of mucus</td>
<td>Interleukin-4, interleukin-9, and interleukin-13</td>
<td>Histamine, leukotriene C₄, leukotriene D₄, substance P, and calcitonin-gene–related peptide</td>
</tr>
</tbody>
</table>
promote the overproduction of mucus (Table 1). Eosinophils can injure mucosal surfaces by releasing toxic basic proteins, cysteinyl leukotrienes, and platelet-activating factor. They also damage inhibitory M2 muscarinic receptors, which may allow unchecked cholinergic responses in patients with asthma. By contrast, eosinophils may also repair damage, since they produce fibrogenic growth factors and matrix metalloproteinase, which remodel airway tissue in asthma.

Interleukin-5 releases both mature and immature eosinophils from the bone marrow, regulates the expression of the transmembrane isoform of its own receptor, and is essential for the terminal differentiation of committed eosinophil precursors. The preferential accumulation of eosinophils occurs through the interactions between selective adhesion molecules (αβ integrin and vascular-cell adhesion molecule), the migration of eosinophils toward receptors for CC chemokines as a result of recruitment by eotaxin-1, eotaxin-2, eotaxin-3, RANTES, monocyte chemotactic protein (MCP) 3 and MCP-4; prolonged survival (delayed apoptosis) under the influence of interleukin-5, interleukin-3, and granulocyte–macrophage colony-stimulating factor; and the local differentiation of tis-

Figure 3. Pathways Leading to Acute and Chronic Allergic Reactions.
Acute allergic reactions are due to the antigen-induced release of histamine and lipid mediators from mast cells. In the skin and upper airways, basophils (not shown) may also participate in allergic tissue reactions. Chronic allergic reactions, including the late-phase reaction, may depend on a combination of pathways, including the recruitment of eosinophils, the liberation of mast-cell products by histamine-releasing factors, and neurogenic inflammation involving neurotrophins and neuropeptides. MHC denotes major histocompatibility complex.
sue-infiltrating cosinophil precursors induced by inter-leukin-5. These neurotrophins are secreted by macrophages, T cells, eosinophils, and mast cells. Neuropeptides, particularly substance P, calcitonin-gene-related peptide, and neuropeitin A (all of which are located predominantly in sensory neurons, but also in inflammatory cells), cause characteristic features of allergic inflammation, including vasodilatation, increased vascular permeability, and in the lung, contraction of the smooth muscles of the airway and hypersecretion of mucus. They also release histamine from mast cells in the lung. Tryptase can also trigger nerve cells to release neuropeptides by binding to protease-activated receptors. Further amplifications of chronic allergic reactions may be mediated by histamine-releasing factor or factors. Pathways leading to acute and chronic allergic reactions are shown in Figure 3.

REFERENCES


55. Clutterbuck EJ, Hirst EM, Sanderson CJ. Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GMCSF. Blood 1989;73:1504-12.


