

## Review Articles

*Advances in Immunology*

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**ALLERGY AND ALLERGIC DISEASES****First of Two Parts**

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**A**LLERGIC 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,<sup>1</sup> and in the United States the annual cost of treating asthma is about \$6 billion.<sup>2</sup>

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.<sup>3</sup> 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

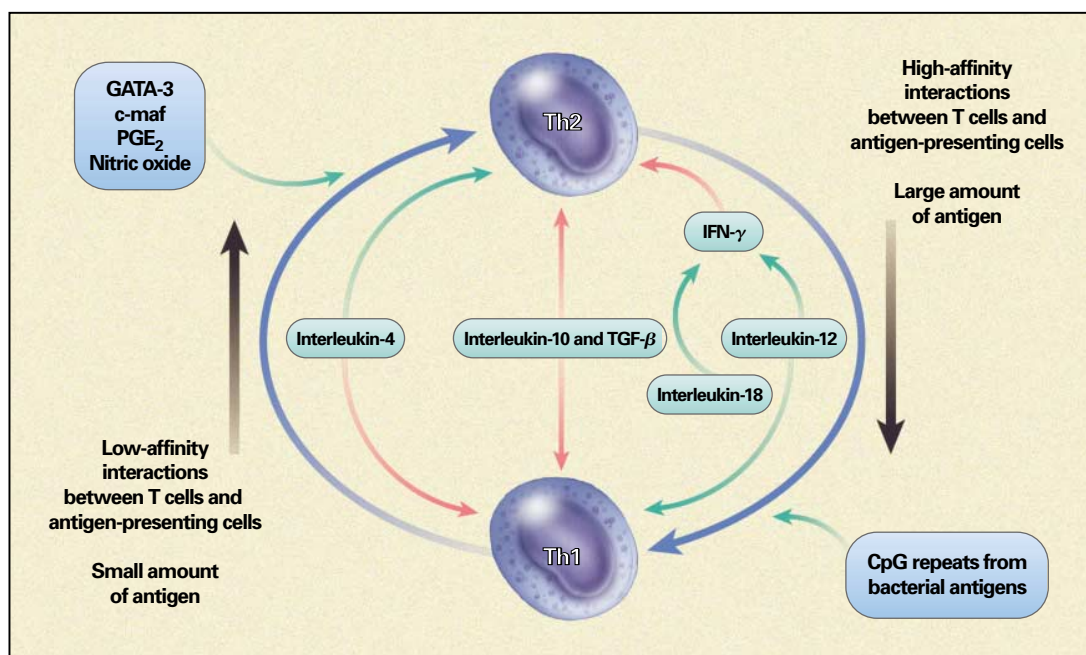
and children without atopy mount a low-grade immunologic response; they produce allergen-specific IgG1 and IgG4 antibodies,<sup>4</sup> and in vitro their T cells respond to the allergen with a moderate degree of proliferation and the production of interferon- $\gamma$  by type 1 helper T (Th1) cells.<sup>5-7</sup> 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),<sup>5,7</sup> rather than cytokines produced by Th1 cells (interferon- $\gamma$  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.<sup>8-10</sup>

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.<sup>11</sup> 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"),<sup>12</sup> 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- $\gamma$ , 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<sup>13,14</sup> (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,<sup>16</sup> 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-

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**Figure 1.** Immunologic and Cellular Factors Regulating the Expression of Th1 and Th2 Cells.

Whether the immune response is dominated by Th1 or Th2 cells is dependent on interleukin-12 and interleukin-4, respectively, as well as on the avidity of interactions between T cells and antigen-presenting cells and the amount of allergen to which the immune system is exposed (antigen).<sup>13,14</sup> In addition, the presence of cytidine–phosphate–guanosine (CpG) repeats derived from bacteria favors the Th1 phenotype, whereas the presence of transcription factors such as GATA-3 favors the Th2 phenotype,<sup>15</sup> as does the presence of c-maf and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Nitric oxide favors the expression of Th2 cells by being less inhibitory to Th2 cells than Th1 cells, whereas in humans interleukin-10 and transforming growth factor β (TGF-β) generally dampen the responses of both types of cells. Interferon-γ (IFN-γ) inhibits Th2-mediated responses; both interleukin-12 and interleukin-18 release interferon-γ from T cells. Interleukin-4 inhibits the expression of Th1 cells and promotes Th2-mediated responses. Green arrows indicate stimulatory effects, and red arrows inhibitory effects, of the cytokines.

many.<sup>17</sup> 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.<sup>18</sup>

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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup>

Other factors that may favor the Th2 phenotype in infants include diet and being born when pollen counts are high.<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup>

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.<sup>25,26</sup> However, we need more data on the rates of infection 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 example, the cofactors required for an asthma attack may include respiratory virus infections and exposure to allergens, tobacco smoke, and air pollutants.<sup>27</sup> These factors, alone or in combination, may alter immunoregulatory mechanisms at mucosal surfaces in ways that promote a Th2-mediated allergic inflammatory response (Fig. 2).

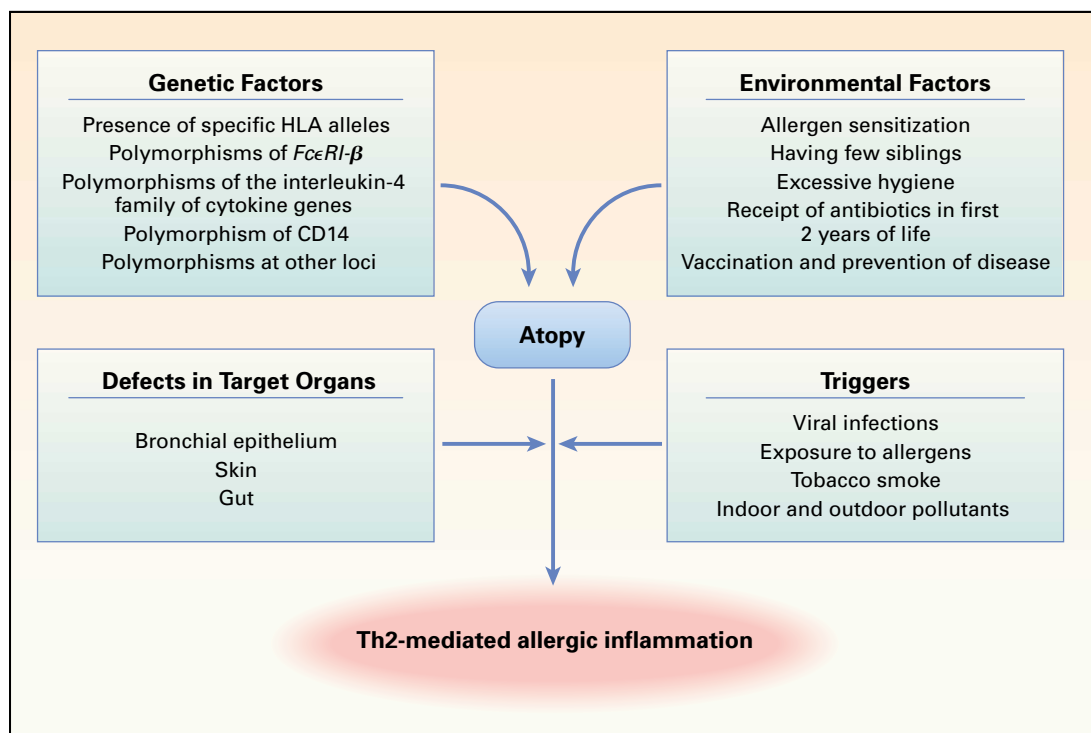
### ALLERGENS

Many allergens are soluble proteins that function in their natural state as enzymes, by, for example, inducing proteolysis. Allergenic properties may be related to the enzymatic activity (e.g., increased mucosal 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 (*Dermatophagoides pteronyssinus*); Fel d 1, from the cat (*Felis domesticus*); several tree allergens, including Bet v 1 from the birch tree (*Betula verrucosa*); and many grasses, such as Phl p 1 and Phl p 5 from timothy (*Pleum pratense*). The ragweed allergens Amb a 1, 2, 3, 5, and 6 from short ragweed (*Ambrosia artemisiifolia*) and Amb t 5 from giant ragweed (*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 (*Hevea brasiliensis*), and Ara h 1, 2, and 3, which are highly allergenic peanut proteins, are increasingly important problems.<sup>28</sup>

### GENETICS

Atopic allergic diseases are familial and have a genetic basis. The difficulties of conducting genetic studies 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 together.



**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. *FcεRI-β* denotes the gene for the β 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.<sup>22</sup> 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<sup>29</sup> and the linkage of atopy to a polymorphism of the gene for the  $\beta$  chain of the high-affinity receptor for IgE (*Fc $\epsilon$ RI- $\beta$* )<sup>30</sup> and to the interleukin-4 family of cytokine genes on chromosome 5.<sup>31</sup> 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.<sup>32</sup>

Polymorphisms of the *Fc $\epsilon$ RI- $\beta$*  gene appear to be associated with equal frequency to severe atopy, asthma, and eczema. Also, positional cloning indicates that chromosomes 2q, 5q, 6q, 12q, and 13q contain loci linked to both asthma and atopy.<sup>22</sup> 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.<sup>33</sup>

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).<sup>22</sup> There has been recent interest in loci with pharmacologic relevance. Polymorphisms within the promoter region of the 5-lipoxygenase gene<sup>34</sup> and in the  $\beta$ -adrenergic receptor gene may regulate the response to inhibitors of 5-lipoxygenase or  $\beta$ -adrenergic agonists, respectively.<sup>22,34</sup> 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  $\alpha$  chain of the high-affinity IgE receptor (*Fc $\epsilon$ RI- $\alpha$* ).<sup>35</sup> This receptor also occurs on antigen-presenting cells, where it can facilitate the IgE-dependent trapping and presentation of allergen to T cells.<sup>36</sup> Eosinophils also possess *Fc $\epsilon$ RI- $\alpha$* , 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.<sup>37</sup>

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 ( $C_{\epsilon}$ ) of the immunoglobulin heavy chain. The production of IgE also

requires two transcription factors, nuclear factor  $\kappa$ B and STAT-6; the former pathway involves the costimulatory molecules CD40 and the CD40 ligand (CD154), and the latter is activated when interleukin-4 binds to the high-affinity  $\alpha$  chain of the interleukin-4 receptor.<sup>38</sup>

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- $\gamma$  produced by activated Th1 cells<sup>39</sup> and interleukin-18, produced by macrophages,<sup>39</sup> join forces to suppress the production of IgE antibodies.<sup>40</sup> Therefore, at least theoretically, interferon- $\gamma$ , 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.<sup>41</sup> 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.<sup>42</sup>

### 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-

**TABLE 1.** THE ROLE OF CYTOKINES PRODUCED BY Th2 CELLS IN CHRONIC ALLERGIC INFLAMMATION.

EVENT	Th2-TYPE CYTOKINES INVOLVED	OTHER FACTORS INVOLVED
Production of IgE	Interleukin-4, interleukin-9, and interleukin-13	Interferon- $\gamma$ , interleukin-12, and interleukin-18
Development and accumulation of eosinophils and basophils	Interleukin-4, interleukin-5, interleukin-9, and interleukin-13	Interleukin-3, granulocyte-macrophage colony-stimulating factor, eotaxin-1, eotaxin-2, eotaxin-3, RANTES, monocyte chemoattractant protein 3, monocyte chemoattractant protein 4, and vascular-cell adhesion molecule 1
Development of mast cells	Interleukin-4, interleukin-9, and interleukin-13	Interleukin-3 and stem-cell factor
Airway hyperresponsiveness	Interleukin-9 and interleukin-13	Interleukin-11 and growth factors involved in remodeling
Overproduction of mucus	Interleukin-4, interleukin-9, and interleukin-13	Histamine, leukotriene C <sub>4</sub> , leukotriene D <sub>4</sub> , substance P, and calcitonin-gene-related peptide

bound IgE. The complex of allergen, IgE, and Fc $\epsilon$ RI on the surface of the mast cell triggers a noncytotoxic, 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 mediators have a critical role in anaphylaxis, rhinoconjunctivitis, and urticaria. The role of histamine in chronic asthma and eczema is probably minimal, however, as shown by the relative ineffectiveness of histamine antagonists in controlling these conditions.

Mast cells produce the three cysteinyl leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>, which cause the contraction of smooth muscles, vasodilatation, increased vascular permeability, and the hypersecretion of mucus when they bind to specific receptors.<sup>43</sup>

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 endothelial and epithelial cells. The activation of these receptors initiates a cascade of events, including the up-regulation of adhesion molecules that selectively attract eosinophils and basophils.<sup>27</sup>

In the cutaneous late-phase reaction, eosinophils and neutrophils accumulate, and then CD4<sup>+</sup> T cells and basophils infiltrate the site.<sup>44</sup> Late-phase asthmatic<sup>45</sup> and nasal<sup>10</sup> reactions have a similar pattern of cellular infiltration, although basophils are not prominent in the lower airways.<sup>46</sup>

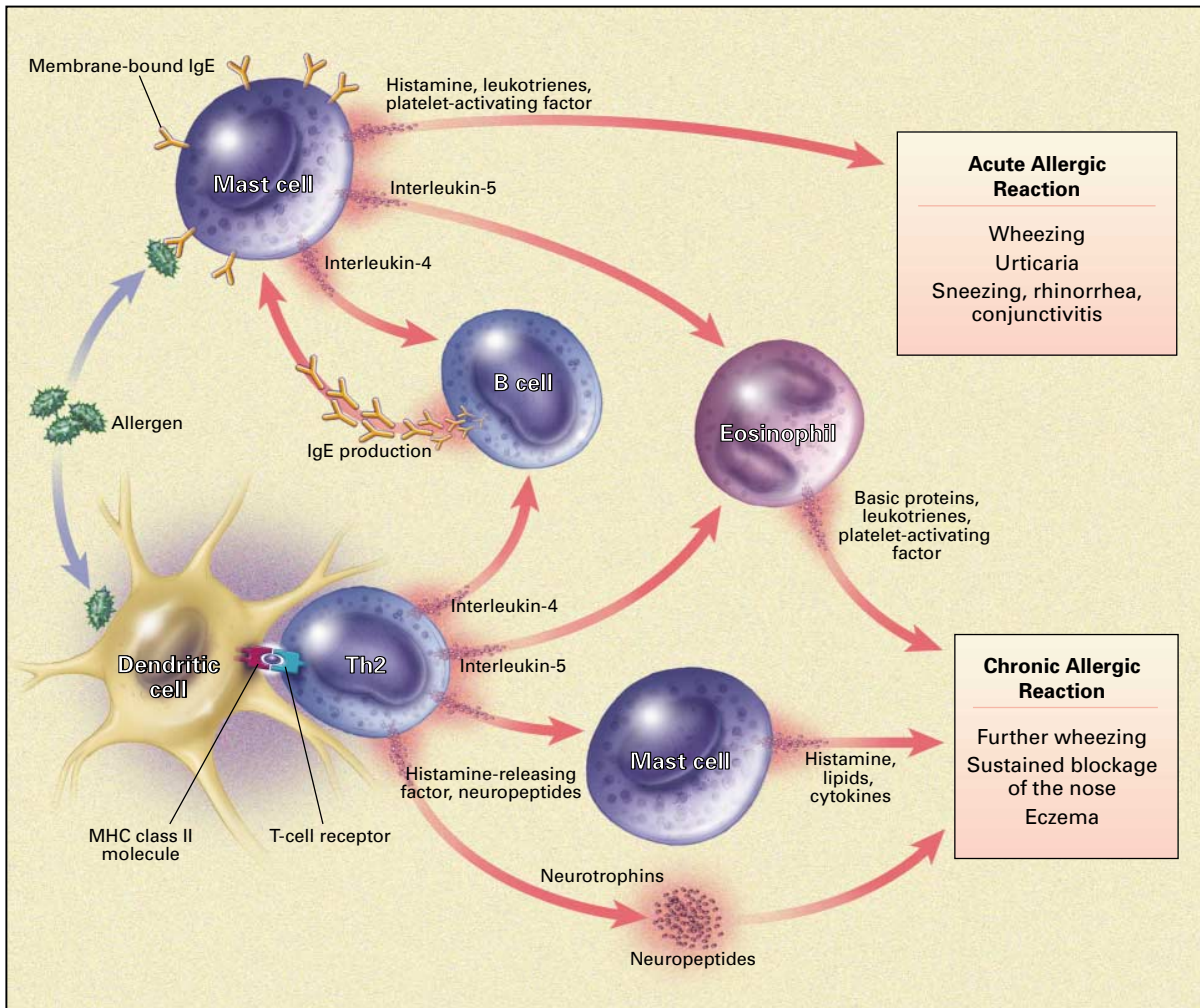
Depending on the target organ, late-phase reactions can be provoked by the activation of mast cells or T cells. In the skin of atopic subjects and normal subjects, cross-linking of mast-cell-bound IgE with an antibody against IgE provokes both immediate hyper-

sensitivity and late-phase reactions.<sup>47</sup> Late-phase reactions 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 intradermal injection of peptides derived from a cat allergen.<sup>48</sup> The fact that these late-phase reactions were independent of IgE and were major-histocompatibility-complex (MHC)-restricted indicates that the activation of T cells alone is sufficient to initiate airway narrowing in patients with allergic asthma.

Antigen-presenting cells are critical in initiating and controlling allergic inflammation. Dendritic cells and cutaneous Langerhans' cells are particularly important in asthma and atopic eczema, respectively. They present antigen to CD4<sup>+</sup> 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 accumulation of macrophages.<sup>12</sup> Alveolar macrophages obtained from patients with asthma by bronchoalveolar lavage present allergen to CD4<sup>+</sup> T cells and stimulate the production of Th2-type cytokines,<sup>49</sup> whereas alveolar 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 interleukin-9 are involved in the development of eosinophils; interleukin-4 and interleukin-9 promote the development of mast cells; interleukin-9 and interleukin-13 help promote airway hyperresponsiveness<sup>50</sup>; and interleukin-4, interleukin-9, and interleukin-13





**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,<sup>62</sup> and neurogenic inflammation involving neurotrophins and neuropeptides. MHC denotes major histocompatibility complex.

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.<sup>51</sup> By contrast, eosinophils may also repair damage, since they produce fibrogenic growth factors and matrix metalloproteinase, which remodel airway tissue in asthma.<sup>52</sup> Interleukin-5 releases both mature and immature eosinophils from the bone marrow,<sup>53</sup> regulates the expression of the transmembrane isoform of its own re-

ceptor,<sup>54</sup> and is essential for the terminal differentiation of committed eosinophil precursors.<sup>55</sup> The preferential accumulation of eosinophils occurs through the interactions between selective adhesion molecules ( $\alpha_4\beta_1$  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 chemoattractant 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-

sue-infiltrating eosinophil precursors induced by interleukin-5.<sup>56</sup>

Allergic inflammation may also follow the release of neuropeptides from nerve cells by the action of nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3.<sup>57,58</sup> These neurotrophins are secreted by macrophages, T cells, eosinophils, and mast cells.<sup>58</sup> Neuropeptides, particularly substance P, calcitonin-gene-related peptide, and neurokinin 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.<sup>59</sup> They also release histamine from mast cells in the lungs.<sup>60</sup> 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.<sup>61</sup> Pathways leading to acute and chronic allergic reactions are shown in Figure 3.

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