Immunology of the Upper Airway and Pathophysiology and Treatment of Allergic Rhinitis

Fuad M. Baroody
Robert M. Naclerio

Key Points

- The immune system protects the organism from infectious microbes and avoids responses that produce damage to host tissues.
- The immune system is divided into the innate and adaptive systems. The adaptive immune system recognizes different specific antigens, adapts to changing environments, and provides immunologic memory.
- The innate immune system includes all aspects of the host defense mechanisms, such as barrier mechanisms (epithelium, mucus layer, mucociliary transport) and soluble bioactive molecules (complement proteins, defensins, cytokines, mediators, and enzymes).
- Cell-mediated immune responses are orchestrated by T cells and their cytokines and mount appropriate reactions to offending antigens.
- Allergic rhinitis is an example of a type I, IgE-dependent, mast cell–mediated immune reaction, whereby the release of mast cell or basophil mediators creates responses to sensitizing allergens.
- Allergic rhinitis is a common disease that, although benign, leads to significant impairment of quality of life and a large health care expenditure.
- The pathophysiology of allergic rhinitis revolves around mast cell release of inflammatory mediators followed by a chronic inflammatory response, in which the eosinophil plays a predominant role and which leads to hyperresponsiveness of the nasal mucosa to subsequent stimulation.
- H1 antihistamines are effective agents for the treatment of allergic rhinitis but often do not completely control the bothersome symptom of nasal congestion.
- Leukotriene receptor antagonists are also effective in controlling the symptoms of allergic rhinitis, and their efficacy parallels that of antihistamines.
- Intranasal steroids are potent anti-inflammatory agents that control allergic nasal inflammation and are superior in efficacy to antihistamines and leukotriene receptor antagonists in controlling symptoms of the disease and improving quality of life.
- Immunotherapy is effective in the treatment of refractory allergic rhinitis and can be administered subcutaneously or by the sublingual route.
- Immunotherapy is the only allergic rhinitis therapy that has been shown to alter the natural course of the disease.

The importance of the immune system in health and disease has long been recognized. Not only does the immune system—with its diverse collection of pathogenic mechanisms—protect the organism from infectious microbes; it also avoids responses that produce damage to host tissues. This basic property of the immune system relies on detecting structural features of the pathogens that are distinct from those of host cells.

The immune system is divided into the innate and adaptive systems. The following features of the adaptive immune system distinguish it from the innate system: specificity of antigen recognition, diversity of the antigen receptor repertoire, rapid clonal expansion, adaptiveness to the changing environment, and immunologic memory. The innate immune system recognizes foreign invaders immediately via pattern recognition receptors, whereas the adaptive immune system takes time to mount a response. Evidence also suggests that activation of the innate immune system triggers the direction of the adaptive immune responses, illustrating the relationship between the two systems.

Innate Immunity and Adaptive Immunity

Broadly defined, the innate immune system consists of all aspects of the host defense mechanisms that are encoded in the germline genes of
the host. These include barrier mechanisms, such as epithelial cell layers that express tight cell-cell contact, the secreted mucus layer that overlays the epithelium, and the epithelial cilia that sweep away this mucus layer. The innate response also includes soluble proteins and small bioactive molecules that either are constitutively present in biologic fluids (such as the complement proteins and defensins) or are released from activated cells (including cytokines, chemokines, lipid mediators of inflammation, and bioactive amines and enzymes). Activated phagocytes (including neutrophils, monocytes, and macrophages) are also part of the innate immune system.

Mucosal surfaces of the upper airway are less resistant than the skin and are thus more common portals for offending pathogens. The innate immune system reduces that vulnerability through the presence of various physical and biochemical factors. A good example is the enzyme lysozyme, which is distributed widely in secretions and can split the cell walls of most bacteria. If an offending organism penetrates this first line of defense, bone marrow–derived phagocytic cells attempt to engulf and destroy it. Lastly, the innate immune system includes cell-surface receptors that bind molecular patterns expressed on the surfaces of invading microbes.

Unlike the innate mechanisms of defense, the adaptive immune system manifests exquisite specificity for its target antigens. Adaptive responses are based primarily on the antigen-specific receptors expressed on the surfaces of T and B lymphocytes. These antigen-specific receptors in the adaptive immune response are assembled by somatic rearrangement of germline gene elements to form intact T-cell receptor (TCR) and B-cell antigen receptor genes. The assembly of antigen receptors from a collection of a few hundred germline-encoded gene elements permits the formation of millions of different antigen receptors, each with a potentially unique specificity for a different antigen.

Because the recognition molecules used by the innate system are expressed broadly on a large number of cells, this system is poised to act rapidly after an invading pathogen is encountered. The second set of responses constitutes the adaptive immune response. Because the adaptive system is composed of small numbers of cells with specificity for any individual pathogen, the responding cells must proliferate after encountering the pathogen to attain sufficient numbers to mount an effective response against the microbe. Thus the adaptive response generally expresses itself temporally after the innate response in host defense. A key feature of the adaptive system is that it produces long-lived cells that persist in an apparently dormant state but that can re-express effector functions rapidly after repeated encounter with an antigen. This feature provides the adaptive response with immune memory, permitting it to contribute to a more effective host response against specific pathogens when they are encountered a second time. This chapter first discusses the innate immune system and its components, followed by the different cells and effector responses of the adaptive immune system.

**Innate Immune System**

Innate immune effectors are critical for effective host defense. In addition to local defenses at mucosal surfaces, such as mucus and mucociliary transport, the effectors of innate immunity include Toll-like receptors (TLRs), antimicrobial peptides, phagocytic cells, natural killer (NK) cells, and complement.

**Toll-Like Receptors**

An important advance in our understanding of innate immunity to microbial pathogens was the identification of a human homolog of the *Drosophila* Toll receptor. Mammalian TLR family members are transmembrane effectors containing repeated leucine-rich motifs in their extracellular portions. Mammalian TLR proteins contain a cytoplasmic portion that is homologous to the interleukin-1 (IL-1) receptor, and can therefore trigger intracellular signaling pathways. TLRs are pattern recognition receptors that recognize pathogen-associated molecular patterns present on a variety of bacteria, viruses, and fungi. The activation of TLRs induces expression of costimulatory molecules and the release of cytokines that instruct the adaptive immune response. Finally, TLRs directly activate host defense mechanisms that directly combat the foreign invader or contribute to tissue injury.

**Expression and Distribution of Toll-Like Receptors**

TLRs were initially found to be expressed in all lymphoid tissue but are most highly expressed in peripheral blood leukocytes. Expression of TLR messenger RNA (mRNA) has been found in monocytes, B cells, T cells, and dendritic cells. The expression of TLRs on cells of the monocyte-macrophage lineage is consistent with the role of TLRs in modulating inflammatory responses via cytokine release. Some TLRs are located intracellularly, like TLR9.

**Activators of the Different Toll-Like Receptors**

Lipopolysaccharides (LPSs) of gram-negative bacteria generate responses mediated via the TLR4 receptor. Microbial lipoproteins and lipopeptides have been shown to activate cells in a TLR2-dependent manner. Lipoproteins have been found extensively in both gram-positive and gram-negative bacteria as well as spirochetes. Mammalian TLR9 mediates the immune response to a specific pattern in bacterial DNA, an unmethylated cytidine-phosphate-guanosine ( CpG) dinucleotide with appropriate flanking regions. These CpG-DNA sequences are 20-fold more common in microbial than in mammalian DNA; thus, mammalian TLR9 is more likely to be activated by bacterial DNA than by mammalian DNA. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. Mammalian TLR5 has been shown to mediate the response to flagellin, a component of bacterial flagella. Mammalian TLR3 mediates the response to double-stranded RNA, a molecular pattern expressed by many viruses during infection. Activation of TLR3 induces interferons IFN-α and IFN-β, cytokines important for antiviral responses. Finally, single-stranded RNA binds to TLR7 and TLR8.

**Toll-Like Receptors and the Adaptive Immune Response**

Critical proinflammatory and immunomodulatory cytokines, such as IL-1, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor-α (TNF-α) have been shown to be induced after activation of TLRs by microbial ligands. Activation of TLRs on dendritic cells triggers their maturation, leading to cell surface changes that enhance antigen presentation, thus promoting the ability of these cells to present antigen to T cells and generate type 1 helper T cell (TH1) responses critical for cell-mediated immunity. Therefore, activation of TLRs as part of the innate response can influence and modulate the adaptive T-cell response and modify the shaping of the TH1/TH2 balance.

**Toll-Like Receptors and the Host**

Like the *Drosophila* Toll receptor, mammalian TLRs have been shown to play a prominent role in directly activating host defense mechanisms. For example, activation of TLR2 by microbial lipoproteins induces activation of the inducible nitric oxide synthase promoter that leads to the production of nitric oxide, a known antimicrobial agent. In *Drosophila*, activation of Toll leads to the nuclear factor κB (NF-κB)–dependent induction of a variety of antimicrobial peptides. In a similar fashion, it has been shown that LPS induces β-defensin-2 in tracheobronchial epithelium, suggesting similar pathways in humans. The activation of TLRs can also be detrimental, causing tissue injury. The administration of LPS to mice can result in shock, a feature that depends on TLR4, and microbial lipoproteins induce features of apoptosis via TLR2. Thus, microbial lipoproteins have the ability to induce both TLR-dependent activation of host defense and tissue pathology. This might be one way for the immune system to activate host defenses and then down-regulate the response to avoid causing tissue injury.

**Antimicrobial Peptides**

The function of antimicrobial peptides (AMPs) is essential to the mammalian immune response. They participate primarily in the innate immune system and are used as a first-line immune defense by many organisms, including plants, bacteria, insects, and vertebrates. AMPs directly kill a broad spectrum of microbes, including gram-positive and gram-negative bacteria, fungi, and certain viruses. In addition, these peptides interact with the host itself, triggering events that complement their role as antibiotics. AMPs can be divided into several categories on the basis of their structures, but most of them maintain certain common structural features, such as a cationic charge and the ability to interact
with bacterial membranes through hydrophobic amino acids. Two major families of AMPs have been characterized in mammals—defensins and cathelicidins.

**Cathelicidins**
Most cathelicidins undergo extracellular proteolytic cleavage that releases their C-terminal peptide containing the antimicrobial activity. The only known human cathelicidin, hCAP-18 (human cationic antimicrobial peptide, 18 kDa), was initially identified in granules of human neutrophils. Its free C-terminal peptide is called LL-37 and has a broad spectrum of antimicrobial activity in vitro against *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Listeria monocytogenes*, and *Staphylococcus aureus*. LL-37, a chemoattractant for mast cells and human neutrophils, monocytes, and T cells, induces degranulation and histamine release in mast cells. Thus, this AMP has the potential to participate in the innate immune response both by killing bacteria and by recruiting a cellular immune response and promoting tissue inflammation.

**Defensins**
Defensins are a broadly dispersed family of gene-encoded antimicrobials that exhibit antimicrobial activity against bacteria, fungi, and enveloped viruses. Defensins are classified into three distinct families: the α-defensins, the β-defensins, and the θ-defensins.

**α-Defensins**
The α-defensins are 29 to 35 amino acids in length. Human neutrophils express a number of distinct defensins. To date, six α-defensins have been identified. Of these, four are known as α-defensins 1, 2, 3, and 4 (also referred to as human neutrophil peptides HNP-1 through -4). The other two α-defensins, known as human defensins 5 and 6 (HD-5, HD-6), are abundantly expressed in Paneth cells of the small intestinal crypts, in epithelial cells of the female urogenital tract, and in nasal and bronchial epithelial cells. HNP-1 through HNP-4 are localized in azurphilic granules of neutrophils and contribute to the oxygen-independent killing of phagocyted microorganisms. Furthermore, HNP-1 through HNP-3 can either increase the expression of TNF-α and IL-1 in human monocytes that have been activated by *S. aureus* or reduce the expression of vascular cellular adhesion molecule-1 (VCAM-1) in human umbilical vein endothelial cells activated by TNF-α.

**β-Defensins**
In human beings, four types of β-defensins have been identified thus far; they are referred to as human β-defensins (HBDs) 1 through 4. They have a broad spectrum of antimicrobial activity, bind to CCR6, and are chemotactic for immature dendritic cells and memory T cells. Human β-defensin 2 can also promote histamine release and prostaglandin (PG) D₂ production in mast cells, suggesting a role in allergic reactions. Thus, the defensins, like the cathelicidins, can contribute to the immune response by both killing bacteria and influencing the cellular innate and adaptive immune response.

**θ-Defensins**
θ-defensins have been isolated from rhesus monkey neutrophils, but no data about the presence of these molecules in different tissues are currently available.

**Tissue Distribution of Antimicrobial Peptides**
All of the β-defensins are present in the respiratory system. These are expressed at various levels in the epithelia of the trachea and lung as well as in the serous cells of the submucosal glands. Cathelicidins are also present in the conducting airway epithelium, pulmonary epithelium, and submucosal glands. Investigations have also documented the presence of these peptides in the nose and paranasal sinuses in health and diseases including rhinitis, chronic rhinosinusitis, and nasal polyps.

Self and Nonself
The essence of specific immunity is the ability to discriminate between self and nonself. This ability allows the immune system to attack and destroy potentially harmful microorganisms without simultaneously destroying the person infected by these agents, a process also known as self-tolerance. Failure of self-tolerance underlies the broad class of autoimmune diseases. This crucial function is mediated by the molecules determined by the human leukocyte antigen (HLA) complex. Initial study of the HLA system focused on the role of these antigens in determining the success of organ and tissue transplantation. The HLA complex and its homologs in other species were thus termed the major histocompatibility complex (MHC). In humans, the MHC occupies about 4000 kDAs of DNA on the short arm of chromosome 6 and contains many genes that encode molecules for various functions. Among these molecules, a group of glycoproteins belonging to the immunoglobulin (Ig) supergene family are present on the cell surface and play a major role in allowing the immune system to distinguish between self and nonself. These are MHC class I molecules (HLA-A, -B, and -C) and class II molecules (HLA-DR, -DQ, and -DP).

MHC class I molecules are present on the surface of most nucleated somatic cells. They are responsible for presenting endogenous antigens to cytotoxic T cells, allowing the recognition and elimination of virus-infected cells and cells containing autoantibodies. A class I molecule and an antigenic (e.g., viral) peptide are recognized as a complex by the TCR. When cytotoxic T-lymphocyte precursors recognize the combination of a particular foreign peptide and a particular class I molecule on a sensitizing cell, they proliferate and differentiate to become mature cytotoxic T lymphocytes (CD8⁺). These mature lymphocytes recognize and kill only target cells that bear the same class I molecule and the same viral peptide as were present on the sensitizing cells. Cytotoxic T-lymphocyte killing is peptide specific (lymphocytes will not lyse a target cell bearing the same class I molecule infected with a different virus). Cytotoxic T-lymphocyte killing is also class I restricted (lymphocytes will not lyse a cell bearing a different class I molecule infected with the same virus).

In contrast to class I molecules, MHC class II molecules are expressed primarily on immunocompetent antigen-presenting cells (APCs), including macrophages, monocytes, dendritic cells, and B lymphocytes. Class II molecules can be up-regulated by IFN-γ, permitting these cells to present antigens to CD4⁺ cells at sites of inflammation. Class II molecules allow binding of peptides of 10 to 25 amino acids, and the bound peptide and the class II molecule constitute the ligand for the receptor on a CD4⁺ T lymphocyte (helper T cell). Thus, just as class I molecules restrict the recognition of peptides by CD8⁺ T cells, class II molecules restrict the recognition of peptides by CD4⁺ T cells. Therefore, class II molecules are necessary for the presentation of exogenous antigen to helper T cells.

**Adaptive Immunity: Cells of the Immune System and Their Responses**
The human immune system consists of dispersed organs (spleen, thymus, lymph nodes) and of cells capable of moving from the bone marrow to the blood and the lymphatic system. An intact immune response includes many subsets of leukocytes that can be discriminated morphologically through the use of conventional histologic stains and, more accurately, by surface phenotype as defined by monoclonal antibody binding to registered differentiation antigens. These differentiation antigens are assigned cluster of differentiation (CD) numbers; updates are issued by the International Workshop on Human Leukocyte Differentiation Antigens (published at http://www.hcdm.org/ Home/tabid/36/Default.aspx).

The pluriptotent stem cells, which are derived from the yolk sac and ultimately reside in the bone marrow, are the progenitor cells from which all cells of the immune system are derived (Fig. 40-1). These pluriptotent stem cells give rise to lymphoid and myeloid stem cells. Lymphoid stem cells differentiate further into the three major populations: T cells, B cells, and NK cells. T cells are defined by their cell surface expression of the TCR, a transmembrane heterodimeric protein that binds processed antigen displayed by APCs. B cells are phenotypically defined by their expression of the B-cell receptor for antigen, membrane-bound immunoglobulin. NK cells are defined morphologically as large granular lymphocytes. They are distinguished by their lack
of either TCR or surface immunoglobulin. They recognize their virus-infected or tumor cell targets through the use of a complex collection of activating and inhibitory cell surface receptors. Lymphocytes represent about 25% of leukocytes in the peripheral blood. The relative contribution of each subtype to this percentage is as follows: T lymphocytes, 80%; B lymphocytes, 10%; NK large granular lymphocytes, 10%.

Myeloid stem cells give rise to different forms of granulocytes, megakaryocytes and erythrocytes. Cells of the granulocyte lineage that play prominent immune roles include neutrophils, monocytes, eosinophils, basophils, and mast cells. Differentiation of the myeloid stem cell occurs in the bone marrow, as does the development of B lymphocytes and NK lymphocytes. In contrast, T-cell progenitors leave the bone marrow and migrate to the thymus, where they differentiate into mature T lymphocytes.

Differentiation of lymphoid and myeloid stem cells depends on their interaction through their surface receptors with soluble ligands (cytokines) or surface ligands (cell interaction molecules). Therefore, proliferation and differentiation along one of the myeloid or lymphoid lineages are controlled (1) through the spatially and temporally regulated exposure of these stem cells to different ligands or factors and (2) through the differential expression of receptors on the stem cells. Cytokines have pleiotropic effects on the development of lymphoid and myeloid cells, affecting both growth and maintenance of pluripotent stem cells and their development and differentiation to specific lineages. Stromal cells within the bone marrow and thymus also regulate cell growth and differentiation by releasing cytokines, such as IL-4, IL-6, IL-7, IL-11, and granulocyte-macrophage colony-stimulating factor (GM-CSF). They also participate in cell-cell interactions with progenitors through engagement of cell surface molecules that provide additional regulatory stimuli and participate in the development of the intercellular matrix (e.g., collagen, fibronectin).

**T Cells**

The development of the various cells that are important in the immune response from their pluripotent stem cell origin to their final stages of maturation. BFU, burst-forming unit; BM, basophil mast cell; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; GM, granulocyte-macrophage; Ig, immunoglobulin; MEG, megakaryocyte; NK, natural killer; TCR, T-cell receptor.

Figure 40-1. The development of the various cells that are important in the immune response from their pluripotent stem cell origin to their final stages of maturation. BFU, burst-forming unit; BM, basophil mast cell; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; GM, granulocyte-macrophage; Ig, immunoglobulin; MEG, megakaryocyte; NK, natural killer; TCR, T-cell receptor.
thymic compartment. Alternatively, successful αβ loci recombination results in βTCR expression, which pairs with the surrogate α receptor and forms the pre-TCR. The pre-TCR provides ligand-independent signals enabling commitment to the αβ T-cell lineage and CD4/CD8 coexpression (double-positive). Assembly of the pre-TCR is followed by recombination at the α loci, which, if successful, generates the αβTCR. Ligand-dependent selection follows and is determined by double-positive cells binding peptide-loaded MHC molecules on thymic cortical epithelia. Double-positive cells that bind MHC with sufficient affinity are selected to survive (positive selection), whereas those that do not are eliminated by apoptosis. The interaction between the TCR and MHC molecules is restricted by the specificity of the TCR and the T-cell coreceptor: CD4 restricts interaction to class II MHC and CD8 to class I MHC. Surviving double-positive cells then lose the CD4 or CD8 coreceptor not involved in MHC recognition. These single-positive cells traffic to the thymic medulla, and those that react too strongly with self-antigens presented by medullary epithelia and bone marrow-derived APCs are deleted by apoptosis (negative selection). These processes of positive and negative selection promote viable T cells capable of recognizing and responding to peptide antigen in MHC while checking those that have autoreactivity. This is a rigorous selection, with approximately only 2% of the double-positive cells surviving. Approximately 90% to 95% of circulating T cells use the αβ TCR and are divided into two major subpopulations, CD4+ helper T cells and CD8+ cells.

**T-Cell Priming**

When T cells recognize their specific peptide/MHC ligand on APCs, TCR signals result in adhesion molecule changes that strengthen and prolong APC contact. During this interaction, a second costimulatory signal is provided by CD28 on T cells binding B7 molecules on APCs and facilitates activation and proliferation of naïve T cells. After costimulation, activated T cells produce IL-2, leading to T-cell proliferation and differentiation. Once primed, naïve T cells differentiate into effector cells that perform antigen-specific functions without the need for costimulation.17

**Effector T Cells**

In the blood and secondary lymphoid organs, 60% to 70% of T cells are CD4+, and 30% to 40% are CD8+. The best understood function of CD8+ cells is that of cytotoxic effectors (cytotoxic T lymphocytes [CTLs]). Their function as suppressors of the immune response is more controversial, and the mechanism of this activity is not very well understood; in some instances, it is thought to be mediated by the production of nonspecific inhibitory cytokines. Although both CD4+ and CD8+ lymphocytes can act as cytotoxic effectors, the CD8+ population has a higher frequency of cytotoxic effectors than the CD4+ population. CD8+ cells show a major cytotoxic activity against cells infected with intracellular microbes and against tumor cells and are the pillars of the cell-mediated immune response. CD8+ effector T-cell function is distinguished by antigen-specific cytotoxicity restricted by MHC class I. On priming, CD8+ T cells produce cytotoxic proteins, including perforin and granzymes, and secrete them at the point of contact with the target cell, resulting in specific killing without bystander cell damage. Perforin is a membrane-disrupting protein that facilitates the ability of granzymes to induce apoptosis in the target cell. Another mechanism for the induction of cytotoxicity, which is thought to play a key role in many inflammatory processes, involves the secretion of cytolytic cytokines by CD8+ cells (e.g., TNF). The perforin-dependent pathway of cytotoxicity is largely responsible for cell-mediated clearance of infectious agents (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus-1, and influenza A and B, measles, mumps, respiratory syncytial, rubella, and vaccinia viruses) and certain intracellular bacterial infections, and for the rejection of allogeneic tissue grafts and tumors.

Another pathway for cytotoxic cell function involves the cell surface molecule Fas, which is a member of the TNF receptor–nervous growth factor receptor superfamily and mediates apoptosis.26 Binding of the cell surface Fas molecule on a target cell to the Fas ligand on the cytotoxic effector leads to apoptosis of the target cell. Fas-mediated cytolysis is thought to play a role in the negative selection process in T-cell development; however, the role of this pathway for cytology in various infectious diseases has not been defined.

Generally designated helper cells, CD4+ cells work to activate both humoral immune responses (B-cell help) and cellular responses (delayed-type hypersensitivity responses). After recognizing antigens presented by MHC class II molecules, CD4+ cells become activated to secrete IL-2, partly in response to monocyte-derived IL-1 and partly in response to autocrine stimulation by IL-2 as part of a positive feedback loop (Fig. 40-2). Activated CD4+ cells interact with other CD4+ or CD8+ cells by secreting IL-2, and with B cells by secreting B-cell growth and differentiation factors (IL-2, IL-4, IL-6). Thus, CD4+ cells augment immune responses by stimulating B cells sensitized by antigen, and by stimulating CD8+ cells sensitized by binding of antigen in the context of MHC class I molecules. CD4+ T-cell priming, unlike CD8+ T-cell priming, results in the differentiation of various subsets distinguished by the production of particular cytokines and effector functions. The activities of these CD4+ cells are largely mediated via the secretion of these cytokines, which are small protein hormones that control the growth and differentiation of cells in the microenvironment. Classically, CD4+ effector cells were viewed in the context of the TH1/TH2 paradigm, but other subsets have emerged, including IL-17–producing T cells (TH17) and T cells with regulatory functions (regulatory T cells [Tregs]).

TH2 cells produce cytokines, such as IL-4, IL-5, and IL-13, and specialize in facilitating B-cell antibody responses. They drive B-cell proliferation by IL-4 and contact-dependent CD40:CD40 ligand binding, increasing humoral defenses against extracellular pathogens. Moreover, IL-4 and IL-5 enable IgE production and eosinophilic inflammation, both of which are important for the clearance of helminthic disease and the allergic response. TH2 differentiation is initiated by weak TCR signals coupled with IL-4 receptor signaling and signal transducer and activator of transcription (STAT) 6 activation. This results in up-regulation of GATA-3 transcription factor, the master regulator of TH2 differentiation. GATA-3 enhances TH2 cytokine production and inhibits TH1 developmental pathways.

TH1 cells specialize in macrophage activation by IFN-γ production and contact-dependent stimulation through the use of a variety of cell surface costimulatory ligands, thus playing a major role in intracellular pathogen clearance and delayed-type hypersensitivity (DTH). TH1 differentiation is directed by interferons generated by the innate response to infection, which ultimately leads to up-regulation of T-bet, the master regulator of TH1 differentiation. T-bet directs IFN-γ production and IL-12 receptor expression. The presence of IL-12 results in activation of signal transducer and activator of transcription (STAT) 4, further enhancing IFN-γ production and TH1 effector formation. IFN-γ is an essential contributor to the generation of chronic inflammatory responses characterized by monocellular cellular infiltration and activated macrophages. In addition to orchestrating the immune response by secreting various cytokines and contributing to CTL activities, the characteristic inflammatory reaction induced by CD4+ T lymphocytes is DTH. DTH is elicited by challenge with antigen in immune, sensitized persons. The typical example is the cutaneous reaction to challenge with the purified protein derivative (PPD) of Mycobacterium tuberculosis in previously infected or vaccinated persons. Clinically, DTH is manifested by local erythema and induration 24 to 48 hours after challenge. Microscopically, the lesion shows perivascular accumulations of leukocytes (initially neutrophils, later lymphocytes and activated macrophages), edema, and fibrin deposition. Chronic DTH reactions result in granulomas (nodular collections of macrophages and lymphocytes) and possibly fibrosis as a result of the cytokines produced by macrophages, which stimulate fibroblast proliferation and collagen synthesis.

TH17 cells are a subset of T cells that fills an essential gap in our understanding of inflammatory processes, because it was unclear how TH1 cells actually mediate inflammation in the tissues by the expression of IFN-γ. TH17 cells secret IL-17 (or IL-17A), IL-17F, IL-6, TNF-α, and IL-22. Neutralization of IL-17, but not genetic deletion of TH1 cells, resolves tissue pathology in autoimmune models. IL-17...
is a potent inflammatory cytokine involved in the recruitment and proliferation of neutrophils. It is also known to induce proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, as well as chemokines CXCL1, 2, and 8, which together are hallmarks of acute inflammatory processes. The chemokines mobilize neutrophil recruitment, which is a characteristic feature of TH17-mediated inflammation. Anti–IL-17 reduces joint destruction in experimental arthritis, and decreases neutrophil infiltration in an experimental asthma model while increasing eosinophil infiltration. Exogenously administered IL-17 reduces pulmonary eosinophil recruitment and bronchial hyperreactivity, suggesting a regulatory role for this interleukin. Thus, the TH17-directed neutrophil infiltration is inversely linked to the TH2-mediated eosinophil direction, much like the inverse relationships between TH1 and TH2 cells. In the upper airways, IL-17 has been found in nasal polyps and, interestingly, is expressed in polyps from patients in South China, which have a neutrophil-predominant infiltration, in contrast to polyps from patients from Belgium, which express IL-5 and have an eosinophil-predominant infiltration.

CD4+ T cells can also differentiate into cells characterized by the ability to suppress T-cell responses and prevent autoimmunity, or Figure 40-2. Summary of the cell-mediated immune response showing the events that follow exposure to an immunogen and the role of the helper T (TH) cell in orchestrating these events. Ag, antigen; APC, antigen-processing cell; BCGF, B-cell differentiation factor; BCGF, B-cell growth factor; IL, interleukin; MHC, major histocompatibility complex; Tc cell, cytotoxic T cell; TCR, T-cell receptor. (From Stites DP, Terr AI, eds. Basic and Clinical Immunology. 7th ed. Norwalk, CT: Appleton & Lange; 1991.)
B Cells

B-Cell Development

B cells constitute approximately 10% of peripheral blood leukocytes. They develop in the bone marrow from hematopoietic stem cells but achieve maturity in peripheral lymphoid organs. Early progenitors committed to the B-cell lineage (pre-B cells) begin recombination at the Ig heavy-chain locus. Successful recombination leads to expression of μ heavy chain, distinguishing them from pre-B cells. With the surrogate light chain and the Igα/β signaling machinery, an Ig-like heterodimer is expressed on the surface (pre-B-cell receptor [pre-BCR]). Pre-BCR signals a halt to μ heavy-chain recombination, and Igκ or Igλ light-chain recombination begins. The surrogate light chain is replaced by successfully formed κ or λ light chain, and the BCR is expressed as surface IgM distinguishing the immature B cell.

B-Cell Responses

B cells provide humoral immunity against extracellular pathogens through the production of antibodies that neutralize pathogens and toxins, facilitate opsonization, and activate complement. Primary infection or vaccination results in prolonged production of high-affinity specific antibodies, the basis of adaptive humoral immunity. On the other hand, IgM antibodies are produced in the absence of infection, are of lower affinity, play a role in first-line defense against bacterial infection, and assist in clearance of endogenous cellular debris. Naïve follicular B cells reside in the follicles of secondary lymphoid tissues. Antigen arrives into these lymphoid organs through circulation of soluble molecules or immune complexes or via transportation by dendritic cells. The B cells, via BCR, process the antigens in the context of MHC class II and then migrate to the T-B cell interface, the border between the T-cell zone and B-cell follicle, where they encounter primed TH cells of cognate specificity. This generates signals from T cell–derived cytokines and binding between CD40 ligand (CD40L) (on T cells) and CD40 (on B cells) that sustain B-cell activation and promote Ig class switching. Signaling through CD40 and its interaction with CD40 ligand on T cells is essential for the induction of isotype switching. The effector T-cell cytokines are as follows: IL-1 and IL-2 promote B-cell activation and growth, IL-4 and IL-13 cause switching to IgG1 and IgG3, IL-4 and IL-13 cause switching to IgE, and TGF-β causes switching to IgA. IFN-γ, or some other undefined product of TH1 cells, appears to induce switching to IgG2. Activated B cells either migrate into the follicle and, with continued T-cell help, initiate the germinal center reaction or migrate to the marginal zone and differentiate into short-lived plasma cells. These latter cells secrete antibody for 2 to 3 weeks, providing a rapid, but transient, source of effector molecules. The B cells in the germinal center undergo specificity diversification through somatic hypermutation, and high-affinity variants are selected by survival advantage, a process termed affinity maturation. Thus within the germinal centers, sequential cycles of proliferation, BCR diversification, and selection amplify high-affinity variants of the original activated B cell. The cells that then exit the germinal center reaction give rise to the memory compartment, consisting of affinity-matured memory B cells and long-lived plasma cells. When memory cells re-encounter antigen, they divide rapidly and expand their numbers or differentiate into antibody-secreting plasma cells. These long-lived plasma cells are terminally differentiated B cells incapable of further division that home to the bone marrow and secrete high-affinity class-switched antibodies. Natural Killer Cells (Large Granular Lymphocytes) and Natural Killer Cell Cytotoxicity

Large granulocytes, the third major subtype of lymphocytes, are referred to as natural killer cells. NK cells are distinct from T cells or B cells and can manufacture and release various cytokines, including IFN-γ, TNF-α, and GM-CSF. They are present in the peripheral circulation and in the spleen, lungs, and liver. They are not found in lymph nodes and do not recirculate through the thoracic duct lymph. These cells are usually larger than typical lymphocytes and display less nuclear material and more cytoplasm. They possess electron-dense, peroxidase-negative granules and a well-developed Golgi apparatus. NK cells lack rearranged immunoglobulin and TCR genes and therefore do not express surface immunoglobulin or primary TCR complex. They express a unique pattern of surface molecules not usually expressed on other lymphocytes, including CD16 (FcγRIII), a receptor for the Fc portion of immunoglobulin, and CD56, an adhesion molecule that is also expressed on neural cells. In addition, they express CD2, which is also expressed on T cells. The ability of CD4+ and CD8+ T cells to recognize only peptides presented by self MHC molecules is termed MHC restriction, and cytolitic activity mediated by these cells is known as MHC-restricted cytotoxicity. In contrast to these two cell types, NK cells are capable of...
cytotoxic activity that is not restricted to recognition of target cells that
display MHC molecules. This process is termed unrestricted toxicity.
NK cells can mediate antibody-dependent cellular cytotoxicity (ADCC)
by activation through their IgG Fc receptors and the subsequent pro-
duction of cytokines such as IFN-γ, which can affect the proliferation and
differentiation of other cell types. They also produce cytokoty
by mechanisms similar to those of CTLs, including perforin-mediated
destruction of cells, receptor-induced apoptosis, and release of cytokines
such as TNF-α. NK cells have no antigen-specific receptors. Their
cytotoxic activity is inhibited by encounter with self MHC molecules
through inhibitory receptors on the surface of NK cells that recognize
class I. They thus kill self cells that have down-regulated class I molecule
expression. This factor is important in host defense, because several
viruses have developed mechanisms to down-regulate class I expression
in infected cells as a strategy to avoid CD8+ cell killing, NK cells have
prominent antitumor effects and are potent killers of virally infected
cells. 74

Monocytes and Macrophages
Monocytes and macrophages arise from colony-forming unit–
graunulocyte-monocyte-colony-stimulating factor (CFU-GM) progenitors, which differentiate
into monoblasts, promonocytes, and monocytes. Monocytes account
for about 10% of circulating leukocytes. Several cytokoty—including
stem cell factor (SCF), IL-3, IL-6, IL-11, and GM-CSF—promote the
development of myeloid-lineage cells from CD34+ stem cells, pre-
dominantly in the early stages of differentiation. The macrophage
colony-stimulating factor (M-CSF) acts at the later stages of develop-
mint and induces maturation of macrophages. 75 Mature monocytes
leave the bone marrow and circulate in the bloodstream until they enter
tissues, where they develop into macrophages. These cells include Lang-
erhans cells in the epidermis, Kupffer cells in the liver, microglial cells
in the central nervous system, and the broad class of dendritic cells that
are present in most tissues of the body and are concentrated in the
secondary lymphoid tissues. All of these cells express both class I and
class II MHC molecules that are used to permit recognition of proc-
essed antigen by the TCR on T cells. Dendritic cells appear to be the
most potent APCs, but macrophages, Langerhans cells, and Kupffer
cells are also prominent APCs.

Like neutrophils, monocytes and macrophages are also highly
phagocytic for microbes and particles that have been marked for clear-
ance by binding immunoglobulin, complement, or both. Phagocytosis
is facilitated by opsonization, which coats foreign material with anti-
bodies. After phagocytosis, an intracellular vacuole forms around the
foreign material and lysosomal enzymes released into the vacuole
destroy the foreign invader. These cells appear to be mobilized shortly
after neutrophils and they persist for long periods at sites of chronic
inflammation and infection. They use production of nitric oxide as a
major mechanism for killing microbial pathogens and produce large
amounts of cytokines, such as IL-12 and INF-γ, giving them a regulato-
ry role in adaptive immune responses. 76

Neutrophils
Neutrophils arise from colony-forming unit–granulocyte-monocyte-colony
progenitor cells that give rise to myeloblasts, which differentiate into
promyelocytes, myelocytes, and finally, mature neutrophils. After mat-
uration in the bone marrow, neutrophils circulate in the peripheral
blood, where they account for 60% to 65% of leukocytes. As for
monocytes, SCF, IL-3, IL-6, IL-11, and GM-CSF promote the growth
and development of neutrophil precursors. Other cytokines that exhibit
more specific effects on neutrophils include granulocyte colony-
stimulating factor (G-CSF), which induces maturation of neutrophil
precursors into neutrophils. 77 IL-4 also enhances neutrophil differen-
tiation induced by granulocyte CSF. Neutrophils produce large quan-
tities of oxygen species that are cytotoxic to bacterial pathogens and
enzymes that appear to participate in tissue remodeling and repair after
injury. They accumulate in large quantities at sites of bacterial infection
and tissue injury and possess prominent phagocytic capabilities that
permit them to sequester microbes and particulate antigens internally,
where they can be destroyed and degraded. Thus, neutrophils play a
major role in the clearance of microbial pathogens and repair of tissue
injury. 78 Neutrophils have also been recognized to produce substantial
amounts of the cytokines TNF and IL-12 as well as certain chemokines;
this finding supports an additional immunoregulatory role for these
cells.

Eosinophils
Eosinophils are derived from colony-forming unit–eosinophil (CFU-
Eo), a progenitor that differentiates into an eosinophilic myeloblast,
promyelocyte, myelocyte, and finally a mature eosinophil. Eosinophils
constitute 2% to 5% of circulating leukocytes in normal individuals
and are readily recognized from their prominent cytoplasmic granules,
which contain toxic molecules and enzymes that are particularly active
against helminths and other parasites. 79 GM-CSF and IL-3 promote
eosinophil growth and differentiation. 80 The production of eosinophils
from the bone marrow and their survival in peripheral tissues are
enhanced by the cytokine IL-5, which maintains their viability through
inhibition of apoptosis. 81

Eosinophils are prominent cells in most allergic responses. 82 Eo-
sinophils possess several surface markers and receptors involved in
differentiation, recruitment into tissues, activation, and synthesis and
release of their multiple mediators. Receptors for immunoglobulins
include those for IgG, IgE, and IgA. Eosinophils have receptors for
complement components, including C1q (CR1), C3b/C4b (CR1),
iC3b (CR3), C5a, and C5a. Both C3a and C5a are eosinophil chemo-
attractors that stimulate production of oxygen radicals by eosinophils.
Eosinophils potentially express several receptors for chemokines. CCR1
is a receptor for macrophage inflammatory protein-1α (MIP-1α),
monocyte chemotactic protein-3 (MCP-3), and the chemokine regu-
lated on activation, normal T cell expressed and secreted (RANTES);
CCR3 is a receptor for eotaxin, eotaxin-2, eotaxin-3, monocyte chem-
otactic protein-3, and RANTES. 83 Mature eosinophils, like their immu-

nocyte precursors, express functional heterodimeric receptors for the three
cytokines—GM-CSF, IL-3, and IL-5—that promote eosinophilopi-
cesis and stimulate the functioning of mature eosinophils.

The eosinophil's cationic granule proteins include major basic
protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic
protein (ECP), and eosinophil-derived neutrotoxin (EDN). Another
prominent protein of the eosinophil is the Charcot-Leyden crystal
(CLC) protein, which constitutes an estimated 7% to 10% of total
cellular protein, possesses lyso phospholipase activity, and forms the
distinctive hexagonal bipyramidal crystals that are the hallmark of
eosinophil-associated inflammation. MBP is a potent cytotoxin and
helminth toxin in vitro. It can kill bacteria and many types of normal
and neoplastic mammalian cells, stimulate histamine release from
basophils and mast cells, activate neutrophils and platelets, and augment
superoxide generation by alveolar macrophages. It can also induce
bronchoconstriction and transient airway hyperreactivity when instilled
into the monkey trachea. 79 ECP, like MBP, has marked toxicity for
helminth parasites, blood hemoflagellates, bacteria, and mammalian
cells and tissues and has been shown in several studies to produce
respiratory epithelial damage similar to that seen in severe asthma. As
with MBP and ECP, EPO is highly cationic and exerts some cytotoxic
effects on parasites and mammalian cells in the absence of hydrogen
peroxide. However, EPO is highly effective in combination with hydro-
gen peroxide and a halide cofactor (iodide, bromide, or chloride), from
which EPO catalyzes the production of the toxic hypohalous acid. In
the presence of these compounds, EPO is highly toxic to various unicel-
lar, multicellular, and other targets, including viruses, mycoplasma,
bacteria, fungi, and parasites. EDN is a poor cationic toxin, with only
limited toxicity for helminths and mammalian cells, but it induces
significant neutrophil damage when injected intratracheally or intracere-
brally into experimental rabbits or guinea pigs. In allergic conditions,
eosinophils may play a dual role. They can suppress the local tissue
response to inflammatory mediators involved in IgE-mediated hyper-
sensitivity reactions by inactivating histamine, platelet-activating
factor, and heparin. On the other hand, eosinophils can augment
destruction through the toxic effects of the products they release upon
degranulation. The balance between these two seemingly contradictory
functions of eosinophils in IgE-mediated reactions is still under
investigation.
Basophils and Mast Cells

Basophils mature from a progenitor colony-forming unit–basophil mast cell (CFU-BM) into basophilic myeloblasts, promyelocytes, myelocytes, and then mature basophils. Mast cells are thought to develop from the same progenitor, but less is known about their specific stages of development. IL-3 and SCF have the most consistent effects on human basophil and mast cell growth and differentiation. These cytokines act synergistically to induce basophil and mast cell development from CD34+ progenitor cells.84 SCF induces functional maturation of human mast cells. Nerve growth factor and GM-CSF affect basophil growth, and IL-5 enhances basophil differentiation.85 Basophils and mast cells are morphologically similar and both exhibit cell surface expression of high-affinity receptors for IgE (FcεRI), making them key initiators of immediate hypersensitivity responses and the host response to helminthic parasites; these cells release histamine and other preformed mediators from their granules and produce important quantities of lipid mediators that stimulate tissue inflammation, edema, and smooth muscle contraction. Studies have shown that in addition to this role, mast cells play prominent roles in the host response to bacterial infections.86

Platelets and Erythrocytes

Platelets and erythrocytes are derived from stem cell progenitors, which differentiate into burst-forming units–megakaryocytes (BFU-MEG) in the case of platelets and into burst-forming units–erythroid (BFU-E) in the case of erythrocytes. Burst-forming units–megakaryocytes then differentiate into colony-forming units–megakaryocytes (CFU-MEG), promegakaryoblasts, megakaryocytes, and platelets. IL-1, IL-3, GM-CSF, IL-6, and IL-11 affect the growth and differentiation of platelets.87-89 The erythrocyte precursors burst-forming units–erythroid differentiate into colony-forming units–erythroid (CFU-E), pronormoblasts, basophilic normoblasts, polychromatophilic normoblasts, orthochromic normoblasts, reticulocytes, and erythrocytes. Cytokines important in the various stages of erythrocyte differentiation and development include GM-CSF, SCF, IL-9, and erythropoietin.90

Lymphoid Organs

The primary lymphoid organs, sites where lymphocytes differentiate and mature from stem cells into effector cells, include the thymus and bone marrow. The secondary lymphoid organs are sites where mature lymphocytes reside and immune responses are generated. They are divided into the systemic immune system (spleen and lymph nodes) and the mucosal immune system (tonsils, Peyer's patches, and isolated lymphoid follicles) and the diffuse mucosal immune system (including intraepithelial lymphocytes and lamina propria). The spleen and lymph nodes are divided into two major regions, the cortex and the medulla.

Lymph Nodes

Lymph nodes occur as chains or groups. Blood vessels enter and leave them through the hilus, and lymph nodes also receive afferent lymphatic vessels from the structures that they drain. The lymphatic vessels carry APCs and foreign antigens that are subsequently transported into the substance of the lymph node. Lymph nodes are divided into two major regions, the cortex and the medulla. The cortex contains numerous primary and secondary lymphoid follicles in which B cells predominate. Primary follicles, consisting of a mantle zone without germinal centers, contain resting B cells expressing surface IgM or IgD and CD23. In addition to an outer mantle zone, secondary follicles contain inner germinal centers, which form in response to antigen stimulation. Immunoglobulin class switching, affinity maturation through somatic mutation, and development of memory B cells occur within germinal centers. CD4+ T cells are also found in these centers and play a key role in the B-cell responses through interactions between CD40 (expressed on the B cell) and the ligand for CD40 (present on activated CD4+ cells). The paracortical region of the lymph node cortex surrounds the lymphoid follicles and contains mostly T cells (both CD4+ and CD8+) and some macrophages, dendritic cells, and B cells (accessory cells). The accessory cells present peptide antigens in association with MHC molecules to the TCR on T cells, resulting in their activation.

The medulla, the region at the center of the lymph node, is divided into medullary cords surrounded by medullary sinuses that drain into the hilus. Medullary cords contain B cells, T cells, macrophages, and many plasma cells. These cells are joined by B and T cells that migrate from the cortex to the medulla. Effector lymphatic vessels leave the hilus carrying antibodies and mature B and T cells that migrate to other tissues and act as memory cells during subsequent immune exposure. The lymphatic system eventually drains into the thoracic duct and into the circulation, therefore allowing lymphocytes to circulate throughout the body.

Mucosal Immune System

Mucosal surfaces and skin encounter the environment and possess an immune system capable of responding to pathogens and foreign antigens. The mucosal immune system is composed of the organized mucosal immune system (including tonsils, Peyer's patches, and isolated lymphoid follicles) and the diffuse mucosal immune system (including intraepithelial lymphocytes and lamina propria).

Tonsils

Three lymphoid structures surround the entrance to the throat: the adenoids, the palate tonsils, and the lingual tonsils. These structures reach full development in childhood and begin to involute around puberty. The palatine tonsils are surrounded by a poorly organized capsule, except at the pharyngeal surface, which is covered with stratified squamous epithelium. Trabeculae extend from the capsule and divide the tonsils into lobules. Blood vessels and nerves enter through the capsule and extend within the trabeculae. The tonsillar surface is covered by pits, which open into crypts that branch downward into the tissue of the tonsil, maximizing the surface area exposed to the pharynx. Each lobule contains numerous lymphoid follicles with germinal centers that contain predominantly B cells.91 The lymphoid tissue that surrounds the follicles contains T cells, macrophages, dendritic cells, and B cells. These structures are strategically located at sites of entry of airborne particles through the nose (adenoids) and at sites of food particle entry (tonsils). The structures filter unwanted organisms and antigens and function as a mucosal immune barrier.

Peyer's Patches and Lymphoid Follicles

Peyer's patches are aggregates of lymphoid follicles within the mucosa of the jejunum and ileum, with most in the terminal ileum. The full development of this component of the mucosal immune system, including the formation of follicles containing germinal centers, occurs several weeks after birth; their number increases until puberty and then decreases. Lymphoid follicles, another component of the mucosal immune system with structures similar to follicles of a Peyer's patch, are scattered throughout the mucosa of the gastrointestinal, respiratory, and genitourinary tracts. These lymphoid organs facilitate antigen presentation from the intestinal lumen to T and B cells.

Intraepithelial Lymphocytes and Lamina Propria

Intraepithelial lymphocytes are found at the basal surface of the epithelium and are interdigitated with epithelial cells. Most are T cells (CD8+ or CD4+ CD8+), and although most express the TCRβ8, some express the TCRγδ. The function of intraepithelial lymphocytes is not understood, but studies have shown their capacity to generate cytotoxic activity.92 The lamina propria, located beneath the epithelium, is populated by various groups of cells. One of the key functions of this tissue is the secretion of IgA antibody from the many IgA plasma cells into the lumen.93 The lamina propria also contains many CD4+ and CD8+ T lymphocytes in a ratio of about 2:1 and other effector cells, including IgG B cells, macrophages, dendritic cells, eosinophils, mast cells, and neutrophils.
**Antigen Presentation**

Follicular dendritic cells, specialized APCs in the B-cell areas of lymph nodes and the spleen, are important in the generation and maintenance of memory B cells, which they achieve by trapping antigen-antibody complexes. Peripheral tissue dendritic cells engulf and process antigen, leave the tissues, then go home to T-cell areas in draining lymph nodes or the spleen. In the lymph nodes, these APCs can directly present processed antigens to resting T cells to induce the latter’s proliferation and differentiation. Monocytes-macrophages exist as monocytes in blood and as macrophages (a more differentiated form) in various tissues, such as the lungs, liver, and brain. In addition to phagocytic and cytotoxic functions, these cells have receptors for various cytokines (IL-4, IFN-γ), which can regulate their function. Activated macrophages are also a major source of several cytokines (IFN, IL-1, TNF), complement proteins, and prostaglandins. All APCs have MHC class II surface molecules.

Foreign or self proteins undergo hydrolytic cleavage within the APCs and become oligopeptides, which are then loaded onto antigen-binding grooves of MHC molecules before expression at the cell surface (Fig. 40-3). Class I molecules usually bind peptides that are 8 to 10 amino acids long and are derived from proteins synthesized intracellularly (e.g., tumor antigens and viruses), whereas class II molecules bind peptides that are 14 to 22 amino acids long and are derived from proteins synthesized extracellularly (e.g., nonreplicating vaccines and extracellular bacteria). Lipid and lipid derivatives are processed much like extracellular proteins in endosomes, combined with CD1 (an MHC-like molecule) and presented to double-negative T cells frequently bearing γδ TCRs. In addition to the mechanism of presentation of oligopeptide antigens to lymphocytes via MHC molecules, T cells can recognize haptens, which are covalently or noncovalently complexed with peptides residing in the MHC-binding groove. Another exception is the presentation of super antigens, which are about 30-kDa proteins produced by a broad spectrum of microbes ranging from retroviruses to bacteria. These antigens do not undergo processing to oligopeptides but bind intact to MHC class II molecules and the TCR outside the antigen-binding grooves. They can activate more T cells than conventional peptide antigens.

**Humoral Immune Response**

**T Cell–Dependent and T Cell–Independent B-Cell Responses.**

Humoral immunity consists of responses that are T cell–dependent (TD) and T cell–independent. Follicular B cells present MHC-restricted protein antigens and receive T-cell help that promotes immunoglobulin class switching, affinity maturation, and memory differentiation as discussed previously. These antigen responses are referred to as T cell–dependent. T cell–independent B-cell responses occur with large antigens that have repeating antigenic determinants, such as carbohydrates, which constitute the capsule and cell wall components of bacteria and cannot be presented in MHC class II molecules. This B-cell response represents a major protective role against bacterial pathogens such as *Streptococcus pneumoniae*. These pathogens bridge immunoglobin on the B-cell surface, causing activation and the subsequent secretion of antibodies, primarily of the IgM class. Antibodies to *S. pneumoniae* mediate the opsonization of bacteria by binding to the bacterial cell surface, thereby targeting them for destruction by Fc receptor–bearing macrophages. Young children and the elderly, who generally show poor response to T cell–independent antigens, are at increased risk for these bacterial infections. Protective immunity against *Haemophilus influenzae* and meningococcal infections is also mediated by T cell–independent B-cell responses.

**Antibody-Dependent Cellular Cytotoxicity**

ADCC can lead to the destruction of invading foreign organisms (bacteria and helminths), virus-infected cells, or tumor cells. In the process of destruction of invading organisms, ADCC involves the targeting of effector cells to these organisms by antibodies. The antibody's variable regions provide specificity for the organism, whereas the antibody's constant region focuses effector cells to the site via various Fc receptors. In ADCC directed against altered self cells, the process involves the reaction of antibodies with cell surface receptors producing antibody-coated target cells for reaction with NK cells that secondarily destroy these altered self cells. The process occurs via binding of the antibody to FcγRIII receptor (CD16) on NK cells.

**Immunoglobulins**

The antibodies (immunoglobulins) secreted by activated B cells are glycoproteins composed of polypeptide (82%-96%) and carbohydrate (4%-18%). Immunoglobulin molecules are composed of two identical 50-kDa heavy chains and two identical 25-kDa κ or λ light chains (Fig. 40-4). The amino terminal portions of the heavy and light chains vary in amino acid sequence from one antibody molecule to another. These variable portions are designated V_{H} and V_{L}, respectively. The juxtaposition of one V_{H} segment and one V_{L} or V_{κ} segment creates the antigen-binding portion of the immunoglobulin molecule, and each immunoglobulin molecule has two identical antigen-binding sites. The carboxyl terminal portions of the heavy and light chains are constant in each subclass of antibody. The heavy-chain constant regions pair to form the Fc domain of the molecule that is responsible for most of the effector functions of the immunoglobulin molecule, including binding to Fc receptors and activating complement.

The isotype of a heavy or light chain is defined by the constant region antigenic determinants, which in turn are defined by the par-

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*Figure 40-3. Antigen processing and presentation. Antigen undergoes hydrolytic cleavage within antigen-presenting cells, and the resultant oligopeptides are loaded on antigen-binding grooves of major histocompatibility complex (MHC) molecules and expressed at the cell surface.*
Immunoglobulin G

IgG constitutes approximately 75% of the total serum immunoglobulins and consists of four subclasses (IgG1, IgG2, IgG3, IgG4). It is a monomer with a molecular weight of 150,000 Da. IgG1, IgG3, and, to a lesser extent, IgG2 can bind and fix complements. Specific Fc receptors for IgG are present on monocytes, macrophages, and neutrophils. IgG is usually bound to the Fc receptor before binding with antigen. IgG functions as an opsonin that facilitates phagocytosis. The Fc receptors for IgG include FcγRI on monocytes and macrophages, FcγRII on most hematopoietic cells except erythrocytes, and FcγRIII on NK cells, eosinophils, neutrophils, and macrophages. In general, the IgG antibody response to soluble protein antigens involves the IgG1 and IgG3 subclasses, whereas polysaccharide antigens elicit primarily IgG2 antibodies. IgG is the immunoglobulin primarily involved in secondary or recall immune responses and is the only immunoglobulin that can cross the placenta and protect the neonate. IgG can fix complement, leading to neutralization, opsonization, bacteriolysis, agglutination, and hemolysis.

Immunoglobulin M

IgM constitutes approximately 10% of serum immunoglobulins. It normally exists as a pentamer of five IgM subunits linked by disulfide bonds and J chains with a molecular weight of 900,000 Da. It is the major immunoglobulin (along with IgD) expressed on the surface of B cells. Membrane IgM functions as the earliest antigen receptor on B cells. Antigen binding results in B-cell activation and differentiation, leading to pentameric IgM secretion. IgM predominates in the early humoral response, and levels then decline rapidly; the IgM is replaced by IgG of the same specificity. IgM is the most efficient complement-fixing antibody, a feature that, with IgG, increases its array of biological activities.

Complement System

The complement system is an important effector of both the innate and adaptive immune responses. It consists of more than 25 plasma and cell surface proteins that are sequentially activated and can interact with one another, with antibodies, and with cell membranes. These interactions mediate functions such as immune adherence, phagocytosis, chemotaxis, and cytotoxicity. Complement system proteins constitute about 15% of the globulin fraction of plasma and circulate as inactive molecules. Complement activation centers on cleavage of C3, which can be achieved by classic, alternative, or lectin pathways (Fig. 40-5).

The classic pathway comprises C1, C4, and C2. C1, in turn, consists of C1q, C1r, and C1s. Antibody-complexed proteins (containing IgG1, IgG2, and IgG3, or IgM) provide the activating signal for the classic pathway of complement activation. Sequential activation of complement components C1, C4, and C2 produces the C3 convertase enzyme that then cleaves C3 into C3a and C3b. At this point, the classic and alternative pathways merge. The alternative pathway is activated in the absence of specific antibody-complex molecules by microorganisms that neutralize inhibitors of spontaneous complement activation. In this pathway, C3 interacts with factors B and D to generate the alternative pathway C3 convertase, which also cleaves C3 into C3a and C3b. The third pathway of complement activation, the lectin pathway, is triggered by microbial cell wall components containing mannans. The interaction of mannann-containing microbes with plasma mannann-binding lectin (MBL) activates the zymogenic plasma proteases MBL-associate serine proteases 1 and 2 (MASP-1, MASP-2). These form a protease analogous to the activated C1 of the classic pathway that then goes on to
activate C4, C2, and the remainder of the pathway leading to C3 convertase.

Cleavage of C3 results in the release of the small C3a fragment—a potent anaphylatoxin that induces mast cell degranulation, creates edema, and recruits phagocytic cells—and the larger C3b fragment, which covalently attaches to the activating antigen, marking it for destruction. C3b serves both as a site for attack of the complement membrane attack complex (MAC), a self-assembling pore-forming complex of the plasma proteins C5, C6, C7, C8, and C9 that kills targets by osmotic lysis, and as an opsonin, enhancing phagocytosis by its binding to complement receptors on the surfaces of neutrophils and macrophages. The effector mechanism of complement is potent and recruits intense local inflammation; its importance is underscored by the phenotypes of inherited deficiencies of individual components. For example, deficiencies of components of the membrane attack complex lead to increased susceptibility to Neisseria infections, deficiency of C3 results in life-threatening susceptibility to pyogenic infections, often fatal during childhood, deficiency of C4 or C2 causes a lupus-like immune complex disease, and deficiency of the serum inhibitor of C1 leads to episodic mast cell–independent episodes of angioedema.

**Cytokines**

Cytokines are a diverse group of small, secreted protein mediators that mediate interactions among different effector cells. Each cytokine may have multiple activities on different cell types, and several cytokines often have related functions. They can also have synergistic or antagonistic activities and can inhibit or induce the synthesis of other cytokines. Cytokines can be divided into several groups: the interleukins, the interferons, tumor necrosis factor and related molecules, TGFs, and hematopoietic growth factors. Each of these different cytokines, their principal cell sources, and their main effects in humans are summarized in Table 40-1.

**Chemokines**

The chemokines are a superfamily of low-molecular-weight, secreted, heparin-binding molecules that serve as potent chemoattractants for cells of the immune system. More than 50 chemokines are currently recognized, and they are characterized by the presence of three or four conserved cysteine residues. They can be divided into four families on the basis of the positioning of the N-terminal cysteine residues. The CXC family is characterized by the separation of the first two cysteines by a variable amino acid. In the CC family, the cysteine residues are adjacent to each other. The majority of these chemokines are contained in these two families. Chemokines of the C family lack the first and third cysteines, containing a single cysteine residue in the conserved position. Members of the CX3C family have the two N-terminal cysteine residues separated by three variable amino acids. The C and CX3C families are small, with one or fewer members per family. Table 40-2 lists the new systematic names of these chemokines as well as their common names and their target cells.

**Immunopathology**

The two major effector arms of the adaptive immune response are humoral and cellular. In the defense against infections, antibodies are operative against bacteria or bacterial products; cell-mediated immunity operates primarily against viral, fungal, and mycotic infections. With few exceptions, antibody-mediated immune mechanisms work best when directed to extracellular infections, whereas cell-mediated immunity is effective against intracellular infections. The killing effects of immune reactions are extremely efficient and, when specifically directed, can eliminate organisms quickly. However, these same immune mechanisms may cause host-tissue destruction and therefore lead to disease states. In some situations, this destructive effect of immune reactions is termed allergy or hypersensitivity and is considered an immunopathologic reaction.

These reactions are divided into four types. Type I, mast cell–mediated reactions, use the release of mast cell or basophil mediators to create responses to sensitizing allergens and can be IgE-dependent (anaphylaxis) or IgE-independent (sensitivity to iodide contrast media). Type II, cytotoxic, antibody-mediated reactions (IgG-, IgM-mediated), involve the binding of IgG and IgM antibodies to antigens on the surface of target cells (e.g., erythrocytes, neutrophils, platelets, and epithelial cells of glandular or mucosal surfaces) or to antigens on tissues such as basement membranes. This interaction between IgG and IgM antibodies and cell surface antigens leads to destruction of these cells by opsonization, complement activation, or cell lysis and ADCC. These mechanisms can damage self antigens in various tissues. One clinical example is known as penicillin-induced autoimmune hemolytic anemia.
### Table 40-1

#### Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Sources</th>
<th>Predominant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Interleukins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1α, IL-1β</td>
<td>Functionally equivalent isoforms</td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>Activated T cells</td>
<td>T-cell proliferation</td>
</tr>
<tr>
<td>IL-3</td>
<td>CD4+ T cells, thymic epithelial cells, mast cells</td>
<td>Synergistic action in early hematopoiesis; activates and promotes recruitment of basophils in late allergic reactions</td>
</tr>
<tr>
<td>IL-4</td>
<td>TH2 cells, mast cells, basophils, NK T cells</td>
<td>Differentiation and growth of TH2 subset, B-cell activation, isotype switch to IgE and IgG1, suppression of TH1 cells, growth factor for mast cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>Activated TH2 cells and mast cells, NK cells, eosinophils</td>
<td>Eosinophil survival, differentiation, and chemotaxis</td>
</tr>
<tr>
<td>IL-6</td>
<td>T cells, mononuclear phagocytes, vascular endothelial cells, fibroblasts</td>
<td>T- and B-cell growth and differentiation, acute phase protein production, fever</td>
</tr>
<tr>
<td>IL-7</td>
<td>Stromal cells in bone marrow and thymus, B cells, monocytes, macrophages</td>
<td>Growth of pre-B cells and pre-T cells</td>
</tr>
<tr>
<td>IL-8, CXC chemokine</td>
<td>Activated mononuclear phagocytes, fibroblasts, and endothelial cells</td>
<td>Neutrophil chemoattractant; promotes neutrophil inflammatory responses</td>
</tr>
<tr>
<td>IL-9</td>
<td>TH2 cells</td>
<td>Stimulation of growth and differentiation of hematopoietic cells and mast cells</td>
</tr>
<tr>
<td>IL-10</td>
<td>Activated monocytes, macrophages, and TH2 cells</td>
<td>Important in innate and adaptive immunity; has immunosuppressive or immunostimulatory effects on various cell types</td>
</tr>
<tr>
<td>IL-11</td>
<td>Bone marrow stromal cells and osteoblasts</td>
<td>Synergistic action with IL-3 and IL-4 in hematopoiesis; stimulates fibroblasts to promote collagen deposition</td>
</tr>
<tr>
<td>IL-12</td>
<td>Mainly activated macrophages; some production by neutrophils, dendritic cells, monocytes, and B cells</td>
<td>Activates NK cells; induces TH1 differentiation and secretion of IFN-γ</td>
</tr>
<tr>
<td>IL-13</td>
<td>Activated T cells (TH2), mast cells, and basophils</td>
<td>Biologic functions closely related to those of IL-4 but of lower magnitude</td>
</tr>
<tr>
<td>IL-14</td>
<td>Activated T cells</td>
<td>Growth factor for B cells</td>
</tr>
<tr>
<td>IL-15</td>
<td>Monocytes, macrophages</td>
<td>Stimulates growth and development of NK cells; stimulates activation and proliferation of T and B cells</td>
</tr>
<tr>
<td>IL-16</td>
<td>T cells, mast cells, eosinophils, airway epithelial cells</td>
<td>Immunomodulatory and chemoattractant for CD4+ T cells</td>
</tr>
<tr>
<td>IL-17</td>
<td>Activated memory CD4+ cells</td>
<td>Induces cytokine production by epithelial and endothelial cells, and fibroblasts; promotes neutrophilic inflammation</td>
</tr>
<tr>
<td>IL-18</td>
<td>Activated macrophages and Kupffer cells</td>
<td>Induces IFN-γ production by T cells and NK cells; favors TH1 induction</td>
</tr>
<tr>
<td>IL-19</td>
<td>Monocytes</td>
<td>Suspected to participate in the regulation of pro-inflammatory cytokine expression</td>
</tr>
<tr>
<td>IL-20</td>
<td>Cell type unknown</td>
<td>Appears to have a role in skin development and is suspected of regulating inflammation in the skin</td>
</tr>
<tr>
<td>IL-21</td>
<td>Activated CD4+ T cells</td>
<td>TH1 cytokine; stimulates proliferation of activated T cells and cytotoxicity of NK cells</td>
</tr>
<tr>
<td>IL-22</td>
<td>TH1 cells and mast cells</td>
<td>Increases production of acute phase proteins in hepatocytes</td>
</tr>
<tr>
<td>IL-23</td>
<td>Activated dendritic cells</td>
<td>Acts on memory CD4+ T cells to promote their proliferation and differentiation into TH1 effectors during a secondary immune response</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Cell Sources</td>
<td>Predominant Effects</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>IL-24</td>
<td>Human melanoma and other tumor cells</td>
<td>Promotes induction of apoptosis in some cancer cells</td>
</tr>
<tr>
<td>IL-25</td>
<td>Activated TH2 cells, mast cells</td>
<td>Enhances allergic responses and promotes TH2 inflammation</td>
</tr>
<tr>
<td>IL-26</td>
<td>Activated memory T cells</td>
<td>May act as an autocrine growth factor for transformed and/or virus-infected T cells</td>
</tr>
<tr>
<td>IL-27</td>
<td>Activated monocytes, dendritic cells, and macrophages serving as antigen-presenting cells</td>
<td>Promotes development along the TH1 phenotype and suppresses the TH2 phenotype</td>
</tr>
<tr>
<td>IL-28 and 29</td>
<td>Induced by viral infection in various cell lines</td>
<td>Induce an antiviral state in infected cells</td>
</tr>
</tbody>
</table>

**The Interferons**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Sources</th>
<th>Predominant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>T cells, NK cells</td>
<td>Macrophage activation, increased expression of MHC molecules and antigen-presenting components, Ig class switching, suppression of TH2 response</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Leukocytes</td>
<td>Antiviral; increases MHC class I expression</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Fibroblasts</td>
<td>Antiviral; increases MHC class I expression</td>
</tr>
</tbody>
</table>

**Tumor Necrosis Factor and Related Molecules**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Sources</th>
<th>Predominant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>Activated monocytes/macrophages, T, B, and NK cells</td>
<td>Major inflammatory mediator induced by the presence of gram-negative bacteria and their components; potent immunoregulatory, cytotoxic, antiviral, and procoagulatory activities</td>
</tr>
<tr>
<td>LTα (lymphotoxinα) Previously called TNF-β</td>
<td>Activated TH1, B, and NK cells</td>
<td>Promotes inflammation, has antiviral activity, and kills tumor cells by apoptosis</td>
</tr>
<tr>
<td>LTαβ</td>
<td>Activated TH1, B, and NK cells</td>
<td>Has a specialized role in secondary lymphoid organ development</td>
</tr>
<tr>
<td>OPGL (osteoprotegerin ligand)</td>
<td>Osteoblasts, bone marrow stromal cells, activated T cells</td>
<td>Stimulates osteoclasts and bone resorption</td>
</tr>
<tr>
<td>BAFF (B-lymphocyte–activating factor belonging to the TNF family)</td>
<td>Monocytes, macrophages, dendritic cells</td>
<td>Survival factor required for the maturation of B cells</td>
</tr>
</tbody>
</table>

**Transforming Growth Factor (TGF)**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Sources</th>
<th>Predominant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β</td>
<td>Chondrocytes, monocytes, T cells</td>
<td>Inhibits cell growth; is anti-inflammatory; induces IgA secretion by B cells; plays a role in adhesion, proliferation, differentiation, transformation, chemotaxis, and immunoregulation</td>
</tr>
</tbody>
</table>

**Hematopoietic Growth Factors**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Sources</th>
<th>Predominant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCF (stem cell factor)</td>
<td>Stromal cells in the fetal liver, bone marrow, and thymus, in the central nervous system, and in the gut mucosa</td>
<td>Supports the survival and growth of the earliest hematopoietic precursors in vivo</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Activated T cells, macrophages, stromal cells, and endothelial cells</td>
<td>Stimulates growth and differentiation of myelomonocytic lineage cells, particularly dendritic cells and inflammatory leukocytes</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Activated T cells, endothelial cells, fibroblasts, and mononuclear phagocytes</td>
<td>Stimulates neutrophil development and differentiation</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Endothelial cells, fibroblasts, mononuclear phagocytes</td>
<td>Influences CFU-GM cells to differentiate into monocytes and macrophages in vitro</td>
</tr>
</tbody>
</table>

CFU, colony-forming unit; CSF, colony-stimulating factor; G, granulocyte; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LT, lymphotoxin; M, macrophage; MHC, major histocompatibility class; NK, natural killer; TH, helper T; TNF, tumor necrosis factor.
### Table 40-2

#### Chemokines

<table>
<thead>
<tr>
<th>Systematic Name</th>
<th>Common Name(s)/Ligand(s)</th>
<th>Target Cell(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CXC Chemokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL1</td>
<td>GROα/MGSAα</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL2</td>
<td>GROβ/α/MGSAβ</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL3</td>
<td>GROδ/α/MGSAα</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL4</td>
<td>Platelet factor-4</td>
<td>Fibroblast</td>
</tr>
<tr>
<td>CXCL5</td>
<td>Epithelial neutrophil activating-78</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL6</td>
<td>Granulocyte chemotactic protein-2</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL7</td>
<td>Neutrophil-activating peptide-2</td>
<td>Neutrophil</td>
</tr>
<tr>
<td>CXCL8</td>
<td>Interleukin-8</td>
<td>Neutrophil, basophil, T cell</td>
</tr>
<tr>
<td>CXCL9</td>
<td>Monokine induced by IFN-γ</td>
<td>Activated T cell</td>
</tr>
<tr>
<td>CXCL10</td>
<td>IFN-γ-inducible protein-10</td>
<td>Activated T cell</td>
</tr>
<tr>
<td>CXCL11</td>
<td>IFN-inducible T-cell α chemoattractant</td>
<td>Activated T cell</td>
</tr>
<tr>
<td>CXCL12</td>
<td>Stromal cell–derived factor-1α/b</td>
<td>CD34+ bone marrow cell, T cell, dendritic cell, B cell, activated CD4 cell</td>
</tr>
<tr>
<td>CXCL13</td>
<td>B-cell–attracting chemokine-1</td>
<td>Naïve B cell, activated CD4 cell</td>
</tr>
<tr>
<td>CXCL14</td>
<td>Breast and kidney–expressed chemokine</td>
<td></td>
</tr>
<tr>
<td>CXCL15</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>CXCL16</td>
<td>Unknown</td>
<td>T cell, NK T cell</td>
</tr>
<tr>
<td><strong>CC Chemokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL1</td>
<td>I-309 (a nameless human chemokine)</td>
<td>Neutrophil, T cell</td>
</tr>
<tr>
<td>CCL2</td>
<td>MCP-1/monocyte chemotactic and activating factor/tumor-derived chemotactic factor</td>
<td>T cell, monocyte, basophil</td>
</tr>
<tr>
<td>CCL3</td>
<td>MIP-1α/LD78α</td>
<td>Monocyte, macrophage, T cell, NK cell, basophil</td>
</tr>
<tr>
<td>CCL3L1</td>
<td>LD78β</td>
<td></td>
</tr>
<tr>
<td>CCL4</td>
<td>MIP-1β</td>
<td>Monocyte, macrophage, T cell, NK cell, basophil</td>
</tr>
<tr>
<td>CCL5</td>
<td>Regulated upon activation, normal T cell–expressed and secreted (RANTES)</td>
<td>Monocyte, macrophage, T cell, NK cell, basophil, eosinophil, dendritic cell</td>
</tr>
<tr>
<td>CCL6</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>CCL7</td>
<td>MCP-3</td>
<td>T cell, monocyte, eosinophil, basophil, dendritic cell</td>
</tr>
<tr>
<td>CCL8</td>
<td>MCP-2</td>
<td>T cell, monocyte, eosinophil, basophil</td>
</tr>
<tr>
<td>CCL9/10</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>CCL11</td>
<td>Eotaxin</td>
<td>Eosinophil</td>
</tr>
<tr>
<td>CCL12</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>CCL13</td>
<td>MCP-4</td>
<td>T cell, monocyte, eosinophil, basophil, dendritic cell</td>
</tr>
<tr>
<td>CCL14</td>
<td>HCC-1</td>
<td>Monocyte</td>
</tr>
<tr>
<td>CCL15</td>
<td>HCC-2/leukotactin-1/MIP-1δ</td>
<td>T cell, monocyte, dendritic cell</td>
</tr>
</tbody>
</table>

*Continued*
Type III, immune complex–mediated reactions (IgG, IgM complex mediated), involve antibody-mediated inflammation whereby the antibody and its antigen form low-solubility immune complexes, which are deposited in normal tissues, activate complement, and set off an inflammatory response characterized primarily by neutrophil influx, which inflicts tissue injury. Knowledge of this immunologic disease became widespread in the early 1900s, when physicians began using immune animal sera, usually equine sera, to treat bacterial infections, a practice that led to serious illness and even death of the treated subjects, a disease known as serum sickness. Immune complex vasculitis in the skin can also occur in a series of clinical conditions, such as systemic lupus erythematosus, rheumatoid arthritis, drug reactions, and infections.

Type IV, delayed hypersensitivity (DTH) reactions (T cell–mediated), are caused by antibody-independent mechanisms involving T cells or NK cells. These reactions are the pathologic variants of a normal T cell–mediated immune response in which the T-cell response to an environmental antigen becomes exaggerated. A clinical example of such a reaction, as previously described, is the cutaneous reaction to challenge with the purified protein derivative of M. tuberculosis in previously infected or vaccinated patients.

Allergic Rhinitis

Allergic rhinitis is a clinical hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies. It has a prevalence of between 10% and 20% and affects 20 to 40 million individuals in the United States annually. The prevalence of seasonal allergic rhinitis is higher in children and adolescents than in adults, and in childhood, boys outnumber girls; the gender ratio becomes approximately equal in adults, however, and may even favor women. Because individuals require low-dose exposure to an offending allergen over many years before development of symptoms, seasonal rhinitis rarely occurs in children younger than 2 years. Most patients with allergic rhinitis have symptoms before age 20. The severity of the disease remains relatively constant throughout childhood and early adulthood, usually improves in middle age, and is seldom a problem in the elderly. A family history of allergic rhinitis increases the odds that a child will have the disease. Atopy, the predisposition to respond to environmental allergens with the production of specific IgE antibodies, occurs in only 13% of children for whom neither parent is atopic, but in 29% of children with one atopic parent or sibling and in 47% for whom both parents are atopic. A history of asthma is also important.
Hygiene Hypothesis

Epidemiologic data provide strong evidence of a steady rise in the incidence of allergic (asthma, rhinitis, and atopic dermatitis)\(^{1,2,3}\) and autoimmune diseases (multiple sclerosis,\(^{4}\) insulin-dependent diabetes mellitus,\(^{5}\) and Crohn’s disease\(^{6}\)) in developed countries since the beginning of the 1970s. Concomitantly, the incidence of many infectious diseases in developed countries has decreased as a result of antibiotics, vaccination, or improved hygiene. A hypothesis thus emerged that the decrease in infectious diseases is causally linked to the increase in the incidence of allergic disease, the “hygiene hypothesis.” Strachan\(^{7}\) observed that the risk of allergic rhinitis was inversely linked to birth order and the size of the family. He proposed that infections within households in early childhood have a role in preventing allergic rhinitis.

The geographic distribution of allergic and autoimmune diseases in the world also shows interesting patterns. The incidence of disease decreases from north to south in the Northern Hemisphere and reciprocally from south to north in the Southern Hemisphere. Underdiagnosis of allergic and autoimmune diseases in underdeveloped countries could explain these geographical differences but it is not likely. Although this explanation might be proposed for allergic rhinitis and atopic dermatitis, relatively benign diseases, it is not likely to apply to type I diabetes and multiple sclerosis, which lead to significant symptoms and are not likely to go undiagnosed. Environment seems to play an important role in this incidence gradient.

In developed and industrialized countries, a higher prevalence of atopy and asthma is observed than in undeveloped and less affluent countries. Immigrant to allergy-prevalent countries causes more allergies and asthma in immigrants in comparison with the prevalence of atopy in their countries of origin. This difference probably involves exposure to a new set of pollutants and allergens and several socioeconomic and cultural issues, such as housing conditions, diet, and accessibility to medical services, all of which are likely to affect migrants’ health. The increase in allergy and asthma is usually not related to ethnicity but in certain populations may play an important role. Studies on migrants support the notion that lifestyle and environmental factors in Western industrialized countries facilitate atopy and asthma.\(^{8}\) An obvious factor in the north–south gradient is socioeconomic differences. Several studies have found a lower frequency of immunologic diseases in populations with a low socioeconomic status. Some infections have been found to be distributed according to a south–north gradient in European countries that mirrors the gradient for autoimmune diseases. Low socioeconomic levels and high temperatures, two common features in populations with a low socioeconomic status. Some infections have been found to be distributed according to a south–north gradient in European countries that mirrors the gradient for autoimmune diseases. Low socioeconomic levels and high temperatures, two common features of southern countries, may predispose to infections in a number of ways: Less stringent control of microbial contamination of water and food, an increased risk of bacterial proliferation with higher ambient temperatures, and poorer housing conditions may all affect the risk of contamination between persons.

When infections are an incriminating factor, they often occur in childhood. Young children with older brothers and sisters at home and those who attend a daycare center during the first 6 months of life subsequently have a lower incidence of asthma\(^{9}\) and type I diabetes\(^{10}\) than children who do not attend a daycare center and have no older siblings. The administration of antibiotics to children has been suspected to raise the risk of asthma and allergy. Droste and colleagues\(^{11}\) observed that the use of antibiotics in the first year of life increased the risk of asthma or other allergic diseases in children with a genetic predisposition to asthma. Multiple studies\(^{12}\) have shown that increasing the number of infections or by modifying intestinal flora.

The increase in atopic diseases in the northern parts of the hemisphere in comparison with the southern parts has been linked to sun exposure and levels of vitamin D. In addition to its traditional role in the endocrine system, vitamin D diminishes the risk of many chronic illnesses, including cancer, autoimmunity, infection, and cardiovascular disease.\(^{13}\) This vitamin has also been implicated in the development of atopic diseases, such as asthma, allergic rhinitis, and anaphylaxis.\(^{13,14}\) In a later study, our group demonstrated lower levels of vitamin D in a cohort of African Americans with chronic rhinosinusitis than in same-race controls.\(^{15}\) Anaphylaxis, measured in proxy on the basis of prescription of EpiPens (Dey Laboratories, Napa, Calif), varies with geographic latitude; the finding of higher levels being found in areas with less sun exposure supports the preceding theory.\(^{16}\) The possible mechanisms by which vitamin D might affect these diseases, characterized by chronic inflammation, could be related to its immunologic effects, including those on T cells, dendritic cells, and macrophages,\(^{17}\) as well as to the ability to promote IL-10 production by regulatory T cells.\(^{18}\)

Differences in disease incidence between urban and suburban dwellers have been observed, and factors other than air pollution have been implicated. In 1999, Braun-Fahrländer and colleagues found that children whose parents were farmers and who lived on the farm were less likely to become allergic than children from the same rural region who were not raised on a farm.\(^{19}\) Since then, a large number of studies has documented that people raised on farms have a lower prevalence of hay fever and atopic sensitization in childhood, as well as in adulthood, whereas effects on asthma are more consistent for the atopic than the nonatopic phenotype.\(^{20}\) The timing of the exposure played a crucial role because the protection was strongest when the exposures occurred in the first years of life rather than in later years.\(^{21}\) One such study showed that allergies were less frequent when the children were exposed early and for a prolonged period to farm animals and cow’s milk.\(^{22}\) In that study, a clear maternal effect was also seen because the mother’s exposure to animal sheds during her pregnancy had a protective effect of the offspring.\(^{23}\) An inverse correlation between endotoxin levels in bedding and the incidence of atopic diseases among children living in rural areas was also found, suggesting that a subject’s environmental exposure to endotoxin may have a crucial role in the development of tolerance to ubiquitous allergens found in natural environments.\(^{24}\) However, although endotoxin was inversely related to atopy and related phenotypes, it was a risk factor for nonatopic asthma, increased airway hyperresponsiveness, and low lung function.\(^{25}\)

Animal studies support the preceding epidemiologic observations, because autoimmune diseases in susceptible strains of mice or rats develop earlier and at a higher rate among animals bred in a specific pathogen-free environment than among animals bred in a conventional environment. The same has been observed relating to allergic diseases. Administration of Mycobacterium bovis and Mycobacterium avium can attenuate the late phase response, airway hyperresponsiveness, and bronchoalveolar lavage eosinophilia in a mouse model of bronchial asthma.\(^{26}\)

Several mechanisms might explain these relationships. The development of most autoimmune diseases depends on the TH1 cytokines IL-2 and IFN-γ, whereas the development of allergic diseases requires the TH2 cytokines IL-4 and IL-5. Initial reports that suggested an inverse relationship between the incidences of autoimmune diseases and allergic diseases\(^{27}\) led to speculation that the reciprocal down-regulation of TH1 cytokines by TH2 cytokines, and the reverse, might account for these observations. However, later evidence supports an association between the incidences of allergic and autoimmune diseases.\(^{28,29}\) These observations would fit with the concept of common mechanisms underlying infection-mediated protection against autoimmunity and allergy.

Another potential mechanism involves Tregs and cytokines. The decrease in antigenic stimulation related to the decreased frequency of childhood infections has resulted in a decrease in the levels of regulatory cytokines, specifically, IL-10 and IFN-γ, whereas the development of allergic diseases requires the TH2 cytokines IL-4 and IL-5. Initial reports that suggested an inverse relationship between the incidences of autoimmune diseases and allergic diseases\(^{27}\) led to speculation that the reciprocal down-regulation of TH1 cytokines by TH2 cytokines, and the reverse, might account for these observations. However, later evidence supports an association between the incidences of allergic and autoimmune diseases.\(^{28,29}\) These observations would fit with the concept of common mechanisms underlying infection-mediated protection against autoimmunity and allergy.
their components. Pathogen-associated molecular patterns that are structural components of microbes are recognized by receptors of the host’s innate immune system, the pattern recognition receptors (PRRs). Examples for pathogen-associated molecular patterns are LPS, a component of endotoxin, and muramic acid, a component of peptidoglycan that is part of the cell wall of most bacteria. Examples of human pattern recognition receptors are CD14 and the human TLRs discussed previously. In the context of the development of allergies, TLR4, serving as a receptor for LPS, and TLR2, which recognizes peptidoglycan of gram-positive bacteria, have been implicated. Polymorphisms in the genes for TLR4 and TLR2 have been shown to interact with these environments, modulating the allergic protective effect. The observation that the peripheral blood leukocytes of farmers’ children, who live in an environment with a high load of microbial compounds even in the absence of infection, express higher levels of TLR2 and CD14 than those of less exposed children supports a modulation of the innate immune response by microbial compounds even in the absence of infection.

Another interesting observation relates to the presence of pets in the house and the risk of asthma. Farm animals have not been common in big European and American cities, but domestic pets are extremely common. They are a prolific source of allergen, and sensitization to these allergens is strongly associated with asthma. Reports from Europe suggest that the presence of a cat in the home decreases the risk of sensitization to cat allergens. Because of studies that suggest that the same effect occurs in countries where domestic animals are equally common in the homes of families with a history of asthma as in the homes of families without such history, the initially proposed explanation that this effect could be secondary to decisions by families with allergic disease not to have pets is unlikely. Ownby and colleagues strengthened these initial observations. They reported that children in a birth cohort raised in a house with two or more dogs or cats in the first year of life have not only less allergic sensitization to dog and cat, as determined by skin prick tests and allergen-specific IgE levels, but also less sensitization to allergens in general at age 6 to 7 years. Because domestic animals can be a source of endotoxin, this finding suggests the possibility that the effects of pets as these researchers described in the United States could be comparable to those of cows and farm animals in Europe. Mechanisms similar to those discussed earlier in this chapter involving regulatory T cells and inhibitory cytokines are being investigated to explain these findings.

Therefore, the interesting relationships between infections and immune-mediated diseases, such as allergic and autoimmune diseases, and between early exposure to some allergens and the lowered risk of future allergic sensitization, potentially create new therapeutic strategies. The challenge will be to elucidate the responsible immune mechanisms involved and to determine the extent of exposure that will ensure safety and the desired outcome—the development of healthy children with a very low risk of allergic and autoimmune disease.

**Burden of the Disease**

Health-related quality of life (HRQL) is the component of overall quality of life that is determined primarily by a person’s health and that can be influenced by clinical interventions. Using both generic and disease-specific tools, several investigations have documented a significant impairment of quality of life in allergic rhinitis.

The disease-specific tools are more sensitive to change in health-related quality of life than the generic instruments. The most commonly used disease-specific tool is the rhinoconjunctivitis quality of life questionnaire (RQLQ) developed and validated by Juniper and Guyatt. Modifications of this questionnaire are also validated and tested for patients with perennial rhinitis, adolescents (12-17 years old), and children (6-12 years old).

Poorly controlled allergic rhinitis has been shown to contribute to sleep loss or disturbance, and seasonal allergic rhinitis leads to increased daytime sleepiness. Allergic rhinitis also contributes to learning problems during school in children either through direct interference or indirectly through its adverse effect on sleep. Treatment with sedating H1 antihistamines aggravates these problems, and nonsedating antihistamines only partially reverses this effect. In adults, similar adverse effects on proper functioning ability lead to an impairment in work ability and induce both work absenteeism as well as reduction in work productivity and presenteeism. In one study, the mean total productivity losses per employee per year were $595 for allergic rhinitis, which was more costly than all other prevalent and chronic disorders, such as migraine, depression, respiratory infections, diabetes, asthma, and coronary artery disease.

For all these reasons, allergic rhinitis is a costly disease. Estimates of the annual health care costs have ranged from $2 billion to $5 billion with the wide range related to the parameters used to make these estimates.

**Pathophysiology of Allergic Rhinitis**

**Sensitization and Immunoglobulin E Production**

During the initial stage of the disease, low-dose exposure leads to the production of specific IgE antibodies. Antigen that is deposited on the nasal mucosa is engulfed by APCs (macrophages, dendritic cells, Langhans cells) and partially degraded within their phagolysosomes. Portions of the antigen are then exteriorized on the surfaces of APCs and are recognized by helper T cells and class II MHC molecules. IL-1-activated helper T cells then secrete cytokines, which promote the growth and differentiation of other cells involved in the immune response. TH2 CD4 cells are important contributors to allergic reactions. They secrete the cytokines IL-4, IL-5, and IL-13, which are all central to the production of IgE and to the recruitment and survival of eosinophils at sites of allergic reactions. Antigen-specific IgE then attaches to high-affinity receptors on mast cells and basophils and to low-affinity receptors on other cells, thereby sensitizing the nasal mucosa. On subsequent exposure to the offending antigen, the IgE antibodies on the surfaces of these cells serve as receptors for the antigen molecules. Cross-linking of adjacent IgE molecules on mast cells leads to the release of inflammatory mediators that stimulate nerves, glands, and blood vessels to cause the clinical manifestations of the disease, namely, sneezing, pruritus, rhinorrhea, and nasal obstruction. These events are known as the early allergic response.

**Early Response to Antigen**

Within minutes after exposure of an allergic patient to antigen, an inflammatory response occurs. The patient first senses tingling and pruritus, followed by sneezing, rhinorrhea, and, last, nasal congestion. These subjective feelings correlate with physiologic changes that are measured after antigen provocation, such as increases in nasal secretions and nasal airway resistance (NAR). In addition to these physiologic changes, increases are noted in the levels of several mediators, including histamine, kinins, tryptase, PGD2, leukotriene C4 (LTC4), leukotriene B4 (LTB4), MBP, and platelet-activating factor (PAF). These mediators lead to the various symptoms of allergic rhinitis by their effects on end-organs and nerves of the nasal mucosa. Histamine and tryptase are found in mast cell granules, and their detection in nasal secretions after antigen provocation provides support for mast cell degranulation during the nasal allergic reaction. PGD2, and the cysteinyl leukotrienes, newly synthesized mediators of the arachidonic acid pathway, are also secreted by mast cells. Further evidence for the role of nasal mast cells in the immediate allergic reaction was provided by the demonstration of degranulated mast cells in nasal mucosal biopsies of allergic patients after allergen challenge.

**Neuronal Contribution**

Sneezing and itching during the early response to allergen provocation involve the nervous system. Unilateral intranasal antigen challenge experiments have supported the role of the nervous system in amplifying the allergic response as challenge leads not only to an increase in sneezes, rhinorrhea, nasal secretions, histamine, nasal airway resistance, and PGD2 on the side of challenge but also to an increase in rhinorrhea, secretion weights, and PGD2 contralateral to the challenge. The contralateral secretory response was rich in glandular markers and was inhibited by atropine, an anticholinergic, suggesting that the efferent limb was cholinergically mediated. It has also become clear that the nasal response to allergen is accompanied by an ocular, pulmonary, and even a sinus response that can, at least in part,
be explained by a neural reflex. Monitoring ocular symptoms and secretions after unilateral allergen challenge has shown an ocular symmetric and secretory response that is inhibited by pretreatment with an intranasal antihistamine, suggesting that histamine’s action on nasal afferent nerves initiates this reflex. This nasal ocular reflex has also been shown to be potentiayed by repeated allergen challenges, which lead to priming, a process inhibited by pretreatment with intranasal steroids because of their anti-inflammatory actions. Similar unilateral challenge studies with allergen have shown an influx of eosinophils into the ipsilateral maxillary sinus hours after allergen provocation that parallels the increase in these cells seen in nasal secretions, albeit of a lesser magnitude. Similarly, challenge of the nose with allergen has been shown to lead to up-regulation of inflammatory markers in bronchial biopsy specimens obtained 24 hours later. Besides a reflex initiated in the nose, another possible explanation of these findings has included the theory of systemic allergic inflammation, whereby an allergic reaction at one site generates an inflammatory response that reaches the systemic circulation and then leads to the involvement of other predisposed end-organs.

Several neuropeptides—in addition to sympathetic and parasympathetic nerves and their transmitters—are found in the nasal mucosa. These neuropeptides are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene-related peptide [CGRP], neurokinin [NK], gastrin-releasing peptide), parasympathetic nerve endings (vagal nerve, intestinal peptide [VIP], peptide histidine methionine), and sympathetic nerve endings (neuropeptide Y). Substance P (SP), a member of the tachykinin family, is often found as a co-transmitter with neurokinin A and calcitonin gene-related peptide; it has been found in high density in arterial vessels and, to some extent, in veins, gland acini, and epithelium. Several studies support the concept that neuronal mechanisms mediated by these peptides amplify the inflammatory allergic reaction.

Mosemann and colleagues were able to demonstrate significant increases in the levels of substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide immediately after antigen challenge in allergic individuals; in patients who experienced a late reaction, only substance P increased slightly. These experiments suggest that neuropeptides are released in vivo in humans after allergen challenge and might be partly responsible for symptoms of the allergic reaction. Repetitive application of capsaicin, the essence of chili peppers, releases substance P and calcitonin gene-related peptide from sensory nerves and initiates both central and axonal reflexes. Capsaicin causes a burning sensation and profuse bilateral rhinorhena when applied to one side of the nasal cavity, and repeated administration causes tachyphylaxis. The capsaicin-induced nasal secretory response in humans is glandular and is not caused by increased vascular permeability. Furthermore, capsaicin desensitization reduces sneezing in response to antigen and histamine challenges. All these findings point to the importance of the participation of neurogenic elements to the allergic response, and more specific delineation of the role of each of these neuropeptides awaits the development of specific antagonists.

**Late Response to Antigen**

The response to allergen exposure is not limited to the acute events that occur minutes after exposure. Hours after antigen challenge, some patients experience a recurrence of symptoms, most notably nasal congestion. This is termed the late response. Several investigators have documented elevations in nasal airway resistance 4 to 10 hours after antigen challenge, with a peak around 6 hours and resolution by 24 hours. After nasal challenge with antigen, the early response was followed by a process of inflammation and increases in the levels of histamine, tryptase, and eosinophils. These events, including eosinophil products, have also been detected. Other mediators, including byosinophilic granule proteins, have also been detected. These events are accompanied by an inflammatory cellular influx.

In addition to the different preformed and newly generated inflammatory mediators secreted by mast cells and other inflammatory cells during the allergic reaction, cytokines have been identified in the nasal mucosa and in nasal secretions of allergic patients during natural exposure and allergen provocation. In different allergen challenge experiments, increased levels of IL-1β, TNF-α, and GM-CSF were detected during the early hours after provocation and levels of IL-5, IL-6, IL-8, GM-CSF, TNF, and soluble intercellular adhesion molecule-1 (ICAM-1) were detected during the late phase response. Furthermore, significantly elevated baseline levels of IL-1β, IL-6, and IL-8 were detected in nasal lavages of patients with seasonal allergic rhinitis compared with those of healthy subjects.

Investigations relating to the role of cytokines in allergic rhinitis have been performed using nasal biopsies during the season or after challenge looking either for protein expression using immunohistochemistry or mRNA using in situ hybridization. Compared to healthy subjects, nasal biopsies from patients with perennial allergic rhinitis show significantly more IL-4+ cells, which seems to be primarily (78-100%) localized to mast cells as evidenced by positive staining of the same cells on consecutive sections with an antibody against mast cell tryptase. Immunoactivity for IL-5, IL-6, and IL-8 was present in most biopsy specimens from perennial rhinitis patients and healthy subjects with no significant differences between the two populations. Most IL-5+ cells were mast cells, with some eosinophils. IL-6 also colocalized to mast cells, and IL-8 was localized to the cytoplasm of epithelial cells. No cytokine reactivity was localized to CD3+ or CD4+ cells. These data suggest that IL-4, IL-5, and IL-6 proteins are localized to mast cells in the nasal mucosa of patients with perennial allergic rhinitis. The lack of localization of any of the cytokines to T lymphocytes is attributed to the authors to the fact that cytokines generated by activated T cells are rapidly transported from the cell, and do not accumulate in sufficient concentrations to be detected by the techniques used. This work supports the role of mast cells in contributing to the cytokines released in the local milieu after exposure to allergen. The same investigators, studying seasonal allergic rhinitis, showed that pretreatment with intranasal corticosteroids suppressed the increases in mucosal eosinophils and epithelial mast cells, and also led to a significant suppression of IL-4+ cells in the nasal submucosa, without significant effects on the number of IL-5 and IL-6 immunoreactive cells.

Looking for mRNA for the different cytokines in nasal biopsy specimens after allergen challenge of allergic subjects, Durham and others found significant increases in cells bearing mRNA for IL-3, IL-4, IL-5, and GM-CSF, but not for IL-2 or IFN-γ compared with biopsies obtained after a control challenge. Activated eosinophils (EG2+) increased significantly after allergen challenge and correlated positively with mRNA for IL-5, IL-4, GM-CSF, IL-3, and IL-2 but not for IFN-γ. Most IL-5 mRNA+ cells were also shown to be CD3 (83%), and the rest were positive for tryptase (16.4%). The same investigators demonstrated that pretreatment with flunisolide prevented before allergen challenge resulted in significant inhibition of an allergen-induced increase in activated eosinophils (EG2+) and cells expressing mRNA for IL-4 but not for IL-5. Immunotherapy, in addition to inhibiting cellular influx into the nasal mucosa, also induced a TH1 cell response, with a significant increase in cells expressing mRNA for IFN-γ. Other biopsy studies have also shown significant increases in mRNA positive cells for IL-10 and IL-13 after allergen challenge.

These findings suggest that both T lymphocytes and mast cells are contributors to cytokine production during the allergic reaction, with technical differences in detection probably accounting for the differences in the quantitative distribution of the cytokines between these two cell types. The cytokine profile observed after exposure to allergen emphasizes the importance of TH2 cells and their cytokines in the allergic reaction. The effects of TH2 cytokines are all conducive to the promotion of allergic inflammation: IL-5 promotes the differentiation, vascular adhesion, and in vitro survival of eosinophils and enhances histamine release from basophils; IL-4 is a mast cell growth factor and promotes the switching of B cells to the production of IgE and IL-13, independent from the other two cytokines, is necessary and sufficient to induce key features of inflammation such as eosinophil recruitment, mucus hyperproduction, and airway hypersensitivity.

**Cellular Events**

Along with the physiologic changes and inflammatory mediator production that occur hours after antigen provocation, inflammatory cel...
lular influx occurs in the nasal mucosa and in recovered nasal secretions after experimental provocation and in seasonally exposed patients. The sampling techniques in the various studies differ, with some targeting nasal secretions and the superficial layers of the mucosa (lavage, scraping, brushing) and others targeting the actual mucosa and submucosa (biopsy). Studies suggest that these techniques yield different cellular predilections for allergic inflammation, with polymorphonuclear cells and eosinophils predominating in nasal secretions, and mononuclear cells predominating in the nasal mucosa. Basophils that reside in the epithelial lamina propria and nasal secretions have been identified.265 Eosinophils are more abundant in the epithelium and lamina propria of allergic patients exposed to antigen either experimentally or naturally.249 Numbers of CD4+ T lymphocytes and CD25+ cells are significantly increased during allergic patients during the pollen season showed significant increases in total MBP and activated (EG2+) eosinophils in the submucosa compared with presessional eosinophil numbers and with numbers in biopsy specimens from nonallergic subjects. Basophilic mast cells were observed in nasal secretions during season exposure of allergic patients, lending credibility to the observations after experimental allergen challenge. Nasal biopsy specimens collected from allergic patients during the pollen season showed significant increases in total MBP and activated (EG2+) eosinophils in the submucosa compared with presessional eosinophil numbers and with numbers in biopsy specimens from nonallergic subjects.252 Basophilic mast cells were observed in nasal secretions during seasonal exposure of allergic patients to pollen. In contrast to nasal secretions, examination of nasal mucosal scrapings116,243 or biopsy specimens,243,244 which sample deeper layers, showed that most metachromatic cells in these compartments were mast cells. A seasonal increase in mast cells occurs on the surface of the nasal epithelium after 4 or 5 days of exposure to pollen, which seems to be the result of migration of mast cells from the deeper layers of the lamina propria to the surface.237 The consensus of most researchers is that basophils predominate in nasal secretions, whereas mast cells are more abundant in the epithelium and lamina propria of allergic patients exposed to antigen either experimentally or naturally. Although eosinophils and mast cells are found in the nasal submucosa, most cells in this location are mononuclear cells (lymphocytes and monocytes). Numbers of CD4+ (helper T) lymphocytes and CD25+ cells are significantly higher after antigen challenge than after sham challenge.245 The preceding discussion of cytokines stresses that a significant source of cytokine production in the nasal mucosa in allergic inflammation are helper T cells of the TH2 subtype. Another important cell type detected in the nasal mucosa of allergic patients is Langerhans cells, large mononuclear dendritic cells that are important in antigen presentation. Although the numbers of intraepithelial CD1+ (Langerhans) cells in healthy subjects and grass-allergic patients before and after the pollen season are not different, the numbers of intraepithelial CD1+ cells are significantly increased during the allergy season.246 In a study involving patients with perennial allergic rhinitis, a significant decrease in numbers of Langerhans cells in the epithelium was seen after 3 months of treatment with fluticasone propionate.247 Thus, Langerhans cells appear important in the allergic reaction and seem to not be constitutively more numerous in patients with allergic rhinitis but are more likely to be up-regulated upon exposure to allergen.

Adhesion Molecules and Cellular Recruitment

Cellular trafficking is integral to human immune response because it allows cells to be selectively recruited from the bloodstream into sites of tissue inflammation. Cellular recruitment into sites of allergic reactions is an example of such trafficking. Numerous inflammatory cells are present in the nasal mucosa and in nasal secretions of allergic patients during allergen exposure but not in healthy subjects. Mechanisms should therefore exist for the migration and accumulation of these effector cells during allergic inflammation. Recruitment of cells such as eosinophils and activated T lymphocytes are mediated, in part, by interactions between adhesion molecules on the cells themselves and those on vascular endothelial cells, with cytokines playing various regulating roles in these interactions.

The molecules responsible for adhesion on leukocytes belong to different families, such as the integrin family, the very late antigen (VLA) family, and the selectin adhesion molecule family.248-256 Adhesion molecules on the vascular endothelial cell surface include ICAM-1,257 CD54, ICAM-2, E-selectin, P-selectin (granule membrane protein-140 [GMP-140], CD62), and VCAM-1.258 Receptor–counter-receptor pairs for adhesion molecules include leukocyte function-associated antigen-1 (LFA-1) with ICAM-1 and ICAM-2, the macrophage differentiation antigen Mac-1 with ICAM-1, VLA-4 with VCAM-1, the carbohydrate structure sialyl–Lewis X with E-selectin and P-selectin, and glycosylation-dependent cell adhesion molecule 1 (GlyCAM-1) for P-selectin.248-250

It is currently thought that a series of events occurs during the migration of circulating leukocytes into tissues (Fig. 10.6). The cells initially undergo reversible margination and can be seen rolling along the endothelial surface on intravital microscopy.251 These changes are mediated by interactions between carbohydrates and selectins. Leukocyte activation occurs next, presumably as a result of exposure to chemotactic agents or other activating factors released by endothelial cells or by nearby tissue-dwelling cells. Leukocyte activation is associated with changes in affinity and expression of adhesion molecules on the leukocyte surface. Leukocytes may also be activated directly by their interaction with adhesion molecules on activated endothelial cells.252 Activated leukocytes then attach to endothelial cells and migrate across the endothelium into the extravascular space. These events are mediated by one or more members of the integrin, selectin, and immunoglobulin families of adhesion molecules. Furthermore, it is likely that the preferential recruitment of leukocytes involves multiple steps, such as leukocyte activation, vascular endothelial cell expression of adhesion molecules, adhesion of leukocytes to vascular endothelium, transendothelial migration, chemotaxis, and localized survival within the tissues. Multiple cytokines and other factors are important in up-regulating adhesion molecules on circulating leukocytes and vascular endothelium and are crucial in chemotaxis and leukocyte survival within the tissues. Clear evidence shows that endothelial activation occurs during allergic rhinitis in vivo. Enhanced expression of ICAM-1 and VCAM-1, but not E-selectin, has been described in the mucosa of allergic patients.253 The expression of VCAM-1 was found to be significantly up-regulated in biopsy specimens obtained from allergic patients 24 hours after antigen challenge concomitantly with a significant increase in the number of eosinophils,254 These studies of adhesion molecules in vivo suggest that these molecules, along with their counter-ligands on circulating leukocytes, have an important role in cellular recruitment to allergic inflammatory sites. Further studies are needed for better definition of the role of these adhesion mechanisms in allergic rhinitis and for determination of whether interfering with the process of adhesion would modify the course and severity of the disease.

Hyperresponsiveness

One of the hallmarks of allergic rhinitis is the hyperresponsiveness of allergic patients to specific stimuli such as antigen (a phenomenon known as priming) and nonspecific stimuli.

Specific Hyperresponsiveness

Many allergic patients report worsening of symptoms as the allergy season progresses, despite unchanged or decreased pollen counts. This phenomenon is probably caused by a shift in the threshold of responsiveness of the patient. Connell266 found that the dose of pollen necessary to cause symptoms decreased more than fivefold by the fourth day of consecutive antigen challenges. Consecutive nasal allergen challenges have also demonstrated the priming phenomenon, in that patients challenged 24 hours after earlier exposure had significantly more sneezes and a reduction in the threshold dose necessary to elicit the response.256 Concomitant with the priming response observed for sneezes, significantly higher levels of histamine and kinins and an increase in the number of neutrophils, eosinophils, and basophils were observed in nasal lavage samples. These observations suggest that mechanisms of priming...
Figure 40-6. Cellular adhesion and recruitment. An eosinophil is seen from the early stage of free circulation to rolling, adhesion to the vascular endothelium, transendothelial migration, and, finally, tissue migration. In the case of the eosinophil, these events are regulated and mediated by multiple cytokines and adhesion molecules. GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; LTB, leukotriene B; PAF, platelet-activating factor; VCAM, vascular cellular adhesion molecule. (From Mygind N, Dahl R, Pedersen S, Thestrup-Pedersen K, eds. Essential Allergy. 2nd ed. Oxford: Blackwell Scientific Publications; 1996.)

involve cellular infiltration, increased mediator production, and possibly increased end-organ responsiveness. Inflowing inflammatory cells are hypothesized to alter the mucosal penetration of antigen and to provide additional targets for antigen stimulation and increased generation of inflammatory mediators, which would, in turn, encounter more responsive end organs, thus leading to the exaggerated response noted after repeated antigen exposure.

**Nonspecific Hyperresponsiveness**

Increased reactivity to irritant stimuli is often reported by allergic patients. This phenomenon has been studied by observation of the nasal response to nonantigenic nasal secretagogues, such as histamine and the cholinergic agonist methacholine. Patients who underwent an antigen challenge followed 24 hours later by a histamine challenge showed increased sensitivity to histamine compared with those undergoing only a baseline histamine challenge. This response was inhibited by pretreatment with topical corticosteroids. The number of eosinophils in nasal secretions 24 hours after antigen challenge correlated with the magnitude of reactivity to histamine, and inhibition by topical corticosteroids was accompanied by an inhibition of the increase in eosinophils. Similar studies show nasal hyperresponsiveness to the cholinomimetic agonist methacholine. In allergic patients during the allergy season, the hyperresponsiveness caused by nonspecific irritants probably reflects complex interactions among inflammatory cellular influx, epithelial injury, and increased end-organ responsiveness caused by exposure to antigen.

The pathophysiologic mechanisms in allergic rhinitis can be synthesized in the following scenario (Fig. 40-7): Sensitization of the nasal mucosa to a certain allergen entails multiple interactions among APCs, T lymphocytes, and B cells that lead to the production of antigen-specific IgE antibodies, which then localize to mast cells and basophils. Subsequent exposure leads to cross-linking of specific IgE receptors on mast cells and their resultant degranulation, with the release of a host of inflammatory mediators that are, in large part, responsible for allergic nasal symptoms. Other proinflammatory substances are also generated after antigen exposure, the most prominent being eosinophil products and cytokines. Cytokines are thought to be generated in part by lymphocytes, which are abundant in restituting and stimulated nasal mucosa, and also by mast cells, which have an important role in the storage, production, and secretion of cytokines. Cytokines up-regulate adhesion molecules on the vascular endothelium, and possibly on marginating leukocytes, leading to the migration of these inflammatory cells into the site of tissue inflammation. Various cytokines also promote the chemotaxis and survival of these recruited inflammatory cells, leading to a secondary immune response by virtue of their capability to promote IgE synthesis by B cells. Also important is the nervous system, which amplifies the allergic reaction by central and peripheral reflexes that result in changes at sites distant from those of antigen deposition, such as the eye, sinuses, and lower airway. These inflammatory changes lower the threshold of mucosal responsiveness to various specific and nonspecific stimuli, making allergic patients more responsive to stimuli to which they are exposed every day.

**Evaluation and Diagnosis**

**History**

The classic symptoms of seasonal allergic rhinitis are recurrent episodes of sneezing, pruritus, rhinorrhea, nasal congestion, and lacrimation that occur after exposure to the offending allergen. Itching is the symptom most suggestive of an allergic etiology and involves not only the nose but also the palate, throat, eyes, and ears. Rhinorrhea is usually clear and can be anterior, resulting in sniffing and nose blowing, or posterior, resulting in snorting, throat clearing, and postnasal drip. If the rhinorrhea is purulent, the physician should consider other etiologies, such as viral upper respiratory infections and bacterial rhinosinusitis. Nasal obstruction may be bilateral or could manifest as exaggeration of the nasal cycle with alternating unilateral obstruction. If the obstruction is constant and fixed, the physician should think about coexisting mechanical causes for the obstruction, such as septal deviation. If the congestion is severe, it can be associated with a loss of smell secondary to obstruction to airflow or to inflammation in the olfactory cleft and usually manifests as a loss of taste. Ocular symptoms, including itching, tearing, and conjunctival injection, occur frequently. Eustachian tube dysfunction, manifested as ear popping and clicking, is an occasional manifestation. Systemic symptoms that may accompany allergic rhinitis include general malaise, fatigue, irritability, snoring, and sleep problems. The history for rhinitis should also include query about family history of allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis, because a positive family history for allergic diseases makes it more likely that the patient’s nasal symptoms are secondary to allergic rhinitis.

The traditional classification of allergic rhinitis is seasonal, perennial, or episodic. *Seasonal allergic rhinitis* is defined by symptoms that occur during exposure to seasonal allergens, such as ragweed, grasses, outdoor molds, and tree pollens. *Perennial allergic rhinitis*, defined as nasal symptoms for more than 2 hours per day for more than 9 months
of the year, occurs when allergies develop to house dust mites, indoor molds, animal danders, and cockroaches. *Episodic rhinitis* refers to symptoms on exposure to allergens that are not normally present in the environment, such as a cat-allergic individual becoming symptomatic upon entering the home of relatives who have a cat.

A newer classification was proposed in 1999, during the ARIA (Allergic Rhinitis and its Impact on Asthma) World Health Organization (WHO) workshop, on the basis of the facts that the preceding, more traditional, classification did not always fit all disease presentations and that most patients were polysensitized with both perennial and seasonal allergens.265 The new definition introduced the terms intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER), with the emphasis that these terms were not synonymous with *seasonal allergic rhinitis* and *perennial allergic rhinitis*, respectively. A degree of severity was also attached to this classification. Thus according to the ARIA classification, *intermittent allergic rhinitis* refers to symptoms present for less than 4 days a week, or for less than 4 consecutive weeks, and *persistent allergic rhinitis* refers to symptoms present for more than 4 days a week and for more than 4 consecutive weeks, with the realization that patients usually suffer almost every day. The severity is designated as mild or moderate to severe. *Mild* implies that the symptoms are present but not troublesome. Importantly, there is the absence of sleep disturbance and of impairment of leisure/sport/school/work daily activities. *Moderate to severe* implies the presence of one or more of the following: sleep disturbance, impairment of leisure/sport/school/work daily activities, and troublesome symptoms. The ARIA classification is used to suggest a treatment algorithm, whereas the traditional classification is used to help define the offending antigens.

It is important for the treating physician to familiarize himself or herself with the pattern of environmental allergens in the area of practice. Once allergic symptoms are present, they may be exacerbated by irritants such as strong odors or perfumes, tobacco smoke, paint, newspaper ink, soap powders, and air pollutants. This exacerbation represents nonspecific hyperresponsiveness. Several clinical entities should be considered in the differential diagnosis of the patient who presents with nasal obstruction and rhinorrhea; they are listed in Box 40-1.

### Physical Examination

A complete ear, nose, and throat examination is essential in the workup of every patient suspected of having allergic rhinitis and is useful in identifying other problems rather than in confirming the diagnosis. The ear examination may show otitis media with effusion, suggesting nasopharyngeal problems. Examination of the face may show puffiness of the eyelids and periorbital cyanosis, usually due to venous stasis secondary to chronic nasal obstruction and often referred to as “allergic shiners.” Other facial anomalies associated with long-standing obstruction are elongated facies, open mouth, flattened malar eminences, pinched nostrils, raised upper lips, high arched palate, and retracted jaws, a complex of signs usually referred to as “adenoid faces.” Localized facial tenderness on palpation, especially in conjunction with purulent anterior or posterior nasal discharge, suggests rhinosinusitis.

External nasal examination may show a gross deformity due to previous trauma or bony expansion by an underlying lesion. A supra tip crease at the junction of the upper and lower lateral cartilages is a result of frequent pushing upward of the nasal tip, the “allergic salute.”

A nasal speculum or an otoscope, fitted with the largest speculum, is then used to inspect the inner aspect of the nasal cavities. The anterior portion of the nose is examined for possible folliculitis and anterior septal deviations. The inferior turbinates are then inspected along the lateral nasal wall. These structures are often described as being pale, bluish, and edematous, and coated with thin, clear secretions. It is important to remember that there is no pathognomonic appearance of the nasal mucosa in allergic rhinitis. A topical decongestant, such as oxymetazoline, can be applied and the nasal cavity examined a few minutes later. This step allows evaluation of the reversibility of nasal congestion and facilitates inspection of the area of the middle meatus.

For better examination of the nasal cavity, and in cases in which the existence of pathology not readily accessible to anterior rhinoscopy...
is suspected, nasal endoscopy should be performed. This procedure is usually done with the use of a flexible or rigid fiberoptic instrument and is well tolerated by adults and by children older than 5 years. Nasal endoscopy allows visualization of the middle meatus to rule out the existence of purulent discharge or small polyps originating from the sinuses. In cases in which adenoidal hypertrophy or choanal atresia is suspected, endoscopy can visualize the nasopharynx.

**Diagnostic Tests**

The two most common tests used to confirm the diagnosis of allergic rhinitis are skin testing and in vitro testing for serum levels of specific IgE antibodies. Skin testing is performed by applying antigen extracts to the skin either epidermaneously (puncture skin tests) or intradermally (intradermal tests). Intradermal testing is usually not required for the diagnosis of inhalant allergy when standardized extracts are available\(^{166,262}\) and might induce false-positive reactions. Testing is always accompanied by an introduction of the diluent for the allergen extract, used as negative control, and histamine or codeine (a mast cell degranulating agent), used as a positive control. A wheal and flare reaction, seen within 15 minutes of injection, occurs if a patient is sensitive to a specific antigen. A positive reaction indicates the existence of specific IgE antibodies on intradermal mast cells and the reaction of the skin to released mediators.

Skin testing is rapid and inexpensive but, like all clinical tests, has certain disadvantages, as follows: (1) skin reactivity might be affected by previous ingestion of antihistamines or other drugs, (2) children often do not tolerate multiple skin needle pricks, (3) prior or coexisting dermatologic conditions, such as eczema or dermatographism, may preclude the performance of skin tests, (4) the potency of antigen extracts needs to be maintained, and (5) systemic reactions may occur. Potentially interfering medications must be discontinued prior to skin testing; montelukast does not appear to affect skin test reactivity, however, and does not need to be discontinued prior to skin testing.\(^{260}\) Most physicians test with a panel of allergens that are prevalent in their areas in addition to allergens that seem relevant from the history, such as cat, dog, and cockroach.

Both total and specific serum IgE levels can be measured in vitro. Total IgE is elevated in 30% to 40% of patients with allergic rhinitis, and can be elevated in patients with nonallergic conditions and normal subjects; thus, total IgE determination is of limited use in the diagnosis of allergic rhinitis. The detection of specific IgE antibodies in the patient's serum is useful in the diagnosis of allergic rhinitis. Although less sensitive than skin testing, in vitro IgE measurements correlate well with the results of skin testing and the clinical picture. These tests eliminate the need for multiple skin pricks but are more expensive, and the results take longer to obtain than those of skin testing. It is important to obtain simultaneous total IgE levels because false-positive radioallergosorbent test (RAST) results may occur in sera with extremely high levels of IgE because of nonspecific binding. Other tools, such as nasal challenges and measurement of blood basophil histamine release, other peripheral blood activation markers, or eosinophils in nasal smears, are primarily utilized for research purposes.

The clinical history should guide the clinician to test the patient with a panel of the most relevant antigens. Testing with the six most common antigens is effective in picking up 95% of the allergens to which a patient is sensitive. It is always important to remember that a positive in vitro or skin test result alone does not confirm the diagnosis of allergic rhinitis in the absence of supporting clinical history, particularly because the last National Health and Nutrition Examination Survey study showed that a prevalence of positive test results exceeded 50% but full expression of allergic disease affected only 20% of the study population.

**Therapeutic Options**

**Avoidance**

Avoiding the offending allergens is potentially an effective treatment for allergic rhinitis. Multiple measures for avoidance have been advocated over the years, including removing a pet from the house, covering pillows and mattresses, washing bedding with hot water, and vacuuming mattresses and pillows. These measures are targeted toward indoor allergens, especially dust mites. Unfortunately a systematic review of many of these avoidance measures has shown that single measures are not effective in reducing symptoms in patients with allergic rhinitis.\(^{210}\) A single, large study investigating the effects of the use of allergen-impermeable bedding covers in the bedrooms of patients with dust mite–associated perennial allergic rhinitis, these covers reduced the concentrations of mattress Dermatophagoides pteronyssinus by 30% of baseline but resulted in no difference in the clinical symptoms of allergic rhinitis.\(^{270}\) Limited evidence suggests that preventive measures (removing carpeting, using tannic acid, washing bedding, washing the cat) result in a reduction of levels of the allergen Fel d 1 in the house and a subsequent improvement of clinical symptoms of allergic rhinitis due to cat allergy.\(^{271}\) Good evidence supporting the use of...
high-efficiency particulate air (HEPA) filters is also lacking. Outdoor allergens such as grasses, trees, and weeds are even more difficult to control, and some of the proposed measures that lack scientific evidence for efficacy include avoiding lawn mowing and driving with the car windows closed. The lack of effectiveness of avoidance measures makes it less important to define what specific allergens patients are sensitive to, if pharmacotherapy is the planned treatment.

**Antihistamines**

H₁ antihistamines block histamine at the H₁ receptor level and are commonly used in the treatment of allergic rhinitis. They include older first-generation drugs, such as diphenhydramine, which are lipophilic and have varying degrees of anticholinergic and sedating side effects, and newer, second-generation, antihistamines, such as loratadine, which have minimal or no sedative effect. The latter are less lipophilic with a reduced ability to cross the blood-brain barrier and have lower sedating and anticholinergic side effects. Oral H₁ antihistamines are effective in controlling histamine-mediated symptoms such as sneezing, itching, rhinorrhea, and eye symptoms such as itchy and watery eyes, but are not as effective in alleviating nasal congestion. Furthermore, several agents in this category have been demonstrated to improve quality of life as measured by generic and disease-specific tools.

Both cetirizine and levocetirizine are labeled by the U.S. Food and Drug Administration (FDA) as sedating, and a low reported incidence of sedation. The second-generation antihistamines include loratadine, cetirizine (both available over the counter), and a low reported incidence of sedation. The second-generation antihistamines in the 1980s eliminated this problem. The newer nonsedating antihistamines have few effects on performance and memory, but do not seem to translate into enhanced clinical efficacy and thus their clinical importance is not clear.

The side effects of first-generation antihistamines can be bothersome. The most important of these is sedation, which is reported in approximately 20% of patients. It is therefore important to warn the patient receiving such a drug about its potential effect on daily activities, such as driving or operating heavy machinery. The development of non-sedating antihistamines in the 1980s eliminated this problem. The newer non-sedating antihistamines have few effects on performance and a low reported incidence of sedation. The second-generation antihistamines include loratadine, cetirizine (both available over the counter), desloratadine, fexofenadine, and the latest, levocetirizine. Both cetirizine and levocetirizine are labeled by the U.S. Food and Drug Administration (FDA) as sedating, but they cause less sedation than the first-generation antihistamines.

H₁ antihistamines are also available for intranasal administration. Azelastine, a pthalazinone derivative, is available in the United States for the treatment of allergic rhinitis. It is comparable in efficacy to other antihistamines, is usually given twice daily, can cause somnolence, and may cause a sensation of altered taste immediately after use. This agent has been shown to be effective in reducing itching, sneezing, runny nose, and nasal congestion. Olopatafatine hydrochloride (0.06%) has been shown to be safe and effective for the treatment of seasonal allergic rhinitis and is usually administered as 2 puffs/nose daily. The most commonly reported adverse reaction to this drug is bitter taste, and the incidence of somnolence is minimally higher than that for the placebo vehicle.

**Decongestants**

Both topical and systemic decongestants act by α-adrenergic stimulation. They cause vascular constriction and a reduction of both the nasal blood supply and the volume of blood in the sinusoids. Topical decongestants, which can be either catecholamines (such as phenylephrine) or imidazoline derivatives (such as xylometazoline or oxymetazoline), have a rapid onset of action and are usually more efficacious than systemic decongestants. They do not have systemic side effects except in children, in whom seizures have been reported. Continued use of these agents leads to progressively shorter duration of action, until almost continued application provides no relief—a condition known as rhinitis medicamentosa. Therefore, the use of topical decongestants in allergic rhinitis should be limited to a short duration for the following purposes: to facilitate the penetration of intranasal steroids in patients in whom severe congestion precludes it, to allow proper physical examination, and to facilitate sleep during severe rhinitic exacerbations.

Commonly used in the United States, oral decongestants do not cause rhinitis medicamentosa but are not as effective as their topical counterparts. Pseudoephedrine hydrochloride and phenylephrine are the most commonly used. Phenylephrine has been taken off the market in the United States because of the increased risk of hemorrhagic stroke in women associated with its use as an appetite suppressant. Pseudoephedrine decongestant–containing products are now sold from behind the pharmacy counter in the United States because of the potential for their conversion into stimulants. They are used most frequently in combination preparations with antihistamines (pseudoephedrine) or over the counter in cough and cold products in combination with analgesics and antitussives. Phenylephrine is another over-the-counter decongestant also used in combination products, but a 2007 meta-analysis showed lack of efficacy for this agent on both objective and subjective measures of nasal congestion in comparison with placebo. In addition to nasal vasoconstriction, oral decongestants cause vasoconstriction in other vascular beds, accounting for their side effects, the most common of which is insomnia and irritability, which can be seen in as many as 25% of patients. An overdose of these agents causes hypertension, nervousness, renal failure, arrhythmias, psychosis, strokes, and seizures. They should therefore be administered with caution to patients who have hypertension, heart disease, seizure disorders, hyperthyroidism, or prostatic hypertrophy or who are undergoing monoamine oxidase inhibitor therapy.

**Anticholinergics**

Anticholinergic drugs are useful in the treatment of those subjects in whom rhinorrhea is the predominant complaint. Ipratropium bromide has little or no systemic effects when administered intranasally and has been shown to be effective in controlling watery nasal discharge in perennial allergic and nonallergic rhinitis. It has no effect on sneezing or nasal obstruction. This agent can be used in conjunction with other modalities, such as antihistamines or intranasal steroids, for the satisfactory control of rhinorrhea.

**Cromolyn Sodium**

Cromolyn sodium, which is available over the counter as a 4% solution for intranasal use, has been shown to be clinically effective in the treatment of allergic rhinitis. Like antihistamines, it is more helpful for sneezing, itching, and rhinorrhea and less effective in relieving nasal congestion. Its mode of action is unclear, and it is most effective when started before the onset of symptoms. The dosage is four to six times daily, causing compliance problems, but cromolyn sodium is very safe, especially in children and pregnant women.

**Leukotriene Modifiers**

Because leukotrienes are generated in allergic rhinitis, the effects of inhibitors of the 5-lipoxygenase pathway (zileuton) and leukotriene receptor antagonists (montelukast and zafirlukast) have been investigated. By far the most commonly used agent in this category is montelukast, which is approved in the United States for the treatment of seasonal and perennial allergic rhinitis in adults and children. In placebo-controlled studies, montelukast has repeatedly been shown to be more effective than placebo and equal in effectiveness to antihistamines for all ocular and nasal symptoms of allergic rhinitis, including congestion, rhinorrhea, and sneezing. Furthermore, the combination of montelukast and loratadine was found to be superior to each agent alone in the treatment of seasonal allergic rhinitis in one study, although these results have not been duplicated consistently in subsequent investigations. Ciebiada and colleagues conducted a placebo-controlled, crossover study to evaluate the effect of montelukast, desloratadine, and levocetirizine, alone or in combination, in patients with persistent allergic rhinitis. These researchers showed that all treatments were superior to placebo in the control of total nasal symptoms and that the
combination of either of the antihistamines with montelukast was more effective than each of the treatments used individually. A combination product containing loratadine and montelukast was not approved by the FDA.

Intranasal Steroids
Intranasal steroids (INSs) are the most potent drugs available for allergic rhinitis, a feature likely related to their diverse anti-inflammatory effects. In nasal allergen challenge models of allergic rhinitis, pretreatment with INSs results in significant inhibition of mediator release during both the early and late phase reactions along with a significant inhibition of the influx of basophils, eosinophils, neutrophils, and mononuclear cells in nasal secretions. Intranasal steroids, such as growth retardation and interference with the disease. They are best reserved for patients who present in the middle of the pollen season with total nasal obstruction. Because oral decongestants, with or without antihistamines, would not be effective in these patients and the intranasal steroid preparations cannot be delivered because of nasal obstruction, a short course of systemic steroids is effective in relieving nasal obstruction. A short course of systemic steroids is also useful in reducing the nasal obstruction associated with rhinitis medicamentosa and facilitates weaning of patients from topical decongestants. Treatment with intramuscular injections of depot-steroids should not be used for the treatment of seasonal allergic rhinitis unless there are extenuating circumstances, because there is always a potential for decreased resistance to infection during the 4 to 6 weeks after the injection. Furthermore, depot-steroid injections have long-term effects on bone density, cause systemic suppression of the hypothalamic-pituitary axis, and have other systemic effects associated with systemic steroids.

Immunotherapy
Allergen-specific immunotherapy involves the repeated administration, sublingually or subcutaneously, of increasing doses of antigen extract in an attempt to alter patients’ immunologic responses and improve their symptoms. Immunotherapy is usually reserved for patients who find it difficult to avoid allergens and who have not experienced adequate responses to pharmacologic treatment.

Subcutaneous Immunotherapy
Since the introduction of subcutaneous immunotherapy (SCIT) in 1911, many studies have supported its effectiveness in the treatment of pollen allergies. Several immunologic changes occur in patients receiving SCIT; they include (1) a rise in serum-specific IgG, (2) an increase in the levels of IgG and IgA antibodies in nasal secretions, (3) a variable reduction in the reactivity and sensitivity of peripheral basophils to antigens, (4) reduced in vitro lymphocyte responsiveness to allergens, (5) a reduction in inflammatory cells in the nasal mucosa and nasal secretions and a shift from the TH2 to the TH1 cytokine profile, and (6) suppression of the seasonal rise in IgE antibodies followed by a slow decline in the level of specific antibodies during the following several years of treatment. The clinical efficacy of SCIT is well established for allergic rhinitis, and the therapy improves quality of life of patients with allergic rhinitis. The treatment offers relief, but the onset of action is slow, with improvement starting within 12 weeks and increasing over a period of 1 to 2 years after treatment. Because the treatment involves multiple visits, requires a high degree of patient compliance, has significant adverse effects, such as death, is highly specific and effective only for the allergens administered, and needs months to achieve clinical improvement, careful identification of all allergens responsible for the patient’s symptoms before initiation of treatment is important.

The duration of SCIT is usually 3 to 5 years, and several studies have shown persistence of benefit for various periods of time after cessation of therapy, supporting the conclusion that SCIT alters the natural history of allergic rhinitis. In one such blinded, placebo-controlled study, Durham and colleagues showed that 3 to 4 years of immunotherapy with grass pollen extract resulted in prolonged clinical remission accompanied by a persistent alteration in immunologic reactivity as demonstrated by reduction in the late skin response and associated CD3+ T-cell infiltration and IL-4 mRNA expression 3 years after discontinuation of therapy. SCIT has also been shown to prevent the development of new sensitizations in monosensitized children, and it may reduce the development of asthma in patients treated for rhinitis.

Immunotherapy causes local and systemic adverse reactions. Lockey and associates reported 46 fatalities associated with immunotherapy and skin testing in the United States for the period 1945 to 1985 and 17 fatalities associated with immunotherapy for the years 1985 to 1989. Analysis of these data with special attention to risk factors suggested that, although death from immunotherapy is uncommon (risk estimated at 1 fatality for every 2 million injections), special precautions must be taken in patients with asthma, and a waiting period of 20 minutes after the administration of the shot is recommended for all patients, with longer intervals (30 minutes) being appropriate for high-risk patients. Treatment should also be administered in an office ready to handle anaphylaxis.

Sublingual Immunotherapy
Sublingual immunotherapy (SLIT), whereby extracts are administered sublingually, was controversial for many years but has gained wide
acceptance in European and other countries and is starting to be investigated in the United States. In 2005, Wilson and colleagues performed a meta-analysis, the results of which supported the safety and efficacy of SLIT in allergic rhinitis. Multiple other studies have been published since then with results to the same effect. A meta-analysis has also supported the efficacy of SLIT in children with allergic rhinitis and patients with asthma. Limited data support the potential of SLIT in altering natural history of the disease.

The obvious advantage of this treatment over SCIT is ease of administration and the avoidance of coming to a doctor’s office to receive the treatment. This is primarily related to the safety of SLIT. Indeed, safety has been demonstrated in multiple studies in adults and children. Described local side effects have included itching and swelling of the lips and the sublingual oral mucosa that resolve without treatment. Systemic anaphylactic reactions have been described, one with latex immunotherapy, one with an ill-defined multi-allergen vaccine, and the last with pollen mix administered in conjunction with dust mite extract during the peak of the spring season in a child. Clear directions should therefore be given to parents about what to do in the event of an adverse reaction, and the extracts should be kept in a safe place out of the reach of children. It is of note that no extracts are currently approved by the FDA for immunotherapy using the sublingual route. However, a couple of leading developers and providers of allergy immunotherapy are in the process of performing clinical trials with SLIT using their standardized antigenic extracts in an effort to bring an approved sublingual-oral immunotherapy treatment to the United States.

SCIT is probably best reserved for patients with perennial rhinitis because they are symptomatic all through the year and are willing to undergo prolonged treatment. Medical treatment is probably more suitable for patients with seasonal or episodic rhinitis who have symptoms for much shorter periods of the year. SLIT has been studied primarily in and is available mostly for seasonal allergens; its use with multiple allergens has not been fully evaluated.

Novel Extracts
Recombinant DNA technology has allowed the production of allergens with improved purity, consistency, composition, and dosage. The use of such extracts is being investigated for the immunotherapy of allergic rhinitis, and initial results are promising. Animal studies are also ongoing to test the efficacy of a mucosal adhesive formulation of allergens that would enhance adhesion of allergen extracts to the sublingual mucosal membrane and would thus augment treatment via the sublingual route.

Anti-IgE
Recombinant, humanized, monoclonal anti-IgE antibody forms complexes with free IgE and blocks its interaction with mast cells and basophils. Anti-IgE has been shown to be beneficial and cost-effective in the treatment of moderate to severe asthma, for which it is currently indicated in the United States. Although it has also been shown to be effective in decreasing nasal symptoms and improving quality of life in patients with allergic rhinitis, the lack of cost-effectiveness as well as the inconvenient route of administration (subcutaneous) make this agent ill-suited as the mainstream of treatment of allergic rhinitis. In a clinical trial in patients with ragweed allergic rhinitis, anti-IgE therapy was shown to enhance the safety of a rush (accelerated dosage increase) immunotherapy regimen, allowing a significant reduction in the time required for treatment.

Treatment of Eye Symptoms in Allergic Rhinoconjunctivitis
Allergic rhinitis involves eye symptoms that are probably a combination of the direct effects of allergen deposition on the conjunctiva and reflexes between the nose and the eye. Oral H1 antihistamines and leukotriene receptor antagonists are effective in controlling eye symptoms. Antihistamines given intraocularly have been shown to be effective for the control of allergic eye symptoms. They have a rapid onset of action and are associated with lower rates of sedation and dry eye than first-generation oral H1-antihistamines. They usually require twice-a-day dosing, although a newer preparation (olopatadine) is effective when used once daily.

Interestingly, multiple studies have shown that the administration of intranasal steroids is effective in controlling ocular symptoms in seasonal allergic rhinitis. In a meta-analysis comparing H1 antihistamines with INSs, there was no difference in the efficacy of these two agent classes in the control of ocular symptoms, suggesting that INSs were at least as effective as H1 antihistamines in the control of ocular symptoms in patients with allergic rhinitis. Furthermore, another meta-analysis examining the findings from clinical trials that compared the effects of INSs and intranasal antihistamines on ocular symptoms in allergic rhinitis demonstrated no overall significant difference between the two treatment modalities. The mechanism of this favorable effect of INSs is speculated to be reduced intranasal inflammation, which in turn inhibits the nasal ocular reflex initiated by allergen contact with the nasal mucosa.

Combination Treatments
Combinations of drugs have been tested for treatment of allergic rhinitis, and results were partly covered in the discussions of decongestants and leukotriene modifiers. Additionally, the use of antihistamines, in various forms, with INSs has been investigated. Addition of intranasal azelastine to intranasal fluticasone propionate in patients with Texas mountain cedar allergic rhinitis showed a synergistic effect of the combination treatments in comparison with each agent alone in the control of nasal symptoms. Studies on the combination of systemic H1 antihistamines and INSs have reported variable results, with one study showing no additional benefit in the control of nasal symptoms for fluticasone and loratadine given in combination over fluticasone administered alone. A similar study showed no palatable added benefit for the addition of cetirizine or montelukast to intranasal fluticasone propionate in comparison with the nasal spray alone for the control of seasonal allergic rhinitis. Furthermore, in the same study, intranasal fluticasone propionate was more effective than the combination of cetirizine and montelukast. In an ocular allergen challenge study combining intranasal fluticasone propionate and intraocular olopatadine produced significantly greater improvements in ocular itching after challenge than the combination of fluticasone and fexofenadine. Finally, an older study showed additive efficacy of intranasal beclomethasone and ipratropium bromide in comparison with the individual agents in the control of severity and duration of rhinorrhea in perennial rhinitis. It is common in clinical practice to use combination treatments in patients with symptoms that are difficult to control; these treatments typically include an INS with an additional agent such as an H1 antihistamine (systemic, intranasal, or intraocular) or a leukotriene modifier.

General Treatment Planning
Various organizations have published guidelines for the management of allergic rhinitis, including a joint effort by the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology; ARIA; and the Global Allergy and Asthma European Network (GAALEN). The interested reader is referred to these publications for more detail. We have tried to keep the discussion of management simple and recommend the following general guidelines for the treatment of allergic rhinitis. If disease is mild, we treat with as-needed (PRN) intranasal steroids, and if it is moderate to severe, we recommend the regular use of INSs. If patients are not willing to use an intranasal medication, or are bothered by local irritation, we recommend treatment with antihistamines.

We generally reevaluate patients after 2 weeks to assess the response to therapy. If they have an excellent response, we consider their anticipated exposure and treat accordingly. If there is a partial response, we identify residual complaints and add agents targeting these symptoms. For residual eye symptoms, we treat with intraocular antihistamines/mast cell stabilizers. If there is significant redness of the eye, we refer the patient to an ophthalmologist. For residual nasal congestion, we consider the addition of an antihistamine decongestant combination or montelukast. For residual rhinorrhea, we consider adding
ipratropium bromide. If the patients do not improve after maximal medical therapy, we reconsider the diagnosis. If they have significant perennial disease and have no response to maximal medical treatment, we evaluate the patients for immunotherapy. We do not routinely perform allergy testing unless immunotherapy is planned, because avoidance is great in theory but not proven in practice.

We also consider special patient groups. In pregnant women, we use budesonide as the INS of choice and loratadine, cetirizine, and levocetirizine as the antihistamines of choice, because these agents are all considered pregnancy category B agents by the FDA. In the elderly, we avoid sedating antihistamines because of the increased risks of falls in such patients. In competitive athletes, systemic decongestants are banned substances and are therefore avoided. In patients taking ritonavir, an inhibitor of human immunodeficiency virus protease, and potentially other protease inhibitors, we avoid INSs. Concomitant use of ritonavir and intranasal/inhaled fluticasone propionate may increase plasma concentrations of fluticasone, resulting in possible systemic corticosteroid effects and adrenal suppression with reduced serum cortisol concentrations.399 In patients taking protease inhibitors, safer options appear to be budesonide, triamcinolone, and flunisolide.399

Conclusion
This chapter provides an overview of immunology of the upper airway and discusses innate and adaptive immunity as well as cell-mediated immune responses. As a model of an immunologic disease involving IgE antibodies to foreign substances, allergic rhinitis, an important and frequently encountered disease in otolaryngology practices, is also discussed. A detailed review of the pathophysiology, diagnosis, and treatment options of this disease are presented.

SUGGESTED READINGS
Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122(2 Suppl):S1-S84.

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