patients can have superimposed polymyalgia rheumatica. Therapy with high-dose steroid should be started promptly if GCA is suspected. Many patients require steroid-sparing agents.

_Takayasu’s arteritis._11 Takayasu’s arteritis is a granulomatous vasculitis of unknown cause affecting predominantly young women, especially Asians. The presence of 3 or more of the following ACR criteria yields a 91% sensitivity and 98% specificity for diagnosis: age less than 40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference between the extremities of greater than 10 mm Hg, bruit over subclavian artery or aorta, and/or arteriographic narrowing-occlusion of the aorta and its primary branches. Patients are treated similarly to those with GCA.

_Kawasaki’s syndrome (mucocutaneous lymph node syndrome)._ Kawasaki’s syndrome is the most common vasculitis of childhood, with a peak incidence at the age of 1 year. It is a self-limited, immune-mediated vasculitis of unknown cause with a predilection for Asians. Classically, children present with fever, bilateral conjunctivitis, mucusitis, polymorphous rash, lymphadenopathy, and desquamation of palms-soles. Children treated with high-dose aspirin and intravenous immunoglobulin (2 g/kg) within the first 10 days of fever are less likely to have potentially life-threatening coronary artery aneurysm. Unlike other types of vasculitis, steroids are contraindicated because of an association with the development of coronary aneurysm.12

**CONCLUSION**

Autoimmune diseases encompass a wide spectrum of diseases, but all are characterized by alterations in normal immune responsiveness, such that there is a loss of tolerance to particular host constituents reflected by the production of autoantibodies (Table II).13,14 Recent research has identified several key changes in components of the immune response (eg, upregulation in proinflammatory cytokines) relevant to the propagation and sustenance of many autoimmune conditions. With this greater understanding of pathogenesis, several novel immunomodulatory therapies targeting specific components of the inflammatory and immune systems have been introduced into the clinic. This has resulted in improved disease outcomes for patients with a number of autoimmune conditions.

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affinity to FcεRI found in its complete form (αβγδ) on mast cells and basophils.1-3

The concentration of IgE in serum is the lowest of the 5 human immunoglobulin isotypes and is age dependent; cord blood IgE levels are low (<2 kIU/L; <4.8 mg/L) and then increase up to 10 to 15 years of age. Those with an allergic predisposition show an earlier and steeper increase. Levels decrease from the second to the eighth decade of life. Approximately 50% of total body IgE is intravascular, with a half-life of 1 to 5 days.1,4

**IgE synthesis**

Two signals are required for IgE synthesis. Signal 1 is provided by IL-4 or IL-13, which activate transcription at a specific immunoglobulin locus. The second signal is provided by ligation of CD40 on B cells, which activates DNA switch recombination. T cells are the principal source of these signals.2,4,5

The process is initiated when an allergen is taken up by an antigen-presenting cell (APCs), such as a dendritic cell or B cell, which then processes and presents the allergen to the T_{H}2 cell. The peptide-MHC complex is recognized by the T-cell receptor, resulting in activation of the T cell and its expression of IL-4, IL-13, and CD154 (CD40 ligand). CD154 engages CD40 expressed on the APC, resulting in activation of the APC, which, in the case of the B cell, results in isotype class switching to IgE, followed by secretion of allergen-specific IgE.

IL-4 activation of α-germline transcription is initiated when it binds to B-cell IL-4 receptor (IL-4R). Ligand-dependent dimerization of the IL-4R leads to Janus kinase–signal transducer and activator of transcription (STAT) signaling, resulting in STAT6 homodimerization and consequent STAT6 translocation to the nucleus, where it binds to IL-4–responsive promoter elements and activates transcription.5 In addition to STAT6, nuclear factor κB-responsive element proteins play an essential role in IL-4–dependent responses, as does B-cell lineage–specific activator protein.

A critical role for CD40-CD154 interactions in IgE synthesis and in isotype switching in general is shown by patients with the X-linked hyper-IgM syndrome.6 These patients have mutations in CD154 and do not undergo class switching, and thus their B cells are unable to produce IgA, IgG, or IgE in response to thymus-dependent antigens.

**IgE receptors**

There are 2 receptors for IgE: the low-affinity IgE receptor (FcεRII; CD23) present on B cells and the high-affinity IgE receptor (FcεRI). FcεRI on mast cells and basophils is a tetramer (αβγδ). It is expressed in a trimeric form (αγδ) on APCs.3,6,7 Expression of the β-chain results in increased FcεRI surface expression and enhances signaling. The density of human basophil FcεRI α expression correlates with serum levels of IgE,8 where binding of IgE to FcεRI stabilizes the receptor at the cell surface.

The Fc fragment of IgE binds to the α-chain of FcεRI. The β-chain is associated with lyn. Two disulfide-linked γ-chains contain immunoreceptor tyrosine-based activation motifs (ITAMs), which are phosphorylated after aggregation of receptor-bound IgE. Syk kinase then binds to the γ-chain ITAM, leading to its activation. Protein levels of syk are undetectable in nonreleasable basophils that do not degranulate in response to FcεRI cross-linking.9 Lyn bound to the β ITAM is also phosphorylated after FcεRI aggregation.

The lyn-syk–dependent signaling cascade involves phosphorylation of adaptor molecules, such as Ssrc homology 2 domain-containing (SHC), vav, non–T-cell activation linker (NTAL), and linker for activation of T cells (LAT); phospholipases, such as PLC_{γ}1, and PLC_{γ}2; tyrosine kinases, such as focal adhesion kinase and Bruton’s tyrosine kinase; and protein and/or inositol phosphatases, such as SHP1, SHP2, and Ssrc homology 2 domain-containing inositol phosphatase (SHIP). Coligation of inhibitory receptors, such as FcεRIIB, with FcεRI results in downregulation of secretory responses.

**Measurements of total and specific IgE**

Total IgE levels are influenced by age, genetic makeup and race, immune status, environmental factors (eg, season of the year), and disease process. Increased IgE levels are found in parasitic diseases, such as schistosomiasis; infections, such as EBV mononucleosis; cutaneous diseases, such as bullous pemphigoid; neoplastic diseases, such as Hodgkin’s disease; immunodeficiency diseases (eg, Wiskott–Aldrich syndrome); hyperimmunoglobulinemia E syndrome; thymic hypoplasia (Di George’s syndrome); Nezelof syndrome; Omenn syndrome; and several other diseases, including nephrotic syndrome, cystic fibrosis, Kawasaki’s disease, and infantile polyarteritis nodosa.

Total IgE is measured with a 2-site, noncompetitive immunometric assay. Here a solid-phase anti-IgE is used to capture IgE and a different anti-human IgE labeled with...
enzyme, fluorophor, or radionuclide is added to detect bound IgE. The minimum amount of IgE detectable in serum with such assays is usually 0.5 to 1 μg/L, where 1 kIU/L equals 2.4 μg/L of IgE.

The presence of antigen-specific IgE is determined by means of skin testing or through the measurement of allergen-specific IgE in serum. Assays to detect allergen-specific IgE antibody are particularly useful when skin testing cannot be used due to extensive skin disease or current medical therapy, significant dermatographism, or use of an extract believed to have a high probability of inducing a systemic reaction in the subject to be tested. The general principle used in such assays is to detect IgE that will bind to allergen fixed on a surface. The assays are influenced by the amount and quality of allergen coupled to the solid support, the degree of nonspecific IgE binding, the affinity of the anti-IgE antibody, and the degree of blocking of allergen-specific IgE binding by allergen-specific IgG.

Allergen-specific IgE levels depend on the degree and duration of exposure to both allergen and cross-reactive allergens. Allergen-specific IgE levels generally peak 4 weeks into seasonal pollen exposure and gradually decrease until the next pollen season. IgE levels usually decrease during immunotherapy. Many individuals have positive test results to allergens but show no clinical reactivity to these allergens. However, as a general rule, the more strongly positive the test result, the more likely the risk of symptoms.

MAST CELLS

The mast cell is a tissue-based inflammatory cell of bone marrow origin that responds to signals of innate and acquired immunity with immediate and delayed release of inflammatory mediators. Mast cells are implicated in the pathogenesis of allergic diseases by their ability to be activated through FcεRI-bound antigen-specific IgE.

The human mast cell is ovoid or irregularly elongate with an oval nucleus and contains metachromatic cytoplasmic granules. In the lungs mast cells are found in bronchial airway connective tissues and in peripheral intra-alveolar spaces. In the skin mast cells appear in greatest numbers near blood vessels, hair follicles, sebaceous glands, and sweat glands.

Human mast cells are divided into 2 major subtypes termed MC\textsubscript{T} or MC\textsubscript{TC} on the basis of the presence of tryptase, chymase, or both. Tryptase staining identifies all mast cells in tissues and has become the principal method to visualize mast cells. MC\textsubscript{TC} cells predominate in skin and small bowel submucosa. MC\textsubscript{T} cells predominate in normal airway and small bowel mucosa.\textsuperscript{10} MC\textsubscript{T} cells appear selectively attenuated in the small bowel of patients with end-stage immunodeficiency diseases. Mast cells are Kit\textsuperscript{+} (receptor for stem cell factor [SCF]) and FcεRI\textsuperscript{+} and express a variety of membrane receptors depending on the state of differentiation and location. Human resting mast cells express FcεRI and FcγRIIb (CD32) and express FcγRI (CD64) in the presence of IFN-γ. Mast cells might also express C3a and C5a receptors, IL-3R, IL-4R, IL-5R, IL-9R, IL-10R, GM-CSFR, IFN-γR, CCR3, CCR5, CXCR2, CXCR4, and nerve growth factor receptor, among others.

Development

Human mast cells arise from CD34\textsuperscript{+} pluripotent stem cells. Mast cell precursors circulate in the blood and home to tissues, where they mature under the influence of SCF produced by stromal cells, including fibroblasts and endothelial cells.\textsuperscript{11} Mast cell phenotype and behavior is altered by cytokines, such as IL-4, IL-5, and IFN-γ. For example, IL-4 upregulates expression of FcεRI. IL-5 promotes proliferation in the presence of SCF, and IFN-γ decreases mast cell numbers.

Mast cells increase in number several-fold in association with IgE-dependent immediate hypersensitivity reactions, including rhinitis, urticaria, and asthma; connective tissue disorders, such as rheumatoid arthritis and scleroderma; infectious diseases, such as tuberculosis and syphilis; neoplastic diseases, such as lymphoma and leukemias; and osteoporosis, chronic liver disease, and chronic renal disease.\textsuperscript{11} The most striking increase in mast cells occurs with parasitic disorders and in mastocytosis.

Activation

In addition to aggregation of FcεRI (αβγ\textsubscript{2}), mast cells are also activated by C3a and C5a through C3aR and C5aR (CD88), nerve growth factor through TRKA, and IgG through FcγRI.\textsuperscript{12} Mast cells might also be activated through Toll-like receptors (TLRs). For example, activation through TLR-3 with double-stranded RNA induces human mast cells to produce type 1 interferons.\textsuperscript{13} The extent and pattern of mediators released depends on the signal, its intensity, and the cytokine milieu. For instance, mediator release is enhanced in the presence of SCF.

Mediators

Mediators produced by mast cells are divided into preformed mediators, newly synthesized lipid mediators, and cytokines. These categories are not absolutely exclusive because at least one cytokine, TNF-α, occurs both preformed and as a newly synthesized molecule.\textsuperscript{11} Preformed mediators are packaged within secretory granules and, on activation, are released into the extracellular environment within minutes. Principal granule constituents include histamine, serine proteases, carboxypeptidase A, and proteoglycans (heparin and chondroitin sulfate E). Histamine in granules is found in ionic association with acidic residues of the glycosaminoglycan side chains of heparin and chondroitin sulfate E and dissociates in extracellular fluids by exchanging with sodium ions. Histamine has effects on smooth muscle (constriction), endothelial cells, nerve endings, and mucous secretion. It is degraded to N-methyl histamine, methylimidazole acetic acid, and imidazole acetic acid.

The majority of the protein in granules is made up of neutral proteases: tryptase, chymase, and carboxypeptidase.
Tryptase is a tetramer with a molecular weight of 110 to 130 kd with subunits of 31 to 36 kd that is stabilized by its association with proteoglycans. The function of tryptase in vivo is unknown, but in vitro it can cleave C3 and C3a, activate fibroblasts, and promote accumulation of inflammatory cells. Lipid mediators include prostaglandin (PG) D2, the major cyclooxygenase product, and lipoxigenase products, including leukotriene (LT) C4 and the peptidolytic products LTD4 and LTE4. Skin mast cells produce more PGD2 than LTC4, whereas the opposite is true of mast cells from the lung. PDG2 and LTC4, LTD4, and LTE4 are all bronchoconstrictors. LTC4, LTD4, and LTE4 enhance vascular permeability. PGD2 is a neutrophil chemoattractant. TNF-α is a major cytokine produced by mast cells; it upregulates endothelial and epithelial adhesion molecules, increases bronchial responsiveness, and has antitumor effects. Other cytokines produced by mast cells include IL-4, which is associated with Tfh2 cell differentiation and IgE synthesis; IL-3, GM-CSF, and IL-5, which are critical for eosinophil development and survival; and IL-6, IL-8, and IL-16. Human mast cells also produce chemokines, such as CCL3 (macrophage inflammatory protein 1α).

Role in health and disease

Mast cell activation through FcεRI initiates an immediate hypersensitivity reaction, as well as a late-phase reaction. The immediate reaction in the skin presents as erythema, edema, and itch; in the upper airways as sneezing, rhinorrhea, and mucous secretion; in the lungs as cough, bronchospasm, edema, and mucous secretion; and in the gastrointestinal tract as nausea, vomiting, diarrhea, and cramping. Such reactions might be followed 6 to 24 hours later by persistent edema and a leukocytic influx, termed a late-phase reaction. In the lungs the late-phase reaction is believed to play a major role in the genesis of persistent asthma. Mast cells might contribute to the downregulation of the allergic response in that they produce and release IL-1 receptor antagonist, heparin, and other molecules with anti-inflammatory properties. Mast cells are also implicated in innate immunity. Mast cells are capable of phagocytosis and are activated through pattern-recognition receptors to produce inflammatory mediators.

Pathologic excess of mast cells, usually caused by activating mutations in Kit, leads to mastocytosis. This disease can occur in any age group, and in the majority of situations is first identified by the appearance of fixed pigmented skin lesions termed urticaria pigmentosa. The clinical presentation might also include episodes of unexplained flushing and hypotension. Mastocytosis varies from benign or indolent forms to mastocytosis associated with bone marrow pathology, including myelodysplasia. This disease is diagnosed on the basis of characteristic skin findings, an increased serum tryptase level, and specific bone marrow findings.

BASOPHILS

Basophils are granulocytes that comprise a separate lineage from mast cells, although both cells share common features, such as FcεRI expression, metachromatic staining, Tph2 cytokine expression, and histamine release. After activation, basophils rapidly produce IL-4 and IL-13, supporting their contribution to allergic inflammation.

Morphology and phenotype

Basophils exhibit a segmented nucleus and are identified by means of metachromatic staining with basic dyes, such as toluidine blue. Basophils express a variety of cytokines (IL-3R, IL-5R, and GM-CSFR), chemokine (CCR2 and CCR3), complement (CD11b, CD11c, CD35, and CD88), prostaglandin (CRTH2), and immunoglobulin Fc (FcrRI and FcyRII) receptors.

Development

Basophils develop from CD34+ pluripotent stem cells, differentiate and mature in the bone marrow, and circulate in the periphery. IL-3 is the dominant cytokine driving basophil differentiation and is sufficient to differentiate stem cells into basophils. Basophils comprise less than 1% of peripheral blood leukocytes.

Activation

Basophils express a complete and functional FcεRI receptor (αβγ2), cross-linking of which leads to basophil activation, granule exocytosis, and mediator release. C3a and C5a also activate basophils through specific receptors. Activation through any of the above receptors leads to histamine release, eicosanoid synthesis, and IL-4/IL-13 gene expression. Additional mediators, such as CC chemokines (eotaxins [CCL11, CCL24, and CCL26], monocyte chemoattractant protein 3 [CCL7], monocyte chemoattractant protein 4 [CCL13], and RANTES [CCL5]), formyl-methionine-leucine-phenylalanine, IL-3, IL-5, GM-CSF, and histamine-releasing factor, do not directly cause basophil mediator release-production but potentiate FcεRI effects.

Mediators

Basophils produce a spectrum of mediators, including histamine, leukotrienes, IL-4, and IL-13. Basophils are a dominant and rapid source of IL-4 in both allergen- and helminth-specific responses in both human and mouse systems. Conversely, the mast cell mediators PGD2 and IL-5 are not produced by basophils.

Role in health and disease

The physiologic role of basophils is not known, although presumably they fulfill a host defense function. A role for basophils in innate immunity is suggested by their expression of a functional TLR-2 receptor, as well as their non–IgE-dependent activation by proteases from Der p 1 and hookworm. Basophils are known to play a role in rejection of ticks and are a component of the inflammatory response to many parasites. Basophils produce...
IL-4 in response to parasites through both IgE-dependent and IgE-independent mechanisms. Basophils are the predominant source of IL-4 in allergen- and helminth parasite–activated human PBMCs, as well as in corresponding mouse models. Basophils have been identified in cutaneous and pulmonary late-phase allergic responses and are found in increased numbers in the lungs of patients who die of asthma.

**EOSINOPHILS**

Eosinophils are granulocytes that were first described to stain with acid aniline dyes, such as eosin. Blood and tissue eosinophilia are hallmark signs of helminth infection, allergy, and asthma.

**Morphology and phenotype**

Eosinophils exhibit a bilobed nucleus, with highly condensed chromatin and cytoplasm containing 2 major types of granules, specific and primary. Specific granules have a distinctive ultrastructural appearance consisting of an electron-dense crystalloid core and contain cationic proteins that give eosinophils their unique staining properties. Primary granules are similar to those found in other granulocyte lineages and are formed early in eosinophil development. Eosinophils also contain lipid bodies, which play a role in the generation of eicosanoid mediators.

Eosinophils express an array of cell-surface molecules, including B family cytokine receptors (IL-3R, IL-5R, and GM-CSFR), chemokine receptors (CCR1 and CCR3), FcγRII (CD32), FcεRI (secretory IgA), complement receptors (C3aR, CD88 and CD35), and adhesion molecules (very late antigen 4 and α4β7 integrin). Eosinophil expression of FcεRI is minimal and is of unclear functional significance (see below).

**Development and trafficking**

Eosinophils develop and mature in the bone marrow from CD34+ progenitor cells and are released to the peripheral blood as mature cells. IL-5, the major eosinophil-active cytokine, increases the differentiation and proliferation of eosinophil precursors in the bone marrow. In this manner IL-5 produced at sites of allergic inflammation or helminth infection acts distally on the bone marrow. Additionally, allergen challenge or the experimental administration of CCL11 (eotaxin) causes bone marrow release of mature eosinophils and eosinophil precursors.

Once released from the bone marrow, eosinophils circulate in the blood and traffic to tissue. The peripheral blood half-life is 8 to 18 hours. Although eosinophils are best known as peripheral blood leukocytes, the vast majority of eosinophils are located in the gut and lungs. The steps required for eosinophil trafficking from the peripheral circulation to tissue have been characterized, and there is an emphasis on exploiting these mechanisms to treat asthma.

**Mediators and effector function**

Eosinophils release proinflammatory mediators, including granule-stored cationic proteins, newly synthesized eicosanoids, and cytokines. Highly cationic (isoelectric point pH 9-11) granule proteins play a role in host defense and in the pathogenesis of eosinophil-mediated diseases.

Major basic protein (MBP) accounts for more than 50% of the eosinophil granule protein mass. MBP has in vitro toxicity against parasites, including helminths and schistosomula. In patients with asthma, serum and bronchoalveolar lavage fluid MBP correlate with bronchial hyperresponsiveness.

Additional eosinophil granule proteins include eosinophil-derived neurotoxin and eosinophil cationic protein, both of which have RNAse activity and demonstrate in vitro toxicity to parasites, as well as single-stranded RNA pneumoviruses, such as respiratory syncytial virus. Both the eosinophil-derived neurotoxin and eosinophil cationic protein genes show exceedingly high rates of molecular evolution, suggesting the molecules are under extraordinary selective pressure, as might be expected of genes responding to the rapid evolution of microbial pathogens.

Eosinophils are also a major source of cysteinyl leukotrienes, particularly LTC4, and are the principal LTC4-synthase producing cells in asthmatic bronchial mucosa. Eosinophils are capable of producing a number of cytokines, including IL-1, TGF-β, IL-3, IL-4, IL-5, IL-8, and TNF-α. However, eosinophils generally produce lower amounts of cytokines than other inflammatory cells, such as T cells. Eosinophils demonstrate immunomodulatory

**Activation**

There is no consensus on the major signaling mechanism for eosinophil activation. Eosinophils are activated by cross-linking of agarose beads coated with either IgG, IgA, or secretory IgA, the latter being the most potent. Most reports have not demonstrated expression of functional FcεRI by eosinophils. Eosinophils express a number of TLRs. Their function on eosinophils has not been clearly defined.

Eosinophils can be primed by a number of mediators, including IL-3, IL-5, GM-CSF, CC chemokines, and platelet-activating factor. Eosinophils obtained from bronchoalveolar lavage fluid after allergen challenge demonstrate a primed phenotype, supporting the in vivo relevance of this priming phenomenon. In contrast to the importance of IL-5 on eosinophil differentiation and bone marrow release, GM-CSF might play a greater role in promoting eosinophil survival in the tissue.
activity through multiple mechanisms, including secretion of cytokines, antigen presentation, or expression of indolamine 2,3 dioxygenase, leading to kynurenine production, which has anti-T$_H$1 activity.\textsuperscript{23,31}

**Role in health and disease**

Peripheral blood eosinophil counts are increased in allergic disease, asthma, and helminth infections, and tissue eosinophilia is often found at inflammatory sites associated with these diseases. Despite their in vitro activity against parasites, in vivo studies in IL-5 gene knockout mice have generally not supported an essential role for eosinophils in clearing parasitic infections.\textsuperscript{24}

In allergic disease and asthma eosinophils play a pro-inflammatory role, in which eosinophil mediators, such as MBP, are thought to cause mucosal inflammation and consequent bronchial hyperresponsiveness.\textsuperscript{23} Anti-IL-5 has been used as an investigational asthma therapy and decreases peripheral blood eosinophil counts by more than 90%, but only decreased lung eosinophil counts by approximately 50%. These findings suggest that anti-IL-5 alone might not be sufficient to abrogate pulmonary eosinophilia in asthma.\textsuperscript{25} Results from both a clinical trial of anti-IL-5 in asthma and from an eosinophil knockout mouse asthma model suggest that eosinophils contribute to airway remodeling, possibly through the elaboration of TGF-$\beta$.

A subset of patients with hypereosinophilic syndrome has a translocation resulting in a FIP1L1-PDGFR fusion protein that acts like an oncogene, resulting in increased numbers of eosinophils. The resulting fusion protein receptor kinase is sensitive to the drug imatinib.\textsuperscript{32}

Eosinophil knockout mice have been used in asthma models, with results supporting a role for eosinophils in airway remodeling and in mucus production and hyperreactivity.\textsuperscript{2,34} Further studies with these eosinophil-deficient mice, as well as antieosinophil pharmacologic strategies in human asthma, will ultimately result in a clearer picture of eosinophil contributions to human disease.
Asthma is a heterogeneous disorder that is characterized by variable airflow obstruction, airway inflammation and hyperresponsiveness, and reversibility either spontaneously or as a result of treatment. Multiple causes no doubt exist for both its inception and symptom exacerbation once the disease is established. Factors underlying inception can range from viral respiratory tract infections in infancy to occupational exposures in adults. Factors underlying asthma exacerbations include allergen exposure in sensitized individuals, viral infections, exercise, irritants, and ingestion of nonsteroidal anti-inflammatory agents among others. Exacerbating factors might include one or all of these exposures and vary both among and within patients. Asthma treatment is determined to a large extent after an assessment of severity, which can be variable over time and assessed in 2 domains: impairment (current) and risk (long-term consequences). Unfortunately, despite the availability of effective therapies, suboptimal asthma control exists in many patients on a worldwide basis. The future development of novel therapies and treatment paradigms should address these disparities. (J Allergy Clin Immunol 2006;117:S456-61.)

Key words: Asthma, respiratory syncytial virus, rhinovirus, allergen, prevention, exacerbation, inception, treatment

NATURAL HISTORY (INCEPTION AND PROGRESSION)

For many asthmatic patients, the disease has its roots during infancy and early childhood. Viral respiratory tract infections produce wheezing episodes during the first 3 years of life in about 50% of children. Some of these children will stop wheezing (transient wheezers), whereas others will go on to have persistent symptoms that will either dissipate before adolescence (primarily nonatopic individuals) or continue into adolescence (atopic wheezers). Once in remission, the disease process might remain quiescent or the individual could relapse in later life.

The pattern and rate of loss of lung function in asthmatic subjects has been of interest and concern to many investigators. A number of groups have reported that the greatest absolute loss of lung function appears to occur very early in childhood. Some have reported that the peak in lung function that is achieved at about 20 years of age in patients with asthma might be decreased and that the rate of further loss during adulthood might be increased in asthmatic subjects. About one fourth of children with asthma could experience greater rates of loss of lung function, and these children have certain phenotypic characteristics: younger age, male sex, higher postbronchodilator FEV1 percent predicted, and greater airway eosinophilic inflammation.

The precise timing for the inception of the inflammatory response characteristic of asthma is unknown. Although recent biopsy studies in wheezing infants who have documented reversible airflow obstruction do not show any consistent inflammatory or structural changes (ie, remodeling), other groups have demonstrated increased numbers of inflammatory cells and mediators in wheezing preschool children. Despite these advances in our understanding of factors contributing to mild persistent asthma in children and their potential for long-term consequences, much still needs to be learned.

Risk factors

Risk factors in relationship to asthma have been evaluated in the context of disease inception (eg, viral infections, environmental exposures [eg, aeroallergens, pollution, and tobacco smoke], lifestyle [eg, living on a farm, diet, and antibiotic use], comorbid conditions [eg, atopic dermatitis and obesity], and occupational exposures among others), as well as disease severity (as defined by the risk domain, which is discussed subsequently: hospitalizations, frequency and severity of exacerbations, and loss of lung function). Genetic factors also contribute significantly to disease expression and severity. Asthma is genetically classified...