

## SECTION 2, DEFINITION, PATHOPHYSIOLOGY AND PATHOGENESIS OF ASTHMA, AND NATURAL HISTORY OF ASTHMA

### KEY POINTS: DEFINITION, PATHOPHYSIOLOGY AND PATHOGENESIS OF ASTHMA, AND NATURAL HISTORY OF ASTHMA

- Asthma is a chronic inflammatory disorder of the airways. This feature of asthma has implications for the diagnosis, management, and potential prevention of the disease.
- The immunohistopathologic features of asthma include inflammatory cell infiltration:
  - Neutrophils (especially in sudden-onset, fatal asthma exacerbations; occupational asthma, and patients who smoke)
  - Eosinophils
  - Lymphocytes
  - Mast cell activation
  - Epithelial cell injury
- Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.
- In some patients, persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.
- Gene-by-environment interactions are important to the expression of asthma.
- Atopy, the genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.
  - Viral respiratory infections are one of the most important causes of asthma exacerbation and may also contribute to the development of asthma.

## KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses.
- Gene-by-environmental interactions are important to the development and expression of asthma. Of the environmental factors, allergic reactions remain important. Evidence also suggests a key and expanding role for viral respiratory infections in these processes.
- The onset of asthma for most patients begins early in life with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.
- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease severity.

## Introduction

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. This interaction can be highly variable among patients and within patients over time. This section presents a definition of asthma, a description of the processes on which that definition is based—the pathophysiology and pathogenesis of asthma, and the natural history of asthma.

## Definition of Asthma

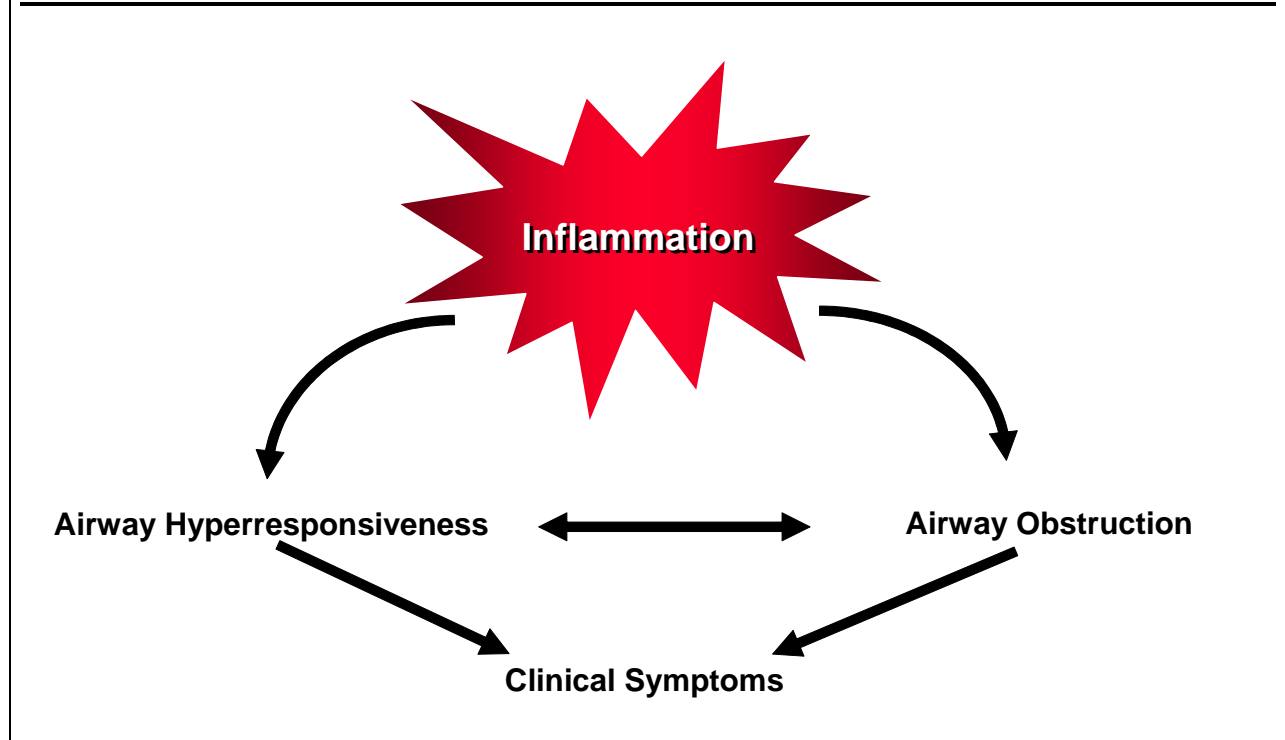
Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation (box 2–1). The interaction of these features of asthma determines the clinical manifestations and severity of asthma (figure 2–1) and the response to treatment.

The concepts underlying asthma pathogenesis have evolved dramatically in the past 25 years and are still undergoing evaluation as various phenotypes of this disease are defined and greater insight links clinical features of asthma with genetic patterns (Busse and Lemanske 2001; EPR—2 1997). Central to the various phenotypic patterns of asthma is the presence of underlying airway inflammation, which is variable and has distinct but overlapping patterns that reflect different aspects of the disease, such as intermittent versus persistent or acute versus chronic manifestations. Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which enhances susceptibility to bronchospasm (Cohn et al. 2004).

### BOX 2–1. CHARACTERISTICS OF CLINICAL ASTHMA

- Symptoms
- Airway obstruction
- Inflammation
- Hyperresponsiveness

**FIGURE 2–1. THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA**



Treatment with anti-inflammatory drugs can, to a large extent, reverse some of these processes; however, the successful response to therapy often requires weeks to achieve and, in some situations, may be incomplete (Bateman et al. 2004; O'Byrne and Parameswaran 2006). For some patients, the development of chronic inflammation may be associated with permanent alterations in the airway structure—referred to as airway remodeling—that are not prevented by or fully responsive to currently available treatments (Holgate and Polosa 2006). Therefore, the paradigm of asthma has been expanded over the last 10 years from bronchospasm and airway inflammation to include airway remodeling in some persons (Busse and Lemanske 2001).

The concept that asthma may be a continuum of these processes that can lead to moderate and severe persistent disease is of critical importance to understanding the pathogenesis, pathophysiology, and natural history of this disease (Martinez 2006). Although research since the first NAEPP guidelines in 1991 (EPR 1991) has confirmed the important role of inflammation in asthma, the specific processes related to the transmission of airway inflammation to specific pathophysiologic consequences of airway dysfunction and the clinical manifestations of asthma have yet to be fully defined. Similarly, much has been learned about the host–environment factors that determine airways' susceptibility to these processes, but the relative contributions of either and the precise interactions between them that leads to the initiation or persistence of disease have yet to be fully established. Nonetheless, current science regarding the mechanisms of asthma and findings from clinical trials have led to therapeutic approaches that allow most people who have asthma to participate fully in activities they choose. As we learn more about the pathophysiology, phenotypes, and genetics of asthma, treatments will become available to ensure adequate asthma control for all persons and, ideally, to reverse and even prevent the asthma processes.

As a guide to describing asthma and identifying treatment directions, a working definition of asthma put forth in the previous Guidelines remains valid: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma (EPR 1991; EPR—2 1997).*

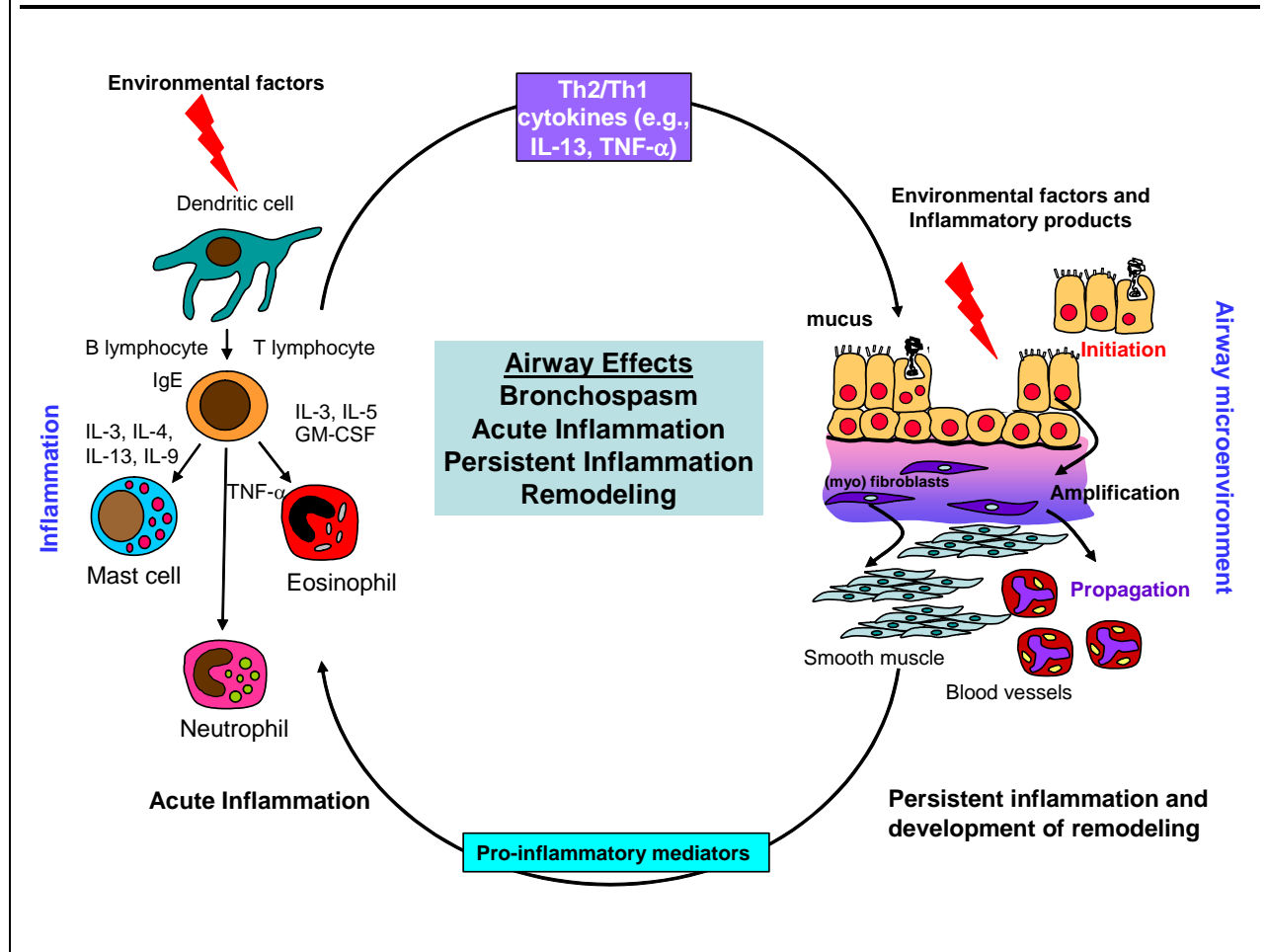
This working definition and its recognition of key features of asthma have been derived from studying how airway changes in asthma relate to the various factors associated with the development of airway inflammation (e.g., allergens, respiratory viruses, and some occupational exposures) and recognition of genetic regulation of these processes. From these descriptive approaches has evolved a more comprehensive understanding of asthma pathogenesis, the processes involved in the development of persistent airway inflammation, and the significant implications that these immunological events have for the development, diagnosis, treatment, and possible prevention of asthma.

## Pathophysiology and Pathogenesis of Asthma

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

- **Bronchoconstriction.** In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle (Busse and Lemanske 2001). Aspirin and other nonsteroidal anti-inflammatory drugs (see section 3, component 3) can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells (Stevenson and Szczeklik 2006). In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines.
- **Airway edema.** As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow (figure 2–2). These include edema, inflammation, mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle. These latter changes may not respond to usual treatment.

**FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA**



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF- $\alpha$ , tumor necrosis factor-alpha

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- **Airway hyperresponsiveness.** Airway hyperresponsiveness—an exaggerated bronchoconstrictor response to a wide variety of stimuli—is a major, but not necessarily unique, feature of asthma. The degree to which airway hyperresponsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyperresponsiveness are multiple and include inflammation, dysfunctional neuroregulation, and structural changes; inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control.
- **Airway remodeling.** In some persons who have asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway (figure 2–2); these are associated with a progressive loss of lung function that is not prevented by or fully

reversible by current therapy. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy (Holgate and Polosa 2006). These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion (box 2–2). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response.

#### **BOX 2–2. FEATURES OF AIRWAY REMODELING**

- Inflammation
- Mucus hypersecretion
- Subepithelial fibrosis
- Airway smooth muscle hypertrophy
- Angiogenesis

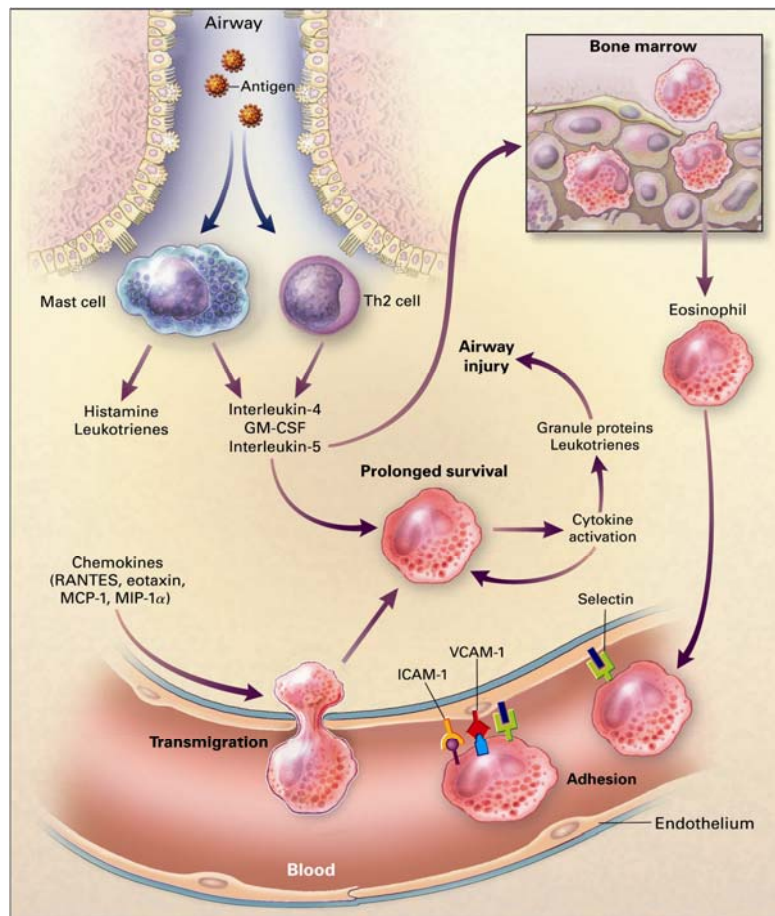
### **PATHOPHYSIOLOGIC MECHANISMS IN THE DEVELOPMENT OF AIRWAY INFLAMMATION**

Inflammation has a central role in the pathophysiology of asthma. As noted in the definition of asthma, airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Moreover, although distinct phenotypes of asthma exist (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent.

### **Inflammatory Cells**

**Lymphocytes.** An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2), with distinct inflammatory mediator profiles and effects on airway function (figure 2–3). After the discovery of these distinct lymphocyte subpopulations in animal models of allergic inflammation, evidence emerged that, in human asthma, a shift, or predilection, toward the Th2-cytokine profile resulted in the eosinophilic inflammation characteristic of asthma (Cohn et al. 2004). In addition, generation of Th2 cytokines (e.g., interleukin-4 (IL-4), IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines (Akbari et al. 2006; Larche et al. 2003). T lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an oversimplification of a complex process to describe asthma as a Th2 disease, recognizing the importance of *n* families of cytokines and chemokines has advanced our understanding of the development of airway inflammation (Barnes 2002; Zimmermann et al. 2003).

**FIGURE 2-3. AIRWAY INFLAMMATION**



Inhaled antigen activates mast cells and Th2 cells in the airway. They in turn induce the production of mediators of inflammation (such as histamine and leukotrienes) and cytokines including interleukin-4 and interleukin-5. Interleukin-5 travels to the bone marrow and causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). As the eosinophils enter the matrix of the airway through the influence of various chemokines and cytokines, their survival is prolonged by interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, the eosinophil releases inflammatory mediators, such as leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribution to persistent airway inflammation. MCP-1, monocyte chemotactic protein; and MIP-1 $\alpha$ , macrophage inflammatory protein.

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**Mast cells.** Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinyl-leukotrienes, prostaglandin D<sub>2</sub>) (Boyce 2003; Galli et al. 2005; Robinson 2004). Although allergen activation occurs through high-affinity IgE receptors and is likely the most relevant reaction, sensitized mast cells also may be activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB). Increased numbers of mast cells in airway smooth muscle may be linked to airway hyperresponsiveness (Brightling et al. 2002). Mast cells also

can release a large number of cytokines to change the airway environment and promote inflammation even though exposure to allergens is limited.

**Eosinophils.** Increased numbers of eosinophils exist in the airways of most, but not all, persons who have asthma (Chu and Martin 2001; Sampson 2000; Williams 2004). These cells contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. Increases in eosinophils often correlate with greater asthma severity. In addition, numerous studies show that treating asthma with corticosteroids reduces circulating and airway eosinophils in parallel with clinical improvement. However, the role and contribution of eosinophils to asthma is undergoing a reevaluation based on studies with an anti-IL-5 treatment that has significantly reduced eosinophils but did not affect asthma control (Leckie et al. 2000). Therefore, although the eosinophil may not be the only primary effector cell in asthma, it likely has a distinct role in different phases of the disease.

**Neutrophils.** Neutrophils are increased in the airways and sputum of persons who have severe asthma, during acute exacerbations, and in the presence of smoking. Their pathophysiological role remains uncertain; they may be a determinant of a lack of response to corticosteroid treatment (Fahy et al. 1995). The regulation of neutrophil recruitment, activation, and alteration in lung function is still under study, but leukotriene B<sub>4</sub> may contribute to these processes (Jatakanon et al. 1999; Wenzel et al. 1997; Wenzel 2006).

**Dendritic cells.** These cells function as key antigen-presenting cells that interact with allergens from the airway surface and then migrate to regional lymph nodes to interact with regulatory cells and ultimately to stimulate Th2 cell production from naïve T cells (Kuipers and Lambrecht 2004).

**Macrophages.** Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response (Peters-Golden 2004).

**Resident cells of the airway.** Airway smooth muscle is not only a target of the asthma response (by undergoing contraction to produce airflow obstruction) but also contributes to it (via the production of its own family of pro-inflammatory mediators). As a consequence of airway inflammation and the generation of growth factors, the airway smooth muscle cell can undergo proliferation, activation, contraction, and hypertrophy—events that can influence airway dysfunction of asthma.

**Epithelial cells.** Airway epithelium is another airway lining cell critically involved in asthma (Polito and Proud 1998). The generation of inflammatory mediators, recruitment and activation of inflammatory cells, and infection by respiratory viruses can cause epithelial cells to produce more inflammatory mediators or to injure the epithelium itself. The repair process, following injury to the epithelium, may be abnormal in asthma, thus furthering the obstructive lesions that occur in asthma.

### **Inflammatory Mediators**

**Chemokines** are important in recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelial cells (Zimmermann et al. 2003). Eotaxin is relatively selective for eosinophils, whereas thymus and activation-regulated chemokines (TARCs) and macrophage-derived chemokines (MDCs) recruit Th2 cells. There is an increasing appreciation



for the role this family of mediators has in orchestrating injury, repair, and many aspects of asthma.

**Cytokines** direct and modify the inflammatory response in asthma and likely determine its severity. Th2-derived cytokines include IL-5, which is needed for eosinophil differentiation and survival, and IL-4 which is important for Th2 cell differentiation and with IL-13 is important for IgE formation. Key cytokines include IL-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which amplify the inflammatory response, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which prolongs eosinophil survival in airways. Recent studies of treatments directed toward single cytokines (e.g., monoclonal antibodies against IL-5 or soluble IL-4 receptor) have not shown benefits in improving asthma outcomes.

**Cysteinyl-leukotrienes** are potent bronchoconstrictors derived mainly from mast cells. They are the only mediator whose inhibition has been specifically associated with an improvement in lung function and asthma symptoms (Busse 1996; Leff 2001). Recent studies have also shown leukotriene B<sub>4</sub> can contribute to the inflammatory process by recruitment of neutrophils (Gelfand and Dakhama 2006).

**Nitric oxide** (NO) is produced predominantly from the action of inducible NO synthase in airway epithelial cells; it is a potent vasodilator (Deykin et al. 2002; Strunk et al. 2003). Measurements of fractional exhaled NO (FeNO) may be useful for monitoring response to asthma treatment because of the purported association between FeNO and the presence of inflammation in asthma (Green et al. 2002).

### **Immunoglobulin E**

IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of inflammation. IgE attaches to cell surfaces via a specific high-affinity receptor. The mast cell has large numbers of IgE receptors; these, when activated by interaction with antigen, release a wide variety of mediators to initiate acute bronchospasm and also to release pro-inflammatory cytokines to perpetuate underlying airway inflammation (Boyce 2003; Sporik et al. 1995). Other cells, basophils, dendritic cells, and lymphocytes also have high-affinity IgE receptors.

The development of monoclonal antibodies against IgE has shown that the reduction of IgE is effective in asthma treatment (Busse et al. 2001; Holgate et al. 2005). These clinical observations further support the importance of IgE to asthma.

### **Implications of Inflammation for Therapy**

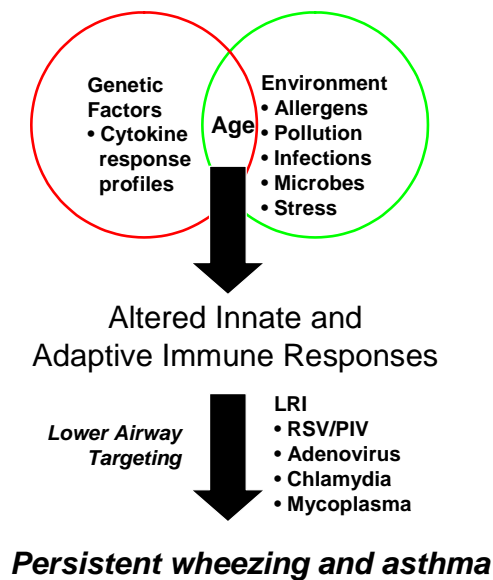
Recent scientific investigations have focused on translating the increased understanding of the inflammatory processes in asthma into therapies targeted at interrupting these processes (Barnes 2002). Some investigations have yielded promising results, such as the development leukotriene modifiers and anti-IgE monoclonal antibody therapy. Other studies, such as those directed at IL-4 or IL-5 cytokines, underscore the relevance of multiple factors regulating inflammation in asthma and the redundancy of these processes. All of these clinical studies also indicate that phenotypes of asthma exist, and these phenotypes may have very specific patterns of inflammation that require different treatment approaches. Current studies are investigating novel therapies targeted at the cytokines, chemokines, and inflammatory cells farther upstream in the inflammatory process. For example, drugs designed to inhibit the Th2 inflammatory pathway may cause a broad spectrum of effects such as airway

hyperresponsiveness and mucus hypersecretion. Further research into the mechanisms responsible for the varying asthma phenotypes and appropriately targeted therapy may enable improved control for all manifestations of asthma, and, perhaps, prevention of disease progression.

## **PATHOGENESIS**

What initiates the inflammatory process in the first place and makes some persons susceptible to its effects is an area of active investigation. There is not yet a definitive answer to this question, but new observations suggest that the origins of asthma primarily occur early in life. The expression of asthma is a complex, interactive process that depends on the interplay between two major factors—host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system (figure 2–4).

**FIGURE 2–4. HOST FACTORS AND ENVIRONMENTAL EXPOSURES**

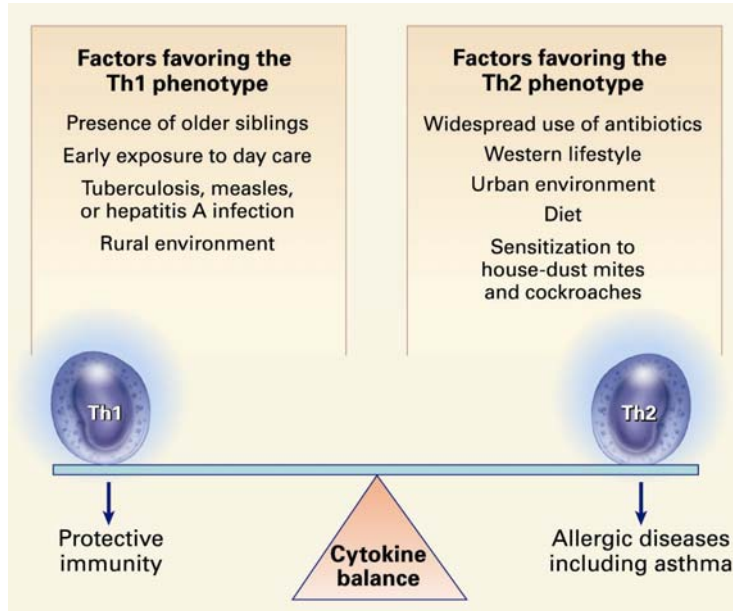


Key: LRI, lower respiratory illnesses; RSV, respiratory syncytial virus; PIV, parainfluenza virus

### **Host Factors**

**Innate immunity.** There is considerable interest in the role of innate and adaptive immune responses associated with both the development and regulation of inflammation (Eder et al. 2006). In particular, research has focused on an imbalance between Th1 and Th2 cytokine profiles and evidence that allergic diseases, and possibly asthma, are characterized by a shift toward a Th2 cytokine-like disease, either as overexpression of Th2 or underexpression of Th1 (figure 2–5). Airway inflammation in asthma may represent a loss of normal balance between two “opposing” populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce IL-2 and interferon- $\gamma$  (IFN- $\gamma$ ), which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, -5, -6, -9, and -13) that can mediate allergic inflammation. The current “hygiene hypothesis” of asthma illustrates how this cytokine imbalance may explain some of the

**FIGURE 2–5. CYTOKINE BALANCE**



Numerous factors, including alterations in the number or type of infections early in life, the widespread use of antibiotics, adoption of the Western lifestyle, and repeated exposure to allergens, may affect the balance between Th1-type and Th2-type cytokine responses and increase the likelihood that the immune response will be dominated by Th2 cells and thus will ultimately lead to the expression of allergic diseases such as asthma.

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dramatic increases in asthma prevalence in westernized countries. This hypothesis is based on the assumption that the immune system of the newly born is skewed toward Th2 cytokine generation. Following birth, environmental stimuli such as infections will activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. Evidence indicates that the incidence of asthma is reduced in association with certain infections (*M. tuberculosis*, measles, or hepatitis A), exposure to other children (e.g., presence of older siblings and early enrollment in childcare), and less frequent use of antibiotics (Eder et al. 2006; Gern et al. 1999; Gern and Busse 2002; Horwood et al. 1985; Sears et al. 2003). Furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child who has a cytokine imbalance toward Th2 will set the stage to promote the production of IgE antibodies to key environmental antigens, such as house-dust mite, cockroach, *Alternaria*, and possibly cat. Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs. Precisely why the airways of some individuals are susceptible to these allergic events has not been established.

There also appears to be a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternatively, recent studies have suggested the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished. The focus on actions of cytokines and chemokines to regulate and activate the inflammatory profile in asthma has provided

ongoing and new insight into the pattern of airway injury that may lead to new therapeutic targets.

**Genetics.** It is well recognized that asthma has an inheritable component to its expression, but the genetics involved in the eventual development of asthma remain a complex and incomplete picture (Holgate 1999; Ober 2005). To date, many genes have been found that either are involved in or linked to the presence of asthma and certain of its features. The complexity of their involvement in clinical asthma is noted by linkages to certain phenotypic characteristics, but not necessarily the pathophysiologic disease process or clinical picture itself. The role of genetics in IgE production, airway hyperresponsiveness, and dysfunctional regulation of the generation of inflammatory mediators (such as cytokines, chemokines, and growth factors) has appropriately captured much attention. In addition, studies are investigating genetic variations that may determine the response to therapy. The relevance of polymorphisms in the beta-adrenergic and corticosteroid receptors in determining responsiveness to therapies is of increasing interest, but the widespread application of these genetic factors remains to be fully established.

**Sex.** In early life, the prevalence of asthma is higher in boys. At puberty, however, the sex ratio shifts, and asthma appears predominantly in women (Horwood et al. 1985). How specifically sex and sex hormones, or related hormone generation, are linked to asthma has not been established, but they may contribute to the onset and persistence of the disease.

### **Environmental Factors**

Two major environmental factors have emerged as the most important in the development, persistence, and possibly severity of asthma: airborne allergens and viral respiratory infections. In the susceptible host, and at a critical time of development (e.g., immunological and physiological), both respiratory infections and allergens have a major influence on asthma development and its likely persistence. It is also apparent that allergen exposure, allergic sensitization, and respiratory infections are not separate entities but function interactively in the eventual development of asthma.

**Allergens.** The role of allergens in the development of asthma has yet to be fully defined or resolved, but it is obviously important. Sensitization and exposure to house-dust mite and *Alternaria* are important factors in the development of asthma in children. Early studies showed that animal danders, particularly dog and cat, were associated with the development of asthma. Recent data suggest that, under some circumstances, dog and cat exposure in early life may actually protect against the development of asthma. The determinant of these diverse outcomes has not been established. Studies to evaluate house-dust mite and cockroach exposure have shown that the prevalence of sensitization and subsequent development of asthma are linked (Huss et al. 2001; Sporik et al. 1990; Wahn et al. 1997). Exposure to cockroach allergen, for example, a major allergen in inner-city dwellings, is an important cause of allergen sensitization, a risk factor for the development of asthma (Rosenstreich et al. 1997). In addition, allergen exposure can promote the persistence of airway inflammation and likelihood of an exacerbation.

**Respiratory infections.** During infancy, a number of respiratory viruses have been associated with the inception or development of the asthma. In early life, respiratory syncytial virus (RSV) and parainfluenza virus in particular, cause bronchiolitis that parallels many features of childhood asthma (Gern and Busse 2002; Sigurs et al. 2000). A number of long-term prospective studies of children admitted to hospital with documented RSV have shown that

approximately 40 percent of these infants will continue to wheeze or have asthma in later childhood (Sigurs et al. 2000). Symptomatic rhinovirus infections in early life also are emerging as risk factors for recurrent wheezing. On the other hand, evidence also indicates that certain respiratory infections early in life—including measles and even RSV (Stein et al. 1999) or repeated viral infections (other than lower respiratory tract infections) (Illi et al. 2001; Shaheen et al. 1996)—can protect against the development of asthma. The “hygiene hypothesis” of asthma suggests that exposure to infections early in life influences the development of a child’s immune system along a “nonallergic” pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this association may explain observed associations between large family size, later birth order, daycare attendance, and a reduced risk of asthma (Eder et al. 2006; Illi et al. 2001).

The influence of viral respiratory infections on the development of asthma may depend on an interaction with atopy. The atopic state can influence the lower airway response to viral infections, and viral infections may then influence the development of allergic sensitization. The airway interactions that may occur when individuals are exposed simultaneously to both allergens and viruses are of interest but are not defined at present.

**Other environmental exposures.** Tobacco smoke, air pollution, occupations, and diet have also been associated with an increased risk for the onset of asthma, although the association has not been as clearly established as with allergens and respiratory infections (Malo et al. 2004; Strachan and Cook 1998a; Strachan and Cook 1998b).

In utero exposure to environmental tobacco smoke increases the likelihood for wheezing in the infant, although the subsequent development of asthma has not been well defined. In adults who have asthma, cigarette smoking has been associated with an increase in asthma severity and decreased responsiveness to inhaled corticosteroids (ICSs) (Dezateux et al. 1999).

The role of air pollution in the development of asthma remains controversial and may be related to allergic sensitization (American Thoracic Society 2000). One recent epidemiologic study showed that heavy exercise (three or more team sports) outdoors in communities with high concentration of ozone was associated with a higher risk of asthma among school-age children (McConnell et al. 2002). The relationship between increased levels of pollution and increases in asthma exacerbations and emergency care visits has been well documented.

An association of low intake of antioxidants and omega-3 fatty acids has been noted in observational studies, but a direct link as a causative factor has not been established.

Increasing rates of obesity have paralleled increasing rates in asthma prevalence, but the interrelation is uncertain (Ford 2005). Obesity may be a risk factor for asthma due to the generation of unique inflammatory mediators that lead to airway dysfunction.

In summary, our understanding of asthma pathogenesis and underlying mechanisms now includes the concept that gene-by-environmental interactions are critical factors in the development of airway inflammation and eventual alteration in the pulmonary physiology that is characteristic of clinical asthma.

## **Natural History of Asthma**

If the persistence and severity of asthma involves a progression of airway inflammation to airway remodeling and some eventual irreversible airway obstruction, then an important

question is whether anti-inflammatory medication (i.e., ICSs), given early in the course of disease might interrupt this process and prevent permanent declines in lung function. For early initiation of ICSs to be more beneficial than delayed initiation, two assumptions must be valid: (1) as a group, people who have mild or moderate persistent asthma experience a progressive decline in lung function that is measurable and clinically significant, and (2) treatment with ICSs prevents or slows this decline, in addition to providing long-term control of asthma. Reviews were conducted in 2002 (EPR—Update 2002) and for the current report to evaluate the literature on the effect of intervention with ICSs in altering the progression of disease.

## **NATURAL HISTORY OF PERSISTENT ASTHMA**

### **Children**

It is well established that asthma is a variable disease. Asthma can vary among individuals, and its progression and symptoms can vary within an individual's experience over time. The course of asthma over time, either remission or increasing severity, is commonly referred to as the natural history of the disease. It has been postulated that the persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung function. Recent research suggests that this may not be the case. Rather, the course of asthma may vary markedly between young children, older children and adolescents, and adults, and this variation is probably more dependent on age than on symptoms.

A prospective cohort study in which followup began at birth revealed that, in children whose asthma-like symptoms began before 3 years of age, deficits in lung growth associated with the asthma occurred by 6 years of age (Martinez et al. 1995). Continued followup on lung function measures taken at 11–16 years of age found that, compared to the group of children who experienced no asthma symptoms for the first 6 years of life, the group of children whose asthma symptoms began before 3 years of age experienced significant deficits in lung function at 11–16 years of age; however, no further loss in forced expiratory volume in 1 second (FEV<sub>1</sub>) occurred compared to children who did not have asthma (Morgan et al. 2005). The group whose asthma symptoms began after 3 years of age did not experience deficits in lung function.

A longitudinal study of children 8–10 years of age found that bronchial hyperresponsiveness was associated with declines in lung function growth in both children who have active symptoms of asthma and children who did not have such symptoms (Xuan et al. 2000). Thus, symptoms neither predicted nor determined lung function deficits in this age group.

A study by Sears and colleagues (2003) assessed lung function repeatedly from ages 9 to 26 in almost 1,000 children from a birth cohort in Dunedin, New Zealand. They found that children who had asthma had persistently lower levels of FEV<sub>1</sub>/forced vital capacity (FVC) ratio during the followup. Regardless of the severity of their symptoms, however, their levels of lung function paralleled those of children who did not have asthma, and no further losses of lung function were observed after age 9.

Baseline data from the Childhood Asthma Management Program (CAMP) study support the finding that the individual's age at the time of asthma onset influences declines in lung function growth. At the time of enrollment of children who had mild or moderate persistent asthma at 5–12 years of age, an inverse association between lung function and duration of asthma was noted (Zeiger et al. 1999). Although the analysis did not distinguish between age of onset and duration of asthma, it can be inferred that, because the average duration of asthma was 5 years and the average age of the children was 9 years, most children who had the longer duration of

asthma started experiencing symptoms before 3 years of age. The data suggest that these children had the lowest lung function levels. After 4–6 years of followup, the children in the CAMP study, on average, did not experience deficits in lung growth (as defined by postbronchodilator FEV<sub>1</sub>), regardless of their symptom levels or the treatment they received (CAMP 2000). However, a followup analysis of the CAMP data showed that a subgroup of the children experienced progressive (at least 1 percent a year) reductions in lung growth, regardless of treatment group (Covar et al. 2004). Predictors of this progressive reduction, at baseline of the study, were male sex and younger age.

The CAMP study noted that when measures other than FEV<sub>1</sub> are used to assess lung function measures over time in childhood asthma, progressive declines are observed: the FEV<sub>1</sub>/FVC ratio before bronchodilator use was smaller at the end of the treatment period than at the start in all three treatment groups; the decline in the ICS group was less than that of the placebo group (0.2 percent versus 1.8 percent) (CAMP 2000). In a comparison of lung function measures of CAMP study participants with lung function measures of children who did not have asthma, by year from ages 5 through 18, the FEV<sub>1</sub>/FVC ratio was significantly lower for the children who had asthma compared to those who did not have asthma at age 5 (mean difference 7.3 percent for boys and 7.1 percent for girls), and the difference increased with age (9.8 percent for boys and 9.9 percent for girls) (Strunk et al. 2006).

Cumulatively, these studies suggest that most of the deficits in lung function growth observed in children who have asthma occur in children whose symptoms begin during the first 3 years of life, and the onset of symptoms after 3 years of age usually is not associated with significant deficits in lung function growth. Thus, a promising target for interventions designed to prevent deficits in lung function, and perhaps the development of more severe symptoms later in life, would be children who have symptoms before 3 years of age and seem destined to develop persistent asthma. However, it is important to distinguish this group from the majority of children who wheeze before 3 years of age and do not experience any more symptoms after 6 years of age (Martinez et al. 1995). Until recently, no validated algorithms were available to predict which children among those who had asthma-like symptoms early in life would go on to have persistent asthma. Data obtained from long-term longitudinal studies of children who were enrolled at birth have generated such a predictive index. The studies first identified an index of risk factors for developing persistent asthma symptoms among children younger than 3 years of age who had more than three episodes of wheezing during the previous year. The index was then applied to a birth cohort that was followed through 13 years of age. Seventy-six percent of the children who were diagnosed with asthma after 6 years of age had a positive asthma predictive index before 3 years of age; 97 percent of the children who did not have asthma after 6 years of age had a negative asthma predictive index before 3 years of age (Castro-Rodriguez et al. 2000). The index was subsequently refined and tested in a clinical trial to examine if treating children who had a positive asthma predictive index would prevent development of persistent wheezing (Guilbert et al. 2006). The asthma predictive index generated by these studies identifies the following risk factors for developing persistent asthma among children younger than 3 years of age who had four or more episodes of wheezing during the previous year: either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens, or (2) two of the following: evidence of sensitization to foods,  $\geq 4$  percent peripheral blood eosinophilia, or wheezing apart from colds.

## **Adults**

Accelerated loss of lung function appears to occur in adults who have asthma. In a study of adults who have asthma and who received 2 weeks of high-dose prednisone if airflow

obstruction persisted after 2 weeks of bronchodilator therapy, the degree of persistent airflow obstruction correlated with both the severity and the duration of their asthma (Finucane et al. 1985).

Two large, prospective epidemiological studies evaluated the rate of decline in pulmonary function in adults who had asthma. In an 18-year prospective study of 66 nonsmokers who had asthma, 26 smokers who had asthma, and 186 control participants who had no asthma, spirometry was performed at 3-year intervals (Peat et al. 1987). Seventy-three percent of the study group underwent at least six spirometric evaluations. The slope for decline in lung function (FEV<sub>1</sub>) was approximately 40 percent greater for the participants who had asthma than for those who had no asthma. This did not appear to result from extreme measurement produced by a few participants, because fewer than 25 percent of the participants who had asthma were measured with a slope less steep than the mean for those who did not have asthma. In another study, three spirometry evaluations were performed in 13,689 adults (778 had asthma, and 12,911 did not have asthma) over a 15-year period (Lange et al. 1998). The average decline in FEV<sub>1</sub> was significantly greater (38 mL per year) in those who had asthma than in those who did not have asthma (22 mL per year). Although, in this study, asthma was defined simply by patient report, the researchers noted that, because the 6 percent prevalence rate for asthma did not increase in this cohort as they increased in age, it is likely that the subjects who reported having asthma did indeed have asthma rather than chronic obstructive pulmonary disease (COPD). It is not possible to determine from these studies whether the loss of pulmonary function occurred in those who had mild or moderate asthma or only in those who had severe asthma. Nevertheless, the data support the likelihood of potential accelerated loss of pulmonary function in adults who have asthma.

New studies have addressed this issue since the “Expert Panel Review—Update 2002” (EPR—Update 2002). James and colleagues (2005) reanalyzed the data from the study of decline in lung function from Busselton, Australia (Peat et al. 1987), after adding a new survey in 1994–1995. Subjects (N = 9,317) had participated as adults (19 years or older) in one or more of the cross-sectional Busselton Health Surveys between 1966 and 1981 or in the followup study of 1994–1995. Using the whole data sample, James and colleagues found that subjects who had asthma showed significantly lower lung function during the whole followup period, but most of the differences were due to deficits in lung function present at the beginning of followup (when subjects were age 19). Once the effect of smoking was taken into account, the excess decline in FEV<sub>1</sub> attributable to asthma was 3.78 mL per year for women and 3.69 mL per year for men. Although these results were statistically significant, their clinical relevance is debatable. Sherrill and coworkers (2003) reanalyzed the data from the Tucson Epidemiologic Study of Airway Obstructive Disease. A total of 2,926 subjects, with longitudinal data for lung function assessed in up to 12 surveys spanning a period of up to 20 years, were included. They found that, unlike subjects who had a diagnosis of COPD, in those who had diagnosis of longstanding asthma, FEV<sub>1</sub> did not decline at a more rapid rate than normal. This was also true for subjects who had asthma and COPD. Griffith and colleagues (2001) studied decline in lung function in 5,242 participants in the Cardiovascular Health Study who were over age 65 at enrollment. Each participant had up to three lung function measurements over a 7-year interval. Subjects who had asthma had lower levels of FEV<sub>1</sub> than those who reported no asthma. However, after adjustment for emphysema and chronic bronchitis, there were no significant increases in the rate of decline in FEV<sub>1</sub> in participants who had asthma.



## Summary

Taken together, these longitudinal epidemiological studies and clinical trials indicate that the progression of asthma, as measured by declines in lung function, varies in different age groups. Declines in lung function growth observed in children appear to occur by 6 years of age and occur predominantly in those children whose asthma symptoms started before 3 years of age. Children 5–12 years of age who have mild or moderate persistent asthma, on average, do not appear to experience declines in lung function through 11–17 years of age, although a subset of these children experience progressive reductions in lung growth as measured by FEV<sub>1</sub>. Furthermore, there is emerging evidence of reductions in the FEV<sub>1</sub>/FVC ratio, apparent in young children who have mild or moderate asthma compared to children who do not have asthma, that increase with age. There is also evidence of progressively declining lung function in adults who have asthma, but the clinical significance and the extent to which these declines contribute to the development of fixed airflow obstruction are unknown.

## EFFECT OF INTERVENTIONS ON NATURAL HISTORY OF ASTHMA

Data on the effect of interventions on the progression of asthma, as measured by declines in lung function, airway hyperresponsiveness, or the severity of symptoms, were evaluated for EPR—Update 2002 and the current update. The Expert Panel does not recommend using ICSs for the purpose of modifying the underlying disease process (e.g., preventing persistent asthma). Evidence to date indicates that daily long-term control medication does not alter the underlying severity of the disease. Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term randomized control trial (RCT) in 1,041 children 5–12 years of age (CAMP 2000). This study does not support the assumption that, on average, children 5–12 years of age who have mild or moderate persistent asthma have a progressive decline in lung function. Children in the placebo group did not experience a decline in postbronchodilator FEV<sub>1</sub> over the 5-year treatment period, and they had postbronchodilator FEV<sub>1</sub> levels similar to children in the ICS and nedocromil treatment groups at the end of the study. Observational prospective data from other studies of large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in childhood asthma appears to occur in the first 3–5 years of life (Martinez et al. 1995). However, in a recent randomized, controlled prospective study, children 2–3 years of age who were at high risk of developing persistent asthma were treated for 2 years with ICSs and observed for 1 additional year after treatment was discontinued. That study demonstrated that the intervention group had lung function and asthma symptom levels similar to the placebo group at the end of the study (Guilbert et al. 2006).

Two recent studies addressed the possibility that ICSs may prevent the putative declines in lung function believed to occur shortly after the beginning of the disease in adults who have late-onset asthma. A retrospective study (Selroos et al. 2004) reported the results of an observational study of adults who had mild-to-moderate asthma and were treated for 5 years with an ICS. One group, treated early in the disease (less than 2 years after diagnosis), had better outcomes in terms of lung function than those who started treatment more than 2 years after diagnosis. The group in which treatment was started more than 2 years after diagnosis, however, had lower levels of lung function at the beginning of the trial. Therefore, it is not possible to determine from these data what the results would have been in a randomized trial. Two recent long-term observational studies report an association between ICS therapy and reduced decline in FEV<sub>1</sub> in adults who have asthma (Dijkstra et al. 2006; Lange et al. 2006). However, long-term RCTs will be necessary to confirm a causal relationship.

The START study (Pauwels et al. 2003) enrolled 7,241 subjects, 5–66 years of age, who had mild asthma of less than 2 years' duration, according to each subject's report. Participants were randomized to a low-dose ICS or placebo and were followed prospectively for 3 years. The study found a slightly better level of postbronchodilator lung function in participants in the active arm than in the placebo arm, but the difference was more prominent after 1 year of treatment (+1.48 percent predicted FEV<sub>1</sub>) than at the end of the treatment period (+0.88 percent predicted FEV<sub>1</sub>), suggesting no effect in the putative progressive loss in lung function in these subjects.

With respect to the potential role of ICSs in changing the natural course of asthma, the relevant clinical question is: Are ICSs associated with less disease burden *after* discontinuation of therapy? The best available evidence in children 5–12 years of age (CAMP 2000) and 2–3 years of age (Guilbert et al. 2006) demonstrated that, although ICSs provide superior control and prevention of symptoms and exacerbations during treatment, symptoms and airway hyperresponsiveness worsen when treatment is withdrawn (EPR—Update 2002; Guilbert et al. 2006). This evidence suggests that currently available therapy controls but does not modify the underlying disease process.

## **IMPLICATIONS OF CURRENT INFORMATION ABOUT PATHOPHYSIOLOGY AND PATHOGENESIS, AND NATURAL HISTORY FOR ASTHMA MANAGEMENT**

Airway inflammation is a major factor in the pathogenesis and pathophysiology of asthma. The importance of inflammation to central features of asthma continues to expand and underscore this characteristic as a primary target of treatment. It has also become apparent, however, that airway inflammation is variable in many aspects including intensity, cellular/mediator pattern, and response to therapy. As knowledge of the various phenotypes of inflammation become apparent, it is likely that treatment also will also have greater specificity and, presumably, effectiveness.

It is also apparent that asthma, and its persistence, begin early in life. Although the factors that determine persistent versus intermittent asthma have yet to be ascertained, this information will become important in determining the type of treatment, its duration, and its effect on various outcomes of asthma. Early studies have indicated that although current treatment is effective in controlling symptoms, reducing airflow limitations, and preventing exacerbations, present treatment does not appear to prevent the underlying severity of asthma.

Despite these unknowns, the current understanding of basic mechanisms in asthma has greatly improved appreciation of the role of treatment. The Expert Panel's recommendations for asthma treatment, which are directed by knowledge of basic mechanisms, should result in improved control of asthma and a greater understanding of therapeutic effectiveness.

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