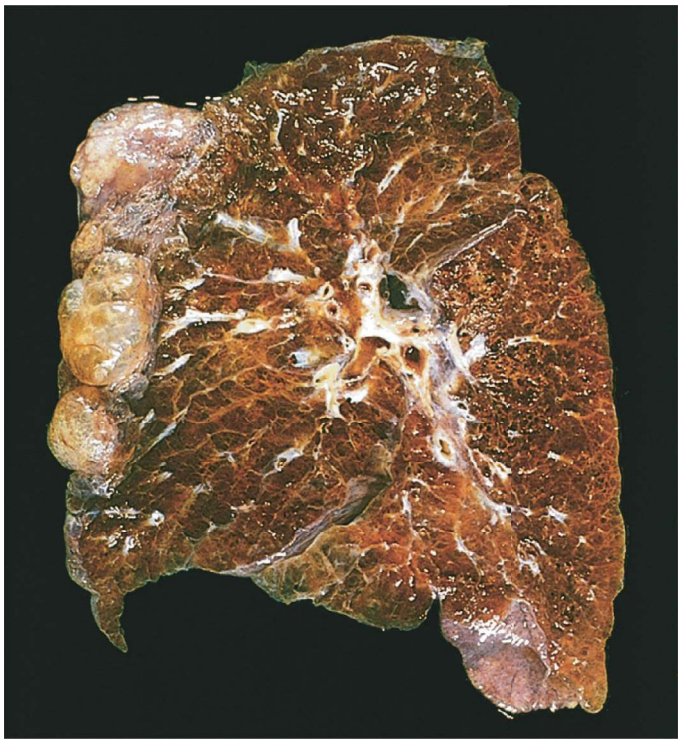

Figure 15.9 Bullous emphysema. Note the large subpleural bullae *(upper left)*.

tissue produces *interstitial emphysema.* In most instances, it is caused by alveolar tears that occur in patients with pulmonary emphysema due to transient increases in intra-alveolar pressure, for example, during coughing. Less commonly, chest wounds or fractured ribs that puncture the lung provide the portal for entrance of air into surrounding soft tissues.

Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and variable expiratory airflow obstruction that produces symptoms such as wheezing, shortness of breath, chest tightness, and cough, which vary over time and in intensity. Symptomatic episodes are most likely to occur at night or in the early morning and are produced by bronchoconstriction that is at least partly reversible, either spontaneously or with treatment. Rarely, an unremitting attack called *acute severe asthma* (formerly known as *status asthmaticus*) may prove fatal; usually, such patients have a long history of asthma. Between the attacks, patients may be virtually asymptomatic. Of note, there has been a significant increase in the incidence of asthma in the Western world over the past 40 to 50 years, a trend that has now started to abate. However, the prevalence of asthma continues to increase in lower income countries and in some ethnic groups in which its prevalence was previously low.

Asthma has several distinct clinical phenotypes, each with different underlying pathogenic mechanisms. It may be categorized as *atopic* (evidence of allergen sensitization and immune activation, often in a patient with allergic rhinitis or eczema) or *nonatopic* (no evidence of allergen sensitization), of which several subtypes exist. In all types, episodes of bronchospasm may have diverse triggers, such as respiratory infections (especially viral infections), irritants (e.g., smoke, fumes), cold air, stress, and exercise. One biologically meaningful and clinically useful way to classify asthma is based on its triggers. We will first briefly describe the various major subtypes of asthma, and then will delve more deeply into its pathogenesis.

Atopic Asthma. This type of asthma is a classic example of an IgE-mediated (type I) hypersensitivity reaction (discussed in Chapter 6). The disease usually begins in childhood and is triggered by environmental allergens, such as dusts, pollens, cockroach or animal dander, and foods, which most frequently act in synergy with other proinflammatory environmental cofactors, most notably respiratory viral infections. A positive family history of asthma is common, and a skin test with the offending antigen in these patients results in an immediate wheal-and-flare reaction. Atopic asthma may also be diagnosed based on high total serum IgE levels or evidence of allergen sensitization by serum radioallergosorbent tests (RASTs), which can detect the presence of IgE antibodies that are specific for individual allergens.

Non-Atopic Asthma. Individuals with non-atopic asthma do not have evidence of allergen sensitization, and skin test results are usually negative. A positive family history of asthma is less common in these patients. Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus, and respiratory syncytial virus) are common triggers in non-atopic asthma. Inhaled air pollutants such as tobacco smoke, sulfur dioxide, ozone, and nitrogen dioxide may also contribute to the chronic airway inflammation and hyperreactivity in some cases. As already mentioned, in some instances attacks may be triggered by seemingly innocuous events, such as exposure to cold and even exercise.

Drug-Induced Asthma. Several pharmacologic agents provoke asthma. Aspirin-sensitive asthma is an uncommon type, occurring in individuals with recurrent rhinitis and nasal polyps. These individuals are exquisitely sensitive to small doses of aspirin as well as other non-steroidal anti-inflammatory medications, and they experience not only asthmatic attacks but also urticaria. Aspirin and related drugs trigger asthma in these patients by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism, leading to a rapid decrease in prostaglandin E_2. Normally prostaglandin E_2 inhibits enzymes that generate proinflammatory mediators such as leukotrienes B_4, C_4, D_4, and E_4, which are believed to have central roles in aspirin-induced asthma.

Occupational Asthma. This form of asthma may be triggered by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), or other chemicals (formaldehyde, penicillin products). Only minute quantities of chemicals are required to induce the attack, which usually occurs after repeated exposure. The

underlying mechanisms vary according to stimulus and include type I reactions, direct liberation of bronchoconstrictor substances, and hypersensitivity responses of unknown origin.

Pathogenesis

Atopic asthma, the most common form of the disease, is caused by a Th2-mediated IgE response to environmental allergens in genetically predisposed individuals. Airway inflammation is central to the disease pathophysiology and causes airway dysfunction partly through the release of potent inflammatory mediators and partly through remodeling of the airway wall. As the disease becomes more severe, there is increased local secretion of growth factors, which induce mucous gland enlargement, smooth muscle proliferation, angiogenesis, and fibrosis. Varying combinations of these processes help explain the different asthma subtypes, their response to treatment, and their natural history over a person's lifetime.

The contributions of the immune response, genetics, and environment are discussed separately below, although they are closely intertwined.

Th2 Responses, IgE, and Inflammation. **A fundamental abnormality in asthma is an exaggerated Th2 response to normally harmless environmental antigens** (Fig. 15.10). Th2 cells secrete cytokines that promote inflammation and stimulate B cells to produce IgE and other antibodies. These cytokines include IL-4, which stimulates the production of IgE; IL-5, which activates locally recruited eosinophils; and IL-13, which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells. The T cells and epithelial cells secrete chemokines that recruit more T cells and eosinophils, thus exacerbating the reaction. As in other allergic reactions (Chapter 6), IgE binds to the Fc receptors on submucosal mast cells, and repeat exposure to the allergen triggers the mast cells to release granule contents and produce cytokines and other mediators, which collectively induce the early-phase (immediate hypersensitivity) reaction and the late-phase reaction.

The early-phase reaction is dominated by bronchoconstriction, increased mucus production, variable degrees of vasodilation, and increased vascular permeability. Bronchoconstriction is triggered by direct stimulation of subepithelial vagal (parasympathetic) receptors through both central and local reflexes triggered by mediators produced by mast cells and other cells in the reaction. The late-phase reaction is dominated by recruitment of leukocytes, notably eosinophils, neutrophils, and more T cells. Although Th2 cells are the dominant T-cell type involved in the disease, other T cells that contribute to the inflammation include Th17 (IL-17 producing) cells, which recruit neutrophils.

Many mediators produced by leukocytes and epithelial cells have been implicated in the asthmatic response. The long list of "suspects" in acute asthma can be ranked based on the clinical efficacy of pharmacologic intervention with antagonists of specific mediators.

- Mediators whose role in bronchospasm is clearly supported by efficacy of pharmacologic intervention are (1) *leukotrienes C_4, D_4,* and *E_4,* which cause prolonged bronchoconstriction as well as increased vascular permeability and increased mucus secretion; (2) *acetylcholine,* released from intrapulmonary parasympathetic nerves, which can cause airway smooth muscle constriction by directly stimulating muscarinic receptors; (3) *IL-5,* antagonists of which are effective in treating severe forms of asthma that are associated with peripheral blood eosinophilia; and (4) *galectin-10* (GAL10), which is released from eosinophils and forms crystals known as *Charcot-Leyden crystals*. Long recognized as a feature of asthma, recent studies have shown that these crystals are strong inducers of inflammation and mucus production.
- A second group of agents are present at the "scene of the crime" but seem to have relatively minor contributions on the basis of lack of efficacy of potent antagonists or synthesis inhibitors. These include (1) *histamine,* a potent bronchoconstrictor; (2) *prostaglandin D_2,* which elicits bronchoconstriction and vasodilation; and (3) *platelet-activating factor,* which causes aggregation of platelets and release of serotonin from their granules. These mediators might yet prove important in certain types of chronic or non-allergic asthma.
- Finally, a large third group comprises "suspects" for whom specific antagonists or inhibitors are not available or have been insufficiently studied as yet. These include IL-4, IL-13, TNF, chemokines (e.g., eotaxin, also known as CCL11), neuropeptides, nitric oxide, bradykinin, and endothelins.

It is thus clear that multiple mediators contribute to the acute asthmatic response. Moreover, the composition of this "mediator soup" likely varies among individuals or different types of asthma. The appreciation of the importance of inflammatory cells and mediators in asthma has led to greater emphasis on anti-inflammatory drugs, such as corticosteroids, in its treatment.

Genetic Susceptibility. Susceptibility to atopic asthma is multigenic and often associated with increased incidence of other allergic disorders, such as allergic rhinitis (hay fever) and eczema. Genetic polymorphisms linked to asthma and other allergic disorders were described in Chapter 6. Suffice it to say here that many of these are likely to influence immune responses and the subsequent inflammatory reaction. Some of the stronger or more interesting genetic variants associated with asthma include the following:

- A susceptibility locus for asthma located on chromosome 5q, near the gene cluster encoding the cytokines IL-3, IL-4, IL-5, IL-9, and IL-13 and the IL-4 receptor. Among the genes in this cluster, polymorphisms in the *IL13* gene have the strongest and most consistent associations with asthma or allergic disease, while IL-4 receptor gene variants are associated with atopy, elevated total serum IgE, and asthma.
- Particular class II HLA alleles linked to production of IgE antibodies against some antigens, such as ragweed pollen.
- Variants associated with the genes encoding IL-33, a member of the IL-1 family of cytokines, and its receptor, ST2, which induce the production of Th2 cytokines.
- Variants associated with the gene encoding thymic stromal lymphopoietin (TSLP), a cytokine produced by epithelium that may have a role in initiating allergic reactions.

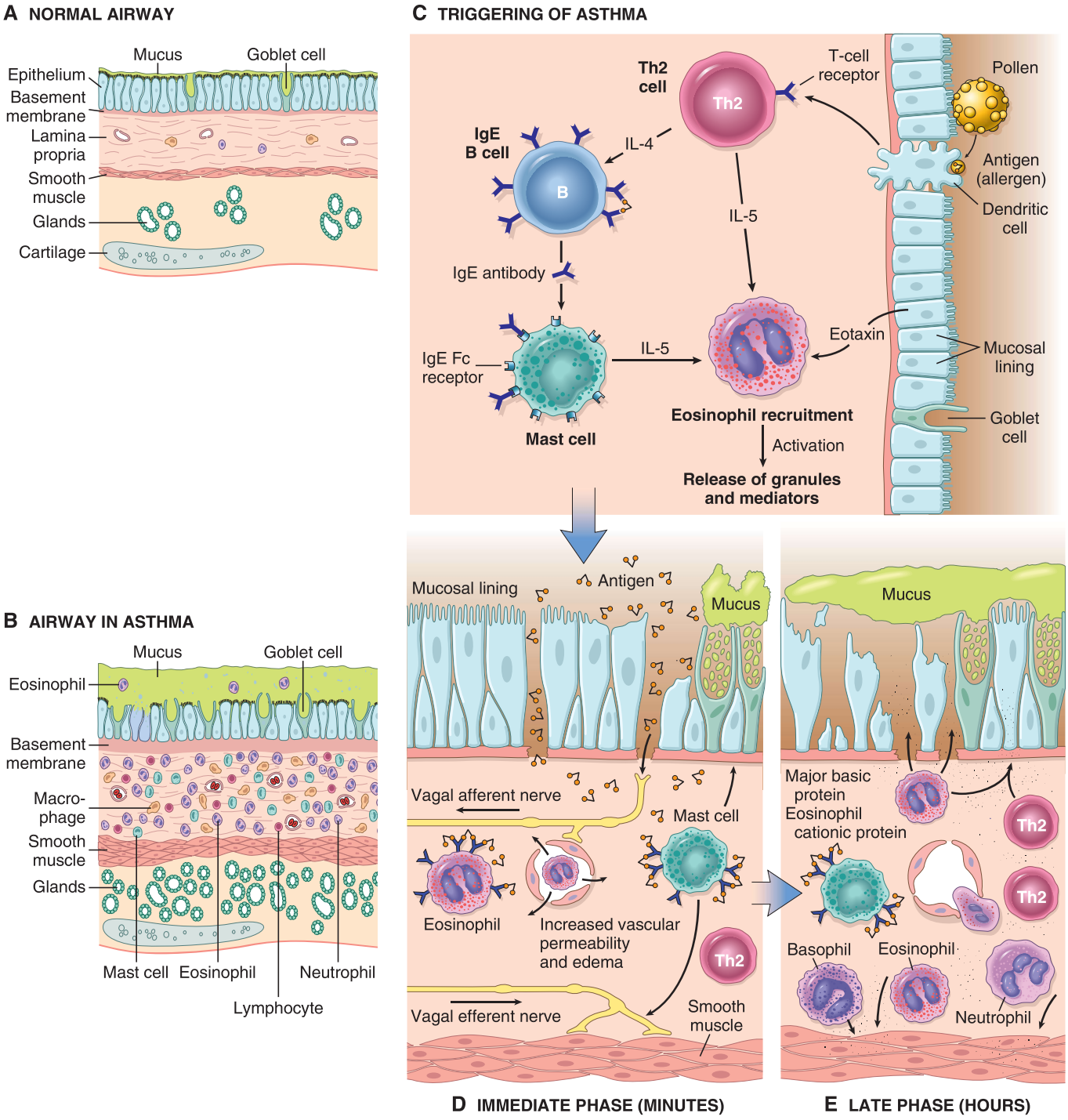

Figure 15.10 (A and B) Comparison of a normal airway and an airway involved by asthma. The asthmatic airway is marked by accumulation of mucus in the bronchial lumen secondary to an increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal glands; intense chronic inflammation due to recruitment of eosinophils, macrophages, and other inflammatory cells; thickened basement membrane; and hypertrophy and hyperplasia of smooth muscle cells. (C) Inhaled allergens (antigen) elicit a Th2-dominated response favoring IgE production and eosinophil recruitment. (D) On re-exposure to antigen, the immediate reaction is triggered by antigen-induced cross-linking of IgE bound to Fc receptors on mast cells. These cells release preformed mediators that directly and via neuronal reflexes induce bronchospasm, increased vascular permeability, mucus production, and recruitment of leukocytes. (E) Leukocytes recruited to the site of reaction (neutrophils, eosinophils, and basophils; lymphocytes and monocytes) release additional mediators that initiate the late phase reaction. Several factors released from eosinophils (e.g., major basic protein, eosinophil cationic protein) also cause damage to the epithelium. *IL-5,* Interleukin-5.

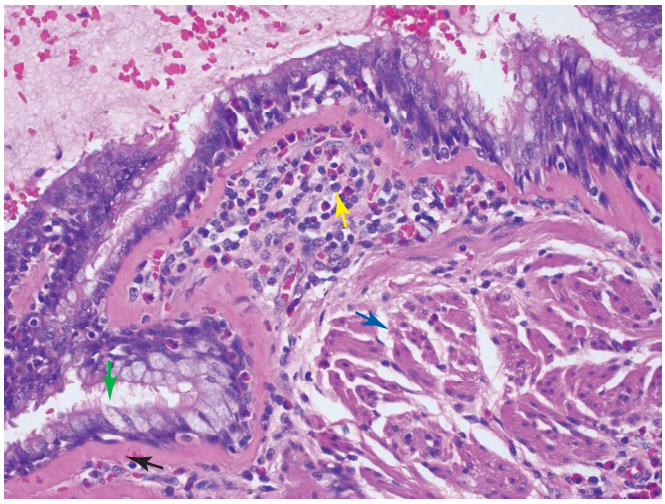

Figure 15.11 Bronchus from an asthmatic patient showing goblet cell hyperplasia *(green arrow)*, sub–basement membrane fibrosis *(black arrow)*, eosinophilic inflammation *(yellow arrow)*, and muscle hypertrophy *(blue arrow)*.

Environmental Factors. Asthma is a disease of industrialized societies where the majority of people live in cities. Two ideas, neither wholly satisfying, have been proposed to explain this association. First, industrialized environments contain many airborne pollutants that can serve as allergens to initiate the Th2 response. Second, city life tends to limit the exposure of very young children to certain antigens, particularly microbial antigens, and exposure to such antigens may protect children from asthma and atopy. The idea that microbial exposure during early life reduces the later incidence of allergic (and some autoimmune) diseases has been popularized as the hygiene hypothesis. Although the underlying mechanisms of this protective effect are unclear, it has spurred trials of probiotics and intentional early exposure of children to putative allergens to decrease their risk of later developing allergies.

Infections do not cause asthma by themselves, but may be important co-factors. Young children with aeroallergen sensitization who develop lower respiratory tract viral infections (rhinovirus type C, respiratory syncytial virus) have a 10- to 30-fold increased risk of developing persistent and/or severe asthma. Both viral and bacterial infections (identified by cultures and non-culture tools) are associated with acute exacerbations of the disease.

Over time, repeated bouts of allergen exposure and immune reactions result in structural changes in the bronchial wall, referred to as *airway remodeling*. These changes, described later in greater detail, include hypertrophy and hyperplasia of bronchial smooth muscle, epithelial injury, increased airway vascularity, subepithelial mucous gland enlargement, and subepithelial fibrosis.

A small subset of patients with asthma, many of whom have severe disease that is refractory to glucocorticoids, has inflammatory infiltrates that are enriched for neutrophils rather than eosinophils. This form of the disease may be driven by a Th17 T-cell response to chronic bacterial colonization of the lung.

MORPHOLOGY

In patients dying of acute severe asthma (status asthmaticus), the lungs are overinflated and contain small areas of atelectasis. The most striking gross finding is occlusion of bronchi and bronchioles by thick, tenacious mucus plugs, which often contain shed epithelium. A characteristic finding in sputum or bronchoalveolar lavage specimens of patients with atopic asthma is **Curschmann spirals,** which may result from extrusion of mucus plugs from subepithelial mucous gland ducts or bronchioles. Also present are numerous eosinophils and **Charcot-Leyden crystals** composed of the eosinophil-derived protein galectin-10. The other characteristic histologic findings of asthma, collectively called **airway remodeling** (Figs. 15.10B and 15.11), include:

- Thickening of airway wall
- Sub–basement membrane fibrosis (due to deposition of type I and III collagens)
- Increased vascularity
- Increase in the size of the submucosal glands and number of airway goblet cells
- Hypertrophy and/or hyperplasia of the bronchial wall muscle with increased extracellular matrix

While acute airflow obstruction is primarily attributed to muscular bronchoconstriction, acute edema, and mucus plugging, airway remodeling may contribute to chronic irreversible airway obstruction.

Clinical Features

A classic acute asthmatic attack lasts up to several hours. In some patients, however, the cardinal symptoms of chest tightness, dyspnea, wheezing, and coughing (with or without sputum production) are present at a low level constantly. In its most severe form, acute severe asthma, the paroxysm persists for days or even weeks, sometimes causing airflow obstruction that is so extreme that marked cyanosis or even death ensues.

The diagnosis is based on demonstration of an increase in airflow obstruction (from baseline levels); difficulty with exhalation (prolonged expiration, wheeze); and (in those with atopic asthma) identification of eosinophilia in the peripheral blood and eosinophils, Curschmann spirals, and Charcot-Leyden crystals in the sputum. In the usual case with intervals of freedom from respiratory difficulty, the disease is more discouraging and disabling than lethal, and most individuals are able to maintain a productive life.

Therapy is based on the severity of the disease. The centerpieces of standard therapy are bronchodilators, glucocorticoids, and leukotriene antagonists. For severe and difficult-to-treat asthma in adolescents and adults, novel biologic therapies targeting inflammatory mediators such as IL-5 blocking antibodies, which is effective in severe asthma associated with Th2 immune responses and peripheral blood eosinophilia, are now available. Up to 50% of childhood asthma remits in adolescence only to return in adulthood in a significant number of patients. In other cases there is a variable decline in baseline lung function over time.

KEY CONCEPTS

ASTHMA

- Asthma is characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli.
- Atopic asthma is caused by a Th2 and IgE-mediated immunologic reaction to environmental allergens and is characterized by acute-phase (immediate) and late-phase reactions. The Th2 cytokines IL-4, IL-5, and IL-13 are important mediators.
- Triggers for non-atopic asthma are less clear but include viral infections and inhaled air pollutants, which can also trigger atopic asthma.
- Eosinophils are key inflammatory cells in atopic asthma; other inflammatory cells implicated in its pathogenesis include mast cells, neutrophils, and T lymphocytes.
- Airway remodeling (sub–basement membrane fibrosis, hypertrophy of bronchial glands, and smooth muscle hyperplasia) adds an irreversible component to the obstructive disease.

Bronchiectasis

Bronchiectasis is a disorder in which destruction of smooth muscle and elastic tissue by inflammation stemming from persistent or severe infections leads to permanent dilation of bronchi and bronchioles. Because of better control of lung infections, bronchiectasis is now uncommon, but may still develop in association with the following:

- *Congenital or hereditary conditions that predispose to chronic infections,* including cystic fibrosis, intralobar sequestration of the lung, immunodeficiency states, primary ciliary dyskinesia, and Kartagener syndrome.
- *Severe necrotizing pneumonia* caused by bacteria, viruses, or fungi; this may be a single severe episode or recurrent infections.
- *Bronchial obstruction,* due to tumor, foreign body, or mucus impaction; in each instance the bronchiectasis is localized to the obstructed lung segment.
- *Immune disorders,* including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and the posttransplant setting (chronic rejection after lung transplant and chronic graft-versus-host disease after hematopoietic stem cell transplantation).
- Up to 50% of cases are *idiopathic,* lacking the aforementioned associations, in which there appears to be dysfunctional host immunity to infectious agents leading to chronic inflammation.

Pathogenesis

Obstruction and infection are the major conditions associated with bronchiectasis. **The infections that lead to bronchiectasis are usually the result of a defect in airway clearance.** Sometimes this defect stems from airway obstruction, leading to distal pooling of secretions.

Both mechanisms are readily apparent in a severe form of bronchiectasis that is associated with cystic fibrosis (Chapter 10). In cystic fibrosis the primary defect in ion transport results in thick viscous secretions that perturb mucociliary clearance and lead to airway obstruction. This sets the stage for chronic bacterial infections, which cause widespread damage to airway walls. With destruction of supporting smooth muscle and elastic tissue, the bronchi become markedly dilated, while smaller bronchioles are progressively obliterated as a result of fibrosis (bronchiolitis obliterans).

Primary ciliary dyskinesia is an autosomal recessive disease with a frequency of 1 in 10,000 to 20,000 births. The disease-causing mutations result in ciliary dysfunction due to defects in ciliary motor proteins (e.g., mutations involving dynein), again preventing mucociliary clearance, setting the stage for recurrent infections that lead to bronchiectasis. Ciliary function also is necessary during embryogenesis to ensure proper rotation of the developing organs in the chest and abdomen; in its absence, their location becomes a matter of chance. As a result, approximately half of patients with primary ciliary dyskinesia have *Kartagener syndrome,* marked by situs inversus or a partial lateralizing abnormality associated with bronchiectasis and sinusitis. Males with this condition also tend to be infertile as a result of sperm dysmotility.

Allergic bronchopulmonary aspergillosis occurs in patients with asthma or cystic fibrosis and frequently leads to the development of bronchiectasis. It is a hyperimmune response to the fungus *Aspergillus fumigatus.* Sensitization to *Aspergillus* leads to activation of Th2 helper T cells, which release cytokines that recruit eosinophils and other leukocytes. Characteristically, there are high serum IgE levels, serum antibodies to *Aspergillus,* intense airway inflammation with eosinophils, and formation of mucus plugs, which play a primary role in the development of bronchiectasis.

MORPHOLOGY

Bronchiectasis usually affects the lower lobes bilaterally, particularly air passages that are vertical, and is most severe in the more distal bronchi and bronchioles. When tumor or aspiration of foreign bodies leads to bronchiectasis, the involvement is localized. **The airways are dilated, sometimes up to four times normal size.** Characteristically, the bronchi and bronchioles are so dilated that they can be followed almost to the pleural surfaces. By contrast, in the normal lung, the bronchioles cannot be followed by eye beyond a point 2 to 3 cm from the pleural surfaces. On the cut surface of the lung, the dilated bronchi appear cystic and are filled with mucopurulent secretions (Fig. 15.12).

The histologic findings vary with the activity and chronicity of the disease. In the full-blown, active case there is an intense acute and chronic inflammatory exudation within the walls of the bronchi and bronchioles, associated with desquamation of the lining epithelium and extensive ulceration. There also may be squamous metaplasia of the remaining epithelium in response to chronic inflammation, further diminishing mucociliary clearance. In some instances, necrosis destroys the bronchial or bronchiolar walls and forms a lung abscess. Fibrosis of the bronchial and bronchiolar walls and peribronchiolar fibrosis develop in more chronic cases, leading to varying degrees of subtotal or total obliteration of bronchiolar lumens.

Haemophilus influenzae is found in approximately half and *Pseudomonas aeruginosa* in 12% to 30% of sputum cultures from patients with bronchiectasis, with four other types of bacteria