- One susceptibility locus for asthma is 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.
- Particular class II HLA alleles are linked to production of IgE antibodies against some antigens, such as ragweed pollen.
- Polymorphisms in the gene encoding ADAM33, a metalloproteinase, may be linked to increased proliferation of bronchial smooth muscle cells and fibroblasts, thus contributing to bronchial hyperreactivity and subepithelial fibrosis.
- β_2-adrenergic receptor gene variants are associated with differential in vivo airway hyper-responsiveness and in vitro response to β-agonist stimulation.
- IL-4 receptor gene variants are associated with atopy, elevated total serum IgE, and asthma.
- Variants in several members of the mammalian family of chitinases, enzymes that cleave chitin, a polysaccharide contained in many human parasites and the cell walls of fungi, have been associated with asthma. Increased serum levels and lung expression of YKL-40 (a chitinase-like glycoprotein expressed and secreted by a variety of cells) are correlated with disease severity, airway remodeling, and decreased pulmonary function.

Environmental Factors. **Asthma is a disease of industrialized societies where the majority of people live in cities.** This likely has two main explanations. Firstly, industrialized environments contain many airborne pollutants that can serve as allergens to initiate the T_H2 response. Secondly, city life tends to limit the exposure of very young children to certain antigens, particularly microbial antigens, and exposure to such antigens seems to protect children from asthma and atopy. This protective effect is even more apparent if the microbial exposure occurred throughout the mother's pregnancy. The idea that microbial exposure during early development 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 putative allergens given to children to decrease their risk of later developing allergies.

Infections themselves are not a cause or trigger for asthma, but 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, increased subepithelial mucus gland hypertrophy, and deposition of subepithelial collagen.

MORPHOLOGY

In patients dying of acute severe asthma (status asthmaticus) the lungs are distended by overinflation 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 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**; the latter are composed of an eosinophil protein called galectin-10. The other characteristic histologic findings of asthma, collectively called **"airway remodeling"** (Fig. 15-10*B*, and 15-11), include:

- Thickening of airway wall
- Subbasement membrane fibrosis (due to deposition of type I and III collagen)
- Increased vascularity
- An increase in the size of the submucosal glands and number of airway goblet cells
- Hypertrophy and/or hyperplasia of the bronchial wall muscle

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

Clinical Course. 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, *status asthmaticus*, the paroxysm persists for days and 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), peripheral blood eosinophilia, and the finding of eosinophils, Curschmann spirals, and Charcot-Leyden crystals in the sputum (particularly in patients with atopic asthma). In the usual case with intervals of freedom from respiratory difficulty, the disease is more discouraging and disabling than lethal, and most individuals with asthma are able to maintain a productive life. Therapy is based on severity of the disease. 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.

KEY CONCEPTS

Asthma

- Asthma is characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli.
- Atopic asthma is caused by a T_H2 and IgE-mediated immunologic reaction to environmental allergens and is characterized by acute-phase (immediate) and late-phase