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CHAPTER 12

Lung

CHAPTER CONTENTS

The major function of the lung is to replenish oxygen and excrete carbon dioxide from blood. Developmentally, the respiratory system is an outgrowth from the ventral wall of the foregut. The midline trachea develops two lateral outpocketings, the lung buds. The right lung bud eventually divides into three main bronchi, and the left into two main bronchi, thus giving rise to three lobes on the right and two on the left. The main bronchi branch dichotomously, giving rise to progressively smaller airways, termed *bronchioles,* which are distinguished from bronchi by the lack of cartilage and submucosal glands within their walls. Additional branching of bronchioles leads to *terminal bronchioles*; the part of the lung distal to the terminal bronchiole is called an *acinus.* Pulmonary acini are composed of *respiratory bronchioles* (emanating from the terminal bronchiole) that proceed into *alveolar ducts,* which immediately branch into *alveolar sacs,* the blind ends of the respiratory passages, whose walls are formed entirely of *alveoli,* the ultimate site of gas exchange. The microscopic structure of the alveolar walls (or alveolar septa) consists of the following components, proceeding from blood to air (Fig. 12–1):

- The capillary endothelium and basement membrane.
- The pulmonary interstitium is composed of fine elastic fibers, small bundles of collagen, a few fibroblast-like cells, smooth muscle cells, mast cells, and rare mononuclear cells. It is most prominent in thicker portions of the alveolar septum.
- Alveolar epithelium contains a continuous layer of two principal cell types: flattened, platelike type I pneumocytes covering 95% of the alveolar surface and rounded type II pneumocytes. The latter synthesize pulmonary surfactant and are the main cell type involved in repair of alveolar epithelium after damage to type I pneumocytes. The alveolar walls are not solid but are perforated by numerous pores of Kohn, which permit passage of air, bacteria, and exudates between adjacent alveoli.
- A few alveolar macrophages usually lie free within the alveolar space. In the adult, these macrophages often contain phagocytosed carbon particles.

There are multiple primary lung diseases that can broadly be divided into those primarily affecting (1) the airways,

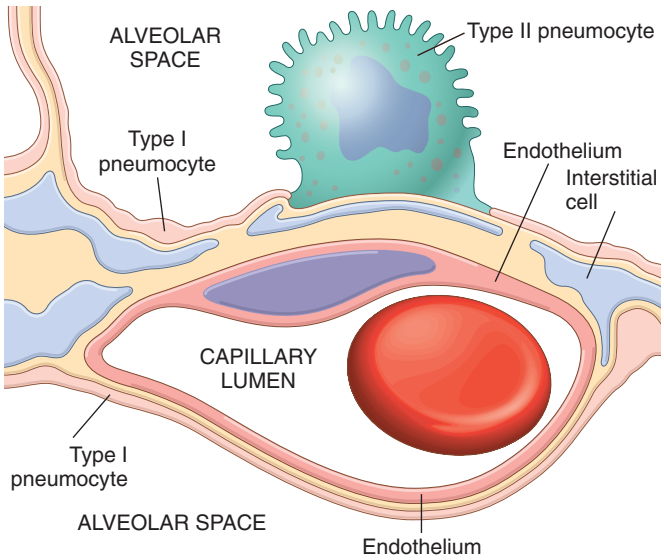

Figure 12–1 Microscopic structure of the alveolar wall. Note that the basement membrane *(yellow)* is thin on one side and widened where it is continuous with the interstitial space. Portions of interstitial cells are shown.

(2) the interstitium, and (3) the pulmonary vascular system. This division into discrete compartments is, of course, deceptively neat. In reality, disease in one compartment often causes secondary alterations of morphology and function in other areas.

ATELECTASIS (COLLAPSE)

Atelectasis, also known as collapse, is loss of lung volume caused by *inadequate expansion of air spaces.* It results in shunting of inadequately oxygenated blood from pulmonary arteries into veins, thus giving rise to a ventilation-perfusion imbalance and hypoxia. On the basis of the underlying mechanism or the distribution of alveolar collapse, atelectasis is classified into three forms (Fig. 12–2).

- *Resorption atelectasis.* Resorption atelectasis occurs when an obstruction prevents air from reaching distal airways. The air already present gradually becomes absorbed, and alveolar collapse follows. Depending on the level of airway obstruction, an entire lung, a complete lobe, or one or more segments may be involved. The most common cause of resorption collapse is obstruction of a bronchus by a mucous or mucopurulent plug. This frequently occurs postoperatively but also may complicate bronchial asthma, bronchiectasis, chronic bronchitis, tumor, or foreign body aspiration, particularly in children.
- *Compression atelectasis.* Compression atelectasis (sometimes called *passive* or *relaxation atelectasis*) is usually associated with accumulation of fluid, blood, or air within the pleural cavity, which mechanically collapses the adjacent lung. This is a frequent occurrence with pleural effusion, caused most commonly by congestive heart failure (CHF). Leakage of air into the pleural cavity (pneumothorax) also leads to compression atelectasis. Basal atelectasis resulting from the elevated position of the diaphragm commonly occurs in bedridden patients, in patients with ascites, and during and after surgery.
- *Contraction atelectasis.* Contraction (or *cicatrization*) atelectasis occurs when either local or generalized fibrotic changes in the lung or pleura hamper expansion and increase elastic recoil during expiration.

Atelectasis (except when caused by contraction) is potentially reversible and should be treated promptly to prevent hypoxemia and superimposed infection of the collapsed lung.

ACUTE LUNG INJURY

The term *acute lung injury* encompasses a spectrum of bilateral pulmonary damage (endothelial and epithelial), which can be initiated by numerous conditions. Clinically, acute lung injury manifests as (1) acute onset of dyspnea, (2) decreased arterial oxygen pressure (hypoxemia), and (3) development of bilateral pulmonary infiltrates on the chest radiograph, all in the absence of clinical evidence of primary left-sided heart failure. Since the pulmonary infiltrates in acute lung injury are usually caused by damage to the alveolar capillary membrane, rather than by left-sided heart failure (Chapter 10), such accumulations constitute

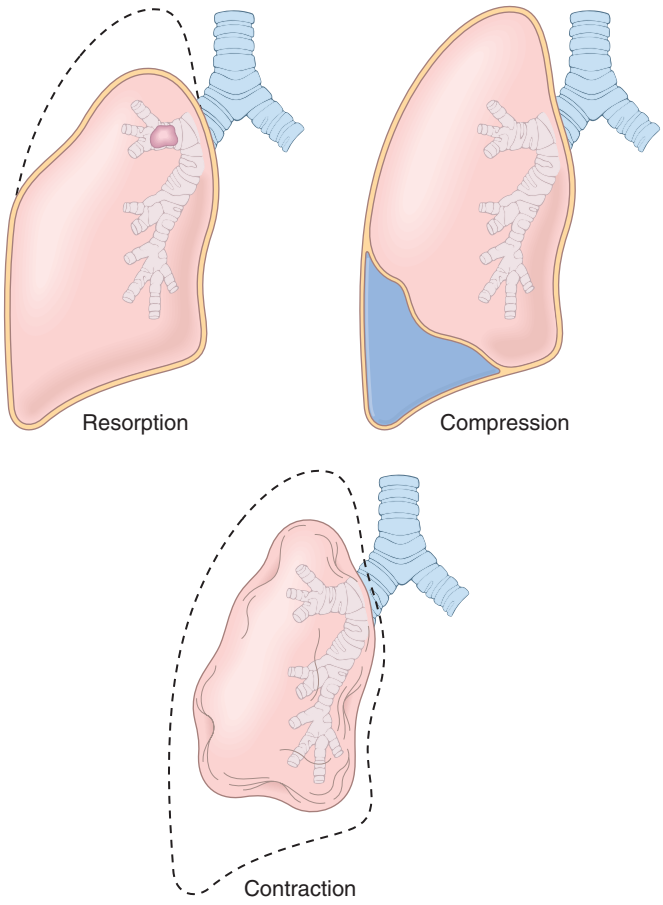

Figure 12–2 Various forms of acquired atelectasis.

Table 12–1 Clinical Disorders Associated with the Development of Acute Lung Injury/Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Common Causes	
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock
Uncommon Causes	
Pulmonary contusion	Cardiopulmonary bypass
Fat embolism	Acute pancreatitis
Near-drowning	Drug overdose
Inhalational injury	Transfusion of blood products
Reperfusion injury after lung transplantation	Uremia

Modified from Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334, 2000.

an example of *noncardiogenic pulmonary edema.* Acute lung injury can progress to the more severe *acute respiratory distress syndrome,* described next.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage. The usual course is characterized by rapid onset of life-threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy and may progress to multisystem organ failure. The histologic manifestation of ARDS in the lungs is known as *diffuse alveolar damage* (DAD). ARDS can occur in a multitude of clinical settings and is associated with either direct injury to the lung or indirect injury in the setting of a systemic process (Table 12–1). It should be recalled that respiratory distress syndrome of the newborn is pathogenetically distinct; it is caused by a primary deficiency of surfactant.

PATHOGENESIS

The alveolar-capillary membrane is formed by two separate barriers: the microvascular endothelium and the alveolar epithelium. **In ARDS, the integrity of this barrier is compromised by either endothelial or epithelial injury, or, more commonly, both.** The acute consequences of damage to the alveolar capillary membrane include increased vascular permeability and alveolar flooding, loss of diffusion capacity, and widespread surfactant abnormalities caused by damage to type II pneumocytes (Fig. 12–3). Although the cellular and molecular basis of acute lung injury and ARDS remains an area of active investigation, recent work suggests that in ARDS, **lung injury is caused by an imbalance of pro-inflammatory and anti-inflammatory mediators.** As early as 30 minutes after an acute insult, there is increased synthesis of interleukin 8 (IL-8), a potent neutrophil chemotactic and activating agent, by pulmonary macrophages. Release of this and similar mediators, such as IL-1 and tumor necrosis factor (TNF), leads to endothelial activation as well as sequestration and activation of neutrophils in pulmonary capillaries. **Neutrophils are thought to have an important role in the pathogenesis of ARDS.** Histologic examination of lungs early in the disease process shows increased numbers of neutrophils within the vascular space, the interstitium, and the alveoli. Activated neutrophils release a variety of products (e.g., oxidants, proteases, platelet-activating factor, leukotrienes) that cause damage to the alveolar epithelium and endothelium. Combined assault on the endothelium and epithelium perpetuates vascular leakiness and loss of surfactant that render the alveolar unit unable to expand. Of note, the destructive forces unleashed by neutrophils can be counteracted by an array of endogenous antiproteases, antioxidants, and anti-inflammatory cytokines (e.g., IL-10) that are upregulated by pro-inflammatory cytokines. In the end, it is the balance between the destructive and protective factors that determines the degree of tissue injury and clinical severity of ARDS.

MORPHOLOGY

In the **acute phase of ARDS,** the lungs are dark red, firm, airless, and heavy. Microscopic examination reveals capillary congestion, necrosis of alveolar epithelial cells, interstitial and intra-alveolar edema and hemorrhage, and (particularly with sepsis) collections of neutrophils in capillaries. The most characteristic finding is the presence of **hyaline membranes,** particularly lining the distended alveolar ducts (Fig. 12–4). Such membranes consist of fibrin-rich edema fluid admixed with remnants of necrotic epithelial cells. Overall, the picture is remarkably similar to that seen in respiratory distress syndrome in the newborn (Chapter 6). In the **organizing stage,** vigorous proliferation of type II pneumocytes occurs in an attempt to regenerate the alveolar lining. Resolution is unusual; more commonly, there is organization of the fibrin exudates, with resultant intra-alveolar fibrosis. Marked thickening of the alveolar septa ensues, caused by proliferation of interstitial cells and deposition of collagen.

Clinical Features

Approximately 85% of patients develop the clinical syndrome of acute lung injury or ARDS within 72 hours of the initiating insult. With improvements in supportive therapy, the mortality rate for the 190,000 ARDS cases occurring yearly has decreased from 60% to 40% in the last decade. Predictors of poor prognosis include advanced age, underlying bacteremia (sepsis), and the development of multisystem (especially cardiac, renal, or hepatic) failure. Should the patient survive the acute stage, diffuse interstitial fibrosis may occur, with continued compromise of respiratory function. However, in most patients who survive the acute insult and are spared the chronic sequelae, normal respiratory function returns within 6 to 12 months.

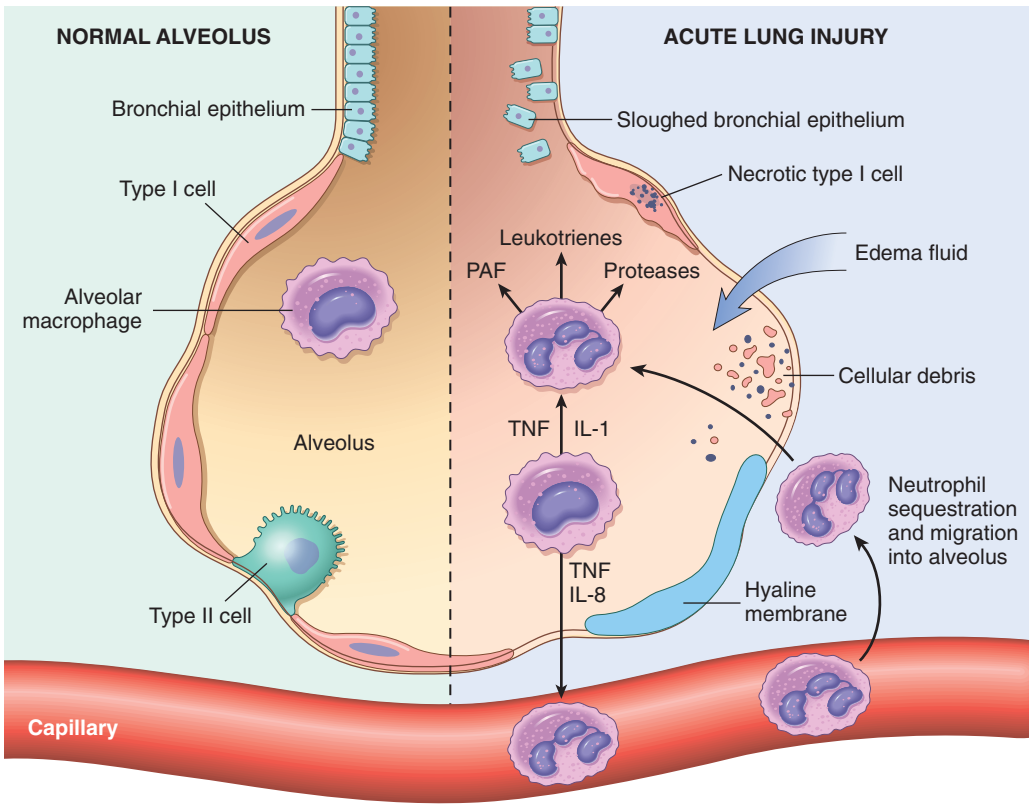

Figure 12–3 The normal alveolus *(left)*, compared with the injured alveolus in the early phase of acute lung injury and the acute respiratory distress syndrome. Under the influence of proinflammatory cytokines such as interleukins IL-8 and IL-1 and tumor necrosis factor (TNF) (released by macrophages), neutrophils initially undergo sequestration in the pulmonary microvasculature, followed by margination and egress into the alveolar space, where they undergo activation. Activated neutrophils release a variety of factors such as leukotrienes, oxidants, proteases, and platelet-activating factor (PAF), which contribute to local tissue damage, accumulation of edema fluid in the air spaces, surfactant inactivation, and hyaline membrane formation. Subsequently, the release of macrophage-derived fibrogenic cytokines such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PGDF) stimulate fibroblast growth and collagen deposition associated with the healing phase of injury.
(Modified from Ware LB: Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Semin Respir Crit Care Med 27:337, 2006.)

SUMMARY

Acute Respiratory Distress Syndrome

- ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, or diffuse pulmonary infection.
- Neutrophils and their products have a crucial role in the pathogenesis of ARDS by causing endothelial and epithelial injury.
- The characteristic histologic picture is that of alveolar edema, epithelial necrosis, accumulation of neutrophils, and presence of hyaline membranes lining the alveolar ducts.

OBSTRUCTIVE VERSUS RESTRICTIVE PULMONARY DISEASES

Diffuse pulmonary diseases can be classified into two categories: (1) obstructive (airway) disease, characterized by limitation of airflow, usually resulting from an increase in resistance caused by partial or complete obstruction at any level, and (2) restrictive disease, characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.

The major diffuse obstructive disorders are *emphysema, chronic bronchitis, bronchiectasis, and asthma.* In patients with these diseases, forced vital capacity (FVC) is either normal or slightly decreased, while the expiratory flow rate, usually measured as the forced expiratory volume at 1 second (FEV_1), is significantly decreased. Thus, *the ratio of FEV to FVC is characteristically decreased.* Expiratory obstruction may result either from anatomic airway narrowing, classically observed in asthma, or from loss of elastic recoil, characteristic of emphysema.

By contrast, in *diffuse restrictive diseases,* FVC is reduced and the expiratory flow rate is normal or reduced proportionately. Hence, *the ratio of FEV to FVC is near normal.* The restrictive defect occurs in two general conditions: (1) *chest wall disorders in the presence of normal lungs* (e.g., with severe obesity, diseases of the pleura, and neuromuscular disorders, such as the Guillain-Barré syndrome [Chapter 21], that affect the respiratory muscles) and (2) *acute or chronic interstitial lung diseases.* The classic *acute* restrictive disease is ARDS, discussed earlier. *Chronic* restrictive diseases

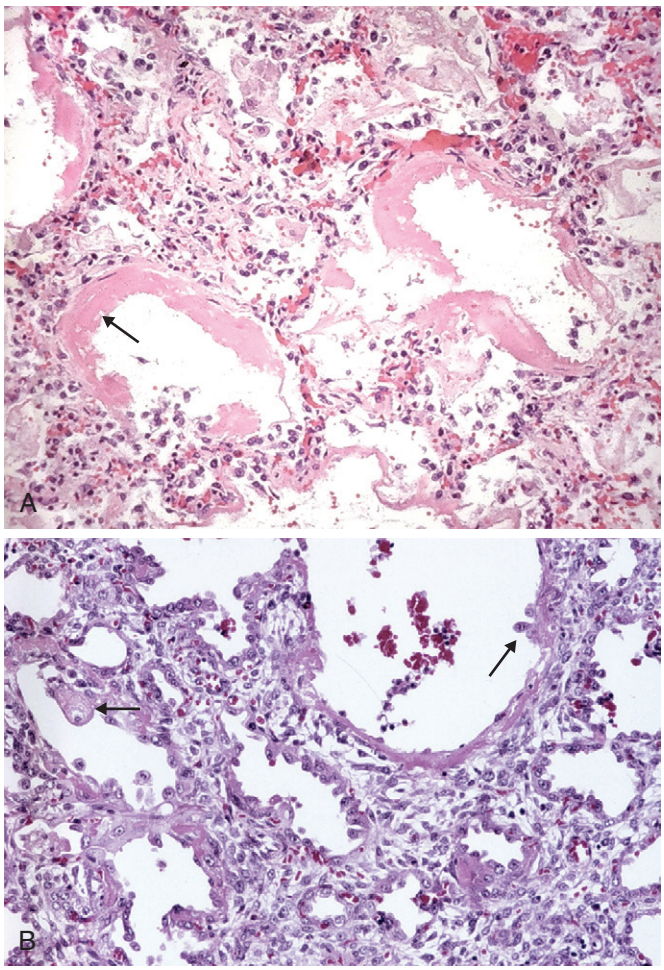

Figure 12–4 A, Diffuse alveolar damage in acute lung injury and acute respiratory distress syndrome. Some alveoli are collapsed; others are distended. Many are lined by bright pink hyaline membranes *(arrow)*. **B,** The healing stage is marked by resorption of hyaline membranes with thickening of alveolar septa containing inflammatory cells, fibroblasts, and collagen. Numerous reactive type II pneumocytes also are seen at this stage (*arrows*), associated with regeneration and repair.

(discussed later) include the pneumoconioses, interstitial fibrosis of unknown etiology, and most of the infiltrative conditions (e.g., sarcoidosis).

OBSTRUCTIVE LUNG (AIRWAY) DISEASES

In their prototypical forms, the four disorders in this group—emphysema, chronic bronchitis, asthma, and bronchiectasis—have distinct clinical and anatomic characteristics (Table 12–2), but overlaps between emphysema, bronchitis, and asthma are common.

At the outset, it should be recognized that *the definition of emphysema is morphologic, whereas chronic bronchitis is defined on the basis of clinical features* such as the presence of chronic and recurrent cough with excessive mucus secretion. Second, the anatomic distribution is partially different; chronic bronchitis initially involves the large airways, whereas emphysema affects the *acinus.* In severe or advanced cases of both, small airway disease (chronic bronchiolitis) is characteristic. Although chronic bronchitis may exist without demonstrable emphysema, and almost pure emphysema may occur (particularly in patients with inherited α_1-antitrypsin deficiency) (discussed later), the two diseases usually coexist. This is almost certainly because the major cause—cigarette smoking, especially long-term, heavy tobacco exposure—is common to both disorders. In view of their propensity to coexist, emphysema and chronic bronchitis often are clinically grouped together under the rubric of *chronic obstructive pulmonary disease* (COPD). COPD affects more than 10% of the U.S. adult population and is the fourth leading cause of death in this country. The primarily *irreversible* airflow obstruction of COPD distinguishes it from asthma, which, as described later, is characterized largely by *reversible* airflow obstruction; however, patients with COPD commonly have some degree of reversible obstruction as well (Fig. 12–5).

Emphysema

Emphysema is characterized by *abnormal permanent enlargement of the air spaces* distal to the terminal bronchioles, accompanied by *destruction of their walls* without significant fibrosis.

Table 12–2 Disorders Associated with Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Entity	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hypertrophy and hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hypertrophy and hyperplasia, excessive mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Air space enlargement, wall destruction	Tobacco smoke	Dyspnea
Small airway disease, bronchiolitis*	Bronchiole	Inflammatory scarring, partial obliteration of bronchioles	Tobacco smoke, air pollutants	Cough, dyspnea

*Can be present in all forms of obstructive lung disease or by itself.

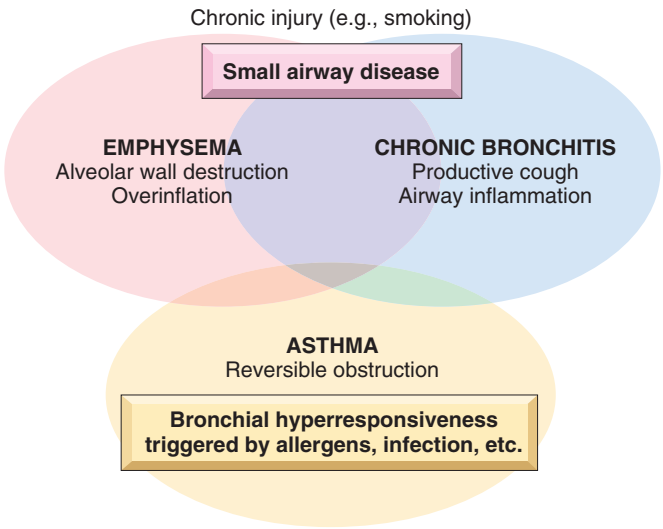

Figure 12–5 Schematic representation of overlap between chronic obstructive lung diseases.

Types of Emphysema

Emphysema is classified according to its *anatomic distribution* within the *lobule*; as described earlier, the acinus is the structure distal to terminal bronchioles, and a cluster of three to five acini is called a *lobule* (Fig. 12–6, *A*). There are four major types of emphysema: (1) centriacinar, (2) panacinar, (3) distal acinar, and (4) irregular. Only the first two types cause clinically significant airway obstruction, with centriacinar emphysema being about 20 times more common than panacinar disease.

Centriacinar (Centrilobular) Emphysema

The distinctive feature of centriacinar (centrilobular) emphysema is the pattern of involvement of the lobules: *The central or proximal parts of the acini, formed by respiratory bronchioles, are affected, while distal alveoli are spared.* Thus, both emphysematous and normal air spaces exist within the same acinus and lobule (Fig. 12–6, *B*). The lesions are more common and severe in the upper lobes, particularly in the apical segments. In severe centriacinar emphysema the distal acinus also becomes involved, and thus, the differentiation from panacinar emphysema becomes difficult. This type of emphysema is most commonly seen as a consequence of cigarette smoking in people who do not have congenital deficiency of α_1-antitrypsin.

Panacinar (Panlobular) Emphysema

In panacinar (panlobular) emphysema, the acini are uniformly enlarged, from the level of the respiratory bronchiole to the terminal blind alveoli (Fig. 12–6, *C*). In contrast with centriacinar emphysema, panacinar emphysema tends to occur more commonly in the lower lung zones and is the type of emphysema that occurs in α_1-antitrypsin deficiency.

Distal Acinar (Paraseptal) Emphysema

In distal acinar (paraseptal) emphysema, the proximal portion of the acinus is normal but the distal part is primarily involved. The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules. It occurs adjacent to areas of fibrosis, scarring, or atelectasis and is usually more severe in the upper half of the lungs. The characteristic finding is the presence of multiple, contiguous, enlarged air spaces ranging in diameter from less than 0.5 mm to more than 2.0 cm, sometimes forming cystic structures that, with progressive enlargement, are referred to as *bullae.* The cause of this type of emphysema is unknown; it is seen most often in cases of spontaneous pneumothorax in young adults.

Irregular Emphysema

Irregular emphysema, so named because the acinus is irregularly involved, is almost invariably associated with scarring, such as that resulting from healed inflammatory diseases. Although clinically asymptomatic, this may be the most common form of emphysema.

PATHOGENESIS

Exposure to toxic substances such as tobacco smoke and inhaled pollutants induces ongoing inflammation with accumulation of neutrophils, macrophages and lymphocytes in the lung. Elastases, cytokines (including IL-8) and oxidants are released causing epithelial injury and proteolysis of the extracellular matrix (ECM). Elastin degradation products further increase the inflammation. Unless checked by antielastases

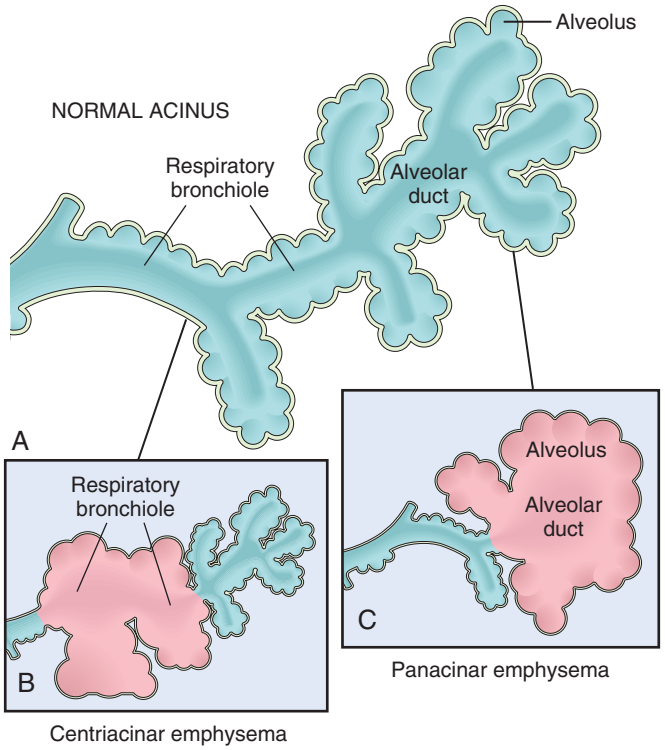

Figure 12–6 Major patterns of emphysema. **A,** Diagram of normal structure of the acinus, the fundamental unit of the lung. **B,** Centriacinar emphysema with dilation that initially affects the respiratory bronchioles. **C,** Panacinar emphysema with initial distention of all the peripheral structures (i.e., the alveolus and alveolar duct); the disease later extends to affect the respiratory bronchioles.

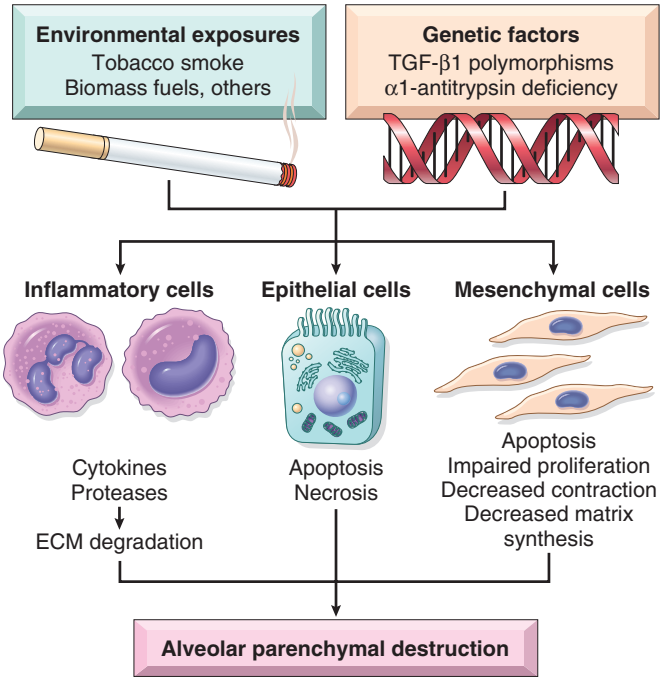

Figure 12–7 Loss of cellular homeostasis in emphysema pathogenesis. Exposure to inhaled toxins (such as cigarette smoke) leads to epithelial cell death, inflammation, and extracellular matrix proteolysis. In susceptible persons, mesenchymal cell survival and reparative functions are impaired by direct effects of inhaled toxic substances and inflammatory mediators and by the loss of the peri- and extracellular matrix. The result is loss of structural cells of the alveolar wall and the associated matrix components.

(Reproduced with permission from Horowitz JC, Martinez FJ, Thannickal VJ: Mesenchymal cell fate and phenotypes in the pathogenesis of emphysema. COPD 6:201, 2009.)

(e.g., α_1-antitrypsin) and antioxidants, the cycle of inflammation and ECM proteolysis continues. Indeed, more than 80% of patients with congenital α_1-antitrypsin deficiency develop symptomatic panacinar emphysema, which occurs at an earlier age and with greater severity if the affected person smokes.

There is marked individual variation in susceptibility to the development of emphysema/COPD. Multiple genetic factors control the response to injury after smoking. For example, the *TGFB* gene exhibits polymorphisms that influence susceptibility to the development of COPD by regulating the response of mesenchymal cells to injury. For example, with certain polymorphisms, mesenchymal cell response to TGF-β signaling is reduced, which in turn results in inadequate repair of elastin injury caused by inhaled toxins. Matrix metalloproteinases (MMPs), especially MMP-9 and MMP-12, have also been shown to have a pathogenic role in emphysema. MMP-9 gene polymorphisms and higher levels of both MMP-9 and MMP-12 have been found in some emphysema patients. Moreover, MMP-12–deficient mice are protected from cigarette smoke–induced emphysema. Although much remains to be studied, the current understanding of emphysema pathogenesis is summarized in Figure 12–7.

Complex interactions between inflammatory mediators, cell signaling and inappropriate activation of repair mechanisms may result in very different diseases: tissue destruction without fibrosis (emphysema) or interstitial fibrosis (discussed later). Recent data indicate that mesenchymal cell response may be a key factor in determining which of these two processes ensues. In emphysema there is loss of not only epithelial and endothelial cells but also mesenchymal cells, leading to lack of extracellular matrix, the scaffolding upon which epithelial cells would have grown. Thus, **emphysema can be thought of as resulting from insufficient wound repair.** By contrast, patients with fibrosing lung diseases have excessive myofibroblastic or fibroblastic response to injury, leading to unchecked scarring.

MORPHOLOGY

The diagnosis and classification of emphysema depend largely on the macroscopic appearance of the lung. **Panacinar emphysema,** when the pathologic process is well developed, produces pale, voluminous lungs that often obscure the heart when the anterior chest wall is removed at autopsy. The macroscopic features of **centriacinar emphysema** are less impressive. The lungs are a deeper pink than in panacinar emphysema and less voluminous, unless the disease is well advanced. Generally, in centriacinar emphysema the upper two thirds of the lungs are more severely affected than the lower lungs. Histologic examination reveals **destruction of alveolar walls without fibrosis, leading to enlarged air spaces** (Fig. 12–8). In addition to alveolar loss, the number of alveolar capillaries is diminished. Terminal and respiratory bronchioles may be deformed because of the loss of septa that help tether these structures in the parenchyma. With the **loss of elastic tissue** in the surrounding alveolar septa, radial traction on the small airways is reduced. As a result, they tend to collapse during expiration—an important cause of chronic airflow obstruction in severe emphysema. Bronchiolar inflammation and submucosal fibrosis are consistently present in advanced disease.

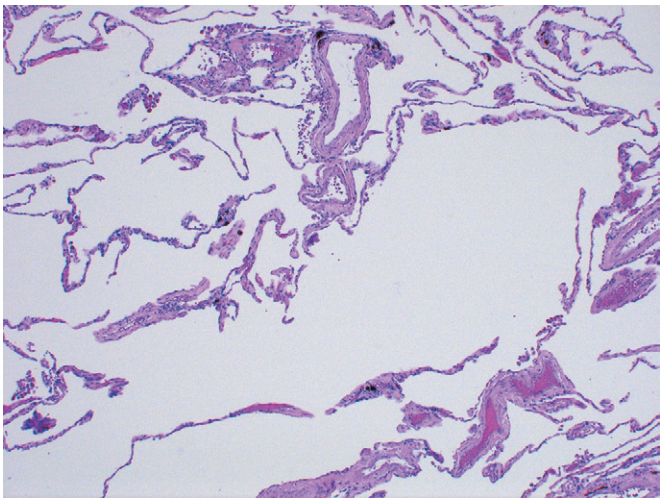

Figure 12–8 Pulmonary emphysema. There is marked enlargement of air spaces, with destruction of alveolar septa but without fibrosis. Note presence of black anthracotic pigment.

Clinical Features

Dyspnea usually is the first symptom; it begins insidiously but is steadily progressive. In patients with underlying chronic bronchitis or chronic asthmatic bronchitis, cough and wheezing may be the initial complaints. Weight loss is common and may be so severe as to suggest a hidden malignant tumor. Pulmonary function tests reveal reduced FEV_1 with normal or near-normal FVC. *Hence, the ratio of FEV_1 to FVC is reduced.*

The classic presentation in emphysema with no "bronchitic" component is one in which the patient is barrel-chested and dyspneic, with obviously prolonged expiration, sitting forward in a hunched-over position, attempting to squeeze the air out of the lungs with each expiratory effort. In these patients, air space enlargement is severe and diffusing capacity is low. Dyspnea and hyperventilation are prominent, so that until very late in the disease, gas exchange is adequate and blood gas values are relatively normal. Because of prominent dyspnea and adequate oxygenation of hemoglobin, these patients sometimes are called "pink puffers."

At the other extreme of the clinical presentation in emphysema is a patient who also has pronounced chronic bronchitis and a history of recurrent infections with purulent sputum. Dyspnea usually is less prominent, with diminished respiratory drive, so the patient retains carbon dioxide, becomes hypoxic, and often is cyanotic. For reasons not entirely clear, such patients tend to be obese—hence the designation "blue bloaters." Often they seek medical help after the onset of CHF (cor pulmonale) (Chapter 10) and associated edema.

Most patients with emphysema and COPD, however, fall somewhere between these two classic extremes. In all cases, *secondary pulmonary hypertension develops gradually,* arising from both hypoxia-induced pulmonary vascular spasm and loss of pulmonary capillary surface area from alveolar destruction. Death from emphysema is related to either pulmonary failure, with respiratory acidosis, hypoxia, and coma, or right-sided heart failure (cor pulmonale).

Conditions Related to Emphysema

Several conditions resemble emphysema only superficially but nevertheless are (inappropriately) referred to as such:

- *Compensatory emphysema* is a term used to designate the compensatory dilation of alveoli in response to loss of lung substance elsewhere, such as occurs in residual lung parenchyma after surgical removal of a diseased lung or lobe.
- *Obstructive overinflation* refers to the condition in which the lung expands because air is trapped within it. A common cause is subtotal obstruction by a tumor or foreign object. Obstructive overinflation can be a life-threatening emergency if the affected portion extends sufficiently to compress the remaining normal lung.
- *Bullous emphysema* refers merely to any form of emphysema that produces large subpleural blebs or bullae (spaces greater than 1 cm in diameter in the distended state) (Fig. 12–9). Such blebs represent localized accentuations of one of the four forms of emphysema; most often the blebs are subpleural, and on occasion they may rupture, leading to pneumothorax.
- *Mediastinal (interstitial) emphysema* is the condition resulting when air enters the connective tissue stroma of the lung, mediastinum, and subcutaneous tissue. This may occur spontaneously with a sudden increase in intra-alveolar pressure (as with vomiting or violent coughing) resulting in a tear, with dissection of air into the interstitium. Sometimes it develops in children with whooping cough. It is particularly likely to occur in patients on respirators who have partial bronchiolar obstruction or in persons who suffer a perforating injury (e.g., a fractured rib). When the interstitial air enters the subcutaneous tissue, the patient may literally blow up like a balloon, with marked swelling of the head and neck and crackling crepitation all over the chest. In most instances, the air is resorbed spontaneously after the site of entry is sealed.

SUMMARY

Emphysema

- Emphysema is a chronic obstructive airway disease characterized by permanent enlargement of air spaces distal to terminal bronchioles.
- Subtypes include centriacinar (most common; smoking-related), panacinar (seen in α_1-antitrypsin deficiency), distal acinar, and irregular.
- Smoking and inhaled pollutants cause ongoing accumulation of inflammatory cells, releasing elastases and oxidants, which destroy the alveolar walls without adequate mesenchymal repair response.
- Most patients with emphysema demonstrate elements of chronic bronchitis concurrently, since cigarette smoking is an underlying risk factor for both; patients with pure emphysema are characterized as "pink puffers."

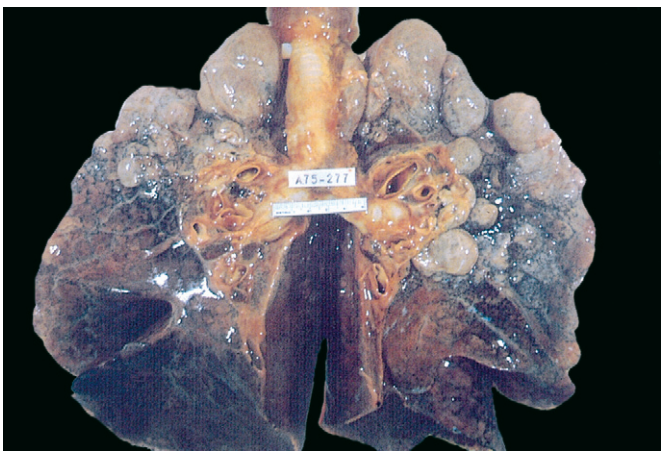

Figure 12–9 Bullous emphysema with large apical and subpleural bullae. *(From the Teaching Collection of the Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

Chronic Bronchitis

Chronic bronchitis is common among cigarette smokers and urban dwellers in smog-ridden cities; some studies indicate that 20% to 25% of men in the 40- to 65-year-old age group have the disease. The diagnosis of chronic bronchitis is made on clinical grounds: it is defined by the *presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.* In early stages of the disease, the productive cough raises mucoid sputum, but airflow is not obstructed. Some patients with chronic bronchitis may demonstrate hyperresponsive airways with intermittent bronchospasm and wheezing. A subset of bronchitic patients, especially heavy smokers, develop chronic outflow obstruction, usually with associated emphysema.

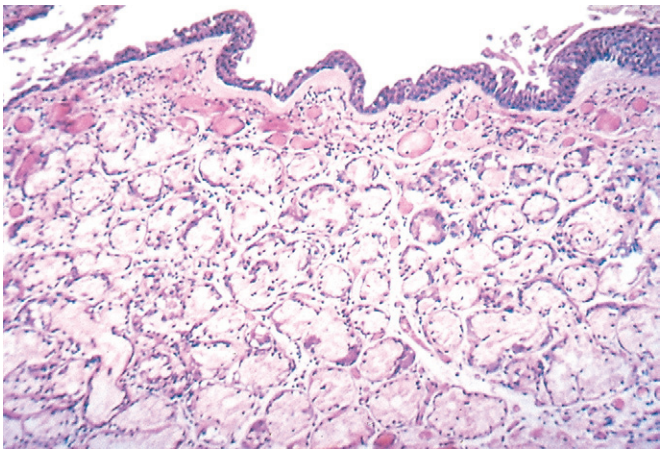

Figure 12–10 Chronic bronchitis. The lumen of the bronchus is *above*. Note the marked thickening of the mucous gland layer (approximately twice-normal) and squamous metaplasia of lung epithelium.

(From the Teaching Collection of the Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Texas.)

PATHOGENESIS

The distinctive feature of chronic bronchitis is **hypersecretion of mucus,** beginning in the large airways. Although the single most important cause is cigarette smoking, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may contribute. These environmental irritants induce hypertrophy of mucous glands in the trachea and main bronchi, leading to a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles. In addition, these irritants cause inflammation with infiltration of CD8+ lymphocytes, macrophages, and neutrophils. In contrast with asthma, there are no eosinophils in chronic bronchitis. Whereas the defining feature of chronic bronchitis (mucus hypersecretion) is primarily a reflection of large bronchial involvement, **the morphologic basis of airflow obstruction in chronic bronchitis is more peripheral** and results from (1) **small airway disease,** induced by goblet cell metaplasia with mucous plugging of the bronchiolar lumen, inflammation, and bronchiolar wall fibrosis, and (2) **coexistent emphysema.** In general, while small airway disease (also known as chronic bronchiolitis) is an important component of early and relatively mild airflow obstruction, chronic bronchitis with significant airflow obstruction is almost always complicated by emphysema.

It is postulated that many of the respiratory epithelial effects of environmental irritants (e.g., mucus hypersecretion) are mediated by local release of T cell cytokines such as IL-13. The transcription of the mucin gene *MUC5AC* in bronchial epithelium and the production of neutrophil elastase are increased as a consequence of exposure to tobacco smoke. **Microbial infection** often is present but has a secondary role, chiefly by maintaining the inflammation and exacerbating symptoms.

MORPHOLOGY

As seen in gross specimens, the mucosal lining of the larger airways usually is **hyperemic and swollen** by edema fluid. It often is covered by a layer of mucinous or mucopurulent **secretions.** The smaller bronchi and bronchioles also may be filled with similar secretions. On histologic examination, the diagnostic feature of chronic bronchitis in the trachea and larger bronchi is **enlargement of the mucus-secreting glands** (Fig. 12–10). The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall (the Reid index—normally 0.4). Inflammatory cells, largely mononuclear but sometimes admixed with neutrophils, are frequently present in variable density in the bronchial mucosa. **Chronic bronchiolitis** (small airway disease), characterized by goblet cell metaplasia, mucous plugging, inflammation, and fibrosis, is also present. In the most severe cases, there may be complete obliteration of the lumen as a consequence of fibrosis (bronchiolitis obliterans). It is the submucosal fibrosis that leads to luminal narrowing and airway obstruction. Changes of emphysema often co-exist.

Clinical Features

In patients with chronic bronchitis, a prominent cough and the production of sputum may persist indefinitely without ventilatory dysfunction. As alluded to earlier, however, some patients develop significant COPD with outflow obstruction. This clinical syndrome is accompanied by hypercapnia, hypoxemia, and (in severe cases) cyanosis (hence the term "blue bloaters"). Differentiation of this form of COPD from that caused by emphysema can be made in the classic case, but many such patients have both conditions. With progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure (Chapter 10). Recurrent infections and respiratory failure are constant threats.

SUMMARY

Chronic Bronchitis

- Chronic bronchitis is defined as persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
- Cigarette smoking is the most important underlying risk factor; air pollutants also contribute.

- Chronic obstructive component largely results from small airway disease (chronic bronchiolitis) and coexistent emphysema.
- Histologic examination demonstrates enlargement of mucus-secreting glands, goblet cell metaplasia, and bronchiolar wall fibrosis.

Asthma

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning. The hallmarks of the disease are *intermittent and reversible airway obstruction, chronic bronchial inflammation with eosinophils, bronchial smooth muscle cell hypertrophy and hyperreactivity, and increased mucus secretion.* Some of the stimuli that trigger attacks in patients would have little or no effect in persons with normal airways. Many cells play a role in the inflammatory response, in particular eosinophils, mast cells, macrophages, lymphocytes, neutrophils, and epithelial cells. Of note, there has been a significant increase in the incidence of asthma in the Western world over the past four decades. This epidemiologic observation has led to the "hygiene hypothesis," according to which the eradication of infections may alter immune homeostasis and promote allergic and other harmful immune responses.

Asthma may be categorized into *atopic* (evidence of allergen sensitization, often in a patient with a history of allergic rhinitis, eczema) and *nonatopic.* In either type, episodes of bronchospasm can be triggered by diverse mechanisms, such as respiratory infections (especially viral), environmental exposure to irritants (e.g., smoke, fumes), cold air, stress, and exercise. There is emerging evidence for differing patterns of inflammation: eosinophilic, neutrophilic, mixed inflammatory, and pauci-granulocytic. These subgroups may differ in etiology, immunopathology, and response to treatment. Asthma also may be classified according to the agents or events that trigger bronchoconstriction.

PATHOGENESIS

The major etiologic factors of asthma are genetic predisposition to type I hypersensitivity (atopy), acute and chronic airway inflammation, and bronchial hyperresponsiveness to a variety of stimuli. **The inflammation involves many cell types and numerous inflammatory mediators, but the role of type 2 helper T (T_H2) cells may be critical to the pathogenesis of asthma.** The classic atopic form of asthma is associated with an excessive T_H2 reaction against environmental antigens. Cytokines produced by T_H2 cells account for most of the features of asthma—IL-4 stimulates IgE production, IL-5 activates eosinophils, and IL-13 stimulates mucus production and also promotes IgE production by B cells. IgE coats submucosal mast cells, which, on exposure to allergen, release granule contents. This induces two waves of reaction: an early (immediate) phase and a late phase (Fig. 12-11). The early reaction is dominated by bronchoconstriction, increased mucus production and variable vasodilation. Bronchoconstriction is triggered by direct stimulation of subepithelial vagal receptors. The late-phase reaction consists of inflammation, with activation of eosinophils, neutrophils, and T cells. In addition, epithelial cells are activated to produce chemokines that promote recruitment of more T_H2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils), as well as other leukocytes, thus amplifying the inflammatory reaction. Repeated bouts of inflammation lead to structural changes in the bronchial wall, collectively referred to as **airway remodeling.** These changes include hypertrophy of bronchial smooth muscle and mucus glands, and increased vascularity and deposition of subepithelial collagen, which may occur as early as several years before initiation of symptoms.

Asthma is a complex genetic disorder in which multiple susceptibility genes interact with environmental factors to initiate the pathologic reaction. There is significant variation in the expression of these genes and in the combinations of polymorphisms that effect the immune response or tissue remodeling. One of the susceptibility loci is on the long arm of chromosome 5 (5q), where several genes involved in regulation of IgE synthesis and mast cell and eosinophil growth and differentiation map. The genes at this locus include *IL13* (genetic polymorphisms linked with susceptibility to the development of atopic asthma), CD14 (single-nucleotide polymorphisms associated with occupational asthma), class II HLA alleles (tendency to produce IgE antibodies), β_2-adrenergic receptor gene, and IL-4 receptor gene (atopy, total serum IgE level, and asthma). Another important locus is on 20q where ADAM-33 that regulates proliferation of bronchial smooth muscle and fibroblasts is located; this controls airway remodeling. Upregulation of various chitinase enzymes has been shown to be important in T_H2 inflammation and severity of asthma; high serum YKL-40 levels (a chitinase family member with no enzymatic activity) correlate with the severity of asthma.

Types of Asthma

Atopic Asthma

This is the most common type of asthma, usually beginning in childhood, and is a classic example of *type I IgE–mediated hypersensitivity reaction* (Chapter 4). A positive family history of atopy and/or asthma is common, and asthmatic attacks are often preceded by allergic rhinitis, urticaria, or eczema. The disease is triggered by environmental antigens, such as dusts, pollen, animal dander, and foods. Infections can also trigger atopic asthma. A skin test with the offending antigen results in an immediate wheal-and-flare reaction. Atopic asthma also can be diagnosed based on serum radioallergosorbent tests (RASTs) that identify the presence of IgE specific for a panel of allergens.

Non-Atopic Asthma

Patients with nonatopic forms of asthma do not have evidence of allergen sensitization, and skin test results usually are negative. A positive family history of asthma is less common. Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants (e.g., sulfur dioxide, ozone, nitrogen dioxide) are common triggers. *It is thought that virus-induced inflammation of the*

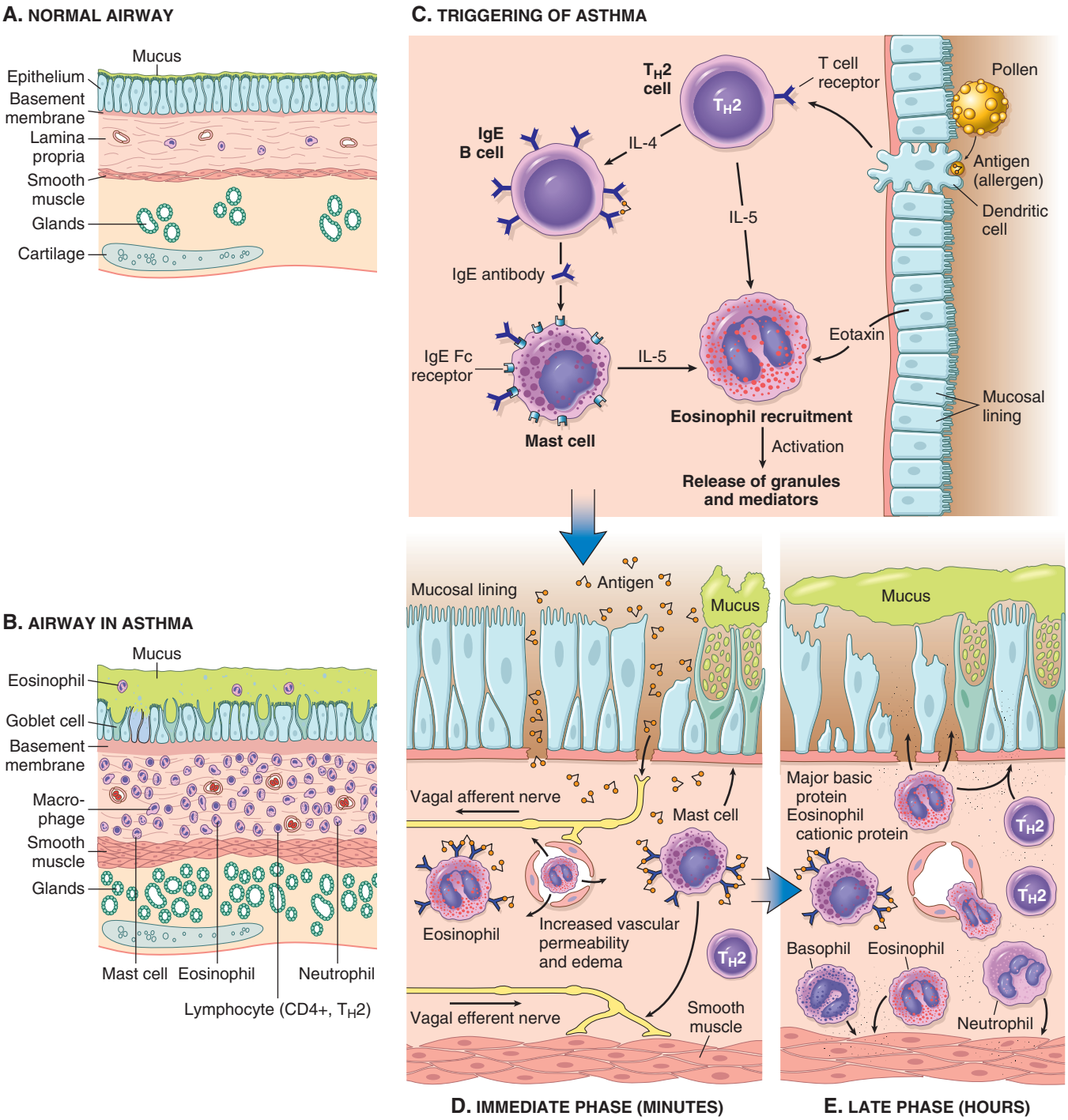

Figure 12–11 **A** and **B**, Comparison of a normal bronchus with that in a patient with asthma. Note the accumulation of mucus in the bronchial lumen resulting from an increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal glands. In addition, there is intense chronic inflammation due to recruitment of eosinophils, macrophages, and other inflammatory cells. Basement membrane underlying the mucosal epithelium is thickened, and smooth muscle cells exhibit hypertrophy and hyperplasia. **C,** Inhaled allergens (antigens) elicit a T_H2-dominated response favoring IgE production and eosinophil recruitment (priming or sensitization). **D,** On reexposure to antigen (Ag), the immediate reaction is triggered by antigen-induced cross-linking of IgE bound to IgE receptors on mast cells in the airways. These cells release preformed mediators. Collectively, either directly or through neuronal reflexes, the mediators induce bronchospasm, increase vascular permeability and mucus production, and recruit additional mediator-releasing cells from the blood. **E,** The arrival of recruited leukocytes (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) signals the initiation of the late phase of asthma and a fresh round of mediator release from leukocytes, endothelium, and epithelial cells. Factors, particularly from eosinophils (e.g., major basic protein, eosinophil cationic protein), also cause damage to the epithelium. IgE, immunoglobulin E.

respiratory mucosa lowers the threshold of the subepithelial vagal receptors to irritants. Although the connections are not well understood, the ultimate humoral and cellular mediators of airway obstruction (e.g., eosinophils) are common to both atopic and nonatopic variants of asthma, so they are treated in a similar way.

Drug-Induced Asthma

Several pharmacologic agents provoke asthma, *aspirin* being the most striking example. Patients with aspirin sensitivity present with recurrent rhinitis and nasal polyps, urticaria, and bronchospasm. The precise mechanism remains unknown, but it is presumed that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance of production toward leukotrienes that cause bronchial spasm.

Occupational Asthma

This form of asthma is stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals. Asthma attacks usually develop after repeated exposure to the inciting antigen(s).

MORPHOLOGY

The morphologic changes in asthma have been described in persons who die of prolonged severe attacks (status asthmaticus) and in mucosal biopsy specimens of persons challenged with allergens. In gross specimens obtained in fatal cases, the lungs are overdistended because of overinflation, and there may be small areas of atelectasis. The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick, tenacious **mucous plugs.** Histologically, the mucous plugs contain whorls of shed epithelium **(Curschmann spirals).** Numerous eosinophils and **Charcot-Leyden crystals** (collections of crystalloids made up of eosinophil proteins) also are present. Other characteristic morphologic changes in asthma, collectively called "airway remodeling," include (Fig. 12–11, *B*):

- Thickening of airway wall
- Sub-basement membrane fibrosis (Fig. 12–12)
- Increased vascularity in submucosa
- An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium
- Hypertrophy and/or hyperplasia of the bronchial muscle (this is the basis for the novel therapy of bronchial thermoplasty, which involves controlled delivery of thermal energy during bronchoscopy; this reduces the mass of smooth muscles which in turn reduces airway hyperresponsiveness)

Clinical Features

An attack of asthma is characterized by severe dyspnea with wheezing; the chief difficulty lies in expiration. The victim labors to get air into the lungs and then cannot get it out, so that there is progressive hyperinflation of the lungs with air trapped distal to the bronchi, which are constricted and filled with mucus and debris. In the usual case, attacks last from 1 to several hours and subside either spontaneously or with therapy, usually bronchodilators and corticosteroids. Intervals between attacks are characteristically free from overt respiratory difficulties, but persistent, subtle deficits can be detected by spirometry. Occasionally a severe paroxysm occurs that does not respond to therapy and persists for days and even weeks (*status asthmaticus*). The associated hypercapnia, acidosis, and severe hypoxia may be fatal, although in most cases the condition is more disabling than lethal.

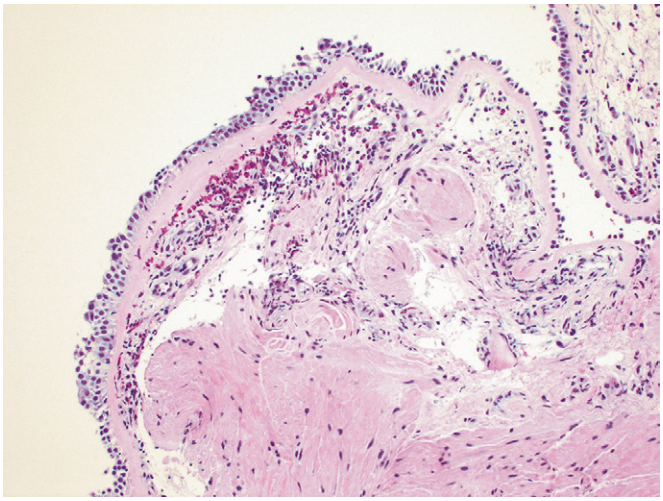

Figure 12–12 Bronchial biopsy specimen from an asthmatic patient showing sub-basement membrane fibrosis, eosinophilic inflammation, and smooth muscle hyperplasia.

SUMMARY

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 reactions. The T_H2 cytokines IL-4, IL-5, and IL-13 are important mediators.
- Triggers for nonatopic asthma are less clear but include viral infections and inhaled air pollutants, which can also trigger atopic asthma.
- *Eosinophils* are key inflammatory cells found in almost all subtypes of asthma; eosinophil products such as major basic protein are responsible for airway damage.
- Airway remodeling (sub-basement membrane thickening and hypertrophy of bronchial glands and smooth muscle) adds an irreversible component to the obstructive disease.

Bronchiectasis

Bronchiectasis is the permanent dilation of bronchi and bronchioles caused by destruction of the muscle and the supporting elastic tissue, resulting from or associated with

chronic necrotizing infections. It is not a primary disease but rather secondary to persisting infection or obstruction caused by a variety of conditions. Once developed, it gives rise to a characteristic symptom complex dominated by cough and expectoration of copious amounts of purulent sputum. Diagnosis depends on an appropriate history along with radiographic demonstration of bronchial dilation. The conditions that most commonly predispose to bronchiectasis include:

- *Bronchial obstruction.* Common causes are tumors, foreign bodies, and occasionally impaction of mucus. With these conditions, the bronchiectasis is localized to the obstructed lung segment. Bronchiectasis can also complicate atopic asthma and chronic bronchitis.
- Congenital or hereditary conditions—for example:
  - In *cystic fibrosis,* widespread severe bronchiectasis results from obstruction caused by the secretion of abnormally viscid mucus thus predisposing to infections of the bronchial tree. This is an important and serious complication (Chapter 6).
  - In *immunodeficiency states,* particularly immunoglobulin deficiencies, localized or diffuse bronchiectasis is likely to develop because of an increased susceptibility to repeated bacterial infections.
  - *Kartagener syndrome* is a rare autosomal recessive disorder that is frequently associated with bronchiectasis and with sterility in males. In this condition, structural abnormalities of the cilia impair mucociliary clearance in the airways, leading to persistent infections, and reduce the mobility of spermatozoa.
- *Necrotizing,* or *suppurative, pneumonia,* particularly with virulent organisms such as *Staphylococcus aureus* or *Klebsiella* spp., may predispose affected patients to development of bronchiectasis. Posttuberculosis bronchiectasis continues to be a significant cause of morbidity in endemic areas.

PATHOGENESIS

Two processes are crucial and intertwined in the pathogenesis of bronchiectasis: **obstruction** and **chronic persistent infection.** Either of these may come first. Normal clearance mechanisms are hampered by obstruction, so secondary infection soon follows; conversely, chronic infection over time causes damage to bronchial walls, leading to weakening and dilation. For example, obstruction caused by a primary lung cancer or a foreign body impairs clearance of secretions, providing a favorable substrate for superimposed infection. The resultant inflammatory damage to the bronchial wall and the accumulating exudate further distend the airways, leading to irreversible dilation. Conversely, a persistent necrotizing inflammation in the bronchi or bronchioles may cause obstructive secretions, inflammation throughout the wall (with peribronchial fibrosis and traction on the walls), and eventually the train of events already described.

MORPHOLOGY

Bronchiectasis usually affects the **lower lobes** bilaterally, particularly those air passages that are most vertical. When caused by tumors or aspiration of foreign bodies the involvement may be sharply localized to a single segment of the lungs. Usually, the most severe involvement is found in the more distal bronchi and bronchioles. The airways may be **dilated** to as much as four times their usual diameter and on gross examination of the lung can be followed almost to the pleural surfaces (Fig. 12–13). By contrast, in normal lungs, the bronchioles cannot be followed by ordinary gross examination beyond a point 2 to 3 cm from the pleural surfaces. The histologic findings vary with the activity and chronicity of the disease. In the full-blown active case, an **intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles** and the desquamation of lining epithelium cause extensive areas of ulceration. In the usual case, a **mixed** flora can be cultured from the involved bronchi, including staphylococci, streptococci, pneumococci, enteric organisms, anaerobic and microaerophilic bacteria, and (particularly in children) *Haemophilus influenzae* and *Pseudomonas aeruginosa.* When healing occurs, the lining epithelium may regenerate completely; however, usually so much injury has occurred that abnormal dilation and scarring persist. Fibrosis of the bronchial and bronchiolar walls and **peribronchiolar fibrosis** develop in more chronic cases. In some instances, the necrosis destroys the bronchial or bronchiolar walls resulting in the formation of an abscess cavity within which a fungus ball may develop.

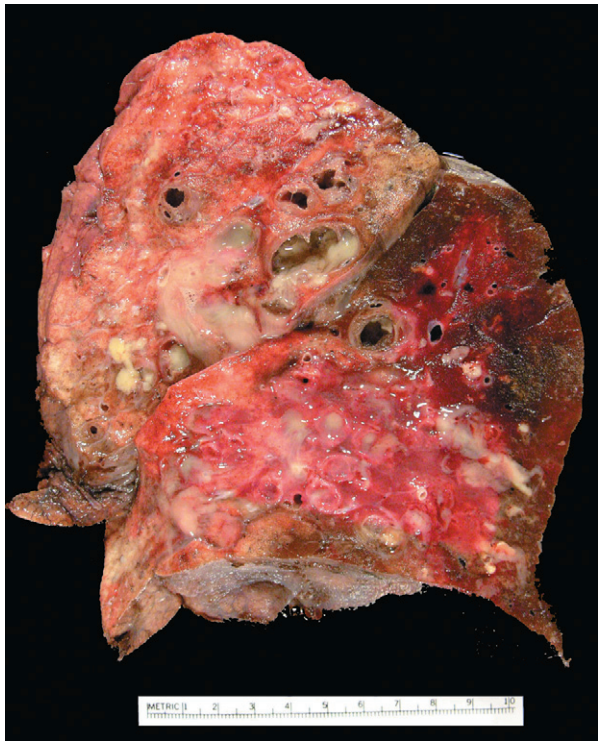

Figure 12–13 Bronchiectasis in a patient with cystic fibrosis who underwent lung resection for transplantation. Cut surface of lung shows markedly dilated bronchi, filled with purulent mucus, which are seen extending to subpleural regions.

Clinical Features

The clinical manifestations consist of severe, persistent cough with expectoration of mucopurulent, sometimes fetid, sputum. The sputum may contain flecks of blood; frank hemoptysis can occur. Symptoms often are episodic and are precipitated by upper respiratory tract infections or the introduction of new pathogenic agents. Clubbing of the fingers may develop. In cases of severe, widespread bronchiectasis, significant obstructive ventilatory defects are usual, with hypoxemia, hypercapnia, pulmonary hypertension, and (rarely) cor pulmonale. Metastatic brain abscesses and reactive amyloidosis (Chapter 4) are other, less frequent complications of bronchiectasis.

CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES

Chronic interstitial diseases are a heterogeneous group of disorders characterized predominantly by bilateral, often patchy, and usually chronic involvement of the pulmonary connective tissue, principally the most peripheral and delicate interstitium in the alveolar walls. The pulmonary interstitium is composed of the basement membrane of the endothelial and epithelial cells (fused in the thinnest portions), collagen fibers, elastic tissue, fibroblasts, a few mast cells, and occasional mononuclear cells (Fig. 12–1). Many of the entities in this group are of unknown cause and pathogenesis; some have an intra-alveolar as well as an interstitial component, and there is frequent overlap in histologic features among the different conditions. Nevertheless, the similarity in clinical signs, symptoms, radiographic alterations, and pathophysiologic changes justifies their consideration as a group. *The hallmark feature of these disorders is reduced compliance (i.e., more pressure is required to expand the lungs because they are stiff), which in turn necessitates increased effort of breathing (dyspnea).* Furthermore, damage to the alveolar epithelium and interstitial vasculature produces abnormalities in the ventilation–perfusion ratio, leading to hypoxia. Chest radiographs show diffuse infiltration by small nodules, irregular lines, or "ground-glass shadows." With progression, patients can develop respiratory failure, often in association with pulmonary hypertension and cor pulmonale (Chapter 10). Advanced forms of these diseases may be difficult to differentiate because they result in scarring and gross destruction of the lung, referred to as end-stage or "honeycomb" lung. Chronic interstitial lung diseases are categorized based on clinicopathologic features and characteristic histology (Table 12–3).

Table 12–3 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Associated with collagen vascular disease
Pneumoconiosis
Associated with therapies (drugs, radiation)
Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome
Drug allergy–related
Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

Fibrosing Diseases

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), also known as *cryptogenic fibrosing alveolitis,* refers to a pulmonary disorder of unknown etiology. It is characterized by patchy but progressive bilateral interstitial fibrosis, which in advanced cases results in severe hypoxemia and cyanosis. Males are affected more often than females, and approximately two thirds of patients are older than 60 years of age at presentation. The radiologic and histologic pattern of fibrosis is referred to as *usual interstitial pneumonia* (UIP), which is required for the diagnosis of IPF. Of note, however, similar pathologic changes in the lung may be present in well-defined entities such as asbestosis, the collagen vascular diseases, and a number of other conditions. Therefore, known causes must be ruled out before the appellation of *idiopathic* is used.

PATHOGENESIS

The current concept is that IPF is caused by "repeated cycles" of epithelial activation/injury by some unidentified agent (Fig. 12–14). Histopathologic features include inflammation and induction of T_H2 type T cell response with eosinophils, mast cells, IL-4, and IL-13 in the lesions. There has been considerable interest in the idea that "alternatively activated macrophages" are dominant in patients with lung fibrosis and may be important in its pathogenesis (Chapter 2). Abnormal epithelial repair at the sites of damage and inflammation gives rise to exuberant fibroblastic or myofibroblastic proliferation, leading to the characteristic fibroblastic foci. Although the mechanisms of abnormal repair are incompletely understood, recent data point to TGF-β1, which is released from injured type I pneumocytes and induces transformation of fibroblasts into myofibroblasts leading to excessive and continuing deposition of collagen and ECM. Some patients with familial IPF have mutations that shorten telomeres (Chapter 1) leading to rapid senescence and apoptosis of pneumocytes. TGF-β1 also downregulates fibroblast caveolin-1, which acts as an endogenous inhibitor of pulmonary fibrosis.

MORPHOLOGY

Grossly, the pleural surfaces of the lung have the appearance of cobblestones because of the retraction of scars along the interlobular septa. The cut surface shows fibrosis (firm, rubbery white areas), with lower lobe predominance and a

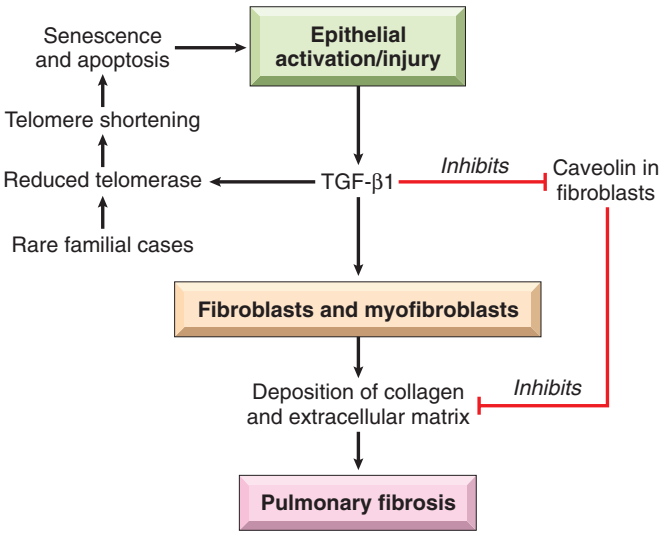

Figure 12–14 Schematic representation of current understanding of the pathogenesis of idiopathic pulmonary fibrosis.

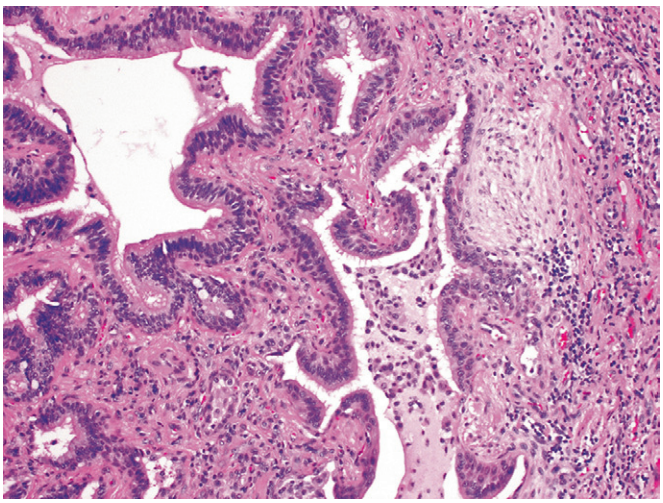

Figure 12–16 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix. Honeycombing is present to the *left*.

distinctive distribution in the subpleural regions and along the interlobular septa. The pattern of fibrosis in IPF is referred to as **usual interstitial pneumonia** (UIP). The histologic hallmark of UIP is **patchy interstitial fibrosis,** which varies in intensity (Fig. 12–15) and worsens with time. The earliest lesions demonstrate exuberant fibroblastic proliferation and appear as **fibroblastic foci** (Fig. 12–16). Over time these areas become more collagenous and less cellular. Quite typical is the existence of both early and late lesions **(temporal heterogeneity).** The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium **(honeycomb fibrosis).** The interstitial inflammation usually is patchy and consists of an alveolar septal infiltrate of mostly lymphocytes and occasional plasma cells, mast cells, and eosinophils. Secondary pulmonary hypertensive changes (intimal fibrosis and medial thickening of pulmonary arteries) are often present.

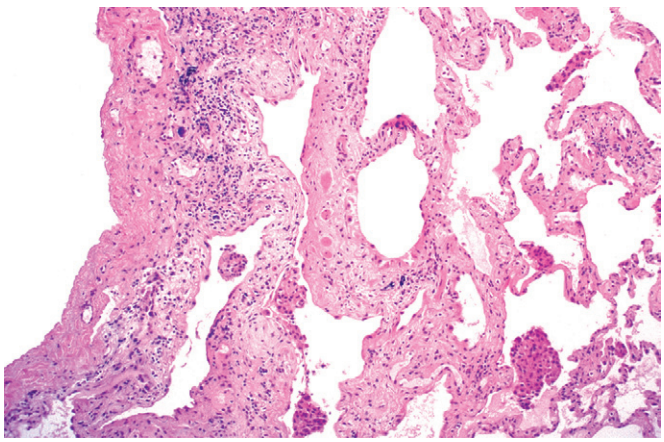

Figure 12–15 Usual interstitial pneumonia. The fibrosis, which varies in intensity, is more pronounced in the subpleural region.

Clinical Features

IPF usually manifests insidiously, with the gradual onset of a nonproductive cough and progressive dyspnea. On physical examination, most patients with IPF have characteristic "dry" or "Velcro"-like crackles during inspiration. Cyanosis, cor pulmonale, and peripheral edema may develop in later stages of the disease. The clinical and radiologic findings often are diagnostic; surgical lung biopsy is needed for diagnosis in selected cases. Unfortunately, progression of IPF is relentless despite medical therapy, and the mean survival is 3 years or less. Lung transplantation is the only definitive therapy available.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is a chronic bilateral interstitial lung disease of unknown etiology, which despite its nonspecific name, has distinct clinical, radiologic, and histologic features. It is important to recognize this disease, since it carries a much better prognosis than that for IPF. On the basis of the histologic appearance, NSIP is divided into cellular and fibrosing patterns. The *cellular pattern* features mild-to-moderate chronic interstitial inflammation (lymphocytes and a few plasma cells) in a uniform or patchy distribution. The *fibrosing pattern* consists of diffuse or patchy interstitial fibrosis, *without the temporal heterogeneity characteristic of UIP.* Fibroblastic foci and honeycombing are typically absent in both variants. Patients present with dyspnea and cough of several months' duration. Patients with the cellular pattern have a better outcome than those with the fibrosing pattern and UIP.

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia is synonymous with the previously popular designation *bronchiolitis obliterans organizing pneumonia* ("BOOP"); the former term is now preferred, however, because it emphasizes the unknown etiology of this clinicopathologic entity. Patients present with cough and dyspnea, and chest radiographs demonstrate subpleural or peribronchial patchy areas of air space

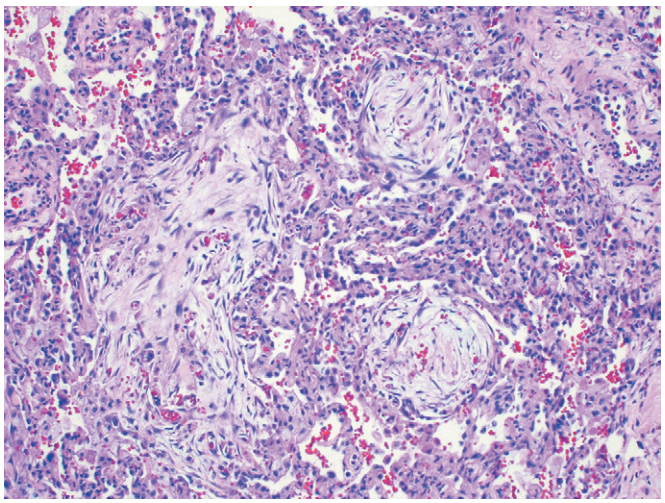

Figure 12–17 Cryptogenic organizing pneumonia. Some alveolar spaces are filled with balls of fibroblasts (Masson bodies). Although compressed, adjacent alveoli are relatively normal.

consolidation. On histologic examination, cryptogenic organizing pneumonia is characterized by the presence of polypoid plugs of loose organizing connective tissue within alveolar ducts, alveoli, and often bronchioles (Fig. 12–17). The connective tissue is all of the same age, and the underlying lung architecture is normal. Some patients recover spontaneously, but most require treatment with oral steroids for 6 months or longer. Of note, organizing pneumonia with intra-alveolar fibrosis also can be seen as a response to infection (e.g., pneumonia) or inflammatory injury (e.g., collagen vascular disease, transplantation injury) to the lung; in such cases, the etiology obviously is not "cryptogenic," and the outcome is determined by the underlying disease.

Pulmonary Involvement in Collagen Vascular Diseases

Many collagen vascular diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, dermatomyositis-polymyositis) are associated with pulmonary manifestations. Several histologic variants can be seen, depending on the underlying disorder, with NSIP, UIP pattern (similar to that seen in IPF), vascular sclerosis, organizing pneumonia, and bronchiolitis (small airway disease, with or without fibrosis) being the most common. Pleural involvement (pleuritis, pleural nodules, and pleural effusion) may also be present. Pulmonary involvement in these diseases is usually associated with a poor prognosis, although it is still better than that with IPF.

SUMMARY

Chronic Interstitial Lung Diseases

- Diffuse interstitial fibrosis of the lung gives rise to restrictive lung diseases characterized by reduced lung compliance and reduced forced vital capacity (FVC). The ratio of FEV to FVC is normal.
- The diseases that cause diffuse interstitial fibrosis are heterogeneous. The unifying pathogenetic factor is injury to the alveoli with activation of macrophages and release of fibrogenic cytokines such as TGF-β.
- Idiopathic pulmonary fibrosis is prototypic of restrictive lung diseases. It is characterized by patchy interstitial fibrosis, fibroblastic foci, and formation of cystic spaces (honeycomb lung). This histologic pattern is known as *usual interstitial pneumonia* (UIP).

Pneumoconioses

Pneumoconiosis is a term originally coined to describe the non-neoplastic lung reaction to inhalation of mineral dusts. The term has been broadened to include diseases induced by organic as well as inorganic particulates, and some experts also regard chemical fume- and vapor-induced non-neoplastic lung diseases as pneumoconioses. The mineral dust pneumoconioses—the three most common of which result from exposure to coal dust, silica, and asbestos—nearly always result from exposure in the workplace. However, the increased risk of cancer as a result of asbestos exposure extends to family members of asbestos workers and to other persons exposed to asbestos outside of the workplace. Table 12–4 indicates the pathologic conditions associated with each mineral dust and the major industries in which the dust exposure is sufficient to produce disease.

PATHOGENESIS

The reaction of the lung to mineral dusts depends on many variables, including size, shape, solubility, and reactivity of the particles. For example, particles greater than 5 to 10 μm are unlikely to reach distal airways, whereas particles smaller than 0.5 μm move into and out of alveoli, often without substantial deposition and injury. **Particles that are 1 to 5 μm in diameter are the most dangerous, because they get lodged at the bifurcation of the distal airways.** Coal dust is relatively inert, and large amounts must be deposited in the lungs before lung disease is clinically detectable. Silica,

Table 12–4 Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, progressive massive fibrosis.

asbestos, and beryllium are more reactive than coal dust, resulting in fibrotic reactions at lower concentrations. Most inhaled dust is entrapped in the mucus blanket and rapidly removed from the lung by ciliary movement. However, some of the particles become impacted at alveolar duct bifurcations, where macrophages accumulate and engulf the trapped particulates. **The pulmonary alveolar macrophage is a key cellular element in the initiation and perpetuation of lung injury and fibrosis.** Many particles activate the inflammasome and induce IL-1 production. The more reactive particles trigger the macrophages to release a number of products that mediate an inflammatory response and initiate fibroblast proliferation and collagen deposition. Some of the inhaled particles may reach the lymphatics either by direct drainage or within migrating macrophages and thereby initiate an immune response to components of the particulates and/or to self-proteins that are modified by the particles. This then leads to an amplification and extension of the local reaction. **Tobacco smoking worsens the effects of all inhaled mineral dusts,** more so with asbestos than with any other particle.

Coal Worker's Pneumoconiosis

Worldwide dust reduction in coal mines has greatly reduced the incidence of coal dust–induced disease. The spectrum of lung findings in coal workers is wide, ranging from *asymptomatic anthracosis,* in which pigment accumulates without a perceptible cellular reaction, to *simple coal worker's pneumoconiosis* (CWP), in which accumulations of macrophages occur with little to no pulmonary dysfunction, to *complicated CWP* or *progressive massive fibrosis* (PMF), in which fibrosis is extensive and lung function is compromised (Table 12–4). Although statistics vary, it seems that less than 10% of cases of simple CWP progress to PMF. Of note PMF is a generic term that applies to a confluent fibrosing reaction in the lung; this can be a complication of any one of the pneumoconioses discussed here.

Although coal is mainly carbon, coal mine dust contains a variety of trace metals, inorganic minerals, and crystalline silica. The ratio of carbon to contaminating chemicals and minerals ("coal rank") increases from bituminous to anthracite coal; in general, anthracite mining has been associated with a higher risk of CWP.

MORPHOLOGY

Pulmonary anthracosis is the most innocuous coal-induced pulmonary lesion in coal miners and also is commonly seen in all urban dwellers and tobacco smokers. Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue along the lymphatics, including the pleural lymphatics, or in lymph nodes.

Simple CWP is characterized by **coal macules** and the somewhat larger **coal nodule.** The coal macule consists of dust-laden macrophages; in addition, the nodule contains small amounts of collagen fibers arrayed in a delicate network. Although these lesions are scattered throughout the lung, the upper lobes and upper zones of the lower lobes are more heavily involved. In due course, **centrilobular emphysema** can occur. Functionally significant emphysema is more common in the United Kingdom and Europe, probably because the coal rank is higher than in the United States.

Complicated CWP (PMF) occurs on a background of simple CWP by coalescence of coal nodules and generally requires many years to develop. It is characterized by usually multiple, intensely blackened scars larger than 2 cm, sometimes up to 10 cm in greatest diameter. On microscopic examination the lesions are seen to consist of dense collagen and pigment (Fig. 12–18).

Clinical Features

CWP is usually a benign disease that produces little decrement in lung function. In those in whom PMF develops, there is increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale. Progression from CWP to PMF has been linked to a variety of conditions including coal dust exposure level and total dust burden. Unfortunately, PMF has a tendency to progress even in the absence of further exposure. Once smoking-related risk has been taken into account, there is no increased frequency of lung carcinoma in coal miners, a feature that distinguishes CWP from both silica and asbestos exposures (discussed next).

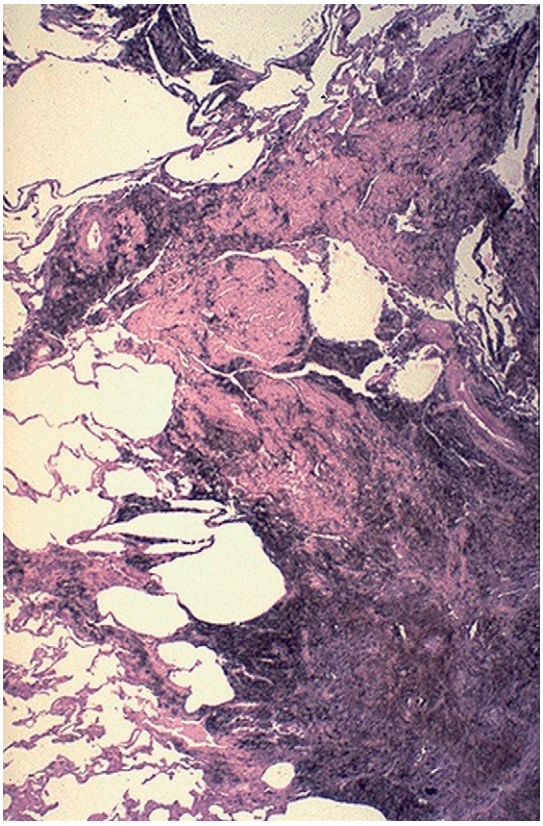

Figure 12–18 Progressive massive fibrosis in a coal worker. Large amount of black pigment is associated with fibrosis.
(From Klatt EC: Robbins and Cotran atlas of pathology, ed 2, Elsevier, p. 121.)

Silicosis

Silicosis *is currently the most prevalent chronic occupational disease in the world.* It is caused by inhalation of crystalline silica, mostly in occupational settings. Workers in several occupations but especially those involved in sandblasting and hard-rock mining are at particular risk. Silica occurs in both crystalline and amorphous forms, but crystalline forms (including quartz, cristobalite, and tridymite) are by far the most toxic and fibrogenic. Of these, quartz is most commonly implicated in silicosis. After inhalation the particles interact with epithelial cells and macrophages. *Ingested silica particles cause activation and release of mediators by pulmonary macrophages,* including IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines. Especially compelling is the evidence incriminating TNF, since anti-TNF monoclonal antibodies can block lung fibrosis in mice that are given silica intratracheally. *When mixed with other minerals, quartz has been observed to have a reduced fibrogenic effect.* This phenomenon is of practical importance, because quartz in the workplace is rarely pure. Thus, miners of the iron-containing ore hematite may have more quartz in their lungs than some quartz-exposed workers and yet have relatively mild lung disease, because the hematite provides a protective effect.

MORPHOLOGY

Silicotic nodules are characterized grossly in their early stages by tiny, barely palpable, discrete, pale-to-blackened (if coal dust is also present) nodules in the upper zones of the lungs (Fig. 12–19). Microscopically, the silicotic nodule demonstrates **concentrically arranged hyalinized collagen fibers** surrounding an amorphous center. The "whorled" appearance of the collagen fibers is quite distinctive for silicosis (Fig. 12–20). Examination of the nodules by **polarized microscopy reveals weakly birefringent silica** particles, primarily in the center of the nodules. As the disease progresses, the individual nodules may coalesce into hard, collagenous scars, with eventual progression to PMF. The intervening lung parenchyma may be compressed or overexpanded, and a honeycomb pattern may develop. Fibrotic lesions may also occur in the hilar lymph nodes and pleura. Sometimes, thin sheets of calcification occur in the lymph nodes and are appreciated radiographically as "eggshell" calcification (e.g., calcium surrounding a zone lacking calcification).

Clinical Features

Silicosis usually is detected on routine chest radiographs obtained in asymptomatic workers. The radiographs typically show a fine nodularity in the upper zones of the lung, but pulmonary function is either normal or only moderately affected. Most patients do not develop shortness of breath until late in the course, after PMF is present. At this time, the disease may be progressive, even if the person is no longer exposed. Many patients with PMF develop pulmonary hypertension and cor pulmonale, as a result of chronic hypoxia-induced vasoconstriction and parenchymal destruction. The disease is slow to kill, but impaired pulmonary function may severely limit activity. *Silicosis is associated with an increased susceptibility to tuberculosis.* It is postulated that silicosis results in a depression of cell-mediated immunity, and crystalline silica may inhibit the ability of pulmonary macrophages to kill phagocytosed mycobacteria. Nodules of silicotuberculosis often contain a central zone of caseation. The relationship between silica and *lung cancer* has been a contentious issue. In 1997, based on evidence from several epidemiologic studies, the International Agency for Research on Cancer concluded that *crystalline silica* from occupational sources is carcinogenic in humans. However, this subject continues to be controversial.

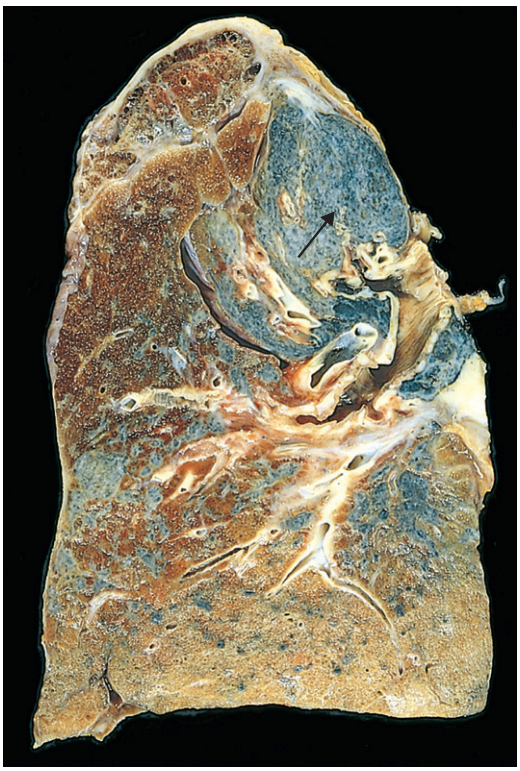

Figure 12–19 Advanced silicosis seen on transection of lung. Scarring has contracted the upper lobe into a small dark mass (*arrow*). Note the dense pleural thickening.
(Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, Massachusetts.)

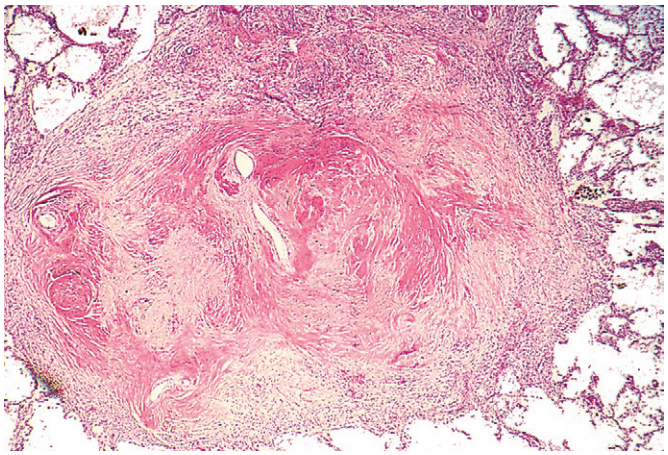

Figure 12–20 Several coalescent collagenous silicotic nodules.
(Courtesy of Dr. John Godleski, Brigham and Women's Hospital, Boston, Massachusetts.)

Asbestosis and Asbestos-Related Diseases

Asbestos is a family of crystalline hydrated silicates with a fibrous geometry. On the basis of epidemiologic studies, occupational exposure to asbestos is linked to (1) parenchymal interstitial fibrosis (*asbestosis*); (2) localized fibrous plaques or, rarely, diffuse fibrosis in the pleura; (3) pleural effusions; (4) lung carcinomas; (5) malignant pleural and peritoneal mesotheliomas; and (6) laryngeal carcinoma. An increased incidence of asbestos-related cancers in family members of asbestos workers has alerted the general public to the potential hazards of asbestos in the environment.

PATHOGENESIS

Concentration, size, shape, and solubility of the different forms of asbestos dictate whether inhalation of the material will cause disease. There are two distinct forms of asbestos: **serpentine,** in which the fiber is curly and flexible, and **amphibole,** in which the fiber is straight, stiff, and brittle. Several subtypes of curly and straight asbestos fibers are recognized. The serpentine **chrysotile** accounts for most of the asbestos used in industry. Amphiboles, even though less prevalent, are more pathogenic than the serpentine chrysotile, but both types can produce asbestosis, lung cancer, and mesothelioma. The greater pathogenicity of straight and stiff amphiboles is apparently related to their structure. The serpentine chrysotiles, with their more flexible, curled structure, are likely to become impacted in the upper respiratory passages and removed by the mucociliary elevator. Those that are trapped in the lungs are gradually leached from the tissues, because they are more soluble than amphiboles. The straight, stiff amphiboles, in contrast, align themselves in the airstream and are hence delivered deeper into the lungs, where they may penetrate epithelial cells to reach the interstitium. Despite these differences, both asbestos forms are fibrogenic, and increasing exposure to either is associated with a higher incidence of all asbestos-related diseases. Asbestosis, like other pneumoconioses, causes fibrosis by a process involving interaction of particulates with lung macrophages.

In addition to cellular and fibrotic lung reactions, asbestos probably also functions as both a tumor initiator and a promoter. Some of the oncogenic effects of asbestos on the mesothelium are mediated by reactive free radicals generated by asbestos fibers, which preferentially localize in the distal lung close to the mesothelial layer. However, potentially toxic chemicals adsorbed onto the asbestos fibers undoubtedly contribute to the pathogenicity of the fibers. For example, **the adsorption of carcinogens in tobacco smoke onto asbestos fibers may well be important to the remarkable synergy between tobacco smoking and the development of lung carcinoma in asbestos workers.**

MORPHOLOGY

Asbestosis is marked by diffuse pulmonary interstitial fibrosis. These changes are indistinguishable from UIP, except for the presence of **asbestos bodies,** which are seen as golden brown, fusiform or beaded rods with a translucent center.

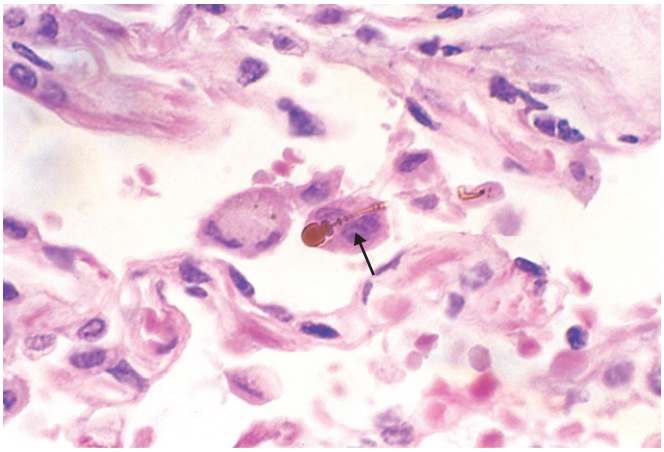

Figure 12–21 High-power detail of an asbestos body, revealing the typical beading and knobbed ends *(arrow)*.

They consist of asbestos fibers coated with an iron-containing proteinaceous material (Fig. 12–21). Asbestos bodies apparently are formed when macrophages attempt to phagocytose asbestos fibers; the iron is derived from phagocyte ferritin. Asbestos bodies sometimes can be found in the lungs of normal persons, but usually in much lower concentrations and without an accompanying interstitial fibrosis.

In contrast with CWP and silicosis, asbestosis begins in the lower lobes and subpleurally, but the middle and upper lobes of the lungs become affected as fibrosis progresses. Contraction of the fibrous tissue distorts the normal architecture, creating enlarged air spaces enclosed within thick fibrous walls. In this way the affected regions become honeycombed. Simultaneously, fibrosis develops in the visceral pleura, causing adhesions between the lungs and the chest wall. The scarring may trap and narrow pulmonary arteries and arterioles, causing pulmonary hypertension and cor pulmonale.

Pleural plaques are the most common manifestation of asbestos exposure and are well-circumscribed plaques of dense collagen (Fig. 12–22), often containing calcium. They develop most frequently on the anterior and posterolateral aspects of the **parietal pleura** and over the domes of the diaphragm. They do not contain asbestos bodies, and only rarely do they occur in persons with no history or evidence of asbestos exposure. Uncommonly, asbestos exposure induces pleural effusion or diffuse pleural fibrosis.

Clinical Features

The clinical findings in asbestosis are indistinguishable from those of any other chronic interstitial lung disease. Typically, progressively worsening dyspnea appears 10 to 20 years after exposure. The dyspnea is usually accompanied by a cough associated with production of sputum. The disease may remain static or progress to congestive heart failure, cor pulmonale, and death. Pleural plaques are usually asymptomatic and are detected on radiographs as circumscribed densities. *Both lung carcinoma and malignant mesothelioma develop in workers exposed to asbestos.* The risk of lung carcinoma is increased about five-fold for asbestos workers; the relative risk for mesothelioma, normally a very rare tumor (2 to 17 cases per 1 million persons), is more than 1000 times greater. Concomitant cigarette

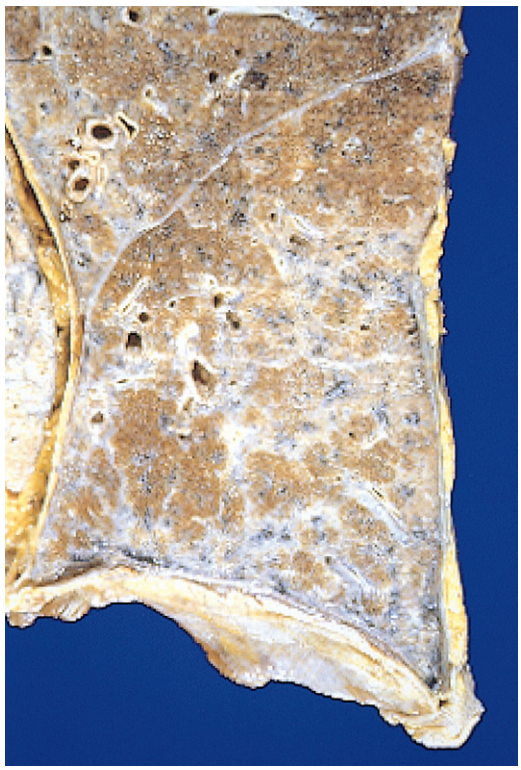

Figure 12–22 Asbestosis. Markedly thickened visceral pleura covers the lateral and diaphragmatic surface of lung. Note also severe interstitial fibrosis diffusely affecting the lower lobe of the lung.

smoking greatly increases the risk of lung carcinoma but not that of mesothelioma. Lung or pleural cancer associated with asbestos exposure carries a particularly grim prognosis.

SUMMARY

Pneumoconioses

- Pneumoconioses encompass a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.
- Pulmonary alveolar macrophages play a central role in the pathogenesis of lung injury by promoting inflammation and producing reactive oxygen species and fibrogenic cytokines.
- Coal dust–induced disease varies from *asymptomatic anthracosis*, to *simple coal worker's pneumoconiosis* (coal macules or nodules, and centrilobular emphysema), to progressive massive fibrosis (PMF), manifested by increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- Silicosis is the most common pneumoconiosis in the world, and crystalline silica (e.g., quartz) is the usual culprit.
- The manifestations of silicosis can range from asymptomatic silicotic nodules to PMF; persons with silicosis also have an increased susceptibility to tuberculosis. The relationship between silica exposure and subsequent lung cancer is controversial.
- Asbestos fibers come in two forms; the stiff *amphiboles* have a greater fibrogenic and carcinogenic potential than the serpentine *chrysotiles*.
- Asbestos exposure is linked with six disease processes: (1) parenchymal interstitial fibrosis (*asbestosis*); (2) localized fibrous plaques or, rarely, diffuse pleural fibrosis; (3) pleural effusions; (4) lung cancer; (5) malignant pleural and peritoneal mesotheliomas; and (6) laryngeal cancer.
- Cigarette smoking increases the risk of lung cancer in the setting of asbestos exposure; moreover, even family members of workers exposed to asbestos are at increased risk for cancer.

Drug- and Radiation-Induced Pulmonary Diseases

Drugs can cause a variety of both acute and chronic alterations in respiratory structure and function. For example, *bleomycin,* an anticancer agent, causes pneumonitis and interstitial fibrosis, as a result of direct toxicity of the drug and by stimulating the influx of inflammatory cells into the alveoli. Similarly, *amiodarone,* an antiarrhythmic agent, also is associated with risk for pneumonitis and fibrosis. *Radiation pneumonitis* is a well-known complication of therapeutic irradiation of pulmonary and other thoracic tumors. *Acute radiation pneumonitis,* which typically occurs 1 to 6 months after therapy in as many as 20% of the patients, is manifested by fever, dyspnea out of proportion to the volume of irradiated lung, pleural effusion, and development of pulmonary infiltrates corresponding to the area of radiation. These signs and symptoms may resolve with corticosteroid therapy or progress to *chronic radiation pneumonitis,* associated with pulmonary fibrosis.

Granulomatous Diseases

Sarcoidosis

Although sarcoidosis is considered here as an example of a restrictive lung disease, it is important to note that sarcoidosis is a *multisystem disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs.* Other diseases, including mycobacterial or fungal infections and berylliosis, sometimes also produce noncaseating granulomas; therefore, the histologic *diagnosis of sarcoidosis is one of exclusion.* Although the multisystem involvement of sarcoidosis can manifest in many clinical guises, bilateral hilar lymphadenopathy or lung involvement (or both), visible on chest radiographs, is the major presenting manifestation in most cases. Eye and skin involvement each occurs in about 25% of cases, and either may occasionally be the presenting feature of the disease.

Epidemiology

Sarcoidosis occurs throughout the world, affecting both genders and all races and age groups. There are, however, certain interesting epidemiologic trends, including:

- There is a consistent predilection for adults younger than 40 years of age.
- A high incidence has been noted in Danish and Swedish populations, and in the United States among African

Americans (in whom the frequency of involvement is 10 times greater than in whites).
- Sarcoidosis is one of the few pulmonary diseases with a higher prevalence among *nonsmokers.*

ETIOLOGY AND PATHOGENESIS

Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed persons exposed to certain environmental agents. The role of each of these contributory influences is summarized in the following discussion.

Several **immunologic abnormalities** in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen. The process is driven by CD4+ helper T cells. These abnormalities include:

- Intra-alveolar and interstitial accumulation of CD4+ T_H1 cells
- Oligoclonal expansion of T cell subsets as determined by analysis of T cell receptor rearrangement
- Increases in T cell–derived T_H1 cytokines such as IL-2 and IFN-γ, resulting in T cell expansion and macrophage activation, respectively
- Increases in several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein-1α) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas
- Anergy to common skin test antigens such as *Candida* or purified protein derivative (PPD), that may result from pulmonary recruitment of CD4+ T cells and consequent peripheral depletion
- Polyclonal hypergammaglobulinemia, another manifestation of T_H cell dysregulation
- The role of genetic factors is suggested by familial and racial clustering of cases and association with certain human leukocyte antigen (HLA) genotypes (e.g., class I HLA-A1 and HLA-B8)

After lung transplantation, sarcoidosis recurs in the new lungs in 75% of patients. Finally, several putative "antigens" have been proposed as the inciting agent for sarcoidosis (e.g., viruses, mycobacteria, *Borrelia,* pollen), but thus far **there is no unequivocal evidence to suggest that sarcoidosis is caused by an infectious agent.**

MORPHOLOGY

The diagnostic histopathologic feature of sarcoidosis is the **noncaseating epithelioid granuloma,** irrespective of the organ involved (Fig. 12–23). This is a discrete, compact collection of epithelioid cells rimmed by an outer zone of largely CD4+ T cells. The epithelioid cells are derived from macrophages and are characterized by abundant eosinophilic cytoplasm and vesicular nuclei. It is not uncommon to see intermixed multinucleate giant cells formed by fusion of macrophages. A thin layer of laminated fibroblasts is present peripheral to the granuloma; over time, these proliferate and lay down collagen that replaces the entire granuloma with a hyalinized scar. Two other microscopic features are sometimes seen in the granulomas: (1) **Schaumann bodies,** laminated concretions composed of calcium and proteins; and (2) **asteroid bodies,** stellate inclusions enclosed within giant cells. Their presence is not required for diagnosis of sarcoidosis—they also may occur in granulomas of other origins. Rarely, foci of central necrosis may be present in sarcoid granulomas, suggesting an infectious process. Caseation necrosis typical of tuberculosis is absent.

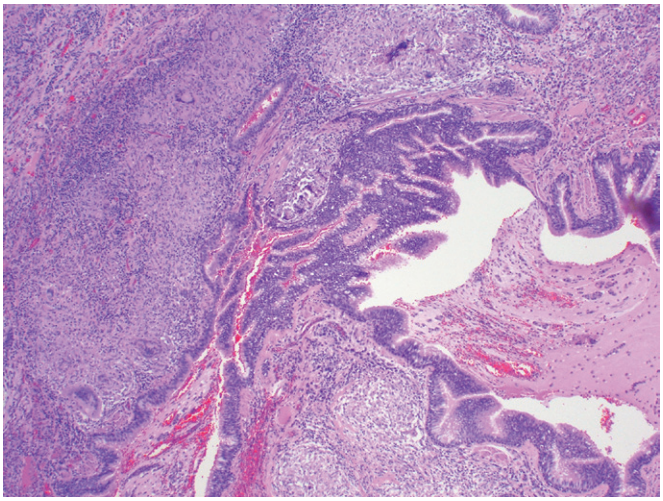

Figure 12–23 Sarcoid. Characteristic peribronchial noncaseating granulomas with many giant cells.

The **lungs** are involved at some stage of the disease in 90% of patients. The granulomas predominantly involve the interstitium rather than air spaces, with some tendency to localize in the connective tissue around bronchioles and pulmonary venules and in the pleura ("lymphangitic" distribution). The bronchoalveolar lavage fluid contains abundant CD4+ T cells. In 5% to 15% of patients, the granulomas eventually are replaced by **diffuse interstitial fibrosis,** resulting in a so-called honeycomb lung.

Intrathoracic **hilar and paratracheal lymph nodes** are enlarged in 75% to 90% of patients, while a third present with peripheral lymphadenopathy. The nodes are characteristically painless and have a firm, rubbery texture. Unlike in tuberculosis, lymph nodes in sarcoidosis are "nonmatted" (nonadherent) and do not ulcerate.

Skin lesions are encountered in approximately 25% of patients. **Erythema nodosum,** the hallmark of acute sarcoidosis, consists of raised, red, tender nodules on the anterior aspects of the legs. Sarcoidal granulomas are uncommon in these lesions. By contrast, discrete painless subcutaneous nodules can also occur in sarcoidosis, and these usually reveal abundant noncaseating granulomas.

Involvement of the eye and lacrimal glands occurs in about one fifth to one half of patients. The ocular involvement takes the form of iritis or iridocyclitis and may be unilateral or bilateral. As a consequence, corneal opacities, glaucoma, and (less commonly) total loss of vision may develop. The posterior uveal tract also is affected, with resultant **choroiditis, retinitis,** and **optic nerve involvement.** These ocular lesions are frequently accompanied by inflammation in the lacrimal glands, with suppression of lacrimation **(sicca syndrome). Unilateral or bilateral parotitis with painful enlargement of the parotid glands**

occurs in less than 10% of patients with sarcoidosis; some go on to develop xerostomia (dry mouth). Combined uveoparotid involvement is designated **Mikulicz syndrome.**

The spleen may appear unaffected grossly, but in about three fourths of cases, it contains granulomas. In approximately 10%, it becomes clinically enlarged. **The liver** demonstrates microscopic granulomatous lesions, usually in the portal triads, about as often as the spleen, but only about one third of the patients demonstrate hepatomegaly or abnormal liver function. Sarcoid involvement of **bone marrow** is reported in as many as 40% of patients, although it rarely causes severe manifestations. Other findings may include hypercalcemia and hypercalciuria. These changes are not related to bone destruction but rather are caused by increased calcium absorption secondary to production of active vitamin D by the mononuclear phagocytes in the granulomas.

Clinical Features

In many affected persons the disease is entirely asymptomatic, discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy. In others, peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly may be presenting manifestations. In about two thirds of symptomatic cases, there is gradual appearance of respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort) or constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats). Because of the variable and nondiagnostic clinical features, resort is frequently made to lung or lymph node biopsies. *The presence of noncaseating granulomas is suggestive of sarcoidosis, but other identifiable causes of granulomatous inflammation must be excluded.*

Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions. The remissions may be spontaneous or initiated by steroid therapy and often are permanent. Overall, 65% to 70% of affected persons recover with minimal or no residual manifestations. Another 20% develop permanent lung dysfunction or visual impairment. Of the remaining 10% to 15%, most succumb to progressive pulmonary fibrosis and cor pulmonale.

SUMMARY

Sarcoidosis

- Sarcoidosis is a multisystem disease of unknown etiology; the diagnostic histopathologic feature is the presence of noncaseating granulomas in various tissues.
- Immunologic abnormalities include high levels of CD4+ T cells in the lung that secrete T_H1-dependent cytokines such as IFN-γ and IL-2 locally.
- Clinical manifestations include lymph node enlargement, eye involvement (sicca syndrome [dry eyes], iritis, or iridocyclitis), skin lesions (erythema nodosum, painless subcutaneous nodules), and visceral (liver, skin, marrow) involvement. Lung involvement occurs in 90% of cases, with formation of granulomas and interstitial fibrosis.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an immunologically mediated inflammatory lung disease that primarily affects the alveoli and is therefore often called *allergic alveolitis.* Most often it is an occupational disease that results from heightened sensitivity to inhaled antigens such as in moldy hay (Table 12–5). Unlike bronchial asthma, in which *bronchi are the focus of immunologically mediated injury, the damage in hypersensitivity pneumonitis occurs at the level of alveoli.* Hence, it manifests as a predominantly restrictive lung disease with decreased diffusion capacity, lung compliance, and total lung volume. The occupational exposures are diverse, but the syndromes share common clinical and pathologic findings and probably have a very similar pathophysiologic basis.

Several lines of evidence suggest that hypersensitivity pneumonitis is an immunologically mediated disease:

- Bronchoalveolar lavage specimens consistently demonstrate increased numbers of T lymphocytes of both CD4+ and CD8+ phenotype.

Table 12–5 Selected Causes of Hypersensitivity Pneumonitis

Syndrome	Exposure	Antigens
Fungal and Bacterial Antigens		
Farmer's lung	Moldy hay	*Micropolyspora faeni*
Bagassosis	Moldy pressed sugar cane (bagasse)	Thermophilic actinomycetes
Maple bark disease	Moldy maple bark	*Cryptostroma corticale*
Humidifier lung	Cool-mist humidifier	Thermophilic actinomycetes, *Aureobasidium pullulans*
Malt worker's lung	Moldy barley	*Aspergillus clavatus*
Cheese washer's lung	Moldy cheese	*Penicillium casei*
Insect Products		
Miller's lung	Dust-contaminated grain	*Sitophilus granarius* (wheat weevil)
Animal Products		
Pigeon breeder's lung	Pigeon droppings	Pigeon serum proteins in droppings
Chemicals		
Chemical worker's lung	Chemical industry	Trimellitic anhydride, isocyanates

- Most patients with hypersensitivity pneumonitis have specific precipitating antibodies in their serum, and complement and immunoglobulins have been demonstrated within vessel walls by immunofluorescence, indicating type III hypersensitivity. The presence of noncaseating granulomas in two thirds of patients with this disorder suggests a role for type IV hypersensitivity as well.

In summary, hypersensitivity pneumonitis is an immunologically mediated response to an extrinsic antigen that involves both immune complex and delayed-type hypersensitivity reactions.

MORPHOLOGY

The histopathologic picture in both acute and chronic forms of hypersensitivity pneumonitis includes patchy mononuclear cell infiltrates in the pulmonary interstitium, with a characteristic peribronchiolar accentuation. Lymphocytes predominate, but plasma cells and epithelioid cells also are present. In acute forms of the disease, variable numbers of neutrophils may also be seen. **Interstitial noncaseating granulomas** are present in more than two thirds of cases, usually in a peribronchiolar location (Fig. 12–24). In advanced chronic cases, diffuse interstitial fibrosis occurs.

Clinical Features

Hypersensitivity pneumonitis may manifest either as an *acute reaction,* with fever, cough, dyspnea, and constitutional signs and symptoms arising 4 to 8 hours after exposure, or as a *chronic disease* characterized by insidious onset of cough, dyspnea, malaise, and weight loss. With the acute form of this disease, the diagnosis is usually obvious because of the temporal relationship of symptom onset to exposure to the incriminating antigen. *If antigenic exposure is terminated after acute attacks of the disease,* complete resolution of pulmonary symptoms occurs within days. Failure to remove the inciting agent from the environment eventually results in an irreversible chronic interstitial pulmonary disease.

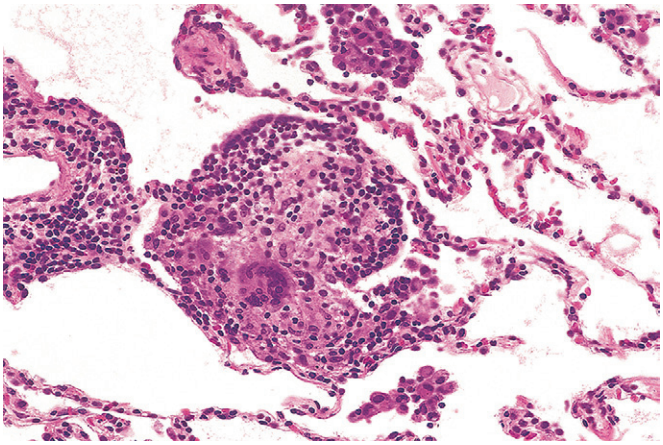

Figure 12–24 Hypersensitivity pneumonitis, histologic appearance. Loosely formed interstitial granulomas and chronic inflammation are characteristic.

Pulmonary Eosinophilia

A number of clinical and pathologic pulmonary entities are characterized by an infiltration and activation of eosinophils, the latter by elevated levels of alveolar IL-5. These diverse diseases generally are of immunologic origin, but the etiology is not understood. Pulmonary eosinophilia is divided into the following categories:

- *Acute eosinophilic pneumonia with respiratory failure,* characterized by rapid onset of fever, dyspnea, hypoxia, and diffuse pulmonary infiltrates on chest radiographs. The bronchoalveolar lavage fluid typically contains more than 25% eosinophils. There is prompt response to corticosteroids.
- *Simple pulmonary eosinophilia* (Loeffler syndrome), characterized by transient pulmonary lesions, eosinophilia in the blood, and a benign clinical course. The alveolar septa are thickened by an infiltrate containing eosinophils and occasional giant cells.
- *Tropical eosinophilia,* caused by infection with microfilariae and helminthic parasites
- *Secondary eosinophilia,* seen, for example, in association with asthma, drug allergies, and certain forms of vasculitis
- *Idiopathic chronic eosinophilic pneumonia,* characterized by aggregates of lymphocytes and eosinophils within the septal walls and the alveolar spaces, typically in the periphery of the lung fields, and accompanied by high fever, night sweats, and dyspnea. This is a disease of exclusion, once other causes of pulmonary eosinophilia have been ruled out.

Smoking-Related Interstitial Diseases

The role of cigarette smoking in causing obstructive pulmonary disease (emphysema and chronic bronchitis) has been discussed. Smoking also is associated with restrictive or interstitial lung diseases. *Desquamative interstitial pneumonia* (DIP) and *respiratory bronchiolitis* are the two related examples of smoking-associated interstitial lung disease. The most striking histologic feature of DIP is the accumulation of large numbers of macrophages with abundant cytoplasm containing dusty-brown pigment (*smoker's macrophages*) in the air spaces (Fig. 12–25). The alveolar septa are thickened by a sparse inflammatory infiltrate (usually lymphocytes), and interstitial fibrosis, when present, is mild. Pulmonary functions usually show a mild restrictive abnormality, and patients with DIP typically have a good prognosis with excellent response to steroid therapy and smoking cessation. Respiratory bronchiolitis is a common histologic lesion found in smokers, characterized by the presence of pigmented intraluminal macrophages akin to those in DIP, but in a "bronchiolocentric" distribution (first- and second-order respiratory bronchioles). Mild peribronchiolar fibrosis also is seen. As with DIP, affected patients present with gradual onset of dyspnea and dry cough, and the symptoms recede with cessation of smoking.

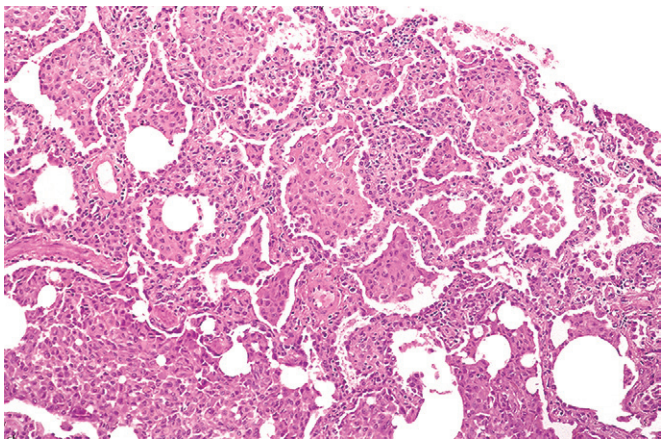

Figure 12–25 Desquamative interstitial pneumonia. There is accumulation of large numbers of macrophages within the alveolar spaces with only slight fibrous thickening of the alveolar walls.

PULMONARY DISEASES OF VASCULAR ORIGIN

Pulmonary Embolism, Hemorrhage, and Infarction

Blood clots that occlude the large pulmonary arteries are almost always embolic in origin. More than 95% of all pulmonary emboli arise from thrombi within the large deep veins of the lower legs, typically originating in the popliteal vein and larger veins above it. Thromboembolism causes approximately 50,000 deaths per year in the United States. Even when not directly fatal, it can complicate the course of other diseases. The true incidence of nonfatal pulmonary embolism is not known. Some cases of embolism undoubtedly occur outside the hospital in ambulatory patients, in whom the emboli are small and clinically silent. Even among hospitalized patients, no more than one third are diagnosed before death. Autopsy data on the incidence of pulmonary embolism vary widely, ranging from 1% in the general hospitalized population, to 30% in persons dying after severe burns, trauma, or fractures.

The influences that predispose the patient to venous thrombosis in the legs are discussed in Chapter 3, but the following risk factors are paramount: (1) prolonged bedrest (particularly with immobilization of the legs); (2) surgery, especially orthopedic surgery, of knee and hip; (3) severe trauma (including burns or multiple fractures); (4) congestive heart failure; (5) in women, the period around parturition or oral contraception using birth control pills with high estrogen content; (6) disseminated cancer; and (7) primary disorders of hypercoagulability (e.g., factor V Leiden) (Chapter 3).

The pathophysiologic consequences of thromboembolism in the lung depend largely on the size of the embolus, which in turn dictates the size of the occluded pulmonary artery, and on the cardiopulmonary status of the patient. There are two important consequences of embolic pulmonary arterial occlusion: (1) an increase in pulmonary artery pressure from blockage of flow and, possibly, vasospasm caused by neurogenic mechanisms and/or release of mediators (e.g., thromboxane A_2, serotonin); and (2) ischemia of the downstream pulmonary parenchyma. Thus, occlusion of a *major vessel* results in a sudden increase in pulmonary artery pressure, diminished cardiac output, right-sided heart failure (*acute cor pulmonale*), or even death. Usually hypoxemia also develops, as a result of multiple mechanisms:

- *Perfusion of lung zones that have become atelectatic.* The alveolar collapse occurs in the ischemic areas because of a reduction in surfactant production and because pain associated with embolism leads to reduced movement of the chest wall; in addition, some of the pulmonary blood flow is redirected through areas of the lung that normally are hypoventilated.
- The decrease in cardiac output causes a *widening of the difference in arterial-venous oxygen saturation.*
- *Right-to-left shunting* of blood may occur through a patent foramen ovale, present in 30% of normal persons.
- If *smaller vessels* are occluded, the result is less catastrophic, and the event may even be clinically silent.

Recall that the lungs are oxygenated not only by the pulmonary arteries but also by bronchial arteries and directly from air in the alveoli. Thus, ischemic necrosis (infarction) is the exception rather than the rule, occurring in as few as 10% of patients with thromboemboli. It occurs only if there is compromise in cardiac function or bronchial circulation, or if the region of the lung at risk is underventilated as a result of underlying pulmonary disease.

MORPHOLOGY

The morphologic consequences of pulmonary embolism, as noted, depend on the size of the embolic mass and the general state of the circulation. A large embolus may embed in the main pulmonary artery or its major branches or lodge astride the bifurcation as a **saddle embolus** (Fig. 12–26). Death usually follows so suddenly from hypoxia or acute failure of the right side of the heart (acute cor pulmonale) that there is no time for morphologic alterations in the lung. Smaller emboli become impacted in medium-sized and small pulmonary arteries. With adequate circulation and bronchial arterial flow, the vitality of the lung parenchyma is maintained, but alveolar hemorrhage may occur as a result of ischemic damage to the endothelial cells.

With compromised cardiovascular status, as may occur with congestive heart failure, **infarction** results. The more peripheral the embolic occlusion, the higher the risk of infarction. About three fourths of all infarcts affect the lower lobes, and more than half are multiple. Characteristically, they are wedge-shaped, with their base at the pleural surface and the apex pointing toward the hilus of the lung. Pulmonary infarcts typically are hemorrhagic and appear as raised, red-blue areas in the early stages (Fig. 12–27). The adjacent pleural surface often is covered by a fibrinous exudate. If the occluded vessel can be identified, it usually is found near the apex of the infarcted area. The red cells begin to lyse within 48 hours, and the infarct pales, eventually becoming red-brown as hemosiderin is produced. In time, fibrous replacement begins at the margins as a gray-white peripheral zone and eventually converts the infarct into a scar. On histologic examination, the hallmark of fresh infarcts is coagulative necrosis of the lung parenchyma and hemorrhage.

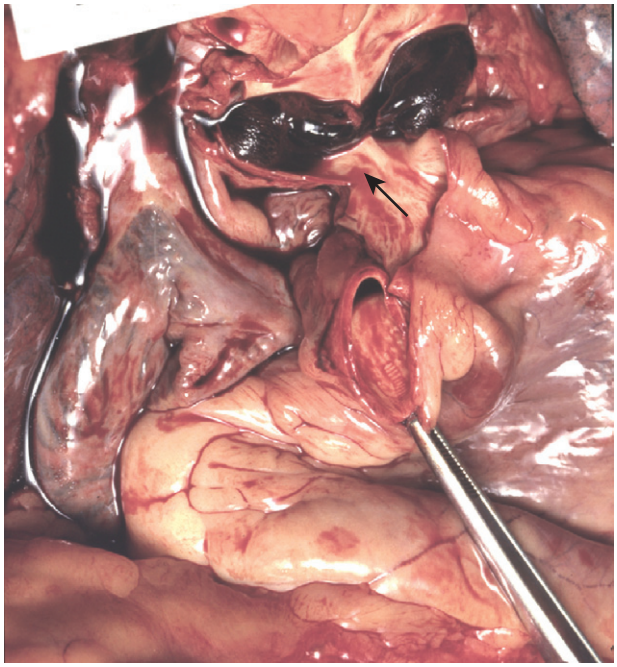

Figure 12–26 Large saddle embolus from the femoral vein lying astride the main left and right pulmonary arteries.
(Courtesy of Dr. Linda Margraf, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Clinical Features

The clinical consequences of pulmonary thromboembolism are summarized as follows:

- Most pulmonary emboli (60% to 80%) are clinically silent because they are small; the embolic mass is rapidly removed by fibrinolytic activity, and the bronchial circulation sustains the viability of the affected lung parenchyma until this is accomplished.
- In 5% of cases, sudden death, acute right-sided heart failure (acute cor pulmonale), or cardiovascular collapse (shock) may occur typically when more than 60% of the total pulmonary vasculature is obstructed by a large embolus or multiple simultaneous small emboli. Massive pulmonary embolism is one of the few causes of literally instantaneous death, even before the person experiences chest pain or dyspnea.
- Obstruction of relatively small to medium pulmonary branches (10% to 15% of cases) that behave as end arteries causes pulmonary infarction when some element of circulatory insufficiency is present. Typically, persons who sustain such infarction manifest dyspnea.
- In a small but significant subset of patients (accounting for less than 3% of cases), recurrent multiple emboli lead to pulmonary hypertension, chronic right-sided heart strain (chronic cor pulmonale), and, in time, pulmonary vascular sclerosis with progressively worsening dyspnea.

Emboli usually resolve after the initial acute event. They contract, and endogenous fibrinolytic activity may cause total lysis of the thrombus. However, in the presence of an underlying predisposing factor, a small, innocuous embolus may presage a larger one, and *patients who have experienced one pulmonary embolism have a 30% chance of developing a second.* Prophylactic therapy may include anticoagulation, early ambulation for postoperative and postparturient patients, application of elastic stockings, intermittent pneumatic calf compression, and isometric leg exercises for bedridden patients. Patients with pulmonary embolism are given anticoagulation therapy. Patients with massive pulmonary embolism are candidates for thrombolytic therapy.

Nonthrombotic forms of pulmonary embolism include several uncommon but potentially lethal forms, such as air, fat, and amniotic fluid embolism (Chapter 3). Intravenous drug abuse often is associated with foreign body embolism in the pulmonary microvasculature; the presence of magnesium trisilicate (talc) in the intravenous mixture elicits a granulomatous response within the interstitium or pulmonary arteries. Involvement of the interstitium may lead to fibrosis, while the latter leads to pulmonary hypertension. Residual talc crystals can be demonstrated within the granulomas using polarized light. Bone marrow embolism (presence of hematopoietic and fat elements within pulmonary circulation) can occur after massive trauma and in patients with bone infarction secondary to sickle cell anemia.

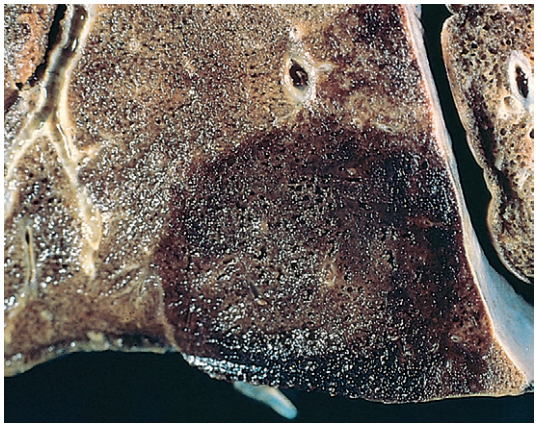

Figure 12–27 A small, roughly wedge-shaped hemorrhagic pulmonary infarct of recent occurrence.

SUMMARY

Pulmonary Embolism

- Almost all large pulmonary artery thrombi are embolic in origin, usually arising from the deep veins of the lower leg.
- Risk factors include prolonged bedrest, leg surgery, severe trauma, CHF, use of oral contraceptives (especially those with high estrogen content), disseminated cancer, and genetic causes of hypercoagulability.
- The vast majority (60% to 80%) of emboli are clinically silent, a minority (5%) cause acute cor pulmonale, shock, or death (typically from large "saddle emboli"), and the remaining cause pulmonary infarction.
- Risk of recurrence is high.

Pulmonary Hypertension

The pulmonary circulation normally is one of low resistance; pulmonary blood pressures are only about one eighth of systemic pressures. Pulmonary hypertension (when mean pulmonary pressures reach one fourth or more of systemic levels) is most often *secondary* to a decrease in the cross-sectional area of the pulmonary vascular bed, or to increased pulmonary vascular blood flow. The causes of secondary pulmonary hypertension include:

- *Chronic obstructive or interstitial lung disease,* which is accompanied by destruction of lung parenchyma and consequent reduction in alveolar capillaries. This causes increased pulmonary arterial resistance and secondarily, elevated arterial pressure.
- *Recurrent pulmonary emboli.* Presence of these emboli leads to a reduction in the functional cross-sectional area of the pulmonary vascular bed, leading in turn to increased vascular resistance.
- *Antecedent heart disease,* for example, *mitral stenosis,* which increases left atrial pressure, leading to higher pulmonary venous pressures, and ultimately pulmonary arterial hypertension. *Congenital left-to-right shunts* are another cause of secondary pulmonary hypertension.

Uncommonly, pulmonary hypertension exists even though all known causes of increased pulmonary pressure have been excluded; this is referred to as *primary,* or *idiopathic, pulmonary arterial hypertension.* Of these, the vast majority of cases are sporadic, and only 6% are familial with an autosomal dominant mode of inheritance.

PATHOGENESIS

According to current thinking, **pulmonary endothelial cell and/or vascular smooth muscle dysfunction** is the probable underlying basis for most forms of pulmonary hypertension.

- In states of **secondary pulmonary hypertension,** endothelial cell dysfunction arises as a consequence of the underlying disorder (e.g., shear and mechanical injury due to increased blood flow in left-to-right shunts, or biochemical injury produced by fibrin in recurrent thromboembolism). Endothelial cell dysfunction reduces production of vasodilatory agents (e.g., nitric oxide, prostacyclin) while increasing synthesis of vasoconstrictive mediators like endothelin. In addition, there is production of growth factors and cytokines that induce the migration and replication of vascular smooth muscle and elaboration of extracellular matrix.
- In **primary pulmonary hypertension,** especially in the uncommon **familial form,** the TGF-β signaling pathway has emerged as a key mediator of endothelial and smooth muscle dysfunction. Specifically, germline mutations of **bone morphogenetic protein receptor type 2** (BMPR-2), a cell surface molecule that binds to a variety of TGF-β pathway ligands, have been demonstrated in 50% of familial cases. The *BMPR2* gene product is inhibitory in its effects on proliferation; hence, loss-of-function mutations of this gene result in abnormal vascular endothelial and pulmonary smooth muscle proliferation. The endothelial proliferations in these instances usually are **monoclonal,** reiterating the genetic basis of their origin. However, not all persons with germline mutations of *BMPR2* develop primary pulmonary hypertension, suggesting the existence of **modifier genes** that probably affect penetrance of this particular phenotype.
- Studies on sporadic forms of primary pulmonary hypertension point to a possible role for the **serotonin transporter gene** (*5HTT*). Specifically, pulmonary smooth muscle cells from some patients with primary pulmonary hypertension demonstrate increased proliferation on exposure to serotonin or serum. Genetic polymorphisms of *5HTT* that lead to enhanced expression of the transporter protein on vascular smooth muscle are postulated to cause their proliferation.

MORPHOLOGY

Vascular alterations in all forms of pulmonary hypertension (primary and secondary) involve the entire arterial tree (Fig. 12–28) and include (1) in the **main elastic arteries,** atheromas similar to those in systemic atherosclerosis; (2) **in medium-sized muscular arteries,** proliferation of myointimal cells and smooth muscle cells, causing thickening of the intima and media with narrowing of the lumina; and (3) in **smaller arteries and arterioles,** thickening, medial hypertrophy, and reduplication of the internal and external elastic membranes. In these vessels, the wall thickness may exceed the diameter of the lumen, which is sometimes narrowed to the point of near-obliteration. Persons with idiopathic pulmonary arterial hypertension have characteristic **plexiform lesions,** in which endothelial proliferation forms multiple lumina within small arteries where they branch from a medium-sized artery.

Clinical Features

Secondary pulmonary hypertension may develop at any age. The clinical features reflect the underlying disease, usually pulmonary or cardiac, with accentuation of respiratory insufficiency and right-sided heart strain. Primary pulmonary hypertension, on the other hand, is almost always encountered in young adults, more commonly women, and is marked by fatigue, syncope (particularly on exercise), dyspnea on exertion, and sometimes chest pain. Eventually severe respiratory insufficiency and cyanosis develop, and death usually results from right-sided heart failure (decompensated cor pulmonale) within 2 to 5 years of diagnosis. Some amelioration of the respiratory distress can be achieved by vasodilators and antithrombotic agents, and continuous prostacyclin infusions may prolong life (months to years), but without lung transplantation the prognosis is still grim.

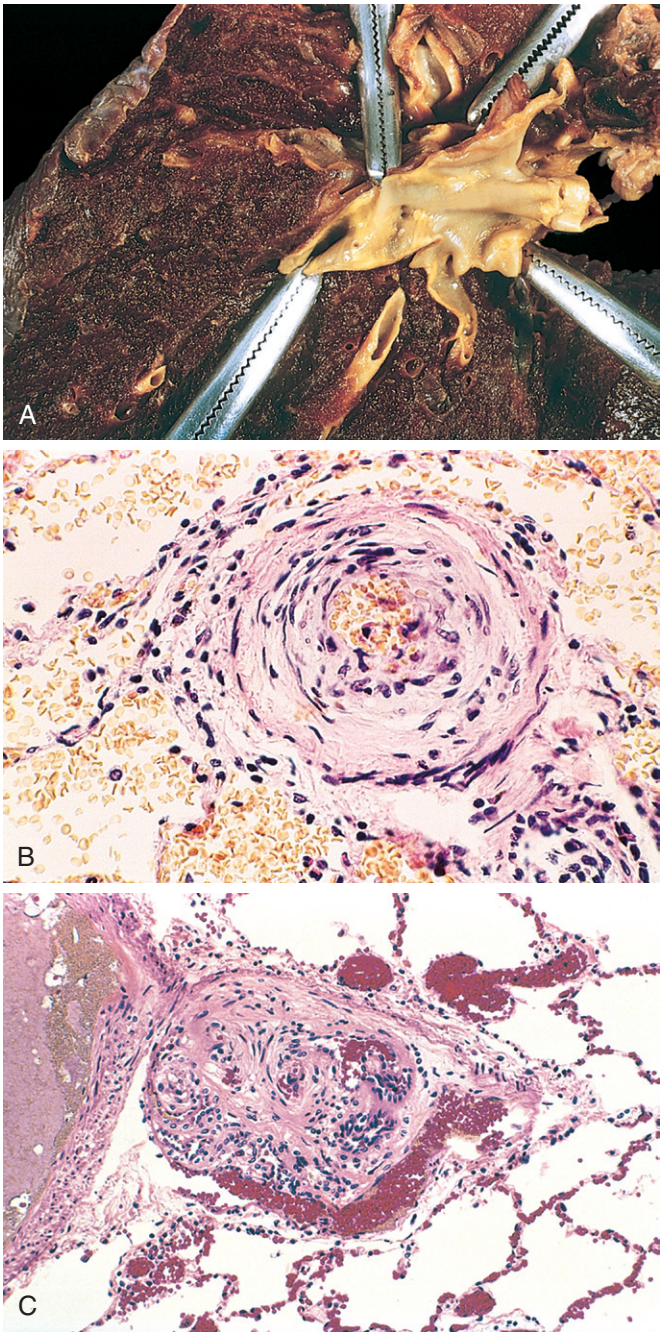

Figure 12–28 Vascular changes in pulmonary hypertension. **A,** Gross photograph of atheroma, a finding usually limited to large vessels. **B,** Marked medial hypertrophy. **C,** Plexiform lesion characteristic of advanced pulmonary hypertension seen in small arteries.

Diffuse Alveolar Hemorrhage Syndromes

While there may be several "secondary" causes of pulmonary hemorrhage (necrotizing bacterial pneumonia, passive venous congestion, bleeding diathesis), the diffuse alveolar hemorrhage syndromes constitute a group of "primary" immune-mediated diseases that manifest as the *triad of hemoptysis, anemia, and diffuse pulmonary infiltrates.*

Goodpasture Syndrome

Goodpasture syndrome, the prototype disorder of this group, is an uncommon but intriguing condition characterized by a *proliferative, usually rapidly progressive, glomerulonephritis* (Chapter 13) and *hemorrhagic interstitial pneumonitis.* Both the renal and the pulmonary lesions are caused by antibodies targeted against the noncollagenous domain of the α3 chain of collagen IV. These antibodies can be detected in the serum of more than 90% of persons with Goodpasture syndrome.

MORPHOLOGY

The lungs are heavy, with areas of red-brown consolidation, due to **diffuse alveolar hemorrhage.** Microscopic examination demonstrates focal necrosis of alveolar walls associated with intra-alveolar hemorrhages, fibrous thickening of the septa, and hypertrophic type II pneumocytes. Presence of **hemosiderin,** both within macrophages and extracellularly, is characteristic, indicating earlier episode(s) of hemorrhage (Fig. 12–29). The characteristic **linear pattern of immunoglobulin deposition** (usually IgG, sometimes IgA or IgM) that is the hallmark diagnostic finding in renal biopsy specimens (Chapter 13) also may be seen along the alveolar septa.

Plasmapheresis and immunosuppressive therapy have markedly improved the once-dismal prognosis for this disease. Plasma exchange removes offending antibodies, and immunosuppressive drugs inhibit antibody production. With severe renal disease, renal transplantation is eventually required.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis is a rare disease of uncertain etiology that has pulmonary manifestations and histologic features similar to those of Goodpasture syndrome, but there is no associated renal disease or circulating anti-basement membrane antibody. Most cases occur in children, although the disease is reported in adults as well, who have a better prognosis. With steroid and immunosuppressive therapy, survival has markedly improved from the historical 2.5 years; thus, an immune-mediated etiology is postulated.

Pulmonary Angiitis and Granulomatosis (Wegener Granulomatosis)

More than 80% of patients with Wegener granulomatosis (WG) develop upper respiratory or pulmonary manifestations at some time in the course of their disease. It is described in Chapter 9. Here we list the salient pulmonary features. The lung lesions are characterized by a combination of necrotizing vasculitis ("angiitis") and parenchymal necrotizing granulomatous inflammation. The manifestations of WG can include both upper respiratory symptoms (chronic sinusitis, epistaxis, nasal perforation) and pulmonary signs and symptoms (cough, hemoptysis, chest pain). PR3-ANCAs are present in close to 95% of cases (Chapter 9).

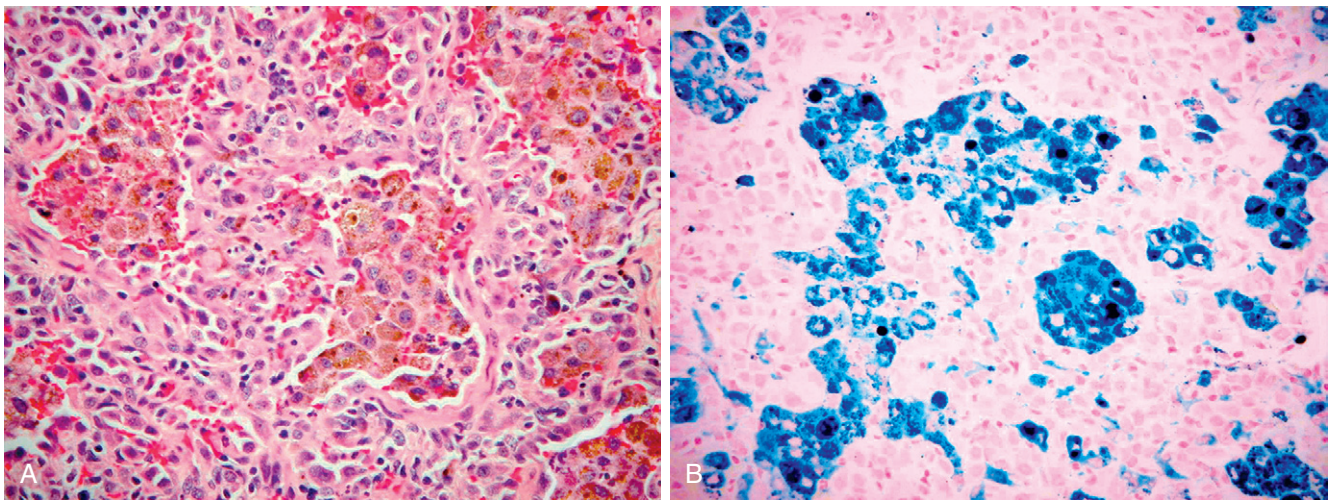

Figure 12–29 A, Lung biopsy specimen from a person with a diffuse alveolar hemorrhage syndrome demonstrates large numbers of intra-alveolar hemosiderin-laden macrophages on a background of thickened fibrous septa. **B,** The tissue has been stained with Prussian blue, an iron stain that highlights the abundant intracellular hemosiderin.

(From the Teaching Collection of the Department of Pathology, Children's Medical Center, Dallas, Texas.)

PULMONARY INFECTIONS

Pulmonary infections in the form of pneumonia are responsible for one sixth of all deaths in the United States. This is not surprising because (1) the epithelial surfaces of the lung are constantly exposed to many liters of air containing various levels of microbial contaminants; (2) nasopharyngeal flora are regularly aspirated during sleep, even by healthy persons; and (3) other common lung diseases render the lung parenchyma vulnerable to virulent organisms. The normal lung parenchyma remains sterile because of the efficiency of a number of immune and nonimmune defense mechanisms in the respiratory system, extending from the nasopharynx all the way into the alveolar air spaces (Fig. 12–30).

Despite the multitude of defense mechanisms, "chinks in the armor" do exist, predisposing even healthy persons to infections. Defects in innate immunity (including neutrophil and complement defects) and humoral immunodeficiency typically lead to an increased incidence of infections with pyogenic bacteria. For example, it has been shown that patients with mutations in MyD88, the adaptor protein downstream of many Toll-like receptors (microbial sensors in innate immunity), are extremely susceptible to severe necrotizing pneumococcal infections (and not most other infections). On the other hand, defects in T_H1 cell–mediated immunity lead mainly to increased infections with intracellular microbes such as atypical mycobacteria. In addition to inherited anomalies, several aspects of lifestyle interfere with host immune defense mechanisms and facilitate infections. For example, cigarette smoke compromises mucociliary clearance and pulmonary macrophage activity, and alcohol not only impairs cough and epiglottic reflexes, thereby increasing the risk of aspiration, but also interferes with neutrophil mobilization and chemotaxis.

Pneumonia can be very broadly defined as any infection in the lung. The clinical presentation may be as an acute, fulminant clinical disease or as a chronic disease with a more protracted course. The histologic spectrum of pneumonia may range from a fibrinopurulent alveolar exudate seen in acute bacterial pneumonias, to mononuclear interstitial infiltrates in viral and other atypical pneumonias, to granulomas and cavitation seen in many of the chronic pneumonias. Acute bacterial pneumonias can manifest as one of two anatomic and radiographic patterns, referred to as *bronchopneumonia* and *lobar pneumonia*. Bronchopneumonia implies a patchy distribution of inflammation that generally involves more than one lobe (Fig. 12–31). This pattern results from an initial infection of the bronchi and bronchioles with extension into the adjacent alveoli. By contrast, in lobar pneumonia the contiguous air spaces of part or all of a lobe are homogeneously filled with an exudate that can be visualized on radiographs as a lobar or segmental consolidation (Fig. 12–31). *Streptococcus pneumoniae* is responsible for more than 90% of lobar pneumonias. The anatomic distinction between lobar pneumonia and bronchopneumonia can often become blurry, because (1) many organisms cause infections that can manifest with either of the two patterns of distribution, and (2) confluent bronchopneumonia can be hard to distinguish radiologically from lobar pneumonia. *Therefore, it is best to classify pneumonias either by the specific etiologic agent or, if no pathogen can be isolated, by the clinical setting in which infection occurs.* The latter approach considerably narrows the list of suspected pathogens for administering empirical antimicrobial therapy. Pneumonia can arise in seven distinct clinical settings, and the implicated pathogens are reasonably specific to each category, as summarized in Table 12–6.

Community-Acquired Acute Pneumonias

Most community-acquired acute pneumonias are bacterial in origin. Not uncommonly, the infection follows a viral upper respiratory tract infection. The onset usually is abrupt, with high fever, shaking chills, pleuritic chest pain,

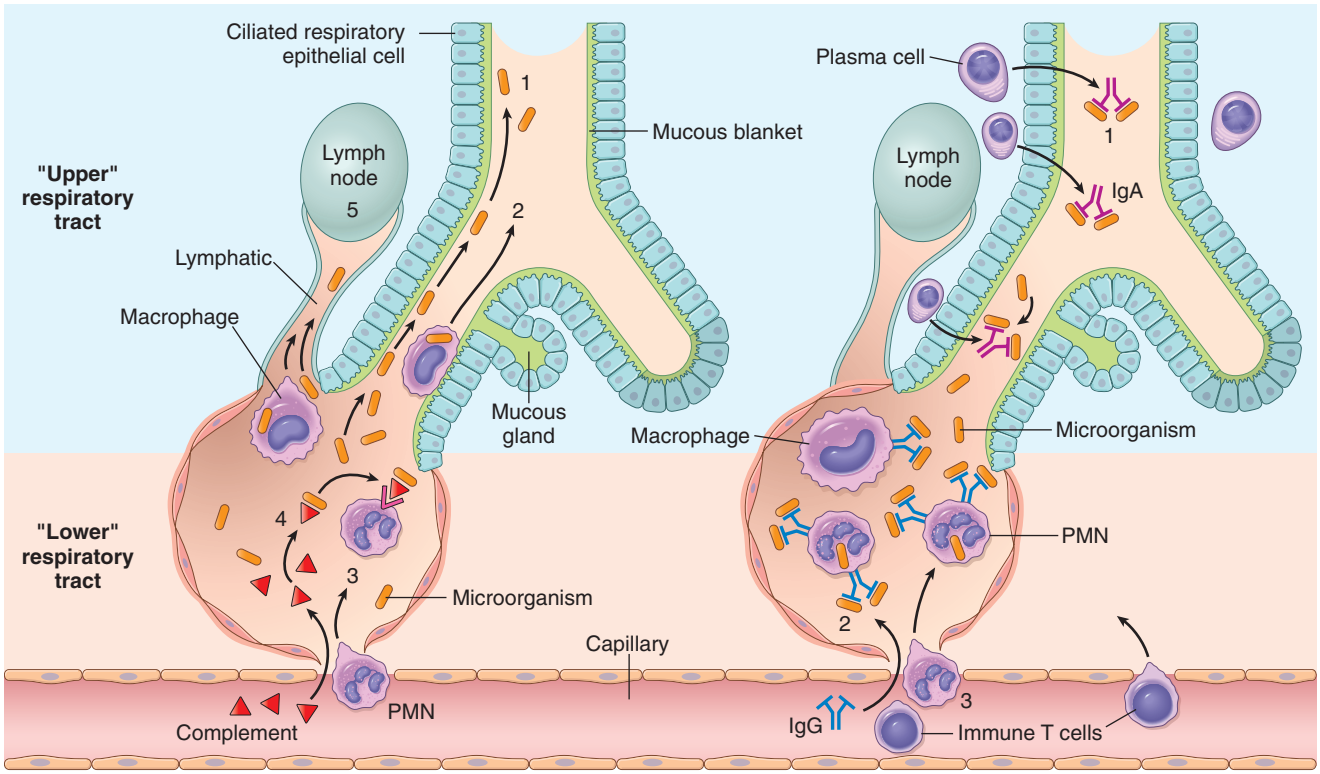

Figure 12–30 Lung defense mechanisms. **A,** Innate defenses against infection: *1*, In the normal lung, removal of microbial organisms depends on entrapment in the mucous blanket and removal by means of the mucociliary elevator; *2*, phagocytosis by alveolar macrophages that can kill and degrade organisms and remove them from the air spaces by migrating onto the mucociliary elevator; or *3*, phagocytosis and killing by neutrophils recruited by macrophage factors. *4*, Serum complement may enter the alveoli and be activated by the alternative pathway to provide the opsonin C3b, which enhances phagocytosis. *5*, Organisms, including those ingested by phagocytes, may reach the draining lymph nodes to initiate immune responses. **B,** Additional mechanisms operate after development of adaptive immunity. *1*, Secreted IgA can block attachment of the microorganism to epithelium in the upper respiratory tract. *2*, In the lower respiratory tract, serum antibodies (IgM, IgG) are present in the alveolar lining fluid. They activate complement more efficiently by the classic pathway, yielding C3b *(not shown)*. In addition, IgG is opsonic. *3*, The accumulation of immune T cells is important for controlling infections by viruses and other intracellular microorganisms. PMN, polymorphonuclear cell.

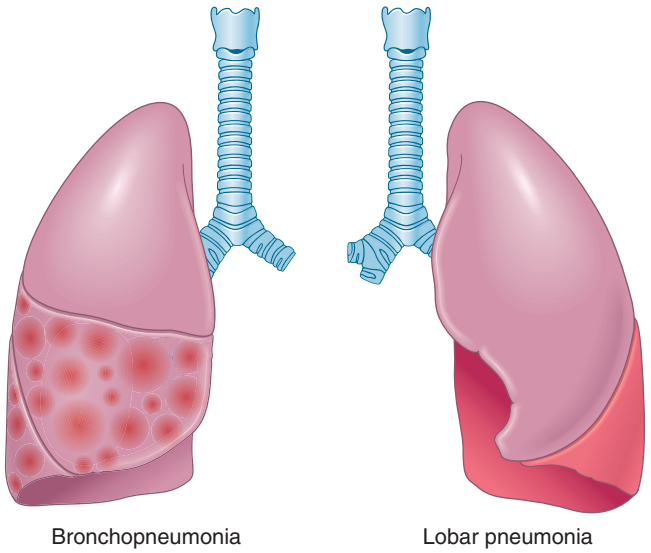

Figure 12–31 The anatomic distribution of bronchopneumonia and lobar pneumonia.

and a productive mucopurulent cough; occasional patients may have hemoptysis. *S. pneumoniae* (i.e., the pneumococcus) is the most common cause of community-acquired acute pneumonia; hence, pneumococcal pneumonia is discussed as the prototype for this subgroup.

Streptococcus pneumoniae *Infections*

Pneumococcal infections occur with increased frequency in three subsets of patients: (1) those with underlying chronic diseases such as CHF, COPD, or diabetes; (2) those with either congenital or acquired immunoglobulin defects (e.g., with the acquired immune deficiency syndrome [AIDS]); and (3) those with decreased or absent splenic function (e.g., sickle cell disease or after splenectomy). In the last group, such infections are more likely because the spleen contains the largest collection of phagocytes and is therefore the major organ responsible for removing pneumococci from the blood. The spleen is also an important organ for production of antibodies against polysaccharides, which are the dominant protective antibodies against encapsulated bacteria.

Table 12–6 The Pneumonia Syndromes and Implicated Pathogens

Community-Acquired Acute Pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Legionella pneumophila
Enterobacteriaceae *(Klebsiella pneumoniae)* and Pseudomonas spp.
Community-Acquired Atypical Pneumonia
Mycoplasma pneumoniae
Chlamydia spp.—Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia trachomatis
Coxiella burnetii (Q fever)
Viruses: respiratory syncytial virus, human metapneumovirus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits)
Nosocomial Pneumonia
Gram-negative rods belonging to Enterobacteriaceae (*Klebsiella* spp., *Serratia marcescens, Escherichia coli*) and *Pseudomonas* spp.
S. aureus (usually methicillin-resistant)
Aspiration Pneumonia
Anaerobic oral flora (*Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus*), admixed with aerobic bacteria (*S. pneumoniae, S. aureus, H. influenzae,* and *Pseudomonas aeruginosa*)
Chronic Pneumonia
Nocardia
Actinomyces
Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis*
Necrotizing Pneumonia and Lung Abscess
Anaerobic bacteria (extremely common), with or without mixed aerobic infection
S. aureus, K. pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)
Pneumonia in the Immunocompromised Host
Cytomegalovirus
Pneumocystis jiroveci
Mycobacterium avium complex (MAC)
Invasive aspergillosis
Invasive candidiasis
"Usual" bacterial, viral, and fungal organisms (listed above)

MORPHOLOGY

With pneumococcal lung infection, either pattern of pneumonia, lobar or bronchopneumonia, may occur; the latter is much more prevalent at the extremes of age. Regardless of the distribution of the pneumonia, because pneumococcal lung infections usually are acquired by aspiration of pharyngeal flora (20% of adults harbor *S. pneumoniae* in the throat), the lower lobes or the right middle lobe is most frequently involved.

In the era before antibiotics, pneumococcal pneumonia involved entire or almost entire lobes and evolved through four stages: **congestion, red hepatization, gray hepatization,** and **resolution.** Early antibiotic therapy alters or halts this typical progression.

During the first stage, that of **congestion,** the affected lobe(s) is (are) heavy, red, and boggy; histologically, vascular congestion can be seen, with proteinaceous fluid, scattered neutrophils, and many bacteria in the alveoli. Within a few days, the stage of **red hepatization** ensues, in which the lung lobe has a liver-like consistency; the alveolar spaces are packed with neutrophils, red cells, and fibrin (Fig. 12–32, *A*). In the next stage, **gray hepatization,** the lung is dry, gray, and firm, because the red cells are lysed, while the fibrinosuppurative exudate persists within the alveoli (Fig. 12–33; see also Fig. 12–32, *B*). **Resolution** follows in uncomplicated cases, as exudates within the alveoli are enzymatically digested to produce granular, semifluid debris that is resorbed, ingested by macrophages, coughed up, or organized by fibroblasts growing into it (Fig. 12–32, *C*). The pleural reaction (fibrinous or fibrinopurulent **pleuritis**) may similarly resolve or undergo organization, leaving fibrous thickening or permanent adhesions.

In the **bronchopneumonic** pattern, foci of inflammatory consolidation are distributed in patches throughout one or several lobes, most frequently bilateral and basal. Well-developed lesions up to 3 or 4 cm in diameter are slightly elevated and are gray-red to yellow; confluence of these foci may occur in severe cases, producing the appearance of a lobar consolidation. The lung substance immediately surrounding areas of consolidation is usually hyperemic and edematous, but the large intervening areas are generally normal. Pleural involvement is less common than in lobar pneumonia. Histologically, the reaction consists of focal suppurative exudate that fills the bronchi, bronchioles, and adjacent alveolar spaces.

With appropriate therapy, complete restitution of the lung is the rule for both forms of pneumococcal pneumonia, but in occasional cases complications may occur: (1) tissue destruction and necrosis may lead to **abscess** formation; (2) suppurative material may accumulate in the pleural cavity, producing an **empyema;** (3) organization of the intra-alveolar exudate may convert areas of the lung into solid fibrous tissue; and (4) bacteremic dissemination may lead to **meningitis, arthritis,** or **infective endocarditis.** Complications are much more likely with serotype 3 pneumococci.

Examination of gram-stained sputum is an important step in the diagnosis of acute pneumonia. The presence of numerous neutrophils containing the typical gram-positive, lancet-shaped diplococci is good evidence of pneumococcal pneumonia; of note, however, *S. pneumoniae* is a part of the endogenous flora, so false-positive results may be obtained by this method. Isolation of pneumococci from blood cultures is more specific. During early phases of illness, blood cultures may be positive in 20% to 30% of persons with pneumonia. Whenever possible, antibiotic sensitivity should be determined. Commercial pneumococcal vaccines containing capsular polysaccharides from the common serotypes of the bacteria are available, and their proven efficacy mandates their use in persons at risk for pneumococcal infections (see earlier).

Pneumonias Caused by Other Important Pathogens

Other organisms commonly implicated in community-acquired acute pneumonias include the following.

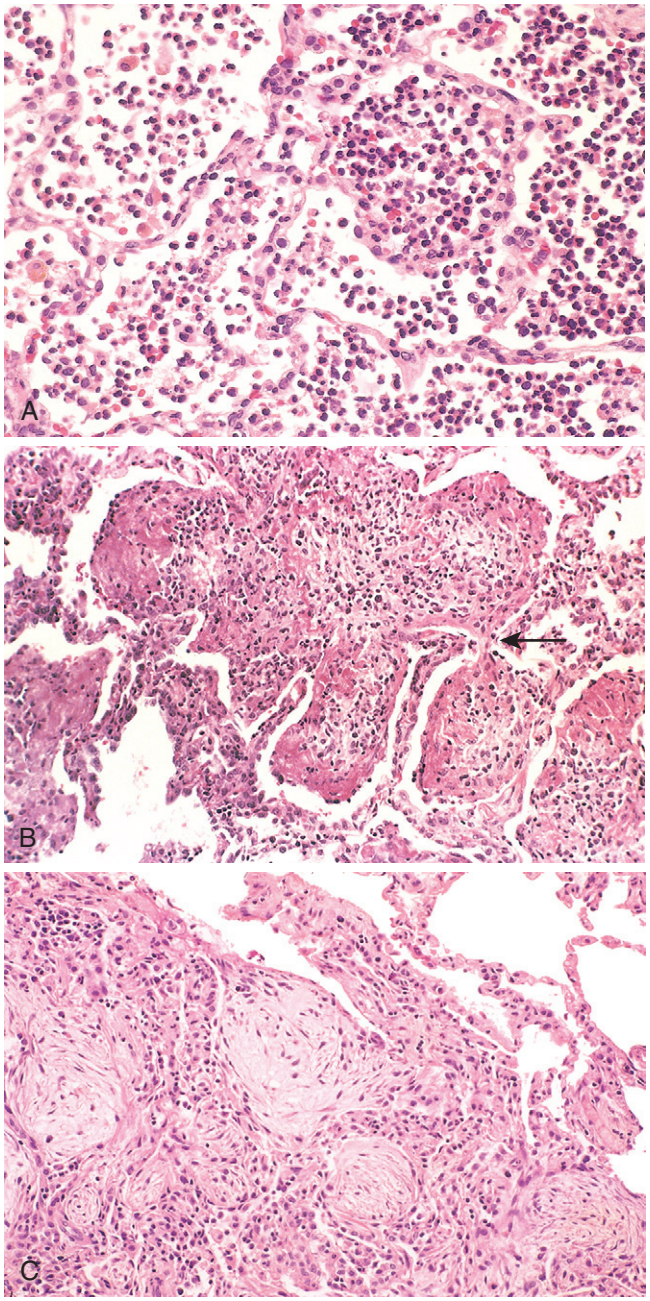

Figure 12–32 A, Acute pneumonia. The congested septal capillaries and extensive neutrophil exudation into alveoli correspond to early red hepatization. Fibrin nets have not yet formed. **B,** Early organization of intra-alveolar exudates, seen in areas to be streaming through the pores of Kohn (*arrow*). **C,** Advanced organizing pneumonia, featuring transformation of exudates to fibromyxoid masses richly infiltrated by macrophages and fibroblasts.

Haemophilus influenzae

- Both *encapsulated* and *unencapsulated* forms are important causes of community-acquired pneumonias. The former can cause a particularly life-threatening form of pneumonia in children, often after a respiratory viral infection.
- Adults at risk for developing infections include those with chronic pulmonary diseases such as chronic bronchitis, cystic fibrosis, and bronchiectasis. *H. influenzae is the most common bacterial cause of acute exacerbation of COPD.*
- Encapsulated *H. influenzae* type b was formerly an important cause of epiglottitis and suppurative meningitis in children, but vaccination against this organism in infancy has significantly reduced the risk.

Moraxella catarrhalis

- *M. catarrhalis* is being increasingly recognized as a cause of bacterial pneumonia, especially in elderly persons.
- It is the second most common bacterial cause of acute exacerbation of COPD in adults.
- Along with *S. pneumoniae* and *H. influenzae, M. catarrhalis* constitutes one of the three most common causes of otitis media (infection of the middle ear) in children.

Staphylococcus aureus

- *S. aureus* is an important cause of secondary bacterial pneumonia in children and healthy adults after viral respiratory illnesses (e.g., measles in children and influenza in both children and adults).
- Staphylococcal pneumonia is associated with a high incidence of complications, such as lung abscess and empyema.
- Staphylococcal pneumonia occurring in association with right-sided staphylococcal endocarditis is a serious complication of *intravenous drug abuse.*
- It is also an important cause of nosocomial pneumonia (discussed later).

Klebsiella pneumoniae

- *K. pneumoniae* is the most frequent cause of gram-negative bacterial pneumonia.

Figure 12–33 Gross view of lobar pneumonia with gray hepatization. The lower lobe is uniformly consolidated.

- *Klebsiella*-related pneumonia frequently afflicts debilitated and malnourished persons, particularly *chronic alcoholics.*
- Thick and gelatinous sputum is characteristic, because the organism produces an abundant viscid capsular polysaccharide, which the patient may have difficulty coughing up.

Pseudomonas aeruginosa

- Although discussed here with community-acquired pathogens because of its association with infections in cystic fibrosis, *P. aeruginosa* most commonly is seen in nosocomial settings (discussed later).
- *Pseudomonas* pneumonia also is common in persons who are neutropenic, usually secondary to chemotherapy; in victims of extensive burns; and in patients requiring mechanical ventilation.
- *P. aeruginosa* has a propensity to invade blood vessels at the site of infection, with consequent extrapulmonary spread; *Pseudomonas* bacteremia is a fulminant disease, with death often occurring within a matter of days.
- Histologic examination reveals coagulative necrosis of the pulmonary parenchyma with organisms invading the walls of necrotic blood vessels (*Pseudomonas* vasculitis).

Legionella pneumophila

- *L. pneumophila* is the agent of Legionnaire disease, an eponym for the epidemic and sporadic forms of pneumonia caused by this organism. Pontiac fever is a related self-limited upper respiratory tract infection caused by *L. pneumophila,* without pneumonic symptoms.
- *L. pneumophila* flourishes in artificial aquatic environments, such as water-cooling towers and within the tubing system of domestic (potable) water supplies. The mode of transmission is thought to be either inhalation of aerosolized organisms or aspiration of contaminated drinking water.
- *Legionella* pneumonia is common in persons with some predisposing condition such as cardiac, renal, immunologic, or hematologic disease. *Organ transplant recipients are particularly susceptible.*
- *Legionella* pneumonia can be quite severe, frequently requiring hospitalization, and immunosuppressed persons may have a fatality rate of 30% to 50%.
- Rapid diagnosis is facilitated by demonstration of *Legionella* antigens in the urine or by a positive fluorescent antibody test on sputum samples; culture remains the standard diagnostic modality. PCR-based tests can be used on bronchial secretions in atypical cases.

Community-Acquired Atypical Pneumonias

The term *primary atypical pneumonia* initially was applied to an acute febrile respiratory disease characterized by patchy inflammatory changes in the lungs, largely confined to the alveolar septa and pulmonary interstitium. The designation *atypical* denotes the moderate amounts of sputum, absence of physical findings of consolidation, only moderate elevation of white cell count, and lack of alveolar exudates. Atypical pneumonia is caused by a variety of organisms, *Mycoplasma pneumoniae* being the most common. *Mycoplasma* infections are particularly common among children and young adults. They occur sporadically or as local epidemics in closed communities (schools, military camps, prisons). Other etiologic agents are *viruses,* including influenza types A and B, the respiratory syncytial viruses, human metapneumovirus, adenovirus, rhinoviruses, rubeola virus, and varicella virus, and *Chlamydia pneumoniae* and *Coxiella burnetii* (the agent of Q fever) (Table 12–6). Nearly all of these agents can also cause a primarily upper respiratory tract infection ("common cold").

The common pathogenetic mechanism is attachment of the organisms to the respiratory epithelium followed by necrosis of the cells and an inflammatory response. When the process extends to alveoli, there is usually *interstitial* inflammation, but some outpouring of fluid into alveolar spaces may also occur, so that on chest films the changes may mimic those of bacterial pneumonia. Damage to and denudation of the respiratory epithelium inhibits mucociliary clearance and predisposes to secondary bacterial infections. Viral infections of the respiratory tract are well known for this complication. More serious lower respiratory tract infection is more likely to occur in infants, elderly persons, malnourished patients, alcoholics, and immunosuppressed persons. Not surprisingly, viruses and mycoplasmas frequently are involved in outbreaks of infection in hospitals.

MORPHOLOGY

Regardless of cause, the morphologic patterns in atypical pneumonias are similar. The process may be patchy, or it may involve whole lobes bilaterally or unilaterally. Macroscopically, the affected areas are red-blue, congested, and subcrepitant. On histologic examination, the **inflammatory reaction is largely confined within the walls of the alveoli** (Fig. 12–34). The septa are widened and edematous; they usually contain a mononuclear inflammatory infiltrate of lymphocytes, histiocytes, and, occasionally, plasma cells. In contrast with bacterial pneumonias, alveolar spaces in atypical pneumonias are remarkably free of cellular exudate. In severe cases, however, full-blown diffuse alveolar damage with hyaline membranes may develop. In less severe, uncomplicated cases, subsidence of the disease is followed by reconstitution of the native architecture. Superimposed bacterial infection, as expected, results in a mixed histologic picture.

Clinical Features

The clinical course of primary atypical pneumonia is extremely varied. It may masquerade as a severe upper respiratory tract infection or "chest cold" that goes undiagnosed, or it may manifest as a fulminant, life-threatening infection in immunocompromised patients. The initial presentation usually is that of an acute, nonspecific febrile illness characterized by fever, headache, and malaise and, later, cough with minimal sputum. Because the edema and exudation are both in a strategic position to cause an alveolocapillary block, there may be *respiratory distress seemingly out of proportion to the physical and radiographic findings.*

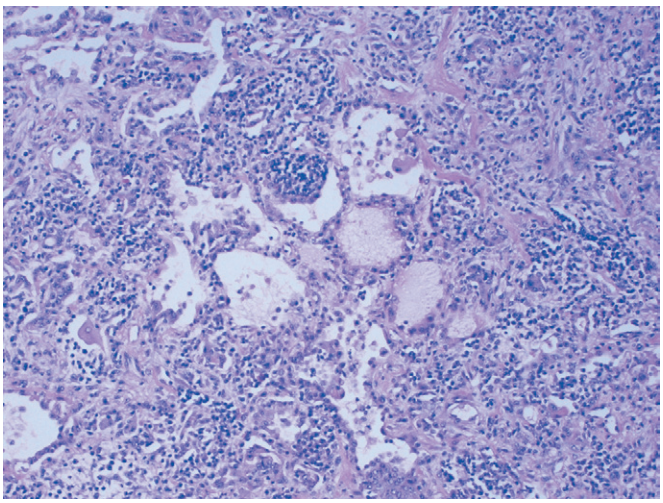

Figure 12–34 Viral pneumonia. The thickened alveolar walls are infiltrated with lymphocytes and some plasma cells, which are spilling over into alveolar spaces. Note focal alveolar edema in the *center* and early fibrosis at *upper right*.

Identifying the causative agent can be difficult. Tests for *Mycoplasma* antigens and polymerase chain reaction (PCR) testing for *Mycoplasma* DNA are available. As a practical matter, patients with community-acquired pneumonia for which a bacterial agent seems unlikely are treated with a macrolide antibiotic effective against *Mycoplasma* and *Chlamydia pneumoniae,* because these are the most common pathogens producing treatable disease.

Influenza Infections

Perhaps no other communicable disorder causes as much public distress in the developed world as the threat of an influenza epidemic. The influenza virus is a single-stranded RNA virus, bound by a nucleoprotein that determines the virus type—A, B, or C. The spherical surface of the virus is a lipid bilayer containing the viral hemagglutinin and neuraminidase, which determine the subtype (e.g., H1N1, H3N2). Host antibodies to the hemagglutinin and neuraminidase prevent and ameliorate, respectively, future infection with the influenza virus. The type A viruses infect humans, pigs, horses, and birds and are the major cause of *pandemic* and *epidemic* influenza infections. Epidemics of influenza occur through mutations of the hemagglutinin and neuraminidase antigens that allow the virus to escape most host antibodies (*antigenic drift*). Pandemics, which last longer and are more widespread than epidemics, may occur when both the hemagglutinin and neuraminidase are replaced through recombination of RNA segments with those of animal viruses, making all animals susceptible to the new influenza virus (*antigenic shift*). Commercially available influenza vaccines provide reasonable protection against the disease, especially in vulnerable infants and elderly persons. A particular subtype of avian influenza—"bird flu," caused by strain H5N1—has caused massive outbreaks in domesticated poultry in parts of Southeast Asia in the last several years; this strain is particularly dangerous, since it has the potential to "jump" to humans and thereby cause a worldwide influenza pandemic.

Influenza Virus Type A/H1N1 Infection

In March 2009, a novel swine-origin influenza A virus, strain H1N1, was identified, which spread in the United States and worldwide, leading to a pandemic affecting more than half a million patients, with more than 6200 deaths by November 2009.

Most patients have only a self-limiting illness, with viral replication limited to pharynx and tracheobronchial tree. Pneumonia occurs in severe disease. Comorbid conditions such as obesity, heart disease, and COPD are seen in fatal cases. Unlike the usual seasonal influenza in which older patients are more at risk of dying, the H1N1 pandemic killed only a few patients over 60 years of age, suggesting that immunity is achieved with previous exposure. Pathologic findings at autopsy include acute tracheobronchitis, bronchiolitis, diffuse alveolar damage, pulmonary thrombosis, and alveolar hemorrhage. In addition, approximately half have bacterial superinfection.

SUMMARY

Acute Pneumonias

- *S. pneumoniae* (the pneumococcus) is the most common cause of community-acquired acute pneumonia, and the distribution of inflammation is usually lobar.
- Morphologically, lobar pneumonias evolve through four stages: congestion, red hepatization, gray hepatization, and resolution.
- Other common causes of acute pneumonias in the community include *H. influenzae* and *M. catarrhalis* (both associated with acute exacerbations of COPD), *S. aureus* (usually secondary to viral respiratory infections), *K. pneumoniae* (observed in patients who are chronic alcoholics), *P. aeruginosa* (seen in persons with cystic fibrosis, in burn victims, and in patients with neutropenia), and *L. pneumophila,* seen particularly in organ transplant recipients.
- In contrast with acute pneumonias, *atypical pneumonias* are characterized by respiratory distress out of proportion to the clinical and radiologic signs, and by inflammation that is predominantly confined to alveolar septa, with generally clear alveoli.
- The most common causes of atypical pneumonias include those caused by *M. pneumoniae*, viruses including influenza viruses types A and B, human metapneumovirus, *C. pneumoniae*, and *C. burnetii* (agent of Q fever).

Hospital-Acquired Pneumonias

Nosocomial, or hospital-acquired, pneumonias are defined as pulmonary infections acquired in the course of a hospital stay. The specter of nosocomial pneumonia places an immense burden on the burgeoning costs of health care, in addition to the expected adverse impact on illness outcome. Nosocomial infections are common in hospitalized persons with severe underlying disease, those who are immunosuppressed, or those on prolonged antibiotic regimens. Those on mechanical ventilation represent a particularly high-risk group, and infections acquired in this setting

are given the distinctive designation *ventilator-associated pneumonia.* Gram-negative rods (members of Enterobacteriaceae and *Pseudomonas* spp.) and *S. aureus* are the most common isolates; unlike with community-acquired pneumonias, *S. pneumoniae* is not a major pathogen in nosocomial infections.

Aspiration Pneumonia

Aspiration pneumonia occurs in debilitated patients or those who aspirate gastric contents either while unconscious (e.g., after a stroke) or during repeated vomiting. These patients have abnormal gag and swallowing reflexes that facilitate aspiration. The resultant pneumonia is partly chemical, resulting from the extremely irritating effects of the gastric acid, and partly bacterial. Although it is commonly assumed that anaerobic bacteria predominate, more recent studies implicate aerobes more commonly than anaerobes (Table 12–6). This type of pneumonia is often necrotizing, pursues a fulminant clinical course, and is a frequent cause of death in persons predisposed to aspiration. In those who survive, abscess formation is a common complication. Microaspiration, by contrast, occurs in many people, especially those with gastro-esophageal reflux, and may exacerbate other lung diseases but does not lead to pneumonia.

Lung Abscess

Lung abscess refers to a localized area of suppurative necrosis within the pulmonary parenchyma, resulting in the formation of one or more large cavities. The term *necrotizing pneumonia* has been used to describe a similar process resulting in multiple small cavitations; necrotizing pneumonia often coexists or evolves into lung abscess, making this distinction somewhat arbitrary. The causative organism may be introduced into the lung by any of the following mechanisms:

- *Aspiration of infective material* from carious teeth or infected sinuses or tonsils, particularly likely during oral surgery, anesthesia, coma, or alcoholic intoxication and in debilitated patients with depressed cough reflexes
- *Aspiration of gastric contents,* usually accompanied by infectious organisms from the oropharynx
- *As a complication of necrotizing bacterial pneumonias,* particularly those caused by *S. aureus, Streptococcus pyogenes, K. pneumoniae, Pseudomonas* spp., and, rarely, type 3 pneumococci. Mycotic infections and bronchiectasis may also lead to lung abscesses.
- *Bronchial obstruction,* particularly with bronchogenic carcinoma obstructing a bronchus or bronchiole. Impaired drainage, distal atelectasis, and aspiration of blood and tumor fragments all contribute to the development of abscesses. An abscess may also form within an excavated necrotic portion of a tumor.
- *Septic embolism,* from septic thrombophlebitis or from infective endocarditis of the right side of the heart
- In addition, lung abscesses may result from *hematogenous spread of bacteria* in disseminated pyogenic infection. This occurs most characteristically in staphylococcal bacteremia and often results in multiple lung abscesses.

Anaerobic bacteria are present in almost all lung abscesses, sometimes in vast numbers, and they are the exclusive isolates in one third to two thirds of cases. The most frequently encountered anaerobes are commensals normally found in the oral cavity, principally species of *Prevotella, Fusobacterium, Bacteroides, Peptostreptococcus,* and microaerophilic streptococci.

MORPHOLOGY

Abscesses range in diameter from a few millimeters to large cavities 5 to 6 cm across. The localization and number of abscesses depend on their mode of development. Pulmonary abscesses resulting from aspiration of infective material are much **more common on the right side** (with its more vertical airways) than on the left, and most are single. On the right side, they tend to occur in the posterior segment of the upper lobe and in the apical segments of the lower lobe, because these locations reflect the probable course of aspirated material when the patient is recumbent. Abscesses that develop in the course of pneumonia or bronchiectasis commonly are multiple, basal, and diffusely scattered. Septic emboli and abscesses arising from hematogenous seeding are commonly multiple and may affect any region of the lungs.

As the focus of suppuration enlarges, it almost inevitably ruptures into airways. Thus, the contained exudate may be partially drained, producing an air-fluid level on radiographic examination. Occasionally, abscesses rupture into the pleural cavity and produce bronchopleural fistulas, the consequence of which is **pneumothorax** or **empyema.** Other complications arise from embolization of septic material to the brain, giving rise to meningitis or brain abscess. On histologic examination, as expected with any abscess, the suppurative focus is surrounded by variable amounts of fibrous scarring and mononuclear infiltration (lymphocytes, plasma cells, macrophages), depending on the chronicity of the lesion.

Clinical Features

The manifestations of a lung abscess are much like those of bronchiectasis and include a prominent cough that usually yields copious amounts of foul-smelling, purulent, or sanguineous sputum; occasionally, hemoptysis occurs. Spiking fever and malaise are common. Clubbing of the fingers, weight loss, and anemia may all occur. Infective abscesses occur in 10% to 15% of patients with bronchogenic carcinoma; thus, when a lung abscess is suspected in an older person, underlying carcinoma must be considered. Secondary amyloidosis (Chapter 4) may develop in chronic cases. Treatment includes antibiotic therapy and, if needed, surgical drainage. Overall, the mortality rate is in the range of 10%.

Chronic Pneumonias

Chronic pneumonia most often is a localized lesion in an immunocompetent person, with or without regional lymph node involvement. There is typically granulomatous inflammation, which may be due to bacteria (e.g., *M. tuberculosis*) or fungi. In immunocompromised patients,

such as those with debilitating illness, on immunosuppressive regimens, or with human immunodeficiency virus (HIV) infection (see below), systemic dissemination of the causative organism, accompanied by widespread disease, is the usual presentation. Tuberculosis is by far the most important entity within the spectrum of chronic pneumonias; the World Health Organization (WHO) estimates that tuberculosis causes 6% of all deaths worldwide, *making it the most common cause of death resulting from a single infectious agent.*

Tuberculosis

Tuberculosis is a communicable chronic granulomatous disease caused by *Mycobacterium tuberculosis.* It usually involves the lungs but may affect any organ or tissue in the body. Typically, the centers of tubercular granulomas undergo *caseous necrosis.*

Epidemiology

Among medically and economically deprived persons throughout the world, tuberculosis remains a leading cause of death. It is estimated that 1.7 billion people are infected worldwide, with 8 to 10 million new cases and 3 million deaths per year. In the Western world, deaths from tuberculosis peaked in 1800 and steadily declined throughout the 1800s and 1900s. However, in 1984 the decline in new cases stopped abruptly, a change that resulted from the increased incidence of tuberculosis in HIV-infected persons. As a consequence of intensive public health surveillance and tuberculosis prophylaxis among immunosuppressed persons, the incidence of tuberculosis in U.S.-born persons has declined since 1992. Currently, it is estimated that about 25,000 new cases with active tuberculosis arise in the United States annually, and nearly 40% of these are in immigrants from countries where tuberculosis is highly prevalent.

Tuberculosis flourishes under conditions of poverty, crowding, and chronic debilitating illness. Similarly, elderly persons, with their weakened defenses, are vulnerable. In the United States, tuberculosis is a disease of the elderly, the urban poor, patients with AIDS, and members of minority communities. African Americans, Native Americans, the Inuit (from Alaska), Hispanics, and immigrants from Southeast Asia have higher attack rates than those typical for other segments of the population. *Certain disease states also increase the risk:* diabetes mellitus, Hodgkin lymphoma, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression. In areas of the world where HIV infection is prevalent, *it has become the single most important risk factor for the development of tuberculosis.*

It is important that *infection* be differentiated from *disease.* Infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage (i.e., disease). Although other routes may be involved, most infections are acquired by direct person-to-person transmission of airborne droplets of organisms from an active case to a susceptible host. In most persons, an asymptomatic focus of pulmonary infection appears that is self-limited, although uncommonly, primary tuberculosis may result in the development of fever and pleural effusions. Generally, the only evidence of infection, if any remains, is a tiny, telltale fibrocalcific nodule at the site of the infection. Viable organisms may remain dormant in such loci for decades, and possibly for the life of the host. Such persons are infected but do not have active disease and therefore cannot transmit organisms to others. Yet when their immune defenses are lowered, the infection may reactivate to produce communicable and potentially life-threatening disease.

Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test. About 2 to 4 weeks after the infection has begun, intracutaneous injection of 0.1 mL of PPD induces a visible and palpable induration (at least 5 mm in diameter) that peaks in 48 to 72 hours. Sometimes, more PPD is required to elicit the reaction, and unfortunately, in some responders, the standard dose may produce a large, necrotizing lesion. *A positive tuberculin skin test result* signifies cell-mediated hypersensitivity to tubercular antigens. It does not differentiate between infection and disease. A well-recognized limitation of this test is that *false-negative reactions (or skin test anergy) may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression, and (notably) overwhelming active tuberculous disease.* False-positive reactions may result from infection by atypical mycobacteria.

About 80% of the population in certain Asian and African countries is tuberculin-positive. In contrast, in 1980, 5% to 10% of the U.S. population was positive, indicating the marked difference in rates of exposure to the tubercle bacillus. In general, 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter. Thus, *only a small fraction of those who contract an infection develop active disease.*

Etiology

Mycobacteria are slender rods that are acid-fast (i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen [carbol fuchsin] stain and subsequently stubbornly resist decolorization). *M. tuberculosis hominis* is responsible for most cases of tuberculosis; the reservoir of infection typically is found in persons with active pulmonary disease. Transmission usually is direct, by inhalation of airborne organisms in aerosols generated by expectoration or by exposure to contaminated secretions of infected persons. Oropharyngeal and intestinal tuberculosis contracted by drinking milk contaminated with *Mycobacterium bovis* infection is now rare in developed nations, but it is still seen in countries with tuberculous dairy cows and sales of unpasteurized milk. Other mycobacteria, particularly *Mycobacterium avium complex,* are much less virulent than *M. tuberculosis* and rarely cause disease in immunocompetent persons. However, they cause disease in 10% to 30% of patients with AIDS.

PATHOGENESIS

The pathogenesis of tuberculosis in the previously **unexposed immunocompetent** person is centered on the development of a targeted cell-mediated immunity that confers **resistance** to the organism and results

in development of **tissue hypersensitivity** to tubercular antigens. The pathologic features of tuberculosis, such as caseating granulomas and cavitation, are the result of the destructive tissue hypersensitivity that is part and parcel of the host immune response. Because the effector cells for both processes are the same, the appearance of tissue hypersensitivity also signals the acquisition of immunity to the organism. The sequence of events from inhalation of the infectious inoculum to containment of the primary focus is illustrated in Fig. 12–35, A and B and is outlined next:

- Once a virulent strain of mycobacteria gains entry into the macrophage endosomes (a process mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls), the organisms are able to inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole. The prevention of phagolysosome formation allows unchecked mycobacterial proliferation. Thus, the earliest phase of primary tuberculosis (in the first 3 weeks) in the nonsensitized patient is characterized by bacillary proliferation within the pulmonary alveolar macrophages and air spaces, with resulting bacteremia and seeding of multiple sites. **Despite the bacteremia, most persons at this stage are asymptomatic or have a mild flu-like illness.**
- The genetic makeup of the patient may influence the course of the disease. In some people with polymorphisms of the **NRAMP1** (**n**atural **r**esistance–**a**ssociated **m**acrophage **p**rotein **1**) gene, the disease may progress from this point without development of an effective immune response. NRAMP1 is a transmembrane ion transport protein found in endosomes and lysosomes that is believed to contribute to microbial killing.
- The development of **cell-mediated immunity** occurs approximately 3 weeks after exposure. Processed mycobacterial antigens reach the draining lymph nodes and are presented to CD4 T cells by dendritic cells and macrophages. Under the influence of macrophage-secreted IL-12, CD4+ T cells of the T_H1 subset are generated that are capable of secreting IFN-γ.
- **IFN-γ released by the CD4+ T cells of the T_H1 subset is crucial in activating macrophages.** Activated macrophages, in turn, release a variety of mediators and upregulate expression of genes with important downstream effects, including (1) TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the "epithelioid histiocytes"

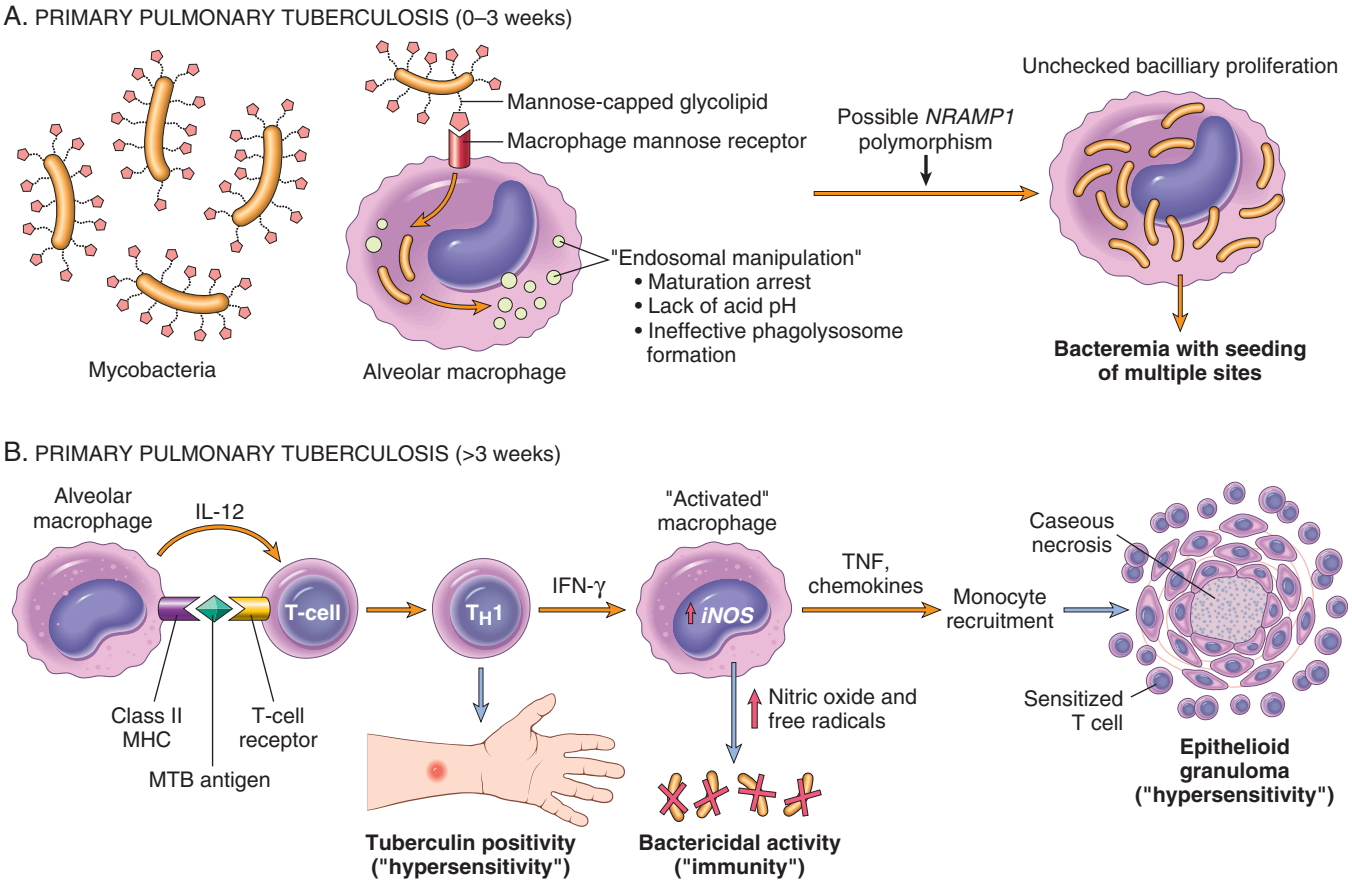

Figure 12–35 Sequence of events in the natural history of primary pulmonary tuberculosis. This sequence commences with inhalation of virulent strains of *Mycobacterium* and culminates in the development of immunity and delayed hypersensitivity to the organism. **A,** Events occurring in the first 3 weeks after exposure. **B,** Events thereafter. The development of resistance to the organism is accompanied by conversion to a positive result on tuberculin skin testing. Cells and bacteria are not drawn to scale. IFN-γ, interferon γ; iNOS, inducible nitric oxide synthase; MHC, major histocompatibility complex; MTB, *Mycobacterium tuberculosis*; *NRAMP1*, gene encoding natural resistance–associated macrophage protein 1; TNF, tumor necrosis factor.

that characterize the granulomatous response; (2) expression of the **inducible nitric oxide synthase** *(iNOS)* gene, which results in elevated **nitric oxide** levels at the site of infection, with excellent antibacterial activity; and (3) generation of reactive oxygen species, which can have antibacterial activity. You will recall that nitric oxide is a powerful oxidizing agent that results in generation of reactive nitrogen intermediates and other free radicals capable of oxidative destruction of several mycobacterial constituents, from cell wall to DNA.

- Defects in any of the steps of a T_H1 response (including IL-12, IFN-γ, TNF, or nitric oxide production) result in poorly formed granulomas, absence of resistance, and disease progression. Persons with inherited mutations in any component of the T_H1 pathway are extremely susceptible to infections with mycobacteria.

In summary, immunity to a tubercular infection is primarily mediated by T_H1 cells, which stimulate macrophages to kill bacteria. This immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction. Reactivation of the infection or reexposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis. Just as hypersensitivity and resistance appear in parallel, so, too, the loss of hypersensitivity (indicated by tuberculin negativity in a tuberculin-positive patient) may be an ominous sign that resistance to the organism has faded.

Primary Tuberculosis

Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized patient. Elderly persons and profoundly immunosuppressed patients may lose their sensitivity to the tubercle bacillus, so they may develop primary tuberculosis more than once. About 5% of those newly infected acquire significant disease.

MORPHOLOGY

In countries in which bovine tuberculosis and infected milk have largely disappeared, primary tuberculosis almost always begins in the lungs. Typically, the inhaled bacilli implant in the distal air spaces of the lower part of the upper lobe or the upper part of the lower lobe, usually close to the pleura. As sensitization develops, a 1- to 1.5-cm area of gray-white inflammatory consolidation emerges, the **Ghon focus.** In most cases the center of this focus undergoes caseous necrosis. Tubercle bacilli, either free or within phagocytes, travel in lymph drainage to the regional nodes, which also often caseate. **This combination of parenchymal lesion and nodal involvement** is referred to as the Ghon complex (Fig. 12–36). During the first few weeks, there is also lymphatic and hematogenous dissemination to other parts of the body. In approximately 95% of cases, development of cell-mediated immunity controls the infection. Hence, the Ghon complex undergoes progressive fibrosis, often followed by radiologically detectable calcification **(Ranke complex),** and despite seeding of other organs, no lesions develop.

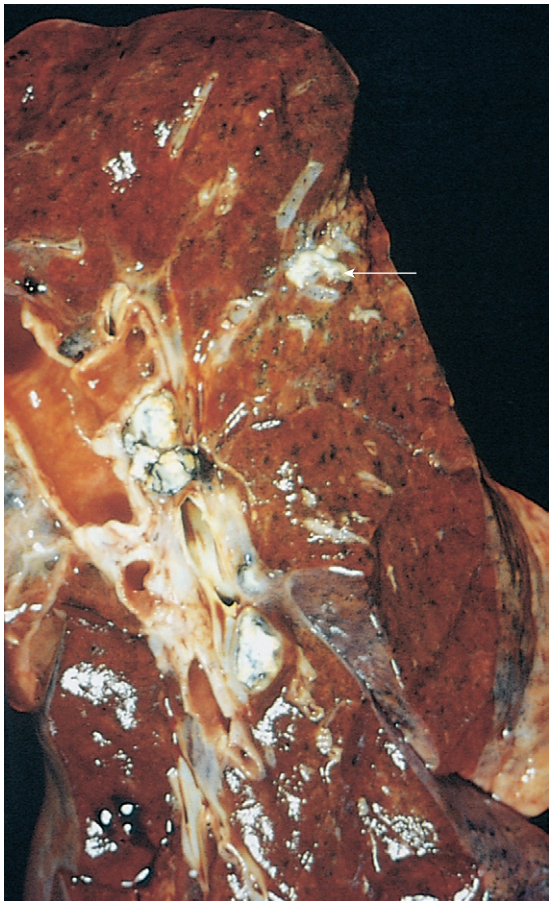

Figure 12–36 Primary pulmonary tuberculosis, Ghon complex. The gray-white parenchymal focus *(arrow)* is under the pleura in the *lower part* of the upper lobe. Hilar lymph nodes with caseation are seen on the *left.*

On histologic examination, sites of active involvement are marked by a characteristic granulomatous inflammatory reaction that forms both caseating and noncaseating granulomas (Fig. 12–37, *A* to *C*), which consist of epithelioid histiocytes and multinucleate giant cells.

The major consequences of primary tuberculosis are that (1) it induces hypersensitivity and increased resistance; (2) the foci of scarring may harbor viable bacilli for years, perhaps for life, and thus be the nidus for *reactivation* at a later time when host defenses are compromised; and (3) uncommonly, it may lead to *progressive primary tuberculosis.* This complication occurs in patients who are immunocompromised or have nonspecific impairment of host defenses, as characteristic in malnourished children or in elderly persons. Certain racial groups, such as the Inuit, also are more prone to the development of progressive primary tuberculosis. The incidence of progressive primary tuberculosis is particularly high in HIV-positive patients with an advanced degree of immunosuppression (i.e., CD4+ counts below 200 cells/μL). Immunosuppression results in an inability to mount a CD4+ T cell–mediated immunologic reaction that would contain the primary focus; because hypersensitivity and resistance are most often concomitant factors, the lack of a tissue hypersensitivity reaction results

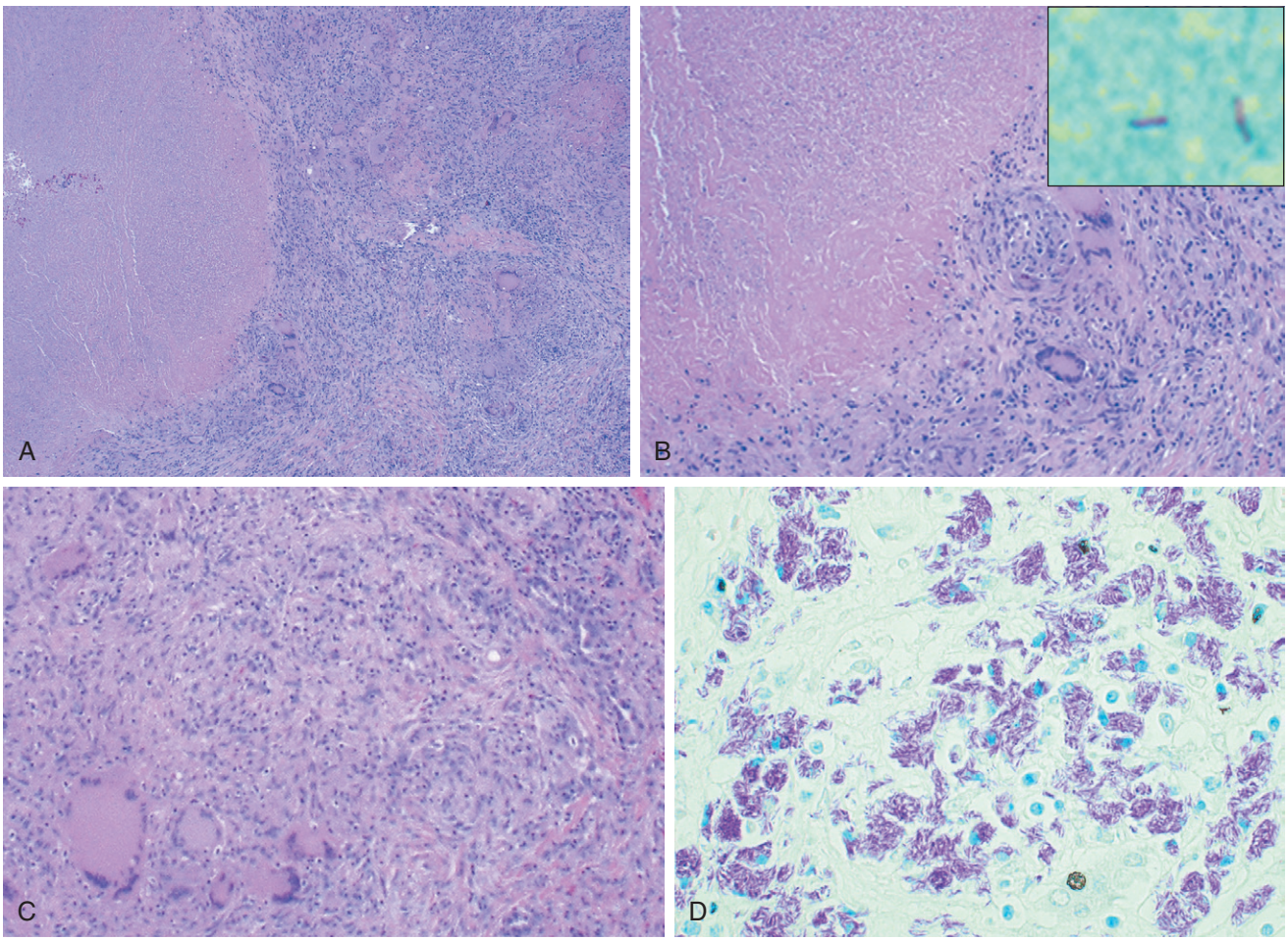

Figure 12–37 The morphologic spectrum of tuberculosis. **A** and **B,** A characteristic tubercle at low magnification **(A)** and at higher power **(B)** shows central granular caseation surrounded by epithelioid and multinucleate giant cells. This is the usual response seen in persons who have developed cell-mediated immunity to the organism. *Inset:* Acid-fast stain shows rare positive organisms. **C,** Occasionally, even in immunocompetent patients, tubercular granulomas may not show central caseation; hence, irrespective of the presence or absence of caseous necrosis, use of special stains for acid-fast organisms is indicated when granulomas are present. **D,** In this specimen from an immunosuppressed patient, sheets of foamy macrophages packed with mycobacteria are seen (acid-fast stain).

in the absence of the characteristic caseating granulomas (*nonreactive tuberculosis*) (Fig. 12–37, *D*).

Secondary Tuberculosis (Reactivation Tuberculosis)

Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host. It may follow shortly after primary tuberculosis, but more commonly it arises from reactivation of dormant primary lesions many decades after initial infection, particularly when host resistance is weakened. It also may result from exogenous reinfection because of waning of the protection afforded by the primary disease or because of a large inoculum of virulent bacilli. Whatever the source of the organism, only a few patients (less than 5%) with primary disease subsequently develop secondary tuberculosis.

Secondary pulmonary tuberculosis is classically localized to the apex of one or both upper lobes. The reason is obscure but may relate to high oxygen tension in the apices. Because of the preexistence of hypersensitivity, the bacilli excite a prompt and marked tissue response that tends to wall off the focus. As a result of this localization, the regional lymph nodes are less prominently involved early in the disease than they are in primary tuberculosis. On the other hand, *cavitation occurs readily in the secondary form,* leading to erosion into and dissemination along airways. Such changes become an important source of infectivity, because the patient now produces sputum containing bacilli.

Secondary tuberculosis should always be an important consideration in HIV-positive patients who present with pulmonary disease. Of note, *although an increased risk of tuberculosis exists at all stages of HIV disease, the manifestations differ depending on the degree of immunosuppression.* For example, patients with less severe immunosuppression (CD4+ counts greater than 300 cells/mm^3) present with "usual" secondary tuberculosis (apical disease with cavitation) while those with more advanced immunosuppression (CD4+ counts below 200 cells/mm^3) present with a clinical picture that resembles progressive primary tuberculosis (lower and middle lobe consolidation, hilar lymphadenopathy, and noncavitary disease). The extent of immunosuppression also determines the frequency of extrapulmonary involvement, rising from 10% to 15% in mildly immunosuppressed patients to greater than 50% in those with severe immune deficiency.

MORPHOLOGY

The initial lesion usually is a small focus of consolidation, less than 2 cm in diameter, within 1 to 2 cm of the **apical pleura.** Such foci are sharply circumscribed, firm, gray-white to yellow areas that have a variable amount of central caseation and peripheral fibrosis. In favorable cases, the initial parenchymal focus undergoes progressive fibrous encapsulation, leaving only fibrocalcific scars. Histologically, the active lesions show characteristic coalescent tubercles with central caseation. Although tubercle bacilli can be demonstrated by appropriate methods in early exudative and caseous phases of granuloma formation, it is usually impossible to find them in the late, fibrocalcific stages. Localized, apical, secondary pulmonary tuberculosis may heal with fibrosis either spontaneously or after therapy, or the disease may progress and extend along several different pathways.

Progressive pulmonary tuberculosis may ensue. The apical lesion enlarges with expansion of the area of caseation. Erosion into a bronchus evacuates the caseous center, creating a ragged, **irregular cavity lined by caseous material** that is poorly walled off by fibrous tissue (Fig. 12–38). Erosion of blood vessels results in hemoptysis. With adequate treatment, the process may be arrested, although healing by fibrosis often distorts the pulmonary architecture. Irregular cavities, now free of caseation necrosis, may remain or collapse in the surrounding fibrosis. If the treatment is inadequate, or if host defenses are impaired, the infection may spread by direct expansion, by means of dissemination through airways, lymphatic channels, or within the vascular system. **Miliary pulmonary disease** occurs when organisms drain through lymphatics into the lymphatic ducts, which empty into the venous return to the right side of the heart and thence into the pulmonary arteries. Individual lesions are either microscopic or small, visible (2 mm) foci of yellow-white consolidation scattered through the lung parenchyma (the word *miliary* is derived from the resemblance of these foci to millet seeds). With progressive pulmonary tuberculosis, the pleural cavity is invariably involved and serous **pleural effusions, tuberculous empyema,** or **obliterative fibrous pleuritis** may develop.

Endobronchial, endotracheal, and **laryngeal tuberculosis** may develop when infective material is spread either through lymphatic channels or from expectorated infectious material. The mucosal lining may be studded with minute granulomatous lesions, sometimes apparent only on microscopic examination.

Systemic miliary tuberculosis ensues when the organisms disseminate through the systemic arterial system to almost every organ in the body. Granulomas are the same as in the lung. Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis (Fig. 12–39).

Isolated-organ tuberculosis may appear in any one of the organs or tissues seeded hematogenously and may be the presenting manifestation of tuberculosis. Organs typically involved include the meninges (tuberculous meningitis), kidneys (renal tuberculosis), adrenals, bones (osteomyelitis), and fallopian tubes (salpingitis). When the vertebrae are affected, the condition is referred to as Pott disease. Paraspinal "cold" abscesses may track along the tissue planes to present as an abdominal or pelvic mass.

Lymphadenitis is the most frequent form of extrapulmonary tuberculosis, usually occurring in the cervical region ("scrofula"). Lymphadenopathy tends to be unifocal, and most patients do not have concurrent extranodal disease. HIV-positive patients, on the other hand, almost always have multifocal disease, systemic symptoms, and either pulmonary or other organ involvement by active tuberculosis.

In years past, **intestinal tuberculosis** contracted by the drinking of contaminated milk was fairly common as a primary focus of tuberculosis. In developed countries today, intestinal tuberculosis is more often a complication of protracted advanced secondary tuberculosis, secondary to the swallowing of coughed-up infective material. Typically, the organisms are trapped in mucosal lymphoid aggregates of the small and large bowel, which then undergo inflammatory enlargement with ulceration of the overlying mucosa, particularly in the ileum.

The many patterns of tuberculosis are depicted in Figure 12–40.

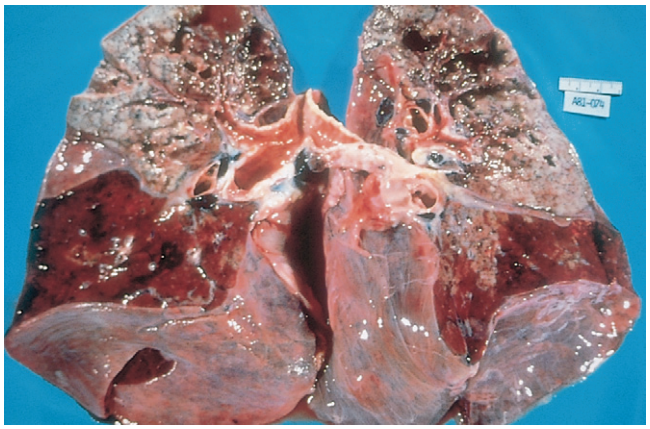

Figure 12–38 Secondary pulmonary tuberculosis. The upper parts of both lungs are riddled with gray-white areas of caseation and multiple areas of softening and cavitation.

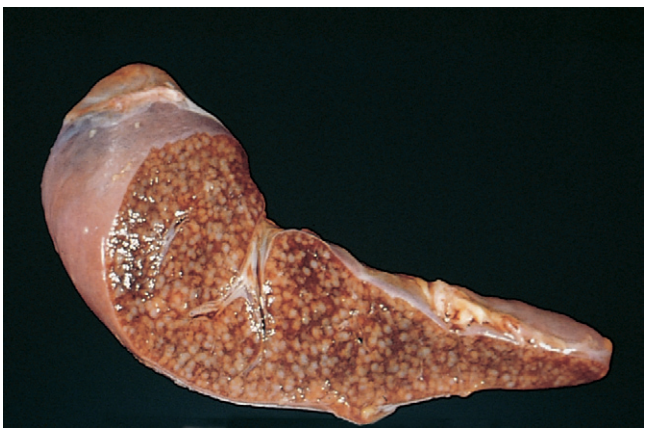

Figure 12–39 Miliary tuberculosis of the spleen. The cut surface shows numerous gray-white granulomas.

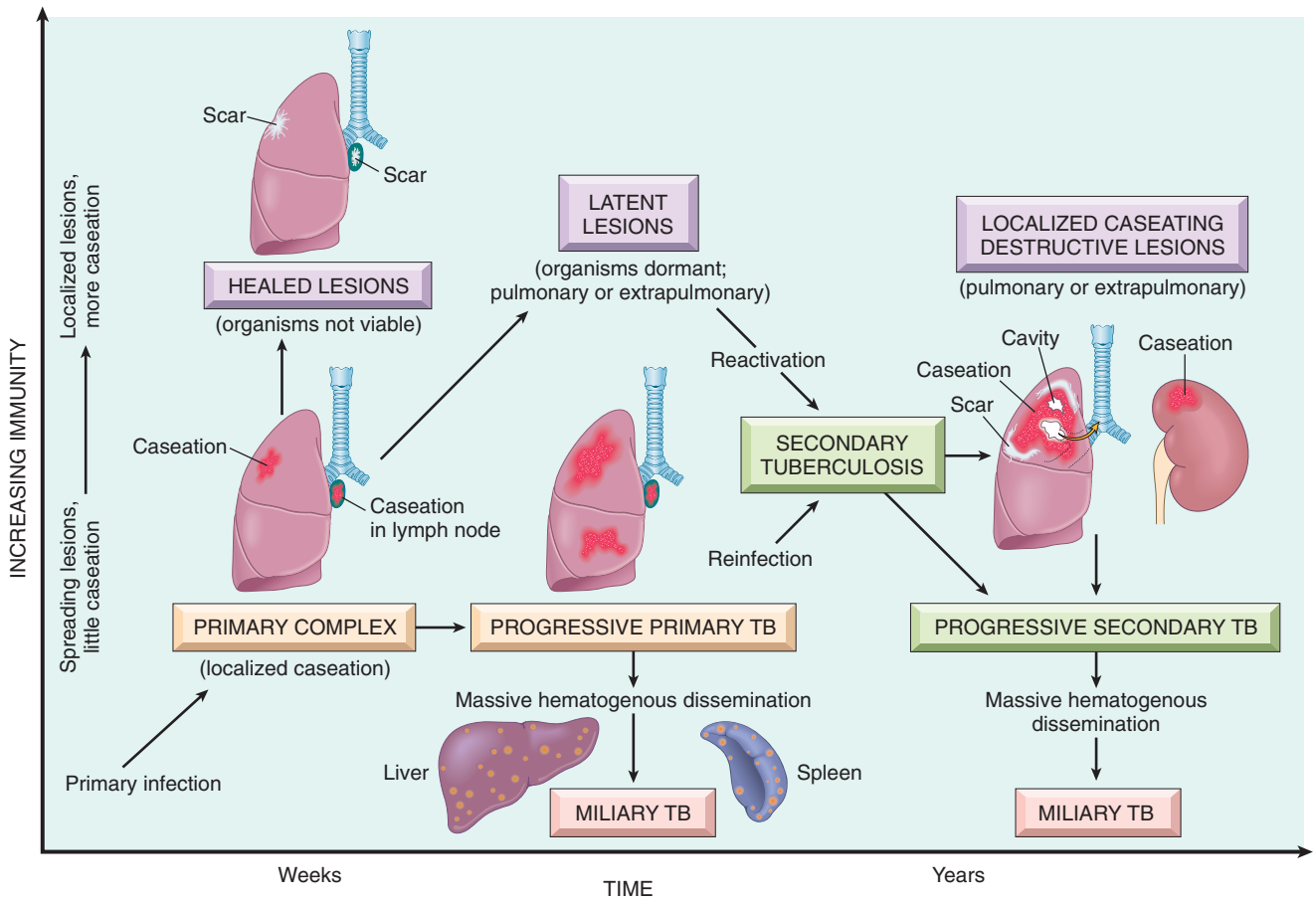

Figure 12–40 The natural history and spectrum of tuberculosis.
(Adapted from a sketch provided by Dr. R.K. Kumar, The University of New South Wales, School of Pathology, Sydney, Australia.)

Clinical Features

Localized secondary tuberculosis may be asymptomatic. When manifestations appear, they are usually *insidious* in onset, with gradual development of both systemic and localizing symptoms and signs. Systemic manifestations, probably related to the release of cytokines by activated macrophages (e.g., TNF and IL-1), often appear early in the disease course and include malaise, anorexia, weight loss, and fever. Commonly, the *fever is low grade* and remittent (appearing late each afternoon and then subsiding), and *night sweats* occur. With progressive pulmonary involvement, increasing amounts of sputum, at first mucoid and later purulent, appear. When cavitation is present, the sputum contains tubercle bacilli. Some degree of *hemoptysis* is present in about half of all cases of pulmonary tuberculosis. *Pleuritic pain* may result from extension of the infection to the pleural surfaces. Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved (for example, tuberculous salpingitis may present as infertility, tuberculous meningitis with headache and neurologic deficits, Pott disease with back pain and paraplegia). The diagnosis of pulmonary disease is based in part on the history and on physical and radiographic findings of *consolidation or cavitation in the apices of the lungs.* Ultimately, however, *tubercle bacilli must be identified.*

The most common methodology for diagnosis of tuberculosis remains demonstration of acid-fast organisms in sputum by acid-fast stains or by use of fluorescent auramine rhodamine. Conventional cultures for mycobacteria require up to 10 weeks, but liquid media–based radiometric assays that detect mycobacterial metabolism are able to provide an answer within 2 weeks. PCR amplification can be performed on positive liquid media, as well as on tissue sections, to identify the mycobacterium. However, culture remains the standard diagnostic modality because it can identify the occasional PCR-negative case and also allows testing of drug susceptibility. Multidrug resistance (MDR), defined as resistance of mycobacteria to two or more of the primary drugs used for treatment of tuberculosis, is now seen more commonly, and the WHO estimates that 50 million people worldwide may be infected with multidrug-resistant tuberculosis.

The prognosis with tuberculosis generally is favorable if infection is localized to the lungs, but it worsens significantly when the disease occurs in aged, debilitated, or immunosuppressed persons, who are at high risk for the development of miliary tuberculosis, and in those with multidrug-resistant tuberculosis. Amyloidosis may develop in persistent cases.

SUMMARY

Tuberculosis

- Tuberculosis is a chronic granulomatous disease caused by *M. tuberculosis*, usually affecting the lungs, but virtually any extrapulmonary organ can be involved in isolated infection.
- Initial exposure to mycobacteria results in development of an immune response that confers resistance but also leads to hypersensitivity (as determined by a positive result on the *tuberculin skin test*).
- CD4+ T cells of the T_H1 subset have a crucial role in cell-mediated immunity against mycobacteria; mediators of inflammation and bacterial containment include IFN-γ, TNF, and nitric oxide.
- The histopathologic hallmark of host reaction to tuberculosis in immunocompetent persons is the presence of *granulomas*, usually with central caseating necrosis.
- Secondary (reactivation) tuberculosis arises in previously exposed persons when host immune defenses are compromised, and usually manifests as cavitary lesions in the lung apices.
- Both progressive primary tuberculosis and secondary tuberculosis can result in systemic seeding, causing life-threatening forms of disease such as miliary tuberculosis and tuberculous meningitis.
- HIV-seropositive status is a well-known risk factor for development or recrudescence of active tuberculosis.

Nontuberculous Mycobacterial Disease

Nontuberculous mycobacteria most commonly cause chronic but clinically localized pulmonary disease in immunocompetent persons. In the United States, strains implicated most frequently include *Mycobacterium avium-intracellulare* (also called *M. avium* complex), *Mycobacterium kansasii,* and *Mycobacterium abscessus.* It is not uncommon for nontuberculous mycobacterial infection to manifest as upper lobe cavitary disease, mimicking tuberculosis, especially in patients with a long history of smoking or alcohol abuse. Concomitant chronic pulmonary disease (COPD, cystic fibrosis, pneumoconiosis) is often present.

In *immunosuppressed persons* (primarily HIV-seropositive patients), *M. avium* complex infection manifests as disseminated disease, associated with systemic signs and symptoms (fever, night sweats, weight loss). Hepatosplenomegaly and lymphadenopathy, signifying involvement of the mononuclear phagocyte system by the opportunistic pathogen, is common, as are gastrointestinal symptoms such as diarrhea and malabsorption. Pulmonary involvement is often indistinguishable from tuberculosis in patients with AIDS. Disseminated *M. avium* complex infection in patients with AIDS tends to occur late in the clinical course, when CD4+ counts have fallen below 100 cells/μL. Hence, tissue examination usually does not reveal granulomas; instead, foamy histiocytes "stuffed" with atypical mycobacteria typically are seen.

Histoplasmosis, Coccidioidomycosis, and Blastomycosis

Infections caused by the dimorphic fungi, which include *Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis,* manifest either with isolated pulmonary involvement, as commonly seen in infected immunocompetent persons, or with disseminated disease in immunocompromised persons. T cell–mediated immune responses are critical for containing the infection, so persons with compromised cell-mediated immunity, such as those with HIV, are more prone to systemic disease. In part because of the overlap in clinical presentations, infectious diseases due to all three dimorphic fungi are considered together in this section.

Epidemiology

Each of the dimorphic fungi has a typical geographic distribution, as follows:

- *H. capsulatum*: This fungus is endemic in the Ohio and central Mississippi River valleys and along the Appalachian mountains in the southeastern United States. Warm, moist soil, enriched by droppings from bats and birds, provides the ideal medium for the growth of the mycelial form, which produces infectious spores.
- *C. immitis*: This organism is endemic in the southwestern and far western regions of the United States, particularly in California's San Joaquin Valley, where coccidial infection is known as "valley fever."
- *B. dermatitidis*: The endemic area is confined in the United States to areas overlapping with those in which histoplasmosis is found.

MORPHOLOGY

The yeast forms are fairly distinctive, which helps in the identification of individual fungi in tissue sections:

- *H. capsulatum*: round to oval, small yeast forms measuring 2 to 5 μm in diameter (Fig. 12–41, *A*)
- *C. immitis*: thick-walled, nonbudding spherules, 20 to 60 μm in diameter, often filled with small endospores (Fig. 12–41, *B*)
- *B. dermatitidis*: round to oval and larger than *Histoplasma* (5 to 25 μm in diameter); reproduce by characteristic broad-based budding (Fig. 12–41, *C* and *D*)

Clinical Features

Clinical manifestations may take the form of (1) *acute (primary) pulmonary infection,* (2) *chronic (granulomatous) pulmonary disease,* or (3) *disseminated miliary disease.* The primary pulmonary nodules, composed of aggregates of macrophages stuffed with organisms, are associated with similar lesions in the regional lymph nodes. These lesions evolve into small granulomas complete with giant cells and may develop central necrosis and later fibrosis and calcification. *The similarity to primary tuberculosis is striking,* and differentiation requires identification of the

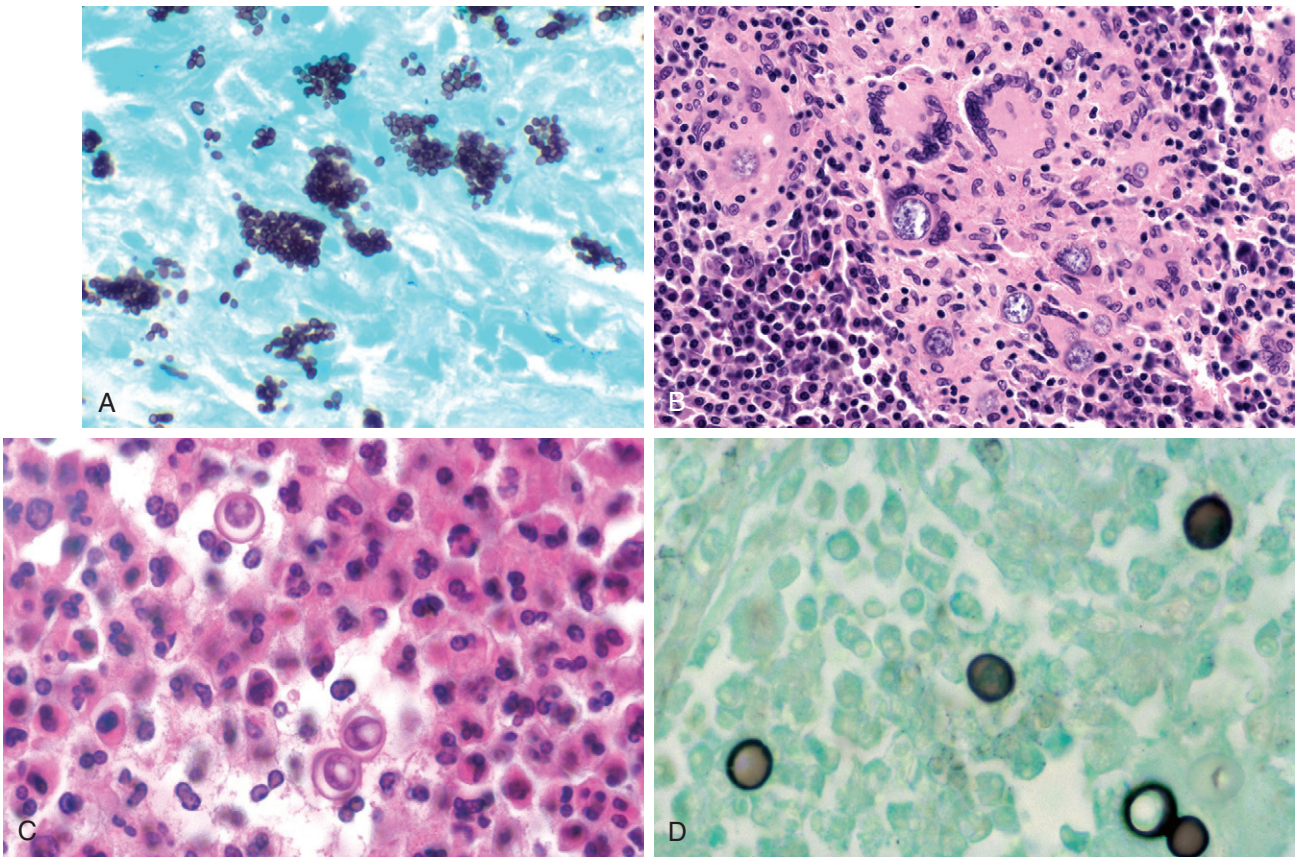

Figure 12–41 A, *Histoplasma capsulatum* yeast forms fill phagocytes in a lymph node of a patient with disseminated histoplasmosis (silver stain). **B,** Coccidioidomycosis with intact spherules within multinucleated giant cells. **C,** Blastomycosis, with rounded budding yeasts, larger than neutrophils. Note the characteristic thick wall and nuclei (not seen in other fungi). **D,** Silver stain highlights the broad-based budding seen in *Blastomyces immitis* organisms.

yeast forms (best seen with silver stains). The clinical symptoms and signs resemble those of a "flulike" syndrome, most often self-limited. In the vulnerable host, chronic cavitary pulmonary disease develops, with a predilection for the upper lobe, resembling the secondary form of tuberculosis. It is not uncommon for these fungi to give rise to perihilar mass lesions that resemble bronchogenic carcinoma radiologically. At this stage, manifestations may include cough, hemoptysis, and even dyspnea and chest pain.

In infants or immunocompromised adults, particularly those with HIV infection, disseminated disease (analogous to miliary tuberculosis) may develop. Under these circumstances there are no well-formed granulomas. Instead, focal collections of phagocytes stuffed with yeast forms are seen within cells of the mononuclear phagocyte system, including in the liver, spleen, lymph nodes, lymphoid tissue of the gastrointestinal tract, and bone marrow. The adrenals and meninges may also be involved, and in a minority of cases, ulcers form in the nose and mouth, on the tongue, or in the larynx. Disseminated disease is a hectic, febrile illness marked by hepatosplenomegaly, anemia, leukopenia, and thrombocytopenia. Cutaneous infections with disseminated *Blastomyces* organisms frequently induce striking epithelial hyperplasia, which may be mistaken for squamous cell carcinoma.

Pneumonia in the Immunocompromised Host

The appearance of a pulmonary infiltrate and signs of infection (e.g., fever) are some of the most common and serious complications in a person in whom the immune and defense systems are suppressed by disease, by immunosuppression for organ transplantation and antitumor therapy, or by irradiation. A wide variety of so-called opportunistic pathogens, many of which rarely cause infection in normal persons, can be the infecting agents with these pneumonias, and often more than one agent is involved. Some of the more common pulmonary pathogens are (1) the bacterial agents *P. aeruginosa*, *Mycobacterium* spp., *L. pneumophila,* and *Listeria monocytogenes*; (2) the viral agents cytomegalovirus and herpesvirus; and (3) the fungal agents *P. jiroveci, Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans.*

Cytomegalovirus Infections

Cytomegalovirus (CMV), a member of the herpesvirus family, may produce a variety of disease manifestations, depending partly on the age of the infected host but even more on the host's immune status. Cells infected by the virus exhibit gigantism of both the entire cell and its nucleus. Within the nucleus is an enlarged inclusion surrounded by a clear halo ("owl's eye"), which gives the

name to the classic form of symptomatic disease that occurs in neonates—cytomegalic inclusion disease. Although classic cytomegalic inclusion disease involves many organs, CMV infections are discussed here because in immunosuppressed adults, particularly patients with AIDS and recipients of allogeneic bone marrow transplants, CMV pneumonitis is a serious problem.

Transmission of CMV can occur by several mechanisms, depending on the age group affected:

- A fetus can be infected transplacentally from a newly acquired or reactivated infection in the mother (*congenital* CMV infection).
- The virus can be transmitted to the baby through cervical or vaginal secretions at birth, or, later, through breast milk from a mother who has active infection (*perinatal* CMV infection).
- Preschool children, especially in day care centers, can acquire it through saliva. Toddlers thus infected readily transmit the virus to their parents.
- In patients older than 15 years of age, the venereal route is the dominant mode of transmission, but spread also may occur through contact with respiratory secretions and by the fecal-oral route.
- Iatrogenic transmission can occur at any age through organ transplantation or blood transfusions.

MORPHOLOGY

Histologically, the characteristic enlargement of cells can be appreciated. In the glandular organs, the parenchymal epithelial cells are affected; in the brain, the neurons; in the lungs, the alveolar macrophages and epithelial and endothelial cells; and in the kidneys, the tubular epithelial and glomerular endothelial cells. **Affected cells are strikingly enlarged, often to a diameter of 40 μm, and exhibit cellular and nuclear polymorphism.** Prominent intranuclear basophilic inclusions spanning half the nuclear diameter are usually set off from the nuclear membrane by a clear halo (Fig. 12–42). Within the cytoplasm of these cells, smaller basophilic inclusions may also be seen.

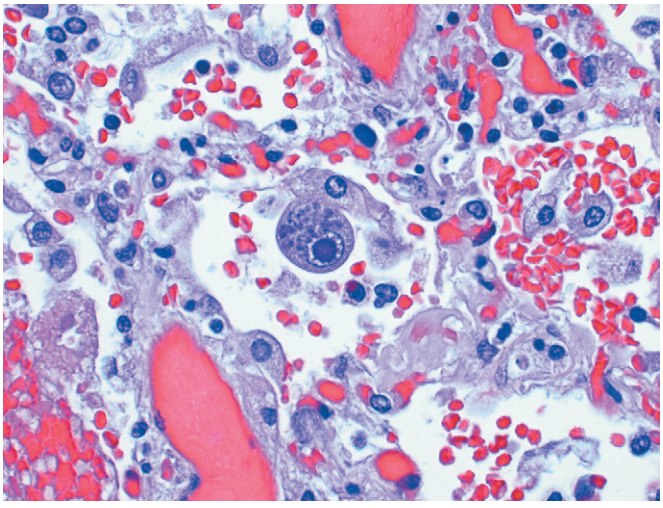

Figure 12–42 Cytomegalovirus infection of the lung. A typical distinct nuclear and multiple cytoplasmic inclusions are seen in an enlarged cell.

Cytomegalovirus Mononucleosis

In healthy young children and adults, the disease is nearly always asymptomatic. In surveys around the world, 50% to 100% of adults demonstrate anti-CMV antibodies in the serum, indicating previous exposure. The most common *clinical manifestation of CMV infection* in immunocompetent hosts beyond the neonatal period is an infectious mononucleosis–like illness, with fever, atypical lymphocytosis, lymphadenopathy, and hepatomegaly accompanied by abnormal liver function test results, suggesting mild hepatitis. Most patients recover from CMV mononucleosis without any sequelae, although excretion of the virus may occur in body fluids for months to years. Irrespective of the presence or absence of symptoms after infection, a person once infected becomes seropositive for life. The virus remains latent within leukocytes, which are the major reservoirs.

Cytomegalovirus Infection in Immunosuppressed Persons

Immunosuppression-related CMV infection occurs most commonly in recipients of transplants (such as heart, liver, kidney, lung, or allogeneic stem cell) and in patients with AIDS. This can be either primary infection or reactivation of a latent infection. CMV is the most common opportunistic viral pathogen in AIDS.

In all of these settings, serious, life-threatening disseminated CMV infections primarily affect the lungs (pneumonitis), gastrointestinal tract (colitis), and retina (retinitis); the central nervous system usually is spared. In pneumonitis, an interstitial mononuclear infiltrate with foci of necrosis develops, accompanied by the typical enlarged cells with inclusions, which can progress to ARDS. Intestinal necrosis and ulceration can develop and be extensive, leading to the formation of "pseudomembranes" (Chapter 14) and debilitating diarrhea. CMV retinitis, by far the most common form of opportunistic CMV disease, can occur either alone or in combination with involvement of the lungs and intestinal tract. Diagnosis of CMV infection is made by demonstration of characteristic viral inclusions in tissue sections, successful viral culture, rising antiviral antibody titer, and qualitative or quantitative PCR assay–based detection of CMV DNA. The latter has revolutionized the approach to monitoring patients after transplantation.

Pneumocystis *Pneumonia*

P. jiroveci (formerly known as *P. carinii*), an opportunistic infectious agent formerly considered to be a protozoan, is now classified as a fungus. Serologic evidence indicates that virtually all persons are exposed to *Pneumocystis* during the first few years of life, but in most the infection remains latent. Reactivation with development of clinical disease occurs almost exclusively in persons who are immunocompromised. Indeed, *P. jiroveci* is an extremely common cause of infection in patients with AIDS, and it also may infect severely malnourished infants and immunosuppressed persons (especially after organ transplantation or in persons receiving cytotoxic chemotherapy or corticosteroids). In patients with AIDS, the risk of acquiring *P. jiroveci* infections increases in inverse proportion to the CD4+ count, with counts less than 200 cells/μL having

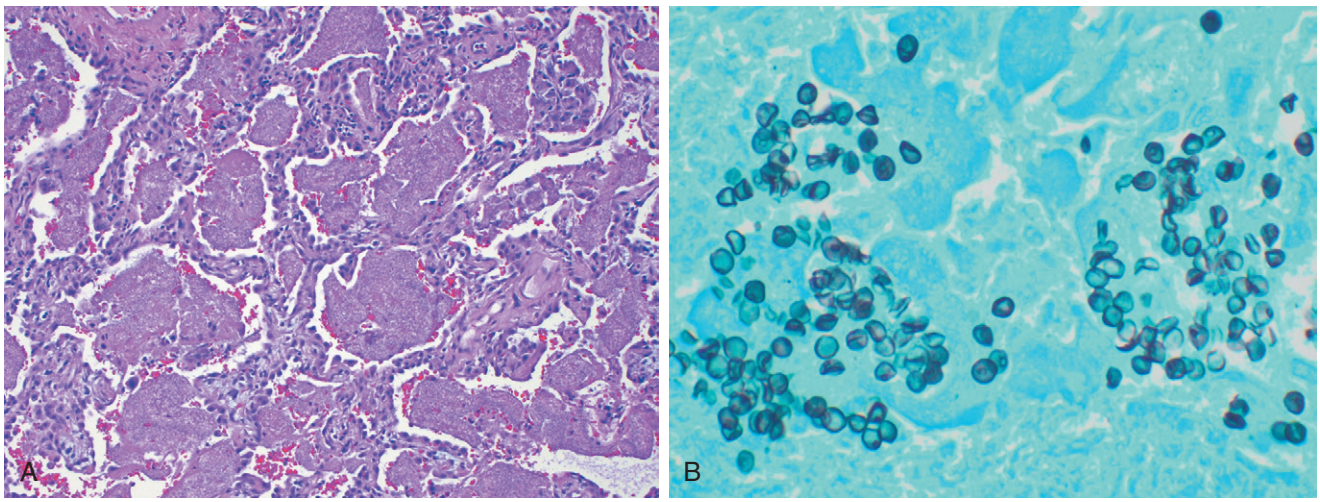

Figure 12–43 *Pneumocystis* pneumonia. **A,** The alveoli are filled with a characteristic foamy acellular exudate. **B,** Silver stain demonstrates cup-shaped and round cysts within the exudate.

a strong predictive value. *Pneumocystis* infection is largely confined to the lung, where it produces an interstitial pneumonitis.

MORPHOLOGY

Microscopically, involved areas of the lung demonstrate a characteristic **intra-alveolar foamy, pink-staining exudate** with hematoxylin-eosin (H&E) stain ("cotton candy" exudate) (Fig. 12–43, *A*). The septa are thickened by edema and a minimal mononuclear infiltrate. Special stains are required to visualize the organism. Silver stain of tissue sections reveals **round to cup-shaped cysts** (4 to 10 μm in diameter), often with intracystic bodies but without budding, in the alveolar exudates (Fig. 12–43, *B*).

The diagnosis of *Pneumocystis* pneumonia should be considered in any immunocompromised patient with respiratory symptoms and abnormal findings on the chest radiograph. Fever, dry cough, and dyspnea occur in 90% to 95% of patients, in whom radiographic evidence of bilateral perihilar and basilar infiltrates is typical. Hypoxia is frequent; pulmonary function studies show a restrictive lung defect. The most sensitive and effective method of diagnosis is to identify the organism in induced sputum or bronchoalveolar lavage fluid using immunofluorescence. If treatment is initiated before widespread involvement, the outlook for recovery is good; however, because residual organisms are likely to persist, particularly in patients with AIDS, relapses are common unless the underlying immunodeficiency is corrected or prophylactic therapy is given.

Opportunistic Fungal Infections

Candidiasis

Candida albicans is the most common disease-causing fungus. It is a normal inhabitant of the oral cavity, gastrointestinal tract, and vagina in many people. Even though systemic candidiasis (with associated pneumonia) is a disease that is restricted to immunocompromised patients, the protean manifestations of infections caused by *Candida* spp. are described in this section.

MORPHOLOGY

In tissue sections, *C. albicans* demonstrates yeastlike forms (blastoconidia), pseudohyphae, and true hyphae (Fig. 12–44, *A*). Pseudohyphae are an important diagnostic clue for *C. albicans* and represent budding yeast cells joined end to end at constrictions, thus simulating true fungal hyphae. The organisms may be visible with routine H&E stains, but a variety of special "fungal" stains (Gomori methenamine-silver, periodic acid–Schiff) commonly are used to better highlight the pathogens.

Clinical Features

Candidiasis can involve the mucous membranes, skin, and deep organs (invasive candidiasis).

- The most common presentation with candidiasis is that of a superficial infection on mucosal surfaces of the oral cavity (thrush). Florid proliferation of the fungi creates gray-white, dirty-looking pseudomembranes composed of matted organisms and inflammatory debris. Deep to the surface, there is mucosal hyperemia and inflammation. This form of candidiasis is seen in newborns, debilitated patients, and children receiving oral corticosteroids for asthma, and after a course of broad-spectrum antibiotics that destroy competing normal bacterial flora. The other major risk group includes HIV-positive patients; patients with oral thrush not associated with an obvious underlying condition should be evaluated for HIV infection.
- *Candida* vaginitis is an extremely common form of vaginal infection in women, especially those who are diabetic or pregnant or on oral contraceptive pills.
- *Candida* esophagitis is common in patients with AIDS and in those with hematolymphoid malignancies. These

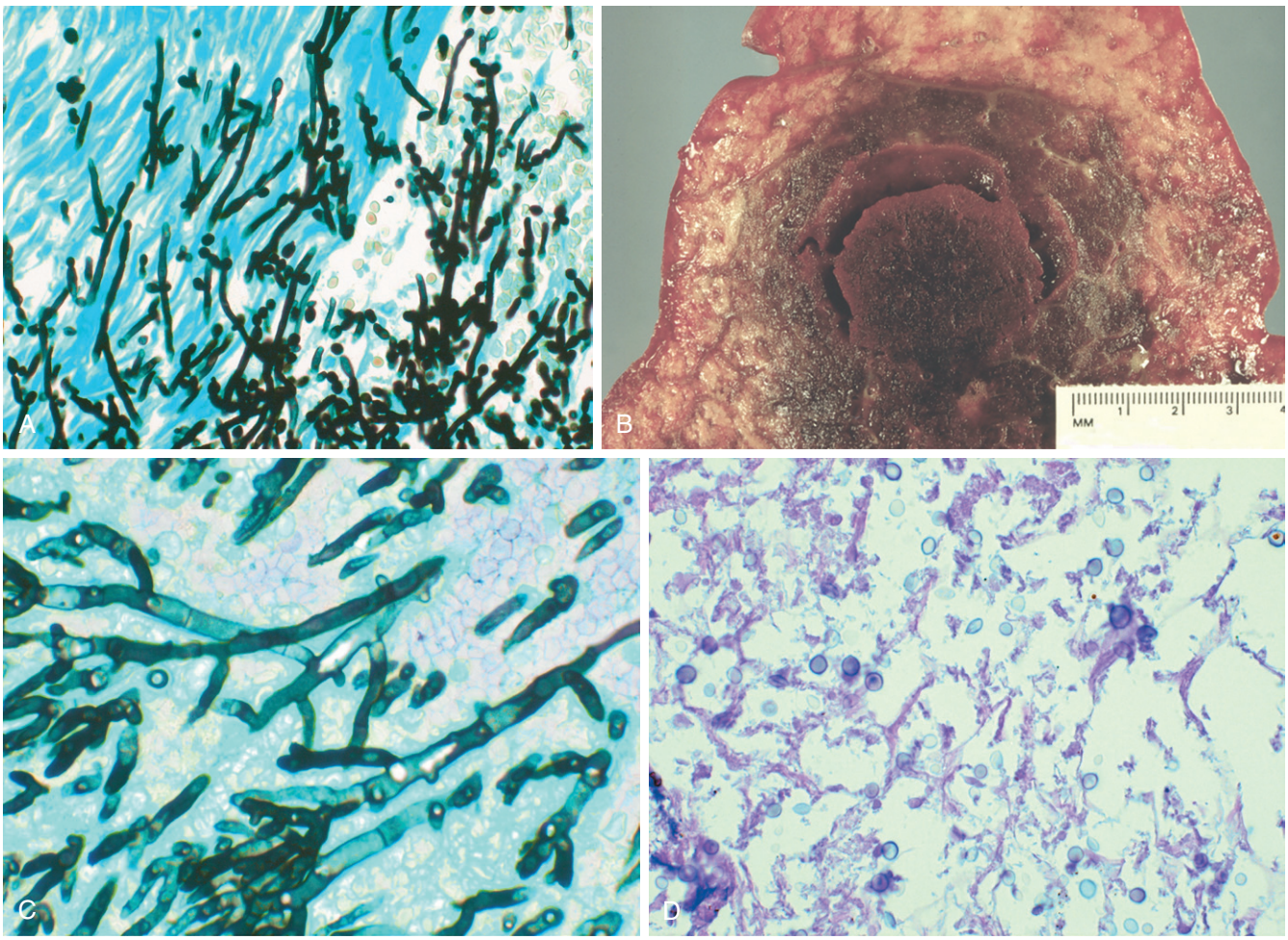

Figure 12–44 The morphology of fungal infections. **A,** *Candida* organism has pseudohyphae and budding yeasts (silver stain). **B,** Invasive aspergillosis (gross appearance) of the lung in a bone marrow transplant recipient. **C,** Gomori methenamine-silver (GMS) stain shows septate hyphae with acute-angle branching, consistent with *Aspergillus*. **D,** Cryptococcosis of the lung in a patient with AIDS. The organisms are somewhat variable in size.

(B, Courtesy of Dr. Dominick Cavuoti, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

patients present with dysphagia (painful swallowing) and retrosternal pain; endoscopy demonstrates white plaques and pseudomembranes resembling the changes of oral thrush on the esophageal mucosa.

- Cutaneous candidiasis can manifest in many different forms, including infection of the nail proper (*onychomycosis*), nail folds (*paronychia*), hair follicles (*folliculitis*), moist, intertriginous skin such as armpits or webs of the fingers and toes (*intertrigo*), and penile skin (*balanitis*). *Diaper rash* often is a cutaneous candidal infection seen in the perineum of infants, in the region of contact of wet diapers.
- Chronic mucocutaneous candidiasis is a chronic refractory disease afflicting the mucous membranes, skin, hair, and nails; it is associated with underlying T cell defects. Associated conditions include endocrinopathies (most commonly hypoparathyroidism and Addison disease) and the presence of autoantibodies. Disseminated candidiasis is rare in this disease. A recent finding is that the T_H17 subset of CD4+ T cells plays an especially important role in defense against *Candida* and a few other fungi. Patients with mutations affecting T_H17 responses are highly susceptible to severe mucocutaneous candidiasis (e.g., "Job syndrome").
- Invasive candidiasis implies blood-borne dissemination of organisms to various tissues or organs. Common patterns include (1) renal abscesses, (2) myocardial abscesses and endocarditis, (3) brain involvement (most commonly meningitis, but parenchymal microabscesses occur), (4) endophthalmitis (virtually any eye structure can be involved), (5) hepatic abscesses, and (6) *Candida* pneumonia, usually manifesting as bilateral nodular infiltrates, resembling *Pneumocystis* pneumonia (see earlier). Patients with acute leukemias who are profoundly neutropenic after chemotherapy are particularly prone to the development of systemic disease. *Candida* endocarditis is the most common fungal endocarditis, usually occurring in patients with prosthetic heart valves or in intravenous drug abusers.

Cryptococcosis

Cryptococcosis, caused by *C. neoformans,* rarely occurs in healthy persons. It almost exclusively manifests as an opportunistic infection in immunocompromised hosts,

particularly patients with AIDS or hematolymphoid malignancies.

MORPHOLOGY

The fungus, a 5- to 10-μm yeast, has a thick, gelatinous capsule and reproduces by budding (Fig. 12–44, *D*). Unlike in *Candida* infections, however, pseudohyphal or true hyphal forms are not seen. **The capsule is invaluable to diagnosis:** (1) In routine H&E stains, the capsule is not directly visible, but often a clear "halo" can be seen surrounding the individual fungi representing the area occupied by the capsule. India ink or periodic acid–Schiff staining effectively highlights the fungus. (2) The capsular polysaccharide antigen is the substrate for the cryptococcal latex agglutination assay, which is positive in more than 95% of patients infected with the organism.

Clinical Features

Human cryptococcosis usually manifests as pulmonary, central nervous system, or disseminated disease. Cryptococcus is most likely to be acquired by inhalation from the soil or from bird droppings. The fungus initially localizes in the lungs and then disseminates to other sites, particularly the meninges. Sites of involvement are marked by a variable tissue response, which ranges from florid proliferation of gelatinous organisms with a minimal or absent inflammatory cell infiltrate (in immunodeficient hosts) to a granulomatous reaction (in the more reactive host). In immunosuppressed patients, fungi grow in gelatinous masses within the meninges or expand the perivascular Virchow-Robin spaces, producing the so-called soap-bubble lesions.

The Opportunistic Molds

Mucormycosis and *invasive aspergillosis* are uncommon infections almost always limited to immunocompromised hosts, particularly those with hematolymphoid malignancies or profound neutropenia, those undergoing corticosteroid therapy, or allogeneic stem cell transplant recipients.

MORPHOLOGY

Mucormycosis is caused by the class of fungi known as Zygomycetes. Their hyphae are **nonseptate** and branch at right angles; by contrast, the hyphae of *Aspergillus* organisms are **septate** and branch at more acute angles (Fig. 12–44, *C*). *Rhizopus* and *Mucor* are the two fungi of medical importance within the Zygomycetes class. Both zygomycetes and *Aspergillus* cause a nondistinctive, suppurative, sometimes granulomatous reaction with a **predilection for invading blood vessel walls, causing vascular necrosis and infarction.**

Clinical Features

In *rhinocerebral* and *pulmonary mucormycosis,* zygomycetes have a propensity to colonize the nasal cavity or sinuses and then spread by direct extension into the brain, orbit, and other head and neck structures. Patients with diabetic ketoacidosis are most likely to develop a fulminant invasive form of rhinocerebral mucormycosis. Pulmonary disease can be localized (e.g., cavitary lesions) or may manifest radiologically with diffuse "miliary" involvement.

Invasive aspergillosis occurs almost exclusively in patients who are immunosuppressed. The fungus preferentially localizes to the lungs, and infection most often manifests as a necrotizing pneumonia (Fig. 12–44, *B*). Systemic dissemination, especially to the brain, is an often fatal complication.

Allergic bronchopulmonary aspergillosis occurs in patients with asthma who develop an exacerbation of symptoms caused by a type I hypersensitivity against the fungus growing in the bronchi. Such patients often have circulating IgE antibodies against *Aspergillus* and peripheral eosinophilia.

Aspergilloma ("fungus ball") formation occurs by colonization of preexisting pulmonary cavities (e.g., ectatic bronchi or lung cysts, posttuberculosis cavitary lesions) by the fungus. These masses may act as ball valves to occlude the cavity, thereby predisposing the patient to infection and hemoptysis.

Pulmonary Disease in Human Immunodeficiency Virus Infection

Pulmonary disease continues to be the leading contributor to morbidity and mortality in HIV-infected persons. Although the use of potent antiretroviral agents and effective chemoprophylaxis has markedly decreased incidence and improved outcome, the plethora of entities involved makes diagnosis and treatment a distinct challenge.

- Despite the emphasis on "opportunistic" infections, it should be recognized that bacterial lower respiratory tract infection caused by the "usual" pathogens is one of the most serious pulmonary disorders in HIV infection. The implicated organisms include *S. pneumoniae, S. aureus, H. influenzae,* and gram-negative rods. Bacterial pneumonias in HIV-infected persons are more common, more severe, and more often associated with bacteremia than in those without HIV infection.
- Not all pulmonary infiltrates in HIV-infected persons are infectious. A host of noninfectious diseases, including Kaposi sarcoma (Chapters 4 and 9), pulmonary non-Hodgkin lymphoma (Chapter 11), and primary lung cancer, occur with increased frequency and must be excluded.
- *The CD4+ T cell count often is useful in narrowing the differential diagnosis.* As a rule of thumb, bacterial and tubercular infections are more likely at higher CD4+ counts (more than 200 cells/mm^3); *Pneumocystis* pneumonia usually occurs at CD4+ counts below 200 cells/mm^3, while CMV and *M. avium* complex infections are uncommon until the very late stages of immunosuppression (CD4+ counts below 50 cells/mm^3).

Finally, an important point is that pulmonary disease in HIV-infected persons may result from more than one cause, and that even common pathogens may be responsible for disease with atypical manifestations.

LUNG TUMORS

Although lungs frequently are the site of metastases from cancers arising in extrathoracic organs, primary lung cancer is also a common disease. Roughly 95% of primary lung tumors are carcinomas; the remaining 5% constitute a miscellaneous group that includes carcinoids, mesenchymal malignancies (e.g., fibrosarcomas, leiomyomas), lymphomas, and a few benign lesions. The most common benign tumor is a spherical, small (3 to 4 cm), discrete "hamartoma" that often shows up as a so-called coin lesion on chest radiographs. It consists mainly of mature cartilage, but this is often admixed with fat, fibrous tissue, and blood vessels in various proportions. Clonal cytogenic abnormalities have been demonstrated, indicating that it is a benign neoplasm, although still commonly referred to as hamartoma.

Carcinomas

Carcinoma of the lung (also known as "lung cancer") is without doubt the single most important cause of cancer-related deaths in industrialized countries. It has long held this position among males in the United States, accounting for about one third of cancer deaths in men, and has become the leading cause of cancer deaths in women as well. American Cancer Society estimates for 2011 included approximately 221,100 new cases of lung cancer and 156,900 deaths. The incidence among males is gradually decreasing, but it continues to increase among females, with more women dying each year from lung cancer than from breast cancers, since 1987. These statistics undoubtedly reflect the causal relationship of cigarette smoking and lung cancer. The peak incidence of lung cancer is in persons in their 50s and 60s. At diagnosis, more than 50% of patients already have distant metastatic disease, while a fourth have disease in the regional lymph nodes. The prognosis with lung cancer is dismal: The 5-year survival rate for all stages of lung cancer combined is about 16%, a figure that has not changed much over the last 30 years; even with disease localized to the lung, a 5-year survival rate of only 45% is typical.

The four major histologic types of carcinomas of the lung are adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma (Table 12–7). In some cases there is a combination of histologic patterns (e.g., small cell carcinoma and adenocarcinoma). Of these, squamous cell and small cell carcinomas show the strongest association with smoking. Possibly because of changes in smoking patterns in the U.S., adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung tumor in recent years. Adenocarcinomas also are by far the most common primary tumors arising in women, in never-smokers, and in persons younger than 45 years.

- Until recently, carcinomas of the lung were classified into two broad groups: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), with the latter including adenocarcinomas and squamous and large cell carcinomas.
- *The key reason for this historical distinction was that virtually all SCLCs have metastasized by the time of diagnosis and hence are not curable by surgery. Therefore, they are best treated by chemotherapy, with or without radiation therapy.* By contrast, NSCLCs were more likely to be resectable and usually responded poorly to chemotherapy; however, now therapies are available that target specific mutated gene products present in the various subtypes of NSCLC, mainly in adenocarcinomas. Thus, NSCLC must be subclassified into histologic and molecular subtypes.

Table 12–7 Histologic Classification of Malignant Epithelial Lung Tumors

Adenocarcinoma*
Acinar, papillary, micropapillary, solid, lepidic predominant, mucinous subtypes
Squamous cell carcinoma
Large cell carcinoma
Large cell neuroendocrine carcinoma
Small cell carcinoma
Combined small cell carcinoma
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Spindle cell carcinoma
Giant cell carcinoma
Carcinoid tumor
Typical, atypical
Carcinomas of salivary gland type
Unclassified carcinoma

*Adenocarcinoma and squamous cell and large cell carcinoma are collectively referred to as non–small cell lung carcinoma (NSCLC).

ETIOLOGY AND PATHOGENESIS

Smoking-related carcinomas of the lung arise by a stepwise accumulation of a multitude of genetic abnormalities (estimated to be in the thousands for small cell carcinoma) that result in transformation of benign progenitor cells in the lung into neoplastic cells.

The sequence of molecular changes is not random but follows a predictable sequence that parallels the histologic progression toward cancer. Thus, inactivation of the putative tumor suppressor genes located on the short arm of chromosome 3 (3p) is a very early event, whereas *TP53* mutations or activation of the *KRAS* oncogene occurs relatively late. More important, it seems that certain genetic changes, such as loss of chromosomal material on 3p, can be found even in benign bronchial epithelium of persons with lung cancer, as well as in the respiratory epithelium of smokers **without** lung cancer, suggesting that large areas of the respiratory mucosa are mutagenized after exposure to carcinogens ("field effect"). On this fertile soil, those cells that accumulate additional mutations ultimately develop into cancer.

A subset of adenocarcinomas, particularly those arising in nonsmoking women of Far Eastern origin, harbor activating mutations of the **epidermal growth factor receptor (EGFR).** Of note, these tumors are sensitive to a class of agents that inhibit EGFR signaling, although the response often is short-lived. EGFR and K-RAS mutations (in 30% of adenocarcinomas) are mutually exclusive. Other mutations occurring in 4% to 6% of adenocarcinomas are EML4-ALK tyrosine kinase fusion genes and c-MET tyrosine kinase gene amplifications. These abnormalities, while rare, are important because of their therapeutic implications, as they can be targeted with tyrosine kinase inhibitors. Indeed, the identification of genetic alterations producing overactive EGFR, ALK, and MET has opened up a new era of "personalized" lung cancer therapy, in which the genetics of the tumor guides the selection of drugs.

With regard to carcinogenic influences, there is strong evidence that **cigarette smoking** and, to a much lesser extent, other environmental insults are the main culprits responsible for the genetic changes that give rise to lung cancers.

About 90% of lung cancers occur in active smokers or those who stopped recently. A nearly linear correlation has been recognized between the frequency of lung cancer and pack-years of cigarette smoking. The increased risk becomes 60 times greater among habitual heavy smokers (two packs a day for 20 years) than among nonsmokers. Since only 11% of heavy smokers develop lung cancer, however, other predisposing factors must be operative in the pathogenesis of this deadly disease. For reasons not entirely clear, women have a higher susceptibility to carcinogens in tobacco than men. Although cessation of smoking decreases the risk of developing lung cancer over time, it may never return to baseline levels. In fact, genetic changes that predate lung cancer can persist for many years in the bronchial epithelium of former smokers. Passive smoking (proximity to cigarette smokers) increases the risk of developing lung cancer to approximately twice that of nonsmokers. The smoking of pipes and cigars also increases the risk, but only modestly.

Other influences may act in concert with smoking or may by themselves be responsible for some lung cancers; witness the increased incidence of this form of neoplasia in miners of radioactive ores; asbestos workers; and workers exposed to dusts containing arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas. Exposure to asbestos increases the risk of lung cancer fivefold in nonsmokers. By contrast, **heavy smokers exposed to asbestos have an approximately 55 times greater risk for development of lung cancer than that for nonsmokers not exposed to asbestos.**

Even though smoking and other environmental influences are paramount in the causation of lung cancer, it is well known that all persons exposed to tobacco smoke do not develop cancer. It is very likely that the mutagenic effect of carcinogens is conditioned by hereditary (genetic) factors. Recall that many chemicals (procarcinogens) require metabolic activation via the P-450 monooxygenase enzyme system for conversion into ultimate carcinogens (Chapter 5). There is evidence that persons with specific genetic polymorphisms involving the P-450 genes have an increased capacity to metabolize procarcinogens derived from cigarette smoke, and thus conceivably incur the greatest risk for development of lung cancer. Similarly, persons whose peripheral blood lymphocytes undergo chromosomal breakages after exposure to tobacco-related carcinogens (mutagen sensitivity genotype) have a greater than 10-fold risk of developing lung cancer over that of control subjects.

The sequential changes leading to cancer have been best documented for squamous cell carcinomas, but they also are present in other histologic subtypes. In essence, there is a linear correlation between the intensity of exposure to cigarette smoke and the appearance of ever more worrisome epithelial changes that begin with rather innocuous basal cell hyperplasia and squamous metaplasia and progress to squamous dysplasia and carcinoma in situ, before culminating in invasive cancer. **Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure.**

MORPHOLOGY

Carcinomas of the lung begin as small mucosal lesions that typically are firm and gray-white. They may arise as intraluminal masses, invade the bronchial mucosa, or form large bulky masses pushing into adjacent lung parenchyma. Some large masses undergo cavitation secondary to central necrosis or develop focal areas of hemorrhage. Finally, these tumors may extend to the pleura, invade the pleural cavity and chest wall, and spread to adjacent intrathoracic structures. More distant spread can occur by way of the lymphatics or the hematogenous route.

Squamous cell carcinomas are more common in men than in women and are closely correlated with a smoking history; they tend to **arise centrally in major bronchi** and eventually spread to local hilar nodes, but they disseminate outside the thorax later than do other histologic types. Large lesions may undergo central necrosis, giving rise to **cavitation.** The preneoplastic lesions that antedate, and usually accompany, invasive squamous cell carcinoma are well characterized. Squamous cell carcinomas often are preceded by the development, over years, of **squamous metaplasia or dysplasia** in the bronchial epithelium, which then transforms to **carcinoma in situ,** a phase that may last for several years (Fig. 12–45). By this time, atypical cells may be identified in cytologic smears of sputum or in bronchial lavage fluids or brushings, although the lesion is asymptomatic and undetectable on radiographs. Eventually, the small neoplasm reaches a symptomatic stage, when a well-defined tumor mass begins to obstruct the lumen of a major bronchus, often producing distal atelectasis and infection. Simultaneously, the lesion invades surrounding pulmonary substance (Fig. 12–46, *A*). On histologic examination, these tumors range from well-differentiated squamous cell neoplasms showing keratin pearls (Fig. 12–46, *B*) and intercellular bridges to poorly differentiated neoplasms exhibiting only minimal residual squamous cell features.

Adenocarcinomas may occur as central lesions like the squamous cell variant but usually are more **peripherally located,** many with a central scar. Adenocarcinomas are the most common type of lung cancer in women and nonsmokers. In general, adenocarcinomas grow slowly and form smaller masses than do the other subtypes, but they tend to metastasize widely at an early stage. On histologic examination, they may assume a variety of forms, including **acinar (gland-forming)** (Fig. 12–47, *C*), **papillary, mucinous** (formerly mucinous bronchioloalveolar carcinoma, which often is multifocal and may manifest as pneumonia-like consolidation), and **solid types.** The solid variant often requires demonstration of intracellular mucin production by special stains to establish its adenocarcinomatous lineage.

Although foci of squamous metaplasia and dysplasia may be present in the epithelium proximal to resected adenocarcinomas, these are not the precursor lesions for this tumor. The putative precursor of peripheral adenocarcinomas is thought to be **atypical adenomatous hyperplasia** (AAH) (Fig. 12–47, *A*) which progresses to adenocarcinoma in situ (formerly bronchioloalveolar carcinoma), minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component measuring 5 mm or less), and invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm). On microscopic examination, AAH is recognized as a

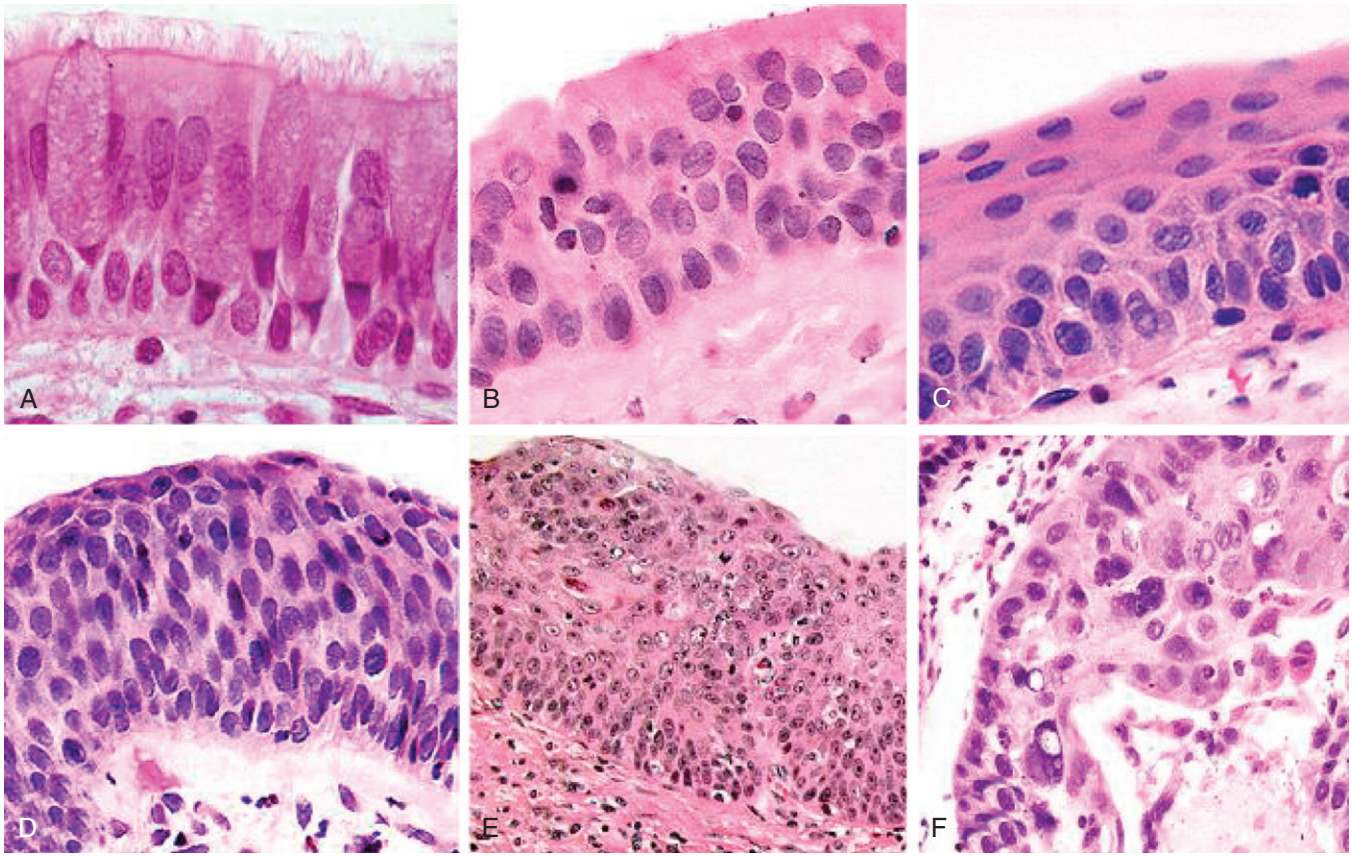

Figure 12–45 Precursor lesions of squamous cell carcinomas that may antedate the appearance of invasive tumor by years. **A–C,** Some of the earliest (and "mild") changes in smoking-damaged respiratory epithelium include goblet cell hyperplasia (**A**), basal cell (or reserve cell) hyperplasia (**B**), and squamous metaplasia (**C**). **D,** More ominous changes include the appearance of squamous dysplasia, characterized by the presence of disordered squamous epithelium, with loss of nuclear polarity, nuclear hyperchromasia, pleomorphism, and mitotic figures. **E** and **F,** Squamous dysplasia may, in turn, progress through the stages of mild, moderate, and severe dysplasia. Carcinoma in situ (CIS) (**E**) is the stage that immediately precedes invasive squamous carcinoma (**F**). Apart from the lack of basement membrane disruption in CIS, the cytologic features of CIS are similar to those in frank carcinoma. Unless treated, CIS eventually progresses to invasive cancer.

(A–E, Courtesy of Dr. Adi Gazdar, Department of Pathology, University of Texas Southwestern Medical School, Dallas. F, Reproduced with permission from Travis WD, Colby TV, Corrin B, et al [eds]: World Health Organization Histological Typing of Lung and Pleural Tumours. Heidelberg, Springer, 1999.)

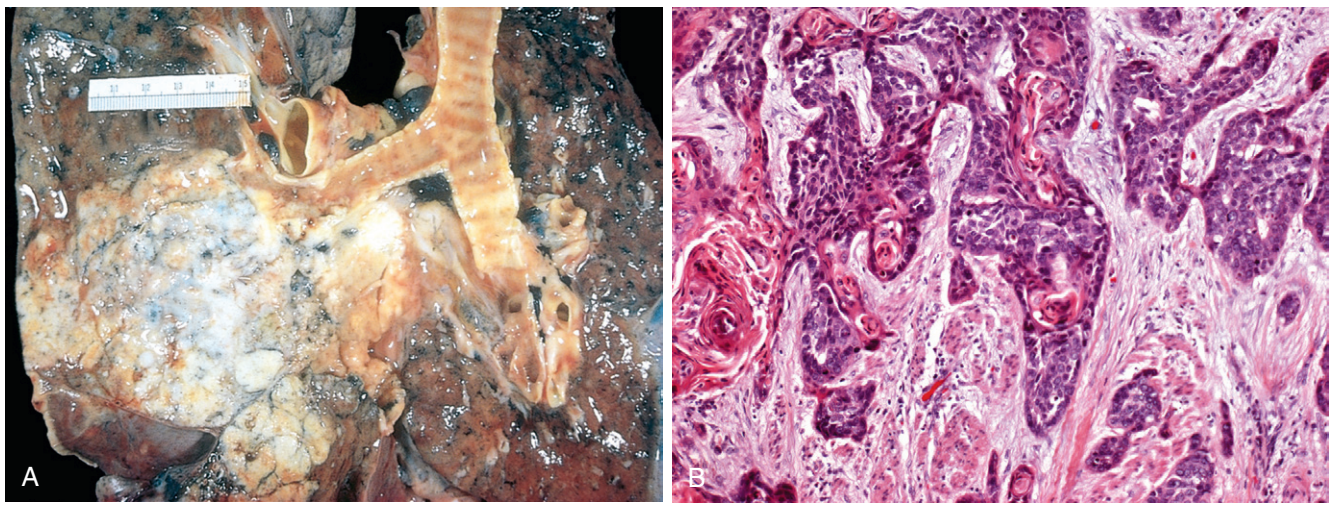

Figure 12–46 **A**, Squamous cell carcinoma usually begins as a central (hilar) mass and grows contiguously into the peripheral parenchyma as seen here. **B,** Well-differentiated squamous cell carcinoma showing keratinization and pearls.

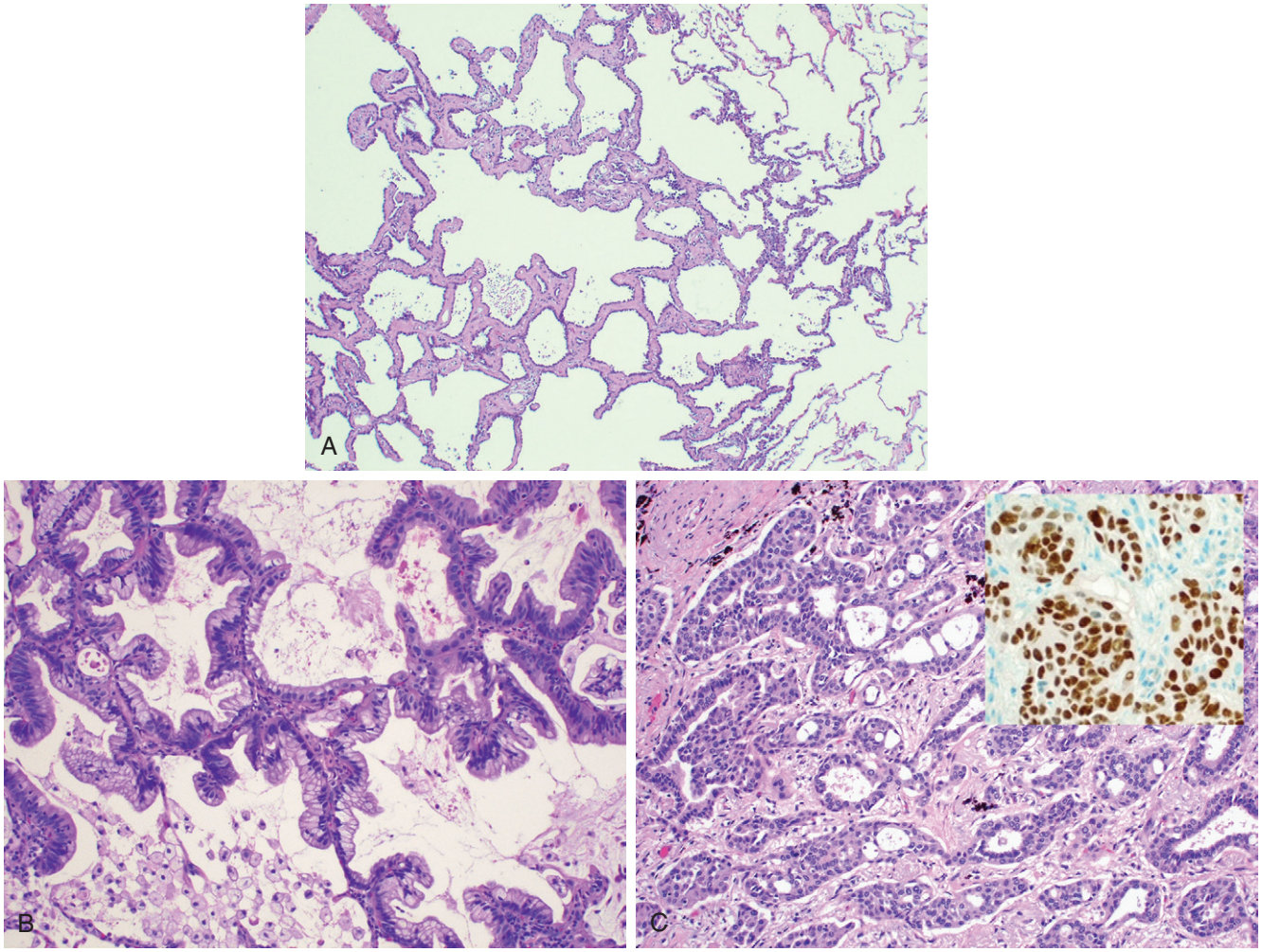

Figure 12–47 Glandular lesions of the lung. **A,** Atypical adenomatous hyperplasia with cuboidal epithelium and mild interstitial fibrosis. **B,** Adenocarcinoma in situ, mucinous subtype, with characteristic growth along preexisting alveolar septa, without invasion. **C,** Gland-forming adenocarcinoma; inset shows thyroid transcription factor 1 (TTF-1) positivity, which is seen in a majority of pulmonary adenocarcinomas.

well-demarcated focus of epithelial proliferation (with a thickness of 5 mm or less) composed of cuboidal to low-columnar cells, which demonstrate cytologic atypia of variable degree such as nuclear hyperchromasia, pleomorphism, prominent nucleoli, but not to the extent seen in adenocarcinoma. Genetic analyses have shown that lesions of AAH are monoclonal, and they share many of the molecular aberrations associated with adenocarcinomas (e.g., *K-RAS* mutations).

Adenocarcinoma in situ (AIS), formerly called bronchioloalveolar carcinoma, often involves peripheral parts of the lung, as a single nodule. **The key features of AIS are diameter of 3 cm or less, growth along preexisting structures, and preservation of alveolar architecture** (Fig. 12–47, *B*). The tumor cells, which may be nonmucinous, mucinous, or mixed, grow in a monolayer along the alveolar septa, which serve as a scaffold (this has been termed a "lepidic" growth pattern, an allusion to the resemblance of neoplastic cells to butterflies sitting on a fence). By definition, AIS does not demonstrate destruction of alveolar architecture or stromal invasion with desmoplasia, features that would merit the diagnosis of frank adenocarcinoma. By analogy to the adenoma–carcinoma sequence in the colon, it is proposed that some invasive adenocarcinomas of the lung may arise through an atypical adenomatous hyperplasia–adenocarcinoma in situ–invasive adenocarcinoma sequence. Studies of lung injury models in mice have now identified a population of multipotent cells at the bronchioloalveolar duct junction, termed bronchioalveolar stem cells (BASCs). After peripheral lung injury, the multipotent BASCs undergo expansion, replenishing the normal cell types (bronchiolar Clara cells and alveolar cells) found in this location, thereby facilitating epithelial regeneration. It is postulated that BASCs incur the initiating oncogenic event (for example, a somatic *K-RAS* mutation) that enables these cells to escape normal "checkpoint" mechanisms and results in pulmonary adenocarcinomas.

Large cell carcinomas are undifferentiated malignant epithelial tumors that lack the cytologic features of small cell carcinoma and have no glandular or squamous differentiation. The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm. Large cell carcinomas probably represent squamous cell or adenocarcinomas that are so undifferentiated that they can no longer be recognized by means of light microscopy. On ultrastructural examination, however, minimal glandular or squamous differentiation is common.

Small cell lung carcinomas (SCLCs) generally appear as pale gray, **centrally located masses** with extension into

the lung parenchyma and early involvement of the hilar and mediastinal nodes. These cancers are composed of tumor cells with a round to fusiform shape, scant cytoplasm, and finely granular chromatin. Mitotic figures frequently are seen (Fig. 12–48). Despite the appellation of **small,** the neoplastic cells are usually twice the size of resting lymphocytes. Necrosis is invariably present and may be extensive. The tumor cells are markedly fragile and often show fragmentation and "crush artifact" in small biopsy specimens. Another feature of small cell carcinomas, best appreciated in cytologic specimens, is nuclear molding resulting from close apposition of tumor cells that have scant cytoplasm. These tumors often express a variety of neuroendocrine markers (Table 12–8) in addition to secreting a host of polypeptide hormones that may result in paraneoplastic syndromes (see below).

Combined patterns require no further comment. Of note, however, a significant minority of lung carcinomas reveal more than one line of cellular differentiation, sometimes several (Table 12–7), suggesting that all are derived from a multipotential progenitor cell.

For all of these neoplasms, it is possible to trace involvement of successive chains of nodes about the carina, in the mediastinum, and in the neck (scalene nodes) and clavicular regions and, sooner or later, distant metastases. Involvement of the left supraclavicular node (Virchow node) is particularly characteristic and sometimes calls attention to an occult primary tumor. These cancers, when advanced, often extend into the pleural or pericardial space, leading to inflammation and effusion. They may compress or infiltrate the superior vena cava to cause either venous congestion or the vena caval syndrome (Chapter 9). Apical neoplasms may invade the brachial or cervical sympathetic plexus to cause severe pain in the distribution of the ulnar nerve or to produce Horner syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis). Such apical neoplasms sometimes are called **Pancoast tumors,** and the combination of clinical findings is known as Pancoast syndrome. Pancoast tumor often is accompanied by destruction of the first and second ribs and sometimes thoracic vertebrae. As with other cancers, tumor-node-metastasis (TNM) categories have been established to indicate the size and spread of the primary neoplasm.

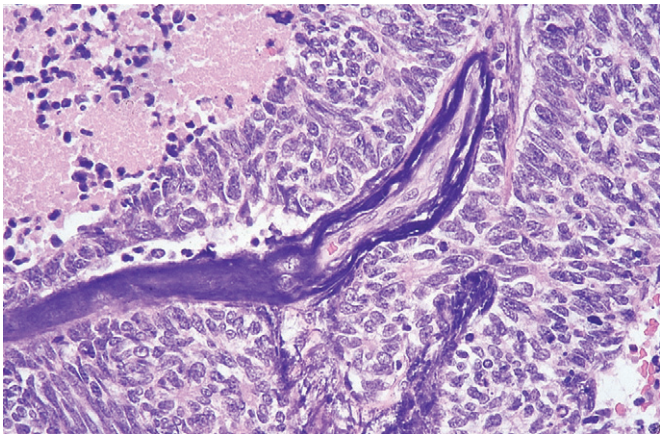

Figure 12–48 Small cell carcinoma with small deeply basophilic cells and areas of necrosis (*top left*). Note basophilic staining of vascular walls due to encrustation by DNA from necrotic tumor cells (Azzopardi effect).

Table 12–8 Comparison of Small Cell Lung Carcinoma (SCLC) and Non–Small Cell Lung Carcinoma (NSCLC)

Feature	SCLC	NSCLC
Histology	Scant cytoplasm; small, hyperchromatic nuclei with fine chromatin pattern; nucleoli indistinct; diffuse sheets of cells	Abundant cytoplasm; pleomorphic nuclei with coarse chromatin pattern; nucleoli often prominent; glandular or squamous architecture
Neuroendocrine markers For example, dense core granules on electron microscopy; expression of chromogranin, neuron-specific enolase, and synaptophysin	Usually present	Usually absent
Epithelial markers Epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin intermediate filaments	Present	Present
Mucin	Absent	Present in adenocarcinomas
Peptide hormone production	Adrenocorticotropic hormone, antidiuretic hormone, gastrin-releasing peptide, calcitonin	Parathyroid hormone–related peptide (PTH-rp) in squamous cell carcinoma
Tumor suppressor gene abnormalities		
3p deletions	>90%	>80%
Rb mutations	~90%	~20%
p16/CDKN2A mutations	~10%	>50%
P53 mutations	>90%	>50%
Dominant oncogene abnormalities		
KRAS mutations	Rare	~30% (adenocarcinomas)
EGFR mutations	Absent	~20% (adenocarcinomas, nonsmokers, women)
ALK rearrangements	Absent	4%–6% adenocarcinomas, nonsmokers, often have signet ring morphology
Response to chemotherapy and radiotherapy	Often complete response but recur invariably	Uncommonly, complete response

Clinical Course

Carcinomas of the lung are silent, insidious lesions that in many cases have spread so as to be unresectable before they produce symptoms. In some instances, chronic cough and expectoration call attention to still localized, resectable disease. By the time hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion, or persistent segmental atelectasis or pneumonitis makes its appearance, the prognosis is grim. Too often, the tumor presents with symptoms emanating from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain). Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon, because islands of cortical cells sufficient to maintain adrenal function usually persist.

Overall, NSCLCs carry a better prognosis than SCLCs. When NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, cure is possible by lobectomy or pneumonectomy. SCLCs, on the other hand, have invariably spread by the time they are first detected, even if the primary tumor appears small and localized. Thus, surgical resection is not a viable treatment. They are very sensitive to chemotherapy but invariably recur. Median survival even with treatment is 1 year.

It is variously estimated that 3% to 10% of all patients with lung cancer develop clinically overt *paraneoplastic syndromes.* These include (1) hypercalcemia caused by secretion of a parathyroid hormone–related peptide (osteolytic lesions may also cause hypercalcemia, but this would not be a paraneoplastic syndrome [Chapter 5]); (2) Cushing syndrome (from increased production of adrenocorticotropic hormone); (3) syndrome of inappropriate secretion of antidiuretic hormone; (4) neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis; (5) clubbing of the fingers and hypertrophic pulmonary osteoarthropathy; and (6) coagulation abnormalities, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation. Secretion of calcitonin and other ectopic hormones also has been documented by assays, but these products usually do not provoke distinctive syndromes. Hypercalcemia most often is encountered with squamous cell neoplasms, the hematologic syndromes with adenocarcinomas. The remaining syndromes are much more common with small cell neoplasms, but exceptions abound.

SUMMARY

Carcinomas of the Lung

- The four major histologic subtypes are adenocarcinomas (most common), squamous cell carcinoma, large cell carcinoma, and small cell carcinoma.
- Each of these is clinically and genetically distinct. SCLCs are best treated by chemotherapy, because almost all are metastatic at presentation. The other carcinomas may be curable by surgery if limited to the lung. Combination chemotherapy also is available along with anti-EGFR therapy for those adenocarcinomas with EGFR mutations, and ALK inhibitors for those with ALK mutations.
- Smoking is the most important risk factor for lung cancer; in women and nonsmokers, adenocarcinomas are the most common cancers.
- Precursor lesions include squamous dysplasia (for squamous cancer) and atypical adenomatous hyperplasia and adenocarcinoma in situ (formerly bronchioloalveolar carcinoma) (for some adenocarcinomas).
- Tumors 3 cm or less in diameter characterized by pure growth along preexisting structures (lepidic pattern) without stromal invasion are now called adenocarcinoma in situ.
- Lung cancers, particularly SCLCs, can cause *paraneoplastic syndromes*.

Carcinoid Tumors

Carcinoid tumors are malignant tumors composed of cells that contain dense-core neurosecretory granules in their cytoplasm and, rarely, may secrete hormonally active polypeptides. They are classified into typical (low-grade) and atypical (intermediate-grade) carcinoids; both are often resectable and curable. They occasionally occur as part of the multiple endocrine neoplasia syndrome (Chapter 19). Bronchial carcinoids occur at an early age (mean 40 years) and represent about 5% of all pulmonary neoplasms.

MORPHOLOGY

Most carcinoids originate in main bronchi and grow in one of two patterns: (1) an obstructing polypoid, spherical, intraluminal mass (Fig. 12–49, *A*); or (2) a mucosal plaque penetrating the bronchial wall to fan out in the peribronchial tissue—the so-called collar-button lesion. Even these penetrating lesions push into the lung substance along a broad front and are therefore reasonably well demarcated. Peripheral carcinoids are less common. Although 5% to 15% of carcinoids have metastasized to the hilar nodes at presentation, distant metastases are rare. Histologically, **typical carcinoids,** like their counterparts in the intestinal tract, are composed of nests of uniform cells that have regular round nuclei with "salt-and-pepper" chromatin, absent or rare mitoses, and little pleomorphism (Fig. 12–49, *B*). **Atypical carcinoid** tumors display a higher mitotic rate (but less than small or large cell carcinomas) and focal necrosis. The atypical tumors have a higher incidence of lymph node and distant metastasis than typical carcinoids. Unlike typical carcinoids, the atypical subset demonstrates *TP53* mutations in 20% to 40% of cases. **Typical carcinoid, atypical carcinoid, and small cell carcinoma can be considered to represent a continuum of increasing histologic aggressiveness and malignant potential within the spectrum of pulmonary neuroendocrine neoplasms.**

Most carcinoid tumors manifest with signs and symptoms related to their intraluminal growth (i.e., they cause cough, hemoptysis, and recurrent bronchial and pulmonary infections). Peripheral tumors are often asymptomatic, being discovered incidentally on chest radiographs.

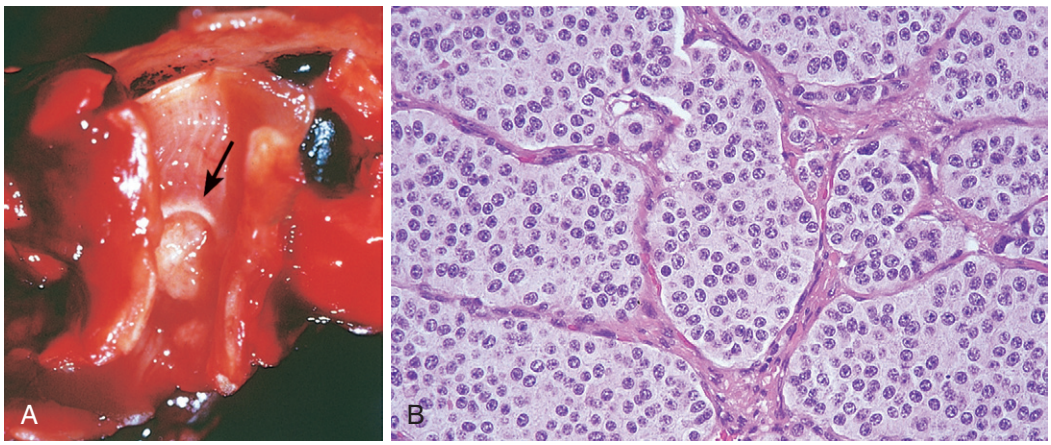

Figure 12-49 Bronchial carcinoid. **A,** Carcinoid growing as a spherical, pale mass *(arrow)* protruding into the lumen of the bronchus. **B,** Histologic appearance demonstrating small, rounded, uniform nuclei and moderate cytoplasm.
(Courtesy of Dr. Thomas Krausz, Department of Pathology, University of Chicago Pritzker School of Medicine, Chicago, Illinois.)

Only rarely do they induce the *carcinoid syndrome,* characterized by intermittent attacks of diarrhea, flushing, and cyanosis. The reported 5- and 10-year survival rates for typical carcinoids are above 85%, while these rates drop to 56% and 35%, respectively, for atypical carcinoids. Only 5% of patients with the most aggressive neuroendocrine lung tumor—SCLC—are alive at 10 years.

PLEURAL LESIONS

Pathologic involvement of the pleura is, with rare exceptions, a secondary complication of an underlying pulmonary disease. Evidence of secondary infection and pleural adhesions are particularly common findings at autopsy. Important primary disorders are (1) primary intrapleural bacterial infections and (2) a primary neoplasm of the pleura known as *malignant mesothelioma.*

Pleural Effusion and Pleuritis

In pleural effusion (the presence of fluid in the pleural space) the fluid can be either a transudate or an exudate. When the pleural fluid is a transudate, the condition is termed *hydrothorax.* Hydrothorax from CHF probably is the most common cause of fluid accumulation in the pleural cavity. An exudate, characterized by protein content greater than 2.9gm/dL and, often, inflammatory cells, suggests pleuritis. The four principal causes of *pleural exudate* formation are (1) microbial invasion through either direct extension of a pulmonary infection or blood-borne seeding (*suppurative pleuritis* or *empyema*); (2) cancer (lung carcinoma, metastatic neoplasms to the lung or pleural surface, mesothelioma); (3) pulmonary infarction; and (4) viral pleuritis. Other, less common causes of exudative pleural effusions are systemic lupus erythematosus, rheumatoid arthritis, and uremia, as well as previous thoracic surgery. Malignant effusions characteristically are large and frequently bloody (*hemorrhagic pleuritis*). Cytologic examination may reveal malignant and inflammatory cells.

Whatever the cause, transudates and serous exudates usually are resorbed without residual effects if the inciting cause is controlled or remits. By contrast, fibrinous, hemorrhagic, and suppurative exudates may lead to fibrous organization, yielding adhesions or fibrous pleural thickening, and sometimes minimal to massive calcifications.

Pneumothorax, Hemothorax, and Chylothorax

Pneumothorax refers to presence of air or other gas in the pleural sac. It may occur in young, apparently healthy adults, usually men without any known pulmonary disease (simple or spontaneous pneumothorax), or as a result of some thoracic or lung disorder (secondary pneumothorax), such as emphysema or a fractured rib. Secondary pneumothorax is the consequence of rupture of any pulmonary lesion situated close to the pleural surface that allows inspired air to gain access to the pleural cavity. Such pulmonary lesions include emphysema, lung abscess, tuberculosis, carcinoma, and many other, less common processes. Mechanical ventilatory support with high pressure also may trigger secondary pneumothorax.

There are several possible complications of pneumothorax. A ball-valve leak may create a tension pneumothorax that shifts the mediastinum. Compromise of the pulmonary circulation may follow and may even be fatal. If the leak seals and the lung is not reexpanded within a few weeks (either spontaneously or through medical or surgical intervention), so much scarring may occur that it can never be fully reexpanded. In these cases, serous fluid collects in the pleural cavity, creating hydropneumothorax. With prolonged collapse, the lung becomes vulnerable to infection, as does the pleural cavity when communication between it and the lung persists. Empyema is thus an important complication of pneumothorax (pyopneumothorax).

Hemothorax, the collection of whole blood (in contrast with bloody effusion) in the pleural cavity, is a complication of a ruptured intrathoracic aortic aneurysm that is almost always fatal. With hemothorax, in contrast with bloody pleural effusions, the blood clots within the pleural cavity.

Chylothorax is a pleural collection of a milky lymphatic fluid containing microglobules of lipid. The total volume

of fluid may not be large, but chylothorax is always significant because it implies obstruction of the major lymph ducts, usually by an intrathoracic cancer (e.g., a primary or secondary mediastinal neoplasm, such as a lymphoma).

Malignant Mesothelioma

Malignant mesothelioma is a rare cancer of mesothelial cells, usually arising in the parietal or visceral pleura, although it also occurs, much less commonly, in the peritoneum and pericardium. It has assumed great importance because it is related to occupational exposure to asbestos in the air. Approximately 50% of persons with this cancer have a history of exposure to asbestos. Those who work directly with asbestos (shipyard workers, miners, insulators) are at greatest risk, but malignant mesotheliomas have appeared in persons whose only exposure was living in proximity to an asbestos factory or being a relative of an asbestos worker. The latent period for developing malignant mesothelioma is long, often 25 to 40 years after initial asbestos exposure, suggesting that multiple somatic genetic events are required for neoplastic conversion of a mesothelial cell. As stated earlier, *the combination of cigarette smoking and asbestos exposure greatly increases the risk of lung carcinoma, but it does not increase the risk of developing malignant mesothelioma.*

MORPHOLOGY

Malignant mesotheliomas are often preceded by extensive **pleural fibrosis and plaque formation,** readily seen on computed tomography scans. These tumors begin in a localized area and over time spread widely, either by contiguous growth or by diffusely seeding the pleural surfaces. At autopsy, the affected lung **typically is ensheathed by a yellow-white, firm, sometimes gelatinous layer of tumor** that obliterates the pleural space (Fig. 12–50). Distant metastases are rare. The neoplasm may directly invade the thoracic wall or the subpleural lung tissue. Normal mesothelial cells are biphasic, giving rise to pleural lining cells as well as the underlying fibrous tissue. Therefore, histologically, mesotheliomas conform to one of three patterns: (1) **epithelial,** in which cuboidal cells line tubular and microcystic spaces, into which small papillary buds project; this is the most common pattern and also the one most likely to be confused with a pulmonary adenocarcinoma; (2) **sarcomatous,** in which spindled and sometimes fibroblastic-appearing cells grow in nondistinctive sheets; and (3) **biphasic,** having both sarcomatous and epithelial areas.

Asbestos is not removed or metabolized from the lung, so the fibers remain in the body for life. Thus, the lifetime risk after exposure does not diminish over time (unlike with smoking, in which the risk decreases after cessation). It has been hypothesized that asbestos fibers preferentially gather near the mesothelial cell layer, where they generate reactive oxygen species, which cause DNA damage with potentially oncogenic mutations. Somatic mutations of two tumor suppressor genes (*p16/CDKN2A,* at chromosomal locus 9p21, and *NF2,* at chromosomal locus 22q12) have been observed in malignant mesotheliomas.

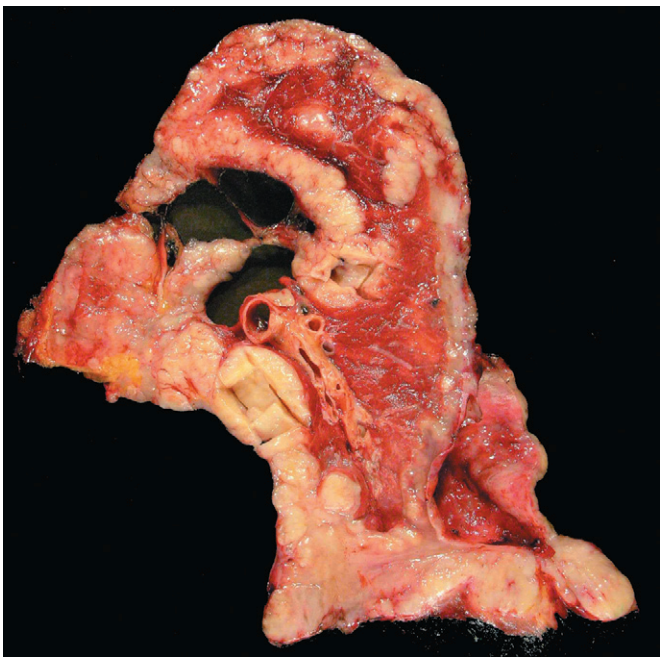

Figure 12–50 Malignant mesothelioma. Note the thick, firm, white pleural tumor that ensheathes this bisected lung.

LESIONS OF THE UPPER RESPIRATORY TRACT

Acute Infections

Acute infections of the upper respiratory tract are among the most common afflictions of humans, most frequently manifesting as the "common cold." The clinical features are well known: nasal congestion accompanied by watery discharge; sneezing; scratchy, dry sore throat; and a slight increase in temperature that is more pronounced in young children. The most common pathogens are rhinoviruses, but coronaviruses, respiratory syncytial viruses, parainfluenza and influenza viruses, adenoviruses, enteroviruses, and sometimes even group A β-hemolytic streptococci have been implicated. In a significant number of cases (around 40%) the cause cannot be determined; perhaps new viruses will be discovered. Most of these infections occur in the fall and winter and are self-limiting (usually lasting for a week or less). In a minority of cases, colds may be complicated by the development of bacterial otitis media or sinusitis.

In addition to the common cold, infections of the upper respiratory tract may produce signs and symptoms localized to the pharynx, epiglottis, or larynx. *Acute pharyngitis,* manifesting as a sore throat, may be caused by a host of agents. Mild pharyngitis with minimal physical findings frequently accompanies a cold and is the most common form of pharyngitis. More severe forms with tonsillitis, associated with marked hyperemia and exudates, occur with β-hemolytic streptococcal and adenovirus infections. Streptococcal tonsillitis is important to recognize and treat early, because of the associated potential for development of peritonsillar abscesses ("quinsy") or for progression to poststreptococcal glomerulonephritis and acute rheumatic

fever. Coxsackievirus A infection may produce pharyngeal vesicles and ulcers (herpangina). Infectious mononucleosis, caused by Epstein-Barr virus (EBV), is an important cause of pharyngitis and bears the moniker of "kissing disease"—reflecting the common mode of transmission in previously nonexposed persons.

Acute *bacterial epiglottitis* is a syndrome predominantly affecting young children who have an infection of the epiglottis caused by *H. influenzae,* in which pain and airway obstruction are the major findings. The onset is abrupt. Failure to appreciate the need to maintain an open airway for a child with this condition can have fatal consequences. The advent of vaccination against *H. influenzae* has greatly decreased the incidence of this disease.

Acute laryngitis can result from inhalation of irritants or may be caused by allergic reactions. It may also be caused by the agents that produce the common cold and usually involve the pharynx and nasal passages as well as the larynx. Brief mention should be made of two uncommon but important forms of laryngitis: *tuberculous* and *diphtheritic.* The former is almost always a consequence of protracted active tuberculosis, during which infected sputum is coughed up. Diphtheritic laryngitis has fortunately become uncommon because of the widespread immunization of young children against diphtheria toxin. After it is inhaled, *Corynebacterium diphtheriae* implants on the mucosa of the upper airways, where it elaborates a powerful exotoxin that causes necrosis of the mucosal epithelium, accompanied by a dense fibrinopurulent exudate, to create the classic superficial, dirty-gray pseudomembrane of diphtheria. The major hazards of this infection are sloughing and aspiration of the pseudomembrane (causing obstruction of major airways) and absorption of bacterial exotoxins (producing myocarditis, peripheral neuropathy, or other tissue injury).

In children, parainfluenza virus is the most common cause of laryngotracheobronchitis, more commonly known as *croup,* but other agents such as respiratory syncytial virus also may precipitate this condition. Although self-limited, croup may cause frightening inspiratory stridor and harsh, persistent cough. In occasional cases, the laryngeal inflammatory reaction may narrow the airway sufficiently to result in respiratory failure. Viral infections in the upper respiratory tract predispose the patient to secondary bacterial infection, particularly by staphylococci, streptococci, and *H. influenzae.*

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is a rare neoplasm that merits comment because of (1) the strong epidemiologic links to EBV and (2) the high frequency of this form of cancer among the Chinese, which raises the possibility of viral oncogenesis on a background of genetic susceptibility. It is thought that EBV infects the host by first replicating in the nasopharyngeal epithelium and then infecting nearby tonsillar B lymphocytes. In some persons this leads to transformation of the epithelial cells. Unlike the case with Burkitt lymphoma (Chapter 11), another EBV-associated tumor, the EBV genome is found in virtually all nasopharyngeal carcinomas, including those that occur outside the endemic areas in Asia.

The three histologic variants are keratinizing squamous cell carcinoma, nonkeratinizing squamous cell carcinoma, and undifferentiated carcinoma; the last-mentioned is the most common and the one most closely linked with EBV. The undifferentiated neoplasm is characterized by large epithelial cells with indistinct cell borders (reflecting "syncytial" growth) and prominent eosinophilic nucleoli. As described in Chapter 11, in infectious mononucleosis, EBV directly infects B lymphocytes, after which a marked proliferation of reactive T lymphocytes causes atypical lymphocytosis, seen in the peripheral blood, and enlarged lymph nodes. Similarly, in nasopharyngeal carcinomas, a striking influx of mature lymphocytes often can be seen. These neoplasms are therefore referred to as "lymphoepitheliomas"—a misnomer, because the lymphocytes are not part of the neoplastic process, nor are the tumors benign. The presence of large neoplastic cells in a background of reactive lymphocytes may give rise to an appearance similar to that in non-Hodgkin lymphomas, and immunohistochemical stains may be required to prove the epithelial nature of the malignant cells. Nasopharyngeal carcinomas invade locally, spread to cervical lymph nodes, and then metastasize to distant sites. They tend to be radiosensitive, and 5-year survival rates of 50% are reported even for patients with advanced cancers.

Laryngeal Tumors

A variety of non-neoplastic, benign, and malignant neoplasms of epithelial and mesenchymal origin may arise in the larynx, but only vocal cord nodules, papillomas, and squamous cell carcinomas are sufficiently common to merit comment. In all of these conditions, the most common presenting feature is hoarseness.

Nonmalignant Lesions

Vocal cord nodules ("polyps") are smooth, hemispherical protrusions (usually less than 0.5 cm in diameter) located, most often, on the true vocal cords. The nodules are composed of fibrous tissue and covered by stratified squamous mucosa that usually is intact but can be ulcerated from contact trauma with the other vocal cord. These lesions occur chiefly in heavy smokers or singers (singer's nodes), suggesting that they are the result of chronic irritation or abuse.

Laryngeal papilloma or *squamous papilloma* of the larynx is a benign neoplasm, usually located on the true vocal cords, that forms a soft, raspberry-like excrescence rarely more than 1 cm in diameter. Histologically, it consists of multiple, slender, finger-like projections supported by central fibrovascular cores and covered by an orderly, typical, stratified squamous epithelium. When the papilloma is on the free edge of the vocal cord, trauma may lead to ulceration that can be accompanied by hemoptysis.

Papillomas usually are single in adults but often are multiple in children, in whom the condition is referred to as *recurrent respiratory papillomatosis* (RRP), since they typically tend to recur after excision. These lesions are caused by human papillomavirus (HPV) types 6 and 11, do not become malignant, and often spontaneously regress at puberty. Cancerous transformation is rare. The most likely cause for their occurrence in children is vertical

transmission from an infected mother during delivery. Therefore, the recent availability of an HPV vaccine that can protect women of reproductive age against infection with types 6 and 11 provides an opportunity for prevention of RRP in children.

Carcinoma of the Larynx

Carcinoma of the larynx represents only 2% of all cancers. It most commonly occurs after age 40 years and is more common in men than in women (with a gender ratio of 7:1). Environmental influences are very important in its causation; nearly all cases occur in smokers, and alcohol and asbestos exposure may also play roles. Human papillomavirus sequences have been detected in about 15% of tumors, which tend to have a better prognosis than other carcinomas.

About 95% of laryngeal cancers are typical squamous cell carcinomas. Rarely, adenocarcinomas are seen, presumably arising from mucous glands. The tumor develops directly on the vocal cords (glottic tumors) in 60% to 75% of cases, but it may arise above the cords (supraglottic; 25% to 40%) or below the cords (subglottic; less than 5%). Squamous cell carcinomas of the larynx begin as in situ lesions that later appear as pearly gray, wrinkled plaques on the mucosal surface, ultimately ulcerating and fungating (Fig. 12–51). The glottic tumors are usually keratinizing, well- to moderately differentiated squamous cell carcinomas, although nonkeratinizing, poorly differentiated carcinomas may also be seen. As expected with lesions arising from recurrent exposure to environmental carcinogens, adjacent mucosa may demonstrate squamous cell hyperplasia with foci of dysplasia, or even carcinoma in situ.

Carcinoma of the larynx manifests itself clinically with persistent hoarseness. The location of the tumor within the larynx has a significant bearing on prognosis. For example, about 90% of glottic tumors are confined to the larynx at diagnosis. First, as a result of interference with vocal cord mobility, they develop symptoms early in the course of disease; second, the glottic region has a sparse lymphatic supply, and spread beyond the larynx is uncommon. By contrast, the supraglottic larynx is rich in lymphatic spaces, and nearly a third of these tumors metastasize to regional (cervical) lymph nodes. The subglottic tumors tend to remain clinically quiescent, usually manifesting as advanced disease. With surgery, radiation therapy, or combination treatment, many patients can be cured, but about one third die of the disease. The usual cause of death is infection of the distal respiratory passages or widespread metastases and cachexia.

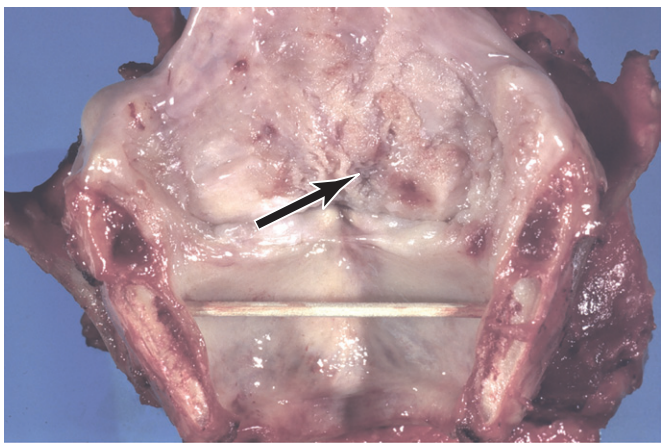

Figure 12–51 Laryngeal squamous cell carcinoma *(arrow)* arising in a supraglottic location (above the true vocal cord).

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