to deficient granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling, which results in the accumulation of surfactant in the intra-alveolar and bronchiolar spaces. PAP is characterized radiologically by bilateral patchy asymmetric pulmonary opacifications. There are three distinct classes of disease—autoimmune (formerly called acquired), secondary, and congenital—each with a similar spectrum of histologic changes.

- *Autoimmune PAP* is caused by autoantibodies that bind and neutralize the function of GM-CSF. It occurs primarily in adults, represents 90% of all cases of PAP, and lacks any familial predisposition. Knockout of the GM-CSF gene in mice induces PAP, and these mice are "cured" by treatment with GM-CSF. Loss of GM-CSF signaling blocks the terminal differentiation of alveolar macrophages, impairing their ability to catabolize surfactant.
- *Secondary PAP* is uncommon and is associated with diverse diseases, including hematopoietic disorders, malignancies, immunodeficiency disorders, lysinuric protein intolerance (an inborn error of amino acid metabolism), and acute silicosis and other inhalational syndromes. It is speculated that these diseases somehow impair GM-CSF–dependent signaling or downstream events involved in macrophage maturation or function, again leading to inadequate clearance of surfactant from alveolar spaces.
- *Hereditary PAP* is extremely rare, occurs in neonates, and is caused by loss-of-function mutations in the genes that encode GM-CSF or the GM-CSF receptor.

MORPHOLOGY

The disease is characterized by the accumulation of intra-alveolar precipitates containing surfactant proteins, causing focal-to-confluent consolidation of large areas of the lungs with minimal inflammatory reaction (Fig. 15.25). As a consequence there is a marked increase in the size and weight of the lung. The alveolar precipitate is pink, homogeneous, and periodic acid–Schiff–positive and contains cholesterol clefts and surfactant proteins (which can be demonstrated by immunohistochemical stains). Ultrastructurally, the surfactant lamellae in type II pneumocytes are normal, in contrast to surfactant dysfunction disorders (described next).

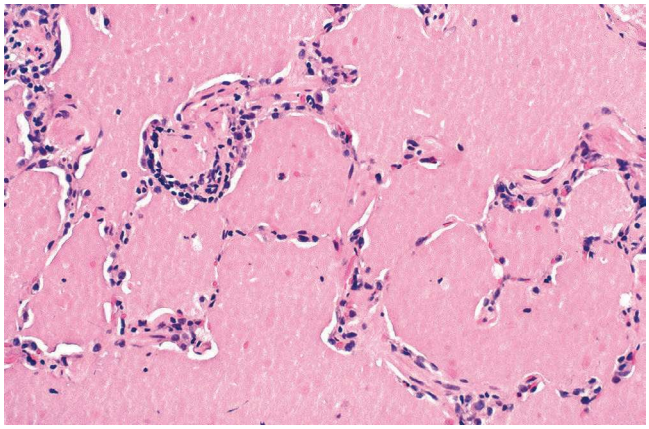

Figure 15.25 Pulmonary alveolar proteinosis. The alveoli are filled with a dense, amorphous, protein-lipid granular precipitate, while the alveolar walls are normal.

Clinical Features

Adult patients, for the most part, present with cough and abundant sputum that often contains chunks of gelatinous material. Some have symptoms lasting for years, often with intermittent febrile illnesses caused by secondary pulmonary infections with a variety of organisms. Progressive dyspnea, cyanosis, and respiratory insufficiency may occur, but other patients follow a benign course, with eventual resolution of the lesions. Whole-lung lavage is the standard of care and provides benefit regardless of the underlying defect. GM-CSF therapy is safe and effective in more than half of patients with autoimmune PAP, and therapy directed at the underlying disorder may also be helpful. Primary disease is treated with GM-CSF replacement therapy, sometimes followed by allogeneic hematopoietic stem cell transplantation, which can be curative.

Surfactant Dysfunction Disorders

Surfactant dysfunction disorders are diseases caused by diverse mutations in genes encoding proteins involved in surfactant trafficking or secretion. Clinical manifestations range from neonatal respiratory failure to adult-onset interstitial lung disease. The most commonly mutated genes are the following:

- *ATP-binding cassette protein member 3 (ABCA3)* is the most frequently mutated gene in surfactant dysfunction disorders. Mutations in *ABCA3* are associated with an autosomal recessive disorder that usually presents in the first few months of life with rapidly progressive respiratory failure followed by death. Less commonly, it comes to attention in older children and in adults with chronic interstitial lung disease.
- The second most commonly mutated gene in surfactant dysfunction disorders encodes *surfactant protein C*. This form has an autosomal dominant mode of inheritance and has a highly variable course.
- The third most commonly mutated gene in surfactant dysfunction disorders encodes *surfactant protein B*. This form has an autosomal recessive mode of inheritance. Typically, the infant is full term and develops progressive respiratory distress shortly after birth. Death ensues between 3 and 6 months of age unless lung transplantation is performed.

MORPHOLOGY

There is a variable amount of intra-alveolar pink granular material, type II pneumocyte hyperplasia, interstitial fibrosis, and alveolar simplification. Immunohistochemical stains show the lack of surfactant proteins C and B in their respective deficiencies. Ultrastructurally, abnormalities in lamellar bodies in type II pneumocytes can be seen in all three; small lamellar bodies with electron dense cores are diagnostic for *ABCA3* mutation (Fig. 15.26).

DISEASES OF VASCULAR ORIGIN

Pulmonary Embolism and Infarction

Pulmonary embolism is an important cause of morbidity and mortality, particularly in patients who are bedridden,

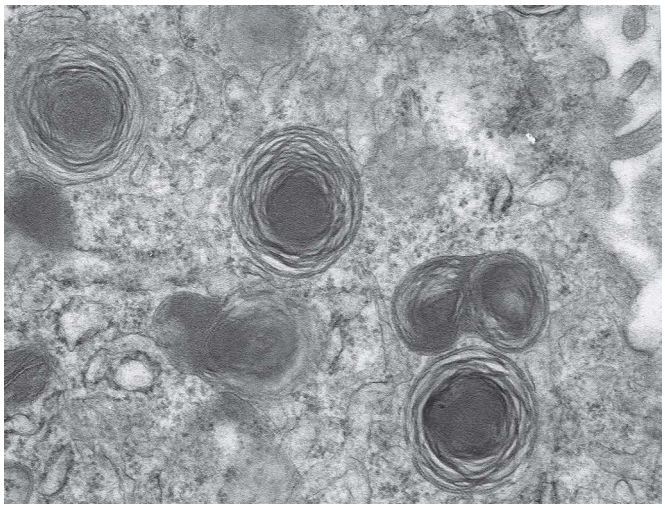

Figure 15.26 Pulmonary alveolar proteinosis associated with mutation of the *ABCA3* gene. An electron micrograph shows type 2 pneumocytes containing small surfactant lamellae with electron dense cores, an appearance that is characteristic of cases associated with *ABCA3* mutations.

but also in a wide range of conditions that are associated with hypercoagulability. Blood clots that occlude the large pulmonary arteries are almost always embolic in origin. The usual source—thrombi in the deep veins of the leg (>95% of cases)—and the magnitude of the clinical problem were discussed in Chapter 4. Pulmonary embolism causes more than 50,000 deaths in the United States each year. Its incidence at autopsy has varied from 1% in the general population of hospital patients to 30% in patients dying after severe burns, trauma, or fractures. It is the sole or major contributing cause of death in about 10% of adults who die acutely in hospitals. By contrast, large-vessel pulmonary thromboses are rare and develop only in the presence of pulmonary hypertension and heart failure.

Pathogenesis

Pulmonary embolism usually occurs in patients with a predisposing condition that produces an increased tendency to clot (thrombophilia). Patients often have cardiac disease or cancer or have been immobilized for several days or weeks prior to the appearance of a symptomatic embolism. Patients with hip fractures are at particularly high risk. Hypercoagulable states, either primary (e.g., factor V Leiden, prothrombin mutations, and antiphospholipid syndrome) or secondary (e.g., obesity, recent surgery, cancer, oral contraceptive use, pregnancy), are important risk factors. Indwelling central venous lines can be a nidus for formation of right atrial thrombi, which can embolize to the lungs. Rarely, pulmonary embolism may consist of fat, air, or tumor. Small bone marrow emboli are often seen in patients who die after chest compressions performed during resuscitative efforts.

The pathophysiologic response and clinical significance of pulmonary embolism depend on the extent to which pulmonary artery blood flow is obstructed, the size of the occluded vessels, the number of emboli, and the cardiovascular health of the patient. Emboli have two deleterious pathophysiologic consequences: *respiratory compromise* due to the nonperfused, although ventilated, segment; and *hemodynamic compromise* due to increased resistance to pulmonary blood flow caused by the embolic obstruction. Sudden death often ensues, largely as a result of the blockage of blood flow through the lungs. Death may also be caused by acute right-sided heart failure *(acute cor pulmonale)*.

MORPHOLOGY

Large emboli lodge in the main pulmonary artery or its major branches or at the bifurcation as a saddle embolus (Fig. 15.27). Smaller emboli travel out into the more peripheral vessels, where they may cause hemorrhage or infarction. In patients with adequate cardiovascular function, the bronchial arterial supply sustains the lung parenchyma; in this instance, hemorrhage may occur, but there is no infarction. In those in whom cardiovascular function is already compromised, such as patients with heart or lung disease, infarction is more likely. Overall, about 10% of emboli cause infarction. About 75% of infarcts affect the lower lobes, and in more than half, multiple lesions occur. They vary in size from barely visible to massive lesions involving large parts of a lobe. Typically, they extend to the periphery of the lung as a wedge with the apex pointing toward the hilus of the lung. In many cases, an occluded vessel is identified near the apex of the infarct. Pulmonary embolus can be distinguished from a postmortem clot by the presence of the lines of Zahn in the thrombus (Chapter 4).

The pulmonary infarct is classically hemorrhagic and appears as a raised, red-blue area in the early stages (Fig. 15.28). Often, the apposed pleural surface is covered by a fibrinous exudate. The red cells begin to lyse within 48 hours, and the infarct becomes paler and eventually red-brown as hemosiderin is produced. With the passage of time, fibrous replacement begins at the margins as a gray-white peripheral zone and eventually converts the infarct into a contracted scar. Histologically, the hemorrhagic area shows ischemic necrosis of the alveolar walls, bronchioles, and vessels. If the infarct is caused by an infected embolus, the neutrophilic inflammatory reaction can be intense. Such lesions are referred to as **septic infarcts,** some of which turn into abscesses.

Clinical Features

A large pulmonary embolus is one of the few causes of virtually instantaneous death. During cardiopulmonary resuscitation in such instances, the patient frequently is said

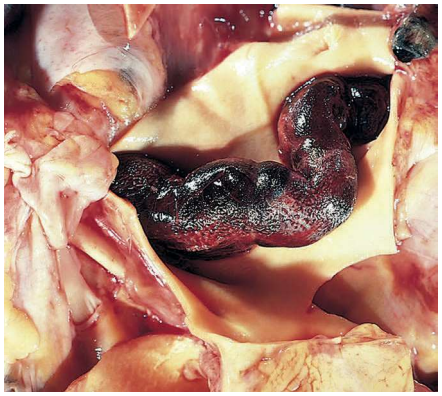

Figure 15.27 Large saddle embolus from the femoral vein lying astride the main left and right pulmonary arteries. (From the teaching collection of the Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex.)

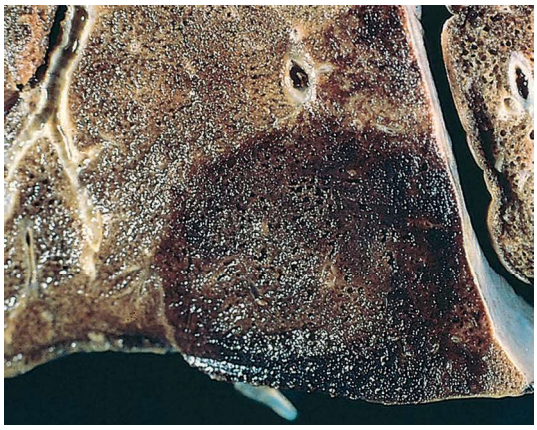

Figure 15.28 Acute hemorrhagic pulmonary infarct.

to have electromechanical dissociation, in which the electrocardiogram has a rhythm, but no pulses are palpated because no blood is entering the pulmonary arterial circulation. If the patient survives after a sizable pulmonary embolus, however, the clinical syndrome may mimic myocardial infarction, with severe chest pain, dyspnea, and shock. Small emboli are silent or induce only transient chest pain and cough. In the remaining group of patients with symptomatic pulmonary embolism, the most common presenting symptoms (in descending order) are dyspnea, pleuritic pain, and cough, accompanied in about half of cases by calf or thigh swelling or pain. Emboli that lead to pulmonary infarction may additionally produce fever and hemoptysis. An overlying fibrinous pleuritis may produce a pleural friction rub.

In hemodynamically stable patients with a low to moderate risk of pulmonary embolism, D-dimer measurement is a useful screening test, as a normal D-dimer level excludes pulmonary embolism. Definitive diagnosis is usually made by computed tomographic pulmonary angiogram, which identifies obstructed pulmonary arteries. Rarely, other diagnostic methods, such as ventilation-perfusion scanning, are required. Deep vein thrombosis can be diagnosed with duplex ultrasonography. Chest radiography may be normal or disclose a pulmonary infarct, usually 12 to 36 hours after it has occurred, as a wedge-shaped infiltrate.

After the initial acute insult, emboli often resolve via contraction and fibrinolysis, particularly in relatively young patients. If unresolved, with time multiple small emboli may lead to pulmonary hypertension and chronic cor pulmonale. Perhaps most important is that a small embolus may presage a larger one. In the presence of an underlying predisposing condition, patients with a pulmonary embolus have a 30% chance of suffering a second embolus.

Prevention of pulmonary embolism is a major clinical challenge for which there is no easy solution. Prophylactic therapy includes early ambulation in postoperative and postpartum patients, elastic stockings and graduated compression stockings for bedridden patients, and anticoagulation in high-risk individuals. Treatment of pulmonary embolism includes anticoagulation and supportive measures; thrombolysis may have some benefit in patients with severe complications (e.g., shock), but carries a high risk of bleeding. Those at risk of recurrent pulmonary embolism in whom anticoagulation is contraindicated may be fitted with an inferior vena cava filter (an "umbrella") that catches clots before they reach the lungs.

KEY CONCEPTS
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 bed rest, leg surgery, severe trauma, congestive heart failure, use of oral contraceptives (especially those with high estrogen content), disseminated cancer, and inherited forms 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 remainder cause symptoms related to ventilation-perfusion mismatch and/or pulmonary infarction, particularly dyspnea and pleuritic chest pain.
- Risk of recurrence is high, and recurrent embolism may eventually lead to pulmonary hypertension and cor pulmonale.

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest. Based on underlying mechanisms, the WHO has classified pulmonary hypertension into five groups: (1) pulmonary arterial hypertension, a diverse collection of disorders that all primarily impact small pulmonary muscular arteries; (2) pulmonary hypertension due to left heart failure; (3) pulmonary hypertension due to lung diseases and/or hypoxia; (4) chronic thromboembolic pulmonary hypertension and other obstructions; and (5) pulmonary hypertension with unclear and/or multifactorial mechanisms.

Pathogenesis

As can be gathered from the above classification, pulmonary hypertension has diverse causes even within each group. It is most frequently associated with structural cardiopulmonary conditions that increase either pulmonary blood flow, pulmonary vascular resistance, or left heart resistance to blood flow. Some of the more common causes are the following:

- *Chronic obstructive or interstitial lung diseases* (group 3). These diseases obliterate alveolar capillaries, increasing pulmonary resistance to blood flow and, secondarily, pulmonary blood pressure.
- *Antecedent congenital or acquired heart disease* (group 2). Mitral stenosis, for example, causes an increase in left atrial pressure and pulmonary venous pressure that is eventually transmitted to the arterial side of the pulmonary vasculature, leading to hypertension.
- *Recurrent thromboemboli* (group 4). Recurrent pulmonary emboli may cause pulmonary hypertension by reducing the functional cross-sectional area of the pulmonary vascular bed, which in turn leads to an increase in pulmonary vascular resistance.
- *Autoimmune diseases* (group 1). Several of these diseases (most notably systemic sclerosis) involve the pulmonary vasculature and/or the interstitium, leading to increased vascular resistance and pulmonary hypertension.