membrane antibodies is unknown. In addition to autoreactive B cells, some experimental evidence suggests that T cells also contribute, both by enhancing B-cell function and by participating directly in glomerular damage and crescent formation. As with other autoimmune disorders, there is an association with certain HLA subtypes (e.g., HLA-DRB1*1501 and HLA-DRB1*1502).

MORPHOLOGY

In the classic case, the lungs are heavy, with areas of red-brown consolidation. Histologically, there is focal necrosis of alveolar walls associated with intra-alveolar hemorrhages. Often the alveoli contain hemosiderin-laden macrophages (see Fig. 15.31). In later stages there may be fibrous thickening of the septa, hyperplasia of type II pneumocytes, and organization of blood in alveolar spaces. In many cases, immunofluorescence studies reveal linear deposits of immunoglobulins along the basement membranes of the septal walls. The kidneys have the characteristic findings of focal proliferative glomerulonephritis in early cases or crescentic glomerulonephritis in patients with rapidly progressive glomerulonephritis. Diagnostic linear deposits of immunoglobulins and complement are seen by immunofluorescence studies along the glomerular basement membranes even in the few patients without renal disease.

Clinical Features

Most cases begin with respiratory symptoms, principally hemoptysis, and radiographic evidence of focal pulmonary consolidations. Soon, manifestations of glomerulonephritis appear, leading to rapidly progressive renal failure. The most common cause of death is uremia. The once dismal prognosis for this disease has been markedly improved by intensive plasmapheresis. This procedure is thought to be beneficial by removing anti–basement membrane antibodies and possibly other mediators of immunologic injury. Simultaneous immunosuppressive therapy inhibits further antibody production, ameliorating both lung hemorrhage and glomerulonephritis.

Polyangiitis With Granulomatosis

Previously called Wegener granulomatosis, this autoimmune disease most often involves the upper respiratory tract and/or the lungs, with hemoptysis being the common presenting symptom. Its features are discussed in Chapter 11. Here, it suffices to emphasize that a transbronchial lung biopsy might provide the only tissue available for diagnosis. Since the amount of tissue is small, necrosis and granulomatous vasculitis might not be present. Rather, the diagnostically important histologic features are capillaritis and scattered, poorly formed granulomas (unlike those of sarcoidosis, which are rounded and well-defined).

PULMONARY INFECTIONS

Respiratory tract infections are more frequent than infections of any other organ and account for the largest number of workdays lost in the general population. The vast majority consist of upper respiratory tract infections caused by viruses (common cold, pharyngitis), but bacterial, viral, mycoplasmal, and fungal infections of the lung (pneumonia) account for an enormous amount of morbidity and are responsible for 2.3% of all deaths in the United States. Pneumonia can be very broadly defined as any infection of the lung parenchyma.

Pulmonary antimicrobial defense mechanisms are described in Chapter 8. Pneumonia can result whenever these local defense mechanisms are impaired or the systemic resistance of the host is lowered. Factors that impair resistance include chronic diseases, immunologic deficiencies, treatment with immunosuppressive agents, and leukopenia. Local pulmonary defense mechanisms may also be compromised by many factors, including:

- *Loss or suppression of the cough reflex,* as a result of altered sensorium (e.g., coma), anesthesia, neuromuscular disorders, drugs, or chest pain, any of which may lead to *aspiration* of gastric contents.
- *Dysfunction of the mucociliary apparatus,* which can be caused by cigarette smoke, inhalation of hot or corrosive gases, viral diseases, or genetic defects of ciliary function (e.g., immotile cilia syndrome).
- *Accumulation of secretions* in conditions such as cystic fibrosis and bronchial obstruction.
- *Interference with the phagocytic and bactericidal activities of alveolar macrophages* by alcohol, tobacco smoke, anoxia, or oxygen intoxication.
- *Pulmonary congestion and edema.*

Defects in innate immunity (including neutrophil and complement defects) and humoral immunodeficiency typically lead to an increased incidence of infections with pyogenic bacteria. Germline mutations in MyD88 (an adaptor for several Toll-like receptors [TLRs] that is important for activation of the transcription factor nuclear factor kappa B [NF-κB]) are also associated with destructive bacterial (pneumococcal) pneumonias. On the other hand, cell-mediated immune defects (congenital and acquired) lead to increased infections with intracellular microbes such as mycobacteria and herpesviruses as well as with microorganisms of very low virulence, such as the fungus *Pneumocystis jiroveci*.

Several other points should be emphasized. First, to paraphrase the French physician Louis Cruveilhier in 1919 (during the Spanish flu epidemic), "flu condemns, and additional infection executes." The most common cause of death in viral influenza epidemics is superimposed bacterial pneumonia. Second, although the portal of entry for most bacterial pneumonias is the respiratory tract, hematogenous seeding of the lungs from another organ may occur and may be difficult to distinguish from primary pneumonia. Finally, many patients with chronic diseases acquire terminal pneumonia while hospitalized *(nosocomial infection)* because of several factors: bacteria common to the hospital environment may have acquired resistance to antibiotics; opportunities for spread are increased; invasive procedures, such as intubations and injections, are common; and bacteria may contaminate equipment used in respiratory care units.

Pneumonia is classified based on the etiologic agent or, if no pathogen can be isolated (which occurs in about 50% of cases), by the clinical setting in which the infection occurs.

Table 15.7 Pneumonia Syndromes

Community-Acquired Acute Pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Legionella pneumophila
Enterobacteriaceae *(Klebsiella pneumoniae)* and *Pseudomonas* spp.
Mycoplasma pneumoniae
Chlamydia spp. *(C. pneumoniae, C. psittaci, C. trachomatis)*
Coxiella burnetii (Q fever)
Viruses: respiratory syncytial virus, parainfluenza virus, and human metapneumovirus (children); influenza A and B (adults); adenovirus (military recruits)
Health Care–Associated Pneumonia
Staphylococcus aureus, methicillin-sensitive
Staphylococcus aureus, methicillin-resistant
Pseudomonas aeruginosa
Streptococcus pneumoniae
Hospital-Acquired Pneumonia
Gram-negative rods, Enterobacteriaceae (*Klebsiella* spp., *Serratia marcescens*, *Escherichia coli*) and *Pseudomonas* spp.
Staphylococcus aureus (usually methicillin-resistant)
Aspiration Pneumonia
Anaerobic oral flora *(Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus)*, admixed with aerobic bacteria *(Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, 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
Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)
Pneumonia in the Immunocompromised Host
Cytomegalovirus
Pneumocystis jiroveci
Mycobacterium avium-intracellulare complex
Invasive aspergillosis
Invasive candidiasis
"Usual" bacterial, viral, and fungal organisms (listed herein)

The latter considerably narrows the list of suspected pathogens, providing a guide for empirical antimicrobial therapy. As Table 15.7 indicates, pneumonia can arise in seven distinct clinical settings ("pneumonia syndromes"), and the implicated pathogens are fairly specific to each category.

Community-Acquired Bacterial Pneumonias

Community-acquired acute pneumonia refers to lung infection in otherwise healthy individuals that is acquired from the normal environment (in contrast to hospital-acquired pneumonia). It may be bacterial or viral. Clinical and radiologic features are usually insensitive in differentiating between viral and bacterial infections. One marker of inflammation, procalcitonin, an acute-phase reactant produced primarily in the liver, is more significantly elevated in bacterial than viral infections and has some predictive value, but is not specific, as it is also markedly elevated in other severe inflammatory disorders, such as systemic inflammatory response syndrome (SIRS) (Chapter 4).

Often, a bacterial infection follows an upper respiratory tract viral infection. Bacterial invasion of the lung parenchyma causes the alveoli to be filled with an inflammatory exudate, thus causing consolidation ("solidification") of the pulmonary tissue. Many variables, such as the specific etiologic agent, the host reaction, and the extent of involvement, determine the precise form of pneumonia. Predisposing conditions include extremes of age, chronic diseases (congestive heart failure, COPD, and diabetes), congenital or acquired immune deficiencies, and decreased or absent splenic function. The latter puts the patient at risk for infection with encapsulated bacteria such as pneumococcus.

Streptococcus pneumoniae

***Streptococcus pneumoniae*, or *pneumococcus*, is the most common cause of community-acquired acute pneumonia.** 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 supports the diagnosis of pneumococcal pneumonia, but it must be remembered that *S. pneumoniae* is a part of the endogenous flora in 20% of adults, and therefore false-positive results may be obtained. Isolation of pneumococci from blood cultures is more specific but less sensitive (in the early phase of illness, only 20% to 30% of patients have positive blood cultures). Pneumococcal vaccines containing capsular polysaccharides from the common serotypes are used in individuals at high risk for pneumococcal sepsis.

Haemophilus influenzae

Haemophilus influenzae is a pleomorphic, gram-negative organism that occurs in encapsulated and nonencapsulated forms. There are six serotypes of the encapsulated form (types a to f), of which type b is the most virulent. Antibodies against the capsule protect the host from *H. influenzae* infection; hence the capsular polysaccharide b is incorporated in the widely used vaccine against *H. influenzae*. With routine use of *H. influenzae* vaccines, the incidence of disease caused by the b serotype has declined significantly. By contrast, infections with nonencapsulated forms, also called *nontypeable forms*, are increasing. These are less virulent and tend to spread along the surface of the upper respiratory tract, producing otitis media (infection of the middle ear), sinusitis, and bronchopneumonia. Neonates and children with comorbidities such as prematurity, malignancy, and immunodeficiency are at high risk for development of invasive infection.

H. influenzae pneumonia, which may follow a viral respiratory infection, is a pediatric emergency and has a high mortality rate. Descending laryngotracheobronchitis results in airway obstruction as the smaller bronchi are plugged by dense, fibrin-rich exudates containing neutrophils, similar to that seen in pneumococcal pneumonias. Pulmonary consolidation is usually lobular and patchy but may be confluent and involve the entire lung lobe. Before a vaccine became widely available, *H. influenzae* was a common cause of suppurative meningitis in children up to

5 years of age. *H. influenzae* also causes an acute, purulent conjunctivitis (pink eye) in children and, in predisposed older patients, may cause septicemia, endocarditis, pyelonephritis, cholecystitis, and suppurative arthritis. Finally, *H. influenzae* is the most common bacterial cause of acute exacerbations of COPD.

Moraxella catarrhalis

Moraxella catarrhalis is recognized as a cause of bacterial pneumonia, especially in the elderly. It is the second most common bacterial cause of acute exacerbation of COPD. Along with *S. pneumoniae* and *H. influenzae, M. catarrhalis* is one of the three most common causes of otitis media in children.

Staphylococcus aureus

Staphylococcus aureus is an important cause of secondary bacterial pneumonia in children and healthy adults following 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. *Intravenous drug users* are at high risk for development of staphylococcal pneumonia in association with endocarditis. It is also an important cause of hospital-acquired pneumonia.

Klebsiella pneumoniae

Klebsiella pneumoniae is the most frequent cause of gram-negative bacterial pneumonia. It commonly afflicts debilitated and malnourished people, particularly *chronic alcoholics*. Thick, mucoid (often blood-tinged) sputum is characteristic because the organism produces an abundant viscid capsular polysaccharide, which the patient may have difficulty expectorating.

Pseudomonas aeruginosa

Although *Pseudomonas aeruginosa* most commonly causes hospital-acquired infections, it is mentioned here because of its occurrence in cystic fibrosis and immunocompromised patients. It is common in patients who are neutropenic, and it has a propensity to invade blood vessels with consequent extrapulmonary spread. *Pseudomonas* septicemia is a very fulminant disease.

Legionella pneumophila

Legionella pneumophila is the agent of legionnaires' disease, the form of pneumonia caused by this organism. It also causes Pontiac fever, a related self-limited upper respiratory tract infection. This organism flourishes in artificial aquatic environments, such as water-cooling towers and the tubing systems of domestic (potable) water supplies. It is transmitted by either inhalation of aerosolized organisms or aspiration of contaminated drinking water. *Legionella* pneumonia is common in individuals with predisposing conditions such as cardiac, renal, immunologic, or hematologic disease. Organ transplant recipients are particularly susceptible. It can be quite severe, frequently requiring hospitalization, and immunosuppressed patients have fatality rates of up to 50%. The diagnosis can be made rapidly by detecting *Legionella* DNA in sputum using a polymerase chain reaction (PCR)–based test or by identification of *Legionella* antigens in the urine; culture remains the diagnostic gold standard, but takes 3 to 5 days.

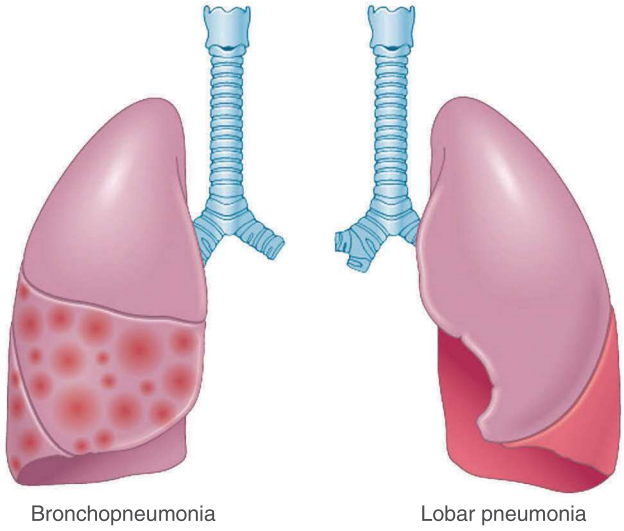

Figure 15.32 Comparison of bronchopneumonia and lobar pneumonia.

Mycoplasma pneumoniae

Mycoplasma infections are particularly common among children and young adults. They occur sporadically or as local epidemics in closed communities (schools, military camps, and prisons).

MORPHOLOGY

Bacterial pneumonia has two patterns of anatomic distribution: lobular bronchopneumonia and lobar pneumonia (Fig. 15.32). Patchy consolidation of the lung is the dominant characteristic of **bronchopneumonia** (Fig. 15.33), while consolidation of a large portion of a lobe or of an entire lobe defines **lobar**

Figure 15.33 Bronchopneumonia. Section of lung showing patches of consolidation *(arrows)*.

Figure 15.34 Lobar pneumonia—gray hepatization. The lower lobe is uniformly consolidated.

pneumonia (Fig. 15.34). These anatomic categorizations may be difficult to apply in individual cases because patterns overlap. The patchy involvement may become confluent, producing lobar consolidation. Moreover, the same organisms may produce either pattern depending on patient susceptibility. **Most important from the clinical standpoint are identification of the causative agent and determination of the extent of disease.**

In lobar pneumonia, four stages of the inflammatory response have classically been described: congestion, red hepatization, gray hepatization, and resolution. In the first stage of **congestion,** the lung is heavy, boggy, and red. It is characterized by vascular engorgement, intra-alveolar edema fluid containing a few neutrophils, and the presence of bacteria, which may be numerous. In the next stage of **red hepatization**, there is massive confluent exudation, as neutrophils, red cells, and fibrin fill the alveolar spaces (Fig. 15.35A). On gross examination, the lobe is red, firm, and airless, with a liver-like consistency, hence the name hepatization. The third stage of **gray hepatization** is marked by progressive disintegration of red cells and the persistence of a fibrinosuppurative exudate (Fig. 15.35B), resulting in a color change to grayish-brown. In the final stage of **resolution,** the exudate within the alveolar spaces is broken down by enzymatic digestion to produce granular, semifluid debris that is resorbed, ingested by macrophages, expectorated, or organized by fibroblasts growing into it (Fig. 15.35C). Pleural fibrinous reaction to the underlying inflammation, often present in the early stages if the consolidation extends to the lung surface **(pleuritis)**, may similarly resolve. More often it undergoes organization, leaving fibrous thickening or permanent adhesions.

Foci of **bronchopneumonia** are consolidated areas of acute suppurative inflammation. The consolidation may be confined to one lobe but is more often multilobar and frequently bilateral and basal because of the tendency of secretions to gravitate to the lower lobes. Well-developed lesions are slightly elevated, dry, granular, gray-red to yellow, and poorly delimited at their margins (see Fig. 15.33). Histologically, the reaction usually elicits a neutrophil-rich exudate that fills the bronchi, bronchioles, and adjacent alveolar spaces (see Fig. 15.35A).

Complications of pneumonia include (1) tissue destruction and necrosis, causing **abscess formation** (particularly common with pneumococcal or *Klebsiella* infections); (2) spread of infection

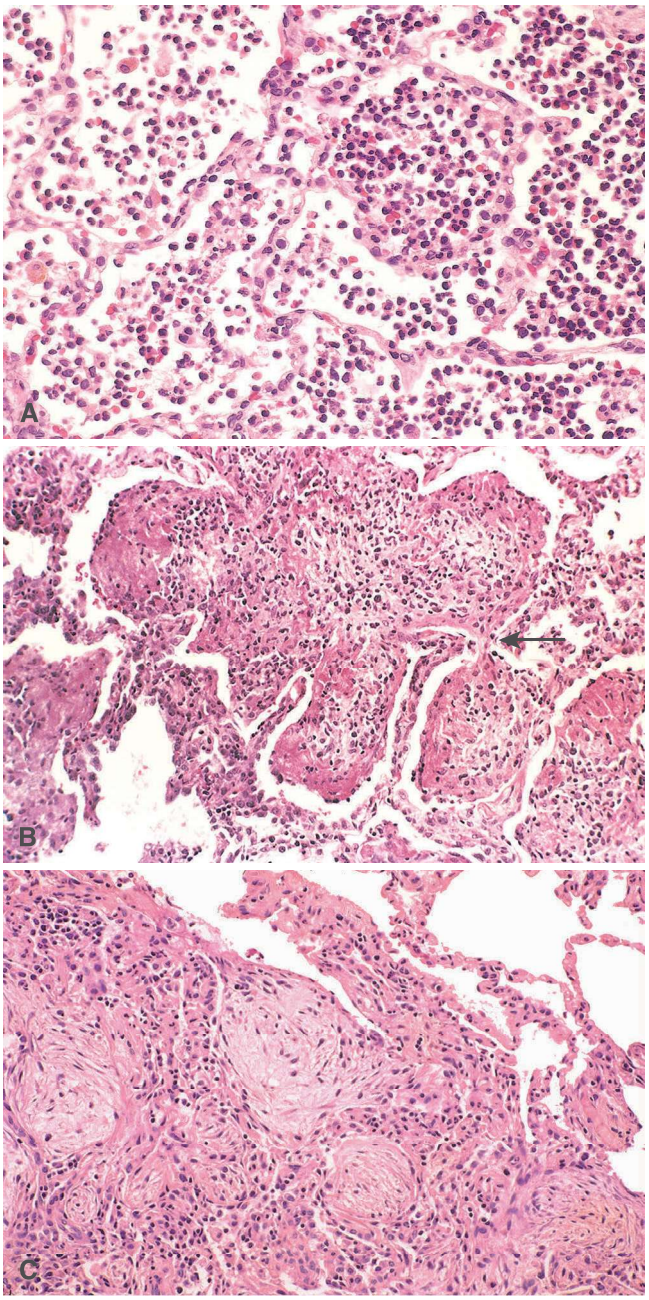

Figure 15.35 Stages of bacterial pneumonia. (A) Acute pneumonia. The congested septal capillaries and numerous intra-alveolar neutrophils are characteristic of early red hepatization. Fibrin nets have not yet formed. (B) Early organization of intra-alveolar exudate, seen focally to be streaming through the pores of Kohn *(arrow)*. (C) Advanced organizing pneumonia. The exudates have been converted to fibromyxoid masses rich in macrophages and fibroblasts.

to the pleural cavity, causing an intrapleural fibrinosuppurative reaction known as **empyema;** and (3) **bacteremic dissemination** to the heart valves, pericardium, brain, kidneys, spleen, or joints, causing abscesses, endocarditis, meningitis, or suppurative arthritis.

Clinical Features

The major symptoms of community-acquired acute bacterial pneumonia are abrupt onset of high fever, shaking chills, and cough producing mucopurulent sputum and occasionally hemoptysis. When pleuritis is present it is accompanied by pleuritic pain and pleural friction rub. The whole lobe is radiopaque in lobar pneumonia, whereas there are focal opacities in bronchopneumonia.

The clinical picture is markedly modified by the administration of effective antibiotics. Appropriately treated patients may become afebrile with few clinical signs 48 to 72 hours after the initiation of antibiotics. The identification of the organism and the determination of its antibiotic sensitivity are the keystones of therapy. Fewer than 10% of patients with pneumonia severe enough to merit hospitalization now succumb, and in most instances death results from a complication, such as empyema, meningitis, endocarditis, or pericarditis, or is attributable to some predisposing influence, such as debility or chronic alcoholism.

Community-Acquired Viral Pneumonia

Common viral infections include influenza virus types A and B, respiratory syncytial viruses, human metapneumovirus, adenovirus, rhinoviruses, rubeola, and varicella viruses. Any of these agents can cause a relatively mild upper respiratory tract infection, recognized as the common cold, or a more severe lower respiratory tract infection. Factors that favor extension of the infection to the lung include extremes of age, malnutrition, alcoholism, and underlying debilitating illnesses.

Although the molecular details vary, all of the viruses that cause pneumonia produce disease through similar general mechanisms. These viruses have tropisms that allow them to attach to and enter respiratory lining cells. Viral replication and gene expression leads to cytopathic changes, inducing cell death and secondary inflammation. The resulting damage and impairment of local pulmonary defenses, such as mucociliary clearance, may predispose to bacterial superinfections, which are often more serious than the viral infection itself.

Influenza

Influenza viruses of type A infect humans, pigs, horses, and birds and are the major cause of pandemic and epidemic influenza infections. The influenza genome encodes several proteins, but the most important from the vantage point of viral virulence are the hemagglutinin and neuraminidase proteins. Hemagglutinin has three major subtypes (H1, H2, H3), while neuraminidase has two (N1, N2). Both proteins are embedded in a lipid bilayer, which constitutes the influenza virus envelope. Hemagglutinin is particularly important, as it serves to attach the virus to its cellular target via sialic acid residues on surface polysaccharides. Following uptake of the virus into endosomal vesicles, acidification of the endosome triggers a conformation change in hemagglutinin that allows the viral envelope to fuse with the host cell membrane, releasing the viral genomic RNAs into the cytoplasm of the cell. Neuraminidase in turn facilitates the release of newly formed virions that are budding from infected cells by cleaving sialic acid residues. Neutralizing host antibodies against viral hemagglutinin and neuraminidase prevent and ameliorate, respectively, infection with influenza virus.

The viral genome is composed of eight single-stranded RNAs, each encoding one or more proteins. The RNAs are packaged into helices by nucleoproteins that determine the influenza virus type (A, B, or C). A single subtype of influenza virus A predominates throughout the world at a given time. Epidemics of influenza are caused by spontaneous mutations that alter antigenic epitopes on the viral hemagglutinin and neuraminidase proteins. These antigenic changes *(antigenic drift)* result in new viral strains that are sufficiently different to elude, at least in part, anti-influenza antibodies produced in members of the population in response to prior exposures to other flu strains. Usually, however, these new strains bear sufficient resemblance to prior strains that some members of the population are at least partially resistant to infection. By contrast, pandemics, which are longer and more widespread than epidemics, occur when both the hemagglutinin and the neuraminidase genes are replaced through recombination with animal influenza viruses *(antigenic shift)*. In this instance, essentially all individuals are susceptible to the new influenza virus.

If the host lacks protective antibodies, the virus infects pneumocytes and elicits several cytopathic changes. Shortly after entry into pneumocytes, the viral infection inhibits sodium channels, producing electrolyte and water shifts that lead to fluid accumulation in the alveolar lumen. This is followed by the death of the infected cells through several mechanisms, including inhibition of host cell messenger RNA translation and activation of caspases leading to apoptosis. The death of epithelial cells exacerbates the fluid accumulation and releases "danger signals" that activate resident macrophages. In addition, prior to their death, infected epithelial cells release a variety of inflammatory mediators, including several chemokines and cytokines, adding fuel to the inflammatory fire. In addition, mediators released from epithelial cells and macrophages activate the nearby pulmonary endothelium and serve as chemoattractants for neutrophils, which migrate into the interstitium within the first day or two of infection. In some cases viral infection may cause sufficient lung injury to produce ARDS, but more often severe pulmonary disease stems from a superimposed bacterial pneumonia. Of these, secondary pneumonias caused by *S. aureus* are particularly common and often life-threatening.

Control of the infection relies on several host mechanisms. The presence of viral products induces innate immune responses in infected cells, such as the production of α- and β-interferon. These mediators upregulate the expression of the *MX1* gene, which encodes a guanosine triphosphatase that interferes with viral gene transcription and viral replication. As with other viral infections, natural killer cells and cytotoxic T cells can recognize and kill infected host cells, limiting viral replication and viral spread to adjacent pneumocytes. The cellular immune response is eventually

augmented by development of antibody responses to the viral hemagglutinin and neuraminidase proteins.

Insight into future pandemics has come from studying past pandemics. DNA analysis of viral genomes retrieved from the lungs of a soldier who died in the great 1918 influenza pandemic that killed between 20 million and 40 million people worldwide identified swine influenza sequences, consistent with this virus having its origin in a "antigenic shift." The first flu pandemic of this century, in 2009, was also caused by an antigenic shift involving a virus of swine origin. It caused particularly severe infections in young adults, apparently because older adults had antibodies against past influenza strains that conveyed at least partial protection. Comorbidities such as diabetes, heart disease, lung disease, and immunosuppression were also associated with a higher risk of severe infection.

What then might be the source of the next great pandemic? There is no certainty, but one concern is centered on avian influenza, which normally infects birds. One such strain, type H5N1, has spread throughout the world in wild and domestic birds. Fortunately, the transmission of the current H5N1 avian virus is inefficient. However, if H5N1 influenza recombines with an influenza that is highly infectious for humans, a strain might result that is capable of sustained human-to-human transmission (and thus of causing the next great pandemic).

Human Metapneumovirus

Human metapneumovirus, a paramyxovirus discovered in 2001, is found worldwide and is associated with upper and lower respiratory tract infections. Infections can occur in any age group but are most common in young children, elderly adults, and immunocompromised patients. Some infections, such as bronchiolitis and pneumonia, are severe; overall, metapneumovirus is responsible for 5% to 10% of hospitalizations and 12% to 20% of outpatient visits of children suffering from acute respiratory tract infections. Such infections are clinically indistinguishable from those caused by human respiratory syncytial virus and are often mistaken for influenza. The first human metapneumovirus infection occurs during early childhood, but reinfections are common throughout life, especially in older subjects. Diagnostic methods include PCR tests for viral RNA. Treatment generally focuses on supportive measures. Although work is ongoing, a clinically effective and safe vaccine has yet to be developed.

Human Coronaviruses

Coronaviruses are enveloped, positive-sense RNA viruses that infect humans and several other vertebrate species. Weakly pathogenic coronaviruses cause mild cold-like upper respiratory tract infections, while highly pathogenic ones may cause severe, often fatal pneumonia. An example of a highly pathogenic type is SARS-CoV-2, a strain that emerged in late 2019 in China that is producing a still evolving pandemic as of early 2020 (discussed in Chapter 8). Highly pathogenic coronaviruses like SARS-CoV-2 bind the ACE2 protein on the surface of pulmonary alveolar epithelial cells, explaining the tropism of these viruses for the lung. With highly pathogenic forms in susceptible hosts, typically older individuals with comorbid conditions, the host immune response and locally released cytokines often produce acute lung injury and ARDS.

MORPHOLOGY

All viral infections produce similar morphologic changes. Upper respiratory infections are marked by mucosal hyperemia and swelling, infiltration of the submucosa by mononuclear cells (mainly lymphocytes and monocytes), and overproduction of mucus secretions. The swollen mucosa and viscous exudate may plug the nasal channels, sinuses, or the Eustachian tubes, leading to suppurative secondary bacterial infection. Virus-induced tonsillitis causing hyperplasia of the lymphoid tissue within the Waldeyer ring is frequent in children.

In viral **laryngotracheobronchitis** and **bronchiolitis** there is vocal cord swelling and abundant mucus production. Impairment of bronchociliary function invites bacterial superinfection with more marked suppuration. Plugging of small airways may give rise to focal lung atelectasis. With more severe bronchiolar involvement, widespread plugging of secondary and terminal airways by cell debris, fibrin, and inflammatory exudate may, if prolonged, lead to organization and fibrosis, resulting in obliterative bronchiolitis and permanent lung damage.

Lung involvement may be quite patchy or may involve whole lobes bilaterally or unilaterally. The affected areas are red-blue and congested. Pleuritis or pleural effusions are infrequent. The histologic pattern depends on the severity of the disease. **Predominant is an interstitial inflammatory reaction involving the walls of the alveoli.** The alveolar septa are widened and edematous and usually contain a mononuclear inflammatory infiltrate of lymphocytes, macrophages, and occasionally plasma cells. In severe cases, neutrophils may also be present. The alveoli may be free of exudate, but in many patients there is intra-alveolar proteinaceous material and a cellular exudate. When complicated by ARDS, pink hyaline membranes line the alveolar walls (see Fig. 15.4). Eradication of the infection is followed by reconstitution of the normal lung architecture.

Superimposed bacterial infection modifies this picture by causing ulcerative bronchitis, bronchiolitis, and bacterial pneumonia. Some viruses, such as herpes simplex, varicella, and adenovirus, may be associated with necrosis of bronchial and alveolar epithelium and acute inflammation. Characteristic viral cytopathic changes are described in Chapter 8.

Clinical Features

The clinical course of viral pneumonia is extremely varied. Many cases masquerade as severe upper respiratory tract infections or as chest colds. Even individuals with well-developed atypical pneumonia have few localizing symptoms. Cough may be absent, and the major manifestations may consist only of fever, headache, and myalgia. The edema and exudation often cause ventilation-perfusion mismatch leading to hypoxemia and thus evoke symptoms out of proportion to the scant physical findings.

Viral pneumonias are usually mild and resolve spontaneously without any lasting sequelae. However, interstitial viral pneumonias may assume epidemic proportions, and in such instances even a low rate of complications can lead to significant morbidity and mortality, as is typically true of influenza epidemics.

Health Care–Associated Pneumonia

Health care–associated pneumonia was recently described as a distinct clinical entity associated with several risk factors. These are hospitalization of at least 2 days within the recent

past; presentation from a nursing home or long-term care facility; attending a hospital or hemodialysis clinic; and recent intravenous antibiotic therapy, chemotherapy, or wound care. The most common organisms isolated are methicillin-resistant *S. aureus* and *P. aeruginosa*. These patients have a higher mortality than those with community-acquired pneumonia.

Hospital-Acquired Pneumonia

Hospital-acquired pneumonias are defined as pulmonary infections acquired in the course of a hospital stay. They are common in patients with severe underlying disease, immunosuppression, prolonged antibiotic therapy, or invasive access devices such as intravascular catheters. Patients on mechanical ventilation are at particularly high risk. Superimposed on an underlying disease (that caused hospitalization), hospital-acquired infections are serious and often life-threatening. Gram-positive cocci (mainly *S. aureus*) and gram-negative rods (Enterobacteriaceae and *Pseudomonas* species) are the most common isolates. The same organisms predominate in ventilator-associated pneumonia, with gram-negative bacilli being somewhat more common in this setting.

KEY CONCEPTS

ACUTE PNEUMONIA

- *S. pneumoniae* (the pneumococcus) is the most common cause of community-acquired acute pneumonia; the distribution of inflammation is usually lobar.
- Lobar pneumonias evolve through four stages: congestion, red hepatization, gray hepatization, and resolution.
- Other common causes of acute bacterial 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 and in those with neutropenia), and *L. pneumophila*, seen particularly in individuals with co-morbid conditions (e.g., heart or lung disease) and in organ transplant recipients.
- Important causes of community-acquired viral pneumonia include influenza virus, metapneumonia virus, and coronavirus COVID-19, the latter a newly emergent pathogen.
- Bacterial pneumonias are characterized by predominantly intra-alveolar neutrophilic inflammation, while viral pneumonia shows interstitial lymphocytic inflammation.

Aspiration Pneumonia

Aspiration pneumonia occurs in markedly 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 predispose to aspiration. The resultant pneumonia is partly chemical due to the irritating effects of gastric acid and partly bacterial (from the oral flora). Typically, more than one organism is recovered on culture, aerobes being more common than anaerobes. This type of pneumonia is often necrotizing, pursues a fulminant clinical course, and is a frequent cause of death. In patients who survive, lung abscess is a common complication.

Microaspiration, in contrast, occurs frequently in almost all people, especially those with gastroesophageal reflux disease. It usually results in small, poorly formed non-necrotizing granulomas with multinucleated foreign body giant cell reaction. It is usually inconsequential, but may exacerbate other pre-existing lung diseases such as asthma, interstitial fibrosis, and lung rejection.

Lung Abscess

The term *pulmonary abscess* describes a local suppurative process that produces necrosis of lung tissue. Oropharyngeal surgical or dental procedures, sinobronchial infections, and bronchiectasis play important roles in their development.

Etiology and Pathogenesis

Under appropriate circumstances any bacterial pathogen can produce an abscess; those that do so most commonly include aerobic and anaerobic streptococci, *S. aureus*, and a host of gram-negative organisms. Mixed infections often occur because of the important causal role played by inhalation of foreign material. Anaerobic organisms normally found in the oral cavity, including members of the *Bacteroides, Fusobacterium,* and *Peptococcus* genera, are the exclusive isolates in about 60% of cases. The causative organisms are introduced by the following mechanisms:

- *Aspiration of infective material* (the most frequent cause). Risk factors include suppressed cough reflexes (e.g., acute alcohol intoxication, opioid abuse, coma, anesthesia, seizure disorders), severe dysphagia (e.g., neurologic deficits, esophageal disease), protracted vomiting, and poor dental hygiene. Aspiration first causes pneumonia, which progresses to tissue necrosis and formation of lung abscess.
- *Antecedent primary lung infection.* Postpneumonic abscess formations are usually associated with *S. aureus, K. pneumoniae,* and pneumococcus. Posttransplant or otherwise immunosuppressed individuals are at special risk.
- *Septic embolism.* Infected emboli may arise from thrombophlebitis in any portion of the systemic venous circulation or from the vegetations of infective bacterial endocarditis on the right side of the heart and lodge in the lung.
- *Neoplasia.* Secondary infection is particularly common in bronchopulmonary segments obstructed by a primary or secondary malignancy *(postobstructive pneumonia)*.
- *Miscellaneous.* Traumatic penetrations of the lungs; direct extension of suppurative infections from the esophagus, spine, subphrenic space, or pleural cavity; and hematogenous seeding of the lung by pyogenic organisms all may lead to lung abscess formation.

When all these causes are excluded, there are still cases in which no discernible basis for the abscess formation can be identified. These are referred to as *primary cryptogenic lung abscesses*.

MORPHOLOGY

Abscesses vary in diameter from a few millimeters to large cavities of 5 to 6 cm (Fig. 15.36). They may affect any part of the lung and may be single or multiple. Pulmonary abscesses due to aspiration are more common on the right (because of the more vertical right main bronchus) and are most often single. Abscesses that

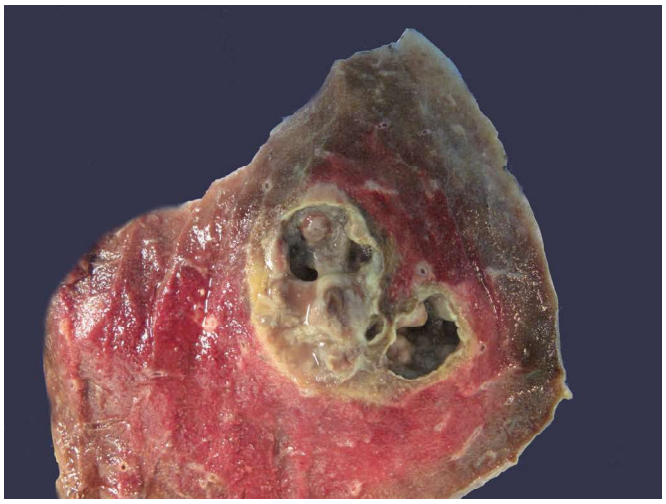

Figure 15.36 Cut surface of lung showing two abscesses. (Courtesy Dr. M. Kamran Mirza, University of Chicago, Chicago, Ill.)

develop in the course of pneumonia or bronchiectasis are usually multiple, basal, and diffusely scattered. Septic emboli and pyemic abscesses are multiple and may affect any region of the lungs.

The **cardinal histologic change in all abscesses is suppurative destruction of the lung parenchyma within the central area of cavitation.** The abscess cavity may be filled with suppurative debris or, if there is communication with an air passage, may be partially drained to create an air-containing cavity. Superimposed saprophytic infections are prone to develop within the necrotic debris. Continued infection leads to large, poorly demarcated, fetid, green-black, multilocular cavities designated gangrene of the lung. In chronic cases considerable fibroblastic proliferation produces a fibrous wall.

Clinical Features

The manifestations of pulmonary abscesses are much like those of bronchiectasis and characteristically include cough, fever, and copious amounts of foul-smelling purulent or sanguineous sputum. Fever, chest pain, and weight loss are common. Clubbing of the fingers and toes may appear. The diagnosis can be only suspected from the clinical findings and must be confirmed radiologically. Whenever an abscess is discovered in older individuals, it is important to rule out an underlying carcinoma, which is present in 10% to 15% of cases.

The course of abscesses is variable. With antimicrobial therapy, most resolve, leaving behind a scar. Complications include extension of the infection into the pleural cavity, hemorrhage, the development of *brain abscesses* or *meningitis* from septic emboli, and (rarely) secondary amyloidosis (type AA).

Chronic Pneumonia

Chronic pneumonia is most often a localized lesion in the immunocompetent patient, with or without regional lymph node involvement. Typically the inflammatory reaction is granulomatous and is caused by bacteria (e.g., *Mycobacterium tuberculosis*) or fungi (e.g., *Histoplasma capsulatum*). Tuberculosis of the lung and other organs is described in Chapter 8. Chronic pneumonias caused by fungi are discussed here.

Histoplasmosis

H. capsulatum infection is acquired by inhalation of dust particles from soil contaminated with bird or bat droppings that contain small spores (microconidia), the infectious form of the fungus. It is endemic along the Ohio and Mississippi rivers and in the Caribbean. It is also found in Mexico, Central and South America, parts of eastern and southern Europe, Africa, eastern Asia, and Australia. Like *M. tuberculosis, H. capsulatum* is an intracellular pathogen that is found mainly in phagocytes. The clinical presentations and morphologic lesions of histoplasmosis bear a striking resemblance to those of tuberculosis, including (1) a self-limited and often latent primary pulmonary involvement, which may result in coin lesions on chest radiography; (2) chronic, progressive, secondary lung disease, which is localized to the lung apices and causes cough, fever, and night sweats; (3) spread to extrapulmonary sites, including mediastinum, adrenal glands, liver, or meninges; and (4) widely disseminated disease in immunocompromised patients. Histoplasmosis can occur in immunocompetent individuals but as per usual is more severe in those with depressed cell mediated immunity.

The pathogenesis of histoplasmosis is incompletely understood. The portal of entry is virtually always the lung. Macrophages ingest but cannot kill the organism without T-cell help, and this allows the organism to multiply within phagolysosomes and disseminate prior to the development of T-cell immunity, which takes 1 to 2 weeks. In individuals with adequate cell-mediated immunity, the infection is controlled by Th1 helper T cells that recognize fungal antigens and subsequently secrete IFN-γ, which activates macrophages and enables them to kill intracellular yeasts. In addition, *Histoplasma* induces macrophages to secrete TNF, which recruits and stimulates other macrophages to kill *Histoplasma.*

MORPHOLOGY

In the lungs of otherwise healthy adults, *Histoplasma* infections produce **granulomas,** which usually become necrotic and may coalesce to produce areas of consolidation. With spontaneous resolution or effective treatment, these lesions undergo fibrosis and concentric calcification (tree-bark appearance) (Fig. 15.37A). Histologic differentiation from tuberculosis, sarcoidosis, and coccidioidomycosis requires identification of the 3- to 5-μm thin-walled yeast forms, which may persist in tissues for years. In **fulminant disseminated histoplasmosis,** which occurs in immunosuppressed individuals, granulomas do not form; instead, there are focal accumulations of mononuclear phagocytes filled with fungal yeasts throughout the body (Fig. 15.37B).

The diagnosis of histoplasmosis may be established by serologic tests for antibodies and fungal antigens, culture, or identification of the fungus in tissue biopsies. The majority of cases resolve spontaneously. Progressive disease or disease in immunocompromised patients is treated with antifungal agents.

Blastomycosis

Blastomyces dermatitidis is a soil-inhabiting dimorphic fungus. It causes disease in the central and southeastern United States; infection also occurs in Canada, Mexico, the Middle East, Africa, and India. There are three clinical forms: *pulmonary*