

# Alterations in Respiratory Function: Infectious Disorders and Neoplasia

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**R**espiratory illnesses represent one of the more common reasons for visits to the physician, admission to the hospital, and forced inactivity among all age groups. Pneumonia is the sixth leading cause of death in the United States, particularly among the elderly and those with compromised immune function. Tuberculosis remains one of the deadliest diseases in the world. It has been estimated that between 19% and 43% of the world population is infected with tuberculosis. Of all neoplasms, lung cancer remains the leading cause of death in the United States.

## RESPIRATORY TRACT INFECTIONS

Respiratory tract infections can involve the upper respiratory tract (*i.e.*, nose, oropharynx, and larynx), the lower respiratory tract (*i.e.*, lower airways and lungs), or the upper and lower airways. The discussion in this section of the chapter focuses on influenza, pneumonia, tuberculosis, and fungal infections of the lung. Acute respiratory infections in children are discussed in the last section of the chapter.

### Influenza

Influenza is a viral infection that can affect the upper and lower respiratory tracts. It usually occurs in epidemics or pandemics. Until the advent of acquired immunodeficiency syndrome (AIDS), it was the last uncontrolled pandemic killer of humans. More persons died in the 1918 and 1919 influenza pandemic than in World War I. In the United States, approximately 20,000 persons die each year of influenza-related illness during nonpandemic years.<sup>1</sup> Most deaths are caused by pneumonia or exacerbation of cardiopulmonary or other conditions; 80% to 90% of those who die are 65 years of age or older.

There are two types of influenza viruses that cause epidemics in humans: types A and B. Infection with type A is most common and causes the most severe disease. Influenza A is further divided into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B has not been categorized

into subtypes. Host antibodies to the surface antigens, which provide entrance in host cells, prevent future infection with influenza virus. New variants result from frequent mutations or antigenic shifts in the surface antigens.<sup>1</sup> Influenza B undergoes less frequent shifts than influenza A. The incubation period for influenza is 1 to 4 days, with 2 days being the average. Persons become infectious starting 1 day before their symptoms begin and remain infectious through approximately 5 days after illness onset. Children can be infectious for a longer time.

The influenza viruses can cause three types of infections: an uncomplicated rhinotracheitis, a respiratory viral infection followed by a bacterial infection, and viral pneumonia. In the early stages, the symptoms of influenza often are indistinguishable from other viral infections. There is an abrupt onset of fever and chills, malaise, muscle aching, headache, profuse, watery nasal discharge, nonproductive cough, and sore throat. One distinguishing feature of an influenza viral infection is the rapid onset, sometimes in as little as 1 to 2 minutes, of profound malaise.<sup>2</sup> The infection causes necrosis and shedding of the serous and ciliated cells that line the respiratory tract, leaving gaping holes between the underlying basal cells and allowing extracellular fluid to escape. This is the reason for the “runny nose” that is characteristic of this phase of the infection. During recovery, the serous cells are replaced more rapidly than the ciliated cells. Mucus is produced, but the ciliated cells are unable to move it adequately; people recovering from influenza continue to blow their nose to clear the nasopharynx and cough to clear the trachea.

The symptoms of uncomplicated rhinotracheitis usually peak by days 3 to 5 and disappear by days 7 to 10. Persons who have secondary complications usually report that they were beginning to feel better when they experienced a return of symptoms. Complications typically include sinusitis, otitis media, bronchitis, and bacterial pneumonia. The clinical course of influenza pneumonia progresses rapidly. It can cause hypoxemia and death within a few days of onset. The rapid onset is thought to be related to the mode of spread and the absence of an initial rhinotracheitis. If the virus is spread by fingers or large-droplet spray, as from sneezing or coughing, only the upper respiratory tract is involved. Infection of the upper respiratory tract is thought to give the immune system enough time to build the defenses needed to protect against viral pneumonia. When the virus is contained in small droplets, it can bypass the upper respiratory tract and travel directly into the lungs to establish infection.<sup>2</sup>

The goals of treatment for influenza are designed to limit the infection to the upper respiratory tract. The symptomatic approach, which uses rest, keeping warm, and drinking large amounts of liquids, helps to accomplish this. Rest decreases the oxygen requirements of the body and reduces the respiratory rate and the chance of moving the virus from the upper to lower respiratory tract. Keeping warm helps maintain the respiratory epithelium at a core body temperature of 37°C (or higher if fever is present), thereby inhibiting viral replication, which is optimal at 35°C. Drinking large amounts of liquids ensures that the function of the epithelial lining of the respiratory tract is not further compromised by dehydration.

The appropriate pharmacologic treatment of people with influenza depends on accurate and timely diagnosis. Rapid antigen detection tests are available to confirm a diagnosis of influenza A or B infection. These tests allow health care providers to monitor influenza type and its prevalence in their

community, to diagnose influenza more accurately, and to consider treatment options more carefully.<sup>3</sup>

Four antiviral drugs are available for the treatment of influenza.<sup>3,4</sup> The first-generation antiviral drugs amantadine and rimantadine are similarly effective against influenza A but not influenza B. These agents inhibit the uncoating of viral RNA in the host cells and prevent its replication. Both drugs are effective in prevention of influenza A in high-risk groups and in the treatment of persons who acquire the disease. The second-generation antiviral drugs zanamivir and oseltamivir are inhibitors of neuraminidase, a viral glycoprotein that is necessary for viral replication and release. These drugs, which have been approved for treatment of acute uncomplicated influenza infection, are effective against both influenza A and B viruses. To be effective, the antiviral drugs should be initiated within 30 hours after onset of symptoms.

Vaccines are available to protect against influenza infections. The formulation of the vaccine must be changed yearly in response to changes in the influenza virus. Immunization is recommended for high-risk groups who, because of their age or underlying health problems, are unable to cope well with the infection and often require medical attention, including hospitalization. Immunization is also recommended for persons who can transmit the infection to high-risk groups (*e.g.*, health care worker and care givers).

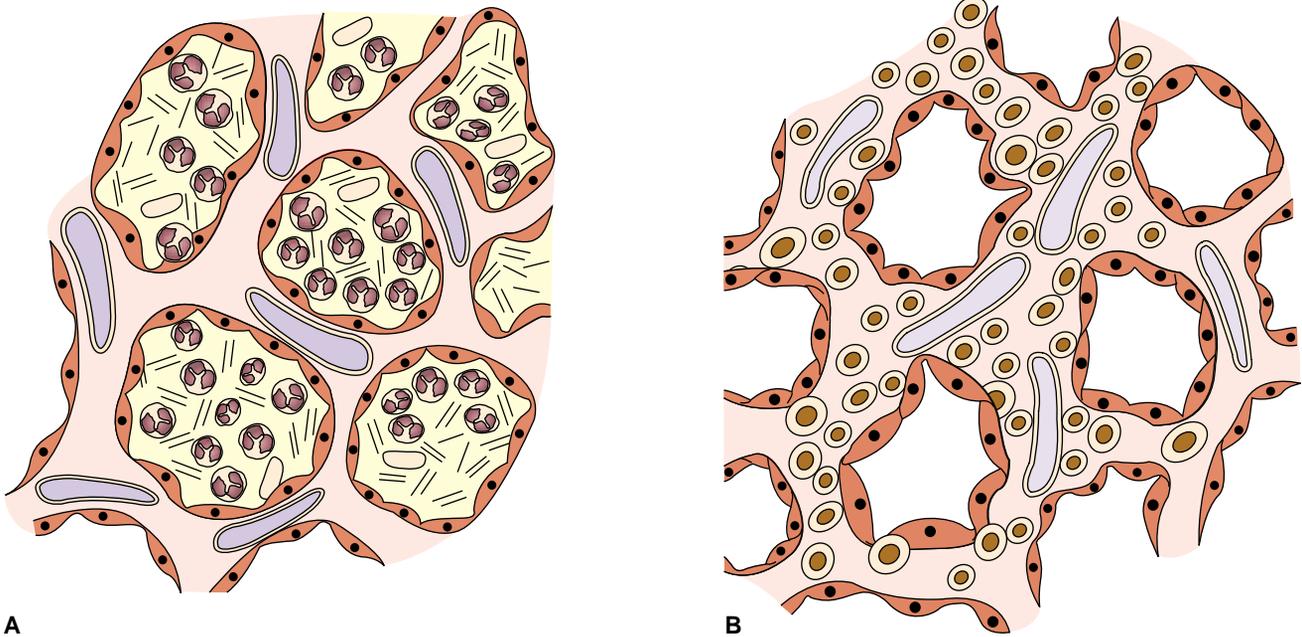
## Pneumonias

The term *pneumonia* describes inflammation of parenchymal structures of the lung, such as the alveoli and the bronchioles.<sup>5</sup> Pneumonia is the sixth leading cause of death in the United States and the most common cause of death from infectious disease, particularly among the elderly and persons with debilitating diseases. Etiologic agents include infectious and non-infectious agents. Although much less common than infectious pneumonia, inhalation of irritating fumes or aspiration of gastric contents can result in severe pneumonia.

Pneumonias can be classified as typical (*i.e.*, bacterial) or atypical (*i.e.*, viral or mycoplasmal) pneumonias (Fig. 20-1). Typical pneumonia results from infection by bacteria that multiply extracellularly in the alveoli and cause inflammation and exudation of fluid into the air-filled spaces of the alveoli. Acute bacterial pneumonias are also classified according to two anatomic and radiologic patterns: *lobar pneumonia* (affecting part or all of a lung lobe) and *bronchopneumonia* (a patchy distribution involving more than one lobe). Atypical pneumonias produce patchy inflammatory changes that are confined to the alveolar septum and the interstitium of the lung. They usually produce less striking symptoms and physical findings than bacterial pneumonia; there is a lack of alveolar infiltration and purulent sputum, leukocytosis, and lobar consolidation on the radiograph.

Because of the overlap in symptomatology and changing spectrum of infectious organisms involved, pneumonias are increasingly being classified as community-acquired and hospital-acquired pneumonias. Persons with compromised immune function constitute a special concern in both categories.

*Community-acquired pneumonia* results from organisms found in the community, rather than in the hospital or nursing home.<sup>6,7</sup> Common causes of community-acquired pneumonia include *Streptococcus pneumoniae* (single most common cause), *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumo-*



**FIGURE 20-1** ■ Location of inflammatory processes in (A) typical and (B) atypical forms of pneumonia.

*niae* and other gram-negative bacilli, *Legionella pneumophila*, and the influenza and respiratory syncytial viruses.

*Hospital-acquired*, or *nosocomial*, pneumonia is defined as a lower respiratory tract infection that was not present or incubating on admission to the hospital. Usually, infections occurring 48 hours or more after admission are considered hospital acquired.<sup>6,8</sup> Most hospital-acquired pneumonias are bacterial. The organisms are those present in the hospital environment and include *Pseudomonas aeruginosa*, *S. aureus*, *Enterobacter* species, *Klebsiella* species, *Escherichia coli*, and *Serratia*. The organisms that are responsible for hospital-acquired pneumonias are different from those responsible for community-acquired pneumonia, and many of them have acquired antibiotic resistance and are more difficult to treat. Persons requiring mechanical ventilation are particularly at risk, as are those with compromised immune function, chronic lung disease, or airway instrumentation, such as endotracheal intubation or tracheotomy.

Although almost all types of microorganisms can cause pulmonary infection in immunocompromised persons, certain types of immunologic defects tend to favor certain types of infection. Defects in humoral immunity predispose to bacterial infections against which antibodies play an important role; defects in cellular immunity predispose to infections with viruses, fungi, mycobacteria, and protozoa. Neutropenia and impaired granulocyte function, as occurs in persons with leukemia, chemotherapy, and bone marrow metaplasia, predispose to infections caused by *S. aureus*, *Aspergillus*, gram-negative bacilli, and *Candida*. Pneumocystis pneumonia is an opportunistic, often fatal form of lung infection that occurs in persons with impaired cell-mediated immunity, particularly those with AIDS (see Chapter 10).

### Acute Bacterial (Typical) Pneumonias

Most of the bacteria that cause pneumonia are normal inhabitants of the nasopharynx or oropharynx and are aspirated into the lung.<sup>5,9</sup> Most persons unknowingly aspirate small amounts

of organisms that have colonized their upper airways, particularly during sleep. Normally, these organisms do not cause infection because of the small numbers that are aspirated and because of the respiratory tract's defense mechanisms (Table 20-1). Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, or impaired immune defenses predispose to colonization and infection of the lower respiratory system. Immune defenses include the bronchial-associated lymphoid tissue, phagocytic cells (*i.e.*, polymorphonuclear cells and macrophages), immunoglobulins (*i.e.*, IgA and IgG), and T-cell-mediated cellular immunity

## KEY CONCEPTS

### PNEUMONIAS

- Pneumonias are respiratory disorders involving inflammation of the lung structures, such as the alveoli and bronchioles.
- Pneumonia can be caused by infectious agents, such as bacteria and viruses, and noninfectious agents, such as gastric secretions that are aspirated into the lungs.
- The development of pneumonia is facilitated by an exceedingly virulent organism, large inoculum, and impaired host defenses.
- Pneumonias caused by infectious agents commonly are classified according to the source of infection (community- vs. hospital-acquired) and according to the immune status of the host (pneumonia in the immunocompromised person).

**TABLE 20-1** Respiratory Defense Mechanisms and Conditions That Impair Their Effectiveness

Defense Mechanism	Function	Factors That Impair Effectiveness
Nasopharyngeal defenses	Remove particles from the air; contact with surface lysosomes and immunoglobulins (IgA) protects against infection	IgA deficiency state, hay fever, common cold, trauma to the nose, others
Glottic and cough reflexes	Protect against aspiration into tracheo-bronchial tree	Loss of cough reflex due to stroke or neural lesion, neuromuscular disease, abdominal or chest surgery, depression of the cough reflex due to sedation or anesthesia, presence of a nasogastric tube (tends to cause adaptation of afferent receptors)
Mucociliary blanket	Removes secretions, microorganisms, and particles from the respiratory tract	Smoking, viral diseases, chilling, inhalation of irritating gases
Pulmonary macrophages	Remove microorganisms and foreign particles from the lung	Chilling, alcohol intoxication, smoking, anoxia

(see Chapter 8). Bacterial adherence also plays a role in colonization of the lower airways. The epithelial cells of critically and chronically ill persons are more receptive to binding microorganisms that cause pneumonia. Other clinical risk factors favoring colonization of the tracheobronchial tree include antibiotic therapy that alters the normal bacterial flora, diabetes, smoking, chronic bronchitis, and viral infection.

**Pneumococcal Pneumonia.** *Streptococcus pneumoniae* (pneumococcus) remains the most common cause of bacterial pneumonia. *S. pneumoniae* colonizes the upper respiratory system and, in addition to pneumonia and lower respiratory tract infections, the organism is an important cause of upper respiratory infections, including sinusitis and otitis media, and of disseminated invasive infections such as bacteremia and meningitis.<sup>10</sup> It is among the leading causes of illness and death of young children, persons with other health problems, and the elderly worldwide.

*S. pneumoniae* are gram-positive diplococci, possessing a capsule of polysaccharide. There are 90 serologically distinct types of *S. pneumoniae* based on the antigenic properties of their capsular polysaccharides. The virulence of *S. pneumoniae* is a function of its capsule, which prevents or delays digestion by phagocytes. The polysaccharide is an antigen that primarily elicits a B-cell response with antibody production. In the absence of antibody, clearance of the pneumococci from the body relies on the reticuloendothelial system, with the macrophages in the spleen playing a major role in elimination of the organism.<sup>11</sup> This, along with the spleen's role in antibody production, increases the risk of pneumococcal bacteremia in persons who are anatomically or functionally asplenic, such as children with sickle cell disease.

The initial step in the pathogenesis of pneumococcal infection is the attachment and colonization of the organism to the mucus and cells of nasopharynx. Colonization does not equate with signs of infection. Perfectly healthy people can be colonized and carry the organism without evidence of infection. The spread of particular strains of pneumococci, particularly antibiotic-resistant strains, is largely by healthy colonized individuals. The factors that permit the pneumococci to spread beyond the nasopharynx vary depending on the virulence of

organism, impaired host defense mechanisms, and the existence of preceding viral infection.

The signs and symptoms of pneumococcal pneumonia vary widely, depending on the age and health status of the infected person. In previously healthy persons, the onset usually is sudden and is characterized by malaise; a severe, shaking chill; and fever. The temperature may go as high as 106°F. During the initial or congestive stage, the sputum is watery and breath sounds are limited, with fine crackles. As the disease progresses, the character of the sputum changes; it may be blood tinged or rust colored to purulent. Pleuritic pain, a sharp pain that is more severe with respiratory movements, is common. Elderly persons are less likely to experience marked elevations in temperature; in these persons, the only sign of pneumonia may be a loss of appetite and deterioration in mental status.

Treatment includes the use of antibiotics that are effective against *S. pneumoniae*. In the past, *S. pneumoniae* was uniformly susceptible to penicillin. However, penicillin-resistant and multidrug-resistant strains have been emerging in the United States and other countries.<sup>12</sup>

Pneumococcal pneumonia can be prevented through immunization. A 23-valent pneumococcal vaccine, composed of antigens from 23 types of *S. pneumoniae* capsular polysaccharides, is used. The vaccine is recommended for persons 65 years of age or older and persons aged 2 to 65 years with chronic illnesses, immunocompromised persons 2 years of age or older, and for residents in special environments or social settings in which the risk for invasive pneumococcal disease is increased, and for residents of nursing homes and long-term care facilities. Because their immune system is immature, the antibody response to most pneumococcal capsular polysaccharides usually is poor or inconsistent in children younger than 2 years.<sup>10</sup> A 7-valent pneumococcal polysaccharide-protein conjugate vaccine (Prevnar) is now available for use among infants and children.<sup>13</sup>

**Legionnaire's Disease.** Legionnaire's disease is a bacterial pneumonia caused by a gram-negative rod, *Legionella pneumophila*. It ranks among the three or four most common causes of community-acquired pneumonia.<sup>6</sup> Although more than 14 serotypes of *L. pneumophila* have been identified, serotype 1

accounts for more than 80% of reported cases of legionellosis.<sup>14</sup> The organism frequently is found in water, particularly in warm, standing water. The disease was first recognized and received its name after an epidemic of severe and, for some, fatal pneumonia that developed among delegates to the 1976 American Legion convention held in a Philadelphia hotel. The spread of infection was traced to a water-cooled air-conditioning system. Although healthy persons can contract the infection, the risk is greatest among smokers, persons with chronic diseases, and those with impaired cell-mediated immunity.<sup>6,15</sup>

Symptoms of the disease typically begin approximately 2 to 10 days after infection, with malaise, weakness, lethargy, fever, and dry cough. Other manifestations include disturbances of central nervous system function, gastrointestinal tract involvement, arthralgias, and elevation in body temperature, sometimes to more than 104 °F. The presence of pneumonia along with diarrhea, hyponatremia, and confusion is characteristic of Legionella pneumonia. The disease causes consolidation of lung tissues and impairs gas exchange.

Diagnosis is based on clinical manifestations, radiologic studies, and specialized laboratory tests to detect the presence of the organism. Of these, the Legionella urinary antigen test is a relatively inexpensive, rapid test that detects antigens of *L. pneumophila* in the urine.<sup>14,15</sup> The urine test usually is easier to obtain because people with legionellosis often have a non-productive cough and the results remain positive for weeks despite antibiotic therapy.

Treatment consists of administration of antibiotics that are known to be effective against *L. pneumophila*. Delay in instituting antibiotic therapy significantly increases mortality rates, so antibiotics known to be effective against *L. pneumophila* usually are included in the treatment regimen for severe community-acquired pneumonia.<sup>14</sup>

### Primary Atypical Pneumonias

The primary atypical pneumonias are characterized by patchy involvement of the lung. They are usually preceded by pharyngitis and systemic flulike symptoms that evolve into laryngitis and finally tracheobronchitis and pneumonia. The most common pathogens are *Mycoplasma pneumoniae*, viruses, and *Chlamydia pneumoniae*.

**Mycoplasma and Viral Pneumonias.** The mycoplasmas are the smallest free-living agents of disease, having characteristics of viruses and bacteria. The influenza virus is the most common cause of viral pneumonia. Less common offenders are parainfluenza and respiratory syncytial viruses. Other viruses sometimes are implicated, including the measles and chickenpox viruses.

The clinical course among persons with mycoplasmal and viral pneumonias varies widely from a mild infection (e.g., influenza types A and B, adenovirus) that masquerades as a chest cold to a more serious and even fatal outcome (e.g., chickenpox pneumonia). The symptoms may remain confined to fever, headache, and muscle aches and pains. Cough, when present, is characteristically dry, hacking, and nonproductive. Viruses impair the respiratory tract defenses and predispose to bronchopneumonia. Some viruses such as herpes simplex, varicella, and adenovirus may be associated with necrosis of the alveolar epithelium and acute inflammation.

## Tuberculosis

Tuberculosis is the world's foremost cause of death from a single infectious agent, causing 25% of avoidable deaths in developing countries. With the introduction of antibiotics in the 1950s, the United States and other Western countries enjoyed a long decline in the number of infections until the mid-1980s. Since that time, the rate of infection has increased, particularly among people with the human immunodeficiency virus (HIV). In the United States, the biggest increase in new cases was from 1985 to 1993, after which the rate of cases reported yearly has again declined.<sup>16</sup> Tuberculosis is more common among foreign-born persons from countries with a high incidence of tuberculosis and among residents of high-risk congregate settings, such as correctional facilities, drug treatment facilities, and homeless shelters. Outbreaks of a drug-resistant form of tuberculosis are being reported, complicating the selection of drugs and affecting the duration of treatment.

Tuberculosis is an infectious disease caused by the mycobacterium *M. tuberculosis*. The mycobacteria are slender, rod-shaped, aerobic bacteria that do not form spores. They are similar to other bacterial organisms except for an outer waxy capsule that makes them more resistant to destruction; the organism can persist in old necrotic and calcified lesions and remain capable of reinitiating growth. The waxy coat also causes the organism to retain red dye when treated with acid in acid-fast staining.<sup>17</sup> Thus, the mycobacteria are often referred to as *acid-fast bacilli*. Although *M. tuberculosis* can infect practically any organ of the body, the lungs are most frequently involved. The tubercle bacilli are strict aerobes that thrive in an oxygen-rich environment. This explains their tendency to cause disease in the upper lobe or upper parts of the lower lobe of the lung, where ventilation is greatest.

Tuberculosis is an airborne infection spread by minute, invisible particles, called *droplet nuclei*, that are harbored in the respiratory secretions of persons with active tuberculosis.<sup>17,18</sup> Coughing, sneezing, and talking all create respiratory droplets; these droplets evaporate, leaving the organisms (droplet nuclei), which remain suspended in the air and are circulated by air currents. Living in crowded and confined conditions increases the risk for spread of the disease.

The tubercle bacillus incites a distinctive chronic inflammatory response referred to as *granulomatous inflammation*. The destructiveness of the disease results from the hypersensitivity response that the bacillus evokes, rather than its inherent destructive capabilities. Cell-mediated immunity and hypersensitivity reactions contribute to the evolution of the disease. Tuberculosis can manifest as a primary or reactivated infection.

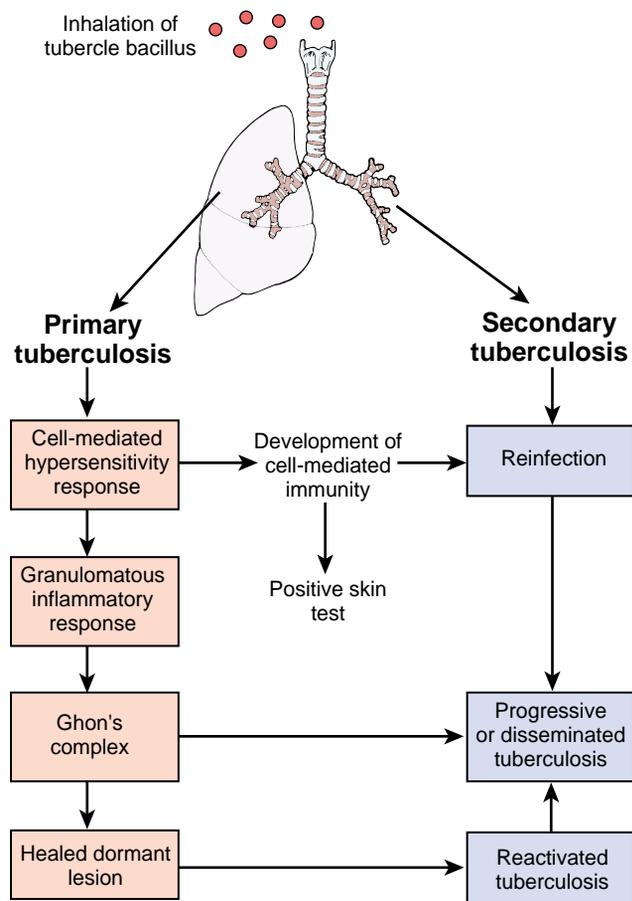
### Primary Tuberculosis

Primary tuberculosis occurs in a person lacking previous contact with the tubercle bacillus. It typically is initiated as a result of inhaling droplet nuclei that contain the tubercle bacillus (Fig. 20-2).<sup>18</sup> Inhaled droplet nuclei pass down the bronchial tree without settling on the epithelium and implant in a respiratory bronchiole or alveolus beyond the mucociliary system. Soon after entering the lung, the bacilli are surrounded and engulfed by macrophages. *M. tuberculosis* has no known endotoxins or exotoxins; therefore, there is no early immunoglobulin response to infection.

## KEY CONCEPTS

## TUBERCULOSIS

- Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*, a rod-shaped aerobic bacteria that is resistant to destruction and can persist in necrotic and calcified lesions for prolonged periods and remain capable of reinstating growth.
- The organism is spread by inhaling the mycobacterium-containing droplet nuclei that circulate in the air.
- The cell-mediated response plays a dominant role in walling off the tubercle bacilli and preventing the development of active tuberculosis. People with impaired cell-mediated immunity are more likely to experience active tuberculosis when infected.
- A positive tuberculin skin test results from a cell-mediated immune response and implies that a person has been infected with *M. tuberculosis* and has mounted a cell-mediated immune response. It does not mean that the person has active tuberculosis.



■ **FIGURE 20-2** ■ Pathogenesis of TB Infection

The tubercle bacillus grows slowly, dividing every 25 to 32 hours in the macrophage.<sup>18</sup> As the bacilli multiply, the macrophages degrade some mycobacteria and present antigen to the T lymphocytes for development of a cell-mediated immune response. The organisms grow for 2 to 12 weeks until they reach sufficient numbers to elicit a cellular immune response. In persons with intact cell-mediated immunity, this action is followed by the development of a single, gray-white, circumscribed granulomatous lesion, called a *Ghon's focus*, that contains the tubercle bacilli, modified macrophages, and other immune cells. Within 2 to 3 weeks, the central portion of the Ghon's focus undergoes soft, caseous (cheeselike) necrosis. This occurs at approximately the time that the tuberculin test result becomes positive, suggesting that the necrosis is caused by the cell-mediated hypersensitivity immune response (see Chapter 10). During this same period, tubercle bacilli, free or inside macrophages, drain along the lymph channels to the tracheobronchial lymph nodes of the affected lung and there evoke the formation of caseous granulomas. The combination of the primary lung lesion and lymph node granulomas is called *Ghon's complex* (Fig. 20-3).

The cell-mediated hypersensitivity response plays a dominant role in limiting further replication of the bacilli. The immune response also provides protection against additional tubercle bacilli that may be inhaled at a later time. People with HIV infection and others with disorders of cell-mediated immunity are more likely to acquire active tuberculosis if they become infected.

When the number of organisms inhaled is small and the body's resistance is adequate, scar tissue forms and encapsu-



■ **FIGURE 20-3** ■ Primary tuberculosis. A healed Ghon's complex is represented by a subpleural nodule and involved hilar lymph nodes. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 606]. Philadelphia: Lippincott Williams & Wilkins)

lates the primary lesion. In time, most of these lesions become calcified and are visible on a chest radiograph.

Primary tuberculosis usually is asymptomatic, with the only evidence of the disease being a positive tuberculin skin test result and calcified lesions seen on the chest radiograph. Occasionally, primary tuberculosis may progress, causing more extensive destruction of lung tissue and spreading through the airways and lymphatics to multiple sites within the lung. As the disease spreads, the organism gains access to the sputum, allowing the person to infect others.

In rare instances, tuberculosis may erode into a blood vessel, giving rise to hematogenous dissemination. *Miliary tuberculosis* describes minute lesions, resembling millet seeds, which can involve almost any organ, resulting from this type of dissemination.

### Secondary Tuberculosis

Secondary tuberculosis represents either reinfection from inhaled droplet nuclei or reactivation of a previously healed primary lesion (Fig. 20-2). It often occurs in situations of impaired body defense mechanisms. The partial immunity that follows primary tuberculosis affords protection against reinfection and to some extent aids in localizing the disease should reactivation occur. In secondary tuberculosis, the hypersensitivity reaction can be an aggravating factor, as evidenced by the frequency of cavitation and bronchial dissemination. The cavities may coalesce to a size as large as 10 to 15 cm in diameter (Fig. 20-4).<sup>6</sup> Pleural effusion and tuberculous empyema are common as the disease progresses.

Persons with secondary tuberculosis commonly present with low-grade fevers, night sweats, easy fatigability, anorexia, and weight loss. A cough initially is dry but later becomes productive with purulent and sometimes blood-tinged sputum. Dyspnea and orthopnea develop as the disease advances.

### Diagnosis and Treatment

The most frequently used screening methods for pulmonary tuberculosis are the tuberculin skin tests and chest radiographic studies. The tuberculin skin test measures delayed hypersensitivity (*i.e.*, cell-mediated, type IV) that follows exposure

to the tubercle bacillus. Persons who become tuberculin positive usually remain so for the remainder of their lives. A positive reaction to the skin test does not mean that a person has active tuberculosis, only that there has been exposure to the bacillus and that cell-mediated immunity to the organism has developed. False-positive and false-negative skin test reactions can occur. False-positive reactions often result from cross-reactions with nontuberculous mycobacteria, such as *M. avium-intracellulare* complex. Because the hypersensitivity response to the tuberculin test depends on cell-mediated immunity, a false-negative test result can occur because of immunodeficiency states that result from HIV infection, immunosuppressive therapy, lymphoreticular malignancies, or aging. This is called *anergy*. In the immunocompromised person, a negative tuberculin test result can mean that the person has a true lack of exposure to tuberculosis or is unable to mount an immune response to the test. Because of the problem with anergy in persons with HIV infection and other immunocompromised states, the use of control tests is recommended. Three antigens that can be used for control testing are *Candida*, mumps virus, and tetanus toxoid. Most healthy persons in the population have been exposed to these antigens and will display a positive response to these control tests.

Diagnosis of active pulmonary tuberculosis requires identification of the organism in respiratory tract secretions. Bacteriologic studies (*i.e.*, acid-fast stain and cultures) of early-sputum specimens, gastric aspirations, or bronchial washings obtained during fiber-optic bronchoscopy may be used. Genotyping can be done to identify different strains of *M. tuberculosis*. It is useful in investigating outbreaks of tuberculosis, tracing the sources of infection, and determining whether new episodes of the disease are caused by reinfection or reactivation. In addition, genotyping is useful in determining sites and patterns of *M. tuberculosis* transmission in communities.

The primary drugs used in the treatment of tuberculosis are isoniazid (INH), rifampin, pyrazinamide, ethambutol, and streptomycin. Two groups meet the criteria established for the use of antimycobacterial therapy for tuberculosis: (1) persons with an active form of the disease and (2) those who have had contact with cases of active tuberculosis and who are at risk for development of active tuberculosis.

The tubercle bacillus is an aerobic organism that multiplies slowly and remains relatively dormant in oxygen-poor caseous material. It undergoes a high rate of mutation and tends to acquire resistance to any one drug. For this reason, multidrug regimens are used for treating persons with active tuberculosis. Tuberculosis is an unusual disease in that chemotherapy is required for a relatively long period of time. Short-course programs of therapy (usually for 6 to 12 months) have replaced the earlier 18- to 24-month multidrug regimens. Treatment may need to be prolonged in persons with HIV infection and in those with drug-resistant strains of *M. tuberculosis*. Drug susceptibility tests are used to guide treatment in drug-resistant forms of the disease.

Prophylactic treatment is used for persons who are infected with *M. tuberculosis* but do not have active disease (*e.g.*, persons with a positive skin test or those who have had close contact with an active case of tuberculosis).<sup>19</sup>

Success of chemotherapy for prophylaxis and treatment of tuberculosis depends on strict adherence to a lengthy drug regimen. This often is a problem, particularly for asymptomatic



■ **FIGURE 20-4** ■ Cavitory tuberculosis in the apex of the left upper lobe of the lung. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 607]. Philadelphia: Lippincott Williams & Wilkins)

persons with tuberculosis infections and for poorly motivated groups, such as intravenous drug abusers. Directly observed therapy, which requires that a health care worker observe while the person takes the antituberculosis drug, is recommended for some persons and for certain types of treatment protocols.

## Fungal Infections

Fungal infections are commonly classified as superficial, subcutaneous, deep-seated, and opportunistic pathogenic fungi. The superficial and subcutaneous fungi almost always limit their infections to the skin and subcutaneous tissues. Opportunistic fungi are organisms of low virulence that cause localized or systemic infections in people who are immunocompromised, such as those with AIDS (see Chapter 10). Examples of opportunistic fungi include molds (e.g., *Aspergillus* species) as well as yeast-like species (e.g., *Candida* species).

The deep-seated fungal infections are caused by highly virulent dimorphic fungi, with the ability to invade deeply into tissues and cause systemic disease. They include *Histoplasma capsulatum* (histoplasmosis), *Coccidioides immitis* (coccidioidomycosis), and *Blastomyces capsulatum* (blastomycosis). Isolated, self-limited pulmonary involvement is commonly seen in people with normal immune function, whereas immunocompromised people often present with disseminated disease. In HIV-infected persons in endemic areas, coccidioidomycosis is now a common opportunistic infection.

Each of the dimorphic fungi has a typical geographic distribution. *H. capsulatum* is endemic along the major river valleys of the Midwest—the Ohio, the Mississippi, and the Missouri.<sup>20</sup> The organism grows in soil and other areas that have been enriched with bird excreta: old chicken houses, pigeon lofts, barns, and trees where birds roost. The infection is acquired by inhaling the fungal spores that are released when the dirt or dust from the infected areas is disturbed. *C. immitis* is most prevalent in the southwestern United States, principally in California, Arizona, and Texas.<sup>21</sup> Because of its prevalence in the San Joaquin Valley, the disease is sometimes referred to as *San Joaquin fever* or *valley fever*. The *C. immitis* organism lives in soil and can establish new sites in the soil. Events such as dust storms and digging for construction have been associated with increased incidence of the disease. *B. capsulatum* is most commonly found in the southern and north central United States, especially in areas bordering the Mississippi and Ohio River basins and the Great Lakes.<sup>22</sup>

The signs and symptoms of the fungal infections commonly resemble those of tuberculosis. Depending on the host's resistance and immunocompetence, the diseases usually take one of three forms: (1) an acute primary disease, (2) a chronic (cavitary) pulmonary disease, or (3) a disseminated infection. The primary pulmonary lesions consist of nodules containing aggregates of macrophages with engulfed microorganisms. Similar nodules develop in the regional lymph nodes. There is a striking similarity to the primary lesions of tuberculosis. The clinical manifestations consist of a mild, self-limited flulike syndrome.

In the vulnerable host, chronic cavitary lesions develop, with a predilection for the upper lobe, resembling the secondary form of tuberculosis. The most common manifestations are productive cough, fever, night sweats, and weight loss.

Disseminated disease most often develops as an acute and fulminating infection in the very old or the very young or in persons with compromised immune function. Although the macrophages of the reticuloendothelial system can remove the fungi from the bloodstream, they are unable to destroy them. Characteristically, this form of the disease presents with a high fever, generalized lymph node enlargement, hepatosplenomegaly, muscle wasting, anemia, leukopenia, and thrombocytopenia. There may be hoarseness, ulcerations of the mouth and tongue, nausea, vomiting, diarrhea, and abdominal pain. Often, meningitis becomes a dominant feature of the disease. Persons with blastomycosis may experience cutaneous infections that induce pseudoepitheliomatous hyperplasia, which may be mistaken for squamous cell carcinoma.

Skin tests similar to the tuberculin test can be used to detect exposure to *Histoplasma* and *Coccidioides*. There is no reliable skin test for *Blastomyces*. The diagnosis of acute infection is usually made by direct visualization of the organism in tissue sections or sputum culture. Serologic tests, detecting antibodies against the specific fungi are available, but lack sensitivity and specificity.

Treatment depends on the severity of infection. Persons without associated risk factors such as HIV infection or without specific evidence of progressive disease usually can be treated without antifungal therapy. The oral or intravenous antifungal drugs are used in the treatment of persons with progressive disease.

**In summary**, respiratory infections are the most common cause of respiratory illness. The influenza virus causes three syndromes: an uncomplicated rhinotracheitis, a respiratory viral infection followed by a bacterial infection, and viral pneumonia.

Pneumonia describes an infection of the parenchymal tissues of the lung. Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, or impaired immune defenses predispose to pneumonia. Pneumonia is being increasingly classified as community acquired or hospital acquired. Community-acquired pneumonia involves infections from organisms that are present more often in the community than in the hospital or nursing home. Hospital-acquired, or nosocomial, pneumonia is defined as a lower respiratory tract infection occurring 72 hours or more after hospital admission. Persons with compromised immune function constitute a special concern in both categories. Typical or bacterial pneumonias result from infection by bacteria such as *Streptococcus pneumoniae* that multiply extracellularly in the alveoli and cause inflammation and exudation of fluid into the air-filled spaces of the alveoli. Atypical pneumonias, such as those caused by *Mycoplasma pneumoniae* and respiratory viruses, involve the interstitium of the lung and often masquerade as chest colds.

Tuberculosis is a chronic respiratory infection caused by *M. tuberculosis*, which is spread by minute, invisible particles called *droplet nuclei*. Tuberculosis is a particular threat among persons with HIV infection, foreign-born persons from countries with a high incidence of tuberculosis, and residents of high-risk congregate settings, such as correctional facilities, drug treatment facilities, and homeless shelters. The tubercle bacillus incites a distinctive chronic inflammatory response re-

ferred to as *granulomatous inflammation*. The destructiveness of the disease results from the hypersensitivity response that the bacillus evokes, rather than its inherent destructive capabilities. Cell-mediated immunity and hypersensitivity reactions contribute to the evolution of the disease. The treatment of tuberculosis has been complicated by outbreaks of drug-resistant forms of the disease.

Infections caused by the fungi *H. capsulatum* (histoplasmosis), *C. immitis* (coccidioidomycosis), and *B. dermatitidis* (blastomycosis) produce pulmonary manifestations that resemble tuberculosis. These infections are common but seldom serious unless they produce progressive destruction of lung tissue or the infection disseminates to organs and tissues outside the lungs.

## CANCER OF THE LUNG

Lung cancer is the leading cause of cancer deaths among men and women in the United States, accounting for 25% of all cancer deaths. The increases in lung cancer incidence and deaths during the past 50 years have coincided closely with the increase in cigarette smoking during the same period. Industrial hazards also contribute to the incidence of lung cancer. A commonly recognized hazard is exposure to asbestos, with the mean risk of lung cancer being significantly greater in asbestos workers than in the general population. Tobacco smoke contributes heavily to the development of lung cancer in persons exposed to asbestos; the risk in this population group is estimated to be 50 to 90 times greater than that for nonsmokers.<sup>9</sup> Because cancer of the lung usually is far advanced before it is discovered, the prognosis in general is poor. The overall 5-year survival rate is 13% to 15%, a dismal statistic that has not changed since the late 1960s.<sup>23</sup>

### Bronchogenic Carcinoma

Bronchogenic carcinoma, which has its origin in the bronchial or bronchiolar epithelium, constitutes 90% to 95% of all lung cancers. Bronchogenic carcinomas are aggressive, locally invasive, and widely metastatic tumors that arise from the epithelial lining of the major bronchi. These tumors begin as small mucosal lesions that may follow one of several patterns of growth. They may form masses within the lumen of the bronchi that invade the mucosal layer and surrounding connective tissue layer, or they may form large, bulky masses that extend into the adjacent lung tissue. Some large tumors undergo central necrosis and acquire local areas of hemorrhage, and some invade the pleural cavity and chest wall and spread to adjacent intrathoracic structures.<sup>9</sup>

Bronchogenic carcinomas can be subdivided into four major categories: squamous cell lung carcinoma (25% to 40%), adenocarcinoma (20% to 40%), small cell carcinoma (20% to 25%), and large cell carcinoma (10% to 15%).<sup>9</sup> *Squamous cell carcinoma* is found most commonly in men and is closely correlated with a smoking history. Squamous cell carcinoma tends to originate in the central bronchi as an intraluminal growth and thus is more amenable to early detection through cytologic examination of the sputum than other forms of lung cancer



■ **FIGURE 20-5** ■ Squamous cell carcinoma of the lung. The tumor grows within the lumen of a bronchus and invades the adjacent intrapulmonary lymph node. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 656]. Philadelphia: Lippincott Williams & Wilkins)

(Fig. 20-5). It tends to spread centrally into major bronchi and hilar lymph nodes and disseminates outside the thorax later than other types of bronchogenic cancers.

*Adenocarcinoma* is the most common type of lung cancer in women and nonsmokers. Its association with cigarette smoking is weaker than for squamous cell carcinoma. Adenocarcinomas can have their origin in either the bronchiolar or alveolar tissues of the lung. These tumors tend to be located more peripherally than squamous cell sarcomas and sometimes are associated with areas of scarring (Fig. 20-6). The scars may be attributable to old infarcts, metallic foreign bodies, wounds, or



■ **FIGURE 20-6** ■ Adenocarcinoma of the lung. A peripheral tumor in the upper right lobe of the lung. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 657]. Philadelphia: Lippincott Williams & Wilkins)

granulomatous infections such as tuberculosis. In general, these tumors grow more slowly than squamous cell carcinomas.

The *small cell carcinomas* are more common in men than women and are strongly associated with smoking. They are characterized by a distinctive cell type—small, dark, round-to-oval shape, lymphocyte-like cells that have a scant cytoplasm and highly colored nuclei. Because of their cellular appearance, these cancers are sometimes referred to as “oat cell” tumors.<sup>9</sup> The small cell carcinomas are highly malignant, tend to infiltrate widely, disseminate early in their course, and rarely are resectable. These tumors are sensitive to chemotherapy and irradiation, and newer protocols have improved the outlook somewhat.

*Large cell carcinomas* have large polygonal cells. They constitute a group of neoplasms that are highly anaplastic and difficult to categorize as squamous or adenocarcinoma. They are associated with a poor prognosis because of their tendency to spread to distant sites early in their course.

In general, adenocarcinoma and squamous cell carcinoma tend to remain localized longer and have a better prognosis than do other, less differentiated cancers, which usually are far advanced at the time of diagnosis. All varieties of bronchogenic carcinomas, especially small cell lung carcinoma, have the capacity to synthesize bioactive products and produce paraneoplastic syndromes, including adrenocorticotrophic hormone (ACTH), antidiuretic hormone (ADH), parathyroid-like hormone, gonadotropins, and gastrin-releasing peptide.

## Manifestations

Cancer of the lung develops insidiously, often giving little or no warning of its presence. Because its symptoms are similar to those associated with smoking and chronic bronchitis, they often are disregarded.

The manifestations of lung cancer can be divided into three categories: those caused by involvement of the lung and adjacent structures, the effects of local spread and metastasis, and the nonmetastatic paraneoplastic manifestations involving endocrine, neurologic, and connective tissue function. As with other cancers, lung cancer causes nonspecific symptoms such as anorexia and weight loss.

Many of the manifestations of lung cancers result from local irritation and obstruction of the airways and from invasion of the mediastinum and pleural space. The earliest symptoms usually are chronic cough, shortness of breath, and wheezing because of airway irritation and obstruction. Hemoptysis (*i.e.*, blood in the sputum) occurs when the lesion erodes blood vessels. Pain receptors in the chest are limited to the parietal pleura, mediastinum, larger blood vessels, and peribronchial afferent vagal fibers. Dull, intermittent, poorly localized retrosternal pain is common in tumors that involve the mediastinum. Pain becomes persistent, localized, and more severe when the disease invades the pleura.

Tumors that invade the mediastinum may cause hoarseness because of the involvement of the recurrent laryngeal nerve and cause difficulty in swallowing because of compression of the esophagus. An uncommon complication called the *superior vena cava syndrome* can occur in some persons with mediastinal involvement. Interruption of blood flow in this vessel usually results from compression by the tumor or involved lymph nodes. The disorder can interfere with venous drainage from

the head, neck, and chest wall. The outcome is determined by the speed with which the disorder develops and the adequacy of the collateral circulation.

Tumors adjacent to the visceral pleura often insidiously produce pleural effusion. This effusion can compress the lung and cause atelectasis and dyspnea. It is less likely to cause fever, pleural friction rub, or pain than pleural effusion resulting from other causes.

Metastatic spread occurs by way of lymph channels and the vascular system. Metastases already exist in 50% of patients presenting with evidence of lung cancer and develop eventually in 90% of patients. The most common sites of these metastases are the brain, bone, and liver.

Paraneoplastic disorders are those that are unrelated to metastasis. These include hypercalcemia from secretion of parathyroid-like peptide, Cushing’s syndrome from ACTH secretion, inappropriate secretion of ADH, neuromuscular syndromes (*e.g.*, myasthenic syndromes, peripheral neuropathy, polymyositis), and hematologic disorders (*e.g.*, migratory thrombophlebitis, nonbacterial endocarditis, disseminated intravascular coagulation). Neurologic or muscular symptoms can develop 6 months to 4 years before the lung tumor is detected. One of the more common of these problems is weakness and wasting of the proximal muscles of the pelvic and shoulder girdles, with decreased deep tendon reflexes but without sensory changes. Hypercalcemia is seen most often in persons with squamous cell carcinoma, hematologic syndromes in persons with adenocarcinomas, and the remaining syndromes in persons with small cell neoplasms.<sup>9</sup> Manifestations of the paraneoplastic syndrome may precede the onset of other signs of lung cancer and may lead to discovery of an occult tumor.

## Diagnosis and Treatment

The diagnosis of lung cancer is based on a careful history and physical examination and other tests such as chest radiography, bronchoscopy, cytologic studies (Papanicolaou’s test) of the sputum or bronchial washings, percutaneous needle biopsy of lung tissue, and scalene lymph node biopsy. Computed tomography scans, magnetic resonance imaging studies, and ultrasonography are used to locate lesions and evaluate the extent of the disease. The carcinoembryonic antigen (CEA) is produced by undifferentiated lung tumor cells; high CEA titers usually correlate with extensive disease. This test often is used to follow the progress of the disease and its response to treatment.

Like other types of cancer, lung cancers are classified according to cell type (*i.e.*, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma) and staged according to the TNM system. These classifications are used for treatment planning. Small cell carcinoma is not evaluated by the TNM system but staged as limited (confined to the one hemithorax and hilar, mediastinal, and supraclavicular nodes) and extensive (spread to more distant sites).<sup>6,9</sup>

Treatment methods for lung cancer include surgery, radiation therapy, and chemotherapy.<sup>6</sup> These treatments may be used singly or in combination. Surgery is used for the removal of small, localized tumors. It can involve a lobectomy, pneumonectomy, or segmental resection of the lung. Radiation therapy can be used as a definitive or main treatment modality, as part of a combined treatment plan, or for palliation of symptoms. Because of the frequency of metas-

tases, chemotherapy often is used in treating lung cancer. Combination chemotherapy, which uses a regimen of several drugs, usually is used. Chemotherapy is the treatment of choice for small cell carcinoma. Advances in the use of combination chemotherapy have improved the outlook for persons with small cell carcinoma.

**In summary,** cancer of the lung is a leading cause of death among men and women between the ages of 50 and 75 years, and the death rate is increasing among women. In the United States, the increased death rate has coincided with an increase in cigarette smoking. Industrial hazards, such as exposure to asbestos, increase the risk for development of lung cancer. Of all forms of lung cancer, bronchogenic carcinoma is the most common, accounting for 90% to 95% of cases. Because lung cancer develops insidiously, it often is far advanced before it is diagnosed, a fact that is used to explain the poor 5-year survival rate.

The manifestations of lung cancer can be attributed to the involvement of the lung and adjacent structures, the effects of local spread and metastasis, and the nonmetastatic paraneoplastic manifestations involving endocrine, neurologic, and connective tissue function. As with other cancers, lung cancer causes nonspecific symptoms such as anorexia and weight loss. Treatment methods for lung cancer include surgery, irradiation, and chemotherapy.



## RESPIRATORY DISORDERS IN INFANTS AND CHILDREN

Acute respiratory disease is the most common cause of illness in infancy and childhood, accounting for 50% of illness in children younger than 5 years.<sup>24</sup> This section focuses on respiratory disorders in the neonate and respiratory infections in children. Discussions of bronchial asthma in children and cystic fibrosis are included in Chapter 21.

### Lung Development

Although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs require much longer. Immaturity of the respiratory system is a major cause of morbidity and mortality in infants born prematurely. Even at birth, the lungs are not fully mature, and additional growth and maturation continue well into childhood.

Lung development may be divided into five stages: the embryonic, glandular, canicular, saccular, and alveolar periods.<sup>25</sup> The first three phases are devoted to development of the conducting airways, and the last two phases are devoted to development of the gas exchange portion of the lung. By the 25th to 28th weeks of gestation, sufficient terminal air sacs are present to permit survival. It is also during this period that the type II alveolar cells, which produce surfactant, begin to function. Lung development is incomplete at birth; an infant is born with only one eighth to one sixth the adult number of alveoli. Alveoli continue to be formed during early childhood, reaching the adult number of 300 million alveoli by 5 to 6 years of age.<sup>25</sup>

### Breathing in the Fetus and Neonate

Effective ventilation in infants, older children, and adults requires coordinated interaction between the muscles of the upper airways, including those of the pharynx and larynx, the diaphragm, and the intercostal muscles of the chest wall. In the infant, the diaphragm inserts more horizontally than in the adult. As a result, contraction of the diaphragm tends to draw the lower ribs inward, especially if the infant is placed in the horizontal position. The intercostal muscles, which normally lift the ribs during inspiration, are not fully developed in the infant. Instead, they function largely to stabilize the chest. Under circumstances such as crying, the intercostal muscles of the neonate function together with the diaphragm to splint the chest wall and prevent its collapse.

The chest wall of the neonate is highly compliant. A striking characteristic of neonatal breathing is the paradoxical inward movement of the upper chest during inspiration, especially during active sleep. Normally, the infant's lungs also are compliant, which is advantageous to the infant with its compliant chest cage because it takes only small changes in inspiratory pressure to inflate a compliant lung. However, with respiratory disorders that decrease lung compliance, the diaphragm must generate more negative pressure; as a result, the compliant chest wall structures are sucked inward. *Retractions* are abnormal inward movements of the chest wall during inspiration; they may occur intercostally (between the ribs), in the substernal or epigastric area, and in the supraclavicular spaces.

**Airway Resistance.** Normal lung inflation requires uninterrupted movement of air through the extrathoracic airways (*i.e.*, nose, pharynx, larynx, and upper trachea) and intrathoracic airways (*i.e.*, bronchi and bronchioles). The neonate (0 to 4 weeks of age) breathes predominantly through the nose and does not adapt well to mouth breathing. Any obstruction of the nose or nasopharynx may increase upper airway resistance and increase the work of breathing.

The airways of the infant and small child are much smaller than those of the adult. Because the resistance to airflow is directly related to the fourth power of the radius, relatively small amounts of mucus secretion, edema, or airway constriction can produce marked changes in airway resistance and airflow. Nasal flaring is a method that infants use to take in more air. This method of breathing increases the size of the nares and decreases the resistance of the small airways.

The airways of infants and small children are also less rigid than those of older children and adults. Cartilaginous support of the extrathoracic (*e.g.*, larynx, trachea) airways is poorly developed in infants and small children. These structures are soft and tend to collapse when the airway is obstructed and the child cries, causing the inspiratory pressures to become more negative.

### Lung Volumes and Gas Exchange

In infants, the functional residual capacity (FRC), which is the air left in the lungs at the end of normal expiration, plays an important role in gas exchange (see Chapter 19). The FRC occurs at a higher lung volume in the infant than in the older child or adult.<sup>26</sup> This higher end-expiratory volume results from a more rapid respiratory rate, which leaves less time for expiration. The increased end-expiratory volume is important

to the neonate because it holds the airways open throughout all phases of respiration to maintain a more uniform lung expansion and gas exchange. During sleep the tone of the upper airway muscles in the neonate is reduced, the intercostal activity that stabilizes the chest wall is less, and the time spent in expiration is increased. As a result, end-expiratory volume decreases and there is less optimal gas exchange during active sleep.<sup>26</sup>

### Control of Ventilation

Fetal blood oxygen (PO<sub>2</sub>) levels normally range from 25 to 30 mm Hg, and carbon dioxide (PCO<sub>2</sub>) levels range from 45 to 50 mm Hg, independent of any respiratory movements. Any decrease in oxygen levels induces quiet sleep in the fetus, with subsequent cessation of breathing movements, both of which lead to a decrease in oxygen consumption. Switching to oxygen derived from the aerated lung at birth causes an immediate increase in PO<sub>2</sub> to approximately 50 mm Hg; within a few hours, it increases to approximately 70 mm Hg.<sup>27</sup> These levels, which greatly exceed fetal levels, cause the chemoreceptors (see Chapter 19) to become silent for several days. Although the infant's PO<sub>2</sub> may fluctuate during this critical time, the chemoreceptors do not respond appropriately. It is not until several days after birth that the chemoreceptors "reset" their PO<sub>2</sub> threshold; only then do they become the major controller of breathing. However, the response seems to be biphasic, with an initial hyperventilation followed by a decreased respiratory rate and even apnea. In neonates, particularly in preterm infants, breathing patterns and respiratory reflexes depend on the arousal state. Periodic breathing and apnea are characteristic of premature infants and reflect patterns of fetal breathing. The fact that they occur with sleep and disappear during wakefulness underscores the importance of arousal.

**Alterations in Breathing Patterns.** Most lung diseases in infants and small children produce a decrease in lung compliance with manifestations of restrictive lung disease or airway obstruction. Children with restrictive lung disease breathe at faster rates, and their respiratory excursions are shallow. Grunting is an audible noise that occurs as the child tries to raise the FRC and improve gas exchange by closing the glottis at the end of expiration. Airway obstruction produces turbulence. When it occurs in the extrathoracic airways (larynx and trachea) it produces an increase in inspiratory effort and a crowing sound called *stridor*. With intrathoracic (*e.g.*, bronchi and bronchioles) obstruction, as in bronchiolitis and bronchial asthma, the intrapleural pressure becomes more positive during expiration because of air trapping; this causes collapse of intrathoracic airways. Expiration is prolonged, and the child uses the accessory muscles to aid in expiration. Often an audible wheezing or whistling sound is heard during expiration.

### Respiratory Disorders in the Neonate

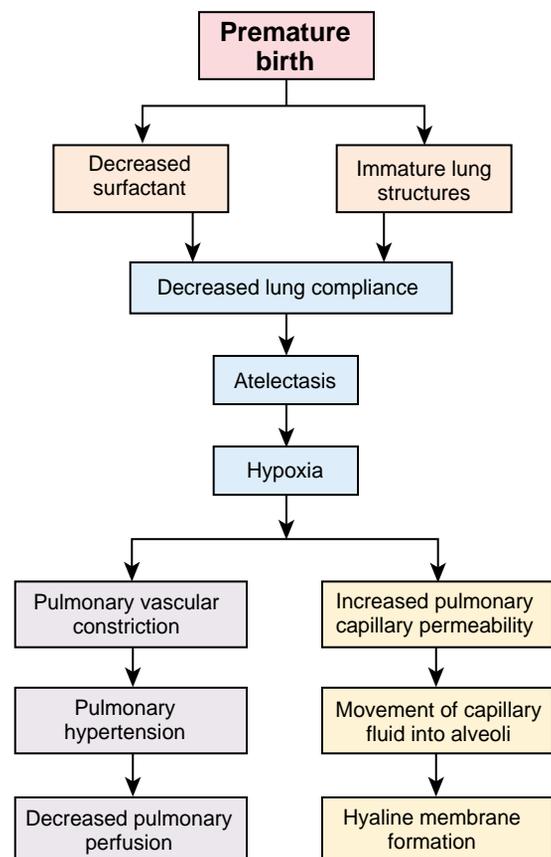
The neonatal period is one of transition from placental dependency to air breathing. This transition requires functioning of the surfactant system, conditioning of the respiratory muscles, and establishment of parallel pulmonary and systemic circulations. Respiratory disorders develop in infants who are born prematurely or who have other problems that impair this transition. Among the respiratory disorders of the neonate are the

respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).

### Respiratory Distress Syndrome

Respiratory distress syndrome, also known as *hyaline membrane disease*, is one of the most common causes of respiratory disease in premature infants. In these infants, pulmonary immaturity, together with surfactant deficiency, leads to alveolar collapse (Fig. 20-7). The type II alveolar cells that produce surfactant do not begin to mature until approximately the 25th to 28th weeks of gestation, and consequently, many premature infants are born with poorly functioning type II alveolar cells and have difficulty producing sufficient amounts of surfactant.<sup>25</sup> The incidence of RDS is higher among preterm male infants, white infants, infants of mothers with diabetes, and those who experience asphyxia, cold stress, precipitous deliveries, and delivery by cesarean section (when performed before the 38th week of gestation).

Surfactant synthesis is influenced by several hormones, including insulin and cortisol. Insulin tends to inhibit surfactant production; this explains why infants of mothers with insulin-dependent diabetes are at increased risk for the development of RDS. Cortisol can accelerate maturation of type II cells and formation of surfactant. The reason premature infants born by cesarean section presumably are at greater risk for the development of RDS is because they are not subjected to the stress of vaginal delivery, which is thought to increase the infants'



■ **FIGURE 20-7** ■ Pathogenesis of respiratory distress syndrome (RSD) in the infant.

cortisol levels. These observations have led to administration of corticosteroid drugs before delivery to mothers with infants at high risk for the development of RDS.<sup>27</sup>

Surfactant reduces the surface tension in the alveoli, thereby equalizing the retractive forces in the large and small alveoli and reducing the amount of pressure needed to inflate and hold the alveoli open (see Chapter 19). At birth, the first breath requires high inspiratory pressures to expand the lungs. With normal levels of surfactant, the lungs retain as much as 40% of the residual volume after the first breath, and subsequent breaths require far lower inspiratory pressures.<sup>9</sup> With a surfactant deficiency, the lungs collapse between breaths, making the infant work as hard with each successive breath as with the first breath. The airless portions of the lungs become stiff and non-compliant. The pulmonary capillary membranes become more permeable, allowing fibrin-rich fluids to be pulled into the alveolar spaces and form a hyaline membrane. The hyaline membrane constitutes a barrier to gas exchange, leading to hypoxemia and carbon dioxide retention, a condition that further impairs surfactant production.

Infants who have RDS present with multiple signs of respiratory distress, usually within the first 24 hours of birth. Central cyanosis is a prominent sign. Breathing becomes more difficult, and retractions occur as the infant's soft chest wall is pulled in as the diaphragm descends. Grunting sounds occur during expiration. As the tidal volume drops because of airway obstruction and alveolar collapse, the respiration rate increases (usually to 60 to 120 breaths/minute) in an effort to maintain normal minute ventilation. Fatigue may develop rapidly because of the increased work of breathing. The stiff lung of infants with RDS also increases the resistance to blood flow in the pulmonary circulation, leading to the development of pulmonary hypertension and decreased pulmonary perfusion.

Infants with suspected RDS require continuous cardiorespiratory monitoring. Oxygen levels can be assessed through an arterial line (umbilical) or by a transcutaneous oxygen sensor. Treatment includes administration of supplemental oxygen, continuous positive airway pressure through nasal prongs, and often assisted mechanical ventilation. A neutral thermal environment and prevention of hypoglycemia are recommended.

Surfactant therapy is used to prevent and treat RDS. There are two types of surfactants available in the United States: surfactants prepared from animal sources and synthetic surfactants.<sup>28</sup> The surfactants are suspended in saline and administered into the airways, usually through an endotracheal tube. The treatment often is initiated soon after birth in infants who are at high risk for RDS.

### Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops in premature infants who were treated with mechanical ventilation, mainly for RDS. The condition is considered to be present if the neonate is oxygen dependent at 36 weeks after gestation. The disorder is thought to be a response of the premature lung to early injury. High concentrations of inspired oxygen and injury from positive-pressure ventilation (*i.e.*, barotrauma) have been implicated. Newer therapies, such as administration of surfactants, high-frequency ventilation, and prenatal or postnatal administration of corticosteroids, may have altered the severity of BPD, but the condition remains a major health problem.<sup>29,30</sup>

BPD is characterized by chronic respiratory distress, persistent hypoxemia when breathing room air, reduced lung compliance, increased airway resistance, and severe expiratory flow limitation. There is a mismatching of ventilation and perfusion with development of hypoxemia and hypercapnia. An increase in pulmonary vascular resistance may lead to the development of pulmonary hypertension and cor pulmonale (*i.e.*, right heart failure associated with lung disease). The infant with BPD may have tachycardia, shallow breathing, chest retractions, cough, barrel chest, and poor weight gain. Clubbing of the fingers occurs in children with severe disease. In infants with right heart failure, tachycardia, tachypnea, hepatomegaly, and periorbital edema develop.

The treatment is mechanical ventilation and administration of adequate oxygenation. Weaning from ventilation is accomplished gradually, and some infants may require ventilation at home. Rapid lung growth occurs during the first year of life, and lung function usually improves. Adequate nutrition is essential for the recovery of infants with BPD.

Most adolescents and young adults who had severe BPD during infancy have some degree of pulmonary dysfunction, consisting of airway obstruction, airway hyperreactivity, or hyperinflation.

## Respiratory Infections in Children

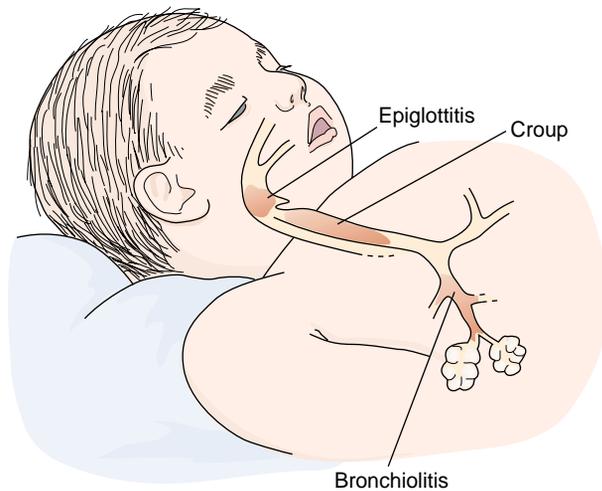
In children, respiratory tract infections are common, and although they are troublesome, they usually are not serious. Frequent infections occur because the immune system of infants and small children has not been exposed to many common pathogens; consequently, they tend to contract infections with each new exposure.

### Upper Airway Infections

Acute inflammation of the upper airway is of particular importance in infants and small children because the airway is smaller, predisposing young children to a relatively greater narrowing than is produced by the same degree of inflammation in an older child. Two acute upper respiratory tract infections are relatively common during early childhood—croup and epiglottitis. Croup, the most common form of acute respiratory obstruction in children, is usually relatively benign and self-limited. Epiglottitis is a rapidly progressive and life-threatening condition. The site of involvement is illustrated in Figure 20-8.

Obstruction of the upper airways because of infection tends to exert its greatest effect during the inspiratory phase of respiration. Movement of air through an obstructed upper airway, particularly the vocal cords in the larynx, causes stridor.<sup>31,32</sup> Impairment of the expiratory phase of respiration also can occur, causing wheezing. With mild to moderate obstruction, inspiratory stridor is more prominent than expiratory wheezing because the airways tend to dilate with expiration. When the swelling and obstruction become severe, the airways no longer can dilate during expiration, and both stridor and wheezing occur.

**Viral Croup.** Viral croup, more appropriately called *acute laryngotracheobronchitis*, is a viral infection that affects the larynx, trachea, and bronchi. It is characterized by a brassy or "croupy" cough, which may or may not be accompanied by inspiratory stridor, hoarseness, and signs of respiratory distress



■ **FIGURE 20-8** ■ Location of airway obstruction in epiglottitis, acute laryngotracheobronchitis (croup), and bronchiolitis. (Courtesy of Carole Russell Hilmer, C.M.I.)

caused by various degrees of laryngeal swelling. The parainfluenza viruses account for approximately 75% all cases; the remaining 25% are caused by adenoviruses, respiratory syncytial virus, influenza A and B viruses, and measles virus.<sup>32</sup>

Viral croup usually is seen in children 3 months to 5 years of age. The condition may affect the entire laryngotracheal tree, but because the subglottic area is the narrowest part of the respiratory tree in this age group, the obstruction usually is greatest in this area. Although the respiratory manifestations of croup often appear suddenly, they usually are preceded by upper respiratory infections that cause rhinorrhea (*i.e.*, runny nose), coryza (*i.e.*, common cold), hoarseness, and a low-grade fever. In most children, the manifestation of croup advances only to stridor and slight dyspnea before they begin to recover.

Airway obstruction may progress in some children. As obstruction increases, the stridor becomes continuous and is associated with nasal flaring with substernal and intercostal retractions. Agitation and crying aggravate the signs and symptoms, and the child prefers to sit up or be held upright. In the cyanotic, pale, or obstructed child, any manipulation of the pharynx, including use of a tongue depressor, can cause cardiorespiratory arrest and should be done only in a medical setting that has the facilities for emergency airway management.

Viral croup does not respond to antibiotics. The child should be disturbed as little as possible and carefully monitored for signs of respiratory distress. The use of steam from a shower or bath in a closed bathroom often brings prompt and dramatic relief of symptoms. Exposure to cold air also seems to relieve airway spasm; often, the severe symptoms are relieved simply because the child is exposed to cold air on the way to the hospital emergency room. Other treatment methods may be required when a humidifier or cold mist is ineffective. Administration of a racemic mixture of epinephrine (*L*-epinephrine and *D*-epinephrine) by positive-pressure breathing through a face mask often results in transient relief of symptoms.<sup>34</sup> Inhaled or systemically administered (oral or intramuscular) corticosteroid therapy may also be used. Children with progressive stridor or signs of respiratory distress may re-

quire hospitalization. Establishment of an artificial airway may become necessary in severe airway obstruction.

**Spasmodic Croup.** Spasmodic croup manifests with symptoms similar to those of acute viral croup. Because the child is afebrile and lacks other manifestations of the viral prodrome, it is thought that it may have an allergic origin. Spasmodic croup characteristically occurs at night and tends to recur with respiratory tract infections. The episode usually lasts several hours and may recur several nights in a row.

Most children with spasmodic croup can be effectively treated at home. An environment of high humidification (*i.e.*, cold-water room humidifier or taking the child into a bathroom with a warm, running shower) lessens irritation and prevents drying of secretions.

**Epiglottitis.** Acute epiglottitis is a dramatic, potentially fatal condition most often caused by the *H. influenzae* type B bacterium. It is usually seen in children 2 to 7 years of age, with a peak incidence at approximately 3.5 years.<sup>32</sup> Epiglottitis is seen less commonly since the widespread use of immunization against *H. influenzae* type B.

Epiglottitis is characterized by inflammatory edema of the supraglottic area, including the epiglottis and pharyngeal structures, that comes on suddenly, bringing danger of airway obstruction and asphyxia. Within a matter of hours, epiglottitis may progress to complete obstruction of the airway and death unless adequate treatment is instituted.

The child appears pale, toxic, and lethargic and assumes a distinctive position—sitting up with the mouth open and the chin thrust forward. The child has difficulty in swallowing, a muffled voice, drooling, fever, and extreme anxiety. Moderate to severe respiratory distress is evident. There is inspiratory and sometimes expiratory stridor, flaring of the nares, and inspiratory retractions of the suprasternal notch and supraclavicular and intercostal spaces. Usually, no other family members are ill with acute respiratory disease.

The child with epiglottitis requires immediate hospitalization. Establishment of an airway by endotracheal tube or tracheotomy usually is needed. If epiglottitis is suspected, the child should never be forced to lie down because this causes the epiglottis to fall backward and may lead to complete airway obstruction. Examination of the throat with a tongue blade or other instrument may cause cardiopulmonary arrest and should be done only by medical personnel experienced in intubation of small children. It also is unwise to attempt any procedure, such as drawing blood, which would heighten the child's anxiety, because this also could precipitate airway spasm and cause death. Recovery from epiglottitis usually is rapid and uneventful after an adequate airway has been established and appropriate antibiotic therapy has been initiated.

### Lower Airway Infections

Lower airway infections produce air trapping with prolonged expiration. The child presents with increased expiratory effort, increased respiratory rate, and wheezing. If the infection is severe, there also are marked intercostal retractions and signs of impending respiratory failure.

**Acute Bronchiolitis.** Acute bronchiolitis is a viral infection of the lower airways, most commonly caused by the respiratory

syncytial virus (RSV).<sup>33</sup> Other viruses, such as parainfluenza 3 virus and some adenoviruses, as well as mycoplasma, also are causative. The infection produces inflammatory obstruction of the small airways and necrosis of the cells lining the lower airways. Because the resistance to airflow in a tube is related to the fourth power of the radius, even minor swelling of bronchioles in an infant can produce profound changes in airflow.

Acute bronchiolitis usually occurs during the first 2 years of life, with a peak incidence between 3 to 6 months of age. The source of infection usually is a family member with a minor respiratory illness. Older children and adults tolerate bronchiolar edema much better than do infants and do not manifest the clinical picture of bronchiolitis.

Most affected infants in whom bronchiolitis develops have a history of a mild upper respiratory tract infection. These symptoms usually last several days and may be accompanied by fever and diminished appetite. There is then a gradual development of respiratory distress, characterized by a wheezy cough, dyspnea, and irritability. The infant usually is able to take in sufficient air but has trouble exhaling it. Air becomes trapped in the lung distal to the site of obstruction and interferes with gas exchange. Hypoxemia and, in severe cases, hypercapnia may develop. Airway obstruction may produce air trapping and hyperinflation of the lungs or collapse of the alveoli.

Infants with acute bronchiolitis have a typical appearance, marked by breathlessness with rapid respirations, a distressing cough, and retractions of the lower ribs and sternum (see Table 20-2). Crying and feeding exaggerate these signs. Wheezing and rales may or may not be present, depending on the degree of airway obstruction. In infants with severe airway obstruction, wheezing decreases as the airflow diminishes.

Usually, the most critical phase of the disease is the first 48 to 72 hours. Cyanosis, pallor, listlessness, and sudden diminution or absence of breath sounds indicate impending respiratory failure. Hospitalization is often indicated during this period. Treatment is largely supportive and includes administration of humidified oxygen to relieve hypoxia. Elevation of the head facilitates respiratory movements and avoids

airway compression. Handling is kept at a minimum to avoid tiring. Because the infection is viral, antibiotics are not effective and are given only for a secondary bacterial infection. Dehydration may occur as the result of increased insensible water losses because of the rapid respiratory rate and feeding difficulties, and measures to ensure adequate hydration are needed. Recovery usually begins after the first 48 to 72 hours and usually is rapid and complete.

There is a reported increase in hyperactive airways during later childhood in infants who have had bronchiolitis.<sup>34</sup> The reason this occurs is not understood, and further investigation is needed.

### Signs of Impending Respiratory Failure

Respiratory problems of infants and small children often are of sudden origin, and recovery usually is rapid and complete. Infants and children are at risk for the development of airway obstruction and respiratory failure resulting from obstructive disorders or lung infection. The child with epiglottitis is at risk for airway obstruction. The child with bronchiolitis is at risk for respiratory failure resulting from impaired gas exchange. Children with impending respiratory failure caused by airway or lung disease have rapid breathing, exaggerated use of the accessory muscles, retractions (which are more pronounced in the child than in the adult because of more compliant chest), nasal flaring, and grunting during expiration.<sup>35</sup> The signs and symptoms of impending respiratory failure are listed in Chart 20-1.

**In summary,** acute respiratory disease is the most common cause of illness in infancy and childhood. Although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs take longer. Immaturity of the respiratory system is a major cause of morbidity and mortality in premature infants. RDS is one of the most common causes of respiratory disease in premature infants. In these infants, pulmonary immaturity, together with surfactant deficiency, leads to alveolar collapse. BPD is a chronic

**TABLE 20-2** Characteristics of Epiglottitis, Croup, and Bronchiolitis in Small Children

Characteristics	Epiglottitis	Croup	Bronchiolitis
Common causative agent	<i>Haemophilus influenzae</i> type B bacterium	Mainly parainfluenza virus	Respiratory syncytial virus
Most commonly affected age group	2–7 years (peak 3–5 years)	3 months to 5 years	Less than 2 years (most severe in infants younger than 6 months)
Onset and preceding history	Sudden onset	Usually follows symptoms of a cold	Preceded by stuffy nose and other signs
Prominent features	Child appears very sick and toxic Sits with mouth open and chin thrust forward Low-pitched stridor, difficulty swallowing, fever, drooling, anxiety <i>Danger of airway obstruction and asphyxia</i>	Stridor and a wet, barking cough Usually occurs at night Relieved by exposure to cold or moist air	Breathlessness, rapid, shallow breathing, wheezing, cough, and retractions of lower ribs and sternum during inspiration
Usual treatment	Hospitalization Intubation or tracheotomy Treatment with appropriate antibiotic	Mist tent or vaporizer Administration of oxygen	Supportive treatment, administration of oxygen and hydration

### CHART 20-1 Signs of Respiratory Distress and Impending Respiratory Failure in the Infant and Small Child

Severe increase in respiratory effort, including severe retractions or grunting, decreased chest movement  
 Cyanosis that is not relieved by administration of oxygen (40%)  
 Heart rate of 150 per minute or greater and increasing  
 Bradycardia  
 Very rapid breathing (rate 60 per minute in the newborn to 6 months or above 30 per minute in children 6 months to 2 years)  
 Very depressed breathing (rate 20 per minute or below)  
 Retractions of the supraclavicular area, sternum, epigastrium, and intercostal spaces  
 Extreme anxiety and agitation  
 Fatigue  
 Decreased level of consciousness

pulmonary disease that develops in premature infants who were treated with mechanical ventilation.

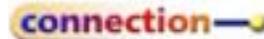
Because of the smallness of the airway of infants and children, respiratory tract infections in these groups often are more serious. Infections that may cause only a sore throat and hoarseness in the adult may produce serious obstruction in the child. Obstruction of the extrathoracic airways often produces turbulence of airflow and an audible inspiratory crowing sound called *stridor*, and obstruction of the intrathoracic airways produces an audible expiratory wheezing or whistling sound. Among the respiratory tract infections that produce airway obstruction in small children are croup, epiglottitis, and bronchiolitis. Epiglottitis is a life-threatening supraglottic infection that may cause airway obstruction and asphyxia. Bronchiolitis is a viral infection of the lower airways; infants and small children with bronchiolitis are at risk for respiratory failure resulting from impaired gas exchange.

Infants and children with impending respiratory failure caused by airway or lung disease have rapid and shallow breathing, exaggerated use of the accessory muscles, retractions (which are more pronounced in the child than in the adult because of more compliant chest), and grunting during expiration.

### REVIEW QUESTIONS

- Differentiate among community-acquired pneumonia, hospital-acquired pneumonia, and pneumonia in immunocompromised persons in terms of pathogens, manifestations, and prognosis.
- Explain the rationale for using the 7-valent, rather than the 23-valent, pneumococcus vaccine for children younger than 2 years.
- Explain the difference between primary tuberculosis and reactivated tuberculosis on the basis of their pathophysiology and symptoms.

- Describe the manifestations of lung cancer and list two symptoms of lung cancer that are related to the invasion of the mediastinum.
- Define the term *paraneoplastic* and cite three paraneoplastic manifestations of lung cancer.
- Characterize the 5-year survival rate for lung cancer.
- Cite the function of surfactant in lung function in the neonate and relate it to the development of respiratory distress syndrome.
- Cite the possible causes and manifestations of bronchopulmonary dysplasia.
- Describe the physiologic basis for sternal and chest wall retractions and grunting, stridor, and wheezing as signs of respiratory distress in infants and small children.
- Compare croup, epiglottitis, and bronchiolitis in terms of incidence by age, site of infection, and signs and symptoms.
- List the signs of impending respiratory failure in small children.



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