CHAPTER
21

Alterations in Respiratory Function: Disorders of Gas Exchange

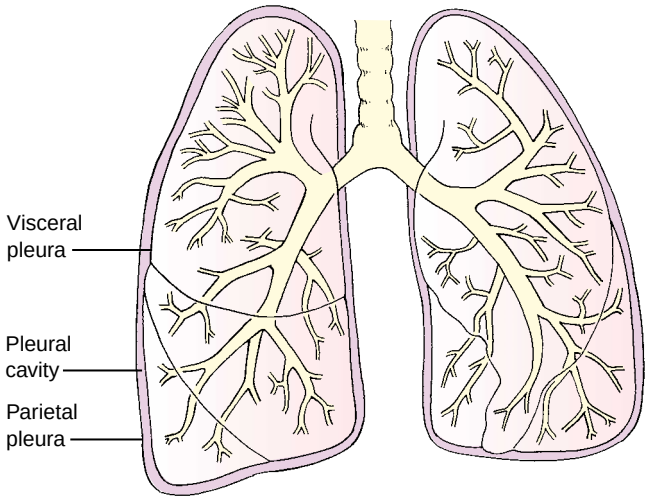
The major function of the lungs is to oxygenate and remove carbon dioxide from the blood as a means of supporting the metabolic functions of body cells. The gas exchange function of the lungs depends on a system of open airways, expansion of the lungs, an adequate area for gas diffusion, and blood flow that carries the gases to the rest of the body. This chapter focuses on diseases that disrupt ventilation and gas exchange and on respiratory failure and hyperventilation.

DISORDERS OF LUNG INFLATION

Air entering through the airways inflates the lung, and the negative pressure in the pleural cavity keeps the lung from collapsing. Disorders of lung inflation are caused by conditions that produce lung compression or lung collapse. There can be compression of the lung by an accumulation of fluid in the intrapleural space, complete collapse of an entire lung as in pneumothorax, or collapse of a segment of the lung as in atelectasis.

Disorders of the Pleura

The pleura is a thin, double-layered membrane that encases the lungs. The two layers of the pleurae are separated by a thin layer of serous fluid (Fig. 21-1). The right and left pleural cavities are separated by the mediastinum, which contains the heart and other thoracic structures. Both the chest wall and the lungs have elastic properties. The pressure in the pleural cavity, which is negative in relation to atmospheric pressure, holds the lungs



■ **FIGURE 21-1** ■ The parietal and visceral pleura and site of fluid accumulation in pleural effusions.

against the chest wall and keeps them from collapsing (see Chapter 19). Disorders of the pleura include pleural pain, pleural effusion, and pneumothorax.

Pleuritis and Pleural Pain

Pain is a common symptom of pleuritis, or inflammation of the pleura. Pleuritis is common in infectious processes such as viral respiratory infections or pneumonia that extend to involve the pleura. Most commonly the pain is abrupt in onset, such that the person experiencing it can cite almost to the minute when the pain started. It usually is unilateral and tends to be localized to the lower and lateral part of the chest. When the central part of the diaphragm is irritated, the pain may be referred to the shoulder. The pain is usually made worse by chest movements, such as deep breathing and coughing, that exaggerate pressure changes in the pleural cavity and increase movement of the inflamed or injured pleural surfaces. Because deep breathing is painful, tidal volumes usually are kept small, and breathing becomes more rapid. Reflex splinting of the chest muscles may occur, causing a lesser respiratory excursion on the affected side.

It is important to differentiate pleural pain from pain produced by other conditions, such as musculoskeletal strain of chest muscles, bronchial irritation, and myocardial disease. Musculoskeletal pain may occur as the result of frequent, forceful coughing. This type of pain usually is bilateral and located in the inferior portions of the rib cage, where the abdominal muscles insert into the anterior rib cage. It is made worse by movements associated with contraction of the abdominal muscles. The pain associated with irritation of the bronchi usually is substernal and dull, rather than sharp, in character. It is made worse with coughing but is not affected by deep breathing. Myocardial pain, which is discussed in Chapter 17, usually is located in the substernal area and is not affected by respiratory movements.

Pleural Effusion

Pleural effusion refers to an abnormal collection of fluid in the pleural cavity (see Fig. 21-1). The fluid may be a transudate, exudate, purulent drainage (empyema), chyle, or blood. Normally, only a thin layer (<10 to 20 mL) of serous fluid separates the visceral and parietal layers of the pleural cavity. Like fluid developing in other transcellular spaces in the body, pleural effusion occurs when the rate of fluid formation exceeds the rate of its removal (see Chapter 6). Five mechanisms have been linked to the abnormal collection of fluid in the pleural cavity: (1) increased capillary pressure, as in congestive heart failure; (2) increased capillary permeability, which occurs with inflammatory conditions; (3) decreased colloidal osmotic pressure, such as the hypoalbuminemia occurring with liver disease and nephrosis; (4) increased negative intrapleural pressure, which develops with atelectasis; and (5) impaired lymphatic drainage of the pleural space, which results from obstructive processes such as mediastinal carcinoma.

The accumulation of a serous transudate (clear fluid) in the pleural cavity often is referred to as *hydrothorax*. The condition may be unilateral or bilateral. The most common cause of hydrothorax is congestive heart failure.[1] Other causes are renal failure, nephrosis, liver failure, and malignancy. An *exudate* is a pleural fluid that has a specific gravity greater than 1.020 and, often, inflammatory cells. Conditions that produce exudative pleural effusions are infections, pulmonary infarction, malignancies, rheumatoid arthritis, and lupus erythematosus.

Empyema refers to pus in the pleural cavity. It is caused by direct infection of the pleural space from an adjacent bacterial pneumonia, rupture of a lung abscess into the pleural space, invasion from a subdiaphragmatic infection, or infection associated with trauma.

Chylothorax is the effusion of lymph in the thoracic cavity.[2] Chyle, a milky fluid containing chylomicrons, is found in the lymph fluid originating in the gastrointestinal tract. The thoracic duct transports chyle to the central circulation. Chylothorax also results from trauma, inflammation, or malignant infiltration obstructing chyle transport from the thoracic duct into the central circulation. It also can occur as a complication of intrathoracic surgical procedures and use of the great veins for total parenteral nutrition and hemodynamic monitoring.

Hemothorax is the presence of blood in the pleural cavity. Bleeding may arise from chest injury, a complication of chest surgery, malignancies, or rupture of a great vessel such as an aortic aneurysm. It is usually diagnosed by the presence of blood in the pleural fluid. Hemorrhagic pleural fluid is a mixture of blood and pleural fluid. Hemothorax usually requires drainage, and if the bleeding continues, surgery to control the bleeding may be required.

The manifestations of pleural effusion vary with the cause. Hemothorax may be accompanied by signs of blood loss and empyema by fever and other signs of inflammation. Fluid in the pleural cavity acts as a space-occupying mass; it causes a decrease in lung expansion on the affected side that is proportional to the amount of fluid that is present. The effusion may cause a shift in the mediastinal structures toward the opposite side of the chest with a decrease in lung volume on that side as well as the side with the pneumothorax. Characteristic signs of pleural effusion are dullness or flatness to percussion and diminished breath sounds. Dyspnea, the most common symptom, occurs when fluid compresses the lung, resulting in decreased ventilation. Pleuritic pain usually occurs only when inflammation is present, although constant discomfort may be

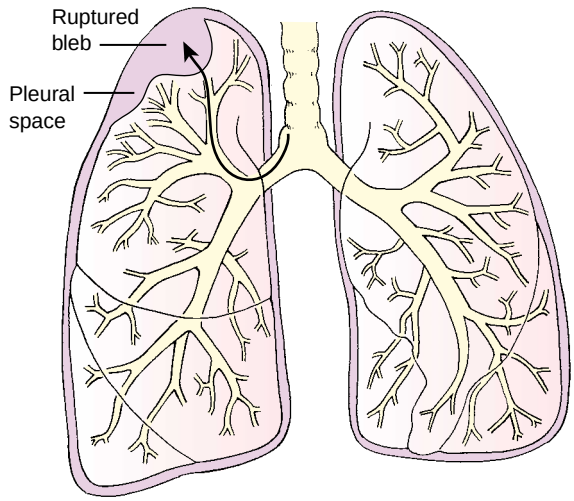
felt with large effusions. Mild hypoxemia may occur and usually is corrected with supplemental oxygen.

Diagnosis of pleural effusion is based on chest radiographs, chest ultrasound, and computed tomography (CT). Thoracentesis is the aspiration of fluid from the pleural space. It can be used to obtain a sample of pleural fluid for diagnosis, or it can be used for therapeutic purposes. The treatment of pleural effusion is directed at the cause of the disorder. With large effusions, thoracentesis may be used to remove fluid from the intrapleural space and allow for re-expansion of the lung. A palliative method used for treatment of pleural effusions caused by a malignancy is the injection of a sclerosing agent into the pleural cavity. This method of treatment causes obliteration of the pleural space and prevents the reaccumulation of fluid. Open surgical drainage may be necessary in cases of continued effusion.

Pneumothorax

Normally, the pleural cavity is free of air and contains only a thin layer of fluid. When air enters the pleural cavity, it is called *pneumothorax*. Pneumothorax causes partial or complete collapse of the affected lung. Pneumothorax can occur without an obvious cause or injury (*i.e.*, spontaneous pneumothorax) or as a result of direct injury to the chest or major airways (*i.e.*, traumatic pneumothorax). Tension pneumothorax describes a life-threatening condition of excessive pressure in the pleural cavity.

Spontaneous Pneumothorax. Spontaneous pneumothorax occurs when an air-filled bleb, or blister, on the lung surface ruptures. Rupture of these blebs allows atmospheric air from the airways to enter the pleural cavity (Fig. 21-2). Because alveolar pressure normally is greater than pleural pressure, air flows from the alveoli into the pleural space, causing the involved portion of the lung to collapse as a result of its own recoil. Air continues to flow into the pleural space until a pressure gradient no longer exists or until the decline in lung size causes the leak to seal. Spontaneous pneumothoraces can be divided into primary and secondary pneumothoraces.[3] Primary spontaneous pneumothorax occurs in otherwise healthy persons. Secondary spontaneous pneumothorax occurs in persons with underlying lung disease.



■ **FIGURE 21-2** ■ Mechanism for development of spontaneous pneumothorax.

In primary spontaneous pneumothorax, the air-filled bleb that ruptures is usually on the top of the lung. The condition is seen most often in tall boys and young men between 10 and 30 years of age.[3] It has been suggested that the difference in pleural pressure from the top to the bottom of the lung is greater in tall persons and that this difference in pressure may contribute to the development of blebs. Another factor that has been associated with primary spontaneous pneumothorax is smoking. Disease of the small airways related to smoking probably contributes to the condition.

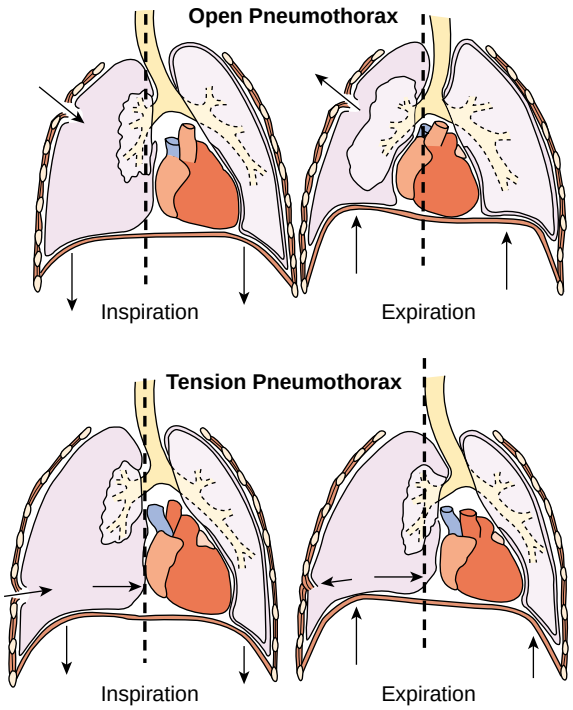
Secondary spontaneous pneumothoraces usually are more serious because they occur in persons with lung disease. They are associated with many different types of lung conditions that cause trapping of gases and destruction of lung tissue, including asthma, tuberculosis, cystic fibrosis, sarcoidosis, bronchogenic carcinoma, and metastatic pleural diseases. The most common cause of secondary spontaneous pneumothorax is emphysema.

Traumatic Pneumothorax. Traumatic pneumothorax may be caused by penetrating or nonpenetrating chest injuries. Fractured or dislocated ribs that penetrate the pleura are the most common cause of pneumothorax from nonpenetrating chest injuries. Hemothorax often accompanies these injuries. Pneumothorax also may accompany fracture of the trachea or major bronchus or rupture of the esophagus. Persons with pneumothorax caused by chest trauma frequently have other complications and may require chest surgery. Medical procedures such as transthoracic needle aspirations, intubation, and positive-pressure ventilation occasionally may cause pneumothorax. Traumatic pneumothorax also can occur as a complication of cardiopulmonary resuscitation.

Tension Pneumothorax. Tension pneumothorax occurs when the intrapleural pressure exceeds atmospheric pressure. It is a life-threatening condition and occurs when injury to the chest or respiratory structures permits air to enter but not leave the pleural space (Fig. 21-3). This results in a rapid increase in pressure in the chest with a compression atelectasis of the unaffected lung, a shift in the mediastinum to the opposite side of the chest, and compression of the vena cava with impairment of venous return to the heart.[4] Although tension pneumothorax can develop in persons with spontaneous pneumothoraces, it is seen most often in persons with traumatic pneumothoraces.

With tension pneumothorax, the structures in the mediastinal space shift toward the opposite side of the chest (see Fig. 21-3). When this occurs, the position of the trachea, normally located in the midline of the neck, deviates with the mediastinum. There may be distention of the neck veins and subcutaneous emphysema (*i.e.*, air bubbles in the subcutaneous tissues of the chest and neck) and clinical signs of shock.

Clinical Features. The manifestations of pneumothorax depend on its size and the integrity of the underlying lung. In spontaneous pneumothorax, manifestations of the disorder include development of ipsilateral (same side) chest pain in an otherwise healthy person. There is an almost immediate in-



■ **FIGURE 21-3** ■ Open or communicating pneumothorax (**top**) and tension pneumothorax (**bottom**). In an open pneumothorax, air enters the chest during inspiration and exits during expiration. There may be slight inflation of the affected lung due to a decrease in pressure as air moves out of the chest. In tension pneumothorax, air can enter but not leave the chest. As the pressure in the chest increases, the heart and great vessels are compressed and the mediastinal structures are shifted toward the opposite side of the chest. The trachea is pushed from its normal midline position toward the opposite side of the chest, and the unaffected lung is compressed.

crease in respiratory rate, often accompanied by dyspnea that occurs as a result of the activation of receptors that monitor lung volume. Heart rate is increased. Asymmetry of chest movement may occur because of the air trapped in the pleural cavity on the affected side. Percussion of the chest produces a more hyperresonant sound, and breath sounds are decreased or absent over the area of the pneumothorax.

Hypoxemia usually develops immediately after a large pneumothorax, followed by vasoconstriction of the blood vessels in the affected lung, causing the blood flow to shift to the unaffected lung. In persons with primary spontaneous pneumothorax, this mechanism usually returns oxygen saturation to normal within 24 hours. Hypoxemia usually is more serious in persons with underlying lung disease in whom secondary spontaneous pneumothorax develops. In these persons, the hypoxemia caused by the partial or total loss of lung function can be life threatening.

Diagnosis of pneumothorax can be confirmed by chest radiograph or CT scan. Blood gas analysis may be done to determine the effect of the condition on blood oxygen levels. Treatment varies with the cause and extent of the disorder. Even without treatment, air in the pleural space usually reabsorbs after the pleural leak seals. In small spontaneous pneumothoraces, the air usually reabsorbs, and observation and follow-up chest radiographs are all that is required. Supplemental oxygen may be used to increase the rate at which the air is reabsorbed. In larger pneumothoraces, the air is removed by needle aspiration or a closed drainage system used with or without an aspiration pump. This type of drainage system uses a one-way valve or a tube submerged in water to allow air to exit the pleural space and prevent it from re-entering the chest. In secondary pneumothorax, surgical closure of the chest wall defect, ruptured airway, or perforated esophagus may be required.

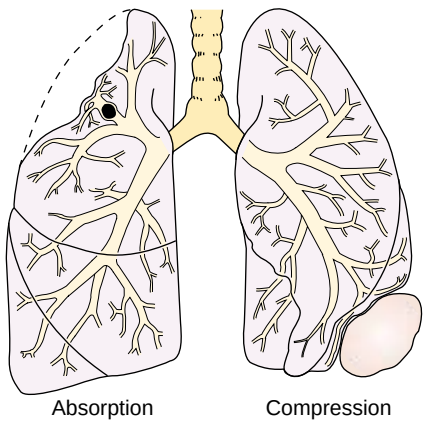
Emergency treatment of tension pneumothorax involves the prompt insertion of a large-bore needle or chest tube into the affected side of the chest along with one-way valve drainage or continuous chest suction to aid in lung expansion. Sucking chest wounds, which allow air to pass in and out of the chest cavity, should be treated by promptly covering the area with an airtight covering. Chest tubes are inserted as soon as possible.

Atelectasis

Atelectasis refers to the incomplete expansion of a lung or portion of a lung. It can be caused by airway obstruction, lung compression such as occurs in pneumothorax or pleural effusion, or the increased recoil of the lung caused by inadequate pulmonary surfactant (see Chapter 19).

Atelectasis is caused most commonly by airway obstruction (Fig. 21-4). Obstruction can be caused by a mucus plug in the airway or by external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway. A small segment of lung or an entire lung lobe may be involved in obstructive atelectasis. Complete obstruction of an airway is followed by the absorption of air from the dependent alveoli and collapse of that portion of the lung. The danger of obstructive atelectasis increases after surgery. Anesthesia, pain, administration of narcotics, and immobility tend to promote retention of viscid bronchial secretions and thus airway obstruction.

Another cause of atelectasis is compression of lung tissue. It occurs when the pleural cavity is partially or completely filled with fluid, exudate, blood, a tumor mass, or air. It is observed most commonly in persons with pleural effusion from



■ **FIGURE 21-4** ■ Atelectasis caused by airway obstruction and absorption of air from the involved lung area on the *left* and by compression of lung tissue on the *right*.

congestive heart failure or cancer. In compression atelectasis, the mediastinum shifts away from the affected lung.

The clinical manifestations of atelectasis include tachypnea, tachycardia, dyspnea, cyanosis, signs of hypoxemia, diminished chest expansion, absence of breath sounds, and intercostal retractions. Fever and other signs of infection may develop. Both chest expansion and breath sounds are decreased on the affected side. There may be intercostal retraction (pulling in of the intercostal spaces) over the involved area during inspiration. If the collapsed area is large, the mediastinum and trachea shift to the affected side. Signs of respiratory distress are proportional to the extent of lung collapse.

The diagnosis of atelectasis is based on signs and symptoms. Chest radiographs are used to confirm the diagnosis. CT scans may be used to show the exact location of the obstruction. Treatment depends on the cause and extent of lung involvement. It is directed at reducing the airway obstruction or lung compression and at reinflating the collapsed area of the lung. Ambulation and body positions that favor increased lung expansion are used when appropriate. Administration of oxygen may be needed to treat the hypoxemia. Bronchoscopy may be used as a diagnostic and treatment method.

In summary, lung inflation depends on a negative intrapleural pressure and unobstructed intrapulmonary airways. Disorders of the pleura include pleuritis and pain, pleural effusion, and pneumothorax. Pain is commonly associated with conditions that produce inflammation of the pleura. Characteristically, it is unilateral, abrupt in onset, and exaggerated by respiratory movements. Pleural effusion refers to the abnormal accumulation of fluid in the pleural cavity. The fluid may be a transudate (*i.e.*, hydrothorax), exudate (*i.e.*, empyema), blood (*i.e.*, hemothorax), or chyle (*i.e.*, chylothorax). Pneumothorax refers to an accumulation of air in the pleural cavity with the partial or complete collapse of the lung. It can result from rupture of an air-filled bleb on the lung surface or from penetrating or nonpenetrating injuries. A tension pneumothorax is a life-threatening event in which air progressively accumulates in the thorax, collapsing the lung on the injured side and progressively shifting the mediastinum to the opposite side of the thorax, producing severe cardiorespiratory impairment.

Atelectasis refers to an incomplete expansion of the lung. In adults, atelectasis usually results from airway obstruction caused by mucus plug or because of external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway.

OBSTRUCTIVE AIRWAY DISORDERS

Obstructive airway diseases are caused by disorders that limit expiratory airflow. Bronchial asthma represents a reversible form of airway disease caused by narrowing of airways due to bronchospasm, inflammation, and increased airway secretions. Chronic obstructive airway disease can be caused by a variety of airway diseases, including chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis.

Physiology of Airway Disease

Air moves through the upper airways (*i.e.*, trachea and major bronchi) into the lower or pulmonary airways (*i.e.*, bronchi and alveoli), which are located in the lung. In the pulmonary airways, the cartilaginous layer that provides support for the trachea and major bronchi gradually disappears and is replaced with crisscrossing strips of smooth muscle (see Chapter 19). The contraction and relaxation of the smooth muscle layer, which is innervated by the autonomic nervous system (ANS), controls the diameter of the airways and consequent resistance to airflow. Parasympathetic stimulation, through the vagus nerve and cholinergic receptors, produces bronchoconstriction, and sympathetic stimulation, through β_2-adrenergic receptors, increases bronchodilation. Normally, a slight vagal-mediated bronchoconstrictor tone predominates. When there is need for increased airflow, as during exercise, the vagal-mediated bronchoconstrictor tone is inhibited, and the bronchodilator effects of the sympathetic nervous system are increased.

Bronchial smooth muscle also responds to inflammatory mediators, such as histamine, that act directly on smooth muscle cells to produce bronchoconstriction. During an antigen-antibody response, inflammatory mediators are released by a special type of cell, called the *mast cell*, which is present in the airways. The binding of immunoglobulin E (IgE) antibodies to receptors on mast cells prepares them for an allergic response when antigen appears (see Chapter 10).

Bronchial Asthma

Bronchial asthma is a chronic inflammatory airway disease. According to 1998 data, an estimated 26 million Americans have received diagnoses of asthma, and 10.6 million have had

KEY CONCEPTS

AIRWAY DISORDERS

- Airway disorders involve the movement of gases into and out of the lung. They involve bronchial smooth muscle tone, mucosal injury, and obstruction due to secretions.
- The tone of the bronchial smooth muscles surrounding the airways determines airway radius, and the presence or absence of airway secretions influences airway patency.
- Bronchial smooth muscle is innervated by the autonomic nervous system—the parasympathetic nervous system, via the vagus nerve, produces bronchoconstriction and the sympathetic nervous system produces bronchodilation.
- Inflammatory mediators that are released in response to environmental irritants, immune responses, and infectious agents increase airway responsiveness by producing bronchospasm, increasing mucus secretion, and producing injury to the mucosal lining of the airways.

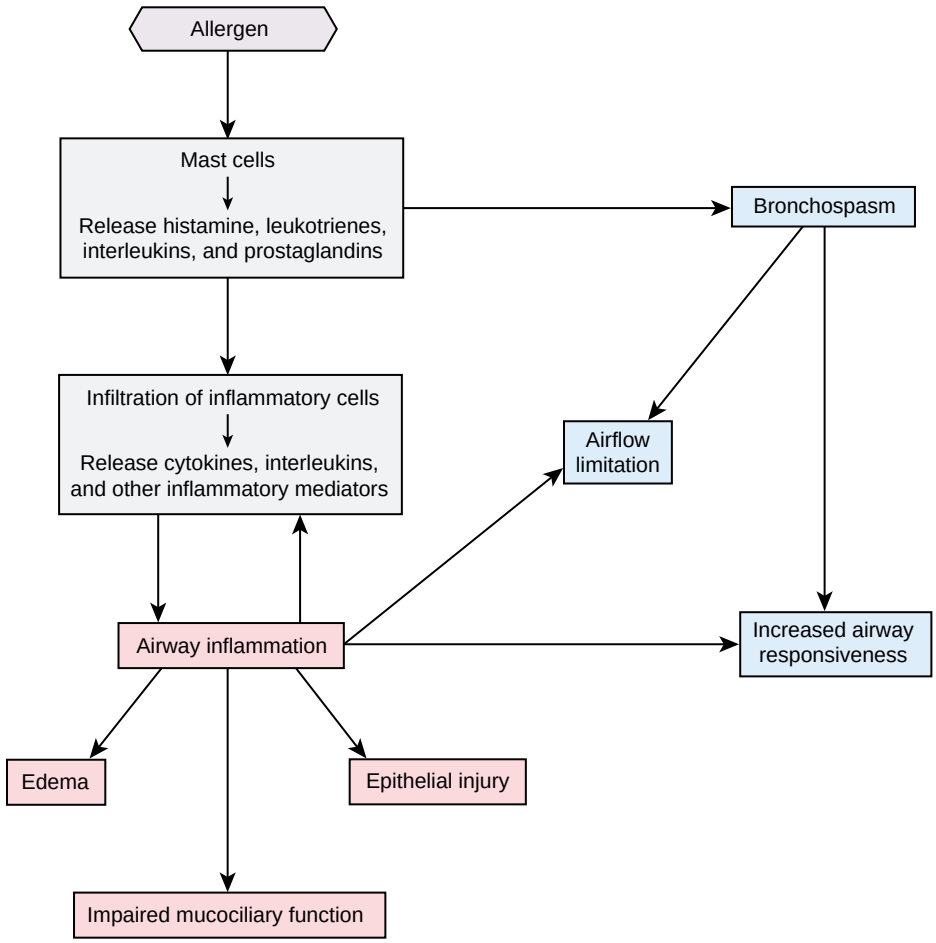
an asthma episode during the past 12 months.[5] Of the 26 million Americans with diagnoses of asthma, 8.6 million are younger than 18 years. In the general population, asthma prevalence rates increased 102% between 1980 and 1994.[5] There also has been a reported increase in incidence and mortality associated with asthma during the past several decades.

The National Heart, Lung, and Blood Institute's Second Expert Panel on the Management of Asthma defined bronchial asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, and epithelial cells."[6] This inflammatory process produces recurrent episodes of airway obstruction, characterized by wheezing, breathlessness, chest tightness, and a cough that often is worse at night and in the early morning. These episodes, which usually are reversible either spontaneously or with treatment, also cause an associated increase in bronchial responsiveness to a variety of stimuli.[6]

Pathogenesis

In susceptible persons, an asthma attack can be triggered by a variety of stimuli that do not normally cause symptoms. Based on their mechanism of response, these triggers can be divided into two categories—bronchospastic or inflammatory. Bronchospastic triggers depend on the existing level of airway responsiveness. They do not normally increase airway responsiveness but produce symptoms in persons who already are predisposed to bronchospasm. *Bronchospastic triggers* include cold air, exercise, emotional upset, and exposure to bronchial irritants such as cigarette smoke. *Inflammatory triggers* exert their effects through the inflammatory response. They cause inflammation and prime the sensitive airways so they are hyperresponsive to nonallergic stimuli. The mechanisms whereby these two types of triggers produce an asthmatic attack can be further described as the early or acute response versus the late phase response.[7] The *acute* or *early response* results in immediate bronchoconstriction on exposure to an inhaled antigen or irritant (Fig. 21-5). The symptoms of the acute response, which usually develop within 10 to 20 minutes, are caused by the release of chemical mediators from IgE-sensitized mast cells. In the case of airborne antigens, the reaction occurs when antigen binds to sensitized mast cells on the mucosal surface of the airways. Mediator release results in the infiltration of inflammatory cells and opening of the mucosal intercellular junctions and enhancement of antigen movement to the more prevalent submucosal mast cells (Fig. 21-5). In addition, there is bronchoconstriction caused by direct stimulation of parasympathetic receptors, mucosal edema caused by increased vascular permeability, and increased mucus secretions.

The *late phase response* develops 4 to 8 hours after exposure to an asthmatic trigger.[7,8] The late phase response involves inflammation and increased airway responsiveness that prolong



■ **FIGURE 21-5** ■ Mechanisms of early and late phase Ig-E mediated bronchospasm.

the asthma attack and set into motion a vicious cycle of exacerbations. Typically, the response reaches a maximum within a few hours and may last for days or even weeks. An initial trigger in the late phase response causes the release of inflammatory mediators from mast cells, macrophages, and epithelial cells. These substances induce the migration and activation of other inflammatory cells (*e.g.*, basophils, eosinophils, neutrophils), which then produce epithelial injury and edema, changes in mucociliary function and reduced clearance of respiratory tract secretions, and increased airway responsiveness (see Fig. 21-6). Responsiveness to cholinergic mediators often is heightened, suggesting changes in parasympathetic control of airway function. Chronic inflammation can lead to airway remodeling, with more permanent changes in airway resistance.[6]

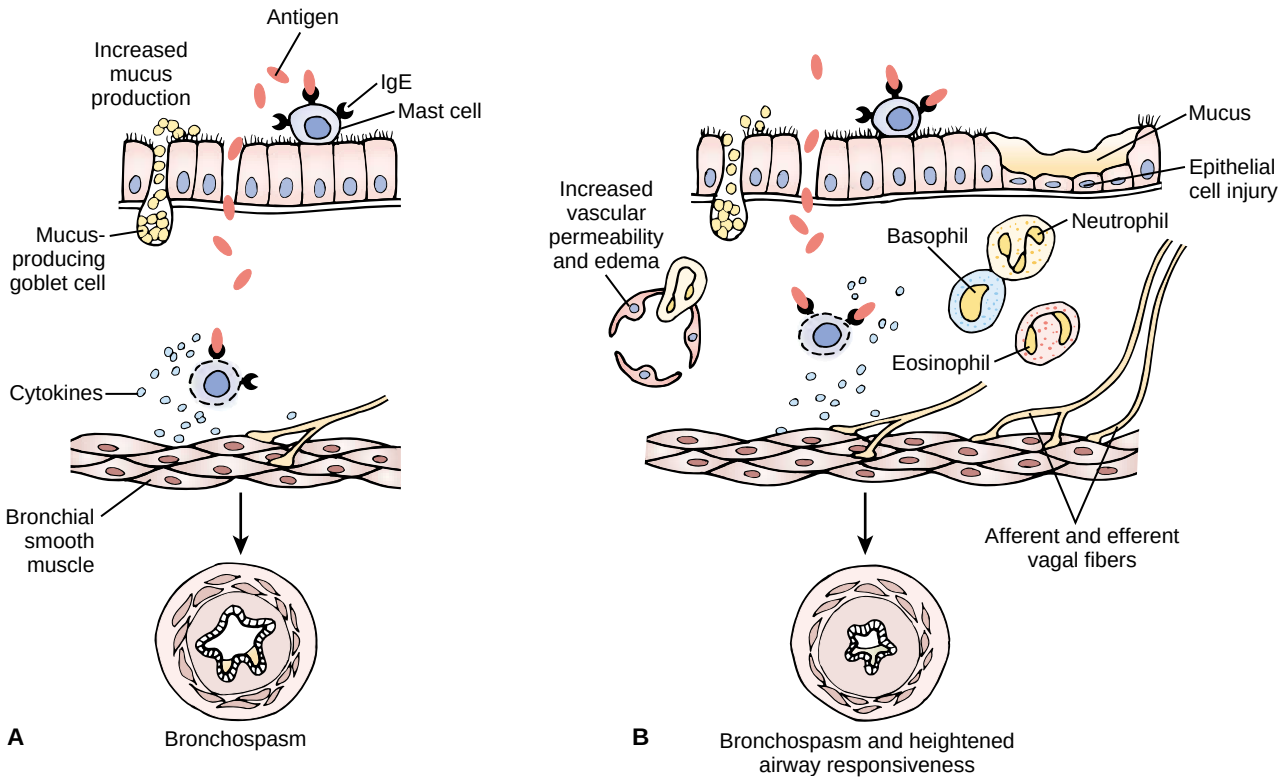
Causes. A number of factors can contribute to an asthmatic attack, including allergens, respiratory tract infections, hyperventilation, cold air, exercise, drugs and chemicals, hormonal changes and emotional upsets, airborne pollutants, and gastroesophageal reflux.

Inhalation of allergens is a common cause of asthma. Usually, this type of asthma has its onset in childhood or adolescence and is seen in persons with a family history of atopic allergy (see Chapter 10). Persons with allergic asthma often have other allergic disorders, such as hay fever, hives, and eczema. Attacks are related to exposure to specific allergens. Among airborne allergens implicated in perennial (year-around) asthma are house dust mite allergens, cockroach allergens, animal danders, and the fungus *Alternaria*.

Respiratory tract infections, especially those caused by viruses, may produce their effects by causing epithelial damage and stimulating the production of IgE antibodies directed toward the viral antigens. In addition to precipitating an asthmatic attack, viral respiratory infections increase airway responsiveness to other asthma triggers that may persist for weeks beyond the original infection.

Exercise-induced asthma occurs in 40% to 90% of persons with bronchial asthma.[9] The cause of exercise-induced asthma is unclear. It has been suggested that during exercise, bronchospasm may be caused by the loss of heat and water from the tracheobronchial tree because of the need for conditioning (*i.e.*, warming and humidification) of large volumes of air. The response is commonly exaggerated when the person exercises in a cold environment.

Inhaled irritants, such as tobacco smoke and strong odors, are thought to induce bronchospasm by way of irritant receptors and a vagal reflex. Exposure to parental smoking has been reported to increase asthma severity in children.[10] High doses of irritant gases such as sulfur dioxide, nitrogen dioxide, and ozone may induce inflammatory exacerbations of airway responsive-



■ **FIGURE 21-6** ■ The pathogenesis of bronchial asthma. (**A**) The acute or early phase response. On exposure to an antigen, the immediate reaction is triggered by an IgE-mediated release of chemical mediators from sensitized mast cells. The release of chemical mediators results in increased mucus secretion, opening of mucosal intercellular junctions with increased antigen exposure of submucosal mast cells, and bronchoconstriction. Inhaled antigen produces release of chemical mediators from sensitized mast cells. (**B**) The late phase response involves release of inflammatory mediators from mast cells, macrophages, basophils, neutrophils, and eosinophils; epithelial cell injury and edema, decreased mucociliary function, and accumulation of mucus; and increased airway responsiveness.

ness (*e.g.*, smog-related asthma). Occupational asthma is stimulated by fumes and gases (*e.g.*, epoxy resins, plastics, toluene), organic and chemical dusts (*i.e.*, wood, cotton, platinum), and other chemicals (*e.g.*, formaldehyde) in the workplace.[11]

There is a small group of persons with asthma in whom aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with asthmatic attacks, the presence of nasal polyps, and recurrent episodes of rhinitis.[12] An addition to the list of chemicals that can provoke an asthmatic attack are the sulfites used in food processing and as a preservative added to beer, wine, and fresh vegetables.

Both emotional factors and changes in hormone levels are thought to contribute to an increase in asthma symptoms. Emotional factors produce bronchospasm by way of vagal pathways. They can act as a bronchospastic trigger, or they can increase airway responsiveness to other triggers through noninflammatory mechanisms. The role of sex hormones in asthma is unclear, although there is much circumstantial evidence to suggest they may be important. As many as 40% of women with asthma report a premenstrual increase in asthma symptoms.[13] Female sex hormones have a regulatory role on β_2-adrenergic function, and it has been suggested that abnormal regulation may be a possible mechanism for premenstrual asthma.[13]

Symptoms of gastroesophageal reflux are common in both adults and children with asthma, suggesting that reflux of gastric secretions may act as a bronchospastic trigger. Reflux during sleep can contribute to nocturnal asthma.[6]

Clinical Features

Persons with asthma exhibit a wide range of signs and symptoms, from episodic wheezing and feelings of chest tightness to an acute, immobilizing attack. The attacks differ from person to person, and between attacks, many persons are symptom free. Attacks may occur spontaneously or in response to various triggers, respiratory infections, emotional stress, or weather changes. Asthma is often worse at night. Nocturnal asthma attacks usually occur at approximately 4 AM because of the occurrence of the late response to allergens inhaled during the evening and because of circadian variations in bronchial reactivity.[14]

During an asthmatic attack, the airways narrow because of bronchospasm, edema of the bronchial mucosa, and mucus plugging. Expiration becomes prolonged because of progressive airway obstruction. The amount of air that can be forcibly expired in 1 second (forced expiratory volume [$FEV_{1.0}$]) and the peak expiratory flow rate (PEF), measured in liters per second, are decreased (see Chapter 19). A fall in the PEF to levels below 50% of the predicted value during an acute asthmatic attack indicates a severe exacerbation and the need for emergency room treatment.[6] With a prolonged attack, air becomes trapped behind the occluded and narrowed airways, causing hyperinflation of the lungs and an increase in the residual volume (RV). As a result, more energy is needed to overcome the tension already present in the lungs, and the accessory muscles (*i.e.*, sternocleidomastoid muscles) are used to maintain ventilation and gas exchange. This causes dyspnea and fatigue. Because air is trapped in the alveoli and inspiration is occurring at higher residual lung volumes, the cough becomes less effective. As the condition progresses, the effectiveness of alveolar ventilation declines, and mismatching of ventilation and perfusion occurs, causing hypoxemia and hypercapnia. Pulmonary vascular resistance may increase as a result of the hypoxemia and hyperinflation, leading to a rise in pulmonary artery pressure and increased work demands on the right heart.

The physical signs of bronchial asthma vary with the severity of the attack. A mild attack may produce a feeling of chest tightness, a slight increase in respiratory rate with prolonged expiration, and mild wheezing. A cough may accompany the wheezing. More severe attacks are associated with use of the accessory muscles, distant breath sounds caused by air trapping, and loud wheezing. As the condition progresses, fatigue develops, the skin becomes moist, and anxiety and apprehension are obvious. Dyspnea may be severe, and often the person is able to speak only one or two words before taking a breath. At the point at which airflow is markedly decreased, breath sounds become inaudible with diminished wheezing, and the cough becomes ineffective despite being repetitive and hacking. This point often marks the onset of respiratory failure.

With increased air trapping, a greater negative intrapleural pressure is needed to inflate the lungs. This increased negative pressure, which is transmitted to the heart and blood vessels, causes the systolic blood pressure to fall during inspiration, a condition called *pulsus paradoxus*. It can be detected by using a blood pressure cuff and a mercury manometer (see Chapter 17).

Diagnosis and Management. The diagnosis of asthma is based on a careful history and physical examination, laboratory findings, and pulmonary function studies. Spirometry provides a means for measuring the PEF, $FEV_{1.0}$, forced vital capacity (FVC), and other indices of lung function (see Chapter 19). The level of airway responsiveness can be measured by inhalation challenge tests using methacholine (a cholinergic agonist), histamine, or exposure to a nonpharmacologic agent such as cold air. The Expert Panel of the National Education and Prevention Program of the National Heart, Lung, and Blood Institute has developed an asthma severity classification system intended for use in directing asthma treatment and identifying persons at high risk for the development of life-threatening asthma attacks[6] (Table 21-1).

Small, inexpensive, portable meters that measure PEF are available. Although not intended for use in diagnosis of asthma, they can be used in clinics and physicians' offices and in the home to provide frequent measures of flow rates. Day-night (circadian) variations in asthma symptoms and PEF variability can be used to indicate the severity of bronchial hyperreactivity. A *person's best performance* (personal best) is established from readings taken throughout several weeks and is used as a reference to indicate changes in respiratory function.[6]

The treatment of bronchial asthma focuses on control of factors contributing to asthma severity and pharmacologic treatment.[6] Measures to control factors contributing to asthma severity are aimed at prevention of exposure to irritants and factors that increase asthma symptoms and precipitate asthma exacerbations.

Pharmacologic treatment is used to prevent or treat reversible airway obstruction and airway hyperreactivity caused by the inflammatory process. The medications used in the treatment of asthma include those with bronchodilator and anti-inflammatory actions. The bronchodilators include the β_2-adrenergic agonists and ipratroprium. The β_2-adrenergic agonists, which are usually administered by inhalation methods,

TABLE 21-1 Classification of Asthma Severity

	Symptoms	Nighttime Symptoms	Lung Function
Mild intermittent	Symptoms ≤2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations brief (from a few hours to a few days); intensity may vary	≤2 times a month	$FEV_{1.0}$ or PEF ≥80% predicted PEF variability <20%
Mild persistent	Symptoms >2 times a week but <1 time a day Exacerbations may affect activity	>2 times a month	$FEV_{1.0}$ or PEF ≥80% predicted PEF variability 20%–30%
Moderate persistent	Daily symptoms Daily use of inhaled short-acting β_2-agonist Exacerbations affect activity Exacerbations ≥2 times a week; may last days	>1 time a week	$FEV_{1.0}$ or PEF >60%–<80% predicted PEF variability >30%
Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	$FEV_{1.0}$ or PEF ≤60% predicted PEF variability >30%

$FEV_{1.0}$, forced expiratory volume in 1 second; PEF, peak expiratory flow rate.
(Adapted from National Education and Prevention Program. [1997]. *Expert Panel report 2: Guidelines for the diagnosis and management of asthma.* National Institutes of Health publication no. 97-4051. Bethesda, MD: National Institutes of Health.)

relax bronchial smooth muscle. *Ipratropium* is an inhaled anticholinergic drug that blocks the postganglionic efferent vagal pathways that cause bronchoconstriction. The anti-inflammatory drugs include the corticosteroids, mast cell stabilizers, and leukotriene modifiers. The *corticosteroids*, which are often administered by inhalation methods, are considered the most effective anti-inflammatory agents for use in the long-term treatment of asthma. The anti-inflammatory agents *sodium cromolyn* and *nedocromil* are used to prevent an asthmatic attack. These agents, which are used prophylactically, act by stabilizing mast cells, thereby preventing release of the inflammatory mediators that cause an asthmatic attack. A newer group of drugs called the *leukotriene modifiers* are available for use in the treatment of asthma. The leukotrienes are potent biochemical mediators released from mast cells that cause bronchoconstriction, increased mucus secretion, and attraction and activation of inflammatory cells in the airways of people with asthma.

Status Asthmaticus and Fatal Asthma

Status asthmaticus is severe, prolonged asthma that is refractory to conventional methods of therapy. Most asthma deaths have occurred outside the hospital. Persons at highest risk are those with previous exacerbations resulting in respiratory failure, respiratory acidosis, and the need for intubation. Risk factors for fatal asthma are described in Chart 21-1.[6] Although the cause of death during an acute asthmatic attack is largely unknown, both cardiac dysrhythmias and asphyxia caused by severe airway obstruction have been implicated. It has been suggested that an underestimation of the severity of the attack may be a contributing factor. Deterioration often occurs rapidly during an acute attack, and underestimation of its severity may lead to a life-threatening delay in seeking medical attention. Frequent and repetitive use of β_2-agonist inhalers (more than twice in a month) far in excess of the recommended doses may temporarily blunt symptoms and mask the severity of the condition. Lack of access to medical care is another risk factor associated with asthma-related death. Distance, as in rural areas, or lack of financial resources, as in the uninsured or underinsured, may limit access to emergency care.

Bronchial Asthma in Children

Asthma is a leading cause of chronic illness in children and is responsible for a significant number of lost school days. It is the most frequently occurring admitting diagnosis in children's hospitals. As many as 10% to 15% of boys and 7% to 10% of girls have asthma at some time during childhood.[15] Asthma

CHART 21-1 Risk Factors for Death From Asthma

- Past history of sudden severe exacerbations
- Prior intubation for asthma
- Two or more hospitalizations for asthma in the past year
- Three or more emergency care visits for asthma in the past year
- Hospitalization or an emergency care visit for asthma within the past month
- Use of more than two canisters per month of inhaled short-acting β_2-agonist
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids
- Difficulty perceiving airflow obstruction or its severity
- Comorbidity, as from cardiovascular diseases or chronic obstructive pulmonary disease
- Serious psychiatric disease or psychosocial problems
- Low socioeconomic status and urban residence
- Illicit drug use
- Sensitivity to *Alternaria*

(From National Education and Prevention Program. [1997]. *Expert Panel report 2: Guidelines for the diagnosis and management of asthma.* National Institutes of Health publication no. 97-4051. Bethesda, MD: National Institutes of Health.)

may have its onset at any age; 30% of children are symptomatic by 1 year of age, and 80% to 90% are symptomatic by 4 to 5 years of age.[15]

As with adults, asthma in children commonly is associated with an IgE-related reaction. It has been suggested that IgE directed against respiratory viruses in particular may be important in the pathogenesis of the wheezing illnesses in infants (*i.e.*, bronchiolitis), which often precede the onset of asthma. The respiratory syncytial virus and parainfluenza viruses are the most commonly involved.[15] Other contributing factors include exposure to environmental allergens such as pet danders, dust mite antigens, and cockroach allergens. Exposure to environmental tobacco smoke also may contribute to asthma in children. Of particular concern is the effect of in utero exposure to maternal smoking on lung function in infants and children.[16]

The signs and symptoms of asthma in infants and small children vary with the stage and severity of an attack. Because airway patency decreases at night, many children have acute signs of asthma at this time. Often, previously well infants and children experience what may seem to be a cold with rhinorrhea, rapidly followed by irritability, a tight and nonproductive cough, wheezing, tachypnea, dyspnea with prolonged expiration, and use of accessory muscles of respiration. Cyanosis, hyperinflation of the chest, and tachycardia indicate increasing severity of the attack. Wheezing may be absent in children with extreme respiratory distress. The symptoms may progress rapidly and require a trip to the emergency room or hospitalization.

The Expert Panel of the National Heart, Lung, and Blood Institute's National Asthma Education Program has developed guidelines for the management of asthma in infants and children younger than 5 years and for adults and children older than 5 years.[6] The Panel recommends that adolescents (and younger children when appropriate) be directly involved in developing their asthma management plans. Active participation in physical activities, exercise, and sports should be encouraged. A written asthma management plan should be prepared for the student's school, including plans to ensure reliable, prompt access to medications.[6]

Chronic Obstructive Pulmonary Disease

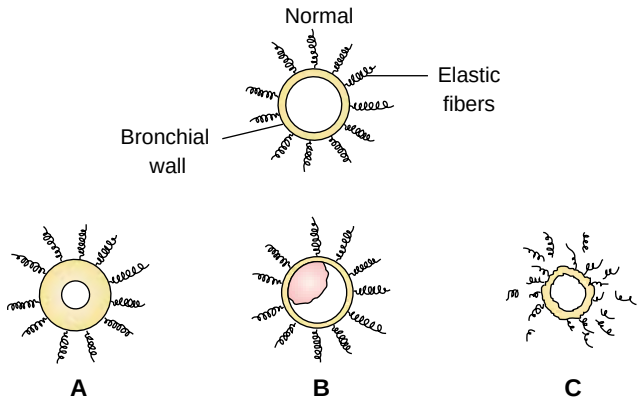
Chronic obstructive pulmonary disease (COPD) denotes a group of respiratory disorders characterized by chronic and recurrent obstruction of airflow in the pulmonary airways. Airflow obstruction usually is progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.[17] The most common cause of COPD is smoking.[17,18] Thus, the disease is largely preventable. Unfortunately, clinical findings are almost always absent during the early stages of COPD, and by the time symptoms appear, the disease usually is far advanced. For smokers with early signs of airway disease, there is hope that early recognition, combined with appropriate treatment and smoking cessation, may prevent or delay the usually relentless progression of the disease.

The term *chronic obstructive pulmonary disease* encompasses two types of obstructive airway disease: *emphysema*, with enlargement of air spaces and destruction of lung tissue, and *chronic obstructive bronchitis*, with obstruction of small airways. The mechanisms involved in the pathogenesis of COPD usually are multiple and include inflammation and fibrosis of the bronchial wall, hypertrophy of the submucosal glands and hypersecretion of mucus, and loss of elastic lung fibers and alveolar tissue (Fig. 21-7).[18] Inflammation and fibrosis of the bronchial wall, along with excess mucus secretion, obstruct airflow and cause mismatching of ventilation and perfusion. Destruction of alveolar tissue decreases the surface area for gas exchange, and the loss of elastic fibers leads to airway collapse. Normally, recoil of the elastic fibers that were stretched during inspiration provides the force needed to move air out of the lung during expiration. Because the elastic fibers are attached to the airways, they also provide radial traction to hold the airways open during expiration. In persons with COPD, the loss of elastic fibers impairs the expiratory flow rate, increases air trapping, and predisposes to airway collapse.

Emphysema

Emphysema is characterized by a loss of lung elasticity and abnormal enlargement of the air spaces distal to the terminal bronchioles, with destruction of the alveolar walls and capillary beds. Enlargement of the air spaces leads to hyperinflation of the lungs and produces an increase in total lung capacity (TLC). Two of the recognized causes of emphysema are smoking, which incites lung injury, and an inherited deficiency of α_1-*antitrypsin*, an antiprotease enzyme that protects the lung from injury. Genetic factors, other than an inherited α_1-antitrypsin deficiency, also may play a role in smokers who experience COPD at an early age.[19]

Emphysema is thought to result from the breakdown of elastin and other alveolar wall components by enzymes, called *proteases*, that digest proteins. These proteases, particularly elastase, which is an enzyme that digests elastin, are released from polymorphonuclear leukocytes (*i.e.*, neutrophils), alveolar macrophages, and other inflammatory cells.[18] Normally, the lung is protected by antiprotease enzymes, including α_1-antitrypsin. Cigarette smoke and other irritants stimulate the movement of inflammatory cells into the lungs, resulting in increased release of elastase and other proteases. In smokers in whom COPD develops, antiprotease production and release may be inadequate to neutralize the excess protease production



■ **FIGURE 21-7** ■ Mechanisms of airflow obstruction in chronic obstructive lung disease. (**Top**) The normal bronchial airway with elastic fibers that provide traction and hold the airway open. (**Bottom**) Obstruction of the airway caused by (**A**) hypertrophy of the bronchial wall, (**B**) inflammation and hypersecretion of mucus, and (**C**) loss of elastic fibers that hold the airway open.

such that the process of elastic tissue destruction goes unchecked (Fig. 21-8).

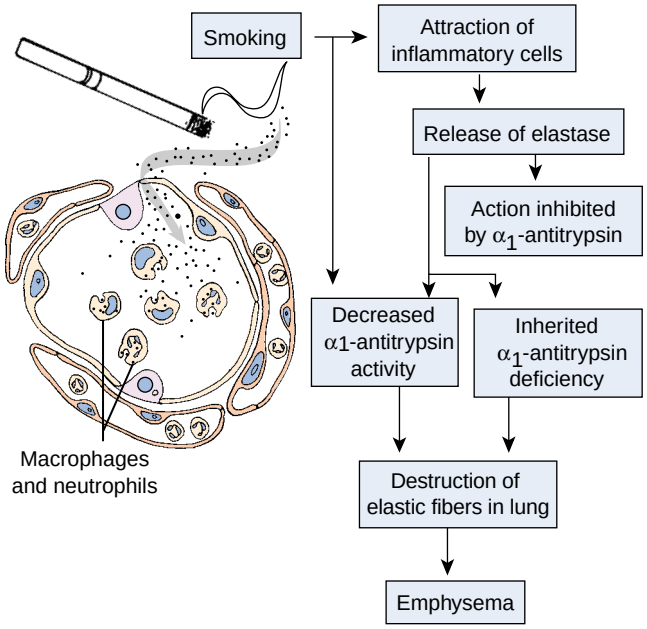
A hereditary deficiency in α_1-antitrypsin accounts for approximately 1% of all cases of COPD and is more common in young persons with emphysema.[18] An α_1-antitrypsin deficiency is inherited as an autosomal recessive disorder. Homozygotes who carry two defective genes have only about 15% to 20% of the normal plasma concentration of α_1-antitrypsin. It is most common in persons of Scandinavian descent and is rare in Jews, blacks, and the Japanese.[20] Smoking and repeated respiratory tract infections, which also decrease α_1-antitrypsin levels, contribute to the risk of emphysema in persons with an α_1-antitrypsin deficiency. Laboratory methods are available for measuring α_1-antitrypsin levels. Human α_1-antitrypsin is available for replacement therapy in persons with a hereditary deficiency of the enzyme.

There are two commonly recognized types of emphysema: centriacinar and panacinar (Fig. 21-9). The centriacinar type affects the bronchioles in the central part of the respiratory lobule, with initial preservation of the alveolar ducts and sacs[20] (Fig. 21-10). It is the most common type of emphysema and is seen predominantly in male smokers. The panacinar type produces initial involvement of the peripheral alveoli and later extends to involve the more central bronchioles. This type of emphysema is more common in persons with α_1-antitrypsin deficiency. It also is found in smokers in association with centrilobular emphysema. In such cases, panacinar changes are seen in the lower parts of the lung and the centriacinar changes in the upper parts of the lung.

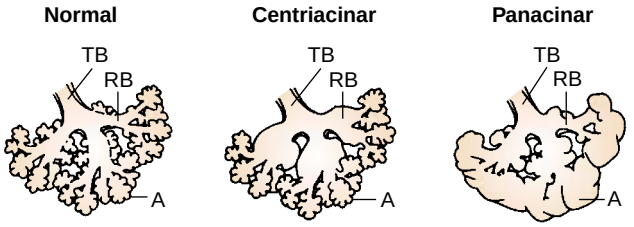
Chronic Bronchitis

In chronic bronchitis, airway obstruction is caused by inflammation of the major and small airways. There is edema and hyperplasia of submucosal glands and excess mucus excretion into the bronchial tree. A history of a chronic productive cough of more than 3 months' duration for more than 2 consecutive years is necessary for the diagnosis of chronic bronchitis.[17,18] Typically, the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum. Chronic bronchitis without airflow obstruction often is referred to as *simple bronchitis*, and chronic bronchitis with airflow obstruction as *chronic obstructive bronchitis*. The outlook for persons with simple bronchitis is good, compared with the premature morbidity and mortality associated with chronic obstructive bronchitis.

Chronic bronchitis is seen most commonly in middle-aged men and is associated with chronic irritation from smok-



■ **FIGURE 21-8** ■ Protease (elastase)-antiprotease (antitrypsin) mechanisms of emphysema. The effects of smoking and an inherited α_1-antitrypsin deficiency on the destruction of elastic fibers in the lung and development of emphysema.



■ **FIGURE 21-9** ■ Centriacinar and panacinar emphysema. In centriacinar emphysema, the destruction is confined to the terminal (TB) and respiratory bronchioles (RB). In panacinar emphysema, the peripheral alveoli (A) are also involved. (West J.B. [1997]. *Pulmonary pathophysiology* [5th ed., p. 53]. Philadelphia: Lippincott-Raven)

■ **FIGURE 21-10** ■ Centrilobular emphysema. A whole mount of the left lung of a smoker with mild emphysema shows enlarged air spaces scattered throughout both lobes, which represent destruction of terminal bronchioles in the central part of the pulmonary lobule. These abnormal spaces are surrounded by intact pulmonary parenchyma. (Rubin E., Farber J.L. [1999]. Pathology [3rd ed., p. 628]. Philadelphia: Lippincott Williams & Wilkins)

ing and recurrent infections. In the United States, smoking is the most important cause of chronic bronchitis. Viral and bacterial infections are common in persons with chronic bronchitis and are thought to be a result, rather than a cause, of the problem.

Clinical Features

The mnemonics "pink puffer" and "blue bloater" have been used to differentiate the clinical manifestations of emphysema and chronic obstructive bronchitis. The important features of these two forms of COPD are described in Table 21-2. In practice, differentiation between the two types is not as vivid as presented here. This is because persons with COPD often have some degree of both emphysema and chronic bronchitis.

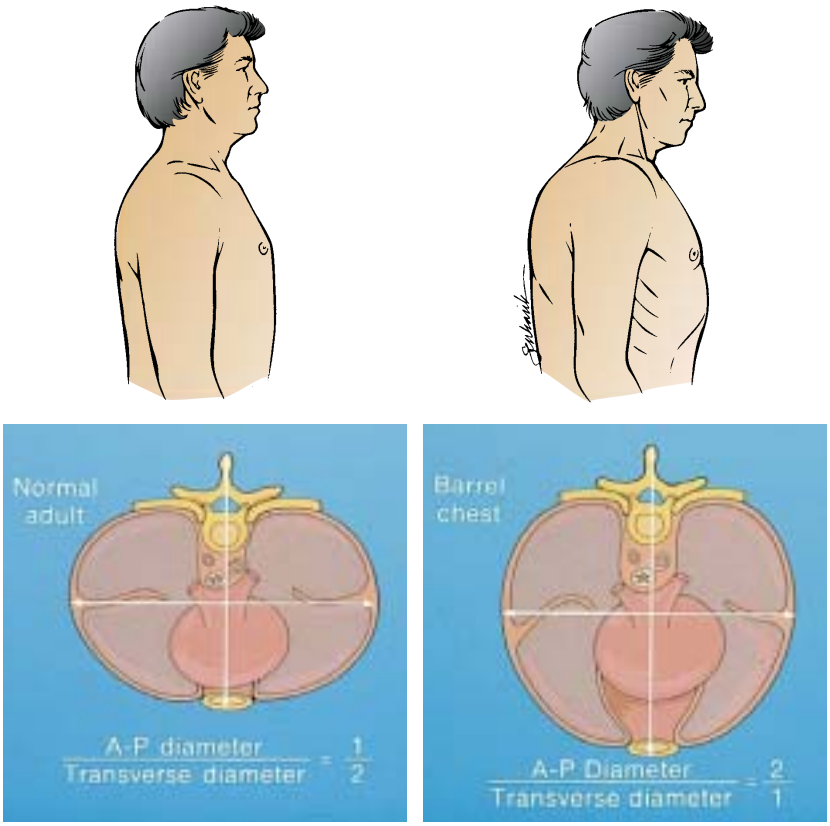
A major difference between the pink puffers and the blue bloaters is the respiratory responsiveness to the hypoxic stimuli. With pulmonary emphysema, there is a proportionate loss of ventilation and perfusion area in the lung. These persons are pink puffers, or fighters, who are able to overventilate and thus maintain relatively normal blood gas levels until late in the disease. Chronic obstructive bronchitis is characterized by excessive bronchial secretions and airway obstruction that causes mismatching of ventilation and perfusion. Thus, persons with chronic bronchitis are unable to compensate by increasing their ventilation; instead, hypoxemia and cyanosis develop. These are the blue bloaters, or nonfighters.

Persons with emphysema have marked dyspnea and struggle to maintain normal blood gas levels with increased breathing effort, including prominent use of the accessory muscles. The seated position, which stabilizes chest structures and allows for maximum chest expansion and use of accessory muscles, is preferred. With loss of lung elasticity and hyperinflation of the lungs, the airways often collapse during expiration because pressure in surrounding lung tissues exceeds airway pressure. Air becomes trapped in lungs, producing an increase in the anteroposterior dimensions of the chest, the so-called *barrel chest* that is typical of persons with emphysema (Fig. 21-11). Expiration often is accomplished through pursed lips. Pursed-lip breathing, which increases the resistance to the outflow of air, helps to prevent airway collapse by increasing airway pressure. The work of breathing is greatly increased in persons with emphysema, and eating often is difficult. As a result, there often is considerable weight loss.

Chronic obstructive bronchitis is characterized by shortness of breath with a progressive decrease in exercise tolerance. As the disease progresses, breathing becomes increasingly more labored, even at rest. The expiratory phase of respiration is prolonged, and expiratory wheezes and crackles can be heard on auscultation. In contrast to persons with emphysema, those with chronic obstructive bronchitis are unable to maintain normal blood gases by increasing their breathing effort. Hypoxemia, hypercapnia, and cyanosis develop, reflecting an imbalance between ventilation and perfusion. Hypoxemia, in which arterial PO_2 levels fall below 55 mm Hg, causes reflex vasoconstriction of the pulmonary vessels and further impairment of gas exchange in the lung. Hypoxemia also stimulates red blood cell production, causing polycythemia. As a result, persons with chronic obstructive bronchitis develop pulmonary hypertension and, eventually, right-sided heart failure with peripheral edema (*i.e.*, cor pulmonale).

TABLE 21-2 Characteristics of Chronic Bronchitis and Emphysematous Types of Chronic Obstructive Lung Disease

Characteristic	Type A Pulmonary Emphysema ("Pink Puffers")	Type B Chronic Bronchitis ("Blue Bloaters")
Smoking history	Usual	Usual
Age of onset	40 to 50 years of age	30 to 40 years of age; disability in middle age
Clinical features		
Barrel chest (hyperinflation of the lungs)	Often dramatic	May be present
Weight loss	May be severe in advanced disease	Infrequent
Shortness of breath	May be absent early in disease	Predominant early symptom, insidious in onset, exertional
Decreased breath sounds	Characteristic	Variable
Wheezing	Usually absent	Variable
Rhonchi	Usually absent or minimal	Often prominent
Sputum	May be absent or may develop late in the course	Frequent early manifestation, frequent infections, abundant purulent sputum
Cyanosis	Often absent, even late in the disease when there is low PO_2	Often dramatic
Blood gases	Relatively normal until late in the disease process	Hypercapnia may be present Hypoxemia may be present
Cor pulmonale	Only in advanced cases	Frequent Peripheral edema
Polycythemia	Only in advanced cases	Frequent
Prognosis	Slowly debilitating disease	Numerous life-threatening episodes due to acute exacerbations



■ **FIGURE 21-11** ■ Characteristics of normal chest wall and chest wall in emphysema. The normal chest wall and its cross section are illustrated on the left (**A**). The barrel-shaped chest of emphysema and its cross section are illustrated on the right (**B**). (Smeltzer S.C., Bare B.G. [2000]. *Medical-surgical nursing.* [9th ed., p. 454]. Philadelphia: Lippincott Williams & Wilkins)

Persons with combined forms of COPD (*i.e.*, some degree of both emphysema and chronic bronchitis) characteristically seek medical attention in the fifth or sixth decade of life, complaining of cough, sputum production, and shortness of breath. The symptoms typically have existed to some extent for 10 years or longer. The productive cough usually occurs in the morning. Dyspnea becomes more severe as the disease progresses. Frequent exacerbations of infection and respiratory insufficiency are common, causing absence from work and eventual disability.

The late stages of COPD are characterized by pulmonary hypertension, cor pulmonale, recurrent respiratory infections, and chronic respiratory failure. Death usually occurs during an exacerbation of illness associated with infection and respiratory failure.

Diagnosis and Treatment. The diagnosis of COPD is based on a careful history and physical examination, pulmonary function studies, chest radiographs, and laboratory tests. Airway obstruction prolongs the expiratory phase of respiration and affords the potential for impaired gas exchange because of the mismatching of ventilation and perfusion. The FVC is the amount of air that can be forcibly exhaled after maximal inspiration (see Chapter 19, Fig. 19-16). In an adult with normal respiratory function, this should be achieved in 4 to 6 seconds. In patients with COPD, the time required for FVC is increased, the $FEV_{1.0}$ is decreased, and the ratio of $FEV_{1.0}$ to FVC is decreased. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal a marked increase in residual volume (RV), an increase in TLC, and elevation of the RV to TLC ratio. These and other measurements of expiratory flow are determined by spirometry and are used in the diagnosis of COPD.

The treatment of COPD depends on the stage of the disease and often requires an interdisciplinary approach. Smoking cessation is the only measure that slows the progression of the disease.[20] Persons in more advanced stages of the disease often require measures to maintain and improve physical and psychosocial functioning, pharmacologic interventions, and oxygen therapy. Respiratory tract infections can prove life threatening to persons with severe COPD. A person with COPD should avoid exposure to others with known respiratory tract infections. Immunization for influenza and pneumococcal infections decreases the likelihood of their occurrence.

Pharmacologic treatment includes the use of bronchodilators, including β_2-adrenergic agonist drugs; the anticholinergic drug, ipratropium; and theophylline preparations. A long-term pulmonary rehabilitation program can significantly reduce episodes of hospitalization and add measurably to a person's ability to manage and cope with his or her impairment in a positive way.

Oxygen therapy is prescribed for selected persons with significant hypoxemia (arterial PO_2 <55 mm Hg). The use of continuous low-flow oxygen decreases dyspnea, helps to prevent pulmonary hypertension, and improves neuropsychological function and activity tolerance. Portable oxygen administration units, which allow mobility and the performance of activities of daily living, usually are used. The overall goal of oxygen therapy is to maintain the hemoglobin oxygen saturation at 89% to 90%, representing an arterial PO_2 of approximately

60 mm Hg (see Chapter 19, Fig. 19-18). Because the ventilatory drive associated with hypoxic stimulation of the peripheral chemoreceptors does not occur until the arterial PO_2 has been reduced to about 60 mm Hg or less, the oxygen flow rate usually is titrated to provide an arterial PO_2 of 55 to 65 mm Hg. Increasing the arterial PO_2 above that level tends to depress ventilation, leading to hypoventilation and carbon dioxide retention.

Bronchiectasis

Bronchiectasis is a chronic obstructive lung disease characterized by an abnormal dilatation of the large bronchi associated with infection and destruction of the bronchial walls (Fig. 21-12). To be diagnosed as bronchiectasis, the dilatation must be permanent, as compared with the reversible bronchial dilatation that sometimes accompanies viral and bronchial pneumonias.

The pathogenesis of bronchiectasis can be either obstructive or nonobstructive.[20] Obstructive bronchiectasis is confined to a segment of the lung distal to a mechanical obstruction. It is caused by conditions such as tumors, foreign bodies, and mucus plugs in asthma. Nonobstructive bronchiectasis can be either localized or generalized. The use of immunizations and antibiotics has largely eliminated localized bronchiectasis caused by childhood bronchopulmonary infections such as measles, pertussis, and other bacterial infections.[21]

■ **FIGURE 21-12** ■ Bronchiectasis. The resected upper lobe shows widely dilated bronchi, with thickening of the bronchial walls and collapse and fibrosis of the pulmonary parenchyma. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 601]. Philadelphia: Lippincott Williams & Wilkins)

Generalized bronchiectasis is attributable largely to inherited impairments of host mechanisms or acquired disorders that permit introduction of infectious organisms into the airways. They include inherited conditions such as cystic fibrosis, in which airway obstruction is caused by impairment of normal mucociliary function; congenital and acquired immunodeficiency states, which predispose to respiratory tract infections; lung infection (*e.g.*, tuberculosis, fungal infections, lung abscess); and exposure to toxic gases that cause airway obstruction.

Generalized bronchiectasis usually is bilateral and most commonly affects the lower lobes. Localized bronchiectasis can affect any area of the lung, the area being determined by the site of obstruction or infection. As the disease progresses, airway obstruction leads to smooth muscle relaxation with dilatation and eventual destruction of the bronchial walls. Infection produces inflammation, impairs mucociliary function, and causes weakening and further dilatation of the walls of the bronchioles. Pooling of secretions produces a vicious cycle of chronic inflammation and development of new infections.

Bronchiectasis is associated with an assortment of abnormalities that profoundly affect respiratory function, including atelectasis, obstruction of the smaller airways, and diffuse bronchitis. Affected persons have fever, recurrent bronchopulmonary infection, coughing, production of copious amounts of foul-smelling, purulent sputum, and hemoptysis. Weight loss and anemia are common. The physiologic abnormalities that occur in bronchiectasis are similar to those seen in chronic bronchitis and emphysema. As in the latter two conditions, chronic bronchial obstruction leads to marked dyspnea and cyanosis. Clubbing of the fingers is common in moderate to advanced bronchiectasis and is not seen in other types of obstructive lung diseases.[21]

Diagnosis is based on history and imaging studies. The condition often is evident on chest radiographs. High-resolution CT scanning of the chest allows for definitive diagnosis. Treatment consists of early recognition and treatment of infection along with regular postural drainage and chest physical therapy. Persons with this disorder benefit from many of the rehabilitation and treatment measures used for chronic bronchitis and emphysema. Localized bronchiectasis may be treated surgically.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder involving fluid secretion in the exocrine glands and epithelial lining of the respiratory, gastrointestinal, and reproductive tracts. Most of the clinical manifestations of the disease are related to abnormal secretions that result in obstruction of organ passages such as the respiratory airways and pancreatic ducts. It is the most common fatal hereditary disorder of whites in the United States and is the most common cause of chronic lung disease in children.[22]

The cystic fibrosis gene, present on the long arm of chromosome 7, encodes the production of a single protein, the cystic fibrosis transmembrane conductance regulator (CFTR),

which functions in chloride transport across cell membranes.[23,24] Because of defective chloride transport, there is a threefold increase in sodium reabsorption. Water moves out of the extracellular fluid with the sodium, causing exocrine (*e.g.*, mucus) secretions to become exceedingly viscid. The cystic fibrosis gene is rare in African blacks and Asians. Homozygotes (*i.e.*, persons with two defective genes) have all or substantially all of the clinical symptoms of the disease, compared with heterozygotes, who are carriers of the disease but have no recognizable symptoms.

Clinically, cystic fibrosis is manifested by (1) chronic respiratory disease, (2) pancreatic exocrine deficiency, and (3) elevation of sodium chloride in the sweat. Nasal polyps, sinus infections, pancreatitis, and cholelithiasis also are common. Excessive loss of sodium in the sweat predisposes young children to salt depletion episodes. Most males with cystic fibrosis have congenital bilateral absence of the vas deferens with azoospermia.[23]

Respiratory manifestations are caused by an accumulation of viscid mucus in the bronchi, impaired mucociliary clearance, and lung infections. Chronic bronchiolitis and bronchitis are the initial lung manifestations, but after months and years, structural changes in the bronchial wall lead to bronchiectasis. Widespread bronchiectasis is common by 10 years of age; large bronchiectatic cysts and abscesses develop in later stages of the disease. Infection and ensuing inflammation are causes of lung destruction in cystic fibrosis. *Staphylococcus aureus* and *Pseudomonas* infections are common. With advanced disease, 80% of persons harbor the *Pseudomonas* organism. New findings suggest that absence of CFTR predisposes to *Pseudomonas* infections, and once established, *Pseudomonas* is not easily cleared from the lungs, producing a cycle of chronic inflammation, tissue damage, and obstruction.

Pancreatic function is abnormal in approximately 80% to 90% of affected persons.[24] Steatorrhea, diarrhea, and abdominal pain and discomfort are common. In the newborn, meconium ileus may cause intestinal obstruction. The degree of pancreatic involvement is highly variable. In some children, the defect is relatively mild, and in others the involvement is severe and impairs intestinal absorption.

Early diagnosis and treatment are important in delaying the onset and severity of chronic illness. Diagnosis is based on the presence of respiratory and gastrointestinal manifestations typical of cystic fibrosis, a history of cystic fibrosis in a sibling, or a positive newborn screening test. Newborn screening consists of a test for determination of immunoreactive trypsinogen. Newborns with cystic fibrosis have elevated blood levels of immunoreactive trypsinogen, presumably because of secretory obstruction in the pancreas. Confirmatory tests include the sweat test to detect increased electrolytes in the sweat and genetic tests to detect the presence of the mutant CFTR genes.

The treatment of cystic fibrosis usually consists of replacement of pancreatic enzymes, physical measures to improve the clearance of tracheobronchial secretions (*i.e.*, postural drainage and chest percussion), bronchodilator therapy, and prompt treatment of respiratory tract infections. Lung transplantation is being used as a treatment for persons with end-stage lung disease.

Progress of the disease is variable. Improved medical management has led to longer survival—approximately half of children live beyond 20 years, and approximately one third of the nearly 30,000 persons with cystic fibrosis are adults.

In summary, obstructive ventilatory disorders are characterized by airway obstruction and limitation in expiratory airflow. Bronchial asthma is a chronic inflammatory disorder of the airways, characterized by airway hypersensitivity and episodic attacks of airway narrowing. An asthmatic attack can be triggered by a variety of stimuli. Based on their mechanism of response, these triggers can be divided into two types: bronchospastic and inflammatory. Bronchospastic triggers depend on the level of airway responsiveness. There are two types of responses in persons with asthma: the acute or early response and the late phase response. The acute response results in immediate bronchoconstriction on exposure to an inhaled antigen and usually subsides within 90 minutes. The late phase response usually develops 3 to 5 hours after exposure to an asthmatic trigger; it involves inflammation and increased airway responsiveness that prolong the attack and cause a vicious cycle of exacerbations.

COPD describes a group of conditions characterized by obstruction to airflow in the lungs. Among the conditions associated with COPD are emphysema, chronic bronchitis, and bronchiectasis. Emphysema is characterized by a loss of lung elasticity; abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles; and hyperinflation of the lungs. Chronic bronchitis is caused by inflammation of major and small airways and is characterized by edema and hyperplasia of submucosal glands and excess mucus secretion into the bronchial tree. A history of a chronic productive cough that has persisted for at least 3 months and for at least 2 consecutive years in the absence of other disease is necessary for the diagnosis of chronic bronchitis. Emphysema and chronic bronchitis are manifested by the eventual mismatching of ventilation and perfusion. As the condition advances, signs of respiratory distress and impaired gas exchange become evident, with development of hypercapnia and hypoxemia. Bronchiectasis is a form of COPD that is characterized by an abnormal dilatation of the large bronchi associated with infection and destruction of the bronchial walls.

Cystic fibrosis is an autosomal recessive genetic disorder manifested by chronic lung disease, pancreatic exocrine deficiency, and elevation of sodium chloride in the sweat. Respiratory manifestations are caused by an accumulation of viscid mucus in the bronchi, impaired mucociliary clearance, lung infections, bronchiectasis, and dilatation. Mucus plugs can result in the total obstruction of an airway, causing atelectasis.

INTERSTITIAL LUNG DISEASES

The diffuse interstitial lung diseases are a diverse group of lung disorders that produce similar inflammatory and fibrotic changes in the interstitium or interalveolar septa of the lung. The disorders may be acute or insidious in onset; they may be rapidly progressive, slowly progressive, or static in their course. They include hypersensitivity pneumonitis (see Chapter 10), lung diseases caused by exposure to toxic drugs (*e.g.*, amio-

darone) and radiation, and occupational lung diseases including the pneumoconioses that are caused by the inhalation of inorganic dusts such as silica, coal dust, and asbestos. Some of the most common interstitial lung diseases are caused by exposure to the inhaled dust and particles. In many cases, no specific cause can be found.[25,26] Examples of interstitial lung diseases and their causes are listed in Chart 21-2.

Current theory suggests that most interstitial lung diseases, regardless of the causes, have a common pathogenesis. It is thought that these disorders are initiated by some type of injury to the alveolar epithelium, followed by an inflammatory process that involves the alveoli and interstitium of the lung. An accumulation of inflammatory and immune cells causes continued damage of lung tissue and the replacement of normal, functioning lung tissue with fibrous scar tissue.

Because the interstitial lung diseases result in a stiff and noncompliant lung, they are commonly classified as fibrotic or restrictive lung disorders. In contrast to obstructive lung diseases, the lungs are stiff and difficult to expand, despite normal functioning airways. Persons with interstitial lung diseases experience dyspnea, tachypnea, and eventual cyanosis, without evidence of wheezing or signs of airway obstruction. Usually there is an insidious onset of breathlessness that initially occurs during exercise and may progress to the point that the person is totally incapacitated. A nonproductive cough may develop, particularly with continued exposure to the inhaled irritant. Typically, a person with a restrictive lung disease breathes with a pattern of rapid, shallow respirations. This tachypneic pattern of breathing, in which the respiratory rate is increased and the tidal volume is decreased, reduces the work of breathing because it takes less work to move air through the airways at an increased rate than it does to stretch a stiff lung to accommodate a larger tidal volume.

Although resting arterial blood gases usually are normal early in the course of the disease, arterial PO_2 levels may fall during exercise, and in cases of advanced disease, hypoxemia often is present, even at rest. In the late stages of the disease, hypercapnia and respiratory acidosis develop. Clubbing of the fingers and toes may develop because of chronic hypoxemia.

The diagnosis of interstitial lung disease requires a careful personal and family history, with particular emphasis on exposure to environmental, occupational, and other injurious agents. Chest radiographs may be used as an initial diagnostic method, and serial chest films often are used to follow the progress of the disease. A biopsy specimen for histologic study and culture may be obtained by surgical incision or bronchoscopy using a fiberoptic bronchoscope. Gallium lung scans often are used to detect and quantify the chronic alveolitis that occurs in interstitial lung disease. Gallium does not localize in normal lung tissue, but uptake of the radionuclide is increased in interstitial lung disease and other diffuse lung diseases.

The treatment goals for persons with interstitial lung disease focus on identifying and removing the injurious agent, suppressing the inflammatory response, preventing progression of the disease, and providing supportive therapy for persons with advanced disease. In general, the treatment measures vary with the type of lung disease. Corticosteroid drugs frequently are used to suppress the inflammatory response. Many of the supportive treatment measures used in the late stages of the disease, such as oxygen therapy and measures to prevent infection, are similar to those discussed for persons with COPD.

In summary, the interstitial lung diseases are characterized by fibrosis and decreased compliance of the lung. They include the occupational lung diseases, lung diseases caused by toxic drugs and radiation, and lung diseases of unknown origin, such as sarcoidosis. These disorders are thought to result from an inflammatory process that begins in the alveoli and extends to involve the interstitial tissues of the lung.

KEY CONCEPTS

INTERSTITIAL OR RESTRICTIVE LUNG DISEASES

- Interstitial lung diseases result from inflammatory conditions that affect the interalveolar structures of the lung and produce lung fibrosis and a stiff lung.
- A stiff and noncompliant lung is difficult to inflate, increasing the work of breathing and causing decreased exercise tolerance due to hypoxemia.
- Because of the increased effort needed for lung expansion, persons with interstitial lung disease tend to take small but more frequent breaths.

CHART 21-2 Causes of Interstitial Lung Diseases*

Occupational and Environmental Inhalants

Inorganic dusts
- Asbestosis
- Silicosis
- Coal miner's pneumoconiosis

Organic dusts
- Hypersensitivity pneumonitis

Gases and fumes
- Ammonia, phosgene, sulfur dioxide

Drugs and Therapeutic Agents

Cancer chemotherapeutic agents
- Busulfan
- Bleomycin
- Methotrexate

Ionizing radiation

Immunologic Lung Disease

Sarcoidosis

Collagen vascular diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Scleroderma
- Dermatomyositis-polymyositis

Miscellaneous

Postacute respiratory distress syndrome

Idiopathic pulmonary fibrosis

*This list is not intended to be inclusive.

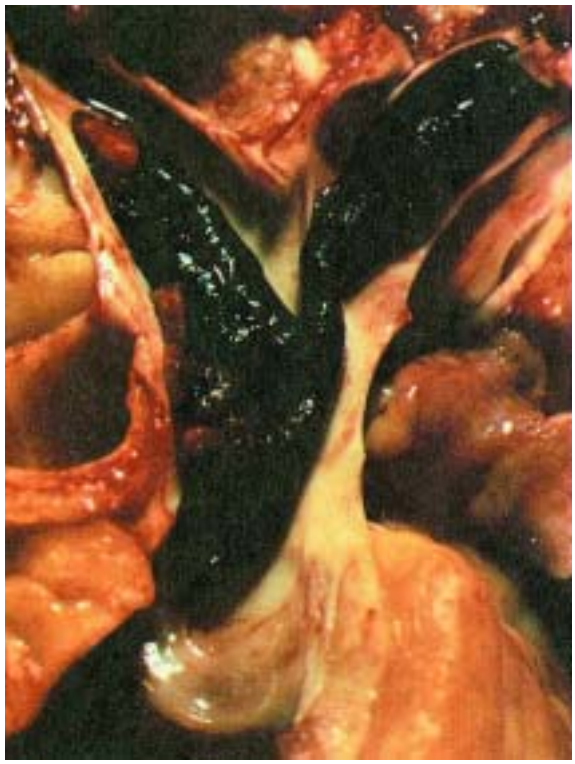
Unlike COPD, which affects the airways, interstitial lung diseases affect the supporting collagen and elastic tissues that lie between the airways and blood vessels. These lung diseases decrease lung volumes, reduce the diffusing capacity of the lung, and cause various degrees of hypoxia. Because lung compliance is reduced, persons with this form of lung disease have a rapid, shallow breathing pattern.

PULMONARY VASCULAR DISORDERS

As blood moves through the lung, blood oxygen levels are raised, and carbon dioxide is removed. These processes depend on the matching of ventilation (*i.e.*, gas exchange) and perfusion (*i.e.*, blood flow). This section discusses three major disorders of the pulmonary circulation: pulmonary embolism, pulmonary hypertension, and acute respiratory distress syndrome. Pulmonary edema, another major problem of the pulmonary circulation, is discussed in Chapter 18.

Pulmonary Embolism

Pulmonary embolism develops when a blood-borne substance lodges in a branch of the pulmonary artery and obstructs the flow. The embolism may consist of a thrombus (Fig. 21-13), air that has accidentally been injected during intravenous infusion, fat that has been mobilized from the bone marrow after a fracture or from a traumatized fat depot (see Chapter 42), or amniotic fluid that has entered the maternal circulation after rupture of the membranes at the time of delivery.



■ **FIGURE 21-13** ■ Pulmonary embolism. The main pulmonary artery and its bifurcation have opened to reveal a large saddle embolus. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 289]. Philadelphia: Lippincott Williams & Wilkins)

Almost all pulmonary emboli arise from deep vein thrombosis (DVT) in the lower extremities (see Chapter 15). The presence of thrombosis in the deep veins of the legs or pelvis often is unsuspected until embolism occurs. The effects of emboli on the pulmonary circulation are related to mechanical obstruction of the pulmonary circulation and neurohumoral reflexes causing vasoconstriction. Obstruction of pulmonary blood flow causes reflex bronchoconstriction in the affected area of the lung, wasted ventilation and impaired gas exchange, and loss of alveolar surfactant. Pulmonary hypertension and right heart failure may develop when there is massive vasoconstriction because of a large embolus. Although small areas of infarction may occur, frank pulmonary infarction is uncommon.

Persons at risk for DVT also are at risk for thromboemboli. Among the physiologic factors that contribute to venous thrombosis are venous stasis, venous endothelial injury, and hypercoagulability states. Venous stasis and venous endothelial injury can result from prolonged bed rest, trauma, surgery, childbirth, fractures of the hip and femur, myocardial infarction and congestive heart failure, and spinal cord injury. Persons undergoing orthopedic surgery and gynecologic cancer surgery are at particular risk, as are bedridden patients in an intensive care unit. Cancer cells can produce thrombin and synthesize procoagulation factors, increasing the risk of thromboembolism. Use of oral contraceptive, pregnancy, and hormone replacement therapy are thought to increase the resistance to endogenous anticoagulants. The risk of pulmonary embolism among users of oral contraceptives is approximately three times the risk of nonusers.[27] Women who smoke are at particular risk.

The manifestations of pulmonary embolism depend on the size and location of the obstruction. Chest pain, dyspnea, and increased respiratory rate are the most frequent signs and symptoms of pulmonary embolism. Pulmonary infarction often causes pleuritic pain that changes with respiration; it is more severe on inspiration and less severe on expiration. Moderate hypoxemia without carbon dioxide retention occurs as a result of impaired gas exchange. Small emboli that become lodged in the peripheral branches of the pulmonary artery may exert little effect and go unrecognized. However, repeated small emboli often result in a gradual the size of the pulmonary capillary bed, resulting in pulmonary hypertension. Moderate-size emboli often present with breathlessness accompanied by pleuritic pain, apprehension, slight fever, rapid and shallow breathing, and cough productive of blood-streaked sputum. Persons with massive emboli usually present with sudden collapse, crushing substernal chest pain, shock, and sometimes loss of consciousness. The pulse is rapid and weak, the blood pressure is low, the neck veins are distended, and the skin is cyanotic and diaphoretic. Massive pulmonary emboli often are fatal.

The diagnosis of pulmonary embolism is based on clinical signs and symptoms, blood gas determinations, venous thrombosis studies, lung scans, CT scans, and in selected cases, pulmonary angiography. Laboratory studies and radiologic films are useful in ruling out other conditions that might give rise to similar symptoms. The electrocardiogram (ECG) may be used to detect signs of right heart strain resulting in an increase in pulmonary vascular resistance. Because almost all

pulmonary emboli originate from DVT, venous studies such as *lower limb compression ultrasonography*, *impedance plethysmography*, and *contrast venography* often are used as initial diagnostic procedures.

The treatment goals for pulmonary emboli focus on the prevention DVT and the development of thromboemboli, protecting the lungs from exposure to thromboemboli when they occur, and in the case of large and life-threatening pulmonary emboli, sustaining life and restoring pulmonary blood flow. Thrombolytic therapy may be indicated in persons with multiple or large emboli. Restoration of blood flow in persons with life-threatening pulmonary emboli can often be accomplished through the surgical removal of the embolus or emboli.

Prevention focuses on identification of persons at risk, avoidance of venous stasis and hypercoagulability states, and early detection of venous thrombosis. For persons at risk, graded compression elastic stockings and intermittent pneumatic compression (IPC) boots can be used to prevent venous stasis. Pharmacologic prophylaxis involves the use of anticoagulant drugs.

Pulmonary Hypertension

The term *pulmonary hypertension* describes the elevation of pressure in the pulmonary arterial system. The pulmonary circulation is a low-pressure system designed to accommodate varying amounts of blood delivered from the right heart and to facilitate gas exchange. The normal mean pulmonary artery pressure is approximately 15 mm Hg (*e.g.*, 28 systolic/8 diastolic). The main pulmonary artery and major branches are relatively thin-walled, compliant vessels. The distal pulmonary arterioles also are thin walled and have the capacity to dilate, collapse, or constrict, depending on the presence of vasoactive substances released from the endothelial cells of the vessel, neurohumoral influences, flow velocity, oxygen tension, and alveolar ventilation.

Pulmonary hypertension can be caused by an elevation in left atrial pressure, increased pulmonary blood flow, or increased pulmonary vascular resistance. Because of the increased pressure in the pulmonary circulation, pulmonary hypertension increases the workload of the right heart. Although pulmonary hypertension can develop as a primary disorder, most cases develop secondary to some other condition.

Secondary Pulmonary Hypertension

Secondary pulmonary hypertension refers to an increase in pulmonary pressures associated with other disease conditions, usually cardiac or pulmonary. Secondary causes, or mechanisms, of pulmonary hypertension can be divided into four major categories: (1) elevation of pulmonary venous pressure, (2) increased pulmonary blood flow, (3) pulmonary vascular obstruction, and (4) hypoxemia.[28] Often more than one factor, such as COPD, heart failure, and sleep apnea, contributes to the elevation in pulmonary pressures.

Elevation of pulmonary venous pressure is common in conditions such as mitral valve stenosis and left ventricular heart failure, in which an elevated left atrial pressure is transmitted to the pulmonary circulation. Continued increases in left atrial pressure can lead to medial hypertrophy and intimal thickening of the small pulmonary arteries, causing sustained hypertension.

Increased pulmonary blood flow results from increased flow through left-to-right shunts in congenital heart diseases such as atrial or ventricular septal defects and patent ductus arteriosus. If the high-flow state is allowed to continue, morphologic changes occur in the pulmonary vessels, leading to sustained pulmonary hypertension. The pulmonary vascular changes that occur with congenital heart disorders are discussed in Chapter 17.

Obstruction of pulmonary blood vessels is most commonly the result of pulmonary emboli. Once initiated, the pulmonary hypertension that develops is self-perpetuating because of hypertrophy and proliferation of vascular smooth muscle.

Hypoxemia is another common cause of pulmonary hypertension. Unlike the vessels in the systemic circulation, most of which dilate in response to hypoxemia and hypercapnia, the pulmonary vessels constrict. The stimulus for constriction is thought to originate in the air spaces near the smaller branches of the pulmonary arteries. In situations in which certain regions of the lung are hypoventilated, the response is adaptive in that it diverts blood flow away from the poorly ventilated areas to more adequately ventilated portions of the lung. However, this effect becomes less beneficial as more and more areas of the lung become poorly ventilated. Pulmonary hypertension is a common problem in persons with advanced COPD. It also may develop at high altitudes in persons with normal lungs. Persons who experience marked hypoxemia during sleep (*i.e.*, those with sleep apnea) may also experience marked elevations in pulmonary arterial pressure.

The signs and symptoms of secondary pulmonary hypertension reflect not only the underlying cause, but the effect that the elevated pressures have on right heart function and oxygen transport. Dyspnea and fatigue are common. Peripheral edema, ascites, and signs of right heart failure (cor pulmonale, to be discussed) develop as the condition progresses.

Diagnosis is based on radiographic findings, echocardiography, and Doppler ultrasonography. Precise measurement of pulmonary pressures can be obtained only through right heart cardiac catheterization. Treatment measures are directed toward the underlying disorder. Vasodilator therapy may be indicated for some persons.

Primary Pulmonary Hypertension

Primary pulmonary hypertension is a relatively rare and rapidly progressive form of pulmonary hypertension that leads to right ventricular failure and death within a few years. Estimates of incidence range from 1 to 2 cases per million people in the general population.[29] The disease can occur at any age, and familial occurrences have been reported. Persons with the disorder usually have a steadily progressive downhill course, with death occurring in 3 to 4 years. Overall, the 5-year survival rate of untreated primary pulmonary hypertension is approximately 20%.[30]

Primary pulmonary hypertension is thought to be associated with a number of factors, including an autosomal dominant genetic predisposition along with an exogenous trigger.[30] Triggers include low oxygen levels that occur at high altitudes, exposure to certain drugs, human immunodeficiency virus infection, and autoimmune disorders.

The disorder is characterized by endothelial damage, coagulation abnormalities, and marked intimal fibrosis leading to obliteration or obstruction of the pulmonary arteries and

arterioles. Most of the manifestations of the disorder are attributable to increased work demands on the right heart and a decrease in cardiac output. Symptoms are the same as those for secondary hypertension. The most obvious are dyspnea and fatigue that is out of proportion to other signs of a person's well being.

The diagnosis of primary pulmonary hypertension is based on an absence of disorders that cause secondary hypertension and mean pulmonary artery pressures greater than 25 mm Hg at rest or 30 mm Hg with exercise.

Treatment consists of measures to improve right heart function to reduce fatigue and peripheral edema. Supplemental oxygen may be used to increase exercise tolerance. The most widely used drugs for long-term therapy are the calcium channel blockers. Anticoagulant (warfarin) therapy may be used to decrease the risk of thrombosis caused by sluggish pulmonary blood flow. Epoprostenol, a short-acting (half-life, 3 to 5 minutes) analog of the naturally occurring vasodilator prostacyclin (prostaglandin I_2), is increasingly used in the long-term care of persons with the disorder. Because of its short half-life, the drug must be administered by continuous infusion, usually through an indwelling venous catheter with an automatic ambulatory pump. Lung transplantation may be an alternative for persons who do not experience response to other forms of treatment.

Cor Pulmonale

The term *cor pulmonale* refers to right heart failure resulting from primary lung disease and longstanding primary or secondary pulmonary hypertension. It involves hypertrophy and the eventual failure of the right ventricle. The manifestations of cor pulmonale include the signs and symptoms of the primary lung disease and the signs of right-sided heart failure (see Chapter 18). Signs of right-sided heart failure include venous congestion, peripheral edema, shortness of breath and a productive cough, which becomes worse during periods of worsening failure. Plethora (*i.e.*, redness) and cyanosis and warm, moist skin may result from the compensatory polycythemia and desaturation of arterial blood that accompany chronic lung disease. Drowsiness and altered consciousness may occur as the result of carbon dioxide retention. Management of cor pulmonale focuses on the treatment of the lung disease and the heart failure. Low-flow oxygen therapy may be used to reduce the pulmonary hypertension and polycythemia associated with severe hypoxemia caused by chronic lung disease.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS), first described in 1967, is a devastating syndrome of acute lung injury. Initially called the *adult respiratory distress syndrome*, it is now called the *acute respiratory distress syndrome* because it also affects children. ARDS affects approximately 150,000 to 200,000 persons each year; at least 50% to 60% of these persons die, despite the most sophisticated intensive care.[31]

ARDS is the final common pathway through which many serious localized and systemic disorders produce diffuse injury to the alveolar-capillary membrane. It may result from a number of conditions, including aspiration of gastric contents, major trauma (with or without fat emboli), sepsis secondary to pulmonary or nonpulmonary infections, acute pancreatitis, hematologic disorders, metabolic events, and reactions to drugs and toxins[31,32] (Chart 21-3).

Although a number of conditions may lead to ARDS, they all produce similar pathologic lung changes that include diffuse endothelial and epithelial cell injury with increased permeability of the alveolar-capillary membrane (Fig. 21-14). The increased permeability permits fluid, protein, cellular debris and blood cells to move out of the vascular compartment into the interstitium and alveoli of the lung. Alveolar cell damage leads to accumulation of edema fluid, surfactant inactivation, and formation of a hyaline membrane that is impervious to gas exchange. The lungs become very stiff and difficult to inflate. There is increased intrapulmonary shunting of blood, impaired gas exchange, and profound hypoxia. Gas exchange is further compromised by alveolar collapse resulting from abnormalities in surfactant production. When injury to the alveolar epithelium is severe, disorganized epithelial repair may lead to fibrosis.

The pathogenesis of ARDS is unclear. Neutrophils accumulate early in the course of the disorder and are thought to play a role in the pathogenesis of ARDS. Activated neutrophils release a variety of products, including oxidants, proteases, platelet activating factor, and leukotrienes that damage the alveolar capillary endothelium and alveolar cells.

Clinically, the syndrome consists of progressive respiratory distress, an increase in respiratory rate, and signs of respiratory failure. Radiologic findings usually show extensive bilateral consolidation of the lung tissue. Severe hypoxia persists despite increased inspired oxygen levels.

The treatment goals in ARDS are to supply oxygen to vital organs and provide supportive care until the condition causing the pathologic process has been reversed and the lungs have had a chance to heal. Assisted ventilation using high concentrations of oxygen may be required to overcome the hypoxia.

CHART 21-3 Conditions in Which ARDS Can Develop*

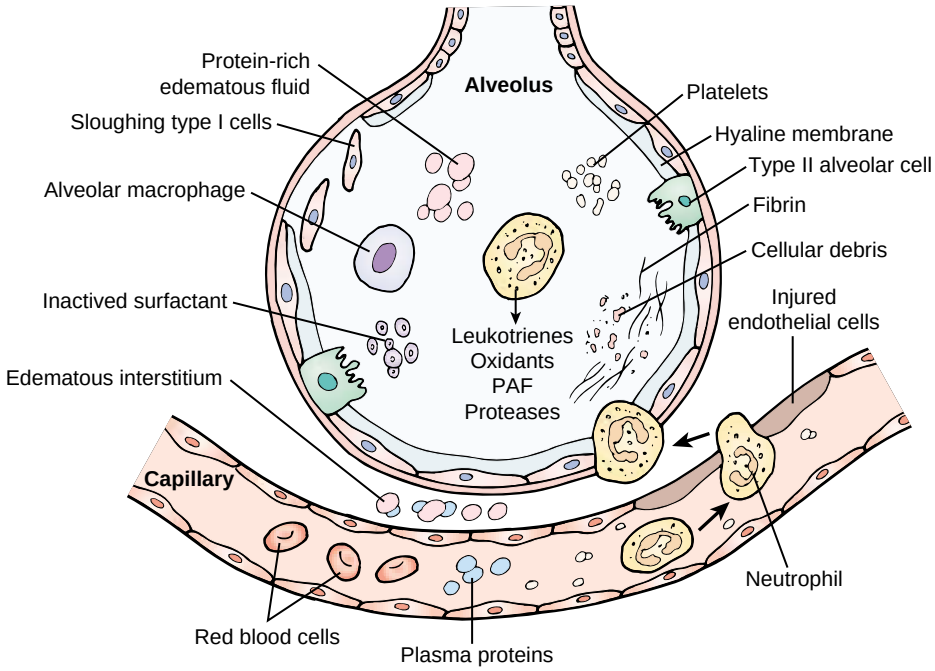
Aspiration
- Near drowning
- Aspiration gastric contents

Drugs, Toxins, Therapeutic Agents
- Heroin
- Inhaled gases (*e.g.*, smoke, ammonia)
- Oxygen
- Radiation

Infections
- Gram-negative septicemia
- Other bacterial infections
- Viral infections

Trauma and Shock
- Burns
- Fat embolism
- Chest trauma

*This list is not intended to be inclusive.



■ **FIGURE 21-14** ■ The mechanism of lung changes in ARDS. Injury and increased permeability of the alveolar capillary membrane allow fluid, protein, cellular debris, platelets, and blood cells to move out of the vascular compartment and enter the interstitium and alveoli. Activated neutrophils release a variety of products that damage the alveolar cells and lead to edema, surfactant inactivation, and formation of a hyaline membrane.

Positive end-expiratory pressure breathing, which increases the pressure in the airways during expiration, may be used to assist in reinflating the collapsed areas of the lung and to improve the matching of ventilation and perfusion.

In summary, pulmonary vascular disorders include pulmonary embolism and pulmonary hypertension. Pulmonary embolism develops when a blood-borne substance lodges in a branch of the pulmonary artery and obstructs blood flow. The embolus can consist of a thrombus, air, fat, or amniotic fluid. The most common form is a thromboembolus arising from the deep venous channels of the lower extremities. Pulmonary hypertension is the elevation of pulmonary arterial pressure. It can be caused by an elevated left atrial pressure, increased pulmonary blood flow, or increased pulmonary vascular resistance secondary to lung disease. The term *cor pulmonale* describes right heart failure caused by primary pulmonary disease and longstanding pulmonary hypertension.

ARDS is a devastating syndrome of acute lung injury resulting from a number of serious localized and systemic disorders that damage the alveolar-capillary membrane of the lung. It results in interstitial edema of lung tissue, an increase in surface tension caused by inactivation of surfactant, collapse of the alveolar structures, a stiff and noncompliant lung that is difficult to inflate, and impaired diffusion of the respiratory gases with severe hypoxia that is resistant to oxygen therapy.

RESPIRATORY FAILURE

Respiratory failure is a condition in which the lungs fail to oxygenate the blood adequately and prevent carbon dioxide retention. It is not a specific disease but the result of a number of conditions that impair ventilation, compromise the matching of ventilation and perfusion, or disrupt blood flow in the lung. These conditions include impaired ventilation caused by impaired function of the respiratory center, weakness and paralysis of the respiratory muscles, chest wall deformities, airway obstruction, and disease of the airways and lungs. It may occur in previously healthy persons as the result of acute disease or trauma involving the respiratory system, or it may develop in the course of a chronic neuromuscular or respiratory disease. The causes of respiratory failure are summarized in Chart 21-4.

Alterations in Blood Gases

The term *hypoxia* refers to a reduction in oxygen supply to the tissues; *hypoxemia*, to a low level of oxygen in the blood; and *hypercapnia* (sometimes referred to as *hypercarbia*), to excess carbon dioxide in the blood. The abbreviation PO_2 often is used to indicate the partial pressure of oxygen in arterial blood, and the abbreviation PCO_2, the partial pressure of carbon dioxide. The common manifestations of respiratory failure are hypoxemia and hypercapnia. There is no absolute definition of the levels of arterial PO_2 and PCO_2 that indicate respiratory failure. As a general rule, *respiratory failure* refers to an arterial PO_2 level of 50 mm Hg or less and an arterial PCO_2 level greater than 50 mm Hg. However, these values are not reliable when dealing with persons who have chronic lung disease because many of these persons are alert and functioning with blood gas levels outside this range.

Mechanisms of Altered Gas Exchange

Various types of respiratory failure are associated with different degrees of hypoxemia or hypercapnia.[33] For example, pure hypoventilation, as occurs in conditions such as drug overdose, favors retention of CO_2. Severe ventilation-perfusion mismatching that is inadequate to maintain the PO_2 results in

CHART 21-4 Causes of Respiratory Failure*

Impaired Ventilation

Upper airway obstruction
- Infection (*e.g.*, epiglottitis)
- Foreign body
- Laryngospasm
- Tumors

Weakness or paralysis of respiratory muscles
- Brain injury
- Drug overdose
- Guillain-Barré syndrome
- Muscular dystrophy
- Spinal cord injury

Chest wall injury

Impaired Matching of Ventilation and Perfusion

Chronic obstructive pulmonary disease
Restrictive lung disease
Severe pneumonia
Atelectasis

Impaired Diffusion

Pulmonary edema
Acute respiratory distress syndrome

*This list is not intended to be inclusive.

hypoxemia that is more severe in relation to hypercapnia. This pattern of respiratory failure is seen most commonly in persons with advanced COPD. In interstitial lung disease, there is severe hypoxemia but no hypercapnia because of increased ventilation. In ARDS, the arterial PCO_2 is typically low, but hypoxemia is severe. In this case, administration of oxygen can produce an increase in PO_2 without producing an increase in PCO_2.

KEY CONCEPTS

DISORDERS OF BLOOD GASES IN RESPIRATORY FAILURE

- Respiratory failure represents failure of the lungs to adequately oxygenate the blood and prevent carbon dioxide retention.
- Hypoxemia results from decreased concentration of oxygen in the inspired air, airway diseases that impair ventilation, respiratory disorders that impair ventilation and/or perfusion, and cardiovascular disorders that impair movement of blood through the respiratory portions of the lung.
- Carbon dioxide retention is characteristic of conditions that produce hypoventilation.
- Conditions such as acute respiratory distress syndrome that impede the diffusion of gases in the lung impair the oxygenation of blood but do not interfere with the elimination of carbon dioxide.

Hypoventilation. Hypoventilation occurs when the volume of "fresh" air moving into and out of the lung is significantly reduced. Hypoventilation is commonly caused by conditions outside the lung such as depression of the respiratory center (*e.g.*, drug overdose), diseases of the nerves supplying the respiratory muscles (*e.g.*, Guillain-Barré syndrome), disorders of the respiratory muscles (*e.g.*, muscular dystrophy), or thoracic cage disorders (*e.g.*, severe scoliosis or crushed chest).

Hypoventilation has two important effects on arterial blood gases. First, hypoventilation almost always causes an increase in PCO_2. The rise in PCO_2 is directly related to the level of ventilation. For example, the PCO_2 doubles when alveolar ventilation is reduced by one half. Thus, the PCO_2 level is a good diagnostic measure for hypoventilation. Second, hypoxemia caused by hypoventilation can be easily corrected by increasing the oxygen content of the inspired air.[33]

Ventilation-Perfusion Mismatching. The mismatching of ventilation and perfusion occurs when areas of the lung are ventilated but not perfused or when areas are perfused but not ventilated. Usually the hypoxemia that is seen in situations of ventilation-perfusion mismatching is more severe in relation to hypercapnia than that seen in hypoventilation. Severe mismatching of ventilation and perfusion often is seen in persons with advanced COPD. These disorders contribute to the retention of carbon dioxide by reducing the effective alveolar ventilation, even when total ventilation is maintained. This occurs because a region of the lung is not perfused and gas exchange cannot take place or because an area of the lung is not being ventilated. Maintaining a high ventilation rate effectively prevents hypercapnia but also increases the work of breathing.

The hypoxemia associated with ventilation-perfusion disorders often is exaggerated by conditions such as hypoventilation and decreased cardiac output. For example, sedation can cause hypoventilation in persons with severe COPD, resulting in further impairment of ventilation. Likewise, a decrease in cardiac output because of myocardial infarction can exaggerate the ventilation-perfusion impairment in a person with mild pulmonary edema.

The beneficial effect of oxygen administration on PO_2 levels in ventilation-perfusion disorders depends on the degree of mismatching that is present. Because oxygen administration increases the diffusion gradient in ventilated portions of the lung, it usually is effective in raising arterial PO_2 levels but may decrease the respiratory drive and produce an increase in PCO_2.

Impaired Diffusion. Diffusion impairment describes a condition in which gas exchange between the alveoli and the red blood cells is impeded because of an increase in the distance for diffusion or a decrease in the permeability of the alveolar capillary membrane to movement of gases. Impaired diffusion is caused by conditions such as interstitial lung disease, ARDS, pulmonary edema, and pneumonia. These conditions alter the thickness or permeability of the alveolar capillary membrane, rather than the time that the blood spends in pulmonary capillaries.

Hypoxemia resulting from impaired diffusion can be partially or completely corrected by the administration of 100% oxygen. This occurs because the increase in alveolar oxygen establishes a large alveolar-capillary diffusion gradient that overcomes the resistance to diffusion.

Shunt. Shunt occurs when blood reaches the arterial system without passing through the ventilated portion of the lung. Most shunts, such as those that occur with congenital heart disease, are extrapulmonary. However, a completely unventilated portion of the lung, as occurs with atelectasis, can result in the shunting of blood in the pulmonary circulation. Administration of oxygen usually increases arterial oxygen levels with intrapulmonary shunting but not with extrapulmonary shunting, such as occurs in children with intracardiac shunts. Because unoxygenated venous blood is being mixed with oxygenated blood in persons with intrapulmonary shunts, the rise in PO_2 levels depends on the degree of shunt.

Hypoxemia

Hypoxemia refers to a reduction in blood oxygen levels. Hypoxemia can result from an inadequate amount of oxygen in the air, disease of the respiratory system, or alterations in circulatory function. The mechanisms whereby respiratory disorders lead to a significant reduction in PO_2 are hypoventilation, impaired diffusion of gases, shunt, and mismatching of ventilation and perfusion.[33] Another cause of hypoxemia, reduction of the partial pressure of oxygen in the inspired air, occurs only under special circumstances, such as at high altitudes. Often more than one mechanism contributes to hypoxemia in a person with respiratory or cardiac disease.

Clinical Manifestations. Hypoxemia produces its effects through tissue hypoxia and the compensatory mechanisms that the body uses to adapt to the lowered oxygen level. Body tissues vary considerably in their vulnerability to hypoxia; those with the greatest need are the nervous system and heart. Cessation of blood flow to the cerebral cortex results in loss of consciousness within 10 to 20 seconds. If the PO_2 of the tissues falls below a critical level, aerobic metabolism ceases and anaerobic metabolism takes over, with the formation and release of lactic acid.

The signs and symptoms of hypoxemia can be grouped into two categories: those resulting from impaired function of vital centers and those resulting from activation of compensatory mechanisms. Mild hypoxemia produces few manifestations. There may be slight impairment of mental performance and visual acuity and sometimes hyperventilation. This is because hemoglobin saturation still is approximately 90% when the PO_2 is only 60 mm Hg (see Chapter 19, Fig. 19-18). More pronounced hypoxemia may produce personality changes, restlessness, agitated or combative behavior, muscle incoordination, euphoria, impaired judgment, delirium, and, eventually, stupor and coma. Recruitment of sympathetic compensatory mechanisms produces tachycardia, cool skin (*i.e.*, peripheral vasoconstriction), diaphoresis, and a mild increase in blood pressure. Profound acute hypoxemia can cause convulsions, retinal hemorrhages, and permanent brain damage. Hypotension and bradycardia often are preterminal events in persons with hypoxemia, indicating the failure of compensatory mechanisms.

In conditions of chronic hypoxemia, the manifestations may be insidious in onset and attributed to other causes, particularly in chronic lung disease. There may be a gradual increase in red blood cells (polycythemia) and development of pulmonary hypertension. Polycythemia increases the red blood cell concentration and the oxygen-carrying capacity of the blood. Pulmonary vasoconstriction occurs as a local response to alveolar hypoxia; it increases pulmonary arterial pressure and improves the matching of ventilation and blood flow.

Cyanosis. Cyanosis refers to the bluish discoloration of the skin and mucous membranes that results from an excessive concentration of reduced or deoxygenated hemoglobin in the small blood vessels. It usually is most marked in the lips, nail beds, ears, and cheeks. The degree of cyanosis is modified by the amount of cutaneous pigment, skin thickness, and the state of the cutaneous capillaries. Cyanosis is more difficult to distinguish in persons with dark skin and in areas of the body with increased skin thickness.

Although cyanosis may be evident in persons with respiratory failure, it often is a late sign. A concentration of approximately 5 g/dL of deoxygenated hemoglobin is required in the circulating blood for cyanosis to occur.[34] The absolute quantity of reduced hemoglobin, rather than the relative quantity, is important in producing cyanosis. Persons with anemia and low hemoglobin levels are less likely to exhibit cyanosis (because they have less hemoglobin to deoxygenate), even though they may be relatively hypoxic because of their decreased ability to transport oxygen, than persons who have high hemoglobin concentrations. Someone with a high hemoglobin level because of polycythemia may be cyanotic without being hypoxic.

Cyanosis can be divided into two types: central or peripheral. *Central cyanosis* is evident in the tongue and lips. It is caused by an increased amount of deoxygenated hemoglobin in the arterial blood. *Peripheral cyanosis* occurs in the extremities and on the tip of the nose or ears. It is caused by slowing of blood flow to an area of the body, with increased extraction of oxygen from the blood. It results from vasoconstriction and diminished peripheral blood flow, as occurs with cold exposure, shock, congestive heart failure, and peripheral vascular disease.

Diagnosis. Diagnosis of hypoxemia is based on clinical observation and diagnostic tests to determine blood oxygen levels. The analysis of arterial blood gases provides a direct measure of the oxygen content of the blood and is a good indicator of the lungs' ability to oxygenate the blood. Noninvasive measurement of hemoglobin saturation can be obtained using the pulse oximeter. The pulse oximeter uses light-emitting diodes and light-receiving sensors to quantify the light absorbed by oxygenated/deoxygenated hemoglobin in arterial blood.[85] Sensors that can be placed on the ear, finger, toe, or forehead are available. Pulse oximetry cannot distinguish between oxygen-carrying hemoglobin and carbon monoxide-carrying hemoglobin, a factor that should be considered when treating persons with carbon monoxide poisoning. It is also inaccurate in persons with pronounced vasoconstriction.

Hypercapnia

Hypercapnia refers to an increase in the carbon dioxide content of the blood. The diagnosis of hypercapnia is based on physiologic manifestations, arterial pH, and blood gas levels. The carbon dioxide level in the arterial blood, or PCO_2, is proportional to carbon dioxide production and inversely related to alveolar ventilation. The diffusing capacity of carbon dioxide is 20 times that of oxygen; therefore, hypercapnia is observed only in situations of hypoventilation sufficient to cause hypoxia.

Causes. Hypercapnia can occur in a number of disorders that cause hypoventilation or mismatching of ventilation and perfusion. Hypoventilation is a cause of hypercapnia in respiratory failure caused by depression of the respiratory center in drug overdose, neuromuscular diseases such as Guillain-Barré syndrome, or chest wall deformities such as those seen with severe scoliosis. Hypercapnia caused by ventilation-perfusion inequalities is seen most commonly in persons with COPD.

The respiratory center, which controls the activity of the muscles of respiration, is a crucial determinant of ventilation and elimination of carbon dioxide. It is composed of widely dispersed groups of neurons located in the medulla oblongata and pons (see Chapter 19). The activity of the respiratory center is regulated by chemoreceptors that monitor changes in the chemical composition of the blood. The most important chemoreceptors in terms of the minute-by-minute control of ventilation are the central chemoreceptors that respond to changes in the hydrogen ion (H^+) concentration of the cerebrospinal fluid. Although the blood-brain barrier is impermeable to H^+ ions, CO_2 crosses it with ease. The CO_2, in turn, reacts with water to form carbonic acid, which dissociates to form H^+ and bicarbonate (HCO_3^-) ions. When the CO_2 content of the blood rises, CO_2 crosses the blood-brain barrier, liberating H^+ ions that stimulate the central chemoreceptors. The excitation of the respiratory center caused by CO_2 is greatest during the first 1 to 2 days that blood levels are elevated, but it gradually declines during the next 1 to 2 days.[34]

In persons with respiratory problems that cause chronic hypoxia and hypercapnia, the peripheral chemoreceptors become the driving force for ventilation. These chemoreceptors, which are located in the bifurcation of the common carotid arteries and in the aortic arch, respond to changes in PO_2. Administration of high-flow oxygen to these persons can abolish the input from these peripheral receptors, causing a decrease in alveolar ventilation and a further increase in PCO_2 levels.

Respiratory muscle fatigue can contribute to carbon dioxide retention in persons with various primary respiratory diseases and in those with neuromuscular disorders. In these persons, respiratory muscle fatigue develops when energy requirements exceed the energy supply. A number of factors increase energy requirements or decrease the energy supply. The energy demands of the respiratory muscles are increased by high levels of ventilation or by factors that increase the work of breathing, such as high levels of airway resistance. The energy supply depends on blood flow and the oxygen content of the blood. Low cardiac output, anemia, and decreased oxygen saturation contribute to a decreased energy supply and increase the likelihood of respiratory muscle fatigue. With malnutrition, the energy stores of the muscles are diminished, and there may be structural changes in the muscle as well. Electrolyte imbalances, especially hypokalemia and hypophosphatemia, contribute to respiratory muscle weakness.[36]

Clinical Manifestations. Hypercapnia affects many body functions, including renal, neural, and cardiovascular function, as well as the acid-base balance. Elevated levels of PCO_2 produce a decrease in pH and respiratory acidosis (see Chapter 6). The body normally compensates for an increase in PCO_2 by increasing renal bicarbonate retention. As long as the pH is in an acceptable range, the main complications of hypercapnia are those resulting from the accompanying hypoxia. Because the body compensates for chronic increases in blood levels of carbon dioxide, persons with chronic hypercapnia may not have symptoms until the PCO_2 is markedly elevated.

Carbon dioxide has a direct vasodilatory effect on many blood vessels and a sedative effect on the nervous system. When the cerebral vessels are dilated, headache develops. The conjunctivae are hyperemic and the skin flushed. Hypercapnia has nervous system effects similar to those of an anesthetic, thus the term *carbon dioxide narcosis*. There is progressive somnolence, disorientation, and if the condition is untreated, coma. Mild to moderate increases in blood pressure are common. Air hunger and rapid breathing occur when alveolar PCO_2 levels rise to approximately 60 to 75 mm Hg; as PCO_2 levels reach 80 to 100 mm Hg, the person becomes lethargic and sometimes becomes semicomatose. Anesthesia and death can result when PCO_2 levels reach 100 to 150 mm Hg.

Treatment of Respiratory Failure

The treatment of respiratory failure focuses on correcting the problems causing impaired gas exchange when possible and on relieving the hypoxemia and hypercapnia. A number of treatment modalities are available, including treatment of drug overdose, use of bronchodilating drugs, and antibiotics to treat severe respiratory tract infections. The insertion of an artificial airway and use of mechanical ventilation may be necessary.

Therapy for hypercapnia is directed at decreasing the work of breathing and improving the ventilation-perfusion balance. Intermittent rest therapy, such as nocturnal negative-pressure ventilation, applied to patients with hypercapnia and chronic obstructive disease or chest wall disease may be effective in increasing the strength and endurance of the respiratory muscle and improving the PCO_2. Respiratory muscle retraining aimed at improving the respiratory muscles, their endurance, or both has been used to improve exercise tolerance and diminish the likelihood of respiratory fatigue.

Hypoxemia is usually treated with oxygen therapy. Oxygen may be delivered by nasal cannula or mask. It also may be administered directly into an endotracheal or tracheostomy tube in persons who are being ventilated. The oxygen must be humidified as it is being administered. The concentration of oxygen that is being administered (usually determined by the flow rate) is based on the PO_2. The rate must be carefully monitored in persons with chronic lung disease because increases in PO_2 above 60 mm Hg are likely to depress the ven-

tilatory drive. There also is the danger of oxygen toxicity with high concentrations of oxygen. Continuous breathing of oxygen at high concentrations can lead to diffuse parenchymal lung injury.

In summary, the lungs enable inhaled air to come in proximity to the blood flowing through the pulmonary capillaries so that the exchange of gases between the internal environment of the body and the external environment can take place. Respiratory failure is a condition in which the lungs fail adequately to oxygenate the blood or prevent undue retention of carbon dioxide. The causes of respiratory failure are many. It may arise acutely in persons with previously healthy lungs, or it may be superimposed on chronic lung disease. Respiratory failure is defined as a PO_2 of 50 mm Hg or less and a PCO_2 of 50 mm Hg or more.

Hypoxia refers to an acute or chronic reduction in tissue oxygenation. It can occur as the result of hypoventilation, diffusion impairment, shunt, and ventilation-perfusion impairment. Acute hypoxemia incites sympathetic nervous system responses such as tachycardia and produces symptoms that are similar to those of alcohol intoxication. In conditions of chronic hypoxia, the manifestations may be insidious in onset and attributed to other causes, particularly in chronic lung disease. The development of cyanosis requires a concentration of 5 g/dL of deoxygenated hemoglobin.

Hypercapnia refers to an increase in carbon dioxide levels. In the clinical setting, four factors contribute to hypercapnia: alterations in carbon dioxide production, disturbance in the gas exchange function of the lungs, abnormalities in respiratory function of the chest wall and respiratory muscles, and changes in neural control of respiration. The manifestations of hypercapnia consist of those associated with the vasodilation of blood vessels, including those in the brain, and depression of the central nervous system (*e.g.*, carbon dioxide narcosis).

REVIEW QUESTIONS

- Differentiate among the causes and manifestations of spontaneous pneumothorax, secondary pneumothorax, and tension pneumothorax.
- Describe the causes and manifestations of atelectasis.
- Describe the physiology of bronchial smooth muscle as it relates to the early phase and late phase responses in the pathogenesis of bronchial asthma.
- Explain the distinction between chronic bronchitis and emphysema in terms of pathology and clinical manifestations.
- Describe the genetic abnormality responsible for cystic fibrosis and state the disorder's effect on lung function.
- Compare the physiology changes that occur with COPD and interstitial lung diseases.
- State the most common cause of pulmonary embolism and the clinical manifestations of the disorder.
- Describe the pathophysiology of pulmonary arterial hypertension and three causes of secondary pulmonary hypertension.
- Describe the pathologic lung changes that occur in acute respiratory distress syndrome and relate them to the clinical manifestations of the disorder.
- Define the terms *hypoxia, hypoxemia,* and *hypercapnia* and characterize the mechanisms whereby respiratory disorders cause hypoxemia and hypercapnia.
- Compare the manifestations of hypoxia and hypercapnia.

connection

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REFERENCES

1. Chestnut M.S., Prendergast T.J. (2002). Lung. In Tierney L.M., McPhee S.J., Papadakis M.A. (Eds.), *Current medical diagnosis and treatment* (41st ed., pp. 350–355). New York: Lange Medical Books/McGraw-Hill.
2. Romero S. (2000). Nontraumatic chylothorax. *Current Opinion in Pulmonary Medicine* 6, 287–291.
3. Sahn S.A., Heffner J.E. (2000). Spontaneous pneumothorax. *New England Journal of Medicine* 342, 868–874.
4. Light R.W. (1995). Diseases of the pleura, mediastinum, chest wall, and diaphragm. In George R.B., Light R.W., Matthay M.A., et al. (Eds.), *Chest medicine* (3rd ed., pp. 501–520). Baltimore: Williams & Wilkins.
5. American Lung Association. (2000). *Asthma statistics*. [On-line.] Available: http://lungusa.org/data.
6. National Asthma Education and Prevention Program. (1997,2002). *Expert Panel report 2: Guidelines for the diagnosis and management of asthma,* and *Guidelines for the diagnosis and management of asthma—Update on selected topics 2002*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute. Available: http://www.nhlbi.nih.gov/guidelines/asthma.
7. Cotran R.S., Kumar V., Collins T. (1999). *Robbins pathologic basis of disease* (6th ed., p. 713). Philadelphia: W.B. Saunders.
8. Busse W.W., Lemanske R.F. (2001). Asthma. *New England Journal of Medicine* 344, 350–362.
9. McFadden E.R., Gilbert I.A. (1994). Exercise-induced asthma. *New England Journal of Medicine* 330, 1362–1366.
10. Young S., LeSouef P.N., Geelhoed G.C., et al. (1991). The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *New England Journal of Medicine* 324, 1168–1173.
11. Chan-Yeung M., Malo J. (1995). Occupational asthma. *New England Journal of Medicine* 333, 107–112.
12. Babu K.S., Salvi S.S. (2000). Aspirin and asthma. *Chest* 118, 1470–1476.
13. Tan K.S., McFarlane L.C., Lipworth B.J. (1997). Loss of normal cyclical B_2 adrenoreceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. *Thorax* 52, 608–611.
14. Dubuske D.M. (1994). Asthma: Diagnosis and management of nocturnal symptoms. *Comprehensive Therapy* 20, 628–639.
15. Sly M. (2000). Allergic disorders. In Behrman R.E., Kliegman R.M., Jenson H.B. (Eds.), *Nelson textbook of pediatrics* (16th ed., pp. 664–685). Philadelphia: W.B. Saunders.
16. Gilliland F.D., Berhane K., McConnell R., et al. (2000). Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 55, 271–276.

17. American Thoracic Society. (1995). Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *American Journal of Respiratory Critical Care Medicine* 152, S77–S120.
18. Barnes P.J. (2000). Medical progress: Chronic obstructive pulmonary disease. *New England Journal of Medicine* 343, 269–280.
19. Silverman E.K., Chapman H.A., Drazen J.M., et al. (1998). Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. *American Journal of Critical Care Medicine* 157, 1770–1778.
20. Travis W.D., Farber J.L., Rubin E. (1999). The respiratory system. In Rubin E., Farber J.L. (Eds.), *Pathology* (3rd ed., pp. 600–601, 623–630). Philadelphia: Lippincott Williams & Wilkins.
21. Mysliwiec V., Pina J.S. (1999). Bronchiectasis: The "other" obstructive lung disease. *Postgraduate Medicine* 106, 123–131.
22. Cystic Fibrosis Foundation. (2000). *Facts about cystic fibrosis*. [Online.] Available: http://www.cff.org/facts.htm.
23. Rubin E., Farber J.L. (1999). Developmental and genetic diseases. In Rubin E., Farber J.L. (Eds.), *Pathology* (3rd ed., pp. 246–249). Philadelphia: Lippincott Williams & Wilkins.
24. Stern R.C. (1997). The diagnosis of cystic fibrosis. *New England Journal of Medicine* 336, 487–491.
25. Reynolds H.V., Matthay R.A. (1995). Diffuse interstitial and alveolar inflammatory diseases. In George R.B., Light R.W., Matthay M.A., et al. (Eds.), *Chest medicine* (3rd ed., pp. 303–323). Baltimore: Williams & Wilkins.
26. Kobzik L. (1999). The lung. In Cotran R.S., Kumar V., Collins T. (Eds.), *Robbins pathologic basis of disease* (6th ed., pp. 697–755). Philadelphia: W.B. Saunders.
27. Goldhaber S.Z. (1998). Pulmonary embolism. *New England Journal of Medicine* 339, 93–104.
28. Richardi M.J., Rubenfire M. (1999). How to manage secondary pulmonary hypertension. *Postgraduate Medicine* 105 (2), 183–190.
29. Rubin L.J. (1997). Primary pulmonary hypertension. *New England Journal of Medicine* 336, 111–117.
30. Richardi M.J., Rubenfire M. (1999). How to manage primary pulmonary hypertension. *Postgraduate Medicine* 105 (2), 45–56.
31. Kollef M.H., Schuster D.P. (1995). The acute respiratory distress syndrome. *New England Journal of Medicine* 332, 27–36.
32. Ware L.B., Matthay M.A. (2000). The acute respiratory distress syndrome. *New England Journal of Medicine* 342, 1334–1348.
33. West J.B. (1997). *Pulmonary pathophysiology: The essentials* (5th ed., pp. 18–40, 132–142, 151). Philadelphia: Lippincott-Raven.
34. Guyton A.C., Hall J.E. (2000). *Textbook of medical physiology* (10th ed., pp. 477–478, 491, 804). Philadelphia: W.B. Saunders.
35. St. John R.E., Thomson P.D. (1999). Noninvasive respiratory monitoring. *Critical Care Nursing Clinics of North America* 11, 423–434.
36. Weinberger S.E., Schwartzstein R.M., Weiss J.W. (1989). Hypercapnia. *New England Journal of Medicine* 321, 1223–1230.