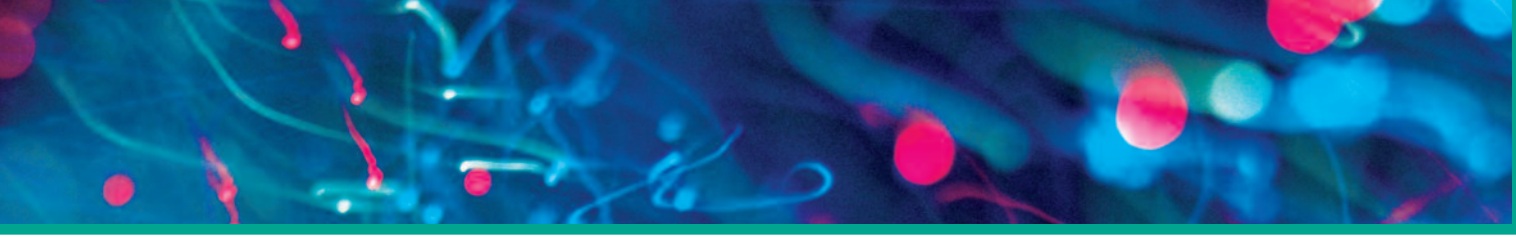

Chapter 22

Disorders of Ventilation and 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. The content in this chapter focuses on disorders of lung inflation, obstructive airway disorders, interstitial lung disease, pulmonary vascular disorders, and respiratory failure.

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 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 serous membrane that encases the lungs (Fig. 22-1). The outer *parietal layer* lines the thoracic wall and superior aspect of the diaphragm. It continues around the heart and between the lungs, forming the lateral walls of the mediastinum. The inner *visceral layer* covers the lung and is adherent to all its surfaces. It provides the lung with a slippery surface, enabling it to move freely on the parietal pleura. The pleural cavity or space between the two layers contains a thin layer of serous fluid, which lubricates the pleural surfaces and allows the pleurae to slide smoothly over each other during breathing movements. The pressure in the pleural cavity, which is negative in relation to atmospheric pressure,

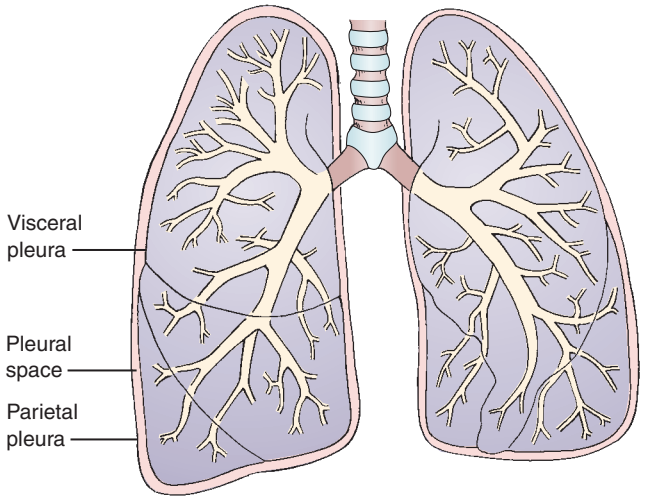

FIGURE 22-1 The relationship between the parietal and visceral pleurae and the pleural space, which is the site of fluid accumulation in pleural effusions.

holds the lungs against the chest wall and keeps them from collapsing (see Chapter 20). Disorders of the pleura include pleuritic chest pain, pleural effusion, and pneumothorax.

Pleuritic Chest Pain

Chest pain caused by respiratory diseases usually originates from involvement of the parietal pleura. Causes include primary pleural disorders, such as neoplasms or inflammatory disorders affecting the pleura, or pulmonary disorders that extend to the pleural surface, such as pneumonia. 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 part of the pleura that covers 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 accentuate 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. It is made worse with coughing but is not affected by deep breathing. Myocardial pain, which is discussed in Chapter 18, 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. 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 purulent drainage (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 represents the effusion of lymph in the thoracic cavity.[2] Chyle, a milky fluid containing chylomicrons (fat-carrying lipoproteins), is found in the lymph fluid originating in the gastrointestinal tract. Chylothorax can result from trauma, inflammation, or malignant infiltration of the thoracic duct that transports chyle to the central circulation (see Chapter 16, Fig. 16-21). 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. 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 ultrasonography, and computed tomography (CT) scans. 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 reexpansion 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 wall 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. 22-2). 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.

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.

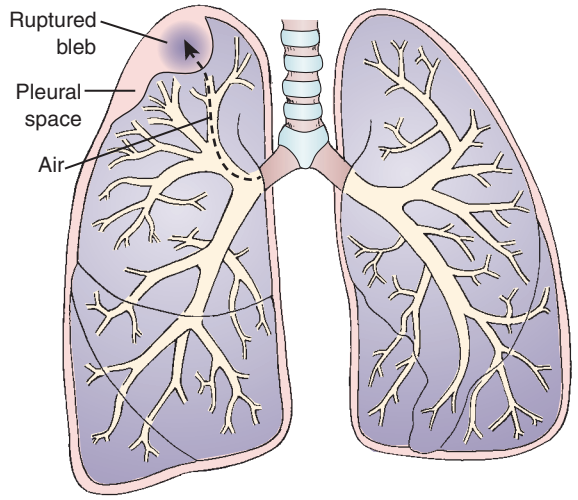

FIGURE 22-2 Mechanism for development of spontaneous pneumothorax in which an air-filled bleb on the surface of the lung ruptures, allowing atmospheric air to enter the pleural space.

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. 22-3). 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

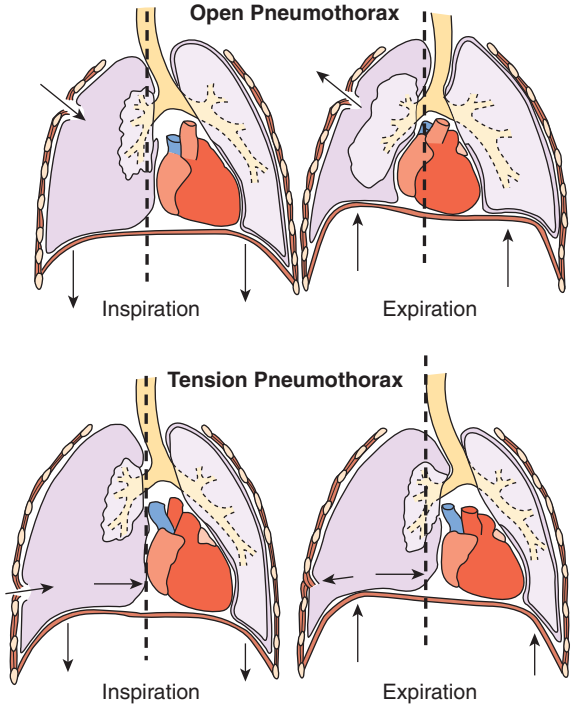

FIGURE 22-3 Open or communicating pneumothorax (**top**) and tension pneumothorax (**bottom**). In an open pneumothorax, air enters the chest during inspiration and exits during expiration. There may be slight inflation of the affected lung because of a decrease in pressure as air moves out of the chest. 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.

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. 22-3). 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, 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 increase 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 traumatic pneumothoraces, 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 20).

Atelectasis is caused most commonly by airway obstruction (Fig. 22-4). 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 com-

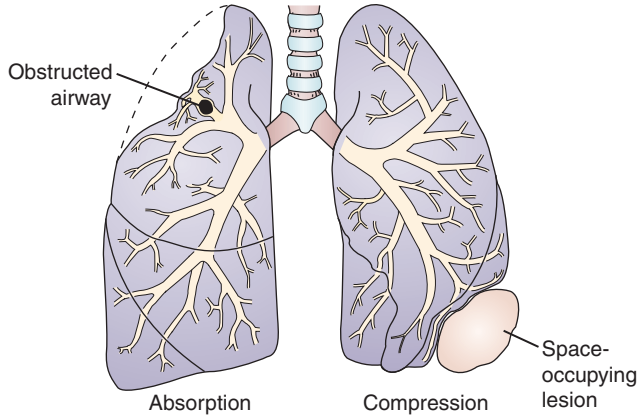

FIGURE 22-4 Atelectasis caused by airway obstruction and absorption of air from the involved lung area (**left**) and by compression of lung tissue (**right**).

pletely filled with fluid, exudate, blood, a tumor mass, or air. It is observed most commonly in persons with pleural effusion from 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 pleuritic chest 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 a mucus plug or 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 increase the resistance to 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 20). The contraction and relaxation of the smooth muscle layer, which is innervated by the autonomic nervous system (ANS), controls the diameter of the pulmonary 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.

BRONCHIAL ASTHMA

Bronchial asthma is a chronic disorder of the airways that causes episodes of airway obstruction, bronchial hyperresponsiveness, and airway inflammation that usually

KEY CONCEPTS

Airway Disorders

- Airway disorders affect 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.

are reversible.[5,6] According to 2001 data, an estimated 20.3 million Americans have been diagnosed with asthma.[5] Although the prevalence rates for asthma have increased over the past several decades, the mortality rate and hospitalizations due to asthma have plateaued during the last few years, indicating a higher level of disease management.

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]

In susceptible persons, an asthma attack can be triggered by a variety of stimuli that do not normally cause symptoms. Typically, asthma has been categorized into extrinsic asthma (initiated by a type I hypersensitivity [atopic] response to an extrinsic antigen) and intrinsic asthma (initiated by diverse nonimmune mechanisms, including respiratory tract infections, exercise, ingestion of aspirin, emotional upset, and exposure to bronchial irritants such as cigarette smoke).[7] Although this distinction is useful from a pathophysiologic point of view, it is less useful clinically because many persons with asthma manifest overlapping characteristics of both extrinsic and intrinsic asthma.

Pathogenesis

The common denominator underlying all forms of asthma is an exaggerated hypersensitivity response to a variety of stimuli. Most current information suggests that airway inflammation manifested by the presence of inflammatory cells (particularly eosinophils, lymphocytes, and mast cells) and by damage to the bronchial epithelium contributes to the pathogenesis of the disease.

Recent interest has focused on the role of the T lymphocytes in the pathogenesis of bronchial asthma. It is now known that there are two subsets of T helper cells (T_H1 and T_H2) that develop from the same precursor CD4+ T lymphocyte.[7] T_H1 cells differentiate in response to microbes and stimulate the differentiation of B cells into immunoglobulin M (IgM)- and IgG-producing plasma cells, whereas T_H2 cells respond to allergens and helminths (intestinal parasites) by stimulating differentiation of B cells into IgE-producing plasma cells, acting as growth factors for mast cells, and recruiting and activating eosinophils (see Chapter 15, Fig. 15-1). It appears that in persons with allergic asthma, T-cell differentiation is skewed toward T_H2 cells. Although the molecular basis for this preferential differentiation is unclear, it seems likely that both genetic and environmental factors play a role.

Extrinsic (Atopic) Asthma. Extrinsic or atopic asthma is typically initiated by a type I hypersensitivity reaction induced by exposure to an extrinsic antigen or allergen.[7–10] It usually has its onset in childhood or adolescence and is seen in persons with a family history of atopic allergy (see Chapter 15). Candidate genes for predisposition to atopy and airway hyperresponsiveness are currently subjects for intensive research and include genes involved in antigen presentation, T-cell activation, regulation of cytokine production or function, and receptors for bronchodilating substances.[7]

Persons with atopic 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-round) asthma are house dust mite allergens, cockroach allergens, animal danders, and the fungus *Alternaria*.

The mechanisms of response to antigens in atopic asthma can be described in terms of the early- and the late-phase responses[7] (Fig. 22-5). Recall that IgE-mediated hypersensitivity responses (discussed in Chapter 15) involve an initial antigen (allergen) sensitization, which leads to the production of presensitized IgE-coated mast cells. The symptoms of the *acute response,* which usually develop within 10 to 20 minutes, are caused by the release of chemical mediators from the presensitized mast cells. In the case of airborne antigens, the reaction occurs when antigen binds to previously sensitized mast cells on the mucosal surface of the airways (Fig. 22-6). Mediator release results in the infiltration of inflammatory cells and opening of the mucosal intercellular junctions and increased access of antigen to the more prevalent submucosal mast cells. In addition, there is bronchospasm

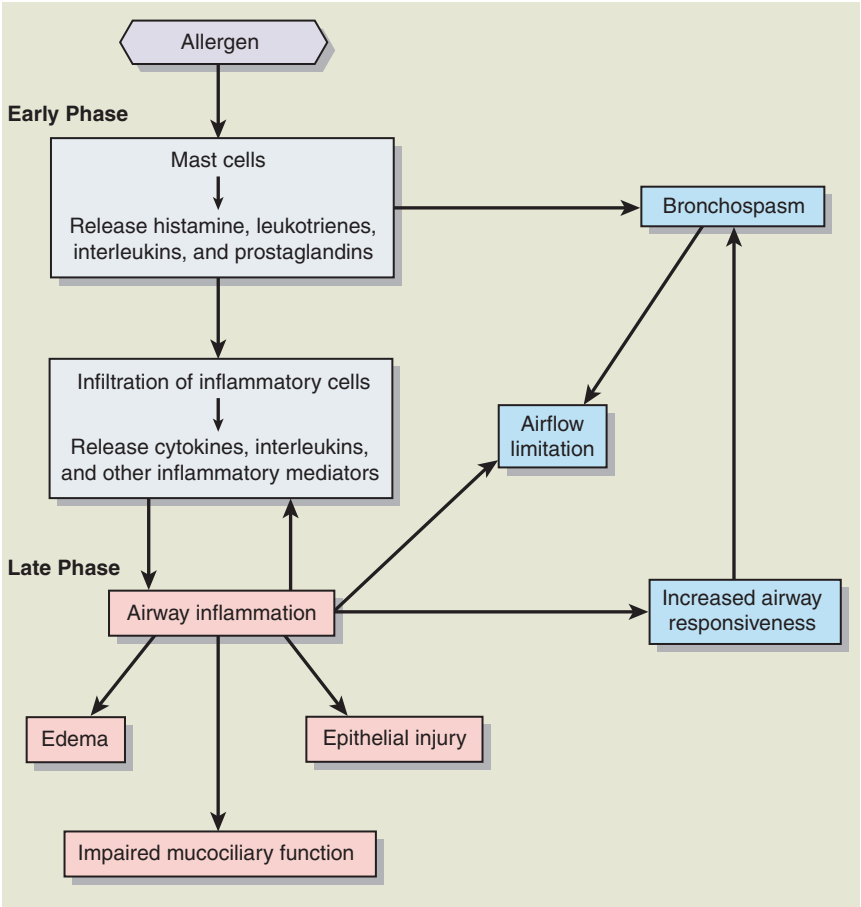

FIGURE 22-5 Mechanisms of early- and late-phase IgE-mediated bronchospasm.

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] The late-phase response involves inflammation and increased airway responsiveness that prolong 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 cell injury, changes in mucociliary function and reduced clearance of respiratory tract secretions, increased vascular permeability and edema, and continued bronchospasm and heightened airway responsiveness (see Fig. 22-6). Responsiveness to cholinergic mediators often is increased, suggesting changes in parasympathetic control of airway function. Chronic inflammation can lead to airway remodeling, with more permanent changes in airway resistance.[6]

Intrinsic (Nonatopic) Asthma. Intrinsic or nonatopic asthma triggers include respiratory tract infections, exercise, hyperventilation, cold air, exercise, drugs and chemicals, hormonal changes and emotional upsets, airborne pollutants, and gastroesophageal reflux.

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.[11] 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.[12] High doses of irritant gases such as sulfur dioxide, nitrogen dioxide, and ozone may induce inflammatory

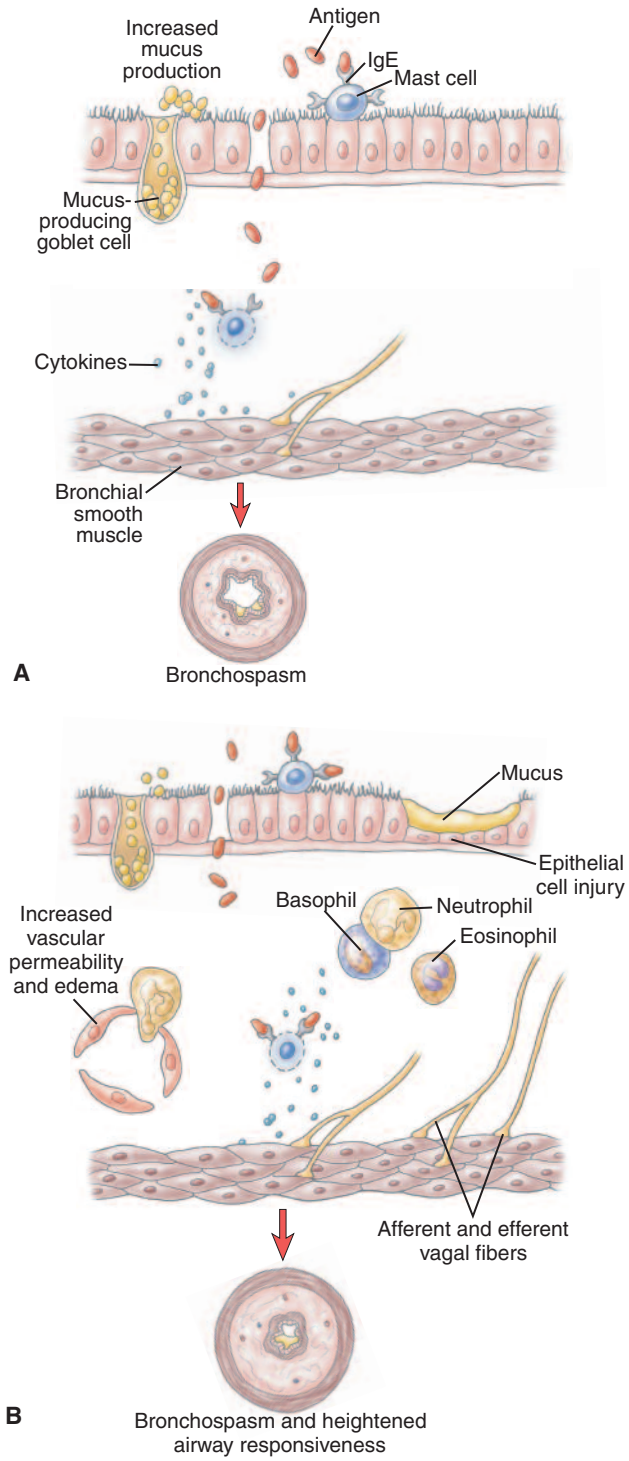

FIGURE 22-6 Pathogenesis of bronchial asthma. (**A**) The immediate or early-phase response triggered by an IgE-mediated release of mediators from sensitized mast cells. The release of chemical mediators results in increased mucous production, opening of mucosal intercellular junctions with exposure of submucosal mast cells to antigen, and bronchospasm. (**B**) The late-phase response involves epithelial cell injury with decreased mucociliary function and accumulation of mucus; release of inflammatory mediators with recruitment of neutophils, eosinophils, and basophils; increased vascular permeability and edema; and increased airway responsiveness and bronchospasm.

exacerbations of airway responsiveness (*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.[13]

There is a small group of persons with the clinical triad of asthma, chronic rhinosinusitis with nasal polyps, and precipitation of asthma and rhinitis attacks in response to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).[14,15] The mechanism of the hypersensitivity reaction is complex and not fully understood, but most evidence points toward an abnormality in arachidonic acid (AA) metabolism (see Chapter 14). Cyclooxygenase (COX), the rate-limiting enzyme in AA metabolism, exists in two main forms: COX-1 and COX-2. COX-1 is responsible for the synthesis of protective prostaglandins and COX-2 for the synthesis of mediators of inflammation and bronchoconstriction. It has been hypothesized that in persons with aspirin-induced asthma, the inhibition of COX-1 shunts the metabolism of AA away from the production of protective prostaglandins and toward the generation of COX-2 and other mediators of inflammation and bronchoconstriction.[15] Avoidance of aspirin and all NSAIDs is a necessary part of the treatment program. An addition to the list of chemicals that can provoke an asthmatic attack is the sulfites used in food processing and as preservatives 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 much as 40% of women with asthma report a premenstrual increase in asthma symptoms.[16] Female sex hormones have a regulatory role in β_2-adrenergic function, and it has been suggested that abnormal regulation may be a possible mechanism for premenstrual asthma.[16]

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 is thought to 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.[17]

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. 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.

Manifestations. 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. Fatigue develops as the attack progresses, 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.[6] This point often marks the onset of respiratory failure.

Diagnosis and Treatment. 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 20). 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 22-1).

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 by persons with asthma to provide frequent measures of flow rates. 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] Day-night (circadian) variations in asthma symptoms and PEF variability can be used to indicate the severity of bronchial hyperreactivity. For example, 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 department treatment.[6]

TABLE 22-1 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.

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 allergens and factors that increase asthma symptoms and precipitate asthma exacerbations.

Pharmacologic treatment is used to prevent or treat reversible airway obstruction and airway hyperresponsiveness caused by the inflammatory process. The Expert Panel recommends a stepwise approach to pharmacologic therapy based on frequency and severity of disease symptoms.[6] The medications used in the treatment of asthma include those with bronchodilator and anti-inflammatory actions. They are categorized into two general categories: quick-relief medications and long-term–control medications.

The *quick-relief medications* include the short-acting β_2-adrenergic agonists, anticholinergic agents, and systemic corticosteroids. The short-acting β_2-adrenergic agonists relax bronchial smooth muscle and provide prompt relief of symptoms, usually within 30 minutes. They are administered by inhalation (*i.e.*, metered-dose inhaler [MDI] or nebulizer). The short-acting β_2-agonists are used for treating acute attacks of asthma but are not recommended for daily use because of concern over safety.[6] Ipratropium is an inhaled anticholinergic agent that blocks the parasympathetic pathways that cause bronchoconstriction. A short course of corticosteroids administered orally or parenterally may be used for treating the inflammatory reaction associated with the late-phase response.

The *long-term medications* are taken on a daily basis to achieve and maintain control of persistent asthma symptoms. They include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers. The corticosteroids are considered the most effective anti-inflammatory agents for use in long-term treatment of asthma. Inhaled corticosteroids that are administered by MDI usually are preferred because of minimal systemic absorption and disruption of hypothalamic-pituitary-adrenal function. In severe cases, oral or parenterally administered corticosteroids may be necessary.

The long-acting β_2-agonists, which are available in inhalation or oral forms, act by relaxing bronchial smooth muscle. These agents have a duration of action of at least 12 hours and should not be used to treat acute symptoms or exacerbations.[6] The anti-inflammatory agents sodium cromolyn and nedocromil are also used to prevent an asthmatic attack. These agents act by stabilizing mast cells, thereby preventing release of the inflammatory mediators that cause an asthmatic attack. They are used prophylactically to prevent early and late responses. A newer group of drugs called the *leukotriene modifiers* have become 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 (see Chapter 14, Fig. 14-3). A particular advantage of the leukotriene modifiers is that they are taken orally.

Severe Asthma

Severe or refractory asthma represents a subgroup (probably less than 5%) of persons with asthma who have more troublesome disease as evidenced by high medication requirements to maintain good disease control or persistent symptoms despite high medication use.[18,19] These persons are at increased risk for fatal or near-fatal asthmatic attacks.

Fatal and near-fatal asthmatic attacks, although uncommon, have increased in frequency over the past several decades. 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. Although the cause of death during an acute asthmatic attack is largely unknown, both cardiac dysrhythmias and asphyxia due to 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. It has been suggested that persons who have fatal or near-fatal asthmatic attacks may have impaired perception of dyspnea and its severity.[20] Thus, they may not realize the severity of their condition and may not take the appropriate measures in terms of securing appropriate emergency treatment. 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 frequent admitting diagnosis in children's hospitals. According to statistics collected by the United States Center for Health Statistics in 1998, 8.65 million children (12.1%) were reported to have physician- or health care professional–diagnosed asthma at some time during childhood.[21] Although childhood asthma may have its onset at any age, 80% of children are symptomatic by 6 years of age.[21,22] Asthma is more prevalent in African-American than white children, and results in more frequent disability and more frequent hospitalizations in African-American children.[22]

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 wheezing illnesses in infants (*i.e.*, bronchiolitis), which often precedes the onset of asthma. The respiratory syncytial virus and parainfluenza viruses are the most commonly involved.[23] Other contributing factors include exposure to environ-

mental allergens such as pet dander, 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.[24]

The signs and symptoms of asthma in infants and small children vary with the stage and the 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 develop 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 emergency department treatment or hospitalization.

The Expert Panel of the National Heart, Lung, and Blood Institute's National Asthma Education Program has developed guidelines for management of asthma in infants and children younger than 5 years of age and for adults and children older than 5 years of age.[6,25] As with adults and older children, the Expert Panel recommends a stepwise approach to diagnosing and managing asthma in infants and children younger than 5 years of age. The anti-inflammatory agents cromolyn and nedocromil are recommended as an initial therapy for mild to moderate persistent asthma in infants and children. Inhaled short-acting β_2-agonists may be used for mild intermittent symptoms or exacerbations. More severe symptoms may require the use of inhaled corticosteroids. Systemic corticosteroids may be required during an episode of severe disease. Growth velocity should be monitored in children and adolescents receiving long-term corticosteroid therapy by any route because these drugs may suppress growth.[6]

Special delivery systems for administration of inhalation medications are available for infants and small children, including nebulizers with face masks and spacers/holding chambers for use with an MDI. For children younger than 2 years of age, nebulizer therapy usually is preferred. Children between 3 and 5 years of age may begin using an MDI with a spacer/holding chamber. The child's caregiver should be carefully instructed in the appropriate use of these devices.

The Expert Panel recommends that adolescents (and younger children when appropriate) be directly involved in developing their asthma management plans.[6] Active participation in physical activities, exercise, and sports should be encouraged.

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.[26–28] The airflow obstruction is usually progressive, may be accompanied by airway hyperresponsiveness, and may be partially reversible. COPD affects over 11 million Americans and now represents the fourth leading cause of death in the United States, accounting for over 100,000 deaths annually.[29] The death rate from COPD is increasing rapidly, especially among older men.

The most common cause of COPD is smoking.[26–28] 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. Persons with COPD often have overlapping features of both disorders.

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 alveolar tissue and elastic lung fibers[26] (Fig. 22-7). 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 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

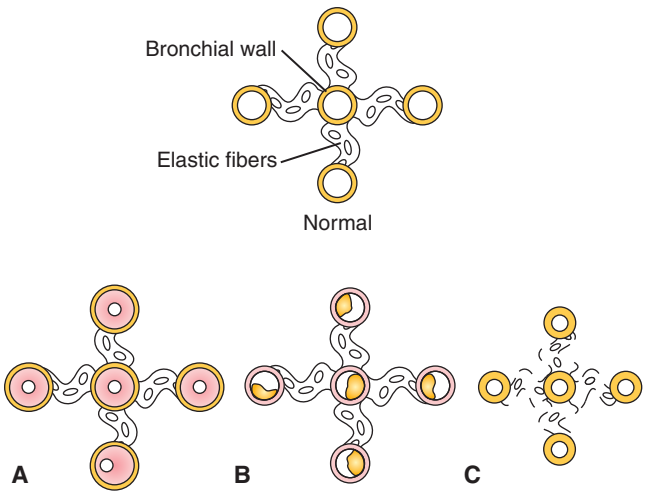

FIGURE 22-7 Mechanisms of airflow obstruction in chronic obstructive lung disease. (**Top**) Normal bronchial airway with elastic fibers that provide traction and hold the airway open. (**Bottom**) Obstruction of the airway caused by (**A**) hypertrophy of the bronchial wall, (**B**) inflammation and hypersecretion of mucus, and (**C**) loss of elastic fibers that hold the airway open.

walls and capillary beds. Enlargement of the alveolar 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 develop COPD at an early age.[30]

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, are released from polymorphonuclear leukocytes (*i.e.,* neutrophils), alveolar macrophages, and other inflammatory cells.[26] 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 such that the process of elastic tissue destruction goes unchecked (Fig. 22-8).

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.[26] An α_1-antitrypsin deficiency is inherited as an autosomal recessive disorder. It is most common in persons of Scandinavian descent and is rare in Jews, blacks, and Japanese.[30] Homozygotes who carry two defective genes have only about 15% to 20% of the normal plasma concentration of α_1-antitrypsin. Almost all persons who have emphysema before the age of 40 years have an α_1-antitrypsin deficiency. 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. A recombinant human α_1-antitrypsin is available for replacement therapy in persons with a hereditary deficiency of the enzyme.

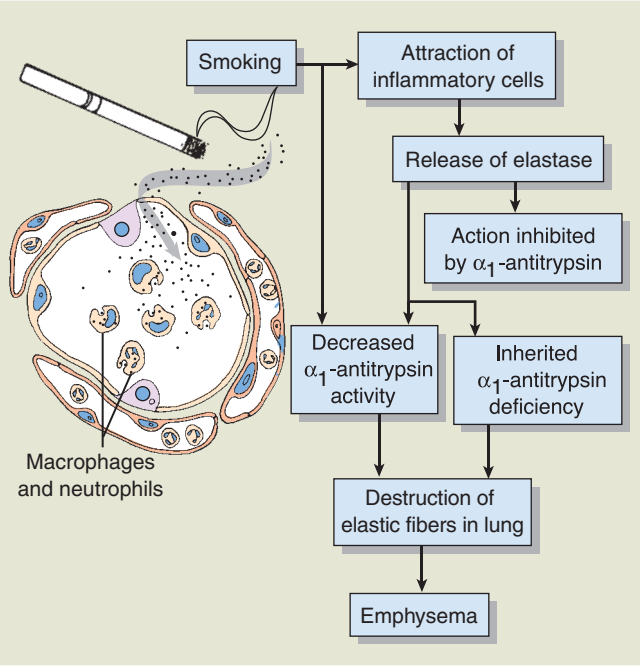

FIGURE 22-8 Protease (elastase)-antiprotease (antitrypsin) mechanisms of emphysema. The effects of smoking and an inherited α_1-antitrypsin deficiency on the destruction of elastic fibers in the lung and development of emphysema.

There are two commonly recognized types of emphysema: centriacinar and panacinar (Fig. 22-9). The centriacinar type affects the bronchioles in the central part of the respiratory lobule, with initial preservation of the alveolar ducts and sacs[30] (Fig. 22-10). 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 commonly seen in the lower parts of the lung and centriacinar changes in the upper parts of the lung.

Chronic Bronchitis

Chronic bronchitis represents airway obstruction of the major and small airways. The condition is seen most commonly in middle-aged men and is associated with chronic irritation from smoking and recurrent infections. A clinical diagnosis of chronic bronchitis requires the history of a chronic productive cough for at least 3 consecutive months in at least 2 consecutive years.[27] Typically, the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum.

The earliest feature of chronic bronchitis is hypersecretion of mucus in the large airways, associated with hypertrophy of the submucosal glands in the trachea and bronchi.[30] Although mucus hypersecretion in the large airways is the cause of sputum overproduction, it is now thought that accompanying changes in the small airways (small bronchi and bronchioles) are physiologically important in the airway obstruction that develops in chronic

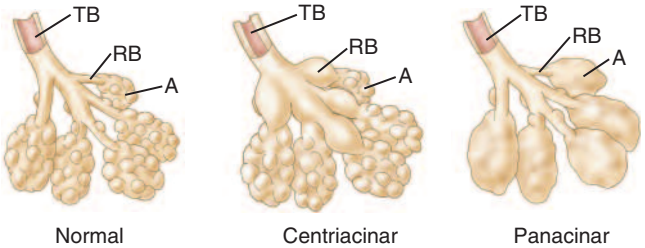

FIGURE 22-9 Centriacinar and panacinar emphysema. In centriacinar emphysema, the destruction is confined to the terminal (TB) and respiratory bronchioles (RB). In panacinar emphysema, the peripheral alveoli (A) are also involved. (Adapted from West J. B. [1997]. *Pulmonary pathophysiology* [5th ed., p. 53]. Philadelphia: Lippincott-Raven.)

FIGURE 22-10 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. (From Travis W. D., Beasley M. B., Rubin E. [2005]. The respiratory system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 618]. Philadelphia: Lippincott Williams & Wilkins.)

bronchitis.[7] Histologically, these changes include a marked increase in goblet cells and excess mucus production with plugging of the airway lumen, inflammatory infiltration, and fibrosis of the bronchiolar wall. It is thought that both the submucosal hypertrophy in the larger airways and the increase in goblet cells in the smaller airways are protective metaplastic reactions against tobacco smoke and other pollutants. 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. Although infections are not responsible for initiating the problem, they are probably important in maintaining it and may be critical in producing acute exacerbations.[7]

Clinical Features

The mnemonics "pink puffer" and "blue bloater" have been used to differentiate the clinical manifestations of emphysema and chronic obstructive bronchitis.[1] The important features of these forms of COPD are described in Table 22-2. In practice, differentiation between the two types is often difficult because persons with COPD usually 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 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 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 ventilatory 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. 22-11). Expiration often is accomplished through pursed lips. Pursed-lip ("puffer") 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 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 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 bronchitis develop pulmonary hypertension and, eventually, right-sided heart failure (*i.e.,* cor pulmonale) with peripheral edema ("bloater").

Persons with combined forms of COPD 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 (to be discussed),

TABLE 22-2 Characteristics of Emphysema and Chronic Bronchitis

Characteristic	Type A Pulmonary Emphysema ("Pink Puffers")	Type B Chronic Bronchitis ("Blue Bloaters")
Smoking history	Usual	Usual
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

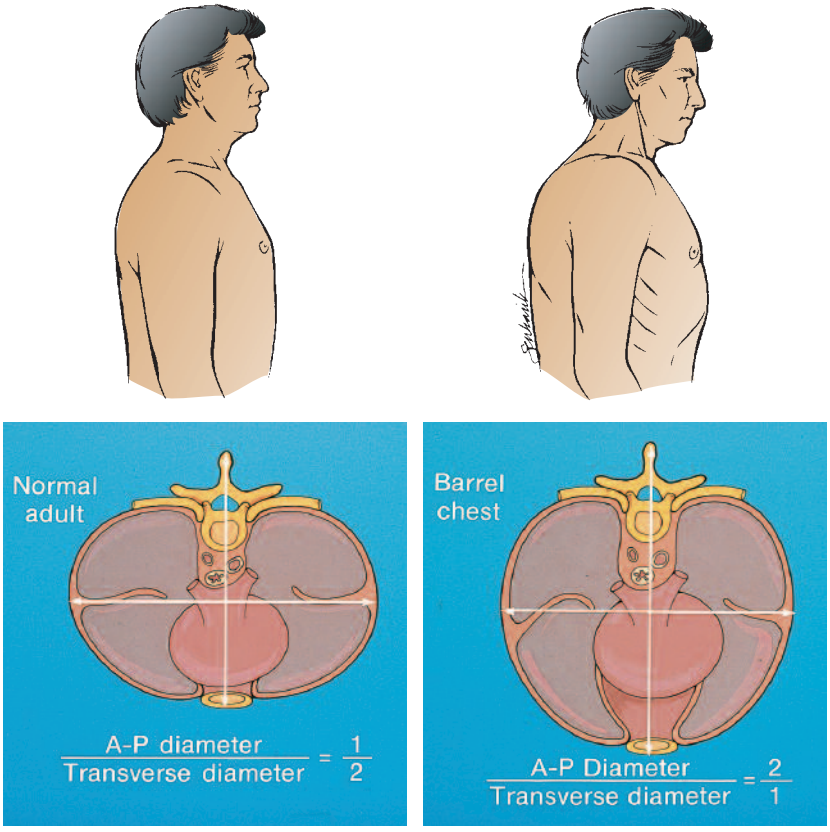

FIGURE 22-11 Characteristics of normal chest wall and chest wall in emphysema. The normal chest wall and its cross-section are illustrated on the left. The barrel-shaped chest of emphysema and its cross-section are illustrated on the right. (From Smeltzer S. C., Bare B. G. [2004]. *Medical-surgical nursing* [10th ed., p. 572]. Philadelphia: Lippincott Williams & Wilkins.)

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 mismatching of ventilation and perfusion. The FVC is the amount of air that can be forcibly exhaled after maximal inspiration. In an adult with normal respiratory function, this should be achieved in 4 to 6 seconds. In patients with chronic lung disease, 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 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 (see Chapter 20, Fig. 20-16). Other diagnostic measures become important as the disease advances. Measures of exercise tolerance, nutritional status, hemoglobin saturation, and arterial blood gases can be used to assess the overall impact of COPD on health status and to direct treatment.

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. 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.

The pharmacologic treatment of COPD includes the use of bronchodilators, including inhaled adrenergic and anticholinergic agents.[26–28] Inhaled β_2-adrenergic agonists have been the mainstay of treatment for COPD for many years. The anticholinergic drugs (*e.g.*, ipratropium), which are administered by inhalation, produce bronchodilation by blocking parasympathetic cholinergic receptors that induce contraction of bronchial smooth muscle. They also reduce the volume of sputum without altering its viscosity. Inhalers that combine an anticholinergic drug with a β_2-adrenergic agonist are available. Oral theophylline, a bronchodilator, may be used in treatment of persons who fail to respond to inhaled bronchodilators. The long-acting theophylline preparations may be used to reduce overnight declines in respiratory function.

Oxygen therapy is prescribed for selected persons with significant hypoxemia (arterial $PO_2 \leq 55$ mm Hg or hemoglobin saturation $\leq 88\%$).[31] 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 a hemoglobin oxygen saturation of at least 90%, representing an arterial PO_2 of approximately 60 mm Hg (see Chapter 20, Fig. 20-18). 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 60 to 65 mm Hg. Increasing the arterial PO_2 above that level tends to depress ventilation, which can lead to carbon dioxide retention.

BRONCHIECTASIS

Bronchiectasis is an uncommon type of COPD characterized by a permanent dilatation of the bronchi and bronchioles caused by destruction of the muscle and elastic supporting tissue resulting from a vicious cycle of infection and inflammation.[32] It is not a primary disease but occurs secondary to persistent infection or obstruction.[7] In the past, bronchiectasis often followed a necrotizing bacterial pneumonia that frequently complicated measles, pertussis, or influenza. Tuberculosis was also commonly associated with bronchiectasis. Thus, with the advent of antibiotics that more effectively treat respiratory infections such as tuberculosis and immunizations against pertussis and measles, there has been a marked decrease in the prevalence of bronchiectasis.

Pathogenesis

Two processes are critical to the pathogenesis of bronchiectasis: obstruction and chronic persistent infection.[7] Regardless of which may come first, both cause damage to the bronchial walls, leading to weakening and dilatation. On gross examination, bronchial dilatation is classified as saccular, cylindrical, or varicose. Saccular bronchiectasis involves the proximal third to fourth generation of bronchi[30] (see Chapter 20, Fig. 20-5). These bronchi become severely dilated and end blindly in dilated sacs with collapse and fibrosis of more distal lung tissue (Fig. 22-12). Cylindrical bronchiectasis involves uniform and moderate dilatation of the sixth to eighth generations of airways. It is a milder form of disease than saccular bronchiectasis and leads to fewer symptoms. Varicose bronchiectasis involves the second through eighth branchings of bronchi and results in bronchi that resemble varicose veins. Bronchiolar obliteration is not as severe and symptoms are variable.

Bronchiectasis can present in either of two forms: a local obstructive process involving a lobe or segment of a lung or a diffuse process involving much of both lungs.[32] *Localized bronchiectasis* is most commonly caused by conditions such as tumors, foreign bodies, and mucus plugs that produce atelectasis and infection due to obstructed drainage of bronchial secretions. It can affect any area of the lung, the area being determined by the site

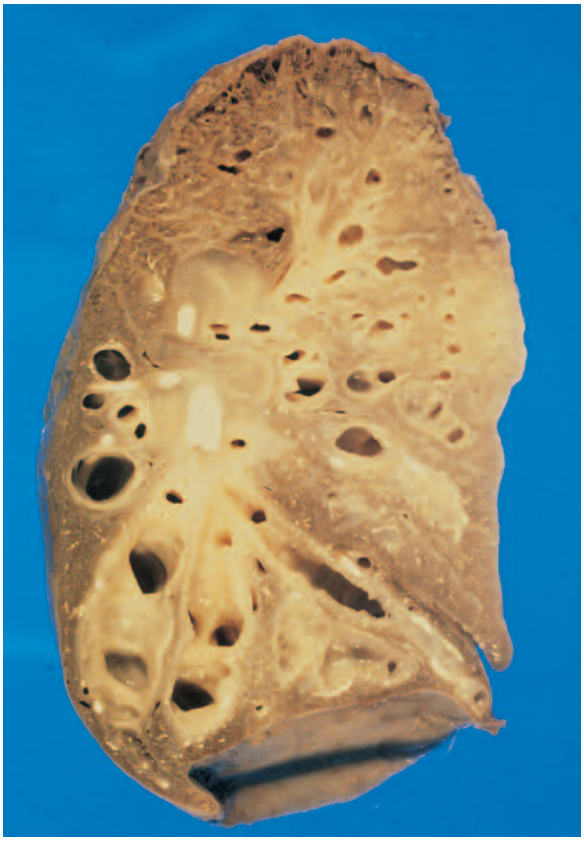

FIGURE 22-12 Bronchiectasis. The resected upper lobe shows widely dilated bronchi, with thickening of the bronchial walls and collapse and fibrosis of the pulmonary parenchyma. (From Travis W. D., Beasley M. B., Rubin E. [2005]. The respiratory system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 591]. Philadelphia: Lippincott Williams & Wilkins.)

of obstruction or infection. *Generalized bronchiectasis* usually is bilateral and most commonly affects the lower lobes. It is due 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.

Clinical Features

Bronchiectasis is associated with a number of abnormalities that profoundly affect respiratory function, including atelectasis, obstruction of the smaller airways, and diffuse bronchitis. Affected persons have recurrent bronchopulmonary infection; coughing; production of copious amounts of foul-smelling, purulent sputum; and hemoptysis. Weight loss and anemia are common.

The manifestations of 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, which is not usually seen in other types of obstructive lung disease, is common in moderate to advanced bronchiectasis.

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. Accuracy of diagnosis is important because interventional bronchoscopy or surgery may be palliative or curative in some of the more obstructive forms of the disease.

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.

CYSTIC FIBROSIS

Cystic fibrosis (CF), which is the major cause of severe chronic respiratory disease in children, is an autosomal recessive disorder involving fluid secretion in the exocrine glands in the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts.[32–36] In addition to chronic respiratory disease, CF is manifested by pancreatic exocrine deficiency and 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 boys with CF have congenital bilateral absence of the vas deferens with azoospermia.

The disease affects approximately 30,000 children and adults in the United States, and more than 10 million persons are asymptomatic carriers of the defective gene.[33] The 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.

Pathogenesis

Cystic fibrosis is caused by mutations in a single gene on the long arm of chromosome 7 that encodes for the cystic fibrosis transmembrane regulator (CFTR), which functions as a chloride (Cl^-) channel in epithelial cell membranes. Mutations in the CFTR render the epithelial membrane relatively impermeable to the chloride ion (Fig. 22-13).

The impact on transport function is relatively tissue specific. In the sweat glands, the concentration of sodium (Na^+) and Cl^- secreted into the lumen of the gland remains unaffected, whereas the reabsorption of Cl^- through the CFTR and accompanying reabsorption of Na^+ in the ducts of the gland fails to occur. This accounts for the high concentration of NaCl in the sweat of persons with CF.[35] In the normal airway epithelium, Cl^- is secreted into the airway lumen through the CFTR. In CF, the

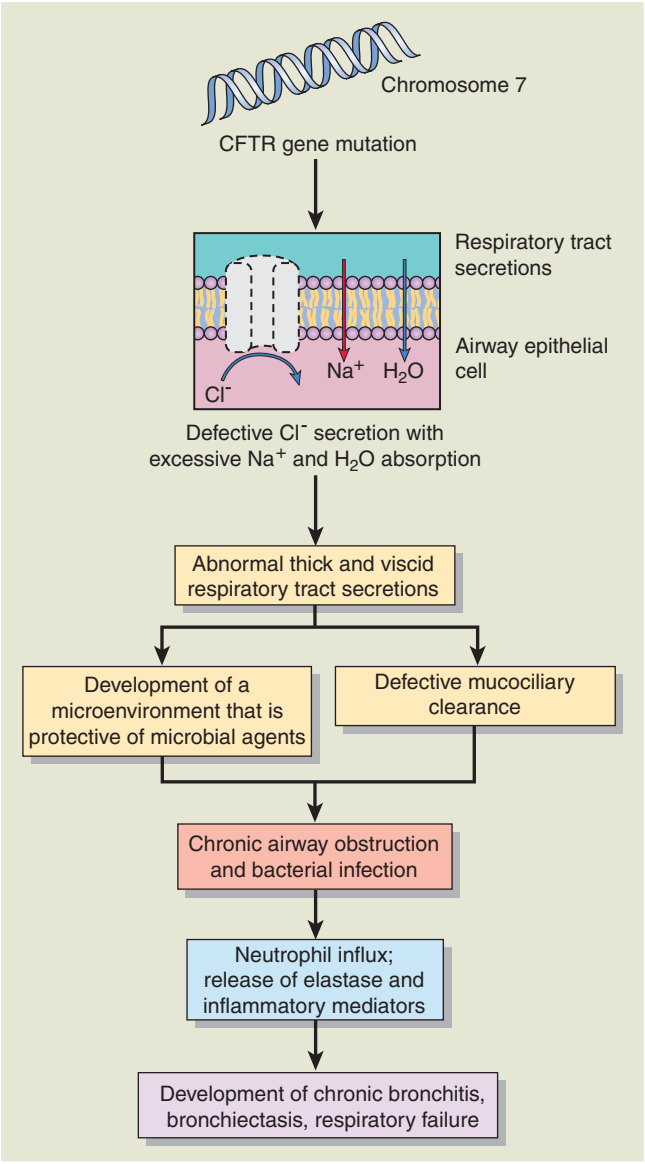

FIGURE 22-13 Pathogenesis of cystic fibrosis.

impaired transport of Cl^- ultimately leads to a series of secondary events that includes increased absorption of Na^+ and water from the airway lumen. This lowers the water content of the mucociliary blanket coating the respiratory epithelium, causing it to become more viscid. The resulting dehydration of the mucus layer leads to defective mucociliary action and accumulation of viscid secretions that obstruct the airways and predispose to recurrent pulmonary infections. Similar transport abnormalities and pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens).

Clinical Features

Respiratory manifestations of CF 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. In addition to airway obstruction, the basic genetic defect that occurs with CF predisposes to chronic infection with a surprisingly small number of organisms, the most common being *Pseudomonas aeruginosa, Staphylococcus aureus, and Burkholderia cepacia,* that rarely affect the lungs of other individuals.[35] Soon after birth, initial infection with bacterial pathogens occurs and is associated with an excessive neutrophilic inflammatory response that appears to occur independent of infection. There is evidence that the CF airway epithelial cells or surface liquids provide a favorable environment for harboring these organisms. *P. aeruginosa,* in particular, has a propensity to undergo mucoid transformation in this environment.[35] The complex polysaccharide produced by these organisms provides a hypoxic environment and generates a biofilm that protects *P. aeruginosa* against antimicrobial agents.

Pancreatic function is abnormal in approximately 80% to 90% of persons with CF.[35] 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. In addition to exocrine pancreatic insufficiency, hyperglycemia may occur, especially after 10 years of age, when approximately 8% of persons with CF develop diabetes mellitus.[35]

Diagnosis and Treatment. Early diagnosis and treatment are important in delaying the onset and severity of chronic illness in children with CF. Diagnosis is based on the presence of respiratory and gastrointestinal manifestations typical of CF, a history of CF in a sibling, or a positive newborn screening test. Confirmatory laboratory tests include the sweat test, assessment of bioelectrical properties of respiratory epithelia by measurement of transepithelial potential differences in the nasal membrane, and genetic tests for CFTR gene mutations.[35] The *sweat test,* using pilocarpine iontophoresis to collect the sweat and chemical analysis of its chloride content, remains the standard approach to diagnosis. Newborns with CF have elevated blood levels of immunoreactive trypsinogen, presumably because of secretory obstruction in the pancreas. *Newborn screening* consists of a test for determination of immunoreactive trypsinogen. The test can be done on blood spots collected for routine newborn screening tests.

At present there are no approved treatments for correcting the genetic defects in CF or to reverse the ion transport abnormalities associated with the dysfunctional CFTR. Thus, treatment measures are directed toward slowing the progression of secondary organ dysfunction and sequelae such as chronic lung infection and pancreatic insufficiency. They include the use of antibiotics to prevent and manage infections; the use of chest physical therapy (chest percussion and postural drainage) and mucolytic agents to prevent airway obstruction; and pancreatic enzyme replacement and nutritional therapy. Routine

laboratory evaluations are crucial for assessing pulmonary function and response to therapeutic interventions. These studies include radiologic examinations, pulmonary function testing, and microbiologic cultures of respiratory secretions.

The abnormal viscosity of airway secretions is attributed largely to the presence of polymorphonuclear white blood cells and their degradation products. A purified recombinant human deoxyribonuclease (rhDNase), an enzyme that breaks down these products, has been developed.[32,36] Clinical trials have shown that the drug, which is administered by inhalation, can improve pulmonary symptoms and reduce the frequency of respiratory exacerbations. Although many persons benefit from the therapy, the drug is costly, and recommendations for its use are evolving.

Up to 90% of patients with CF have complete loss of exocrine pancreas function and inadequate digestion of fats and proteins. They require diet adjustment, pancreatic enzyme replacement, and supplemental vitamins and minerals. Pancreatic enzyme dosage and product are individualized for each patient. Enteric-coated, pH-sensitive enzyme microspheres are available.

Progress of the disease is variable. Improved medical management has led to longer survival. Currently, the median age for survival of people with CF has increased to 35.1 years.[32] Current hopes reside in research that would make gene therapy a feasible alternative for persons with the disease.

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. Typically, asthma has been categorized into extrinsic (initiated by a type I hypersensitivity [atopic] response to an extrinsic antigen) and intrinsic (initiated by diverse nonimmune mechanisms, including respiratory tract infections, exercise, ingestion of aspirin, emotional upset, and exposure to bronchial irritants such as cigarette smoke). There are two types of response in persons with atopic asthma: the acute or early-phase 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 4 to 8 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.

Chronic obstructive pulmonary disease 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.

Chronic 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. Because the interstitial lung diseases result in a stiff and noncompliant lung, they are commonly classified as restrictive lung disorders. In contrast to obstructive lung diseases, the lungs are stiff and difficult to expand, despite normal functioning airways.

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.

The interstitial lung diseases 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 15), lung diseases caused by exposure to toxic drugs (*e.g.,* the cancer drug bleomycin and the antiarrhythmic drug amiodarone) and radiation, sarcoidosis, 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 inhaled dust and particles. In many cases, no specific cause can be found.[37–39] Examples of interstitial lung diseases and their causes are listed in Chart 22-1.

PATHOGENESIS

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.

CHART 22-1

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.

CLINICAL FEATURES

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. 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 19.

PULMONARY EMBOLISM

Pulmonary embolism develops when a blood-borne substance lodges in a branch of the pulmonary artery and obstructs the flow.[40–42] The embolism may consist of a thrombus (Fig. 22-14), 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.

Almost all pulmonary thromboemboli arise from a deep vein thrombosis (DVT) in the lower extremities (see Chapter 17). 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 by the blood clot and associated reflex vasoconstriction. Obstruction of pulmonary blood flow also 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.

Among the physiologic factors that contribute to DVT 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 contraceptives, 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.[40] Women who smoke are at particular risk.

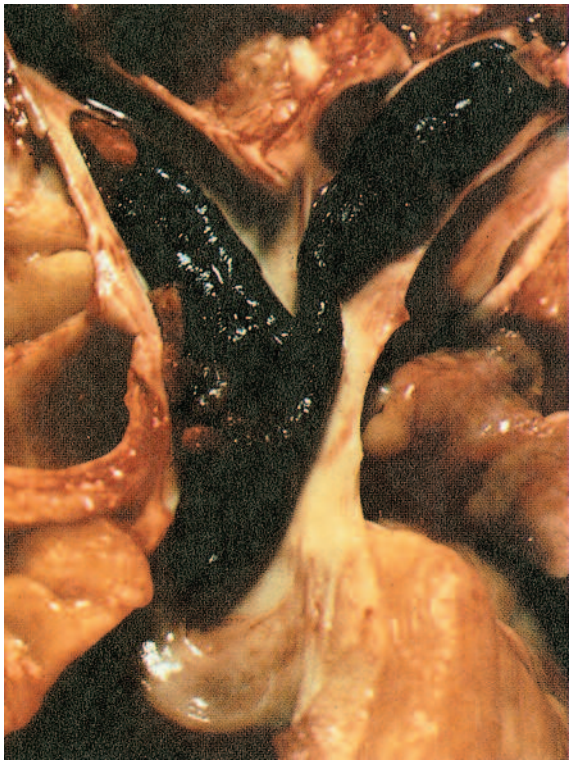

FIGURE 22-14 Pulmonary embolism. The main pulmonary artery and its bifurcation have opened to reveal a large saddle embolus. (From McManus B. M., Allard M. F., Yanagawa B. [2005]. Hemodynamic disorders. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 291]. Philadelphia: Lippincott Williams & Wilkins.)

Clinical Features

Manifestations. 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 reduction in the size of the pulmonary capillary bed, resulting in pul-

monary 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.

Diagnosis and Treatment. The diagnosis of pulmonary embolism is based on clinical signs and symptoms, blood gas determinations, venous thrombosis studies, D-dimer testing, lung scans, helical CT scans of the chest, and, in selected cases, pulmonary angiography.[41,42] Laboratory studies and radiologic films are useful in ruling out other conditions that might give rise to similar symptoms. Because emboli can cause an increase in pulmonary vascular resistance, the electrocardiogram (ECG) may be used to detect signs of right heart strain. There has been recent interest in combining several noninvasive methods (lower limb compression ultrasonography, D-dimer measurements, and clinical assessment measures) as a means of establishing a diagnosis of pulmonary embolism.

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. *D-dimer testing* involves the measurement of plasma D-dimer, a degradation product of coagulation factors that have been activated as the result of a thromboembolic event. The *ventilation-perfusion scan* uses radiolabeled albumin, which is injected intravenously, and a radiolabeled gas, which is inhaled. A scintillation (gamma) camera is used to scan the various lung segments for blood flow and distribution of the radiolabeled gas. *Helical (spiral) CT angiography* requires administration of an intravenous radiocontrast media. It is sensitive for the detection of emboli in the proximal pulmonary arteries and provides another method of diagnosis. *Pulmonary angiography* involves the passage of a venous catheter through the right heart and into the pulmonary artery under fluoroscopy. Although it remains the most accurate method of diagnosis, it is an invasive procedure; therefore, its use is reserved for selected cases. An embolectomy sometimes is performed during this procedure.

The treatment goals for pulmonary emboli focus on preventing 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 using streptokinase, urokinase, or recombinant tissue plasminogen activator may be indicated in persons with multiple or large emboli. Thrombolytic therapy is followed by administration of heparin and then warfarin. Restoration of blood flow in persons with life-threatening pulmonary emboli can be accomplished through the surgical removal of the embolus or emboli.

Prevention. Prevention focuses on identification of persons at risk, avoidance of venous stasis and hypercoagulability states, and early detection of venous thrombosis. For patients at risk, graded compression elastic stockings and intermittent pneumatic compression (IPC) boots can be used to prevent venous stasis. Both of these devices are safe and practical ways to prevent venous thrombosis. IPC boots provide intermittent inflation of air-filled sleeves that prevent venous stasis. Some devices produce sequential gradient compression that moves blood upward in the leg.

Pharmacologic prophylaxis involves the use of anticoagulant drugs (see Chapter 10). Anticoagulant therapy may be used to decrease the likelihood of DVT, thromboembolism, and fatal pulmonary embolism after major surgical procedures. Low–molecular-weight heparin, which can be administered subcutaneously on an outpatient basis, often is used. Warfarin, an oral anticoagulation drug, may be used for persons with long-term risk of developing thromboemboli.

PULMONARY HYPERTENSION

The pulmonary circulation is a low-pressure system designed to accommodate varying amounts of blood delivered to the right heart and to facilitate gas exchange. 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.

The term *pulmonary hypertension* describes the elevation of pressure in the pulmonary arterial system. The normal mean pulmonary artery pressure is approximately 15 mm Hg (*e.g.,* 28 mm Hg systolic/8 mm Hg diastolic). Pulmonary hypertension is defined as a sustained elevation of the mean pulmonary artery pressure to more than 25 mm Hg at rest or to more 30 mm Hg with exercise.[43] 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.[44] 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 18. *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 pressure has 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 often leads to right ventricular failure and death within a few years. Estimates of incidence range from one to two cases per million people in the general population.[45] 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%.[45]

Primary pulmonary hypertension is thought to be associated with a number of factors, including an autosomal dominant genetic predisposition along with an exogenous trigger. Triggers include low oxygen levels that occur at high altitudes, exposure to certain drugs, human immunodeficiency virus infection, and autoimmune disorders. Studies of a rare familial form of the disease point to a mutation in the transforming growth factor-β (TGF-β) superfamily of receptors as being responsible for the vascular thickening.[46] Mutations in these receptors are thought to prevent TGF-β and related molecules from exerting an inhibitory effect on smooth muscle and endothelial cell proliferation. A potent endogenous peptide, endothelin-1, is also thought to have a role in pulmonary hypertension.[47] Endothelin-1 acts on two receptors, endothelin-A and endothelin-B receptors. Activation of endothelin-B receptors causes vasodilatation, and activation of endothelin-A receptors results in vasoconstriction and smooth muscle growth.

Primary pulmonary hypertension 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 the person's well-being.

Treatment consists of measures to improve right heart function to reduce fatigue and peripheral edema. Supplemental oxygen may used to increase exercise tolerance. The calcium channel blockers may be effective early in the course of the disease, but offer little relief in advanced stages. More advanced disease has been managed with epoprostenol, a prostacyclin that has potent pulmonary vasodilator effects.[45,47] Because of its short half-life (3 to 5 minutes), the drug must be administered by continuous infusion through an indwelling catheter with an automatic ambulatory pump. Properties of the drug other than its vasodilating effects include inhibition of platelet aggregation and beneficial vascular remodeling effects. This agent often improves symptoms, sometimes dramatically, in persons who have not responded to other vasodilators. Bosentan, an oral endothelin antagonist, has proved to be effective in treating moderate to severe primary pulmonary hypertension and may become the treatment of choice for all stages of the disease.[47]

Cor Pulmonale

The term *cor pulmonale* refers to right heart failure resulting from primary lung disease and long-standing 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 19). 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.[48–50] The disorder is the final common pathway through which many serious localized and systemic disorders produce diffuse injury to the alveolar-capillary membrane.

Acute respiratory distress syndrome 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[48–50] (Chart 22-2).

Although a number of conditions may lead to ARDS, they all produce similar pathologic lung changes that include diffuse epithelial cell injury with increased permeability of the alveolar-capillary membrane (Fig. 22-15). The increased permeability permits fluid, protein, 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. As the disease progresses,

CHART 22-2

Conditions in Which ARDS Can Develop*

Aspiration

Near drowning
Aspiration of 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.

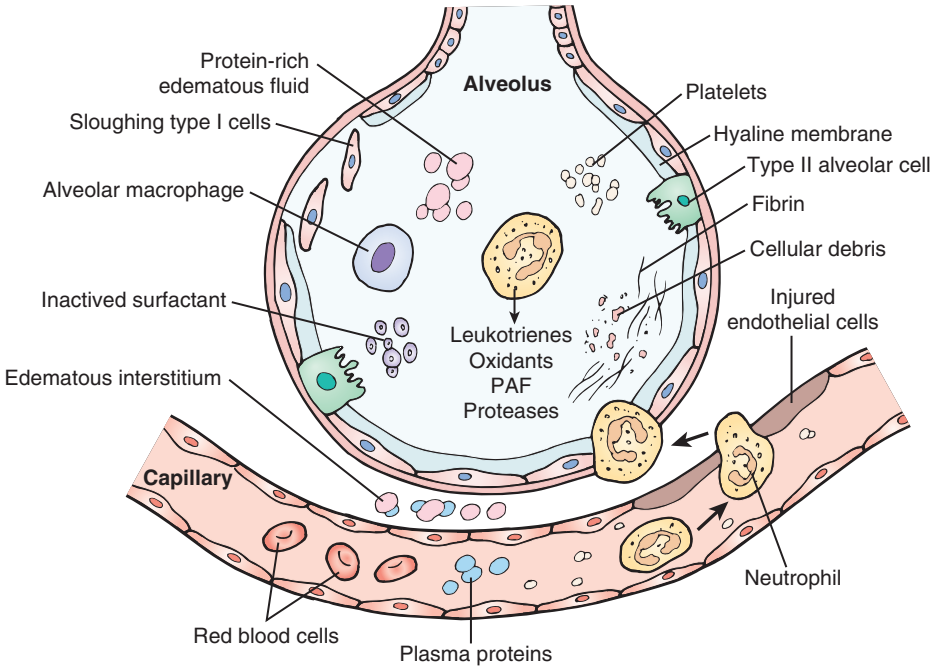

FIGURE 22-15 The mechanism of lung changes in ARDS. Injury and increased permeability of the alveolar capillary membrane allow fluid, protein, cellular debris, platelets, and blood cells to move out of the vascular compartment and enter the interstitium and alveoli. Activated neutrophils release a variety of products including toxic oxygen species (*e.g.*, oxidants), phospholipid products (*e.g.*, leukotrienes), proteolytic enzymes (proteases), and platelet-activating factor (PAF) that damage alveolar cells, inactivate surfactant, and lead to formation of a hyaline membrane.

the work of breathing becomes greatly increased as the lung stiffens and becomes more 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 its pathogenesis. Activated neutrophils synthesize and release a variety of products, including proteolytic enzymes, toxic oxygen species, and phospholipid products, that increase the inflammatory response and cause injury to the capillary endothelium and alveolar epithelium.

Clinically, ARDS is marked by a rapid onset, usually within 12 to 18 hours of the initiating event, of respiratory distress, an increase in respiratory rate, and signs of respiratory failure. Chest radiography shows diffuse bilateral consolidation of the lung tissue. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen therapy. Many persons with ARDS demonstrate multiple organ failure, particularly involving the kidneys and gastrointestinal, central nervous, and cardiovascular systems.

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. 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.

Most survivors of ARDS are left with some pulmonary symptoms (cough, dyspnea, sputum production) that may improve over time. Mild abnormalities of oxygenation, diffusing capacity, and lung mechanics persist in some individuals.

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 occur secondary to cardiac or pulmonary diseases that produce elevated left atrial pressure, increased pulmonary blood flow, pulmonary vascular obstruction, or hypoxemia. Primary pulmonary hypertension is a relatively rare and rapidly progressive form of pulmonary hypertension. The term *cor pulmonale* describes right heart failure caused by primary pulmonary disease and long-standing pulmonary hypertension.

Acute respiratory distress syndrome 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 lung edema; 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 respiratory system fails in one or both of its gas exchange functions (*i.e.*, oxygenation of or elimination of carbon dioxide from the mixed venous blood).[51,52] 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 common result of respiratory failure is *hypoxemia,* or a low level of oxygen in the blood, and *hypercapnia* (sometimes referred to as *hypercarbia*), or excess carbon dioxide in the blood. The abbreviation PO_2 often is used to indicate the partial pressure of oxygen in arterial

KEY CONCEPTS

Disorders of Blood Gases in Respiratory Failure

- Respiratory failure represents failure of the lungs adequately to oxygenate the blood (hypoxemia) and prevent carbon dioxide retention (hypercarbia.)
- Hypoxemia results from decreased concentration of oxygen in the inspired air, airway diseases that impair ventilation, respiratory disorders that impair ventilation 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.

blood, and the abbreviation PCO_2, the partial pressure of carbon dioxide.

CAUSES

Respiratory failure is not a specific disease, but the result of a number of conditions that impair ventilation, compromise the matching of ventilation and perfusion, or impair gas diffusion. The causes of respiratory failure are summarized in Chart 22-3.

Hypoventilation

Hypoventilation or ventilatory failure occurs when the volume of "fresh" air moving into and out of the lung is significantly reduced. It is commonly caused by conditions outside the lung such as depression of the respiratory center (*e.g.*, drug overdose, high-flow oxygen therapy in persons with advanced COPD), 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). (Other causes of hypoventilation are discussed later in the section on Hypercapnia.)

Hypoventilation has two important effects on arterial blood gases. First, it almost always causes an increase in PCO_2. The rise in PCO_2 is directly related to the level of ventilation; reducing the ventilation by one half causes a doubling of the PCO_2. Thus, the PCO_2 level is a good diagnostic measure for hypoventilation.[51] Second, hypoxemia that is caused by hypoventilation can be readily abolished by increasing the oxygen content of the inspired air.

CHART 22-3

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.

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 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. However, it may also decrease the respiratory drive and produce an increase in PCO_2.

Impaired Diffusion

Impaired diffusion describes a condition in which gas exchange between the alveolar air and pulmonary blood is impeded because of an increase in the distance for diffusion or a decrease in the permeability of the respiratory membranes to the movement of gases. It most commonly occurs in conditions such as interstitial lung disease, ARDS, pulmonary edema, and pneumonia.

Conditions that impair diffusion may produce severe hypoxemia but no hypercapnia because of increased ventilation. Hypoxemia resulting from impaired diffusion can be partially or completely corrected by the administration of high concentrations of oxygen. In this case, the high concentration of oxygen serves to overcome the resistance to diffusion by establishing a large alveolar-to-capillary diffusion gradient.

MANIFESTATIONS

Respiratory failure is manifested by varying degrees of hypoxemia and hypercapnia. There is no absolute definition of the levels of PO_2 and PCO_2 that indicate respira-

tory failure. Respiratory failure is conventionally defined by an arterial PO_2 of less than 60 mm Hg, an arterial PCO_2 of more than 50 mm Hg, or both.[51] It is important to emphasize that these cut-off values are not rigid, but simply serve as a general guide in combination with history and physical assessment information.

Hypoxemia

The signs and symptoms of acute 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. More pronounced hypoxemia may produce personality changes, restlessness, agitated or combative behavior, uncoordinated muscle movements, euphoria, impaired judgment, delirium, and, eventually, stupor and coma. Recruitment of sympathetic nervous system compensatory mechanisms produces an increase in heart rate, 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. Decreased sensory function, such as impaired vision or fewer complaints of pain, may be an early sign of worsening hypoxemia. This is probably because the involved sensory neurons have the same need for high levels of oxygen as do other parts of the nervous system. Pulmonary hypertension is common because of associated alveolar hypoxia.

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.[53] It is the absolute quantity (gm/dL) of reduced hemoglobin rather than the relative quantity (%) of reduced hemoglobin that 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 or an abnormal hemoglobin derivative 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. The diagnosis of hypoxemia is based on clinical observation and diagnostic measures of 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 measurements of arterial oxygen saturation of hemoglobin can be obtained using an instrument called the *pulse oximeter*. The pulse oximeter uses light-emitting diodes and combines plethysmography (*i.e.*, changes in light absorbance and vasodilatation) with spectrophotometry.[54,55] Spectrophotometry uses a red-wavelength light that passes through oxygenated hemoglobin and is absorbed by deoxygenated hemoglobin and an infrared-wavelength light that is absorbed by oxygenated hemoglobin and passes through deoxygenated hemoglobin. Sensors that can be placed on the ear, finger, toe, or forehead are available. These methods, although not as accurate as the invasive methods, provide a means for continuous monitoring of oxygen levels and are useful indicators of respiratory and circulatory status. Pulse oximeters do not measure hemoglobin levels and the oxygen-carrying capacity of blood nor can they distinguish between oxygen-carrying hemoglobin and carbon monoxide–carrying hemoglobin. In addition, the pulse oximeter cannot detect elevated levels of methemoglobin.

Hypercapnia

Hypercapnia refers to an increase in the CO_2 content of the arterial blood.[56] The respiratory center, which is located in the brain stem, controls the activity of the muscles of respiration and plays a critical role in the regulation of ventilation and elimination of CO_2 (see Chapter 20). 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. Stimulation of the respiratory center is greatest during the first 1 to 2 days that PCO_2 levels are elevated, but it gradually declines over the next 1 to 2 days.[56] Part of this decline results from renal compensatory mechanisms that readjust the blood pH by increasing blood HCO_3^- levels.

An important cause of carbon dioxide retention in respiratory failure is the injudicious use of oxygen therapy. 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 a decrease in arterial 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 rise in PCO_2 levels.

Manifestations. Hypercapnia affects a number of body functions, including renal function, neural function, cardiovascular function, and acid-base balance. Elevated levels of PCO_2 produce a decrease in pH and respiratory acidosis (see Chapter 6). The kidneys normally compensate for an increase in PCO_2 by increasing bicarbonate reabsorption. 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 adapts to chronic increases in blood levels of carbon dioxide, persons with chronic hypercapnia may not have symptoms until the PCO_2 becomes markedly elevated.

Carbon dioxide has a direct vasodilating effect on many blood vessels and a sedative effect on the nervous system. In acute respiratory failure, elevated PCO_2 levels greatly increase cerebral blood flow, causing headache, increased cerebrospinal fluid pressure, and sometimes papilledema. There is headache due to dilatation of the cerebral vessels; the conjunctivae are hyperemic; and the skin is warm and flushed. Hypercapnia has nervous system effects similar to those of an anesthetic—hence 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 semicomatose. Anesthesia and death can result when PCO_2 levels reach 100 to 150 mm Hg.[53]

Diagnosis. The diagnosis of hypercapnia is based on physiologic manifestations, arterial blood gas levels, and arterial pH. At the end of exhalation, arterial PCO_2 measurements approximate alveolar carbon dioxide measurements. Therefore, samples of exhaled carbon dioxide, measured at the end of exhalation, can be used as estimates of alveolar carbon dioxide, and because arterial and alveolar carbon dioxide levels are similar, as estimates of arterial PCO_2. Methods for monitoring samples of expired gas from an oral airway or endotracheal tube are available and are sometimes used for monitoring patients during weaning from a ventilator or cardiopulmonary resuscitation.

TREATMENT OF RESPIRATORY FAILURE

The treatment of respiratory failure focuses on correcting the problem causing impaired gas exchange when possible and on relieving the hypoxemia and hypercapnia. A number of treatment modalities are available, including the establishment of an airway, use of bronchodilating drugs, and antibiotics for respiratory infections. Controlled oxygen therapy and mechanical ventilation are used in treating blood gas abnormalities associated with respiratory failure.

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. A high-flow administration system is one in which the flow rate and reserve capacity are sufficient to provide all the inspired air.[55] A low-flow oxygen system delivers less than the total inspired air.[55] The oxygen should 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 ventilatory 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. Persons with healthy lungs begin to experience respiratory symptoms such as cough, sore throat, substernal distress, nasal congestion, and painful inspiration after breathing pure oxygen for 24 hours.[51]

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 hypercapnic patients with COPD or chest wall disease may be effective in increasing the strength and endurance of the respiratory muscles 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.

When alveolar ventilation is inadequate to maintain PO_2 or PCO_2 levels because of respiratory or neurologic failure, mechanical ventilation may be lifesaving. Usually a nasotracheal, orotracheal, or tracheotomy tube is inserted into the trachea to provide the patient with the airway needed for mechanical ventilation. There has been recent interest in noninvasive forms of mechanical ventilation that use a face mask to deliver positive-pressure ventilation.[57]

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 to oxygenate the blood adequately and prevent carbon dioxide retention. It can result from a number of conditions that impair ventilation, compromise the matching of ventilation and perfusion, or impair gas diffusion and 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 less than 60 mm Hg, a PCO_2 of more than 50 mm Hg, or both.

Hypoxia refers to an acute or chronic reduction in tissue oxygenation. Acute hypoxia 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. The manifestations of hypercapnia consist of those associated with dilatation of blood vessels, including those in the brain, and depression of the central nervous system (*e.g.,* carbon dioxide narcosis).

Review Exercises

A 30-year-old man is brought to the emergency department with a knife wound to the chest. On visual inspection, the asymmetry of chest movement during inspiration, displacement of the trachea, and absence of breath sounds on the side the wound are noted. His neck veins are distended and his pulse is rapid and thready. A rapid diagnosis of tension pneumothorax is made.

A. Explain the observed respiratory and cardiovascular function in terms of the impaired lung expansion and air that has entered the chest as a result of the injury.
B. What type of emergent treatment is necessary to save this man's life?

A 10-year-old boy who is having an acute asthmatic attack is brought to the emergency department by his parents. The boy is observed to be sitting up and struggling to breathe. His breathing is accompanied by use of the accessory muscles, a weak cough, and audible wheezing sounds. His pulse is rapid and weak and both heart and breath sounds are distant on auscultation. His parents relate that his asthma began to worsen after he developed a "cold" and now he does not even get relief from his "albuterol" inhaler.

A. Explain the changes in physiologic function underlying this boy's signs and symptoms.
B. What is the most probable reason for the progression of this boy's asthma in terms of the early- and late-phase responses?
C. The boy is treated with a systemic corticosteroid, and an inhaled anticholinergic agent and β_2-adrenergic agonist, and then transferred to the intensive care unit. Explain the action of each of these medications in terms of relieving this boy's symptoms.

A 62-year-old man with an 8-year history of chronic bronchitis reports to his health care provider with complaints of increasing shortness of breath, ankle swelling, and a feeling of fullness in his upper abdomen.

The expiratory phase of his respirations is prolonged and expiratory wheezes and crackles are heard on auscultation. His blood pressure is 160/90 mm Hg, his red blood cell count is 6.0 x 10^6/µl (normal 4.2 to 5.4 x 10^6/µl), his hematocrit is 65% (normal male value 40% to 50%), his arterial PO_2 is 55 mm Hg, and his O_2 saturation, which is 85% while he is resting, drops to 55% during walking exercise.

A. Explain the physiologic mechanisms responsible for his edema, hypertension, and elevated red blood cell count.
B. His arterial PO_2 and O_2 saturation indicate that he is a candidate for continuous low-flow oxygen. Explain the benefits of this treatment in terms of his activity tolerance, blood pressure, and red blood cell count.
C. Explain why the oxygen flow rate for persons with COPD is normally titrated to maintain the arterial PO_2 between 60 to 65 mm Hg.

An 18 year-old female is admitted to the emergency room with a suspected drug overdose. Her respiratory rate is slow (4 to 6 times/minute) and shallow. Arterial blood gases reveal a PCO_2 of 80 mm Hg and a PO_2 of 60 mm Hg.

A. What is the cause of this woman's high PCO_2 and low PO_2?
B. Hypoventilation almost always causes an increase in PCO_2. Explain.
C. Even though her PO_2 increases to 90 mm Hg with institution of oxygen therapy, her PCO_2 remains elevated. Explain.

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