Steven E. **Weinberger**
Barbara A. **Cockrill**
Jess **Mandel**

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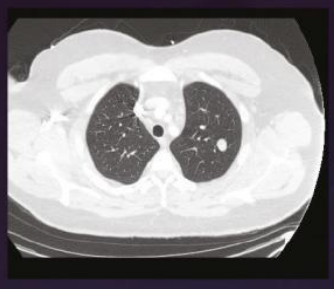
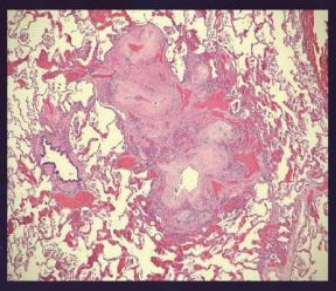
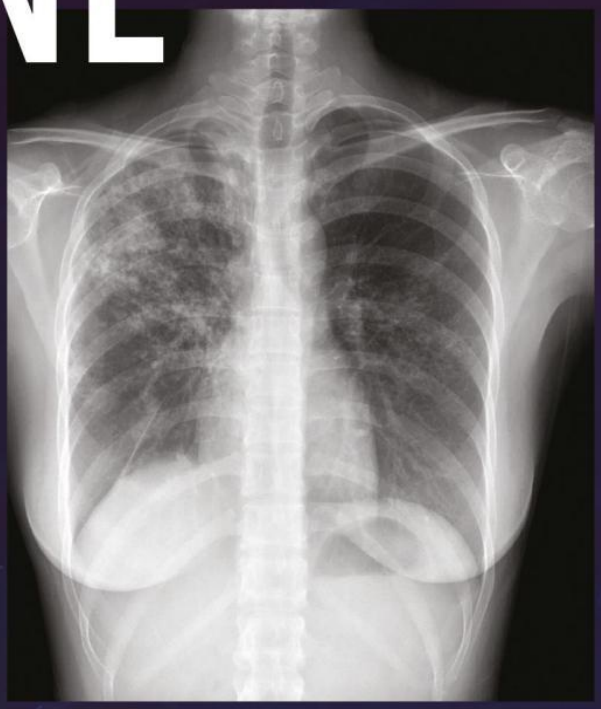
# *Principles of* PULMONARY MEDICINE







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EIGHTH EDITION

# Principles of Pulmonary Medicine

EIGHTH EDITION


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# Dedication

*To our families and to the students and trainees we have had the privilege of teaching over many years.*

# Introduction to the eighth edition

Steven E. Weinberger, MD, MACP, FRCP, Barbara A. Cockrill, MD, Jess Mandel, MD, MACP, FRCP

*Principles of Pulmonary Medicine* was first published in 1986 as a "concise, core reference [that] emphasizes pathophysiology and diagnosis as the basis for optimal management of respiratory disorders. Physiologic, radiologic, and pathologic features of diseases are correlated with clinical findings providing an integrated, comprehensive approach." Much has changed over eight editions of the book and the more than 35 years that have elapsed since the first edition. Our understanding of many disease processes has improved, our diagnostic tests have become more sophisticated, and our therapeutic armamentarium has been expanded and improved. The single author of the first four editions, Steven E. Weinberger, MD, MACP, FRCP, was joined starting with the fifth edition by two additional authors, Barbara A. Cockrill, MD, and Jess Mandel, MD, MACP, FRCP; their knowledge, experience, and perspectives have greatly enhanced the quality of the book. Since the fifth edition, we added and subsequently expanded supplementary images and self-assessment questions accessible on the internet, recognizing the importance of learners being able to assess their knowledge and their understanding of concepts that can at times be difficult to grasp.

Although the primary audience has always been the medical student taking a respiratory pathophysiology course, the book has also been extensively used by residents and practicing physicians and by other healthcare professionals who care for patients with pulmonary disease. A persistent goal throughout all editions of the book has been to present physiologic concepts, pathogenetic and pathophysiologic mechanisms, and radiologic and pathologic correlates of disease in a clear fashion that can be easily understood even by the beginning student of pulmonary medicine. We have also continued to include margin notes throughout the text, which summarize the major points and concepts and allow the reader to quickly review the material. Starting with the second edition, we included three appendices that provide simplified methods for interpreting pulmonary function tests and arterial blood gases, while also presenting sample problems that test the reader's ability to use respiratory equations, assess pulmonary function abnormalities, and interpret arterial blood gases.

Many changes and updates have been incorporated in the eighth edition. Whereas histopathologic and other images were printed in black and white in previous editions, these and additional images are shown in color in the current edition. We have also added more images—particularly plain chest radiographs and computed tomographic scans—to provide additional examples of the appearance of many clinical disorders on

imaging studies. Finally, in the era of COVID-19 and new diagnostic and therapeutic options for a number of disorders, we have updated the text to include information about organisms such as SARS-CoV-2 and expanded coverage of new biologic and immunologic treatments available for a variety of diseases.

We have been most gratified by the popularity of the textbook, which has been used extensively not only in the United States and Canada but also in other countries throughout the world. Various editions have been translated into Spanish, Portuguese, Italian, Japanese, Chinese, and Polish. Although there may be some differences in diagnostic and therapeutic approaches to pulmonary diseases in different countries, the conceptual underpinnings of physiology, pathophysiology, and disease mechanisms that we are trying to convey in a readable fashion are universal.

It has been a pleasure to work with the editorial staff at Elsevier in development of this edition, just as it has been for past editions. We particularly want to express our appreciation to Robin Carter, Content Strategist; Vasowati Shome, Content Development Specialist; Nandhini Thanga Alagu, Project Manager; Bridget Hoette, Book Designer; and the efforts of Elsevier. Finally, we are most grateful to our families for their support and understanding as we had to sacrifice time with them to prepare this new edition of the book.

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# List of Tables

# 1: Pulmonary anatomy and physiology: The basics

OUTLINE



To be effective at gas exchange, the lungs cannot act in isolation. They must interact with the central nervous system (which provides the rhythmic drive to breathe), the diaphragm and muscular apparatus of the chest wall (which respond to signals from the central nervous system and act as a bellows for movement of air), and the circulatory system (which provides blood flow and thus gas transport between the tissues and lungs). The processes of oxygen uptake and carbon dioxide elimination by the lungs depend on proper functioning of all these systems, and a disturbance in any of them can result in clinically important abnormalities in gas exchange. This chapter begins with an initial overview of pulmonary anatomy, followed by a discussion of the mechanical properties of the lungs and chest wall and a consideration of some aspects of the contribution of the lungs and the circulatory system to gas exchange. Additional discussion of pulmonary and circulatory physiology is presented in Chapters 4, 8, and 12; neural, muscular, and chest wall interactions with the lungs are discussed further in

Chapter 17.

## Anatomy

It is appropriate when discussing the anatomy of the respiratory system to include the entire pathway for airflow from the mouth or nose down to the alveolar sacs. En route to the alveoli, gas flows through the oropharynx or nasopharynx, larynx, trachea, and finally a progressively arborizing system of bronchi and bronchioles of diminishing diameter (Fig. 1.1). The trachea divides at the carina into right and left mainstem bronchi, which branch into lobar bronchi (three on the right, two on the left), segmental bronchi, and an extensive system of subsegmental and smaller bronchi. These conducting airways divide approximately 15 to 20 times down to the level of terminal bronchioles, which are the smallest units that do not actually participate in gas exchange.

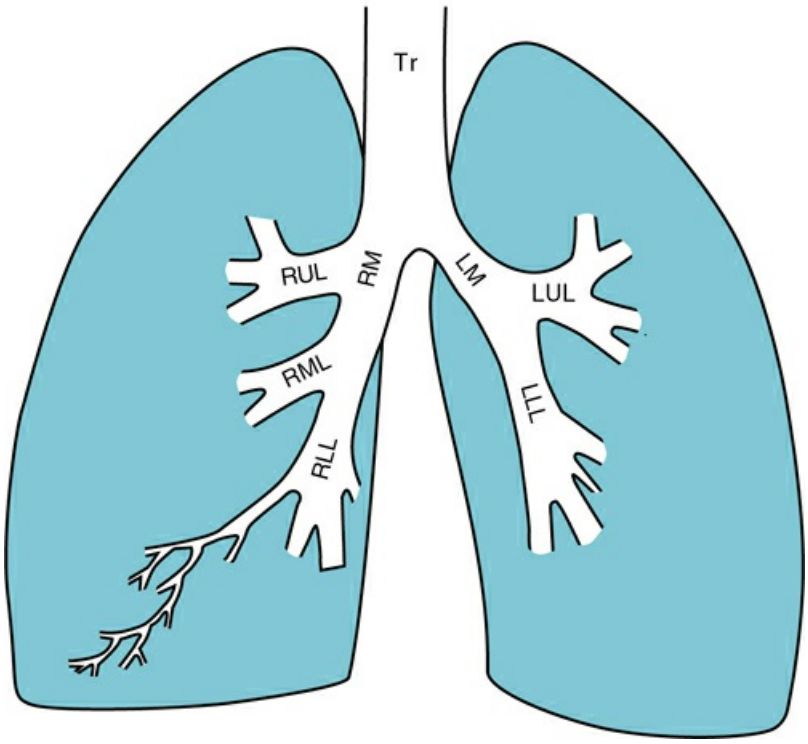


**FIGURE 1.1** Schematic diagram of airway branching. *LLL*, left lower lobe bronchus; *LM*, left mainstem bronchus; *LUL*, left upper lobe bronchus; *RLL*, right lower lobe bronchus; *RM*, right mainstem bronchus; *RML*, right middle lobe bronchus; *RUL*, right upper lobe bronchus; *Tr*, trachea.

Conducting airways include all airways down to the level of the terminal bronchioles.

Beyond the terminal bronchioles, further divisions include the respiratory bronchioles, alveolar ducts, and alveoli. From the respiratory bronchioles on, these divisions form the portion of the lung involved in gas exchange and constitute the terminal respiratory unit or *acinus*. At this level, inhaled gas comes into contact with alveolar walls (septa), and pulmonary capillary blood loads $O_2$ and unloads $CO_2$ as it courses through the septa.

The acinus includes structures distal to a terminal bronchiole: respiratory bronchioles, alveolar ducts, and alveoli (alveolar sacs).

The surface area for gas exchange provided by the alveoli is enormous. It is estimated that the adult human lung has on the order of 300 million alveoli, with a total surface area approximately the size of a tennis court, more than 2000 square feet or 200 $m^2$. This vast surface area of gas in contact with alveolar walls is a highly efficient mechanism for $O_2$ and $CO_2$ transfer between alveolar spaces and pulmonary capillary blood.

The pulmonary circulation and blood within provide the other crucial requirement for gas exchange: a transportation system for $O_2$ and $CO_2$ to and from other body tissues and organs. After blood arrives at the lungs via the pulmonary artery, it courses through a widely branching system of smaller pulmonary arteries and arterioles to the major locale for gas exchange, the pulmonary capillary network. The capillaries generally allow red blood cells to flow through in single file only, so that gas exchange between each cell and alveolar gas is facilitated. Upon completion of gas exchange and travel through the pulmonary capillary bed, the oxygenated blood flows through pulmonary venules and veins and arrives at the left side of the heart for pumping to the systemic circulation and distribution to the tissues.

Further details about the anatomy of airways, alveoli, and the pulmonary vasculature, particularly with regard to structure–function relationships and cellular anatomy, are given in Chapters 4, 8, and 12.

# Physiology

## Mechanical aspects of the lungs and chest wall

The discussion of pulmonary physiology begins with an introduction to a few concepts about the mechanical properties of the respiratory system, which have important implications for assessment of pulmonary function and its derangement in disease states.

Both the lungs and chest wall have elastic properties. Each has a particular resting size (or volume) it would assume if no internal or external pressure were exerted on it, and any deviation from this volume requires some additional influencing force. If the lungs were removed from the chest and no longer had the external influences of the chest wall and pleural space acting on them, they would collapse to the point of being almost airless; they would have a much lower volume than they have within the thoracic cage. To expand these lungs, positive pressure would have to be exerted on the air spaces, as could be done by putting positive pressure through the airway. (It is similar to

a balloon, which is essentially airless unless positive pressure is exerted on the opening to distend the elastic wall and fill it with air.)

Alternatively, instead of positive pressure exerted on alveoli through the airways, negative pressure could be applied outside the lungs to cause their expansion. Thus, what increases the volume of the isolated lungs from the resting, essentially airless, state is application of a positive *transpulmonary pressure*—the pressure inside the lungs relative to the pressure outside. Either the internal pressure can be made positive or the external pressure can be made negative; the net effect is the same. With the lungs inside the chest wall, the internal pressure is alveolar pressure ($P_{alv}$), whereas external pressure is the pressure within the pleural space (Fig. 1.2). Therefore, transpulmonary pressure is defined as $P_{alv}$ minus pleural pressure ($P_{pl}$). For air to be present in the lungs, $P_{pl}$ must be negative compared with $P_{alv}$, resulting in a positive transpulmonary pressure.

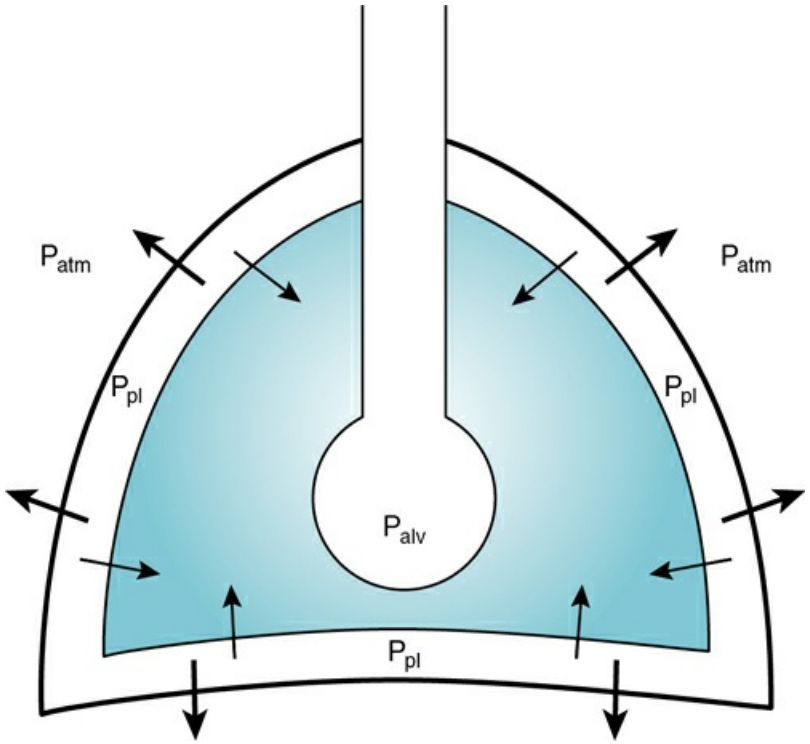


**FIGURE 1.2** Simplified diagram showing pressures on both sides of chest wall *(heavy line)* and lung *(shaded area)*. Thin arrows show direction of elastic recoil of lung (at resting end-expiratory position). Thick arrows show direction of elastic recoil of chest wall. $P_{alv}$, alveolar pressure; $P_{atm}$, atmospheric pressure; $P_{pl}$, pleural pressure.

Transpulmonary pressure = Alveolar pressure ($P_{alv}$) – Pleural pressure ($P_{pl}$)

The relationship between transpulmonary pressure and lung volume can be described

for a range of transpulmonary pressures. The plot of this relationship is the *compliance curve* of the lung (Fig. 1.3A). As transpulmonary pressure increases, lung volume naturally increases. However, the relationship is not linear but curvilinear. At relatively high volumes, the lungs reach their limit of distensibility, and even large increases in transpulmonary pressure do not result in significant increases in lung volume.

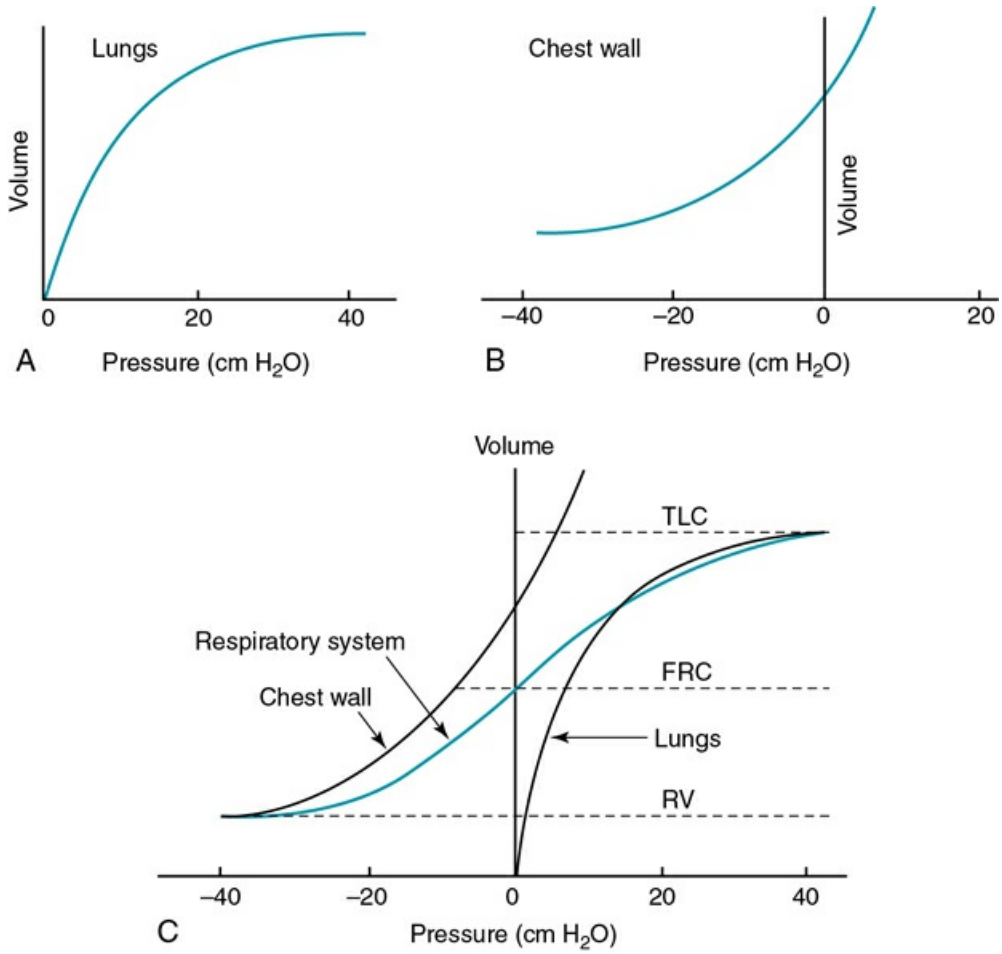


**FIGURE 1.3** **A,** Relationship between lung volume and distending (transpulmonary) pressure, the compliance curve of the lung. **B,** Relationship between volume enclosed by chest wall and distending (transchest wall) pressure, the compliance curve of the chest wall. **C,** Combined compliance curves of lung and chest wall showing relationship between respiratory system volume and distending (transrespiratory system) pressure. *FRC*, functional residual capacity; *RV*, residual volume; *TLC*, total lung capacity.

The chest wall also has an effect on lung volume. If the lungs were removed from the chest, the chest wall would expand to a larger size when no external or internal

pressures were exerted on it. Thus, the chest wall has a springlike character that is not intuitively obvious. The resting volume is relatively high, and distortion to either a smaller or larger volume requires alteration of either the external or internal pressures acting on it. The pressure across the chest wall is akin to the transpulmonary pressure. With the lungs inside the chest wall, the pressure across the chest wall is the $P_{pl}$ (internal pressure) minus the external pressure surrounding the chest wall (atmospheric pressure).

The compliance curve of the chest wall relates the volume enclosed by the chest wall to the pressure across the chest wall (see Fig. 1.3B). The curve becomes relatively flat at low lung volumes, at which the chest wall becomes stiff. Further decrease in pressure across the chest wall causes little further decrement in volume.

To examine how the lungs and chest wall behave in the living human, remember that the elastic properties of each are coupled and are acting in opposite directions. At the normal resting end-expiratory position of the respiratory system (*functional residual capacity* [FRC]), the lung is expanded to a volume greater than the resting volume it would have in isolation, whereas the chest wall is contracted to a volume smaller than it would have in isolation. However, at FRC the tendency of the lung to become smaller (the inward or elastic recoil of the lung) is exactly balanced by the tendency of the chest wall to expand (the outward recoil of the chest wall). The transpulmonary pressure at FRC is equal in magnitude to the pressure across the chest wall but acts in an opposite direction (see Fig. 1.3C). Therefore, $P_{pl}$ is negative, a consequence of the inward recoil of the lungs and the outward recoil of the chest wall.

At FRC, the inward elastic recoil of the lung is balanced by the outward elastic recoil of the chest wall.

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*FRC*, Functional residual capacity.

The chest wall and lungs can be considered as a unit, the *respiratory system*. The respiratory system has its own compliance curve, which is essentially a combination of the individual compliance curves of the lungs and chest wall (see Fig. 1.3C). The transrespiratory system pressure, again defined as internal pressure minus external pressure, is airway pressure minus atmospheric pressure. At a transrespiratory system pressure of 0, the respiratory system is at its normal resting end-expiratory position and the volume within the lungs is FRC.

Two additional lung volumes can be defined, as can the factors that determine each of them. *Total lung capacity* (TLC) is the volume of gas within the lungs at the end of a maximal inhalation. At this point the lungs are stretched well above their resting position, and even the chest wall is stretched beyond its resting position. We are able to distort both the lungs and chest wall so far from FRC by using our inspiratory muscles, which exert an outward force to counterbalance the inward elastic recoil of the lung and, at TLC, the chest wall. However, at TLC it is primarily the extreme stiffness of the lungs that prevents even further expansion by inspiratory muscle action. Therefore, the primary determinants of TLC are the expanding action of the inspiratory musculature balanced by the inward elastic recoil of the lung.

At TLC, the expanding action of the inspiratory musculature is limited primarily by the inward elastic recoil of the lung.

*TLC*, Total lung capacity.

At the other extreme, when we exhale as much as possible, we reach *residual volume* (RV). At this point a significant amount of gas still is present within the lungs (i.e., we can never exhale enough to empty the lungs entirely of gas). Again, the reason can be seen by looking at the compliance curves in Fig. 1.3C. The chest wall becomes so stiff at low volumes that additional effort by the expiratory muscles is unable to decrease the volume any further. Therefore, RV is determined primarily by the balance of the outward recoil of the chest wall and the contracting action of the expiratory musculature. However, this simple model for RV applies only to young individuals with normal lungs and airways. With age or airway disease, further expulsion of gas during expiration is limited not only by the outward recoil of the chest wall but also by the tendency for airways to close during expiration and for gas to be trapped behind the closed airways.

At RV, either outward recoil of the chest wall or closure of airways prevents further expiration.

*RV*, Residual volume.

## Ventilation

To maintain normal gas exchange to the tissues, an adequate volume of air must pass through the lungs for provision of $O_2$ to and removal of $CO_2$ from the blood. An average-sized adult male at rest typically breathes approximately 500 mL and an average adult female approximately 400 mL of air per breath at a frequency of 12 to 16 times per minute, resulting in a ventilation of 6 to 8 L/min (*minute ventilation* [ $\dot{V}_E$ ]) for males and slightly less for females.[a] (The subscript "E" indicates that the minute ventilation is measured from expired gas, rather than by how much gas is inspired; these values are slightly different if the patient's respiratory quotient is not exactly 1.)

The volume of each breath (*tidal volume* [$V_T$]) is not used entirely for gas exchange; a portion stays in the conducting airways and does not reach the distal part of the lung where gas exchange occurs. The portion of the $V_T$ that is "wasted" (in the sense of gas exchange) is termed the *volume of dead space* ($V_D$), and the volume that reaches the gas-exchanging portion of the lung is the *alveolar volume* ($V_A$). The *anatomic dead space*, which includes the larynx, trachea, and bronchi down to the level of the terminal bronchioles, is approximately 150 mL in an average-sized male; thus, 30% of a $V_T$ of 500 mL is wasted.

The volume of each breath (tidal volume [$V_T$]) is divided into dead space volume ($V_D$) and alveolar volume ($V_A$).

As for $CO_2$ elimination by the lung, alveolar ventilation ( $\dot{V}_A$ ), which is equal to the breathing frequency (f) multiplied by $V_A$, bears a direct relationship to the amount of $CO_2$ removed from the body. In fact, the partial pressure of $CO_2$ ($Paco_2$) in arterial blood is inversely proportional to $\dot{V}_A$ ; as $\dot{V}_A$ increases, $Paco_2$ decreases. In addition, $Paco_2$ is affected by the body's rate of $CO_2$ production ( $\dot{V}co_2$ ); if $\dot{V}co_2$ increases without any change in $\dot{V}_A$ , $Paco_2$ shows a proportional increase. Thus, it is easy to understand the relationship given in Eq. 1.1:

$$(\text{Eq. 1.1}) Paco_2 \propto \dot{V}co_2/\dot{V}A$$

Arterial $P_{CO_2}$ ($Paco_2$) is inversely proportional to alveolar ventilation ( $\dot{V}_A$ ) and directly proportional to $CO_2$ production ( $\dot{V}co_2$ ).

This defines the major factors determining $Paco_2$. When a normal individual exercises, $\dot{V}co_2$ increases, but $\dot{V}_A$ increases proportionately so that $Paco_2$ remains relatively constant.

As mentioned earlier, the dead space comprises that amount of each breath going to parts of the tracheobronchial tree not involved in gas exchange. The anatomic dead space consists of the conducting airways. However, in disease states, areas of lung that normally participate in gas exchange (parts of the terminal respiratory unit) may not receive normal blood flow, even though they continue to be ventilated. In these areas, some of the ventilation is wasted; such regions contribute additional volume to the dead space.

Hence, a more useful clinical concept than anatomic dead space is *physiologic dead space*, which takes into account the volume of each breath not involved in gas exchange, whether at the level of the conducting airways or the terminal respiratory units. Primarily in certain disease states, in which there may be areas with normal ventilation but decreased or no perfusion, the physiologic dead space is larger than the anatomic dead space.

Quantitation of the physiologic dead space or, more precisely, the fraction of the $V_T$ represented by the dead space ($V_D/V_T$), can be made by measuring $P_{CO_2}$ in arterial blood ($Paco_2$) and expired gas ($P_{ECO_2}$) and by using Eq. 1.2, known as the *Bohr equation* for physiologic dead space:

$$(\text{Eq. 1.2}) VD/VT = (Paco_2 - PEco_2)/Paco_2$$

The Bohr equation can be used to quantify the fraction of each breath that is wasted, the dead space-to-tidal volume ratio ($V_D/V_T$).

For gas coming directly from alveoli that have participated in gas exchange, $P_{CO_2}$

approximates that of arterial blood. For gas coming from the dead space, $P_{CO_2}$ approximates 0 because the expired gas from that region never came into contact with pulmonary capillary blood.

Consider the two extremes. If the expired gas came entirely from perfused alveoli, $P_{ECO_2}$ would equal $P_{aCO_2}$, and according to the equation, $V_D/V_T$ would equal 0. On the other hand, if expired gas came totally from the dead space, it would contain no $CO_2$, $P_{ECO_2}$ would equal 0, and $V_D/V_T$ would equal 1. In practice, this equation is used in situations between these two extremes, and it quantifies the proportion of expired gas coming from alveolar gas ($P_{CO_2} = P_{aCO_2}$) versus dead space gas ($P_{CO_2} = 0$).

In summary, each normal or $V_T$ breath can be divided into alveolar volume ($V_A$) and dead space ($V_D$), just as the total ventilation ( $\dot{V}_E$ ) can be divided into alveolar ventilation ( $\dot{V}_A$ ) and wasted (or dead space) ventilation ( $\dot{V}_D$ ). Elimination of $CO_2$ by the lungs is proportional to $\dot{V}_A$ ; therefore, $P_{aCO_2}$ is inversely proportional to $\dot{V}_A$ and not to $\dot{V}_E$ . The wasted ventilation can be quantified by the Bohr equation, using the principle that increasing amounts of dead space ventilation augment the difference between $P_{CO_2}$ in arterial blood and expired gas.

## Circulation

Normally, because the entire cardiac output flows from the right ventricle to the lungs and back to the left side of the heart, the pulmonary circulation handles a blood flow of approximately 5 L/min. If the pulmonary vasculature were similar in structure to the systemic vasculature, large pressures would have to be generated because of the thick walls and high resistance offered by systemic-type arteries. However, pulmonary arteries are quite different in structure from systemic arteries, with thin walls that provide much less resistance to flow. Thus, despite equal right and left ventricular outputs, the normal mean pulmonary artery pressure of 15 mm Hg is much lower than the normal mean aortic pressure of approximately 95 mm Hg.

One important feature of blood flow in the pulmonary capillary bed is the distribution of flow in different areas of the lung. The pattern of flow is explained to a large degree by the effect of gravity and the necessity for blood to be pumped “uphill” to reach the apices of the lungs. In an upright person the apex of each lung is approximately 25 cm higher than the base, so the pressure in pulmonary vessels at the apex is 25 cm $H_2O$ (19 mm Hg) lower than that in pulmonary vessels at the bases. Because flow through these vessels depends on the perfusion pressure, the capillary network at the bases receives much more flow than the capillaries at the apices. In fact, flow at the lung apices falls to 0 during the part of the cardiac cycle when pulmonary artery pressure is insufficient to pump blood up to the apices.

As a result of gravity, there is more blood flow to dependent regions of the lung.

West developed a model of pulmonary blood flow that divides the lung into zones, based on the relationships among pulmonary arterial, venous, and alveolar pressures (Fig. 1.4). As stated earlier, the vascular pressures (i.e., pulmonary arterial and venous)

depend in part on the vertical location of the vessels in the lung because of the hydrostatic effect. Apical vessels have much lower pressure than basilar vessels, the difference being the vertical distance between them (divided by a correction factor of 1.3 to convert from cm $H_2O$ to mm Hg).

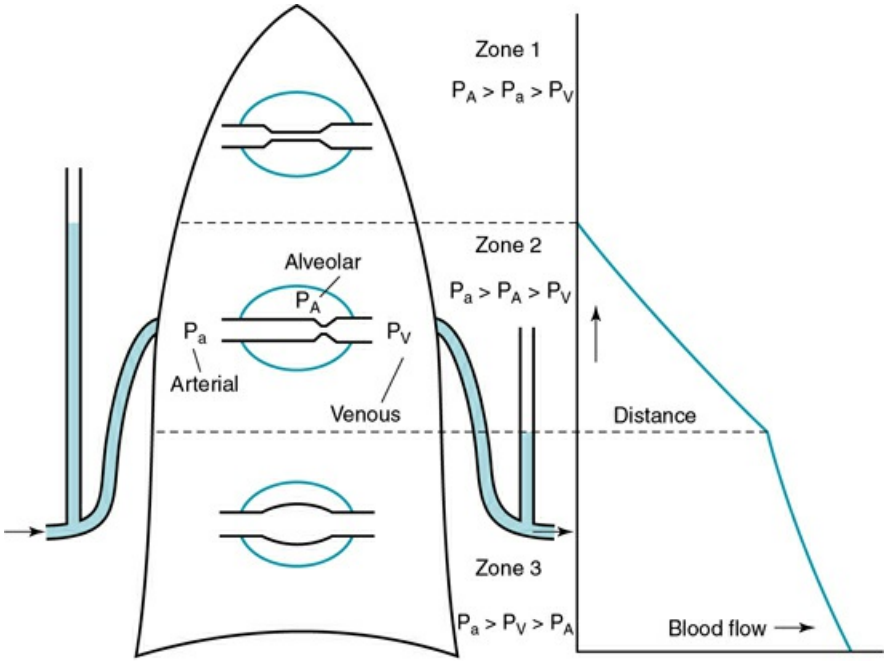


**FIGURE 1.4** Three-zone model of pulmonary blood flow showing relationships among alveolar pressure *($P_A$)*, arterial pressure *($P_A$)*, and venous pressure *($P_V$)* in each zone. Blood flow (per unit volume of lung) is shown as function of vertical distance on the right. *Source:* (From West, J. B., Dollery, C. T., & Naimark, A. (1964). Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *Journal of Applied Physiology*, *19*, 713–724.)

At the apex of the lung (see zone 1 in Fig. 1.4), alveolar pressure exceeds arterial and venous pressures and no flow results. Normally, such a condition does not arise unless pulmonary arterial pressure is decreased or alveolar pressure is increased (by exogenous pressure applied to the airways and alveoli). In zone 2, arterial but not venous pressure exceeds alveolar pressure, and the driving force for flow is determined by the difference between arterial pressure and alveolar pressure. In zone 3, arterial and venous pressures exceed alveolar pressure, and the driving force is the difference between arterial and venous pressures, as is the case in the systemic vasculature.

When cardiac output is increased (e.g., during exercise), the normal pulmonary vasculature is able to handle the increase in flow by recruiting previously unperfused vessels and distending previously perfused vessels. The ability to expand the pulmonary vascular bed and thus decrease vascular resistance allows major increases in cardiac output with exercise to be accompanied by only small increments in mean pulmonary

artery pressure. However, in disease states that affect the pulmonary vascular bed, the ability to recruit additional vessels with increased flow may not exist, and significant increases in pulmonary artery pressure may result.

## Diffusion

For $O_2$ and $CO_2$ to be transferred between the alveolar space and blood in the pulmonary capillary, diffusion must take place through several compartments: alveolar gas, alveolar and capillary walls, plasma, and membrane and some cytoplasm of the red blood cell. Although diffusion of $O_2$ is less efficient than $CO_2$, in normal circumstances the process of diffusion of both gases is relatively rapid, and full equilibration occurs during the transit time of blood flowing through the pulmonary capillary bed. In fact, the $P_{O_2}$ in capillary blood rises from the mixed venous level of 40 mm Hg[b] to the end-capillary level of 100 mm Hg in approximately 0.25 second, or one-third the total transit time (0.75 second) an erythrocyte normally spends within the pulmonary capillaries. Carbon dioxide diffusion occurs more rapidly, and transfer is complete in a shorter amount of time.

Normally, equilibration of $O_2$ and $CO_2$ between alveolar gas and pulmonary capillary blood is complete in one-third the time spent by blood in the pulmonary capillary bed.

Diffusion of $O_2$ is normally a rapid process, but it is not instantaneous. Resistance to diffusion is provided primarily by the alveolar–capillary membrane and by the reaction that forms oxygenated hemoglobin within the erythrocyte. Each factor provides approximately equal resistance to the transfer of $O_2$, and each can be disturbed in various disease states. However, as discussed later in this chapter, even when diffusion is measurably impaired, it rarely is a cause of impaired gas exchange. Sufficient time still exists for full equilibration of $O_2$ or $CO_2$ unless blood is flowing faster and transit time is significantly shortened, as with exercise.

Even though diffusion limitation rarely contributes to hypoxemia, an abnormality in diffusion may be a useful marker for diseases of the pulmonary parenchyma that affect the alveolar–capillary membrane, the volume of blood in the pulmonary capillaries, or both. Rather than using $O_2$ to measure diffusion within the lung, clinicians generally use carbon monoxide, which avidly binds to hemoglobin and provides a technically easier test to perform and interpret. The usefulness and meaning of the measurement of diffusing capacity are discussed in Chapter 3.

## Oxygen transport

Because the eventual goal of tissue oxygenation requires transport of $O_2$ from the lungs to the peripheral tissues and organs, any discussion of oxygenation is incomplete without consideration of transport mechanisms.

In preparation for this discussion, an understanding of the concepts of *partial pressure*, *gas content*, and *percent saturation* is essential. The *partial pressure* of any gas is the product of the ambient total gas pressure and the proportion of total gas composition made up by the specific gas of interest. For example, air is composed of

approximately 21% $O_2$. Assuming a total pressure of 760 mm Hg at sea level and no water vapor pressure, the partial pressure of $O_2$ ($P_{O_2}$) is 0.21 × 760, or 160 mm Hg. If the gas is saturated with water vapor at body temperature (37°C), the water vapor has a partial pressure of 47 mm Hg. The partial pressure of $O_2$ is then calculated on the basis of the remaining pressure: 760 − 47 = 713 mm Hg. Therefore, when room air is saturated at body temperature, $P_{O_2}$ is 0.21 × 713 = 150 mm Hg. Because inspired gas is normally humidified by the upper airway, it becomes fully saturated by the time it reaches the trachea and bronchi, where inspired $P_{O_2}$ is approximately 150 mm Hg.

In clinical situations, we also must consider the concept of partial pressure of a gas within a body fluid, primarily blood. When a gas mixture is in contact with a liquid, the partial pressure of a particular gas in the liquid is the same as its partial pressure in the gas mixture, assuming full equilibration has taken place. Some of the gas molecules will dissolve in the liquid, and the amount of dissolved gas reflects the partial pressure of gas in the liquid. Therefore, the partial pressure of the gas acts as the driving force for the gas to be taken up by the liquid phase.

However, the quantity of a gas carried by a liquid medium depends not only on the partial pressure of the gas in the liquid but also on the "capacity" of the liquid for that particular gas. If a specific gas is quite soluble within a liquid, more of that gas is carried for a given partial pressure than a less soluble gas. In addition, if a component of the liquid is also able to bind the gas, more of the gas is transported at a particular partial pressure. For example, this is true of the interaction of hemoglobin and $O_2$. Hemoglobin in red blood cells vastly increases the capacity of blood to carry $O_2$, as a more detailed discussion will show.

The *content* of a gas in a liquid, such as blood, is the actual amount of the gas contained within the liquid. For $O_2$ in blood, the content is expressed as milliliters of $O_2$ per 100 mL blood. The *percent saturation* of a gas is the ratio of the actual content of the gas to the maximal possible content if there is a limit or plateau in the amount that can be carried.

Oxygen is transported in blood in two ways: either dissolved in the blood or bound to the heme portion of hemoglobin. Oxygen is not very soluble in plasma, and only a small amount of $O_2$ is carried this way under normal conditions. The amount dissolved is proportional to the partial pressure of $O_2$, with 0.0031 mL dissolved for each millimeter of mercury of partial pressure. The amount bound to hemoglobin is a function of the *oxyhemoglobin dissociation curve*, which relates the driving pressure ($P_{O_2}$) to the quantity of $O_2$ bound. This curve reaches a plateau, indicating that hemoglobin can hold only so much $O_2$ before it becomes fully saturated (Fig. 1.5). At $P_{O_2}$ = 60 mm Hg, hemoglobin is approximately 90% saturated, so only relatively small amounts of additional $O_2$ are transported at a $P_{O_2}$ above this level.

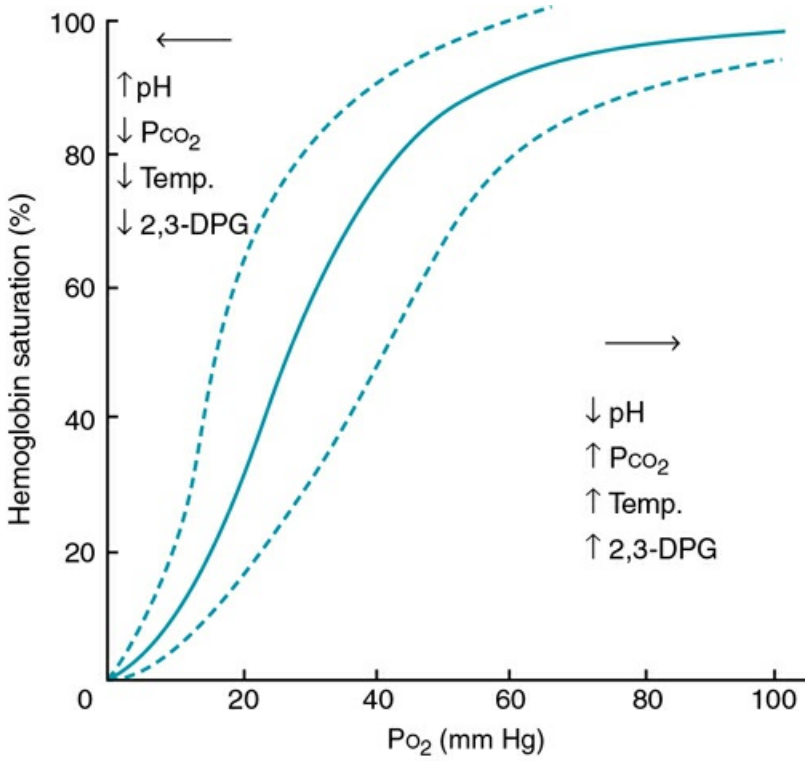


**FIGURE 1.5** Oxyhemoglobin dissociation curve, relating percent hemoglobin saturation and partial pressure of oxygen *($Po_2$)*. Oxygen content can be determined on the basis of hemoglobin concentration and percent hemoglobin saturation (see text). Normal curve is depicted with solid line. Curves shifted to right or left (and conditions leading to them) are shown with broken lines. *2,3-DPG*, 2,3-diphosphoglycerate; *$Pco_2$*, partial pressure of carbon dioxide.

Almost all $O_2$ transported in the blood is bound to hemoglobin; only a small fraction is dissolved in plasma.

Hemoglobin is 90% saturated with $O_2$ around an arterial $Po_2$ of 60 mm Hg.

This curve can shift to the right or left, depending on a variety of conditions. Thus, the relationships between arterial $Po_2$ and saturation are not fixed. For instance, a decrease in pH or an increase in $Pco_2$ (largely by a pH effect), temperature, or 2,3-bisphosphoglycerate (2,3-BPG; also called 2,3-diphosphoglycerate [2,3-DPG]) shifts the oxyhemoglobin dissociation curve to the right, making it easier to unload (or harder to bind) $O_2$ for any given $Po_2$ (see Fig. 1.5). The opposite changes in pH, $Pco_2$, temperature, or 2,3-BPG shift the curve to the left and make it harder to unload (or easier to bind) $O_2$ for any given $Po_2$. These properties help to ensure that oxygen is released preferentially

to tissues that are more metabolically active because intense anaerobic metabolism results in decreased pH and elevations in 2,3-BPG, whereas increased heat and $CO_2$ are generated by intense aerobic metabolism.

Perhaps the easiest way to understand $O_2$ transport is to follow $O_2$ and hemoglobin as they course through the circulation in a normal person. When blood leaves the pulmonary capillaries, it has already been oxygenated by equilibration with alveolar gas, and the $P_{O_2}$ should be identical to that in the alveoli. Because of $O_2$ uptake and $CO_2$ excretion at the level of the alveolar–capillary interface, alveolar $P_{O_2}$ is less than the 150 mm Hg that was calculated for inspired gas within the airways (see discussion on Hypoxemia and Eq. 1.7). Alveolar $P_{O_2}$ in a normal individual (breathing air at sea level) is approximately 100 mm Hg. However, the $P_{O_2}$ measured in arterial blood is actually slightly lower than this value for alveolar $P_{O_2}$, partly because of the presence of small amounts of "shunted" blood that do not participate in gas exchange at the alveolar level, such as (1) desaturated blood from the bronchial circulation draining into pulmonary veins and (2) venous blood from the coronary circulation draining into the left side of the heart via thebesian veins. Ventilation–perfusion mismatch, as discussed below, also contributes to the difference between alveolar and arterial $P_{O_2}$.

Assuming $P_{O_2}$ = 95 mm Hg in arterial blood, the total $O_2$ content is the sum of the quantity of $O_2$ bound to hemoglobin plus the amount dissolved. To calculate the quantity bound to hemoglobin, the patient's hemoglobin level and the percent saturation of the hemoglobin with $O_2$ must be known. Because each gram of hemoglobin can carry 1.34 mL $O_2$ when fully saturated, the $O_2$ content is calculated by Eq. 1.3:

$$\text{(Eq. 1.3)} \quad \begin{aligned} &O_2 \text{ content bound to hemoglobin} \\ &= 1.34 \times \text{Hemoglobin} \times \text{Saturation} \end{aligned}$$

Assume that hemoglobin is 97% saturated at $P_{O_2}$ = 95 mm Hg and the individual has a hemoglobin level of 15 g/100 mL blood (Eq. 1.4):

$$\text{(Eq. 1.4)} \quad \begin{aligned} O_2 \text{ content bound to hemoglobin} &= 1.34 \times 15 \times 0.97 \\ &= 19.5 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

In contrast, the amount of dissolved $O_2$ is much smaller and is proportional to $P_{O_2}$, with 0.0031 mL $O_2$ dissolved per 100 mL blood per mm Hg $P_{O_2}$. Therefore, at an arterial $P_{O_2}$ of 95 mm Hg (Eq. 1.5):

$$\text{(Eq. 1.5)} \quad \begin{aligned} \text{Dissoloed } O_2 \text{ content} &= 0.0031 \times 95 \\ &= 0.3 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

The total $O_2$ content is the sum of the hemoglobin-bound $O_2$ plus the dissolved $O_2$, or 19.5 + 0.3 = 19.8 mL $O_2$/100 mL blood.

Arterial $P_{O_2}$ is not the sole determinant of $O_2$ content; because most of the oxygen is bound to hemoglobin, the hemoglobin level is also crucial. With anemia (reduced

hemoglobin level), fewer binding sites are available for $O_2$, and the $O_2$ content falls even though $P_{O_2}$, which reflects the amount of $O_2$ dissolved in the plasma, remains unchanged. In addition, the $O_2$ content of blood is a static measurement of the quantity of $O_2$ per 100 mL blood. The actual delivery of oxygen to tissues is dynamic and depends on blood flow (determined primarily by cardiac output, but also influenced by regulation at the microvascular level of the receiving tissue or organ) as well as $O_2$ content. Thus, three main factors determine tissue $O_2$ delivery: arterial $P_{O_2}$, hemoglobin level, and cardiac output. Disturbances in any one of these factors can result in decreased or insufficient $O_2$ delivery.

Oxygen content in arterial blood depends on arterial $P_{O_2}$ and the hemoglobin level; tissue oxygen delivery depends on these two factors and cardiac output.

When blood reaches the systemic capillaries, $O_2$ is unloaded to the tissues and $P_{O_2}$ falls. The extent to which $P_{O_2}$ falls depends on the balance of $O_2$ supply and demand: The local venous $P_{O_2}$ of blood leaving a tissue falls to a greater degree if more $O_2$ is extracted per volume of blood because of increased tissue requirements or decreased supply (e.g., due to decreased cardiac output).

On average in a resting individual, $P_{O_2}$ falls to approximately 40 mm Hg after $O_2$ extraction occurs at the tissue-capillary level. Because $P_{O_2}$ = 40 mm Hg is associated with 75% saturation of hemoglobin, the total $O_2$ content in venous blood is calculated by Eq. 1.6:

$$\text{(Eq. 1.6)} \quad \begin{aligned} \text{Venous } O_2 \text{ content} &= (1.34 \times 15 \times 0.75) + (0.0031 \times 40) \\ &= 15.2 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

The quantity of $O_2$ consumed at the tissue level is the difference between the arterial and venous $O_2$ contents, or 19.8 – 15.2 = 4.6 mL $O_2$ per 100 mL blood. The total $O_2$ consumption ( $\dot{V}_{O_2}$ ) is the product of cardiac output and this difference in arterial–venous $O_2$ content. Because (1) normal resting cardiac output for a young individual depends on size and is approximately 5 to 6 L/min and (2) 46 mL $O_2$ is extracted per liter of blood flow (note difference in units), the resting $O_2$ consumption is approximately 250 mL/min.

When venous blood returns to the lungs, oxygenation of this desaturated blood occurs at the level of the pulmonary capillaries, and the entire cycle can repeat.

## Carbon dioxide transport

Carbon dioxide is transported through the circulation in three different forms: (1) as bicarbonate ($HCO_3^-$), quantitatively the largest component; (2) as $CO_2$ dissolved in plasma; and (3) as carbaminohemoglobin bound to terminal amino groups on hemoglobin. The first form, bicarbonate, results from the combination of $CO_2$ with $H_2O$ to form carbonic acid ($H_2CO_3$), catalyzed by the enzyme carbonic anhydrase, and

subsequent dissociation to $H^+$ and $HCO_3^-$ (Eq. 1.7). This reaction takes place primarily within the red blood cell, but $HCO_3^-$ within the erythrocyte is then exchanged for $Cl^-$ within plasma.

$$(\text{Eq. 1.7})\quad CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

Carbon dioxide is carried in blood as (1) bicarbonate, (2) dissolved $CO_2$, and (3) carbaminohemoglobin.

Although dissolved $CO_2$, the second transport mechanism, constitutes only a small portion of the total $CO_2$ transported, it is quantitatively more important for $CO_2$ transport than dissolved $O_2$ is for $O_2$ transport, because $CO_2$ is approximately 20 times more soluble than $O_2$ in plasma. Carbaminohemoglobin, formed by the combination of $CO_2$ with hemoglobin, is the third transport mechanism. The oxygenation status of hemoglobin is important in determining the quantity of $CO_2$ that can be bound, with deoxygenated hemoglobin having a greater affinity for $CO_2$ than oxygenated hemoglobin (known as the *Haldane effect*). Therefore, oxygenation of hemoglobin in the pulmonary capillaries decreases its ability to bind $CO_2$ and facilitates elimination of $CO_2$ by the lungs.

In the same way the oxyhemoglobin dissociation curve depicts the relationship between the $P_{O_2}$ and $O_2$ content of blood, a curve can be constructed relating the total $CO_2$ content to the $P_{CO_2}$ of blood. However, within the range of gas tensions encountered under physiologic circumstances, the $P_{CO_2}$–$CO_2$ content relationship is almost linear compared with the curvilinear relationship of $P_{O_2}$ and $O_2$ content (Fig. 1.6).

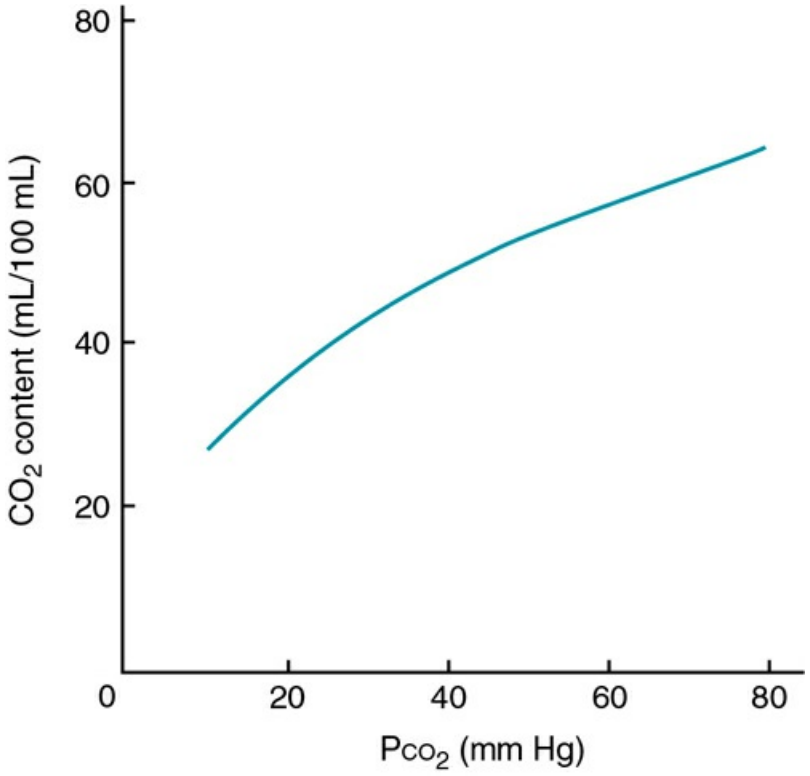


**FIGURE 1.6** Relationship between partial pressure of carbon dioxide *($P_{CO_2}$)* and $CO_2$ content. Curve shifts slightly to left as $O_2$ saturation of blood decreases. Curve shown is for blood completely saturated with $O_2$.

$P_{CO_2}$ in mixed venous blood is approximately 46 mm Hg, whereas normal arterial $P_{CO_2}$ is approximately 40 mm Hg. The decrease of 6 mm Hg when going from mixed venous to arterial blood, combined with the effect of oxygenation of hemoglobin on release of $CO_2$, corresponds to a change in $CO_2$ content of approximately 3.6 mL per 100 mL blood (or 36 mL/L). Assuming a cardiac output of 5 to 6 L/min, $CO_2$ production can be calculated as the product of the cardiac output and arteriovenous $CO_2$ content difference, or approximately 200 mL/min.

## Ventilation–perfusion relationships

Ventilation, blood flow, diffusion, and their relationship to gas exchange ($O_2$ uptake and $CO_2$ elimination) are more complicated than initially presented because the distribution of ventilation and blood flow within the lung was not considered. Effective gas exchange critically depends on the relationship between ventilation and perfusion in individual gas-exchanging units. A disturbance in this relationship, even if the total amounts of ventilation and blood flow are normal, is frequently responsible for abnormal gas exchange in disease states.

The optimal efficiency for gas exchange would be provided by a perfectly even distribution of ventilation and perfusion throughout the lung so that a matching of

ventilation and perfusion is always present. In reality, such a circumstance does not exist, even in normal lungs. Because blood flow is determined to a large extent by hydrostatic and gravitational forces, the dependent regions of the lung receive a disproportionately larger share of the total perfusion, whereas the uppermost regions are relatively underperfused. Similarly, there is a gradient of ventilation throughout the lung, with greater amounts also going to the dependent areas. However, even though ventilation and perfusion are both greater in the gravity-dependent regions of the lung, this gradient is more marked for perfusion than for ventilation. Consequently, the ratio of ventilation ( $\dot{V}$ ) to perfusion ( $\dot{Q}$ ) is higher in apical regions of the lung than in basal regions. As a result, gas exchange throughout the lung is not uniform but varies depending on the $\dot{V}/\dot{Q}$ ratio of each region.

From top to bottom of the lung, the gradient is more marked for perfusion ( $\dot{Q}$ ) than for ventilation ( $\dot{V}$ ), so the $\dot{V}/\dot{Q}$ ratio is lower in the dependent regions of the lung.

To understand the effects on gas exchange of altering the $\dot{V}/\dot{Q}$ ratio, first consider the individual alveolus and then the more complex model with multiple alveoli and variable $\dot{V}/\dot{Q}$ ratios. In a single alveolus, a continuous spectrum exists for the possible relationships between $\dot{V}$ and $\dot{Q}$ (Fig. 1.7). At one extreme, where $\dot{V}$ is maintained and $\dot{Q}$ approaches 0, the $\dot{V}/\dot{Q}$ ratio approaches ∞. When there is actually no perfusion ( $\dot{Q}$ = 0), ventilation is wasted insofar as gas exchange is concerned, and the alveolus is part of the dead space. At the other extreme, $\dot{V}$ approaches 0 and $\dot{Q}$ is preserved, and the $\dot{V}/\dot{Q}$ ratio approaches 0. When there is no ventilation ( $\dot{V}$ = 0), a “shunt” exists, oxygenation does not occur during transit through the pulmonary circulation, and the hemoglobin still is desaturated when it leaves the pulmonary capillary.

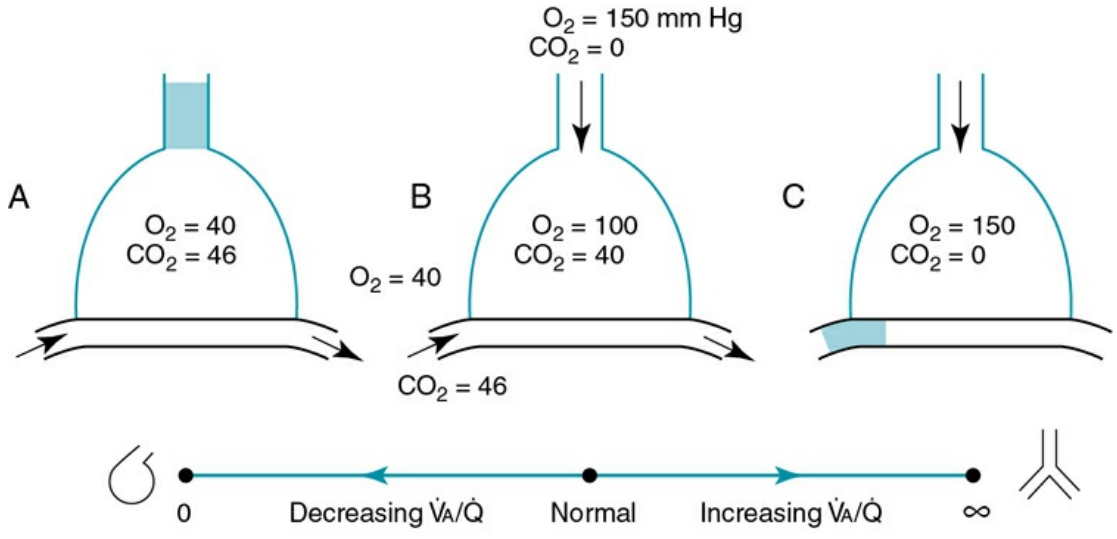

**FIGURE 1.7 Spectrum of ventilation–perfusion ratios within single alveolar–capillary unit. A,** Ventilation is obstructed, but perfusion is preserved. Alveolar–capillary unit is behaving as a shunt. **B,** Ventilation and perfusion are well matched. **C,** No blood flow is reaching the alveolus, so ventilation is wasted, and the alveolus behaves as dead space. $\dot{V}A/\dot{Q}$ , Ventilation–perfusion ratio. *Source:* (Modified from West, J. B. (1977). *Ventilation/blood flow and gas exchange* (3rd ed., p. 36). Oxford, UK: Blackwell Scientific Publications.)

Ventilation–perfusion ratios within each alveolar–capillary unit range from $\dot{V}/\dot{Q}$ = ∞ (dead space) to $\dot{V}/\dot{Q}$ = 0 (shunt).

Again, dealing with the extremes, for an alveolar–capillary unit acting as dead space (ventilation but no perfusion, or $\dot{V}/\dot{Q}$ = ∞), $P_{O_2}$ in the alveolus is equal to that in air (i.e., 150 mm Hg, taking into account the fact that air in the alveolus is saturated with water vapor), whereas $P_{CO_2}$ in the alveolus approaches 0 because no blood and therefore no $CO_2$ is in contact with alveolar gas. With a region of true dead space, there is no blood flow, so no gas exchange has occurred between this alveolus and blood. If there were a minute amount of blood flow (i.e., if the $\dot{V}/\dot{Q}$ ratio approached but did not reach ∞), the blood also would have a $P_{O_2}$ approaching (but slightly less than) 150 mm Hg and a $P_{CO_2}$ approaching (but slightly more than) 0 mm Hg. At the other extreme, for an alveolar–capillary unit acting as a shunt (perfusion but no ventilation or $\dot{V}/\dot{Q}$ = 0), blood leaving the capillary has gas tensions identical to those in mixed venous blood. Normally, mixed venous blood has a $P_{O_2}$ = 40 mm Hg and $P_{CO_2}$ = 46 mm Hg.

In reality, alveolar–capillary units fall anywhere along this continuum of $\dot{V}/\dot{Q}$ ratios. The higher the $\dot{V}/\dot{Q}$ ratio in an alveolar–capillary unit, the closer the unit comes to behaving like an area of dead space and the more $P_{O_2}$ approaches 150 mm Hg and $P_{CO_2}$ approaches 0 mm Hg. The lower the $\dot{V}/\dot{Q}$ ratio, the closer the unit comes to behaving like a shunt, and the more the $P_{O_2}$ and $P_{CO_2}$ of blood leaving the capillary approach the gas tensions in mixed venous blood (40 and 46 mm Hg, respectively). This continuum is depicted in Fig. 1.8, in which moving to the left signifies decreasing the $\dot{V}/\dot{Q}$ ratio, and moving to the right means increasing the $\dot{V}/\dot{Q}$ ratio. The ideal circumstance lies between these extremes, in which $P_{O_2}$ = 100 mm Hg and $P_{CO_2}$ = 40 mm Hg.

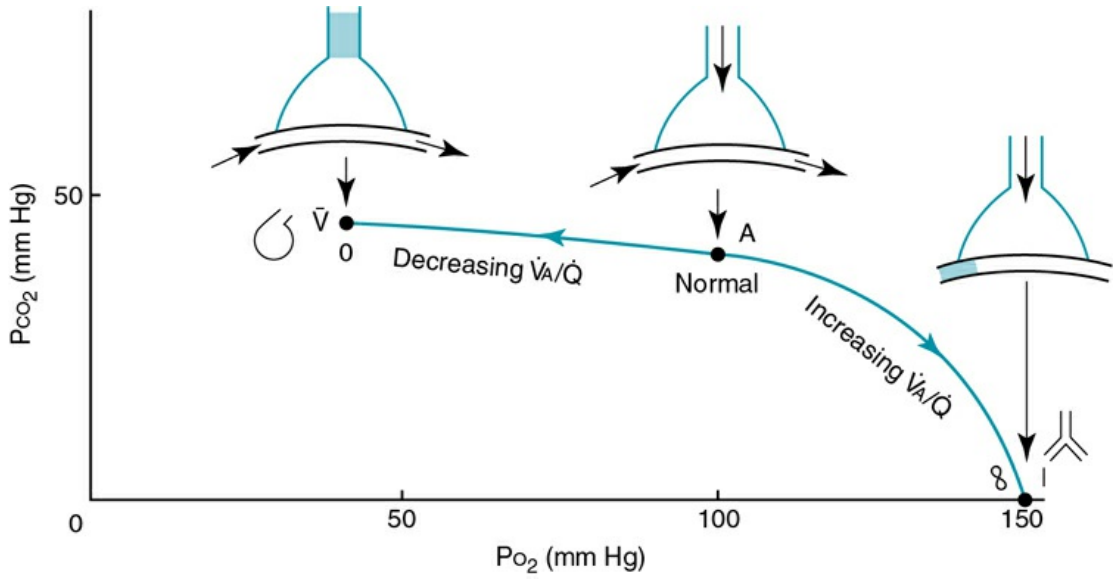


**FIGURE 1.8** Continuum of alveolar gas composition at different ventilation–perfusion ratios within a single alveolar–capillary unit. The line is the "ventilation–perfusion ratio line." At extreme left side of the line, $\dot{V}/\dot{Q} = 0$ (shunt). At extreme right side of the line, $\dot{V}/\dot{Q} = \infty$ (dead space). $P_{CO_2}$, partial pressure of carbon dioxide; $P_{O_2}$, partial pressure of oxygen. *Source:* (Modified from West, J. B. (1977). *Ventilation/blood flow and gas exchange* (3rd ed., p. 37). Oxford, UK: Blackwell Scientific Publications.)

When multiple alveolar–capillary units are considered, the net $P_{O_2}$ and $P_{CO_2}$ of the resulting pulmonary venous blood returning to the left atrium depend on the $O_2$ or $CO_2$ content and the volume of blood collected from each of the contributing units. Considering $P_{CO_2}$ first, areas with relatively high $\dot{V}/\dot{Q}$ ratios contribute blood with a lower $P_{CO_2}$ than do areas with low $\dot{V}/\dot{Q}$ ratios. Recall that the relationship between $CO_2$ content and $P_{CO_2}$ is nearly linear over the physiologic range (see Fig. 1.6). Therefore, if blood having a higher $P_{CO_2}$ and $CO_2$ content mixes with an equal volume of blood having a lower $P_{CO_2}$ and $CO_2$ content, an intermediate $P_{CO_2}$ and $CO_2$ content (approximately halfway between) results.

Regions of the lung with a high $\dot{V}/\dot{Q}$ ratio and a high $P_{O_2}$ cannot compensate for regions with a low $\dot{V}/\dot{Q}$ ratio and low $P_{O_2}$.

In marked contrast, a high $P_{O_2}$ in blood coming from a region with a high $\dot{V}/\dot{Q}$ ratio cannot fully compensate for blood with a low $P_{O_2}$ from a region with a low $\dot{V}/\dot{Q}$ ratio. The difference stems from the shape of the oxyhemoglobin dissociation curve, which is

curvilinear (rather than linear) and becomes nearly flat at the top (see Fig. 1.5). After hemoglobin is nearly saturated with $O_2$ (on the relatively flat part of the oxyhemoglobin dissociation curve), increasing $P_{O_2}$ only contributes to the very small amount of oxygen dissolved in blood and does not significantly boost the $O_2$ content. In other words, because most of the oxygen content in blood is due to $O_2$ bound to hemoglobin, once the hemoglobin is fully saturated, blood with a higher than normal $P_{O_2}$ does not have a correspondingly higher $O_2$ content and cannot compensate for blood with a low $P_{O_2}$ and low $O_2$ content.

In the normal lung, regional differences in the $\dot{V}/\dot{Q}$ ratio affect gas tensions in blood coming from specific regions, as well as gas tensions in the resulting arterial blood. At the apices, where the $\dot{V}/\dot{Q}$ ratio is approximately 3.3, $P_{O_2}$ = 132 mm Hg and $P_{CO_2}$ = 28 mm Hg. At the bases, where the $\dot{V}/\dot{Q}$ ratio is approximately 0.63, $P_{O_2}$ = 89 mm Hg and $P_{CO_2}$ = 42 mm Hg. As discussed, the net $P_{O_2}$ and $P_{CO_2}$ of the combined blood coming from the apices, bases, and the areas between are a function of the relative amounts of blood from each of these areas and the gas contents of each.

In disease states, ventilation–perfusion mismatch frequently is much more extreme, resulting in clinically significant gas exchange abnormalities. When an area of lung behaves as a shunt or even as a region having a very low $\dot{V}/\dot{Q}$ ratio, blood coming from this area has a low $O_2$ content and saturation, which cannot be compensated for by blood from relatively preserved regions of lung. $\dot{V}/\dot{Q}$ mismatch that is severe, particularly with areas of a high $\dot{V}/\dot{Q}$ ratio, can effectively produce dead space and therefore decrease the $\dot{V}_A$ to other areas of the lung carrying a disproportionate share of the perfusion. Because $CO_2$ excretion depends on $\dot{V}_A$, $P_{CO_2}$ may rise unless an overall increase in the $\dot{V}_E$ restores the effective $\dot{V}_A$.

## Abnormalities in gas exchange

The net effect of disturbances in the normal pattern of gas exchange can be assessed by measurement of the gas tensions ($P_{O_2}$ and $P_{CO_2}$) in arterial blood. The information that can be obtained from arterial blood gas measurement is discussed further in Chapter 3, but the mechanisms of hypoxemia (decreased arterial $P_{O_2}$) and hypercapnia (increased $P_{CO_2}$) are considered here because they relate to the physiologic principles just discussed.

### Hypoxemia

Blood that has traversed pulmonary capillaries leaves with a $P_{O_2}$ that should be in equilibrium with and almost identical to the $P_{O_2}$ in companion alveoli. Although it is difficult to measure the $O_2$ tension in alveolar gas, it can be conveniently calculated by a formula known as the *alveolar gas equation*. A simplified version of this formula is relatively easy to use and can be extremely useful in the clinical setting, particularly

when trying to deduce why a patient is hypoxemic. The alveolar $O_2$ tension ($P_{AO_2}$)[c] can be calculated by Eq. 1.8:

$$(\text{Eq. } 1.8) P_{AO_2} = F_{IO_2}(P_B - P_{H_2O}) - P_{ACO_2}/R$$

where $F_{IO_2}$ = fractional content of inspired $O_2$ ($F_{IO_2}$ of air = 0.21), $P_B$ = barometric pressure (approximately 760 mm Hg at sea level), $P_{H_2O}$ = vapor pressure of water in the alveoli (at full saturation at 37°C, $P_{H_2O}$ = 47 mm Hg), $P_{ACO_2}$ = alveolar $CO_2$ tension (which can be assumed to be identical to arterial $CO_2$ tension, $P_{aCO_2}$), and R = respiratory quotient ($CO_2$ production divided by $O_2$ consumption, usually approximately 0.8). In practice, for the patient breathing room air ($F_{IO_2}$ = 0.21), the equation often is simplified. When numbers are substituted for $F_{IO_2}$, $P_B$, and $P_{H_2O}$ and when $P_{aCO_2}$ is used instead of $P_{ACO_2}$, the resulting equation (at sea level) is Eq. 1.9:

$$(\text{Eq. } 1.9) P_{AO_2} = 150 - 1.25 \times P_{aCO_2}$$

The simplified alveolar gas equation (see Eq. 1.9) can be used to calculate alveolar $P_{O_2}$ ($P_{AO_2}$) for the patient breathing room air.

By calculating $P_{AO_2}$, the expected $P_{aO_2}$ can be determined. Even in a normal person, $P_{AO_2}$ is greater than $P_{aO_2}$ by an amount called the *alveolar-arterial oxygen difference* or *gradient* ($AaDO_2$). A gradient exists even in normal individuals for two main reasons: (1) A small amount of cardiac output behaves as a shunt, without ever going through the pulmonary capillary bed. This includes venous blood from the bronchial circulation, a portion of which drains into the pulmonary veins, and coronary venous blood draining via thebesian veins directly into the left side of the heart. Desaturated blood from these sources lowers $O_2$ tension in the resulting arterial blood. (2) Ventilation–perfusion gradients from the top to the bottom of the lung result in somewhat less oxygenated blood from the bases combining with better oxygenated blood from the apices.

$AaDO_2$ normally is less than 15 mm Hg, but it increases with age. $AaDO_2$ may be elevated in disease for several reasons. First, a shunt may be present so that some desaturated blood combines with fully saturated blood and lowers $P_{O_2}$ in the resulting arterial blood. Common causes of a shunt are as follows:

1. Intracardiac lesions with a right-to-left shunt at the atrial or ventricular level (e.g., an atrial or ventricular septal defect). Note that although a left-to-right shunt can produce severe long-term cardiac consequences, it does not affect either $AaDO_2$ or arterial $P_{O_2}$ because its net effect is to recycle already oxygenated blood through the pulmonary vasculature, not to dilute oxygenated blood with desaturated blood.
2. Structural abnormalities of the pulmonary vasculature that result in direct communication between pulmonary arterial and venous systems (e.g., pulmonary arteriovenous malformations).

3. Pulmonary diseases that result in filling of the alveolar spaces with fluid (e.g., pulmonary edema) or complete alveolar collapse. Either process can result in complete loss of ventilation to the affected alveoli, although some perfusion through the associated capillaries may continue. Although perfusion of poorly ventilated lung units is detrimental to gas exchange, it can be helpful for immunologic reasons, such as delivering white blood cells to an area of pneumonia.

Ventilation–perfusion mismatch and shunting are the two important mechanisms for elevation of $AaDo_2$.

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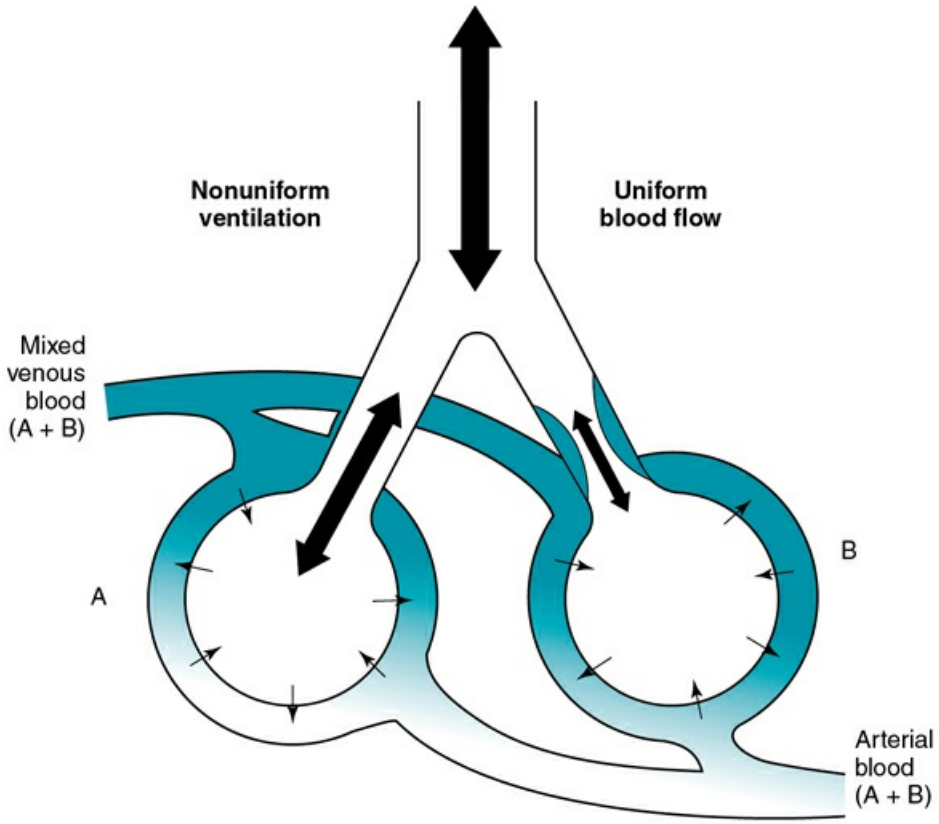
*AaDo2*, Alveolar-arterial O2 difference.

Another cause of elevated $AaDo_2$ is ventilation–perfusion mismatch. Even when total ventilation and total perfusion to both lungs are normal, if some areas receive less ventilation and more perfusion (low $\dot{V}/\dot{Q}$ ratio) whereas others receive more ventilation and less perfusion (high $\dot{V}/\dot{Q}$ ratio), $AaDo_2$ increases and hypoxemia results. As just mentioned, the reason for this phenomenon is that areas having a low $\dot{V}/\dot{Q}$ ratio provide relatively desaturated blood with a low $O_2$ content. Blood coming from regions with a high $\dot{V}/\dot{Q}$ ratio cannot compensate for this problem because the hemoglobin is already fully saturated and cannot increase its $O_2$ content further by increased ventilation (Fig. 1.9).




| | A | B | A + B |
|---|---|---|---|
| Alveolar ventilation (L/min) | 3.2 | 0.8 | 4.0 |
| Pulmonary blood flow (L/min) | 2.5 | 2.5 | 5.0 |
| Ventilation–blood flow ratio | 1.3 | 0.3 | 0.8 |
| Mixed venous $O_2$ saturation (%) | 75.0 | 75.0 | 75.0 |
| Arterial $O_2$ saturation (%) | 98.2 | 91.7 | 95.0 |
| Mixed venous $O_2$ tension (mm Hg) | 40.0 | 40.0 | 40.0 |
| Alveolar $O_2$ tension (mm Hg) | 116.0 | 66.0 | 106.0 |
| Arterial $O_2$ tension (mm Hg) | 116.0 | 66.0 | 84.0 |
| Alveolar-arterial $P_{O_2}$ difference (mm Hg) | 0.0 | 0.0 | 22.0 |

**FIGURE 1.9** Example of nonuniform ventilation producing $\dot{V}/\dot{Q}$ mismatch in two-alveolus model. In this instance, perfusion is equally distributed between the two alveoli. Calculations demonstrate how $\dot{V}/\dot{Q}$ mismatch lowers arterial $P_{O_2}$ and causes elevated alveolar-arterial oxygen difference. *Source:* (Modified from Comroe, J. H. (1962). *The lung* (2nd ed., p. 94). Chicago, IL: Year Book Medical Publishers.)

In practice, the contribution to hypoxemia of true shunt ( $\dot{V}/\dot{Q}$ = 0) and $\dot{V}/\dot{Q}$ mismatch (with areas of $\dot{V}/\dot{Q}$ that are low but not 0) can be distinguished by having the patient inhale 100% $O_2$. In the former case, increasing inspired $P_{O_2}$ does not add more $O_2$ to the shunted blood and $O_2$ content does not increase significantly. In the latter

case, alveolar and capillary $P_{O_2}$ rise considerably with additional $O_2$, fully saturating blood coming even from regions with a low $\dot{V}/\dot{Q}$ ratio, and arterial $P_{O_2}$ rises substantially.

A third cause of elevated $AaD_{O_2}$ occurs primarily in specialized circumstances. This cause is a "diffusion block" in which $P_{O_2}$ in pulmonary capillary blood does not reach equilibrium with alveolar gas. If the interface (i.e., the tissue within the alveolar wall) between the capillary and the alveolar lumen is thickened, one can hypothesize that $O_2$ does not diffuse as readily and that the $P_{O_2}$ in pulmonary capillary blood never reaches the $P_{O_2}$ of alveolar gas. However, even with a thickened alveolar wall, there is still sufficient time for this equilibrium. Unless the transit time of erythrocytes through the lung is significantly shortened, failure to equilibrate does not appear to be a problem. A specialized circumstance, in which a diffusion block plus more rapid transit of erythrocytes together contribute to hypoxemia, occurs during exercise in a patient with interstitial lung disease, as will be discussed later. However, for most practical purposes in the nonexercising patient, a diffusion block should be considered only a hypothetical rather than a real mechanism for increasing $AaD_{O_2}$ and causing hypoxemia.

Increasing the difference between alveolar and arterial $P_{O_2}$ is not the only mechanism that results in hypoxemia. Alveolar $P_{O_2}$ can be decreased, which must necessarily lower arterial $P_{O_2}$ if $AaD_{O_2}$ remains constant. Referring to the alveolar gas equation, it is relatively easy to see that alveolar $P_{O_2}$ drops if barometric pressure falls (e.g., with altitude) or if alveolar $P_{CO_2}$ rises (e.g., with hypoventilation). In the latter circumstance, when total $\dot{V}_A$ falls, $P_{CO_2}$ in alveolar gas rises at the same time alveolar $P_{O_2}$ falls. Hypoventilation is relatively common in lung disease and is defined by the presence of a high $P_{CO_2}$ accompanying the hypoxemia. If $P_{CO_2}$ is elevated and $AaD_{O_2}$ is normal, then hypoventilation is the exclusive cause of low $P_{O_2}$. If $AaD_{O_2}$ is elevated, either $\dot{V}/\dot{Q}$ mismatch or shunting also contributes to hypoxemia.

## WHEN HYPOVENTILATION IS THE SOLE CAUSE OF HYPOXEMIA, $AaD_{O_2}$ IS NORMAL

Mechanisms of hypoxemia:

1. Shunt
2. $\dot{V}/\dot{Q}$ mismatch
3. Hypoventilation
4. Low inspired $P_{O_2}$

In summary, lung disease can result in hypoxemia for multiple reasons. Shunting and ventilation–perfusion mismatch are associated with elevated $AaD_{O_2}$. They often can be distinguished, if necessary, by inhalation of 100% $O_2$, which markedly increases $Pa_{O_2}$ with $\dot{V}/\dot{Q}$ mismatch but not with true shunting. In contrast, hypoventilation (identified by high $Pa_{CO_2}$) and low inspired $P_{O_2}$ lower alveolar $P_{O_2}$ and cause hypoxemia, although

$AaDO_2$ remains normal. Because many of the disease processes examined in this text lead to several pathophysiologic abnormalities, it is not at all uncommon to see more than one of the aforementioned mechanisms producing hypoxemia in a particular patient.

## Hypercapnia

As discussed earlier in the section on Ventilation, $\dot{V}_A$ is the prime determinant of arterial $P_{CO_2}$, assuming $CO_2$ production remains constant. It is clear that $\dot{V}_A$ is compromised either by decreasing the total $\dot{V}_E$ (without changing the relative proportion of dead space and alveolar ventilation) or by keeping the total $\dot{V}_E$ constant and increasing the relative proportion of dead space to alveolar ventilation. A simple way to produce the latter circumstance is to change the pattern of breathing (i.e., decrease $V_T$ and increase frequency of breathing). With a lower $V_T$, a larger proportion of each breath ventilates the fixed amount of anatomic dead space, and the proportion of alveolar ventilation to total ventilation must decrease.

In addition, if significant ventilation–perfusion mismatching is present, well-perfused areas may be underventilated, whereas underperfused areas receive a disproportionate amount of ventilation. The net effect of having a large proportion of ventilation go to poorly perfused areas is similar to that of increasing the dead space. By wasting this ventilation, the remainder of the lung with the large share of the perfusion is underventilated, and the net effect is to decrease the effective alveolar ventilation. However, in many disease conditions, when such significant $\dot{V}/\dot{Q}$ mismatch exists, any increase in $P_{CO_2}$ stimulates breathing, increases total minute ventilation, and can compensate for the effectively wasted ventilation.

Therefore, several causes of hypercapnia can be defined, all of which have in common a decrease in effective alveolar ventilation. Causes include a decrease in minute ventilation, an increase in the proportion of wasted ventilation, and significant ventilation–perfusion mismatch. However, by increasing the total minute ventilation, a patient often is capable of compensating for the latter two situations so $CO_2$ retention does not result.

Decrease in alveolar ventilation is the primary mechanism that causes hypercapnia.

Increasing $CO_2$ production necessitates an increase in alveolar ventilation to avoid $CO_2$ retention. Thus, if alveolar ventilation does not rise to compensate for additional $CO_2$ production, it will also result with hypercapnia.

As is the case with hypoxemia, pathophysiologic explanations for hypercapnia do not necessarily follow such simple rules so that each case can be fully explained by one mechanism. In reality, several of these mechanisms may be operative, even in a single patient.

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[a]By convention, a dot over a letter adds a time dimension. Hence, $\dot{V}_E$ stands for volume of expired gas per minute—that is, *minute ventilation*. Similar abbreviations used in this chapter are $\dot{V}co_2$ (volume of $CO_2$ produced per minute) and $\dot{Q}$ (blood flow per minute).

[b]The units torr and mm Hg can be used interchangeably: 1 torr = 1 mm Hg.

[c]By convention, *A* refers to alveolar and *a* to arterial.

# 2: Presentation of the patient with pulmonary disease

OUTLINE



The patient with a pulmonary problem generally comes to the attention of the clinician for one of two reasons: (1) complaint of a symptom that can be traced to a respiratory cause or (2) incidental finding of an abnormality on an imaging study, such as a chest radiograph or computed tomography (CT) scan. Although the former presentation is more common, the latter is not uncommon when a radiograph or CT scan is obtained either for evaluation of a seemingly unrelated problem or as a screening study in a patient at risk for pulmonary disease, such as lung cancer. This chapter focuses on the first case, the patient who comes to the physician with a respiratory-related complaint. In the next and subsequent chapters, frequent references are made to abnormal imaging findings as a clue to the presence of a pulmonary disorder.

Four particularly common symptoms bring the patient with lung disease to the physician: dyspnea (and its variants), cough (with or without sputum production), hemoptysis, and chest pain. Each of these symptoms, to a greater or lesser extent, may result from a nonpulmonary disorder, especially primary cardiac disease. For each symptom, a discussion of some of the important clinical features is followed by the pathophysiologic features and the differential diagnosis.

## Dyspnea

Dyspnea, or shortness of breath, is frequently a difficult symptom for the physician to evaluate because it is such a subjective feeling experienced by the patient. It is perhaps best defined as an uncomfortable sensation (or awareness) of one's own breathing, to which little attention normally is paid. However, the term *dyspnea* subsumes several

sensations that are qualitatively distinct. As a result, when patients are asked to describe in more detail their sensation of breathlessness, their descriptions tend to fall into three primary categories: (1) air hunger or suffocation, (2) increased effort or work of breathing, and (3) chest tightness.

Not only is the symptom of dyspnea highly subjective and describable in different ways, but the patient's appreciation of it and its importance to the physician also depend heavily on the stimulus or amount of activity required to precipitate it. The physician must consider how the stimulus, when quantified, compares with the patient's usual level of activity. For example, a marathon runner who experiences a new symptom of shortness of breath after running 5 miles may warrant more concern than would an elderly man who for many years has had a stable symptom of shortness of breath after walking three blocks. On the other hand, a patient who is limited in exertion by a nonpulmonary problem (e.g., severe arthritis of the hips) may not experience any shortness of breath even in the presence of advanced lung disease. If the person were more active, however, dyspnea would become readily apparent. Such considerations become particularly important when joint replacement or other surgical procedures are being considered to try to improve a given patient's functional status.

Dyspnea should be distinguished from several other signs or symptoms that may have an entirely different significance. *Tachypnea* is a rapid respiratory rate (greater than the usual value of 12-20/min). Tachypnea may be present with or without dyspnea, just as dyspnea does not necessarily entail the finding of tachypnea on physical examination. *Hyperventilation* is ventilation that is greater than the amount required to maintain normal $CO_2$ elimination. Hence, the criterion that defines hyperventilation is a decrease in the $P_{CO_2}$ of arterial blood. Finally, the symptom of exertional fatigue must be distinguished from dyspnea. Fatigue may be due to cardiovascular, neuromuscular, or other nonpulmonary diseases, and the implication of this symptom may be quite different from that of shortness of breath.

Dyspnea is distinct from tachypnea, hyperventilation, and exertional fatigue.

There are some variations on the theme of dyspnea. *Orthopnea*, or shortness of breath on assuming the recumbent position, is often quantified by the number of pillows or angle of elevation necessary to relieve or prevent the sensation. One of the main causes of orthopnea is an increase in venous return and central intravascular volume on assuming the recumbent position. In patients with cardiac decompensation and either overt or subclinical heart failure, the incremental increase in left atrial and left ventricular filling may result in pulmonary vascular congestion and pulmonary interstitial or alveolar edema. Thus, orthopnea frequently suggests cardiac disease and some element of heart failure. However, orthopnea may be seen in other, non-cardiac disorders. For example, some patients with primary pulmonary disease experience orthopnea, such as individuals with a significant amount of secretions who have more difficulty handling their secretions when they are recumbent. Bilateral diaphragmatic weakness may also cause orthopnea because of greater pressure on the diaphragm by abdominal contents and more difficulty inspiring when the patient is supine rather than upright.

*Paroxysmal nocturnal dyspnea* is waking from sleep with dyspnea. As with

orthopnea, the recumbent position is important, but this symptom differs from orthopnea in that it does not occur immediately or shortly after lying down. Although the implication regarding underlying cardiac decompensation still applies, the increase in central intravascular volume is because of a slow mobilization of tissue fluid, such as peripheral edema, rather than to a rapid redistribution of intravascular volume from peripheral to central vessels. Patients with obstructive sleep apnea also may report awakening during the night with a gasping or choking sensation, but this symptom usually occurs in the context of other features of this condition, such as loud snoring, witnessed apneas during sleep, and excessive daytime somnolence.

Orthopnea, often associated with left ventricular failure, may also accompany some forms of primary pulmonary disease.

Variants that are much more uncommon are only briefly mentioned here. *Platypnea* is shortness of breath when the patient is in the upright position; it is the opposite of orthopnea. *Trepopnea* is shortness of breath when the patient lies on either the right side or the left side. The symptom can be relieved by moving to the opposite lateral decubitus position.

Returning to the more general symptom of dyspnea, several mechanisms are proposed rather than a single common thread linking the diverse responsible conditions. In particular, neural output reflecting central nervous system respiratory drive is integrated with input from a variety of mechanical receptors in the chest wall, respiratory muscles, airways, and pulmonary vasculature. If central neural output to the respiratory system is not associated with the expected responses in ventilation and gas exchange, the patient experiences a sensation of dyspnea. Presumably, the relative contributions of each source differ from disease to disease and from patient to patient, and they are responsible for the qualitatively different sensations all included under the term *dyspnea*. Detailed discussions of the mechanisms of dyspnea can be found in the references at the end of this chapter.

The sensation of dyspnea has a number of underlying pathophysiologic mechanisms.

Studies have attempted to link descriptions of dyspnea with underlying pathophysiologic mechanisms. Although the correlations are not perfect, a patient's description can sometimes help guide the clinician to the correct diagnosis. Patients who describe their breathlessness as a sense of air hunger or suffocation often have increased respiratory drive, which can be related in part to either a high $P_{CO_2}$ or a low $P_{O_2}$, but this also can occur in the absence of respiratory system or gas exchange abnormalities. The sensation of increased effort or work of breathing is commonly experienced by patients who have high resistance to airflow or abnormally stiff lungs. The sensation of chest tightness, frequently noted by patients with asthma, probably arises from intrathoracic receptors that are stimulated by bronchoconstriction. Because many disorders may produce breathlessness by more than one mechanism (e.g., asthma may have components of all three mechanisms), overlap or a mixture of these different sensations often occurs.

The differential diagnosis includes a broad range of disorders that result in dyspnea

(Table 2.1). The disorders can be separated into the major categories of respiratory disease and cardiovascular disease. Dyspnea also may be present in the absence of underlying respiratory or cardiovascular disease in conditions associated with increased respiratory drive, such as pregnancy or hyperthyroidism, or in metabolic disorders, such as mitochondrial myopathies. In addition, dyspnea may be experienced by individuals in several common settings or situations that do not readily fall into the above-mentioned categories, such as patients experiencing panic attacks.

**TABLE 2.1**
**Differential Diagnosis of Dyspnea**

| **Respiratory Disease** |
| --- |
| Airway disease<br>Asthma<br>Chronic obstructive lung disease<br>Upper airway obstruction<br>Parenchymal lung disease<br>Acute respiratory distress syndrome<br>Pneumonia<br>Interstitial lung disease<br>Pulmonary vascular disease<br>Pulmonary emboli<br>Pulmonary arterial hypertension<br>Pleural disease<br>Pneumothorax<br>Pleural effusion<br>"Bellows" disease<br>Neuromuscular disease (e.g., polymyositis, myasthenia gravis, and Guillain-Barré syndrome)<br>Chest wall disease (e.g., kyphoscoliosis) |
| **Cardiovascular Disease** |

| |
|---|
| Elevated pulmonary venous pressure<br>Left ventricular failure<br>Mitral stenosis<br>Decreased cardiac output<br>Severe anemia |
| **Increased Respiratory Drive** |
| Hyperthyroidism<br>Pregnancy |
| **Disorders of Oxidative Metabolism** |
| Mitochondrial myopathies<br>Metabolic myopathies |
| **Other Patient Factors** |
| Deconditioning<br>Obesity<br>Anxiety |

The first major category consists of disorders at many levels of the respiratory system (airways, pulmonary parenchyma, pulmonary vasculature, pleura, and bellows) that can cause dyspnea. Airway diseases that cause dyspnea result primarily from obstruction to airflow, occurring anywhere from the upper airway to the large, medium, and small intrathoracic bronchi and bronchioles. Upper airway obstruction, which is defined here as obstruction above or including the vocal cords, is caused primarily by foreign bodies, tumors, laryngeal edema (e.g., with anaphylaxis), and stenosis. A clue to upper airway obstruction is the presence of disproportionate difficulty during inspiration and an audible, prolonged, monophonic gasping sound called *inspiratory stridor*. The pathophysiology of upper airway obstruction is discussed in Chapter 7.

Airways below the level of the vocal cords, from the trachea down to the small bronchioles, are commonly involved with disorders that produce dyspnea. A localized problem, such as an airway tumor, usually does not by itself cause dyspnea unless it occurs in the trachea or a major bronchus. In contrast, diseases such as asthma and chronic obstructive pulmonary disease are widespread throughout the tracheobronchial tree, with airway narrowing resulting from spasm, edema, secretions, or loss of radial support (see Chapter 4). With this type of obstruction, difficulty with expiration predominates over that with inspiration, and the physical findings associated with obstruction (polyphonic wheezing and prolongation of airflow) are more prominent on expiration.

The category of pulmonary parenchymal disease includes disorders causing inflammation, infiltration, fluid accumulation, or scarring of the alveolar structures. Such disorders may be diffuse in nature, as with the many causes of interstitial or diffuse parenchymal lung disease, or they may be more localized, as occurs with a bacterial pneumonia.

Pulmonary vascular disease results in obstruction or loss of functional blood vessels in the lung. The most common acute type of pulmonary vascular disease is *pulmonary embolism*, in which one or many pulmonary vessels are occluded by thrombi originating

in systemic veins. Chronically, large pulmonary arteries may be blocked by abnormally organized pulmonary emboli, or small pulmonary arteries may be blocked by inflammatory or scarring processes that result in thickening of vessel walls or obliteration of the vascular lumen, ultimately causing pulmonary hypertension.

Two major disorders affecting the pleura may result in dyspnea: *pneumothorax* (air in the pleural space) and *pleural effusion* (liquid in the pleural space). With pleural effusions, a substantial amount of fluid must be present in the pleural space to result in dyspnea, unless the patient also has significant underlying cardiopulmonary disease or additional complicating features.

The term *bellows* is used here for the final category of respiratory-related disorders causing dyspnea. It refers to the pump system that works under the control of a central nervous system generator to expand the lungs and produce airflow. This pump system includes muscles (primarily but not exclusively diaphragm and intercostals) and the chest wall. Primary disease affecting the muscles, their nerve supply, or neuromuscular interaction, including polymyositis, myasthenia gravis, and Guillain-Barré syndrome, may result in dyspnea. Deformity of the chest wall, particularly kyphoscoliosis, produces dyspnea by several pathophysiologic mechanisms, primarily through increased work of breathing. Disorders of the respiratory bellows are discussed in Chapter 19.

The second major category of disorders that produce dyspnea is cardiovascular disease. In the majority of cases, the feature that patients have in common is an elevated hydrostatic pressure in the pulmonary veins and capillaries that leads to a transudation or leakage of fluid into the pulmonary interstitium and alveoli. Left ventricular failure, from either ischemic or valvular heart disease, is the most common example. In addition, mitral stenosis, with increased left atrial pressure, produces elevated pulmonary venous and capillary pressures even though left ventricular function and pressure are normal. A frequent accompaniment of the dyspnea associated with these forms of cardiac disease is orthopnea, paroxysmal nocturnal dyspnea, or both. Although worsening of dyspnea in the supine position is not specific to pulmonary venous hypertension and can also be found in some patients with pulmonary disease, improvement of dyspnea in the supine position is argues against left ventricular failure as the causative factor. Severe anemia is frequently included under cardiac causes of dyspnea because the decreased oxygen content of anemic blood mandates an increased cardiac output to maintain adequate oxygen delivery; dyspnea on exertion may result, depending on the patient's cardiac reserve.

A third category of conditions associated with dyspnea includes those characterized by increased respiratory drive but no underlying cardiopulmonary disease. Both thyroid hormone and progesterone augment respiratory drive, and patients with hyperthyroidism and pregnant women commonly report dyspnea. Dyspnea during pregnancy often starts before the abdomen is noticeably distended, indicating that diaphragmatic elevation from the enlarging uterus is not the primary explanation for the dyspnea.

Dyspnea may also be due to or exacerbated by several factors, such as deconditioning and obesity, that do not readily fall into the above-mentioned clinical categories. An individual who is deconditioned, often because of a sedentary lifestyle and little exercise, is less able than the well-conditioned individual to augment cardiac output for delivering oxygen to exercising muscles. Though significant obesity is often

accompanied by deconditioning, it may also be associated with increased ventilatory requirements as well as increased work of breathing, leading to the exertional dyspnea commonly experienced by significantly obese individuals even in the absence of underlying cardiopulmonary disease. Finally, anxiety may also contribute to or cause a sensation of dyspnea, which may be disproportionately noticed during rest rather than during exercise. Because the sensation of dyspnea is so subjective, any awareness of one's breathing may start a self-perpetuating problem. The patient breathes faster, becomes more aware of breathing, and finally has a sensation of shortness of breath. At the extreme, a person can hyperventilate and lower arterial $P_{CO_2}$ sufficiently to cause additional symptoms of lightheadedness and tingling, particularly of the fingers and around the mouth. Of course, patients who seem anxious can also have lung disease, just as patients with lung or heart disease can have dyspnea with a functional cause unrelated to their underlying disease process.

## Cough

Cough is a symptom everyone has experienced at some point. It is a physiologic mechanism for clearing and protecting the airway and does not necessarily imply disease. Normally, cough is protective against food or other foreign material entering the airway. It also is responsible for helping clear secretions produced within the tracheobronchial tree. Generally, mucociliary clearance is adequate to propel secretions upward through the trachea and into the larynx so that the secretions can be removed from the airway and swallowed. However, if the mucociliary clearance mechanism is temporarily damaged or not functioning well, or if the mechanism is overwhelmed by excessive production of secretions, coughing becomes an important additional mechanism for clearing the tracheobronchial tree.

Cough usually is initiated by stimulation of receptors (called *irritant receptors*) at several locations. Irritant receptor nerve endings are found primarily in the larynx, trachea, and major bronchi, particularly at points of bifurcation. However, sensory receptors are also located in other parts of the upper airway as well as on the pleura, the diaphragm, and even the pericardium. Irritation of these nerve endings initiates an impulse that travels via afferent nerves (primarily the vagus, but also trigeminal, glossopharyngeal, and phrenic) to a poorly defined cough center in the medulla. The efferent signal is carried in the recurrent laryngeal nerve (a branch of the vagus), which controls closure of the glottis, and in phrenic and spinal nerves, which effect contraction of the diaphragm and the expiratory muscles of the chest and abdominal walls. The initial part of the cough sequence is a deep inspiration to a high lung volume, followed by closure of the glottis, contraction of the expiratory muscles, and opening of the glottis. When the glottis suddenly opens, contraction of the expiratory muscles and relaxation of the diaphragm produce an explosive rush of air at high velocity, which transports airway secretions or foreign material out of the tracheobronchial tree.

Irritant receptors triggering cough are located primarily in larger airways.

The major causes of cough are listed in Table 2.2. Cough commonly results from an airway irritant, regardless of whether the person has respiratory system disease. The

most common inhaled irritant is cigarette smoke. Noxious fumes, dusts, and chemicals also stimulate irritant receptors and result in cough. Secretions resulting from postnasal drip are a particularly common cause of cough, presumably triggering the symptom via stimulation of laryngeal cough receptors. Reflux of gastric contents or aspiration of upper airway secretions, which amounts to "inhalation" of liquid or solid material, can result in cough, the cause of which may be unrecognized if the aspiration has not been clinically apparent. In the case of gastroesophageal reflux, in which gastric acid flows retrograde into the esophagus, cough may be due not only to aspiration of gastric contents from the esophagus or pharynx into the tracheobronchial tree, but also to reflex mechanisms triggered by acid entry into the lower esophagus and mediated by the vagus nerve.

**TABLE 2.2**
**Differential Diagnosis of Cough**

| |
|---|
| **Airway Irritants** |
| Inhaled smoke, dusts, and fumes<br>Aspiration<br>Gastric contents<br>Oral secretions<br>Foreign bodies<br>Postnasal drip (upper airway cough syndrome) |
| **Airway Disease** |
| Upper respiratory tract infection<br>Postinfectious cough<br>Acute or chronic bronchitis<br>Eosinophilic bronchitis<br>Bronchiectasis<br>Neoplasm<br>External compression by node or mass lesion<br>Reactive airway disease (asthma) |
| **Parenchymal Disease** |
| Pneumonia and other lower respiratory tract infections (e.g., tuberculosis)<br>Lung abscess<br>Interstitial lung disease |
| **Congestive Heart Failure** |
| **Miscellaneous** |
| Drug-induced (angiotensin-converting enzyme inhibitors)<br>Cough hypersensitivity syndrome |

Cough caused by respiratory system disease derives mainly but not exclusively from disorders affecting the airway. Upper airway infections, most commonly caused by viruses or certain bacteria (especially *Mycoplasma, Chlamydophila*, and *Bordetella*

*pertussis*), also affect parts of the tracheobronchial tree, and the airway inflammation results in a bothersome cough that sometimes lasts from weeks to months. Bacterial infections of the lung, either acute (pneumonia and acute bronchitis) or chronic (bronchiectasis, chronic bronchitis, and lung abscess), generally have an airway component and an impressive amount of associated coughing. Space-occupying lesions in the tracheobronchial tree (tumors, foreign bodies, and granulomas) and external lesions compressing the airway (mediastinal masses, lymph nodes, and other tumors) commonly manifest as cough secondary to airway irritation. Hyperirritable airways with airway constriction, such as in asthma, are frequently associated with cough, even when a specific inhaled irritant is not identified. The more readily recognized manifestations of asthma (wheezing and dyspnea) may not be apparent, and cough may be the sole presenting symptom, in which case the term *cough variant asthma* is applied. An entity of unknown etiology called *nonasthmatic eosinophilic bronchitis*, characterized by eosinophilic inflammation of the airway in the absence of asthma, has also been identified as a cause of chronic cough.

Patients with diffuse parenchymal (interstitial) lung disease may have cough, probably owing more to secondary airway or pleural involvement, because very few irritant receptors are present in the lung parenchyma. In heart failure, cough may be related to the same unclear mechanism operative in patients with diffuse parenchymal lung disease, or it may be secondary to bronchial edema.

A variety of miscellaneous causes of cough, such as irritation of the tympanic membrane by wax or a hair or stimulation of one of the afferent nerves by osteophytes or neural tumors, have been identified but are not discussed in further detail here. With the widespread use of angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril and lisinopril) for treatment of hypertension and heart failure, cough has been recognized as a relatively common side effect of these agents. Because ACE breaks down bradykinin and other inflammatory peptides, accumulation of bradykinin or other peptides in patients taking these inhibitors may be responsible by stimulating receptors capable of initiating cough. Of note, cough is a far less common side effect of angiotensin II receptor antagonists such as losartan, although it may occur. Coughing may be a nervous habit that can be especially prominent when the patient is anxious, although the physician must not neglect the possibility of an organic cause.

A relatively recently recognized entity of *cough hypersensitivity syndrome* describes an increased sensitivity of airway sensory receptors to irritant stimuli. It can manifest clinically as a chronic, unexplained cough or as a generalized increased sensitivity to environmental or other stimuli that can provoke coughing.

The symptom of cough is generally characterized by whether it is productive or nonproductive of sputum. Virtually any cause of cough may be productive at times of small amounts of clear or mucoid sputum. However, thick yellow or green sputum indicates the presence of numerous leukocytes in the sputum, either neutrophils or eosinophils. Neutrophils may be present with just an inflammatory process of the airways or parenchyma, but they also frequently reflect the presence of a bacterial infection. Specific examples include bacterial bronchitis, bronchiectasis, lung abscess, and pneumonia. Eosinophils, which can be seen after special preparation of the sputum, often occur with bronchial asthma, whether or not an allergic component plays a role, and in the much less common entity of nonasthmatic eosinophilic bronchitis.

Yellow or green sputum reflects the presence of numerous leukocytes, either neutrophils or eosinophils.

In clinical practice, cough is often divided into three major temporal categories: acute, subacute, or chronic, depending on the duration of the symptom. *Acute cough*, defined by a duration of less than 3 weeks, is most commonly due to an acute viral infection of the respiratory tract, such as the common cold. *Subacute cough* is defined by a duration of 3 to 8 weeks, and *chronic cough* lasts 8 or more weeks. Chronic bronchitis is a particularly frequent cause of cough in smokers, whereas common causes of either subacute or chronic cough in nonsmokers are postnasal drip (also called *upper airway cough syndrome*), gastroesophageal reflux, and asthma. An important subacute cough is postinfectious cough that lasts for more than 3 weeks following an upper respiratory tract infection. It often is due to persistent airway inflammation, postnasal drip, or bronchial hyperresponsiveness (as seen with asthma). In all cases, however, the clinician must keep in mind the broader differential diagnosis of cough outlined in Table 2.2, recognizing that cough may be a marker and the initial presenting symptom of a more serious disease, such as tuberculosis or carcinoma of the lung.

## Evaluation and management of cough

When cough is acute, accompanied by other symptoms of an upper respiratory tract infection, and not associated with other concerning findings (e.g., high fever, chills, or hemoptysis), further evaluation is not needed. A mild cough often needs no treatment, but if it is particularly bothersome, an over-the-counter antitussive (cough suppressant) can be used. In many cases of a lingering, subacute cough after an upper respiratory tract infection, the cough can be particularly bothersome but will ultimately resolve. The possibility of persistent cough from *Bordetella pertussis* (whooping cough) can also be considered in these cases suggestive of a postinfectious cough. If the patient is on an ACE inhibitor, the patient should ideally be switched to a medication acting by another mechanism.

When cough extends beyond 8 weeks and becomes chronic, further evaluation and/or management may be indicated. The patient's history and physical examination may provide clues to an etiology, particularly if there is a suggestion or evidence of underlying pulmonary disease. In the absence of a likely cause of the subacute or chronic cough, a chest radiograph is typically indicated to look for underlying intrathoracic disease (pulmonary or cardiac) to explain the cough. If the chest radiograph does not show pathology that could be responsible for the cough, then the patient may be tried sequentially on therapy to address the three most common causes of chronic cough—upper airway cough syndrome (postnasal drip), asthma, and gastroesophageal reflux disease (GERD). Empiric therapy for any of these common diagnoses serves not only as a therapeutic trial but also as a diagnostic trial that can potentially clinch the diagnosis. Other diagnostic tests that can be applied to look for specific diagnoses include pulmonary function testing (for asthma), chest CT (for bronchiectasis), and esophageal pH monitoring (for GERD).

When no etiology of cough is found and empiric therapeutic trials have failed, a centrally acting neuromodulatory drug used for neuropathic pain (gabapentin or pregabalin) is sometimes tried, though often limited by side effects. With recognition of

the cough hypersensitivity syndrome as an explanation for unexplained, persistent cough in some patients, there is now interest in developing a therapeutic approach targeting a variety of chemical mediators (e.g., P2X3 and TRPV-1) involved in activation of sensory nerves leading to cough.

## Hemoptysis

Hemoptysis refers to coughing up blood derived from airways or the lung itself. When the patient complains of coughing or spitting up blood, whether the blood actually originated from the respiratory system is not always apparent. Other sources of blood include the nasopharynx (particularly from the common nosebleed), mouth (even lip or tongue biting can be mistaken for hemoptysis), and upper gastrointestinal tract (esophagus, stomach, and duodenum). The patient often can distinguish some of these causes of pseudohemoptysis, but the physician also should search by examination for an oral or nasopharyngeal source.

The major causes of hemoptysis can be divided into three categories based on location: airways, pulmonary parenchyma, and vasculature (Table 2.3). Airway disease is the most common cause, with bronchitis, bronchiectasis, and bronchogenic carcinoma leading the list. Bronchial carcinoid tumor (formerly called *bronchial adenoma*), a less common neoplasm with variable malignant potential, also originates in the airway and may cause hemoptysis. In patients with advanced acquired immunodeficiency syndrome (AIDS), hemoptysis may be due to endobronchial (and/or pulmonary parenchymal) involvement with Kaposi sarcoma.

**TABLE 2.3**
**Differential Diagnosis of Hemoptysis**

| **Airway Disease** |
| --- |
| Acute or chronic bronchitis<br>Bronchiectasis<br>Bronchogenic carcinoma<br>Bronchial carcinoid tumor (bronchial adenoma)<br>Other endobronchial tumors (Kaposi sarcoma and metastatic carcinoma) |
| **Parenchymal Disease** |
| Tuberculosis<br>Lung abscess<br>Pneumonia<br>Mycetoma (“fungus ball”)<br>Miscellaneous<br>Goodpasture syndrome<br>Idiopathic pulmonary hemosiderosis<br>Granulomatosis with polyangiitis (Wegener granulomatosis) |
| **Vascular Disease** |
| Pulmonary embolism<br>Elevated pulmonary venous pressure<br>Left ventricular failure<br>Mitral stenosis<br>Vascular malformation |
| **Miscellaneous/Rare Causes** |
| Impaired coagulation<br>Pulmonary endometriosis |

Diseases of the airways (e.g., bronchitis) are the most common causes of hemoptysis.

Parenchymal causes of hemoptysis frequently are infectious in nature: tuberculosis, lung abscess, pneumonia, and localized fungal infection (generally attributable to *Aspergillus* organisms), termed *mycetoma* (“fungus ball”) or *aspergilloma*. Rarer causes of parenchymal hemorrhage, some of which are discussed in Chapter 11, are Goodpasture syndrome, idiopathic pulmonary hemosiderosis, and granulomatosis with polyangiitis (formerly called Wegener granulomatosis).

Vascular lesions resulting in hemoptysis are generally related to problems with the pulmonary circulation. Pulmonary embolism, with either frank infarction or transient bleeding without infarction, is often a cause of hemoptysis. Elevated pressure in the pulmonary venous and capillary bed may also be associated with hemoptysis. Acutely elevated pressure, such as in pulmonary edema, may have associated low-grade hemoptysis, commonly seen as pink- or red-tinged frothy sputum. Chronically elevated pulmonary venous pressure results from mitral stenosis, but this valvular lesion is a relatively infrequent cause of significant hemoptysis in developed countries. Vascular anomalies, such as arteriovenous malformations, may also be associated with coughing of blood.

Other miscellaneous etiologic factors in hemoptysis should be considered. Some of

these belong in more than one of the aforementioned categories; others are included here because of their rarity. Cystic fibrosis affects both airways and pulmonary parenchyma. Although either component theoretically can cause hemoptysis, bronchiectasis (a common complication of cystic fibrosis) is most frequently responsible. Patients with impaired coagulation, either from disease or from anticoagulant therapy, rarely may have pulmonary hemorrhage in the absence of other obvious causes of hemoptysis. An interesting but rare disorder is pulmonary endometriosis, in which implants of endometrial tissue in the lung can bleed coincident with the time of the menstrual cycle. Other causes are even more rare, and discussion of them is beyond the scope of this chapter.

## Chest pain

Chest pain as a reflection of respiratory system disease does not originate in the lung itself, which is free of sensory pain fibers. When chest pain does occur in this setting, its origin usually is the parietal pleura (lining the inside of the chest wall), diaphragm, or mediastinum, each of which has extensive innervation by nerve fibers capable of pain sensation. Although cardiac disease is of course an extremely important cause of chest pain, it will not be included in this discussion.

Chest pain can be associated with pleural, diaphragmatic, or mediastinal disease.

For the parietal pleura or the diaphragm, an inflammatory or infiltrating malignant process generally produces the pain. When the diaphragm is involved, the pain commonly is referred to the shoulder. In contrast, pain from the parietal pleura usually is relatively well localized over the area of involvement. Pain involving the pleura or diaphragm is often worsened on inspiration; in fact, chest pain that is particularly pronounced on inspiration is described as *pleuritic*.

Inflammation of the parietal pleura producing pain is often secondary to pulmonary embolism or to pneumonia extending to the pleural surface. A pneumothorax may result in the acute onset of pleuritic pain, although the mechanism is not clear because an acute inflammatory process is unlikely to be involved. Some diseases, particularly connective tissue disorders such as lupus, may result in episodes of pleuritic chest pain from a primary inflammatory process involving the pleura. Inflammation of the parietal pleura as a result of a viral infection (e.g., viral pleurisy) is a common cause of pleuritic chest pain in otherwise healthy individuals.

Infiltrating tumor can produce chest pain by affecting the parietal pleura or adjacent soft tissue, bones, or nerves. In the case of malignant mesothelioma, the tumor arises from the pleura itself. In other circumstances, such as lung cancer, the tumor may extend directly to the pleural surface or involve the pleura after bloodborne (hematogenous) metastasis from a distant site.

A variety of disorders originating in the mediastinum may result in pain, but they may or may not be associated with additional problems in the lung itself. These disorders of the mediastinum are discussed in Chapter 16.

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# 3: Evaluation of the patient with pulmonary disease

OUTLINE



In evaluating a patient with pulmonary disease, the physician is concerned with three levels of evaluation: macroscopic, microscopic, and functional. The methods for assessing each of these levels range from simple and readily available studies to highly sophisticated and elaborate techniques requiring state-of-the-art technology.

Each level is considered here, with an emphasis on the basic principles and utility of the studies. Subsequent chapters repeatedly refer to these methods because they form the backbone of the physician's approach to the patient.

# Evaluation on a macroscopic level

## Physical examination

The most accessible and efficient method for evaluating the patient with respiratory disease is the physical examination, which requires only a stethoscope; the eyes, ears, and hands of the examiner; and the examiner's skill in eliciting and recognizing abnormal findings. Because the purpose of this discussion is not to elaborate the details of a chest examination but to review a few of the basic principles, the primary focus is on selected aspects of the examination and what is known about mechanisms that produce abnormalities.

Apart from general observation of the patient, precise measurement of the patient's respiratory rate, and interpretation of the patient's pattern of and difficulty with breathing, the examiner relies primarily on palpation and percussion of the chest and auscultation with a stethoscope. Palpation is useful for comparing the expansion of the two sides of the chest. The examiner can determine whether the two lungs are expanding symmetrically or if some process is affecting expansion much more on one side than on the other. Palpation of the chest wall is also useful for feeling the vibrations created by spoken sounds. When the examiner places a hand over an area of lung and asks the patient to speak (e.g., "say the word 'ninety-nine'"), vibration normally should be felt as the sound is transmitted to the chest wall. This vibration is called *vocal* or *tactile fremitus*. Some disease processes increase transmission of sound and augment the intensity of the vibration. Other conditions diminish transmission of sound and reduce the intensity of the vibration or eliminate it altogether. Elaboration of this concept of sound transmission and its relation to specific conditions is provided in the discussion of chest auscultation.

When percussing the chest, the examiner notes the quality of sound produced by tapping a finger of one hand against a finger of the opposite hand pressed close to the patient's chest wall. The principle is similar to that of tapping a surface and judging whether what is underneath is solid or hollow. Normally, percussion of the chest wall overlying air-containing lung gives a resonant sound, whereas percussion over a solid organ such as the liver produces a dull sound. This contrast allows the examiner to detect areas with something other than air-containing lung beneath the chest wall, such as fluid in the pleural space (pleural effusion) or airless (consolidated) lung, each of which sounds dull to percussion. At the other extreme, air in the pleural space (pneumothorax) or a hyperinflated lung (as in emphysema) may produce a hyperresonant or more "hollow" sound, approaching what the examiner hears when percussing over a hollow viscus such as the partially gas-filled stomach. In addition, the examiner can locate the approximate position of the diaphragm by a change in the quality of the percussed note, from resonant to dull, at the bottom of the lung. A convenient aspect of the whole-chest examination is the largely symmetric nature of the two sides of the chest; a difference in the findings between the two sides suggests a localized abnormality.

When auscultating the lungs with a stethoscope, the examiner listens for two major features: the quality of the breath sounds and the presence of any abnormal (commonly called *adventitious*) sounds. As the patient takes a deep breath, the sound of airflow can be heard through the stethoscope. When the stethoscope is placed over normal lung

tissue, sound is heard primarily during inspiration, and the quality of the sound is relatively smooth and soft. These breath sounds heard over normal lung tissue are called either *normal* or *vesicular breath sounds*. Laennec, the inventor of the stethoscope, thought that normal breath sounds were generated by air movement into and out of alveoli ("vesicles"), and therefore the phrase *vesicular breath sounds* has often been used to describe these sounds. However, our current understanding is that these sounds are more likely generated in lobar or segmental airways rather than at the level of the alveoli, so there has been a movement toward replacing the phrase *vesicular breath sounds* with *normal breath sounds*.

Goals of auscultation:

1. Assessment of intensity and quality of breath sounds
2. Detection of adventitious sounds

When the examiner listens over consolidated lung—that is, lung that is airless and filled with liquid or inflammatory cells—the findings are different. The sound generally is louder and harsher, more tubular in quality, and the most characteristic feature is that expiration is at least as loud and as long as inspiration. Such breath sounds are called *bronchial breath sounds*, as opposed to the normal or vesicular sounds. This difference in quality of the sound is due to the ability of consolidated lung to transmit sound better than normally aerated lung. As a result, sounds generated by turbulent airflow in the central airways (trachea and major bronchi) are transmitted to the periphery of the lung and can be heard through the stethoscope. Normally, these sounds are not heard in the lung periphery; they can be reasonably well demonstrated, however, by listening near their site of origin—for example, over the upper part of the sternum or the suprasternal notch. These normal *tracheal breath sounds* approximate the quality of abnormal bronchial breath sounds heard over consolidated lung. Finally, when the stethoscope is placed over large airways that are not quite as central as the trachea, or over an area of partially consolidated lung, the breath sounds are intermediate in quality between bronchial and normal (vesicular) sounds and therefore are often termed *bronchovesicular*.

Consolidated lung does not transmit sound in the same way as air-containing lung.

Improved transmission of sound through consolidated rather than normal lung can also be demonstrated when the patient whispers or speaks. The enhanced transmission of whispered sound results in more distinctly heard syllables and is termed *whispered pectoriloquy*. Spoken words can be heard more distinctly through the stethoscope placed over the involved area, a phenomenon commonly called *bronchophony*. Because of differences in acoustic filtering between normal and consolidated lung, when the patient says the vowel "E," the resulting sound through consolidated lung has a nasal "A" quality. This "E-to-A change" is termed *egophony*. All these findings are variations on the same theme—enhanced transmission of sound through consolidated lung—and basically have the same significance.

Two qualifications are important in interpreting the quality of breath sounds. First,

normal transmission of sound depends on patency of the airway. If a relatively large bronchus is occluded, such as by tumor, secretions, or a foreign body, airflow into that region of lung is diminished or absent, and the examiner hears decreased or absent breath sounds over the affected area. A blocked airway proximal to consolidated or airless lung also eliminates the increased transmission of sound described previously. Second, air or fluid in the pleural space acts as a barrier to sound transmission, so a pneumothorax or pleural effusion causes diminution of breath sounds.

The second major feature the examiner listens for is adventitious sounds. Although there is some variation in how different adventitious sounds are described, the most commonly used terms are *crackles, wheezes*, and *friction rubs*. Because several additional terms—*stridor, rhonchi,* and *squawks*—are also sometimes used, we have described them as well.

*Crackles*, also called *rales*, are a series of individual clicking or popping noises heard with the stethoscope over an involved area of lung. Their quality can range from the sound produced by rubbing hairs together to that generated by opening a hook-and-loop (Velcro) fastener or crumpling a piece of cellophane. These sounds are "opening" sounds of small airways or alveoli that have been collapsed or decreased in volume during expiration because of fluid, inflammatory exudate, or poor aeration. On each subsequent inspiration, opening of these distal lung units creates the series of clicking or popping sounds heard either throughout or at the latter part of inspiration. The most common disorders producing crackles are pulmonary edema, pneumonia, some causes of diffuse parenchymal lung disease (especially idiopathic pulmonary fibrosis), and atelectasis. Although some clinicians believe the quality of the crackles ("fine" or "coarse") helps distinguish the different disorders, others think that such distinctions in quality are of little clinical value.

Crackles (or rales), heard during inspiration, are "opening" sounds of small airways and alveoli.

*Wheezes* are high-pitched, continuous sounds generated by airflow through narrowed airways. Causes of such narrowing include airway smooth muscle constriction, edema, secretions, intraluminal obstruction, and collapse because of poorly supported bronchiolar walls. These individual pathophysiologic features are discussed in Chapters 4 through 7. For reasons that are also described later, the diameter of intrathoracic airways is less during expiration than inspiration, and wheezing generally is more pronounced or exclusively heard in expiration. However, because sufficient airflow is necessary to generate a wheeze, wheezing may no longer be heard if airway narrowing is severe. In conditions such as asthma and chronic obstructive pulmonary disease, wheezes originate in multiple narrowed airways and are generally *polyphonic*, meaning they are a combination of different musical pitches that start and stop at different times during the expiratory cycle. In contrast, wheezing sounds tend to be monophonic when they result from focal narrowing of the trachea or large bronchi. When the site of narrowing is the extrathoracic airway (e.g., in the larynx or the extrathoracic portion of the trachea), the term *stridor* is used to describe the inspiratory wheezing-like sound that results from such narrowing. Physiologic factors that relate the site of narrowing and the phase of the respiratory cycle most affected are described later in this chapter

and shown in Figs. 3.20 and 3.21.

Wheezes reflect airflow through narrowed airways.

Clinicians commonly use the term *rhonchi* when referring to a variety of noises and musical sounds that cannot readily be classified within the more generally accepted categories of crackles and wheezes, but often appear to have airway secretions as a common underlying cause. The term sometimes describes a snoring-like sound, but also sometimes refers to sounds that could be characterized as coarse, low-pitched wheezing. Because secretions can move with coughing, rhonchi will often change or disappear following a cough.

The term *squawk* is used to describe a short, inspiratory, wheeze-like sound, often thought to reflect disease in small or peripheral airways. It is heard most commonly in patients with hypersensitivity pneumonitis or pneumonia.

A *friction rub* is the term for the sounds generated by inflamed or roughened pleural surfaces rubbing against each other during respiration. It describes a series of creaky or rasping sounds heard during both inspiration and expiration. The most common causes are primary inflammatory diseases of the pleura or parenchymal processes that extend out to the pleural surface, such as pneumonia and pulmonary infarction.

Table 3.1 summarizes some of the pulmonary findings commonly seen in selected disorders affecting the respiratory system. Many of these are mentioned again in subsequent chapters when the specific disorders are discussed in more detail.

## TABLE 3.1
## Typical Chest Examination Findings in Selected Clinical Conditions

| Condition | Percussion | Fremitus | Breath Sounds | Voice Transmission | Crackles |
|---|---|---|---|---|---|
| Normal | Resonant | Normal | Normal (vesicular; at lung bases) | Normal | Absent |
| Consolidation or atelectasis (with patent airway) | Dull | Increased | Bronchial | Bronchophony, whispered pectoriloquy, egophony | Present |
| Consolidation or atelectasis (with blocked airway) | Dull | Decreased | Decreased | Decreased | Absent |
| Emphysema | Hyperresonant | Decreased | Decreased | Decreased | Absent |
| Pneumothorax | Hyperresonant | Decreased | Decreased | Decreased | Absent |
| Pleural effusion | Dull | Decreased | Decreased* | Decreased* | Absent |

*May be altered by collapse of underlying lung, which will increase transmission of sound.

Although the focus here is the chest examination itself as an indicator of pulmonary disease, other nonthoracic manifestations of primary pulmonary disease may be

detected on physical examination. Clubbing (with or without hypertrophic osteoarthropathy) and cyanosis are briefly discussed here.

*Clubbing* is a change in the normal configuration of the nails and the distal phalanx of the fingers or toes (Fig. 3.1). Several features may be seen: (1) loss of the normal angle between the nail and the skin, (2) increased curvature of the nail, (3) increased sponginess of the tissue below the proximal part of the nail, and (4) flaring or widening of the terminal phalanx. Although several nonpulmonary disorders can result in clubbing (e.g., congenital heart disease with right-to-left shunting, endocarditis, chronic liver disease, inflammatory bowel disease), the most common causes are clearly pulmonary. Occasionally, clubbing is familial and of no clinical significance. Carcinoma of the lung (or mesothelioma of the pleura) is the single leading etiologic factor. Other pulmonary causes include chronic intrathoracic infection with suppuration (e.g., bronchiectasis, lung abscess, empyema) and some types of diffuse parenchymal lung disease. Uncomplicated chronic obstructive lung disease is not associated with clubbing, so the presence of clubbing in this setting should suggest coexisting malignancy or suppurative disease.

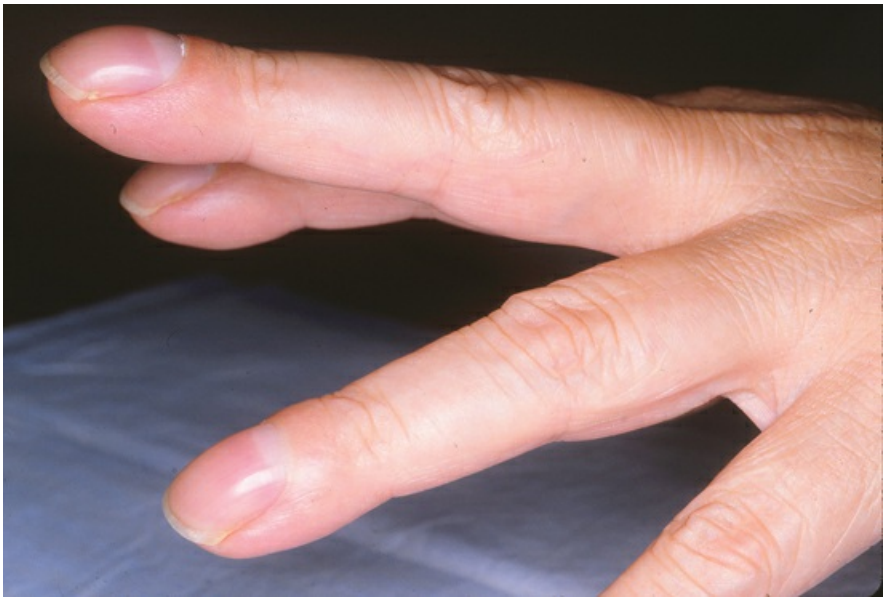

**FIGURE 3.1 Clubbing.** Curvature of nail and loss of angle between nail and adjacent skin can be seen.

Respiratory system diseases associated with clubbing:

1. Carcinoma of the lung (or mesothelioma of the pleura)
2. Chronic intrathoracic infection
3. Diffuse parenchymal lung disease

Clubbing may be accompanied by *hypertrophic osteoarthropathy*, characterized by

periosteal new bone formation, particularly in the long bones, and arthralgias and arthritis of any of several joints. With coexistent hypertrophic osteoarthropathy, either pulmonary or pleural tumor is the likely cause of the clubbing, because hypertrophic osteoarthropathy is relatively rare with the other causes of clubbing.

The mechanism of clubbing and hypertrophic osteoarthropathy is not clear. It has been observed that clubbing is associated with an increase in digital blood flow, whereas the osteoarthropathy is characterized by an overgrowth of highly vascular connective tissue. Why these changes occur is a mystery. One interesting theory suggests an important role for stimuli coming through the vagus nerve, because vagotomy frequently ameliorates some of the bone and nail changes. Another theory proposes that megakaryocytes and platelet clumps, bypassing the pulmonary vascular bed and lodging in the peripheral systemic circulation, release growth factors responsible for the soft-tissue changes of clubbing.

*Cyanosis*, the second extrapulmonary physical finding arising from lung disease, is a bluish discoloration of the skin (particularly under the nails) and mucous membranes. Whereas oxygenated hemoglobin gives mucous membranes and nail beds their usual pink color, a sufficient amount of deoxygenated hemoglobin produces cyanosis. Cyanosis may be either generalized, owing to a low $P_{O_2}$ or low systemic blood flow resulting in increased extraction of oxygen from the blood, or localized, owing to low blood flow and increased $O_2$ extraction within the localized area. In lung disease, the common factor causing cyanosis is a low $P_{O_2}$, and several different types of lung disease may be responsible. The total amount of hemoglobin affects the likelihood of detecting cyanosis. In an anemic patient, if the total quantity of deoxygenated hemoglobin is less than the amount needed to produce the bluish discoloration, even a very low $P_{O_2}$ may not be associated with cyanosis. In a patient with polycythemia, in contrast, much less depression of $P_{O_2}$ is necessary before sufficient deoxygenated hemoglobin exists to produce cyanosis. In patients with darker skin, cyanosis may only be evident in mucous membranes or nail beds, whereas more widespread bluish discoloration of skin may be evident in lighter skinned individuals.

## Chest radiography

The chest radiograph is used to evaluate patients with suspected respiratory disease and also sometimes in the routine evaluation of asymptomatic patients. Of all the viscera, the lungs are the best suited for radiographic examination. The reason is straightforward: air in the lungs provides an excellent background against which abnormalities can stand out. In addition, the presence of two lungs allows each to serve as a control for the other so that unilateral abnormalities can be more easily recognized.

A detailed description of interpretation of the chest radiograph is beyond the scope of this text. However, a few principles can aid the reader in viewing films presented in this and subsequent chapters.

First, the appearance of any structure on a radiograph depends on the structure's density; the denser the structure, the whiter it appears on the film. At one extreme is air, which is radiolucent and appears black on the film. At the other extreme are metallic densities, which appear white. In between is a spectrum of increasing density from fat to water to bone. On a chest radiograph, the viscera and muscles fall within the range of

water-density tissues and cannot be distinguished in radiographic density from water or blood.

Second, for a line or an interface to appear between two adjacent structures on a radiograph, the two structures must differ in density. For example, within the cardiac shadow, the heart muscle cannot be distinguished from the blood coursing within the chambers because both are of water density. In contrast, the borders of the heart are visible against the lungs because the water density of the heart contrasts with the density of the lungs, which is closer to that of air. However, if the lung adjacent to a normally denser structure (e.g., heart or diaphragm) is airless, either because of collapse or consolidation, the neighboring structures are now both of the same density, and no visible interface or boundary separates them. This principle is the basis of the useful *silhouette sign*. If an expected border with an area of lung is not visualized or is not distinct, the adjacent lung is abnormal and lacks full aeration.

Chest radiographs usually are taken in two standard views—posteroanterior (PA) and lateral (Fig. 3.2). For a PA image, the x-ray beam goes from the back to the front of the patient, and the patient's anterior chest is adjacent to the image receptor (which may be film or a digital device). The lateral view is typically taken with the patient's left side against the image receptor, and the beam is directed through the patient to the image receptor. If an image cannot be taken with the patient standing and the chest adjacent to the image receptor, as in the case of a bedridden patient, then an anteroposterior (AP) view is taken. For this view, which is generally obtained using a portable chest radiograph machine in the patient's hospital room, the image receptor is placed behind the patient (generally between the patient's back and the bed), and the beam is directed through the patient from front to back. Lateral decubitus views, either right or left, are obtained with the patient in a side-lying position, with the beam directed horizontally. Decubitus views are particularly useful for detecting free-flowing fluid within the pleural space and therefore are often used when a pleural effusion is suspected.

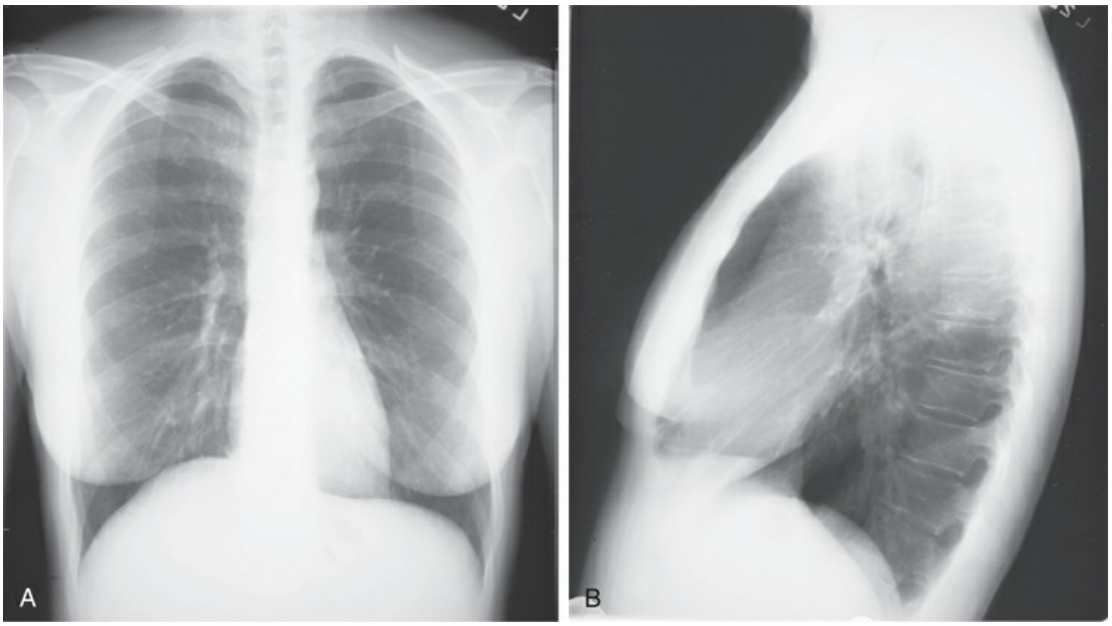

**FIGURE 3.2 Normal chest radiograph. A,** Posteroanterior view. **B,** Lateral view. Compare with Fig. 3.3 for position of each lobe.

Knowledge of radiographic anatomy is fundamental for interpretation of consolidation or collapse (atelectasis) and for localization of other abnormalities on the chest film. Lobar anatomy and the locations of fissures separating the lobes are shown in Fig. 3.3. Localization of an abnormality often requires information from both the PA and lateral views, both of which should be taken and interpreted when an abnormality is being evaluated. As can be seen in Fig. 3.3, the major fissure separating the upper (and middle) lobes from the lower lobe runs obliquely through the chest. Thus, it is easy to be misled about location on the basis of the PA film alone; a lower lobe lesion may appear in the upper part of the chest, whereas an upper lobe lesion may appear much lower in position.

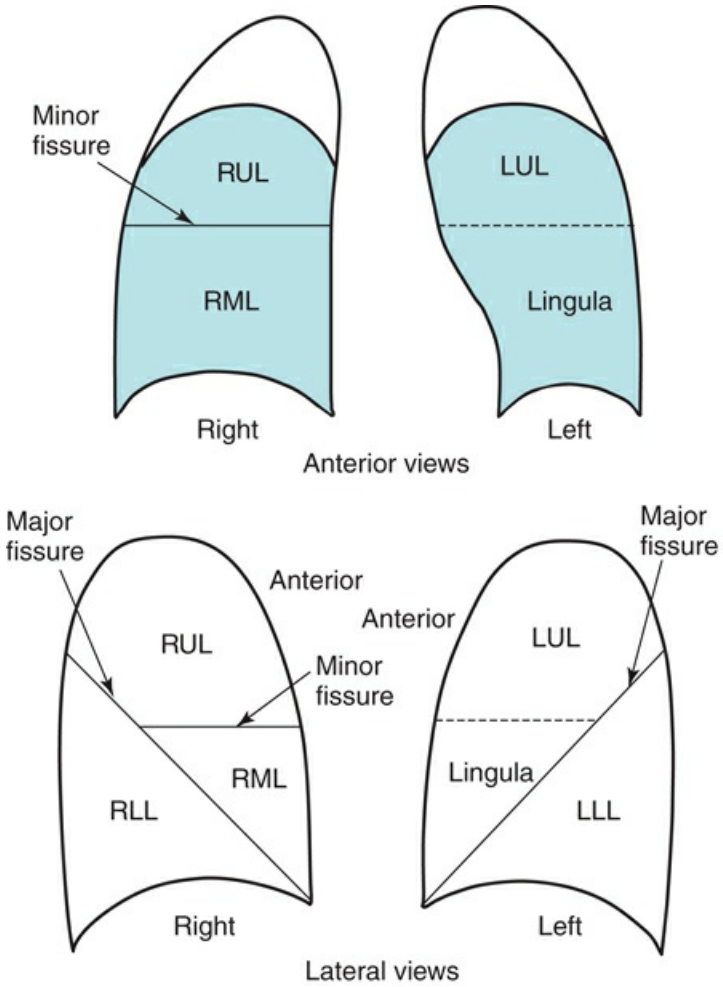


**FIGURE 3.3 Lobar anatomy as seen from anterior and lateral views.** In anterior views, shaded regions represent lower

lobes and are behind upper and middle lobes. Lingula is part of the left upper lobe; dashed line between the two does not represent a fissure. *LLL*, left lower lobe; *LUL*, left upper lobe; *RLL*, right lower lobe; *RML*, right middle lobe; *RUL*, right upper lobe.

Both posteroanterior and lateral radiographs are often necessary for localization of an abnormality.

When a lobe becomes filled with fluid or inflammatory exudate, as in pneumonia, it contains water rather than air density and therefore is easily delineated on the chest radiograph. With pure consolidation the lobe does not lose volume, so it occupies its usual position and retains its usual size. An example of lobar consolidation on PA and lateral radiographs is shown in Fig. 3.4.

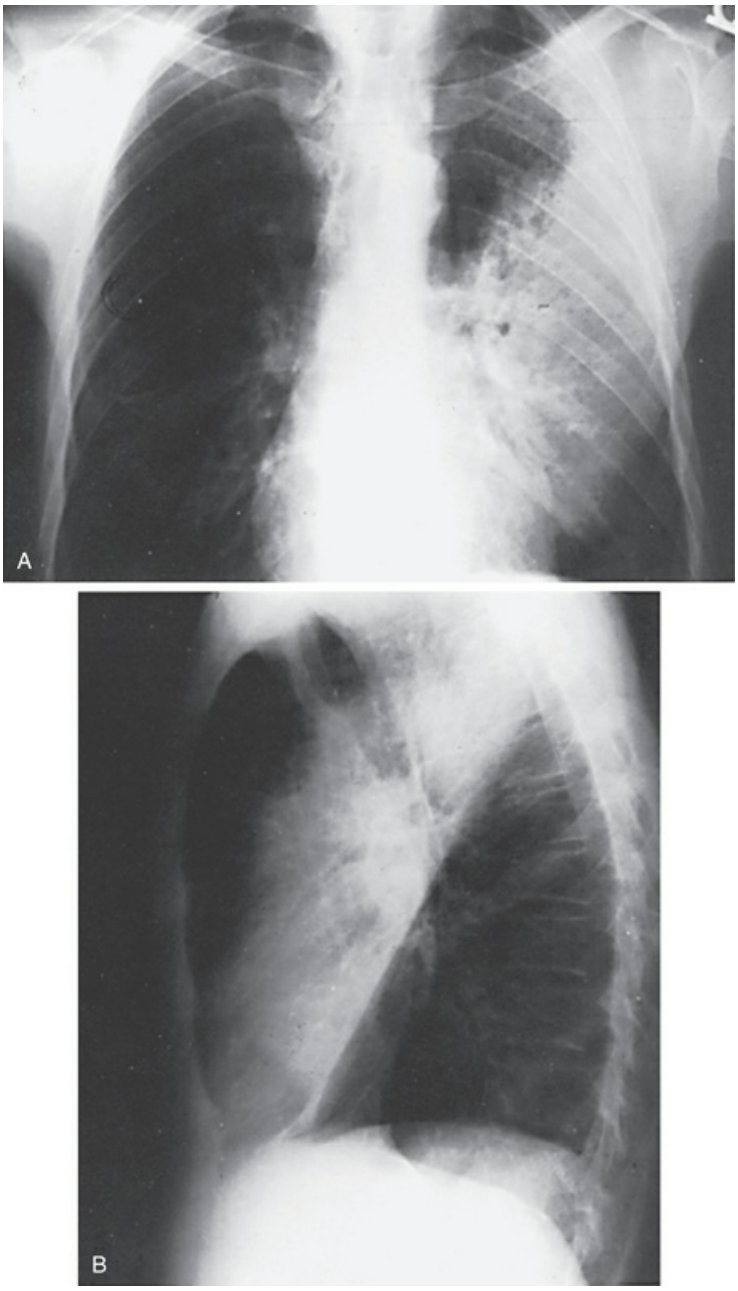


**FIGURE 3.4** Posteroanterior **(A)** and lateral **(B)** chest radiographs of a patient with left upper lobe consolidation due to pneumonia. Anatomic boundary is best appreciated on the lateral view, where it is easily seen that a normally positioned major fissure defines the lower border of consolidation (compare with Fig. 3.5). Part of left upper lobe is spared. *Source:* (Courtesy Dr. T. Scott Johnson.)

In contrast, when a lobe has airless alveoli and collapses, it not only becomes denser but also has features of volume loss characteristic for each individual lobe. Such features of volume loss include change in position of a fissure or the indirect signs of

displacement of the hilum, diaphragm, trachea, or mediastinum in the direction of the volume loss (Fig. 3.5). A common mechanism of atelectasis is occlusion of the airway leading to the collapsed region of lung, caused, for example, by a tumor, aspirated foreign body, or mucous plug. All the aforementioned examples reflect either pure consolidation or pure collapse. In practice, however, a combination of these processes often occurs, leading to consolidation accompanied by partial volume loss.

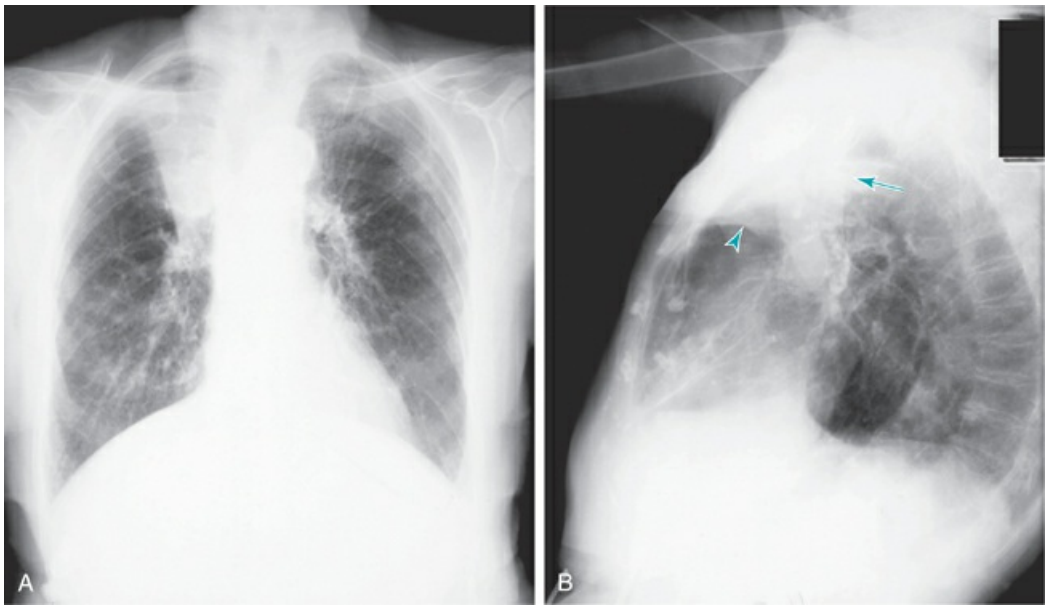


**FIGURE 3.5** Posteroanterior **(A)** and lateral **(B)** chest radiographs demonstrating right upper lobe collapse. **A,** Displaced minor fissure outlines the airless (dense) right upper lobe. **B,** Right upper lobe is outlined by an elevated minor fissure *(arrowhead)* and an anteriorly displaced major fissure *(long arrow)*.

When the chest radiograph shows a diffuse or widespread pattern of increased density within the lung parenchyma, it is often useful to characterize the process further, depending on the pattern of the radiographic findings. The two primary patterns are *interstitial* and *alveolar*. Although the naming of these patterns suggests a correlation with the type of pathologic involvement (i.e., interstitial, affecting the alveolar walls and the interstitial tissue; alveolar, involving filling of the alveolar spaces), such radiographic-pathologic correlations are often lacking. Nevertheless, many diffuse lung diseases are characterized by one of these radiographic patterns, and the particular pattern may provide clues about the underlying type or cause of disease.

Diffuse increase in density on the radiograph can often be categorized as either alveolar or interstitial.

An interstitial pattern is generally described as *reticular* or *reticulonodular*, consisting of an interlacing network of linear and small nodular densities. In contrast,

an alveolar pattern appears fluffier, and the outlines of air-filled bronchi coursing through the alveolar densities are often seen. This latter finding is called an *air bronchogram* and is due to air in the bronchi being surrounded and outlined by alveoli that are filled with fluid. This finding does not occur with a purely interstitial pattern. Examples of chest radiographs that show diffuse abnormality as a result of interstitial disease and alveolar filling are shown in Figs. 3.6 and 3.7, respectively.

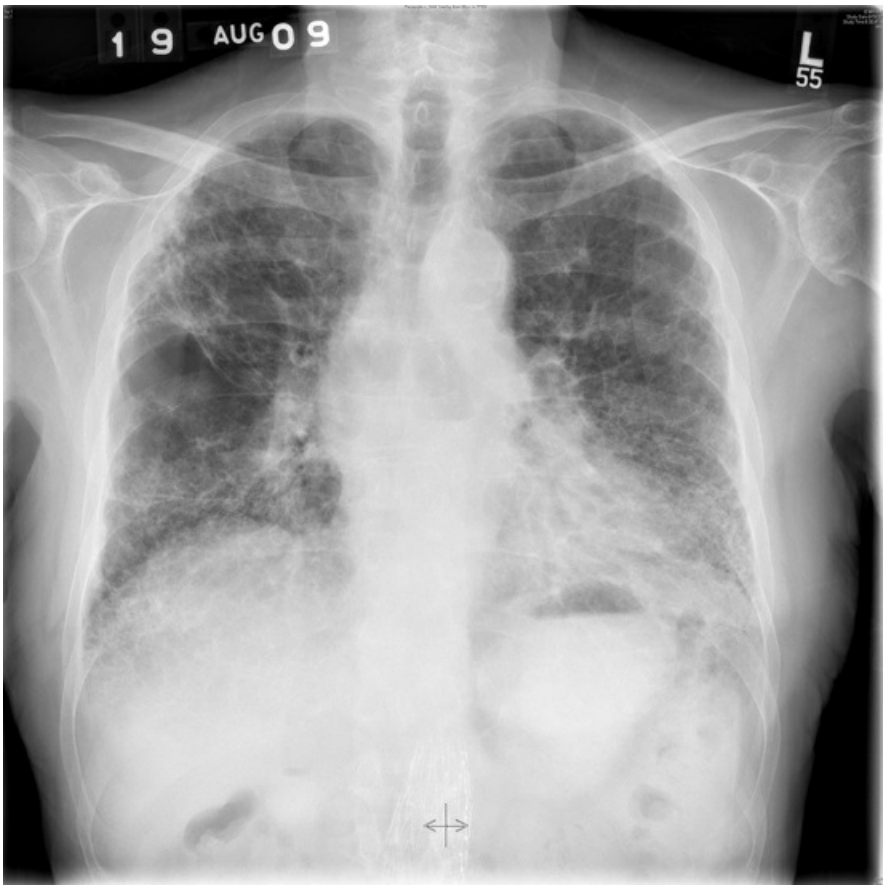


**FIGURE 3.6** Posteroanterior (PA) chest radiograph demonstrating a diffuse interstitial (reticulonodular) pattern in a patient with idiopathic pulmonary fibrosis (IPF).

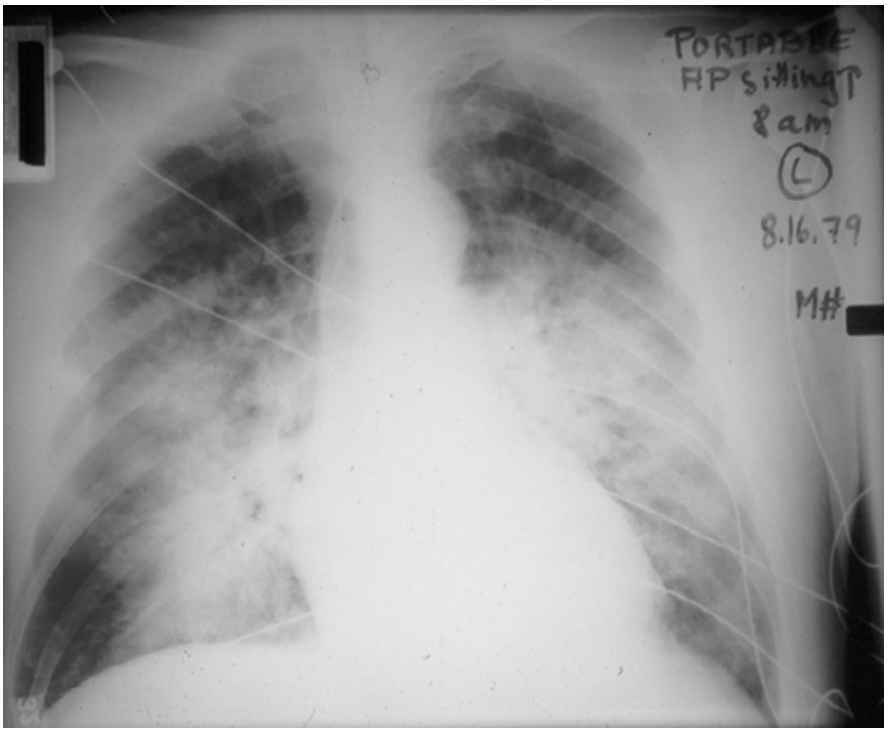


**FIGURE 3.7** Chest radiograph showing a diffuse alveolar filling pattern, most prominent in middle and lower lung fields.

Two additional terms that describe patterns of increased density are commonly used. A *nodular pattern* refers to the presence of multiple discrete, typically spherical, nodules. A uniform pattern of relatively small nodules several millimeters or less in diameter is often called a *miliary pattern*, as can be seen with hematogenous (bloodborne) dissemination of tuberculosis throughout the lungs. Alternatively, the nodules can be larger (e.g., >1 cm in diameter), as seen with hematogenous metastasis of carcinoma to the lungs (Fig. 3.8). Another common term is *ground-glass*, used to describe a hazy, translucent appearance to the region of increased density. Unlike the more opaque appearance of consolidated lung tissue, which obscures lung (primarily vascular) markings, a ground-glass pattern does not obscure underlying lung markings. Although the term can be used to describe a region or a pattern of hazy increased density on a plain chest radiograph, it is more commonly used when describing abnormalities seen on computed tomography (CT) of the chest (Fig. 3.9).

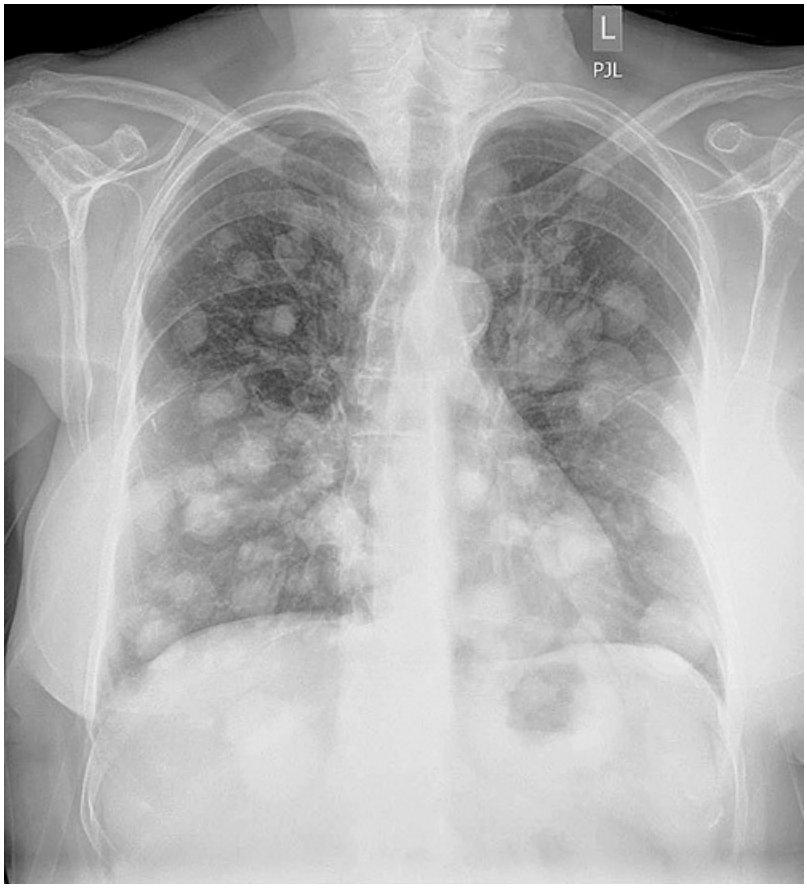


**FIGURE 3.8** Chest radiograph showing a diffuse nodular pattern in a patient with metastatic melanoma. *Source:* (Courtesy Dr. Laura Avery, Massachusetts General Hospital.)

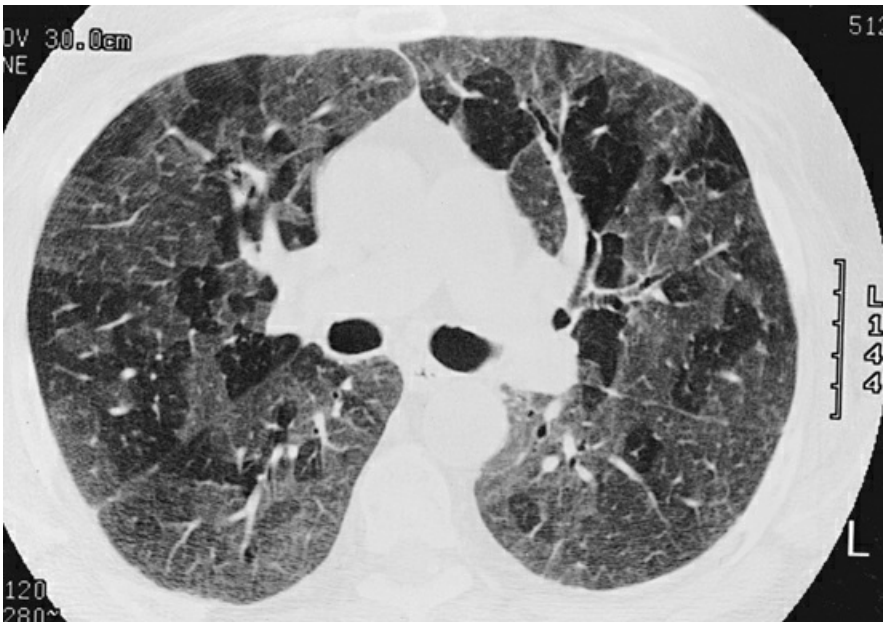


**FIGURE 3.9** High-resolution computed tomography scan of patient with dyspnea and normal chest radiograph. There are well-demarcated areas of lower density (either normal lung or areas of air trapping) interspersed between hazy areas of increased ("ground-glass") density. Biopsy specimen showed findings of hypersensitivity pneumonitis.

The preceding focus on some typical abnormalities provides an introduction to pattern recognition on a chest radiograph. However, the careful examiner must also use a systematic approach in analyzing the image. A chest radiograph shows not only the lungs; radiographic examination may also reveal changes in bones, soft tissues, the heart, other mediastinal structures, and the pleural space.

## Computed tomography

Compared with the plain chest radiograph, CT of the chest provides greater anatomic detail but is more expensive and exposes patients to a significantly higher dose of radiation. With this technique, a narrow beam of x-rays is passed through the patient and sensed by a rotating detector on the other side of the patient. The beam is partially absorbed within the patient, depending on the density of the intervening tissues. Computerized analysis of the information received by the detector allows a series of cross-sectional images to be constructed. Use of different "windows" allows different displays of the collected data, depending on the densities of the structures of interest (Fig. 3.10). With the technique of helical (spiral) CT scanning, the entire chest is scanned continuously (typically during a single breath-hold and using multiple detectors) as the patient's body is moved through the CT apparatus (the gantry).

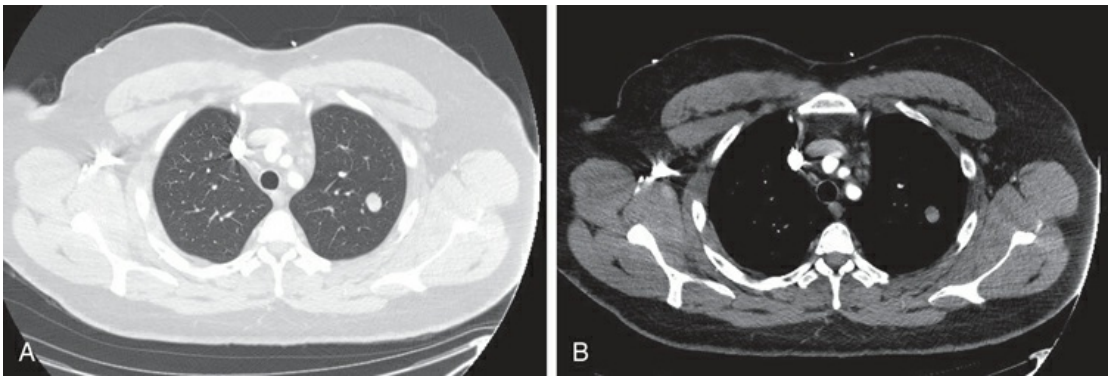


**FIGURE 3.10** Cross-sectional (axial) images from a computed tomography (CT) scan showing a solitary pulmonary nodule in the left lung. Images are displayed using different "windows" at the same cross-sectional level. **A,** Settings were chosen to optimize visualization of lung parenchyma. **B,** Settings were chosen to distinguish different densities of soft tissues, such as structures within mediastinum. Iodinated contrast allows vascular structures in the mediastinum to be readily identified.

CT is particularly useful for detecting subtle differences in tissue density that cannot be distinguished by conventional radiography. In addition, the resolution of the images and the cross-sectional views obtained from the slices provide better definition and more precise three-dimensional spatial location of abnormalities.

CT provides cross-sectional views of the chest and detects subtle differences in tissue density.

Chest CT is used extensively in evaluating pulmonary nodules and the mediastinum. It is also quite valuable in characterizing chest wall and pleural disease. As the technology has advanced, CT has become progressively more useful in the diagnostic evaluation of various diseases affecting the pulmonary parenchyma and the airways. With high-resolution CT, the thickness of individual cross-sectional images is reduced to 1 to 2 mm instead of the traditional 5 to 10 mm. As a result, exceptionally fine detail can be seen, allowing earlier recognition of subtle disease and better characterization of specific disease patterns (see Fig. 3.9).

Over a number of years, computed tomographic pulmonary angiography (CTPA) has become the standard imaging test for the diagnosis of pulmonary thromboembolism. This technique, in which the pulmonary arterial system is visualized by helical CT scanning following injection of radiographic contrast into a peripheral vein, has been increasingly used in place of both perfusion lung scanning and traditional pulmonary angiography (see later). Its use is attractive because CTPA is more likely to be diagnostic than perfusion scanning, and it is less invasive than traditional pulmonary angiography. Although CTPA may not be as sensitive as traditional angiography for detecting emboli in relatively small pulmonary arteries, ongoing improvements in CT scanner technology

have led to better identification of thromboemboli in progressively smaller pulmonary arteries.

Sophisticated software protocols now allow images obtained by CT scanning to be reconstructed and presented in any plane that best displays the abnormalities of interest. In addition, three-dimensional images are produced from the data acquired by CT scanning. For example, a three-dimensional view of the airways can be displayed in a manner resembling what is seen inside the airway lumen during bronchoscopy (described later in this chapter). This methodology creates an imaging tool that has been dubbed *virtual bronchoscopy*.

## Magnetic resonance imaging

Another technique available for evaluation of intrathoracic disease is magnetic resonance imaging (MRI). The physical principles of MRI are complicated and beyond the training of most physicians and students, but are discussed here briefly. The interested reader is referred to other sources for an in-depth discussion of MRI (see Suggested Readings). In brief, the technique depends on the way nuclei within a stationary magnetic field change their orientation and release energy delivered to them by a radiofrequency pulse. The time required to return to the baseline energy state can be analyzed by a complex computer algorithm, and a visual image created.

MRI has several important features in the evaluation of intrathoracic disease. First, flowing blood produces a "signal void" and appears black, so blood vessels can be readily distinguished from nonvascular structures without the need to use intravenous contrast agents. Second, images can be constructed in any plane so that the information obtained can be displayed as sagittal, coronal, or transverse (cross-sectional) views. Third, differences can be seen between normal and diseased tissues that are adjacent to each other, even when they are of the same density and therefore cannot be distinguished by routine radiography or CT. Some of these features are illustrated in Fig. 3.11.

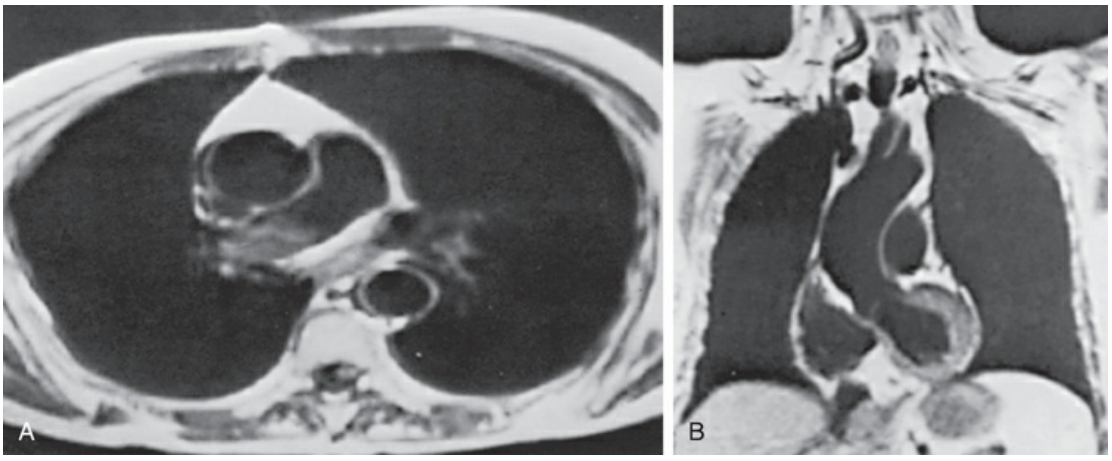


**FIGURE 3.11** Magnetic resonance images of normal chest in cross-sectional **(A)** and coronal **(B)** views. Lumen of structures that contain blood appears black because flowing blood produces a signal void.

MRI scanning is expensive and time-consuming, so it generally is used when it can provide information not otherwise obtainable by less expensive, equally noninvasive means. MRI does not replace CT; rather, it often provides complementary diagnostic information. It can be a valuable tool in evaluating hilar and mediastinal disease and in defining intrathoracic disease that extends to the neck or the abdomen. On the other hand, it is less useful than CT in evaluating both pulmonary parenchymal disease and pulmonary emboli. However, knowledge about the power and limitations of this technique continues to grow, and applications are likely to expand with further refinements in technology.

## Radionuclide lung scanning

Injected or inhaled radioisotopes readily provide information about pulmonary blood flow and ventilation. Imaging of the γ radiation from these isotopes produces a picture showing the distribution of blood flow and ventilation throughout both lungs. Other isotopes have been used for detecting increased metabolic activity at sites of intrathoracic malignancy, though with the caveat that increased activity can also be seen in infectious and inflammatory processes.

### Perfusion and ventilation scanning

For lung perfusion scanning, the most common technique involves injecting aggregates or microspheres of human albumin labeled with a radionuclide, usually technetium-99m, into a peripheral vein. These particles, which are approximately 10 to 60 μm in diameter, travel through the right side of the heart, enter the pulmonary vasculature, and become lodged in small pulmonary vessels (Fig. 3.12). Only areas of the lung receiving perfusion from the pulmonary arterial system demonstrate uptake of the tracer, whereas nonperfused regions show no uptake of the labeled albumin.

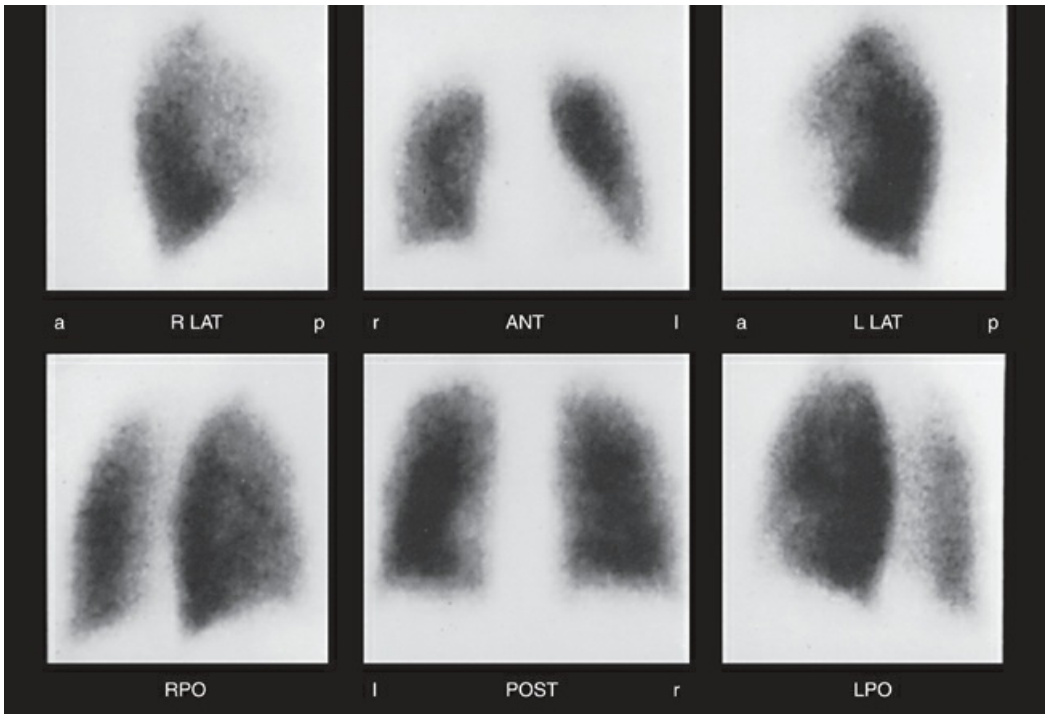


**FIGURE 3.12** Normal perfusion lung scan shown in six views. *a*, anterior; *ANT*, anterior view; *l*, left; *LAT*, lateral view; *LPO*, left posterior oblique view; *p*, posterior; *POST*, posterior view; *r*, right; *RPO*, right posterior oblique view. *Source:* (Courtesy Dr. Henry Royal.)

For ventilation scanning, the gaseous radioisotope xenon-133 or an aerosol of technetium-99m-diethylenetriamine pentaacetate (DTPA) is inhaled, and the sequential pictures obtained show how the gas or aerosol distributes within the lung. Pictures obtained at different times after inhalation reveal information about gas distribution after the first breath (wash-in phase), after a longer time of breathing the gas (equilibrium phase), and after the patient again breathes air to eliminate the radioisotope (wash-out phase). Ventilation scanning shows which regions of the lungs are being ventilated and any significant localized problems with expiratory airflow and "gas trapping" of the radioisotope during the wash-out phase.

Perfusion and ventilation scans are chiefly performed for two reasons: detection of pulmonary emboli and assessment of regional lung function. When a pulmonary embolus occludes a pulmonary artery, blood flow ceases to the lung region normally supplied by that vessel, and a corresponding perfusion defect results. Generally, ventilation is preserved, and a ventilation scan does not show a corresponding ventilation defect. In practice, many pieces of information are considered in the interpretation of the scan, including the appearance of the chest radiograph and the size and distribution of the defects on the perfusion scan. These issues are discussed in greater detail in Chapter 13.

Perfusion and ventilation lung scans are useful for detecting pulmonary emboli and

evaluating regional lung function.

Scans to assess regional lung function are sometimes performed before surgery involving resection of a part of the lung, usually one or more lobes. By visualizing which areas of lung receive ventilation and perfusion, the physician can determine how much the area to be resected is contributing to overall lung function. When the scanning techniques are used in conjunction with pulmonary function testing, the physician can approximately predict postoperative pulmonary function, which is a guide to postoperative respiratory problems and impairment.

### Positron emission tomography (fluorodeoxyglucose scanning)

Positron emission tomography (PET) scanning detects areas of increased metabolic activity. On the basis of the principle that malignant tumors typically exhibit increased metabolic activity, scanning following injection of the radiolabeled glucose analog 18-fluorodeoxyglucose (FDG) has been used as a way of identifying malignant lesions in the lungs and mediastinum (Fig. 3.13). Malignant cells, as a consequence of their increased uptake and use of glucose, take up the FDG more rapidly than surrounding normal cells. Because the FDG has been chemically modified, it cannot be metabolized beyond the initial phosphorylation step and is trapped within the cell. The radiolabeled FDG emits positrons that are detected by PET using a specialized imaging system, or by adapting a γ camera for imaging of positron-emitting radionuclides.

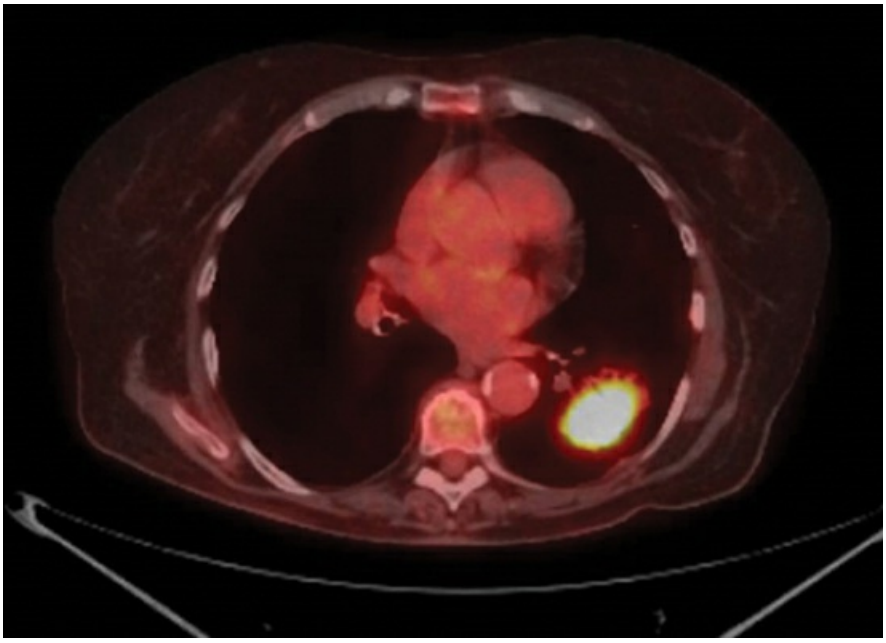

**FIGURE 3.13** Combined positron emission tomography–computed tomography (PET-CT) scan showing uptake of 18-fluorodeoxyglucose in a left lower lobe adenocarcinoma of the lung.

PET imaging with FDG has been used primarily for evaluation of solitary pulmonary

nodules and for staging of lung cancer, particularly for mediastinal lymph node involvement. However, the distinction between benign and malignant disease is not perfect, and false-negative and false-positive results can be seen with slower growing malignant lesions and highly active inflammatory lesions, respectively. PET scans can be performed in conjunction with CT scans, allowing direct correlation of specific lesions visible on CT scan with their corresponding FDG uptake.

## Pulmonary angiography

Pulmonary angiography is a radiographic technique in which a catheter is guided from a systemic vein through the right atrium and ventricle and into the main pulmonary artery or one of its branches. Radiopaque contrast material is injected, and the pulmonary arterial tree is visualized via digital angiography (Fig. 3.14). This test has primarily been used in the past for diagnosing pulmonary embolism. A thromboembolus in a pulmonary vessel appears either as an abrupt termination ("cutoff") of the vessel or as a filling defect within its lumen. Previously, pulmonary angiography was often used when the diagnosis of acute pulmonary embolism was uncertain after lung scanning, or CTPA was inconclusive. However, with advances in CT techniques, a conventional pulmonary angiogram is now rarely needed.

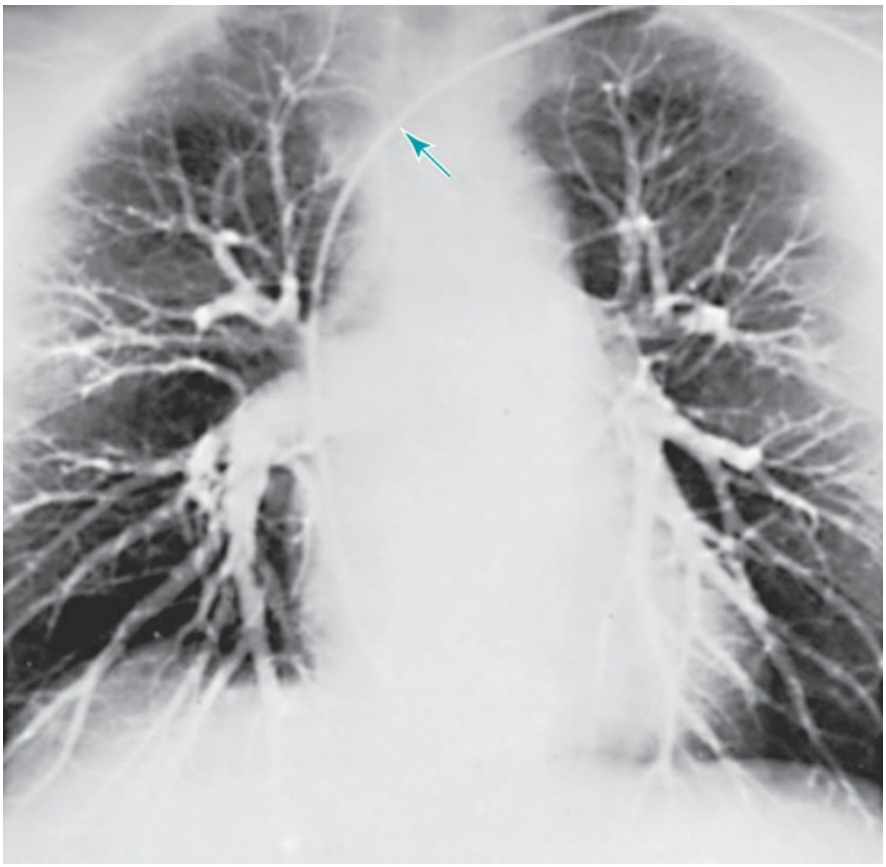

**FIGURE 3.14 Normal pulmonary angiogram.** Radiopaque dye was injected directly into the pulmonary artery, and the pulmonary

arterial tree is well visualized. Catheter used for injecting dye is indicated by arrow. *Source:* (Courtesy Dr. Morris Simon.)

The pulmonary angiogram has other uses, including investigation of congenital vascular anomalies, chronic thromboembolic disease, and invasion of a vessel by tumor. However, use of the angiogram in these situations is also quite infrequent.

## Ultrasonography

The ability of different types of tissue to transmit sound and of tissue interfaces to reflect sound has made ultrasonography useful for evaluating a variety of body structures. A piezoelectric crystal generates sound waves, and the reflected echoes are detected and recorded by the same crystal. Images are displayed on a screen and can be captured for a permanent record.

The heart is the intrathoracic structure most frequently studied by ultrasonography, but the technique is also useful in evaluating pleural disease and can be performed at the patient's bedside (point-of-care ultrasound, or POCUS). In particular, ultrasonography can detect small amounts of pleural fluid and is often used to guide placement of a needle for sampling the fluid. In addition, it can detect walled-off compartments (loculations) within pleural effusions, distinguish fluid from pleural thickening, identify pleural-based nodules or masses, and detect pneumothorax with high sensitivity.

Ultrasonography can localize the diaphragm and detect disease immediately below the diaphragm, such as a subphrenic abscess. Ultrasonography is not useful for defining structures or lesions within the pulmonary parenchyma, because the ultrasound beam penetrates air poorly.

## Bronchoscopy

Direct visualization of the airways is possible by bronchoscopy, originally performed with a hollow, rigid metal tube, but now primarily with a thin, flexible instrument (Fig. 3.15). The flexible bronchoscope transmits images via flexible fiberoptic bundles (traditional fiberoptic bronchoscope) or more commonly via a digital camera at the tip of the bronchoscope that displays the images on a monitor screen. Because the bronchoscope is flexible, the bronchoscopist can bend the tip with a control lever and maneuver into airways at least down to the subsegmental level.

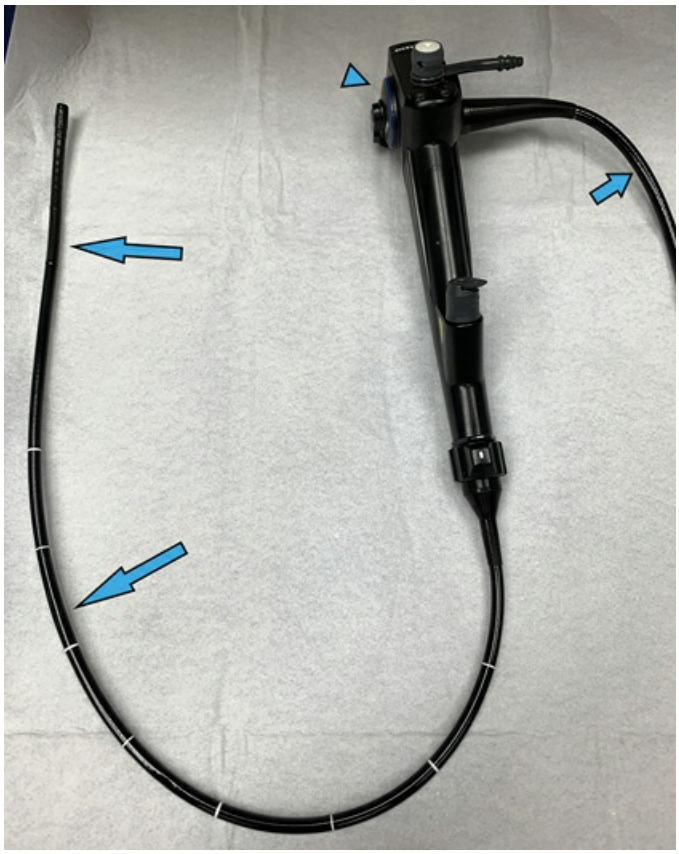

**FIGURE 3.15 Flexible bronchoscope.** Long arrows point to the flexible part passed into the patient's airways. Short arrow points to the portion of bronchoscope connected to the light source. Arrowhead points to controls for the clinician performing the procedure. *Source:* (Courtesy of Dr. George Cheng.)

The bronchoscopist can obtain an excellent view of the airways (Fig. 3.16) and collect a variety of samples for cytologic, pathologic, and microbiologic examination. Sterile saline can be injected through a small hollow channel in the bronchoscope and suctioned back into a collection chamber. This technique, called *bronchial washing*, samples cells and, if present, microorganisms from the lower respiratory tract. When the bronchoscope is passed as far as possible and wedged into an airway before saline is injected, the washings are able to sample the contents of the alveolar spaces; this technique is called *bronchoalveolar lavage* (BAL).

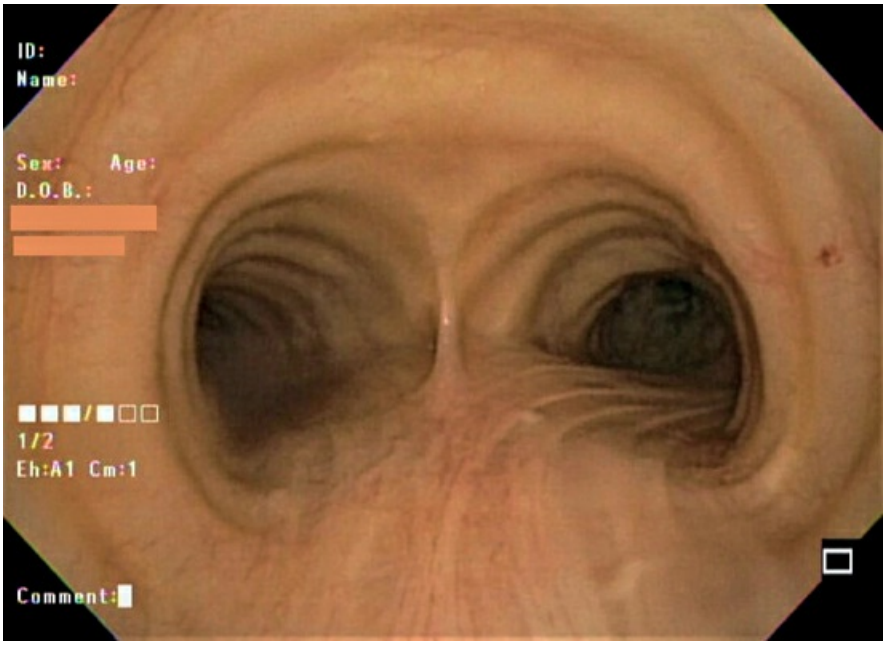


**FIGURE 3.16** Airways as seen through a fiberoptic bronchoscope. At this level, the carina can be seen separating the right and left mainstem bronchi. *Source:* (Courtesy of Dr. George Cheng.)

With the flexible bronchoscope, airways are visualized and laboratory samples are obtained.

A long, flexible wire instrument with a small brush at the tip can be passed through the hollow channel of the bronchoscope. The surface of a lesion within a bronchus can be brushed and the cells collected or smeared onto a slide for cytologic examination. Brushes are frequently passed into diseased areas of the lung parenchyma, and the material collected by the bristles is subjected to cytologic and microbiologic analysis.

A needle at the end of a long catheter passed through the bronchoscope can puncture an airway wall and sample cells from lymph nodes or lesions adjacent to the airway. This technique, called *transbronchial needle aspiration*, can be used to obtain malignant cells from mediastinal lymph nodes in the staging of known or suspected lung cancer. Using an ultrasound probe within the airway during bronchoscopy *(endobronchial ultrasound* or *EBUS)* can help the bronchoscopist localize mediastinal or hilar lymph nodes or solid mass lesions adjacent to the airway and therefore greatly assist with accurate needle placement into the node or the lesion for transbronchial needle aspiration.

With a small biopsy forceps passed through the bronchoscope, the clinician can extract a biopsy specimen from a lesion visualized on the bronchial wall *(endobronchial biopsy)*. The forceps can also be passed through a small bronchus into the lung parenchyma to obtain a small specimen of lung tissue. This procedure, known as *transbronchial biopsy*, yields specimens that are small but have a sizable number of alveoli. Fluoroscopy can be used during the procedure to better localize the position of

the biopsy forceps relative to the desired biopsy site, either a discrete lesion or an area representative of more diffuse disease. EBUS can also be used to help guide placement of the biopsy forceps into relatively peripheral lesions in the lungs.

An additional, specialized technique that has been developed within the past decade is called *electromagnetic navigational bronchoscopy* (often shortened to *navigational bronchoscopy*). Using a previously obtained CT scan of the chest, sophisticated software creates a three-dimensional image of the chest and a "map" with directions for guiding a steerable navigation catheter, advanced through a flexible bronchoscope, into a small peripheral nodule. Without this type of guidance, it is very difficult for the bronchoscopist to choose the correct path for steering the bronchoscope and any sampling tools to a peripheral lesion through the progressively branching system of airways. Because of the tiny size of the distal airways, a technique called *robotic bronchoscopy* has been developed that permits the bronchoscopist to make smaller, more accurate manipulations using a computer-assisted device that holds and directly moves the bronchoscope.

There are many indications for bronchoscopy, usually with a flexible instrument, although the rigid instrument is used under some circumstances. When appropriate, the flexible instrument is preferred because the procedure can be performed using only mild sedation and the patient need not be hospitalized. In contrast, rigid bronchoscopy is performed only under general anesthesia. Some indications for bronchoscopy include (1) evaluation of a suspected endobronchial malignancy, (2) sampling of an area of parenchymal disease by BAL, brushings, or biopsy, (3) evaluation of hemoptysis, and (4) removal of a foreign body (with special instruments that can be passed through the bronchoscope and are capable of retrieving objects). A variety of newer therapeutic modalities are being delivered to the airways via either flexible or rigid bronchoscopic techniques. These modalities include laser techniques for shrinking endobronchial tumors causing airway obstruction; placement of stents to maintain patency of airways having a compromised or obstructed lumen; procedures for dilation of strictures; placement of radioactive seeds directly into malignant airway lesions (brachytherapy); and delivery of electric current (electrocautery), low temperature (cryotherapy), or certain wavelengths of light (photodynamic therapy) to endobronchial masses. Deployment of these novel therapeutic opportunities has spawned a relatively new and rapidly evolving area of subspecialization within pulmonary medicine called *interventional pulmonology*.

Since the invention of the fiberoptic bronchoscope in 1966, flexible bronchoscopy has become a common and useful technique in evaluating and managing pulmonary disease. Even though the physician who first suggested placing a tube into the larynx and bronchi was censured in 1847 for proposing a technique that is "an anatomical impossibility and an unwarrantable innovation in practical medicine," bronchoscopy is generally well tolerated, and complications are infrequent.

## Evaluation on a microscopic level

Microscopy often provides the definitive diagnosis of pulmonary disease suggested by the history, physical examination, or imaging of the chest. Several types of disorders are particularly amenable to diagnosis by microscopy: lung tumors (by either histology or

cytology), pulmonary infection (by microscopic identification of a specific organism), and a variety of miscellaneous pulmonary diseases, particularly those affecting the interstitium of the lung (by histology). Frequently, when a diagnosis is uncertain, the same techniques are used to obtain samples that are processed both for histologic (or cytologic) examination and for identification of microorganisms. This section provides a discussion of how specimens are obtained and then considers how the specimens are processed. The more recent identification and use of tumor markers on lung cancer specimens, which has become important for developing targeted therapeutic plans, will be discussed in Chapters 20 and 21.

## Obtaining specimens

The three main types of specimens the physician uses for microscopic analysis in diagnosing the patient with lung disease are (1) tracheobronchial secretions, (2) tissue from the lung parenchyma, and (3) fluid or tissue from the pleura. A number of methods are available for obtaining each of these types of specimens, and knowledge of the yield and the complications determines the most appropriate method.

The easiest way to obtain a specimen of tracheobronchial secretions is to collect sputum expectorated spontaneously by the patient. The sample can be used for identifying inflammatory or malignant cells and for staining (and culturing) microorganisms. Collecting sputum sounds simple, but it presents several potential problems. First, the patient may not have any spontaneous cough and sputum production. If this is the case, a strong cough that produces sputum can frequently be induced by having the patient inhale an irritating aerosol, such as hypertonic saline ("induced sputum"). Second, what is thought to be sputum originating from the tracheobronchial tree is frequently either nasal secretions or "spit" expectorated from the mouth or the back of the throat. Finally, as a result of passage through the mouth, even a good, deep sputum specimen is contaminated by the multiplicity of microorganisms that reside in the mouth. Because of this contamination, care is required in interpreting the results of sputum culture, particularly with regard to the normal flora of the upper respiratory tract. Despite these limitations, sputum remains a valuable resource when looking for an infectious process such as bacterial pneumonia and tuberculosis. Its role in diagnosing lung cancer is more limited due to its low sensitivity.

Tracheobronchial secretions can also be obtained by two other routes: transtracheal aspiration and bronchoscopy. With transtracheal aspiration, a small plastic catheter is passed inside (or over) a needle inserted through the cricothyroid membrane and into the trachea. The catheter induces coughing, and secretions are collected with or without the additional instillation of saline through the catheter. This technique avoids the problem of contamination by mouth and upper airway flora. It also allows collection of a sample even when the patient has no spontaneous sputum production. However, the technique is not without risk. Bleeding complications and, to a lesser extent, subcutaneous emphysema (air dissecting through tissues in the neck) are potentially serious sequelae. Because of these potential complications, the availability of alternative methods of sampling, and physicians' inexperience with the procedure, transtracheal aspiration is now rarely performed.

Tracheobronchial secretions are provided by:

1. Expectorated sputum (either spontaneous or induced by hypertonic saline)
2. Transtracheal aspiration (rarely used)
3. Flexible bronchoscopy

Flexible bronchoscopy is a suitable and direct way to obtain secretions from the tracheobronchial tree. It has the additional benefit of allowing visualization of the airways. Bronchoscopy has distinct advantages in collecting material for cytologic analysis because specimens can be collected from a localized area directly visualized with the bronchoscope. However, because the instrument passes through the upper respiratory tract, collection of specimens for culture is subject to contamination by upper airway flora. Specially designed systems with a protected brush can decrease contamination, and quantifying the bacteria recovered can be helpful in distinguishing upper airway contamination from true lower respiratory infection.

BAL has become a widely employed method for obtaining specimens from the lower respiratory tract. The fluid obtained by BAL has been used quite effectively for detecting *Pneumocystis jirovecii*, particularly in patients with acquired immunodeficiency syndrome (AIDS) or other causes of immunocompromise. In some diffuse parenchymal lung diseases (see Chapters 9 and 11), analysis of the cellular and biochemical components of BAL may provide information that is useful diagnostically and for research about basic disease mechanisms.

As is true of tracheobronchial secretions, tissue specimens for microscopic examination can be collected in numerous ways. A brush or a biopsy forceps can be passed through a bronchoscope. The brush is often used to scrape cells from the surface of an airway lesion, but it can also be passed more distally into the lung parenchyma to obtain specimens directly from a diseased area. The biopsy forceps is used in a similar fashion to sample tissue from a lesion in the airway (*endobronchial biopsy*) or from an area of disease in the parenchyma (*transbronchial biopsy*, so named because the forceps must puncture a small bronchus to sample the parenchyma). In the case of bronchial brushing, the specimen that adheres to the brush is smeared onto a slide for staining and microscopic examination. For both endobronchial and transbronchial biopsies, the tissue obtained can be fixed and sectioned, and slides can be made for subsequent microscopic examination.

A lesion or diseased area in the lung parenchyma can also sometimes be reached with a needle through the chest wall, particularly when the lesion is near the periphery of the lung. This type of biopsy, called a percutaneous needle biopsy, is typically performed using simultaneous CT imaging to ensure placement of the needle in the desired area. Depending on the type of needle used, a small sample may be either aspirated or taken by biopsy. Bleeding and pneumothorax are potential complications, just as they are for a transbronchial biopsy through a bronchoscope.

Lung biopsy specimens can be obtained by:

1. Flexible bronchoscopy
2. Percutaneous needle aspiration or biopsy

3. Video-assisted thoracic surgery
4. Open surgical procedure

Lung tissue is frequently obtained by a surgical procedure involving an approach through the chest wall. Traditionally, a surgeon made an incision in the chest wall, allowing direct visualization of the lung surface and removal of a small piece of lung tissue. This type of open lung biopsy has largely been supplanted by a less invasive procedure called *thoracoscopy (video-assisted thoracic surgery* or *VATS)*. VATS involves placement of a thoracoscope and biopsy instruments through small incisions in the chest wall; a high-quality image obtained through the thoracoscope can be displayed on a monitor screen. The surgeon uses the video image as a guide for manipulating the instruments to obtain a biopsy sample of peripheral lung tissue or to remove a peripheral lung nodule.

Finally, fluid in the pleural space is frequently sampled in the evaluation of a patient with a pleural effusion. A small needle is inserted through the chest wall and into the pleural space, usually with ultrasound guidance, and fluid is withdrawn. The fluid can be examined for malignant cells and microorganisms. Chemical analysis of the fluid (see Chapter 15) often provides additional useful diagnostic information. A biopsy specimen of the parietal pleural surface (the tissue layer lining the pleural space) may also be obtained blindly, with a special needle passed through the chest wall, or under direct visualization using a thoracoscope. The tissue can be used for microscopic examination and microbiologic studies.

## Processing specimens

Once specimens are obtained, the techniques of processing and types of examination performed are common to those used for many types of tissue and fluid specimens.

Diagnosis of pulmonary infections depends on smears and cultures of the material obtained, such as sputum, other samples of tracheobronchial secretions, or pleural fluid. The standard Gram stain technique often allows initial identification of microorganisms, and inspection may reveal inflammatory cells (particularly polymorphonuclear leukocytes) and upper airway (squamous epithelial) cells, the latter indicating contamination of sputum by upper airway secretions. Final culture results provide definitive identification of an organism, but the results must always be interpreted with the knowledge that the specimen may be contaminated and that what is grown is not necessarily causally related to the clinical problem.

Specimens can be processed for staining and culture of microorganisms and for cytologic and histopathologic examination.

Identification of mycobacteria, including the causative agent for tuberculosis, traditionally required special staining and culturing techniques. Mycobacteria are stained by agents such as carbolfuchsin or auramine-rhodamine, and the organisms are almost unique in their ability to retain the stain after acid is added. Hence, the expression *acid-fast bacilli* is used commonly when referring to mycobacteria. Frequently used staining methods are the Ziehl-Neelsen stain or a modification called

the *Kinyoun stain*. A more sensitive and faster way to detect mycobacteria involves use of a fluorescent dye such as auramine-rhodamine. Mycobacteria take up the dye and fluoresce and can be detected relatively easily even when present in small numbers. Because mycobacteria grow slowly, they may require 6 to 8 weeks for growth and identification on culture media. More recently, genetic probes have been employed to identify the presence of specific mycobacterial species with much greater speed and precision (see later). However, culture is generally still performed to confirm the initial genetic test results and to allow drug sensitivity testing.

Organisms other than the common bacterial pathogens and mycobacteria often require other specialized staining and culture techniques. Fungi may be diagnosed by special stains, such as methenamine silver or periodic acid–Schiff stains, applied to tissue specimens. Fungi can also be cultured on special media favorable to their growth. *P. jirovecii,* a pathogen now classified as a unique category of fungi (see Chapter 26) and most common in patients with impaired defense mechanisms, is stained in tissue and tracheobronchial secretions by methenamine silver, toluidine blue, or Giemsa stain. An immunofluorescent stain using monoclonal antibodies against *Pneumocystis* is particularly sensitive for detecting the organism in sputum and BAL fluid. The organism identified in 1976 as *Legionella pneumophila*, the causative agent of Legionnaires disease, can be diagnosed by silver impregnation or immunofluorescence staining. The organism also can be grown (with difficulty) on some special media.

Cytologic examination for malignant cells is available for expectorated sputum, specimens obtained by needle aspiration, bronchial washings or brushings obtained with a bronchoscope, and pleural fluid. A specimen can be smeared directly onto a slide (as with a bronchial brushing), subjected to concentration (bronchial washings, pleural fluid), or digested (sputum) prior to being smeared on the slide. The slide is then stained by the Papanicolaou technique, and the cells are examined for findings suggestive or diagnostic of malignancy.

Pathologic examination of tissue sections obtained by biopsy is most useful for diagnosis of malignancy or infection, as well as for a variety of other processes affecting the lungs and pleura. In many circumstances, examination of tissue obtained by biopsy is the gold standard for diagnosis, although even biopsy results can show false-negative findings or yield misleading information.

Tissue obtained by biopsy is routinely stained with hematoxylin and eosin for histologic examination. A wide assortment of other stains is available that specifically stain collagen, elastin, and a variety of microorganisms. Immunohistochemical stains applied to neoplasms in the lung are useful to identify and characterize specific tumors, and testing for genetic mutations may help guide treatment of certain types of lung cancer, as discussed in Chapter 21.

Recently, state-of-the-art molecular biology techniques have been applied to respiratory specimens for diagnosis of certain types of respiratory tract infection. When compared with traditional culture methods, the advantages of molecular techniques include rapid detection and specific identification of pathogens, as well as minimizing the hazard to laboratory personnel of exposure to growing pathogens. Techniques based on nucleic acid amplification can be used directly on respiratory specimens for rapid (3-4 hours) detection of the DNA or RNA of some pathogens. For example, the polymerase chain reaction uses specific synthetic oligonucleotide “primer” sequences and DNA

polymerase to amplify DNA unique to a specific organism. If the particular target DNA sequence is present, even if only from a single organism, sequential amplification allows production of millions of copies that can be detected by gel electrophoresis. This technique can be applied to samples such as sputum and BAL, providing an exquisitely sensitive test for identifying organisms such as mycobacteria, *P. jirovecii*, and cytomegalovirus. In addition, oligonucleotide hybridization probes enable rapid identification of organisms that have been cultured from clinical specimens. These newer molecular techniques are becoming more readily available and have seen increasing clinical use over time.

## Assessment on a functional level

Pulmonary evaluation on a macroscopic or microscopic level aims at a diagnosis of lung disease, but neither can determine the extent to which normal lung functions are impaired. This final aspect of evaluation adds an important dimension to overall patient assessment because it reflects how much the disease may limit daily activities. The two most common methods for determining a patient's functional status are pulmonary function testing and evaluation of gas exchange (using either arterial blood gases or pulse oximetry). In addition, a variety of measurements taken during exercise can help determine how much exercise a patient can perform and what factors contribute to any limitation of exercise.

### Pulmonary function tests

Pulmonary function testing provides an objective method for assessing functional changes in a patient with known or suspected lung disease. With the results of tests that are widely available, the physician can answer several questions: (1) Does the patient have significant lung disease sufficient to cause respiratory impairment and account for his or her symptoms? (2) What functional pattern of lung disease does the patient have —restrictive or obstructive disease?

In addition, serial evaluation of pulmonary function enables the physician to quantify any improvement or deterioration in a patient's functional status. Information obtained from such objective evaluation may be essential in deciding when to treat a patient with lung disease and in assessing whether a patient has responded to therapy. Preoperative evaluation of patients can be useful in predicting which patients are likely to have significant postoperative respiratory problems and which are likely to have adequate pulmonary function after lung resection.

Three main categories of information can be obtained with routine pulmonary function testing:

1. Lung volumes, which provide a measurement of the size of the various compartments within the lung
2. Flow rates, which measure maximal flow within the airways
3. Diffusing capacity, which indicates how readily gas transfer occurs from the alveolus to pulmonary capillary blood

Before examining how these tests indicate what type of functional lung disease a

patient has, we briefly describe the tests themselves and how they are performed.

## Lung volumes

Although the lung can be subdivided into compartments in different ways, four volumes are particularly important (Fig. 3.17):

1. Total lung capacity (TLC): total volume of gas within the lungs after a maximal inspiration
2. Residual volume (RV): volume of gas remaining within the lungs after a maximal expiration
3. Vital capacity (VC): volume of gas expired when going from TLC to RV
4. Functional residual capacity (FRC): volume of gas within the lungs at the resting state—that is, at the end of expiration during the normal tidal breathing pattern

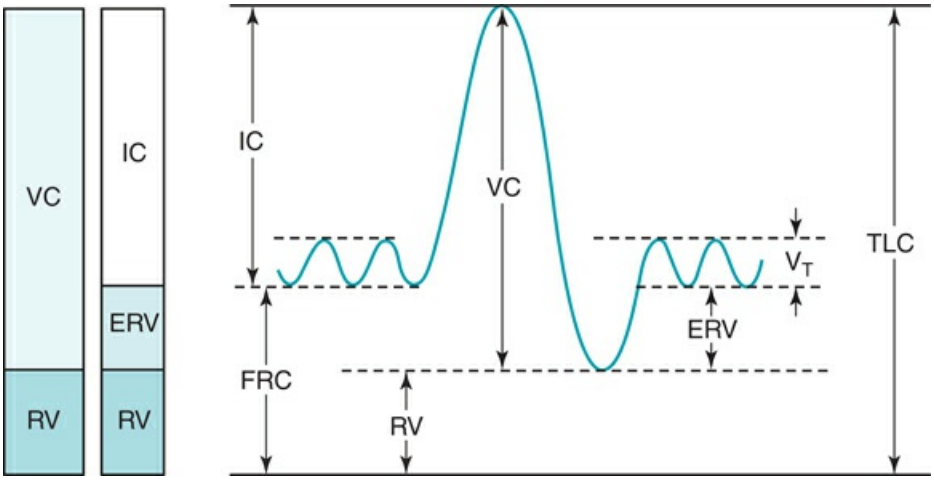


**FIGURE 3.17** Subcompartments of the lung (lung volumes). *Right,* Lung volumes are labeled on spirographic tracing. *Left,* Block diagrams show two ways in which total lung capacity can be subdivided. *ERV*, expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *RV*, residual volume; *TLC*, total lung capacity; *VC*, vital capacity; $V_T$, tidal volume.

VC can be measured by having the patient exhale into a spirometer from TLC down to RV. By definition, the volume expired in this manner is the VC. However, because RV, FRC, and TLC all include the amount of gas left within the lungs even after a maximal expiration, these volumes cannot be determined simply by having the patient breathe into a spirometer. To quantify these volumes, a variety of methods can measure one of the three volumes, and the other two can then be calculated or derived from the spirometric tracing. Two methods are described here:

1. Dilution tests: A known volume of an inert gas (usually helium) at a known concentration is inhaled into the lungs. This gas is diluted by the volume of gas

already present within the lungs, and the concentration of expired gas (relative to inspired), therefore, reflects the initial volume of gas in the lungs.

2. Body plethysmography: The patient, sitting inside an airtight box, performs a maneuver that causes expansion and compression of gas within the thorax. By measuring volume and pressure changes and by applying Boyle's law, the volume of gas in the thorax can be calculated.

Lung volumes are determined by spirometry and either gas dilution or body plethysmography.

In many circumstances, dilution methods are adequate for determining lung volumes. However, for patients who have air spaces within the lung that do not communicate with the bronchial tree (e.g., bullae), the inhaled gas is not diluted in these noncommunicating areas, and the measured lung volumes determined by dilution methods are falsely low. In such situations, body plethysmography gives a more accurate reflection of intrathoracic gas volume because it does not depend on ready communication of all peripheral air spaces with the bronchial tree.

## Flow rates

Measurement of flow rates on routine pulmonary function testing involves assessing airflow during maximal forced expiration—that is, with the patient blowing out as hard and as fast as possible from TLC down to RV. The volume expired during the first second of such a forced expiratory maneuver is called the *forced expiratory volume in 1 second* ($FEV_1$) (Fig. 3.18). When pulmonary function tests are interpreted, $FEV_1$ is routinely compared with VC, or with VC specifically measured during the forced expiratory maneuver, called the *forced vital capacity* (FVC). In interpreting flow rates, the ratio between these two measurements ($FEV_1$/VC or $FEV_1$/FVC) is the most important number used to determine the presence of obstruction to airflow. Another parameter often calculated from the forced expiratory maneuver is the maximal mid-expiratory flow rate (MMFR), which is the rate of airflow during the middle one-half of the expiration (between 25% and 75% of the volume expired during the FVC). MMFR is frequently called the *forced expiratory flow* (FEF) *between 25% and 75% of VC* ($FEF_{25\%–75\%}$). The MMFR or $FEF_{25\%–75\%}$ is a relatively sensitive index of airflow obstruction and may be abnormal when the $FEV_1$/FVC ratio is still preserved.

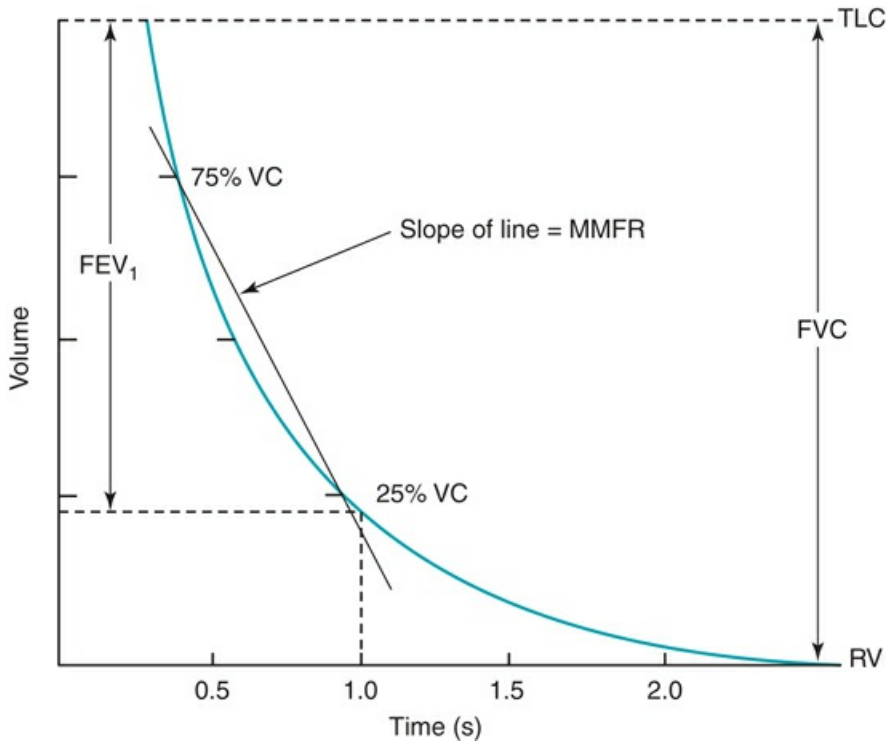


**FIGURE 3.18** Forced expiratory spirogram. Volume is plotted against time while the patient breathes out as hard and fast as possible from total lung capacity *(TLC)* to residual volume *(RV)*. *$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *MMFR*, maximal mid-expiratory flow rate (also called *forced expiratory flow from 25%–75%* [$FEF_{25\%–75\%}$]); *VC*, vital capacity.

Maximal expiratory airflow is assessed by the $FEV_1$/FVC (or $FEV_1$/VC) ratio and MMFR ($FEF_{25\%–75\%}$).

## Diffusing capacity

The diffusing capacity is a measurement of the rate of transfer of gas from the alveolus to hemoglobin within a capillary, measured in relation to the driving pressure of the gas across the alveolar-capillary membrane. Small concentrations of carbon monoxide are generally used for this purpose. Carbon monoxide combines readily with hemoglobin, and the rate of transfer of gas from the alveolus to hemoglobin depends on movement through the alveolar-capillary membrane and the amount of hemoglobin available for binding the carbon monoxide.

The measurement obtained during a diffusing capacity test is primarily dependent on the number of functioning alveolar-capillary units—that is, the surface area available for gas exchange—and the volume of blood (hemoglobin) in the pulmonary capillaries available to bind carbon monoxide. Because the uptake of carbon monoxide by

hemoglobin is dependent on the hemoglobin concentration in the blood, patients with anemia may have a depressed diffusing capacity measurement even if the lungs are normal. Therefore, the observed value is generally corrected for the patient's hemoglobin level.

In practice, the diffusing capacity is commonly decreased in three categories of disease in which surface area for gas exchange is lost, pulmonary capillary blood volume is decreased, or both: (1) emphysema, (2) diffuse parenchymal lung disease, and (3) pulmonary vascular disease. In disorders that affect only the airways and not pulmonary parenchymal tissue (e.g., asthma, chronic bronchitis), diffusing capacity is generally preserved. On the other hand, the diffusing capacity may be elevated in cases of recent intrapulmonary hemorrhage as a result of uptake of carbon monoxide by hemoglobin in the erythrocytes within the alveolar spaces.

Diffusing capacity of carbon monoxide depends largely on the surface area for gas exchange and the pulmonary capillary blood volume.

## Interpretation of normality in pulmonary function testing

Interpretation of pulmonary function tests necessarily involves a qualitative judgment about normality or abnormality on the basis of quantitative data obtained from these tests. To arrive at a relatively objective judgment, the patient's values are compared with normal standards established for each test, based on measurements in large numbers of asymptomatic nonsmoking control subjects without known cardiopulmonary disease. Separate regression equations for men and women have been constructed to fit the data obtained from these normal control subjects. A "normal" or predicted value for a test in a given patient can be determined by inputting the patient's age and height into the appropriate regression equation. Separate race-/ethnicity-specific equations may be used because of population data showing slight differences in pulmonary function in normal individuals of different races and ethnicities. Although the intent is to ensure comparison of each individual to a relevant normal standard, previous studies have not clearly accounted for the contribution of social determinants of health. Therefore, the utility of race-/ethnicity-specific equations is controversial.

The standards for determining what constitutes the "lower limits of normal" for a particular test vary among laboratories. Most laboratories now consider values below the bottom 5th percentile of a normal reference group (also called the "95% confidence interval") to be abnormal, whereas others consider an observed value to be abnormal if it is less than 80% of the predicted value. No matter which criteria are used, all the data must be considered to determine whether certain patterns are consistently present. Interpretation of any test in isolation, with the assumption that a patient with a value of 79% has lung disease, but a patient with a value of 81% is disease-free, is obviously dangerous.

As a general rule, the normal $FEV_1/VC$ or $FEV_1/FVC$ ratio is 0.70 or greater. This means that an individual without obstructive lung disease should, during the first second of a maximal exhalation, be able to exhale at least 70% of the total volume exhaled. However, because the normal ratio can decrease with age, the actual value ideally should be considered abnormal if it is less than the 95% confidence interval for that patient's age.

## Patterns of pulmonary function impairment

In the analysis of pulmonary function tests, abnormalities are usually categorized as one of two patterns (or a combination of the two): (1) an *obstructive* pattern, characterized mainly by obstruction to airflow, and (2) a *restrictive* pattern, with evidence of decreased lung volumes but no airflow obstruction.

An obstructive pattern, as seen in patients with asthma, chronic bronchitis, and emphysema, consists of a decrease in rates of expiratory airflow and usually manifests as a decrease in $FEV_1/FVC$ ratio, accompanied by a decrease in MMFR ($FEF_{25\%–75\%}$) (Fig. 3.19). There is generally a high RV and an increased RV/TLC ratio, indicating air trapping due to closure of airways during forced expiration (Fig. 3.20). Hyperinflation, reflected by an increased TLC, is often found in patients with emphysema. Diffusing capacity is decreased in patients who have loss of alveolar-capillary bed (as seen in emphysema) but not in those without loss of available surface area for gas exchange (as in chronic bronchitis and asthma).

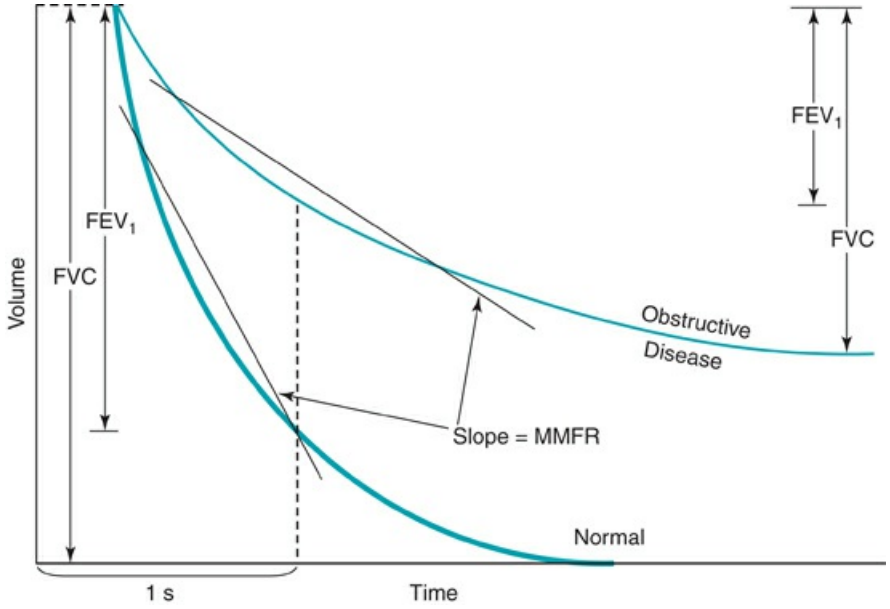


**FIGURE 3.19** Forced expiratory spirograms in a normal individual and a patient with airflow obstruction. Note the prolonged expiration and changes in forced vital capacity *(FVC)* and forced expiratory volume in 1 second *($FEV_1$)* in a patient with obstructive disease. *MMFR*, maximal mid-expiratory flow rate.

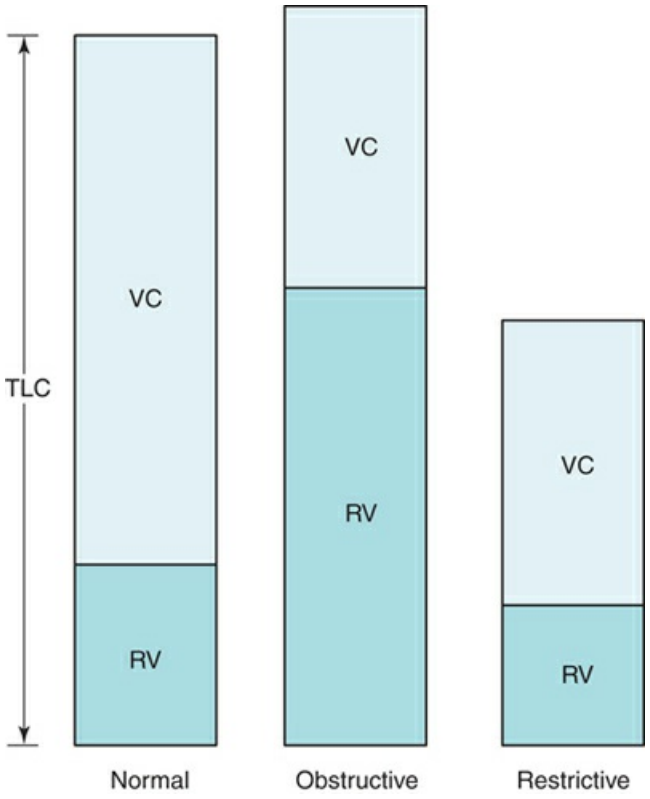


**FIGURE 3.20** Diagram of lung volumes (total lung capacity *[TLC]* and its subcompartments, vital capacity *[VC]* and residual volume *[RV]*) in a normal individual and patients with obstructive and restrictive disease.

In a patient with evidence of airflow obstruction, additional testing is often performed to assess whether the obstruction is at least partially reversible with an inhaled bronchodilator, typically an inhaled β-agonist. Clinically significant improvement or reversibility with bronchodilators is said to be present if either the $FEV_1$ or FVC improves over baseline by at least 10% of the predicted value.

A restrictive pattern is defined by a low TLC, and the hallmark of restrictive disease is a reduction in lung volumes, although expiratory airflow is normal (see Fig. 3.20). Therefore, in addition to TLC, other volumes (RV, VC, and FRC) all tend to be reduced, whereas MMFR and $FEV_1$/FVC are preserved. In some patients with significant loss of volume resulting from restrictive disease, MMFR is decreased because less volume is available to generate a high flow rate. Interpreting a low MMFR in the face of significant restrictive disease is difficult unless MMFR is clearly decreased out of proportion to the decrease in lung volumes.

Patterns of impairment:

1. Obstructive: diminished rates of expiratory airflow (↓ $FEV_1$/FVC, ↓ MMFR)
2. Restrictive: diminished lung volumes (↓ TLC and often other volumes) and preserved expiratory airflow

A wide variety of parenchymal, pleural, neuromuscular, and chest wall diseases can demonstrate a restrictive pattern. Certain clues are useful in distinguishing among these causes of restriction. For example, a decrease in the diffusing capacity for carbon monoxide suggests loss of alveolar-capillary units and points toward diffuse parenchymal lung disease as the cause of the restrictive pattern. The finding of a relatively high RV can indicate either expiratory muscle weakness or a chest wall abnormality that makes the thoracic cage particularly stiff (noncompliant) at low volumes.

Although lung diseases often occur with one or the other of these patterns, a mixed picture of obstructive and restrictive disease can be present, making interpretation of the tests much more complex. These tests do not directly reflect a patient's overall capability for $O_2$ and $CO_2$ exchange, which is assessed by measurement of arterial blood gases.

A simplified guide to the interpretation of pulmonary function tests is presented along with several sample problems in Appendix B.

## Other tests

A significant amount of work was performed in the past to develop tests that detect early obstruction to airflow, particularly when it is due to small or peripheral airway obstruction. Such tests include maximal expiratory flow-volume loops, analysis of closing volume, and frequency-dependent dynamic compliance. Unfortunately, pathologic studies have shown that the correlation between tests of "small airway function" and the actual presence of disease in small airways (as demonstrated by histopathologic specimens) is inconsistent, making the value of these tests unclear. Despite this limitation, the maximal expiratory flow-volume loop is a test with sufficient routine clinical applicability to warrant a short discussion here.

The flow-volume loop is a graphic record of maximal inspiratory and maximal expiratory maneuvers. However, rather than the graph of volume versus time that is given with usual spirometric testing, the flow-volume loop has a plot of flow (on the *Y*-axis) versus volume (on the *X*-axis). Although the initial flows obtained during the early part of a forced expiratory maneuver are effort dependent, the flows during the latter part of the maneuver are effort independent and primarily reflect the mechanical properties of the lungs and the resistance to airflow.

In patients with evidence of airflow obstruction, flow rates at a given volume are decreased, often giving the curve a "scooped out" or coved appearance. The flow data obtained from maximal expiratory flow-volume loops can be interpreted quantitatively (comparing observed flow rates at specified volumes with predicted values) or qualitatively (visually analyzing the shape and concavity of the expiratory portion of the curve). When routine spirometric parameters reflecting airflow obstruction ($FEV_1$/FVC, MMFR) are abnormal, the flow-volume loop is generally abnormal. However, in patients with early airflow obstruction, perhaps localized to small airways, the contour of the terminal part of the expiratory curve may be abnormal even when the $FEV_1$/FVC ratio is normal. Examples of flow-volume loops in a normal patient and in a patient with obstructive lung disease are shown in Fig. 3.21.

In obstructive lung disease, the expiratory portion of the flow-volume curve typically has a “scooped out” or coved appearance.

Another important application of flow-volume loops is for diagnosing and localizing upper airway obstruction. By analyzing the contour of the inspiratory and expiratory portions of the curve, the obstruction can be categorized as *fixed* or *variable*, as well as *intrathoracic* or *extrathoracic*. In a fixed lesion, changes in pleural pressure do not affect the degree of obstruction, and a limitation in peak airflow (a plateau) is seen on both the inspiratory and expiratory portions of the curve. In a variable lesion, the amount of obstruction is determined by the location of the lesion and the effect of alterations in pleural and airway pressure with inspiration and expiration (Fig. 3.22). A variable intrathoracic lesion is characterized by expiratory limitation of airflow and a plateau on the expiratory portion of the flow-volume curve, whereas a variable extrathoracic lesion demonstrates inspiratory limitation of airflow and a plateau on the inspiratory portion of the flow-volume curve (Fig. 3.23).

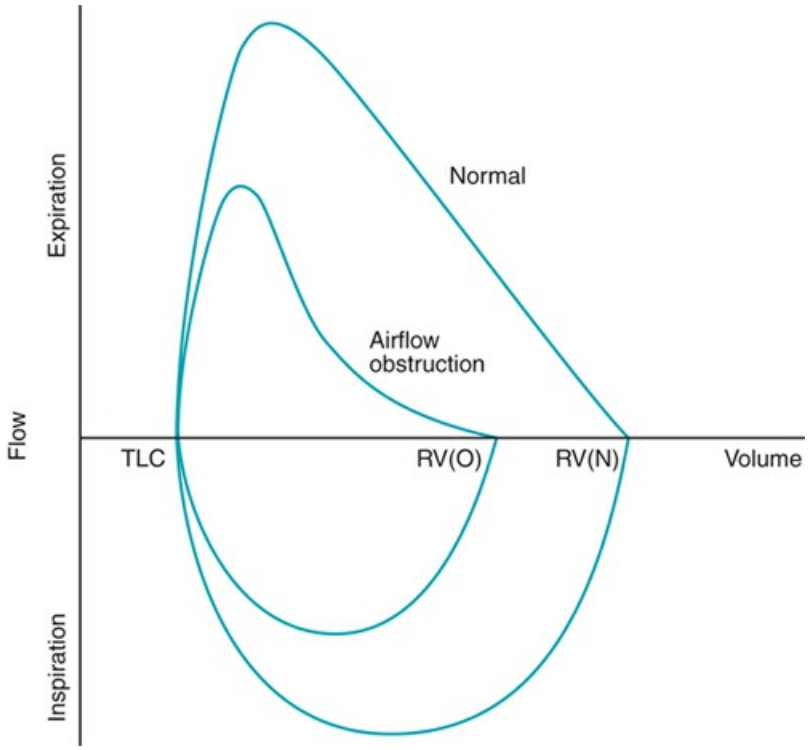


**FIGURE 3.21** Flow-volume loops in a normal individual and a patient with airflow obstruction. Expiratory “coving” is apparent on tracing of a patient with airflow obstruction. *RV(N)*, residual volume in normal individual; *RV(O)*, residual volume in a patient with obstructive disease; *TLC*, total lung capacity.

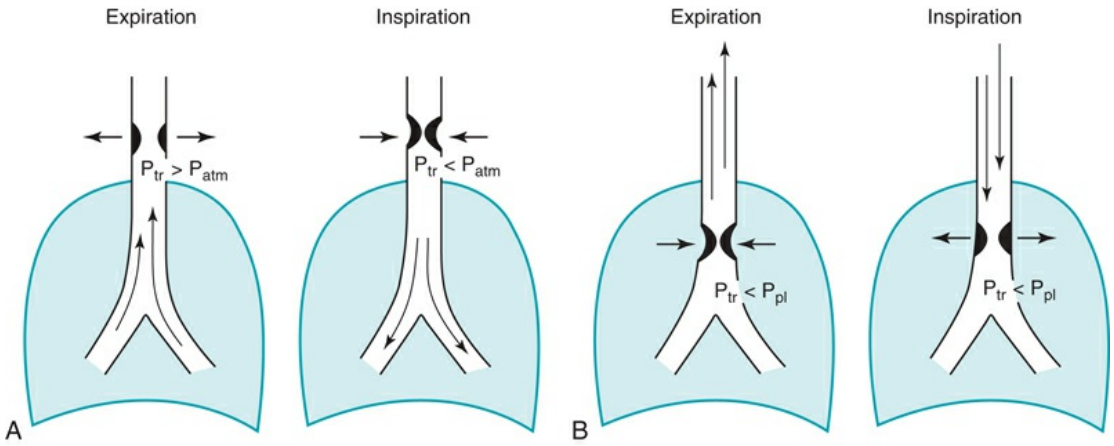


**FIGURE 3.22 Effect of phase of respiration on upper airway obstruction. A,** Variable extrathoracic obstruction. During forced inspiration, airway or tracheal pressure ($P_{tr}$) becomes more negative than surrounding atmospheric pressure ($P_{atm}$), and airway diameter decreases. During forced expiration, more positive intratracheal pressure distends the airway and decreases the magnitude of obstruction. **B,** Variable intrathoracic obstruction. Pleural pressure ($P_{pl}$) surrounds and acts on large intrathoracic airways, affecting the airway diameter. During forced expiration, pleural pressure is markedly positive, and airway diameter is decreased. During forced inspiration, negative pleural pressure causes intrathoracic airways to be increased in size, and obstruction is decreased. *Source:* (From Kryger, M., Bode, F., Antic, R., & Anthonisen, N. (1976). Diagnosis of obstruction of the upper and lower airways. *American Journal of Medicine*, 61, 85–93, with permission from Excerpta Medica Inc.)

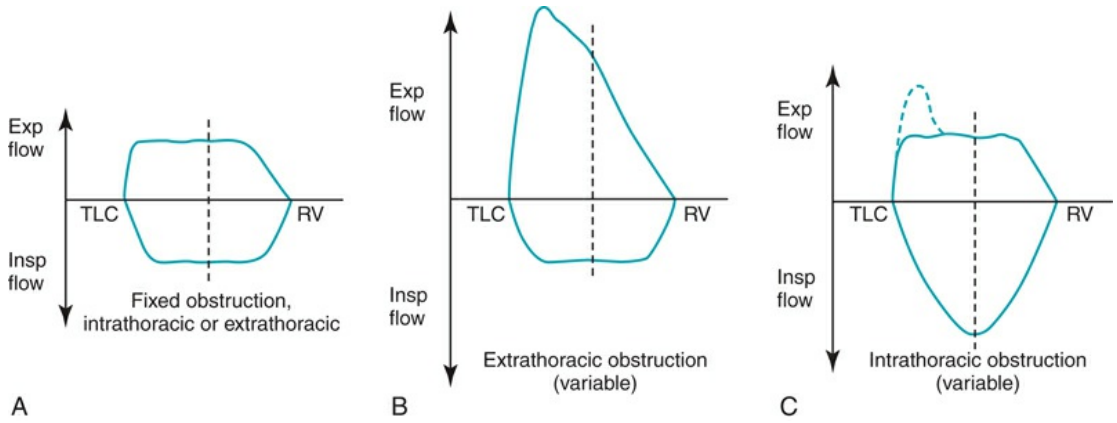


**FIGURE 3.23 Maximal inspiratory and expiratory flow-volume curves in three types of upper airway obstruction.** **A,** Fixed obstruction, either intrathoracic or extrathoracic. Obstruction is equivalent during inspiration and expiration, so maximal inspiratory and expiratory flows are limited to the same extent. **B,** Variable extrathoracic obstruction. Obstruction is more marked during inspiration, and only the inspiratory part of the curve demonstrates a plateau. **C,** Variable intrathoracic obstruction. Obstruction is more marked during expiration, and only the expiratory part of the curve demonstrates a plateau. Dashed line represents higher initial flow occasionally observed before the plateau in intrathoracic obstruction. *Source:* (From Kryger, M., Bode, F., Antic, R., & Anthonisen, N. (1976). Diagnosis of obstruction of the upper and lower airways. *American Journal of Medicine*, *61*, 85–93, with permission from Excerpta Medica Inc.)

Upper airway obstruction can be evaluated and characterized by maximal inspiratory and expiratory flow-volume curves.

An easy and inexpensive test of airflow that is commonly used in clinical practice, particularly in patients with asthma as a method to follow severity of disease, is the *peak expiratory flow rate*. In performing this test, the patient blows out from TLC as hard and rapidly as possible into a simple, readily available device that records the maximal (or peak) expiratory flow rate achieved. Patients with asthma frequently perform and record serial measurements of the test at home as a way of self-monitoring their disease. A significant drop in the peak flow rate from the usual baseline often indicates an exacerbation of the disease and the need for escalating or intensifying the therapeutic regimen.

## Arterial blood gases

Despite the extensive information provided by pulmonary function tests, they do not show the net effect of lung disease on gas exchange, which is easily assessed by studies performed on arterial blood. Arterial blood is usually sampled by needle puncture of a radial artery or, less commonly and with more potential risk, of a brachial or femoral artery. The blood is collected into a heparinized syringe (to prevent clotting), and care is taken to expel air bubbles from the syringe and analyze the sample quickly (or to keep it on ice until analyzed). Three measurements are routinely obtained: arterial $P_{O_2}$, $P_{CO_2}$, and pH.

Arterial $P_{O_2}$ is normally between 80 and 100 mm Hg, but the expected value depends significantly on the patient's age and the simultaneous level of $P_{CO_2}$ (reflecting alveolar ventilation, an important determinant of alveolar and, secondarily, arterial $P_{O_2}$). From the arterial blood gases, the alveolar-arterial oxygen gradient ($AaD_{O_2}$) can be calculated, as discussed in Chapter 1. Normally, the difference between alveolar and arterial $P_{O_2}$ is less than 10 to 15 mm Hg in a healthy young person, and this difference increases with patient age. The oxygen content of the blood does not begin to fall significantly until the arterial $P_{O_2}$ drops below approximately 60 mm Hg (see Chapter 1). Therefore, an abnormally low $P_{O_2}$ generally does not affect $O_2$ transport to the tissues until it drops below this level and the saturation falls.

The range of normal arterial $P_{CO_2}$ is approximately 36 to 44 mm Hg, with a corresponding pH between 7.44 and 7.36. Respiratory and metabolic factors interact closely in determining these numbers and a patient's acid-base status. $P_{CO_2}$ and pH should be interpreted simultaneously because both pieces of information are necessary to distinguish respiratory from metabolic abnormalities.

When $P_{CO_2}$ rises acutely, carbonic acid is formed and the concentration of $H^+$ also rises; therefore pH falls. As a general rule, pH falls approximately 0.08 for each 10 mm Hg increase in $P_{CO_2}$. Such a rise in $P_{CO_2}$ with an appropriate decrease in pH indicates an *acute respiratory acidosis*. Conversely, a drop in $P_{CO_2}$ resulting from hyperventilation, with the attendant increase in pH, indicates an *acute respiratory alkalosis*. With time (hours to days), the kidneys attempt to compensate for a prolonged respiratory acidosis by retaining bicarbonate ($HCO_3^-$), or by excreting bicarbonate in the case of a prolonged respiratory alkalosis. In either case, the compensation returns the pH value toward but not entirely to normal, and the disturbance is termed a *chronic* (i.e., compensated) *respiratory acidosis* or *alkalosis*.

On the other hand, a patient who is producing too much (or excreting too little) acid has a *primary metabolic acidosis*. Conversely, an excess of $HCO_3^-$ (equivalent to a decrease in $H^+$) defines a *primary metabolic alkalosis*. In the same way the kidneys attempt to compensate for a primary respiratory acid-base disturbance, respiratory elimination of $CO_2$ is adjusted to compensate for metabolic acid-base disturbances. Hence, metabolic acidosis stimulates ventilation, $CO_2$ elimination, and a rise in the pH toward the normal level, whereas metabolic alkalosis suppresses ventilation and $CO_2$ elimination, and the pH falls toward the normal range.

Arterial $P_{CO_2}$ and pH together determine the nature of an acid-base disorder and the presence or absence of compensation.

In practice, the clinician considers three fundamental questions in defining all acid-base disturbances: (1) Is there an acidosis or alkalosis? (2) Is the primary disorder of respiratory or metabolic origin? (3) Is there evidence for respiratory or metabolic compensation? Table 3.2 summarizes the findings in the major types of acid-base disturbances. Unfortunately, matters are not always so simple in clinical practice, and it is quite common to see complex mixtures of acid-base disturbances in patients who have several diseases and are receiving a variety of medications.

**TABLE 3.2**
**Acid-Base Disturbances**

| Condition | $P_{CO_2}$ | pH | $HCO_3$ |
|---|---|---|---|
| Normal | 36–44 torr | 7.36–7.44 | 23–30 mEq/L |
| **Respiratory Acidosis** | | | |
| No metabolic compensation | ↑ | ↓ | Normal (or ↑) |
| With metabolic compensation | ↑ | Lesser ↓ | ↑ |
| **Respiratory Alkalosis** | | | |
| No metabolic compensation | ↓ | ↑ | Normal (or ↓) |
| With metabolic compensation | ↓ | Lesser ↑ | ↓ |
| **Metabolic Acidosis** | | | |
| No respiratory compensation | Normal | ↓ | ↓ |
| With respiratory compensation | ↓ | Lesser ↓ | ↓ |
| **Metabolic Alkalosis** | | | |
| No respiratory compensation | Normal | ↑ | ↑ |
| With respiratory compensation | ↑ | Lesser ↑ | ↑ |

Because of the discomfort and small risk of vessel injury with arterial puncture, a venous blood sample is sometimes used as a surrogate for arterial blood gas analysis. The $P_{CO_2}$ in venous blood is typically slightly higher than in arterial blood, whereas the venous pH is slightly lower than arterial pH. Because venous $P_{O_2}$ is largely dependent on how much $O_2$ has been extracted at the local tissue level, it does not reflect arterial $P_{O_2}$ and therefore is not clinically useful.

A simplified guide to the interpretation of arterial blood gases is presented along with several sample problems in Appendix C.

## Pulse oximetry

Although direct measurement of arterial blood gases provides the best method for assessing gas exchange, it requires collection of blood by arterial puncture. As already

noted, sampling of arterial blood is uncomfortable for patients, and a small but finite risk of complications is associated with arterial puncture. As a result, pulse oximetry, a noninvasive method for assessing arterial oxygen saturation of hemoglobin, has come into widespread use, particularly for hospitalized patients. The pulse oximeter is clipped onto a patient's finger, and specific wavelengths of light are passed through the finger (Fig. 3.24). Oxygenated and deoxygenated hemoglobin have different patterns of light absorption, and measurement of the pulsatile absorption of light by arteriolar blood passing through the finger allows quantifying the two forms of hemoglobin. However, certain limitations are inherent in pulse oximetry: (1) the oximeter measures $O_2$ saturation rather than $Po_2$, (2) no information is provided about $CO_2$ elimination and acid-base status, and (3) the results are typically inaccurate in the presence of an abnormal hemoglobin such as carboxyhemoglobin, as seen in carbon monoxide poisoning. Theoretically, skin pigmentation should not affect pulse oximetry because it measures the difference in absorption of oxygenated and deoxygenated hemoglobin for an *individual* patient. However, recent studies have suggested that pulse oximetry is less accurate in patients with darker skin as opposed to lighter skin. Thus, for all the reasons outlined above, pulse oximetry values must be considered as only part of the clinical picture.


**FIGURE 3.24 Pulse oximeter.** The two numbers shown on the digital display represent the oxygen saturation and the heart rate.

## Exercise testing

Because limited exercise tolerance is frequently the most prominent symptom of patients with a variety of pulmonary problems, study of patients during exercise may

provide valuable information about how much these patients are limited and why. Adding measurements of arterial blood gases during exercise provides an additional dimension and shows whether gas exchange problems (either hypoxemia or hypercapnia) contribute to the impairment. Pulse oximetry commonly is also used during exercise, particularly because it is noninvasive, but it provides less information than direct measurement of arterial blood gases.

Although any form of exercise is theoretically possible for the testing procedure, the patient usually is studied while exercising on a treadmill or stationary bicycle. Measurements that can be made at various points during exercise include work output, heart rate, ventilation, $O_2$ consumption, $CO_2$ production, expired gas tensions, and arterial blood gases. Analysis of these data can often distinguish whether ventilation, cardiac output, or problems with gas exchange (particularly hypoxemia) provide the major limitation to exercise tolerance. The results can guide the physician to specific therapy on the basis of the type of limitation found.

A simpler form of exercise often used to assess functional limitation is the 6-minute walk test. This test measures the distance a patient is able to walk (not jog or run) in 6 minutes and whether there is a change in the patient's oxygen saturation (as measured by pulse oximetry) during the exercise. However, other than potentially identifying a decrease in the patient's oxygen saturation, the test does not provide information about the mechanism of exercise limitation and cannot distinguish limitation due to lung disease from that attributable to other medical problems such as heart disease, peripheral vascular disease, or muscle weakness. Nevertheless, it does provide an easily performed objective measure of a patient's exercise tolerance and can be used to follow how a patient is doing over time, with or without treatment.

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# 4: Anatomic and physiologic aspects of airways

OUTLINE



In its transit from the nose or the mouth to the gas-exchanging region of the lung, air passes through the larynx and then along a series of progressively branching tubular structures from the trachea down to the smallest bronchioles. In preparation for a discussion of diseases affecting the airways, this chapter describes the structure of these airways and then considers how they function.

## Structure

The trachea, bronchi, and bronchioles down to the level of the terminal bronchioles constitute the *conducting airways*. Their functions are to transport gas and protect the distal lung from inhaled contaminants, but they do not directly participate in gas exchange. Beyond the terminal bronchioles are the *respiratory bronchioles*. They mark the beginning of the *respiratory zone* of the lung, where gas exchange takes place. Respiratory bronchioles are considered part of the gas-exchanging region of lung because some alveoli are present along part of their walls. With successive generations of respiratory bronchioles, more alveoli appear along the walls up to the site of the alveolar ducts, which are entirely "alveolarized" (Fig. 4.1). The discussion in this chapter is limited to the conducting airways and those aspects of the more distal airways that affect air movement but not gas exchange. Alveolar structure is discussed further in Chapter 8.

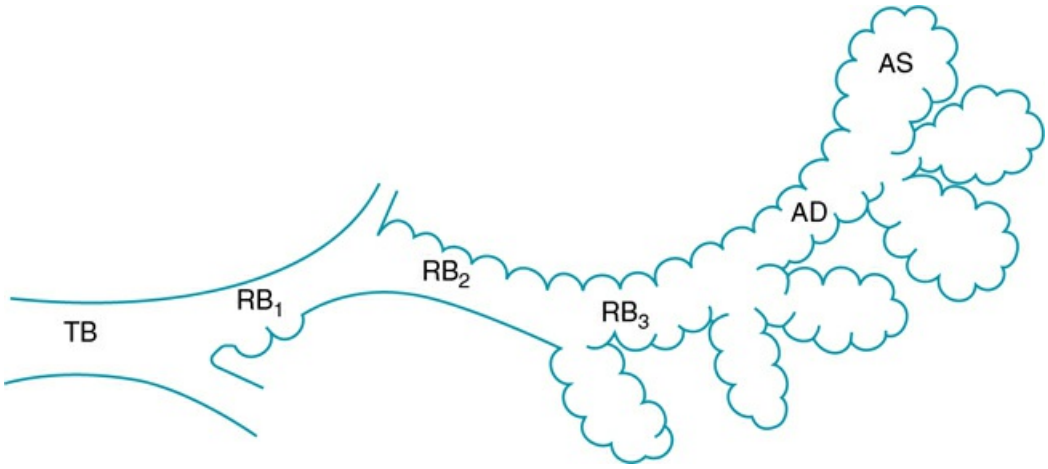


**FIGURE 4.1** Schematic diagram of the most distal portion of the respiratory tree. Each terminal bronchiole *(TB)* supplies several generations of respiratory bronchioles ($RB_1$ through $RB_3$) that have progressively more respiratory (alveolar) epithelium lining their walls. Alveolar ducts *(AD)* are entirely lined by alveolar epithelium, as are alveolar sacs *(AS)*. The region of lung distal to and supplied by the terminal bronchiole is termed the *acinus*. *Source:* (From Thurlbeck, W. M. (1968). Chronic obstructive lung disease. In S. C. Sommers (Ed.), *Pathology annual* (Vol. 3). New York, NY: Appleton-Century-Crofts.)

Conducting airways: trachea, bronchi, bronchioles down to the level of terminal bronchioles
Respiratory zone: respiratory bronchioles, alveolar ducts, and alveoli

The airways are composed of several layers of tissue (Fig. 4.2). Adjacent to the airway lumen is the mucosa, beneath which is a basement membrane separating the epithelial cells of the mucosa from the submucosa. Within the submucosa are mucous glands (the contents of which are extruded through the mucosa into the airway lumen), smooth muscle, and loose connective tissue with some nerves and lymphatic vessels. Surrounding the submucosa is a fibrocartilaginous layer that contains the cartilage rings that support several generations of airways. Finally, a layer of peribronchial tissue with fat, lymphatics, vessels, and nerves encircles the rest of the airway wall. Each of these layers is considered here, with a description of the component cells and the way the structure changes in the distal progression through the tracheobronchial tree.

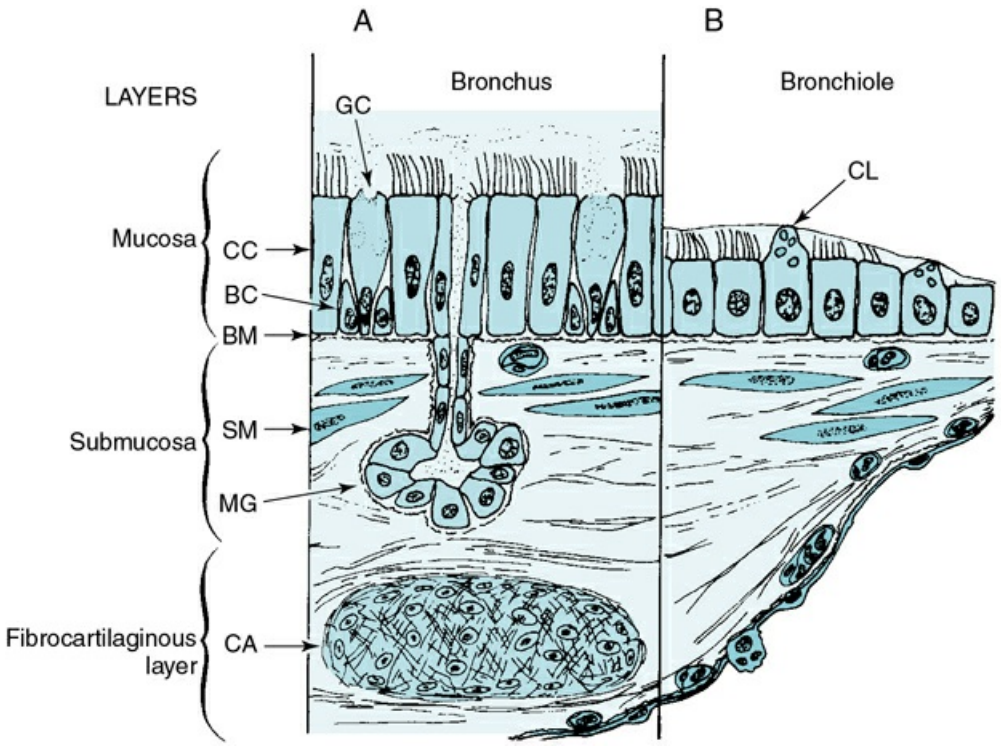


**FIGURE 4.2 Schematic diagram of components of airway wall. A,** Level of large airways (trachea and bronchi). **B,** Level of small airways (bronchioles). *BC*, basal cell; *BM*, basement membrane; *CA*, cartilage; *CC*, ciliated columnar epithelial cell; *CL*, club cell; *GC*, goblet cell; *MG*, mucous gland; *SM*, smooth muscle. *Source:* (Adapted from Weibel, E. R., & Burri, P. H. (1973). Funktionelle Aspekte der Lungenmorphologie. In W. A. Fuchs, & E. Voegeli (Eds.), *Aktuelle Probleme der Roentgendiagnostik* (Vol. 2). Bern, Switzerland: Huber.)

The surface layer (mucosa) consists predominantly of pseudostratified columnar epithelial cells. It is termed “pseudostratified” because the mucosa appears to be several cells thick in the trachea and large bronchi, owing to the columnar shape and variable positions of the nuclei; however, each cell is actually resting on the basement membrane (see Fig. 4.2A). The cilia that line the airway lumen are responsible for protecting the deeper airways by propelling tracheobronchial secretions (and inhaled particles that become trapped within them) toward the pharynx. The cilia of airway epithelial cells have the characteristic ultrastructure seen in other ciliated cells: a central pair of microtubules and an outer ring of nine double microtubules (see Fig. 22.1). Small side arms called *dynein arms*, which contain the adenosine triphosphatase (ATPase) *dynein*, are found on the outer double microtubules. Proper configuration and function of dynein arms are necessary for normal ciliary functioning, and patients with cilia lacking fully functional dynein side arms have impaired ciliary action and thus develop recurrent bronchopulmonary infections.

Scattered between the ciliated epithelial cells are mucin-secreting epithelial cells called *goblet cells* that produce and discharge mucins into the airway lumen. Normally, goblet cells are more prevalent in the proximal airways. Their numbers decrease peripherally, and they are not present in terminal bronchioles. Mucins are very large glycoproteins, some of which are bound to airway epithelial cell membranes, whereas others are secreted into the airways. Secreted mucins can polymerize, physically expand greatly, and bind with water, electrolytes, and other molecules to form a viscous mucous gel that is essential for normal ciliary motion and hence for airway clearance of inhaled particles and microorganisms. In humans, there are seven major airway mucins; the two most important appear to be MUC5AC, produced primarily by goblet cells, and MUC5B, produced primarily by cells in the submucosal glands (see later). In normal healthy airway secretions, MUC5AC is the most abundant mucin present.

The mucosal layer of large airways consists of pseudostratified ciliated columnar epithelial cells.

The surface epithelium appears to have other important functions that may be altered in certain clinical conditions. By virtue of tight junctions between epithelial cells at the luminal surface, the epithelium prevents access of inhaled foreign material to deeper levels of the airway wall. There is evidence that inflammation-induced disruption in this barrier function, which allows antigens to penetrate the epithelial surface, is important in asthma. Another important function of the epithelium involves active transport and regulation of ions, particularly chloride and bicarbonate, to maintain a favorable ionic environment in the mucous layer lining the airway wall. In cystic fibrosis, an abnormality in chloride transport by surface epithelial cells plays a crucial role in the pathogenesis of the disease (see Chapter 7).

*Basal cells* are interspersed deep within the epithelium, abutting the basement membrane. The function of basal cells is to differentiate into and replenish the more superficial cells of the mucosa, either the ciliated cells or the secretory goblet cells. In more distal airways and terminal bronchioles, *club cells* are found interspersed among the ciliated epithelial cells. Club cells, which act as progenitor cells for themselves and for ciliated cells, have several protective functions, including synthesis of immune molecules and small amounts of mucus and surfactant proteins, as well as metabolism of inhaled chemicals. Another important cell type found in the airway epithelium is the *pulmonary neuroendocrine cell (Kulchitsky cell)*. These cells are part of the amine precursor uptake and decarboxylation system and are therefore capable of producing amine hormones (serotonin, dopamine, norepinephrine) and polypeptide products. In addition, pulmonary neuroendocrine cells have cytoplasmic processes that extend to the luminal surface. As a result, these cells may be involved in sensing the composition of inspired gas and have been postulated to play a role in regional control of ventilation and perfusion. The different cell types in the airway mucosa are significant not only because of their normal physiologic roles but also because of the way they respond to airway irritation and their potential for becoming neoplastic.

The submucosal layer has two major components: *bronchial mucous glands* and *bronchial smooth muscle*. Mucus is a gel-like substance composed mostly of water (97%) and mucins. Other proteins including immunomodulators are also present, as

well as electrolytes, lipids, and cellular debris. The mucous glands are located between bands of smooth muscle. The base of the glands is lined by *mucous cells* and *serous cells* and is connected to the airways by ducts lined by ciliated cells. The duct transports the secretions through the mucosa and discharges them into the airway lumen. As noted earlier, the primary mucin produced by mucous glands is MUC5B. In disease states such as chronic obstructive pulmonary disease and cystic fibrosis, where there is mucous gland hyperplasia and hypertrophy, MUC5B becomes more prominent than MUC5AC in bronchial secretions. However, whether the functions of MUC5AC and MUC5B are different is not yet understood. In addition, a common polymorphism in the MUC5B gene is associated with susceptibility to idiopathic pulmonary fibrosis (IPF), a disease of the lung parenchyma that is discussed in Chapter 11. Serous cells also line the mucous gland; these cells secrete proteoglycans and numerous antimicrobial substances involved in innate immunity (see Chapter 22). Airway smooth muscle is present from the trachea down to the level of the bronchioles and even the alveolar ducts. Disturbances in the quantity and function of the smooth muscle are important in disease, particularly in the case of bronchial asthma.

Bronchial secretions are produced by submucosal glands and goblet cells in the mucosa.

The fibrocartilaginous layer is important because of the structural support cartilage provides to the airways. The configuration of the cartilage varies significantly at different levels of the tracheobronchial tree, but the function at all levels is probably similar.

Airway structure changes considerably in the distal progression through the tracheobronchial tree.

We have thus far described the general structure of the airways, but structure varies considerably at different levels. Some of these differences are illustrated in Fig. 4.2. In the progression distally through the tracheobronchial tree, the following changes are normally seen:

1. The epithelial layer of cells becomes progressively thinner until there is a single layer of cuboidal cells at the level of the terminal bronchioles.
2. Goblet cells decrease in number until they disappear about at the level of the terminal bronchiole. Dome-shaped club cells appear in the smaller airways, where they contribute to mucus production and other functions.
3. Mucous glands, which are present in the trachea and large bronchi, are most numerous in the medium-sized bronchi. They become progressively fewer in number more distally and are absent from the bronchioles.
4. Smooth muscle changes in configuration at different levels of the tracheobronchial tree. In the trachea and large bronchi, smooth muscle is found as either bands or a spiral network, whereas in the smaller bronchi and bronchioles, a continuous layer of smooth muscle encircles the airway. As airway size decreases distally in the tracheobronchial tree, smooth muscle generally

occupies a larger portion of the total thickness of the airway wall. The proportion of smooth muscle to airway wall thickness becomes maximal at the level of the terminal bronchiole.

5. Cartilage also changes in configuration. In the trachea, the cartilaginous rings are horseshoe shaped, with the posterior aspect of the trachea being free of cartilage. In the bronchi, plates of cartilage become smaller and less numerous distally until cartilage is absent in the bronchioles.

The preceding discussion describes many of the structural features of normal airways. However, a variety of changes occur with chronic exposure to an irritant such as cigarette smoke. Some of these changes, particularly in the epithelial cells, are important because of the potential for eventual malignancy (see Chapter 20). Other changes are apparent in the mucus-secreting structures (bronchial mucous glands and goblet cells) and are important features of chronic bronchitis. With chronic irritation, the mucous glands hypertrophy, and goblet cells become more numerous and are found more distally than usual, even in the terminal bronchioles. The implications of these changes in disease states are discussed in Chapter 6.

## Neural control of airways

Innervation (neural control) of airways is an important aspect of airway structure, with particular clinical relevance in asthma (see Chapter 5). Neural control of airways affects contraction and relaxation of bronchial smooth muscle and the activity of bronchial mucous glands. An understanding of the innervation, receptors, and mediators involved in neural control of airway function is important both because of the potential role of neural control in the pathogenesis of asthma and because of the well-established role of pharmacotherapy in stimulating or blocking airway receptors. The following discussion focuses on three components of the neural control of airways: the parasympathetic (cholinergic) system, the sympathetic (adrenergic) system, and the nonadrenergic, noncholinergic inhibitory system (Fig. 4.3).

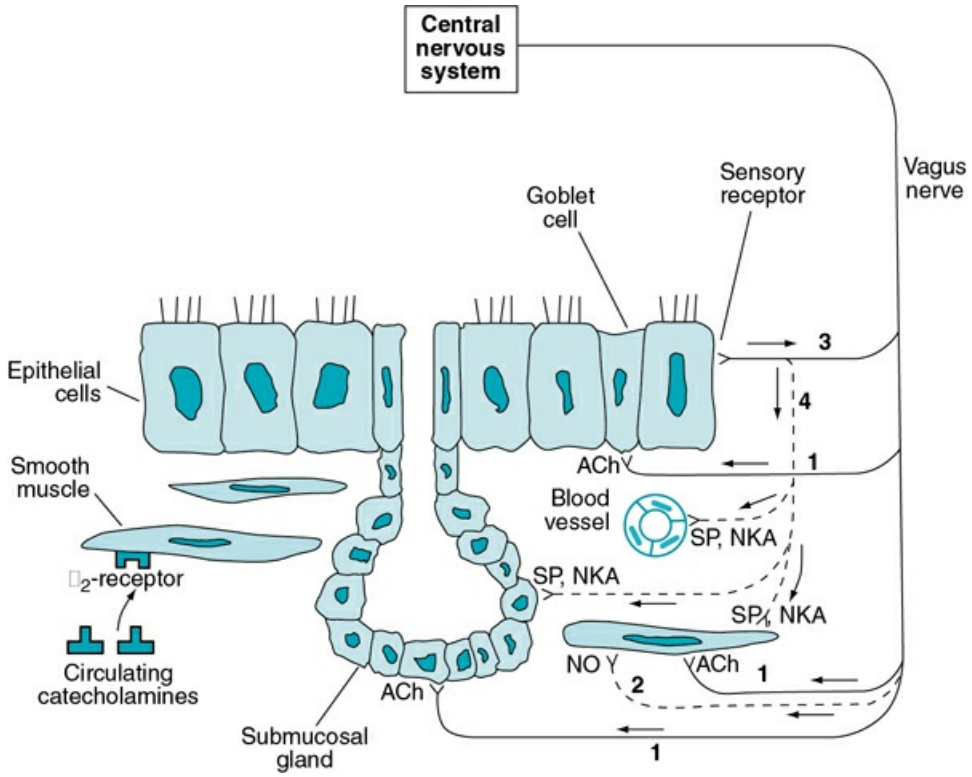


**FIGURE 4.3 Schematic diagram of neural control of airways.** Parasympathetic fibers innervating airway smooth muscle cells, submucosal glands, and goblet cells are labeled *1;* nonadrenergic, noncholinergic innervation of airway smooth muscle cells is labeled *2;* afferent innervation of airway epithelial cells is labeled *3;* and neural traffic along the pathway labeled *4* goes to the vagus nerve but also has effects on airway smooth muscle cells, submucosal glands, and blood vessels via local reflexes. *ACh*, acetylcholine; *NKA*, neurokinin A; *NO*, nitric oxide; *SP*, substance P.

The *parasympathetic nervous system* provides the primary bronchoconstrictor tone to the airways via branches of the vagus nerve (cranial nerve X, also known as the pneumogastric nerve). Stimulation of these vagal branches causes contraction of smooth muscle in the airway wall; in addition, vagal fibers innervate bronchial mucous glands and goblet cells, resulting in increased secretions from both components of the mucus-secreting apparatus. The receptors on smooth muscle and the mucus-secreting apparatus are muscarinic cholinergic receptors; the neurotransmitter is acetylcholine. These cholinergic receptors are more dense in central than in peripheral airways. Identification of multiple subtypes of muscarinic receptors, elucidation of a variety of effects on both airway smooth muscle and on nerves supplying smooth muscle, and evidence of “cross-talk” among muscarinic and adrenergic receptors have demonstrated that muscarinic receptor signaling is actually much more complicated. However, the simplified schema described earlier provides a practical framework for later discussions

about pathophysiology and treatment of airway diseases. For example, inhaled anticholinergic medications such as ipratropium and tiotropium block the muscarinic cholinergic receptors, resulting in bronchodilation and decreased mucus production (see Chapter 6).

The role of the *sympathetic (adrenergic) nervous system* in controlling airway tone is much less clear because there is sparse if any adrenergic innervation of human airways. Despite the paucity of innervation by sympathetic nerves, there are adrenergic, primarily $\beta_2$, receptors on bronchial smooth muscle that are stimulated by circulating catecholamines. When stimulated, $\beta_2$-receptors activate adenylate cyclase, increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP) and causing relaxation of bronchial smooth muscle. In contrast, stimulation of the less numerous α-adrenergic receptors results in a degree of bronchoconstriction. Receptor density of $\beta_2$-adrenergic receptors is opposite that of cholinergic receptors; $\beta_2$-adrenergic receptors are more dense in peripheral than in central airways. Inhaled β-adrenergic agonists cause bronchodilation and are a critical part of asthma and COPD treatment (see Chapter 6).

A search for innervation of the airways with a smooth muscle relaxant (bronchodilating) effect has demonstrated a third component of neural control, often called the *nonadrenergic, noncholinergic inhibitory system*. Similar to parasympathetic airway nerves, these nerve fibers run in the vagal trunk, but when stimulated they cause bronchial smooth muscle to relax, not constrict. Evidence suggests that important bronchodilator transmitters for these nerves are nitric oxide and vasoactive intestinal peptide.

Parasympathetic innervation provides bronchoconstrictor tone to the airways; nonadrenergic, noncholinergic inhibitory innervation provides bronchodilator tone. Adrenergic receptors are present on bronchial smooth muscle despite the absence of significant sympathetic innervation.

Thus far, only the neural output to (i.e., efferent control of) the airways has been discussed. In addition, there are airway receptors with sensory (afferent) nerve innervation. These receptors, which are located in the airway epithelial layer and are responsive to various chemical and mechanical stimuli, include myelinated cough ("irritant") receptors and unmyelinated C fibers. Neural traffic is carried from these sensory endings in afferent fibers of the vagus nerve. This sensory information is not only communicated to the central nervous system via the afferent vagal fibers but also responsible for activation of local reflexes causing release of mediators called *tachykinins* from nerve endings in the airway wall. The tachykinins, which include substance P and neurokinin A, can cause bronchoconstriction, increased submucosal gland secretion, and increased vascular permeability (see Fig. 4.3). However, the magnitude of their importance in disease states such as asthma is not known with certainty.

## Function

With each breath, air flows from the nose or mouth, through the bronchial tree, to the

regions of the lung responsible for gas exchange. To generate this flow of air during inspiration, the pressure must be lower in the alveoli than at the nose or mouth because air flows from a region of higher pressure to one of lower pressure. The diaphragm and inspiratory muscles of the chest wall cause expansion of the chest and lungs, producing negative pressure in the pleural space and in the alveoli, thereby initiating airflow.

Flow in the airways can be considered analogous to the flow of current in an electrical system. However, rather than a voltage drop when electrons flow across a resistance, airways have a pressure difference between two points of airflow, and resistance to flow is provided primarily by the limited cross-sectional area of the airways themselves. The rate of airflow depends in part on the pressure difference between the two points and in part on the airway resistance. During inspiration, alveolar pressure is negative relative to nose or mouth pressure (which is atmospheric), and air flows inward. In contrast, during expiration, alveolar pressure is positive relative to nose or mouth pressure, and air flows outward from the alveoli toward the nose and mouth.

## Airway resistance

Airflow is in fact a much more complex phenomenon than we have just described. For instance, consider in more detail the problem of resistance. Normal airway resistance is approximately 0.5 to 2 cm $H_2O$/L/s—that is, a pressure difference of 0.5 to 2 cm $H_2O$ between nose or mouth and alveoli is required for air to flow at a rate of 1 L/s between these two points. Which airways provide most of the resistance? Although a single smaller airway provides more resistance to airflow than a single larger airway, it does not follow that the aggregate of smaller airways provides the bulk of the resistance. In fact, the opposite is true. For example, even though the trachea is large, there is only one trachea, and the total cross-sectional area of the airways at this level is quite small. In contrast, at the level of small airways (e.g., <2 mm in diameter), the enormous number of these airways makes up for the small diameter of each one and results in a very large total cross-sectional area.

Fig. 4.4 shows how much resistance to flow is provided by airways at different levels of the tracheobronchial tree. The major site of resistance (the smallest total cross-sectional area) is at the level of medium-sized bronchi. The small or peripheral airways, generally defined as airways less than 2 mm in diameter, contribute only approximately 10% to 20% of the total resistance. Hence, these airways are frequently called the “silent zone” because disease in them can affect their size without significantly altering the total airway resistance. Unfortunately, despite a great deal of work by physiologists to develop methods capable of detecting increased resistance in small airways, the usefulness of such tests has not met original expectations. The correlation between these functional studies and histopathologic confirmation of disease in small airways has been inconsistent; consequently, these tests are used infrequently.

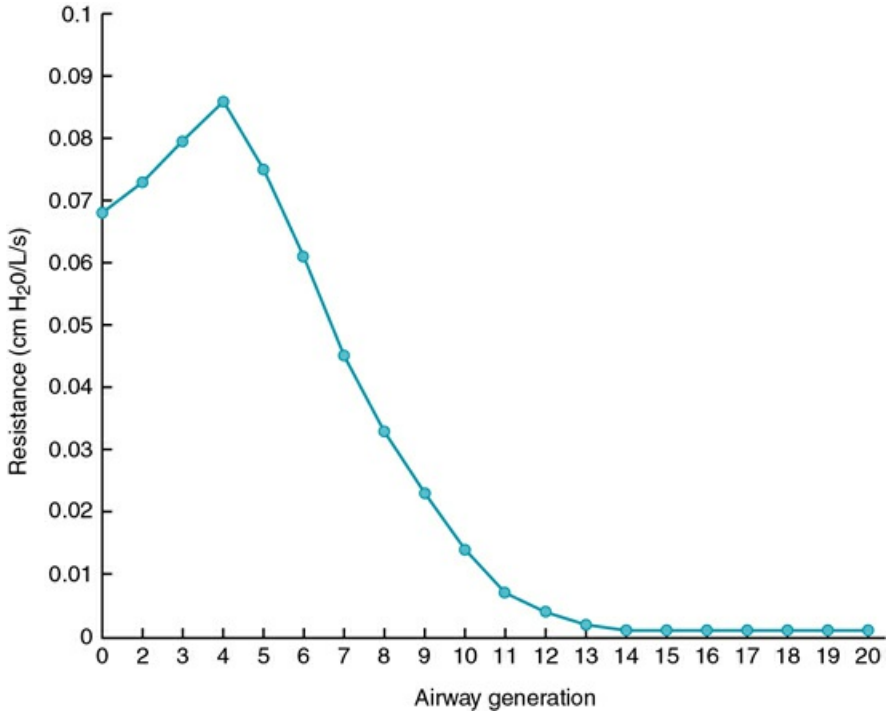


**FIGURE 4.4 Contribution to resistance by airways at different levels of the tracheobronchial tree.** The greatest contribution to resistance is provided by medium-sized bronchi (generations 3-5), whereas smaller airways (approximately generation 9 and beyond) provide significantly less contribution to total resistance because of their much larger total cross-sectional area.

Because resistance to airflow in the tracheobronchial tree depends on the total cross-sectional area of the airways, large- and medium-sized airways provide greater resistance than the more numerous small airways.

## Maximal expiratory effort

The next important aspect of the physiology of airflow is the distinction between normal breathing and forced or maximal respiratory efforts. A great deal of information can be obtained by looking at flow during a forced expiration (i.e., breathing out from total lung capacity down to residual volume as hard and as fast as possible). In a discussion of this concept, it is useful to consider the flow-volume curve mentioned in Chapter 3 and shown again in Fig. 4.5. In this figure, a series of expiratory curves shows the kind of flow rates generated by progressively greater expiratory efforts. Curve A shows expiratory flow with a relatively low effort, whereas curve D shows flow with a maximal expiratory effort.

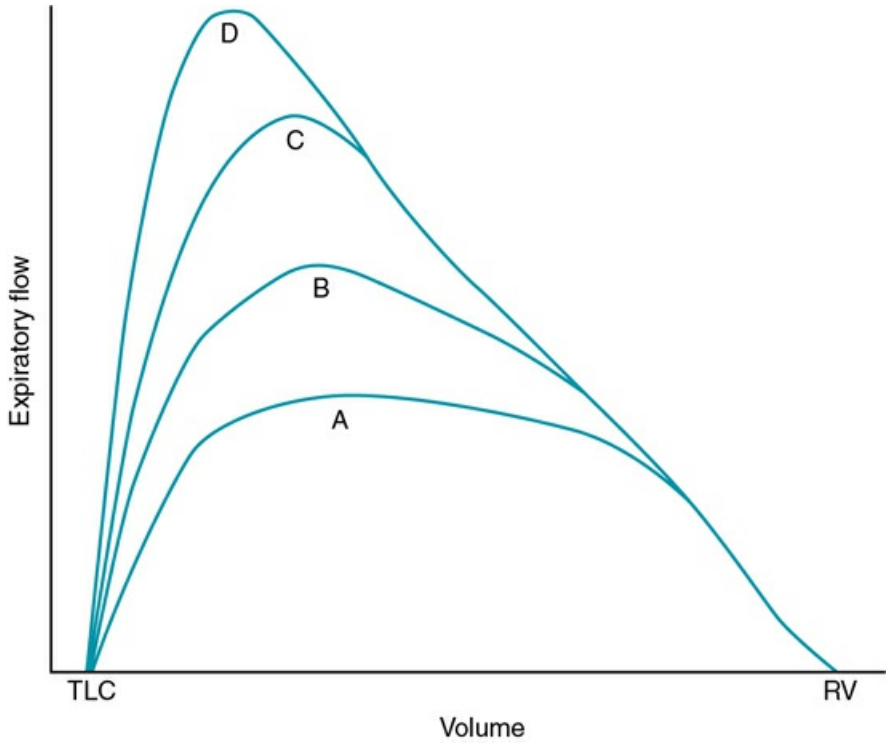


**FIGURE 4.5 Expiratory flow-volume curves with progressively greater effort.** Curve *A* represents least effort; curve *D* represents maximal expiratory effort. On the downsloping part of curve, beyond the point at which approximately 30% of vital capacity has been exhaled, flow is limited by mechanical properties of airways and lungs, not by muscular effort. *RV*, residual volume; *TLC*, total lung capacity.

During the first part of this curve, until approximately 30% of vital capacity has been exhaled, the flow rate is quite dependent on the effort expended—that is, greater expiratory efforts cause a continuing increase of expiratory flow rates, which results from increased pleural pressure and thus an increased driving force for expiratory airflow. This region of the vital capacity during maximal expiratory flow is often termed the *effort-dependent portion*.

Below 70% of vital capacity comes a point at which we can no longer increase the flow rate with increasing effort. Something other than our muscular strength (hence, other than the positive pleural pressure we can generate) limits flow. In fact, the limiting factor is a critical narrowing of the airways. When we try harder, all we do is compress the airway further without any increase in the flow rate. This part of the flow-volume curve is frequently termed the *effort-independent portion* because beyond a certain level of effort, further effort does not result in an augmented flow rate.

During most of a forced expiration, flow is limited by critical narrowing of the airway; further effort does not result in augmented flow.

Two unanswered questions about maximal expiratory flow remain. First, why does critical narrowing of the airways occur such that increasing effort proves fruitless in augmenting flow? Second, at what level in the airways does this critical narrowing occur? Answers to these questions, which have been of great interest to pulmonary physiologists, must be distilled from a large amount of theory and research.*

During a forced expiration, there are several determinants of airway diameter. First and most obvious is the inherent size of the airway, which depends on its level in the tracheobronchial tree and the tone of the airway smooth muscle. In disease, smooth muscle tone may be increased (as in asthma), or secretions in the airway may narrow the lumen (as in asthma or chronic bronchitis). Second is the potential collapsibility of the airway, which, in small airways, is affected by the amount of radial traction exerted by surrounding lung tissue on the airway walls. The trachea and larger bronchi are supported by cartilage, but small airways are surrounded by a supporting framework of alveolar walls that are constantly "pulling" or "tethering" the airways open. When lung parenchyma is destroyed, as in emphysema, the small airways lose some of this normal support and are more likely to collapse during a forced expiration (see Chapter 6). Third is the combination of external and internal pressures acting on the small airways. This balance of pressures is crucial in determining whether a particular airway remains open or closed during a forced expiration.

Airway diameter depends on the level of the airway in the tracheobronchial tree, airway smooth muscle tone, radial traction on the airway from surrounding lung tissue, and internal and external pressures on the airway.

The external pressure acting on an airway is determined by pleural pressure (Fig. 4.6). When pleural pressure is strongly positive, as with a forced expiration, the airway becomes compressed. It is only because of a counteracting pressure within the airways that they remain open in the face of a strongly positive external pressure. Two factors contribute to the internal airway pressure: (1) the elastic recoil of the lungs and (2) pleural pressure transmitted to the alveoli and airways. Fig. 4.6 shows that the alveolar wall is like a stretched balloon trying to expel its air. In the same way a balloon, in trying to collapse, exerts pressure on the air inside, the alveolar wall has its elastic recoil that exerts pressure on the gas within. This pressure results in flow from the alveoli through the airways. However, remember that flow through an airway is accompanied by a pressure drop along the airway. At a certain point along the airway, the pressure falls enough so that pressure within the airway becomes equal to the pressure outside the airway (i.e., pleural pressure). This point where the pressure inside the airway is the same as the pressure outside the airway is called the *equal pressure point*. Increased effort causes increased pleural pressure, which is exerted both on the alveolus and on the airway wall. The increased pressure on the alveoli (which would increase flow) is therefore matched by the increased external pressure on the airway. Thus, the driving pressure (i.e., the difference between alveolar pressure and the pressure at the equal pressure point) is determined *only* by the elastic recoil pressure of the lung. With additional effort, the increased alveolar driving pressure is exactly balanced by the increased external pressure on the airway, which promotes airway collapse (see Fig. 4.6). As a net result, the elastic recoil pressure, not the pleural pressure produced by a

maximal expiratory effort, is the important determinant of maximal expiratory flow, at least in the effort-independent or latter part of a forced expiration. Subsequent chapters show that in diseases with altered elastic recoil, maximal expiratory flow rates are affected by this change in the effective driving pressure for airflow.

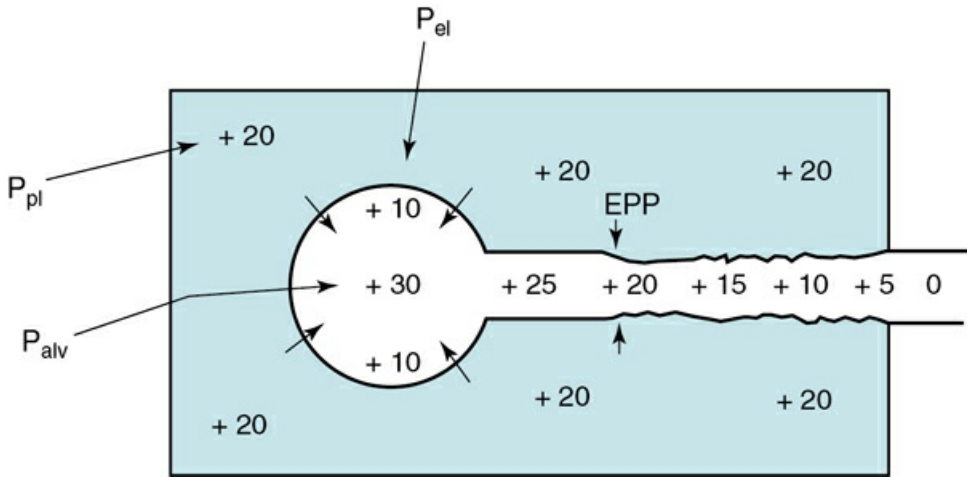


**FIGURE 4.6 Schematic diagram of the equal pressure point concept during a forced (maximal) expiration.** Alveolus and its airway are shown inside the box, which represents pleural space. Alveolar pressure *($P_{alv}$)* has two contributing components: pleural pressure *($P_{pl}$)* and elastic recoil pressure of lung *($P_{el}$)*. In this diagram, $P_{pl}$ = 20 cm $H_2O$ and $P_{el}$ = 10 cm $H_2O$, so $P_{alv}$, the sum of $P_{pl}$ and $P_{el}$, is 30 cm $H_2O$.

At the equal pressure point, internal and external pressures on the airway are equal. The net driving pressure from the alveolus to the equal pressure point is the elastic recoil pressure of the lung.

The final question to be addressed here is the level at which this critical narrowing (i.e., the equal pressure point) occurs. The answer depends on lung volume. The equal pressure point does not remain at a constant position as an individual exhales to residual volume. At higher lung volumes, the elastic recoil pressure is greater (the alveoli are more stretched), and a longer distance separates the alveoli from the equal pressure point. At lung volumes above functional residual capacity, this critical point of narrowing is within relatively large airways, segmental bronchi or larger. At lower lung volumes, the elastic recoil pressure is lower, the distance from alveoli to the equal pressure point is smaller, and critical narrowing occurs in smaller, more peripheral airways. Because maximal airflow depends on elastic recoil and the resistance of the airways peripheral ("upstream") to the equal pressure point, the resistance of the small airways is a larger component of the upstream resistance at small lung volumes and is therefore a greater determinant of maximal expiratory flow at lower volumes along the

flow-volume curve.

The equal pressure point moves peripherally (toward smaller airways) as lung volume decreases during a forced expiration; hence, the resistance of small airways limits maximal expiratory flow more at low than at high lung volumes.

In summary, flow through the tracheobronchial tree reflects a combination of factors: airway size, support or radial traction exerted by the surrounding lung parenchyma, and driving pressure provided by the elastic recoil of the lung. Although pleural pressure contributes to the driving pressure for airflow, it also exerts a counterbalancing external pressure on the airway, promoting airway collapse. Later discussion of specific disorders will show how these different factors are interrelated as determinants of maximal expiratory airflow and how they can be altered in disease states.

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*This discussion uses a model based on the equal pressure point concept. A different model based on wave speed theory probably provides a more accurate conceptual framework for expiratory flow limitation, but it is far more complicated and beyond the scope of this discussion.

# 5: Asthma

## OUTLINE



Chapter 4 discussed the normal structure of airways and considered several aspects of airway function. The most common disorders disrupting the normal structure and function of the airways—asthma and chronic obstructive pulmonary disease (COPD)—are discussed here and in Chapter 6, respectively. Several other miscellaneous diseases affecting airways are covered in Chapter 7.

Asthma is an inflammatory condition characterized by episodes of reversible airway narrowing due to contraction of smooth muscle within the airway wall. It is a common disorder that affects approximately 7% to 10% of the population. Although asthma can occur in any age group, it is particularly common in children and young adults and

probably is the most common chronic disease in these age groups.

The primary feature patients with asthma appear to have in common is *hyperresponsiveness* of the airways, that is, an exaggerated constriction of airway smooth muscle and consequent narrowing of airways in response to a wide variety of stimuli. The hyperresponsiveness is likely due in part to underlying airway inflammation with several types of inflammatory cells, especially lymphocytes and eosinophils. The particular constellation of stimuli triggering attacks often varies among patients, but the net effect (bronchoconstriction) is qualitatively similar. Because asthma is by definition a disease with at least some reversibility, the patient experiences exacerbations (attacks) interspersed between intervals of diminished symptoms or symptom-free periods. During an attack, the diagnosis is usually straightforward. During a symptom-free period, the diagnosis may be more difficult to establish and may require provocation or challenge tests to induce airway constriction.

Asthma is characterized by hyperreactivity of the airways and reversible episodes of bronchoconstriction.

# Etiology and pathogenesis

Despite the high prevalence of asthma in the general population and the many advances that have been made in treating the manifestations of the disease, a great deal about its etiology and pathogenesis remains uncertain. In fact, it is likely that what we call asthma may not represent a single disease process, but rather may encompass several pathogenetic pathways (endotypes) that have somewhat different expressions (phenotypes) despite common features of airway inflammation and episodic bronchoconstriction. While recognizing the difficulty of presenting a unifying framework for understanding asthma, this section focuses on two major questions that are relevant across the spectrum of what we call asthma: (1) What causes certain people to have airways that hyperreact to various stimuli? (2) What factors appear to be important from the time of exposure to the stimulus until the time of clinical response?

## Predisposition to asthma

Potential factors that may predispose an individual to developing asthma are both inherited and acquired. There has been significant interest in and investigation of genetic and environmental factors that may contribute to the development of asthma, but the roles of these factors and their possible interactions have not been fully elucidated.

### Genetics

A substantial proportion of patients with asthma, particularly children and young adults, have a history of allergic rhinitis and eczema along with accompanying markers for allergic disease, such as positive skin tests and elevated immunoglobulin E (IgE) levels. In these patients, the asthma is frequently exacerbated by exposure to allergens to which the patients have been previously sensitized. Patients who have an allergic phenotype to their asthma often have a strong family history of asthma or other allergies, suggesting that genetic factors may play a role in the development of asthma as

well as the underlying allergic diathesis (often called *atopy*). However, no simple pattern of Mendelian inheritance suggesting a single gene responsible for either atopy or asthma has been identified.

Epidemiologic studies have confirmed an increased frequency of asthma and atopy in first-degree relatives of subjects with asthma compared with control subjects, and studies in twins indicate a much higher concordance for asthma in monozygotic than in dizygotic twins. Attempts to identify genes associated with asthma have found over 128 independently associated genetic loci, most of which represent single nucleotide polymorphisms. Nevertheless, variations in any of these single genes appear to explain only a small portion of the overall heritability. This may be in part because any genetic influence involves multiple genes, and in part because genetic studies often combine individuals with different phenotypes and presumably different endotypes, thus potentially diluting the effect of a genetic variant that may play a strong role only in a specific subset of the total asthma population. The latter issue is illustrated by the fact that variants at the 17q21 locus appear associated with childhood asthma, but not with adult-onset asthma. Despite whatever intriguing genetic associations are found with asthma, there is general agreement that the genetic influences in asthma are complex, varying according to the population being studied, and that multiple genes, gene products, and environmental exposures likely interact in the pathogenesis of the disease.

## Acquired (environmental) factors

A variety of environmental factors that might predispose an individual to develop asthma, most likely interacting with one or more genetic factors, have been proposed. Exposure to allergens, possibly at a critical time during childhood, may be an important environmental factor. Some of these exposures are to common environmental allergens, such as those derived from house dust mites, domestic animals, and cockroaches. These allergens are found indoors, often concentrated in bedding and carpets, and are present throughout the year. Another potential environmental factor is maternal cigarette smoking. An increased risk for early-onset asthma is found in children whose mothers smoke, possibly related to altering the normal development of the child's immune system.

Viral respiratory tract infections precipitate airway inflammation and trigger acute exacerbations of asthma, but their potential role as an inducer or cause of asthma in the absence of other factors is controversial. One theory suggests that early childhood viral infections are causally associated with later development of asthma. On the other hand, the so-called *hygiene hypothesis* suggests that exposure to microbes and microbial byproducts (e.g., endotoxin) during childhood may protect against development of asthma by shifting the immunologic profile of helper T ($T_H$) cells toward a $T_H1$ response (responsible for cellular defense) and away from a $T_H2$ response (which mediates allergic inflammation). It is likely that some infections increase the chance of developing asthma, whereas others decrease the risk, and that timing of the infection and other factors may play a role in this interaction.

Finally, one line of inquiry to explain the increasing prevalence of asthma throughout industrialized parts of the world has turned to a possible role for vitamin D deficiency among pregnant women. Vitamin D is believed to have an immunoregulatory role, and it has been hypothesized that deficiency of vitamin D during pregnancy may predispose to

asthma in the offspring.

## Airway inflammation, cytokine mediators, and bronchial hyperresponsiveness

No single factor or cell appears to be responsible for asthma. Instead, a complex and interrelated series of events, including cellular infiltration, epithelial injury, cytokine release, and airway remodeling, likely culminates in airway hyperresponsiveness and episodes of airflow obstruction (Fig. 5.1). A further complication is the recognition that specific mechanistic pathways and the role of various cells and mediators differ depending on the particular asthma phenotype. The explosion of research relating to pathogenetic mechanisms and potential chemical mediators means that we can only scratch the surface in this discussion. However, the interested reader can find more detailed information in the Suggested Readings at the end of this chapter.

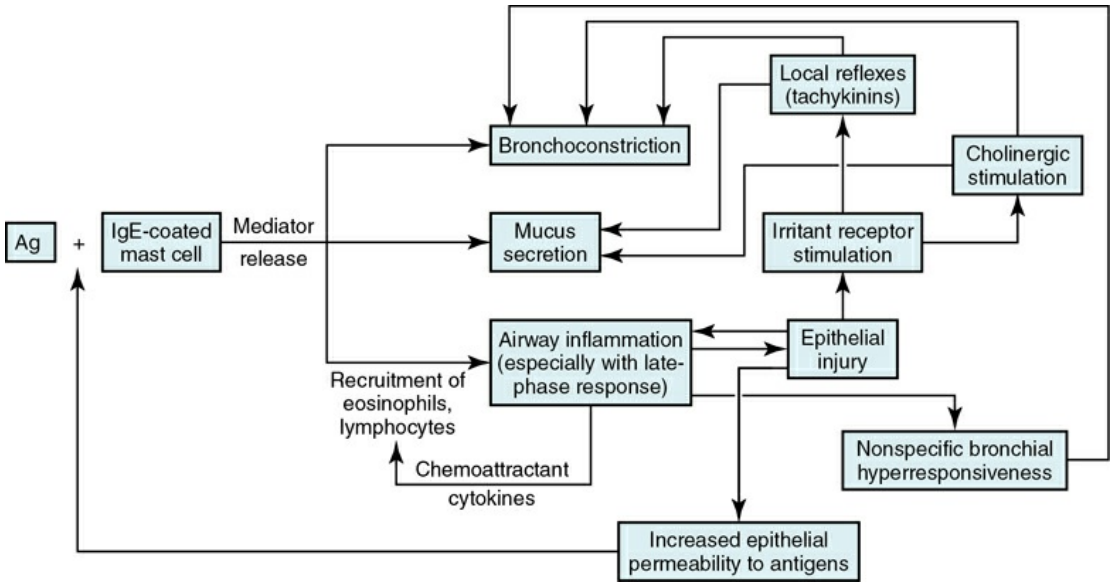


**FIGURE 5.1 Schematic Diagram of Events in Pathogenesis of Antigen-Induced Asthma.** A hypothetical series of complex interactions is shown, focusing on bronchoconstriction, mucus secretion, and airway inflammation. *Ag*, antigen; *IgE*, immunoglobulin E.

As noted, a feature that is common to patients with asthma, independent of their age at presentation or their specific phenotype, is hyperresponsiveness of the airways to a variety of stimuli. When exposed to such stimuli, the airways often demonstrate bronchoconstriction, which can be measured as an increase in airway resistance or a decrease in forced expiratory flow rates.

A myriad of cytokine mediators, produced and released by inflammatory cells and by the airway epithelium, are responsible for recruitment and activation of other inflammatory cells and amplification of cytokine production, thus perpetuating the

inflammatory response. For example, lymphocytes of the $T_H2$ phenotype, which are thought to be a prominent component of the inflammatory response in many patients with asthma, release interleukin (IL)-5, which has a chemoattractant effect for eosinophils. IL-5 also stimulates growth, activation, and degranulation of eosinophils. IL-4, another cytokine released from $T_H2$ lymphocytes, exerts a different type of proinflammatory effect by activating B lymphocytes, enhancing synthesis of IgE, and promoting differentiation of naïve $T_H$ lymphocytes ($T_H0$) to $T_H2$ cells. These and several other of the many cytokine mediators thought to be of particular importance in asthma are summarized in Table 5.1.

**TABLE 5.1**
**Important Cytokines in Asthma Pathogenesis**

| Cytokine | Origin | Effect |
|---|---|---|
| IL-4 | $T_H2$ cells | Differentiation of naïve $T_H0$ cells to $T_H2$ cells; differentiation of B cells to IgE-producing plasma cells |
| IL-5 | $T_H2$ cells | Eosinophil recruitment |
| IL-13 | $T_H2$ cells | Similar to IL-4; airway remodeling |
| IL-17 | $T_H17$ cells | Neutrophil recruitment |
| IL-25 | Epithelial cells | Stimulation of $T_H2$ cytokine production |
| IL-33 | Epithelial cells | Activation of group 2 innate lymphoid cells (ILC2) and production of IL-5 and IL-13 by ILC2 |
| TSLP | Epithelial cells | Activation and mobilization of antigen-processing dendritic cells |

*IL,* interleukin; *TSLP*, thymic stromal lymphopoietin.

Another typical finding in many patients with asthma is *airway remodeling*, which likely results from chronic airway inflammation and the associated production and release of a multitude of mediators including growth factors. Such remodeling changes include epithelial disruption, airway fibrosis, and smooth muscle hyperplasia. These histologic findings, particularly the increase in airway smooth muscle, also likely contribute to the hyperresponsiveness that can be documented in individuals with asthma, even when they are free of obvious bronchospasm.

Airway inflammation and remodeling are believed to contribute to nonspecific bronchial hyperresponsiveness.

A variety of other mediators released from inflammatory cells can alter the extracellular milieu of bronchial smooth muscle, increasing its responsiveness to bronchoconstrictive stimuli. Mediators that have been proposed to play such a role

include prostaglandin and leukotriene products of arachidonic acid metabolism. Mediators released from inflammatory cells may also produce tissue damage that contributes to asthma pathogenesis. For example, when eosinophils degranulate, they release several toxic proteins from their granules, such as major basic protein and eosinophil cationic protein. These and other eosinophil products may contribute to the epithelial damage found in the asthmatic airway. Once the epithelium is injured or denuded, its barrier function is disrupted, allowing access of inhaled material into deeper layers of the mucosa. The epithelial cells become actively involved in amplifying the inflammatory process (through production of cytokine and chemokine mediators) and in perpetuating airway edema (through vasodilation mediated by release of nitric oxide, leukotrienes, and prostaglandins). Finally, sensory nerve endings in the airway epithelial layer may become exposed, triggering a reflex arc and release of tachykinin mediators (e.g., substance P, neurokinin A), as shown in pathway 4 of Fig. 4.3. These peptide mediators, released at bronchial smooth muscle, submucosal glands, and blood vessels, can cause bronchoconstriction and airway edema.

Mediators from inflammatory cells may recruit and activate other inflammatory cells and promote epithelial injury.

## Asthma phenotypes

The association between asthma and allergies is significant but not universal. Many individuals with asthma have no other evidence of atopy and do not experience exacerbations as a result of antigen exposure. In this group, asthma attacks often are precipitated by other stimuli, as will be described later. A common framework used in the past has distinguished two "types" of asthma: (1) "extrinsic" (atopic) asthma, typically seen in younger patients and having a significant allergic component; and (2) "intrinsic" (nonatopic) asthma, typically in adults and lacking a significant allergic component.

Although many patients with asthma have allergies, heterogeneity in asthma presentation (phenotypes) has been increasingly recognized and suggests multiple underlying mechanistic pathways.

More recently, the recognition of differences in asthma presentation has led to an evolution of this framework and a number of proposed asthma phenotypes, potentially with different underlying pathogenetic mechanisms (endotypes). However, whether these phenotypes are truly distinct and have different endotypes or whether they represent different manifestations of a continuous spectrum of disease is uncertain. A particularly common phenotype is an "allergic" phenotype, roughly corresponding to what was previously described as extrinsic asthma. The allergic phenotype is typically associated with atopy and asthma developing early in life. Another phenotype, which describes severe asthma presenting during adulthood, accompanied by tissue and often peripheral eosinophilia as well as sinusitis, but not identifiable allergies or atopy, has been called an "eosinophilic" phenotype. An association of obesity with asthma, particularly in women and developing during adulthood, has defined an "obesity-related" phenotype. These and other asthma phenotypes are described in more detail in

the Suggested Readings at the end of this chapter.

## Common provocative stimuli

A substantial amount is known about the sequence of events from the time of exposure to a stimulus until the clinical response of bronchoconstriction in persons with asthma. Four specific types of stimuli that can result in bronchoconstriction are considered here: (1) allergen (antigen) exposure, (2) inhaled irritants, (3) respiratory tract infection, and (4) exercise.

Common stimuli that precipitate bronchoconstriction in a patient with asthma are as follows:

1. Exposure to an allergen
2. Inhaled irritants
3. Respiratory tract infection
4. Exercise

### Allergen exposure

The pathogenetic mechanisms leading to bronchoconstriction are best defined for allergen-induced asthma. Allergens to which a person with asthma may be sensitized are widespread throughout nature. Although patients and clinicians often first consider seasonal outdoor allergens such as pollen, many indoor allergens may play a more critical role. These allergens include antigens from house dust mites (*Dermatophagoides* and others), domestic animals, and cockroaches. Inhaled antigens are initially identified and processed by antigen-presenting cells called *dendritic cells*, which in turn present the antigenic material to T lymphocytes. Chemical mediators released by $T_H2$ cells, especially IL-4 and IL-13, signal B lymphocytes to produce antigen-specific IgE antibodies. When a person with asthma has the IgE antibody against a particular antigen, the antibody binds to high-affinity IgE receptors on the surface of tissue mast cells and circulating basophils (see Fig. 5.1). If that particular antigen is inhaled, it binds to and cross-links the IgE antibody (against the antigen) bound to the surface of mast cells in the bronchial lumen. The mast cell is then activated, leading to release of both preformed and newly synthesized mediators. Mediators released from the mast cell induce bronchoconstriction and increase airway epithelial permeability, allowing the antigen access to the much larger population of specific IgE-containing mast cells deeper within the epithelium. Binding of antigen to antibody on this larger population of mast cells again initiates a sequence of events leading to release of mediators which induce bronchoconstriction and inflammation. Several mediators have been recognized (Table 5.2), but the discussion here is limited to the few that have been primarily implicated in the pathogenesis of allergic asthma; major mediators include histamine and leukotrienes.

**TABLE 5.2**
**Additional Potential Chemical Mediators in Asthma**

Histamine
Leukotrienes ($LTC_4$, $LTD_4$, $LTE_4$)
Platelet-activating factor
Prostaglandins ($PGD_2$)
Eosinophil chemotactic factor of anaphylaxis
Neutrophil chemotactic factor of anaphylaxis
Bradykinin
Serotonin
Kallikrein

### Histamine.

This relatively small (molecular weight 111) compound is found preformed within the mast cell and is released on exposure to specific antigens. Histamine has several effects that are important in asthma, including contraction of bronchial smooth muscle, augmentation of vascular permeability with formation of airway edema, and stimulation of irritant receptors (which can trigger a reflex neurogenic pathway via the vagus nerve, causing secondary bronchoconstriction). Despite these varied effects, the fact that the clinical manifestations of asthma do not respond to antihistamines suggests that histamine is not the most important chemical mediator involved.

### Leukotrienes.

The leukotrienes include a series of compounds ($LTC_4$, $LTD_4$, and $LTE_4$) that formerly were called *slow-reacting substance of anaphylaxis* (SRS-A). Unlike histamine, leukotrienes are not preformed in the mast cell but are synthesized after antigen exposure and then released. To some extent, their actions are similar to those of histamine; they also have a direct bronchoconstrictor action on smooth muscle, increase vascular permeability, and stimulate excess production of airway mucus. Leukotrienes are synthesized from arachidonic acid (also the precursor for prostaglandins) but along a different pathway involving a lipoxygenase enzyme, as opposed to the cyclooxygenase enzyme used for prostaglandin synthesis (Fig. 5.2). $LTC_4$ and $LTD_4$ in particular are extraordinarily potent bronchoconstrictors and have an important role in the pathogenesis of some cases of bronchial asthma. A noteworthy insight is provided by knowledge that some persons with asthma experience exacerbations of their disease after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are known inhibitors of the cyclooxygenase enzyme and may result in preferential shifting of the pathway shown in Fig. 5.2 toward production of the bronchoconstrictor leukotrienes.

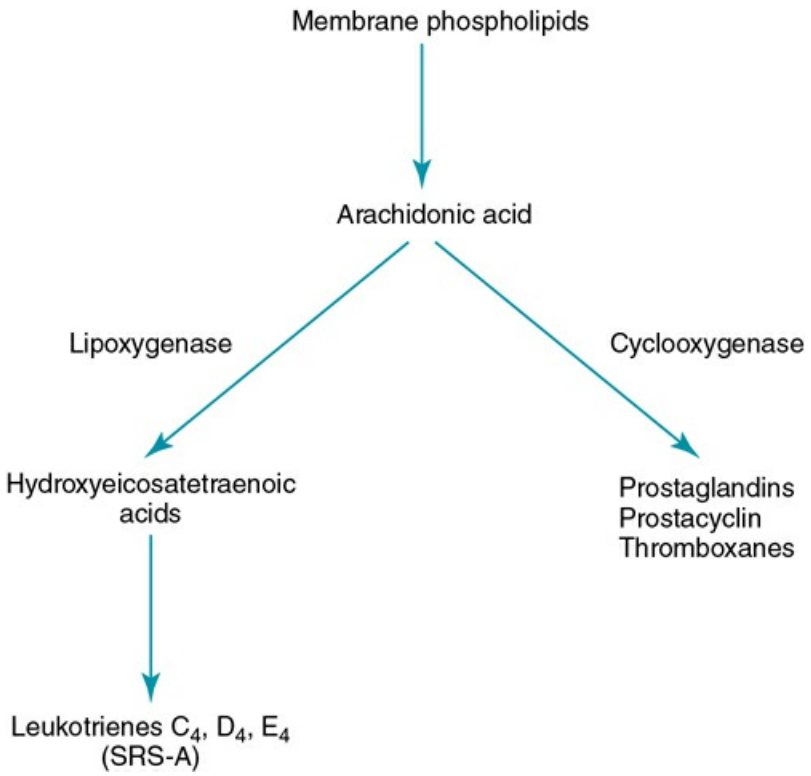


**FIGURE 5.2** Outline of the pathway for formation of leukotrienes (slow-reacting substance of anaphylaxis *[SRS-A]*) and prostaglandins. Aspirin and other nonsteroidal anti-inflammatory drugs are inhibitors of the enzyme cyclooxygenase.

The role of other mediators listed in Table 5.2 in asthma pathogenesis is less clear. Platelet-activating factor has been proposed to play a role in recruiting eosinophils to the lung, activating them, and stimulating them to release proteins toxic to airway epithelial cells.

### Late-phase asthmatic response.

The airway response to antigen challenge, as measured by changes in forced expiratory volume in 1 second ($FEV_1$), is more complicated and involves more than just the rapid mediator-induced bronchoconstriction seen within the first half-hour following exposure. In many patients, the return of $FEV_1$ to normal is followed by a secondary delayed fall in $FEV_1$ occurring hours after antigen exposure (Fig. 5.3). This delayed fall in $FEV_1$ is accompanied histologically by inflammatory changes in the airway wall. At the same time, increased bronchial hyperresponsiveness to nonspecific stimuli, such as histamine or methacholine, can be demonstrated and can last for days.

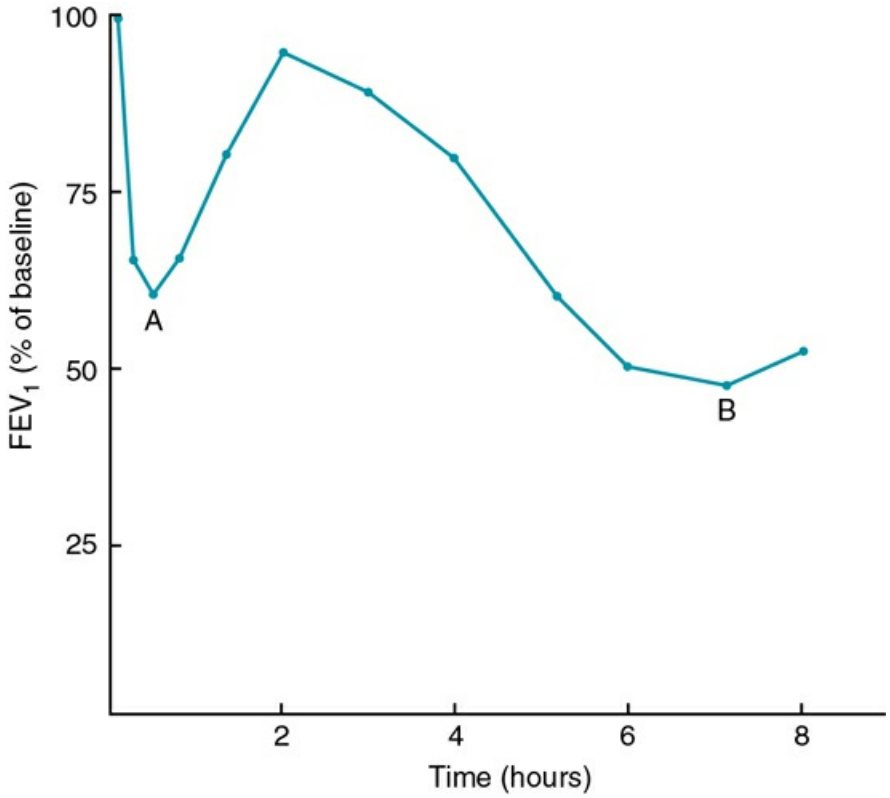


**FIGURE 5.3** Response of forced expiratory volume in 1 second *($FEV_1$)* after antigen challenge in a patient who demonstrates a biphasic response. Early bronchoconstrictive response is at point *A*. Slower onset late-phase asthmatic response is at point *B*.

This "late-phase response," as it has been called, depends on the presence of antigen-specific IgE. Release of mediators after allergen binding to IgE-coated mast cells results in an influx of inflammatory cells, especially eosinophils, into the airway wall. Experimental data suggest that this heightened airway inflammation is responsible for the increased nonspecific bronchial hyperresponsiveness seen at the time of the late-phase response.

## Inhaled irritants

Inhaled irritants such as cigarette smoke, inorganic dusts, and environmental pollutants are common precipitants of bronchoconstriction in persons with asthma. These airborne irritants appear to stimulate *irritant receptors* located primarily in the walls of the larynx, trachea, and large bronchi. Stimulation of the receptors initiates a reflex arc that travels to the central nervous system and back to the bronchi via the vagus nerve. This efferent vagal stimulation of the bronchi completes the reflex arc and induces bronchoconstriction. As mentioned in the discussion about chemical mediators, histamine can stimulate irritant receptors, and at least part of its bronchoconstrictive effect may be mediated indirectly via stimulation of the irritant receptors.

## Respiratory tract infection

Respiratory tract infection is an exacerbating factor for patients with either nonallergic or allergic asthma. Viral infections are the most common causes in this category, but bacterial infections of the tracheobronchial tree also can be implicated. The mechanism by which respiratory infections precipitate bronchoconstriction in persons with asthma is not entirely clear but is likely related to epithelial damage and airway inflammation. Potential consequences of epithelial injury include release of mediators from inflammatory cells, stimulation of irritant receptors, and nonspecific bronchial hyperresponsiveness.

### Exercise

Exercise can frequently provoke bronchoconstriction in patients with hyperreactive airways. The crucial factor in the pathogenesis appears to be heat movement from the airway wall, resulting in cooling and drying of the airway. During exercise, individuals have a high minute ventilation, and the large amounts of relatively cool and dry inspired air must be warmed and humidified by the tracheobronchial mucosa. When the air is warmed and humidified, water evaporates from the epithelial surface, resulting in cooling and drying of the airway epithelium. The phenomenon of exercise-induced bronchoconstriction can be reproduced by having a person with asthma voluntarily breathe cold dry air at a high minute ventilation. Inhalation of warm saturated air at the same minute ventilation does not produce a similar effect. The mechanism that links airway cooling and drying with bronchoconstriction is less clear. Alteration of the ionic environment after drying of the mucosa, mediator release, hyperemia of the mucosa following airway rewarming, and stimulation of irritant receptors have all been proposed as mechanisms, but none is universally accepted.

Airway cooling and drying are important in exercise-induced bronchoconstriction.

As might be expected from the description of exercise-induced bronchoconstriction, inhalation of cold air during the winter months can cause asthma exacerbations or worsening of symptoms in selected patients. The mechanism of airway narrowing in these patients following inhalation of cold air is also believed to be due to airway cooling and drying and is therefore analogous to the mechanism of exercise-induced bronchoconstriction.

## Pathology

Pathologic findings in asthma traditionally have been described from autopsy studies and thus represent the consequences of particularly severe disease. In these cases, marked overdistention of the lungs is seen, and the airways are occluded by thick, tenacious mucous plugs. However, information regarding the histologic appearance of airways in patients with stable mild disease more recently has become available. Examination of the airways by microscopy demonstrates the following findings of variable severity that are apparent in both mild and more severe disease:

1. Edema and cellular infiltrates within the bronchial wall, especially with eosinophils and lymphocytes

2. Epithelial damage, with a “fragile” appearance of the epithelium and detachment of surface epithelial cells from basal cells
3. Hypertrophy and hyperplasia of the smooth muscle layer
4. Increased deposition of collagen in a layer beneath the epithelium (referred to in the past as *basement membrane thickening*)
5. Enlargement of the mucus-secreting apparatus, with hypertrophy of mucous glands and an increased number of goblet cells

As described earlier in this chapter, the presence of histologic abnormalities presumably contributes to the nonspecific bronchial hyperresponsiveness in patients, even when they are free of an acute attack. In addition to the bronchial hyperresponsiveness that results from airway inflammation and remodeling, the more long-standing structural changes that characterize airway remodeling contribute to the component of persistent airflow obstruction that can be seen in some patients with longstanding asthma.

## Pathophysiology

The pathophysiologic features of asthma largely follow from the pathologic abnormalities. Contraction of smooth muscle in the bronchial walls, mucosal and submucosal inflammation and edema, and secretions within the airway lumen all contribute to decreased airway diameter, which increases airway resistance. Pathologic changes are present at many levels of the tracheobronchial tree, from large airways down to peripheral airways less than 2 mm in diameter.

As a result of narrowed airways with increased resistance, patients have difficulty with airflow during both inspiration and expiration. However, because intrathoracic airways are subjected to relatively negative external pressure (transmitted from negative pleural pressure) during inspiration, lumen size is larger during the inspiratory phase of the respiratory cycle. During expiration, relatively positive pleural pressure is transmitted to intrathoracic airways, thus decreasing their diameter. Therefore, greater difficulty with airflow on expiration than on inspiration is characteristic of asthma, as it is of any of the diseases that cause obstruction or narrowing of airways within the thorax. The greatest difficulty with expiration occurs when the patient is asked to perform a forced expiration (i.e., breathe out as hard and fast as possible). With forced expiration, pleural pressure becomes much more positive, thereby promoting airway narrowing, closure, and air trapping.

In asthma and other diseases associated with obstruction of intrathoracic airways, airflow is most compromised during expiration.

The effects of increased airway resistance are readily seen by measuring pulmonary function in persons with asthma. Pulmonary function studies performed during an attack show decreases in forced expiratory flow rates and evidence of air trapping. On the forced expiratory spirogram, patients typically exhibit a decrease in both forced vital capacity (FVC) and $FEV_1$, with the decrease in $FEV_1$ more pronounced than the decrease in FVC. Hence, the ratio $FEV_1/FVC$, which reflects the proportion of FVC that can be

exhaled during the first second, is decreased. In addition, the maximal midexpiratory flow rate (also called the *forced expiratory flow between 25% and 75% of the vital capacity* [$FEF_{25\%-75\%}$]) is diminished.

Pulmonary function tests in patients with asthma generally demonstrate decreased $FEV_1$, FVC, and $FEV_1$/FVC ratio. Air trapping is demonstrated by increases in RV and measured FRC.

Measurement of lung volumes during an exacerbation shows evidence of air trapping, with an increase in residual volume (RV) and functional residual capacity (FRC) as determined by plethysmography. The most impressive increase is seen in RV, the volume left in the lungs at the end of a maximal exhalation, which may be greater than 200% of the predicted value. The increase in RV is believed to be due to premature small airway closure with expiration as a result of smooth muscle constriction, mucous plugs, and inflammatory changes of the mucosa.

FRC, the resting point of the lungs at the end of expiration, is increased in the setting of an asthma flare due to air trapping. In addition, patients may experience *dynamic hyperinflation* because more time is required for expiration when airways are obstructed, and patients may not have sufficient time before the next breath to fully exhale the volume from the previous breath. Dynamic hyperinflation is a particular problem when the person with asthma is breathing at a rapid respiratory rate. During an asthma exacerbation, it is also hypothesized that patients have persistent activity of the inspiratory muscles during expiration, maintaining lung volume at a level higher than expected throughout expiration. A physiologic advantage to breathing at higher-than-normal lung volumes is having airways held open at a greater diameter. A disadvantage is increased work of breathing due to reduced compliance of the respiratory system at higher lung volumes (see Fig. 1.3C) and a mechanical disadvantage for diaphragmatic function when the diaphragm is lower and flatter (see Mechanisms of Abnormal Gas Exchange in Chapter 6).

The focus so far has been on pulmonary function and physiologic abnormalities seen with a typical asthmatic attack. Between attacks, pulmonary function, as measured by $FEV_1$ and FVC, often returns to normal. However, even when a person is not having an acute attack, subtle abnormalities in pulmonary function may be present, such as a decrease in maximal midexpiratory flow rate and a mild increase in RV. These abnormalities may reflect some residual disease in the small airways of the lung, frequently the last region to become normal after an attack.

A subgroup of persons with asthma, generally those with long-standing disease, have pulmonary function that does not return fully to normal. Instead, they have demonstrable physiologic abnormalities (e.g., abnormal $FEV_1$ and FVC) that persist between attacks. Even though asthma is generally characterized by reversible episodes of airflow obstruction, these individuals also appear to have a component of irreversible disease, particularly after decades with asthma. Nevertheless, they still generally experience episodes of reversible airflow obstruction and worsening of expiratory flow rates superimposed upon whatever irreversible disease is present.

The increased resistance to airflow in asthma exerts a toll on gas exchange, which is generally disturbed during acute attacks. The most common pattern of arterial blood

gases consists of a low $P_{O_2}$ accompanied by a low $P_{CO_2}$ (respiratory alkalosis). The mechanism for the hypoxemia is ventilation-perfusion mismatch. The increased airway resistance in asthma is not evenly distributed, such that some airways are affected more than others. Therefore, inspired air is not distributed evenly but tends to go to less diseased areas. However, blood flow remains relatively preserved in the regions that are ventilating poorly due to the suppression of normal hypoxic vasoconstriction by inflammatory mediators. The regions of low ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) ratio contribute blood with a low $P_{O_2}$ that cannot be compensated for by increases in the $\dot{V}/\dot{Q}$ ratio from other regions of the lung (see Chapter 1).

Patients are typically able to hyperventilate if an acute asthma attack is not too severe, and $P_{CO_2}$ is usually low. The stimulus or mechanism for the hyperventilation is not clear. During an acute attack, activation of irritant receptors may stimulate ventilation, or other reflexes originating in the airways, lung, or chest wall may stimulate ventilation. $P_{CO_2}$ that increases to either a normal or a frankly elevated level often indicates worsening airflow obstruction or fatigue of the respiratory muscles in a tiring individual who is no longer able to maintain normal or high minute ventilation in the face of significant airflow obstruction. Thus, the clinician should view a normal or high $P_{CO_2}$ as a potentially serious warning sign of progressive respiratory failure.

The most common pattern of arterial blood gases in asthma is low $P_{O_2}$ (due primarily to $\dot{V}/\dot{Q}$ mismatch) and low $P_{CO_2}$.

## Clinical features

Asthma is clinically recognized most frequently during childhood and young adulthood, although asthma can develop for the first time in older patients. In many patients, particularly those in whom asthma started before age 16 years, the disease eventually regresses, and patients are no longer subject to repeated episodes of reversible airway obstruction.

The symptoms most commonly noted by patients during an exacerbation of asthma are cough, dyspnea, wheezing, and chest tightness. However, some patients may only have unexplained cough or breathlessness on exertion. At times, patients can clearly identify a precipitating factor for an attack, such as exposure to an allergen, respiratory tract infection, exercise, exposure to cold air, emotional stress, or exposure to irritating dusts, fumes, or odors. In other circumstances, no precipitant can be identified. Exposures in the workplace, related to proteins or other chemicals to which the patient may be sensitized, are important precipitants in a subgroup of patients who are said to have *occupational asthma*. Some persons with asthma are particularly sensitive to ingestion of aspirin, which is believed to favor production of leukotrienes from arachidonic acid. Some patients with aspirin sensitivity also have nasal polyps, leading to a well-recognized triad of asthma, aspirin sensitivity, and nasal polyposis (sometimes referred to as *triad asthma, Samter syndrome*, or *aspirin-exacerbated respiratory disease*). Other NSAIDs (which also inhibit the cyclooxygenase enzyme) can also produce bronchoconstriction in patients who are aspirin sensitive.

Major symptoms during an acute asthma attack are as follows:

1. Cough
2. Dyspnea
3. Wheezing
4. Chest tightness

On physical examination, patients experiencing an asthma attack usually have tachypnea and, on chest auscultation, prolonged expiration and evidence of wheezing. Wheezing is more prominent during expiration than during inspiration and may be triggered by having the patient exhale forcefully. Although the tendency is to equate wheezing and asthma, the presence of wheezing does not necessarily indicate a diagnosis of asthma. Wheezing only reflects airflow through narrowed airways and is not synonymous with asthma; it can also be seen in such diverse disorders as congestive heart failure and COPD or in the case of a foreign body in the airway. On the other hand, not all persons with asthma wheeze. It is a common observation that severe asthma may be associated with no wheeze at all if airflow is too impaired to generate an audible wheeze.

Despite its prominence, the presence of wheezing is not synonymous with asthma and merely reflects turbulent airflow through narrowed airways.

During a particularly severe attack that is refractory to initial treatment with bronchodilators, persons with asthma are said to be in *status asthmaticus*. These patients present difficult therapeutic challenges, may require assisted ventilation, and may even die as a result of the acute attack.

The overall severity of an individual's asthma can be characterized based on the frequency of exacerbations, nocturnal symptoms, and magnitude of abnormality and variability in pulmonary function. The features used to define four categories of severity (intermittent asthma, mild persistent asthma, moderate persistent asthma, and severe persistent asthma) are listed in Table 5.3.

**TABLE 5.3**
**Classification of Asthma by Severity: Clinical Aspects and Treatment**

| Asthma Severity | Clinical Features Before Treatment | Nighttime Symptoms | Lung Function | Treatment |
|---|---|---|---|---|
| Intermittent | • Symptoms no more than twice per week<br>• No interference with normal activity<br>• Exacerbations brief | • No more than twice per month | • $FEV_1$ > 80% predicted<br>• $FEV_1$/FVC normal | • Combination glucocorticoid/$\beta_2$-agonist inhaler as needed<br>Alternative: Inhaled short-acting β2-agonist as needed |
| Mild persistent | • Symptoms > twice per week but < once per day<br>• Minor limitation with normal activity | • 3 or 4 times per month | • $FEV_1$ or PEFR > 80% predicted<br>• $FEV_1$/FVC normal | • As needed use of a combination inhaled corticosteroid/long-acting $\beta_2$-agonist<br>Alternative: Regular use of an inhaled corticosteroid<br>Alternative: Leukotriene modifier, cromoglycate, or sustained-release theophylline<br>As needed inhaled combination glucocorticoid/β2-agonist or short-acting β2-agonist if an alternative is used |
| Moderate persistent | • Daily symptoms<br>• Daily use of inhaled short-acting $\beta_2$-agonist<br>• Some limitation with normal activity<br>• Exacerbations at least twice per week; may last days | • More than once per week but not nightly | • $FEV_1$ > 60% but < 80% predicted<br>• $FEV_1$/FVC reduced 5% | • Low-dose inhaled corticosteroid plus long-acting $\beta_2$-agonist<br>In addition, inhaled combination glucocorticoid/β2-agonist or short-acting β2-agonist as needed |

| | | | | |
|---|---|---|---|---|
| Severe persistent | • Continual symptoms<br>• Extremely limited with normal activity<br>• Frequent exacerbations | • Often nightly | • $FEV_1$ < 60% predicted<br>• $FEV_1$/FVC reduced > 5% | • Medium- or high-dose inhaled corticosteroid plus long-acting $\beta_2$-agonist<br>• Consider addition of leukotriene modifier, cromoglycate, sustained-release theophylline, inhaled long-acting anticholinergic agent, or macrolide antibiotic<br>• Consider use of a biologic agent<br>• Consider short course of oral corticosteroid<br>• In addition, inhaled combination glucocorticoid/$\beta_2$-agonist inhaler or short-acting $\beta_2$-agonist as needed |

*$FEV_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *PEFR*, peak expiratory flow rate.

Adapted from National Asthma Education and Prevention Program. *Guidelines for the diagnosis and management of asthma: Expert panel report 3*, NIH publication 08-4051. Bethesda, MD: National Institutes of Health; 2007 and Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma Strategy 2021: Executive Summary and Rationale for Key Changes. Am J Respir Crit Care Med. 2022;205:17-35.

## Diagnostic approach

A clinical history of reversible episodes of dyspnea and wheezing brought on by characteristic triggers is often crucial to the diagnosis of asthma. Other helpful features in the history include other evidence for atopy (e.g., hay fever or eczema) or a family history of allergies or asthma. Physical examination demonstrating wheezes during an attack often provides confirmatory evidence for airflow obstruction.

The chest radiograph, although sometimes useful for excluding other causes of wheezing or complications of asthma, generally is not particularly helpful in the diagnosis. It usually shows normal findings but may demonstrate a flattened diaphragm suggestive of air trapping.

If the patient is producing sputum, microscopic examination of the sputum frequently shows many eosinophils on the smear. An increased number of eosinophils in peripheral blood is also relatively common, even when the asthma has no clear relationship to allergies.

The clinical usefulness of skin testing and inhalation testing with allergens in an attempt to identify antigens to which the patient is sensitized is controversial. Allergy skin testing with antigens and blood testing for specific IgE antibodies are available to help confirm or refute suspected allergic sensitivities to common aeroallergens. Unfortunately, neither is useful for the diagnosis of asthma, because persons with

asthma may have no allergic sensitivities, and persons with allergic sensitivities may not have asthma but rather manifest with symptoms affecting the nose and conjunctivae.

A measure of airway inflammation that is sometimes used clinically is the *fraction of exhaled nitric oxide (FENO)*. Nitric oxide, which is produced and released by airway epithelial cells, is increased in exhaled gas in the presence of airway inflammation, particularly with eosinophils. This occurs as a result of augmenting the levels of the inducible nitric oxide synthase (iNOS) enzyme in the airway epithelium. This measure of eosinophilic airway inflammation has been used as a marker of how active the inflammatory response is, as a guide to the likelihood of response to corticosteroids, and as an indicator of response to therapy.

Although the diagnosis of asthma is usually made based on clinical features, spirometry, and response to therapy, provocation tests are sometimes used to establish or confirm the diagnosis of asthma. These tests rely on the principle that persons with asthma have hyperreactive airways. Therefore, when tested with inhalation of methacholine (a cholinergic agent) or histamine, persons with asthma develop bronchoconstriction to lower doses of either agent compared with normals. Inhalation of cold air at high minute ventilations with $P_{CO_2}$ kept constant (termed *isocapnic hyperpnea*) can also be used as a challenge test to induce transient bronchoconstriction in patients in whom the diagnosis of asthma is uncertain.

Measurements of pulmonary function, especially $FEV_1$ and FVC, are particularly useful in the patient with suspected or known asthma. Documentation of reversible airflow obstruction, either during attacks or with a challenge test, is frequently sufficient to make the diagnosis. In practice, the diagnosis of asthma is most commonly made by the history of episodic dyspnea, wheezing, or cough, with documentation of reversible airflow obstruction by pulmonary function testing.

A diagnosis of asthma includes a history of episodic dyspnea, wheezing, or cough, along with reversible airflow obstruction documented by pulmonary function testing.

Patients can conveniently test their own pulmonary function through measurement of the peak expiratory flow rate on a simple, inexpensive hand-held device. Such testing is particularly useful for monitoring the course of the disease and alerting the patient to adjust the medication regimen, seek attention from a physician, or both. In addition, the efficacy of treatment or changes in the therapeutic regimen can readily be assessed by serial measurement of the peak expiratory flow rate.

## Treatment

The major categories of drugs used to treat asthma are those that dilate smooth muscle of the bronchial wall and those that have an anti-inflammatory action. Agents that decrease the production or activity of specific mediators and are developed from biological sources are termed *biologic* agents, and include monoclonal antibodies against IgE, IL-5, and other important mediators of asthmatic inflammation. The main categories of drugs used to treat asthma are listed in Table 5.4. Several of the drugs are also used for treatment of other types of pulmonary disease, particularly COPD, and are mentioned in other chapters.

## TABLE 5.4
## Drug Therapy in Asthma

| | Examples | Possible Routes of Administration | Mechanism of Action |
|---|---|---|---|
| **Bronchodilators** | | | |
| Sympathomimetics | Epinephrine<br>Albuterol<br>Salmeterol<br>Formoterol<br>Arformoterol<br>Vilanterol | Inhaled, oral, parenteral (depending on particular drug) | ↑ cAMP via stimulation of adenylate cyclase |
| Xanthines | Theophylline<br>Aminophylline | Oral<br>Oral, parenteral | ? ↑cAMP via inhibition of phosphodiesterase; ? anti-inflammatory |
| Anticholinergics | Ipratropium<br>Tiotropium | Inhaled | Blockade of cholinergic (bronchoconstrictor) effect on airways |
| **Anti-Inflammatory Drugs** | | | |
| Corticosteroids | Prednisone<br>Methylprednisolone<br>Dexamethasone | Systemic (oral or parenteral, depending on particular drug) | Decreased inflammatory response in airways; ? additional mechanisms |
| | Beclomethasone<br>Triamcinolone<br>Flunisolide<br>Fluticasone<br>Budesonide | Inhaled | |
| Cromolyn | | Inhaled | Inhibition of mediator release from mast cells;? additional mechanisms |
| **Drugs Directed at Specific Targets** | | | |
| 5-Lipoxygenase inhibitors | Zileuton | Oral | Decreased production of leukotrienes |
| Leukotriene antagonists | Zafirlukast<br>Montelukast | Oral | Leukotriene $D_4$ receptor antagonism |
| Anti-IgE antibody | Omalizumab | Subcutaneous | Binds and decreases levels of circulating IgE antibody |
| Anti-IL-4 receptor alpha subunit antibody | Dupilumab | Subcutaneous | Blocks binding of both IL-4 and IL-13 to their receptors |
| Anti-IL-5 antibody | Mepolizumab<br>Reslizumab | Subcutaneous<br>Intravenous | Binds and decreases levels of circulating IL-5 |
| Anti-IL-5 receptor alpha antibody | Benralizumab | Subcutaneous | Blocks binding of IL-5 to its receptor |
| Anti-TSLP antibody | Tezepelumab | Subcutaneous | Decreases TSLP levels and consequently decreases signaling in multiple downstream cytokine pathways |

*cAMP*, cyclic adenosine monophosphate; *IgE*, immunoglobulin E; *IL-4,* interleukin-4; *IL-5*, interleukin-5; *IL-13,* interleukin-13; *TSLP,* thymic stromal lymphopoietin.

## Bronchodilators

The most common bronchodilator agents used for the treatment of asthma are the sympathomimetic agents, which act on $\beta_2$-receptors to activate adenylate cyclase and increase intracellular cyclic adenosine monophosphate (cAMP). Increased levels of cAMP in bronchial smooth muscle, resulting specifically from stimulation of $\beta_2$-receptors, activate protein kinase A, which phosphorylates several regulatory proteins that mediate bronchodilation. In addition, β-receptor stimulation increases intracellular cAMP in mast cells, inhibiting release of chemical mediators that secondarily cause bronchoconstriction. Specific examples of available sympathomimetic drugs are listed in Table 5.4. To avoid some of the adverse cardiac effects induced by stimulation of $\beta_1$-receptors (primarily tachycardia), the preferred agents act preferentially on $\beta_2$-receptors. The $\beta_2$-specific agents most commonly used are albuterol (short-acting $\beta_2$-agonist) and salmeterol or formoterol (long-acting $\beta_2$-agonists), and the typical route of administration is inhalation. In addition to its long duration, formoterol also has a rapid onset of action. Although some sympathomimetic agents can be given orally or parenterally, the inhaled route is preferred because it has fewer systemic side effects and provides direct delivery to the site of action in the airways.

Sympathomimetic agents increase intracellular cAMP by activating adenylate cyclase. Preferred agents preferentially stimulate $\beta_2$-receptors and decrease potential adverse cardiac effects caused by stimulation of $\beta_1$-receptors.

Short-acting inhaled $\beta_2$-agonists, such as albuterol, are typically used on an as-needed basis to reverse an acute episode of bronchoconstriction. They may be the only agents needed to control the patient's asthma when episodes are infrequent. Short-acting $\beta_2$-agonist drugs can also be used prophylactically before activities or exposure to stimuli known to precipitate bronchoconstriction, such as exercise. Effects of the long-acting $\beta_2$-agonists salmeterol, formoterol, and arformoterol last for approximately 12 hours, whereas newer ultra-long-acting $\beta_2$-agonists such as vilanterol can last up to 24 hours. If asthma severity necessitates frequent use of an inhaled $\beta_2$-agonist, then an anti-inflammatory agent (see following section) should be incorporated in the treatment regimen.

The second class of bronchodilator agents, which are less commonly used in asthma, consists of drugs that have an anticholinergic action. Anticholinergic agents dilate bronchial smooth muscle by decreasing bronchoconstrictor cholinergic tone to airways. Ipratropium, available as an aerosol for inhalation, is the primary short-acting example of this class of agents. The major use of ipratropium for asthma has been as adjunctive therapy to inhaled $\beta_2$-agonists in patients during a severe acute asthma attack. Tiotropium, a long-acting anticholinergic agent frequently used in patients with COPD, is also used in patients with asthma and has been increasingly used as adjunctive therapy in patients with severe asthma already on an inhaled glucocorticoid and a long-

acting $\beta_2$-agonist.

The third class of bronchodilator agents, the methylxanthines, is used much less frequently than either $\beta_2$-agonists or anticholinergic agents. Theophylline, the prototype of this class, is generally believed to act by inhibiting the enzyme phosphodiesterase (PDE), which is normally responsible for metabolic degradation of cAMP. When degradation is inhibited, the levels of cAMP in smooth muscle and mast cells increase, resulting again in bronchodilation and decreased mediator release from mast cells. However, the serum levels of methylxanthines needed to inhibit PDE are higher than those actually achieved in patients, so whether PDE inhibition is the major or exclusive mechanism of action of theophylline as a bronchodilator is uncertain. In addition, theophylline may have a component of anti-inflammatory activity, mediated by inhibition of the PDE-4 isozyme in inflammatory cells. Theophylline is available only for oral administration, whereas aminophylline (a water-soluble salt of theophylline) can be given orally or intravenously. Because methylxanthines can be administered only systemically (as opposed to locally in the airway), systemic side effects (gastrointestinal, cardiac, neurologic) are more problematic than with inhaled sympathomimetic or anticholinergic agents. In addition, methylxanthines have a narrow therapeutic window and require monitoring of serum levels. For these reasons, methylxanthines are now used relatively infrequently compared with other medications.

Methylxanthines (aminophylline, theophylline) increase cAMP by inhibiting the enzyme PDE, which degrades cAMP. This mechanism may be responsible for bronchodilation.

## Anti-inflammatory drugs

As opposed to the bronchodilator agents, which act by relaxing bronchial smooth muscle, anti-inflammatory agents are targeted to control the underlying process of airway inflammation and are therefore categorized as *controller* medications. The primary category of anti-inflammatory controller agents are corticosteroids, ideally given by inhalation. They suppress the inflammatory response by decreasing the number of eosinophils and lymphocytes infiltrating the airway and decrease production of a number of inflammatory mediators. Despite the general rationale for corticosteroid use, many aspects of their anti-inflammatory action remain poorly understood. Glucocorticoids are thought to bind to a cytoplasmic receptor present in nearly all cell types. After the receptor binds to its glucocorticoid ligand, it moves to the cell nucleus, where it interacts with transcription factors such as activator protein (AP)-1 and nuclear factor (NF)-κB, which regulate transcription of other target genes. Important target genes whose transcription is suppressed by the action of glucocorticoids include a variety of inflammatory cytokines (e.g., IL-1, IL-3, IL-4, IL-5, IL-6, and tumor necrosis factor [TNF]-α), the inducible form of iNOS, and an inducible form of cyclooxygenase.

Because airway inflammation plays an important role in asthma pathogenesis, particularly in the patient with more frequent attacks or more persistent airflow obstruction, inhaled corticosteroids have assumed a central role in the management of most cases of asthma. By decreasing airway inflammation, inhaled corticosteroids are thought to ameliorate the underlying disease process in asthma, not just the bronchoconstriction resulting from airway inflammation.

Corticosteroids have an important place in both management of acute asthma exacerbations and as part of maintenance therapy. Frequently, systemic corticosteroids such as prednisone or methylprednisolone are started at high doses during an acute attack and then tapered relatively rapidly. Because of the potential for significant adverse effects with long-term use of systemic (oral) corticosteroids, chronic administration of oral corticosteroids is avoided if the asthma can be managed with other modes of therapy. Foremost among these alternative forms of therapy are inhaled forms of corticosteroids that deliver the drug locally to the airway but have minimal systemic absorption and limited side effects. Inhaled corticosteroids are currently incorporated into the regimen of most patients with asthma. Traditionally, scheduled daily use of an inhaled corticosteroid was started if the condition required more than infrequent use of a short-acting β-agonist. More recently, the field has moved toward using inhaled corticosteroids in conjunction with formoterol (a long-acting β-agonist with an onset of action that is short enough to be used for quick relief) on an as-needed basis if possible, rather than committing patients with less severe asthma to scheduled daily inhaled corticosteroids. However, patients with more severe asthma may require daily in addition to as-needed therapy with a combination corticosteroid-formoterol inhaler. This latter approach has been called SMART (Single Maintenance And Reliever Therapy).

Systemic and inhaled corticosteroids have an important role in acute therapy and preventive management, respectively.

A different anti-inflammatory drug that is rarely used is disodium cromoglycate (cromolyn). Its mode of action was traditionally thought to be inhibition of mediator release from mast cells, but this mechanism has been disputed. Alternative mechanisms proposed include inhibitory effects on other types of inflammatory cells or on the action of tachykinins. Cromolyn is available in most countries only as a solution for inhalation using a nebulizer; it is not a bronchodilator and therefore has no role in the treatment of acute attacks. Rather, it is given as an ongoing medication, with the goal of preventing future exacerbations.

Anti-inflammatory therapy is important when treatment of asthma requires more than infrequent use of an inhaled $\beta_2$-agonist.

## Agents with specific targeted action

Agents are increasingly being developed that block the synthesis or action of a particular type of mediator. Accompanying the recent interest in identifying discrete asthma phenotypes is a goal of targeting therapy toward individual mediators that may have a central role in one or more underlying endotypes. This rationale is supported by the observation that such agents are often effective only in specific subgroups of patients with asthma. We will consider three categories of chemical mediators in asthma that are the targets of currently available drugs—leukotrienes, IgE, and cytokines that are important in the asthmatic response.

Drugs that are directed at modifying leukotrienes or leukotriene pathways include zafirlukast and montelukast, which antagonize the action of leukotrienes at their

receptor, and zileuton, which inhibits the enzyme 5-lipoxygenase and thus limits leukotriene production. Because of their mode of action, drugs that either block leukotriene synthesis or antagonize their action have a particularly important role in patients who are sensitive to aspirin or other NSAIDs.

Omalizumab, a monoclonal antibody to IgE, prevents binding of IgE to receptors on mast cells, thus inhibiting the release of mast cell mediators which are important components of the pathobiology of allergic asthma. Omalizumab is administered every 2 to 4 weeks by subcutaneous injection in a healthcare setting (e.g., outpatient medical office) and is expensive. Its use has been limited to selected patients with particularly severe asthma who have elevated levels of IgE and continue to be symptomatic and prone to asthmatic attacks despite other treatment.

More recently, monoclonal antibodies against important cytokine mediators of asthma, such as IL-4, IL-5, IL-13, and thymic stromal lymphopoietin, have become available and reduce $T_H2$-related inflammation. Like omalizumab, these drugs are extremely expensive. They are administered subcutaneously or intravenously and have limited use, but can be very effective in some patients with severe asthma, particularly when requiring ongoing treatment with corticosteroids. Of note, the effectiveness of some of these agents is limited to specific phenotypes of asthma based on eosinophil count and other factors.

## Bronchial thermoplasty

In bronchial thermoplasty, a relatively new procedure performed via a flexible bronchoscope, thermal energy is delivered to the airways in an effort to reduce airway smooth muscle mass. Studies indicate that the procedure can produce sustained benefit in patients with moderate and severe asthma, but experience is limited. Further trials should better define the optimal role of this procedure in asthma management.

## Management strategy

At present, the overall strategy for management of asthma commonly proceeds in the following manner. In a patient with relatively infrequent attacks and with symptom-free periods and normal pulmonary function between attacks, preferred management is with the use of an inhaled $\beta_2$-agonist or a combined inhaled corticosteroid and $\beta_2$-agonist on an as-needed basis. These drugs are used both for management of bronchospasm once it occurs and before exposure to stimuli often known to precipitate attacks (e.g., exercise or allergen exposure). These general guidelines are summarized in Table 5.3 according to the categories of clinical severity of disease.

When a patient's asthma cannot be managed successfully with just infrequent use of an as-needed inhaler, maintenance (ongoing) therapy is provided with an anti-inflammatory agent to suppress the underlying airway inflammation, administered either alone or with an inhaled long-acting $\beta_2$-agonist. Inhaled corticosteroids are used most frequently and appear to be the most effective anti-inflammatory agents, although leukotriene antagonists are alternatives.

Importantly, long-acting $\beta_2$-agonist therapy should never be used in asthma without concomitant inhaled corticosteroid therapy because control of the disease may deteriorate and increased mortality may result. Options other than the regular use of a

combined long-acting inhaled $\beta_2$-agonist and inhaled corticosteroid are the addition of an antileukotriene agent to the regularly used inhaled corticosteroid, escalation of the dose of inhaled corticosteroids, or addition of the methylxanthine theophylline.

Long-acting inhaled anticholinergic medications and macrolide antibiotics (used primarily for anti-inflammatory rather than antimicrobial effects) can be useful additions to the chronic treatment of severe asthma. Drugs that are targeted toward antagonizing specific biologic mediators, such as IgE, IL-4, IL-5 and others, are reserved for a very limited group of patients, typically those who have severe disease refractory to more traditional and cost-effective therapy.

When patients have a significant acute attack or an attack that occurs despite adequate therapy as described, intensive bronchodilator therapy plus a short course of systemic corticosteroids is typically effective. Particularly severe asthma exacerbations (i.e., *status asthmaticus*) often require high doses of systemic corticosteroids along with frequently administered bronchodilator therapy. In the extreme, patients with respiratory failure may require intubation and mechanical ventilation until their bronchospasm is reversed.

For patients in whom allergen exposure is an exacerbating factor for their asthma, allergen avoidance is a fundamental component of the management regimen. Environmental control measures to minimize allergen exposure include removing carpets, encasing mattresses and pillows in allergen-impermeable covers (to minimize dust mite exposure), and removing pets from the home (to minimize exposure to animal antigens). Immunotherapy with repeated injections of antigen extract is sometimes used to desensitize the patient to the offending allergen. Although immunotherapy is effective in allergic rhinitis, its efficacy in patients with asthma is controversial and its role uncertain.

Because of the availability of effective forms of therapy, patients with asthma and access to good medical care generally lead normal lives with relatively little or no alteration in their daily activities. However, not all patients with asthma are so fortunate. Even with treatment, some patients will experience refractory disease, persistent airflow obstruction, and rapid development of life-threatening attacks that pose a continuing challenge to physicians caring for these patients.

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# 6: Chronic obstructive pulmonary disease

OUTLINE



The term *chronic obstructive pulmonary disease* (COPD) refers to chronic disorders that disturb airflow, whether the most prominent process is within the airways or within the lung parenchyma. The two most common disorders included in this category are chronic bronchitis and emphysema. Although the pathophysiology of airflow obstruction is somewhat different in the two disorders, patients frequently have features of both, so it is appropriate to discuss them together. Asthma could logically also be in this category, but it is discussed in Chapter 5 because the term *COPD*, as commonly used, does not usually include bronchial asthma. Importantly, although patients with

asthma typically regain normal lung function between exacerbations, patients with COPD have obstructive lung disease that is “chronic,” that is, their lung function is always abnormal.

Other terms synonymous with COPD are *chronic airflow limitation, chronic airflow obstruction, chronic obstructive airways disease*, and *chronic obstructive lung disease*. Because *COPD* is the term in most common use, it is used here as well. Emphysema is discussed in this section of the textbook dealing with airway disease, even though the most obvious and visible pathologic manifestations of emphysema affect the lung parenchyma via alveolar destruction.

*Chronic bronchitis* is a clinical diagnosis used for patients with chronic cough and sputum production. The condition has certain pathologic features, but the diagnostic label refers to the specific clinical presentation. For epidemiologic purposes, the formal definition is the presence of a chronic productive cough on most days during at least 3 months per year for 2 or more consecutive years. However, for clinical purposes, the physician does not necessarily adhere to this formal time requirement. Patients with chronic bronchitis frequently have periods of worsening or exacerbation, often precipitated by respiratory tract infection. Unlike patients with asthma, however, patients with pure chronic bronchitis have residual clinical disease even between exacerbations, and their disease is not primarily one of airway hyperreactivity. The diagnosis of *asthmatic bronchitis* has often been given to patients with chronic bronchitis and a prominent component of airway hyperreactivity, because features of both chronic bronchitis and asthma are present. More recently, the label of *asthma-COPD overlap syndrome* has begun to be applied to these patients who have features of both asthma and COPD.

Chronic bronchitis is a diagnosis made on the basis of chronic cough and sputum production.

In contrast to the clinical diagnosis of chronic bronchitis, emphysema is formally a pathologic diagnosis, although certain clinical, radiographic, and laboratory features are also highly suggestive of the disease. Pathologically, emphysema is characterized by the destruction of alveolar walls and larger regions of lung parenchyma, and the enlargement of air spaces distal to the terminal bronchiole. The region of the lung from the respiratory bronchioles down to the alveoli is involved, and determination of the particular type of emphysema depends on the pattern of destruction within the acinus. Antemortem diagnosis of emphysema obviously does not have the kind of confirmation offered by postmortem examination of the lung, and the diagnosis is based on clinical and radiographic evidence.

Emphysema is a diagnosis made on the basis of destruction of lung parenchyma and enlargement of air spaces distal to the terminal bronchiole.

Because chronic bronchitis and emphysema coexist to a variable extent in different patients, the broader term *COPD* is frequently more accurate. That these two disorders are tied so closely together is not surprising. A single etiologic factor—cigarette smoking—is primarily responsible for both processes. Inflammation induced by cigarette smoke,

from the large airways down to the alveolar walls of the pulmonary parenchyma, is believed to be the common thread that ties together many of the varied manifestations of COPD. Throughout this chapter, specific reference is made to chronic bronchitis or to emphysema because some of the clinical and pathophysiologic features are distinct enough to warrant separate consideration. However, patients usually do not fit neatly into these separate diagnostic categories.

The public health problems posed by COPD are enormous. Globally, the World Health Organization estimates that approximately 65 million people have moderate or severe COPD, accounting for approximately 3 million deaths per year. In the United States alone, approximately 15 million people have a diagnosis of COPD, and it is the third most common cause of death. Morbidity in terms of chronic symptoms, days lost from work, and permanent disability is even more staggering. Unlike many diseases encountered by the physician, COPD is preventable in the majority of cases, because the main etiologic factor is well established and totally avoidable. Fortunately, since 1964, when the first Surgeon General's report on smoking and health was published, the prevalence of smoking among American adults has decreased from 40% to approximately 14%. Nevertheless, there are still more than 36 million current smokers and a large reservoir of former smokers who have placed themselves at high risk for COPD and other smoking-related diseases. It is important to note that the vast majority of smokers start smoking in their teens and early 20s; smoking avoidance programs are most effective when aimed at this age group. Worldwide, an increasing prevalence of smoking in developing countries has made COPD the third most common cause of death worldwide since 2019.

## Etiology and pathogenesis

Factors that have been implicated in causing or contributing to the risk of COPD include smoking, including second-hand smoke, environmental and indoor air pollution, infection, and genetics. Of these four, smoking is clearly the most important, and the one that will receive most attention here. Yet the fact that symptomatic COPD develops in only approximately 20% of smokers indicates that other factors modify an individual's risk. One well-defined genetic risk factor for COPD, inherited deficiency of the protein $\alpha_1$-antitrypsin, is discussed in detail in this section, but it is likely that other as yet unidentified polygenetic factors also affect the risk.

Smoking is the key etiologic factor for chronic bronchitis. Environmental and indoor pollutants and genetics are potential additional factors in exposed individuals. Respiratory tract infection is an important cause of disease exacerbations.

### Smoking

Smoking affects the lung at multiple levels: bronchi, bronchioles, and pulmonary parenchyma. In the larger airways—the bronchi—smoking has a prominent effect on the structure and function of the mucus-secreting apparatus, the bronchial mucous glands. An increase in the number and size of these glands is responsible for excessive mucus within the airway lumen. The airway wall becomes thickened because of the hypertrophied and hyperplastic mucous glands as well as an influx of inflammatory cells

(especially macrophages, neutrophils, and cytotoxic [$CD8^+$] T lymphocytes) into the airway wall. Thickening of the wall diminishes the size of the airway lumen, and mucus within the lumen further compromises its cross-sectional area. Release of a variety of mediators from the inflammatory cells, including leukotriene $B_4$, interleukin-8, and tumor necrosis factor-α, contributes to tissue damage and amplifies the inflammatory process in both the airways and the lung parenchyma. Similarly, oxidative stress due to reactive oxygen species present in cigarette smoke or released from inflammatory cells contributes to the overall pathologic process.

At the same time as more mucus is produced in the larger airways, clearance of mucus is altered by the effects of cigarette smoke on the cilia lining the bronchial lumen. Structural changes in cilia after long-term exposure to cigarette smoke have been well documented, and functional studies have demonstrated impaired mucociliary clearance as a consequence of cigarette smoking.

The combined effects of smoking on mucus production, mucociliary clearance, and airway inflammation easily explain the epidemiologic data demonstrating a significant correlation between cigarette smoking and the symptoms of chronic bronchitis: cough and sputum production. Pipe and cigar smoking are also predisposing factors in the development of chronic bronchitis, but the risk is significantly less than that from cigarette smoking, probably because pipe and cigar smoke is generally not inhaled as extensively.

Small airways (bronchioles less than approximately 2 mm in diameter) are prominently affected by smoking. Smoking induces bronchiolar narrowing, inflammation, and fibrosis, with resulting airflow obstruction. These changes in the small airways or bronchioles are responsible for an important component of the airflow obstruction in COPD and are likely the primary factor in patients with mild COPD (discussed later under Pathophysiology).

In the pulmonary parenchyma, smoking results in the eventual development of emphysema. An understanding of the concepts about how smoking leads to the destruction of alveolar walls, which is characteristic of emphysema, requires familiarity with the *protease-antiprotease hypothesis*. According to this theory, emphysema results from destruction of the connective tissue matrix of alveolar walls by proteolytic enzymes (proteases) released by inflammatory cells in the alveoli. Studies in animals have demonstrated that the injection of certain proteolytic (i.e., capable of breaking down protein) enzymes into the airways of animals results in pathologic and physiologic changes similar to those of clinical emphysema.

Cigarette smoking is responsible for most cases of emphysema. Deficiency of serum $\alpha_1$-antitrypsin is a predisposing factor for emphysema in a small proportion of cases.

The particular proteolytic enzymes thought to contribute to emphysema are those capable of breaking down elastin, a complex structural protein found in the walls of the alveoli. Elastase, one of several enzymes within the category of serine proteases, appears to be the most important of the proteolytic enzymes. Neutrophils are the major source of elastase within the lungs; therefore, the enzyme is commonly called *neutrophil elastase*. If elastase were allowed to exert its proteolytic effect on elastin whenever it was released from a neutrophil, destruction of this important structural protein of the alveolar wall

would ensue. Fortunately, an inhibitor of neutrophil elastase, usually called *$\alpha_1$-antitrypsin*, but also sometimes called *$\alpha_1$-antiprotease* or *$\alpha_1$-protease inhibitor*, is normally produced in the liver, released into the bloodstream, and is present in the lung. It is believed that a balance between neutrophil elastase and its inhibitor prevents diffuse destruction of the alveolar walls. When this balance is disturbed, either by an increase in neutrophil elastase activity or by a decrease in antielastase activity, damage to elastin and to the alveolar wall can result, with the eventual production of emphysema.

Theories postulate that proteolytic enzymes (especially elastase) are balanced by $\alpha_1$-antitrypsin. If smoking or $\alpha_1$-antitrypsin deficiency disturbs this balance in favor of proteolytic enzymes, emphysema can result.

The damage induced by cigarette smoke is believed to be mediated, in part, by disturbing the balance between elastases and antielastases. An increased number of neutrophils can be found in the lungs of smokers, providing a source for increased amounts of neutrophil elastase, which, therefore, shifts the balance toward a more proteolytic destruction of elastin. In addition, oxidant stress related to oxidants derived from cigarette smoke and inflammatory cells is thought to be injurious to the airway epithelium as well as to important structural components of the lung, including elastin and collagen. This pathogenetic sequence hypothesized for the development of COPD, including emphysema, is summarized in Fig. 6.1.

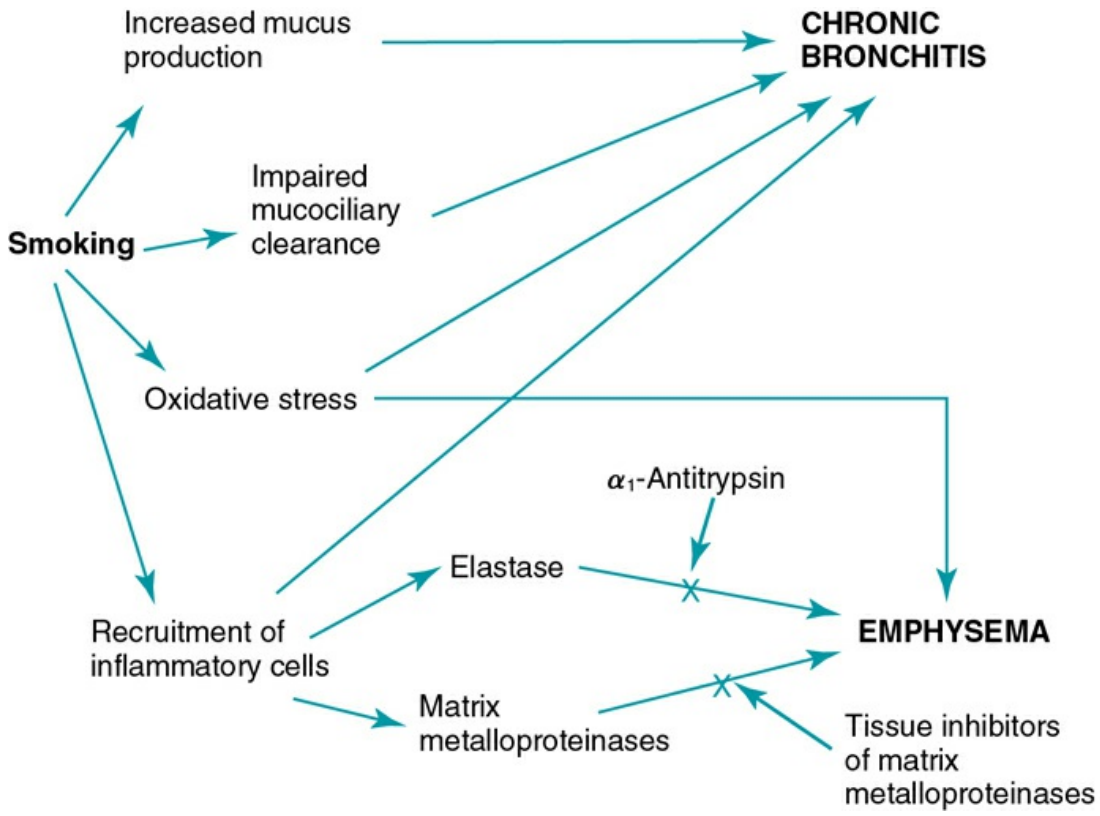

**FIGURE 6.1** Schematic diagram of the effect of smoking on airway inflammation and structural components of alveolar walls—the latter by altering the relationship between elastase and $\alpha_1$-antitrypsin (also called *$\alpha_1$-protease inhibitor*).

In addition to degrading elastin in the alveolar wall, neutrophil elastase, when released in the airways, stimulates the secretion of mucus. The primary defense against the action of neutrophil elastase in the airway is provided by *secretory leukoprotease inhibitor*, an antiprotease produced by airway epithelial and mucus-secreting cells.

Elastase is not the only proteolytic enzyme that has been implicated in the development of smoking-related damage and emphysema. Additional interest has focused on a group of enzymes called the *matrix metalloproteinases*, which are produced by macrophages and neutrophils and are capable of breaking down a variety of structural components of the alveolar wall. Like the relationship between elastase and its inhibitor $\alpha_1$-antitrypsin, the matrix metalloproteinases have a number of natural inhibitors, appropriately called *tissue inhibitors of matrix metalloproteinases (TIMP)*. Because of the influx of neutrophils and macrophages induced by cigarette smoke, it is believed that an increased burden of matrix metalloproteinases may result from smoking, potentially overwhelming the capability of the TIMPs and contributing to the breakdown of alveolar walls.

## Environmental and indoor pollution

Other factors implicated in the pathogenesis of COPD (environmental pollution, infection, and genetics) are quantitatively much less important than smoking. Air pollution is important primarily because of its potential for causing exacerbations of preexisting disease, not for initiating COPD. However, occupational exposure to pollutants or organic antigens (e.g., in miners or agricultural workers, respectively) does appear to be an important factor contributing to COPD, particularly chronic bronchitis. In addition, in parts of the world where biomass fuels are used for indoor cooking, environmental exposure to pollutants in confined indoor spaces may play an important role in development of COPD and may help explain the greater risk for women to develop COPD in these circumstances because of greater time spent in the home environment.

## Infection

Infections do not initiate COPD, but they do cause transient worsening of symptoms and pulmonary function in patients with preexisting COPD. Of the different types of respiratory tract infection, viral infection appears to be responsible for a large number of clinical exacerbations of symptoms. Bacterial infections probably play a less important role but can cause superinfection of patients already harboring an acute viral infection.

An interesting additional role for infection is suggested by data indicating that childhood respiratory tract infections may increase the risk for subsequent development of COPD. This may be one of the factors helping explain why development of COPD is not uniform in all smokers. Childhood respiratory infection might contribute to later

risk for developing COPD by affecting lung growth and function during childhood. The smoker who starts with a lower level of function because of childhood respiratory infections may be more likely to suffer functionally important consequences from heavy smoking in later life.

## Genetic factors

Genetic factors presumably contribute to the risk for development of COPD, but the nature of the predisposition is poorly defined. The one hereditary factor best established as predisposing to emphysema is deficiency of the serum protein $\alpha_1$-antitrypsin. $\alpha_1$-Antitrypsin is a glycoprotein of the serine protease inhibitor (serpin) family that is produced by the liver and normally circulates in blood. Minor changes in the *SERPINA1* gene, which codes for $\alpha_1$-antitrypsin, produce alterations in the structure of the protein that can be detected by biochemical methods. More than 100 different alleles of $\alpha_1$-antitrypsin have been identified. Each person has two genes coding for $\alpha_1$-antitrypsin: one of maternal origin and one of paternal origin. The normal (and most common) allele is the *M* allele, and the normal complement of two *M* genes is called *MM*. A person with the *MM* genotype has approximately 200 mg/dL (2.0 g/L) of the *M* type of protease inhibitor circulating in the blood. With one of the variant alleles, termed *Z*, the amino acid sequence of the protein is slightly altered, impairing secretion of the protein from its site of production in the liver. Hence, the abnormal protein remains in globules in the liver, where it may result in liver disease, and only small amounts enter the blood. Individuals who are homozygous for the *Z* gene (i.e., with the *ZZ* genotype) have circulating levels of $\alpha_1$-antitrypsin that are approximately 15% of normal. Heterozygotes with one *M* and one *Z* gene (the *MZ* genotype) have intermediate levels of circulating $\alpha_1$-antitrypsin in the range of 50% to 60% of normal levels. In the presence of a genotype associated with $\alpha_1$-antitrypsin deficiency, a blood level less than 1.1 g/L puts a patient at risk for development of clinical disease. It should be noted, however, that not all individuals with levels below this threshold ultimately develop clinical disease.

The most important form of $\alpha_1$-antitrypsin deficiency is associated with the *ZZ* genotype.

The *ZZ* genotype is a strong risk factor for premature development of emphysema, particularly if the individual is a smoker. Emphysema frequently develops as early as the third or fourth decade of life in persons with the *ZZ* genotype (who are commonly said to have $\alpha_1$-antitrypsin deficiency because of low serum levels). As mentioned earlier, the structural integrity of alveolar walls appears to depend on the balance between elastin degradation by elastase and protection from this destruction afforded by $\alpha_1$-antitrypsin. In patients with $\alpha_1$-antitrypsin deficiency, lack of the elastase inhibitor is believed to permit elastase action to proceed in an unchecked fashion, and early development of emphysema is the consequence.

Another factor of interest, one that presumably is at least partially genetically determined, is the degree of the patient's preexisting bronchial hyperresponsiveness. Data support the hypothesis that accelerated decline in lung function occurs in patients who have greater levels of bronchial responsiveness. However, this is an area of

controversy, in part because the potential for smoking to induce changes in bronchial responsiveness makes it difficult to determine cause/effect relationships.

## Pathology

Much of the pathology in chronic bronchitis relates to mucus and the mucus-secreting apparatus in the airways. Mucus-secreting glands and goblet cells are responsible for the production of bronchial secretions, but the mucous glands are the more important source (see Chapter 4). In chronic bronchitis, enlargement (hypertrophy) of the mucus-secreting glands has been objectively assessed by comparing the relative thickness of the mucous glands with the total thickness of the airway wall. This ratio, known as the *Reid index*, is increased in patients with chronic bronchitis. In general, the number of goblet cells in the airways is increased as well (hyperplasia), and these cells are abundant in airways more peripheral than normal. These alterations in the mucus-secreting apparatus increase the quantity of airway mucus, and its composition is likely altered as well. In practice, the secretions found in patients are often thick and more viscous than usual. Bronchial walls demonstrate evidence of an inflammatory process, with cellular infiltration and variable degrees of fibrosis.

Chronic bronchitis is characterized by enlargement of the mucus-secreting glands and an increased number of goblet cells.

In the smaller airways (e.g., bronchioles), inflammation, fibrosis, intraluminal mucus, and an increase in goblet cells all contribute to a decrease in luminal diameter. Because the resistance of airways varies inversely with the fourth power of the radius, even small changes in bronchiolar size may result in major impairment to airflow at the level of the small airways. These pathologic changes in the small airways are thought to be a major contributor to the airflow obstruction in COPD, particularly in patients with mild disease.

In patients with severe chronic airflow obstruction, the most important process responsible for airflow obstruction is emphysema. As mentioned earlier, the pathology of emphysema is characterized by the destruction of alveolar walls and the enlargement of terminal air spaces. Several types of emphysema have distinct pathologic features, which are primarily dependent on the distribution of the lesions. The most important types are panacinar (panlobular) emphysema and centriacinar (centrilobular) emphysema (Figs. 6.2 and 6.3). Panacinar emphysema is characterized by a relatively uniform involvement of the acinus, the region beyond the terminal bronchiole, including respiratory bronchioles, alveolar ducts, and alveolar sacs. Examination of a section of lung with panacinar emphysema shows that the damage in an involved area is relatively diffuse (Fig. 6.4). Typically, the lower zones of the lung are more involved than the upper zones. Panacinar emphysema is the usual type of emphysema described in patients who have $\alpha_1$-antitrypsin deficiency, although the condition is not limited to this clinical setting.

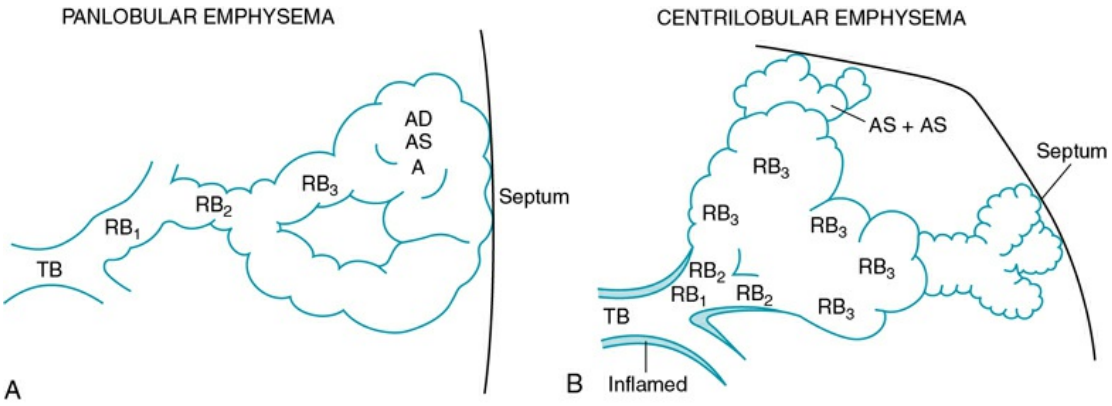


**FIGURE 6.2** Diagrams of panlobular **(A)** and centrilobular **(B)** emphysema. In panlobular (panacinar) emphysema, enlargement of air spaces is relatively uniform throughout the acinus. In centrilobular (centriacinar) emphysema, the enlargement of air spaces is primarily at the level of respiratory bronchioles. *A,* alveolus; *AD,* alveolar duct; *AS,* alveolar sac; *$RB_1$, $RB_2$, $RB_3$,* three generations of respiratory bronchioles; *TB,* terminal bronchiole. *Source:* (From Thurlbeck, W. M. (1968). Chronic obstructive lung disease. In S. C. Sommers (Ed.), *Pathology annual* (Vol 3). New York, NY: Appleton-Century-Crofts)

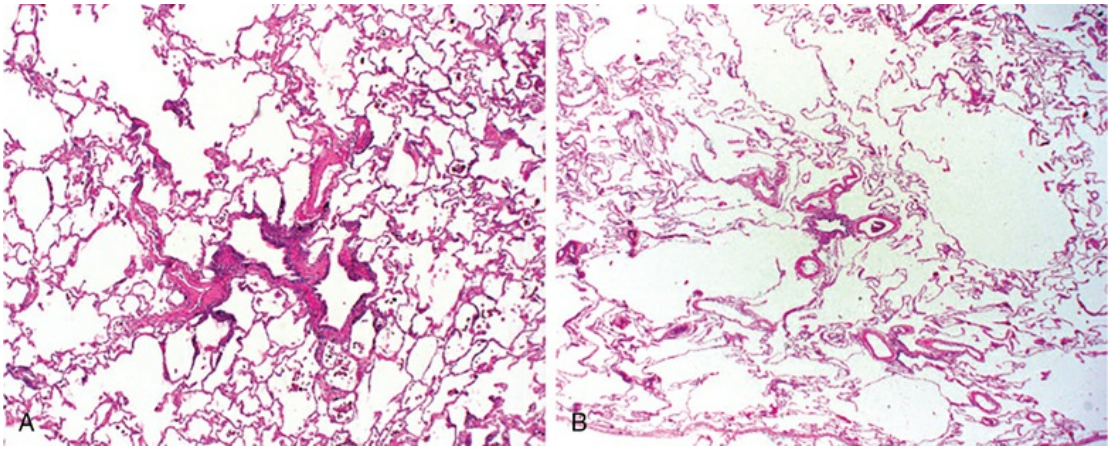


**FIGURE 6.3** Low-power photomicrographs of emphysema. **A,** Centrilobular (centriacinar) emphysema with dilation of airspaces surrounding a bronchiole. **B,** Panlobular (panacinar) emphysema with more diffuse airspace dilation. *Source:* (From Leslie, K. O., & Wick, M. R. (2018). *Practical pulmonary pathology. A diagnostic approach* (3rd ed.). Philadelphia, PA: Elsevier.)

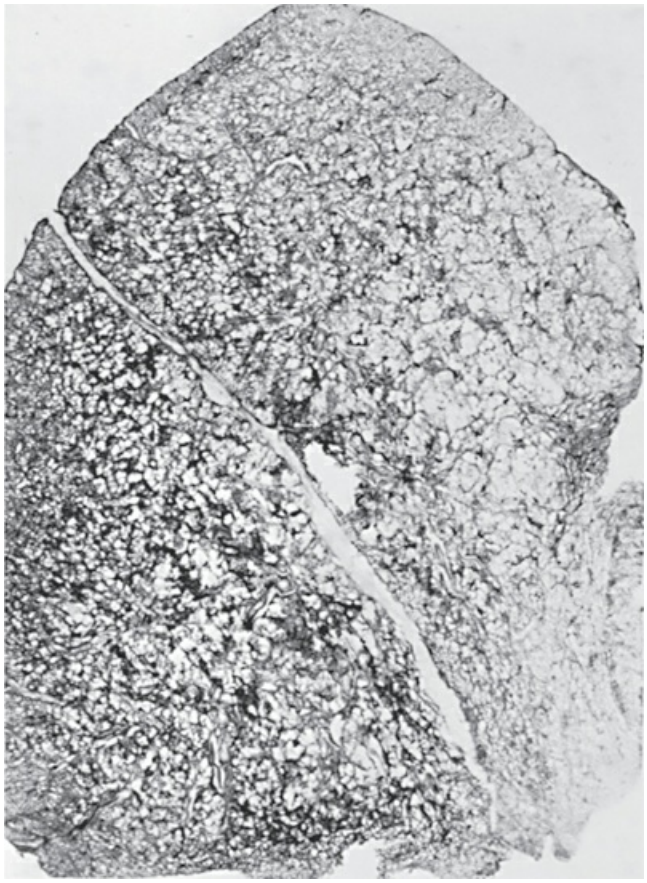

**FIGURE 6.4** The mounted section of the whole lung shows diffuse involvement seen with panacinar emphysema. *Source:* (From Thurlbeck, W. M. (1976). *Chronic airflow obstruction in lung disease*. Philadelphia, PA: WB Saunders.)

Pathologic changes from smoking often start in small airways, predating the advanced findings associated with chronic bronchitis and emphysema.

In centrilobular emphysema, the predominant involvement and dilation are found in the proximal part of the acinus, the respiratory bronchiole. The appearance of a lung section with centrilobular emphysema is different from that with panacinar emphysema. In centrilobular emphysema, involvement in an affected area seems to be more irregular, with apparently spared alveolar tissue between the dilated respiratory bronchioles at the center of the acinus (Fig. 6.5). This type of emphysema is the typical form seen in smokers. It is reasonable to speculate that the prominent involvement focused around the respiratory bronchiole is a consequence of extension of the bronchiolar inflammation in mild COPD.


**FIGURE 6.5** The mounted section of the whole lung shows centrilobular emphysema. Adjacent to emphysematous spaces (which represent dilated respiratory bronchioles) are spared areas of lung parenchyma (representing alveolar ducts and alveolar spaces). *Source:* (From Thurlbeck, W. M. (1967). Internal surface area and other measurements in emphysema. *Thorax*, *22*, 483–496. BMJ Publishing Group.)

## Pathophysiology

Underlying a discussion of the pathophysiology of COPD is the fact that cigarette smoking affects the large airways, small airways, and pulmonary parenchyma. The pathophysiologic consequences resulting from disease at each of these levels contribute to the overall clinical picture of COPD. In addition, the degree of airway reactivity, which probably is affected by genetic and environmental factors, appears to modify the clinical expression of disease in a given patient. This section simplifies, summarizes, and places into a conceptual framework some of the information regarding structure–function correlations for each of these aspects of COPD.

## Functional abnormalities in airways disease

In the larger airways (bronchi), an increase in the mucus-secreting apparatus and the amount of mucus produced results in the symptoms of excessive cough and sputum production characteristic of chronic bronchitis. However, these symptoms do not necessarily correlate with the degree of airflow obstruction, as some patients with typical symptoms of chronic bronchitis do not exhibit abnormally high resistance or changes in other measurements of airflow. When airflow obstruction exists, in general, additional pathologic factors, either in the small airways (inflammation and fibrosis) or pulmonary parenchyma (emphysema), are critical for the presence of obstruction. In relatively mild airflow obstruction associated with chronic bronchitis, disease in the small airways is likely the important factor responsible for airflow obstruction. When airflow obstruction is more marked, coexisting emphysema, with decreased caliber of small airways due to loss of airway tethering, is often the primary reason for the obstruction.

Small airways disease, emphysema, or both contribute significantly to decreased expiratory flow rates in COPD.

In patients who have a component of airway hyperreactivity contributing to their disease, often the clinical expression is that of an asthma-COPD overlap syndrome. Airway smooth muscle constriction adds more reversible airflow obstruction than is typically seen in the patient without airway hyperreactivity.

The common problem produced by the processes affecting airways is a decrease in the overall cross-sectional area of the airways. Airways resistance is increased (i.e., worsened) by anything that reduces the cross-sectional area of the lumen of the airways: intraluminal secretions, bronchospasm, or thickening of the airway wall caused by edema, inflammatory cells, fibrosis, or enlargement of the mucus-secreting apparatus, for example. When disease is located primarily in the peripheral airways and is mild, the functional consequences may be relatively subtle. Because the peripheral airways contribute only approximately 10% to 20% of overall airways resistance, total resistance is preserved unless small airways disease is considerable, or additional disease affects the larger airways.

As another consequence of airway disease, expiratory flow rates—including forced expiratory volume in 1 second ($FEV_1$), $FEV_1$/forced vital capacity (FVC) ratio, and maximal mid-expiratory flow rate (MMFR)—are generally decreased. The use of inhaled bronchodilators may or may not result in significantly improved flow rates in COPD. Patients with asthma-COPD overlap syndrome and greater airway reactivity generally have the most striking improvement in flow rates after receiving an inhaled bronchodilator.

Before a discussion of how lung volumes change in patients having the airway disease associated with COPD, it is useful to review the factors that determine major lung volumes: *total lung capacity* (TLC), *functional residual capacity* (FRC), and *residual volume* (RV). TLC is the point at which the maximal force of the inspiratory muscles acting to expand the lungs is equaled by the elastic recoil of the respiratory system (primarily lung recoil) resisting expansion (see Chapter 1). At FRC, the resting point of the respiratory system, there is a balance between the elastic recoil of the lungs and the

elastic recoil of the chest wall, which are acting in opposite directions—the lungs inward and the chest wall outward. The determinants of RV depend to some extent on age. In a normal young person, RV is the point at which the relatively stiff chest wall can be compressed no further by the expiratory muscles. With increasing age, a sufficient number of airways close at low lung volumes to limit further expiration, and airway closure is an important determinant of RV. In disease states in which airways are likely to close at low lung volumes, airway closure is associated with an elevated RV, even in young patients.

In patients with pure airway disease, TLC theoretically remains close to normal because neither the elastic recoil of the lung nor inspiratory muscle strength is altered. Similarly, FRC should remain normal because the recoil of the lung and the recoil of the chest wall are unchanged. However, if expiratory flow rates are decreased and the respiratory rate is high, the patient may not have sufficient time during expiration to reach the normal resting end-expiratory point. When this occurs, the end-expiratory lung volume is increased, resulting in an increase in the measured FRC. RV is generally also increased with processes that involve airways, because the narrowing and occlusion of small airways by secretions and inflammation result in air trapping during expiration.

## Functional abnormalities in emphysema

Although emphysema (i.e., destruction of alveolar walls) leads to decreased expiratory flow rates, the pathophysiology is different from the situation in pure airway disease. The primary problem in emphysema is loss of elastic recoil (i.e., loss of the lung's natural tendency to resist and recover from expansion). An important consequence of decreased elastic recoil is a decreased driving pressure that expels air from the alveoli during expiration. A simple analogy is a balloon filled with air, in which the elastic recoil is the "stiffness" of the balloon. With a given volume of air inside an unsealed balloon, a stiffer balloon will expel air more rapidly than a less stiff balloon. An emphysematous lung is like a less stiff balloon: a smaller than normal force drives air out of the lungs during expiration.

In emphysema, decreased expiratory flow rates are largely due to loss of elastic recoil of the lung, resulting in:

1. Lower driving pressure for expiratory airflow
2. Loss of radial traction on the airways provided by supporting alveolar walls, thus promoting airway collapse during expiration

Loss of driving pressure during exhalation is not the only consequence of emphysema. There is also an indirect effect on the collapsibility of airways. Normally, the walls of airways are held open and pulled radially outward from the center of their lumen by a supporting structure of tissue from the adjacent lung parenchyma. When the alveolar tissue is disrupted, as in emphysema, the supporting structure for the airways is diminished, and less radial traction is exerted to prevent airway collapse (Fig. 6.6). During a forced expiration, the strongly positive pleural pressure promotes collapse. Airways lacking an adequate supporting structure are more likely to collapse (and have

diminished flow rates and air trapping) than normally supported airways.

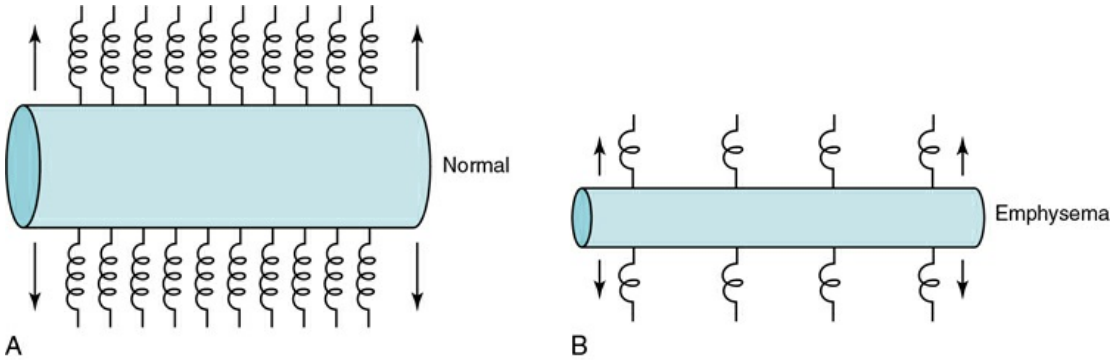


**FIGURE 6.6** Schematic diagram of radial traction exerted by alveolar walls (represented as springs), acting to keep the airways open. **A,** Normal situation. **B,** Loss of radial traction as seen in emphysema.

The decrease in elastic recoil in emphysema also alters the compliance curve of the lung and measured lung volumes. The *compliance curve* relates transpulmonary pressure and the associated volume of gas within the lung (see Chapter 1). Because an emphysematous lung has less elastic recoil (i.e., is less stiff), it resists expansion less than its normal counterpart, the compliance curve is shifted upward and to the left, and the lung has more volume at any particular transpulmonary pressure (Fig. 6.7). TLC is increased because loss of elastic recoil results in a smaller force opposing the action of the inspiratory musculature. FRC is also increased because the balance between the outward recoil of the chest wall and the inward recoil of the lung is shifted in favor of the chest wall. As in bronchitis, RV is substantially increased in emphysema because poorly supported airways are more susceptible to closure during a maximal expiration.

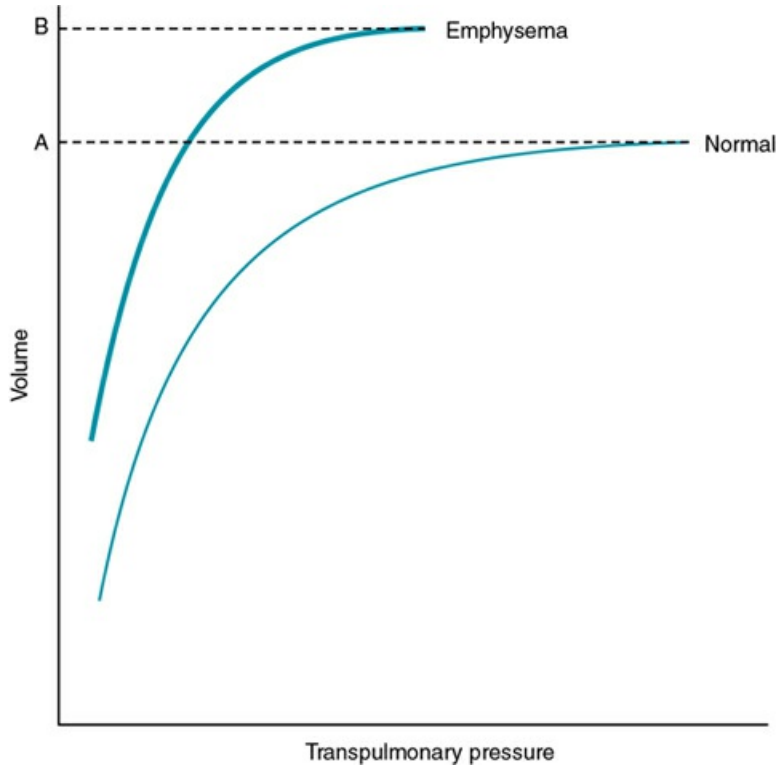


**FIGURE 6.7** Compliance curve of lung in emphysema compared with that of normal lung. In addition to shift of curve upward and to left, total lung capacity in emphysema (point *B* on volume axis) is greater than normal total lung capacity (point *A*). In pure chronic bronchitis without emphysema, the compliance curve is normal.

## Mechanisms of abnormal gas exchange

In obstructive lung disease, many of the observed pathologic changes affecting airflow are not uniformly distributed. For example, in chronic bronchitis, some airways are extensively affected by secretions and plugging, but others remain relatively uninvolved, so ventilation is not uniformly distributed throughout the lung. Regions of the lung supplied by more diseased airways receive diminished ventilation in comparison with regions supplied by less diseased airways. Although there may be a compensatory decrease in blood flow to underventilated alveoli, the compensation is not totally effective, and inequalities and mismatching of ventilation and perfusion result. This type of ventilation-perfusion disturbance, with some areas of lung having low ventilation-perfusion ratios and contributing desaturated blood, leads to arterial hypoxemia.

In obstructive lung disease, nonuniformity of the disease process results in $\dot{V}/\dot{Q}$ mismatch and hypoxemia.

Carbon dioxide elimination is impaired in some patients with obstructive lung

disease. The mechanism of alveolar hypoventilation and $CO_2$ retention is less clear than the mechanism of hypoxemia. Several factors probably contribute, including increased work of breathing (due to impaired airflow), abnormalities of central ventilatory drive, and ventilation-perfusion mismatch creating some areas with high ventilation-perfusion ratios that effectively act as dead space.

Mechanisms that contribute to alveolar hypoventilation and $CO_2$ retention in obstructive lung disease are as follows:

1. Increased work of breathing
2. Abnormalities of ventilatory drive
3. $\dot{V}/\dot{Q}$ mismatch
4. Decreased effectiveness of the diaphragm

An additional problem—fatigue of inspiratory muscles—has received attention as a factor contributing to acute $CO_2$ retention when affected patients are in respiratory failure (see Chapter 19). The importance of diaphragmatic fatigue in the stable patient with chronic hypercapnia is less certain. However, it is clear that contraction of the diaphragm, the major muscle of inspiration, is less efficient and less effective in patients with obstructive lung disease. When FRC is increased, the diaphragm is lower and flatter, and its fibers are shortened even before the initiation of inspiration. A shortened, flattened diaphragm is at a mechanical disadvantage compared with a longer, curved diaphragm and is less effective as an inspiratory muscle.

## Pulmonary hypertension

A potential complication of COPD is the development of pulmonary hypertension (i.e., abnormally high pressures within the pulmonary arterial system). Long-standing pulmonary hypertension places an added workload onto the right ventricle, which hypertrophies and eventually may fail. The term *cor pulmonale* is used to describe the disease of the right ventricle secondary to lung disease (either COPD or other forms of lung disease); this topic is discussed in Chapter 14. The primary feature of COPD that leads to pulmonary hypertension and eventually to cor pulmonale, is chronic hypoxia. A decrease in $P_{O_2}$ is a strong stimulus to the constriction of pulmonary arterioles (see Chapter 12). If hypoxia is corrected, the element of pulmonary vasoconstriction may be reversible, but vascular remodeling from chronic hypoxia may not fully reverse.

The major cause of pulmonary hypertension in COPD is hypoxia. Additional factors include hypercapnia, polycythemia, and destruction of the pulmonary vascular bed.

Several other but relatively less important factors that may contribute to elevated pulmonary artery pressure are hypercapnia, polycythemia, and reduction in the area of the pulmonary vascular bed. Hypercapnia, like hypoxia, can cause pulmonary vasoconstriction. To a large extent, this effect may be mediated by the change in pH resulting from an increase in $P_{CO_2}$. An elevation in hematocrit (i.e., polycythemia) is

often found in the chronically hypoxemic patient, producing increased blood viscosity and contributing to elevated pulmonary artery pressure. Finally, in emphysema, destruction of alveolar walls is accompanied by a loss of pulmonary capillaries. Therefore, in extensive disease, the limited pulmonary vascular bed may result in a high resistance to blood flow and, consequently, an increase in pulmonary artery pressure.

## COPD phenotypes

In the past, clinicians and researchers often distinguished two pathophysiologic types of COPD: *type A* and *type B*. These subtypes are no longer included in the definition of COPD, but the terms are embedded in older literature, so a brief discussion is given here. As originally conceived, type A (so-called "pink puffer") physiology was associated with underlying emphysema, high minute ventilation, and relatively normal arterial $Po_2$. Type B (so-called "blue bloater") physiology was equated with chronic bronchitis, hypoxemia, hypercapnia, and cor pulmonale. These two types were thought to represent the two ends of the spectrum of COPD: "pure" emphysema or "pure" airways disease. It is now recognized that this framework is not useful in classifying patients, because the vast majority of patients with COPD have both aspects of the disease.

Currently, there is intense interest in developing a better understanding of COPD phenotypes, with the goal of identifying different clinically relevant classifications of the disease. An important current classification system, using categories A through D, relies upon an assessment of the patient's symptoms as well as the risk for future exacerbations, based on the history of previous exacerbations (Fig. 6.8). Where the patient falls with respect to these two factors can then be used to personalize the approach to the patient's therapeutic regimen.

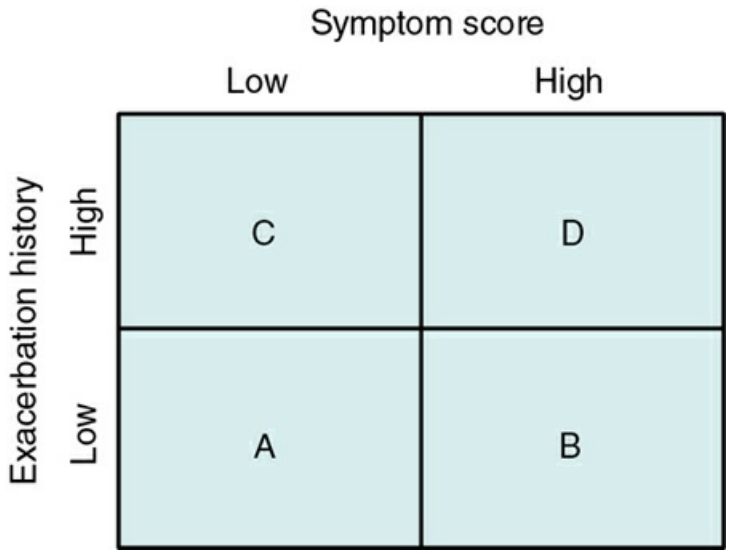


**FIGURE 6.8** Simplified depiction of the clinical classification scheme for COPD defining phenotypes A to D based on the symptoms and history of exacerbations. *Source:* (From the Global Strategy for Diagnosis, Management and Prevention of COPD 2022,

©.)

## Clinical features

Symptoms most commonly experienced by patients with COPD include dyspnea and cough, frequently with sputum production. Cough and sputum production may precede the development of dyspnea by many years. Most patients are symptomatic, but some are symptom-free, and the diagnosis of COPD is determined on the basis of pulmonary function tests.

Frequently, patients have a certain level of chronic symptoms, but their disease course is punctuated by periods of exacerbation. An *exacerbation* is defined as an acute event characterized by worsening of symptoms that requires a change in medication. The precipitating factor producing an exacerbation is often a respiratory tract infection of either viral or bacterial origin. A variety of bacteria are often chronically present in the tracheobronchial tree of patients with COPD, and an acute exacerbation can sometimes be due to the acquisition of a new strain of a colonizing bacterium. Other factors that cause acute deterioration in patients include exposure to a variety of air pollutants, bronchospasm (particularly if patients have a superimposed asthmatic component to their disease), and heart failure. However, in up to one-third of cases, the cause of an exacerbation cannot be identified. When exacerbations are severe, patients may develop frank respiratory failure, a complication discussed in Chapter 28.

The precipitating factor for an exacerbation of COPD is often either a viral or bacterial infection.

In addition to chronic symptoms of dyspnea, cough, or both, which may worsen during periods of acute exacerbation, patients may experience secondary cardiovascular complications of their lung disease (i.e., cor pulmonale). Patients with chronic hypoxemia and hypercarbia are particularly at increased risk for cor pulmonale.

Early in the course of the disease, physical examination may be normal or show only a prolonged expiratory time. As the process becomes more severe, characteristic findings are common. Breath sounds are generally decreased in intensity diffusely, and expiration is prolonged. Wheezing may be heard but does not necessarily reflect reversible bronchospasm. Some patients do not wheeze during normal tidal breathing, but do so when asked to give a forced exhalation. In patients with profuse airway secretions, coarse gurgling sounds labeled as *rhonchi* are frequently appreciated. Examination of the chest often discloses an increased anteroposterior diameter, indicating hyperinflation of the lungs. When diaphragmatic excursion is assessed by percussion of the lung bases during inspiration and expiration, diminished movement is noted.

In advanced COPD, patients may use accessory muscles of respiration (e.g., sternocleidomastoid and trapezius muscles), and the intercostal muscles may retract with each inspiration. The patient may assume a characteristic “tripod” position, leaning forward on straight arms allowing fixation of the clavicles and more effective use of accessory muscles. Pursed lip breathing may be observed. Severe disease may also be

complicated by weight loss and muscle wasting. When cor pulmonale is present, with or without frank right ventricular failure, patients have the cardiac findings described in Chapter 14.

Smoking is not only the primary factor that initiates COPD but also a major risk factor that determines the prognosis of a patient's illness. Patients who continue to smoke have the greatest progressive deterioration of pulmonary function over time. Exacerbations and respiratory tract infections frequently cause acute deterioration in lung function, but their effect on the long-term rate at which pulmonary function declines is not well established. Nonetheless, infections are the most important cause of acute mortality in patients with COPD, pointing to the need for influenza, COVID-19, and pneumococcal vaccination, as well as rapid appropriate treatment of bacterial respiratory infections and influenza.

Continuation of smoking is a major risk factor affecting the prognosis of COPD.

A wide spectrum of severity is characteristic of COPD, so morbidity from the disease varies tremendously among patients. Patients with mild disease are able to continue their usual work and lifestyle with minimal, if any, changes. Patients with severe disease are quite limited in their capacity for any exertion, are subject to frequent hospitalizations, and may have a life expectancy of less than 5 years.

## Diagnostic approach and assessment

In most cases, the diagnosis of COPD is suspected on the basis of history and physical examination, but spirometry with evidence of persistent airflow obstruction is still required to confirm the diagnosis in this clinical context. Chronic bronchitis is a clinical diagnosis, and the history is particularly crucial. Although emphysema is formally a pathologic diagnosis, a lung biopsy is not performed to make the diagnosis. Pathologic confirmation is generally obtained only at postmortem examination, if one is performed.

Chest radiographs have poor sensitivity in detecting COPD but are valuable in excluding other processes that cause dyspnea, such as heart failure, pulmonary fibrosis, or pleural disease. Patients with chronic bronchitis alone frequently have a normal chest radiograph. When present, chest radiographic findings suggestive of COPD include signs of hyperinflation, such as large lung volumes, flat diaphragms, an increased retrosternal air space, increased anteroposterior diameter (seen on the lateral view), and a paucity of vascular markings (Fig. 6.9). Hyperinflation associated with decreased vascular markings in the lungs results from the destruction of alveolar septa and enlargement of alveolar spaces, and has been called the *arterial deficiency pattern* of emphysema. In patients with $\alpha_1$-antitrypsin deficiency and early onset of emphysema, the arterial deficiency pattern is quite striking in the lower lobes, where there may be almost a complete loss of vascular markings.

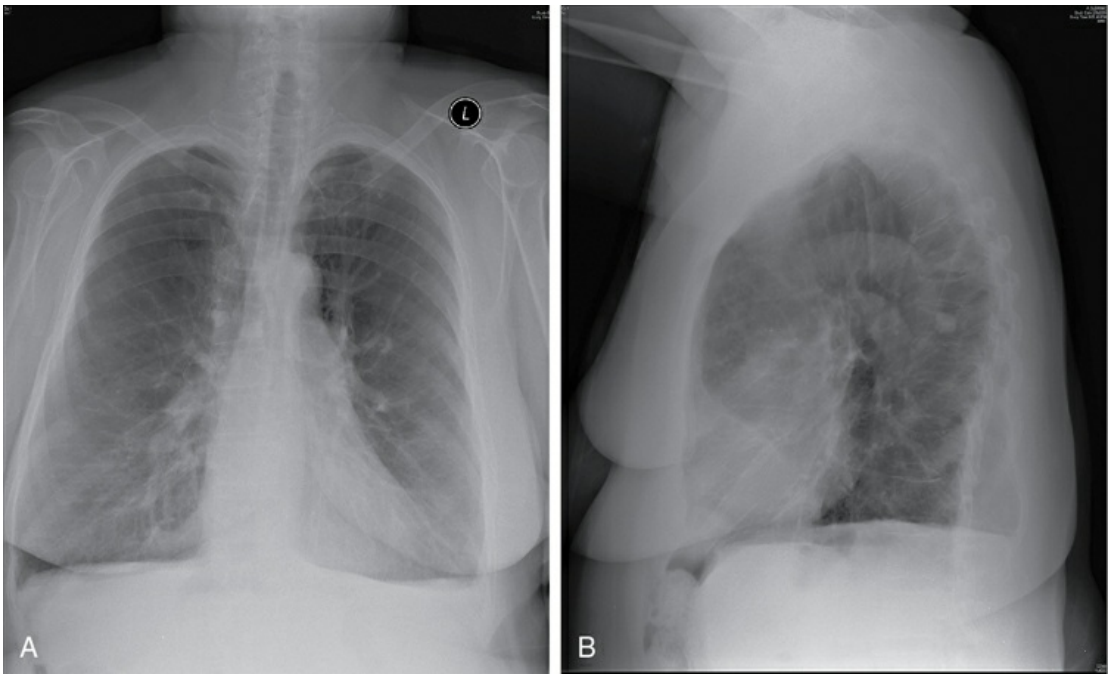


**FIGURE 6.9** Chest radiographs of a patient with severe chronic obstructive pulmonary disease. The lungs are hyperinflated and the diaphragms are low and flat. **A,** Posteroanterior view. **B,** Lateral view.

Characteristic radiographic findings in the more frequently recognized arterial deficiency pattern of COPD are as follows:

1. Large lung volumes
2. Flat diaphragms
3. Increased anteroposterior diameter
4. Loss of vascular markings

When cor pulmonale develops in patients with COPD, findings of pulmonary hypertension may be seen. These include enlargement of the proximal pulmonary arteries, pronounced tapering of the distal vessels, and cardiomegaly indicative of right ventricular hypertrophy or dilation.

High-resolution computed tomography (HRCT) is recognized as a more sensitive imaging method than plain chest radiography for detecting emphysema. Because it is expensive and rarely changes the management plan in this setting, it should not be considered part of the usual diagnostic evaluation for most patients with COPD. However, HRCT is an important step in characterizing the extent and distribution of emphysema in patients for whom lung volume reduction surgery is being considered.

The most useful physiologic adjuncts in evaluating patients with COPD are pulmonary function tests and arterial blood gas analysis. Spirometry demonstrates airflow

obstruction, with decreases in FVC, $FEV_1$, $FEV_1$/FVC ratio, and MMFR. Measurements of lung volume generally give evidence of air trapping, with an elevation in RV. In patients whose lung compliance is increased (i.e., patients with emphysema), TLC is generally elevated. Measured FRC can be elevated as a result of either increased compliance (decreased elastic recoil) in emphysema or insufficient expiratory time in the face of significant airflow obstruction, leading to an elevation in end-expiratory lung volume. Whether emphysema is present can be indirectly assessed by measuring the diffusing capacity for carbon monoxide. In patients with emphysema, in whom the surface area for gas exchange is reduced, the diffusing capacity is decreased. In pure airway disease (e.g., chronic bronchitis without emphysema), the diffusing capacity is generally normal.

Pulmonary function tests in COPD show:

1. Airflow obstruction (decreased FVC, $FEV_1$, $FEV_1$/FVC, MMFR)
2. Air trapping and often hyperinflation (increased RV, FRC, and often TLC)
3. Diffusing capacity generally decreased in emphysema, normal in chronic bronchitis

Pulse oximetry is routinely used to evaluate patients with COPD, because supplemental oxygen is an important treatment in patients with hypoxemia (see later). If the clinician is concerned about $CO_2$ retention or the accuracy of pulse oximetry, then measurement of arterial blood gases is necessary. Typically, patients with mild to moderate COPD have an increased alveolar-arterial oxygen gradient and mild hypoxemia. In more severe disease, hypoxemia worsens, and hypercarbia ($CO_2$ retention) may develop. With chronic elevation in $P_{CO_2}$, the kidneys adjust bicarbonate excretion in an attempt to compensate and return the pH toward normal. With acute exacerbations of COPD, hypoxemia frequently worsens and $CO_2$ retention becomes more pronounced, so the pH may drop from the stable compensated value.

In severe COPD, arterial blood gases typically show hypoxemia with or without hypercapnia.

## Treatment

Several modalities of treatment—used either individually or in combination—are available for patients with COPD. Although bronchoconstriction in these patients is considerably less than in patients with bronchial asthma, bronchodilators remain an important part of the treatment of many patients with COPD. The agents used are identical to those discussed in Chapter 5, including sympathomimetic agents ($\beta_2$-agonists), anticholinergic drugs, and methylxanthines. Short-acting inhaled $\beta_2$-agonists (e.g., albuterol), short-acting anticholinergic agents (e.g., ipratropium), or both are most commonly used as needed for patients with mild disease who require only infrequent therapy. For patients with more severe disease who require regular therapy, either a

long-acting $\beta_2$-agonist (e.g., salmeterol, formoterol, arformoterol, indacaterol), a long-acting anticholinergic (antimuscarinic) agent (e.g., tiotropium, aclidinium, umeclidinium), or both are commonly used, although regular use of short-acting agents is an alternative. The methylxanthine theophylline is another option, but concern for systemic side effects has relegated it to a secondary role in comparison with the inhaled bronchodilators.

Corticosteroid use for COPD treatment is dependent on the clinical setting. A 5- to 14-day course of systemic corticosteroids is frequently administered at the time of an acute exacerbation, and most studies suggest the benefit of improved pulmonary function and reduced treatment failure in this setting. On the other hand, only a minority of patients with chronic, stable, but severe disease show improved pulmonary function after a regimen of oral corticosteroids. Inhaled corticosteroids have little use in the setting of acute exacerbations of COPD. However, a trial of inhaled corticosteroids should be considered in patients with moderate to severe COPD who have frequent exacerbations, because some evidence indicates that inhaled corticosteroids may reduce the frequency or severity of exacerbations. In patients with frequent exacerbations, an alternative to combination therapy with a long-acting $\beta_2$-agonist and an inhaled corticosteroid is combination therapy with a long-acting $\beta_2$-agonist and a long-acting anticholinergic (antimuscarinic) agent, or a combination of all three drug classes.

Roflumilast, a phosphodiesterase-4 inhibitor, represents a relatively new class of medications for COPD. Phosphodiesterase-4 inhibitors decrease inflammation and promote airway smooth muscle relaxation and bronchodilation. Roflumilast is typically used in patients with more severe disease and frequent exacerbations.

Modalities available for treatment of COPD are as follows:

1. Bronchodilators
2. Antibiotics
3. Corticosteroids
4. Phosphodiesterase-4 inhibitors
5. Supplemental oxygen
6. Exercise rehabilitation
7. Chest physiotherapy
8. Surgery (selected cases)

Patients with COPD who develop an acute respiratory tract infection, or patients with an exacerbation of their disease without a clear precipitant, are often treated with antibiotics. The primary usefulness of antibiotics is treatment of bacterial infections. However, a bacterial cause is difficult to document with certainty, and many exacerbations are thought to be either noninfectious or triggered by viral respiratory infections. In practice, patients are frequently treated with antibiotics when a change in quantity, color, and/or thickness of sputum is noted in comparison with the usual pattern of sputum production, regardless of whether a bacterial infection is documented. Of the potential bacterial pathogens, those most frequently implicated are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. As a

result, the choice of an empiric antibiotic should provide coverage for these organisms. An area of investigation is the use of C-reactive protein levels and other biomarkers to help guide the use of antibiotics.

More recently, there has also been interest in the chronic use of a macrolide antibiotic (e.g., azithromycin) for its anti-inflammatory as well as antibacterial properties as another option for decreasing exacerbations in patients with COPD and a history of frequent exacerbations. However, as with chronic use of virtually any antibiotic, there is an associated risk of selecting out more resistant bacterial strains.

An important therapy for patients with significant hypoxemia (i.e., systemic arterial oxygen saturation ≤ 88% or arterial $P_{O_2}$ ≤ 55 mm Hg) is administration of supplemental $O_2$. Fortunately, the $P_{O_2}$ of hypoxemic patients with COPD usually responds quite well to relatively small amounts of supplemental $O_2$ (range, 24%-28% $O_2$). A low flow rate of $O_2$ (1-2 L/min) given by nasal prongs is an effective, well-tolerated method for achieving these concentrations of inspired $O_2$. Oxygen is particularly important in patients with pulmonary hypertension and in those with secondary polycythemia, because each of these complications is largely due to hypoxemia and is responsive to treatment for it. For significantly hypoxemic patients, as defined earlier, administering supplemental $O_2$ has been shown to alter the natural history of the disease and improve long-term survival. However, no such benefit appears to accrue in patients with less severe or episodic hypoxemia.

The goal of $O_2$ therapy is to shift $P_{O_2}$ into the range where hemoglobin is almost fully saturated (i.e., $P_{O_2}$ > 60-65 mm Hg). Ideally, $O_2$ saturation should be well maintained on a continuous basis throughout the day and night. In some COPD patients who are not significantly hypoxemic during the day, a substantial drop in $P_{O_2}$ and $O_2$ saturation can occur at night. In these patients, nocturnal $O_2$ theoretically may be of benefit, although this has not been proven. In addition to oxygen therapy, there is also an emerging role for nocturnal noninvasive positive pressure ventilation in some patients with severe COPD, particularly if hypercapnia is present.

For patients in whom airway secretions cause significant symptoms, chest physiotherapy and postural drainage are sometimes used to help mobilize and clear secretions. These techniques use percussion of the chest wall to loosen secretions and induce cough, followed by positional changes to allow gravity to aid in the drainage of secretions. Hand-held mucus-clearing devices are also available. To use these devices, the patient exhales into the apparatus, which applies oscillatory positive end-expiratory pressure, allowing more efficient clearance of secretions. However, the general usefulness of chest physiotherapy, postural drainage, or mucus-clearing devices is not generally accepted because outcome studies have not clearly supported their benefit.

In a small subgroup of patients with COPD who have $\alpha_1$-antitrypsin deficiency, therapy is available in the form of intravenous $\alpha_1$-antitrypsin concentrate, which is prepared from pooled human plasma. The rationale for this therapy is to replace the deficient protease inhibitor and attempt to inhibit or prevent unchecked proteolytic destruction of alveolar tissue. Although intravenous infusions of $\alpha_1$-antitrypsin have been shown to increase concentrations of this antiprotease in alveolar epithelial lining fluid, whether such replacement therapy alters the accelerated decline in pulmonary function is less definitively known.

In patients with impaired exercise tolerance secondary to COPD, a rehabilitation program focusing on education and a regimen of exercise training is often quite beneficial. Most patients participating in such a program report an improved sense of well-being at the same time they experience an improvement in exercise tolerance. Smoking cessation education and assistance are absolutely critical parts of any comprehensive therapeutic program. Pharmacologic assistance to ameliorate the effects of nicotine withdrawal—nicotine replacement therapy, bupropion, or varenicline—is often a valuable component of smoking cessation efforts. Vaccination against influenza, SARS-CoV-2, and pneumococcus is indicated for all patients as a preventive strategy and a component of the overall therapeutic regimen.

Two surgical approaches have been used for patients with severe COPD who remain markedly symptomatic despite optimal therapy. One approach, *lung volume reduction surgery*, initially seems counterintuitive because it involves removing portions of both lungs from patients whose pulmonary reserve is marginal at best. However, two interesting pathophysiologic rationales underlie this approach. First, removal of some lung tissue diminishes overall intrathoracic volume, allowing the flattened and foreshortened diaphragm to return toward its normal position and resume its usual curved configuration. A flattened, foreshortened diaphragm is an inefficient respiratory muscle, and the changes in its position and shape following surgery facilitate its effectiveness during inspiration. Second, when the most diseased regions of lung are selectively removed (i.e., the regions with the least elastic recoil), the overall elastic recoil of the lung improves. Lung elastic recoil is an important determinant of expiratory flow and airway collapse, and improving elastic recoil has secondary benefits on airway patency and expiratory flow. Although lung volume reduction, either via surgery or via implantation of endobronchial valves through a bronchoscope, is a novel and potentially attractive approach, it appears to be beneficial only in well-selected patients. Critical aspects of patient selection include the severity of disease and the anatomic distribution of emphysematous changes.

The other surgical approach to treatment of end-stage COPD is *lung transplantation*. However, this approach is limited for large numbers of individuals because of the resources needed, the shortage of donor organs, the age of most patients with COPD, and the presence of disqualifying comorbid conditions. Patients whose emphysema is due to $\alpha_1$-antitrypsin deficiency, in whom the disease occurs at an early age, may be a particularly appropriate subgroup to consider for lung transplantation.

When acute respiratory failure supervenes as a part of COPD, mechanical ventilation may be necessary to support gas exchange and maintain acceptable arterial blood gas values. Such ventilatory assistance with intermittent positive pressure may be delivered via either a mask (noninvasive positive-pressure ventilation) or an endotracheal tube, but the former noninvasive method is preferred. More detailed information about the treatment of acute respiratory failure superimposed on chronic disease of the obstructive variety is covered in Chapter 28. Mechanical ventilation is discussed in Chapter 30.

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# 7: Miscellaneous airway diseases

## OUTLINE



This chapter considers several disorders that affect airways, chosen because of their clinical or physiologic importance. The first of these disorders, bronchiectasis, is defined by chronic structural changes of airways that are often a consequence of prior

respiratory tract infection and/or a variety of underlying predisposing conditions. The second disorder, cystic fibrosis, is a genetic disease that usually first manifests in childhood and is notable for the serious clinical consequences that ensue. Finally, abnormalities of the upper airway (which for our purposes here includes the airway at or above the level of the trachea) are discussed briefly to acquaint the reader with the physiologic principles that allow detection of these disorders.

# Bronchiectasis

*Bronchiectasis* is an irreversible dilation of airways caused by inflammatory destruction of airway walls. Because the most common etiologic factor is infection, which triggers the destructive inflammatory process, the involved area with bronchiectasis depends on the location and extent of the underlying infection. In some cases, bronchiectasis is localized to a specific region of the lung. In other cases, the process involves more than one area or even is diffuse, involving a large portion of both lungs.

## Etiology and pathogenesis

Infection and impairment of drainage (frequently due to obstruction) are the two underlying problems that contribute to development of dilated or bronchiectatic airways. The responsible infection(s) may be viral or bacterial. Up until the mid-20th century in developed nations, measles and pertussis (whooping cough) pneumonia were common respiratory infections resulting in bronchiectasis. Currently, a variety of other viral and bacterial infections often are associated; important examples are tuberculosis and *Mycobacterium avium* complex. At times, inflammation resulting from hypersensitivity to fungal organisms is the underlying cause, as with *allergic bronchopulmonary aspergillosis*. This condition, found almost exclusively in patients with clinically apparent asthma or cystic fibrosis, is characterized by colonization of airways with *Aspergillus* organisms and by thick mucus plugs and bronchiectasis in relatively proximal airways.

Prior infection, obstruction, or both are the most common problems leading to bronchiectasis.

When an airway is obstructed, a superimposed infection is likely to develop behind the obstruction, causing injury to the airway wall and leading to bronchiectasis. Slow-growing tumors, thick mucus, or foreign bodies commonly cause bronchial obstruction that results in bronchiectasis. As will be described later in this chapter, poor airway clearance of thick mucus as well as impaired antimicrobial defenses are factors that make bronchiectasis an important consequence of cystic fibrosis.

A factor that plays a role in some patients is a defect in the ability of the airway to clear itself of, or protect itself against, bacterial pathogens (see Chapter 22). Such a defect predisposes a person to recurrent infections and eventually to airway dilation and bronchiectasis. The abnormality may involve inadequate humoral immunity and insufficient antibody production (hypogammaglobulinemia) or defective leukocyte function. Another potential cause is primary ciliary dyskinesia, in which ciliary dysfunction impairs the ability of the ciliary blanket that lines the airway to clear

bacteria and protect the airway against infection. The ciliary dysfunction is not limited to the lower airways; it also affects the nasal mucosa and, in males, may affect sperm motility and hence fertility. Pathologically, the dynein arms that are a characteristic feature of the ultrastructure of cilia are frequently absent in this disorder. One specific syndrome associated with bronchiectasis and ciliary dysfunction is *Kartagener syndrome*, which includes a triad of sinusitis, bronchiectasis, and situs inversus (usually discovered because of the presence of dextrocardia) (Fig. 7.1).

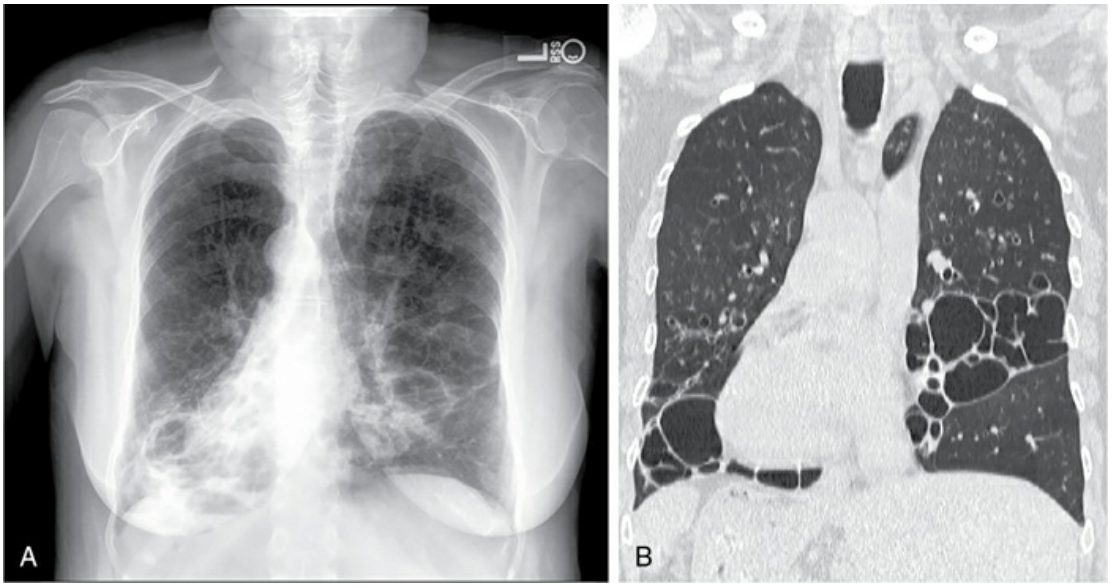


**FIGURE 7.1** Chest imaging studies from a patient with Kartagener syndrome, showing dextrocardia and bronchiectasis. **A,** Posteroanterior (PA) chest x-ray. Note the "L" at the top of the image, identifying the left side of the chest and documenting that the heart is on the opposite (right) side. **B,** Coronal slice from the chest CT scan. In addition to dextrocardia, multiple dilated airways are readily visible. *Source:* (Courtesy Dr. Seth Kligerman.)

Whatever the underlying cause, a "vicious cycle" of events has been proposed to explain the evolution and potential for progression of disease. The cycle starts with infection or another injury to the airway wall leading to an inflammatory response, resulting in structural changes to the airway wall and impaired mucus clearance, which then facilitates ongoing or progressive infection, inflammation, and perpetuation of the cycle.

Abnormalities of ciliary structure and function can result in recurrent infections and bronchiectasis.

## Pathology

The primary pathologic feature of bronchiectasis is evident on gross inspection of the airways, which are markedly dilated in the involved region (Fig. 7.2). Three specific patterns of dilation have been described: *cylindrical* (appearing as uniform widening of the involved airways), *varicose* (having irregularly widened airways resembling varicose veins), and *saccular bronchiectasis* (characterized by widening of peripheral airways in a balloon-like fashion). These terms are used when describing radiographic patterns but are not relevant clinically. The dilated airways typically are filled with a considerable amount of secretions that may be grossly purulent. Microscopic changes of the bronchial wall can be seen, including epithelial ulceration and squamous metaplasia, as well as infiltration by inflammatory cells (both lymphocytes and neutrophils) in the mucosa and submucosa.

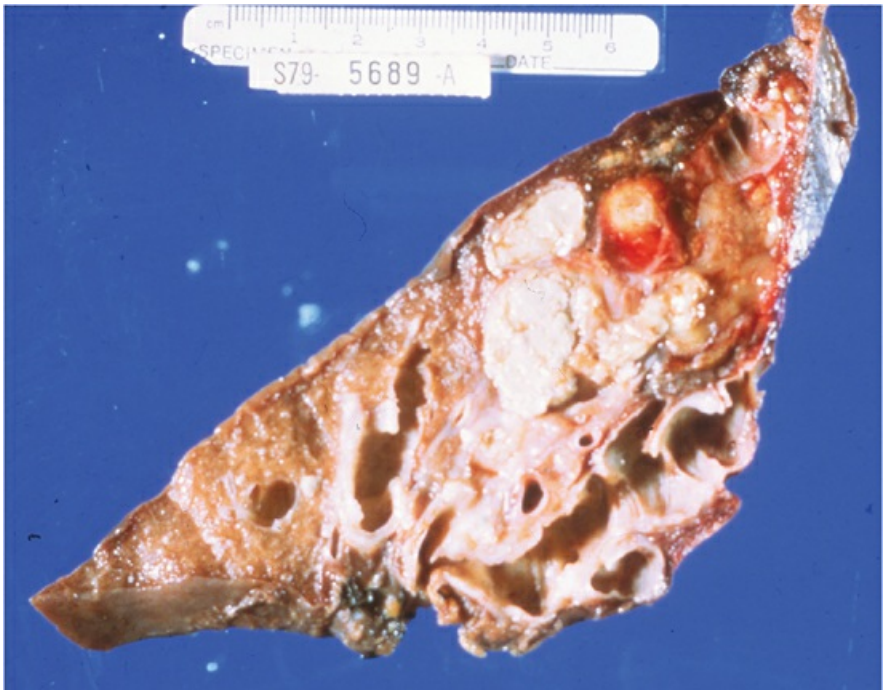


**FIGURE 7.2** Surgically removed specimen of lung shows extensive bronchiectasis. Some grossly dilated airways are filled with large amounts of mucoid and purulent material.

As a result of the exuberant inflammatory changes in the bronchial wall, the blood supply, provided by the bronchial arteries, is increased. The arteries enlarge and increase in number, and new anastomoses may form between the bronchial and pulmonary artery circulations. Inflammatory erosion or mechanical trauma at the site of these vascular changes is often responsible for the hemoptysis seen frequently in patients with bronchiectasis.

Vessels from the bronchial arterial circulation supplying a bronchiectatic region are often a source of bleeding and hemoptysis.

Coexisting disease in the remainder of the tracheobronchial tree is common. Other areas of bronchiectasis may be present, or generalized changes of chronic bronchitis may be seen (see Chapter 6).

## Pathophysiology

After the airways have become irreversibly dilated, their defense mechanisms against infection are disturbed. The normal propulsive action of cilia in the involved area is lost, even if it was intact before development of bronchiectasis. Bacteria colonize the enlarged airways, and secretions pool in the dilated sacs of patients with saccular bronchiectasis. Cough becomes much less effective at clearing secretions because of the abnormally collapsible airways. In many cases, the relationship established between the colonizing bacteria and the host is relatively stable over time, but the course may be punctuated by acute exacerbations of airway infection.

Functionally, patients with a localized area of bronchiectasis are not impaired to the same extent as patients with generalized obstructive lung disease. Measurement of pulmonary function may reveal surprisingly few if any abnormalities. When present, functional abnormalities are the result of either extensive bronchiectasis involving a large area of one or both lungs or coexistent generalized airway disease, primarily chronic bronchitis.

## Clinical features

The most prominent symptoms in patients with bronchiectasis are generally cough and copious sputum production. The sputum may be frankly purulent and tenacious, and often the profuse amount of yellow or green sputum production raises the physician's suspicion of bronchiectasis. However, not all patients with bronchiectasis have significant sputum production. It has been estimated that approximately 10% to 20% of patients are free of copious sputum production; these patients are said to have "dry" bronchiectasis.

Common clinical features of bronchiectasis are as follows:

1. Cough
2. Copious and purulent sputum
3. Hemoptysis
4. Localized rales or rhonchi
5. Clubbing

The other frequent symptom in patients with bronchiectasis is hemoptysis, which may be massive and life-threatening. Hypertrophied bronchial arterial circulation to the involved area is responsible for this symptom in most cases. Because bronchial arteries are branches of the aorta and therefore perfused at systemic blood pressure, bleeding from these vessels can be brisk. Physical examination of the patient with bronchiectasis may reveal few abnormalities, even over the area of involvement. When present, abnormal findings, such as wheezes, crackles, or rhonchi in a localized area, are heard. Clubbing is frequently observed. Although the mechanism is not clear, clubbing is

thought to be associated with the chronic suppurative process.

Whether gas exchange is abnormal in these patients often depends on the extent of involvement and the presence or absence of underlying chronic bronchitis. With well-localized disease, both $P_{O_2}$ and $P_{CO_2}$ may be normal. At the other extreme, patients with more severe disease may develop hypoxemia and hypercapnia. Cor pulmonale may subsequently develop.

## Diagnostic approach

The diagnosis of bronchiectasis is usually suggested by a history of copious sputum production, frequent respiratory tract infections, hemoptysis, or all three. A chest radiograph often reveals nonspecific abnormalities in the involved area. The radiograph may show an area of increased markings, crowded vessels, or "ring" shadows corresponding to dilated or saccular airways. However, none of the findings on the routine radiograph is considered diagnostic of bronchiectasis.

High-resolution computed tomography (HRCT) provides a definitive diagnosis and is the initial procedure used to define the presence, location, and extent of bronchiectasis (Fig. 7.3). HRCT (with sections 1-2 mm thick) provides excellent detail and is particularly useful for detecting subtle bronchiectasis. In the past, the definitive diagnosis depended on bronchography, a radiographic procedure in which an inhaled opaque contrast material was used to outline part of the tracheobronchial tree (Fig. 7.4). This procedure is uncomfortable, can induce bronchospasm, and is not currently performed.

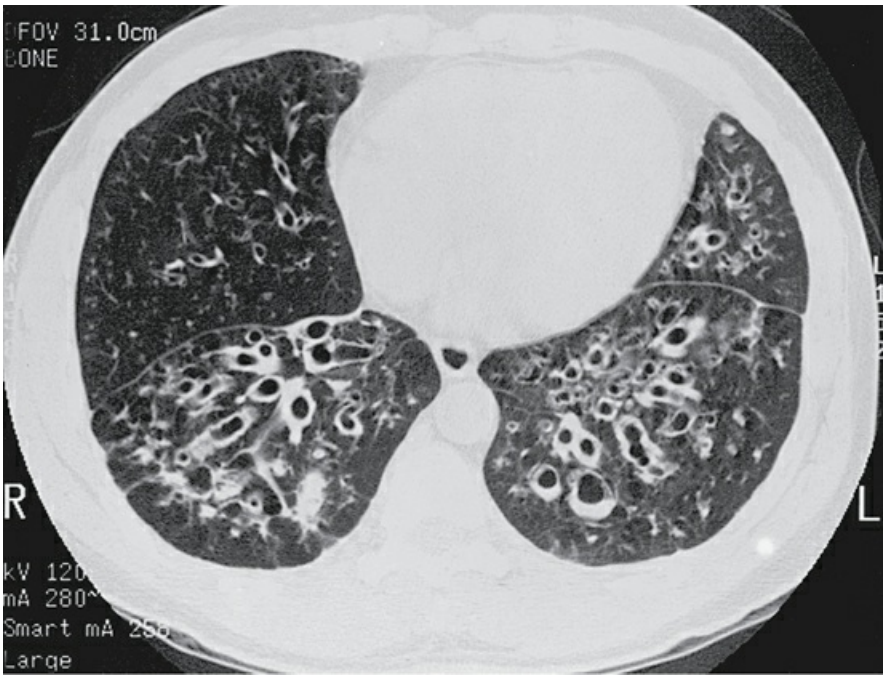


**FIGURE 7.3** High-resolution computed tomography scan of bronchiectasis shows dilated airways in both lower lobes and in the lingula. When seen in cross-section, dilated airways have a ringlike

appearance.

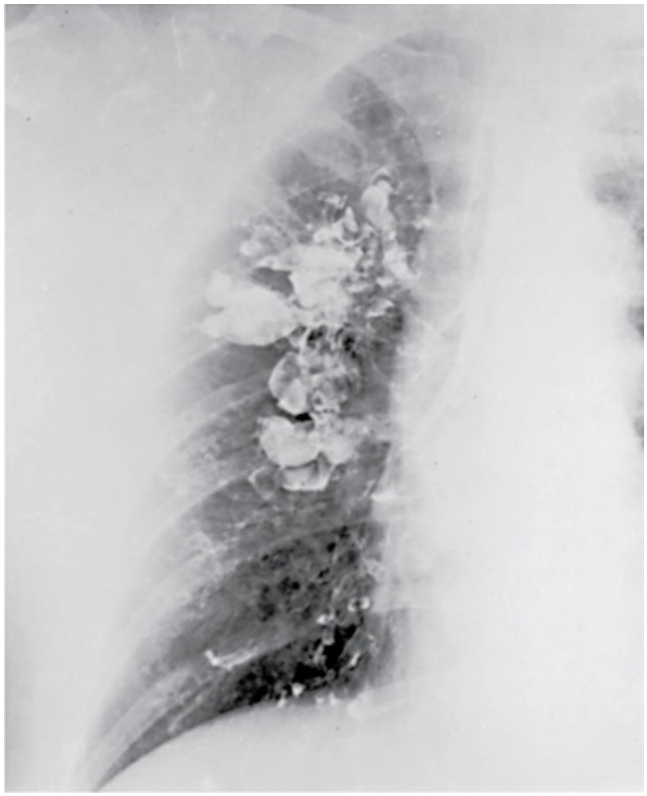

**FIGURE 7.4** Bronchogram of patient with extensive saccular bronchiectasis, primarily in right upper lobe.

Examination of the sputum for microorganisms may be helpful, particularly during an acute exacerbation of the disease. Patients with bronchiectasis frequently become colonized and infected with *Pseudomonas aeruginosa* or nontuberculous mycobacteria (see Chapter 25), and the finding of these otherwise relatively unusual pathogens may be a clue to the presence of underlying bronchiectasis. The effects of bronchiectasis on functional evaluation were discussed in the sections on pathophysiology and clinical features.

## Treatment

The three major aspects of treatment of bronchiectasis are control of infection, mobilization and clearance of airway secretions, and suppression of the inflammatory response. Bronchodilators are also frequently used in the patient who has functional evidence of airflow obstruction. Antibiotics to control infection are used and are dependent on the particular organisms cultured from the airways. Patients are typically treated during an exacerbation of their disease (i.e., when the quantity or appearance of the sputum unequivocally changes). In addition, some patients also are treated on a more chronic or intermittent basis with antibiotics in an attempt to suppress or even

eradicate colonizing bacteria, with the intent of reducing symptoms and exacerbations. Oral agents that are typically effective against many strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* are often used in patients with bronchiectasis in whom *Pseudomonas aeruginosa* has not yet become problematic. When these patients are infected with *Pseudomonas* organisms, treatment is generally more difficult. Inhaled tobramycin is sometimes used to suppress the growth of *Pseudomonas* and other Gram-negative organisms. Parenteral antibiotic therapy with either one or two antibiotics active against *Pseudomonas* is often administered, particularly during acute exacerbations. Oral fluoroquinolones such as ciprofloxacin can be useful as an alternative to parenteral antibiotics for treatment of *Pseudomonas* infection, but development of resistance to this class of antibiotics is common. Infection with nontuberculous mycobacteria such as *M. avium* complex may require prolonged therapy with multiple drugs (see Chapter 25). Just as for patients with other chronic lung diseases, pneumococcal, SARS-CoV-2, and seasonal influenza vaccines are particularly important for patients with bronchiectasis.

Chest physical therapy and positioning to allow better drainage of secretions (postural drainage), often preceded by inhalation of a mist of hypertonic saline, are frequently used for patients with copious sputum. Alternatively, mucus-clearing devices that provide oscillating positive pressure during exhalation, inflatable vests, or mechanical vibrators on the chest are commonly used to facilitate clearance of secretions. Inhaled deoxyribonuclease (DNase) has been used to decrease the viscosity of pulmonary secretions in patients with cystic fibrosis (see section on cystic fibrosis) but has not proven effective in bronchiectasis resulting from other causes.

Because ongoing airway inflammation is an important feature of bronchiectasis, there is great interest in anti-inflammatory treatment. Both oral and inhaled corticosteroid medications have been investigated, but large studies do not support their routine use. Oral macrolides (e.g., azithromycin) are increasingly being used in bronchiectasis because anti-inflammatory actions and immunomodulatory effects can be attributed to macrolides when administered for long term in low doses. Studies have demonstrated a significant reduction in exacerbations in patients receiving chronic macrolide therapy, although there is a potential for emergence of resistant bacteria from the long-term use of antibiotics and a risk of adverse cardiac effects due to QT interval prolongation. Other more targeted approaches to anti-inflammatory interventions are under study, but none have yet been proven safe and effective.

Treatment of bronchiectasis includes antibiotics, mobilization and clearance of secretions, suppression of the inflammatory response, and bronchodilators. Surgical therapy with resection of the diseased area is infrequent.

In the past, surgery was used for many patients with localized bronchiectasis. Because medical therapy is frequently effective in limiting symptoms and impairment, resection of a discrete diseased area now is performed infrequently. Surgery is reserved for selected patients who have significant poorly controlled symptoms attributable to a single localized area and who do not have other areas of bronchiectasis or significant evidence of generalized chronic obstructive pulmonary disease.

# Cystic fibrosis

*Cystic fibrosis*, an autosomal recessive genetic disorder that affects all races and ethnic groups, is the most common lethal genetic disease affecting persons of European ancestry. An epidemiologic survey of cystic fibrosis in the United States found a frequency in newborns of approximately 1 in 3200 whites, 1 in 9200 Hispanics, 1 in 11,000 Native Americans, 1 in 15,000 African Americans, and 1 in 30,000 Asian Americans. Manifestations of the disease are usually seen in childhood, although increasingly more cases are being recognized in adults, and children with the disease are living longer into adulthood. The clinical presentation is dominated by severe lung disease and pancreatic insufficiency resulting from thick and tenacious secretions produced by exocrine glands.

## Etiology and pathogenesis

Cystic fibrosis is caused by mutations in the gene that codes for the 1480-amino-acid protein *cystic fibrosis transmembrane conductance regulator* (CFTR), which resides on the long arm of chromosome 7. A member of the adenosine triphosphate (ATP)-binding cassette transporter protein superfamily, CFTR is an epithelial ion channel critically important in regulation of chloride, sodium, bicarbonate, and water absorption and secretion. CFTR mutations are categorized into six different classes according to the resultant functional or processing abnormality in the protein (Table 7.1). The specific defects in each class are potential targets for different approaches to therapy (see Treatment).

**TABLE 7.1**

**Classes of Cystic Fibrosis Transmembrane Conductance Regulator Mutations**

| Class | Effect on CFTR | Functional CFTR | Presence of CFTR on Cell Membrane |
|---|---|---|---|
| I | Defective protein production due to premature termination of CFTR messenger RNA | No | No |
| II | Impaired protein processing due to misfolding (e.g., ΔF508 deletion) | No | No, CFTR is degraded in the cytoplasm |
| III | Defective regulation with reduced channel opening time (e.g., G551D mutation) | No | Yes |
| IV | Impaired function causing reduced chloride transport | Yes, but reduced in function | Yes |
| V | Reduced synthesis of normally functioning CFTR | Yes, but reduced in number | Reduced in number |
| VI | Impaired membrane insertion or stability | Yes, but reduced in number | Reduced in number |

*CFTR,* cystic fibrosis transmembrane conductance regulator.

The most common mutation causing cystic fibrosis, ΔF508, is a three-nucleotide

deletion causing a single phenylalanine residue to be missing at position 508. The ΔF508 mutation causes the protein to misfold and be retained in the endoplasmic reticulum. Whatever the responsible mutation, a deficiency in the quantity or function of CFTR leads to decreased secretion of chloride into airways and increased reabsorption of sodium from airway secretions. As movement of water follows the concentration of ions, the decrease in sodium and chloride in the liquid covering the airway surface leads to a dehydrated airway surface, viscous mucous secretions, and impaired mucociliary clearance. The defective CFTR also leads to decreased secretion of bicarbonate into the airways, resulting in a lower pH in the mucus layer and impaired bacterial killing. Although a double copy (i.e., homozygous) ΔF508 mutation is responsible for approximately 50% of cases of cystic fibrosis, at least one allele with the ΔF508 mutation, when combined with another abnormal allele, is present in approximately 90% of cases. To date, more than 2000 different cystic fibrosis mutations have been identified.

Two major consequences of abnormal CFTR function are responsible for the clinical manifestations of cystic fibrosis. The first relates to the quality of secretions produced by various exocrine glands, which are thick and tenacious and block the tubes into which they are normally deposited (especially airways and pancreatic ducts). Second, because of disrupted sodium and chloride transport and reabsorption along the sweat duct, the sweat produced by affected patients has elevated concentrations of sodium, chloride, and potassium. The abnormal electrolyte composition of sweat has proven to be crucial in diagnosing the disorder.

Major consequences of abnormal CFTR in cystic fibrosis are as follows:

1. Production of thick, tenacious secretions from exocrine glands
2. Decreased pH of mucus
3. Elevated concentrations of sodium, chloride, and potassium in sweat

The mechanisms by which abnormal CFTR leads to all manifestations of the disease are not completely understood. Thick, tenacious secretions appear to play a major role, predisposing to difficulty clearing microbes and chronically infected airways. Inflammation and release of mediators from inflammatory cells, particularly neutrophils, not only are triggered by chronic infection but may result from abnormalities in mucosal defenses that are related to CFTR dysfunction. In addition, CFTR-related changes in cellular fatty acid metabolism causing abnormalities in control of inflammation and susceptibility to infection may also contribute. Other genetic differences, such as variants in tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-$\beta$ genes, appear to influence disease severity.

## Pathology

The pathologic findings in cystic fibrosis result from obstruction of ducts or airways by tenacious secretions and the accompanying inflammation. In the pancreas, obstruction of the ducts eventually produces fibrosis, atrophy of the acini, and cystic changes. In the lungs, thick mucus plugs appear in the airways, obstructing both airflow and normal

drainage of the tracheobronchial tree. Early in the course of the disease, airway changes are found predominantly in the bronchioles, which are plugged and obliterated by secretions. Later, the findings are more extensive. Bacterial and sometimes fungal colonization of the airways and secondary infection results, accompanied by infiltration primarily with neutrophils. Superimposed areas of pneumonitis appear, and frank bronchiectasis and areas of abscess formation may be found.

## Pathophysiology

In the pancreas, the pathologic process leads to exocrine pancreatic insufficiency, with maldigestion and malabsorption of foodstuffs, particularly fat and the fat-soluble vitamins A, D, E, and K. Diabetes mellitus due to destruction of islet cells may develop in later stages. In the lung, the major problem is recurrent episodes of tracheobronchial infection and bronchiectasis resulting from bronchial obstruction and defective mucociliary transport. In addition, evidence suggests that the CFTR mutation contributes to airway infection by altering the binding and clearance of microorganisms by airway epithelial cells, and the altered chloride concentration of airway fluid appears to impair the activity of antimicrobial peptides (especially human β-defensin-1). The major organisms that eventually colonize the airways are *Staphylococcus aureus, Pseudomonas aeruginosa, Stenotrophomonas (Xanthomonas) maltophilia,* and *Burkholderia cepacia*. Difficulty with these organisms seems to be entirely the result of local (airway) host defense mechanisms; the humoral immune system (i.e., ability to form antibodies) appears to be intact.

Major clinical problems from cystic fibrosis are as follows:

1. Pancreatic insufficiency
2. Recurrent episodes of tracheobronchial infection
3. Bronchiectasis
4. Intestinal obstruction
5. Sterility in males

As a result of airway obstruction, functional changes characteristic of obstructive airways disease and air trapping develop and can be tracked longitudinally with pulmonary function testing. Patients also exhibit ventilation-perfusion mismatch, hypoxemia (sometimes with $CO_2$ retention), pulmonary hypertension, and cor pulmonale.

## Clinical features

Approximately 10% to 20% of patients with cystic fibrosis develop their first clinical problem in the neonatal period, manifested as intestinal obstruction with thick meconium (the newborn's intestinal contents composed of ingested amniotic fluid). This obstruction is called *meconium ileus*. The remainder of patients usually have a childhood presentation, manifested as pancreatic insufficiency, recurrent bronchial infections, or both. Occasionally, patients are first diagnosed when they are adults. Almost all males with the disease are infertile because of congenital bilateral absence of

the vas deferens. Females have reduced fertility due to abnormally tenacious cervical mucus as well as malnutrition, which is frequently present to some degree.

Physical examination of patients with cystic fibrosis reveals the findings expected with severe airflow obstruction and plugging of airways by secretions. Wheezing and coarse crackles or rhonchi occur frequently, and clubbing is common.

Several problems may complicate the course of cystic fibrosis. Pneumothorax and hemoptysis, which may be massive, can pose major challenges in management. Eventually, progressive respiratory insufficiency and cor pulmonale develop. Although most patients with access to good care live into adult life, their life span is significantly reduced, with a current median survival of approximately 40 years. As noted below, with the recent introduction of CFTR modulator drugs, improvement in life expectancy is forecast.

Serious complications of cystic fibrosis are as follows:

1. Pneumothorax
2. Massive hemoptysis
3. Respiratory insufficiency
4. Cor pulmonale

## Diagnostic approach

In the United States and many countries in Europe, all newborns now are screened for cystic fibrosis, which is leading to earlier diagnosis and intervention. The definitive diagnosis of cystic fibrosis is made by the combination of compatible clinical features and one of the following: (1) identification of mutations known to cause cystic fibrosis in both CFTR genes, (2) characteristic abnormalities in measurements of nasal mucosal electrical potential difference, or (3) abnormal sweat electrolytes. The concentrations of sodium, chloride, and potassium are elevated in sweat from these patients, and a sweat chloride concentration greater than 60 mEq/L is generally considered diagnostic. Only individuals homozygous for the cystic fibrosis gene demonstrate this abnormality; heterozygous carriers have normal sweat electrolytes. Identification of heterozygotes (i.e., carriers of the cystic fibrosis gene) and in utero detection of homozygotes are possible with current DNA analytic techniques.

The chest radiograph often shows an increase in markings and the findings of bronchiectasis described in the previous section (Fig. 7.5). Evidence of focal pneumonitis may be seen during the course of the disease.

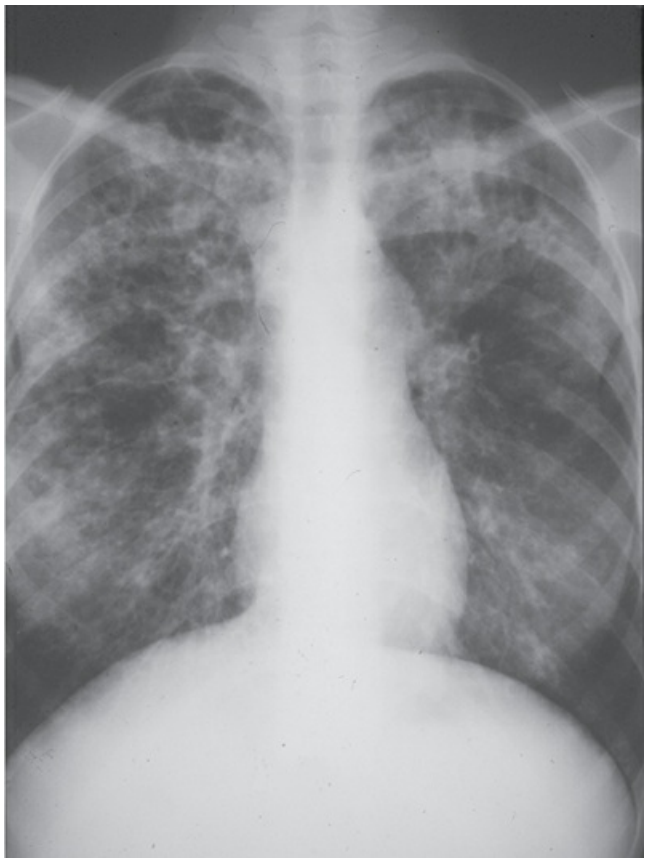

**FIGURE 7.5** Posteroanterior chest radiograph of patient with cystic fibrosis shows diffuse increase in markings throughout both lungs. These findings represent extensive fibrotic changes and bronchiectasis.

Diagnosis of cystic fibrosis is made by demonstration of an elevated concentration of sweat chloride, a culprit mutation in the CFTR gene, or an abnormal electrical potential difference in the nasal mucosa.

Functional assessment of these patients early in the disease shows evidence of obstruction of small airways. As the disease progresses, evidence of more generalized airway obstruction (decreased forced expiratory volume in 1 second [$FEV_1$], forced vital capacity [FVC], and $FEV_1$/FVC ratio) and air trapping (increased residual volume [RV]/total lung capacity [TLC] ratio) is seen. The elastic recoil of the lung is generally preserved, and TLC most commonly is within the normal range. Because emphysematous changes generally are not seen in patients with cystic fibrosis and the alveolar-capillary interface remains relatively preserved, most frequently the diffusing capacity is relatively normal. Arterial blood gas values often indicate hypoxemia, and hypercapnia may be seen as the disease progresses.

## Treatment

Therapy for cystic fibrosis has been focused on diminishing the clinical consequences and managing complications when they occur. In addition to a sustained focus on adequate nutrition, the principles of therapy were traditionally similar to those used for bronchiectasis of other causes: bronchopulmonary drainage (using chest physiotherapy and postural drainage, a mucus-clearing device, or a vibrating vest), antibiotics, and bronchodilators. Agents used to decrease the viscosity of the sputum appear to offer benefit in some patients. In particular, because DNA released from inflammatory cells contributes significantly to the viscosity of mucus, inhalation of recombinant DNase has been used to degrade DNA, decrease mucus viscosity, and improve clearance of secretions. Inhaled hypertonic saline also may be useful as a mucolytic agent. Oral macrolide antibiotics such as azithromycin may offer some benefit that is believed related to their anti-inflammatory effects rather than their antimicrobial properties.

More recently, therapy of cystic fibrosis has been revolutionized by the development of medications that improve the function of abnormal CFTR in most patients, frequently to within the normal range. These CFTR modulator drugs, such as ivacaftor, tezacaftor, and elexacaftor, can be used individually or in combination (depending on the specific mutation[s] present) to restore normal CFTR function and improve respiratory symptoms, lung function, nutritional status, and quality of life, frequently with normalization of sweat chloride testing.

Although current forms of therapy have significantly improved prognosis in cystic fibrosis, the natural history of the disease at present without disease-modifying therapy is still one of progressive pulmonary dysfunction and eventual death due to the disease or its complications. However, there is great optimism that the introduction of CFTR modulator medications earlier in the course of the disease, perhaps even in presymptomatic infants identified via newborn screening, may markedly improve prognosis. Importantly, even in adults with established advanced disease, the number of pulmonary exacerbations and hospitalizations tends to fall quickly after CFTR modulator therapy is initiated.

Bilateral lung transplantation may be considered for advanced cystic fibrosis. Despite initial concern for infectious complications due to preexisting chronic sinopulmonary infections, experience with bilateral lung transplantation in cystic fibrosis suggests post-transplantation survival is similar to that of patients with other diagnoses undergoing this procedure. Unfortunately, median survival after lung transplantation in cystic fibrosis remains less than 10 years, emphasizing that transplantation in this young population cannot be viewed as a cure.

Identification of the genetic basis for the disease in the majority of patients raised hopes that gene therapy would provide a means for reversing the primary defect, as well as the characteristic abnormality in airway secretion. Unfortunately, initial enthusiasm for gene therapy as a “cure” for cystic fibrosis has been tempered by difficulty finding an effective and nontoxic method (vector) for delivering the gene to the airway and achieving sufficient and durable expression of the normal gene. With the correction of ion transport abnormalities with CFTR modulators such as ivacaftor, cystic fibrosis may become a less optimal candidate disease for gene therapy approaches to treatment.

## Upper airway disease

The obstructive diseases considered so far primarily affect the airways below the level of the main carina—the bronchi and bronchioles. In contrast to disease of these lower airways, a variety of other disorders affect the pharynx, larynx, and trachea and produce what is termed *upper airway obstruction*. The discussion of these disorders includes a brief consideration of representative etiologic factors and some of the tests used to make the diagnosis. In particular, use of the flow-volume loop to define the location of upper airway obstruction is considered.

## Etiology

The upper airway can be affected by either acute problems or those following a more subacute or chronic course. On an acute basis, the larynx is probably the major area subject to obstruction. Potential causes include infection (epiglottitis, often due to *H. influenzae*), thermal injury and the resulting laryngeal edema from smoke inhalation, aspiration of a foreign body, laryngeal edema from an allergic (anaphylactic) reaction, or physical trauma associated with endotracheal intubation.

On a chronic basis, the upper airway may be partially obstructed by hypertrophy of the tonsils, by tumors (particularly of the trachea), by strictures of the trachea (often resulting from prior instrumentation of the trachea), or by vocal cord paralysis. Tracheomalacia, another chronic condition that may be congenital or acquired, is characterized by flaccidity of supporting airway cartilage and results in upper airway narrowing, especially on forced exhalation. The entity of obstructive sleep apnea, which is considered further in Chapter 18, is characterized by recurrent episodes of upper airway obstruction during sleep, resulting from anatomic factors and/or abnormal control of upper airway musculature.

## Pathophysiology

The resistance of a tube to airflow varies inversely to the fourth power of the radius; hence, even small changes in airway size may produce dramatic changes in resistance and in the work of breathing. There are three pathophysiologic categories of upper airway obstruction which depend on the rigidity and site of the obstruction (intrathoracic vs. extrathoracic). A *fixed obstruction* occurs when the involved airway is rigidly narrowed, without any change in the size of the lumen during the respiratory cycle. In this case, inspiration and expiration are impaired by the same amount, and the flow rate generated during inspiration is essentially identical to the flow rate during expiration.

On the other hand, if airway diameter changes during the respiratory cycle, the greatest impairment to airflow occurs when the airway diameter is smallest. This type of obstruction is termed a *variable obstruction*. If the obstruction is located within the thorax, changes in pleural pressure during the respiratory cycle affect the size of the airway and therefore the magnitude of the obstruction. During a forced expiration, the positive pleural pressure causes airway narrowing, making the obstructing lesion more critical. In contrast, during inspiration, the airways increase their diameter, and the effects of a partial obstruction are less pronounced (see Fig. 3.22).

The location and respiratory variability of an upper airway obstruction affect the appearance of the flow-volume curve and the findings on physical examination.

In contrast, if the obstruction is located above the level of the thorax (i.e., outside the thorax), changes in pleural pressure are not directly transmitted to the airway in question. Rather, the negative airway pressure during inspiration tends to create a vacuum-like effect on extrathoracic upper airways, narrowing them and augmenting the effect of any partial obstruction. During expiration, the pressure generated by the flow of air from the intrathoracic airways tends to widen the extrathoracic airways and decrease the net effect of a partially obstructing lesion (see Fig. 3.22).

## Clinical features

Patients with upper airway obstruction may have dyspnea or cough. On physical examination, they may have evidence of flow through narrowed airways. If the lesion is variable and intrathoracic, the primary difficulty with airflow occurs during expiration, and patients demonstrate expiratory wheezing. If the lesion is variable and extrathoracic, obstruction is more marked during inspiration, and patients frequently manifest inspiratory stridor, a high-pitched, monophonic, continuous inspiratory sound often best heard over the trachea. With acute upper airway obstruction, such as that seen with inhalation of a foreign body, anxiety and respiratory distress often are apparent, signaling a medical emergency. In patients with epiglottitis, respiratory distress often is accompanied by sore throat, change in voice, dysphagia, and drooling.

## Diagnostic approach

In the evaluation of suspected disorders of the upper airway, radiography and direct visualization provide the most useful information about the macroscopic appearance of the airway. Lateral neck radiographs or CT scans of the upper airway may reveal the localization, extent, and character of a partially obstructing lesion. A CT scan may offer particularly useful information by providing a cross-sectional view of the airways from the larynx down to the carina. Direct visualization of the upper airway may be obtained by laryngoscopy or bronchoscopy, which may reveal the presence of edema, vocal cord paralysis, or an obstructing lesion such as a tumor. However, direct visualization of the airways by these techniques includes some risk. The instrument used occupies part of the already compromised airway and may induce airway spasm or swelling that further obstructs the airway. This is especially true in cases of suspected epiglottitis, in which direct visualization should *not* be attempted unless the examiner is prepared to perform an emergency tracheostomy.

Because the functional consequences of a fixed versus a variable obstruction and an extrathoracic versus an intrathoracic obstruction are quite different, functional assessment of the patient with presumed upper airway obstruction can be useful in quantifying and localizing the obstruction. To recognize these distinctions, the flow-volume loop and the principles discussed in the pathophysiology section must be understood. This type of physiologic evaluation is appropriate for chronic upper airway obstruction, not for acute life-threatening obstruction.

When a fixed lesion is causing a relatively critical obstruction, maximal flow rates generated during inspiration and expiration are approximately equal, and a “plateau” marks both the inspiratory and expiratory parts of the flow-volume curve. When the lesion is variable, the effect of the obstruction depends on whether the lesion is

intrathoracic or extrathoracic. With an intrathoracic obstruction, critical narrowing occurs during expiration, and the expiratory part of the flow-volume curve displays a plateau. With an extrathoracic obstruction, the expiratory part of the loop is preserved, and the inspiratory portion displays the plateau. A schematic diagram of the flow-volume loops observed in these types of upper airway obstruction is shown in Fig. 3.23.

### Treatment

Because many different types of disorders result in upper airway obstruction, treatment varies greatly depending on the underlying problem, particularly its acuteness and severity. In acute severe upper airway obstruction, an emergency procedure such as endotracheal intubation or tracheostomy may be necessary to maintain a patent airway. A procedure such as bronchoscopic laser therapy or airway stenting also may be used. Discussion of each disorder and further consideration of management can be found in other textbooks and in some articles listed in the Suggested Readings.

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# 8: Anatomic and physiologic aspects of the pulmonary parenchyma

OUTLINE



Chapters 8 through 11 focus on the region of the lung directly involved in gas exchange, often called the *pulmonary parenchyma*. This region includes the alveolar walls and spaces (with the alveolar-capillary interface) at the level of the alveolar sacs, ducts, and respiratory bronchioles. Although the broad group of disorders involving these structures traditionally has been described under the category of *interstitial lung disease*, the term *diffuse parenchymal lung disease* is increasingly used and more accurately reflects the breadth of the pathologic involvement.

This chapter provides a description of the normal anatomy of the gas-exchanging region of the lung and some aspects of its normal physiology. Chapter 9 provides an overview of the diffuse parenchymal lung diseases, emphasizing how disturbances in alveolar structure are closely linked with aberrations in function. Chapters 10 and 11 focus on specific disorders, mostly subacute or chronic, in which the main pathologic features reside within the alveolar wall. Pneumonia, acute lung injury (acute respiratory distress syndrome), and diseases of the pulmonary vasculature are deliberately excluded because of their different pathologic appearance and are considered separately in other parts of this text.

Although a wide variety of disorders affect the alveolar wall, many of the pathophysiologic features are common to many individual diseases. Knowledge of these common pathophysiologic features and their effects on the normal function of the lung is useful for understanding the consequences of individual disease entities. For specific diseases with special characteristics, a consideration of these individual features is included.

## Anatomy

For the lung to function efficiently as a gas-exchanging organ, a large surface area must be available where $O_2$ can be taken up and $CO_2$ released. At the alveolar wall, where gas

exchange occurs, an extensive network of capillaries coursing through and coming into close contact with alveolar gas facilitates the exchange. In the normal lung, the alveolar septa are extremely thin and delicate, with the capillaries closely apposed to the alveolar lumen, and there is little tissue extraneous to the gas-exchanging process (Fig. 8.1).

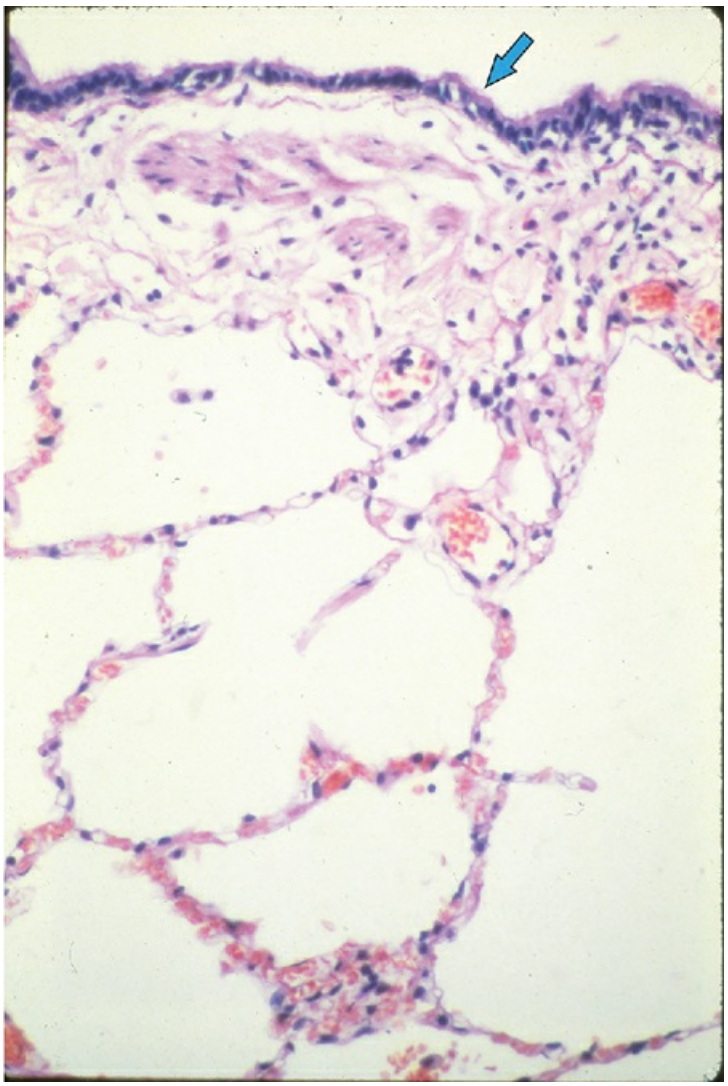

**FIGURE 8.1** Photomicrograph of alveolar walls shows a normal thin, lacy appearance. At top of photo is bronchial lumen, lined by bronchial epithelial cells *(arrow)*. Peribronchial tissue lies between bronchial epithelium and alveolar walls. *Source:* (Courtesy Dr. Earl Kasdon.)

The surface of the alveolar walls (the region bordering the alveolar lumen) is lined by a continuous layer of epithelial cells. Two different types of these lining epithelial cells, called *type I* and *type II cells*, can be identified. Type I cells are less numerous than type II cells but account for a much larger surface area. They have strikingly long and delicate

cytoplasmic extensions that line more than 95% of the alveolar surface (Fig. 8.2). Type I cells function as a barrier preventing free movement of material, such as fluid, from the alveolar wall into the alveolar lumen. Although they have few cytoplasmic organelles, evidence indicates that type I cells play an important role in the regulation of ion and fluid balance in the lung, in part because they cover such a large part of the alveolar surface area.

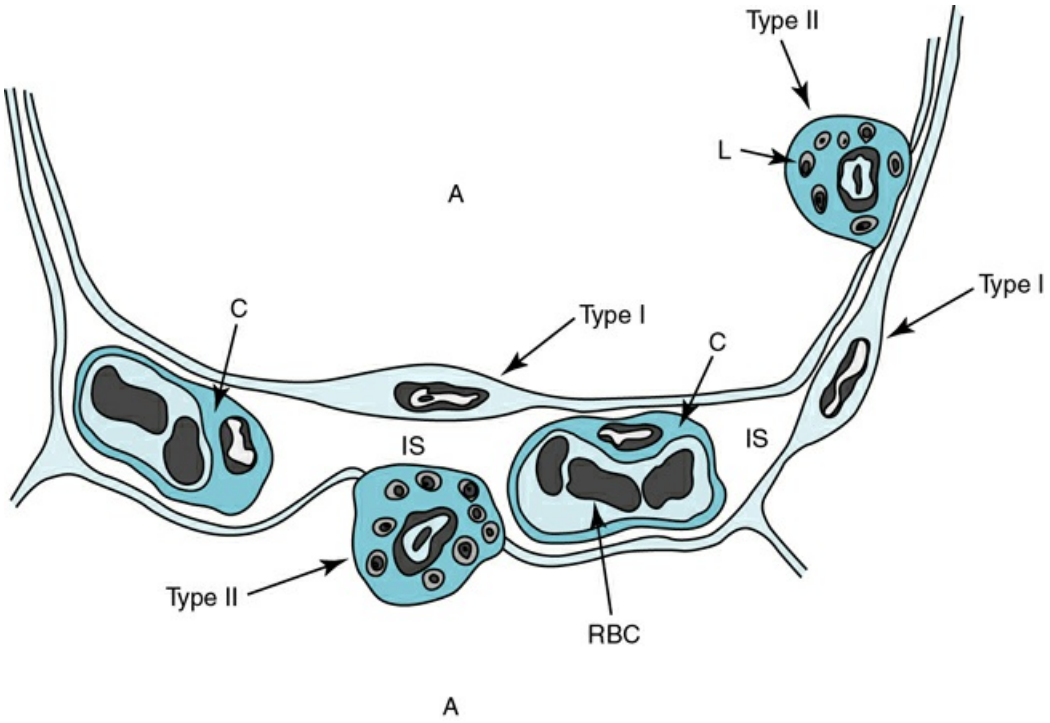


**FIGURE 8.2** Schematic diagram of normal alveolar structure. Type I and type II epithelial cells line alveolar wall. Type I cells are relatively flat and characterized by long cytoplasmic processes. Type II cells are cuboidal. Two capillaries are shown. A, alveolar space; C, capillary endothelial cells; IS, interstitial space (relatively acellular region of the alveolar wall); L, type II cell cytoplasmic lamellar bodies (source of surfactant); RBC, erythrocytes in capillary lumen.

Type I alveolar epithelial cells have long cytoplasmic processes that line almost the entire alveolar surface.

The second lining epithelial cell is the type II cell. Type II cells have three well-defined functions: synthesis of surfactant, alveolar epithelial repair, and ion and fluid transport. In contrast to type I cells, type II epithelial cells have a cuboidal shape and often bulge into the alveolar lumen. Type II cells are more numerous, but because they do not have long cytoplasmic extensions, they cover less than 5% of the alveolar surface. Type II cells

have many cytoplasmic organelles (mitochondria, rough endoplasmic reticulum, Golgi apparatus), which relate to their important synthetic role.

Type II cells produce surfactant, are important in the reparative process for type I cells, and are active in ion and fluid transport.

The primary product of the type II cells is *surfactant*. Specific inclusion bodies within the type II cells, termed *lamellar inclusions*, contain the packaged form of surfactant that eventually is released into the alveolar lumen. Surfactant is a complex of molecules composed of a high proportion of lipids, associated proteins, and carbohydrates, all of which are necessary for effective function. Surfactant reduces the surface tension of the alveoli. It stabilizes the alveolus in the same way a bubble is prevented from collapsing by a detergent material, thereby preventing microatelectasis (alveolar collapse on a microscopic level). During fetal development, surfactant is not synthesized until the third trimester. Defective or insufficient surfactant synthesis in premature infants may result in infant respiratory distress syndrome, and exogenous surfactant replacement therapy given shortly after birth improves outcomes.

Four types of protein are associated with surfactant: surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, and SP-D, respectively). The function of surfactant in maintaining a low surface tension is critically dependent on the hydrophobic proteins SP-B and SP-C. Although SP-A and SP-D also affect surface tension, they additionally have an important role in the innate immunity of the lung by opsonizing as well as directly inhibiting the growth of some microbial pathogens (see Chapter 22).

Type II cells have a significant role in maintenance and repair of the injured alveolar epithelium. Type I epithelial cells are quite susceptible to injury, whether from an external source via the airways or an internal source via the bloodstream. When type I cells are damaged, the reparative process involves hyperplasia of the type II cells and eventual differentiation into cells with the characteristics of type I cells. Normally, this orderly process results in some hyperplastic type II cells undergoing apoptosis, whereas the remainder transdifferentiate into thin, delicate, type I cells. As discussed in Chapter 11, defects in this process have been identified in idiopathic pulmonary fibrosis, a disease of progressive parenchymal scarring.

The third function of type II cells is regulation of alveolar fluid via transepithelial sodium and chloride transport. Proper regulation of ion and fluid balance requires an intact epithelium. Inhibition of this function occurs during inflammation and probably contributes to the edema formation seen in acute lung injury (see Chapter 29).

Type II cells are also involved in the synthesis of a number of other proteins. They have been reported to elaborate several growth factors and cytokines, cytokine receptors, and proteins involved in innate immunity, such as β-defensins. These additional activities of type II cells are areas of active research.

Pulmonary capillaries course through the alveolar walls as part of an extensive network of intercommunicating vessels. Unlike the alveolar epithelial cells, which are quite impermeable under normal circumstances, junctions between capillary endothelial cells permit passage of small-molecular-weight proteins. The importance of the permeability features of the alveolar epithelial and capillary endothelial cells will become apparent in the discussion of acute respiratory distress syndrome in Chapter 29,

because this disorder is characterized by increased permeability and leakage of fluid and protein into alveolar spaces.

The alveolar epithelial and capillary endothelial cells rest on a basement membrane. At some regions of the alveolar wall, nothing stands between the epithelial and endothelial cells other than the basement membranes, which are fused to form a single structure. At other regions, the *interstitial space*, which consists of relatively acellular material (see Fig. 8.2), intervenes. The major components of the interstitial space are collagen, elastin, proteoglycans, a variety of macromolecules involved with cell-cell and cell-matrix interactions, some nerve endings, and some fibroblast-like cells. There are also small numbers of lymphocytes as well as cells that appear to be in a transition state between blood monocytes and alveolar macrophages (which are derived from circulating monocytes).

Within the alveolar lumen, a thin layer of liquid covers the alveolar epithelial cells. This extracellular alveolar lining layer is composed of an aqueous phase immediately adjacent to the epithelial cells, covered by a surface layer of lipid-rich surfactant produced by the type II epithelial cells. The alveolar lining layer also contains alveolar macrophages, phagocytic cells that are important in protecting the distal lung against bacteria and in clearing inhaled particulate matter. Alveolar macrophages and the innate immunity of the lung are discussed further in Chapter 22.

## Physiology

Some of the physiologic principles relating to the pulmonary parenchyma were covered briefly in Chapter 1. This chapter further discusses two topics that are important in the pathophysiologic abnormalities resulting from diffuse parenchymal lung disease: gas exchange at the alveolar-capillary level and how disturbances within the pulmonary parenchyma affect the mechanical properties of the lung.

Gas exchange between the alveolus and the capillary depends on passive diffusion of gas from a region of higher partial pressure to one of lower partial pressure. As discussed in Chapter 1, the $Po_2$ in the alveolus normally is approximately 100 mm Hg, and in the blood entering the pulmonary capillary is approximately 40 mm Hg. This difference results in a driving pressure for $O_2$ to diffuse from the alveolus to the pulmonary capillary, where it binds with hemoglobin within the erythrocyte. The barrier to diffusion—which includes the thin cytoplasmic extension of the type I cell, the basement membrane of type I and capillary endothelial cells, and the capillary endothelial cell itself—is extremely thin, measuring approximately 0.5 μm. Some areas of the alveolar wall also contain a thin layer of interstitium, but presumably diffusion and gas exchange occur preferentially at the thinnest region, where the interstitium is sparse or absent.

Although the rate of gas transfer across the alveolar-capillary interface depends on the thickness of the barrier, $O_2$ uptake by the blood is normally complete early during the transit through the capillaries. The total time spent by a red blood cell traveling through the pulmonary capillaries is approximately 0.75 second, and equilibration with $O_2$ occurs within the first third of this time. Therefore, extra time is available for diffusion should disease affect the alveolar-capillary interface and impair the normal process of diffusion. Because $CO_2$ diffuses much more readily than $O_2$, even more ample reserve

time is available for its diffusion.

Oxygen uptake and $CO_2$ elimination at the alveolar-capillary interface are completed early during transit of an erythrocyte through the pulmonary vascular bed.

Consequently, although diffuse parenchymal lung diseases do affect gas exchange, impaired diffusion across an abnormal alveolar-capillary interface is not the primary contributor to the disturbance in gas exchange when the patient is at rest. However, when these patients exercise and cardiac output increases, blood flows more rapidly through the pulmonary capillaries, and the combination of a diffusion impairment and a shorter time for diffusion of oxygen may lead to hypoxemia. This issue is considered further in Chapter 9 as part of the discussion of abnormalities in gas exchange in patients with diseases affecting the alveolar wall.

Another important aspect of physiology relating to the lung parenchyma is compliance. As stated in Chapter 1, the lung is elastic and resists expansion like a balloon or a rubber band. Lung compliance relates the volume of gas within the lung and the distending pressure (i.e., *transpulmonary pressure*) needed to expand the lung to that volume. Diseases affecting the alveolar walls commonly disturb this pressure-volume relationship, making the lung either more stiff (less compliant, more resistant to expansion), or less stiff (more compliant, easier to expand). For the stiffer, less compliant lung, the compliance curve is shifted to the right: a lower volume is achieved for any given transpulmonary pressure. Most of the diseases discussed in this section, which are included in the category of diffuse parenchymal lung disease, affect the compliance of the lung in this way (Fig. 8.3). In contrast, as discussed in Chapter 6 and illustrated in Fig. 6.7, patients with emphysema, whose lungs are less resistant to expansion (i.e., are more compliant), have compliance curves that are shifted to the left. This principle of compliance is important in pulmonary physiology. Chapters 1 and 6 discussed the role of compliance in determining lung volumes measured by pulmonary function testing, particularly total lung capacity and functional residual capacity. This principle is cited again in Chapter 9, which discusses the pathophysiology of diseases that affect the alveolar walls.

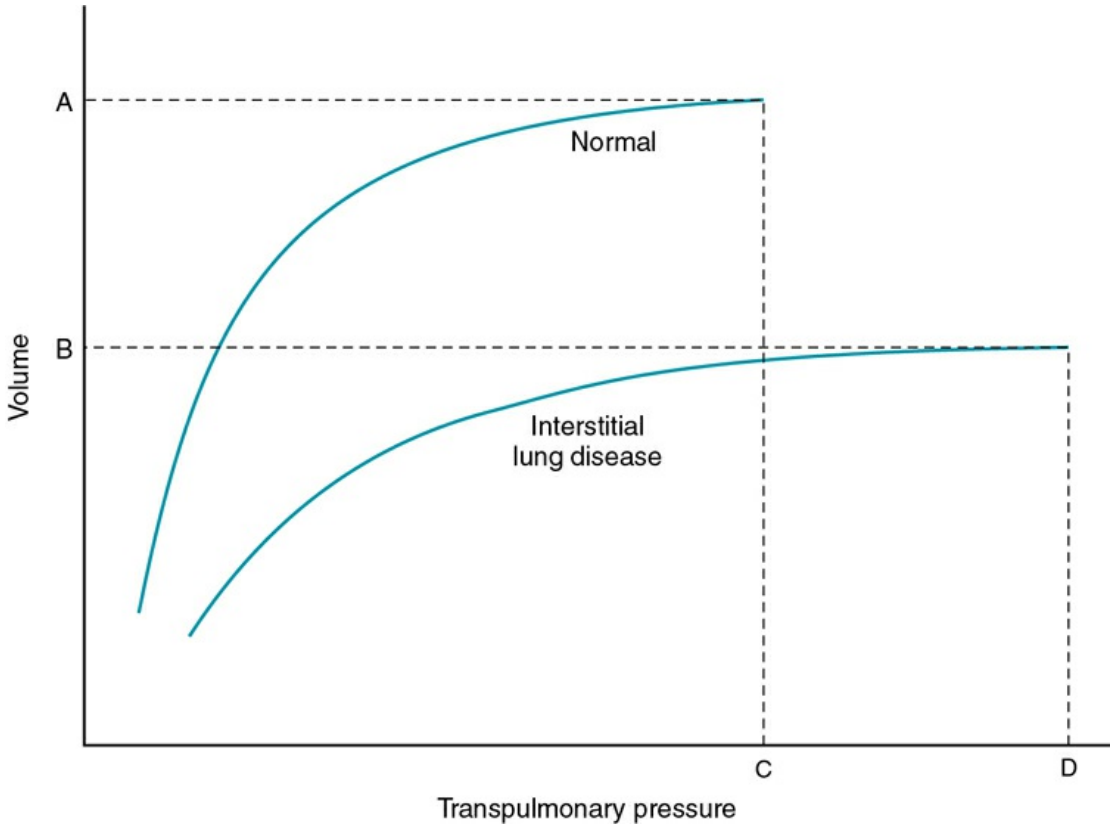


**FIGURE 8.3** Compliance curve of lung in diffuse parenchymal lung disease compared with that of normal lung. In addition to shift of the curve downward and to right, total lung capacity (TLC) in diffuse parenchymal lung disease *(point B on volume axis)* is characteristically less than normal TLC *(point A)*. Maximal pressure at TLC is called *maximal static recoil pressure* ($Pst_{max}$), represented for normal lung and lung with interstitial disease by points C and D, respectively. *Source:* (Compare with Fig. 6.7.)

The compliance curve of the lung in interstitial lung disease is shifted downward and to the right.

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# 9: Overview of diffuse parenchymal lung diseases

OUTLINE



A large group of disorders affects the alveolar wall in a fashion that ultimately may lead to diffuse scarring or fibrosis. These disorders traditionally have been referred to as *interstitial lung diseases*, although the term is somewhat of a misnomer (see Chapter 8). The *interstitium* formally refers only to the region of the alveolar wall exclusive of and separating the alveolar epithelial and capillary endothelial cells. However, interstitial lung diseases affect all components of the alveolar wall: epithelial cells, endothelial cells, and cellular and noncellular components of the interstitium. In addition, the disease process often extends into the alveolar spaces and therefore is not limited to the alveolar wall. Many authors now prefer the expression *diffuse parenchymal lung disease*, which is the term generally used in this book. However, for practical purposes, the reader should recognize that the expressions *diffuse parenchymal lung disease* and *interstitial*

*lung disease* typically refer to the same group of disorders causing inflammation and fibrosis of alveolar structures. Another label, the *idiopathic interstitial pneumonias,* identifies a group of pathologic entities that represent a subcategory of diffuse parenchymal lung disease. The disorders included within that label will be discussed in more detail in the Pathology section of this chapter, as well as in Chapter 11, where we consider those diffuse parenchymal lung diseases that do not have a well-defined etiology.

The idiopathic interstitial pneumonias represent a subgroup of disorders within the broader category of diffuse parenchymal lung disease.

There are more than 150 diffuse parenchymal lung diseases. Table 9.1 lists the most common of these disorders, grouped by broad categories according to whether the underlying etiology of the disease is currently known or unknown. A third category of "mimicking disorders" is included in recognition of the fact that a number of additional well-defined clinical problems can produce diffuse parenchymal abnormalities on chest imaging. Even though these mimicking disorders often are not included in traditional lists of diffuse parenchymal lung diseases, the clinician must remember to consider them in the appropriate clinical settings.

**TABLE 9.1**
**Classification of Selected Diffuse Parenchymal Lung Diseases**

| |
|---|
| **Known Etiology** |
| Resulting from inhaled inorganic dusts (pneumoconiosis [e.g., asbestosis, silicosis])<br>Caused by organic antigens (hypersensitivity pneumonitis)<br>Iatrogenic (drugs, radiation pneumonitis) |
| **Unknown Etiology** |
| Idiopathic interstitial pneumonias<br>Associated with systemic rheumatic (connective tissue) disease<br>Sarcoidosis<br>Less common:<br>Pulmonary Langerhans cell histiocytosis<br>Lymphangioleiomyomatosis<br>Goodpasture syndrome<br>Granulomatosis with polyangiitis[a]<br>Chronic eosinophilic pneumonia<br>Pulmonary alveolar proteinosis |
| **Mimicking Disorders** |
| Heart failure<br>Disseminated carcinoma (lymphangitic carcinomatosis)<br>Pulmonary infection (e.g., *Pneumocystis*, viral pneumonia) |

[a]Typically associated with focal or multifocal disease rather than diffuse disease.

Familiarity with this large number of specific diseases is difficult even for the

pulmonary specialist, so the novice in pulmonary medicine cannot be expected to amass deep knowledge regarding each individual entity. Rather, the reader is urged to first develop an understanding of the pathologic, pathogenetic, pathophysiologic, and clinical features common to these disorders. This chapter is an overview of general aspects of diffuse parenchymal lung disease and refers to individual diseases only when necessary. Chapter 10 discusses disorders associated with an identifiable etiologic agent; the minority of patients with diffuse parenchymal lung disease are in this category. Chapter 11 discusses diseases for which a specific etiologic agent has not been identified, representing the majority of patients with diffuse parenchymal lung disease. These chapters focus on only a small number of the described types of diffuse parenchymal disease. The goal throughout is to consider those disorders the reader most likely will encounter.

The entities covered in these three chapters are primarily *chronic* (although sometimes *subacute* and rarely *acute*) diseases affecting the alveolar structures. Another process associated with diffuse disease, the *acute respiratory distress syndrome (ARDS),* is due to acute injury to various components of the alveolus. ARDS, which is of clinical importance as a major cause of acute respiratory failure, is discussed in detail in Chapter 29.

## Pathology

Typically, the diffuse parenchymal lung diseases, regardless of cause, have two major pathologic components: an inflammatory process in the alveolar wall and alveolar spaces (sometimes called an *alveolitis*) and a scarring or fibrotic process (Fig. 9.1). Both features frequently occur simultaneously, although the relative proportions of inflammation and fibrosis vary with the particular cause and phase of disease. The general presumption has been that active inflammation is the primary process and that fibrosis follows as a secondary feature. However, idiopathic pulmonary fibrosis (IPF) is a major exception to this generalization. As discussed in Chapter 11, the primary process in IPF appears to be epithelial cell injury and fibrosis (representing an abnormal repair of injury) rather than alveolar inflammation (see Pathogenesis).

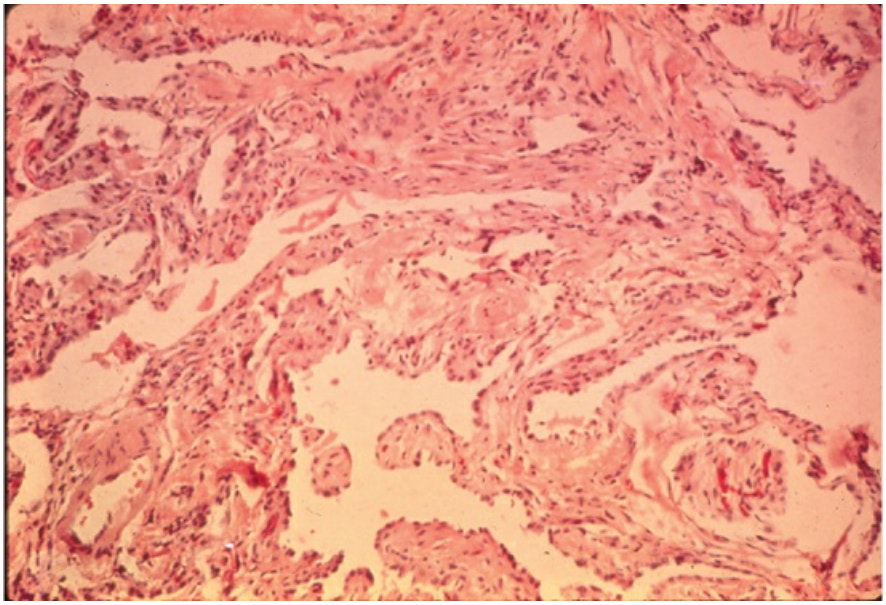

**FIGURE 9.1** Photomicrograph of diffuse parenchymal lung disease showing markedly thickened alveolar walls. Cellular inflammatory process and fibrosis are present. Compare with appearance of normal alveolar walls in Fig. 8.1.

Diffuse parenchymal (interstitial) lung diseases are characterized pathologically by variable amounts of inflammation and fibrosis.

When active alveolitis is present, a variety of inflammatory cells (e.g., macrophages, lymphocytes, neutrophils, eosinophils, and plasma cells) infiltrate the alveolar wall. Individual types of diffuse parenchymal lung disease may be associated with a prominence of a specific inflammatory cell type, such as eosinophils in chronic eosinophilic pneumonia. In addition to the presence of inflammatory cells, other characteristic pathologic features that help to define a specific disorder may be associated with the alveolitis. These individual patterns are useful in, and in many cases critical to, the diagnosis of a specific pathologic entity.

One of the most important and distinctive pathologic features associated with several of the diffuse parenchymal lung diseases is the granuloma. A *granuloma* is a localized collection of cells called *epithelioid histiocytes*, which are tissue cells of monocyte/macrophage lineage (Fig. 9.2A). These cells are generally accompanied by T lymphocytes within the granuloma, often also forming a rim around it. When cellular necrosis is present in the center of a granuloma, the entity is termed a *caseating or necrotizing granuloma*, but diffuse parenchymal lung diseases are associated almost exclusively with *noncaseating granulomas* (i.e., granulomas in which the central area is not necrotic). In contrast, caseating granulomas are characteristically seen in infectious diseases, especially tuberculosis (see Chapter 25, Pathology). The granuloma typically also has multinucleated giant cells, which result from fusion of several phagocytic cells into a single large cell with abundant cytoplasm and many nuclei (see Fig. 9.2B).

Examples of diffuse parenchymal lung disease in which granulomas are part of the pathologic process include sarcoidosis and hypersensitivity pneumonitis. Granulomas are often considered to reflect some underlying immune process, specifically an immune reaction to an exogenous agent. In the case of hypersensitivity pneumonitis, many agents have been identified. In contrast, in the case of sarcoidosis, no specific exogenous agent has been definitively identified. Granulomas in the lung have many other causes (e.g., tuberculosis, certain fungal infections, and foreign bodies), but they are not covered here because the granulomas are generally not associated with diffuse parenchymal lung disease.

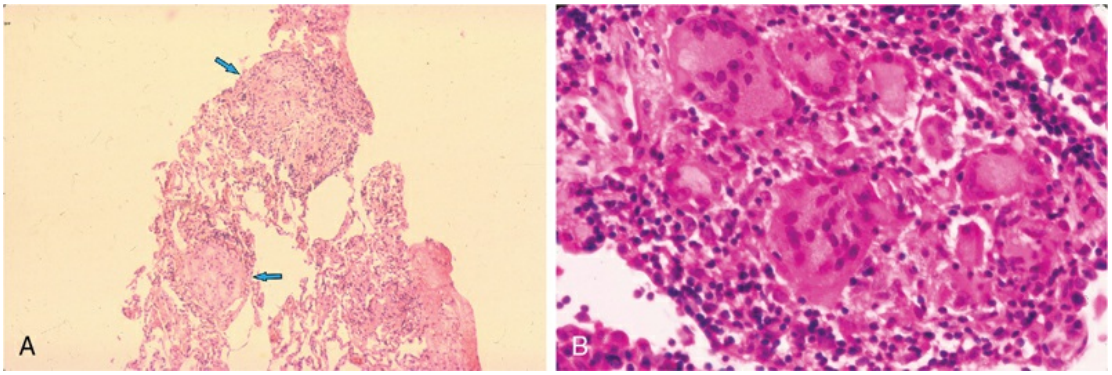


**FIGURE 9.2** Granulomas. **A,** Low-power photomicrograph of transbronchial lung biopsy showing characteristic non-necrotizing granulomas (arrows) from a patient with sarcoidosis. **B,** High-power photomicrograph showing several multinucleated giant cells within a granuloma.

Diffuse parenchymal lung diseases with granulomas include sarcoidosis and hypersensitivity pneumonitis.

## Pathology of idiopathic interstitial pneumonias

The *idiopathic interstitial pneumonias* represent a subgroup that includes several types of diffuse parenchymal lung disease. Although the term “idiopathic” in this subgroup label indicates that a specific etiologic agent has not been identified for these disorders, there is now recognition that smoking plays a significant contributory role or adds to the risk of developing several of the idiopathic interstitial pneumonias. The individual idiopathic interstitial pneumonias were initially defined by their histopathologic appearance; however, the terms used to describe the pathology and the associated clinical disorder may be different. A good example is the pathologic description of usual interstitial pneumonia (UIP) being associated with the clinical label of IPF. As we have gained experience with radiographic imaging studies, we also have recognized that specific pathologic descriptions are often associated with characteristic patterns on high-resolution computed tomography (HRCT) scanning. Table 9.2 summarizes the pathologic–clinical–radiographic correlations for the idiopathic interstitial pneumonias,

which will also be discussed further in Chapter 11.

**TABLE 9.2**

**Pathologic, Clinical, and Radiographic Correlations for the Idiopathic Interstitial Pneumonias**

| Subcategory | Clinical Diagnosis | Pathologic Pattern | Common Radiographic Description |
|---|---|---|---|
| Chronic fibrosing interstitial pneumonias | Idiopathic pulmonary fibrosis (IPF) | Usual interstitial pneumonia (UIP) | Reticular (fibrosis), honeycombing |
| | Idiopathic nonspecific interstitial pneumonia | Nonspecific interstitial pneumonia (NSIP) | Ground glass |
| Smoking-related interstitial pneumonias | Respiratory bronchiolitis–interstitial lung disease (RB-ILD) | Respiratory bronchiolitis | Bronchial wall thickening, centrilobular nodules, ground glass |
| | Desquamative interstitial pneumonia (DIP) | Desquamative interstitial pneumonia (DIP) | Ground glass |
| Acute/subacute interstitial pneumonias | Cryptogenic organizing pneumonia (COP) | Organizing pneumonia (formerly bronchiolitis obliterans with organizing pneumonia, BOOP) | Patchy consolidation, often peripheral (subpleural) |
| | Acute interstitial pneumonia (AIP) | Diffuse alveolar damage (DAD) | Diffuse alveolar filling |



Pathologists and clinicians have spent considerable time and effort refining and intermittently updating the description and categorization of the idiopathic interstitial pneumonias. These disorders display variable amounts of nonspecific inflammation and fibrosis, and they lack granulomas or specific pathologic features characteristic of other previously well-defined diseases. Classification of the idiopathic interstitial pneumonias and determination of whether the various pathologic appearances represent different diseases or, in some cases, different stages or parts of the spectrum of a single disease have been subject to uncertainty and confusion, particularly when a biopsy specimen

may contain more than one of these pathologic appearances. Although the field is still evolving, this chapter attempts to present a simplified framework based on current pathologic and clinical concepts about these disorders.

The pathologic categories subsumed under the idiopathic interstitial pneumonias include:

1. Usual interstitial pneumonia (UIP)
2. Nonspecific interstitial pneumonia (NSIP)
3. Respiratory bronchiolitis–interstitial lung disease (RB-ILD)
4. Desquamative interstitial pneumonia (DIP)
5. Cryptogenic organizing pneumonia (COP)
6. Acute interstitial pneumonia (AIP)

Confusion also sometimes arises from the fact that several of the same pathologic appearances associated with the idiopathic interstitial pneumonias can be seen in lung disease associated with some of the systemic rheumatic (also called connective tissue or collagen vascular) diseases. A good example is the pathologic appearance of NSIP, which can be idiopathic but is also a common pathologic expression of pulmonary involvement with diseases such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis (scleroderma).

This chapter discusses six pathologic entities subsumed under the broad term *idiopathic interstitial pneumonias*: (1) UIP, (2) NSIP, (3) RB-ILD, (4) DIP, (5) COP, and (6) AIP. This section briefly describes the pathologic characteristics defining these six entities, whereas Chapter 11 expands upon their clinical and radiographic features. Table 9.2 also groups these six disorders into three categories—chronic fibrosing interstitial pneumonias, smoking-related interstitial pneumonias, and acute/subacute interstitial pneumonias—and correlates their pathologic, clinical, and radiographic features.

*UIP* is characterized by patchy areas of parenchymal fibrosis and interstitial inflammation interspersed between areas of relatively preserved lung tissue (Fig. 9.3). Fibrosis is the most prominent component of the pathology, with focal collections of proliferating fibroblasts called *fibroblastic foci*. The fibrosis often is associated with *honeycombing*, which represents cystic air spaces that result from retraction of surrounding fibrotic lung tissue. The inflammatory process in the alveolar walls is nonspecific, not prominent, and typically composed of a variety of cell types, including lymphocytes, macrophages, and plasma cells. Hyperplasia of type II pneumocytes (alveolar epithelial cells) presumably reflects an attempt to replenish damaged type I cells. Importantly, the pathology of UIP is characterized by the simultaneous presence of all stages of fibrosis: from early fibrosis with actively proliferating fibroblasts to end-stage acellular collagenous scarring. It is thought the fibrotic process in UIP is ongoing and not related to a single event. By far the most important of the clinical disorders associated with the histopathologic pattern of UIP is IPF, and the terms are often used synonymously. However, the pathologic appearance of UIP can also result from exposure to certain inhaled dusts (especially asbestos), from a number of drug-induced lung diseases, and as a form of parenchymal lung disease associated with some systemic rheumatic diseases. It is important to remember that the term UIP refers to the

*histologic pattern* seen under the microscope, whereas IPF refers to the *clinical disease* associated with idiopathic UIP.

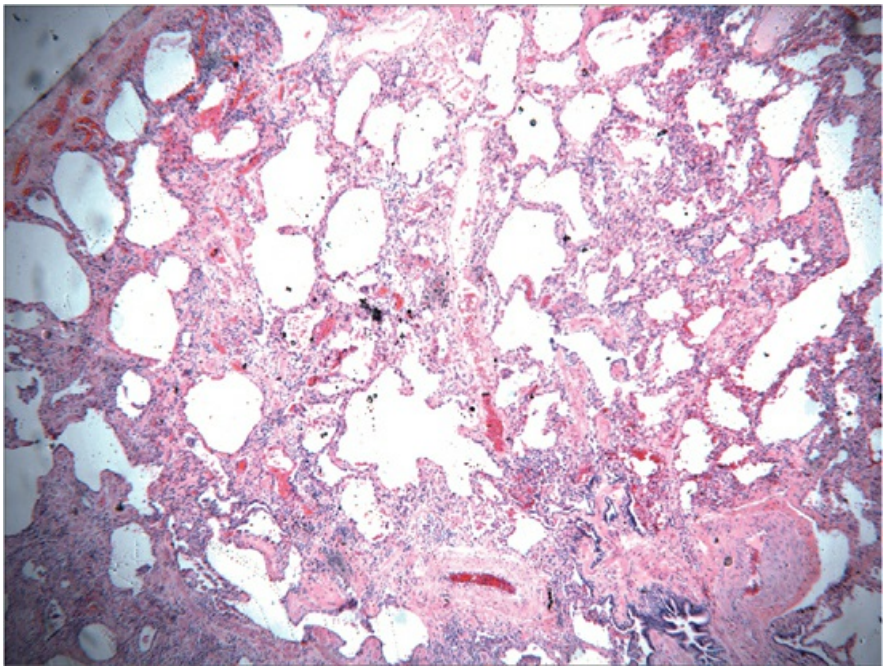

**FIGURE 9.3** Low-power photomicrograph of usual interstitial pneumonia shows prominent fibrosis accompanied by honeycombing. *Source:* (Courtesy Dr. Olivier Kocher.)

*NSIP* is characterized by a prominent histopathologic component of mononuclear cell infiltration within the alveolar walls (Fig. 9.4). Despite the designation "nonspecific," NSIP is a distinct pathologic entity that presents either in an idiopathic form or in association with a number of systemic rheumatic diseases. In contrast to UIP, the pathologic process in NSIP appears relatively uniform, fibrosis is variable but generally less apparent, and the prognosis is better. In the past, this pattern was often not recognized as separate from UIP. As a result, its inclusion in many clinical studies of IPF served to confound our understanding of the natural history and treatment of IPF.

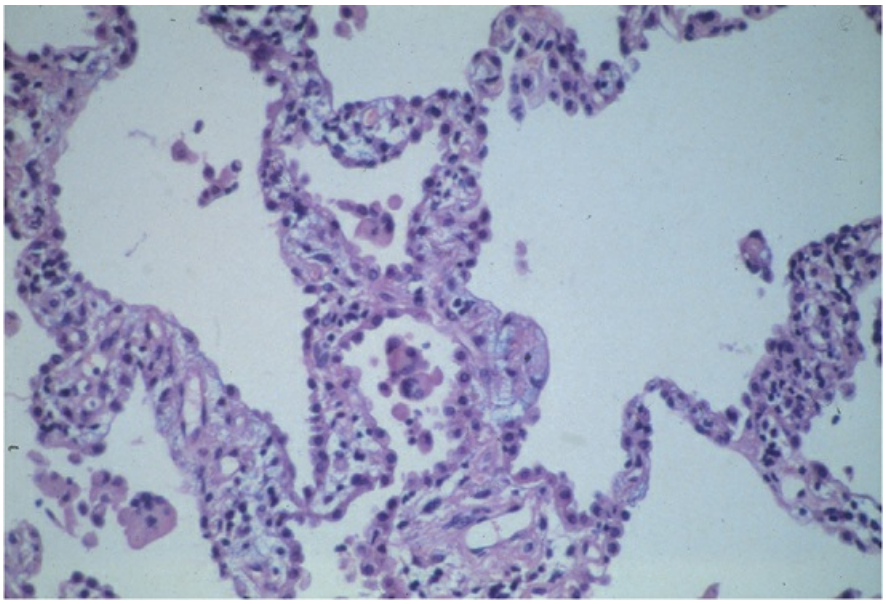

**FIGURE 9.4** High-power photomicrograph of nonspecific interstitial pneumonitis showing characteristic mononuclear cell infiltrate in alveolar walls without significant fibrosis.

*RB-ILD* and DIP are thought to be related, in that both are typically associated with tobacco smoking. RB-ILD is characterized by pigmented macrophages within the lumen of respiratory bronchioles, accompanied by an infiltrate of lymphocytes and macrophages. However, in contrast to DIP, alveolar inflammation is not present. RB-ILD is nearly always associated with smoking. The most important clinical intervention is assisting patients to successfully quit smoking. At times, the distinction between RB-ILD and DIP is difficult and somewhat arbitrary, and both pathologic appearances may be present in the same individual.

*DIP* is characterized by large numbers of intra-alveolar mononuclear cells (Fig. 9.5). Although originally thought to represent desquamated alveolar epithelial cells (hence the name), these cells are now known to be intra-alveolar macrophages. A less prominent component of the histology is inflammation within alveolar walls, and there is little associated fibrosis. In contrast to UIP, the process is temporally uniform, and architectural distortion is minimal. Based on a strong (although not universal) association of this histologic pattern with a history of smoking, as well as an apparent overlap in some patients with smoking-induced inflammation of respiratory bronchioles with pigmented macrophages, smoking is believed to be an important underlying etiology for this pathologic pattern.

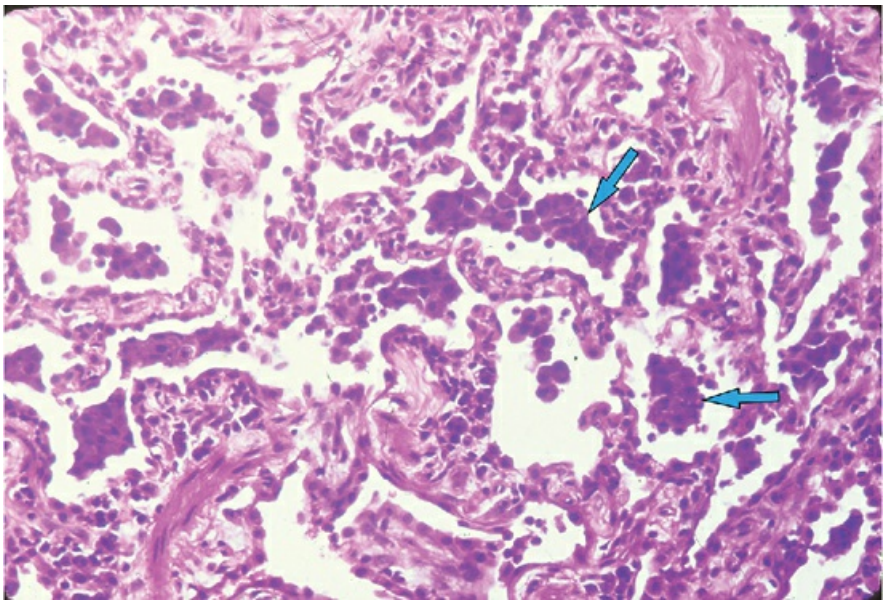

**FIGURE 9.5** High-power photomicrograph showing macrophages within respiratory bronchioles and alveolar spaces (arrows), characteristic of the spectrum that includes respiratory bronchiolitis-interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP).

*COP* is characterized by organizing fibrosis (also referred to as "granulation tissue") in small airways, associated with a mild degree of chronic interstitial inflammation (Fig. 9.6). Intraluminal small airway involvement is a key feature and distinguishes COP from the other idiopathic interstitial pneumonias. This histologic pattern has also been called *bronchiolitis obliterans organizing pneumonia* (BOOP). The histologic findings in BOOP are either idiopathic or associated with specific known causes (e.g., infections, toxic inhalants, systemic rheumatic disease). Although the terms have sometimes been used interchangeably, the term *COP* generally refers to the idiopathic form of BOOP.

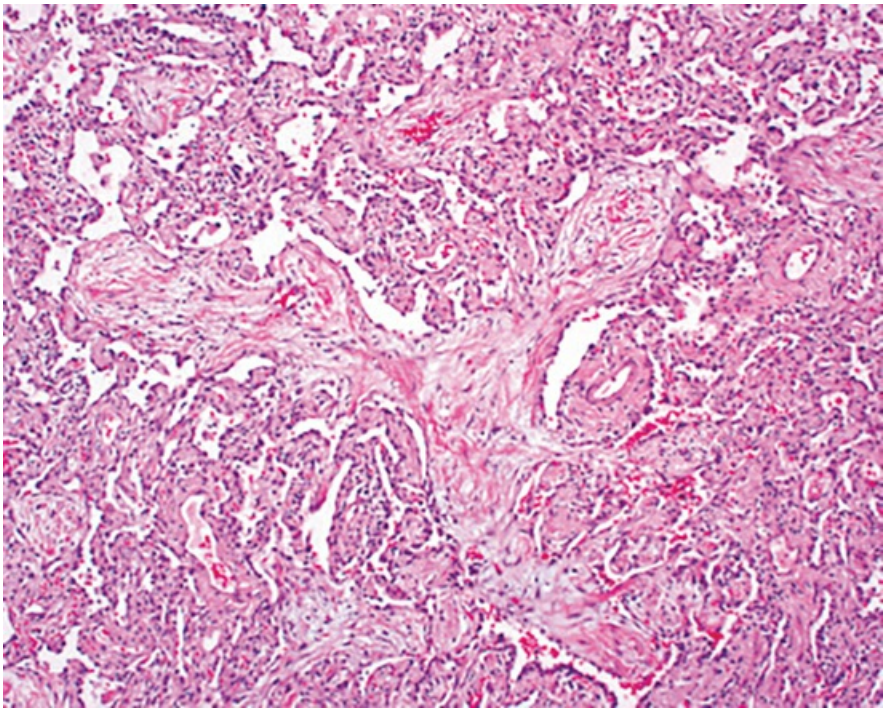

**FIGURE 9.6** Low-power photomicrograph of organizing pneumonia pattern, as seen in cryptogenic organizing pneumonia (COP). In addition to an inflammatory interstitial infiltrate, there is a branching tongue of fibroblastic tissue occupying a small airway. *Source:* (From Leslie, K. O., & Wick, M. R. (2018). *Practical pulmonary pathology. A diagnostic approach* (3rd ed.). Philadelphia, PA: Elsevier.)

*AIP* is believed to represent the organizing or fibrotic stage of diffuse alveolar damage, which is the histologic pattern seen in ARDS (see Chapter 29). In most cases of ARDS an inciting cause is apparent, whereas in AIP no initiating trigger for ARDS can be identified. The histology is similar to the later phases of ARDS, and shows fibroblast proliferation and type II pneumocyte hyperplasia in the setting of what appears to be organizing diffuse alveolar damage.

## End-stage diffuse parenchymal lung disease

When diffuse parenchymal lung disease has been present for an extended time and is associated with significant fibrosis, distinctive features of prior interstitial inflammation or alveolitis are often lost. For example, after sufficient time has elapsed and a substantial degree of fibrosis has developed, granulomas may no longer be identifiable in the granulomatous lung diseases. Therefore, at a certain point, many of the diffuse parenchymal lung diseases, if sufficiently severe and chronic, can follow a final common pathway toward *end-stage* diffuse parenchymal lung disease. At end-stage, severe fibrosis leads to significant architectural distortion of the lung that can be seen both grossly and microscopically, with areas of contraction and other areas showing

formation of cystic spaces. In many cases, the result is “honeycomb lung,” in which the dense scarring and intervening cystic regions make areas of the lung resemble a honeycomb (Fig. 9.7).

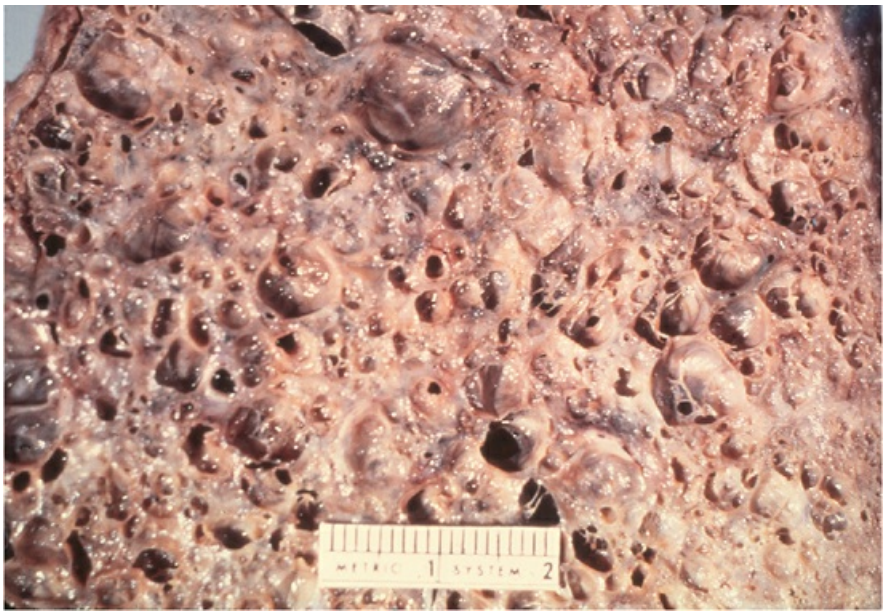

**FIGURE 9.7** Appearance of honeycomb lung from patient with severe pulmonary fibrosis. Many cystic areas are seen between bands of extensively scarred and retracted pulmonary parenchyma.

## Pathogenesis

Much research during the past 2 decades has attempted to clarify the pathogenetic sequence of events in various types of diffuse parenchymal lung disease. However, in most cases the factors that initiate and propagate these diseases remain unknown, and our understanding of the cellular and biochemical events producing inflammation and fibrosis remains mostly at the descriptive level. More recently, there has been greater interest in the potential role of genetic factors in development of some of the diffuse parenchymal lung diseases, either as a primary determinant or as an important modifier of the patient’s response to a potentially injurious exposure. Some gene variants of particular interest have been ones involved in coding for mucins (especially MUC5B), surfactant proteins A and C, and telomerase components.

This section outlines the general scheme of events thought to be operative in the production of parenchymal inflammation and fibrosis. Chapters 10 and 11 discuss specific diseases and provide additional information believed to be relevant to the pathogenesis of each disease. The general scheme outlined here has features similar to that of other forms of lung injury described elsewhere in this book (e.g., emphysema in Chapter 6 and ARDS in Chapter 29). A fundamental but unanswered question is what determines whether an injurious agent eventually leads to emphysema, acute lung

injury (with ARDS), or chronic parenchymal inflammation and fibrosis.

Fig. 9.8 summarizes the general sequence of events presumed to be common to many of the diffuse parenchymal lung diseases. The events can be divided into three stages: initiation, propagation, and final pathologic consequences. Each of these stages is considered in turn.

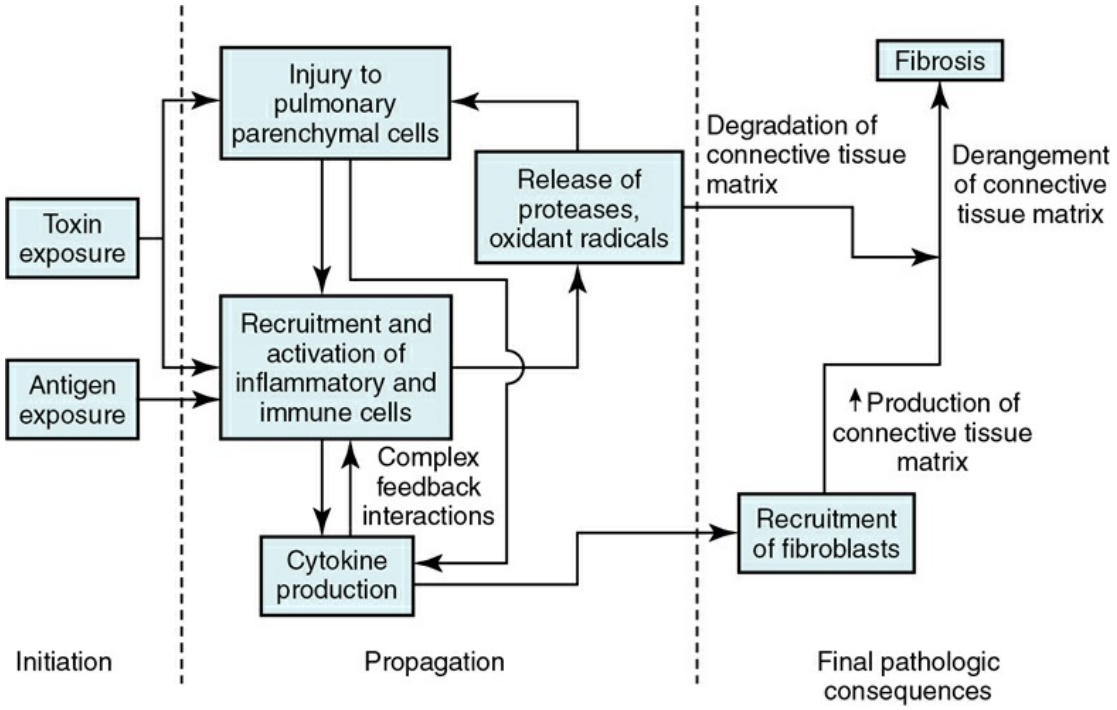


**FIGURE 9.8** Schematic diagram illustrating general aspects of pathogenesis of diffuse parenchymal lung diseases.

Pathogenetic features of diffuse parenchymal lung disease are as follows:

1. Initiation—by antigens, toxins
2. Propagation—with inflammatory cells, proteases, cytokines
3. Final pathologic consequence—fibrosis

The initiating stimulus for the diffuse parenchymal lung diseases is generally believed to be either a toxin or an antigen. The most obvious presumed toxins include some of the inhaled inorganic particles (e.g., asbestos) responsible for producing the pneumoconioses. Smoking also appears to be an important factor for development of the smoking-related interstitial pneumonias (RB-ILD and DIP) as well as pulmonary Langerhans cell histiocytosis (eosinophilic granuloma, discussed in Chapter 11), and is a risk factor for IPF. Inhaled antigens have been best identified as the cause of hypersensitivity pneumonitis. In sarcoidosis and perhaps in IPF, exposure to one or more antigens may initiate the disease, but no specific antigens have been identified.

After exposure to an initiating stimulus occurs, a complex series of interrelated events is responsible for propagation of the disease. At the microscopic level, the consequence of these propagating events is inflammation, a hallmark of many but not all of the diffuse parenchymal lung diseases. Toxins may be directly injurious to pulmonary parenchymal (alveolar epithelial) cells, whereas either toxins or antigens may result in activation and recruitment of inflammatory and immune cells. Inflammatory cells can release a variety of mediators (e.g., proteolytic enzymes, toxic oxygen radicals) that can secondarily further injure pulmonary parenchymal cells. In addition, a wide variety of cytokine mediators produced by epithelial, inflammatory, and immune cells have been identified. These cytokines have complex secondary effects on other inflammatory and immune cells, often acting either to amplify or diminish the inflammatory response.

Some cytokines (e.g., transforming growth factor [TGF]-β and platelet-derived growth factor) are capable of recruiting and stimulating replication of fibroblasts, which are critical for the eventual production of new connective tissue. Action of proteases from inflammatory cells may also be responsible for degradation of connective tissue components. The combination of new synthesis and degradation of connective tissue defines the derangement of the connective tissue matrix that is seen histologically as fibrosis, the final pathologic consequence of diffuse parenchymal lung disease. In IPF, the most recent (and now prevailing) concept is that alveolar epithelial injury results in epithelial cell expression of cytokine mediators that promote fibrosis, and that inflammation, although present in variable degrees, is not the critical trigger for the development of fibrosis.

## Pathophysiology

With minor exceptions and variations, the pathophysiologic features of the chronic diffuse parenchymal lung diseases are similar and therefore are discussed here as a single group. As a result of the inflammation and fibrosis affecting the alveolar walls, the following abnormalities are generally seen (Fig. 9.9): (1) decreased compliance (increased stiffness) of the lung, (2) generalized decrease in lung volumes, (3) loss of alveolar-capillary surface area resulting in impaired diffusing capacity, (4) abnormalities in small airway function without generalized airflow obstruction, (5) disturbances in gas exchange, usually consisting of hypoxemia without $CO_2$ retention, and (6) in some cases, pulmonary hypertension. Each of these features is briefly considered in turn.

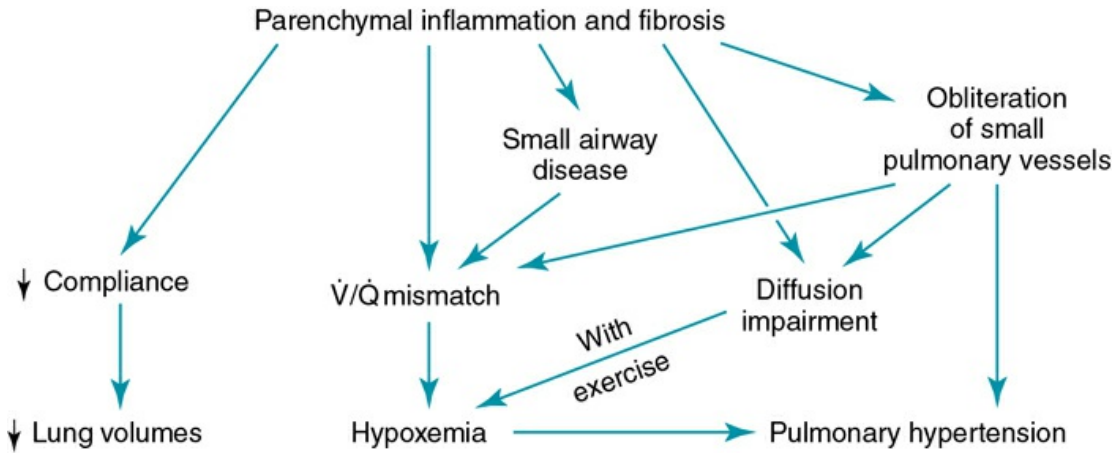


**FIGURE 9.9** Schematic diagram illustrating interrelationships between various pathologic and physiologic features of diffuse parenchymal lung disease.

## Decreased compliance

Lung distensibility is significantly altered by processes involving inflammation and fibrosis of the alveolar walls. The lungs become much stiffer, have greatly increased elastic recoil, and therefore require greater distending (transpulmonary) pressures to achieve any given lung volume. The pressure-volume or compliance curve is shifted to the right (see Fig. 8.3), and at any given lung volume, a much higher elastic recoil pressure is found than in normal lungs. Because wider swings in transpulmonary pressure are required to achieve a normal tidal volume during inspiration, the patient's work of breathing is increased. As a result, patients with diffuse parenchymal lung disease tend to breathe with smaller tidal volumes but increased respiratory frequency. This method allows the patient to expend less energy per breath but maintain adequate alveolar ventilation.

Compliance curves in diffuse parenchymal lung disease are shifted downward and to the right, reflecting increased stiffness of the lung.

## Decrease in lung volumes

Early in the course of diffuse parenchymal lung disease, lung volumes may be normal. However, in most cases, some reduction in lung volumes is seen shortly thereafter, including a reduction in total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and, to a lesser extent, residual volume (RV). The decreases in TLC, FRC, and RV are direct consequences of the change in lung compliance. At TLC, the force generated by the inspiratory muscles is balanced by the inward elastic recoil of the lung. Because the recoil pressure is increased, this balance is achieved at a lower lung volume or lower TLC. At FRC, the outward recoil of the chest wall is balanced by the inward elastic recoil of the lung. This balance is achieved at a lower lung volume or lower FRC because of the greater elastic recoil of the lung. As discussed in Chapter 1, RV

is primarily determined by the strength of the expiratory muscles, but a small component is determined by the inward elastic recoil of the lungs. Because the elastic recoil is greater in diffuse parenchymal lung disease, the RV is slightly smaller. In general, TLC is reduced more than RV, so it follows that VC (representing the difference between TLC and RV) is also decreased.

Lung volumes are characteristically decreased in diffuse parenchymal lung disease.

## Impairment of diffusion

Measurement of diffusion by the usual techniques involving carbon monoxide typically shows a decrease in diffusing capacity. Although thickening of the alveolar-capillary interface (due to interstitial inflammation and fibrosis) might be expected to be responsible for this decrease, in fact it is not the major factor. Rather, the processes of inflammation and fibrosis destroy a portion of the alveolar-capillary interface and reduce the surface area available for gas exchange. This decrease in surface area is the primary mechanism responsible for the observed diffusion abnormality.

Diffusing capacity is reduced, with destruction of a portion of the alveolar-capillary interface and reduced surface area for gas exchange.

## Abnormalities in small airway function

Large airways generally function normally in these patients, and the forced expiratory volume in 1 second to forced vital capacity ratio ($FEV_1/FVC$) is usually normal or even increased. However, frequently the pathologic process occurring in the alveolar walls also affects small airways within the lung. Light microscopy commonly demonstrates inflammation and fibrosis in the peribronchiolar regions, with narrowing of the lumen of the small airways or bronchioles. Tests of small airway function often show the physiologic effects of this narrowing. The clinical importance of small airway dysfunction in the absence of larger airway abnormalities is uncertain, but it is likely that ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) mismatching and hypoxemia are consequences. Evidence of more significant airflow obstruction may be seen in a few disorders causing diffuse parenchymal lung disease. This relatively infrequent problem sometimes results from severe fibrosis and airway distortion.

Small airway function is often disturbed in diffuse parenchymal lung disease. Large airway function is generally preserved.

## Disturbances in gas exchange

The gas exchange consequences of diffuse parenchymal lung disease most frequently consist of hypoxemia without $CO_2$ retention, and in fact hypocapnia typically is present. The pathologic process in the alveolar walls is uneven, and normal matching of ventilation and perfusion is disrupted. As a result, $\dot{V}/\dot{Q}$ mismatch is the primary factor contributing to hypoxemia. In patients with small airway disease, dysfunction at this

level probably also contributes to $\dot{V}/\dot{Q}$ mismatch and hypoxemia. Characteristically, patients with diffuse parenchymal lung disease become even more hypoxemic with exercise. Again, the primary mechanism of oxygen desaturation associated with exertion is worsening $\dot{V}/\dot{Q}$ mismatch, but diffusion limitation may also be a contributing factor, particularly with higher levels of exercise and with exercise performed at higher altitudes. The combination of impaired diffusion and decreased transit time of the red blood cell during exercise may prevent complete equilibration of $P_{O_2}$ in pulmonary capillary blood with alveolar $P_{O_2}$. Despite the often profound hypoxemia in patients with severe pulmonary fibrosis, $P_{CO_2}$ is usually normal or low because patients are able to increase minute ventilation sufficiently to compensate for a decrease in tidal volume and for any additional dead space. Elevation of $P_{CO_2}$ does not generally occur until the very late stages of the disease.

Arterial blood gases in diffuse parenchymal lung disease generally show hypoxemia (due to $\dot{V}/\dot{Q}$ mismatch) and normal or decreased $P_{CO_2}$. $P_{O_2}$ falls even further with exercise.

### Pulmonary hypertension

Eventually, patients with severe diffuse parenchymal lung disease may develop some degree of pulmonary hypertension. Typically, the two main contributing factors are (1) hypoxemia and (2) obliteration of small pulmonary vessels by the fibrotic process within the alveolar walls. During exercise, pulmonary hypertension becomes more marked; this is due partly to worsening hypoxemia and partly to limited ability of the pulmonary capillary bed to recruit new vessels and normally distend to accommodate the increase in cardiac output associated with exercise. Importantly, however, a subset of patients with diffuse parenchymal lung diseases will develop more severe pulmonary hypertension, and the pulmonary vascular changes are similar to those in patients with idiopathic pulmonary arterial hypertension (see Chapter 14). In these patients, the pulmonary hypertension is due to a primary process affecting pulmonary vessels in addition to the destruction and fibrosis of alveolar walls. Notably, the level of pulmonary hypertension does not correlate well with the degree of fibrosis in patients with diffuse parenchymal lung diseases but is independently associated with a worse prognosis. Thus, although there is a clear association between pulmonary hypertension and diffuse parenchymal lung diseases, the exact pathophysiologic and clinical relationships are not fully elucidated.

Pulmonary hypertension is common in severe diffuse parenchymal lung disease, resulting from hypoxemia and obliteration of small pulmonary vessels.

## Clinical features

Patients with diffuse parenchymal lung disease most commonly have dyspnea as the presenting symptom. Dyspnea is noticed initially on exertion but, with severe disease, may be experienced even at rest. Cough, usually nonproductive, is also common. On

physical examination, auscultation of the chest characteristically reveals dry crackles or rales, which often are most prominent on inspiration at the lung bases. However, the likelihood of hearing crackles depends on the particular diagnosis; for example, crackles are especially prominent in IPF and less frequent in sarcoidosis. Clubbing may be present, particularly with certain types of diffuse parenchymal lung disease. If cor pulmonale develops, cardiac physical findings may be associated with pulmonary hypertension and right ventricular hypertrophy.

Chest examination is often notable for inspiratory crackles, particularly at the lung bases.

## Diagnostic approach

The chest radiograph is the most important means for making the initial macroscopic assessment of diffuse parenchymal lung disease. The characteristic radiographic picture of diffuse parenchymal involvement that primarily involves alveolar walls is described as either *reticular* (increased linear markings) or *reticulonodular* (increased linear and small nodular markings; see Fig. 3.6). The pattern has also previously been called an "interstitial pattern" because it was believed to reflect a process limited to the alveolar walls. However, histopathology often indicates that some of these processes extend into alveolar spaces as well. The absence of chest x-ray abnormalities does not exclude the presence of diffuse parenchymal disease; entirely normal chest radiographic findings have been reported in up to 10% of patients. The pattern on chest radiograph is not particularly useful for gauging the relative amounts of inflammation versus fibrosis, each of which may result in a similar pattern.

Reticular or reticulonodular changes are frequently diffuse throughout both lung fields, although individual causes of diffuse parenchymal lung disease may be more likely to result in either an upper or a lower lung field predominance of the abnormal markings. In addition to the reticular or reticulonodular pattern, certain diseases may reveal other associated findings on chest radiograph, such as hilar adenopathy or pleural disease. These additional features noted with some diseases are discussed in Chapters 10 and 11.

A reticular or reticulonodular pattern on chest radiograph is characteristic of many diffuse parenchymal lung diseases, but up to 10% of patients have normal radiographic findings.

With long-standing and severe disease, the lungs may become grossly distorted. In addition, regions of cyst formation between scarred and retracted areas of lung often occur (see Fig. 9.7). A corresponding pattern of honeycombing on chest radiograph may be apparent. Cor pulmonale may be suspected on chest radiograph by the presence of right ventricular enlargement, best appreciated on the lateral view (see Fig. 14.3).

HRCT of the chest is an important step in the evaluation of diffuse parenchymal lung disease (see Figs. 3.9 and 11.2). Because of the quality of images of the pulmonary parenchyma, early changes that are not evident on routine chest radiography often can be seen by HRCT. In addition, the specific pattern of abnormality on an HRCT scan may

be suggestive of a particular underlying diagnosis such as IPF and may help to distinguish inflammation from fibrosis.

*Bronchoalveolar lavage* (BAL) is a relatively noninvasive procedure for sampling the cell population of the alveolitis. A flexible bronchoscope is placed as distally as possible into an airway, and an irrigation or lavage of normal saline through the bronchoscope enables collection of cells from the alveolar spaces. These cells are thought to be representative of the cell populations responsible for the alveolitis. Although this technique has been useful as a relatively noninvasive means of obtaining cells for research studies on diffuse parenchymal lung disease, its clinical usefulness for making a diagnosis or for sequential evaluation of disease activity is limited. Samples obtained by BAL in the evaluation of diffuse parenchymal lung disease are primarily useful for ruling out pulmonary hemorrhage or infection.

When a careful evaluation of the clinical, radiographic, laboratory, and pulmonary function findings does not allow the clinician to make a confident diagnosis, a lung biopsy is considered. A variety of biopsy procedures have been used to obtain tissue specimens from the lung, which are subjected to several routine staining techniques. The most frequently used biopsy procedures for this purpose are thoracoscopic lung biopsy and transbronchial biopsy (via flexible bronchoscopy). More recently, cryobiopsies with a bronchoscope, using a liquid cooling agent to freeze the tissue being biopsied, are being investigated as a means of obtaining larger, more useful specimens nonsurgically. Thoracoscopic biopsy often is the most appropriate procedure for obtaining a sufficiently large specimen of tissue for examination. However, when sarcoidosis (or several other specific forms of diffuse parenchymal disease) is suspected, transbronchial biopsy is a particularly suitable initial procedure because the characteristic pathology is present in tissue adjacent to the airways.

Findings on functional assessment of the patient with diffuse parenchymal lung disease were reviewed under Pathophysiology. Briefly, patients have a restrictive pattern on pulmonary function testing, with decreased lung volumes and preserved airflow. Diffusing capacity usually is reduced, which is indicative of loss of surface area for gas exchange. Hypoxemia is usually (although not necessarily) present, and $Po_2$ falls even further with exercise. Hypercapnia is rarely a feature of the disease. When it occurs, hypercapnia usually reflects preterminal disease or an additional unrelated process.

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# 10: Diffuse parenchymal lung diseases associated with known etiologic agents

OUTLINE



This chapter focuses on several of the major categories of diffuse parenchymal (interstitial) lung disease for which an etiologic agent has been identified. The general principles discussed in Chapter 9 apply to most of these conditions, and the features emphasized here are those peculiar to or characteristic of each cause. Considering the vast number of diffuse parenchymal lung diseases, this chapter only scratches the surface of information available. When a physician is confronted with a patient having a particular type of diffuse parenchymal lung disease, it is best to relearn the details of the disease at that time.

## Diseases caused by inhaled inorganic dusts

Many types of diffuse parenchymal lung disease are caused by inhalation of inorganic dusts; the term *pneumoconiosis* is used for these conditions. Examples of the many responsible agents include silica, asbestos, coal, talc, mica, aluminum, and beryllium. In most cases, exposure has occurred for a prolonged time as a result of the occupational environment. In some of these diseases, the parenchymal process progresses even in the

absence of continued exposure.

For an inhaled inorganic dust to initiate injury to the lung parenchyma, it must be deposited at an appropriate area of the lower respiratory tract. If particle size is too large or too small, deposition tends to be in the upper airway or in the larger airways of the tracheobronchial tree. Particles with a diameter of approximately 0.5 to 5 μm are most likely to deposit in the respiratory bronchioles or the alveoli.

Particles with a diameter of 0.5 to 5 μm are most likely to be deposited in respiratory bronchioles or alveoli.

No effective treatment is available for parenchymal lung disease caused by most inhaled inorganic dusts. Therefore, the important issues facing physicians are recognition and prevention of these disorders. Total avoidance of exposure is the optimal form of prevention, but when exposure is necessary, appropriate precautions with effective masks or respirators are essential.

Four types of pneumoconiosis are considered here: silicosis, coal worker's pneumoconiosis (CWP), asbestosis, and berylliosis. For information about the numerous other agents, consult the more detailed Suggested Readings at the end of this chapter.

## Silicosis

*Silicosis* is the diffuse parenchymal lung disease resulting from exposure to silica (silicon dioxide). Of several crystalline forms of silica, quartz is the one most frequently encountered, usually as a component of rock or sand. Despite the known toxicity, silica exposure continues to be a problem world-wide. Persons at risk include sandblasters, hard rock miners, quarry workers, and stonecutters. More recently, severe disease is recognized in those working in the manufacture of engineered stone typically used in countertops. In most cases, development of disease requires at least 20 years of exposure. However, with particularly heavy doses of inhaled silica, as can occur in sandblasters, an acute form of the disease may occur with much shorter periods of exposure.

The pathogenetic effect of silica is due to generation of oxygen radicals and toxicity to macrophages. Inhaled silica particles that reach the lower respiratory tract are phagocytosed by pulmonary macrophages. Freshly cut silica particles are more pathogenic than older particles, likely because the freshly cut surface is highly reactive and generates more reactive oxygen species. After engulfing the silica particle, the macrophage is activated and releases inflammatory mediators, including tumor necrosis factor (TNF)-α and interleukin (IL)-1. Phagocytosis of silica particles leads to apoptotic cell death of the macrophage and release of the previously engulfed toxic silica particles, with repeat of the process after the particles are re-ingested by other macrophages. With each cycle of activation and destruction, the macrophages release chemical mediators that initiate or perpetuate an alveolitis, eventually leading to development of fibrosis.

Pathologically, the inflammatory process initially is localized around the respiratory bronchioles but eventually becomes more diffuse throughout the parenchyma. The ongoing inflammatory process causes scarring and results in characteristic acellular nodules called *silicotic nodules* that are composed of connective tissue (Fig. 10.1).

Silicotic nodules are believed to be areas in which the cycle of macrophage ingestion, activation and destruction, and release of the toxic silica particles occurs. At first the nodules are small and discrete. With disease progression, they become larger and may coalesce.

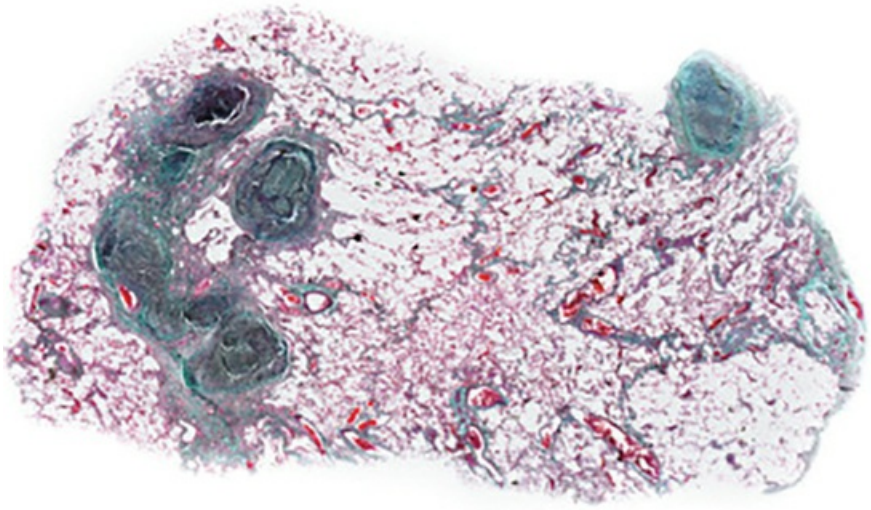

**FIGURE 10.1** Silicosis (low-power photomicrograph). The silicotic nodules are sharply circumscribed and densely collagenous (Masson trichrome stain). *Source:* (From Leslie, K. O., & Wick, M. R. [2018]. *Practical pulmonary pathology. A diagnostic approach* [3rd ed.]. Philadelphia, PA: Elsevier.)

The pulmonary effects of silica are related in part to a toxic effect on macrophages that ingest the particles.

The most common radiographic appearance of silicosis is notable for small, rounded opacities or nodules. This pattern is described as *simple chronic silicosis*. Uncommonly, the nodules become larger and coalescent, in which case the pneumoconiosis is called *complicated*; the term *progressive massive fibrosis* has also been used (Fig. 10.2). Typically, the upper lung zones in patients with silicosis are affected more heavily than the lower zones. Enlargement of the hilar lymph nodes, which frequently calcify, may be seen.

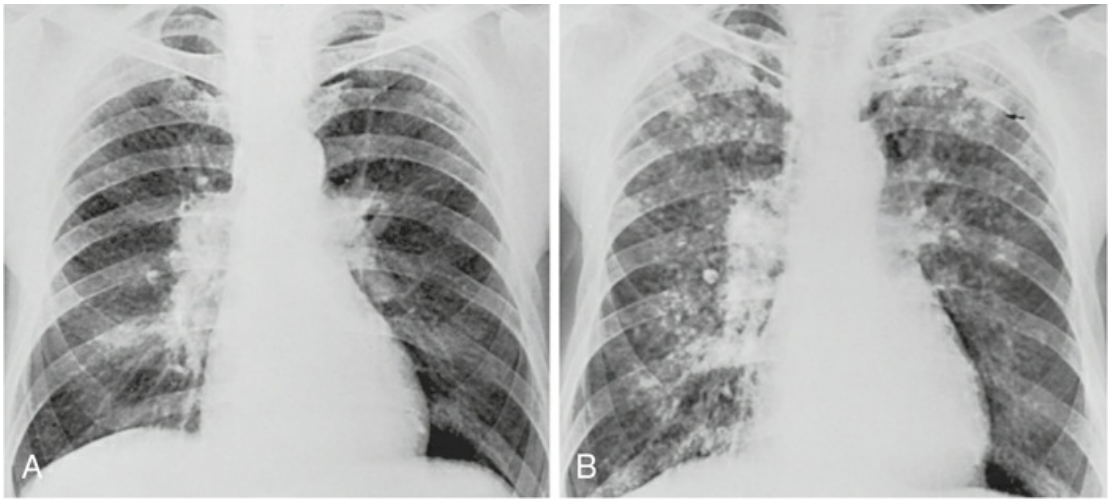


**FIGURE 10.2** Radiographic appearance of (**A**) simple and (**B**) complicated silicosis in same patient. **A,** Small nodules are present throughout both lungs, particularly in upper zones. A reticular component is also seen. **B,** Nodules have become larger and are coalescent in upper zones. One of the confluent shadows on left shows cavitation *(arrow)*. Interval between radiographs shown in **A** and **B** is 11 years. *Source:* (From Fraser, R. G., Müller, N. L., Colman, N., Paré, P. D. [1999]. *Diagnosis of diseases of the chest* [Vol. 4, 4th ed.]. Philadelphia, PA: WB Saunders.)

In addition to the potential problem of progressive pulmonary involvement and eventual respiratory failure, abnormal immune regulation is associated with silicosis. Patients are at increased risk for certain autoimmune diseases, including rheumatoid arthritis and systemic sclerosis. Patients with silicosis are also particularly susceptible to infections with mycobacteria, perhaps because of impaired macrophage function. The specific organisms may be either *Mycobacterium tuberculosis*, the etiologic agent for tuberculosis, or other species of mycobacteria, often called *atypical* or *nontuberculous mycobacteria* (see Chapter 25). The term *silicotuberculosis* is used when pulmonary tuberculosis develops in a patient with background silicosis, and longer courses of antituberculous medications may be required for treatment versus when silicosis is absent.

Silicosis is associated with immune dysregulation and is a predisposing factor for secondary infection by mycobacteria.

## Coal worker's pneumoconiosis

Individuals who have worked as part of the coal mining process and have been exposed to large amounts of coal dust are at risk for development of *CWP*. In comparison with silica, coal dust is a less fibrogenic material, and the tissue reaction is much less marked for equivalent amounts of dust deposited in the lungs. In addition to its role in the

development of CWP, coal mining also appears to be associated with an increased risk of chronic obstructive pulmonary disease (COPD), including anatomic evidence of emphysema that is most commonly centrilobular in distribution.

Tissue reaction to inhaled coal dust is much less than that to silica.

The pathologic hallmark of CWP is the *coal macule*, which is a focal collection of coal dust surrounded by relatively little cellular infiltration or fibrosis (Fig. 10.3). The initial lesions tend to be distributed primarily around respiratory bronchioles. Small associated regions of emphysema, termed *focal emphysema*, may be seen.

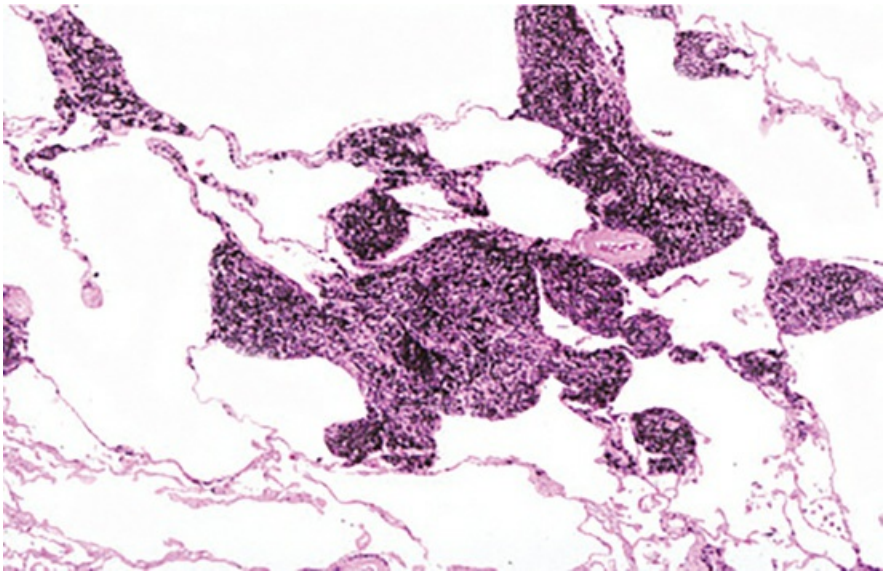

**FIGURE 10.3** Histologic appearance of a coal dust macule shows focal interstitial pigment deposition. In this example, destruction of the adjacent alveolar septa is also seen. *Source:* (From Leslie, K. O., & Wick, M. R. [2018]. *Practical pulmonary pathology. A diagnostic approach* [3rd ed.]. Philadelphia, PA: Elsevier.)

As with silicosis, the disease is often separated into simple and complicated forms. In *simple CWP,* the chest radiograph consists of relatively small and discrete densities that usually are more nodular than linear. In this phase of the disease, patients have few symptoms, and pulmonary function usually is relatively preserved. In later stages of the disease, to which only a small minority of individuals progress, chest radiographic findings and clinical symptoms are more pronounced. With extensive disease and coalescent opacities on chest radiographs, patients are said to have *complicated CWP*, also called *progressive massive fibrosis*. Pulmonary function may show restrictive disease, obstructive disease, or a mixed pattern, depending on the relative amounts of fibrosis, airway disease, and emphysema.

Why complicated disease develops in some patients with CWP is not clear. At one time, it was speculated that patients with progressive massive fibrosis had also been

exposed to toxic amounts of silica and that the simultaneous silica exposure was responsible for most of the fibrotic process. However, although some patients do have a mixed form of pneumoconiosis from both coal dust and silica exposure, progressive massive fibrosis can result from coal dust in the absence of concomitant exposure to silica. Some studies indicate that genetic polymorphisms may help to explain the different clinical responses to inhalational exposures.

Symptoms and pulmonary function changes in CWP are related to the extent of fibrosis and coexistent COPD, if present.

## Asbestosis

Asbestos, widely used because of its thermal and fire resistance, is a fibrous derivative of silica, termed a *fibrous silicate*. It is a naturally occurring mineral that, because of its long narrow shape, can be woven into cloth. Among the health hazards it presents are the development of diffuse interstitial fibrosis, benign pleural plaques and effusions, and the potential for inducing several types of neoplasms, particularly bronchogenic carcinoma and mesothelioma. These latter problems are discussed in Chapters 15, 20, and 21. The term *asbestosis* is reserved for the diffuse parenchymal lung disease that occurs due to asbestos exposure, not simply asbestos exposure itself.

Asbestos still presents a major health issue in many developing countries where the mineral is mined and used in industrial applications. Individuals at risk for development of asbestosis include asbestos miners; insulation, shipyard, and construction workers; and persons who have been exposed by working with brake linings. Even though the health hazards of asbestos are well recognized and use of asbestos has been curtailed in industrialized countries, workers still may be exposed in the course of demolishing, remodeling, or reinsulating pipes or buildings in which asbestos had been used. The duration of exposure necessary for development of asbestosis usually is more than 10 to 20 years but can vary depending on the intensity of the exposure.

One theory for the pathogenesis of asbestosis suggests that asbestos fibers directly injure pulmonary epithelial cells in the respiratory bronchioles and alveolar duct bifurcations, inducing the release of mediators that attract inflammatory cells, including macrophages, neutrophils, and lymphocytes. Unlike silica, asbestos probably is not cytotoxic to macrophages. That is, it does not seem to destroy or “kill” macrophages in the way that silica does. The mechanism of the fibrotic reaction that occurs with asbestos may be related to the release of mediators from macrophages (e.g., transforming growth factor [TGF]-β, TNF-α, fibronectin, insulin-like growth factor [IGF]-1, and platelet-derived growth factor) that can promote fibroblast recruitment and replication. An area of active research involves studying the effects of asbestos fibers on initiating abnormalities in alveolar epithelial cell apoptosis and proliferation. Genetic polymorphisms in TGF-β and TNF-α have been associated with increased susceptibility to the toxic effects of asbestos.

The earliest microscopic lesions appear around respiratory bronchioles, with inflammation that progresses to peribronchiolar fibrosis. The fibrosis subsequently becomes more generalized throughout the alveolar walls and can become quite marked. Areas of the lung that are heavily involved by the fibrotic process include the lung bases and subpleural regions.

A characteristic finding of asbestos exposure is the *ferruginous body*, a microscopic rod-shaped body with clubbed ends (Fig. 10.4) that appears yellow-brown in stained tissue. Ferruginous bodies represent asbestos fibers that have been coated by macrophages with an iron-protein complex. Although large numbers of these structures are commonly seen by light microscopy in patients with asbestosis, not all such coated fibers are asbestos, and ferruginous bodies may be seen even in the absence of parenchymal lung disease. Uncoated asbestos fibers, which are long and narrow, cannot be seen by light microscopy and require electron microscopy for detection.

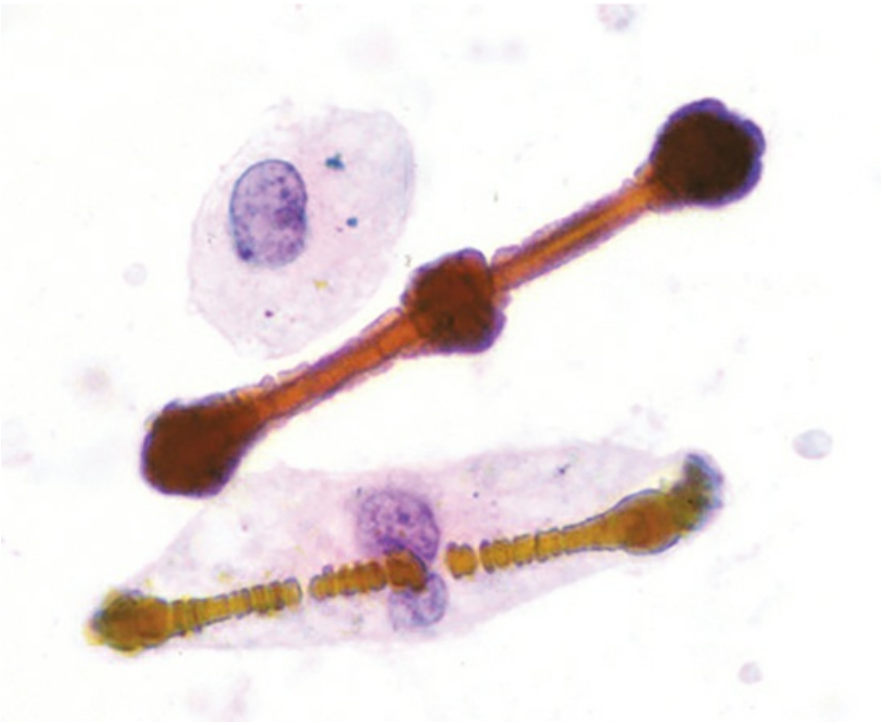

**FIGURE 10.4** High-power photomicrograph of asbestos bodies in a sputum cytology specimen. Rod-shaped bodies with clubbed ends represent "coated" asbestos fibers. *Source:* (From Leslie, K. O., & Wick, M. R. [2018]. *Practical pulmonary pathology. A diagnostic approach* [3rd ed.]. Philadelphia, PA: Elsevier.)

In asbestosis, light microscopic examination of lung tissue often shows large numbers of ferruginous bodies.

The chest radiograph in patients with asbestosis shows a pattern of linear streaking that is generally most prominent at the lung bases (Fig. 10.5A). In advanced cases, the findings may be quite extensive and associated with cyst formation and honeycombing. Commonly there is evidence of associated pleural disease, either in the form of diffuse pleural thickening or localized plaques (which may be calcified) or, much less frequently, in the form of pleural effusions (Fig. 10.5B). Because asbestos is a

predisposing factor in development of malignancies of the lung and pleura, either of these complications may be seen on the chest radiograph.

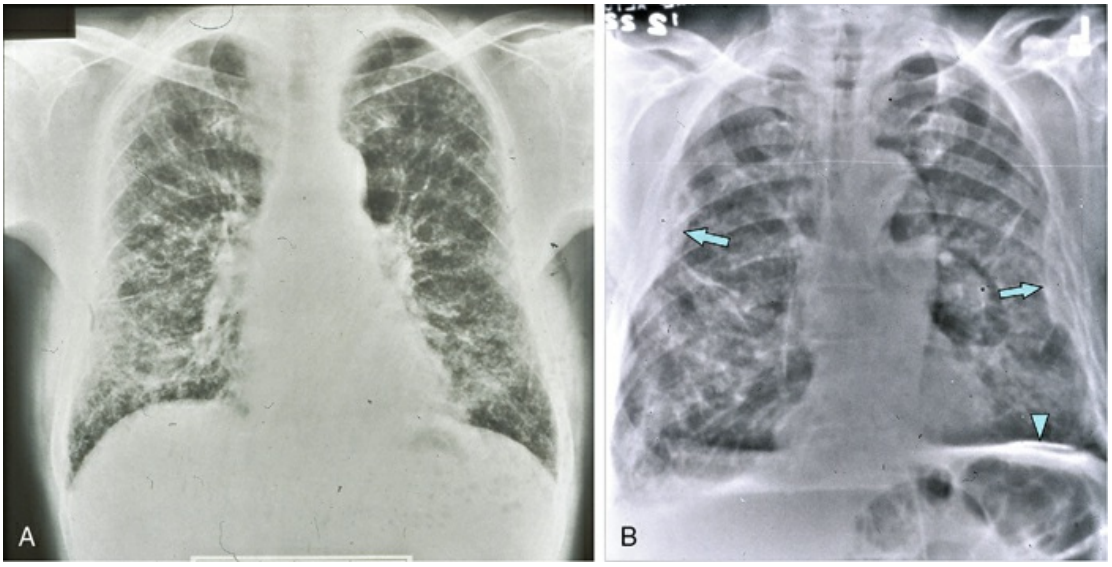


**FIGURE 10.5** Chest radiographs showing parenchymal and pleural disease secondary to asbestos exposure. **A,** Extensive interstitial lung disease in a patient with asbestosis. **B,** Increased interstitial markings and pleural disease (arrows) with diaphragmatic calcification (arrowhead), due to prior asbestos exposure. *Source:* (Courtesy Dr. Paul Stark.)

Pulmonary complications of asbestos exposure are as follows:

1. Diffuse parenchymal lung disease (asbestosis)
2. Diffuse pleural thickening
3. Localized pleural plaques
4. Pleural effusions
5. Lung cancer
6. Pleural malignancy (mesothelioma)

The clinical, pathophysiologic, and diagnostic features of asbestosis usually follow the general description of diffuse parenchymal lung disease discussed in Chapter 9. However, of the pneumoconioses already discussed, asbestosis is much more likely than either silicosis or CWP to be associated with clubbing of digits seen on physical examination.

## Berylliosis

*Berylliosis* is a pneumoconiosis that results from inhalation of dust of the metal beryllium. The disease initially was described in individuals who manufactured fluorescent light bulbs, but more recent cases involve workers in the aerospace, nuclear weapons, and electronics industries and other businesses where beryllium is used. The histologic appearance of disease caused by beryllium is quite different from that seen with the other pneumoconioses described earlier. In berylliosis, the pathologic reaction is found in the lungs as well as hilar and mediastinal lymph nodes and involves formation of granulomas resembling those seen in sarcoidosis.

Berylliosis, which resembles sarcoidosis in many respects, represents a cellular immune response to beryllium.

Berylliosis is now known to represent a cellular immune (delayed hypersensitivity) response to beryllium. Lymphocytes harvested from blood or bronchoalveolar lavage (BAL) fluid of patients with berylliosis demonstrate proliferation and transformation when exposed to beryllium salts in vitro. This "beryllium lymphocyte proliferation test" not only suggests the pathogenesis of the disease but also serves as a useful diagnostic test in individuals with a clinical picture consistent with berylliosis. In addition, sensitization to beryllium can be demonstrated in some workers before the onset of clinical disease, a finding that may be important for prevention or early intervention to arrest progression from subclinical to clinical disease.

Aspects of the pathogenesis of beryllium lung disease are still being elucidated. According to current understanding, after being inhaled, beryllium reaches the alveoli, associates with human leukocyte antigens on the surface of antigen-presenting cells (APCs), and sensitizes $CD4^+$ lymphocytes. In the lymph nodes. APCs promote the expansion of beryllium-specific $CD4^+$ cells, which release several cytokines, including IL-2, IFN-γ, and TNF-α. The secretion of IFN-γ and TNF-α is important in the recruitment of macrophages and the formation of granulomas. Only a minority of people exposed to beryllium develop disease. Innate variability in major histocompatibility complexes affects the response of APCs to beryllium. One form of this susceptibility is identified by the presence of glutamate in position 69 of the human leukocyte antigen DPB1 molecule.

Clinically and radiographically, the disease closely mimics sarcoidosis (see Chapter 11). Specifically, patients with berylliosis demonstrate granulomatous inflammation in the pulmonary parenchyma and intrathoracic lymph nodes. Although extrathoracic involvement can occur, it is less common than in sarcoidosis. Unlike CWP and asbestosis, in which fibrosis is the primary pathology and immunosuppression is not effective, berylliosis represents delayed hypersensitivity to beryllium. Thus, patients with symptoms and pulmonary function abnormalities due to berylliosis are often treated with systemic corticosteroids, typically oral prednisone, to suppress the immune response.

## Hypersensitivity pneumonitis

In *hypersensitivity pneumonitis*, immunologic phenomena directed against an antigen are responsible for the production of diffuse parenchymal lung disease. This disorder is

sometimes referred to as *extrinsic allergic alveolitis*.

The antigens that induce the series of immunologic events are inhaled particulates and aerosolized antigens from a variety of sources. Almost all the antigens are derived from microorganisms, plant proteins, and animal proteins. Exposure often is related either to the patient's occupation or to some avocation. The first of the hypersensitivity pneumonitides to be described was *farmer's lung*, which is due to antigens from microorganisms (thermophilic actinomycetes) that may be present on moldy hay. The list of antigens and types of exposure is quite extensive and includes entities such as air conditioner or humidifier lung (caused by antigens from microorganisms contaminating a forced air system) and bird breeder's or bird fancier's lung (attributable to avian proteins). In an entity called "hot tub lung," the responsible antigens are from nontuberculous mycobacteria, most commonly organisms classified as *Mycobacterium avium* complex, that are contaminating the water in the hot tub.

Hypersensitivity pneumonitis represents an immunologic response to an inhaled organic antigen.

Interestingly, even when a large number of individuals are exposed to a given antigen by virtue of their occupation or avocation, disease develops in only a small percentage. Current understanding of the pathogenesis of hypersensitivity pneumonitis indicates that, in genetically susceptible individuals, repeated exposure to a specific environmental antigen (an "inducer") triggers a cascade of immunologically mediated events which result in the clinical manifestations. Most of the genetic polymorphisms associated with hypersensitivity pneumonitis involve pathways associated with processing or presenting antigens.

Despite much research, we do not yet have a complete understanding of the pathogenesis of hypersensitivity pneumonitis. A first step appears to be that, in genetically susceptible individuals, repeated antigen recognition by pattern recognition receptors on APCs of the innate immune system leads to transcription of proinflammatory cytokines and interferons. A type IV immune reaction (cell-mediated or delayed hypersensitivity, mediated by T lymphocytes) causing a lymphocytic alveolitis is known to be of prime importance in producing the disease. A type III (immune complex disease) mechanism plays a contributory role, especially in acute disease. Evidence suggests that T lymphocytes in the lower respiratory tract become sensitized to the particular organic antigen. They may then release soluble cytokines that attract macrophages and possibly induce them to form granulomas in the lung. Antigen-antibody immune complexes also may be involved, with binding of complement and the resulting production of chemotactic factors and activation of macrophages.

Pathologic examination of the lung in patients with hypersensitivity pneumonitis reveals an alveolitis composed primarily of lymphocytes and macrophages, as well as the presence of granulomas (Fig. 10.6). The granulomas often are loosely formed, unlike the well-defined granulomas characteristic of berylliosis and sarcoidosis (see Chapter 11). Often the pathologic changes have a peribronchiolar prominence, thus accounting for the frequent physiologic evidence for obstruction of small airways.

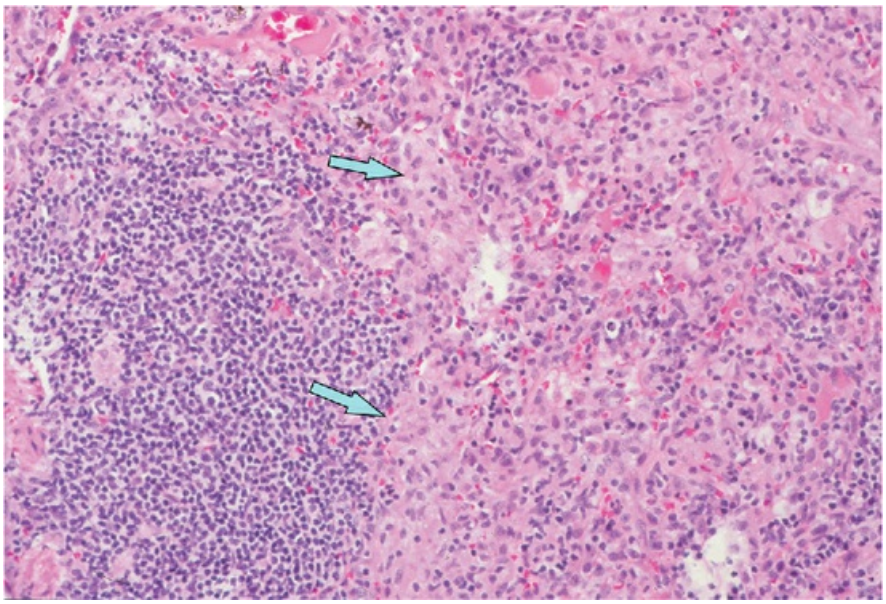

**FIGURE 10.6** Pathology of hypersensitivity pneumonitis, showing a chronic inflammatory process with small lymphocytes, macrophages, and poorly formed granulomas (arrows).

Clinically, hypersensitivity pneumonitis manifests in different ways, ranging from acute episodes of dyspnea, cough, fever, and infiltrates on chest radiograph (occurring approximately 4-6 hours after exposure to the offending antigen) to a chronic form of diffuse parenchymal lung disease. The latter presentation is more insidious. The patient often reports gradual onset of shortness of breath and cough, along with systemic symptoms of fatigue, loss of appetite, and weight loss. Long-term antigen exposure has been occurring in these circumstances, and, because acute episodes are not necessarily an important feature, the patient does not associate the symptoms with any particular exposure.

Hypersensitivity pneumonitis occurs either with acute episodes 4 to 6 hours after exposure to the offending antigen or with the more insidious course of chronic diffuse parenchymal lung disease.

Unlike the acute form, the chronic form of hypersensitivity pneumonitis can behave like other forms of fibrotic diffuse parenchymal lung disease, resembling and mimicking idiopathic pulmonary fibrosis. Unless the physician is attuned to the possibility that hypersensitivity to an antigen in the environment might be responsible for the patient's lung disease, the entity may easily be missed, and exposure to the antigen may continue.

With an acute episode of hypersensitivity pneumonitis, the chest radiograph shows patchy or diffuse infiltrates. As the disease becomes chronic, the abnormality may take on a more nodular quality, eventually appearing as the reticulonodular pattern characteristic of the other chronic diffuse parenchymal lung diseases. In the chronic form of disease, an upper lobe predominance to the radiographic changes is often seen. High-resolution chest computed tomography (CT) scanning may be particularly helpful

in suggesting the diagnosis, often demonstrating a mosaic ground-glass pattern (see Fig. 3.9). An important distinction, which may be suggested by the radiographic appearance, is whether or not fibrosis is present. This has led to a currently used framework that characterizes hypersensitivity pneumonitis as either fibrotic or nonfibrotic. The distinction between fibrotic and nonfibrotic hypersensitivity pneumonitis has implications relating both to prognosis and to the likelihood of improvement with removal of the antigen and response to therapy.

The diagnosis is more likely to be considered if the patient gives a history of acute episodes that either occur by themselves or punctuate a more chronic illness. Historic features concerning the patient's occupation, hobbies, and other environmental exposures may provide valuable clues for detecting the responsible factor. One diagnostic test is a search for precipitating antibodies to the common organic antigens known to cause hypersensitivity pneumonitis. Unfortunately, the presence of antibodies indicates exposure but not necessarily disease. For example, the finding of precipitins to thermophilic actinomycetes, the agent responsible for farmer's lung, is relatively common in healthy farmers without any evidence of the disease. In addition, supporting a diagnosis of hypersensitivity pneumonitis by the finding of precipitins requires that the responsible antigen be included in the panel of antigens tested, which is not always possible.

If a lung biopsy is performed for diagnosis of diffuse parenchymal lung disease, findings on microscopic examination typically include chronic inflammation and small, indistinct non-necrotizing granulomas, as described above.

The best treatment is avoidance of exposure. Unfortunately, the chronic form of the disease often leads to irreversible fibrotic changes in the lung that persist after exposure is terminated. For patients with severe disease or for those in whom antigen avoidance does not lead to resolution, corticosteroid administration is considered, but the results are variable. Trials with antifibrotic agents are underway in patients who develop chronic fibrotic changes.

## Drug-induced parenchymal lung disease

As the list of available pharmacologic agents expands every year, so does the list of potential complications. The lung is certainly one of the target organs for these adverse effects, and diffuse parenchymal lung disease is a particularly important manifestation of drug toxicity. It is imperative that drug toxicity be considered in all patients who develop diffuse parenchymal lung disease. Each drug cannot be considered in detail here, nor can a complete list of the growing number of drugs that have been implicated be provided. However, this chapter briefly discusses the general principles of drug-induced parenchymal lung disease and the major agents responsible.

The major categories of drugs associated with disease of the alveolar wall, along with examples of each, are shown in Table 10.1. A large category includes the traditional chemotherapeutic or cytotoxic agents, drugs designed primarily as antitumor agents. Individual drugs that have been commonly implicated in the development of lung disease include bleomycin, mitomycin, busulfan, cyclophosphamide, gemcitabine, taxanes, and the nitrosoureas, although several others have been described in smaller numbers of cases. Recently, severe and potentially fatal pneumonitis has been

recognized due to checkpoint inhibitor immunotherapy that targets cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) or proteins inhibiting programmed cell death (PD-1 and PD-L1). In general, the risk of developing diffuse parenchymal lung disease increases with higher cumulative doses of a particular agent, but occasional cases with relatively low cumulative doses are described. In most cases, diffuse parenchymal lung disease develops in a period ranging from 1 month to several years after use of the agent, but some agents can also be associated with the development of more acute disease. Busulfan is particularly notable for late development of complications, often several years after onset of therapy.

**TABLE 10.1**

**Selected Drugs Potentially Causing Diffuse Parenchymal Lung Disease**

| |
|---|
| **Cytotoxic Chemotherapy** |
| Bleomycin<br>Busulfan<br>Cyclophosphamide<br>Gemcitabine<br>Nitrosoureas<br>Taxanes (e.g., paclitaxel, docetaxel) |
| **Antimetabolites** |
| Methotrexate |
| **Targeted Biologic Agents** |

| |
|---|
| Tumor necrosis factor (TNF)-α inhibitors or soluble receptors<br><br>Infliximab<br>Adalimumab<br>Certolizumab pegol<br>Etanercept<br><br>Tyrosine kinase inhibitors<br><br>Afatinib<br>Dasatinib<br>Erlotinib<br>Gefitinib<br>Idelalisib<br>Imatinib<br>Osimertinib<br>Trametinib<br><br>Immune checkpoint inhibitors (antibodies against PD-1, PD-1 ligand, or CTLA-4)<br><br>Ipilimumab<br>Nivolumab<br>Pembrolizumab<br><br>Inhibitors of anaplastic lymphoma kinase (ALK)<br><br>Alectinib<br>Ceritinib<br>Crizotinib |
| **Miscellaneous** |
| Trastuzumab (monoclonal antibody against HER2)<br>Rituximab (monoclonal antibody against CD20)<br>Inhibitors of mechanistic target of rapamycin (mTOR, e.g., everolimus) |
| **Miscellaneous Other Drugs** |
| Nitrofurantoin<br>Amiodarone |
| **Drug-Induced Syndromes** |
| Drug-induced lupus (e.g., procainamide, hydralazine)<br>Drug-induced pulmonary infiltrates with eosinophilia (e.g., sulfa-containing drugs) |

A wide variety of different drug classes are associated with diffuse parenchymal lung disease.

The pathogenesis of chemotherapy-induced diffuse parenchymal lung disease often appears to involve either direct toxicity to normal lung parenchymal cells, especially epithelial cells, or oxidant injury induced by generation of toxic oxygen radicals. When oxidant damage is involved, as with bleomycin, other agents that promote formation of oxygen free radicals (e.g., radiation therapy, high concentrations of inhaled oxygen) can augment the injury caused by the chemotherapeutic agent.

The pathologic appearance of diffuse parenchymal lung disease caused by cytotoxic agents frequently is notable for the presence of atypical bizarre-appearing type II

alveolar epithelial cells with large hyperchromatic nuclei. When this feature is associated with the other usual findings of diffuse parenchymal lung disease, the pathologist should suspect that a chemotherapeutic agent may be responsible.

Cytotoxic drug–induced diffuse parenchymal lung disease shows atypical bizarre-appearing alveolar type II epithelial cells.

Methotrexate, an antimetabolite affecting folic acid metabolism, is used in low doses for treatment of rheumatoid arthritis and other rheumatologic diseases, and in higher doses as an antineoplastic agent, especially for treatment of hematologic malignancies. A hypersensitivity mechanism appears to play an important role in the pathogenesis of methotrexate pneumonitis, as evidenced by the frequent presence of granulomas on pathology.

Biologic agents, a large and rapidly increasing category of drugs developed from biologic sources and often involving use of recombinant gene technology, are commonly monoclonal antibodies or other inhibitors targeted against cytokines and a variety of signaling pathways. In addition to treatment of cancer, some of these agents are used for the treatment of systemic inflammatory or immune-related diseases. Although the frequency of pulmonary toxicity with most of these agents is quite low, the possibility of a drug-related complication should be considered in any patient on one of these agents who develops parenchymal lung disease.

Several drugs that are not chemotherapeutic or biologic agents have been implicated in the development of parenchymal lung disease. Nitrofurantoin, an antibiotic, has been associated with both acute and chronic reactions. The acute problem, which presumably is a hypersensitivity phenomenon, often is characterized by pulmonary infiltrates, pleural effusions, fever, and eosinophilia in peripheral blood. The chronic problem, which does not appear to be related to prior acute episodes, is characterized by a nonspecific interstitial pneumonitis and fibrosis akin to that of the other diffuse parenchymal lung diseases.

The commonly used antiarrhythmic agent amiodarone is associated with clinically significant parenchymal lung disease in approximately 1% to 5% of treated patients. Amiodarone pulmonary toxicity is dose-related and may be fatal. In addition to nonspecific inflammation and fibrosis, the pathologic appearance of amiodarone-induced diffuse parenchymal lung disease is notable for macrophages that appear foamy because of cytoplasmic phospholipid inclusions. However, similar foamy macrophages with cytoplasmic inclusions may be seen in lung tissue from amiodarone-treated patients without interstitial inflammation and fibrosis. This finding suggests that the phospholipid inclusions are a marker of amiodarone use but are not necessarily directly responsible for the other pathologic and clinically important pulmonary consequences of amiodarone. Radiographically, patients with amiodarone-induced lung disease can develop either focal or diffuse infiltrates. CT scanning commonly shows a relatively high density of the infiltrates, resulting from a high iodine content within the amiodarone molecule.

Amiodarone-induced lung disease is an important cause of either focal or diffuse pulmonary infiltrates.

A large number of drugs have been linked with development of an illness that resembles systemic lupus erythematosus, and patients with this “drug-induced lupus” may have parenchymal lung disease as one manifestation. In addition, a variety of drugs have been associated with pulmonary infiltrates and peripheral blood eosinophilia. This constellation of pulmonary infiltrates with eosinophilia, of which drugs are just one of several possible causes, is often abbreviated as the *PIE syndrome*.

Clinically, fever is a common accompaniment to the respiratory symptoms associated with drug-induced diffuse parenchymal lung disease. An increase in eosinophils in peripheral blood is often noted in patients with methotrexate-induced lung disease and is characteristic of patients with the PIE syndrome.

When pulmonary infiltrates develop in patients with malignancy or anyone receiving a drug associated with suppression of the immune response, several diagnostic considerations arise, especially when the clinical presentation is accompanied by fever. In addition to the possibility of drug toxicity, there is concern about infection (because host defenses may be impaired by the drug or the underlying malignancy), dissemination of the malignancy through the lung, bleeding into the lung, and, in patients who have received radiation therapy, toxic effects from irradiation. When the diagnosis is not clear, a diagnostic procedure such as a lung biopsy or BAL often is performed, primarily to rule out an infectious process. If atypical epithelial cells but no infectious agents are found, a drug-induced process is suspected.

For patients who are believed to have drug-related diffuse parenchymal lung disease, the drug ideally should be discontinued. Corticosteroids may be administered, but, as with their use in other diffuse parenchymal diseases, the results are variable.

## Radiation-induced lung disease

Parenchymal lung disease is a potential complication of radiation therapy for tumors within or in close proximity to the thorax, particularly lymphoma (Hodgkin lymphoma) and carcinoma of the breast or lung. The incidence of clinically apparent injury is increased with higher radiation dose, a larger radiation field, and the use of concomitant chemotherapy. The risk is highest in lung cancer (5%–25%), followed by mediastinal lymphoma (5%–10%) and breast cancer (1%–5%). However, radiographic changes in the absence of symptoms are seen even more frequently, in 20% to 70% of exposed patients.

Radiation-induced pulmonary disease is generally divided into two phases: early pneumonitis and late fibrosis. The acute phase of radiation pneumonitis typically develops 1 to 3 months after completion of a course of therapy and depends on the total dose and the volume of lung irradiated. The later stage of radiation fibrosis may directly follow earlier radiation-induced pneumonitis, may occur after a symptom-free latent interval, or occasionally may develop without any prior clinical evidence of acute pneumonitis. Fibrosis, when it occurs, does so generally 6 to 12 months after radiation therapy has been completed.

Radiation-induced lung disease includes an early period of radiation pneumonitis and a later period of radiation fibrosis.

Radiation-induced lung injury results from a combination of direct injury to normal pulmonary cells and induction of fibrotic pathways. Early injury to pulmonary capillary endothelial cells leads to increased permeability. Damage to type I and type II cells ensues, leading to production of cytokines and recruitment of inflammatory cells. In the period preceding chronic fibrosis, an alveolitis develops and the body's attempt at injury repair leads to development of fibrotic changes. The possibility of hypersensitivity also playing a role in the pathogenesis of the alveolitis has been suggested by the finding of increased lymphocytes in the BAL fluid of the nonirradiated lung in patients with radiation-induced pneumonitis.

Early pathologic changes include swelling of endothelial cells, interstitial edema, mononuclear cell infiltrates, and atypical hyperplastic epithelial cells. Subsequent changes during the fibrotic stage consist of progressive fibrosis (indistinguishable from pulmonary fibrosis from other causes) and sclerosis of small vessels, with obliteration of a major portion of the capillary bed in the involved area.

Clinically, patients may have fever with the acute pneumonitis in conjunction with respiratory symptoms, and distinguishing radiation pneumonitis from an atypical pneumonia is often difficult. On chest radiograph, the acute pneumonitis is often characterized by an infiltrate that conforms in shape and location to the region of lung irradiated. Chest CT scanning may be particularly useful, both because it may detect subtle abnormalities earlier than can be seen on chest radiograph and because the cross-sectional views more readily show the correspondence of the radiographic abnormalities to the radiation ports. However, for reasons that are unclear, additional changes outside the field of radiation may develop in some patients. As radiation delivery has become more sophisticated and is using three-dimensional approaches, an additional complication is that the radiation beam may be delivered through a variety of different orientations to maximize delivery to the tumor and limit exposure to normal lung tissue. This means that relatively linear borders of disease corresponding with the orientation of a fixed radiation beam may no longer be apparent.

The pattern of chronic radiation fibrosis is an increase in interstitial markings, again generally corresponding in location to the irradiated region of lung, often with associated volume loss. With newer modes of delivery that do not have a fixed orientation of the radiation beam, the area of fibrosis may be primarily in the region of the irradiated tumor and may have rather indistinct margins. The acute changes of the pneumonitis are potentially reversible, whereas the chronic fibrotic changes are permanent.

The interstitial pattern in radiation-induced lung disease may conform in distribution to the region of lung irradiated.

Diagnostic considerations are usually similar to those for drug-induced parenchymal lung disease. A history of recent irradiation occurring at the appropriate time is crucial to the diagnosis. In addition, the finding of radiographic changes that conform to the radiation port, if there happens to be a relatively linear border, is strongly suggestive of the diagnosis.

Corticosteroids are frequently used to treat radiation-induced pneumonitis, often with reasonably good results. When the chronic changes of fibrosis have developed,

corticosteroids are much less effective.

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# 11: Diffuse parenchymal lung diseases of unknown etiology

OUTLINE



Approximately 65% of patients with diffuse parenchymal lung disease are victims of a process for which no etiologic agent has been identified, even though a specific name may be attached to the disease entity. Included in this category are idiopathic pulmonary fibrosis (IPF), parenchymal lung disease associated with systemic rheumatic disease (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis), sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH), and a variety of other disorders. Many general aspects of these problems were discussed in Chapter 9. This chapter focuses on the specific diseases and their particular characteristics.

## Idiopathic pulmonary fibrosis

Although the name *idiopathic pulmonary fibrosis* has often been used nonspecifically to describe fibrotic interstitial lung disease without an identifiable diagnosis, most

clinicians and investigators believe IPF represents a specific disease entity. This chapter adopts that assumption and considers pulmonary fibrosis associated with an underlying systemic rheumatic disease a separate entity. Another name that has been used interchangeably with IPF is *cryptogenic fibrosing alveolitis*. The term *usual interstitial pneumonia* (UIP) is not a clinical disease but refers to the pathologic pattern associated with IPF, but also can be seen in clinical settings other than IPF, such as when lung disease is associated with a systemic rheumatic disease.

As implied by the name, IPF does not have a recognizable inciting agent, although most studies demonstrate an association with tobacco smoke exposure. The theory behind the pathogenesis of IPF has changed considerably over the past 25 years. For many years the prevailing thought was that exposure to an unknown agent (perhaps an antigen leading to formation of antigen-antibody complexes) led to alveolar inflammation, which was perpetuated by release of chemotactic factors from inflammatory cells. The ongoing inflammation was believed to be responsible for subsequent development of fibrosis.

However, the current widely accepted paradigm is that recurrent microinjuries to susceptible alveolar epithelial cells result in an abnormal wound healing process, ultimately causing fibrosis. According to this current theory, alveolar inflammation does *not* play a critical role in the eventual development of fibrosis, and injury to alveolar epithelial cells is the primary initiating event. Although injury to type I alveolar epithelial cells normally would be followed by a repair process that includes proliferation of type II cells and differentiation into type I cells, this repair process is impaired, at least in part because of disruption of the basement membrane, which normally is important for the re-epithelialization process. Several defects in type II cell function have been associated with IPF pathogenesis, including abnormalities in autophagy, apoptosis, and progenitor cell function. At the same time, alveolar epithelial cells express a variety of profibrotic cytokines and growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β1, which enhance fibroblast migration and proliferation. Fibroblastic foci develop at sites of alveolar injury and appear to be responsible for increased extracellular matrix deposition. This process is summarized in Fig. 11.1.

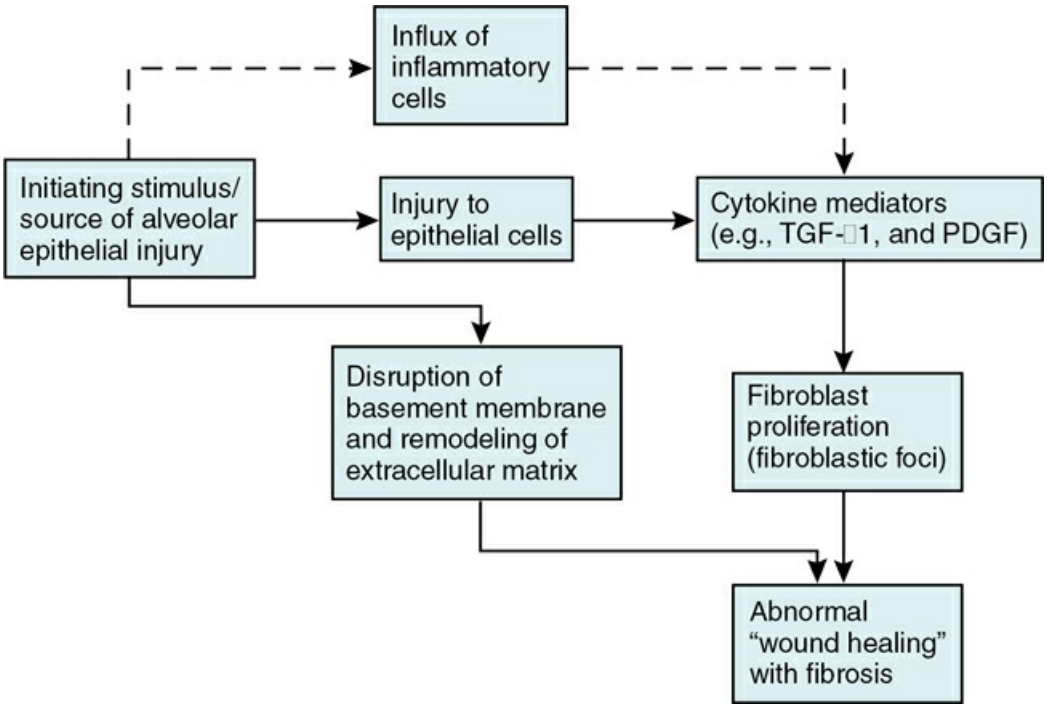


**FIGURE 11.1** Proposed pathogenetic sequence in idiopathic pulmonary fibrosis. *Dotted lines* indicate that although there is an influx of inflammatory cells, this is not thought to be a primary component of pathogenesis. *PDGF*, platelet-derived growth factor; *TGF-β1*, transforming growth factor-β1.

The development of IPF is associated with gene mutations in several biological pathways known to be related to lung injury, lung repair, or production of mucins in peripheral airways. Mutations in the first pathway affect genes encoding surfactant proteins A2 (SFP-A2) and C (SFP-C), which may act to increase susceptibility to chronic lung injury by causing increased endoplasmic reticulum stress in alveolar type II epithelial cells. Mutations in the second pathway affect genes encoding telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC), the multimeric enzyme system that repairs shortened telomeres. Abnormalities in telomerase function appear to impair wound healing by decreasing replication of progenitor cells. Finally, a variant that leads to overexpression of the MUC5B gene, involved in mucin production in peripheral airways, has also been associated with an increased risk of IPF by one or more mechanisms that have not yet been elucidated. Although these various mutations are not present in many patients with IPF, identification of these involved pathways has led to better understanding of the mechanism of disease in at least some IPF patients, raising hopes of new therapies.

Idiopathic pulmonary fibrosis is thought to represent a dysregulated pattern of fibrosis in response to alveolar epithelial injury.

Clinically, the most common age at presentation of patients with IPF is between 50

and 70 years. Disease onset is generally insidious, and symptoms are similar to those of other interstitial lung diseases; dyspnea is the most prominent complaint. In addition to the classic finding of dry inspiratory crackles or rales on physical examination, patients frequently display clubbing of the digits.

The chest radiograph shows an interstitial (reticular) pattern that is generally bilateral and relatively diffuse but typically is more prominent at the lung bases, particularly in the peripheral subpleural regions (see Fig. 3.6). Neither hilar enlargement nor pleural effusions are common. High-resolution computed tomography (HRCT) scanning typically has a characteristic appearance, showing interstitial densities that are patchy, peripheral, subpleural, and associated with small cystic spaces (Fig. 11.2). The pattern of small cystic peripheral abnormalities on HRCT is termed *honeycombing* and indicates irreversible fibrosis. Many patients have serologic abnormalities, such as a positive test result for antinuclear antibodies, which are generally found in patients with autoimmune or systemic rheumatic disease. However, in the absence of other suggestive clinical features, these abnormalities are thought to be nonspecific and not indicative of an underlying rheumatologic disease.

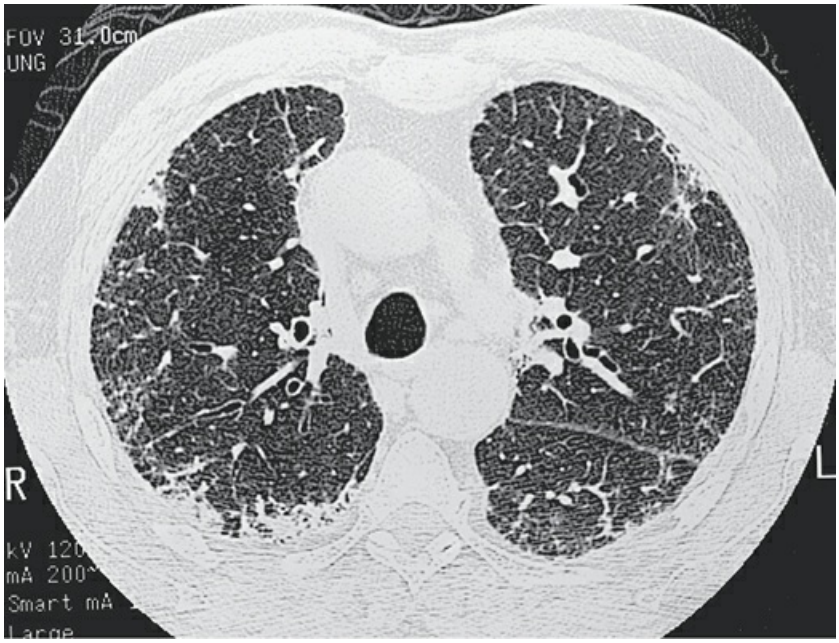


**FIGURE 11.2** High-resolution computed tomography scan of idiopathic pulmonary fibrosis shows scattered reticular densities, especially in subpleural regions.

The chest radiograph in IPF demonstrates a diffuse interstitial pattern without pleural disease or hilar enlargement.

The diagnosis is definitively established by surgical lung biopsy. However, if the HRCT scan shows a classic pattern that includes honeycombing and several other

features, the diagnosis can be made with relative certainty without a lung biopsy. Traditional methods of bronchoscopic lung biopsy do not yield sufficiently large samples to establish the diagnosis, although a newer technique called transbronchial cryobiopsy, which obtains a larger tissue sample, appears more useful. The histologic expression of IPF is in the form of UIP (see Fig. 9.3), and patients who have a pathologic pattern more compatible with desquamative interstitial pneumonia (DIP) or NSIP (see Other Idiopathic Interstitial Pneumonias; also see Chapter 9) should not be considered to have IPF. Granulomas should not be seen on an IPF biopsy specimen and, if present, suggest another disorder.

Although IPF represents a chronic, fibrotic disease, some patients develop an *acute exacerbation of IPF*. This intercurrent problem is characterized by a relatively acute increase in symptoms, radiographic findings of a ground-glass pattern superimposed over their preexisting disease, and a pathologic appearance consistent with acute lung injury that resembles the acute respiratory distress syndrome (ARDS) (see Chapter 29). Acute exacerbations are frequently treated with corticosteroids and antibiotics (because of the difficulty in definitively excluding infection), although it is unclear whether they provide any benefit, and the mortality associated with an acute exacerbation is relatively high.

Currently, there is no proven effective therapy to arrest or reverse the progressive fibrosis of IPF. Although corticosteroids and cytotoxic agents have been used frequently in the past for IPF, subsequent studies unfortunately demonstrated that these agents are ineffective and appear to be harmful. It is now thought that the small subgroup of patients previously believed to respond to corticosteroids actually had a corticosteroid-responsive diffuse parenchymal lung disease that was misidentified as IPF. Treatment for IPF now focuses on agents that suppress fibrosis or interfere with mediators involved in the fibrotic process. Two available drugs have been shown to reduce (but not stop) progression of disease, as measured by loss of pulmonary function. One of these, pirfenidone, inhibits TGF-β-mediated collagen synthesis and fibroblast proliferation. The other agent, nintedanib, a tyrosine kinase inhibitor, blocks the receptors and the downstream signaling of several fibrogenic growth factors, including PDGF, fibroblast growth factor, and vascular endothelial growth factor. In some patients with severe IPF, especially those who are younger, lung transplantation is the only therapeutic alternative to progressive respiratory failure and death. Although the overall prognosis is generally poor, with average survival less than 5 years, some patients have a more prolonged course, with survival that can exceed a decade.

Prognosis in idiopathic pulmonary fibrosis is generally poor. Treatment options include drugs aimed at slowing progression of disease (nintedanib, pirfenidone) or, in selected patients, lung transplantation.

## Other idiopathic interstitial pneumonias

Several other disorders besides IPF fall under the category of the idiopathic interstitial pneumonias and previously have often been confused with IPF. Although these disorders are uncommon, some are briefly described here, largely to clarify how their pathologic features differ from UIP and how their clinical features differ from IPF. They

are also mentioned in Chapter 9 as part of the discussion on the pathology of the interstitial pneumonias (see Table 9.2).

*Respiratory bronchiolitis–interstitial lung disease* (RB-ILD) and DIP are often considered together as part of a spectrum because of their strong association with smoking, although they are currently classified as separate smoking-related interstitial pneumonias. RB-ILD typically has relatively mild symptoms, occurs exclusively in smokers, and usually is reversible with cessation of smoking. HRCT scans in RB-ILD often show a ground-glass (hazy) pattern of opacification accompanied by centrilobular nodules. The pathologic pattern that corresponds to this appearance on HRCT is an accumulation of pigmented macrophages in the lumen of small airways accompanied by some peribronchiolar inflammation with lymphocytes and macrophages (see Fig. 9.5).

DIP is almost always associated with smoking, although rarely cases have also been described in nonsmokers. It generally has a subacute rather than a chronic onset. Imaging studies with chest radiography and HRCT scanning often show a ground-glass pattern. On lung biopsy, there is a uniform accumulation of intra-alveolar macrophages, with little or no fibrosis. In comparison with the peribronchiolar distribution in RB-ILD, DIP demonstrates more diffuse parenchymal involvement. The prognosis is better than in IPF, and patients often can improve after cessation of smoking and may respond to corticosteroids.

*NSIP* differs from UIP in its radiographic pattern, histologic appearance, prognosis, and response to treatment. As with DIP, imaging studies often show a ground-glass pattern reflecting inflammation rather than fibrosis. Lung biopsy shows a predominantly inflammatory response in the alveolar walls, with relatively little fibrosis (see Fig. 9.4). Although NSIP is often idiopathic, it can represent the histologic appearance of parenchymal lung disease associated with one of the systemic rheumatic diseases or with drug-induced pulmonary toxicity. The prognosis of NSIP appears to depend on the degree of fibrotic involvement present on both imaging and pathology. If inflammation predominates rather than fibrosis, the prognosis is significantly better than in IPF, and patients often respond to treatment with corticosteroids.

*Cryptogenic organizing pneumonia* (COP) is a disorder characterized by connective tissue plugs in small airways accompanied by mononuclear cell infiltration of the surrounding pulmonary parenchyma (see Fig. 9.6). As noted in Chapter 9, the terms *cryptogenic organizing pneumonia* (*COP*) and *bronchiolitis obliterans with organizing pneumonia* (*BOOP*) have often been used interchangeably, but the term BOOP is best reserved for the pathologic picture rather than the clinical syndrome. Although the pathologic pattern of BOOP can be associated with systemic rheumatic disease, toxic fume inhalation, or infection, the majority of cases have no identifiable cause and are considered idiopathic. The term *COP* is most appropriate for patients who have "idiopathic BOOP"—that is, the histologic findings of BOOP without an apparent cause.

On chest radiograph, cryptogenic organizing pneumonia (COP) often mimics a pneumonia with one or more alveolar infiltrates.

Like chronic eosinophilic pneumonia (see later), COP often has a subacute presentation (over weeks to months) with systemic (constitutional) as well as respiratory symptoms. Chest imaging studies show patchy infiltrates, generally with an

alveolar rather than an interstitial pattern, often mimicking a community-acquired pneumonia (Fig. 11.3). Like chronic eosinophilic pneumonia, the response to corticosteroids is often dramatic and occurs over days to weeks. Therapy is usually maintained for months in order to prevent relapse.

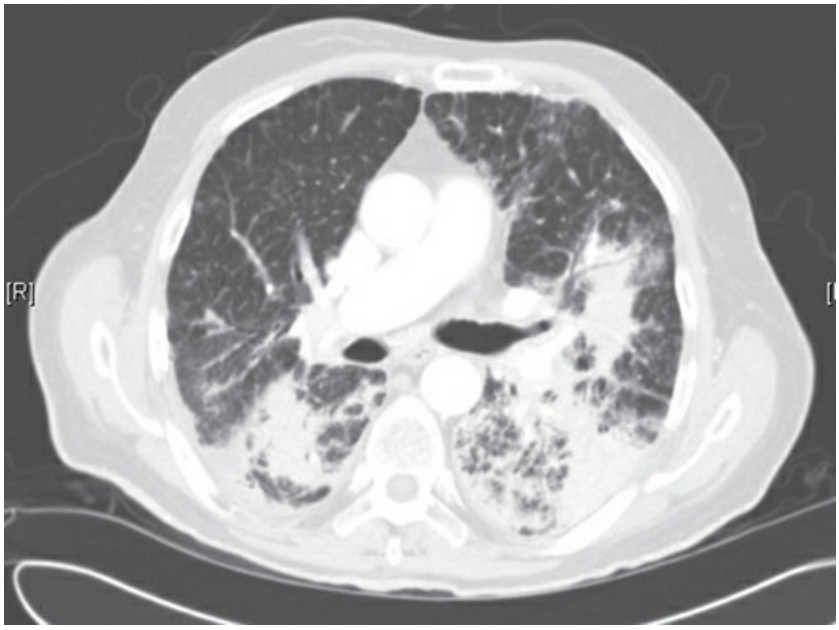


**FIGURE 11.3** Chest CT scan demonstrating patchy alveolar opacities in a patient with cryptogenic organizing pneumonia.

*Acute interstitial pneumonia* (AIP) is a more acute or fulminant type of pulmonary parenchymal disease characterized by the clinical picture of ARDS (see Chapter 29) but without any of the usual inciting events associated with development of ARDS. Imaging studies of AIP typically show features of ARDS, including areas of ground-glass opacification and alveolar filling (as opposed to a purely interstitial pattern). The histologic pattern is that of diffuse alveolar damage, often showing some organization and fibrosis. Although mortality is high overall, a small percentage of patients do well, with clinical resolution of the disease and no long-term sequelae.

One confusing aspect of the nomenclature of the idiopathic interstitial pneumonias is the relationship underlying AIP, UIP (or IPF), and a disorder called *Hamman-Rich syndrome*. More than 80 years ago, Hamman and Rich described a number of cases of parenchymal lung disease that subsequently were thought to represent the first described cases of IPF, and for many years the term *Hamman-Rich syndrome* was used synonymously with *IPF*. However, the cases described by Hamman and Rich are now believed to be cases of AIP rather than IPF, and it is more appropriate that Hamman-Rich syndrome be considered synonymous with AIP rather than either UIP or IPF.

## Pulmonary parenchymal involvement complicating systemic rheumatic disease

The systemic rheumatic diseases, also commonly called *collagen vascular* or *connective tissue diseases*, include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma), polymyositis-dermatomyositis, Sjögren syndrome, and overlap syndromes that have features of more than one of these disorders. Although they comprise a diverse group, all are multisystem inflammatory diseases that are mediated immunologically and often considered as autoimmune disorders. The organ systems likely involved vary with each disease and are mentioned briefly in the following discussion of each entity.

Each disease is complicated and has been the focus of extensive research into etiology and pathogenesis. However, because none of them primarily affects the lung, they are not considered in detail here. Rather, a brief discussion notes how they affect the respiratory system, particularly with regard to development of parenchymal lung disease. Some clinicians include additional disorders under the label of connective tissue diseases, but this discussion is limited to those in the preceding paragraph, each of which has the potential for pulmonary involvement.

Four assertions are true about each of these disorders. First, although patients generally have evidence of the underlying systemic rheumatic disease before pulmonary manifestations develop, some patients have lung disease as the presenting problem, occasionally predating other manifestations of their illness by several years. Second, detailed histologic, physiologic, or autopsy evaluation of patients with these diseases shows that pulmonary involvement is much more common in these autoimmune conditions than clinically suspected. Third, the histopathology of interstitial lung disease associated with the systemic rheumatic diseases is usually either NSIP or UIP and is indistinguishable from idiopathic NSIP or IPF, respectively. Occasionally, however, the histopathology demonstrates organizing pneumonia that is indistinguishable from COP. Fourth, the interstitial lung disease that may develop with each of these entities preferentially affects the lower rather than the upper lung zones. This fact usually is apparent on examination of the chest radiograph.

Histologic and physiologic changes suggest that pulmonary involvement in most systemic rheumatic diseases is common, usually with a histologic pattern of nonspecific interstitial pneumonia or usual interstitial pneumonia.

*Rheumatoid arthritis* is a disorder with primary manifestations consisting of inflammatory joint disease. The most common site of involvement within the thorax is the pleura. Involvement takes the form of pleurisy, pleural effusions, or both. The lung parenchyma may become involved, with one or multiple nodules or with development of interstitial lung disease. A pathologic picture of UIP is most common, NSIP is slightly less common, and occasional patients have a pattern of organizing pneumonia resembling COP. Less commonly, patients with rheumatoid arthritis develop airway complications in the form of bronchiolitis (an inflammatory process involving small airways) or bronchiectasis. Because patients with rheumatoid arthritis are frequently treated with drugs that can be associated with pulmonary toxicity, such as methotrexate or rituximab, the possibility of drug-induced lung disease must also be considered.

In rheumatoid arthritis and lupus, pleural disease is more common than clinically evident diffuse parenchymal lung disease.

*Systemic lupus erythematosus* is a multisystem disease that primarily affects joints and skin but often has more serious involvement of several organ systems, including the kidneys, lungs, nervous system, and heart. Its most frequent presentation within the chest takes the form of pleural disease, specifically pleuritic chest pain, pleural effusion, or both. The lung parenchyma may be involved by an acute pneumonitis that resembles AIP, with infiltrates often involving the alveolar spaces as well as the alveolar walls. Another acute pulmonary complication in lupus is the development of diffuse alveolar hemorrhage. Less frequently, patients with lupus can develop chronic interstitial lung disease that has either NSIP or UIP pathology, although extensive fibrosis is relatively uncommon in lupus.

*Systemic sclerosis*, or *scleroderma*, is a disease with the most obvious manifestations located in the skin and small blood vessels. Other organ systems, including the gastrointestinal tract, lungs, kidneys, and heart, are involved relatively frequently. As with other systemic rheumatic disease, the pulmonary parenchymal involvement with scleroderma can represent either NSIP or UIP. Pulmonary fibrosis complicating scleroderma appears to be strongly associated with the presence of a particular serologic marker, an autoantibody to topoisomerase I (antitopoisomerase I, also called *Scl70*). Another potential pulmonary manifestation of scleroderma is disease of the small pulmonary blood vessels, producing pulmonary arterial hypertension, which is discussed in Chapter 14. This involvement appears to be independent of the fibrotic process affecting the alveolar walls. Because patients with scleroderma commonly have esophageal disease leading to gastroesophageal reflux, recurrent aspiration may play a role in the development or progression of apparent interstitial lung disease.

In addition to interstitial fibrosis, patients with scleroderma may develop pulmonary vascular disease involving the small pulmonary vessels that is independent of the interstitial process.

In *polymyositis-dermatomyositis*, muscles and skin are the primary sites of the inflammatory process. The interstitial lung disease of polymyositis-dermatomyositis is relatively infrequent and often has no particular distinguishing features. Patients may also have respiratory problems due to muscle disease, with weakness of the diaphragm or other inspiratory muscles. Involvement of striated muscle in the proximal esophagus may lead to difficulty in swallowing and recurrent episodes of aspiration pneumonia.

In *Sjögren syndrome*, a lymphocytic infiltration affects salivary and lacrimal glands and is associated with dry mouth and dry eyes (keratoconjunctivitis sicca). When patients with Sjögren syndrome have pulmonary parenchymal involvement, the histologic appearance is most commonly either NSIP or a lymphocytic infiltrate within the alveolar walls called *lymphocytic interstitial pneumonia*. Other lymphocytic complications of the lung can develop in patients with Sjögren syndrome, specifically either a localized nodular lesion called a *pseudolymphoma* or a full-fledged lymphoma.

Finally, a number of overlap syndromes, often called *undifferentiated connective tissue disease*, have features of several of these disorders, particularly scleroderma, lupus, and polymyositis. Patients may develop any of the complications noted with the more classic individual disorders, including parenchymal lung disease, pleural disease,

and pulmonary vascular disease.

## Sarcoidosis

*Sarcoidosis* is a systemic disorder in which granulomas, typically noncaseating, can be found in affected tissues or organ systems. An important qualification is that these granulomas occur in the absence of any exogenous (infectious or environmental) agents known to be associated with granulomatous inflammation. The lung is the most frequently involved organ, with potential manifestations including parenchymal lung disease, enlargement of hilar and mediastinal lymph nodes, or both.

Sarcoidosis is a systemic granulomatous disease that most commonly affects the lungs, the hilar and mediastinal lymph nodes, or both.

Sarcoidosis is a relatively common disorder that particularly affects young adults between the ages of 20 and 40 years. It is slightly more common in women than in men. In the United States, it is more common in the Black population than in the White population. However, this predilection is not seen throughout the world because the disease is notably prevalent in the White population of Scandinavia. Of all the disorders of unknown cause affecting the alveolar walls, sarcoidosis is the most prevalent.

Despite increasing knowledge about the cells involved in the inflammatory and granulomatous response in sarcoidosis and the identification of multiple cytokines and chemokines that appear to be involved in the pathogenesis of disease, the fundamental etiology of sarcoidosis remains as mysterious as it was when the disease was first described more than 125 years ago. It is hypothesized that sarcoidosis represents an immunologic response to an exogenous agent in a genetically susceptible individual. Multiple exogenous antigens and a number of human leukocyte antigens and other candidate genes have been associated with susceptibility to sarcoidosis. However, neither a particular exogenous agent nor a specific genetic susceptibility has been consistently demonstrated. Interest in potential exogenous inciting agents has focused on microorganisms such as viruses, mycobacteria, and other bacteria (e.g., *Propionibacterium acnes*), as well as inorganic dusts such as silica. Nevertheless, the identity of a trigger for sarcoidosis remains elusive, and whether such an agent or group of agents even exists is not known. At present, it seems most likely that sarcoidosis represents a complex interaction among a variety of antigens or particles and the effects of multiple genes.

In contrast, substantial information is available about cells and mediators that appear to be important in the inflammatory and granulomatous tissue reaction in sarcoidosis (Fig. 11.4). The critical cells are antigen-presenting cells and T lymphocytes. Processing of the still unidentified responsible antigen(s) by alveolar macrophages or dendritic cells results in recruitment of helper T lymphocytes ($CD4^+$ cells) with a $T_H1$ profile. Markedly increased expression of interferon (IFN)-$\gamma$ is characteristic, and other proinflammatory cytokines and chemokines, such as interleukin (IL)-2, tumor necrosis factor (TNF)-α, and IL-12, appear to be important in recruiting and activating inflammatory cells, perpetuating the inflammatory response, and inducing the formation of granulomas. Profibrotic cytokines, such as TGF-β, PDGF, and insulin-like growth factor (IGF)-1,

subsequently may result in fibrosis as a complication of the initial inflammatory reaction.

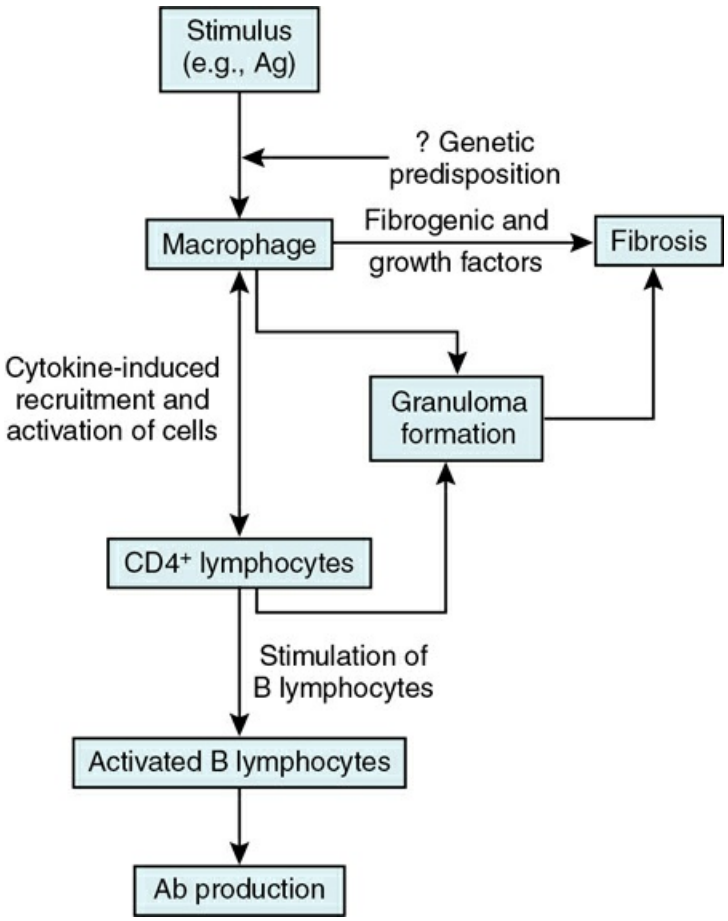


**FIGURE 11.4** Simplified proposed pathogenetic sequence in sarcoidosis. *Ab*, antibody; *Ag*, antigen.

The accumulation of $CD4^+$ lymphocytes at sites of active disease appears to result in secondary immunologic phenomena that are well recognized in sarcoidosis. First, presumably because of this concentration of activated lymphocytes in affected tissues, there is a relative depletion of $CD4^+$ cells in peripheral blood. The depletion leads to an apparent depression of cell-mediated immunity, at least as measured by cutaneous delayed hypersensitivity (skin testing). However, patients with sarcoidosis are not unduly susceptible to opportunistic infections that characteristically affect the immunosuppressed host with impaired cellular immunity. Second, T lymphocytes in sarcoidosis nonspecifically activate B lymphocytes and the humoral immune system, leading to production of a variety of immunoglobulins and the common finding of polyclonal hypergammaglobulinemia.

The characteristic histopathologic feature of sarcoidosis is the noncaseating granuloma (see Fig. 9.2). These typically well-formed granulomas represent a collection of tissue macrophages (also called *epithelioid histiocytes*), multinucleated giant cells,

and T lymphocytes, particularly toward the periphery or at the rim of the granuloma. In contrast to the histopathology seen in tuberculosis or histoplasmosis, the center of a sarcoid granuloma does not show evidence of frank necrosis or caseation. An alveolitis often accompanies the granulomas in the lung parenchyma or intrathoracic lymph nodes. The alveolitis is composed primarily of $CD4^+$ T-helper lymphocytes, which are presumed to be of particular importance in the pathogenesis of disease.

The characteristic pathologic feature of sarcoidosis is the noncaseating granuloma. An alveolitis composed primarily of mononuclear cells may occur.

Patients with sarcoidosis most frequently are identified due to abnormalities detected on an incidental chest radiograph or because of respiratory symptoms, mainly dyspnea or a nonproductive cough. Unlike the common and early finding of crackles in patients with IPF, crackles are often absent in sarcoidosis, even in the presence of significantly abnormal imaging studies. The lung is the site most commonly involved, but many other organs may be involved with noncaseating granulomas. Eye involvement (e.g., anterior uveitis [inflammation in the anterior chamber of the eye]) and skin involvement (e.g., skin papules or plaques) are particularly common extrathoracic manifestations of sarcoidosis, but cardiac, neurologic, hematologic, hepatic, endocrine, and peripheral lymph node findings also may be seen.

Although symptoms often are insidious in onset, some patients with sarcoidosis have a more acute presentation called *Löfgren syndrome*, in which the chest radiographic finding of bilateral hilar lymphadenopathy is accompanied by erythema nodosum (painful red nodules, typically on the anterior surface of the lower legs) and acute onset of fever and lower extremity arthralgias. For unknown reasons, patients who present with Löfgren syndrome typically have an excellent prognosis, with a spontaneous remission rate greater than 80%.

The chest radiograph in sarcoidosis generally shows one of the following patterns: (1) enlargement of lymph nodes, most commonly bilateral hilar lymphadenopathy with or without paratracheal node enlargement (Fig. 11.5); (2) parenchymal lung disease (in the form of interstitial disease, nodules, or alveolar infiltrates) (Fig. 11.6); or (3) both adenopathy and parenchymal disease. HRCT scanning is more sensitive than plain chest radiography in detecting parenchymal lung disease. It may show a particularly characteristic pattern of small nodules preferentially distributed along bronchovascular bundles (Fig. 11.7). In addition, HRCT often demonstrates mediastinal lymphadenopathy that cannot be discerned on plain chest radiography.

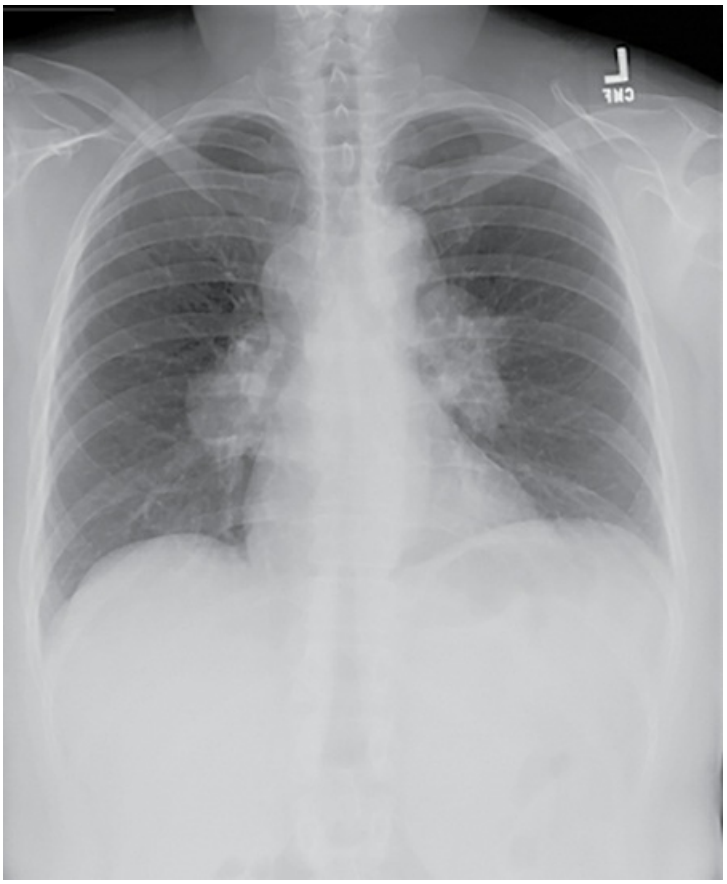

**FIGURE 11.5** Posteroanterior (PA) chest radiograph of stage I sarcoidosis showing bilateral hilar and paratracheal adenopathy without apparent pulmonary parenchymal involvement.

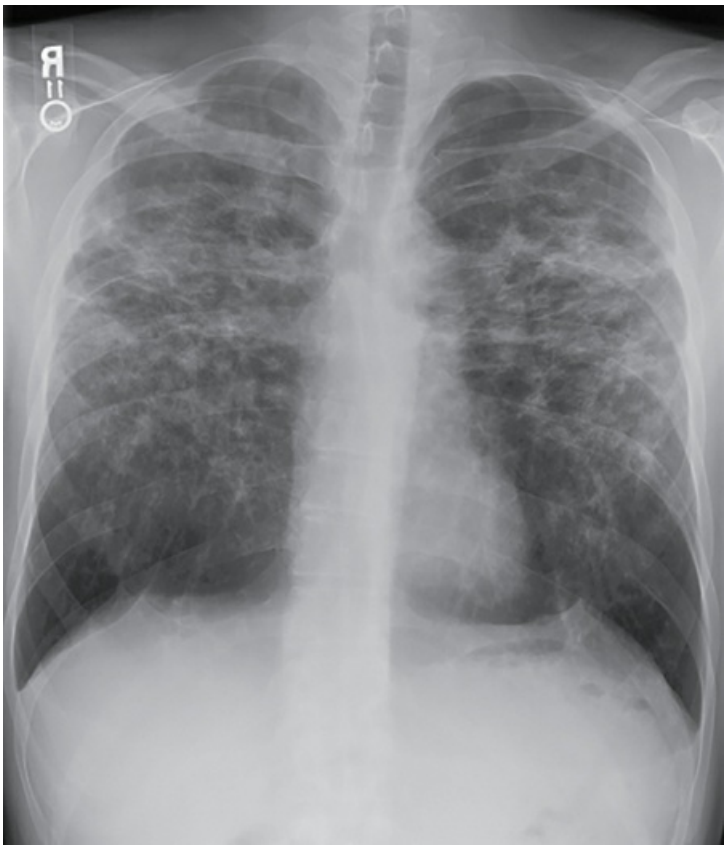

**FIGURE 11.6** Posteroanterior (PA) chest radiograph of stage III sarcoidosis. There are bilateral interstitial infiltrates, most prominent in the upper lung zones. There is no apparent hilar or mediastinal lymphadenopathy.

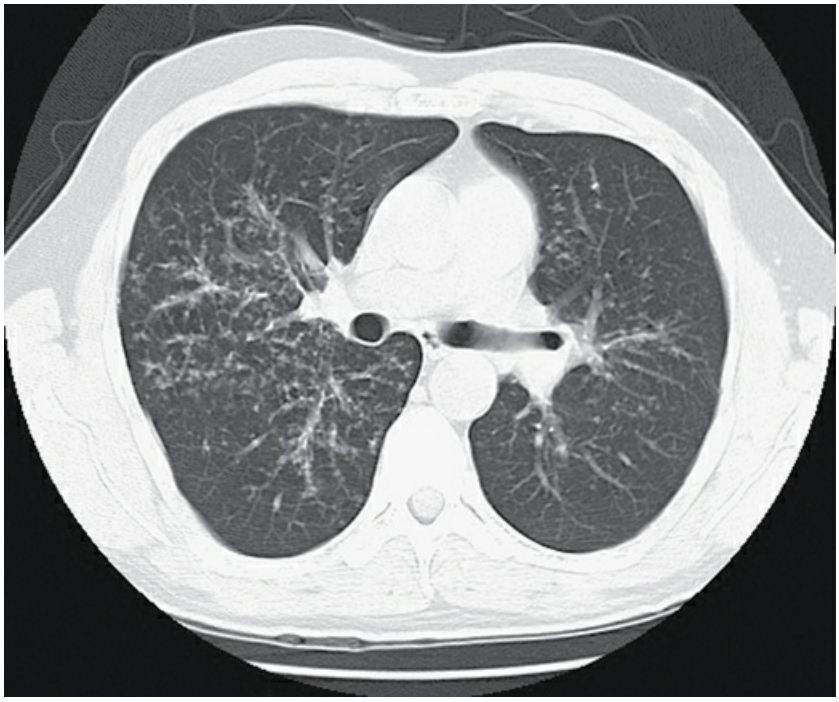

**FIGURE 11.7** Chest computed tomography scan demonstrates micronodular pattern in a patient with sarcoidosis.

The chest radiograph in sarcoidosis shows symmetrically enlarged hilar lymph nodes, interstitial lung disease, or both. The CT scan often shows a characteristic pattern of small peribronchovascular nodules accompanied by hilar and mediastinal adenopathy.

The course of the radiographic findings in sarcoidosis is quite variable. Over time, both the adenopathy and the interstitial lung disease may regress spontaneously. At the other extreme, the interstitial disease may progress to a condition of extensive scarring and end-stage lung disease, at which time the patient has severe respiratory compromise.

Patients often display immune system abnormalities. Clinically, these patients may have *anergy*, failure to respond to skin tests requiring intact delayed hypersensitivity. They also may have hypergammaglobulinemia, which is evidence of a hyperactive humoral immune system. Calcium metabolism may be abnormal in sarcoidosis, due to increased formation of the active form of vitamin D (1,25-dihydroxy-$D_3$) by activated macrophages in granulomas. Increased amounts of the active form of vitamin D lead to enhanced calcium absorption from the gastrointestinal tract, potentially causing hypercalciuria or, less frequently, hypercalcemia.

The diagnosis of sarcoidosis can be established in several ways. When the clinical diagnosis strongly suggests sarcoidosis, tissue confirmation is sometimes unnecessary. An example of such a presentation is the patient who presents with a classic picture of Löfgren syndrome. In contrast, when the patient has other symptoms or findings or when there is a question about the diagnosis, tissue sampling usually is undertaken to

look for noncaseating granulomas and rule out other causes. The lung or a lymph node in the mediastinum is generally the most appropriate source of tissue, assuming an easily accessible biopsy site such as a skin lesion or an enlarged peripheral lymph node is not available. Samples of lung tissue are frequently obtained by transbronchial biopsy through a flexible bronchoscope. Interestingly, even when the chest radiograph shows only hilar adenopathy without obvious parenchymal lung disease, the alveolar walls and small airways are often studded with granulomas that may be seen on transbronchial lung biopsy. With the increasing use of endobronchial ultrasound during bronchoscopy, needle aspiration through the airway wall into an adjacent mediastinal or hilar lymph node has become a frequent option for obtaining cellular material to identify granulomatous inflammation. Other, more invasive ways of obtaining tissue include performing a biopsy of a lymph node in the mediastinum (via mediastinoscopy) or a thoracoscopic lung biopsy. Potential biopsy sites outside the thorax depend on the presence of apparent disease in those sites. These can include the skin, peripheral lymph nodes, conjunctiva, minor salivary glands, and liver.

In sarcoidosis, transbronchial lung biopsy through a flexible bronchoscope usually demonstrates granulomas in the lung parenchyma, even when the chest radiograph does not show interstitial lung disease.

Elevated serum levels of angiotensin-converting enzyme (ACE) have been found in a large percentage of patients with sarcoidosis. This enzyme, which normally is synthesized by vascular endothelial cells, appears to be produced in the granulomas of sarcoidosis. However, because it is not specific for sarcoidosis and often is normal in the presence of relatively inactive disease, ACE levels are not considered reliable in either diagnosing sarcoidosis or assessing its response to treatment.

The natural history of sarcoidosis is quite variable. In some patients, all clinical and radiographic manifestations resolve within 1 to 2 years. Other patients have persistent radiographic changes, either with or without persisting symptoms. In general, nearly two-thirds of patients have spontaneous remissions. A minority of patients (10%-30%) show continued progression of radiographic abnormalities, with or without additional extrathoracic disease, and may have debilitating respiratory symptoms. Clinical factors associated with a worse prognosis include age at onset older than 40 years, chronic uveitis, chronic hypercalcemia, certain genetic variants, progressive pulmonary parenchymal fibrosis, and the presence of lupus pernio, a skin lesion affecting the face. In the United States, multiple studies show that Black race and low-income status are adverse prognostic factors; the degree to which socioeconomic factors explain an association with prognosis is an area of current interest.

Pulmonary function tests are most useful for quantifying functional impairment. Spirometry, lung volumes, and diffusing capacity all are measured. Perhaps surprisingly, abnormalities on pulmonary function testing do not necessarily correlate well with the severity of the findings on chest radiography or HRCT scanning. Although a restrictive pattern is most common, some patients develop either isolated or concomitant airflow obstruction, often resulting from granulomas involving airways or from distortion of airways in patients with extensive fibrosis.

The initial treatment decision confronting the clinician is whether to institute therapy

for the patient with sarcoidosis. Many patients do not require treatment, especially when the disease is not causing significant symptoms or significant functional organ involvement. The fact that the disease may improve or resolve spontaneously also complicates decisions about instituting therapy. When treatment is indicated because of symptoms and significant tissue involvement affecting organ function, first-line treatment is usually systemic corticosteroids. Because long-term treatment with systemic glucocorticoids is associated with significant adverse side effects, early consideration of steroid-sparing agents is recommended if a patient requires prolonged therapy. Commonly used nonsteroidal medications include methotrexate, azathioprine, mycophenolate mofetil, and leflunomide. In patients with refractory disease, monoclonal antibodies targeting TNF-α, particularly infliximab and adalimumab, can be employed.

The variable natural history of sarcoidosis often makes decisions about treatment difficult.

# Miscellaneous disorders involving the pulmonary parenchyma

An exhaustive description of all the remaining diseases of unknown etiology affecting the pulmonary parenchyma cannot be presented here. Instead, a brief description of several additional diseases will acquaint the reader with their major features. They include (1) PLCH, (2) lymphangioleiomyomatosis (LAM), (3) Goodpasture syndrome, (4) granulomatosis with polyangiitis (GPA), (5) chronic eosinophilic pneumonia, and (6) pulmonary alveolar proteinosis (PAP). For each of these relatively uncommon disorders, certain pathologic, clinical, or radiographic features distinguish them from the diffuse parenchymal lung diseases described earlier in this chapter. However, the defining feature for each of these disorders is a relatively specific pathologic appearance involving various components of the pulmonary parenchyma.

## Pulmonary langerhans cell histiocytosis

PLCH, previously called *eosinophilic granuloma of the lung* or *pulmonary histiocytosis X*, is thought to represent part of a spectrum of disorders involving histiocytic infiltration of one or more organ systems. Although multisystem involvement in Langerhans cell histiocytosis or histiocytosis X is typically seen with the childhood disorders called *Letterer-Siwe disease* or *Hand-Schüller-Christian disease* (not discussed here), isolated or predominant pulmonary involvement in PLCH occurs mainly in young to middle-aged adults.

Pulmonary Langerhans cell histiocytosis (previously called *eosinophilic granuloma of the lung* or *pulmonary histiocytosis X*) enters into the differential diagnosis of unexplained interstitial disease, particularly in the young or middle-aged adult.

The responsible histiocytic cell is a dendritic cell of monocyte/macrophage lineage called a *Langerhans cell*. Recently, mutations in mitogen-activated protein kinase

(MAPK) pathways and clonal origins have been identified in these dendritic cells leading to the classification of PLCH as an inflammatory myeloid neoplasm. An interesting ultrastructural feature of these cells is the presence of cytoplasmic rodlike structures called *X bodies* (hence the name *histiocytosis X*) or *Birbeck granules*, which can be seen by electron microscopy. These cells are also notable for positive immunohistochemical staining for S-100 protein. Light microscopic examination of the lung, in addition to demonstration of these histiocytes, reveals infiltration by eosinophils, lymphocytes, macrophages, and plasma cells. The process initially involves the lungs in a peribronchiolar distribution and subsequently becomes more diffuse. The disease occurs almost exclusively in current and former smokers, and it appears that dendritic cells harboring the MAPK mutations accumulate in the lungs in response to cigarette smoke. This leads to activation and migration of immune cells and to the formation of peribronchiolar nodules and the destruction of tissue.

Patients often present clinically with dyspnea, cough, or both. On chest radiograph, PLCH typically features a pattern of nodular or reticulonodular disease, which tends to be more prominent in the upper lung zones. HRCT scans show small cysts in addition to the nodular or reticulonodular changes (Fig. 11.8). The cysts occasionally rupture, leading to a spontaneous pneumothorax, which may be the presenting feature of the disease. In some cases, progression results in a pattern of extensive cystic disease and honeycombing. Unlike the typical restrictive pattern in most of the diffuse parenchymal lung diseases, pulmonary function testing in PLCH may show restrictive changes, obstructive changes, or both. The presence of air-filled cysts typically leads to normal or large lung volumes on chest radiography, despite the presence of interstitial disease.

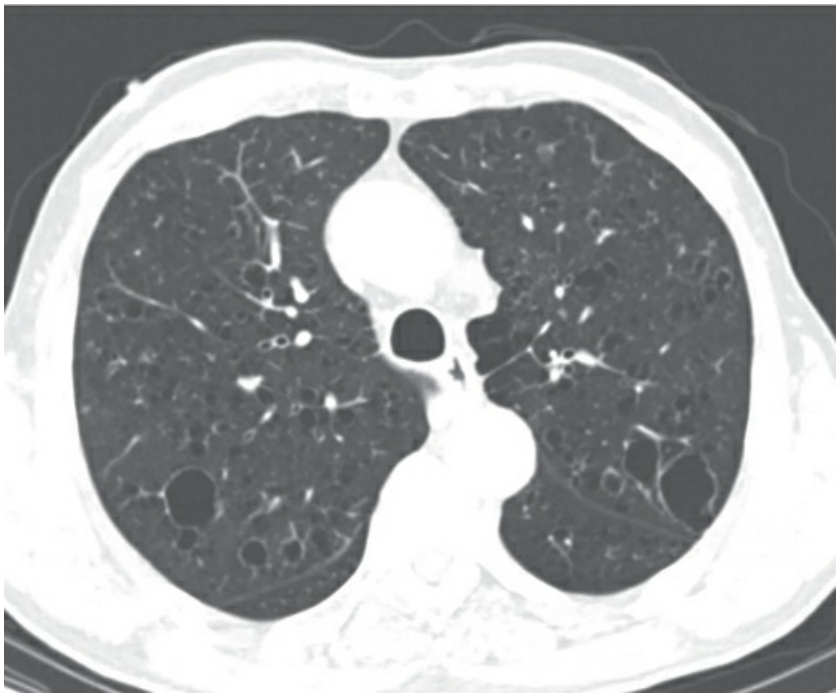

**FIGURE 11.8** Chest CT scan demonstrates multiple cysts of variable size in a patient with pulmonary Langerhans cell

histiocytosis. *Source:* (Courtesy Dr. Seth Kligerman.)

The natural history of the disease is variable. In some patients, the disease is self-limited, and the radiographic and functional changes may stabilize over time, especially with cessation of smoking. In other patients, extensive disease and significant functional impairment follow. No clearly effective treatment is available, although corticosteroids are sometimes tried if smoking cessation alone is ineffective.

## Lymphangioleiomyomatosis

*LAM* is a rare pulmonary disease, now considered to be a neoplasm, that is characterized by proliferation of atypical smooth muscle cells around lymphatics, blood vessels, and airways, accompanied by numerous small cysts throughout the pulmonary parenchyma. LAM occurs almost exclusively in women of childbearing age. This demographic, as well as the fact that LAM cells express receptors for estrogen and progesterone, suggests that hormonal influences play a role in the development of disease. In addition to occurring sporadically, LAM also develops in 30% to 40% of female patients with the genetic condition tuberous sclerosis complex (TSC). An interesting aspect is that the pathologic process seen in the lungs in LAM is essentially identical to that seen in multiple organ systems in TSC, suggesting a common pathogenetic mechanism. Germ cell mutations in two genes, *TSC1* and *TSC2*, are associated with TSC, whereas in LAM the abnormal smooth muscle cells have a mutation in the *TSC2* gene.

Lymphangioleiomyomatosis is characterized by proliferation of atypical smooth muscle cells within the lung.

The normal products of *TSC1* and *TSC2* are proteins forming a complex that acts as a potent suppressor of cell growth and proliferation through the mechanistic target of rapamycin (mTOR) pathway. Thus, the abnormal proteins lead to loss of this suppressor activity, resulting in uncontrolled growth. Patients with LAM appear to have developed an acquired mutation in smooth muscle cells in the lung, whereas patients with TSC appear to have an inborn genetic error. Furthermore, the gene product of *TSC2* also interacts directly with intracellular estrogen receptors to cause inhibition of cell growth. Presumably, a mutation in the TSC2 gene leads to loss of this function accounting for some of the hormonal influences in LAM. The LAM cells also express a lymphangiogenic growth factor called vascular endothelial growth factor D, and the finding of elevated levels of this growth factor may be helpful in establishing the diagnosis.

The clinical manifestations of LAM result from the presence of cysts and disease involvement of lymphatics, blood vessels, and airways. The overall pathologic process in the pulmonary parenchyma may lead to dyspnea and cough. Vascular involvement may result in hemoptysis, lymphatic obstruction may produce chylous (milky-appearing) pleural effusions, and airway involvement may produce airflow obstruction. Rupture of subpleural cysts can lead to development of a spontaneous pneumothorax. LAM is also often accompanied by benign tumors of the kidney called *angiomyolipomas*.

The chest radiograph typically shows a reticular pattern, and cystic changes may be seen. HRCT scanning is far superior to plain chest radiography for demonstrating cystic

disease throughout the pulmonary parenchyma (Fig. 11.9). The mechanism of cyst formation is thought to be a combination of a ball-valve phenomenon resulting from small airway obstruction by the abnormal smooth muscle proliferation and destruction of tissue attributable to elaboration of metalloproteinases by LAM cells. As is true for PLCH, results of pulmonary function testing are not typical of most diffuse parenchymal diseases, because patients may demonstrate obstructive disease, restrictive disease, or both. Similarly, lung volumes on chest radiograph appear normal or increased rather than decreased due to air trapping in the cystic regions.

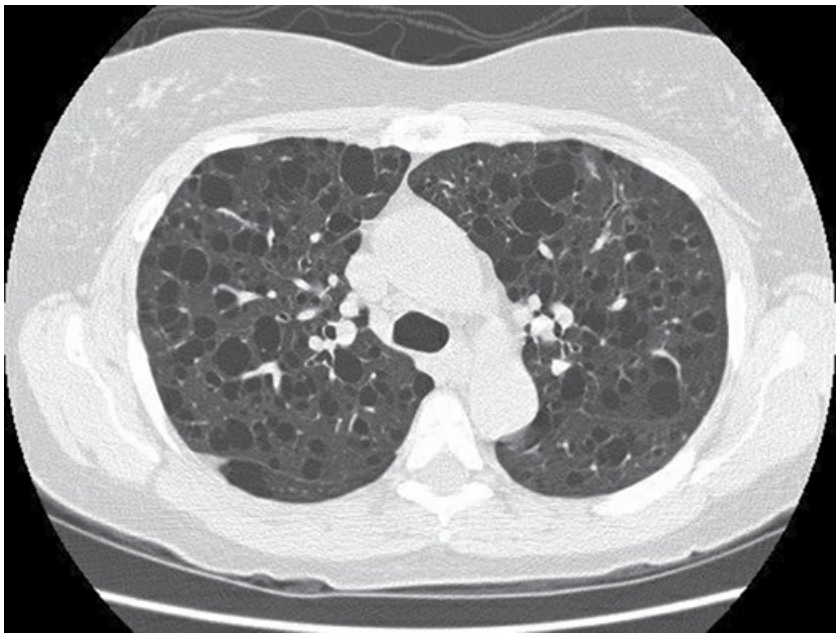

**FIGURE 11.9** Chest CT scan showing countless cysts bilaterally in a patient with lymphangioleiomyomatosis. *Source:* (Courtesy Dr. Seth Kligerman.)

Pharmacological treatment targets enhancement of the mTOR pathway-mediated suppression of smooth muscle cell proliferation, which is lost with TSC2 gene mutations. Sirolimus is an inhibitor of cell growth and proliferation through the same pathway as the *TSC2* gene products. Sirolimus (also called *rapamycin*) blocks mTOR signaling and thus restores some of the functions of the abnormal *TSC2* gene product. Sirolimus has been shown to be effective in stabilizing lung function and improving symptoms and quality of life in patients with LAM. Previously, patients were commonly treated with hormonal manipulation to block the effects of estrogen on the aberrant smooth muscle growth; however, routine anti-estrogen treatment is no longer recommended.

## Goodpasture syndrome

*Goodpasture syndrome* is a disease that has become well known not because of its incidence, which is extremely low, but because of its interesting pathogenetic and

immunologic features. Two organ systems are involved in this syndrome: the lungs and the kidneys. In the lungs, patients have episodes of pulmonary hemorrhage, and pulmonary fibrosis may develop, presumably as a consequence of the recurrent episodes of bleeding. In the kidneys, patients have a glomerulonephritis characterized by linear deposits of antibody along the glomerular basement membrane (GBM). Studies on peripheral blood have demonstrated that patients have circulating antibodies against a component of type IV collagen in their own GBM, often abbreviated as anti-GBM antibodies. These antibodies cross-react with antigens within the basement membrane of the alveolar wall, causing injury that is responsible for the clinical manifestations of the disease in both organ systems.

In Goodpasture syndrome, autoantibodies directed against the glomerular basement membrane may cross-react with the basement membrane of alveolar walls.

Why these true autoantibodies develop in patients with Goodpasture syndrome is not clear. In some patients, onset of disease appears to follow influenza infection or exposure to a toxic hydrocarbon. Presumably, injury to basement membranes and release of previously unexposed antigenic determinants are involved, or incidental formation of antibodies (against an unrelated antigen) may cross-react with alveolar and glomerular basement membranes. The disease is associated with certain human leukocyte antigens, suggesting an underlying genetic susceptibility.

Unlike many diseases associated with autoantibodies, the anti-GBM antibodies are clearly pathogenetic. Therapy for Goodpasture syndrome is based on decreasing the burden of anti-GBM antibodies presented to the lung and kidney. Plasmapheresis is capable of directly removing anti-GBM antibodies from the circulation. Immunosuppressive therapy (e.g., glucocorticoids plus cyclophosphamide), aimed at decreasing the formation of anti-GBM antibodies, usually is given in conjunction with plasmapheresis.

## Granulomatosis with polyangiitis

A group of disorders termed the *granulomatous vasculitides* may affect the alveolar wall as part of a more generalized disease. The most well known of these disorders is *GPA* (formerly called *Wegener granulomatosis*), a disease characterized primarily but not exclusively by involvement of the upper respiratory tract, lungs, and kidneys. The pathologic process in the lungs and upper respiratory tract consists of a necrotizing small-vessel granulomatous vasculitis, whereas a focal glomerulonephritis is present in the kidney. On chest radiograph, patients commonly have one or several nodules (often large) or infiltrates, often with associated cavitation of the lesion(s) (Fig. 11.10). Pulmonary hemorrhage is another potential manifestation of respiratory tract involvement. Unlike most of the other disorders of the pulmonary parenchyma discussed in Chapter 10 and this chapter, diffuse parenchymal lung disease is not common in this entity.

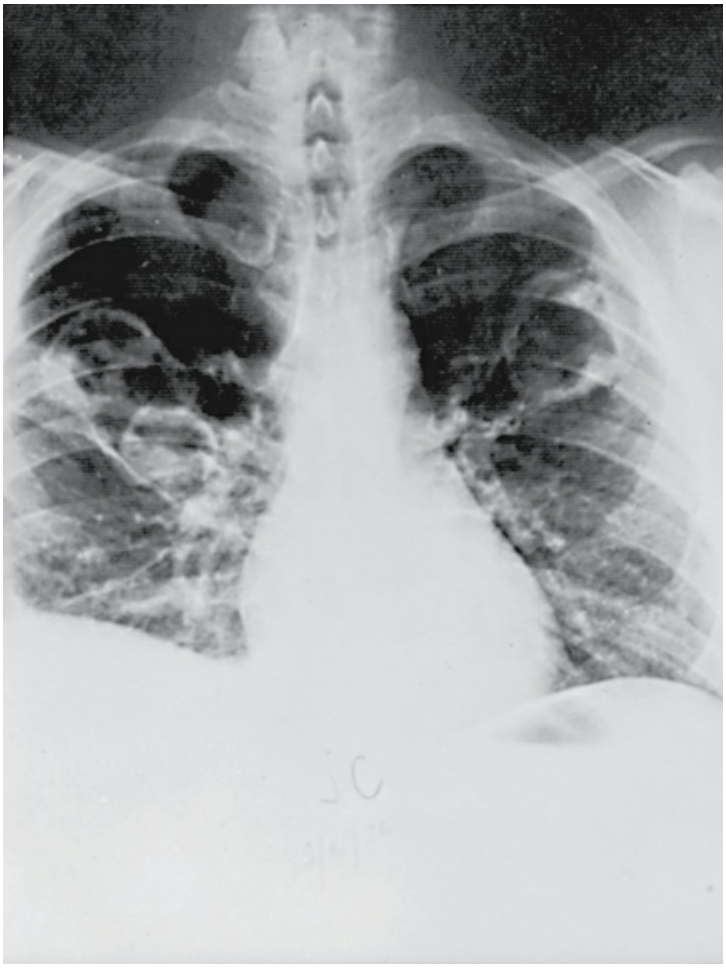

**FIGURE 11.10** Chest radiograph shows multiple cavitary pulmonary nodules in a patient with granulomatosis with polyangiitis.

Granulomatosis with polyangiitis is characterized pathologically by granulomatous vasculitis of the lung and upper respiratory tract and by glomerulonephritis. The clinical corollary is pulmonary, upper respiratory tract, and renal disease.

Patients with GPA typically have antibodies in the serum directed against proteinase 3, a serine protease present in the azurophil granules found in the cytoplasm of neutrophils. These antibodies can be detected by immunofluorescent techniques, which demonstrate a coarse, diffuse cytoplasmic pattern of staining when the patient's serum is incubated with normal neutrophils. The presence of antineutrophil cytoplasmic antibodies (ANCA), specifically with a cytoplasmic staining pattern (c-ANCA), is an important component of the diagnostic evaluation for GPA, although some patients may have negative results, especially with limited disease. Antibody levels correlate with disease activity, and these antibodies likely play some role in the pathogenesis of disease. However, other factors are probably involved as well.

Although GPA once was considered an aggressive and fatal disease, its prognosis has improved dramatically since cytotoxic agents, specifically cyclophosphamide, have been used in its treatment. Prednisone is also generally added for the initial period of therapy. More recently, rituximab, a monoclonal antibody directed against CD20 antigen found primarily on B lymphocytes, has come to play an important role in treating this disease. Although the mean survival time without treatment was 5 months, patients frequently achieve complete and long-term remissions with institution of appropriate therapy. Most patients require maintenance therapy, and rituximab is most commonly used due to a better side-effect profile compared with cyclophosphamide.

## Chronic eosinophilic pneumonia

*Chronic eosinophilic pneumonia* is a disorder in which the pulmonary interstitium and alveolar spaces are infiltrated primarily by eosinophils and, to a lesser extent, by macrophages. The clinical presentation typically occurs over weeks to months, with systemic symptoms such as fever and weight loss accompanying dyspnea and a nonproductive cough. The clues suggesting this diagnosis are often found on the chest radiograph and the routine white blood cell differential count. The radiograph frequently shows pulmonary infiltrates with a peripheral distribution and a pattern more suggestive of alveolar filling than of interstitial disease (Fig. 11.11). Because the typical radiographic pattern of pulmonary edema with congestive heart failure has central pulmonary infiltrates with sparing of the lung periphery, the prominent peripheral pattern often seen in chronic eosinophilic pneumonia has been described as the “photographic negative of pulmonary edema.” The majority of patients also have increased numbers of eosinophils in peripheral blood, although this finding is not uniformly present and therefore is not critical for the diagnosis. Bronchoalveolar lavage typically shows a high percentage of eosinophils, reflecting the pathologic process within the pulmonary parenchyma.

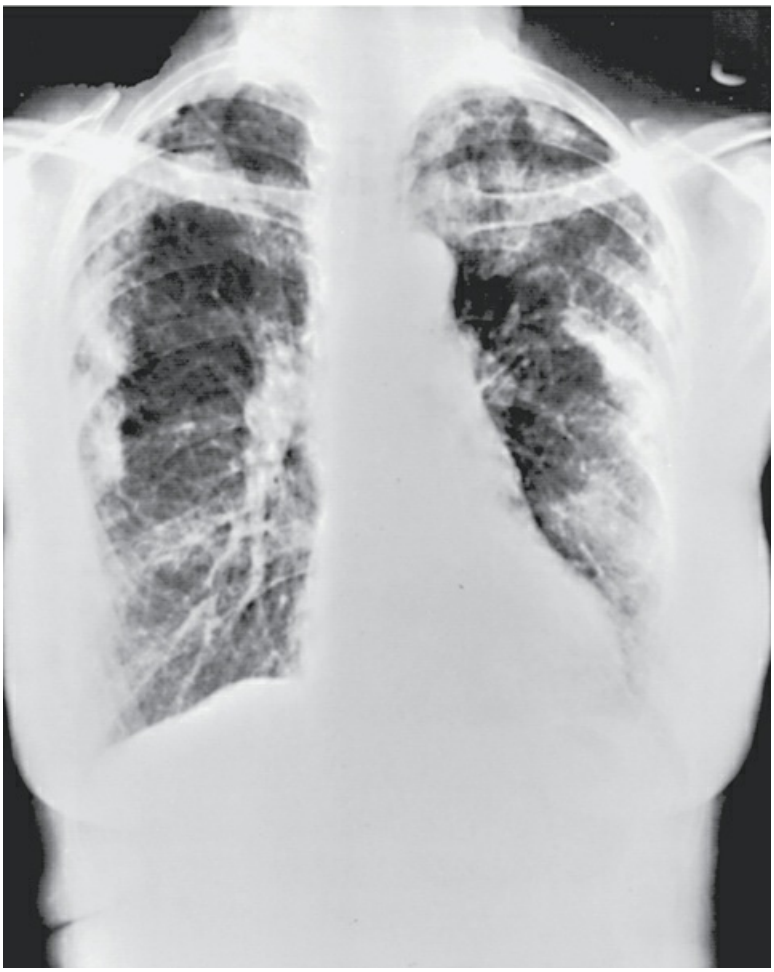

**FIGURE 11.11** Chest radiograph shows pattern of peripheral pulmonary infiltrates characteristic of chronic eosinophilic pneumonia.

Chronic eosinophilic pneumonia is often suggested on chest radiograph by a pattern of peripheral pulmonary infiltrates.

Treatment is gratifying for both patients and physicians alike because chronic eosinophilic pneumonia characteristically shows a dramatic response to corticosteroid therapy. Clinical improvement and radiographic resolution generally occur within days to weeks, although therapy often must be prolonged for months to prevent recurrence.

## Pulmonary alveolar proteinosis

*PAP* is a parenchymal lung disease in which the primary pathologic process affects the alveolar spaces, not the alveolar walls. Alveolar spaces are filled with a proteinaceous phospholipid material that represents components of pulmonary surfactant. Accumulation of surfactant components is due to either decreased degradation or surfactant dysfunction. PAP is classified as autoimmune, secondary (usually related to

hematologic malignancies), or congenital/hereditary. Autoimmune PAP (formerly known as primary or idiopathic PAP) is by far the most common of the three types and is discussed here.

In autoimmune PAP, the underlying mechanism is production of an autoantibody to granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF, acting through alveolar macrophage-specific transcription factors, affects several essential macrophage functions, including regulation of surfactant degradation, intracellular lipid metabolism, and phagocytosis. Thus, inhibiting the activity of GM-CSF via autoantibodies leads to abnormal macrophage function and decreased clearance of surfactant from the alveolar spaces. The disease mechanism was fortuitously discovered when it was noted that GM-CSF knockout mice (in which both alleles for GM-CSF are disabled) consistently developed a pulmonary process with pathology essentially identical to that seen in human PAP.

Defective uptake of surfactant by alveolar macrophages, attributable to a decreased amount or effect of GM-CSF, underlies the pathogenesis of pulmonary alveolar proteinosis.

Patients with alveolar proteinosis present primarily with dyspnea and cough. The chest radiograph is notable for bilateral alveolar infiltrates. HRCT generally shows a distinctive but not entirely pathognomonic appearance called a *crazy paving pattern* (produced by thickening of interlobular septa accompanied by ground-glass alveolar filling) that suggests the diagnosis (Fig. 11.12). Patients are susceptible to certain types of superimposed respiratory infections that are uncommon in normal hosts, especially with the organism *Nocardia*. The susceptibility to unusual pathogens appears due to abnormal macrophage function as well as to abnormalities in neutrophil function also mediated by GM-CSF.

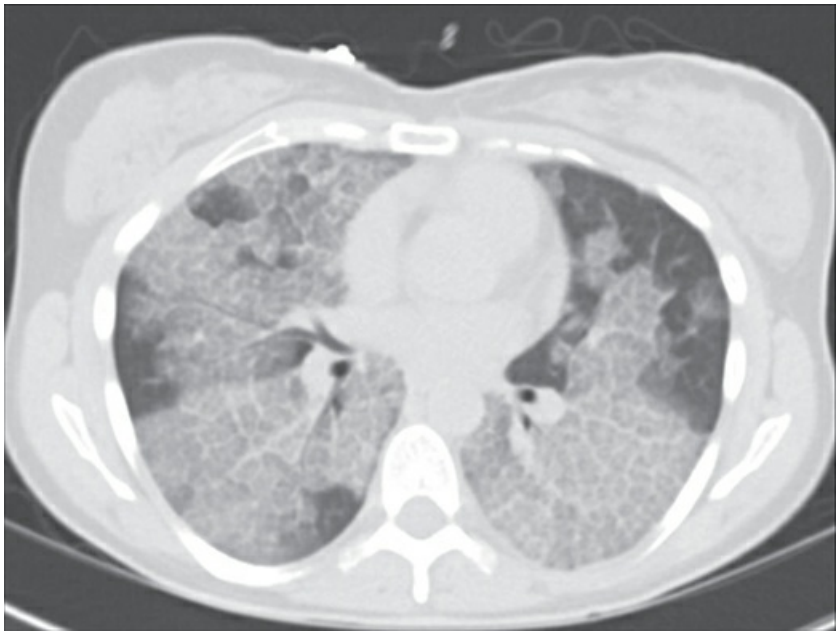

**FIGURE 11.12** Chest CT scan in a patient with pulmonary alveolar proteinosis showing the characteristic "crazy paving" pattern representing thickened interlobular septa superimposed upon ground-glass opacification.

For patients with moderate to severe disease, the primary treatment of PAP is whole-lung lavage, which involves washing out the material filling the alveolar spaces while the patient is under general anesthesia. Administration of inhaled or subcutaneous recombinant GM-CSF may be used as an alternative therapy but is still under investigation. The prognosis of the disease is relatively good, although patients may require additional treatments with whole-lung lavage. The long-term effects of exogenous GM-CSF in this disease are unknown.

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# 12: Anatomic and physiologic aspects of the pulmonary vasculature

OUTLINE



The pulmonary vasculature is responsible for transporting deoxygenated blood to the alveoli and then carrying freshly oxygenated blood back to the left atrium and ventricle for pumping through the aorta to the systemic arterial circulation. Although the pulmonary circulation is often called the "lesser circulation," the lungs are the only organ system that receives the entire cardiac output. This extensive system of pulmonary vessels is susceptible to a variety of disease processes, ranging from those that primarily affect the vasculature to those that are either secondary to airway or pulmonary parenchymal disease or due to the transport of material that is foreign to the pulmonary vessels, including blood clots.

Before diseases of the pulmonary vasculature are considered in Chapters 13 and 14, this chapter discusses a few of the general anatomic and physiologic aspects of the pulmonary vessels. Included in the discussion on physiology are several topics relating to the hemodynamics of the pulmonary circulation, as well as a brief consideration of some nonrespiratory metabolic functions of the pulmonary circulation.

## Anatomy

In contrast to the systemic arteries, which carry blood from the left ventricle to the rest of the body, the pulmonary arteries, which carry blood from the right ventricle into the lungs, are relatively low-pressure, thin-walled vessels. Under normal circumstances, the mean pressure within the main pulmonary arteries is approximately 15 mm Hg, roughly

one-sixth of the pressure in the aorta. The pulmonary trunk, which carries the outflow from the right ventricle, divides almost immediately into the right and left main pulmonary arteries, which subsequently divide into smaller branches. Throughout these progressive divisions, the pulmonary arteries and their branches travel with companion airways, closely following the course of the progressively dividing bronchial tree. By the time the vessels are considered arterioles, the outer diameter is less than approximately 0.1 mm. An important feature of the smaller pulmonary arteries is the presence of smooth muscle within the walls, which permits a vasoconstrictive response to various stimuli, particularly hypoxia, resulting in preferential routing of perfusion to well-ventilated lung units. (See Chapter 1 for discussion of $\dot{V}/\dot{Q}$ mismatch.)

The pulmonary capillaries form an extensive network of communicating channels coursing through alveolar walls. Rather than being described as a series of separate vessels, the capillary system can be viewed as a continuous meshwork or sheet bounded by alveolar walls on each side and interrupted by "posts" of connective tissue, akin to the appearance of an underground parking garage. The capillaries are in close proximity to alveolar gas, separated only by alveolar epithelial cells and a small amount of interstitium present in some regions of the alveolar wall (see Figs. 8.1 and 8.2). Overall, the capillary surface area is approximately 125 $m^2$ and represents approximately 85% of the available alveolar surface area. The architecture of this capillary system is extraordinarily well suited to the requirements of gas exchange, inasmuch as it contains an enormous effective surface area of contact between pulmonary capillaries and alveolar gas.

The pulmonary veins, which are responsible for transporting oxygenated blood from the pulmonary capillaries to the left atrium, progressively combine into larger vessels until four major pulmonary veins enter the left atrium. Unlike the pulmonary arteries and their branches, the pulmonary venous system does not follow the course of the corresponding bronchial structures until the level of the hila.

The bronchial arteries, which are part of the systemic circulation, provide nutrient blood flow to a variety of nonalveolar structures, such as the bronchi and the visceral pleural surface. There is significant variability in the anatomy of the bronchial circulation. Generally, a single bronchial artery of variable origin (upper right intercostal, right subclavian, or internal mammary artery) supplies the right lung. Two bronchial arteries, usually arising from the thoracic aorta, supply the left lung. Venous blood from the large extrapulmonary airways drains via bronchial veins into the azygos vein and eventually into the right atrium. In contrast, venous blood from intrapulmonary airways drains into the pulmonary venous system emptying into the left atrium. This blood leaving the intrapulmonary airways and draining back to the left atrium never enters the pulmonary capillary bed and thus provides a small amount of anatomic shunting of deoxygenated blood into the systemic arterial circulation.

An extensive network of lymphatic channels is also located primarily within the connective tissue sheaths around small vessels and airways. Although these channels do not generally course through the interstitial tissue of the alveolar walls, they are in sufficiently close proximity to be effective at removing liquid and some solutes that constantly pass into the interstitium of the alveolar wall.

# Physiology

## Pulmonary vascular resistance

Although the pulmonary circulation handles the same cardiac output from the right ventricle as the systemic circulation handles from the left ventricle, the former operates under much lower pressures and has substantially less resistance to flow than the latter. The systolic and diastolic pressures in the pulmonary artery are normally approximately 25 and 10 mm Hg, respectively, in contrast to 120 and 80 mm Hg in the systemic arteries. The pulmonary vascular resistance (PVR) can be calculated according to Eq. 12.1:

$$R = \text{Change in pressure} / \text{Flow} \qquad \textbf{(Eq. 12.1)}$$

The change or drop in pressure across the pulmonary circuit is the mean pulmonary artery (mPA) pressure minus the mean left atrial (mLA) pressure, and the flow is the cardiac output $\dot{Q}$ (Eq. 12.2). Thus:

$$PVR = (mPA - mLA)/\dot{Q} \qquad \text{(Eq. 12.2)}$$

Left atrial pressure is difficult to measure directly. However, a special catheter called a *pulmonary artery balloon occlusion catheter* or *Swan-Ganz catheter* is clinically used for indirect left atrial pressure measurements (Fig. 12.1). This catheter is inserted into a large vein (usually the internal jugular vein in the neck or the femoral vein in the groin) and passed through the right heart into a pulmonary artery. The catheter tip is equipped with a small soft balloon that, when inflated, lodges in a segmental pulmonary artery and temporarily blocks flow to the segment, creating a static, minimally compressible column of blood between the catheter and the left atrium. After a short period of equilibration, because there is no blood flow passing the catheter tip, the pressure measured at the tip of the catheter reflects the pressure “downstream” in the pulmonary veins and left atrium.

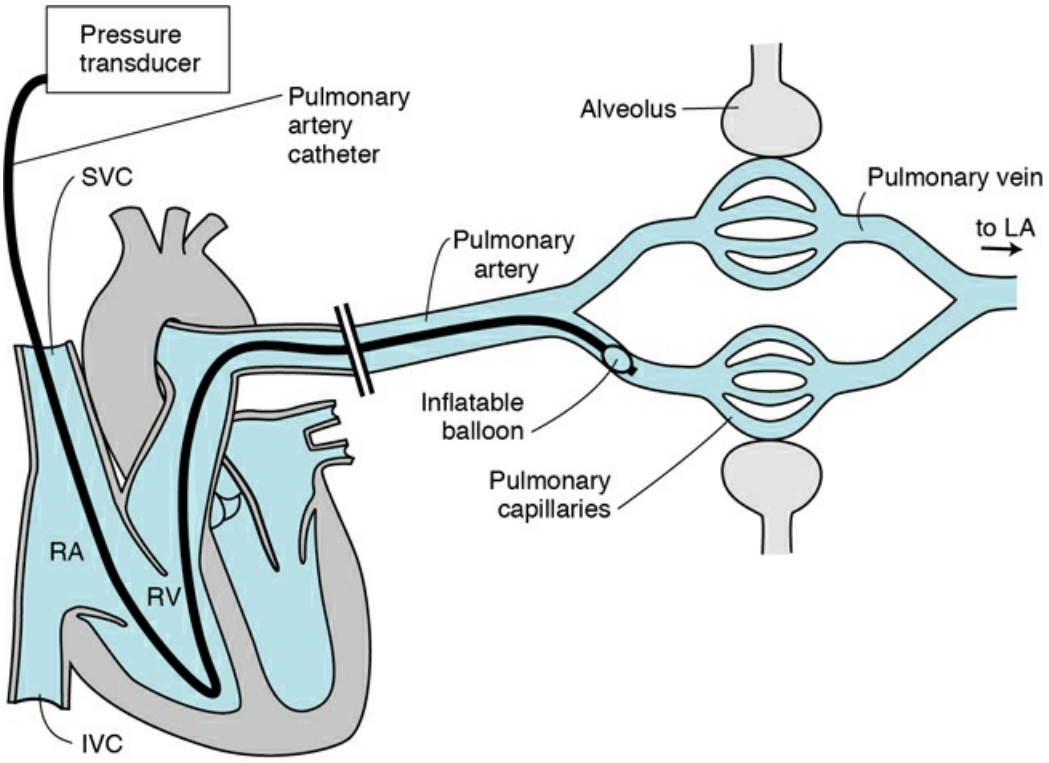


**FIGURE 12.1** Schematic diagram of pulmonary artery (Swan-Ganz) catheter positioned in a pulmonary artery. The catheter is shown with the balloon inflated, so forward flow is occluded and pressure measured at catheter tip (pulmonary artery occlusion, or pulmonary capillary wedge pressure) is pressure transmitted from pulmonary veins, which reflects simultaneous left atrial pressure. When the balloon is deflated, the pressure measured at the catheter tip is pulmonary artery pressure. *IVC*, inferior vena cava; *LA*, left atrium; *RA*, right atrium; *RV*, right ventricle; *SVC*, superior vena cava.

Pulmonary vascular resistance = (mean PA pressure – mean LA pressure)/cardiac output. LA pressure is indirectly determined from occluded PA pressure.

Assuming normal mean pulmonary artery (PA) and left atrial (LA) pressures of 15 and 6 mm Hg, respectively, along with a cardiac output of 6 L/min, the PVR is (15 – 6)/6 mm Hg/L/min = 1.5 mm Hg/L/min. This resistance is approximately one-tenth that found in the systemic circulation. (A source of confusion is that PVR may be reported in either mm Hg/L/min [also called *Wood units* in honor of physiologist Earl Wood] or in dyn·s/cm$^5$. The value in Wood units is multiplied by 80 to convert to dyn·s/cm$^5$.)

When cardiac output increases (e.g., during exercise), the pulmonary circulation is able to decrease its resistance and handle the extra flow with only a minimal increase in

pulmonary artery pressure. Two mechanisms appear to be responsible: recruitment (opening) of vessels that had not been perfused at rest and, to a lesser extent, distention of previously perfused vessels. Under normal resting conditions, many pulmonary vessels receive no blood flow, but they are capable of carrying part of the pulmonary blood flow should the pressure increase. In addition, because pulmonary vessels have relatively thin walls, they are distensible and can enlarge their diameter under increased pressure to accommodate additional blood flow. With a means for increasing the total cross-sectional area of the pulmonary vasculature on demand, the pulmonary circulation is capable of lowering its resistance when the need for increased flow arises.

When cardiac output increases, recruitment and distention of pulmonary vessels decrease pulmonary vascular resistance and prevent a significant increase in pulmonary artery pressure.

Another factor that affects PVR is lung volume. In discussing the nature of this effect, it is useful to distinguish two categories of pulmonary vessels on the basis of their size and location. One category, called *alveolar vessels*, includes the capillary network coursing through alveolar walls. When alveoli are expanded and lung volume is raised, these vessels are compressed within the stretched alveolar walls, and their contribution to PVR increases. In contrast, when alveoli are emptied and lung volume is lowered, the resistance of these alveolar vessels decreases. The other category consists of the larger vessels called *extra-alveolar vessels*. They are not compressed by air-filled alveoli. The supporting structure that surrounds the walls of these vessels has attachments to alveolar walls, and the elastic recoil of the alveolar walls provides radial traction to keep these vessels open. This concept is similar to that discussed in Chapter 6 concerning the effect of alveolar wall attachments on airway diameter (see Fig. 6.6). When lung volume is increased, elastic recoil of the alveolar walls increases, the extra-alveolar vessels become larger, and their resistance decreases. When lung volume is decreased, elastic recoil of the alveolar walls decreases, extra-alveolar vessels narrow, and their resistance increases. This differential effect of lung volume on the resistance of alveolar versus extra-alveolar vessels is shown in Fig. 12.2. The total PVR is least at the normal resting expiratory position of the lung (i.e., at functional residual capacity).

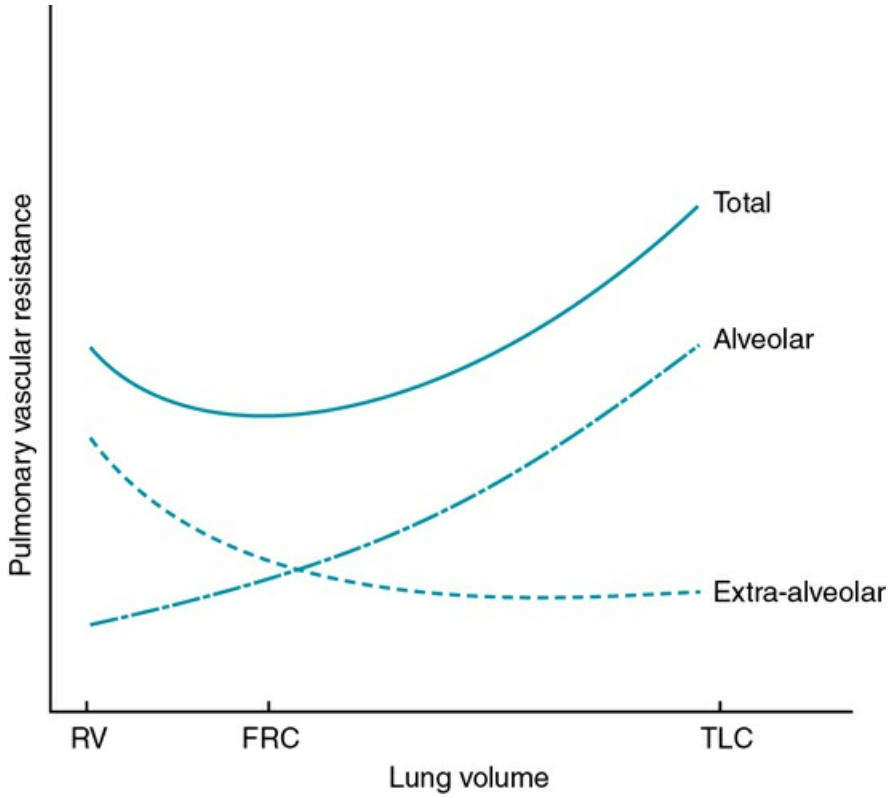


**FIGURE 12.2** Effect of lung volume on total pulmonary vascular resistance *(solid line)*, alveolar vessel resistance *(dashed-dotted line)*, and extra-alveolar vessel resistance *(dashed line)*. Note that total resistance is least at the functional residual capacity *(FRC)*. *RV*, residual volume; *TLC*, total lung capacity. *Source:* (From Taylor, A. E., Rehder, K., Hyatt, R. E., & Parker, J. C. (1989). *Clinical respiratory physiology* (p. 75). Philadelphia, PA: WB Saunders.)

## Distribution of pulmonary blood flow

The relatively low pressure in the pulmonary arteries has important implications regarding the way blood flow is distributed in the lung. When a person is in the upright position, blood going to the upper zones of the lung is flowing against gravity and must be under sufficient pressure in the pulmonary artery to make this antigravitational journey. Because the top of the lungs is approximately 15 cm above the level of the main pulmonary arteries, a pressure of 15 cm $H_2O$ is required to achieve perfusion of the apices. The mPA of 15 mm Hg (approximately 19 cm $H_2O$) is normally just sufficient to achieve flow to this region. In contrast, flow to the lower lung zones—that is, below the level of the main pulmonary arteries—is assisted by gravity. Therefore, in the upright individual, gravity provides a normal gradient of blood flow from the apex to the base of the lung, with the base receiving substantially greater flow than the apex (see Fig. 1.4). As discussed in Chapter 1, this distribution of blood flow in the lung has major

implications regarding the manner in which ventilation and perfusion are matched.

The distribution of blood flow within the lung is strongly influenced by gravity.

The three-zone model for describing the determinants of pulmonary blood flow discussed in Chapter 1 actually is more complicated now that a zone 4 has been recognized. In this zone, which occupies the base of the lung at low lung volumes, blood flow progressively diminishes as the most dependent region of the lung is approached. To explain why a zone 4 exists, we must return to the concept of extra-alveolar pulmonary vessels. At the lung bases, the weight of the lung results in decreased alveolar volume, accompanied by distortion and compression of extra-alveolar vessels. As a result, the resistance of the extra-alveolar vessels considerably increases, the total vascular resistance in this zone increases, and blood flow diminishes.

The distribution of blood flow in the lung can be measured with radioactive isotopes. A *perfusion scan* is a particularly useful technique that involves intravenous injection of radiolabeled particles, specifically macroaggregates of albumin, that are of sufficient size to lodge in the pulmonary capillaries. An external counter over the lung records the distribution of lodged particles and, hence, the distribution of blood flow to the lung. This technique, when performed in the upright individual, not only confirms the expected gradient of blood flow in the lung but also detects regions of decreased or absent perfusion in disease states, such as pulmonary embolism (see Chapter 3).

## Pulmonary vascular response to hypoxia

An important physiologic feature of the pulmonary circulation is its response to hypoxia. When alveoli in an area of lung contain gas with a low $P_{O_2}$, generally less than 60 to 70 mm Hg, the vessels supplying that region of lung undergo vasoconstriction. This response occurs primarily at the level of the small arteries or arterioles and serves as a protective mechanism by decreasing perfusion to poorly ventilated alveoli. Hence, ventilation-perfusion mismatch is decreased, and blood flow to areas with a low ventilation-perfusion ratio, from which hypoxemic blood would return to the left heart, is minimized. When localized regions of lung have a low $P_{O_2}$, the vasoconstrictive response also is localized. In these circumstances, the overall PVR does not significantly increase. However, with a more generalized decrease in $P_{AO_2}$, as in many forms of lung disease or in persons exposed to high altitude, pulmonary vasoconstriction is more generalized. In this circumstance, PVR and pulmonary artery pressure are both increased. What would be a protective response in the case of localized disease is thus detrimental in the case of generalized disease and widespread alveolar hypoxia.

Pulmonary vasoconstriction occurs in response to alveolar hypoxia. This protective mechanism reduces blood flow to poorly ventilated alveoli, minimizing ventilation-perfusion mismatch.

However, there is one setting in which such generalized pulmonary vasoconstriction in response to alveolar hypoxia is most beneficial: the fetus. In utero, the alveoli receive no aeration, making the entire lung hypoxic. The result is marked pulmonary

vasoconstriction, which is accompanied by very high PVR and diversion of blood away from the lung. Blood preferentially flows through the foramen ovale from the right to the left atrium and through the ductus arteriosus from the pulmonary artery to the aorta. This allows the majority of the blood oxygenated by the placenta to go directly into the systemic circulation of the fetus, bypassing the nonaerated lungs.

At birth, when the first few breaths are taken, the lungs expand and oxygen flows into the alveoli. The PVR falls, allowing blood to flow into the lungs. The fall in PVR is due to both the reversal of diffuse hypoxic pulmonary vasoconstriction and the mechanical effects of the inflated lung helping to open previously compressed vessels. As a result of this pulmonary vasodilation (as well as constriction of the ductus arteriosus), right ventricular output passes through the lungs, where the blood is oxygenated. Interestingly, the hypoxic vasoconstriction that persists throughout adult life may be directly related to this important fetal response.

The mechanism of hypoxic vasoconstriction is incompletely understood. One theory suggests that alveolar hypoxia is sensed by a redox sensor in the endothelial mitochondria, which generates a diffusible mediator—likely a reactive oxygen species. The mediator then acts on pulmonary vascular smooth muscle cells by inhibiting a membrane potassium ion channel, which leads to membrane depolarization and a subsequent influx of calcium ions. The increase in intracellular calcium then induces pulmonary vascular smooth muscle cell contraction. Alternatively, hypoxia may alter the release of vasoactive mediators, either increasing the release of vasoconstrictors or decreasing the release of vasodilators. Popular candidates are mediators released from vascular endothelial cells, such as the vasodilating factors nitric oxide (previously called *endothelial-derived relaxing factor*) and endogenously derived carbon monoxide, as well as the constricting factor known as *endothelin*. Nitric oxide, which is produced by vascular endothelial cells, acts via increasing cyclic guanosine monophosphate to produce vascular smooth muscle relaxation.

## Other aspects of pulmonary vascular physiology

An additional stimulus for pulmonary vasoconstriction is a low blood pH value. Although this effect is less important than the effect of hypoxia, the two stimuli appear to have a synergistic effect on increasing PVR. Any direct effect of $P_{CO_2}$ on the pulmonary vasculature appears to be small. Although hypercapnia may increase PVR, the effect is mediated by changes in blood and intracellular pH. Animal studies indicate that hypoxic vasoconstriction is attenuated by hypothermia and is enhanced by hyperthermia but there are few data in humans with regard to this phenomenon.

A low pH value in blood is an additional stimulus for pulmonary vasoconstriction.

A variety of other factors that influence pulmonary vascular tone are being increasingly recognized. Autonomic innervation of the pulmonary arterial system is present but not extensive. Sympathetic and parasympathetic stimulation have the expected opposing effects, causing vasoconstriction and vasodilation, respectively. Humoral stimuli altering vascular tone are numerous; examples include histamine and the prostaglandin products of arachidonic acid metabolism. Most recently, interest has focused on two molecules mentioned earlier in the discussion of hypoxic

vasoconstriction, each of which is known to have important effects on the pulmonary vasculature: nitric oxide (a potent vasodilator) and endothelin (a potent vasoconstrictor). Recognition of the role of these vasoactive compounds in the pathophysiology of disease states involving the pulmonary vasculature has led to the development of drugs targeting these actions that have therapeutic benefits in patients with pulmonary arterial hypertension (see Chapter 14).

Another important aspect of pulmonary vascular physiology relates to fluid movement from pulmonary capillaries into the interstitium of the alveolar wall. Because of the importance of abnormalities in fluid transport across the capillaries in acute respiratory distress syndrome and respiratory failure, this topic is discussed in detail in Chapter 29.

Finally, although the transport of blood between the heart and lungs is the most obvious function of the pulmonary vasculature, these vessels have other, nonrespiratory, metabolic functions. The pulmonary circulation has an important role in the inactivation of certain circulating bioactive chemicals. For example, serotonin (5-hydroxytryptamine) and bradykinin are primarily inactivated in the lung at the level of the vascular endothelium. In addition, angiotensin I, an inactive decapeptide that is produced in the kidney, is converted to the active octapeptide angiotensin II by angiotensin-converting enzyme, which is produced by pulmonary vascular endothelial cells. Although the metabolic functions of the pulmonary vasculature are important in modifying the effects of these substances, whether derangements in these functions are important consequences of diseases affecting the vasculature is not known.

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# 13: Pulmonary embolism

OUTLINE



Pulmonary embolism is one of the most important disorders that affect the pulmonary vasculature. It not only is found in a significant number of unselected autopsies in which a careful search is made but also has the potential both for "overdiagnosis" when not present and "underdiagnosis" when present.

The term *pulmonary embolism* or, more precisely, *pulmonary thromboembolism,* refers to movement of a blood clot from a systemic vein through the right side of the heart to the pulmonary circulation, where it lodges in one or more branches of the pulmonary artery. The clinical consequences of this common problem are quite variable, ranging from none to sudden death, depending on the size of the embolus and the underlying cardiopulmonary condition of the patient. Although pulmonary embolism is intimately associated with the development of a thrombus elsewhere in the circulation, this chapter focuses on the pulmonary manifestations of thromboembolic disease, and not on the clinical effects or diagnosis of the clot at the site of formation, usually in the deep veins of the lower extremities.

## Etiology and pathogenesis

A thrombus—that is, a blood clot—is the material that travels to the pulmonary circulation in pulmonary thromboembolic disease. Other material can also travel via the vasculature to the pulmonary arteries, including tumor cells or fragments, fat, amniotic fluid, and a variety of foreign materials that can be introduced into the circulation. This text does not consider these other (much less common) types of embolism, which usually have quite different clinical presentations than thromboemboli.

In the majority of cases, the lower extremities are the source of thrombi that embolize to the lungs. Although these thrombi frequently originate in the veins of the calf, extension of the clots proximally to involve the larger veins of the thigh is necessary to produce sufficiently sized thromboemboli that can obstruct major portions of the pulmonary vascular bed and become clinically important. Rarely do pulmonary emboli originate in the arms, pelvis, or right-sided chambers of the heart; combined, these sources probably account for less than 10% of all pulmonary emboli. However, the source of thrombi in embolic disease may not be clinically apparent. In fact, only about 50% of patients with pulmonary emboli have previous clinical evidence of venous thrombosis in the lower extremities or elsewhere.

Thrombi in the deep veins of the lower extremities are the usual source of pulmonary emboli.

Three factors are commonly cited as potential contributors to the genesis of venous thrombosis: (1) alteration in the mechanism of blood coagulation (i.e., hypercoagulability), (2) damage to the vessel wall endothelium, and (3) venous stasis or stagnation of blood flow. In practice, many specific risk factors for thromboemboli have been identified, including immobilization (e.g., bed rest, prolonged sitting during travel, immobilization of an extremity after fracture), the postoperative state, heart failure, obesity, underlying malignancy, pregnancy and the postpartum state, the use of oral contraceptives, and chronic deep venous insufficiency. Patients at particularly high risk are those who had trauma or surgery related to the pelvis or lower extremities, especially hip fracture, or hip or knee replacement.

A number of genetic predispositions to hypercoagulability are recognized. They include deficiency or abnormal function of proteins with antithrombotic activity (e.g., antithrombin III, protein C, protein S) or the presence of abnormal variants of some of the clotting factors that are part of the coagulation cascade, especially factor V and prothrombin (factor II). The most common genetic defect associated with hypercoagulability is called *factor V Leiden*. It is usually due to a single base pair substitution leading to replacement of an arginine residue by glutamine, causing the activated factor V protein to become more resistant to degradation by activated protein C. Individuals who are heterozygous for factor V Leiden have a three- to fivefold increased lifetime risk for venous thrombosis. The much less common homozygous state confers a significantly higher risk. In the genetic variant of prothrombin often called the *prothrombin gene mutation*, there is a single base pair deletion that appears to affect posttranslational mRNA processing, leading to increased plasma levels of prothrombin and predisposition to venous thrombosis.

Although deficiencies of the antithrombotic proteins (antithrombin III, protein C, and protein S) are rare, factor V Leiden may have a prevalence of up to 5% in European, North American, Lebanese, and Greek populations. Both factor V Leiden and the prothrombin gene mutation are relatively common in the North American White population but are rare among Black and Asian populations in the United States. The fact that factor V Leiden is found in some 20% of patients with a first episode of venous thromboembolism suggests that it is an important risk factor.

## Pathology

Pathologic changes that result from occlusion of a pulmonary artery branch depend to a large extent on the location of the occlusion and the presence of other disorders that compromise $O_2$ supply to the pulmonary parenchyma. There are two major consequences of vascular occlusion in the lung parenchyma distal to the site of occlusion. First, if minimal or no other $O_2$ supply reaches the parenchyma, either from the airways or from the bronchial arterial circulation, frank necrosis of lung tissue (pulmonary infarction) will result. According to one estimate, only 10% to 15% of all pulmonary emboli result in pulmonary infarction. It is sometimes said that compromise of two of the three $O_2$ sources to the lung (pulmonary artery, bronchial artery, and alveolar gas) is necessary before infarction results. Second, even when parenchymal integrity is maintained and infarction does not result, hemorrhage and edema often occur in lung tissue supplied by the occluded pulmonary artery.

Embolic occlusion of a vessel may lead to infarction, hemorrhage, and/or edema of the lung parenchyma.

Either with or without frank pulmonary infarction, the pathologic process generally extends to the visceral pleural surface, so corresponding radiographic changes are often pleura-based. In some cases, pleural effusion also may result. As part of the natural history of infarction, there is generally contraction of the infarcted parenchyma and eventual formation of a scar. When infarction of the affected lung has not occurred, resolution of the process and resorption of the blood may leave few or no permanent pathologic sequelae.

In many cases, neither of these pathologic changes occurs, and relatively little alteration of the distal lung parenchyma is found, presumably because of incomplete occlusion or sufficient oxygen from other sources. Frequently, the thrombus quickly fragments or undergoes a process of lysis, with smaller fragments moving progressively distally in the pulmonary arterial circulation. Whether this rapid process of clot dissolution occurs is important in determining the pathologic consequences of pulmonary embolism.

With clots that do not fragment or lyse, generally a slower process of organization in the vessel wall and eventual recanalization are seen. Webs may form within the arterial lumen and sometimes are detected on a pulmonary arteriogram or on postmortem examination as the only evidence for prior embolic disease.

## Pathophysiology

When a thrombus migrates to and lodges within a pulmonary vessel, a variety of consequences ensue. They relate not only to mechanical obstruction of one or more vessels but also to the secondary effects of various mediators released from the thrombus and ischemic tissue. The effects of mechanical occlusion of the vessels are discussed first, followed by a consideration of how chemical mediators contribute to the clinical effects.

When a vessel is occluded by an embolus and forward blood flow through the vessel

stops, the perfusion of pulmonary capillaries normally supplied by that vessel ceases. If ventilation to the corresponding alveoli continues, it is wasted and this region of lung serves as dead space. The combination of wasted ventilation and redistribution of blood flow away from the embolized region of lung can contribute to $\dot{V}/\dot{Q}$ mismatch, which is the primary mechanism for hypoxemia in pulmonary embolism. As discussed in Chapter 1, assuming that total minute ventilation remains constant, increasing the dead space automatically decreases alveolar ventilation and hence $CO_2$ elimination. However, despite the potential for $CO_2$ retention in pulmonary embolic disease, hypercapnia is an unusual consequence of pulmonary embolism, mainly because patients routinely increase their minute ventilation after an embolism occurs and more than compensate for any increase in dead space. In fact, the usual consequence of a pulmonary embolus is hyperventilation and *hypocapnia*, rather than hypercapnia. Hyperventilation is believed to occur because of the stimulation of respiratory drive by mediator release and activation of irritant receptors in the lung. However, if minute ventilation is fixed (e.g., in an unconscious or anesthetized patient whose ventilation is controlled by a mechanical ventilator), a $P_{CO_2}$ rise may result from the increase in dead space caused by a relatively large pulmonary embolus.

In addition to creating an area of dead space, another potential consequence of mechanical occlusion of one or more vessels is an increase in pulmonary vascular resistance. As discussed in Chapter 12, the pulmonary vascular bed is capable of recruitment and distention of vessels. Experimental evidence indicates that there is no increase in resistance or pressure in the pulmonary vasculature until approximately 50% to 70% of the vascular bed is occluded. However, the experimental model is somewhat different from the clinical setting because the release of chemical mediators may cause vasoconstriction and additional compromise of the pulmonary vasculature.

Pulmonary emboli are typically associated with hypocapnia resulting from an increase in overall minute ventilation.

With further limitation of the vascular bed by the combination of mechanical occlusion and the effects of chemical mediators, the pulmonary vascular resistance may increase enough that the right ventricle cannot overcome the acute increase in its afterload. As a result, the forward output of the right ventricle may diminish, blood pressure may fall, and the individual may have a syncopal (fainting) episode or develop cardiogenic shock. In addition, “backward” failure of the right ventricle may occur, which manifests acutely with an elevation of systemic venous pressure and appears on physical examination as distention of the jugular veins.

The hemodynamic consequences of acute pulmonary embolism depend, to a large extent, on the presence of preexisting emboli and whether underlying pulmonary vascular disease or cardiac disease is present. When emboli have occurred previously, the right ventricular wall has already thickened (hypertrophied), and higher pressures can be generated and maintained. On the other hand, an additional embolus in an already compromised pulmonary vascular bed may act as “the straw that broke the camel’s back” and induce decompensation of the right ventricle.

In addition to the direct mechanical effects of vessel occlusion, thrombi result in the release of chemical mediators that have secondary effects on both the airways and blood

vessels of the lung. Platelets that adhere to the thrombus are an important source of mediators, such as histamine, serotonin, and prostaglandins. Injury to the pulmonary arterial endothelium by the clot results in the increased release of endothelin-1, a potent vasoconstrictor, and the decreased production of nitric oxide, a vasodilator. Bronchoconstriction—largely at the level of small airways—appears to be an important consequence of mediator release and is thought to contribute to the hypoxemia that commonly accompanies pulmonary embolism. In addition, areas of low ventilation and inappropriately high perfusion appear to develop because the process of hypoxic vasoconstriction becomes compromised by mediators related to thromboemboli. However, if vasoconstriction of pulmonary arteries and arterioles predominates, this adds to the likelihood of significant cardiovascular compromise.

Three additional features of the pathophysiology of pulmonary embolism are noteworthy. First, as a result of vascular compromise to one or more regions of lung, synthesis of the surface-active material surfactant in the affected alveoli is compromised. Consequently, alveoli may be more likely to collapse, and liquid more likely may leak into alveolar spaces. Second, hypocapnia appears to have the effect of inducing secondary bronchoconstriction of small airways. With the hypocapnia that occurs in pulmonary embolism, and particularly with the low alveolar $P_{CO_2}$ in the dead space regions of lung, secondary bronchoconstriction results. Both of these mechanisms, along with the small airway constriction induced by chemical mediators, may contribute to the volume loss or atelectasis frequently observed on chest radiographs of patients with pulmonary embolism. Shunt physiology also may contribute to hypoxemia because of either perfusion of the atelectatic lung or elevation of the right heart pressures producing intracardiac shunting across a patent foramen ovale.

A variety of bioactive substances are inactivated in the lung (see Chapter 12). Whether pulmonary embolism disturbs some of these nonrespiratory metabolic functions of the lung is not clear, and whether clinical consequences might ensue from such a potential disturbance is unknown.

## Clinical features

Most frequently, pulmonary embolism develops in the setting of one of the risk factors mentioned earlier. Commonly, the embolus produces no significant symptoms, and the entire episode may go unnoticed by the patient and physician. When the patient does have symptoms, acute onset of dyspnea is the most frequent complaint. Less common is pleuritic chest pain or hemoptysis. Syncope is an occasional presentation, particularly in the setting of a *massive pulmonary embolism*, defined as acute pulmonary embolism causing hemodynamic instability and sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support).

On physical examination, the most common findings are tachycardia and tachypnea. The chest examination may be entirely normal or may reveal a variety of nonspecific findings such as decreased air entry, localized crackles, or wheezing. With pulmonary infarction extending to the pleura, a pleural friction rub may be detected, and evidence of a pleural effusion may be found. Cardiac examination may reveal acute right ventricular overload (i.e., acute cor pulmonale), in which case the pulmonic component of the second heart sound ($P_2$) is increased, a right-sided $S_4$ is heard, and a right

ventricular heave may be present. If the right ventricle fails, a right-sided $S_3$ may be heard and jugular veins may be distended. Examination of the lower extremities may reveal changes suggesting a thrombus, including tenderness, swelling, or a cord (palpable clot within a vessel). However, only a minority of patients (approximately 10%) with emboli arising from leg veins have clinical evidence of deep venous thrombosis, so the absence of these findings should not be surprising or overly reassuring.

Common symptoms of pulmonary embolism:

1. Dyspnea
2. Pleuritic chest pain
3. Hemoptysis
4. Syncope

## Diagnostic evaluation

Diagnosis of acute pulmonary embolism can be challenging, and the approach depends on the clinician's level of suspicion, or *pretest probability*, of pulmonary embolism. As an example, for patients in whom the diagnosis is considered less likely, the clinician may start with a D-dimer assay (discussed later). Most patients who present with acute dyspnea or chest pain will have a chest radiograph and oxygen saturation checked by pulse oximetry. The radiographic findings in an acute pulmonary embolism are quite variable. Usually, the chest radiograph is normal. When it is not, the abnormalities often are nonspecific, including areas of atelectasis or elevation of a hemidiaphragm, indicating volume loss. Volume loss may be related to decreased ventilation to the involved area due to small airways constriction and possibly loss of surfactant. If pleuritic chest pain is present, the patient may try to reduce pain by breathing more shallowly, which contributes to atelectasis.

Occasionally, the chest radiograph reveals a localized area of decreased lung vascular markings corresponding to the region where the vessel has been occluded. This finding is called the *Westermark sign*, but it is often difficult to read unless prior radiographs are available for comparison. With a large proximal embolus, enlargement of a pulmonary artery near the hilum occasionally occurs secondary to distention of the vessel by the clot itself. An apparent abrupt termination of the vessel may occur, although this is usually difficult to see on a plain chest radiograph.

Both infarction and pulmonary hemorrhage may appear as an opacified region on the radiograph. Classically, the density is shaped like a truncated cone, fanning out toward and reaching the pleural surface. This finding, called a *Hampton hump*, is relatively infrequent. Pleural effusions may be seen as an accompaniment of pulmonary embolic disease. Pleural effusions associated with pulmonary embolism may be either exudative or transudative and contain a variable number of red blood cells.

Arterial blood gas values typically show a widened alveolar-arterial difference in partial pressure of oxygen ($P_{AO_2}$–$Pa_{O_2}$ [$AaD_{O_2}$]), a low $Pa_{O_2}$, and respiratory alkalosis, with hypocapnia occurring in more than 80% of cases. As $P_{CO_2}$ is decreased, arterial $P_{O_2}$

is higher than it would be if hyperventilation was not present. Occasionally, $P_{O_2}$ is normal, so the presence of a normal $P_{O_2}$ does not exclude the diagnosis of pulmonary embolism. Unfortunately, because of the variability in values, arterial blood gases are not very useful in determining the likelihood of pulmonary embolism.

Characteristic arterial blood gas values in pulmonary embolic disease:

1. Decreased $P_{O_2}$ and widened $AaD_{O_2}$
2. Decreased $P_{CO_2}$
3. Increased pH

The measurement of plasma D-dimer levels is commonly used as part of the diagnostic strategy for venous thromboembolic disease, especially in patients who are less likely to have a pulmonary embolism. D-dimer is a degradation product of cross-linked fibrin; therefore, levels are increased in the setting of thrombosis of any type. Plasma levels of D-dimer typically are increased in the setting of venous thrombosis but also are increased in many other conditions including trauma, surgery, pregnancy, cancer, and inflammation. Thus, D-dimer testing for venous thrombosis or pulmonary embolism is very sensitive, but the test is quite nonspecific. Previously, the interpretation of D-dimer testing was complicated by the use of different assays with varying sensitivity and specificity. However, the superior sensitivity and high negative predictive value of the quantitative enzyme-linked immunosorbent assay (ELISA) have established it as the standard D-dimer test. When the D-dimer measurement is used in clinical practice, normal levels are considered as strong evidence against thromboembolic disease. Thus, a normal D-dimer level is helpful in excluding the diagnosis, especially in the patient with a low pretest probability of having a pulmonary embolus, but an elevated level is considered nonspecific and therefore does not establish the diagnosis definitively.

Recommendations for the best radiologic test to diagnose pulmonary embolism have shifted in the last three decades. Traditionally, the major screening test for pulmonary embolism had been the perfusion lung scan (described in Chapter 3), but contrast computed tomographic angiography (CTA) is now used either instead of, or in addition to, perfusion lung scanning. Evaluation of the large veins in the lower extremities, typically using ultrasound techniques, is another commonly used diagnostic strategy. Identification of a clot in a vein above the popliteal fossa warrants the same treatment acutely as a documented pulmonary embolus and often obviates the need for further evaluation.

The technique of CTA (discussed in Chapter 3) is the most commonly used modality in the diagnosis of pulmonary embolism (Fig. 13.1). CTA offers the significant advantage of high-quality visualization of the lung parenchyma, which is helpful in considering the likelihood of competing diagnoses, such as pneumonia. In addition, in many centers, CTA can be performed more quickly and is more readily available than ventilation-perfusion scanning. However, the radiation dose associated with CTA, especially to the breast and chest, is significantly higher than with ventilation-perfusion scanning, so despite its advantages CTA has not completely replaced perfusion scanning as a diagnostic modality. The clinician must weigh the risks and benefits, as well as the

practical issues of test availability and interpretation, for each patient in whom the diagnosis of pulmonary embolism is being considered.

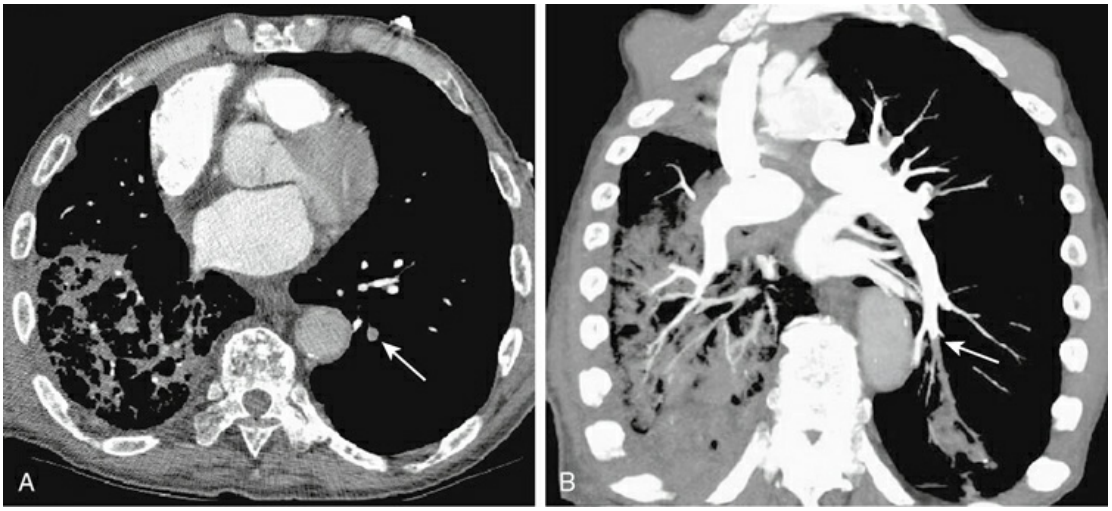


**FIGURE 13.1** Chest computed tomographic angiography shows pulmonary embolus in the midsized vessel in the left lung. **A,** Standard cross-sectional view shows a blood vessel (seen on end) filled by a clot rather than radiopaque contrast dye *(arrow)*. **B,** Image displayed in a reformatted oblique view shows the same vessel in its longitudinal course. The *arrow* marks the absence of radiopaque dye in the vessel at the edge of the clot.
*Source:* (Courtesy Dr. Phillip Boiselle.)

A perfusion lung scan is performed by injecting radiolabeled macroaggregated albumin particles into a peripheral vein. In areas of normal blood flow in the lungs, the albumin particles lodge in a fraction of the small vessels that have been perfused. When blood flow is obstructed by a clot within the pulmonary arterial system, perfusion lung scanning demonstrates no labeled albumin and, therefore, an absence of perfusion to the region of lung supplied by the occluded vessel (Fig. 13.2). If the results of the scan are normal, pulmonary embolism can be excluded. However, perfusion abnormalities do not automatically indicate the presence of embolic disease. False-positive lung scans are common because local decreases in blood flow may result from primary disease of the lung parenchyma or the airways. A ventilation scan, which involves inhalation of a xenon radioisotope, is often added because if regions of decreased blood flow are secondary to airway disease, corresponding abnormalities should be seen on the ventilation scan. If a defect in perfusion is due to a pulmonary embolism, ventilation still will be present in the area, and the perfusion defect will be *mismatched* (i.e., will not have a corresponding ventilation defect). If parenchymal disease (e.g., pneumonia) is the cause of a perfusion defect, the corresponding abnormality should be seen on the chest radiograph.

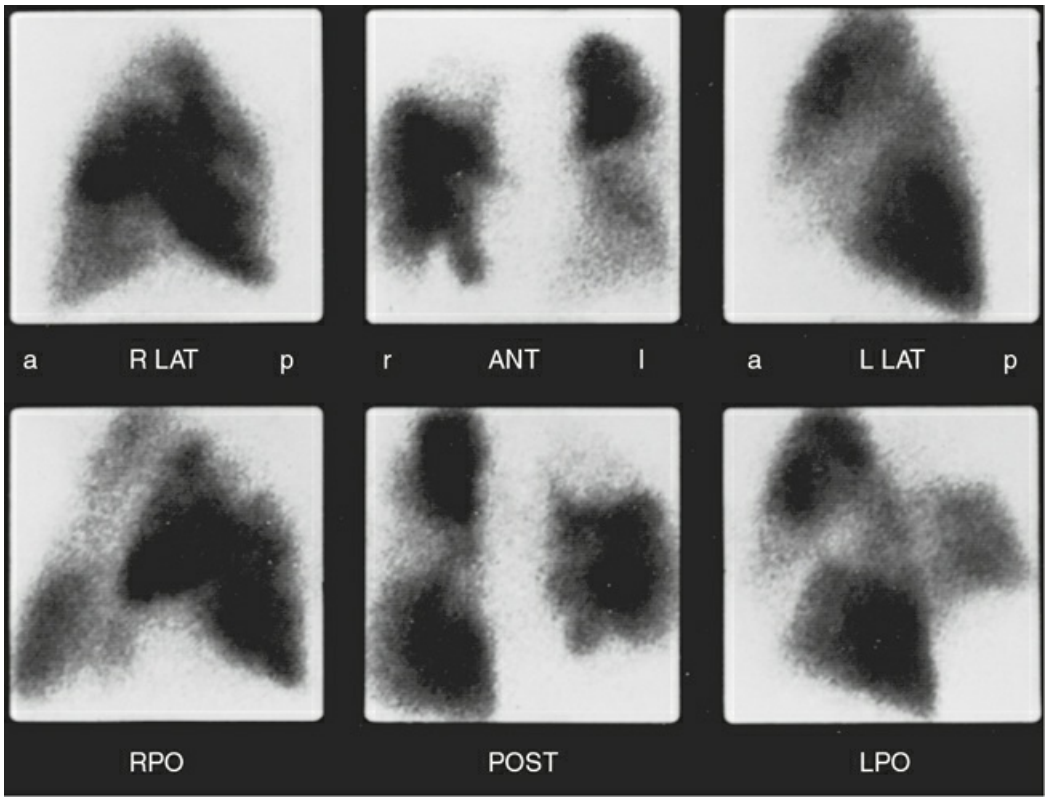


**FIGURE 13.2** Positive perfusion scan shows multiple perfusion defects in a patient with pulmonary emboli. Six views of complete scan are shown: right lateral *(R LAT)*, anterior *(ANT)*, left lateral *(L LAT)*, right posterior oblique *(RPO)*, posterior *(POST)*, and left posterior oblique *(LPO)*. Compare with normal scan results in Fig. 3.12. *a,* anterior; *l,* left; *p,* posterior; *r,* right. *Source:* (Courtesy Dr. Henry Royal.)

Interpretation of the perfusion lung scan is a complicated process that depends on the clinical setting, results of the chest radiograph, and frequently the findings on a ventilation lung scan. As the perfusion scan often is not definitive, a probability is placed on the likelihood of pulmonary embolism, taking into account the size and number of defects and the presence or absence of corresponding abnormalities on the radiograph and ventilation lung scan. The scan results are analyzed in conjunction with the *pretest probability* of pulmonary embolism, the term used to represent the clinician's assessment of the likelihood of pulmonary embolism based on the patient's clinical presentation.

When the lung scan is inconclusive, it is critical that additional diagnostic evaluation be performed. Different options for further investigation are available, focusing either on the veins of the lower extremities or on the pulmonary vasculature itself. However, because lower extremity studies are often negative even in the presence of documented pulmonary embolism, a negative lower extremity study does not preclude the need for further evaluation of the pulmonary arteries if there is a reasonably high suspicion of

pulmonary thromboembolism.

Major techniques for the diagnosis of pulmonary emboli include chest computed tomographic angiography (CTA), ventilation–perfusion lung scanning, and conventional pulmonary angiography.

Long considered the gold standard for confirmation of pulmonary embolism, *conventional pulmonary angiography* is now rarely performed for this indication (Fig. 13.3). In this technique, direct evaluation of the pulmonary arterial system to identify intraluminal thrombus is accomplished invasively by advancing a catheter through a jugular or femoral vein through the right heart and injecting radiographic contrast material directly into the pulmonary arteries. Compared with CTA, pulmonary angiography is invasive, more expensive, and requires higher doses of radiation; therefore, it is not recommended in a standard evaluation.

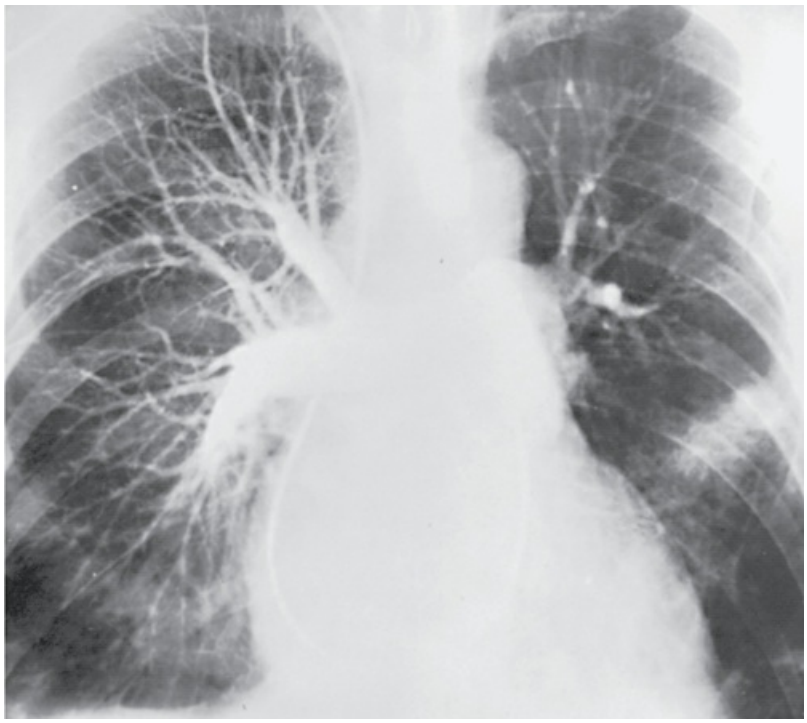

**FIGURE 13.3** Positive results of pulmonary angiogram show occlusion of the vessel supplying the left lower lobe. The area of density left mid-lung probably represents pulmonary infarction. *Source:* (Courtesy Dr. Morris Simon.)

Although echocardiography is not useful for diagnosis of pulmonary embolism, it is commonly performed as a supplementary test to assess the impact of documented embolic disease on pulmonary artery pressure and right ventricular function. In addition, in a patient with suspected pulmonary embolism who is hemodynamically unstable, evidence of right ventricular failure on echocardiography serves as

presumptive evidence that the hemodynamic instability is due to acute pulmonary thromboembolism unless another cause is implicated.

## Treatment

In addition to supporting oxygenation and circulation as needed, the standard treatment of a pulmonary embolus involves prompt initiation of anticoagulant therapy, usually beginning with subcutaneous low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin, followed by an oral agent administered for at least 3 to 6 months. LMWH has a number of potential advantages over unfractionated heparin, including a lower risk of heparin-induced thrombocytopenia and more reliable pharmacokinetics. Consequently, in most cases, LMWH does not require frequent laboratory monitoring of coagulation tests to guide dosage adjustment, and it can be given subcutaneously in one or two daily doses, avoiding the need for continuous intravenous infusion. For many years, the only oral agents used to complete therapy were coumarin-derived vitamin K antagonists, such as warfarin, which required frequent laboratory monitoring and dose adjustments. However, many newer oral anticoagulants that do not require routine laboratory monitoring are now available. These newer agents include direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g., apixaban and rivaroxaban).

Therapeutic options for pulmonary embolism:

1. Anticoagulation (heparin, warfarin, direct thrombin inhibitors, factor Xa inhibitors)
2. Thrombolysis (tPA, streptokinase, urokinase)
3. Inferior vena caval filter
4. Catheter-based or surgical removal of the clot (embolectomy)

By far the most important aspect of treating pulmonary embolism is achieving prompt, adequate anticoagulation. For the most part, after a patient with an embolus that has already entered the pulmonary circulation has sought medical attention, the biggest danger derives from a recurrent embolus that leads to hemodynamic instability. Therefore, treatment in high-risk patients is frequently started before the diagnosis is confirmed.

The rationale for the use of anticoagulants is to prevent the formation of new thrombi or the propagation of existing thrombi (in the legs), not to dissolve clots that have already embolized to the lungs. In the setting of massive pulmonary embolism and hemodynamic compromise, pharmacologic and/or catheter-based mechanical options are available to dissolve, break up, or remove clots and decrease their hemodynamic impact. Thrombolytic agents, particularly recombinant tissue plasminogen activator (rtPA), can lyse recent blood clots; they are ideally given within the first hours after the embolic event but may have some effect even up to 2 weeks after the embolism. Catheter-based options to decrease clot burden include both local delivery of a thrombolytic agent and mechanical fragmentation or removal of the clot. Use of a thrombolytic agent or catheter-based intervention is then followed by standard

anticoagulant therapy.

In some circumstances, the treatment of pulmonary embolism involves placement of a filtering device into the inferior vena cava (IVC), with the goal of trapping thrombi from the lower extremities en route to the pulmonary circulation. This type of device, often called an *IVC filter*, is used most frequently (1) if there are contraindications to anticoagulant therapy (e.g., bleeding problems), (2) if thromboemboli have recurred despite adequate anticoagulation, or (3) if the patient already has such limited pulmonary vascular reserve that an additional clot to the lungs likely would be fatal. If there is no contraindication, anticoagulation is continued after the device is in place to decrease the risk of clotting in the veins distal to the filter. Once in place, some filters can be removed once the need for the filter has resolved.

No discussion of the treatment of pulmonary embolism is complete without considering prophylactic methods to prevent deep venous thrombosis in the high-risk patient. For low-risk patients, external compression of the lower extremities with an intermittently inflating pneumatic device is considered. For higher risk patients, pharmacologic prophylaxis is used. Options include LMWH, unfractionated heparin, or fondaparinux administered subcutaneously in low dosage. Prophylaxis is generally used in patients following thoracic, abdominal, or orthopedic surgery and in a variety of other at-risk patients who are relatively immobile in the hospital. In situations such as high-risk orthopedic surgeries when prophylaxis needs to be continued beyond the inpatient setting, generally an oral agent is used.

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# 14: Pulmonary hypertension

OUTLINE



Elevation of intravascular pressure within the pulmonary circulation is the hallmark of pulmonary hypertension (PH). This elevation of pressure may be due to either a pathologic process that affects the pulmonary vasculature or a variety of forms of cardiac disease that lead to increased pulmonary blood flow or increased back pressure from the left atrium. PH has most recently been defined as a mean pulmonary artery pressure (PAP) > 20 mm Hg, usually confirmed by right heart catheterization. An additional criterion of an elevation in pulmonary vascular resistance (PVR), specifically a PVR ≥ 3 Wood units (i.e., mm Hg/L/min), identifies the presence of pulmonary vascular pathology causing or contributing to the elevation in mean PAP. Based on hemodynamic data, PH has been subdivided into three hemodynamic subgroups, as shown in Table 14.1.

## TABLE 14.1
## Hemodynamic Subgroups of Pulmonary Hypertension

| | Precapillary PH | Isolated Postcapillary PH | Combined Pre- and Postcapillary PH |
|---|---|---|---|
| **Pulmonary vascular resistance (PVR)** | ≥3 Wood units[a] | <3 Wood units | >3 Wood units |
| **Pulmonary artery wedge pressure[b]** | ≤15 mm Hg | >15 mm Hg | >15 mm Hg |
| **Example** | Pulmonary artery hypertension (PAH) | Left ventricular failure without pulmonary vascular remodeling | Cardiac disease with secondary pulmonary vascular remodeling |

[a] 1 Wood unit = 1 mm Hg/L/min.

[b] Also called pulmonary capillary wedge pressure (PCWP) or pulmonary artery occlusion pressure (PAOP).

Because PH has many possible causes that presumably act by several different mechanisms, this chapter begins with a consideration of features relevant to PH in general, and follows with a discussion of some important specific causes of PH.

The current classification of PH is summarized in Table 14.2. The clarification of a few points is pertinent. First, the term *pulmonary hypertension* simply refers to elevated pulmonary arterial pressure, which may be due to a number of different mechanisms. The term *pulmonary arterial hypertension* (PAH) is reserved for specific types of PH—those categorized under Group 1 in the classification system in Table 14.2. The elevation of pulmonary arterial pressure may be acute or chronic and either reversible or irreversible, depending on the causative factors. In some cases, chronic PH is punctuated by further acute elevations in pressure, often as a result of exacerbations of underlying disease. Second, the development of right ventricular hypertrophy and eventual dysfunction is the consequence of chronic PH, whatever the primary cause of the latter. When PH is due to disorders of any part of the respiratory apparatus (airways, parenchyma and blood vessels, chest wall, respiratory musculature, or central nervous system controller), the term *cor pulmonale* is used to refer to the resulting alterations in the right ventricle. This term is not to be used to describe the right ventricular changes occurring as a consequence of primary cardiac disease or increased flow to the pulmonary vascular bed.

## TABLE 14.2
## Updated Clinical Classification of Pulmonary Hypertension (6th World Symposium)

1. **PULMONARY ARTERIAL HYPERTENSION (PAH)**
   1.1. Idiopathic PAH
   1.2. Heritable PAH
   1.3. Drug- and toxin-induced PAH
   1.4. PAH associated with
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
   1.5. PAH long-term responders to calcium channel blockers
   1.6. PAH with overt features of venous or capillary involvement
   1.7. Persistent pulmonary hypertension of the newborn
2. **PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE**
   2.1. Heart failure with preserved left ventricular ejection fraction
   2.2. Heart failure with reduced left ventricular ejection fraction
   2.3. Valvular heart disease
   2.4. Congenital/acquired cardiovascular conditions leading to postcapillary pulmonary hypertension
3. **PULMONARY HYPERTENSION DUE TO LUNG DISEASES AND/OR HYPOXIA**
   3.1. Obstructive lung disease
   3.2. Restrictive lung disease
   3.3. Other lung disease with mixed restrictive/obstructive pattern
   3.4. Hypoxia without lung disease
   3.5. Developmental lung disorders
4. **PULMONARY HYPERTENSION DUE TO PULMONARY ARTERY OBSTRUCTIONS**
   4.1. Chronic thromboembolic pulmonary hypertension
   4.2. Other pulmonary artery obstructions
5. **PULMONARY HYPERTENSION WITH UNCLEAR AND/OR MULTIFACTORIAL MECHANISMS**
   5.1. Hematological disorders
   5.2. Systemic and metabolic disorders
   5.3. Others
   5.4. Complex congenital heart disease



## Pathogenesis

A number of potential factors contribute to the pathogenesis of PH, both acutely and chronically. First, occlusion of a sufficient cross-sectional area of the pulmonary arteries by material (e.g., pulmonary emboli) within the vessels is an important factor (discussed in Chapter 13). In acute embolism where massive pulmonary emboli occlude more than approximately one-half to two-thirds of the vasculature, pulmonary arterial pressure is elevated. The right ventricle may dilate in response to its acutely increased workload because of insufficient time for hypertrophy to occur; consequently, in this acute circumstance, death may ensue prior to the right ventricle being able to generate adequately elevated PAPs to maintain cardiac output. In contrast, in chronic thromboembolic disease, multiple and recurrent pulmonary emboli may organize over a period sufficiently long for right ventricular hypertrophy to occur and markedly elevated pulmonary arterial pressures to result.

Second, remodeling of the pulmonary arterial walls causing diminution of the overall

cross-sectional area of the pulmonary vascular bed is a potential factor causing PH. Disorders acting by this mechanism are characterized by intimal and medial changes (see Pathology) that lead to thickening of the arterial and arteriolar walls and narrowing or obliteration of the lumen. This group of disorders with pulmonary arterial pathology includes *idiopathic pulmonary arterial hypertension* (IPAH, formerly called *primary PH*). The familial form of this condition, called *heritable pulmonary arterial hypertension*, in most cases is related to mutations of the gene on chromosome 2 that encodes the bone morphogenetic protein receptor type 2 (*BMPR2*). Abnormalities in this receptor are believed to lead to the dysregulation of proliferative responses in the endothelium and pulmonary arterial smooth muscle cells, producing the well-described pathologic changes in small pulmonary arteries and arterioles (again, see Pathology). Lesions pathologically similar to those seen in IPAH are also observed in other conditions associated with PAH (e.g., scleroderma, portal hypertension, and human immunodeficiency virus [HIV] infection) or with exposure to drugs and toxins (e.g., cocaine, methamphetamine, and certain diet drugs). When compromise of the pulmonary vasculature and increased resistance to flow are sufficiently pronounced in these primary disorders of the vessel wall, the level of PH can be quite severe, both at rest and with exercise.

Factors contributing to pulmonary hypertension (PH):

1. Occlusion of vessels by emboli
2. Primary remodeling and thickening of arterial walls
3. Loss of vessels by scarring or destruction of alveolar walls
4. Pulmonary vasoconstriction
5. Increased pulmonary vascular flow (left-to-right shunt)
6. Elevated left atrial and pulmonary venous pressure

Third, the total cross-sectional area of the pulmonary vascular bed can be compromised by parenchymal lung disease, with loss of blood vessels from either a scarring or a destructive process affecting the alveolar walls. Interstitial lung disease and emphysema can affect the pulmonary vasculature via this mechanism, although the underlying disorder in the parenchyma is quite different. Because of the significant capacity of the normal pulmonary vascular bed to accept increased blood flow, a large amount of the pulmonary vascular bed must be lost before resulting in an elevation in pulmonary arterial pressure. With these diseases, pulmonary arterial pressure is often normal at rest, but becomes mildly to moderately elevated with exercise because of insufficient recruitment or distention of vessels to handle the increase in cardiac output.

A fourth mechanism of PH is vasoconstriction, which may be present in all forms of PH. It is most prominent in response to hypoxia and, to a lesser extent, to acidosis. The importance of this mechanism is related to its potential reversibility when normal $P_{O_2}$ and pH values are restored. In several causes of cor pulmonale, particularly chronic obstructive pulmonary disease (COPD), hypoxia is the single most important factor leading to PH, and is potentially the most treatable. Acidosis—either respiratory or metabolic—causes pulmonary vasoconstriction and, although it is less important than hypoxia, may augment the vasoconstrictive response to hypoxia (discussed in Chapter

12). Some degree of vasoconstriction is seen in a minority of patients with PAH and is assessed during vasodilator testing (see below), and is also typically present in patients with PH associated with longstanding left ventricular dysfunction.

A fifth mechanism is chronically increased blood flow through the pulmonary vascular bed. When flow through the pulmonary vascular bed is increased (as occurs in patients with congenital left-to-right intracardiac shunts), the vasculature is initially able to handle the augmented flow without any anatomic changes in the arteries or arterioles. However, in most patients with a significant left-to-right shunt over a prolonged period, the pulmonary arterial walls remodel and pulmonary arterial resistance increases. The precise mechanism by which chronically increased pulmonary blood flow leads to vascular remodeling is not known. Eventually, as a result of the high PVR, right-sided cardiac pressures may become so elevated that the intracardiac shunt reverses in direction. This conversion to a right-to-left shunt, commonly called *Eisenmenger syndrome*, is a potentially important consequence of an atrial or ventricular septal defect or a patent ductus arteriosus.

A final and especially common mechanism of PH is the elevation of pressure distally, due to abnormalities at the level of the left atrium or left ventricle. This leads to progressive elevation of the "back pressure," first in the pulmonary veins and capillaries, and then in the pulmonary arterioles and arteries. As is the case with PH induced by increased flow in the pulmonary vasculature, the initial elevation in pressure may be accompanied by an element of vasoconstriction, but is not accompanied by anatomic changes in the pulmonary arteries. However, structural changes are eventually seen, and measured PVR may be substantially increased. The major disorders that result in PH by this final mechanism are mitral stenosis and chronic left ventricular failure, with either preserved or reduced systolic function.

## Pathology

Although PH is classified into different clinical categories (see Table 14.2), as the disease progresses and remodeling occurs, many of the pathologic findings in the pulmonary arteries of patients with PH are similar regardless of the underlying cause. This section focuses on these general changes, which are particularly well illustrated in the lungs of patients with IPAH.

Pathologic features of pulmonary hypertension (PH):

1. Intimal hyperplasia and medial hypertrophy of small arteries and arterioles
2. Eventual obliteration of the lumen of small arteries and arterioles
3. Thickening of the walls of larger (elastic) pulmonary arteries
4. Right ventricular hypertrophy

The most prominent abnormalities are seen in pulmonary arterial tree vessels with a diameter of less than 1 mm: the small muscular arteries (0.1-1 mm) and the arterioles (<0.1 mm). The muscular arteries show hypertrophy of the media, composed of smooth muscle, and hyperplasia of the endothelial cells that make up the intimal layer lining the vessel lumen. In the arterioles, a significant muscular component to the vessel wall is

not normally present, but with PH these vessels undergo “neomuscularization” of their walls (Fig. 14.1A). In addition, cells in the arteriolar intima proliferate. As a result of medial hypertrophy and encroachment of proliferating endothelial cells into the vessel, the luminal diameter is significantly decreased and the PVR becomes elevated. Ultimately, the lumen may be completely obliterated and the overall number of patent small vessels greatly diminished. In some cases of severe PH, particularly when due to IPAH or secondary to congenital intracardiac shunts, cells originating in the vessel wall (smooth muscle cells, endothelial cells, and fibroblasts) will form so-called plexiform lesions, appearing as a plexus of small, slit-like vascular channels (see Fig. 14.1B and C). Although the pathogenesis of these lesions is not precisely understood, disordered endothelial cell growth has been documented in patients with IPAH. It appears likely that the endothelial cells in many patients with severe PH have acquired a dysfunctional pro-proliferative phenotype that is resistant to apoptosis (programmed cell death).

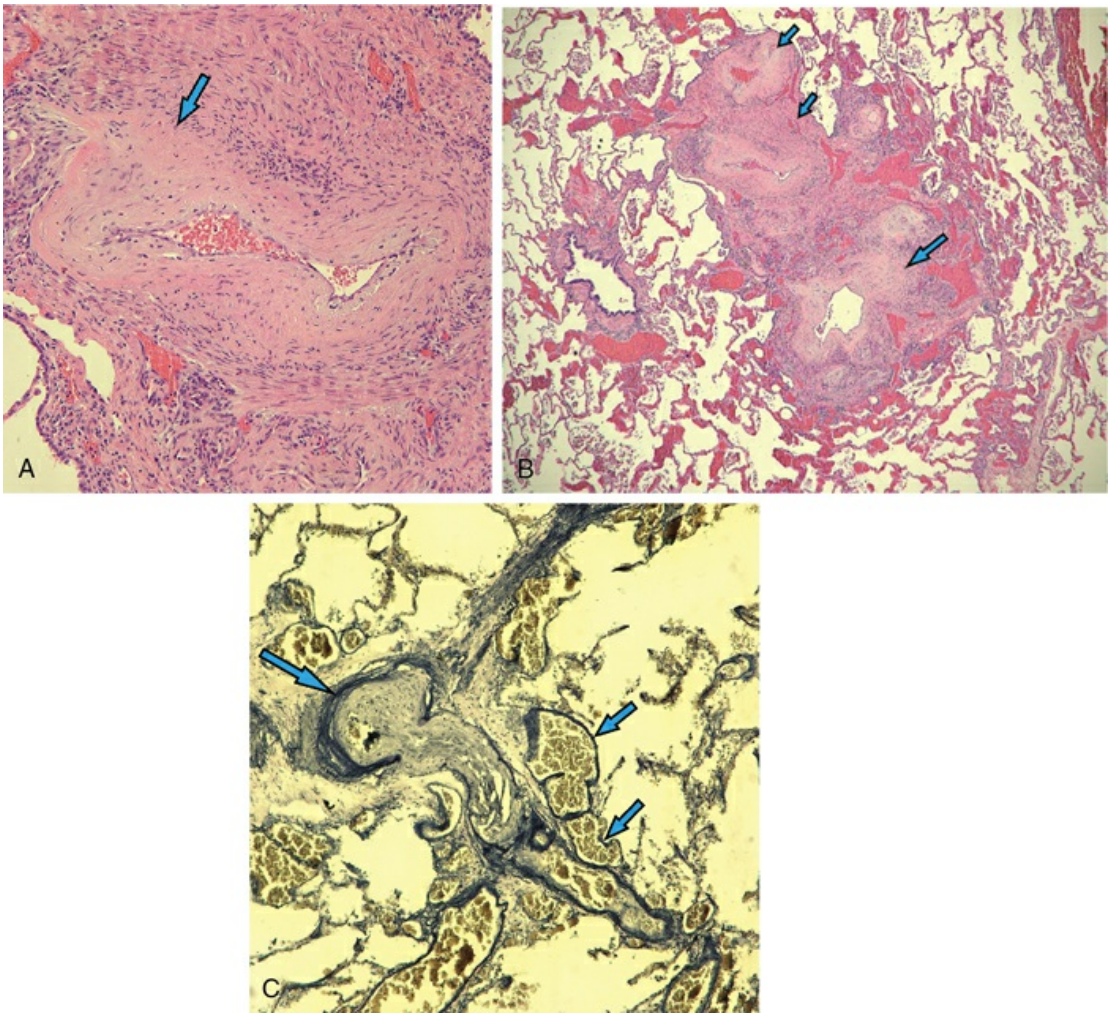


**FIGURE 14.1** Histologic changes in pulmonary hypertension. **A,** Moderate-power photomicrograph showing the thickened wall of a pulmonary arteriole *(arrow)*. **B,** Low-power photomicrograph

showing a thickened artery *(large arrow)* with an adjacent plexiform lesion *(small arrows)*. **C,** Elastic stain highlights thickened vessel walls *(large arrow)* and adjacent plexiform lesions *(small arrows)*. *Source:* (Courtesy Dr. Lester Kobzik.)

When PH becomes marked, other changes are commonly seen in the larger (elastic) pulmonary arteries. These vessels, which normally have much thinner walls than comparably sized vessels in the systemic circulation, develop thickening of the wall, particularly in the media. They also develop the types of atherosclerotic plaques generally seen only in the higher pressure systemic circulation.

Another finding that may develop in patients with PH of any cause is in situ thrombosis in the small pulmonary arterioles. It is likely that primary endothelial cell dysfunction causing loss of normal intraluminal antithrombotic mechanisms, as well as secondary endothelial damage and sluggish blood flow, contribute to in situ thrombus formation. Development of extensive in situ thrombosis will worsen the degree of PH by further compromising the pulmonary vascular bed.

The cardiac consequences of PH are manifest pathologically as changes in the right ventricular wall. The magnitude of the changes depends primarily on the severity and chronicity of the PH rather than the nature of the underlying disorder. The major finding is concentric hypertrophy of the right ventricular wall. If the right ventricle fails as a result of an increase in workload, then dilation of the right ventricle is observed.

## Pathophysiology

The pathophysiologic hallmark of PH is, by definition, an increase in pressure within the pulmonary circulation. If the primary component of the vascular change occurs at the precapillary level in the pulmonary arteries or arterioles, as in the case of IPAH or cor pulmonale, pulmonary arterial pressures (both systolic and diastolic) rise, but the pressure within pulmonary capillaries remains normal. On the other hand, if PH is secondary to pulmonary venous and pulmonary capillary hypertension, as in the case of mitral stenosis or left ventricular dysfunction, pulmonary capillary pressure is elevated above its normal level. Of note, fluid leaks from the pulmonary capillaries and accumulates in the interstitium or alveolar spaces when either intracapillary pressures are elevated (cardiogenic pulmonary edema) or pulmonary capillary permeability is increased (noncardiogenic pulmonary edema; see Chapter 29). In contrast, patients with precapillary PH and with normal pulmonary capillary pressures typically do not develop pulmonary edema.

As the architectural changes of PH progress, both right ventricular and pulmonary arterial pressures rise because of increased PVR. Cardiac output usually remains normal early in the course of the process. When the right ventricle begins to fail, right ventricular end-diastolic pressure rises, and cardiac output may decrease as well. Right atrial pressure also rises, which may be apparent on physical examination of the neck veins as elevation in the jugular venous pressure.

## Clinical features

Although the overall constellation of symptoms in patients with PH depends on the underlying disease, certain characteristic complaints can be attributed to the PH itself. Dyspnea on exertion and fatigue are frequently observed in all forms of PH, even in the absence of any gas exchange abnormalities. The mechanism of the dyspnea is likely due to activation of stretch receptors in the pulmonary arteries and right ventricle, which are stimulated as cardiac output increases with exertion. In patients with PH related to underlying parenchymal lung disease, it is often difficult to know how much of the dyspnea is due to the PH as opposed to the underlying lung disease. Cardiopulmonary exercise testing may be useful in partitioning the relative contributions of each process to the patient's dyspnea. Patients may have substernal chest pain that is difficult if not impossible to distinguish from classic angina pectoris, particularly because the pain is frequently precipitated by exertion. In most instances, the chest pain is presumed to be related to the increased workload of the right ventricle and to right ventricular ischemia, although, in some cases, an enlarged pulmonary artery can compress the left main coronary artery and produce true left ventricular ischemia. If PH is severe and the right ventricle cannot overcome the high PVR to increase cardiac output with exertion, patients may experience exertional lightheadedness or frank syncope. These represent very poor prognostic signs.

Clinical features of pulmonary hypertension (PH):

1. Symptoms: dyspnea, substernal chest pain, fatigue, and syncope
2. Physical signs: loud pulmonic component of the second heart sound ($P_2$), tricuspid insufficiency murmur, prominent parasternal (right ventricular) impulse, right-sided $S_4$ gallop; also, right-sided $S_3$ gallop, jugular venous distention, and peripheral edema in the case of right ventricular failure

Physical examination shows several features more related to the cardiac consequences of PH than to actual disease of the pulmonary vessels. PH itself does not cause any changes that can be noted on examination of the lungs, although patients with underlying lung disease often have findings related to their primary disease. On cardiac examination, patients frequently exhibit an accentuation of the pulmonic component of the second heart sound ($P_2$) because of earlier and more forceful valve closure attributable to high pressure in the pulmonary artery. A murmur of tricuspid insufficiency is commonly heard, and a pulmonic insufficiency (Graham Steell) murmur may be appreciated. When the pulmonary artery is enlarged, a pulsation may be felt between the ribs at the left upper sternal border (pulmonary artery tap). With right ventricular hypertrophy, there is often a prominent lift or heave in the region immediately to the left of the lower sternum, corresponding to a prominent right ventricular impulse during systole. As the right atrium contracts and empties its contents into the poorly compliant, hypertrophied right ventricle, a presystolic gallop ($S_4$) originating from the right ventricle may be heard. When the right ventricle fails, a mid-diastolic gallop ($S_3$) in the parasternal region is frequently heard, and the jugular veins become distended. Both lower extremity peripheral edema and ascites may develop.

## Diagnostic features

Echocardiography is usually the first test to suggest a diagnosis of PH. When PH is present, echocardiography can also often identify if left-sided cardiac disease is responsible. Key findings of PH are right ventricular hypertrophy and elevated right ventricular and pulmonary artery systolic pressures by Doppler estimates. A detailed description of these echocardiographic techniques is beyond the scope of this chapter, but can be found in standard cardiology textbooks.

The definitive diagnosis of PH and the precise quantification of its hemodynamics require cardiac catheterization. Measurements of right ventricular, pulmonary arterial, pulmonary capillary wedge, and in some cases left ventricular end-diastolic pressures are important in confirming the diagnosis, determining the disease severity, and assessing the response to acute vasodilator testing to guide the patient's subsequent management (see Chapter 12 for discussion of pulmonary artery catheterization).

Clues to the status of the pulmonary vessels can be provided by chest radiography in some patients. With mild PH originating at the arterial or arteriolar level, abnormalities are not usually seen. As PAH becomes more significant, the central (hilar) pulmonary arteries increase in size, and the vessels often rapidly taper, so the distal vasculature appears attenuated (Fig. 14.2). With hypertrophy of the right ventricle, the cardiac silhouette may enlarge (Fig. 14.3A). This feature is most apparent on the lateral radiograph, which shows bulging of the anterior cardiac border that is formed by the right ventricle (Fig. 14.3B).

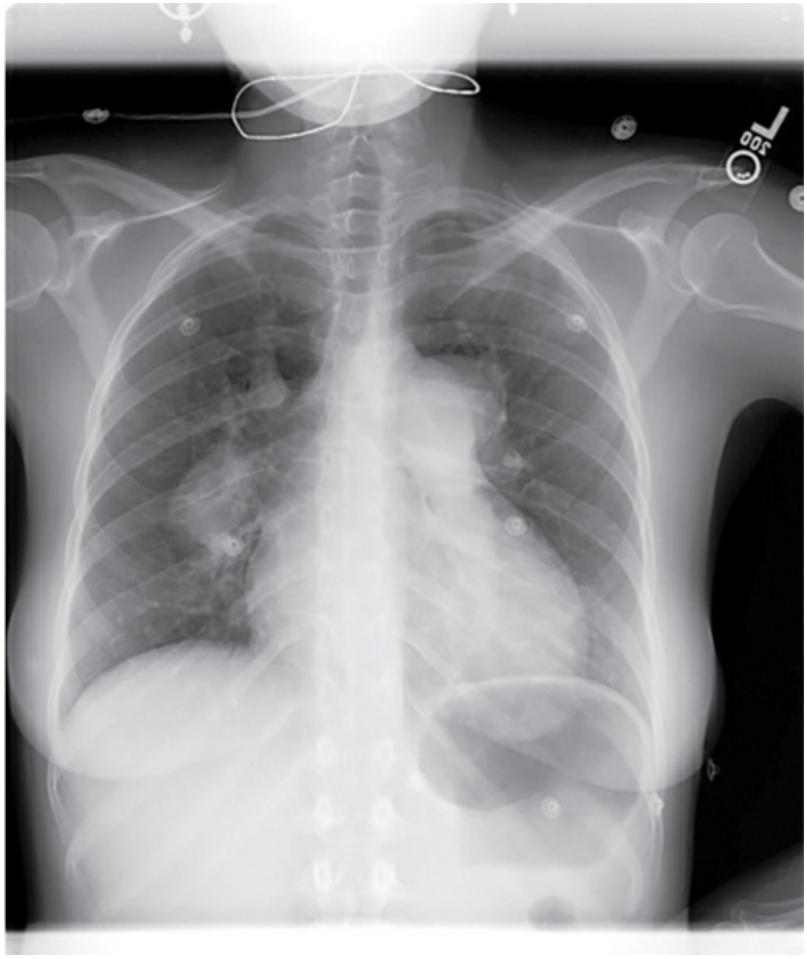

**FIGURE 14.2** Chest radiograph of a patient with pulmonary hypertension attributable to recurrent thromboemboli. Central pulmonary arteries are large bilaterally, but rapid tapering of vessels occurs distally.

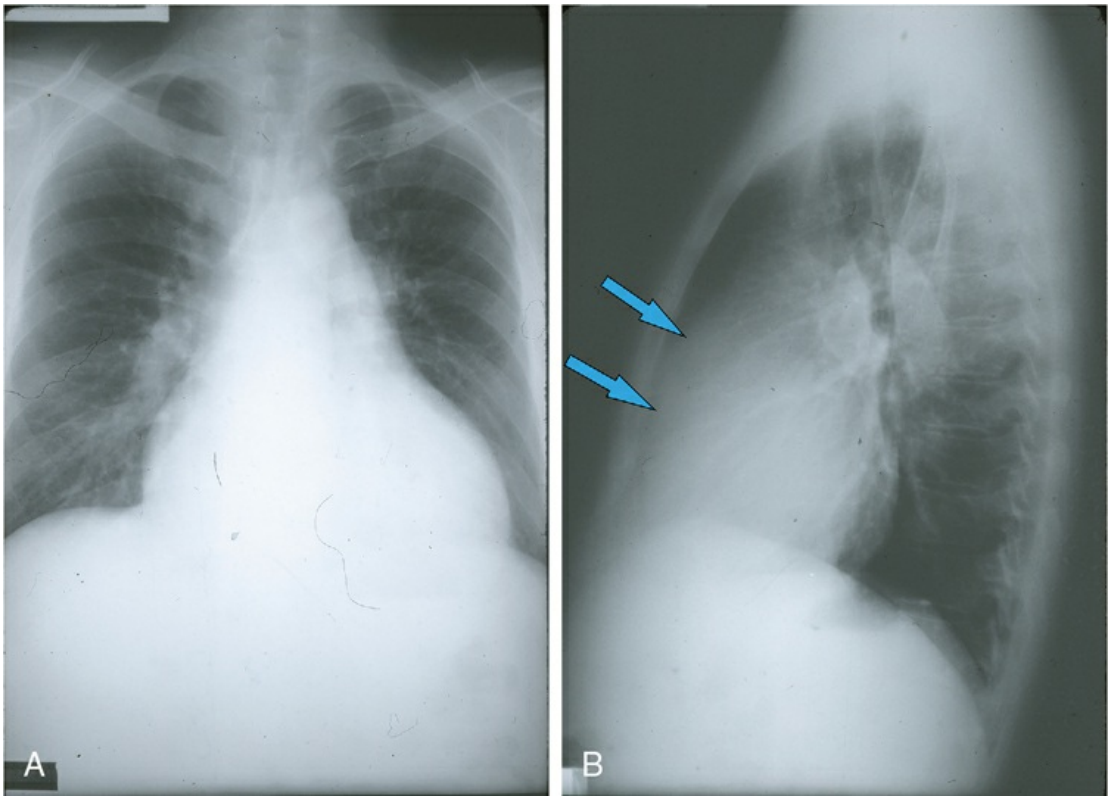


**FIGURE 14.3** Chest radiograph of a patient with right ventricular enlargement due to pulmonary hypertension. **A,** Posteroanterior (PA) view showing cardiomegaly. **B,** Lateral view demonstrating bulging of the anterior cardiac border due to an enlarged right ventricle (arrows).

When PH is a consequence of either increased flow to the pulmonary vasculature (as in congenital heart disease with initial left-to-right shunting) or increased back pressure from the pulmonary veins and pulmonary capillaries (as in mitral stenosis or left ventricular failure), the findings are significantly different. In the case of congenital heart disease with left-to-right shunting, the pulmonary vasculature is prominent due to the increased blood flow until reversal of the left-to-right shunt occurs. When there is elevation of pulmonary venous pressure from mitral stenosis or left ventricular failure, the chest radiograph often shows a redistribution of blood flow from the lower to the upper lung zones, accompanied by evidence of interstitial or alveolar edema and small pleural effusions.

Computed tomographic angiography (CTA) or perfusion lung scanning can be valuable adjuncts in the assessment of patients with PH, primarily to look for chronic thromboembolic disease. Computed tomography scanning can also identify occult parenchymal disease that is not evident on chest radiograph (see Chapters 3 and 13). When chronic thromboembolic disease is suspected and CTA or perfusion scanning is positive, conventional pulmonary angiography may be useful to confirm the diagnosis and assess the surgical accessibility of the obstructing lesions.

When evaluating the patient with PH, pulmonary function tests are useful primarily for detecting underlying airflow obstruction (from COPD) or restricted lung volumes (from interstitial lung disease). As a result of the PH itself and the reduction of the functional pulmonary vascular bed, the diffusing capacity is often decreased and may be the only abnormality noted.

Pulmonary function tests may demonstrate underlying restrictive or obstructive disease. Tests may also show decreased diffusing capacity due to loss of the pulmonary vascular bed.

Arterial blood gas analysis is highly useful for determining whether hypoxemia or acidosis plays a role in PH pathogenesis. Arterial $P_{O_2}$ may be mildly decreased as a result of pulmonary vascular disease, apparently because of the nonuniform distribution of disease and the resultant worsened ventilation-perfusion matching.

## Specific disorders associated with pulmonary hypertension

PH is currently classified according to the scheme given in Table 14.2, which is very useful in categorizing patients based on clinical aspects of their disease. However, it is important to recognize that there is much pathophysiologic overlap among the categories, and as we better understand the pathobiology of PH, the classification system will likely evolve.

On a population basis, PH is most commonly the result of either left heart failure or parenchymal lung disease (most commonly COPD). Treatment directed specifically at PH has not been shown to be beneficial in these disorders. In contrast, patients with IPAH and some other types of PAH now have a variety of medications that can be used for effective treatment.

### Idiopathic pulmonary arterial hypertension and related disorders (group 1 PAH)

In general, diseases categorized as PAH are associated with pathology primarily in the pulmonary vasculature, without accompanying lung or left-sided cardiac abnormalities to explain the elevated PVR. Unfortunately, the nomenclature can be confusing; according to convention, only diseases in Group 1 are termed *PAH*.

As noted earlier, IPAH was once referred to as *primary PH* and is a disease of unknown cause found most commonly in women (up to 80% of patients are female), with a mean age of 50 years at diagnosis. However, IPAH also occurs in children, teens, and adults of all ages and both sexes. The diagnosis of IPAH cannot be made until other causes of PH have been excluded. Other types of PAH have a pathologic appearance and clinical presentation similar to those of IPAH, but with an accompanying process or etiologic agent known to be associated with this disease pattern. Such underlying processes or agents include connective tissue disease (particularly systemic sclerosis, also termed scleroderma), portal hypertension accompanying cirrhosis, HIV infection, and exposure to certain drugs or toxins, especially methamphetamines. In the past,

several appetite suppressants were associated with PH; they include aminorex (withdrawn from the market many years ago) and the drugs fenfluramine and dexfenfluramine (withdrawn from the market in 1997).

Often, idiopathic pulmonary arterial hypertension (IPAH) occurs in women, is associated with Raynaud syndrome, and has a poor prognosis.

IPAH, by definition, occurs as a sporadic (i.e., nonfamilial) disorder. However, PAH does occur as an inherited disease in 10% or more of all cases. When the disease has a familial basis, it is termed *heritable PAH*. Clinically, IPAH and heritable PAH are indistinguishable. Understanding the genetic basis of heritable PAH likely has relevance to the pathogenesis of sporadic nonfamilial cases of IPAH. In approximately 80% of patients with a familial basis to the disease, a germline mutation in the *BMPR2* gene can be detected. The gene product of *BMPR2* is a receptor in the transforming growth factor (TGF)-β superfamily. It has been proposed that under the proper conditions, the presence of the mutant *BMPR2* leads to partial loss of an inhibitory effect of *BMPR2* on vascular smooth muscle cell growth. The smooth muscle cell changes may also lead indirectly to endothelial cell injury and proliferation. Importantly, up to 20% of patients who present with no family history and apparently idiopathic disease have *BMPR2* mutations. Once a mutation is found, the patient is considered to have heritable disease; thus, the distinction between idiopathic and heritable PAH is also evolving. More rarely, mutations in other genes involved in the TGF-β superfamily are identified in patients with PAH. Specifically, the genes for endoglin or activin receptor-like kinase type 1 are abnormal in many patients with PAH associated with the heritable disorder hereditary hemorrhagic telangiectasia.

Without treatment, the prognosis in IPAH is poor; patients frequently die within several years of diagnosis. Treatment has focused on the use of vasoactive medications—both vasodilators and antiremodeling agents—in an attempt to reduce PVR and pulmonary arterial pressure. Typically, before a particular medication is initiated, patients undergo acute vasodilator testing (commonly with inhaled nitric oxide) in the setting of right heart catheterization to assess the resulting immediate changes in pulmonary arterial pressure, cardiac output, and systemic blood pressure in a controlled setting. Patients who have some degree of reactivity (i.e., pulmonary arterial pressure and vascular resistance fall in response to an acute pulmonary vasodilator) generally have a better prognosis.

Historically, the first vasodilator medications shown to be effective in a small subset of patients were calcium channel antagonists, such as nifedipine and diltiazem, which are administered orally. These medications are still used but are indicated only in the small subset of patients (<10%) who normalize their pulmonary arterial pressure in response to acute vasodilator testing. Currently, four other classes of drugs are available specifically to treat PAH: prostacyclin derivatives, endothelin-1 receptor antagonists, phosphodiesterase inhibitors, and guanylate cyclase stimulators. Prostacyclin derivatives administered by continuous intravenous (e.g., epoprostenol and treprostinil) or subcutaneous (treprostinil) infusion have been associated with clinical and hemodynamic improvement as well as improved survival. The long-term effect of these drugs indicates that they reverse some of the vascular remodeling and proliferative

changes in the pulmonary arterial system separate from their vasodilator effects. However, these drugs are extremely expensive, and the need for continuous infusion makes them inconvenient and logistically more difficult to administer than oral agents. The prostacyclin derivatives iloprost and treprostinil also can be administered by inhalation using specialized nebulizers. Selexipag, an orally active nonprostanoid agonist of the prostacyclin receptor, has more recently been approved for use.

The endothelin-1 receptor antagonists (bosentan, ambrisentan, and macitentan), the phosphodiesterase-5 inhibitors (sildenafil and tadalafil), and a guanylate cyclase stimulator (riociguat) are available in pill form. The oral medications are attractive therapeutic alternatives, particularly in patients with less advanced disease.

Although not based on randomized trials, patients with IPAH may be placed on long-term anticoagulation therapy. The rationale is to decrease in situ thrombosis in the pulmonary arterial system. Some, but not all, observational data suggest that anticoagulation may improve survival, especially in patients with severe disease.

For some patients with debilitating disease and a poor response to therapy, lung transplantation or combined heart-lung transplantation is indicated. However, this form of therapy has very limited availability and does not offer long-term survival for most patients. A more detailed discussion of treatment options for patients with PAH is beyond the scope of this text; the reader is referred to the excellent review articles given in the Suggested Readings at the end of this chapter.

## Pulmonary hypertension due to left heart disease (group 2 PH)

Mitral stenosis and chronic left ventricular failure are the two disorders most frequently associated with pulmonary venous, and subsequently pulmonary arterial, hypertension. The resulting right ventricular hypertrophy is not included in the category of cor pulmonale because the underlying problem resulting in PH is clearly of cardiac, not pulmonary, origin.

With pulmonary venous hypertension, the pathologic and many of the clinical and diagnostic features are different from PAH in a relatively predictable way. Pathologically, dilated and tortuous capillaries and small veins may result from high pressures in the pulmonary veins and capillaries, along with chronic extravasation of red blood cells into the pulmonary parenchyma. During the process of handling the interstitial and alveolar hemoglobin, macrophages may become loaded with hemosiderin, which is a breakdown product of hemoglobin. These macrophages can be detected by appropriate staining of sputum for iron. Often, the alveolar walls have a fibrotic response, which is presumably secondary to the long-standing extravasation of blood, so a component of interstitial lung disease with fibrosis may be seen.

Long-standing pulmonary venous hypertension is associated with the extravasation of erythrocytes into the pulmonary parenchyma, hemosiderin-laden macrophages, and a fibrotic interstitial response.

As mentioned in the discussion of radiographic abnormalities, the presence of pulmonary venous hypertension adds several features to the chest radiograph, including the redistribution of blood flow to the upper lobes and interstitial and alveolar edema. Another frequent finding is Kerley B lines, which are small, horizontal lines extending to

the pleura at both lung bases that reflect the thickening of, or fluid in, lymphatic vessels in the interlobular septa, which is a consequence of interstitial edema.

Radiographic evidence of pulmonary venous hypertension includes:

1. Redistribution of blood flow to the upper zones
2. Interstitial and alveolar edema
3. Kerley B lines

Treatment of these disorders revolves around attempts to optimize therapy for the cardiac disease and to decrease pulmonary venous and capillary pressures. The potential reversibility of PH depends on disease chronicity and the degree to which venous hypertension can be alleviated. Occasionally, a patient will have a persistent elevation in PVR even after the left-sided heart disease has been treated (e.g., a patient with long-standing mitral stenosis who has had valve replacement surgery). In these patients, treatment with therapies directed specifically at PAH may be effective in treating the PH.

## Pulmonary hypertension due to lung disease and/or hypoxia (group 3 PH)

The most common causes of cor pulmonale are COPD and interstitial lung disease. Hypoxia is the single most important etiologic factor in patients with COPD. Other contributory factors include respiratory acidosis, which may worsen vasoconstriction; secondary polycythemia, a consequence of chronic hypoxemia, which further increases PAPs as a result of increased blood viscosity; and reduction of the pulmonary vascular bed caused by coexistent emphysema.

Any of the interstitial lung diseases, when relatively severe, may be associated with cor pulmonale. Major contributing factors appear to be loss of the vascular bed, as a result of the scarring process in the alveolar walls, and hypoxia. However, a subset of patients develops a disproportionate degree of pulmonary vascular disease, and these patients may progress to more severe PH.

Obstructive disease, interstitial disease, and a variety of neural, muscular, and chest wall diseases may produce PH and cor pulmonale.

The most important aim of treatment for cor pulmonale in the setting of obstructive and interstitial disease is correction of alveolar hypoxia and hypoxemia by the administration of supplemental $O_2$. The goal is to maintain arterial $P_{O_2}$ at a level greater than approximately 60 mm Hg, above which hypoxic vasoconstriction is largely eliminated. Other forms of therapy aimed more specifically at the underlying disease are discussed in Chapters 6, 10, and 11.

In addition to these two categories of lung disease, other disorders of the respiratory apparatus associated with hypoxemia and hypercapnia may be complicated by the development of cor pulmonale. Specifically, disorders of the control of breathing, of the chest bellows, and of the neural apparatus controlling the chest bellows may be

complicated by cor pulmonale. These disorders are discussed in more detail in Chapters 18 and 19.

### Chronic thromboembolic pulmonary hypertension (group 4 PH)

The typical presentation of chronic thromboembolic pulmonary hypertension (CTEPH) is with insidious onset of dyspnea and findings related to PH, rather than with a history suggesting one or more known acute episodes of pulmonary embolism (see Chapter 13). Presumably, by the time a patient presents with CTEPH, the emboli have been occurring and organizing with fibrosis over months to years. Because chronic thrombi are organized and extensively remodeled with fibroblasts and connective tissue, anticoagulation alone is not an effective therapy. In most cases, the organized thromboemboli are primarily located within the large proximal pulmonary arteries, causing significant obstruction. In these patients, surgical removal of the proximal organized thrombi (pulmonary thromboendarterectomy) may be a feasible and highly effective therapeutic option. More recently, balloon pulmonary angioplasty is employed as an alternative to surgery in some cases. In other patients, there is extensive thromboembolic occlusion of smaller, inaccessible vessels. Although this type of small vessel occlusion has generally been assumed to result from multiple small pulmonary emboli, primary thrombosis of the microvasculature—perhaps secondary to endothelial damage—also has been suggested to play a role. For the small vessel or microvascular form of chronic pulmonary thromboembolism, therapy involves anticoagulation and agents similar to those used for IPAH.

### Pulmonary hypertension with unclear multifactorial mechanisms (group 5 PH)

A miscellaneous group of diseases listed in Table 14.2 under Group 5 may be associated with PH. The most common disorder in this category is sarcoidosis. The underlying mechanisms responsible for PH in these disorders are not entirely clear and are often believed to be multifactorial.

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# 15: Pleural disease

OUTLINE



In moving from the lung to other structures that are part of the process of respiration, we next consider the adjacent pleura. In clinical medicine, the pleura is important not only because diseases of the lung commonly cause secondary abnormalities in the pleura, but also because the pleura is a major site of disease in its own right. Not infrequently, pleural disease is a manifestation of a multisystem process that is inflammatory, autoimmune, or malignant.

In this chapter, the anatomy of the pleura is discussed, followed by a presentation of several physiologic principles of fluid formation and absorption by the pleura and a discussion of two types of abnormalities that affect the pleura: liquid in the pleural space *(pleural effusion)* and air in the pleural space *(pneumothorax)*. The chapter concludes

with a brief discussion of a primary malignancy of the pleura, *malignant mesothelioma*. A comprehensive treatment of all the disorders that affect the pleura is beyond the scope of this text. Rather, this chapter aims to cover the major categories and give the reader an understanding of how different factors interact in producing pleural disease.

## Anatomy

The term *pleura* refers to the thin lining layer on the outer surface of the lung *(visceral pleura),* the corresponding lining layer on the inner surface of the chest wall *(parietal pleura),* and the space between them *(pleural space)* (Fig. 15.1). Because the visceral and parietal pleural surfaces normally touch each other, the space between them is usually only a potential space. It contains a thin layer of serous fluid that coats the apposing surfaces and acts as a lubricant during lung movement with respiration. When air or a larger amount of fluid accumulates in the pleural space, the visceral and parietal pleural surfaces are separated, and the space between the lung and the chest wall becomes more apparent.

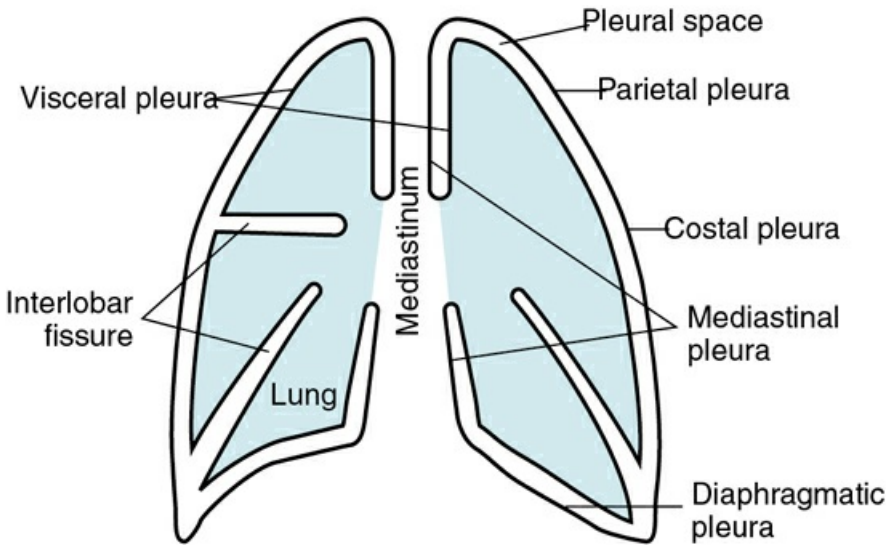


**FIGURE 15.1** Anatomic features of pleura. The pleural space is located between visceral and parietal pleural surfaces. The pleura lines surfaces of lung in contact with chest wall (costal pleura) and mediastinal and diaphragmatic borders (mediastinal and diaphragmatic pleura, respectively). *Source:* (From Lowell, J. R. (1977). *Pleural effusions: a comprehensive review* (p. 77). Baltimore, MD: University Park Press.)

The pleura lines the surfaces of the lung in direct contact with the chest wall and also the diaphragmatic and mediastinal borders of the lung. These surfaces are called the *diaphragmatic* and *mediastinal pleura*, respectively (see Fig. 15.1). Visceral pleura also separates the lobes of the lung from each other; therefore, the major and minor fissures

are defined by two apposing visceral pleural surfaces.

Each of the two pleural surfaces, visceral and parietal, is a thin membrane, the surface of which consists of specific lining cells called *mesothelial cells*. Beneath the mesothelial cell layer is a thin layer of connective tissue. Blood vessels and lymphatic vessels course throughout the connective tissue and are important in the dynamics of liquid formation and resorption in the pleural space. On the parietal but not the visceral pleural surface, openings called *stomata* are located between the mesothelial cells. Each stoma leads to lymphatic channels, allowing a passageway for liquid from the pleural space into the lymphatic system. Sensory nerve endings in the parietal and diaphragmatic pleura are responsible for the characteristic "pleuritic chest pain" arising from the pleura.

Blood vessels supplying the parietal pleural surface originate from the systemic arterial circulation, primarily the intercostal arteries. Venous blood from the parietal pleura drains to the systemic venous system. The visceral pleura is also supplied primarily by systemic arteries, specifically branches of the bronchial arterial circulation. However, unlike the parietal pleura, the visceral pleura has venous drainage into the pulmonary venous system. Depending on their location, the lymphatic vessels that drain the pleural surfaces transport their fluid contents to different lymph nodes. Ultimately, any liquid transported by the lymphatic channels finds its way to the thoracic or right lymphatic duct, which empties into the systemic venous circulation.

## Physiology

The pleural space normally contains only a small quantity of liquid (~10 mL), which lubricates the apposing surfaces of the visceral and parietal pleurae. According to the current concept of pleural fluid formation and resorption, formation of fluid is ongoing primarily from the parietal pleural surface, and fluid is resorbed through the stomata into the lymphatic channels of the parietal pleura (Fig. 15.2). The normal rates of formation and resorption of fluid, which must be equal if the quantity of fluid within the pleural space is not changing, are believed to be approximately 15 to 20 mL/day.

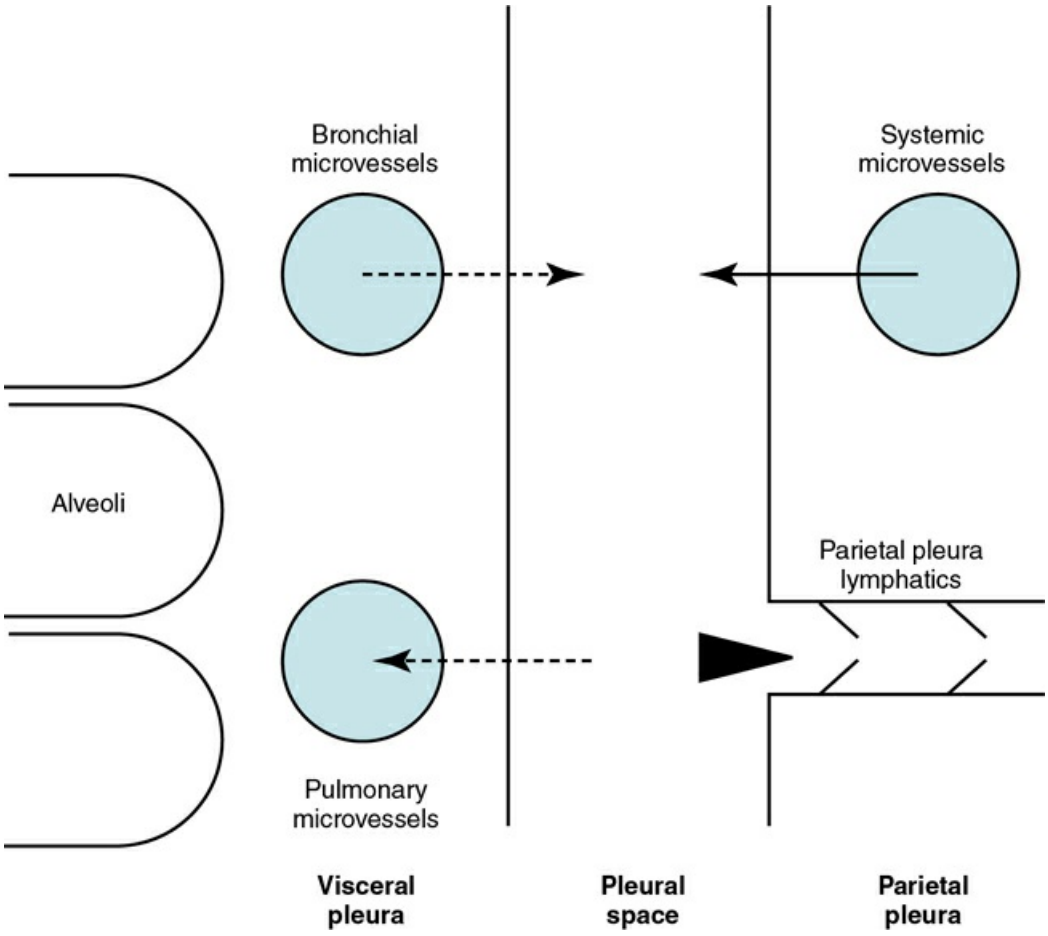


**FIGURE 15.2** Schematic diagram of normal filtration and resorption of fluid in pleural space. *Solid arrow* shows filtration of fluid from parietal pleural microvessels into pleural space. *Arrowhead* indicates removal of fluid through stomata and into parietal pleural lymphatics. *Dashed arrows* indicate a minor role for filtration and resorption of fluid by visceral pleural microvessels. *Source:* (Modified from Pistolesi, M., Miniati, M., & Giuntini, C. (1989). Pleural liquid and solute exchange. *American Review of Respiratory Disease, 140*, 825–847.)

The normally occurring liquid in the pleural space is a low-protein transudate produced by ultrafiltration from the pleural capillaries. Several different forces either promote or oppose fluid filtration. The net movement of fluid from the pleural capillaries to the pleural space depends on the magnitudes of these counterbalancing forces. The hydrostatic pressure in the capillary promotes movement of fluid out of the vessel and into the pericapillary space, whereas the colloid osmotic pressure (the osmotic pressure exerted by protein drawing in fluid) hinders movement of liquid out of the capillary. Likewise, hydrostatic and colloid osmotic pressures in the pericapillary space comprise the opposing forces that act on liquid within the pericapillary region.

The effect of these forces is summarized in the *Starling equation*, which describes the movement of fluid between vascular and extravascular compartments of any part of the body, not just the pleura:

$$\text{Fluid movement} = K[(P_c - P_{is}) - \sigma(COP_c - COP_{is})] \quad \textbf{(Eq. 15.1)}$$

The Starling equation can be applied to the parietal pleura:

$P_c = 30$ cm $H_2O$

$P_{is}$ (mean intrapleural pressure) $= -5$ cm $H_2O$

$COP_c = 32$ cm $H_2O$

$COP_{is} = 6$ cm $H_2O$

$\sigma = 1$, $K = 1$

Fluid movement at parietal pleura $= [30 - (-5)] - 1(32 - 6) = 9$ cm $H_2O$

where K = filtration coefficient (a function of the permeability of the pleural surface), P = hydrostatic pressure, COP = colloid osmotic pressure, σ = measure of capillary permeability to protein (called the *reflection coefficient*), and the subscripts "c" and "is" refer to the capillary and pericapillary interstitial space, respectively. In this case, the pericapillary interstitial space is essentially the pleural space; therefore, $P_{is}$ and $COP_{is}$ refer to intrapleural pressure and the colloid osmotic pressure of pleural fluid, respectively. The intrapleural pressure—that is, the hydrostatic pressure within the pleural space—is negative, reflecting the outward elastic recoil of the chest wall and the inward elastic recoil of the lung.

When values obtained by direct measurement or by estimation are put into the Starling equation, a net pressure of approximately 9 cm $H_2O$ (6.6 mm Hg) favors movement of fluid from the parietal pleura to the pleural space. The critical factor responsible for the forces favoring formation of pleural fluid is the difference between the positive hydrostatic pressure in the pleural capillaries and the negative hydrostatic pressure within the pleural space.

Applying the same equation to fluid filtration from the visceral pleura is more difficult. The visceral pleural capillaries are supplied primarily by the systemic arterial circulation but are drained into the pulmonary venous circulation rather than the systemic venous circulation. Although currently unknown, the hydrostatic pressure in the visceral pleural capillaries is estimated to be less than in the parietal pleural capillaries. As a result, the driving pressure for formation of pleural fluid is normally greater at the parietal than at the visceral pleural surface, and most of the small amount of normal pleural fluid is thought to originate from filtration through the systemic capillaries of the parietal pleura.

Resorption of pleural fluid, including protein and cells in the fluid, occurs through the stomata between mesothelial cells on the parietal pleural surface. The fluid enters lymphatic channels, and valves within these channels ensure unidirectional flow. Movement of fluid through the valved lymphatics is believed to be aided by respiratory motion. When pleural fluid formation is increased, as occurs in many of the pathologic states to be discussed, the parietal pleural lymphatics can augment their flow substantially to accommodate some or all of the excess fluid formed.

The liquid normally lubricating the pleural surfaces is filtered from the parietal pleura into the pleural space and reabsorbed through stomata into the parietal pleural lymphatics.

# Pleural effusion

In the normal individual, resorption of pleural fluid maintains pace with pleural fluid formation, so fluid does not accumulate. However, a variety of diseases affect the forces governing pleural fluid filtration and resorption, resulting in fluid formation exceeding fluid removal—that is, development of pleural effusion. The pathogenesis (dynamics) of fluid accumulation is discussed first, followed by a consideration of some of the etiologic factors, clinical features, and diagnostic approaches to pleural effusions.

## Pathogenesis of pleural fluid accumulation

In theory, a change in magnitude of any of the factors in the Starling equation can cause sufficient imbalance of pleural fluid dynamics to result in pleural fluid accumulation. In practice, it is easiest to divide these changes into two categories: (1) alteration of the permeability of the pleural surface (i.e., changes in the filtration coefficient [K] and reflection coefficient [σ] such that the pleura is more permeable to fluid and larger molecular weight components of blood, including proteins), and (2) alteration in the driving pressure, encompassing a change in hydrostatic or colloid osmotic pressures of the parietal or visceral pleura, without any change in pleural permeability.

The most common types of disease causing a change in the filtration and reflection coefficients are inflammatory or neoplastic diseases involving the pleura. In these circumstances, the pleural surface becomes more permeable to both fluid and proteins, so the accumulated fluid has a relatively high protein content compared to normal pleural fluid. This type of fluid, because of a change in permeability and its association with a relatively high protein content, is termed an *exudate*.

Increased permeability of the pleural surface is associated with exudative pleural fluid. Changes in pleural hydrostatic or colloid osmotic pressures are associated with transudative pleural fluid.

In contrast, an increase in hydrostatic pressure within pleural capillaries (as might be seen with high pulmonary venous pressure from heart failure) or a decrease in plasma colloid osmotic pressure (as in hypoproteinemia) results in accumulation of fluid with a low protein content because the pleural barrier is still relatively impermeable to the movement of proteins. This type of fluid, formed because of a change in the driving pressure (without increased permeability) or the presence of a low protein content, is termed a *transudate*.

Another general mechanism accounting for some pleural effusions reflects neither altered permeability nor altered driving pressure. Rather, the fluid originates in the peritoneum as ascitic fluid and travels to the pleural space primarily via small diaphragmatic defects and perhaps also by diaphragmatic lymphatics. Considering that intrapleural pressure is more negative than intraperitoneal pressure, it is not surprising that fluid is drawn from the peritoneum into the pleural space when such defects exist.

Interference with the resorptive process for pleural fluid can contribute to development of effusions. This is seen primarily with blockage of the lymphatic drainage from the pleural space, as may occur when tumor cells invade the lymphatic channels or draining lymph nodes.

## Etiology of pleural effusion

The numerous causes of pleural fluid accumulation are best divided into transudative and exudative categories (Table 15.1). This distinction is generally easy to make and is most important in guiding the physician along the best route for further evaluation. Transudative fluid usually implies that the pathologic process does not primarily involve the pleural surfaces, whereas exudative fluid often suggests that the pleura itself is affected by the disease process causing the effusion.

**TABLE 15.1**

**Major Causes of Pleural Effusion**

| |
|---|
| **Transudate** |
| Increased hydrostatic pressure; "overflow" of liquid from the lung interstitium |
| • Heart failure |
| Decreased plasma oncotic pressure |
| • Nephrotic syndrome |
| Movement of transudative ascitic fluid through the diaphragm |
| • Cirrhosis |
| **Exudate** |
| Inflammatory |
| • Infection (tuberculosis, bacterial pneumonia)<br>• Pulmonary embolus (infarction)<br>• Connective tissue disease (lupus, rheumatoid arthritis)<br>• Adjacent to subdiaphragmatic disease (pancreatitis, subphrenic abscess) |
| Malignant |

### Transudative pleural fluid

Most frequently, transudative pleural fluid is associated with left ventricular failure. The source of pleural fluid in heart failure appears primarily to be liquid leaking out of the *pulmonary* capillaries and accumulating in the lung interstitium. This interstitial fluid then leaks across the visceral pleura and into the pleural space, akin to leakage of fluid from the surface of a wet sponge. Previously, it was thought that increased hydrostatic pressure in the *parietal* pleural capillaries, due to elevated right atrial pressure, was responsible for increased flux of fluid from these vessels into the pleural space.

However, clinical studies indicate that pulmonary venous hypertension (with left-sided heart failure), leading to increased hydrostatic pressure in the pulmonary capillaries, is the more important factor contributing to effusions rather than systemic venous hypertension (with right-sided failure). Pleural effusion is particularly likely to occur when both ventricles are failing and pulmonary and systemic venous hypertension coexist. In contrast, pleural effusion is rare in isolated right ventricular dysfunction.

Patients with hypoproteinemia have decreased plasma colloid osmotic pressure, and pleural fluid may accumulate because hydrostatic pressure in pleural capillaries now is less opposed by the osmotic pressure provided by plasma proteins. The most common circumstance resulting in hypoproteinemia and pleural effusion is nephrotic syndrome, with excessive renal losses of protein.

Movement of transudative ascitic fluid through diaphragmatic defects and into the pleural space appears to be the most important mechanism for the pleural effusions sometimes seen in liver disease, especially cirrhosis. Although patients also may have decreased hepatic synthesis of protein, hypoproteinemia has only a minor role in the pathogenesis of these effusions.

Ascitic fluid may travel through diaphragmatic defects into the pleural space.

## Exudative pleural fluid

Exudative pleural fluid generally implies an increase in permeability of pleural surfaces, allowing protein and fluid to more readily enter the pleural space. Although a wide variety of processes can result in exudative pleural effusions, the two main etiologic categories are inflammatory and neoplastic diseases. Inflammatory processes often originate within the lung but extend to the visceral pleural surface. Infection (especially bacterial pneumonia and tuberculosis) and pulmonary embolism (often with infarction) are two common examples. In the case of pneumonia extending to the pleural surface, an associated pleural effusion is called a *parapneumonic effusion*. When the effusion itself harbors organisms or has the appearance of pus (due to an exuberant inflammatory response with many thousands of neutrophils), the effusion is called an *empyema*, or more properly, *empyema thoracis*. Although infection within the pleural space is commonly secondary to pneumonia, empyema also may result from infection introduced through the chest wall, as occurs with trauma or surgery involving the thorax.

In tuberculosis, a focus of infection adjacent to the pleura may rupture into the pleural space, with an ensuing inflammatory response of the pleura (with or without growth of the tubercle bacilli within the pleural space). In some cases, the pulmonary focus is not apparent, and pleural involvement is the major manifestation of tuberculosis within the thorax, either as a tuberculous empyema in advanced disease or as an inflammatory but largely sterile pleural effusion seen in early tuberculosis.

Other forms of inflammatory disease affecting the pleura primarily involve the pleural surface as opposed to the lung. Several connective tissue diseases, particularly systemic lupus erythematosus and rheumatoid arthritis, are associated with pleural involvement that occurs independent of changes within the pulmonary parenchyma. Inflammatory processes below the diaphragm, such as pancreatitis and subphrenic abscess, are often accompanied by “sympathetic” pleural inflammation and development of an exudative

pleural effusion. With these disorders, inflammation of the diaphragm itself may lead to increased permeability of vessels in the diaphragmatic pleura and leakage of fluid into the pleural space. When ascites is present, as may occur in pancreatitis, transport of fluid from the abdomen through defects in the diaphragm may contribute to pleural fluid accumulation.

Malignancy may cause pleural effusion by several mechanisms, but the resulting fluid is usually exudative. Commonly, malignant cells are found on the pleural surface, arriving there either by direct extension from an intrapulmonary malignancy or by hematogenous (bloodstream) dissemination from a distant source. In other cases, lymphatic channels or lymph nodes become occluded by foci of tumor, impairing the normal lymphatic clearance mechanism for protein and fluid from the pleural space. In these latter cases, malignant cells are generally not found on examination of the pleural fluid.

A host of other disorders may have pleural effusion as a clinical manifestation. The list includes such varied processes as hypothyroidism, benign ovarian tumors (Meigs syndrome), asbestos exposure, and primary disorders of the lymphatic channels. Detailed discussion of the various disorders with potential for pleural fluid accumulation can be found in the Suggested Readings at the end of this chapter.

## Clinical features

A patient with pleural fluid may or may not have symptoms caused by the pleural disease. Whether symptoms are present depends on the size of the effusion(s), the rate of accumulation, the nature of the underlying process, and the degree of a given patient's cardiopulmonary reserve. Inflammatory processes affecting the pleura frequently result in pleuritic chest pain—that is, sharp pain aggravated by respiration. When an effusion is large, patients may experience dyspnea resulting from compression of the underlying lung. With small- or moderate-sized effusions, a patient with otherwise normal lungs may not have any symptoms from the presence of fluid in the pleural space. When the pleural fluid has an inflammatory nature or is frankly infected, fever is commonly present.

On physical examination of the chest, the region overlying the effusion is dull to percussion. Breath sounds are usually decreased in this region due to fluid in the pleural space interfering with the transmission of breath sounds from the lung to the chest wall. However, at the upper level of the effusion, egophony, bronchial breath sounds, and other findings usually associated with consolidation may be heard as manifestations of increased transmission of sound resulting from compression (atelectasis) of the underlying lung parenchyma. A scratchy pleural friction rub may be present, particularly with an inflammatory process involving the pleural surfaces.

Common clinical features with pleural effusion(s):
- Symptoms: pleuritic chest pain, dyspnea
- Physical signs: dullness to percussion, decreased breath sounds, egophony at upper level, pleural friction rub

## Diagnostic approach

Posteroanterior and lateral chest radiographs are typically most important in the initial evaluation of the patient with suspected pleural effusion (Fig. 15.3). With a small effusion, blunting of the normally sharp angle between the diaphragm and chest wall (costophrenic angle) is seen. Often this blunting is first apparent on inspection of the posterior costophrenic angle on the lateral radiograph, because this is the most dependent area of the pleural space. With a larger effusion, a homogeneous opacity of liquid density appears and is most obvious at the lung base(s) when the patient is upright. The fluid may track along the lateral chest wall, forming a meniscus. Ultrasonography and computed tomography (CT) scanning of the chest are more sensitive than plain film in detecting pleural effusions (Fig. 15.4). With imaging for these studies performed in the supine position, small, free-flowing effusions will be seen posteriorly at the bases of the lung and track up the lung fields posteriorly and laterally as the effusion becomes larger.

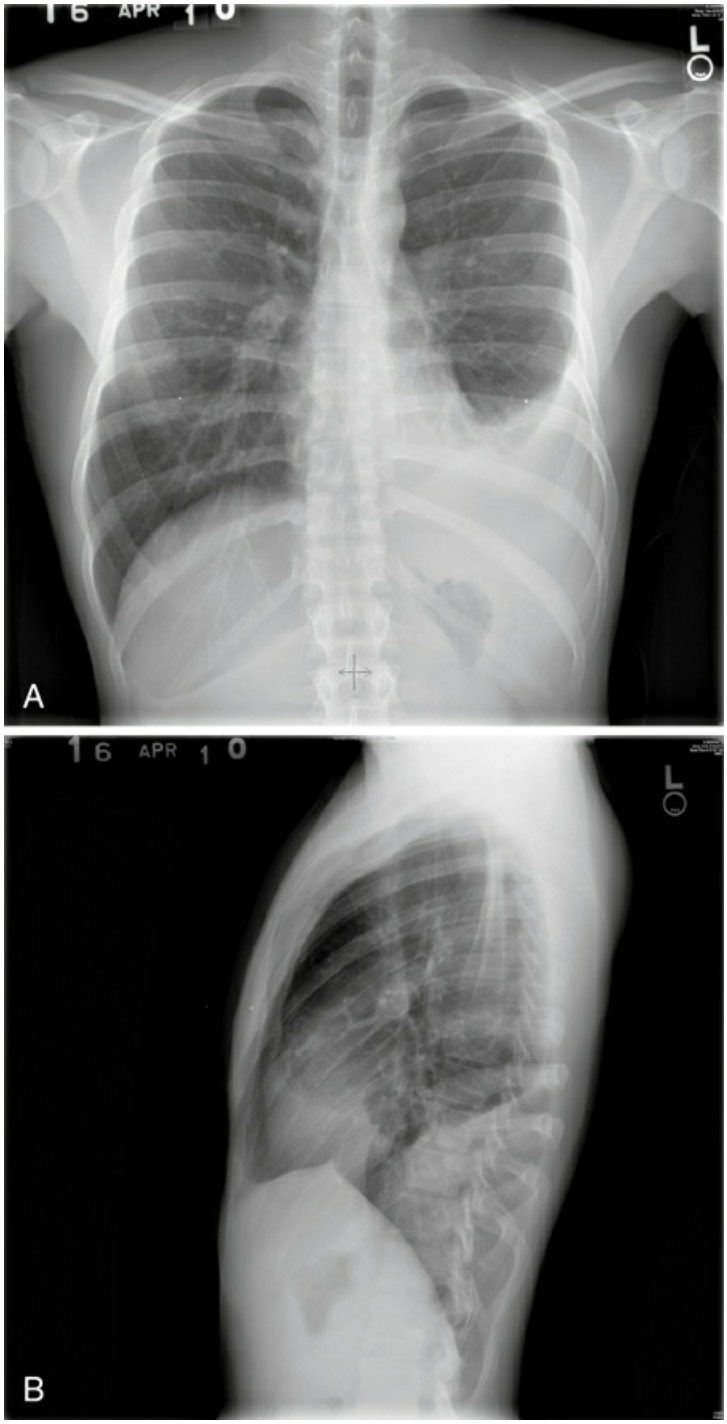


**FIGURE 15.3** Posteroanterior **(A)** and lateral **(B)** chest radiographs demonstrating left pleural effusion.

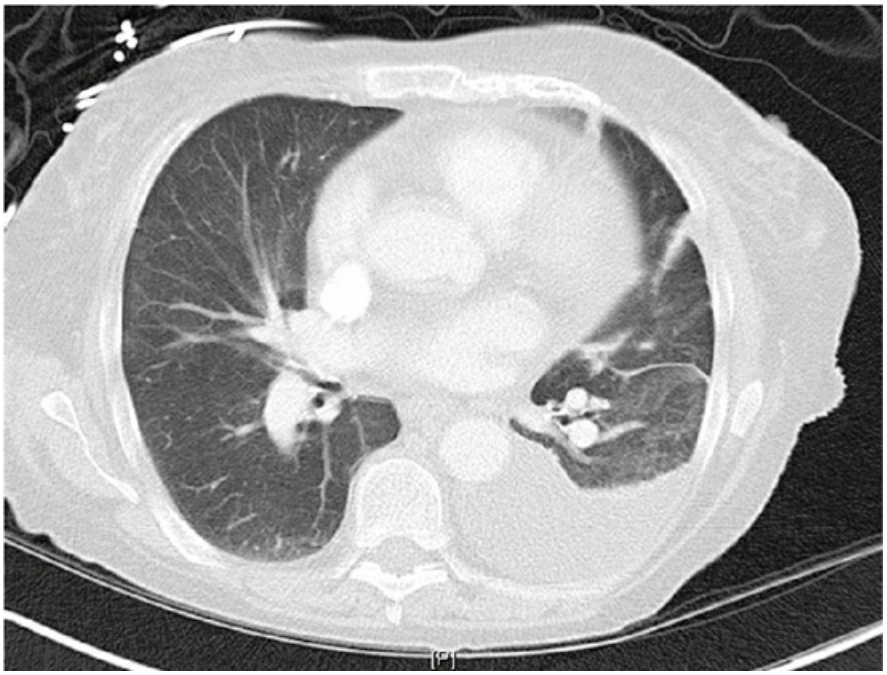

**FIGURE 15.4** Chest computed tomography scan showing a left pleural effusion. With the patient supine, the fluid lies posteriorly against the chest wall in the dependent portion of the left hemithorax.

When inflammatory effusions persist for a time, fluid may no longer be free-flowing as fibrous bands of tissue (loculations) form within the pleural space. In such circumstances, fluid is not necessarily positioned as expected from the effects of gravity, and atypical appearances may be found. To detect whether fluid is free-flowing or whether small costophrenic angle densities represent pleural fluid, a lateral decubitus chest radiograph may be extremely useful. In this view, the patient lies on a side, and free-flowing fluid shifts position to line the most dependent part of the pleural space (Fig. 15.5).

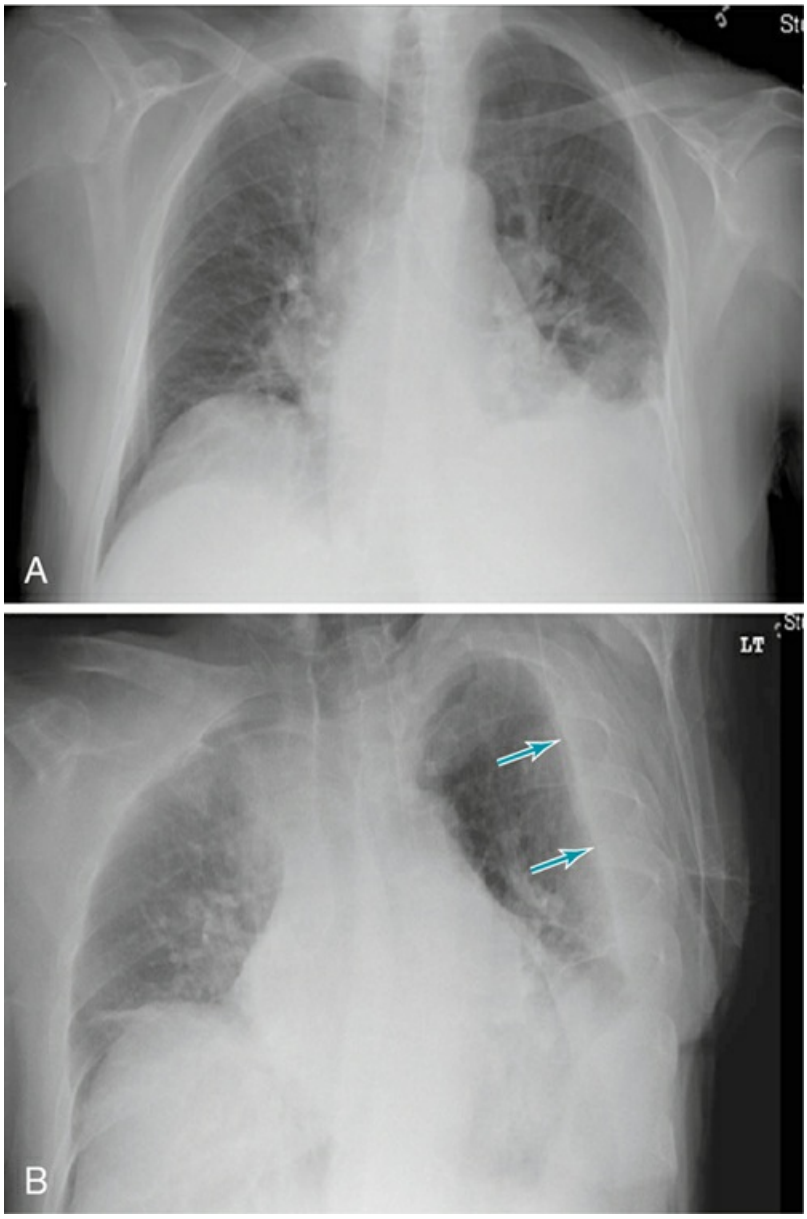


**FIGURE 15.5** Posteroanterior **(A)** chest radiograph suggesting presence of left pleural effusion. Left lateral decubitus **(B)** chest radiograph of patient shown in **A**. With patient lying on left side, pleural fluid *(arrows)* flows freely to dependent part of pleural space adjacent to left lateral chest wall. Film is shown upright for convenience of comparison with **A**.

Ultrasonography is another technique frequently used to evaluate the presence and location of pleural fluid. When pleural fluid is present, a characteristic echo-free space can be detected between the chest wall and lung. Ultrasonography is particularly useful in locating a loculated effusion or a small effusion not apparent on physical examination, and in guiding the physician to a suitable site for thoracentesis.

When a pleural effusion is present and the etiologic diagnosis is uncertain, sampling the fluid by *thoracentesis* (withdrawal of fluid through a needle or catheter) allows determination of the cellular and chemical characteristics of the fluid. These features define whether the fluid is transudative or exudative and frequently give other clues about the cause. Although different criteria have been used, the most common criteria rely on levels of protein and the enzyme lactate dehydrogenase (LDH) within the fluid. Exudative fluid has high levels of protein, LDH, or both, whereas transudative fluid has low levels of protein and LDH.

An exudative effusion is defined by one or more of the following:

1. Pleural fluid/serum protein ratio > 0.5
2. Pleural fluid/serum LDH ratio > 0.6
3. Pleural fluid LDH > $^{2}/_{3}$ × upper limit of normal serum LDH

Pleural fluid obtained by thoracentesis routinely is analyzed for absolute numbers and types of cellular constituents, for microorganisms (by stains and cultures), and for glucose level. In many cases, amylase level and pH value of the pleural fluid are measured. Special slides are prepared for cytologic examination to search for malignant cells. Detailed discussions of the findings in different disorders can be found in the Suggested Readings at the end of this chapter.

When pleural tissue is needed for diagnostic purposes, it is most commonly obtained under direct vision with the aid of a thoracoscope passed through the chest wall and into the pleural space while the patient is under general anesthesia. Formerly, pleural tissue was often sampled by closed pleural biopsy, generally performed with a relatively large cutting needle inserted through the skin of the chest wall in an awake patient. Histologic examination of these small biopsies is most useful for demonstrating granulomas of tuberculosis but also can reveal implants of tumor cells from a malignant process in some cases.

Pulmonary function tests are generally not part of the routine evaluation of patients with pleural effusion. However, a significant effusion may impair lung expansion sufficiently to cause a restrictive pattern (with decreased lung volumes) on pulmonary function testing.

## Treatment

Treatment of pleural effusion depends entirely on the nature of the underlying process and usually is directed at this process rather than the effusion itself. If the effusion is likely to progress to extensive fibrosis or loculation of the pleural space (e.g., with an empyema or a hemothorax [blood in the pleural space, often secondary to trauma]), a chest tube is placed through the chest wall into the pleural space to drain the fluid as completely as possible. If loculation has already occurred, thoracoscopy or an open surgical approach may be necessary to break up fibrous adhesions and allow effective drainage of the fluid and full reexpansion of the lung.

When the effusion is recurrent and large enough to cause dyspnea, the fluid is initially drained with a tube passed into the pleural space, and an irritating agent (e.g., talc or a

tetracycline derivative) is instilled via the tube into the pleural space to induce inflammation and cause the visceral and parietal pleural surfaces to become adherent. This process of sclerosis (also called *pleurodesis*) is most commonly used for recurrent malignant effusions and, if effective, obliterates the pleural space and prevents recurrence of pleural effusion on the side where the procedure was performed. When the effusion is loculated or pleurodesis via a chest tube is unsuccessful, the procedure can be performed under general anesthesia through a thoracoscope. Another option for management of a recurrent effusion is placement of a tunneled pleural catheter that can remain in place for many months and through which the patient or a caregiver can drain fluid as needed to palliate dyspnea related to the effusion.

# Pneumothorax

Air is not normally present between the visceral and parietal pleural surfaces, but it can be introduced into the pleural space by a break in the surface of either pleural membrane, creating a *pneumothorax*. Because pressure within the pleural space is subatmospheric, air readily enters the space if there is any communication with air at atmospheric pressure.

## Etiology and pathogenesis

When a pneumothorax is created by entry of air through the chest wall and parietal pleura, the most common causes are (1) trauma (e.g., knife or gunshot wound) and (2) introduction of air via a needle, catheter, or incision through the chest wall and into the pleural space. Alternatively, air may enter the pleura through a break in the visceral pleura, allowing communication between the airways or alveoli and the pleural space. Examples of the latter circumstance include rupture of a subpleural air pocket (e.g., bleb, cyst, or bulla) into the pleural space or necrosis of the lung adjacent to the pleura by a destructive pneumonia or neoplasm.

A pneumothorax can result from a break in the parietal pleura (e.g., from trauma, needle, or catheter insertion) or in the visceral pleura (e.g., from rupture of a subpleural air pocket or necrosis of lung adjacent to the pleura).

When a reason for the pneumothorax is apparent, such as an underlying abnormality in the lung, the pneumothorax is called a *secondary spontaneous pneumothorax*. Common causes include lung diseases known to be associated with subpleural air pockets (emphysema or interstitial lung disease with honeycombing and subpleural cysts), or destruction of lung tissue adjacent to the pleural surface (necrotizing pneumonia or neoplasm). In contrast, some patients do not have a defined abnormality of the lung adjacent to the pleura and therefore are said to have a *primary spontaneous pneumothorax*. Even in this circumstance, patients frequently have small subpleural pockets of air (blebs), especially at the lung apices, that have gone unrecognized clinically and on routine radiographic examination. If a bleb eventually ruptures, air is released from the lung parenchyma into the pleural space, creating a pneumothorax.

Patients who receive positive pressure to the tracheobronchial tree and alveoli (e.g., with mechanical ventilation) are subject to development of a pneumothorax. In this

case, positive pressure may lead to rupture of a preexisting subpleural bleb or penetration of air through an alveolar wall into the interstitial space. The air then tracks through the lung parenchyma to the subpleural surface and eventually ruptures into the pleural space. Alternatively, and perhaps more commonly, the air following alveolar rupture tracks retrograde to the mediastinum alongside blood vessels and airways to produce a pneumomediastinum (see Chapter 16). A pneumothorax can result when air subsequently ruptures through the mediastinal pleura into the pleural space.

## Pathophysiology

The pathophysiologic consequences of a pneumothorax are variable, ranging from none to the development of acute cardiovascular collapse. The size of the pneumothorax (i.e., amount of air within the pleural space) is an important determinant of the clinical effects. Because the lung is enclosed within a relatively rigid chest wall, accumulation of a substantial amount of pleural air is accompanied by collapse of the underlying lung parenchyma. In extreme cases, air in the pleural space occupies almost the entire hemithorax, and the lung is totally collapsed and functionless until the pleural air is resorbed or removed.

Air in the pleural space is generally under atmospheric or subatmospheric pressure. In some cases the air may be under positive pressure, creating a *tension pneumothorax*. This tension within the pleural space develops due to a "one-way valve" mechanism by which air is free to enter the pleural space during inspiration but the site of entry is closed during expiration. When air repeatedly enters the pleural space but does not exit, the intrapleural pressure increases, and the underlying lung collapses further. When pleural pressure is sufficiently high, the mediastinum and trachea may be shifted away from the side of the pneumothorax. In extreme cases, cardiovascular collapse and respiratory failure may result, with a marked fall in cardiac output and blood pressure. These hemodynamic changes are commonly stated to result from inhibition of venous return into the superior and inferior venae cavae as a consequence of positive intrathoracic pressure. However, in animal models, the predominant pathophysiologic mechanism appears to be progressive respiratory failure with severe hypoxemia and ventilatory compromise. Whatever the mechanism, emergent treatment is necessary to release the air under tension and reverse the process. A particularly important risk factor for development of a tension pneumothorax is positive-pressure ventilation with a mechanical ventilator. When a pneumothorax occurs in this situation, the ventilator may continue to introduce air under high pressure through the site of rupture in the visceral pleura.

A tension pneumothorax may be associated with total collapse of the underlying lung, mediastinal shift, and cardiovascular collapse.

For most cases of pneumothorax, after the site of entry into the pleural space is closed, the air is spontaneously resorbed. The reason is that the pressure of gases in the air in a pneumothorax is higher than the combined partial pressure of those gases in surrounding venous or capillary blood. For example, air within the pleural space might have a pressure a few millimeters of mercury below atmospheric pressure, or approximately 755 to 758 mm Hg. In contrast, gas pressures in mixed venous blood are

approximately as follows: $P_{O_2}$ = 40 mm Hg, $P_{CO_2}$ = 46 mm Hg, $P_{N_2}$ = 573 mm Hg, and $P_{H_2O}$ = 47 mm Hg. Therefore, the total gas pressure in mixed venous blood is 706 mm Hg, which is approximately 50 mm Hg below that of air in the pleural space. Consequently, there is a gradient for diffusion of gas from the pleural space into mixed venous blood. With continued diffusion of gas from the pleural space into the blood, the size of the pneumothorax is slowly reduced, the gas pressures within the pleural space are maintained, and the gradient favoring absorption of gas continues until all the air is resorbed.

If high levels of supplemental $O_2$ are administered to the patient with a pneumothorax, the process of resorption can be hastened. Following application of oxygen, most of the nitrogen in arterial blood is replaced by $O_2$. As a result, $P_{N_2}$ in the capillary blood surrounding the pneumothorax becomes quite low, and the gradient for resorption of nitrogen from the pleural space is increased considerably. At the same time, although arterial $P_{O_2}$ is high after inhalation of pure $O_2$, $P_{O_2}$ falls substantially in capillary and venous blood because of $O_2$ consumption by the tissues. Therefore, a large partial pressure gradient from pleural gas to pleural capillary blood remains for $O_2$ as well. The net result is that $O_2$ administration favors more rapid resorption of nitrogen (the main component of gas in ambient air and thus in the pneumothorax) without significantly compromising the gradient promoting resorption of $O_2$.

When a pneumothorax is causing important clinical problems, the physician need not wait for spontaneous resorption of the air but can actively remove the air with a needle, catheter, or tube inserted into the pleural space.

## Clinical features

In many cases, the patient has obvious risk factors for developing a pneumothorax (e.g., predisposing underlying lung disease, receiving positive-pressure ventilation with a mechanical ventilator). The group of patients in whom a primary spontaneous pneumothorax develops shows a striking predominance of males. In addition, the patients are often smokers, are young adults, and frequently are tall and thin.

Clinical features of pneumothorax:
- Symptoms: chest pain and dyspnea
- Physical signs: asymmetric (decreased) breath sounds, hyperresonance, tracheal deviation (tension), and ↓ blood pressure (tension)

The most common complaint at the time of pneumothorax is acute onset of chest pain, dyspnea, or both, but some patients may be totally symptom-free, particularly if the pneumothorax is small. On physical examination, findings depend to a large extent on the size of the pneumothorax. Because of decreased transmission of sound, breath sounds and tactile fremitus are diminished or absent. With a significant amount of air in the pleural space, increased resonance to percussion over the affected lung may be observed.

When the pneumothorax is under tension, the patient is often in acute distress, and a decrease in blood pressure or even frank cardiovascular collapse may be present.

Palpation of the trachea frequently demonstrates deviation away from the side of the pneumothorax.

## Diagnostic approach

The diagnosis of pneumothorax most commonly is established or confirmed by chest radiograph, although CT scan and ultrasound have greater sensitivities for small pneumothoraces. The characteristic finding is a curved line representing the edge of the lung (the visceral pleura) separated from the chest wall. Between the edge of the lung and the chest wall, the pleural space is lucent, and none of the normal vascular markings of the lung are seen in this region (Figs. 15.6 and 15.7). When the pneumothorax is small, separation of the visceral and parietal pleura appears on upright chest films only at the apex of the lung, where the pleural air generally accumulates first. If the pneumothorax is substantial, the lung loses a significant amount of volume and therefore has a greater density than usual.

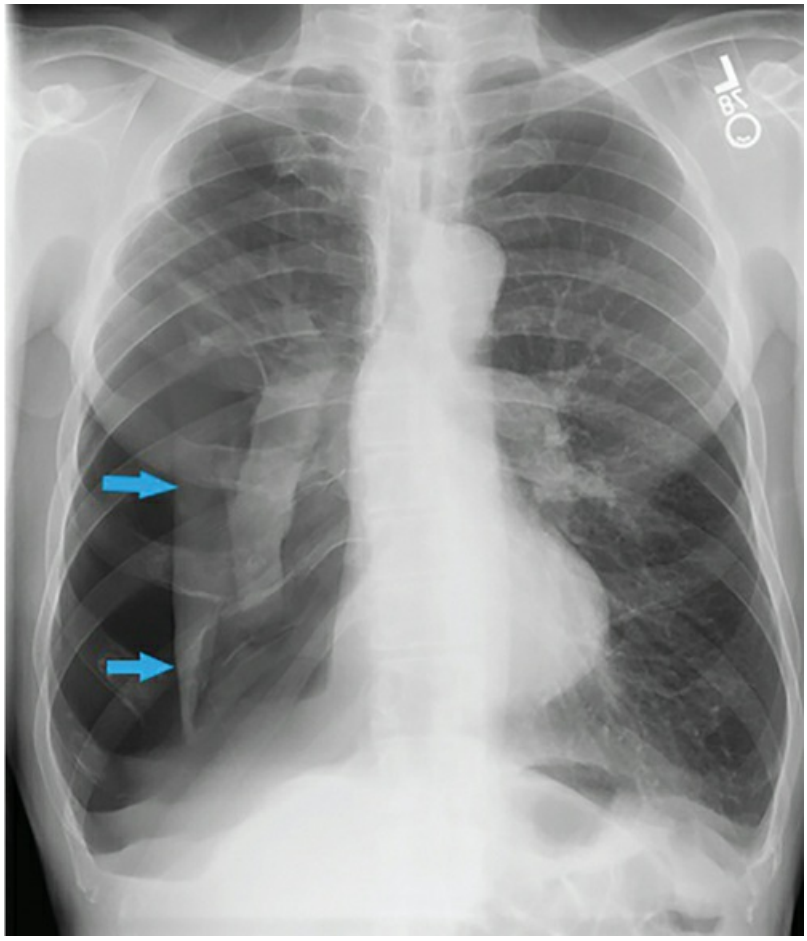

**FIGURE 15.6** Chest radiograph of patient with right-sided spontaneous pneumothorax and underlying COPD. *Arrows* point to visceral pleural surface of lung. Beyond visceral pleura is air within pleural space. No lung markings can be seen in this region.

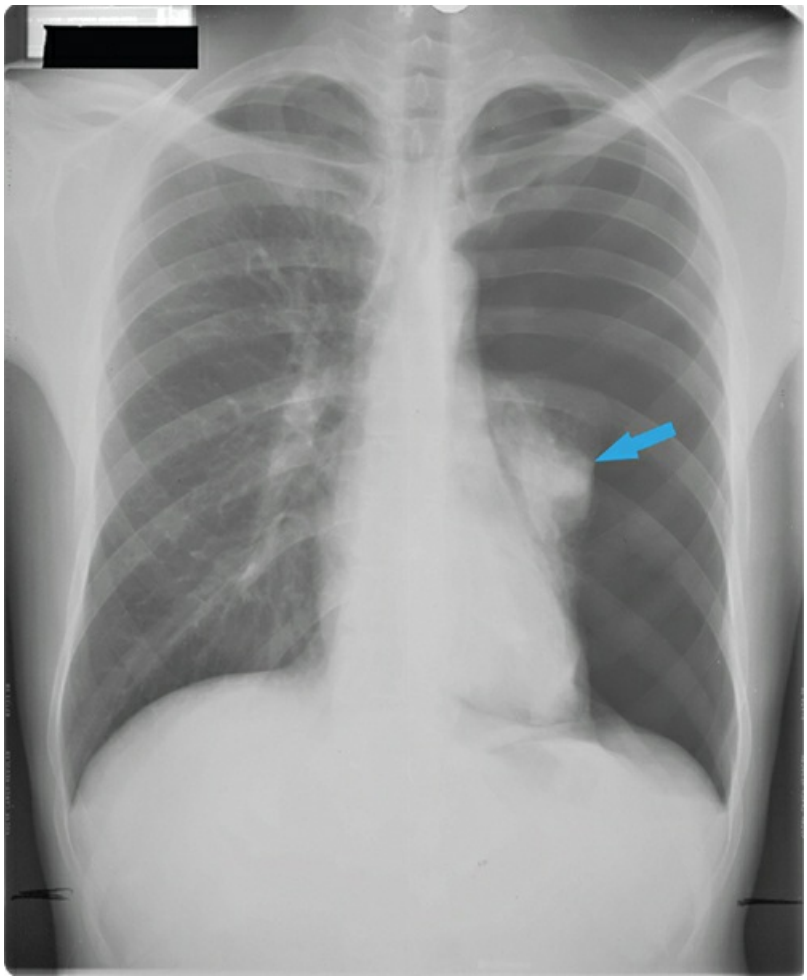

**FIGURE 15.7** Chest radiograph of left spontaneous pneumothorax. *Arrow* points to edge of the completely collapsed left lung.

When both fluid and air are present in the pleural space *(hydropneumothorax),* the fluid no longer appears as a meniscus tracking up along the lateral chest wall. Rather, the fluid falls to the most dependent part of the pleural space and appears as a liquid density with a perfectly horizontal upper border, above which is the air in the pleural space (see Fig. 15.8). Finally, when gas in the pleural space is under tension, evidence is often seen of structures (e.g., trachea and mediastinum) being "pushed" away from the side of the pneumothorax (Fig. 15.9).

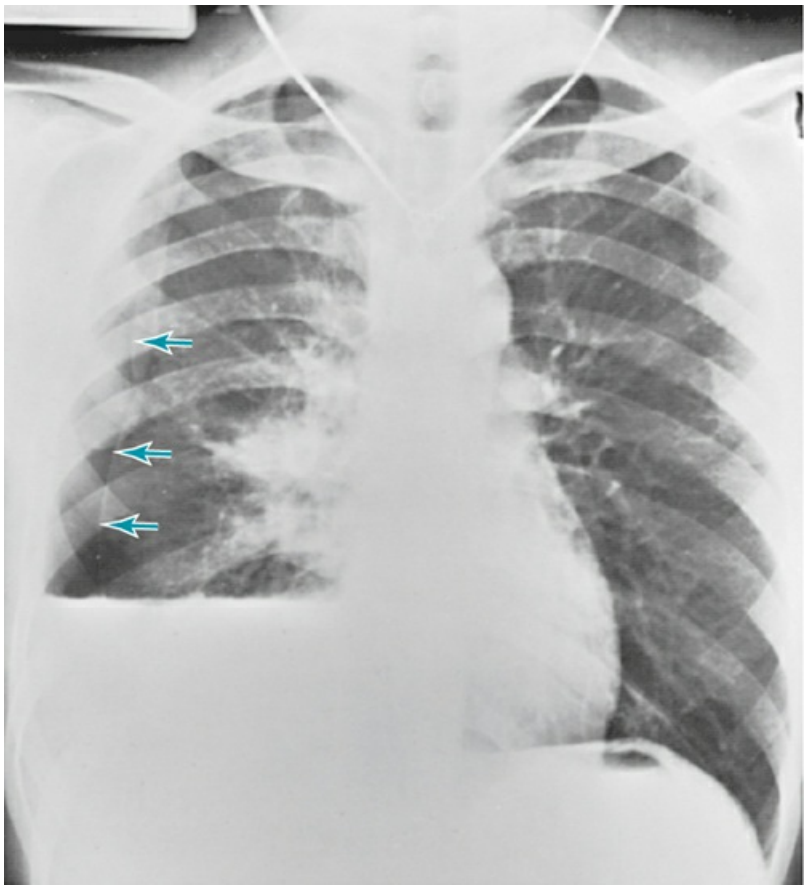

**FIGURE 15.8** Chest radiograph shows right hydropneumothorax. Horizontal line in lower right hemithorax is interface between air and liquid in pleural space. *Arrows* point to visceral pleura above level of effusion. There is air in pleural space between visceral pleura and chest wall.

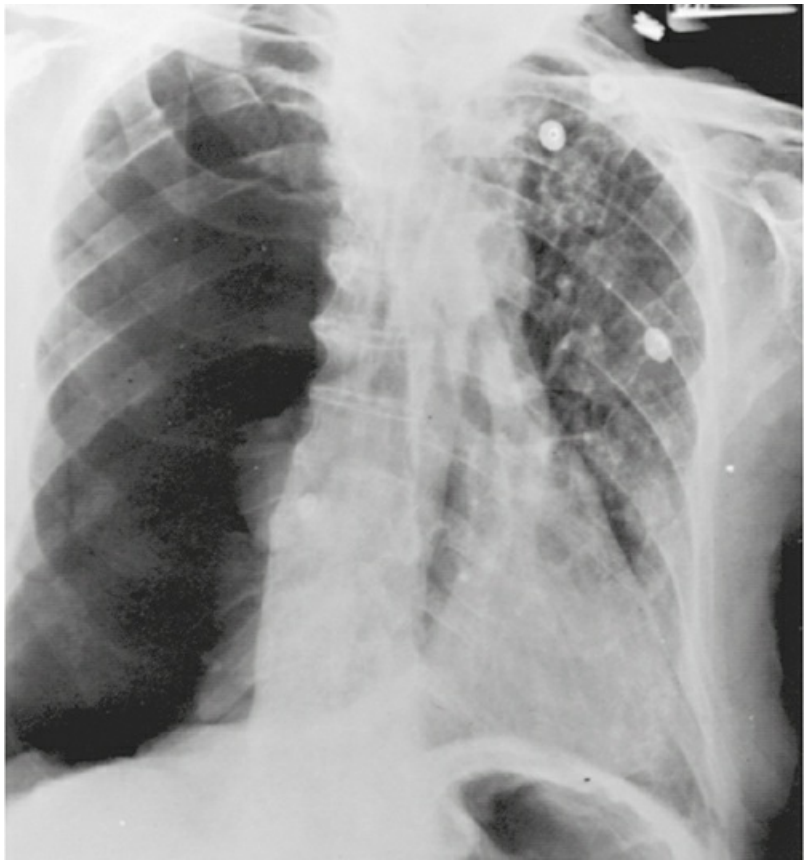

**FIGURE 15.9** Chest radiograph shows right-sided tension pneumothorax. No lung markings are seen in right hemithorax, and mediastinum is shifted to left.

## Treatment

Treatment of a pneumothorax is based on the type of pneumothorax as well as by the size and the ensuing clinical consequences. With a primary spontaneous pneumothorax causing few symptoms, it is best to wait for spontaneous resolution. With a large but minimally symptomatic primary spontaneous pneumothorax (involving >20% of the hemithorax), the options are either to evacuate the air with a needle or catheter, or wait for spontaneous resolution. Resolution can be hastened by administration of 100% $O_2$, which alters the partial pressures of gases in capillary blood, favoring resorption of pleural air.

When the pneumothorax is secondary to identifiable underlying lung disease (secondary spontaneous pneumothorax) or the patient has significant clinical sequelae, the air is best removed, usually by a catheter or chest tube inserted into the pleural space. Patients with secondary spontaneous pneumothorax and those with recurrent primary spontaneous pneumothorax often require obliteration of the pleural space by instilling agents, such as talc, into the pleura to promote pleural inflammation and sclerosis. Concomitant thoracoscopic resection of subpleural apical blebs is frequently performed, giving the opportunity to achieve pleurodesis via mechanical irritation of the

pleura rather than by agents such as talc.

If a patient has hemodynamic compromise because of a tension pneumothorax, a needle, catheter, or tube must be inserted immediately to relieve the pressure. When this technique is performed, the sound of air under pressure escaping from the pleural space can readily be heard. The most important results of decompression are improvements in gas exchange, venous return to the thorax, cardiac output, and arterial blood pressure.

## Malignant mesothelioma

Unlike primary lung cancer (discussed in Chapters 20 and 21), *malignant mesothelioma* is a malignant neoplasm that primarily involves the pleura rather than the airways or the pulmonary parenchyma. Malignant mesothelioma is relatively uncommon compared to lung cancer, and unlike lung cancer, smoking is not a risk factor. The primary risk factor for development of malignant mesothelioma is a history of exposure to asbestos, generally in the range of 30 to 40 years earlier. Individuals who have worked in the types of jobs that expose them to asbestos (see Chapter 20) are the persons at highest risk, but a heavy exposure is not necessary to increase the risk for malignant mesothelioma. In fact, mesothelioma develops in spouses of asbestos workers, presumably because of inhalation of asbestos dust while exposed to their partners' clothes.

In patients with malignant mesothelioma, the main symptoms are chest pain, dyspnea, and sometimes cough. Chest imaging studies are most notable for the presence of pleural fluid and often irregular or lobulated thickening of the pleura (Fig. 15.10). Diagnosis requires biopsy of the pleura and histologic demonstration of the malignancy. Because the tumor originates in the pleura and does not directly communicate with airways, malignant cells are not shed into the tracheobronchial tree and cannot be found on cytologic examination of sputum or bronchoscopy specimens.

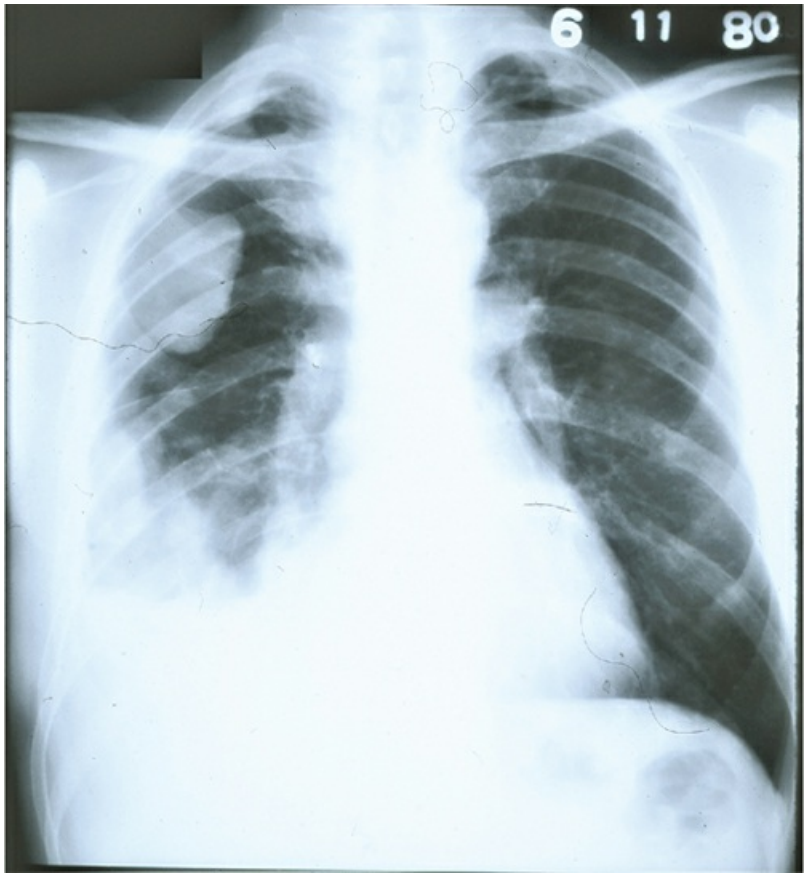


**FIGURE 15.10** Chest radiograph of patient with mesothelioma. Note several lobulated, pleural-based masses in right hemithorax accompanied by right pleural effusion.

Mesothelioma is suggested by pleural fluid, irregular or lobulated pleural thickening, and a distant history of asbestos exposure.

The prognosis for malignant mesothelioma is poor. The tumor eventually entraps the lung and spreads to mediastinal structures. Death generally results from respiratory failure. No clearly effective form of therapy is available, and fewer than 10% of patients survive 3 years. Although improved mortality has not been demonstrated in randomized trials, surgical approaches to treatment have included unilateral removal of the visceral and parietal pleura and any visible tumor (called pleurectomy and decortication), or unilateral removal of the pleura and visible tumor as well as removal of the entire ipsilateral lung (called extrapleural pneumonectomy). Chemotherapy and/or radiotherapy have also been used, either alone or in combination with one of the surgical options. As a palliative measure for patients with persistent symptomatic pleural effusions, obliteration of the pleural space (pleurodesis) with a sclerosing agent can be performed in an attempt to prevent reaccumulation of large amounts of pleural fluid. Because of the poor prognosis, mesothelioma has become a target for a variety of new types of investigational therapy, including immunotherapy using immune

checkpoint inhibitors, cellular therapy using genetically engineered T lymphocytes, and therapy aimed at specific molecular targets.

## Suggested readings

### General reviews


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# 16: Mediastinal disease

OUTLINE



The mediastinum is the region of the thoracic cavity located between the two lungs. Included within the mediastinum are numerous structures, ranging from the heart and great vessels (aorta, superior and inferior venae cavae) to lymph nodes and nerves. The physician dealing with diseases of the lung is confronted with mediastinal disease in two main ways: (1) an imaging study (chest radiograph or computed tomography [CT]) shows an abnormal mediastinum or (2) the patient has symptoms similar to those originating from primary pulmonary disease. This chapter describes some of the anatomic features of the mediastinum and discusses two of its most common clinical problems: mediastinal masses and pneumomediastinum.

## Anatomic features

The mediastinum is bounded superiorly by bony structures of the thoracic inlet (specifically the manubrium, first ribs, and first thoracic vertebra) and inferiorly by the diaphragm. Laterally, the mediastinal pleura on each side serves as a membrane

separating the medial aspect of the lung (with its visceral pleura) from the structures contained within the mediastinum. The mediastinum most frequently is divided into three anatomic compartments: anterior, middle, and posterior (Table 16.1). This division is particularly useful for characterizing mediastinal masses because specific etiologic factors have a predilection for a particular compartment. Normal structures located within or coursing through each of the compartments may serve as the origin of a mediastinal mass. Consequently, knowledge of the structures contained in each of the three compartments is important for the clinician in evaluating a patient with a mediastinal mass.

**TABLE 16.1**
**Mediastinal Compartments: Anatomy and Pathology**

| Compartment | Borders | Normal Structures | Masses |
|---|---|---|---|
| Anterior | Anterior: sternum<br>Posterior: pericardium, ascending aorta, brachiocephalic vessels | Lymph nodes<br>Connective tissue<br>Thymus (remnant in adults) | Thymoma<br>Germ cell neoplasm<br>Lymphoma<br>Thyroid enlargement (intrathoracic goiter)<br>Other tumors |
| Middle | Anterior: anterior pericardium, ascending aorta, brachiocephalic vessels<br>Posterior: posterior pericardium | Pericardium<br>Heart<br>Vessels: ascending aorta, venae cavae, main pulmonary arteries<br>Trachea<br>Lymph nodes<br>Nerves: phrenic, upper vagus | Carcinoma<br>Lymphoma<br>Pericardial cyst<br>Bronchogenic cyst<br>Benign lymph node enlargement (granulomatous disease) |
| Posterior | Anterior: posterior pericardium<br>Posterior: posterior chest wall | Vessels: descending aorta<br>Esophagus<br>Vertebral column<br>Nerves: sympathetic trunk, lower vagus<br>Lymph nodes<br>Connective tissue | Neurogenic tumor<br>Diaphragmatic hernia |

The borders of the three mediastinal compartments are visualized more easily on the lateral chest radiograph than on the posteroanterior view (Fig. 16.1). Several descriptions exist for the limits defining each compartment. According to the scheme used here, the anterior mediastinum extends from the sternum to the anterior border of the pericardium. Included within this region are the thymus, lymph nodes, and loose connective tissue.

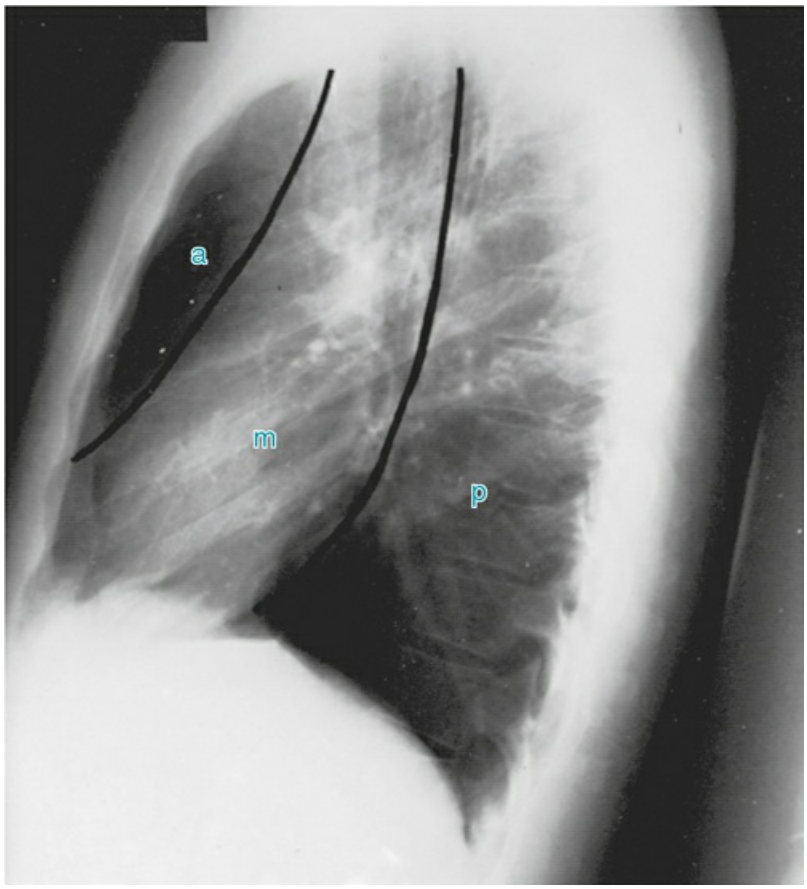


**FIGURE 16.1** Lateral chest radiograph shows borders of three mediastinal compartments. *a*, anterior; *m*, middle; *p*, posterior.

The borders of the middle mediastinum are the anterior and posterior pericardium. This region includes the heart, pericardium, great vessels, trachea, lymph nodes, and phrenic nerves. The upper portion of the vagus nerve also courses through the middle mediastinum.

The posterior mediastinum extends from the posterior pericardium to the posterior chest wall. This compartment normally includes the vertebral column, neural structures (including the sympathetic trunks and lower portion of the vagus nerve), esophagus, and descending aorta. Some lymph nodes and loose connective tissue may also be found in the posterior mediastinum.

Another classification scheme is based on position within the mediastinum as seen on cross-sectional CT images. The three compartments defined in this scheme are prevascular, visceral, and paravertebral, corresponding roughly to anterior, middle, and posterior. The primary difference is that the esophagus is included in the visceral compartment, which extends more posteriorly than the corresponding middle mediastinal compartment. In our discussion below, we will use the anterior, middle, and posterior classification scheme.

## Mediastinal masses

## Etiology

Because of the predilection for certain types of masses to occur in specific mediastinal compartments, it is easiest to separately consider masses occurring in each of the three anatomic regions. However, a fair amount of overlap occurs; that is, many types of mediastinal masses are not exclusively limited to the one compartment where they most frequently appear. A summary of the types of mediastinal masses, arranged by anatomic compartment, is provided in Table 16.1.

### Anterior mediastinal masses

The major types of anterior mediastinal mass are thymoma, germ cell tumor, lymphoma, thyroid gland enlargement, and miscellaneous other tumors.

Thymomas, or tumors of the epithelium of the thymus gland, are the most common type of neoplasm originating in the anterior compartment. They may be benign or malignant in behavior, depending more on whether they exhibit local invasion than on any specific morphologic features. Thymomas are diagnosed most commonly in patients between 40 and 60 years of age and have a similar incidence among men and women. These tumors are notable for their association with a variety of systemic paraneoplastic syndromes. The best known and most common of these is myasthenia gravis, which is found in 10% to 50% of patients with thymic tumors. Myasthenia gravis is characterized clinically by abnormally rapid muscle fatigue and weakness and pathophysiologically by a decrease in functional acetylcholine receptors at neuromuscular junctions caused by autoantibodies against the acetylcholine receptor. Other systemic syndromes associated with thymoma include pure red blood cell aplasia, hypogammaglobulinemia, and thymoma-associated multiorgan autoimmunity, which is similar to graft-versus-host disease and characterized by skin rash, enterocolitis, and hepatitis.

Myasthenia gravis and other paraneoplastic syndromes occur frequently in patients with thymoma.

Germ cell tumors are believed to originate from primitive germ cells that underwent abnormal migration during an early developmental period. Several types of germ cell tumors have been described. The most common is the teratoma, a tumor composed of ectodermal, mesodermal, and endodermal derivatives. The types of tissue seen are clearly foreign to the area from which the tumor arose and may include elements such as skin, hair, cartilage, and bone. Like thymomas, these tumors may be benign or malignant, with approximately 80% described as benign. Other less common but more reliably malignant mediastinal germ cell tumors include seminomas and choriocarcinomas.

Lymphomas may involve the mediastinum, either as part of a disseminated process, in which the mediastinum is only one locus of the disease, or as primary mediastinal masses without other clinically apparent areas of involvement. Hodgkin lymphoma, particularly the nodular sclerosis subtype, is well described as manifesting solely as a mediastinal mass, although non-Hodgkin lymphoma may have a similar presentation. Lymphoma involving the mediastinum is most common in either the anterior or the middle mediastinal compartment.

Lymphoma and carcinoma commonly affect anterior or middle mediastinal compartments. Malignant mediastinal disease may be isolated or part of more widespread involvement.

The thyroid gland may be the origin of a mediastinal mass as a result of extension of thyroid tissue from its normal location in the neck into the mediastinum. Because these masses are typically not functional, patients do not have clinical or laboratory evidence of hyperthyroidism. Only rarely do these masses of thyroid origin prove to be malignant.

Other tumors, including carcinomas, may produce a mediastinal mass. In many cases, mediastinal involvement is secondary to a primary neoplasm found elsewhere, particularly in the lung. In occasional cases, no other tumor is apparent, and patients are believed to have a primary carcinoma originating in the mediastinum. Carcinomatous involvement of the mediastinum is not limited to the anterior mediastinum but is also common in the middle mediastinal compartment.

A variety of less common neoplasms may occur in the anterior mediastinum, including parathyroid tumors and tumors of fatty or connective tissue origin. Given the infrequency of these tumors, they are not discussed in this book.

### Middle mediastinal masses

Carcinomas and lymphomas may be found in the middle mediastinum, as mentioned in the discussion of anterior mediastinal masses. In addition, the middle mediastinum is frequently the location of benign cysts originating from structures found within this region. For example, fluid-filled pericardial and bronchogenic cysts originate from the embryonic formation of the pericardium and tracheobronchial tree, respectively. However, these cysts are generally self-contained and usually do not directly communicate with either the pericardium or airways. Nonmalignant enlargement of lymph nodes in the middle mediastinum, often in the hilar regions, is commonly found in granulomatous diseases such as sarcoidosis, histoplasmosis, and tuberculosis.

### Posterior mediastinal masses

The posterior mediastinum is characteristically the location of tumors of neurogenic origin. These tumors may arise from a variety of nerve elements found in peripheral nerves, the sympathetic nervous system chain, or paraganglionic tissue. Examples include neurilemomas (arising from the Schwann sheath), ganglioneuromas and neuroblastomas (benign and malignant lesions arising from the sympathetic nervous system, respectively), and pheochromocytomas. Diaphragmatic hernias, either congenital or acquired, frequently are posterior, with the herniated intraabdominal organ appearing as a posterior mediastinal mass.

## Clinical features

Almost one-half of patients with a mediastinal mass have no symptoms, and the mass is first detected on incidentally performed chest imaging. In patients who develop symptoms, the most common are chest pain, cough, and dyspnea. Occasionally, evidence is seen of esophageal or superior vena caval compression, leading to difficulty swallowing (dysphagia) or to facial and upper extremity edema attributable to impairment of venous return (superior vena cava syndrome). Thymic tumors may

manifest with one of the associated paraneoplastic syndromes described previously such as muscle weakness (from myasthenia gravis) or anemia (from pure red cell aplasia). A variety of systemic symptoms may be related to the presence of a lymphoma or other malignancy or to hormone production by hormonally active mediastinal tumors.

## Diagnostic approach

In almost all cases, a mediastinal mass is initially identified by either a posteroanterior and lateral chest radiograph or a chest CT scan. In addition to showing the mass, these studies allow determination of its location within the mediastinum (Fig. 16.2). When the mass is first detected on chest radiograph, a chest CT scan is then performed for further characterization (Fig. 16.3). A contrast-enhanced CT scan is particularly useful for defining the cross-sectional appearance of the lesion, its density, and its relationship to other structures within the mediastinum (Fig. 16.4).

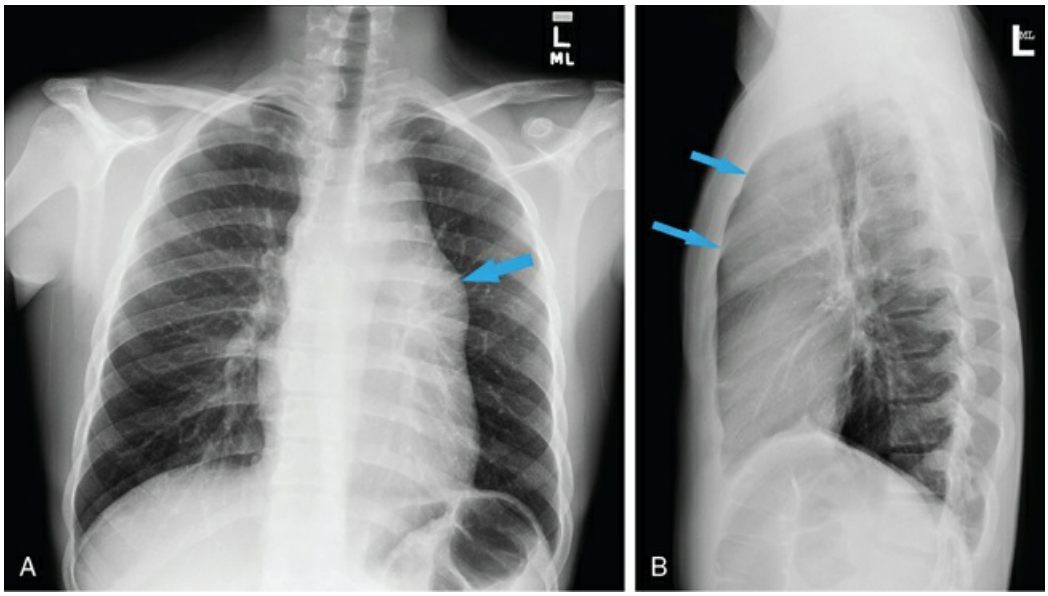


**FIGURE 16.2** Chest radiographs of patient with large mediastinal mass shown in posteroanterior **(A)** and lateral **(B)** views. The mass, proved at surgery to be a germ cell tumor (seminoma), involves anterior and middle mediastinal compartments. In (A), the mass is above the left heart border, including the bulge in the area of the left hilum (arrow). In (B), the mass occupies the retrosternal space above the heart, which normally should have air rather than soft tissue (arrows).

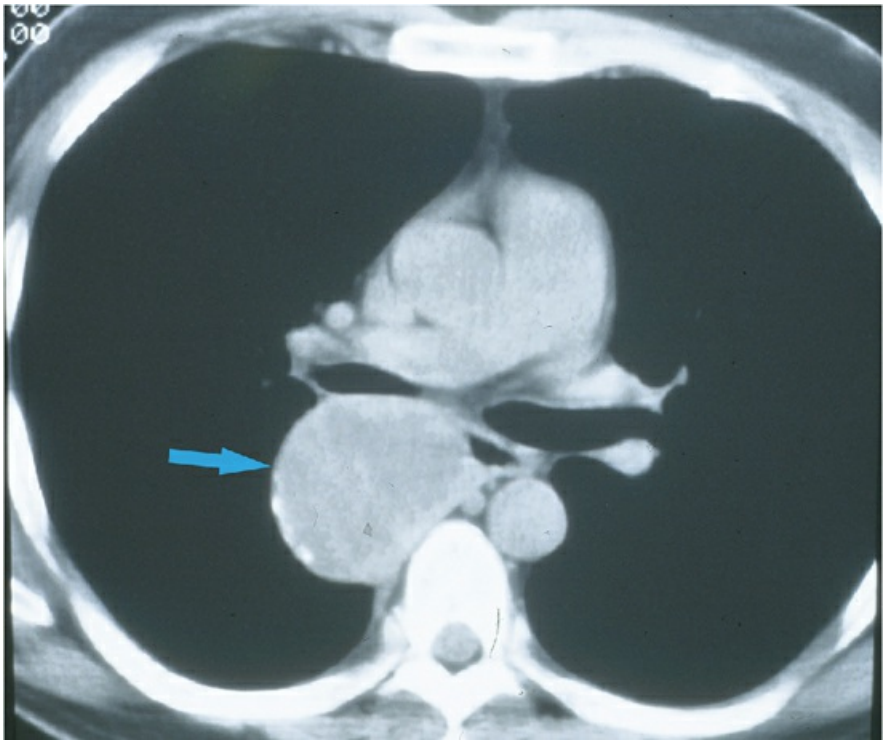

**FIGURE 16.3** Chest computed tomography scan of a patient with a bronchogenic cyst appearing as a mass in the middle and posterior mediastinum (arrow). *Source:* (Courtesy of Dr. Paul Stark.)

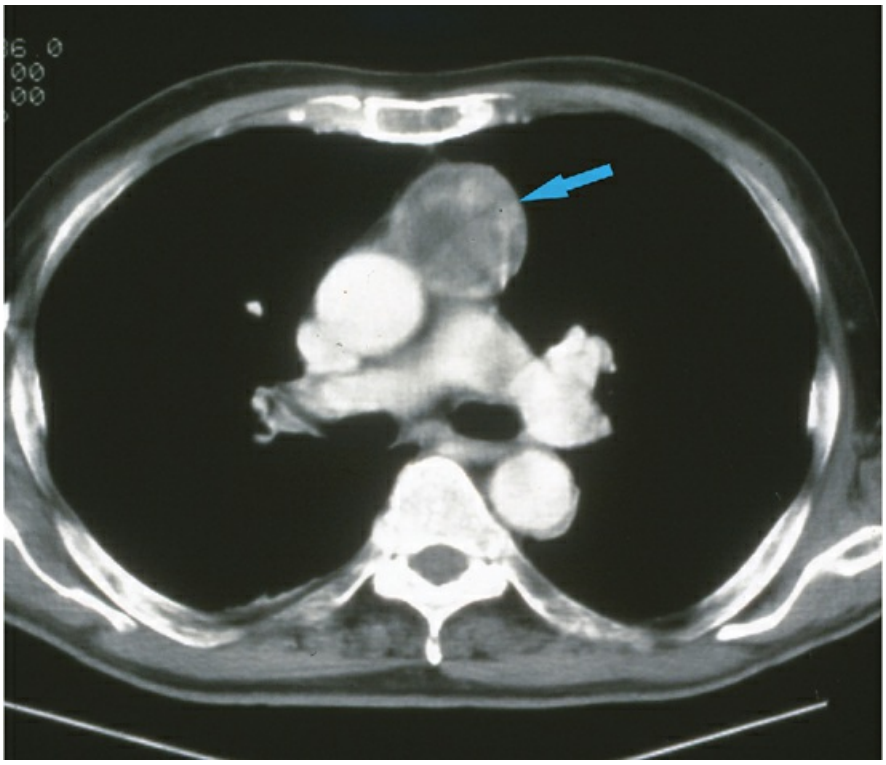

**FIGURE 16.4** Contrast-enhanced chest computed tomography scan showing an anterior mediastinal mass due to a cystic thymoma (arrow). *Source:* (Courtesy of Dr. Paul Stark.)

Several other diagnostic tests may be useful in specific clinical situations. With magnetic resonance imaging (MRI), blood vessels can be distinguished from other mediastinal structures without the use of radiographic contrast. Like a CT scan, MRI can display images in coronal and sagittal planes, as well as cross-sectional axial views. $^{18}$F-fluorodeoxyglucose positron emission tomography (PET) yields information about tissue metabolism, which is generally increased in active neoplastic or infectious processes, and thus may narrow the differential diagnosis of the anatomic lesion.

Computed tomography (CT) is generally the most valuable modality in the evaluation of mediastinal masses.

The definitive diagnosis of a mediastinal mass typically requires examination of tissue by histopathologic techniques. If tissue cannot be obtained via a percutaneous or endobronchial ultrasound approach, it is frequently obtained either by mediastinoscopy, in which a rigid scope is inserted into the mediastinum via an incision at the suprasternal notch, or by exploration of the mediastinum by a surgical approach that is anterior and adjacent to the sternum (parasternal mediastinotomy, also referred to as a Chamberlain procedure). The technique of video-assisted thoracic surgery also can be used to obtain tissue from the mediastinum. In some cases, the patient undergoes a more extensive procedure that allows biopsy and removal of the mass at the same time.

Techniques for histologic sampling of a mediastinal mass:

1. Percutaneous needle aspiration or biopsy
2. Endobronchial ultrasound-guided aspiration
3. Mediastinoscopy
4. Parasternal mediastinotomy
5. Video-assisted thoracic surgery

### Treatment

Treatment of the various mediastinal masses depends to a large extent on the nature of the lesion. In many cases, complete removal of the mass by surgery is the preferred procedure if technically feasible. Because benign lesions may slowly enlarge and compress vital mediastinal structures, excision of even low-grade neoplasms is frequently indicated. In addition, there may be complicating hemorrhage or infection of a benign lesion and eventually even malignant transformation of an initially benign tumor; these factors also favor removal, if possible, following initial diagnosis.

Treatment of malignant tumors depends on the type of tumor and the presence or absence of invasion of other mediastinal structures. Because surgical removal of malignant lesions often is not possible, chemotherapy and radiotherapy are frequently the primary forms of treatment.

## Pneumomediastinum

Normally, free air is not present within the mediastinum. When air enters the mediastinum for any number of reasons, *pneumomediastinum* is said to be present.

### Etiology and pathogenesis

The three major sources of air entry to the mediastinum are (1) through the skin and chest wall, as occurs commonly in the setting of penetrating trauma; (2) from a tear or defect in the esophagus or the trachea, allowing air to enter the mediastinum directly; and (3) from a localized loss of integrity of the alveoli. In the last circumstance, an increase in intraalveolar pressure may induce air entry into interstitial tissues of the alveolar wall. This interstitial air may then dissect alongside the wall of blood vessels coursing through the interstitium. After air tracks back proximally, it can eventually enter the mediastinum at the site of origin of the vessels in the mediastinum. When pneumomediastinum occurs as a result of this final mechanism, it is termed the *Macklin effect*.

Sources of air entry in a pneumomediastinum:

1. External (penetrating trauma)
2. Tracheal or esophageal tear
3. Alveolar rupture and tracking of air proximally

Proximal dissection of extraalveolar air is probably the most common cause of a pneumomediastinum. In some cases, the reason for the increase in intraalveolar pressure is obvious—for example, severe coughing, vomiting, or straining. In patients receiving mechanical ventilation, the positive pressure produced by the ventilator may result in alveolar rupture and a pneumomediastinum, particularly if the patient's spontaneous breathing is dyssynchronous with the ventilator. A pneumomediastinum may develop in persons with asthma, presumably because of the development of high intraalveolar pressure in a lung unit behind a partially obstructed bronchus through which air can enter more easily than exit. In other circumstances, the immediate cause of the pneumomediastinum is not apparent, and the patient truly has a "spontaneous pneumomediastinum."

## Pathophysiology

With accumulation of air in the mediastinum, an increase in pressure might be expected to cause a decrease in venous return to the great veins, with resulting cardiovascular compromise. However, when pressure builds up within the mediastinum, air usually dissects further along fascial planes into the neck, allowing release of the pressure and preventing disastrous cardiovascular complications. In addition, an increase in mediastinal pressure sometimes results in rupture of the mediastinal pleura and escape of air into the pleural space, with consequent development of a pneumothorax (see Chapter 15).

After air has entered the soft tissues of the neck, the patient is said to have *subcutaneous emphysema*. With continued entry of air from the mediastinum into the neck, the air dissects further over soft tissues of the chest and abdominal walls, producing more extensive subcutaneous emphysema.

Mediastinal air often results in subcutaneous emphysema.

Because of the escape route available for mediastinal air and the opportunity for decompression, major cardiovascular complications are quite uncommon. The development of subcutaneous emphysema, although unsightly and frequently uncomfortable, usually is not associated with major clinical sequelae.

## Clinical features

At the onset, patients with a pneumomediastinum often experience relatively sudden substernal chest pain. They may have dyspnea and (very rarely) cardiovascular compromise and hypotension. In some cases, the pneumomediastinum causes no symptoms, and the problem is detected on chest radiograph (e.g., on a film obtained during an acute asthma exacerbation).

Physical examination may reveal a crunching or clicking sound synchronous with the heartbeat on cardiac auscultation (Hamman sign). If the patient has subcutaneous emphysema associated with the pneumomediastinum, popping and crackling sounds (crepitations) may be heard and palpated over the affected skin and subcutaneous tissue.

## Diagnostic approach

The chest radiograph and chest CT scan are the most important studies for documenting a pneumomediastinum. Gas may be seen within the mediastinal tissues and is frequently accompanied by gas within and tracking along soft tissues of the neck and/or chest wall (subcutaneous emphysema) (Fig. 16.5).

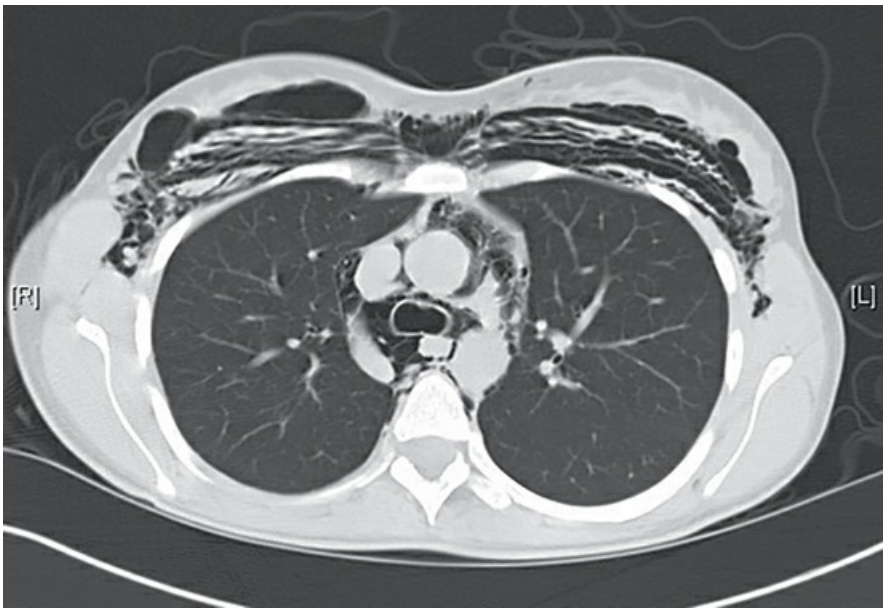


**FIGURE 16.5** Chest computed tomography scan shows air within the mediastinum (pneumomediastinum) and air in subcutaneous tissues of the anterior chest wall (subcutaneous emphysema).

## Treatment

Generally, no treatment is necessary for a pneumomediastinum, even when accompanied by subcutaneous emphysema. The air is usually resorbed spontaneously over time. When a pneumomediastinum is a consequence of tracheobronchial or esophageal rupture, surgery may be necessary to repair the underlying tear. Esophageal rupture can result in a rapidly progressive and fatal bacterial mediastinitis, and urgent surgical intervention must be considered if esophageal perforation is suspected. In the rare circumstance when pressure builds up within the mediastinum, an incision or placement of a catheter or chest tube into the mediastinum may be necessary to allow escape of air from the mediastinum and release of positive pressure.

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# 17: Anatomic and physiologic aspects of neural, muscular, and chest wall interactions with the lungs

OUTLINE



Movement of gas into and out of the lungs requires the action of a pump capable of creating negative intrathoracic pressure, expanding the lungs, and initiating airflow with each inspiration, whereas expiration is largely passive under most circumstances. This cyclical pump-like action is provided by the respiratory muscles, including the diaphragm, working in conjunction with the chest wall. However, the muscles themselves have no intrinsic rhythmic activity in the way cardiac muscle does; they must be driven by rhythmic impulses provided by a "controller."

This chapter focuses on the anatomic and physiologic features of the controlling system and the respiratory muscles to provide background for the discussion in Chapters 18 and 19. Those chapters discuss disorders affecting respiratory control, respiratory musculature, and the chest wall. Although much of the physiology and many of the clinical problems discussed here and in the next two chapters do not directly involve the lungs, they are so closely intertwined with respiratory function and dysfunction that they are appropriately considered in a textbook of pulmonary disease.

## Respiratory control

Although the process of breathing is a normal rhythmic activity that occurs without conscious effort, it involves an intricate controlling mechanism at the level of the central nervous system (CNS). The CNS transmits signals to the respiratory muscles, initiating inspiration approximately 12 to 20 times per minute under normal circumstances.

Remarkably, this controlling system is normally able to respond to varied needs of the individual, appropriately increasing ventilation during exercise and maintaining arterial blood gas parameters within a narrow range.

This section begins with a description of the structural organization of neural control of ventilation and proceeds to a consideration of how various stimuli may interact with and adjust the output of the respiratory controller. The ways the output of the controller can be quantified and how these techniques have proved useful in evaluating patients with a variety of clinical disorders are briefly discussed.

## Organization of respiratory control

The basic organization of the respiratory control system is shown in Fig. 17.1. Crucial to this system is the CNS "generator." Signals that originate from the generator travel down the spinal cord to the various respiratory muscles. The inspiratory muscles, the most important of which is the diaphragm, respond to the signals by contracting and initiating inspiration. This process is described later in more detail under the section "Respiratory Muscles."

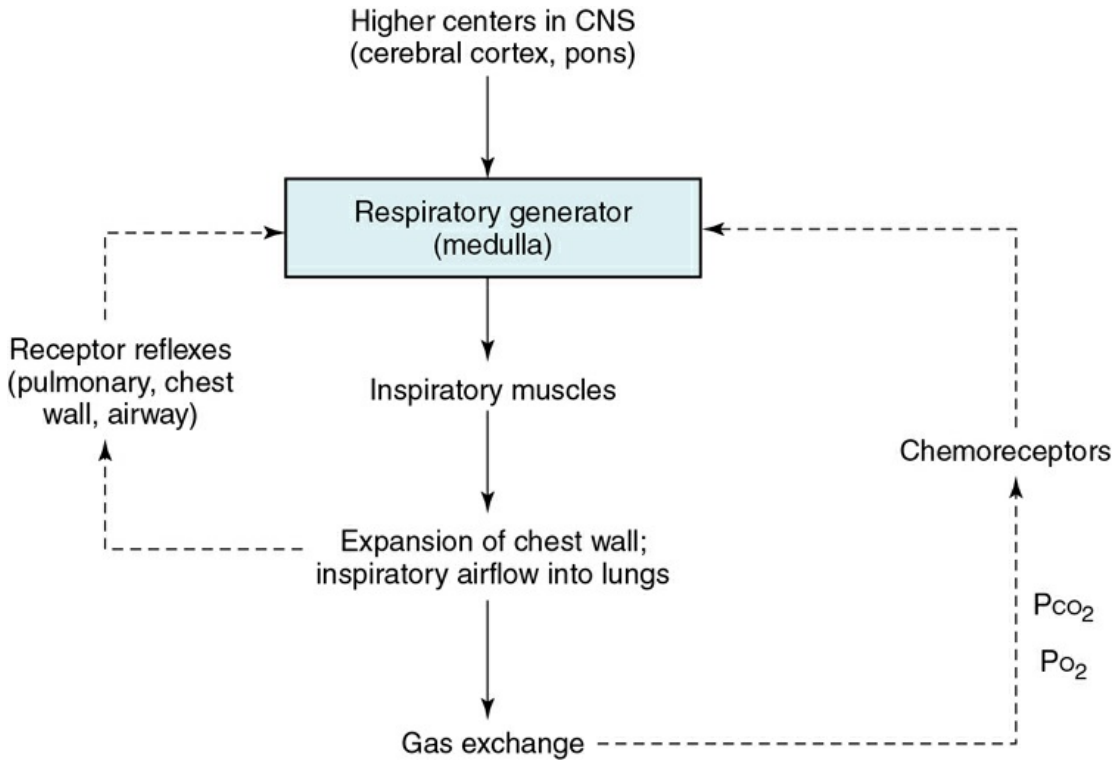


**FIGURE 17.1** Schematic diagram showing organization of respiratory control system. Dashed lines show feedback loops affecting respiratory generator. *CNS*, central nervous system.

As a result of inspiratory muscular contraction, the diaphragm descends, the chest wall expands, and air flows down a pressure gradient from the mouth through the tracheobronchial tree to the alveolar spaces. Gas exchange in the distal parenchyma

allows movement of $O_2$ into the blood and release of $CO_2$ from the blood into gas within the alveoli.

Although this sequence of events sounds relatively straightforward, it is regulated by an intricate and complicated feedback system that adjusts the output of the generator to achieve the desired effect. If the response of the respiratory muscles to the generator's signal is inadequate, as judged by a variety of respiratory "reflexes," the generator increases its output to compensate for the lack of expected effect. If the arterial blood gas variables deviate from appropriate values, input from chemosensors for pH, $O_2$, and $CO_2$ to the respiratory generator is altered, ultimately affecting its output. In addition, input from other regions of the CNS, particularly the cerebral cortex and pons, can adjust the generator's net output.

## The respiratory generator

Considering the importance of the respiratory generator in this scheme of respiratory control, its anatomy and mode of action are described here. Much of the work clarifying the location of the respiratory generator involved animal experiments with transections at various levels of the CNS and assessment of the effects on ventilation. Because transection between the brain and brainstem does not significantly alter ventilation, the generator apparently resides somewhere at the level of the brainstem or lower and does not require interaction with higher cortical centers. When transections are made at various points within the brainstem, the breathing pattern is substantially altered, but ventilation is not eliminated. Only when a transection is made between the medulla and the spinal cord does ventilation cease, indicating that the respiratory generator resides within the medulla. In humans and other mammals, the collection of neurons in the ventrolateral medulla that appears to be essential for respiratory pattern generation is termed the pre-Bötzinger complex.

A central respiratory generator within the medulla controls activity of the respiratory muscles.

Although the respiratory center (or generator) has been referred to as a single region, more than one network of neurons within the medulla are involved in initiating and coordinating respiratory activity. According to a popular model, one group of neurons is responsible for initiating inspiration and regulating its speed as a result of the intensity of neuronal activity; another group of neurons controls "switching off" inspiration and hence determines the onset of expiration.

Therefore, there are two aspects of ventilatory control: (1) the degree of inspiratory drive or central inspiratory activity (which regulates the inspiratory flow rate), and (2) the timing mechanism (which controls the termination of inspiration). These two determining factors act in concert to set the respiratory rate and tidal volume and thus the minute ventilation and specific pattern of breathing.

## Input from other regions of the central nervous system

Even though the medullary respiratory center does not require additional input to drive ventilation, it does receive other information that contributes to a regular pattern of breathing and more precise ventilatory control. For example, input from the pons

appears to be necessary for a normal, coordinated breathing pattern. When the influence of the pons is lost, irregularities in the breathing pattern ensue.

In addition to pathways involved in the "automatic" or involuntary control of ventilation, the cerebral cortex exerts a conscious or voluntary control over ventilation. Cortical overriding of automatic control can be seen with either voluntary breath-holding or voluntary hyperventilation. Its usefulness is readily apparent in a person's need for voluntary control of breathing during such activities as speaking, eating, and swimming. Interestingly, the automatic control of ventilation may be disturbed while conscious control remains intact. In these cases, during wakefulness the cerebral cortex exerts sufficient voluntary control over ventilation to maintain normal arterial blood gas values. During periods when the patient is dependent on automatic ventilatory control (e.g., during sleep), marked hypoventilation or apnea may occur. This rare condition, called *congenital central hypoventilation syndrome*, has also been known as *Ondine's curse*, after a mythologic tale in which the suitor of Neptune's daughter was cursed to lose automatic control over all bodily functions when he fell asleep. Defects in the *PHOX2b* gene mapped to chromosome 4p12 have been identified in most cases. *PHOX2b* encodes a highly conserved domain for transcription factors important in neural development. Further research into the pathogenesis of this condition undoubtedly will lead to better understanding of the mechanisms of normal ventilatory control.

## Chemoreceptors

Maintenance of normal arterial blood gas parameters is the ultimate goal of ventilatory control, and an important feedback loop adjusts respiratory center output if these parameters are not maintained (see Fig. 17.1). Elevation of $P_{CO_2}$ (hypercapnia) and depression of $P_{O_2}$ (hypoxemia) will both stimulate ventilation. In each case, one or more chemoreceptors detect alterations in $P_{CO_2}$ or $P_{O_2}$ and accordingly vary their input to the medullary respiratory center.

Changes in $P_{CO_2}$ are sensed primarily at a central chemoreceptor in the medulla.

The primary sensor regulating $CO_2$ is located near but separate from the medullary respiratory center on the ventrolateral surface of the medulla and is called the *central chemoreceptor*. The central chemoreceptor does not respond directly to blood $P_{CO_2}$ but rather to the pH of the extracellular fluid (ECF) surrounding the chemoreceptor. The pH, in turn, is determined by the concentration of hydrogen ($H^+$) and bicarbonate ($HCO_3^-$) ions, as well as $P_{CO_2}$ in the ECF (see Appendix C for further discussion). The composition of cerebrospinal fluid (CSF) and brain ECF is influenced by the permeability properties of the blood-brain barrier: $CO_2$ diffuses freely, whereas the movement of either $H^+$ or $HCO_3^-$ from blood to brain ECF is constrained. Thus, blood $CO_2$ level indirectly affects the central chemoreceptor by affecting the composition of the ECF. The feedback loop for changes in $P_{CO_2}$ can be summarized as follows:

Increased arterial blood $P_{CO_2}$ → Increased brain ECF $P_{CO_2}$
→ Decreased brain ECF pH → Decreased pH at central chemoreceptor
→ Stimulation of central chemoreceptor
→ Stimulation of medullary respiratory center → Increased ventilation
→ Decreased arterial blood $P_{CO_2}$

There are two primary sensors for $O_2$, the *carotid body* and *aortic body chemoreceptors,* which are both located in peripheral blood vessels, not the CNS. The carotid chemoreceptors, which are quantitatively much more important than the aortic chemoreceptors, are located just beyond the bifurcation of each common carotid artery into the internal and external carotid branches. The aortic chemoreceptor is found between the pulmonary artery and the aortic arch. These chemoreceptors are sensitive to changes in $P_{O_2}$, with hypoxia stimulating chemoreceptor discharge. In adults, the peripheral carotid body chemoreceptors also have a role in sensing $P_{CO_2}$. Under normoxic conditions, the peripheral chemoreceptors play a much less important regulatory function than the central chemoreceptors for maintaining $P_{CO_2}$. However, arterial hypoxemia increases the sensitivity of the peripheral $P_{CO_2}$ receptors, so if hypoxemia and hypercarbia are both present, the carotid body chemoreceptor will be maximally stimulated to increase ventilation. Peripheral chemoreceptor discharge is transmitted back to the CNS by cranial nerves: the glossopharyngeal nerve (cranial nerve IX) in the case of the carotid bodies and the vagus nerve (cranial nerve X) for the aortic body chemoreceptor. The information ultimately is transmitted to the medullary respiratory center so that its output is augmented.

The major sensors for $P_{O_2}$ are the peripheral (carotid and aortic body) chemoreceptors.

## Input from other receptors

In addition to chemoreceptor effects, input from receptors in the lung (including the airways), which are carried via the vagus nerve to the CNS, can influence ventilation. Stretch receptors located within the smooth muscle of airway walls respond to changes in lung inflation. As the lung is inflated, receptor discharge increases. In diving animals, this *stretch receptor reflex* (the *Hering-Breuer reflex*) is responsible for apnea that occurs as a result of lung inflation. In contrast, conscious human adults do not readily demonstrate the Hering-Breuer reflex, but in human infants the reflex is strong enough to limit tidal volumes and control the respiratory rate, preventing overinflation of the lungs in early infancy. Presumably, stretch receptors contribute to switching off inspiration and initiating expiration after a critical level of inspiratory inflation has been reached.

Irritant receptors located superficially along the lining of airways may initiate tachypnea, usually in response to some noxious inhaled stimulus such as a chemical or irritating dust. Juxtacapillary (or J) receptors are found within the pulmonary interstitium, adjacent to capillaries. One of their effects is to cause tachypnea, and they may be responsible for the respiratory stimulation caused by inflammatory processes or accumulation of fluid within the pulmonary interstitium.

Receptors in the chest wall, particularly in the intercostal muscles, appear to play a role in fine-tuning ventilation. The muscle spindles are part of a reflex arc that adjusts the output of respiratory muscles if the desired degree of muscular work has not been achieved. When a mismatch occurs between the output from the CNS controller and the amount of "stretch" sensed by these receptors, feedback from the receptors is involved in causing dyspnea. For example, in the patient with severe emphysema and lung hyperinflation, the increased output from the brain does not produce an "appropriate" change in lung inflation. Because the neural output is not matched by the resultant lung expansion, feedback is transmitted through the stretch receptors in the chest wall to the brain, and the patient experiences dyspnea. The precise mechanisms of these pathways are incompletely understood.

## Ventilatory response to hypercapnia and hypoxia

Two of the stimuli for ventilation that have been best studied are well-defined chemical stimuli: hypercapnia and hypoxia. As discussed above, hypercapnia is sensed primarily but not exclusively by the central chemoreceptor, and the stimulus appears to be the pH level of brain ECF. In contrast, hypoxia stimulates ventilation by acting on peripheral chemoreceptors, carotid much more than aortic.

When arterial $P_{O_2}$ is held constant, ventilation increases by approximately 3 L/min for each millimeter of mercury rise in arterial $P_{CO_2}$ in adults. This relatively linear response, the magnitude of which varies considerably among individuals, is shown in Fig. 17.2. Also shown is the effect of $P_{O_2}$ on the response to increments in $P_{CO_2}$. At a lower $P_{O_2}$, the response to hypercapnia is heightened.

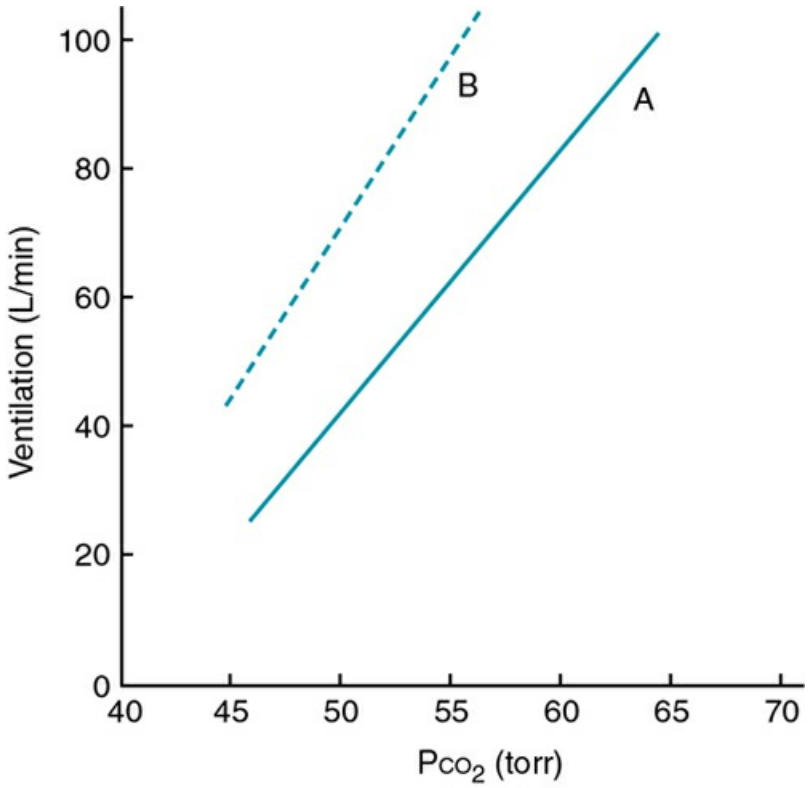


**FIGURE 17.2** Ventilatory response to progressive elevation of $P_{CO_2}$ in a normal individual. Solid line (A) shows response when simultaneous $P_{O_2}$ is high (hyperoxic conditions). Dashed line (B) shows heightened response when simultaneous $P_{O_2}$ is low (hypoxic conditions).

With chronic hypercapnia, the ventilatory response to further increases in $P_{CO_2}$ is diminished. The reason for the blunted $CO_2$ responsiveness is relatively straightforward. When $CO_2$ retention persists for days, the kidneys compensate for the more acidic pH by excreting more hydrogen ions and less bicarbonate, and the levels of bicarbonate rise in both plasma and brain ECF. The elevated bicarbonate level can buffer any acute changes in $P_{CO_2}$ more successfully, so that the brain ECF pH value changes less for any given increment in $P_{CO_2}$.

Ventilatory responsiveness to $CO_2$ is blunted in patients with chronic hypercapnia.

With hypoxemia, the same linear relationship does not exist between alterations in partial pressure and ventilation. Rather, the ventilatory response is relatively small until $P_{O_2}$ falls to approximately 60 mm Hg, below which the rise in ventilation is much more dramatic (Fig. 17.3). The curvilinear relationship between $P_{O_2}$ and ventilation can be made linear if ventilation is plotted against $O_2$ saturation instead of partial pressure (Fig. 17.4). However, despite the linear relationship between ventilation and $O_2$

saturation, it is the partial pressure of $O_2$, not the oxygen content or saturation, that is sensed by the chemoreceptor.

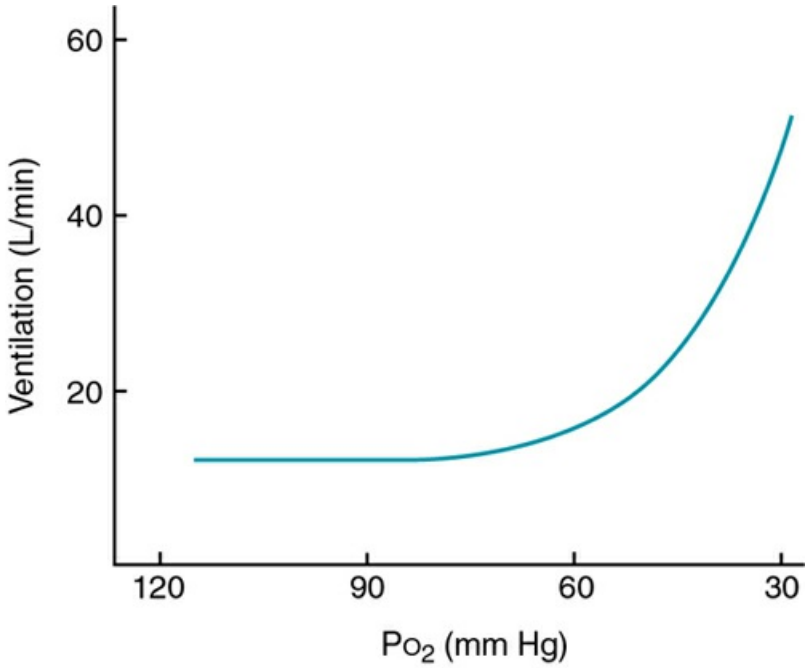


**FIGURE 17.3** Ventilatory response to progressively decreasing $P_{O_2}$ with $P_{CO_2}$ kept constant in a normal individual. Ventilation does not rise significantly until $P_{O_2}$ falls to approximately 60 mm Hg.

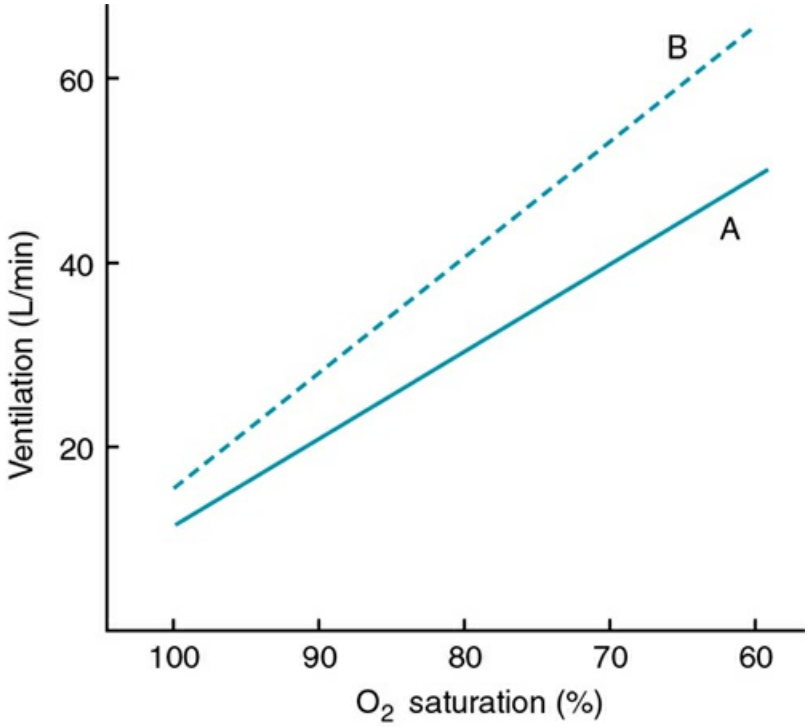


**FIGURE 17.4** Ventilatory response to hypoxia, plotted using $O_2$ saturation rather than $P_{O_2}$. Relationship between ventilation and $O_2$ saturation during progressive hypoxia is linear. Solid line (A) shows response when measured at normal $P_{CO_2}$. Dashed line (B) shows augmented response at elevated $P_{CO_2}$.

$P_{CO_2}$ also has an effect on a patient's response to hypoxia. The sensitivity to hypoxia is increased as $P_{CO_2}$ is raised and is decreased as $P_{CO_2}$ is lowered (see Fig. 17.4). This feature is important to consider when testing for responsiveness to hypoxia. As the patient hyperventilates in response to a low $P_{O_2}$, $P_{CO_2}$ drops, and ventilation is stimulated less than it would be if $P_{CO_2}$ were unchanged. Therefore, $P_{CO_2}$ should be kept constant so that the condition for testing actually is "isocapnic" hypoxia.

When the clinician suspects a disorder of ventilatory control, the ventilatory response to hypercapnia or hypoxia can be quantified. However, the responses to these stimuli vary widely even in seemingly normal individuals, presumably due to genetic variation. This fact must be taken into account in the interpretation of ventilatory response data.

## Ventilatory response to other stimuli

One of the most important times for a rapid and appropriate increase in ventilation is in response to a change in metabolic requirements. For example, with the metabolic needs of exercise, a normal individual can increase ventilation from a resting value of 5 L/min to 60 L/min or more, without any demonstrable change in arterial blood gas values. According to one popular theory, the initial rapid increase in ventilation at the onset of exercise (i.e., before $P_{aO_2}$ or $P_{aCO_2}$ begin to change) is due to a neural stimulus, although

the origin is not clear. After the initial rapid augmentation in ventilation, there occurs a later and slower rise that probably is due to a bloodborne chemical stimulus. However, many questions about the remarkably precise way ventilation responds to the demands of exercise remain unanswered.

Another important ventilatory response occurs to alterations in acid-base status. When oxygen delivery can no longer meet tissue metabolic needs, anaerobic metabolism ensues and causes excess metabolic acid production (i.e., metabolic acidosis). Ventilation increases as pH is lowered, and elimination of additional $CO_2$ aids in returning the blood pH toward normal. The peripheral chemoreceptors appear to be primarily responsible for sensing acute metabolic acidosis and stimulating the increase in ventilation, but the degree to which the central chemoreceptors modify or contribute to this response is not entirely settled.

## Respiratory muscles

The purpose of signals emanating from the respiratory generator is to initiate inspiratory muscle activity. Although the primary inspiratory muscle is the diaphragm, other muscle groups contribute to optimal movement of the chest wall under a variety of conditions and needs. Notable among these other inspiratory muscle groups are the scalene and parasternal intercostal muscles, which display inspiratory activity even during normal quiet breathing. The so-called accessory muscles of inspiration (e.g., sternocleidomastoid and trapezius muscles) are not normally used during quiet inspiration but can be recruited when necessary, either when diaphragm function is impaired or when ventilation is significantly increased. Another set of intercostal muscles, the external intercostal muscles, are also inspiratory muscles, but their overall importance during inspiration is less clear. Finally, additional muscles coordinate upper airway activity during inspiration. Proper functioning of these muscles maintains patency of the upper airway, whereas dysfunction may be important in the pathogenesis of certain clinical disorders associated with upper airway obstruction, such as obstructive sleep apnea (see Chapter 18).

The diaphragm is the major muscle of inspiration. The less important inspiratory and accessory muscle activity is increased during exercise and disease states.

During inspiration, the diaphragm contracts and its muscle fibers shorten. To understand the effect of this contraction, consider the configuration of the diaphragm within the chest. At its lateral aspect, the diaphragm is adjacent to the inner part of the lower rib cage. This portion of the chest wall and the diaphragm is known as the *zone of apposition* (Fig. 17.5). In this region, the muscle fibers of the diaphragm are oriented vertically. When the diaphragm contracts, shortening of these vertically oriented fibers diminishes the zone of apposition and causes the more medial dome of the diaphragm to descend. At the same time, by pushing abdominal contents downward, diaphragmatic contraction increases both intraabdominal pressure and the lateral pressure on the lower rib cage transmitted through the apposed diaphragm. The effect of diaphragmatic contraction is thus to lift the lower ribs and expand the lower chest wall at the same time the abdominal wall moves outward. The external intercostal muscles, located between

the ribs, also contract during inspiration, contributing as well to the lower rib cage being lifted and rotated outward.

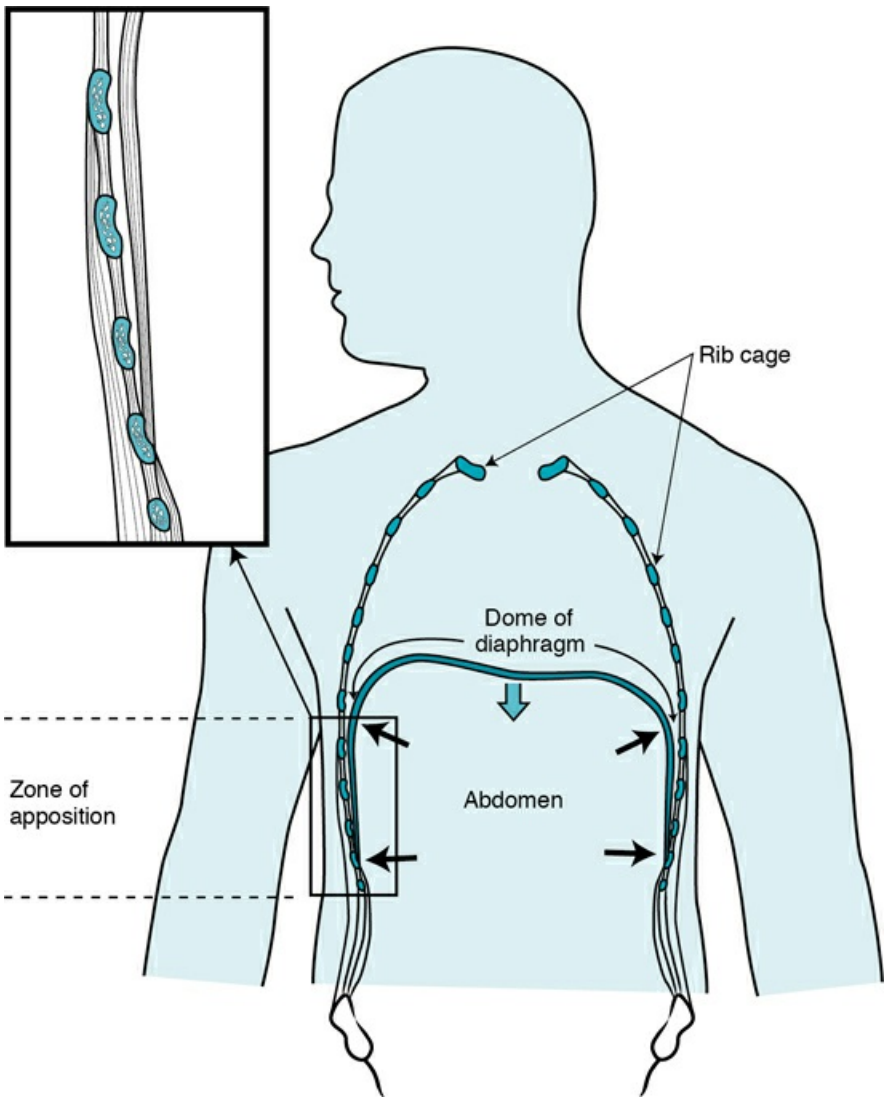


**FIGURE 17.5** Functional anatomy and action of diaphragm during breathing. At zone of apposition, fibers of diaphragm are oriented vertically alongside inner aspect of lower rib cage. During inspiration, descent of diaphragm *(open arrow)* causes increase in abdominal pressure that is transmitted through apposed diaphragm to expand lower rib cage *(solid arrows)*. *Source:* (Modified from De Troyer, A., & Estenne, M. (1988). Functional anatomy of the respiratory muscles. *Clinics in Chest Medicine, 9*, 175–193.)

As the reader can now appreciate, the act of inspiration is more complex than it initially seemed. Whereas the diaphragm acts on the abdomen and the lower chest wall,

the scalene muscles and parasternal intercostals (perhaps along with the external intercostals) act to expand the upper chest wall. The net effect is that abdominal contents are pushed downward, intraabdominal pressure is increased, the chest wall expands, intrathoracic pressure is lowered, and air flows into the lungs. With normal resting breathing, the most apparent inspiratory motion is the outward movement of the abdomen, which results from diaphragmatic descent and increased abdominal pressure. In the face of high workloads, increased ventilation, or certain disease states, the accessory muscles are additionally recruited to assist the primary inspiratory muscles.

An important determinant of the efficacy of diaphragmatic contraction is the initial shape and length of the diaphragm. For any muscle, the strength of contraction is decreased when its initial length is shorter. The diaphragm is no exception. Therefore, at high lung volumes, the diaphragm is lower and foreshortened before its active contraction, so the strength of contraction is diminished. At the same time, the lower, flatter diaphragm means that the zone of apposition is decreased, with less downward movement of the diaphragm and outward movement of the lower chest wall associated with inspiration. At the extreme, the diaphragm is flattened and horizontally (axially) oriented, there is no zone of apposition, and contraction draws in the lower rib cage but provides no useful inspiratory function. The importance of these factors will become apparent in the discussion of diaphragmatic function in obstructive lung disease, in which resting lung volume may be abnormally high and, even before contraction, the diaphragm is in a flatter, more horizontal and less efficient position.

The effectiveness of diaphragmatic contraction is decreased at high resting lung volumes when the diaphragm is flatter and shorter.

In contrast to inspiration, expiration is a relatively passive process in which the lung and chest wall return to their resting positions. However, when breathing is deep and forceful, when airway resistance is increased during expiration, or when a person coughs, the action of expiratory muscles may be important in aiding expiratory airflow. In particular, abdominal muscles (transverse abdominis, internal and external obliques) and internal intercostals are important in this role.

In summary, normal operation of the respiratory apparatus depends on signals generated by the respiratory center which are translated into an efficient pattern of respiratory muscle contraction. Although feedback and control systems ensure optimal functioning of this process, this finely coordinated mechanism may fail in numerous ways. Chapters 18 and 19 examine clinically important dysfunction occurring at various levels of this complex system.

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# 18: Disorders of ventilatory control

OUTLINE



The finely tuned system of ventilatory control described in Chapter 17 is altered in a variety of clinical circumstances. In some cases, a primary disorder of the nervous system affects the neurologic network involved in ventilatory control and therefore may either diminish or increase the "drive" to breathe. In other instances, the controlling system undergoes a process of adaptation in response to primary lung disease, so any alteration in function is a secondary phenomenon.

This chapter considers primary and secondary disturbances in ventilatory control, as well as alteration in breathing patterns. A common disturbance in the pattern of breathing, termed *Cheyne-Stokes breathing*, is covered, along with a brief discussion of its pathogenesis. Secondary disorders are most commonly associated with chronic obstructive pulmonary disease (COPD); therefore, the discussion of secondary disorders of ventilatory control focuses on this particular disorder. The final topic is ventilatory disorders associated with sleep because alteration of ventilatory control is an important component of the pathogenesis of sleep-related respiratory dysfunction.

## Primary neurologic disease

Several diseases of the nervous system alter ventilation, apparently by affecting regions involved in ventilatory control. However, the results are variable, depending on the type of disorder and the region involved. In some cases, hyperventilation is prominent, whereas in others hypoventilation is significant. In a third category, the most apparent change occurs in the pattern of breathing.

## Presentation with hyperventilation

With certain acute disorders of the central nervous system (CNS), hyperventilation (i.e., decreased $P_{CO_2}$ and respiratory alkalosis) is relatively common. Acute infections (meningitis, encephalitis), strokes, and trauma affecting the CNS are notable examples. The exact mechanism of hyperventilation in these situations is not known with certainty. Patients with hyperthyroidism frequently present with hyperventilation that resolves after treatment. Increased sensitivity of the chemoreceptors in the brain due to hyperthyroidism appears to account for the effect. Hyperventilation frequently complicates advanced hepatic disease, presumably because of increased concentrations of circulating substances stimulating ventilation that normally are cleared by the healthy liver. Some proposed substances causing central stimulation of respiration in patients with hepatic disease include progesterone, ammonia, and glutamate.

Many acute disorders of the CNS are associated with hyperventilation.

## Presentation with hypoventilation

A presentation with hypoventilation presumably results from a primary insult to the nervous system that affects centers involved with control of breathing. In such circumstances, patients have an elevated $P_{CO_2}$, but because the clinical problems are generally not acute, the pH level has returned closer toward normal due to renal compensation. When no specific etiologic factor or prior event can be found to explain the hypoventilation, the patient is said to have *idiopathic hypoventilation* or *primary alveolar hypoventilation*. Other patients have suffered a significant insult to the nervous system at some time in the past (e.g., encephalitis), and chronic hypoventilation presumably is a sequela of the past event.

Patients with these syndromes of hypoventilation are characterized by depressed ventilatory responses to the chemical stimuli of hypercapnia and hypoxia. Measurement of arterial blood gases reveals an elevation in arterial $P_{CO_2}$ accompanied by a decrease in $P_{O_2}$, the latter primarily attributable to hypoventilation. As in other disorders associated with these blood gas abnormalities, cor pulmonale may result and be the presenting problem in these syndromes. The term *congenital central hypoventilation syndrome* or *Ondine's curse* (see Chapter 17) has been applied to a rare subset of patients with congenital alveolar hypoventilation. However, less severe decreases in ventilatory response to hypercapnia and hypoxia are commonly seen in clinical practice and probably represent a spectrum of abnormalities in ventilatory response.

The most common therapy for patients with clinically significant hypoventilation is noninvasive positive-pressure (i.e., assisted) ventilation, usually applied nocturnally. This topic is discussed in Chapter 30. In the past, treatment of alveolar hypoventilation generally centered around two modalities: drugs (most commonly the hormone

progesterone) and electrical stimulation of the phrenic nerve. In the latter approach, the diaphragm can be induced to contract by repetitive electrical stimulation of the phrenic nerve, which can be achieved by intermittent current applied via an implanted electrode. Although both of these modalities are still used, noninvasive positive-pressure (i.e., assisted) ventilation, usually applied during sleep, is a more effective and better tolerated treatment in most cases.

Treatment of alveolar hypoventilation due to depressed central respiratory drive consists of:

1. Assisted ventilation, generally with nocturnal noninvasive ventilation
2. Pharmacotherapy (e.g., progesterone)
3. Electrical stimulation of phrenic nerve

### Abnormal patterns of breathing

In addition to disturbances in overall alveolar ventilation, patients with neurologic disease may demonstrate abnormal patterns of breathing. The term *ataxic breathing* is applied to a grossly irregular breathing pattern observed with some types of lesions in the medulla. In contrast, certain lesions in the pons result in a breathing pattern characterized by a prolonged inspiratory pause; this pattern is called *apneustic breathing*.

Another type of abnormal breathing pattern is termed *Cheyne-Stokes breathing*. Unlike the other patterns, Cheyne-Stokes breathing is common and warrants further description and discussion of what is known about its pathogenesis.

## Cheyne-stokes breathing

Cheyne-Stokes breathing is a cyclic pattern in which periods of gradually increasing ventilation alternate with periods of gradually decreasing ventilation (sometimes to the point of apnea). This type of ventilation is shown schematically in Fig. 18.1. It has been known for many years that two main types of disorders are associated with this pattern of breathing: heart failure and some forms of CNS disease. Cheyne-Stokes breathing can also be seen under certain physiologic situations even in the absence of underlying disease. Examples include the onset of sleep and exposure to high altitude.

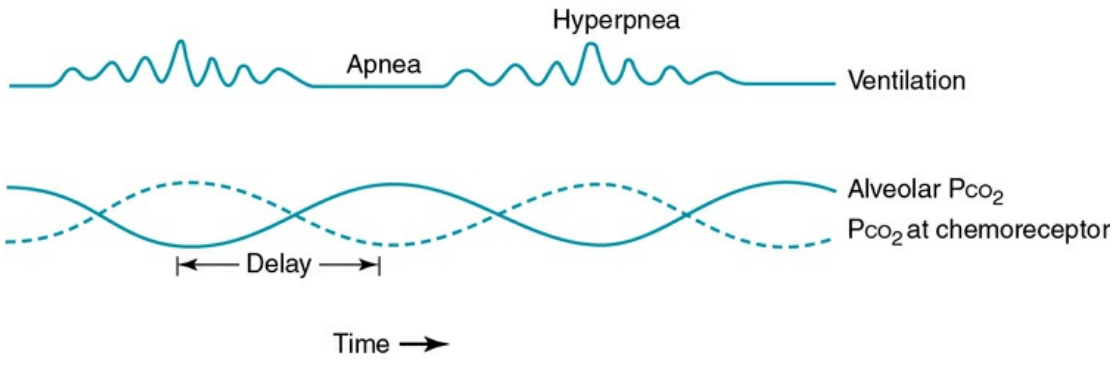

**FIGURE 18.1** Cheyne-Stokes breathing shows cyclic pattern of ventilation. In patients with prolonged circulation time, delay between signal to chemoreceptor ($P_{CO_2}$ at chemoreceptor) and ventilatory output (reflected by alveolar $P_{CO_2}$) is shown.

Common causes of Cheyne-Stokes ventilation are heart failure and some forms of CNS disease.

Central to the pathogenesis of Cheyne-Stokes ventilation is a problem with the feedback system of ventilatory control. Normally, the controlling system can adjust its output to compensate for arterial blood gas values that differ from the ideal or desired state. For example, with an elevated arterial $P_{CO_2}$, the central chemoreceptor signals the medullary respiratory center to increase its output to augment ventilation and restore $P_{CO_2}$ to normal. Similarly, the peripheral chemoreceptor responds to hypoxemia by increasing its output, signaling the medullary respiratory center to augment ventilation and restore $P_{O_2}$ to normal.

At times, this feedback system may fail, especially if there is a delayed response to the signal or if the system responds more than necessary and overshoots the mark. Such defects in the feedback process appear to be at work in Cheyne-Stokes breathing. This section touches on a few aspects of theories proposed to explain Cheyne-Stokes ventilation, but for further discussion, the interested reader is referred to the Suggested Readings.

Decreased cardiac output produces a slowed circulation time, which results in an abnormal delay between events in the lung and sensing of $P_{CO_2}$ changes by the central chemoreceptor. This is one mechanism postulated to play a role in generating Cheyne-Stokes breathing in heart failure. Due to this abnormal delay, medullary respiratory output is out of phase with gas exchange at the lungs, and oscillations in ventilation occur as the central chemoreceptor and the medullary respiratory center make belated attempts to maintain a stable $P_{CO_2}$ (see Fig. 18.1).

An alternative explanation for Cheyne-Stokes breathing that occurs with heart failure is an accentuated ventilatory response to hypercapnia. This type of heightened responsiveness of the feedback system produces “instability” of respiratory control and a cyclic overshooting and undershooting of ventilation. Such increased responsiveness of the ventilatory control system may also play a role in patients with CNS disease who exhibit periods of Cheyne-Stokes respiration.

A similar type of instability of ventilatory control occurs at high altitude, when hypoxia is driving the feedback system. The ventilatory response to hypoxia is nonlinear. For the same drop in $P_{O_2}$, the increment in ventilation is larger at a lower absolute $P_{O_2}$ (see Fig. 17.3). This means that at a relatively high initial $P_{O_2}$, the system is less likely to respond to small changes in $P_{O_2}$ but then is apt to overshoot as $P_{O_2}$ falls further. This instability of the respiratory control system results in a widely oscillating output from the respiratory center and thus a cyclic pattern of ventilation.

## Control abnormalities secondary to lung disease

Ventilatory control mechanisms often respond to various forms of primary lung disease by altering respiratory center output. Either stimulation of peripheral chemoreceptors by hypoxemia or stimulation of receptors by diseases affecting the airways or pulmonary interstitium can induce the respiratory center to increase its output, resulting in respiratory alkalosis. For example, patients with asthma commonly demonstrate increased respiratory drive and hyperventilation during acute attacks, due to stimulation of airway receptors. Similarly, patients with acute pulmonary embolism, pneumonia, or chronic interstitial lung disease often hyperventilate, presumably as a result of stimulation of one or more types of intrathoracic receptors, with or without the additional ventilatory stimulus contributed by hypoxemia.

In contrast, patients with COPD have variable levels of $P_{CO_2}$. The development of hypercapnia is inconsistent in patients with COPD (see Chapter 6). In patients with COPD who demonstrate elevated levels of carbon dioxide, the ventilatory control mechanism appears to be recalibrated to operate at a higher set point for $P_{CO_2}$, rather than the hypercapnia being solely due to reduced function of the lung. When responsiveness to increased levels of $P_{CO_2}$ is measured in hypercapnic patients, it is apparent that their ventilatory response is diminished. Patients with chronic compensated respiratory acidosis have higher levels of plasma and cerebrospinal fluid bicarbonate because of bicarbonate retention by the kidneys. Therefore, for any increment in $P_{CO_2}$, the effect on pH at the medullary chemoreceptor is attenuated by the increased buffering capacity available. A "chicken and egg" question then becomes important: is $CO_2$ retention secondary to an underlying ventilatory control abnormality in these patients, or is the diminution in ventilatory sensitivity merely secondary to chronic $CO_2$ retention? Although this question remains unanswered, some evidence suggests that hereditary factors may be important and that $CO_2$ retention is more likely to develop in patients with a genetically lower respiratory sensitivity.

Whatever the answer to this question, there is a clinically important corollary to this depression in $CO_2$ sensitivity, irrespective of the cause of $CO_2$ retention. When $O_2$ is administered to the chronically hypoxemic and hypercapnic patient, $P_{CO_2}$ may rise even further. Three factors account for this well-recognized clinical event: changes in minute ventilation, changes in ventilation-perfusion matching, and the Haldane effect. To understand this phenomenon, each of these factors should be appreciated. The easiest factor to understand is the change in minute ventilation. If a patient is hypoxemic, low $Pa_{O_2}$ is sensed by the peripheral chemoreceptors, causing stimulation of the respiratory center. When supplemental oxygen is given and the patient is no longer hypoxemic, this stimulation abates. This was previously thought to be the sole explanation for the rise in $P_{CO_2}$ seen in hypoxic, hypercapnic patients who were given supplemental oxygen. However, it now is known that hypoxic drive and a decrease in ventilation play only a small role in the frequently observed increase in $P_{CO_2}$ occurring in this situation. More important is a worsening of ventilation-perfusion matching. Recall that alveolar hypoxia results in decreased perfusion to the hypoxic lung segments, an effect that is mediated through hypoxic vasoconstriction of those pulmonary arterioles supplying hypoxic alveoli. However, administration of supplemental $O_2$ may alleviate alveolar hypoxia in

these poorly ventilated regions, thus inhibiting the compensatory localized vasoconstriction. Ventilation-perfusion mismatch becomes more marked in the absence of hypoxic vasoconstriction, leading to less efficient elimination of $CO_2$ and increased levels of $P_{CO_2}$. The third factor contributing to the rise in $P_{CO_2}$ is the Haldane effect, in which deoxygenated hemoglobin has a higher affinity for $CO_2$ (see Chapter 1). When supplemental oxygen is administered, the more oxygenated hemoglobin has a lower affinity for $CO_2$, leading to enhanced release of $CO_2$ from hemoglobin into plasma and a higher $P_{CO_2}$.

Administration of $O_2$ to the chronically hypoxemic and hypercapnic patient may elevate $P_{CO_2}$.

Significant elevations in $P_{CO_2}$ on administration of supplemental $O_2$ to the chronically hypercapnic patient can generally be prevented by avoiding excessive concentrations of supplemental $O_2$ beyond those needed to raise oxygen saturation to approximately 90% to 94%. In the presence of significant hypoxemia, the clinician should not withhold supplemental $O_2$ from patients who have chronic hypercapnia, because significant hypoxemia poses a greater risk than a further increase in $P_{CO_2}$. Nevertheless, such patients usually are given relatively limited amounts of supplemental $O_2$ to minimize the degree of further hypercapnia. In the hospital setting, oxygen can be administered via noninvasive positive-pressure ventilation, which generally attenuates any hypercapnia that may develop.

## Sleep apnea syndrome

Sleep apnea is a common disorder in which patients have repetitive episodes of apnea (cessation of breathing) during sleep that lead to gas exchange abnormalities and disruption of normal sleep architecture. In subjects older than 50 years, studies estimate the prevalence of moderate to severe sleep apnea to be 17% in men and 9% in women. Obesity is a strong risk factor for sleep apnea, and the prevalence of sleep apnea increases with higher body mass indices.

A period of more than 10 seconds without airflow is considered to constitute an apneic episode, and patients with this syndrome often have hundreds of such episodes during the course of a night's sleep. The term *hypopnea* is used to describe a reduction in airflow of 50% or more without the complete cessation of airflow implied by the term *apnea*. Because episodes of apnea and hypopnea commonly coexist, the broader term *sleep apnea–hypopnea syndrome* is sometimes used.

### Types

Sleep apnea syndrome is commonly divided into two types, obstructive and central, depending on the nature of the episodes. In addition, some patients have a mixture of the two types. Obstructive sleep apnea (OSA), which is much more common, is characterized by transient collapse and obstruction of the pharyngeal airway that prevents inspiratory airflow. Inspiratory muscles are still active during the obstructive

episodes, but initiation of airflow is unsuccessful due to the obstruction. Some degree of decreased upper airway muscle tone and narrowing occurs in all people during sleep, but in patients with OSA this reaches the point of airway occlusion.

In contrast, central sleep apnea (CSA) is characterized by apneas due to lack of respiratory efforts—that is, there is no signal from the respiratory center to initiate inspiration. Hence, no respiratory muscle activity can be observed when airflow ceases. CSA is rare in the general population but commonly seen in patients with heart failure, where Cheyne-Stokes breathing is grouped under CSA. Some patients may have episodes of apnea that have features of both central and obstructive apnea, a condition called *mixed apnea*. Typically, such episodes start without ventilatory effort (central apnea), but upper airway obstruction occurs when ventilatory effort resumes (obstructive apnea). Because OSA is more common than CSA, the focus here is on the clinical features, pathophysiology, and treatment of obstructive apnea, with only a brief discussion of CSA.

Categories of sleep apnea syndrome:

1. Obstructive
2. Central
3. Mixed

## Clinical features

Patients with sleep apnea syndrome may seek medical consultation because of (1) symptoms or signs that they or their partner have noticed during a night's sleep, (2) daytime hypersomnolence, or (3) complications that arise from the repetitive apneic episodes. During sleep, patients with OSA are often noted to have loud snoring and may have obvious snorting, gasping, and agitation as a result of trying to breathe against the obstructed airway. They also may have violent movements during periods of obstruction. The sleep partner may report being hit or injured due to these violent movements. On awakening, patients often report a severe headache, presumably related to cerebral vasodilation associated with derangements in gas exchange that occur during the apneic episodes. However, it is important to note that many patients, especially those with milder cases, will not report any problems to their physician. Symptoms may be noted only when the physician specifically inquires about sleep issues.

With such a disordered pattern of sleep, patients are effectively sleep deprived and, not surprisingly, frequently are somnolent during normal waking hours. Even though the patient is in bed and "asleep," only the lighter phases of sleep are entered, and adequate amounts of the deeper restorative phases of sleep are not achieved because of repeated "microarousals." The degree of daytime hypersomnolence can be debilitating and even dangerous. Patients may fall asleep while driving, eating, or working, or during a variety of other usual daytime activities. Patients may appear to have a psychiatric disorder, partially because of their extreme hypersomnolence and partially because of psychological changes that have presumably resulted from their disease. Inability to concentrate and depression are common symptoms.

Clinical features of sleep apnea syndrome:

1. Disordered respiration during sleep
2. Daytime hypersomnolence
3. Morning headaches
4. Cardiovascular complications

Secondary cardiovascular complications are associated with OSA and are believed to be mediated in part by increased sympathetic nervous system activity. OSA is a risk factor for systemic hypertension, pulmonary arterial hypertension, coronary artery disease, atrial fibrillation, heart failure, and stroke. Treatment of OSA is associated with improved blood pressure control in patients with systemic hypertension. Atrial fibrillation is strongly associated with OSA, and during the episodes of apnea, patients may have a variety of other cardiac conduction disturbances, although they rarely are life threatening. As a result of multiple episodes of hypoxemia at night, pulmonary hypertension can result, and unexplained cor pulmonale may be the presenting clinical problem.

## Pathophysiology

During the past 3 decades, a great deal has been learned about the pathogenesis and risk factors leading to OSA. Normally, inspiration is characterized by contraction of the diaphragm, resulting in negative airway pressure accompanied by increased activity of upper airway muscles acting to keep the pharynx patent. The genioglossus muscle is particularly important in this regard because it prevents the tongue from falling against the posterior pharyngeal wall and occluding the pharynx.

In patients with OSA, structural and functional factors often work together to allow the upper airway to close during inspiration. In most patients, an excess of soft tissue in the upper airway, often as a consequence of obesity, reduces the size of the pharyngeal opening. During sleep, particularly rapid eye movement sleep, loss of activity of the upper airway muscles results in inspiratory collapse of the soft tissues and obstruction of the upper airway. Airflow eventually resumes after each episode of obstruction as the patient arouses (although these microarousals often are not evident to the patient), when activity of the upper airway muscles is restored and when the airway temporarily becomes patent. However, as the patient falls asleep again, upper airway muscle activity is again lost, and the cycle repeats itself. Because of the importance of structural factors contributing to a small upper airway, patients who are obese or who have a small jaw (micrognathia), a large tongue, or large tonsils are at particular risk for OSA.

In contrast, CSA can be further characterized as one of two subtypes: hyperventilation-associated and hypoventilation-associated. The former type is more common and frequently seen in heart failure. The pathophysiology is similar to that of Cheyne-Stokes respiration, with ventilatory instability leading to both episodic overshooting (hyperventilation) and periods of apnea. The latter, on the other hand, is seen in patients with chronic hypoventilation, usually in the setting of CNS disease, neuromuscular disease, or severe pulmonary disease.

In CSA, during an episode of central apnea, monitoring of chest wall motion reveals

no movement, corresponding to cessation of airflow and a fall in $O_2$ saturation (Fig. 18.2A). With OSA, chest wall and abdominal movement can be detected during an ineffective attempt to move air through the obstructed airway. Airflow measured simultaneously is found to be absent (tidal volume = 0), and $O_2$ saturation drops, often to profoundly low levels (see Fig. 18.2B). When $O_2$ saturation drops significantly during sleep, disturbances in cardiac rhythm can occur, and elevation of pulmonary artery pressure may be seen as a consequence of hypoxia-induced pulmonary vasoconstriction.

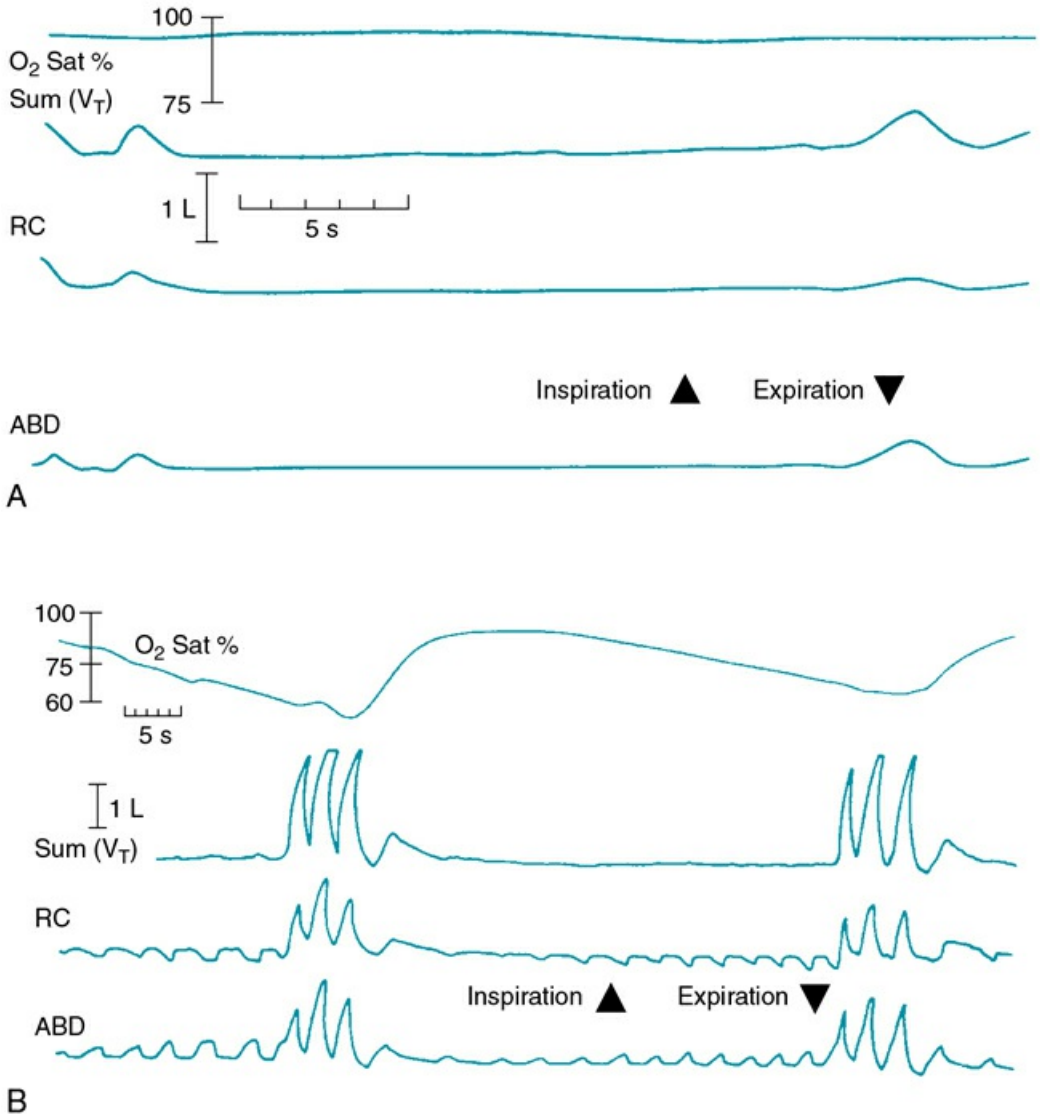


**FIGURE 18.2** Examples of recordings in sleep apnea syndrome. **A,** Central sleep apnea. Absence of abdominal, rib cage, and sum movements are associated with a small fall in arterial oxygen saturation. **B,** Obstructive sleep apnea. Apneas at beginning and midportion of recording are marked by absence of sum movements

($V_T$) despite respiratory efforts. When diaphragm contracts and upper airway is obstructed during attempted inspiration, abdomen moves out *(upward on tracing)* while rib cage moves inward *(downward)*. Each apnea shown is associated with marked fall in $O_2$ saturation and is terminated by three deep breaths. *ABD*, abdominal movement; *$O_2$ Sat*, $O_2$ saturation; *RC*, rib cage; *$V_T$*, tidal volume (monitored as sum of rib cage and abdominal movements).
*Source:* (From Tobin, M. J., Cohn, M. A., & Sackner, M. A. (1983). Breathing abnormalities during sleep. *Archives of Internal Medicine, 143*, 1221–1228. Copyright 1983, American Medical Association.)

## Treatment

The first-line therapy used in most patients with OSA is continuous positive airway pressure, commonly called *CPAP*. A mask connected to an air compressor is placed over the nose or the full face of the patient at bedtime. The compressor maintains positive pressure in the upper airway throughout the respiratory cycle, thus providing a pneumatic splint to prevent the airway from collapsing. For patients who are obese, an attempt at significant weight loss is recommended. Although weight loss can sometimes dramatically improve the number and severity of apneic episodes, long-term weight reduction is difficult for most patients to maintain, making other forms of therapy necessary. In all patients, respiratory depressants, including alcohol and sedative-hypnotic drugs, should be avoided because they may worsen OSA. An alternative but less effective form of therapy involves nocturnal use of an oral appliance to maintain the tongue and/or the jaw in a relatively anterior position. This mechanical form of therapy facilitates airway patency by keeping the tongue away from the posterior pharyngeal wall.

Nasal or full-face mask CPAP is often applied at night to patients with OSA to prevent upper airway closure.

Because CPAP and oral appliances are so often effective, other forms of therapy now are used less frequently. Nevertheless, surgical modes of therapy may be beneficial in selected patients. For example, some patients are treated by a surgical procedure called *uvulopalatopharyngoplasty*, which involves removal of redundant soft tissue in the upper airway. Because the procedure is not without a risk of complications, this surgery is generally reserved for patients who cannot tolerate CPAP.

A newer surgical technique called *hypoglossal nerve stimulation* requires surgical implantation of a neurostimulator device that can be turned on before sleep. Electrical impulses from the device activate the hypoglossal nerve to in turn stimulate the protrusion muscles of the tongue and maintain patency of the lower pharyngeal airway.

Rare patients with particularly severe obstructive apnea whose disease is refractory to other forms of therapy can be treated with a tracheostomy, which involves placement of

a tube in the trachea to allow air to bypass the site of upper airway obstruction. Despite the drastic nature of tracheostomy as a form of treatment, for patients who have failed other treatment, the therapeutic response can be quite significant. Patients may have a dramatic reversal of symptoms and a striking improvement in their lifestyle, which previously was limited by intractable daytime sleepiness.

In patients with CSA, treatment is primarily focused on addressing the underlying disease. In the appropriate clinical setting, respiratory stimulants, an electrical implanted phrenic nerve pacemaker to stimulate the diaphragm, or mechanical ventilation, either noninvasive via a face mask or invasive via a tracheostomy tube, may all be considered.

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# 19: Disorders of the respiratory pump

OUTLINE



The chest wall, diaphragm, and related neuromuscular (NM) apparatus moving the chest wall act in concert to translate signals from the ventilatory controller into expansion of the thorax. Together these structures constitute the respiratory pump, an important system that may fail as a result of diseases affecting any of its parts. Because disorders of the respiratory pump include a variety of problems, this discussion is limited to those disorders that are most common and most important clinically: (1) NM disease affecting the muscles of respiration (Guillain-Barré syndrome, myasthenia gravis, poliomyelitis, and amyotrophic lateral sclerosis), (2) diaphragmatic fatigue, (3) diaphragmatic paralysis, and (4) disorders affecting the chest wall (kyphoscoliosis, obesity).

## Neuromuscular disease affecting the muscles of respiration

Several NM diseases have the potential for affecting the muscles of respiration. In some cases, the underlying process is acute and generally reversible (e.g., Guillain-Barré syndrome), and the muscles of respiration are transiently affected. In other cases the

NM damage is permanent, and any consequences that impair function of the muscles of respiration are chronic and irreversible. This chapter provides brief definitions of some specific neurologic disorders with respiratory sequelae, followed by a discussion of the pathophysiology and clinical consequences of these diseases as they relate to the respiratory system.

## Specific diseases

The major NM diseases that can affect the muscles of respiration are listed in Table 19.1; several are discussed here.

**TABLE 19.1**
**Disorders of the Respiratory Pump**

| Neuromuscular Diseases | Chest Wall Diseases |
|---|---|
| Guillain-Barré syndrome | Kyphoscoliosis |
| Myasthenia gravis | Obesity |
| Poliomyelitis | Ankylosing spondylitis |
| Postpolio syndrome | |
| Amyotrophic lateral sclerosis | |
| Cervical or thoracic spinal cord injury | |
| Polymyositis | |
| Muscular dystrophies | |

*Guillain-Barré syndrome* is a heterogeneous disorder with different variants all involving immune injury to peripheral nerves. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common variant accounting for 85% to 90% of cases, is a disorder characterized by demyelination of peripheral nerves. It is thought to be triggered by exposure to an antigen (typically an infectious agent such as *Campylobacter jejuni*) resulting in production of an antibody that cross-reacts with similar antigenic determinants (epitopes) on neural tissue or Schwann cells. Patients frequently report a history of a recent viral or bacterial illness followed by development of ascending paralysis and variable sensory symptoms. *C. jejuni* is the most frequently identified infection, but human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, Zika virus, and other infections also have been implicated. Typically, weakness or paralysis starts symmetrically in the lower extremities and progresses or ascends proximally to the upper extremities and trunk. In up to one-third of cases, the disease is more severe, with respiratory muscle weakness or paralysis accompanying the more usual limb and trunk symptoms. Respiratory muscle involvement may progress to respiratory failure, which is usually reversible over the course of weeks to months. In general, the natural history of the disease leads to recovery, although mortality is 3% to 8% and up to 10% of survivors have permanent sequelae.

In *myasthenia gravis*, patients experience weakness and fatigue of skeletal muscles, most frequently those innervated by cranial nerves, but peripheral (limb) and respiratory muscles also may be affected. The primary abnormality is found at the NM junction, where transmission of impulses from nerve to muscle is impaired by a decreased number of receptors on the muscle for the neurotransmitter acetylcholine and by the presence of antibodies against these receptors. Although myasthenia gravis is a chronic illness, the manifestations often can be controlled by appropriate therapy, and individual episodes of respiratory failure are potentially reversible.

*Poliomyelitis* is a viral disease in which the poliovirus attacks motor nerve cells of the spinal cord and brainstem. Both the diaphragm and intercostal muscles can be affected, with resulting weakness or paralysis and respiratory failure. Surviving patients usually recover respiratory muscle function, although some patients have chronic respiratory insufficiency from prior disease. Mass vaccination of the population in developed countries makes new cases rare. In *postpolio syndrome*, patients develop new or progressive symptoms of weakness that occur decades after the initial episode of poliomyelitis. Involvement typically occurs in muscles originally affected by the disease, so respiratory muscle involvement is more likely in patients who had respiratory failure with their initial disease.

*Amyotrophic lateral sclerosis* is a degenerative disease of the nervous system that involves both upper and lower motor neurons. Commonly, muscles innervated by either cranial nerves or spinal nerves are affected. Clinically, progressive muscle weakness and wasting develop, eventually leading to profound weakness of respiratory muscles and death. Although the time course of the disease is variable among patients, the natural history is one of progressive and irreversible deterioration. As a result, patients and families must confront the difficult decision of whether to use mechanical ventilation either noninvasively or through a tracheostomy tube when the patient develops respiratory failure, knowing that no treatment will arrest the progressive neurologic deterioration.

## Pathophysiology and clinical consequences

Weakness of respiratory muscles is the hallmark of respiratory involvement in the NM diseases. Depending on the specific disease, chest wall (intercostal) muscles, diaphragm, and expiratory muscles of the abdominal wall can be affected to variable extents.

Impairment of inspiratory muscle strength may render patients unable to maintain sufficient minute ventilation for adequate $CO_2$ elimination. In addition, patients often alter their pattern of breathing, taking shallower and more frequent breaths. Although this pattern of breathing may require less muscular effort and be more comfortable, it is also less efficient because a greater proportion of each breath is wasted on ventilating the anatomic dead space (see Chapter 1). Therefore, even if total minute ventilation is maintained, alveolar ventilation (and thus $CO_2$ elimination) is impaired by this altered pattern of breathing.

The respiratory difficulty that develops in patients with NM disease is exacerbated by weakness of expiratory muscles leading to ineffective cough. Recurrent respiratory tract infections, accumulation of secretions, and areas of collapse or atelectasis significantly contribute to the clinical problems seen in these patients. Respiratory failure usually occurs in the context of a respiratory infection and impaired secretion clearance rather

than as a result of simple progression of weakness beyond a critical point in the absence of these factors.

Symptoms include dyspnea and anxiety. Patients may also have a feeling of suffocation. Often the presence of generalized muscle weakness severely limits patients' activity and lessens the degree of dyspnea that would be present if they were capable of more exertion.

Features of NM disease:

1. Altered pattern of breathing (↑ rate, ↓ tidal volume)
2. Ineffective cough
3. Restrictive pattern on pulmonary function tests
4. Decreased maximal inspiratory/expiratory pressures
5. ↑ $P_{CO_2}$, often with ↓ $P_{O_2}$

With severe NM disease, pulmonary function tests show a restrictive pattern of impairment. Although muscle weakness is the primary cause of restriction, compliance of the lung and chest wall may be secondarily affected, further contributing to the restrictive pattern. The decrease in pulmonary compliance presumably is due to microatelectasis (i.e., multiple areas of alveolar collapse) resulting from the shallow tidal volumes. At the same time, stiffening of various components of the chest wall (e.g., tendons, ligaments, and joints) over time is thought to be responsible for decreased distensibility of the chest wall. Functional residual capacity (FRC) is normal or decreased, depending on how much respiratory system compliance is altered. Total lung capacity (TLC) is decreased primarily due to inspiratory muscle weakness, but changes in respiratory system compliance may also contribute. Residual volume (RV) frequently is increased due to expiratory muscle weakness (Fig. 19.1). The degree of muscle weakness can be quantified by measuring the maximal inspiratory and expiratory pressures the patient is able to generate with maximal inspiratory and expiratory efforts against a closed mouthpiece. Both maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) may be significantly depressed.

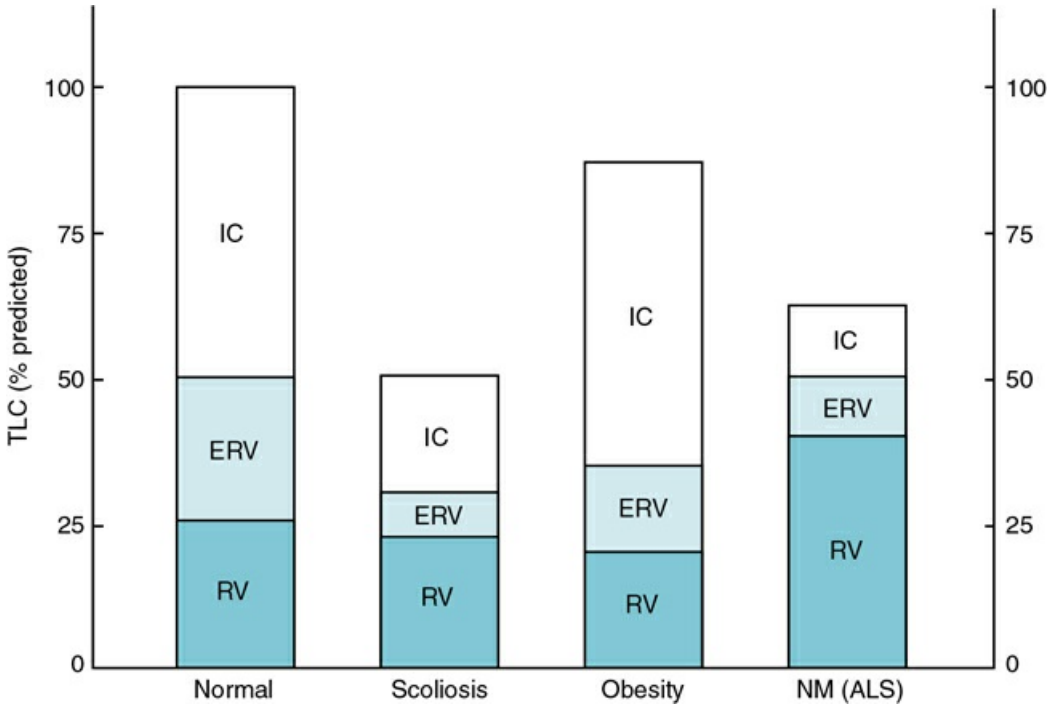


**FIGURE 19.1** Examples of lung volumes (total lung capacity *[TLC]* and its subdivisions) in patients with chest wall and neuromuscular *(NM)* disease compared with values in a normal subject. Nonshaded area represents vital capacity and its subdivisions. *ALS*, amyotrophic lateral sclerosis; *ERV*, expiratory reserve volume; *IC*, inspiratory capacity; *RV*, residual volume. *Source:* (Modified from Bergofsky, E. H. (1979). Respiratory failure in disorders of the thoracic cage. *American Review of Respiratory Disease, 119*, 643–669.)

In the setting of severe muscle weakness, arterial blood gas analysis is most notable for hypercapnia. Hypoxemia due to alveolar hypoventilation and atelectasis also occurs. When hypoventilation is the sole cause of hypoxemia, the alveolar-arterial oxygen difference ($AaDo_2$) is normal. However, complications such as atelectasis, respiratory tract infections, and inadequately cleared secretions may add a component of ventilation-perfusion mismatch or shunt that further depresses $Po_2$ and increases $AaDo_2$.

## Diaphragmatic disease

Although diaphragmatic involvement is a significant component of many of the NM diseases that affect the muscles of respiration, additional etiologic and clinical considerations justify a separate discussion of diaphragmatic disease. First, we consider *diaphragmatic fatigue*, a potential consequence of disorders affecting other parts of the respiratory system that significantly increase the workload placed on the diaphragm. We then discuss *diaphragmatic paralysis*, with separate considerations of unilateral and

bilateral paralysis, because the causes and clinical manifestations are often quite different.

## Diaphragmatic fatigue

Excluding cardiac muscle, the diaphragm is the single muscle used most consistently and repetitively throughout the course of a person's lifetime. It is well suited for sustained activity and aerobic metabolism, and under normal circumstances the diaphragm does not become fatigued.

However, if the diaphragm is required to perform an excessive amount of work or if its energy supplies are limited, fatigue may develop and may contribute to respiratory dysfunction in certain clinical settings. For example, if a healthy individual repetitively uses the diaphragm to generate 40% or more of its maximal force, fatigue develops and prevents this degree of effort from being sustained indefinitely. For patients with diseases that increase the work of breathing, particularly obstructive lung disease and disorders of the chest wall (described in the section on disorders affecting the chest wall), the diaphragm works at a level much closer to the point of fatigue. When a superimposed acute illness further increases the work of breathing or when an intercurrent problem (e.g., depressed cardiac output, anemia, or hypoxemia) decreases the energy supply available to the diaphragm, diaphragmatic fatigue may contribute to the development of hypoventilation and respiratory failure.

Inefficient diaphragmatic contraction is another factor that may contribute to diaphragmatic fatigue, especially in patients with obstructive lung disease. When the diaphragm is flattened and its fibers are shortened as a result of hyperinflated lungs, the force or negative pleural pressure developed during contraction is less for any given level of diaphragmatic excitation (see Chapter 17). Therefore, a higher degree of stimulation is necessary to generate comparable pressure by the diaphragm, and increased energy consumption results.

Factors contributing to diaphragmatic fatigue:

1. Increased work of breathing
2. Decreased energy supply to the diaphragm
3. Inefficient diaphragmatic contraction

Diaphragmatic fatigue is often difficult to detect because the force generated by the diaphragm cannot be measured conveniently. Ideally, diaphragmatic fatigue is documented by measuring the pressure across the diaphragm (i.e., the difference between abdominal and pleural pressure, called the *transdiaphragmatic pressure*) during diaphragmatic stimulation or contraction. As an alternative to measurement of transdiaphragmatic pressure, the strength of the inspiratory muscles in general can be assessed by measuring the pressure that a patient can generate with a maximal inspiratory effort against a closed mouthpiece (i.e., MIP). A useful finding on physical examination is the pattern of motion of the abdomen during breathing when the patient is supine. If diaphragmatic contraction is especially weak or absent, pleural pressure falls during inspiration mainly due to contraction of other inspiratory muscles. The

negative pleural pressure is transmitted across the relatively flaccid diaphragm to the abdomen, which then moves paradoxically inward during inspiration. Once a patient has reached the point of respiratory failure due to diaphragmatic fatigue, the most important intervention is mechanical ventilatory support, either noninvasive or invasive, while the diaphragm recovers and the acute cause of respiratory failure is treated.

Diaphragmatic weakness can be demonstrated in the supine position by inward motion of the abdomen during inspiration.

## Unilateral diaphragmatic paralysis

Paralysis of the diaphragm on one side of the thorax (also called a *hemidiaphragm*) typically results from disease affecting the ipsilateral phrenic nerve. A particularly common cause of unilateral diaphragmatic paralysis is invasion of the phrenic nerve by malignancy. The underlying tumor is frequently lung cancer that has invaded or metastasized to the mediastinum, and either the primary tumor itself or mediastinal lymph node metastases of tumor invade the phrenic nerve somewhere along its course through the mediastinum. With treatment, some diaphragmatic function may return, but frequently diaphragmatic paralysis resulting from malignancy is irreversible.

Paralysis of the left hemidiaphragm may be seen following cardiac surgery, attributable to either a stretch injury or a cooling injury to the phrenic nerve. The latter type of injury relates to instillation of a cold potassium-rich solution into the pericardium during the procedure to stop cardiac contraction (cold cardioplegia) and allow surgery on a nonbeating heart while circulation is maintained by cardiopulmonary bypass. However, the cardioplegia solution also can cause injury to the left phrenic nerve, leading to diaphragmatic paralysis of variable severity and duration. With changes in surgical and cardiac anesthesia techniques, phrenic nerve injury has become less common following cardiac surgery. When it does occur, function usually recovers within 1 year.

In some patients with unilateral diaphragmatic paralysis, no underlying reason for the paralysis can be identified, and the problem is considered *idiopathic*. A viral infection affecting the phrenic nerve may be responsible in such cases. Many but not all of these patients recover some function over time.

The possibility of unilateral diaphragmatic paralysis is usually first suggested by a characteristic appearance on the chest radiograph (Fig. 19.2). The affected hemidiaphragm is elevated above its usual position in the absence of any associated lobar atelectasis or other reason for volume loss on the affected side. Standard chest radiographs taken during a full inspiration (to TLC) reveal that the normal hemidiaphragm descends fully during inspiration, whereas the paralyzed hemidiaphragm cannot. Patients may or may not be symptomatic with dyspnea as a result of the paralyzed hemidiaphragm, often depending on the presence or absence of additional underlying lung disease.

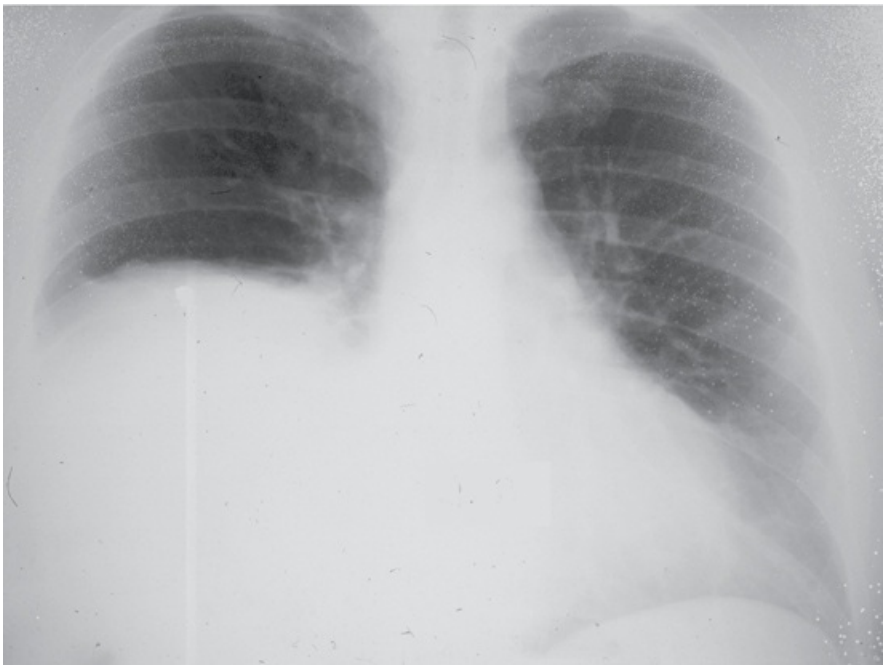

**FIGURE 19.2** Chest radiograph shows elevation of right hemidiaphragm resulting from unilateral *(right)* phrenic nerve paralysis.

Because an elevated diaphragm may result from causes other than diaphragmatic paralysis (e.g., processes below the diaphragm, such as a subphrenic abscess), it is important to confirm objectively that diaphragmatic paralysis is the cause of diaphragmatic elevation. This can be achieved relatively easily by real-time observation of diaphragmatic movement during a "sniff test." With this technique, a radiologist observes diaphragmatic motion under fluoroscopy while the patient sniffs. During the act of sniffing, which is a rapid inspiratory activity, the normal diaphragm contracts and therefore descends, but the paralyzed diaphragm moves passively (and paradoxically) upward due to rapid development of negative intrathoracic pressure during the sniff. Ultrasonographic assessment of diaphragmatic motion may also be useful but requires considerable operator skill.

Many patients do not have symptoms related to unilateral diaphragmatic paralysis. For appropriate patients who are dyspneic in this setting, a treatment option is *diaphragmatic plication*; in this surgical procedure, the hemidiaphragm is fixed in a flattened position. Although the hemidiaphragm still does not move, the lung is maintained at a higher volume, and the hemidiaphragm can no longer move paradoxically upward during inspiration, thus improving ventilatory efficiency.

## Bilateral diaphragmatic paralysis

Paralysis of both hemidiaphragms has much more serious clinical implications than unilateral paralysis because the patient must depend on the accessory muscles of inspiration to maintain minute ventilation. The causes of bilateral diaphragmatic paralysis are the NM diseases listed in Table 19.1, with bilateral diaphragmatic paralysis

being the most severe consequence of respiratory involvement by these disorders.

A characteristic clinical manifestation of bilateral diaphragmatic paralysis is dyspnea that is significantly exacerbated when the patient assumes the recumbent position (i.e., severe orthopnea). In the supine patient, the abdominal contents push on the flaccid diaphragm when the beneficial effects of gravity on abdominal contents and on lowering the position of the diaphragm are lost. On physical examination, patients typically demonstrate paradoxical inward motion of the abdomen during inspiration while they are supine, as described in the discussion on diaphragmatic fatigue. Pulmonary function testing will show the vital capacity measured in the supine position is significantly lower than that measured in the upright position.

## Disorders affecting the chest wall

With certain diseases of the chest wall, difficulty in expanding the chest may impede normal inspiration (see Table 19.1). This section focuses on two specific disorders that pose the greatest clinical problems: kyphoscoliosis and obesity.

### Kyphoscoliosis

*Kyphoscoliosis* is an abnormal curvature of the spine in both the anterior (kyphosis) and lateral (scoliosis) directions (Fig. 19.3). This deformity causes the rib cage to become stiffer and more difficult to expand (i.e., chest wall compliance is decreased). Respiratory difficulties are common in patients with significant kyphoscoliosis. In severe cases, chronic respiratory failure ensues. Although some cases of kyphoscoliosis are secondary to NM disease such as poliomyselitis, the majority of severe cases associated with respiratory impairment are idiopathic.

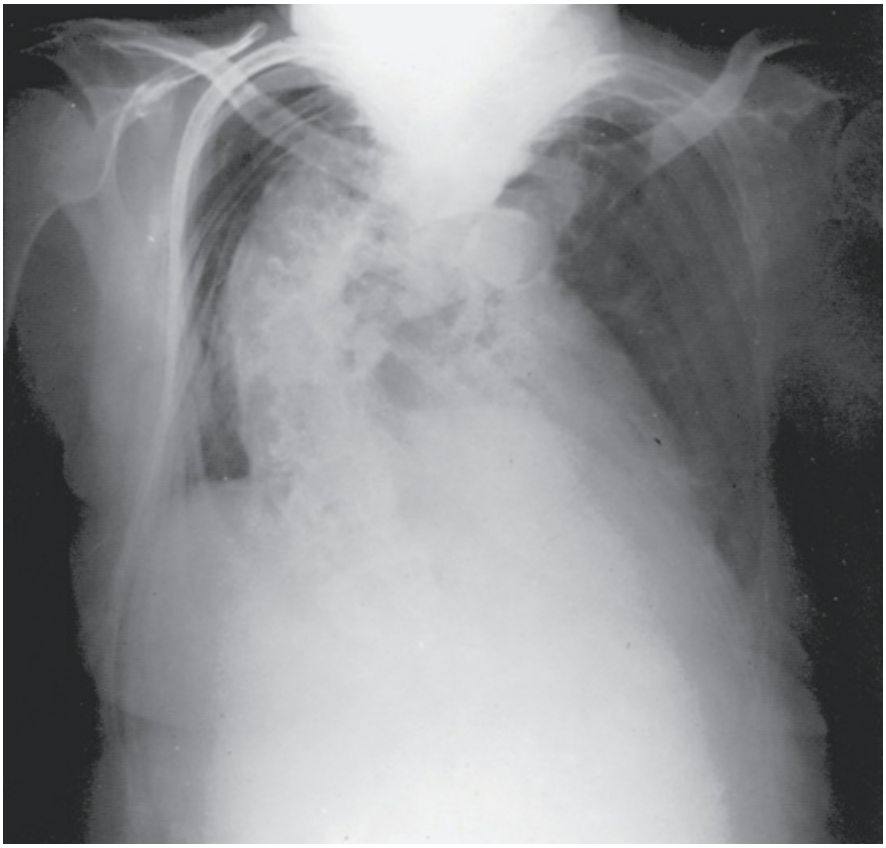

**FIGURE 19.3** Chest radiograph of patient with severe kyphoscoliosis. Note marked spinal curvature and chest wall distortion.

Several pathophysiologic features contribute to respiratory dysfunction in patients with kyphoscoliosis. A crucial underlying problem is the increased work of breathing resulting from the poorly compliant chest wall. To maintain a normal minute ventilation, the work expenditure of the respiratory muscles is greatly increased. In addition, patients decrease their tidal volume and increase respiratory frequency because of difficulty expanding the abnormally stiff chest wall. Consequently, the proportion of dead space ventilation rises, and alveolar ventilation falls unless total ventilation undergoes a compensatory increase. Hence, the increased work of breathing acts together with the altered pattern of breathing to decrease alveolar ventilation and increase $P_{CO_2}$. Chest wall compliance further decreases with age, and respiratory complications of uncorrected kyphoscoliosis become increasingly prevalent as the patient grows older.

Marked distortion of the chest wall causes underventilation of some regions of the lung, microatelectasis, ventilation-perfusion mismatch, and hypoxemia. Thus, two frequent causes of hypoxemia in kyphoscoliosis are hypoventilation and ventilation-perfusion mismatch.

A common complication of severe kyphoscoliosis is pulmonary hypertension and cor pulmonale. Hypoxemia is the most important trigger for the development of pulmonary hypertension. However, increased resistance of the pulmonary vessels also results from

compression and possibly from impaired development in regions where the chest wall is especially distorted. Long-standing hypoxemia and pulmonary hypertension eventually result in remodeling of the pulmonary vasculature, and the pulmonary hypertension becomes irreversible, even with correction of hypoxemia.

Features of severe kyphoscoliosis:

1. Increased work of breathing
2. Altered pattern of breathing (↑ rate, ↓ tidal volume)
3. Exertional dyspnea
4. Ventilation-perfusion mismatch
5. ↑ $P_{CO_2}$, often with ↓ $P_{O_2}$
6. Pulmonary hypertension, cor pulmonale
7. Restrictive pattern on pulmonary function tests

Exertional dyspnea is probably the most common symptom experienced by patients with severe kyphoscoliosis and respiratory impairment. Unlike patients with NM disease, those with a chest wall deformity such as kyphoscoliosis have normal skeletal muscle strength and therefore are capable of normal levels of exertion. Unlike patients with NM disease, patients with kyphoscoliosis are not subject to the same difficulty in generating an effective cough. Expiratory muscle function is preserved, an effective cough is maintained, and problems with secretions and recurrent respiratory tract infections are not prominent clinical features.

Pulmonary function tests in patients with kyphoscoliosis are notable for a restrictive pattern of impairment with a decrease in TLC. Vital capacity is significantly decreased, whereas RV tends to be relatively preserved. FRC, determined by the outward recoil of the chest wall balanced by the inward recoil of the lung, is decreased because the poorly compliant chest wall has a diminished propensity to recoil outward (see Fig. 19.1).

Severe cases of kyphoscoliosis are generally characterized by hypercapnia and hypoxemia. The latter usually is due to both hypoventilation and ventilation-perfusion mismatch. Chronic respiratory insufficiency and cor pulmonale are the end results of severe kyphoscoliosis, and the level of respiratory difficulty appears to correlate with the severity of chest wall deformity.

Surgical therapy aimed at improving or correcting the spinal deformity may be useful in children or adolescents but rarely is effective in adults. Supportive therapy that may be beneficial includes a variety of measures that provide ventilatory assistance to the patient. Treatments with an intermittent positive-pressure breathing machine augment tidal volume by delivering positive pressure to the patient during inspiration. The increase in tidal volume improves microatelectasis and lung compliance, affording the patient several hours with decreased work of breathing after each treatment. At night, ventilatory assistance with inspiratory positive pressure delivered via a mask or through a tracheostomy tube allows the respiratory muscles to rest. Nocturnal ventilatory support may provide sufficient rest for the inspiratory muscles to diminish daytime respiratory muscle fatigue. This type of ventilatory support is discussed further in Chapter 30.

## Obesity

Obesity has many consequences for health, and respiratory symptoms are one aspect. Obesity can produce a wide spectrum in severity of respiratory impairment, ranging from no symptoms to marked limitation in function. Surprisingly, the degree of obesity does not correlate very well with the presence or severity of respiratory dysfunction. Some patients who are massively obese have little difficulty in comparison with much less obese patients who may be severely limited. This is partially explained by the distribution of body fat: central (abdominal) distribution of fat is more associated with decreased lung function as measured by pulmonary function testing. A full explanation of the discrepancies in symptoms among different patients is based on several factors, including smoking history, underlying lung disease, effects of obesity on the cardiovascular system, and underlying physical deconditioning.

The problem of respiratory impairment in obesity was popularly known for years as the *Pickwickian syndrome* or *obesity-hypoventilation syndrome* (OHS). The term *Pickwickian* was applied because of the description of Joe, the obese character in Charles Dickens' *Pickwick Papers*, who had many of the characteristics described in this syndrome. Specifically, Joe had features of massive obesity, hypersomnolence, and peripheral edema, the latter presumably related to cor pulmonale and right ventricular failure. With the accumulation of knowledge about the pathogenesis of respiratory impairment in obesity, the term *Pickwickian syndrome* has become less meaningful.

Obesity appears to exert two main mechanical effects on the respiratory system. As a result of excess soft tissue, more work is necessary for expansion of the thorax. In addition, the massive accumulation of soft tissue in the abdominal wall exerts pressure on abdominal contents, forcing the diaphragm up to a higher resting position. The high resting position of the diaphragm in obesity is associated with decreased expansion of the lung and closure of small airways and alveoli at the bases. Thus, the dependent regions are hypoventilated relative to their perfusion, and this ventilation-perfusion mismatch contributes to arterial hypoxemia.

Similar to kyphoscoliosis, obesity results in lower tidal volumes and increased wasted or dead space ventilation. To maintain adequate alveolar ventilation, overall minute ventilation must increase in the face of increased work of breathing. Most patients compensate appropriately by increasing their overall minute ventilation, and $P_{CO_2}$ remains normal. Other patients do not compensate fully, and hypercapnia is the consequence.

Exactly what distinguishes these two types of patients is not clearly understood. Most obese patients have increased central respiratory drive in response to the added mechanical load. However, patients with OHS do not develop this increased drive. Patients with OHS also show decreased sensitivity to hypoxemia and hypercapnia. This appears to be an acquired phenomenon and may develop in conjunction with sleep-disordered breathing. In addition, the obesity-associated hormone leptin may influence the development of OHS. After hypercapnia develops, it is much more difficult to assess the innate responsiveness of the patient's ventilatory controller because chronic hypercapnia (i.e., chronic respiratory acidosis with a compensatory metabolic alkalosis) blunts the responsiveness of the central chemoreceptor.

Features of obesity:

1. Increased work of breathing
2. High diaphragm (low FRC)
3. Altered pattern of breathing (↑ rate, ↓ tidal volume)
4. Ventilation-perfusion mismatch
5. Variable ↑ $P_{CO_2}$, ↓ $P_{O_2}$
6. Obstructive apnea (common)

Another distinguishing feature between normocapnic and hypercapnic obese patients may relate to inspiratory muscle strength. Although inspiratory muscle strength is normal in obese patients with normal $P_{CO_2}$, it is reduced by approximately 30% in patients with OHS, perhaps as a result of respiratory muscle fatigue.

Another factor that contributes to the overall clinical picture in many massively obese patients is upper airway obstruction during sleep (i.e., the obstructive form of sleep apnea syndrome). Soft tissue deposition in the neck and tissues surrounding the upper airway presumably predisposes the person to episodes of upper airway obstruction during sleep (see Chapter 18). The somnolence that occurs in patients who have OHS is primarily related to the presence of obstructive sleep apnea and its disruption of normal sleep architecture.

Although obesity, abnormal respiratory drive, respiratory muscle weakness, and sleep apnea syndrome contribute to respiratory dysfunction, exactly how they all interact in individual patients is often difficult to assess. Because sleep apnea syndrome and abnormal respiratory drive also occur in patients who are not obese, it is reasonable to view some of the contributing pathophysiologic factors in terms of a Venn diagram (Fig. 19.4). Probably the most marked symptoms and respiratory dysfunction are seen in patients who are represented at the intersection of the three circles.

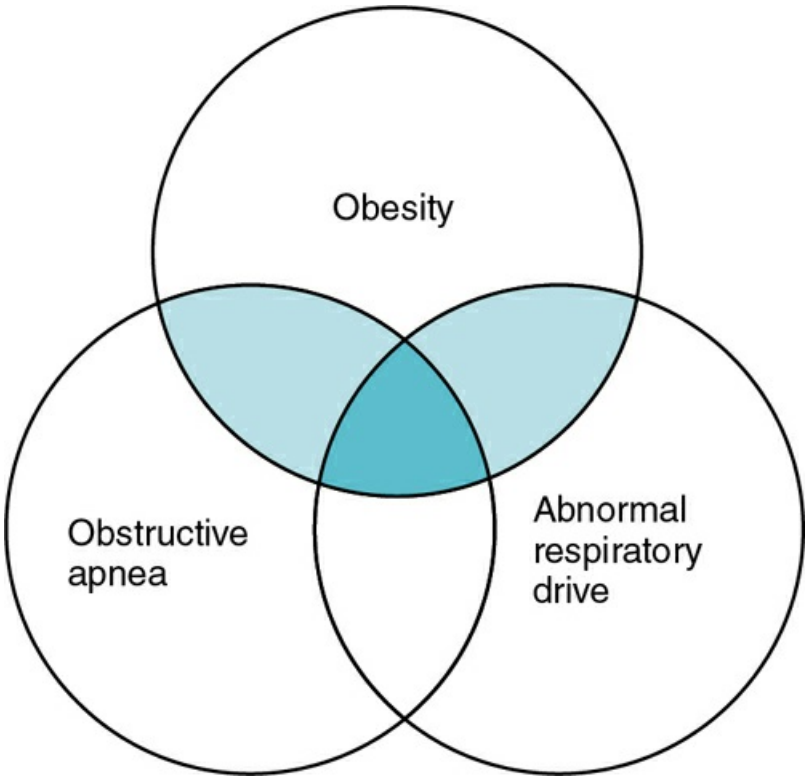


**FIGURE 19.4** Venn diagram shows hypothetical indication of the way obesity interacts with obstructive apnea and abnormal respiratory drive. Overlap on left indicates obese normocapnic patients with obstructive apnea. Overlap on right indicates hypercapnic obese patients without obstructive apnea. Overlap at center indicates obese hypercapnic patients with obstructive apnea.

The symptoms that may occur in obese patients can be associated with increased work of breathing (e.g., dyspnea) or sleep apnea syndrome (e.g., daytime somnolence and disordered sleep with profound snoring). Patients may have clinical manifestations related to the complications of pulmonary hypertension, cor pulmonale, and right ventricular failure. These complications are largely related to arterial hypoxemia both during the day and at night, particularly if patients have sleep apnea syndrome.

Pulmonary function tests typically demonstrate a restrictive pattern, with a decrease in TLC. The diaphragm is pushed up in massively obese patients, reducing FRC, which in these patients is much closer to RV; thus, spirometric examination shows the expiratory reserve volume is greatly reduced. This pattern of functional impairment is shown in Fig. 19.1.

In most obese patients, arterial blood gases show a decrease in $P_{O_2}$ and an increase in $AaD_{O_2}$ as a consequence of high diaphragms, airway and alveolar closure, and ventilation-perfusion mismatch. When patients have OHS and $P_{CO_2}$ is elevated, hypoventilation is another factor contributing to hypoxemia. If patients have sleep apnea syndrome, arterial blood gas values become even more deranged at night due to

episodes of disordered breathing.

Weight loss is crucial in the treatment of obese patients with respiratory dysfunction. If weight loss is successfully achieved by either diet or bariatric surgery, respiratory problems may resolve in some patients. Unfortunately, attempts at significant and sustained weight loss are often unsuccessful, and some patients who successfully lose weight do not manifest respiratory benefits. Thus, in most patients, other modes of therapy must be instituted. Nocturnal positive-pressure ventilation is generally helpful in improving daytime sleepiness, particularly if the patient has concomitant obstructive sleep apnea syndrome (see Chapter 18). In some patients with impaired respiratory drive, respiratory stimulants, especially progesterone (a centrally acting respiratory stimulant), have been used with limited success.

## Suggested readings

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**Diseases affecting the chest wall**

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# 20: Lung cancer: Etiologic and pathologic aspects

OUTLINE



Carcinoma of the lung is a public health problem of immense proportions; it has been a source of great frustration to individual physicians and the medical profession in general. More than 70 years ago, the primary cause of carcinoma of the lung—cigarette smoking—was conclusively identified. Fortunately, the global prevalence of smoking has been falling, albeit gradually, after peaking in the mid-1970s. The World Health Organization (WHO) reports that the number of smokers in the world decreased from 1.397 billion in 2000 to 1.337 billion in 2018. This decline has been driven largely by a reduction in the number of female smokers, but the number of male smokers appears to have reached a plateau and is also starting to decline. In the United States, the percentage of adults who smoke has decreased from 42% in 1965 to 21% in 2005 and 14% in 2019.

Lung cancer has been one of the most common cancers worldwide for several decades. In 2020, there were an estimated 2,200,000 new cases of lung cancer globally. Lung

cancer is also the most common cause of cancer-related death worldwide, with an estimated 1,800,000 deaths (18% of all cancer deaths) in 2020. For 2022, the American Cancer Society estimates that 236,740 new cases of lung cancer will be diagnosed in the United States, and approximately 130,000 individuals will die as a result of the disease. For many years, carcinoma of the lung has been the leading cause of cancer deaths among men, and in 1985 lung cancer surpassed breast cancer as the leading cause of cancer deaths among women. Lung cancer is responsible for 21% of all deaths in the United States attributable to cancer and approximately 5% of all deaths from any cause, killing more people than cancers of breast, prostate, and colon *combined*.

The number of cases and the number of deaths related to lung cancer have increased dramatically over the last several decades. For no other form of cancer has the increase approached that of lung cancer. For men, the death rate appears to have reached a peak in 1990; fortunately, it has been decreasing since then. In women, the death rate increased fivefold in the 30 years from 1960 to 1990, and reached a plateau around 2002.

Despite the magnitude of the problem and some innovative new therapies, our ability to treat most carcinomas of the lung has not yet improved dramatically. In the United States, where treatment is available to most patients, 5-year survival has increased from roughly 7% to 22% during the last several decades, making the prognosis of this disease still dismal in the majority of cases. There is some recent cautious optimism as a result of earlier detection by screening of high-risk patients as well as development and use of new tumor genotype-directed therapies and immunotherapies.

This chapter's discussion of carcinoma of the lung is presented in two parts. First, the etiology and pathogenesis of lung cancer are considered; this is followed by a description of the pathologic aspects and classification of the different types of tumors. Chapter 21 continues with a discussion of the clinical aspects of the disease, including diagnostic and therapeutic considerations. Chapter 21 concludes with a brief discussion of an additional type of neoplastic disease affecting the respiratory system, bronchial carcinoid tumor, along with a consideration of the common problem of the patient with a solitary pulmonary nodule. Malignant mesothelioma, a neoplasm that originates in the pleura, is discussed in Chapter 15, Pleural Disease.

## Etiology and pathogenesis

For no other common cancer affecting humans have the causative factors been identified as well as for lung cancer. Cigarette smoking clearly is responsible for the vast majority of cases (80%–85% according to most estimates), and additional risk factors associated with occupational exposure have been identified. This chapter begins with a discussion of the two major risk factors—cigarette smoking and occupational exposure—and considers genetic factors as a potential contributor to lung cancer risk. Next is a brief description of the importance of previous scarring within the pulmonary parenchyma, which has been implicated in the development of "scar carcinomas," and several miscellaneous proposed risk factors are mentioned. Finally, the role of oncogenes and tumor suppressor genes in the pathogenesis of lung cancer is discussed.

### Smoking

Cigarette smoking is the single most important risk factor for the development of carcinoma of the lung. As might be expected, the duration of smoking history, number of cigarettes smoked each day, depth of inhalation, and amount of each cigarette smoked, all correlate with the risk for developing lung cancer. As a rough but easy way to quantify prior cigarette exposure, the number of years of smoking can be multiplied by the average number of packs smoked per day, giving the number of "pack-years."

Although the evidence linking smoking with lung cancer is incontrovertible, the responsible components of cigarette smoke have not been identified with certainty. Cigarette smoke consists of a gaseous phase and a particulate phase, and at least 69 known carcinogens have been found in both phases, ranging from nitrosamines to benzo[a]pyrene and other polycyclic hydrocarbons. Filters appear to decrease but certainly not eliminate the potential carcinogenic effects of cigarettes. A substantially lower risk for lung cancer is associated with cigar and pipe smoking, presumably related to the fact that cigar and pipe smoke is generally not inhaled deeply into the lungs in the same manner as cigarette smoke. The smoking of marijuana and cocaine is also associated with the precancerous histologic changes observed among cigarette smokers, and both are believed to be risk factors for lung cancer. The use of e-cigarettes, commonly known as *vaping*, is still relatively new, and the long-term risk it poses for development of lung cancer is unknown. Although many of the carcinogenic components of cigarette smoke are not found in e-cigarettes, there are still some potential carcinogens in the constituents of the vaping liquid as well as the organic products produced by the e-cigarette device.

Development of lung cancer due to smoking requires many years of exposure. However, histologic abnormalities before the development of a frank carcinoma are well documented in the bronchial epithelium of smokers with lesser degrees of exposure. These changes—including loss of bronchial cilia, hyperplasia of bronchial epithelial cells, and nuclear abnormalities—may be the pathologic forerunners of a true carcinoma.

In contrast to smoking-related emphysema, which is irreversible, if a person stops smoking many of the precancerous changes begin to regress. Epidemiologic studies have shown that the risk for developing lung cancer begins to decrease within 5 years and continues to decline progressively after cessation of smoking. Case-control studies show that abstinence for more than 15 years reduces the risk of lung cancer in former smokers by 80% to 90%, but unfortunately the risk never fully returns to the level of lifetime nonsmokers. In some cases, the initial cellular changes leading to or predisposing to malignant transformation have already developed by the time the patient stops smoking, and it is merely a matter of time before the carcinoma develops or becomes clinically apparent.

Smoking-induced histopathologic abnormalities in bronchial epithelium precede the development of carcinoma.

Data indicate that the risk of lung cancer is increased for nonsmoking spouses because of their exposure to sidestream or "secondhand" smoke. Although the risk attributable to "passive smoking" is relatively small compared with the risk of active smoking, involuntary exposure to cigarette smoke is likely responsible for some cases of lung cancer occurring in nonsmokers. The comparably small but real risk of lung cancer

from passive smoking has been a major justification for legislation prohibiting smoking in shared spaces such as commercial aircraft, restaurants, and offices.

## Occupational factors

A number of potential environmental risk factors for lung cancer have been identified, most of which occur with occupational exposure. Perhaps the most widely studied of the environmental or occupationally related carcinogens is asbestos, a fibrous silicate formerly in wide use because of its properties of fire resistance and thermal insulation. Shipbuilders, construction workers, and those who worked with insulation and brake linings are among those who may have been exposed to asbestos.

Carcinoma of the lung is the most likely malignancy to result from occupational asbestos exposure, although other tumors, especially mesothelioma (see Chapter 15), are also strongly associated with prior asbestos contact. Low-level nonoccupational exposures to asbestos in schools or among residents living near asbestos mines or processing facilities are of much lesser significance. The risk for development of lung cancer is particularly high among smokers exposed to asbestos, in which case these two risk factors have a multiplicative rather than a simple additive effect. Specifically, asbestos alone appears to confer a 2- to 5-fold increased risk for lung cancer, whereas smoking alone is associated with an approximately 10-fold increased risk. Together, the two risk factors make the person who smokes and has had asbestos exposure 20 to 50 times more likely to have carcinoma of the lung than a nonsmoking, nonexposed counterpart. Like other forms of asbestos-related disease, many years elapse before complications develop. In the case of lung cancer, the tumor generally becomes apparent more than two decades after exposure.

The combined risk factors of asbestos exposure and smoking markedly increase the risk of lung cancer.

Several other occupational exposures have been associated with an increased risk of lung cancer. Examples include exposure to arsenic (in workers making pesticides, glass, pigments, and paints), ionizing radiation (especially in uranium miners), haloethers (bis[chloromethyl] ether and chloromethyl methyl ether in chemical industry workers), and polycyclic aromatic hydrocarbons (in petroleum, coal tar, and foundry workers). As is the case with asbestos, there is generally a latent period of at least two decades from the time of exposure until presentation of the tumor.

## Genetic factors

Why lung cancer develops in some heavy smokers and not in others is a question of great importance but with no definite answer at present. The assumption is that genetic factors must place some individuals at higher risk for lung cancer after exposure to carcinogens. The finding of an increased risk of lung cancer among first-degree relatives of lung cancer patients—even after confounding factors have been taken into account—supports this hypothesis.

Candidate genetic factors have included specific enzymes of the cytochrome P450 system. These enzymes may have a role in metabolizing products of cigarette smoke to potent carcinogens, and genetically determined increased activity or expression of the

enzymes may be associated with a greater risk of developing lung cancer following exposure to cigarette smoke. One example is the enzyme aryl hydrocarbon hydroxylase, which can convert hydrocarbons to carcinogenic metabolites. This enzyme is induced by smoking, and genetically determined inducibility of this enzyme by smoking may correlate with the risk for lung cancer.

In some families with high rates of lung cancer in nonsmokers, germline mutations in the epithelial growth factor receptor (EGFR) have been identified and are postulated to be a risk factor for lung cancer. Other as yet unidentified genetic factors potentially affect susceptibility to environmental carcinogens and may include the activity of tumor suppressor genes. If such factors are eventually recognized, then preventing susceptible individuals from being exposed to the known environmental carcinogens or targeting more aggressive screening techniques toward the populations at greatest risk may be possible.

## Parenchymal scarring

Scar tissue within the lung can be a locus for the subsequent occurrence of lung cancer, called a *scar carcinoma*. The scarring may be either localized (e.g., resulting from an old focus of tuberculosis or another infection) or diffuse (e.g., from pulmonary fibrosis, whether idiopathic or associated with a specific cause). Mechanistically, it is thought that fibrosis and malignancy share some dysregulated pathways of cell proliferation, although the precise relationship is uncertain. Most frequently, scar carcinoma of the lung is a peripherally located adenocarcinoma.

Although it is easy to consider carcinomas occurring within or adjacent to scar tissue to be scar carcinomas, adenocarcinomas of the lung may also develop fibrotic areas within the tumor. Therefore, in some cases, it may be impossible to know whether the scar preceded or followed development of the carcinoma.

## Miscellaneous factors

Exposure to radon, a gas that is a decay product of radium-226 (itself a decay product of uranium-238), is a clear risk factor for the development of lung cancer. Epidemiologic studies of uranium miners exposed to high levels of radon working in the United States and Europe prior to the 1980s, when the risk was identified, demonstrated an increased incidence of both small-cell and squamous cell carcinoma (see discussion of pathology further on). The risk appears to be mitigated by improved working conditions and ventilation in mines.

Exposure to much lower levels of this known carcinogen may occur indoors in homes built on soil that has a high radium content resulting in release of radon into the surrounding environment. The finding of unacceptably high levels of radon in some home environments has sparked concern about the risk of lung cancer and interest in widespread testing of houses. Household levels of radon never come close to the level experienced by miners, so some uncertainty remains about the overall risk posed by exposure to household radon. However, most authorities agree there is a small but real increased risk of lung cancer associated with elevated home levels. It has been suggested that radon is the second most important factor contributing to lung cancer and is potentially responsible for 20,000 lung cancer deaths per year in the United States.

Some evidence suggests that dietary factors may affect the risk of lung cancer. Several

studies have reported an association between low intake and serum levels of β-carotene, the provitamin form of vitamin A, with an increased risk of lung cancer. However, the data relating to this issue are controversial. An increased risk associated with low dietary intake of β-carotene, if it exists, is relatively minor compared with the risk posed by cigarette smoking. Three large randomized trials have failed to demonstrate a protective effect of β-carotene, α-tocopherol, or retinoid supplementation on lung cancer risk. The issue is further complicated by data suggesting an *increase* in the incidence of lung cancer in some trials of individuals given supplements.

Human immunodeficiency virus (HIV) infection increases the risk of lung cancer; this association has become more important as effective antiretroviral treatment has decreased mortality from infectious causes in this population. Patients who have received radiation therapy to the thorax (e.g., as treatment for breast cancer or Hodgkin lymphoma) are at increased risk for lung cancer. Finally, in developing countries, chronic exposure to wood smoke is believed to be responsible for a sizable fraction of lung cancers, particularly among women.

## Concepts of lung cancer pathogenesis

There has been a great deal of interest in identifying the cell or cells of origin (i.e., histogenesis) of the various types of lung cancer and elucidating the genetic changes involved in malignant transformation of these cells. For many years it was assumed that the different histopathologic types of lung cancer (described in the section on pathology, further on) were each associated with a different cell of origin. It was thought that previously well-differentiated normal cells underwent a process of dedifferentiation and unrestricted growth when exposed to a carcinogenic stimulus. However, based in part on the common finding of cellular heterogeneity (i.e., more than one cell type within a single tumor), it is currently believed that many if not all types of lung cancer arise from a relatively undifferentiated precursor or stem cell. During this cell's malignant transformation, it differentiates along one or more particular pathways that determine its ultimate histologic appearance—that is, its cell type or types.

Alterations in genes that code for proteins controlling or regulating cell growth have been found in a high proportion of patients with lung cancer. These molecular changes may play a central role in lung cancer pathogenesis. Two types of oncogenes have been identified: proto-oncogenes (which code for growth-promoting factors) and tumor suppressor genes (which code for factors having a negative regulatory effect on cell proliferation). A mutation in one of the paired alleles of a proto-oncogene can result in production of a protein with a growth-promoting effect such that a "dominant" behavior or effect would be observed. In contrast, both alleles of a tumor suppressor gene must be altered before the absence of the gene product would be clinically manifested as increased cell growth or malignant transformation. This requirement produces a "recessive" pattern of clinical expression.

Alterations in proto-oncogenes and tumor suppressor genes have been found in many patients with lung cancer.

Examples of specific alterations in proto-oncogenes that have been identified in lung cancer include mutations in the epidermal growth factor receptor *(EGFR)*, activin

receptor-like kinase *(ALK)*, and *KRAS* families of dominant oncogenes. A variety of mutations in recessive tumor suppressor genes also have been identified, including the retinoblastoma *(rb)* and *p53* genes. In addition, deletion of genetic material from chromosome 3p (the short arm of chromosome 3) has been recognized in lung cancer, and it is thought that deletion may involve loss of one or more tumor suppressor genes. Efforts to elucidate the pathobiology of oncogenes in lung and other cancers constitute an exploding area of intense investigation that is beyond the scope of this textbook. Readers are referred to excellent review articles in the Suggested Readings at the end of this chapter. Importantly, the presence of some of these alterations affects treatment choices, as discussed in Chapter 21.

## Pathology

The term *bronchogenic carcinoma* is often used interchangeably with the term *lung cancer*, implying that lung cancers arise from bronchi or bronchial structures. Many cancers do originate within airways, but other tumors arise in the periphery of the lung and may not necessarily originate in an airway. This section focuses on the currently accepted classification of lung cancer, which was updated in 2015 and then again in 2021, and summarizes what is known about the behavior patterns of the various types of tumors. Of note, whereas older classification schemes of lung cancer relied exclusively upon microscopic examination of stained specimens, immunohistochemistry and genetic analysis now play a central role in characterizing lung malignancies.

Most lung cancers fall within one of four histologic categories: (1) squamous cell carcinoma, (2) adenocarcinoma, (3) large-cell carcinoma, and (4) small-cell carcinoma (now considered a subcategory of neuroendocrine tumors). Within each histologic category are several subcategories that, for our purposes, are less important. Of note, nearly 15% of lung cancers are considered “other non–small-cell” tumors, a category that includes malignancies too anaplastic to permit further subtyping, as well as rarer variants that are not discussed here.

Major histologic categories of lung cancer:

1. Squamous cell carcinoma
2. Adenocarcinoma
3. Large-cell carcinoma
4. Small-cell carcinoma (subcategory of neuroendocrine tumors)

A major distinction to make is between *small-cell lung carcinoma (SCLC)* and all the other cell types, which are grouped together as *non–small-cell lung carcinoma (NSCLC)*. The importance of this distinction relates to the propensity of small-cell carcinoma for early clinical and subclinical metastasis, which affects the approaches to staging and treatment of this tumor compared with those of all the other cell types. Within non–small-cell carcinomas, a second important distinction is between squamous cell carcinoma and other non–small-cell carcinomas, especially adenocarcinoma, because of differences in responsiveness to certain drugs, such as EGFR tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors (discussed in Chapter 21).

Each of the four major categories of lung cancer is associated with cigarette smoking, but the statistical association between smoking and the individual cell types is strongest for squamous cell carcinoma and small-cell carcinoma, which are seen almost exclusively in smokers. Even though smoking also increases the risk for adenocarcinoma and large-cell carcinoma, these cell types also occur with some regularity in nonsmokers.

## Squamous cell carcinoma

Formerly the most common histopathologic type encountered, squamous cell tumors currently account for approximately only 20% to 25% of all primary lung cancers. These malignancies originate within the epithelial layer of the bronchial wall, in which a series of progressive histologic abnormalities result from chronic or repetitive cigarette smoke–induced injury.

Initially, there is metaplasia of normal bronchial columnar epithelial cells, which are replaced by squamous epithelial cells. Over time these squamous cells become more and more atypical in appearance until a well-localized noninvasive carcinoma (i.e., carcinoma in situ) develops. Eventually the carcinoma extends beyond the bronchial mucosa and becomes frankly invasive. After the tumor reaches this stage, it generally comes to eventual clinical attention by producing either symptoms or radiographic changes. In some cases, detection of the carcinoma is made at the earlier in situ stage, usually by recognition of the malignant cells in a specimen of sputum obtained for cytologic examination or by biopsy of grossly abnormal-appearing bronchial mucosa during bronchoscopic evaluation undertaken for other reasons.

Specific histologic features of squamous cell carcinoma are common and point the pathologist to this diagnosis. These tumors are characterized by the visible presence of keratin, “squamous pearls,” and intercellular desmosomes or bridges (Fig. 20.1).

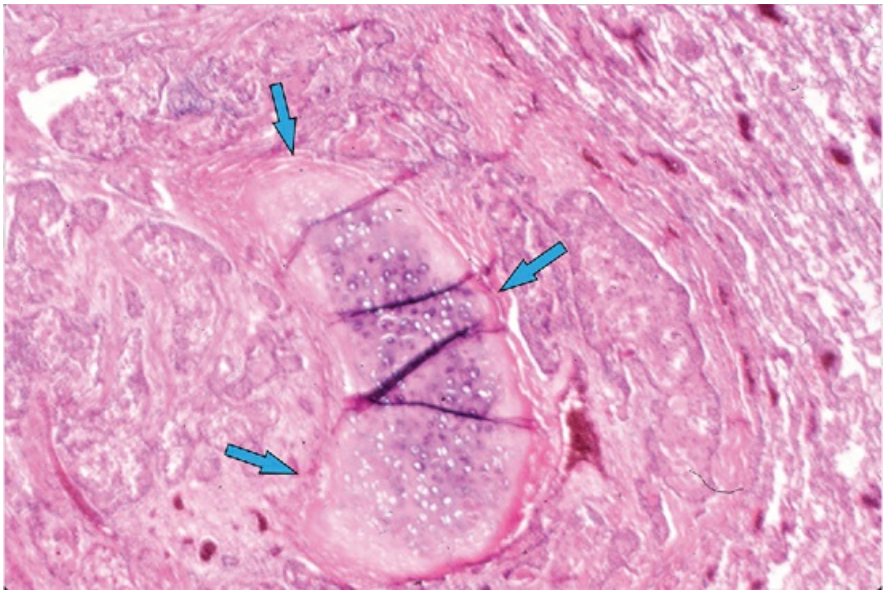

**FIGURE 20.1** Photomicrograph of squamous cell carcinoma. Arrows outline a “keratin pearl,” a characteristic of squamous cell

carcinoma.

Squamous cell carcinomas tend to be located in relatively large or proximal airways, most commonly at the subsegmental, segmental, or lobar level. With growth of the tumor into the bronchial lumen, the airway may become obstructed. The lung distal to the obstruction frequently collapses (becomes atelectatic), and a postobstructive pneumonia may develop. Sometimes a cavity develops within the tumor mass; this finding of cavitation is much more common with squamous cell than with other types of bronchogenic carcinoma.

Features of squamous cell carcinomas:

1. Generally arise in proximal airways
2. May cause airway obstruction, leading to distal atelectasis or pneumonia
3. May cavitate
4. Intrathoracic spread rather than distant metastases

Spread of squamous cell carcinoma beyond the airway usually involves (1) direct extension to the pulmonary parenchyma or other neighboring structures or (2) invasion of lymphatic vessels, with spread to local lymph nodes in the hilum or mediastinum. These tumors have a tendency to remain within the thorax and cause problems by intrathoracic complications rather than by distant metastasis. Although the stage at presentation is the primary determinant of survival, some studies suggest the overall prognosis in terms of 5-year survival is better for patients with squamous cell carcinoma than for those with other cell types.

## Adenocarcinoma

Adenocarcinoma has surpassed squamous cell carcinoma as the most frequent cell type, accounting for approximately 50% of primary lung tumors. Because most adenocarcinomas occur in the lung periphery, it is much harder to relate their origin to the bronchial wall. At present, these tumors are believed to arise at the level of bronchioles or alveolar walls. Adenocarcinomas sometimes appear at a site of parenchymal scarring that is either localized or part of a diffuse fibrotic process.

Adenocarcinoma is the most common type of lung cancer to develop among nonsmokers. Nearly 18% of lung adenocarcinomas are diagnosed in nonsmokers, versus less than 2% of squamous cell carcinomas and less than 1% of small-cell carcinomas. Although the risk factors are not well understood, secondhand smoke exposure may be a contributing factor in some cases. A link between human papillomavirus and adenocarcinoma of the lung has been hypothesized but not definitively established.

The characteristic appearance defining adenocarcinoma is the tendency to form glands, and in many cases produce mucus (Fig. 20.2). When the malignant cells seem to grow and spread along the preexisting alveolar walls, almost as though they were using the alveolar wall as scaffolding for their growth, the tumors are described as having a *lepidic* pattern of growth (Fig. 20.3). The term *lepidic carcinoma* is now used for an invasive carcinoma with this growth pattern, but a similar growth pattern is also seen in

earlier, noninvasive tumors that are classified as either adenocarcinoma in situ or minimally invasive adenocarcinoma. Prior to the 2015 WHO classification of lung tumors, these different tumor types that exhibit lepidic growth were labeled as *bronchioloalveolar carcinoma*, but this term has been eliminated from the current classification system.

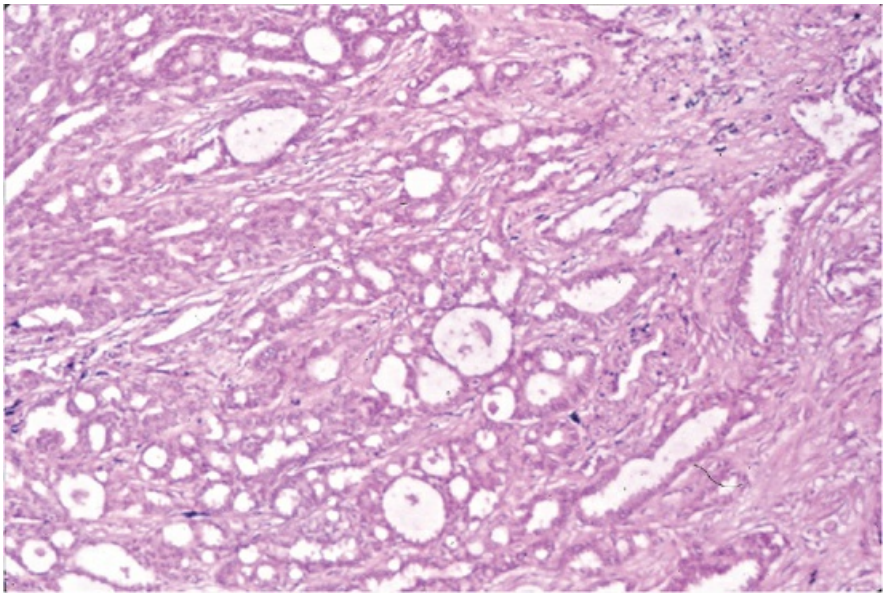

**FIGURE 20.2** Low-power photomicrograph of adenocarcinoma of lung. Malignant cells form gland-like structures.

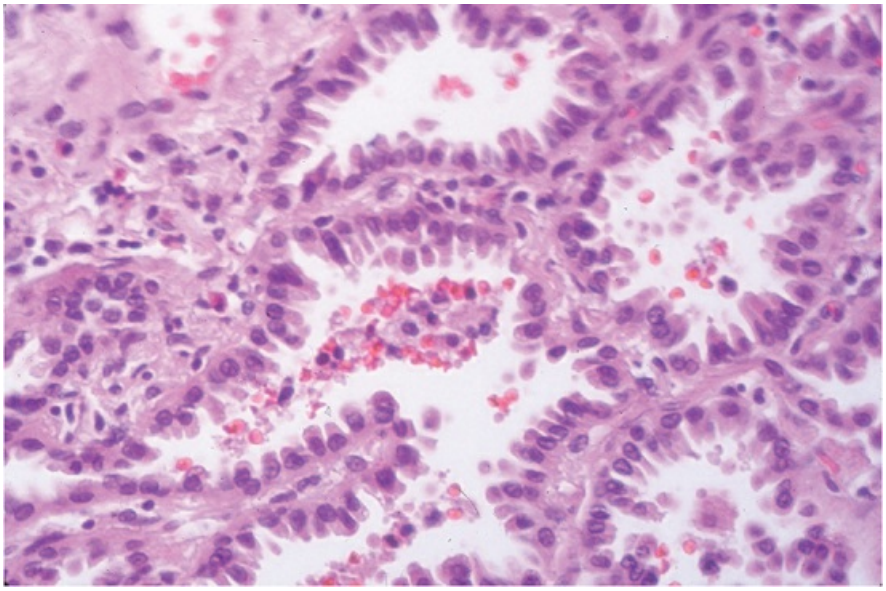

**FIGURE 20.3** High-power photomicrograph showing lepidic growth of tumor along preexisting alveolar walls. This pattern can be

seen in some cases of adenocarcinoma as well as in adenocarcinoma in situ and minimally invasive adenocarcinoma.

The usual presenting pattern of adenocarcinoma is a peripheral lung nodule or mass. Occasionally, the tumors arise within a relatively large bronchus and therefore may become apparent clinically because of complications of localized bronchial obstruction, as seen with squamous cell carcinoma. The lepidic subcategory can manifest in several ways: as a nodule or mass lesion, as a localized infiltrate simulating a pneumonia, or as widespread parenchymal disease.

Although adenocarcinoma may spread locally to adjacent regions of lung or to pleura, it also has a propensity for hilar and mediastinal lymph node involvement and distant metastatic spread. Like small-cell carcinoma, it spreads to liver, bone, central nervous system, and adrenal glands. In comparison with small-cell carcinoma, however, adenocarcinoma is more likely to be localized at the time of presentation, particularly when it manifests as a solitary peripheral lung nodule.

Features of adenocarcinomas:

1. Often manifest as a solitary peripheral pulmonary nodule
2. May arise in an old parenchymal scar
3. Generally localized when presenting as a peripheral lung nodule
4. Spread to hilar and mediastinal nodes and to distant sites

## Large-cell carcinoma

Large-cell carcinoma accounts for approximately 2% of all lung cancers. Essentially a diagnosis of exclusion, it is the most difficult carcinoma to describe microscopically because the tumors often are defined by the characteristics they lack—that is, the specific features, both by light microscopy and histochemistry, that would otherwise classify them as one of the other three cell types. Microscopically, they appear as collections of large polygonal cells with prominent nucleoli and a moderate amount of cytoplasm.

The behavior of these tumors is similar to that of adenocarcinoma. They often appear in the periphery of the lung as mass lesions, although they tend to be somewhat larger than adenocarcinomas. Their natural history is also similar to that of adenocarcinoma in terms of both propensity for spread and overall prognosis.

## Small-cell carcinoma

Small-cell carcinoma, constituting 10% to 15% of all lung cancers, is classified as a neuroendocrine tumor, along with several other less common tumors. Like squamous cell carcinomas, small-cell carcinomas are strongly associated with cigarette smoking and generally originate within the bronchial wall, most commonly at the level of the proximal airways. Small-cell carcinomas, like other lung cancers, originate from a pluripotent stem cell. The eventual cell type then depends on the pattern and degree of differentiation from this precursor cell. Molecular and chromosomal studies have shown

that more than 90% of small-cell carcinomas demonstrate deletions on the short arm of chromosome 3 (3p).

In small-cell carcinoma, the malignant cells appear as small, darkly stained cells with sparse cytoplasm (Fig. 20.4). Local growth of the tumor often follows a submucosal pattern, but the tumor quickly invades lymphatics and submucosal blood vessels. Hilar and mediastinal nodes are involved and enlarged early in the course of the disease and frequently are the most prominent aspect of the radiographic presentation.

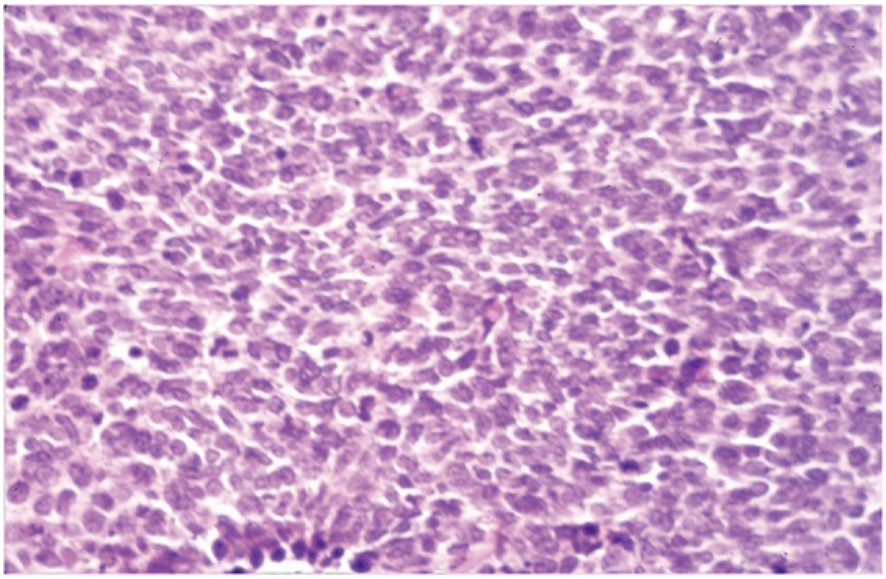

**FIGURE 20.4** High-power photomicrograph of small-cell carcinoma. Malignant cells have irregular, darkly stained nuclei and sparse cytoplasm.

Features of small-cell carcinomas:

1. Generally arise in proximal airways
2. Commonly associated with hilar and mediastinal node involvement
3. Manifest early, distant metastatic disease

Due to the characteristic rapid dissemination, most small-cell carcinomas have already metastasized to distant sites at the time of diagnosis. Distant disease, which may be clinically occult at the time of presentation, often affects the brain, liver, bone (and bone marrow), and adrenal glands. It is this propensity for early metastatic involvement that gives small-cell carcinoma the worst prognosis among the four major categories of bronchogenic carcinoma. Table 20.1 summarizes the distinguishing features of each cell type and reiterates many of the points discussed in this chapter.

**TABLE 20.1**

**Lung Cancer: Comparative Features**

| Cell Type | Frequency (%)[a] | Location[b] | Radiographic Appearance[c] | Spread |
|---|---|---|---|---|
| **Non-Small-Cell Lung Cancer (NSCLC)** | | | | |
| Squamous cell | 20–25 | Proximal, endobronchial | 1. Central mass<br>2. Obstructive atelectasis<br>3. Postobstructive pneumonia | Contiguous intrathoracic spread; nodal metastasis |
| Adenocarcinoma (and other adenocarcinoma spectrum lesions) | 50 | Peripheral | Solitary peripheral nodule or mass | Contiguous intrathoracic spread; nodal and distant metastasis |
| Large cell | 2–5 | Variable | Variable; often large peripheral mass | Contiguous intrathoracic spread; nodal and distant metastasis |
| **Small-Cell Lung Cancer (SCLC)** | | | | |
| Small cell (including oat cell) | 10–15 | Proximal, endobronchial (submucosal) | 1. Central mass<br>2. Hilar, mediastinal adenopathy | Hilar, mediastinal nodes; distant metastasis |

[a]Approximate percent of all lung cancers.

[b]Most common location; for all cell types, variable locations are seen.

[c]Common presentations on chest radiograph.

# Suggested readings

## Etiology and pathogenesis


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# 21: Lung cancer: Clinical aspects

OUTLINE



The goal of this chapter is to extend the discussion of lung cancer into the clinical realm and to relate how the pathologic processes considered in Chapter 20 are encountered in a clinical setting. An outline of the major clinical features of lung cancer is followed by a discussion of the diagnostic approach and general principles of management. The chapter concludes with a brief discussion of bronchial carcinoid tumors and the clinical problem of the solitary pulmonary nodule.

## Clinical features

Because lung cancer presumably starts with a single malignant cell, a long period of

repetitive divisions and doubling of cell number must occur before the tumor becomes clinically apparent. During this preclinical period, an estimated 30 divisions take place before the tumor reaches a diameter of 1 cm. This process most likely requires several years, during which time the patient and the physician are unaware of the tumor.

The possibility of lung cancer is often raised because of findings on imaging studies such as a chest radiograph or computed tomography (CT) scan, or because of an assortment of symptoms that develop. This section focuses primarily on symptoms; imaging studies and diagnostic sampling are discussed in the section "Diagnostic Approach." The symptoms at the time of presentation may relate to the primary lung lesion, to metastatic disease (either in intrathoracic lymph nodes or at distant sites), or to what are commonly called "paraneoplastic syndromes."

## Symptoms relating to primary lung lesion

Perhaps the most common symptoms associated with lung cancer are cough and hemoptysis. Because bronchogenic carcinoma generally develops in smokers, these patients often dismiss their symptoms (particularly cough) as routine complications of smoking and chronic bronchitis. With tumors originating in large airways, such as squamous cell carcinoma or small-cell carcinoma, patients may also have problems related to bronchial obstruction, such as pneumonia behind the obstruction or shortness of breath secondary to occlusion of a major bronchus. In contrast, with tumors that arise in the periphery of the lung, including many adenocarcinomas and large-cell carcinomas, patients tend not to have symptoms related to bronchial involvement, and their lesions are often found on imaging obtained for unrelated purposes.

When tumors involve the pleural surface, either by direct extension or by metastatic spread, patients may have chest pain, often pleuritic in nature, or dyspnea resulting from substantial accumulation of pleural fluid. Other adjacent structures, particularly the heart and esophagus, can be involved by direct invasion or extrinsic compression by the tumor. Resulting complications include pericardial effusion, cardiac dysrhythmias, and dysphagia.

Tumors originating in the most apical portion of the lung, which are called *superior sulcus* or *Pancoast tumors*, often produce a characteristic constellation of symptoms and physical findings caused by direct extension to adjacent structures. Involvement of the nerves composing the brachial plexus can result in pain and weakness of the shoulder and arm. Involvement of the cervical sympathetic chain produces the typical features of Horner syndrome—ptosis (a drooping upper eyelid), miosis (a constricted pupil), and anhidrosis (loss of sweat) over the forehead and face—all occurring on the same side as the lung mass. Invasion of neighboring bony structures (e.g., ribs and vertebrae) is a common complication.

Potential clinical problems with lung cancer:

1. Symptoms of endobronchial tumor: cough, hemoptysis
2. Problems of bronchial obstruction: postobstructive pneumonia, dyspnea
3. Pleural involvement: chest pain, pleural effusion, dyspnea
4. Involvement of adjacent structures: heart, esophagus
5. Complications of mediastinal involvement: phrenic or recurrent laryngeal nerve

paralysis, superior vena cava obstruction
6. Distant metastases: brain, bone or bone marrow, liver, adrenals
7. Ectopic hormone production: ACTH, ADH, parathyroid hormone-related peptide
8. Other paraneoplastic syndromes: neurologic, clubbing, hypertrophic osteoarthropathy
9. Nonspecific systemic effects: anorexia, weight loss

## Symptoms relating to nodal and distant metastasis

When a primary lung cancer metastasizes to mediastinal lymph nodes, symptoms often arise from invasion or compression of important structures within the mediastinum, such as the phrenic nerve, recurrent laryngeal nerve, or superior vena cava. As a consequence, the following conditions, respectively, may develop: diaphragmatic paralysis (often with accompanying dyspnea), vocal cord paralysis (with hoarseness), and superior vena cava obstruction (with edema of the face and upper extremities resulting from obstruction to venous return).

Distant metastases, most commonly to the brain, bone or bone marrow, liver, and adrenal gland(s), frequently are asymptomatic. In other cases, symptoms depend on the particular organ system involved, and manifestations such as seizures or bone pain may develop. Small-cell carcinoma is the cell type most likely to generate distant metastases (see Chapter 20). Squamous cell carcinoma is least likely, and both adenocarcinoma and large-cell carcinoma occupy an intermediate position.

## Paraneoplastic syndromes

Many lung tumors are associated with clinical syndromes that are *not* attributable to the space-occupying nature of the tumor or to direct invasion of other structures or organs. These syndromes are called the "paraneoplastic" manifestations of malignancy and frequently are due to either production of a hormone or a hormone-like substance by the tumor or the presence of autoantibodies stimulated by antigens on the tumor.

When a hormone is produced by the lung tumor (or, for that matter, by any type of tumor), the patient is said to have "ectopic" hormone production. Sometimes clinical symptoms result from high circulating levels of the hormone; in other cases, only sensitive techniques of measurement can detect production of the hormone. Why some tumors produce ectopic hormones is not clear. Genetic information coding for the particular hormone is present but not expressed in normal, nonmalignant cells, and it has been hypothesized that in the course of becoming malignant, the cell undergoes a process of gene dysregulation. As a result, the malignant cell regains the ability to express this normally silent genetic material coding for hormone production.

The lung cancer type most frequently associated with ectopic production of humoral substances is small-cell lung cancer (SCLC), presumably because of its neuroendocrine features. Antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH) are the most common hormones produced by SCLC. The syndrome of inappropriate ADH (SIADH) causing hyponatremia is seen in approximately 10% of patients with SCLC, and SCLC is the cause of most malignancy-associated cases of SIADH. Ectopic production of

ACTH occurs in approximately 1% of patients with SCLC. A paraneoplastic syndrome commonly associated with squamous cell lung cancer, rather than SCLC, is hypercalcemia due to production of parathyroid hormone–related peptide, a peptide with parathyroid hormone-like activity. Production of other hormones, such as calcitonin and human chorionic gonadotropin, also are well described with bronchogenic carcinoma.

SCLC is the most common cause of autoimmune-mediated paraneoplastic syndromes affecting the nervous system. The mechanism is best understood for Lambert-Eaton myasthenic syndrome in which the tumor expresses a voltage-gated calcium channel protein on its surface. This protein is normally present at the neuromuscular junction and is important in calcium regulation. Autoantibodies are stimulated by the protein on the tumor, and these antibodies cross-react with the normal protein at the neuromuscular junction, disrupting neuromuscular transmission and causing skeletal muscle weakness.

The soft tissue and bony manifestations of clubbing and hypertrophic osteoarthropathy (see Chapter 3) are most commonly associated with adenocarcinoma of the lung and may relate to abnormal megakaryocyte fragmentation in the lung in patients with this complication. Nonspecific systemic effects of malignancy, such as anorexia, weight loss, and fatigue, are potential consequences of lung cancer, and it has been hypothesized that production of various mediators, such as tumor necrosis factor, may mediate these systemic effects.

# Diagnostic approach

A wide variety of diagnostic methods are used in evaluating cases of known or suspected lung cancer. Many of the studies assessing the lung on a macroscopic level aim to demonstrate the presence, location, and probability of spread of bronchogenic carcinoma. Evaluation on a microscopic level is essential for defining the histologic type of lung cancer and analyzing its immunohistochemical and genetic signatures, which are important factors in determining which modalities of therapy are most appropriate. Functional assessment of the patient with lung cancer plays a role primarily in establishing the severity of underlying lung disease, particularly chronic obstructive lung disease resulting from prior heavy smoking. Knowledge of a patient's functional limitation from lung disease is essential before the clinician can decide whether operative removal of a lung cancer is even feasible without precipitating disabling respiratory insufficiency.

## Macroscopic evaluation

The initial test for detection and macroscopic evaluation of bronchogenic carcinoma is typically the posteroanterior and lateral chest radiograph. The presence of a nodule or mass within the lung on a chest radiograph always raises the question of lung cancer, especially when the patient has a significant smoking history. The location of the lesion may give an indirect clue about its histology: peripheral lesions are more likely to be adenocarcinoma or large-cell carcinoma, whereas central lesions are statistically more likely to be squamous cell carcinoma or small-cell carcinoma (Figs. 21.1 and 21.2). The chest radiograph is also useful for determining the presence of additional suspicious

lesions, such as a second primary tumor or metastatic spread from the original carcinoma. Involvement of hilar or mediastinal nodes or the pleura (with resulting pleural effusion) may be detected on the chest radiograph, and such a finding will substantially affect the overall approach to therapy.

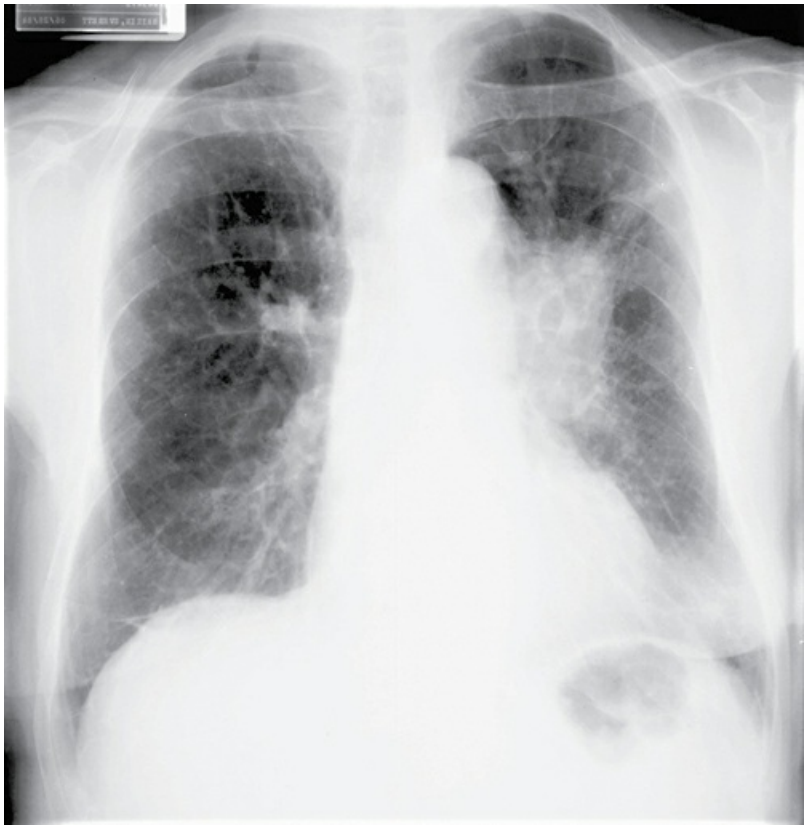

**FIGURE 21.1** Chest radiograph shows small-cell carcinoma of lung manifesting as a left hilar mass.

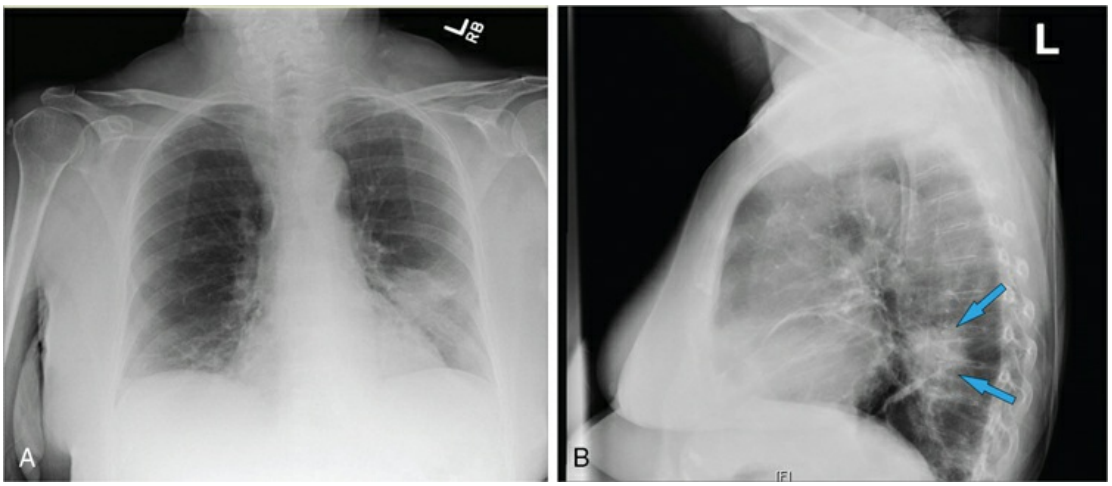

**FIGURE 21.2** **A,** Posteroanterior (PA) chest radiograph shows adenocarcinoma presenting as a left lower lobe mass. **B,** Lateral chest radiograph of the same patient shows the mass posterior to the cardiac silhouette (arrows).

CT of the chest and upper abdomen is a standard part of the diagnostic evaluation of patients with lung cancer (Fig. 21.3). Besides helping to define the location, extent, and spread of tumor within the chest, this technique is particularly useful for the detection of enlarged, potentially malignant, lymph nodes within the mediastinum, which are often not seen with conventional radiography. However, even though CT effectively identifies enlarged mediastinal nodes, it cannot determine whether such nodes simply are hyperplastic or are enlarged because of tumor involvement. Consequently, histologic sampling of enlarged mediastinal nodes is still necessary to confirm tumor involvement of the nodes. CT is also crucial in evaluating the liver and adrenal glands because these are common sites of lung cancer metastasis.

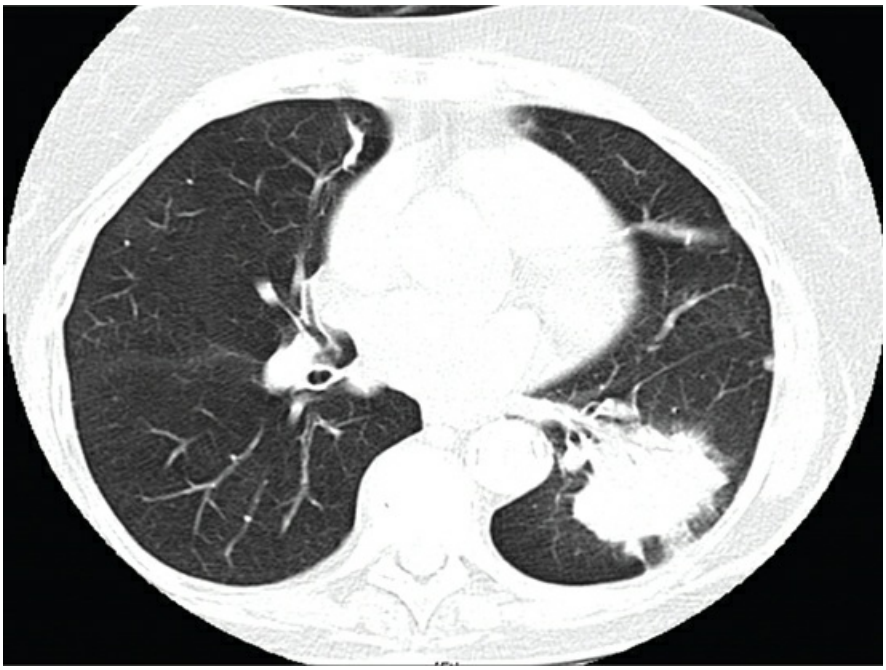

**FIGURE 21.3** Chest CT cross-sectional (axial) scan image of the same patient in Fig. 21.2 demonstrating the appearance of the left lower lobe adenocarcinoma.

Positron emission tomography (PET) scanning (see Chapter 3) is often combined with CT scanning in staging evaluations of lung cancer. Because of their high metabolic activity, malignant lesions typically exhibit high uptake of the tracer $^{18}$F-fluorodeoxyglucose (FDG) (see Fig. 3.13). Focal uptake in the region of a parenchymal nodule or mass suggests that the lesion is malignant, and uptake in the mediastinum or at distant sites often reflects spread of the tumor to those sites. However, other

metabolically active lesions, such as localized areas of infection, also may show FDG uptake. Thus, a positive PET scan in the appropriate clinical scenario is very suggestive but is not diagnostic of malignancy.

The best way to directly examine the airways of a patient with presumed or known bronchogenic carcinoma is by bronchoscopy with a flexible bronchoscope (see Chapter 3). The location and intrabronchial extent of many tumors can be directly observed, and samples can be obtained from the lesion, either for cytologic or histopathologic examination (Fig. 21.4). In addition, the bronchoscopist can assess whether an intrabronchial carcinoma is impinging significantly on the bronchial lumen and causing either partial or complete airway occlusion. Diagnostic specimens can be obtained in many cases even when the lesion is beyond direct visualization with the bronchoscope. Electromagnetic navigational bronchoscopy, particularly when combined with a robotic platform, is particularly useful in obtaining specimens that are distal to the visual range of the bronchoscope.

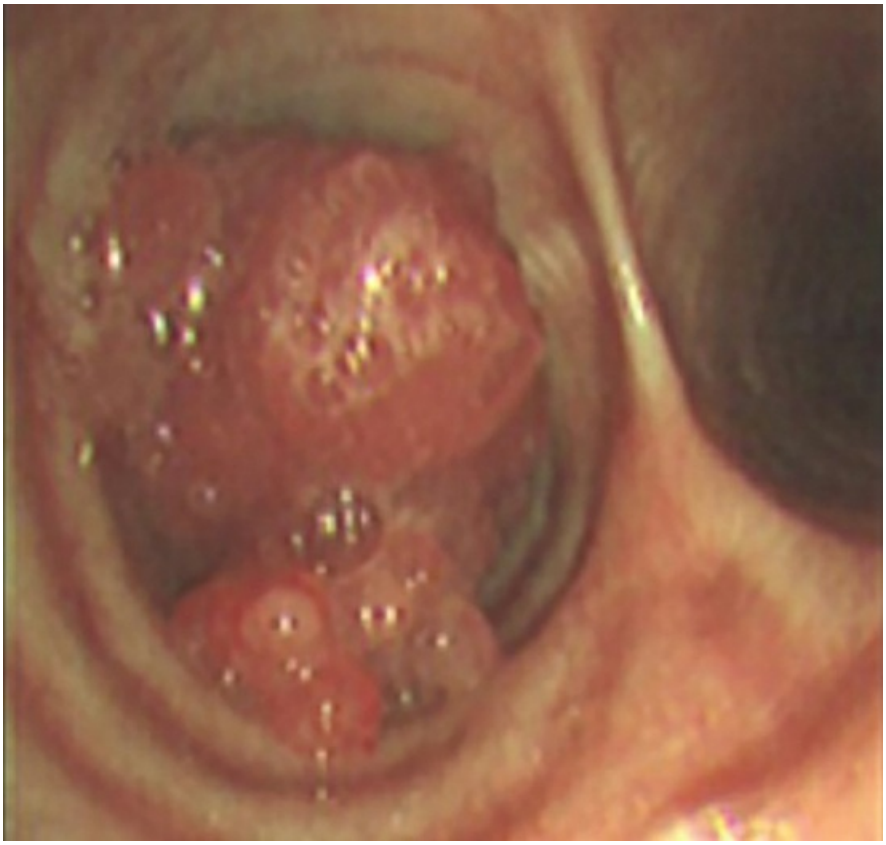

**FIGURE 21.4** Bronchoscopic appearance of a large, lobulated lung cancer obstructing the left mainstem bronchus.

## Staging of lung cancer

After a tumor has been documented, evaluation of the extent and spread of the malignancy is formally achieved by staging. Staging uses a TNM classification, which is

based on (1) the primary intrathoracic tumor (T)—its size, location, and local complications, such as direct extension to adjacent structures or obstruction of the airway lumen; (2) the presence or absence of tumor within hilar and mediastinal lymph nodes (N); and (3) the distant spread of tumor (i.e., metastasis) beyond the thorax to other tissues or organ systems (M) (Table 21.1). Based on the pattern of T, N, and M characteristics of a particular tumor, a specific tumor stage (I-IV) is assigned (Table 21.2).

**TABLE 21.1**

**Overview of TNM Classification of Lung Cancer[a]**

| |
|---|
| **T Component—Size of Primary Tumor** |
| T1: ≤3 cm |
| T2: >3 cm but ≤5 cm |
| T3: >5 cm but ≤7 cm |
| T4: >7 cm |
| **N Component—Regional Lymph Node Involvement** |
| N0: no regional lymph node involvement |
| N1: ipsilateral peribronchial and/or hilar nodes |
| N2: ipsilateral mediastinal and/or subcarinal nodes |
| N3: contralateral hilar or mediastinal nodes; any scalene or supraclavicular nodes |
| **M Component—Distant Metastasis** |
| M0: no distant metastasis |
| M1: distant metastasis present |

[a]The complete classification system has subcategories as well as additional criteria relating to some of the above categories.

Adapted from J Thorac Oncol. 2016;11:39-51.

**TABLE 21.2**

**Overview of Lung Cancer Stages and Prognosis Based on TNM Classification[a]**

| Stage | T Category | N Category | M Category | 5-Year Survival |
|---|---|---|---|---|
| I | T1 or T2 | N0 | M0 | ~70%–90% |
| II | T1 or T2 | N1 | M0 | ~50%–60% |
| | T3 | N0 | M0 | |
| IIIA | T1 or T2 | N2 | M0 | ~35% |
| | T3 | N1 | M0 | |
| | T4 | N0 or N1 | M0 | |
| IIIB | T1 or T2 | N3 | M0 | ~25% |
| | T3 or T4 | N2 | M0 | |
| IIIC | T3 or T4 | N3 | M0 | ~15% |
| IV | Any T | Any N | M1 | ~0%–10% |

[a]The complete staging system also has substages.

Adapted from J Thorac Oncol. 2016;11:39-51.

Basis for formal TNM classification and staging of lung cancer includes the following:

1. Size, location, and local complications of the primary tumor (T)
2. Hilar and mediastinal lymph node involvement (N)
3. Distant metastasis (M)

The first component of staging is defining the characteristics of the primary tumor itself, and it is typically accomplished with a combination of chest imaging and bronchoscopy. The second component, based on involvement of mediastinal lymph nodes by tumor, is typically assessed initially by CT complemented by fluorodeoxyglucose positron emission tomography (FDG-PET) scanning. The FDG-PET scan can identify metabolically active tumor (>1 cm in size) in the mediastinum and elsewhere. Superimposing the image of FDG-PET uptake over the corresponding CT image allows precise anatomic localization of the uptake. Definitive evaluation of nodal enlargement and/or FDG uptake requires biopsy and histologic evaluation of the node(s), and this may be accomplished by endobronchial ultrasound-guided *transbronchial needle aspiration* via a flexible bronchoscope, or by surgical biopsy, either via mediastinoscopy or mediastinotomy. Performed as part of a flexible bronchoscopic procedure, transbronchial needle aspiration is an option for needle sampling of cellular material from lymph nodes adjacent to major airways. In *suprasternal mediastinoscopy*, the mediastinum is visualized with a scope placed through an incision made just above the sternal notch, and biopsy specimens can be obtained by this technique. In *parasternal mediastinotomy*, the mediastinum is examined through a small incision made adjacent to the sternum, and samples of suspicious nodes can be taken. Ultrasound-guided biopsy of certain mediastinal lymph nodes can be performed via an endoscope introduced into the esophagus rather than the tracheobronchial tree. When available, endobronchial ultrasound-guided transbronchial

needle aspiration is preferred to surgical mediastinoscopy to obtain tissue samples because it is less invasive and does not always require general anesthesia.

The third component of staging involves determining whether the tumor has disseminated to distant sites. If available, a total body FDG-PET scan often will indicate sites of distant metastasis in the bones, liver, and adrenal glands. If an FDG-PET scan is not available, metastatic disease in bone can be well demonstrated with radioisotope bone scanning. CT is particularly suitable for detection of metastases to the liver, brain, and adrenal glands. Importantly, FDG-PET scanning is not very useful for assessing intracranial metastasis because brain tissue is so metabolically active at baseline that distinguishing between a metastasis and surrounding normal brain tissue is difficult. Instead, a CT scan or magnetic resonance imaging is best for detecting intracranial metastasis.

Although this formal staging system can be applied to all types of lung cancer, a more simplified system for classifying SCLC is commonly used for treatment purposes. Specifically, SCLC is categorized as *limited stage* or *extensive stage* disease. Limited stage disease is defined as tumor that is limited to an ipsilateral thorax and regional lymph nodes. In contrast, extensive stage disease represents spread outside this region.

## Microscopic and molecular evaluation

An initial diagnosis of lung cancer can be determined from inspection of cytology specimens obtained from sputum, from washings or brushings obtained through a bronchoscope, or from material aspirated from the tumor with a small-gauge needle. However, full characterization of the tumor requires a larger biopsy specimen, which can be obtained by passing a biopsy forceps through a bronchoscope, by using a cutting needle passed through the chest wall directly into the tumor, or by directly sampling tissue at the time of a surgical procedure.

Over a number of years, there has been a paradigm shift in the evaluation and treatment of lung cancer. Previously, the primary distinction was between SCLC and NSCLC, which includes adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Distinguishing among the subtypes of NSCLC was less important because the principles of treatment were generally identical for all patients with NSCLC, that is, based on stage rather than the specific cell type. Although the distinction between SCLC and NSCLC remains critical, the recognition that specific mutations within a NSCLC tumor allow targeted therapy (discussed below) has made more complete molecular analysis of lung tumors an additional component of the diagnostic evaluation. Although histologic examination of a tumor is still performed and is of some value, further immunohistochemical and genetic analysis for specific abnormalities—including epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations—is now standard practice in most centers.

In addition to genetic characterization, the tumor may be examined to determine if it is likely to respond to immunotherapy, anticancer medications that stimulate the patient's immune system to attack the malignancy. Typically, this involves assessing the percentage of tumor cells that express programmed cell death ligand-1 (PD-L1); if greater than 50% of malignant cells express PD-L1, there is a high likelihood of response to a category of drugs called *immune checkpoint inhibitors (ICI)*.

## Functional assessment

Functional assessment of the patient with lung cancer provides important information to guide the clinician in the choice of treatment. As discussed in the section "Principles of Therapy," surgery usually is the procedure of choice if staging has shown that the disease is limited and potentially curable surgically. However, when surgery is performed, usually a lobe and sometimes an entire lung must be removed. Because patients are generally smokers, they are at high risk for having significant underlying chronic obstructive pulmonary disease, and they may not tolerate removal of a substantial amount of lung tissue. Spirometry is helpful as the initial step in determining whether a patient is a suitable surgical candidate. If the results of spirometry are marginal and do not clearly define whether the patient will be able to tolerate lung resection, other tests are used to determine exercise tolerance or the relative amount of function contributed by the area of lung to be removed.

Assessment of pulmonary function helps to determine whether surgical resection can be tolerated by the functionally compromised patient.

## Screening for lung cancer

Given that the likelihood of curing lung cancer through surgical resection is greatest when the lesion has not yet metastasized to lymph nodes or distant sites, it seems logical that screening high-risk individuals for early, small lesions that have not yet caused symptoms would improve overall survival. In the past, controlled studies of sputum cytology and chest radiography in a high-risk population of smokers were not able to demonstrate improved mortality from lung cancer with use of these screening techniques. However, in a major change from previous recommendations, based on the results of the National Lung Screening Trial (NSLT), lung cancer screening with low-dose computed tomography (LDCT) of the chest is now recommended for high-risk individuals. NSLT randomized over 50,000 patients at high risk for lung cancer to screening with either LDCT or standard chest radiographs. The trial was stopped early when a 20% mortality reduction was detected in the LDCT group. Screening with LDCT is currently recommended by the US Preventive Services Task Force and other organizations for adults aged 50 to 80 years with a greater than 20 pack-year history of smoking who are still smoking or have quit less than 15 years prior.

However, there are additional considerations that are essential for both clinicians and patients to understand. It is important to note that almost 40% of patients in the LDCT group had a false-positive finding—that is, a lesion found on screening that proved not to be a lung cancer. Of all lesions found, 96% were not lung cancers. The diagnosis of lung cancer requires microscopic evaluation of tissue samples; thus, many patients were subjected to psychological distress and invasive procedures only to discover the lesion was benign. Another potential consequence is overdiagnosis—this refers to the possibility that a lung cancer is discovered that is slow-growing and would otherwise not influence mortality. It is hoped that ongoing studies to refine the criteria for screening and improve the diagnostic techniques will minimize any disadvantages of lung cancer screening.

# Principles of therapy

The choice of treatment for lung cancer depends on functional status, cell type, staging, and the molecular characteristics of the tumor. In general, treatment algorithms start with the distinction between SCLC and NSCLC. With recent advances in understanding of the molecular biology of lung cancer, the development of targeted therapy for some tumors, and the use of immunotherapy with ICI, the approach to treatment of patients with lung cancer is continuously evolving.

The five major forms of treatment available for lung cancer are surgery, radiation therapy, chemotherapy, molecularly targeted therapy directed toward driver mutations, and immunotherapy. In addition to the patient's functional status and the presence or absence of comorbid disease, four primary tumor-related factors determine how a particular tumor should be treated: its staging (i.e., size, location, and extent of spread), its cell type, the presence of "driver mutations" (genetic mutations within tumor cells that drive cell growth and can be targeted by specific inhibitors), and the extent of PD-L1 expression (which correlates with the expected response to treatment with ICI).

## Treatment of non–small-cell lung cancer

As long as a patient has sufficient pulmonary function reserve, surgery remains the treatment of choice for localized NSCLC regardless of the presence or absence of activating mutations such as EGFR. Complete resection of the entire tumor, usually by removing the entire lobe with the tumor (lobectomy), affords the best chance for cure. Thus, patients with stages I, II, and IIIA are considered for surgery with curative intent. For patients with stage I or II disease who decline surgery or are considered inoperable because of comorbid disease or limited pulmonary function, stereotactic body radiation therapy (SBRT) is an increasingly used alternative. SBRT delivers high doses of radiation that are precisely targeted to the tumor while attempting to minimize delivery of radiation to adjacent normal tissue.

Depending on the stage, chemotherapy may be used as adjunctive therapy before or after surgery as well. When the tumor has extended directly to the pleura (with malignant cells found in the pleural fluid) or to lymph nodes outside of the hemithorax, it usually is considered unresectable, and chemotherapy, radiation, molecularly targeted therapy, immunotherapy, or a combination of modalities is used. There is great interest in trying to determine the best modes of therapy for patients in whom the benefit of surgery is debatable, such as those with ipsilateral mediastinal node involvement or chest wall involvement.

If metastasis to distant tissues or organs has occurred, surgery usually is not an appropriate form of therapy; however, in carefully chosen patients with a solitary metastasis, both the primary tumor and the metastatic lesion may be resected. For example, surgical removal of an isolated brain metastasis in selected cases may be associated with improved survival. In virtually all patients with stage IV (metastatic) disease, the management options include chemotherapy, molecularly targeted therapy, and immunotherapy.

Previously, the typical chemotherapy for all types of NSCLC was a cytotoxic platinum-based regimen, which was often difficult for patients to tolerate. With recognition of the importance of the tumor's molecular characteristics, the recommended treatment for

inoperable or recurrent NSCLC has changed dramatically in recent years. Now, when available, molecular subtyping is performed to evaluate for driver mutations that can be targeted by specific drugs to inhibit their function. The first and best characterized is the EGFR mutation, although many others are clinically targeted or currently being studied. Mutations in EGFR occur in approximately 15% of patients with adenocarcinoma in the United States and up to 60% of such patients from regions in Asia. EGFR mutations also appear to be more common in women and in lung cancer patients who have not smoked.

EGFR is a normally occurring, highly regulated cell surface receptor; when activated, it triggers an intracellular tyrosine kinase, resulting in cellular proliferation. The mutated EGFR receptor does not respond to normal inhibitory signals, resulting in continuous activation of tyrosine kinase and uncontrolled cell growth. When an EGFR mutation is present, treatment with specific tyrosine kinase inhibitors (e.g., osimertinib) is associated with longer progression-free survival.

The newest therapeutic approach for patients with advanced NSCLC involves immunotherapy targeted to the programmed death (PD) pathway. Many lung tumors express PD-L1, which interacts with the programmed death receptor (PD-1) on immune effector cells to serve as a checkpoint limiting the immune response to tumor cells. A number of monoclonal antibodies have now been developed that block the binding of PD-L1 to PD-1, thus upregulating the immune response and allowing T lymphocytes to recognize and kill tumor cells. These antibodies, called ICI, have become a mainstay of therapy for advanced NSCLC, either alone or in combination with standard chemotherapy. For patients with advanced NSCLC whose tumors do not demonstrate an activating mutation, treatment options include standard cytotoxic therapy with consideration of the addition of immunotherapy with an ICI. Finally, bevacizumab, a monoclonal antibody directed at vascular endothelial growth factor (VEGF), is another agent that has been used in combination with cytotoxic chemotherapy in a subset of NSCLC patients.

When NSCLC is unresectable on the basis of any criteria and contains no targetable mutations or viable immunotherapy options, the clinician is faced with a choice of no treatment, radiotherapy, or chemotherapy. The final strategy often is highly influenced not only by the particular tumor but also by the physician's judgment and the patient's preferences. In some cases, radiation therapy treatments are instituted early in an attempt to shrink the tumor and delay local complications. In other circumstances, therapy is withheld until a complication ensues, such as bleeding or airway obstruction. Radiation treatments then are given with the goal of tumor size reduction for temporary alleviation of the acute problem. Unfortunately, this is not curative, and further problems with the tumor are certain to develop.

A general overview of treatment of NSCLC has been presented here. Because the details of treatment for NSCLC are nuanced, constantly evolving, and beyond the scope of this text, the reader is referred to detailed Suggested Readings at the end of the chapter.

## Treatment of small-cell lung cancer

Because SCLC has already disseminated at the time of diagnosis in almost all patients, surgery is not considered the treatment of choice unless the particular small-cell tumor is a solitary peripheral nodule without any evidence of mediastinal or distant spread. In

the typical presentation of SCLC as a central mass, unresectable disease is virtually assured, and chemotherapy (with or without radiotherapy) is considered the primary mode of therapy. For limited stage disease, a platinum-based regimen of combination chemotherapy is typically used, supplemented by thoracic radiation. Patients who respond to this initial treatment will also often receive prophylactic cranial radiation. Patients with extensive stage disease are treated with a combination chemotherapeutic regimen, often supplemented by immunotherapy with an ICI. As with limited stage disease, selected patients with a good response may sometimes receive thoracic or prophylactic cranial radiation.

For all patients with lung cancer, the formal principles of palliative care should be incorporated early as part of their management. These include a focus on symptom management, psychosocial health, and goals of care, and are associated with improved quality of life.

### Restoration of airway patency

For both NSCLC and SCLC, other forms of therapy are being used to reestablish patency of an airway that has been partially or completely occluded or compressed by tumor. The treatment typically is accomplished with either flexible or rigid bronchoscopy, using techniques such as laser, argon plasma coagulation, photodynamic therapy, cryotherapy, or electrocautery to diminish the size of the endobronchial tumor and reestablish an effective lumen. Alternatively or as a combined approach used in addition to those techniques, an endobronchial stent (i.e., a hollow and relatively rigid plastic or metal sheath) can be positioned within the airway lumen to help maintain airway patency.

## Bronchial carcinoid tumors

Bronchial carcinoid tumors, which are classified as a type of *bronchial neuroendocrine tumor*, constitute approximately 5% of primary lung tumors. Previously thought to be benign lesions, bronchial carcinoids now are recognized to be a low-grade malignancy. Lung carcinoids are classified as either *typical*, with a low mitotic rate and indolent growth, or *atypical*, with an intermediate mitotic rate and clinical behavior. As noted above, SCLC and large-cell neuroendocrine carcinomas are also tumors with neuroendocrine features; however, based on molecular, genetic analysis and clinical behavior, bronchial carcinoids are considered by many authorities to be in a different family of neoplasms. Most patients with these tumors have an excellent prognosis and are cured by surgical removal.

Two important epidemiologic features distinguish bronchial carcinoid tumors from the other pulmonary neoplasms discussed here. First, smoking does not appear to be a risk factor. Second, as a group, patients with bronchial carcinoid tumors are younger than those with other pulmonary malignancies; frequently, young adults are affected.

Bronchial carcinoid tumors arise most commonly in central airways of the tracheobronchial tree and are often discovered on either an abnormal chest radiograph or during episodes of hemoptysis or pneumonia distal to an obstructing airway tumor. Ectopic hormone production may be found, relating to the presumed neurosecretory origin of the neoplastic cells. The carcinoid syndrome, generally involving episodic

flushing, diarrhea, and wheezing that results from the effects of serotonin produced by the tumor, is uncommon, being found in less than 5% of all cases of bronchial carcinoid tumors.

Treatment of these tumors is surgical resection if at all possible. For many patients, the prognosis is excellent, and recurrent or distant disease does not occur after surgical removal. However, metastatic disease is found more commonly in patients whose tumors have atypical histology, and the prognosis is worse for these patients.

Common features of bronchial carcinoid tumors:

1. Often found in young adults
2. Hemoptysis
3. Pneumonia distal to an obstructing endobronchial mass

## Solitary pulmonary nodule

A solitary pulmonary nodule on chest radiograph or CT scan (defined as a single, rounded lesion 3 cm or less in diameter) is a common presentation of lung cancer (Fig. 21.5). However, there is actually a broad differential diagnosis for this radiographic abnormality, and only approximately 5% of incidentally identified nodules turn out to be malignant. The physician is faced with judging the likelihood that a nodule is malignant and choosing the appropriate pathway for diagnosis and management. Because lung cancer that manifests as a pulmonary nodule may be curable by surgical resection, management of such a lesion should not be neglected until the lesion is no longer curable. On the other hand, to subject a patient to thoracotomy, which is a major surgical procedure, for removal of a benign lesion requiring no therapy is likewise undesirable.

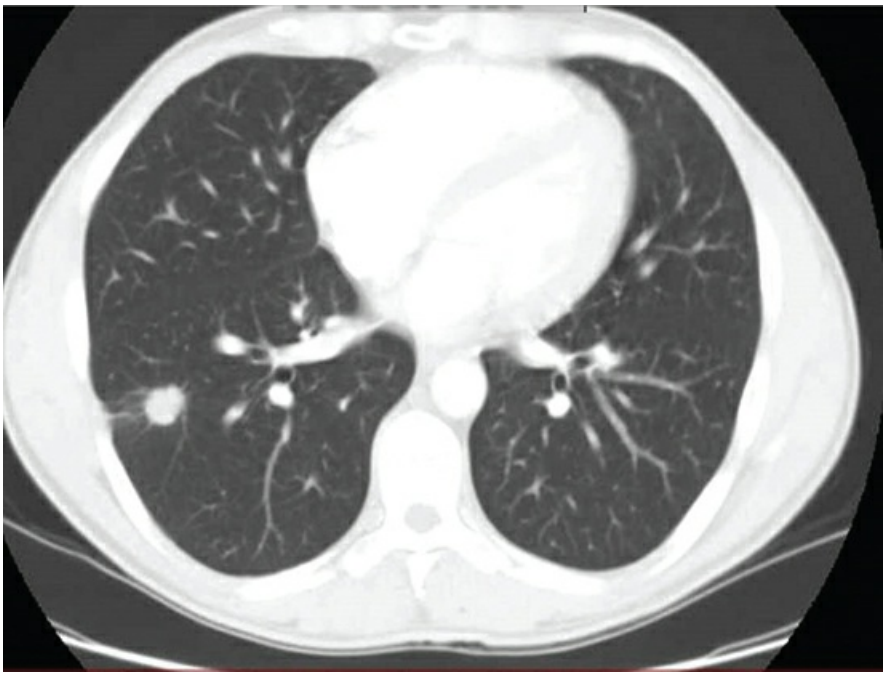

**FIGURE 21.5** Chest CT cross-sectional (axial) scan image showing a right lower lobe adenocarcinoma presenting as a solitary pulmonary nodule.

The diagnostic possibilities for the solitary pulmonary nodule are listed in Table 21.3. Besides primary lung cancer, the major alternative diagnoses are benign pulmonary neoplasms, solitary metastases to the lung from a distant primary carcinoma, and infections (especially healed granulomatous lesions from tuberculosis or fungal disease). Estimating the likelihood of a malignant versus a benign lesion from its radiographic appearance on CT scan is based on six major factors:

1. ***Size.*** The larger the nodule, the more likely it is to be malignant. Nodules less than 5 mm in diameter are malignant in less than 1%, whereas nodules greater than 20 mm represent a malignancy over 50% of the time.
2. ***Growth.*** Perhaps the most helpful piece of information a physician can have is a prior chest radiograph or CT scan. Comparison of old and new images shows whether a lesion is stable and gives an approximation of the rate of growth. Although it is difficult to say with certainty whether a lesion is benign or malignant based on the rate of growth, the absence of any increase in size for at least 2 years is an extremely good (but not infallible) indication that a lesion is benign.
3. ***Attenuation.*** Nodules are classified as solid or subsolid, and some lesions are mixed solid and subsolid (also called part solid). A nodule that is part solid has a higher risk of being malignant.
4. ***Calcification.*** The presence of calcification within a pulmonary nodule, best demonstrated on CT scan, may favor the diagnosis of a benign lesion, especially a granuloma or hamartoma. If certain patterns of calcification are found—diffuse speckling, dense calcification, laminated (onion-skin) calcification, or “popcorn”

calcification—then the lesion almost assuredly is benign. On the other hand, calcification at the periphery of a lesion or amorphous calcification within the lesion may be suggestive of malignancy. For example, a peripheral area of calcification is entirely consistent with a scar carcinoma arising in the region of an old, calcified parenchymal scar (e.g., an old calcified granuloma).

5. ***Border appearance.*** An irregular or spiculated margin is suggestive of a malignant lesion, whereas a benign lesion commonly has a smooth and discrete border.
6. ***Location.*** A nodule in the upper lobes has a higher likelihood of malignancy than nodules in the lower lobes.

**TABLE 21.3**
**Differential Diagnosis of the Solitary Pulmonary Nodule**

| |
|---|
| **Neoplasms** |
| Malignant<br>Primary lung cancer<br>Solitary pulmonary metastasis from distant carcinoma<br>Bronchial carcinoid (bronchial adenoma)<br>Benign<br>Hamartoma<br>Miscellaneous (e.g., fibroma, lipoma) |
| **Vascular Abnormality** |
| Arteriovenous malformation |
| **Infection** |
| Infectious granuloma<br>Tuberculosis (“tuberculoma”)<br>Histoplasmosis (“histoplasmoma”)<br>Bacterial abscess<br>Miscellaneous (e.g., hydatid cyst, canine heartworm) |
| **Miscellaneous** |
| Rounded atelectasis<br>Hematoma<br>Intrapulmonary lymph node<br>Pseudotumor (fluid loculated in a fissure) |

Criteria for assessing the likelihood that a solitary pulmonary nodule is malignant are as follows:

1. Size
2. Stability or change in size of the lesion
3. Attenuation—solid, subsolid, or part solid

4. Presence or absence of calcification; pattern of calcification
5. Smooth versus irregular appearance of the border
6. Location

Additional clinical features are suggestive of a benign versus a malignant lesion but are somewhat less reliable. In individuals younger than 35 years, primary lung cancer is an unlikely but certainly not impossible diagnosis. A history of heavy smoking and/or exposure to asbestos indicates a high risk for a malignant lesion; however, the absence of a smoking history does not rule out the diagnosis of lung cancer, particularly a peripheral adenocarcinoma. Finally, the presence of a previously diagnosed distant carcinoma obviously raises the possibility that a lung nodule is a metastatic focus of tumor.

The practical question of how to evaluate and manage these cases often is difficult, and the decision-making process must be individualized for each patient. A number of online calculators are available that estimate the likelihood of malignancy based on patient and nodule characteristics. This estimate may be helpful to both the physician and the patient when discussing and deciding how aggressively to pursue the diagnostic evaluation. Based on the estimated likelihood of malignancy, the options for management include no further work-up, follow-up (serial) CT scans to look for growth of the lesion, immediate sampling via a biopsy procedure, or even surgical removal of the nodule.

A simple noninvasive test such as sputum cytologic examination is helpful if results are positive; however, the yield is low, even with peripheral nodules that eventually are proven to be carcinoma. Unless the lesion has been stable on chest radiograph for more than 2 years, chest CT scanning is performed routinely to look at border characteristics, assess the presence and pattern of calcification, and identify other abnormalities, especially lymph nodes within the mediastinum. If a nodule is larger than 1 cm, FDG-PET scanning (see Chapter 3), if available, is helpful when the diagnosis is uncertain after evaluation of the clinical information and other imaging studies. Uptake of labeled FDG suggests that the lesion has high metabolic activity and could be malignant, whereas lack of uptake suggests a metabolically inactive, benign lesion.

More invasive procedures, such as percutaneous needle aspiration or biopsy and transbronchial biopsy (through a flexible bronchoscope), may be used to make a histologic diagnosis. However, in many cases biopsy findings that are negative for malignancy do not obviate the need for surgery because malignant cells may be missed by the limited sampling of a needle or biopsy forceps. Hence, a commonly used approach with a lesion suspicious for carcinoma is to proceed directly to resection with video-assisted thoracic surgery (VATS) using a thoracoscope, assuming no contraindications to surgery and no clinical evidence that the lesion has spread elsewhere or has metastasized from a distant primary malignancy. A more definitive resection, such as a lobectomy performed by thoracotomy, then is performed if the nodule is found to be malignant.

When lung cancer presents as a solitary peripheral nodule, the prognosis is much better than for the general group of patients with lung cancer. As a result of frequently curative surgical resection, more than 50% of patients with an initial solitary peripheral

lung cancer survive 5 years, compared with less than 10% of lung cancer patients if the disease has metastasized outside the chest.

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# 22: Lung defense mechanisms

## OUTLINE



In the process of exchanging thousands of liters of air each day for $O_2$ uptake and $CO_2$ elimination, the lung is exposed to a multitude of microorganisms and foreign substances transported with the inhaled air. Some of these are potentially injurious; others are relatively harmless. Inhaled air is not the only source of foreign material. Secretions from the mouth and pharynx frequently are aspirated into the tracheobronchial tree, especially during sleep, even in healthy individuals. This myriad of intruders foreign to the lung is perhaps best classified into three major categories: small particulate material, noxious gases, and microorganisms. Because the oropharynx is rich with bacteria, aspirated secretions are particularly important as a source of

unwanted bacteria entering the airways.

To protect itself against potentially toxic inhaled material, the respiratory system has evolved complex protective mechanisms that can be conceptualized as different groups of components. Each appears to have a distinct role, but a tremendous degree of redundancy and interaction exists among different components. That the distal lung parenchyma is normally not infected serves as testimony to the effectiveness of the defense system. However, the protective mechanisms can break down, resulting in respiratory infection. Such a breakdown in defense can occur as a result of certain diseases, a large inoculum of microorganisms that overwhelms a normal host, an especially virulent organism, or frequently as a consequence of medical treatment that impairs the immune system.

Before the discussion of infectious disorders of the respiratory system in Chapters 23 through 27, it is appropriate to first consider how the lung protects itself against the infectious agents to which it is exposed. Although this chapter focuses on protective mechanisms against infection, defenses against noninfectious substances, especially inhaled particulate material, also are addressed. The major categories of defense mechanisms to be discussed include (1) physical or anatomic factors relating to deposition and clearance of inhaled material, (2) antimicrobial peptides, (3) phagocytic and inflammatory cells that interact with the inhaled material, and (4) adaptive immune responses, which depend on prior exposure to and recognition of the foreign material. The chapter concentrates on the aspects of the host defense system specific to the lung and then proceeds with a discussion of several ways the system breaks down, resulting in an inability to handle microorganisms and an increased risk for certain types of respiratory tract infection. The chapter concludes by briefly considering how we can activate or augment specific immune responses through immunization, thus enhancing defenses against selected respiratory pathogens.

## Physical or anatomic factors

The pathway from the mouth or nose down to the alveoli requires that inhaled air traverse a series of progressively branching airways. The laminar flow of air through the airways becomes more turbulent at the branch points (subcarinae), thus enhancing deposition of particulate material on bronchial mucosal surfaces at these locations. Hence, inhaled particulates frequently are deposited at various points along the airway, never reaching the most distal region of lung, the alveolar spaces. Particle size is an important determinant of deposition along the airway and thus affects the likelihood of a particle's reaching the distal parenchyma. When an inhaled particle is greater than 10 μm in diameter, it is likely to settle high in the upper airway (e.g., in the nose). For particles 5 to 10 μm in diameter, settling tends to occur somewhat lower, in the trachea or the conducting airways, but not down to the level of the small airways and alveoli. The particles most likely to reach the distal lung parenchyma range in size from 0.5 to 5 μm. Many bacteria fall within this size range, so deposition along the airways is not very effective for excluding bacteria from the lower respiratory tract. However, large particles of dust and other inhaled material are effectively prevented from reaching the distal lung parenchyma by virtue of their size. Of note, the target size for particles of inhaled medications, such as bronchodilators, is less than 5 μm so the medication can bypass the

conducting airways and reach the more distal lung.

When particles are deposited in the trachea or bronchi, two major processes, cough and mucociliary transport, are responsible for physical removal of these particles from the airways. Cough is an important protective mechanism, frequently triggered by stimulation of airway irritant receptors, which are most prominent in the proximal airways and are activated by inhaled or aspirated foreign material. Rapid acceleration and high flow rates of air achieved by a cough are often effective in clearing irritating foreign material from the airways.

Factors affecting deposition and physical clearance of particles:

1. Particle size
2. Cough
3. Mucociliary transport

The term *mucociliary transport* or *mucociliary clearance* refers to a process in which coordinated waves of beating cilia move a blanket of mucus (and any material trapped within the mucus) progressively upward along the tracheobronchial tree. From the trachea down to the respiratory bronchioles, the most superficial layer of epithelial cells lining the airway has cilia projecting into the airway lumen. These cilia have a structure identical to that of cilia found elsewhere in the body, consisting of longitudinal microtubules with a characteristic architecture. Specifically, a cross-sectional view of cilia shows two central microtubules surrounded by nine pairs of microtubules arranged around the periphery (Fig. 22.1). Small projecting side arms from each doublet, called *dynein arms*, are crucial to the contractile function of the microtubules and hence to the beating of the cilia.

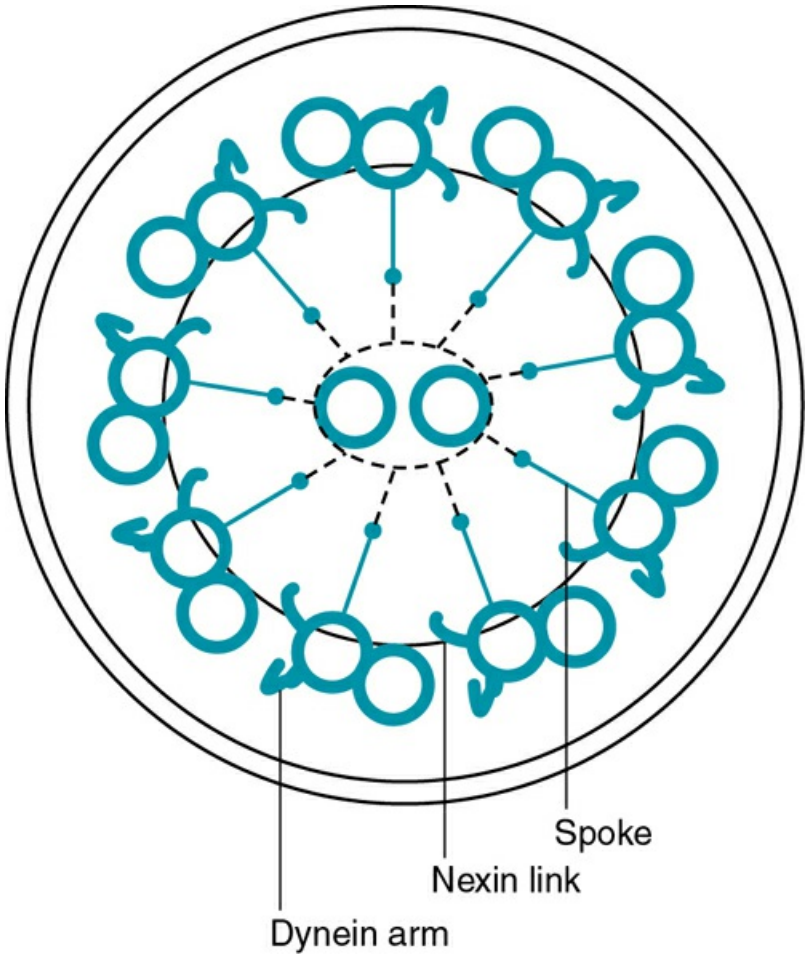


**FIGURE 22.1 Schematic diagram of the cross-section of cilium.** Two central microtubules and nine pairs of peripheral microtubules are shown. A dynein arm projects from each peripheral doublet, and nexin links and radial spokes provide connections within microtubular structure. *Source:* (From Eliasson, R., Mossberg, B., Camner, P., & Afzelius, B. A. (1977). The immotile-cilia syndrome. A congenital ciliary abnormality as an etiologic factor in chronic airway infections and male sterility. *New England Journal of Medicine, 297*, 1–6. Copyright 1977 Massachusetts Medical Society. All rights reserved.)

The movement of cilia on a particular cell and the movement between cells are strikingly coordinated, producing actual "waves" of ciliary motion. Exactly how such a pattern of ciliary motion is coordinated from cell to cell or even within the same cell is not entirely known. This wavelike motion accomplishes movement of the overlying mucous layer in a cephalad direction (i.e., from distal to more proximal parts of the tracheobronchial tree) at the remarkable estimated speed of 6 to 20 mm/min in the trachea. Inhaled particles that are trapped in the mucous layer are also transported

upward and eventually either expectorated or swallowed.

Two layers comprise the mucous blanket bathing the epithelial cells. Directly adjacent to the cells is the *sol layer*, within which the cilia are located. The aqueous sol layer contains several molecules in solution that are part of the innate immune system and are discussed in the "Antimicrobial Peptides" section. Superficial to the sol layer is the more viscous *gel layer*, which is produced by both submucosal mucous glands and goblet cells. The viscous gel layer floats on top of the sol layer and is propelled in a cephalad direction as the cilia beat more freely within the less viscous sol layer.

## Antimicrobial peptides

The sol layer contains a number of substances that are important in innate immunity. The innate immune system can be thought of as a fast-acting system that is ready to quickly protect the lungs without prior sensitization and ideally avoid activation of the adaptive immune system (discussed in the "Adaptive Immune Responses" section). In addition to mucociliary clearance, the innate immune system is composed of small molecules, proteins, and cells capable of responding to inhaled particles in a way that does not require any previous exposure to the particle. These molecules are generally highly conserved in evolution and are present in many invertebrate species as well as in humans. They are able to immediately interact with microorganisms through pattern recognition receptors that are stimulated by conserved structures on microbes, and they can act directly to kill the invader and initiate an additional host immune response. The innate immune response provides a fast, energy-efficient, effective frontline defense, with broad overlap in actions. There are many components of innate immunity in the lung and more than 2000 naturally occurring antimicrobial peptides. A full description is beyond the scope of this chapter; however, the interested reader is referred to the in-depth reviews listed in the Suggested Readings. This chapter focuses on a few of the best described of these molecules: lysozyme, lactoferrin, defensins, collectins (surfactant protein A [SP-A] and surfactant protein D [SP-D]), and immunoglobulin (Ig)A.

Airway innate immunity substances include:

1. Lysozyme
2. Lactoferrin
3. Defensins
4. Collectins (surfactant proteins A and D)
5. IgA

*Lysozyme* is present throughout the respiratory tract but is most prominent in the proximal airways. It is synthesized by respiratory epithelial cells, serous glandular cells, and macrophages. As the name implies, lysozyme causes bacterial cell death by inducing lysis. It is most active against Gram-positive organisms. Decreased levels of lysozyme have been correlated with increased susceptibility to acute bronchitis.

*Lactoferrin* is present in airway fluid. It is produced by serous cells and neutrophils. Lactoferrin acts to agglutinate and kill bacteria, enhance neutrophil adherence, and prime neutrophil superoxide production. Its name derives from the fact that lactoferrin

also functions to block iron from supporting bacterial metabolism. Lactoferrin binds to bacteria through the recognition of highly conserved carbohydrate moieties on the microbial cell surface.

*Defensins* are a family of small proteins with intrinsic antimicrobial activity that are found in the lung and on other mucosal surfaces, including the gastrointestinal and reproductive tracts. Two important types of defensins in the lung are α-defensins and β-defensins. α-Defensins are synthesized by resident neutrophils; β-defensins are made by respiratory epithelial cells. Defensins have broad antimicrobial activity against both Gram-positive and Gram-negative organisms. They act by making the microbial cell wall permeable, thus causing release of microbial cell contents and destruction of the membrane potential. The activity of defensins is highly sensitive to ionic concentrations, and they are inactivated in the abnormal milieu in the lungs of patients with cystic fibrosis.

*SP-A* and *SP-D* are members of the *collectin* family of proteins. Their antimicrobial function is a result of binding and aggregating microbes and facilitating interaction with phagocytic cells. They also appear to be important in the regulation of pulmonary macrophage activity and cytokine production. Animal models indicate that defects in either of these proteins increase the susceptibility to respiratory infection.

*Respiratory IgA* can be considered part of the innate immune system because it is also constitutively produced by the respiratory epithelium and does not require prior exposure. IgA is further discussed in the “Humoral Immune Mechanisms” section.

# Phagocytic and inflammatory cells

## Pulmonary alveolar macrophages

In the airways and at the level of the alveoli, particles and bacteria can be scavenged by mononuclear phagocytic cells called *pulmonary alveolar macrophages*. These cells constitute a major form of defense against material that has escaped deposition in the upper airway and has reached the intrathoracic airways or the alveolar structures.

Pulmonary alveolar macrophages are large mobile cells approximately 15 to 50 μm in diameter. They are descendants of circulating monocytes derived from bone marrow. These cells adhere to the alveolar epithelium. Their cytoplasm contains a variety of granules of various shapes and sizes, many of which are packages of digestive enzymes that can dispose of ingested foreign material. Alveolar macrophages have a major role in killing microorganisms that have reached the lower respiratory tract. They also release chemoattractant cytokines (chemokines) that recruit other inflammatory cells.

When an alveolar macrophage is exposed to inhaled particles or bacteria, attachment of the foreign material to the surface of the macrophage is the first step in the processing sequence. The particles or bacteria are engulfed within the plasma membrane, which invaginates and pinches off within the cell to form a cytoplasmic phagosome containing the now isolated foreign material. In some circumstances, this sequence of attachment and phagocytosis is facilitated by *opsonins*, which coat the foreign material. Opsonins are proteins that bind to extracellular materials and make them more adherent to phagocytic cells and more amenable to engulfment or ingestion. Opsonins can be specific for the particular foreign substance, such as antibodies directed against

antigenic material, or they may demonstrate nonspecific binding to a variety of substances. Particularly important specific opsonins are antibodies of the IgG class directed against antigenic foreign material, either bacteria or other antigenic particles. Nonspecific opsonins in the lung include secretory IgA, complement, and fibronectin. All these opsonins greatly promote attachment to and ingestion by macrophages.

After bacteria or other foreign material is isolated within phagosomes, a process of intracellular digestion occurs within the macrophage. Often the phagosomes combine with lysosomes to form phagolysosomes, in which proteolytic enzymes supplied by the lysosome digest, detoxify, or destroy the phagosomal contents. In addition to lysosomal enzymes, a variety of oxidation products, such as hydrogen peroxide and other intermediate products of oxidative metabolism, are toxic to bacteria and play a role in the ability of the macrophage to kill ingested microorganisms.

After they are activated, the resident pulmonary macrophages participate in orchestrating further immune responses. Macrophages release inflammatory mediators such as tumor necrosis factor-α and interleukin-1β, as well as other cytokines and chemokines that are active in recruiting additional inflammatory cells.

The macrophage does not always kill or totally eliminate inhaled foreign material to which it is exposed. In some cases, such as with inhaled silica particles, the ingested material is toxic to the macrophage and eventually may kill the phagocytic cell. In other cases, ingested material is inert but essentially indigestible and may persist indefinitely in the form of a residue that cannot be broken down further or cleared. Some organisms are especially capable of persistent infection of macrophages without being killed or deactivated, including *Mycobacterium tuberculosis* and the human immunodeficiency virus (HIV).

Alveolar macrophages are also important in *suppression* of inflammation in the lung. The lung is unique in that it is constantly exposed to inhaled foreign substances but at the same time must maintain an exquisitely delicate gas-exchange apparatus. Even a small amount of inflammation within the alveolar wall would have a negative effect on gas exchange, and a fine balance keeps the distal airways free of infection but not in a state of constant harmful inflammation. Alveolar macrophages are able to process a large amount of inhaled substances without inciting an immune response external to the macrophage itself. It is estimated that the normal pool of alveolar macrophages can handle up to $10^9$ inhaled bacteria before the bacteria overwhelm the macrophages and cause infection in the alveoli. In addition, alveolar macrophages, through complex signaling mechanisms, function to keep dendritic cell and T-cell activation in check. The detailed working of this fine equilibrium between inflammation and quiescence in the lung is an area of active research.

Major phagocytic and resident inflammatory cells:

1. Pulmonary alveolar macrophages
2. Dendritic cells (airway and parenchymal)
3. Polymorphonuclear leukocytes
4. Natural killer cells

### Dendritic cells

*Dendritic cells* are present throughout the body in various forms. They are bone marrow–derived cells that, in the lung, are located in the airway epithelium as well as in alveolar walls and peribronchial connective tissue. These cells have long and irregular cytoplasmic extensions that form a contiguous network. The primary function of dendritic cells is to sample the airway microenvironment, ingest and process antigens, and then migrate to regional lymph nodes. In the lymph nodes, dendritic cells present antigen to T cells, a critical step for the later immunologic defense provided by lymphocytes. *Langerhans cells*, a type of dendritic cell with a particular ultrastructural appearance, are the cells with abnormal proliferation that appear to be responsible for Langerhans cell histiocytosis of the lung (also called *eosinophilic granuloma*; see Chapter 11).

### Polymorphonuclear leukocytes

Another important cell involved in pulmonary defense is the *polymorphonuclear leukocyte* (PMN). The PMN is a particularly important component of the defense mechanism for an established bacterial infection of the lower respiratory tract. Normally, few PMNs reside in the small airways and alveoli. When bacteria overwhelm the initial defense mechanisms already discussed, they may replicate within alveolar spaces, causing a bacterial pneumonia. Examination of the histologic features of a bacterial pneumonia reveals that a prominent component of the inflammatory response is an outpouring of PMNs into the alveolar spaces. These cells probably are attracted to the lung by a variety of stimuli, particularly products of complement activation and chemotactic factors released by alveolar macrophages.

The eventual movement of PMNs out of the vasculature and into the lung parenchyma depends on the initial adherence of PMNs to the vascular endothelium. A variety of factors mediate this process of adhesion, including *integrins* (on the surface of the PMNs) and *adhesion molecules* (on the surface of the vascular endothelial cells).

When PMNs are involved, they play a crucial role in phagocytosis and killing of the population of invading and proliferating bacteria. Neutrophil granules contain several antimicrobial substances, including defensins, lysozyme, bacterial permeability–increasing protein, and lactoferrin. In addition, neutrophils can generate products of oxidative metabolism that are toxic to microbes.

### Natural killer cells

*Natural killer* (NK) cells are part of the rapid initial response and are capable, without prior sensitization, of killing cells infected by microorganisms, particularly viruses. NK cells lack surface markers characteristic of either T or B lymphocytes (discussed in the "Cellular Immune Mechanisms" section). They act by recognizing and killing virus-infected cells that have been transformed and express different markers of cellular health on the cell surface. NK cells also are important in surveillance for neoplasms, and they use the same methods to detect and kill malignantly transformed cells.

## Adaptive immune responses

The final category of defense mechanisms for the respiratory system is the adaptive immune response, which involves recognizing and responding to specific antigenic material after prior sensitization. Bacteria, viruses, and other microorganisms are perhaps the most important antigens to which the respiratory tract is repetitively exposed. Presumably, immune defense mechanisms are particularly important in protecting the individual against these agents. The processes of the adaptive immune response are not unique to the lung, and only a superficial discussion of general principles is provided here as a basis for understanding the adaptive immune responses in the lung. For more detailed information, the reader is referred to specialized texts and review articles on immunology.

The two major components of the adaptive immune system are humoral (or B-lymphocyte related) and cellular (or T-lymphocyte related). *Humoral immunity* involves the activation of B lymphocytes (which do not require the thymus for differentiation) and the production of antibodies by plasma cells (which are derived from B lymphocytes). *Cellular immunity* refers to the activation of T lymphocytes (which depend on the thymus for differentiation) and the execution of certain specific T-lymphocyte functions, including the production of soluble mediators or cytokines. The two lymphocyte systems are not independent of each other. In particular, T lymphocytes appear to have an important role in regulating immunoglobulin or antibody synthesis by the humoral immune system.

Both humoral and cellular immunity are important in the protection of the respiratory system against microorganisms. For certain infectious agents, humoral immunity is the primary mode of protection. For other agents, cellular immunity appears to be paramount. In the lung and in blood, T lymphocytes are more numerous than B lymphocytes, but both systems are essential for effective defense against the spectrum of potentially harmful microorganisms.

Lymphocytes can be found in many locations within the respiratory tract, extending from the nasopharynx down to distal regions of the lung parenchyma. True lymph nodes are present around the trachea and carina, and at the hilum of each lung in the region of the mainstem bronchi. These lymph nodes receive lymphatic drainage from most of the airways and lung parenchyma. Lymphoid tissue is present in the nasopharynx, and collections of lymphocytes arranged in nodules are found along medium to large bronchi. These latter collections are called *bronchus-associated lymphoid tissue* and may be responsible for intercepting and handling antigens deposited along the conducting airways. Smaller aggregates of lymphocytes can be found in more distal airways and even scattered throughout the pulmonary parenchyma.

Major components of the adaptive immune system operative in the respiratory tract:

1. T lymphocytes
2. B lymphocytes
3. IgG

## Humoral immune mechanisms

Humoral immunity in the respiratory tract appears in the form of two major classes of

immunoglobulins: IgA and IgG. Antibodies of the IgA class are particularly important in the nasopharynx and upper airways, where they constitute the primary antibody type. The form of IgA present in these areas is secretory IgA, which includes a dimer of IgA molecules (joined by a polypeptide) plus an extra glycoprotein component termed the *secretory component*. Secretory IgA appears to be synthesized locally, and the quantities of IgA are much greater in the upper respiratory tract than in the serum.

Evidence suggests that secretory IgA plays an important role in the respiratory defense system. By virtue of its ability to bind to antigens, IgA may bind to viruses and bacteria, preventing their attachment to epithelial cells. In addition, IgA is efficient in agglutinating microorganisms; the agglutinated microbes are more easily cleared by the mucociliary transport system. Finally, IgA appears to have the ability to neutralize a variety of respiratory viruses as well as some bacteria. Nonetheless, many of the functions of IgA are redundant with other parts of the immune system, as the majority of individuals with selective IgA deficiency are asymptomatic, whereas fewer than 10% develop recurrent sinopulmonary infections.

In contrast to IgA, IgG is particularly abundant in the lower respiratory tract. It is synthesized locally to a large extent, although a fraction also originates from serum IgG. It has a number of biological properties, such as agglutinating particles, neutralizing viruses and bacterial toxins, serving as an opsonin for macrophage phagocytosis of bacteria, activating complement, and causing lysis of Gram-negative bacteria in the presence of complement.

The overall role of the humoral immune system in respiratory defenses includes protecting the lung against a variety of bacterial and, to some extent, viral infections. The clinical implications of this role and the consequences of impairment in the humoral immune system are discussed in the "Defects in the Adaptive Immune System" section.

## Cellular immune mechanisms

Cellular immune mechanisms, those mediated by thymus-dependent (T) lymphocytes, also operate as part of the overall defense system of the lungs. Sensitized T lymphocytes produce a variety of soluble, biologically active mediators called *cytokines*, some of which (e.g., interferon [IFN]-γ) function to attract or activate other protective cell types, particularly macrophages. T lymphocytes also can interact with the humoral immune system and modify antibody production.

Two important types of T lymphocytes have been well characterized based on specific cell surface markers and functional characteristics. One type consists of cells that are positive for the CD4 surface marker, commonly called *$CD4^+$* or *helper T cells*. $CD4^+$ cells, in turn, are divided into $T_H1$ and $T_H2$ subsets, which mediate cellular immune defense and allergic inflammation, respectively. The other major type of T lymphocyte consists of cells that are positive for the CD8 surface marker. These $CD8^+$ cells include suppressor and cytotoxic T cells. On exposure to specific antigens, both $CD4^+$ and $CD8^+$ cells produce a variety of cytokines that interact with other components of the immune system, particularly B lymphocytes and macrophages.

One important role for the cellular immune system is to protect against bacteria that have a pattern of intracellular growth, especially *M. tuberculosis* (see discussion of tuberculosis in Chapter 25). In addition, the cellular immune system has a critical role in

the handling of many viruses, fungi, and protozoa.

Although separating the immune protection of the lung into different categories is important for discussion purposes, these functions are deeply intertwined, and dysfunction in one aspect will likely cause problems in other parts of the system. Development of a respiratory infection generally indicates that a number of defense mechanisms have been overcome by the infecting organism.

# Failure of respiratory defense mechanisms

Clinically important deficiencies have been recognized for each of the major categories of respiratory defense mechanisms. As a result, respiratory infections may ensue, and an analysis of the specific types of infections associated with each type of defect is clinically useful.

## Impairment of physical clearance

The simplest impairment of physical clearance to understand is the inability to cough effectively. Three factors are required to generate the high velocities of an effective cough: (1) a large inspiration, (2) an increase in intrathoracic pressure against a closed glottis, and (3) a coordinated expiratory blast during which the glottis opens. Considering each of these steps, it becomes easier to appreciate why certain patients have difficulty with clearing inhaled particles and respiratory secretions. The patient with a weakened or paralyzed diaphragm will not be able to take a deep breath. The patient with weak expiratory muscles, such as the person with quadriplegia, will not be able to generate the large increase in intrathoracic pressure. The patient with a chronic tracheostomy or paralyzed vocal cord will not be able to effectively close the glottis to increase intrathoracic pressure. All these patients are prone to respiratory tract infections, even if the underlying immune systems are normal.

Other physical or anatomic factors that influence deposition and clearance of particles include genetic abnormalities and environmental factors affecting the mucociliary transport system. Especially interesting information has been provided by a genetic abnormality termed *primary ciliary dyskinesia*, also sometimes called either the *dyskinetic cilia syndrome* or the *immotile cilia syndrome*. In this disorder, a defect in ciliary structure and function leads to absent or impaired ciliary motility and hence to ineffective mucociliary clearance. More than 20 types of defects are recognized, but the most common is the absence of dynein arms on the microtubules (Fig. 22.1). Clinically, the impairment in mucociliary clearance is associated with chronic sinusitis, chronic bronchitis, and bronchiectasis. In males, the sperm tail, which has a structure similar to that of cilia, is abnormal, resulting in poor sperm motility and infertility. The disorder called *Kartagener syndrome*, which consists of the triad of chronic sinusitis, bronchiectasis, and situs inversus, is a variant of primary ciliary dyskinesia (see Chapter 7). Normal ciliary motion in a specific direction is believed to be responsible for the normal rotation of the heart and positioning of intraabdominal organs during embryogenesis. When ciliary function is significantly disturbed, positioning of the heart and intraabdominal organs becomes random, thus accounting for the situs inversus found in approximately 50% of patients with primary ciliary dyskinesia.

Causes of impaired mucociliary clearance:

1. Primary ciliary dyskinesia
2. Viral respiratory tract infection
3. Cigarette smoking
4. High concentrations of $O_2$ for prolonged periods
5. General anesthesia

Viral respiratory tract infections frequently cause temporary structural damage to the tracheobronchial mucosa. The injured mucosa is associated with impaired mucociliary clearance, which may retard the transport of invading bacteria out of the tracheobronchial tree. This is one of the mechanisms by which viral respiratory tract infections predispose the individual to complicating bacterial superinfections.

Environmental factors also may cause impairment of mucociliary clearance. Exposure to cigarette smoke is the most important clinically and probably contributes to the predisposition of heavy smokers to recurrent respiratory tract infections. Some atmospheric pollutants, such as sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), and ozone ($O_3$), appear to depress mucociliary clearance, but the clinical consequences are not entirely clear. High concentrations of $O_2$, such as 90% to 100% inhaled for more than several hours, appear to be associated with impaired mucociliary function. Here, the consequences may be relevant to patients with respiratory failure who require these extremely high concentrations. In addition, general anesthesia with inhalational drugs administered during surgery is associated with short-term ciliary dysfunction and contributes to the increased risk of pneumonia in patients during the postoperative period.

Management of patients with respiratory failure often involves the insertion of a tube into the trachea (an endotracheal tube) and the support of gas exchange with a mechanical ventilator (see Chapter 30). Endotracheal tubes pose a significant risk for bacterial infection of the lower respiratory tract, often called *ventilator-associated pneumonia*, in part by preventing glottic closure, a critical component of the sequence of events leading to an effective cough. In addition, the endotracheal tube provides a direct conduit into the trachea for bacteria that have colonized or contaminated the ventilator tubing or the endotracheal tube itself.

## Impairment of antimicrobial peptides

There is substantial overlap in function of the antimicrobial substances present in the sol layer. Thus, an isolated defect in any one component is unlikely to cause catastrophic consequences. Deficiencies of lysozyme have been associated with an increased risk of acute bacterial bronchitis. In patients with cystic fibrosis, the high sodium and chloride content in their respiratory secretions appears to inactivate defensins and contributes to the severe respiratory infections that commonly occur. In animals, defects in SP-A or SP-D are associated with an increase in respiratory infections, but analogous problems in humans have not been identified.

## Impairment of phagocytic and inflammatory cells

Clinical problems result from deficiencies in the number or function of the two major phagocytic and inflammatory cell types: alveolar macrophages and PMNs. One of the more important ways in which macrophage function can be impaired is by viral respiratory tract infections. These infections may paralyze the ability of the macrophage to kill bacteria, another reason why patients with viral infections are more susceptible to superimposed bacterial bronchitis or pneumonia.

Cigarette smoking depresses the ability of alveolar macrophages to take up and kill bacteria. Hypoxia, HIV infection, starvation, alcoholism, and cold exposure similarly appear to be conditions in which impaired bacterial killing is at least partly due to depressed macrophage function. Treatment with corticosteroids, given for myriad diseases, seems to depress migration and function of macrophages, and this may compound additional adverse effects of steroids on lymphocytes and the immune system. HIV can infect alveolar macrophages, both serving as a reservoir for viral particles and resulting in impaired macrophage function in patients with AIDS, likely complicating the other host defense defects recognized in the disease (see Chapter 27).

Clinical situations that potentially depress macrophage function include:

1. Viral respiratory tract infections
2. Cigarette smoking
3. Alcoholism
4. Starvation
5. Cold exposure
6. Hypoxia
7. Corticosteroid therapy
8. HIV/AIDS

PMNs are reduced in number in several clinical circumstances, often due to underlying bone marrow disease (e.g., leukemia) or to the treatment administered. Chemotherapeutic agents used to treat malignancy commonly destroy rapidly proliferating cells of the bone marrow, resulting in temporary loss of PMN precursors and marked depression in the number of circulating PMNs. When PMNs are present at abnormally low concentrations, the risk of bacterial infection begins to rise, becoming particularly marked when the count drops below 500/mm$^3$. Although opportunistic fungal infections are generally associated with impairment of cellular immunity rather than with neutropenia, the fungus *Aspergillus* is an important respiratory pathogen in the neutropenic patient.

Causes of decreased numbers of PMNs:

1. Bone marrow replacement by tumor
2. Cancer chemotherapeutic agents

## Defects in the adaptive immune system

The adaptive immune system is subject to defects in function that affect its humoral and cellular components. In comparison with innate immunity, there is much less redundancy in the adaptive immune system, and as a general principle, defects in adaptive immunity result in a much greater risk of infection. Deficiencies in the humoral immune system, such as decreased or absent immunoglobulin production (i.e., hypogammaglobulinemia or agammaglobulinemia), are associated with recurrent bacterial and viral respiratory infections, often leading to bronchiectasis. The risk of infection is best defined for individuals with IgG or global immunoglobulin deficiency. Although some individuals with selective IgA deficiency seem to have an increased risk of respiratory infections, either viral or bacterial, this risk may be at least partly related to a coexisting deficiency of one of the four recognized IgG subclasses. The majority of patients with selective IgA deficiency do not develop recurrent sinopulmonary infections, likely because of redundancy in the immune system.

Causes of adaptive immune deficiency:

1. Humoral: decreased or absent immunoglobulins
2. Cellular: corticosteroids, cytotoxic drugs, Hodgkin disease and other lymphomas, HIV/AIDS

Cellular immunity is disturbed most frequently by treatment with corticosteroids, cytotoxic agents, or other immunosuppressive drugs and in some well-defined disease states, such as Hodgkin lymphoma and AIDS. A number of congenital immunodeficiency syndromes are characterized by profound impairments in cellular immunity as well. Unlike most other deficits in respiratory defenses, problems with cell-mediated immunity may lead to infection with a specific group of microorganisms, including intracellular bacteria (especially mycobacteria), fungi, *Pneumocystis*, and certain viruses, particularly cytomegalovirus. Some of these organisms, such as *Pneumocystis* and several of the fungi, rarely affect individuals with normal cellular immunity, whereas other organisms, such as *M. tuberculosis*, can affect individuals without any defined defects in cellular immunity.

In summary, the defense mechanisms available to protect the respiratory tract from invading microorganisms are varied and complex. These defenses can be thwarted by exposure to damaging influences, such as cigarette smoke and ethanol. Equally important, pharmacological and other forms of treatment provided by physicians can disrupt host defense mechanisms, making it essential that physicians be aware of the potential infectious complications of therapy.

In the clinical setting, deficiencies in immunoglobulins and PMNs are strongly associated with an increased risk of bacterial infections. Although problems with mucociliary clearance and macrophage function are somewhat less well defined in terms of the specific infectious risk, bacterial infections also appear to be prominent in these settings. In contrast, disturbances in cellular immunity are characterized by an increased risk of a different subset of infections, especially those caused by mycobacteria, *Pneumocystis*, fungi, and certain viruses.

## Augmentation of respiratory defense mechanisms

Importantly, there are significant opportunities to augment defense mechanisms and protect against some forms of respiratory tract infection. Immunization against certain respiratory pathogens has induced the production of antibodies against the organisms and has conferred either relative or complete protection against infection by these microbes.

Perhaps the most notable examples are immunization against SARS-CoV-2 (which causes COVID-19), influenza viruses, and many subtypes of the common bacterium *Streptococcus pneumoniae* (pneumococcus) as well as to toxins of *Bordetella pertussis* (which causes whooping cough). Appropriate vaccination is critical for any patient with an underlying condition which increases their risk for severe disease. At the time of publication, SARS-CoV-2 vaccination is recommended for all individuals 5 years and older. Universal immunization against pertussis is recommended during childhood and a booster shot recommended for all adults. Annual influenza vaccination is indicated for all individuals aged 6 months and older. Pneumococcal vaccination is now recommended universally both for young children and for adults older than 65 years. Pneumococcal vaccination is also recommended for individuals outside of those age groups who are at increased risk of invasive pneumococcal disease.

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**Augmentation of respiratory defense mechanisms**

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# 23: Pneumonia

OUTLINE



Infection of the pulmonary parenchyma (pneumonia) is one of the most important categories of disease affecting the respiratory system. Of note:

- Pneumonia is very common; even prior to the COVID-19 pandemic, it was the sixth most common reason for hospital admission in the United States.
- Pneumonia in combination with influenza was the 9th most common cause of death in the United States in 2019, just prior to the COVID-19 pandemic.
- In the United States, the direct annual cost of community-acquired pneumonia has been estimated to be at least $17 billion, and in Europe, overall annual costs are estimated to be 10.1 billion.
- It is the world's leading cause of death among children younger than 5 years, and it is the most common reason for children to be hospitalized in the United States.
- Worldwide, pneumonia afflicts an estimated 450 million people per year and results in 3–4 million deaths.

It is no wonder that Sir William Osler referred to pneumonia as "the captain of the men of death," particularly as he spoke before the era of effective antibiotic therapy. For many types of pneumonia, medical therapy with antibiotics (along with supportive care)

has great impact on the duration and outcome of the illness. Because of the effectiveness of treatment, pneumonia is typically gratifying to treat for the patient and for medical personnel. Unfortunately, with the COVID-19 pandemic and the emerging trend of antibiotic resistance, it is a struggle to ensure that treatment of pneumonia continues to evolve to keep pace.

This chapter is organized primarily as a general discussion of the clinical problem of pneumonia. The approach to initial assessment and treatment of pneumonia is addressed according to the categorization of pneumonia based on the clinical setting: community-acquired versus nosocomial (hospital-acquired) pneumonia. In current clinical practice, the approach to evaluation and management of these two types of pneumonia is quite different. As appropriate, specific etiologic agents are discussed as examples; however, a more in-depth discussion of specific organisms is given in Chapter 24.

## Etiology and pathogenesis

The host defenses of the lung are constantly challenged by a variety of organisms, including both viruses and bacteria (see Chapter 22). Viruses in particular are likely to avoid or overwhelm some of the upper respiratory tract defenses, causing a transient, relatively mild clinical illness with symptoms limited to the upper respiratory tract. When host defense mechanisms of the upper and lower respiratory tracts are overwhelmed, microorganisms may establish residence, proliferate, and cause a distinct infectious process within the pulmonary parenchyma. With particularly virulent organisms, no major impairment of host defense mechanisms is needed; pneumonia may occur in normal and otherwise healthy individuals. At the other extreme, if host defense mechanisms are impaired, microorganisms that are not particularly virulent and are unlikely to cause disease in a healthy host may produce a life-threatening pneumonia.

In practice, several factors frequently cause enough impairment of host defenses to contribute to the development of pneumonia, even though individuals with such impairment are not considered “immunosuppressed.” Viral upper respiratory tract infections, alcohol use disorder, cigarette smoking, heart failure, and preexisting chronic obstructive pulmonary disease (COPD) are important risk factors. More severe impairment of host defenses is caused by diseases associated with immunosuppression (e.g., advanced HIV/AIDS), various underlying malignancies (particularly leukemia and lymphoma), and the use of corticosteroids and other immunosuppressive drugs. In cases associated with impairment of host defenses, individuals are susceptible to both bacterial and more unusual nonbacterial infections (see Chapters 24-27).

Common contributing factors for pneumonia in the immunocompetent host:

1. Viral upper respiratory tract infection
2. Alcohol use disorder
3. Cigarette smoking
4. Heart failure
5. Chronic obstructive pulmonary disease

Microorganisms, especially bacteria, primarily access the lower respiratory tract in two major ways. The first is by inhalation, whereby organisms are usually carried in small droplet particles inhaled into the tracheobronchial tree. The second is by aspiration, whereby secretions from the oropharynx pass through the larynx and into the tracheobronchial tree. Aspiration is usually thought of as a process occurring in individuals unable to protect their airways from secretions by glottic closure and coughing. Although clinically significant aspiration is more likely to occur in such individuals, everyone is subject to aspirating small amounts of oropharyngeal secretions, particularly during sleep. Defense mechanisms cope with this nightly onslaught of bacteria, and frequent bouts of aspiration pneumonia are not experienced in most healthy individuals.

Less commonly, bacteria reach the pulmonary parenchyma through the bloodstream rather than by the airways. This occurs when a distant primary source of bacterial infection is present (e.g., cellulitis or abscess) or when bacteria are introduced directly into the bloodstream (e.g., with intravenous drug use). This route is especially important for the spread of certain organisms, particularly *Staphylococcus*.

## Pathology

The pathologic process common to all pneumonias is infection and inflammation of the distal pulmonary parenchyma. An influx of polymorphonuclear leukocytes (PMNs), edema fluid, erythrocytes, mononuclear cells, and fibrin develops to a variable extent in all cases. Bacterial pneumonias in particular are characterized by an exuberant outpouring of PMNs into alveolar spaces as they attempt to limit proliferation of the invading bacteria.

Individual types of pneumonia may differ in exact location and mode of spread of the infection. In the past, a distinction was often made between pneumonias that follow a "lobar" distribution, those that behave more like a "bronchopneumonia," and those with the pattern of an "interstitial pneumonia." However, these distinctions are often difficult to make because individual cases of pneumonia frequently do not adhere to any one particular pattern but have mixtures of the three patterns in varying proportions. Given this limitation, a brief mention of the three major types follows:

***Lobar pneumonia.*** Lobar pneumonia has classically been described as a process which spreads contiguously throughout part of, or an entire lobe of the lung (Fig. 23.1; see also Fig. 3.4). Spread of the infection is believed to occur from alveolus to alveolus and from acinus to acinus through interalveolar pores known as the *pores of Kohn*. The classic example of a lobar pneumonia is that due to *Streptococcus pneumoniae* (see Chapter 24), although many cases of pneumonia documented as being due to pneumococcus do not necessarily follow this typical pattern.

***Bronchopneumonia***. In bronchopneumonia, distal airway inflammation is prominent along with alveolar disease, and spread of the infection and the inflammatory process tends to occur through airways rather than through adjacent alveoli and acini (Fig. 23.2). Whereas lobar pneumonias appear as dense consolidations involving part or all of a lobe, bronchopneumonias are more patchy in distribution, depending on where spread by airways has

occurred. Many bacteria, such as staphylococci and a variety of Gram-negative bacilli, may produce this patchy pattern.

***Interstitial pneumonia***. Interstitial pneumonias are characterized by an inflammatory process within the interstitial walls rather than alveolar spaces (Fig. 23.3). Although viral pneumonias classically start as interstitial pneumonias, severe cases generally show extension of the inflammatory process to alveolar spaces as well.

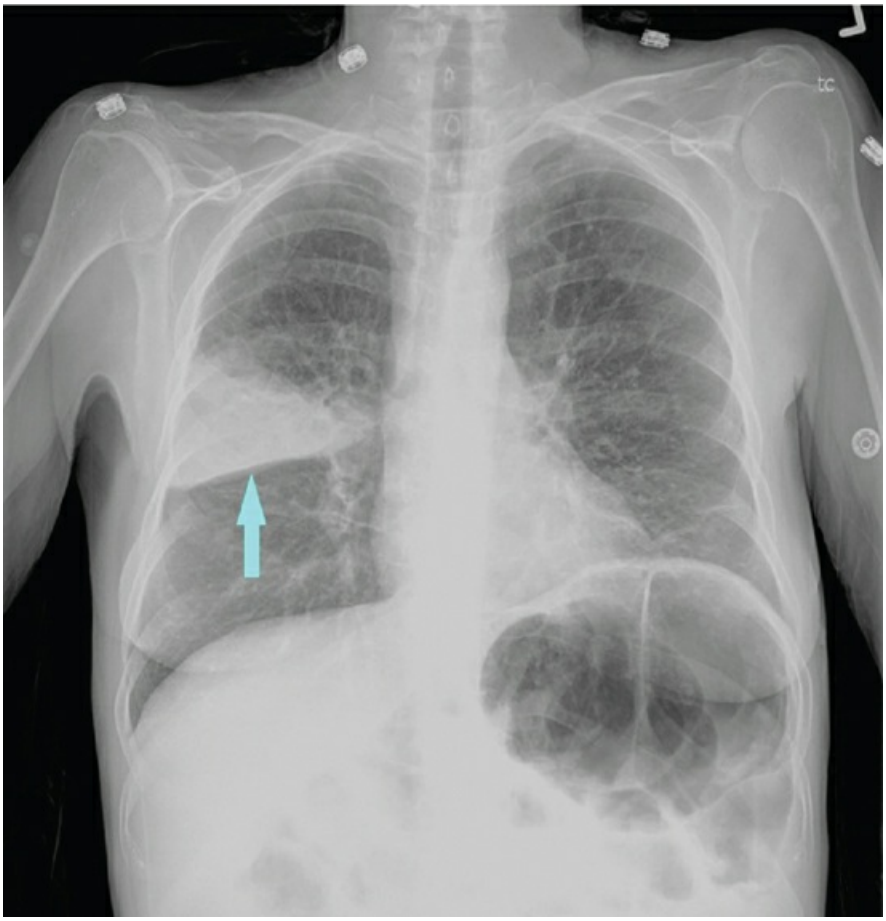

**FIGURE 23.1** Posteroanterior chest radiograph shows homogeneous consolidation from a lobar pneumonia (probably caused by *Streptococcus pneumoniae*) affecting part of the right upper lobe. The arrow points to the minor (horizontal) fissure separating the right upper lobe from the right middle lobe. Also seen is a significant amount of air in the colon. *Source:* (Courtesy of Dr. Laura Avery.)

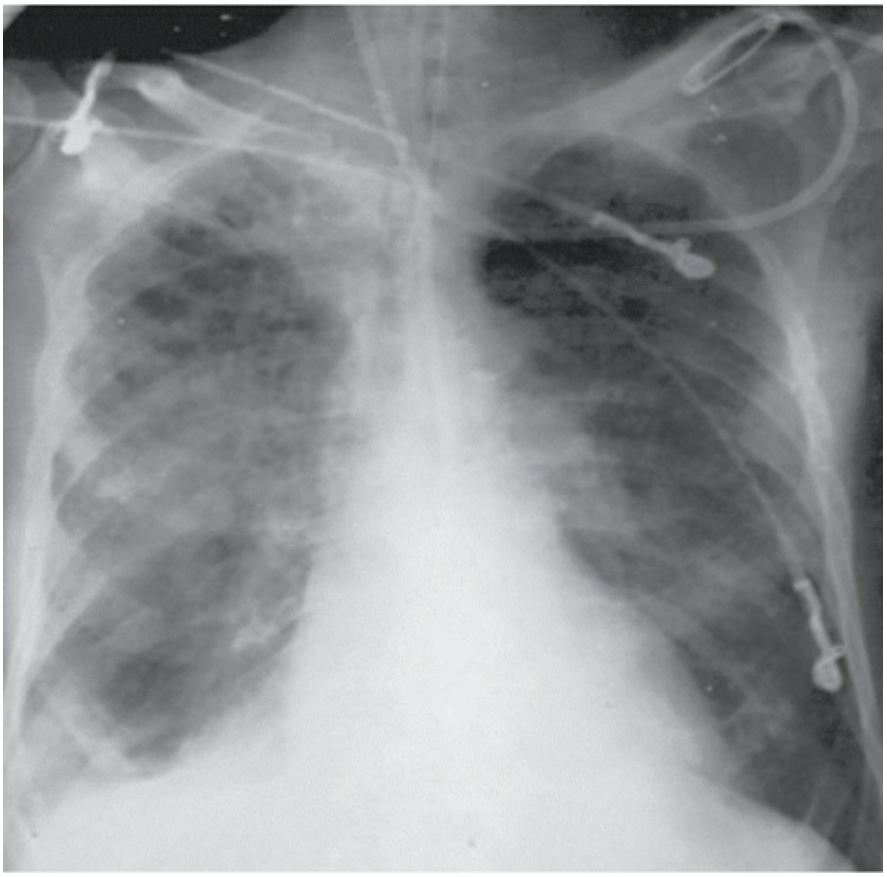

**FIGURE 23.2** Posteroanterior chest radiograph of a patient with extensive Gram-negative bronchopneumonia. Note the patchy infiltrates throughout both lungs, which are more prominent on the right.

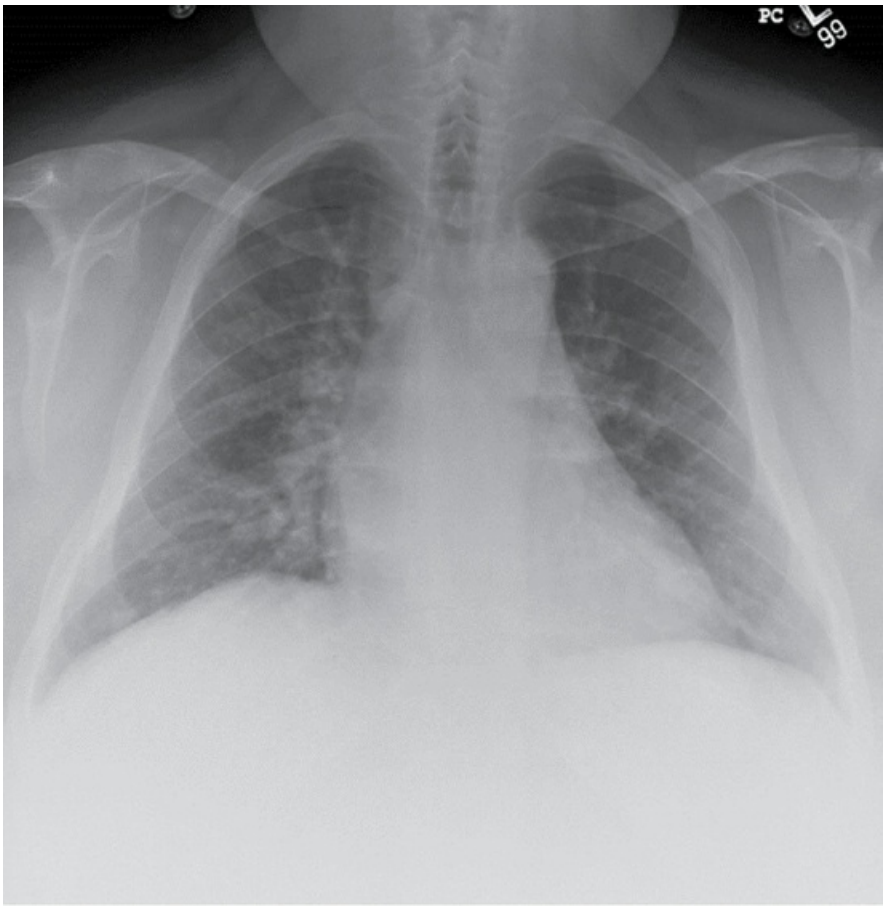


**FIGURE 23.3** Posteroanterior chest radiograph showing diffuse but subtle bilateral interstitial infiltrates caused by influenza pneumonia. *Source:* (Courtesy of Dr. Laura Avery.)

In some cases of pneumonia, the organisms are not highly destructive to lung tissue even though an exuberant inflammatory process may be seen. Pneumococcal pneumonia classically (although not always) behaves in this way, and the healing process is associated with restoration of relatively normal parenchymal architecture. In other cases, when the organisms are more destructive, tissue necrosis may occur, with resulting cavity formation or scarring of the parenchyma. Many cases of staphylococcal and anaerobic pneumonias follow this more destructive course.

## Pathophysiology

In addition to altering the normal function of the lung, infections of the pulmonary parenchyma also produce their clinical sequelae by inducing a more generalized systemic response to invading microorganisms. The major pathophysiologic consequence of inflammation and infection involving the distal air spaces is decreased ventilation to affected areas. If perfusion is relatively maintained, as it often is because of the vasodilatory effects of inflammatory mediators, ventilation-perfusion mismatch results, with low ventilation-perfusion ratios in diseased regions. When alveoli are

totally filled with inflammatory exudate, there may be no ventilation to these regions, and a pulmonary shunt results (see Chapter 1).

Pneumonia commonly results in ventilation-perfusion mismatch (with or without shunting) and hypoxemia.

Ventilation-perfusion inequality generally manifests as hypoxemia. Although shunt may explain part of the hypoxemia, ventilation-perfusion mismatch with areas of low ventilation-perfusion ratio is usually a more important factor. Carbon dioxide retention is not typically a feature of pneumonia unless the patient already has extremely limited reserve, especially from underlying COPD. In fact, otherwise healthy patients with pneumonia frequently hyperventilate and have a $P_{CO_2}$ less than 40 mm Hg, especially early in the course of the disease.

The systemic response to pneumonia is not unique but rather a reflection of the body's response to serious infection. Perhaps the most apparent aspects of this response are fever, an outpouring of PMNs into the circulation (particularly with bacterial pneumonia), and often a "toxic" appearance of the patient. These indirect systemic responses can be clues that an infectious process is the cause of a new pulmonary infiltrate.

## Clinical features and initial diagnosis

Most patients with pneumonia, especially younger and immunocompetent individuals, typically present with fever, cough, and often shortness of breath. The cough is nonproductive in some cases, particularly in pneumonias due to viruses or *Mycoplasma*; in others, especially bacterial pneumonias, sputum production is a prominent feature. When the inflammatory process in the pulmonary parenchyma extends out to the pleural surface, the patient often reports pleuritic chest pain. If the fever is high and "spiking," patients frequently experience shaking chills associated with the rapid rise in body temperature. Importantly, older patients and those with chronic illness may not mount a robust immune response; thus, fever and cough may be lacking. Such patients may present with only nonrespiratory symptoms such as confusion, lethargy, poor oral intake, and an exacerbation of underlying disease (especially congestive heart failure or COPD).

Physical examination reflects the systemic response to infection and the ongoing inflammatory process in the lung. Patients often have tachycardia, tachypnea, and fever. Examination of the chest typically reveals inspiratory crackles overlying the region of the pneumonia. If dense consolidation is present and the bronchus supplying the area is patent, sound transmission is greatly increased through the consolidated pneumonic area. As a result, breath sounds may be increased and bronchial in quality, fremitus is increased, and egophony is present. The consolidated area is characteristically dull to percussion of the overlying chest wall (see Chapter 3). Examination of peripheral blood typically shows an increase in white blood cell count (leukocytosis). Especially in patients with bacterial pneumonia, the leukocytosis is composed primarily of PMNs, and a shift toward greater numbers of immature neutrophils such as band forms may be seen.

Frequent clinical features in patients with pneumonia:

1. Fever (with or without chills)
2. Cough (with or without sputum)
3. Dyspnea
4. Pleuritic chest pain
5. Crackles overlying affected region
6. Dullness, bronchial breath sounds, and egophony with frank consolidation
7. Polymorphonuclear leukocytosis

As with other disorders affecting the pulmonary parenchyma, the single most cost-effective tool for assessing pneumonia at the macroscopic level is the chest radiograph in both posteroanterior and lateral views. Even in the presence of a consistent history and physical examination, the clinical diagnosis of pneumonia is often inaccurate. The radiograph is required to confirm the presence of a pneumonia and also show the distribution and extent of disease, sometimes providing clues about the nature of the etiologic agent.

Chest radiographs are also important for demonstrating potential complications of pneumonia, including lung abscess or the presence of pleural fluid, which frequently accompanies pneumonia, particularly of bacterial origin (Fig. 23.4) (see Chapter 24, section “Intrathoracic Complications of Pneumonia”).

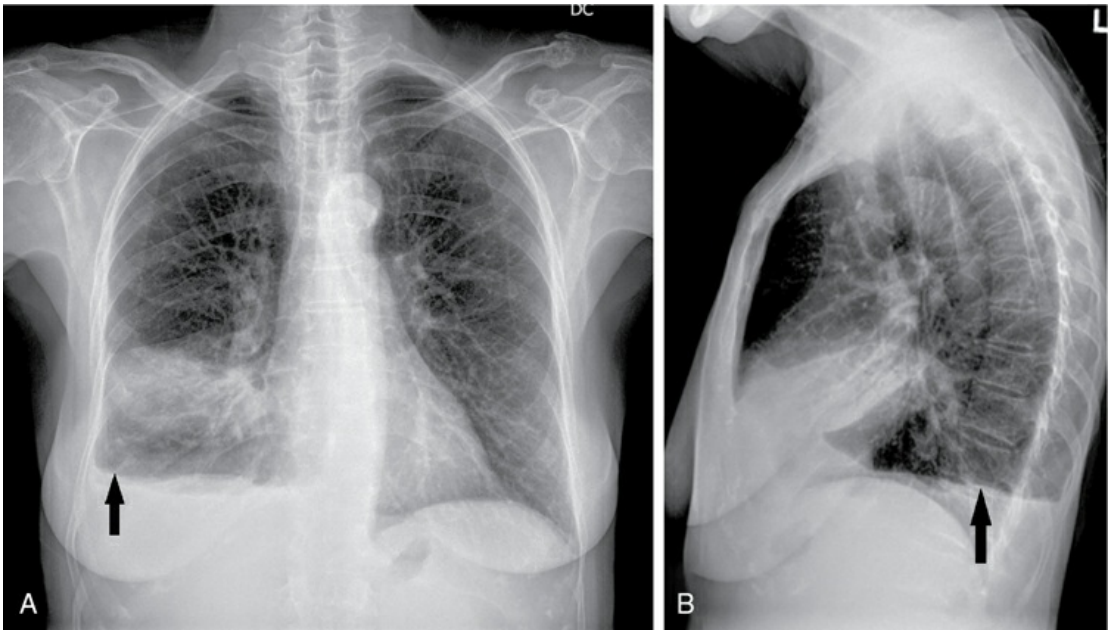


**FIGURE 23.4** Posteroanterior **(A)** and lateral **(B)** chest radiographs showing a lobar pneumonia in the right middle lobe with an associated pleural effusion. Arrows point to the top level of the pleural effusion. *Source:* (Courtesy of Dr. Laura Avery.)

Functional assessment of patients with acute infectious pneumonia is usually limited to evaluating gas exchange. Assessment of oxygen saturation by finger oximetry may suffice, but if there is concern for more significant gas exchange disturbances, an arterial blood gas may be required. Arterial blood gas values characteristically demonstrate hypoxemia accompanied by normal or decreased $P_{CO_2}$, as well as a widened alveolar-arterial (A-a) oxygen gradient. Pulmonary function tests have little usefulness in this acute setting.

## Therapeutic approach: General principles and antibiotic susceptibility

The cornerstone of treatment of bacterial pneumonia is prompt and effective antibiotic therapy directed at the infecting organism. However, the causative organism is identified in less than 40% of cases, even after extensive testing, Therefore, initial treatment strategies have been developed on the basis of the clinical setting (i.e., community-acquired vs. nosocomial pneumonia). The specifics of the treatment strategies are outlined later under "Initial Management Strategies Based on Clinical Setting of Pneumonia." These guidelines were developed by expert consensus through consideration of the most likely organisms to be involved, the principles of antibiotic stewardship, and to some extent, the risk of delayed treatment. The concept of antibiotic stewardship has grown from the recognition that overuse of antibiotics leads to marked increases in antibiotic resistance. The goal is to use the most narrow spectrum antibiotic regimen possible to treat an infection in an effort to limit the development of resistant organisms.

As the risk of infection by any of multiple different organisms becomes greater, the spectrum of the recommended antibiotic regimen(s) increases. Implicit in these guidelines is an understanding of the risk of delayed treatment. In addition, there will be some patients with an infection for whom the guidelines recommend initial treatment that will not be effective. This potential risk reinforces the need to carefully assess each patient for risk factors for unusual organisms. The guidelines attempt to balance these three goals: treating the most likely organism, using the most narrow spectrum antibiotic regimen, and minimizing the risk of starting treatment that is ineffective. Thus, the recommended antibiotic regimens escalate from a very narrow treatment focused primarily on *S. pneumoniae* (amoxicillin) in younger healthy individuals, to a broad-spectrum regimen that is unlikely to miss any bacteria in patients who are severely ill. Table 23.1 summarizes the etiology of four broad subcategories of patients with community-acquired pneumonia. If and when an organism is identified, the regimen is narrowed to allow for more focused or more effective antibiotic coverage. Because knowledge of antibiotic susceptibility of specific organisms helps with understanding the rationale behind initial treatment strategies, this section will consider some of the general patterns of antibiotic susceptibility for the major organisms causing pneumonia.

**TABLE 23.1**

**Community-Acquired Pneumonia: Common Organisms**[a]

| Patient Category | Common Organisms | Other Miscellaneous Organisms |
|---|---|---|
| Outpatient, no cardiopulmonary disease or other modifying risk factors | *S. pneumoniae*<br>*M. pneumoniae*<br>*C. pneumoniae*<br>Respiratory viruses (including SARS-CoV-2 and influenza)<br>*H. influenzae* (in smokers) | *Legionella*<br>*M. tuberculosis*<br>Endemic fungi |
| Outpatient with cardiopulmonary disease and/or other modifying factors | *S. pneumoniae*<br>*M. pneumoniae*<br>*H. influenzae*<br>Aerobic Gram-negative bacilli<br>Respiratory viruses (including SARS-CoV-2 and influenza)<br>Anaerobes<br>*C. pneumoniae* | *M. catarrhalis*<br>*Legionella*<br>*M. tuberculosis*<br>Endemic fungi |
| Hospitalized | *S. pneumoniae*<br>*H. influenzae*<br>Polymicrobial (including anaerobes)<br>Aerobic Gram-negative bacilli<br>*Legionella*<br>*C. pneumoniae*<br>Respiratory viruses (including SARS-CoV-2 and influenza) | *M. pneumoniae*<br>*M. catarrhalis*<br>*M. tuberculosis*<br>Endemic fungi |
| Hospitalized, severe pneumonia | *S. pneumoniae*<br>*Legionella*<br>*H. influenzae*<br>Aerobic Gram-negative bacilli<br>*M. pneumoniae*<br>Respiratory viruses (including SARS- | *M. tuberculosis*<br>*C. pneumoniae*<br>Endemic fungi |

| | | |
|---|---|---|
| | CoV-2 and influenza)<br>*S. aureus* | |

[a]Excludes patients with human immunodeficiency virus infection.

*C. pneumoniae, Chlamydophila pneumoniae; H. influenzae, Haemophilus influenzae; M. catarrhalis, Moraxella catarrhalis; M. pneumoniae, Mycoplasma pneumoniae; M. tuberculosis, Mycobacterium tuberculosis; S. aureus, Staphylococcus aureus; S. pneumoniae, Streptococcus pneumoniae*.

Modified from Mandell, L. A., Wunderink, R. G., Anzueto, A., Bartlett, J. G., Campbell, G. D., Dean, N. C., et al. (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases, 44* (Suppl. 2), S27–S72.

Before moving on, however, we will define two confusing terms: *typical pneumonia* and *atypical pneumonia*. These are historical terms that actually do not provide a clear distinction and in general should be avoided. However, the terms are so embedded in the literature that we will define them here. The origin of these terms is likely based on the historical recognition of mycoplasma pneumonia (i.e., due to *Mycoplasma pneumoniae*). *Streptococcus pneumoniae* was the first organism recognized to cause an acute pneumonia (i.e., pneumococcal pneumonia) and for many years was the only known cause. Pneumococcal pneumonia classically presents with a high fever, lobar infiltrate, a Gram stain of sputum revealing organisms consistent with the diagnosis, and response to penicillin or other β-lactam antibiotics. Soon after radiographs were more commonly used, it was recognized that some patients with symptoms of pneumonia had chest x-rays that showed patchy, scattered infiltrates, were not as ill, had no organisms seen on Gram stain of sputum, and did not respond to penicillin. In retrospect, it is likely that many of these cases were due to *M. pneumoniae*. This "new" pattern was labeled "atypical pneumonia," and pneumococcal pneumonia was considered "typical pneumonia." Thus, "atypical pneumonia" has come to mean pneumonia caused by bacterial organisms that cannot be seen on Gram stain or cultured by standard techniques and are intrinsically resistant to β-lactam antibiotics. *Mycoplasma*, *Chlamydophila*, and *Legionella* are included in this category. "Typical pneumonia" includes other common respiratory bacterial pathogens, most notably *S. pneumoniae* (the most common bacterial cause), *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and other aerobic Gram-negative rods.

Because *S. pneumoniae* is the most common cause of bacterial pneumonia, initial treatment for all patients should cover this organism. Penicillin has traditionally been the most appropriate agent, assuming the patient is not allergic to it, and amoxicillin (an oral penicillin derivative) is recommended for uncomplicated pneumonia in otherwise healthy patients. However, amoxicillin is not effective against some of the other common causes of community-acquired pneumonia (e.g., *M. pneumoniae*, *Chlamydophila pneumoniae*). Previously, macrolide antibiotics were recommended as a single agent for empiric outpatient therapy in uncomplicated pneumonia, but the prevalence of macrolide-resistant *S. pneumoniae* has caused a change in this recommendation.

Staphylococci generally produce penicillinase, which requires the use of a penicillinase-resistant semisynthetic derivative of penicillin, such as oxacillin or nafcillin, or a first-generation cephalosporin such as cefazolin. Unfortunately, many staphylococci (methicillin-resistant *S. aureus,* or MRSA) are also resistant to these agents, in which case vancomycin is the antibiotic of choice. *H. influenzae* may be sensitive to ampicillin, but the high frequency of organisms resistant to this antibiotic generally justifies alternative coverage, such as a second- or third-generation cephalosporin, an extended-spectrum macrolide, trimethoprim-sulfamethoxazole, a quinolone, or a β-lactam/β-lactamase inhibitor combination. Many of the other Gram-negative bacillary pneumonias often display resistance to a variety of antibiotics. Aminoglycosides (e.g., gentamicin and tobramycin), third- or fourth-generation cephalosporins, quinolones, carbapenems (e.g., meropenem), or an extended-spectrum penicillin with a β-lactamase inhibitor (e.g., piperacillin/tazobactam) may be used initially while antibiotic sensitivity testing is performed. Pneumonia caused by anaerobes is treated most commonly with either penicillin or clindamycin. A macrolide or a quinolone is the antibiotic of choice for pneumonias caused by either *Legionella* or *Mycoplasma*.

Frequently used targeted antibiotics for common organisms causing pneumonia:

1. *S. pneumoniae* (penicillin or ampicillin, first- or second-generation cephalosporin, selected quinolones, macrolide in areas where resistance is low)
2. *Staphylococcus* (oxacillin, nafcillin, cefazolin, vancomycin)
3. *Haemophilus influenzae* (second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole, quinolone, macrolide)
4. Gram-negative rods (aminoglycosides, third- or fourth-generation cephalosporins, carbapenems, extended-spectrum penicillin with β-lactamase inhibitor)
5. Anaerobes (penicillin, clindamycin)
6. *Mycoplasma* organisms (macrolide, quinolone)
7. *Legionella* (macrolide, quinolone)
8. *Chlamydophila pneumoniae* (tetracycline, macrolide)

## Initial management strategies based on clinical setting of pneumonia

Greater emphasis on the cost-effective use of medical resources has spurred development of algorithms and guidelines for the clinician approaching common clinical problems. Pneumonia is a particularly good example of an important clinical problem for which such management strategies relating to both diagnostic evaluation and initiation of therapy have been developed. Importantly, even when rigorous diagnostic testing is pursued, the specific cause of pneumonia is frequently not identified, thus necessitating empiric treatment. In large studies done prior to the COVID-19 pandemic, the specific etiology of pneumonia in patients admitted to the hospital with pneumonia was identified in less than 40% of patients. When an etiology was found, respiratory

viruses were the most common cause, accounting for approximately 25%. Specific bacterial causes were found in 13%, with *S. pneumoniae* accounting for over one-third of bacterial infections. It is likely that the proportion of organisms is different in the COVID-19 era. There is some early indication that the incidence of illness due to other respiratory viruses, including influenza, has decreased as the protective measures taken for COVID-19 (mask-wearing and social distancing) also protect against transmission of other viruses.

Separate strategies are endorsed for two distinct groups of patients with pneumonia, depending on the setting where the pneumonia developed: (1) community-acquired pneumonia or (2) nosocomial (hospital-acquired) pneumonia. These guidelines apply to patients who do not have significant underlying impairment of systemic host defense mechanisms, such as patients with HIV/AIDS or those receiving immunosuppressive drugs or cancer chemotherapy.

## Community-acquired pneumonia

*Community-acquired pneumonia* refers to pneumonia that develops in the community setting (i.e., in an individual who is not hospitalized). Although this category is not meant to include patients with significant impairment of systemic host defense mechanisms, it can include patients with other coexisting illnesses or risk factors that alter the profile of organisms likely to be responsible for pneumonia.

As noted above, because the cause of community-acquired pneumonia is never identified in more than 60% of patients, even after extensive testing, guidelines specify empiric antibiotic treatment. The recommended empiric therapy is determined by a number of modifying factors: the presence of coexisting illness, recent treatment with antibiotics, and the severity of illness at the initial presentation. If a specific pathogen is identified, the initial empiric antibiotic regimen is modified to avoid use of unnecessary antibiotics.

A presumptive diagnosis of pneumonia is made when the patient presents with signs and symptoms of a respiratory infection, and a chest radiograph confirms a pulmonary infiltrate. Fig. 23.5 summarizes the recommended initial approach to testing once a diagnosis of pneumonia is made. All patients should be tested for SARS CoV-2 and seasonally for influenza. The next steps are assessing for comorbidities and establishing the severity of illness, which determines whether the patient requires hospital admission or can be treated as an outpatient. A number of scoring systems have been developed to assess the need for hospitalization or ICU admission for an individual patient based on demographic characteristics and the severity of the illness at presentation. A detailed discussion of these algorithms is beyond the scope of this chapter, but references to the most common management algorithms are provided. Further testing and treatment are based on specific subcategories of patients specified by these algorithms.

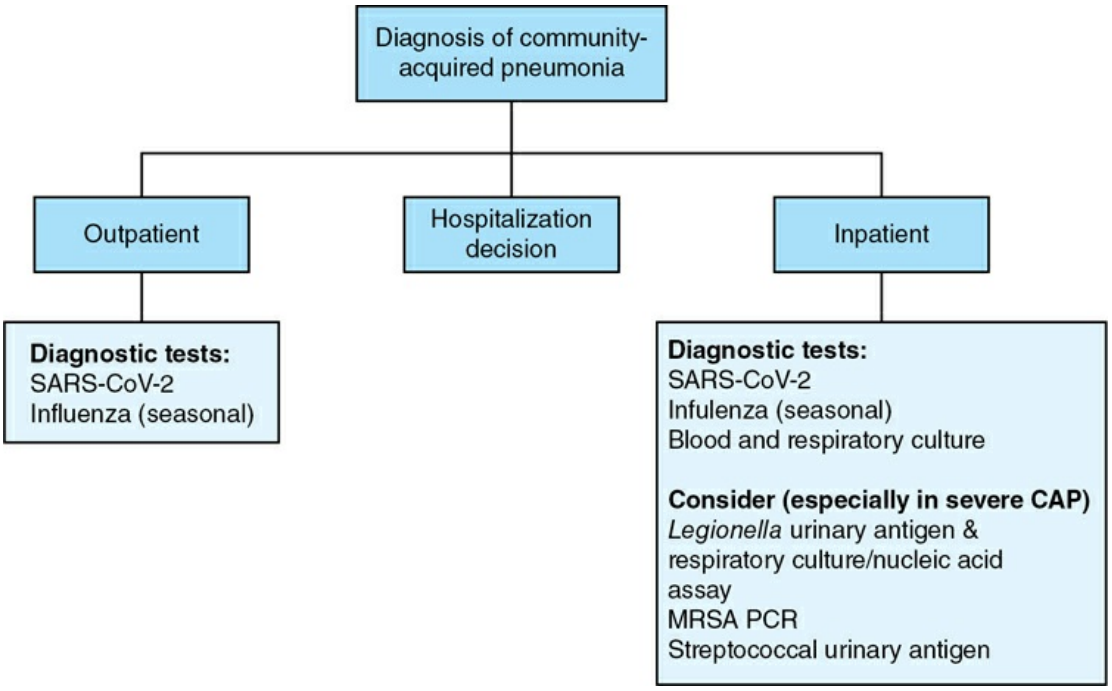


**FIGURE 23.5** Approach to diagnostic testing for community-acquired pneumonia. CAP, community-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction. *Source:* (Recommendations are adapted from Jones, B. E., Herman, D. D., Dela Cruz, C. S., Waterer, G. W., Metlay, J. P., Ruminjo, J. K., et al. (2020). Summary for clinicians: Clinical practice guideline for the diagnosis and treatment of community-acquired pneumonia. *Annals of the American Thoracic Society, 17*, 133–138.)

Importantly, each patient must be considered on an individual basis, and the recommendations are intended as guidelines to help with decision-making rather than as strict rules. One important aspect of empiric treatment is the need for careful follow-up. Most patients respond to treatment within 48 to 72 hours. If a patient does not respond within this time frame, reassessment with consideration of a change in therapy is indicated.

The first group of patients with community-acquired pneumonia who are specified in guidelines are those who do not have coexisting cardiopulmonary disease or other modifying factors, and who do not require hospitalization. The most common pathogens in this group of patients include *S. pneumoniae, M. pneumoniae, C. pneumoniae*, respiratory viruses, and in smokers, *H. influenzae*. The most widely accepted therapeutic regimens are monotherapy with either amoxicillin or doxycycline. A macrolide, such as azithromycin or clarithromycin, should be used only in areas where the incidence of pneumococcal resistance to macrolides is less than 25%. Unfortunately, this excludes the United States and many other countries. An issue with using

amoxicillin as monotherapy in this population is that amoxicillin does not treat either *Mycoplasma* or *Chlamydophila* pneumonia, which are common pathogens, and has led some authorities to recommend both amoxicillin and a macrolide, or doxycycline alone as initial therapy in this population.

In community-acquired pneumonia, factors influencing the likelihood of certain organisms and therefore the therapeutic approach include age, the presence of coexisting illness, and the severity of pneumonia at the initial presentation.

The second group includes patients who have coexisting cardiopulmonary disease or other modifying risk factors but still can be treated in an outpatient setting. Important comorbidities that place a patient in this category include chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcohol use disorder; malignancies; asplenia; immunosuppressive conditions or drugs; or the use of antibiotics within the prior 3 months (in which case antibiotics from a different class should be used). Again, local resistance patterns of *S. pneumoniae* should be taken into account, and residence in a nursing home or other healthcare facility should be considered a factor that increases the risk of pneumonia caused by a Gram-negative organism. Poor dentition (leading to an increased burden of anaerobic organisms in the mouth), problems with swallowing, or impaired consciousness increase the risk of an anaerobic aspiration pneumonia. Recommended options for management of patients with comorbidities include a β-lactam antibiotic (e.g., amoxicillin/clavulanic acid or cefuroxime) given in combination with a macrolide (particularly an advanced-generation macrolide, e.g., azithromycin or clarithromycin) or doxycycline, or monotherapy with an oral respiratory quinolone (e.g., levofloxacin, moxifloxacin).

The third and fourth groups differ from the first two on the basis of severity of the pneumonia. The third group is defined by a need for hospitalization. The fourth group includes patients with the most severe disease, which usually necessitates admission to an intensive care unit (ICU). These patients still commonly have pneumonia caused by *S. pneumoniae* or the other organisms found in outpatients, but with additional concern for Gram-negative bacilli, *Legionella*, and sometimes *S. aureus*, including MRSA. Therapy for these patients is adjusted accordingly. Recommended antibiotic regimens include a β-lactam antibiotic plus a macrolide or a respiratory fluoroquinolone. If there is concern for MRSA, vancomycin typically is added. If there is a history of documented *Pseudomonas* infection within the past year, then anti-*Pseudomonas* treatment is included.

There are some data to suggest that adjunctive treatment with corticosteroids may be beneficial in patients with severe pneumonia. However, this practice has not been uniformly adopted, and some data suggest that patients with pulmonary infection due to influenza or *Aspergillus* may have worse outcomes if corticosteroids are used. Currently, the routine use of corticosteroids in patients with severe pneumonia is not recommended except when it is due to COVID-19, a situation where corticosteroids appear to improve outcomes in patients with severe disease.

## Further diagnostic testing

As noted, all patients presenting with community-acquired pneumonia should be tested

for SARS-CoV-2 and seasonally for influenza. Additional diagnostic testing is reserved for patients with pneumonia requiring hospital admission. Among outpatients with community-acquired pneumonia, extensive testing adds significant cost, does not change treatment or outcomes, and usually does not result in a specific diagnosis. Here we describe the general guidelines for further diagnostic testing of inpatients with community-acquired pneumonia, but recognize that clinical decisions must be based on the individual patient.

Routine testing with Gram stain and culture of lower respiratory specimens was previously the standard of care for patients with pneumonia. It is now recognized that these tests are of low yield and typically do not affect treatment decisions or outcome. Thus, sputum testing is only recommended in patients admitted to the hospital. Similarly, routine blood cultures are also recommended only for hospitalized patients with community-acquired pneumonia unless MRSA or *Pseudomonas aeruginosa* is suspected. When a sputum specimen is obtained, it is important to evaluate the quality of the specimen, because a poor quality specimen may provide inadequate or inaccurate information. In an appropriate sputum specimen (i.e., one that contains few squamous epithelial cells picked up in transit through the oropharynx), inflammatory cells and bacteria can be seen.

In most bacterial pneumonias, large numbers of PMNs are seen in the sputum. In contrast, mycoplasmal and viral pneumonias have fewer PMNs and more mononuclear inflammatory cells. Pneumococcal, staphylococcal, and Gram-negative bacillary pneumonias commonly demonstrate a relatively homogeneous population of the infecting bacteria. Anaerobic aspiration pneumonias, caused by a mixture of organisms from the oropharynx, show a mixed population of bacteria of many different morphologies. In Legionnaires disease, the bacterium does not stain well with the usual Gram stain reagent, and visualization requires special stains. In mycoplasmal and viral pneumonia, the infecting agent is not detected on light microscopy, and only the predominantly mononuclear cell inflammatory response is seen.

When sputum is not spontaneously expectorated by the patient, other methods for obtaining respiratory secretions (or even material directly from the lung parenchyma) may be necessary. Techniques that can be used—flexible bronchoscopy, needle aspiration of the lung, and surgical lung biopsy—are described in greater detail in Chapter 3. Further recommendations for patients admitted to the hospital with severe pneumonia include urinary antigen testing for *S. pneumoniae* and *Legionella* as well as specialized respiratory cultures for *Legionella* species.

## Nosocomial (hospital-acquired) pneumonia

In contrast to community-acquired pneumonia, nosocomial pneumonia is defined as pneumonia which develops in a hospital setting. Nosocomial pneumonia, also called hospital-acquired pneumonia, is defined as a pneumonia that occurred 48 hours or more after admission and did not appear to be developing at the time of presentation. Patients in ICUs, especially those receiving mechanical ventilation, are at particularly high risk for developing this category of pneumonia. When a patient develops a new pneumonia 48 hours or more after endotracheal intubation, the patient is considered to have a *ventilator-associated pneumonia*, which is a subset of hospital-acquired pneumonia.

The primary route of infection for both hospital-acquired pneumonia and ventilator-associated pneumonia is microaspiration of organisms from the oropharynx into the tracheobronchial tree. The hospital environment and treatment with antibiotics lead to a change in the normal oropharyngeal flora; thus, the organisms associated with hospital-acquired pneumonia are different from those commonly causing community-acquired pneumonia. Patients at risk often have other underlying medical problems, have been receiving antibiotics, or have an endotracheal tube in their airway that bypasses some of the normal protective mechanisms of the respiratory tract. Gastric acid–reducing medications, particularly proton-pump inhibitors, have been implicated as a risk factor for nosocomial pneumonia in some studies; an increase in gastric pH allowing increased bacterial growth is the presumed mechanism. Contamination of the apparatus for respiratory support, including tubing and humidification reservoirs, is also implicated.

Organisms of particular concern in nosocomial pneumonia include *Staphylococcus aureus*, Gram-negative bacilli, and *Legionella*.

Organisms of particular concern in patients who develop hospital-acquired pneumonia are Gram-negative bacilli (e.g., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*) and Gram-positive cocci (*S. aureus*, including MRSA), but other organisms such as respiratory viruses and *Legionella* can be involved. Diagnostic evaluation is difficult and often complicated by the need to distinguish bacterial colonization of the tracheobronchial tree from true bacterial pneumonia. Detailed consideration of the clinical issues involved with diagnostic testing and optimal therapy of nosocomial pneumonia are beyond the scope of this discussion but can be found in Suggested Readings at the end of this chapter.

# Suggested readings

### General reviews and community-acquired pneumonia


Aliberti S, Dela Cruz C.S, Amati F, Sotgiu G. & Restrepo M.I. *Community-acquired pneumonia* Lancet 2021;398: 906-919.

Chee E, Huang K, Haggie S. & Britton P.N. *Systematic review of clinical practice guidelines on the management of community acquired pneumonia in children* Paediatric Respiratory Reviews 2022;42: 59-68.

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Evans S.E, Jennerich A.L, Azar M.M, Cao B, Crothers K, Dickson R.P., et al. *Nucleic acid-based testing for noninfluenza viral pathogens in adults with suspected community-acquired pneumonia. An official American Thoracic Society clinical practice guideline* American Journal of Respiratory and Critical Care Medicine 2021;203: 1070-1087.

Fabre V, Spivak E.S. & Keller S.C. *Viewing the community-acquired pneumonia guidelines through an antibiotic stewardship lens* American

Journal of Respiratory and Critical Care Medicine 2020;201: 745-746.
Huttner B, Cappello B, Cooke G, Gandra S, Harbarth S, Imi M., et al. *2019 Community-acquired pneumonia treatment guidelines: There is a need for a change toward more parsimonious antibiotic use* American Journal of Respiratory and Critical Care Medicine 2020;201: 1315-1316.
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# 24: Bacterial and viral organisms causing pneumonia

OUTLINE



In this chapter, we expand upon the general discussion of pneumonia in Chapter 23 to consider some of the specific and common responsible organisms. The most clinically relevant pathogens are addressed here, with the focus on individual etiologic agents and characteristic features of each that are particularly useful to the clinician. Importantly,

as discussed in Chapter 23, the clinician usually must decide about a treatment regimen before knowing which specific organism is causing disease. This decision is based on patient characteristics and whether the infection was acquired in the community (community-acquired pneumonia [CAP]) or in the hospital or other healthcare setting (hospital-acquired pneumonia [HAP]). Even when extensive testing protocols are used for patients requiring hospital admission, the specific pathogen is identified in fewer than 60% of cases. Lung abscess and empyema, two of the more common complications of pneumonia, are also addressed.

The chapter concludes with a brief discussion of several infections that are relevant as the threat of bioterrorism has emerged. In addition to reviewing inhalational anthrax, the chapter briefly describes two other organisms considered to be of concern as potential weapons of bioterrorism: *Yersinia pestis* (the cause of plague) and *Francisella tularensis* (the cause of tularemia).

# Bacteria

## *Streptococcus pneumoniae*

Of the bacteria, the organism most frequently associated with pneumonia is *Streptococcus pneumoniae*; in common parlance, it is often called *pneumococcus*. It has been estimated that in adults, approximately one-half of all pneumonias serious enough to require hospitalization are caused by this organism. *S. pneumoniae*, a normal inhabitant of the oropharynx in a large proportion of adults and children, is a Gram-positive coccus typically seen in pairs, or diplococci. Pneumococcal pneumonia is the most common cause of CAP and frequently occurs following a viral upper respiratory tract infection. The organism has a polysaccharide capsule that interferes with immune recognition and phagocytosis; this is an important factor in its virulence. There are many different antigenic types of capsular polysaccharide, and for host defense cells to phagocytize the organism, antibody against the particular capsular type must be present. Antibodies contributing in this way to the phagocytic process are called *opsonins* (see Chapter 22).

In pneumococcal pneumonia, onset of the clinical illness is often abrupt, with the sudden development of shaking chills and high fever. The cough may be productive of yellow, green, or blood-tinged (rusty-colored) sputum. Before the development of pneumonia, patients often have experienced a viral upper respiratory tract infection, which is an important predisposing feature. Chest radiographs commonly show a dense lobar infiltrate, although more patchy patterns are also seen (Fig. 24.1).

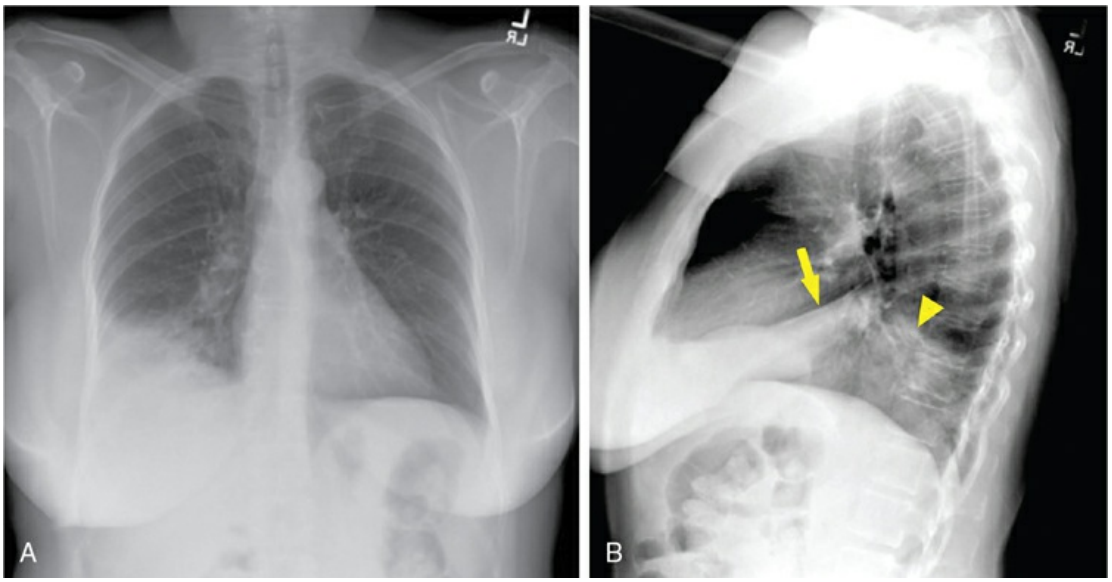


**FIGURE 24.1** Posteroanterior (**A**) and lateral (**B**) chest radiographs show lobar pneumonia caused by *Streptococcus pneumoniae* affecting most of the right lower lobe (RLL). In (**A**), visualization of the right diaphragm has been lost because it is adjacent to consolidated rather than air-containing lung (the "silhouette sign"). In (**B**), the arrow points to the right lung major fissure, and the arrowhead points to increased opacity over the spine posteriorly (often called the "spine sign"). *Source:* (Courtesy of Dr. Laura Avery.)

*Streptococcus pneumoniae* (pneumococcus) is the most common cause of bacterial pneumonia. The polysaccharide capsule is an important factor in its virulence.

Typically, outpatients with clinical findings and a chest x-ray consistent with suspected pneumococcal pneumonia are treated empirically with antibiotics appropriate for a CAP, and do not require further testing. Adult patients who are hospitalized should have sputum Gram stain and culture, blood cultures, and a urine pneumococcal antigen test, which detects polysaccharide components of the cell wall. Notably, there is a high rate of false-positive urine antigen tests in healthy children due to nasopharyngeal colonization by *S. pneumoniae*; therefore, this test is not recommended in children. Definitive diagnosis of pneumococcal infection requires culture of the organism from blood or pleural fluid, which are both normally sterile. If the pneumococcus is identified, treatment is with a β-lactam antibiotic if possible. Vaccines have been available against pneumococcus for many years and have been improved more recently by conjugating pneumococcal polysaccharides to proteins, which produces a more robust immune response. Vaccination is indicated for all adults older than 65 years and for individuals with a specified chronic medical condition or risk factor.

## *Staphylococcus aureus*

*Staphylococcus aureus* is another Gram-positive coccus, but is found in clusters when examined microscopically. Three major settings in which this organism is seen as a cause of pneumonia are as follows: (1) as a secondary complication of respiratory tract infection with the influenza virus; (2) in the hospitalized patient, who often has some impairment of host defense mechanisms and whose oropharynx has been colonized by *Staphylococcus*; and (3) as a complication of widespread dissemination of staphylococcal organisms through the bloodstream.

*S. aureus* is an uncommon cause of CAP, but accounts for up to 30% of nosocomial pneumonia cases. Notably, community-acquired methicillin-resistant *S. aureus* (MRSA) is a significant problem, and antibiotic choice should target MRSA if it is suspected. Patients with *S. aureus* are typically acutely ill with high fever and may develop rapid deterioration. Because *S. aureus* can cause a necrotizing infection, purulent bloody sputum is often seen.

When *S. aureus* pneumonia is suspected, because of the propensity of the organism to spread to the lung from a bloodstream infection, a search for a nonpulmonary site (especially endocarditis) is indicated. Chest radiographs typically show a bronchopneumonia pattern with a patchy distribution; however, a lobar infiltrate may also be seen (Fig. 24.2). When the pneumonia is due to hematogenous spread, multiple small abscesses may be present.

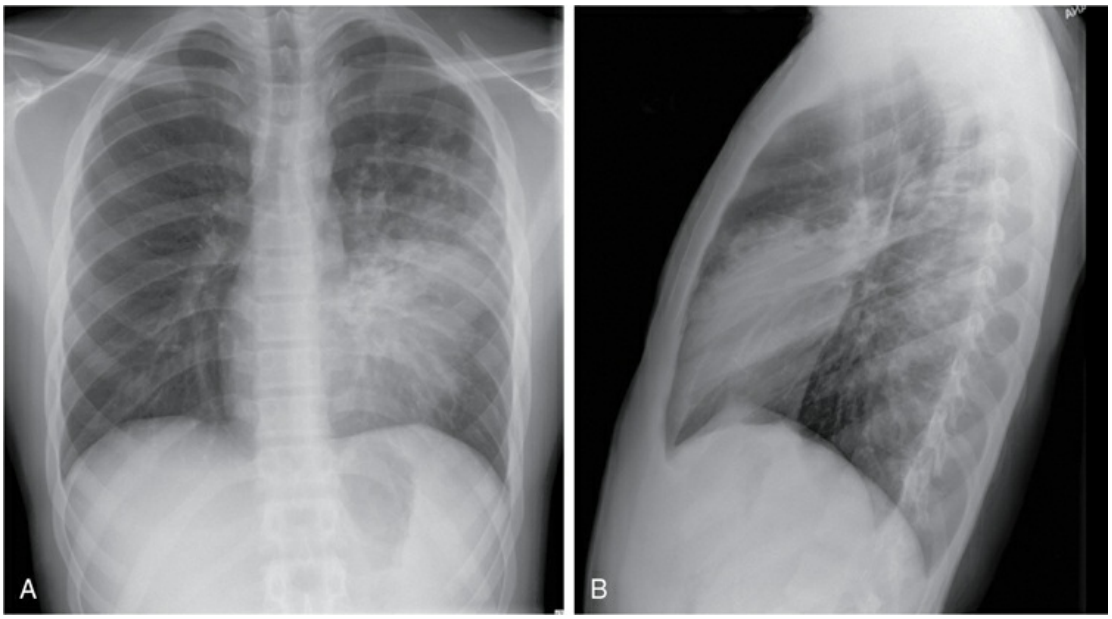


**FIGURE 24.2** Posteroanterior **(A)** and lateral **(B)** chest radiographs show a patchy lobar pneumonia in the lingular segments of the left upper lobe due to *Staphylococcus aureus*. In (**A**), the consolidation in the lingula is adjacent to the heart and has caused loss of the left heart border (another example of a silhouette sign, as also shown in Fig. 24.1). *Source:* (Courtesy of Dr. Laura Avery.)

## Gram-negative organisms

Many Gram-negative organisms are potential causes of pneumonia, but only a few of the most important examples are mentioned here. *Haemophilus influenzae*, a small coccobacillary Gram-negative organism, is often found in the nasopharynx of normal individuals and in the lower airways of patients with COPD. It can cause pneumonia in children and adults—the latter often with underlying COPD as a predisposing factor. *Klebsiella pneumoniae*, a relatively large Gram-negative rod normally found in the gastrointestinal tract, is most associated with pneumonia in the setting of an underlying alcohol use disorder. *Pseudomonas aeruginosa*, found in a variety of environmental sources (including the hospital environment), is seen primarily in patients who are debilitated, hospitalized, and often previously treated with antibiotics. *P. aeruginosa* is also a very common cause of respiratory tract infection in patients with underlying bronchiectasis or cystic fibrosis.

Factors predisposing to oropharyngeal colonization and pneumonia with Gram-negative organisms:

1. Hospitalization or residence in a chronic care facility
2. Underlying disease and compromised host defenses
3. Recent antibiotic therapy

The bacterial flora normally present in the mouth are potential etiologic agents in the development of pneumonia. A multitude of organisms (both Gram-positive and Gram-negative) that favor or require anaerobic conditions for growth are the major organisms comprising mouth flora. The most common predisposing factor for anaerobic pneumonia is the aspiration of secretions from the oropharynx into the tracheobronchial tree, especially in patients with poor dentition or gum disease because of the larger burden of organisms in their oral cavities. Patients with impaired consciousness (e.g., as a result of coma, alcohol or drug ingestion, or seizures) and those with difficulty swallowing (e.g., as a result of stroke or diseases causing muscle weakness) are prone to aspirate and are at greatest risk for pneumonia caused by anaerobic or mixed mouth organisms.

Anaerobes normally found in the oropharynx are a frequent cause of aspiration pneumonia.

In some settings, such as prolonged hospitalization or recent use of antibiotics, the type of bacteria residing in the oropharynx may change. Specifically, aerobic Gram-negative bacilli and *S. aureus* are more likely to colonize the oropharynx, and any subsequent pneumonia resulting from aspiration of oropharyngeal contents may include these aerobic organisms as part of the process.

## *Mycoplasma*

*Mycoplasma pneumoniae* is a common respiratory pathogen, especially in young adults. It usually causes upper respiratory tract infections or bronchitis, but may also cause pneumonia. Some of the smallest free-living organisms yet identified, mycoplasmas are similar in size to large viruses, and unlike other bacteria, do not possess a rigid cell wall. This feature is clinically important because the lack of a cell wall means that *Mycoplasma* does not stain with a Gram stain and is not susceptible to antibiotics that inhibit cell wall synthesis (e.g., β-lactams). These organisms are now recognized as a common cause of pneumonia and are perhaps responsible for 10% to 20% of all cases.

*Pneumonia due to Mycoplasma* occurs most frequently in young adults but is not limited to this age group. The pneumonia is generally acquired in the community—that is, by previously healthy, nonhospitalized individuals—and may occur in either isolated cases or localized outbreaks. Patients are typically only mildly ill, leading to the lay term of "walking pneumonia" when referring to pneumonia due to *Mycoplasma*.

Symptoms include a low-grade fever and a prominent cough, with or without sputum production. The chest x-ray typically shows reticulonodular infiltrates and/or patchy opacities (Fig. 24.3); however, it may be remarkably clear, especially in early disease. As with other CAPs in individuals who do not require hospitalization, specific diagnostic testing is not routinely recommended. If specific testing is needed, a *Mycoplasma* PCR test on respiratory secretions can be performed.

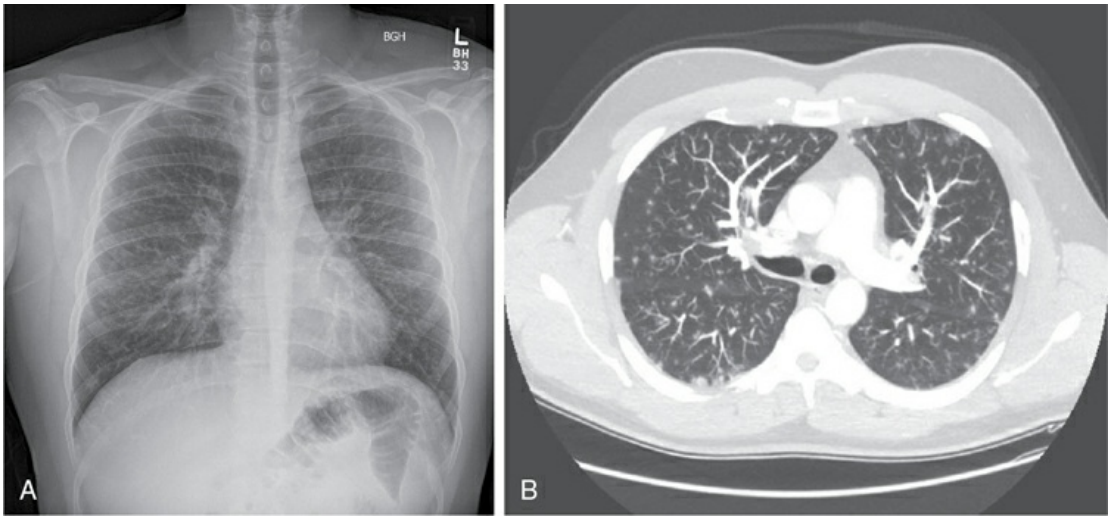


**FIGURE 24.3** Posteroanterior chest radiograph **(A)** and chest CT scan (**B**) of a patient with *Mycoplasma* pneumonia. Note patchy opacities throughout both lungs. *Source:* (Courtesy of Dr. Laura Avery.)

*Mycoplasma*, one of the smallest known free-living organisms, is a frequent cause of pneumonia with relatively mild symptoms in young adults.

### *Legionella pneumophila*

*Legionella pneumophila* is an important cause of serious pneumonia occurring in epidemics as well as in isolated, sporadic cases. It is estimated to account for up to 10% of cases of CAP, and primarily affects older individuals and those with prior impairment of respiratory defense mechanisms. It also occurs as a sporadic cause of nosocomial pneumonia and is linked to the presence of the organisms in facility water supplies.

*L. pneumophila* was first identified as the cause of a mysterious outbreak of pneumonia in 1976 affecting American Legion members at a convention in Philadelphia. Thus, pneumonia due to *L. pneumophila* is often labeled "Legionnaires disease." Since then, it has been retrospectively recognized as the cause of several prior outbreaks of unexplained pneumonia. Although the organism is technically a Gram-negative bacillus, it is poorly visualized by conventional staining methods and is not seen on Gram stain.

Clinically, patients present with fever, cough, and shortness of breath, and can be quite ill. Extrapulmonary manifestations, including gastrointestinal symptoms, hyponatremia, and liver function test abnormalities, are common and can be a clue to etiology. Radiographically, patchy unilobar infiltrates are typical early during the illness, often progressing to multilobar consolidations. Diagnosis is usually accomplished through PCR testing of respiratory secretions (sputum or bronchoalveolar lavage). Urine antigen testing is widely available and highly specific, but only detects *L. pneumophila* serotype 1. Although this serotype causes most infections worldwide, some regions (especially New Zealand and Australia) have a high prevalence of other serotypes. Drugs of choice for treatment are levofloxacin or azithromycin. Notably, β-lactam antibiotics are not effective in treating this organism.

### *Chlamydophila pneumoniae*

*Chlamydophila pneumoniae* is an obligate intracellular organism that is recognized in epidemiologic studies as a cause of CAP. The reported incidence ranges from less than 1% to 20%, depending on the series and methods of diagnosis. *C. pneumoniae* typically causes a mild illness. There are no distinguishing clinical and radiographic features, and the organism is not readily cultured. Diagnosis is rarely made clinically because most patients are treated empirically for CAP without specific testing. In patients who are more severely ill, diagnosis with PCR testing of respiratory secretions can be pursued. Serologic studies can provide retrospective diagnosis, but are not useful for acute diagnosis.

Many other types of bacteria can cause pneumonia. Because all of them cannot be covered in this chapter, the interested reader should consult some of the more detailed publications listed in the Suggested Readings at the end of this chapter.

## Viruses

Although viruses are extremely common causes of upper respiratory tract infections, previously they were diagnosed relatively infrequently as a cause of frank pneumonia. Here we focus on two viruses which are common and can be associated with severe disease: SARS-CoV-2 and influenza virus.

### SARS-CoV-2/COVID-19

In late 2019, SARS-CoV-2, a novel viral pathogen that ultimately resulted in a devastating and wide-reaching global viral pandemic, was identified. SARS CoV-2, the virus that causes COVID-19, is a highly contagious member of the coronavirus family. Since its initial identification, SARS-CoV-2 has undergone a number of mutations, leading to variants that have been called Alpha, Beta, Gamma, Delta, and most recently (as of 2022) Omicron. These variants differ to some extent in the likelihood of transmissibility as well as the risk of severe disease.

The spectrum of disease due to SARS-CoV-2 runs from completely asymptomatic to progressive and fatal lung disease. Risk factors for severe disease include older age, obesity, and other comorbid medical conditions. Population data indicated that COVID-19 has disproportionately affected Black, Hispanic, and South Asian individuals in the United States and the United Kingdom. This appears to be related to underlying disparities in the social determinants of health, as early studies which control for these determinants do not find a discrepancy. Although SARS-CoV-2 infection is also associated with many less frequent extrapulmonary manifestations, most notably kidney and cardiac dysfunction and a hypercoagulable state, this discussion will focus solely on the pulmonary manifestations.

SARS-CoV-2 primarily infects cells when the viral spike protein attaches to the angiotensin-converting enzyme-2 (ACE-2) receptor. ACE-2 is widely distributed in epithelial and endothelial cells throughout the body, including in the respiratory tract (in nasal mucosa, bronchi, and particularly type II pneumocytes and macrophages). When COVID-19 pneumonia was first recognized, many clinicians noted that patients infected with COVID-19 had much more prominent hypoxemia and relatively more compliant lungs than typical patients who developed the acute respiratory distress syndrome (ARDS, see Chapter 29). Research has subsequently shown that SARS-CoV-2 caused direct injury by infecting type II pneumocytes and pulmonary vascular endothelial cells at the onset of disease, and hypoxic vasoconstriction (HPVC) appears to be severely impaired. The direct injury to the lung parenchyma and vasculature combined with the abnormal HPVC leads to hypoxemia because of severe $\dot{V}/\dot{Q}$ mismatch early in the disease before the chest x-ray becomes densely consolidated and the lungs become markedly less compliant. Because surfactant is made by the type II pneumocyte, surfactant dysfunction and scattered microatelectasis likely also play an early role.

Patients with COVID-19 pneumonia typically present with fever, cough, shortness of breath, and bilateral pulmonary infiltrates. Loss of smell and/or taste was common with earlier variants but appears to be less frequent with the Omicron variant. A typical chest x-ray in early COVID-19 pneumonia shows diffuse, hazy, nonlobar infiltrates (Fig. 24.4). The diagnosis is confirmed by nasal swab PCR or antigen testing.

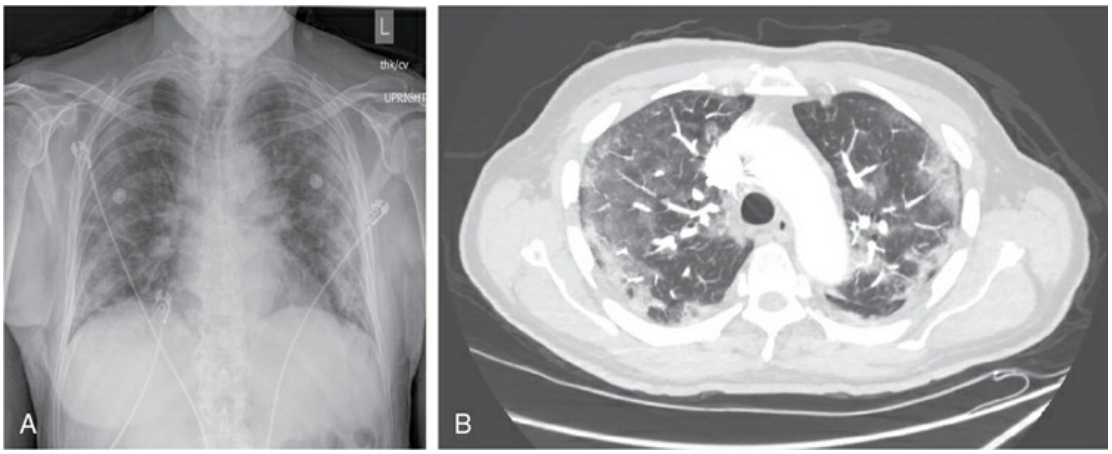


**FIGURE 24.4** Posteroanterior chest radiograph **(A)** and chest CT scan (**B**) of a patient with COVID-19 pneumonia showing a typical pattern of bilateral, diffuse, and predominantly peripheral ground-glass opacities with some areas of more dense consolidation.
*Source:* (Courtesy of Dr. Laura Avery.)

Treatment depends on the timing and severity of disease. Although the information provided here is current as of 2022, it will likely change as our understanding of the disease is continually evolving. Younger, healthy individuals usually require no treatment. In individuals at risk for severe disease, early treatment with monoclonal antibodies directed at SARS-CoV-2 or oral antiviral drugs (combination therapy with nirmatrelvir-ritonavir) are indicated. The antiviral remdesivir is also an option, but is only available intravenously and thus is typically reserved for hospitalized patients.

In severely ill patients, it is recognized that the host inflammatory and cytokine response in addition to the virus itself is responsible for many of the manifestations. Thus, for patients hospitalized with COVID-19, medications which target the inflammatory and/or cytokine response are often used, including dexamethasone (a corticosteroid), tocilizumab (an antibody against the IL-6 receptor), and baricitinib (a JAK protein inhibitor).

Vaccines against SARS-CoV-2 are available and provide marked protection from severe disease. These vaccines are indicated and approved for all individuals aged 6 months and older. Notably, some of these vaccines have used a novel approach involving mRNA that encodes for a target protein on the virus. Administration of the specific mRNA leads to the individual producing and developing an immune response to the target protein.

Several other coronaviruses have caused much more limited epidemics of severe viral pneumonia in recent years. An outbreak of a highly contagious and highly lethal pneumonia was reported in 2003 in East Asia and Canada. The outbreak, termed *severe acute respiratory syndrome* (SARS), was attributed to a novel coronavirus (SARS-CoV) that may have evolved from a type normally found in the civet (a weasel-like mammal found in Chinese markets). In 2012, *Middle East respiratory syndrome* (MERS) coronavirus (MERS-CoV) caused an outbreak of severe pneumonia with a nearly 75% mortality rate. The causative agent is related to a virus that normally infects camels, and

most cases have been traced to initial exposures in the Arabian Peninsula.

### Influenza

Two types of influenza virus cause significant respiratory disease, influenza A and influenza B. Epidemics of influenza occur almost every year, and the severity depends on the viral antigenic characteristics, which change regularly. The most notable pandemic in the modern era was the 1918 influenza pandemic, which is estimated to have resulted in 50 to 100 million deaths, or 3% to 5% of the world's population. Since the onset of the COVID-19 pandemic, the incidence of influenza infections has decreased, likely due to changes in behavior such as mask-wearing and social distancing, which protect from both SARS-CoV-2 and influenza.

Clinically, influenza is usually characterized by the abrupt onset of fever, chills, and malaise. Muscle aches (myalgias) are prominent. Most patients do not develop pneumonia; however, when present, pneumonia may be a primary influenza pneumonia or due to secondary bacterial infection. Primary influenza appears as diffuse bilateral reticular or reticulonodular infiltrates. The presence of more lobar consolidations should raise concern for complicating bacterial infection, especially with *S. pneumoniae* or *S. aureus*. Diagnosis is made by PCR testing of nasopharyngeal specimens.

Oseltamivir is the preferred treatment for influenza and is shown to be effective in reducing the duration and severity of disease if given within 48 hours of symptom onset. Several types of influenza vaccines are formulated every year according to the prevalent and anticipated strains, and annual vaccination is recommended for all adults and children aged 6 months and older.

### Other viruses

Outbreaks of pneumonia caused by adenovirus also are well described, particularly among military recruits. *Hantavirus*, a relatively rare cause of a fulminant and often lethal pneumonia, was first described in the southwest United States, but cases in other locations have also been recognized. Related viruses are found in rodents and were previously described as a cause of fever, hemorrhage, and acute renal failure in other parts of the world.

## Intrathoracic complications of pneumonia

As part of the discussion of pneumonia, two specific intrathoracic complications of pneumonia—lung abscess and empyema—are briefly considered because they represent important clinical sequelae.

### Lung abscess

A lung abscess, like an abscess elsewhere, represents a localized collection of pus. In the lung, abscesses generally result from tissue destruction complicating a pneumonia. The abscess contents are primarily neutrophils, often with collections of bacterial organisms. When antibiotics have been administered, organisms may no longer be culturable from the abscess cavity.

Etiologic agents associated with formation of a lung abscess are generally those

bacteria that cause significant tissue necrosis. Most commonly, anaerobic organisms are responsible, suggesting that aspiration of oropharyngeal contents is the predisposing event. However, aerobic organisms, such as *Staphylococcus* or enteric Gram-negative rods, can also cause significant tissue destruction with cavitation of a region of lung parenchyma and abscess formation (Fig. 24.5). Right-sided endocarditis can be associated with multiple lung abscesses, as small infectious particles are released into the blood from the infected valve and lodge in the pulmonary parenchyma.

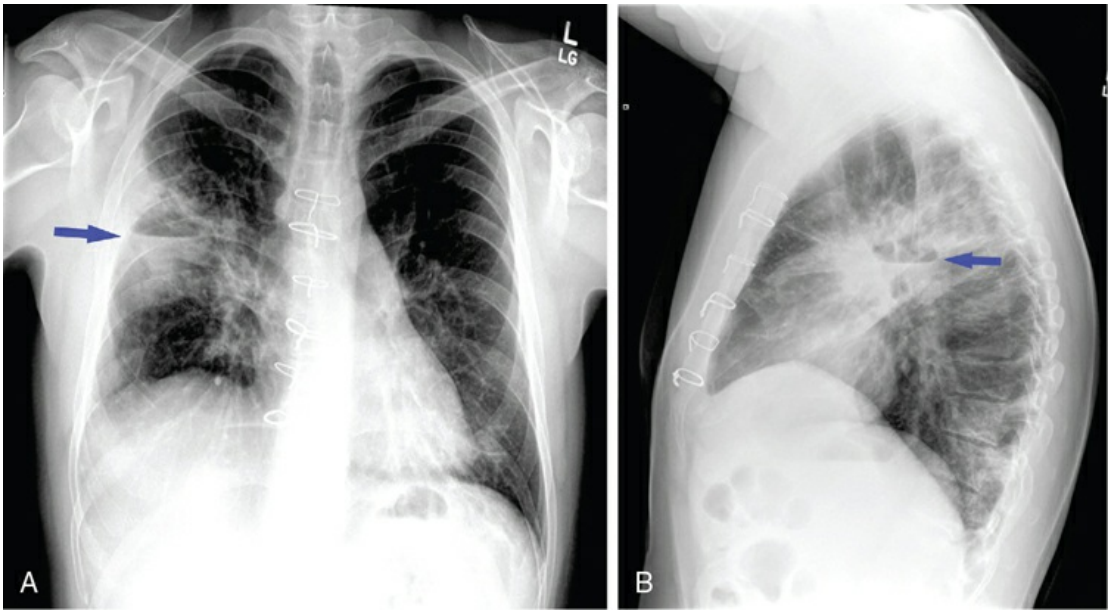


**FIGURE 24.5** Posteroanterior (**A**) and lateral (**B**) chest radiographs showing a cavitary lung abscess with an air-fluid level (arrows) in the right upper lobe. Note the sternal wires. The patient had a history of intravenous drug use and had undergone tricuspid valve surgery for endocarditis. *Source:* (Courtesy of Dr. Laura Avery.)

Anaerobic bacteria are the agents most frequently responsible for lung abscesses.

Treatment of a lung abscess involves antibiotic therapy, given for longer than for an uncomplicated pneumonia. Although abscesses elsewhere in the body are drained by surgical incision or catheter placement, lung abscesses generally drain through the tracheobronchial tree, and surgical intervention or placement of a drainage catheter is needed only rarely.

## Empyema

When pneumonia extends to the pleural surface, the inflammatory process eventually may lead to empyema, another intrathoracic complication of pneumonia. The term

*empyema* (or more properly, *empyema thoracis*) refers to pus in the pleural space. In its most florid form, an empyema represents thick, creamy, or yellow fluid within the pleural space. The fluid is comprised of leukocytes, primarily neutrophils, often accompanied by bacterial organisms. With a true empyema or often even with other grossly inflammatory pleural effusions accompanying pneumonia (parapneumonic effusions), pleural inflammation can result in formation of localized pockets of fluid or substantial scarring and subsequent limited mobility of the underlying lung.

Several different bacterial organisms may be associated with development of an empyema. Anaerobes are particularly common, but *S. pneumoniae*, *S. aureus,* and other aerobic organisms are also potential causes. After an empyema has been documented, usually by thoracentesis and sampling of pleural fluid, drainage of the fluid is required. In many cases thoracoscopic surgery is performed to completely drain the pleural space. Alternative techniques are used in some specific clinical situations and can include open surgical procedures or placement of large-bore chest tubes with repeated instillation of fibrinolytic agents (e.g., alteplase and DNase) into the pleural space.

Adequate drainage of pleural fluid is critical in the management of empyema.

## Respiratory infections associated with bioterrorism

The magnitude of society's concerns about bioterrorism has increased abruptly in recent years. In 2001, recognition of cases of both cutaneous and inhalational anthrax contracted by handling mail containing anthrax spores in the United States illustrated all too vividly not only the danger posed by some otherwise uncommon biological agents but also the widespread fear elicited by the threat of bioterrorism. This section briefly discusses three biological agents with life-threatening effects that can be mediated by infection involving the respiratory system: *Bacillus anthracis, Y. pestis,* and *F. tularensis*.

### Anthrax

*B. anthracis*, a Gram-positive spore-forming rod found in soil, causes infection in farm stock and wild animals. Human cases occur due to exposure to infected animals, contaminated animal products, and inhalation of aerosolized spores. The virulence and potential lethality of the organism are related to elaboration of three polypeptides that come together to form two toxins, lethal factor and edema factor. In early infection, these toxins interfere with innate immune cells, especially neutrophils, macrophages, and dendritic cells. In later disseminated disease, the toxins are widespread and intracellular, leading to circulatory collapse. Whereas cutaneous anthrax results from spores introduced through a break in the skin (including from contaminated needles used by injection drug users), inhalational anthrax follows the inhalation of spores into alveolar spaces and the transport of viable spores via lymphatics to the mediastinal lymph nodes. Germination of the spores in the mediastinum is associated with toxin release and a hemorrhagic lymphadenitis and mediastinitis.

Clinically, patients with inhalational anthrax typically present with a flulike illness with symptoms of mild fever, myalgias, nonproductive cough, malaise, and chest discomfort. Several days later, they become acutely and severely ill with fever, dyspnea,

cyanosis, septic shock, and often findings of meningitis. The most prominent abnormality on chest radiograph is mediastinal widening from hemorrhagic lymphadenitis and mediastinitis. Because viable spores are present in the mediastinum and not the alveoli, anthrax is generally not transmitted from person to person via droplet nuclei. Treatment must be instituted urgently and includes bactericidal antibiotics as well as antitoxin. Despite treatment with antibiotics (typically ciprofloxacin, levofloxacin, or doxycycline), mortality is extremely high after the onset of clinical illness due to the persistent effects of intracellular anthrax toxins. Public health guidelines have focused on antibiotic prophylaxis to prevent inhalational anthrax following confirmed or suspected exposure to aerosolized spores. An available anthrax vaccine requires a complex administration schedule and annual booster injections, and is recommended for individuals at high risk for exposure (e.g., anthrax investigation laboratory workers, veterinarians, and some military personnel).

Inhalational anthrax characteristically produces a widened mediastinum on chest radiograph. Treatment includes the administration of both antibiotics and antitoxins.

## Plague

Despite its association with epidemics of devastating proportions, such as the Black Death of the 14th century, plague is now an uncommon disease. However, plague is one of the conditions thought to be of major concern as a possible weapon of bioterrorism. The causative organism, *Y. pestis*, a Gram-negative rod transmitted by fleas from rodents to humans, is endemic in many parts of the world, including southwestern and western United States, and focused areas in Africa, Asia, and South America. The three most endemic countries are the Democratic Republic of Congo, Madagascar, and Peru. Infection through the skin disseminates to regional lymph nodes, leading to the clinical syndrome of *bubonic plague*. Infection of the lungs *(pneumonic plague)* can occur either secondary to bacteremic spread from skin or lymph nodes or via airborne transmission of the organism from person to person. Pneumonic plague is highly contagious through aerosolization of the organisms during cough.

Clinically, patients become acutely ill with high fever, malaise, myalgias, rigors, dyspnea, and cyanosis. Chest radiography shows widespread bronchopneumonia that can have regions of diffuse homogeneous consolidation resembling ARDS. Mortality is high unless antibiotic treatment is initiated soon after the onset of symptoms. First-line agents are an aminoglycoside (streptomycin, gentamicin), a fluoroquinolone, or doxycycline.

## Tularemia

Tularemia is caused by *F. tularensis*, a Gram-negative coccobacillary organism that infects small mammals and is transmitted to humans by insect vectors (e.g., ticks), exposure to contaminated animals, or the inhalation of aerosolized organisms. Although several different clinical presentations may occur with tularemia, depending on the mechanism of transmission and the site of entry, pulmonary tularemia secondary to inhalation of *F. tularensis* is the primary concern for the use of this organism as a bioterrorist weapon.

Pulmonary tularemia is characterized by patchy inflammation and consolidation of the lung parenchyma, sometimes with the enlargement of hilar lymph nodes and the development of pleural effusions. Patients develop fever, chills, malaise, and headache. Chest radiography shows patchy consolidation that may be accompanied by hilar lymphadenopathy and pleural effusions. Oral fluoroquinolones are the treatment of choice for mild to moderate infections, whereas an aminoglycoside (streptomycin or gentamicin) is indicated for severe infections. With appropriate treatment, cure is achieved in more than 90% of patients, even in severe disease. Mortality is estimated to be approximately 35% without treatment.

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# 25: Tuberculosis and nontuberculous mycobacteria

OUTLINE



Throughout the centuries, few diseases have claimed so many lives, caused so much morbidity, and been so dreaded as tuberculosis. At the beginning of the 20th century, tuberculosis was the single most common cause of death in the United States, and more than 80% of the population was infected before the age of 20 years. At the beginning of the 21st century, tuberculosis provided a stark example of the disparity in health resources between industrialized nations and the developing world. In countries with widely available healthcare, such as in North America and Europe, few diseases have declined so greatly in frequency and mortality as tuberculosis. Two main factors have been responsible: overall improvement in living conditions and the development of effective antituberculous chemotherapy, which transformed tuberculosis into a routinely curable disease. However, in countries with fewer resources, the disease, especially with drug-resistant tuberculosis, continues to be a health crisis, often striking the young, most productive members of society.

Now more than 140 years since identification of the tubercle bacillus by Robert Koch in 1882, we must not become complacent about the disease. It is estimated that approximately 25% of the world's current population, or over 2 billion people, have been infected (i.e., have either latent or active infection) with the tubercle bacillus. According to the World Health Organization (WHO), the global incidence of tuberculosis peaked in

2003 with a slow decline until 2019. In 2020, the COVID-19 pandemic led to decreased access to healthcare in under-resourced countries, resulting in a drop in reported newly diagnosed cases of tuberculosis. However, the reduced access was associated with an increase in tuberculosis deaths (1.5 million deaths worldwide). This was the first increase in annual deaths worldwide due to tuberculosis since 2003.

Tuberculosis occurs in every part of the world; however, the incidence varies globally, with the majority of cases of active tuberculosis occurring in resource-limited countries. Poverty, HIV infection, and the presence of drug-resistant organisms are major factors in the variation. In 2020, the largest number of new tuberculosis cases occurred in the WHO South-East Asian Region, with 43% of new cases, followed by the WHO African Region, with 25% of new cases, and the WHO Western Pacific Region, with 18%. In the United States, tuberculosis remains an important public health problem, even though in 2020 the CDC reported the lowest number of cases on record. As with previous years, new cases were more common in individuals born outside the United States from areas with a higher prevalence of tuberculosis (72%). The COVID-19 pandemic probably influenced these numbers, and it is uncertain if this trend will continue.

## Etiology and pathogenesis

The etiologic agent that causes tuberculosis, *Mycobacterium tuberculosis*, is an aerobic rod-shaped bacterium. A distinctive property of the tubercle bacillus is its ability to retain certain stains even after exposure to acid (discussed under Diagnostic Approach); thus, mycobacteria are said to be *acid-fast*.

Transmission of the disease occurs via small aerosol droplets, generally from 1 to 5 μm in size, that contain the microorganism. The source of these droplets is an individual with tuberculosis who harbors the organism, often excreting tubercle bacilli in the sputum or in small droplets produced during commonplace activities such as speaking, coughing, singing, and laughing. Most commonly, transmission occurs with relatively close contact, often between related individuals or others living in the same household. The disease is not transmitted by fomites (e.g., articles of clothing, eating utensils); direct inhalation of aerosolized droplets is the exclusive mode of spread.

Transmission of tuberculosis is by inhalation of small aerosol droplets containing the organism.

When droplets containing mycobacteria are inhaled, reach the alveoli, and are not immediately cleared by innate host defenses, a small focus of *primary infection* develops, consisting of the organisms and an inflammatory process mounted by the host. Alveolar macrophages represent the initial primary defense against organisms, and they are a particularly important component of the resulting inflammatory response. Tubercle bacilli proliferate inside alveolar macrophages, which release cytokines and chemokines that result in recruitment of more macrophages and other inflammatory cells. If the infection is not controlled, organisms spread via lymphatic vessels to draining hilar lymph nodes as well as via the bloodstream to distant organs and other regions of the lung, particularly the apices. Even though lymphatic and hematogenous spread may occur, the host immune defense mechanisms (in the lung and elsewhere)

control and limit the primary infection in more than 90% of cases. An important component of the body's acquired defense against *M. tuberculosis* is the development of cell-mediated immunity (delayed hypersensitivity) against the mycobacterial organisms. This sensitization and development of a cell-mediated immune response typically occur within several weeks of initial infection.

The patient often is unaware of the primary infection, although a mild, self-limited febrile illness may be reported. The only residua left by the organism are those related to the host's response to the bacillus: either the local tissue response or evidence that the host has become sensitized to the tubercle bacillus, which is evidenced by a positive delayed hypersensitivity skin test reaction or interferon (IFN)-$\gamma$ release assay. In a small minority of patients, probably 5% or fewer, defense mechanisms are unable to control the primary infection, and clinically apparent primary tuberculosis results. This is most common in the setting of immunocompromise, treatment with immunosuppressive medications, alcoholism, HIV/AIDS, malnutrition, or malignancy.

Despite apparent control of the primary infection, tubercle bacilli may persist in the host. A small number of organisms often remain in a dormant or latent state, not proliferating or causing any apparent active disease, but still potentially viable. These patients are considered to have *latent infection*. Most patients with latent infection will never develop clinically active tuberculosis. However, in some patients, the delicate balance between the organism and the host defense mechanisms eventually breaks down, sometimes after many years, and a dormant focus of infection becomes active. Patients with active disease occurring at a time removed from the primary infection are said to have *reactivation tuberculosis*. Over the course of a lifetime, it is estimated that approximately 10% of individuals with a normal immune system who have been infected with *M. tuberculosis* (and have not received treatment for latent tuberculosis infection to eradicate dormant organisms) will develop active disease. The risk of developing active tuberculosis is greatest within the first 2 years after the initial infection; approximately one-half of patients who develop active disease do so within this time frame. The other half who develop active disease do so at some later point in life. These estimates of risk apply to patients with normal host defenses. The risk of developing active tuberculosis is dramatically higher in patients with defects in host immunity such as advanced HIV infection, chronic corticosteroid use, and treatment with tumor necrosis factor (TNF)-α receptor blockers.

For both primary and reactivation disease, the lungs are most commonly affected. However, with either type of disease, other organs may be involved due to hematogenous spread during the primary phase of the infection. When the host immune response is overwhelmed, whether due to primary or reactivation disease, extensive hematogenous spread of organisms leads to disseminated disease known as *miliary tuberculosis* (Fig. 25.1).

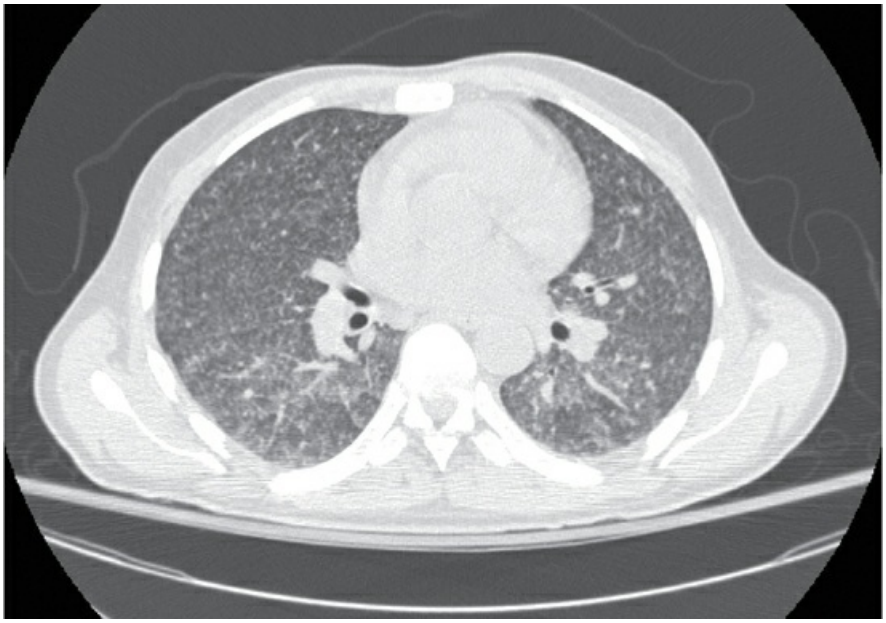

**FIGURE 25.1** Chest CT image from a patient with miliary tuberculosis. There are countless small nodules resulting from hematogenous dissemination of *M. tuberculosis*. *Source:* (Courtesy Dr. Seth Kligerman.)

The majority of active tuberculosis cases involve reactivation of a previously dormant focus within the lungs.

## Definitions

On the basis of our understanding of disease pathogenesis, a few terms are worth clarifying. First is the distinction between tuberculous infection and tuberculous disease. *Tuberculous infection* (or *latent tuberculous infection*) is defined by a positive tuberculin skin test or a positive blood IFN-γ release assay (IGRA; described under Diagnostic Approach) but no clinical evidence of active disease. Patients with latent tuberculous infection have been infected by the organism, but the initial infection was controlled by the body's host defense mechanisms and subsequently can be traced only by a positive delayed hypersensitivity skin test or positive IGRA response. The small number of remaining organisms are in a dormant or latent state, but do pose a risk for reactivation at a later time, especially with any impairment in the host's cellular immunity. *Tuberculous disease* (or *active tuberculosis*), on the other hand, is defined by the presence of clinically active disease in one or more organ systems, ideally with confirmation of the diagnosis by isolation of *M. tuberculosis*.

Other terms worth defining are those that describe different subsets of tuberculous disease. Most common are the terms *primary* and *reactivation tuberculosis*, which refer to disease following the initial exposure and disease that reactivates after a period of latency, respectively. The term *progressive primary tuberculosis* reflects primary

disease that has not been controlled by host defense mechanisms and has continued to be active beyond the point at which delayed hypersensitivity has developed. Typically, cellular immunity develops 2 to 10 weeks after the initial infection, and continuing active disease beyond this time has many of the features of reactivation tuberculosis. The term *postprimary tuberculosis* refers to disease beyond the initial primary infection. Although this term usually refers to reactivation disease, it sometimes includes cases of progressive primary tuberculosis.

The term *reinfection tuberculosis* refers to disease in a previously infected person that results from an infection due to exposure to new organisms rather than from reactivation of dormant tubercle bacilli. This type of infection traditionally has been considered uncommon. It is believed that individuals with prior infection with tuberculosis who manifest delayed hypersensitivity to the organism are relatively resistant to exogenous reinfection from another source. However, studies using DNA fingerprinting techniques suggest that reinfection with another organism is more common than previously thought, particularly in highly endemic regions and in patients who are infected with HIV.

## Pathology

The pathologic features of pulmonary tuberculosis vary according to the stage of infection. The primary infection in the lung consists of the organisms and an inflammatory response involving alveolar macrophages, neutrophils, and monocyte-derived macrophages in the involved region of parenchyma. If the inflammatory response does not control the infection, the organisms spread to regional lymph nodes, leading to ipsilateral hilar and mediastinal lymphadenopathy. The combination of the primary area in the lung (the *Ghon lesion*) and involved lymph nodes is termed a *Ghon complex*.

When delayed hypersensitivity is present, either weeks after the primary infection or during a period of reactivation disease, a different pathologic pattern emerges. The hallmarks are the presence of (1) granulomas (collections of activated blood- and tissue-derived macrophages termed *epithelioid histiocytes* surrounded by a rim of lymphocytes), and (2) caseous necrosis (foci of necrosis and softening at the center of a granuloma). Within the region of caseous necrosis, the contents can liquefy and slough, leaving behind a cavity, another hallmark of tuberculosis. Other microscopic features of the granulomas include multinucleated giant cells and the frequent presence of visible tubercle bacilli when proper stains are employed.

After the development of delayed hypersensitivity, the pathologic hallmarks of tuberculosis are granulomas and caseous necrosis, often with cavity formation.

A process of healing tends to occur at the sites of disease. Fibrosis or scarring ensues, often associated with contraction of the affected area and the deposition of calcium. When the Ghon complex undergoes progressive fibrosis and calcification, it is referred to as a *Ranke complex*. With severe disease, extensive destruction of lung tissue results from large areas of inflammation, granuloma formation, caseous necrosis, and cavitation, along with fibrosis, contraction, and foci of calcification. Importantly, much

of the destruction that occurs during tuberculosis requires an intact cellular immune system and appears to be due to the host inflammatory response attempting to contain the infection. Thus, patients with advanced HIV disease and other marked immune defects often have an atypical presentation in which the organism is widely disseminated but there is little evidence of cavitation and fibrosis.

Tuberculosis can spread hematogenously, and dissemination of organisms through the bloodstream at the time of primary infection is probably the rule rather than the exception. When defense mechanisms break down, disease can become apparent at other sites (e.g., liver, kidney, adrenal glands, bones, central nervous system). Spread also occurs to other regions of the lung, either due to hematogenous seeding during the primary infection or because of the spilling of infected secretions or caseous material into the bronchi and other regions of the lung.

Within the lung, characteristic locations for reactivation tuberculosis are the apical regions of the upper lobes and, to a lesser extent, the superior segment of the lower lobes. It is believed these are not sites of primary infection but rather the favored location for implantation of organisms after hematogenous spread. These regions have a relatively high ventilation-perfusion ratio, resulting in a high $P_{O_2}$ and making them particularly suitable for survival of the aerobic tubercle bacilli.

## Pathophysiology

Most of the clinical features of pulmonary tuberculosis can be attributed to one of two aspects of the disease: the presence of a poorly controlled chronic infection, or a chronic destructive process within the lung parenchyma. A variety of other manifestations result from extrapulmonary spread of tuberculosis, but these consequences are not considered here.

Chronic tuberculosis infection within the lung is associated with systemic manifestations of widespread inflammation. As implied by the term “consumption,” which was so frequently used in the past, tuberculosis is a disease in which systemic manifestations, such as fatigue, weight loss, cachexia, and loss of appetite, are prominent features. These and other systemic effects of tuberculosis are discussed in the section on clinical manifestations.

The chronic destructive process involving the pulmonary parenchyma entails progressive scarring and loss of lung tissue. However, respiratory function is generally preserved more than would be expected, perhaps because the disease often is limited to the apical and posterior regions of the upper lobes as well as to the superior segment of the lower lobes. Oxygenation also tends to be surprisingly preserved, presumably because ventilation and perfusion are destroyed simultaneously in the affected lung. Consequently, ventilation-perfusion mismatch is not nearly so great as in many other parenchymal and airway diseases.

## Clinical manifestations

There is an important distinction—and important clinical differences—between latent tuberculous infection and tuberculous disease (active tuberculosis). Latent tuberculous infection is the consequence of primary exposure, by which the bacilli have become

established in the patient; however, host defense mechanisms have prevented any clinically apparent disease. Specific immunity to the tubercle bacillus can be demonstrated by a positive reaction to a skin test for delayed hypersensitivity or a positive IGRA; otherwise, there is no evidence for proliferation of bacteria or for tissue involvement by disease. Patients with infection but without disease are not contagious. In contrast, tuberculous disease is associated with proliferation of organisms, accompanied by a tissue response and generally (although not always) clinical problems of which the patient is aware.

Patients with pulmonary tuberculosis can manifest (1) systemic symptoms, (2) symptoms referable to the respiratory tract, or (3) an abnormal finding on chest radiograph but no clinical symptoms. When symptoms occur, they are generally insidious or subacute rather than acute in onset.

Systemic symptoms are often relatively nonspecific: weight loss, anorexia, fatigue, low-grade fever, and night sweats. The most common symptoms resulting from pulmonary involvement are cough, sputum production, and hemoptysis; chest pain occasionally is present. Many patients have neither systemic nor pulmonary symptoms, and come to the attention of a physician because of an abnormal finding on chest radiograph, which is often performed for an unrelated reason.

Patients with extrapulmonary involvement frequently have pulmonary tuberculosis as well, but occasional cases are limited to an extrapulmonary site. The pericardium, pleura, kidney, peritoneum, adrenal glands, bones, and central nervous system each may be involved, with symptoms resulting from the organ or region affected. With miliary tuberculosis, the disease is disseminated, and patients usually are systemically quite ill.

Physical examination of the patient with pulmonary tuberculosis may show the ravages of a chronic infection with evidence of wasting and weight loss. This presentation is uncommon in patients with access to treatment, but it is frequently seen in under-resourced settings. Findings on chest examination tend to be relatively insignificant, although sometimes crackles or rales are heard over affected areas. If a tuberculous pleural effusion is present, the physical findings characteristic of an effusion may be found.

Common presenting problems with tuberculosis:

1. Systemic symptoms: fatigue, weight loss, fever, night sweats
2. Pulmonary symptoms: cough, sputum production, hemoptysis
3. Abnormal chest radiographic findings

## Diagnostic approach

The tuberculin skin test, a commonly used diagnostic tool, documents tuberculous infection rather than active disease. A small amount of protein derived from the tubercle bacillus (purified protein derivative [PPD]) is injected intradermally on the inner surface of the forearm. Individuals who have been infected by *M. tuberculosis* and have acquired cellular immunity to the organism demonstrate a positive test reaction, seen as induration or swelling at the site of injection after 48 to 72 hours. The criteria for

determining a positive skin test reaction vary according to the clinical setting, specifically the presence or absence of immunosuppression and/or epidemiologic risk factors affecting the likelihood of previous exposure to tuberculosis. Importantly, the test does not distinguish between individuals who have active tuberculosis and those who merely have acquired delayed hypersensitivity from previous infection. However, because reactivation tuberculosis occurs in patients with previous tuberculous infection, a positive skin test reaction does identify individuals at higher risk for the subsequent development of active disease.

As with most diagnostic tests, false-negative results can occur with the tuberculin skin test. Faulty administration, a less bioactive batch of skin-testing material, and underlying diseases that depress cellular immunity, such as HIV or even advanced tuberculosis itself, are several causes of false-negative skin test reactions. On the other hand, not all patients who react to tuberculoprotein have been exposed to *M. tuberculosis*. Infection with nontuberculous mycobacteria, often called *atypical mycobacteria*, is sometimes associated with a positive or a borderline positive skin test reaction to PPD.

The IGRA, a blood test, is an alternative to skin testing. Blood is drawn, and the patient's T cells are incubated with *M. tuberculosis* antigens. Cells from previously sensitized individuals will release IFN-$\gamma$ in response to the antigens, and the IFN-$\gamma$ is detected by an enzyme-linked assay. Tuberculin skin testing does not require laboratory facilities and globally remains more commonly performed than IFN-$\gamma$ assays. However, because the blood tests do not require the patient to return for an additional office visit for interpretation, IGRA has the advantages of fewer patients lost to follow-up. These assays are unaffected by prior bacille Calmette-Guérin (BCG) vaccination (see section on principles of therapy) or exposure to most atypical mycobacteria, but false-positive results still can occur in individuals exposed to or infected with *Mycobacterium marinum* and *Mycobacterium kansasii*.

For the diagnosis of tuberculosis (i.e., actual tuberculous disease), an important initial diagnostic tool is the chest radiograph. In primary disease, the chest radiograph may show a nonspecific infiltrate, often—but certainly not exclusively—in the lower lobes (in contrast to the upper lobe predominance of reactivation disease). Hilar (and sometimes paratracheal) lymph node enlargement may be present, reflecting involvement of the draining node by the organism and by the primary infection. Pleural involvement may be seen, with the development of a pleural effusion.

Common features of the chest radiograph in primary tuberculosis:

1. Nonspecific infiltrate (often lower lobe)
2. Hilar (and paratracheal) node enlargement
3. Pleural effusion

When the primary disease heals, the chest radiograph frequently shows some residua of the healing process. Most common are small, calcified lesions within the pulmonary parenchyma, reflecting a collection of calcified granulomas. Calcification within hilar or paratracheal lymph nodes may be seen. The radiographic terminology can be confusing as it is commonly used. The term *granuloma* is a pathologic term that describes a

microscopic collection of lymphocytes and histiocytes. A calcified nodule on a chest radiograph is frequently called a *calcified granuloma*, but it really represents a small mass of numerous microscopic granulomas.

With reactivation tuberculosis, the most common sites of disease are the apical and posterior segments of the upper lobes and, to a lesser extent, the superior segment of the lower lobes. A variety of patterns can be seen: infiltrates, cavities, nodules, and scarring and contraction (Fig. 25.2). The presence of abnormal findings on a chest radiograph does not necessarily indicate active disease. The disease may be old, stable, and currently inactive, and it is difficult, if not impossible, to gauge activity solely based on radiographic appearance.

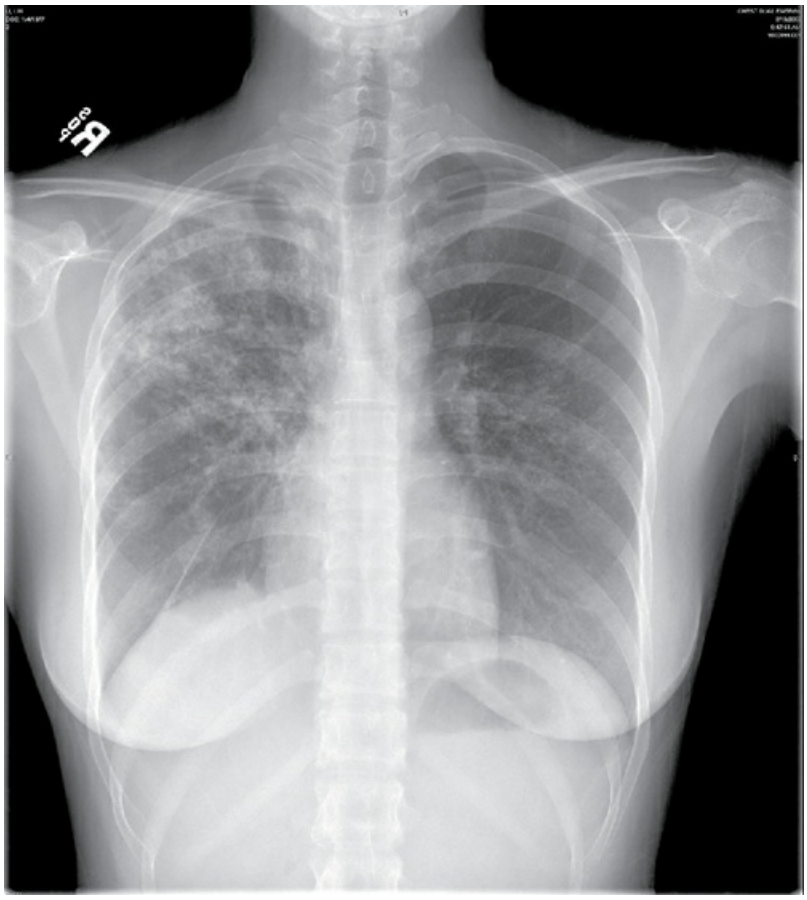

**FIGURE 25.2** Chest radiograph of patient with reactivation tuberculosis. Note infiltrates in the right lung, primarily in the right upper lobe.

Radiographic location of reactivation tuberculosis: most commonly apical and posterior segments of upper lobe(s), superior segment of lower lobe(s).

The definitive diagnosis of tuberculosis rests on culturing the organism from either

secretions (e.g., sputum) or tissue, but the organisms are slow growing, with up to 6 weeks required for growth and final identification. Culture of the organism is important for confirmation of the diagnosis and for testing sensitivity to antituberculous drugs, particularly considering rising resistance to some of the commonly used antituberculous agents. Molecular genetic testing now permits earlier identification of certain types of drug resistance than do traditional methods of culture and sensitivity testing.

Another extremely useful procedure that can provide results almost immediately is staining of material obtained from the tracheobronchial tree. The specimens obtained can be sputum, expectorated either spontaneously or following inhalation of an irritating aerosol (sputum induction), or washings or biopsy samples obtained by flexible bronchoscopy. Although they stain positive with Gram stain, a hallmark of mycobacterial organisms is their ability to retain certain dyes even after exposure to acid. Their acid-fast property is generally demonstrated with Ziehl-Neelsen or Kinyoun stain, or with a fluorescent stain that uses auramine-rhodamine. The finding of a single acid-fast bacillus from sputum or tracheobronchial washings is clinically significant in the majority of cases. One qualification is that nontuberculous mycobacteria, which either cause less severe disease or are present as colonizing organisms or contaminants, have the same staining properties. Therefore, it is critical to determine whether acid-fast bacilli seen on smear represent *M. tuberculosis* or nontuberculous mycobacteria. This distinction can be made either by certain growth characteristics on culture or molecular biologic techniques.

For a single tubercle bacillus to be seen on smear, large numbers of organisms must be present in the lungs. Thus, even in the setting of active disease, if relatively few organisms are present in the lungs, the smear results may be negative, although culture results will often be positive. In general, the infectiousness of a patient with tuberculosis correlates with the number of organisms the patient is harboring and the presence of organisms on smear. Patients whose sputum is positive by smear tend to be much more infectious than patients whose sputum is positive by culture but negative by smear.

Because of the insensitivity of sputum smears and the time required for *M. tuberculosis* to grow in culture, rapid and more sensitive methods for establishing the diagnosis of tuberculosis have been developed. Nucleic acid amplification assays have been developed that can detect *M. tuberculosis* in respiratory specimens in less than 12 hours and with greater sensitivity and specificity than are generally available by staining techniques. Another technique involves detecting radiolabeled $CO_2$ after incubation of the specimen with radiolabeled palmitic acid, a metabolic substrate for mycobacteria. Results can be obtained much more quickly with this technique than by conventional cultures.

Functional assessment of the patient with tuberculosis often shows surprisingly little impairment of pulmonary function. Such testing is useful primarily for the patient who already has compromised pulmonary function, when there is concern about how much of the patient's reserve has been lost. However, a patient who is potentially contagious should not be evaluated with pulmonary function testing because of the possibility of infecting others during the testing maneuvers. Arterial blood gases are often relatively preserved, with normal or decreased $P_{O_2}$, depending on the amount of ventilation–perfusion mismatch that has resulted.

## Principles of therapy

Effective chemotherapy is available for almost all cases of tuberculosis. Before the 1950s, treatment for tuberculosis was only marginally effective, involving prolonged hospitalization (usually in a sanatorium) or a variety of surgical procedures, whereas now most cases are curable with appropriate drug therapy. However, the rise in incidence of multidrug-resistant tuberculosis is again threatening the ability to effectively treat the disease. Patients are treated for a prolonged period, generally with a minimum of two effective antituberculous agents to which the organisms are sensitive. There are numerous different recommended drug regimens depending on the probability of resistant organisms and patient tolerability. In areas where the concern for drug resistance is low, the traditional regimen includes an intensive phase of four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) for the first 2 months followed by 4 more months of two drugs. If susceptibility data become available, the initial choice of drugs is adjusted accordingly.

A common treatment of pulmonary tuberculosis is isoniazid and rifampin given for 6 months, supplemented by pyrazinamide for the first 2 months and ethambutol until the organism's antimicrobial sensitivity is known.

Treatment can be administered in an outpatient setting unless the patient is sufficiently ill to require hospitalization. Patients whose sputum smears initially were positive are usually considered no longer infectious after they have demonstrated a clinical response to antituberculous therapy and their sputum has become smear-negative on three successive samples. A critical issue determining the success of antituberculous therapy is the patient's adherence to the medical regimen. Erratic or incomplete therapy is associated with a risk of treatment failure and the emergence of resistant organisms, with potentially disastrous consequences. As a result, the use of *directly observed therapy*, in which adherence is monitored in the outpatient setting with either video or in-person observation of the patient taking their medicines, has become an important component of treatment for most cases of tuberculosis. Hepatotoxicity can occur with antituberculous medications, necessitating appropriate monitoring of patients during therapy.

Treatment of active tuberculosis in patients with concomitant HIV/AIDS presents unique challenges. Such patients are at increased risk for drug interactions and adverse reactions to antituberculous medications. In addition, immune reconstitution inflammatory syndrome can develop if combination antiretroviral therapy is started concurrent with treatment of tuberculosis. With antiretroviral treatment, as the depleted immune system recovers and confronts the tuberculosis infection, intense inflammation may develop causing transient higher fever, malaise, weight loss, and worsening respiratory symptoms. This syndrome may be difficult to clinically differentiate from tuberculosis treatment failure.

Thus, effective therapy for tuberculosis requires long-term chemotherapy for all patients and directly observed therapy for as many as possible. Treatment is labor intensive, and it is most successful with a well-funded and effective public health system. Even in industrialized nations, this presents difficulties. Many parts of the world are under-resourced and this type of public health system is nonexistent.

In addition to multiple-drug therapy administered for active tuberculosis, therapy is indicated for select patients with latent tuberculous infection that is detected via tuberculin skin testing or IGRA. Currently, the Centers for Disease Control and Prevention (CDC) recommends a rifampin-based regimen for 3–4 months, as this is safe and effective with higher completion rate than the older regimen of isoniazid for 6 to 9 months. Such therapy substantially decreases the chances of developing active tuberculosis, especially in individuals who are at particularly high risk.

Single-drug therapy with rifampin or isoniazid is indicated for selected patients with latent tuberculous infection (with a positive tuberculin skin test or interferon-$\gamma$ release assay but no evidence of active disease).

In addition to close contacts of patients with active tuberculosis, certain other patients with latent tuberculous infection documented by a positive tuberculin skin test reaction or IGRA but no evidence of active disease are considered candidates for treatment with a single-drug regimen. Specifically, this category includes patients who satisfy additional criteria that put them at high risk for reactivation of a dormant infection. Examples include the presence of stable radiographic findings of old active tuberculosis but no prior therapy, or the presence of underlying diseases or treatment that impairs host defense mechanisms. Although this form of single-drug therapy was often called "prophylactic" or "preventive," it actually represents treatment aimed at eradicating a small number of dormant but viable organisms, and only a single drug is required because there is less concern about resistance when organism numbers are low. Treatment of latent tuberculosis is very effective in decreasing the rate of reactivation tuberculosis.

As noted, a recent major public health issue has been the development of organisms resistant to one or more of the commonly used antituberculous agents. When a strain is resistant to both isoniazid and rifampin, it is termed *multidrug resistant* (MDR). If a strain is resistant to isoniazid and rifampin plus any fluoroquinolone and at least one of the injectable drugs, it is termed *extensively drug resistant* (XDR). This problem underscores the importance of public health measures to limit person-to-person transmission of tuberculosis, as well as efforts to improve patient adherence with antituberculous medication. When treating a patient with tuberculosis caused by MDR or XDR organisms, close coordination between the treating physicians and the public health authorities is essential. Molecular diagnostic techniques have been developed to immediately identify some drug resistance at the time tuberculosis is diagnosed, and they may significantly improve the management of these patients.

The goal of developing an effective vaccine against *M. tuberculosis* remains an important step toward achieving worldwide eradication of tuberculosis. Vaccination with BCG, a live, attenuated strain of *Mycobacterium bovis*, has been used for many years in various countries around the world, but it has not been recommended for use in the United States except in selected rare circumstances. Although BCG vaccination appears to decrease the risk of serious and potentially life-threatening forms of tuberculosis in children, its efficacy in preventing pulmonary tuberculosis in adults is questionable. Of note, patients treated with a BCG vaccination will at least initially have a positive response to a PPD test, although the accuracy of IGRAs for tuberculosis is

unaffected in this setting.

## Nontuberculous mycobacteria

A variety of nontuberculous mycobacteria, sometimes called *atypical mycobacteria*, are potential pulmonary pathogens. They are generally found in water and soil, which appear to be the sources of infection rather than person-to-person transmission. The most common organisms in this group are classified as belonging to the *Mycobacterium avium* complex (MAC), which includes *Mycobacterium avium, Mycobacterium intracellulare* and other genetically similar organisms. Nontuberculous organisms which may also cause lung disease include *M. kansasii, M. abscessus, M. xenopi*, and *M. fortuitum*.

The nontuberculous mycobacteria are primarily responsible for disease in two settings: (1) the patient with underlying structural lung disease, most commonly bronchiectasis, cystic fibrosis, or severe COPD, in whom local host defense mechanisms are impaired, and (2) the patient with acquired or inherited defects in the host immune response, including HIV/AIDS and genetic defects in the interferon-γ pathway. Importantly, treatment with immunosuppressive agents, especially glucocorticoids and biological therapy against TNF-α, is similarly associated with increased risk. However, nontuberculous mycobacteria may also cause disease in a small number of patients without any of these risk factors.

Nontuberculous mycobacteria are most frequently pathogens in patients with underlying lung disease or defects in host immune response.

Disease caused by nontuberculous mycobacteria can be localized to the lung, where it can mimic tuberculosis, or it can be found after hematogenous dissemination throughout the body, particularly in patients with AIDS or other immunodeficiencies. Confirmation of disease caused by these organisms is difficult. In patients with underlying lung disease, these organisms can colonize the respiratory system without being responsible for invasive disease and can be found as laboratory contaminants.

Unlike tuberculosis, where recovery of organisms is evidence for active disease that requires treatment, isolation of nontuberculous mycobacteria does not automatically mean treatment is indicated. Because treatment can be associated with side effects, the toxicity of treatment may outweigh its potential benefit. Consequently, the decision whether to treat is based on the presence and severity of disease, the risk of progression, and patient priorities. When treatment is given, it typically involves multiple agents for an extended period, usually longer than 1 year. The organisms are frequently resistant to some of the standard antimycobacterial drugs, so treatment regimens are complicated, difficult to tolerate, and often unsuccessful. All treatment should be based on drug sensitivity data. For patients with MAC, macrolide antibiotics (e.g., clarithromycin, azithromycin) are recommended as part of a three-drug regimen, depending on sensitivities. A more complete discussion of this topic is beyond the scope of this text, so the reader is referred to the review articles in the references.

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# 26: Miscellaneous infections caused by fungi, including Pneumocystis

OUTLINE



This chapter continues the discussion of infectious diseases involving the lungs and considers miscellaneous infections caused by fungi, including *Pneumocystis*. For some of the organisms discussed, infection is a common potential problem for the individual with intact immunologic defense mechanisms. Histoplasmosis, coccidioidomycosis, and blastomycosis are the major fungal infections in this category. Yet, even for these diseases, impairment of normal defense mechanisms may substantially alter the presentation, clinical consequences, and natural history of the illness. As an example, after the introduction of tumor necrosis factor-α inhibitor agents for the treatment of autoimmune diseases, it was recognized that they impart a substantial risk for developing pulmonary and disseminated histoplasmosis, coccidioidomycosis, and blastomycosis. For many other fungi, including *Pneumocystis*, the normal host is essentially protected from the organism. Disease occurs almost exclusively as a consequence of an underlying illness or a breakdown of normal defense mechanisms. *Aspergillus* is perhaps the most important fungus of this sort and is the main one considered in this chapter. *Pneumocystis* is considered both in this chapter and in the discussion of acquired human immunodeficiency syndrome (AIDS) in Chapter 27.

## Fungal infections

## Histoplasmosis

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*, which is found primarily in the soil of river valleys in temperate zones throughout the world. In North America, the Mississippi and Ohio River valleys of the central United States and the St. Lawrence River valley in Canada have a particularly high incidence of the disease. However, the organism is present in many regions of the world; as examples, case series from Brazil, Argentina, Australia, India, South Africa, China, and other countries have been reported. *Histoplasma* is a *dimorphic fungus*; it exhibits one of two types of morphology depending on the conditions for growth. In the soil, the organism takes the form of branching hyphae. In the body at 37°C, the organism appears as a round or oval yeast.

Features of *Histoplasma capsulatum*:

1. Common in river valleys of central North America and other regions
2. Found in soil contaminated by bird droppings
3. Present in yeast form in tissue
4. Elicits granulomatous response in tissue

*Histoplasma* organisms flourish best in soil that has been contaminated by nitrogen-rich bird droppings, which promote sporulation of the fungus. When the soil becomes dry or disrupted (e.g., with construction equipment), the infectious spores become airborne and are inhaled by humans, potentially reaching the distal regions of the lung. Contact with chicken houses, bat-infested caves, or starling, blackbird, or pigeon roosts often exposes individuals or groups working in the contaminated area to the fungus. Riverbanks lined with trees are frequent places for blackbird nesting.

Once *H. capsulatum* has entered the lung, the organism (at body temperature) undergoes conversion to the yeast phase. An inflammatory response ensues in the lung parenchyma, with recruitment of phagocytic macrophages. Commonly, the yeast is not killed within the macrophage, and the organism spreads to regional lymph nodes and via the bloodstream to other organs, such as the spleen. Within 3 weeks, lymphocyte-mediated delayed hypersensitivity against *Histoplasma* typically develops, and the pathologic response becomes granulomatous. Central areas of caseous necrosis can occur within the granulomas, making the pathologic appearance similar to that of tuberculosis.

When the initial or primary lesions heal, residua are absent or take the form of small fibrotic pulmonary nodules that may contain areas of calcification. Similarly, small foci of calcification within the spleen (seen on computed tomography [CT] scan) may suggest prior infection. However, in some cases, particularly in the immunosuppressed host or in the infant or young child, the host defense mechanisms do not control the initial infection, the organism disseminates more widely, and the patient is said to have *progressive disseminated histoplasmosis*. In other cases, particularly in patients with significant underlying airway disease or emphysema, progressive parenchymal inflammation, destruction, and cavity formation occur in the lung, often called *progressive* or *chronic pulmonary histoplasmosis*.

## Types of infection

Three clinical syndromes associated with histoplasmosis correspond to the three types of pathologic response just mentioned. In the normal immunocompetent host, a benign self-limited infection called *acute* or *primary histoplasmosis* develops, with relatively few if any clinical sequelae. Often, the affected person is symptom-free during the acute infection, particularly when the level of exposure has been relatively low. Other individuals with primary histoplasmosis have nonspecific symptoms that may include some combination of cough, fever, chills, chest pain, headache, malaise, myalgias, and weight loss. The chest radiograph most commonly reveals a pulmonary infiltrate with or without hilar adenopathy. The typical clinical syndrome resolves within a few weeks without therapy. The only clues remaining from the acute infection are often one or several pulmonary nodules (which can be calcified) seen on chest radiograph. The nodules represent an encapsulated focus of granulomatous inflammation. Immunologic testing by means of skin tests or serologic studies typically indicates prior exposure to the organism. Rarely, and generally following a particularly intense acute exposure, patients may develop a serious or fatal clinical course as a result of acute histoplasmosis.

Clinical syndromes with histoplasmosis:

1. Acute (primary) histoplasmosis
2. Progressive disseminated histoplasmosis
3. Chronic pulmonary histoplasmosis

The syndrome of *progressive disseminated histoplasmosis* usually occurs in immunocompromised hosts or in infants or young children. These patients appear to have in common some impairment of cell-mediated immunity that predisposes them to progressive disseminated histoplasmosis. Thus, progressive disseminated histoplasmosis is now seen most commonly in patients treated with corticosteroids or cytotoxic agents, or in those who have human immunodeficiency virus (HIV)/AIDS. This potentially life-threatening illness is often associated with widespread pulmonary involvement accompanied by prominent systemic symptoms and infection of other organ systems.

*Chronic pulmonary histoplasmosis* is generally seen in individuals with preexisting structural abnormalities of the lung, primarily chronic obstructive lung disease with emphysema. The clinical and radiographic patterns often resemble those of tuberculosis. Patients may have cough, sputum production, fever, fatigue, and weight loss. The chest radiograph shows disease localized mainly to the upper lobes, with parenchymal infiltrates, often streaky in appearance, and cavity formation.

A rare but devastating complication of histoplasmosis is *fibrosing mediastinitis,* a condition characterized by progressive dense fibrosis of the mediastinum that can produce compression of the great vessels, bronchi, or the esophagus with severe clinical sequelae. The pathogenesis of this condition is not well understood, but the fact that the condition is progressive in the absence of viable *Histoplasma* organisms has led to the hypothesis that it results from ongoing immune stimulation by nondigestible fungal antigens that are present in mediastinal lymph nodes. Unfortunately, because the

presence of living fungi is not required for the disease to worsen, antifungal therapy has little impact on the progression of the disease.

The diagnosis of histoplasmosis depends on the type of infection: acute, disseminated, or chronic. The options available to the clinician are culture of the organism; identification in tissue; detection of *Histoplasma* antigen in the urine, bronchoalveolar lavage (BAL) fluid, or blood; or documentation of an immunologic response by serologic studies. To identify the organism microscopically, special stains, such as methenamine silver, are required. The specific usefulness and limitations of each of these methods can be found in resources listed in the references.

Treatment of pulmonary histoplasmosis also depends on the specific clinical syndrome. Acute histoplasmosis generally requires no therapy and is a self-limited illness. Disseminated histoplasmosis generally requires treatment with a regimen using amphotericin B, typically followed by itraconazole. Chronic pulmonary histoplasmosis is generally treated with itraconazole alone or with amphotericin B followed by itraconazole, depending on disease severity.

## Coccidioidomycosis

Like histoplasmosis, coccidioidomycosis also affects normal hosts, but the risk for severe disease is much higher in patients with impaired immunity. The causative organism, *Coccidioides immitis*, is a dimorphic fungus. In soil, the organisms show mycelia, whereas staining of tissue specimens shows characteristic round, thick-walled structures called *spherules* often containing multiple endospores.

Features of *Coccidioides immitis*:

1. Present in yeast form in tissue
2. Endemic in western and southwestern United States, Mexico, Central and South America
3. Elicits granulomatous response in tissue

Unlike *Histoplasma* organisms, the organisms of *Coccidioides* are limited to the western hemisphere. In the United States, the highest incidence is in California, especially within the San Joaquin Valley region of California (where disease caused by *Coccidioides* is referred to as “Valley Fever”). Other areas where the organism is endemic include parts of New Mexico, Nevada, Texas, and Arizona, as well as regions of Mexico, Central America, and South America.

After the host inhales contaminated material, some spores may evade nonspecific host defenses and reach the alveoli, leading to the development of primary disease. Pathologically, once delayed hypersensitivity to *Coccidioides* has developed, the inflammatory response to the organism is also a granulomatous one.

The normal host generally has a self-limited illness resulting from the primary infection with *C. immitis* or may be asymptomatic, with the disease going undetected. When symptoms do occur, they often include fever, cough, headache, and chest pain. Skin manifestations, presumably representing a form of hypersensitivity, are common. One example is *erythema nodosum*, which consists of tender red nodules on the

anterior surface of the lower legs. Some patients develop polyarthritis, another manifestation of hypersensitivity. The chest radiograph taken during the primary infection typically shows a pulmonary infiltrate, often with associated hilar adenopathy and sometimes with a pleural effusion.

Clinical syndromes with coccidioidomycosis:

1. Acute (primary) coccidioidomycosis
2. Disseminated coccidioidomycosis
3. Chronic pulmonary coccidioidomycosis

The acute (primary) infection usually resolves within a few weeks without treatment. Residual findings on chest radiograph may be absent or may consist of one or more pulmonary nodules or thin-walled cavities. Calcification of the nodules can occur but is less common than with histoplasmosis, and the nodules may resemble and be mistaken for a primary pulmonary malignancy.

Disseminated disease, resulting from hematogenous spread of the organism outside of the lungs, occurs in less than 5% of recognized cases and probably less than 1% of all cases because many go unrecognized. Disseminated coccidiomycosis is often associated with an ominous prognosis. Certain ethnic groups (patients of Filipino or African ancestry) are at higher risk for developing disseminated disease, as are pregnant women and immunosuppressed patients, especially organ transplant recipients and patients with HIV/AIDS.

Chronic pulmonary involvement by coccidioidomycosis can take several forms, including one or more chronic cavities or upper lobe disease with streaky infiltrates and/or nodules resembling tuberculosis. Patients often have fever, cough (sometimes with hemoptysis), malaise, and weight loss, and may appear subacutely or chronically ill.

As with histoplasmosis, the diagnosis of coccidioidomycosis depends on the type of clinical presentation and relies on culture, demonstration in tissue (e.g., with methenamine silver staining), or evidence of an immune response to the organism. Diagnosis is commonly based on serology, used in combination with the clinical presentation. Because of the dangers posed to hospital personnel when culturing the organism, the microbiology laboratory should be notified if there is a high clinical suspicion for coccidioidomycosis in specimens sent for culture.

Treatment considerations are similar to those for histoplasmosis. Primary infections generally do not require therapy, although patients at high risk for dissemination are commonly treated with an oral azole antifungal agent (e.g., itraconazole fluconazole). Chronic pulmonary disease requires therapy, usually with an oral azole, and surgery plays an occasional role in specific clinical settings. Disseminated disease is treated with an azole or amphotericin B. Patients who are undergoing prolonged immunosuppressive therapy commonly receive an oral azole.

## Blastomycosis

Blastomycosis is due to the soil-dwelling fungus *Blastomyces dermatitidis*. It occurs

primarily in the midwestern and southeastern United States, often overlapping the areas in which histoplasmosis is seen. Blastomycosis has been reported much less frequently outside of North America, most commonly in Africa, with a few cases identified in Mexico, Central and South America, India, and the Middle East. Infection is initiated by inhalation of spores that have become airborne. The primary inflammatory response in the lung consists largely of phagocytosis by neutrophils, monocytes, and alveolar macrophages. Once in the tissue, the spores convert to a yeast phase, which is much more resistant to phagocytosis. The acquired host response is primarily cellular and mediated by antigen-specific T cells and activated macrophages. As a result, the findings on histopathology show a combination of granulomas and a pyogenic (neutrophilic) response. If the latter is prominent, the response may mimic a bacterial infection. The organism can disseminate in an estimated 20% of patients, especially to the skin, usually in conjunction with an active pulmonary infection.

Acute infection with *Blastomyces* may resemble a bacterial pneumonia.

Acute pulmonary infection with *Blastomyces* often resembles a bacterial pneumonia. Patients frequently have a relatively abrupt onset of symptoms including fever, chills, and cough accompanied by purulent sputum production. However, subacute or chronic cases can be seen. Studies during outbreaks indicate that up to 50% of blastomycosis cases are asymptomatic. As with the other fungi, patients with impaired cellular immunity are at increased risk for the development of more rapidly progressive or severe disease. Skin lesions are common, usually appearing as a characteristic irregular patch with a crusted or verrucous surface, but nodules and ulcers also may occur.

The chest radiograph of patients with blastomycosis is variable. It may show unilateral or bilateral pulmonary infiltrates that can resemble bacterial pneumonia, or localized densities that can resemble carcinoma. Diagnosis can often be confirmed by demonstrating the characteristic yeast forms in sputum or tissue, or by culture of sputum. Antigen testing can be performed on urine, serum, bronchoalveolar lavage, and cerebrospinal fluid. Of note, the *Blastomyces* urine antigen test has significant cross-reactivity with *Histoplasma* antigens, but treatment is similar for both infections. Serologic testing is not useful because of low sensitivity and specificity.

Mild to moderate blastomycosis is generally treated with itraconazole. Patients with severe or disseminated disease are treated with amphotericin B. However, many cases of blastomycosis are self-limited. Whether all cases require treatment, particularly if the diagnosis is made as the disease seems to be resolving clinically, is not clear. Most authorities agree that a patient with active symptoms when the disease is diagnosed should receive treatment.

## Aspergillosis

Of all the fungi, *Aspergillus* is particularly notable for the variety of clinical presentations seen and the types of individuals predisposed. Unlike *Histoplasma, Coccidioides*, and *Blastomyces*, *Aspergillus* species are widespread throughout nature, not limited to particular geographic areas, and not dimorphic in appearance but always occur as mycelia (i.e., branching hyphal forms). *Aspergillus* is ubiquitous, and virtually everyone is exposed at some point. However, the disease only develops in patients with

certain predisposing factors, as discussed later.

Features of *Aspergillus* infection:

1. Widespread distribution
2. Present as branching hyphae in tissue

Four major clinical forms of disease caused by *Aspergillus* and the different settings in which these diseases occur are considered here. The first form, *allergic bronchopulmonary aspergillosis (ABPA)*, is a hypersensitivity reaction to airway colonization with *Aspergillus*, seen almost exclusively in patients with underlying asthma or cystic fibrosis. The second form, *aspergilloma*, is a saprophytic colonization of a preexisting cavity in the lung by a mycetoma ("fungus ball") composed of a mass of *Aspergillus* hyphae. The third form, *invasive aspergillosis*, involves tissue invasion by the organism and is seen in patients with significant impairment of their immune defense mechanisms. The fourth and least well-recognized form, *chronic necrotizing pulmonary aspergillosis*, involves a subacute to chronic invasion and destruction of the pulmonary parenchyma by *Aspergillus*, which is often complicated by cavity formation and secondary development of a mycetoma.

Clinical syndromes with aspergillosis:

1. Allergic bronchopulmonary aspergillosis
2. Mycetoma (aspergilloma)
3. Invasive aspergillosis
4. Chronic necrotizing pulmonary aspergillosis

## Allergic bronchopulmonary aspergillosis

The presence of underlying reactive airway disease—asthma—appears to be the important predisposing factor for development of ABPA. This condition does not represent a true infection, in that the organism does not invade the tissues; rather, the organism colonizes the patient's airways, where it provides intense antigenic stimulation. Both type I (immediate, immunoglobulin [Ig]E-mediated) and type III (immune complex, IgG-mediated) immune reactions to the organism develop in affected persons.

Clinically, patients with ABPA have manifestations of difficult to control asthma (wheezing, dyspnea, and cough) and often low-grade fever and production of characteristic brownish plugs of sputum. *Aspergillus* species frequently can be cultured from these plugs of sputum. The chest radiograph may show transient pulmonary infiltrates, which can be a consequence of bronchial obstruction by the plugs or a result of eosinophilic infiltration of lung tissue. Bronchiectasis of proximal airways with mucoid impaction is a frequent manifestation.

Diagnosis is made in the proper clinical setting of underlying asthma, and is based on culturing the organism, demonstrating the host's immune response to the fungus, or both. For example, skin tests against *Aspergillus* antigen show a positive immediate

reaction (reflecting type I immunity), often accompanied by a delayed reaction (called an *Arthus reaction*) after several hours (reflecting type III immunity). Precipitins in the blood and specific IgE against the organism frequently can be identified.

Treatment of ABPA is aimed primarily at controlling the host's immunologic response to the organism. Therefore, corticosteroids are the mainstay of treatment of this syndrome. Concomitant therapy with a well-tolerated oral azole agent is recommended for patients who develop an acute exacerbation or are unable to taper corticosteroids, with some authorities recommending azoles in all patients with ABPA at presentation. Patients with mild disease or those who are unable to tolerate corticosteroids may be treated with an azole alone. For patients with severe or refractory disease, advanced biologic agents such as omalizumab (anti-IgE) or mepolizumab (anti-IL-5) may be considered, although clear data on the benefits are not yet available.

## Aspergilloma

The second type of clinical problem resulting from *Aspergillus* is the *aspergilloma*, also referred to as a *mycetoma* or "fungus ball." The major predisposing feature for this entity is the presence of a preexisting cavity within the pulmonary parenchyma. The fungus ball itself represents a mass of fungal mycelia lying within the cavity proper. Tuberculosis, sarcoidosis, and non-*Aspergillus* fungal infections are a few examples of diseases in which cavities may be seen and, therefore, in which an aspergilloma may become a complicating problem. In these cases, the organism is essentially a saprophyte or colonizer of the cavity, with little tissue invasion. Fungi other than *Aspergillus* can occasionally result in a mycetoma.

Clinically, patients with an aspergilloma present either with hemoptysis or with no symptoms, but with suggestive findings on chest radiograph. Classically the radiograph demonstrates an apparent mass in the upper lobes surrounded by a lucent rim, representing air in the cavity around the fungus ball (Fig. 26.1). When the patient changes position, the fungus ball often changes position within the cavity, owing to the effects of gravity.

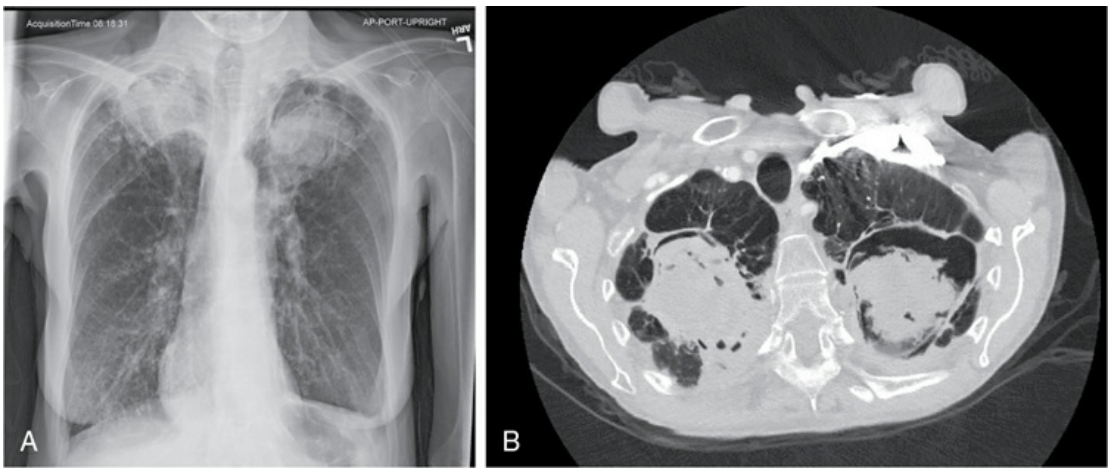


**FIGURE 26.1** Posteroanterior radiograph **(A)** and axial chest CT section **(B)** show bilateral upper lobe aspergillomas. Each fungus

ball appears as a mass sitting within a radiolucent thin-walled cavity.
*Source:* (Courtesy of Dr. Laura Avery.)

Diagnosis of an aspergilloma is strongly suggested by the characteristic radiographic appearance and is confirmed by culture of the organism or demonstration of the presence of precipitins against *Aspergillus* species. Treatment may be unnecessary when the patient has no symptoms from the lesion, but continued follow-up is required to confirm stability. In some patients, particularly those with significant amounts of hemoptysis, surgery is performed to remove the diseased area containing the fungus ball. For patients with severe lung disease who are unable to tolerate surgery, bronchial artery embolization can be performed. In this procedure, the bleeding vessels are identified angiographically, and small pieces of synthetic material are released into one or more vessels to occlude them and stop the bleeding. Administration of an oral azole may provide some benefit in reducing symptoms of cough, but is rarely a cure and requires months of therapy.

## Invasive aspergillosis

Invasive aspergillosis is the third clinical presentation of *Aspergillus* infection in the lung. This is the most life-threatening manifestation, occurring almost exclusively in patients with marked impairment of host immune defense mechanisms. The most important risk factor is neutropenia, but patients often also have impairment of cellular immunity as a consequence of hematopoietic stem cell transplantation or treatment with chemotherapeutic agents or high-dose corticosteroids.

Pathologically, the organism invades and spreads through lung tissue, but it also tends to invade blood vessels within the lung. As a result of vascular invasion by the fungus, hemoptysis is common, vessels can become occluded, and areas of pulmonary infarction can develop.

Clinically, patients are extremely ill, with fever, cough, dyspnea, and often pleuritic chest pain and septic shock. The chest radiograph may show localized or diffuse pulmonary infiltrates, reflecting either parenchymal invasion or pulmonary infarction secondary to vascular occlusion. Once vascular invasion occurs, embolic infectious foci may develop, including brain abscesses and endophthalmitis.

A definitive diagnosis is made by using special stains—for example, by methenamine silver to demonstrate tissue invasion by the organism on lung biopsy. However, biopsy may not be practical due to the risks of complications, especially hemorrhage, in these very ill patients. Thus, less invasive diagnostic testing is usually utilized first. Stain and culture of sputum or bronchoalveolar lavage fluid is typically done. Positive assays of serum or bronchoalveolar lavage fluid for the fungal cell wall constituents galactomannan or β-D-glucan support the diagnosis, as does a positive polymerase chain reaction (PCR) detecting fungal nucleic acid. In the setting of clinical and radiographic findings which are suggestive of invasive aspergillosis, detection of the organism in sputum or BAL combined with positive biomarkers is generally sufficient for a presumptive diagnosis. Treatment consists of voriconazole, posaconazole, isavuconazole, an echinocandin, or amphotericin B, but the mortality rate is extremely high even with appropriate use of one of these agents.

### Chronic necrotizing pulmonary aspergillosis

The final type of *Aspergillus* infection involving the lung is *chronic necrotizing pulmonary aspergillosis*. In this form, patients frequently have underlying lung disease or some relatively mild impairment of either pulmonary or systemic host defense mechanisms, as occurs with diabetes mellitus or treatment with low-dose corticosteroids. The clinical process is characterized by an indolent localized invasion of pulmonary parenchyma by *Aspergillus* organisms. Necrosis of the involved tissue often results in cavity formation, which may become the site for an aspergilloma. Because of tissue invasion, the infection is treated with oral voriconazole or itraconazole, or intravenous micafungin or amphotericin B.

## Cryptococcosis

Cryptococcosis is primarily due to infection with *Cryptococcus neoformans* or *Cryptococcus gattii*, which are encapsulated yeasts that can be recovered worldwide, particularly in soil contaminated with bird droppings. Human disease is initiated by inhalation of infectious particles. Pulmonary defense mechanisms are generally quite effective in clearing this infection. However, in some normal individuals as well as in those with impaired cell-mediated immunity as a result of HIV/AIDS, malignancy, organ transplantation, or treatment with corticosteroids, a focal pneumonia can develop, which is inconsistently symptomatic with a productive cough and fever. Dissemination of the organism to other organs may then occur—the most common and feared of which is development of meningoencephalitis.

The diagnosis of cryptococcosis is definitively established by demonstrating the presence of *Cryptococcus* within tissues. Ideally this is achieved by culture, but a positive cryptococcal antigen test or visualization of yeast forms in the proper clinical setting is considered highly suggestive of the diagnosis.

Pulmonary cryptococcosis has a high likelihood of resolution without treatment in an immunocompetent host. However, because of the risk of dissemination and central nervous system infection, treatment with fluconazole is generally recommended if infection is documented. Central nervous system, severe pulmonary, or extrapulmonary disease due to *Cryptococcus* requires treatment with intravenous amphotericin B, frequently with concomitant flucytosine. To reduce the risk of disease recurrence, immunosuppressed patients generally require prolonged (and sometimes lifetime) courses of oral fluconazole after the acute phase of treatment.

## Other fungi

Other fungi are less frequent causes of respiratory infection. *Candida albicans* is an extraordinarily common contaminant of sputum (particularly in patients treated with antibiotics), but it is an uncommon cause of pneumonia, even in immunosuppressed patients. In contrast, *Mucor* and other zygomycetes are opportunistic fungi that may cause life-threatening pulmonary infection in the immunocompromised host, including patients with underlying diabetes mellitus.

# *Pneumocystis* infection

Although *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*) has been recognized for decades as a cause of pneumonia in immunocompromised patients, its clinical importance as a major pathogen in patients with HIV/AIDS sparked renewed interest in the organism, its treatment, and prevention of infection in high-risk patients. The use of combination antiretroviral therapy (cART) regimens to treat HIV and preserve immune system function has considerably decreased the number of AIDS-related *Pneumocystis* cases. Nevertheless, it remains an important pulmonary pathogen, not only in HIV-infected patients but also in a variety of other immunosuppressed patients.

The taxonomy of *Pneumocystis* has changed a number of times since its discovery in 1909. For many years, the organism was considered a protozoan, but techniques involving nucleic acid sequencing of ribosomal RNA and studies of enzyme structure and cell wall composition have shown that the organism is more closely related to fungi than to protozoa. *Pneumocystis* is now classified as a unique category of fungi. The nomenclature change of *P. carinii* to *P. jiroveci* recognizes the pathologist Otto Jirovec, who first described the organism in humans.

Features of *Pneumocystis jiroveci*:

1. Ubiquitous distribution
2. Seen on methenamine silver stain rather than routine tissue and Gram stains
3. Tissue response in the lung is primarily exudation of foamy fluid into alveoli

*Pneumocystis* appears to be widely distributed in nature. Normally, it can be found in the lungs of a variety of animals as well as in humans. Yet the organisms only cause disease in individuals with impaired cellular immunity. The key cell appears to be the helper T lymphocyte $CD4^+$, whose numbers, function, or both can be diminished by specific diseases or immunosuppressive drugs. Before the recognition of HIV/AIDS, *P. jiroveci* pneumonia was seen most commonly in patients with severe malnutrition, malignancy, organ transplantation, or other diseases requiring treatment with corticosteroids or other immunosuppressive agents. However, after the identification of AIDS and before the introduction of cART, the majority of cases were seen in patients with AIDS and greatly reduced numbers of $CD4^+$ lymphocytes. The problem of *Pneumocystis* pneumonia as it occurs in AIDS is discussed in more detail in Chapter 27.

*Pneumocystis* cysts, which are seen in the lung tissue of infected patients, appear on light-microscopic examination as round or cup-shaped structures. They do not stain well with routine hematoxylin and eosin stains and require special stains, such as methenamine silver (Fig. 26.2). The tissue response to the organism seen on microscopic examination of lung tissue includes infiltration of mononuclear cells within the pulmonary interstitium and exudation of foamy fluid (containing cysts) into alveolar spaces. An exuberant host inflammatory response to the organism contributes to the pulmonary injury. As a result, many patients with *Pneumocystis* pneumonia are treated with corticosteroids in addition to antimicrobial therapy against *Pneumocystis* early in the course of the disease to suppress this transiently deleterious response.

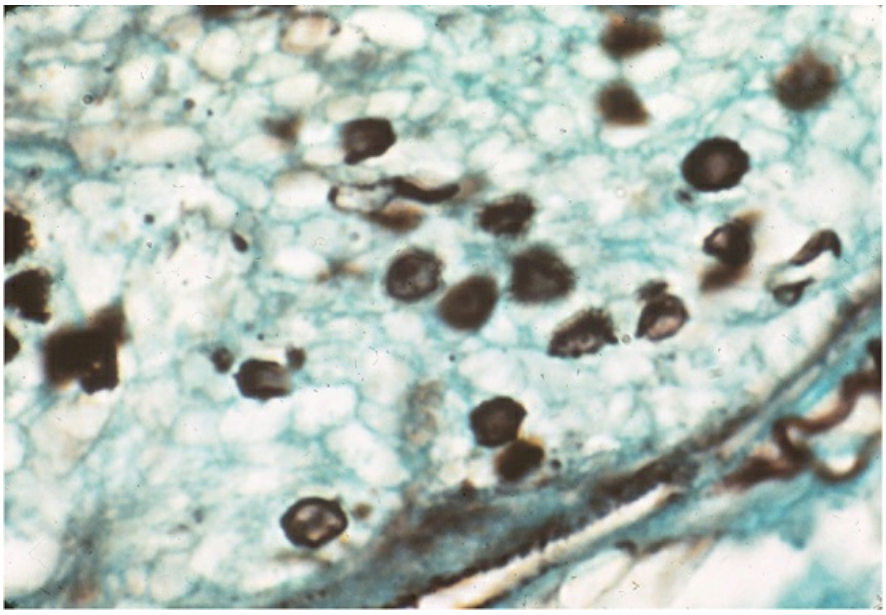

**FIGURE 26.2** High-power photomicrograph of many *Pneumocystis* cysts as seen with methenamine silver staining. Darkly staining cysts are within the alveolar lumen. Note the foamy exudate in the alveolar lumen.

Clinically, *Pneumocystis* pneumonia usually manifests with cough, dyspnea, and fever in immunocompromised patients. Notably, in patients for whom treatment with corticosteroids was the risk factor for developing *Pneumocystis* pneumonia, symptoms frequently develop (and the infection is recognized) as the dose of corticosteroids is being tapered. This observation further supports the concept that the host inflammatory reaction to the organism, which is suppressed by corticosteroids and surges only as the corticosteroid dose is being tapered, is responsible for much of the clinical presentation. The chest radiograph commonly shows diffuse bilateral infiltrates, which can have the appearance of either an interstitial or an alveolar filling pattern (Fig. 26.3). Alveolar filling and resultant areas of shunting often make hypoxemia a particularly prominent clinical feature in these patients. Although the disease is often insidious in onset in AIDS patients, it commonly manifests in other immunocompromised patients as a relatively acute-onset pneumonia that, if untreated, can rapidly progress to respiratory failure and death within days.

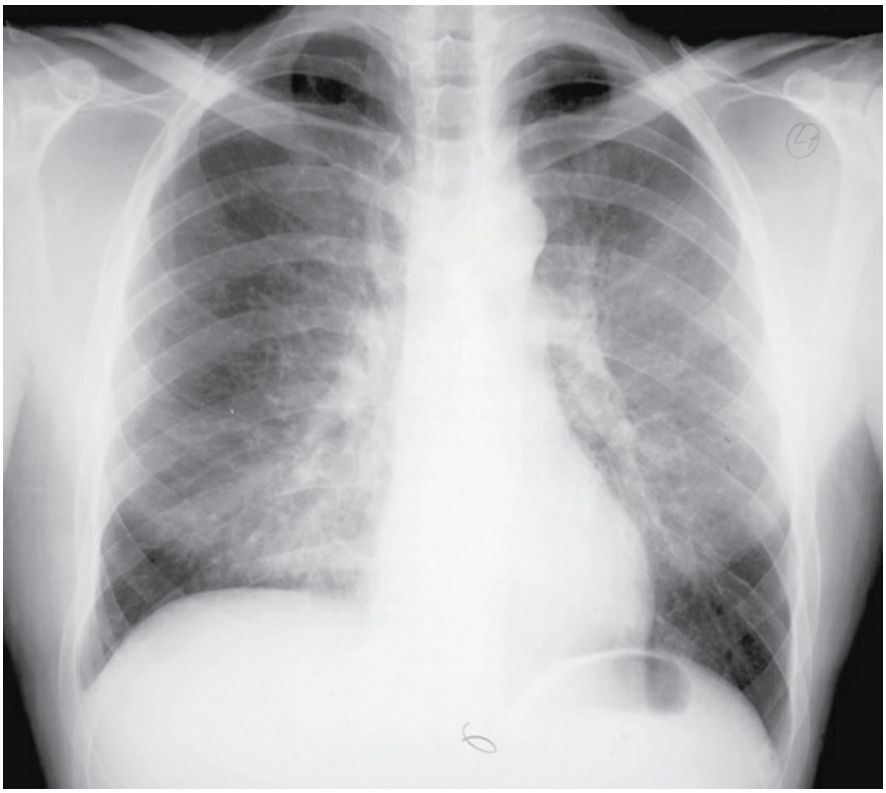

**FIGURE 26.3** Chest radiograph of a patient with AIDS and pneumonia due to *Pneumocystis jiroveci*. Infiltrates representing the alveolar filling are most prominent at the right base, but also appear in the left midlung field as diffuse haziness.

Clinical features of *Pneumocystis* pneumonia:

1. Symptoms: cough, dyspnea, fever
2. Chest radiograph: frequently diffuse interstitial or alveolar infiltrates
3. Hypoxemia

Because the organism is extremely difficult to cultivate in the laboratory setting, diagnosis depends on demonstrating the organism on stains of tissue sections, BAL fluid, or sputum that has been induced by having the patient inhale a hypertonic saline aerosol. The use of monoclonal antibodies and polymerase chain reaction technology as a means of detecting the organism in sputum or BAL fluid has improved the detection rate compared with the use of previous staining methods. No serologic or skin testing methods are available for diagnosis. A positive β-D-glucan assay is observed in many patients and is a useful adjunctive test; a negative test has good predictive value.

The treatment of choice for *Pneumocystis* infection is a combination of trimethoprim and sulfamethoxazole. Primaquine/clindamycin, pentamidine, atovaquone, or one of several other regimens are alternative options in patients who cannot tolerate

trimethoprim-sulfamethoxazole. In high-risk patients, such as transplant recipients or individuals receiving antineoplastic chemotherapy for leukemia, low doses of the same agents are used prophylactically to prevent the infection.

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# 27: Pulmonary complications in the immunocompromised host

OUTLINE



Physicians are frequently faced with patients who have impaired host defense mechanisms that increase the risk of specific infections. HIV/AIDS, neutropenia, and depressed cellular and/or humoral immunity, as frequently occurs due to either chemotherapy (given for malignancy) or immunosuppressive agents (administered for inflammatory diseases or suppression of rejection following organ transplantation), all predispose patients to particular pathogens. This chapter is devoted to the spectrum of respiratory complications potentially associated with several of the more commonly encountered forms of impaired immunity.

Immunocompromised patients are extremely susceptible to respiratory tract infections with a variety of organisms, some of which rarely cause disease in the immunocompetent host. When the immunosuppressed patient has fever and new pulmonary infiltrates, the possibility of an “opportunistic” infection comes immediately

to mind. However, immunocompromised patients are also susceptible to common respiratory pathogens and noninfectious complications, both of which must be seriously considered in the differential diagnosis.

## Acquired immunodeficiency syndrome

In 1981, a number of cases of immunodeficiency of unknown cause in men who had sex with men and in intravenous drug users were reported. These patients had a variety of unusual infections, including *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, mucosal candidiasis, and several types of viral infections. In some cases, the unusual neoplasm Kaposi sarcoma also occurred. Evaluation of these patients revealed marked impairment of cellular immunity, characterized by anergy to skin tests for delayed hypersensitivity and decreased numbers of lymphocytes, specifically with loss of $CD4^+$ T lymphocytes and a reversal in the normal ratio of $CD4^+$ helper and $CD8^+$ suppressor T cells. This disease subsequently was given the name *acquired immunodeficiency syndrome* (*AIDS*).

What initially seemed to be an unusual problem that might be relegated to the realm of medical curiosities has since become one of the major worldwide public health problems confronting the medical profession in the 21st century. Roughly 37 million individuals around the world (including approximately 1.2 million in the United States) are currently infected with HIV. With effective antiretroviral therapy (ART), the mortality from HIV/AIDS has declined in areas where the treatment is available. However, the World Health Organization estimates almost 700,000 deaths worldwide were attributable to HIV-related diseases in 2020. In some parts of sub-Saharan Africa, HIV/AIDS is the leading cause of death.

In the more than four decades since HIV/AIDS was recognized, an enormous amount of research has resulted in identification of the retrovirus responsible for this catastrophic attack on the cellular immune system. At the same time, a wide and unexpected spectrum of clinical problems has been posed by a myriad of opportunistic infections and neoplasms resulting from the profound immunodeficiency in these patients. Fortunately, the development of current antiretroviral therapies and effective prophylactic regimens against several opportunistic infections has significantly decreased many of the clinical complications of the disease, and the global death rate has declined by almost 40% since 2010. Nevertheless, although substantial and rapid progress has been made in therapy for the disease, as well as prevention and treatment of secondary complications, management of patients with AIDS continues to present a major challenge to the medical community. The critical concern is at the worldwide level, primarily because of limited availability of therapeutic and prophylactic agents for the large number of affected individuals in under-resourced regions.

In the United States, the largest category of individuals affected by AIDS is men who have sex with men, in whom HIV is transmitted by sexual contact. Heterosexual transmission also occurs, and intravenous drug users are at risk due to use of sharing of infected needles or syringes. In other areas of the world (e.g., sub-Saharan Africa and Asia), AIDS is common in both sexes and is transmitted primarily by heterosexual contact.

Although AIDS can lead to complications in almost any organ system, the lungs are

the organ system most commonly affected.

## Etiology and pathogenesis

The etiologic agent responsible for AIDS is the human immunodeficiency virus (HIV), a retrovirus formerly called *human T-cell lymphotropic virus type III* (HTLV-III). The virus appears to mediate its pathogenic effect by binding to the CD4 receptor on cells that carry this surface receptor, then entering and destroying the cells. Although the predominant cell type affected is the $CD4^+$ helper T lymphocyte, cells of the monocyte-macrophage series and certain neural cells are also infected because they carry the CD4 receptor on their cell surface.

The immunodeficiency occurring with HIV infection results primarily from lysis and depletion of infected $CD4^+$ T lymphocytes. Macrophages and monocytes are also infected, leading to dysfunctional cytokine production. Because macrophages are relatively resistant to the cytotoxic effects of the virus, they appear to provide a viral reservoir.

HIV binds to the CD4 receptor of T lymphocytes.

The major consequence of the immunodeficiency is opportunistic infection with organisms normally handled by an adequately functioning cellular immune system. When $CD4^+$ T lymphocytes fall below $200/mm^3$, the most common infection involving the lungs in the absence of prophylaxis is pneumonia caused by *P. jiroveci* infection. Pulmonary infection can similarly result from a wide variety of other respiratory pathogens normally controlled by cell-mediated immune mechanisms, including cytomegalovirus (CMV), mycobacteria (*Mycobacterium tuberculosis* and nontuberculous or atypical mycobacteria), and fungi (especially *Cryptococcus, Histoplasma*, and *Coccidioides*). Patients with HIV have also been more likely to develop severe illness if they contract COVID-19.

Certain types of bacterial pneumonia, primarily due to *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*, are also seen with increased frequency in AIDS. Although these types of bacterial pneumonia normally might not be predicted to result from the cellular immunodeficiency of AIDS, these infections probably can be explained by secondary dysregulation of the humoral immune system and impaired antibody production against these organisms.

Major pulmonary infections with AIDS:

1. *Pneumocystis jiroveci* (formerly *carinii*)
2. Cytomegalovirus
3. Mycobacteria (tuberculosis, nontuberculous mycobacteria)
4. Fungi *(Cryptococcus, Histoplasma, Coccidioides)*
5. Bacteria *(Streptococcus pneumoniae, Haemophilus influenzae)*

## Infectious complications of acquired immunodeficiency

## syndrome

### *Pneumocystis jiroveci* pneumonia

Since the first identification of cases in 1981, *Pneumocystis* infection has been the most common respiratory complication in untreated patients with AIDS in the United States, frequently representing the initial opportunistic infection that establishes the diagnosis of AIDS in the absence of other known causes of immunosuppression. The risk of developing this opportunistic infection is highly dependent on the patient's peripheral blood $CD4^+$ count—with a level less than 200 cells/$mm^3$ associated with a high risk for infection. Fortunately, the availability of increasingly effective antiretroviral agents and more frequent use of prophylaxis against *Pneumocystis* have significantly decreased the likelihood of infection and death resulting from this opportunistic infection.

A general discussion of *Pneumocystis* as a respiratory pathogen was given in Chapter 26. Although *Pneumocystis* is a fungus, it is discussed separately from other fungi (see later in this chapter) due to its distinct clinical characteristics. In patients with AIDS, onset of the disease is often more indolent than in immunosuppressed patients without AIDS. Fever, cough, and dyspnea are the usual symptoms bringing the patient to medical attention. The typical chest radiograph shows diffuse interstitial or alveolar infiltrates. Often the lung fields look hazy, a pattern that may be difficult to characterize specifically as either interstitial or alveolar and is commonly described as looking like "ground glass" (see Fig. 26.3). However, atypical radiographic presentations are clearly recognized with documented *Pneumocystis* pneumonia, including even the finding of a normal chest radiograph. High-resolution computed tomographic (CT) scanning is particularly sensitive for demonstrating subtle changes associated with *Pneumocystis* pneumonia and generally shows abnormal results even in patients with a normal chest radiograph.

*Pneumocystis jiroveci* pneumonia often has an indolent onset in AIDS.

A presumptive diagnosis of *Pneumocystis* pneumonia may be made in a patient with HIV/AIDS who develops dyspnea and hypoxemia if the $CD4^+$ T-lymphocyte count is less than 200 cells/$mm^3$, chest radiology is consistent, and the serum 1,3-β-D-glucan is more than 80 pg/mL. However, a definitive diagnosis requires demonstrating the organism in respiratory secretions or tissue—typically by immunofluorescent staining with a monoclonal antibody or by nucleic acid amplification methods. Patients with *Pneumocystis* pneumonia in the setting of AIDS often have a large burden of organisms, making specimens that are diagnostic easier to obtain than from patients without AIDS. Inducing sputum by having the patient inhale a solution of hypertonic saline is frequently effective and often is used as the initial diagnostic method when *Pneumocystis* is suspected. Flexible bronchoscopy with bronchoalveolar lavage (BAL) is another means for recovering the organism, with a positive yield of greater than 85% in patients eventually proven to have *Pneumocystis* pneumonia. Transbronchial biopsy provides a small incremental increase in sensitivity over BAL alone.

Definitive diagnosis of *Pneumocystis jiroveci* is made most commonly on samples obtained by induction of sputum or bronchoalveolar lavage.

Trimethoprim-sulfamethoxazole, given either orally or intravenously, is the preferred treatment of pneumonia due to *Pneumocystis*. For patients unable to tolerate trimethoprim-sulfamethoxazole, the combination of clindamycin and primaquine, the combination of trimethoprim and dapsone, or either atovaquone or pentamidine as single agents are considered. Because patients with HIV/AIDS have a higher incidence of allergic reactions to sulfonamides, making a switch from trimethoprim-sulfamethoxazole to other drugs is necessary in a relatively high proportion of patients. In patients without AIDS treated for *Pneumocystis* pneumonia, the combination trimethoprim-sulfamethoxazole also is generally preferred and tends to be complicated by fewer drug reactions.

Trimethoprim-sulfamethoxazole is the preferred therapy for *Pneumocystis jiroveci* pneumonia.

In patients with moderate to severe disease caused by *Pneumocystis* pneumonia, adjunctive therapy with corticosteroids is indicated to avert respiratory failure. Although corticosteroid therapy might be expected to cause more immunosuppression and make the infection worse, this has not been the case when administered along with antimicrobial agents directed at the organism. The presumed benefit of reducing the inflammatory response in the lung to lysing organisms outweighs any negative effects of the corticosteroids.

In patients with AIDS, oral administration of trimethoprim-sulfamethoxazole (in low doses) or dapsone (either alone or with pyrimethamine) is used to prevent *Pneumocystis* pneumonia. Alternatively, patients can receive aerosolized or intravenous pentamidine once a month or daily oral atovaquone. Such prophylactic therapy is routinely recommended in HIV-infected patients who have a $CD4^+$ count less than 200 cells/$mm^3$ and in selected other circumstances. When *Pneumocystis* pneumonia develops despite use of aerosolized pentamidine prophylaxis, the clinical presentation may be atypical. Unusual radiographic patterns are often seen, especially pulmonary infiltrates limited to the upper lung zones rather than the more typical pattern of diffuse pulmonary infiltrates.

Atypical presentations of *Pneumocystis jiroveci* infections are commonly seen in patients receiving aerosolized pentamidine.

## Mycobacterial infection

*M. tuberculosis* is an important respiratory pathogen in patients with AIDS. Clinical disease may result from primary infection, reactivation of previous infection, or exogenous reinfection. Disease due to *M. tuberculosis* is a particular problem in those groups of individuals with a high background prevalence of tuberculosis—for example, much of the population of sub-Saharan Africa, intravenous drug users, homeless or incarcerated individuals, and some immigrant populations in the United States.

Because *M. tuberculosis* is a relatively virulent organism that does not require the same degree of immunosuppression to produce disease as do many of the other opportunistic infections, it is often seen early in the course of the disease in patients

with HIV infection. The clinical presentation is similar to that seen in the non-HIV-infected patient with tuberculosis. However, it also may occur in HIV/AIDS patients who are in an advanced stage of their disease with more severe immunosuppression, in which case the clinical manifestations are often atypical. In this latter circumstance, upper lobe cavitary disease is less frequent, and disseminated disease is more frequent than is usually seen in patients without AIDS. Importantly, for patients with AIDS and tuberculosis (or, for that matter, with other opportunistic infections), improvement in the patient's overall immune status, particularly as a result of antiretroviral therapy, can be associated with a paradoxical clinical worsening of symptoms from the opportunistic infection. In these cases, "reconstitution" of the immune system results in an augmented inflammatory reaction to the opportunistic infection, leading to the apparent clinical worsening known as *immune reconstitution inflammatory syndrome*.

Tuberculosis may be an early opportunistic infection in HIV/AIDS.

Treatment considerations for tuberculosis in AIDS patients are similar to those for patients without AIDS, but with some differences. Because of the risk for disease with nontuberculous mycobacteria, an expanded list of drugs is sometimes given initially to AIDS patients until the organism and its sensitivities are firmly identified. In addition, treatment may be given for a longer duration to AIDS patients, especially if the response to therapy appears slow. Drug interactions with antiretroviral therapy must be carefully considered. Similar to recommendations in patients without HIV infection, treatment of latent tuberculosis is indicated. For patients with HIV infection who have a positive tuberculin skin test reaction (defined as 5 mm or more of induration) or a positive interferon-γ release assay but no evidence of active disease, one of the recommended treatment regimens for latent tuberculosis should be administered.

The other types of mycobacteria that frequently cause opportunistic infection in AIDS are members of the *Mycobacterium avium* complex (MAC). What is surprising in patients with MAC infection is that the organism is associated primarily with disseminated disease, not with pulmonary disease. Even when disseminated disease is present, pulmonary involvement is not generally a significant part of the clinical picture. Previously, in patients with HIV/AIDS, prophylactic treatment against MAC with a macrolide antibiotic such as azithromycin or clarithromycin was indicated when the $CD4^+$ count fell below 50/$mm^3$. However, with potent antiretroviral therapy, the risk of disease due to MAC is significantly reduced and routine prophylaxis is no longer recommended.

## Other bacterial infection

Patients with AIDS, particularly intravenous drug users, have an increased frequency of bacterial pneumonia, primarily due to either *S. pneumoniae* or *H. influenzae*. The risk is increased at all levels of $CD4^+$ count and is highest when the count falls below 200 cells/$mm^3$. As with other opportunistic infections in HIV disease, the risk of bacterial pneumonia is also greatly decreased with the use of antiretroviral therapy.

Bacterial pneumonias might not be predicted as a complication of AIDS, because impairment in cellular immunity should not by itself predispose an individual to these infections. However, dysregulation of the humoral immune system accompanies the

impairment in cellular immunity. Patients frequently have polyclonal hyperglobulinemia at the same time they demonstrate a poor antibody response after antigen exposure. Presumably, loss of $CD4^+$ cells results in alteration of the normal interaction between these cells and B lymphocytes that regulates antibody production.

## Viral infection

One of the most common viruses afflicting patients with AIDS is CMV, a member of the herpesvirus family. The most common sites of clinical involvement are the eye (CMV retinitis) and gastrointestinal tract. Although CMV can frequently be cultured from lung tissue or BAL fluid of patients with AIDS, its role as a clinically important respiratory pathogen is not clear. When patients with CMV in the lungs have clinical respiratory system disease, they almost always have a coexistent organism such as *Pneumocystis* that is thought to be the primary pathogen. Even when typical nuclear and cytoplasmic inclusions are present, the role played by CMV is uncertain in the presence of these other important pathogens, and the usefulness of adding specific treatment for CMV in this setting is unclear.

Evidence regarding the interaction between HIV infection and infection with COVID-19 is rapidly evolving. HIV, especially with a low $CD4^+$ count, appears to be an independent risk factor for the development of severe COVID-19, even in patients on effective antiretroviral therapy. Individuals with HIV infection should receive COVID-19 vaccination on the same schedule as recommended for non-HIV individuals.

Other viruses such as herpes simplex, varicella-zoster, and Epstein-Barr virus have been described as potential respiratory pathogens in AIDS, but they are distinctly uncommon and are not considered here.

## Fungal infection

In addition to *Pneumocystis*, discussed previously, several other fungi are recognized as causes of respiratory involvement in patients with advanced AIDS, either as isolated respiratory system disease or as part of a disseminated infection. The most common of these fungal infections is due to *Cryptococcus neoformans*. Although the initial infection starts in the lungs, meningitis is the most common clinical manifestation rather than clinically apparent respiratory disease. When respiratory involvement is present, the radiograph may show localized or diffuse disease and sometimes an associated pleural effusion or intrathoracic lymph node involvement. Optimal treatment consists of amphotericin B combined with flucytosine.

Histoplasmosis and coccidioidomycosis, fungal infections that occur in specific endemic regions, are described in detail in Chapter 26. Consequently, histoplasmosis and coccidioidomycosis in AIDS patients are seen primarily but not exclusively in their respective endemic areas. In patients with AIDS, pulmonary involvement with these organisms is most commonly a manifestation of disseminated disease that resulted either from reactivation of previous disease or, in those with advanced AIDS, from progressive primary infection. Treatment with antiretroviral therapy greatly decreases the risk from either of these organisms. As is the case in patients without AIDS, amphotericin B (or an oral azole such as itraconazole) is the primary agent used to treat either of these infections.

Other fungal infections of the lung are much less common in AIDS patients. Perhaps

surprisingly, even though oral candidiasis (thrush) is extremely common in AIDS, pulmonary infection with *Candida albicans* is extremely uncommon and rarely described, except at autopsy. *Aspergillus* infection has been described in AIDS, but generally it occurs in patients who have other predisposing factors for invasive aspergillosis, especially neutropenia.

## Noninfectious complications of acquired immunodeficiency syndrome

Although infectious complications affecting the respiratory system are much more common, noninfectious complications are also recognized in patients with AIDS. They fall into the broad categories of neoplastic disease (which includes Kaposi sarcoma and non-Hodgkin lymphoma), inflammatory disease (which includes lymphocytic interstitial pneumonitis and nonspecific interstitial pneumonitis), and pulmonary vascular disease (pulmonary hypertension). As with infections, the incidence of these noninfectious complications is also markedly decreased in patients receiving antiretroviral therapy. A brief discussion of each of these potential complications follows.

### Neoplastic disease

Kaposi sarcoma, a vascular tumor that is associated with human herpesvirus-8, is an AIDS-defining illness and the most common malignancy in patients with HIV. Prior to the AIDS epidemic, it was a rare diagnosis in the United States, typically occurring in elderly men and characterized by slowly progressive cutaneous lesions of the lower extremities. A more aggressive form with frequent visceral involvement was seen in certain parts of Africa. In the early descriptions of AIDS patients in 1981, Kaposi sarcoma was one of the unusual clinical manifestations accompanying the profound cellular immunodeficiency. Since then, Kaposi sarcoma is recognized as one of the common manifestations, typically occurring with skin involvement but often complicated by dissemination to the lungs and other organ systems. The incidence of HIV-related Kaposi sarcoma has decreased substantially with antiretroviral therapy.

Kaposi sarcoma is most commonly observed in AIDS patients as violaceous vascular-appearing skin lesions. Histologically, these lesions consist of spindle-shaped cells with intervening slit-like vascular spaces. Visceral involvement indicates the presence of dissemination, and commonly involved organ systems include the gastrointestinal tract and lungs. Pulmonary involvement has a variable presentation on chest radiograph. It can appear as diffuse infiltrates, localized disease, or pulmonary nodules. Pleural involvement with resulting pleural effusions can be present and is often helpful diagnostically to distinguish pulmonary Kaposi sarcoma from *Pneumocystis* pneumonia because pleural effusions are uncommon with the latter diagnosis. Involvement of the airways or mediastinal lymph nodes can be seen with intrathoracic Kaposi sarcoma.

Kaposi sarcoma in the thorax can manifest with parenchymal, airway, lymph node, and pleural involvement.

Definitive diagnosis of Kaposi sarcoma in the lung may be difficult, because BAL and even transbronchial biopsy infrequently provide sufficient diagnostic material. A surgical lung biopsy typically provides sufficient diagnostic material but is preferably

avoided because of its invasive nature. When endobronchial involvement is present, the gross appearance of airway lesions may be highly suggestive of the diagnosis. Although rarely used now, a gallium lung scan may provide another useful clinical clue by demonstrating pulmonary uptake in most opportunistic infections but not in Kaposi sarcoma.

The primary therapy for Kaposi sarcoma in patients with AIDS is antiretroviral treatment. Prior to effective antiretroviral medications, the prognosis for AIDS-associated Kaposi sarcoma was quite poor, with typical survival of less than 1 year. For patients who show progression of disease despite antiretroviral therapy, systemic chemotherapy is considered.

Another common neoplasm associated with AIDS is non-Hodgkin lymphoma. Although extranodal involvement and advanced disease are common when this malignancy occurs in AIDS patients, isolated intrathoracic involvement is uncommon. Lung cancer also appears to occur with increased frequency in AIDS patients. As with Kaposi sarcoma, antiretroviral therapy does appear to significantly diminish the incidence of non-Hodgkin lymphoma and lung cancer, but to a lesser extent.

### Inflammatory disease

An occasional patient with AIDS and diffuse pulmonary infiltrates has neither an opportunistic infection nor a neoplasm affecting the lung. Instead, the process is an inflammatory one without any known cause, although viral etiologies (especially Epstein-Barr virus and HIV) have been proposed. In some cases, the microscopic appearance is notable for the prominence of lymphocytes and plasma cells infiltrating alveolar septa. In these cases, a diagnosis of lymphocytic interstitial pneumonitis is made. This particular histologic pattern is a relatively common pulmonary complication seen in children with perinatally acquired HIV infection who do not receive antiretroviral therapy. The primary treatment for these children is the institution of antiretroviral therapy, with the addition of corticosteroids when necessary.

Lymphocytic interstitial pneumonitis is a common pulmonary complication of AIDS in children.

The other histologic pattern is a nonspecific one with a mixed inflammatory cell infiltrate. Patients with this pattern are diagnosed as having nonspecific interstitial pneumonitis. This is an uncommon complication of AIDS, about which little is known.

### Pulmonary vascular disease

Pulmonary arterial hypertension (PAH) is a potential complication of HIV infection, although the exact pathophysiologic explanation is poorly understood. A number of viral proteins have been implicated, and one hypothesis holds that circulating monocytes infected with HIV abnormally release high levels of endothelin-1, leading to pulmonary artery vasoconstriction and remodeling. The histopathology and clinical features are indistinguishable from those of idiopathic pulmonary arterial hypertension (IPAH). Antiretroviral therapy is indicated as part of the therapeutic approach, although the effect of antiretroviral agents on progression of PAH is unclear. Treatment is similar to that of IPAH (see Chapter 14), but use of endothelin-1 receptor antagonists and

phosphodiesterase-5 inhibitors is frequently problematic because of concerns about drug interactions.

### Diagnostic evaluation of pulmonary infiltrates in acquired immunodeficiency syndrome

Pulmonary infiltrates, often accompanied by fever, dyspnea, and cough, present a common problem in patients known to have either HIV infection or risk factors for exposure to HIV. Although typical radiographic presentations may suggest a particular diagnosis, findings are often nonspecific. In addition, with accumulation of experience with AIDS, more atypical presentations of many of these respiratory complications have been recognized. For example, with *Pneumocystis* infection, use of aerosolized pentamidine decreases the likelihood of infection but increases the frequency of atypical radiographic presentations when the infection occurs despite prophylactic therapy. Likewise, pulmonary tuberculosis in patients with advanced HIV infection may present with minimal or atypical radiographic manifestations.

Initial evaluation of diffuse pulmonary infiltrates frequently focuses on the diagnosis of *Pneumocystis* pneumonia in patients at high risk because of a $CD4^+$ count less than $200/mm^3$, especially if they are not receiving adequate prophylaxis. An elevated serum β-D-glucan level also supports the diagnosis of *Pneumocystis*. Induction of sputum accompanied by appropriate staining for *Pneumocystis* is often the first diagnostic procedure because of its noninvasive nature. When sputum induction produces negative findings, flexible bronchoscopy is usually the next procedure performed, typically with BAL and sometimes with transbronchial biopsy. The yield for *Pneumocystis* is excellent with BAL, but making a diagnosis of some of the other infections, neoplasms, and inflammatory processes may require transbronchial biopsy. During bronchoscopy, Kaposi sarcoma is strongly suspected if typical lesions are observed in the airways. Surgical lung biopsy is the most invasive of the diagnostic procedures and is usually reserved for situations where a diagnosis is crucial but not forthcoming by less invasive means.

## Pulmonary complications in non–HIV immunocompromised patients

Over the past several decades, increasing numbers of patients have been rendered immunocompromised due to organ transplantation, antineoplastic chemotherapy, or the use of immunosuppressive medications for inflammatory conditions. In addition, improved diagnostic tools have resulted in better identification of patients with primary disorders of one or more limbs of the immune system.

### Organ transplant recipients

With very rare exceptions, organ transplantation necessitates some degree of suppression of the recipient's immune system in order to prevent rejection of the transplanted organ. A necessary consequence of this immunosuppression is an increased risk of infection. Because the lungs communicate with the outside environment with every breath, pulmonary infections are very common in this

population and are a major cause of morbidity and mortality following organ transplantation.

## Solid organ transplantation

Lung transplantation is increasingly performed to treat a variety of end-stage lung diseases (see Chapter 30). In addition to the effects of immunosuppressive medications, the transplanted lung has impaired lymphatic drainage, decreased cough and mucociliary function, and constant exposure to organisms from the environment, all leading to an increased risk of a variety of types of pulmonary infection. The propensity of specific organisms to cause infections in the post–lung transplant period varies somewhat during the time course following transplantation.

In the first month after lung transplantation, pulmonary infections are most commonly caused by healthcare-associated pneumonia organisms such as Gram-negative rods and *Staphylococcus aureus*. Between months 1 and 6 after transplantation, patients are at maximal risk for opportunistic infections such as CMV, *P. jiroveci*, toxoplasmosis, *Aspergillus*, endemic fungi, and mycobacteria. By 6 months posttransplant, most patients are receiving stable and reduced levels of immunosuppression. These patients are most frequently subject to community-acquired pneumonias due to pneumococcus, *Mycoplasma*, *Legionella*, respiratory viruses (e.g., influenza, parainfluenza, RSV, adenovirus, and metapneumovirus), or other common respiratory pathogens. Information about the incidence and clinical course of COVID-19 infection in transplant recipients is evolving; however, full vaccination is required by most programs.

Similar patterns are observed among patients who receive transplants of other solid organs, such as the heart, liver, or kidney. However, the overall incidence of pneumonia is less common in these groups, both because their native lung defenses remain intact and because lower levels of immunosuppression are required. Notably, the widespread practice of prophylaxis against *P. jiroveci*, CMV, and other pathogens has helped reduce the overall incidence of pulmonary infections among solid organ transplant recipients over the past decade.

## Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) has largely replaced bone marrow transplantation as a treatment modality because of the ease of harvesting circulating hematopoietic stem cells by pheresis. HSCT is used to treat primary hematopoietic malignancies such as acute myelogenous leukemia and is also indicated for treating some solid organ malignancies and some chronic nonmalignant diseases of the bone marrow.

Most patients receiving HSCT undergo pretransplant treatment with antineoplastic agents or radiation therapy to destroy the native bone marrow so that transplanted bone marrow precursors can take residence with less risk of immunologic destruction. This usually imparts a prolonged period of neutropenia, in addition to other impairment of cell-mediated and humoral immunity.

As a consequence, HSCT recipients are at very high risk for infections, including respiratory tract infections. During the several weeks of profound neutropenia that follow transplantation, pulmonary infections are most commonly due to bacteria such as

*S. aureus* and Gram-negative rods or to fungi such as *Aspergillus*. After approximately 30 days, when neutrophil numbers have returned to normal but additional immunosuppression may be required to suppress graft-versus-host disease, viral infections become more common. Community-acquired pneumonia due to organisms such as *S. pneumoniae* is a constant concern. As with solid organ transplant recipients, appropriate prophylaxis against CMV and *P. jiroveci* has reduced the incidence of these specific infections in this population.

## Treatment of inflammatory conditions

Many inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and glomerulonephritis require chronic treatment with immunosuppressive medications. In many cases, oral corticosteroids can result in significant improvement in the inflammatory condition but do so at the expense of multiple adverse effects and an increased susceptibility to infection because of actions on multiple components of the immune response. Pulmonary infections in patients receiving chronic corticosteroids are most commonly due to routine community-acquired pneumonia pathogens, but there is also an increased risk of reactivation tuberculosis and infections due to *P. jiroveci*, *Aspergillus*, *Nocardia*, and other opportunistic pathogens.

Tumor necrosis factor (TNF)-α inhibitors are increasingly employed to treat chronic inflammatory disorders because of their greater efficacy and fewer adverse effects compared with corticosteroids. However, these medications also increase the risk for pulmonary and other infections. Increased risk for development of reactivation tuberculosis is well described, and it is essential that patients be tested and appropriately treated for latent tuberculous infection *before* starting therapy with TNF-α inhibitors. The risk of infection with nontuberculous mycobacteria or fungi such as *Coccidioides* also is increased.

## Primary immunodeficiencies

Primary immunodeficiencies are genetic disorders that result in dysfunction of one or more limbs of the immune response. *Antibody deficiencies* may be due to conditions such as X-linked agammaglobulinemia, common variable immunodeficiency, or immunoglobulin (Ig)G subclass deficiencies, and the diagnosis is usually confirmed by quantitative measurement of immunoglobulins. Patients with antibody deficiencies may suffer from recurrent sinopulmonary infections, most commonly from encapsulated bacteria such as *S. pneumoniae* and *H. influenzae*. Increased rates of infection with *Mycoplasma pneumoniae* have also been reported. Diffuse bronchiectasis may develop due to repeated infections (see Chapter 7). If the bronchiectasis is sufficiently severe, hypoxemia and cor pulmonale may ultimately ensue. Amelioration of many manifestations of antibody deficiencies may be possible by regular administration of intravenous human IgG.

*Cellular immunodeficiencies* are characterized by either reduced T cell numbers or function. Cellular immunodeficiencies are observed in conditions such as DiGeorge syndrome (in which a deletion on chromosome 22 leads to thymic hypoplasia) or severe combined immunodeficiency syndrome, a heterogeneous group of conditions characterized by absent or severely impaired T-cell function and some element of concomitant B-cell hypofunction. Patients usually present in early infancy with

recurrent gastrointestinal and pulmonary infections due to common and opportunistic pathogens (e.g., *P. jiroveci*), as well as thrush and impaired growth. Patients have a high mortality due to disseminated infections. HSCT from a human leukocyte antigen (HLA) identical donor is successful in reversing the immunodeficiency state in some patients.

*Phagocytic cell disorders* may also lead to recurrent pulmonary infections. For example, patients with chronic granulomatous disease lack NADPH oxidase function and frequently develop pulmonary infections due to catalase-positive organisms such as *Aspergillus*, *S. aureus*, and *Burkholderia cepacia*. Patients with hyper-IgE syndrome (also called *Job syndrome*) have defects in immunologic signaling pathways causing impaired T-cell function and leading to increased susceptibility to pulmonary infections due to *S. aureus*, *H. influenzae*, *Aspergillus*, and *Pseudomonas*.

## Diagnostic evaluation of pulmonary infiltrates in non–HIV immunocompromised patients

As for patients with HIV infection, the approach to the non-HIV immunocompromised patient with pulmonary infiltrates revolves around the attempt to identify an infectious agent or noninfectious etiology. Because the differential diagnosis of pulmonary infiltrates in these patients is so broad, clues from the exposure history and radiographic patterns may be even more useful. Noninvasive assessment with antigen detection, PCR assays, β-1,3-glucan levels, sputum examination, and other tests is typically performed. However, invasive testing with specimens obtained by bronchoscopy or thoracoscopic lung biopsy may also be necessary. The procedure chosen is based on specific clinical features relevant to each patient, such as the nature of the underlying disease, suspected cause of the pulmonary infiltrate, presence or absence of other predisposing factors, and potential risks of a diagnostic procedure. However, in some immunocompromised patients with pulmonary infiltrates, empirical treatment is given without a definitive diagnosis, particularly when patients are at high risk for complications from invasive procedures.

The spectrum of infectious and noninfectious causes of pulmonary infiltrates in the immunosuppressed host is given in Table 27.1. Although fungi and other relatively unusual types of organisms are commonly thought to be the major causes of infectious infiltrates in patients receiving treatment for malignancy, bacterial pneumonia is still the most frequent problem in this setting. Neutropenia is an important predisposing factor for bacterial pneumonias, which frequently are due to Gram-negative rods or *Staphylococcus*.

**TABLE 27.1**

**Common Causes of Pulmonary Infiltrates in the Immunocompromised Host**

| **Infections** |
| --- |
| ***Bacteria*** |
| Gram-positive cocci, especially *Staphylococcus*<br>Gram-negative bacilli |

| |
|---|
| *Mycobacterium tuberculosis*<br>Nontuberculous mycobacteria<br>*Nocardia* |
| ***Viruses*** |
| Cytomegalovirus<br>Herpesvirus<br>SARS-CoV-2 (likely) |
| ***Fungi*** |
| *Aspergillus*<br>*Cryptococcus*<br>*Candida*<br>*Mucor*<br>*Pneumocystis jiroveci* |
| ***Protozoa*** |
| *Toxoplasma gondii* (rare) |
| ***Pulmonary Effects of Therapy*** |
| Drug toxicity (chemotherapy, molecularly targeted agents including monoclonal antibodies)<br>Radiation therapy |
| **Pulmonary Hemorrhage** |
| **Heart Failure** |
| **Disseminated Malignancy** |
| **Nonspecific Interstitial Pneumonitis (No Defined Etiology)** |

Other bacteria, namely mycobacteria (either *M. tuberculosis* or nontuberculous mycobacteria) and *Nocardia*, mainly cause problems in the patient with impaired cellular immunity. Defective cellular immunity also predisposes the individual to infections with *P. jiroveci*, other fungi, and viruses. The fungus *Aspergillus*, which causes an invasive pneumonia in the immunosuppressed patient, is commonly found in the patient who is neutropenic (and also has impaired cellular immunity) from cytotoxic chemotherapy.

Common noninfectious diagnoses are interstitial lung diseases due to side effects of radiation therapy or a variety of chemotherapeutic and other agents with specific molecular targets (see Chapter 10). Among lung transplant recipients, development of pulmonary infiltrates and fever is highly suggestive of an infectious pneumonia, although acute lung transplant rejection can present in a similar fashion. Heart failure (often secondary to cardiac toxicity from chemotherapeutic agents), pulmonary dissemination of the underlying malignancy, and hemorrhage into the pulmonary parenchyma are other causes of infiltrates that can closely mimic infectious etiologies. In many circumstances, an interstitial inflammatory process can be proved

histologically, but no definite cause can be identified. These cases often are diagnosed as nonspecific interstitial pneumonitis, with the realization that neither the pathology nor the clinical history provides a specific etiologic diagnosis.

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# 28: Classification and pathophysiologic aspects of respiratory failure

OUTLINE



Many types of respiratory disease may impair the normal function of the lung as a gas-exchanging organ. In some cases, the degree of impairment is mild, and the patient suffers relatively few consequences. In other cases, dysfunction is marked, and the patient experiences disabling or life-threatening clinical sequelae. When the respiratory system can no longer function to keep gas exchange at an acceptable level, the patient is said to be in *respiratory failure*, irrespective of the underlying cause.

The tempo for development of respiratory failure varies, depending on the nature of the underlying problem. Many of the diseases discussed so far, such as chronic obstructive pulmonary disease (COPD) and diffuse parenchymal (interstitial) lung diseases, are characterized by a chronic clinical course accompanied by relatively slow deterioration of pulmonary function and gas exchange. However, because of limited pulmonary reserve, patients with preexisting pulmonary disease are also susceptible to episodes of acute respiratory failure, either from a superimposed intercurrent illness or from transient worsening of their underlying disease. On the other hand, acute or

subacute respiratory failure also can develop in individuals without preexisting lung disease. The initiating problem in these patients is often a primary respiratory illness or a disorder of another organ system accompanied by major respiratory complications.

This chapter presents an overview of the problem of respiratory failure and discusses the different pathophysiologic types and consequences of respiratory insufficiency. Chapter 29 addresses a specific form of acute respiratory failure known as *acute respiratory distress syndrome* (ARDS), which does not require the presence of preexisting lung disease. Chapter 30 considers some principles of management of respiratory failure, as well as specific modalities of current therapy.

# Definition of respiratory failure

Respiratory failure is best defined as the inability of the respiratory system to maintain adequate gas exchange. Exactly where to draw the line for "adequate gas exchange" is somewhat arbitrary, but in a previously normal individual, arterial $P_{O_2}$ less than 60 mm Hg or $P_{CO_2}$ greater than 50 mm Hg generally is considered evidence for acute respiratory failure. In the individual with preexisting lung disease, the situation is more complicated because the patient chronically has impaired gas exchange and abnormal blood gas values.

For patients with normal baseline arterial blood gas measurements, criteria for respiratory failure are $P_{O_2}$ less than 60 mm Hg or $P_{CO_2}$ more than 50 mm Hg.

For example, it would not be unusual for a patient with significant COPD to perform daily activities with $P_{O_2}$ approximately 60 mm Hg and $P_{CO_2}$ 50 to 55 mm Hg. By the blood gas criteria just mentioned, this patient is always in respiratory failure, but the condition obviously is chronic, not acute. A look at the patient's pH value shows that the kidneys have compensated for the $CO_2$ retention, and the pH is not far from the normal value of 7.40.

At which point is the condition called acute respiratory failure? Certainly if an acute respiratory illness such as an acute pneumonia develops, the patient's gas exchange becomes even worse. $P_{O_2}$ falls further, and $P_{CO_2}$ may rise even higher. In this case, acute respiratory failure is defined as a significant change from the patient's baseline gas exchange status. If the patient's usual arterial blood gases are known, the task is easier. If the blood gases are not known, the pH value can provide a clue about whether the patient's $CO_2$ retention is acute or chronic. When a patient is seen initially with $P_{CO_2}$ 70 mm Hg, the implications are quite different if the accompanying pH value is 7.15 as opposed to 7.36.

# Classification of acute respiratory failure

## Hypoxemic type

In practice, it is most convenient to classify acute respiratory failure into two major categories based on the pattern of gas exchange abnormalities. In the first category,

hypoxemia is the major problem, with the patient's $P_{CO_2}$ normal or low. This condition is the hypoxemic variety of acute respiratory failure. For example, localized diseases of the pulmonary parenchyma (e.g., pneumonia) can result in this type of respiratory failure if the disease is sufficiently severe. However, an even broader group of etiologic factors causes hypoxemic respiratory failure by means of increased permeability of pulmonary capillaries, leading to leakage of fluid from the pulmonary capillaries into alveolar spaces and a generalized increase in fluid within alveoli. The latter problem is frequently called ARDS and can be the consequence of a wide variety of disorders that cause an increase in pulmonary capillary permeability.[1] Because of the importance of this syndrome as a major form of acute respiratory failure, Chapter 29 focuses entirely on the problem of ARDS. Another relatively common cause of hypoxemic respiratory failure is hydrostatic pulmonary edema due to heart failure or renal failure.

Categories of acute respiratory failure:

1. Hypoxemic (with normal or low $P_{CO_2}$)
2. Hypercapnic/hypoxemic

Examples of hypoxemic respiratory failure:

1. Severe pneumonia
2. ARDS
3. Hydrostatic pulmonary edema from decompensated heart failure or renal failure

## Hypercapnic/hypoxemic type

In the second category, hypercapnia is present. For the respiratory failure to be considered acute, the pH must show absent or incomplete metabolic compensation for the respiratory acidosis. From the discussion of alveolar gas composition and the alveolar gas equation in Chapter 1, it is apparent that hypercapnia is associated with decreased arterial $P_{O_2}$ because of altered alveolar $P_{O_2}$. Therefore, even if ventilation and perfusion are relatively well matched and the fraction of blood shunted across the pulmonary vasculature is not increased, arterial $P_{O_2}$ falls in the presence of hypoventilation and consequent hypercapnia. In practice, many cases of hypercapnic respiratory failure also have marked ventilation-perfusion mismatch, which further accentuates the hypoxemia. With these concepts in mind, it is clear that the hypercapnic form of respiratory failure typically involves both hypercapnia and hypoxemia, and thus is more appropriately considered the hypercapnic/hypoxemic form of respiratory failure.

A number of types of respiratory disease are potentially associated with this second form of respiratory failure. How the various disorders result in hypercapnic/hypoxemic respiratory failure is explained in the "Pathogenesis of Gas Exchange Abnormalities" section of this chapter. These disorders primarily include: (1) depression of the neurologic system responsible for respiratory control; (2) disease of the respiratory

bellows, either the chest wall or the neuromuscular apparatus responsible for thoracic expansion; and (3) COPD. More than one of these three problems commonly ares present, compounding the potential for respiratory insufficiency.

Causes of hypercapnic/hypoxemic respiratory failure:

1. Depression of central nervous system ventilatory control
2. Disease of the respiratory bellows
3. COPD

In the hypercapnic/hypoxemic form of respiratory failure, patients often have preexisting disease causing either chronic respiratory insufficiency or limitations in respiratory reserve, making them much more susceptible to decompensation with an acute superimposed problem. This form of respiratory failure is called *acute-on-chronic respiratory failure*, reflecting prior problems or limitations with respiratory reserve. This expression is used most commonly to describe the patient with COPD in whom acute respiratory failure develops at the time of an infection or another acute respiratory insult.

## Presentation of gas exchange failure

When acute respiratory failure develops, the patient's symptom complex generally includes the manifestations of hypoxemia, hypercapnia, or both, accompanied by the specific symptoms related to the precipitating disorder. Dyspnea is present in the majority of cases and is the symptom that often suggests to the physician the possibility of respiratory failure.

Clinical presentation with respiratory failure may consist of:

1. Dyspnea
2. Impaired mental status
3. Headache
4. Tachycardia
5. Papilledema (with ↑ $P_{CO_2}$)
6. Variable findings on lung examination
7. Cyanosis (with severe hypoxemia)

Changes in mental status are frequent results of either hypoxemia or hypercapnia. Patients may become disoriented, confused, and unable to conduct their normal level of activity. With profound hypercapnia, patients may become stuporous and eventually lapse into a coma. Headache is a common finding in patients with hypercapnia; dilation of cerebral blood vessels as a consequence of increased $P_{CO_2}$ is probably an important factor in its pathogenesis.

Physical findings associated with abnormal gas exchange are relatively few. Patients may be tachypneic, tachycardic, and restless, findings that are relatively nonspecific.

Examination of the optic fundi may reveal papilledema (swelling and elevation of the optic disk) resulting from hypercapnia, cerebral vasodilation, and increased intracranial pressure. Findings in the lung are related to the specific form of disease present—for example, wheezing and/or rhonchi in COPD, or crackles due to fluid in the small airways and alveolar spaces. When hypoxemia is severe, patients may become cyanotic, which is apparent as a dusky or bluish hue to the nail beds and mucous membranes. Of note, a critical amount of deoxygenated hemoglobin is required for cyanosis to manifest, and anemic patients may not become cyanotic despite profound hypoxemia.

# Pathogenesis of gas exchange abnormalities

The basic principles of abnormal gas exchange were discussed in Chapter 1. The focus here is on applying these principles to patients with respiratory failure. A discussion of hypoxemic respiratory failure is followed by a discussion of hypercapnic/hypoxemic failure.

## Hypoxemic respiratory failure

In patients with hypoxemic respiratory failure, two major pathophysiologic factors contribute to lowering of arterial $P_{O_2}$: ventilation-perfusion mismatch and shunting. In patients with significant ventilation-perfusion mismatch, regions with a low ventilation-to-perfusion ratio return relatively desaturated blood to the systemic circulation. What sorts of problems cause a decrease in ventilation relative to perfusion in a particular region of the lung? If an alveolus or a group of alveoli is partially filled with fluid, only a limited amount of ventilation reaches that particular area, whereas perfusion to the region may remain relatively preserved. Similarly, if an airway supplying a region of lung is diseased, either by pathology affecting the airway wall or by secretions occupying the lumen, then ventilation is limited.

When these problems become extreme, ventilation to a region of perfused lung may be totally absent so that a true shunt—perfusion without ventilation—exists. For example, alveoli may be completely filled with fluid, or an airway may be completely obstructed, preventing any ventilation to the involved area. Although the response of the pulmonary vasculature is to constrict and thereby limit perfusion to an underventilated or unventilated portion of the lung, this protective mechanism often cannot fully compensate for the loss of ventilation, and hypoxemia results. Of note, inflammation in the lung, as occurs in the presence of pneumonia, tends to decrease the effectiveness of hypoxic vasoconstriction and further worsen ventilation-perfusion matching. Alveolar filling with fluid and collapse of small airways and alveoli seem to be the main pathogenetic features leading to ventilation-perfusion mismatch and shunting in ARDS (see Chapter 29). An earlier consideration of the ability of supplemental $O_2$ to raise $P_{O_2}$ in conditions of ventilation-perfusion mismatch versus shunt indicated that $O_2$ cannot improve $P_{O_2}$ substantially for truly shunted blood (see Chapter 1). Therefore, when the shunt fraction of cardiac output is quite high, oxygenation may be helped much less than expected by administration of high concentrations of supplemental $O_2$.

Despite the marked derangement of oxygenation in ARDS, $CO_2$ elimination typically remains adequate because, at least early in the course of the syndrome, patients are able

to maintain alveolar ventilation at an acceptable level. Even when regions of the lung have a high ventilation-perfusion ratio and thus effectively act as dead space, patients are generally able to compensate by increasing their overall minute ventilation.

## Hypercapnic/hypoxemic respiratory failure

In the hypercapnic form of respiratory failure, patients are unable to maintain a level of alveolar ventilation sufficient to eliminate $CO_2$ and keep arterial $P_{CO_2}$ within the normal range. Because ventilation is determined by a sequence of events ranging from generation of impulses by the respiratory controller to movement of air through the airways, there are multiple stages at which problems can adversely affect alveolar ventilation. This sequence is shown in Fig. 28.1, which also lists some of the disorders that can interfere at each level. Recall that only alveolar ventilation participates in gas exchange. Thus, if the proportion of each breath going to dead space (i.e., ratio of volume of dead space to tidal volume [$V_D/V_T$]) increases substantially, alveolar ventilation may fall to a level sufficient to cause elevated $P_{CO_2}$, even if total minute ventilation is preserved.

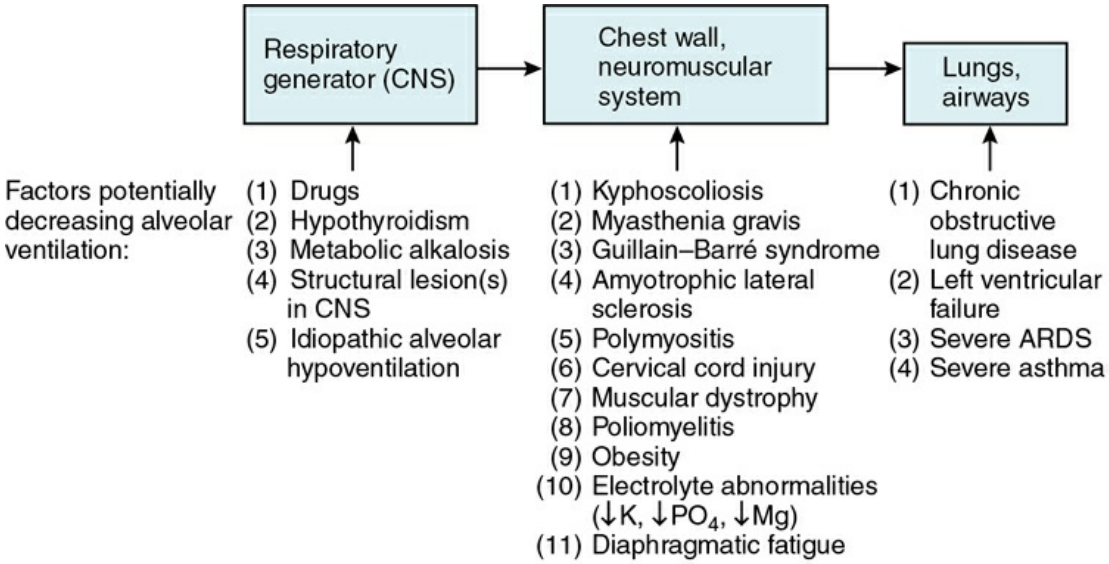


**FIGURE 28.1** Levels at which interference with normal ventilation give rise to alveolar hypoventilation. Factors contributing to decreased ventilation are listed under each level. *ARDS*, acute respiratory distress syndrome; *CNS*, central nervous system.

In the hypercapnic form of respiratory failure, hypoventilation also leads to a decrease in alveolar $P_{O_2}$. As a result, arterial $P_{O_2}$ falls even if ventilation-perfusion matching and gas exchange at the alveolar level are well maintained. In practice, however, many of the diseases associated with alveolar hypoventilation, ranging from neuromuscular and chest wall disease to chronic airflow obstruction, are accompanied by significant ventilation-perfusion mismatch. Therefore, patients generally have two major reasons

for hypoxemia: hypoventilation and ventilation-perfusion mismatch. Interestingly, true shunts usually play a limited role in causing hypoxemia in these disorders, unlike the situation in ARDS.

Given the causes of hypoxemia in the hypercapnic/hypoxemic form of respiratory failure, patients frequently respond to supplemental $O_2$ with a substantial rise in arterial $P_{O_2}$. However, most of these patients have at least mild chronic $CO_2$ retention, with their acute respiratory failure resulting from some precipitating insult or worsening of their underlying disease. Administration of supplemental $O_2$ to these chronically hypercapnic patients may lead to a further increase in arterial $P_{CO_2}$ for a number of pathophysiologic reasons (see Chapter 18). With judicious use of supplemental $O_2$, substantial additional elevation of arterial $P_{CO_2}$ can usually be avoided.

An elaboration of further features of the hypercapnic/hypoxemic form of respiratory failure follows.

## Clinical and therapeutic aspects of hypercapnic/hypoxemic respiratory failure

Whether the underlying disease is chest wall disease (e.g., kyphoscoliosis) or COPD, this type of respiratory failure often develops in patients who already have some degree of chronic respiratory insufficiency. However, this is not true of all cases. In certain neurologic conditions such as Guillain-Barré syndrome, hypercapnic respiratory failure occurs in a previously healthy, eucapnic individual.

As noted earlier, when the patient has chronic disease upon which acute respiratory failure is superimposed, the phrase *acute-on-chronic respiratory failure* is frequently used. In such cases, a specific different problem often precipitates the acute deterioration, and identification of the problem is important.

Frequent precipitants of acute-on-chronic respiratory failure:

1. Respiratory infection
2. Drugs (e.g., sedatives, narcotics)
3. Heart failure
4. Exacerbation of underlying neuromuscular disease (e.g., myasthenic crisis)

What are some of the intercurrent problems or factors that precipitate acute respiratory failure in these patients? Perhaps the most common is an acute respiratory infection, such as bronchitis, usually caused by a virus. However, bacterial causes must always be considered because they are amenable to antibiotic therapy. The use of drugs that suppress the respiratory center, such as sedatives or narcotics, may precipitate hypercapnic respiratory failure by depressing central respiratory drive in a person whose condition already was marginal. Other intercurrent problems include heart failure, pulmonary emboli, and exposure to environmental pollutants, each of which may be sufficient to induce further $CO_2$ retention in the patient with previously borderline compensation.

The general therapeutic approach to these patients has three main components: (1) support of gas exchange, (2) treatment of the acute precipitating event, and (3) treatment of the underlying pulmonary disease. The support of gas exchange involves maintaining adequate oxygenation and elimination of $CO_2$ (see Chapter 30). Briefly, supplemental $O_2$, generally in a concentration only slightly higher than that found in ambient air, is administered to raise $P_{O_2}$ and $SaO_2$ to acceptable levels (i.e., more than 60 mm Hg and more than 90%, respectively). If $CO_2$ elimination deteriorates and $P_{CO_2}$ rises much beyond its usual level, then an acute respiratory acidosis is superimposed on the patient's usual acid-base status. If significant acidemia develops or if the patient's mental status changes significantly due to $CO_2$ retention, some form of ventilatory assistance, either intubation and mechanical ventilation or noninvasive positive-pressure ventilation with a mask, may be required.

Treating the factor precipitating acute respiratory failure is most successful when bacterial infection or heart failure is responsible for the acute deterioration. Antibiotics for suspected bacterial infection, or diuretics and afterload reduction for heart failure, are appropriate forms of therapy in these circumstances. For patients in whom respiratory secretions seem to be playing a role either chronically or in an acute exacerbation of their disease, attempts to assist with clearance of secretions may be beneficial. In particular, chest physical therapy, in which percussion and vibration of the chest are performed and cough is assisted mechanically, may be beneficial.

Treatment of the underlying pulmonary disease depends on the nature of the disease. For patients with obstructive lung disease, intensive therapy with bronchodilators and corticosteroids may be helpful in reversing whatever components of bronchoconstriction and inflammation are present. If neuromuscular or chest wall disease is the underlying problem, specific therapy may be available, as is the case with myasthenia gravis. Unfortunately, for many neuromuscular or chest wall diseases, no specific form of therapy exists, and support of gas exchange and treatment of any precipitating factors are the major modes of therapy.

When patients with irreversible chest wall or neuromuscular disease are in frank respiratory failure, they may require some form of ventilatory assistance on a chronic basis. (Modalities for chronic ventilatory support are discussed in Chapter 30.) It is important to emphasize that the primary decision to be made is whether chronic ventilatory support is acceptable to a patient with this type of irreversible disease. In many cases the patient, family, and physician make the joint decision that life should not be prolonged with chronic ventilator support, given the projected poor quality of life and irreversible nature of the process.

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The abbreviation *ARDS* formerly was used for *adult respiratory distress syndrome*, but *acute* has now replaced *adult* because the entity can occur in individuals of any age.

# 29: Acute respiratory distress syndrome

OUTLINE



This chapter continues the discussion of respiratory failure with more detailed consideration of one important type of acute respiratory failure: *acute respiratory distress syndrome* (ARDS). This entity was initially called *adult respiratory distress syndrome*, but it is not limited to adults, so *acute* rather than *adult* is now the preferred terminology. ARDS represents a common and important form of acute hypoxemic respiratory failure. Its clinical and pathophysiologic features differ considerably from those noted for acute-on-chronic respiratory failure. ARDS is characterized by the presence of severe arterial hypoxemia and diffuse bilateral pulmonary infiltrates, not exclusively due to cardiogenic or hydrostatic causes. The full criteria for establishing the diagnosis of ARDS are shown in Table 29.1. This chapter describes in detail each of these

criteria and the associated pathology and pathophysiology.

**TABLE 29.1**

**2012 Berlin Definition of Acute Respiratory Distress Syndrome (All Components Must be Present)**

| | | | |
|---|---|---|---|
| Timing | Within 1 week of a known clinical insult or new/worsening respiratory symptoms | | |
| Chest imaging | Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules | | |
| Origin of edema | Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor for ARDS is present | | |
| Oxygenation | *Mild ARDS* | *Moderate ARDS* | *Severe ARDS* |
| | 200 < $Pao_2/Fio_2$ ≤ 300 with PEEP or CPAP ≥ 5 cm $H_2O$ | 100 < $Pao_2/Fio_2$ ≤ 200 with PEEP ≥ 5 cm $H_2O$ | $Pao_2/Fio_2$ ≤ 100 with PEEP ≥ 5 cm $H_2O$ |

*ARDS*, acute respiratory distress syndrome.

ARDS is characterized by the presence of acute, severe arterial hypoxemia and bilateral pulmonary infiltrates not attributable exclusively to cardiogenic or hydrostatic causes.

Rather than a specific disease, ARDS truly is a syndrome resulting from any of a number of etiologic factors. It is perhaps simplest to consider this syndrome as the nonspecific result of acute injury to the lungs, characterized by breakdown of the normal barrier that prevents leakage of fluid out of the pulmonary capillaries and into the interstitium and alveolar spaces. Another term, *acute lung injury*, was formerly used to describe a similar process of lung injury in which the disturbance in oxygenation is less severe, whereas ARDS represented the more severe end of the spectrum. However, the current classification eliminates “acute lung injury” as a specific term and instead grades ARDS as mild, moderate, or severe based on the degree of hypoxemia that is present. A number of other names have been used to describe ARDS, including *noncardiogenic pulmonary edema*, *shock lung*, and *posttraumatic pulmonary insufficiency*.

This chapter first considers the dynamics of fluid transfer between the pulmonary vessels and alveolar interstitium because alterations in this process are important in the pathogenesis of ARDS. Next is an outline of the many types of injury that can result in ARDS and some of the theories proposed to explain how such a diverse group of disorders can produce this syndrome. We then proceed with a discussion of the pathologic, pathophysiologic, and clinical consequences of ARDS. The chapter concludes with a general approach to treatment. More specific details about support of impaired gas exchange are provided in Chapter 30.

## Physiology of fluid movement in alveolar interstitium

Despite the diverse group of disorders that can cause ARDS, the net result of the syndrome is the same: a disturbance in the normal barrier that limits movement of fluid normally contained within the pulmonary capillaries into the alveoli. Before a discussion of some of the theories explaining how this barrier is damaged, a brief consideration of the determinants of fluid transport among the pulmonary vessels, interstitium, and alveolar space may be helpful. The pulmonary parenchyma (Fig. 29.1) consists of (1) small vessels coursing through the alveolar walls, which are referred to as the *pulmonary capillaries*; (2) *pulmonary capillary endothelium*, the lining cells that normally limit but do not completely prevent fluid movement out of the capillaries; (3) *pulmonary interstitium*, which is considered here as the alveolar wall exclusive of vessels and the epithelial cells lining the alveolar lumen; (4) *lymphatic channels*, which are found mainly in perivascular connective tissue in the lungs; (5) *alveolar epithelial cells*, which line the surface of the alveolar lumen; and (6) *alveolar lumen* or alveolar space.

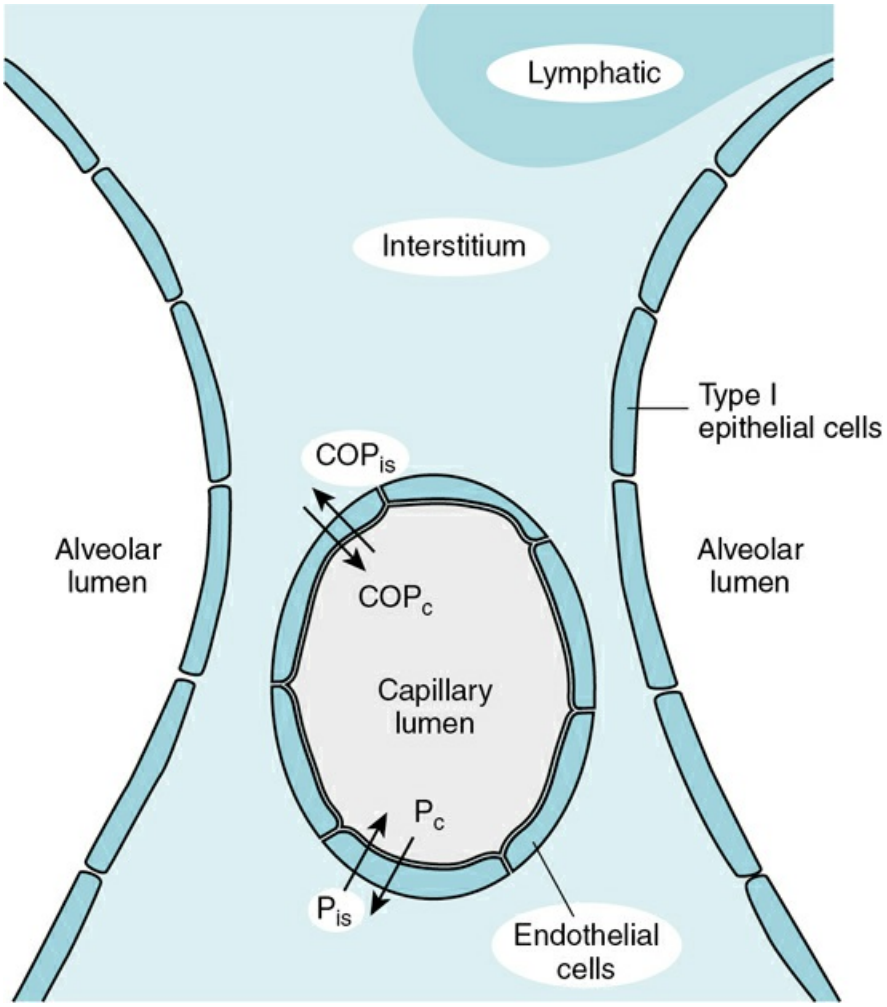


**FIGURE 29.1** Schematic diagram of the lung's gas-exchanging region. Forces governing fluid movement between pulmonary

capillary lumen and alveolar interstitium are shown. Arrows show direction of fluid movement favored by each of the important forces. Lymphatic vessels are located in perivascular connective tissue rather than within alveolar walls. $COP_c$, pulmonary capillary colloid osmotic pressure; $COP_{is}$, interstitial space colloid osmotic pressure; $P_c$, pulmonary capillary hydrostatic pressure; $P_{is}$, interstitial space hydrostatic pressure.

Movement of fluid out of the pulmonary capillaries and into the interstitial space is determined by the hydrostatic pressures in the vessels and the pulmonary interstitium, the colloid osmotic pressures in these same two compartments, and the permeability of the endothelium. The effect of these factors in determining fluid transport is summarized in the Starling equation, examined in Chapter 15 with regard to fluid transport across the pleural space. The Starling equation is repeated here as Eq. 29.1:
(Eq. 29.1)

$$F = K\left[(P_C - P_{is}) - \sigma(COP_C - COP_{is})\right]$$

where F is the fluid movement; $P_c$ and $P_{is}$ the pulmonary capillary and interstitial space hydrostatic pressure, respectively; $COP_c$ and $COP_{is}$ the pulmonary capillary and interstitial space colloid osmotic (oncotic) pressure, respectively; K the filtration coefficient; and σ the reflection coefficient (measure of permeability of endothelium for protein).

Fluid normally moves from the pulmonary capillaries to the interstitial space. Resorption by lymphatics prevents accumulation.

If estimates of the actual numbers are substituted for normal hydrostatic and oncotic pressures in Eq. 29.1, F is a positive number, indicating that fluid normally moves out of the pulmonary capillaries and into the interstitial space. Even though the rate of fluid movement out of the pulmonary capillaries is estimated to total approximately 20 mL/h, this fluid does not accumulate. Under normal conditions, the lymphatic vessels are effective in absorbing both protein and fluid that have left the vasculature and entered the interstitial space. However, if fluid movement into the interstitium increases substantially or if lymphatic drainage is impeded, fluid accumulates within the interstitial space, resulting in interstitial edema. When sufficient fluid accumulates or the alveolar epithelium is damaged, fluid also moves across the epithelial cell barrier and into the alveolar spaces, resulting in alveolar edema.

## Two mechanisms of fluid accumulation

In practice, the forces described in the Starling equation become altered in two main ways, producing interstitial and often alveolar edema (Table 29.2). The first occurs when hydrostatic pressure within the pulmonary capillaries ($P_c$) is increased, generally due to

elevated left atrial pressure (e.g., in left ventricular failure or mitral stenosis). The resulting pulmonary edema is called *cardiogenic* or *hydrostatic pulmonary edema*, and the cause is essentially an imbalance between the hydrostatic and oncotic forces governing fluid movement. In this form of edema, the permeability barrier that limits movement of protein out of the capillaries is intact, and the fluid that leaks out has a very low protein content.

**TABLE 29.2**
**Categories of Pulmonary Edema**

| Feature | Cardiogenic | Noncardiogenic |
|---|---|---|
| Major causes | Left ventricular failure, mitral stenosis | Acute respiratory distress syndrome |
| Pulmonary capillary pressure | Increased | Normal |
| Pulmonary capillary permeability | Normal | Increased |
| Protein content of edema fluid | Low | High |

In the second mechanism by which fluid accumulates, hydrostatic pressures are normal, but the permeability of the capillary endothelial and alveolar epithelial barriers is increased as a result of damage to one or both of these cell populations. Movement of proteins out of the intravascular space occurs as a consequence of the increase in permeability. Due to the increase in permeability to large molecules, the fluid that leaks out has a relatively high protein content, often close to that found in plasma. This second mechanism is the one operative in ARDS. Because an elevation in pulmonary capillary pressure from cardiac disease is not involved, this form of edema is called *noncardiogenic pulmonary edema*.

Although cardiogenic and hydrostatic pulmonary edema are mentioned here, subsequent parts of this chapter focus on noncardiogenic edema (i.e., ARDS). However, it is important to remember that hydrostatic pressures still have an important impact on fluid movement, even when the primary problem is a defective permeability barrier. Specifically, higher pulmonary capillary hydrostatic pressures result in more fluid leaking through an abnormally permeable pulmonary capillary endothelium than occurs at lower pressures. At the extreme, some patients with a permeability defect of the pulmonary capillary bed simultaneously have a grossly elevated pulmonary capillary pressure due to concurrent left ventricular failure. In these cases, the permeability defect and the elevated hydrostatic pressure work synergistically in contributing to leakage of fluid out of the pulmonary vasculature. Not only is the fluid leak compounded, but when both factors are involved, sorting out the relative importance of each and thus determining the optimal treatment priorities in a given patient can be difficult.

## Etiology

Numerous and varied disorders are associated with the potential to produce ARDS (Table 29.3). What these diverse etiologic factors in ARDS have in common is their ability to cause diffuse injury to the pulmonary parenchyma. Beyond that, defining other features that link the underlying causes is difficult based on our present knowledge. Even the route of injury varies. Some etiologic factors involve inhaled injurious agents; others appear to mediate their effects on the lungs via the circulation rather than the airway.

**TABLE 29.3**

**Causes of Diffuse Alveolar Damage and Acute Respiratory Distress Syndrome**

| |
|---|
| Aspiration |
| Gastric contents |
| Salt/fresh water (near drowning) |
| Hydrocarbons |
| Toxic gas inhalation |
| Nitrogen dioxide ($NO_2$) |
| Smoke |
| E-cigarette or vaping use-associated lung injury (EVALI) |
| Ammonia |
| Phosgene |
| Bilateral pneumonia |
| Viral (e.g., COVID-19, influenza) |
| Bacterial |
| *Pneumocystis jiroveci* |
| Sepsis |
| Shock (accompanied by other etiologic factors) |
| Trauma |
| Disseminated intravascular coagulation |
| Embolism |
| Fat embolism |
| Amniotic fluid embolism |
| Drugs |
| Narcotics |
| Sedatives |
| Aspirin (rare) |
| Thiazides (rare) |
| Multiple transfusions |
| Pancreatitis |
| Neurogenic |
| Head trauma |
| Intracranial hemorrhage |
| Seizures |
| Mechanical ventilation (overdistention and/or cyclic opening and closing of alveoli)[a] |

*ARDS*, acute respiratory distress syndrome.

[a]Generally not a primary cause of acute respiratory distress syndrome but a potential secondary contributor to alveolar damage (see Chapter 30).

## Inhaled injurious agents

Numerous injurious agents that reach the pulmonary parenchyma through the airway have been identified. In some cases, a liquid is responsible; examples include gastric contents, salt or fresh water, and hydrocarbons. With acidic gastric contents, especially when pH is lower than 2.5, patients sustain a "chemical burn" to the pulmonary parenchyma, resulting in damage to the alveolar epithelium. In the case of near drowning in either fresh or salt water, not only does the inhaled water fill alveolar spaces, but secondary damage to the alveolar-capillary barrier causes fluid to leak from the pulmonary vasculature. Because salt water is hypertonic to plasma, it draws fluid from the circulation as a result of an osmotic pressure gradient. Fresh water, on the other hand, is hypotonic to plasma and cellular contents and thus may enter pulmonary parenchymal cells, with resulting cellular edema. In addition, fresh water appears to inactivate surfactant, a complicating factor discussed in more detail under Pathophysiology. Finally, aspirated hydrocarbons can be toxic to the distal parenchyma, perhaps in part because they also inactivate surfactant and cause significant changes in surface tension.

A number of inhaled gases have been identified as potential acute toxins and precipitants of ARDS. Nitrogen dioxide is one example, as are some chemical products of combustion when smoke inhalation occurs. A more recently described cause is e-cigarette or vaping use-associated lung injury (EVALI), in which inhaled vaporized chemicals initiate the development of ARDS among susceptible individuals, particularly if vitamin E acetate is among the inhaled agents. A high concentration of inhaled oxygen, particularly when given for prolonged periods, can contribute to alveolar injury. The mechanism of $O_2$ toxicity is believed to be the generation of free radicals and superoxide anions, byproducts of oxidative metabolism that are toxic to pulmonary epithelial and endothelial cells. It is ironic that $O_2$ can contribute to lung injury, given that it is so important in supportive treatment of ARDS. Chapter 30 discusses an additional way in which treatment of ARDS may worsen alveolar damage through overdistention and/or cyclic opening and closing of alveoli induced by mechanical ventilation.

Infectious agents may produce injury via airway access to the pulmonary parenchyma. Bacterial pneumonia is a common underlying clinical problem associated with development of ARDS. Another important cause of ARDS is viral pneumonia such as COVID-19 or influenza pneumonia, which damages parenchymal cells and adjacent endothelial cells, thus altering alveolar-capillary permeability. In the initial decade of the AIDS epidemic, pneumonia due to *Pneumocystis jiroveci* became a common cause of ARDS. However, with the advent of highly active antiretroviral therapy in the mid-1990s and the availability of effective prophylactic regimens against *Pneumocystis*, it is now an uncommon cause of ARDS.

## Injury via pulmonary circulation

For causes of ARDS that do not involve inhaled agents or toxins, the pulmonary circulation is believed to be the route of injury. However, in most cases a specific circulating factor has not been identified with certainty, even though several possibilities

have been proposed. One of the most common precipitants for ARDS is sepsis, in which microorganisms or their products (especially endotoxin) circulating through the bloodstream initiate a sequence of events resulting in toxicity to parenchymal cells.

Although the term *shock lung* was used many years ago to describe what is now called ARDS, the presence of hypotensive shock alone is probably insufficient for development of ARDS. Patients in whom ARDS develops seemingly as a result of hypotension usually have complicating potential etiologic factors (e.g., trauma, sepsis) or have received therapy (e.g., blood transfusions) associated with cellular damage.

Patients with the coagulation disorder known as *disseminated intravascular coagulation* (DIC) appear to have the potential for development of ARDS. In DIC, patients have ongoing activation of both the clotting mechanism and the protective fibrinolytic system that prevents clot formation and propagation. Like ARDS, DIC is a syndrome and can occur because of a variety of primary or underlying causes; although these two problems are frequently associated, whether and exactly how one causes the other is uncertain.

When fat or amniotic fluid enters the circulation, the material is transported to the lungs, resulting in the clinical problems of fat embolism and amniotic fluid embolism, respectively. Presumably these materials are toxic to endothelial cells of the pulmonary capillaries, and the development of ARDS is well described in these clinical settings.

A variety of drugs, many of which fall into the class of narcotics, are potential causes of ARDS. In most cases an overdose of the drug has been taken, although this is not always the situation. One of the agents most frequently recognized has been heroin, and the name “heroin pulmonary edema” sometimes is used. In addition to heroin and other narcotics, several other drugs occasionally cause ARDS, including aspirin and thiazide diuretics. Although the syndrome of drug-induced pulmonary edema has been well described, the mechanism by which it occurs is not certain.

Some patients with acute pancreatitis develop a clinical picture consistent with noncardiogenic pulmonary edema. In this situation, enzymes released into the circulation from the damaged pancreas have been proposed to directly injure pulmonary parenchymal cells or initiate other indirect pathways, resulting in injury.

Certain disorders of the central nervous system, particularly trauma and intracerebral bleeding associated with increased intracranial pressure, are known to be associated with development of ARDS. Similarly, ARDS occasionally occurs after generalized seizures. An interesting and commonly accepted hypothesis to explain this so-called neurogenic pulmonary edema is that intense sympathetic nervous system discharge in response to intracranial hypertension produces vasospasm and extremely high pulmonary capillary pressures, resulting in mechanical damage to the endothelium and subsequent exudation of fluid out of the intravascular space.

## Pathogenesis

How do these diverse clinical problems all result in the syndrome of increased pulmonary capillary permeability in ARDS? One important factor appears to be injury to pulmonary capillary endothelial and alveolar epithelial cells (primarily type I epithelial cells, the cytoplasmic processes of which provide most of the surface area lining the alveolar walls). Given the wide variety of insults that can damage these cell types, it

seems unlikely that a single common mechanism is operative for all kinds of injury.

The initial injury in ARDS affects alveolar epithelial (type I) cells, capillary endothelial cells, or both.

In the discussion of some specific causes of ARDS, brief mention was made of a few of the theories of pathogenesis for individual disorders. Here the more generalized cellular and biochemical mechanisms that are operative during the course of injury to the pulmonary epithelial and capillary endothelial cells are considered. A particularly important component of the pathogenesis of acute lung injury and ARDS appears to be recruitment of inflammatory cells to the lungs, especially neutrophils. An early theory explaining recruitment of neutrophils to the lungs focused on the complement pathway. When complement is activated by sepsis, C5a is released and is responsible for aggregation of neutrophils within the pulmonary vasculature. These neutrophils may release a variety of substances that are potentially destructive to cellular and noncellular components of the alveolar wall. Superoxide radicals, other byproducts of oxidative metabolism, an array of cytokines, and various proteolytic enzymes all can be released by neutrophils and may be important pathogenetically in producing structural and functional injury to the alveolar wall. Examples of specific mediators include endotoxin, products of arachidonic acid metabolism, and cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-8, endothelin, and transforming growth factor (TGF)-β. An inflammatory response also can be augmented by a reduction in anti-inflammatory mediators, including cytokines such as IL-10 and IL-11.

Proposed important components of the pathogenesis of ARDS include:

1. Inflammation in the pulmonary parenchyma, particularly with neutrophils
2. Activation of the vascular endothelium and expression of leukocyte adhesion molecules
3. Release of multiple cytokine mediators, proteases, and oxidants
4. Release of procoagulants and activation of the coagulation system

Activation of complement is just one of multiple potential mechanisms for recruiting and sequestering neutrophils in the lungs. Other important factors include various cytokines and other mediators that influence neutrophil trafficking in the lungs. Vascular endothelial cells, particularly in the pulmonary vascular system, also become activated, express leukocyte adhesion molecules, and lead to accumulation of neutrophils within the pulmonary vasculature.

Another important process appears to be activation of the coagulation system. Several factors are responsible for what has been called a “procoagulant state,” including release of procoagulant tissue factors, a decreased concentration of factors with anticoagulant activity (e.g., protein C and protein S), and increased activity of proteins that inhibit fibrinolysis (e.g., plasminogen activator inhibitor-1). The result is increased production of thrombin and fibrin, as well as evidence of thrombosis within pulmonary capillaries.

Despite extensive research efforts over the past decades to explain the mechanisms of acute lung injury, a complete understanding of ARDS remains elusive. Recently,

potential roles for the innate immune system (including alveolar macrophages and dendritic cells), toll-like receptors, and mitochondrial damage–associated molecular patterns (DAMPs) are actively being investigated. Further clarification of pathogenesis and the importance of various pathways and mediators will be critical to the development of effective forms of prevention and therapy.

## Pathology

Despite the number of etiologic factors in ARDS, the pathologic findings are relatively similar regardless of the underlying cause. As observed by the pathologist, this pattern of injury accompanying ARDS is labeled *diffuse alveolar damage*.

Pathologic features of ARDS:

1. Damage to alveolar type I epithelial cells
2. Interstitial and alveolar fluid
3. Areas of alveolar collapse
4. Inflammatory cell infiltrate
5. Hyperplasia of alveolar type II epithelial cells
6. Hyaline membranes
7. Fibrosis
8. Pulmonary vascular changes

Injury to type I alveolar epithelial cells and pulmonary capillary endothelial cells appears to be the primary factor in pathogenesis. Type I epithelial cells frequently appear necrotic and may slough from the surface of the alveolar wall. Damage to capillary endothelial cells is generally more difficult if not impossible to recognize with light microscopy; electron microscopy may be necessary to appreciate their subtle ultrastructural changes.

Early in the course of ARDS, often called the *exudative phase*, fluid can be seen in the interstitial space of the alveolar septum as well as in the alveolar lumen. Scattered bleeding and regions of alveolar collapse, which are at least partly related to inactivation of surfactant (by protein-rich alveolar exudates) and decreased surfactant production resulting from injury to alveolar type II epithelial cells, are seen. The lung parenchyma shows an influx of inflammatory cells, both in the interstitial space and often in the alveolar lumen. The cellular response is relatively nonspecific, consisting of neutrophils and macrophages. Fibrin and cellular debris may be seen in or around alveoli.

A characteristic finding in the pathology of ARDS is the presence of *hyaline membranes*. They are not true “membranes” in the biological sense; rather, these findings represent the protein-rich edema fluid that has filled the alveoli. Hyaline membranes are composed of a combination of fibrin, cellular debris, and plasma proteins that are deposited on the alveolar surface. Although they are nonspecific, their presence suggests that alveolar injury and increased capillary permeability, rather than elevated hydrostatic pressures, are the cause of pulmonary edema.

After approximately 1 to 2 weeks, the exudative phase evolves into a *proliferative phase*. As an important part of the reparative process that occurs during the

proliferative phase, alveolar type II epithelial cells replicate in an attempt to replace the damaged type I epithelial cells. The resulting overabundance of type II epithelial cells often figures quite prominently in the pathologic picture of ARDS.

Another component of the proliferative phase is accumulation of fibroblasts in the pulmonary parenchyma. In some severe and prolonged cases of ARDS, this fibroblastic response becomes progressive and a *fibrotic phase* occurs. In these cases, the damaged lung parenchyma is not repaired but goes on to develop significant scar tissue (fibrosis). Often accompanying the fibrosis are changes in the pulmonary vasculature, which include extensive remodeling and compromise of the lumen of small vessels by intimal and medial proliferation and by the formation of in situ thrombi.

# Pathophysiology

## Effects on gas exchange

Most of the clinical consequences of ARDS follow in reasonably logical fashion from the presence of interstitial and alveolar edema. The most striking early problem is *alveolar flooding*, which effectively prevents ventilation of affected alveoli, even though perfusion may be relatively preserved. These alveoli, perfused but not ventilated, act as regions where blood is shunted from the pulmonary arterial to pulmonary venous circulation without being oxygenated. This type of shunting is one of the mechanisms of hypoxemia (see Chapter 1), and there is perhaps no better example of intrapulmonary shunting than ARDS.

Pathophysiologic features of ARDS:

1. Shunt and mismatch
2. Secondary alterations in function of surfactant
3. Increased pulmonary vascular resistance
4. Decreased pulmonary compliance
5. Decreased FRC

In ARDS, there are regions of not only true shunt but also ventilation-perfusion mismatch. To some extent, this phenomenon results from a nonuniform distribution of the pathologic process within the lungs. In areas where the interstitium is more edematous or where more fluid is present in the alveoli, ventilation is more impaired (even though some ventilation remains) than in areas that have been relatively spared. Changes in blood flow do not necessarily follow the same distribution as changes in ventilation, and thus ventilation-perfusion mismatch results.

In addition to the direct effects of interstitial and alveolar fluid on oxygenation, other changes appear to be secondary to alterations in the production and effectiveness of surfactant. Chapter 8 refers to *surfactant* as a mixture of lipids, specific proteins, and carbohydrates responsible for decreasing surface tension and maintaining alveolar aeration. When surfactant is absent, as is seen in the respiratory distress syndrome of neonates, there is extensive collapse of alveoli. In ARDS, surfactant production is adversely affected by injury to alveolar type II epithelial cells. In addition, the high

protein fluid within the alveoli makes surfactant dysfunctional and therefore less effective in preventing alveolar collapse.

In terms of oxygenation, both ventilation-perfusion mismatch (with regions of low ventilation-perfusion ratio) and true shunt (ventilation-perfusion ratio = 0) contribute to hypoxemia. Insofar as shunt is responsible for much of the drop in $P_{O_2}$, supplemental $O_2$ alone may not restore oxygenation to normal. In practice, $P_{O_2}$ does rise somewhat with administration of 100% $O_2$, but not nearly to the level expected after such high concentrations of $O_2$. Considering the nature of the problem of ARDS, this response to supplemental $O_2$ should not be surprising. Oxygen improves the component of hypoxemia that is due to ventilation-perfusion mismatch, but it is ineffective for a true shunt.

On the other hand, the absolute level of ventilation in the patient with ARDS initially remains intact or even increases. As a result, the patient typically does not have difficulty with $CO_2$ retention, except in very severe disease or in the presence of another underlying pulmonary process. Even though substantial amounts of what is effectively dead space may be present (as part of the overall ventilation-perfusion mismatch), the patient with early ARDS is able to increase total ventilation to compensate for the regions of maldistribution. If the patient progresses to the later stages of ARDS, dead space is increased, pulmonary fibrosis ensues, and $CO_2$ elimination may be impaired.

## Changes in pulmonary vasculature

The pulmonary vasculature is subject to changes resulting from the overall pathologic process. Pulmonary vascular resistance increases, probably for a variety of reasons. Hypoxemia produces vasoconstriction within the pulmonary arterial system, and fluid in the interstitium may increase interstitial pressure, resulting in a decrease in size and an increase in resistance of the small pulmonary vessels. The lumen of small vessels may be compromised by microthrombi and proliferative changes in vessel walls (discussed earlier under Pathogenesis and Pathology).

One consequence of the pulmonary vascular changes is alteration in the normal distribution of pulmonary blood flow. Blood flows preferentially to areas with lower resistance, which often do not correspond to the regions receiving the most ventilation. Hence ventilation-perfusion mismatch again results, with some areas having high and other areas low ventilation-perfusion ratios.

## Effects on mechanical properties of the lungs

When considering the mechanical properties of the lungs in ARDS, we must recognize that computed tomography scanning has demonstrated the distribution of disease to be more heterogeneous than expected based on the diffuse changes seen on chest radiograph. Although some regions have been damaged and are quite abnormal, others appear spared from injury. As a result, the alveoli are not diffusely and homogeneously affected. Rather, some regions of the lungs have significantly diseased alveoli that are noncompliant and ventilate poorly or not at all, whereas others have relatively preserved and well-ventilated alveoli. The net result of having fewer effectively “functional” alveoli is that less volume enters the lungs for any given inflation pressure; by definition, this means lung compliance is decreased.

The decreased compliance and low FRC in ARDS are not associated with homogeneously affected alveoli but rather with heterogeneous disease involvement.

The volume of gas contained within the lungs at functional residual capacity (FRC; i.e., resting end-expiratory position of the lungs) is also significantly decreased. Again, the pathologic process is heterogeneous, so the decreased FRC is not due to a uniform decrease in volume over all alveoli but rather to a group of alveoli containing little or no gas and another group containing a relatively normal volume of gas. The net result is that patients breathe at a much lower overall lung volume than normal, preferentially ventilating those alveoli that are relatively preserved. The typical breathing pattern resulting from these mechanical changes is characterized by rapid but shallow breaths. This type of breathing pattern is inefficient and demands increased energy expenditure by the patient, which probably contributes to the dyspnea so characteristic of ARDS patients.

## Clinical features

Because ARDS is a clinical syndrome with many different causes, the clinical picture reflects the presence of not only noncardiogenic pulmonary edema but also the underlying disease. In this section, we examine the respiratory consequences of ARDS, irrespective of the cause, and direct our focus to the clinical effects of the syndrome itself rather than to those of the underlying disorder.

Clinical features of ARDS:

1. Dyspnea, tachypnea
2. Rales
3. ↓$P_{O_2}$, normal or ↓$P_{CO_2}$, ↑$AaD_{O_2}$
4. Radiographic findings of interstitial and alveolar edema

After the initial insult, whatever it may be, there is generally a lag of several hours to a day or more before respiratory consequences fully develop. In most cases, the first symptom experienced by the patient is dyspnea. As this manifests, examination often shows the patient to be tachypneic, although the chest radiograph may not reveal significant findings. However, arterial blood gases reflect a disturbance of oxygenation, often with an increase in the alveolar-arterial difference in partial pressure of oxygen ($AaD_{O_2}$). Initially, alveolar ventilation is either normal or (more frequently) increased, so $P_{CO_2}$ is generally below baseline. As fluid and protein continue to leak from the vasculature into the interstitial and alveolar spaces, clinical findings become florid. Patients may become extremely dyspneic and tachypneic, and rales may be heard on chest auscultation. Chest radiographic findings become highly abnormal, revealing extensive interstitial and alveolar edema. The radiographic aspects of ARDS are discussed under Diagnostic Approach.

Our improved ability over the past 50 years to provide respiratory support for these patients has now made death directly due to respiratory failure relatively uncommon.

Rather, the high mortality seen with ARDS, currently estimated at 25% to 40%, is related to the underlying cause (particularly sepsis) or to failure of multiple organ systems in these critically ill patients. Patients fortunate enough to recover may have surprisingly few respiratory sequelae that are both serious and permanent. Pulmonary function may essentially return to normal, although sophisticated assessment frequently shows persistent subtle abnormalities. However, there is increasing recognition that a significant portion of survivors may suffer from impaired neurocognitive function, depression, anxiety, weakness, and posttraumatic stress disorder related to critical care.

## Diagnostic approach

The diagnosis of ARDS is generally based on a combination of clinical and radiographic information (assessment at a macroscopic level) and arterial blood gas values (assessment at a functional level). Although at one time, some clinicians and investigators advocated lung biopsy in patients with presumed ARDS, these procedures were performed primarily for research purposes. Lung biopsies are now rarely performed unless a process other than ARDS is suspected.

The chest radiograph in patients with incipient ARDS may not reveal abnormal findings at the onset of clinical presentation. However, within a short period of time, evidence of interstitial and alveolar edema generally develops, the latter being the most prominent finding on chest radiograph. Edema appears diffuse, affecting both lungs relatively symmetrically. As an indication that fluid is filling alveolar spaces, air bronchograms often appear within the diffuse infiltrates. Unless the patient has prior heart disease and cardiac enlargement unrelated to the present problem, heart size remains normal. A characteristic example of a chest radiograph in a patient with severe ARDS is shown in Fig. 3.7.

Arterial blood gas values in early ARDS show hypoxemia and hypocapnia (respiratory alkalosis). Calculation of $AaDO_2$ shows that gas exchange is actually worse than it may appear at first glance, with alveolar $PO_2$ elevated as a result of hyperventilation. As the amount of interstitial and alveolar edema increases, oxygenation becomes progressively more abnormal, and severe hypoxemia results. Because true shunting of blood across unventilated alveoli is important in the pathogenesis of hypoxemia, arterial $PO_2$ may be relatively unresponsive to administration of supplemental $O_2$. As a standardized method for interpreting $PO_2$ in patients receiving different amounts of supplemental oxygen, a ratio of $PaO_2$ to fractional concentration of inspired oxygen ($PaO_2/FiO_2$) is used to define the severity of ARDS. A $PaO_2/FiO_2$ ratio ≤300 but greater than 200 is considered mild ARDS (and was categorized as acute lung injury under previous criteria), a $PaO_2/FiO_2$ between 100 and 200 defines moderate ARDS, and a $PaO_2/FiO_2$ ratio of less than 100 is classified as severe ARDS (see Table 29.1).

Most patients will have a central venous catheter (a catheter inserted into a systemic vein and then advanced to the superior vena cava) placed, allowing for delivery of medications and measurement of central venous pressure (as a gauge of overall volume status). If there is concern about the presence of a component of hydrostatic pulmonary edema from left heart dysfunction, measuring pressures with a pulmonary artery catheter (commonly known as a *Swan-Ganz catheter*), advanced further and passed

through the right atrium and right ventricle into the pulmonary artery, may be used (see Chapter 12). The pressure measured by a pulmonary artery catheter with the balloon inflated (and forward flow blocked) reflects pressure from the left atrium and is commonly called the *pulmonary artery occlusion pressure* (PAOP) or *pulmonary capillary wedge pressure*.

Measurements from a central venous catheter gauge volume status, and a pulmonary artery (Swan-Ganz) catheter can estimate left ventricular preload.

Measurement of pulmonary artery occlusion pressure, which estimates left ventricular preload, can help distinguish whether the observed pulmonary edema is cardiogenic or noncardiogenic in origin. In cardiogenic pulmonary edema, the hydrostatic pressure within the pulmonary capillaries is high as a result of increased pressure in the pulmonary veins and left atrium. In pure noncardiogenic pulmonary edema or ARDS, the pressure within the left atrium (measured as the PAOP) is normal, indicating that the interstitial and alveolar fluid results from increased permeability of the pulmonary capillaries and not from high intravascular pressure.

Although use of a pulmonary artery catheter for measurement of intravascular pressures is not essential to the diagnosis of ARDS, the information obtained may be useful for determining whether elevated hydrostatic pressure within the pulmonary capillary bed is contributing to the observed pulmonary edema. However, despite the potential for providing helpful information for management of these complicated cases, use of pulmonary artery catheters has not been unequivocally demonstrated to improve mortality. Because of this lack of impact on patient outcomes, placement of pulmonary artery catheters for assessment and management of patients with presumed ARDS has declined significantly in recent years.

## Treatment

Management of ARDS centers on three main issues: (1) treatment of the precipitating disorder, (2) interruption of or interference with the pathogenetic sequence of events involved in the development of capillary leak, and (3) support of gas exchange with ventilator strategies that minimize further lung injury until the pulmonary process improves. Although treatment of the precipitating disorder is not always possible or successful, the principle is relatively simple: as long as the underlying problem persists, the pulmonary capillary leak may remain. In the case of a disorder such as sepsis, management of the infection with appropriate antibiotics (and drainage of closed space infections if necessary) is crucial to allowing the pulmonary vasculature to reestablish the normal permeability barrier for protein and fluid.

Meticulous supportive management, particularly support of gas exchange, is critical for patients with ARDS to survive the acute illness. Given the life-threatening nature of ARDS, patients typically are endotracheally intubated, mechanically ventilated, and managed in an intensive care unit. Failure of other organ systems besides the respiratory system is common, and patients often present some of the most complex and challenging management problems handled in intensive care units. Because of the importance of mechanical ventilation and ventilatory support in the management of

respiratory failure associated with ARDS and with other disorders, Chapter 30 is devoted to a more detailed consideration of mechanical ventilation in the management of respiratory failure.

In patients who are mechanically ventilated (as almost all patients with ARDS are), the most effective strategy involves applying lower tidal volumes than had been the traditional practice prior to the turn of the millennium. This so-called lung-protective ventilation has a significant mortality benefit that has been documented in a large, well-designed randomized trial. However, the exact reasons why this approach is beneficial remain somewhat speculative. It is hypothesized that ventilating the lungs at lower lung volumes avoids overdistention of alveoli and the consequent deleterious release of inflammatory mediators. For patients with severe ARDS who do not have adequate gas exchange despite early institution of lung-protective ventilation strategies, turning the patient and ventilating in the prone (face down) position can improve oxygenation and appear to reduce mortality. The mechanisms by which gas exchange improves with prone ventilation are complicated, but include more even distribution of ventilation and perfusion. A more complete discussion of ARDS ventilator strategies is included in the Suggested Readings for this chapter.

Approaches aimed at altering the pathogenetic sequence of events in ARDS have focused on developing agents that block the effect of various cytokines or other initiating stimuli, such as endotoxin, in patients with septic shock. However, to date this approach has been unsuccessful, and no agents blocking the effect of a particular mediator have been useful. A more nonspecific approach has been use of corticosteroids in an attempt to block a variety of mediators and control or reverse the capillary permeability defect allowing fluid and protein to leak into the interstitium and alveolar spaces. This approach is based in part on experimental evidence suggesting that corticosteroids inhibit aggregation of neutrophils induced by activated complement. Many studies have been conducted on the use of corticosteroids in ARDS with mixed results. The current thinking is that corticosteroids should be administered only to patients whose ARDS is due to COVID-19 pneumonia or a known steroid-responsive disease; they are otherwise not recommended.

Inhaled nitric oxide and inhaled epoprostenol are selective pulmonary vasodilators and have been used in the treatment of ARDS. By producing preferential vasodilation in areas of the lungs that are well ventilated (because these are the areas to which the inhaled medications can penetrate to the alveoli), inhaled nitric oxide or epoprostenol can facilitate better perfusion of well-ventilated areas, leading to better ventilation-perfusion matching and improved oxygenation. Unfortunately, however, these beneficial physiologic effects on gas exchange have not been accompanied by documentation of improved survival in clinical trials conducted to date.

In some severe cases of ARDS where life-threatening gas exchange abnormalities cannot be addressed by other means, extracorporeal membrane oxygenation (ECMO) is employed. With this technique, venous blood is removed through a cannula, pumped through a circuit outside of the body that adds oxygen and removes carbon dioxide through a gas-permeable membrane, and then returned to the patient's circulation. ECMO is not unequivocally associated with improved survival, and because of the expertise and resources required for this technique, it is available only at specialized centers.

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# 30: Management of respiratory failure

OUTLINE



Supportive therapy aimed at maintaining adequate gas exchange is critical in the management of both acute respiratory failure and chronic respiratory insufficiency. In acute respiratory failure, survival depends on the ability to provide supportive therapy until the patient recovers from the acute illness that precipitated the need to support the respiratory system. In patients with chronic respiratory insufficiency, the goal is to maximize the patient's function and minimize symptoms and cor pulmonale on a long-term basis. This chapter outlines the goals and methods of supportive therapy, focusing

on various aspects of mechanical ventilation and strategies for maintaining adequate gas exchange. Because the principles for supportive management differ in acute hypoxemic respiratory failure (e.g., acute respiratory distress syndrome [ARDS]) and in hypercapnic respiratory failure (e.g., acute-on-chronic respiratory failure, as in chronic obstructive pulmonary disease [COPD] or neuromuscular disease), these categories are considered separately. The chapter concludes with a consideration of two specific topics applicable to patients with chronic respiratory insufficiency: chronic ventilatory assistance and lung transplantation.

## Goals and principles underlying supportive therapy

Adequate uptake of $O_2$ by the blood, delivery of $O_2$ to the tissues, and elimination of $CO_2$ all are components of normal gas exchange. In terms of $O_2$ uptake by the blood, almost all of the $O_2$ carried by blood is bound to hemoglobin, and only a small portion is dissolved in plasma. It is apparent from the oxyhemoglobin dissociation curve that elevating $P_{O_2}$ beyond the point at which hemoglobin is almost completely saturated does not significantly increase the $O_2$ content of blood (see Chapter 1). On average, assuming that the oxyhemoglobin dissociation curve is not shifted, hemoglobin is approximately 90% saturated at a $P_{O_2}$ of 60 mm Hg. Increasing $P_{O_2}$ to this level is important for tissue oxygen delivery, but a $P_{O_2}$ much beyond this level does not provide that much incremental benefit. In practice, patients with respiratory failure often are maintained at a $P_{O_2}$ slightly higher than 60 mm Hg (or an $O_2$ saturation slightly > 90%) to allow a "margin of safety" for fluctuations in oxygenation.

Goals of optimizing $O_2$ transport to tissues:

1. Arterial $O_2$ saturation greater than 90% (i.e., $P_{O_2}$ > 60 mm Hg)
2. Acceptable hemoglobin level (e.g., ≥7 g/dL)
3. Appropriate cardiac output

Oxygen delivery to the tissues, however, depends not only on arterial $P_{O_2}$ but also on hemoglobin concentration and cardiac output. In patients who are anemic, $O_2$ content and thus $O_2$ transport can be compromised as much by the low hemoglobin level as by hypoxemia (see Eq. 1.3). In selected circumstances, blood transfusion may be useful in raising the hemoglobin and $O_2$ content to more desirable levels, usually in order to maintain a hemoglobin concentration ≥ 7 g/dL.

Similarly, when cardiac output is impaired, tissue $O_2$ delivery also decreases, and measures to augment cardiac output may improve overall $O_2$ transport and delivery. Unfortunately, the use of positive-pressure ventilation, particularly with positive end-expiratory pressure (PEEP), may have a detrimental effect on cardiac output. As a result, tissue $O_2$ delivery may not improve (and even may worsen) despite an increase in $P_{O_2}$. The use of PEEP is discussed in more detail later in this chapter.

Elimination of $CO_2$ by the lungs is important for maintaining adequate acid-base

homeostasis. However, achieving an acceptable pH value, not a "normal" $P_{CO_2}$ of 40 mm Hg, is the primary goal in managing respiratory failure with impaired elimination of $CO_2$. In patients with chronic hypercapnia (and metabolic compensation), abruptly restoring $P_{CO_2}$ to 40 mm Hg may cause significant alkalosis and thus risk precipitating either arrhythmias or seizures.

$CO_2$ elimination is manipulated to maintain acceptable pH rather than "normal" $P_{CO_2}$ of 40 mm Hg.

## Acute hypoxemic respiratory failure

In the patient with acute hypoxemic respiratory failure such as due to ARDS, ventilation-perfusion mismatch and shunting are responsible for the hypoxemia. Because a large fraction of the cardiac output is being shunted through areas of unventilated lung and is therefore not oxygenated during passage through the lungs, supplemental $O_2$ is relatively ineffective at raising $P_{O_2}$ to an acceptable level. In these cases, patients may require inspired $O_2$ concentrations in the range of 60% to 100% and still may have difficulty maintaining $P_{O_2}$ greater than 60 mm Hg.

Such patients with ARDS typically require ventilatory assistance for support of oxygenation and relief from a high work of breathing resulting from stiff, noncompliant lungs that are filled with fluid. Although oxygenation is extremely difficult to support, $CO_2$ retention is much less frequent in patients with ARDS, and hypoxemia rather than hypercapnia is the primary indication for mechanical ventilation.

For patients with acute hypoxemic respiratory failure, inability to achieve a $P_{O_2}$ of 60 mm Hg or greater on supplemental $O_2$ readily administered by face mask or heated high-flow nasal cannula with an oxygen blender (generally delivering a fractional concentration of inspired oxygen [$FiO_2$] of 70%-100%) is often considered a justification for intubation (i.e., placement of a flexible plastic endotracheal tube through the nose or mouth, between the vocal cords, and into the trachea). A mechanical ventilator is then connected to the endotracheal tube to provide the desired inspiratory gas under positive pressure. However, such decisions for ventilatory support are not based on just one number. Other factors taken into consideration include the nature of the underlying problem and the likelihood of a rapid response to therapy.

Mechanical ventilation is often indicated when $P_{O_2} \geq 60$ mm Hg cannot be achieved with inspired $O_2$ concentration $\leq$ 70% to 100%.

In the setting of ARDS, intubation and mechanical ventilation serve several useful purposes. First, higher concentrations of $O_2$ can be administered much more reliably through a tube inserted into the trachea than through a mask placed over the face. Second, administration of positive pressure by a ventilator relieves the patient of the high work of breathing (see section "Reducing Work of Breathing"), allowing patients to receive more reliable tidal volumes than they would spontaneously take, particularly because the poorly compliant lungs of ARDS promote shallow breathing and low tidal volumes. Finally, when a tube is in place in the trachea, positive pressure can be

maintained in the airway throughout the entire respiratory cycle rather than in just roughly one-half of it. In common usage, positive airway pressure maintained at the end of expiration in a mechanically ventilated patient is termed PEEP, which is described in more detail later in this chapter.

Beneficial effects of ventilatory assistance in acute respiratory distress syndrome (ARDS):

1. More reliable administration of high concentrations of inspired $O_2$
2. Delivery of more reliable tidal volumes than those achieved spontaneously by the patient
3. Use of positive end-expiratory pressure (PEEP)

Why is positive pressure throughout the respiratory cycle beneficial for ARDS patients? In ARDS, fluid occupying alveolar spaces, low tidal volumes, and probably both decreased production and inactivation of surfactant result in microatelectasis and in decreased or absent ventilation to involved areas of the lung. The resting end-expiratory volume (i.e., functional residual capacity [FRC]) is decreased, and continued perfusion of nonventilated alveoli results in an elevation of the fraction of blood that is shunted through the lungs without being oxygenated. With administration of PEEP, FRC is increased, and many small airways and alveoli that formerly were collapsed and received no ventilation are now opened and available for gas exchange. Measurement of the "shunt fraction" shows that PEEP is quite effective at decreasing the amount of blood that otherwise would not be oxygenated during passage through the lungs.

PEEP is effective in ARDS by increasing functional residual capacity (FRC), preventing closure of small airways and alveoli, and decreasing the shunt fraction.

When the shunt fraction is decreased by PEEP, supplemental $O_2$ is much more effective at elevating the patient's $P_{O_2}$ to an acceptable level. The concentration of inspired $O_2$ thus can be lowered, and the patient is less likely to experience $O_2$ toxicity from sustained exposure to very high concentrations of $O_2$.

## Hypercapnic respiratory failure

$CO_2$ retention is an important aspect of respiratory failure in several types of patients. Most frequently, these patients have some degree of chronic $CO_2$ retention, and their acute problem is appropriately termed *acute-on-chronic respiratory failure*. Patients with chronic obstructive lung disease, chest wall disease, and neuromuscular disease are all subject to the development of hypercapnia. Hypercapnia may be purely acute in certain other groups of patients—individuals who have suppressed respiratory drive resulting from ingestion of certain drugs, especially narcotics, or occasional patients with severe asthma and status asthmaticus.

If the degree of $CO_2$ retention is sufficiently great to cause a marked decrease in the patient's pH (<7.25 to 7.30) or a change in mental status, ventilatory assistance with a

mechanical ventilator is often necessary. Traditionally, ventilator support has been initiated following endotracheal intubation. Although this type of *invasive mechanical ventilation* through an endotracheal tube may be required for patients with more extreme hypercapnia or with changes in mental status, most patients with hypercapnia from an acute exacerbation of chronic obstructive lung disease, neuromuscular disease, chest wall disease, or heart failure now are managed initially using *noninvasive positive-pressure ventilation* (NIPPV). With NIPPV, the mechanical ventilator delivers positive pressure via a tight-fitting face mask rather than an endotracheal tube, and the need for intubating the trachea and sedating the patient can often be averted.

Mechanical ventilation for patients with hypercapnic respiratory failure often is provided initially with noninvasive positive-pressure ventilation.

Most cases of hypercapnic respiratory failure are also associated with some degree of hypoxemia, due to hypoventilation as well as ventilation-perfusion mismatch that accompanies the underlying disease. For these mechanisms of hypoxemia, administration of supplemental $O_2$ is quite effective in improving $P_{O_2}$, and high concentrations of inspired $O_2$ are usually not necessary. As previously noted in Chapter 18, patients with chronic hypercapnia may be subject to further increases in $P_{CO_2}$ when they receive supplemental $O_2$. If $P_{CO_2}$ rises significantly after administration of supplemental $O_2$ in a patient not already receiving ventilatory assistance, NIPPV should be started. Fortunately, this complication of significant hypercapnia is infrequent with judicious use of supplemental $O_2$.

## Reducing work of breathing

One pathophysiologic feature shared by most patients with respiratory failure is an imbalance in the work of breathing relative to the ability of the respiratory muscles to perform that work. In the case of acute-on-chronic respiratory failure in the patient with chronic obstructive lung disease, the diaphragm is flattened and mechanically disadvantaged at the same time the work of breathing may be increased. In acute or acute-on-chronic neuromuscular disease, respiratory muscle strength may be insufficient to handle even a relatively normal work of breathing. In the patient with ARDS, the noncompliant, stiff lungs require an inordinately high work of breathing even though respiratory muscle strength may be intact.

Consequently, ventilatory assistance in the patient with respiratory failure is important for temporary support of gas exchange as well as for mechanical support of inspiration, allowing the respiratory muscles to rest. Dyspnea is often alleviated when such support is provided and the patient no longer must expend so much energy on the act of breathing. Fatigued respiratory muscles have an opportunity to recover, and the relatively large amount of blood flow required by overworking respiratory muscles can be shifted to perfusion of other organ systems.

Reducing the work of breathing is a benefit of mechanical ventilation in all forms of acute respiratory failure.

# Mechanical ventilation

Mechanical ventilators are critical to effective management of respiratory failure. By supporting gas exchange and assisting with the work of breathing for as long a period as necessary, mechanical ventilators can keep a patient alive while the acute process precipitating respiratory failure is treated or spontaneously resolves. This section briefly describes the operation of mechanical ventilators, basic modes of ventilation, and common complications that can result from mechanical ventilation.

Ventilators currently used for management of acute respiratory failure are positive-pressure devices: they deliver gas under positive pressure during inspiration. However, the ventilator settings are often quite different, depending on the type of respiratory failure. As an example, in hypercapnic patients who are receiving ventilatory support via NIPPV, each delivered breath is often *pressure-limited*, meaning the ventilator is set to provide a specified amount of pressure to assist the work of breathing during inspiration. In contrast, in patients with ARDS and hypoxemic respiratory failure who are receiving ventilatory support through an endotracheal tube, the ventilator is more often used in a *volume-cycled* mode, delivering a specified volume for each breath. We will separately consider these different modes of delivery.

## Pressure-limited ventilation

Two types of pressure-limited ventilation are used commonly in certain clinical settings. The first is *pressure support ventilation* (PSV). With PSV, the ventilator senses when the patient initiates a breath, at which time the ventilator assists the patient's efforts by providing a specified amount of positive pressure to the airway. This level of pressure support is reached rapidly and maintained throughout most of inspiration. The ventilator stops providing inspiratory assistance when the patient's inspiratory flow rate falls below a specified target level, such as 25% of the peak inspiratory flow rate. The volume of each breath can be quite variable and is dependent on the preset level of inspiratory pressure support, the patient's pattern of breathing, and the mechanical properties of the lungs. This type of ventilatory support is intended to assist a patient's own spontaneous breathing efforts; if the patient stops making inspiratory efforts, no backup breaths are provided by the ventilator. PSV is generally the most comfortable form of mechanical ventilation in conscious patients because they have the greatest freedom to determine the timing and depth of each breath.

In *pressure-controlled ventilation* (PCV), the targeted pressure level is set by the clinician and achieved rapidly, as is the case with PSV. However, in PSV, the patient's spontaneously initiated flow triggers the breath, and a decrease in flow terminates the breath. In contrast, with PCV the initiation of the breath, duration of inspiration, and duration of expiration are determined by the clinician and set on the ventilator. However, changes in lung compliance and airway resistance do alter the volume of gas delivered as the specified target pressure is reached. Because the ventilator rather than the patient primarily controls the breathing pattern, PCV can be uncomfortable for the patient, who must be heavily sedated to tolerate the imposed ventilatory pattern. PCV is used primarily in patients with ARDS in whom problems with oxygenation and decreased lung compliance are particularly severe. In these cases, the clinician's control of peak pressure and the relative timing of inspiration and expiration can facilitate

improved oxygenation and reduce the risk of complications from high pressure delivered by the ventilator.

## Volume-cycled ventilation

When the ventilator is used in a *volume-cycled* fashion, each inspiration is terminated (and passive expiration allowed to occur) after a specified volume has been delivered by the machine. Volume cycling is much more reliable than pressure-limited ventilation in delivering constant, specified tidal volumes. However, the pressure required to deliver a particular volume will vary depending on lung compliance and airway resistance and may change over time as these parameters get better or worse.

A hybrid mode termed *volume-targeted pressure-control* is sometimes employed. In this mode, initial pressure control settings are entered, but these are then automatically and continuously adjusted by the ventilator in order to achieve a selected tidal volume.

With volume-cycled ventilation, inspiration terminates after a specified tidal volume has been delivered by the ventilator. With pressure-limited ventilation, inspiration terminates after the targeted airway pressure has been achieved.

Several ventilatory patterns or modes are available with most mechanical ventilators when used in a volume-cycled fashion (Fig. 30.1). In *controlled ventilation*, ventilation is supplied entirely by the ventilator at a respiratory rate, tidal volume, PEEP, and inspired $O_2$ concentration chosen by the physician. If the patient attempts to take a spontaneous breath between the machine-delivered breaths, he or she does not receive any inspired gas. Rarely used anymore, this type of ventilation is extremely uncomfortable for the conscious patient capable of initiating inspiration and therefore can only be used for patients who are comatose, anesthetized, or unable to make any inspiratory effort.

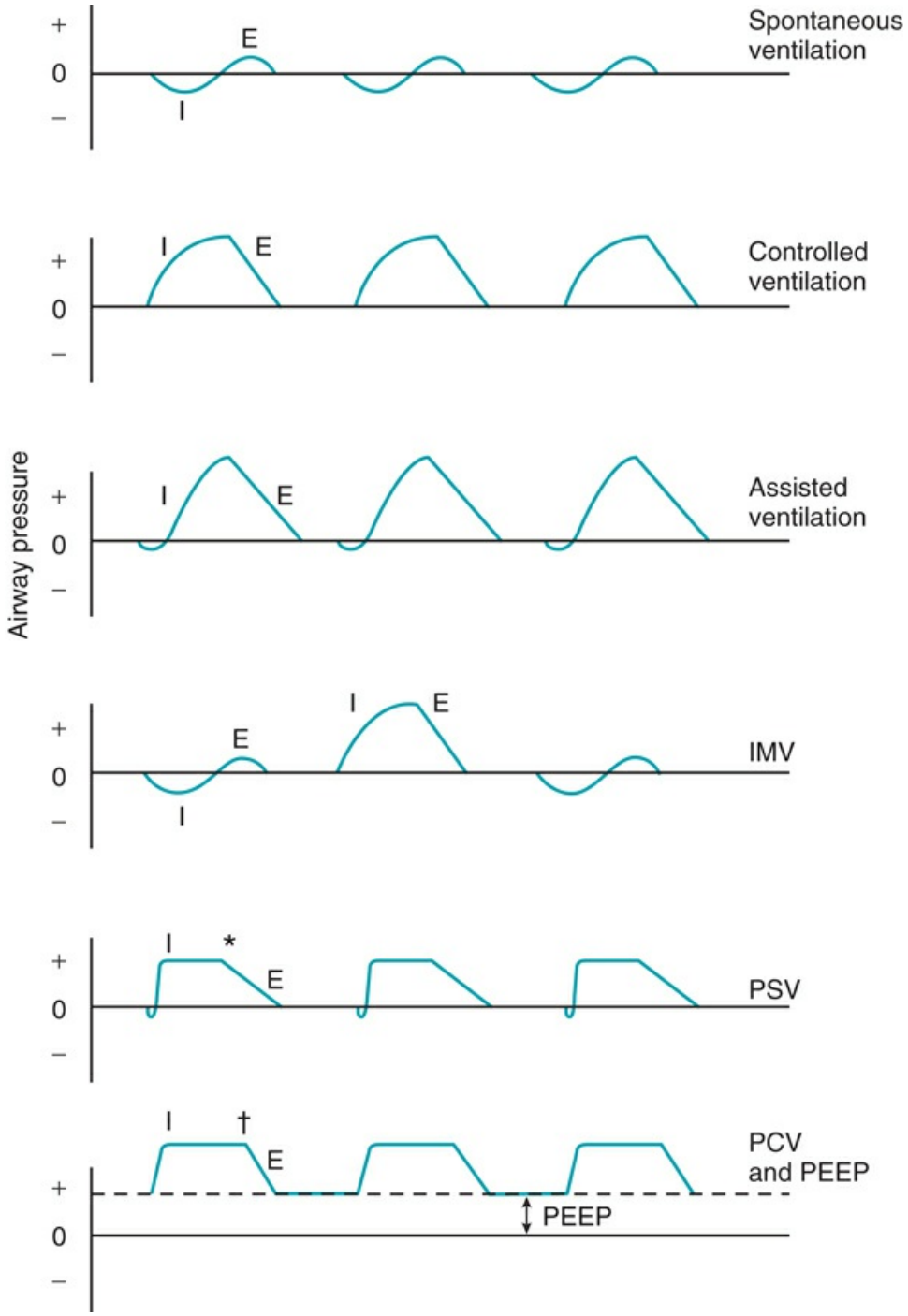


**FIGURE 30.1** Airway pressure during spontaneous ventilation and during mechanical ventilation with several different ventilatory patterns. *E*, expiration; *I*, inspiration; *IMV*, intermittent mandatory ventilation; *PCV*, pressure-controlled ventilation; *PEEP*, positive end-expiratory pressure; *PSV*, pressure support ventilation. *Inspiratory positive-pressure support ceases when patient's flow

rate falls below a threshold level. †Relative timing of inspiration and expiration is controlled by physician-determined ventilator settings.

In the *assist-control mode* of ventilation, the ventilator is set to "sense" when the patient initiates inspiration, at which point the machine assists by delivering a specified tidal volume. Although the tidal volume is set by the machine, the respiratory rate is determined by the number of spontaneous inspiratory efforts made by the patient. However, should the patient's spontaneous respiratory rate fall below a specified level, the machine provides backup by delivering at least this minimal number of breaths. For example, if the backup rate set on the machine is 10 breaths/min, the ventilator will automatically deliver a breath if and when 6 seconds have elapsed from the previous breath. In this example, if the patient is spontaneously initiating breaths at 16 breaths/min, all breaths are triggered by the patient. Because the respiratory rate with assist-control mode is determined by the patient (after the rate exceeds the specified minimal level), fluctuations in minute ventilation can occur if the patient's respiratory rate changes significantly.

Available modes of volume-cycled mechanical ventilation are controlled ventilation, assist-control ventilation, and synchronized intermittent mandatory ventilation (SIMV).

A third ventilatory mode is *intermittent mandatory ventilation* (IMV). With IMV, the machine delivers a preset number of breaths per minute at a specified tidal volume and inspired $O_2$ concentration. Between the machine-delivered breaths, the patient can breathe spontaneously from a gas source providing the same inspired $O_2$ concentration given during the machine-delivered breaths. However, the machine does not assist the spontaneous breaths; therefore, the tidal volume for these breaths is determined by the patient. In a much more commonly used variant of IMV called *synchronized IMV* (SIMV), each of the machine-delivered breaths is timed to coincide with and assist a patient-initiated breath. If the patient being ventilated by IMV or SIMV modes changes his or her spontaneous respiratory rate significantly, the variation in minute ventilation theoretically is less than in the assist-control mode of ventilation, because each breath has not been supplemented by a comparatively large tidal volume delivered by the ventilator. In practice, both assist-control and SIMV are clinically useful and effective modes of ventilation. The assist-control mode is used more commonly because the problem of patient-ventilator dyssynchrony is more likely to occur in the SIMV mode.

## Positive end-expiratory pressure

PEEP is an important option available for the intubated patient with hypoxemic respiratory failure (especially when it is due to ARDS). PEEP consists of the maintenance of positive pressure during expiration, which functions to keep small airways open and avoid microatelectasis. When a patient is assisted by a mechanical ventilator without PEEP, airway (and alveolar) pressure falls during expiration from the positive level achieved at the height of inspiration down to zero. However, if the expiratory portion of the tubing is connected to a valve requiring a pressure of at least 10

cm $H_2O$, for example, to open it, the valve closes and expiration ceases when the airway pressure falls to 10 cm $H_2O$. Consequently, airway pressure at the end of expiration does not fall to zero but remains at the level determined by the settings of the expiratory valve. The level of PEEP can be set as desired by adjusting the pressure required to open the expiratory valve.

A variation of PEEP that works on the same principle is *continuous positive airway pressure* (CPAP, see Chapter 18). The term *CPAP* is used when the patient is breathing spontaneously (without machine-assisted breaths) and expiratory tubing is connected to a PEEP valve. To use CPAP, the patient can be either intubated or given a tightly fitting face mask. Although no positive pressure is provided by a mechanical ventilator during inspiration, inspired gas is delivered from a reservoir bag under tension or at a sufficiently high flow rate to keep airway pressure positive during inspiration as well as expiration.

With PEEP or CPAP, the benefit comes from the positive pressure within airways and alveoli at the end of expiration. FRC is increased by the positive pressure, and closure of airways and alveoli at the end of expiration is diminished.

## Other ventilatory strategies

In complicated cases of respiratory failure, such as patients with ARDS, a variety of ventilatory strategies can be used. Important goals of these particular strategies are to prevent closure of alveoli during expiration while simultaneously avoiding delivery of excessive volume and pressure to the airways and alveoli, with the potential for secondary complications (see later). A particularly common strategy is called a *protective open lung strategy*, in which sufficient PEEP is given to diminish airway closure during expiration, and relatively low tidal volumes (6 mL/kg) are used to protect the lung from higher volumes and pressures delivered during inspiration. In some cases, $P_{CO_2}$ may rise when these relatively low tidal volumes are used, but the elevation in $P_{CO_2}$ above normal levels is considered an acceptable strategy of *permissive hypercapnia*. By minimizing the need for high ventilation requirements, this strategy theoretically decreases the risks of developing high alveolar pressures leading to overdistention and injury of some alveolar units. Importantly, the use of low tidal volume ventilation has been demonstrated to significantly improve mortality among patients with ARDS and acute hypoxemic respiratory failure. In contrast, the use of higher levels of PEEP in the protective open lung strategy has not consistently shown such benefit.

Another important approach that is used in patients with severe ARDS involves having the patient spend the majority of time in the *prone position* (face down on the bed) rather than the more customary supine position (face up on the bed) while receiving mechanical ventilation. Prone positioning can improve oxygenation, enhance clearance of secretions, and decrease ventilator-induced lung injury. Several studies have shown improved survival when prone ventilation is used in ARDS patients.

An adjunctive therapy that may improve oxygenation but has not been shown to improve survival is the use of inhaled pulmonary vasodilators, such as nitric oxide (a gas) or epoprostenol (an aerosol). Because these medications are delivered via inhalation, they preferentially travel to more ventilated alveoli and increase relative blood flow to these better-functioning lung units. Local vasodilation in these lung units results in improved ventilation-perfusion matching and a higher $P_{O_2}$ in blood returning

from the lungs to the left side of the heart.

Finally, for the most severe cases of ARDS or when the patient continues to do poorly with the other strategies mentioned previously, some centers are equipped to support gas exchange through *extracorporeal membrane oxygenation (ECMO)*. With this technique, venous blood is removed through a cannula, pumped through a circuit outside of the body that adds oxygen and removes carbon dioxide through a gas-permeable membrane, and then returned to the patient's circulation. However, because of the complexity of this process and the potential for complications, it is performed only in centers that have the experience and personnel well trained in applying this technique.

A protective open lung strategy (using PEEP and avoiding excessive inspiratory inflation pressure and volume) is commonly used in patients with ARDS.

Patients with severe refractory hypoxemic respiratory failure are sometimes treated with inhaled pulmonary vasodilators or extracorporeal membrane oxygenation (ECMO).

## Discontinuation of ventilatory support

When the underlying problem that precipitated the need for mechanical ventilation has improved, ventilatory support is discontinued, typically after observing the patient during a short (30-120 minutes) trial of spontaneous breathing with minimal or no positive pressure delivered by the mechanical ventilator. A useful guideline for assessing the patient's initial response to the spontaneous breathing trial and predicting successful discontinuation of mechanical ventilation is provided by the *rapid shallow breathing index*. This index is the ratio of the patient's respiratory rate divided by the tidal volume (expressed in liters) measured when the patient is not receiving assistance from the ventilator (i.e., during the spontaneous breathing trial). An index less than 105 is predictive of successful extubation (i.e., removal of the endotracheal tube), whereas an index greater than 105 is associated with a much higher likelihood of recrudescent respiratory failure after extubation.

Although the term *weaning* is still applied to discontinuation of mechanical ventilation, the older technique of slowly decreasing the amount of support provided by the ventilator is generally no longer used. As rational as it seems to wean the patient gradually from ventilatory support, an alternative strategy that tends to discontinue mechanical ventilation more rapidly is to perform an empiric daily trial of spontaneous breathing. If the patient tolerates the trial, then the patient is extubated. In many cases, the patient continues to receive some ventilatory assistance following extubation through NIPPV applied with a tight-fitting face mask, as described earlier, with the goal of avoiding the need for reintubation.

Mechanical ventilation can be discontinued after a successful trial of spontaneous breathing.

## Noninvasive ventilatory support for acute respiratory failure

When patients with acute respiratory failure require mechanical ventilation, support traditionally has been provided by positive pressure administered through a tube placed into the trachea (i.e., endotracheal tube). However, use of an endotracheal tube is associated with risks and complications, such as patient discomfort from the tube itself, injury to the larynx or trachea, and development of lower respiratory tract infection (Table 30.1). An alternative to endotracheal intubation is to provide positive pressure noninvasively through a tightly fitting mask placed over the mouth and nose. This approach has been used for support of patients with a variety of types of acute respiratory failure, including patients with cardiogenic pulmonary edema, those with hypercapnic acute exacerbation of COPD, and patients who are not considered suitable candidates for intubation. High-flow (up to 60 L/min) warmed, humidified oxygen delivered via large nasal prongs may be another option to avoid endotracheal intubation in patients with less severe forms of acute hypoxemic respiratory failure in whom hypercapnia is not a prominent concern. However, noninvasive ventilatory support is not appropriate if a patient is unable to protect the airway; it is most useful when respiratory failure most likely is readily reversible and therefore of relatively short duration.

## TABLE 30.1
## Complications of Intubation and Mechanical Ventilation

| **Associated With Intubation** |
|---|
| Malposition of tube<br>Tube in esophagus<br>Tube in mainstem bronchus (usually right mainstem bronchus)<br>Dysrhythmias<br>Hypoxemia<br>Laryngospasm |
| **Associated With Endotracheal or Tracheostomy Tubes** |
| Vocal cord ulcers<br>Laryngeal stenosis/granulomas<br>Tracheal stenosis<br>Nasal necrosis<br>Sinusitis/otitis media (with nasotracheal tubes)<br>Occlusion or kinking of tube<br>Infection (ventilator-associated pneumonia) |
| **Associated With Mechanical Ventilation** |
| Barotrauma (volutrauma)<br>Pneumothorax<br>Pneumomediastinum<br>Subcutaneous emphysema<br>Biotrauma (alveolar injury related to overdistention and cytokine release)<br>Atelectrauma (associated with cyclic alveolar opening and closing)<br>Decreased cardiac output (hypotension)<br>Alveolar hypoventilation or hyperventilation |

## Complications of intubation and mechanical ventilation

Intubation and mechanical ventilation of patients in respiratory failure are associated with potential risks and complications (see Table 30.1). The procedure of intubation can be complicated acutely by problems such as arrhythmias, laryngospasm, and malposition of the endotracheal tube (either in the esophagus or in a mainstem bronchus). When a tube remains in the trachea for days to weeks, complications affecting the larynx and trachea can occur. Vocal cord ulcerations and laryngeal stenosis and granulomas may develop. The trachea is subject to ulcerations, stenosis, and tracheomalacia (degeneration of supporting tissues in the tracheal wall) resulting from pressure applied by the inflated balloon at the end of the tube. As a precaution to decrease tracheal complications, tubes are made with cuffs that minimize the pressure exerted on the tracheal wall and the resulting pressure necrosis. For prolonged ventilatory support (weeks to months), a tracheostomy tube placed directly into the trachea through an incision in the neck has some advantages over prolonged orotracheal or nasotracheal intubation, including patient comfort, reduced need for sedation, and prevention of further vocal cord and laryngeal injury.

The presence of an endotracheal tube puts the patient at significant risk for nosocomial pneumonia, usually called *ventilator-associated pneumonia*. Several factors appear to contribute to the patient's increased risk for developing pneumonia when intubated and receiving mechanical ventilation. They include bypassing of the normal anatomic barriers and upper airway clearance mechanisms that prevent organisms from reaching the lower respiratory tract, aspiration of oropharyngeal secretions around the endotracheal tube and into the lower respiratory tract, and bacterial contamination of the endotracheal tube or the ventilator circuitry connected to the endotracheal tube. Organisms causing ventilator-associated pneumonia are often relatively antibiotic-resistant bacteria that are resident in the hospital environment, including Gram-negative bacilli and *Staphylococcus aureus*, leading to significant increases in both duration of hospitalization and mortality.

Administration of positive pressure by a mechanical ventilator has its own attendant problems. Patients receiving positive-pressure ventilation are subject to *barotrauma*—development of pneumothorax or pneumomediastinum as a result of high alveolar pressures. Because alveolar overdistention with rupture is currently thought to be the cause of these complications, the term *volutrauma* is now often used instead of *barotrauma*. Development of a pneumothorax in patients receiving mechanical ventilation can have catastrophic consequences if not detected and treated quickly. The ventilator continues to deliver gas under positive pressure, and the gas enters the pleural space through the rupture. The pressure in the pleural space and thorax increases, and a *tension pneumothorax* can result (see Chapter 15), which severely diminishes venous return and cardiac output and causes rapid cardiovascular collapse. In such situations, a tube, catheter, or needle must be immediately inserted through the chest wall in order to decompress the pleural space, allow resumption of venous return, and enable reexpansion of the lung.

Barotrauma/volutrauma, atelectrauma, biotrauma, and impairment of systemic venous return to the heart are important adverse effects of positive-pressure

ventilation.

Prolonged exposure to excessive volumes and high levels of pressure delivered to the alveoli is injurious to alveolar structures. Because lung injury in ARDS is often heterogeneously distributed (see Chapter 29), inspired gas is preferentially distributed to the more normal, more compliant alveoli than to the abnormal, less compliant alveoli. This puts the more normal alveoli at particular risk for overdistention. At the same time, more diseased alveoli are subject to collapse (atelectasis) during the expiratory phase of the respiratory cycle because of intraalveolar fluid and/or a disrupted or insufficient surfactant layer. Alveoli that are open during inspiration but collapse during expiration are subject to abnormal shear stresses during the repetitive process of opening and closing, a complication termed *atelectrauma*.

Repeated alveolar overdistention and atelectrauma are accompanied by microscopic injury to cells of the alveolar wall and to intercellular attachments, leading to disruption of the normal permeability barrier provided by alveolar epithelial and capillary endothelial cells. In addition, proinflammatory cytokines may be released, a phenomenon that has been called *biotrauma,* resulting in ongoing alveolar injury and also systemic effects, such as increasing the likelihood of developing multiorgan dysfunction syndrome. As a result, positive-pressure ventilation for respiratory failure, especially ARDS, can potentially compound or worsen the process for which it was initiated. Therefore, the pattern of ventilation should avoid both alveolar closure (atelectasis) during expiration and overdistention during inspiration, the former by use of PEEP and the latter by limiting tidal volume to 6 to 8 mL/kg of predicted body weight and alveolar distending pressure to no more than 30 cm $H_2O$. As noted above, the use of a low tidal volume ventilatory strategy in patients with ARDS has been demonstrated to decrease mortality, whereas the use of higher levels of PEEP has not resulted in decreased mortality versus using lower levels of PEEP.

Use of a low tidal volume ventilatory strategy in patients with ARDS has been demonstrated to decrease mortality.

Another major adverse effect of positive-pressure ventilation is potential impairment of cardiovascular function. At least two mechanisms are thought to play a role. The first involves a decrease in venous return to the heart. Whereas the normally negative intrathoracic pressure during inspiration promotes venous return from the periphery, positive inspiratory pressure from a ventilator impedes venous return. The hemodynamic consequences of low cardiac output and blood pressure are even more likely when the patient is also receiving PEEP and is somewhat volume depleted. In many cases, judicious administration of fluids can restore the effective intravascular volume and reverse the adverse hemodynamic consequences of positive-pressure ventilation.

The second mechanism involves an increase in pulmonary vascular resistance. When alveolar volume is increased with positive-pressure mechanical ventilation, alveolar vessels are compressed, compromising the overall cross-sectional area of the pulmonary vascular bed. As a result, pulmonary vascular resistance and the workload placed on the right ventricle increase. Right ventricular output is potentially compromised, and the

right ventricle may dilate. This shifts the interventricular septum toward the left ventricular cavity, also impairing left ventricular filling and stroke volume.

Management of patients receiving positive-pressure ventilation, particularly those with hypoxemic respiratory failure who require PEEP, is complicated. Many factors interact in a complex way, specifically oxygenation, cardiac output, and fluid status. Optimal care requires both sophisticated patient monitoring and substantial expertise from the team responsible for patient care. Such care is necessary for proper support of vital functions and to minimize the complications of therapy.

# Selected aspects of therapy for chronic respiratory failure

## Chronic ventilatory support

Working with patients who have chronic irreversible respiratory or neuromuscular disease and require continuous long-term ventilatory support involves difficult clinical decisions. The first question is whether the patient wishes "to be on a machine" for the rest of his or her life. Some patients clearly wish to prolong life even if it means permanent ventilatory support; others choose not to be dependent on a ventilator for the remainder of their lives. When the patient chooses to be maintained on a ventilator, support usually is given by positive-pressure ventilation administered through a tracheostomy tube. The care of some patients can be handled at home with the proper support of family and visiting healthcare personnel. Management of other cases continues in chronic care hospitals or other facilities equipped to care for such patients.

A subgroup of patients with chronic respiratory insufficiency does not require continuous ventilatory support but benefits from nocturnal assistance with ventilation. These patients often have chronic neuromuscular or chest wall disease accompanied by chronic hypercapnia. More recent data suggest that some patients with COPD and hypercapnia may also benefit from chronic nocturnal ventilation. Although the degree to which respiratory muscle fatigue contributes to the hypercapnia experienced by these patients is not clear, at least part of the rationale for using nocturnal ventilatory support is to afford these patients a number of hours each day when their inspiratory muscles are allowed to rest. After a period of nocturnal rest, the respiratory muscles presumably are better able to handle the work of breathing during the day, and daytime hypercapnia may be improved.

When ventilatory support is needed only during the night, it is generally preferable to avoid a chronic tracheostomy. Several options are available, and the most appropriate depends on the particular patient. Positive pressure can be administered at night through nasal pillows, a mouthpiece, or a mask (i.e., NIPPV). Much less commonly, lung inflation can be achieved by *negative-pressure ventilation*, intermittent negative pressure applied outside the chest wall, causing it to expand and the lungs to inflate. The original type of negative-pressure ventilator was the "iron lung," used for ventilatory support from the late 1920s through the polio epidemics of the 1950s. The two most common types of negative pressure ventilators currently used are the *raincoat* (or "poncho") *ventilator* and the *cuirass* (or "chest shell") *ventilator*. Unlike the iron lung, which enclosed the entire body below the neck, raincoat and cuirass ventilators do not

enclose or limit movement of the lower half of the body.

Continuous chronic ventilatory support is typically provided through a tracheostomy tube, whereas chronic nocturnal ventilatory support is provided using noninvasive positive-pressure ventilation.

## Lung transplantation

First performed successfully in 1983, lung transplantation is an option for some patients with severe and disabling chronic pulmonary disease. However, availability of a lung transplant is limited, primarily because suitable donor organs are scarce, and difficulties with posttransplant infections and chronic rejection limit the long-term utility of the procedure. The most common clinical problems leading to lung transplantation are COPD (including $\alpha_1$-antitrypsin deficiency), idiopathic pulmonary fibrosis, cystic fibrosis, and pulmonary arterial hypertension.

Several types of transplantation can be performed: single lung, bilateral lung, lobar transplantation from living donors, and heart-lung transplantation. Although single lung transplantation allows more potential recipients to receive a donor lung than bilateral lung transplantation, survival is better following bilateral lung transplantation, and there has been a trend away from single lung and toward bilateral lung transplantation. For patients with cystic fibrosis, in whom chronic bilateral pulmonary infection complicates their lung disease, bilateral lung transplantation is essential to avoid infection of the new lung by spillover of infected secretions from a remaining diseased native lung. When severe cardiac disease accompanies end-stage lung disease, combined heart-lung transplantation may be required. The most recent lung transplantation technique is lobar transplantation from living donors. In this technique, which is used primarily in younger patients with cystic fibrosis, the recipient is given bilateral implants of a lower lobe from each of two living donors.

In many ways, the lung transplant patient trades the primary lung disease for another disease state: that of the transplant recipient. The major potential complications of lung transplantation fall under the general categories of rejection and infection. Because of the risk of rejection, patients are routinely given immunosuppressive drugs, such as prednisone, mycophenolate mofetil (or azathioprine), and tacrolimus (or cyclosporine), as a regimen to prevent rejection. Nevertheless, acute or chronic rejection can occur despite maintenance immunosuppression. *Acute rejection* is often characterized by fever, impairment of pulmonary function and gas exchange, and pulmonary infiltrates on chest radiograph. Episodes typically occur during the first several months after transplantation and are difficult to differentiate from infection on clinical grounds alone. Acute rejection is treated by short-term intensification of the immunosuppressive regimen, especially with increased doses of corticosteroids. *Chronic rejection* is usually manifested as bronchiolitis obliterans, which is characterized by progressive inflammation, fibrosis, and obstruction of small airways. The physiologic consequence of this process is progressive airflow obstruction, which typically is unresponsive to augmentation of immunosuppressive therapy. As a result, bronchiolitis obliterans is the major cause of graft failure and death occurring later in the course after lung transplantation. Pharmacologic treatment of severe bronchiolitis obliterans has been disappointing, and the main treatment option for posttransplant patients with this

syndrome is repeat transplantation.

The major complications occurring after lung transplantation are rejection and infection.

Progressive airflow obstruction from bronchiolitis obliterans is thought to represent chronic transplant rejection.

Another major complication of lung transplantation is infection, the risk of which is greatly increased by the need for immunosuppressive therapy. In some cases, organisms (e.g., bacteria, cytomegalovirus) accompanied the donor organ, and development of a complicating infection was precipitated by immunosuppression and impairment of the recipient's defense mechanisms. Patients are also subject to the variety of opportunistic infections common to patients with impaired cell-mediated immunity, including other viruses, fungi, and *Pneumocystis*. Finally, there is also an increased risk of malignancy in lung transplant recipients, notably with what has been called *posttransplant lymphoproliferative disease*, a type of malignant expansion of lymphocytes that is usually related to Epstein-Barr virus infection and frequently can be controlled by reducing the intensity of immunosuppression.

Accompanying the growing experience with lung transplantation over the past decade has been a modest improvement in survival. Survival is approximately 75% to 80% at 1 year after transplantation; however, median survival is only approximately 5 to 7 years. Lung transplantation is an accepted but expensive therapeutic option for a highly selected group of patients, and future improvements in donor organ preservation and immunosuppression may lead to improved outcomes and broader application of the procedure.

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## Mechanical ventilation


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# Appendix A: Sample problems using respiratory equations

A comatose patient with no spontaneous respiration is placed on mechanical ventilation with the following settings:

Tidal volume ($V_T$) = 1000 mL
Respiratory frequency (f) = 10 breaths/min
Inspired $O_2$ concentration = 40% ($Fi_{O_2}$ = 0.4)

The following measurements are made:

Arterial $P_{CO_2}$ ($Pa_{CO_2}$) = 40 mm Hg
Mixed expired $P_{CO_2}$ ($P_{E}CO_2$) = 30 mm Hg
Arterial $P_{O_2}$ ($Pa_{O_2}$) = 95 mm Hg

1. Calculate minute ventilation ( $\dot{V}_E$ ), dead space–to–tidal volume ratio ($V_D/V_T$), alveolar volume ($V_A$), and alveolar ventilation ( $\dot{V}_A$ ).
2. If extra tubing with a volume of 250 mL were added to the system in a position such that it provided additional dead space, what would be the new $V_D/V_T$?
3. With the new system as described in Question 2, what would be the new $Pa_{CO_2}$?
4. Going back to the original conditions (without added extra tubing), the ventilator settings are changed to new settings:
   $V_T$ = 500 mL
   f = 20 breaths/min
   a. Calculate the new $\dot{V}_E$ , $V_A$, $\dot{V}_A$ , and $V_D/V_T$.
   b. What would happen to $Pa_{CO_2}$ on the new settings?
   c. What would you expect $P_{E}CO_2$ to be if you now measured it?
5. Using the original ventilator settings and arterial blood gases as given, calculate the alveolar-arterial difference in partial pressure of oxygen ($AaDo_2$).
6. After the patient is improved, arterial blood gases measured with the patient breathing room air are as follows:
   $P_{O_2}$ = 75 mm Hg
   $P_{CO_2}$ = 40 mm Hg
   pH = 7.40
   Calculate $AaDo_2$.
7. The next day, the patient's arterial blood gas values on room air are as follows:
   $P_{O_2}$ = 80 mm Hg
   $P_{CO_2}$ = 20 mm Hg

pH = 7.55
What is $AaDO_2$?

## Answers

1. $\dot{V}_E$ = 1000 mL/breath × 10 breaths/min = 10, 000 mL/min = 10 L/min
   $V_D/V_T$ = (40 mm Hg – 30 mm Hg)/40 mm Hg = 0.25
   $V_A = V_T - V_D$ = 1000 mL – (0.25 × $V_T$) = 1000 mL – 250 mL = 750 mL
   $\dot{V}_A = V_A \times f$ = 750 mL/breath × 10 breaths/min = 7.5 L/min
2. New $V_D$ = 250 mL + 250 mL = 500 mL
   New $V_D/V_T$ = 500 mL/1000 mL = 0.5
3. Because $PaCO_2$ is inversely proportional to $\dot{V}_A$, the new $PaCO_2$ can be calculated from the old and the new $\dot{V}_A$ (assuming $\dot{V}CO_2$ remains constant).
   As per Problem 1, old $\dot{V}_A$ = 7.5 L/min
   New $V_A$ = 1000 mL – new $V_D$ = 1000 mL – 500 mL = 500 mL
   New $\dot{V}_A$ = 500 mL/breath × 10 breaths/min = 5 L/min
   New $\dot{V}_A$ = 2/3 × old $\dot{V}_A$
   New $PaCO_2$ = 3/2 × old $PaCO_2$ = 3/2 × 40 mm Hg = 60 mm Hg
4. On the basis of the new settings:
   a. $\dot{V}_E$ = 500 mL/breath × 20 breaths/min = 10 L/min
      $V_A$ = 500 mL – 250 mL = 250 mL
      $\dot{V}_A$ = 250 mL/breath × 20 breaths/min = 5 L/min
      $V_D/V_T$ = 250 mL/500 mL = 0.5
   b. New $PaCO_2$ is inversely proportional to the ratio of the new $\dot{V}_A$ to the old $\dot{V}_A$.
      New $\dot{V}_A$ /old $\dot{V}_A$ = (5 L/min)/(7.5 L/min) = 2/3
      New $PaCO_2$ = 3/2 × old $PaCO_2$ = 3/2 × 40 mm Hg = 60 mm Hg
   c. Because $V_D/V_T = (PaCO_2 - PECO_2)/PaCO_2$, substitute the known values and solve the equation for $PECO_2$.
      0.5 = (60 mm Hg – $PECO_2$)/60 mm Hg
      $PECO_2$ = 30 mm Hg
5. $PAO_2$ = (0.4 × 713 mm Hg) – (40 mm Hg/0.8) = 285 mm Hg – 50 mm Hg = 235 mm Hg
   $AaDO_2 = PAO_2 - PaO_2$ = 235 mm Hg – 95 mm Hg = 140 mm Hg
6. $PAO_2$ = 150 mm Hg – (40 mm Hg/0.8) = 100 mm Hg
   $AaDO_2$ = 100 mm Hg – 75 mm Hg = 25 mm Hg
7. $PAO_2$ = 150 mm Hg – (20 mm Hg/0.8) = 125 mm Hg
   $AaDO_2$ = 125 mm Hg – 80 mm Hg = 45 mm Hg

# Appendix B: Pulmonary function tests: Guidelines for interpretation and sample problems

This appendix provides an outline of a simplified approach to interpreting pulmonary function tests and gives several examples of test results presented as unknown problems. Because details of the interpretation of these tests may vary among laboratories, the approach here focuses on the general concepts rather than the specific details, providing a step-by-step approach to analyzing pulmonary function tests. The concepts underlying this step-by-step approach are covered in the relevant section on pulmonary function tests in Chapter 3.

## Analysis of pulmonary function tests

1. Examination of lung volumes:
    a. A decrease in total lung capacity (TLC) generally indicates the presence of a restrictive pattern. However, TLC measured by helium dilution (as opposed to body plethysmography) may also be artificially depressed when there are poorly communicating or noncommunicating regions within the lung (e.g., in bullous lung disease).
    b. Are lung volumes symmetrically reduced (i.e., are TLC, residual volume [RV], functional residual capacity [FRC], and vital capacity [VC] all decreased to approximately the same extent)? If so, this suggests diffuse parenchymal lung disease as the cause of the restrictive pattern. A low diffusing capacity also supports the diagnosis of diffuse parenchymal lung disease as the cause of the restrictive pattern.
    c. A relatively preserved RV and a normal diffusing capacity suggest another cause of restrictive disease, such as neuromuscular or chest wall disease. Poor effort from the patient may also create this type of pattern.
2. Examination of the mechanics—that is, flow rates measured from the forced expiratory spirogram:
    a. A decrease in the ratio of forced expiratory volume in 1 second to forced vital capacity ($FEV_1/FVC$) indicates obstruction. In some cases of airflow obstruction, both $FEV_1$ and FVC are reduced by approximately the same extent, and $FEV_1/FVC$ may be preserved. Clues to the presence of obstructive disease in this setting are a low forced expiratory flow from 25% to 75% of vital capacity ($FEF_{25\%-75\%}$), a normal to high TLC with a high ratio

of RV to TLC, and the configuration of the flow-volume curve.

b. Interpretation of $FEF_{25\%-75\%}$ (also called *maximal midexpiratory flow* [MMF]):

(1) $FEF_{25\%-75\%}$ is subject to more variability than most other measurements obtained during a forced expiration, so guidelines for normal values are less well established.

(2) When lung volumes are low, $FEF_{25\%-75\%}$ can also be decreased without necessarily indicating coexisting airflow obstruction. Therefore, in the presence of decreased lung volumes, a low $FEF_{25\%-75\%}$ indicates obstruction, primarily if the decrease in $FEF_{25\%-75\%}$ is out of proportion to the decrease in lung volumes.

(3) Taking into account the aforementioned qualifications, $FEF_{25\%-75\%}$ may be a relatively sensitive measurement for airway obstruction. An isolated abnormality in $FEF_{25\%-75\%}$ has sometimes been considered a marker for early or very mild airflow obstruction, theoretically reflecting "small airway disease."

c. The criteria for a significant response to a bronchodilator, indicating at least partial reversibility of airflow obstruction, are an improvement over baseline of either the $FEV_1$ or FVC by 10% of the predicted value. Patients with asthma characteristically fulfill at least one of these criteria, as do some patients with chronic obstructive pulmonary disease (COPD) who have a reversible component to their disease.

3. Interpretation of the flow-volume curve:

a. An obstructive pattern is reflected by decreased flow relative to lung volume, generally accompanied by a "scooped out" or "coved" appearance to the descending part of the expiratory curve (see Fig. 3.21).

b. A restrictive pattern is characterized by decreased volumes (i.e., narrowing of the curve along the volume or *X*-axis) and relatively preserved flow rates. The flow rates often appear increased relative to the small lung volumes, producing a tall, narrow curve.

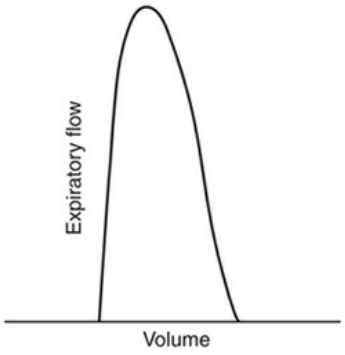
4. Interpretation of diffusing capacity of the lung for carbon monoxide (DLCO):

a. Ensure that the value has been corrected for the patient's hemoglobin level. If not, the value will be falsely low if the patient is anemic.

b. A decrease in the diffusing capacity reflects disease affecting the alveolar-capillary membrane (decreased surface area for gas exchange and/or abnormal thickness of the membrane) or a decrease in pulmonary capillary blood volume.

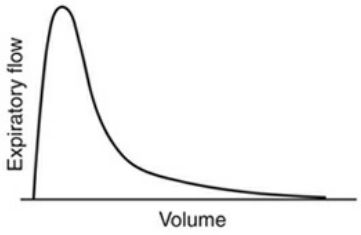
c. An increase in the diffusing capacity can reflect increased pulmonary capillary blood volume or erythrocytes within alveolar spaces (pulmonary hemorrhage).

**Sample pulmonary function test results**



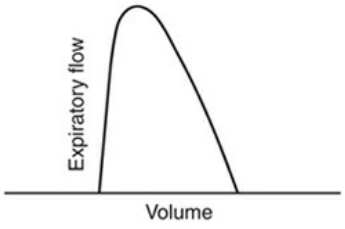

**Flow–volume curve**

| 1. Female aged 32 years | Actual | Predicted | % Predicted |
|---|---|---|---|
| *Lung mechanics* | | | |
| FVC (L) | 1.03 | 3.86 | 27 |
| $FEV_1$ (L) | 0.97 | 3.05 | 32 |
| $FEV_1/FVC \times 100$ ($FEV_1$ %) | 95 | 79 | 120 |
| $FEF_{25\%-75\%}$ (L/s) | 2.39 | 3.49 | 68 |
| *Lung volumes* | | | |
| VC (L) | 1.07 | 3.86 | 28 |
| FRC (L) | 1.59 | 2.89 | 55 |
| TLC (L) | 1.99 | 5.51 | 36 |
| RV (L) | 0.92 | 1.65 | 55 |
| $RV/TLC \times 100$ (%) | 46 | 30 | 153 |
| $D_{LCO}$ (mL/min/mm Hg) | 6.5 | 11.4 | 57 |




**Flow–volume curve**

| 2. Male aged 60 years | Actual | Predicted | % Predicted |
|---|---|---|---|
| *Lung mechanics* | | | |
| FVC (L) | 2.42 | 4.62 | 52 |
| $FEV_1$ (L) | 0.78 | 3.26 | 24 |
| $FEV_1/FVC \times 100$ ($FEV_1$ %) | 32 | 71 | 45 |
| $FEF_{25\%-75\%}$ (L/s) | 0.27 | 3.10 | 9 |
| *Lung volumes* | | | |
| VC (L) | 3.23 | 4.62 | 70 |
| FRC (L) | 5.08 | 3.94 | 129 |
| TLC (L) | 6.90 | 7.02 | 98 |
| RV (L) | 3.67 | 2.40 | 153 |
| $RV/TLC \times 100$ (%) | 53 | 34 | 156 |
| $D_{LCO}$ (mL/min/mm Hg) | 6.8 | 24.5 | 28 |




**Flow–volume curve**

| 3. Female aged 55 years | Actual | Predicted | % Predicted |
|---|---|---|---|
| *Lung mechanics* | | | |
| FVC (L) | 0.93 | 2.73 | 34 |
| $FEV_1$ (L) | 0.80 | 2.03 | 39 |
| $FEV_1/FVC \times 100$ ($FEV_1$ %) | 86 | 75 | 115 |
| $FEF_{25\%-75\%}$ (L/s) | 1.60 | 2.50 | 64 |
| *Lung volumes* | | | |
| VC (L) | 0.90 | 2.73 | 33 |
| FRC (L) | 1.50 | 2.29 | 66 |
| TLC (L) | 2.14 | 4.18 | 51 |
| RV (L) | 1.24 | 1.46 | 85 |
| $RV/TLC \times 100$ (%) | 58 | 35 | 166 |
| $D_{LCO}$ (mL/min/mm Hg) | 14 | 12.9 | 109 |

# Answers

1. All measurements of lung volume (TLC, VC, FRC, RV) are significantly decreased, indicative of restrictive disease. $FEV_1$ and FVC are decreased because of low lung volumes, but $FEV_1/FVC$ is preserved. This finding, along with the fact

that $FEF_{25\%–75\%}$ is not decreased out of proportion to the decrease in lung volumes, indicates there is no obstruction. Diffusing capacity is decreased, suggesting that the restrictive disease is secondary to an abnormality of the pulmonary parenchyma rather than a result of chest wall or neuromuscular disease. The flow-volume curve is tall and narrow, consistent with a restrictive pattern. *Diagnosis:* Diffuse parenchymal lung disease secondary to pulmonary sarcoidosis.

2. $FEV_1$ and FVC are both decreased. Because $FEV_1$ is decreased more than FVC, $FEV_1$/FVC is decreased. $FEF_{25\%–75\%}$ is also decreased. These values are indicative of obstructive lung disease. TLC is normal, and RV and FRC are increased. RV/TLC ratio is also increased. Therefore, there is no restriction, but the high RV/TLC ratio indicates there is "air trapping, " as is often expected with airflow obstruction. The diffusing capacity is decreased, reflecting loss of alveolar-capillary bed. The flow-volume curve shows an obstructive pattern characterized by a striking decrease in flow rates, well seen throughout most of the expiratory curve after the initial peak flow rate. This combination of significant airflow obstruction with normal or increased volumes and a low diffusing capacity suggests emphysema.
3. TLC and FRC are reduced, indicating restrictive disease. RV is relatively preserved. $FEV_1$ and FVC both are decreased, but $FEV_1$/FVC ratio is preserved. There is no evidence for coexisting obstructive disease. Diffusing capacity is normal, suggesting the alveolar-capillary bed is preserved. The flow-volume curve is relatively tall and narrow, without any evidence of obstructive disease. *Diagnosis:* Restrictive pattern secondary to chest wall disease (kyphoscoliosis).

# Appendix C: Arterial blood gases: Guidelines for interpretation and sample problems

The following guidelines are meant to expand on the material presented in Chapter 3 and to simplify the interpretation of arterial blood gas values. Because memorizing a "cookbook" approach can sometimes be counterproductive if the reason why the approach is being used is not clear, these guidelines are meant to supplement a basic understanding of the underlying physiologic principles.

Numerous formulas are used to assess the appropriateness of compensation for a primary acid-base disorder. These formulas are particularly useful for suggesting whether a mixed acid-base disorder is present. Table C.1 lists commonly used formulas that predict the expected degree of respiratory compensation for a primary metabolic problem and metabolic compensation for a primary respiratory problem. These formulas relate arterial $P_{CO_2}$ and measured $HCO_3$–. However, measured values from arterial blood gases include arterial $P_{CO_2}$ and pH, not serum $HCO_3$–. Therefore, to use the formulas in the table, one must either measure serum $HCO_3$– (as part of serum electrolyte values) or use a value calculated from $P_{CO_2}$ and pH according to the Henderson-Hasselbalch equation.

**Table C.1**

**Expected Compensation for Primary Acid-Base Disorders**

| Primary Disorder | Compensatory Response | Expected Magnitude of Response |
|---|---|---|
| Metabolic acidosis | ↓ $P_{CO_2}$ | $P_{CO_2} = 1.5 \times (HCO_3^-) + 8 \pm 2$ |
| Metabolic alkalosis | ↑ $P_{CO_2}$ | $P_{CO_2}$ increases 6 mm Hg for each 10 mEq/L increase in $HCO_3^-$ |
| Respiratory acidosis | ↑ $HCO_3^-$ | Acute: $HCO_3^-$ increases 1 mEq/L for each 10 mm Hg increase in $P_{CO_2}$<br>Chronic: $HCO_3^-$ increases 3.5 mEq/L for each 10 mm Hg increase in $P_{CO_2}$ |
| Respiratory | | |

| | | |
|---|---|---|
| alkalosis | ↓ $HCO_3^-$ | Acute: $HCO_3^-$ falls 2 mEq/L for each 10 mm Hg decrease in $Pco_2$<br>Chronic: $HCO_3^-$ falls 5 mEq/L for each 10 mm Hg decrease in $Pco_2$ |

Modified from Narins, R. G., & Emmett, M. (1980). Simple and mixed acid-base disorders: A practical approach. *Medicine (Baltimore)*, *59*, 161–187. © by Williams & Wilkins, 1980.

Alternatively, one can use other guidelines relating $Pco_2$ and pH values. Because these latter guidelines are based on direct measurements obtained with arterial blood gases—and because they are relatively easy to remember—they are used in the method outlined here. It is worth noting that formulas relating $Pco_2$ and pH become less accurate at the extremes of $Pco_2$ and pH values and provide only rough guidelines. The human body does not respond to physiologic disturbances with mathematical precision.

## Analysis of acid-base status

1. Look at the pH value to determine the net disturbance in acid-base balance. An alkalotic pH (>7.44) indicates the presence of a primary respiratory alkalosis, a metabolic alkalosis, or both. An acidotic pH (<7.36) indicates the presence of a primary respiratory acidosis, a metabolic acidosis, or both. A normal pH (approximately 7.36-7.44) indicates normal acid-base status or a mixed disturbance (of two balancing problems).
2. Look at $Pco_2$. A high $Pco_2$ (>44) indicates that a *respiratory acidosis* is present. A low $Pco_2$ (<36) indicates that a *respiratory alkalosis* is present. If the pH value moves in the appropriate direction for the $Pco_2$ change (i.e., ↓ pH with ↑ $Pco_2$; ↑ pH with ↓ $Pco_2$), the respiratory disorder is the primary disturbance. If the pH value does not move in the appropriate direction for the $Pco_2$ change, a metabolic disorder is the primary disorder.
3. When a primary respiratory disorder is present, the pH value should change approximately 0.08 units for each 10 mm Hg change in $Pco_2$ if the process is acute. If the process is chronic, the kidneys compensate (by retaining or losing $HCO_3^-$) and blunt the pH change in response to any change in $Pco_2$. The resulting change in pH when the respiratory disorder is chronic is slightly different for acidosis versus alkalosis. With a chronic respiratory acidosis, the expected pH decrease is approximately 0.03 for each 10 mm Hg increase in $Pco_2$. With a chronic respiratory alkalosis, the expected pH increase is approximately 0.02 for each 10 mm Hg decrease in $Pco_2$.
4. If a pH change cannot be explained by an alteration in $Pco_2$, a primary metabolic disturbance is present. A low pH value with a low $Pco_2$ indicates a *primary metabolic acidosis* with respiratory compensation. A high pH value with a high $Pco_2$ can indicate a *primary metabolic alkalosis* with secondary suppression of respiratory drive. However, in many patients the latter pattern of a high pH

value with a high $P_{CO_2}$ often represents a complex acid-base disturbance, such as a chronic compensated respiratory acidosis with a superimposed primary metabolic alkalosis (e.g., as a result of diuretics, vomiting, or nasogastric suction).

5. To determine whether there has been appropriate respiratory compensation for a primary metabolic disorder, a rough guideline is that $P_{CO_2}$ should approximate the last two digits of the pH value. For example, a $P_{CO_2}$ of 25 mm Hg accompanying a pH value of 7.25 indicates appropriate respiratory compensation for a primary metabolic acidosis. However, the degree of compensatory hyperventilation (i.e., lowering of $P_{CO_2}$) for a metabolic acidosis tends to be more predictable than the degree of compensatory hypoventilation (i.e., $CO_2$ retention) accompanying a metabolic alkalosis.

## Analysis of oxygenation

1. When analyzing arterial $P_{O_2}$, first calculate alveolar $P_{O_2}$ according to the following equation: $PAO_2 = \left(713 \times FiO_2\right) - \frac{PCO_2}{0.8}$

   For ambient air ($Fi_{O_2}$ = 0.21), the equation can be simplified as follows: $P_{AO_2}$ = 150 – (1.25 × $P_{CO_2}$). Then calculate the alveolar-arterial $O_2$ gradient ($AaD_{O_2}$), which is the difference between the calculated $P_{AO_2}$ and the measured $P_{AO_2}$: $AaD_{O_2} = P_{AO_2} - Pa_{O_2}$.
2. If the patient is hypoxemic, $P_{CO_2}$ is elevated, and $AaD_{O_2}$ is normal (<15 mm Hg on ambient air in a young person, although it increases with age), *hypoventilation* is the cause of the hypoxemia.
3. If the patient is hypoxemic, $P_{CO_2}$ is normal or low, and $AaD_{O_2}$ is increased, either $\dot{V}/\dot{Q}$ *mismatch* or *shunting* is present. With $\dot{V}/\dot{Q}$ mismatch, the patient's $Pa_{O_2}$ has a good response to administration of supplemental $O_2$. With a true shunt, $Pa_{O_2}$ does not rise appropriately with supplemental $O_2$ (even 100% $O_2$).
4. If the patient is hypoxemic, $P_{CO_2}$ is high, and $AaD_{O_2}$ is increased, the patient has both hypoventilation *and* either $\dot{V}/\dot{Q}$ mismatch or shunt as the cause of the low $Pa_{O_2}$.

## Sample problems

Determine the acid-base status and calculate the alveolar-arterial oxygen difference ($AaD_{O_2}$) for each numbered problem. All blood gases are drawn with the patient breathing room air ($Fi_{O_2}$ = 0.21), except as otherwise noted.

,

| | | | |
|---|---|---|---|
| 1. Room air | $Po_2$ = 45 mm Hg | $Pco_2$ = 30 mm Hg | pH = 7.47 |
| (100% $O_2$) | $Po_2$ = 65 mm Hg | $Pco_2$ = 32 mm Hg | pH = 7.46 |
| 2. Room air | $Po_2$ = 45 mm Hg | $Pco_2$ = 30 mm Hg | pH = 7.47 |
| (100% $O_2$) | $Po_2$ = 560 mm Hg | $Pco_2$ = 32 mm Hg | pH = 7.46 |
| 3. | $Po_2$ = 88 mm Hg | $Pco_2$ = 20 mm Hg | pH = 7.55 |
| 4. | $Po_2$ = 65 mm Hg | $Pco_2$ = 60 mm Hg | pH = 7.35 |
| 5. | $Po_2$ = 30 mm Hg | $Pco_2$ = 60 mm Hg | pH = 7.35 |
| 6. | $Po_2$ = 110 mm Hg | $Pco_2$ = 20 mm Hg | pH = 7.30 |
| 7. | $Po_2$ = 55 mm Hg | $Pco_2$ = 48 mm Hg | pH = 7.49 |
| 8. | $Po_2$ = 90 mm Hg | $Pco_2$ = 60 mm Hg | pH = 7.20 |

## Answers

1. Acute respiratory alkalosis. On room air, the patient's $AaDo_2$ = 67.5 mm Hg, which is elevated. The minimal elevation in $Po_2$ with 100% $O_2$ indicates that a shunt is the major cause of the hypoxemia.
2. Identical to Problem 1, except that the dramatic increase in $Po_2$ with 100% $O_2$ indicates that ventilation-perfusion mismatch is the major cause of the hypoxemia.
3. Acute respiratory alkalosis. Even though $Po_2$ appears normal, $AaDo_2$ is elevated to 37 mm Hg, indicating the presence of a disorder impairing normal oxygenation of blood.
4. Chronic respiratory acidosis. $AaDo_2$ = 10 mm Hg, indicating that hypoxemia is due to hypoventilation.
5. Chronic respiratory acidosis, as in Problem 4. However, in contrast to Problem 4, $AaDo_2$ is elevated (to 45 mm Hg), indicating that both hypoventilation and either ventilation-perfusion mismatch or shunting (most likely the former) are responsible for the hypoxemia.
6. Mixed acid-base disorder with a primary metabolic acidosis complicated by a primary respiratory alkalosis. $Pco_2$ is too low to represent only compensation for the metabolic acidosis, indicating the presence of a respiratory alkalosis as well. $AaDo_2$ = 15 mm Hg, the upper limit of normal for a young adult.
7. The simplest explanation of the acid-base status is a compensated metabolic alkalosis. However, this pattern is probably seen more commonly with a mixed acid-base disorder consisting of a compensated respiratory acidosis complicated by a superimposed primary metabolic alkalosis. $AaDo_2$ = 35 mm Hg. Therefore, hypoxemia is partly due to hypoventilation but mostly due to ventilation-perfusion mismatch or shunt, probably the former.
8. Something is wrong because $AaDo_2$ is negative (−15 mm Hg). Several possible explanations are (a) the patient was receiving supplemental $O_2$, (b) a laboratory

error was made, or (c) the blood was not collected or transported properly under anaerobic conditions.

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