PRINCIPLES OF PULMONARY MEDICINE

Seventh Edition

STEVEN E. WEINBERGER

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Seventh Edition

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To Janet, Eric, and Mark
Steven E. Weinberger

To my parents, Fred and Shirley Cockrill
Barbara A. Cockrill

To my parents, Martha and Gerald Mandel
Jess Mandel

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Introduction to the Seventh Edition

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 seven editions of the book and the more than 30 years that have elapsed since the first edition. Our understanding of many disease processes has improved, particularly at a molecular level; 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, has been joined by two additional authors, Barbara A. Cockrill, MD, and Jess Mandel, MD, FACP, since the fifth edition; their knowledge, experience, and perspectives have clearly enhanced the quality of the book. Since the fifth edition, we have expanded the number of 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 daunting to grasp.

At the same time, however, much remains unchanged since the first edition. 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 as well as 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. Finally, starting with the second edition, we have included three appendixes 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.

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 Stephanie Turza, Marybeth Thiel, and Robin Carter, who have been most supportive throughout the development and production process. Finally, we are most grateful to our spouses and children for their support and understanding as we had to sacrifice time with them to prepare this new edition of the book.

Steven E. Weinberger, MD, MACP, FRCP
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Jess Mandel, MD, FACP

Contents

1 Pulmonary Anatomy and Physiology: The Basics 1
2 Presentation of the Patient with Pulmonary Disease 19
3 Evaluation of the Patient with Pulmonary Disease 30
4 Anatomic and Physiologic Aspects of Airways 65
5 Asthma 75
6 Chronic Obstructive Pulmonary Disease 93
7 Miscellaneous Airway Diseases 113
8 Anatomic and Physiologic Aspects of the Pulmonary Parenchyma 126
9 Overview of Diffuse Parenchymal Lung Diseases 132
10 Diffuse Parenchymal Lung Diseases Associated with Known Etiologic Agents 145
11 Diffuse Parenchymal Lung Diseases of Unknown Etiology 158
12 Anatomic and Physiologic Aspects of the Pulmonary Vasculature 177
13 Pulmonary Embolism 184
14 Pulmonary Hypertension 194
15 Pleural Disease 206
16 Mediastinal Disease 221
17 Anatomic and Physiologic Aspects of Neural, Muscular, and Chest Wall Interactions with the Lungs 229
18 Disorders of Ventilatory Control 239
19 Disorders of the Respiratory Pump 248
20 Lung Cancer: Etiologic and Pathologic Aspects 259
21 Lung Cancer: Clinical Aspects 270
22 Lung Defense Mechanisms 285
23 Pneumonia 297
24 Tuberculosis and Nontuberculous Mycobacteria 314
25 Miscellaneous Infections Caused by Fungi and Pneumocystis 325
26 Pulmonary Complications in the Immunocompromised Host 337
27 Classification and Pathophysiologic Aspects of Respiratory Failure 350
28 Acute Respiratory Distress Syndrome 357
29 Management of Respiratory Failure 370

Appendix A Sample Problems Using Respiratory Equations 384
Appendix B Pulmonary Function Tests: Guidelines for Interpretation and Sample Problems 386
Appendix C Arterial Blood Gases: Guidelines for Interpretation and Sample Problems 390

Index 394

Online Contents

Visit expertconsult.com to access online contents.

- **Author Audio Commentary**
  - Introduction
  - Chapter 1 – Pulmonary Anatomy and Physiology: The Basics
  - Chapter 2 – Presentation of the Patient with Pulmonary Disease
  - Chapter 3 – Evaluation of the Patient with Pulmonary Disease
  - Chapter 4 – Anatomic and Physiologic Aspects of Airways
  - Chapter 5 – Asthma
  - Chapter 11 – Diffuse Parenchymal Lung Diseases of Unknown Etiology
  - Chapter 14 – Pulmonary Hypertension
  - Chapter 28 – Acute Respiratory Distress Syndrome
  - Chapter 29 – Management of Respiratory Failure
- **Videos**
  - How to Use an Inhaler
  - How to Use an Inhaler with a Spacer
  - How to Use a Disc Inhaler
  - How to Use an Egg Inhaler
  - Normal Bronchoscopy
- **Audio**
  - Medium Inspiratory Crackles
  - Fine Late Inspiratory Crackles Typical for Pulmonary Fibrosis
  - Mild Expiratory Wheeze
  - Inspiratory Crackles with Moderate Expiratory Wheezes
  - Inspiratory Crackles with Severe Expiratory Wheezes
  - Pleural Friction Rub
  - Normal Voice Sounds followed by Egophony
  - Normal Whispered Sound followed by Whispered Pectoriloquy
- **200 Case-Based Self-Assessment Questions**
- **Image Bank**
- **Fully Searchable Text**

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1

Pulmonary Anatomy and Physiology: The Basics

ANATOMY, 1
PHYSIOLOGY, 3
Mechanical Aspects of the Lungs and Chest Wall, 3
Ventilation, 5
Circulation, 7
Diffusion, 8
Oxygen Transport, 8
Carbon Dioxide Transport, 11
Ventilation-Perfusion Relationships, 12
ABNORMALITIES IN GAS EXCHANGE, 15
Hypoxemia, 15
Hypercapnia, 17

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.

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

Abstract

Chapter 1 provides the fundamentals of pulmonary anatomy and physiology that are critical for understanding both the normal functioning of the lung and the mechanisms for its disruption in the various disease states discussed throughout the book. After a presentation of basic lung anatomy, the relationships between pressure and volume within various compartments of the thorax are explored. An extensive discussion of how ventilation and circulation interact in oxygen uptake and carbon dioxide elimination by the lungs is followed by an explanation of how the relationship between ventilation and perfusion affects gas exchange. The chapter concludes with an explanation of the mechanisms behind abnormal gas exchange resulting in hypoxemia or hypercapnia.

Keywords

Pulmonary anatomy
Lung mechanics
Ventilation-perfusion relationships
Oxygen transport
Carbon dioxide transport
Hypoxemia
Hypercapnia

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.

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

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 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. 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. (Similarly, a balloon 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 internal pressure can be made positive or 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.

Transpulmonary pressure = alveolar pressure (P_{alv}) – pleural pressure (P_{pl}.)

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.

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 rather large increases in transpulmonary pressure do not result in significant increases in lung volume.

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 cause little further decrement in 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.

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.

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 the young individual 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 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

[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).

capable of gas exchange. 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 (P_{aCO_2}) in arterial blood is inversely proportional to $\dot{V}_A$; as $\dot{V}_A$ increases, P_{aCO_2} decreases. In addition, P_{aCO_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 $\dot{V}_A$, P_{aCO_2} shows a proportional increase. Thus it is easy to understand the relationship given in Eq. 1.1:

Arterial P_{CO_2} (P_{aCO_2}) is inversely proportional to alveolar ventilation ($\dot{V}_A$) and directly proportional to CO_2 production ($\dot{V}_{CO_2}$).

$$P_{aCO_2} \propto \dot{V}_{CO_2}/\dot{V}_A \qquad \text{(Eq. 1.1)}$$

This defines the major factors determining P_{aCO_2}. When a normal individual exercises, $\dot{V}_{CO_2}$ increases, but $\dot{V}_A$ increases proportionately so that P_{aCO_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.

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).

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 (P_{aCO_2}) and expired gas (P_{ECO_2}) and by using Eq. 1.2, known as the *Bohr equation* for physiologic dead space:

$$V_D/V_T = (P_{aCO_2} - P_{ECO_2})/P_{aCO_2} \qquad \text{(Eq. 1.2)}$$

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 V_A and dead space, just as the total $\dot{V}_E$ can be divided into $\dot{V}_A$ and wasted (or dead space) ventilation. 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, with use of the principle that increasing amounts of dead space ventilation augment the difference between P_{CO_2} in arterial blood and expired gas.

Circulation

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 the 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 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

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. (From West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol*. 1964;19:713–724.)

the vertical distance between them (divided by a correction factor of 1.3 to convert from cm H_2O to mm Hg).

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., on 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

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.

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. 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. Similarly, CO_2 transfer is complete within approximately the same amount of time.

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 also combines with hemoglobin and is 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

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

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 is 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 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.

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

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.

Hemoglobin is 90% saturated with O_2 around an arterial P_{O_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 P_{O_2} and saturation are not fixed. For instance, a decrease in pH or an increase in P_{CO_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 P_{O_2} (see Fig. 1.5). The opposite changes in pH, P_{CO_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 P_{O_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

Figure 1.5. Oxyhemoglobin dissociation curve, relating percent hemoglobin saturation and partial pressure of oxygen *(P_{O_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; *P_{CO_2}*, partial pressure of carbon dioxide.

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.

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:

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

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):

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

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):

$$\text{Dissolved } O_2 \text{ content} = 0.0031 \times 95 = 0.3 \text{ mL } O_2/100 \text{ mL blood} \quad \text{(Eq. 1.5)}$$

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 Po_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 Po_2 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) as well as O_2 content. Thus three main factors determine tissue O_2 delivery: arterial Po_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 Po_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 Po_2 falls. The extent to which Po_2 falls depends on the balance of O_2 supply and demand: The local venous Po_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, Po_2 falls to approximately 40 mm Hg after O_2 extraction occurs at the tissue-capillary level. Because Po_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:

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

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.

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

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

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).

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 upon 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 markedly 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

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.

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.

Ventilation-perfusion ratios within each alveolar-capillary unit range from $\dot{V}/\dot{Q} = \infty$ (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 $\dot{V}/\dot{Q} = \infty$), 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

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. (Modified from West JB. *Ventilation/Blood Flow and Gas Exchange*. 3rd ed. Oxford, UK: Blackwell Scientific Publications; 1977:36.)

Figure 1.8. Continuum of alveolar gas composition at different ventilation-perfusion ratios within a single alveolar-capillary unit. Line is "ventilation-perfusion ratio line." At extreme left side of line, $\dot{V}/\dot{Q} = 0$ (shunt). At extreme right side of line, $\dot{V}/\dot{Q} = \infty$ (dead space). P_{CO_2}, Partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen. (Modified from West JB. *Ventilation/Blood Flow and Gas Exchange*. 3rd ed. Oxford, UK: Blackwell Scientific Publications; 1977:37.)

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.

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:

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

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:

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

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* (AaD_{O_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)

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

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 Po_2 in the resulting arterial blood. Common causes of a shunt are:

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 Po_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.

Ventilation-perfusion mismatch and shunting are the two important mechanisms for elevation of the alveolar-arterial O_2 difference ($AaDo_2$).

$AaDo_2$, Alveolar-arterial O_2 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) while 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).

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 Po_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 Po_2 rise considerably with additional O_2, fully saturating blood coming even from regions with a low $\dot{V}/\dot{Q}$ ratio, and arterial Po_2 rises substantially.

A third cause of elevated $AaDo_2$ occurs primarily in specialized circumstances. This cause is a "diffusion block" in which Po_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 Po_2 in pulmonary capillary blood never reaches the Po_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 $AaDo_2$ and causing hypoxemia.

Increasing the difference between alveolar and arterial Po_2 is not the only mechanism that results in hypoxemia. Alveolar Po_2 can be decreased, which must necessarily lower arterial Po_2 if $AaDo_2$ remains constant. Referring to the alveolar gas equation, it is relatively easy to see that alveolar Po_2 drops if barometric pressure falls (e.g., with altitude) or if alveolar Pco_2 rises (e.g., with hypoventilation). In the latter circumstance, when total $\dot{V}_A$ falls, Pco_2 in alveolar gas rises at the same time alveolar Po_2 falls. Hypoventilation is relatively common in lung disease and is defined by the presence

	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. (Modified from Comroe JH. *The Lung*. 2nd ed. Chicago, IL: Year Book Medical Publishers; 1962:94.)

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}

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.

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 AaD_{O_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.

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

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.

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, hypercapnia also will result.

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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2

Presentation of the Patient with Pulmonary Disease

DYSPNEA, 19
COUGH, 23
Evaluation and Management of Cough, 25
HEMOPTYSIS, 26
CHEST PAIN, 27

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 and a number of less 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* probably 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

Abstract

Chapter 2 covers the variety of major symptoms that can be experienced by patients with a disorder affecting the respiratory system. In many cases, it is one of these symptoms that leads to the individual's seeking medical care. Dyspnea, or shortness of breath, is a particularly common symptom that results from many acute and chronic pulmonary diseases, but it can also result from cardiovascular disease and a variety of other miscellaneous conditions. Cough, which is normally an important protective mechanism for clearing the airway, can be due to airway irritants, diseases affecting the airways or pulmonary parenchyma, heart failure, and a variety of miscellaneous causes, including use of angiotensin-converting inhibitors. Hemoptysis, which is most commonly from airways disease, can also be a consequence of pulmonary parenchymal or vascular disease. Chest pain, although most commonly resulting from cardiac disease, can occur with irritation, inflammation, or infiltration of pleural, diaphragmatic, or mediastinal surfaces.

Keywords

Respiratory symptoms
Dyspnea
Cough
Hemoptysis
Chest pain

heavily on the stimulus or amount of activity required to precipitate it. The physician must take into account 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.

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 to 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, often is 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 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 due to 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 with regard to underlying cardiac decompensation still applies, the increase in central intravascular volume is due more to a slow mobilization of tissue fluid, such as peripheral edema, than to a rapid redistribution of intravascular volume from peripheral to central vessels.

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

Variants that are much more uncommon are only 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, a number of sources or mechanisms are proposed rather than a single common thread linking the diverse responsible conditions. In particular, neural output reflecting central nervous system respiratory drive appears to be 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 subsumed 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 dyspnea with underlying pathophysiologic mechanisms. While 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 even 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 increased 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 categories, such as patients experiencing panic attacks.

Table 2.1

DIFFERENTIAL DIAGNOSIS OF DYSPNEA

RESPIRATORY DISEASE
Airway disease
Asthma
Chronic obstructive lung disease
Upper airway obstruction
Parenchymal lung disease
Acute respiratory distress syndrome
Pneumonia
Interstitial lung disease
Pulmonary vascular disease
Pulmonary emboli
Pulmonary arterial hypertension
Pleural disease
Pneumothorax
Pleural effusion
"Bellows" disease
Neuromuscular disease (e.g., polymyositis, myasthenia gravis, Guillain-Barré syndrome)
Chest wall disease (e.g., kyphoscoliosis)
CARDIOVASCULAR DISEASE
Elevated pulmonary venous pressure
Left ventricular failure
Mitral stenosis
Decreased cardiac output
Severe anemia
INCREASED RESPIRATORY DRIVE
Hyperthyroidism
Pregnancy
DISORDERS OF OXIDATIVE METABOLISM
Mitochondrial myopathies
Metabolic myopathies
OTHER PATIENT FACTORS
Deconditioning
Obesity
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 more commonly involved with disorders that produce dyspnea. An isolated 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 have widespread effects 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 generally predominates over that with inspiration, and the physical findings associated with obstruction (polyphonic wheezing, 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 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, vessels may be blocked by recurrent pulmonary emboli or by inflammatory or scarring processes that result in thickening of vessel walls or obliteration of the vascular lumen, ultimately causing pulmonary arterial 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 allow airflow. This pump system includes a variety of muscles (primarily but not exclusively diaphragm and intercostal) 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 a point against left ventricular failure as the causative factor.

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 complain of 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 clinical categories. Individuals who are deconditioned, often because of a sedentary lifestyle and little exercise, have less ability 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 frank dyspnea. 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

Table 2.2

DIFFERENTIAL DIAGNOSIS OF COUGH

AIRWAY IRRITANTS
Inhaled smoke, dusts, fumes
Aspiration
Gastric contents
Oral secretions
Foreign bodies
Postnasal drip (upper airway cough syndrome)
AIRWAYS DISEASE
Upper respiratory tract infection
Postinfectious cough
Acute or chronic bronchitis
Eosinophilic bronchitis
Bronchiectasis
Neoplasm
External compression by node or mass lesion
Reactive airways disease (asthma)
PARENCHYMAL DISEASE
Pneumonia and other lower respiratory tract infections (e.g., tuberculosis)
Lung abscess
Interstitial lung disease
CONGESTIVE HEART FAILURE
MISCELLANEOUS
Drug-induced (angiotensin-converting enzyme inhibitors)

Irritant receptors triggering cough are located primarily in larger airways.

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.

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. Aspiration of gastric contents or 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.

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, acute bronchitis) or chronic (bronchiectasis, chronic bronchitis, lung abscess), generally have an airway component and an impressive amount of associated coughing. Space-occupying lesions in the tracheobronchial tree (tumors, foreign bodies, granulomas) and external lesions compressing the airway (mediastinal masses, lymph nodes, other tumors) commonly manifest as cough secondary to airway irritation. Hyperirritable airways with airway constriction, 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, since 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, 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. Finally, 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.

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. Whereas chronic bronchitis is a particularly frequent cause of cough in smokers, 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, 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). Further details about the evaluation and management of chronic cough can be found in references at the end of this chapter.

HEMOPTYSIS

Hemoptysis is coughing or spitting 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 acquired immunodeficiency syndrome (AIDS), hemoptysis may be due to endobronchial (and/or pulmonary parenchymal) involvement with Kaposi sarcoma.

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, 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

Table 2.3

DIFFERENTIAL DIAGNOSIS OF HEMOPTYSIS

AIRWAYS DISEASE
Acute or chronic bronchitis
Bronchiectasis
Bronchogenic carcinoma
Bronchial carcinoid tumor (bronchial adenoma)
Other endobronchial tumors (Kaposi sarcoma, metastatic carcinoma)

PARENCHYMAL DISEASE
Tuberculosis
Lung abscess
Pneumonia
Mycetoma ("fungus ball")
Miscellaneous
- Goodpasture syndrome
- Idiopathic pulmonary hemosiderosis
- Granulomatosis with polyangiitis (Wegener granulomatosis)

VASCULAR DISEASE
Pulmonary embolism
Elevated pulmonary venous pressure
- Left ventricular failure
- Mitral stenosis

Vascular malformation

MISCELLANEOUS/RARE CAUSES
Impaired coagulation
Pulmonary endometriosis

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, inasmuch as 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

EVALUATION ON A MACROSCOPIC LEVEL, 30
Physical Examination, 30
Chest Radiography, 34
Computed Tomography, 37
Magnetic Resonance Imaging, 42
Radionuclide Lung Scanning, 43
Pulmonary Angiography, 45
Ultrasonography, 46
Bronchoscopy, 46

EVALUATION ON A MICROSCOPIC LEVEL, 48
Obtaining Specimens, 49
Processing Specimens, 50

ASSESSMENT ON A FUNCTIONAL LEVEL, 52
Pulmonary Function Tests, 52
Arterial Blood Gases, 58
Exercise Testing, 61

In evaluating the 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 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 examine 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

Abstract

Chapter 3 describes the various tools that the clinician has at his or her disposal to evaluate the patient with known or suspected disease affecting the respiratory system. These tools are placed into three categories: evaluation on a macroscopic level, evaluation on a microscopic level, and assessment on a functional level. Evaluation at a macroscopic level starts with a discussion of the physical examination of the lungs, but also includes such important findings as clubbing and cyanosis. This is followed by a variety of imaging studies, including chest radiography, computed tomography (including CT pulmonary angiography), magnetic resonance imaging, radionuclide lung scanning, traditional pulmonary angiography, and ultrasonography. The section on macroscopic evaluation concludes with a discussion of flexible bronchoscopy, including the use of endobronchial ultrasound and various other techniques that are commonly used during bronchoscopy. Evaluation on a microscopic level describes the various methods for obtaining specimens and then processing them, particularly when looking for infection or tumor. The chapter concludes by considering how lung function and the effects of abnormal lung function on gas exchange are assessed. The techniques used in pulmonary function testing are described, along with interpretation based upon patterns of pulmonary function impairment. Measuring gas exchange by arterial blood gases and pulse oximetry are then followed by a description of exercise testing and its utility in evaluating the patient with exercise limitation.

Keywords

Pulmonary physical examination
Chest radiography
Chest computed tomography (chest CT)
Radionuclide lung scanning
Bronchoscopy
Pulmonary function testing
Arterial blood gases

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 aeration 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, 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. Additionally, the examiner can locate the approximate position of the diaphragm by a change in the quality of the percussed note, from resonant to dull, toward 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 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 is louder and harsher, more hollow or tubular in quality, and 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

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

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*.

Better 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*. 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—an altered 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 will describe 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 helps distinguish the different disorders, others think that such distinctions in quality are of little clinical value.

Crackles, 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 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.

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. Briefly discussed here are clubbing (with or without hypertrophic osteoarthropathy) and cyanosis.

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.

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

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.

Figure 3.1. Clubbing in a patient with carcinoma of the lung. Curvature of nail and loss of angle between nail and adjacent skin can be seen.

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 lighter skin and all mucous membranes 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 the 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 the patient with polycythemia, in contrast, much less depression of P_{O_2} is necessary before sufficient deoxygenated hemoglobin exists to produce cyanosis.

Chest Radiography

The chest radiograph, which is largely taken for granted in the practice of medicine, is used not only in evaluating patients with suspected respiratory disease but 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. Additionally, 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 realm 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 film, the x-ray beam goes from the back to the front of the patient, and the patient's anterior chest is adjacent to the film. The lateral view is typically taken with the patient's left side against the film, and the beam is directed

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

through the patient to the film. If a film cannot be taken with the patient standing and the chest adjacent to the film, 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 film 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.

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.

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

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.

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.

In contrast, when a lobe has airless alveoli and collapses, it not only becomes denser but also has features of volume loss characteristics 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.

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.

Two additional terms used to describe patterns of increased density are worth mentioning. 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. Although the term can be used to describe a region or a pattern of 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).

Although the preceding focus on some typical abnormalities provides an introduction to pattern recognition on a chest radiograph, the careful examiner must also use a systematic approach in analyzing the film. 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

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. (Courtesy Dr. T. Scott Johnson.)

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 *(arrow head)* and an anteriorly displaced major fissure *(long arrow)*.

Figure 3.6. Posteroanterior **(A)** and lateral **(B)** chest radiographs of a patient with interstitial lung disease. Reticulonodular pattern is present throughout but is most prominent in the right lung and at the base of left lung.

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

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

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 breathhold and using multiple detectors) as the patient's body is moved through the CT apparatus (the gantry).

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

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.

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 the last 2 decades, computed tomographic angiography (CTA) has become important in the diagnosis of pulmonary emboli. 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 CTA is more likely to be diagnostic than perfusion scanning, and it is less invasive than traditional pulmonary angiography. Although CTA 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. Additionally, 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*.

Figure 3.10. Cross-sectional (axial) image from a computed tomography scan performed for evaluation of a solitary peripheral pulmonary nodule. The nodule can be seen in the posterior portion of the right lung. Images were taken 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.

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 References). 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

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.

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.

MRI scanning is expensive, so it is generally used when it can provide information not otherwise obtainable by less expensive, equally noninvasive means. Although MRI is newer than CT, it 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 (Fig. 3.12). 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. Only areas of the lung receiving perfusion from the pulmonary arterial system demonstrate uptake of the tracer, whereas non-perfused regions show no uptake of the labeled albumin.

For ventilation scanning, the gaseous radioisotope xenon 133 or an aerosol of technetium 99 diethylenetriamine pentaacetate (DTPA) is inhaled, and the sequential

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. (Courtesy Dr. Henry Royal.)

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)

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. 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 positron emission tomography (PET) using a specialized imaging system, or by adapting a γ camera for imaging of positron-emitting radionuclides.

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 hypometabolic 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 on a series of rapidly exposed chest radiographs (Fig. 3.13). This test is primarily used 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,

Figure 3.13. 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. (Courtesy Dr. Morris Simon.)

or CTA was inconclusive. However, with advances in CT techniques, a pulmonary angiogram is now rarely needed.

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. In particular, ultrasonography is capable of detecting small amounts of pleural fluid and is often used to guide placement of a needle for sampling a small amount of this fluid. Additionally, it can detect walled-off compartments (loculations) within pleural effusions, distinguish fluid from pleural thickening, and detect pneumothorax with high sensitivity.

Ultrasonography is capable of localizing the diaphragm and detecting 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 much more commonly with a thin, flexible instrument (Fig. 3.14). The flexible instrument transmits images via flexible fiberoptic bundles (traditional fiberoptic bronchoscope) or more commonly via a digital chip 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.

The bronchoscopist can obtain an excellent view of the airways (Fig. 3.15) 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).

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*

Figure 3.14. 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. Controls for the clinician performing procedure are shown at the upper left.

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 a *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.

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

Figure 3.15. Airways as seen through a fiberoptic bronchoscope. At this level the carina can be seen separating the right and left mainstem bronchi. A large endobronchial mass (squamous cell carcinoma of the lung) obstructs the right mainstem bronchus.

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. 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 malignancy and infectious processes such as bacterial pneumonia and tuberculosis.

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
2. Transtracheal aspiration
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 jiroveci*, particularly in patients with acquired immunodeficiency syndrome (AIDS). 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.

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

A lesion or diseased area in the lung parenchyma can be reached with a needle through the chest wall. 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 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, 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.

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

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.

Identification of mycobacteria, 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. jiroveci,* a pathogen now classified as a unique category of fungi (see Chapter 25) 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 more or less specifically stain collagen, elastin, and a variety of microorganisms. Further discussion of the specific techniques and stains can be found in standard pathology textbooks.

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 to 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. jiroveci*, 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. Many other types of functional studies are useful for clinical or research purposes, but they are not discussed in this chapter.

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. 3.16):

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

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

Figure 3.16. 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.

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 inasmuch as 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. 3.17). 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 midexpiratory 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

Figure 3.17. 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 ($FEF_{25\%–75\%}$).

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.

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 the capillary 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. Despite the name, as the test is performed in clinical practice, the influence of the thickness of the alveolar-capillary membrane on the measured value is actually minimal. 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 are often used because of 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, the utility of race/ethnicity-specific equations has recently been questioned and can be problematic for individuals with mixed racial/ethnic backgrounds.

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. An individual without 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 MMFR and FEV_1/FVC ratio (Fig. 3.18). There is generally a high RV and an increased RV/TLC ratio, indicating air trapping due to closure of airways during forced expiration (Fig. 3.19). Hyperinflation, reflected by an increased TLC, is often found, particularly in patients with emphysema. Diffusing capacity tends to be 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).

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 by at least 12% and at least 200 mL over baseline.

The hallmark of restrictive disease is a reduction in lung volumes although expiratory airflow is normal (see Fig. 3.19). Therefore, TLC, RV, VC, and FRC all tend to be

Figure 3.18. 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 3.19. Diagram of lung volumes (total lung capacity *[TLC]* and subcompartments vital capacity *[VC]* and residual volume *[RV]*) in a normal individual and patients with obstructive and restrictive disease.

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.

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.

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

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 (MMFR, FEV_1/FVC) 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. 3.20.

In obstructive lung disease, the expiratory portion of the flow-volume curve 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

Figure 3.20. 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.

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

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. 3.21). 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. 3.22).

A test of airflow that is commonly used in clinical practice, particularly in asthmatics 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 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 can be conveniently 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

Figure 3.21. 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. (From Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper and lower airways. *Am J Med*. 1976;61:85–93, with permission from Excerpta Medica Inc.)

Figure 3.22. 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. (From Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper and lower airways. *Am J Med*. 1976;61:85–93, with permission from Excerpta Medica Inc.)

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*.

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

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.

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.

Because of the discomfort and small risk of vessel injury with arterial puncture, there is interest in analyzing venous blood as a surrogate for arterial blood gas analysis. This practice has not been well studied at present. Early studies suggest that in hemodynamically stable patients (i.e., with normal cardiac output and systemic blood pressure), venous blood samples have reasonable correlation with arterial HCO_3^- and pH. However, there is inadequate correlation between arterial and venous P_{CO_2} and P_{O_2}. If the patient is critically ill or hemodynamically unstable, venous blood gases do not provide a good indicator of arterial values.

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,

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 ↑	↑

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. 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 P_{O_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.

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 is also commonly 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 is usually 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. However, the test does not provide any information about the mechanism of exercise limitation. Although this test does not distinguish limitation due to lung disease from that attributable to other medical problems such as heart disease, peripheral vascular disease, or muscle weakness, 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

STRUCTURE, 65
Neural Control of Airways, 68

FUNCTION, 70
Airway Resistance, 70
Maximal Expiratory Effort, 71

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 tubes 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. 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.

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), 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.

Abstract

Chapter 4 focuses on airway anatomy and physiology, providing the background information about airway structure and function that will prove critical in understanding how normal structure and function are affected by diseases involving the airways, particularly asthma and chronic obstructive pulmonary disease. Airway anatomy and histology are presented, followed by a description of neural innervation of the airways and the effect of sympathetic, parasympathetic, and non-adrenergic, non-cholinergic stimulation on airway tone. A discussion of airway function covers the concept of airway resistance and explains the determinants of forced expiratory flow. The difficult conceptual model of the equal pressure point during forced expiration is explained, with implications for effort-dependent and effort-independent components of the forced expiratory flow-volume curve.

Keywords

Airway anatomy
Neural control of airways
Airway resistance
Forced expiratory flow
Equal pressure point
Flow-volume curves

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*. (From Thurlbeck WM. Chronic obstructive lung disease. In: Sommers SC, ed. *Pathology Annual*, vol 3. New York, NY: Appleton-Century-Crofts; 1968.)

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. (Adapted from Weibel ER, Burri PH: Funktionelle Aspekte der Lungenmorphologie. In: Fuchs WA, Voegeli E, eds. *Aktuelle Probleme der Roentgendiagnostik*, vol 2. Bern, Switzerland: Huber; 1973.)

The surface layer (mucosa) consists predominantly of pseudostratified columnar epithelial cells. 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) 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 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. Mucins are very large glycoproteins that, after secretion into the airways, physically expand greatly and bind with water and other molecules to form a viscous mucous gel. In humans, there are two predominant mucins: MUC5AC, produced primarily by goblet cells, and MUC5B, produced primarily by cells in the submucosal glands (see later). Normally goblet cells are more prevalent in the proximal airways. Their numbers decrease peripherally, and they are not present in terminal bronchioles. 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 increasing 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 of ions, particularly chloride, 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, 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 not only contraction and relaxation of bronchial smooth muscle but also 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).

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 denser 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

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.

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 β_2, receptors on bronchial smooth muscle. These receptors are stimulated by circulating catecholamines. When stimulated, β_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 β_2-adrenergic receptors is opposite that of cholinergic receptors; β_2-adrenergic receptors are denser in peripheral than in central airways. Inhaled β-adrenergic agonists cause bronchodilation and are a critical part of asthma treatment (see Chapter 6).

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.

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.

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 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 is 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 per second—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.

Table 4.1 lists the total cross-sectional area of the 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.

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. 4.4. 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.

During the first part of this curve, until about 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

Table 4.1

AIRWAY NUMBERS AND DIMENSIONS

Name	Number	Diameter (mm)	Cross-Sectional Area (cm^2)
Trachea	1	25	5
Main bronchi	2	11–19	3.2
Lobar bronchi	5	4.5–13.5	2.7
Segmental bronchi	19	4.5–6.5	3.2
Subsegmental bronchi	38	3–6	6.6
Terminal bronchi	1000	1	7.9
Terminal bronchioles	35,000	0.65	116
Terminal respiratory bronchioles	630,000	0.45	1000
Alveolar ducts and sacs	4×10^6	0.4	17,100
Alveoli	300×10^6	0.25–0.30	700,000 (surface area)

Modified from Thurlbeck WM: Chronic obstructive lung disease. In Sommers SC, editor: *Pathology annual*, vol 3, New York, 1968, Appleton-Century-Crofts.

Figure 4.4. 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 about 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.

of the vital capacity during maximal expiratory flow is often termed the *effort-dependent portion*.

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

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 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.

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 is affected by the amount of radial traction exerted by surrounding lung tissue on the airway walls. Airways are not isolated structures but 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 airways

*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.

Figure 4.5. 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.

lose some of their normal support and are more likely to collapse during a forced expiration (see Chapter 6). Third, and perhaps most difficult to understand, is the combination of pressures acting on the airway from without and within. 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, 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. 4.5). 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 are able to 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. 4.5 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 internally on the alveolus and externally 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. 4.5). 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.

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 all 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.

going toward 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.

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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5

Asthma

ETIOLOGY AND PATHOGENESIS, 75
- Predisposition to Asthma, 76
- Airway Inflammation, Cytokine Mediators, and Bronchial Hyperresponsiveness, 77
- Asthma Phenotypes, 79
- Common Provocative Stimuli, 79

PATHOLOGY, 82

PATHOPHYSIOLOGY, 83

CLINICAL FEATURES, 84

DIAGNOSTIC APPROACH, 85

TREATMENT, 87
- Bronchodilators, 87
- Antiinflammatory Drugs, 89
- Agents With Specific Targeted Action, 89
- Bronchial Thermoplasty, 90
- Management Strategy, 90

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—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 response of airway smooth muscle to a wide variety of stimuli. The hyperresponsiveness is likely due in part to underlying airway inflammation with a variety of types of inflammatory cells, especially 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

Abstract

Chapter 5 covers the common condition of asthma. The discussion of etiology and pathogenesis focuses on genetic and environmental factors and their contribution to a predisposition to developing asthma. The importance of airway inflammation and bronchial hyperresponsiveness is stressed, with implications for effective treatment. Common stimuli that provoke asthma are presented, such as allergen exposure, inhaled irritants, respiratory tract infection, and exercise, along with a discussion of what is known about the mechanisms underlying each of these triggers. The pathologic findings in asthma are provided along with the pathophysiologic features that lead to abnormal pulmonary function and gas exchange. The clinical discussion of asthma outlines the typical history and physical examination, and diagnostic evaluation stresses the importance of pulmonary function testing. The important treatment modalities are covered, along with the general approach for treatment based upon severity of disease. Newer modalities available for selected patients with particularly severe disease are presented, including bronchial thermoplasty and biological agents targeted to blocking the action of IgE or interleukin (IL)-5.

Keywords

Asthma
Asthma genetics
Leukotrienes
Asthma mediators
Asthma diagnosis
Asthma treatment

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 a number of 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 either inherited or 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 an underlying history of allergies (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 various 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 asthmatic subjects compared with control subjects, and studies in twins indicate a much higher concordance for asthma in monozygotic than in dizygotic twins. Attempts to identify chromosomal regions carrying genes associated with asthma have found the highest association with gene variants at the 17q21 locus. Nevertheless, variations in a single gene appear to explain only a portion of the 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 phenotype. 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 increasing the immune responsiveness of the child.

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.

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 presumption that specific mechanistic pathways and the role of various cells and mediators differ depending upon 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 references at the end of this chapter.

As noted, a feature that is common to asthmatic patients, independent of their age at presentation or their specific phenotype, is hyperresponsiveness of the airways to a

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.

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.

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

Another typical finding in many asthmatics 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 such persons with asthma, even when they are free of obvious bronchospasm.

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 to deeper layers of the mucosa. Additionally, the epithelial cells themselves may 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

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.

mediators, released at bronchial smooth muscle, submucosal glands, and blood vessels, are capable of causing 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 commonly used framework 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 asthmatic patients 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 references 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 asthmatic persons. 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 the asthmatic patient are:

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 an asthmatic person 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 an asthmatic person 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 capable of inducing bronchoconstriction and inflammation. Several mediators have been recognized (Table 5.2), but the discussion

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

here is limited to the few that have been primarily implicated in the pathogenesis of allergic asthma; major mediators include histamine and leukotrienes.

Histamine

This relatively small (molecular weight 111) compound is found preformed within the mast cell and is released on exposure to the appropriate antigen. Histamine has several effects that may be 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 may have an important role in the pathogenesis 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 antiinflammatory 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.

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), appears to be 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

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

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*.

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.

It now appears that this "late-phase response," as it has been called, depends on the presence of antigen-specific IgE. Presumably, 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 asthmatic persons. 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 is capable of stimulating 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 a 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 asthmatic persons 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 an asthmatic person 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 be responsible for 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 have often 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 is also 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 asthmatics.

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 asthmatic persons. 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 generally exhibit a decrease in both forced vital capacity (FVC) and FEV_1, with the decrease in FEV_1 usually 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 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 asthmatic person 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 a higher-than-normal FRC 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 asthmatic persons, generally those with long-standing disease, have pulmonary function that does not return to normal. Instead, they have easily 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. 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 means 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.

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

Onset of asthma occurs 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. Patients do not necessarily have a classic presentation with several or all of these complaints but may merely have an unexplained cough or breathlessness on exertion. In some cases, 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 cases, 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 asthmatic persons 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:
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 chronic obstructive pulmonary disease or in the case of a foreign body in the airway. On the other hand, not all asthmatic persons 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 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 on the basis of 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.

DIAGNOSTIC APPROACH

A clinical history of reversible episodes of bronchoconstriction 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, is generally 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 percentage 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

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 • No interference with normal activity • Exacerbations brief	• No more than twice per month	• FEV_1 > 80% predicted • FEV_1/FVC normal	• Inhaled short-acting β_2 agonist as needed
Mild persistent	• Symptoms > twice per week but < once per day • Minor limitation with normal activity	• Three or 4 times per month	• FEV_1 or PEFR >80% predicted • FEV_1/FVC normal	• Antiinflammatory therapy (inhaled corticosteroid) • Alternative: sustained-release theophylline, leukotriene modifier, or cromoglycate • Inhaled short-acting β_2 agonist as needed
Moderate persistent	• Daily symptoms • Daily use of inhaled short-acting β_2 agonist • Some limitation with normal activity • Exacerbations at least twice per week; may last days	• More than once per week but not nightly	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• Low-dose inhaled corticosteroid plus long-acting β_2 agonist *OR* • Medium-dose inhaled corticosteroid
Severe persistent	• Continual symptoms • Extremely limited with normal activity • Frequent exacerbations	• Often nightly	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%	• Medium- or high-dose inhaled corticosteroid plus long-acting β_2 agonist • Consider short course of oral corticosteroid

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.

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 (F_ENO). 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 both as a marker of how active the inflammatory response is, and as a guide to the likelihood of response to corticosteroids.

Although the diagnosis of asthma is usually made on the basis of 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 asthmatic persons have hyperreactive airways. Therefore, when tested with inhalation of methacholine (a cholinergic agent) or histamine, persons with asthma respond with bronchoconstriction to comparatively small doses of either agent. 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.

Measurement of pulmonary function, especially FEV_1 and FVC, is 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.

Patients can conveniently test their own pulmonary function through measurement of the peak expiratory flow rate. 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.

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

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 antiinflammatory action. Agents that decrease the production or activity of specific mediators are also used, and monoclonal antibodies against IgE and against IL-5 are available for use in selected patients. 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 chronic obstructive pulmonary disease, and are mentioned in other chapters.

Bronchodilators

The most common bronchodilator agents used for treatment of asthma are the sympathomimetic agents, which act on β_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 β_2 receptors, activate protein kinase A, which phosphorylates several regulatory proteins that mediate bronchodilation. Additionally, β 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 β_1 receptors, the preferred agents have action limited primarily to stimulation of β_2 receptors. The β_2-specific agents most commonly used are albuterol (short-acting β_2 agonist) and salmeterol or formoterol (long-acting β_2 agonists), and the typical route of administration is inhalation. 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 β_2 receptors and decrease potential adverse cardiac effects caused by stimulation of β_1 receptors.

Short-acting inhaled β_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 β_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 β_2 agonists salmeterol, formoterol, and arformoterol last for approximately 12 hours, while newer ultra-long-acting β_2 agonists such as vilanterol can last up to 24 hours; none of these agents is appropriate for as-needed use to treat acute symptoms. If asthma severity necessitates frequent use of a short-acting inhaled β_2 agonist or regular use of a long-acting β_2 agonist, then an antiinflammatory agent (see following section) should be incorporated in the treatment regimen.

The second class of bronchodilator agents, which are less commonly used in asthma, often in conjunction with β_2 agonists, 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 β_2 agonists in patients during an acute asthma attack. Tiotropium, a long-acting anticholinergic agent frequently used

Table 5.4

DRUG THERAPY IN ASTHMA

	Examples	Possible Routes of Administration	Mechanism of Action
BRONCHODILATORS			
Sympathomimetics	Epinephrine Albuterol Salmeterol Formoterol Arformoterol Vilanterol	Inhaled, oral, parenteral (depending on particular drug)	↑cAMP via stimulation of adenylate cyclase
Xanthines	Theophylline Aminophylline	Oral Oral, parenteral	? ↑cAMP via inhibition of phosphodiesterase; ? antiinflammatory
Anticholinergics	Ipratropium Tiotropium	Inhaled	Blockade of cholinergic (bronchoconstrictor) effect on airways
ANTIINFLAMMATORY DRUGS			
Corticosteroids	Prednisone Methylprednisolone	Systemic (oral or parenteral, depending on particular drug)	Decreased inflammatory response in airways; ? additional mechanisms
	Beclomethasone Triamcinolone Flunisolide Fluticasone 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 Montelukast	Oral	Leukotriene D_4 receptor antagonism
Anti-IgE antibody	Omalizumab	Parenteral	Binds circulating IgE antibody
Anti-IL-5 antibody	Mepolizumab Reslizumab	Parenteral	Blocks IL-5; reduces eosinophils in sputum and blood

cAMP, Cyclic adenosine monophosphate; *IgE*, immunoglobulin E; *IL-5*, interleukin-5.

in patients with chronic obstructive pulmonary disease (COPD), is also approved for 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 β_2 agonist.

The third class of bronchodilator agents, the methylxanthines, is used much less frequently than either β_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 antiinflammatory 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 is arguably responsible for bronchodilation.

Antiinflammatory Drugs

As opposed to the bronchodilator agents, which act by relaxing bronchial smooth muscle, antiinflammatory agents are targeted to control the underlying process of airway inflammation, and are therefore categorized as *controller* medications. The primary category of antiinflammatory 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 antiinflammatory action are unknown. 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 nitric oxide synthase (iNOS), and an inducible form of cyclooxygenase.

Because airway inflammation is believed to play an important role in asthma pathogenesis, particularly in the patient with more frequent attacks or more persistent airflow obstruction, corticosteroids have assumed a central role in the management of most cases of asthma. By decreasing airway inflammation, 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 attacks and maintenance therapy for disease requiring more than just infrequent use of a β_2-agonist bronchodilator. Frequently, 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 the preferred form of controller or preventive therapy for patients with asthma not adequately managed with infrequent use of a β-agonist inhaler.

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

A different antiinflammatory 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.

Antiinflammatory therapy is important when treatment of asthma requires more than infrequent use of an inhaled β_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 IL-5.

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. On the basis 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.

A monoclonal antibody to IgE, omalizumab, was developed to prevent the binding of IgE to receptors on mast cells, and is based on the principle that IgE is an important component 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 extremely 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.

Most recently, two drugs—mepolizumab and reslizumab—which are monoclonal antibodies against IL-5, are intended to reduce eosinophilic inflammation by blocking IL-5's effect on recruiting and activating eosinophils. Like omalizumab, these drugs are also extremely expensive. They are administered subcutaneously (mepolizumab) or intravenously (reslizumab) and have limited use, but can be particularly effective in the subgroup of adult patients with severe asthma and eosinophilia, particularly when refractory to treatment with corticosteroids. Of note, mepolizumab and reslizumab are of limited effectiveness in patients without the eosinophilic phenotype of asthma.

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. A patient with relatively infrequent attacks, with symptom-free periods and normal pulmonary function between attacks, is managed with inhaled short-acting sympathomimetics (β_2 agonists). These drugs are used on an as-needed basis, 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 infrequent use of a β_2-agonist inhaler, then an antiinflammatory agent is generally added as maintenance (ongoing) therapy to suppress the underlying airway inflammation. Inhaled corticosteroids are used most frequently and appear to be the most effective agents in this class, although leukotriene antagonists are alternatives.

If therapy must be escalated beyond these measures because of inadequate control, addition of a regularly used long-acting inhaled β_2 agonist (e.g., salmeterol or formoterol) is the preferred option. Other options are addition of an antileukotriene agent, escalation of the dose of inhaled corticosteroids, or addition of the methylxanthine theophylline. The drugs that are targeted toward antagonizing IgE or IL-5 are reserved for a very limited group of patients, typically those in whom IgE or IL-5 is thought to be an important mediator and who have severe disease refractory to more traditional 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 generally 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.

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

ETIOLOGY AND PATHOGENESIS, 94
- Smoking, 95
- Environmental and Indoor Pollution, 96
- Infection, 97
- Genetic Factors, 97

PATHOLOGY, 98

PATHOPHYSIOLOGY, 98
- Functional Abnormalities in Airways Disease, 99
- Functional Abnormalities in Emphysema, 102
- Mechanisms of Abnormal Gas Exchange, 102
- Pulmonary Hypertension, 104
- COPD Phenotypes, 104

CLINICAL FEATURES, 105

DIAGNOSTIC APPROACH AND ASSESSMENT, 106

TREATMENT, 107

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 disorders generally included in this category are chronic bronchitis and emphysema. Although the pathophysiology of airflow obstruction is 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.

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.

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, a more formal definition has been used, one requiring 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 usually have residual clinical disease even between exacerbations, and their disease is not primarily one of airway

Abstract

Chapter 6 reviews the common problem of chronic obstructive pulmonary disease (COPD). The various factors contributing to the etiology and pathogenesis of smoking are described, focusing on smoking and the protease-antiprotease hypothesis, but also considering environmental and indoor pollution, infection, and genetic factors. The pathologic features of chronic bronchitis and emphysema are detailed, including the contribution of small airways disease and the distinction between centrilobular and panacinar emphysema. The pathophysiology of airflow obstruction in COPD is explained, with consideration of factors that affect, as well as the effects of, airway resistance and loss of elastic recoil. Various factors potentially contributing to hypoxemia and hypercapnia are described, noting the importance of ventilation-perfusion mismatch. Newer concepts of COPD phenotypes are considered, as well as the factors that can lead to pulmonary hypertension in some patients. Treatment of COPD focuses on the use and roles of β2-agonists, anticholinergic agents, inhaled and systemic corticosteroids, antibiotics, and PDE-4 inhibitors. Lung volume reduction surgery and lung transplantation are considered as treatment options in selected individuals with severe disease, and the roles of pulmonary rehabilitation and long-term oxygen therapy are reviewed.

Keywords

Chronic obstructive pulmonary disease
Chronic bronchitis
Emphysema
Small airways disease
Anticholinergic agents
Alpha-1-antitrypsin deficiency
Lung volume reduction surgery

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

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

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 overlapping features of both asthma and COPD.

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 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, but indirect support for the diagnosis is still useful and reasonably reliable.

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 frequently 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 12 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 in the United States has decreased from 40% to approximately 15%. 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 is contributing to the World Health Organization's prediction that COPD will be the third most common cause of death worldwide in the year 2030.

ETIOLOGY AND PATHOGENESIS

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

Factors that have been implicated in causing or contributing to the risk of COPD include smoking, 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 about 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 α_1-antitrypsin, is discussed in detail in this section, but it is likely that other as yet unidentified genetic factors also affect the risk.

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 patency. 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 several 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 α_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 *α_1-antitrypsin*, but also sometimes called *α_1-antiprotease* or *α_1-protease inhibitor*, is normally 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

Theories postulate that proteolytic enzymes (especially elastase) are balanced by α_1-antitrypsin. If smoking or α_1-antitrypsin deficiency disturbs this balance in favor of proteolytic enzymes, emphysema could result.

antielastase activity, damage to elastin and to the alveolar wall can result, with the eventual production of emphysema.

The damage induced by cigarette smoke is believed to be mediated, in part, by disturbing the balance between elastase and antielastase. 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.

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 α_1-antitrypsin, the matrix metalloproteinases have a number of natural inhibitors, appropriately called *tissue inhibitors of matrix metalloproteinases*. 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 metalloproteinase inhibitors 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

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 α_1-antitrypsin (also called *α_1-protease inhibitor*).

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. Additionally, 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.

Infection

Infections do not initiate the disease, 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 α_1-antitrypsin. α_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 α_1-antitrypsin, produce alterations in the structure of the protein that can be detected by biochemical methods. More than 100 different alleles of α_1-antitrypsin have been identified. Each person has two genes coding for α_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 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 α_1-antitrypsin that are approximately 15% of normal, or 30 mg/dL. Heterozygotes with one *M* and one *Z* gene (the *MZ* genotype) have intermediate levels of circulating α_1-antitrypsin in the range of 50% to 60% of normal levels.

The most important form of α_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 α_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 α_1-antitrypsin. In patients with α_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 and hyperplasia) 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, and these particular cells are abundant in airways more peripheral than usual. 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 (Fig. 6.2). 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 (Fig. 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 α_1-antitrypsin deficiency, although the condition is not limited to this clinical setting.

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.

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

Figure 6.2. Low-power photomicrograph shows the localized region of emphysema in the left half of the figure, adjacent to the pleural surface *(P)*. Because emphysema here is localized, the destruction of alveolar walls and the enlargement of terminal air spaces can be contrasted with the appearance of normal lung in the right half of the figure. (Courtesy Dr. Earl Kasdon.)

Figure 6.3. 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. (From Thurlbeck WM. Chronic obstructive lung disease. In Sommers SC, ed. *Pathology Annual*, vol 3. New York, NY: Appleton-Century-Crofts; 1968.)

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

Figure 6.4. The mounted section of the whole lung shows diffuse involvement seen with panacinar emphysema. (From Thurlbeck WM. *Chronic Airflow Obstruction in Lung Disease*. Philadelphia, PA: WB Saunders; 1976.)

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 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 potentially increased 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

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). (From Thurlbeck WM. Internal surface area and other measurements in emphysema. *Thorax* 1967;22:483–496. BMJ Publishing Group.)

consequences may be relatively subtle. Because the peripheral airways contribute only about 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 airways 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. 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 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 expiration is prolonged 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 these processes that involve airways, because the narrowing and occlusion of small airways by secretions and inflammation result in air trapping 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

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 expansion). One 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.

Loss of driving pressure is not the only consequence of emphysema. There is also an indirect effect on the collapsibility of airways. Normally, the walls of airways are pulled radially outward 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.

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.

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

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.

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.

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

Mechanisms that contribute to alveolar hypoventilation and CO_2 retention in obstructive lung disease are:
1. Increased work of breathing
2. Abnormalities of ventilatory drive
3. $\dot{V}/\dot{Q}$ mismatch
4. Decreased effectiveness of the diaphragm

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.

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

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

A potential complication of COPD is the development of pulmonary hypertension (i.e., 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.

Several other, but 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, is capable of causing 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 the alveoli 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 P_{O_2}. Type B (so-called blue bloater) physiology was equated with chronic bronchitis, hypoxemia, and hypercapnia. 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, since 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 upon the history of previous exacerbations (Fig. 6.8). Where the patient falls in respect of 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 upon the symptoms and history of exacerbations. (Modified from the 2017 Report of the Global Initiative for Chronic Obstructive Lung Disease [GOLD].)

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 the colonizing bacteria. Other factors that cause acute deterioration in patients include exposure to 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 go into frank respiratory failure, a complication discussed in Chapter 27.

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 an 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, 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. 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.

Not only is smoking the primary factor that initiates COPD, but it is also a major risk factor that determines the prognosis of a patient's illness. Patients who continue to smoke appear to have the greatest further 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 is lost is not well established. Nonetheless, infections are the most important cause of acute mortality in patients with COPD, pointing to the need for influenza and pneumococcal vaccination, as well as rapid appropriate treatment of bacterial respiratory infections.

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 actually 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.

Characteristic radiographic findings in the more frequently recognized arterial deficiency pattern of COPD are:
1. Large lung volumes
2. Flat diaphragms
3. Increased anteroposterior diameter
4. Loss of vascular markings

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. 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 (Fig. 6.9). In patients with α_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.

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 COPD patients. 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. Pulmonary function tests demonstrate 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.

Figure 6.9. Chest radiographs of a patient with severe chronic obstructive pulmonary disease, showing the arterial deficiency pattern of emphysema. The lungs are hyperinflated, the diaphragms are low and flat (in this case they are actually inverted on lateral film), and there is a paucity of vascular markings. **(A)** Posteroanterior view. **(B)** Lateral view.

In patients whose lung compliance is increased (i.e., patients with emphysema), TLC is generally elevated. 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 lost, the diffusing capacity typically 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, since 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 retain bicarbonate 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 COPD patients. The agents used are identical

to those discussed in Chapter 5, including sympathomimetic agents (β_2 agonists), anticholinergic drugs, and methylxanthines. Short-acting inhaled β_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 β_2 agonist (e.g., salmeterol, formoterol, arformoterol, indacaterol), a long-acting anticholinergic (antimuscarinic) agent (e.g., tiotropium, aclidinium, umeclidinium, glycopyrrolate), 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 often relegates it to a secondary role in comparison with the inhaled bronchodilators.

Corticosteroid use for COPD treatment is evolving and is dependent on the clinical setting. A 5-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 β_2-agonist and an inhaled corticosteroid that may be even more effective is combination therapy with a long-acting β_2-agonist and a long-acting anticholinergic (antimuscarinic) agent.

Modalities available for treatment of COPD are:
1. Bronchodilators
2. Antibiotics
3. Corticosteroids
4. Phosphodiesterase-4 inhibitors
5. Supplemental oxygen
6. Exercise rehabilitation
7. Chest physiotherapy
8. Surgery (selected cases)

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, particularly those with chronic bronchitis and frequent exacerbations.

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.

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 $\leq$ 88% or arterial $P_{O_2} \leq 55$ mm Hg) is administration of supplemental O_2. Fortunately, the P_{O_2} of hypoxemic patients with COPD usually responds quite well to even relatively small amounts of supplemental O_2 (range, 24% to 28% O_2). A low flow rate of O_2 (1 to 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 Po_2 into the range where hemoglobin is almost fully saturated (i.e., $PO_2 > 60$ to 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 Po_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.

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. Handheld 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 usefulness of chest physiotherapy and postural drainage or mucus-clearing devices is not generally accepted because outcome studies have not clearly supported their benefit.

In the small subgroup of patients with COPD who have α_1-antitrypsin deficiency, therapy is available in the form of intravenous α_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 α_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 not 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 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 surgery 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 is not a practical approach 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 α_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 27. Mechanical ventilation is discussed in Chapter 29.

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7

Miscellaneous Airway Diseases

BRONCHIECTASIS, 113
- Etiology and Pathogenesis, 113
- Pathology, 114
- Pathophysiology, 115
- Clinical Features, 115
- Diagnostic Approach, 116
- Treatment, 116

CYSTIC FIBROSIS, 118
- Etiology and Pathogenesis, 118
- Pathology, 120
- Pathophysiology, 120
- Clinical Features, 120
- Diagnostic Approach, 121
- Treatment, 122

UPPER AIRWAY DISEASE, 122
- Etiology, 123
- Pathophysiology, 123
- Clinical Features, 123
- Diagnostic Approach, 124
- Treatment, 124

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 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. Years ago, measles and pertussis (whooping cough) pneumonia were common respiratory infections resulting in bronchiectasis. Currently, a variety of other viral and bacterial infections often are

Abstract

Chapter 7 covers several miscellaneous diseases affecting the airways. Bronchiectasis, the irreversible dilation of airways caused by inflammatory destruction of airway walls, is often due to infection or problems with airway clearance that result from obstruction or a defect in any of several host defense mechanisms. The various etiologies of bronchiectasis are presented, followed by the clinical and pathophysiologic features that are common to bronchiectasis, independent of etiology. Treatment focuses on the use of bronchodilators, antibiotics, and clearance of airway secretions. Cystic fibrosis, a genetic disorder most commonly associated with pulmonary and pancreatic disease, is discussed in detail, The various types of genetic mutations that can lead to cystic fibrosis are presented, along with a description of what is known about the abnormalities in ion transport across the airway wall that ultimately lead to thick, tenacious sputum and recurrent infection. Therapeutic modalities are described, including antibiotics, bronchopulmonary drainage, and newer options that are directed toward ameliorating the genetic abnormality or its direct effect on ion transport. Finally, the chapter discussed upper airway obstruction, emphasizing the differing effects of intrathoracic versus extrathoracic upper airway obstruction.

Keywords

Bronchiectasis
Ciliary dysfunction
Cystic fibrosis
Airway clearance
Upper airway obstruction

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 mucous 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 may develop behind the obstruction, causing destruction of 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.

Another 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 problem that has received significant attention 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).

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

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.

Pathology

The primary pathologic feature of bronchiectasis is evident on gross inspection of the airways, which are markedly dilated in the involved region (Fig. 7.1). 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 balloonlike fashion). These terms are still used when describing radiographic patterns but are much less relevant clinically. The dilated airways are generally 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.

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

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.

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).

Figure 7.1. Surgically removed specimen of lung shows extensive bronchiectasis. Some grossly dilated airways are filled with large amounts of mucoid and purulent material.

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.

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 the majority of 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

Common clinical features of bronchiectasis are:

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

with bronchiectasis may reveal few abnormalities, even over the area of involvement. On the other hand, the examiner may hear strikingly abnormal findings, such as wheezes, crackles, or rhonchi in a localized area. Clubbing is frequently present. 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. Evaluation on a macroscopic level generally includes a chest radiograph, which 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. 7.2). HRCT (with sections 1 to 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. 7.3). This procedure is uncomfortable, can induce bronchospasm, and is not currently performed.

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 24), 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, bronchopulmonary drainage (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 in various ways and are dependent upon the particular organisms that are cultured from the airways. Patients are typically treated during an exacerbation of their disease (i.e., when the quantity or appearance of the sputum clearly changes). In addition, some patients are also treated on a more chronic or intermittent basis 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

Figure 7.2. 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 7.3. Bronchogram of patient with extensive saccular bronchiectasis, primarily in right upper lobe.

secondary development of resistance to this class of antibiotics is common. Infection with nontuberculous mycobacteria such as *M. avium* complex requires prolonged therapy with multiple drugs (see Chapter 24). Just as for patients with other chronic lung diseases, both pneumococcal and seasonal influenza vaccines are recommended 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, expiratory "flutter valves" that provide oscillating positive pressure during exhalation, inflatable vests, or mechanical vibrators on the chest are commonly used to facilitate clearance of secretions. Inhaled 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.

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

Because ongoing airway inflammation is an important feature of bronchiectasis, there is great interest in antiinflammatory 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, since antiinflammatory actions and immunomodulatory effects can be attributed to macrolides when administered long term in low doses. Studies have demonstrated a significant reduction in exacerbations in patients receiving chronic macrolide therapy, although there is a risk of emergence of resistant bacteria from the long-term use of antibiotics.

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 the diseased area now is performed infrequently. In general, 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).

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

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.

reticulum. Whatever the responsible mutation, a deficiency in the quantity or function of CFTR leads to impermeability of epithelial cells to chloride transport, 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. Although a double copy (i.e., homozygous) ΔF508 mutation is responsible for approximately 70% 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 are recognized as 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 an abnormal electrolyte composition, specifically, elevated concentrations of sodium, chloride, and potassium. These abnormalities in the composition of sweat have proven to be crucial in diagnosing the disorder.

Major consequences of abnormal CFTR in cystic fibrosis are:

1. Production of thick, tenacious secretions from exocrine glands
2. 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)-β genes, appear to influence disease severity.

Pathology

The pathologic findings in cystic fibrosis result from obstruction of ducts or tubes 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 mucous 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. Cardiac complications of cor pulmonale frequently occur, and pathologic examination of the heart shows evidence of right ventricular hypertrophy.

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:
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. 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 sterile because of congenital bilateral absence of the vas deferens. Females are capable of having children, but their fertility rate is decreased as a consequence of the generation of 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.

Serious complications of cystic fibrosis are:
1. Pneumothorax
2. Massive hemoptysis
3. Respiratory insufficiency
4. Cor pulmonale

Several complications may develop as a result of the disease. Pneumothorax and hemoptysis, which may be massive, can be major problems in management. Eventually, frank respiratory insufficiency and cor pulmonale develop. Although most patients live into adult life when good care has been provided, their life span is significantly reduced, with a median survival of approximately 40 years.

Diagnostic Approach

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.

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.

The chest radiograph often shows an increase in markings and the findings of bronchiectasis described in the previous section (Fig. 7.4). Evidence of focal pneumonitis may be seen during the course of the disease.

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

Figure 7.4. Posteroanterior chest radiograph of patient with cystic fibrosis shows diffuse increase in markings throughout both lungs. These findings represent extensive fibrotic changes and bronchiectasis. (Courtesy Dr. Mary Ellen Wohl.)

normal. Arterial blood gas values often indicate hypoxemia, and hypercapnia may be seen as the disease progresses.

Treatment

Therapy for cystic fibrosis is based on an attempt to diminish the clinical consequences and to manage 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: bronchopulmonary drainage (using chest physiotherapy and postural drainage, a flutter valve, 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 deoxyribonuclease (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 antiinflammatory effects rather than their antimicrobial properties.

In a recent conceptual breakthrough a new drug, ivacaftor, has been shown to improve respiratory symptoms and lung function in patients with a less common CFTR mutation (G551D). This mutation results in a protein that is present in typical amounts on the cell surface but does not function normally. Ivacaftor acts as a "potentiator" to increase the time that activated CFTR channels at the cell surface remain open, thus improving the function of the abnormal channel. Unfortunately, the drug does not appear to be effective treatment for patients with the most common defect, ΔF508. Another new drug, lumacaftor, is targeted toward correcting the misfolding of CFTR characteristic of the ΔF508 mutation that prevents CFTR from getting to the epithelial cell surface. It has been approved as combination therapy with ivacaftor for patients who are homozygous for the ΔF508 deletion, with the rationale of lumacaftor's increasing the amount of CFTR on the cell surface and ivacaftor's potentiating its effect. However, ivacaftor and lumacaftor are extremely expensive and only modestly beneficial rather than curative, so it will be important to assess their long-term benefit and define their cost effectiveness.

Although current forms of therapy have significantly improved prognosis in cystic fibrosis, the natural history of the disease at present is still one of progressive pulmonary dysfunction and eventual death due to the disease or its complications. Despite initial concern about lung transplantation in these patients because of their chronic pulmonary infections, experience with bilateral lung transplantation suggests posttransplantation survival is similar to that of other patients undergoing this procedure. Unfortunately, however, 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 true 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. Thus, as with ivacaftor and lumacaftor, much current therapeutic research is focused on posttranslational modifications of the defective protein or its effects.

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. If the airways under consideration were always stiff or if a disorder did not allow any flexibility in the size of the airway, inspiration and expiration would be impaired by the same amount, and the flow rate generated during inspiration would be essentially identical to the flow rate during expiration. This type of obstruction is termed a *fixed obstruction*.

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. 3.21).

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

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. 3.21).

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 is not without 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.

Functional assessment of the patient with presumed upper airway obstruction can be useful in quantifying and localizing the obstruction, because the functional consequences of a fixed versus a variable obstruction and an extrathoracic versus an intrathoracic obstruction are quite different. To understand these differences, 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. 3.22.

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 references.

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8

Anatomic and Physiologic Aspects of the Pulmonary Parenchyma

ANATOMY, 126 PHYSIOLOGY, 129

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 rubric 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, generally subacute or chronic, the main pathologic features of which appear to 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 a large number of individual diseases. Knowledge of these general 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 capillaries are closely apposed to the alveolar lumen, and there is little tissue extraneous to the gas-exchanging process (Fig. 8.1).

Abstract

Chapter 8 describes important anatomic and physiologic aspects of the pulmonary parenchyma, paving the way for an overview in Chapter 9 of how anatomy and physiology are altered by diffuse parenchymal lung diseases. The anatomy focuses on the two major types of epithelial cells comprising alveolar walls—type I and type II epithelial cells. Their appearance and functions are considered, particularly noting the importance of alveolar type I cells as providing the major surface area of the alveolus, whereas type II cells produce surfactant and are important in maintaining and repairing the injured alveolar epithelium. The section on physiology relating to the pulmonary parenchyma expands upon the discussion of gas exchange at the alveolar level that is covered in Chapter 1. Additionally, the concept of compliance as the relationship between distending pressure and lung volume is reviewed, and the shifting of compliance curves in diffuse parenchymal lung disease downward and to the right is described.

Keywords

Alveolar epithelial cells
Pulmonary interstitium
Pulmonary alveolar injury
Surfactant
Oxygen uptake
Lung compliance

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. (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 proportion of alveolar surface area. They have impressively 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, through the alveolar wall into the alveolar lumen. Although they have few cytoplasmic organelles, increasing 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.

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 than type I cells. However, because they do not have long cytoplasmic extensions, type II cells cover less than 5% of the alveolar surface. To support their multiple functions, the more numerous 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*, appear to be the packaged form of surfactant that eventually is released into the alveolar lumen. Surfactant is composed of a high proportion of lipids as well as associated proteins and carbohydrates that are necessary for effective function. Surfactant acts like a detergent, reducing the surface tension of the alveoli. It stabilizes the alveolus in the same way a bubble is prevented

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.

from collapsing by a detergent material, thereby preventing microatelectasis (alveolar collapse on a microscopic level). Four types of protein are associated with surfactant: surfactant protein 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 and directly killing 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, while 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 devastating disease of progressive parenchymal scarring.

The third function of type II cells is regulation of alveolar fluid composition 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.

In addition, type II cells are 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 28, 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. It initially reviews gas exchange at the alveolar-capillary level, followed by a discussion of 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 between 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 usually 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 a 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 or, described more simply, the opposite of the stiffness of the lung. As stated in Chapter 1, the lung is elastic and behaves like a balloon or a rubber band in terms of resisting expansion. During inspiration, contraction of the diaphragm and expansion of the thorax by respiratory muscle function result in negative pressure around the lungs, causing them to expand. Conversely, positive pressure may be applied through the airways to inflate the lungs, as occurs during positive pressure mechanical ventilation. For any given volume of air in the lungs, a certain pressure is required to achieve this degree of inflation, and a curve can be drawn relating volume on the *Y*-axis to pressure on the *X*-axis (see Fig. 1.3A). Because the net pressure producing expansion is the difference between the pressure exerted on the alveoli (via the airway) and the absolute pressure outside the lung, the term *transpulmonary pressure* is used to describe this distending pressure. In vivo, when the lung is sitting within the chest, the pressure outside the lung is pleural pressure. If a lung is removed and studied in isolation, the pressure outside the lung is atmospheric pressure. The normal compliance relationship between transpulmonary pressure and volume in the lung is a curve that flattens out at high distending pressures when the lung reaches its upper limit of expansion. At this point the elastic tissues of the lung can be stretched no further, and additional pressure does not add volume to the lung.

Figure 8.3. Compliance curve of lung in interstitial lung disease compared with that of normal lung. In addition to shift of the curve downward and to right, total lung capacity (TLC) in interstitial 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. (Compare with Fig. 6.7.)

Diseases affecting the alveolar walls commonly disturb this pressure-volume relationship, making the lung either more stiff (more resistant to expansion) or less stiff (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 alluded to 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 Chapter 9, which discusses the pathophysiology of diseases that affect the alveolar walls.

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

PATHOLOGY, 134
- Pathology of Idiopathic Interstitial Pneumonias, 135
- End-Stage Diffuse Parenchymal Lung Disease, 138

PATHOGENESIS, 138

PATHOPHYSIOLOGY, 140
- Decreased Compliance, 141
- Decrease in Lung Volumes, 141
- Impairment of Diffusion, 141
- Abnormalities in Small Airways Function, 142
- Disturbances in Gas Exchange, 142
- Pulmonary Hypertension, 142

CLINICAL FEATURES, 142

DIAGNOSTIC APPROACH, 143

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

Abstract

Chapter 9 describes the common features that unite many of the diffuse parenchymal lung diseases (often referred to as interstitial lung diseases) as well as some specific features that distinguish among these disorders. This overview is followed in Chapters 10 and 11 by more detailed descriptions of specific diseases. The development of the diffuse parenchymal lung diseases is broken down into initiation, propagation, and final pathologic consequences, with consideration of what is known about the underlying cellular and biochemical processes involved in each stage. A summary of the pathology of these disorders emphasizes the relative roles of inflammation, fibrosis, and granuloma formation, depending upon the particular disorder. The subcategory of idiopathic interstitial pneumonias is described in detail, along with the 6 specific pathologic patterns that comprise this subcategory. These disorders generally have common pathophysiologic features, including decreased compliance of the lung, decreased lung volumes, diffusion impairment, abnormalities in small airways function, disturbance in gas exchange that is exacerbated by exercise, and the potential for pulmonary hypertension. Dyspnea is stressed as the mode of clinical presentation of most of these disorders, and the diagnostic approach focuses on the role of chest radiography, high resolution CT scanning, and the need to obtain tissue in some cases when the diagnosis is uncertain.

Keywords

Diffuse parenchymal lung disease
Interstitial lung disease
Idiopathic interstitial pneumonias
Usual interstitial pneumonia
Nonspecific interstitial pneumonia
Restrictive lung disease

Table 9.1

CLASSIFICATION OF SELECTED DIFFUSE PARENCHYMAL LUNG DISEASES

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

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

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 radiograph. 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.

Familiarity with this large number of diseases is difficult even for the pulmonary specialist, so the novice in pulmonary medicine cannot be expected to amass 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 cover 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. Included in the discussion of diseases of unknown etiology in Chapter 11 are several disorders that affect the lung parenchyma but do not characteristically have diffuse findings on chest radiograph. Examples of diseases in which the findings are more typically focal (or multifocal with more than one area of involvement) include granulomatosis with polyangiitis (formerly called Wegener granulomatosis) and cryptogenic organizing pneumonia (COP).

The diseases covered in these three chapters are primarily *chronic* (although sometimes *subacute* and rarely *acute*) diseases affecting the alveolar structures. Another category of disease, which goes under the label *acute respiratory distress syndrome (ARDS)*, is associated with diffuse disease 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 28.

PATHOLOGY

Diffuse parenchymal (interstitial) lung diseases are characterized pathologically by variable amounts of inflammation and fibrosis.

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 duration 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).

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 the phagocytic or macrophage series (Fig. 9.2). 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 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,

Figure 9.1. Photomicrograph of diffuse parenchymal lung disease shows markedly thickened alveolar walls. Cellular inflammatory process and fibrosis are present. Compare with appearance of normal alveolar walls in Fig. 8.1.

Figure 9.2. Low-power photomicrograph of transbronchial lung biopsy sample from patient with sarcoidosis. Numerous confluent granulomas throughout entire specimen obliterate normal pulmonary architecture. Two multinucleated giant cells are marked by *arrows*. (Courtesy Dr. Earl Kasdon.)

caseating granulomas are characteristically seen in infectious diseases, especially tuberculosis (see Chapter 24, 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. 9.2). 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 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.

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 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 pathologic 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

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

Modified and expanded from Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med*. 2013;188:733–748.

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)

correlations for the idiopathic interstitial pneumonias, which will also be discussed further in Chapter 11.

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.

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 nonspecific interstitial pneumonia (NSIP), which can be idiopathic but also can be a particularly 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) respiratory bronchiolitis–interstitial lung disease (RB-ILD), (4) desquamative interstitial pneumonia (DIP), (5) COP, and (6) acute interstitial pneumonia (AIP). This section briefly describes the pathologic characteristics defining these six entities, while 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.

NSIP is characterized by a prominent histopathologic component of mononuclear cell infiltration within the alveolar walls. Despite the designation "nonspecific," NSIP is now considered to be 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

Figure 9.3. Low-power photomicrograph of usual interstitial pneumonia shows prominent fibrosis accompanied by honeycombing. (Courtesy Dr. Olivier Kocher.)

not separated 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.

RB-ILD and DIP are thought to be related, in that both are typically associated with 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. 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.

COP is characterized by organizing fibrosis (also referred to as "granulation tissue") in small airways, associated with a mild degree of chronic interstitial inflammation. 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.

AIP is believed to represent the organizing or fibrotic stage of diffuse alveolar damage, which is the histologic pattern seen in ARDS (see Chapter 28). In most cases of ARDS an inciting cause is apparent, whereas in AIP no initiating trigger for ARDS can be identified. The histology 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 a fairly long time and is associated with significant fibrosis, any distinctive features of prior interstitial inflammation or alveolitis are often lost. For example, any of the granulomatous lung diseases may no longer demonstrate the characteristic granulomas after sufficient time has elapsed and a substantial degree of fibrosis has developed. 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. Along with severe fibrosis, the lung at end stage exhibits much distortion 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. 9.4).

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

Figure 9.4. Appearance of honeycomb lung from patient with severe pulmonary fibrosis. Many cystic areas are seen between bands of extensively scarred and retracted pulmonary parenchyma.

fibrosis remains mostly at the descriptive level. Recently, there has been increasing 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 (especially surfactant protein 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 28). 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.

Pathogenetic features of diffuse parenchymal lung disease are:

1. Initiation—by antigens, toxins
2. Propagation—with inflammatory cells, proteases, cytokines
3. Final pathologic consequence—fibrosis

Fig. 9.5 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.

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 dusts (e.g., asbestos) responsible for producing the pneumoconioses. Smoking also appears to be an important contributing factor for the development of the smoking-related interstitial pneumonias (RB-ILD and DIP), as well as pulmonary Langerhans cell histiocytosis (eosinophilic granuloma), discussed in Chapter 11. Inhaled antigens have been best identified as the cause of chronic 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

Figure 9.5. Schematic diagram illustrates general aspects of pathogenesis of diffuse parenchymal lung diseases.

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. 9.6): (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 9.6. Schematic diagram illustrates 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 less 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. The 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 Airways 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 airways function often show the physiologic effects of this narrowing. The clinical importance of small airways dysfunction in the absence of larger airways 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 airways function is often disturbed in diffuse parenchymal lung disease. Large airways 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. Although a diffusion block once was proposed as the cause of the hypoxemia, evidence supports $\dot{V}/\dot{Q}$ mismatch as the major contributor. The pathologic process in the alveolar walls is uneven, and normal matching of ventilation and perfusion is disrupted. In patients with small airways 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 also appears to be a contributing factor. 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 handle 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, may be present. 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 much 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. Absence of radiographic 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 may occur (see Fig. 9.4). 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 seen on the lateral view.

HRCT of the chest is an important step in the evaluation of diffuse parenchymal lung disease (see Fig. 3.9). 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.

Despite the importance of the macroscopic evaluation, making a diagnostic distinction between the different types of diffuse parenchymal lung disease often requires investigation at the microscopic or histologic level. 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). Thoracoscopic biopsy often is the more appropriate of the two procedures 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.

Another procedure for sampling the cell population of the alveolitis is *bronchoalveolar lavage* (BAL). 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.

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

DISEASES CAUSED BY INHALED INORGANIC DUSTS, 145
- Silicosis, 146
- Coal Worker's Pneumoconiosis, 146
- Asbestosis, 148
- Berylliosis, 150

HYPERSENSITIVITY PNEUMONITIS, 151

DRUG-INDUCED PARENCHYMAL LUNG DISEASE, 153

RADIATION-INDUCED LUNG DISEASE, 155

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 occupational factors. 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.

Abstract

A variety of known etiologic agents can cause diffuse parenchymal lung disease, also referred to as interstitial lung disease. These include inorganic dusts (the pneumoconioses), organic antigens (the cause of hypersensitivity pneumonitis), drugs, and radiation to the thorax. The most common of the disorders classified as pneumoconioses include silicosis, coal worker's pneumoconiosis, asbestosis, and berylliosis. Some of these disorders involve toxicity to, or activation of macrophages, whereas beryllium induces a hypersensitivity reaction that clinically mimics sarcoidosis. Many organic antigens can induce a hypersensitivity pneumonitis, which can have a presentation ranging from an acute illness with transient pulmonary infiltrates to a chronic diffuse parenchymal lung disease. A wide range of drugs are now known to be associated with parenchymal lung disease, with the most important categories being cancer chemotherapeutic agents and a variety of newer biological drugs, but a number of other miscellaneous drugs have also been implicated. Finally, radiation therapy directed to the thorax, most commonly for breast cancer, lung cancer, or Hodgkin disease, can be associated with an acute inflammatory process in the lungs (radiation pneumonitis) or a more chronic fibrotic process (radiation fibrosis).

Keywords

Occupational lung disease
Pneumoconiosis
Silicosis
Asbestosis
Berylliosis
Hypersensitivity pneumonitis
Drug-induced lung disease
Radiation-induced lung disease

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 references 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. Persons at risk include sandblasters, hard rock miners, quarry workers, and stonecutters. In most cases, development of disease requires at least 20 years of exposure. However, with particularly heavy doses of inhaled silica, as are found in sandblasters, an acute form of the disease may occur with much shorter periods of exposure.

The presumed pathogenetic effect of silica has centered around its potential toxicity for macrophages. Silica particles in 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, release of the toxic silica particles, and a repeat of the process after the particles are reingested 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.

The pulmonary effects of silica are related in part to a toxic effect on macrophages that ingest the particles.

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). At first the nodules are small and discrete. With disease progression, they become larger and may coalesce. 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.

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). As a general rule, in patients with silicosis, the upper lung zones are affected more heavily than the lower zones. Enlargement of the hilar lymph nodes, which frequently calcify, may be seen.

Silicosis is associated with immune dysregulation and is a predisposing factor for secondary infection by mycobacteria.

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. In addition, patients with silicosis are 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 *non-tuberculous mycobacteria* (see Chapter 24).

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

Figure 10.1. Low-power micrograph of silicotic lung shows characteristic appearance of silicotic nodules. (From Morgan WKC, Seaton A. *Occupational Lung Diseases*. Philadelphia, PA: WB Saunders; 1975.)

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. (From Fraser RG, Müller NL, Colman N, et al. *Diagnosis of Diseases of the Chest*. Vol 4. 4th ed. Philadelphia, PA: WB Saunders; 1999.)

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, 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 coal macule shows coal dust, dust-laden macrophages, and relatively small amounts of fibrous reaction. (From Morgan WKC, Seaton A. *Occupational Lung Diseases*. Philadelphia, PA: WB Saunders; 1975.)

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 upon the relative amounts of fibrosis, airways disease, and emphysema.

Symptoms and pulmonary function changes in coal worker's pneumoconiosis (CWP) are related to the extent of fibrosis and coexistent chronic obstructive pulmonary disease (COPD), if present.

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. Whether genetic polymorphisms may help to explain the different clinical responses to inhalational exposures is currently unknown.

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 as a result of 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 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 activate macrophages and pulmonary epithelial cells, inducing the release of mediators that attract other inflammatory cells, including neutrophils, lymphocytes, and more alveolar macrophages. 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 often significant 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, insulinlike 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.

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. 10.5). 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. 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.

Pulmonary complications of asbestos exposure are:

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.

Figure 10.4. High-power photomicrograph of ferruginous body. Rod-shaped body with clubbed ends represents "coated" asbestos fiber. (Courtesy Dr. Earl Kasdon.)

Figure 10.5. Chest radiographs of patient with parenchymal and pleural disease secondary to asbestos exposure. Interstitial markings are increased at lung bases, and extensive pleural thickening is present. Diaphragmatic calcification, which strongly suggests prior asbestos exposure, is highlighted by arrows. **A,** Posteroanterior view. **B,** Lateral view.

Berylliosis

Berylliosis, which resembles sarcoidosis in many respects, represents a cellular immune response to beryllium.

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 industries where beryllium is used. The histologic appearance of disease caused by beryllium is quite different from that seen with the other pneumoconioses described earlier. Instead, 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 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. Not only does this "beryllium lymphocyte transformation test" suggest the pathogenesis of the disease, it 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, where it is engulfed by macrophages and other antigen-presenting cells. $CD4^+$ lymphocytes are sensitized to beryllium, and the beryllium-sensitized $CD4^+$ cells release several cytokines, including IL-2, IFN-γ, and TNF-α. The secretion of IFN-γ and TNF-α is thought to be important in the recruitment of macrophages and the formation of granulomas. Studies also suggest a genetic susceptibility to development of the disease in response to beryllium exposure. 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 multiple organ systems, especially the pulmonary parenchyma and intrathoracic lymph nodes. 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. Studies suggest that polymorphisms in TNF-α may be important in determining the development of bird breeder's lung. Clearly, additional factors, perhaps genetic, determine who will develop the disease, but these factors are not yet identified.

Despite much research, we do not yet have a complete understanding of the pathogenesis of hypersensitivity pneumonitis. However, 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 early in the disease process. 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. The granulomas often are loosely formed, unlike the well-defined granulomas characteristic of sarcoidosis (see Chapter 11). Often the pathologic changes have a peribronchiolar prominence, thus accounting for the frequent physiologic evidence for obstruction of small airways.

Hypersensitivity pneumonitis occurs either with acute episodes 4–6 hours after exposure to the offending antigen or with the more insidious course of chronic diffuse parenchymal lung disease.

Clinically, hypersensitivity pneumonitis manifests in different ways, ranging from acute episodes of dyspnea, cough, fever, and infiltrates on chest radiograph (occurring approximately 4 to 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.

Unlike the acute form, the chronic form of hypersensitivity pneumonitis behaves like other forms of diffuse parenchymal lung disease. 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).

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 standard diagnostic test is a search for precipitating antibodies to the common organic antigens known to cause hypersensitivity pneumonitis. Unfortunately, false-positive and false-negative results for precipitins may cause diagnostic confusion. 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, establishing a diagnosis of hypersensitivity pneumonitis by the finding of precipitins requires that the responsible antigen be included in the panel of antigens tested. If a lung biopsy is performed for diagnosis of diffuse parenchymal lung disease, findings on microscopic examination may suggest this entity.

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 even after exposure is terminated. Corticosteroids are sometimes administered to patients with persistent disease, but the results are variable.

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 (although not the only) 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

Table 10.1

SELECTED DRUGS POTENTIALLY CAUSING DIFFUSE PARENCHYMAL LUNG DISEASE

CYTOTOXIC CHEMOTHERAPY
Bleomycin
Busulfan
Cyclophosphamide
Gemcitabine
Nitrosoureas
Taxanes (e.g., paclitaxel, docetaxel)
ANTIMETABOLITES
Methotrexate
TARGETED BIOLOGIC AGENTS
Tumor necrosis factor (TNF)-α inhibitors or soluble receptors
Infliximab
Adalimumab
Certolizumab pegol
Etanercept
Tyrosine kinase inhibitors
Afatinib
Erlotinib
Gefitinib
Idelalisib
Imatinib
Osimertinib
Trametinib
Checkpoint inhibitors (antibodies against PD-1, PD-1 ligand, or CTLA-4)
Ipilimumab
Nivolumab
Pembrolizumab
Inhibitors of anaplastic lymphoma kinase (ALK)
Alectinib
Ceritinib
Crizotinib
MISCELLANEOUS
Trastuzumab (monoclonal antibody against HER2)
Rituximab (monoclonal antibody against CD20)
Inhibitors of mechanistic target of rapamycin (mTOR, e.g., everolimus)
MISCELLANEOUS OTHER DRUGS
Nitrofurantoin
Amiodarone
DRUG-INDUCED SYNDROMES
Drug-induced lupus (e.g., procainamide, hydralazine)
Drug-induced pulmonary infiltrates with eosinophilia (e.g., sulfa-containing drugs)

disease include bleomycin, mitomycin, busulfan, cyclophosphamide, gemcitabine, taxanes, and the nitrosoureas, although several others have been described in smaller numbers of cases. In general, the risk of developing diffuse parenchymal lung disease increases with higher cumulative doses of a particular agent, but occasional cases with even 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.

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.

Cytotoxic drug–induced diffuse parenchymal lung disease shows atypical bizarre-appearing alveolar type II epithelial cells.

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.

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 interstitial pneumonitides.

The commonly used antiarrhythmic agent amiodarone is associated with clinically significant parenchymal lung disease in approximately 5% to 10% 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 have been found in autopsy specimens of 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 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 the 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 particular agent ideally should be discontinued. Steroids 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 the thorax or in close proximity to it, particularly lymphoma (Hodgkin disease) and carcinoma of the breast or lung. It is estimated that signs and symptoms of clinically apparent injury will develop in 5% to 15% of patients whose radiation therapy includes exposure of portions of normal lung. 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 develops approximately 1 to 3 months after completion of a course of therapy, depending to a large extent 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.

Although the pathogenesis of radiation-induced lung disease is not entirely known, toxicity to capillary endothelial cells and, to a lesser extent, to type I alveolar epithelial cells is believed to be the primary mode of injury and is thought to be mediated by oxygen-derived free radicals. In the period preceding chronic fibrosis, an alveolitis probably contributes directly to development of fibrotic changes. The possibility of hypersensitivity 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 dose delivery programs have become more sophisticated and use 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 interstitial pattern in radiation-induced lung disease may conform in distribution to the region of lung irradiated.

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 generally are permanent.

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 supervened, corticosteroids are much less effective.

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11

Diffuse Parenchymal Lung Diseases of Unknown Etiology

IDIOPATHIC PULMONARY FIBROSIS, 158
OTHER IDIOPATHIC INTERSTITIAL PNEUMONIAS, 161
PULMONARY PARENCHYMAL INVOLVEMENT COMPLICATING CONNECTIVE TISSUE DISEASE, 163
SARCOIDOSIS, 164
MISCELLANEOUS DISORDERS INVOLVING THE PULMONARY PARENCHYMA, 169
Pulmonary Langerhans Cell Histiocytosis, 169
Lymphangioleiomyomatosis, 170
Goodpasture Syndrome, 171
Granulomatosis with Polyangiitis, 172
Chronic Eosinophilic Pneumonia, 173
Pulmonary Alveolar Proteinosis, 174

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), pulmonary fibrosis associated with connective tissue disease, sarcoidosis, pulmonary Langerhans cell histiocytosis, 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* (*IPF*) 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 connective tissue disease a separate entity. Other names that have been used interchangeably with IPF are *cryptogenic fibrosing alveolitis* and *usual interstitial pneumonia* (UIP). The latter term is now generally used as a description of the pathologic pattern associated with IPF, a pattern occasionally seen in clinical settings other than IPF.

As implied by the name, IPF does not yet have a recognizable inciting agent, although most studies demonstrate an association with tobacco smoke exposure. Whether the

Abstract

Chapter 11 covers a wide range of diffuse parenchymal or interstitial lung diseases without a known etiologic agent triggering the disease. Idiopathic pulmonary fibrosis (IPF), a generally progressive disease with a relatively poor prognosis, is the most common entity within a broader category of idiopathic interstitial pneumonias. Also classified as an idiopathic interstitial pneumonia is nonspecific interstitial pneumonia (NSIP), which is commonly associated with underlying systemic rheumatic disease but can also be idiopathic. Two other entities within this category are desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-interstitial lung disease (RB-ILD), which are likely related and notable for a strong association with smoking. Rounding out the category of idiopathic interstitial pneumonias are two other disorders, cryptogenic organizing pneumonia (COP) and acute interstitial pneumonia (AIP). Sarcoidosis, a systemic granulomatous disease of unknown etiology, most commonly affects the lungs and/or intrathoracic lymph nodes, and is notable for a variable prognosis and the potential for therapeutic suppression of disease with corticosteroids. The chapter concludes by summarizing what is known about the pathogenesis and clinical aspects of several miscellaneous disorders involving the pulmonary parenchyma. These include pulmonary Langerhans cell histiocytosis (also called eosinophilic granuloma of the lung), lymphangioleiomyomatosis, Goodpasture syndrome, granulomatosis with polyangiitis, chronic eosinophilic pneumonia, and pulmonary alveolar proteinosis.

Keywords

Idiopathic pulmonary fibrosis
Idiopathic interstitial pneumonias
Sarcoidosis
Cryptogenic organizing pneumonia
Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Granulomatosis with polyangiitis
Chronic eosinophilic pneumonia
Pulmonary alveolar proteinosis

primary agent, if one exists, reaches the lung via the airways or bloodstream has not been determined. The theory behind the pathogenesis of IPF has changed considerably over the past decade. 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.

More recently, a different conceptual framework has emerged. According to the current theory, alveolar inflammation does not play a critical role in the eventual development of fibrosis. Rather, fibrosis is believed to result directly from alveolar epithelial injury and is thought to be a manifestation of abnormal wound healing within the lung parenchyma. According to this paradigm, injury to alveolar epithelial cells (still from an unidentified source or agent) is the primary initiating event. Whereas 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 reepithelialization process. 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.

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 (SFPA2) and C (SFPC), 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

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-*β*1.

Idiopathic pulmonary fibrosis is thought to represent a dysregulated pattern of fibrosis in response to alveolar epithelial injury.

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 all patients with IPF, identification of the pathways involved has led to better understanding of the mechanism of disease in at least some IPF patients, raising hopes of new therapies.

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 crackles or rales on physical examination, patients frequently have evidence of 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 pleural effusions nor hilar enlargement is common. High-resolution computed tomography (HRCT) scanning often 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 connective tissue 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.

The chest radiograph in IPF demonstrates a diffuse interstitial pattern without pleural disease or hilar enlargement.

The diagnosis is definitively made by surgical lung biopsy, but only in the appropriate clinical setting when other etiologic factors for interstitial lung disease cannot be identified. Some patients are too frail for lung biopsy, and if HRCT scan shows a classic pattern that includes honeycombing and several other features, then the diagnosis can be made with relative certainty without a lung biopsy. The histologic expression of IPF is in the form of UIP (see Fig. 9.3), and patients who have a pathologic pattern more

Figure 11.2. High-resolution computed tomography scan of idiopathic pulmonary fibrosis shows scattered reticular densities, especially in subpleural regions.

compatible with desquamative interstitial pneumonia (DIP) or nonspecific interstitial pneumonia (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. If they are found, granulomas indicate the presence of another disorder.

From the time of clinical presentation, patients have a relatively poor prognosis; mean survival ranges from 2 to 5 years. Although corticosteroids and cytotoxic agents have been used frequently in the past for IPF, newer studies unfortunately demonstrate that these agents are ineffective and appear to be harmful. It is now thought that the small subgroup of patients previously thought to respond to corticosteroids actually had a corticosteroid-responsive diffuse parenchymal lung disease that was misidentified as IPF.

Although IPF represents a chronic, fibrotic disease, some patients have been recognized to develop what has been called 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 28). 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. Recent efforts to develop treatment for IPF have focused on identifying and testing agents that suppress fibrosis or interfere with mediators involved in the fibrotic process. Two such drugs are now available that appear to reduce (but not stop) progression of disease, as measured by loss of pulmonary function. One of these, pirfenidone, is thought to inhibit a number of profibrotic cytokines, including TGF-β. The other agent, nintedanib, is a tyrosine kinase inhibitor that blocks the receptors and the downstream signaling of several fibrogenic growth factors, including platelet-derived growth factor, 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.

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 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 *desquamative interstitial pneumonia* (DIP) are often considered together and perhaps 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.

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 intraalveolar macrophages, with little or no fibrosis. The prognosis is better than in IPF, and patients often can improve after cessation of smoking and may respond to corticosteroids.

Nonspecific interstitial pneumonia (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. Although NSIP is often idiopathic and not associated with any underlying disease or inciting agent, it can represent the histologic appearance of parenchymal lung disease associated with one of the connective tissue 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. 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 connective tissue 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, bronchiolitis obliterans with organizing pneumonia (BOOP) 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. The chest radiograph shows 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

Figure 11.3. Chest radiograph demonstrating patchy alveolar opacities in a patient with cryptogenic organizing pneumonia. Enlarged cardiac silhouette is due to an unrelated cardiomyopathy.

and occurs over days to weeks. Therapy is usually prolonged for months to prevent relapse.

Acute interstitial pneumonia (AIP) is a more acute or fulminant type of pulmonary parenchymal disease characterized by the clinical picture of acute respiratory distress syndrome (ARDS) (see Chapter 28) 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 CONNECTIVE TISSUE DISEASE

The connective tissue diseases, also commonly called *collagen vascular diseases* or *systemic rheumatic diseases*, include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma), polymyositis-dermatomyositis, Sjögren syndrome, and some overlap syndromes that have features of more than one of these disorders. Although they form a diverse group, all are multisystem inflammatory diseases that are mediated immunologically. 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 among 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 connective tissue 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 than clinically suspected. Third, the histopathology of interstitial lung disease associated with connective tissue disorders 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 connective tissue 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

In rheumatoid arthritis and lupus, pleural disease is more common than clinically evident interstitial lung disease.

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. Occasionally 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 is also often raised in these patients.

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 pulmonary hemorrhage. Chronically, and 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 connective tissue disease, the pulmonary 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, it is unclear what role recurrent aspiration may play 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 as a result of 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 interstitial lung disease, pleural disease, and pulmonary vascular disease.

SARCOIDOSIS

Sarcoidosis is defined as 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 African Americans than in whites. However, this racial predilection is not seen throughout the world, as the disease is notably prevalent in the white population of Scandinavia. Of all the disorders of unknown cause affecting the alveolar wall, 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 a century ago. It has been 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 number 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 macrophages and T lymphocytes. The presumption is that processing of the responsible antigen by alveolar macrophages results in recruitment of helper T lymphocytes ($CD4^+$ cells) with a T_H1 profile. A host of proinflammatory cytokines and chemokines, such as interleukin (IL)-2, interferon (IFN)-γ, 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 insulinlike growth factor (IGF)-1, subsequently may result in fibrosis as a complication of the initial inflammatory reaction.

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. The discrete accumulation of tissue macrophages within the granuloma does not show evidence of frank necrosis or caseation, as would appear in disorders like tuberculosis and histoplasmosis. In addition to granulomas in the lung parenchyma or intrathoracic

Figure 11.4. Simplified proposed pathogenetic sequence in sarcoidosis. *Ab*, Antibody; *Ag*, antigen.

The characteristic pathologic feature of sarcoidosis is the noncaseating granuloma. An alveolitis composed primarily of mononuclear cells may occur.

lymph nodes, an alveolitis often occurs. The alveolitis is composed of mononuclear cells, including macrophages and lymphocytes, with the latter presumed to be of particular importance in the pathogenesis of disease.

Patients with sarcoidosis most frequently seek consultation either as a result of 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. Because many organ systems besides the respiratory system may be involved with noncaseating granulomas, other manifestations occur but are less common. 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 are often 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 often the rather 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); or (3) both adenopathy and parenchymal disease (Fig. 11.6). HRCT scanning, although not generally necessary, is more sensitive than plain chest radiography in detecting parenchymal lung disease. It may show a particularly characteristic pattern of small nodules

Figure 11.5. Radiographic appearance of stage I sarcoidosis shows bilateral hilar and paratracheal adenopathy. Enlarged nodes can be seen on posteroanterior (A) and lateral (B) views.

Figure 11.6. Chest radiograph shows characteristic features of stage II sarcoidosis: bilateral hilar adenopathy and diffuse interstitial lung disease. In stage III sarcoidosis (not shown), patients have diffuse interstitial lung disease without hilar adenopathy.

preferentially distributed along bronchovascular bundles (Fig. 11.7). In addition, HRCT often demonstrates mediastinal lymphadenopathy that cannot be easily seen on plain chest radiography.

The chest radiograph in sarcoidosis shows symmetrically enlarged hilar lymph nodes, interstitial lung disease, or both.

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.

Figure 11.7. Chest computed tomography scan demonstrates micronodular pattern in a patient with sarcoidosis.

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, occurring as a result of 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 bilateral hilar lymphadenopathy found on an incidental chest radiograph in a symptom-free young African American woman. Another example is the patient who presents with a classic picture of Löfgren syndrome. On the other hand, 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 usually are 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 upon 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% to 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, African descent, chronic uveitis, chronic hypercalcemia, progressive pulmonary parenchymal fibrosis, and the presence of lupus pernio, a skin lesion affecting the face.

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 or not to institute therapy for the patient with sarcoidosis. Many patients do not require treatment, especially when the disease is causing neither significant symptoms nor 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, the drug of choice usually is systemic corticosteroids. In patients with refractory disease, a variety of other agents, especially immunosuppressive drugs such as methotrexate or leflunomide, have been used, often with the intention of allowing reduction of corticosteroid dosage. More recently, there has been interest in using infliximab, an antagonist of TNF-α, in selected cases, but its ultimate potential role in treating sarcoidosis is uncertain.

The variable natural history of sarcoidosis often makes decisions about use of corticosteroids 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) pulmonary Langerhans cell histiocytosis, (2) lymphangioleiomyomatosis (LAM), (3) Goodpasture syndrome, (4) granulomatosis with polyangiitis, (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

Pulmonary Langerhans cell histiocytosis, also 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. Whereas 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 pulmonary Langerhans cell histiocytosis occurs mainly in young to middle-aged adults.

Pulmonary Langerhans cell histiocytosis (also 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 appears to be a type of antigen-presenting dendritic or phagocytic cell called a *Langerhans cell*. 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. Although the disease occurs almost exclusively in smokers, the mechanism by which smoking may cause the disease or contribute to its pathogenesis is not well defined.

On chest radiograph, the clinical presentation of pulmonary Langerhans cell histiocytosis typically features a pattern of nodular or reticulonodular disease often accompanied by respiratory symptoms of dyspnea, cough, or both. The radiographic findings tend to be more prominent in the upper lung zones, with HRCT scans showing small cysts in addition to the nodular or reticulonodular changes. 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 pulmonary Langerhans cell histiocytosis may show restrictive changes, obstructive changes, or both. The presence of air-filled cysts typically leads to unusually normal or large lung volumes on chest radiography, despite the presence of interstitial disease.

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

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, suggesting 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 that form a complex that acts as a potent suppressor of cell growth and proliferation. 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. This may account 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 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. 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 pulmonary Langerhans cell histiocytosis, 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.

Because of the apparent hormonal dependence of the disease, treatment had traditionally focused on hormonal manipulation, most commonly with either oophorectomy or administration of progesterone. However, understanding of the role of the *TSC2* gene led to clinical trials of the drug sirolimus, which has now supplanted hormonal therapy as the treatment of choice. Sirolimus is an inhibitor of cell growth and proliferation through the same pathway as the *TSC2* gene products. Loss of *TSC2* gene function in smooth muscle cells leads to unchecked activation of the mechanistic target of rapamycin (mTOR) signaling pathway, which regulates multiple aspects of cell growth. Sirolimus (also called *rapamycin*) blocks mTOR signaling and thus restores some of the functions of the abnormal *TSC2* gene product. Recently sirolimus has been shown to be effective in stabilizing lung function and improving symptoms and quality of life in patients with LAM.

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., prednisone plus cyclophosphamide), aimed at decreasing the formation of anti-GBM antibodies, usually is given in conjunction with plasmapheresis.

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.

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 *granulomatosis with polyangiitis* (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. 11.8). 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 interstitial lung disease is not the characteristic radiographic finding in this entity.

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), has become an important component of the diagnostic evaluation for GPA, although the sensitivity of the test has varied considerably in different series. 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

Figure 11.8. Chest radiograph shows multiple cavitary pulmonary nodules in a patient with granulomatosis with polyangiitis.

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. Whereas the mean survival time without treatment was 5 months, patients are achieving complete and long-term remissions with institution of appropriate therapy. Some data support use of the combination antibiotic trimethoprim-sulfamethoxazole, either for treatment of selected patients or for prevention of relapse following successful immunosuppressive therapy. The mechanism is uncertain but may involve a reduction in nasal carriage of *Staphylococcus*, which has been associated with flares. The meaning of this finding in terms of pathogenesis of the disease is unclear, as is the place of this less toxic therapy in the overall strategy for management.

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. 11.9). 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

Figure 11.9. 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.

not critical for the diagnosis. However, bronchoalveolar lavage typically shows a high percentage of eosinophils, reflecting the pathologic process within the pulmonary parenchyma.

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

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 primary, secondary (usually related to hematologic malignancies), or congenital. Primary PAP is by far the most common of the three types and is discussed here.

An animal model indicates that defective uptake of surfactant by alveolar macrophages, attributable to a decreased amount or effect of GM-CSF, underlies the pathogenesis of pulmonary alveolar proteinosis.

In most cases of primary PAP, the underlying problem has been identified as production of an autoantibody to granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF, acting through alveolar macrophage-specific transcription factors, affects a number of essential macrophage functions, including regulation of surfactant degradation, intracellular lipid metabolism, and phagocytosis. Thus inhibiting the activity of GM-CSF via autoantibodies leads to 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.

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. 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 is probably due to abnormal macrophage function as well as to more recently discovered abnormalities in neutrophil function also mediated by GM-CSF.

Treatment of PAP traditionally has been based on whole-lung lavage, which involves washing out the material filling the alveolar spaces while the patient is under general anesthesia. Preliminary studies suggest that administration of exogenous GM-CSF may be an alternative therapy. The prognosis of the disease is generally 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

ANATOMY, 177
PHYSIOLOGY, 178
Pulmonary Vascular Resistance, 178
Distribution of Pulmonary Blood Flow, 180
Pulmonary Vascular Response to Hypoxia, 181
Other Aspects of Pulmonary Vascular Physiology, 182

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

Abstract

Chapter 12 reviews the anatomy and physiology of the pulmonary vasculature. 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. Pulmonary hemodynamics are measured clinically by means of a balloon-tipped catheter inserted in a large systemic vein and advanced to a wedged position in the pulmonary vasculature. Geographic matching of ventilation and perfusion in the lung is essential for appropriate oxygen exchange and is accomplished in large part via hypoxic pulmonary vasoconstriction, by which blood flow in the lungs is preferentially routed to well ventilated alveoli. The pulmonary capillary endothelium also has important metabolic functions, such as the conversion of angiotensin I to angiotensin II.

Keywords

Pulmonary circulation
Bronchial arteries
Pulmonary artery
Vascular resistance
Endothelins
Nitric oxide

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 is responsible for the vasoconstrictive response to various stimuli, particularly hypoxia, which results 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 has been described 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 non-alveolar 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:

$$R = \text{Change in pressure}/\text{Flow} \qquad \text{(Eq. 12.1)}$$

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 designed for this purpose, called a *pulmonary artery balloon occlusion catheter* or *Swan-Ganz catheter*, is clinically used for indirect 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. 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.

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 pulmonary vascular resistance 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.)

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.

When cardiac output increases, recruitment and distention of pulmonary vessels decrease pulmonary vascular resistance and prevent a significant increase in pulmonary artery pressure.

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, some 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.

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 *extraalveolar 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 extraalveolar vessels become larger, and their resistance decreases. When lung volume is decreased, elastic recoil of the alveolar walls decreases, extraalveolar vessels narrow, and their resistance increases. This differential effect of lung volume on the resistance of alveolar versus extraalveolar 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).

Distribution of Pulmonary Blood Flow

The distribution of blood flow within the lung is strongly influenced by gravity.

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 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 extraalveolar pulmonary vessels. At the lung bases, the weight of the lung results in decreased alveolar volume, accompanied by distortion and compression of extraalveolar vessels. As a result, the

Figure 12.2. Effect of lung volume on total pulmonary vascular resistance *(solid line)*, alveolar vessel resistance *(dashed-dotted line)*, and extraalveolar vessel resistance *(dashed line)*. Note that total resistance is least at the functional residual capacity *(FRC)*. *RV*, Residual volume; *TLC*, total lung capacity. (From Taylor AE, Rehder K, Hyatt RE, et al. *Clinical Respiratory Physiology*. Philadelphia, PA: WB Saunders; 1989:75.)

resistance of the extraalveolar 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 for 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 $P_{A_{O_2}}$, 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, apparently 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 specifically in Chapter 28.

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, probably 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 yet known.

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13

Pulmonary Embolism

ETIOLOGY AND PATHOGENESIS, 184
PATHOLOGY, 185
PATHOPHYSIOLOGY, 186
CLINICAL FEATURES, 187
DIAGNOSTIC EVALUATION, 188
TREATMENT, 191

Pulmonary embolism is one of the most important disorders that affect the pulmonary vasculature. Not only is it found in a significant number of unselected autopsies in which a careful search is made, but it is widely misdiagnosed in terms of "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 upon 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, 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 also can 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, propagation of the clots to 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, not all thrombi resulting in embolic disease are 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),

Abstract

Chapter 13 reviews the common problem of pulmonary thromboembolism, usually referred to simply as pulmonary embolism. Risk factors are described, which fall into the general categories of hypercoagulability, damage to endothelium, and venous stasis. The pathophysiology of cardiopulmonary compromise in pulmonary embolism is explained, with an emphasis on alterations in ventilation-perfusion matching and right ventricular decompensation. The clinical features are outlined, ranging from asymptomatic presentations to dyspnea and frank cardiopulmonary failure. A number of diagnostic strategies may be appropriate depending upon individual patient factors; investigative tools include measurement of plasma d-dimer, CT angiography, and radionuclide ventilation-perfusion scanning. Treatment is reviewed, including the use of intravenous and oral anticoagulants, thrombolytic therapy, and placement of a mechanical filter in the inferior vena cava.

Keywords

Pulmonary embolism
Venous thromboembolism
Thrombophilia
Anticoagulants
Heparin
Warfarin
Thrombolytic therapy
Vena cava filters

(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 carcinoma, 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 commonly found genetic defect that causes 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 threefold 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.

Whereas 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 Caucasian population but are rare among African Americans and Asians 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 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 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 the 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. The name *congestive atelectasis* has sometimes been applied to this process of parenchymal hemorrhage and edema without infarction.

Embolic occlusion of a vessel may lead to infarction or congestive atelectasis of the lung parenchyma.

With either pulmonary infarction or congestive atelectasis, the pathologic process generally extends to the visceral pleural surface, so corresponding radiographic changes often are 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. With congestive atelectasis but no infarction, 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 nutrient O_2 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. As discussed in Chapter 1, assuming that 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. 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.

Pulmonary emboli are typically associated with hypocapnia resulting from an increase in overall minute ventilation.

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. Not surprisingly, experimental evidence indicates 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.

With further limitation of the vascular bed by the combination of mechanical occlusion and the effects of chemical mediators, the pulmonary vascular resistance and pulmonary artery pressure may rise so high that the right ventricle cannot cope with the acute increase in 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 the elevation of systemic venous pressure and appears on physical examination as a 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 previously mentioned. 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

Common symptoms of pulmonary embolism are:
1. Dyspnea
2. Pleuritic chest pain
3. Hemoptysis
4. Syncope

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 (about 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.

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. Frequently, 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 prevent 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 congestive atelectasis and infarction 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 may contain a variable number of red blood cells.

Characteristic arterial blood gas values in pulmonary embolic disease are:
1. Decreased P_{O_2} and widened AaD_{O_2}
2. Decreased P_{CO_2}
3. Increased pH

Arterial blood gas values typically show a widened alveolar-arterial difference in partial pressure of oxygen (P_{AO_2}-P_{aO_2} [AaD_{O_2}]), a low P_{aO_2}, and respiratory alkalosis, with hypocapnia occurring in more than 80% of cases. Because P_{CO_2} is decreased, arterial P_{O_2} is higher than it would be if hyperventilation were 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.

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 not only 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 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, especially in the patient with a low pretest probability of having a pulmonary embolus, but an elevated level is considered nonspecific and, therefore, nondiagnostic.

Recommendations for the best radiologic test to diagnose pulmonary embolism have shifted in the last two 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 as a documented pulmonary embolus and often obviates the need for further evaluation.

The technique of CTA (discussed in Chapter 3) has become 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.

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, 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 is, for all practical purposes, excluded. However, 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.

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. Because 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

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. (Courtesy Dr. Phillip Boiselle.)

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. (Courtesy Dr. Henry Royal.)

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. (Courtesy Dr. Morris Simon.)

further evaluation of the pulmonary arteries if there is a reasonably high suspicion of pulmonary thromboembolism.

Long thought to be 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 less sensitive for pulmonary emboli; it is invasive and more expensive and therefore is not recommended in a standard evaluation. Although its lack of radiation or iodinated contrast exposure makes magnetic resonance imaging (MRI) seem like a potentially attractive option for diagnosing pulmonary emboli, technical aspects of the study currently make it much less useful; thus it is rarely considered for the evaluation of pulmonary emboli.

Major techniques for the diagnosis of pulmonary emboli include chest computed tomographic angiography (CTA), ventilation–perfusion lung scanning, and conventional pulmonary angiography.

TREATMENT

In addition to supporting oxygenation and circulation as needed, the standard treatment of a pulmonary embolus involves anticoagulant therapy, usually beginning with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH), followed by an oral agent given for at least 3 to 6 months. LMWH has a number of potential advantages over unfractionated heparin, including less 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. Until recently, the only oral agents used to complete therapy were coumarin-derived vitamin K antagonists,

Therapeutic options for pulmonary embolism are:
1. Anticoagulation (heparin, warfarin, direct thrombin inhibitors, factor Xa inhibitors)
2. Thrombolysis (tPA, streptokinase, urokinase)
3. Inferior vena caval filter

such as warfarin, which required frequent laboratory monitoring and dose adjustments. A number of 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).

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. For this reason, 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), but not to dissolve clots that have already embolized to the lungs. As a result, there has been a great deal of interest in the use of thrombolytic agents, such as tissue plasminogen activator (tPA), streptokinase, or urokinase, for treatment of pulmonary emboli. These agents, which lyse recent blood clots, ideally are given within the first hours of the embolic event, but they may be effective even up to 2 weeks after the embolism. A difference in overall mortality rate has not been demonstrated when a thrombolytic agent versus heparin is used for the initial therapy. However, there may be specific subgroups of patients more likely to benefit from thrombolytic therapy, particularly patients with massive pulmonary embolism and hemodynamic compromise as a result of vascular occlusion. When one of these agents is used, the intravenous infusion of the thrombolytic agent is followed by standard anticoagulant therapy. While usually administered intravenously, in some cases thrombolytic therapy is delivered via a pulmonary artery catheter and may be coupled with catheter-based mechanical interventions to remove or fragment large pulmonary thromboemboli.

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 newer filters can be removed once the need for the filter has resolved.

No discussion of the treatment of pulmonary embolism is complete without considering the prophylactic methods used to prevent deep venous thrombosis in the high-risk patient. The most common forms of prophylaxis traditionally have been (1) external compression of the lower extremities with an intermittently inflating pneumatic device; and (2) heparin administered subcutaneously in low dosage. LMWH is at least as effective and safe as low-dose unfractionated heparin. Prophylaxis is generally used in patients about to undergo thoracic, abdominal, or orthopedic surgery and in a variety of other at-risk patients who are relatively immobile in the hospital. In the highest-risk patients (i.e., those with hip fracture or hip or knee replacement surgery), either LMWH or warfarin is more effective for prophylaxis than low-dose subcutaneous standard heparin.

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14

Pulmonary Hypertension

PATHOGENESIS, 195
PATHOLOGY, 197
PATHOPHYSIOLOGY, 197
CLINICAL FEATURES, 199
DIAGNOSTIC FEATURES, 199
SPECIFIC DISORDERS ASSOCIATED WITH PULMONARY HYPERTENSION, 201
Idiopathic Pulmonary Arterial Hypertension and Related Disorders (Group 1 PAH), 201
Pulmonary Hypertension Owing to Left Heart Disease (Group 2 PH), 202
Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia (Group 3 PH), 203
Chronic Thromboembolic Pulmonary Hypertension (Group 4 PH), 203
Pulmonary Hypertension with Unclear Multifactorial Mechanisms (Group 5 PH), 204

Elevation of intravascular pressure within the pulmonary circulation is the hallmark of pulmonary hypertension. In this chapter, specific reference is made to elevated pulmonary arterial pressure (defined as mean pulmonary artery pressure > 25 mm Hg at rest, usually confirmed by right heart catheterization). Because pulmonary hypertension has a number of causes that presumably act by several different mechanisms, this chapter begins with a consideration of features relevant to pulmonary hypertension in general, and follows with a discussion of some important specific causes of pulmonary hypertension.

The current classification for clinical categories of pulmonary hypertension is summarized in Table 14.1. The clarification of a few points is pertinent. First, the term *pulmonary hypertension* (PH) 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 14.1. 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 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 right ventricular hypertrophy. This term should not be used to describe the right

Abstract

Chapter 14 reviews the definition, classification, pathology, and pathophysiology of pulmonary hypertension. In addition, representative conditions are discussed in detail, as well as the general diagnostic and therapeutic approach when these disorders are encountered. Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest, usually confirmed by right heart catheterization. However, pulmonary hypertension is a condition rather than a specific disease and can be associated with many different exposures, genetic factors, and other conditions. Patients generally present with dyspnea on exertion and may describe fatigue, chest pain, and syncope. Physical examination may reveal a loud pulmonic component of the second heart sound, various heart murmurs, and findings of right heart failure. In the past two decades, a number of medications with different mechanisms of action have become available to treat pulmonary arterial hypertension.

Keywords

Hypertension, pulmonary
Familial primary pulmonary hypertension
Pulmonary heart disease
Idiopathic pulmonary arterial hypertension
Pulmonary vasodilators
Cor pulmonale

Table 14.1

UPDATED CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION (Nice, 2013)

1. PULMONARY ARTERIAL HYPERTENSION (PAH)
- 1.1. Idiopathic PAH
- 1.2. Heritable
  - 1.2.1. *BMPR2*
  - 1.2.2. ALK1, endoglin, SMAD9, CAV1, KCNK3
  - 1.2.3. Unknown
- 1.3. Drug- and toxin-induced
- 1.4. Associated with
  - 1.4.1. Connective tissue diseases
  - 1.4.2. HIV infection
  - 1.4.3. Portal hypertension
  - 1.4.4. Congenital heart diseases
  - 1.4.5. Schistosomiasis
    - 1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
    - 1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. PULMONARY HYPERTENSION OWING TO LEFT HEART DISEASE
- 2.1. Left ventricular systolic dysfunction
- 2.2. Left ventricular diastolic dysfunction
- 2.3. Valvular disease
- 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PULMONARY HYPERTENSION OWING TO LUNG DISEASES AND/OR HYPOXIA
- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep-disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental abnormalities

4. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

5. PULMONARY HYPERTENSION WITH UNCLEAR MULTIFACTORIAL MECHANISMS
- 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

ALK1, Activin receptor-like kinase type 1; *SMAD9*, mothers against decapentaplegic 9; *CAV1*, caveolin1; *KKCNK3*, potassium channel super family K member-3; *BMPR2*, bone morphogenetic protein receptor type 2; *HIV*, human immunodeficiency virus.

Modified from Simonneau G, Gatzoulis M, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34–D41.

ventricular changes occurring as a consequence of primary cardiac disease or increased flow to the pulmonary vascular bed.

PATHOGENESIS

A number of 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, in which massive pulmonary emboli occlude more than 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 markedly elevated pulmonary artery pressures. 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.

Factors contributing to PAH are:

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 (from hypoxia, acidosis)
5. Increased pulmonary vascular flow (left-to-right shunt)
6. Elevated left atrial and pulmonary venous pressure

Second, remodeling of the pulmonary arterial walls causing the diminution of the cross-sectional area 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 pulmonary hypertension*). 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, human immunodeficiency virus [HIV] infection) or with exposure to drugs and toxins (e.g., cocaine, methamphetamine, 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.

Third, the total cross-sectional area of the pulmonary vascular bed is 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 appears quite different. Because of the large 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 usually relatively normal at rest, but is 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 in response to hypoxia and, to a lesser extent, to acidosis. The importance of this mechanism is related to its potential reversibility when normal Po_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, it may augment the vasoconstrictive response to hypoxia (discussed in Chapter 12).

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. Eventually, as a result of the high pulmonary vascular resistance, 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. The precise mechanism by which chronically increased pulmonary blood flow leads to remodeling is not known.

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 is not accompanied by anatomic changes in the pulmonary arteries. However, structural changes are eventually seen, and measured pulmonary vascular resistance may be substantially increased. The major disorders that result in PH by this final mechanism are mitral stenosis and chronic left ventricular systolic or diastolic failure.

Pathologic features of PH are:

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

PATHOLOGY

Although PH is classified into different clinical categories (see Table 14.1), as the disease progresses and remodeling occurs, 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.

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 to 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 pulmonary vascular resistance is elevated. Ultimately, the lumen may be completely obliterated and the overall number of 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, slitlike vascular channels (see Fig. 14.1B). 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).

When PH becomes marked, other changes are commonly seen in the larger (elastic) pulmonary arteries (see Fig. 14.1C). 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 the chronic 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

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)*. (Courtesy Dr. Lester Kobzik.)

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 28). 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 pulmonary vascular resistance. 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 pulmonary vascular resistance to increase cardiac output with exertion, patients may experience exertional lightheadedness or frank syncope. These represent very poor prognostic signs.

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 of 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. At this stage, both lower extremity peripheral edema and ascites may develop.

Clinical features of pulmonary hypertension (PH) are:

1. Symptoms: dyspnea, substernal chest pain, fatigue, 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

DIAGNOSTIC FEATURES

Echocardiography is usually the first test to suggest a diagnosis of PH. Key findings are right ventricular hypertrophy and elevated right ventricular systolic pressure by Doppler estimates. A detailed description of these echocardiographic techniques is beyond the scope of this chapter, but it 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

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.

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. This feature is most apparent on the lateral radiograph, which shows bulging of the anterior cardiac border.

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, which is not evident on chest radiograph (see Chapters 3 and 13). When CTA or perfusion scanning is positive, pulmonary angiography may be used to confirm the diagnosis and assess the surgical accessibility of the obstructing lesions.

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.

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 loss of the pulmonary vascular bed, the diffusing capacity may be decreased and often may be the only other abnormality noted.

Arterial blood gas analysis is highly useful for determining whether hypoxemia or acidosis plays a role in PH pathogenesis. Arterial Po_2 may be mildly decreased as a result of pulmonary vascular disease, apparently because of the nonuniform distribution of disease and the worsened ventilation-perfusion matching.

SPECIFIC DISORDERS ASSOCIATED WITH PULMONARY HYPERTENSION

PH is currently classified according to the scheme given in Table 14.1, 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.

Numerically, PH is most commonly a 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 pulmonary vascular resistance. 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 pulmonary hypertension* 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. 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. In particular, several appetite suppressants have been 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). The diagnosis of IPAH cannot be made until other causes of PH have been excluded.

Often, 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 up to 70% 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 one-quarter 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 familial 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 pulmonary vascular resistance 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) appear to 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 patients who *normalize* their pulmonary arterial pressure in response to acute vasodilator testing (<10% of patients). 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 (e.g., epoprostenol, treprostinil) administered by continuous intravenous 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 intravenous 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 been recently 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 as pills taken orally. The oral medications are attractive therapeutic alternatives, particularly in patients with less advanced disease.

Patients with IPAH may be placed on long-term anticoagulation therapy, although this practice is controversial. 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 detailed discussion of treatment options for patients with PAH is beyond the scope of this text; the reader is referred to a number of excellent review articles cited in the references at the end of this chapter.

Pulmonary Hypertension Owing 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 pulmonary vascular resistance 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 Owing to Lung Disease and/or Hypoxia (Group 3 PH)

The most common causes of PH and 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 pulmonary artery pressures as a result of increased blood viscosity; and reduction of the pulmonary vascular bed caused by coexistent emphysema.

Obstructive disease, interstitial disease, and a variety of neural, muscular, and chest wall diseases may produce PH and cor pulmonale.

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 develop a disproportionate degree of pulmonary vascular disease, and these patients may progress to more severe PH.

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 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 some 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. In other cases, there is extensive thromboembolic occlusion of smaller, surgically 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 14.1 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

ANATOMY, 206
PHYSIOLOGY, 207
PLEURAL EFFUSION, 209
Pathogenesis of Pleural Fluid Accumulation, 209
Etiology of Pleural Effusion, 210
Clinical Features, 212
Diagnostic Approach, 212
Treatment, 214
PNEUMOTHORAX, 215
Etiology and Pathogenesis, 215
Pathophysiology, 216
Clinical Features, 217
Diagnostic Approach, 217
Treatment, 218

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.

This chapter discusses the anatomy of the pleura, 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)*. 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. The primary malignancy of the pleura, *mesothelioma*, is discussed in Chapter 21, which deals with neoplastic disease of the thorax.

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 coating the apposing surfaces. 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.

The pleura lines not only the surfaces of the lung in direct contact with the chest wall but also the diaphragmatic and mediastinal borders of the lung. These surfaces

Abstract

Chapter 15 discusses the anatomy of the pleura, followed by a presentation of several physiologic principles of fluid formation and absorption, including the role of hydrostatic and oncotic pressures in formation of pleural fluid and the role of pleural lymphatics in removing fluid. Pleural fluid that accumulates because formation exceeds the capacity for resorption can be categorized as either transudate or exudate, and the common causes of each type of fluid are presented. Air can enter the pleural space, causing a pneumothorax, either through the chest wall, as occurs with various kinds of trauma, or from disorders within the thorax. The physiology leading to air being resorbed from a pneumothorax is described, as well as management considerations depending upon the size and consequences of the pneumothorax.

Keywords

Pleural diseases
Pleural effusion
Pleura
Pneumothorax
Pleurodesis

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). (From Lowell JR. *Pleural Effusions: A Comprehensive Review*. Baltimore, MD: University Park Press; 1977:77.)

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 apparently 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. (Modified from Pistolesi M, Miniati M, Giuntini C. Pleural liquid and solute exchange. *Am Rev Respir Dis*. 1989;140:825–847.)

The normally occurring liquid in the pleural space is a low-protein ultrafiltrate 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 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
σ = 1, K = 1
Fluid movement at parietal pleura = [30 – (–5)] – 1(32 – 6) = 9 cm H_2O

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:

$$\text{Fluid movement} = K[(P_c - P_{is}) - \sigma(COP_c - COP_{is})] \qquad \text{(Eq. 15.1)}$$

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 are capable of increasing their flow substantially to accommodate at least some of the excess fluid formed.

Pleural fluid 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.

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.

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*.

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 is affected by the disease process causing the effusion.

Transudative Pleural Fluid

Most frequently, transudative pleural fluid is associated with heart failure. Although traditionally the explanation has been that an elevation of hydrostatic pressure in the pleural capillaries was responsible for increased flux of fluid from these vessels into the pleural space, more recent data suggest an alternative explanation. 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. On the basis of clinical studies, pulmonary venous hypertension (with left-sided heart failure), leading to increased hydrostatic pressure in the pulmonary capillaries, appears to be a more important factor contributing to effusions 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.

Patients with hypoproteinemia have decreased plasma colloid osmotic pressure, and pleural fluid may develop because hydrostatic pressure in pleural capillaries now is less

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)
- Pulmonary embolus (infarction)
- Connective tissue disease (lupus, rheumatoid arthritis)
- Adjacent to subdiaphragmatic disease (pancreatitis, subphrenic abscess)

Malignant

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 (as a result of 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 independently 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 generally exudative in nature. 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 references 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, and the nature of the underlying process. 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 generally does not have dyspnea just 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.

Common clinical features with pleural effusion(s) are:
- Symptoms: pleuritic chest pain, dyspnea
- Physical signs: dullness to percussion, decreased breath sounds, egophony at upper level, pleural friction rub

On physical examination of the chest, the region overlying the effusion is dull to percussion. Breath sounds are usually decreased in this region as a result of 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 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.

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. Computed tomography (CT) scanning of the chest is more sensitive than plain film in detecting pleural effusions (Fig. 15.4). 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.

When certain inflammatory effusions persist for a time, fluid may no longer be free-flowing within the pleural space as fibrous bands of tissue (loculations) form within the pleura. 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).

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.

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 >⅔ × upper limit of normal serum LDH

When pleural fluid 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 include the levels of protein and the enzyme lactate dehydrogenase (LDH) within the fluid, both in absolute numbers and relative to the corresponding values in serum. Exudative fluid has high levels of protein, LDH, or both, whereas transudative fluid has low levels of protein and LDH.

Figure 15.3. Posteroanterior **(A)** and lateral **(B)** chest radiographs demonstrating left pleural effusion.

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, and a search for malignant cells is made. Detailed discussions of the findings in different disorders can be found in the references at the end of this chapter.

In some cases, pleural tissue is sampled by closed pleural biopsy, generally performed with a relatively large cutting needle inserted through the skin of the chest wall. Histologic

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.

examination of this tissue is most useful for demonstrating granulomas of tuberculosis but also can reveal implants of tumor cells from a malignant process in some cases. Currently, pleural tissue more commonly is obtained under direct vision with the aid of a thoracoscope passed through the chest wall and into the pleural space, and this has become the most definitive method for evaluating the pleural space for malignant implants.

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. In cases with a high likelihood of the effusion eventuating in 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]), the fluid is drained with a tube inserted into the pleural space. 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.

In other cases with recurrent large effusions causing dyspnea, especially malignant effusions, 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*) eliminates the pleural space and, if effective, 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 be left 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.

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**.

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

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, necrosis of lung adjacent to the pleura).

(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.

In some cases, a reason for the pneumothorax is apparent, such as an underlying abnormality in the lung, a form of lung disease 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). Pneumothorax in these clinical settings is said to be secondary to the known lung disease.

In patients with AIDS, pneumothorax can develop as a complication of pulmonary infection with *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*), presumably because of necrosis or cyst formation adjacent to the visceral pleura.

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 latter 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, as a result of positive pressure, a preexisting subpleural bleb may rupture, or air may rupture through an alveolar wall into the interstitial space, track through the lung parenchyma to the subpleural surface, and then rupture into the pleural space. Alternatively, and perhaps more commonly, the air following alveolar rupture tracks retrograde to the mediastinum alongside blood vessels and airways and produces 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 is believed to occur as a result of 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. Therefore, only unidirectional movement of air into the pleural space occurs, 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 explanation is 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.

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.

A tension pneumothorax may be associated with total collapse of the underlying lung, mediastinal shift, and cardiovascular collapse.

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). Interestingly, 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.

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.

Clinical features of pneumothorax are:
- Symptoms: chest pain, dyspnea
- Physical signs: asymmetric (decreased) breath sounds, hyperresonance, tracheal deviation (tension), ↓ blood pressure (tension)

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

Figure 15.6. Chest radiograph of patient with spontaneous pneumothorax on left. *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.

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.

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 (see Fig. 15.7). 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. 15.8).

Treatment

Treatment of a pneumothorax is determined by its size and the ensuing clinical consequences. With a small pneumothorax causing few symptoms, it is best to wait for spontaneous resolution. This process 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 large (i.e., involves >20% of the hemithorax) or the patient has significant clinical sequelae, the air is best removed, usually by a needle, catheter, or chest tube inserted into the pleural space. Occasionally, patients have recurrent spontaneous pneumothoraces that 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

Figure 15.7. 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 15.8. Chest radiograph shows right-sided tension pneumothorax. No lung markings are seen in right hemithorax, and mediastinum is shifted to left.

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.

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16

Mediastinal Disease

ANATOMIC FEATURES, 221
MEDIASTINAL MASSES, 223
Etiology, 223
Clinical Features, 224
Diagnostic Approach, 224
Treatment, 225
PNEUMOMEDIASTINUM, 226
Etiology and Pathogenesis, 226
Pathophysiology, 226
Clinical Features, 226
Diagnostic Approach, 227
Treatment, 227

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 often 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.

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.

The borders of the middle mediastinum are the anterior and posterior pericardium. This region includes the heart, pericardium, great vessels, trachea, lymph nodes, and

Abstract

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. Chapter 16 describes some of the anatomic features of the mediastinum and discusses two of its most common clinical problems: mediastinal masses and pneumomediastinum.

Keywords

Mediastinum
Mediastinal emphysema
Pneumomediastinum
Mediastinal diseases
Mediastinal neoplasms
Mediastinal cyst

Table 16.1

MEDIASTINAL COMPARTMENTS: ANATOMY AND PATHOLOGY

Compartment	Borders	Normal Structures	Masses
Anterior	Anterior: sternum Posterior: pericardium, ascending aorta, brachiocephalic vessels	Lymph nodes Connective tissue Thymus (remnant in adults)	Thymoma Germ cell neoplasm Lymphoma Thyroid enlargement (intrathoracic goiter) Other tumors
Middle	Anterior: anterior pericardium, ascending aorta, brachiocephalic vessels Posterior: posterior pericardium	Pericardium Heart Vessels: ascending aorta, venae cavae, main pulmonary arteries Trachea Lymph nodes Nerves: phrenic, upper vagus	Carcinoma Lymphoma Pericardial cyst Bronchogenic cyst Benign lymph node enlargement (granulomatous disease)
Posterior	Anterior: posterior pericardium Posterior: posterior chest wall	Vessels: descending aorta Esophagus Vertebral column Nerves: sympathetic trunk, lower vagus Lymph nodes Connective tissue	Neurogenic tumor Diaphragmatic hernia

Figure 16.1. Lateral chest radiograph shows borders of three mediastinal compartments. *a*, Anterior; *m*, middle; *p*, posterior.

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 nerves), esophagus, and descending aorta. Some lymph nodes and loose connective tissue may also be found in the posterior mediastinum.

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 given 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 particular 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 decreased number of functional acetylcholine receptors at neuromuscular junctions. The latter is due to antibodies 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 probably 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, 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 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 intra-abdominal 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, the initial diagnostic test is the posteroanterior and lateral chest radiograph, which generally shows the mass and allows determination of its location within the mediastinum (Fig. 16.2). The mass can be further characterized by a variety of other techniques, but CT is generally the most valuable. The 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. With magnetic resonance imaging (MRI), blood vessels can be distinguished from other mediastinal

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. *Arrows* outline inferior border of mass on lateral view.

structures without the use of radiographic contrast. Both MRI and CT can display images in coronal and sagittal planes, as well as cross-sectional axial views. ^{18}F-Fluorodeoxyglucose positron emission tomography (PET) yields information on 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). 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 are:

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 neither indicated nor 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

Sources of air entry in a pneumomediastinum are:
1. External (penetrating trauma)
2. Tracheal or esophageal tear
3. Alveolar rupture and tracking of air proximally

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 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*.

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 asthmatic persons, presumably because of the development of high intraalveolar pressure in a lung unit behind an obstructed bronchus. 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 would 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).

Mediastinal air often results in subcutaneous emphysema.

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.

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., 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

Figure 16.3. Chest radiograph shows pneumomediastinum and air in subcutaneous tissues (subcutaneous emphysema). Note numerous radiolucent stripes outlining mediastinal structures; these stripes represent air within mediastinum. *Arrow* points to air around aortic arch.

(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 usually is visible as one or more radiolucent stripes alongside and parallel to the heart border or aorta (Fig. 16.3).

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 infection of the mediastinum, 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

RESPIRATORY CONTROL, 229
Organization of Respiratory Control, 230
Ventilatory Response to Hypercapnia and Hypoxia, 233
Ventilatory Response to Other Stimuli, 235
RESPIRATORY MUSCLES, 235

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. This pumplike 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 gases within a narrow range.

Abstract

The lungs do not act in isolation, but rather are part of an integrated system that also involves the central nervous system (CNS), which controls the action of the muscles of respiration, and the appropriate response of the respiratory muscles to the signals they receive from the CNS. The respiratory generator, located in the medulla, also receives input from the cerebral cortex and higher levels of the brainstem, as well as feedback from central and peripheral chemoreceptors that is targeted to maintaining stable and acceptable levels of Po_2 and Pco_2. This chapter provides an overview of the neural, muscular, and chest wall contributions to respiration. The anatomy of ventilatory control is presented, followed by a description of input that the control system receives from chemoreceptors as well as receptors from the lungs and chest wall. The action of the diaphragm, the main muscle of respiration, is described, including the importance of the zone of apposition and diaphragm length. This presentation of the anatomy and physiology of ventilatory control and the respiratory pump forms the background information for understanding the disorders of ventilatory control and disorders of the respiratory pump that will be presented in Chapters 18 and 19, respectively.

Keywords

Ventilatory control
Respiratory generator
Carotid body chemoreceptors
Aortic body chemoreceptor
Hypercapnic ventilatory response
Hypoxic ventilatory response
Diaphragm
Respiratory muscles

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."

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 complicated by an intricate 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, chemosensors for pH, O_2, and CO_2 alter their input to the respiratory generator, 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

Figure 17.1. Schematic diagram shows organization of respiratory control system. Dashed lines show feedback loops affecting respiratory generator. *CNS*, Central nervous system.

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 may be 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 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 for CO_2 is located near the ventrolateral surface of the medulla and is called the *central chemoreceptor*. Even though it is located in the medulla, the central chemoreceptor is clearly separate from the medullary respiratory center and should not be confused with it. 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 are much less important 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. Since 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.

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.

Figure 17.2. Ventilatory response to progressive elevation of P_{CO_2} in normal individual. **A,** Solid line shows response when simultaneous P_{O_2} is high (hyperoxic conditions). **B,** Dashed line shows heightened response when simultaneous P_{O_2} is low (hypoxic conditions).

Ventilatory responsiveness to CO_2 is blunted in patients with chronic hypercapnia.

When CO_2 retention persists for days, the kidneys compensate for the more acidic pH by excreting 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}.

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 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. **A,** Solid line shows response when measured at normal P_{CO_2}. **B,** Dashed line 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. 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 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 is capable of responding to the demands of exercise remain unanswered.

Another important ventilatory response occurs to alterations in acid-base status. With excess metabolic acid production (i.e., metabolic acidosis), ventilation increases as pH is lowered, and elimination of additional CO_2 aids in returning the 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

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)*. (Modified from De Troyer A, Estenne M. Functional anatomy of the respiratory muscles, *Clin Chest Med*. 1988;9:175–193.)

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.

As the reader can now appreciate, the act of inspiration is more complex than it initially seemed. While 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 whereby 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 a signal generated by the respiratory center and eventually translated into an efficient pattern of respiratory muscle contraction. Although feedback and control systems ensure optimal functioning of this system, 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

PRIMARY NEUROLOGIC DISEASE, 239
- Presentation with Hyperventilation, 239
- Presentation with Hypoventilation, 240
- Abnormal Patterns of Breathing, 240

CHEYNE-STOKES BREATHING, 240

CONTROL ABNORMALITIES SECONDARY TO LUNG DISEASE, 242

SLEEP APNEA SYNDROME, 243
- Types, 243
- Clinical Features, 243
- Pathophysiology, 244
- Treatment, 246

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 may be 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.

Abstract

Chapter 18 builds on Chapter 17 and addresses disorders of ventilatory control. Hyperventilation, most frequently due to an acute disorder of the central nervous system, to a variety of pulmonary diseases, or to hormonal stimulation, is discussed. The primary mechanism leading to hyperventilation is either unknown or appears to be an increased sensitivity or stimulation of the central chemoreceptors or other receptors providing input to the respiratory generator. Hypoventilation disorders, including primary alveolar hypoventilation and congenital central hypoventilation, are reviewed. The pathophysiology of Cheynes-Stokes respiration, an abnormal breathing pattern characterized by cyclic hyper- and hypoventilation, is examined. Finally, obstructive sleep apnea (OSA) and central sleep apnea (CSA) and mixed syndromes are addressed. OSA is more common than CSA. Clinical features of sleep apnea include disordered respiration during sleep, hypersomnolence, morning headaches, and cardiovascular complications. Diagnosis and treatment are reviewed.

Keywords

Hyperventilation
Hypoventilation
Cheyne-Stokes respiration
Sleep apnea
Obstructive sleep apnea
Central sleep apnea
Apnea
Hypopnea
CPAP
Continuous positive airway pressure

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 metabolized 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 as a result of renal compensation with retention of bicarbonate. 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 generally 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 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.

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.

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 29. 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 nocturnally, is a more effective and better tolerated treatment in most cases.

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 a special section to describe it and discuss 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

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.

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.

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. For further discussion, the interested reader is referred to the references.

Decreased cardiac output and slow circulation time, which results in an abnormal delay between events in the lung and sensing of P_{CO_2} changes by the central chemoreceptor, is one mechanism postulated to play a role in heart failure. Hence 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 COPD patients 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}. 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 P_{aO_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} upon 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%. 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 an increasingly recognized disorder in which patients have repetitive episodes of apnea (cessation of breathing) during sleep that lead to gas exchange abnormalities and sleep disruption. 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 increase in prevalence correlates closely with the obesity epidemic.

A period of more than 10 seconds without airflow is generally 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 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. 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 are:
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 as a result of these violent movements. On awakening, patients often complain of 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.

Clinical features of sleep apnea syndrome are:
1. Disordered respiration during sleep
2. Daytime hypersomnolence
3. Morning headaches
4. Cardiovascular complications

With such a disordered pattern of sleep, patients are effectively sleep deprived and, not surprisingly, frequently are overly somnolent during normal waking hours. Even though the patient is in bed and "asleep," only the lightest 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.

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, cardiac arrhythmias, heart failure, and stroke. Systemic hypertension appears to be a consequence of OSA, and treatment of OSA is associated with a decrease in systemic blood pressure. Atrial fibrillation also 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 episodes of prolonged hypoxemia at night, pulmonary hypertension can result and unexplained cor pulmonale may be the presenting clinical problem.

Pathophysiology

During the past 2 decades, a great deal has been learned about the pathogenesis and risk factors leading to OSA. Normally, inspiration is characterized not only by contraction of the diaphragm, resulting in negative airway pressure, but also by increased activity of a number 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, compromises 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 a fruitless 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). (From Tobin MJ, Cohn MA, Sackner MA. Breathing abnormalities during sleep. *Arch Intern Med*. 1983;143:1221–1228. Copyright 1983, American Medical Association.)

Treatment

The first-line therapy used in most patients with OSA is nasal continuous positive airway pressure, commonly called *nasal CPAP*. A mask connected to an air compressor is placed over the nose of the patient at bedtime. The compressor maintains positive pressure in the upper airway throughout the respiratory cycle, thus providing a pneumatic splint to keep the airway open. 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 CPAP is often applied at night to patients with OSA to prevent upper airway closure.

Because nasal 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. 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 invasive via a tracheostomy tube or noninvasive via a face mask, may all be considered.

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19

Disorders of the Respiratory Pump

NEUROMUSCULAR DISEASE AFFECTING THE MUSCLES OF RESPIRATION, 248
Specific Diseases, 248
Pathophysiology and Clinical Consequences, 250
DIAPHRAGMATIC DISEASE, 250
Diaphragmatic Fatigue, 251
Unilateral Diaphragmatic Paralysis, 252
Bilateral Diaphragmatic Paralysis, 253
DISORDERS AFFECTING THE CHEST WALL, 254
Kyphoscoliosis, 254
Obesity, 255

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

A number of 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 for a variable amount of time. 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.

Guillain-Barré syndrome historically was considered a single disease process. It is now recognized that it is a heterogeneous disorder with different variants all involving

Abstract

Chapter 19 addresses disorders affecting the respiratory pump including neuromuscular disease, disorders of the diaphragm, and disorders affecting the chest wall. Four of the more common neuromuscular diseases that influence the respiratory system are discussed: Guillain-Barré syndrome, myasthenia gravis, poliomyelitis, and amyotrophic lateral sclerosis. Respiratory muscle weakness, both inspiratory and expiratory, is the underlying pathophysiology for these disorders. The diaphragm is the most important inspiratory muscle of respiration, and this chapter reviews diaphragmatic muscle fatigue and both unilateral and bilateral diaphragmatic paralysis. Finally, two important processes affecting the chest wall, kyphoscoliosis and obesity, are discussed.

Keywords

Neuromuscular disease
Guillain-Barré syndrome
Myasthenia gravis
Poliomyelitis
Amyotrophic lateral sclerosis
Diaphragm
Kyphoscoliosis
Obesity

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	

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 3% to 8% of patients die and up to 10% of survivors have permanent sequelae.

In *myasthenia gravis*, patients experience weakness and fatigue of voluntary muscles, most frequently those innervated by cranial nerves, but peripheral (limb) and potentially respiratory muscles also are 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 generally 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 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 irreversibility and progressive 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 are 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.

Features of NM disease are:
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}

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.

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.

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 as a result of inspiratory muscle weakness, but changes in respiratory system compliance may also contribute. Residual volume (RV) frequently is increased as a result of 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.

In the setting of severe muscle weakness, arterial blood gas analysis is most notable for the presence of alveolar hypoventilation (i.e., hypercapnia). Hypoxemia due to alveolar hypoventilation and the associated depression in alveolar P_{O_2} also occurs. When hypoventilation is the sole cause of hypoxemia, the alveolar-arterial oxygen difference (AaD_{O_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 P_{O_2} and increases AaD_{O_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

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. (Modified from Bergofsky EH. Respiratory failure in disorders of the thoracic cage. *Am Rev Respir Dis.* 1979;119:643–669.)

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,

Factors contributing to diaphragmatic fatigue are:
1. Increased work of breathing
2. Decreased energy supply to the diaphragm
3. Inefficient diaphragmatic contraction

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.

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 as a result of 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 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. In these cases a cold solution is instilled in 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 cold solution causes temporary paralysis of the left phrenic nerve, leading to diaphragmatic paralysis of variable duration. With changes in surgical 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 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.

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

Figure 19.2. Chest radiograph shows elevation of right hemidiaphragm resulting from unilateral *(right)* phrenic nerve paralysis.

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 the 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 as a result of rapid development of negative intrathoracic pressure during the sniff.

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 does not move, the lung is maintained at a higher volume, and the hemidiaphragm can no longer move paradoxically upward during inspiration.

Bilateral Diaphragmatic Paralysis

Paralysis of both diaphragms 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). When the patient is supine, the abdominal contents push on the flaccid diaphragm as 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. The deleterious effect of assuming the recumbent position is also seen with pulmonary function testing, in that 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 particularly severe cases, chronic respiratory failure is the consequence. Although some cases of kyphoscoliosis actually are secondary to NM disease such as poliomyelitis, the majority of severe cases associated with respiratory impairment are idiopathic.

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 even 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. Therefore two

Figure 19.3. Chest radiograph of patient with severe kyphoscoliosis. Note marked spinal curvature and chest wall distortion.

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.

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 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 29.

Features of severe kyphoscoliosis are:

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

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 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, occurring as a result of pressure from the obese abdomen, 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.

In a fashion similar to that of 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.

Features of obesity are:
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)

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 due to sleep-disordered breathing. In addition, the obesity-associated hormone leptin may influence the development of OHS. After hypercapnia actually 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.

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 complete upper airway obstruction during sleep (see Chapter 18). In a large percentage of cases, somnolence that occurs in patients who have OHS is related to the presence of obstructive sleep apnea.

Although obesity, abnormal respiratory drive, respiratory muscle weakness, and sleep apnea syndrome contribute to respiratory dysfunction, exactly how they 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.

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

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.

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 frequently demonstrate a restrictive pattern of dysfunction, 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 Po_2 and an increase in $AaDo_2$ as a consequence of high diaphragms, airway and alveolar closure, and ventilation-perfusion mismatch. When patients have OHS and Pco_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 during episodes of apnea.

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 who hypoventilate, respiratory stimulants, especially progesterone (a centrally acting respiratory stimulant), have been used with limited success.

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20

Lung Cancer: Etiologic and Pathologic Aspects

ETIOLOGY AND PATHOGENESIS, 260
Smoking, 260
Occupational Factors, 261
Genetic Factors, 261
Parenchymal Scarring, 262
Miscellaneous Factors, 262
Concepts of Lung Cancer Pathogenesis, 263
PATHOLOGY, 263
Squamous Cell Carcinoma, 264
Small Cell Carcinoma, 265
Adenocarcinoma, 266
Large Cell Carcinoma, 268

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 half a century ago, the primary cause of carcinoma of the lung—cigarette smoking—was conclusively identified. Fortunately, the global prevalence of smoking has been falling gradually after peaking in the mid-1970s. Unfortunately, any optimism is tempered by review of World Health Organization (WHO) data indicating that (1) tobacco use is continuing to increase in Africa and eastern Mediterranean countries, where the tobacco industry is focusing its marketing efforts; (2) although global smoking prevalence declined substantially in the years before 1990, it has changed only slowly since then; and (3) even in the United States and Europe, where tobacco education has been available, about 17% of American and 27% of European adults still smoke.

Lung cancer has been the most common cancer worldwide for several decades. In 2012, there were an estimated 1,800,000 new cases of lung cancer, 58% of which occurred in less developed regions. Lung cancer is also the most common cause of cancer-related death worldwide, with an estimated 1,590,000 (19.4%) of cancer deaths in 2012. For 2017, the American Cancer Society estimates that 222,500 new cases of lung cancer will be diagnosed in the United States, and approximately 155,000 individuals will die as a result of the disease. For many years, carcinoma of the lung was 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 25% to 30% 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, colon, liver, kidney, and melanoma *combined.* It is sobering to realize that during the last 5 years, more Americans died from lung cancer than were killed in all the wars in US history.

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

Abstract

Chapter 20 addresses the etiologic and pathologic aspects of lung cancer—the most common cause of cancer and cancer-related death worldwide. Risk factors, including smoking, occupational exposures and genetic predisposition, are explained. Concepts of the underlying pathogenesis of lung cancer are discussed, including the potential importance of proto-oncogenes and tumor suppressor genes. Detailed descriptions of the anatomic and pathological patterns of four major categories of lung cancer, squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma, are examined.

Key words

Carcinoma
Lung cancer
Squamous cell carcinoma
Small cell carcinoma
Adenocarcinoma
Large cell carcinoma
Non-small cell carcinoma
Smoking
Radon
Asbestos

increased fivefold in the 30 years from 1960 to 1990, but more recently it appears to be reaching a plateau. Despite the magnitude of the problem, our ability to treat carcinoma of the lung has not improved dramatically. In the United States, where treatment is available to most patients, 5-year survival has increased from roughly 7% to 18% during the last several decades, making the prognosis of this disease still dismal in the vast majority of cases. There is some recent cautious optimism as new tumor genotype-directed agents are developed. Still, more than half of all individuals with lung cancer will die within 1 year of being diagnosed.

This chapter's discussion of carcinoma of the lung is presented in two parts. First, what is known about the etiology and pathogenesis of lung cancer is 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 two additional types of neoplastic disease affecting the respiratory system, bronchial carcinoid tumor (bronchial adenoma) and mesothelioma, along with a consideration of the common problem of the patient with a solitary pulmonary nodule.

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 (>85% according to some 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 do 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.

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.

If a person stops smoking, many of these precancerous changes appear to be reversible. 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 many 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 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 21), 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 two- to fivefold increased risk for lung cancer, whereas smoking alone is associated with an approximately tenfold 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.

A number of 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 primarily 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.

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 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 and is releasing 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. Some studies have reported an association between low intake and serum levels of beta 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 beta 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 beta carotene, alpha 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 advances in antiretroviral treatment decrease 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 an 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 manifest 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 references 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 if not most lung 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 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 an increasing role in characterizing lung malignancies.

Major histologic categories of lung cancer:
1. Squamous cell carcinoma
2. Small cell carcinoma (subcategory of neuroendocrine tumors)
3. Adenocarcinoma
4. Large cell carcinoma

Most lung cancers fall within one of four histologic categories: (1) squamous cell carcinoma, (2) small cell carcinoma (now considered a subcategory of neuroendocrine tumors), (3) adenocarcinoma, and (4) large cell carcinoma. Within each category are several subcategories that, for our purposes, are less important. Of note, nearly 24% 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.

A major distinction to make is between small cell carcinoma and all the other cell types, which are grouped together as *non–small cell carcinoma.* 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 carcinomas and other non–small cell carcinomas, especially adenocarcinoma, because of differences in responsiveness to certain drugs, such as epidermal growth factor receptor 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 only about 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.

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

Specific histologic features of squamous cell carcinoma allow the pathologist to establish this diagnosis. These tumors are characterized by the visible presence of keratin, "squamous pearls," and intercellular desmosomes or bridges (Fig. 20.1).

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.

Spread of squamous cell carcinoma beyond the airway usually involves (1) direct extension to the pulmonary parenchyma or other neighboring structures or (2) invasion

Figure 20.1. Low-power photomicrograph of squamous cell carcinoma. Note three foci of tumor, each highlighted by *arrowheads*. Intervening regions show connective tissue and inflammatory cells. *Arrows* point to two areas of keratin formation by the tumor. (Courtesy Dr. Earl Kasdon.)

of lymphatic vessels, with spread to local lymph nodes in the hilum or mediastinum. These tumors have a general 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.

Small Cell Carcinoma

Small cell carcinoma, constituting 14% of all lung cancers, was previously considered as a separate group. However, in 2015, small cell carcinomas were reclassified as a subtype in the neuroendocrine tumor category. 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).

Features of small cell carcinomas:

1. Generally arise in proximal airways
2. Commonly produce polypeptide hormones
3. Commonly associated with hilar and mediastinal node involvement
4. Manifest early, distant metastatic disease

In small cell carcinoma, the malignant cells appear as small, darkly stained cells with sparse cytoplasm (Fig. 20.2). 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.

Rapid dissemination of small cell carcinoma makes metastatic spread to distant sites a common early complication. 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.

Figure 20.2. High-power photomicrograph of small cell carcinoma. Malignant cells have irregular, darkly stained nuclei and sparse cytoplasm. Note small area of necrosis *(N)* within tumor. (Courtesy Dr. Earl Kasdon.)

Adenocarcinoma

Adenocarcinoma has surpassed squamous cell carcinoma as the most frequent cell type, accounting for up to half of primary lung tumors. Because the majority of 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. 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. 20.3). 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. 20.4). 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.

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.

Figure 20.3. Low-power photomicrograph of adenocarcinoma of lung. Malignant cells form gland-like structures and produce mucus *(arrows)*. (Courtesy Dr. Earl Kasdon.)

Figure 20.4. Low-power photomicrograph of lepidic adenocarcinoma. Tumor cells appear to be growing along preexisting alveolar walls. Lower right corner of photograph shows normal alveolar walls, which can be contrasted with areas of tumor. (Courtesy Dr. Earl Kasdon.)

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

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.

Large Cell Carcinoma

Large cell carcinoma accounts for approximately 3% 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 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 relatively 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.

Table 21.1 (see Chapter 21) summarizes the distinguishing features of each cell type and reiterates many of the points discussed here.

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21

Lung Cancer: Clinical Aspects

CLINICAL FEATURES, 270
- Symptoms Relating to Primary Lung Lesion, 271
- Symptoms Relating to Nodal and Distant Metastasis, 271
- Paraneoplastic Syndromes, 271

DIAGNOSTIC APPROACH, 272
- Macroscopic Evaluation, 272
- Microscopic and Molecular Evaluation, 275
- Functional Assessment, 275
- Screening for Lung Cancer, 276

PRINCIPLES OF THERAPY, 276
- Treatment of Non–Small Cell Lung Cancer, 276
- Treatment of Small Cell Lung Cancer, 277
- Restoration of Airway Patency, 278

BRONCHIAL CARCINOID TUMORS, 278

MALIGNANT MESOTHELIOMA, 278

SOLITARY PULMONARY NODULE, 281

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, malignant mesothelioma, 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 radiography or computed tomography (CT), 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 on "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."

Abstract

Chapter 21 builds on the discussion of lung cancer presented in Chapter 20, and focuses on clinical aspects and treatment. Symptoms of lung cancer may be due to local disease, metastatic disease, or paraneoplastic syndromes, and specific examples of each are addressed. The clinical evaluation of lung cancer usually starts with radiographic imaging—chest x-rays, computed tomography, and sometimes positron emission tomography. Tissue sampling is required for definitive diagnosis. The principles of lung cancer staging and treatment are considered. The chapter concludes with a brief discussion of bronchial carcinoid tumors, malignant mesothelioma, and the clinical problem of the solitary pulmonary nodule.

Keywords

Lung cancer
Squamous cell carcinoma
Small cell carcinoma
Adenocarcinoma
Large cell carcinoma
Non-small cell carcinoma
Carcinoid tumor
Mesothelioma
Solitary pulmonary nodule
Lung cancer screening

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 (drooping upper eyelid), miosis (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.

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, and 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. 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 are capable of hormone production is not clear. It has been hypothesized that genetic information coding for the particular hormone is present but not expressed

Potential clinical problems with lung cancer are the following:

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

in the normal, nonmalignant cell. In the course of becoming malignant, the cell undergoes a process of gene dysregulation, during which it 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 origin. 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 about 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 on its surface a protein, voltage-gated calcium channel, which is important in calcium regulation at the neuromuscular junction. 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 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, which is an important factor in determining which modalities of therapy are most appropriate. Further molecular characterization of the tumor has also now become essential in determining treatment of many non–small cell lung cancers (NSCLCs). 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 even is 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

Figure 21.1. Chest radiograph shows small cell carcinoma of lung manifesting as left hilar mass.

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.

CT of the chest and upper abdomen is a standard part of the diagnostic evaluation of patients with lung cancer. 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, since these are common sites of lung cancer metastasis.

Positron emission tomographic (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). 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. Diagnostic specimens can be obtained in many cases even when the lesion is beyond direct visualization with the bronchoscope. In addition, the

Figure 21.2. Chest radiograph shows adenocarcinoma of lung manifesting as solitary pulmonary nodule *(arrow)*.

bronchoscopist can assess whether an intrabronchial carcinoma is impinging significantly on the bronchial lumen and causing either partial or complete airway occlusion.

Staging of Lung Cancer

Basis for staging of non–small cell lung cancer includes the following:
1. Size, location, and local complications of the primary tumor
2. Hilar and mediastinal lymph node involvement
3. Distant metastasis

After a tumor has been documented, evaluation of the extent and spread of the malignancy is formally achieved by staging. In the case of NSCLC (i.e., all cell types other than SCLC), staging is based on (1) the primary intrathoracic tumor—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; and (3) the distant spread of tumor beyond the thorax to other tissues or organ systems. In the case of SCLC, the disease is most commonly classified as either limited (localized within one hemithorax) or extensive (beyond the limits of one hemithorax).

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, often is initially assessed by CT, sometimes complemented by PET scanning. Definitive evaluation requires biopsy and histologic evaluation of the nodes, 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 and is especially useful for sampling nodes in the subcarinal region. In *suprasternal mediastinoscopy*, the mediastinum is visualized with a scope placed through an incision made just above the sternal notch. Biopsy specimens can be obtained by this technique if there is any suspicion that abnormal nodes are present. 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 require general anesthesia.

The third component of staging involves determining whether the tumor has disseminated to distant sites. Spread of a lung tumor to other organs is often documented with either radioisotope or CT scanning. If available, a total body PET scan often will indicate sites of distant metastasis in the bones, liver, and adrenal glands. If a 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, 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.

SCLC is typically staged as limited or extensive stage disease. Limited disease is defined as tumor that is limited to an ipsilateral thorax and regional lymph nodes. Extensive stage disease represents spread outside this region.

Microscopic and Molecular Evaluation

Since the last edition of this textbook, 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 between the subtypes of NSCLC was less important because the principles of treatment were generally identical for all patients with NSCLC, i.e., based on stage rather than the specific cell type. While 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. While histologic examination of a tumor is still performed and is of some value, further 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.

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.

Functional Assessment

Functional assessment of the patient with lung cancer provides important information that will guide the clinician in the choice of treatment. As discussed in the section on "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

Assessment of pulmonary function helps to determine whether surgical resection can be tolerated by the functionally compromised patient.

contributed by the area of lung to be removed. Further specification of guidelines precluding surgery is beyond the scope of this chapter but may be found in the references.

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 by most, but not all, expert groups. 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. Although there are some differences between organizations in their specific recommendations, screening with LDCT is generally recommended for adults ages 55 to 80 years with a greater than 30 pack per year history of smoking who are still smoking or have quit less than 15 years prior.

Unfortunately, there are distinct harms related to screening. 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 harm 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 the 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 and development of targeted therapy for some tumors, the approach to treatment has changed significantly for some patients with NSCLC.

The four major forms of treatment available for lung cancer are surgery, radiation therapy, chemotherapy, and molecularly targeted therapy. Three primary factors appear to determine how a particular tumor should be treated: its staging (i.e., size, location, and extent of spread), its cell type, and presence of "driver mutations"—genetic mutations within tumor cells that drive cell growth and can be targeted by specific inhibitors.

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 affords the best chance for cure. Thus, patients with Stage I, II, and IIIA are considered for surgery with curative intent. Depending on the stage, chemotherapy and/or radiation may be used 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, targeted therapy, or a combination of all three 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.

Previously, the typical chemotherapy for all 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 adenocarcinomas in approximately 15% of U.S. patients and in up to 60% of patients from regions in Asia. EGFR mutations also appear to be more common in women and 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., erlotinib, gefitinib, afatinib) is associated with longer progression-free survival.

For advanced NSCLC patients whose tumors do not demonstrate an activating mutation, treatment options include standard cytotoxic therapy with consideration of the addition of immunotherapy with monoclonal antibodies. Bevacizumab, a monoclonal antibody directed at vascular endothelial growth factor, is used in combination with cytotoxic chemotherapy in a subset of NSCLC patients. Finally, the host immune response against the tumor can be stimulated by agents such as pembrolizumab, which is a monoclonal antibody targeting the programmed death 1 (PD-1) receptor. Targeted therapy and immunotherapy are currently areas of very active research.

When an NSCLC is unresectable on the basis of any criteria and contains no targetable mutations or 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 and 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 palliation or tumor size reduction for temporary alleviation of the acute problem. Unfortunately, by definition, palliation is not curative therapy, and further problems with the tumor are certain to develop.

A general overview of treatment of NSCLC has been presented here. Since the details of treatment for NSCLC are nuanced and beyond the scope of this text, the reader is referred to detailed references 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. This regimen may be supplemented by thoracic radiation and/or prophylactic cranial radiation. A combination chemotherapeutic regimen is also used for extensive stage disease, and selected patients with a good response may sometimes receive thoracic or prophylactic cranial radiation.

Restoration of Airway Patency

For both NSCLC and SCLC, other palliative 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.

Table 21.1 summarizes many of the specific features of lung cancer discussed in this chapter and in Chapter 20. Each of the major cell types is considered separately, with emphasis on clinical, radiographic, and therapeutic aspects of each category of tumor.

BRONCHIAL CARCINOID TUMORS

Bronchial carcinoid tumors, also called *bronchial neuroendocrine tumors*, 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 of neuroendocrine origin; 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 relatively 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.

Common features of bronchial carcinoid tumors are the following:

1. Often found in young adults
2. Hemoptysis
3. Pneumonia distal to an obstructing endobronchial mass

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.

MALIGNANT MESOTHELIOMA

Unlike the other tumors discussed, *malignant mesothelioma* primarily involves the pleura rather than the airways or the pulmonary parenchyma. As with bronchial carcinoid tumors, smoking is not a risk factor. Malignant mesothelioma is relatively uncommon

Table 21.1

LUNG CANCER: COMPARATIVE FEATURES

Cell Type	Frequency (%)*	Location†	Radiographic Appearance‡	Spread	Treatment	Miscellaneous
Squamous cell	30–35	Proximal, endobronchial	1. Central mass 2. Obstructive atelectasis 3. Postobstructive pneumonia	Contiguous intrathoracic spread; nodal metastasis	Surgery, combined-modality therapy, or palliative therapy	Hypercalcemia (occasional)
Small cell (including oat cell)	20	Proximal, endobronchial (submucosal)	1. Central mass 2. Hilar, mediastinal adenopathy	Hilar, mediastinal nodes; distant metastasis	Chemotherapy (± radiation therapy)	Ectopic hormone production (ADH, ACTH) relatively common
Adenocarcinoma (including bronchoalveolar cell)	35	Peripheral	Solitary peripheral nodule or mass	Contiguous intrathoracic spread; nodal and distant metastasis	Surgery, combined-modality therapy, or palliative therapy	
Large cell	15–20	Variable	Variable; often large peripheral mass	Contiguous intrathoracic spread; nodal and distant metastasis	Surgery, combined-modality therapy, or palliative therapy	

*Approximate percent of all lung cancers.
†Most common location; for all cell types, variable locations are seen.
‡Common presentations on chest radiograph.
ACTH, Adrenocorticotropic hormone; *ADH*, antidiuretic hormone.

but is important at least partially because in many of the cases a specific etiologic factor can be identified. Specifically, 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.

Mesothelioma is suggested by pleural fluid, irregular or lobulated pleural thickening, and a distant history of asbestos exposure.

In patients with malignant mesothelioma, the main symptoms are chest pain, dyspnea, and sometimes cough. The chest radiograph usually is most notable for the presence of pleural fluid and often irregular or lobulated thickening of the pleura (Fig. 21.3). 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.

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 a randomized trial, extrapleural pneumonectomy in conjunction with chemotherapy and/or radiotherapy may be considered for patients with disease limited to one hemithorax. This procedure involves removal of the entire ipsilateral lung along with both the visceral and parietal pleura. 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, use of biologic response modifiers (e.g., interferons and interleukin-2), and gene therapy.

Figure 21.3. Chest radiograph of patient with mesothelioma. Note several lobulated, pleural-based masses in right hemithorax accompanied by right pleural effusion.

SOLITARY PULMONARY NODULE

Although the solitary pulmonary nodule on chest radiograph (defined as a single, rounded lesion 3 cm or less in diameter) is a common presentation of lung cancer, there is actually a broad differential diagnosis for this radiographic abnormality. 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.

The diagnostic possibilities for the solitary pulmonary nodule are listed in Table 21.2. 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. Comparison of old and new films 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

Table 21.2

DIFFERENTIAL DIAGNOSIS OF THE SOLITARY PULMONARY NODULE

NEOPLASMS
Malignant
Primary lung cancer
Solitary pulmonary metastasis from distant carcinoma
Bronchial carcinoid (bronchial adenoma)
Benign
Hamartoma
Miscellaneous (e.g., fibroma, lipoma)
VASCULAR ABNORMALITY
Arteriovenous malformation
INFECTION
Infectious granuloma
Tuberculosis ("tuberculoma")
Histoplasmosis ("histoplasmoma")
Bacterial abscess
Miscellaneous (e.g., hydatid cyst, canine heartworm)
MISCELLANEOUS
Rounded atelectasis
Hematoma
Pseudotumor (fluid loculated in a fissure)

Criteria for assessing the likelihood that a solitary pulmonary nodule is malignant are the following:
1. Size
2. Stability or change in size of the lesion
3. Attenuation—solid vs. subsolid
4. Presence or absence of calcification; pattern of calcification
5. Smooth versus irregular appearance of the border
6. Location

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.

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 simple noninvasive test such as sputum cytologic examination is most 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, PET scanning (see Chapter 3), when 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 in an attempt 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 with resection with video-assisted thoracic surgery 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 manifests 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

PHYSICAL OR ANATOMIC FACTORS, 286
ANTIMICROBIAL PEPTIDES, 287
PHAGOCYTIC AND INFLAMMATORY CELLS, 288
Pulmonary Alveolar Macrophages, 288
Dendritic Cells, 289
Polymorphonuclear Leukocytes, 290
Natural Killer Cells, 290
ADAPTIVE IMMUNE RESPONSES, 290
Humoral Immune Mechanisms, 291
Cellular Immune Mechanisms, 292
FAILURE OF RESPIRATORY DEFENSE MECHANISMS, 292
Impairment of Physical Clearance, 292
Impairment of Antimicrobial Peptides, 293
Impairment of Phagocytic and Inflammatory Cells, 293
Defects in the Adaptive Immune System, 294
AUGMENTATION OF RESPIRATORY DEFENSE MECHANISMS, 295

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.

Abstract

In the process of exchanging thousands of liters of air each day, the lung is exposed to a multitude of microorganisms and foreign substances transported with the inhaled air. 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. This chapter considers 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 non-infectious substances, especially inhaled particulate material, also are addressed. The major categories of defense mechanisms 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.

Keywords

Cough
Mucociliary clearance
alpha-Defensins
beta-Defensins
Muramidase
Lactoferrin
Collectins
Macrophages, alveolar
Kartagener syndrome
Ciliary motility disorders
Immunity, active
Vaccines

Before the discussion of infectious disorders of the respiratory system in Chapters 23 through 26, 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 excluded from 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.

Factors affecting deposition and physical clearance of particles are:
1. Particle size
2. Cough
3. Mucociliary transport

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.

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. (From Eliasson R, Mossberg B, Camner P, et al. The immotile-cilia syndrome. A congenital ciliary abnormality as an etiologic factor in chronic airway infections and male sterility, *N Engl J Med*. 1977;297:1–6. Copyright 1977 Massachusetts Medical Society. All rights reserved.)

Strikingly, the movement of cilia on a particular cell and the movement between cells are quite 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. What this wavelike motion accomplishes is 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. If inhaled particles are trapped in the mucous layer, they too are transported upward and eventually are 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 a number of 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. Picture the viscous gel layer floating on top of the sol layer and being propelled upward as the cilia are able to 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 that are able to respond 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

Airway innate immunity substances include:
1. Lysozyme
2. Lactoferrin
3. Defensins
4. Collectins (surfactant proteins A and D)
5. IgA

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 references. For the reader to get a sense of the system, 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.

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; however, human disease related to a genetic mutation or deletion has not been identified.

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 section on humoral immune mechanisms.

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. Organisms that are especially capable of persistent infection of macrophages without being killed or deactivated include *Mycobacterium tuberculosis* and the human immunodeficiency virus (HIV).

An increasingly appreciated role of the alveolar macrophage is to *suppress* 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 are:

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 bonemarrow–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 section on cellular immune mechanisms). They act by recognizing and killing virus-infected cells that have been transformed and no longer express certain 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 are:

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 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, while 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 section on defects in the adaptive immune system.

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) have the ability to attract or activate other protective cell types, particularly macrophages. T lymphocytes also are capable of interacting with the humoral immune system and modifying antibody production.

Two important types of T lymphocytes have been well characterized on the basis of 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 24). 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, all of these limbs 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 the 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. 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 are:

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. Functionally, alteration of the 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 29). 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.

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

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. Some data suggest that macrophage migration is impaired in AIDS, possibly complicating the other host defense defects recognized in the disease (see Chapter 26).

Causes of decreased numbers of PMNs are:
1. Bone marrow replacement by tumor
2. Cancer chemotherapeutic agents

PMNs are reduced in number in several clinical circumstances, generally as a result of an underlying bone marrow disease (e.g., leukemia) or as a result of 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.

Defects in the Adaptive Immune System

Causes of adaptive immune deficiency are:
1. Humoral: decreased or absent immunoglobulins
2. Cellular: corticosteroids, cytotoxic drugs, Hodgkin disease and other lymphomas, HIV/AIDS

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 are not at increased risk of sinopulmonary infections, likely because of redundancy in the immune system.

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 special 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. People are capable of thwarting these defenses by exposing themselves to damaging influences, such as cigarette smoke and ethanol. Equally important, physicians often manage patients with pharmacologic agents or other modalities that 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

In contrast to disease and the actions of physicians in treating patients that can lead to the impairment of normal lung defense mechanisms, there are important 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 toxins of *Bordetella pertussis* (which causes whooping cough) and immunization against influenza viruses and many subtypes of the common bacterium *Streptococcus pneumoniae* (pneumococcus). Universal immunization against pertussis is recommended during childhood, and as of 2006, the U.S. Centers for Disease Control and Prevention (CDC) recommend a booster vaccine for all adults. Immunization with influenza and pneumococcal vaccines had been generally targeted to individuals believed to be at relatively high risk for contracting or developing complications from these infections. However, in 2010, the US Advisory Committee on Immunization Practices changed their recommendation for influenza vaccination to include all individuals 6 months of age and older. Likewise, pneumococcal vaccination is now recommended universally both for young children and for adults over 65 years of age. 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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23

Pneumonia

ETIOLOGY AND PATHOGENESIS, 298
Bacteria, 299
Viruses, 300
Mycoplasma, 300
PATHOLOGY, 301
PATHOPHYSIOLOGY, 301
CLINICAL FEATURES, 302
DIAGNOSTIC APPROACH, 303
THERAPEUTIC APPROACH: GENERAL PRINCIPLES AND ANTIBIOTIC SUSCEPTIBILITY, 306
INITIAL MANAGEMENT STRATEGIES BASED ON CLINICAL SETTING OF PNEUMONIA, 307
Community-Acquired Pneumonia, 307
Nosocomial (Hospital-Acquired) Pneumonia, 309
INTRATHORACIC COMPLICATIONS OF PNEUMONIA, 310
Lung Abscess, 310
Empyema, 310
RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM, 310
Anthrax, 311
Plague, 311
Tularemia, 311

By nearly any criteria, pneumonia (infection of the pulmonary parenchyma) must be considered one of the most important categories of disease affecting the respiratory system. Of note:

- Pneumonia is extraordinarily common; it is the most common reason for hospital admission in the United States other than women giving birth.
- Mortality is higher with an admitting diagnosis of pneumonia for adults 65 years of age in the United States than for any of the other top 10 admitting diagnoses.
- In 2011, pneumonia had an aggregate cost of nearly $10.6 billion for 1.1 million hospital stays in the United States.
- It is the world's leading cause of death among children under 5 years of age, 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 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, the diseases discussed in this chapter are typically gratifying to treat for all involved medical personnel. Unfortunately, the emerging trend during the past 20 years has been the acquisition of antibiotic resistance by some of the

Abstract

By nearly any criteria, pneumonia (infection of the pulmonary parenchyma) must be considered one of the most important categories of disease affecting the respiratory system. This chapter is organized primarily as a general discussion of the clinical problem of pneumonia. As appropriate, the focus on individual etiologic agents highlights some characteristic features of each that are particularly useful to the physician. Also covered is a commonly used 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 often quite different. The chapter concludes with a brief discussion of several infections that were uncommon or primarily of historical interest until recently, as the threat of bioterrorism 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).

Keywords

Pneumonia
Streptococcus pneumoniae
Mycoplasma
Chlamydophila
Lung abscess
Empyema, pleural
Anthrax
Plague
Tularemia

organisms causing pneumonia, and treatment of pneumonia has had to evolve to keep pace.

Although many of the specific agents causing pneumonia are considered here, this chapter is organized primarily as a general discussion of the clinical problem of pneumonia. As appropriate, the focus on individual etiologic agents highlights some characteristic features of each that are particularly useful to the physician. Also covered is a commonly used 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 often quite different.

The chapter concludes with a brief discussion of several infections that were uncommon or primarily of historical interest until recently, as the threat of bioterrorism 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).

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 frank infectious process within the pulmonary parenchyma. With particularly virulent organisms, no major impairment of host defense mechanisms is needed; pneumonia may occur even in normal and otherwise healthy individuals. At the other extreme, if host defense mechanisms are quite impaired, microorganisms that are not particularly virulent and are unlikely to cause disease in a healthy host may produce a life-threatening pneumonia.

Common contributing factors for pneumonia in the immunocompetent host are:

1. Viral upper respiratory tract infection
2. Ethanol abuse
3. Cigarette smoking
4. Heart failure
5. Chronic obstructive pulmonary disease

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, ethanol abuse, cigarette smoking, heart failure, and preexisting chronic obstructive pulmonary disease (COPD) are a few of the contributing factors. More severe impairment of host defenses is caused by diseases associated with immunosuppression (e.g., advanced AIDS), various underlying malignancies (particularly leukemia and lymphoma), and the use of corticosteroids and other immunosuppressive drugs. In these cases associated with impairment of host defenses, individuals are susceptible to both bacterial and more unusual nonbacterial infections (see Chapters 24 to 26).

Microorganisms, especially bacteria, find their way to 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 seem able to cope with this nightly onslaught of bacteria, and frequent bouts of aspiration pneumonia are not experienced.

Less commonly, bacteria reach the pulmonary parenchyma through the bloodstream rather than by the airways. This route is important for the spread of certain organisms, particularly *Staphylococcus*. When pneumonia results in this way from bacteremia, the

implication is that a distant primary source of bacterial infection is present or that bacteria were introduced directly into the bloodstream (e.g., with intravenous drug use).

Many individual infectious agents are associated with the development of pneumonia. The frequency with which each agent is involved is difficult to assess and depends to a large extent on the specific population studied. The largest single category of agents is probably bacteria. The other two major categories are viruses and *Mycoplasma*. 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 *S. pneumoniae.*

Streptococcus pneumoniae (pneumococcus) is the most common cause of bacterial pneumonia. The polysaccharide capsule is an important factor in its virulence.

Bacteria

S. pneumoniae, a normal inhabitant of the oropharynx in a large proportion of adults, is a Gram-positive coccus typically seen in pairs, or diplococci. Pneumococcal pneumonia is commonly acquired in the community (i.e., in nonhospitalized patients) and frequently occurs following a viral upper respiratory tract infection. The organism has a polysaccharide capsule that interferes with immune recognition and phagocytosis, and therefore 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, the antibody against the particular capsular type must be present. Antibodies contributing in this way to the phagocytic process are called *opsonins* (see Chapter 22).

Staphylococcus aureus is another gram-positive coccus, but usually appears in clusters when examined microscopically. Three major settings in which this organism is seen as a cause of pneumonia are (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.

A variety of gram-negative organisms are potential causes of pneumonia, but only a few of the most important examples from this group of organisms 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, has been best described as a cause of pneumonia in the setting of underlying alcoholism. *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 infections in patients with underlying bronchiectasis or cystic fibrosis.

Factors predisposing to oropharyngeal colonization and pneumonia with gram-negative organisms are:

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. 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. In addition, patients with poor dentition or gum disease are more likely to develop aspiration pneumonia because of the larger burden of organisms in their oral cavity.

Anaerobes normally found in the oropharynx are the usual 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.

The two final types of bacteria mentioned here are more recent additions to the list of etiologic agents. The first of these organisms, *Legionella pneumophila*, was identified as the cause of a mysterious outbreak of pneumonia in 1976 affecting American Legion members at a convention in Philadelphia. Since then it has been recognized as an important cause of pneumonia occurring in epidemics, as well as in isolated sporadic cases, and seems to affect both previously healthy individuals and those with prior impairment of respiratory defense mechanisms. Retrospectively, several prior outbreaks of unexplained pneumonia have been shown to be due to this organism. Although the organism technically is a gram-negative bacillus, it is poorly visualized by conventional staining methods.

The other organism, *Chlamydophila pneumoniae*, has been recognized in epidemiologic studies as the cause of approximately 5% to 10% of cases of pneumonia. It appears related to gram-negative bacteria, and for part of its life cycle it is an obligate intracellular parasite. Diagnosis is rarely made clinically because of the lack of distinguishing clinical and radiographic features, and the organism is not readily cultured. As a result, serologic studies serve as the primary means of diagnosis, although they are infrequently obtained and may be difficult to interpret.

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 references at the end of this chapter.

Viruses

Although viruses are extremely common causes of upper respiratory tract infections, they are diagnosed relatively infrequently as a cause of frank pneumonia, except in children. In adults, the influenza virus is the most commonly diagnosed agent. The 2010 H1N1 influenza pandemic fortunately caused fewer deaths than originally anticipated and raised the profile of best practices for prevention, diagnosis, and treatment of this virus. In contrast, the 1918 influenza pandemic is estimated to have resulted in 50 to 100 million deaths, or 3% to 5% of the world's population.

Outbreaks of pneumonia caused by adenovirus also are well described, particularly among military recruits. A relatively rare cause of a fulminant and often lethal pneumonia was described in the southwest United States, but cases in other locations have also been recognized. Species of *Hantavirus,* the genus of viruses responsible for this pneumonia, are found in rodents and were previously described as a cause of fever, hemorrhage, and acute renal failure in other parts of the world.

Several other viruses have caused limited epidemics of severe viral pneumonia in recent years. An outbreak of a novel, 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 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 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.

Mycoplasma

Mycoplasma appears to be a class of organisms that is intermediate between viruses and bacteria. Unlike bacteria, they have no rigid cell wall. Unlike viruses, they do not require the intracellular machinery of a host cell to replicate and are capable of free-living growth. Similar in size to large viruses, mycoplasmas are the smallest fully free-living organisms that have been identified thus far. These organisms are now recognized as

a common cause of pneumonia, and are perhaps responsible for a minimum of 10% to 20% of all cases. Mycoplasmal pneumonia 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, non-hospitalized individuals—and may occur in either isolated cases or localized outbreaks.

Mycoplasma, the smallest known free-living organism, is a frequent cause of pneumonia in young adults.

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 not limited to segmental boundaries but rather tending to spread throughout an entire lobe of the lung. 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 *S. pneumoniae*, 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. 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. Although viral pneumonias classically start as interstitial pneumonias, severe cases generally show extension of the inflammatory process to alveolar spaces as well.

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

Infections of the pulmonary parenchyma produce their clinical sequelae not only by altering the normal functioning of the lung parenchyma but also by inducing a more generalized systemic response to invading microorganisms. The major pathophysiologic

Pneumonia commonly results in ventilation-perfusion mismatch (with or without shunting) and hypoxemia.

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 extreme ventilation-perfusion inequality (i.e., shunt) results.

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 a feature of pneumonia unless the patient already has an extremely limited reserve, especially from underlying COPD. In fact, patients with pneumonia frequently hyperventilate and have a P_{CO_2} less than 40 mm Hg.

The systemic response to pneumonia is not unique but rather is 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

In many ways the clinical manifestations of pneumonia are similar, even when different infectious agents are involved. In other ways, the presentations and manifestations are quite different. Although recognition of subtle clinical differences sometimes allows the astute clinician to suggest an etiologic diagnosis, methods for identifying a specific infectious agent are required for a definitive final diagnosis. However, in many cases, a specific agent cannot be clearly identified, and patients often are managed in an empirical way based on the setting in which they present.

Frequent clinical features in patients with pneumonia are:

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

Perhaps the most important constellation of symptoms in almost any type of pneumonia consists of 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.

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 crackles or rales 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. Examination of peripheral blood generally 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.

In pneumococcal pneumonia, the onset of the clinical illness often is relatively 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 can be an important predisposing feature.

Mycoplasmal pneumonia, in contrast to pneumococcal pneumonia, characteristically has a somewhat slower, more insidious onset. Cough is a particularly prominent symptom,

but it often is non-productive. Fever is not as high, and shaking chills are uncommon. Young adults are the individuals most likely to have mycoplasmal pneumonia, although the disease is not limited to this age group.

Patients with either staphylococcal or gram-negative bacillary pneumonias are often quite ill. Frequently these patients have complex underlying medical problems and have already been hospitalized. Many have impaired defense mechanisms or have recently received antibiotics. Staphylococcal pneumonia classically may be seen as a secondary complication of influenza infection or as a result of dissemination of the organism through the bloodstream.

Pneumonia with anaerobic organisms generally occurs in patients with impaired consciousness or difficulty swallowing who cannot adequately protect the airway from aspiration of oropharyngeal secretions. Dentition often is poor, and patients frequently have gingivitis or periodontal abscesses. Clinical onset of the pneumonia tends to be gradual, and sputum may have a particularly foul odor, suggesting anaerobic infection. Successful culture of causative organisms may be difficult. While generally slow growing, anaerobic organisms can cause substantial tissue destruction, and necrosis of affected tissue and abscess formation are relatively common sequelae.

Pneumonia caused by *L. pneumophila*, commonly called *Legionnaires' disease*, can be seen as isolated cases or localized outbreaks. Otherwise healthy hosts may be affected, but patients with impaired respiratory defense mechanisms appear to be predisposed. Patients are often extremely ill, not only with respiratory compromise and even respiratory failure but also with nonrespiratory manifestations; specifically, gastrointestinal, central nervous system, hepatic, and renal abnormalities may accompany the pneumonia.

DIAGNOSTIC APPROACH

As with other disorders affecting the pulmonary parenchyma, the single most useful tool for assessing pneumonia at the macroscopic level is the chest radiograph in both posteroanterior and lateral views. The radiograph not only confirms the presence of a pneumonia but also shows the distribution and extent of disease and sometimes give clues about the nature of the etiologic agent. The classic pattern for *S. pneumoniae* (pneumococcus) and *K. pneumoniae* is a lobar pneumonia (Fig. 23.1). Staphylococcal and many of the gram-negative pneumonias may be localized or extensive and often follow a patchy distribution (Fig. 23.2). *Mycoplasma* organisms can produce a variety of radiographic presentations, which are classically described as being more impressive than the clinical picture would suggest. Pneumonias caused by aspiration of oropharyngeal secretions characteristically involve the dependent regions of lung: the lower lobe in the upright patient or the posterior segment of the upper lobe or superior segment of the lower lobe in the supine patient (Fig. 23.3). *Legionella* pneumonia most commonly presents with a patchy or consolidated unilobar infiltrate, although all patterns have been described.

Chest radiographs also are useful for demonstrating the presence of pleural fluid, which frequently accompanies pneumonia, particularly of bacterial origin. The pleural fluid can be either thin and serous or thick and purulent; in the latter case, the term *empyema* is used (discussed later under Empyema).

Microscopic examination of sputum may play an important role in evaluating patients with pneumonia. However, the importance of obtaining a sputum specimen and using it as a guide to treatment, as opposed to treating the patient empirically without a sputum specimen, is an issue of substantial controversy. For patients who do not require hospitalization, most authorities now recommend basing initial treatment on clinical presentation, without substantial efforts at identifying a causative organism. In contrast, patients who are sick enough to be admitted to the hospital are still treated empirically, but attempts are made to identify the organism in order to further guide therapy. When

Figure 23.1. Posteroanterior **(A)** and lateral **(B)** chest radiographs show lobar pneumonia (probably caused by *Streptococcus pneumoniae*) affecting the right middle lobe. In **A**, the arrow points to a minor fissure, which defines the upper border of the middle lobe. In **B**, the long arrow points to a minor fissure, and the short arrow points to a major fissure.

Figure 23.2. Chest radiograph of a patient with extensive gram-negative pneumonia. Note the patchy infiltrates throughout both lungs, which are more prominent on the right.

Figure 23.3. Chest radiograph of right lower lobe aspiration pneumonia. In addition to the infiltrate at the right base, note the loculated pleural effusion, which represents empyema complicating pneumonia. Arrow points to the edge of the loculated effusion. (Courtesy Dr. T. Scott Johnson.)

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 generally requires special stains to appreciate its presence. In mycoplasmal and viral pneumonia, the infecting agent is not visualized by light microscopy, and only the predominantly mononuclear cell inflammatory response is seen.

In conjunction with the initial Gram stain and microscopic examination of sputum, the specimen is cultured for bacteria. However, some bacteria are relatively difficult to grow, and in many if not most cases the initial Gram stain is just as important in making the etiologic diagnosis. Special culture media are available to facilitate the growth of *Legionella* species.

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 have been used—flexible bronchoscopy, needle aspiration of the lung, and occasionally surgical lung biopsy—are described in greater

detail in Chapter 3. Techniques for testing urine for the presence of antigens related to *S. pneumoniae* and *Legionella* (see below) are becoming increasingly useful.

Routine stains and cultures of sputum are not useful for three of the important causes of pneumonia: *Mycoplasma, Chlamydophila,* and *Legionella.* Sometimes the diagnosis can be confirmed by a variety of serologic techniques that demonstrate a rise in antibody titer against the organism, but these techniques provide a retrospective diagnosis and are not clinically useful. Several newer methods are seeing increasing clinical usefulness over time. For example, direct fluorescent antibody staining can be performed for *Legionella*, especially on tissue specimens, but more recent methods include culture on special supplemented media and a commonly used urinary antigen radioimmunoassay (only for certain *L. pneumophila* serotypes). Nucleic acid amplification methods, including polymerase chain reaction, are now widely used to detect *Mycoplasma, Chlamydophila*, and specific respiratory viruses, such as influenza or coronaviruses.

Functional assessment of patients with acute infectious pneumonia is usually limited to evaluating gas exchange. 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 setting.

THERAPEUTIC APPROACH: GENERAL PRINCIPLES AND ANTIBIOTIC SUSCEPTIBILITY

The cornerstone of treatment of bacterial pneumonia is prompt, effective, antibiotic therapy directed at the infecting organism. However, because the causative organism often is not known when the pneumonia is first diagnosed and, in fact, frequently is not identified at any point during the clinical course, initial treatment strategies have been developed on the basis of the clinical setting (e.g., community-acquired vs. hospital-acquired pneumonia). These initial treatment strategies are outlined later under Initial Management Strategies Based on Clinical Setting of Pneumonia. If and when an organism is identified, the regimen may be changed 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 first considers some of the general patterns of antibiotic susceptibility for the major organisms causing pneumonia.

In the case of pneumococcal pneumonia, penicillin has been the most appropriate agent traditionally, assuming the patient is not allergic to penicillin, although cases with various degrees of resistance to penicillin are encountered with increasing frequency. In addition, because penicillin is not effective against some of the other common causes of community-acquired pneumonia (e.g., *Mycoplasma pneumoniae, C. pneumoniae*), other classes of antibiotics with a broader spectrum against agents causing community-acquired pneumonia are typically used when antibiotics are initiated. They include macrolides (erythromycin or a derivative, such as azithromycin) and quinolones (e.g., moxifloxacin). When high-level resistance of pneumococcus to penicillin is found, either a quinolone or vancomycin is typically necessary. Intermediately resistant strains can often be treated with ceftriaxone.

Staphylococci generally produce penicillinase, which requires the use of a penicillinase-resistant semisynthetic derivative of penicillin, such as oxacillin or nafcillin. Many staphylococci are also resistant to these derivatives, 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*.

No definitive forms of therapy are available for most viral pneumonias, although rapid advances in this field may lead to the development of more clinically useful therapeutic agents. The influenza vaccine (see Chapter 22) is effective in preventing influenza in the majority of individuals who receive it, whereas antiviral agents (amantadine or rimantadine for influenza A, a neuraminidase inhibitor, such as zanamivir or oseltamivir, for influenza A or B) may reduce the duration or severity of the illness if given soon after the onset of clinical symptoms.

Other modalities of therapy are mainly supportive. Chest physical therapy and other measures to assist the clearance of respiratory secretions are useful for some patients with pneumonia, particularly if neuromuscular disease or other factors impair the effectiveness of the patient's cough. If patients have inadequate gas exchange, as demonstrated by significant hypoxemia, administration of supplemental O_2 is beneficial. Occasionally, frank respiratory failure develops, and appropriate supportive measures are instituted (see Chapter 29).

Frequently used antibiotics for common pneumonias are:

1. *S. pneumoniae* (penicillin, first- or second-generation cephalosporin, macrolide, selected quinolones)
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

During the past two decades, 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 have been developed, relating to both diagnostic evaluation and initiation of therapy. Separate strategies are being promulgated for two distinct groups of patients with pneumonia, depending on the setting where the pneumonia developed: community-acquired or nosocomial (hospital-acquired). Guidelines apply to patients who do not have a significant underlying impairment of systemic host defense mechanisms, such as patients with 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 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.

Surprisingly, the cause of community-acquired pneumonia is never identified in a high proportion of patients, estimated to be up to 50%. The likelihood of particular agents is believed to be influenced by a number of modifying factors: the presence of coexisting illness, recent treatment with antibiotics, residence in a nursing home, and the severity of illness at the initial presentation. One issue that has sparked controversy is whether an attempt should be made to identify a specific etiologic agent, using Gram stain and culture, in patients with community-acquired pneumonia, or whether empirical therapy should be used based on the patient's risk factors, clinical characteristics, and local bacterial resistance patterns. If a specific pathogen is identified, modification of

the initial antibiotic regimen is often appropriate, particularly to avoid an overly broad spectrum of coverage.

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.

Table 23.1 summarizes the etiology and initial management of four broad subcategories of patients with community-acquired pneumonia. The first group comprises patients who do not have coexisting cardiopulmonary disease or other modifying risk factors, who have not used antibiotics in the previous 3 months, 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 preferred therapeutic regimen is one of the advanced-generation macrolide antibiotics, such as azithromycin or clarithromycin, but this recommendation is subject to local differences in rates of bacterial resistance. For example, in some regions of the United States, up to 45% of *S. pneumoniae* isolates are resistant to macrolides.

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

Table 23.1

ETIOLOGY AND INITIAL MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA*

Patient Category	Common Organisms	Other Miscellaneous Organisms	Initial Therapy
Outpatient, no cardiopulmonary disease or other modifying risk factors	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* Respiratory viruses *H. influenzae* (in smokers)	*Legionella* *M. tuberculosis* Endemic fungi	Advanced-generation macrolide (e.g., azithromycin or clarithromycin) *OR* Doxycycline
Outpatient with cardiopulmonary disease and/or other modifying factors	*S. pneumoniae* *M. pneumoniae* *H. influenzae* Aerobic gram-negative bacilli Respiratory viruses Anaerobes *C. pneumoniae*	*M. catarrhalis* *Legionella* *M. tuberculosis* Endemic fungi	Oral quinolone (with activity against pneumococcus) *OR* β-Lactam plus macrolide
Hospitalized	*S. pneumoniae* *H. influenzae* Polymicrobial (including anaerobes) Aerobic gram-negative bacilli *Legionella* *C. pneumoniae* Respiratory viruses	*M. pneumoniae* *M. catarrhalis* *M. tuberculosis* Endemic fungi	Intravenous (IV) β-lactam plus IV or oral macrolide or doxycycline *OR* IV quinolone
Hospitalized, severe pneumonia	*S. pneumoniae* *Legionella* *H. influenzae* Aerobic gram-negative bacilli *M. pneumoniae* Respiratory viruses *S. aureus*	*M. tuberculosis* *C. pneumoniae* Endemic fungi	IV β-lactam plus either IV macrolide (azithromycin) or IV quinolone†

*Excludes patients with human immunodeficiency virus infection.
†If there is a high risk for *Pseudomonas*, adjust the regimen to include two antipseudomonal agents.
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 LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.

comorbidities that place a patient in this category include chronic heart, lung, hepatic, or renal disease; diabetes mellitus; alcoholism; 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 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 the management of this group have included either an oral quinolone (used as a single agent) or a β-lactam antibiotic (e.g., second- or third-generation cephalosporin) given in combination with a macrolide (particularly an advanced-generation macrolide, such as azithromycin or clarithromycin).

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 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 the additional concern for gram-negative bacilli, *Legionella*, and sometimes *S. aureus*. Therapy for these patients is adjusted accordingly (see Table 23.1). Antibiotics, such as a quinolone or an advanced-generation macrolide, plus a β-lactam (particularly a third-generation cephalosporin), a carbapenem, or an extended-spectrum penicillin with β-lactamase inhibitor, are typically used in these settings, frequently in combination with vancomycin.

There are increasing data to suggest that adjunctive treatment with corticosteroids may be beneficial in many patients with severe pneumonia. However, the 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.

A number of scoring systems have been developed to assess the need for hospitalization or ICU admission for an individual patient based upon the 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 clinical prediction rules are provided.

Nosocomial (Hospital-Acquired) Pneumonia

In contrast to community-acquired pneumonia, nosocomial pneumonia is acquired by hospitalized patients, generally after more than 48 hours of hospitalization. Patients in ICUs, especially those receiving mechanical ventilation, are at particularly high risk for developing this category of pneumonia. Perhaps the most common problem leading to nosocomial pneumonia is colonization of the oropharynx by organisms not usually present in this site, which is followed by microaspiration of oropharyngeal secretions into the tracheobronchial tree. 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.

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 enteric gram-negative bacilli and *S. aureus*, but other organisms such as *Pseudomonas aeruginosa* 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. The clinical issues involved with diagnostic testing and optimal forms of therapy are beyond the scope of this discussion but can be found in the references at the end of this chapter.

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 PMNs, often with collections of bacterial organisms. When antibiotics have been administered, organisms may no longer be culturable from the abscess cavity.

Anaerobic bacteria are the agents most frequently responsible for lung abscesses.

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.

Treatment of a lung abscess involves antibiotic therapy, often given for longer than for an uncomplicated pneumonia. Although abscesses elsewhere in the body are drained by surgical incision, 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 contains enormous numbers of leukocytes, primarily PMNs, 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 limited mobility of the underlying lung.

Adequate drainage of pleural fluid is critical in the management of empyema.

Several different bacterial organisms may be associated with development of an empyema. Anaerobes are particularly common, but staphylococci 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.

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 previously 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, Yersinia pestis,* and *Francisella tularensis.*

Anthrax

Bacillus anthracis, a gram-positive spore-forming rod found in soil, causes infection in farm stock and wild animals. Human cases have occurred as a result of 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 a toxin that causes prominent edema, inhibits neutrophil function, and alters production of a number of cytokines. Whereas cutaneous anthrax results from spores introduced through a break in the skin, 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. Despite treatment with ciprofloxacin or doxycycline, mortality is extremely high after the onset of clinical illness, and public health guidelines have focused on prophylaxis (with either of these antibiotics) to prevent inhalational anthrax following confirmed or suspected exposure to aerosolized spores. An anthrax vaccine is available but requires a complex administration schedule and annual booster injections.

Inhalational anthrax characteristically produces a widened mediastinum on chest radiograph.

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, *Yersinia pestis*, a gram-negative rod transmitted by fleas from rodents to humans, is still endemic in many parts of the world, including the southwest and Pacific coastal regions of the United States, the former Soviet Union, and focused areas in Africa, Asia, and South America. 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.

Pulmonary involvement is characterized by widespread bronchopneumonia that can have regions of homogeneous consolidation. Clinically, patients become acutely ill with high fever, malaise, myalgias, rigors, dyspnea, and cyanosis. Chest radiography shows widespread bronchopneumonia with a diffuse pattern that can resemble acute respiratory distress syndrome (ARDS). Mortality is high unless antibiotic treatment is initiated soon after the onset of symptoms. Streptomycin and doxycycline are the treatments of choice.

Tularemia

Tularemia is caused by *Francisella 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 forms of clinical presentation 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. Treatment consists of streptomycin, and mortality is estimated to be approximately 35% without treatment.

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24

Tuberculosis and Nontuberculous Mycobacteria

ETIOLOGY AND PATHOGENESIS, 315
DEFINITIONS, 316
PATHOLOGY, 317
PATHOPHYSIOLOGY, 317
CLINICAL MANIFESTATIONS, 318
DIAGNOSTIC APPROACH, 318
PRINCIPLES OF THERAPY, 321
NONTUBERCULOUS MYCOBACTERIA, 322

Throughout the centuries, few diseases have claimed so many lives, caused so much morbidity, and been so dreaded as tuberculosis. At the turn of the 20th century, tuberculosis was the single most common cause of death in the United States; 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 the United States and Europe, few diseases have declined so greatly in frequency of cases and mortality as tuberculosis. Two main factors have been responsible: overall improvement in living conditions and the development of effective antituberculous chemotherapy, which has made tuberculosis a curable disease. However, in countries with fewer resources, the disease continues to be a health crisis, often striking the young, most productive, members of society.

Now more than 135 years since identification of the tubercle bacillus by Robert Koch in 1882, we still cannot become complacent about the disease. It has been estimated that approximately one-third 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, with approximately 10 million new cases of active tuberculosis and approximately 1.8 million deaths occurring worldwide each year. The overwhelming majority of cases of active tuberculosis occur in developing countries. Some 70 million of the 88 million cases of tuberculosis during the 1990s were from Asia and sub-Saharan Africa, where coinfection with the human immunodeficiency virus (HIV) is a major contributor to the increase in infections. Despite this huge burden of disease, the number of global deaths fell 22% between 2000 and 2015 due to the increased availability of diagnostic techniques and medications.

Tuberculosis remains an important public health problem in the United States and other industrialized countries, particularly in indigent and immigrant populations and patients with acquired immunodeficiency syndrome (AIDS; see Chapter 26). Reported cases of tuberculosis in the United States were decreasing until the mid-1980s, at which time the AIDS epidemic and immigration from countries with a high prevalence

Abstract

It has been estimated that approximately one-third 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, with approximately 10 million new cases of active tuberculosis and approximately 1.8 million deaths occurring worldwide each year. The overwhelming majority of cases of active tuberculosis occur in developing countries. Tuberculosis remains an important public health problem in the United States and other industrialized countries, particularly in indigent and immigrant populations and patients with AIDS. This chapter reviews the pathophysiology and clinical manifestations of tuberculosis, as well as diagnosis and management. The epidemiology, diagnosis, and treatment of disease caused by nontuberculous mycobacteria are also reviewed.

Keywords

Tuberculosis
Latent tuberculosis
Tuberculosis, pulmonary
Tuberculosis, miliary
Mycobacterium tuberculosis
Tuberculosis, multidrug-resistant
Extensively drug-resistant tuberculosis
Nontuberculous mycobacteria
Mycobacterium infections, nontuberculous

of tuberculosis combined to result in an increasing frequency of cases. Fortunately, since 1991, the number of cases reported annually in the United States has again been decreasing. Perhaps most alarming is the relatively recent emergence of drug-resistant strains of the organism, some of which are resistant to multiple antituberculous drugs. The World Health Organization estimated approximately 480,000 new cases of multidrug-resistant tuberculosis worldwide in 2015, nearly half of which were from India, China, and Russia.

ETIOLOGY AND PATHOGENESIS

The etiologic agent that causes tuberculosis, *Mycobacterium tuberculosis*, is an aerobic rod-shaped bacterium. An important 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 droplets aerosolized by another individual is almost exclusively the mode of spread.

Transmission of tuberculosis is by inhalation of small aerosol droplets containing the organism.

When droplets containing mycobacteria are inhaled and reach the alveoli, 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 reaching the parenchyma, and they are a particularly important component of the resulting inflammatory response. After the initial infection has started, organisms frequently 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. In the majority of cases, even though lymphatic and hematogenous spread may occur, the body's defense mechanisms (in the lung and elsewhere) are capable of controlling and limiting the primary infection. 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 generally occur within several weeks of initial exposure.

The patient usually 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)-γ 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 if the host is immunocompromised because of immunosuppressive medications, alcoholism, HIV/AIDS, or malignancy.

Even when the primary infection apparently has been controlled, the tubercle bacillus may not be completely eliminated from 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. The majority of patients will never have any further difficulty with development of 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

The majority of active tuberculosis cases involve reactivation of a previously dormant focus within the lungs.

becomes active. Such patients with active disease occurring at a time removed from the primary infection are said to have *reactivation tuberculosis*. For both primary and reactivation disease, the lungs are the most commonly affected site. However, with either type of disease, distant organ systems may be involved as a result of hematogenous spread during the primary phase of the infection. In addition, disseminated disease known as *miliary tuberculosis* may result from the hematogenous spread of the organisms.

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 of 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; about 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 defective cellular immunity due to advanced HIV infection.

DEFINITIONS

On the basis of our understanding of disease pathogenesis, a few additional terms are worth defining. 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 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 they 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. Several other terms are sometimes used to describe clinical disease on the basis of the presumed pathogenesis. 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. As a general rule, 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 not from reactivation of dormant tubercle bacilli but from new exposure to another source of organisms. This type of infection traditionally has been considered uncommon. It is believed that individuals with prior exposure to 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 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 a relatively nonspecific inflammatory response in the involved region of parenchyma. Regional lymph nodes often become involved by local spread of the organism, and 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 tubercle bacilli.

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 full-blown tuberculosis, 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. Interestingly, 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. As a result, patients with advanced HIV disease and 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 is capable of spread, 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 as a result of 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 high P_{O_2} and relatively less perfusion and, therefore, are believed to be 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.

Why chronic infection within the lung produces systemic manifestations is not entirely clear. However, as implied by the term "consumption," which was used so frequently in the past, tuberculosis is a disease in which systemic manifestations, such

as weight loss, wasting, 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 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 particular organ or region affected. With miliary tuberculosis, the disease is disseminated, and patients usually are systemically quite ill.

Common presenting problems with tuberculosis are:

1. Systemic symptoms: weight loss, fever, night sweats
2. Pulmonary symptoms: cough, sputum production, hemoptysis
3. Abnormal chest radiographic findings

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 health care, but it is frequently seen in the developing world. Findings on chest examination tend to be relatively insignificant, although sometimes evidence of crackles or rales over affected areas is observed. If a tuberculous pleural effusion is present, the physical findings characteristic of an effusion may be found.

DIAGNOSTIC APPROACH

One of the most commonly used diagnostic tools, the tuberculin skin test, 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 for 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.

As an alternative to skin testing, blood tests that detect latent tuberculosis involve incubating the patient's T cells with *M. tuberculosis* antigens. Cells from previously sensitized individuals release IFN-γ in response to the antigens, and the IFN-γ is detected by an enzyme-linked assay. Worldwide, tuberculin skin testing remains more commonly performed than IFN-γ assays. However, blood tests have the advantage of fewer patients lost to follow-up and lower labor costs by not requiring patients to return for an additional office visit for interpretation of the skin test. 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*.

Common features of the chest radiograph in primary tuberculosis are:
1. Nonspecific infiltrate (often lower lobe)
2. Hilar (and paratracheal) node enlargement
3. Pleural effusion

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.

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 actually 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.

Radiographic location of reactivation tuberculosis: most commonly apical and posterior segments of upper lobe(s), superior segment of lower lobe(s)

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. 24.1). 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 frequently it is difficult, if not impossible, to gauge activity solely on the basis of radiographic appearance.

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 possibly 6 weeks required for growth and final identification. Culture of the organism is important not only for confirmation of the diagnosis but also for testing sensitivity to antituberculous drugs, particularly in light of concerns about resistance to some

Figure 24.1. Chest radiograph of patient with reactivation tuberculosis. Note infiltrates with cavitation at both apices, which are more prominent on the right.

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, more recently, by molecular biologic techniques.

For even one 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 Po_2, depending on the amount of ventilation–perfusion mismatch that has resulted.

PRINCIPLES OF THERAPY

Effective chemotherapy is available for most 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 the majority of cases are curable with appropriate drug therapy. Recently, 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. Therapy for as few as 6 months with two very effective antituberculous agents, isoniazid and rifampin, supplemented during the first 2 months by a third agent, pyrazinamide, is commonly used in cases of pulmonary tuberculosis, with excellent results in patients with a normal immune system. However, because of concern for organisms resistant to one or more antituberculous agents, a fourth drug (ethambutol) is typically added at the initiation of therapy until drug sensitivity results become available. When resistance to one or more of the usual antituberculous agents is documented, the specific regimen and duration of therapy must be 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 generally considered no longer infectious after they have demonstrated a clinical response to antituberculous therapy and after 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 the drugs are given in a supervised outpatient setting, has become an important component of treatment for many cases of tuberculosis and is essential when there are concerns regarding patient adherence. Hepatotoxicity can occur with antituberculous medications, necessitating appropriate monitoring of patients during therapy.

Tuberculosis is the most common cause of death in HIV-positive patients, and treating patients with concomitant active tuberculosis and HIV/AIDS may present unique challenges. Such patients are at increased risk for drug interactions and for adverse reactions to antituberculous medications. In addition, immune reconstitution inflammatory syndrome can develop if combination antiretroviral therapy is started at the same time as treatment of tuberculosis. The intense inflammation that develops as the depleted immune system recovers and confronts the tuberculosis infection is

apparent clinically as transiently higher fever, malaise, weight loss, and worsening respiratory symptoms and may be difficult to clinically differentiate from 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 expensive and labor intensive, and it is most successful with a well-funded and effective public health system. Even in industrialized nations, this presents difficulties. In many parts of the world, this type of public health system is nonexistent.

Isoniazid alone for 9 months is indicated for selected patients with latent tuberculous infection (with a positive tuberculin skin test or interferon-γ release assay but no evidence of active disease).

In addition to multiple drug therapy administered for active tuberculosis, therapy is typically indicated for patients with latent tuberculous infection that is detected via tuberculin skin testing or IGRA. This generally consists of isoniazid alone (typically for 9 months), although other regimens are also acceptable. Such therapy substantially decreases the chances of active tuberculosis developing in these individuals, who are at particularly high risk.

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 9 months of treatment with isoniazid alone (or an alternative 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. It has been well demonstrated to be effective in achieving its goal of substantially decreasing the eventual risk for 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 bacille Calmette–Guérin (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 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), formerly called *Mycobacterium avium-intracellulare*. Other organisms include *M. kansasii, M. xenopi*, and *M. fortuitum*.

The nontuberculous mycobacteria are primarily responsible for disease in two settings: (1) the patient with underlying lung disease, in whom local host defense mechanisms presumably are impaired, and (2) the patient with a defect in systemic immunity, particularly AIDS (see Chapter 26). Nevertheless, these organisms cause disease in a small number of patients without either of these risk factors. Overall recognition of disease from nontuberculous mycobacteria has increased over the past 10 to 20 years, largely because of its occurrence in patients with AIDS.

Nontuberculous mycobacteria are most frequently pathogens in patients with underlying lung disease or AIDS.

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. Diagnosis of disease caused by these organisms is difficult. They can be found as laboratory contaminants, and in patients with other underlying lung diseases, the organisms can colonize the respiratory system without being responsible for invasive disease.

When these organisms cause disease, treatment typically involves multiple agents. The organisms are frequently resistant to some of the standard antimycobacterial drugs, so treatment regimens traditionally were complicated and often unsuccessful. Fortunately, the newer macrolide antibiotics (e.g., clarithromycin, azithromycin) are often effective as part of a multidrug oral regimen for many of the nontuberculous mycobacteria. 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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25

Miscellaneous Infections Caused by Fungi and *Pneumocystis*

FUNGAL INFECTIONS, 325
Histoplasmosis, 325
Coccidioidomycosis, 327
Blastomycosis, 328
Aspergillosis, 329
Cryptococcosis, 331
Other Fungi, 332
***PNEUMOCYSTIS* INFECTION, 332**

This chapter continues the discussion of infectious diseases involving the lungs and considers miscellaneous infections caused by fungi and *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-alpha 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 and for *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 immunodeficiency syndrome (AIDS) in Chapter 26. The less common fungi (e.g., *Mucor* and *Candida*) and protozoa (e.g., *Toxoplasma*) affecting the immunosuppressed host are not considered in detail here, but further information can be obtained from the references at the end of this chapter.

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,

Abstract

This chapter continues the discussion of infectious diseases involving the lungs, and considers miscellaneous infections caused by fungi and *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. For many other fungi and for *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* also is considered in this chapter.

Keywords

Lung diseases, fungal
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Pulmonary aspergillosis
Invasive pulmonary aspergillosis
Aspergillosis, allergic bronchopulmonary
Cryptococcosis
Pneumocystis infections
Pneumonia, *Pneumocystis*

Features of *Histoplasma capsulatum* are:
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

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 upon 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.

Histoplasma organisms flourish best in soil that has been contaminated by bird droppings. When the soil becomes dry or disrupted (e.g., with construction equipment), the infectious spores become airborne, are inhaled by humans, and eventually reach 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.

After an individual has been exposed and *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 cells (macrophages). Initially, the yeast may not be killed within the macrophage, so the organism commonly 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* generally develops, and the pathologic response becomes granulomatous in nature. Central areas of caseous necrosis often 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, there are alternatives to this benign pathologic course after exposure. In some cases, particularly in the immunosuppressed host or in the infant or young child, dissemination of the organism to other organs is not controlled by host defense mechanisms, and the patient is said to have *progressive disseminated histoplasmosis*. In other cases, particularly in patients with significant underlying airways 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* generally 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 have a variety of nonspecific symptoms that may include some combination of cough, fever, chills, chest pain, headache, malaise, myalgias, and weight loss. The chest radiograph may reveal one of several types of patterns, most commonly 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 may indicate 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 are:
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 originate 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.

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 particular type of infection. 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.

Features of *Coccidioides immitis* are:

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

Coccidioidomycosis

Like histoplasmosis, coccidioidomycosis also affects normal hosts, but its clinical consequences may be altered in special categories of patients, especially those with impairment of host defense mechanisms. 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*, which often contain multiple endospores within them.

Unlike *Histoplasma* organisms, the organisms of *Coccidioides* are limited to the western hemisphere, most classically 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 the nonspecific host defenses and reach the alveoli, leading to the development of primary disease. Pathologically, the inflammatory response to the organism is also a granulomatous one, once delayed hypersensitivity to *Coccidioides* has developed. The normal host generally has a relatively self-limited illness resulting from the primary infection. When dissemination occurs, it usually does so in specific groups of predisposed individuals: immunosuppressed patients, pregnant women, and for unclear reasons, certain ethnic

groups, particularly Filipinos, African Americans, and Native Americans. Chronic pulmonary coccidioidomycosis is found in some patients as a sequela to primary disease, perhaps related to underlying lung disease or immune impairment.

Clinical syndromes with coccidioidomycosis are:
1. Acute (primary) coccidioidomycosis
2. Disseminated coccidioidomycosis
3. Chronic pulmonary coccidioidomycosis

Primary infection with *C. immitis* may be subclinical and unassociated with symptoms, or it may produce respiratory tract symptoms or manifestations of hypersensitivity to the organism. When symptoms 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 frequently shows a pulmonary infiltrate, often with associated hilar adenopathy and sometimes with a pleural effusion.

The acute (primary) infection is usually self-limited, resolving 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, is often associated with an ominous prognosis. Certain ethnic groups are at high risk for this complication, 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. The specific uses and interpretation of skin testing and serologic techniques for diagnosis are discussed in the various more detailed references. 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 neutrophils; the subsequent response includes macrophages and T lymphocytes. 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, especially to form large skin lesions, but the frequency of dissemination is unknown.

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. Asymptomatic cases of blastomycosis have been reported, but their relative frequency compared with symptomatic cases is unknown. 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. An immunoassay for detecting *B. dermatitidis* antigens in urine has been developed, although the sensitivity and specificity of the test are not optimal. Serologic testing is not useful because of low sensitivity and specificity.

Blastomycosis is generally treated with itraconazole, but amphotericin B is employed for life-threatening disease. 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. However, 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 are:
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*, 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 pre-existing 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 are:
1. Allergic bronchopulmonary aspergillosis
2. Mycetoma (aspergilloma)
3. Invasive aspergillosis
4. Chronic necrotizing pulmonary aspergillosis

Allergic Bronchopulmonary Aspergillosis

The presence of underlying reactive airways disease—asthma—appears to be the important predisposing factor for development of allergic bronchopulmonary aspergillosis. In this condition, the organism resides in the patient's airways, where it appears to be important as a source of intense antigenic stimulation rather than as an infectious invasive fungus. 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 allergic bronchopulmonary aspergillosis have manifestations of moderate to severe 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 can be present, and these dilated airways may be filled with mucous casts.

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 allergic bronchopulmonary aspergillosis is aimed primarily at 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 seems to be associated with somewhat more favorable outcomes and is now considered standard treatment.

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. Tuberculosis, sarcoidosis, or 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. The fungus ball itself represents a mass of fungal mycelia lying within the cavity proper. 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. 25.1). When the patient

Figure 25.1. Posteroanterior radiograph **(A)** and tomogram **(B)** show aspergilloma in the left lung. The fungus ball appears as a mass sitting within a radiolucent thin-walled cavity. Arrows outline cavity wall. (Courtesy of Dr. Ferris Hall.)

changes position, the fungus ball often changes position within the cavity, owing to the effects of gravity.

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 is often unnecessary when the patient has no symptoms from the lesion. 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. Systemic administration of antifungal agents is not effective treatment of this syndrome, and direct instillation of amphotericin B into the cavity results only in limited success.

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 (insufficient numbers of polymorphonuclear leukocytes), 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 can occur, vessels can become occluded, and areas of infarction can develop.

Clinically, patients are extremely ill, with fever, cough, dyspnea, and often pleuritic chest pain. The chest radiograph may show localized or diffuse pulmonary infiltrates, reflecting either tissue invasion and a fungal pneumonia or pulmonary infarction secondary to vascular occlusion. Once vascular invasion occurs, embolic infectious foci may develop, including brain abscesses and endophthalmitis.

Diagnosis of invasive aspergillosis generally requires identification of the organism—for example, by methenamine silver staining on a BAL or biopsy specimen of lung tissue. A positive assay for the fungal cell wall constituents galactomannan or β-D-glucan supports the diagnosis, although many false positives and negatives occur. Treatment consists of voriconazole or amphotericin B, but the mortality rate is extremely high even with appropriate use of either agent.

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 due primarily 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, but in some normal individuals, as well as those with HIV/AIDS, malignancy, organ transplantation, or those under 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. Central nervous system or other severe 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

Features of *Pneumocystis jiroveci* are:

1. Ubiquitous distribution
2. Seen on methenamine silver stain rather than routine tissue and Gram stains
3. Tissue response is primarily exudation of foamy fluid into alveoli

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 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 in 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.

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 do not cause disease in normal hosts, only in individuals with significant impairment of host defenses, specifically 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 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 26.

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; instead, they require special stains, such as methenamine silver (Fig. 25.2). 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.

Clinically, *Pneumocystis* pneumonia usually manifests with dyspnea and fever in immunocompromised patients. Interestingly, 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 blossoms only as the steroid 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. 25.3). 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.

Clinical features of *Pneumocystis* pneumonia are:

1. Symptoms: 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

Figure 25.2. 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. (Courtesy of Dr. Earl Kasdon.)

Figure 25.3. 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.

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, although a positive β-D-glucan assay is observed in many patients.

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 children receiving chemotherapy for leukemia, low doses of the same agents are used prophylactically to prevent the infection.

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26

Pulmonary Complications in the Immunocompromised Host

ACQUIRED IMMUNODEFICIENCY SYNDROME, 338
- Etiology and Pathogenesis, 338
- Infectious Complications of Acquired Immunodeficiency Syndrome, 339
- Noninfectious Complications of Acquired Immunodeficiency Syndrome, 342
- Diagnostic Evaluation of Pulmonary Infiltrates in Acquired Immunodeficiency Syndrome, 344

PULMONARY COMPLICATIONS IN NON–HIV IMMUNOCOMPROMISED PATIENTS, 344
- Organ Transplant Recipients, 344
- Treatment of Inflammatory Conditions, 345
- Primary Immunodeficiencies, 346
- Diagnostic Evaluation of Pulmonary Infiltrates in Non–HIV Immunocompromised Patients, 346

During the last several decades, physicians have been faced with increasing numbers of patients who have impaired host defense mechanisms, particularly due to infection with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS). In addition, neutropenia (decreased polymorphonuclear neutrophils [PMNs]) or depressed cellular immunity occurs frequently as a result of either chemotherapy given for malignancy or immunosuppressive agents administered for inflammatory diseases or suppression of rejection following organ transplantation. This chapter is devoted to the spectrum of respiratory complications potentially associated with several of the more commonly encountered forms of immunodeficiency.

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,

Abstract

During the last several decades, physicians have been faced with increasing numbers of patients who have impaired host defense mechanisms, particularly due to infection with the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS). In addition, neutropenia (decreased polymorphonuclear leukocytes) or depressed cellular immunity occurs frequently as a result of either chemotherapy given for malignancy or immunosuppressive agents administered for inflammatory diseases or suppression of rejection following organ transplantation. This chapter is devoted to the spectrum of respiratory complications potentially associated with several of the more commonly encountered forms of immunodeficiency. 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.

Keywords

Acquired immunodeficiency syndrome
Sarcoma, Kaposi
Organ transplantation
Hematopoietic stem cell transplantation
Bone marrow transplantation

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 helper-inducer $CD4^+$ T lymphocytes and a reversal in the normal ratio of helper to 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. It has been estimated that there are nearly 1.1 million deaths worldwide per year from HIV/AIDS. In many parts of sub-Saharan Africa, HIV/AIDS is the leading cause of death.

During the past 35 years, 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 death rate in the United States declined 80% between 1990 and 2003. 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 challenge is at the worldwide level, primarily because of limited availability of therapeutic and prophylactic agents for the large number of affected individuals in developing nations.

In the United States, the largest category of individuals affected by AIDS is men who have sex with men, in whom the responsible virus is transmitted by sexual contact. Heterosexual transmission also occurs, and intravenous drug users may introduce the virus into their circulation via 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 have been the organ system most commonly affected.

Etiology and Pathogenesis

The etiologic agent responsible for AIDS is a retrovirus formerly called *human T cell lymphotropic virus type III* (HTLV-III), now called *HIV*. The virus appears to mediate its pathogenic effect by binding to the CD4 receptor on cells that carry this surface receptor. Although the most important cell type affected is the helper-inducer subset of T lymphocytes, 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. This loss of the helper-inducer cell population may be complicated by altered macrophage function, which probably is secondary to direct effects of the virus and impaired production of cytokines normally affecting macrophage activation and function.

HIV binds to the CD4 receptor of helper-inducer 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 also 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*). Certain types of bacterial pneumonia, primarily due to *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*, are also seen with increased frequency in AIDS. Whereas 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 are:
1. *Pneumocystis jiroveci* (formerly *carinii*)
2. Cytomegalovirus
3. 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 the cutoff below which patients are at 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 25. 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 commonly described as looking like "ground glass" (see Fig. 25.3). 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.

Diagnosis is generally based on finding the organism in respiratory secretions by any number of techniques, especially immunofluorescent staining with a monoclonal antibody. Patients with 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

Diagnosis of *Pneumocystis jiroveci* is made most commonly on samples obtained by induction of sputum or bronchoalveolar lavage.

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. More recently, elevated levels of serum β-d-glucan—a component of fungal cell walls including *Pneumocystis*—have been used as adjunctive evidence to indicate infection with *Pneumocystis*.

Treatment of severe pneumonia caused by *Pneumocystis* organisms usually involves one of the following regimens: the combination antimicrobial trimethoprim-sulfamethoxazole (which is preferred if tolerated), the combination of clindamycin and primaquine, the combination of trimethoprim and dapsone, or pentamidine as a single agent given intravenously. 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. However, patients with AIDS have a peculiar predisposition to allergic reactions to sulfonamides, causing a higher frequency of adverse side effects and making a switch to therapy with other drugs necessary in a relatively high proportion of patients. Other agents such as atovaquone have been used, especially in patients who do not respond to or cannot tolerate one of the more standard agents or have less severe disease.

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 helpful in averting 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, and 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) can be used with reasonable effectiveness 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. Unfortunately, the propensity for development of allergic reactions to trimethoprim-sulfamethoxazole frequently makes this regimen difficult to use in patients with AIDS, so many patients are maintained on one of the other forms of prophylaxis. 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 has emerged as an important respiratory pathogen in patients with AIDS, not only because it is common but also because it is potentially treatable. Clinical disease may result from primary infection, reactivation of previous infection, or exogenous reinfection. Rather than occurring in all categories of AIDS patients, 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 AIDS. In this setting, its clinical presentation is similar to that seen in the typical patient with tuberculosis who does not have AIDS. However, it also may occur in AIDS patients who are in a late 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. Interestingly, 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 AIDS.

Treatment considerations for tuberculosis in AIDS patients are generally 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. Patients with HIV infection who have positive tuberculin skin test reactions (defined as 5 mm or more of induration) but no evidence of active disease should receive 9 months of treatment with isoniazid (or an alternative regimen), similar to the treatment of latent tuberculosis infection in individuals without HIV infection.

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. Because the risk of MAC infection is associated with extremely low $CD4^+$ counts, prophylactic treatment against MAC, typically with a newer macrolide antibiotic such as azithromycin or clarithromycin, is indicated when the $CD4^+$ count falls below $50/mm^3$.

Other Bacterial Infection

Patients with AIDS appear to 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. Intravenous drug users appear to be at particularly high risk.

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 helper-inducer cells results in alteration of the normal interaction between helper-inducer 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.

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 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*, which more commonly causes meningitis 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. The lung may be the only organ involved, or involvement may be accompanied by meningitis or disseminated disease. Treatment traditionally has been with amphotericin B, but fluconazole has been used as an alternative agent.

Histoplasmosis and coccidioidomycosis, fungal infections that occur in specific endemic regions, are described in detail in Chapter 25. 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 from progressive primary infection. Consequently, histoplasmosis and coccidioidomycosis are seen primarily but not exclusively in their respective endemic areas. 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). A brief discussion of each of these potential complications follows.

Neoplastic Disease

Kaposi sarcoma is one of the most common of the neoplastic diseases affecting AIDS patients. In patients without AIDS, typically elderly men, it is characterized by slowly progressive cutaneous lesions of the lower extremities. It was formerly a rare diagnosis in the United States and was seen in a more aggressive form with frequent visceral involvement in certain parts of Africa. In the early descriptions of AIDS patients in 1981, Kaposi sarcoma was one of the peculiar clinical manifestations accompanying the profound cellular immunodeficiency. Since then, Kaposi sarcoma has been recognized as one of the common manifestations, occurring generally with skin involvement but often complicated by dissemination to the lungs and other organ systems. Data from a variety of studies, including identification of herpesvirus-like DNA sequences in patients with Kaposi sarcoma (either with or without AIDS) but not in control subjects, indicate that human herpesvirus 8 is the causative agent responsible for Kaposi sarcoma.

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 slitlike 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, since 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.

Although therapy for Kaposi sarcoma involving the lungs remains palliative rather than curative, treatment options have improved greatly in recent years. 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. Patients may have progressive respiratory involvement, often complicated by pulmonary hemorrhage. Although patients may die of disseminated Kaposi sarcoma, they frequently succumb to coexisting opportunistic infections rather than the neoplasm.

Another common neoplasm associated with AIDS is non-Hodgkin lymphoma. Although extranodal involvement and disseminated disease are common when this malignancy occurs in AIDS patients, intrathoracic involvement is uncommon. Lung cancer also appears to occur with increased frequency in AIDS patients. In contrast to Kaposi sarcoma, antiretroviral therapy does not appear to significantly diminish the incidence of non-Hodgkin lymphoma or lung cancer.

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 AIDS but is found infrequently in adults. When treatment is necessary, corticosteroids are used with variable success.

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

A number of cases of pulmonary arterial hypertension (PAH) in patients with HIV infection have been reported. Although the association is believed to be a true rather than a coincidental relationship, the exact pathophysiologic explanation is not known. One hypothesis holds that circulating monocytes infected with HIV abnormally release cytokines that impact microvascular architecture as they traverse the pulmonary capillaries. The histopathology and clinical features are typically similar to those of idiopathic pulmonary arterial hypertension (IPAH), but the disease may have a more rapid progression than is generally seen in patients without HIV infection. Treatment is similar to that of IPAH (see Chapter 14), but use of endothelin-1 receptor antagonists is frequently problematic because of concomitant hepatic disease or concerns about drug interactions. Antiretroviral therapy is generally indicated as part of the therapeutic approach.

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 of some of the aforementioned diseases 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 are being 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 they have a CD4 count less than 200/mm^3 and are not receiving adequate prophylaxis. 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 often the next procedure performed, usually with BAL and sometimes with transbronchial biopsy. Elevated serum β-d-glucan levels support the diagnosis of *Pneumocystis*. The diagnosis of Kaposi sarcoma is strongly suspected if typical lesions are observed in the airways. 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. 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 29). In addition to the effects of immunosuppressive medications, the immunologic milieu in the transplanted lung is quite abnormal, leading to an increased risk of pulmonary infections of a variety of types. 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 post transplant, 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, metapneumovirus), or other common respiratory pathogens.

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 as a result of repeated infections (see Chapter 7), and 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 increased susceptibility to pulmonary infections due to *S. aureus*, *H. influenzae*, *Aspergillus*, and *Pseudomonas* via a mechanism that remains incompletely characterized.

Diagnostic Evaluation of Pulmonary Infiltrates in Non–HIV Immunocompromised Patients

The approach to the non-HIV immunocompromised patient with pulmonary infiltrates revolves around the attempt to identify an infectious agent or noninfectious etiology. Traditional methods have included examination of sputum and specimens obtained by bronchoscopy or thoracoscopic lung biopsy. There has been great interest in the use of newer, more rapid, more sensitive techniques for identifying a variety of opportunistic pathogens. Improved methods of culture, molecular probes, and nucleic acid amplification technology are being investigated and increasingly used clinically in the diagnosis of specific opportunists. The particular 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 26.1. Although fungi and other

Table 26.1

CAUSES OF PULMONARY INFILTRATES IN THE IMMUNOCOMPROMISED HOST

INFECTIONS

Bacteria

Gram-positive cocci, especially *Staphylococcus*
Gram-negative bacilli
Mycobacterium tuberculosis
Nontuberculous mycobacteria
Nocardia

Viruses

Cytomegalovirus
Herpesvirus

Fungi

Aspergillus
Cryptococcus
Candida
Mucor
Pneumocystis jiroveci

Protozoa

Toxoplasma gondii (rare)

PULMONARY EFFECTS OF THERAPY

Chemotherapeutic agents
Radiation therapy

PULMONARY HEMORRHAGE

HEART FAILURE

DISSEMINATED MALIGNANCY

NONSPECIFIC INTERSTITIAL PNEUMONITIS (NO DEFINED ETIOLOGY)

relatively unusual types of organisms are commonly thought to be the major causes of infiltrates in patients receiving treatment for malignancy, bacterial pneumonia is still the most frequent problem in this setting. Neutropenia is the primary predisposing factor for bacterial pneumonias, which frequently are due to gram-negative rods or *Staphylococcus*.

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, seems to be most 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 agents (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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27

Classification and Pathophysiologic Aspects of Respiratory Failure

DEFINITION OF RESPIRATORY FAILURE, 351
CLASSIFICATION OF ACUTE RESPIRATORY FAILURE, 351
Hypoxemic Type, 351
Hypercapnic/Hypoxemic Type, 352
PRESENTATION OF GAS EXCHANGE FAILURE, 352
PATHOGENESIS OF GAS EXCHANGE ABNORMALITIES, 353
Hypoxemic Respiratory Failure, 353
Hypercapnic/Hypoxemic Respiratory Failure, 353
CLINICAL AND THERAPEUTIC ASPECTS OF HYPERCAPNIC/HYPOXEMIC RESPIRATORY FAILURE, 354

Many types of respiratory disease are capable of impairing 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 an intercurrent illness or from transient worsening of their underlying disease. On the other hand, respiratory failure, generally acute or subacute in onset, 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 complicated by major respiratory problems.

Abstract

Chapter 27 addresses acute and chronic respiratory failure. Respiratory failure is defined as a clinical state in which the respiratory system is not functioning adequately to keep gas exchange (i.e. blood gas values) at an acceptable level. The chapter discusses two types of respiratory failure: hypoxemic and hypercapnic respiratory failure. Because hypercapnia is often accompanied by hypoxemia, the term hypercapnic/hypoxemic respiratory failure is often used. Common causes of hypoxemic respiratory failure include severe pneumonia and acute respiratory distress syndrome (ARDS). Common causes of hypercapnic/hypoxemic respiratory failure include central nervous system depression, diseases of the respiratory muscles, and chronic obstructive pulmonary disease (COPD). Clinical findings in patients with respiratory failure typically include dyspnea, impaired mental status, cyanosis, and headache.

Keywords

Respiratory failure
Hypercapnia
Hypoxemia
Gas exchange

This chapter presents an overview of the problem of respiratory failure and discusses the different pathophysiologic types and consequences of respiratory insufficiency. Chapter 28 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 29 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 even 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 $P_{O_2} < 60$ mm Hg or $P_{CO_2} > 50$ 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. The patient's P_{CO_2} is normal or even 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 *acute respiratory distress syndrome* (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 28 focuses entirely on the problem of ARDS.

Categories of acute respiratory failure are:
1. Hypoxemic (with normal or low P_{CO_2})
2. Hypercapnic/hypoxemic

Examples of hypoxemic respiratory failure are:
1. Severe pneumonia
2. ARDS

[1]The abbreviation *ARDS* was formerly used for *adult respiratory distress syndrome*, but *acute* has now replaced *adult* because the entity can occur in children as well.

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 fact, many cases of hypercapnic respiratory failure have marked ventilation-perfusion mismatch as well, which further accentuates the hypoxemia. With these concepts in mind, it is clear that the hypercapnic form of respiratory failure generally involves not just hypercapnia; it may be more appropriately considered the hypercapnic/hypoxemic form of respiratory failure.

Causes of hypercapnic/hypoxemic respiratory failure are:
1. Depression of central nervous system ventilatory control
2. Disease of the respiratory bellows
3. COPD

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 are present, compounding the potential for respiratory insufficiency.

In the hypercapnic/hypoxemic form of respiratory failure, patients often have preexisting disease that is responsible for either chronic respiratory insufficiency or limitations in respiratory reserve sufficient to make patients much more susceptible to decompensation with an acute superimposed problem. This form of respiratory failure is called *acute-on-chronic respiratory failure*, obviously 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)

Impairment of mental abilities is a frequent result 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 frank 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 pressure at the back of the eye. 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 lips. 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.

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 28). 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} significantly for truly shunted blood (see Chapter 1). Therefore, when the shunt fraction of cardiac output is quite high, oxygenation may be helped surprisingly little by administration 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. 27.1, which also lists some of the disorders that can interfere at each level. Not only is the total ventilation per minute important, the "effectiveness" of the ventilation for CO_2 excretion—that is, the relative amount of alveolar versus dead space ventilation—is also important to ensure proper utilization of inspired gas. 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 27.1. 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

Frequent precipitants of acute-on-chronic respiratory failure are:
1. Respiratory infection
2. Drugs (e.g., sedatives, narcotics)
3. Heart failure
4. Less common: pulmonary emboli, exposure to environmental pollutants

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 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.

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 but not always caused by a virus. Bacterial causes must always be investigated, however, because often they are amenable to specific 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 29). 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., > 60 mm Hg and >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 as a result of 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 followed by appropriate positioning to assist gravity in drainage of secretions, 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 29.) It is important to emphasize here that the primary decision is whether chronic ventilatory support should be given 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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28

Acute Respiratory Distress Syndrome

PHYSIOLOGY OF FLUID MOVEMENT IN ALVEOLAR INTERSTITIUM, 358
Two Mechanisms of Fluid Accumulation, 359
ETIOLOGY, 360
Inhaled Injurious Agents, 360
Injury via Pulmonary Circulation, 362
PATHOGENESIS, 362
PATHOLOGY, 363
PATHOPHYSIOLOGY, 364
Effects on Gas Exchange, 364
Changes in Pulmonary Vasculature, 365
Effects on Mechanical Properties of the Lungs, 365
CLINICAL FEATURES, 365
DIAGNOSTIC APPROACH, 366
TREATMENT, 367

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 used to describe it. ARDS represents a major form of 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 due exclusively to cardiogenic or hydrostatic causes. The full criteria for establishing the diagnosis of ARDS are shown in Table 28.1. This chapter describes in detail each of these criteria and the associated pathology and pathophysiology.

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 upon 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 any alteration in this process is 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

Abstract

Chapter 28 addresses the acute respiratory distress syndrome (ARDS). ARDS is characterized by increased permeability of the pulmonary capillary endothelial and alveolar epithelial barriers, which allows both protein and fluid to move from the pulmonary capillaries into the alveolar space, resulting in a high-protein pulmonary edema. Many disorders may trigger the development of ARDS. The injury may be direct to the lung, as in aspiration, or due to remote inflammation that involves the lungs via the pulmonary circulation. The typical clinical presentation in early ARDS includes hypoxemia and hypocapnia. The lungs become less compliant, but the distribution of injury is not uniform, with some areas relatively spared and other areas severely involved. Treatment is focused on the underlying trigger for ARDS and on supporting the patient with mechanical ventilation.

Keywords

Acute respiratory distress syndrome
ARDS
Noncardiogenic pulmonary edema
Diffuse alveolar damage
Exudative phase
Fibroproliferative phase

Table 28.1

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* $200 < PaO_2/FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H_2O	*Moderate ARDS* $100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cm H_2O	*Severe ARDS* $PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5 cm H_2O

ARDS, Acute respiratory distress syndrome.

of disorders can produce this syndrome. The following is a discussion of the pathologic, pathophysiologic, and clinical consequences. The chapter concludes with a general approach to treatment. More specific details about support of gas exchange are provided in Chapter 29.

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 leakage 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. 28.1) consists of (1) small vessels coursing through the alveolar walls, which for simplicity 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.

Movement of fluid out of the pulmonary capillaries and into the interstitial space is determined by a number of factors, including 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. 28.1:

$$F = K[(P_c - P_{is}) - \sigma(COP_c - COP_{is})]$$

Fluid normally moves from the pulmonary capillaries to the interstitial space. Resorption by lymphatics prevents accumulation.

where F is the fluid movement; P_c and P_{is} the pulmonary capillary and interstitial hydrostatic pressure, respectively; COP_c and COP_{is} the pulmonary capillary and interstitial colloid osmotic (oncotic) pressure, respectively; K the filtration coefficient; and σ the reflection coefficient (measure of permeability of endothelium for protein).

If estimates of the actual numbers are substituted for normal hydrostatic and oncotic pressures in Eq. 28.1, F is a positive number, indicating that fluid normally moves out

Figure 28.1. 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.

Table 28.2

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

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. The lymphatic vessels are quite 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 28.2). The first occurs

when hydrostatic pressure within the pulmonary capillaries (P_c) is increased, generally as a consequence of elevated left ventricular or 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.

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. 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 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 lower pressures. At the extreme, some patients with a permeability defect of the pulmonary capillary bed simultaneously have a grossly elevated pulmonary capillary pressure as a result of 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 28.3). 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.

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 is capable of drawing 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

Table 28.3

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
Ammonia
Phosgene
Bilateral pneumonia
Viral
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)*

ARDS, Acute respiratory distress syndrome.
*Generally not a primary cause of acute respiratory distress syndrome but a potential secondary contributor to alveolar damage (see Chapter 29).

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 inhaled in smoke. A high concentration of inhaled oxygen, particularly when given for prolonged periods, contributes 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 29 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 the most common underlying clinical problem associated with development of ARDS. Another important cause of ARDS is viral pneumonia, which has the capability of damaging parenchymal cells and altering alveolar-capillary permeability. After recognition of AIDS and with the large number of affected patients in the 1980s, pneumonia due to *Pneumocystis jiroveci* became a common cause of ARDS. However, with the advent of antiretroviral therapy 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) also capable of causing 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 they certainly have been associated with development of ARDS.

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 have been described as occasionally causing 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

The initial injury in ARDS affects alveolar epithelial (type I) cells, capillary endothelial cells, or both.

How do these diverse clinical problems all result in the syndrome of increased pulmonary capillary permeability in ARDS? One important factor appears to be the ability to produce 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.

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 antiinflammatory 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 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

Pathologic features of ARDS are:

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

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*.

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 the 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, may be 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 a permeability problem, 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. This 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 particularly important 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.

Pathophysiologic features of ARDS are:

1. Shunt and $\dot{V}/\dot{Q}$ mismatch
2. Secondary alterations in function of surfactant
3. Increased pulmonary vascular resistance
4. Decreased pulmonary compliance
5. Decreased FRC

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 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 ever 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.

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, four specific proteins, and carbohydrates responsible for decreasing surface tension and maintaining alveolar patency. When surfactant is absent, as is seen in the respiratory distress syndrome of neonates, there is extensive collapse of alveoli. In ARDS, surfactant production may be adversely affected by injury to alveolar type II epithelial cells. In addition, evidence suggests that as a result of extensive fluid within the alveoli, surfactant is inactivated and therefore ineffective 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 Po_2, supplemental O_2 alone may not restore oxygenation to normal. In practice, Po_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 whatever component of hypoxemia 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 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 is able to increase total ventilation to compensate for the regions of maldistribution.

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 certainly 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 tomographic scanning has demonstrated the distribution of disease to be more heterogeneous than expected based on the diffuse changes seen on chest radiograph. Whereas some regions have been damaged and are quite abnormal, others appear to have been spared from injury. As a result, the alveoli are not diffusely and relatively homogeneously stiffened. Rather, some regions of the lungs have significantly diseased alveoli that 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 not only the presence of noncardiogenic pulmonary edema but also the presence

Clinical features of ARDS are:
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

of 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.

After the initial insult, whatever it may be, there is generally a lag of several hours to a day or more before respiratory consequences ensue. In most cases, the first symptom experienced by the patient is dyspnea. As this develops, 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. If the process progresses and the case becomes severe, alveolar ventilation cannot be maintained, and P_{CO_2} rises.

As fluid and protein continue to leak from the vasculature into the interstitial and alveolar spaces, clinical findings become even more florid. Patients may become extremely dyspneic and tachypneic, and rales may be heard on chest auscultation. Chest radiographic findings become highly abnormal, revealing interstitial and alveolar edema that can be extensive. The radiographic aspects of ARDS are discussed under Diagnostic Approach.

Our improved ability over the past 40 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 and never achieved general clinical acceptance.

The chest radiograph in patients with incipient ARDS does not necessarily 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 AaD_{O_2} clearly shows that gas exchange is actually worse than it may appear at first glance, with alveolar P_{O_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, P_{O_2} may be relatively unresponsive to administration of supplemental O_2. As a standardized method for interpreting P_{O_2} in patients receiving different amounts of supplemental oxygen, a ratio of Pa_{O_2} to fractional concentration of inspired oxygen (Pa_{O_2}/Fi_{O_2}) is used to

define the three categories 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 28.1).

In many cases of ARDS, direct measurement of pressures within the central circulation is useful. This measurement is facilitated by use of either a central venous catheter (a catheter inserted into a systemic vein and then advanced to the superior vena cava) or a pulmonary artery catheter, which is advanced further and passed through the right atrium and right ventricle into the pulmonary artery. The relatively easy passage of the pulmonary artery catheter (commonly known as a *Swan-Ganz catheter*) results from a balloon at the tip, which can be inflated with air and then carried along with blood flow through the tricuspid and pulmonic valves into the pulmonary artery. The catheter is positioned at a point in the pulmonary artery where inflation of the balloon occludes the lumen and prevents forward flow. Consequently, if pressure is measured at the tip of the catheter when forward flow has been prevented, a static column of blood is created between the catheter and the left atrium, with the measured pressure theoretically reflecting pressure in the left atrium, which in turn corresponds to left ventricular preload. The pressure measured with the balloon inflated is commonly called the *pulmonary artery occlusion pressure* (PAOP) or *pulmonary capillary wedge pressure*. In recent years, central venous catheters are used more commonly than pulmonary artery catheters because they can be placed more quickly and easily, have fewer complications, and have been shown in large trials to produce similar patient outcomes to pulmonary artery catheters by using measurements of central venous pressure as a surrogate marker for left ventricular preload (see Chapter 12, section on Pulmonary Vascular Resistance).

Measurements from a central venous or pulmonary artery (Swan-Ganz) catheter can estimate left ventricular preload.

These measurements 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 "back-pressure" from the pulmonary veins and left atrium. In noncardiogenic pulmonary edema or ARDS, the central venous pressure and the pressure within the left atrium (measured as the PAOP) are 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 these catheters for measurement of intravascular pressures is not essential to the diagnosis of ARDS, the information obtained may be useful for determining whether elevated hydrostatic pressures within the capillaries are contributing to the observed pulmonary edema. In addition, the catheters may provide helpful information during the course of the complicated management of these cases, even though their use has not been unequivocally demonstrated to improve mortality.

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 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 and avoidance of hypervolemia, is critical for patients with ARDS to survive the acute illness. Given the life-threatening nature of ARDS, patients typically are 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 29 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 a 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 (facedown) position improves gas exchange and appears 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 references 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 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 are delivered), inhaled nitric oxide or epoprostenol can facilitate better perfusion of well-ventilated areas, leading to better ventilation-perfusion matching and improved oxygenation. Unfortunately, however, beneficial physiologic effects on gas exchange have not been accompanied by documentation of improved survival in clinical trials conducted to date.

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29

Management of Respiratory Failure

GOALS AND PRINCIPLES UNDERLYING SUPPORTIVE THERAPY, 371
- Hypoxemic Respiratory Failure, 371
- Hypercapnic Respiratory Failure, 372
- Reducing Work of Breathing, 373

MECHANICAL VENTILATION, 373
- Pressure-Limited Ventilation, 373
- Volume-Cycled Ventilation, 374
- Positive End-Expiratory Pressure (PEEP), 376
- Other Ventilatory Strategies, 376
- Discontinuation of Ventilatory Support, 377
- Noninvasive Ventilatory Support for Acute Respiratory Failure, 377
- Complications of Intubation and Mechanical Ventilation, 377

SELECTED ASPECTS OF THERAPY FOR CHRONIC RESPIRATORY FAILURE, 380
- Chronic Ventilatory Support, 380
- Lung Transplantation, 380

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 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.

Abstract

Chapter 29 describes the management of the two broad classes of respiratory failure – hypoxemic respiratory failure and hypercapnic respiratory failure. The goals of each are described in terms of the principles of support and the desired targets for gas exchange. The available types of mechanical ventilation are presented, focusing on pressure support ventilation and pressure-controlled ventilation as the major modes of pressure-limited ventilation, and assist-control ventilation and synchronized intermittent mandatory ventilation as the major modes of volume-cycled ventilation. Positive end-expiratory pressure is explained as a technique to avoid alveolar closure during expiration, increase functional residual capacity, reduce the amount of shunting, and improve oxygenation. When ventilated patients are sufficiently stable, a daily trial of spontaneous breathing is used to assess the patient's ability to be maintained off ventilatory support. The technique of noninvasive ventilation as an alternative to intubation and ventilation through an endotracheal tube is described, along with the clinical scenarios where it may be most applicable. Complications associated with intubation, with endotracheal or tracheostomy tubes, and with use of a mechanical ventilator are described as the major categories of complications associated with intubation and mechanical ventilation. Options for chronic ventilatory support in the home setting are presented, focusing primarily on home noninvasive ventilation. In selected patients with severe lung disease of various etiologies, lung transplantation may be an option, although it does replace the underlying disease with the potential complications of infection and rejection following transplantation.

Keywords

Mechanical ventilation
Pressure support ventilation
Synchronized intermittent mandatory ventilation
Weaning from ventilatory support
Complications of mechanical ventilation
Noninvasive mechanical ventilation
Home mechanical ventilation
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 are:

1. Arterial O_2 saturation > 90% (i.e., P_{O_2} > 60 mm Hg)
2. Acceptable hemoglobin level (e.g., >10 g/dL, corresponding to hematocrit > 30%)
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.

Similarly, when cardiac output is impaired, tissue O_2 delivery also decreases, and measures to augment cardiac output may improve overall O_2 transport. Unfortunately, some of the measures used to improve arterial P_{O_2} 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}. Use of positive-pressure ventilation, particularly with positive end-expiratory pressure (PEEP), may produce such changes in some patients. 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}, 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 normal (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.

Hypoxemic Respiratory Failure

In the patient with hypoxemic respiratory failure such as ARDS, ventilation-perfusion mismatch and shunting are responsible for hypoxemia. When a large fraction of the cardiac output is being shunted through areas of unventilated lung and 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 an inordinately high work of breathing, resulting from noncompliant lungs that are filled with fluid. Although oxygenation is extremely difficult to support, CO_2 retention is much less frequent, and hypoxemia rather than hypercapnia is the primary indication for mechanical ventilation.

For patients with 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 (generally in the fractional concentration of inspired oxygen [F_{iO_2}] range of 40% to 80%) 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

Mechanical ventilation is often indicated when P_{O_2} ≥ 60 mm Hg cannot be achieved with inspired O_2 concentration ≤40% to 80%.

Beneficial effects of ventilatory assistance in acute respiratory distress syndrome (ARDS) are:
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)

PEEP is effective in ARDS by increasing functional residual capacity (FRC), preventing closure of small airways and alveoli, and decreasing the shunt fraction.

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.

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 Reducing Work of Breathing), allowing the patient to receive more reliable tidal volumes than he or she 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 respiratory cycle and not just during the inspiratory phase. 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.

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.

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 then can be lowered, and the patient is less likely to experience O_2 toxicity from extremely 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 are now 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 can often be averted.

Mechanical ventilation for patients with hypercapnic respiratory failure is often 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 to 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 neuromuscular disease in either the purely acute or the acute-on-chronic setting, respiratory muscle strength may be insufficient to handle even a relatively normal work of breathing. In the patient with ARDS, the noncompliant (i.e., 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 not only for temporary support of gas exchange but also 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 are allowed 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 ventilation for as long a period as necessary, mechanical ventilators can keep a patient alive while the acute process precipitating respiratory failure is treated or allowed to resolve spontaneously. This section briefly describes the operation of mechanical ventilators, the available modes of ventilation, and the complications that can ensue from their use.

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 upon 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 level of support is provided by the ventilator. PSV may be the most comfortable form of mechanical ventilation in a conscious patient because he or she has 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 is typically 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 minimize the risk of complications from high pressure delivered by the ventilator.

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.

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.

Several ventilatory patterns or modes are available with most mechanical ventilators when used in a volume-cycled fashion (Fig. 29.1). In *controlled ventilation*, ventilation is supplied entirely by the ventilator at a respiratory rate, tidal volume, 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 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.

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 this mode of ventilation 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 is able to breathe spontaneously from a gas source providing the same inspired O_2

Figure 29.1. 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.

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 frequently 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 application of positive pressure during expiration, which functions to keep small airways open and avoid atelectasis. 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 specifications 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 a mechanical ventilator) 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 and overdistention and injury of some alveolar units.

Another important strategy that is used in patients with severe ARDS involves periods of time with the patient in a *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 the 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 is 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 to 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 and superior strategy 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 the 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 29.1). An alternative form of support for acute respiratory failure does not require use of an endotracheal tube; rather, positive pressure is provided typically through a tightly fitting mask placed over the face but, in some clinical situations, can alternatively be provided with nasal "pillows" or with a mouthpiece. 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. However, noninvasive ventilatory support is not appropriate if a patient is unable to protect his or her airway; it is most useful when respiratory failure most likely is readily reversible and therefore of relatively short duration.

Complications of Intubation and Mechanical Ventilation

Intubation and mechanical ventilation of patients in respiratory failure are associated with potential risks and complications (see Table 29.1). The procedure of intubation can be complicated acutely by problems such as arrhythmias, laryngospasm, and

Table 29.1

COMPLICATIONS OF INTUBATION AND MECHANICAL VENTILATION

ASSOCIATED WITH INTUBATION
Malposition of tube
Tube in esophagus
Tube in mainstem bronchus (usually right mainstem bronchus)
Arrhythmias
Hypoxemia
Laryngospasm
ASSOCIATED WITH ENDOTRACHEAL OR TRACHEOSTOMY TUBES
Vocal cord ulcers
Laryngeal stenosis/granulomas
Tracheal stenosis
Nasal necrosis
Sinusitis/otitis media (with nasotracheal tubes)
Occlusion or kinking of tube
Infection (ventilator-associated pneumonia)
ASSOCIATED WITH MECHANICAL VENTILATION
Barotrauma (volutrauma)
Pneumothorax
Pneumomediastinum
Subcutaneous emphysema
Biotrauma (alveolar injury related to overdistention and cytokine release)
Atelectrauma (associated with cyclic alveolar opening and closing)
Decreased cardiac output (hypotension)
Alveolar hypoventilation or hyperventilation

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 and prevention of further vocal cord 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, 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*—traumatic changes such as pneumothorax or pneumomediastinum occurring 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 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.

Concern has been raised that the excessive volumes and high levels of pressure provided to the alveoli may be injurious to alveolar structures. Because lung injury in ARDS is often heterogeneously distributed (see Chapter 28), 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*.

Both alveolar overdistention and atelectrauma may be 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 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 is being used. 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 mL/kg and alveolar distending pressure to no more than 30 cm H_2O. Of note, the use of a low tidal volume ventilation 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 ventilation 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. 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 not only for proper support of vital functions but also for minimizing the complications of therapy.

SELECTED ASPECTS OF THERAPY FOR CHRONIC RESPIRATORY FAILURE

Chronic Ventilatory Support

Patients with chronic irreversible respiratory or neuromuscular disease who require continuous long-term ventilatory support pose a difficult problem. 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 health care 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. 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). Alternatively, 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 1930s through the polio epidemics of the 1950s. Although nocturnal NIPPV is now the standard rather than negative-pressure ventilation in patients requiring nocturnal ventilator support, rare patients who have successfully used negative-pressure devices continue to use them. The two most common types 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. These negative-pressure ventilatory support devices were used in the past, most frequently for patients with chronic respiratory failure resulting from neuromuscular disease such as muscular dystrophy.

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 α_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: 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, either 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 other 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.*

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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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% (F_{IO_2} = 0.4)

The following measurements are made:

Arterial P_{CO_2} (P_{aCO_2}) = 40 mm Hg
Mixed expired P_{CO_2} (P_{ECO_2}) = 30 mm Hg
Arterial P_{O_2} (P_{aO_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 P_{aCO_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 P_{aCO_2} on the new settings?
   c. What would you expect P_{ECO_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 (AaD_{O_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 AaD_{O_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 AaD_{O_2}?

ANSWERS

1. $\dot{V}_E$ = 1000 mL/breath × 10 breaths/min = 10,000 mL/min = <u>10 L/min</u>
   V_D/V_T = (40 mm Hg − 30 mm Hg)/40 mm Hg = <u>0.25</u>
   $V_A = V_T - V_D$ = 1000 mL − (0.25 × V_T) = 1000 mL − 250 mL = <u>750 mL</u>
   $\dot{V}_A = V_A \times f$ = 750 mL/breath × 10 breaths/min = <u>7.5 L/min</u>

2. New V_D = 250 mL + 250 mL = 500 mL
   New V_D/V_T = 500 mL/1000 mL = <u>0.5</u>

3. Because P_{aCO_2} is inversely proportional to $\dot{V}_A$, the new P_{aCO_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 P_{aCO_2} = 3/2 × old P_{aCO_2} = 3/2 × 40 mm Hg = <u>60 mm Hg</u>

4. On the basis of the new settings:
   a. $\dot{V}_E$ = 500 mL/breath × 20 breaths/min = <u>10 L/min</u>
      V_A = 500 mL − 250 mL = <u>250 mL</u>
      $\dot{V}_A$ = 250 mL/breath × 20 breaths/min = <u>5 L/min</u>
      V_D/V_T = 250 mL/500 mL = <u>0.5</u>
   b. New P_{aCO_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 P_{aCO_2} = 3/2 × old P_{aCO_2} = 3/2 × 40 mm Hg = <u>60 mm Hg</u>
   c. Because $V_D/V_T = (P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$, substitute the known values and solve the equation for P_{ECO_2}.
      0.5 = (60 mm Hg − P_{ECO_2})/60 mm Hg
      P_{ECO_2} = <u>30 mm Hg</u>

5. P_{AO_2} = (0.4 × 713 mm Hg) − (40 mm Hg/0.8) = 285 mm Hg − 50 mm Hg = 235 mm Hg
   $AaD_{O_2} = P_{AO_2} - P_{aO_2}$ = 235 mm Hg − 95 mm Hg = <u>140 mm Hg</u>

6. P_{AO_2} = 150 mm Hg − (40 mm Hg/0.8) = 100 mm Hg
   AaD_{O_2} = 100 mm Hg − 75 mm Hg = <u>25 mm Hg</u>

7. P_{AO_2} = 150 mm Hg − (20 mm Hg/0.8) = 125 mm Hg
   AaD_{O_2} = 125 mm Hg − 80 mm Hg = <u>45 mm Hg</u>

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 of 12% or more and at least 200 mL in either the FEV_1 or the FVC. Patients with asthma characteristically fulfill 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. 3.20).
   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. Make sure 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 32 years of age	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 × 100 (%)	46	30	153
D_{LCO} (mL/min/mm Hg)	6.5	11.4	57

Flow-volume curve

2. Male 60 years of age	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 × 100 (%)	53	34	156
D_{LCO} (mL/min/mm Hg)	6.8	24.5	28

Flow-volume curve

3. Female 55 years of age	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 × 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).

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.

Alternatively, one can use other guidelines relating P_{CO_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 P_{CO_2} and pH become less accurate at the extremes of P_{CO_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 to 7.44) indicates normal acid-base status or a mixed disturbance (of two balancing problems).

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} 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 P_{CO_2} Chronic: HCO_3^- falls 5 mEq/L for each 10–mm Hg decrease in P_{CO_2}

Modified from Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore)*. 1980;59:161–187. © by Williams & Wilkins, 1980.

2. Look at P_{CO_2}. A high P_{CO_2} (>44) indicates that a *respiratory acidosis* is present. A low P_{CO_2} (<36) indicates that a *respiratory alkalosis* is present. If the pH value moves in the appropriate direction for the P_{CO_2} change (i.e., ↓ pH with ↑ P_{CO_2}; ↑ pH with ↓ P_{CO_2}), the respiratory disorder is the primary disturbance. If the pH value does not move in the appropriate direction for the P_{CO_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 P_{CO_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 P_{CO_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 P_{CO_2}. With a chronic respiratory alkalosis, the expected pH increase is approximately 0.02 for each 10–mm Hg decrease in P_{CO_2}.
4. If a pH change cannot be explained by an alteration in P_{CO_2}, a primary metabolic disturbance is present. A low pH value with a low P_{CO_2} indicates a *primary metabolic acidosis* with respiratory compensation. A high pH value with a high P_{CO_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:

$$P_{AO_2} = (713 \times F_{IO_2}) - \frac{P_{CO_2}}{0.8}$$

For ambient air ($F_{IO_2} = 0.21$), the equation can be simplified as follows: $P_{AO_2} = 150 - (1.25 \times P_{CO_2})$. 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}: $AaD_{O_2} = P_{AO_2} - P_{aO_2}$.

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 P_{aO_2} has a good response to administration of supplemental O_2. With a true shunt, P_{aO_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 P_{aO_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 ($F_{IO_2} = 0.21$), except as otherwise noted.

1. Room air	P_{O_2} = 45 mm Hg	P_{CO_2} = 30 mm Hg	pH = 7.47
(100% O_2)	P_{O_2} = 65 mm Hg	P_{CO_2} = 32 mm Hg	pH = 7.46
2. Room air	P_{O_2} = 45 mm Hg	P_{CO_2} = 30 mm Hg	pH = 7.47
(100% O_2)	P_{O_2} = 560 mm Hg	P_{CO_2} = 32 mm Hg	pH = 7.46
3.	P_{O_2} = 88 mm Hg	P_{CO_2} = 20 mm Hg	pH = 7.55
4.	P_{O_2} = 65 mm Hg	P_{CO_2} = 60 mm Hg	pH = 7.35
5.	P_{O_2} = 30 mm Hg	P_{CO_2} = 60 mm Hg	pH = 7.35
6.	P_{O_2} = 110 mm Hg	P_{CO_2} = 20 mm Hg	pH = 7.30
7.	P_{O_2} = 55 mm Hg	P_{CO_2} = 48 mm Hg	pH = 7.49
8.	P_{O_2} = 90 mm Hg	P_{CO_2} = 60 mm Hg	pH = 7.20

ANSWERS

1. Acute respiratory alkalosis. On room air, the patient's AaD_{O_2} = 67.5 mm Hg, which is elevated. The minimal elevation in P_{O_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 P_{O_2} with 100% O_2 indicates that ventilation-perfusion mismatch is the major cause of the hypoxemia.
3. Acute respiratory alkalosis. Even though P_{O_2} appears normal, AaD_{O_2} is elevated to 37 mm Hg, indicating the presence of a disorder impairing normal oxygenation of blood.
4. Chronic respiratory acidosis. AaD_{O_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, AaD_{O_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. P_{CO_2} is too low to represent only compensation for the metabolic acidosis, indicating the presence of a respiratory alkalosis as well. AaD_{O_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. AaD_{O_2} = 35 mm Hg. Therefore, hypoxemia is due partly to hypoventilation but mostly to ventilation-perfusion mismatch or shunt, probably the former.
8. Something is wrong because AaD_{O_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.

Index

Page numbers followed by "*f*" indicate figures, and "*t*" indicate tables.

A
Abscess, lung, as complication of pneumonia, 310
Acid-base status
  analysis of, 390–391, 391*t*
  ventilatory response to, 235
Acidosis
  alkalosis, 60, 61*t*
  metabolic, 60, 61*t*
    ventilatory response to, 235
Acinus, 2
Acquired immunodeficiency syndrome (AIDS), 338–344
  etiology and pathogenesis of, 338–339
  infectious complications of, 339–342
    bacterial pneumonia as, 341
    fungal, 342
    mycobacterial, 340–341
    Pneumocystis jiroveci pneumonia as, 339–340
    viral, 341
  inflammatory disease complicating, 343
  Kaposi sarcoma complicating, 342–343
  lung cancer complicating, 343
  non-Hodgkin lymphoma complicating, 343
  noninfectious complications of, 342–343
  nontuberculous mycobacterial disease and, 323
  pneumothorax in, 216
  pulmonary infiltrates, diagnostic evaluation of, 344
  pulmonary vascular disease complicating, 343
Acute cough, 25
Acute interstitial pneumonia (AIP), 163
  pathology of, 136–137
Acute lung injury, 357
Acute respiratory distress syndrome, 357–369
  clinical features of, 365–366
  definition of, 358*t*
  diagnostic approach to, 366–367
  etiology of, 360–362, 361*t*
  exudative phase of, 363–364
  injury via pulmonary circulation causing, 362
  mortality rate in, 366
  pathogenesis of, 362–363
  pathology of, 363–364
  pathophysiology of, 364–365
  proliferative phase of, 364
  treatment of, 367–368
Acute respiratory failure, 351
  classification of, 351–352
Acute-on-chronic respiratory failure, 352
Adaptive immune responses, in lung defense, 290–292
  defects in, 294–295
Adenocarcinoma, of lung, 266–267, 267*f*, 279*t*
  chest radiograph in, 274*f*
Adenovirus, pneumonia from, 300
Adhesion molecules, in PMN adhesion, 290
Adrenergic nervous system. *see* Sympathetic nervous system, in airway control
Adventitious breath sounds, 31
AIDS. *see* Acquired immunodeficiency syndrome
AIP. *see* Acute interstitial pneumonia
Air bronchogram, 37
Airway disease
  asthma as, 75–92
  bronchiectasis as, 113–114
  cystic fibrosis as, 118–122
  dyspnea in, 22
  functional abnormalities in, 99–102
  hemoptysis in, 26
  upper, 122–124
Airway patency, restoration of, 278
Airway resistance, 70–71
Airways
  anatomic and physiologic aspects of, 65–74
  collapse of, in emphysema, 102, 103*f*
  diameter, determinants of, 72–73
  dilated, in bronchiectasis, 114, 115*f*
  external pressure acting on, 73, 73*f*
  functions of, 70–74
  hyperresponsiveness of, in asthma, 75
  inflammation of, in asthma, 77–79
  irritants of, cough from, 24*t*
  neural control of, 68–70, 69*f*
  numbers and dimensions of, 71*t*
  remodeling of, in asthma, 78
  small, function of, in diffuse parenchymal lung disease, 142
  structure of, 65–70, 66*f*
Alkalosis
  metabolic, 60, 61*t*
  respiratory, 60, 61*t*
    in asthma, 84
Allergen exposure, in asthma, 79–82
Allergic alveolitis, extrinsic, 151
Allergic bronchopulmonary aspergillosis, 329–330
Aluminum, 145
Alveolar damage, diffuse
  in ARDS, 363
  causes of, 361*t*
Alveolar epithelium, repair of, 128
Alveolar flooding, in ARDS, 364
Alveolar fluid, regulation of, 128
Alveolar gas
  composition, continuum of, 14*f*
  equation, 15
Alveolar hypoventilation, 240
  in COPD, mechanisms of, 103–104
Alveolar interstitium, fluid movement in, physiology of, 358–360, 359*f*

Alveolar macrophages
depressed function of, 294
in lung defense, 288–289
Alveolar pattern, on chest radiograph, 37, 40*f*
Alveolar proteinosis, pulmonary, 174
Alveolar ventilation, 5, 18
in ARDS, 366
Alveolar vessels, 180, 181*f*
Alveolar volume (V_A), 5–6
Alveolar wall, in gas exchange, 126, 127*f*
Alveolar-arterial oxygen difference ($AaDo_2$), 15–16, 17*f*
Alveolitis
allergic, extrinsic, 151
in diffuse parenchymal lung disease, 134
sampling the cell population of, 143–144
fibrosing, cryptogenic, 158
in sarcoidosis, 165–166
Aminoglycosides, for pneumonias, 306–307
Amiodarone, parenchymal lung disease from, 154–155
Amniotic fluid embolism, ARDS and, 362
Amyotrophic lateral sclerosis, respiratory pump and, 249–250
Anaerobic bacteria
clinical features of, 303
pneumonia from, 299
antibiotics for, 306–307
Anatomic dead space, 5–6
Anergy, in sarcoidosis, 168
Angiography
computed tomographic
in patient evaluation, 41
in pulmonary embolism diagnosis, 189
pulmonary, 45–46, 45*f*
Angiomyolipomas, 170–171
Angiotensin-converting enzyme (ACE), elevated levels of, in sarcoidosis, 168–169
Angiotensin-converting enzyme (ACE) inhibitors, cough from, 25
Anthrax, 311
Antibiotic susceptibility, of pneumonias, 306–307
Antibiotics, for bronchiectasis, 122
Antibody deficiencies, pulmonary complications of, 346
Anticoagulant therapy, for pulmonary embolism, 191–192
Antigen-induced asthma, 77*f*
Antimicrobial peptides
impairment of, 293
in lung defense, 287–288
α_1-antiprotease, in emphysema pathogenesis, 95–96
α_1-antitrypsin, 95–96
Anxiety
dyspnea in, 23
in respiratory muscle weakness, 250
Aortic body chemoreceptors, for oxygen, 232
ARDS, PEEP in, 372, 376
Arsenic exposure, lung cancer and, 261
Arterial blood gas analysis, 201
Arterial blood gases, 58–61, 61*t*
in ARDS, 366
in asthma, 84
guidelines for interpretation and sample problems, 390–393
in obesity, 257
in pneumonia, 306
in pulmonary embolism, 188
Arterial blood, oxygen content of, 10
Arterial deficiency pattern, in COPD, 106, 107*f*
Arthritis, rheumatoid, pulmonary parenchymal involvement in, 163–164
Asbestos exposure
lung cancer and, 261
malignant mesothelioma from, 278–280
Asbestosis, 148–149, 150*f*
Aspergilloma, 26, 330–331
Aspergillosis, 329–331
Aspergillus, 330
Aspiration
of microorganisms, in lower respiratory tract, 298
needle, transbronchial, in lung cancer staging, 274–275
Aspiration pneumonia, 299
radiographic appearance of, 303, 305*f*
Aspirin sensitivity, 85
Aspirin-exacerbated respiratory disease, 85
Assist-control mode of ventilation, 374, 375*f*
Asthma, 75–92
acquired (environmental) factors in, 76–77
allergen exposure in, 79–82
antigen-induced, 77*f*
bronchial thermoplasty for, 90
bronchodilators for, 87–88, 88*t*
clinical features of, 84–85
diagnostic approach to, 85–87
etiology/pathogenesis of, 75–82
exercise and, 82
genetics and, 76
histamine in, 80
inhaled irritants, 82
late-phase asthmatic response in, 80–82, 81*f*
leukotrienes in, 80, 81*f*
management strategy for, 86*t*, 90–91
occupational, 85
pathogenesis of, 78*t*
pathology of, 82–83
pathophysiology of, 83–84
predisposition to, 76–77
provocative stimuli in, 79–82
respiratory tract infections and, 77
treatment of, 87–91, 88*t*
triad, 85
Asthmatic bronchitis, 93–94
Atelectasis, congestive, from pulmonary embolism, 185
Atelectrauma, complicating mechanical ventilation, 379
Atopy, 76
Atypical mycobacteria, 319

B

Bacille Calmette-Guérin (BCG) vaccination, for tuberculosis, 319
Bacillus anthracis, inhalation anthrax from, 311
"Back-pressure", 196–197
Bacteria, causing pneumonia, 298
BAL. *see* Bronchoalveolar lavage
Barotrauma, from positive pressure ventilation, 378–379
Basal cells, 67
Basement membrane, of alveolar wall, 129
Bellows, 22
Berylliosis, 150–151
Beryllium, 145
Bicarbonate, carbon dioxide transport in blood as, 11
Biologic agents, 154

Biopsy
in diffuse parenchymal lung disease diagnosis, 143
endobronchial, 50
lung, 50
pleural, closed, in pleural effusion diagnosis, 213–214
transbronchial, 50
in sarcoidosis diagnosis, 168
Bioterrorism, respiratory infections associated with, 310–312
Birbeck granules, in pulmonary Langerhans cell histiocytosis, 170
Blastomyces dermatitidis, 328
Blastomycosis, 328–329
Blood clot, in pulmonary circulation, 184
Blood flow, pulmonary, 7–8, 7*f*
distribution of, 180–181
increased, pulmonary hypertension from, 196
Blood tests, for latent tuberculosis, 319
Bloodstream, bacterial access to parenchyma via, 298–299
Blue bloater, 104
BMPR2 gene, 201–202
Body plethysmography, to quantify lung volumes, 53
Bohr equation, 6
Bordetella pertussis, 25–26
Breath sounds, 31
in COPD, 105
in pleural effusion, 212
in pneumonia, 302
Breathing
abnormal patterns of, 240
in kyphoscoliosis, 254–255
in respiratory muscle weakness, 250
work of, in obesity, 256
cessation of, 243
Cheyne-Stokes, 240–241, 241*f*
work of, in respiratory failure, 373
Bronchial adenoma, 26
Bronchial breath sounds, 31–32
Bronchial carcinoid tumors, 278
Bronchial circulation, anatomy of, 178
Bronchial hyperresponsiveness, in asthma, 77–79
Bronchial mucous glands, 67–68
Bronchial obstruction, bronchiectasis and, 114
Bronchial secretions, 68
Bronchial smooth muscle, 67–68
Bronchial thermoplasty, for asthma, 90
Bronchial washing, 46
Bronchiectasis, 113–118
clinical features of, 115–116
in cystic fibrosis, 120
diagnostic approach to, 116, 117*f*
etiology/pathogenesis of, 113–114
pathology of, 114, 115*f*
pathophysiology of, 115
treatment of, 122
Bronchioles, respiratory, function of, in diffuse parenchymal lung disease, 142
Bronchiolitis obliterans with organizing pneumonia (BOOP), 162
Bronchioloalveolar carcinoma, 266
Bronchitis
asthmatic, 93–94
nonasthmatic eosinophilic, 24–25
Bronchoalveolar lavage (BAL), 46
alveolitis in diffuse parenchymal lung disease, 143–144
for specimen collection, 46
Bronchoconstriction
in asthma, 75
exercise-induced, 82
in pulmonary embolism, 187
Bronchodilators
for asthma, 87–88, 88*t*
for bronchiectasis, 122
Bronchogenic carcinoma, 263–264
Bronchography, in bronchiectasis diagnosis, 116, 117*f*
Bronchophony, 32
Bronchopulmonary aspergillosis, allergic, 329–330
Bronchopulmonary drainage, for cystic fibrosis, 122
Bronchoscopy
in lung cancer, 274–275
in patient evaluation, 46–48, 47*f*
in tracheobronchial specimen collection, 49
virtual, 41
Bronchovesicular breath sounds, 31–32
Bronchus-associated lymphoid tissue, 291
Bubonic plague, 311

C

Calcium channel antagonists, 202
Cancer, lung, 259–269
adenocarcinoma as, 266–267, 267*f*
as AIDS complication, 343
clinical aspects of, 270–284
clinical features of, 270–272
relating to nodal and distal metastasis, 271
relating to paraneoplastic syndromes, 271–272
relating to primary lung lesion, 271
comparative features of, by cell type, 279*t*
death rate from, 259–260
diagnostic approach to, 272–276, 273*f*–274*f*
etiology and pathogenesis of, 260–263
functional assessment of, 275–276
genetic factors in, 261–262
histologic categories of, 264
large cell carcinoma as, 268
macroscopic evaluation of, 272–275, 273*f*–274*f*
microscopic and molecular evaluation of, 275
miscellaneous factors in, 262–263
non-small cell carcinoma, 264
occupational factors in, 261
parenchymal scarring and, 262
pathogenesis, concepts of, 263
pathology of, 263–268
prevalence of, 259
screening for, 276
small cell carcinoma as, 265, 266*f*
smoking and, 260–261
squamous cell carcinoma as, 264–265, 265*f*
staging of, 274–275
therapy of, principles of, 276–278
Candida albicans, 332
Candidiasis, oral, as AIDS complication, 342
Capillaries, pulmonary, 178
permeability of, increased, in ARDS, 362
Capillary system, 178
Carbaminohemoglobin, in carbon dioxide transport, 11–12
Carbapenems, for pneumonias, 306–307
Carbon dioxide
dissolved, 11
elimination of, maintenance of, in respiratory failure management, 373–379
partial pressure of, in respiratory failure, 351
radiolabeled, detection of, in tuberculosis diagnosis, 321

Carbon dioxide *(Continued)*
retention of, mechanism of, in COPD, 103–104
sensitivity to, depressed, 242
transport of, 11–12, 12*f*
Carcinoid syndrome, 278
Carcinoid tumors, bronchial, 278
Carcinoma
anterior mediastinal, 223
bronchioalveolar, 266
bronchogenic, 263–264
lepidic, 266, 267*f*
middle mediastinal, 224
scar, 262
Cardiac output, pulmonary vascular resistance and, 179
Cardiogenic pulmonary edema, 197–198, 360
Cardiopulmonary exercise testing, 199
Cardiovascular disease, dyspnea in, 22–23
Carotid body chemoreceptor, 232
cART. *see* Combination antiretroviral therapy
Caseating granuloma, 134–135
Caseous necrosis, in tuberculosis, 317
Catheter
pulmonary artery balloon occlusion, 179, 179*f*
Swan-Ganz, 179, 179*f*
in ARDS evaluation, 367
Cellular immune response, to beryllium in berylliosis, 150
Cellular immunity
defects in, 294
in lung defense, 292
Cellular immunodeficiencies, pulmonary complications of, 346
Central chemoreceptor, 232
Central nervous system (CNS)
disorders of, ARDS in, 362
in respiratory control, 229
Central sleep apnea, 243, 245*f*
Centrilobular emphysema, 98, 99*f*, 101*f*
Cephalosporins, for pneumonias, 306–307
Cerebral cortex, in voluntary respiratory control, 231
Chemical mediators
in asthma, 79–80, 80*t*
in pulmonary embolism, 187
Chemoreceptors, in respiratory control, 231–232
Chemotherapy
for lung cancer, 277
parenchymal lung disease induced by, 154
for tuberculosis, 321
Chest pain, 27–28
in pneumothorax, 217
Chest physical therapy
for bronchiectasis, 122
for cystic fibrosis, 122
Chest radiography
alveolar pattern on, 37, 40*f*
in anthrax, 311
in ARDS, 366
in aspergilloma, 330–331, 330*f*
in aspiration pneumonia, 303, 305*f*
in blastomycosis, 329
in COPD, 106
in diffuse parenchymal lung disease, 143
in idiopathic pulmonary fibrosis, 161–162
interstitial pattern on, 37, 39*f*
in kyphoscoliosis, 254*f*
in lung cancer, 270, 274*f*
in malignant mesothelioma, 280, 280*f*
in mediastinal masses, 225*f*
in patient evaluation, 34–37, 35*f*–36*f*, 38*f*–40*f*
in plague, 311
Chest radiography *(Continued)*
in pleural effusions, 212, 213*f*–215*f*
of *Pneumocystis* cysts, 333, 333*f*–334*f*
in *Pneumocystis* pneumonia, 333, 334*f*
in pneumomediastinum, 227*f*
in pneumonia, 304*f*–305*f*
in pneumothorax, 217–218, 218*f*–219*f*
in pulmonary hypertension, 199–200, 200*f*
in pulmonary Langerhans cell histiocytosis, 170
in tuberculosis, 319, 320*f*
in unilateral diaphragmatic paralysis, 253*f*
Chest wall
diseases of, respiratory pump and, 254–257, 254*f*
irreversible, in respiratory failure, 355
mechanical aspects of, 2*f*–3*f*, 3–5
receptors in, 233
stiff, in obesity, 256
Cheyne-Stokes breathing, 239–241, 241*f*
pathogenesis of, 241
Children, respiratory tract infections in, COPD and, 97
Chills, shaking, in pneumonia, 302
Chlamydophila pneumoniae, pneumonia from, 300
antibiotics for, 306
Chronic bronchitis, 93–94
pathology of, 98
smoking and, 95–96
Chronic cough, 25
Chronic necrotizing pulmonary aspergillosis, 331
Chronic obstructive pulmonary disease (COPD), 93–112
abnormal gas exchange in, mechanisms of, 102–104
blue bloater, subtype of, 104
clinical features of, 105–106
diagnostic approach to, 106–107
environmental pollution and, 96–97
etiology/pathogenesis, 94–98
exacerbations in, 106
functional abnormalities in, 99–102
genetic factors in, 97–98
infection and, 97
pathology of, 98, 99*f*
pathophysiology of, 98–104
phenotypes of, 104, 105*f*
pink puffer subtype of, 104
as public health problem, 94
pulmonary hypertension in, 104
smoking and, 95–96
treatment of, 107–110
ventilatory control abnormalities secondary to, 242
Chronic pulmonary coccidioidomycosis, 327–328
Chronic pulmonary histoplasmosis, 326
Chronic thromboembolic pulmonary hypertension (CTEPH), 203–204
Cilia, of airways
defense function of, 286, 287*f*
dysfunction of
bronchiectasis and, 115
impaired clearance and, 293
Circulation, 7–8, 7*f*
bronchial, anatomy of, 178
Clindamycin, for pneumonias, 306–307
Club cells, 67
Clubbing
in asbestosis, 149
in bronchiectasis, 115–116
in diffuse parenchymal lung disease, 142–143
in pulmonary disease, 33, 34*f*
Coagulation system, activation of, in ARDS, 363

Coal macule, in coal worker's pneumoconiosis, 147, 148*f*
Coal worker's pneumoconiosis, 146–148
Coccidioides immitis, 327
Coccidioidomycosis, 327–328
  as AIDS complication, 342
Collagen vascular diseases, pulmonary parenchymal involvement complicating, 163
Combination antiretroviral therapy (cART), 332
Community-acquired pneumonia
  antibiotics for, 306, 308*t*
  etiology and management of, 307–309, 308*t*
Complement activation, in ARDS, 363
Compliance curve, of lung, 4, 4*f*
  in diffuse parenchymal lung disease, 141
  in emphysema, 102, 103*f*
Compliance of lung, 130, 130*f*
  decreased, in ARDS, 365
  in diffuse parenchymal lung disease, 141
Complicated silicosis, 146
Computed tomographic angiography (CTA)
  in patient evaluation, 41
  in pulmonary embolism diagnosis, 189, 190*f*
  in pulmonary hypertension, 200
Computed tomography (CT)
  in lung cancer, 270
  in mediastinal masses, 227
  in patient evaluation, 37–41, 42*f*
  in pleural effusion, 212, 214*f*
  in solitary pulmonary nodule, 281–282
Conducting airways, 1, 65
Congenital central hypoventilation syndrome, 231, 240
Congestive atelectasis, from pulmonary embolism, 185
Congestive heart failure, cough in, 24*t*
Connective tissue disease, pulmonary parenchymal involvement complicating, 163–164
Consolidated lung, breath sounds in, 31–32
Continuous positive airway pressure (CPAP)
  nasal, for obstructive sleep apnea, 246
  in respiratory failure, 376
Controlled ventilation, 374, 375*f*
Conventional pulmonary angiography, 191
COP. *see* Cryptogenic organizing pneumonia
COPD. *see* Chronic obstructive pulmonary disease
Cor pulmonale
  complicating COPD, 104
    radiographic findings, 105–106
  definition of, 194–195
  in kyphoscoliosis, 255
Corticosteroids
  for allergic bronchopulmonary aspergillosis, 330
  for ARDS management, 368
  for radiation-induced pneumonitis, 152
  for sarcoidosis, 169
Cough, 23–26
  in bronchiectasis, 115
  in COPD, 105
  differential diagnosis of, 24*t*
  in diffuse parenchymal lung disease, 142–143
  inability, impaired clearance and, 292
  ineffective, in respiratory muscle weakness, 250
  in lung cancer, 271
  in pneumonia, 298, 302
Cough variant asthma, 24–25
Coumarin, for pulmonary embolism, 191–192
CPAP. *see* Continuous positive airway pressure
Crackles, 32, 33*t*
  in diffuse parenchymal lung disease, 142–143
  in pneumonia, 302
Crazy paving pattern, in pulmonary alveolar proteinosis, 174
Cryptococcosis, 331–332
Cryptococcus neoformans, 331–332
  infections from, as AIDS complication, 342
Cryptogenic fibrosing alveolitis, 158
Cryptogenic organizing pneumonia (COP), 162, 162*f*
  pathology of, 133
CTA. *see* Computed tomographic angiography
CTEPH. *see* Chronic thromboembolic pulmonary hypertension
Cuirass ventilator, 380
Culture, in tuberculosis diagnosis, 319–320
Cyanosis, in pulmonary disease, 34
Cyclophosphamide, for Wegener granulomatosis, 172–173
Cylindrical bronchiectasis, 114
Cystic fibrosis, 118–122, 121*f*
  clinical features of, 120
  complications of, 120
  diagnostic approach for, 121–122
  etiology and pathogenesis of, 118–119, 119*t*
  hemoptysis in, 26–27
  pathology of, 120
  pathophysiology of, 120
  treatment of, 122
Cystic fibrosis transmembrane conductance regulator (CFTR), mutations of, 118
Cysts, *Pneumocystis*, 333, 333*f*
Cytomegalovirus, AIDS and, 294

D

D-dimer testing, in pulmonary embolism diagnosis, 188–189
Dead space
  anatomic, 5–6
  creation of, by pulmonary embolism, 186
  physiologic, 6
  volume of, 5–6
Defense mechanisms, lung, 285–296
Defensins, in innate immune system, 288
Delayed hypersensitivity, in tuberculosis, 317
Dendritic cells, 79–80
  in lung defense, 289–290
Desquamative interstitial pneumonia, 161
  pathology of, 136–137
Diaphragm
  fatigue
    in COPD, carbon dioxide retention from, 103–104
    respiratory pump and, 251–252
  in inspiration, 235–236, 236*f*
  paralysis of
    impaired clearance and, 292
    respiratory pump and, 252–253, 253*f*
  resting position of, in obesity, 256
  weakened, impaired clearance and, 292
Diaphragmatic pleura, 206–207, 207*f*
Diaphragmatic plication, 253
DIC. *see* Disseminated intravascular coagulation
Dietary factors, lung cancer and, 262–263
Diffuse alveolar damage
  in ARDS, 363
  causes of, 361*t*
Diffuse parenchymal lung disease, 129–130, 132–144
  asbestosis as, 148–149, 150*f*
  associated with known etiologic agents, 145–157
  berylliosis as, 150–151
  chronic eosinophilic pneumonia as, 173–174, 173*f*

Diffuse parenchymal lung disease *(Continued)*
classification of, 133*t*
clinical features of, 142–143
coal worker's pneumoconiosis as, 146–148
compliance in, 141
connective tissue diseases with, 163–164
diagnostic approach to, 143–144
diffusion impairment in, 141
drug-induced, 153–155, 153*t*
end-stage, pathology of, 138, 139*f*
fibrosis in, 132, 134*f*, 141*f*
Goodpasture syndrome as, 171
hypersensitivity pneumonitis as, 151–152
idiopathic interstitial pneumonias as, 135–138
idiopathic pulmonary fibrosis as, 158–161, 159*f*
inhaled inorganic dusts causing, 145–151
initiating stimulus for, 139
lung volumes in, 141
lymphangioleiomyomatosis as, 170–171
miscellaneous disorders involving, 169–174
pathogenesis of, 138–140, 140*f*
pathology of, 134–138
pathophysiology of, 140–142, 141*f*
propagation of, 139
pulmonary alveolar proteinosis as, 174
pulmonary Langerhans cell histiocytosis as, 169–170
radiation-induced, 155–156
sarcoidosis as, 164–169, 166*f*
silicosis as, 146
of unknown etiology, 158–176
Wegener granulomatosis as, 172
Diffuse pulmonary infiltrates, as AIDS complication, 343
Diffusing capacity, in patient evaluation, 54–55
Diffusion, 8
in diffuse parenchymal lung disease, 141
Diltiazem, 202
Dilution tests, to quantify lung volumes, 53
Dimorphic fungus, *Histoplasma capsulatum* as, 325–326
Direct fluorescent antibody staining, in pneumonia diagnosis, 306
Disseminated coccidioidomycosis, 328
Disseminated histoplasmosis, progressive, 326
Disseminated intravascular coagulation (DIC), acute respiratory distress syndrome and, 362
Driving pressure for expiratory airflow, loss of, in emphysema, 102
"Drug-induced lupus", 155
Drug-induced parenchymal lung disease, 153–155
Drugs, ARDS from, 362
Dusts, inorganic, inhaled, diseases caused by, 145–151
Dynamic hyperinflation, in asthma, 83–84
Dynein arms, 67
in lung defense, 286, 287*f*
Dyskinetic cilia syndrome, 292–293
Dyspnea, 20, 23
in ARDS, 366
in COPD, 105
differential diagnosis of, 21, 21*t*
in diffuse parenchymal lung disease, 142–143
exertional, in kyphoscoliosis, 255
mechanisms of, 20–21
paroxysmal nocturnal, 20
from pleural effusion, 212
in pneumomediastinum, 226
in pneumothorax, 217
in pulmonary embolism, 187
in pulmonary hypertension, 199
Dyspnea *(Continued)*
in respiratory failure, 352
in respiratory muscle weakness, 250
signs/symptoms distinguished from, 20

E

Echocardiography, 199
Effort-dependent portion, 71–72
Egophony, 32
in pneumonia, 302
Eisenmenger syndrome, 196
Elastase, in emphysema pathogenesis, 95–96, 96*f*
Elastic recoil pressure, 73
ELISA. *see* Enzyme-linked immunosorbent assay
Embolism, pulmonary, 184–193
Emphysema, 94
focal, in coal worker's pneumoconiosis, 147
functional abnormalities in, 102
pathology of, 98, 99*f*
smoking and, 94
subcutaneous, 226
Empyema, 211, 303
complicating pneumonia, 310
Endobronchial biopsy, 50
Endometriosis, pulmonary, hemoptysis in, 26–27
Endothelial cells, vascular, activation of, in ARDS, 363
Endothelial-derived relaxing factor, 182
Endothelin, 182
in pulmonary embolism, 187
Endothelin-1 receptor antagonists, 202
Environmental factors, in asthma, 76–77
Enzyme-linked immunosorbent assay (ELISA), 188–189
Eosinophilic granuloma of lung, 169
Eosinophilic pneumonia, chronic, 173–174, 173*f*
Epidermal growth factor receptor (EGFR) mutations, lung tumor, chemotherapy for, 275
Epithelioid histiocytes
in diffuse parenchymal lung disease, 134–135
in sarcoidosis, 165–166
in tuberculosis, 317
Equal pressure point, 73
Erlotinib, for tumor from epidermal growth factor receptor mutations, 277
Erythema nodosum, in coccidioidomycosis, 328
Ethambutol, for tuberculosis, 321
Evaluation of patient
arterial blood gases in, 58–61, 61*t*
bronchoscopy in, 46–48, 47*f*–48*f*
chest radiography in, 34–37, 35*f*
computed tomography in, 37–41, 42*f*
exercise testing in, 61
on functional level, 52–61
on macroscopic level, 30–48
magnetic resonance imaging in, 42–43, 43*f*
on microscopic level, 48–52
physical examination in, 30–34
pulmonary angiography in, 45–46, 45*f*
with pulmonary disease, 30–64
pulmonary function tests in, 52–58
pulse oximetry in, 60–61
radionuclide lung scanning in, 43–45, 44*f*
specimen collection for, 49–50
ultrasonography in, 46
Exacerbation, definition of, 105
Exercise
asthma and, 82
testing, in patient evaluation, 61
Exertional fatigue, 20

Expiration, muscle activity in, 237
Expiratory effort, maximal, 71–74, 72*f*
Expiratory pressure, maximal, in respiratory muscle weakness, 250
Extensively drug resistant tuberculosis, 322
Extraalveolar vessels, 180, 181*f*
Extrinsic allergic alveolitis, 151
Exudative pleural fluid, 211

F
Factor V Leiden, 185
Farmer's lung, 151
Fat embolism, ARDS and, 362
Fatigue
  diaphragmatic, respiratory pump and, 250–251
  exertional, 20
FEF. *see* Forced expiratory flow
Ferruginous body, in asbestosis, 149, 150*f*
Fever, in pneumonia, 300, 302
Fibrosing mediastinitis, 327
Fibrosis
  in diffuse parenchymal lung disease, 132, 134*f*
  progressive massive, 148
  radiation, 155
Fibrous silicate, asbestosis from, 148–149
Fixed obstruction, 123
Flow rates, in patient evaluation, 53–54, 54*f*
Flow-volume curves
  forced expiratory, 72, 72*f*
  in upper airway obstruction evaluation, 57–58, 59*f*
Flow-volume loop, 57, 58*f*–59*f*
Fluid accumulation, mechanisms of, 359–360
Fluid movement, in alveolar interstitium, physiology of, 358–360, 359*f*
Fluorescent antibody staining, direct, in pneumonia diagnosis, 306
Fluorodeoxyglucose scanning, 45
Focal emphysema, in coal worker's, pneumoconiosis, 147
Forced expiratory flow (FEF), 53–54
  in asthma, 83
Forced expiratory spirogram, 54*f*, 56*f*
Forced expiratory volume in 1 second (FEV_1), 53–54, 54*f*
  in asthma, 80–81, 81*f*
Forced vital capacity, 53–54
Francisella tularensis, tularemia, 311
FRC. *see* Functional residual capacity
Fremitus, 30–31, 33*t*
Friction rub, 33
Functional residual capacity (FRC), 5
  in airway disease, 99–102
  in asthma, 83
  decreased, in ARDS, 365
  in diffuse parenchymal lung disease, 141
  in emphysema, 102
  factors determining, 101–102
  in patient evaluation, 52
Fungal infections, 325–332
  as AIDS complication, 342
  aspergillosis as, 329–331
  blastomycosis as, 328–329
  coccidioidomycosis as, 327–328
  cryptococcosis as, 331–332
  histoplasmosis as, 325–327
Fungi
  diagnosis of, 51
  miscellaneous infections caused by, 325–336

G
Gas content, 8–9
Gas exchange
  abnormal, 15–18
    in COPD, mechanisms of, 102–104
    pathogenesis of, 353–354
  alveolar wall in, 126, 127*f*
  at capillary-alveolar level, 129
  disturbances, in diffuse parenchymal lung disease, 142
  effects of, ARDS on, 364–365
  failure of, presentation of, 352
  support of, in ARDS management, 368
  ventilation-perfusion relationships and, 12
Gas, percent saturation in, 8–9
Gastric contents, inhaled, ARDS from, 360–361
Gefitinib, for tumor from epidermal growth factor receptor mutations, 277
Gel layer, in lung defense, 287
Genes alteration, lung cancer and, 263
Genetic factors
  in asthma, 76
  in COPD, 97–98
  in lung cancer, 261–262
Germ cell tumors, 223
Ghon complex, in tuberculosis, 317
Ghon lesion, in tuberculosis, 317
Glomerulonephritis
  in Goodpasture syndrome, 171
  in Wegener granulomatosis, 172
Glucocorticoids, for asthma, 89
Goblet cells, 67
Goodpasture syndrome, 171
Graham Steell, 199
Gram-negative pneumonia, 299
  antibiotics for, 306–307
  radiographic appearance of, 303, 304*f*
Gram-positive pneumonia, 299
Granulocyte-macrophage colony-stimulating factor (GM-CSF), autoantibody to, in pulmonary alveolar proteinosis, 174
Granuloma
  in diffuse parenchymal lung disease, 134–135, 135*f*
  eosinophilic, of lung, 169
  noncaseating, 134–135
    in sarcoidosis, 165–166
  in tuberculosis, 317
Granulomatosis with polyangiitis, 172–173, 172*f*
Gravity, pulmonary blood flow distribution and, 180
Ground-glass appearance, on chest radiograph, 37, 41*f*
Guanylate cyclase stimulators, 202
Guillain-Barré syndrome, respiratory pump and, 248–249

H
Haemophilus influenzae pneumonia, 299
  antibiotics for, 306–307
Haldane effect, 11–12, 242
Halo ethers, lung cancer and, 261
Hamman sign, 226–227
Hamman-Rich syndrome, 163
Hampton hump, in pulmonary embolism, 188
Hand-Schüller-Christian disease, 169
Hematopoietic stem cell transplantation, pulmonary complications of, 345
Hemidiaphragm, 252, 253*f*
Hemoglobin, 9
  in oxygen transport, 9

Hemoptysis, 26–27
in bronchiectasis, 115–116
differential diagnosis of, 27*t*
in lung cancer, 271
in pulmonary embolism, 187
Heparin, for pulmonary embolism, 191–192
Hering-Breuer reflex, 232
Heritable pulmonary arterial hypertension, 195–196, 201–202
Heroin, ARDS from, 362
High-resolution computed tomography (HRCT)
in bronchiectasis diagnosis, 116, 117*f*
in COPD diagnosis, 106
in diffuse parenchymal lung disease, 135–136
in idiopathic pulmonary fibrosis, 160, 160*f*
in lymphangioleiomyomatosis, 171
in pulmonary alveolar proteinosis, 174
in sarcoidosis, 160
Hilar lymphadenopathy, in sarcoidosis, 166–167
Histamine, in asthma, 80
Histiocytes, epithelioid
in sarcoidosis, 165–166
in tuberculosis, 317
Histiocytosis, Langerhans cell, of lung, 169–170, 289–290
Histiocytosis X, pulmonary, 169
Histologic examination, 51
Histoplasma capsulatum, 325–326
Histoplasmosis, 325–327
as AIDS complication, 342
HIV. *see* Human immunodeficiency virus
"Honeycomb lung", 138, 139*f*
in idiopathic pulmonary fibrosis, 160
Hormone production, in paraneoplastic syndromes, 271–272
Hospital-acquired pneumonia, management of, 309
HRCT. *see* High-resolution computed tomography
Human immunodeficiency virus (HIV), 337
infection from, lung cancer and, 263
Humoral immunity
defects in, 294
in lung defense, 291
Hyaline membranes, in ARDS, 364
Hydrocarbon aspiration, ARDS from, 360–361
Hydropneumothorax, 218, 219*f*
Hydrostatic pulmonary edema, 359–360
Hypercapnia, 17–18
mental impairment in, 352
permissive, 376
in respiratory failure, 371
ventilatory response to, 233–235, 233*f*
Hypercapnic/hypoxemic respiratory failure, 352
clinical and therapeutic aspects of, 354–355
pathogenesis of, 353–354, 354*f*
Hyperinflation
dynamic, in asthma, 83–84
of lungs, in COPD, 106, 107*f*
Hyperirritable airways, 24–25
Hyperpnea, isocapnic, 86
Hyperresponsiveness, bronchial, in asthma, 77–79
Hypersensitivity, delayed
to beryllium in berylliosis, 151
in tuberculosis, 317
Hypersensitivity pneumonitis, 151–152
granulomas in, 134–135
Hypersomnolence, daytime, in sleep apnea syndrome, 243–244
Hyperthyroidism, dyspnea in, 23
Hypertrophic osteoarthropathy, 33–34
Hyperventilation, 20
neurologic disorders with, 239–240
Hypocapnia
in ARDS, 366–367
in pulmonary embolism, 186
Hypopnea, 243
Hypoventilation, alveolar, 240
in COPD, mechanisms of, 103–104
Hypoxemia, 15–17, 17*f*
in ARDS, 365
mechanisms of, 17
mental impairment in, 352
in respiratory failure, 372–373
Hypoxemic respiratory failure, 351
pathogenesis of, 353
Hypoxia
feedback system in, 241
pulmonary hypertension in COPD from, 104
pulmonary vascular response to, 181–182
ventilatory response to, 233–235, 233*f*–234*f*

I

Idiopathic hypoventilation, 240
Idiopathic interstitial pneumonias, pathology of, 135–138, 136*t*
Idiopathic pulmonary arterial hypertension (IPAH), 195–196
Idiopathic pulmonary fibrosis (IPF), 158–161
clinical presentation of, 161
diagnosis of, 160–161
pathogenesis of, 158–159, 159*f*
prognosis in, 161
treatment of, 161
in usual interstitial pneumonia, 134
Immotile cilia syndrome, 292–293
Immune dysregulation, in silicosis, 146
Immune system, of lung
adaptive
defects in, 294–295
in lung defense, 290–292
innate, 287
Immunity
cellular
defects in, 290–291, 294
in lung defense, 292
humoral
defects in, 294
in lung defense, 291
Immunization, against respiratory pathogens, 295
Immunocompromised host
by acquired immunodeficiency syndrome, 338–344
non-human immunodeficiency virus, pulmonary complications of, 344–347
diagnostic evaluation of, 346–347, 347*t*
inflammatory, treatment of, 345–346
in organ transplant recipients, 344–345
in primary immunodeficiencies, 346
pulmonary complications in, 337–349
Immunodeficiencies, primary, pulmonary complications of, 346
Immunoglobulin A (IgA), respiratory, in innate immune system, 288
Immunoglobulins, in humoral immunity, 291
IMV. *see* Intermittent mandatory ventilation
Infarction, pulmonary, from pulmonary embolism, 185
Infection
bronchiectasis, 113
complicating lung transplantation, 381
diagnosis of
molecular biology techniques in, 51–52
staining and cultures in, 50
opportunistic, in AIDS, 338

Infection *(Continued)*
pulmonary, pleural effusions from, 211
respiratory tract
asthma and, 77
viral, asthma and, 77
Inflammation
airway, in asthma, 77–79
in diffuse parenchymal lung disease, 132, 134*f*
in lung, suppression of, alveolar macrophages in, 289
Inflammatory cells, in lung defense, 288–290
impairment of, 293–294
Inflammatory disease
as AIDS complication, 343
pleural effusions in, 211
Influenza virus
immunization against, 295
pneumonia from, 300
Inhalation, of microorganisms, in lower respiratory tract, 298
Inhaled injurious agents, ARDS from, 360–361
Inhaled irritants, in asthma, 82
Innate immune system of lung, 287
Innervation of airways, 68–69, 69*f*
Inorganic dusts, inhaled, diseases caused by, 145–151
Inspiration, muscle activity in, 235–236, 236*f*
Inspiratory pressure
maximal, in respiratory muscle weakness, 250
for mechanical ventilation, 373–374
Inspiratory stridor, 22
Integrins, on PMNs, 290
Intermittent mandatory ventilation (IMV), 374–375, 375*f*
Interstitial lung disease, 126, 132
Interstitial pattern, on chest radiograph, 37, 39*f*–40*f*
Interstitial space, in alveolar wall, 129
Interstitium, 132
alveolar, fluid movement in, physiology of, 358–360, 359*f*
Intubation, for mechanical ventilation, complications of, 377–379
Invasive aspergillosis, 331
Ionizing radiation, lung cancer and, 261
IPAH. *see* Idiopathic pulmonary arterial hypertension
IPF. *see* Idiopathic pulmonary fibrosis
Irreversible chest wall, in respiratory failure, 355
Irritant receptors
causing cough, 23–24
in respiratory control, 232–233
Irritants, inhaled, in asthma, 82
Isocapnic hyperpnea, 86
Isoniazid, for tuberculosis, 321
IVC filter, for pulmonary embolism, 192

J
Juxtacapillary receptors, in respiratory control, 232–233

K
Kaposi sarcoma, as AIDS complication, 342–343
Kartagener syndrome
bronchiectasis and, 114
impaired clearance in, 292–293
Killer cells, natural, in lung defense, 290
Klebsiella pneumoniae, pneumonia from, 299
Kulchitsky cell. *see* Pulmonary neuroendocrine cell
Kyphoscoliosis, respiratory pump and, 254–255, 254*f*

L
Lactoferrin, in innate immune system, 288
Lamellar inclusions, in surfactant release, 127–128
Langerhans cell, 170, 289–290
Langerhans cell histiocytosis, of lung, 169–170, 289–290
Large cell carcinoma, of lung, 268, 279*t*
Latent tuberculous infection, definition of, 316
Late-phase asthmatic response in, 80–82, 81*f*
Left atrial pressure, measurement of, 179
Legionella pneumophila
diagnosis of, 51
pneumonia from, 300
Legionnaires' disease
antibiotics for, 306–307
clinical features of, 303
Lepidic carcinoma, 266, 267*f*
Letterer-Siwe disease, 169
Leukocytosis, in pneumonia, 302
Leukotrienes, in asthma, 80, 81*f*
Liver disease, transudative pleural fluid in, 211
Lobar pneumonia, radiographic appearance of, 304*f*
Löfgren syndrome, 165–166
Lung
abscess of, as complications of pneumonia, 310
bronchial carcinoid tumors of, 278
elastic recoil pressure of, 73
farmer's, 151
honeycomb, 138
mechanical properties of, effects of ARDS on, 365
solitary nodule, in differential diagnosis of, 281–282, 281*t*
Lung cancer, 259–269
adenocarcinoma as, 266–267, 267*f*
as AIDS complication, 343
clinical aspects of, 270–284
clinical features of, 270–272
relating to nodal and distal metastasis, 271
relating to paraneoplastic syndromes, 271–272
relating to primary lung lesion, 271
comparative features of, by cell type, 279*t*
cytologic examination for, 51
death rate from, 259–260
diagnostic approach to, 272–276, 273*f*–274*f*
etiology and pathogenesis of, 260–263
functional assessment of, 275–276
genetic factors in, 261–262
histologic categories of, 264
large cell carcinoma as, 268
macroscopic evaluation of, 272–275, 273*f*–274*f*
microscopic and molecular evaluation of, 275
miscellaneous factors in, 262–263
non-small cell carcinoma, 264
occupational factors in, 261
parenchymal scarring and, 262
pathogenesis, concepts of, 263
pathologic examination for, 51
pathology of, 263–268
prevalence of, 259
screening for, 276
small cell carcinoma as, 265, 266*f*
smoking and, 260–261
squamous cell carcinoma as, 264–265, 265*f*
staging of, 274–275
therapy of, principles of, 276–278

Lung defense mechanisms, 285–296
adaptive immune responses in, 290–292
defects in, 294–295
antimicrobial peptides as, 287–288
impairment of, 293
augmentation of, 295
cellular immune mechanisms in, 292
dendritic cells in, 289–290
failure of, 292–295
humoral immune mechanisms as, 291
natural killer cells in, 290
phagocytic and inflammatory cells in, 288–290
impairment of, 293–294
physical or anatomic factors in, 286–287
impairment of, 292–293
polymorphonuclear leukocytes in, 290
pulmonary alveolar macrophages in, 288–289
Lung disease
beryllium, 151
chronic obstructive, 93–112
presentation of
chest pain in, 27–28
cough in, 23–26
dyspnea, 19–23
pulmonary hypertension and, 203
ventilatory control abnormalities secondary to, 242–243
Lung injury, acute, 357
Lung transplantation
for chronic respiratory failure, 380–381
complication of, 381
recipients of, pulmonary complications in, 344
Lung volumes, 5
in asthma, 83
in chest wall and neuromuscular diseases, 251*f*
in diffuse parenchymal lung disease, 141
factors determining, 101–102
in patient evaluation, 52–53, 53*f*
pulmonary vascular resistance and, 181*f*
Lymphadenopathy, hilar, in sarcoidosis, 165–166
Lymphangioleiomyomatosis, 170–171
Lymphocytes, T, in cellular immunity, 292
Lymphocytic interstitial pneumonia, in Sjögren syndrome, 164
Lymphocytic interstitial pneumonitis, as AIDS complication, 343
Lymphoma
anterior mediastinal, 223
middle mediastinal, 224
non-Hodgkin, as AIDS complication, 343
Lysozyme, in innate immune system, 288

M

MAC. *see Mycobacterium avium* complex
Macklin effect, 226
Macrolide antibiotics
for bronchiectasis, 122
for pneumonias, 306–307
Macrophages, alveolar, 129
depressed function of, 294
in lung defense, 288–289
Magnetic resonance imaging (MRI)
in mediastinal masses, 224–225
in patient evaluation, 42–43, 43*f*
Malignancy, of lung, 261
Malignant cells, cytologic examination for, 51
Malignant mesothelioma, 278–280, 280*f*
Massive pulmonary embolism, 187
Matrix metalloproteinases, in emphysema pathogenesis, 96
Maximal expiratory effort, 71–74, 72*f*
Maximal expiratory pressure, depressed, in respiratory muscle weakness, 250
Maximal inspiratory pressure, depressed, in respiratory muscle weakness, 250
Maximal midexpiratory flow rate (MMFR), 53–54
Mechanical ventilation
in ARDS management, 368
pneumothorax from, 216
in respiratory failure, 373–379, 375*f*
assist-control mode of, 374, 375*f*
complications of, 377–379, 378*t*
controlled, 374, 375*f*
indication for, 371
intermittent mandatory, 374–375, 375*f*
pressure support, 373–374, 375*f*
pressure-controlled, 374, 375*f*
protective open lung strategy for, 376
volume-cycled, 374–375, 375*f*
weaning from, 377
Meconium ileus, 120
Mediastinal disease, 221–228
Mediastinal masses, 223–225
anterior, 223–224
clinical features of, 224
diagnostic approach to, 224–225, 225*f*
etiology of, 223–224
middle, 224
posterior, 224
treatment of, 225
Mediastinal pleura, 206–207, 207*f*, 221
Mediastinitis, fibrosing, 327
Mediastinoscopy, suprasternal, in lung cancer staging, 274–275
Mediastinotomy, parasternal, in lung cancer staging, 274–275
Mediastinum, 221
air in, 227*f*
anatomic features of, 221–223, 222*t*
compartments of, borders of, 221, 222*f*, 222*t*
masses of, 223–225. *see also* Mediastinal masses
Mediators
chemical
in asthma, 79–80, 80*t*
in pulmonary embolism, 187
from inflammatory cells, in asthma, 77–79
Medullary respiratory generator, 230*f*
Mesothelial cells, on pleural surfaces, 207
Mesothelioma, malignant, 278–280, 280*f*
Metabolic acidosis, 60, 61*t*
expected compensation for, 391*t*
ventilatory response to, 235
Metabolic alkalosis, 60, 61*t*
expected compensation for, 391*t*
Metabolic requirements, ventilatory response to, 235
Methotrexate, 154
Methyl ether exposure, lung cancer and, 261
Methylxanthines, in asthma, 88
Mica, 145
Miliary pattern, on chest radiograph, 37
Miliary tuberculosis, 315–316
Minute ventilation, 5
changes in, 242
increased, in pulmonary embolism, 186
Miscellaneous airway disease, 113–125
Mitral stenosis, 202
Mixed apnea, 243
MMFR. *see* Maximal midexpiratory flow rate
Molecular biology techniques, in respiratory tract infection diagnosis, 51–52

Mucociliary transport/clearance
impairment of, 292–293
in lung defense, 286
Mucor, 332
Mucous glands, enlarged, in chronic bronchitis, 95
Multidrug resistant (MDR) tuberculosis, 322
Murmur of tricuspid, 199
Muscles of respiration, 229, 235–237, 236*f*
neuromuscular disease affecting, 248–250
Muscular arteries, 197
Myasthenia gravis, respiratory pump and, 249
Mycetoma, 26
Mycobacteria
false-positive tuberculin skin test in, 319
identification of, 50–51
nontuberculous, 322–323
Mycobacterial infection, as AIDS complication, 340–341
Mycobacterium avium complex (MAC), 322–323
infection from, as AIDS complication, 341
Mycobacterium avium-intracellulare, 322–323
Mycobacterium tuberculosis, tuberculosis from, 315
Mycoplasmal pneumonia
antibiotics for, 306–307
clinical features of, 302–303

N

Narcotics, ARDS from, 362
Natural killer cells, in lung defense, 290
Necrotizing pulmonary aspergillosis, chronic, 331
"Neomuscularization", 197
Neoplastic disease, as AIDS complication, 342–343
Neural control, of airways, 68–70, 69*f*
Neurologic disease, 239–240
Neuromuscular disease
affecting muscles of respiration, 248–250
in respiratory failure, 355
Neutrophil elastase, in emphysema pathogenesis, 95–96
Neutrophils, recruitment of, to lungs, in ARDS, 363
Nifedipine, 202
NIPPV. *see* Noninvasive positive pressure ventilation
Nitric oxide, 182
inhaled, in ARDS management, 368
in pulmonary embolism, 187
Nitrofurantoin, parenchymal lung disease from, 154
Nitrogen dioxide, inhaled, ARDS from, 361
Nocturnal dyspnea, paroxysmal, 20
Nocturnal positive pressure ventilation, 257
Nodular pattern, on chest radiograph, 37
Nodules, silicotic, 146
Nonadrenergic, noncholinergic inhibitory system, in airway control, 70
Nonasthmatic eosinophilic bronchitis, 24–25
Noncardiogenic pulmonary edema, 360
Noncaseating granuloma, 134–135
in sarcoidosis, 165–166
Non-Hodgkin lymphoma, as AIDS complication, 343
Noninvasive positive pressure ventilation (NIPPV), in respiratory failure, 372
Non-small cell lung cancer, 264
treatment of, 276–277
Nonspecific interstitial pneumonia (NSIP), 162
pathology of, 135–136
Nontuberculous mycobacteria, 314–324
false positive tuberculin skin test in, 319
Nosocomial pneumonia, management of, 309
NSIP. *see* Nonspecific interstitial pneumonia
Nucleic acid amplification assays, in tuberculosis diagnosis, 321

O

Obesity, respiratory pump and, 255–257
Obesity-hypoventilation syndrome, 256
Obstructive pattern, of pulmonary function, 55, 56*f*
Obstructive sleep apnea, 243, 245*f*
in obesity, 256, 257*f*
Occupational asthma, 85
Occupational factors, in lung cancer, 261
Omalizumab, for asthma, 90
Ondine's curse, 231, 240
Opportunistic infections, in AIDS, 338
Opsonins, in lung defense, 289
Oral candidiasis, as AIDS complication, 342
Organ transplant, recipients of, pulmonary complications in, 344–345
Orthopnea, 20
Osteoarthropathy, hypertrophic, 33–34
Oxygen
diffusion of, 8
high concentrations of
ARDS from, 364–365
impaired clearance from, 293
uptake of, by blood in capillaries, 129
Oxygen content, 11
Oxygen transport, 8–11, 10*f*
optimizing, in respiratory failure, 371
Oxygenation
analysis of, 391–392
support of, in respiratory failure management, 371
Oxyhemoglobin dissociation curve, 9, 10*f*

P

Palpation, of chest, 30–31
Panacinar (panlobular) emphysema, 98, 99*f*–100*f*
Pancoast tumors, symptoms of, 271
Pancreatic insufficiency, in cystic fibrosis, 120
PAOP. *see* Pulmonary artery occlusion pressure
PAP. *see* Pulmonary alveolar proteinosis
Paralysis, diaphragmatic, respiratory pump and, 252–253, 253*f*
Paraneoplastic syndromes, 224, 271–272
Parapneumonic effusion, 211
Parasternal mediastinotomy, 225
in lung cancer staging, 274–275
Parasympathetic nervous system, in airway control, 69–70
Parenchyma
anatomy of, 358, 359*f*
destruction of, in tuberculosis, 317
disease of
cough in, 25
hemoptysis in, 26
scarring of, lung cancer and, 262
infection of, 297
Parenchymal lung disease, in pulmonary hypertension, 201
Parietal pleura, 206, 207*f*
inflammation of, chest pain in, 27
Paroxysmal nocturnal dyspnea, 20
Partial pressure, 8–9
of carbon dioxide, in respiratory failure, 351
of oxygen, in respiratory failure, 351
Pathologic examination, of pulmonary disease, 51
PCV. *see* Pressure-controlled ventilation

Peak expiratory flow rate, 58
measurement of, in asthma monitoring, 87
Pectoriloquy, whispered, 32, 33*t*
PEEP. *see* Positive end-expiratory pressure
Penicillin, 306
extended-spectrum, for pneumonias, 306–307
penicillinase-resistant derivative of, for pneumonias, 306–307
Peptides, antimicrobial, impairment of, 293
Percent saturation, 9
of gas, 8–9
Perfusion lung scan, 44*f*, 181
in pulmonary embolism diagnosis, 189, 190*f*
Pertussis, immunization against, 295
PET. *see* Positron emission tomography
Phagocytic cells
disorders of, pulmonary complications of, 346
in lung defense, 288–290
impairment of, 293–294
Phosphodiesterase inhibitors, 202
Phosphodiesterase-4 inhibitors, for COPD, 108
Physical examination, for pulmonary disease, 30–34
Physiologic dead space, 6
Pickwickian syndrome, 256
PIE syndrome, 155
Pink puffer, 104
Plague, pulmonary involvement in, 311
Platypnea, 20
Pleura
anatomy of, 206, 207*f*
malignant mesothelioma involving, 278–280, 280*f*
Pleural disease
anatomy and, 206–207, 207*f*
physiology of, 207–209, 208*f*
pleural effusion in, 209–214
pneumothorax as, 215–220
Pleural effusion, 209–214
causes of, 210*t*
clinical features of, 212
diagnostic approach to, 212–214, 213*f*, 215*f*
dyspnea in, 22
etiology of, 210–211
exudative, 209
malignancy in, 211
pathogenesis of, 209–210
transudative, 210–211
treatment of, 214
Pleural space, 206, 207*f*
air in, 216–217
fluid in, specimen of, collection of, 50
liquid in
accumulation of, 209–210
formation and resorption of, 207, 208*f*
Pleuritic chest pain, 27
from pleural effusion, 212
in pulmonary embolism, 187
Pleurodesis, for pleural effusion, 214
PMNs. *see* Polymorphonuclear leukocytes
Pneumatic splint, 246
Pneumococcal pneumonia, 299
antibiotics for, 306
clinical features of, 302
vaccination for, 295
Pneumoconiosis
asbestosis as, 148–149
berylliosis as, 150–151
coal worker's, 146–148
definition of, 145
Pneumocystis cysts, 333, 333*f*
Pneumocystis infection, 332–334
Pneumocystis jiroveci infection, 332, 333*f*–334*f*
diagnosis of, 49–50
pneumothorax in, 215–220
Pneumocystis jiroveci pneumonia
as AIDS complication, 339–340
ARDS from, 361
diagnosis of, 49–50
Pneumocystis, miscellaneous infections caused by, 325–336
Pneumomediastinum, 226–227, 227*f*
Pneumonia, 297–313
ARDS and, 361
aspiration, 299
bacteria, 299–300
clinical features of, 302–303
community-acquired, 306, 308*t*
contributing factors for, 298
cryptogenic organizing, 162, 162*f*
diagnostic approach to, 303–306, 304*f*–305*f*
eosinophilic, chronic, 173–174, 173*f*
etiology/pathogenesis of, 298–301
idiopathic, pathology of, 135–138
interstitial
acute, 163
desquamative, 161
idiopathic, 161–163
lymphocytic, in Sjögren syndrome, 164
nonspecific, 162
usual, 158
intrathoracic complications of, 310
mycoplasmal, 302–303
nosocomial, management of, 309
pathology of, 301
pathophysiology of, 301–302
pleural effusions in, 211
pneumococcal, 299
Pneumocystis jiroveci, as AIDS complication, 339–340
prevalence of, 297
therapeutic approach
based on clinical setting, 307–309
general principles and antibiotic susceptibility in, 306–307
ventilator-associated, 293, 378
viral, 300
Pneumonic plague, 311
Pneumonitis
hypersensitivity, 151–152
lymphocytic interstitial, as AIDS complication, 343
radiation, 155
Pneumothorax, 215–220
clinical features of, 217
complicating mechanical ventilation, 378–379
diagnostic approach to, 217–218, 219*f*
dyspnea in, 22
etiology and pathogenesis of, 215–216
pathophysiology of, 216–217
primary spontaneous, 216
tension, 216–217
treatment of, 218–220
Poliomyelitis, respiratory pump and, 249
Polycyclic aromatic hydrocarbons, lung cancer and, 261
Polymerase chain reaction, 51–52
Polymorphonuclear leukocytes (PMNs)
in lung defense, 290
reduction of, 294
in pneumonias, 301
Polymyositis-dermatomyositis, 164
pulmonary parenchymal involvement in, 163
Polyphonic wheezes, 32–33

Pores of Kohn, in spread of lobar pneumonia, 301
Positive end-expiratory pressure (PEEP), in ARDS, 372, 376
Positron emission tomography (PET)
  in lung cancer, 273
  in mediastinal masses, 224–225
  in patient evaluation, 45
Postpolio syndrome, respiratory pump and, 249
Postprimary tuberculosis, definition of, 316
Pre-Bötzinger complex, 230–231
Prednisone, for Wegener granulomatosis, 172–173
Pregnancy, dyspnea in, 23
Pressure support ventilation (PSV), 373–374, 375*f*
Pressure-controlled ventilation (PCV), 374, 375*f*
Pressure-limited ventilation, 373–374
Pretest probability, 189
Primary acid-base disorders, expected compensation for, 391*t*
Primary pulmonary hypertension, 195–196
Primary tuberculosis
  definition of, 316
  progressive, definition of, 316
  radiographic appearance of, 319
Progressive disseminated histoplasmosis, 326
Progressive massive fibrosis
  in coal worker's pneumoconiosis, 146
  in silicosis, 146
Progressive primary tuberculosis, 316
Progressive systemic sclerosis, pulmonary parenchymal involvement in, 163
Prostacyclin derivatives, 202
α_1-protease inhibitor, in emphysema pathogenesis, 95–96
Protease-antiprotease hypothesis, of emphysema, 95
Protective open lung strategy, for mechanical ventilation, 376
Proteinosis, alveolar, pulmonary, 174
Proteolytic enzymes, in emphysema pathogenesis, 95
Prothrombin gene mutation, 185
Proto-oncogenes, lung cancer and, 263
Provocation tests, in asthma diagnosis, 86
Pseudolymphoma, in Sjögren syndrome, 164
PSV. *see* Pressure support ventilation
Pulmonary alveolar proteinosis (PAP), 174
Pulmonary angiography, 45–46, 45*f*
  conventional, 191, 191*f*
Pulmonary arterial hypertension, as AIDS complication, 343
Pulmonary arterial pressure, elevated, 194
Pulmonary arterial walls, remodeling of, 195–196
Pulmonary artery, anatomy of, 178
Pulmonary artery balloon occlusion catheter, 179, 179*f*
Pulmonary artery occlusion pressure (PAOP), in ARDS, 367
Pulmonary artery tap, 199
Pulmonary capillary permeability, increased, 197–198
Pulmonary capillary wedge pressure, in ARDS, 367
Pulmonary disease
  evaluation of patient with, 30–64
  presentation of patient with, 19–29
Pulmonary edema, 359–360, 359*t*
Pulmonary embolism
  clinical features of, 187–188
  diagnostic evaluation in, 188–191
  dyspnea in, 22
  etiology and pathogenesis of, 184–185
  pathology of, 185–186
Pulmonary embolism *(Continued)*
  pathophysiology of, 186–187
  prophylaxis for, 192
  treatment of, 191–192
Pulmonary endometriosis, hemoptysis in, 26–27
Pulmonary function testing, 52–58, 200
  in asthma, 86–87
  guidelines for interpretation and sample problems, 386–389, 388*f*
  interpretation of normality in, 55
  in kyphoscoliosis, 255
  patterns of impairment, 55–57, 56*f*
  in pleural effusion, 214
  in respiratory muscle weakness, 250
  in sarcoidosis, 169
Pulmonary hypertension, 194–205
  architectural changes of, 198
  cardiac consequences of, 197
  chronic thromboembolic, 203–204
  classification of, 195*t*
  clinical features of, 199
  in COPD, 104
  diagnostic features of, 199–201
  in diffuse parenchymal lung disease, 142
  heritable, 201–202
  histologic changes in, 198*f*
  idiopathic, 195–196
  in kyphoscoliosis, 255
  left heart disease and, 202–203
  lung disease and, 203
  pathogenesis of, 195–197
  pathology of, 197
  pathophysiology of, 197–198
  specific disorders associated with, 201–204
  with unclear multifactorial mechanisms, 204
Pulmonary infarction, from pulmonary embolism, 185
Pulmonary infiltrates, 155
  diffuse, as AIDS complication, 343
Pulmonary Langerhans cell histiocytosis, 169–170
Pulmonary neuroendocrine cell, 67
Pulmonary parenchyma, 126–131
  anatomy of, 126–129, 127*f*
  physiology of, 129–131
  structure of, 128*f*
Pulmonary vascular bed, 196
Pulmonary vascular disease, 22
  as AIDS complication, 343
Pulmonary vascular resistance (PVR), 178–180, 179*f*
  increased
    in ARDS, 365
    in pulmonary embolism, 186
Pulmonary vasculature
  anatomy of, 177–178
  changes in, in ARDS, 365
  physiology of, 178–183
    aspects of, 182–183
    pulmonary blood flow distribution in, 180–181
    pulmonary vascular resistance in, 178–180, 179*f*
    pulmonary vascular response to hypoxia in, 181–182
Pulmonary vasoconstriction, hypoxic, 182
Pulmonary venous hypertension, 202–203
  transudative pleural fluid and, 210
Pulmonic insufficiency, 199
Pulse oximetry
  in COPD, 107
  in patient evaluation, 60–61

PVR. *see* Pulmonary vascular resistance
Pyrazinamide, for tuberculosis, 321

Q
Quinolones, for pneumonias, 306

R
Radiation treatments, in lung cancer palliation, 277
Radiation-induced lung disease, 155–156
Radiography, chest, 34–37, 35*f*
Radioimmunoassay, urinary antigen, in pneumonia diagnosis, 306
Radionuclide lung scanning, in patient evaluation, 43–45, 44*f*
Radon exposure, lung cancer and, 262
Raincoat ventilator, 380
Rales, 32
  in ARDS, 366
  in diffuse parenchymal lung disease, 142–143
Rapamycin, for lymphangioleiomyomatosis, 171
Rapid shallow breathing index, 377
Raynaud syndrome, pulmonary hypertension and, 201
Reactivation tuberculosis, 315–316
  definition of, 316
  radiographic appearance of, 319, 320*f*
Reflection coefficient, 208–209
Reinfection tuberculosis, definition of, 316
Rejection, complicating lung transplantation, 381
Residual volume (RV), 5
  in airway disease, 101–102
  in asthma, 83
  in diffuse parenchymal lung disease, 141
  in emphysema, 102
  factors determining, 101–102
  in patient evaluation, 52
  result of expiratory muscle weakness, 250, 251*f*
Respiratory acidosis, 60, 61*t*
  expected compensation for, 391*t*
Respiratory alkalosis, 60, 61*t*
  in asthma, 84
  expected compensation for, 391*t*
Respiratory bronchiolitis interstitial lung disease, pathology of, 136–137
Respiratory control, 229–235
  chemoreceptors in, 231–232, 232*f*
  CNS generator in, 230, 230*f*
  disorders of
    Cheyne-Stokes breathing as, 240–241, 241*f*
    secondary to lung disease, 242–243
    sleep apnea syndrome as, 243–246
  feedback system of, 230, 230*f*, 241
  input from other CNS regions in, 231
  input from other receptors in, 232–233
  instability of, 241
  organization of, 230–233, 230*f*
  ventilatory response
    to hypercapnia and hypoxia in, 233–235, 233*f*–234*f*
    to other stimuli in, 235
Respiratory disease, aspirin-exacerbated, 85
Respiratory distress syndrome, acute, 357–369
Respiratory equations, sample problems using, 384–385
Respiratory failure, 350–356
  acute
    classification of, 351–352
    noninvasive ventilatory support for, 377
  acute-on-chronic, 352
    CO_2 retention in, 372
    reducing work of breathing for, 373
Respiratory failure *(Continued)*
  chronic
    lung transplantation for, 380–381
    therapy for, 380–381
    ventilatory support, chronic, 380
  definition of, 351
  development of, 350
  gas exchange abnormalities in, pathogenesis of, 353–354
  hypercapnic, 352
    clinical and therapeutic aspects of, 354–355
    pathogenesis of, 353–354, 354*f*
  hypoxemic, 351
    pathogenesis of, 353
  management of, 370–383
    CO_2 elimination maintenance in, 371
    hypercapnic, 372–373
    hypoxemic, 371–372
    mechanical ventilation in, 373–379, 375*f*
    reducing work of breathing in, 373
    supportive therapy in, 371–373
  presentation of, 352
Respiratory generator, 230–231, 230*f*
Respiratory IgA, in innate immune system, 288
Respiratory infections, associated with bioterrorism, 310–312
Respiratory pump
  disorders of, 248–258, 249*t*
    chest wall diseases as, 254–257, 254*f*
    diaphragmatic disease as, 250–253
    neuromuscular, affecting muscles of respiration, 248–250
    obesity as, 255–257
  specific diseases of, 248–250
Respiratory system, 5
  anatomy of, 1–2
  physiology of, 3–15
    carbon dioxide transport in, 11–12
    circulation in, 7–8, 7*f*
    diffusion in, 8
    mechanical aspects of lungs/chest wall in, 2*f*–3*f*, 3–5
    oxygen transport in, 8–11, 10*f*
    ventilation, 5–6
    ventilation-perfusion relationships in, 12
Respiratory tract infections
  asthma and, 77
  childhood, COPD and, 97
  viral
    asthma and, 77
    impaired clearance in, 293
Restrictive pattern, of pulmonary function, 55, 56*f*
Reticular pattern, on chest radiograph, 37
  in diffuse parenchymal lung disease, 143
Reticulonodular pattern, on chest radiograph, 37
  in diffuse parenchymal lung disease, 143
Rheumatic diseases, systemic, pulmonary parenchymal involvement complicating, 163
Rheumatoid arthritis
  pleural effusions in, 211
  pulmonary parenchymal involvement in, 163
Rhonchi, 33
  in COPD, 105
Rifampin, for tuberculosis, 321
Roflumilast, for COPD, 108

S
Saccular bronchiectasis, 114
Samter syndrome, 85
Sarcoidosis, 164–169, 168*f*
  berylliosis and, 151
  chest radiograph in, 167*f*

Sarcoidosis *(Continued)*
diagnosis of, 168
granulomas in, 134–135, 135*f*
natural history of, 169
pathogenesis of, 165, 166*f*
treatment of of, 169
Sarcoma, Kaposi, as AIDS complication, 342–343
SARS. *see* Severe acute respiratory syndrome
Scar carcinoma, 262
Scleroderma, 201
pulmonary parenchymal involvement in, 163
Secretory IgA, in humoral immunity, 291
Secretory leukoprotease inhibitora1-protease, inhibitor, in emphysema pathogenesis, 96
Selexipag, 202
Severe acute respiratory syndrome (SARS), 300
Shunting
in ARDS, 364
in hypoxemic respiratory failure, 353
Silhouette sign, 35
Silica, 145
phagocytosis of, 146
Silicate, fibrous, asbestosis from, 148–149
Silicosis, 146, 147*f*
Silicotic nodules, 146, 147*f*
Simple chronic silicosis, 146
Sirolimus, for lymphangioleiomyomatosis, 171
Sjögren syndrome, pulmonary parenchymal involvement in, 164
Sleep apnea, obesity and, 256, 257*f*
Sleep apnea-hypopnea syndrome, 243
Sleep apnea syndrome, 123, 243–246
clinical features of, 243–244
pathophysiology of, 244–245, 245*f*
treatment of, 246
types of, 243
Slow-reacting substance of anaphylaxis, 80
Small cell carcinoma, of lung, 265, 266*f*
chest radiograph in, 273*f*, 279*t*
treatment of, 277–278
Smoking
COPD from, 95–96
prognostic significance of, 106
impaired clearance from, 294
lung cancer and, 260–261
Sol layer
antimicrobial peptides in, 287–288
in lung defense, 287
Solitary pulmonary nodule, 281–282, 281*t*
Specimens for diagnostic microscopy
collection of, 49–50
processing of, 48–49
Spherules, 327
Sputum
copious production of, in bronchiectasis, 115
microscopic examination of, in pneumonia diagnosis, 303–305
specimen, collection of, 49
staining of, in tuberculosis diagnosis, 320
Squamous cell carcinoma, of lung, 264–265, 265*f*, 279*t*
Squawk, 33
Staphylococcal pneumonia, 299
antibiotics for, 303, 306–307
clinical features of, 303
Starling equation, 208–209
fluid transport and, 358
Status asthmaticus, 85
Stem cell transplantation, hematopoietic, pulmonary complications of, 345
Stomata, on parietal pleural surface, 207, 209
Streptococcus pneumoniae pneumonia, 299
Stretch receptor reflex, 232
Stridor, 32–33
inspiratory, 22
Subacute cough, 25
Subcutaneous emphysema, 226
Superior sulcus tumors, symptoms of, 271
Supportive therapy, goals and principles of, 371–373
Suprasternal mediastinoscopy, in lung cancer staging, 274–275
Surfactant
production, decreased, in ARDS, 363–364
synthesis and function of, 127
Surfactant protein A (SP-A), in innate immune system, 288
Surfactant protein D (SP-D), in innate immune system, 288
Swan-Ganz catheter, 179, 179*f*
in ARDS evaluation, 367
Sweat chloride concentration, elevated, in cystic fibrosis diagnosis, 121
Sympathetic nervous system, in airway control, 70
Sympathomimetic agents, inhaled, for asthma, 87
Syncope, in massive pulmonary embolism, 187
Systemic lupus erythematosus
pleural effusions in, 211
pulmonary parenchymal involvement in, 163
Systemic rheumatic diseases, pulmonary parenchymal involvement complicating, 163

T

T lymphocytes, in cellular immunity, 292
Tachycardia, in pulmonary embolism, 187–188
Tachykinins, 70
Tachypnea, 20
in pulmonary embolism, 187–188
Tactile fremitus, 30
Talc, 145
Tension pneumothorax, 216–217, 219*f*
complicating mechanical ventilation, 378–379
Thoracentesis, in pleural effusion diagnosis, 212
Thoracoscopy, for lung tissue biopsy, 50
Thromboembolic pulmonary hypertension, chronic, 203–204
Thromboembolism, pulmonary, 184
Thrombolytic agents, for pulmonary embolism, 192
Thrush, as AIDS complication, 342
Thymic tumors, 224
Thymomas, 223
Thyroid gland enlargement, 223
Tidal volume (V_T), 5–6
Tissue inhibitors of matrix metalloproteinases, 96
TLC. *see* Total lung capacity
Total lung capacity (TLC), 5
in airway disease, 101–102
in chest wall and neuromuscular diseases, 250, 251*f*
in diffuse parenchymal lung disease, 141
in emphysema, 102
factors determining, 101–102
in patient evaluation, 52
Tracheal breath sounds, 31–32
Tracheobronchial infection, in cystic fibrosis, 120
Tracheobronchial secretions, collection of, 49
Transbronchial biopsy, 50
in diffuse parenchymal lung disease diagnosis, 143
in sarcoidosis diagnosis, 168
Transbronchial needle aspiration, 46
in lung cancer staging, 274–275
Transdiaphragmatic pressure, 252

Transplantation
hematopoietic stem cell, pulmonary complications of, 345
lung
for chronic respiratory failure, 380–381
complication of, 381
recipient of, pulmonary complications in, 344
organ, recipients of, pulmonary complications in, 344–345
Transpulmonary pressure, 2*f*, 3, 130
Transudative pleural fluid, 210–211
Trepopnea, 20
Triad asthma, 85
Trimethoprim-sulfamethoxazole
for *Pneumocystis* infection, 334
for pneumonias, 306–307
TSC. *see* Tuberous sclerosis complex
Tuberculin skin test, 318–319
Tuberculosis, 314–324
active, definition of, 316
as AIDS complication, 340–341
clinical manifestations of, 318
definitions related to, 316
diagnostic approach to, 318–321, 320*f*
disparity in health resources and, 314
etiology and pathogenesis of, 315–316
extensively drug resistant, 322
extrapulmonary, 318
granulomas in, 134–135
miliary, 315–316
multidrug resistant, 322
pathology of, 317
pathophysiology of, 317–318
pleural effusions from, 211
postprimary, definition of, 316
primary, 315
definition of, 316
progressive, definition of, 316
radiographic appearance of, 319
principles of therapy for, 321–322
reactivation, 315–316
definition of, 316
radiographic appearance of, 319, 320*f*
reinfection, definition of, 316
systemic manifestations of, 317–318
vaccine for, development of, 322
worldwide trends in, 314
Tuberculous disease, definition of, 316
Tuberculous infection
definition of, 316
tuberculin skin test for, 318–319
Tuberous sclerosis complex (TSC), lymphangioleiomyomatosis and, 170
Tularemia, 311–312
Tumor
bronchial carcinoid, 278
infiltrating, chest pain in, 28
Tumor necrosis factor (TNF)-α inhibitors, 345–346
Tumor suppressor genes, lung cancer and, 263
Type I epithelial cells, 128, 128*f*
Type II epithelial cells, 127, 128*f*

U

Ultrasonography
endobronchial, 46
in patient evaluation, 46
in pleural effusion, 212
Undifferential connective tissue disease, 164
Upper airway cough syndrome, 25
Upper airway disease, 122–124
clinical features of, 123–124
diagnostic approach of, 124
etiology of, 123
pathophysiology of, 123
treatment of, 124
Upper airway obstruction, 122–123
Urinary antigen radioimmunoassay, in pneumonia diagnosis, 306
Usual interstitial pneumonia, pathology of, 135–136, 137*f*
Uvulopalatopharyngoplasty, for obstructive sleep apnea, 246

V

Vaccine, tuberculosis, development of, 322
Vagus nerve, in airway control, 69*f*, 70
Vancomycin, for staphylococcal pneumonia, 306–307
Variable obstruction, 123
Varicose bronchiectasis, 114
Vascular disease
dyspnea in, 22
hemoptysis in, 27*t*
Vascular endothelial cells, activation of, in ARDS, 363
Vascular pressures, 7–8
Vasculitis, granulomatous, in Wegener granulomatosis, 172
Vasoconstriction
pulmonary, hypoxic, 182
in response to hypoxia, 196
Vasodilator testing, 202
VATS. *see* Video-assisted thoracic surgery
Vein, pulmonary, anatomy of, 178
Venn diagram, 257*f*
Venous blood, oxygen content of, 11
Ventilation, 5–6
alveolar, in ARDS, 366
Cheyne-Stokes, 240–241, 241*f*
negative-pressure, 380
positive pressure, noninvasive, 377
Ventilation scanning, 43–44
Ventilation-perfusion mismatch, 242
in ARDS, 364
in asthma, 84
in diffuse parenchymal lung disease, 142
in hypercapnia, 18
in hypoxemic respiratory failure, 353
in kyphoscoliosis, 255
in obesity, 256
in pneumonia, 302
Ventilation-perfusion ratio ($\dot{V}/\dot{Q}$), 13, 13*f*
spectrum of, 13*f*
Ventilation-perfusion relationships, 12–15
Ventilator-associated pneumonia, 293, 378
Ventilatory control disorders, 239–247
Ventilatory response
to hypercapnia and hypoxia, 233–235, 233*f*–234*f*
to other stimuli, 235
Ventilatory support
chronic, for chronic respiratory failure, 380–381
discontinuation of, 377
noninvasive, for acute respiratory failure, 377
Vesicular breath sounds, 31, 33*t*
Video-assisted thoracic surgery (VATS), 225
for lung tissue biopsy, 50
Viral infection, as AIDS complication, 341
Viral pneumonias, 300
therapy for, 307

Viral respiratory tract infections, 105
asthma and, 77
impaired clearance in, 293
Virtual bronchoscopy, 41
Visceral pleura, 206, 207*f*
Vital capacity (VC)
in diffuse parenchymal lung disease, 141
effort-independent portion of, 71–72
in patient evaluation, 52
Vocal fremitus, 30
Volume of dead space (V_D), 5–6
Volume-cycled ventilation, 374–375, 375*f*
Volutrauma, from positive pressure ventilation, 378–379

W
Warfarin, for pulmonary embolism, 191–192
Water, inhaled, ARDS from, 360–361
Wegener granulomatosis. *see* Granulomatosis with polyangiitis
Weight loss, in obesity, 257
Westermark sign, 188
Wheezing, 32–33
in asthma, 85
in COPD, 105
Whispered pectoriloquy, 32
Wood units, 179
Work of breathing, reducing, in respiratory failure, 373

X
X bodies, in pulmonary Langerhans cell histiocytosis, 170

Y
Yersinia pestis, plague from, 311

Z
Zone of apposition, 235–236, 236*f*
Zygomycetes, 332
ZZ genotype, emphysema and, 97

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