Fishman's Pulmonary Diseases and Disorders

Volume 1

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Fishman's Pulmonary Diseases and Disorders

Sixth Edition

Volume 1

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DEDICATION

This book is dedicated to the many clinicians worldwide who have devoted themselves to caring for those affected by SARS-CoV-19 and to the scientists who developed vaccines and therapeutic modalities directed against the virus.

MAG: To my wife, Barbara, and to our daughters, Kristen and Amy, for their steadfast support over the years, and to their families—Emily, Ali, Sawyer, Sophie, Levi, and Kieran.

DAO: To my husband, Eric, and our daughters, Orly and Daya. If you are going to spend a pandemic with anyone, you might as well laugh a lot. And to my patients, from whom I learn every day.

CDC: I would like to thank my family, friends, and all the mentors in pulmonary and critical care medicine who helped support me throughout my career. I would also like to thank my patients, from whom I have learned so much and who have been the motivation for my current work.

RMK: To my wife, Debbie, and my sons, Eric, Brian, and Ethan, for their unwavering love and support. And to the memory of my parents, Jean and Leon Kotloff, for instilling in me the principles by which I live my life and practice my profession.

CNK: Thanks to my husband, Darrell Kotton, and to our wonderful sons, David and Benjamin, for their thoughtfulness and support, especially as we navigated our family through the peaks of the COVID-19 pandemic. And thanks to my patients over the years, who have taught me so much about medicine, but also about resilience, optimism, and hope.

AIP: To my very supportive wife, Frances; my long-collaborating Administrative Assistant, Daniel Barrett; my four children, Alison, Angela, Andrew, and Allan Junior; and our 11 grandchildren.

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PART 1

Perspectives

CHAPTER 1

Milestones in the History of Pulmonary Medicine*

Michael A. Grippi

Clinical, scientific, and technologic aspects of medicine have evolved over more than 2000 years, and the study of lung function and pulmonary diseases has been an integral part of its growth and development. About 3 centuries ago, progress toward scientific medicine accelerated markedly, and it has continued to gain speed ever since. In the 17th century, research and experimentation began to tilt clinical medicine toward the exact sciences; by the 18th century, pathology had become an integral part of clinical medicine, and clinical–pathologic correlations succeeded empiricism, dogmatism, and metaphysics. The age of the great clinicians dawned in Europe in the early 19th century, when autopsies became legal and socially acceptable, and when physicians who cared for patients actually *performed* the autopsies.

The road to our current understanding and practice of pulmonary medicine and science has been somewhat convoluted.[1–3] However, it is possible to retrace the scientific trail by examining iconic figures and addressing milestones (Table 1-1). This chapter traces the course of scientific pulmonary medicine over the last two millennia. By necessity, what follows constitutes a limited overview of *selected* aspects of the history of the field, including alveolar–capillary gas exchange, lung volumes, mechanics of breathing, control of breathing, ventilation–perfusion relationships, and scientific advancements impacting clinical medicine, including chest imaging, lung transplantation, bronchoscopic techniques, and advances in critical care. Indeed, much of the content of the book addresses the many advances in respiratory disorders achieved over the last 50 years.

ALVEOLAR–CAPILLARY GAS EXCHANGE

In reflecting on the history of the science and thinkers largely responsible for our current understanding of the central role of the lungs in gas exchange, the following are considered: the ancient Greeks, William Harvey and the Oxford physiologists, the "phlogiston theory," theories of blood gas diffusion and "secretion" of oxygen, and the physical chemistry of blood gas transport.

Ancient Greek Medicine

The beginnings of scientific medicine can be traced to ancient Greece in the sixth century BC. At that time, natural philosophers speculated that air, or an essential ingredient in air, was inspired to generate a "vital essence" for distribution throughout the body.

Hippocrates, the "father of medicine," is as much a symbol of the Greek physician of the fifth and fourth centuries BC as the name of a real figure (Fig. 1-1). As an individual, he exemplified the caring physician who kept accurate records, made cautious inferences, and relied more on nature, rest, and diet than on drugs for treatment. His name has been immortalized by affixing it to three major components of Greek medicine, even though none appears to be the work of a single individual.

The first is the *Hippocratic corpus*, a collection of about 70 works that includes case reports, textbooks, lectures, and notebooks. The collection contains a description of Cheyne–Stokes respiration and the use of *Hippocratic succussion* for the diagnosis of fluid and air in the pleural space. The second is a collection of aphorisms—a compilation of brief generalizations related to medicine. The third, which is more likely attributable to Pythagoras (c. 530 BC) than Hippocrates (who lived about a century later), is the *Hippocratic oath*, which not only represents the spirit of the physician of ancient Greece, but which has endured to modern times as a reflection of the physician's code of ethics.

Another Greek, Aristotle, not only had an enduring influence on the intellect of humankind in his own time, but also for two millennia thereafter. Not until the 17th century were Aristotle's doctrine of the four elements (earth, air, fire, and water) and that of Hippocrates (blood, phlegm, yellow bile, and black bile) laid to rest, thereby clearing the way for modern scientific medicine.

Soon after Aristotle, in about 300 BC, an extraordinary medical school was founded at Alexandria in Egypt. One of the first teachers at the school, Erasistratus, postulated that the "pneuma," or spirit essential for life, is generated from interplay between air and blood.

About four centuries after Erasistratus, Galen (Fig. 1-2) drew upon the medical, philosophic, and anatomic knowledge of his day to fashion a remarkable physiologic schema.[3,4] His construct was largely teleologic. Unfortunately, it was so convincing that even though it was ultimately proved to be fanciful, it sufficed to retard scientific progress for a millennium and a half. Galen was a talented individual who was well educated, well read, and well positioned in society to popularize his beliefs. Moreover, his concepts fit well into the tenets of Christianity, which was then in its ascendency; to controvert his authority was tantamount to blasphemy. Among his long-lasting, albeit erroneous, postulates were the following: invisible pores in the ventricular septum that enabled the bulk of the blood to flow from the right ventricle to the left ventricle, thereby bypassing the lungs; a diminutive pulmonary circulation that served only to nourish the lungs; and two-way traffic in the pulmonary veins that enabled inspired air and "effluent waste vapors" to go their respective ways (Fig. 1-3).

Voices raised in protest to Galen's theories were without lasting effect. In the 13th century, Ibn al-Nafis, writing in his *Canon of Avicenna*, objected that blood does not traverse the ventricular septum from right to left, as Galen had proposed. However, this insight attracted little attention. Three hundred years later, Vesalius voiced similar misgivings. In the 16th century, Michael Servetus, a polymath trained in theology, geography, and anatomy, pictured the pulmonary circulation as the vehicle by which the "inhaled spirit" could be distributed throughout the body. In his theologic treatise, *Christianismi Restitutio*, he pointed out that blood could not traverse the septum between the right and left ventricles, and that the lumen of the pulmonary artery was too large for a nutrient vessel. He became a hunted heretic, wanted for execution by both the Catholic Church and Calvin. He was warned by Calvin to stay out of Geneva. Both Servetus and Calvin then behaved predictably: Servetus showed up at a church where Calvin was preaching, and Calvin had him captured and burned at the stake. In 1559, Realdus Columbus of Cremona, a pupil of Vesalius, rediscovered the pulmonary circulation, as did Andreas Caesalpinus in 1571. Despite these challenging observations, Galen's schema was to last for more than another half century—until the physiologic experiments of William Harvey.

William Harvey and the Oxford Physiologists

William Harvey's (Fig. 1-4) discovery of the circulation of the blood[5] was preceded by anatomic observations on the valves in systemic veins made by his mentor, Fabricus ab Aquapedente. Harvey's

*This chapter is a revision of the original chapter written by Alfred P. Fishman.

TABLE 1-1 Landmark Figures in the Evolution of Modern Pulmonary Medicine

Alveolar–Capillary Gas Exchange

Ancient Greek Medicine
- Hippocrates of Cos (c. 460–359 BC)
- Aristotle (384–322 BC)
- Erasistratus of Chios (c. 300–250 BC)
- Galen of Pergamon (AD 129–99)
- Ibn al-Nafis (c. 1210–1288)
- Leonardo da Vinci (1452–1519)
- Miguel Servetus (1511–1553)
- Andreas Vesalius of Brussels (1514–1564)
- Realdus Columbus of Cremona (1516–1559)
- Andreas Caesalpinus of Pisa (1519–1603)

William Harvey and the Oxford Physiologists
- Galileo Galilei (1564–1642)
- William Harvey (1578–1657)
- Giovanni Alfonso Borelli (1608–1679)
- Marcello Malpighi (1628–1694)
- Robert Boyle (1627–1691)
- Richard Lower (1631–1691)
- Robert Hooke (1635–1703)
- John Mayow (1640–1679)

Phlogiston: The Rise and Fall
- Georg Ernst Stahl (1660–1734)
- John Black (1728–1799)
- Joseph Priestley (1733–1804)
- Carl Wilhelm Scheele (1742–1782)

Respiration and Metabolism
- Antoine Laurent Lavoisier (1743–1794)
- John Dalton (1766–1844)
- Julius Robert von Mayer (1814–1878)
- Carl von Voit (1831–1908)
- Nathan Zuntz (1847–1920)

The Blood Gases
- Joseph Black (1728–1799)
- John Dalton (1766–1844)
- Heinrich Gustav Magnus (1802–1870)
- Felix Hoppe-Seyler (1825–1895)
- Paul Bert (1833–1886)
- Christian Bohr (1855–1911)
- John Scott Haldane (1860–1936)
- August Krogh (1874–1949)

Diffusion or Secretion of Oxygen
- Joseph Barcroft (1872–1947)
- Marie Krogh (1874–1943)

The Physical–Chemical Synthesis
- Lawrence J. Henderson (1878–1942)

Mechanics of Breathing
- John Hutchinson (1811–1861)
- Karl Ludwig (1816–1895)
- Franciscus Cornelius Donders (1818–1889)
- Fritz Rohrer (1888–1926)
- Wallace Osgood Fenn (1893–1971)

Control of Breathing

The Central Respiratory Centers
- Thomas Lumsden (1874–1953)
- Hans Winterstein (1878–1963)
- Merkel Henry Jacobs (1884–1970)

The Peripheral Chemoreceptors
- Ewald Hering (1834–1918)
- Joseph Breuer (1842–1925)
- Cornelius Heymans (1892–1968)

Scientific Basis of Clinical Medicine

Pathologic Anatomy
- Gioranni Battista Morgagni (1682–1771)
- Leopold Auenbrugger (1727–1809)
- Jean Nicolas Corvisart (1755–1821)
- René Théophile Hyacinthe Laënnec (1781–1826)

Microbiology
- Robert Koch (1843–1910)

Physiology of the Pulmonary Circulation
- Claude Bernard (1813–1878)
- Auguste Chauveau (1827–1917)
- Étienne Jules Marey (1830–1904)
- Dickinson W. Richards (1895–1973)
- André Frederic Cournand (1895–1988)
- Werner Forssmann (1904–1979)

Thoracic Imaging
- Wilhelm Conrad Roentgen (1845–1923)
- Godfrey N. Hounsfield (1919–2004)

Bronchoscopy
- Gustav Killian (1860–1921)
- Chevalier Jackson (1865–1958)
- Shigeto Ikeda (1925–2001)

Lung Transplantation
- Vladimir P. Demikhov (1916–1998)
- James D. Hardy (1918–2003)
- Joel D. Cooper

small book, *De Motu Cordis*, published in 1628, not only corrected a self-perpetuating error in Galenical teaching, but also marked the birth of modern physiology. The time, however, was not yet ripe to relate the function of the heart to the physiology of breathing. To his dying day, Harvey clung to the idea that the main function of breathing was to cool the heart. Moreover, since he made no use of the microscope, he could not picture how the pulmonary arteries made connections with the pulmonary veins. Galileo invented the compound microscope in 1610. In 1661, using the compound microscope, Marcello Malpighi reported that alveoli were covered by capillaries and that blood and air were kept separate by the continuous alveolar–capillary barrier.

Figure 1-1 The Hippocrates of Ostia. This damaged bust is believed to represent Hippocrates as perceived in antiquity. It was found in a family tomb in excavations near Ostia. *(Reproduced with permission from Dr. Dickinson W. Richards.)*

Figure 1-2 Galen of Pergamon as depicted in medieval times. No authentic reproduction exists of Galen in ancient times. *(Reproduced with permission from Galen's Therapeutica, published in Venice in 1500.)*

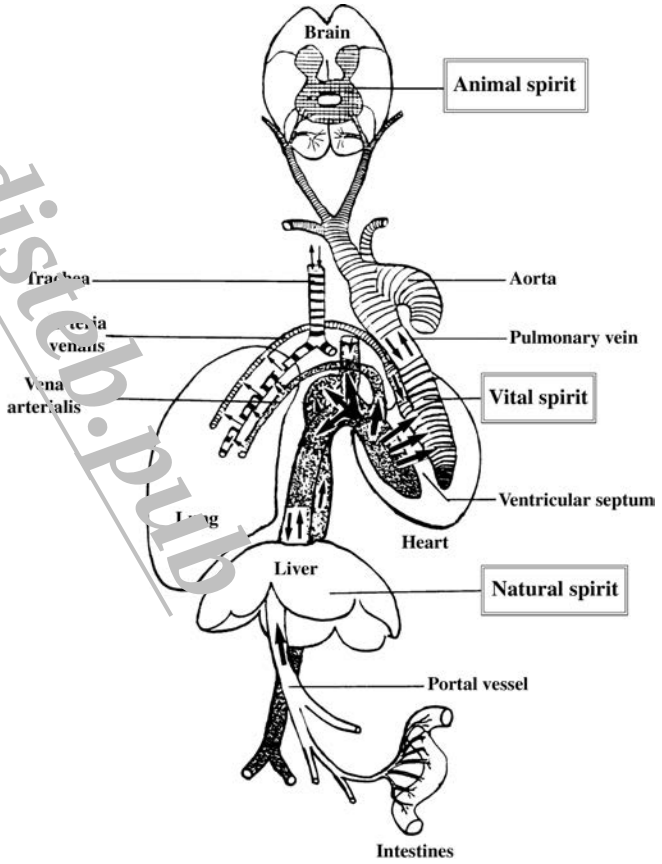

Figure 1-3 Galen's scheme of the circulation. The diagram shows the source and distribution of the three types of spirits. The validity of this scheme depended on invisible pores in the ventricular septum, two-way traffic in the pulmonary vein, and selective permeability of the mitral valve for sooty wastes but not for spirit-containing blood. Vena arterialis, pulmonary vein; arteria venalis, pulmonary artery. *(Modified with permission from Singer C. A Short History of Scientific Ideas to 1900. London: Oxford University Press; 1959.)*

Figure 1-4 William Harvey (1578–1657). This portrait of William Harvey is part of a family group in which William Harvey and his five brothers are gathered around their father, William Harvey.

Figure 1-5 Robert Boyle (1627–1691). This engraving, from an original painting by Johann Kerseboom, hangs in the Royal Society, London. Boyle's invention of a pneumatic air pump and his publications concerning "the spring of air and its effect" stimulated considerable research on the physical properties of air and its role in respiration and combustion. He strongly influenced Hooke, Lower, and Mayow at Oxford.

Harvey's description in 1628 of the circulation of the blood had three major consequences for pulmonary medicine: (1) it oriented pulmonary medicine toward the basic sciences and away from philosophy and empiricism; (2) it demolished the Galenic concept of the movement of the blood; and (3) it set the stage for an upcoming generation of physiologists at Oxford University to explore breathing in chemical and physical terms.

The physiologists working at Oxford in the 1660s were greatly impressed by Harvey's disciplined approach to scientific inquiry. Many were medical practitioners who conducted research as a sideline. Four, in particular, began the systematic study of air and its constituents, thereby laying the foundations for contemporary respiratory physiology and medicine: Robert Boyle (Fig. 1-5), Robert Hooke, Richard Lower, and John Mayow.

In 1660, Robert Boyle proved by means of his air pump that air is necessary for life. In 1667, Robert Hooke showed that insufflation of the lungs with air while breathing movements were arrested could keep an open-chest animal alive; that is, that movement of the lungs was not essential for life. Richard Lower, the first to practice blood transfusion, took advantage of Hooke's continuously inflated lung preparation in the dog to observe that dark venous blood becomes bright red as it traverses lungs insufflated with air. In 1674, Mayow interpreted the change in the color of blood from venous to arterial as due to the uptake of "nitroaerial particles" (later to be called "oxygen") from the air.

Phlogiston: the Rise and Fall

Unfortunately, the discoveries and insights of the Oxford physiologists went largely unnoticed during the century that followed, overshadowed by the "phlogiston theory" of combustion. The theory, advanced by Stahl, postulated that all combustible materials were composed of two ingredients: phlogiston, a principle that transformed into fire when heated, and an ash that was left behind after the fiery phlogiston escaped. The phlogiston theory was sufficiently malleable to accommodate almost every new discovery that could have overthrown it, including the rediscovery of carbon dioxide in 1754 by Joseph Black, and the independent discoveries of oxygen by Priestley and Scheele. Although the respiratory gases had been discovered by the end of the 18th century and many of their properties characterized, the discoveries were misapplied to support, rather than destroy, the phlogiston theory. The phlogiston theory was finally undone by the experiments of Lavoisier.

Respiration and Metabolism

From the time of Hippocrates until early in the 20th century, debate had continued about the site of heat production in the body. In 1777, Lavoisier suggested that air was composed of one respirable gas (which he later named "oxygine") and another (nitrogen) that remained unchanged in the course of respiration. Between 1782 and 1784, Lavoisier and Laplace concluded, on the basis of calorimetric experiments on guinea pigs, that "respiration is therefore a combustion, admittedly very slow, but otherwise exactly similar to that of charcoal" (Fig. 1-6). The similarity between respiration and combustion had previously been recognized by the Oxford physiologists, especially Mayow.[6] By 1783, Lavoisier was accumulating evidence against the phlogiston theory and began to replace it with an entirely new system of chemistry.

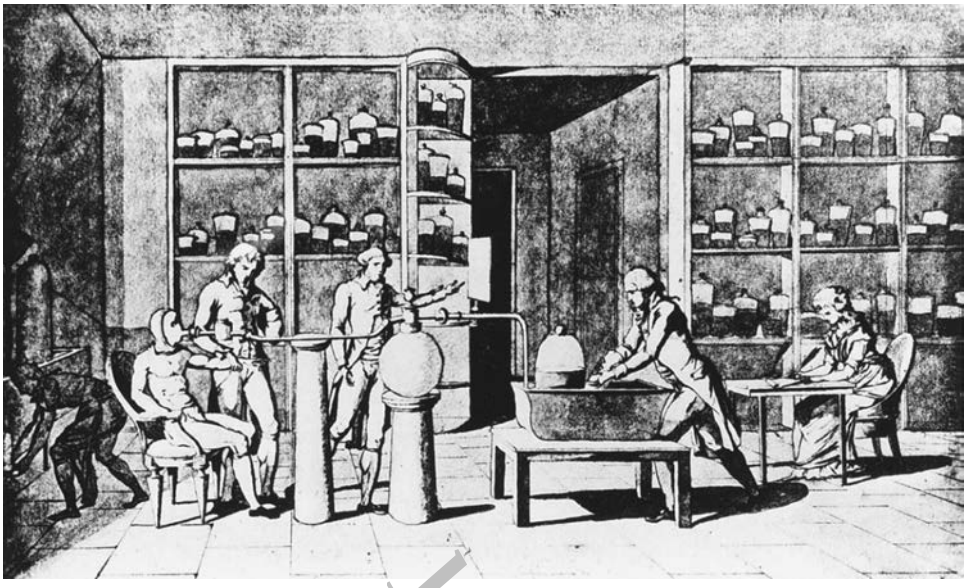

Figure 1-6 Scene from the laboratory of Antoine Laurent Lavoisier (1743–1794). His wife is acting as his assistant, and Sequin is the subject. Studies such as this led to the conclusion that respiration and combustion are similar processes.

As noted previously, the ancients pictured the heart as the heat generator. Lavoisier favored the lungs. Others held that combustion occurred in the blood. Although Spallanzani had shown in the 18th century that isolated tissues take up oxygen and give off carbon dioxide, the idea that combustion occurred in the tissues was slow to gain acceptance. However, the hypothesis gained strength through the work of Pflüger in 1878. He measured oxygen consumption and carbon dioxide production in dogs and calculated respiratory quotients. His research substantiated a concept that had been enunciated, but not named, by Lavoisier.[7]

Once the idea that oxidation occurred in the tissues had become generally accepted, investigators delved into the processes involved in utilization of foodstuffs by the tissues, energetics, growth, and repair. Carl von Voit and Max von Pettenkofer, using a respiration chamber, drew upon chemical balances and respiratory quotients in humans to distinguish the nature of the foodstuffs being burned and to show that the amounts of fat, protein, and carbohydrate burned varied with the mechanical work done by the subject. Between 1842 and 1845, Julius Robert von Mayer formulated the law of conservation of energy. Subsequently, Max Rubner showed that the law applied to the living body, and Herman von Helmholtz showed that its relevance to metabolism could be demonstrated experimentally. Application of these principles at the bedside was greatly facilitated by the development of a portable metabolic apparatus by Nathan Zuntz. Pioneering bedside studies of metabolic states were conducted by a succession of distinguished investigators, including Magnus-Levy, Graham Lusk, F. G. Benedict, and Eugene F. DuBois.

The Blood Gases

The Oxford physiologists set the stage for the discovery of the blood gases. Using his vacuum pump, Robert Boyle extracted "air" from blood. John Mayow came close to discovering oxygen by showing that only a portion of air was necessary for life—the "nitroaerial spirits"—which were removed both by respiration and fire (combustion). One of his famous experiments entailed enclosing a mouse and a lighted lamp in an airtight container; the lamp went out first and then the mouse died. However, Mayow did not realize that the "nitroaerial spirits" could be isolated as a gas.[6]

One hundred years after Mayow, Joseph Priestley (Fig. 1-7) exposed a mouse to the gas released from heated mercuric oxide and found that the gas supported life better than air did; he also noticed that a flame burned more vigorously in this gas than in air. Priestley was not alone in his preoccupation with flame. In 1773, about a year before Priestley had obtained oxygen by heating mercuric oxide, Scheele discovered oxygen independently because of his interest in fire, and he designated oxygen as "fire air."

In 1662, Van Helmont, a Capuchin friar and talented chemist, as well as a mystic with a drive to quantify, discovered carbon dioxide, coined the word *gas*, and called carbon dioxide "wild gas" ("gas sylvestre"). In 1755, Joseph Black rediscovered carbon dioxide. He showed that calcium carbonate (limestone) and magnesium carbonate (magnesia alba) lost weight on heating, releasing "fixed air" (CO_2) in the process. This fixed air extinguished both flame and life. Lavoisier knew of the observations of Black and of Priestley

Figure 1-7 Joseph Priestley (1733–1804), the discoverer of oxygen. This figure shows a silver medal struck in his honor in 1783. A Presbyterian minister, he was radical in his religious and political beliefs, inventive in science, and conservative in the interpretation of his findings. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

Figure 1-8 Christian Bohr (1855–1911). At work in his laboratory, Bohr *(far right)* and his associates systematically explored the interplay between the respiratory gases and hemoglobin that led to the discovery of the "Bohr effect." *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

and Scheele. He decided in 1778 that the gas obtained from heating mercuric oxide was not "fixed air" or "common air," but "highly respirable air" (oxygen).

The story of hemoglobin, the essential element in the transport of the respiratory gases by the blood, begins with Hoppe-Seyler, who, between 1866 and 1871, crystallized hemoglobin, explored its chemical properties, and assigned it a proper role in the transport of oxygen by the blood. At the turn of the 19th century, Dalton reported his experiments with the respiratory gases, which led to the development of his atomic theory. In 1872, taking advantage of Dalton's law, Paul Bert published the first oxygen dissociation curve, that is, oxygen content at different barometric pressures; he pictured the curve as hyperbolic. Christian Bohr (Fig. 1-8) subsequently identified its s-shaped contour, and in 1904, together with Hasselbach and August Krogh, showed that increasing carbon dioxide tension in blood drives out oxygen, that is, the "Bohr effect." Shortly thereafter, the influence of various factors, for example, temperature and electrolytes, on the affinity of oxygen for hemoglobin (and, consequently, on the position of the oxygen dissociation curve) was explored in detail by Barcroft and associates. In 1914, Christiansen, Douglas, and Haldane reported that an increase in the oxygen tension of the blood drives out carbon dioxide, that is, the "Haldane effect." In 1967, a new dimension was added to the understanding of the position and configuration of the oxygen dissociation curve by the demonstration that diphosphoglycerate, a chemical constituent of red cells, regulates the release of oxygen from oxyhemoglobin.

Diffusion or Secretion of Oxygen

Bohr is a central figure as an investigator and mentor in respiratory physiology.[8] In 1904, he raised a troublesome issue that was not easily resolved, primarily because of limitations in methodology at the time. He postulated that even though diffusion could account for oxygen uptake at rest, it could not suffice during strenuous exercise, particularly at altitude. He held that oxygen *secretion* had to be involved.[9] He clung to this misconception during his lifetime, a conviction supported by two major lines of evidence. The first was indirect: Oxygen secretion by the swim bladder of fish showed by extrapolation that active transport of oxygen in the lungs was possible. The second was based on observations made during Bohr's expedition to Pike's Peak in 1912, during which it was erroneously demonstrated that with exercise at altitude, arterial oxygen tension exceeded alveolar oxygen tension.

However, even before the report from high altitude, Bohr's former assistant, August Krogh, and his wife, Marie Krogh (Fig. 1-9) had marshaled new evidence to show that "the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and diffusion alone." The final blow to the secretion theory was delivered by Marie Krogh.[10] Based on the single-breath carbon monoxide method for determining diffusing capacity that she and her husband had developed in 1910,[11] she was able to account for oxygen uptake in the lungs by diffusion alone, even during strenuous exercise under conditions of low oxygen tension. Refinements in the carbon monoxide method by Roughton and others extended

Figure 1-9 August and Marie Krogh in 1922, at the time of their first visit to the United States so that August Krogh could deliver the Silliman Lecture at Yale. They demonstrated that diffusion, without secretion, could account for the transfer of O_2 and CO_2 across the alveolar–capillary membranes of the lungs. *(Reproduced with permission of their daughter, Dr. Bodil Schmidt-Nielsen.)*

Figure 1-10 Two founders of contemporary respiratory physiology in 1936. Sir Joseph Barcroft (1872–1947) *(left)* proved, in experiments on himself, that diffusion was the mechanism for gas exchange in the lungs and pioneered current understanding of the respiratory functions of the blood. Lawrence J. Henderson (1878–1942) *(right)* provided a mathematical analysis of blood as a physiochemical system and stimulated research on the complex interplay involved in respiratory gas exchange during exercise. *(Reproduced with permission from Fishman AP, Richards DW. Circulation of the Blood: Men and Ideas. New York, NY: Oxford University Press; 1964.)*

its clinical applicability and provided further evidence against the secretion theory.[12] Despite these observations, Haldane would not let go. Throughout his life, despite mounting evidence to the contrary, he adhered to the idea that oxygen was secreted by the alveolar membrane.

The issue was finally settled by Joseph Barcroft (Fig. 1-10). Using a chamber to reproduce the circumstances of hypoxia and strenuous exercise assessed during the Pike's Peak expedition, he found that under all conditions, the oxygen saturation of arterial blood was less than that of arterial blood exposed to a sample of alveolar gas obtained at the same time. He subsequently confirmed these results by experiments done at high altitude at Cerro de Pasco (1921–1922).

The Physical–Chemical Synthesis

Lawrence J. Henderson undertook the herculean task of depicting the reactions of oxygen and carbon dioxide in blood, not as cause and effect, but as interplay among physiochemical variables and functions (Fig. 1-10). His theoretical considerations and practical applications in the Fatigue Laboratory at Harvard University were greatly abetted by close collaboration with Van Slyke, Wu, and McLean at the Rockefeller Institute in New York, who were exploring the exchanges of blood constituents between red cells and plasma. In 1828, Henderson presented his synthesis in the form of a d'Ocagne nomogram that displayed changes in the various elements that entered into the exchange of the respiratory gases between alveolar gas and blood: plasma; the red cell; hemoglobin; and chloride, bicarbonate, and hydrogen ions. He presented nomograms not only for the normal subject at rest and during exercises, but also for individuals with anemia, nephritis, diabetic coma, and other major clinical entities. Henderson dealt with steady-state observations. Roughton and associates enlarged the physiochemical horizons

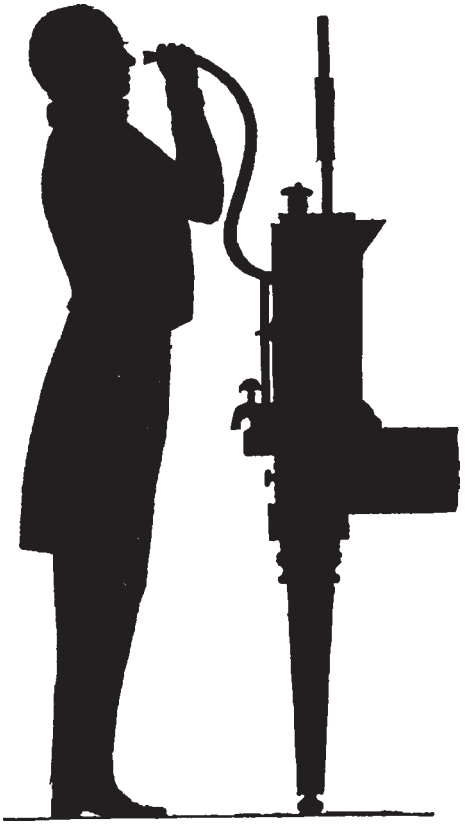

Figure 1-11 John Hutchinson's illustration of a subject about to undergo measurements of lung volumes. *(Reproduced with permission from Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Med Chir Trans. 1846;29:137–252.)*

further by discovering carbonic anhydrase in the red cell and addressing transient phenomena related to transport of respiratory gases and carbon monoxide in blood.

LUNG VOLUMES

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800,[13] it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing. He devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age (Fig. 1-11). The many refinements since then are too numerous for mention in this chapter. A big step forward was the invention of the body plethysmograph many years later, which made possible the determination of the thoracic gas volume and airway resistance.

MECHANICS OF BREATHING

The ancients wondered how air moved into and out of the lungs; as far back as the time of Erasistratus, the diaphragm was recognized as involved in breathing. Galen was aware that the lungs fill the chest cavity and are moved by the actions of the thorax, and that the large airways enlarge and lengthen during inspiration. He marveled at the long course of the nerves to the diaphragm and the innervation of the intercostal muscles. After Galen, interest in the mechanics of breathing waned except for sporadic observations and experiments by anatomists, notably Leonardo da Vinci and Andreas Vesalius. Interest in respiratory mechanics resumed in the 16th century, largely as a result of progress in physics and mathematics, as exemplified in the works of Borelli and Galileo.

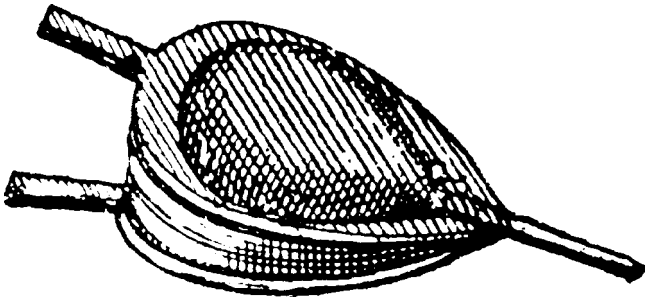

Figure 1-12 Mayow's model of the chest and lungs. The bellows encloses a bladder, the neck of which opens to the outside. A glass window on the upper side makes it possible to observe the bladder during inflation and deflation. *(Reproduced with permission from Mayow J: Medico-Physical Works, Crum A, Brown, Dobbin L [trans]. Edinburgh, Alembic Club, Reprints, no 17, 1957. [Translated from Tractatus quinque medico-physics, 1674.])*

The Respiratory Muscles

Mayow, one of the Oxford physiologists, drew heavily on the work of colleagues, including Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it (Fig. 1-12). He understood that air moved into the lungs as the chest expanded because of the pressure and elasticity of ambient air; he also appreciated that the chest expanded because of the action of the intercostal muscles (internal and external), that the diaphragm is the primary muscle of inspiration, and that normal expiration is passive. After Mayow, little research was done on the role of the respiratory muscles in breathing until the mid-19th century, when Donders distinguished between the respective roles played by the inspiratory muscles and elastic forces.

Elastic Properties of Lungs and Chest Wall

Until the 20th century, observations on the elastic properties of the lungs and chest wall in humans were fragmentary. Access to the pleural space was the major limiting factor. With few exceptions—notably Neergaard and Wirz, who used pleural pressures to determine elastic recoil in normal human subjects, and Christie, who recorded pleural pressures to demonstrate loss of pulmonary elasticity in emphysematous patients—measurements in humans were largely confined either to therapeutic interventions, for example, induction of a pneumothorax or aspiration of pleural fluid, or experiments done at autopsy. The number of observations on the mechanical properties of the lungs increased dramatically when it was shown by Buytendijk, in 1949, and again by Dornhurst and Leathart, in 1952, that esophageal pressures provided an accurate measure of pleural pressures.

The role of alveolar surface tension in determining the elastic forces in the lungs began to be widely appreciated in the late 1950s, although the stage had been set long before. In 1812, Laplace had published the law of surface tension. The implication of this law for the lungs was appreciated initially in 1929 when Neergaard compared pressure–volume curves of lungs filled with air with those filled with fluid. He concluded that unopposed surface tensions would favor alveolar collapse. Then, between 1954 and 1960, a remarkable outpouring of papers from different laboratories showed that a unique surfactant lined the alveoli, and that this material was absent in premature infants with hyaline membrane disease (and alveolar collapse); these papers prompted extensive research on the chemical and physical properties of surfactant and on its sites of formation and removal.

Airway Resistance

A giant step forward occurred in 1916 when Rohrer, as part of his doctoral dissertation, presented a conceptual framework for determining flow and resistance in airways. His equations were based on precise anatomic measurements of airway dimensions in a human cadaver, coupled with aerodynamic principles. During the following decade, he and his coworkers, Neergaard and Wirz, applied Poiseuille's law for laminar flow and his equations to the determination of airway resistance. Use of Fleisch's pneumotachograph, coupled with periodic interruptions of airflow, permitted measurement of alveolar pressure. Clinically useful measurements of alveolar pressure became available in 1956 with the introduction by DuBois and associates of the whole-body plethysmograph, which they coupled with the application of Boyle's law.

Synthesis of Mechanics

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure–volume characteristics of the respiratory system and the work of breathing; they also developed the principle of optimal frequencies of breathing to minimize respiratory work. Together with von Neergaard and Wirz, Rohrer developed and tested, experimentally, concepts involving pressures, flows, and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester, starting in the 1940s. The contributions of W. O. Fenn, H. Rahn, and A. B. Otis to our present understanding of the mechanics of breathing are significant, and there is little doubt that this group shaped much of the contemporary thinking of respiratory physiologists and pulmonary physicians.[14–17]

CONTROL OF BREATHING

The control of breathing is a complex process that depends on the integrity of the entire respiratory system—lungs, airways, circulation, and control systems.[18] Two dominant control systems exist. One is in the central nervous system; the other is outside the brain. Control mechanisms in the central nervous system are influenced by the state of wakefulness or alertness and are subject to voluntary control. These mechanisms are also influenced reflexively by a variety of peripheral receptors.

Localization of the Central Respiratory Centers

In 1812, Legallois, apparently intrigued by the gasping movements of the head after decapitation, identified an area in the medulla that was essential for life. In 1923, Lumsden systematically explored the effects of serial sectioning of the brain stem on respiration, marking the beginning of the era of contemporary research on rhythmic breathing. He designated an area in the caudal pons responsible for a sustained inspiratory drive as the "apneustic center," and an area in the rostral and lateral portions of the pons that presumably inhibited the apneustic drive as the "pneumotaxic center"; sectioning of the vagi exaggerated the inhibition of the apneustic drive by the pneumotaxic center. Sixteen years later, Pitts et al.,[19] using stereotactic stimulation of the cat medulla, identified inspiratory and expiratory centers and proposed a theory that could account for both rhythmic breathing and apneusis.

Chemical Stimulation of the Respiratory Centers

The chemical stimuli to breathing have been known for more than a century. In 1885, Miescher-Ruesch showed in humans that ventilation at rest is primarily regulated by carbon dioxide. Between 1887 and 1901, cross-perfusion experiments by Leon Fredericq underscored the role of carbon dioxide. However, it was not until 1905

to 1909 that Haldane, Priestley, and Douglas paved the way to the modern understanding of the role of carbon dioxide under a variety of experimental conditions.[20] In their experiments on humans, they relied heavily on the Haldane gas analyzer and an alveolar gas sampler of their own invention. However, their experiments did not distinguish clearly between CO_2 and H^+ in the stimulation of the respiratory centers. Winterstein, and later Gesell,[21] advanced the idea that the chemical regulation of respiration is determined by the concentration of hydrogen ions within the respiratory centers.

The Winterstein theories[22] provide a good example of the evolution of ideas prompted by new discoveries and inventions. The original theory in 1911 attributed increments in ventilation caused by hypoxic or hypercapnic inspired mixtures to a single mechanism, that is, acidification of arterial blood by either carbonic acid or lactic acid. In 1921, Jacobs' demonstration of the rapid diffusion of carbon dioxide into starfish eggs implicated acidity within the respiratory centers,[23] as well as arterial blood acidity, as the sites of stimulation. To account for the stimulation of breathing by hypoxia (the peripheral chemoreceptors had not yet been discovered), he invoked the release of asphyxiating substances *(Erstickungsstoffen)* within the respiratory centers themselves. A third theory, postulated in 1949, attempted to incorporate the discovery of the peripheral chemoreceptors, and it finally gave way in 1955 to his fourth theory, which explained the effects of acid or hypoxia on both the central and peripheral chemoreceptors.

A major consequence of Winterstein's research was an impetus to subsequent exploration of the chemical control of breathing. These studies led to the identification of central chemoreceptors, distinct from mechanoreceptors, on the ventral surface of the medulla, and clarification of the role of hydrogen ion activity as the central stimulus to breathing. The studies also prompted a search for a unifying theory for the chemical control of breathing.

The Reflex Regulation of Breathing

A considerable and diverse number of peripheral receptors can influence breathing reflexively by supplying information to respiratory centers located in the brain. These include pain receptors, stretch receptors in the muscles and distensible thoracic structures, and organs and chemoreceptors in major systemic arteries.

Mechanoreceptors

Until the work of Hering and his student, Breuer, little was known about the role of afferent impulses to the central control mechanisms in the control of breathing, other than the fact that electrical stimulation of the vagus nerves influenced respiration.[24] In 1868, Hering and Breuer reported that inflation of the lungs stopped respiration in expiration and promoted expiration, and that, conversely, a decrease in lung volume ended expiration and promoted inspiration. They inferred that inflation mechanically stimulated nerve endings in the lungs and that the resulting impulses ascending the vagi were inhibitory to inspiration.

Peripheral Chemoreceptors

In 1841, Volkmann suggested the existence of chemoreceptors in the systemic circulation that were sensitive to blood-borne stimulants to respiration. In 1927, J. F. Heymans and C. Heymans first showed that the aortic bodies served this function, and in 1930, C. Heymans and Bouckaert demonstrated the peripheral chemoreceptive function of the carotid bodies. These were physiologic observations that tallied well with the observations of F. De Castro, a student and later a colleague of Ramón y Cajal, who was sufficiently impressed by the histologic structure, location, and rich innervation of the carotid body to propose that it might be stimulated by blood-borne substances (Fig. 1-13).[25]

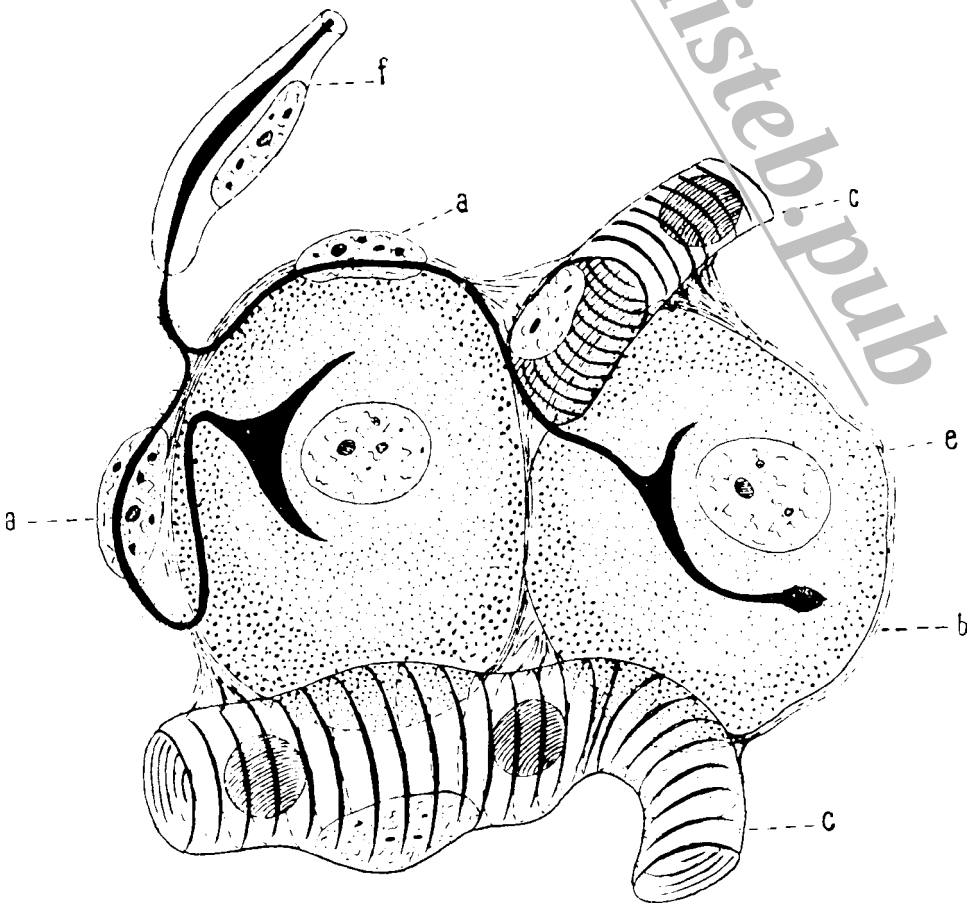

Figure 1-13 Drawing by De Castro showing the structure of the chemoreceptor. The glomus cells (*e*) present an ample cytoplasmic surface for contact with the perfusing blood delivered by the capillary (*c*); sensory nerve fiber (*f*) with sheath of myelin; Schwann cells (*a*) surround the unmyelinated fibers which form the terminal menisci; cell membrane (*b*). *(Reproduced with permission from De Castro F: Sur la structure de la synapse dans les chemocepteurs: leur mécanisme d'Excitation et R™ le dans la circulation sanguine locale. Acta Physiol Scand. 1951;22(1):14–43.)*

Figure 1-14 Giovanni Battista Morgagni (1682–1771). The five volumes of his *De Sedibus* contain the clinical and pathologic descriptions of approximately 700 cases. *(Reproduced with permission from the Library of the College of Physicians of Philadelphia.)*

VENTILATION–PERFUSION RELATIONSHIPS

In 1946, William Dock attributed the apical localization of tuberculosis to hypoperfusion of well-ventilated alveoli in the lung apices in the upright position.[26] Shortly thereafter, ventilation–blood flow relationships were described in quantitative terms in papers by two separate groups: Rahn and Fenn[27] and Riley and Cournand.[28–30]

SCIENTIFIC BASIS OF CLINICAL PULMONARY MEDICINE

Five remarkable figures serve to illustrate different stages in the evolution of the scientific basis of pulmonary medicine: Morgagni, Laënnec, Koch, Cournand, and Richards. They represent key scientists in the areas of pathologic anatomy, microbiology, and physiology.

■ Pathologic Anatomy

Morgagni and Laënnec, almost a century apart, made major contributions to the field of pathologic anatomy. Morgagni (Fig. 1-14), who lived in the 18th century and was a student of Valsalva, veered away from the undisciplined case reports of his predecessors. Instead, he adopted a logical system for relating findings at autopsy to their clinical manifestations. At age 79, he published a compilation of his lifelong experience in his famous work, *De Sedibus et Causis Morborum per Anatomen Indagatis. De Sedibus* includes about 700 cases. The clinical–pathologic correlations in this work benefited greatly from the fact that Morgagni was both a seasoned clinician and a pathologist. One of the compilation's five books is devoted to diseases of the thorax. Among his descriptions were those of a tubercle undergoing liquefaction and the hepatization stage of pneumonia.

René Théophile Laënnec is, perhaps, best known for inventing the stethoscope in 1816 (Fig. 1-15).[31,32] At that time, clinical medicine in Europe, especially in France, was turning from metaphysical concepts

Figure 1-15 Rene T.H. Laënnec (1781–1826). *(Drawn from life in 1825 by Charles James Blasius Williams (1805–1889) and reproduced in his autobiography, Memoirs of Life and Work, London: Smith, Elder & Co; 1884.)*

and doctrinal systems to pathology as its scientific foundation. Eminent physicians, such as Bichat, Bayle, and Corvisart in France, and William and John Hunter and Baillie in England, were turning to anatomic findings at autopsy to understand the signs and symptoms of their patients. Percussion had been rediscovered by Corvisart. Although Auenbrugger had reported in Latin his "new invention" in 1761, the idea had not caught on until Corvisart—eminent clinician and teacher and personal physician to Napoleon—published a translation in French in 1808. Corvisart's approach to medicine strongly influenced Laënnec. Laënnec applied the stethoscope and Corvisart's "sounding of the chest" to study individual patients with diseases of the lungs and heart throughout their clinical course, along with anatomical examination at autopsy. This was no simple matter. Since there were no pathologists in those days, the physician not only had to provide continuous care during the patient's lifetime, but he also had to arrange for and perform, the autopsy; he then had to gather all that he had seen and learned and prepare it for publication.

In 1819, two years after the invention of the stethoscope, Laënnec published his famous monograph, *De l'Auscultation médiate*, which drew lessons from carefully documented cases that were studied throughout their clinical course and at autopsy. In this work, Laënnec built upon the monumental tome of Morgagni, who, a generation before, had related the clinical features of the diseases he described to the morbid anatomy, but who had not been able to take the next step of relating the clinical course of individual patients to the anatomic findings after death.

Laënnec's monograph contains descriptions of physical signs, clinical–pathologic correlations for tuberculosis, pneumonia, bronchiectasis, emphysema, and cancer of the lung, and instructions for the treatment of these conditions. The descriptions of tuberculosis were an outstanding contribution to the field and were reported prior to Koch's discovery of the causative agent.

■ Microbiology

Tuberculosis provides a remarkably illuminating example of the impact of a novel basic science on clinical medicine.[33–35] The disease

can be traced back to the ancients, who were familiar with the diverse clinical syndromes that we now take for granted as due to tuberculosis; however, they had no way to relate them to a common etiologic agent. A synthesis by Morton in 1685 of all that was then known about tuberculosis focused on cavitary lesions, emaciation ("consumption"), and the tubercle, but it was shrouded in Galenic humors. An understanding of the disease accelerated in the 18th century when clinicians, such as William Cullen, began to sort out the various syndromes relating to phthisis, including hemoptysis, empyema, catarrh, and asthma.

The tempo of discovery increased dramatically in the 19th century after the French Revolution. During the Napoleonic era, distinguished Parisian clinicians, including Bichat, Bayle, Louis, Broussais, and Laënnec, reported clinical–pathologic correlations of tuberculosis. (Notably, both Bayle and Laënnec died of tuberculosis.) However, little advance was made in understanding the pathogenesis of tuberculosis until Villemin, who, impressed by the analogy between glanders and syphilis on the one hand, and tuberculosis on the other, and the fact that two of the three diseases had been shown to be infectious in origin, undertook experiments demonstrating that tuberculosis was an infectious disease that could be transmitted from humans to animals, and from animals to animals.

Koch

In 1876, Koch was a general practitioner in the German township of Wollestein in the province of Posen, where he was responsible for the health care of 4000 inhabitants (Fig. 1-16). Between obstetrical deliveries and satisfying the medical and surgical needs of patients of all ages, he managed to conduct research on the microbial causes of communicable diseases. His laboratory was homemade-based in either the barn or his living room; his major instrument was a microscope used to examine bacteriologic and tissue specimens. In pursuing his research, he kept in mind the dictum of Jacob Henle, one of his teachers in medical school, who counseled that, "before microscopic organisms can be regarded as the cause of contagion in man, they must be found constantly in the contagious material, they must be isolated from it and their strength tested." This lesson was to become the keynote of the future "Koch postulates."

In 1876, Koch, the busy medical practitioner, sent a letter to Professor Ferdinand Cohn, director of the Botanical Institute in Breslau, indicating that he had discovered "the process of development of bacillus anthracis" and requesting permission to present his findings to Professor Cohn, "the foremost authority on bacteria." Koch had discovered the spores of anthrax bacilli. Cohn arranged for him to present his results before a room full of formidable, distinguished scientists, including Julius Cohnheim, Carl Weigert, Moritz Traube, Ludwig Lichtheim, and Leopold Auerbach. Koch's demonstration of the complete life history of the anthrax bacillus, including sporulation, was entirely convincing to these scientists. After the meeting, Cohnheim, upon his return home, announced to his colleagues, "This man has made a splendid discovery which is all the more astonishing because Koch has had no scientific connections and has worked entirely on his own initiative and has produced something absolutely complete. There is nothing more to be done. I consider this the greatest discovery in the field of bacteriology."

During the next 2 years, Koch described novel procedures for the examination, preservation, and photography of bacteria and demonstrated the role of microorganisms in traumatic infections, while continuing his dual existence as a country doctor and an independent investigator. In 1880, Cohn and Cohnheim arranged for him to move to Berlin as a member of the Imperial Sanitary Commission. The move freed more time for research. By 1881, he made another breakthrough—the pour-plate method for isolating pure cultures. The opportunity that this technique afforded to

Figure 1-16 Robert Koch (1843–1910), announcing his discovery of the tubercle bacillus as the cause of tuberculosis, Berlin, March 28, 1882. *(Reproduced with permission from Knight D: Robert Koch: Founder of Bacteriology. New York, NY: Franklin Watts, Inc; 1961.)*

produce transparent solid media, coupled with Koch's invention of new staining methods, paved the way for him to tackle the microbial cause of tuberculosis.

Koch's scientific approach, which has been immortalized as "Koch postulates," consisted of four essential steps: (1) To prove that a microbe is the cause of a disease, it must be present in all cases of the disease. (Koch showed this for the tubercle bacillus using methylene blue and a counter stain.) (2) The microbe must be grown outside of the body in pure culture. (Koch devised blood-serum jelly as a culture medium for the slow-growing tubercle bacillus.) (3) The pure culture must be capable of causing the disease in healthy animals. (Koch proved this initially by inoculation and, subsequently, by allowing animals to breathe contaminated air.) (4) The same microbe must then be isolated from the inoculated (infected) animal and grown outside of the body in pure culture.

Koch's discovery of the tubercle bacillus and its modes of transmission revolutionized the treatment of tuberculosis. Before the discovery, tubercular patients were treated in sanitaria, which offered fresh air and altitude. Those who ran the sanitaria did not know that tuberculosis was a contagious disease: Sanitation was unregulated, and neither sterilization nor fumigation was practiced; diagnostic capabilities were limited. Koch's discovery of the tubercle bacillus revolutionized therapy. For the rest of his life, while pursuing the causes of other diseases around the world—rinderpest in South Africa, Texas fever, tropical malaria, blackwater fever, and bubonic

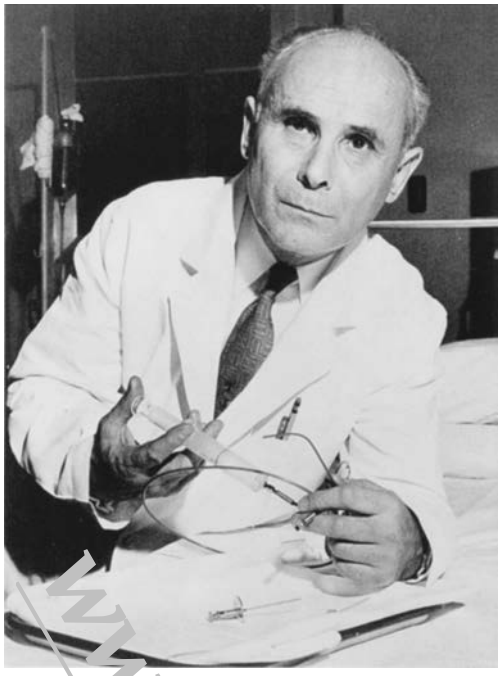

Figure 1-17 André Frederic Cournand (1895–1988) and Dickinson W. Richards (1895–1973). After Forssman's report of the uneventful catheterization of his own right heart, Cournand and Richards pioneered the use of cardiac catheterization for the study of the normal and the abnormal pulmonary circulation and the standardization of pulmonary function tests.

plague in Bombay—Koch maintained his interest in tuberculosis. This interest, however, led him into a major mistake—advocacy of tuberculin as a vaccine instead of as a diagnostic test. In 1905 he was awarded the Nobel Prize. On April 7, 1910, the year of his death, he delivered a final address on the epidemiology of tuberculosis before the Berlin Academy of Sciences.

Physiology of the Pulmonary Circulation

Starting with William Harvey,[5] studies of the pulmonary circulation have gone hand in hand with advances in pulmonary physiology and medicine. For many years, research on the pulmonary circulation was confined to animal experimentation. A giant step forward was made with the introduction of cardiac catheterization in humans.

Accurate measurement of pulmonary blood flow is a sine qua non for assessing pulmonary and cardiac performance in health and disease. The use of nitrous oxide in humans by Krogh and Lindhard was an important beginning in this direction, but not until mixed venous blood could be sampled for application of the Fick principle could reliable determinations of pulmonary blood flow be made.

Claude Bernard in 1846, and Chauveau and Marey in 1861, had catheterized the right side of the heart in animal experiments. Whether this technique could be used safely in humans was not known until 1929, when Werner Forssmann, a young surgeon in Germany, introduced a ureteral catheter into his own right atrium. In the 1940s, Cournand, Richards, and their colleagues resorted to right heart catheterization to obtain mixed venous blood for the determination of cardiac output by application of the Fick principle (Fig. 1-17). The technique opened the way not only to the accurate determination of cardiac output, but also to exploration of the heart and lungs in a wide variety of clinical disorders.

Until 1946, when von Euler and Liljestrand reported the effects of hypoxia and hypercapnia on the pulmonary circulation in an open-chest preparation of an anesthetized cat (Fig. 1-18),[36] there was little understanding of the regulation of the pulmonary circulation. However, these studies, coupled with the proposition of local control of the pulmonary circulation by local concentrations of the respiratory gases, paved the way to understanding pulmonary hypertension and the behavior of the pulmonary circulation in normal individuals at rest, after birth, during exercise, and at altitude, and in individuals with heart or lung disease.

The interposition of the pulmonary circulation between the right and left sides of the heart is a prerequisite for gas exchange. However, it also serves a variety of other functions, for example, a mechanical role, as a filter for particulate matter in blood returning to the heart, and a metabolic role, effecting the synthesis, uptake, and breakdown of biologic compounds. Extensive studies have been

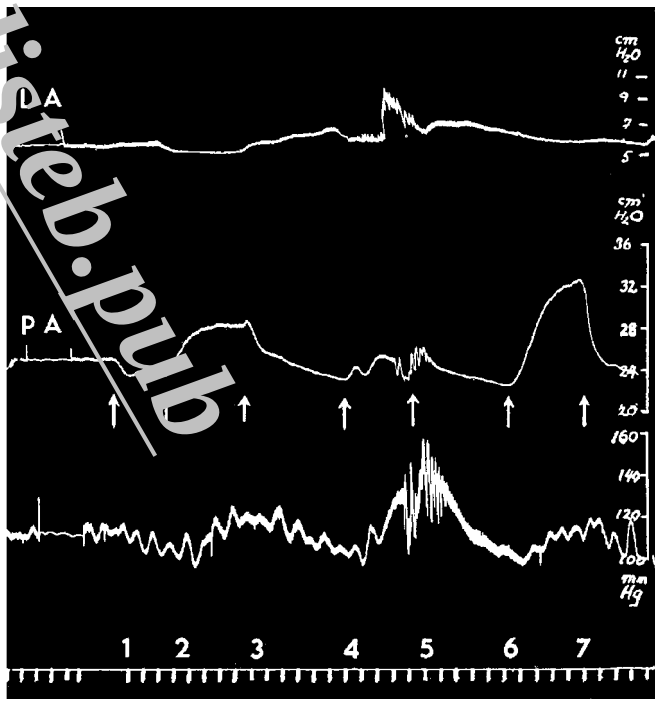

Figure 1-18 Effects of the blood gases on pulmonary arterial pressure in the open-chest cat, artificial respiration. LA, left atrial pressure; PA, pulmonary arterial pressure; lower trace, systemic arterial blood pressure. Numbers along the baseline represent the administration of test gases: 1, O_2 (from air); 2, 6.5% CO_2 in O_2; 3, O_2; 4, 18.7% CO_2 in CO_2; 5, O_2; 6, 10.5% O_2 in N_2; 7, O_2. *(Reproduced with permission from Von Euler US, Liljestrand, G: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand. 1946;12(4):301–320.)*

conducted in recent decades on the nonrespiratory functions of the lungs. From these studies has emerged considerable understanding of the diverse functions served by the branching pulmonary circulation and its components, including the endothelium and smooth muscle and their interplay.

TECHNOLOGIC ADVANCES THROUGH THE EARLY 20TH CENTURY

The road to contemporary pulmonary medicine could be just as easily traced by using technologic advances as landmarks, instead of people and discoveries. For example, the introduction of the manometer for pressure recording, the use of chambers to simulate high altitude, the development of accurate blood gas analyzers, and the application of sophisticated optical systems for viewing the lumens of the airways and the inside of the chest cavity are all notable milestones. However, probably no better example exists than the discovery of radiographs and the application of this discovery to the diagnosis, prevention, and management of pulmonary tuberculosis.

Wilhelm Conrad Roentgen discovered radiographs in 1895 while experimenting with cathode ray tubes in his physics laboratory at the University of Wurzburg. Although others before him had seen radiographs as early as 1890, Roentgen was apparently the first to grasp the full significance of the discovery, and his publication, quite unpretentious, immediately attracted worldwide attention because of its prospects for the study of anatomic structures and pathologic changes.

Within 2 years after Roentgen's discovery, fluoroscopy of the chest had been introduced into clinical practice, and its value in the early detection of tuberculosis and the diagnosis of pleural effusions was appreciated. In 1901, an atlas of chest radiographs was published, and the use of chest radiography increased greatly with each subsequent improvement in hot cathode radiograph tubes and intensifying screens. The radiographic evaluation of tuberculosis was superior to physical examination for diagnosis and characterization of the disease. By 1910, all patients admitted to sanatoriums had a chest radiographic examination, and by 1917 tuberculosis was classified according to radiographic findings.

MAJOR DEVELOPMENTS SINCE THE MID-20TH CENTURY

Many notable developments have occurred over the last 60 years in pulmonary medicine and the related field of critical care. Measured against the metric of having a broad and deep impact on clinical care, several are particularly noteworthy: advances in thoracic imaging, lung transplantation, bronchoscopy and interventional bronchoscopic techniques, and advances in management of the critically ill, including those infected with COVID-19 (SARS-CoV-2).

■ Advances in Thoracic Imaging

Following Roentgen's discovery of the x-ray at the turn of the 20th century, another major diagnostic leap forward in pulmonary medicine occurred with development of computerized tomography (CT) in the 1960s.[37–39] In 1967, the first experimental CT scan was generated, with computer reconstruction of an image of a mouse taking 9 days to complete. The first human application was a head CT that demonstrated a brain tumor (Fig. 1-19). In 1973, Dr. Godfrey Hounsfield published a description of CT scanning in the British Journal of Medicine. Along with Dr. Allan Cormack, Hounsfield (Fig. 1-20) was awarded a Nobel Prize in 1979.

Application of CT to lung imaging arose in the mid-1970s; high-resolution techniques were developed in the 1980s. Multi-slice CT scanning now permits rapid acquisition of high-resolution images from which multiplanar reconstructions can be derived (Fig. 1-21). Elegant characterization and classification of a variety of interstitial and airway diseases is now possible using CT. In addition, when coupled with intravenous contrast injection (CT angiography),

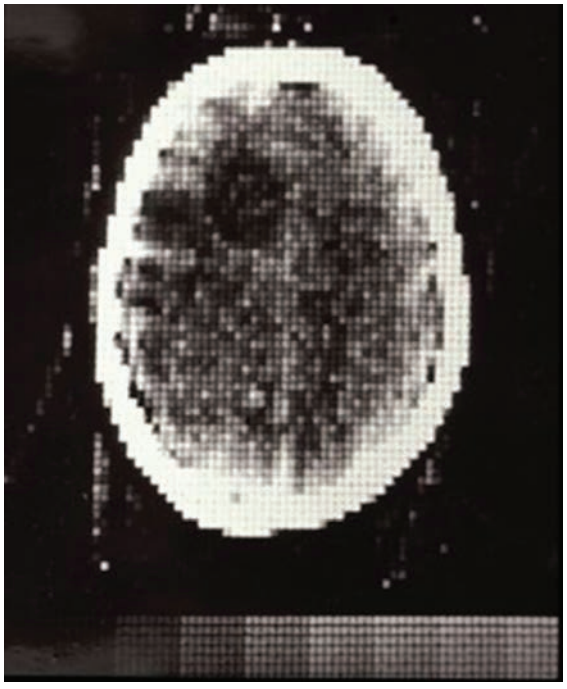

Figure 1-19 The first clinical CT scan, obtained in 1971. The grainy image shows a brain tumor in a frontal lobe (*left side* of image). Advances in image quality over the last four decades have been dramatic. *(Reproduced with permission from impactscan.org.)*

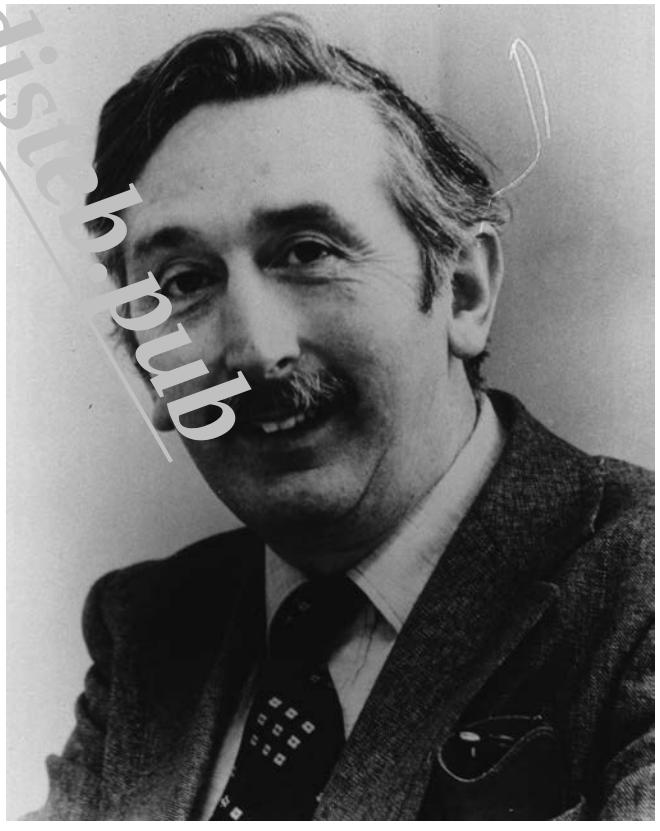

Figure 1-20 Dr. Godfrey Hounsfield, inventor of computerized tomography (CT). Along with Dr. Allan Cormack, Hounsfield was awarded a Nobel Prize in 1979. *(Reproduced with permission from Visible Proofs, National Library of Medicine, National Institutes of Health.)*

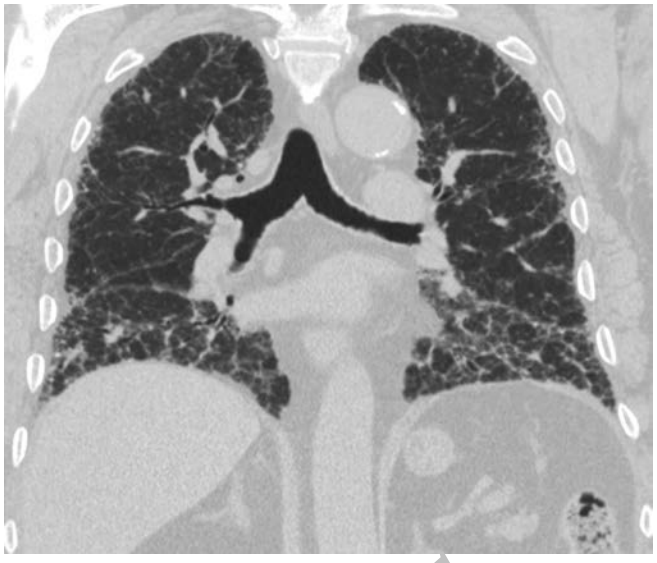

Figure 1-21 A modern-day, coronal reconstruction of the chest using CT in a patient with idiopathic pulmonary fibrosis (IPF). Current scanners are capable of rapidly generating high-resolution images from which a variety of computer-generated reconstructions can be derived. *(Reproduced with permission from Dr. Eduardo J. Mortani Barbosa, Jr.)*

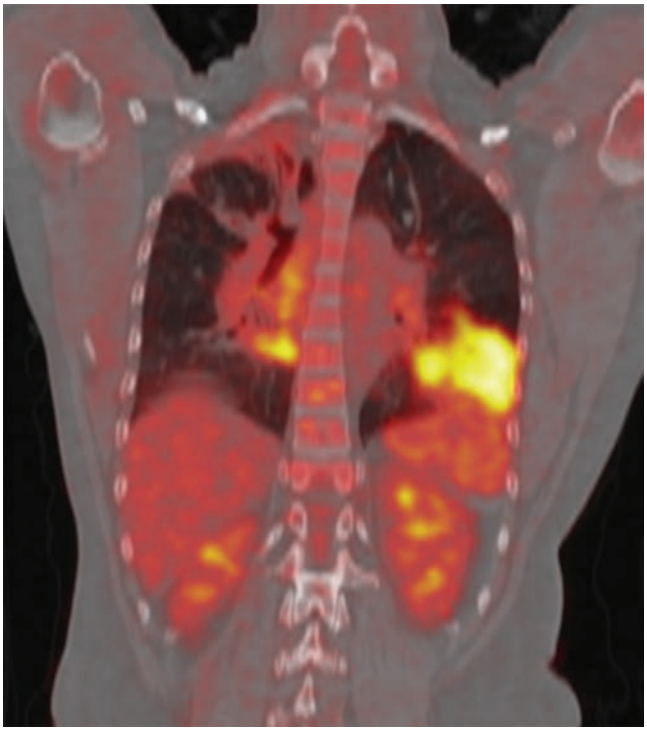

Figure 1-22 A coronal PET/CT image demonstrating metastatic lung cancer, evident as bright areas (in *yellow*) at the left base and the right hilum. The PET and CT images are aligned ("in register") to create precise anatomic localization of the heightened metabolic activity noted in the PET image. *(Reproduced with permission from Dr. Eduardo J. Mortani Barbosa, Jr.)*

rapid, high-resolution scanners provide for the very accurate diagnosis of pulmonary embolism[40] and other pulmonary vascular disorders. Advances in multi-slice techniques (e.g., 320-slice scanners) offer extremely high-quality imaging.

Aligning the anatomic detail provided by CT with functional images afforded by positron emission tomography (PET) has generated useful information on the staging and clinical assessment of bronchogenic carcinoma, particularly non–small-cell carcinoma.[41–] Positively charged electrons (positrons), emitted from injected radionuclides, are destroyed by electrons and, in the process, produce photons that are detected and imaged by the PET scanner. Malignant cells, by virtue of having increased numbers of cell membrane–based glucose transporters compared with normal cells, accumulate greater levels of the radionuclide, ^{18}F-fluorodeoxyglucose (F-FDG), which cannot be metabolized further and is trapped within the cells. The tracer-enriched collection of malignant cells stands out against the background of normal tissue. Coupling of the PET-based and CT images provides precise localization of the area of abnormality (Fig. 1-22). PET/CT imaging has been used to evaluate solitary pulmonary nodules, assess local extent of disease (particularly mediastinal and pleural involvement) in lung cancer, and evaluate distant anatomic sites for metastatic disease.

■ Lung Transplantation

Following on the heels of pioneering animal experimentation conducted by Vladimir Demikhov,[46] the first reported human lung transplantation was conducted by Dr. James Hardy and colleagues in 1963.[47,48] However, it was not until the 1980s that clinically meaningful outcomes were achieved by Dr. Joel Cooper and colleagues with single-lung[49] and bilateral-lung[50] transplantation.

Since the advent of lung transplantation, approximately 70,000 procedures have been performed worldwide. Survival of recipients has improved from 4.0 years in the late 1980s and early 1990s to 5.8 years in the last decade. Contemporary, overall survival rates are 85% at 1 year and 59% at 5 years.[51,52] Lung transplantation is associated with improvements in lung function, exercise tolerance, and hemodynamic parameters. Currently, the primary diagnoses for which lung transplantation is most commonly conducted include idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and other disorders, including alpha-1-antitrypsin deficiency, sarcoidosis, non-CF bronchiectasis, lymphangioleiomyomatosis (LAM), and primary pulmonary hypertension.[53,54]

Despite tremendous advances in the field, complications of lung transplantation are common and include primary graft dysfunction (non-cardiogenic pulmonary edema without other apparent cause occurring in the first 72 hours following transplantation); bronchial stenosis developing at the anastomotic site; a broad array of infectious complications, including CMV infection; acute rejection (occurring in over one-third of recipients); and chronic allograft dysfunction due to bronchiolitis obliterans.[53]

Improved surgical techniques in lung transplantation have been important. However, critical to advances in solid organ transplantation, including lung transplantation, has been development of effective immunosuppressive regimens. The earliest regimens included a limited repertoire of drugs, for example, corticosteroids and azathioprine. Development of calcineurin inhibitors, including cyclosporine in 1977 and tacrolimus in 1983, substantially advanced the field.[55]

While technical and pharmacologic advances in lung transplantation afford many patients with advanced lung disease improved quality of life, a limited supply of suitable donor organs persists. Various approaches have been employed in an attempt to ameliorate the continuous shortage. In addition to obtaining organs from brain-dead donors as the primary source, more recently, many transplant programs have embarked on the somewhat controversial program of donation after cardiac death (DCD) or donation from "non–heart-beating donors," who undergo controlled withdrawal of life support in an operating room. In addition, new technologic developments in organ "reconditioning" offer hope for enlarging the supply of transplantable lungs.[56–58]

Figure 1-23 Gustav Killian (1860–1921), the father of bronchoscopy. *(Reproduced with permission from Klaus D. Peter, Wiehl, Germany. Released to the public domain, via Wikimedia Commons.)*

Bronchoscopy and Interventional Bronchoscopic Techniques

Application of bronchoscopic techniques, both rigid and flexible, has revolutionized the field of pulmonary medicine, from both diagnostic and interventional perspectives. Credit for invention of the rigid bronchoscope is given to Gustav Killian (Fig. 1-23) in Germany in the late 19th century;[59] in the United States, the field of rigid bronchoscopy was pioneered by Chevalier Jackson in Philadelphia (Fig. 1-24).[60] The next major wave in bronchoscopy

Figure 1-24 Chevalier Jackson (1865–1958), a pioneer in American bronchoesophagology. *(Reproduced with permission from Thomas Jefferson University.)*

Figure 1-25 An "iron lung." The patient was placed in the hollow cylinder before the device was sealed, with his or her head protruding from one end. *(Reproduced with permission from CDC/GHO/Mary Hilpertshauser. Photo contributor: Jim Gathany.)*

arose with development of the flexible fiberoptic technique by Shigeto Ikeda in Japan.[61,62] Since then, significant advances in optics, digital technology, and a variety of interventional techniques, including those based on the fiberoptic method, have been reported.

Advances in Critical Care

In parallel with the previously noted advances in imaging, transplantation, and bronchoscopy, significant progress in the management of critically ill patients has occurred over the last several decades. One of the most notable is application of mechanical ventilation.[63–65]

The era of the "iron lung," the first widely used negative pressure ventilator, dates back to 1928 (Fig. 1-25).[66–68] Restricted access to the patient was a major limitation to use of the device. The advent of positive pressure ventilators, dramatically evident during the polio epidemic in Copenhagen in 1952, ushered in the "modern" era of mechanical ventilation.[69] Indeed, the clustering of paralyzed patients needing ventilatory support paved the way for development of medical intensive care units. Subsequent invention of the Bennett valve, a result of efforts to establish a means of facilitating high-altitude flight for military purposes, further enhanced clinical use of positive pressure ventilation.[70–73] Many additional refinements in mechanical ventilation, including microprocessor-controlled functions, have evolved over the last quarter century. One noteworthy development in the field deserves special consideration: use of the "low-stretch protocol."

Based on recognition that application of traditionally used tidal volumes of 10 to 15 mL/kg body weight may cause stretch-induced injury in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), a multicenter prospective trial was undertaken to address whether use of smaller tidal volumes (6 mL/kg), that is, a "low-stretch protocol," would improve outcomes. Indeed, in a landmark study published in 2000, an approximate 25% reduction in mortality using a low-stretch protocol was demonstrated.[74] Additional refinements, including use of higher levels of positive end-expiratory pressure (PEEP)[75] and the so-called "lung recruitment maneuvers"[76] have been added to the contemporary ventilator management scheme for these patients.

In addition to advances in mechanical ventilation, other notable recent refinements in critical care include recognition of the value of venous thromboembolism prophylaxis, prophylaxis against gastrointestinal bleeding, semierect patient positioning to minimize aspiration risk, good (but not excessive) glycemic control, application of spontaneous breathing trials and sedation interruption, and early patient mobilization. However, one particular

development warrants special mention: use of early goal-directed therapy (EGDT) in sepsis.

Sepsis is a severe, systemic response to infection and is associated with high mortality. A reflection of the systemic inflammatory response syndrome (SIRS), sepsis may progress to severe sepsis (end-organ dysfunction in the setting of documented or suspected infection) or septic shock (severe sepsis with hypotension unresponsive to intravenous fluid administration). An important study published in 2000 addressed the value of EGDT in the management of septic patients. Such therapy focuses on early and aggressive fluid administration titrated to a goal central venous pressure (CVP), mean arterial blood pressure (MAP), and target central venous oxygen saturation (Scv_{O2}), and incorporates use of vasoactive agents and transfusion of packed red blood cells as necessary. Application of EGDT has been shown to reduce mortality by as much as one-third[77] and constitutes one of the cornerstones of management of critically ill patients with sepsis, as comprehensively discussed in the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock."[78]

Acute Lung Injury Related to COVID-19

In late 2019, a cluster of cases of pneumonia due to a novel coronavirus emanating from Wuhan, China, was reported.[79] The World Health Organization designated the disease as COVID-19, the causative organism of which is SARS-CoV-2 (Fig. 1-26). We now know that the major morbidity and mortality due to this infection is acute viral pneumonia that may evolve to ARDS.[80,81]

The pandemic has stimulated rapid evaluation of a variety of modalities related to management of the critically ill patient with diffuse lung injury, including prone positioning,[82,83] use of high-flow oxygen therapy and noninvasive mechanical ventilation prior to consideration of intubation, use of adjunctive agents, including corticosteroids, and an alternative to a low-stretch ventilator protocol, based on data suggesting that the disturbed lung mechanics in COVID-19-related ARDS are different from those of other causes of ARDS.[85,86]

The social and economic consequences of COVID-19 pandemic have been extraordinary. With well over 250 million infections and more than 5 million deaths worldwide, the impact of the pandemic has triggered debate over the preparedness of nations globally for dealing with future pandemics. As the world struggles with containing COVID-19, attention has been intensely focused on development of effective vaccines and therapeutics.

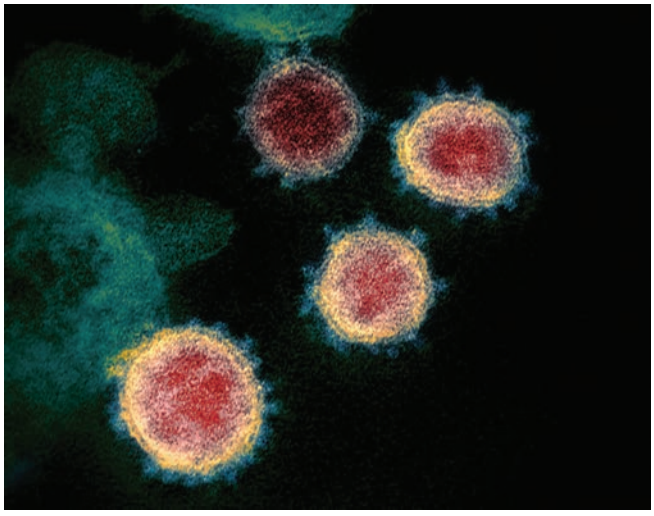

Figure 1-26 Transmission electron microscope image of SARS-CoV-2, the virus that causes COVID-19. The image shows virus particles emerging from laboratory-cultured cells. Spikes on the surface of the virus, appearing as a crown, account for the name, "coronavirus." *(Reproduced with permission from NIH Research Matters: Novel coronavirus structure reveals targets for vaccines and treatments. Bethesda, MD: U.S. Department of Health & Human Services; March 2020.)*

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