RESPIRATORY PHYSIOLOGY

N. BALFOUR SLONIM, M.D., Ph.D.

LYLE H. HAMILTON, Ph.D.

FOURTH EDITION

RESPIRATORY PHYSIOLOGY

N. BALFOUR SLONIM, M.D., Ph.D.

Director, Cardiopulmonary Diagnostic Laboratory,
Denver, Colorado

LYLE H. HAMILTON, Ph.D.

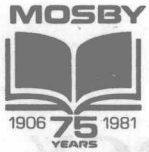
Principal Scientist, Wood VA Center; Professor of Physiology and Director,
Clinical Physiology Section, The Medical College of Wisconsin,
Milwaukee, Wisconsin

FOURTH EDITION

With 111 illustrations and 17 tables

The C. V. Mosby Company

ST. LOUIS • TORONTO • LONDON 1981



A TRADITION OF PUBLISHING EXCELLENCE

Editor: John E. Lotz
Design: Susan Trail
Production: Debbie Wedemeier

FOURTH EDITION

Printed in the United States of America

The C.V. Mosby Company
11830 Westline Industrial Drive, St. Louis, Missouri 63141

Library of Congress Cataloging in Publication Data

Slonim, N. Balfour, 1923-
Respiratory physiology

Bibliography: p.
Includes index.
1. Respiration. I. Hamilton, Lyle H., 1924-
II. Title. [DNLM: 1. Respiration. WF 102 S634r]
QP121.S6 1981 612'.2 81-11055
ISBN 0-8016-4668-5 AACR2

C/VH/VH 9 8 7 6 5 4 3 2 1 01/B/048

PREFACE

The major objective of this text is to present clearly and concisely the physiology of respiration. We have stressed fundamental principles and also indicated the applications of the basic science to the clinical practice of medicine. We have further attempted to identify and to propound the pressing problems of the field and to distinguish established fact from unproved speculation. We hope that the reader will share our fascination with this vital subject. We aim to pique his or her curiosity about the unanswered questions of respiratory physiology.

The traditional rigid boundaries that scientists have drawn between adjacent disciplines in the biomedical field now appear arbitrary, unnatural, and restrictive. Although originally necessary as a scaffold to delineate practical areas of work, these boundaries persist as a tribute to the instinct of territoriality. They cut through the complex structure of the biomedical field, blocking communication, interrupting continuities, obscuring patterns, impeding progress, and hindering recognition of interrelationships. We have expanded and extended this fourth edition in the direction of the new organ system biology. To accomplish this, examples of applied clinical physiology, as well as material from the basic biosciences, are woven into the text where they fit into the development of the central physiologic theme.

The present material is the product of experience gained in both teaching physiology and practicing medicine. This book is designed primarily for medical students, but it should also prove useful to physicians, physiologists, environmental scientists, and bioengineers. Paramedical personnel, such as nurses, anesthetists, respiratory therapists, and physical therapists, will find some sections of particular interest.

Almost all the illustrations have been drawn especially for this book. The illustrative material includes electron micrographs of healthy human lung. In addition to the standard material, the text contains material on the respiratory aspects of hydrogen ion regulation (Chapter 11), the respiratory physiology of the newborn (Chapter 15), respiratory physiology in unusual atmospheres and environments (Chapter 16), and the clinical evaluation of pulmonary function (Chapter 17). The Appendix includes a table of symbols and abbreviations for respiratory physiology and a set of equations for use in respiratory calculations. A glossary of key terms and concepts follows the Appendix.

We are keenly aware that mathematics is the language of science and thus of physiology, lending itself to objective, precisely quantitative, and unambiguous expression. In this regard we have aimed for a realistic balance, to avoid the delusion of mathematical precision on the one hand and the misfortune of unnecessary complication on the other.

We use torr instead of mm Hg and °C instead of °F. To eliminate ambiguity, units that measure different dimensions and imply sequential arithmetic operations including more

than one division are given in the form $A \times B^{-1} \times C^{-2} \times D^{-3}$. For example, the units of respiratory resistance are given as cm $H_2O \times liter^{-1} \times sec^{-1}$ instead of cm H_2O/liter/sec or cm H_2O/(L × sec), and the units of cardiac index are given as liters $\times$ $min^{-1} \times M^{-2}$ instead of liters/min/M^2 or liters/(min × M^2).

Our main objective is to present the current state of the science of respiratory physiology. It is beyond the scope of this book to offer rigorous evidence for our statements and conclusions or to give details of the evolutionary development of the facts, principles, and concepts of respiratory physiology. However, "Historic Review," a section in the Introduction, discusses some of the major contributors to respiratory physiology and their work.

We are sorry to have had to omit, for the sake of brevity, the names of many contributors to the field of respiratory physiology, as well as the specific references to their published works. However, we believe that the inclusion of such a large and constantly increasing volume of detail would defeat the objective of this book. We have attempted to reach a compromise by listing selected references for further study in a section at the end of the book.

We acknowledge with pleasure the capable and dedicated assistance of Luba Ilczyszyn-Horodyskyj and Sylvia Welytok in the preparation of our manuscript and of Carole R. Hilmer for many of the illustrations in this fourth edition. Our sincere appreciation also goes to numerous reviewers whose frank criticism has been invaluable in the revision, and the improvement, of our text.

N. Balfour Slonim
Lyle H. Hamilton

CONTENTS

LIST OF TABLES

INTRODUCTION

ON PHYSIOLOGY

We define physiology broadly as the science of processes and functions of living biologic systems. Its roots are in anatomy, biochemistry, and biophysics, and its spreading branches bear the blossoms and fruit of clinical medicine. The physiologist studies sensors, intercommunicating neurohumoral pathways, effectors, feedback control systems, and the differentiating and integrating intermediation of the central nervous system. All physiologic explanations involve the elements of cell function and biologic control mechanisms that, in turn, reduce to sequences of physicochemical events. The application of feedback control theory to physiology is a step toward thinking in terms of dynamic processes.

There are two stages of conceptualization in the evolution of a science—early static description and entity thinking and a later stage of thinking in terms of dynamic process and function. As knowledge accumulates and the unity of science is discovered, the classic artificial boundaries between the departmentalized disciplines basic to physiology blur and then disappear. Having served their original purpose, these carefully defended borders now appear less and less meaningful. On analysis today, physiologic processes resolve inevitably into the more basic biologic sciences of biochemistry, biophysics, and anatomy—the science of structure. In this resolution process pharmacologic tools are often used as molecular dissecting needles with which to unravel physiologic processes. At molecular level the apparent dichotomy disappears as structure and function fuse into a single identity. Synthetically, physiologic processes are the manifestation of highly organized molecular processes; analytically, physiologic processes resolve inevitably into biochemical and biophysical events.

Of basic importance to physiology are the concepts of internal environment, homeostasis, and steady state. Many different feedback control systems operate to assure the fitness of the internal environment, or *milieu interieur*, and the constancy of its regulated quantities throughout a wide range of environmental conditions. When an environmental influence perturbs a biologic system, appropriate counterreactions begin. Homeostasis is a consequence of successful counterreactions, both physiologic and behavioral, to environmental influences; it is thus the tendency to maintain a condition of relative constancy, or stability, of the internal environment of the organism through a series of interacting physiologic processes. It is this mean physiologic state that maintains the organism as a viable entity distinct from its external environment. The essence of physiology is regulation.

Thermodynamically, a living biologic system is an open system in a steady state. Such a system is to a large extent self-regulatory. If a stimulus is applied to it, it reacts to reestablish the steady state or, if the stimulus continues to act, it assumes a different steady state. The whole organism, its organs, its cells, and the

reaction systems within the cell are all open systems.

Physiologically, a steady state is a balanced condition of responsive adjustment to any particular environmental condition, influence, or stress. In health every environmental change that displaces a biologic system from its mean steady state evokes appropriate countermeasures. Since the dynamic adjustments operating to reestablish a steady state involve many physiologic processes that proceed at different rates, one must define the relevant physiologic parameters for a given condition, and it is more precise to speak of a *nearly* steady state. On close examination a steady state is seen to contain many transient processes for which time is important in terms of fractions of a second.

An unsteady state is characterized by changing physiologic parameters in the course of transition from one nearly steady state to another. Unsteady states may result from breathing unusual gas mixtures, hyperventilation, hypoventilation, breath-holding, exercise, anesthesia, drugs, increasing apparatus dead space, and changes in posture or cardiac output. These causes may occur singly or in combination.

The present forms of terrestrial life have evolved on this rotating, revolving earth out of millions of generations of ancestry. It is not surprising, then, that all living organisms undergo continuous variations, or fluctuations, as does the geophysical environment with which they continuously interact. We are now in the process of discovering and describing the manifestations of this fundamental biologic phenomenon.

Some fluctuations contain no regularly recurring patterns of change with time and are termed *aperiodic*. In contrast, some relatively regular patterns of change repeat at nearly constant intervals; phenomena that recur with such regularity are termed *periodic*, or rhythmic, and can be analyzed in terms of amplitude, frequency, and phase. Some biorhythmic variations are linked to natural fluctuations of the geophysical environment such as the cycles of light and temperature, the ebb and flow of the ocean tides, and the annual rotation of the seasons. A host of periodic phenomena in animals and plants follow these periodic environmental changes. Many such oscillations have periods of approximately 24 hours and, accordingly, are termed *circadian* rhythms.

Biorhythmicity is also manifest as a variation of susceptibility to a variety of stressors, such as drug overdose, endotoxins, and high-intensity noise. Susceptibility is a function of the circadian system phase at the time the stress is applied. Indeed, experiments can be designed so that circadian system phase makes the difference between survival and death.

Biologic rhythms of large amplitude can be a source of considerable error in estimating mean values and normal ranges. Unfortunately, sampling at a fixed clock hour is not a sufficient precaution to control circadian rhythms as a source of variation in experimental studies.

Circadian rhythms persist even in coma and for several months after elimination of the most obvious time cues. However, during prolonged isolation the circadian system as a whole becomes desynchronized from the 24-hour clock (external circadian desynchronization).

Can a circadian rhythm, as some evidence suggests, desynchronize from other physiologic rhythms of the same organ system? What is the etiologic, diagnostic, and therapeutic significance of abnormalities of amplitude, period, or phase of physiologic rhythms? Certainly, we must consider the significance of physiologic rhythms in both health and disease.

ON TEACHING RESPIRATORY PHYSIOLOGY

The process of respiration is different in lower animals from that in mammals. In microscopic forms, such as protozoa, gas exchange involves only simple diffusion; a respiratory system does not exist. In insects, where the

respiratory system is independent of the circulatory system, gases diffuse freely through a tracheal system that terminates in tracheoles in the deeper tissues. Coelenterates, fish, amphibia, and reptiles differ with respect to the coordination of their "ventilatory" and circulatory systems for the function of respiration. Birds have a unique ventilatory system in which a unidirectional flow of gas through the lungs is assisted by air sacs that fill and empty through the action of adjacent skeletal muscles.

The functions of respiration, circulation, electrolyte and water balance, metabolism, and body temperature are so interlocked that alterations of one evoke responsive adjustments in the others to establish a new dynamic steady state. When any such changes occur, respiration adjusts rapidly to metabolic demand, assuring the tissues an adequate supply of O_2 and removing excess CO_2.

Respiratory gas exchange produces arterial blood from mixed venous blood and is the essence of pulmonary function. The regulation of gas exchange to meet the changing *demands of the body* is the essence of respiratory physiology.

In health the mammalian cardiorespiratory system supplies O_2 to the metabolizing tissues of the body and removes excess CO_2 from them, maintaining optimal pressures of these two respiratory gases in the cells. This vital function is accomplished by the coordinated operation of two fluid pump systems—a blood circulatory system and a gas exchange system. The thorax is a variable displacement, variable frequency, air pump that moves air back and forth through the airways by active expansion followed by passive elastic recoil, thus presenting large volumes of inspired gas to large volumes of mixed venous blood. This air pump is devoid of valves and operates by creating a subatmospheric pressure. The right ventricle is a variable displacement, variable frequency, blood pump that drives the cardiac output in one direction through thin-walled capillaries in the alveoli of the lung. This blood pump has valves and operates by creating a positive pressure. Ventilation is phasic, or intermittent, whereas lung perfusion is essentially continuous if pulsatile. In spite of the rather unlikely combination of flows, gas exchange is both efficient and well controlled. Inspired wetted gas moves into contact with moist warm respiratory surfaces convoluted within the lung. Here blood flow matches gas flow.

Respiration in air-breathing animals involves a set of coordinated, regulated physiologic processes. To appreciate the integrated function of the whole set, we must first understand the function of each component process. We will thus dissect the respiratory system into its component processes for presentation and study. However, as we will show, the functioning whole is somewhat greater than the sum of the functions of its separated parts because new functions are derived from the coordinated interaction of various components. The components that comprise the respiratory system include pulmonary ventilation, pulmonary circulation, ventilation/perfusion distribution, diffusion, transport of gases, and regulation of respiration.

Pulmonary ventilation. Ventilation is the process by which air is moved into the lungs toward the alveoli where gas exchange takes place. The muscles of breathing produce the intrathoracic pressure changes that move air into and out of the lung.

Pulmonary circulation. The pulmonary circulation supplies mixed venous blood to the pulmonary capillaries at the rate required for delivery of CO_2 and uptake of O_2 in the gas exchange region of the lung. Since the rate of pulmonary blood flow is normally determined by, and essentially equal to, cardiac output, it is under circulatory control. Thus, pulmonary circulation is as vital to respiratory physiology as pulmonary ventilation.

Ventilation/perfusion distribution. Respiratory gas exchange requires adequate rates of ventilation and perfusion (pulmonary capillary blood

flow) and requires that these two flows be delivered to adjacent areas to minimize the diffusion impediment. If all ventilation went to the right lung and all circulation went to the left lung, respiratory gas exchange would not occur. Although the distribution of neither ventilation nor perfusion is ideal, mechanisms exist to minimize regional variation of ventilation/perfusion ratios. In the consideration of ventilation/perfusion problems, we cannot separate respiratory function from circulatory function.

Diffusion. Gases move by diffusion from regions of high pressure to regions of low pressure through membranes that separate alveolar gas from blood in the pulmonary capillaries. Equalization of gas pressure is achieved more quickly when the capacity for diffusion is large.

Transport of gases. Respiratory processes supply O_2 to the cells and remove the CO_2 produced by metabolism. Efficient transport and delivery of O_2 and CO_2 depend on the remarkably well-adapted properties of hemoglobin, the physical chemistry of blood, and the precise regulation of the systemic arterial circulation that perfuses the body tissues to maintain optimal respiratory gas tensions.

Regulation of ventilation. The central nervous system coordinates and regulates both ventilation and perfusion and, to some degree, their distribution in the lung. This function, together with adjustment of the systemic circulation, controls blood-gas transport and delivery. Ventilation changes efficiently to meet the demands of gas exchange throughout the wide range of conditions to which the body is exposed. Although we study each of the foregoing component processes separately, we must remember that efficient pulmonary gas exchange and circulatory transport and delivery are the result of coordination and regulation of all the foregoing processes.

On teleology. Teleology is a belief that natural phenomena are determined by an overall design or ultimate purpose in nature. As such, it is an aspect of the classic vitalism-versus-mechanism controversy. Because much of physiology appears to "make sense," we are tempted to think in terms of need and purpose. When scientists ask "Why?" they generally mean "How does it happen?" rather than "What is its purpose?" They avoid *teleology*, or *purpose*, as an explanation for natural events. Indeed, not every physiologic occurrence serves a useful purpose. Lack of purpose, however, does not imply lack of cause.

Goose pimples (cutis anserina) may, at one time, have kept furry animals warm, but this erection of skin papillae does nothing for modern man. It is likewise unrewarding to spend time worrying "What are hiccups for?" They are not "for" anything. There are wrong questions as well as wrong answers.

The word "function" is used by some to mean "purpose." If one asks, "what is the function of a yawn?" one is apparently assuming that because people yawn, yawning must serve some useful purpose. Yawning may be useful, but this is not guaranteed by the fact that people yawn.

If we think in terms of need and purpose, then we must conclude that the body makes mistakes. Scar tissue can impair function as well as localize infection; immune mechanisms can kill as well as protect. Books have been written about the "stupidity" as well as the "wisdom" of the body.

The remarkable adaptation of many molecules, processes, and mechanisms to the conditions of life is to be understood in terms of environment, mutations, biologic survival value, and natural selection. The natural selection of effective feedback control systems is the real reason that biologic phenomena appear to be purposeful. This appearance is also the chief argument for teleology. Thus, although teleology is an attractive projection of the mind, in this book we will ask "How?" rather than "Why?"

ON LEARNING RESPIRATORY PHYSIOLOGY

Medical students must learn and physicians must know respiratory physiology for proper diagnosis and effective treatment of bronchopulmonary disease. With the advent of potent and effective therapeutic modalities—the result of advances in pharmacology and medicine—physicians, now more than ever before, have an obligation to understand the physiology of the body systems with which they deal. In the past, therapeutic impotence often made diagnosis academic so that comprehension of pathologic physiology was less a practical necessity. Today, however, it is necessary to know the meaning of alterations of blood-gas tensions, to understand the causes of change in expired gas composition, and to appreciate the factors affecting gas diffusion in the lung so that we can distinguish problems of ventilation/perfusion distribution from problems of diffusing capacity. Today it is useful to understand that spirometric measurements of flow rates and lung volume measurements can differentiate obstruction of airways from loss of lung elasticity. A knowledge of pathologic physiology is basic to the precise diagnosis of the cyanotic patient and is further essential for selection of proper treatment. Compassion is not enough. A good grasp of the material in this text is essential to physicians facing the questions, problems, and decisions of clinical medicine.

Each time we are introduced to a new field, we must learn a new vocabulary to communicate precisely with others in the field. As we learn mathematics, it is first necessary to become familiar with the symbols for addition, subtraction, multiplication, and division; then with those for exponents and logarithms; and later with those for the operations of differentiation and integration. Physics and chemistry require a new vocabulary and a new set of symbols for valences, atomic weights, and isotopes. It is not surprising therefore that there is a special terminology with definitions, abbreviations, and symbols for respiratory physiology. This terminology is generally consistent with that of chemistry, physics, and mathematics. Students must learn this basic vocabulary to comprehend this book as well as the literature of physiology. Table A-1 in the Appendix presents the system. We will define them again where they first appear in the text.

HISTORIC REVIEW

Respiratory physiology has developed enormously since Hippocrates (460-377 BC) first suggested that the main purpose of breathing is to cool the heart. Galen (130-201 AD) almost understood the circulation but continued to believe, as had Hippocrates, that breathing serves to cool the heart. His most significant teachings in respiratory physiology concerned diaphragmatic contraction and chest wall movement.

For centuries no advance was made in the understanding of respiratory physiology. Then, anatomists of the early Renaissance, such as Leonardo da Vinci (1452-1519), set the stage for further progress. Michael Servetus (1511-1553) found that blood passes from the pulmonary artery through the lungs into the pulmonary veins and that during this passage it becomes crimson. Soon thereafter it was realized that as blood passes through the lungs it takes up something from the air.

Jean Baptiste van Helmont (1577-1644) added acids to potash or limestone, collected the "air" thus produced, and observed that it extinguishes flame. He also knew that this "air" is the same as that produced in the process of fermentation and that present in the Grotto del Cane in Italy, a cave in which dogs died, whereas their erect masters survived. Van Helmont coined the word "gas" and named this "air" the "gas sylvestre." In this sense he discovered carbonic acid gas, or carbon dioxide.

William Harvey (1578-1657) described the relationship of the circulation to the lungs in his classic publication, *De Motu Cordis*, which appeared in 1628. Robert Boyle (1627-1691) observed that small animals die promptly in an evacuated chamber, from which he deduced that air contains a vital ingredient.

Joseph Black (1728-1799), a physician, made an important contribution to the chemistry of respiration through his studies of CO_2. Black discovered that when limestone or chalk is heated, a gas evolves as the substances lose weight and that the same volume of gas effervesces when these substances are treated with strong acid. He named this gas "fixed air" and knew that it would extinguish both flame and life. He also found that when limewater is exposed to air, a white precipitate of chalk slowly forms, suggesting that "fixed air" is a natural component of the atmosphere. Again, using limewater as a test, he proved that "fixed air" is produced when charcoal burns, in the fermentation of beer, and during the process of respiration. In 1754 Black published his M.D. dissertation entitled "Experiments on Magnesia Alba, Quicklime, and Some Other Alkaline Substances." He confirmed the metabolic production of "fixed air" by an experiment in 1764 in Glasgow, where he was a professor of chemistry. In an air duct in the ceiling of a church where 1,500 people congregated for a religious service for 10 hours, he dripped a solution of limewater over rags, producing a considerable quantity of crystalline lime ($CaCO_3$). Although from a chemical point of view Black did not characterize "fixed air" completely, he is generally given credit for the discovery of CO_2.

The next important steps were made by Joseph Priestley (1733-1804), who discovered oxygen, and Antoine Laurent Lavoisier (1743-1794), who overthrew the phlogiston theory and recognized the basic chemical similarity of respiration to combustion in the disappearance of O_2 and the appearance of CO_2. Lavoisier observed that animals succumb when confined in a sealed atmosphere as soon as they have absorbed or converted to "aeriform calcic acid" (CO_2) the greater part of the respirable portion of the air. Lazzaro Spallanzani (1729-1799) placed small animals in sealed tubes and measured the rates of O_2 consumption, CO_2 production, and the change of nitrogen volume. He also found that tissues excised from freshly killed animals and the skin and muscle of a recently deceased human being take up O_2 and give off CO_2, indicating that oxidation occurs in the tissues. In 1809 Allen and Pepys found that the volume of CO_2 produced is approximately equal to that of the O_2 consumed.

In 1837 Heinrich Gustav Magnus (1802-1870) improved the methods for blood-gas analysis. He made the first quantitative analyses of arterial and venous blood for O_2 and CO_2 content. He found that both venous and arterial blood contain carbonic acid, oxygen, and nitrogen and that there is more carbonic acid in venous than in arterial blood.

John Hutchinson (1811-1861) devised the spirometer, measured the vital capacity in both health and disease, and described the other subdivisions of the lung volume. Lothar Meyer (1830-1895) showed that blood oxygenation depends on atmospheric pressure. Paul Bert (1833-1886) first demonstrated that reduced inspired O_2 tension (hypoxia) causes hyperventilation, as well as the signs and symptoms of altitude sickness. His work, *La Pression Barométrique: Recherches de Physiologie Experimentale*, was published in 1878.

In 1867 Alexander Schmidt and Eduard Pflüger discovered that shed blood consumes O_2 and produces CO_2. In the same year Strassburg, Pflüger's student, measured the partial pressure of CO_2 in the tissues. In 1868 Pflüger began to study the role of O_2 and CO_2 in the regulation of pulmonary ventilation in dogs. Using improved methods of blood-gas analysis, he found that the arterial blood O_2 content of dogs breathing nitrogen decreased from a control level of 14 to 18 vol% to a level of 1 to 2

vol%, with resulting marked dyspnea. He also found that breathing a mixture of 30% CO_2 and 70% O_2 increased the arterial blood CO_2 content of dogs from a control level of 25 to 28 vol% to a level of 50 to 60 vol%, while only moderate dyspnea resulted. Although aware of the work of Dohmen, who reported enormous increases of tidal volume and moderate increases of breathing frequency during 10% CO_2 inhalation, Pflüger concluded that either CO_2 excess or O_2 lack stimulates breathing. However, he considered O_2 lack the quicker and stronger stimulus, not realizing that inhalation of 30% CO_2 depresses breathing. He also concluded that the normal carbonic acid content of blood excites the medulla oblongata.

In the early 1870s a disagreement arose between the laboratories of Pflüger and Carl Ludwig (1815-1895), which became known as the secretion-versus-diffusion controversy. Pflüger believed that simple diffusion accounts completely for the transfer of O_2 from alveolar gas to arterial blood, whereas Ludwig believed that the lungs pump O_2 from alveolar gas into the blood so that the oxygen pressure is higher in arterial blood than it is in alveolar gas. In the decades that followed, many respiratory physiologists studied this problem and took sides in the controversy.

In 1885 F. Miescher-Rüsch obtained the first quantitative evidence that the resting pulmonary ventilation rate is regulated primarily by carbon dioxide. Analyzing lung gas obtained by deep exhalation, he found an average value of 5.43% CO_2 (on a dry gas basis) in resting human subjects. During dyspnea produced by breathing gas mixtures containing CO_2, he found to his surprise that the CO_2 concentration of lung gas had risen to only 6.0% to 6.4%. He concluded that an increase of lung gas CO_2 concentration of less than 1% increases breathing. Because decreasing lung gas O_2 concentration by an amount greater than the increase of CO_2 concentration that stimulates breathing had no observable effect, Miescher-Rüsch deduced that CO_2 is the normal chemical stimulus for breathing.

Christian Bohr (1855-1911) constructed the first oxyhemoglobin dissociation curve for purified hemoglobin in 1886. Although the shape of this curve resembled a hyperbola (no values below 30% saturation), he later established its true sigmoid shape. G. V. Hüfner in 1890 was the first to consider the detailed shape of the oxyhemoglobin dissociation curve. In 1894 he measured the carbon monoxide capacity of oxyhemoglobin and, after making certain corrections, decided that 1 gm of hemoglobin combines with 1.34 ml of CO, although his value of 0.34% Fe for oxyhemoglobin implied 1.36 ml/gm. Both values are still used in some laboratories today to calculate the hemoglobin content of human blood from analytically determined O_2 or CO capacities.

In 1904 Bohr with K. A. Hasselbalch and A. Krogh discovered that adding CO_2 to blood drives O_2 out. This important effect, linking the processes of O_2 and CO_2 transport, is called the Bohr shift. Bohr's contributions are also honored in the terms *Bohr equation* (for calculation of respiratory dead space) and *Bohr integration* (a graphic integration procedure used to calculate the mean alveolocapillary diffusion gradient for oxygen). Hasselbalch made other contributions to our understanding of the acid-base chemistry of blood.

John Scott Haldane (1860-1936) also investigated the role of CO_2 in the regulation of pulmonary ventilation. In 1893 Haldane and Lorrain Smith observed that dyspnea occurs when the inspired CO_2 concentration in a closed chamber increases to a level of only 3%, whereas if O_2 concentration was reduced and CO_2 was removed, no effects were observed until O_2 concentration decreased to 14%. Working with John Gillies Priestley (1880-1941), Haldane developed a practical method of sampling alveolar gas that facilitated study of alveolar CO_2 concentration under a variety of experimental conditions. They showed that the

resting pulmonary ventilation rate is normally regulated by CO_2, rather than by O_2. Haldane found that the partial pressure of CO_2 in alveolar gas remains relatively constant as barometric pressure varies from 646 to 1,260 torr, despite wide variation of ambient and alveolar O_2 pressure. He also observed that during inhalation of CO_2–enriched air, an alveolar CO_2 concentration increase of only 0.2% doubles alveolar ventilation rate and that breathing 5.5% CO_2 prevents posthyperventilation apnea. In addition to his many other contributions, Haldane developed the science of experimental human physiology. The work of Haldane, Priestley, and Yandell Henderson (1873-1944) demonstrated the importance of blood CO_2 tension, both as a normal stimulus to breathing and as a factor in maintaining respiratory homeostasis.

August Krogh (1874-1949) studied the distribution of capillaries in tissue, calculated coefficients for the diffusion of O_2 and CO_2 through tissue, and derived equations to describe tissue oxygen uptake. He designed a microtonometer for measuring the partial pressure of gases in blood, the tilting spirometer, the electric bicycle ergometer, a gas analyzer accurate to 0.001%, and an osmometer for blood plasma. In 1903 he showed that most of the O_2 used by the frog enters through the lung (short diffusion path), whereas most of the more readily diffusible CO_2 leaves through the moist skin. In 1910, with his wife Marie, he introduced the use of carbon monoxide into respiratory research. Application of the carbon monoxide technic increased knowledge of gas diffusion and uptake in the lungs and led to present clinical laboratory methods for measuring pulmonary diffusing capacity. Regarding the diffusion-versus-secretion controversy, the Kroghs proved experimentally that the process of diffusion alone can account for the transfer of O_2 and CO_2 between lung and blood. In 1910 they wrote, "The absorption of oxygen and the elimination of carbon dioxide in the lungs take place by diffusion and by diffusion alone." However, despite their conclusion, controversy continued as to whether the lungs secrete oxygen under certain conditions.

Joseph Barcroft (1872-1947) contributed to our understanding of the properties of hemoglobin, the oxyhemoglobin dissociation curve, blood-gas transport, the physiologic effects of altitude, the role of the spleen as a blood depot, fetal respiration and circulation in lambs, and initiation of the first breath. In a 6-day experiment performed on himself in 1919 at simulated high altitude (ambient P_{O_2} 84 torr) in a glass chamber, he found that an alveolar-arterial oxygen difference is maintained at all times, even during hypoxia and physical exertion. This experiment, together with his studies in the Andes during the winter of 1921 to 1922 at an elevation of 14,200 feet (4,328 M), demolished the secretion theory and established that pulmonary alveolocapillary oxygen transfer involves only the simple process of diffusion.

Lawrence J. Henderson (1878-1942) calculated the dissociation constants for oxygenated and deoxygenated hemoglobin, finding the former to be the stronger acid. He recognized that deoxygenation of hemoglobin binds the hydrogen ion of carbonic acid without change of blood pH and called this important physiologic mechanism the *isohydric change*.

Advances in the acid-base chemistry of blood clarified the relationship between CO_2 and blood acidity. In 1908 and 1909 Henderson applied the law of mass action to the $CO_2 - HCO_3^-$ system of blood and in 1909 Sorensen introduced the logarithmic pH notation for expressing hydrogen ion concentration. In 1917 Hasselbalch introduced the logarithmic version of the mass law expression known as the Henderson-Hasselbalch buffer equation. This equation interrelates the pH, CO_2 pressure, and total CO_2 content or bicarbonate ion concentration of blood plasma. In 1920 Henderson applied the Gibbs-Donnan equilibrium

concept to blood, predicting the changes that occur in electrolytes and hemoglobin ions within the erythrocyte and in the surrounding plasma. In the same year M. H. Jacobs presented conclusive evidence that the uncharged CO_2 molecule can diffuse into the interior of tadpole cells, *Arbacia* eggs, and the petals of certain carnations, rendering them acid, whereas the charged H^+ enters the cell very slowly.

Donald D. Van Slyke contributed much to our understanding of respiration, metabolism, and quantitative clinical chemistry. To this day the Van Slyke manometric method remains a standard for analysis of blood gases in laboratories throughout the world. By 1928 knowledge of the steady-state reactions for carbon dioxide, oxygen, and electrolytes in blood was fairly complete as a result of intensive research by L. J. Henderson's group at Harvard and D. D. Van Slyke's group at the Rockefeller Institute.

During the 1920s and 1930s there was intensive study of the acid-base chemistry of blood, the biochemistry of CO_2, the interaction of CO_2 with oxyhemoglobin dissociation equilibria, the reaction of CO_2 with hemoglobin to form carbaminohemoglobin, blood CO_2 transport, and CO_2 hydration-dehydration reactions. The investigations of these two decades produced fundamental data on the biochemistry of blood, laid the foundations of clinical chemistry, and developed methods that were used in the following decade of clinical research.

Francis John Worsley Roughton (1899-1972) studied the kinetics of the reaction of molecular O_2 with deoxyhemoglobin to form oxyhemoglobin. With H. Hartridge, he developed the continuous flow rapid reaction method in which a solution of deoxyhemoglobin and a solution of O_2 were rapidly mixed and the streaming liquid observed at varying distances along an observation tube, the distance serving as a measure of the time elapsed since mixing. Having shown that this reaction is rapid compared with the time an erythrocyte spends in a pulmonary capillary, Roughton turned to the problem of gas exchange in heterogeneous systems. He predicted the existence of a catalyst in blood that accelerates the reaction of CO_2 with H_2O to form carbonic acid. With N. U. Meldrum, he discovered the zinc-containing enzyme carbonic anhydrase in erythrocytes, which is essential to the unloading of CO_2 during the brief passage of venous blood through the pulmonary capillaries, and developed the theory of CO_2 transport in blood. He also showed that carbaminohemoglobin is formed by direct reaction of CO_2 with amino groups in the protein. Using recently developed knowledge of the structure of the hemoglobin molecule, he determined the dissociation constants of the active groups in the α and β chains and defined the interaction of CO_2 with 2,3-diphosphoglycerate. To evaluate the four Adair constants that describe the equilibrium of a tetrameric molecule, he developed accurate gasometric methods applicable to the extremes of the oxyhemoglobin dissociation curve, below 2% saturation and above 98% saturation, and found that the equilibrium cannot be fully described by a simple two-state model in which a single conformation change occurs after three ligand molecules have been bound.

Wallace O. Fenn (1893-1971) contributed greatly to our understanding of respiratory physiology by his studies of the mechanics of breathing, the pressure-volume relationships of lungs and chest wall, responses to breathing various gas mixtures, and responses to altitude. With Hermann Rahn he developed an important graphic synthesis, the O_2-CO_2 diagram, for displaying alveolar gas information.

In 1928 Werner Theodor Otto Forssmann performed the first cardiac catheterization, introducing a ureteral catheter into his own right atrium. This courageous experiment, for which he was reprimanded at the time, opened the way for studies of the human cardiopulmonary

system that were previously impossible. Although contributions to knowledge of the cardiovascular system were great, cardiac catheterization also increased our understanding of human respiratory physiology. A wealth of information regarding cardiovascular pressures, cardiac output, and the pH and respiratory gas content of blood in health and disease resulted. The technic of cardiac catheterization was applied and extended in human subjects who had a variety of cardiopulmonary conditions for both diagnostic and research purposes by Andre Cournand and Dickinson W. Richards, who with Forssmann shared the Nobel prize for medicine-physiology in 1956.

Linus Pauling's discovery of sickle cell hemoglobin (Hb S), the cause of sickle cell disease, was the first step toward understanding the molecular biology of hemoglobinopathies. Following this important discovery, many other genetically determined abnormal hemoglobins were identified, some of which are associated with abnormalities of blood-gas transport. Pauling also applied the paramagnetic principle to oxygen analysis, an insight that resulted in a rapid dependable instrument for analysis of oxygen in mixture with diamagnetic gases.

Since the turn of the century, the scientific knowledge of respiratory physiology has grown almost exponentially. The rising flood of contributions challenges teacher and student alike to read, study, evaluate, and assimilate a wealth of new methodologies, data, information, theories, concepts, and models. The inexorable evolutionary expansion of physiology brings with it a number of problems. These include the dissemination and presentation of information, the proper role of computer technology, the emphasis due molecular biology as opposed to classic organ system biology, productivity as opposed to creativity, and the optimal balance of resources to be invested in basic as opposed to applied physiology. As we wrestle with these problems, it is encouraging to know that science is the first common enterprise of mankind. What is the future of the science of physiology?