AREND BOUHUYS, M.D.

# THE PHYSIOLOGY OF BREATHING

A Textbook
for Medical Students

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*To the Memory of Gunnar Lundin*
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*Anaximenes, son of Eurystratus of Miletus, declared that air is the principle of existing things; for from it all things come-to-be and into it they are again dissolved.*

Aetius

# Preface

This book contains the chapters on physiology of breathing, previously published in a book of broader scope.* It appears in response to several suggestions that these chapters might serve as a textbook for medical students. For this edition, all chapters have been updated and revised where necessary. Several illustrations have been replaced or improved. A section on carbon dioxide transport has been added to Chapter 6. Chapter 10 has largely been rewritten to include results of recent work on the control of breathing. Chapter 12 has been written to introduce students to applications of respiratory physiology in studies of environmental lung disease.

The book is intended to provide students of medicine with a comprehensive framework of knowledge concerning respiratory physiology, emphasizing areas which are important in physiopathology. The text is extensively referenced, so that the reader can find his way to the original articles and reviews which I have used in preparing the text. Hence, the critical reader can decide whether or not he agrees with my interpretations and summarizing statements. I welcome comments, particularly from those who disagree, as well as suggestions for additional material that might be covered in a text of this scope.

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* *Breathing—Physiology, Environment and Lung Disease,* by A. Bouhuys, Grune & Stratton, 1974, 511 pp.

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# Introduction

Unless we understand the function of an organ system, we cannot fully understand the diseases that affect it. The physiology of today remains the medicine of tomorrow—and in the years since E. H. Starling first wrote these words, the scope of both physiology and of medicine have greatly expanded and become more diversified. Today, most respiratory physiologists are specialists in one or a few of the areas covered by chapters in this book. They have partitioned the simple act of breathing, which anyone can observe, into its minutest components. They have analyzed the main objective of breathing—transport of oxygen and carbon dioxide—in great detail. They have also discovered how the central nervous system controls the mechanical act of breathing, so that gas transport can be optimal under a variety of conditions.

Unicellular organisms can acquire oxygen and excrete carbon dioxide simply by diffusion between the cell and its medium. Higher organisms, including man and other mammals, need increasingly complex, specialized gas transport systems to supply all tissues with enough oxygen and to remove $CO_2$. They cannot rely on gas exchange by diffusion alone, because of their size and the relative impermeability of the skin to gases. In addition, the diversity of their tissues and their varying demands for oxygen supply and carbon dioxide excretion impose the need for a gas transport system that is regulated to adapt itself to metabolic demands. The development of gas transport systems in the animal kingdom is a main topic of comparative respiratory physiology.[2] This book, on the other hand, concerns itself mainly with the objectives of the student of human health and medicine: to understand how the human gas transport system works, what can go wrong with it, and how one can assess its function in health and disease.

A resting human needs an oxygen supply of about 0.3 liters per minute. During heavy exercise, the need for oxygen may increase to 4 liters per minute or even more. The lungs are a gas-exchanger of a degree of efficiency not yet matched by any "artificial lung" designed by man. In a volume less than 10 liters, they contain a surface area of about 80 $m^2$ where air and blood can exchange $O_2$ and $CO_2$. At rest, only part of this surface area is used; during heavy exercise, increased blood flow through the lung capillaries is a principal device which allows increased gas exchange.

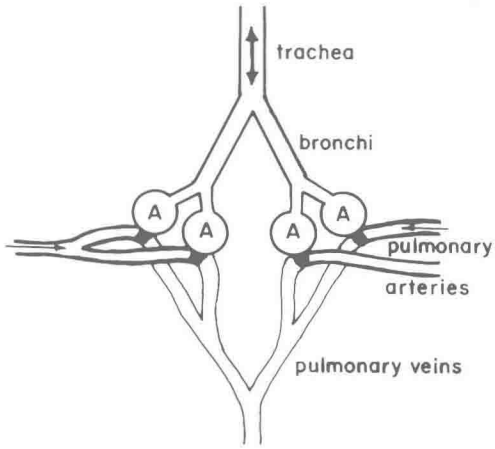


**Fig. 1.** Design of the gas-exchange system in the lungs. A = alveoli, where gas exchange occurs between alveolar gas and blood in capillaries (dark areas in blood vessels).

The large surface area of the air-blood barrier is created by the design shown schematically in Fig. **1**. Atmospheric air is brought to the gas-exchanging surfaces by a system of branched tubes, the bronchial tree, which end in thin-walled sacs, the alveoli. In the alveoli, an extremely thin alveolocapillary membrane (Fig. 6-1, p. 100) separates alveolar air from venous blood, carried to capillary blood vessels in the alveolar walls by a second system of branched tubes, the pulmonary artery and its branches. During the passage of blood through the alveoli, $O_2$ is taken up and $CO_2$ is excreted; i.e., blood becomes arterialized. A third system of branched tubes, the pulmonary veins, collects the arterialized capillary blood and carries it to the left atrium and ventricle. From there, it is distributed to all body tissues through the aorta and its branches, the systemic arteries.

The continuous exchange of gases between alveolar air and pulmonary capillary blood can only be maintained if the partial pressure of oxygen in alveolar air is higher, and that of carbon dioxide lower, than the corresponding partial pressures in venous blood arriving in the lung capillaries. This is accomplished by discontinuous, rhythmic dilution of alveolar air with atmospheric air, which contains almost no $CO_2$ and has a $P_{O_2}$ higher than that of alveolar air. Periodic entry of atmospheric air into the alveoli is assured by cyclical increases of lung volume (inspiration), followed by equal decreases of lung volume (expiration) which remove a portion of alveolar air from the lungs. These rhythmic volume changes—ventilation—of the lungs (at a rate of about 15 per minute and a volume, the tidal volume, of about 500 ml at rest; see Fig. 7-1, p. 150) are brought about by rhythmic volume changes (at the same rate and volume) of the chest cage, the bony and muscular structure which contains the lungs (see Fig. 7-2, p. 157). The chest cage is able to increase and decrease its volume actively, by contraction of inspiratory or expiratory respiratory muscles which are attached to the chest cage.

Hence, ventilation of the lungs is brought about by a pump—the chest cage; the lungs follow the volume changes of the chest cage passively. The rate of ventilation can be altered by changing the rate of the breathing movements or the

tidal volume, or both. The ventilation of the lungs is regulated by the central nervous system, which sends nerve impulses to the respiratory muscles (see, e.g., Fig. 10-4, p. 240). Changes in these nerve impulses can have their origin in our will, e.g., when we voluntarily hold the breath, or when we consciously breathe faster or deeper. But under many other conditions, changes in the signals sent by the central nervous system to the muscles of breathing are initiated unconsciously, automatically. This involuntary control system includes sensors which detect changes in the partial pressures of oxygen and carbon dioxide in blood, other sensors which detect changes in lung volume, and yet others which assess the degree of contraction of respiratory muscles. In this way, the central nervous system receives information on the mechanical process of breathing and on its consequences in terms of changes in blood gas tensions. In response to this information, groups of nerve cells in the brain stem adjust their rate of firing in accordance with changes in requirements for ventilation of the lungs. The impulses generated by the brain stem "centers" (the ventilatory drive) reach other groups of nerve cells, most of them in the spinal cord, which coordinate the signals sent to the respiratory muscles in accordance with the ventilatory drive.

Thus, the main aspects of the human and mammalian breathing apparatus which need to be discussed in detail are:

(1) Gas transport;
(2) Mechanics of breathing;
(3) Control of breathing.

This book begins with two additional topics: the development of the breathing apparatus (Chap. 1) and the morphology and function of the conducting airways, i.e., the upper airways and the part of the bronchial tree which does not participate in gas exchange (Chap. 2). These airways are more than passive conduits for inspired and expired gas: they participate in heat and water exchange and help in protecting the lungs against entry and accumulation of foreign matter.

*Gas transport* between atmospheric air and the tissues is discussed in Chaps. 3–6. First, Chapter 3 deals with gas transport mechanisms in the conducting airways, and with the volume of these airways, the anatomical dead space. Next in the chain of events is the distribution of inspired gas to different regions of the lungs and its mixing with alveolar gas (Chap. 4). Chapter 5 deals with the "dialogue" between air and blood in the alveoli, where $O_2$ and $CO_2$ exchange is chiefly determined by the ratio of alveolar ventilation and lung capillary blood flow. Chapter 6 traces oxygen transport from alveolar gas to the cells' mitochondria by diffusion through alveolocapillary and red cell membranes, binding to hemoglobin, and diffusion from capillary blood into the cells. The second part of Chapter 6 describes the transport of carbon dioxide in the opposite direction, from the cells to the alveoli, through solution and chemical binding of $CO_2$ in blood; it includes discussion of the relations between $CO_2$ transport and the acid-base balance.

The section on *mechanics of breathing* (Chaps. 7–10) focuses, in part, on a simple pumping function: as the lungs and chest suck in atmospheric air and expel air containing less oxygen and more carbon dioxide, alveolar air is renewed. Although, for many purposes, such a simple model is sufficient, lung mechanics is more than the study of an ingenious pump system ventilating through a complex

system of pipes. It also involves the basic physical properties of lung tissue and the details of lung structure which determine transmission of forces; lung mechanics can lead to study of airways and lungs as biological systems. Measurement of mechanical parameters, although an imperfect reflection of the physical system, helps assess changes in lungs and airways which result from disease, drugs, and other agents. In an attempt to treat lung mechanics in this broader sense, Chapter 7 describes the properties of the lungs and chest cage during volume displacements. The relationships between driving pressures and airflow through airways are discussed in Chapter 8. Chapter 9 describes flow-volume curves and their applications.

The *control of breathing* is discussed in two different contexts. Chapter 10 describes breathing mainly as an involuntary motor act, controlled by a neuronal network in the brain stem which initiates rhythmic breathing and modifies its pattern guided by information concerning lung inflation, respiratory muscle tension, and arterial blood gas composition received from different types of sensors. Chapter 11 focuses on breathing as a voluntary motor act in the service of interhuman communication via speech, singing, and wind-instrument playing. This function of the breathing apparatus emphasizes the integration of the control of breathing with the control of other motor acts.

Clinical applications of respiratory physiology are discussed in each chapter. In addition, Chapter 12 contains a more comprehensive discussion of applied respiratory physiology in the study of environmental lung diseases caused by smoking, occupational exposures, and air pollution. It is now clear that morbidity and mortality due to chronic lung diseases and lung cancer could be greatly reduced if everyone at all times inspired air free from smoke, dusts, fumes, and noxious gases. There are many examples of controlled studies in man and in animals, using methods of respiratory physiology, which have shown relations between environmental exposures and lung diseases. Tests which can detect minor changes in lung function, due to inhalation of noxious agents in our environment, can further refine our knowledge of environmental lung diseases.

The subject matter of this book is sometimes called "classical" respiratory physiology, perhaps because it concerns topics in which physiologists have had a long-standing interest. It is therefore possible to present a systematic discussion of concepts, experimental data, and areas of ignorance. More recently, biochemists, pharmacologists, and cell biologists have in increasing numbers turned to the study of the lungs. All lung diseases involve responses of cells to exogenous or endogenous factors. As a tissue, the lungs are a heterogeneous mixture of many different types of cells, involved in a wide variety of activities. Biochemists prefer to study basic principles in simpler systems. Yet, to understand lung diseases one needs to study lung tissue and lung cells. Some biochemical processes (e.g., formation of surfactant, p. 8) are specialized functions of the lungs and cannot be studied in other tissues. Other events, like the ciliary beat (p. 37) are similar in human bronchi, oysters, and unicellular organisms. Yet other processes (e.g., smooth muscle contraction, mucous gland secretion, fibroblast proliferation) are not unique to lung tissue, but their occurrence in lung tissue has special significance for the development of lung diseases. Hence, biochemical studies of these events usually take their cue from questions raised by physicians and physiologists who detect abnormalities in the structure and function of the lungs and wonder how these came about.

Because tissue and cellular responses in the lungs are diverse, it is not surprising that people with a wide variety of expertise are needed to unravel the problems posed by lung diseases. Immunologists and pharmacologists study asthma and other hypersensitivity lung diseases. Protein chemists study the formation of collagen. Lipid chemists investigate the pathways of surfactant formation. Tissue and cell culture specialists try to tease lung tissue apart and to obtain homogeneous cultures of viable cells. Thus, the cell biology of the lungs is highly diverse in its approaches, depending largely on which disease or tissue response one wants to study.

Some of the types of lung cells which the reader will encounter in various chapters of this book are:

Type I alveolar cells, which are destroyed by high concentrations of oxygen, ozone, and other toxic gases (p. 101, 301);

Type II alveolar cells, which are destroyed in repair of the alveolar epithelium when Type I cells have been destroyed, and which normally produce surfactant (see Chap. 1);

Alveolar macrophage cells, which phagocytose bacteria and dust particles (p. 294);

Mast cells, which release histamine and other chemical mediators in allergic reactions (p. 35);

Fibroblasts, which form collagen and may proliferate to form dense fibrous tissue in the lungs (p. 301);

Airway smooth muscle cells, which affect airway caliber in asthma and other diseases with airway obstruction (p. 296);

Mucous glands and goblet cells, which secrete airway mucus (Chap. 2).

Much recent work on lung metabolism and on lung cells is discussed in two recent books.[1,3] There is little question that basic research on lung cell biology holds many promises for the future. I believe that these promises stand the best chance of coming true if, at the same time, the methods and concepts of "classical" respiratory physiology continue to be improved and refined. The combination of the two approaches is a powerful one if one wants to relate responses of cells and tissues to events that can be observed in vivo in animals and in man. In this respect, we are fortunate in having chosen the lungs for our studies: so few other systems in the body yield as much information on their function, with simple methods, as the lungs do. This means that the physiologist can study not just patients, but also large groups of healthy subjects, including those who may have incipient or unrecognized lung disease. The detection and description of these early stages of lung diseases, together with the study of the development of cellular and humoral responses in lung cells and tissue, is just one example of an area where cell biologists and biochemists, on the one hand, and respiratory physiologists, physicians, and epidemiologists, on the other hand, can work together towards prevention and better treatment of lung diseases.

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# Contents

# THE PHYSIOLOGY OF BREATHING

# Chapter 1

## Development of the Breathing Apparatus

Growth and differentiation of tissues and organs are regulated by information contained in the genetic code. How this information is transcribed during the development of a fertilized egg into a full-grown organism remains a mystery. Gross morphological development is well understood in a descriptive sense, but we do not know the mechanisms that bring about the rapid and profound changes in a developing organism. How the biochemical machinery of the body and its capacity to respond to exogenous agents, such as drugs, develop is virtually unknown. The surfactant system of the lungs is a prime example of the difficulties remaining in this field. In this chapter, we will consider chiefly the lungs' morphological development, the maturation of the surfactant system, and the maturation of the neuromuscular system that controls chest motion and affects airway caliber. We will also review aspects of lung and chest growth that can be measured in vivo. Several other developmental aspects of breathing, such as fetal gas exchange and the initiation of breathing in newborn infants, have been discussed in recent monographs and reviews [4, 25, 29] (see also Chap. 10, p. 254).

### MORPHOLOGICAL DEVELOPMENT

When the human fetus is about 3 mm long, the lungs begin to form. A groove develops from the foregut, forming two pouches, with a tissue mass around them: the *primary lung bud.* Next, the proximal foregut divides into esophagus and trachea, with the latter connecting to the primary lung bud. The bronchial tree develops by division of the primary lung bud. During the first four months of fetal life—the *pseudoglandular period*—the whole tissue mass grows rapidly. The primitive airways that are formed are open from the beginning: at no stage of lung development is the tissue solid.[29] The *canalicular period* follows, and the newly formed bronchi divide further and the amount of connective tissue between them decreases. Increased numbers of blood vessels now enter the lungs. Although the epithelium flattens out, there is still enough tissue between epithelium and blood