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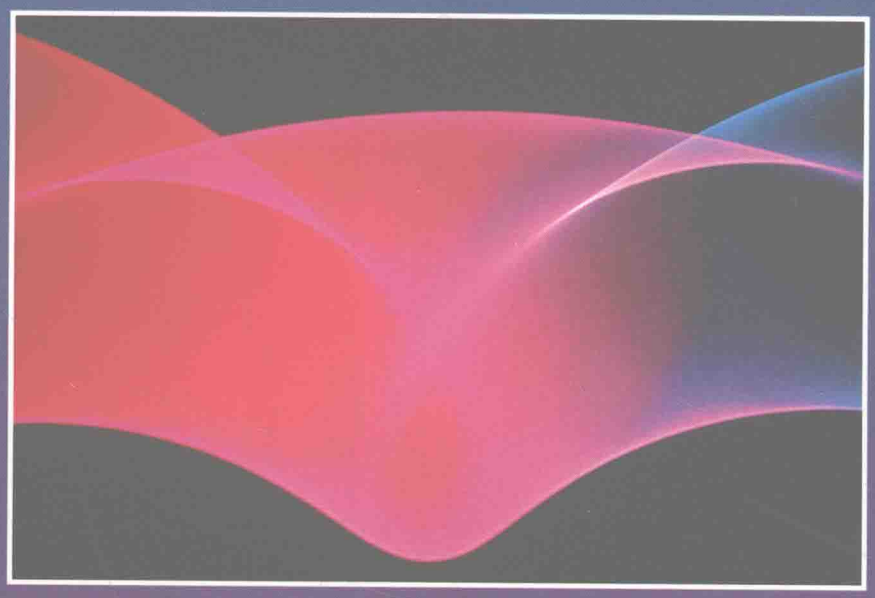
PULMONARY PATHOPHYSIOLOGY



Michael A. Grippi

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Lippincott's Pathophysiology Series

PULMONARY PATHOPHYSIOLOGY

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♾ This paper meets the requirements of ANSI/NISO Z39.48–1992 (Permanence of Paper).

. . . To Barbara, Kristen, and Amy

. . . To Joseph, Catherine, and Jean

. . . To my family

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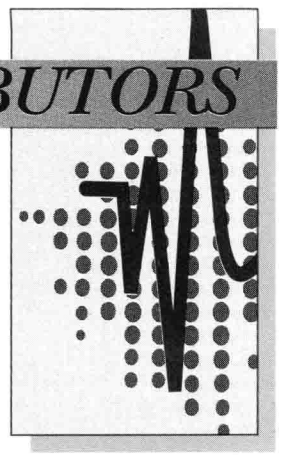

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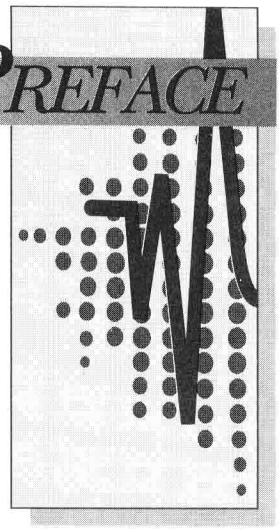
PREFACE



This book is an outgrowth of a core course in pathophysiology designed for second-year medical students at the University of Pennsylvania School of Medicine. It has been written with several goals in mind: (1) to review normal respiratory physiology as the basis for understanding pathophysiologic alterations important in disease states; (2) to provide a framework for understanding commonly used pulmonary diagnostic tests; (3) to develop a rational basis for various therapeutic strategies used in treating respiratory diseases; and (4) to demonstrate the clinical relevance of pathophysiology by anchoring concepts in case presentations grouped along thematic lines.

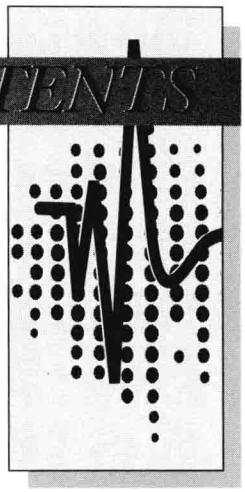
The audience to whom the book is addressed includes medical students, residents and fellows in training, and practicing physicians. The authors' experience has been that although students learn many of the fundamental concepts during their undergraduate medical education, these concepts are not rediscovered or fully understood until later in training, for example, during residency or fellowship. Therefore, although the book is targeted primarily to medical students, it should prove useful to all physicians interested in pulmonary physiology.

The volume is organized in four parts. Part I deals with the structure and mechanical properties of the lungs, chest wall, and airways. Included are respiratory mechanics, obstructive and restrictive pulmonary diseases, and the physiologic basis of pulmonary function testing. Part II addresses gas exchange in the lungs and gas transport to and from peripheral tissues. Part III focuses on the pulmonary circulation and its interface with ventilation. Part IV covers integrated respiratory functions, including control of breathing, respiratory failure, and pulmonary exercise physiology. Each part concludes with a series of clinical presentations, designed to highlight pathophysiologic principles addressed in the preceding chapters. Brief case scenarios are given, along with supporting laboratory studies; an analysis of the information is provided at strategic points.

This book is not an exhaustive review of pulmonary medicine or pathophysiology. Rather, it is a presentation of essential material and is based on the development of important pathophysiologic concepts. Additional information can be found in a number of other publications on the subject, as well as in comprehensive textbooks of pulmonary medicine.

Michael A. Grippi, M.D.

CONTENTS



PART I:

STRUCTURAL–FUNCTIONAL CORRELATES OF THE LUNGS, AIRWAYS, AND CHEST WALL

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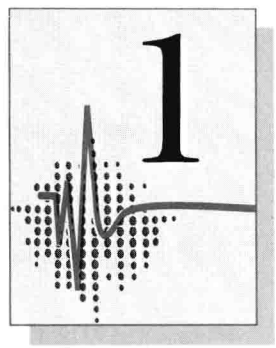
CHAPTER



Structure of the Airways and Lung Parenchyma

Michael A. Grippi

The role of the lung is gas exchange—the extraction of oxygen from the environment and elimination of carbon dioxide. These processes are necessary for cellular metabolism. Multiple organ functions must be integrated and coordinated for successful gas exchange. Ambient gas is pumped to the gas exchanging surfaces of the lung, while carbon dioxide–laden alveolar gas is eliminated by the same pumping mechanism. The pulmonary circulation provides blood flow through the lungs for continuous uptake and delivery of oxygen and, at the same time, unloads carbon dioxide into the alveoli. Furthermore, exquisite coupling between ventilation and circulation is essential for maximal efficiency of gas exchange. Finally, the gas exchange system must be monitored, controlled, and continuously fine tuned to cope with wide variations in metabolic demand, such as during exercise and in a variety of disease states.

In addition to its primary role in gas exchange, the lung serves a number of metabolic functions. These include production of surfactant and other compounds and metabolism of a variety of chemical mediators. Derangements in these functions can have a profound impact on the lung's ability to carry out gas exchange.

Normally, the lung is remarkably able to maintain appropriate levels of oxygen uptake and carbon dioxide elimination in a variety of circumstances. Lung disease, however, can selectively or universally affect the individual physio-

logic steps involved in gas exchange. For example, the obstructive airway diseases (see Chaps. 5 and 6) impede gas flow into and out of the alveoli, whereas the restrictive lung diseases (see Chap. 7) disturb the relationship between ventilation and blood flow or create a barrier for diffusion of gas.

The function of the lung is closely coupled to its structure; that is, form follows function. This chapter provides an overview of lung structure. The configuration of the thorax and its contents are described before airway and alveolar structure is considered. Anatomic relationships among the airways, alveoli, and pulmonary circulation are then reviewed. Finally, brief mention is made of the pulmonary lymphatic system and lung and airway innervation.

OVERALL CONFIGURATION OF THE THORAX AND ITS CONTENTS

The lungs are encompassed by the chest wall on all sides and by the diaphragm inferiorly (Fig. 1-1). The gas-exchanging function of the lungs is profoundly affected by the mechanical properties of the chest wall and diaphragm, as discussed in Chapter 2. Movement of the lungs within the thoracic cavity during inspiration and expiration is facilitated by a space between the two structures—the *pleural space*—created by apposition of the inner lining surface of the chest wall, the *parietal pleura,* and the outer lining surface of the lung, the *visceral pleura.* A thin film of fluid separates the parietal and visceral pleurae and serves as a lubricant. The precise mechanism for pleural fluid formation remains unknown. Removal of the fluid depends, in part, on the pulmonary lymphatic system. Changes in pressure within the pleural space help to determine inspiratory and expiratory airflow in healthy and diseased lungs (see Chap. 2).

The pleural "envelopes" surrounding each lung extend medially to create the *mediastinum,* a centrally located anatomic compartment containing the major

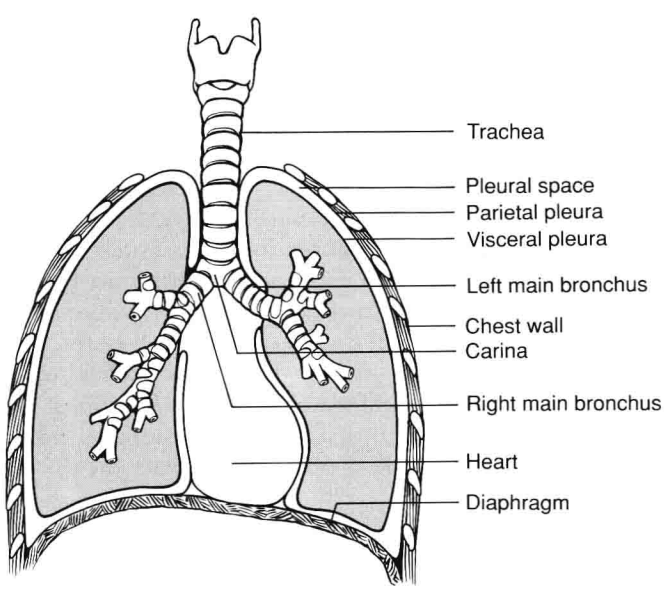


Figure 1-1. Anatomic relationships of the lungs, chest wall, diaphragm, pleural space, and central airways. The pleural space is created by apposition of the visceral and parietal pleurae.

airways and great vessels, including the pulmonary arteries and veins. The main bronchi and pulmonary arteries and veins penetrate each lung at the *hila* (Fig. 1-2). The point of bifurcation of the trachea into left and right main bronchi—the *carina*—lies in close proximity to the aortic arch and the division of the main pulmonary artery into branches supplying the left and right lungs. The *phrenic nerves,* derived from the third, fourth, and fifth cervical nerve roots, innervate the diaphragm and lie along the lateral aspects of the trachea.

AIRWAY STRUCTURE AS RELATED TO FUNCTION

The airways may be viewed as a series of dichotomously branching tubes; each "parent" airway gives rise to two "daughter" branches (Fig. 1-3). On average, there are 23 generations of airways in the human lung. The first 16 are known as *conducting* airways because they provide a conduit for gas flow to and from the gas-exchanging regions of the lung. These airways include bronchi, bronchioles, and terminal bronchioles. The last seven generations include the respiratory bronchioles, alveolar ducts, and alveolar sacs, all of which give rise to alveoli. The first-order respiratory bronchiole ($z = 17$ in Fig. 1-3) and all its distal gas-exchanging airways constitute a pulmonary *acinus.*

The structure of the walls of the conducting airways is quite different from that of the gas-exchanging regions (Fig. 1-4). The walls of the conducting airways are made up of three principal areas: the inner mucosal surface; the smooth muscle layer, separated from the mucosa by submucosal connective tissue; and the outer connective tissue layer, which, in large bronchi, contains cartilage. There are important functional correlates of this airway wall structure, and common clinical disorders are characterized by alterations in one or more components, as discussed in Chapters 5 and 6.

The bronchial epithelium is *pseudostratified,* containing tall cells and shorter

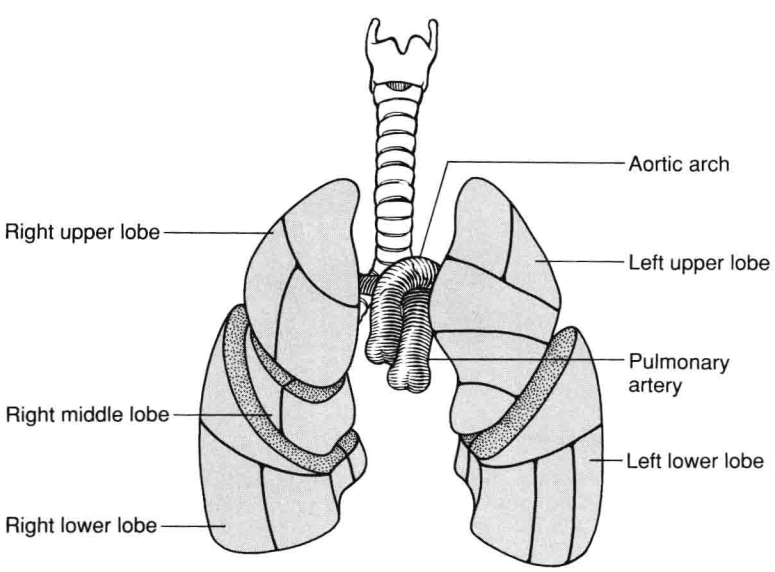


Figure 1-2. Relationship between major airways and great vessels in the chest. In the mediastinum, the trachea divides at the carina into left and right main bronchi, which lie near the aortic arch and pulmonary artery. The phrenic nerves, not shown in the figure, descend along both sides of the trachea and continue in a caudal direction, innervating the two hemidiaphragms. Three lobes constitute the right lung and two the left, including a subdivision of the left upper lobe, the lingula. Each lobe is completely or partially enveloped by visceral pleura and contains two to five segments, the borders of which are shown schematically by the thick lines within each lobe.

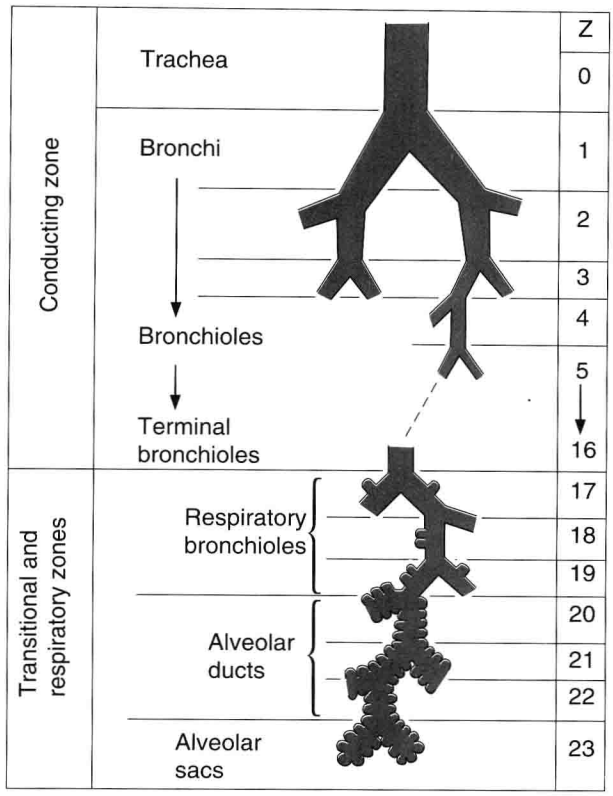


Figure 1-3. The tracheobronchial tree as a system of dichotomously branching tubes. The conducting zone, made up of the first 16 generations of airways to the level of the terminal bronchioles (z = 0–16), does not participate in gas exchange. The transitional and respiratory zones, in which gas exchange occurs, include the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (z = 17–23). (From Weibel ER. Geometry and dimensions of airways of conductive and transitory zones. In: Morphometry of the Human Lung. New York: Springer-Verlag, 1963:111.)

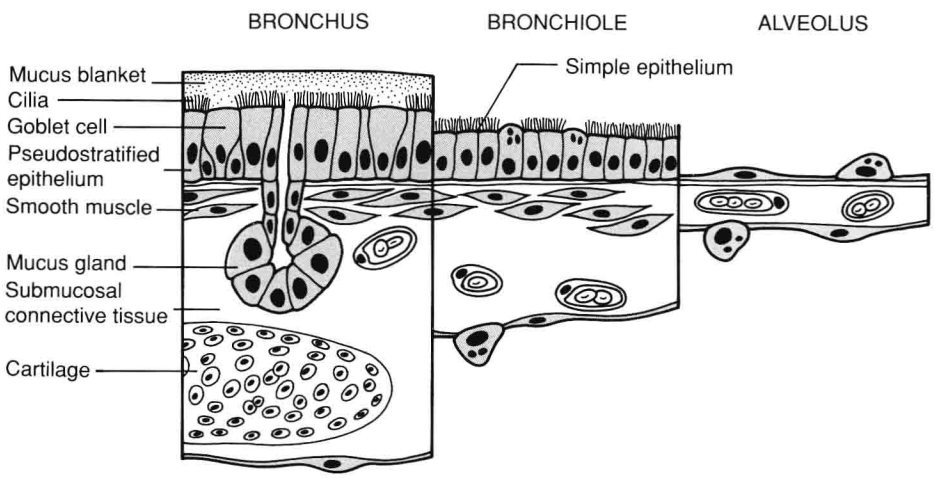


Figure 1-4. Airway wall structure: bronchus, bronchiole, alveolus. The bronchial wall contains ciliated pseudostratified epithelium, smooth muscle cells, mucus glands, connective tissue, and cartilage. In smaller bronchioles, a simple epithelium is found; cartilage is absent, and the wall is thinner. The alveolar wall is designed primarily for gas exchange, rather than structural support. (From Weibel ER, Taylor RC. Design and structure of the human lung. In: Fishman AP, ed. Pulmonary Diseases and Disorders, Vol. 1. New York: McGraw-Hill, 1988:14.)

basal cells, each of which is attached to the basement membrane. In the bronchioles, a *simple epithelium* is present. Airway epithelial cells have cilia at their apical surfaces; the cilia are important elements of the *mucociliary escalator*. The cilia beat in the direction of the airway opening, propelling a blanket of mucus secreted by goblet cells, which are interposed between ciliated epithelial cells. The mucociliary escalator is an important airway clearance mechanism and part of the respiratory host defense system.

Airway smooth muscle lies in continuous bundles within the submucosal connective tissue, extending from the major bronchi to the respiratory bronchioles. Muscle bundles extend into the gas-exchanging regions as well, lying in the walls at the openings of alveoli.

STRUCTURE OF THE GAS-EXCHANGING REGION

The gas-exchanging region must permit efficient diffusion of oxygen and carbon dioxide across alveolar and capillary walls. At the same time, it must support gas exchange over a lifetime and withstand the mechanical forces of lung inflation, deflation, and pulmonary blood flow. The apposition of vascular endothelium and alveolar epithelium in a supportive connective tissue stroma appears ideally suited to fulfill these requirements (Fig. 1-5).

The alveolar epithelium consists of two types of cells: squamous lining cells (type I cells) and secretory cells (type II cells). Type I cells, although significantly fewer in number than type II cells, account for 95% of the alveolar surface area. Type II cells produce and secrete *surfactant*, a substance composed of proteins and phospholipids, which spreads along the alveolar surface and lowers surface tension (see Chap. 2).

The capillary endothelium also consists of a layer of squamous lining cells that rest on the endothelial basement membrane. In parts of the alveoli, the basement membranes of the epithelium and endothelium are fused, creating an ultrathin barrier for gas exchange (see Chap. 9). Unlike the "tight" junctions between adjacent epithelial cells, which constitute a tight seal, the junctions between endothelial cells are "leaky," allowing water and solutes to move back and

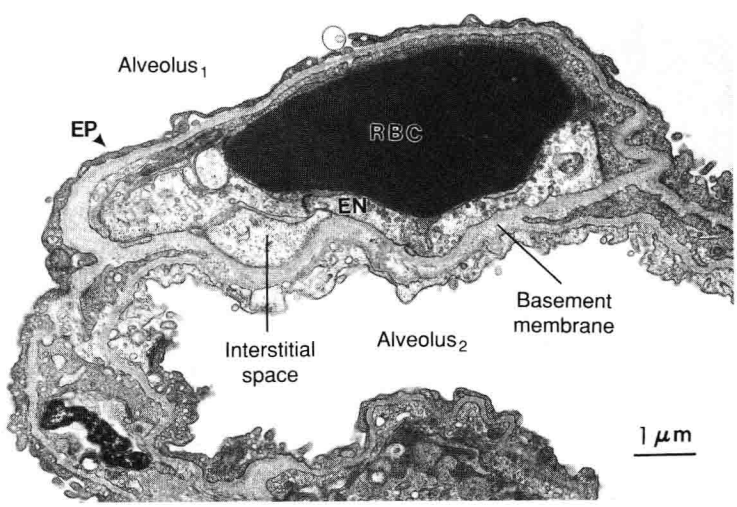


Figure 1-5. The alveolar–capillary membrane. Two adjacent alveoli are shown. Fusion of the basement membranes of the epithelial, type I cell (EP), and endothelial cell (EN) near Alveolus$_1$ creates an ultrathin barrier to diffusion of oxygen and carbon dioxide between the alveolar space and capillary. Near Alveolus$_2$, the epithelial and endothelial cells are separated by the interstitial space. The interstitial space is a potential site for collection of fluid. RBC, red blood cell. (Photomicrograph courtesy of Giuseppe G. Pietra, M.D.)

forth between plasma and the *interstitial space,* the region between epithelial and endothelial basement membranes (see Chap. 14).

Additional cell types exist within the interstitium, including macrophages and lymphocytes, cells important in host defense. These cells are discussed in more detail in Chapter 7.

GAS FLOW IN AIRWAYS

As a series of dichotomously branching tubes, the airways present a somewhat complex route for gas movement to and from the gas-exchanging regions. Although the diameter of each daughter branch is less than the diameter of the parent airway from which it is derived, the total cross-sectional area of each successive airway generation *increases* because of a marked increase in the number of airways (Fig. 1-6).

In the human lung, the airway diameter for each airway generation (z) can be estimated according to the following equation:

$$d(z) = d_0 \cdot 2^{-z/3} \qquad [1\text{-}1]$$

where

$d(z)$ = diameter of airway generation z
d_0 = diameter of the trachea (airway generation "0")

Figure 1-7 shows the average diameter of each generation of human airways.

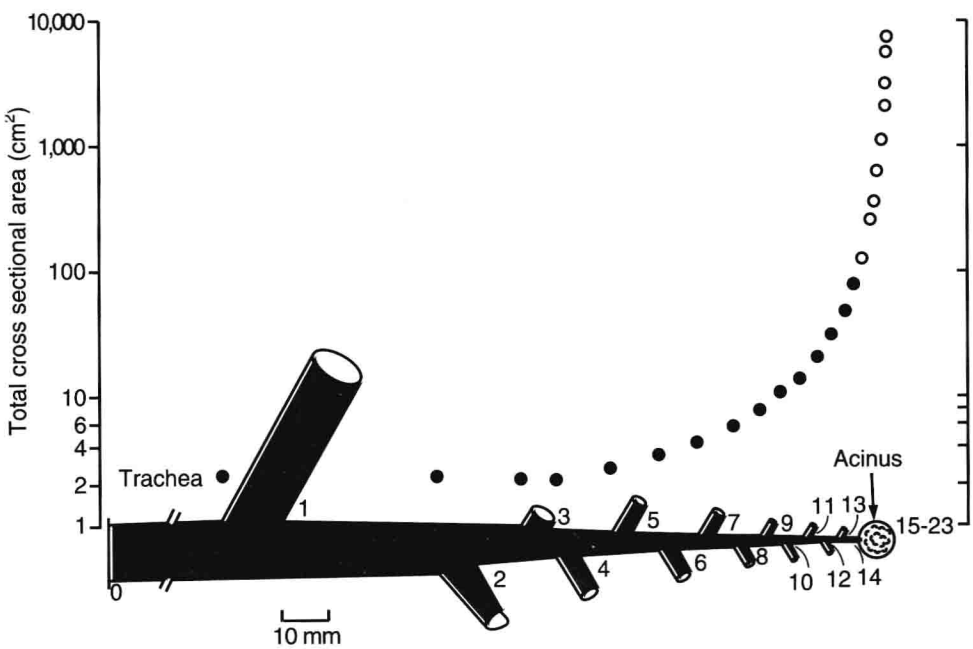


Figure 1-6. Total airway cross-sectional area in relation to airway generation. Although individual airway cross-sectional area decreases in successive airway generations, total cross-sectional area increases markedly because of an increase in the number of airways. (From Weibel ER. Design of the airways and blood vessels considered as branching trees. In: Crystal RG, West JB, eds. The Lung: Scientific Foundations. New York: Raven Press, 1991:717.)