Pulmonary Diseases

Mechanisms of Altered Structure and Function

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Preface

We intend this textbook to serve several purposes by its emphasis on the importance of structure-function relations in the lungs. First, it provides a background for medical students, exposed to the study of the respiratory system for the first time, to understand pulmonary pathophysiology. To facilitate this learning process, we have separated the discussion of the normal anatomy and physiology from the discussion of the pathology and pathophysiology of the diseased lung. Second, we believe that house officers should acquire a physiologic approach to clinical pulmonary medicine, and we have therefore applied this principle to the review of pulmonary diseases. Finally, practicing physicians who are intimately involved with the management of patients with respiratory problems may discover in this book the rationale for some of the diagnostic and therapeutic measures that they are routinely taking.

The text is divided into three parts. The first provides a brief summary of the normal structure and function of the lung to set the stage for the second part, which deals with the commonly used diagnostic techniques in pulmonary medicine, and especially for the third part, which discusses the clinical spectrum of lung disease. Realizing that an encyclopedic review of the subject would be neither possible nor desirable in the context of this series, we deliberately have omitted topics that were not deemed instrumental for the purposes of this book. For example, we have focused the discussion on those clinical entities that are commonly seen in outpatient and inpatient practice. For the description of rarities and oddities in pulmonary medicine, the reader is referred to readily available textbooks. We also have not included some recent observations on disease mechanisms as they are still awaiting confirmation.

We believe that this concise overview of pulmonary diseases represents a didactically effective synthesis of the basic pathophysiology of respiratory disorders and its clinical expression. We are grateful to our editors, DeWitt S. Goodman, M.D., Lin Paterson, and Carol Snarey, whose encouragement and expertise were crucial for the successful completion of this book.

Likewise, we would like to thank Isabel V. Rodriguez for her invaluable secretarial assistance, Lee Rickles for preparing the artwork, and Manuel Viamonte, Jr., M.D., for supplying the roentgenograms.

A. W.
M. A. S.

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I. Normal structure and function of the respiratory system

Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

1 : Relation between structure and function

Structure

Embryology

The lung starts its development on day 24 of fetal life as an outpouching of the embryonic gut. A few days later, this outpouching divides into two branches, and the branching then continues in an irregular dichotomous pattern for about 2 months, each branch giving rise to two daughter branches of unequal size. At this point most of the airways become lined with ciliated columnar epithelium, which consists of rectangular cells whose short edge faces the airway. These cells bear fine projections, *cilia,* which beat with a wavelike motion to move a mucous layer from the smaller to the larger airways and up to the larynx, where the mucus spills over into the esophagus. The mucus originates from mucous glands, which develop beneath the ciliated columnar epithelium through ducts or channels that penetrate the columnar epithelium, and from goblet cells interspersed with ciliated cells of the surface epithelium.

In month 5 of fetal life, small airways develop deep within the lung and are lined by nonciliated cuboidal epithelium. Capillaries that arise from vascular structures in the mesenchyme invest these airways, and the *alveoli,* the ultimate gas-exchanging units of the lungs, appear 1 month later. In the terminal alveoli, the cuboidal epithelium becomes attenuated. Capillaries proliferate around the terminal air spaces. At birth, there are about 24 million alveoli in the lungs. Their number increases to about 300 million by the age of 8 years, but further lung growth is not accompanied by an increase in the number of alveoli.

Anatomy

LARGE AIRWAYS. The airways are the conduits for air passage between the external environment and the gas-exchanging units of the lungs. The passages begin with the oral and nasal cavities and the pharynx. The larynx and the trachea are the immediate entrance to the lungs proper. The larynx contains fibromuscular structures and the vocal cords, which, on vibration, produce sound. The trachea is a fibromuscular tube about 10 to 12 cm in length that lies half in the neck and half in the thorax. The anterior and lateral surfaces are composed of ap-

proximately 20 U-shaped cartilages; the posterior surface is a fibrous membrane that can invaginate during a strenuous cough or exhalation. The average cross-sectional area of the trachea is 1.5 cm^2 during quiet breathing; during a forceful cough, the area may be reduced to 0.25 cm^2. The termination of the trachea within the thorax is called the *carina*; at this point there is a division into the right and left main bronchi. The right bronchus deviates to a lesser degree from the axis of the trachea than does the left.

The right lung accounts for 55 percent of the total gas volume. Each lung has incomplete separations that produce divisions called *lobes;* each lobe is supplied by a *lobar bronchus,* a division of one of the main bronchi. The right lung has three lobes (upper, middle, and lower); the left lung, two (upper and lower). Tertiary branching of the bronchi allows for further classification into bronchopulmonary segments, of which there are ten on the right and nine on the left.

SMALL AIRWAYS. The bronchial tree branches through 16 generations, until the terminal bronchioles are reached. These airways are lined by ciliated columnar epithelium and are the primary site for conduction of air in and out of the lungs: they are termed the *conductive zone* (Fig. 1-1). Branching then proceeds irregularly, either dichotomously or trichotomously, through a *transitional zone* of three generations of respiratory bronchioles. In the transitional zone, both conduction and a limited amount of gas exchange take place, because the walls of the respiratory bronchioles contain a few alveoli.

The terminal unit of the lung, the acinus, functions as the *respiratory zone.* The acinus is composed of the respiratory bronchioles, (generations 17–19), the alveolar ducts (generations 20–22), and the alveolar sacs, whose walls are formed by the terminal alveoli (the final generation—23). Smooth muscle is distributed throughout the bronchioles and proximal alveolar ducts.

ALVEOLI. In humans, the average alveolar size at resting lung volume is between 200 and 300 μm in diameter. At low lung volumes, such as after a maximum exhalation, the alveolar walls fold up to below some critical resting length, whereas in well-inflated lungs, alveolar septa become fairly uniform in thickness, and alveolar diameter becomes much larger. The septal thickness, exclusive of capillaries, ranges from about 2 to 8 μm.

The alveolar epithelium consists predominantly of flat cells (type I pneumocytes). Type II pneumocytes are much fewer in number; they are characterized by granules that contain the

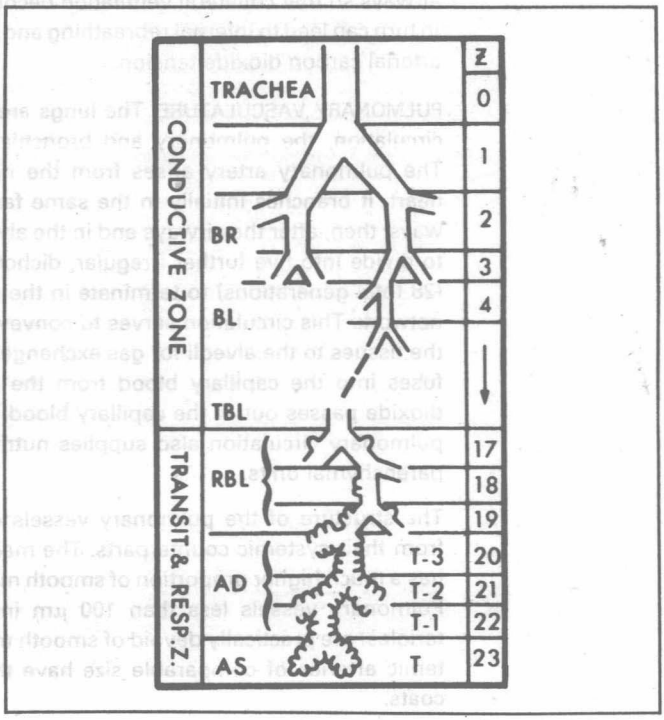

Fig. 1-1 : Branching pattern of the tracheobronchial tree. Z denotes the generation of branching; BR = bronchus; BL = bronchiole; TBL = terminal bronchiole; RBL = respiratory bronchiole; AD = alveolar duct; AS = alveolar sac. (From E. R. Weibel, *Morphometry of the Human Lung.* New York: Academic, 1963.)

precursors of *surfactant*, a phospholipid secreted to line the surface of the alveoli. Surfactant reduces the surface tension at the air-liquid interface of the lung, thereby preventing alveolar collapse. The alveoli and alveolar septa are also populated by pulmonary macrophages, which are migratory and phagocytic and, under normal conditions, serve a defense role.

Because of collateral ventilation, segmental or lobar airway obstruction does not invariably produce collapse of lung tissue owing to absorption of g... The term *collateral ventilation* signifies that gas can enter one area of the lung from another without resorting to conventional anatomic pathways. Anatomic communications between alveoli in normal lungs, namely, pores of Kohn, and bronchiolar channels of Martin and Lambert constitute the collateral pathways. The resistance to gas flow in such communications during tidal breathing is so high that collateral ventilation under normal circumstances is virtually absent. Enlargement of partially open collateral channels or recruitment of previously closed channels occurs with an increase of lung volume to promote collateral ventilation. In patients with emphysema, who have both anatomically disrupted alveoli and pulmonary hyperinflation, the resistance to airflow of the collateral pathways may be lower than the conducting

airways so that collateral ventilation becomes significant. This in turn can lead to internal rebreathing and a concomitant rise in arterial carbon dioxide tension.

PULMONARY VASCULATURE. The lungs are perfused by a dual circulation, the pulmonary and bronchial vascular systems. The pulmonary artery arises from the right ventricle of the heart. It branches initially in the same fashion as do the airways, then, after the airways end in the alveolar sac, continues to divide into five further irregular, dichotomous generations (28 total generations) to terminate in the pulmonary capillary network. This circulation serves to convey venous blood from the tissues to the alveoli for gas exchange; that is, oxygen diffuses into the capillary blood from the alveoli, and carbon dioxide passes out of the capillary blood into the alveoli. The pulmonary circulation also supplies nutrition to the terminal parenchymal units.

The structure of the pulmonary vessels differs considerably from their systemic counterparts. The main pulmonary artery has a much higher proportion of smooth muscle than the aorta. Pulmonary vessels less than 100 μm in diameter (e.g., arterioles) are practically devoid of smooth muscle, whereas systemic arteries of comparable size have thick smooth-muscle coats.

The bronchial arterial system consists of several small vessels that arise from the aorta or intercostal arteries; their total flow normally amounts to less than 1 percent of the cardiac output. This system supplies the nutritional needs of the large conducting airways and pulmonary vessels; the bronchial vessels are not directly distributed to the terminal parenchymal units.

PLEURA. The lungs are separated from the chest wall, diaphragm, and mediastinal structures by a virtual space, the *pleural space.* The pleural space is lined by an epithelium (mesothelium) that covers the lungs (visceral pleura), the mediastinum, the cranial surface of the diaphragm, and the inner surface of the rib cage (parietal pleura).

Function

Respiratory function

The major functions of the respiratory system are shown in Figure 1-2. The process of breathing is called *ventilation.* For the lungs to function efficiently as an organ of gas exchange, there must be a uniform *distribution* of inspired air to mix with the *volume* of air contained in the alveoli, which are perfused with blood. This mechanism operates to ensure optimal matching of ventilation with perfusion (*circulation*). Gas exchange takes place by *diffusion.* Oxygen diffuses from the alveoli into the red

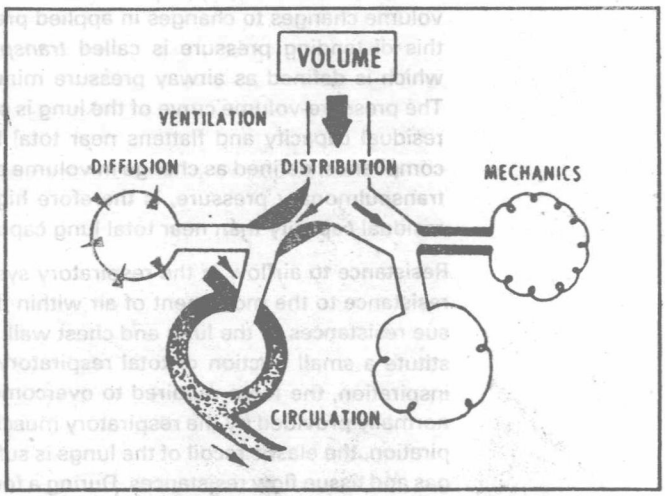

Fig. 1-2 : Major functions of the respiratory system. (From J. Kline, *Biological Foundations of Biomedical Engineering.* Boston: Little, Brown, 1976.)

cells, where it reacts with reduced hemoglobin, and carbon dioxide diffuses from the blood into the alveoli. The interrelationship of pressure, volume, and flow that is developed in the lung and pleural space by the movement of the chest wall muscles and diaphragm constitutes the *mechanics* of breathing.

MECHANICS OF BREATHING AND LUNG VOLUMES. When the respiratory muscles are relaxed at the end of a normal expiration, there remains a volume of air in the lungs. This volume is called *functional residual capacity* and is determined by the balance of the elastic forces exerted by the lungs and chest wall. The maximum excursions of the respiratory apparatus in both inspiratory and expiratory directions are also determined by a balance of forces—the elastic characteristics of the respiratory apparatus and the muscle forces applied to the apparatus. The maximum volume of air that is contained in the lung after a maximum inspiration is called the *total lung capacity,* and the minimum amount of air contained in the lung after a maximum expiration is called the *residual volume.* The *vital capacity* is the maximum amount of air that the subject is able to expire after a maximum inspiration (or vice versa) and is the difference between total lung capacity and residual volume. The volumes that can be displaced between the functional residual capacity position and total lung capacity and residual volume positions are called *inspiratory capacity* and *expiratory reserve volume,* respectively. The *tidal volume* is a component of the inspiratory capacity.

The elastic behavior of the lung–chest wall system can be best described by the pressure-volume curve generated by relating

volume changes to changes in applied pressure. For the lung, this distending pressure is called *transpulmonary pressure,* which is defined as airway pressure minus pleural pressure. The pressure-volume curve of the lung is steep near functional residual capacity and flattens near total lung capacity. Lung compliance, defined as change in volume divided by change in transpulmonary pressure, is therefore higher near functional residual capacity than near total lung capacity.

Resistance to airflow in the respiratory system is the result of resistance to the movement of air within the airways, and tissue resistances of the lung and chest wall. The latter two constitute a small fraction of total respiratory resistance. During inspiration, the force required to overcome flow resistance is normally provided by the respiratory muscles, whereas, on expiration, the elastic recoil of the lungs is sufficient to overcome gas and tissue flow resistances. During a forced and rapid expiration, however, the elastic recoil of the lungs is insufficient to overcome the flow resistance, and additional forces must be applied by contraction of the expiratory muscles. Most of the resistance to airflow is contained in the central airways; in the normal lung, airways smaller than 2 mm in diameter contribute less than 30 percent to total airflow resistance. Airflow resistance is inversely related to lung volume.

During a forced expiration, the flow rates are dependent upon lung volume and are governed by the muscular effort developed and by limitation to airflow that is influenced by dynamic compression of the airways.

The work of breathing is related to the force generated by the respiratory muscles to overcome elastic and resistive forces of the lung–chest wall system. This work can be defined as the cumulative product of pressure and volume.

VENTILATION, DISTRIBUTION OF VENTILATION, AND PERFUSION. The ventilation of the lungs at rest is 6 to 9 liters/minute. However, only part of this quantity has a role in alveolar ventilation and contributes to gas exchange. This phenomenon is due to wasted ventilation in the *dead space*—that is, the sum of air spaces in the lung that do not participate in gas exchange. The *anatomic dead space* is the volume of air contained within the conducting pathways down to the terminal bronchioles. The *physiologic dead space* includes the anatomic dead space and, in addition, those volumes of the lung that should anatomically participate in gas exchange, but functionally do not. The difference between the physiologic and anatomic dead space is the volume of alveoli with no blood flow and volume of alveoli with ventilation in excess of blood flow; this space is also

called the *parallel dead space*. The physiologic dead space has to be related to the tidal volume (dead space–tidal volume ratio) since the alveolar ventilation depends on it. Normally this ratio is less than 0.3. For a given minute ventilation, it is decreased during rapid shallow breathing (decreased alveolar ventilation) and increased during slow deep breathing (increased alveolar ventilation).

During inspiration, the tidal volume is added to the functional residual capacity; for the whole lung, the ratio of the final to the initial volume, the expansion ratio, is around 8:7 during quiet breathing (for example, 4.0:3.5 liters). Within the lung, expansion ratios have a wide range, since the expansion of lung tissue does not take place uniformly. Spatial inequality occurs when some alveoli have larger expansion ratios than others. Temporal inequality occurs in some alveoli that empty and fill earlier than others. These inequalities cause uneven distribution of ventilation. Causes of uneven distribution of ventilation include regional variations in elasticity due to gravity or disease, and regional obstruction. In a normal erect subject, there is a ventilation gradient from the bottom to the top of the lung as a result of gravitational forces.

Similarly, the distribution of blood flow is uneven in the erect normal subject, with a greater perfusion per lung unit at the base than at the apex of the lung. The ventilation and perfusion gradients from the bottom to the top of the lung are not ideally matched even in normal subjects. This discrepancy leads to a slight ventilation-perfusion inequality with an increase in the alveolar-arterial oxygen tension gradient. The extremes of the ventilation-perfusion ratio are 0 (right-to-left shunt) and infinite (dead space ventilation).

DIFFUSION. The rate of diffusion of a gas across the blood gas barrier is dependent on its solubility in liquid, its density, its partial pressure in the alveolus and the blood, and the surface area that is available for diffusion. Even though it is a larger molecule than oxygen, carbon dioxide has a solubility that is almost 25 times that of grease, and it diffuses about 20 times more rapidly between air and blood than oxygen. For this reason, the diffusion of carbon dioxide from the pulmonary capillaries to the alveoli is rarely a clinical problem.

A diffusion abnormality for oxygen is present if the capillary blood fails to achieve equilibrium with alveolar gas during its transit past the alveolus. An alteration in diffusing capacity of the lung can result from changes in the surface area and thickness of the alveolar membrane and the quantity and composition (red cell mass, hemoglobin concentration) of pulmonary

capillary blood. The diffusing capacity of the lung is a direct function of lung volume.

MUSCLES OF RESPIRATION. The diaphragm is the principal muscle involved in the expansion of the lungs during tidal inspiration. Contraction of this muscle causes descent of its dome and expansion of the lower rib cage. Both these actions become less efficient if the diaphragm is depressed (as in emphysema), and the second action may actually be reversed, so that the rib cage moves inward rather than outward. The dome of the diaphragm moves 1.5 cm during quiet breathing and 6 to 10 cm during maximal breathing.

The external intercostal muscles, which are situated between the ribs, contract during inspiration and enlarge the rib cage by their action on the ribs. The internal intercostal muscles contract only during forced expiration. The abdominal muscles are almost always inactive during quiet breathing. They contract vigorously in all voluntary expiratory maneuvers—coughing, for example. During exercise, abdominal muscles come into play when ventilation is in the order of 40 liters/minute (about five times the resting ventilation).

The anterior neck muscles, the scalene and sternocleidomastoids, are the most important accessory muscles of inspiration. However, the scalene muscles and occasionally the sternocleidomastoids contract to a limited extent in the upright position even during quiet tidal breathing, as indicated by electromyography. Contraction of these muscles becomes visually apparent only when inspiration is rapid or when tidal volume exceeds a value of approximately 1 liter.

Nonrespiratory function

PULMONARY DEFENSE MECHANISMS. The pulmonary defense system against cellular debris and inhaled foreign material, including microorganisms, consists of a series of barriers between the upper airway and the alveoli (Fig. 1-3). Not shown on this diagram are the tracheobronchial secretions, which contain several substances that contribute to host defenses, notably secretory immunoglobulin A (IgA). Secretory IgA consists of two serum-derived IgA molecules bridged by a secretory piece that is a product of the airway epithelium. In the normal subject, the primary defense mechanisms are capable of preserving the integrity of the airways. However, if there is a breakdown of one or a combination of the primary defense functions, cough comes into play as a secondary backup system.

Coughing begins with a brief, rapid inspiration of a volume of air greater than the normal tidal volume. The glottis then closes

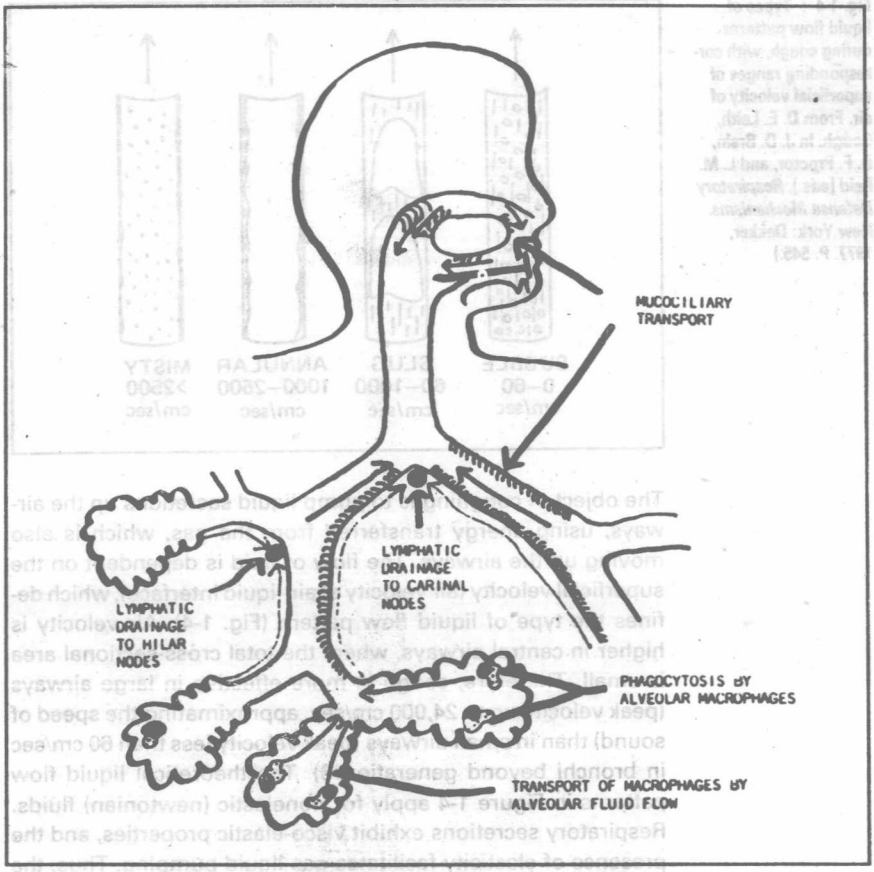

Fig. 1-3 : Defense system of the lung. (From G. Green, *Am. Rev. Respir. Dis.* 102:694, 1970.)

for about 200 msec. The pressure in abdominal, pleural, and alveolar spaces rapidly rises to 50 to 100 mm Hg or more. The glottis opens suddenly as subglottic pressure continues to rise. Expiratory flow at the mouth accelerates rapidly; within 30 to 50 msec, flow reaches a peak that may exceed 12 liters/second in normal subjects. Oscillations of airways, vocal cords, and gas cause a characteristic explosive sound. During this time, the lower trachea and other intrathoracic airways narrow, thereby increasing air velocity. About 500 msec later, after a liter of gas or less has been expired, flow ceases by one of two methods: Either the glottis closes with a characteristic "second sound" or respiratory muscle agonist-antagonist activity is adjusted so that alveolar pressure falls to zero. The sequence may be repeated rapidly several times, sweeping down through the lung volume toward residual volume and progressively narrowing more and more of the intrathoracic airways.