Disorders of the Respiratory System

Edited by

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Preface

Diseases of the respiratory system are diagnosed with increasing frequency and are one of the major causes of morbidity in patients. In recent decades our understanding of the physiologic function of the lung has expanded greatly, and physiologic tools are used continuously in the diagnosis and management of patients with respiratory disorders. The biochemical functions of the lungs in terms of host defense mechanisms, homeostasis of various polypeptides in the body as a whole and in the regulation of pulmonary microcirculation and airway function are becoming better known and understood.

This book is an attempt to bring together the physiologic function and the pathophysiologic alterations in the respiratory system. It is intended primarily for the medical student, house officer, and general physician, not necessarily for the pulmonary specialist, and is the second volume of a projected textbook entitled *The Science and Practice of Clinical Medicine*. The first part of this book describes anatomy, development, and nonrespiratory functions of the lung; physiology of respiration is then presented in some detail. The subsequent chapters on respiratory diseases group together disorders that share certain common physiologic traits, and these disorders, as far as possible, are discussed in relation to their pathophysiologic alterations. These chapters are not an exhaustive compilation of all of the diseases of the respiratory system. Rather, they are reviews of the major pathophysiologic disorders that share a common pattern of physiologic alterations or comparable etiologic factors, such as occupational lung disease. In addition there are sections on diagnostic approaches—physiologic, radiologic, isotopic, and surgical—as well as a section on physical signs and symptoms in pulmonary disease.

Since this book is part of a larger work, there are certain deliberate omissions. Pulmonary infections are included in the section on infections, pulmonary emboli are discussed in the book covering disorders of the cardiovascular system, and H^+ homeostasis is presented only very briefly in this volume since it is dealt with extensively in the book on the disorders of the renal system.

This book is the result of the contributing efforts of several authors, and I am grateful to them for their help. In particular I would like to express my gratitude to my colleague Denise J. Strieder, for not only writing extensively for this book but also for helping to review and edit many of the other chapters. I would also like to thank Lilian Roberts, who supervised and typed the initial manuscript.

Homayoun Kazemi, M.D.

Contents

ANATOMY OF THE LUNG

Gerald Nash

THORAX

Thoracic Skeleton

The thoracic skeleton consists of the 12 vertebrae, the sternum, and the ribs, which articulate with the vertebrae posteriorly and join the sternum anteriorly. The bony thorax is rigid, to provide protection for the thoracic organs; yet it is also pliable, to permit changes in thoracic volume during respiration. The thoracic skeleton forms a truncated cone with a small superior and large inferior opening. Anteriorly the apices of the lungs protrude about 2 in. above the superior opening; posteriorly they extend to the level of the neck of the first rib. Each thoracic vertebra has an articular facet on its superior aspect near the junction of the body and pedicle that receives the head of its corresponding rib. Thoracic vertebrae T2 through T8 also have inferior articulating facets. Each of these vertebrae articulates not only with its own rib, but also with the next lower rib. Each of the other thoracic vertebrae articulates only with its own rib. The vertebrocostal articulations are arranged in such a way that when the ribs are elevated they move outward, increasing both the anteroposterior and transverse dimensions of the thorax.

The sternum consists of three segments: manubrium, body, and xiphoid process. The manubrium receives the clavicles and the first two pairs of ribs. The body of the sternum and the manubrium has a hingelike junction, called the sternal angle, which permits changes in the anteroposterior dimensions of the thorax. The sternal body joins with the costal cartilages of ribs three through seven. The costal cartilages of ribs eight through ten join the seventh costal cartilages and thereby attach only indirectly to the sternum. The costal cartilages below the second rib ascend obliquely to join the sternum. Despite this ascent of the costal cartilages, the sternal ends of the ribs lie below the level of their vertebral connections, giving the ribs a downward inclination as they extend from the vertebrae to the sternum. The last two pairs of ribs articulate only with their vertebrae and do not join the sternum. The xiphoid process of the sternum, which receives part of the seventh costal cartilage at the xiphisternal junction, ends inferiorly in the posterior wall of the rectus sheath.

Muscles of Respiration

The principal muscles of respiration are the diaphragm and the intercostal muscles. The diaphragm is a thin muscle that separates the thoracic and abdominal cavities. It has sternal, costal, and vertebral origins and a central aponeurotic insertion called the central tendon. There are three large openings in the diaphragm through which pass the inferior vena cava, esophagus, and aorta. Each hemidiaphragm receives its motor innervation solely from the ipsilateral phrenic nerve. These motor fibers have their origins in ventral horn cells at spinal levels C3 to C5. The peripheral fringe of the diaphragm is supplied by sensory fibers from the lower intercostal nerves. The phrenic nerves provide sensory fibers to the remainder of the diaphragm. When the muscle fibers of the diaphragm contract on inspiration, the central tendon is pulled down, thereby increasing the thoracic volume. On expiration the diaphragm relaxes and returns to its resting condition. On forced expiration the abdominal muscles are brought into play, the abdominal viscera are forced upward, and the diaphragm may rise as high as the fourth intercostal space.

The intercostal muscles consist of outer and inner layers that crisscross, running in opposite directions. The fibers of each external intercostal muscle slope obliquely anteriorly and inferiorly from the inferior margin of a rib to the superior margin of the rib below. The fibers of each internal intercostal muscle run posteriorly and inferiorly from the lateral border of the sternum to the dorsal angle of the rib below. Each internal intercostal muscle is split into two layers (the internal and the innermost intercostal muscles) by the intercostal nerves and vessels. The mechanical action of the intercostal muscles has been the subject of debate. Some authorities believe that these muscles simply prevent the intercostal spaces from ballooning in and out during inspiration and expiration. Others think that the intercostal muscles play a more active role in respiration by producing movement of the ribs, notably elevation. They may also facilitate the action of other muscles on the rib cage. In addition to the diaphragm and intercostal muscles, many other muscles attached to the bony thorax may be used to augment

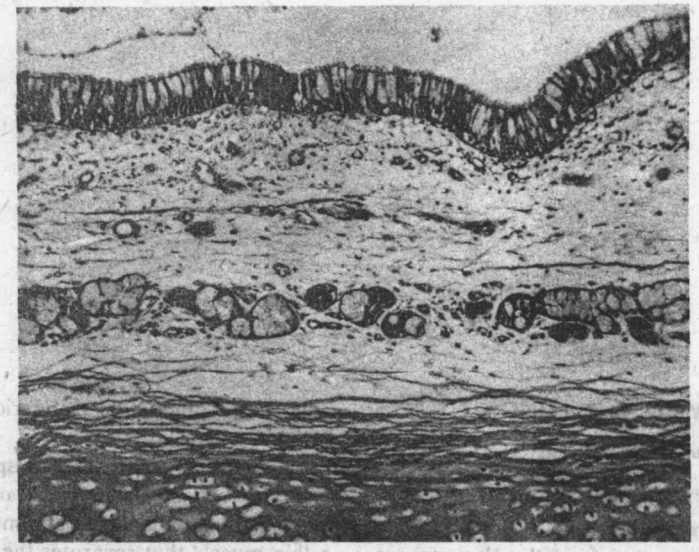


Fig. 1. Microscopic section of trachea showing pseudostratified columnar epithelium with ciliated and goblet cells, submucosal mucous and serous glands, and a portion of a cartilage plate (H&E ×130).

thoracic movements when respiratory efforts increase. These accessory muscles of respiration include the abdominal muscles, erector spinae, scalenes, sternocleidomastoids, and the serratus muscles. A familiar example of the use of accessory muscles of respiration occurs when an individual with air hunger grasps the arms of a chair to increase the force of his respiratory movements. This maneuver fixes the shoulders, enabling the anterior serratus muscles to assist in elevating the ribs.

Pleural Cavities

The pleural cavities contain the lungs and are bordered by the ribs, diaphragm, and mediastinum. The cavities are lined with parietal pleura, which consists of an inner layer of mesothelial cells lying on an outer layer of collagen and elastic fibers. The lungs are enveloped in visceral pleura, which has a structure similar to that of the parietal pleura. The visceral and parietal pleurae merge and become continuous at the root of the lung.

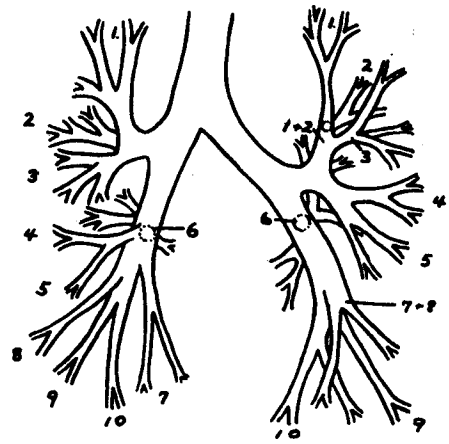
Lungs

The lungs are paired organs that fill most of the pleural cavities and are divided into lobes by deep fissures lined by visceral pleura. Oblique and horizontal fissures separate the right lung into three lobes, and a single oblique fissure divides the left lung into two lobes. Connective-tissue septae divide the pulmonary lobes into lobules, which are most easily recognized at the periphery of the lung, where the septae are most prominent. The bronchi, vessels, and nerves supplying the lungs enter at the pulmonary hila.

Airways

The airways include the trachea and the bronchial tree down to the level of the terminal bronchioles. They function as air conduits and do not participate in respiratory gas exchange. The trachea is a tube about 10 to 12 cm long and about 2 cm wide that begins at the cricoid cartilage. It descends through the superior mediastinum to the level of the junction of the manubrium and body of the sternum, where it bifurcates, giving rise to the main bronchi. The tracheal wall is lined by pseudostratified columnar epithelium that contains ciliated and nonciliated cells (Fig. 1). Among the latter are mucin-producing goblet cells. Against the basement membrane are small cells with oval nuclei, known as basal cells, which are thought to be able to differentiate into either ciliated or nonciliated epithelial cells. The cilia of the tracheobronchial tree have a coordinated whiplike beat that propels an overlying mucus coat upward toward the larynx, where it is either swallowed or expectorated. The mucus layer contains particulate matter from the inspired air, exfoliated epithelial cells, macrophages, and leukocytes. The mucociliary mechanism plays an important role in ridding the respiratory tract of environmental and endogenous contaminants. Beneath the basement membrane on which the tracheal epithelium lies is an elastic lamina propria. The submucosa contains mucus and serous glands whose ducts penetrate the mucosa to reach the surface. Beneath the submucosa, providing support for the wall, are a series of U-shaped cartilage plates that have their open ends facing posteriorly. A flat, transversely arranged layer of smooth-muscle fibers fills the gap between the tips of the cartilages.

The two main bronchi arise at the tracheal bifurcation and enter the lungs at the pulmonary hila. The right main bronchus is shorter than the left and deviates less from the axis of the trachea. This explains why aspirated foreign objects more often lodge in the right lung than in the left. Within the lung the main bronchi divide into lobar bronchi, one for each pulmonary lobe. The lobar bronchi give rise to segmental bronchi, ten in the right lung and eight in the left (Fig. 2). Each segmental bronchus and the portion of lung that it supplies constitute a bronchopulmonary segment. The broncho-



1. Apical	Upper Lobe Bronchus	Apical posterior	1, 2
2. Posterior			
3. Anterior		Anterior	3
4. Lateral	Middle Lobe Bronchus	Superior lingular	4
5. Medial		Inferior lingular	5
6. Superior	Lower Lobe Bronchus	Superior	6
7. Medial basal		Anteromedial basal	7, 8
8. Anterior basal			
9. Lateral basal		Lateral basal	9
10. Posterior basal		Posterior basal	10

Fig. 2. Diagram of normal tracheobronchial tree showing standard numbering of segmental bronchi. (Reproduced by permission from Hinshaw HC: Diseases of the Chest. Philadelphia, WB Saunders, 1969, p 83.)

pulmonary segments are irregular and variable in size and shape, and they are separated from one another by connective-tissue septae. Knowledge of the distribution of the segmental bronchi and bronchopulmonary segments enables one to describe accurately the locations of pulmonary lesions and is important in thoracic surgery, bronchoscopy, and radiology.

The bronchi branch more or less dichotomously into successively smaller tubes, the total cross-sectional area of each generation being greater than that of the preceding one. After 6 to 25 generations the bronchial tree ends in terminal bronchioles. The large bronchi have essentially the same structure as the trachea. Medium-sized bronchi have irregularly shaped cartilage plates. The cartilage plates become smaller and more regular as the bronchi decrease in size, and they disappear at the level of the bronchioles. Bronchioles are generally less than 1 mm in diameter, are devoid of mucous glands, and have cuboidal rather than pseudostratified columnar epithelium. There are three or four orders of bronchioles, which end in terminal bronchioles. Terminal bronchioles still have ciliated epithelium, but goblet cells are few or absent. Nonciliated, heavily granulated cells known as Clara cells are also present in bronchioles. Recent studies have shown that Clara cells have ultrastructural and histochemical features characteristic of secretory cells. Although their function remains unknown it has been postulated that Clara cells are a source of the mucopolysaccharides and proteins that constitute part of the subphase (base layer) of the alveolar surface-active layer (surfactant).

Respiratory Structures

The respiratory unit of the lung is the acinus. It is defined as the lung portion distal to a terminal bronchiole and includes respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (Fig. 3). These are the structures that are involved in gas exchange. Respiratory bronchioles have cuboidal nonciliated epithelium and are devoid of goblet cells. Each respiratory bronchiole contains a few alveoli arising directly from its walls, and each bronchiole gives off from 2 to 11 alveolar ducts. The walls of alveolar ducts are made up entirely of alveoli and exhibit knoblike arrangements of smooth muscle surrounding the alveolar openings. The alveolar ducts terminate in either one or several alveolar sacs that are made up of a variable number of alveoli.

Alveoli are thin-walled sacs that have one open side. Alveolar walls contain a dense network of capillaries, which protrude into the alveolar spaces, as well as a supporting framework of reticulin and elastic fibers. Pores of Kohn, which are openings through the alveolar walls that measure about 7 to 9 μ in diameter, connect adjacent alveoli. These are rare or absent in children and increase in number with age. They may provide a pathway for collateral ventilation in cases of small-airway obstruction and may be involved in the spread of infection from one alveolus to another. The total alveolar surface area of the adult human lung varies between 43 and 102 m^2 de-

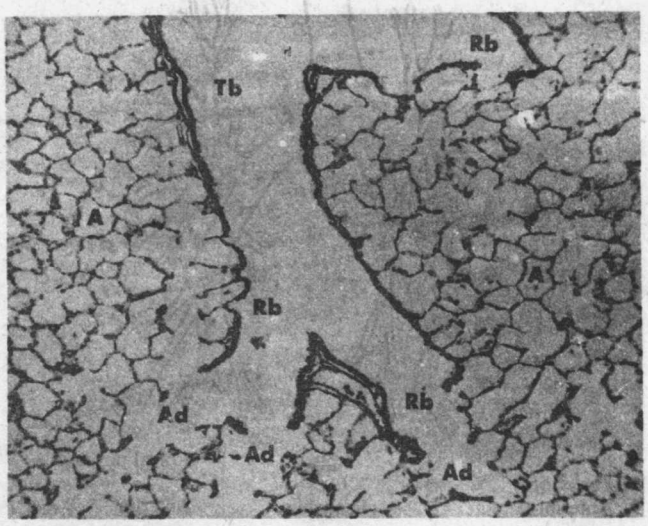


Fig. 3. Microscopic section of lung showing the respiratory structures. A terminal bronchiole (Tb) gives rise to respiratory bronchioles (Rb). The respiratory bronchioles give off alveolar ducts (Ad) that terminate in alveolar sacs made up of a variable number of alveoli (A). (H&E × 130).

pending on body length. This means that gas exchange can occur across a wide surface area and indicates that there is a great deal of reserve in the system.

The structure of the alveolar–capillary membrane was a matter of debate among histologists for many years. The controversy was resolved by the ultrastructural observations of Low and Karrer, who found that the alveolus is lined with a continuous layer of epithelium that in most areas is below the limit of resolution of the light microscope. The alveolar lining epithelium is composed primarily of two cell types (Fig. 4). Most of the alveolar surface is lined with extremely flattened cells that are similar in appearance to endothelial cells. These are membranous pneumocytes, or Type I alveolar cells. Membranous pneumocytes consist largely of thin cytoplasmic extensions that arise from a central nucleated portion. Most of the organelles, such as mitochondria and endoplasmic reticulum, are concentrated around the nucleus. The thin cytoplasmic extensions contain pinocytotic vesicles, but few other organelles. A second cell type, the granular pneumocyte or Type II cell, makes up only a small fraction of the alveolar surface. These cells are rounded and do not have cytoplasmic extensions. They bulge into the alveolar spaces or lie in niches in the alveolar wall, almost covered by adjacent Type I cells. The granular pneumocyte has microvilli on its free surface and is rich in Golgi elements, endoplasmic reticulum, and mitochondria. It also has characteristic cytoplasmic membrane-bound osmiophilic bodies. These structures, which consist largely of concentric lamellae, are called cytosomes or lamellar bodies. Lamellar bodies are rich in phospholipid, and they have been observed apparently discharging their contents onto the surface of the alveolus. These bodies may represent intracellular stores of the phospholipid portion of surfactant. In addition to their supposed contribution to the production of surfactant, the granular pneumocytes may also serve as the reserve cells of the alveolus. When the alveolar epithelium has been damaged, these cells have been shown to proliferate and repopulate the alveolar surface with a cuboidal epithelium.

A rarely seen third type of alveolar epithelial cell is the Type III or alveolar brush cell. It is shaped like a truncated pyramid, with wide apical microvilli that are twice the diameter of those of the Type II cells. Its cytoplasm contains dense bundles of fine filaments. This cell is structurally similar to the chemoreceptor cell found in taste buds. Its function in the lung has yet to be ascertained.

Another cell type found in the alveoli is the alveolar macrophage. Macrophages lie free in the alveolar spaces and are not part of the epithelial lining. As phagocytes they play an important role in respiratory defense mechanisms such as inflammation and the clearing of particulate matter and bacteria from the lung. The origin of alveolar macrophages has been a subject of debate, and recent evidence supports the hypothesis that these cells are derived from marrow stem cells. It is possible that derivatives of marrow stem cells are transported via the bloodstream to the lung where, in the alveolar interstitium, they undergo division-maturation to become mature macrophages.

The endothelium of the alveolar capillaries forms an uninterrupted lining devoid of pores. Endothelial cells have an appearance similar to that of membranous pneumocytes, with central nucleated portions and thin cytoplasmic extensions containing numerous pinocytotic vesicles. Endothelial intercellular junctions permit passage of protein molecules the size of horseradish peroxidase (about 40 Å) and probably play a greater role than pinocytotic vesicles in the exchange of substances between the blood and interstitial space. In contrast, the intercellular junctions of the alveolar epithelium do not allow horseradish peroxidase to pass from the alveolar space into the interstitium.

The alveolar interstitium is the space between the

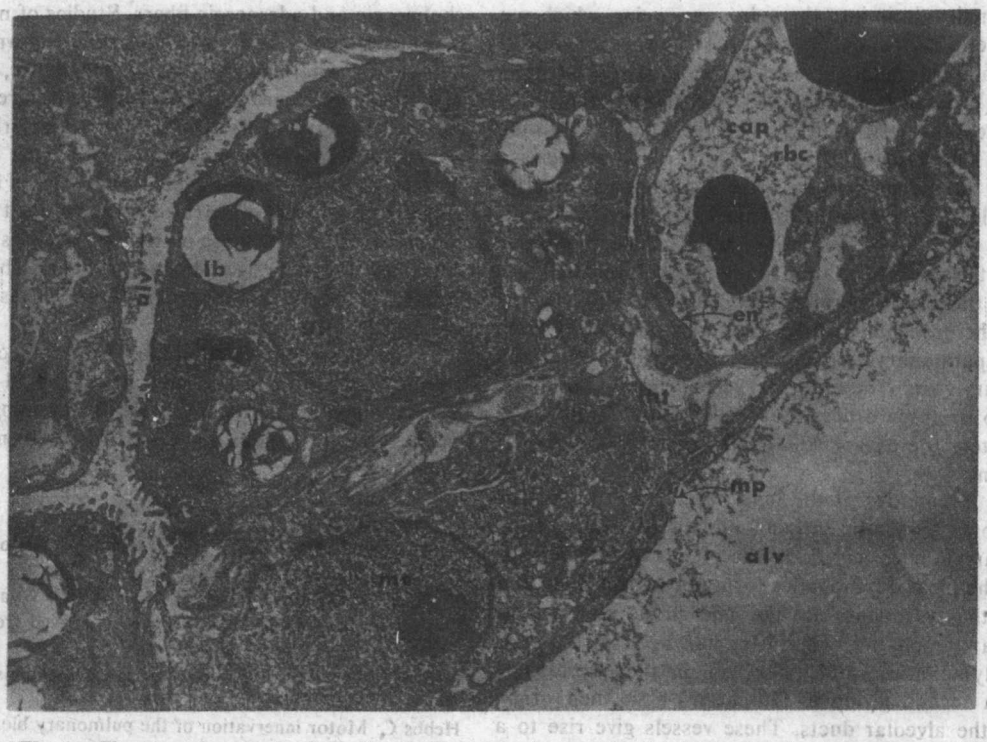


Fig. 4. Electron micrograph of alveolar-capillary membrane. Alveolus (alv) is lined with two types of epithelium: Type I membranous pneumocytes (mp) and Type II granular pneumocytes (gp) with lamellar bodies (lb). Alveolar capillary (cap) is lined with endothelium (en) and contains erythrocytes (rbc). The interstitium (int) lies between the capillary endothelium and alveolar epithelium and varies in thickness. Collagen (c) and a mesenchymal cell (mc) are present where the interstitium is widest (×7800). (Courtesy of Andrea Ceselski, Shriner's Burn Institute, Boston, Mass.)

alveolar–capillary endothelium and the alveolar epithelium. It is continuous with the interstitial space surrounding the airways and vessels. In many areas the basement membranes of the endothelium and epithelium are fused, the interstitial space is minimal, and the alveolar–capillary membrane is very thin. In other regions the endothelial and epithelial basement membranes are separated by a variable space that contains collagen and elastic fibers, fibroblasts, and other mesenchymal cells. In such regions the interstitium and the alveolar–capillary membrane are relatively wide. Thus the thickness of the alveolar–capillary membrane varies from about 0.2 μ to 10 μ with a mean of about 1.5 μ.

Physiologic and biochemical evidence points to the existence of an extracellular surface-active layer overlying the alveolar epithelium. This lining layer, known as pulmonary surfactant, is believed to consist of a superficial phospholipid film lying on a subphase composed of mucopolysaccharides and protein. As mentioned previously, it is believed that the phospholipid film is produced by the granular pneumocytes of the alveolus. Ultrastructural demonstration of such an extracellular layer overlying the alveolar epithelium was not possible when standard techniques were used to prepare lung tissue for electron microscopy; however, recent studies employing new methods of lung fixation have shown a double extracellular layer lining alveoli. This layer has an ultrastructural appearance consistent with the biochemical composition of pulmonary surfactant.

Vessels and Lymphatics

Two arterial systems, pulmonary and bronchial, supply the lungs. The pulmonary arteries carry deoxygenated blood from the right ventricle to the respiratory parenchyma, accompanying the bronchial tree as far as the respiratory bronchioles. The pulmonary arterial tree is a low-resistance system, a fact reflected in the structure of the pulmonary arteries, which have a relatively thin media with more elastic tissue and less muscle than systemic arteries of comparable size. Whereas in the general circulation only the aorta and its major branches are elastic arteries, in the pulmonary circuit elastic arteries may have a diameter as small as 1 mm. Below that size the transition to muscular arteries takes place. Muscular pulmonary arteries accompany terminal and respiratory bronchioles and give rise to arterioles when they reach a diameter of approximately 70 μ. Pulmonary arterioles are devoid of muscle and consist only of endothelium and a single elastic lamina surrounded by a thin layer of collagen fibers. They supply clusters of alveolar ducts. The arterioles give rise to pulmonary capillaries that form a network supplying the alveoli. The pulmonary venules drain blood from the capillaries of the pleura, alveoli, alveolar ducts, respiratory bronchioles, and bronchi, excluding the first two bronchial divisions.

These venules drain into the pulmonary veins, which run in the interlobular connective-tissue septae away from the airways and pulmonary arteries and enter the left atrium.

The bronchial arteries arise from the thoracic aorta or intercostal arteries and carry oxygenated blood to the airways. They supply the bronchial walls and provide vasa vasorum to the pulmonary arteries. Bronchial arteries are smaller in caliber and more muscular than pulmonary arteries. They lie in the peribronchial connective tissue close to the cartilage plates, supplying the bronchial tree as far as the terminal bronchioles. Much of the blood carried by the bronchial arteries enters the pulmonary veins via intrapulmonary anastamoses between bronchial and pulmonary veins. The bronchial veins primarily drain the first two or three orders of bronchi. Blood from these veins enters the azygos, the hemiazygos, or the innominate veins.

The lymphatics of the lung have three major divisions. Some lymphatics originate at the periphery of the pulmonary lobules and lie in the pleura or interlobular septa. The pleural lymphatics form polyhedral rings that outline the pulmonary lobules and drain into the interlobular lymphatics. The latter join to form the perivenous lymphatics, which also run in the interlobular septa. A second group of lymphatics have their origin around the alveolar ducts. These vessels give rise to a lymphatic network that accompanies the bronchial and pulmonary arteries. The lymphatics of the third division lie in the interlobular septa and connect the perivenous lymphatics with the bronchoarterial lymphatics. All pulmonary lymphatics drain to the hilar lymph nodes.

Innervation

Branches from the vagus nerves and the second, third, and fourth ganglia of the thoracic sympathetic chain form anterior and posterior pulmonary plexuses that supply the bronchi, arteries, and veins of the lung. The nerves supplying the bronchi are larger than those of the vessels and consist of bundles of large and small myelinated and unmyelinated fibers. The large myelinated fibers are believed to be afferent; they terminate in muscle spindles or in the bronchial epithelium. Small myelinated fibers, presumably efferent, connect with the vagal ganglion cells that are found throughout the plexus. These ganglion cells give rise to unmyelinated fibers that end in bronchial smooth-muscle and mucous glands. Ganglion cells that are probably of vagal origin have been demonstrated throughout the lung at all levels of the airways, respiratory bronchioles, alveolar ducts, and pulmonary arteries and veins.

Whereas the relatively stout nerve fibers that supply the bronchi are readily identified by the classic histologic techniques of neuroanatomy, the finer fibers that supply the pulmonary vessels have been difficult to trace and even to differentiate from reticulin fibers. In addition, the standard methods cannot distinguish between adrenergic and cholinergic fibers. The recent developments of a histochemical technique for demonstrating acetylcholinesterase and a fluorescence technique for identifying noradrenaline have enabled investigators to differentiate cholinergic and adrenergic fibers. Studies of mammalian lung employing these methods have shown that the pulmonary arteries, bronchial musculature, and large pulmonary veins are innervated by both adrenergic and cholinergic nerve fibers. The pulmonary arterial tree has a dual vasomotor nerve supply down to the level of arterioles 40 to 70 μ in diameter. The density of innervation appears to be greatest in arterial branches just beyond the parent vessel. In the large pulmonary arteries adrenergic nerves predominate over cholinergic fibers. The bronchial arteries of most of the mammalian species tested contain adrenergic fibers only.

The existence of pulmonary stretch receptors and receptors sensitive to pressure and chemical substances has been postulated on the basis of physiologic studies. Such receptor organs have yet to be identified anatomically.

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STRUCTURAL AND FUNCTIONAL DEVELOPMENT OF THE LUNG

Daniel C. Shannon

The fetal lung in utero serves no recognized useful function except for a minor role in water balance. Yet from the moment of birth the lung must immediately and continuously interact with the environment to sustain aerobic metabolism and defend against air pollutants and microorganisms. Previously untested mechanisms must first initiate and then sustain ventilation of air through a system of fluid-filled conduits and air spaces; further, a pulmonary capillary bed, accustomed to carrying 5 percent of cardiac output, must suddenly carry almost the entire output and match it in a reasonable fashion with ventilation to accomplish efficient gas exchange. Once fetal lung fluid is cleared, the alveolar surface and interstitium must be kept relatively dry and the alveoli themselves must remain inflated. Of less immediate but

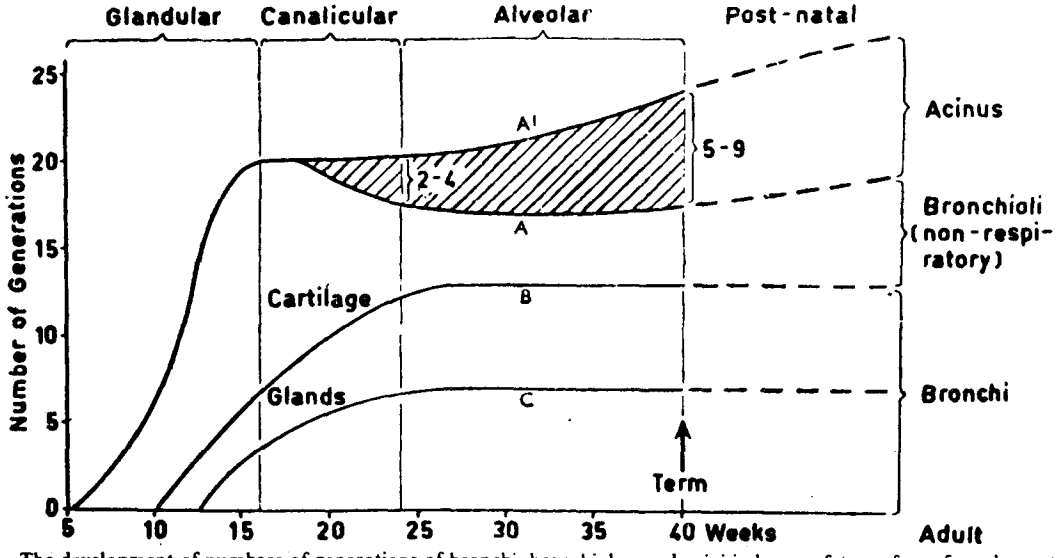

Fig. 1. The development of numbers of generations of bronchi, bronchioles, and acini in human fetuses from 5 weeks gestation to term. [Reproduced by permission from Reid L: in De Reuck AVS, Porter R (eds): Development of the Lung. Boston, Little, Brown, 1967, p 110.]

nonetheless great importance, defense mechanisms must be prepared to filter out large numbers of inhaled particles and microorganisms.

Since successful initiation and maintenance of air breathing is central to survival in man, it is no surprise that failure of development or expression of physiologic processes controlling respiration accounts for a large percentage of neonatal mortality.

BASIC STRUCTURE

Bronchial

The developing lung can be thought of as two trees arborizing toward one another, resulting in apposition of their terminal branches. The tracheobronchial tree begins as a ventral pouch of endoderm from the floor of the primitive foregut in the fourth week of gestation. Within days, precartilage appears and follows bronchial development, so that while the branching of the bronchial system proceeds to completion by the 16th week the full extent of cartilage has appeared by the 24th week (Fig. 1).

Vascular

A transitional system of perfusion of the primitive lung bud is then replaced by the definitive pulmonary vascular tree. The main pulmonary artery is derived from the right ventricle and joins the right and left pulmonary arteries, which are derived from the right and left sixth aortic arches. Branching of the system then parallels airway development and establishes functional connections with capillaries that proliferate in the glandular mesenchyme. Pulmonary venous branching occurs simultaneously and connects to buds from the left atrium, completing the pulmonary vascular system. Most of the primitive blood supply then atrophies except for a variable number of bronchial arteries that supply derivatives of the primitive lung bud down to terminal bronchioles and drain into the pulmonary veins. Origins of lymphatic capillaries, which ultimately extend peripherally to the level of respiratory bronchioles and their more central lymphatic vascular connections which accompany bronchial and arterial branches through interstitial spaces to the right lymphatic duct and the thoracic duct, are not well defined.

As a result the lung contains air spaces approximated to capillaries and appears physically capable of gas exchange by the 28th week. Although there is controversy over whether true alveoli are present even at 40 weeks of gestation, it is clear that most if not all alveoli develop postnatally, reaching their full complement of 300×10^6 at 8 years of age. Even though alveolar epithelium and capillary endothelium are closely apposed at 28 weeks gestation on the average, they will not support gas exchange unless the interstitial space between them can be kept dry by a functional lymphatic system.

Connective Tissue

Elastic tissue elements appear to arise from collagen fibers during the 25th week and are especially prominent around the entrance to alveolar ducts and between capillary and epithelial walls that will later develop into alveoli. Smooth-muscle fibers appear early in airways, and are present as a thin, often unicellular layer, down to terminal bronchioles at 40 weeks' gestation.

Cellular Differentiation: Epithelium

Knowledge of the regulation of orderly elaboration of various cell types with their specialized metabolic functions is recent and incomplete. Mesenchyme is necessary or endoderm will not differentiate into epithelial structures. Epithelium of air conduits becomes pseudostratified columnar in type, with goblet cells that produce mucus and with ciliated cells that propel it toward the trachea. The function of a third type, serous cells, is unknown. Cuboid epithelium characteristic of terminal airways of the 16-week fetus differentiates to form Type I membranous pneumocytes and Type II granular pneu-

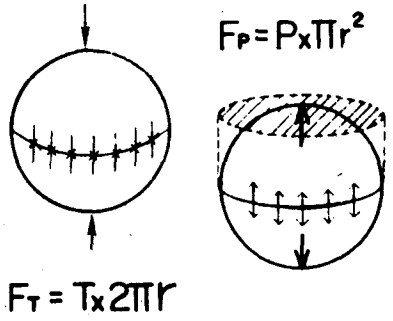

Fig. 2. Forces acting on a bubble. The force of surface tension (FT) acts at the circumference of the sphere $2\pi r$, while the force of pressure within (FP) aots on the surface of the sphere πr^2.

mocytes. While the Type I cell attenuates to provide most of the alveolar surface area, the Type II cell is responsible for production and release of a surface-active material that helps stabilize alveoli and keep them dry once air breathing begins.

Surfactant

Until Clements found that surface forces in lung extracts were directly related to surface area, it seemed perplexing that bubbles expressed from lungs did not recoil and break but were in fact extremely stable. He suggested that the ability of lung surface extracts to approach zero surface tension at low surface areas prevented atelectasis of alveoli at low lung volume, e.g., at expiration. Having observed that air-filled lungs tended to retain volume on deflation whereas saline-filled lungs did not, von Neergard postulated in 1929 that the lung must be lined by a material with low surface tension.

Physiology. The size of the alveoli at any phase in the respiratory cycle depends on a balance between pressures acting across alveolar walls. If alveoli are to remain inflated and stable when the lung is at rest, pressures acting on alveoli that tend toward inflation and surface pressures that tend toward deflation must be balanced. In very simple terms, $2\pi r \times T = \pi r^2 \times P$, or $P = 2T/r$. This is the Laplace relationship (Fig. 2) applied to the lung. P is the pressure difference across alveolar walls necessary to maintain a given size measured as the radius. This relationship predicts that larger pressure differences will be necessary as surface tension increases or alveolar size decreases. Little is known about the relative contributions of factors contributing to normal intraalveolar pressure, but the net pressure must tend toward inflation. The factors involved are interdependent and consist of the supporting effects of elastic tissue, support by the thorax at the pleural surface, intravascular pressure in both capillaries and lymphatics, alveolar interstitial fluid pressure, the geometric relationship of one alveolus to the next, and the pressure transmitted from more central airways. From current knowledge it appears that most if not all of these pressures tend to inflate alveoli; even pulmonary vascular pressure appears to exert an erectile effect (von Bosch effect) that would help inflate alveoli.

Ultimately the summation of all these forces is manifest in the alveolar interstitial pressure, which at resting lung volume (functional residual capacity) is 2–3 cm H_2O subatmospheric. Since intraalveolar pressure at rest is atmospheric, surface forces must balance interstitial pressure with an equivalent collapsing pressure. Thus any increase of alveolar surface forces or increase in interstitial pressure will promote atelectasis. There may be a margin of safety attributable to the presence of a surfactant lining whose surface tension as measured in vitro changes with surface area and approaches zero at a minimal surface area. If the primary deficit increases surface forces, however, only a greater than normal transalveolar pressure, and thus greater work, can support alveoli.

Biochemistry. Only a highly polar molecule could satisfy the requirements of low surface tension at low lung volume. Intermolecular attraction (surface tension) is minimal if polar molecules are arranged in palisade fashion at the surface. Disruption of this arrangement as surface area is increased at increasing lung volume leads to increased intermolecular forces and thus increased surface tension and greater elastic recoil, which assists passive expiration. The behavior of surface forces in a lung at various volumes can be illustrated by considering the pressure difference necessary to inflate a collapsed alveolus on the end of a respiratory bronchiole in the presence of a surfactant compared to its absence. The respiratory bronchiole of a premature infant has a radius of about 20 microns and surface tension in the presence of surfactant is about 5–10 dynes/cm compared to about 55 dynes/cm in its absence. Since one dyne equals 10^3 cm H_2O, the Laplace relationship predicts that a pressure difference of 5–10 cm H_2O will be necessary to open a collapsed alveolus when surfactant is present compared to 55 cm H_2O in its absence (Fig. 3).

Nearly all air-breathing animals share in common a surfactant lining that stabilizes terminal air spaces; it has been characterized as a phospholipid, primarily β,γ-dipalmitoyl lecithin (DPL), but is associated with other highly surface-active components. In vitro analysis has led to the conclusion that cholesterol may promote the spreading of DPL on the surface while the role of apoprotein is still disputed. The biochemical development of the surfactant system in utero has been well defined. Gluck has found that a sharp increase in lecithin, particularly in relation to sphingomyelin, occurs between 28 and 34 weeks in the human amniotic fluid, much of which arises from the lung (Fig. 4). Epstein and Farrell have demonstrated that choline incorporation via pathway I for lecithin synthesis accounts for nearly all of the DPL formed in primates and that a striking increase in activity of this pathway develops after about 85 percent of gestation.

Lamellar inclusions, observed in mitochondria of Type II alveolar lining cells, appear late in fetal life and are probably the major source of surfactant. Kikkawa has suggested that the phospholipid remains in these vessels until birth, when it is suddenly secreted onto the alveolar surface. Whatever the precise mechanism of re-

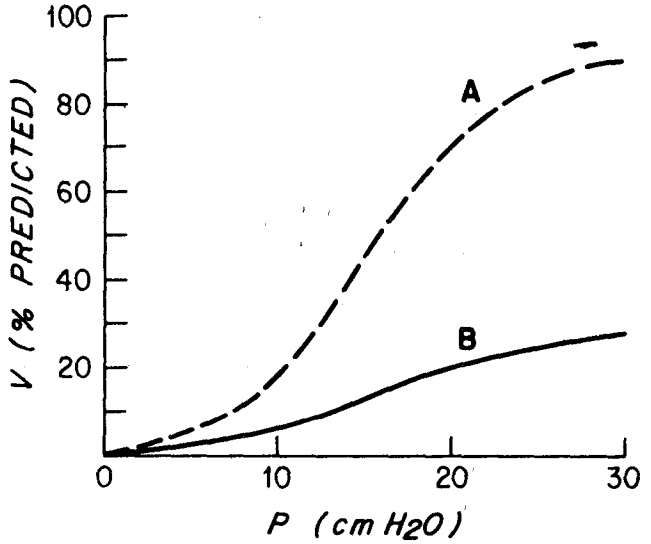

Fig. 3. The inflation limbs of the volume-pressure curves, measured in two infants: A is normal, B has severe RDS. The curves have been normalized for size to permit comparison. Curve A indicates that many alveoli open below 10 cm H_2O pressure difference. Curve B indicates that most alveoli have not yet opened at 30 cm H_2O.

lease; once on the alveolar surface it permits a five- to tenfold decrease in the pressure difference necessary to open an alveolus.

Although various inhalants and alterations in pulmonary perfusion (Table 1) can alter surface forces in the lung, their role in altering these forces in patients, outside of the premature infant, is not well defined. Certainly in a given patient with alveolar disease it is only possible to guess whether any one factor is etiologic.

Clinically, abnormality in the surfactant system is

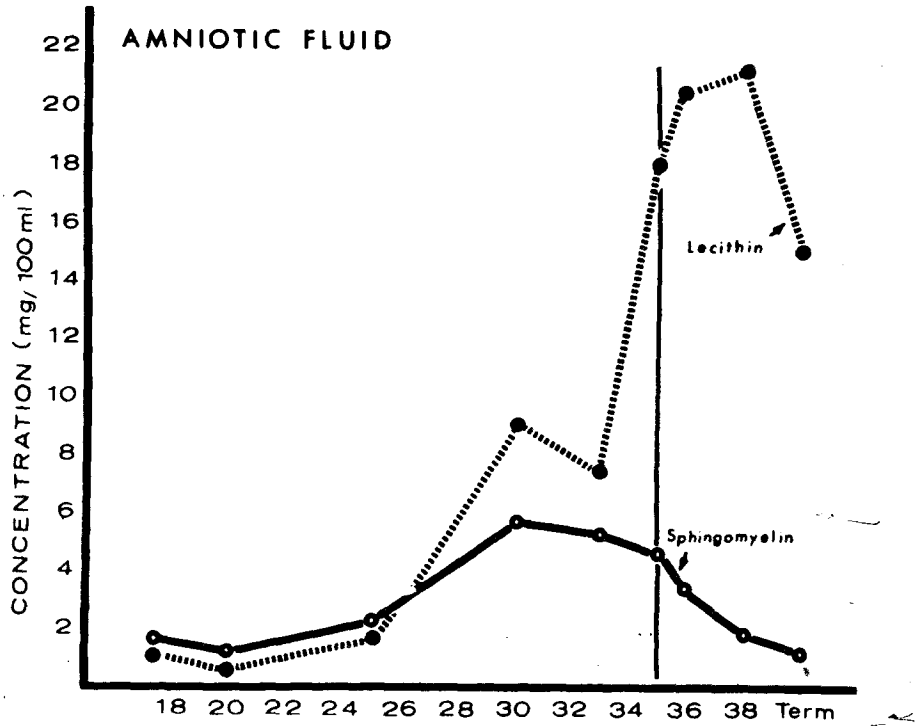

Fig. 4. The concentration of lecithin and sphingomyelin in amniotic fluid obtained from women by amniocentesis at fetal gestational age from 18 weeks to term showing a marked increase in the L/S ratio at 34 weeks. (Reproduced by permission from Gluck L, et al: Am J Obstet Gynecol 109:440, 1970.)

Table 1
Experimental Factors That Alter Surface Tension

INHALANTS		
Gases	Liquids	Perfusion Alterations
100% O_2	Water	Pulmonary artery ligation
15% CO_2	Saline	Pulmonary embolus
Oxides of nitrogen	Hydrocarbons	Cardiopulmonary bypass
Cigarette smoke		Ventilation of unperfused lung
Anesthetics		Pulmonary edema

defined in only a few circumstances (respiratory distress syndrome of the newborn, smoke inhalation, exposure to oxides of nitrogen and cigarette smoke). In a variety of other disease states abnormalities in surface forces of lung extracts have been demonstrated, but their role in the pathophysiology of those diseases remains to be defined.

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NONRESPIRATORY FUNCTIONS OF THE LUNG

Barry W. Levine

In addition to its primary function as an organ of gas exchange, the lung has a significant role in host defense and is an active metabolic organ.

PULMONARY DEFENSE MECHANISMS

The lung has within it a group of defense mechanisms comprised of mechanical factors, surface fluids and epithelium, cellular reserves, immunoglobulins, and alveolar proteins and lipids, all designed to protect the host against environmental insults.

Mechanical Factors

The anatomy of the upper airway, which includes the nasopharynx, trachea, and nonrespiratory bronchi, provides a unique defense against inhaled gases or large particulate matter. The large surface area and rich vascular supply of the nasopharyngeal cavity make it an ideal absorbing surface. Both the nasal passages and tracheobronchial tree act as aerodynamic filters. The filtering property is the result of subjecting inhaled air to turbulence, which causes large particulate matter to adhere to the mucosal membranes by inertial force. Ninety percent of inhaled particles larger than 2 μ are precipitated and then cleared in this fashion.

Surface Fluids and Epithelium

The mucociliary system is composed of ciliated epithelium and a layer of viscoelastic fluid. This system extends from the nasopharynx to the terminal nonrespiratory bronchioles. The epithelium is a pseudostratified ciliated layer composed of 3 to 4 rows of nuclei decreasing in height peripherally into a single layer at the level of the respiratory bronchiole. Within the pseudostratified layer are goblet cells occurring singly without touching each other. There are no goblet cells within the terminal bronchioles. From the goblet cells a viscoelastic fluid emerges and rests upon the ciliated epithelium. This fluid layer is propelled upward by coordinated ciliary motion at a rate of 10–20 mm/min. Ninety percent of foreign material deposited upon this fluid layer can be cleared in 1 hr.

Cellular Reserves

Within the substance of the lung a number of different cells participate in the cleansing system. These include alveolar macrophages and Types I and II alveolar lining epithelial cells. They provide in situ detoxification independent of ciliary motion. The alveolar macrophages number about 600,000. Their phagocytic function is aided by tissue histiocytes, polymorphonculear leukocytes, monocytes, and possibly eosinophils. Although it is a potent defense mechanism, intrapulmonary phagocytosis is very sensitive to changes in host environment. Ethanol ingestion, steroids, acute hypoxia, and hypothermia all have been shown to diminish phagocytic capability within the lung.

Alveolar Proteins and Lipids

In addition to phagocytosis occurring within the alveoli, the numerous lipids and proteins found on the epithelial lining play an important role in host defense through their physiochemical characteristics. Lipids within the alveolus act as traps by absorbing particulate matter. Protein-rich alveolar lining fluid acts as a trap by causing wetting of foreign particulate matter.

Immunoglobulins

Endobronchial secretions are known to contain various immunoblogulins whose antibody properties may play a role in pulmonary defense. The major immunoglobulin component in tracheobronchial secretions is IgA. Within these secretions IgA is 20-fold more concentrated than IgG. The form of IgA in tracheobronchial secretions differs from that in serum. A carbohydrate fragment is coupled to serum IgA, probably within the plasma cells of the bronchial submucosa, forming secretory IgA. Secretory IgA has a molecular weight of 390,000 d, of which 60,000 d is the molecular weight of the carbohydrate component.

The role of secretory IgA in pulmonary defense is not well understood. Approximately 1 of every 500 to 700 births has complete absence of serum IgA and consequently secretory IgA. However, only a third of these individuals are subject to an increased frequency of sinopulmonary disease. Furthermore, in patients with chronic bronchitis, respiratory IgA has been found in normal concentrations. Therefore the role that the presence or absence of secretory IgA plays in the pathogenesis of recurrent pulmonary infection is unclear. The recent discovery of a deficiency in IgE, the circulating antibody that mediates cutaneous anaphylaxis, may help delineate the role of antibody deficiency in pulmonary defense. In patients with combined deficien-

cies of serum IgA and IgE, there appears to be a predisposition to recurrent sinopulmonary infection. IgA and IgE may therefore play a role in an immunologic system that regulates the normal bacterial and viral flora of mucous membranes.

IgG, the dominant serum immunoglobulin, has a molecular weight of 160,000 d. Deficiency of IgG has multiple etiologies, but is characterized by recurrent severe infections, usually bacterial. The deficiency can be secondary to either decreased synthesis or increased catabolism. IgG deficiency may be an inherited defect or an acquired trait. Upper respiratory tract infections with sinusitis, otitis media, and recurrent pneumonia are common. Because of the long in vivo half-life of IgG, the respiratory infections in deficient individuals can be controlled with chronic parenteral γ-globulin therapy. Unfortunately the half-life of IgA in vivo is about 4 hr, and therefore parenteral therapy is of little value in this deficiency.

METABOLIC FUNCTIONS OF THE LUNG

The lung, in addition to playing a critical role in host defense, has important metabolic functions. The lung is known to store abundant amounts of histamine and serotonin; within its vascular endothelium are found potent enzymes that inactivate polypeptides and convert others to more potent forms; and finally the lung plays an important role in maintaining water and electrolyte balance.

INTRAPULMONARY STORAGE

Histamine

The lung has an abundant concentration of histamine within the pulmonary mast cells located around small pulmonary vessels. The enzymes that decarboxylate histidine and then deaminate or methylate the product to form histamine have been identified in mammalian lung tissue. Although the lung is felt to produce and store endogenous histamine, its physiologic role is yet unclear. During anaphylactic shock and tissue injury pulmonary histamine is released. This release may influence the local regulation of the pulmonary microcirculation.

Slow-reacting Substance of Anaphylaxis (SRS-A)

SRS-A is a group of chemical mediators that produce a slow, prolonged contraction of certain smooth muscles. These compounds have the biologic potential of being involved in antigen-induced bronchospasm and immunologic tissue injury due to increased capillary permeability. The release of SRS-A from the lungs when specific antigens are administered to sensitized guinea pigs seems to demonstrate this. Passive sensitization of human lung tissue with reaginic antibody has also resulted in release of SRS-A. When release occurs, there is a reduction in the number of pulmonary mast cells, suggesting that SRS-A originates or is stored in this cell type. At present SRS-A is felt to be involved in the pathogenesis of immediate hypersensitivity in man.

Serotonin

Following pulmonary emboli serotonin is released from the lung either from intrapulmonary clots (platelets) or from pulmonary mast cells. The release of serotonin from the pulmonary mast cells may cause bronchospasm or alter regional pulmonary blood flow.

INTRAPULMONARY METABOLISM

Vasoactive Polypeptides

The lung contains an abundant concentration of kininase and angiotensin-converting enzymes. These enzymes are presumably located on the pulmonary vascular endothelium. Bradykinin, which is a naturally occurring vasoactive polypeptide, is almost completely inactivated by hydrolysis during a single passage through the lung. The enzyme responsible for the inactivation is a kininase that remains potent in face of marked alterations in the physiologic function of the lung. The lung is also capable of converting the relatively inactive polypeptide angiotensin I to the more vasoactive angiotensin II. In a single passage more than 90 percent of angiotensin I is converted to angiotensin II within the pulmonary circulation. Although these are potent functions of the lung, their effects on the physiologic and biochemical homeostais of the organism are not known.

Catecholamines

Most mammalian lungs contain dopamine, norepinephrine, and epinephrine. The concentration of norepinephrine in the lung is proportional to the sympathetic innervation. There is indirect evidence that catecholamines are synthesized within the lung. Catechol-*o*-methyltransferase, the enzyme responsible for the breakdown of various catecholamines, is present within the lung. Therefore the lung may both produce and destroy catecholamines. It is not known what role the lung plays in the total spectrum of catecholamine metabolism.

Lipid Metabolism

The lung contains phospholipids within the interstitial space, and a phospholipid-rich layer (surfactant) coats the alveolar-tissue interface. The predominant lipid is dipalmitoyl lecithin, which is surface-active. Phospholipids are synthesized by either esterification or phosphorylation. The lung has been shown to contain the appropriate enzymes to synthesize phospholipids. The site of this synthesis is not known, although most data point to the alveolar Type II cell. The rate of lipid turnover in the lung is affected by pulmonary edema, pulmonary embolization, occlusion of a pulmonary artery, and nutritional state. Prematurity has also been associated with decreased surfactant activity, as in infant respiratory distress syndrome. It appears that maturity of alveolar cells, blood flow, and an energy source are necessary for pulmonary surfactant metabolism. When insufficient formation occurs, alveolar instability results and there is marked impairment of pulmonary mechanics and gas exchange.

WATER AND ELECTROLYTE BALANCE

Water

During respiration inspired air is conditioned by being warmed and humidified, which are dependent on air-flow dynamics, minute ventilation, and body temperature. Water loss through the lungs is also dependent on these factors. During normal ventilation 250 ml of water and 350 kcal of heat are lost per 24-hr period.

Hyperpnea increases heat transfer and water loss and acts as a homeostatic mechanism during fever. The proper conditioning of inspired air is important in maintaining the function of the ciliated epithelium. Since the nasopharynx is the major site for the appropriate exchange of water and heat, exclusion of this portion of the respiratory system (such as by a tracheostomy) will interfere with the conditioning of inspired air and the recovery of heat and water from expired air.

Solute Balance

Because of the lung's large extracellular fluid volume, it plays an important role in total-body solute balance. Water and solutes are transported across the alveolar–capillary membrane by hydrostatic forces and molecular diffusion. Between 15 and 30 osmols of carbon dioxide are excreted by the lung during a 24-hr period. The effect of various hormones on this solute balance is unknown.

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PHYSICAL FACTORS IN LUNG FUNCTION

Denise J. Strieder

LUNG MECHANICS

Pulmonary lobules are built on a framework made of collagen, elastic fibers, and smooth muscle. The helicoid arrangement of collagen and muscle allows for considerable volume change between collapse and full expansion. The lobules are more or less compliant, depending on whether the smooth muscle is relaxed or contracted; but at all times their volume is determined by external forces, which are needed to unfold and stretch their walls and are measured as a pressure difference.

Pressure–Volume Curve

The fundamental relationship between pressure and volume is clearly demonstrated when excised inflated lungs are allowed to deflate slowly, while the tracheal pressure and the volume of air exhaled are simultaneously recorded. The volume change for equal decrements of pressure is small at first but increases as lung volume decreases. Accordingly the pressure–volume relationship of the lung describes a curve that, as observed during deflation, is stable and reproducible (Fig. 1). The same relationship prevails whether the lungs have been inflated by positive pressure applied to the mouth or trachea or by negative pressure over the pleural surface. In both instances the forces that tend to increase lung volume are reflected in the transpulmonary pressure (P_{tp}), measured by the difference between the pressure inside the lung and the pressure at the pleural surface. When the distending pressure is removed the lungs recoil and collapse. When lung volume remains constant, distending pressure exactly balances lung recoil.

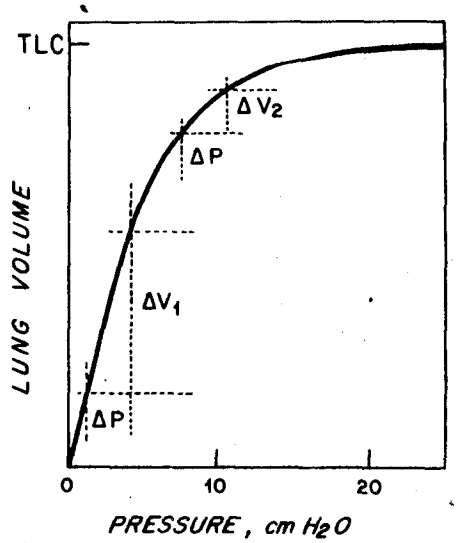

Fig. 1. Pressure–volume curve of the lungs during deflation. Compliance, which is measured by the ratio of volume increments ΔV to pressure increment ΔP decreases with increasing lung distension.

Two factors are known to contribute to lung recoil: the elastic tension within the lung tissue and the surface tension arising at the air–fluid interface. During deflation surface effects are small and lung recoil measures the elastic properties of lung tissue. During inflation the surface area of each alveolar wall increases and surface tension becomes dominant. This variability of surface forces in the lungs is due to the presence of surfactant, a surface-active material that lines the alveolar walls and permits the surface tension to vary with varying surface area from very low (10 dynes/cm) to moderately high values (40–50 dynes/cm). Surface tension is greater when surface area increases, and it falls rapidly when surface area begins to contract. In the lung, therefore, the change in surface tension that accompanies a given change of volume depends not only on the initial volume but also on the immediately preceding events (the volume history), a property known as hysteresis.

Because tension at the surface of alveolar walls is greater during inspiration than during expiration, lung recoil is greater during inspiration than during expiration. The pressure–volume relationship of the lung is best represented by a family of hysteresis loops with a common deflation curve characteristic of the elastic properties of the lung and an infinite number of inflation curves reflecting the variability of surface tension (Fig. 2).

During inhalation of a large tidal volume, transpulmonary pressure increases with increasing lung volume according to the inflation limb of the appropri-