CHAPTER 10

Respiratory Tract

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The function of the respiratory tract of the pig is straightforward: gaseous exchange between inspired air and the blood. However, the cellular mechanisms by which this function occurs are complex and integrated with other bodily functions such as olfaction, deglutition, and phonation. Several features of the respiratory tract in the pig are unique. Most obvious are the shape of the nasal planum and the natural behavior of pigs to root the nose through dirt and surface materials such as feedstuffs, feces, and water. Many other features are similar to a wide cross section of mammals.

The respiratory tract is composed of air passages through the nasal cavity, pharynx, and trachea that conduct and modify inspired air prior to entrance into the lung. Modifications of inspired air include warming and humidification of the air and filtering of particulate matter. The air also activates olfactory receptors in specialized epithelia of the nasal cavity. The flow of inspired air is altered during deglutition of saliva, solid materials, or liquid through contraction of the pharyngeal muscles and the larynx. Gaseous exchange of oxygen and carbon dioxide is the principal function of the lung and occurs deep in the parenchyma across the alveolar septal wall. With expiration, air flow is reversed and pressures of the outflowing air through the laryngeal vocal folds produce phonation.

Developmental Anatomy

Formation of the nasal cavities is related to formation of the face and pharynx. The primordial cavities form from the olfactory placodes, which become indented by mesenchyme of the medial and lateral nasal prominences and form nasal pits. The pits form into primitive nasal cavity and rostral openings and become the external nares of adults. The nasal septum is formed by fusion of the two medial nasal prominences. The hard palate is formed rostrally by fusion of the medial prominences (primary palate).

The caudal portion of the hard palate separates the tongue and oral cavity from the nasal cavity and is formed from fusion of the palatine processes of the maxillary prominences. The caudal portions of the palate do not ossify and become the soft palate. The soft palate does not separate the nasal cavity from the oral cavity but instead divides the rostral pharynx into a dorsal region that is the nasopharynx and a ventral region that is the oropharynx. In the pig, the nasal septum extends to the rostral portion of the nasopharynx and separates the rostral nasopharynx into bilateral regions. Ridges on the medial portions of the nasal cavity form the conchae. The dorsal nasal concha is formed from ethmoid ridges, whereas the ventral nasal concha is formed from the maxillary process. Between the conchae, the nasal cavity is divided into meatuses that conduct the flow of air. The bony core (turbinates) of the conchae develop from the mesenchyme of the nasal prominences. In the pig, the ventral nasal concha has characteristic dorsal and ventral scrolls. Postnatally, bone formation of the ventral scroll occurs in a rostrocaudal direction by enchondral ossification, whereas centrifugally directed growth of the scrolls and elongation of their extremities occur by intramembranous ossification (Martineau-Doizé et al., 1992). The bony portions of these scrolls, along with the nasal septum, are malformed in growing pigs with atrophic rhinitis. Pigs infected with toxigenic strains of *Pasteurella multocida* or virulent strains of *Bordetella bronchiseptica* often develop atrophic rhinitis. The paranasal sinuses are formed by ingrowths of epithelium from the nasal cavity into the mesenchyme of the nasal cavity. The paranasal sinuses are not fully developed at birth and form simultaneously with growth of the face and head. In the pig, the frontal sinus continues to expand even after the animal is fully mature.

The larynx and trachea are formed from the caudal portion of the pharynx. A ventral evagination of the pharynx forms the laryngeotracheal groove, and the tubular primordial trachea is separated from the esophagus by the tracheoesophageal septum. The larynx cartilages form from arytenoid swellings of the ventral part of the pharynx, and the epiglottis forms from the hypobranchial swellings just cranial to the arytenoid swellings. Muscles of the larynx form from a branchial arch. The caudal end of the trachea branches dichotomously, forming the tracheal carinae and primitive bronchi. These elongate and continue to branch, forming lobar buds during the pseudoglandular stage of development between 50 and 80 days of fetal growth. The terminal portions of the buds expand, resulting in the canalicular stage of development at 80 to 92 days of gestation. This is associated with increased vascularity. The buds form into terminal branches or saccules during the terminal saccular stage of development at 92 to 110 days of gestation. These saccules are divided by septa into rudimentary alveoli. This final stage is termed the *alveolar stage* of development. Alveolar formation occurs after 110 days of gestation and continues after birth.

Pulmonary arteries are formed from aortic arch VI, and bronchial vessels extend from the aorta. Prior to birth the blood flow is limited, owing to high intrathoracic pressure and peripheral resistance; however, at birth inspired air expands the chest and dramatically lowers the thoracic cavity pressure and vascular resistance. The epithelium lining the trachea and lung is of endodermal origin and arises from the caudal portion of the pharynx.

An extensive set of nerve fibers from the vagus nerve innervates the bronchial tree. The nerves branch from main nerve trunks and form an extensive plexus that covers the surface of the smooth muscle in fetal pigs and penetrates the smooth muscle cells postnatally (Weichselbaum et al., 1996). Smooth muscle function and innervation of the bronchi occur shortly after differentiation of the smooth muscle at the growing tips of the airways. The fetal lung has many ganglia and extraganglial cell bodies and nerve trunks. Postnatally cell bodies are restricted to the ganglia in the central airways.

Cellular Structure and Function

Gross Structure

The pig lung consists of seven lobes divided by fissures (Figure 10-1). The left side has a cranial, middle, and caudal lobe; the right side has a cranial, middle, and caudal lobe and an intermediate lobe that is located caudal to the heart and medial to the right and left caudal lobes. Eighty percent of the lung parenchyma consists of luminal airspace in the alveolar ducts and alveoli, 9 percent consists of capillary lumina, and 8 to 12 percent consists of interalveolar septal tissue (Winkler and Cheville, 1985). Inspired air inflates all lobes; however, particulate material tends to localize in the cranioventral portions of the lung (right and left cranial lobes) due to gravitation.

Mucosal Histology and Physiology

Conchae and Nasal Cavity

Four types of epithelium are present rostrocaudally from the nares to the ethmoid bones (Larochelle and Martineau-Doizé, 1990): stratified squamous, cuboidal, pseudostratified respiratory, and olfactory. Stratified squamous epithelium covers the nasal plana and vestibule to the first incisor. The epithelium is stratified and in some areas cuboidal with intervening

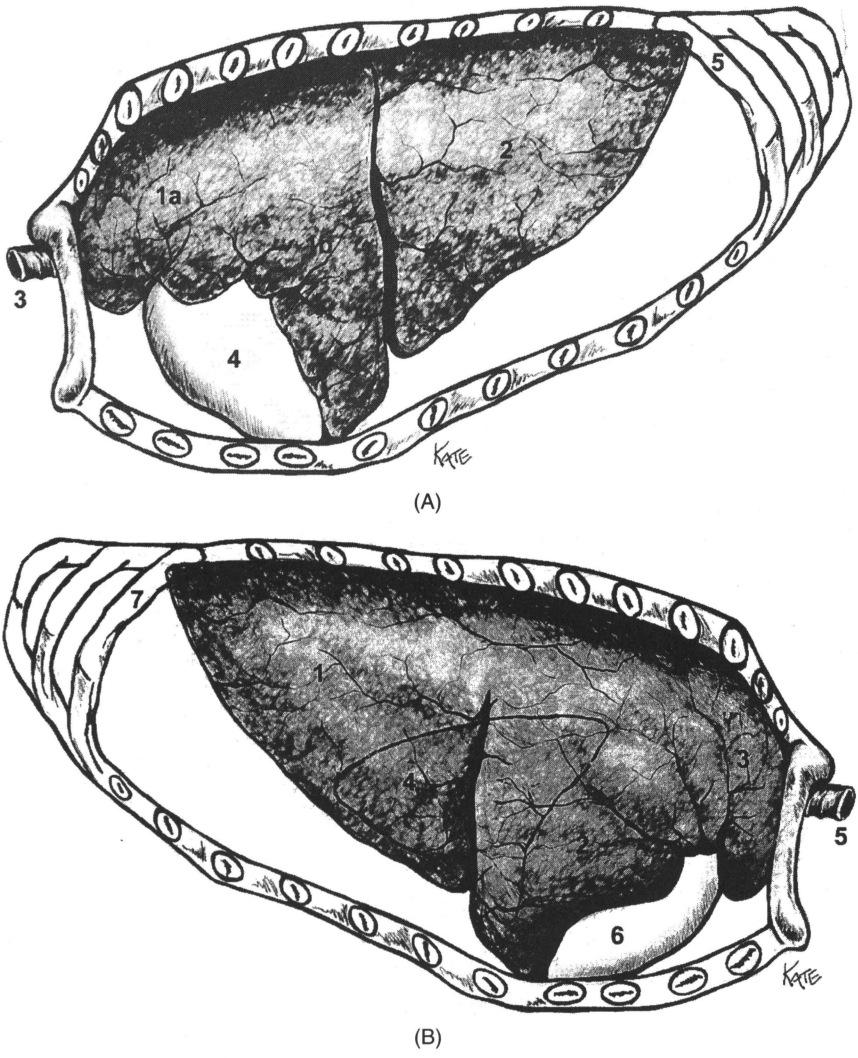


Figure 10-1 Schematic illustrations of the lung lobes in relation to the heart and thoracic cavity. A. Left lobe. 1a = cranial cranial lobe; 1b = caudal cranial lobe; 2 = caudal lobe; 3 = trachea; 4 = heart; 5 = rib cage. B. Right lobe. 1 = caudal lobe; 2 = middle lobe; 3 = cranial lobe; 4 = outline of accessory lobe; 5 = trachea; 6 = heart; 7 = rib cage.

goblet cells between vestibula at approximately the level of the second incisor. A respiratory epithelium with pseudostratified columnar epithelial cells and interspersed goblet cells lines regions caudal to the second incisor and includes the ethmoid conchae and nasopharynx (Figure 10-2). These

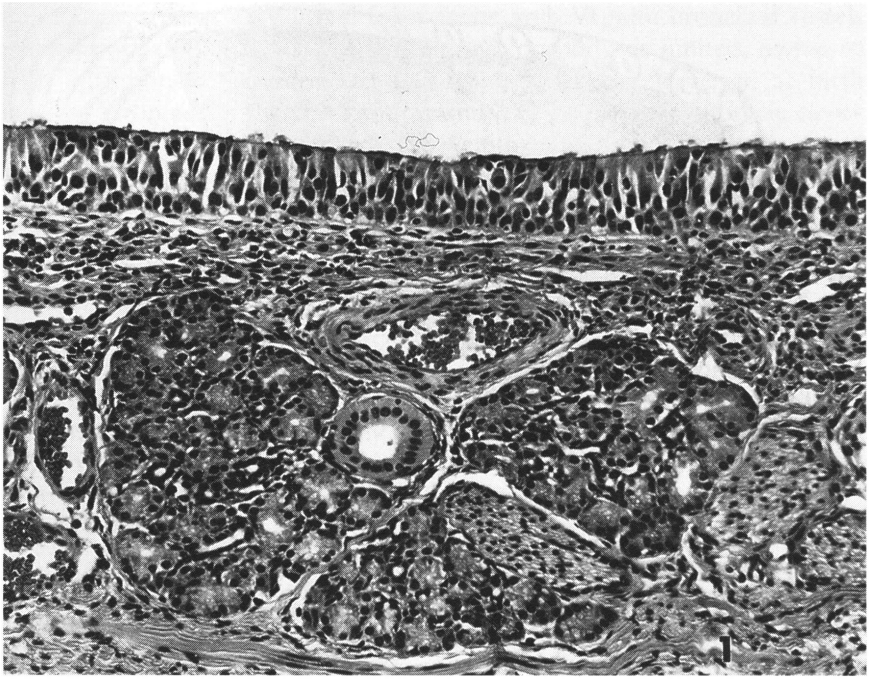


Figure 10-2 Pseudostratified ciliated respiratory epithelium of the ventral nasal meatus. The epithelium is covered by a small amount of mucinous material. The submucosa contains serous and mucous submucosal glands and blood vessels.

epithelial regions change with age. In neonates, ciliated epithelium extends farther in the rostral direction than in 28-day-old pigs. In 28-day-old pigs the rostral portion of the ventral nasal concha is lined by transitional epithelium. Lectin histochemistry suggests that nasal epithelial cells of pigs are rich in *N*-acetylgalactosamine, *N*-acetylglucosamine, and L-fucose residues (Perfumo et al., 1998). Subjacent to much of the nasal cavity respiratory epithelium are glands that open to the epithelial surface (Figure 10-2). These glands support the replication of porcine cytomegalovirus in the disease inclusion body rhinitis.

Olfactory epithelium is present in the caudodorsal portion of the nasal cavity, the ethmoid conchae, dorsal nasal meatus, and nasal septum. It is thicker than respiratory epithelium and composed of basal cells, sustentacular cells, and neurosensory cells. The neurons produce odor receptors on cilia in the nasal cavity. The neurosensory cells have axons that extend to the olfactory lobe of the brain. Mammals have 1000 or more different types of odor receptors, and recent work suggests that each neuron expresses only one type of receptor (Mori and Yoshihara, 1995). In pigs, 11 receptors have

been characterized and classified into three families and seven subfamilies (Matarazzo et al., 1998). Activated neurons in the olfactory epithelium have increased levels of G protein and transmit signals to the olfactory lobe through axons that interact with the dendritic processes of neurons in the olfactory lobe in specialized regions called *glomeruli.* The neural input is transferred to the olfactory cortex of the cerebrum, although the mechanism by which the olfactory cortex interprets this information is poorly understood.

The pigs' ability to use olfactory cues to localize truffles for humans is well known. Olfaction is also important for the pig as well. Piglets learn to identify their mother's odor by 12 hours after birth (Morrow-Tesch and McGlone, 1990b), and they are especially attracted to odors associated with maternal feces and skin secretions. They use this sense to discriminate between mother and nonmother. Piglets use olfaction in combination with tactile stimuli for nipple attachment (Morrow-Tesch and McGlone, 1990a). In older pigs, olfactory cues in urine increase submissive behavior during fighting (McGlone, 1985).

To a certain degree, olfaction influences taste. Taste buds are present on the surface of the tongue of the pig. Ruminants (goats and cattle) have taste buds in the epithelium of the epiglottis; however, the pig, as well as the horse and ass, lack epiglottal taste buds (Palmieri et al., 1983).

The vomeronasal organ is a paired neurosecretory tubular, pouchlike structure of the rostral nasal septum that opens rostrally. It is crescent shaped on cross section, encased in cartilage, and lined by pseudostratified epithelium. The organ functions in chemoreception, although its role and influence on sensory activity and behavior are not fully understood. Cells of the porcine vomeronasal organ are similar to those of other mammals but contain numerous small dense granules with diverse morphology (Adams, 1992).

Paranasal Sinuses

The paranasal sinuses are lined by a pseudostratified epithelium; however, the development and regional differences in epithelium and gland formation in the pig have not been described. The paranasal sinuses are a likely location for the colonization of microbial pathogens, but few reports have investigated this possibility. One Japanese study provided data suggesting that most pigs (69 percent) have inner-ear bacterial infections (Shimada et al., 1992). This infection was likely initiated by the growth of bacteria such as *Mycoplasma* sp. in the auditory tube. The auditory tube is lined by ciliated cells, and its orifice is located within the pharynx. Therefore, the orifice is exposed to the passage of air flow and pathogens of both the respiratory and the upper digestive tract.

Nasopharynx

The epithelium of the pharynx, including the crypts of the palatine and pharyngeal tonsils, is lined by stratified squamous epithelium. The crypts contain laminated keratin, neutrophils, and cell debris. This exudate can be present even in gnotobiotic (germ-free) pigs (Ackermann et al., 1991a). A unique feature of the pig is the pharyngeal diverticulum. This structure can be mistaken for a tonsillar crypt or pouch. During experimental procedures, the crypt also can be mistaken for the esophageal orifice when a laryngotracheal tube is passed. The diverticulum is blind ended, roughly 3 to 4 cm deep, and located on the dorsal surface of the pharynx caudal to the soft palate.

Trachea, Bronchi, and Bronchioles

The trachea and bronchi are lined by pseudostratified respiratory epithelium and also have numerous submucosal glands. The epithelium of these airways actively absorbs sodium to remove fluid (Ballard et al., 1992). This is especially important for newborn pigs and in states of disease (i.e., pneumonia) when fluid accumulates in the airway lumen. Cells of tracheal and bronchial epithelium also secrete chloride, which is vital for ion balance and function.

Glycoprotein (mucin) is secreted in the trachea and bronchi by goblet cells in the epithelium and submucosal glands. The goblet cells of the tracheal and bronchial epithelium produce sulfated and sialylated glycoproteins, and the level of sulfated glycoproteins increases with age. The number of goblet cells decreases during infection with *Mycoplasma hyopneumoniae*, a common respiratory pathogen of swine (Debey and Ross, 1992). In addition, infected pigs have decreased levels of total mucin and sulfated glycoproteins but increased amounts of sialylated glycoproteins. Submucosal glands produce mainly sulfated glycoproteins until age 3 days and predominantly sialylated glycoproteins thereafter (Mills et al., 1986). The submucosal glands of the trachea and bronchi are stained by the L-fucose–binding lectin from *Ulex europeas I* (UEA-I), and this lectin also binds epithelial cells of these airways. Binding of cells by UEA-I is suggestive of the presence of terminal or accessible L-fucose residues (Ackermann et al., 1991a). Other than UEA-I, there have been no extensive studies of lectin-binding affinities in glycoprotein (mucin)-secreting cells of the trachea and lungs in swine. Muscarinic stimulation of the tracheal mucosa induces transient glycoconjugate secretion from submucosal glands (Dwyer et al., 1992). Secretion from submucosal glands of the porcine trachea in response to exogenous cholinergic substances and tachykinin peptides is limited for

the first 22 days of life and increases greatly by age 10 weeks (Haxhiu et al., 1990).

The epithelium of distal conducting airways is lined by ciliated and nonciliated (Clara) cells. The Clara cells extend from the basement membrane to the airway lumen, lack cilia, have apical microvilli, and have dense-cored neurosecretory granules in the apical cytoplasm. Clara cells contain mixed-function oxidases that process toxic compounds. This also makes these cells susceptible to toxic secondary metabolites. Clara cells in pigs express nitric oxide synthetase (NOS) (Shaul et al., 1994). Nitric oxide, the product of NOS, may regulate ion flux or secretory function, as Clara cells in other mammals (bovine, guinea pig, and rat) also produce guanylin, which is a regulator of fluid secretion in the intestine (Cetin et al., 1995). Type II cells of the pulmonary bronchioles and alveoli are ciliated, produce surfactant, and replicate and replace damaged type I cells. Type II cells also take up intraluminal surfactant for resynthesis. Type II cells are adhered to a subjacent basement membrane and also contact fibroblasts through gaps in the basement membrane. The type II cell and fibroblast have reciprocal interactions in vitro. This contact is trophic for type II cells and increases the level of transcription of surfactant protein A (SP-A). The type II cells release factors such as insulin-like growth factor (IGF)-I, which stimulates type I collagen secretion by fibroblasts (Griffin et al., 1993). When damage occurs to type I cells, type II cells replicate and migrate along the basement membrane to cover the denuded region. Numerous microbial pathogens adhere to or invade type II cells. *M. hyopneumoniae*, for example, expresses an adhesion protein (P97) that works in concert with other bacterial proteins to mediate cilia adherence (Hsu and Minion, 1998).

Alveoli

Pulmonary alveoli are lined by flattened, elongated type I cells that allow for gaseous exchange (Figure 10-3). The type I cell is flat, has numerous vesicles and few mitochondria, and is often less than 0.1 μm wide. Although type I cells account for less than 10 percent of the total cell population of the lung, they line more than 70 percent of the surface area, owing to their expansile structure. These physical characteristics make the type I cell conducive to the rapid passage of gases across the alveolar septa. Type I cells are covered on their luminal side by a layer of surfactant, which in turn contacts a moist surface on the inner portion of the alveolar lumen. The type I cell of miniature pigs can be stained with the lectin soybean agglutinin (Kasper et al., 1994).

Immediately after birth the alveoli of the porcine lung appear morphologically mature. This is similar to lungs in the guinea pig, dog, and monkey

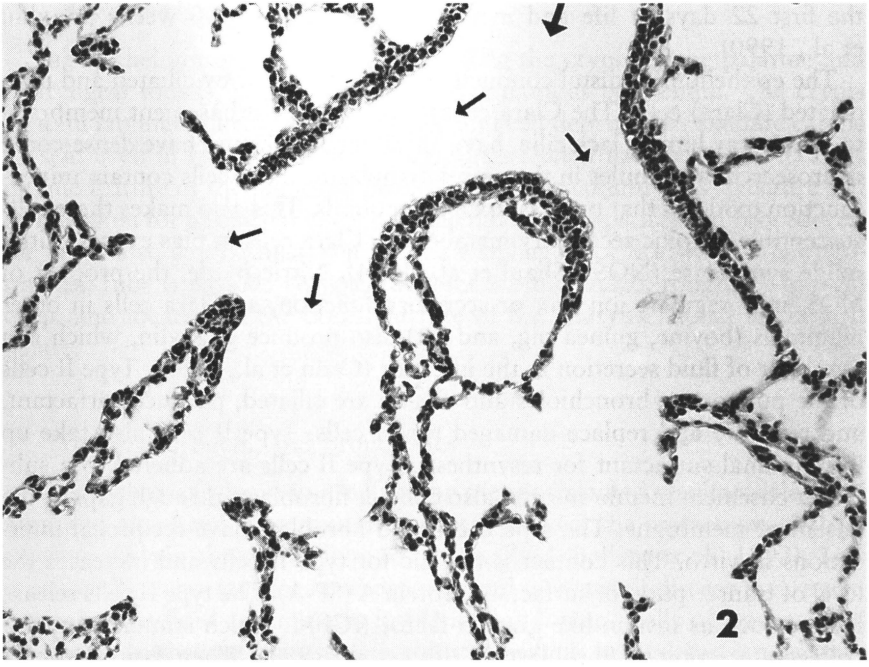


Figure 10-3 Lung parenchyma at the terminus of a bronchiole leading into (arrows) pulmonary alveoli lined by type I pneumocytes.

but differs from those in the mouse and rat. The lungs of newborn pigs are relatively stiff and resistant to shape deformation (Mansell et al., 1995). This stiffness is related to thickened alveolar septa. After 2 to 3 days of life the airspace expands owing to alveolar septal lengthening and thinning, and this expansion results in increased elastic recoil. At ages 2 and 3 months there is septal proliferation and an increase in mean septal thickness but no change in elastic recoil. Therefore, the alveoli are thinner but retain elasticity.

Ciliary Function

A large percentage of the nasal cavity, paranasal sinuses, trachea, and bronchi is lined by ciliated cells. Cilia are vital to the movement of the mucous layer lining the cell surface. This layer is more aqueous in the region of the cell membrane and has properties of a viscoelastic gel at distances farther from the cell. The layer moves at roughly 4 to 15 mm/min. Inspired particulate matter, exfoliated cells, and leukocytes become entrapped in this

layer and are moved up the trachea to the pharynx, where the mucous material is swallowed or coughed out of mouth. The importance of the ciliary function is exemplified by disease such as ciliary dyskinesis in which defects of the dynein arms or structural components of the microtubules impair cilia beat. Children and animals with ciliary dyskinesis often develop bacterial infections of the respiratory tract that can lead to chronic sinusitis, bronchitis, bronchiectasis, and pneumonia.

A study of ciliary beat frequency (CBF) in the nasal cavity, nasopharynx, upper and lower trachea, and main and subsegmental bronchi of pigs used cold light conducted by fiberoptics through a microscope and then directed onto the epithelium, and reflected light was measured in a photodetector tube (Joki and Saano, 1994). The work demonstrated that the CBF was the same for all areas measured and that the CBF in pigs is 11.3 to 16.9 Hz and similar to the frequency in the cow and dog, but faster than that in the rat. The CBF in the pig differs from that in humans; the CBF of human respiratory epithelia ranges from 14.0 Hz in the nose to 10.3 Hz in subsegmental bronchi.

Pulmonary Surfactant

Pulmonary surfactant is produced by type II cells of all mammalian species and stored in specialized organelles known as *lamellar bodies*. Surfactant is a complex substance composed of lipids and proteins that lower the surface tension of the alveolar air-liquid interface and stabilize alveoli during expiration (deflation). The inner surface of the alveolar septum is moist, and there is a tendency of molecules in this location to condense. This surface tension is increased during inhalation and decreased during exhalation. However, during exhalation, the alveolar lumen is condensed, and without surfactant to reduce the surface tension, the lumen would collapse. Surfactant in the alveolar lumen eventually is taken up by type II cells and to a lesser degree, by alveolar macrophages for recycling (Figure 10-4).

The lipid component of the surfactant consists primarily of phospholipids and other lipids such as cholesterol, triacylglycerol, and unesterified fatty acids. Phosphatidylcholine is the most abundant phospholipid and accounts for nearly 70 percent of the total lipids (Table 10-1). The majority of phosphatidylcholine is saturated, containing two palmitic acid moieties.

Surfactant Proteins

The lipid components of surfactant are produced and secreted in concert with surfactant proteins. The surfactant proteins account for 10 percent of

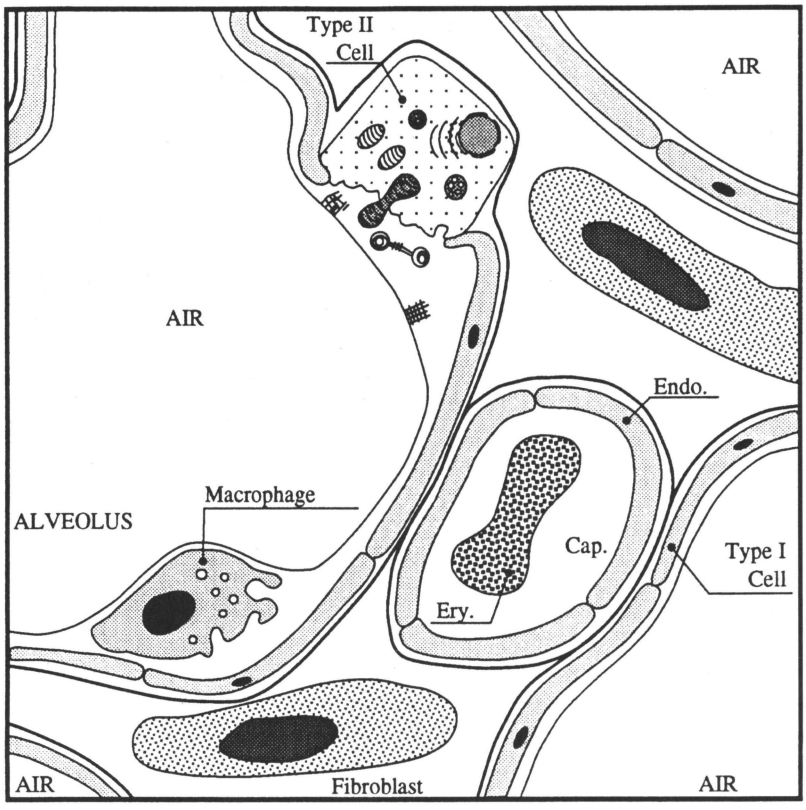


Figure 10-4 Schematic illustrations of surfactant production and recycling. A. Alveolus containing a type II cell and alveolar macrophage and an adjacent alveolar septum that contains a pulmonary capillary. Cap. = capillary; Ery. = erythrocyte; Endo. = endothelial cell. B. Type II cells produce surfactant, which is stored in lamellar bodies (1) and secreted into the alveolar space (2). The surfactant is transformed (3) into tubular myelin (4), from which the monolayer (5) is formed. Surfactant is taken up again (6, 7) by the type II cell and reused. (Reproduced from Creuwels et al. [1997] with permission of Springer-Verlag, Medical Journals.)

the weight of surfactant. Advances in molecular biology have accelerated greatly the understanding of pulmonary surfactant proteins in mammals. There are four types of surfactant proteins (SP): A, B, C, and D. In addition to surfactant phospholipids, SP-B is essential for normal respiratory function. In fact, mutation of SP-B in human infants (congenital alveolar proteinosis) is uniformly fatal. Of the four surfactant proteins, SP-A and SP-D are hydrophilic, whereas SP-B and SP-C are hydrophobic. The synthesis, production, and function of surfactant proteins is reviewed elsewhere (Creuwels et al., 1997; Rooney et al., 1994). Briefly, SP-A induces the for-

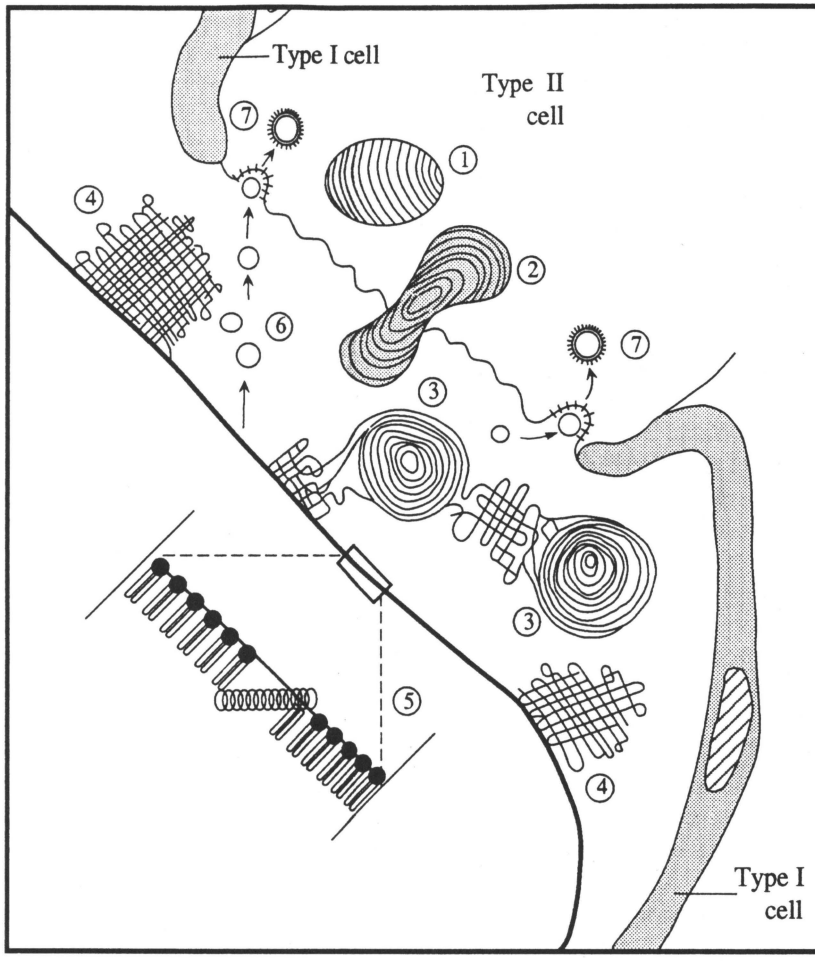


Figure 10-4 *Continued*

mation of tubular myelin, which is the conformational form of extracellular surfactant. SP-A also binds type II cells and macrophages for surfactant uptake and recycling. SP-D does not have a classic role in surfactant homeostasis but may have a role in intracellular lipid sorting or signal transduction. As indicated, SP-B is vital to surfactant function. It mediates insertion of the phospholipid into the air-liquid interface, enhances tubular myelin formation, and increases the spatial arrangement of phospholipid bilayer. SP-C functions similarly to SP-B but does not have a role in tubular myelin formation. In addition to their contribution to surfactant function,

Table 10-1 Lipid Content of Pulmonary Surfactant

Lipid	Percentage of Total Lipid
Phosphatidylcholine	70–80
Phosphatidylethanolamine	5
Phosphatidylinositol	3
Phosphatidylserine	<2
Shingomyelin	<2
Cholesterol	2.4
Triglycerol	*
Free fatty acid	*

* Minor quantities.
Sources: Adapted from Creuwels et al. (1997).

certain surfactant proteins have activity against pathogenic microorganisms. SP-A and SP-D induce activation and chemotaxis of macrophages and can bind certain bacteria and viruses. The binding of microbial pathogens may stimulate complement- or immunoglobulin-mediated phagocytosis by alveolar macrophages.

Control of Surfactant Production

Surfactant production can be induced with glucocorticoids and cyclic AMP. Clinically, glucocorticoids are used to enhance surfactant production in premature infants. Glucocorticoids stimulate the rate of the regulatory enzyme for phosphatidylcholine production, cholinephosphate cytidylyltransferase (Rooney et al., 1994). Glucocorticoids also regulate expression of SP-A, SP-B, and SP-C genes. Compounds that increase cyclic AMP levels also enhance transcription and posttranscriptional events in surfactant production. In addition to inadequate surfactant production due to premature birth or mutations of SP-B, a variety of lung insults can alter surfactant synthesis and production. These insults include adult respiratory distress syndrome (ARDS) in humans and exposure to halothane, polyurethane smoke, drugs, nitrogen dioxide, and ozone (Creuwels et al., 1997). The effects of these insults on surfactant production in pigs have not been determined nor have the effects of exposure to high levels of ammonia, dust, or other airborne substances that also may affect surfactant function.

Pulmonary Vascular and Lymphatic Systems

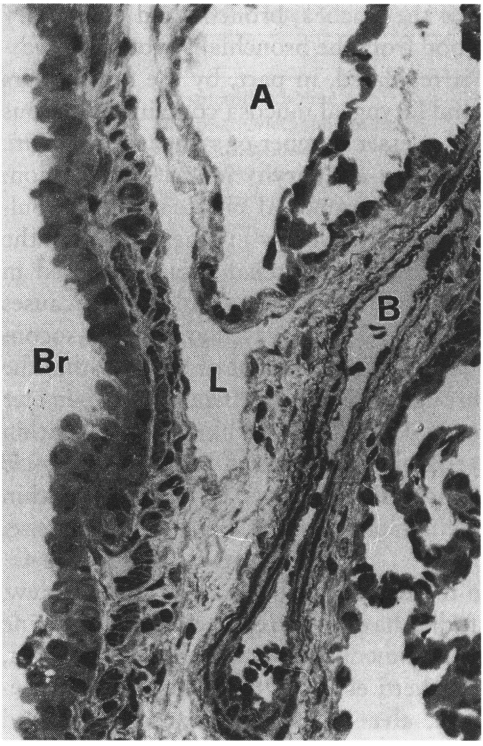
Two vascular systems deliver blood to the lungs. The pulmonary arteries from the right ventricle vascularize the capillary plexuses of the lung

alveoli. The supporting structures of the trachea, bronchi, and pulmonary artery wall are vascularized with blood from the bronchialis artery. The vascular system of the porcine lung is regulated, in part, by the nerve fibers within the mucosae. The tracheal and laryngeal mucosa contains numerous fibers of parasympathetic origin and a lesser number of sympathetic origin. The parasympathetic fibers of the trachea and larynx induce vasodilation. Parasympathetic fibers are lacking in the bronchial mucosa and the pulmonary vasculature. These areas, instead, contain sympathetic fibers in the pig (Matran, 1991). Neuropeptide Y and noradrenaline are costored in sympathetic paravascular nerves, and release of these substances causes vasoconstriction (Franco-Cereceda et al., 1995). Vascular tone (vasoconstriction or vasodilation) not only regulates the amount of blood within the lung but also influences airflow through bronchi by affecting the diameter of the airway lumen (Lockhart et al., 1992). Dilated blood vessels within the bronchial smooth muscle layer limit the amount of smooth muscle shortening and can result in edema. In addition, dilated blood vessels within the lamina propria narrow the bronchial lumen and also can result in edema formation.

Lymphatic vessels are present in the mucosa of the nasal cavity, but few, if any, anatomical or functional studies have been reported. In the porcine lung, lymphatic vessels are present in the connective tissue of the bronchi, bronchioles, and blood vessels (Marchetti et al., 1994). They border alveolar lobules but are not present in the alveolar septa. The vessels are lined by a single layer of endothelial cells and lack muscle cells (Figure 10-5). Therefore, they are not contractile but are supported by anchoring filaments (talin, vinculin), collagen, and elastic fibers that may conduct rhythmic actions to the vessel during respiration. The lymphatic vessels absorb excess fluid of the interlobular septa during normal physiological function, and this is increased with disease, particularly with acute inflammatory exudates and during vascular hypertension. Although lymphatic vessels are not present in the alveolar septa, excess fluid in the alveolar septal interstitium is removed by oncotic pressure. Alveolar capillaries have a low capillary pressure (8 mm Hg) and a relatively high intravascular oncotic pressure (25 mm Hg).

Neural Regulation of Respiration

The respiratory center of the pig, as in other mammalian species, is located in the medulla, ventrocaudal to the caudal part of the fourth ventricle (Figure 10-6). It is composed of bilateral groups of neurons. There is the dorsal respiratory group (dorsomedial inspiratory group) of the nucleus tractus solitarii and ventral respiratory group (ventrolateral expiratory



(A)

Figure 10-5 Lymphatic vessels of the porcine lung. A. Lymphatic vessel (L) adjacent to the lumen of a bronchus (Br), an alveolus (A), and a blood vessel (B). B. Electron micrograph of a lymphatic capillary (L) with an undulated wall. The capillary leads to an outlet (*). Two adjacent endothelial cells are overlapped and form a small saclike structure (inset). (Reproduced from Marchetti et al. [1994] with permission.)

group) of the reticular formation. The dorsal respiratory group is the termination of sensory fibers from the vagus and glossopharyngeal nerves. The ventral respiratory group extends fibers to the phrenic nerve for inspiration. The ventral group extends additional fibers to (1) spinal nerve fibers for the intercostal and abdominal muscles and (2) the vagus nerve for laryngeal, tracheal, and intrapulmonary (bronchus) muscles. Parenchymal innervation is necessary for development of the immature porcine lung; denervation impairs full maturation (Kern et al., 1993).

There is close functional integration between the neural control of the diaphragm and muscles of the thoracic cavity and cholinergic innervation by the vagus of the trachea, pulmonary airways, and pulmonary parenchyma. In young pigs with hypercapnia (Martin et al., 1995), airway and parenchymal resistance increases with expiration, in part due to oscillations of smooth muscle cells in the bronchi. Four types of cholinergic (muscarinic) receptors have been identified (Hislop et al., 1998; Chelala et al., 1998). By in situ hybridization, messenger RNA (mRNA) expression for three of the receptors (M1, M2, and M3) have been localized to smooth

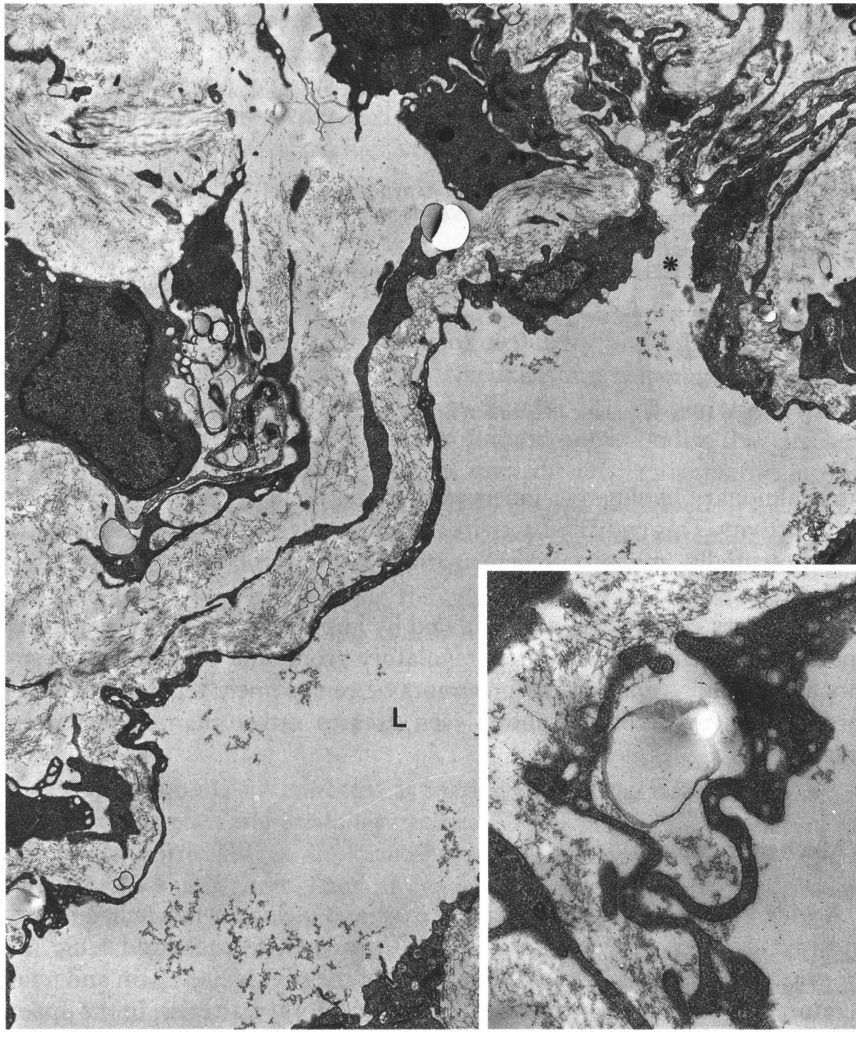


Figure 10-5 *Continued*

muscle cells in the pulmonary blood vessels and airways (Hislop et al., 1998). The mRNA for the M2 receptor is present at all ages but decreases with age. The mRNA for the M1 receptor increases shortly after birth, whereas M3 receptor mRNA is absent by age 3 days. When stimulated, these receptors induce the release of mucus from goblet cells in the epithelium and contraction of bronchial and arterial smooth muscle cells. The

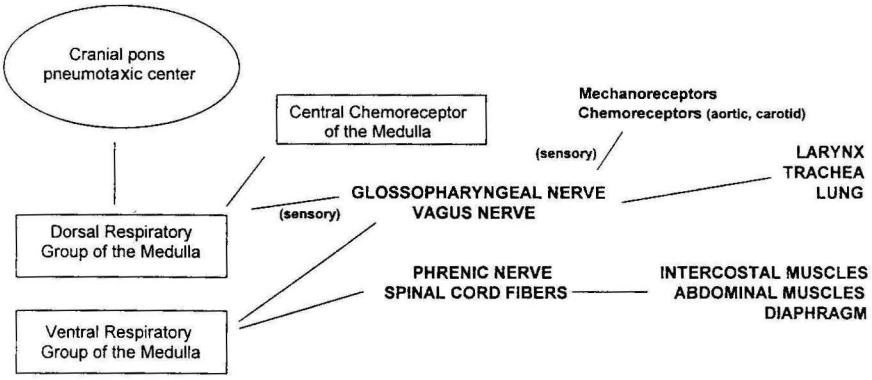


Figure 10-6 Schematic illustration of the neural regulation of respiration.

intrapulmonary cholinergic innervation corresponds closely with phrenic nerve activity. This regulated activity optimizes gas exchange in the neonate and potentially minimizes deformation and alveolar collapse during expiration.

Respiratory centers also are regulated by impulses from the cranial pons pneumotaxic center to the dorsal regulatory group and by mechanoreceptors and chemoreceptors. The pneumotaxic center finely regulates inspiratory efforts and results in short, even breaths rather than slower, deep breaths.

Mechanoreceptors

A wide variety of mechanoreceptors exist and include (1) stretch, irritant, and juxtacapillary receptors of the nasal passages, trachea, and lung; (2) proprioceptors of the muscles and tendons of the rib cage; (3) pain and temperature receptors of the skin; and (4) baroreceptors of arteries. In the upper airways, stimulation of mechanoreceptors by mechanical (i.e., dust) or chemical (i.e., ammonia) agents stimulates afferent nerves that induce sneezing or apnea. Similar stimulants in the larynx and trachea can induce cough and bronchoconstriction. In the lung, stretch receptors are present in the smooth muscle of bronchi and prevent overinflation. Irritant receptors are stimulated by noxious compounds such as pit gases and ammonia in poorly ventilated rooms and confinement units. They induce bronchoconstriction with shallow breathing to reduce additional inspiration of the noxious substance. Juxtacapillary receptors are present in the interstitial tissue of the lung and are stimulated by edema fluid as well as histamine and halothane, resulting in laryngeal closure and apnea. Proprioceptors adjust muscular

and mechanical movements to the inspiratory efforts. Pain receptors induce apnea followed by hyperventilation. Temperature receptors stimulate regions of the hypothalamus to accelerate respirations in order to regulate the body temperature. Arterial baroreceptors of the pig are located in the carotid sinus and aortic arch. Sharp increases in blood pressure induce apnea, whereas hypotension results in hyperpnea.

Chemoreceptors

Two types of chemoreceptors control medullary inspiratory centers: (1) central chemoreceptors located in the medulla that respond to changes in hydrogen ions and indirectly by carbon dioxide, and (2) peripheral (arterial) chemoreceptors located in the carotid and aortic bodies that are sensitive to anoxia. Although hydrogen ions directly activate the central chemoreceptors, hydrogen ions do not easily cross the blood-brain barrier or cerebrospinal fluid to directly contact the receptors. Instead, changes in carbon dioxide levels in these fluids alter the level of hydrogen ions in cells and interstitial fluid surrounding the central receptors through the action of carbonic anhydrase.

$$CO_2 + H_2O \underset{\text{carbonic anhydrase}}{\Leftrightarrow} HCO_3^- + H^+$$

The carotid bodies are located at the junction of the internal and external carotid arteries and are innervated by fibers from the glossopharyngeal nerve. The aortic bodies are located along the aortic arch and are innervated by the vagus nerve. Lack of oxygen stimulates these bodies (but not the central chemoreceptors) and increases the respiration rate.

C fibers, sensory fibers of the airway mucosa loop, send efferent fibers that loop back to the muocsa. These release neuropeptides such as substance P and neurokinin-A. These peptides affect vascular permeability and the degranulation of mast cells.

Inspiration and Expiration

In the resting pig, 10 to 15 percent of the alveolar air volume is exchanged per inspiration. The respiratory rate of pigs varies with age. For piglets and growing pigs, finishing pigs, and sows the rates are 25 to 40, 25 to 35, and 15 to 20 breaths/min, respectively (Christensen and Mousing, 1992). During respiration the volume of air within the upper respiratory tract stays relatively constant, but the resistance changes owing to opening or closing

of the laryngeal glottis. During inspiration the glottis is opened by contraction of the laryngeal muscles. With expiration, the glottis closes partially, resulting in increased intrapulmonary air pressure. In newborn mammals, the glottis can be closed completely during initial moments of expiration, and exacerbation of this process by pigs may explain their characteristic grunting sound. The increased mean airway pressure in the lung during expiration enhances the pulmonary resorption of fluid, the distribution of ventilation, and the diffusion of gases in piglets and other species (Mortola et al., 1987).

The exchange of gases across the air-blood barrier is an essential function of the lungs. Definitions of terms commonly used for respiratory function are summarized in Table 10-2. Inspiration of a volume of air (tidal volume) into the airways is an active process requiring contraction of inspiratory muscles. The elastic recoil of the rib cage tends to exert an outward movement of the rib cage, whereas the elastic recoil of the lung parenchyma tends to collapse the lungs. These contrasting tendencies equilibrate to a pleural pressure less than the atmospheric pressure. The contraction of inspiratory muscles increases intrathoracic volume, which causes the pleural space between the lungs and the rib cage to become more negative, reducing from approximately −2.5 to −6 mm Hg. The lung parenchyma is then

Table 10-2 Definitions of Physiological Parameters for Pulmonary Function

Maximal inspiratory reserve volume	Air inspired during maximal inspiratory effort in excess of the tidal volume
Tidal volume	Volume of air inspired and expired in a breath
Inspiratory capacity	Tidal volume plus maximal inspiratory reserve volume
Expiratory reserve volume	Air expired during maximal expiratory effort in excess of passive expiration (normal effort)
Expiratory capacity	Tidal volume and expiratory reserve volume
Vital capacity	Greatest amount of air that can be expired after maximal inspiration
Functional residual capacity	Amount of air left in lung at the end of normal respiration
Functional anatomical dead space	Volume of inspired air that does not mix with alveolar gas (volume is inspired and humidified but does not reach the alveolus)
Alveolar dead space (parallel dead space)	Volume of inspired air that mixes with the air of the alveoli but does not become a part of gaseous exchange (volume is limited in healthy pigs but increases in pigs with alveolar disease)
Alveolar ventilation-perfusion ratio	Ratio of alveolar ventilation per minute to alveolar perfusion per minute

expanded to admit a tidal volume. The airway pressure is slightly less than atmospheric pressure, which allows inflow. Movement of the diaphragm with slight expansion of the abdominal wall allows virtually all of the changes in intrathoracic volume that occur during resting inspiration. The external intercostal muscles that span individual ribs contract during expansion of the rib cage. This is especially important in swine because of the thick subcutaneous fat layer that encases the rib cage. Full inspiratory efforts require both the diaphragm and the intercostal muscles to allow transverse and longitudinal expansion of the chest cavity.

Lung compliance, or the expansive capability of the lung, is a measure of how easily lungs can be expanded. The compliance depends on two major factors: the tissue elasticity and the surface tension. Compared to lungs in humans, the lungs in pigs have prominent interlobular septa composed of fine fibrous connective tissue and lymphatic vessels. These subdivide pulmonary lung lobes, expand readily, and thereby increase compliance. Tissue elasticity is due to the elastic fibers, extracellular matrix proteins, vascular walls, basement membranes, and epithelium of the alveoli and bronchioles. The elasticity allows recoil of the lung after expansion and in this way directly influences lung compliance. Surface tension is the force at which a surface has a tendency to reduce its area. In the pulmonary alveoli of pigs and virtually all mammals, reduction of surface tension largely depends on function of the surfactant. Avian species have an additional material termed *trilaminar substance* that also may function in reducing surface tension.

The velocity of inspired air decreases after it enters the nasal cavity. The nares of pigs can be closed slightly to prevent inflow; however, the nasal meatuses of healthy pigs are progressively expansive. Once air is in the lung, the branching of air passages due to bifurcations of the bronchi and bronchioles causes in a divergent flow of air. Pig lungs are similar to those in other species in that the increase in airspace area slows the air velocity and allows diffusion of air across the alveolar septa. Resistance to airflow occurs by the turbulence precipitated by turbulence in the nasopharynx, glottis, trachea, and bronchi as well as the elasticity of the lung and rib cage. Parasympathetic (cholinergic) innervation by the vagus nerve increases the resistance to air flow at the level of the bronchi and bronchioles. This occurs through contraction of smooth muscle cells in these airways, resulting in luminal constriction. Compounds such as histamine enhance bronchoconstriction. On the other hand, sympathetic innervation can inhibit the effect of cholinergic stimulation. In addition to bronchoconstriction, fibrosis, mucosal edema, mucous production, intraluminal inflammatory debris, foreign bodies, alveolar septal thickening (by inflammatory cells, fibrosis, edema secondary to hypertension), and neoplastic masses also increase resistance. *M. hyopneumoniae* is a common respiratory pathogen in pigs

that induces dense infiltration of lymphocytes and plasma cells in the adventitial regions of the bronchi and bronchioles. These infiltrates reduce expansion of the airways and can compress adjacent alveoli.

Expiration does not require extensive muscle contraction during resting states of breathing. The elasticity of the lung collapses the parenchyma, and relaxation of the diaphragm presses on the collapsing parenchyma; both induce constriction of the alveoli and airways for the expulsion of air. During deep breathing, exercise, or forced expulsion of air (grunting, coughing), the glottis is closed momentarily while the diaphragm, intercostal, and abdominal muscles contract.

Respiration has a major role in cooling the body of pigs. When pigs become warm, they increase their respirations by increasing diaphragmatic activity. Although respirations are increased, the tidal volume decreases. This allows rapid exchanges of air. The inspired air becomes humidified and when exhaled, results in a loss of moisture from the body. Pigs are sensitive to heat because of their cylindric-like body conformation, thick layer of subcutaneous fat, and inability to cool themselves through perspiration. Therefore, evaporative cooling by the respiratory tract is critical.

Gaseous exchange across the aveolar septa in the pig and other mammals depends on the degree of inspired air reaching the alveolar lumen and the degree of blood flow within the alveolar septal capillaries. The alveolar ventilation-perfusion ratio assesses these two parameters through measurements of per-minute alveolar ventilation divided by per-minute alveolar perfusion (or cardiac output) and in normal pigs is slightly less than or near 1.0. Because of gravity there are regional differences in the ventilation-perfusion ratios in the lungs of the pig. In the dorsocaudal regions, ventilation is increased in relation to blood perfusion. The dorsocaudal region has a ventilation-perfusion ratio that is near 1.0. In contrast, in the ventrocranial regions ventilation is slightly less than perfusion and the ratio is less than 1.0 (0.8–1.0).

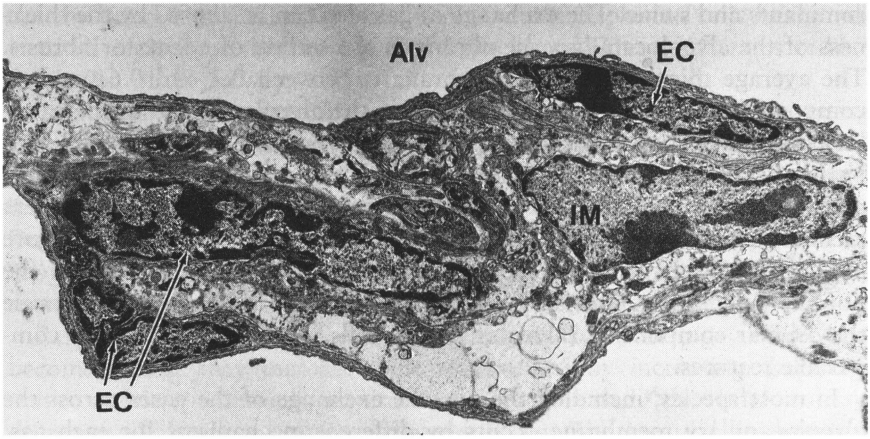
Exchange of Oxygen and Carbon Dioxide

The majority of total inspired air (66 percent) enters the alveoli for gaseous exchange. At the level of the alveolus, incoming air reaches a near standstill due to the wide expanse of the alveolar volume. By diffusion the main gases (nitrogen, oxygen, and carbon dioxide) move toward the alveolar septa. This is regulated by the amount of each gas in the inspired air and the tensions (measured in millimeters of mercury) in the vascular lumen of the alveolar septal capillary. Pores of Kohn, small orifice-like openings that interconnect alveoli, are frequent in carnivores but relatively sparse in

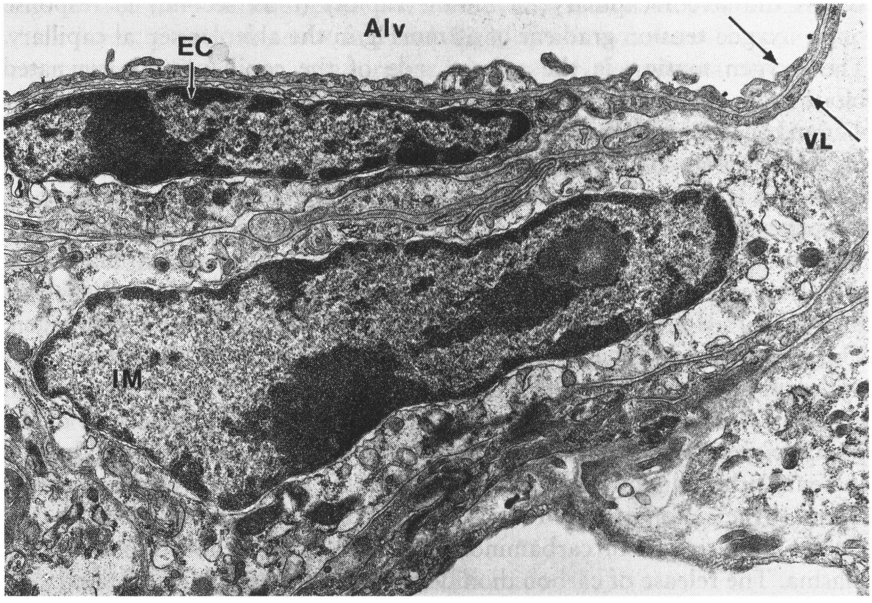
ruminants and swine. The exchange of gas also can be altered by the thickness of the alveolocapillary membrane in the setting of edema or fibrosis. The average thickness of the membrane is between 0.2 and 0.6 μm. It is composed of several layers (in order from the alveolar lumen to the capillary lumen): (1) surfactant layer, (2) alveolar type I cell, (3) basement membrane, (4) interstitial tissue (which includes extracellular matrix proteins, glycosaminoglycans, and fibroblasts in some locations), (5) basement membrane, and (6) endothelial cells of the alveolar septal capillary (Figure 10-7). The mechanisms of oxygen and carbon dioxide exchange in the porcine lung are presumably similar to those of other species because the cellular components (alveolar type II cells, surfactant, etc.) have comparable features.

In most species, including the pig, the exchange of the gases across the alveolocapillary membrane occurs by different mechanisms for each gas. Nitrogen is an inert gas and enters the plasma directly. Oxygen diffuses across the alveolocapillary membrane rapidly (0.25 second) in response to an oxygen tension gradient of 60 mm Hg in the alveolar septal capillary. The oxygen tension in the arterial side of the capillary (unoxygenated blood from the myocardial right ventricle and pulmonary arteries) is near 40 mm Hg, whereas that in the venous side of the capillary and the air in the alveolar lumen is near 100 mm Hg. Nearly 99 percent of the oxygen is associated with hemoglobin, and the remainder is present in the plasma.

Rapid passage of carbon dioxide from the pulmonary capillary into the alveolar lumen is due to a pressure gradient of 5 mm Hg and the fact that the diffusion coefficient for carbon dioxide is 20 times that of oxygen. The pressure gradient is 5 mm Hg because the tension on the arterial side of the pulmonary capillary is near 45 mm Hg and that in the alveolar lumen is nearly 40 mm Hg. The carbon dioxide tension on the venous side of the pulmonary capillary is also 40 mm Hg, identical to that in the alveolar lumen. Carbon dioxide in the vasculature of the pulmonary capillary comes from (1) the action of erythrocytic carbonic anhydrase on bicarbonate and (2) the dissociation of carbaminohemoglobin, and carbon dioxide in the plasma. The release of carbon dioxide from the vascular lumen is increased when oxygen is attached to erythrocytic hemoglobin. Obviously, oxygen saturation is higher in the lungs than in peripheral tissues, and this optimizes expulsion of carbon dioxide into the alveolar lumen. This event is called the *Haldane effect* and is due to the increased acidity of erythrocytes with oxygen-saturated hemoglobin. The additional hydrogen ions lead to increased carbonic acid formation, which dissociates, releasing carbon dioxide. On the other hand, decreased oxygenation in the peripheral tissues has the opposite effect and leads to the accumulation of carbon dioxide in the vascular lumen.



(A)



(B)

Figure 10-7 Electron micrographs of the porcine lung. A. The alveolar lumina (Alv) are lined by a thin layer of cytoplasm of a type I pneumocyte. Subjacent to the pneumocyte is a blood vessel lined by endothelial cells (EC), and in the lumen of the blood vessel is an intravascular macrophages (IM). B. Higher magnification of the alveolus (Alv) reveals a thin layer of type I pneumocyte cytoplasm. The layers of the air-blood barrier are present between the two arrows: the cytoplasm of the type I pneumocyte is supported by a basement membrane that is lined internally by the cytoplasm of a vascular endothelial cell (EC). Within the vascular lumen (VL) is an intravascular macrophage (IM). (Reproduced with permission from Dr. R. Thanawongnuwech, College of Veterinary Medicine, Iowa State University, Ames.)

Defense Mechanisms and Immune Cells

Inspired air can carry particulate matter, microorganisms, subcomponents of microorganisms such as lipopolysaccharide, and toxic gases. The air can also be too warm, excessively cold, too moist, or dry. The respiratory mucosa is an interface to all of these factors. Particulate matter is removed by nasal hairs or gravitation within the respiratory mucous layer. Most particles larger than 10 μm are deposited in the nasal, sinus, and upper respiratory tract mucosa at a level cranial to the larynx. In addition to binding particulate matter, the mucociliary layer is a barrier against temperature changes, noxious gases, and alterations in humidity and also entraps microorganisms. Low numbers of leukocytes such as neutrophils as well as immunoglobulins such as IgA, IgG, IgM, and IgG are present in this layer. With inflammatory processes the airway lumen can accumulate edema fluid and large amounts of cellular debris from neutrophils and sloughed epithelial cells. The degenerate cells release DNA and actin, both of which increase the viscosity of the mucus. The mucous layer also contains antimicrobial substances such as lactoferrin, which binds free iron. Recently, antimicrobial peptides produced by tracheal and bronchial epithelial cells in cattle, mice, and humans have been identified. These peptides, termed *defensins*, are produced at a basal level and increased during bacterial infection and the accompanying acute and chronic inflammation (Stolzenberg et al., 1997). Porcine beta-defensin-1 (pBD) mRNA has been detected in porcine respiratory epithelial cells (Zhang et al., 1998).

Pigs born in germ-free (gnotobiotic) conditions have few inflammatory cells within the respiratory system. The nasal mucosa contains low numbers of lymphocytes subjacent to the epithelium, and these cells extend between submucosal glands. The pharyngeal and palatine tonsils contain dense aggregates of lymphocytes that circumscribe the tonsillar crypts. The lung parenchyma typically lacks significant numbers of lymphocytes. Conventionally reared pigs have increased numbers of lymphocytes and plasma cells in the nasal cavity, trachea, and lung. Lymphocytes and plasma cells often form small aggregates in the adventitia of pulmonary arteries and veins and in the bronchi and bronchioles. The increased numbers of these cells are likely due to the exposure of the lung mucosa to the environmental antigens and pathogens present in dust. Lifetime nonsmoking pig farmers with normal lung function had increased numbers of lymphocytes, neutrophils, and activated macrophages in bronchoalveolar lavage fluids as a response to environmental dust (Pedersen et al., 1996). Mast cells are not seen in gnotobiotic or conventionally reared pigs; however, there have been no studies in pig lungs specially stained for mast cells.

All pigs have alveolar and intravascular macrophages. Alveolar macrophages are mature cells derived from bone marrow monocytes.

Alveolar macrophages have abundant cytoplasm and internalize foreign material and pathogens. Upon activation, they express major histocompatibility antigens (MHC II), release proinflammatory cytokines including interleukin (IL)-1 and tumor necrosis factor (TNF)-α, produce oxidative radicals (hydroxyl radical, nitric oxide), and release chemoactive products. Porcine alveolar macrophage-derived chemotactic factors (AMCFs) I and II induce neutrophil infiltration. There is 74 percent homology of AMCFs with human IL-8, and AMCR II has 53 percent homology with human neutrophil activating peptide 2 (Goodman et al., 1992).

Pulmonary intravascular macrophages (PIMs) are present within the aveolar capillaries and do not migrate into the alveolar lumen. These macrophages are roughly 20 to 80 μm in diameter and have an irregular shape, with a dense glycocalyx that adheres to the endothelial cell membrane (Winkler, 1988). In addition to the special location of PIMs, they differ structurally from alveolar macrophages in that they have cell junctions with endothelial cells, specialized tubular structures termed *micropinocytosis vermiformis*, and phagosomes with ferritin-containing sidersomes (Winkler and Cheville, 1985). Similar to alveolar macrophages, PIMs are derived from monocytes and the number of PIMs increases with age (Winkler, 1988). The PIMs have increased metabolic activity for cyclooxygenase and lipoxygenase metabolism of arachidonic acid when compared to alveolar macrophages, and predominantly utilize the lipoxygenase pathway (Bertram et al., 1989). They are thought to have a role in pulmonary hemodynamics and clearance of substances (such as lipopolysaccharide) from blood. When 3 percent copper (copper phthalocyanine tetrasulfonic acid [CPTA]) is injected intravenously into pigs, the lung levels of copper increase roughly 20 times compared to those in control pigs (Table 10-3). In contrast, liver and spleen levels of copper increase only slightly or decrease. By light microscopy, the majority of the copper is present in intravascular cells, likely PIMs. Studies have demonstrated struc-

Table 10-3 Level of Copper (Copper Phthalocyanine Tetrasulfonic Acid [CPTA]), in ppm, Uptake by Lung Macrophages following Intravenous Injection

	Lung		Liver		Spleen	
Days after Injection	Saline	CPTA	Saline	CPTA	Saline	CPTA
3	2.0	23.3	52.5	40.0	2.2	4.9
7	1.7	25.0	47.3	49.0	2.3	2.9
10	1.9	19.8	21.0	23.3	2.0	2.6
14	2.1	24.3	20.7	18.5	2.1	3.0
28	1.3	20.7	10.6	9.1	1.6	2.4

Source: Contributed by Dr. Roongroje Thanawongnuwech, Veterinary Diagnostic Laboratory, Iowa State University, Ames.

tural changes in PIMs following infections with *Haemophilus* (*Actinobacillus*) *pleuropneumoniae* (Bertram, 1986), African swine fever virus (Sierra et al., 1990), and porcine reproductive and respiratory syndrome virus (PRRSV) (Thanawongnuwech et al., 1998).

Special Respiratory Problems in the Newborn Pig

Pulmonary function is critical in the first moments after birth. Typically, pigs begin to breath after passing through the birth canal and eventually wander to the warmth and nourishment of the sow's mammary gland. Some pigs, however, have difficulty breathing, for any of a variety of reasons. Airway blockage or dyspnea of any type results in inadequate airflow, decreased gaseous exchange, and hypoxia.

Inhalation of meconium (fetal rectal contents that are excreted into the amnionic fluid) can occur with placentation anomalies, placentitis, and dystocia. In these conditions the porcine fetus senses hypoxia, and breathing is initiated as a compensatory mechanism. The meconium lodges in the pulmonary alveoli and induces an inflammatory reaction with accumulation of edema fluid. With large amounts of inhaled meconium, the inflammatory response and physical presence of meconium reduce the alveolar exchange of gases. There can be occlusion of the nares and mouth by placental membranes and fluids because of their slimy, mucoid, and tenacious characteristics. If the young pig is weak or in some way unable to remove this material, the flow of air through these orifices is inhibited.

Respiratory function is compromised in pigs that are born prematurely. Premature pigs have an impaired ability to begin respiratory efforts and also can have inadequate amounts of surfactant. Thus, inspiratory efforts are weak, and the lung parenchyma has a tendency to collapse.

Common Respiratory Pathogens

Acute and chronic infections of the respiratory tract in pigs are common. Most are related to an underlying cause such as inadequate ventilation, improper temperature and humidity, poor nutrition, and high levels of irritant gases such as ammonia. Other infections can be due to managerial practices, and recent efforts of segregated early weaning (SEW) programs to prevent respiratory infections have been successful. This husbandry practice separates groups of young pigs from sows after the pig has received colostrum and learned to live on its own, but before it can become infected with a respiratory pathogen carried by the sow.

Viral infections of pigs include PRRSV, swine influenza virus, porcine res-

piratory coronavirus, porcine circovirus, porcine cytomegalovirus, and porcine herpesvirus (pseudorabies virus). The PRRSV initially infects pulmonary alveolar and intravascular macrophages and induces marked thickening of the alveolar septa by infiltrates of macrophages and lymphocytes. Most of these viruses, including PPRSV, predispose the pig to secondary bacterial infections. Swine influenza virus induces a high fever in pigs and infects the epithelial cells in the bronchi and bronchioles, which results in necrosis of these cells and infiltrates of neutrophils. Porcine respiratory coronavirus can infect the ciliated cells of the nasal cavity and also induce infiltrates of cells into the pulmonary alveolar septa. Porcine circovirus, which was recently described, can infect macrophages, lymphocytes, endothelial cells, and epithelial cells (Morozov et al., 1998). Circovirus can cause a multisystemic wasting syndrome in growing pigs that is characterized by dyspnea, emaciation, and lymph node enlargement. Although serological surveys indicate that antibodies to circovirus are common in North American and European swine, the full impact of circovirus on the health of swine in production units has not been determined. Porcine cytomegalovirus infects the submucosal glands of the nasal cavity. The virus creates very large, easy-to-recognize inclusion bodies within the nucleus of these cells, and the disease is termed *inclusion body rhinitis*. Pseudorabies virus can cause tracheitis and bronchitis.

A number of bacteria are pathogenic to the porcine respiratory tract. *Pasteurella multocida* colonizes the tonsil of pigs and releases toxin (PMT) that impairs the formation of and increases osteolysis of the nasal conchal bone. *Bordetella bronchiseptica* colonizes ciliated cells of the nasal cavity, paranasal sinuses, trachea, and bronchi and induces mucosal damage and infiltrates of inflammatory cells. Ciliated cells of the nasal cavity, trachea, and bronchi also are colonized by *M. hyopneumoniae*. It induces ciliostasis, cilia loss, and nodular infiltrates of lymphocytes and plasma cells in the adventitia of bronchi and bronchioles. *Streptococcus suis* is present in the tonsil of most pigs and can cause suppurative bronchopneumonia; however, the pneumonia is difficult to reproduce consistently in experimental conditions. *Haemophilus parasuis* colonizes the nasal cavity and tonsils and also induces suppurative bronchopneumonia and pleuritis. *A. pleuropneumoniae* causes severe necrohemorrhagic lesions that typically involve more than 40 percent of the lung area. *Salmonella choleraesuis* causes a histiocytic (macrophage) infiltrate in the lung alveoli.

Ascaris suum is a roundworm of swine. Larval forms of *A. suum* penetrate the liver and migrate to the lung. Within the lung the larvae mature but incite a suppurative and eosinophilic pneumonia. *Metastrongylus* sp. is the lungworm of swine and also incites pulmonary damage and inflammation.

A wide range of atypical infections occur in swine and include agents

such as *Pneumocystis carinii*. These infections as well as therapeutic strategies are reviewed elsewhere (Leman et al., 1992).

The Pig as a Model for Pulmonary Research

All of the above-mentioned microbial pathogens of the porcine respiratory tract have been studied in porcine models. This work has clearly benefited the health and well-being of swine and the efficiency of pork production. The porcine respiratory system also is used commonly for the study of human diseases or therapies including ARDS, oxidative stress (reactive oxygen species), surfactant therapy, nitric oxide therapy, smoke inhalation, asthma, and others. The pig lung has increasing potential for xenotransplantation, especially if rejection problems due to major histocompatibility incongruencies can be resolved. The respiratory tract of swine also has potential for studies of gene therapy vectors. Human viral vectors could be tested in swine models. In addition, the porcine adenovirus has potential as a gene therapy vector. It replicates in the respiratory tract when it is administered intranasally, and causes only minor tissue damage and a minimal inflammatory response.

In conclusion, gaseous exchange is the single most important function of the respiratory system. It requires unobstructed flow of air from the environment into the body in order for oxygen and carbon dioxide to pass across the air-blood barrier. Although the respiratory system in the pig has subtle anatomical features that are unique, it has many similarities to the respiratory systems in other mammalian species, including humans.

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