Respiratory System

FORMATION OF THE LUNG BUDS

When the embryo is approximately 4 weeks old, the **respiratory diverticulum (lung bud)** appears as an outgrowth from the ventral wall of the foregut. The appearance and location of the lung bud are dependent upon an increase in **retinoic acid (RA)** produced by adjacent mesoderm. Hence, **epithelium** of the internal lining of the larynx, trachea, and bronchi, as well as that of the lungs, is entirely of **endodermal origin**. The **cartilaginous, muscular**, and **connective tissue** components of the trachea and lungs are derived from **splanchnic mesoderm** surrounding the foregut. Initially, the lung bud is in open communication with the foregut. When the diverticulum expands caudally, however, two longitudinal ridges, the **tracheoesophageal ridges**, separate it from the foregut. Subsequently, when these ridges fuse to form the **tracheoesophageal septum**, the foregut is divided into a dorsal portion, the **esophagus**, and a ventral portion, the **trachea** and **lung buds**. The respiratory primordium maintains its communication with the pharynx through the **laryngeal orifice**.

Larynx

The internal lining of the larynx originates from endoderm, but the cartilages and muscles originate from mesenchyme of the **fourth** and **sixth pharyngeal arches.** As a result of rapid proliferation of this mesenchyme, the laryngeal orifice changes in appearance from a sagittal slit to a T-shaped opening. Subsequently, when mesenchyme of the two arches transforms into the **thyroid, cricoid**, and **arytenoid cartilages**, the characteristic adult shape of the laryngeal orifice can be recognized. At about the time that the cartilages are formed, the laryngeal epithelium also proliferates rapidly, resulting in a temporary occlusion of the lumen. Subsequently, vacuolization and recanalization produce a pair of lateral recesses, the **laryngeal ventricles.** These recesses are bounded by folds of tissue that differentiate into the **false** and **true vocal cords.** Since musculature of the larynx is derived from mesenchyme of the fourth and sixth pharyngeal arches, all laryngeal muscles are innervated by branches of the tenth cranial nerve, the **vagus nerve.** The **superior laryngeal** nerve innervates derivatives of the fourth pharyngeal arch, and the **recurrent laryngeal nerve** innervates derivatives of the sixth pharyngeal arch.

Trachea, Bronchi, and Lungs

During its separation from the foregut, the **lung bud** forms the trachea and two lateral outpocketings, the **bronchial buds**. At the beginning of the fifth week, each of these buds enlarges to form right and left main bronchi. The right then forms three secondary bronchi, and the left, two, thus foreshadowing the three lobes on the right side and two on the left. With subsequent growth in caudal and lateral directions, the lung

buds expand into the body cavity. **The spaces for the lungs, the pericardioperitoneal canals**, are narrow. They lie on each side of the foregut and are gradually filled by the expanding lung buds. Ultimately the pleuroperitoneal and pleuropericardial folds separate the pericardioperitoneal canals fromthe peritoneal and pericardial cavities, respectively, and the remaining spaces form the **primitive pleural cavities**. The mesoderm, which covers the outside of the lung, develops into the **visceral pleura.** The somatic mesoderm layer, covering the body wall from the inside, becomes the **parietal pleura**. The space between the parietal and visceral pleura is the **pleural cavity**. During further development, secondary bronchi divide repeatedly in a dichotomous fashion, forming 10 **tertiary (segmental)** bronchi in the right lung and 8 in the left, creating the **bronchopulmonary segments** of the adult lung. By the end of the sixth month, approximately 17 generations of subdivisions have formed. Before the bronchial tree reaches its final shape, however, **an additional 6 divisions form during postnatal life.** Branching is regulated by epithelial-mesenchymal interactions between the endoderm of the lung buds and splanchnic mesoderm that surrounds them. Signals for branching, which emit from the mesoderm, involve members of the fibroblast growth factor (FGF)family. While all of these new subdivisions are occurring and the bronchial tree is developing, the lungs assume a more caudal position, so that by the time of birth the bifurcation of the trachea is opposite the fourth thoracic vertebra.

Maturation of the Lungs

Up to the seventh prenatal month, the bronchioles divide continuously into more and smaller canals (canalicular phase), and the vascular supply increases steadily. Respiration becomes possible when some of the cells of the cuboidal **respiratory bronchioles** change into thin, flat cells. These cells are intimately associated with numerous blood and lymph capillaries, and the surrounding spaces are now known as **terminal sacs** or **primitive alveoli.** During the seventh month, sufficient numbers of capillaries are present to guarantee adequate gas exchange, and the premature infant is able to survive. During the last 2 months of prenatal life and for several years thereafter, the number of terminal sacs increases steadily. In addition, cells lining the sacs, known as **type I alveolar epithelial cells,** become thinner, so that surrounding capillaries protrude into the alveolar sacs. This intimate contact between epithelial and endothelial cells makes up the **blood-air barrier. Mature alveoli** are not present before birth. In addition to endothelial cells and flat alveolar epithelial cells, another cell type develops at the end of the sixth month. These cells, **type II alveolar epithelial cells,** produce **surfactant,** a phospholipid-rich fluid capable of lowering surface tension at the air-alveolar interface. Before birth the lungs are full of fluid that contains a high chloride concentration, little protein, some mucus from the bronchial glands, and surfactant from the alveolar epithelial cells (type II). The amount of surfactant in the fluid increases, particularly during the last 2 weeks before birth. Fetal **breathing movements** begin before birth and cause aspiration of

amniotic fluid. These movements are important for stimulating lung development and conditioning respiratory muscles. When respiration begins at birth, most of the lung fluid is rapidly resorbed by the blood and lymph capillaries, and a small amount is probably expelled via the trachea and bronchi during delivery. When the fluid is resorbed from alveolar sacs, surfactant remains deposited as a thin phospholipid coat on alveolar cell membranes. With air entering alveoli during the first breath, the surfactant coat prevents development of an air-water (blood) interface with high surface tension. Without the fatty surfactant layer, the alveoli would collapse during expiration (atelectasis). Respiratory movements after birth bring air into the lungs, which expand and fill the pleural cavity. Although the alveoli increase somewhat in size, growth of the lungs after birth is due primarily to an increase in the number of respiratory bronchioles and alveoli. It is estimated that only one-sixth of the adult number of alveoli are present at birth. The remaining alveoli are formed during the first 10 years of postnatal life through the continuous formation of new primitive alveoli.

C L I N I C A L C O R R E L A T E S

Surfactant is particularly important for survival of the **premature infant.** When surfactant is insufficient, the air-water (blood) surface membrane tension becomes high, bringing great risk that alveoli will collapse during expiration. As a result, **respiratory distress syndrome** (RDS) develops. This is a common cause of death in the premature infant. In these cases the partially collapsed alveoli contain a fluid with a high protein content, many hyaline membranes, and lamellar bodies, probably derived from the surfactant layer.

Maturation of the Lungs

period	time	changes
Pseudoglandular period	5–16 weeks	Branching has continued toform terminal bronchioles. No respiratorybronchioles or alveoli are present
Canalicular period	16–26 weeks	Each terminal bronchiole divides into 2 or more respiratory bronchioles,which in turn divide into 3–6 alveolar ducts.
Terminal sac period	26 weeks to birth	Terminal sacs (primitive alveoli) form, and capillaries establish closecontact.
Alveolar period	8 months to childhood	Mature alveoli have well-developed epithelial endothelial (capillary) contacts