

12. LUNG DEVELOPMENT

Peter Rothstein, MD
ptr1@columbia.edu

RECOMMENDED READING: Larsen, Human Embryology, 3rd edition, pp 143-155.

Additional sources:

1. DiFiore JW, Wilson JM. Lung development. *Seminars in Pediatric Surgery* 3:221-32, 1994.
2. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. *J. Appl. Physiol.* 81:209-24, 1996.
3. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N. Eng. J. Med.* 284:1333-40, 1971.

This paper describes how a simple clinical observation led to a tremendous breakthrough in the treatment of neonatal respiratory distress syndrome.

4. Whitsett JA, Weaver TE. Hydrophobic surfactant proteins in lung function and disease. *N. Eng. J Med* 347:2141-48, 2002.

LEARNING OBJECTIVES:

You should be able to:

1. Discuss the growth and functional development of the respiratory system.
2. Discuss the stages of lung development and the major events of each stage.
3. Describe the physical and biochemical requirements for alveolar development and function.
4. Identify the developmental causes of neonatal respiratory failure, tracheoesophageal fistula and diaphragmatic hernia.

GLOSSARY:

Surfactant – Macromolecular complex of phospholipids and hydrophobic proteins present in alveoli that decreases surface tension and prevents alveolar collapse during exhalation. Largest lipid components are phosphatidylcholine (lecithin) and phosphatidylglycerol

Type I cell (pneumocyte) – found in the airways and alveoli

Type II cell (pneumocyte) – site of production of surfactant

Lamellar bodies – inclusions in Type II cells where surfactant is stored. Also known as inclusion bodies

Oligohydramnios – decreased volume of amniotic fluid

Conducting airways – trachea, mainstem bronchi, terminal bronchioles

Acinus – the unit of respiratory function distal to the terminal bronchioles, comprising the respiratory bronchioli, the alveolar ducts and the alveoli

SUMMARY:

Development of the lung can be divided into two phases, lung growth (structural development) and lung maturation (functional development). Lung growth can be influenced by a host of physical factors. Lung maturation and the achievement of functionality is primarily a biochemical process and is under the control of a number of different hormones. Lung growth proceeds through gestation. There is progressive branching of the airways and finally development of alveolar spaces capable of gas exchange in the last trimester. The surfactant system, composed of phospholipids that decrease surface tension within the alveoli and prevent alveolar collapse during exhalation, develops in the last trimester, and reaches maturity by approximately 36 weeks. Lung growth continues after birth as alveolar number continues to increase. The end result of the development of the lung is an organ with a tremendously large surface area that is approximately 50-100 m², capable of exchanging oxygen and carbon dioxide across a very thin membrane.

TEXT:

Successful development and function of the lung requires the completion of both physical development, required for the structure of the lung, and biochemical development of the surfactant system, required for the stability of this very large surface area. The two processes clearly are related. Incomplete development of lung structure and premature birth prior to the development of the surfactant system will lead to respiratory compromise or insufficiency in the newborn. The stages of lung development are summarized in Table 12-1.

Maturation of the Lungs		
Pseudoglandular period	5–16 weeks	Branching has continued to form terminal bronchioles. No respiratory bronchioles 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 close contact.
Alveolar period	8 months to childhood	Mature alveoli have well-developed epithelial endothelial (capillary) contacts.

Table 12-1.

There are five phases of structural lung development that occur at progressive times during gestation. The timing of the phases is approximate, with variation between fetuses, and in fact, there is no absolute agreement about the weeks that comprise each phase among various authors and texts.

The embryonic stage is apparent in the 3 week old embryo. The lung bud develops from the foregut and in communication with it. Separation of the two lung buds comes about with fusion of the esophagotracheal ridges to form the esophagotracheal septum (Figure 12-1).

When the embryo is 5 weeks old, two primary lung buds are identifiable. The lung buds go on to form their first subdivisions, with 2 lobar buds developing in the right lung bud and 2 lobar buds

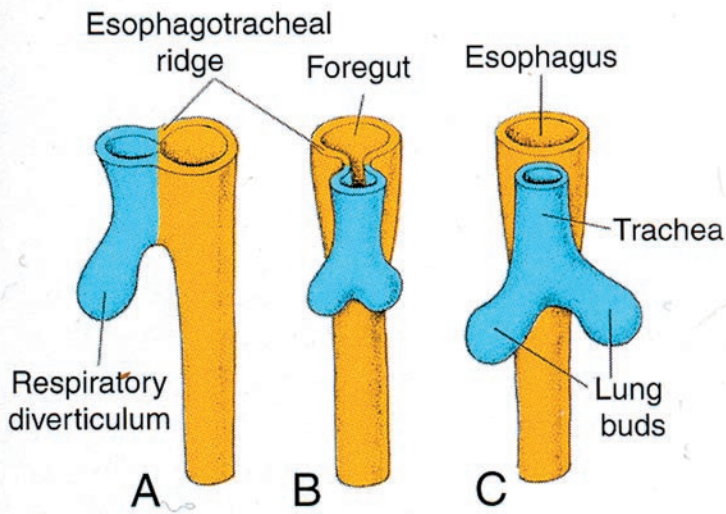


Fig. 12-1. A, B, and C. Successive stages in development of the respiratory diverticulum showing the esophagotracheal ridges and formation of the septum, splitting the foregut into esophagus and trachea with lung buds.

developing in the left. These are the forerunners of the right upper, middle and lower lobes and the left upper and lower lobes (Figure 12-2).

Development progresses in the 8 week old embryo as the lobar buds subdivide and form the bronchopulmonary segments (Figure 12-3).

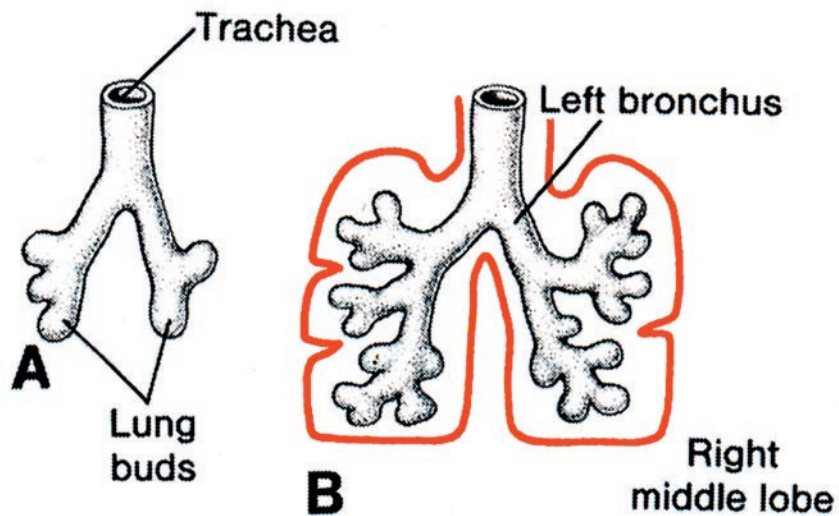


Fig. 12-2. Stages in development of the trachea and lungs. A. 5 weeks. B. 6 weeks.

Lung buds are lined by **endodermally derived epithelium** which differentiates into respiratory epithelium that lines the airways and specialized epithelium that lines the alveoli. The innervation of the

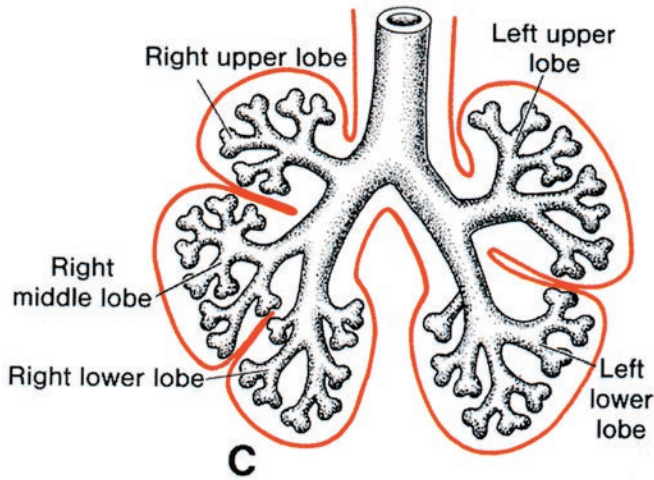


Fig. 12-3. Stages in development of the trachea and lungs. C. 8 weeks.

lungs is derived from **ectoderm**, while the **mesoderm** is the origin of pulmonary blood vessels, smooth muscle, cartilage and other connective tissue.

The **pseudoglandular stage** takes place between the 7th and 16th week of embryonic development. Conducting airways are formed by progressive branching. This is a demonstration of the power of 2ⁿ!! Eventually 16-25 generations of primitive airways are formed (Figure 12-4).

Endodermal lung buds undergo branching only if they are exposed to bronchial mesoderm. The rate and extent of branching appear directly proportional to amount of mesenchyme present. All

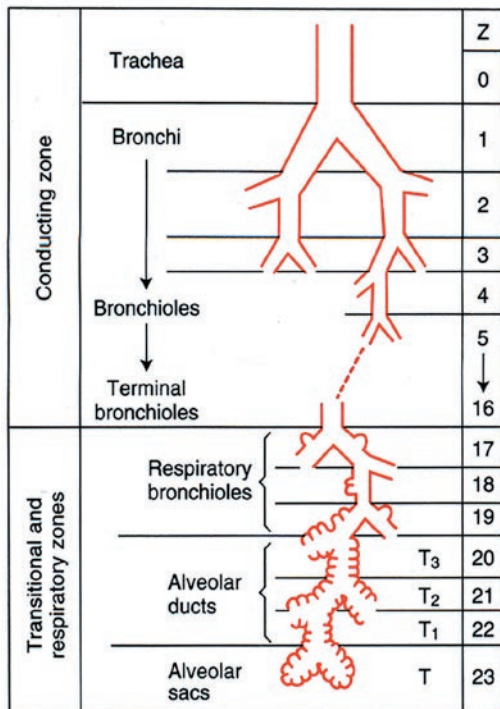


Fig. 12-4. Idealization of the human airways according to Weibel. Note that the first 16 generations (Z) make up the conducting airways, and the last 7, the respiratory zone (or the transitional and respiratory zone).

bronchial airways are formed by 16 weeks. After this time, further growth occurs by elongation and widening of existing airways.

During this stage, the first differentiation of lung epithelium occurs. By 13 weeks cilia appear in the proximal airways. **Mesenchyme** is necessary for this epithelial differentiation to occur and there is a transition from formation of bronchial epithelial cells (ciliated columnar and goblet cells) to alveolar type II cells. Conversely, the differentiation of lung **mesenchyme** requires the presence of lung **epithelium**.

The **canalicular stage** takes place between the 16th and 25th week. At this time the gas exchanging portion of the lung is formed and vascularized. There is a decrease of interstitial tissue and growth of the capillary network. By 20 weeks there is differentiation of the **type I pneumocyte**. The type I pneumocyte is the primary structural cell of the alveolus, and gas exchange will occur across these very thin, membrane-like cells. Capillaries begin to grow in absolutely close proximity to the distal surface of the alveolar cells (if the potential alveolar space is considered proximal) (Figure 12-5A). At about the same time, there is the appearance of **lamellar bodies**, also called inclusion bodies, in **type II alveolar cells**. The lamellar body is the site of surfactant storage, prior to its release into the alveolar space (see below).

The **terminal sac**, or **saccular stage** encompasses the period from 26 weeks until term. During this stage, there is a decrease in interstitial tissue, and a thinning of the airspace (=alveolar) walls (Figure 12-5B). As this stage progresses, there are recognizable **Type I** and **Type II** cells. The lamellar bodies of the Type II cells are the site of storage of **surfactant**, which is rich in phosphatidylinositol (vs. phosphatidyl choline and phosphatidyl glycerol in late gestation lungs), and is necessary for alveolar stability. The stability of the lung at birth correlates with the number of lamellar bodies present. In the absence of surfactant, the lung can maintain alveoli in an open state for only a very short time.

At birth, the air-containing space, later to become the alveolus, has been called a “primitive saccule”. There are approximately 20×10^6 saccules at birth. The saccules continue to mature following

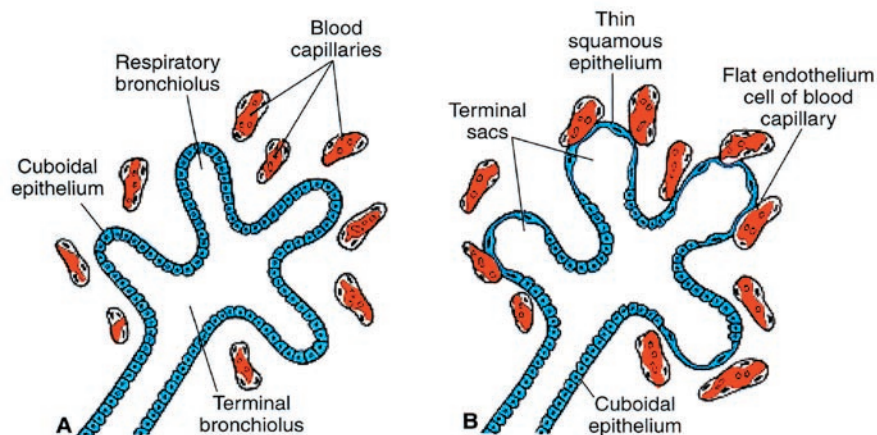


Fig. 12-5. Histological and functional development of the lung. A. The canalicular period lasts from the 16th to the 26th week. Note the cuboidal cells lining the respiratory bronchioli. B. The terminal sac period begins at the end of the sixth and beginning of the seventh prenatal month. Cuboidal cells become very thin and intimately associated

birth in the **postnatal or alveolar stage**. While these saccules are lined by mature Type I cells, the shape or geometry of the saccules does not achieve “adult” configuration until approximately 5 weeks after birth (Figure 12-6). The functioning alveolus is connected to an alveolar duct, is lined with Type I cells, which are in intimate contact to pulmonary capillaries, contain surfactant produced by Type II cells and have pores (pores of Kohn) connecting them to adjacent alveoli. The interstitial capillaries are exposed to two alveoli simultaneously. The air/blood interface consists of the Type I cell, a very thin basement membrane and the pulmonary capillary endothelium. At functional maturity, there are approximately 300×10^6 alveoli in the lung. This number of alveoli appears to be achieved by the age of 8 (Figure 12-7).

The development of the **pulmonary arterial system** follows a similar progression to that of the developing airways. Development of, and branching of the pulmonary artery mirrors bronchial

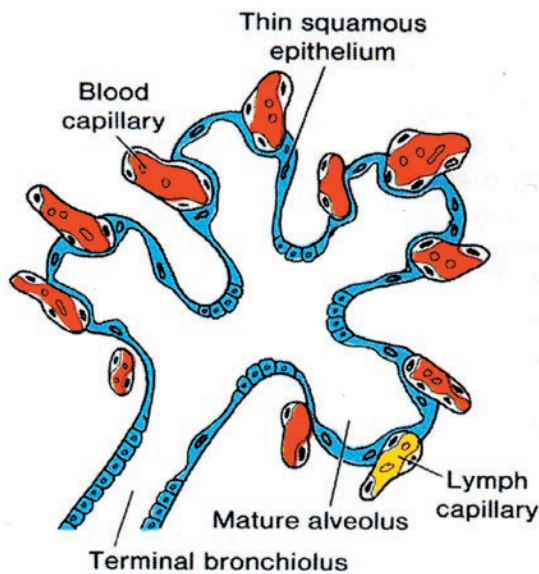
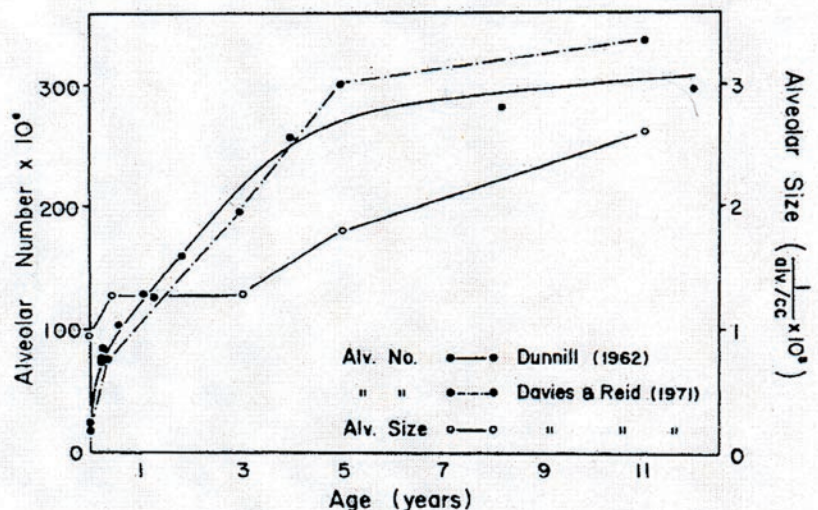


Fig. 12-6. Lung tissue in a newborn. Note the thin squamous epithelial cells (also known as alveolar epithelial cells, type 1) and surrounding capillaries protruding into mature alveoli.

Fig. 12-7. The increase in number and size of alveoli with age using quantitative analysis. Curve of Dunnill’s study is fitted from his figures. Figures for number and size from Davies and Reid are shown; size is shown as a reciprocal. (Reprinted with permission).



branching, and later mirrors alveolar development. By the beginning of the canalicular stage arteries in the preacinar region have formed. The development of muscle within the wall of the pulmonary blood vessels lags behind structural development. Muscularization of intra-acinar arteries does not keep pace with the appearance of new arteries and is not complete until childhood (Figure 12-8). What is the significance of this? Although the control of pulmonary blood flow in terms of distribution within the lung is controlled by a number of factors (physical location of lung units, gravity, oxygen, nitric oxide), alveolar oxygen tension is probably the most important determinant of pulmonary blood flow. The ultimate effector governing the distribution of pulmonary blood flow is pulmonary vascular muscle. The process of **hypoxic pulmonary vasoconstriction** governs this distribution of blood flow (Figure 12-9). Decreased alveolar oxygen tension will cause vasoconstriction in the area of the alveolus with a decreased oxygen tension, thus diverting blood to better oxygenated areas of the lung. During a generalized decrease in oxygen tension, or hypoxia, there is vasoconstriction of pulmonary blood vessels throughout the lung which causes a rise in pulmonary artery pressure.

Why is there so little blood flow in the pulmonary artery in the fetus, and why does this suddenly change with the first breath after birth? The fetal alveolus is filled with liquid not exposed

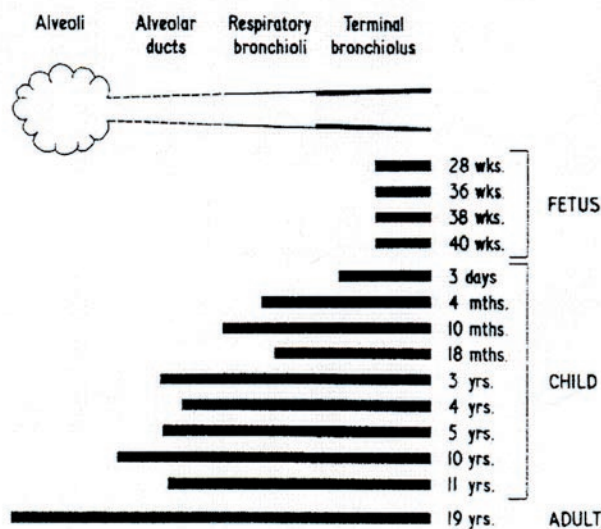
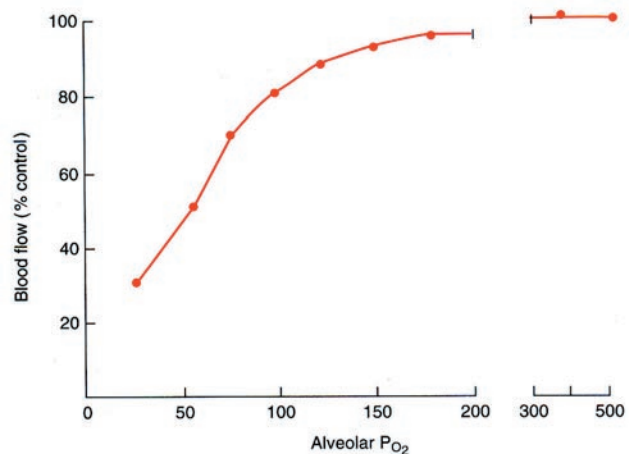


Fig. 12-8. Bar graph showing progression of muscle in the walls of arteries within the acinus. In fetuses there is no muscle within the acinus. With age, there is a gradual extension into the acinar region but, even at 11 years, muscular arteries have not reached the alveolar wall, where they are found in adults. (Reprinted with permission.)

Fig. 12-9. Effect of reducing alveolar P_{O_2} on pulmonary blood flow.



to the atmosphere, and therefore oxygen tension in the alveolus is very low. As a consequence of this low oxygen tension in the alveolus, there is generalized pulmonary vasoconstriction, a rise in pulmonary artery pressure, and diversion of blood from the pulmonary bed, across the ductus arteriosus to the systemic circulation. At birth, as the alveoli become gas filled, and oxygen tension in the alveolus rises, vasoconstriction decreases, and blood flow now increases to the lung. The mediator of vasodilation in the pulmonary bed is **nitric oxide**. Pulmonary artery pressure decreases after birth. In a small number of neonates the nitric oxide system in the pulmonary vascular bed is dysfunctional and pulmonary arterial vasodilation does not occur after birth. When this occurs pulmonary artery pressures remain elevated, the ductus arteriosus remains open, blood with low oxygen tension is shunted into the systemic circulation (a situation analogous to that found in the fetus) and systemic oxygen delivery is compromised. This syndrome, originally called persistent fetal circulation, is now called **persistent pulmonary hypertension of the newborn**.

There are a number of **physical influences on lung growth**. Proper development of the lung is dependent on the presence of both lung liquid and amniotic fluid. The lung liquid is secreted by pulmonary epithelium. The volume of lung fluid is maintained by the activity of the upper airway which acts as a gatekeeper by controlling the resistance to efflux of fluid out of the lung and trachea during non-breathing periods, and by diaphragmatic movement associated with fetal breathing movements. The larynx is the major site of regulation of efflux and therefore of lung liquid volume. During fetal breathing movements, when the upper airway resistance is decreased, diaphragmatic movements help to maintain lung liquid volume (Figure 12-10). The experimental drainage of lung liquid leads to pulmonary hypoplasia.

Amniotic fluid is also required for normal lung development. Amniotic fluid originates in the lung and fetal kidney. **Oligohydramnios** is associated with lung hypoplasia (Potters syndrome-renal

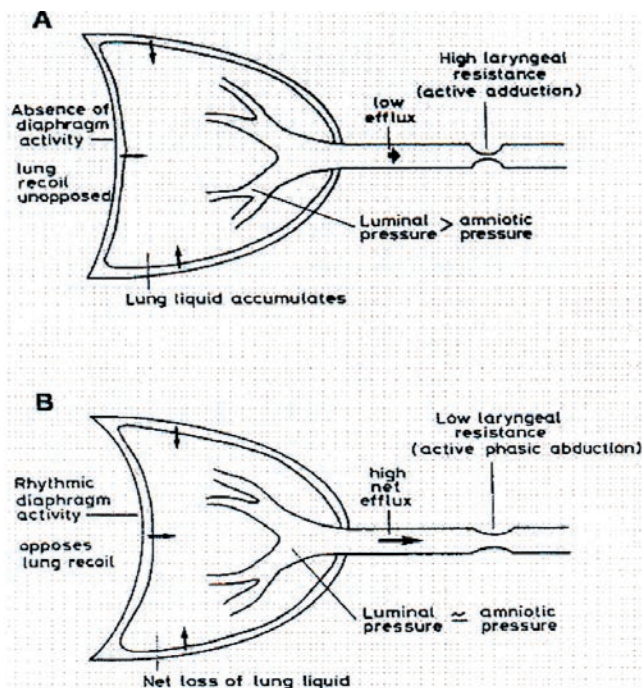


Fig. 12-10. Schematic diagrams showing physical influences on fetal lungs during periods of apnea and episodes of fetal breathing movements (FBM). During apneic periods (A), a high laryngeal resistance opposes lung recoil, shown by 3 arrows, resulting in a low rate of tracheal fluid efflux, an increase in luminal pressure, relative to ambient pressure, and accumulation of liquid in lung lumen. During episodes of FBM (B), laryngeal resistance is reduced, leading to increased efflux of tracheal fluid as a result of lung recoil; rhythmic diaphragmatic contractions tend to oppose effects of lung recoil. That is, pulmonary luminal volume is maintained during apnea by resistance of the upper airway and, during FBM episodes, by the effects of inspiratory efforts in opposing escape of lung liquid via trachea.

agenesis, lack of fetal urine). The mechanism of lung hypoplasia in this syndrome is uncertain but, perhaps it is due to increased efflux of lung liquid into the amniotic space.

Lung hypoplasia may be caused by a number of other factors that restrict or better, compress the fetal lung. Conditions or lesions known to cause lung hypoplasia are:

1. Congenital diaphragmatic hernia, in which usually the left hemithorax is occupied by intestinal contents
2. Musculoskeletal abnormalities of the thorax which do not allow full expansion of the thoracic cage
3. Space occupying lesions of thorax, such as fetal pleural effusions
4. Changes in geometry due to oligohydramnios associated with renal or urinary tract abnormalities

Biochemical maturation, that is, production of surfactant, appears to be independent of lung growth. What is surfactant and why is it so important? Surfactant is a mixture of phospholipids and hydrophobic proteins, produced by Type II cells, and secreted into the alveolar space. The principal lipids are phosphatidylcholine (lecithin) and phosphatidylglycerol, and the principal proteins are surfactant proteins B and C (Figure 12-11).

Surfactant decreases surface tension within alveoli and prevents collapse of alveoli during exhalation. In the absence of surfactant, the alveolus would be unstable and collapse at the end of each breath. Tremendous work would be required to open up the alveolus with each breath (Figure 12-

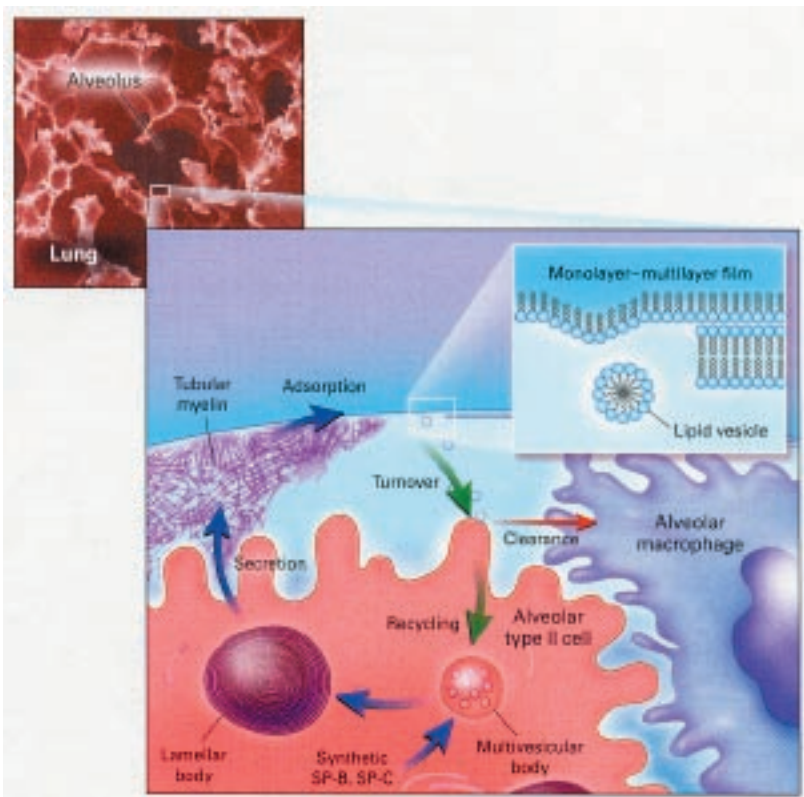


Figure 12-11. Freeze-Frame view of the Alveolar Space with a Magnified View of the Air-Liquid Interface, with Formation of Pulmonary Surfactant Films.

Surfactant phospholipids and proteins are synthesized by alveolar type II cells lining the alveoli. Surfactant lipids and surfactant protein B (SP-B) precursor protein and surfactant protein C (SP-C) are transported to multivesicular bodies and, after proteolytic processing, stored in lamellar bodies. SP-B, SP-C and surfactant lipids are secreted into the alveolar subphase and interact with surfactant protein A to form a tubular myelin reservoir from which multilayers and monolayers form a film, thus reducing surface tension at the air-liquid interface. Surfactant remnants are taken up and reutilized or catabolized by type II epithelial cells. Alveolar macrophages play a critical part in the clearance and catabolism of surfactant lipids and proteins. Formation of the active surface film is required to maintain lung volumes, thereby preventing atelectasis and respiratory failure. The freeze-frame view is courtesy of Debra Yager.

12). In fact, a mutation in the gene coding for surfactant protein B leading to an absence of this crucial protein is an extremely rare cause of respiratory failure in term newborns.

Type II cells and their associated surfactant can develop in the presence of pulmonary hypoplasia. Gas exchange is possible by 26-27 weeks, though not necessarily sustainable. Surfactant production gradually increases with advancing gestational age. The surfactant system matures by

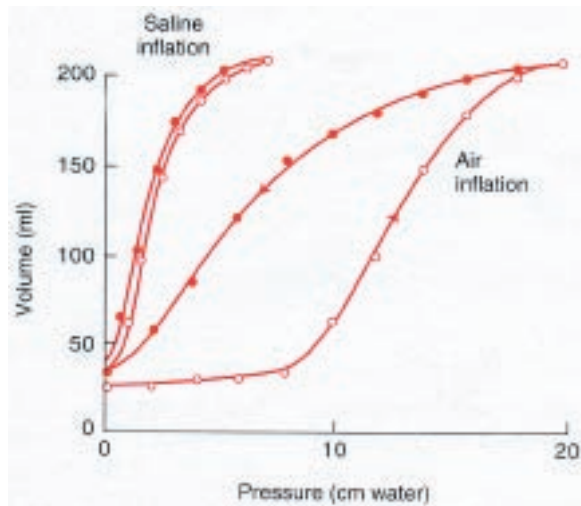


Figure 12-12. Comparison of pressure-volume curves of air-filled and saline-filled lungs (cat). *Open circles, inflation; closed circles, deflation.* Note that the saline-filled lung has a higher compliance and also much less hysteresis than the air-filled lung.

36 weeks in most fetuses (Figure 12-13, Figure 12-14). Production of surfactant by Type II cells is hormonally influenced. **Corticotropin** stimulates lung maturation via **cortisol**. Cortisol induces fetal lung fibroblasts to produce **fibroblast pneumocyte factor** which stimulates surfactant production in Type II cells. Thyroid hormones are also required for development of the surfactant system. At the time of birth, **epinephrine** and **arginine vasopressin** suppress fetal lung liquid formation, and play a role in its reabsorption. These two hormones are in turn dependent on increasing concentrations of glucocorticoids that occur at term.

The development of the surfactant system, to the point that spontaneous respiratory function can occur, usually takes place by 36 weeks of gestation. Birth before 36 weeks may be associated with respiratory compromise and failure. The incidence and severity of the lung disease is greater in proportion to the degree of prematurity. A number of strategies have been developed to try to deal

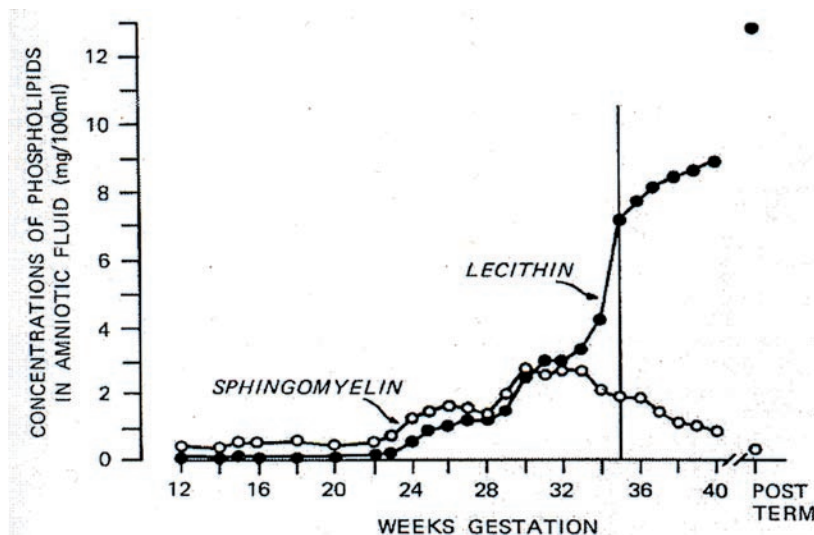


Fig. 12-13 Concentrations of acetone precipitable (surface active) lecithin and sphingomyelin in amniotic fluid are comparable until 30 to 32 weeks gestation. After 32 weeks gestation, concentration of lecithin increases sharply, while sphingomyelin decreases steadily until term. Lung is mature when lecithin concentration reaches 10mg %. (From Gluck, L, and Kulovich, M. V.414)

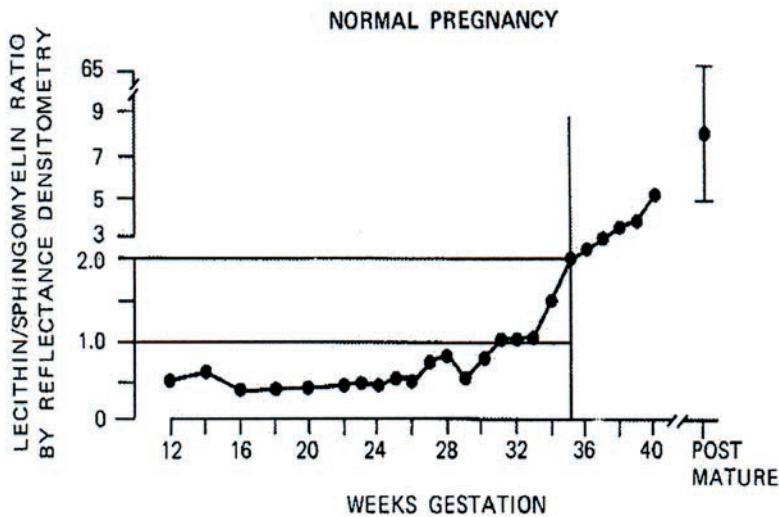


Fig. 12-14. Amniotic fluid L/S ratio increases progressively with gestational age. L/S ratio greater than two signifies maturity of surfactant system of lung. (From Gluck, L, and Kulovich, M. V.414)

with this problem, including the use of antenatal steroids to promote lung maturity, the use of various forms of positive pressure to maintain the lungs in the open state, and the administration of exogenous surfactant. The scope of the problem of prematurity is enormous in terms of neonatal mortality, morbidity among survivors and the costs in emotional and economic terms to society. It is estimated that there are 80,000 cases per year in the United States of neonatal respiratory failure, with 8,500 deaths. The estimated hospital costs for this is \$4.4 billion. The incidence of neonatal respiratory failure is higher in boys than in girls (20 vs. 15.6/1000) and higher in blacks (29/1000). The elimination of a substantial portion of the morbidity and mortality associated with prematurity and neonatal respiratory failure will depend on factors such as education and nutrition. Prematurity is in large part a reflection of disorders of societal structure and function.

There are several well known examples of **failure of normal physical development of the lung**. **Tracheoesophageal fistula** results from the failure of the normal formation of tracheoesophageal septum. The syndrome has an incidence of approximately 1:3000 births. There are five different types of tracheoesophageal fistula (Figure 12-15). Ninety percent have blind upper esophageal pouch and connection of distal esophagus to lower trachea.

Diaphragmatic hernia results from failure of one of the pleuroperitoneal membranes to close. This occurs predominantly on the left side (Figure 12-16). This defect has an incidence of 1:2000 births.

Finally, we cannot ignore the supremacy of the lung compared with other organs (or at least most others). The primacy of the lung is confirmed by conventional wisdom. For example, whereas the kidney and related organs can be pushed to the sidelines, as in “Hold your water!”, and the gut must be constantly controlled, “Don’t get your bowels in an uproar!”, the lung is ignored only at your own peril –“Don’t hold your breath!!!!”

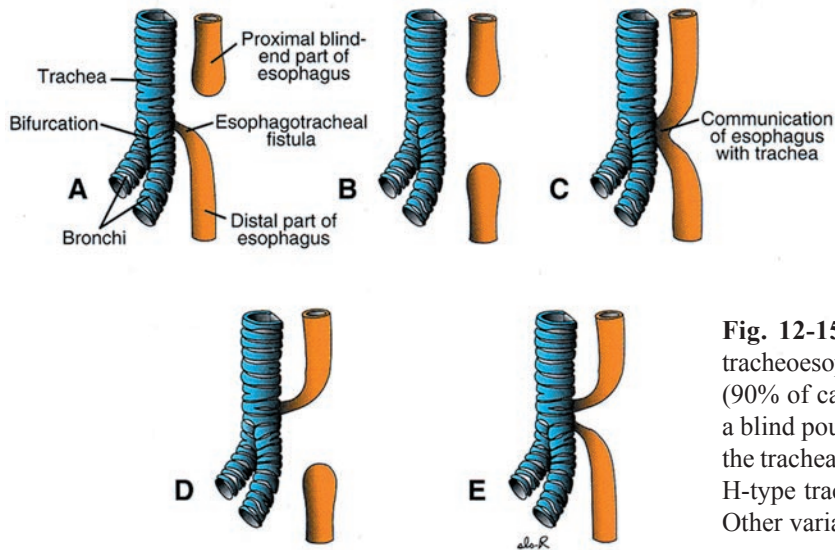


Fig. 12-15. Various types of esophageal atresia and/or tracheoesophageal fistula. **A.** The most frequent abnormality (90% of cases) occurs with the upper esophagus ending in a blind pouch and the lower segment forming a fistula with the trachea. **B.** Isolated esophageal atresia (4% of cases). **C.** H-type tracheoesophageal fistula (4% of cases). **D.** and **E.** Other variations (each 1% of cases).

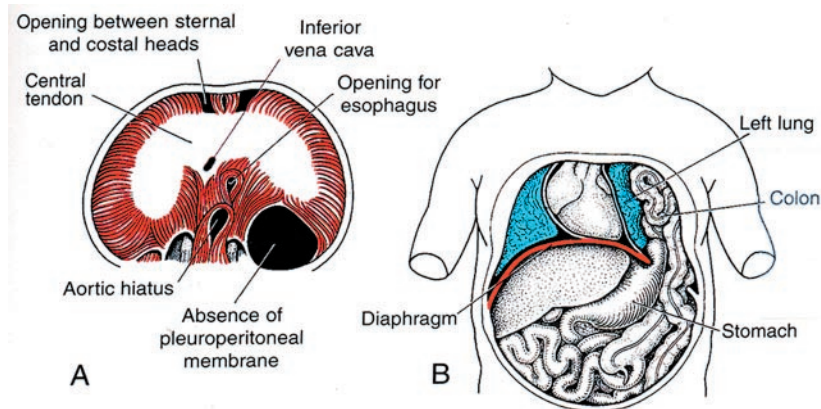


Fig. 12-16. Congenital diaphragmatic hernia. **A.** Abdominal surface of the diaphragm showing a large defect of the pleuroperitoneal membrane. **B.** Hernia of the intestinal loops and part of the stomach into the left pleural cavity. The heart and mediastinum are frequently pushed to the right and the left lung compressed.