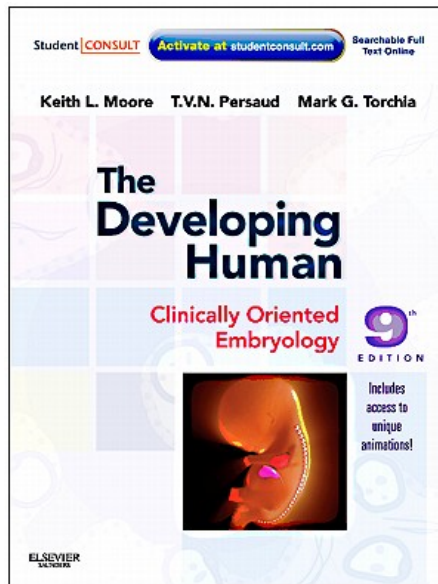


Respiratory development

Lecture Date: 2013-09-03 Lecture Time: 16:00 Venue: Biomed E
Speaker: Steve Palmer

Objectives

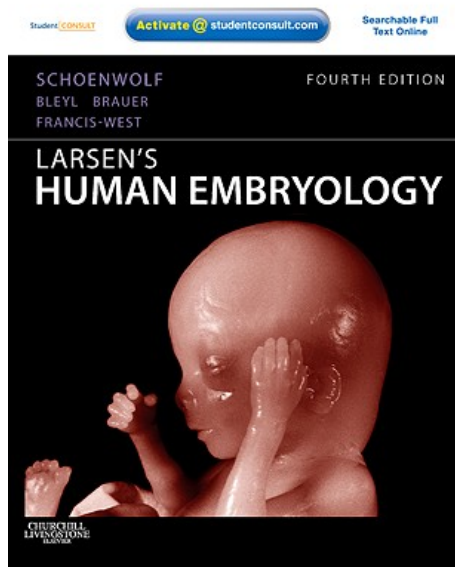
- Understanding of the stages of lung development
- Understanding of diaphragm development
- Understanding of subdivision of the primitive pericardial cavity
- Brief understanding of respiratory vascular development
- Brief understanding of molecular mechanisms



Citation: The Developing Human: clinically oriented embryology 9th ed. Keith L. Moore, T.V.N. Persaud, Mark G. Torchia. Philadelphia, PA: Saunders, 2011.

[Chapter 8 – Body Cavities and Diaphragm](#)

[Chapter 10 – Respiratory System](#)



Citation: Larsen's human embryology 4th ed. Schoenwolf, Gary C; Larsen, William J, (William James). Philadelphia, PA : Elsevier/Churchill Livingstone, c2009.

[Chapter 11 - Development of the Respiratory System and Body Cavities](#)

- The respiratory system does not carry out its physiological function (of gas exchange) until after birth.
- The respiratory tract is divided anatomically into 2 main parts:
- **upper respiratory tract** - consisting of the nose, nasal cavity and the pharynx.
- **lower respiratory tract** - consisting of the larynx, trachea, bronchi and the lungs.
- The respiratory "system" usually includes descriptions of not only the functional development of the lungs, but also related musculoskeletal (diaphragm) and vascular (pulmonary) development.

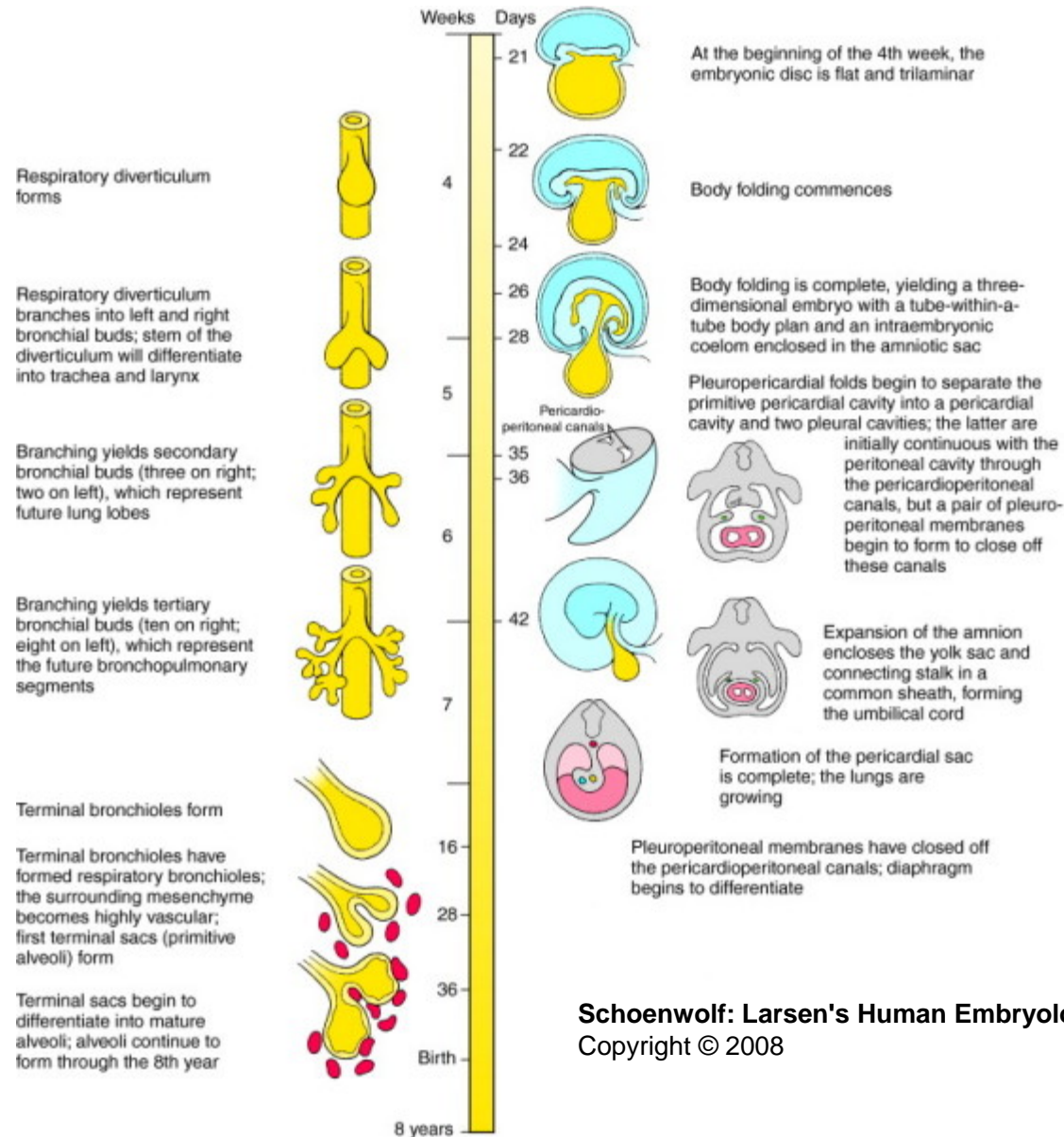
Lung Development

1. week 4 - 6 embryonic
2. week 6 - 16 pseudoglandular
3. week 16 - 28 canalicular
4. week 28 - 36 saccular
5. week 36 – 8 years old alveolar



The 5 stages of lung development

Overview and timeline of respiratory development



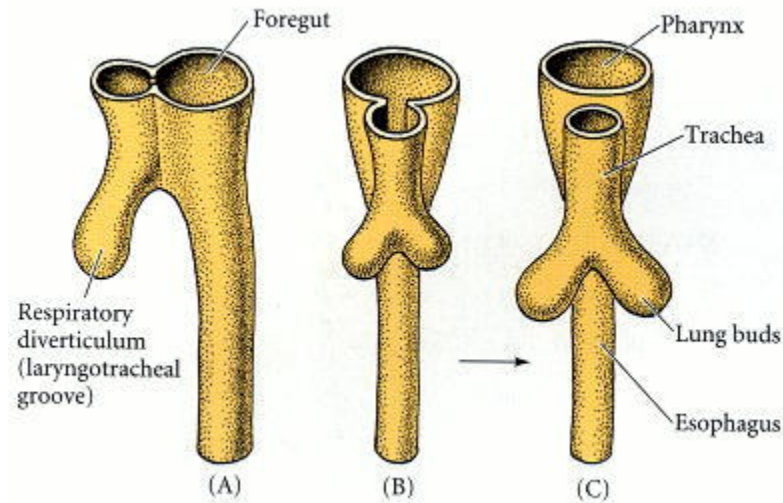
ORGANOGENESIS

Germ Layers

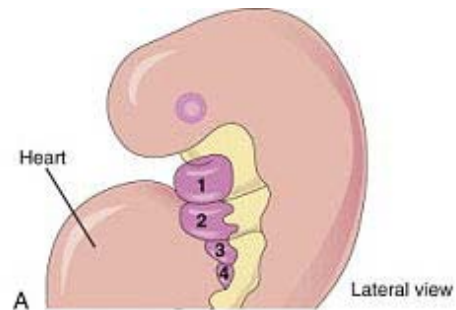
The respiratory system integrates all of the germ layers to some extent

- Endoderm forms the inner lining of the airways and alveoli
- Splanchnic mesoderm forms the surrounding tissue of the lungs and airways
- Neural ectoderm contributes the neural innervation.
- Neural crest derived cells contribute to the larynx
- Somitic mesoderm contributes the supporting musculoskeletal components of the ribcage.
- The diaphragm is made up of 4 different mesodermal components

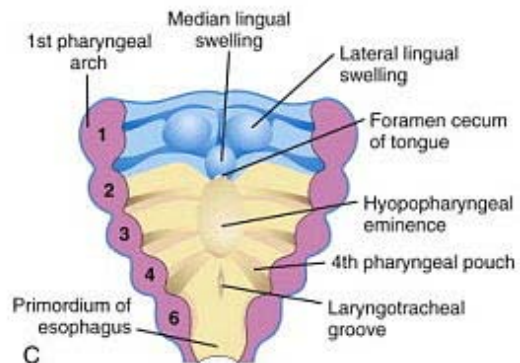
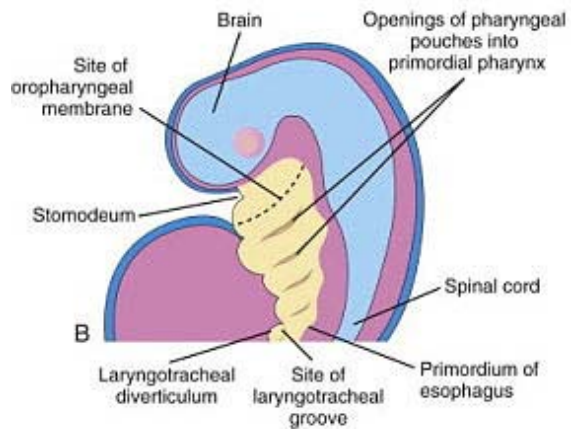
Embryonic stage of lung development week 4-6



The respiratory system starts as an outgrowth on the ventral surface of the gut tube at the level of the 4th pharyngeal arch (see head development later) called the **laryngotracheal groove** or **respiratory diverticulum** that divides at the midline to create the **lung buds (primary bronchial buds)**



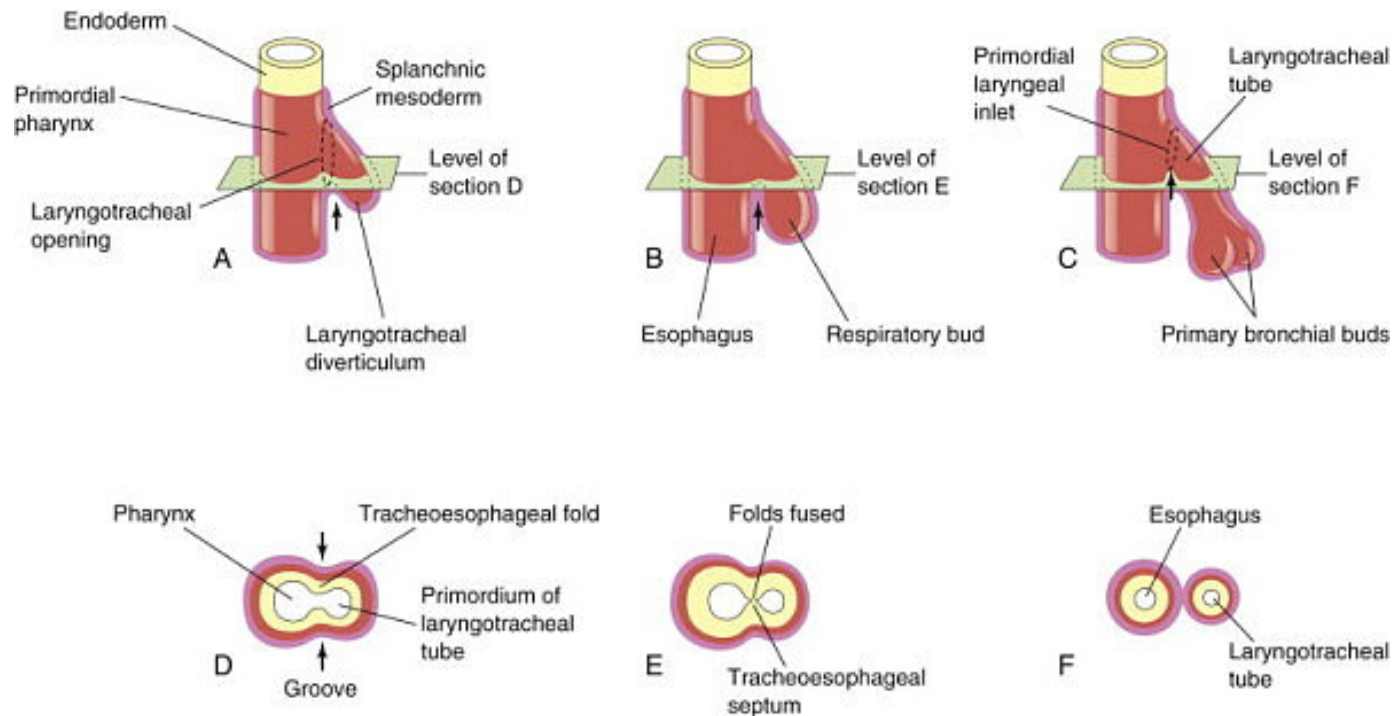
The pharyngeal arches are indicated.



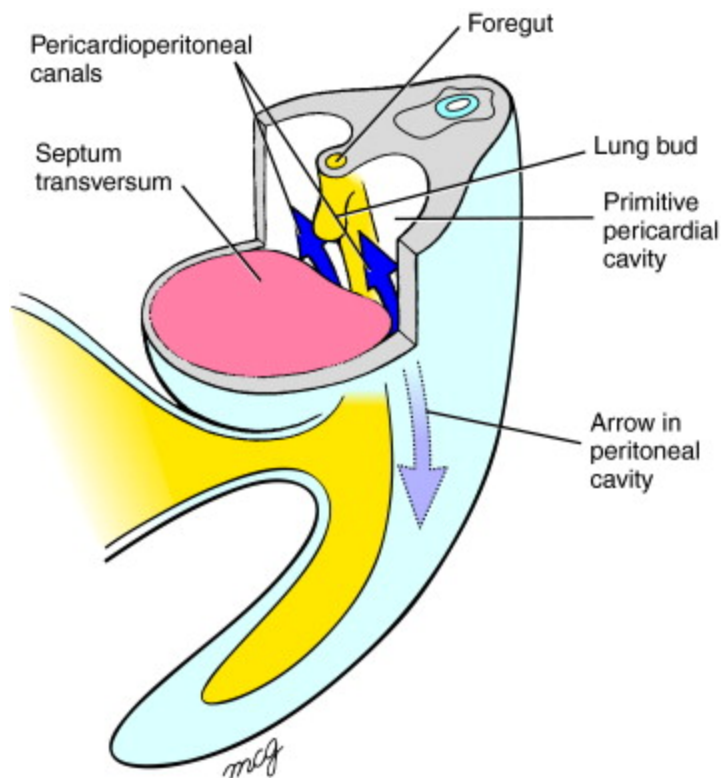
Position of the laryngotracheal groove on the anterior lining of the developing pharynx

From Moore KL, Persaud TVN, Shiota K: *Color Atlas of Clinical Embryology*, 2nd ed. Philadelphia, WB Saunders, 2000.

The outgrowth of the gut tube is endodermal but it is surrounded by splanchnic mesoderm and it is the combination of these two tissues that creates the bulk of the lungs. Distal to the larynx, the endoderm makes the epithelium and glands of the trachea and pulmonary epithelium. The cartilage, connective tissue and muscles of the trachea are derived from the splanchnic mesoderm.

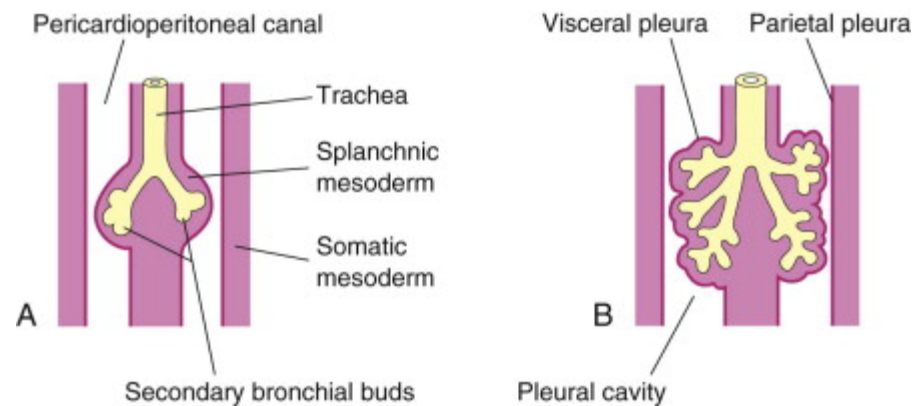


From Moore KL, Persaud TVN, Shiota K: *Color Atlas of Clinical Embryology*, 2nd ed. Philadelphia, WB Saunders, 2000.



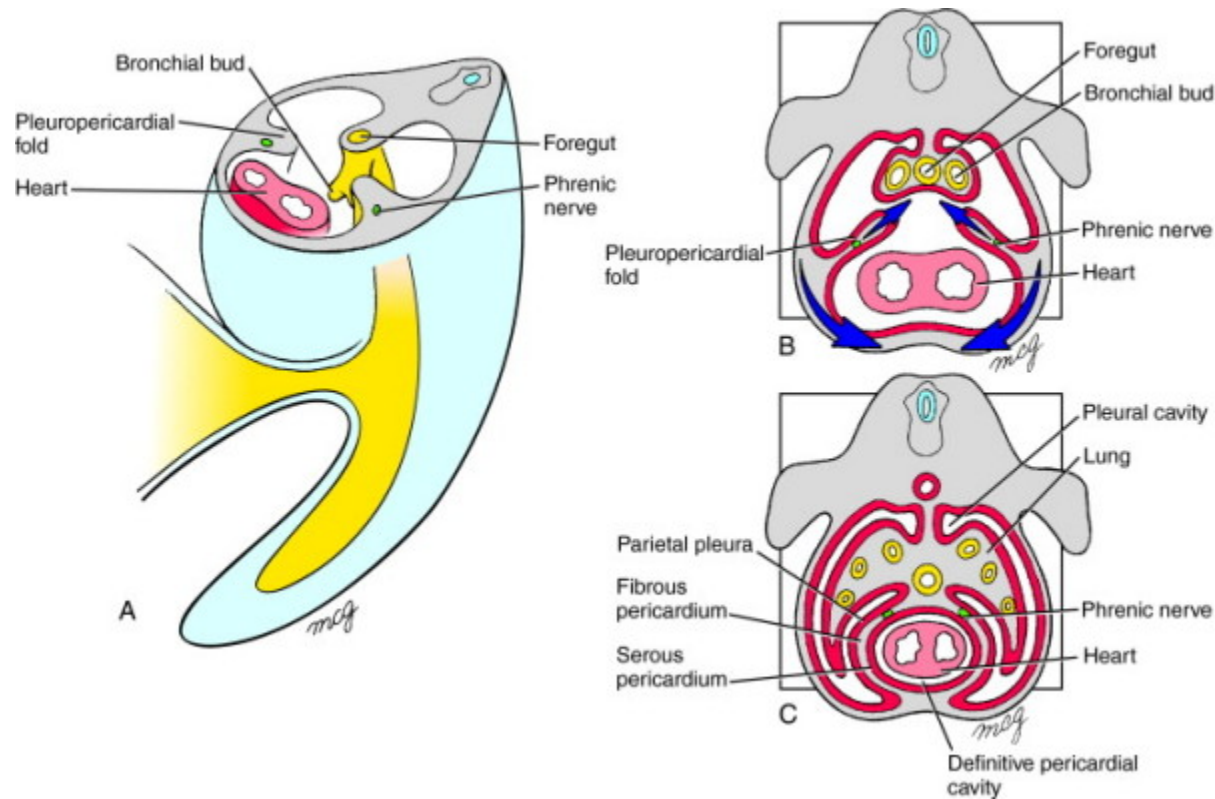
The septum transversum provides the first subdivision of the peritoneal and primitive pericardial cavity

The pleural cavities initially communicate with the peritoneal cavity through a pair of **pericardioperitoneal canals** passing dorsal to the septum transversum. However, a pair of transverse **pleuroperitoneal membranes** grow ventrally from the dorsal body wall to fuse with the transverse septum, thus closing off the pericardioperitoneal canals. Therefore, the septum transversum and the pleuroperitoneal membranes form major parts of the future diaphragm.



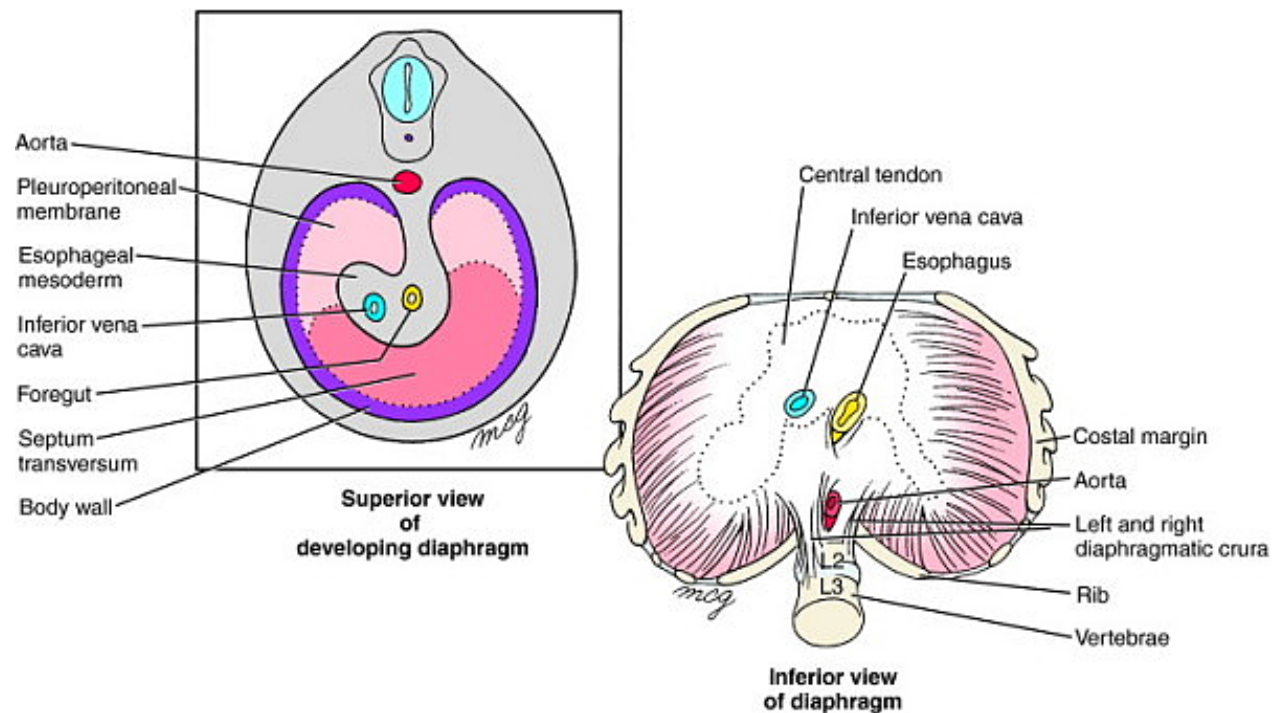
From Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.

The second subdivision of the coelom occurs in the thoracic cavity through the growth and fusion of the **pleuropericardial folds** during the 5th week. The roots of the pleuropericardial folds migrate ventromedially thus extending the pleural cavities around the whole thorax



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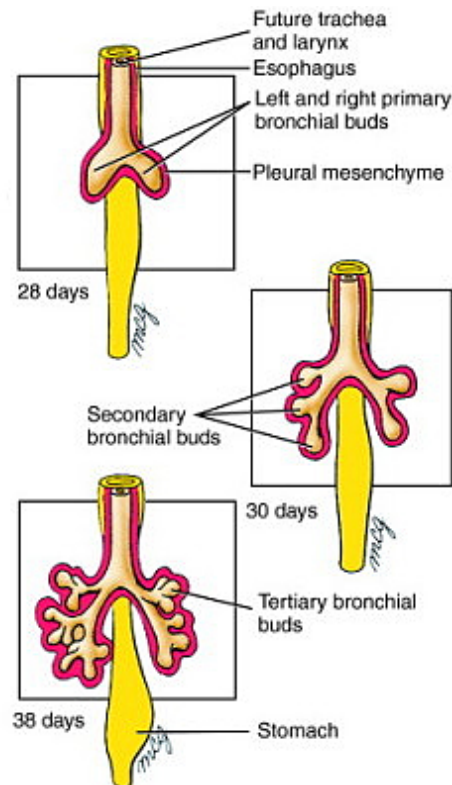
Diaphragm development



Formation of the diaphragm. The definitive diaphragm is a composite structure including elements of the septum transversum, pleuroperitoneal membranes, and esophageal mesenchyme, as well as a rim of body wall mesoderm

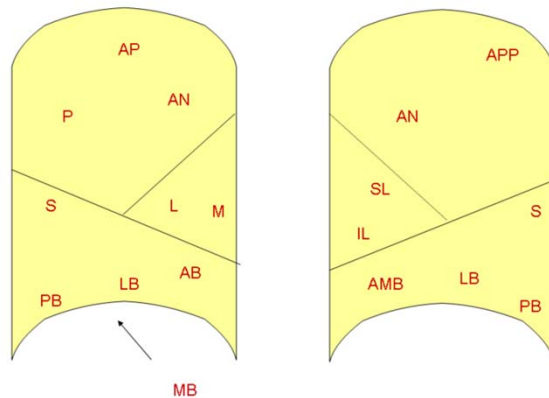
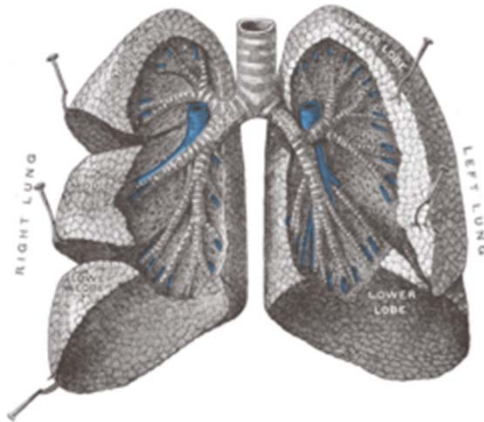
Stages of lung development – embryonic 4-6 weeks

Respiratory diverticulum arises as a ventral outpouching of foregut endoderm and undergoes three initial rounds of branching, producing the primordia successively of the two lungs, the lung lobes, and the bronchopulmonary segments; the stem of the diverticulum forms the trachea and larynx. By the 6th week, secondary bronchial buds branch into tertiary bronchial buds (usually about 10 on each side) to form the **bronchopulmonary segments**.



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Bronchopulmonary segments



Left lung

A PALM Seed Makes Another Little Palm

- superior lobe
 - apical
 - posterior
 - anterior
- middle lobe
 - lateral
 - medial
- inferior lobe
 - superior
 - medial-basal
 - anterior-basal
 - lateral-basal
 - posterior-basal

Left lung

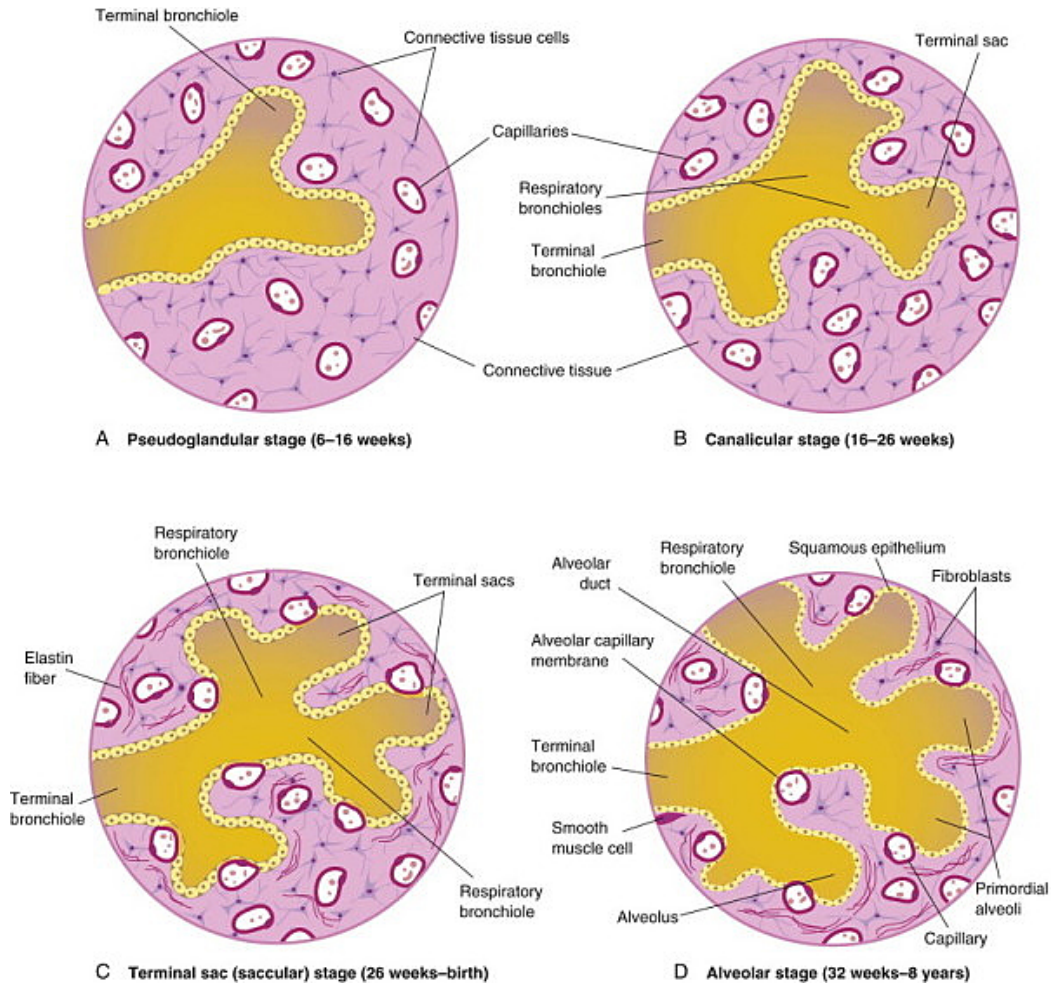
ASIA ALPS

Apoptotic Antlions Stop In, Suddenly Amalgamating Laboratory Posts

AP And Supine alignment Increases Limited Studies And Makes Baseline Pulmonary Bases Look Bad (a radiology mnemonic)

- superior lobe
 - apico-posterior (merger of "apical" and "posterior")
 - anterior
- lingula of superior lobe
 - inferior lingular
 - superior lingular
- inferior lobe
 - superior
 - anteromedial basal (merger of "anterior basal" and "medial basal")
 - posterior basal
 - lateral basal

Stages of lung development – pseudoglandular, canalicular, terminal sac (saccular) and alveolar.

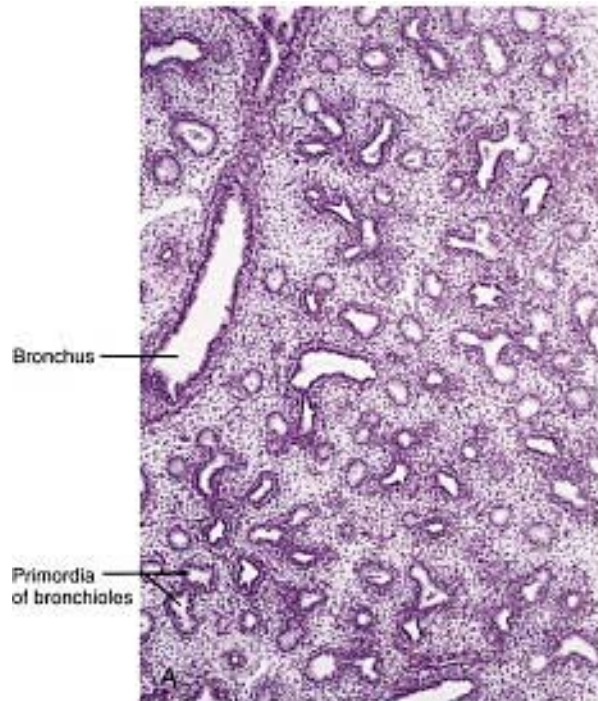


From Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.

Stages of lung development – pseudoglandular week 6-16

After the embryonic stage, the tree undergoes 14 more branchings, resulting in the formation of **terminal bronchioles**. The developing lungs histologically somewhat resemble exocrine glands during this stage. By 16 weeks, all major elements of the lung have formed, except those involved with gas exchange.

Fetuses born during this period are unable to survive.



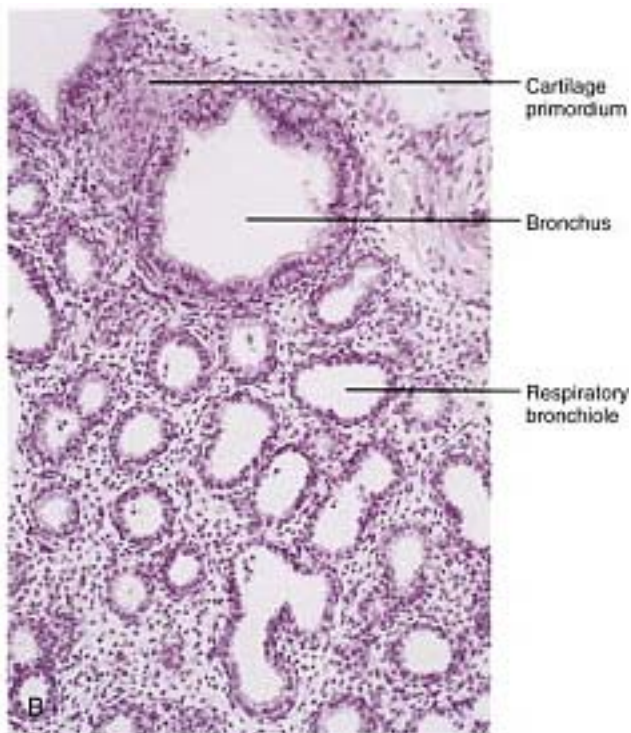
The terminal bronchioles from the end of the **conducting zone** of the respiratory system – made up of nose, pharynx, larynx, trachea, bronchi, bronchioles and terminal bronchioles. The function of the conducting zone is to filter, warm and moisten air

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Stages of lung development – canalicular week 16-24

This period overlaps the pseudoglandular stage because cranial segments of the lungs mature faster than caudal ones. During the canalicular stage, the lumina of the bronchi and **terminal bronchioles** become larger and the lung tissue becomes highly vascular. By 24 weeks, each terminal bronchiole has given rise to two or more **respiratory bronchioles**, each of which then divides into three to six passages—**primordial alveolar ducts**.

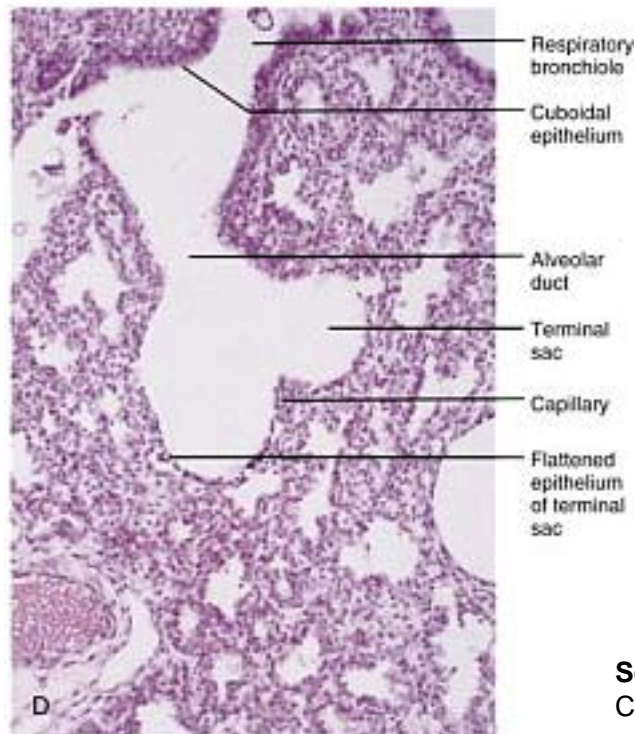
Respiration is possible at the end of the canalicular stage because some thin-walled **terminal sacs** (primordial alveoli) have developed at the ends of the respiratory bronchioles, and *the lung tissue is well vascularized*. Although a fetus born toward the end of this period may survive if given intensive care, it often dies because its respiratory and other systems are still relatively immature.



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Stages of lung development – Terminal sac (saccular) week 28-36

- Respiratory bronchioles subdivide to produce **terminal sacs** (primitive alveoli). Terminal sacs continue to be produced until well into childhood.
- Capillaries begin to bulge into the terminal sacs
- The intimate contact between epithelial and endothelial cells establishes the **blood–air barrier**
- *Surfactant production begins at 20 to 22 weeks*, but it is present in only small amounts in premature infants

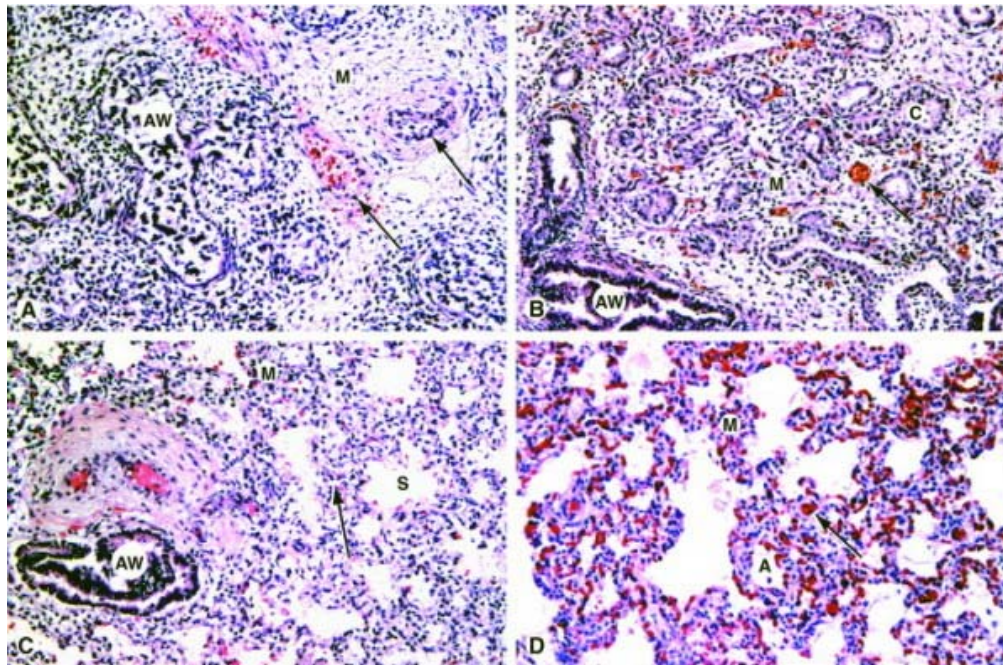


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Stages of lung development – Alveolar week 36-8 yrs

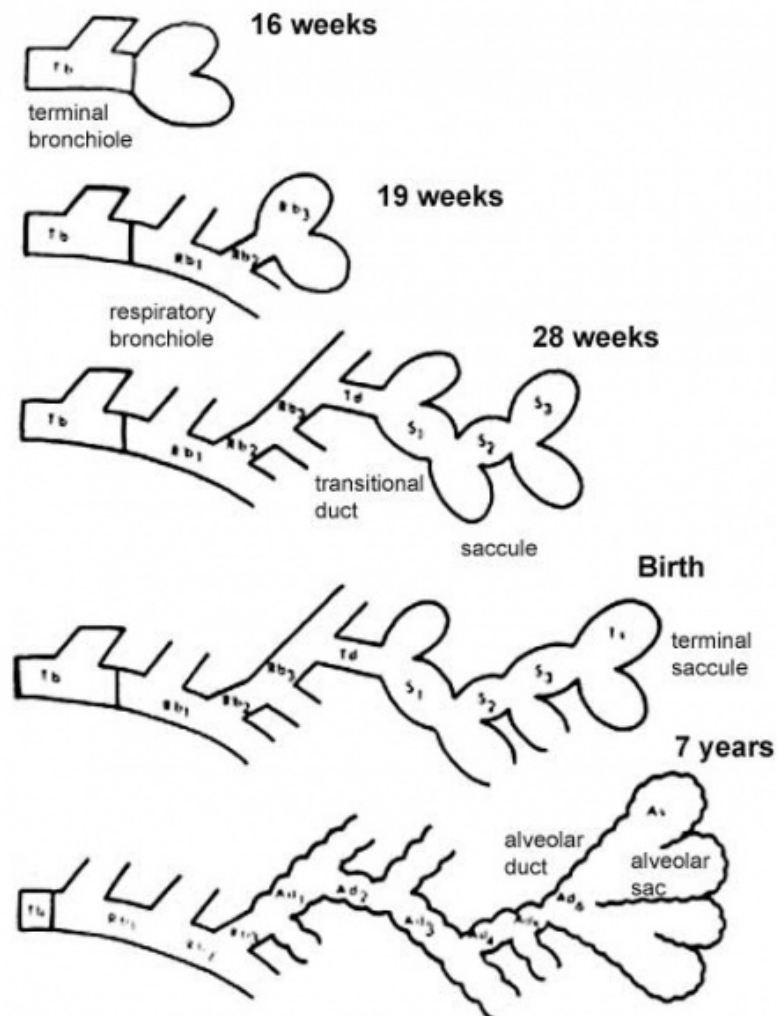
Exactly when the terminal sac stage ends and the alveolar stage begins depends on the definition of the term **alveolus**. Sacs analogous to alveoli are present at 32 weeks. The epithelial lining of the terminal sacs attenuates to a thin squamous epithelial layer. The type I pneumocytes become so thin that the adjacent capillaries bulge into the alveolar sacs

By the late fetal period, the lungs are capable of respiration because the **alveolocapillary membrane** (pulmonary diffusion barrier or respiratory membrane) is sufficiently thin to allow gas exchange.



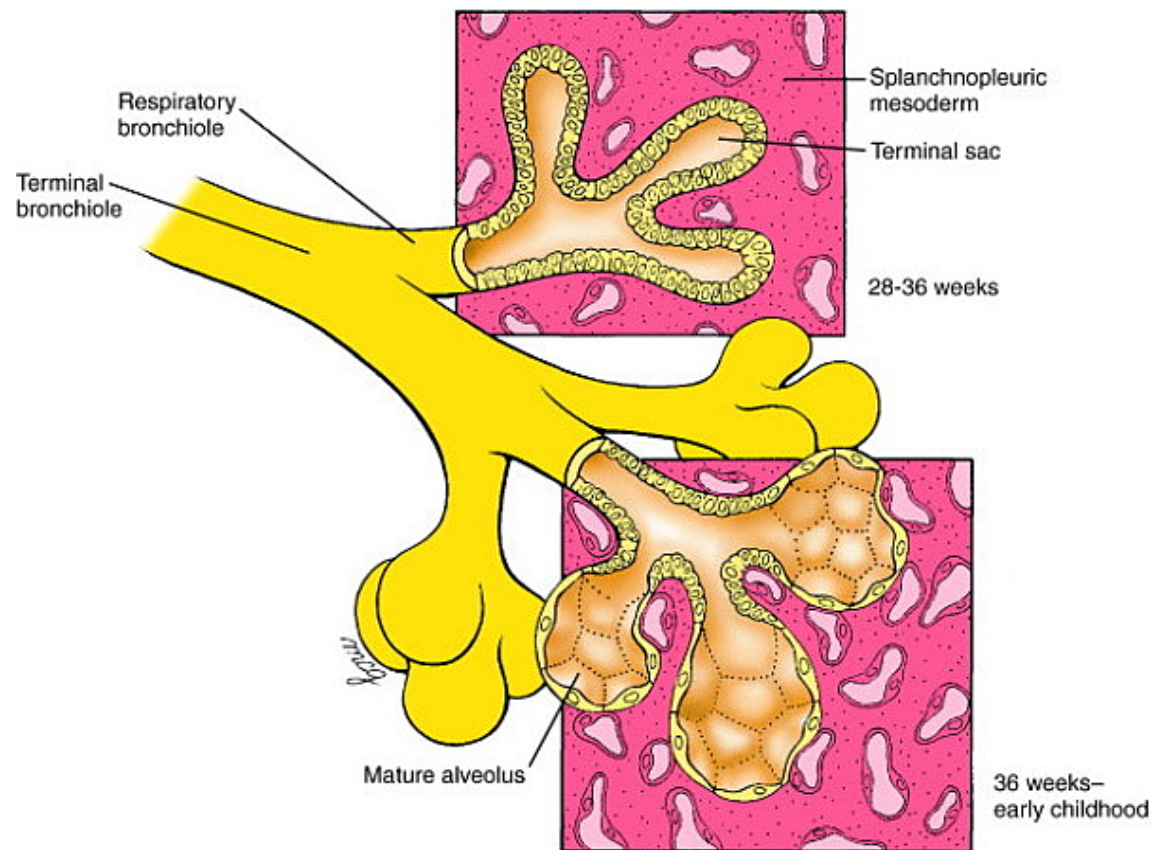
From Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.

The stages track the development of the respiratory tree

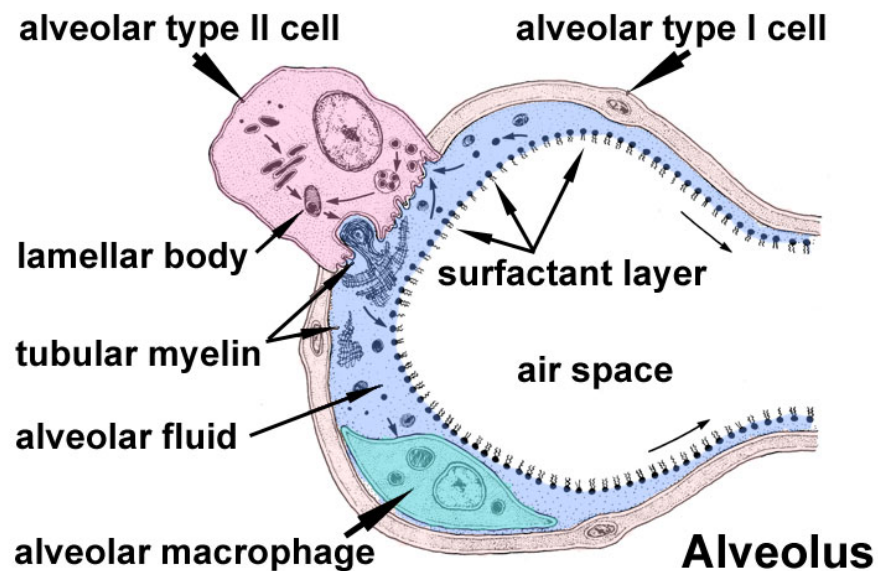


Modified from Dilly SA. Thorax. 1984 Oct;39(10):733-42. PMID: 6495241

Maturation of lung tissue. Terminal sacs (primitive alveoli) begin to form between weeks 28 and 36 and begin to mature between 36 weeks and birth. However, only 5% to 20% of all terminal sacs eventually produced are formed before birth



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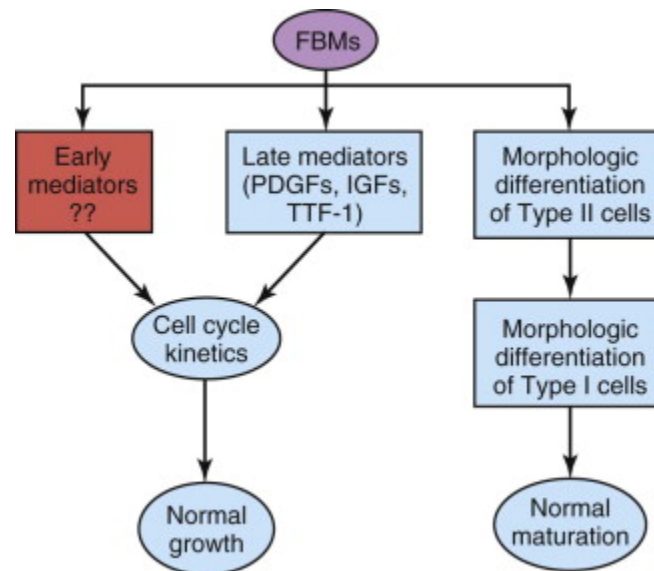
Alveolar Type I cell - (squamous alveolar) cells form the structure of an alveolar wall.

Alveolar Type II cell - (great alveolar) cells secrete pulmonary surfactant.

- surfactant is continuously released by exocytosis
- lowers the surface tension of water and allows the membrane to separate
- increases the capability to exchange gases.

Macrophages - destroy foreign material and debris.

Fetal breathing movements involving aspiration of amniotic fluid into the lungs seem to be important for the control of cell cycle kinetics



Fluid in the lungs is cleared at birth by:

- Through the mouth and nose through pressure from vaginal delivery
- Clearance through the blood vessels
- Clearance through lymphatic drainage

Molecular and cellular control of lung development

Organ culture

Lung primordia can be studied in short-term organ culture systems. These experiments have shown that branching morphogenesis is controlled by interactions with the surrounding mesenchyme. If lung mesenchyme is replaced by mesenchyme around the trachea, branching is inhibited.

Genetic manipulation of animal models

Knockout and transgenic mouse experiments have shown that several growth factors are essential for branching morphogenesis. Fibroblast growth factor 10 (Fgf10) is a crucial player and a knockout of the Thyroid transcription factor 1 (Ttf1) gene blocked formation of the thyroid and the lungs. Transgenic mice expressing mutant human forms of the cystic fibrosis gene (cAMP-stimulated chloride channel) have been made as a means to test human treatments.

Molecular analysis has shown a number of factors are important:

Retinoic acid

- Tgf β
- Bmps
- Shh
- Wnts
- Fgfs
- Epithelial growth factor (Egf)
- Pdgf
- Igf

Don't forget revision of lectures on Early vascular development and Placenta for tomorrow.