

# Lecture - Respiratory Development

## Contents

## Introduction

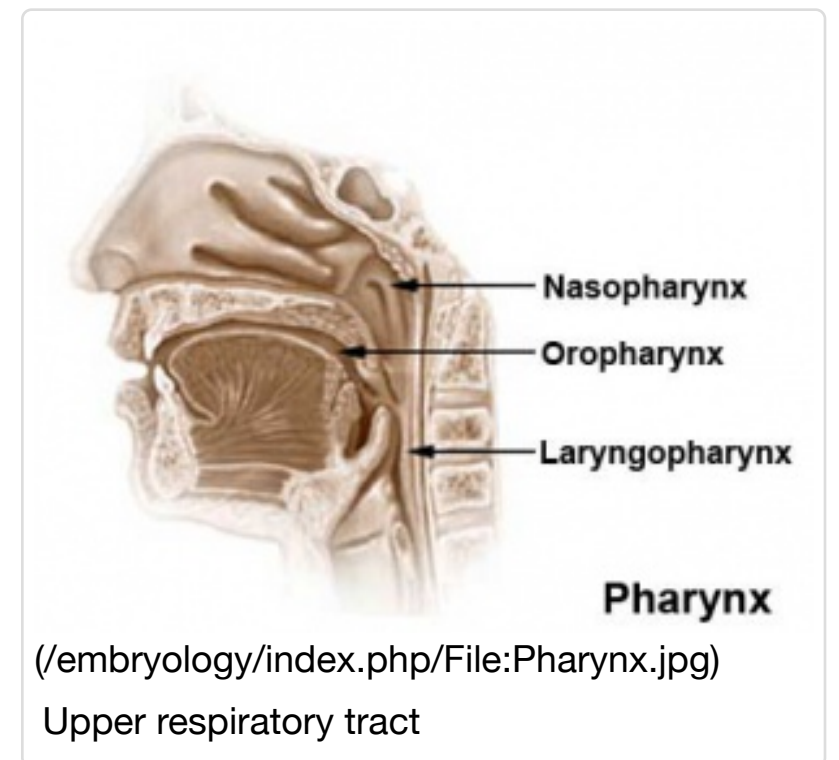
Current research suggests that both genetic and the developmental environment (fetal and postnatal) can influence the growth, differentiation and function of the respiratory system.

The respiratory system does not carry out its physiological function (of gas exchange) until after birth and is filled with liquid and not air until then. Note that most of the respiratory system consists of the conductive "pipes", with the actual functional exchange unit (the **alveolus**, plural alveoli) forming at the very end of this plumbing right at the end of development.

The respiratory tract is divided anatomically into 2 main parts:

1. **upper respiratory tract** - consisting of the nose, nasal cavity and the pharynx.
2. **lower respiratory tract** - consisting of the larynx, trachea, bronchi and the alveoli (respiratory functional unit).

The respiratory "system" usually includes descriptions of not only the functional development of the lungs, but also related musculoskeletal (diaphragm), vascular (pulmonary) and coelomic (pleural cavity) development.



## Lecture Objectives

- Understanding of embryonic lung development
- Understanding of the stages of lung development
- Understanding of diaphragm development
- Brief understanding of respiratory vascular development
- Brief understanding of respiratory abnormalities
- Brief understanding of molecular mechanisms

## Lecture Resources

[Movies\[Expand\]](#)

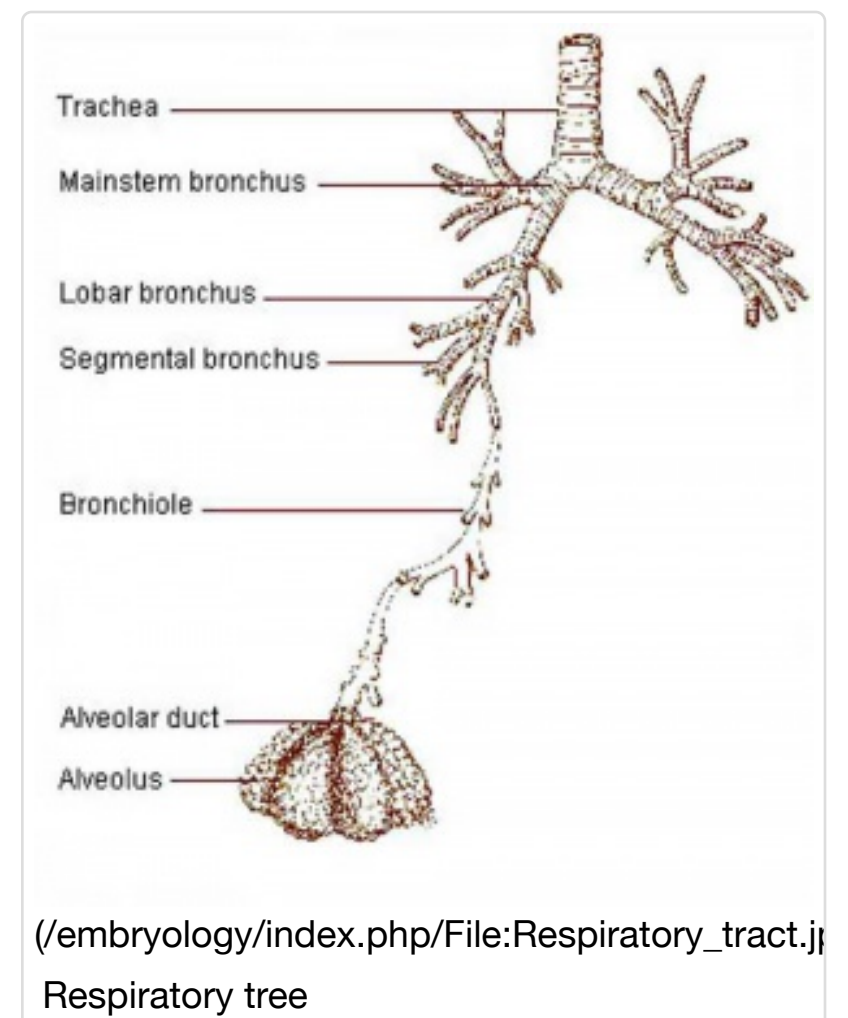
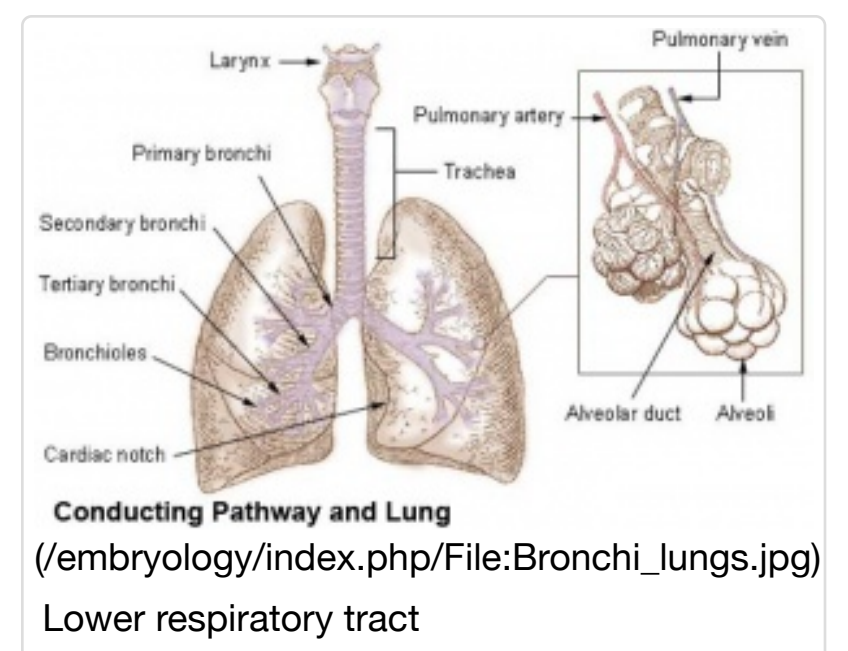
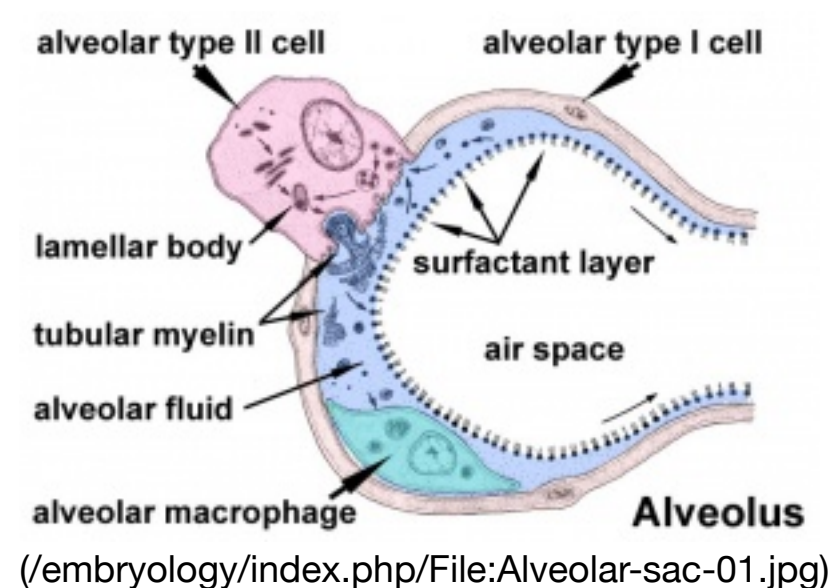
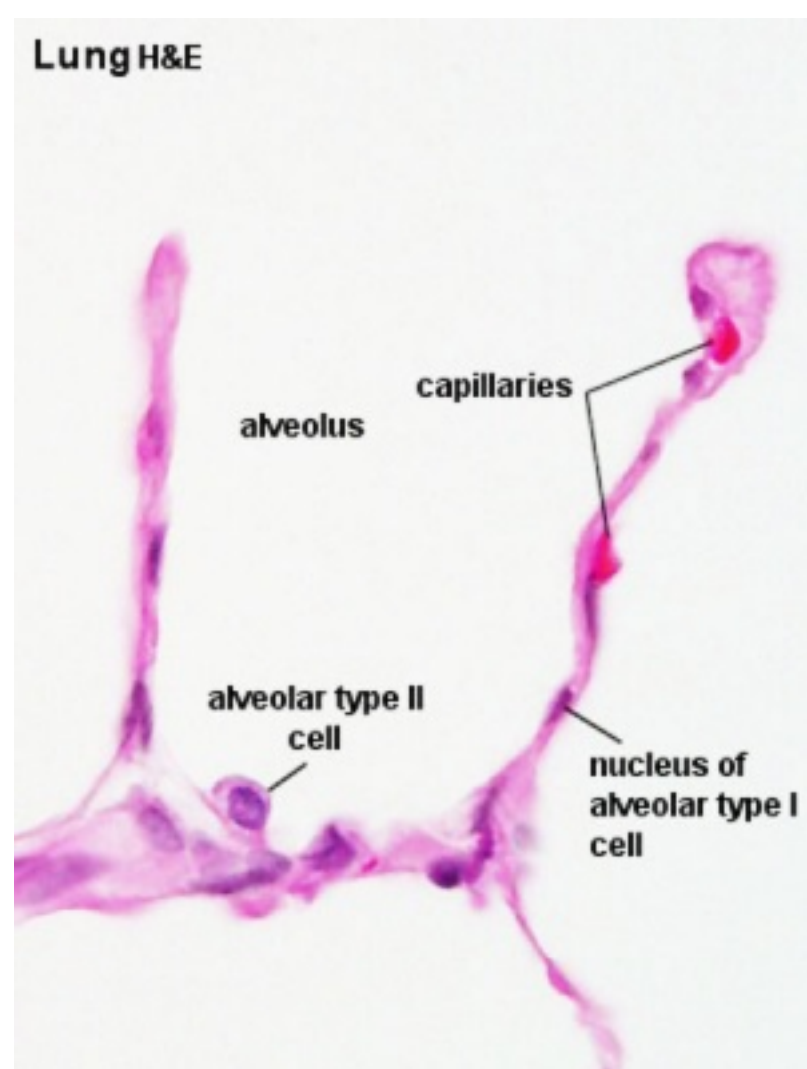
[References\[Expand\]](#)

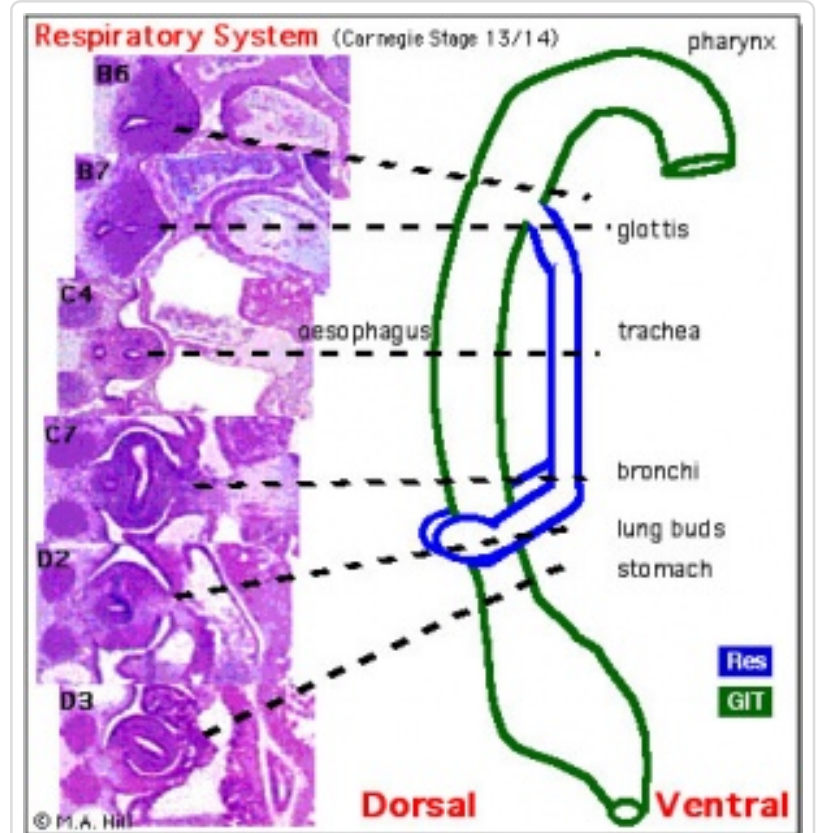
[Recent 2014 Review\[Expand\]](#)

## Respiratory Functional Unit

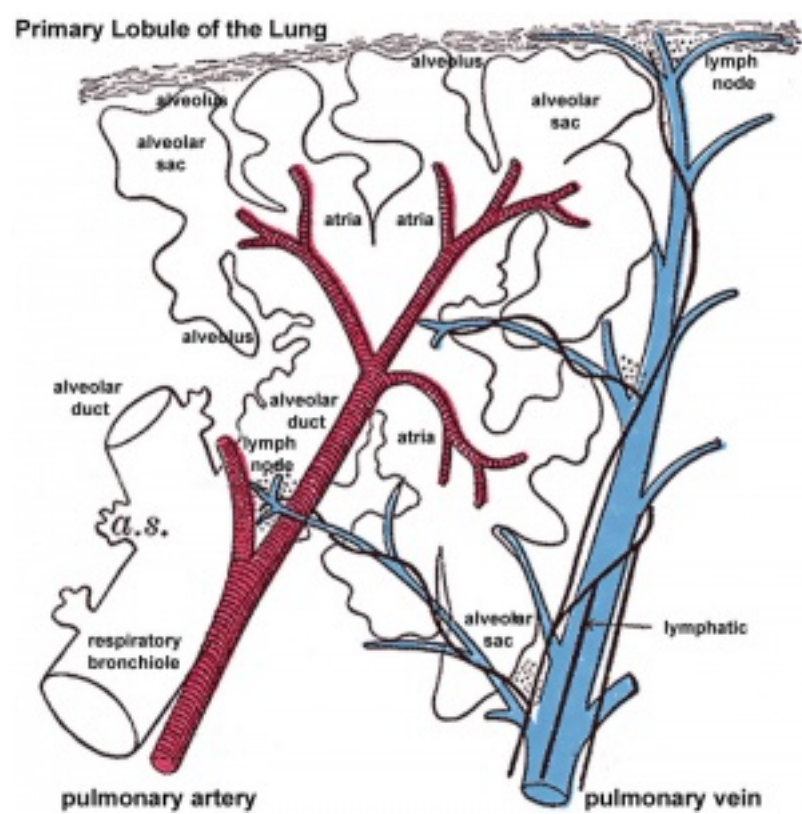
### Alveolus

**Alveolus** (Latin *alveolus* = "little cavity", plural is alveoli)





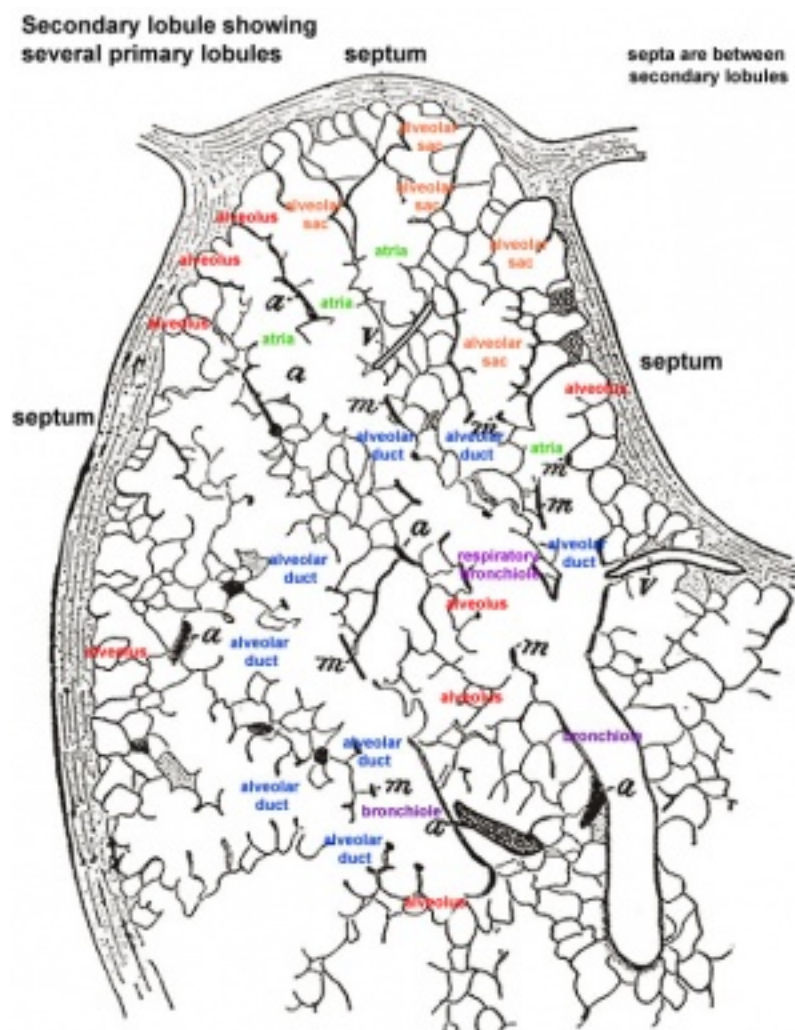
(/embryology/index.php/File:Stage14\_respirator  
Respiratory tract (Week 5)



(/embryology/index.php/File:Lung\_primary\_lobule\_01.jpg)

### Primary Lobule

- region supplied by a respiratory bronchiole



(/embryology/index.php/File:Lung\_secondary\_lobule\_01.jpg)

### Secondary Lobule

- region supplied by a terminal bronchiole
- size - up to 2.5 cm across.
- connective tissue - bounded by fibrous (interlobular) septa and containing internal (interlobular) septa.
- lobule contains a up to 12 acini and 30 - 50 primary lobules (/embryology/index.php/File:Lung\_primary\_lobule\_01.jpg).
- blood supply - pulmonary artery branch
- blood drainage - pulmonary veins located at lobule periphery leave through the interlobular septa.
- lymphatics - arterial and interlobular septa associated (drain to subpleural plexus).

## Developmental Overview

### Germ Layers

- Endoderm and splanchnic mesoderm form majority of conducting and alveoli.
- Ectoderm will contribute the neural innervation.
- Mesoderm also contributes the supporting musculoskeletal components.

**Week 4** - laryngotracheal groove forms on floor foregut.

**Week 5** - left and right lung buds push into the pericardioperitoneal canals (primordia of pleural cavity)

**Week 6** - descent of heart and lungs into thorax. Pleuroperitoneal foramen closes.

**Week 7** - enlargement of liver stops descent of heart and lungs.

**Month 3-6** - lungs appear glandular, end month 6 alveolar cells type 2 appear and begin to secrete surfactant.

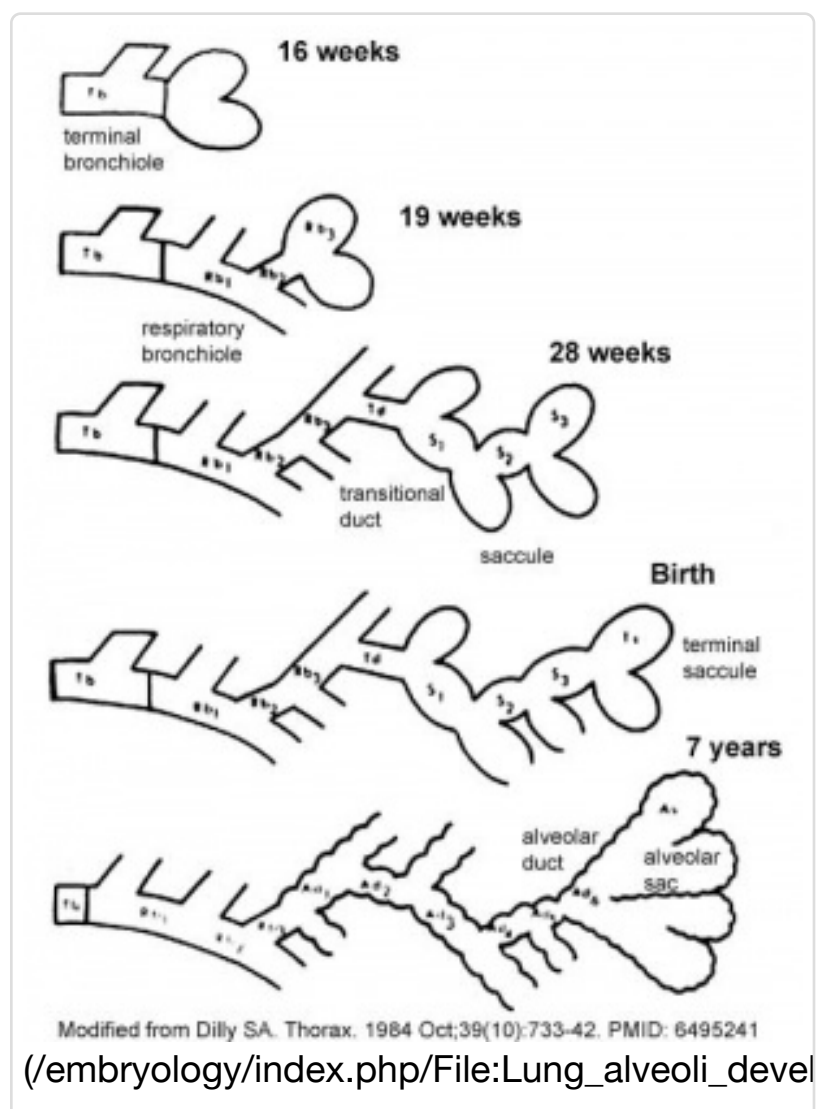
**Month 7** - respiratory bronchioles proliferate and end in alveolar ducts and sacs.

## Development Stages

Note - the sequence is important rather than the actual timing, which is variable in the existing literature.

### Human Lung Stages

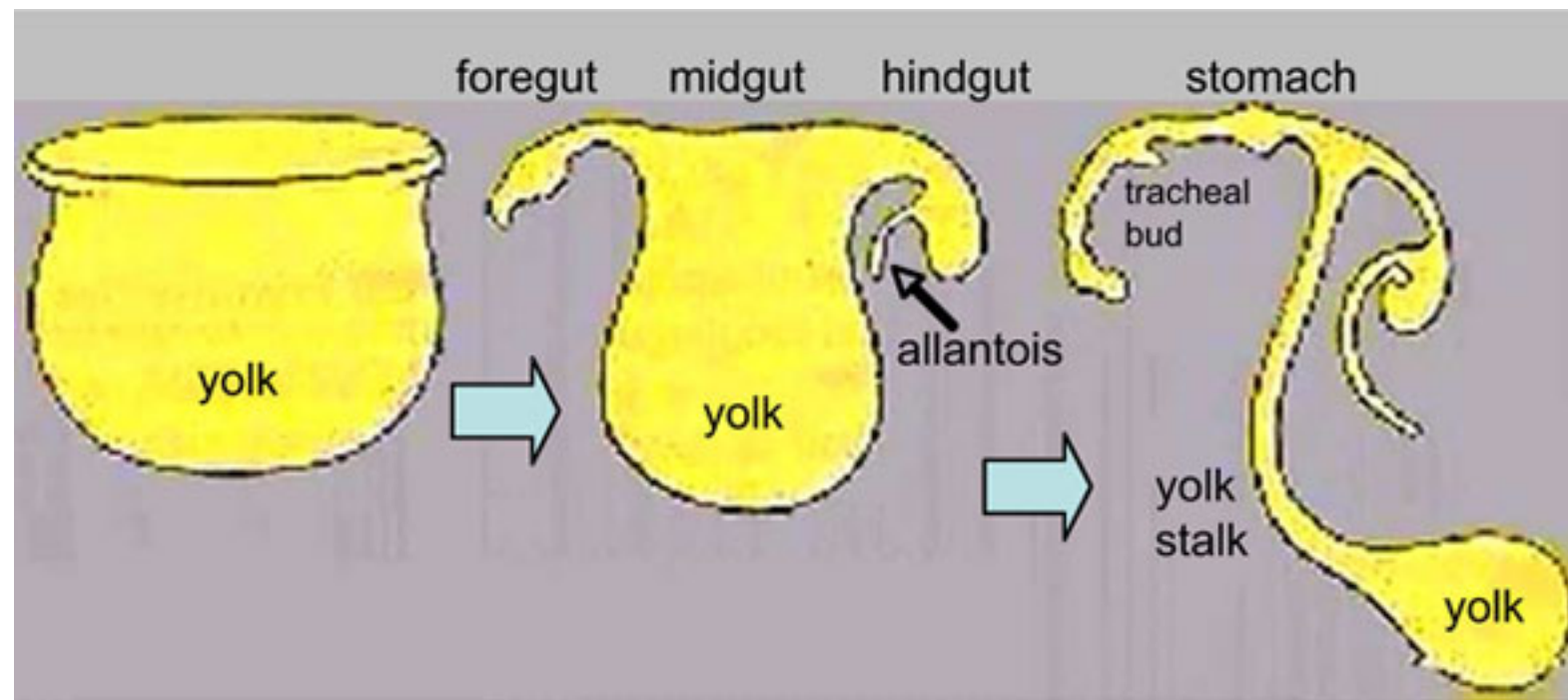
Stage	Human	Features
Embryonic	week 4 to 5	lung buds originate as an outgrowth from the ventral wall of the foregut where lobar division occurs



Modified from Dilly SA. Thorax. 1984 Oct;39(10):733-42. PMID: 6495241  
(/embryology/index.php/File:Lung\_alveoli\_devel

Pseudoglandular	week 5 to 17	conducting epithelial tubes surrounded by thick mesenchyme are formed, extensive airway branching
Canalicular	week 16 to 25	bronchioles are produced, increasing number of capillaries in close contact with cuboidal epithelium and the beginning of alveolar epithelium development
Saccular	week 24 to 40	alveolar ducts and air sacs are developed
Alveolar	late fetal to 8 years	secondary septation occurs, marked increase of the number and size of capillaries and alveoli

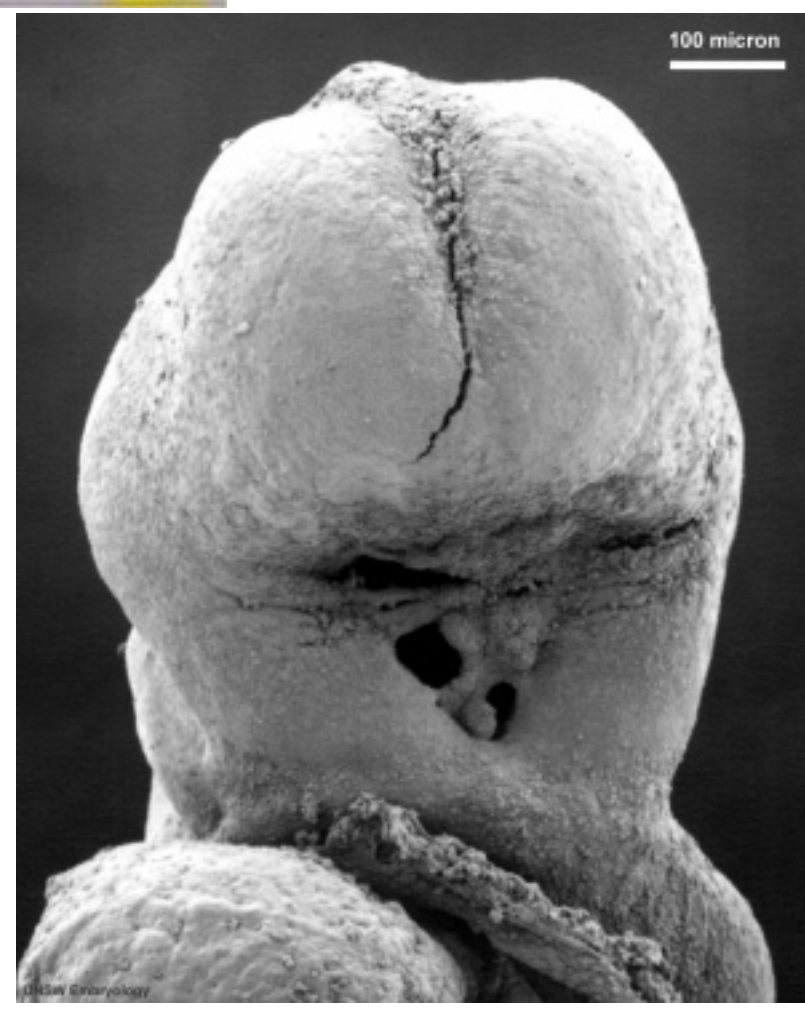
## Embryonic



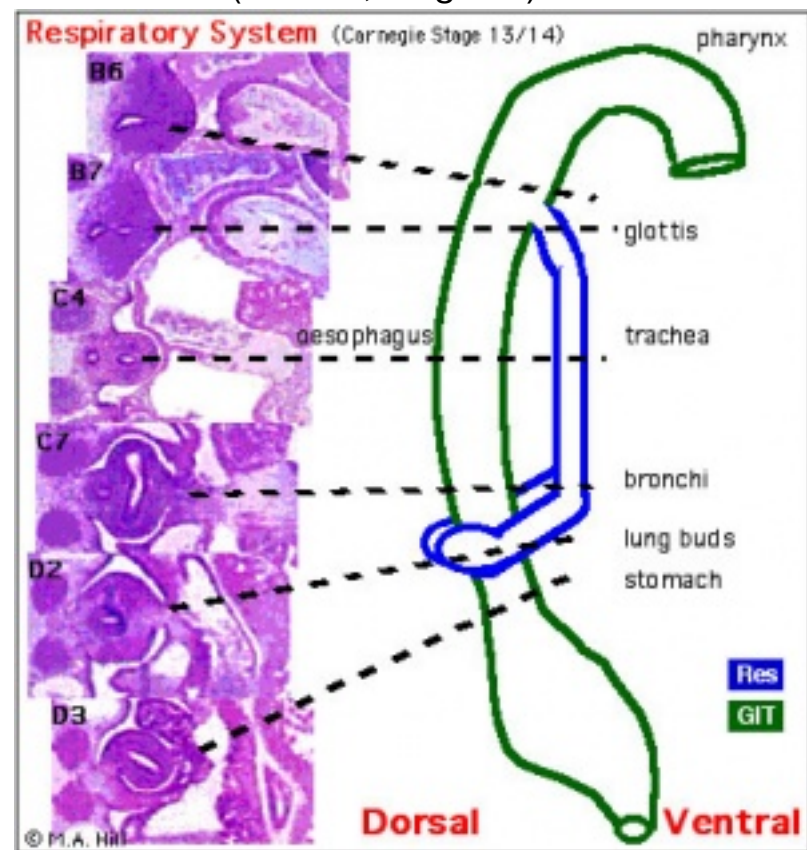
(/embryology/index.php/Endoderm\_Development\_Movie)



(/embryology/index.php/File:Stage11\_bf9.jpg)  
Stomodeum (Week 4, stage 11)



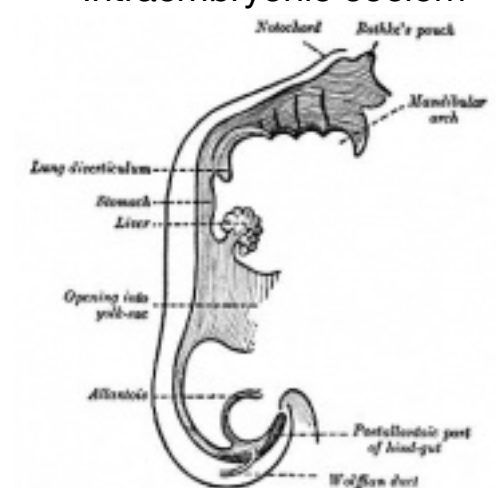
(/embryology/index.php/File:Stage11\_sem4.jpg)  
Buccopharyngeal membrane (Week 4, stage 11)



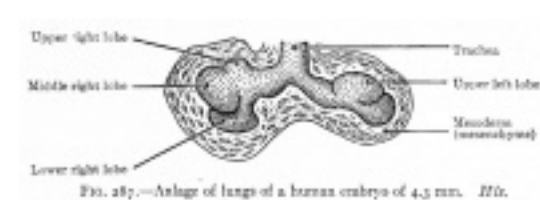
(/embryology/index.php/File:Stage14\_respiratory\_tract.jpg)

(Week 5, stage 14)

- week 4 - 5
- Endoderm - tubular ventral growth from foregut pharynx.
- Mesoderm - mesenchyme of lung buds.
- Intraembryonic coelom - pleural cavities elongated spaces connecting pericardial and peritoneal spaces.



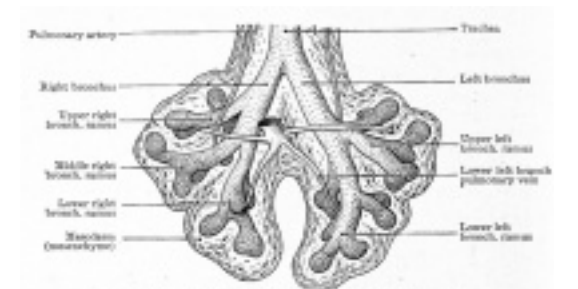
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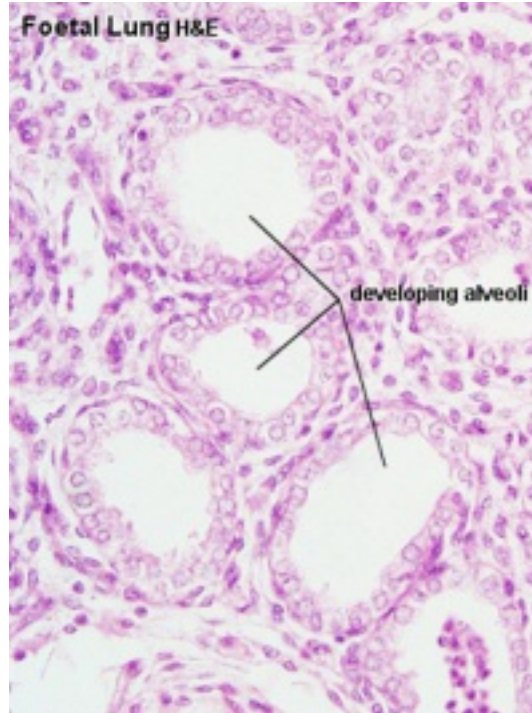
## Molecular - Branching

fibroblast growth factor 10 (FGF10) (/embryology/index.php/Developmental\_Signals\_-\_Fibroblast\_Growth\_Factor) and sonic hedgehog (SHH) (/embryology/index.php/Developmental\_Signals\_-\_Sonic\_hedgehog) form a feedback loop

- FGF10 produced in the mesenchyme signals to the distal epithelium to up regulate SHH expression.
- SHH then feeds back to inhibit Fgf10 expression in the adjacent mesenchyme, dividing in two the Fgf10 expression domain.
- new FGF10 signaling domains serve as two chemoattractant sources, leading to bifurcation of the epithelial tip.

## Pseudoglandular stage

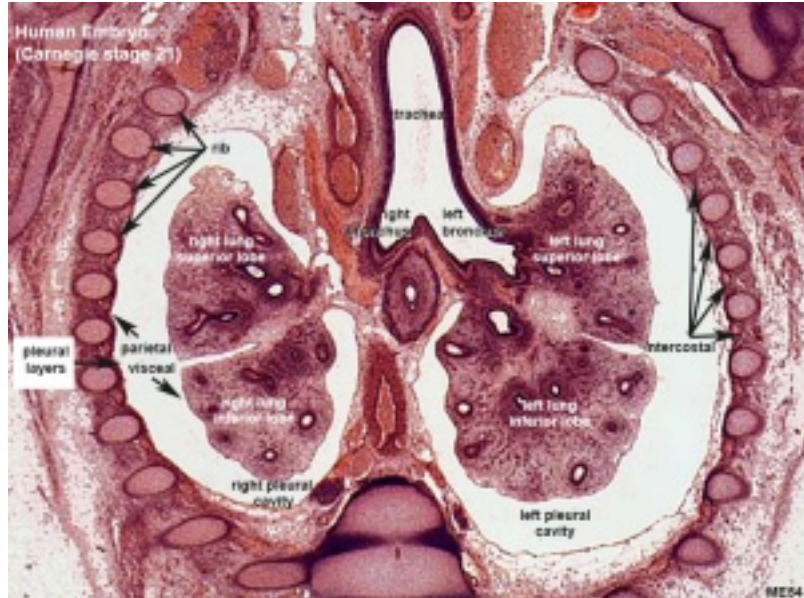
- **week 5 - 17**
- tubular branching of the human lung airways continues
- by 2 months all segmental bronchi are present.
- lungs have appearance of a glandlike structure.
- stage is critical for the formation of all conducting airways.
  - lined with **tall columnar epithelium**
  - more distal structures are lined with **cuboidal epithelium**.



(/embryology/index.php/File:Fetal\_lung\_histology.jpg)

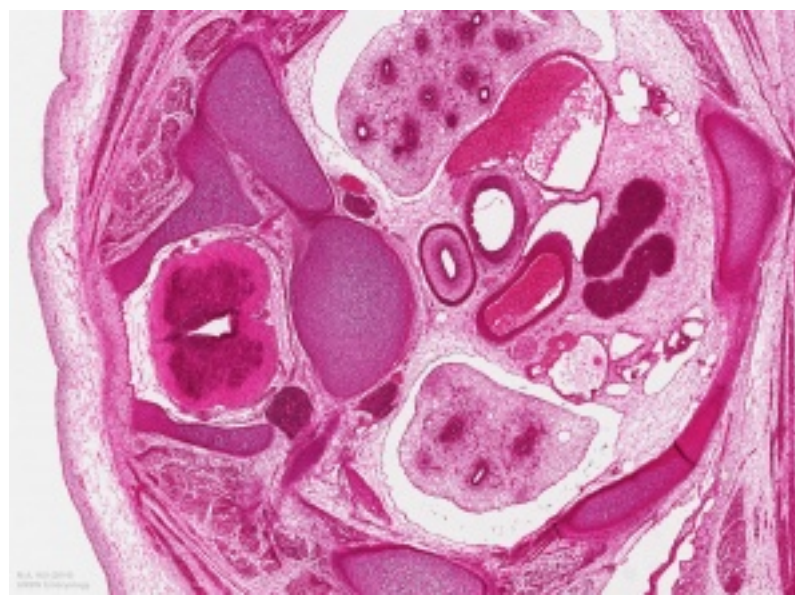
Fetal lung histology

## Embryo (week 8)



(/embryology/index.php/File:ME54\_003.jpg)

Carnegie stage 21 (/embryology/index.php/Carnegie\_stage\_21) coronal



(/embryology/index.php/File:Stage\_22\_image\_200.jpg)

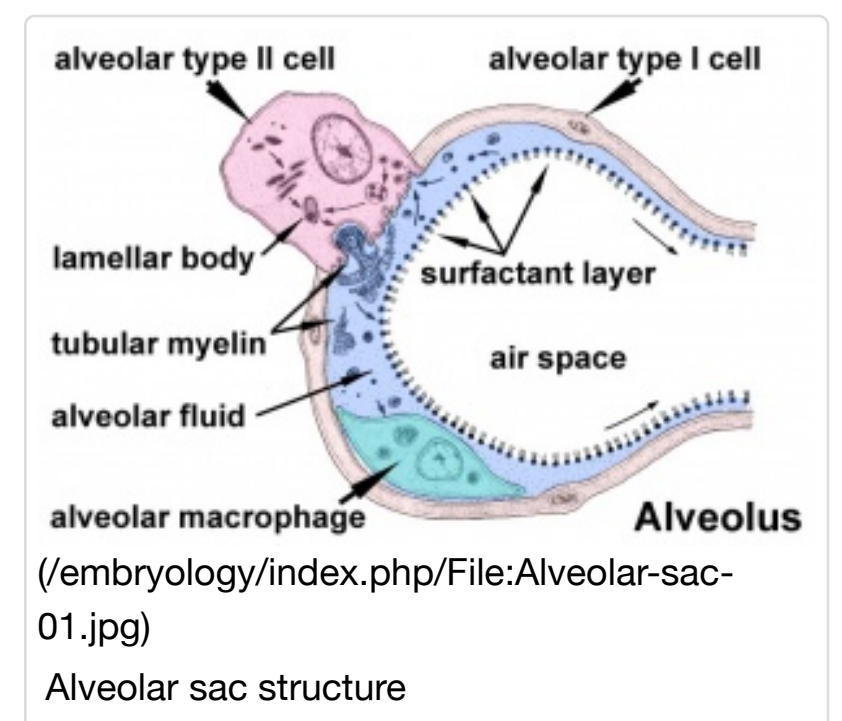
Carnegie stage 22 (/embryology/index.php/Carnegie\_stage\_22) transverse

## Canalicular stage

- **week 16 - 24** lung morphology changes dramatically
- 3+ orders of branching forms canaliculi.
- differentiation of the pulmonary epithelium results in the formation of the future air-blood tissue barrier.
- capillaries organise around airspaces and contact with the overlying cuboidal epithelium.
- **Surfactant** synthesis and the canalization of the lung parenchyma by capillaries begin.
- future gas exchange regions can be distinguished from the future conducting airways of the lungs.
- air-blood barrier development starts peripherally but not does not involve the terminal segment ( required for further growth and branching).

## Saccular stage

- **week 24 to near term.**
- most peripheral airways form widened "airspaces", termed **saccules**.
- saccules widen and lengthen the airspace (by the addition of new generations).
- future gas exchange region expands significantly.
- Fibroblastic cells also undergo differentiation, they produce extracellular matrix, collagen, and elastin.
  - May have a role in epithelial differentiation and control of **surfactant secretion**.
- Alveolar Cells Type II (Type II pneumocytes)
  - begin to secrete **surfactant**, levels of secretion gradually increase to term.
  - allows alveoli to remain inflated
- Vascular tree - also grows in length and diameter during this time.

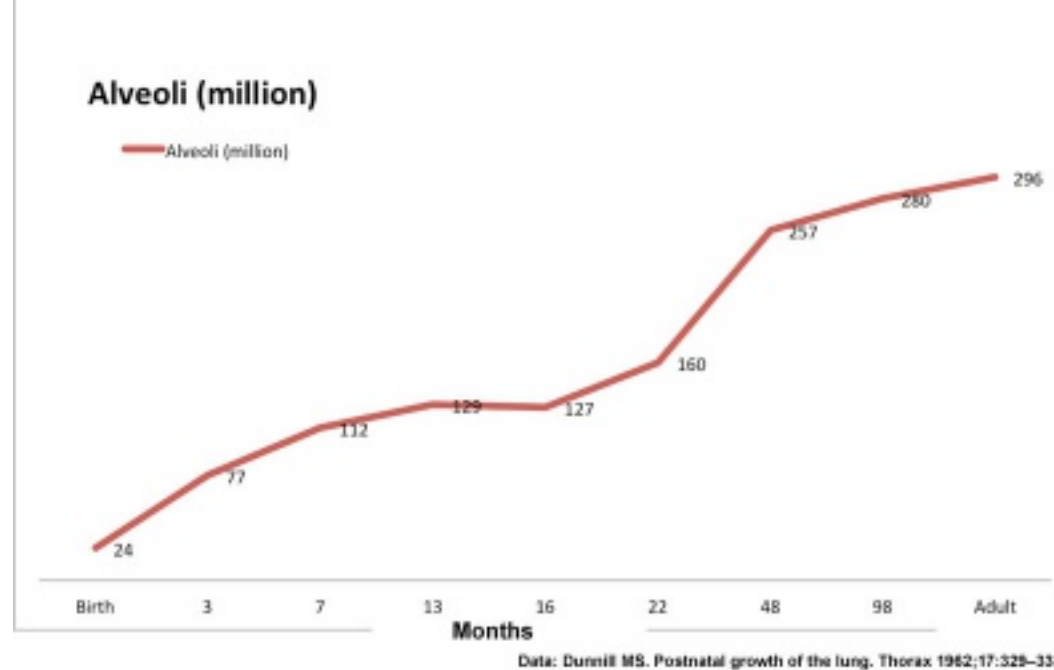


(/embryology/index.php/File:Alveolar-sac-01.jpg)

Alveolar sac structure

## Alveolar stage

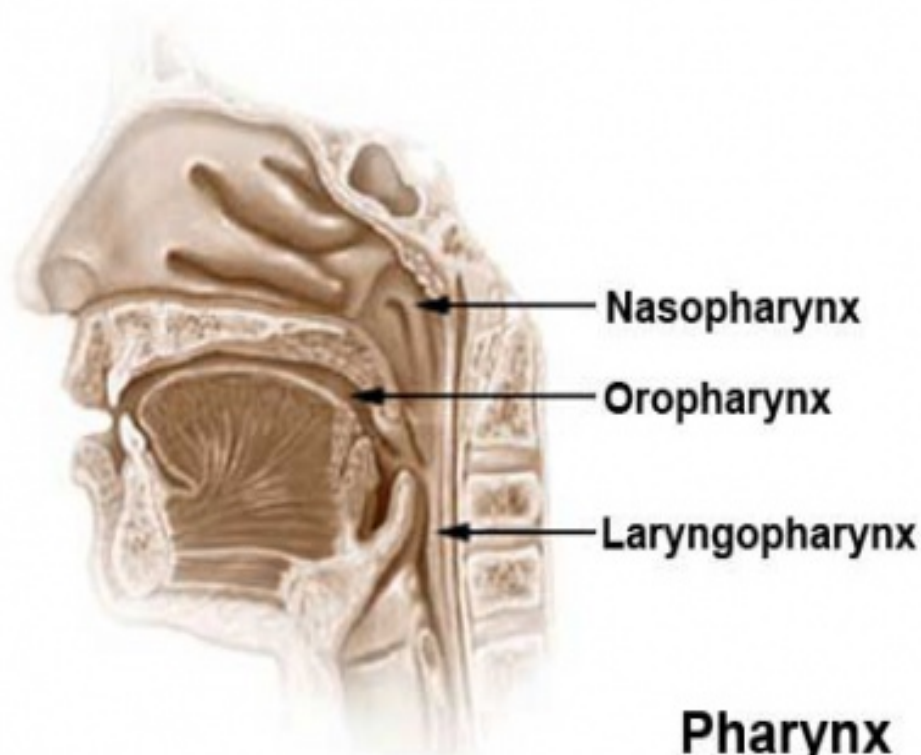
- late fetal to 8 years.
- The postnatal lung, with **alveoli** forming.
- Expansion of gas exchange alveoli, vascular beds (capillaries), lymphatics and innervation.



(/embryology/index.php/File:Postnatal\_alveoli\_number.jpg)

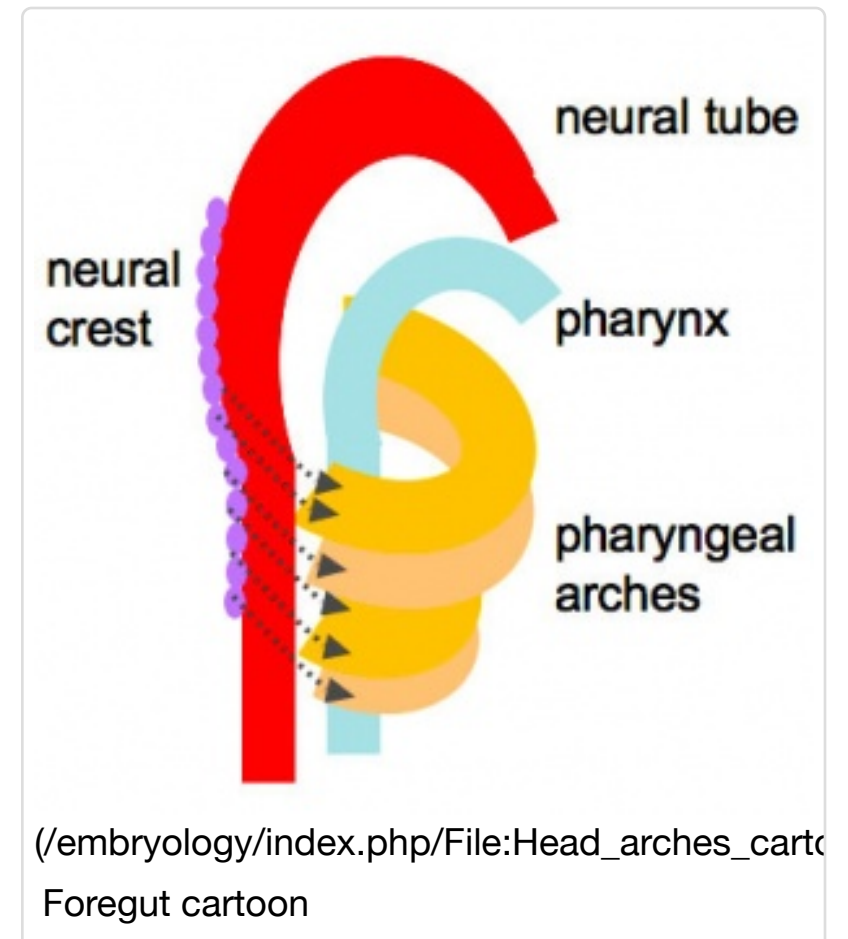
## Upper Respiratory Tract

**Foregut Development** - from the oral cavity the next portion of the foregut is initially a single gastrointestinal (oesophagus) and respiratory (trachea) common tube, the pharynx which lies behind the heart. Note that the respiratory tract will form from a ventral bud arising at this level.



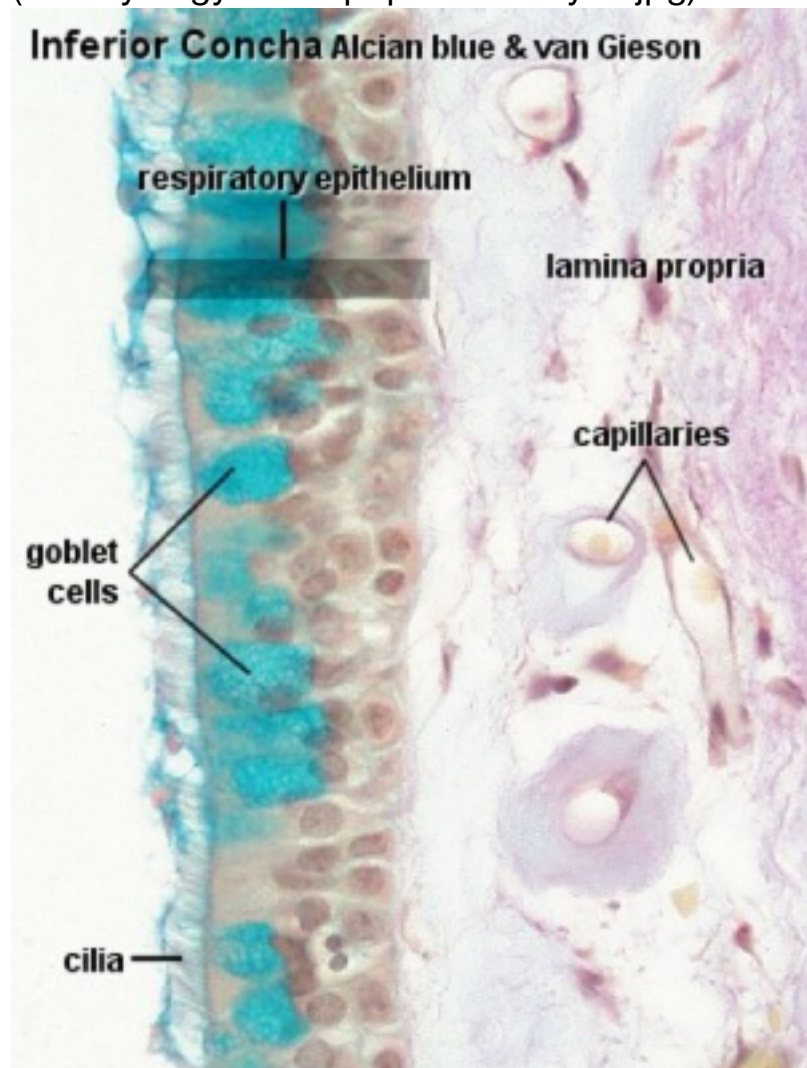
### Pharynx

- part of **foregut** development (Oral cavity, Pharynx (esophagus, trachea), Respiratory tract, Stomach)
- anatomically the nose, nasal cavity and the pharynx
- **pharynx** forms a major arched cavity within the pharyngeal arches (**MH** - pharyngeal arches will be described in head development lecture).
- **palate** - development for mammals, allows breathing while feeding.



(/embryology/index.php/File:Head\_arches\_cartoon)  
Foregut cartoon

(/embryology/index.php/File:Pharynx.jpg)

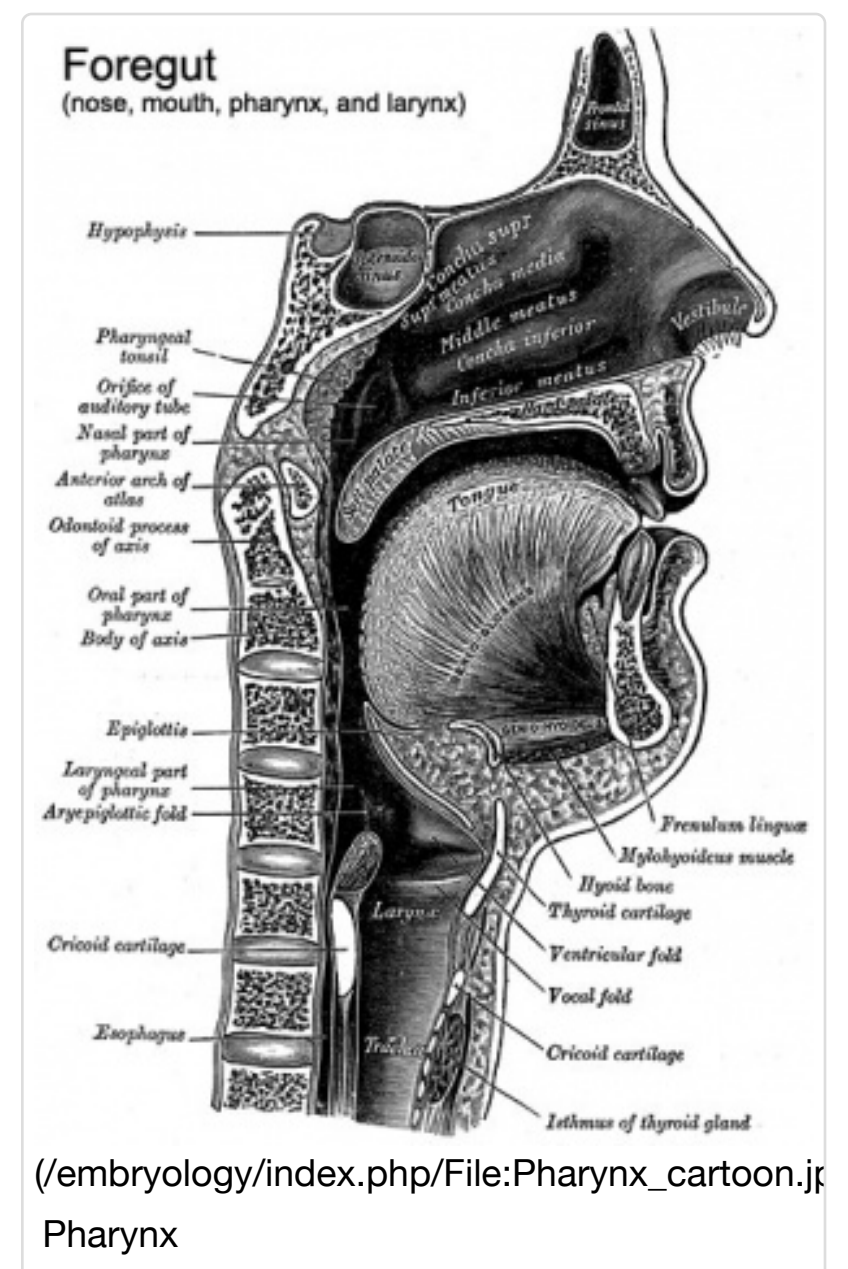


### Respiratory epithelium

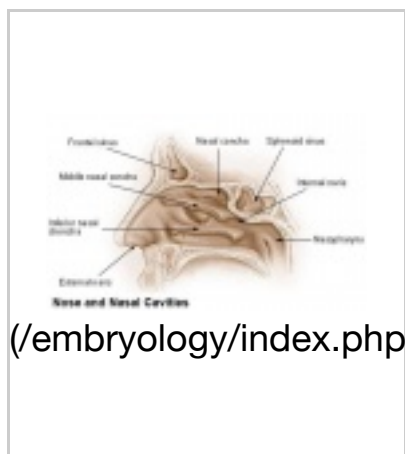
- pseudo-stratified
- ciliated cells
- goblet cells
- basal cells

Note - Specialised **olfactory epithelium** for smell, a small region located in roof of nasal cavity.

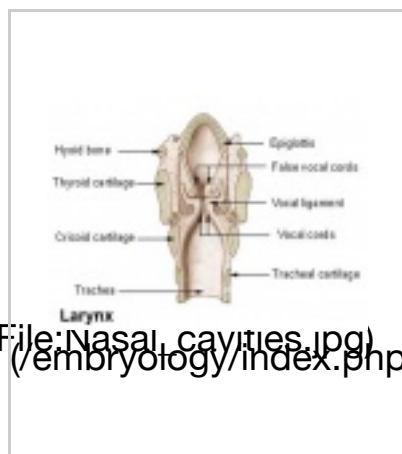
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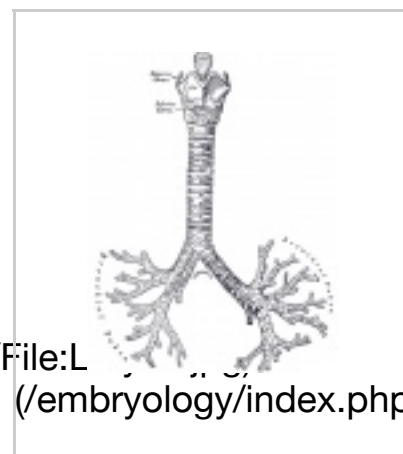
(/embryology/index.php/File:Pharynx\_cartoon.jpg)  
Pharynx



Nasal cavities



Larynx



Adult upper respiratory tract conducting system

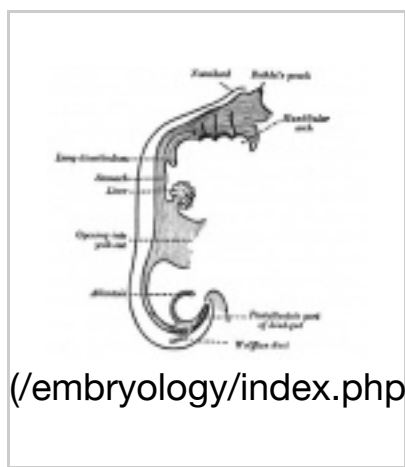
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(/embryology/index.php/File:Larynx.jpg)

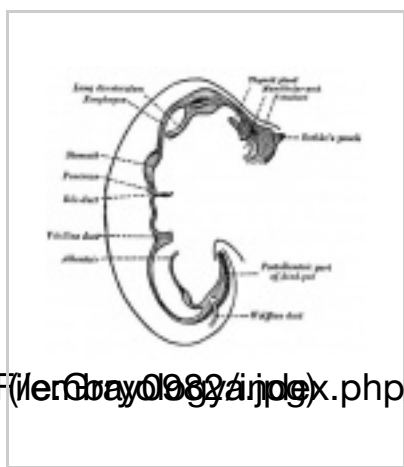
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**Additional Information - Histology[Expand]**

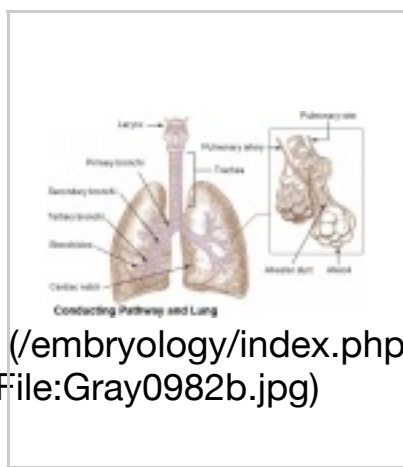
## Lower Respiratory Tract



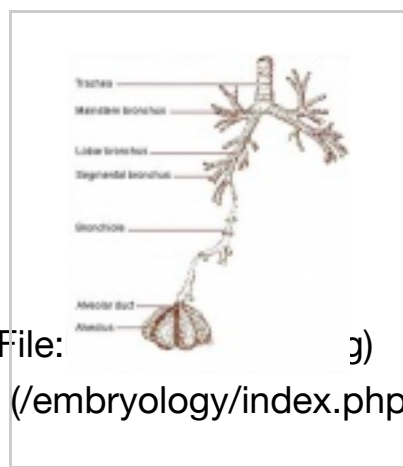
week 4 early respiratory endodermal bud



week 4 later ventral endoderm growth



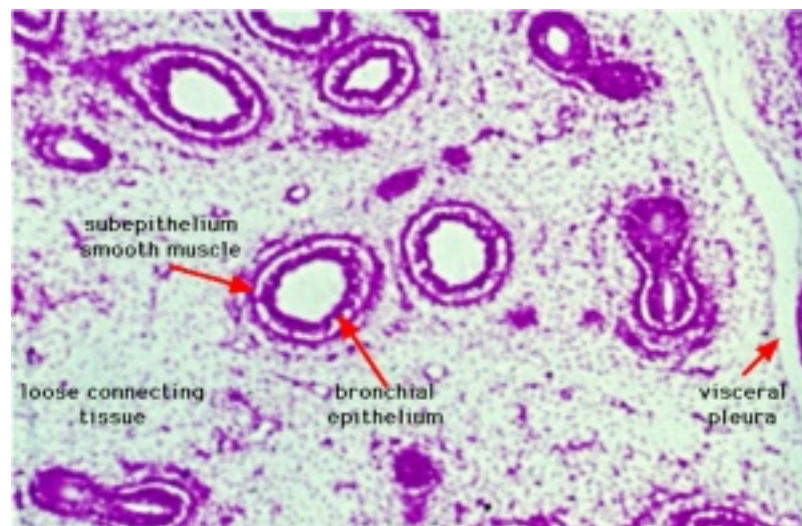
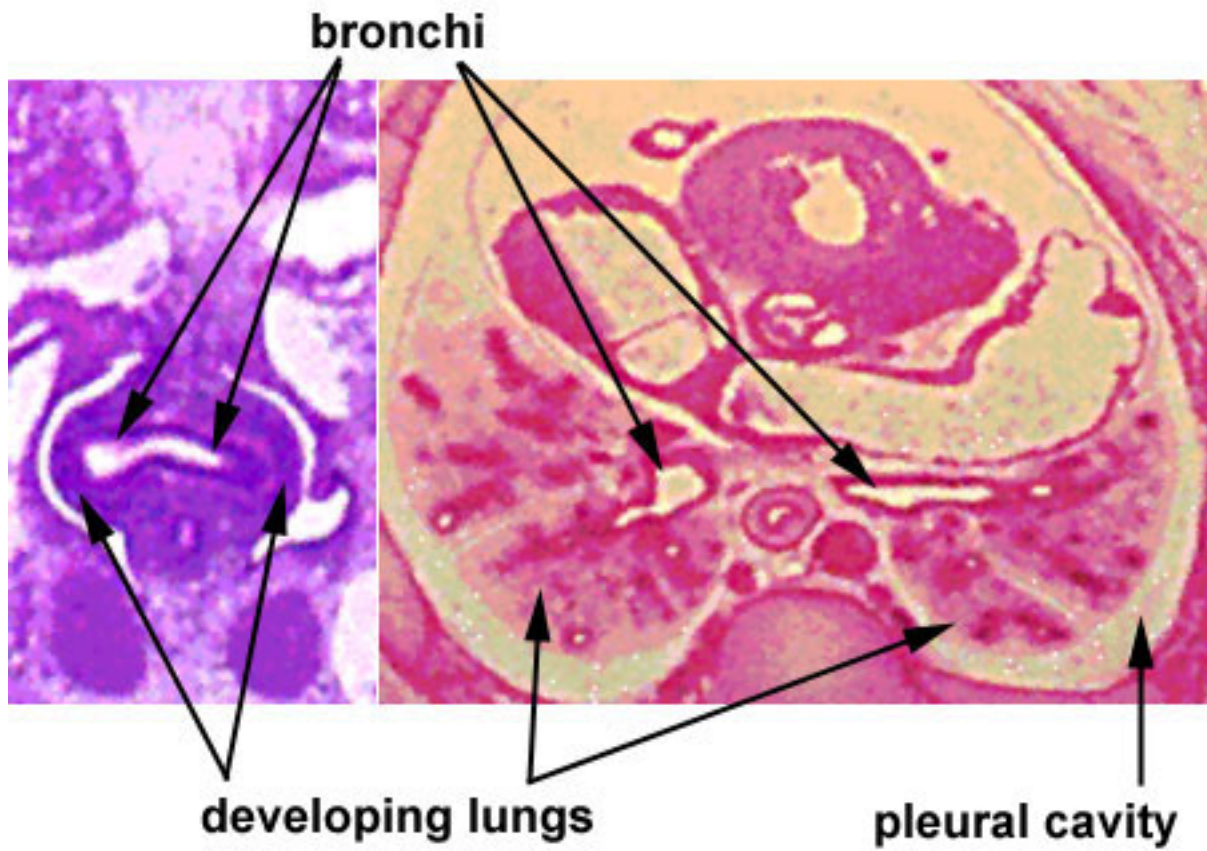
lower respiratory tract



conducting system bronchi to lungs

## stage 13

## stage 22



(/embryology/index.php/File:Stage\_22\_image\_171.jpg)

(/embryology/index.php/File:Lung\_development\_stage13-22.jpg)

Stage 13 (Week 4-5) (/embryology/index.php/Respiratory\_System\_-\_Carnegie\_Stage\_13)

Stage 22 (Week 8) (/embryology/index.php/Respiratory\_System\_-\_Carnegie\_Stage\_22)

- lung buds ( endoderm epithelial tubes) grow/push into mesenchyme covered with pleural cells (lung border)
- generates a tree-like network by repeated:
  1. elongation
  2. terminal bifurcation
  3. lateral budding

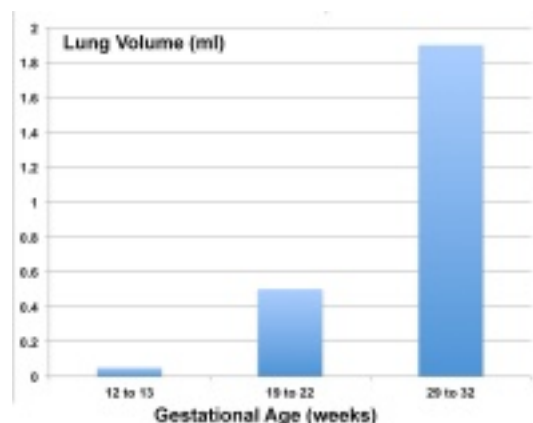
Growth initially of branched "conducting" system of bronchial tree, followed by later development of the "functional units" of the alveoli.

### Additional Information - Histology[Expand]

## Fetal Lung Volume

Each human lung volume as determined by ultrasound and matched to gestational age <sup>[1]</sup>

Weeks (gestational)	Volume (ml)
12 to 13	0.05
19 to 22	0.5
29 to 32	1.9



(/embryology/index.php/File:Lung\_volume\_graph\_01.jpg)



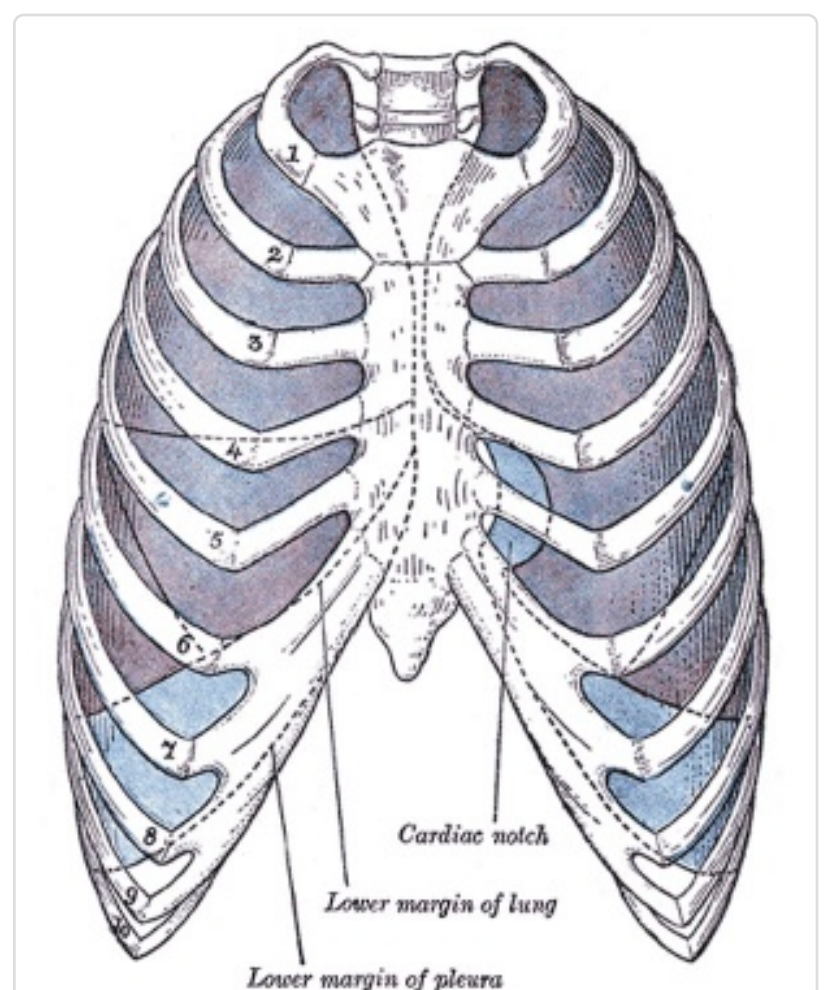
Modified from Dilly SA. Thorax. 1984 Oct;39(10):733-42. PMID: 6495241  
(/embryology/index.php/File:Lung\_alveoli\_devel  
Lung alveoli development cartoon

## Pleural Cavity

- anatomical body cavity in which the lungs develop and lie.
- pleural cavity forms in the **lateral plate mesoderm** as part of the early single **intraembryonic coelom**.
- This cavity is initially continuous with pericardial and peritoneal cavities and form initially as two narrow canals.
  - later becomes separated by folding (pleuropericardial fold, pleuroperitoneal membrane) and the later formation of the diaphragm.
- **pleuropericardial fold** - (pleuropericardial membrane) An early embryonic fold which restricts the communication between pleural cavity and pericardiac cavity, contains both the cardinal vein and phrenic nerve.
- **pleuroperitoneal membrane** - An early embryonic membrane that forms inferiorly at the septum transversum to separate peritoneal cavity from pleural cavity.

## Pleura

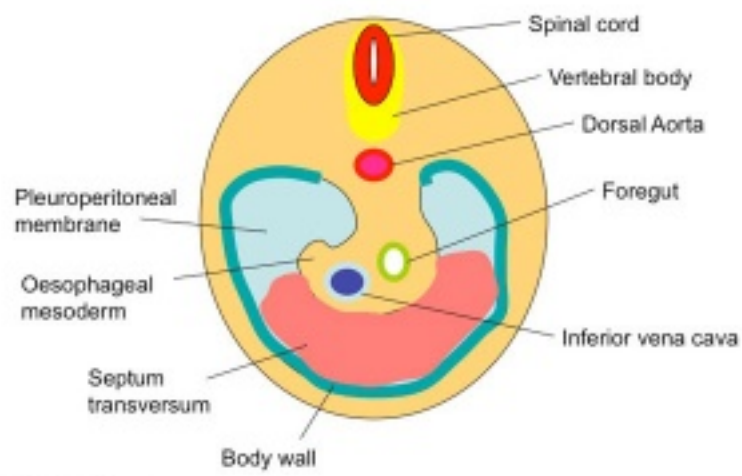
- **serous membrane** covers the surface of the lung and the spaces between the lobes.
- arranged as a closed invaginated sac.
- two layers (**pulmonary**, **parietal**) continuous with each other, the potential space between them is the **pleural cavity**.



# Diaphragm

- Not respiratory tract but musculoskeletal development, there are **5 embryonic elements** that contribute to the diaphragm.

## Developing Diaphragm

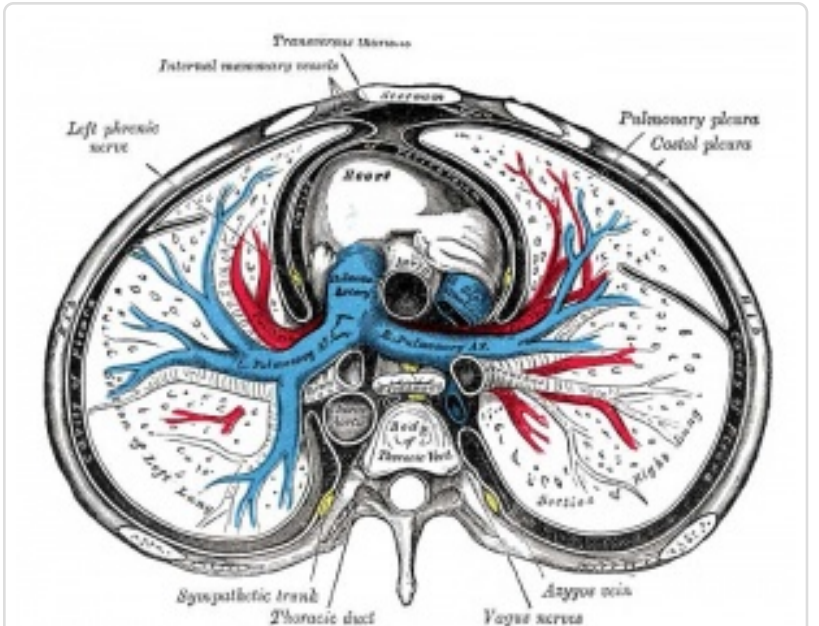


(/embryology/index.php/File:Diaphragm\_components.jpg)

1. septum transversum- central tendon
2. 3rd to 5th somite- musculature of diaphragm
3. ventral pleural sac- connective tissue
4. mesentery of oesophagus- connective tissue around oesophagus and IVC
5. pleuroperitoneal membranes- connective tissue around central tendon

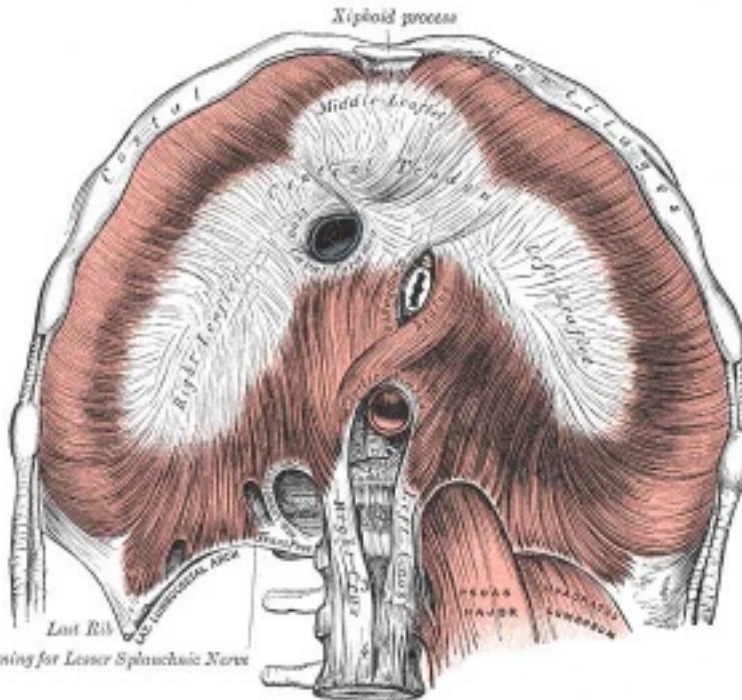
(/embryology/index.php/File:Gray0965.jpg)

pleura



(/embryology/index.php/File:Gray0968.jpg)

pleura

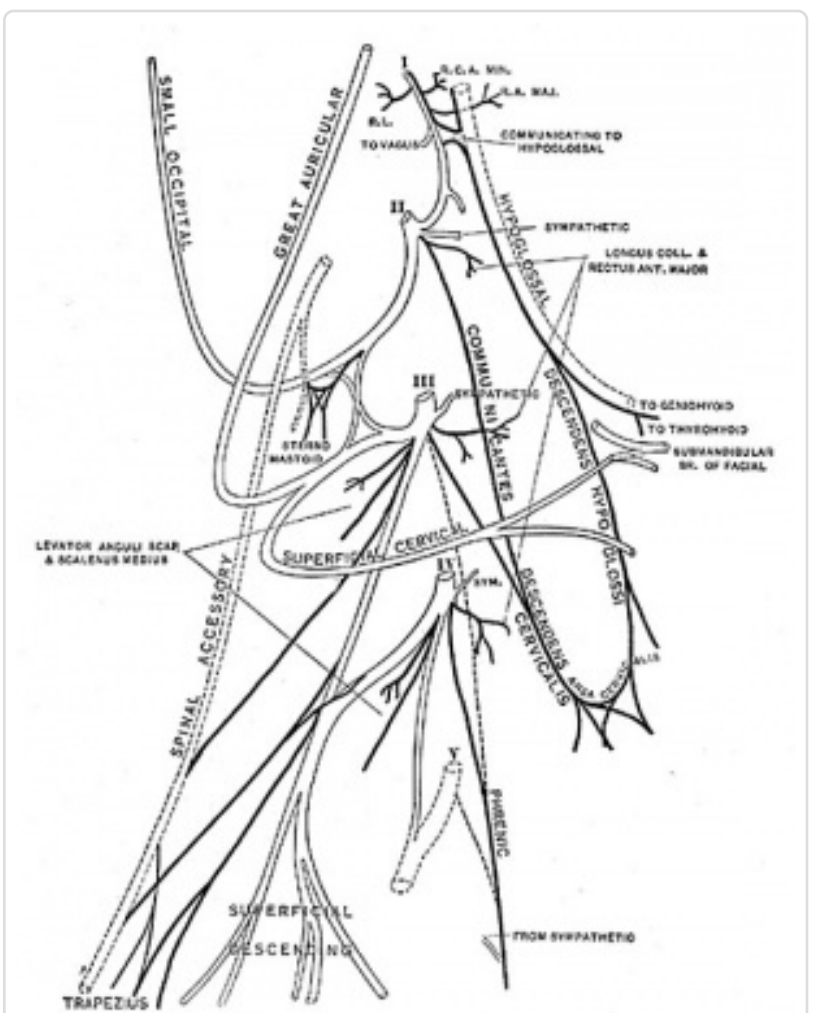


(/embryology/index.php/File:Gray0391.jpg)

- Innervation of the human diaphragm is by the **phrenic nerves**
  - arising from the same segmental levels from which the diaphragm skeletal muscles arise, segmental levels C3 to C5.
- The paired phrenic nerves are **mixed nerves**
  - motor neurons for the diaphragm
  - sensory nerves for other abdominal structures (mediastinum, pleura, liver, gall bladder).

# Pulmonary Circulation

- the pulmonary system not "functional" until after birth
- pulmonary arteries - 6th aortic arch arteries
- pulmonary veins - are incorporated into the left atrium wall
- bronchial arteries - branches from dorsal aorta



(/embryology/index.php/File:Gray0804.jpg)

Adult Cervical Plexus (phrenic nerve shown lower right)

# Fetal

## Fetal Respiratory Movements

- Fetal respiratory movements (FRM) or Fetal breathing movements (FBM) are regular muscular contractions occurring in the third trimester.
- preparing the respiratory muscular system for neonatal function.
- may also have a role in late lung development.

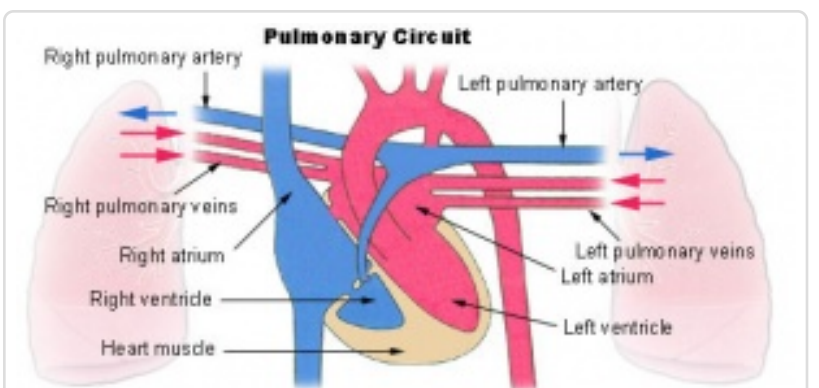
# The First Breath

- The respiratory system does not carry out its physiological function (gas exchange) prenatally and remain entirely fluid-filled until birth.
- At birth, fluid in the upper respiratory tract is expired and fluid in the lung aveoli is rapidly absorbed this event has also been called "dewatering of the lung".
  - The lung epithelia has to now rapidly change from its prenatal secretory function to that of fluid absorption.

The exchange of lung fluid for air leads to:

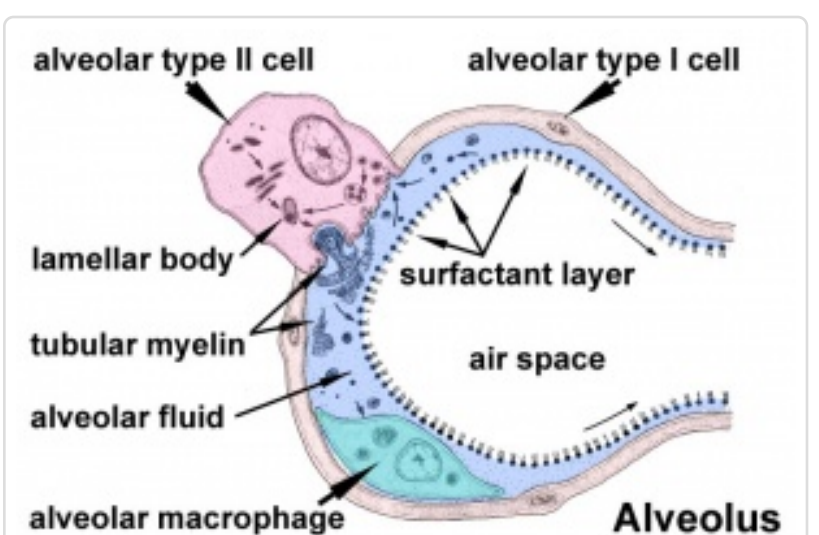
- fall in pulmonary vascular resistance
- increase in pulmonary blood flow
- thinning of pulmonary arteries (stretching as lungs increase in size)
- blood fills the alveolar capillaries

In the heart - pressure in the right side of the heart decreases and pressure in the left side of the heart increases (more blood returning from pulmonary).



(/embryology/index.php/File:Pulmonary\_circulat

Pulmonary circulation



(/embryology/index.php/File:Alveolar-sac-01.jpg)

Alveolar sac structure

# Postnatal

## Alveoli

- At birth about 15% of adult alveoli number have formed
  - 20 - 50 million to in the adult about 300 million.
- remaining subdivisions develop in the first few postnatal years

## Respiratory Rate

- neonatal rate is higher (30-60 breaths/minute) than adult (12-20 breaths/minute).
  - tachypnea - (Greek, rapid breathing) an increased respiratory rate of greater than 60 breaths/minute in a quiet resting baby

Age	Rate (breaths/minute)
Infant (birth - 1 year)	30 - 60
Toddler (1 - 3 years)	24 - 40
Preschool (3 - 6 years)	22 - 34
School age (6 - 12 years)	18 - 30
Adolescent (12 - 18 years)	12 - 16

## Rib Orientation

- Infant rib - is virtually **horizontal**, allowing diaphragmatic breathing only.
- Adult rib - is **oblique** (both anterior and lateral views), allows for pump-handle and bucket handle types of inspiration.

## Respiratory Tract Abnormalities

Respiratory System - Abnormalities (/embryology/index.php/Respiratory\_System\_-\_Abnormalities)

- Meconium Aspiration Syndrome** - (MAS) Meconium is the gastrointestinal contents that accumulate in the intestines during the fetal period. Fetal stress in the third trimester, prior to/at/ or during parturition can lead to premature meconium discharge into the amniotic fluid and subsequent ingestion by the fetus and damage to respiratory function. Damage to placental vessels meconium myonecrosis may also occur.
- Newborn Respiratory Distress Syndrome** - (Hyaline Membrane Disease) membrane-like substance from damaged pulmonary cells, absence of surfactant, if prolonged can be irreversible, intrauterine asphyxia, prematurity and maternal diabetes medline plus (<http://www.nlm.nih.gov/MEDLINEPLUS/ency/article/001563.htm>) | eMedicine (<http://www.medscape.com/article/976034-overview>)
- Tracheoesophageal Fistula** - Tracheo-Oesophageal Fistula, Oesophageal Atresia - Oesophageal Atresia with or without tracheo-oesophageal fistula (/embryology/index.php/F#istula) **Fistula** - an abnormal communication between 2 structures (organs, vessels, cavities) that do not normally connect.
- Lobar Emphysema** (Overinflated Lung) - There is an overinflated left upper lobe There is a collapsed lower lobe The left lung is herniating across the mediastinum
- Congenital Diaphragmatic Hernia** - (1 in 3,000 live births) Failure of the pleuroperitoneal foramen (foramen of Bochdalek) to close (left side), allows viscera into thorax -intestine, stomach or spleen can enter the pleural cavity, compressing the lung. rare (Morgagni hernia) -an opening in the front of the diaphragm. Congenital Diaphragmatic Hernia (/embryology/index.php/Respiratory\_System\_-\_Abnormalities#Congenital\_Diaphragmatic\_Hernia) | GeneReviews (<http://www.ncbi.nlm.nih.gov/books/NBK1359>)
- Azygos Lobe** - Common condition (0.5% of population). The right lung upper lobe expands either side of the posterior cardinal. There is also some course variability of the phrenic nerve in the presence of an azygos lobe.
- Congenital Laryngeal Webs** - Laryngeal abnormality due to embryonic (week 10) incomplete recanalization of the laryngotracheal tube during the fetal period. Rare abnormality occurring mainly at the level of the vocal folds (glottis).
- Hyaline Membrane Disease - (Newborn Respiratory Distress Syndrome) a membrane-like substance from damaged pulmonary cells.
- Bronchopulmonary Dysplasia** - A chronic lung disease which can occur following premature birth and related lung injury. Most infants who develop BPD are born more than 10 weeks before their due dates, weigh less than 1,000 grams (about 2 pounds) at birth, and have breathing problems.
- Asthma** - Flow limitation during tidal expiration in early life significantly associated with the development of physician-diagnosed asthma by the age of 2 years. Infants with abnormal lung function soon after birth may have a genetic predisposition to asthma or other airway abnormalities that predict the risk of subsequent lower respiratory tract illness. PMID 8176553 (<http://www.ncbi.nlm.nih.gov/pubmed/8176553?dopt=Abstract>)
- Cystic Fibrosis** - Inherited disease of the mucus and sweat glands, causes mucus to be thick and sticky. Clogging the lungs, causing breathing problems and encouraging bacterial grow. (Covered elsewhere in the course)
- Environmental Factors** see recent review below.

Mark D Miller, Melanie A Marty **Impact of environmental chemicals on lung development.** Environ. Health Perspect.: 2010, 118(8);1155-64 PubMed 20444669 (<http://www.ncbi.nlm.nih.gov/pubmed/20444669>)

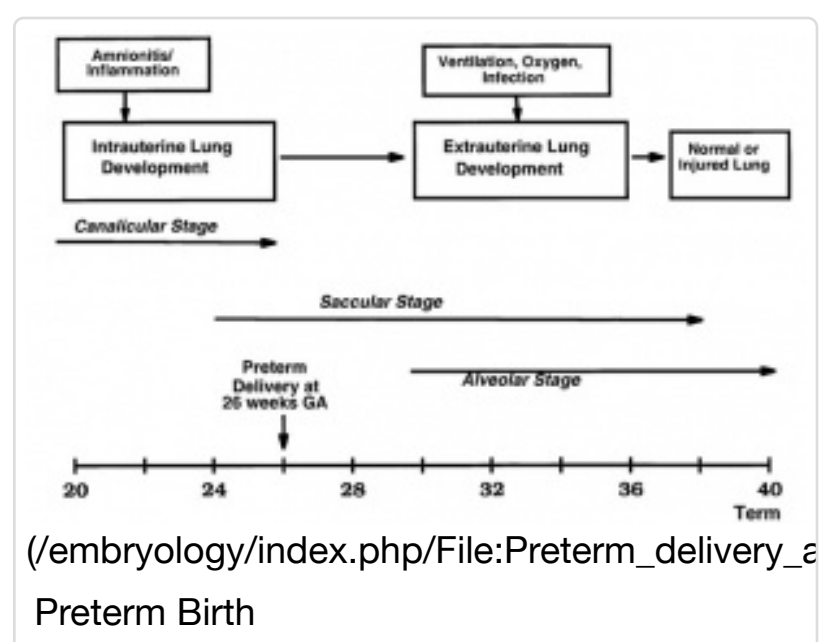
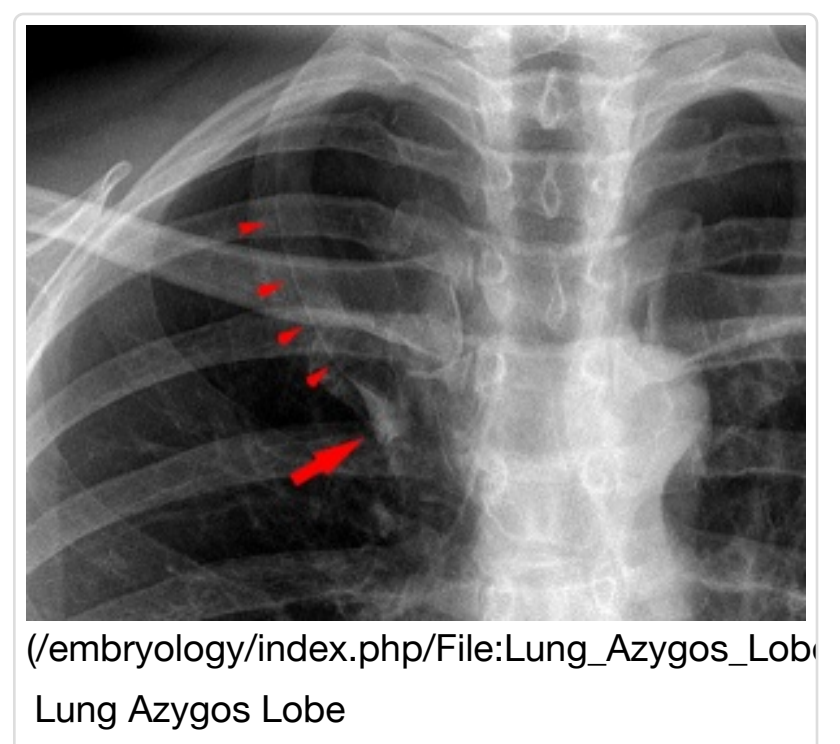
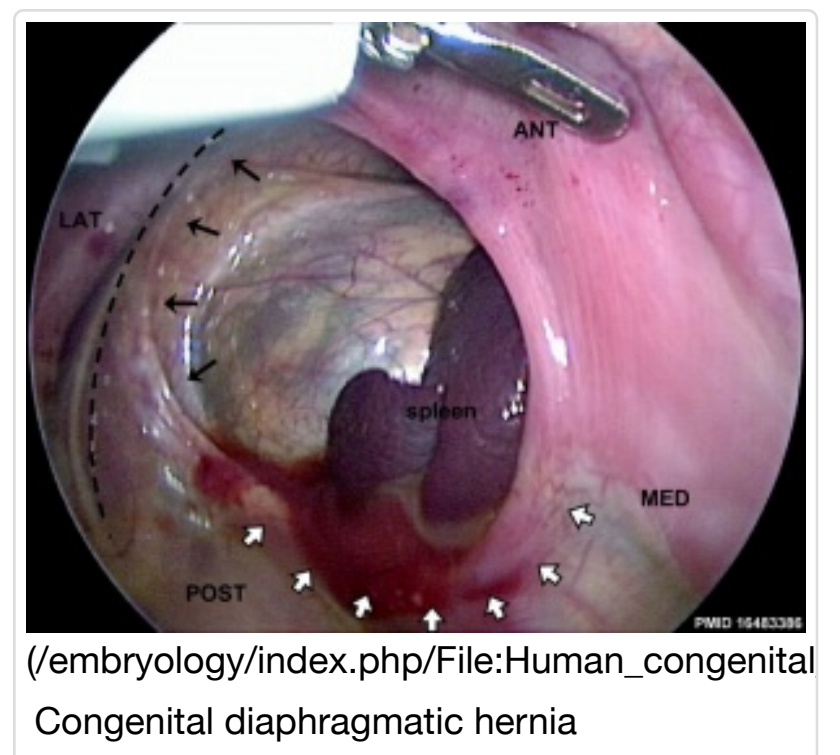
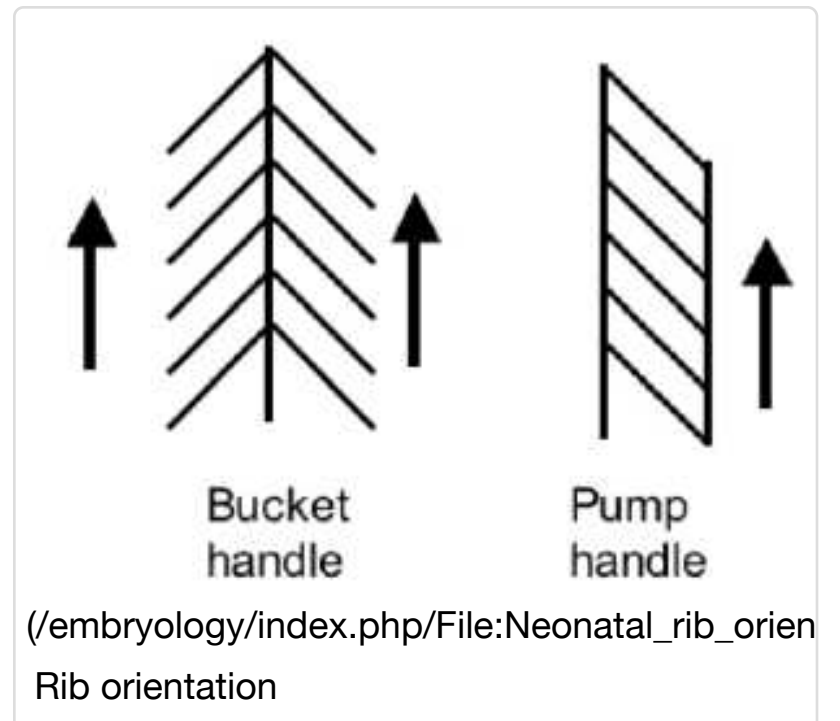
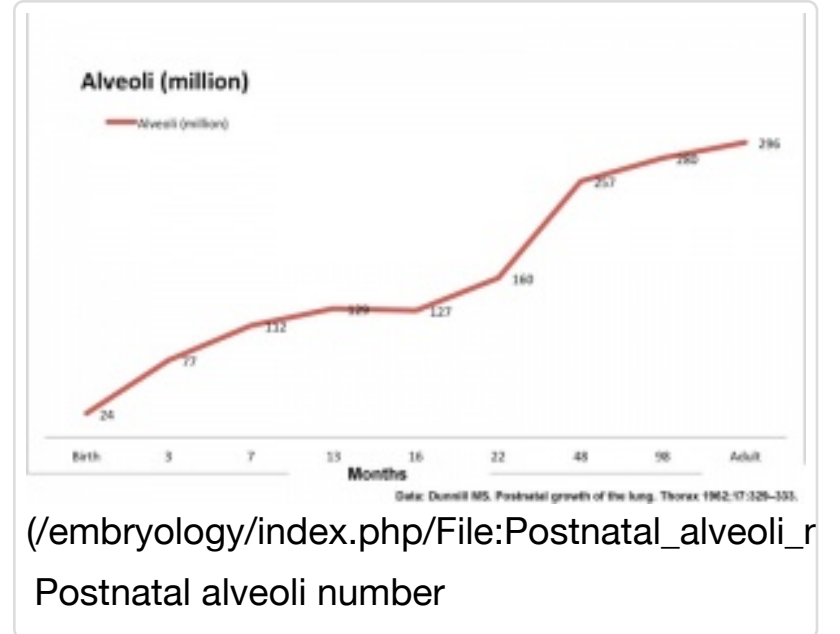
## Additional Information

Respiratory Quiz (/embryology/index.php/Respiratory\_Quiz)

[Grays - Respiratory Images\[Expand\]](#)

[Respiratory Histology\[Expand\]](#)

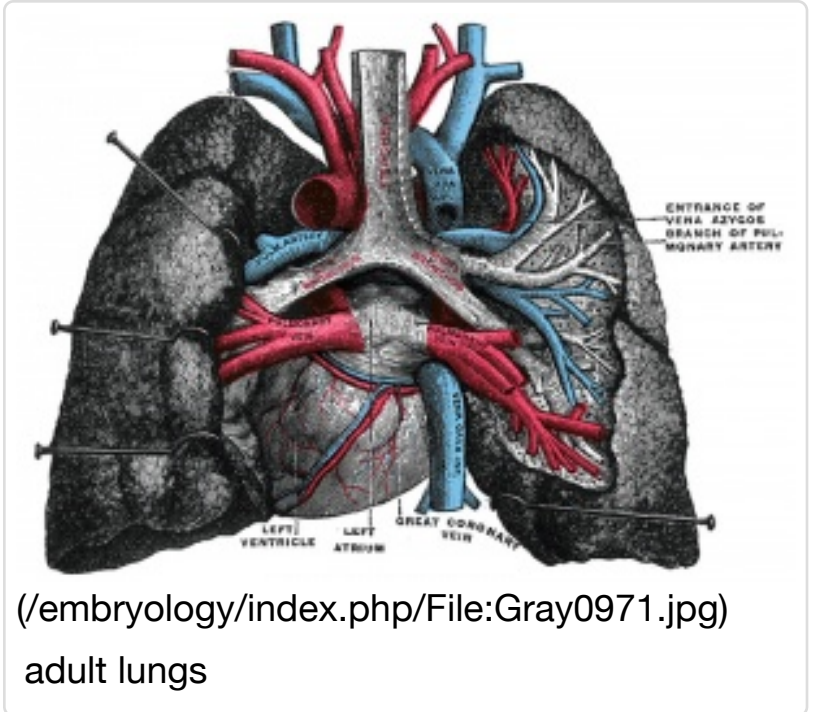
- C F A Peralta, P Cavoretto, B Csapo, O Falcon, K H Nicolaidis **Lung and heart volumes by three-dimensional ultrasound in normal fetuses at 12-32 weeks' gestation.** Ultrasound Obstet Gynecol: 2006,





## Glossary Links

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