Respiratory System Embryology

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Modified Key:

Black Text: Information present in original presentation.

Highlighted Text: Text read by the Doctor.

Red Text: Information stated by the Doctor, not present in original presentation file.

Blue Text: Additional information added for further comprehension.

Development of the nose and Palate

Development = proliferation

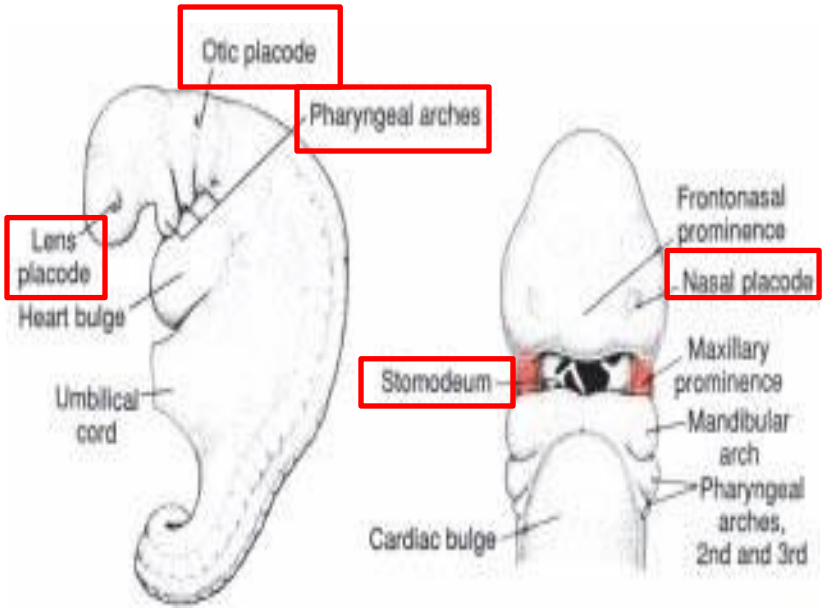
of cells, forming prominences

Development of the nose

- At the end of the fourth week, **facial prominences** consisting primarily of neural crest-derived mesenchyme and formed mainly by the first pair of pharyngeal arches appear

- The **frontonasal prominence,** formed by proliferation of mesenchyme ventral to the brain vesicles, constitutes the upper border of the stomodeum

- On both sides of the frontonasal prominence, local thickenings of the surface ectoderm, the **nasal** (**olfactory**) **placodes,** originate under inductive influence of the ventral portion of the forebrain



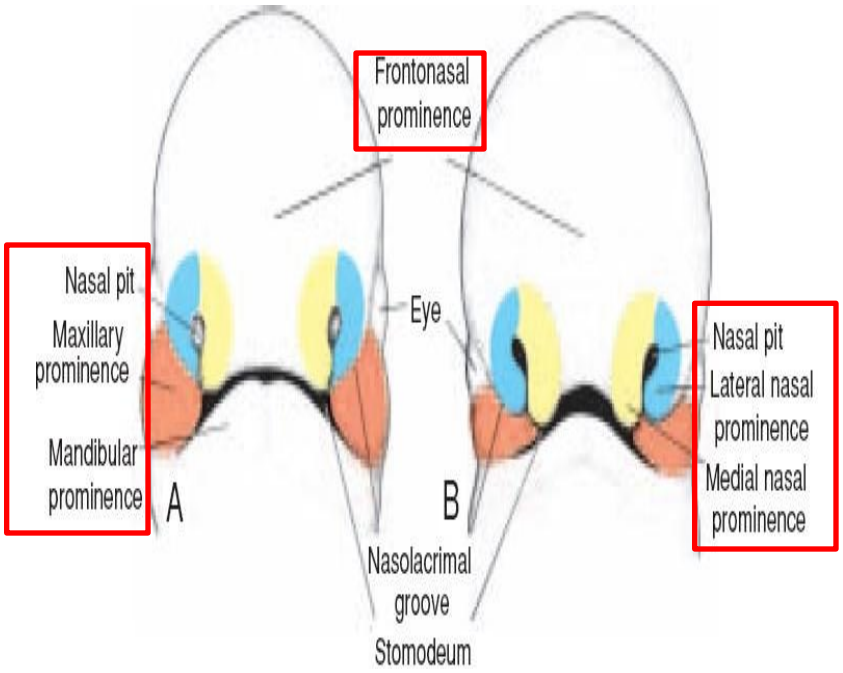
Placode: precursor of a specific organ.
Stomodeum: anterior part of oral cavity, separated from the posterior part by oropharyngeal membrane.
Note: proliferation always occurs in mesenchymal/mesodermal cells.

Development of the nose

- During the fifth week, the nasal placodes invaginate to form **nasal pits (nostril).** **It starts from the skin (the ectoderm), forms the nostrils and then the vestibules (stratified squamous keratinized).**

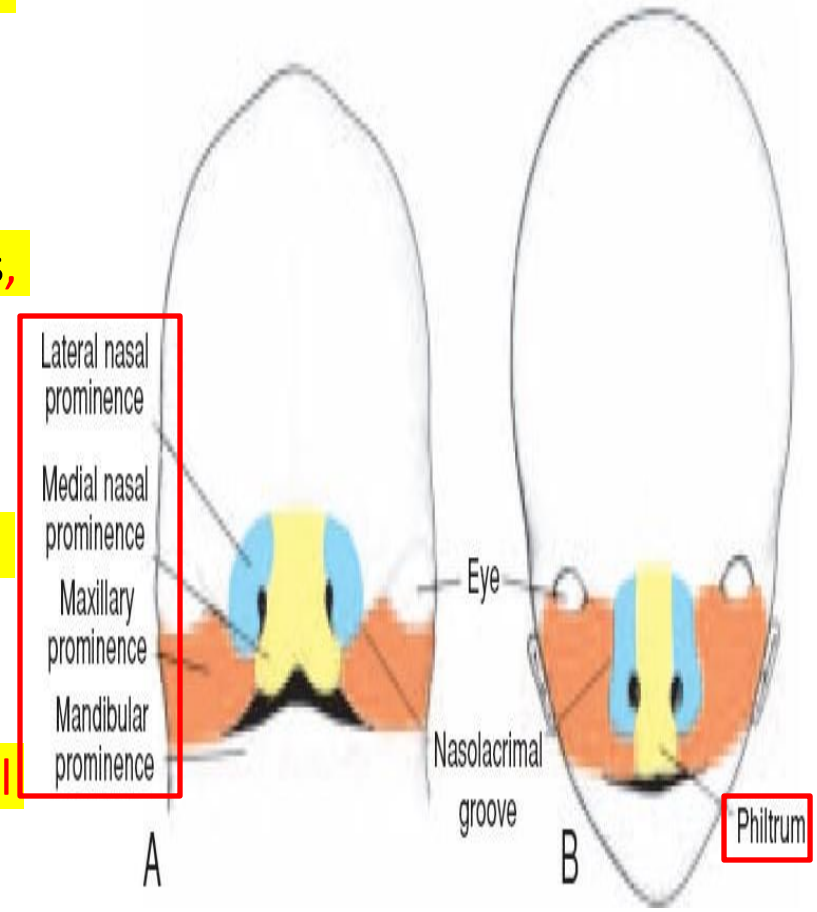
- In so doing, they create a ridge of tissue that surrounds each pit and forms the **nasal prominences.**

- The prominences on the outer edge of the pits are the **lateral nasal prominences;** those on the inner edge are the **medial nasal prominences**



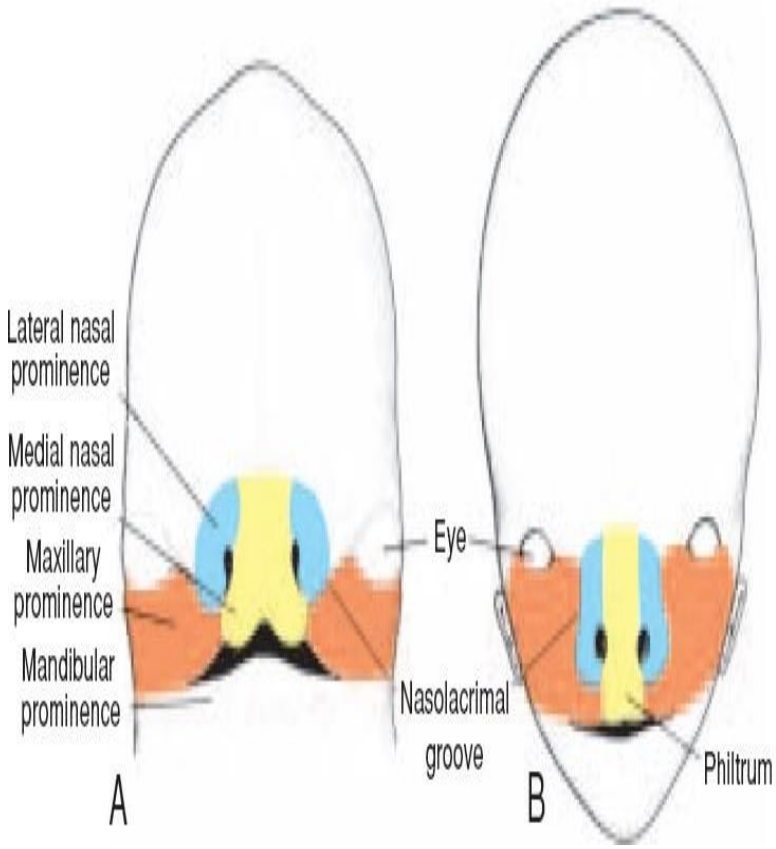
Development of the nose

- During the following 2 weeks, the maxillary prominences continue to increase in size
- Simultaneously, they grow medially, compressing the medial nasal prominences, which also grow medially, toward the midline
- Subsequently the cleft between the medial nasal prominence and the maxillary prominence is lost, and the two fuse, forming the philtrum (vertical depression above the upper lip, formed by medial nasal prominences).
- The meeting of the medial nasal and maxillary prominences forms the upper lip. If they don't fuse, a labial cleft/hare-lip results, and it could be unilateral or bilateral.



Development of the nose

- The **nose** is formed from five facial prominences
- the frontal prominence gives rise to the frontal bone, nose bridge; and **nasal septum** (i.e. medial wall of the nose) by merging with the medial nasal prominences.
- the merged medial nasal prominences provide the crest of the nasal spine and tip;
- the lateral nasal prominences form the sides (alae)
- Olfactory pit forms the nostril and then becomes deeper to form a blind sac (the vestibule)



Development of the nose

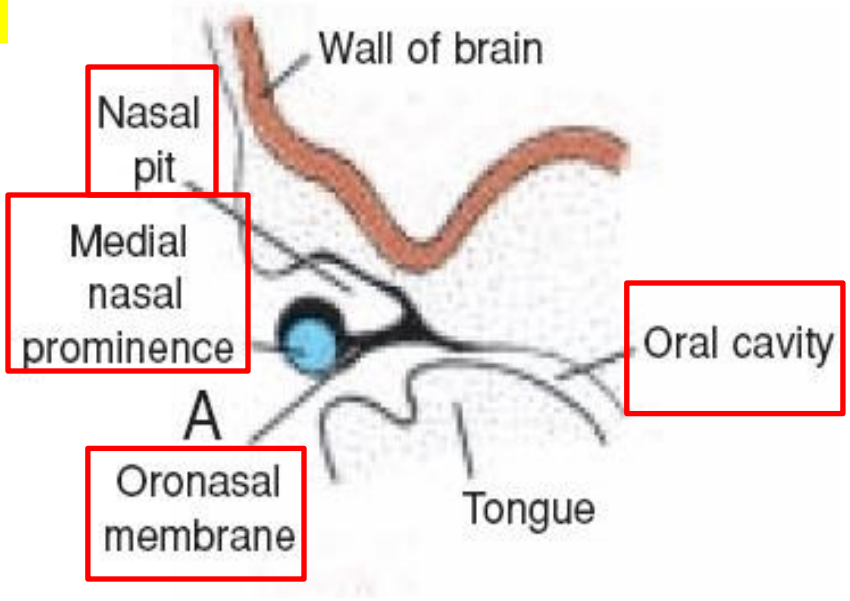
TABLE 15.2 Structures Contributing to Formation of the Face

Prominence	Structures Formed
Frontonasal[a]	Forehead, bridge of nose, medial and lateral nasal prominences
Maxillary	Cheeks, lateral portion of upper lip
Medial nasal	Philtrum of upper lip, crest and tip of nose
Lateral nasal	Alae of nose & lateral wall of the nasal cavity
Mandibular	Lower lip

[a] The frontonasal prominence is a single unpaired structure; the other prominences are paired.

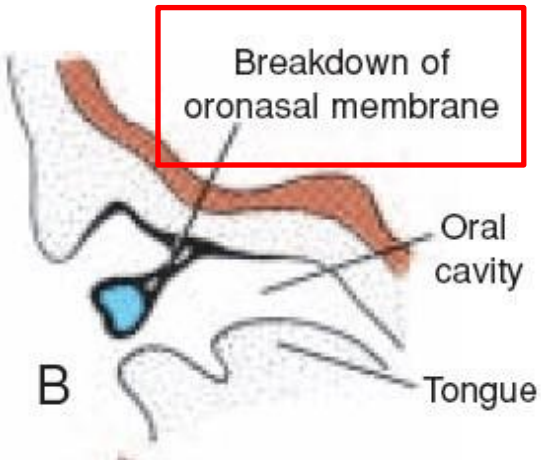
Nasal Cavities

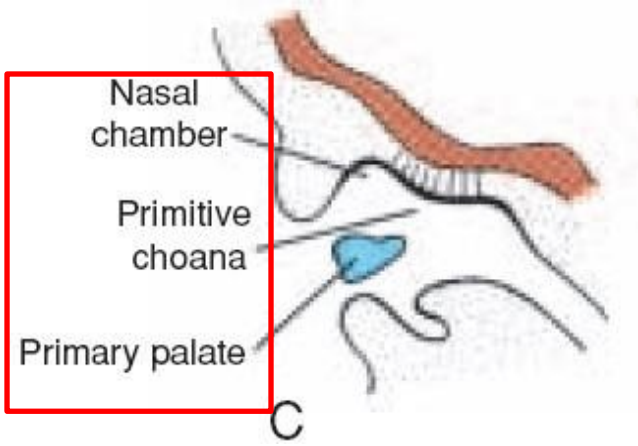
- 1. During the sixth week, the nasal pits deepen considerably by proliferation of the mesenchyme inside the nasal cavity to form the nasal cavity, conchae, meatuses and recess, partly because of growth of the surrounding nasal prominences and partly because of their penetration into the underlying mesenchyme



Nasal Cavities

- 2. At first the **oronasal membrane (floor of the nose)** separates the pits from the primitive oral cavity by way of the newly formed foramina, the **primitive choanae.**
- **It ruptures then forms again, forming a permanent oronasal membrane, by the primary and secondary palates.**



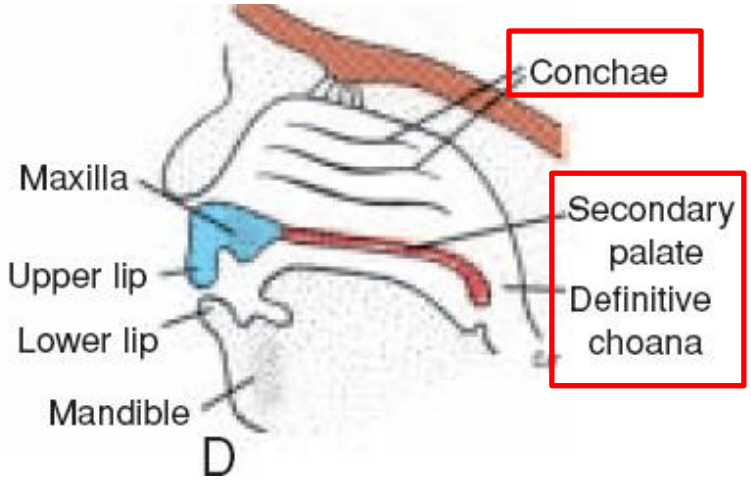


- These choanae lie on each side of the midline and immediately behind the primary palate.

Nasal Cavities

- 3. Later, with formation of the secondary palate and further development of the primitive nasal chambers, it will separate the nasal and oral cavities and form the conchae, meatuses and recess.

- the **definitive choanae will** lie at the junction of the nasal cavity and the pharynx (nasopharynx).



Paranasal air sinuses

- **Paranasal air sinuses** develop as diverticula of the lateral nasal wall, from their site of drainage, and extend as ducts into the maxilla, ethmoid, frontal, and sphenoid bones and their ends form the sinuses.

- They reach their maximum size during puberty with the growth of facial bones and contribute to the definitive shape of the face.

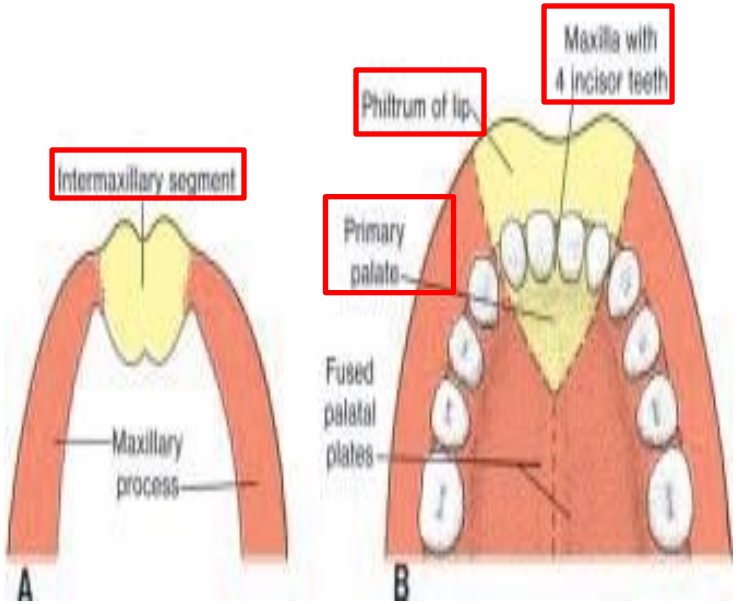
Primary palate

- As a result of medial growth of the maxillary prominences, the two medial nasal prominences merge not only at the surface but also at a deeper level.

- The structure formed by the two merged prominences is the **intermaxillary segment formed by the maxillary and medial nasal prominences.**

- It is composed of (*a*) a **labial component,** which forms the philtrum of the upper lip, mainly by the medial nasal prominences, and takes part in the formation of the intermaxillary segment;
- (*b*) an **upper jaw component,** which carries the upper four incisor teeth within the intermaxillary segment;
- (*c*) a **palatal component,** which forms the triangular primary palate

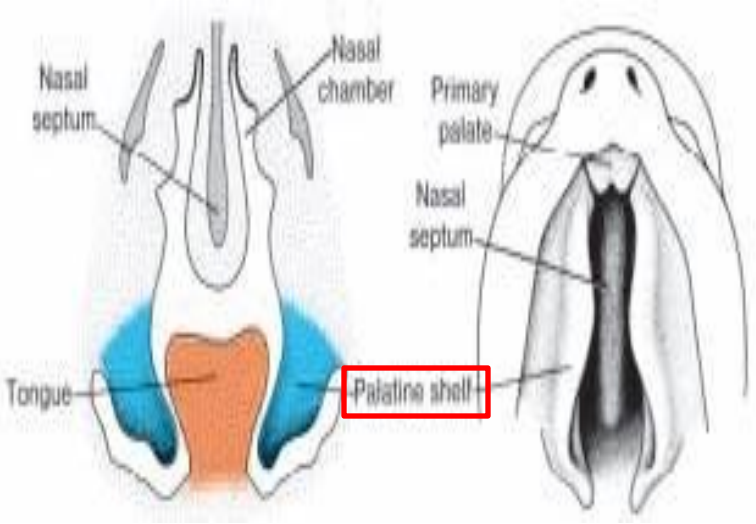
- The intermaxillary segment is continuous with the rostral portion of the **nasal septum,** which is formed by the frontal prominence.



Secondary Palate

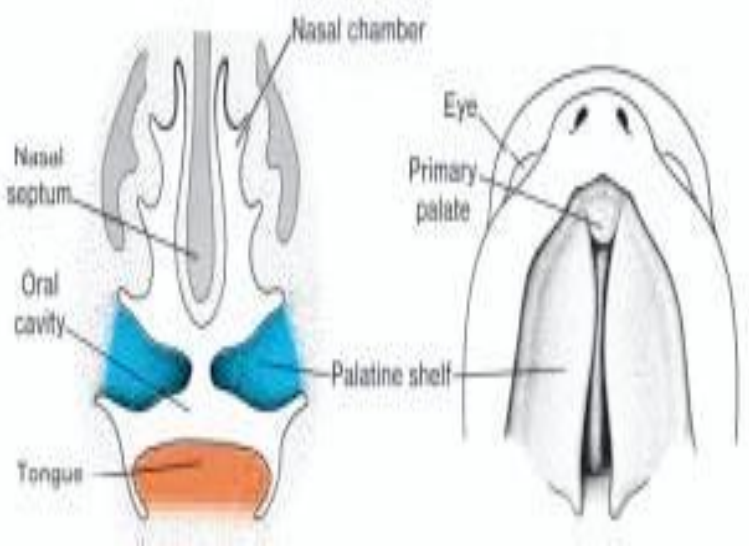
- the main part of the definitive palate is formed by two shelflike outgrowths from the maxillary prominences.

- These outgrowths, the **palatine shelves,** appear in the sixth week of development and are directed obliquely downward on each side of the tongue



Secondary Palate

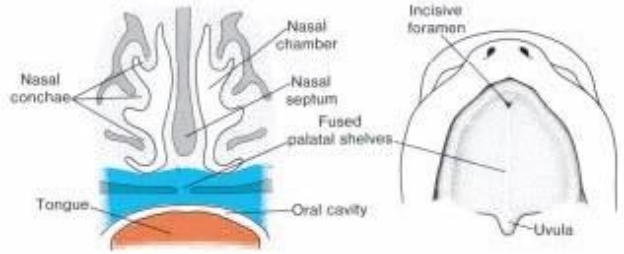
- In the seventh week, however, the palatine shelves ascend to attain a horizontal position above the tongue and fuse, forming the **secondary palate,** which, along with the primary palate, fuses with the frontonasal septum.



Secondary Palate

- Anteriorly, the shelves fuse with the triangular primary palate, and the **incisive foramen** is the midline landmark between the primary and secondary palates

- At the same time as the palatine shelves fuse, the frontonasal septum grows down and joins with the cephalic aspect of the newly formed palate (both primary & secondary palates).



Secondary Palate

- 2 folds grow posteriorly from the edge of the palatine process to form the soft palate and the uvula.
- The union of the 2 folds of the soft palate occurs during the 8th week
- The 2 parts of the uvula fuse in the midline during the 11th week (could occur that they don't fuse and, thus, we find a cleft separating the 2 uvulae)
- Unilateral cleft lip can extend to the nose

Respiratory System

Primitive gut

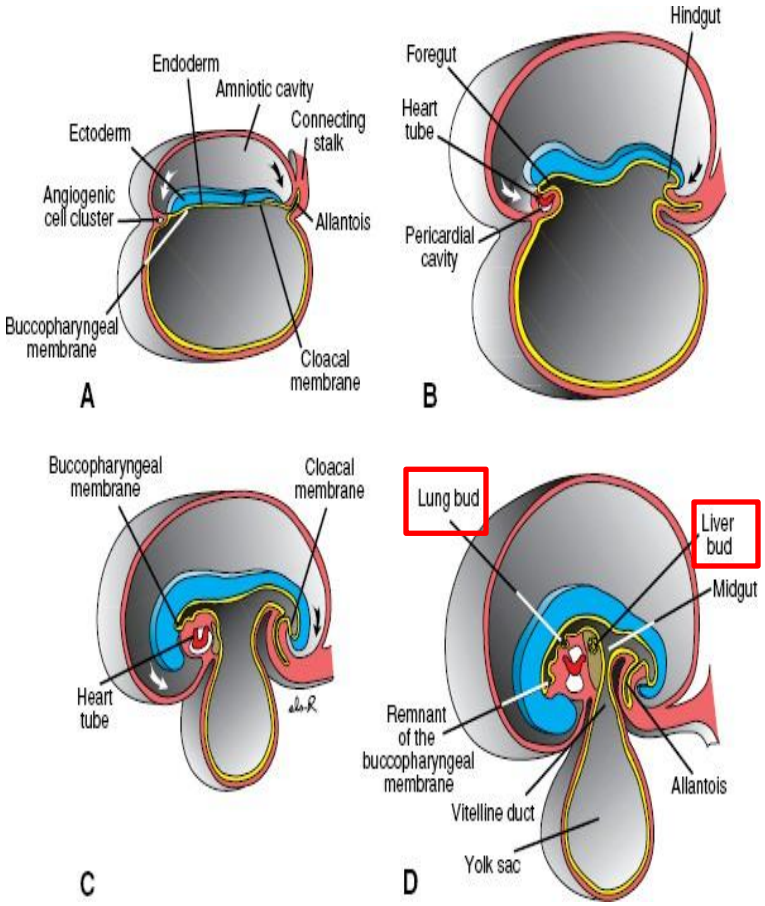
- Development of the primitive gut and its derivatives is in four sections:

- (*a*) The **pharyngeal gut,** or **pharynx,** extends from the buccopharyngeal membrane (membrane separating the oral cavity from the pharynx) to the tracheobronchial diverticulum/lung bud (posterior part of oral cavity + pharynx. Pharynx develops from pharyngeal arches).

- (*b*) The **foregut** lies caudal to the pharyngeal tube and extends as far caudally as the liver outgrowth/liver bud (2nd part of duodenum, upper half).

- (*c*) The **midgut** begins caudal to the liver bud and extends to the junction of the right/proximal two-thirds and left/distal third of the transverse colon in the adult.

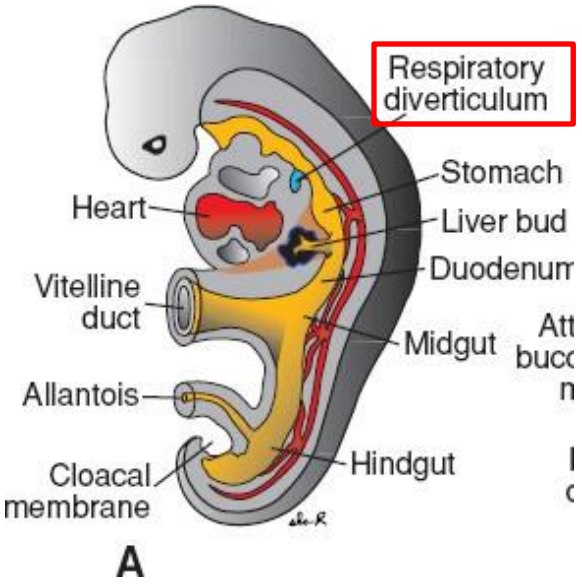
- (*d*) The **hindgut** extends from the left/distal third of the transverse colon, descending colon, sigmoid colon, rectum and upper half of anal canal to the cloacal membrane



Respiratory diverticulum

- 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 location of the bud along the gut tube is determined by signals from the surrounding mesenchyme, including fibroblast growth factors (FGFs) that instruct the endoderm. Any abnormalities in these signals can result in anomalies.

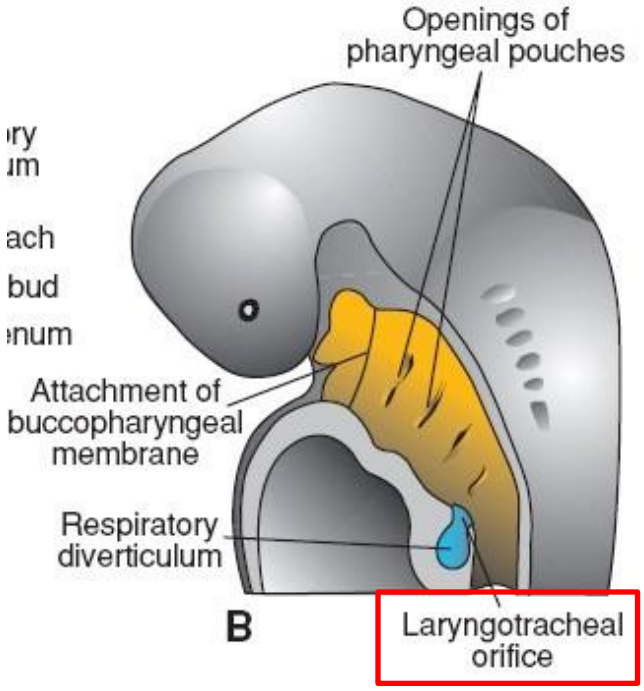


Respiratory diverticulum

- The **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.

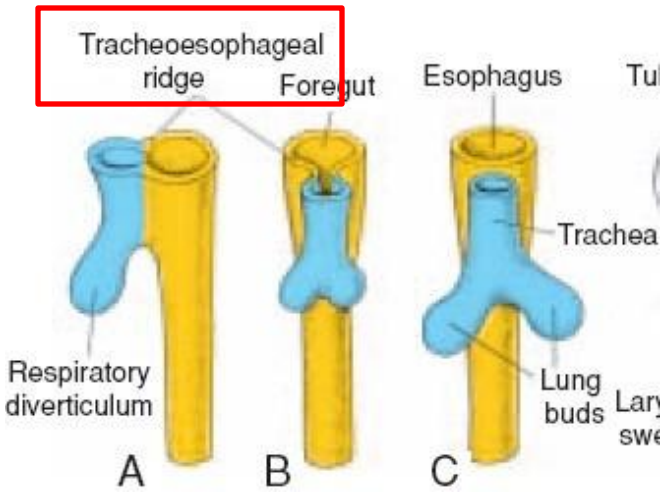
- Initially the lung bud is in open communication with the foregut



Respiratory diverticulum

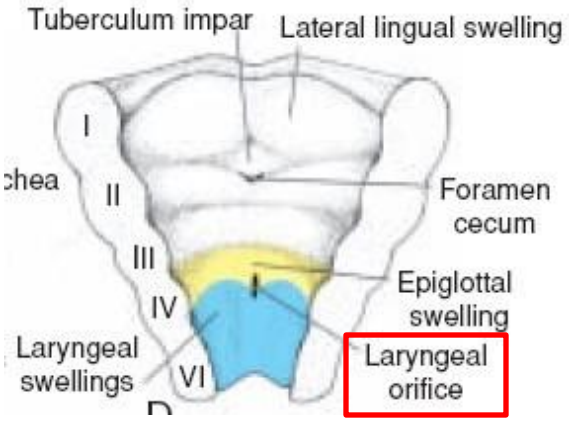
- When the diverticulum expands caudally, two longitudinal ridges, the **tracheoesophageal ridges,** separate it from the foregut

- 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**



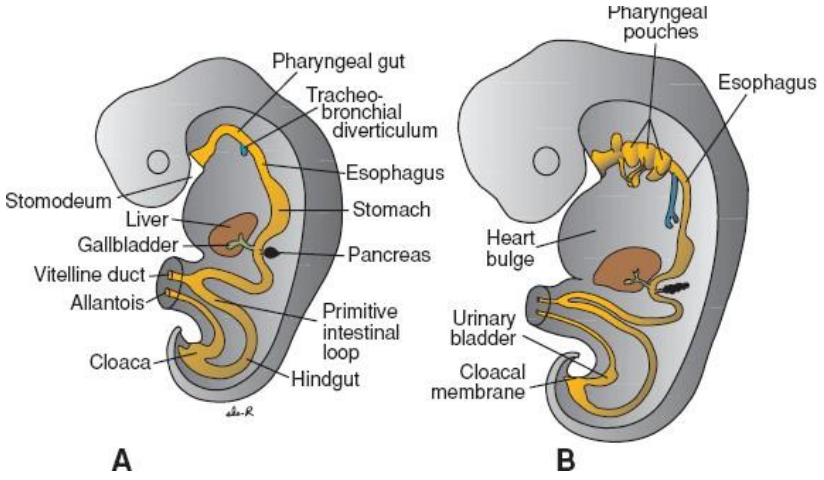
Respiratory diverticulum

- The respiratory primordium maintains its communication with the pharynx and the digestive tract through the **laryngeal orifice** (slit-like) which changes with the development of the larynx (will be discussed soon).



Esophagus

- At first the esophagus is short
- but with descent of the heart, pericardium and lungs it lengthens rapidly
- The muscular coat, which is formed by surrounding splanchnic mesenchyme, is striated in its upper two-thirds and innervated by the vagus the muscle coat is smooth in the lower third and is innervated by the splanchnic plexus.



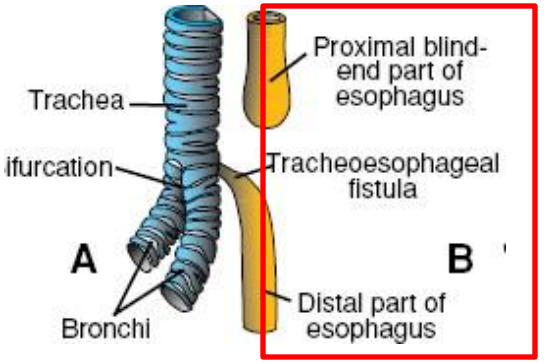
Anomalies of the trachea and esophagus

Tracheoesaphageal fistula (TEF)

- Abnormalities in partitioning of the esophagus and trachea by the tracheoesaphageal septum result in **esophageal atresia** with or without **tracheoesaphageal fistulas**

- These defects occur in approximately in 1/3000 births, and 90% result in the upper portion of the esophagus ending in a blind pouch (i.e., atresia) and the lower segment forming a fistula with the trachea

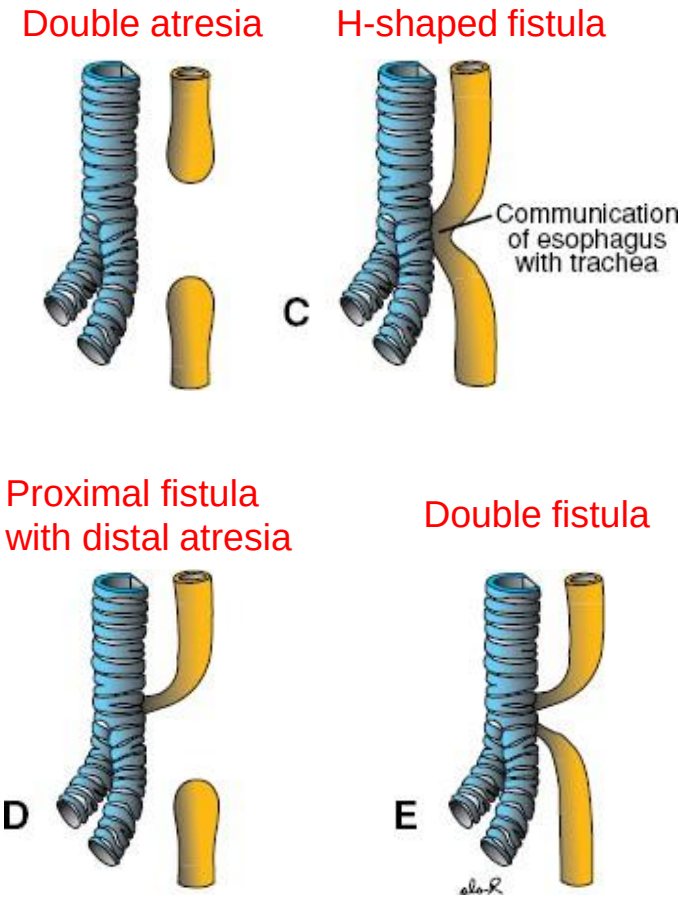
- Predominantly affect male infants



Tracheoesaphageal fistula (TEF)

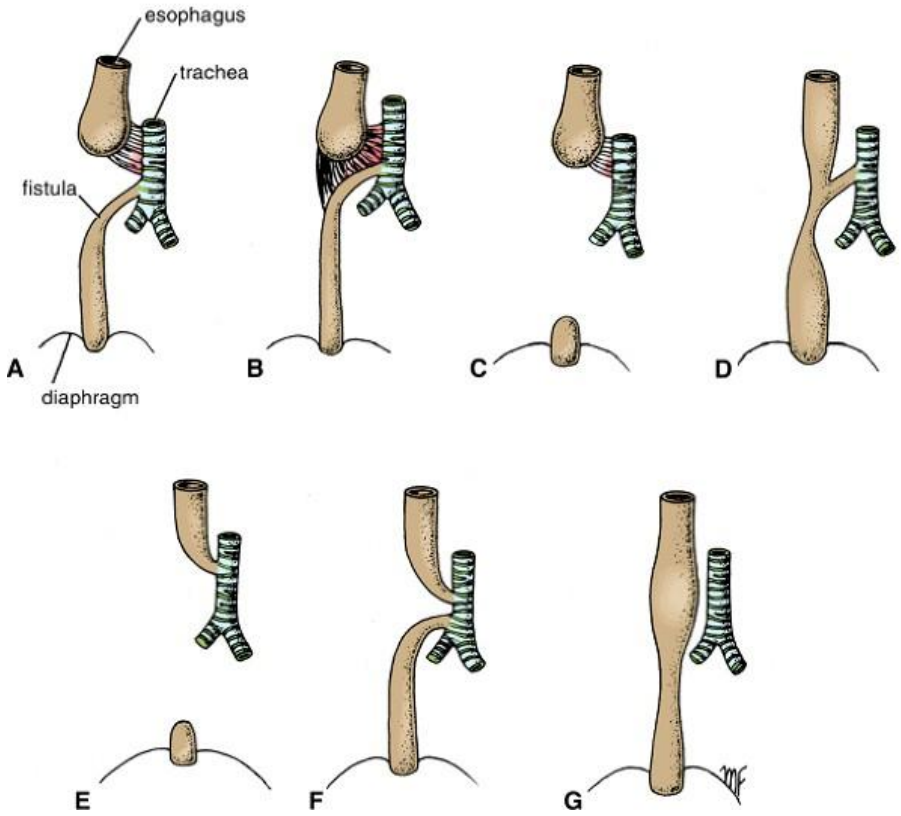
- Isolated esophageal atresia and H-type TEF without esophageal Atresia each account for 4% of these defects.

- Other variations each account for approximately 1% of these defects.



Tracheoesaphageal fistula (TEF)

- TEF is the most common anomaly in the lower respiratory tract
- Infants with common type TEF and esophageal atesia cough and choke because of excessive amounts of saliva in the mouth
- When the infant try to swallow milk it rapidly fills the esophageal pouch and is regurgitated
- A complication of some TEFs is polyhydramnios (excessive amniotic fluid in the amniotic sac), since in some types of TEF amniotic fluid does not pass to the stomach and intestines
- Also, gastric contents and/or amniotic fluid may enter the trachea through a fistula, causing pneumonitis and pneumonia.
- Also, air can pass from the respiratory tract to the digestive tract, causing the abdomen to distend during respiration.



Tracheoesaphageal fistula (TEF)

- These abnormalities are associated with other birth defects, including cardiac abnormalities, which occur in 33% of these cases.

- In this regard TEFs are a component of the **VACTERL** association (**V**ertebral anomalies, **A**nal atresia, **C**ardiac defects, **T**racheoesophageal fistula, **E**sophageal atresia, **R**enal anomalies, and **L**imb defects)

- a collection of defects of unknown causation, but occurring more frequently than predicted by chance alone.

Tracheal atresia and stenosis

- Are uncommon anomalies and usually associated with one of the varieties of TEF

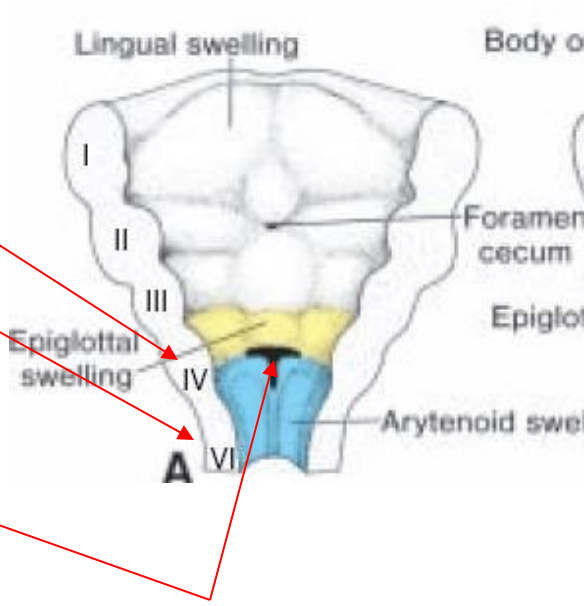
- In some case a web tissue may obstructs the airflow (incomplete/partial tracheal atresia)

Larynx

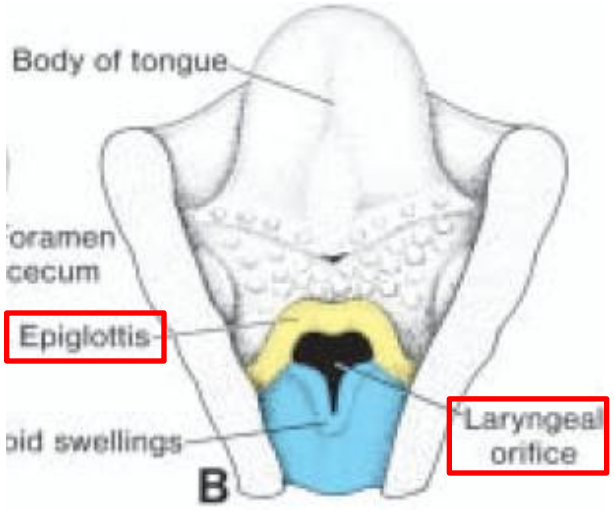
Larynx

- 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 and their saccules.**

- 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, a branch of the vagus nerve, gives the external laryngeal nerve which innervates derivatives of the fourth pharyngeal arch (i.e., cricothyroid muscle which tenses vocal cords to produce high-pitched voice), and the **recurrent laryngeal nerve,** also a branch of the vagus nerve, innervates derivatives of the sixth pharyngeal arch (the rest of the muscles).

Anomalies of the larynx

Laryngeal atresia

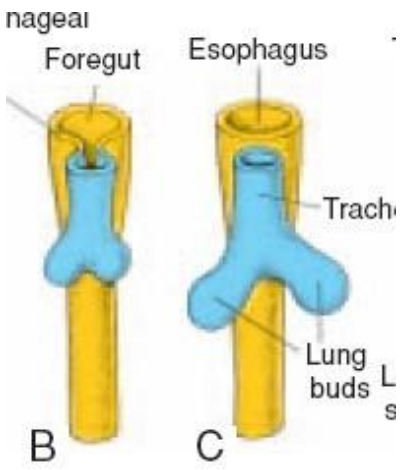
- Laryngeal atresia is a rare anomaly and cause obstruction of the upper fetal airway
- Also known as **congenital high airway obstruction syndrome (chaos)**
- Distal to the atresia or stenosis the lung are enlarged and capable of producing echoes (echogenic)
- Also, the diaphragm is flattened or inverted, and fetal ascites (fluid within the abdominal cavity) and hydrops (accumulation of serous fluid) is present
- Prenatal ultra-sonograpghy permits diagnosis.

Lungs and Bronchial tree development

Trachea, Bronchi, and Lungs

- During its separation from the foregut, the **lung bud** forms the trachea and two lateral outpocketings, the **bronchial buds**

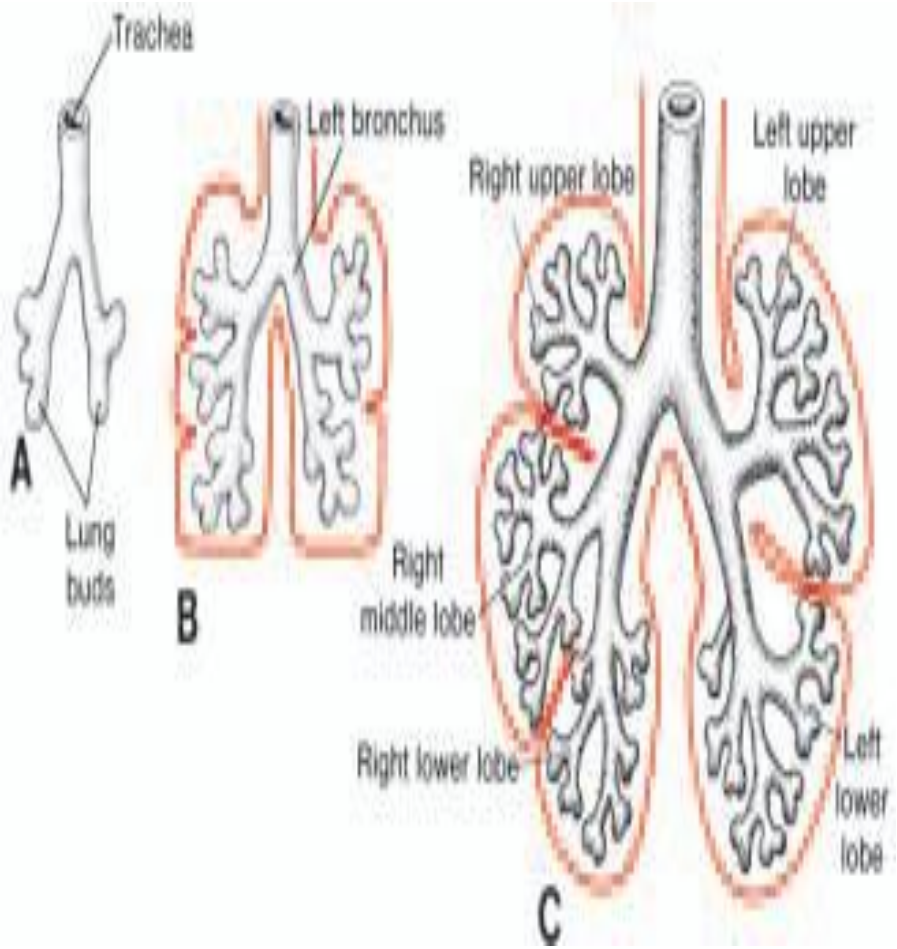
- At the beginning of the fifth week, each of these buds enlarges to form right and left main bronchi



Trachea, Bronchi, and Lungs

- The right then forms three secondary/lobar bronchi, and the left, two

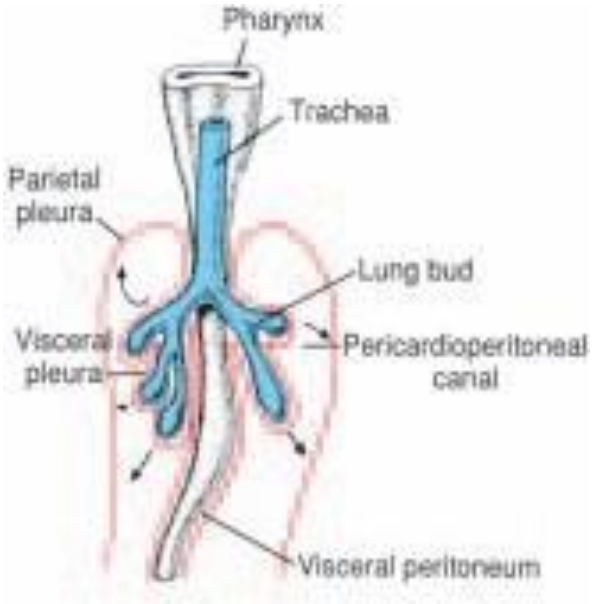
- thus foreshadowing the three lobes on the right side and two on the left



Trachea, Bronchi, and Lungs

- 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 then become pleuropericardial and pleuroperitoneal cavities.

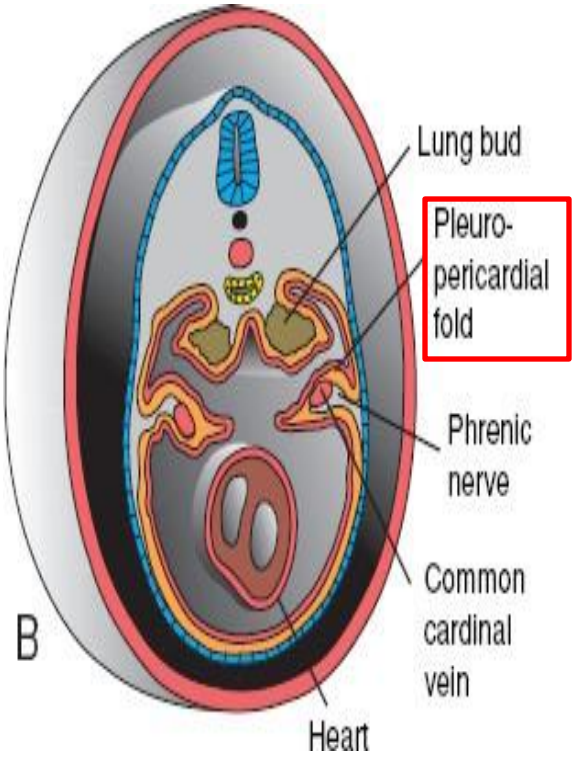


- They lie on each side of the foregut

Trachea, Bronchi, and Lungs

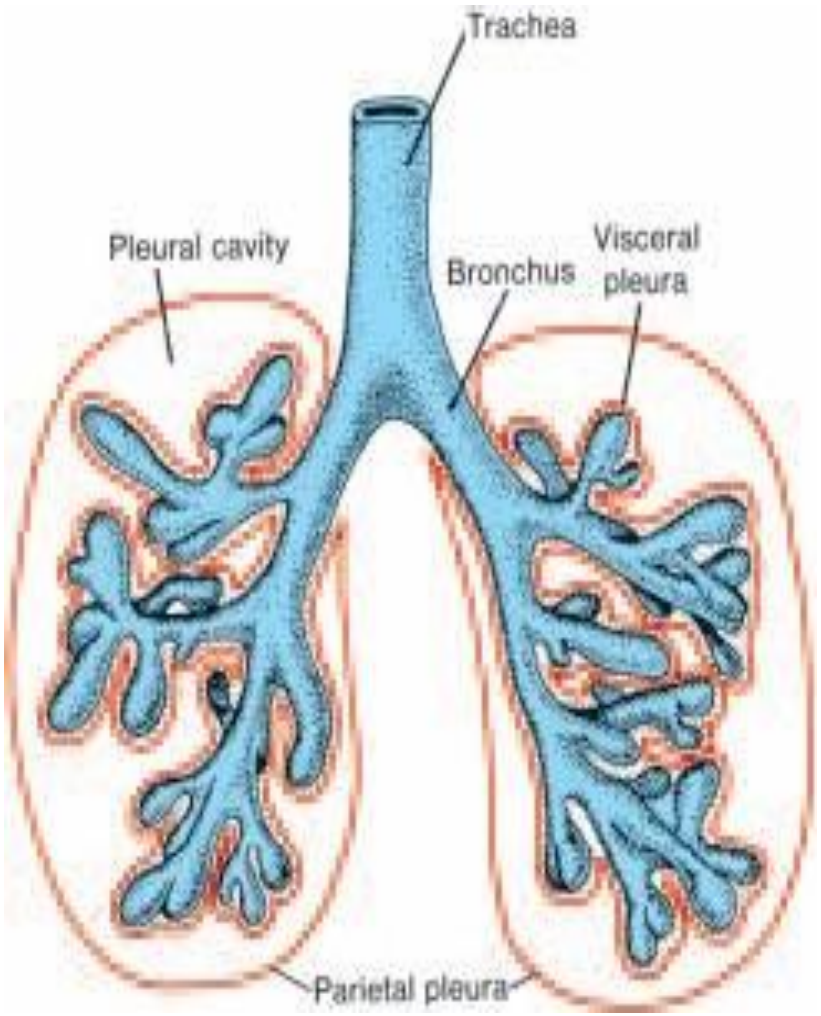
- Ultimately the pleuroperitoneal and pleuropericardial folds separate the pericardioperitoneal canals from the peritoneal and pericardial cavities

- and the remaining spaces form the **primitive pleural cavities**



Trachea, Bronchi, and Lungs

- 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**



Trachea, Bronchi, and Lungs

- 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 (apicoposterior and anteromedial segments separate later on after birth), 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, to end up with the terminal bronchioles. However, the formation and maturation of alveolar ducts, alveolar sacs and alveoli occurs within the lungs primarily after birth.**

- 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 fromthe 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

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.

10 years

Note: no respiratory membrane yet! Any infant born before 26 weeks/7 months cannot survive.

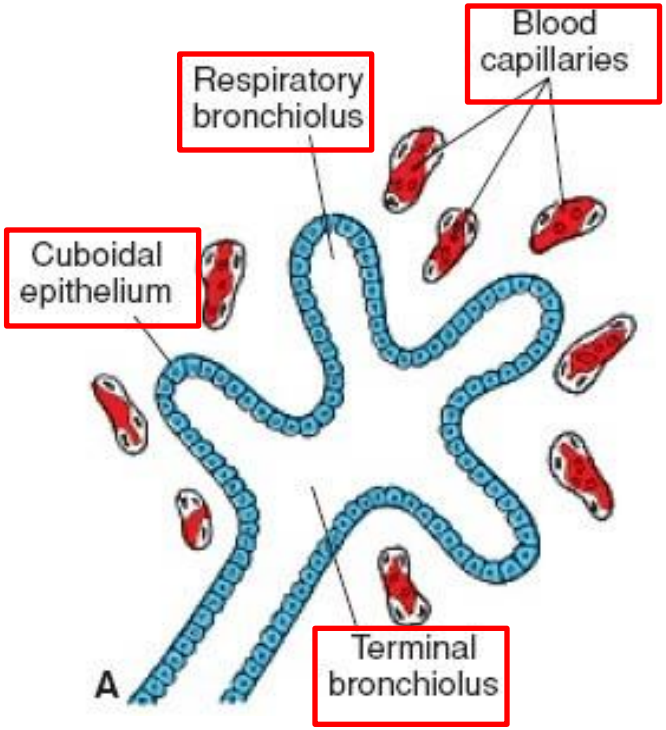
Well-developed respiratory membrane

Maturation of the Lungs

- Up to the seventh prenatal month, the bronchioles divide continuously into more and smaller canals (canalicular phase) which form respiratory bronchioles (note: epithelium is still cuboidal)

- the vascular supply increases steadily; however, there is NO RESPIRATORY MEMBRANE (NO CONTACT).

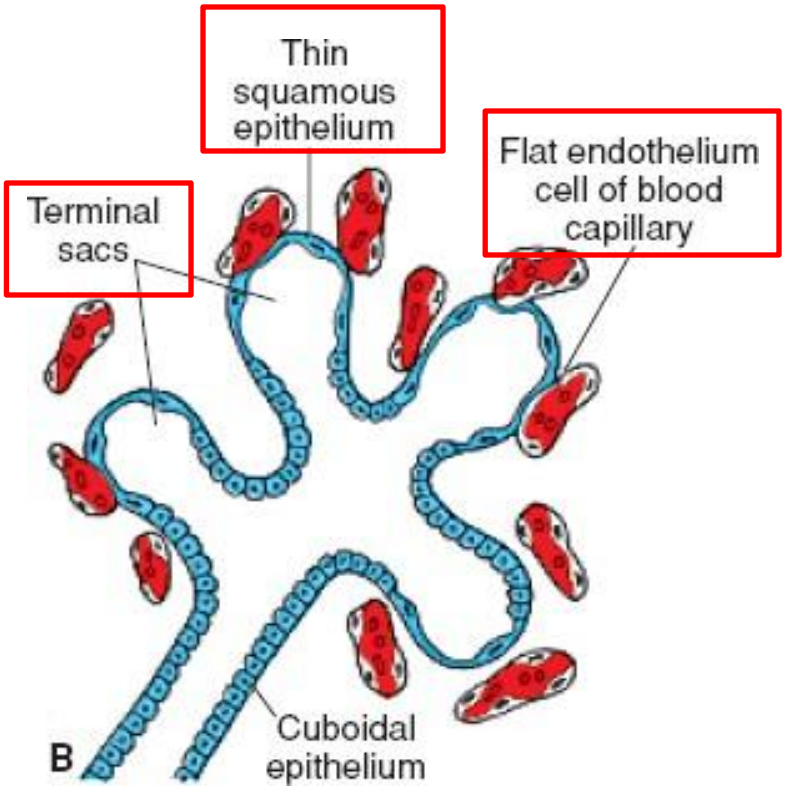
- Respiration becomes possible when some of the cells of the cuboidal **respiratory bronchioles** change into thin, flat cells (i.e. terminal sac period)



Maturation of the Lungs

- These cells are intimately associated with numerous blood and lymph capillaries, and the surrounding spaces are now known as **terminal sacs** or **primitive alveoli (note the thin squamous epithelium)**

- During the seventh month, sufficient numbers of capillaries (i.e. respiratory membrane) are present to guarantee adequate gas exchange, and the premature infant is able to survive.



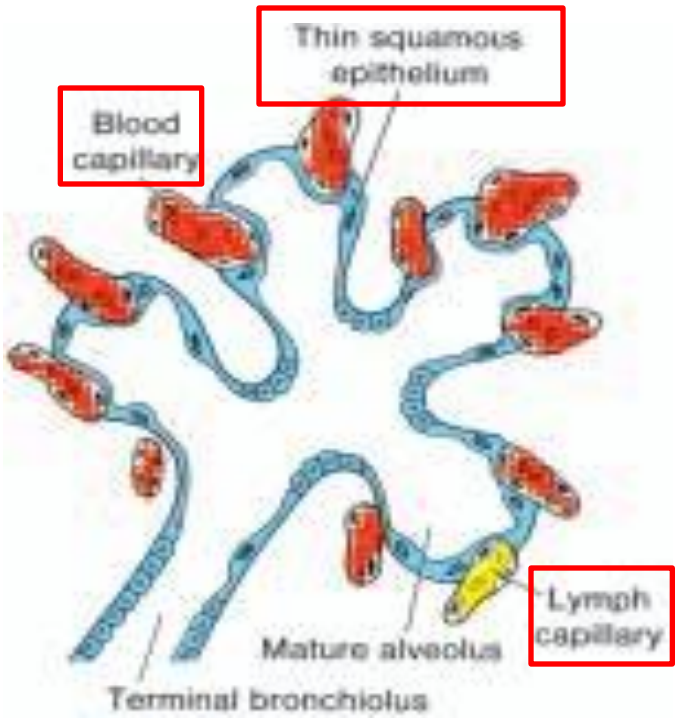
Maturation of the Lungs

- 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/invaginate into the alveolar sacs.
- In addition, type 2 pneumocytes develop to synthesize and secrete the surfactants. Lymphatics also develop here.

- This intimate contact between epithelial and endothelial cells makes up the **blood-air barrier.**

- **Mature alveoli** are not present before birth



Maturation of the Lungs

- 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** **which reduces the surface tension. If it's absent, it causes IRDS. The first breath is indicated with the first cry which occurs during expiration.**

- 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.

Maturation of the Lungs (read it all, Doctor only focused on the highlighted statements, however)

- 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 (suctioning is also done to clear the airways from these fluids) 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).

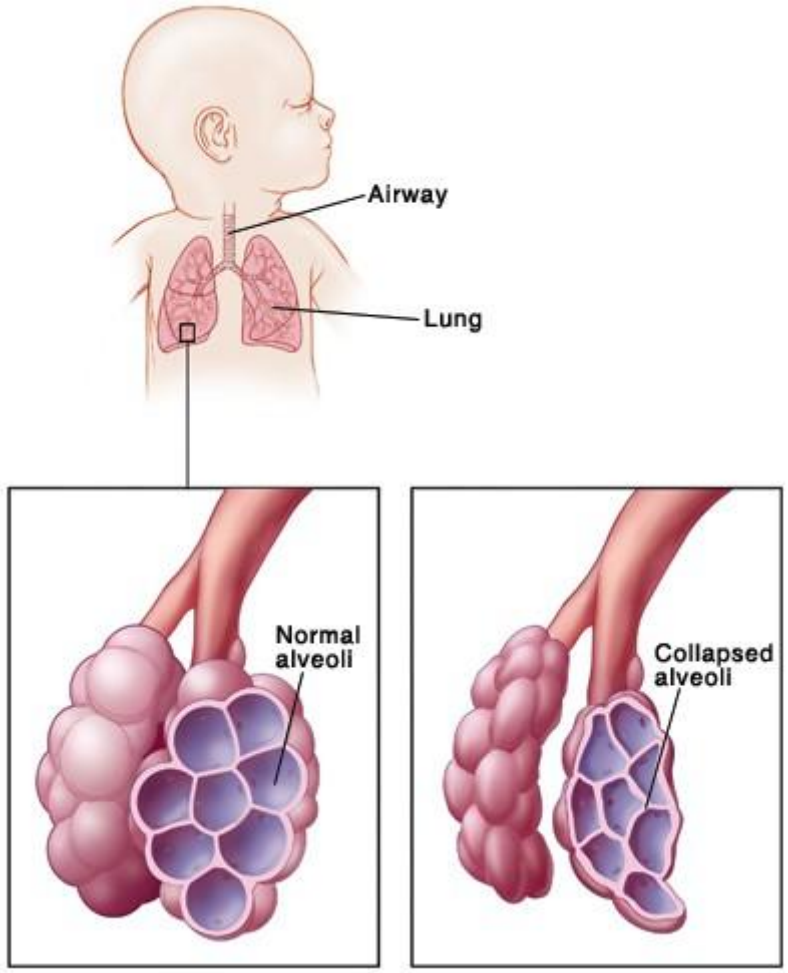
Maturation of the Lungs

- 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.

Anomalies of the lung

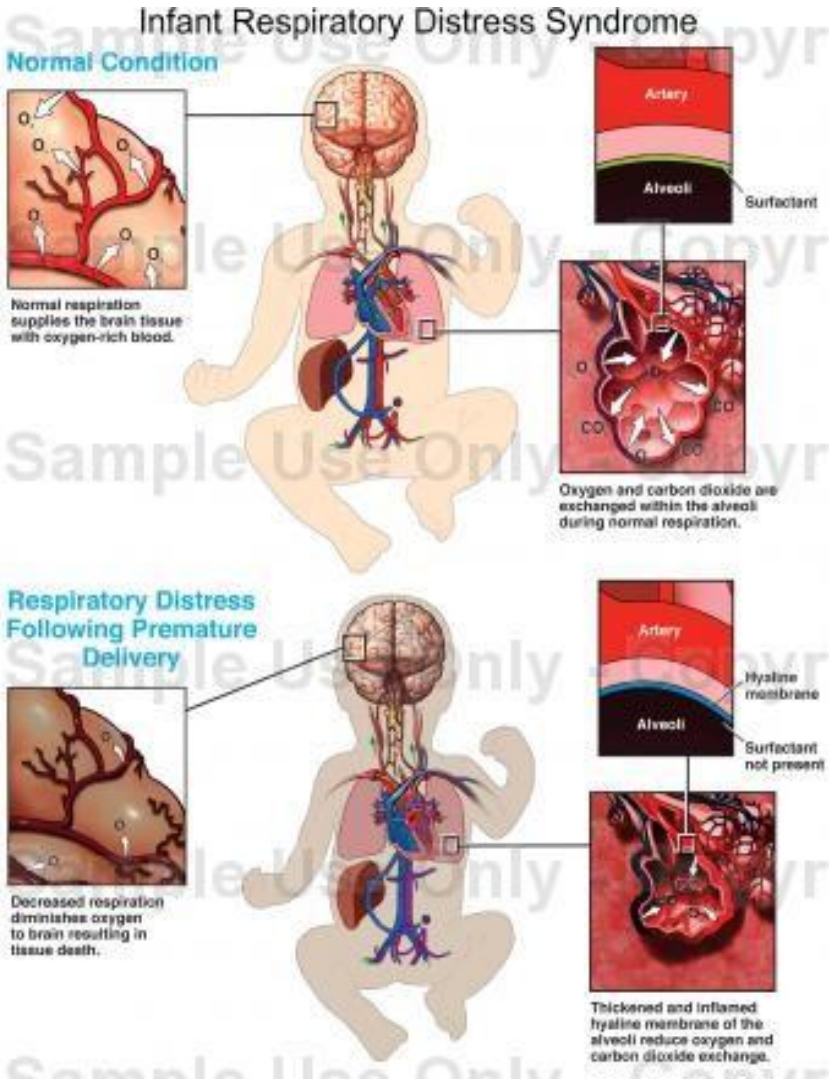
Clinical notes (RDS)

- 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/rupture during expiration (atelectasis).
- As a result, **respiratory distress syndrome** (RDS) develops
- This is a common cause of death in the premature infant (30% of all neonatal diseases)
- 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



Clinical notes (RDS)

- RDS, is therefore also known as **hyaline membrane disease,** accounts for approximately 20% of deaths among newborns
- Intrauterine Asphyxia may produce irreversible changes in type II cells
- Recent development of artificial surfactant and treatment of premature babies with glucocorticoids (betamethasone) to stimulate surfactant production have reduced the mortality associated with RDS
- It Also allowed survival of some babies as young as 5.5 months of gestation
- Thyroxine is the most important stimulator for surfactants production



Clinical notes (Other Anomalies)

- Although many abnormalities of the lung and bronchial tree have been found (e.g., blind-ending trachea with absence of lungs and agenesis of one lung) most of these gross abnormalities are rare

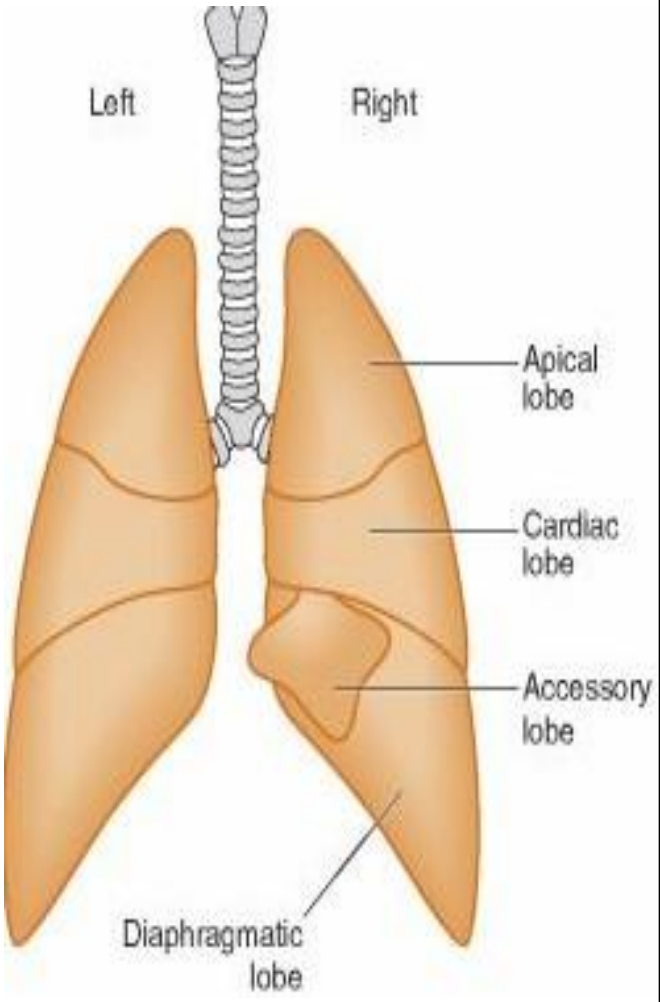
- Abnormal divisions of the bronchial tree are more common; some result in supernumerary lobules.

- These variations of the bronchial tree have little functional significance, but they may cause unexpected difficulties during bronchoscopies.

Clinical notes (Other Anomalies)

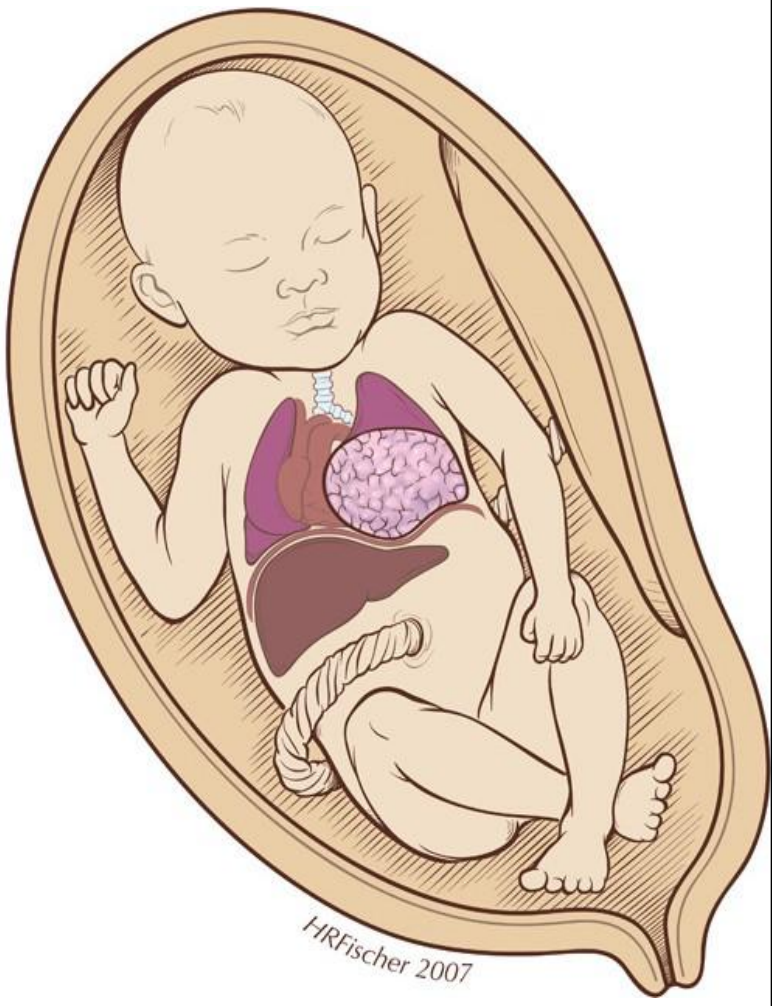
- **Ectopic (i.e. outside the normal site) lung lobes** arising from the trachea or esophagus

- It is believed that these lobes are formed fromadditional respiratory buds of the foregut that develop independently of the main respiratory system.



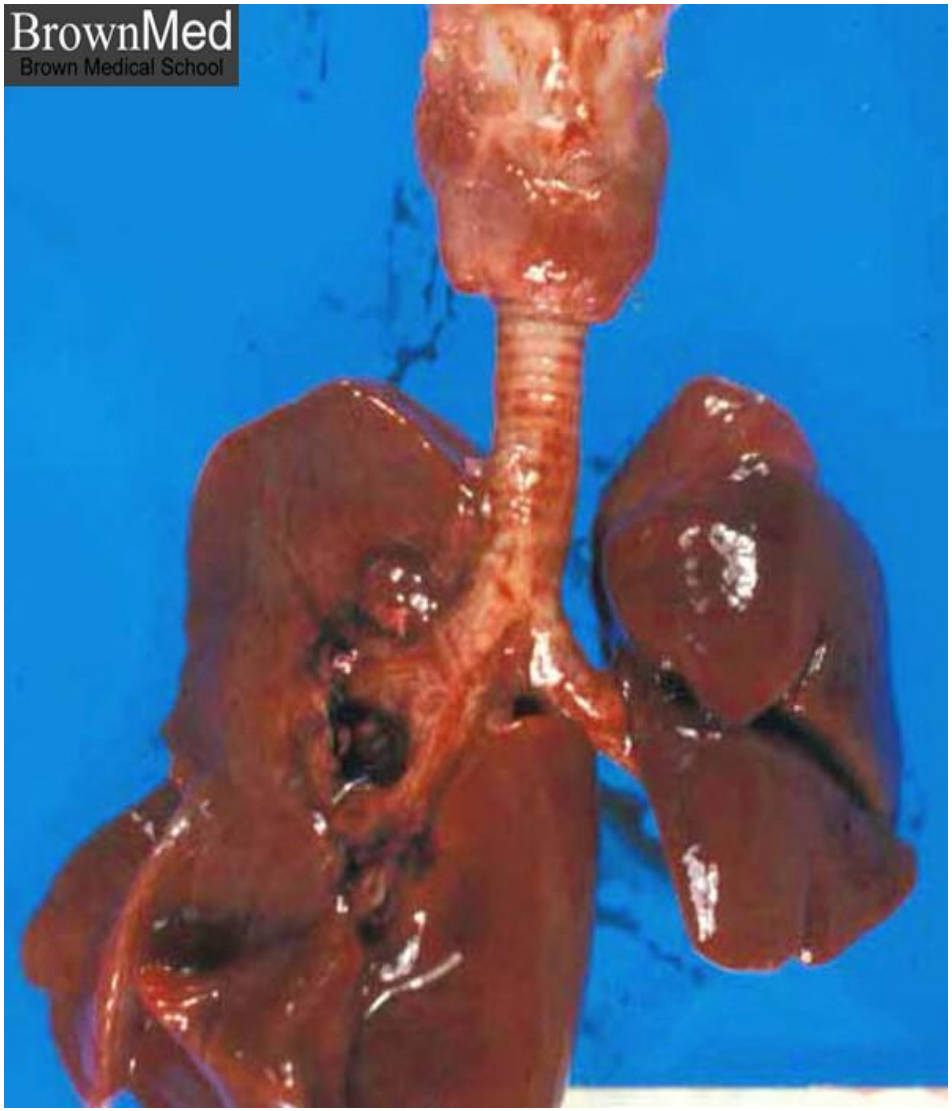
Clinical notes (Other Anomalies)

- Most important clinically are **congenital cysts of the lung**
- which are formed by dilation of terminal or larger bronchi
- These cysts may be small and multiple, giving the lung a honeycomb appearance on radiograph
- Or they may be restricted to one or more larger ones
- Cystic structures of the lung usually drain poorly and frequently cause chronic infections



Lung Hypoplasia

- In infants with congenital diaphragmatic hernia (CDH) the lung is unable to develop normally
- Because it is compressed by the abnormally positioned abdominal viscera (more common on the left side)
- It is characterized by reduced lung volume
- Most infants with CDH die of pulmonary insufficiency as their lungs are too hypoplastic to support life



Oligohydroamnios and lungs

- When oligohydroamnios (reduced amniotic fluid) is severe, lung development is retarded (as we said, the amniotic fluids are essential for stimulating lung development and conditioning respiratory muscles)

- Severe pulmonary hypoplasia results

Lungs of the newborn infants

- Fresh and healthy lungs contain some air so pulmonary samples float in water

- The lungs of the stillborn infants are firm and sink in water because they contain fluids not air.

Thank you