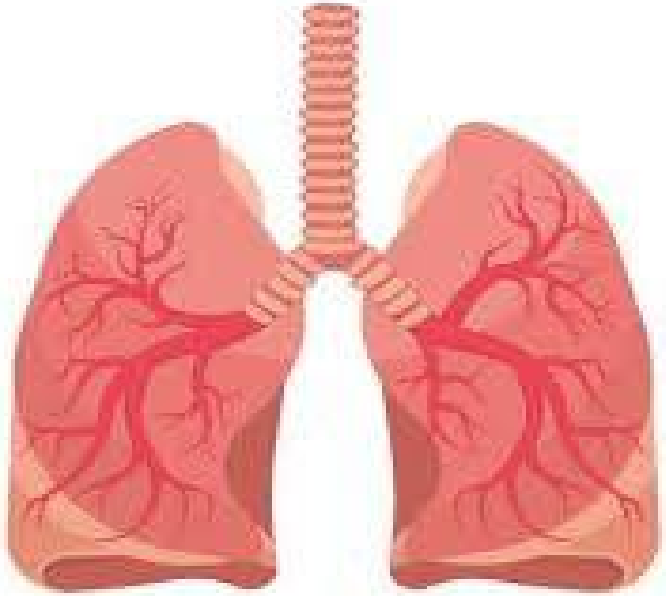
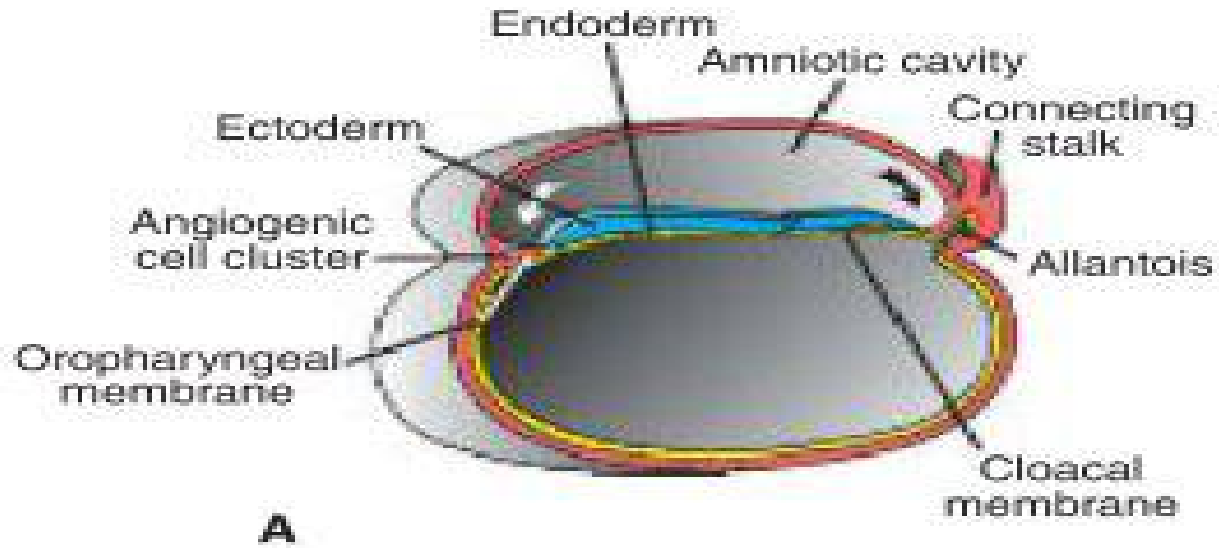
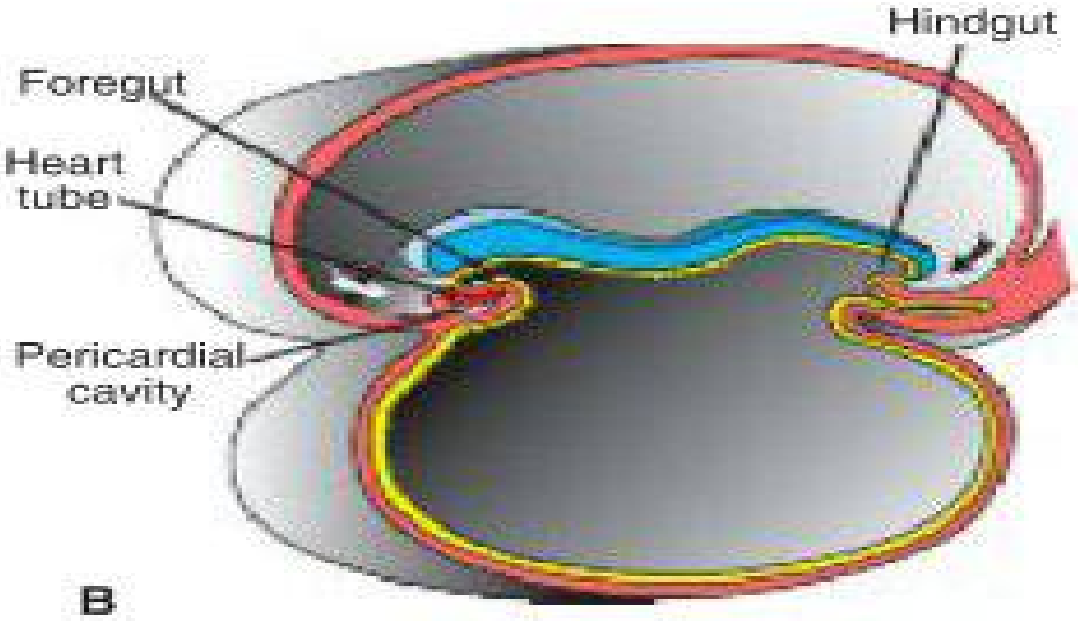
Embryology

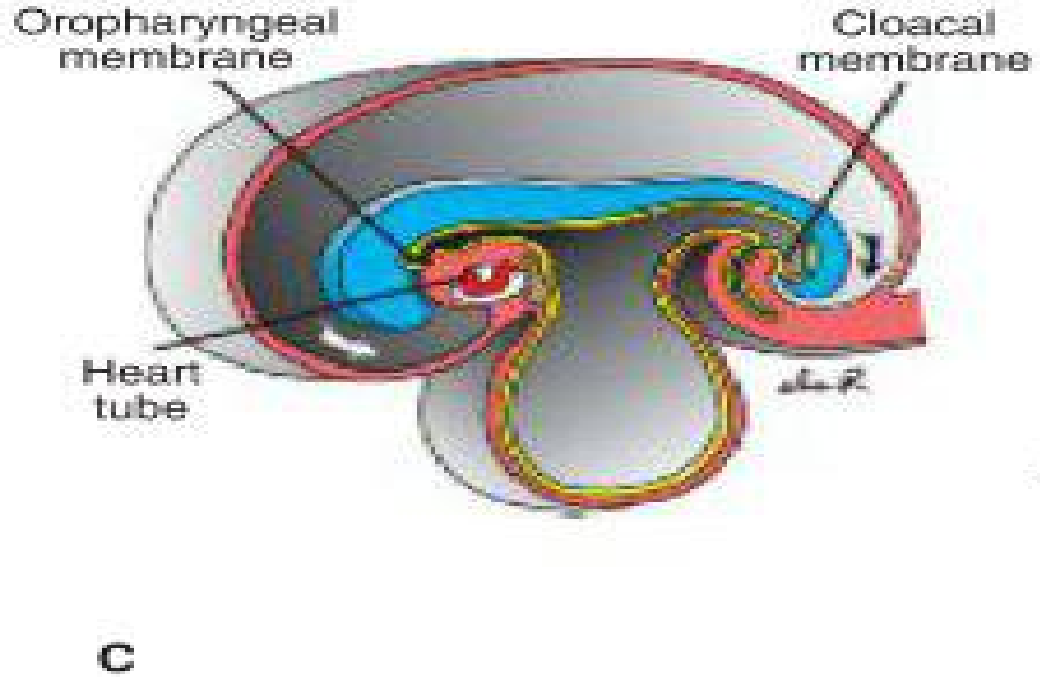
Dr. Sharif Yaser Matar

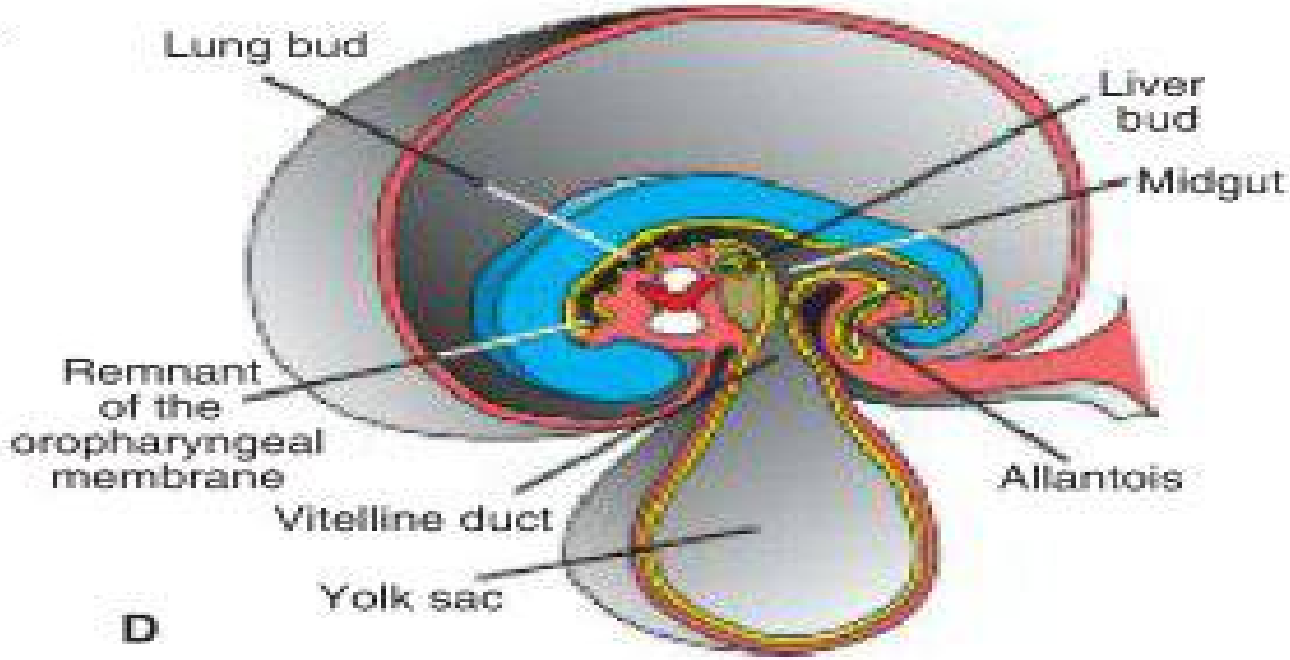


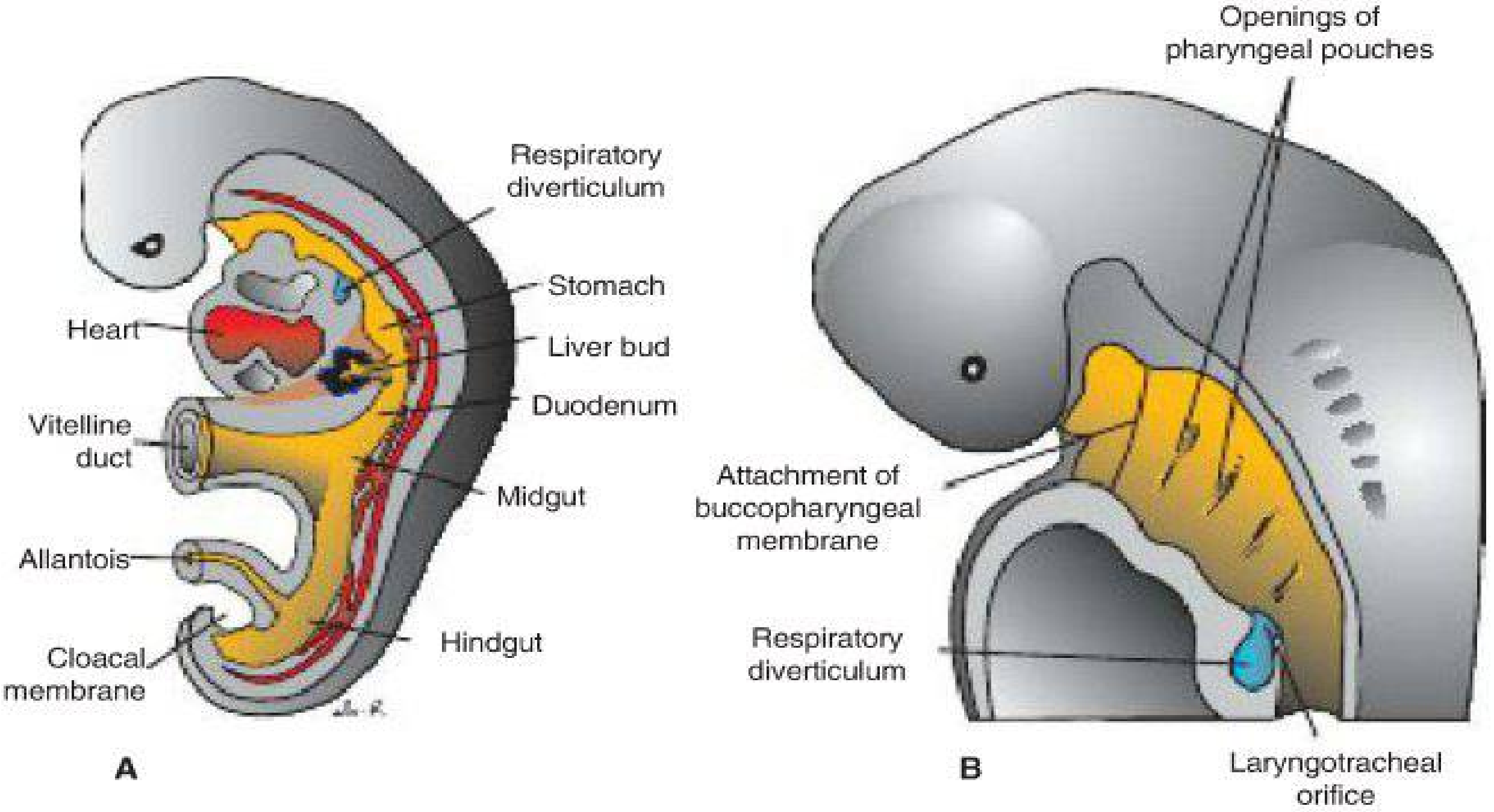
Respiratory System


Endoderm
Amniotic cavity
Connecting stalk
Ectoderm
Angiogenic cell cluster
Allantois
Oropharyngeal membrane
Cloacal membrane
A

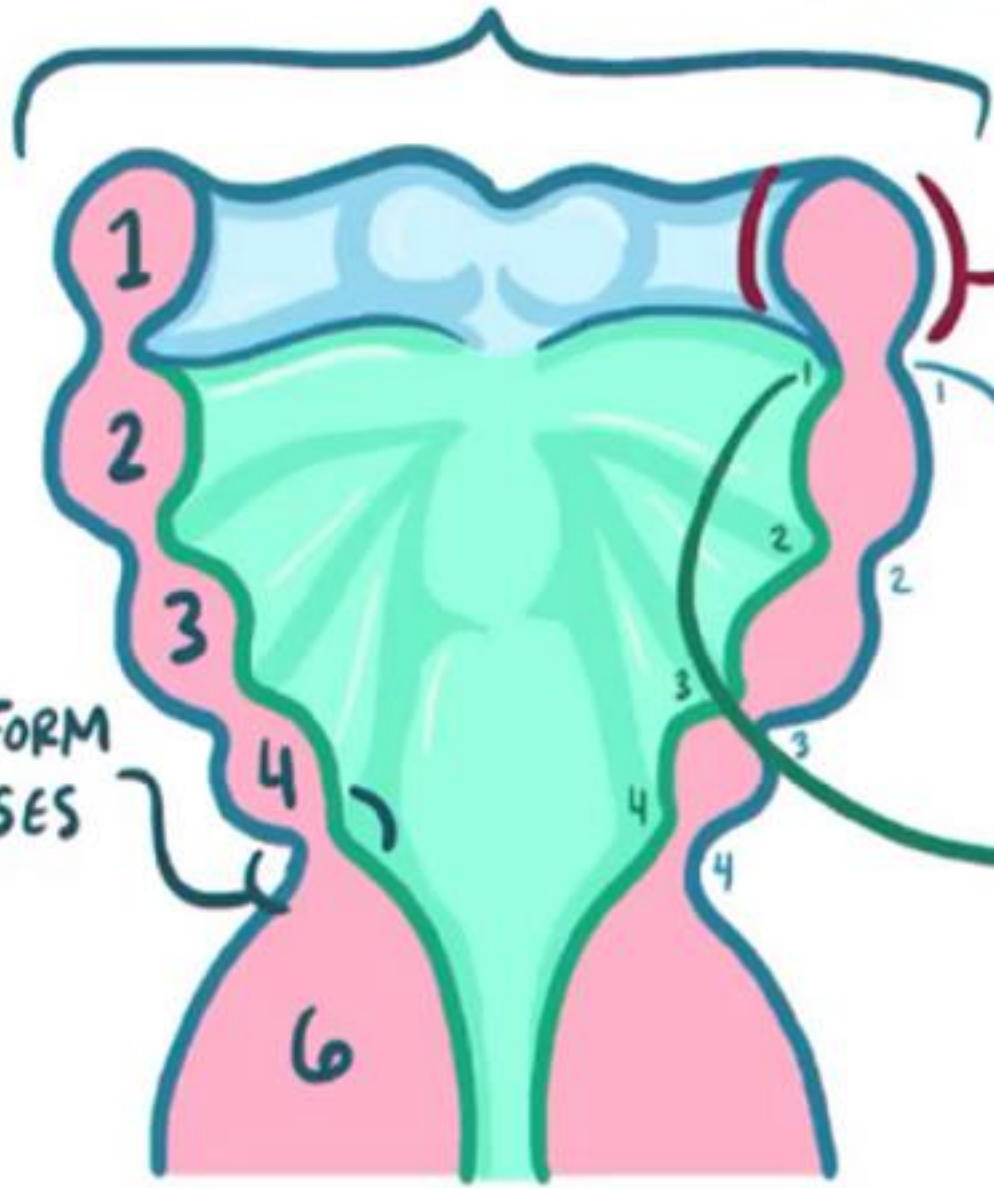

Hindgut
Foregut
Heart tube
Pericardial cavity
B


Oropharyngeal membrane
Cloacal membrane
Heart tube
C


Lung bud
Liver bud
Midgut
Remnant of the oropharyngeal membrane
Allantois
Vitelline duct
Yolk sac
D


Respiratory diverticulum
Stomach
Heart
Liver bud
Duodenum
Vitelline duct
Midgut
Allantois
Hindgut
Cloacal membrane
A
Openings of pharyngeal pouches
Attachment of buccopharyngeal membrane
Respiratory diverticulum
Laryngotracheal orifice
B

PHARYNGEAL APPARATUS



5 DOESN'T FORM or REGRESSES

From PRIMITIVE PHARYNX

ARCH
* MESODERM *
* WEEKS 4-5 *

CLEFT
* ECTODERM *

POUCH
* ENDODERM *

(HEAD) CRANIO-

-CAUDAL (TAIL)

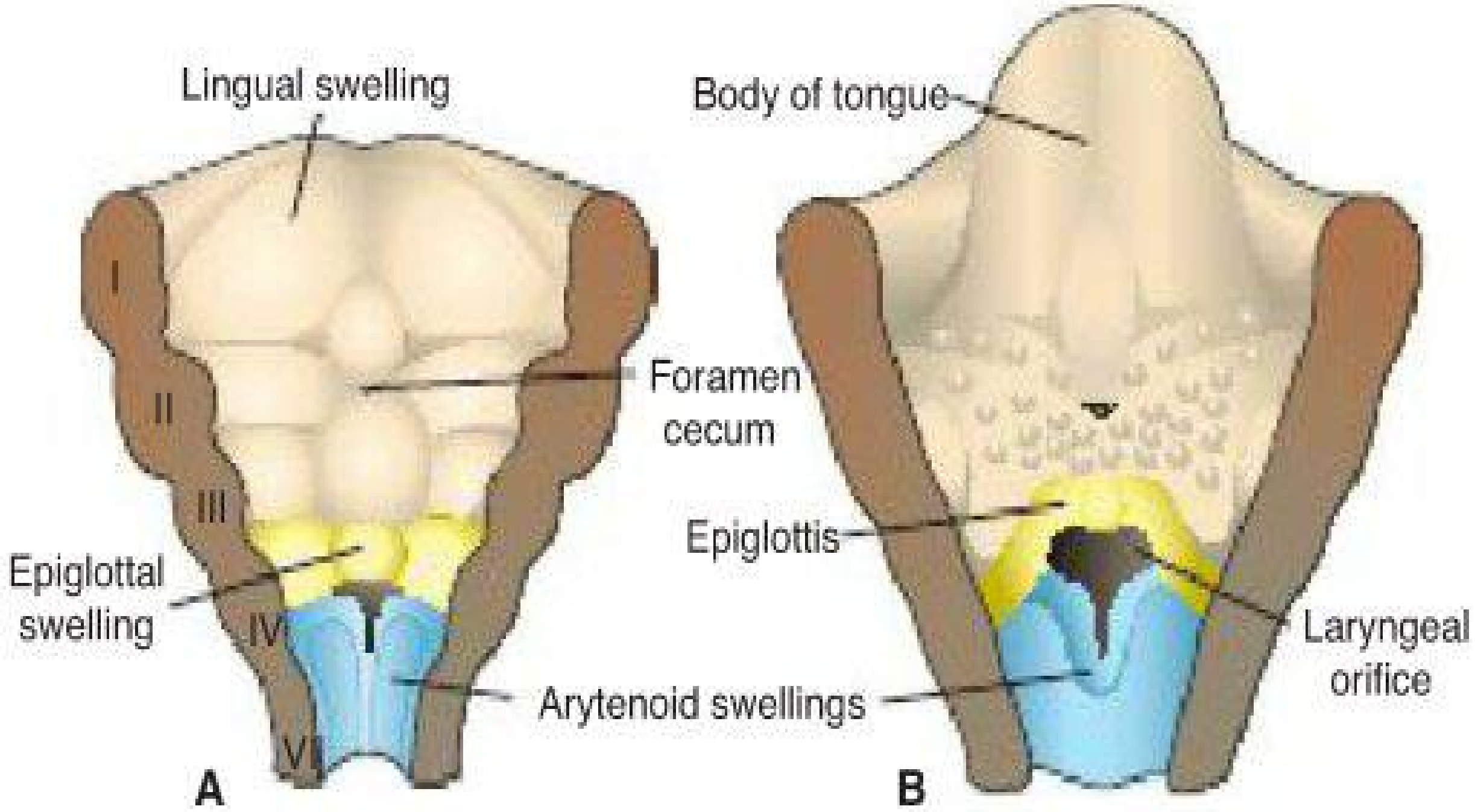
FORMATION OF THE LUNG BUDS

- When the embryo is approximately 4 weeks old, the respiratory diverticulum (lung bud) appears as an outgrowth from the ventral w of the foregut .
- the appearance and location of the lung bud are dependent upon an increase in retinoic acid (RA) produced by adjacent mesoderm
- Initially, the lung bud is in open communication with the foregut
- When the diverticulum expands caudally, however, two longitudinal ridges, the tracheoesophageal ridges, separate it from the foregut
- Subsequently, when these ridges fuse to form the tracheoesophageal

septum, the foregut is divided into a dorsal portion, the esophagus, a a ventral portion, the trachea

LARYNX

- The internal lining of the larynx originates from endoderm, but th cartilages and muscles originate from mesenchyme of the fourth and sixth pharyngeal arches.
- As a result of rapid proliferation of this mesenchyme, the laryngea 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 characteristi 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

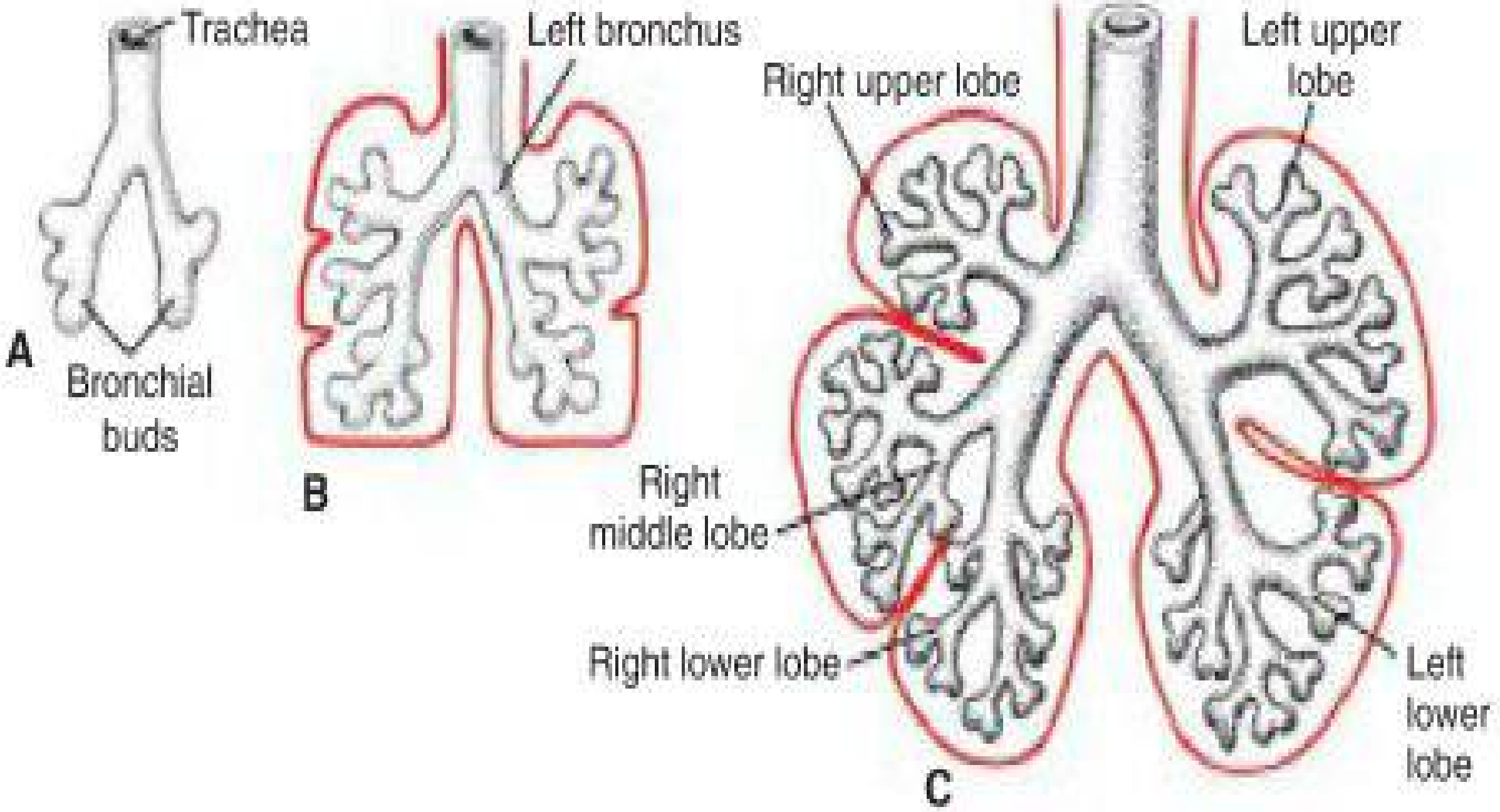

Lingual swelling
Body of tongue
I
II
III
IV
V
VI
Foramen cecum
Epiglottal swelling
Epiglottis
Laryngeal orifice
Arytenoid swellings
A
B

TRACHEA, BRONCHI, AND LUNGS

- During its separation from the foregut, the lung bud forms the trachea and two lateral outpocketings, the primary bronchial buds .
- At the beginning of the fifth week, each of these buds enlarges to form right and left primary

bronchi. The right then forms three secondary bronchi, and the left, two , thus foreshadowing the three lobes of the lung on the right side and two on the left .

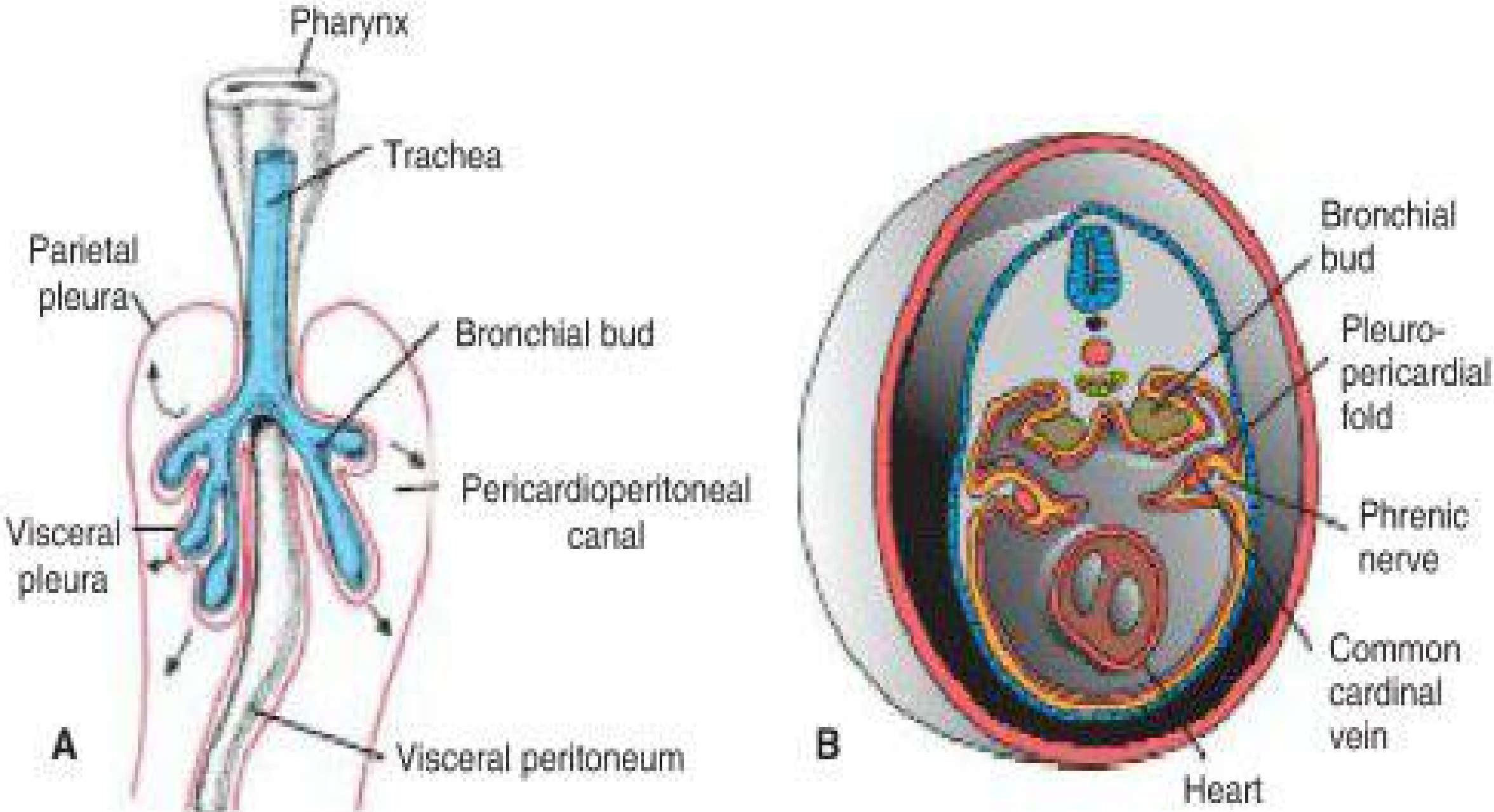
- With subsequent growth in caudal and lateral directions, the lungs expand into the body cavity


Trachea
Bronchial buds
A
Left bronchus
B
Right upper lobe
Left upper lobe
Right middle lobe
Right lower lobe
Left lower lobe
C

- The spaces for the lungs, the pericardioperitoneal canals, are narrow. They lie on each side of the foregut and are gradually filled

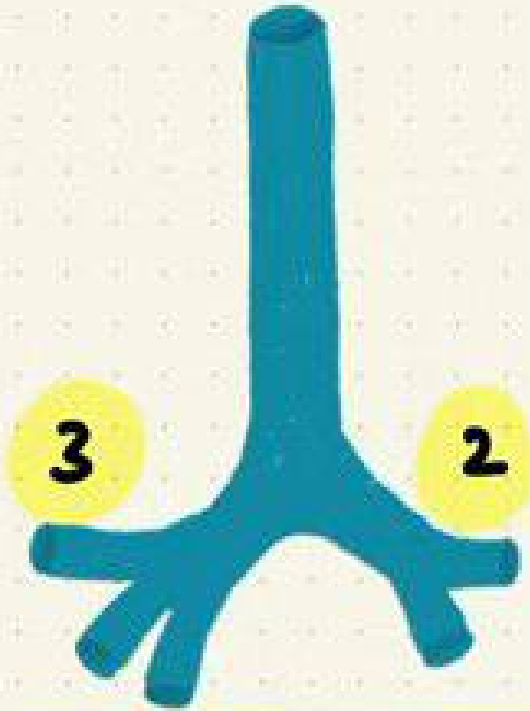
  by the expanding growth of the lungs.
- Ultimately, the pleuroperitoneal and pleuropericardial folds separate the pericardioperitoneal canals from the peritoneal and pericardial cavities, respectively, and the remaining spaces form the primitive pleural cavities
- the mesoderm, which covers the outside of the lung, develops

  into the visceral pleura.
- the somatic mesoderm layer, covering the body wall from the inside, becomes the parietal pleura .
- The space between the parietal and visceral pleura is the

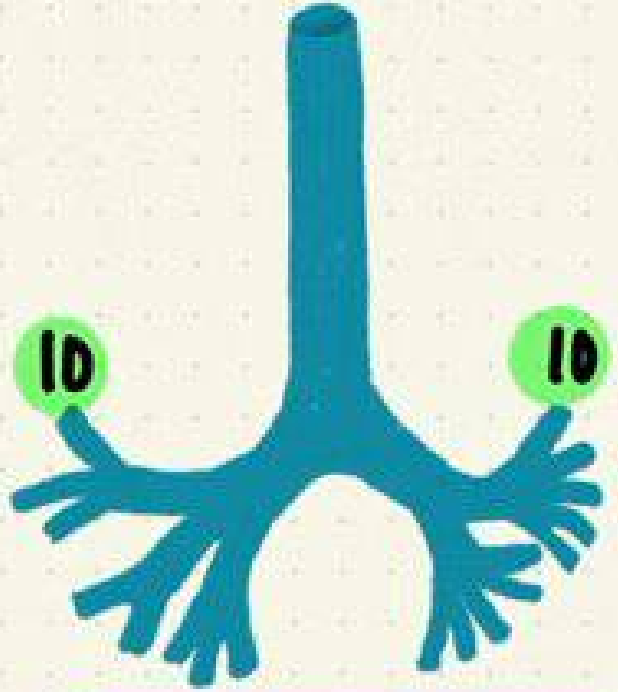

Pharynx
Trachea
Parietal pleura
Bronchial bud
Pericardioperitoneal canal
Visceral pleura
A
Visceral peritoneum
Bronchial bud
Pleuro-pericardial fold
Phrenic nerve
Common cardinal vein
B
Heart

- During further development, secondary bronchi divide repeatedly in a dichotomous fashion, forming 10 tertiary (segmental) bronchi in the right lung and 8 in the left, creating the bronchopulmonary segments of the adult lung.
- By the end of the sixth month, approximately 17 generations of subdivisions have formed.
- Before the bronchial tree reaches its final shape, however, an additional six divisions form during postnatal life.

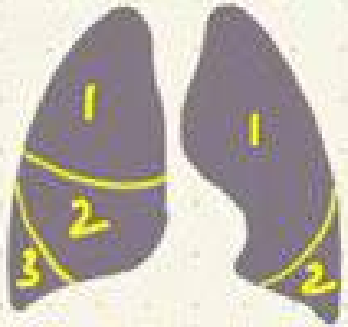
PRIMARY BRONCHI

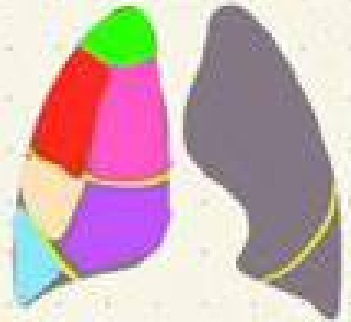


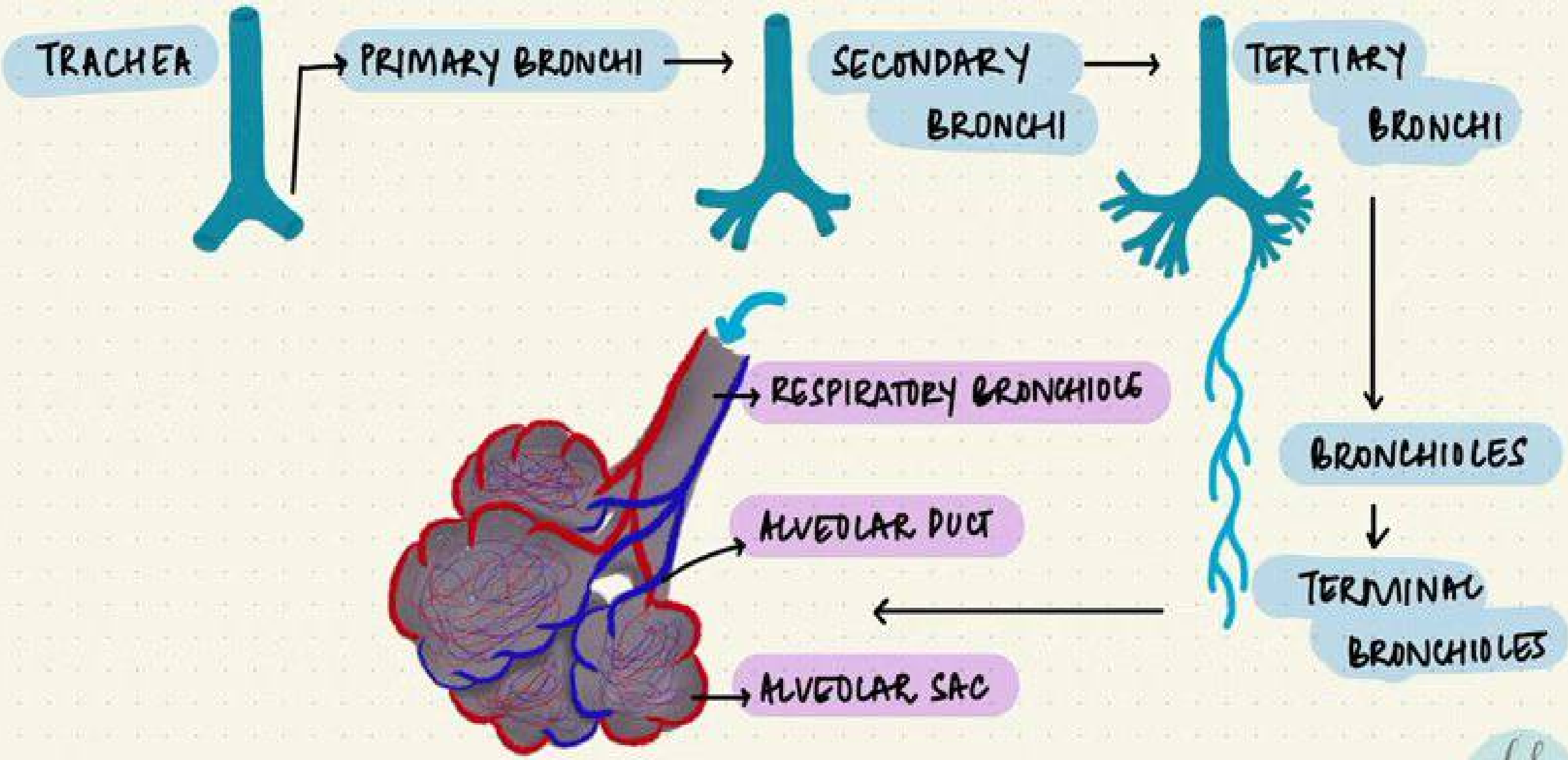
SECONDARY BRONCHI

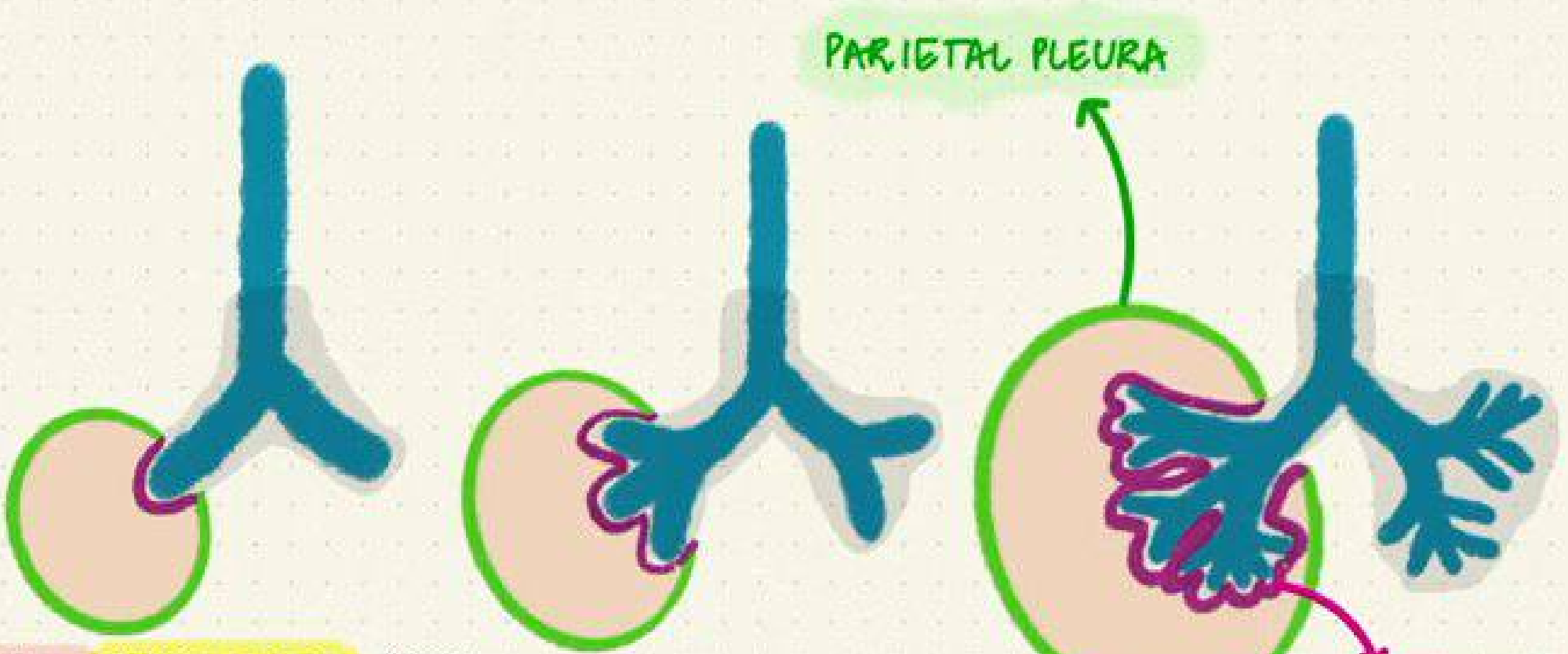


TERTIARY BRONCHI






TRACHEA
PRIMARY BRONCHI
SECONDARY BRONCHI
TERTIARY BRONCHI
BRONCHIOLES
TERMINAL BRONCHIOLES
RESPIRATORY BRONCHIOLE
ALVEOLAR DUCT
ALVEOLAR SAC



PERICARDIOPERITONEAL CANAL

PLEUROPERICARDIAL MEMBRANE

PLEUROPERITONEAL MEMBRANE

MATURATION OF THE LUNGS

- Up to the seventh prenatal month, the bronchioles divide continuously into more and smaller canals (canalicular phase) and the vascular supply increases steadily.
- Terminal bronchioles divide to form respiratory bronchioles, and each of these divides into three to six alveolar ducts . The ducts end in terminal sacs (primitive alveoli) that are surrounded by flat alveolar cells in close contact with neighboring capillaries
- By the end of the seventh month, sufficient numbers of

mature alveolar sacs and capillaries are present to guarantee adequate gas exchange, and the premature infant is able to survive

- During the last 2 months of prenatal life and for several years thereafter, the number of terminal sacs increases steadily. In addition, cells lining the sacs, known as type I alveolar epithelial cells, become thinner, so that surrounding capillaries protrude into the alveolar sacs .
- This intimate contact between epithelial and endothelial cells makes up the blood—air barrier.
- Mature alveoli are not present before birth.
- In addition to endothelial cells and flat alveolar epithelial cells, another cell type develops at the end of the sixth month. These cells, type II alveolar epithelial cells, produce surfactant, a phospholipid-rich fluid capable of lowering surface tension at the air—alveolar interface.

Table 14.1 Maturation of the Lungs

Pseudoglandular period	5–16 wk	Branching has continued to form terminal bronchioles. No respiratory bronchioles or alveoli are present.
Canalicular period	16–26 wk	Each terminal bronchiole divides into two or more respiratory bronchioles, which in turn divide into three to six alveolar ducts.
Terminal sac period	26 wk to birth	Terminal sacs (primitive alveoli) form, and capillaries establish close contact.
Alveolar period	8 mo to childhood	Mature alveoli have well-developed epithelial endothelial (capillary) contacts.

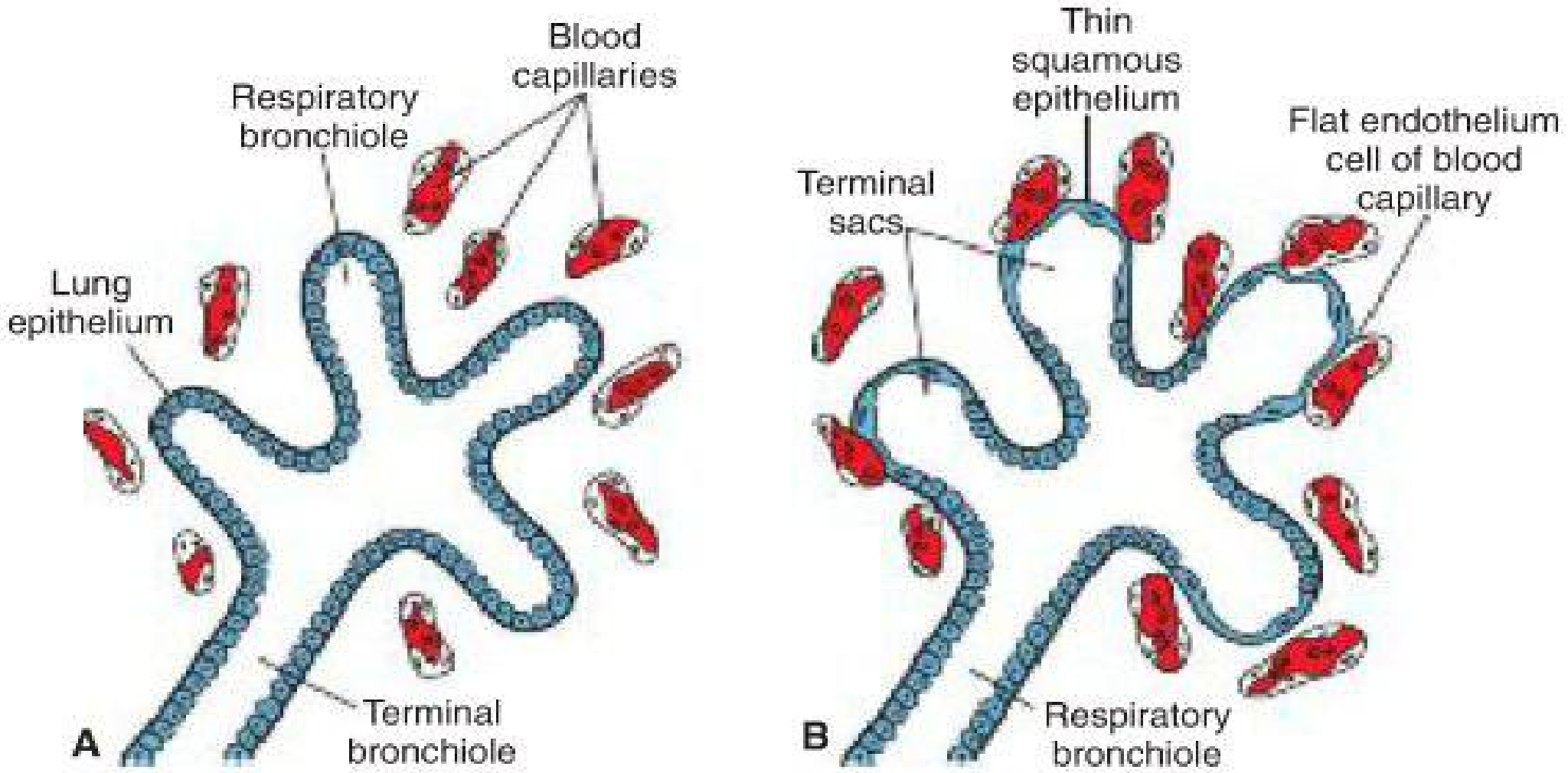


FIGURE 14.8 Histological and functional development of the lung. **A.** The canalicular period lasts from the 16th to the 26th week. Note the cuboidal cells lining the respiratory bronchioli. **B.** The terminal sac period begins at the end of the sixth and beginning of the seventh prenatal month. Cuboidal cells become very thin and intimately associated with the endothelium of blood and lymph capillaries or form terminal sacs [primitive alveoli].

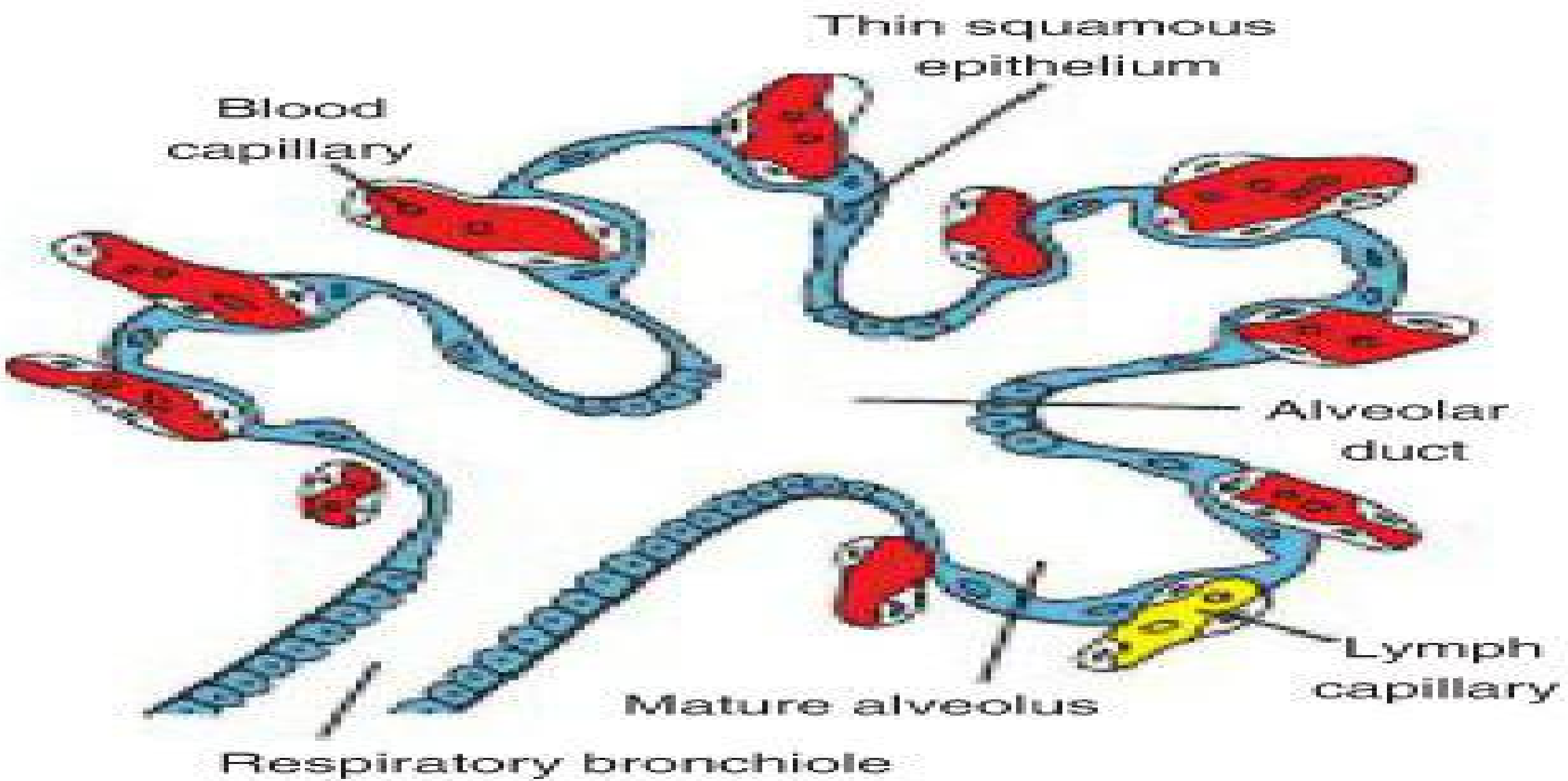
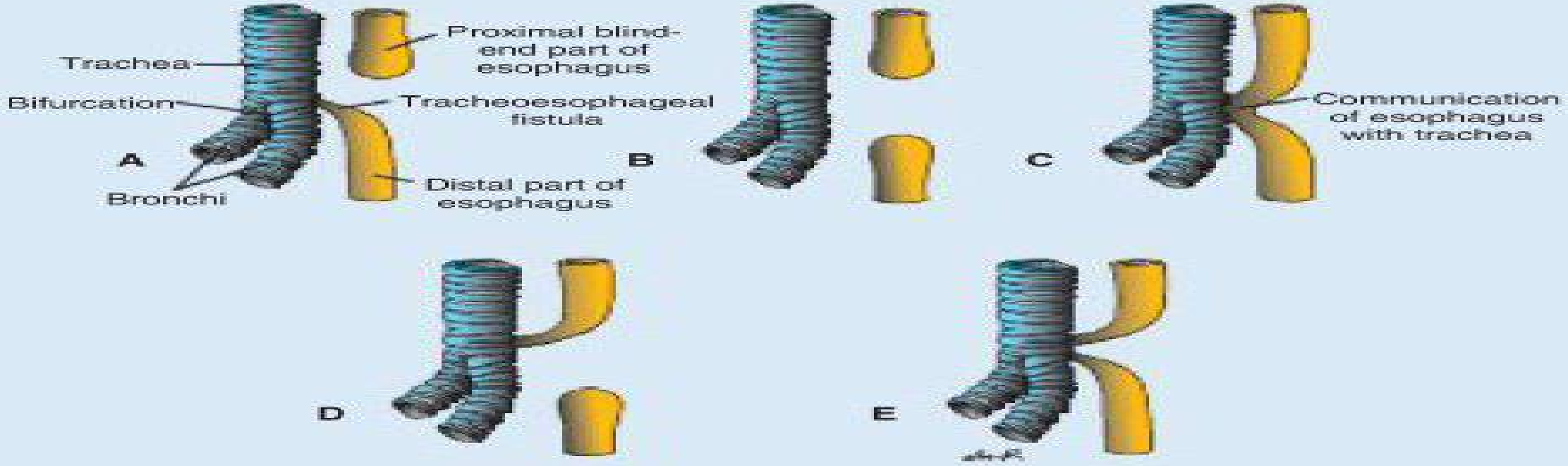


FIGURE 14.9 Lung tissue in a newborn. Note the thin squamous epithelial cells [also known as **alveolar epithelial cells, type I**] and surrounding capillaries protruding into mature alveoli.

- 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. As concentrations of surfactant increase during the 34th week of gestation, some of this phospholipid enters the amniotic fluid and acts on macrophages in the amniotic cavity.
- Once “activated,” evidence suggests that these macrophages migrate across the chorion into the uterus where they begin to produce immune system proteins, including interleukin- 1 B (IL —1 B).
- Upregulation of these proteins results in increased production

Clinical Correlates

Abnormalities in partitioning of the esophagus and trachea by the tracheoesophageal septum result in **esophageal atresia** with or without **tracheoesophageal fistulas (TEFs)**. These defects occur in approximately 1/3,000 births, and 90% result in the upper portion of the esophagus ending in a blind pouch and the lower segment forming a fistula with the trachea (Fig. 14.3*A*). Isolated esophageal atresia (Fig. 14.3*B*) and H-type TEF without esophageal atresia (Fig. 14.3*C*) each account for 4% of these defects. Other variations (Fig. 14.3*D*,*E*)



each account for approximately 1% of these defects. 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.

A complication of some TEFs is polyhydramnios because in some types of TEF, amniotic fluid, when swallowed, does not pass to the stomach and intestines. Also, gastric contents and/or amniotic fluid at birth may enter the trachea through a fistula, causing pneumonitis and pneumonia.

Clinical Correlates

Surfactant is particularly important for survival of the **premature infant**. When surfactant is insufficient, the air–water (blood) surface membrane tension becomes high, bringing great risk that alveoli will collapse during expiration. As a result, **respiratory distress syndrome (RDS)** develops. This is a common cause of death in the premature infant. In these cases, the partially collapsed alveoli contain a fluid with a high protein content, many hyaline membranes, and lamellar bodies, probably derived from the surfactant layer. RDS, which was previously known as **hyaline membrane disease**, accounts for approximately 20% of deaths among newborns. Treatment of preterm babies with artificial surfactant as well as treatment of mothers with premature labor with glucocorticoids to stimulate surfactant production have reduced the mortality associated with RDS.

Although many abnormalities of the lung and bronchial tree have been described (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.

More interesting are **ectopic lung lobes** arising from the trachea or esophagus. It is believed that these lobes are formed from additional respiratory buds of the foregut that develop independent of the main respiratory system.

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.

Development of the Respiratory System

Laryngo-tracheal groove

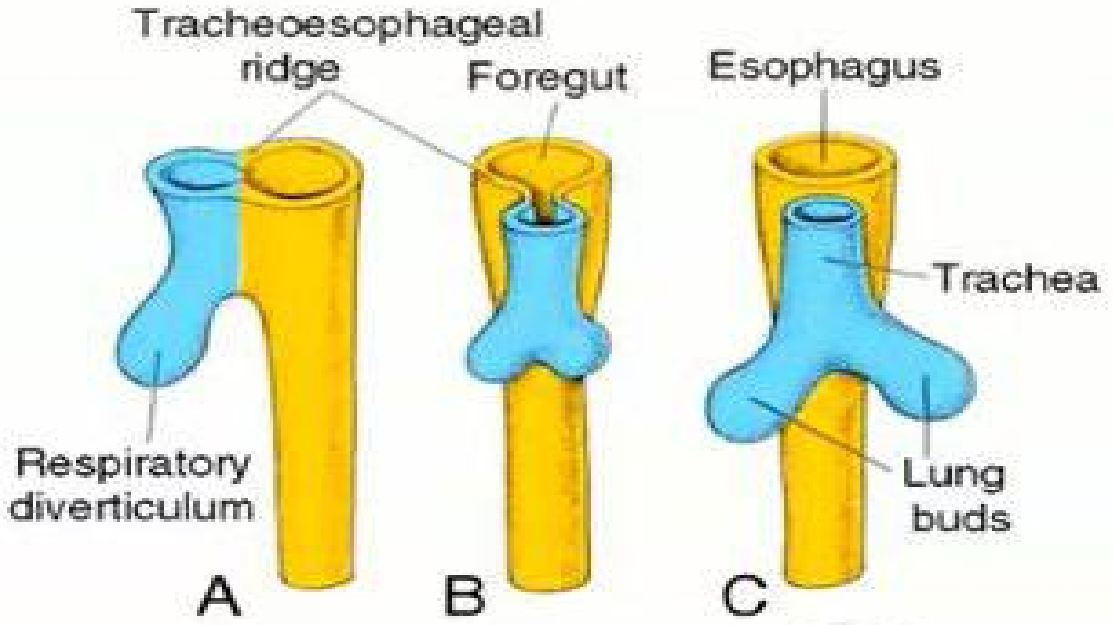
Begins at about the middle of the 4th week

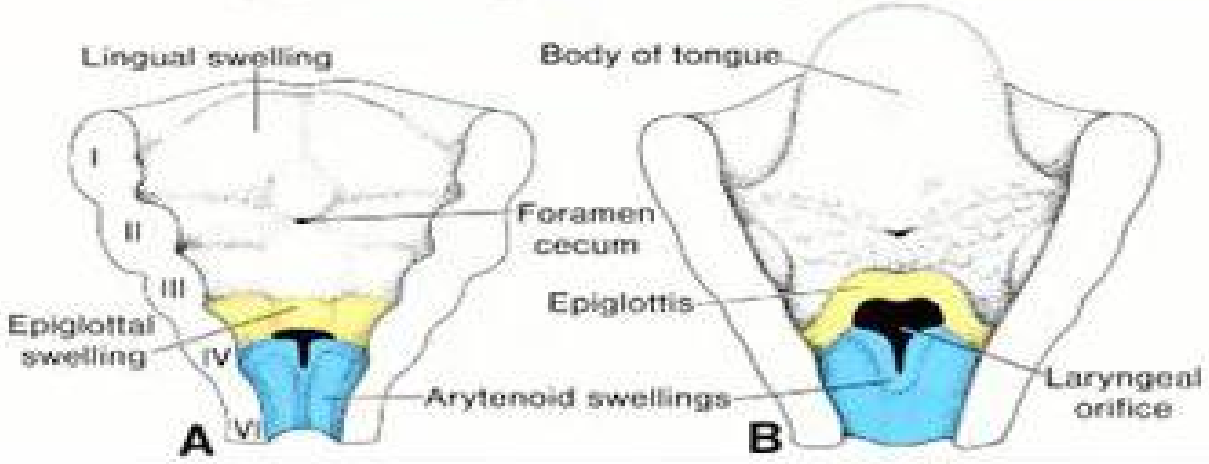
- It appears as a median longitudinal groove in ventral wall of the primitive pharynx (the cranial part of the foregut).
- The 2 margins of the groove (called the tracheo-oesophageal ridges) fuse together in a caudo-cranial direction forming the tracheo-oesophageal septum which separates the lumen of the primitive pharynx into 2 parts:

A. Dorsal part: for the pharynx and esophagus.

B. Ventral part: the laryngo-tracheal tube.

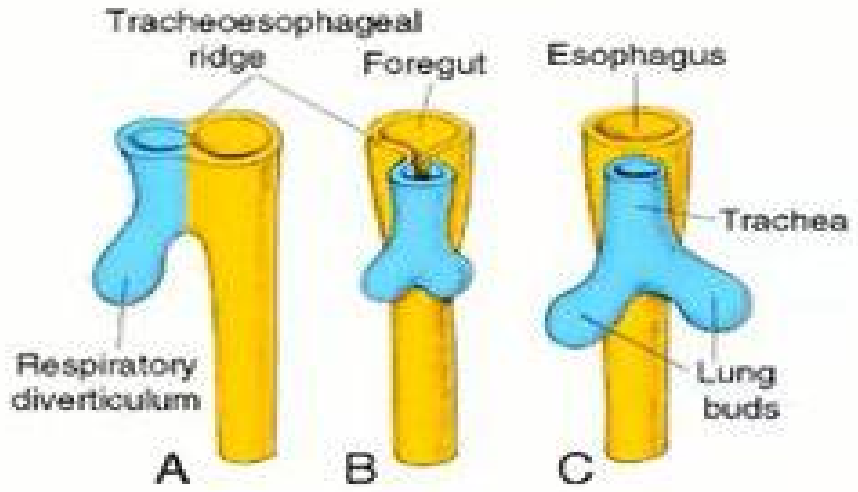
- Fusion of the laryngo-tracheal folds stops cranially leaving a communication between the laryngo-tracheal tube and the pharynx (the laryngeal inlet).





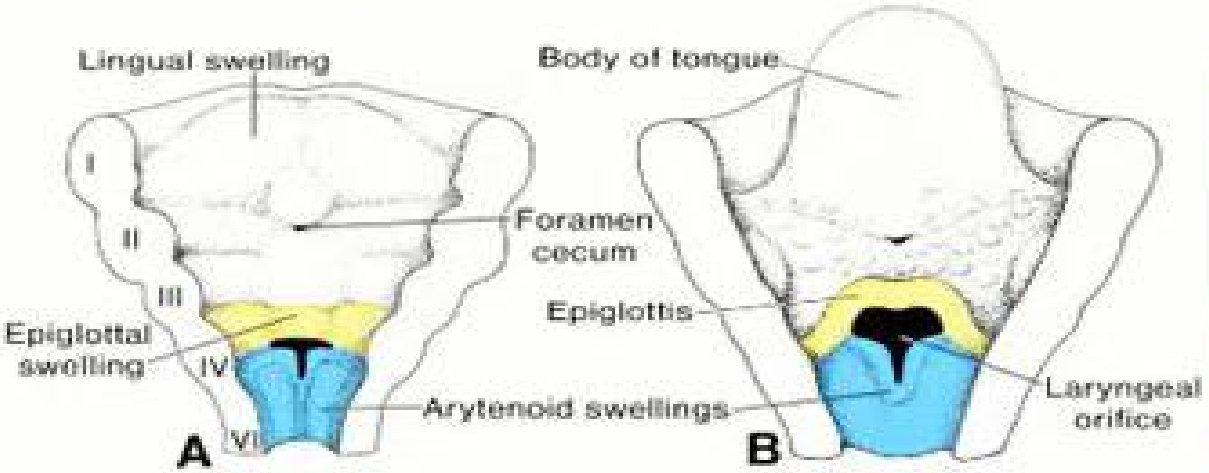
Development of the Respiratory System

Laryngo-tracheal groove



Laryngo-tracheal tube

- It forms the lining epithelium of the larynx, trachea, bronchial tree, and alveoli.
- The caudal end of the laryngo-tracheal tube grows down into the splanchnic mesoderm on the ventral aspect of the foregut, where it divides into right and left lung buds.

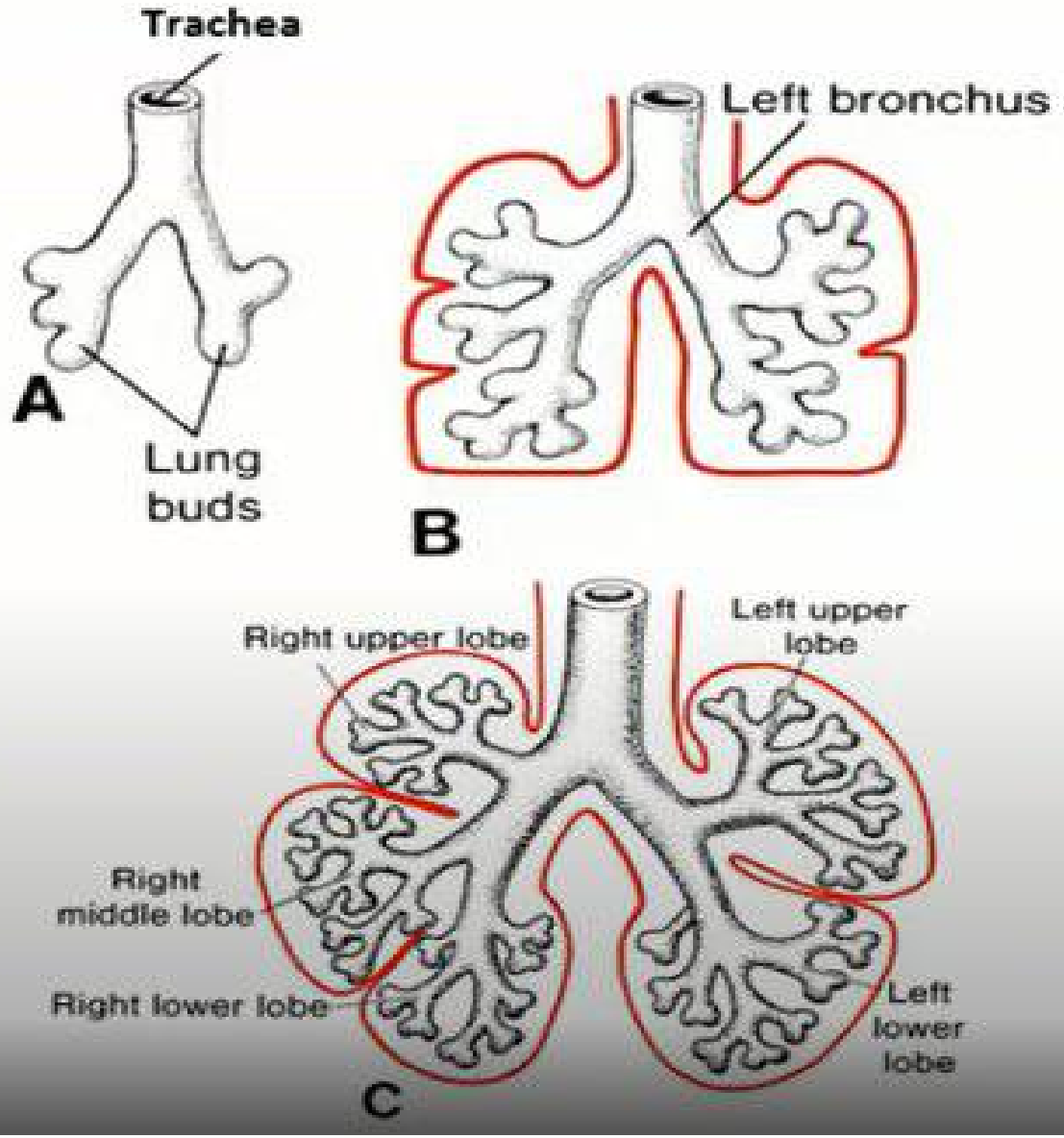


- At beginning, the laryngeal inlet is a vertical slit which ends cranially opposite the copula (which is a median elevation in the floor of the pharynx which will form the epiglottis).
- Later, the inlet becomes T-shaped and is obliterated between the 8th – 10th weeks, then recanalization occur during which the true and false vocal cords appear.

Events of the lung buds

Divisions

- Each lung bud forms a main bronchus (remember that the right bud is wider and more vertical than the left).
- Each main bronchus divides into secondary (lobar) bronchi (3 on the right side and 2 on the left side).
- The secondary bronchi divide giving tertiary (segmental) bronchi, which become surrounded by masses of splanchnic mesoderm forming the broncho-pulmonary segments.
- Repeated division by the 6th month reaching 17 orders of branches ending in terminal bronchioles.
- Further division continues for after birth (up to 8 years) till the respiratory bronchioles and alveoli are formed after 7 additional orders of divisions (total of 24 orders).

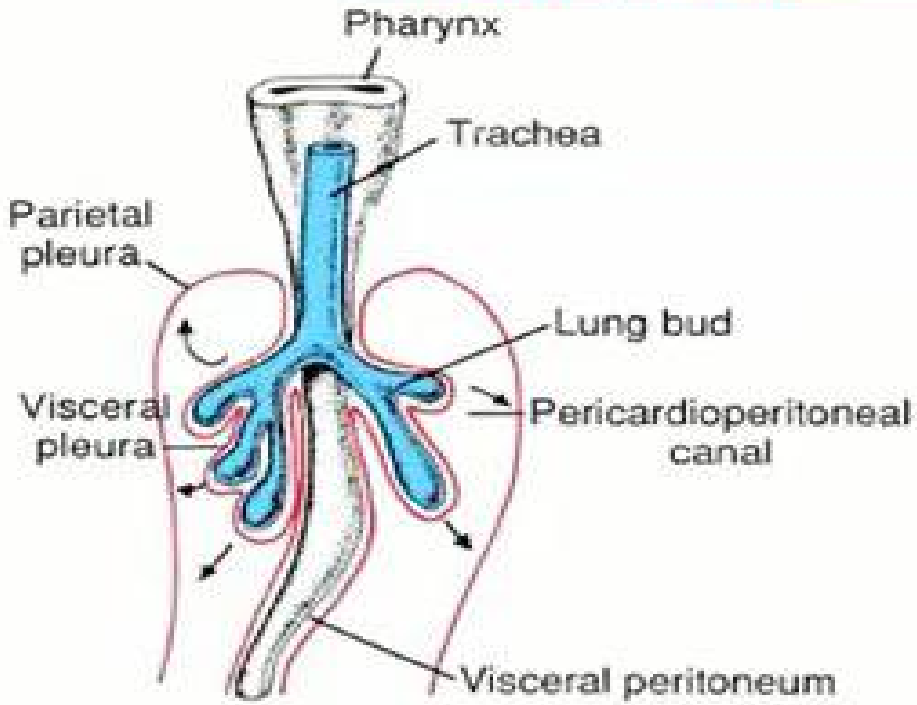


Events of the lung buds

Divisions

Invasion of splanchnic mesoderm

- To form cartilaginous plates, smooth muscles, connective tissue, and all blood capillaries.



Invasion of pleural sac

- Each lung grows laterally and invaginates the pericardio- peritoneal canal of the intraembryonic coelom, which gives the pleural sac.
- The visceral pleura is derived from the splanchnic mesoderm, while the parietal pleura is derived from the somatic mesoderm (hence the nerve supply of the pleura).

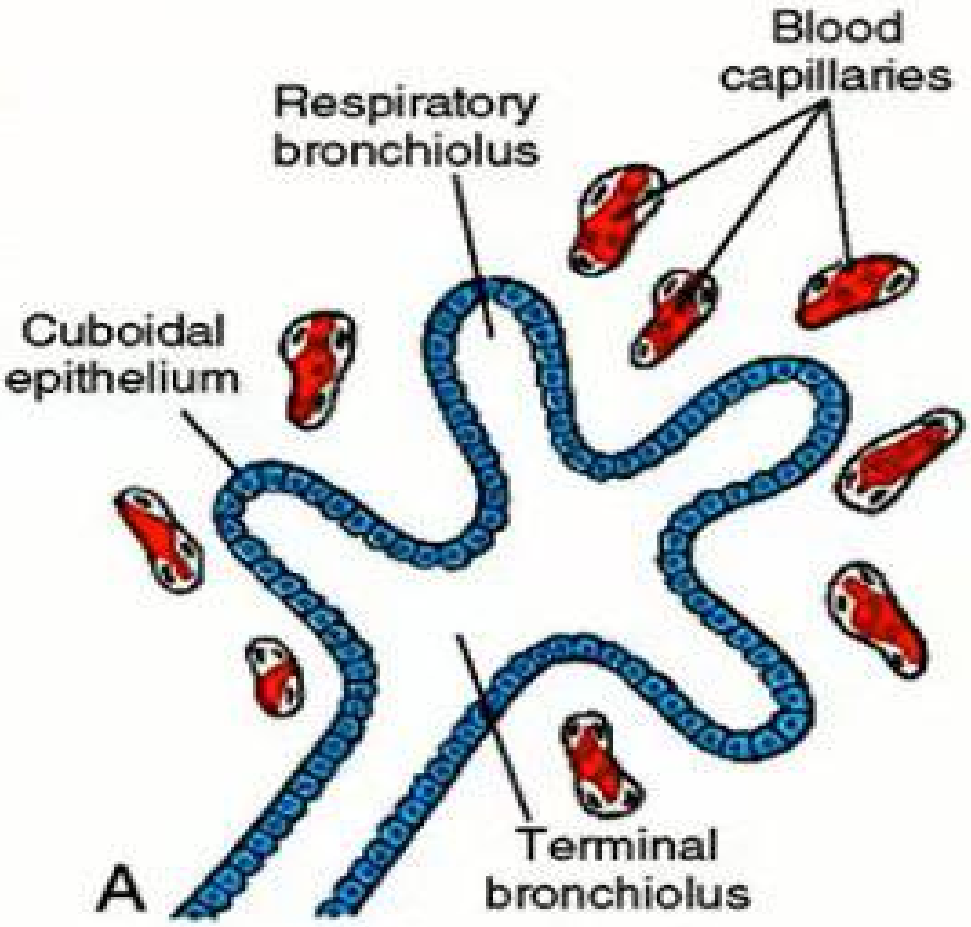
Stages of maturation of the lung

Pseudo-glandular

- Until the 4th month, only the bronchi & terminal bronchioles are formed.
- Elements involved in gaseous exchange are not formed yet (a fetus born at this stage can't survive).

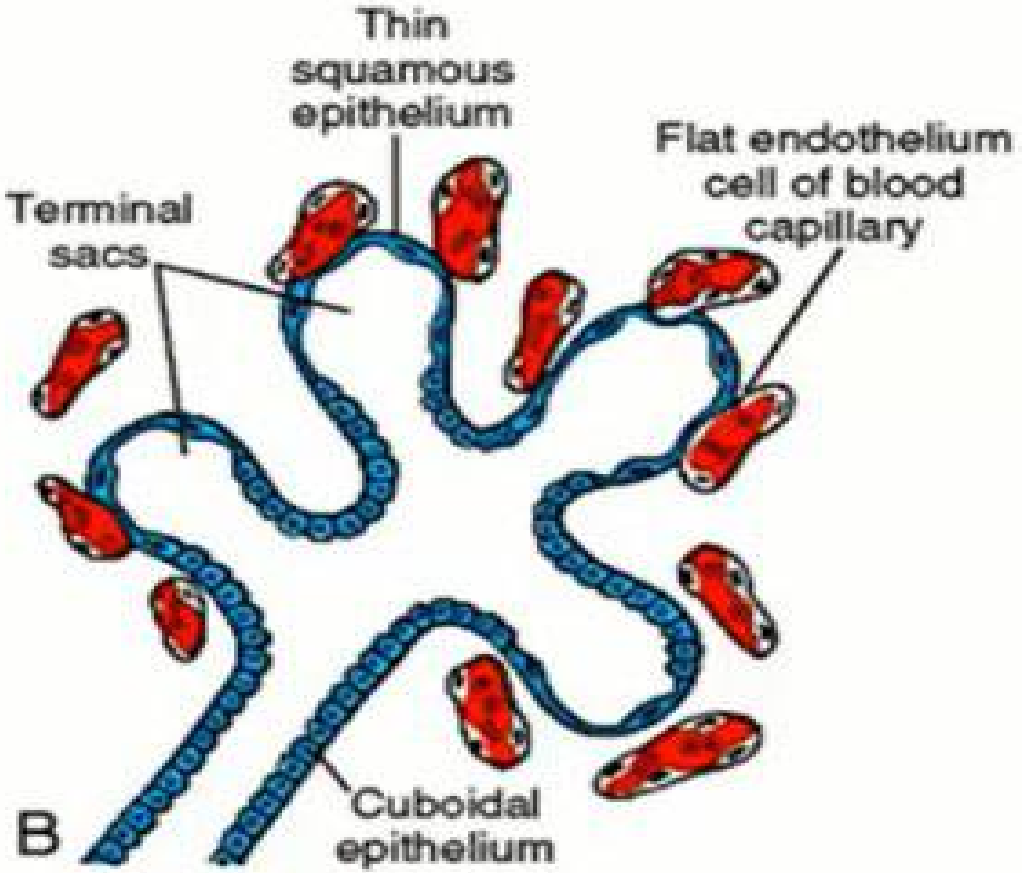
Canalicular stage

- From 4th to 6th month, respiratory bronchioles & alveolar ducts develop.
- Vascularization of the lung occurs, but still a fetus born at this stage can't survive even with intensive care.



Stages of maturation of the lung

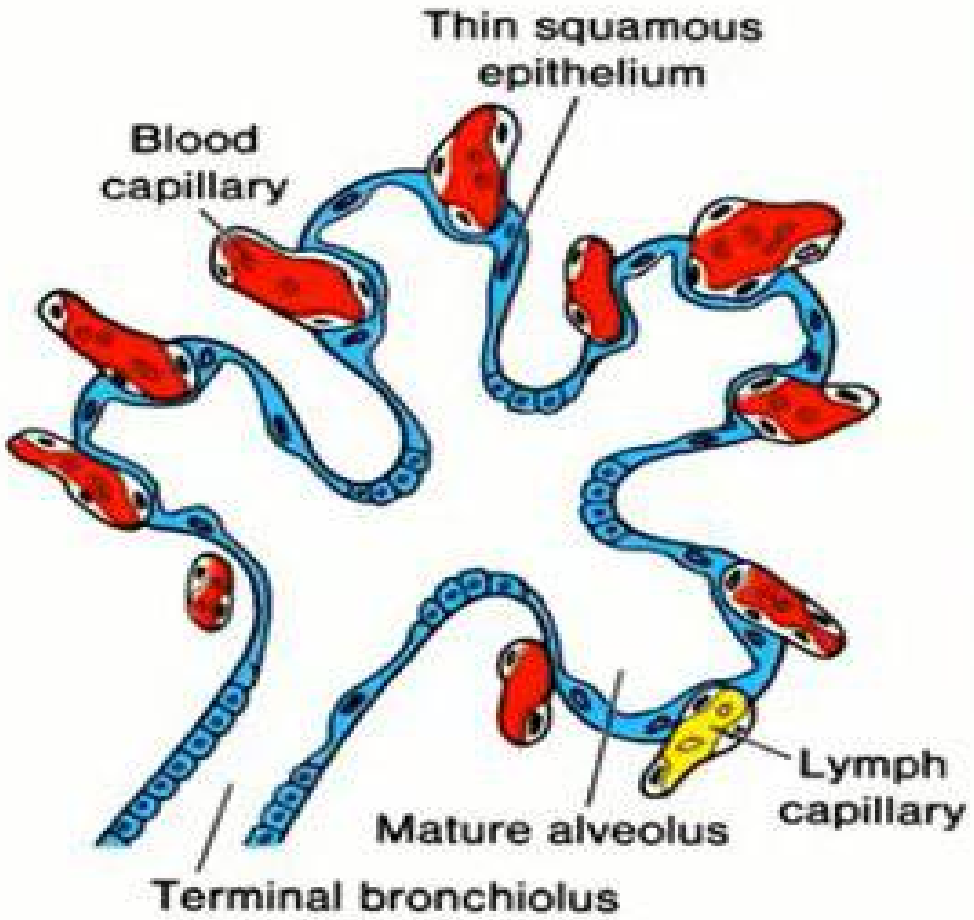
Pseudo-glandular | Canalicular stage | Terminal sac stage



- From 6th month till
- bThe primitive alveoli are formed and lined by cuboidal epithelium.
- Capillaries bulge into the alveoli and surfactant secreting cells appear.
- Surfactant is a phospholipid that lines the alveoli and helps in their expansion after birth. Its production begins in the 20th week and increases gradually till it reaches adequate levels by the 7th month (A fetus born by that time can survive with intensive care).

Stages of maturation of the lung

- Pseudo-glandular
- Canalicular stage
- Terminal sac stage
- Alveolar stage



- Extends till 8 years of age.
- The number of alveoli increases (95% of the alveoli develop after birth), this is the cause of growth of the lung.
- Mature (thin walled) alveoli don't develop except after birth.
- Now, the alveolo-capillary membrane is thin enough to permit sufficient gaseous exchange.

Respiratory movements:

- **Before birth:** prenatal respiratory movements cause suction of amniotic fluid into the airway and training of the respiratory muscles (the lung is not a respiratory organ before birth). These movements can be detected by ultrasound examination.

- **After birth:** the air replaces the fluid in the by two mechanisms: pressure on the thorax during labor and absorption by pulmonary capillaries and pulmonary lymphatics (main mechanism).

Clinical note:

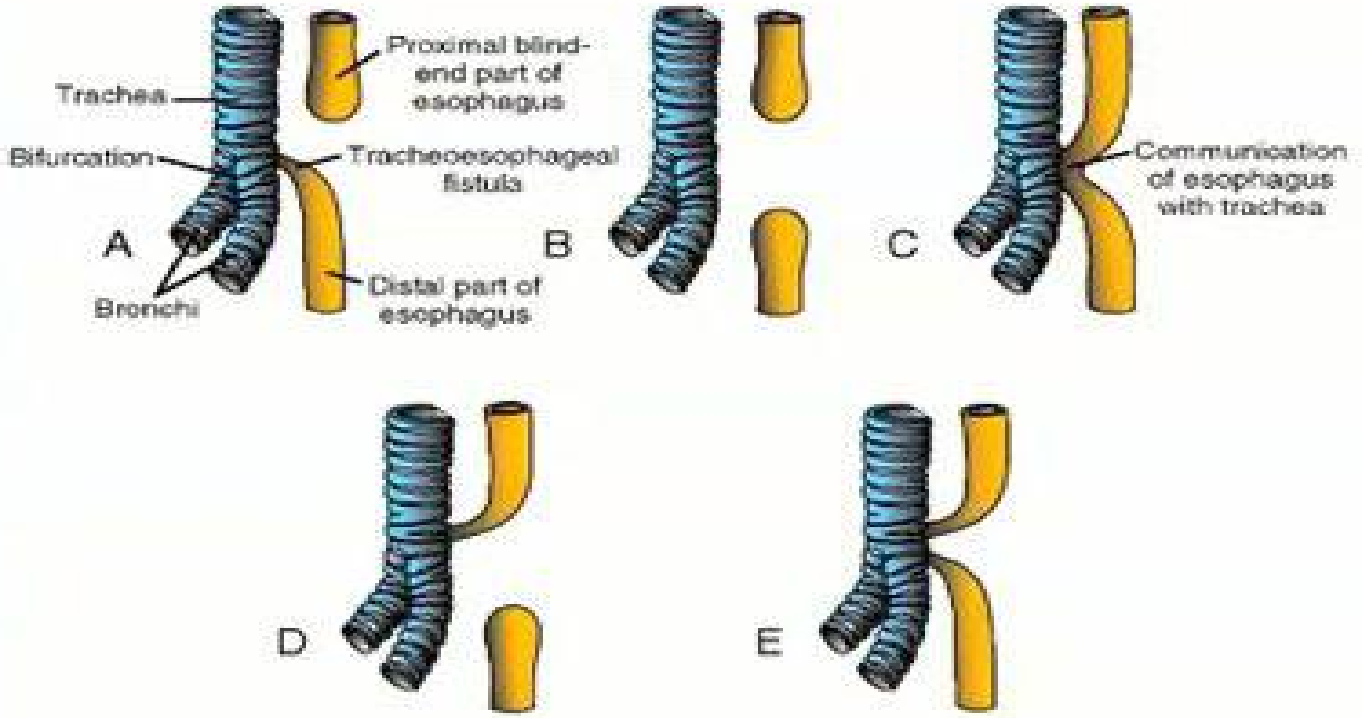
- The lung of a still borne baby (a baby died before birth) will sink in water as this lung doesn't contain air (the lung fluid is not absorbed by pulmonary capillaries and lymphatics).

- If a baby was born alive then died, the lung will float on water as this lung contains air.

Anomalies of the respiratory system

Tracheoesophageal fistula

- It means abnormal communication between trachea and esophagus.
- It is due to incomplete fusion of the tracheo-esophageal ridges.
- It may be accompanied by esophageal atresia (obstruction of a segment of esophagus).
- Four varieties may occur (as shown in the figure).
- The most common is atresia of the upper portion of esophagus and fistula of its lower portion with the trachea. This leads to impossible feeding with aspiration of milk into the lungs. (before birth, it causes polyhydramnios).



Anomalies of the respiratory system

Tracheoesophageal fistula

Surfactant deficiency

- As surfactant is important for alveolar expansion and prevention of their collapse (see before), its deficiency causes respiratory distress.
- The disease is called (hyaline membrane disease), which is the most common cause of respiratory distress syndrome.
- Surfactant production is increased by cortisone and thyroxine hormones.

Anomalies of the respiratory system

Tracheoesophageal fistula

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- Surfactant production is increased by cortisone and thyroxine hormones.

Others

- Agenesis (absent lung)
- Hypoplasia (small lung)
- Dilatation in lobes
- Accessory lung and ectopic lung lobes (from the trachea or esophagus).
- Congenital lung cysts formed by dilatation of terminal or larger bronchi.