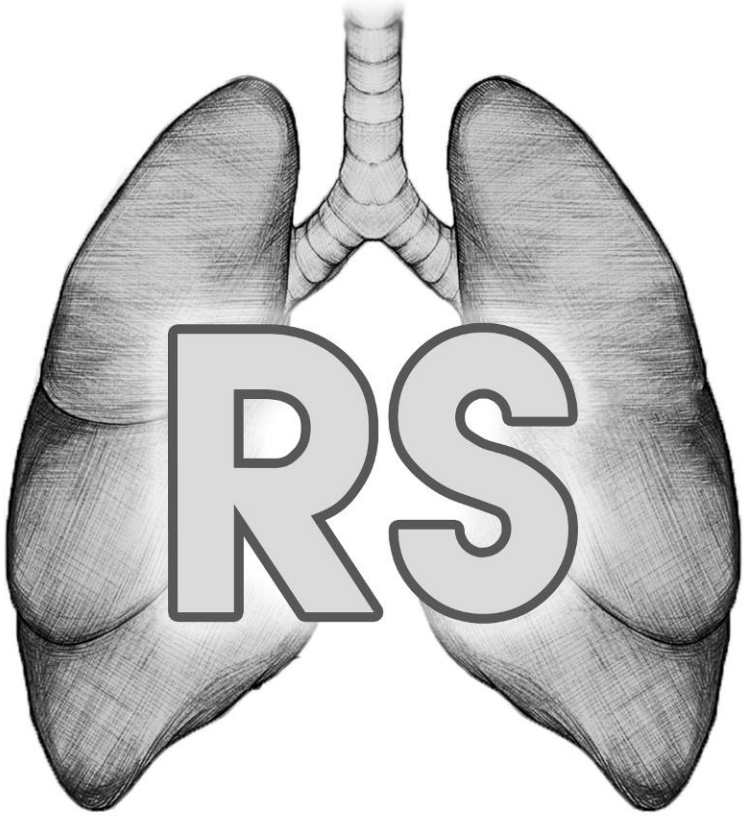

ANATOMY / HISTOLOGY

✓Sheet ○Slide ○Handout

Number

8

Subject

RS Embryology-2

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Date: **00/00/2016**

Price:

-By the name of Allah-

Development and Anomalies of Respiratory System

-In the previous lecture we have talked about development of the nose, palate (primary and secondary) and their related anomalies (cleft lip and palate), development of respiratory system, respiratory diverticulum, and anomalies of the trachea and esophagus.

- Topics of this lecture:

- Development and Anomalies of the **Larynx**.
- **Lungs** and **Bronchial** tree development.
- Anomalies of the lung.
- Lungs of the newborn infants.

Note : in this sheet we've attached an overview each structure in its "adult form" for the sake of completeness and comprehension.
-u can skip these overviews.

Larynx

- Development of the Larynx

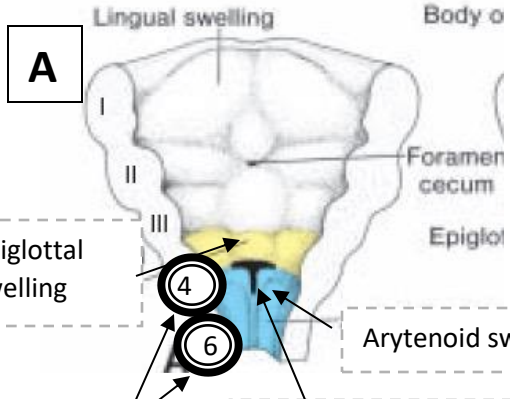
• The internal lining (epithelium) of the larynx originates from endoderm, but the cartilages (thyroid, cricoids, arytenoids) , muscles, and connective tissue (larynx ligaments) originate from mesenchyme of the **fourth** and **sixth pharyngeal arches.**

- This origin explains the nerve supply of the larynx. (vagus nerve)

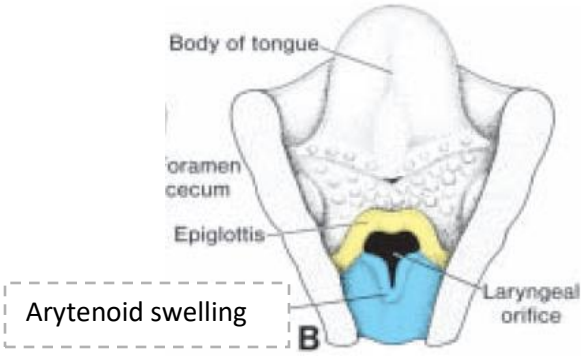
- Notice in figure A : The epiglottis which develops above the larynx, Arytenoid swelling, inlet of the Larynx, and pharyngeal arches fourth and sixth which participate in the development of the Larynx.
- Notice the laryngeal orifice forms the only communication between the gut (Laryngopharynx) and the RS system (the Larynx) , early in embryological development this orifice is slit-like shape.

Overview

in an adult the larynx extends from **C3-C6** and is composed of 9 **cartilages** (3 singles: cricoid, thyroid, epiglottis –and 3 pairs (+6): cuneiforms, arytenoids, Corniculate cartilages)
also composed of **muscles** (extrinsic and intrinsic) and **ligaments**.
it is responsible for **phonation** (as it contains the vocal cords) .
finally, it is innervated by **vagus** nerve (sensory and motor)
*rem. All laryngeal muscles are innervated by recurrent laryngeal except cricothyroid (innervated by external laryngeal)

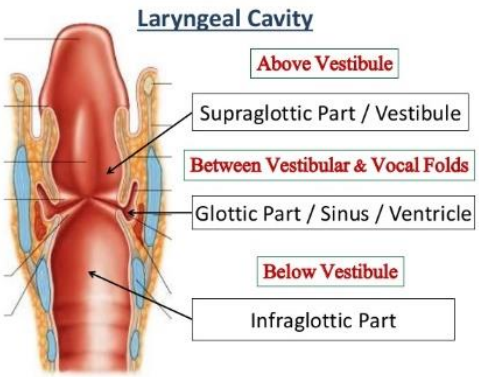


- Rapid proliferation of mesenchyme happens inside the Larynx ; as a result the Larynx will be filled with mesenchymal connective tissue and the laryngeal orifice changes in appearance from a sagittal slit to a T-shaped opening, and finally after development and when the mesenchyme of the two arches transforms into the thyroid, cricoids, and arytenoids cartilages, it gives the adult shaped Laryngeal orifice (Figure B).
- Notice in the figure B: The epiglottis, Laryngeal orifice, Arytenoid cartilage (swelling then proliferation of mesenchymal tissue will produce the cartilage).
- Notice that the shape of Laryngeal orifice changes from slit-like shape to T-shape then to the final adult shape.



- Changes that occur during the development of the Larynx :

- At about the time that the cartilages are formed, the Laryngeal epithelium also proliferates rapidly resulting in **temporary occlusion** of the lumen.
- Then it'll undergo recanalization and vacuolization from medial to lateral side to create a space or a cavity within the Larynx.
- A pair of lateral recesses, the **Laryngeal ventricles** produced at the lateral sides.
- These recesses are bounded by folds of tissue that differentiate into the **false vocal cord** (above the ventricle), and **true vocal cord** (below the ventricle). Look at this figure



Remember : in an adult , the laryngeal cavity is composed of 3 parts :

1. Vestibule (above the vestibular lig. And false vocal cords)
2. Ventricles (glottic region , b/w vestibular lig. and vocal cords)
3. Infraglottic region (below the vocal cords

- **Innervation of the Laryngeal muscles** :

- We've said that the origin reflects the nerve supply; then since the muscles of the Larynx are derived from the mesenchyme of the fourth and sixth pharyngeal arches , they are all innervated by branches of tenth cranial nerve which is the **vagus nerve**.

- All Laryngeal muscles are intrinsic except of one muscle presents outside the larynx which is **cricothyroid**.
- All Laryngeal muscles that developed from the **sixth pharyngeal arch** are innervated by **recurrent laryngeal nerve**.
- Only one muscle which is **cricothyroid** muscle developed from the **fourth pharyngeal arch** and innervated by **external Laryngeal nerve** (branch from **superior Laryngeal nerve**).
- So, the motor nerve supply is determined by the developmental origin of the muscles.

- Anomalies of the Larynx

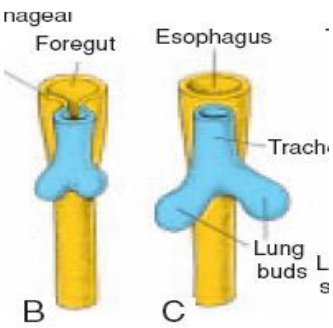
▪ Laryngeal atresia (Also known as **congenital high airway obstruction syndrome (chaos)**) :

- Rare anomaly
- This syndrome causes obstruction of the upper airway, and there is enlargement of the lungs distal to atresia or stenosis.
- The enlargement of the lungs happens because they try to become inflated more than normal to overcome the obstruction. (compensatory complication)
- The enlarged lungs are capable of producing echoes (echogenic); echogenic means giving rise to (echoes) of ultrasound waves.
- This syndrome also accompanied with other complications, such as : the diaphragm is flattened or inverted; raised up (it will ascend upward in the chest rather than descends downward in the abdomen) , and also there is fetal ascites -which is the accumulation of fluids in the abdominal cavity-.

Lungs and Bronchial tree development

- Trachea, Bronchi, and Lungs

▪ Trachea and Bronchi:

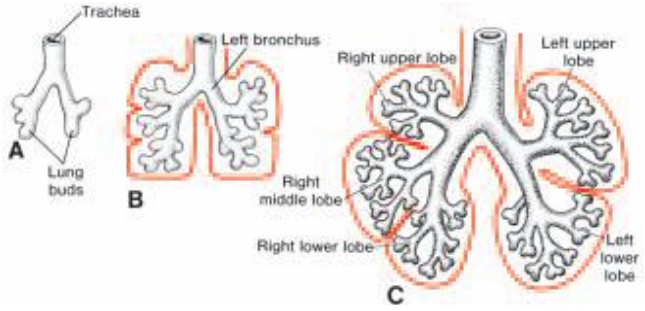


Overview

in an adult the trachea is composed of hyaline cartilage rings , (from C6-T4) –terminate by giving two main bronchi

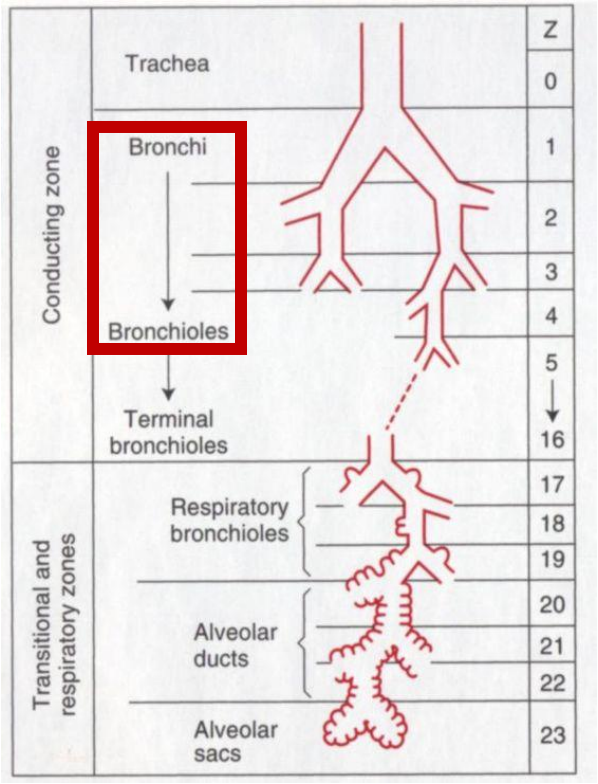
the bronchial tree (main bronchus >>2ry bronchi >> 3ry bronchi>> many bronchioles (No. #16 is the terminal bronchiole, No. #17 is the respiratory bronchiole) >> then alveolar duct >> alveolar sac >> alveoli.

- At the **fourth week** of pregnancy, the respiratory diverticulum (tracheal buds/respiratory buds) forms from the **anterior wall of the foregut** (i.e outgrowth from the ventral wall of the foregut).-this bud will descend downward till it reach T4 ,where the trachea bifurcate.
- Respiratory diverticulum initially communicates with the foregut, but later on, it expands and forms two esophageotracheal ridges. These ridges fuse and form septum which separates the trachea and lung buds anteriorly from the esophagus posteriorly.
- If there is any problem in the separation, the trachea will not well developed and anomalies like TEF (tracheo-esophageal fistula) and atresia may arise.
- Respiratory diverticulum (respiratory bud) descends downward, then it will give two lung buds, and these two lung buds will produce bronchial buds to form right and left main bronchi (primary bronchi) at the beginning of the **fifth week**.
- Then primary bronchi(main bronchi) give the secondary bronchi. The right main bronchus gives three secondary bronchioles, and the left main bronchus gives two; according to the lobes of the lungs (three lobes in the right lung, and two lobes in the left lung).
- So we notice in the figure that the right main bronchus will give upper, middle, and lower secondary bronchi, while the left main bronchus will give only upper and lower secondary bronchi.



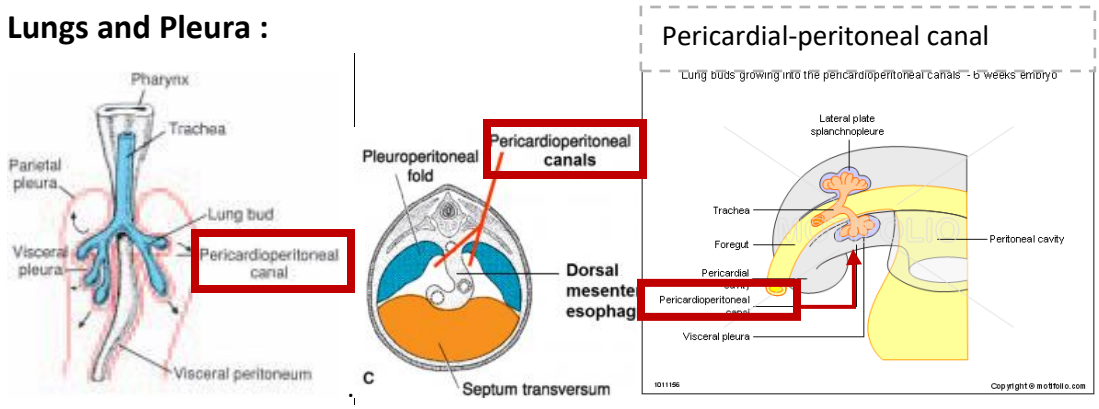
- The secondary bronchi will divide repeatedly forming 10 tertiary bronchi on the right and 8 on the left which are called **bronchopulmonary segments**.
- (they are 8 on the left lung just before birth).
- The ten segments of the right lung are :
- Three segments in the upper lobe(apical, posterior, and anterior).
- Two segments in the middle lobe (lateral, and medial).
- Five segment in the lower lobe (apical (apicobasal) or superior, anterior, medial, lateral, and posterior).
- The eight segments of the left lung are:
- Four segments in the upper lobe (superior lingual, inferior lingual, anterior, and apicoposterior).
- Four segments in the lower lobe (apical (apicobasal) or superior, posterior, lateral, anteromedial).
- During adulthood, on the left lung the apicoposterior tertiary bronchus in left upper lobe divides to apical and posterior segments and the anteromedial tertiary bronchus in the right lower lobe divides to anterior and medial segments .

- So before birth the tertiary bronchi (bronchopulmonary segments) are 10 on the right and 8 on the left, while after birth they become 10 on the right and 10 on the left.
- **3ry bronchi** divides in dichotomous fashion -repeated of division -(2 -4 -8 …) - giving arise to **bronchioles** .



- By the end of the sixth month, approximately **17 generations** of subdivisions have formed.
- Postnatally , there are additional 6 subdivisions , so the **total** number become **23 subdivisions** of bronchopulmonary segments (3ry bronchi) .
- After all these divisions, the bronchi at the end will give the terminal bronchiole #16 (conducting bronchiole)and then respiratory bronchiole #17 –or >17 postnatally - .
- with each division the diameter becomes smaller and smaller.
- When the diameter becomes smaller, histological changes are appeared; i.e. bronchi contain cartilage, while bronchioles don't >> they contain smooth muscles.
- Fibroblast Growth Factor (FGF) is responsible for stimulation and repetition of division.
- 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.

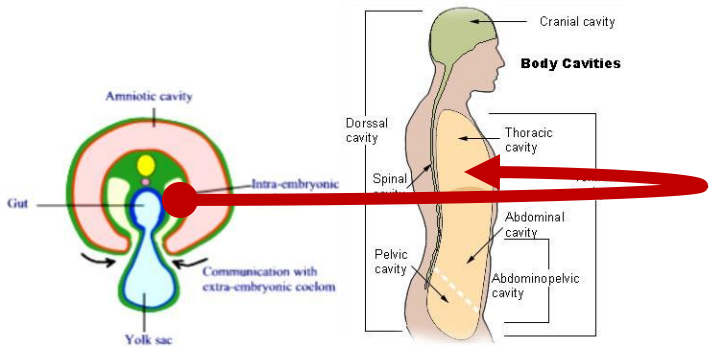
- **Lungs and Pleura :**

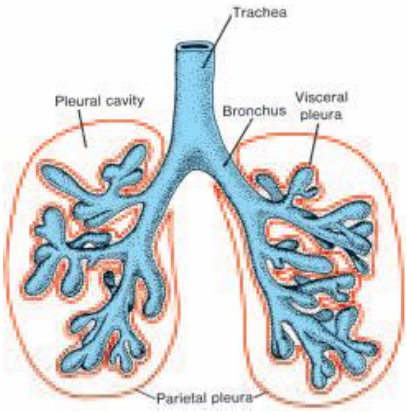


- With subsequent growth in caudal and lateral directions, the lung buds expand into the body cavity (coelomic cavity).
- The coelomic cavity initially is in the form of pericardioperitoneal canal which will be separated into peritoneal cavity in the abdomen and pericardial cavity in the chest.
- Later on; pleuropericardial fold appear on the lateral wall of primitive pericardial cavity which originally came from pericardioperitoneal canal, and as the name implies it will be separated into pericardial cavity in the heart and pleural cavity in the lung.
- The mesoderm, which covers the outside of the lung, develops into the **visceral pleura** (comes from splachnic mesoderm)
- The somatic mesoderm layer, covering the body wall from the inside(It lines the thoracic cavity), becomes the **parietal pleura** (comes from somatic mesoderm).
- Remember that the mesoderm has two layers : splanchnic and somatic.
- The space between the parietal and visceral pleura is the **pleural cavity**, and it contains serous fluid.

Rem.

the intra-embryonic Coelom gives arise to all body cavities.





With each period , focus on:

- ✓ The formed bronchial structure.
- ✓ Would the fetus survive or not if it got born during this period.

- Maturation of the Lungs (alveoli development):

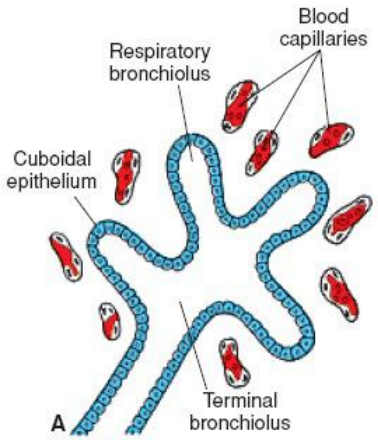
*Divided into four periods:

- **Pseudoglandular period**

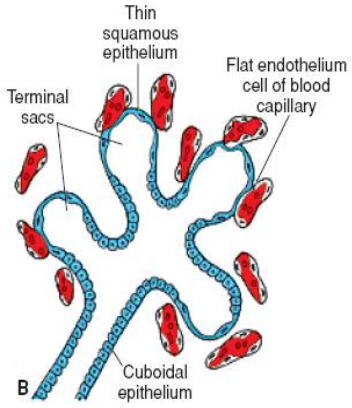
  - From 6th to 16th weeks.
  - During this period, branching has occurred and it stops at the terminal bronchioles (conducting bronchioles). So >>
  - No respiratory bronchioles or alveoli are present; that's **why respiration** is **not possible** during this phase.
  - The lining epithelium in terminal bronchioles is **simple cuboidal** epithelium; so there is no gases exchange.(as gas exchange needs simple squamous epi.)
  - The capillaries are distal.
    why we are concerned with the distance b/w capilleries and alveoli?
    -because for the gas exchange to happen we need >> respiratory membrane [both alveoli and capillary form this membrane]
  - Fetuses born during this period are unable to survive.(no alveoli)

- **Conalicular period**

  - 16th - 26th weeks (by 26th week the fetus is 6 and a half months old).
  - Each **terminal bronchiole** divides into 2 or more **respiratory bronchioles**, which in turn divide into 3-6 **alveolar ducts**.
  - The lining epithelium in both terminal and respiratory bronchioles is **simple cuboidal epithelium**.
  - Although there are respiratory bronchioles and alveolar ducts in this period, there is **no respiration** because the capillaries are still far from the respiratory bronchioles and alveoli (no respiratory membrane).
  - Fetus born during this period can survive with medical interventions; by being placed in an incubator, stimulate surfactant secretion and giving them oxygen (and an appropriate medical treatments to induce his lungs' inflation and maturation.)

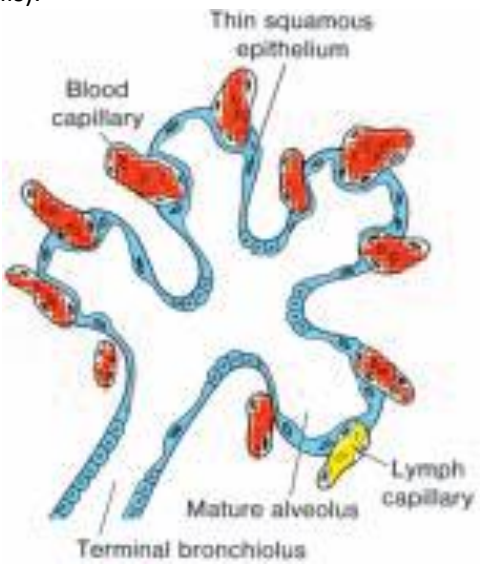


- **Terminal sac period**
  - 26th weeks to birth (from almost 7 months to birth)
  - **Terminal sacs (primitive alveoli)** are formed. –look at the figure below.
  - The lining epithelium in primitive alveoli is **simple squamous** epithelium.
  - Specialized cells appear, including type I alveolar cells across these gas exchange occurs, and type II alveolar cells which secrete surfactant.
  - Capillaries establish close contact; the connection between capillaries and primitive alveoli forming the respiratory membrane; also known as blood-air barrier (respiration is possible in this period).
  - A premature infant born by the 7th month is able to survive; because sufficient numbers of capillaries are present to guarantee adequate gas exchange.
  - Notice in the figure:
    - The cells are changed from simple cuboidal epithelium to thin simple squamous epithelium (these are type I alveolar cells or pneumocytes) .
    - Capillaries are in contact with primitive alveoli (simple squamous epithelium),their BM fuse forming the respiratory membrane(blood-air barrier).



- **Alveolar period**
  - 8 months to childhood (10 years).
  - Mature alveoli become well-developed.
  - The contact between epithelial and endothelial (capillary) is present >> the respiratory membrane is present (blood-air barrier).
  - **Mature alveoli** are not present before birth.
  - Growth of the lung after birth is mainly due to increase in number of alveoli and not in size (even if there is increase in size, it will be very little).
  - The growth of the lung continues to age of 10 years.
  - It is estimated that only **one-sixth** of the adult number of alveoli are present at birth.

  - Notice in the figure:
    - Most of alveoli are simple squamous epithelium (type I cells)
    - More invagination of endothelial cells in the wall of the alveoli forming respiaratory membrane (blood-air barrier).
    - Type II cells which responsible for the secretion of surfactant are also present (the alveoli inflated and become mature by type II cells).



  - At the end of the 6th month with the beginning of the 7th, type II cells are present; but need to be stimulated to secrete surfactant.
    ⇨ Nowadays; they give artificial surfactant as injection and glucocorticoids (betamethazone) to stimulate surfactant production; help in Inflation and maturation of alveoli.
  - Before birth, the lungs (exactly the alveoli) 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 this fluid increases, particularly during the last 2 weeks before birth.

- Fetal breathing movements begin before birth and cause aspiration of amniotic fluid (Amniotic fluid is very important; it stimulates the development of the lung).
- 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 by the blood and lymph capillaries, and a small amount is probably expelled via the trachea and bronchi during delivery.
- The fluid is resorbed; why do I get rid of this fluid?
  because it increases the surface tension and prevents the inflation (opposite to the surfactant), but its presence is important for the development of the lungs initially .
- 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(surfactant decreases surface tention).
- First breathe is taken by stimulating the respiratory center by hitting the baby at his back-skin, then signals go from the respiratory center through the phrenic nerve to the diaphragm .

clinical correlation

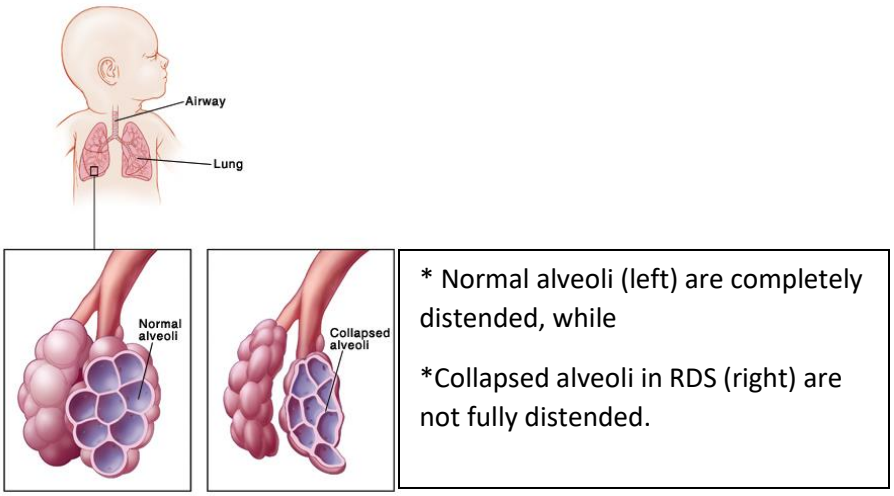
- Without the fatty surfactant layer, the alveoli would collapse during expiration (atelectasis).

Anomalies of the Lung :

- ☑ RDS
- ☑ Agenesis
- ☑ Ectopic lung lobes
- ☑ Congenital cysts
- ☑ Oligohydramnios and lungs

Anomalies of the Lung

- **Respiratory Distress syndrome (RDS)**
  - The most common anomaly of the lung.
  - Surfactant is particularly important for survival of the premature infant (decrease surface tension, alveoli inflation)
  - 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 (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. That's why RDS is also known as **hyaline membrane disease.**
  - Hyaline membrane disease accounts for 20% of **deaths** among newborns(high mortality).
  - **IRDS might complicate and produce Intra-uterine Asphyxia**

- **Intrauterine Asphyxia** (اختناق الجنين داخل الرحم)**:**
  this happen when irreversible changes in **type II cells** occur >>meaning that there is no secretion of surfactant.
  - ⇨ Intrauterine Asphyxia : the baby will die in the uterus because there's no oxygen and secretion.
- 

  * Normal alveoli (left) are completely distended, while

  *Collapsed alveoli in RDS (right) are not fully distended.

- Treatment (How to increase surfactant) :
  - Recent development of **artificial surfactant** and treatment of premature babies with **glucocorticoids (betamethasone**) to stimulate surfactant production have reduced the mortality associated with RDS.
  - Glucocorticoids are not given randomly; usually given according to the weight of the baby to avoid development of complications.
  - It Also allowed survival of some babies as young as 5.5 months of gestation.
  - Thyroxine (secreted from the thyroid gland) is the most important stimulator for surfactants production.

- **Blind-ending trachea with absence of lungs and agenesis of one lung**

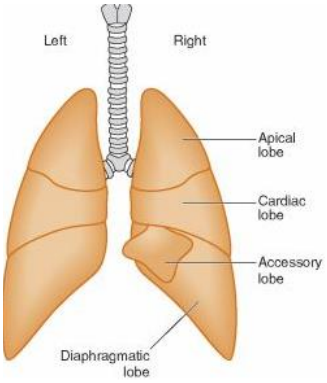
  - Fatal, the baby will not survive since there is no formation of the lung.
  - Although many abnormalities of the lung and bronchial tree have been found (e.g., blind-ending trachea with absence of lungs and agenesis of one lung) most of these gross abnormalities are rare.
  - Agenesis : imperfect organ development.

- **Abnormal divisions of the bronchial tree**

  - More common.
  - Some result in supernumerary lobules (more lobules than expected); e.g. four lobes in one side of the lung.
  - Doesn’t affect respiration.
  - These variations of the bronchial tree have little functional significance, but they may cause unexpected difficulties during bronchoscopies.

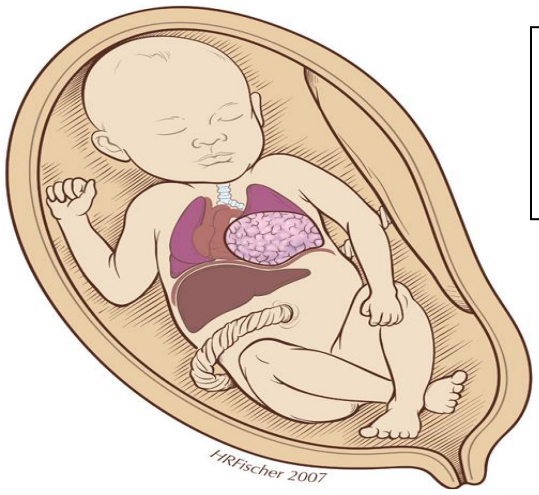
- **Ectopic lung lobes**

  - Means that the lung doesn't arise from its normal position.
  - Arising from the trachea or esophagus.
  - It is believed that these lobes are formed from additional respiratory buds of the foregut that develop independently of the main respiratory system.



- **Congenital cysts of the lung**

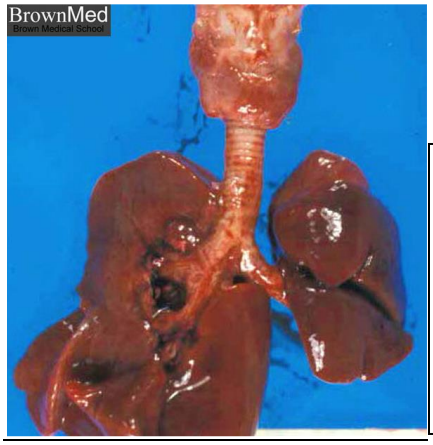
  - Most important clinically.
  - Formed by dilation of terminal or larger bronchi.
  - These cysts could be single or multiple.
    - ⇨ May be **small and multiple**, giving the lung a **honeycomb appearance** on radiograph, or they may be **restricted to one** or more larger ones.
  - The most important complication of it is **chronic infection** in the lung.
  - It can be treated.



*The figure shows fetus with multicysts lung giving it a honeycomb appearance on radiograph.

- **Lung Hypoplasia**

  - Accompanied with the infants of congenital diaphragmatic hernia (CDH). In these infants the lung is unable to develop normally; because it is compressed by the abnormally positioned abdominal viscera.
  - Congenital diaphragmatic hernia (CDH) is more common on the left side; because during development of diaphragm as there's a triangle beneath the lung -which is wider in the left Side than that of the right side- >> this triangle is considered a weak point so the abdominal viscera can ascends upward through this triangle >> this develop extra pressure on the left lung >>then the volume of the Lt lung is reduced as a result of this compression.
  -



* The figure shows **hypoplastic lung.**

* Notice the shrinkage of the left lung; it's smaller in size than the right lung, and this is because of the hernia that caused pressure on the left lung preventing it from development.

  - Most infants with CDH die of pulmonary insufficiency as their lungs are too hypoplastic to support life.

- **Oligohydramnios and lungs**

  - Oligohydramnios means reduced amniotic fluid.
  - Oligohydramnios is the opposite of polyhydramnios .
  - Remember that the polyhydramnios is one of the complications of trecheo-esophegeal fistula (TEF).
  - Normally, there is high amount of amniotic fluid around the baby in the amniotic sac, and this amniotic fluid enters the respiratory tract through the oral cavity, and when it reaches the lungs it will help in their development.
  - Amniotic fluid is very necessary in development of the lungs; that's why insufficient amount of it will affect the function of the lungs.
  - When oligohydramnios is severe, lung development is retarded and severe pulmonary hypoplasia results.

Lungs of the newborn infants

- Intrauterine, Babies take their oxygen from the blood of their mothers. Once the mother delivers the baby, the physician will grip him(it) from his legs, flip him over and slap his back >> to stimulate the respiratory center which in turn via the phrenic nerve will stimulate the diaphragm then>> the diaphragm descend downward, the pleural cavity increase in size >> the intrapleural pressure decreases>> the lungs inflate. – by the inflation of the lungs >> the baby take his first breathe and then start crying.
- Crying of the baby is an indication of breathing (inflation of lungs).
- Intrauterine, the baby Is surrounded by amniotic fluid>>this fluid is viscous >> when delivered some of this fluid will remain at the baby's skin >>his skin will be slippy .
  in the past, physicians faced a real problem because of this .
  as after delivery , they grip the baby >> flip the baby upside down (to slap him on the back to stimulate inspiration) but because the baby is slippy >> it slip , fall into the ground and –most properly killed.
  some irresponsible doctors do not Admit that the baby has fallen and slipped from their hands >> they rather claim that " the baby has already born dead".

  So, how can we determine if the infant was stillborn or die after birth?
  - By applying **lung flow test**; we take a part of the lung and put it in water:
    * If it floats, then the baby has breathed, cried then had died .
      ⇨ Fresh and healthy lungs contain some air so pulmonary samples float in water
    * If it sinks in the bottom of water, then the baby was really born dead.
      ⇨ The lungs of the stillborn infants are firm and sink in water because they contain fluids not air.
    * This is used in **Forensic Medicine** to differentiate between these two cases.

- The truth will be revealed at the end; so physicians should not lie, and they always have to be honest.

. Regret for wasted time is more wasted time.

-All the best