# Development of respiratory system

***Note:*** *I've tried to keep everything together for the sake of keeping information connected and more comprehendible, that being said, not everything written here is mentioned by the order it was said in the lecture.*

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It's important when you're studying the development of an organ to always keep an image of its anatomy/ its last picture.

## *1. Nasal cavity:*

The frontonasal process: a process or prominence means there's growth, and frontonasal means it's coming from the frontal bone and involved in nose development. Since it's descending within the midline, then it will reach the septum and the roof of the nose (involved in their formation).

We have 2 nasal processes; medial (involved in the formation of the medial wall/ septum) and lateral (involved in the formation of the lateral wall of the nose).

The maxillary process will give the maxilla and is also involved in the development of the palate and the nose, while the mandibular process will give the mandible.

***Nostrils***: made by 3 processes. There's something called the olfactory pit, which is a small opening, starts being small and surrounded by medial nasal process medially, lateral nasal process laterally and maxillary process inferiorly, which all then fuse to give the nostril.

***Vestibule***: results from deep invagination (from outside to inside) of the nostril -olfactory pit before-, what proves this is the fact that the lining epithelium of the vestibule is actually of the skin type (stratified squamous non-keratinized) … so after the nostril is formed, invagination occurs.

***Walls, roof and floor:*** the lateral wall of the nose & the roof are made by the lateral nasal process and maxillary process. The floor (the hard palate) is mainly made by the medial nasal process and maxillary process.

***The nasal septum:*** is a down growth of the –fused- medial nasal processes and frontonasal process, that's because the septum has 3 parts;
1. Perpendicular plate of ethmoid -from above-, so it's developed from frontonasal process.
2. The vomer coming from the medial nasal process.

3. Cartilaginous part.

***Choncae***: in the lateral wall, the bones make invaginations in it making the 3 choncae and 3 meatuses (as it's previously mentioned, a chonca is a process of bone covered by mucosa).

- The palatal processes of maxilla are very important because they grow from both sides medially towards the midline and fuse together along with the septum & thus ending the communication between the oral and the nasal cavities by participating in the formation of the hard palate (floor of the nose).
- Note: the meeting between the palatal processes of the maxilla with the septum will result in the formation of the nasal cavity (septum, lateral wall & floor), also, as a result, the posterior opening, aka choana, is formed, opening to the nasopharynx.

## *2. The palate:*

***Hard palate:*** made of a primary palate and a secondary palate. The primary palate is made by the medial nasal process, whereas the secondary is made by the fusion of the medially growing palatal processes of maxilla, then these palatine shelves fuse with the primary palate and the septum. The reason we have **the incisive foramen** & sutures between the primary and the secondary palates is that we have two sources for the development of the palate that later fuse together.

***Soft palate & uvula:*** by growth of the posterior part of the secondary palate –which is part of the hard palate-. Union of the 2 folds of the soft palate happens in the 8th week of development and the 2 parts of uvula, coming from left and right, fuse in the 11$^{th}$ week.

*Clinical point:* Cleft lip and Cleft palate: can be unilateral or bilateral, partial or complete. Cleft lip can extend to the nose because the development of the nose and palate come/ occur together, so any block of this development with no continuation of growth will result in Cleft formation which can extend to the nasal cavity.

## *3. Paranasal sinuses:*

These sinuses are pouches, diverticula, or canals that extend from the lateral wall of the nose to the maxilla, ethmoid, frontal and sphenoid bones. These pouches stay in the form of ducts that have an enlargement at their ends making the sinuses. So, the sinuses begin their development from the lateral wall of the nose & they will have a cavity and a duct that opens into the lateral wall of the nose.

The sinuses begin small in size/ rudimental and take their final picture & size after delivery at the age of 8 years old - puberty along with the development of the face.

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# ***Larynx, trachea and lungs development:***

Lining epithelium of the respiratory tract as a whole is endodermal in origin, whereas the cartilage, the muscles and the bones are mesodermal in origin; specifically from the splanchnic layer of mesoderm.

As it was already mentioned in the GI system, we have a foregut, a midgut and a hindgut.

1. By the 4th week of development, the foregut -from its ventral surface- gives a growth called respiratory diverticulum (aka; lung bud) by the effect of a protein called TBX-4 which acts as an alarm, i.e. once this protein is produced, this diverticulum will proliferate & grow, eventually giving the respiratory tract.

2. At first, the lung bud is in open communication with the foregut, after a while, the bud's growth increases and ridges, known as tracheoesophageal ridges, appear from the lateral sides causing constriction & then fuse together resulting in a septum that separates the trachea & the lung bud anteriorly from the esophagus posteriorly. The lung buds are at the end of the trachea.

## *Clinical Point:*

Some anomalies can develop between the trachea and the esophagus, like **Proximal esophageal atresia and distal fistula with trachea:**

- Proximal means close to the oral cavity.

- Makes 90% of anomalies developing between the esophagus & trachea.

- Has many complications:
    1. The infant will vomit anything that he's given orally after delivery, due to the proximal esophageal atresia –which means that the upper/proximal portion of the esophagus is ending in a blind pouch-.
    2. Polyhydroamnios: where the amniotic fluid around the baby (that's supposed to enter the oral cavity to reach the GI), goes back to the amniotic cavity/ sac resulting in too much amniotic fluid around the baby –polyhydroamnios-. (Opposite to oligohydroamions; too little amniotic fluid around the baby).
    3. Since this case also represents a connection between the respiratory and GI tracts due to distal tracheoesophageal fistula, bacteria from GI can cross to the respiratory tract causing infections, Ex; pneumonia, which can be dangerous.
    4. Also as a result of the fistula, gas can fill the stomach, that's why when babies with this anomaly take their first breath, their stomach will immediately bulge; due to the air crossing to the GI tract by the fistula filling the stomach & their stomach will keep distending with each breath as long as the fistula is present.

- An urgent operation must be done to any baby born with this anomaly, to connect the two portions of esophagus together and close the fistula… all in all, it's a very common anomaly & also the correcting operations are easy & very successful.
- The rest of cases are rare:

1) Isolated esophageal atresia: 4% of anomalies
2) H-type TEF –TracheoEsophageal Fistula-: 4% of anomalies
3) Proximal TEF & distal esophageal atresia: 1% of anomalies
4) Double fistula – type D: 1% of anomalies

- These aforementioned rare anomalies are accompanied by other abnormalities, such as
  1. Cardiac abnormalities in 33% of the cases, ex. Atrial-septal defect, ventricular-septal defect, tetralogy of Fallot.
  2. Renal abnormalities
  3. Limb defects
  4. Anal atresia

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## ***4. Larynx:***

- As it was already mentioned in previous lectures, the larynx is a box of cartilage. The cartilage is mesenchymal in origin, but here the cartilage and the muscles originate from the mesoderm (or mesenchyme) of the **4th** and **6th pharyngeal arches**. This origin reflects the nerve supply of the larynx.

- Notice the laryngeal orifice, which is slit-like & forms a communication between the respiratory primordium and the pharynx. The epiglottis develops above the larynx.

- First, rapid proliferation of mesenchyme happens in the larynx, as a result the larynx will be filled with mesenchymal connective tissue, but the opening stays and changes. The initial shape of it is slit, then that changes into T-shape, and finally gives the adult shaped laryngeal orifice with the epiglottis above and aryepiglottic folds on both sides. This happens by the 12th week.

- After the larynx was filled with connective tissue, it'll undergo recanalization and vacuolization that creates a space or a cavity within it & thus an invagination in the lateral walls will occur & will give a recess that'll be the ventricle and the saccule.

- The quadrangular membrane is mesenchymal in origin coming from above and going downwards, it's free edge will give the false vocal cords.

- The cricothyroid membrane (conus elasticus) is also mesenchymal in origin, it grows upwards & its free edge will give the true vocal cords.

- The 4th pharyngeal arch will give the region that's above the true vocal cords; that's why this region's innervation comes from the superior laryngeal nerve, mostly the internal branch while the external innervates only cricothyroid muscle. So, anything innervated by the superior laryngeal nerve & its branches must have come from the 4th pharyngeal arch.

- Those coming from the 6th pharyngeal arch (mucosa below the true vocal cords & all intrinsic muscles except cricothyroid) are innervated by the recurrent laryngeal nerve.

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## ***5. The trachea:***

- The respiratory diverticulum has grown to give 2 lung buds that will give the right and left main bronchi, which will also divide to give the secondary bronchi according to the number of lobes; right lung 3, left lung 2 .. So the buds located inside the lungs are actually –growing- secondary bronchi.

- So, the laryngotracheal tube will eventually form the trachea and right & left lung buds, then the out pocketing of the lung buds will give the bronchial buds which will be the left & right main bronchi. The main right gives 3 secondary bronchi, the left 2. Now the bronchopulmonary segments develop; 10 on the right and 8 on the left (8 only before birth), they are 8 because there is apicoposterior segment and anteromedial segment in the lower lobe. After birth, they become 10 on the left side too.

***The division of the bronchopulmonary segments:***

Before birth, there are 17 generations of ''Subdivisions/ dichotomous divisions''. It is when 1 bronchus gives 2 or 3 smaller, then 2 or 3 more & so on. This repetition of division is called dichotomous or subdivision. After delivery (postnatally), 6 additional divisions are formed. So, there are 23 divisions in total. Eventually, this division will give the respiratory bronchiole, alveolar ducts and alveoli.

## ***6. Pleura and lung:***

Lung buds will grow towards the coelomic cavity.

***Coelomic cavity:*** is a cavity that came from the pericardio-peritoneal cavity, where the pericardial and the peritoneal cavities were connected, then they separate; peritoneal cavity remains in the abdomen, while pericardial will change its name to pleuro-pericardial cavity which will be divided by the lung bud to pericardium of the heart ventrally/anteriorly and pleural cavity dorsally/ posteriorly. The invagination of the lung bud into the pleural cavity will give parietal and visceral pleura and lung.

Visceral pleura comes from splanchnic mesoderm, while the parietal pleura, that's on the edge of the coelomic cavity, is from the somatic mesoderm, between them is a large space that gets smaller by the growth of the lung tissue called the pleural cavity.

** Please note on the slides: the lungs, their hilum, the costo-diaphragmatic recess.

***Innervation of lung and pleura is connected with their development:***

*1. Parietal pleura:* Phrenic nerve (C3, C4 & C5)... it's a cervical spinal nerve

- This nerve will grow in the mediastinum between the 2 lungs, going down till just above the diaphragm then to the diaphragmatic surface of the lung; resulting in the mediastinal and diaphragmatic pleura to be innervated by it.
- Costal parietal pleura's innervation is from the intercostal nerves; T1-T11, in a segmental fashion.

*2. Visceral pleura and lung tissue*: Autonomic innervation, that is primarily from the pulmonary plexus through the vagus and sympathetic nerves.

- Because visceral pleura is autonomically innervated, it's sensitive to stretch, while parietal pleura is sensitive to pain, touch and temperature.

- Parietal pleura is divided to cervical, costal, diaphragmatic and mediastinal.

## *7. Alveoli development:*

- Last phase of lung development.

- Alveoli are responsible for respiration and gas exchange through the respiratory membrane found in the septum between them (alveoli).

- Alveoli formation determines lung maturation.

- Divided into 4 periods of time:

***1. Pseudo-glandular phase/ period:*** $5^{th}$/ $6^{th}$ -$16^{th}$ week.

- No respiratory bronchioles or alveoli are present… no respiration.

***2. Canalicular period:*** $16^{th}$ - $26^{th}$ week, meaning till the 6th month.

- Here, the lining epithelium is simple cuboidal, in both respiratory & terminal bronchioles.
- Blood vessels –capillaries- are far from the respiratory bronchioles by a space between them; so no respiration.

***3. Terminal sac period:*** $26^{th}$ week - birth

- Here, there are respiratory bronchioles that will divide & give the alveolar ducts.
  All terminal alveolar sacs' epithelium has turned from cuboidal to thin simple squamous.

  Capillaries are adherent to the wall of the alveolar sac, so now flat endothelium (which is simple squamous) is adherent to the flat alveolar cells & thus fusing their basal lamina forming the respiratory membrane can occur. In other words, in this period, primitive alveoli have been formed, making respiration and gas exchange possible.

- **Prenatally by the 6th month, alveolar cell type I & II are formed**, only type II happens at the end of the 6th month with the beginning of the 7th. So surfactants secretion can happen in the 7th month, that's why a premature infant, born by the 7th month, is able to survive, because his capillaries are sufficient in number, and gases exchange can happen.

- In newborns, the capillaries invaginate through the alveolar wall meaning the respiratory membrane has been formed and is **clearly present**.

- Nowadays, even if the infant was born before the 7th month, he can also survive by being placed in an incubator & giving him the appropriate medical injections & treatments to induce his lungs' maturation.

***4. Alveolar period:*** $8^{th}$ month - childhood

- Mature alveoli with well-developed epithelial - endothelial contacts (i.e. respiratory membrane is present).
  Fluid found in the lung consists of protein, mucous and surfactants. All the fluid is absorbed except the surfactants because they're important for coating the inner surface of the alveoli and is responsible for inflation of the lung.

- *Clinical point:* Absent or insufficient amounts of surfactants will result in respiratory distress syndrome, aka hyaline membrane disease. This disease is common and causes a high percentage (20%) of deaths after birth, especially in premature infants. Treated by an injection of glucocorticoids to help in surfactants secretion & subsequently inflation of the lungs. Even infants born by 5th month and a half of gestation can survive by being given a treatment that will help in the maturation of alveoli and respiratory membrane formation for respiration.

- Postnatally, lung growth happens by increase in the number of alveoli ***not*** in their size (even if there is increase in size, it will be very little/ negligible), till the age of 10 years old. Exactly opposite to brain cells; their number is fixed since birth, only size increases. For example, a person that cannot drive has small nerve cells responsible for driving, after learning, the cells grow in size.

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*Clinical point:*

An infant born by the 7th month can live normally while an infant born by the 8th is in a dangerous status, that's because the development of the central nervous system passes in several stages, one of them starts by the 7th month. If the infant is born by the 7th month then put into an incubator, the development will continue normally. By the 8th month, the development has already begun; so when an infant is born & then is taken from the intrauterine atmosphere and put into an incubator (i.e. you changed the surrounding environment), then that can disturb the development of the CNS and affect his life.

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***"The world is complicated and it deserves to be understood complexly.."***
***- Hank Green.***