RESPIRATORY SYSTEM

Embryology

Sheet Slide

Number:	1
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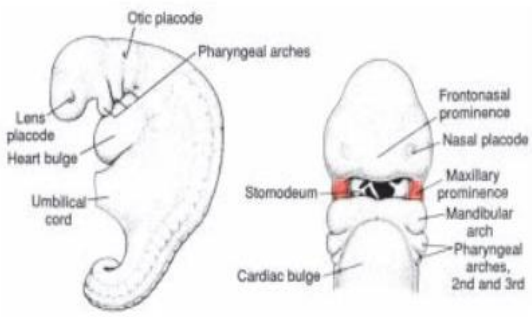
According to the doctor it is very important to link what was explained in the Gross Anatomy lectures to what is going to be described in the two Embryology lectures of this system.

Development of the Nose and Palate:

You are well aware of the Gross Anatomy of the nose and nasal cavity consisting of a Nostril anteriorly, a septum which divides the nasal cavity into two separate cavities, a lateral wall with its designated structures (Conchae and Meatuses), and a Choana posteriorly leading into the Nasopharynx.

The doctor stated a few of the structures located in Figure 1 (A) such as:



A B

Figure 1

1. Otic Placode: Has a relationship with the development of the ear.
2. Lens Placode: Has a relationship with the development of the eye.
3. Nasal Placode: Involved in the development of the nasal orifice otherwise known as the nostrils.
4. Heart bulge: Involved in the development of the heart.

In Figure 1 (B):

1. Stomodeum: meaning oral cavity.
2. Frontonasal Prominence
3. Maxillary Prominence
4. Mandibular Arch
5. Second and Third Pharyngeal Arches

At the end of the **fourth week**, structures known as facial prominences derived primarily of neural-crest mesenchyme formed by the first pair of pharyngeal arches begin to develop. A prominence is defined as “the fact or state of projecting from something.” Therefore, you could say that a prominence is an elevation above the surface of the embryo due to increased proliferation of certain cells compared with their neighbouring

cells. These prominences are thus involved in the development and formation of different structures within the embryo. There are three prominences which are of importance to us in this lecture which are:

1. Frontonasal Prominence: As the name suggest, it is a bony prominence originating from the frontal bone and reaches down to the nose forming the nasal septum. On both sides of this prominence, surface **ectoderm** cells proliferate locally under inductive influence of the ventral portion of the forebrain producing thickenings called the **nasal (olfactory) placodes**.
2. Maxillary Prominence: Grows internally and is involved in the development of the jaw, upper lip, and the nose.
3. Mandibular Prominence: Involved in the development of mandible and lower lip.

Throughout the **<u>fifth week</u>**, the nasal placodes invaginate inwards to form the **nasal pits (nostrils).** This process leads to the formation of the nasal opening, then dilatation of the structure occurs leading to the development of the vestibule.

There is also formation of both the Medial and Lateral nasal prominences/processes.

<u>During the following 2 weeks</u>, the Maxillary prominences continue to grow in size medially, compressing the medial nasal prominence toward the midline, at this instance the maxillary and medial nasal prominences on each side fuse and thus the cleft between them closes. If for any reason this fusion fails a developmental anomaly known as **Cleft Lip** (unilateral or bilateral) arises.

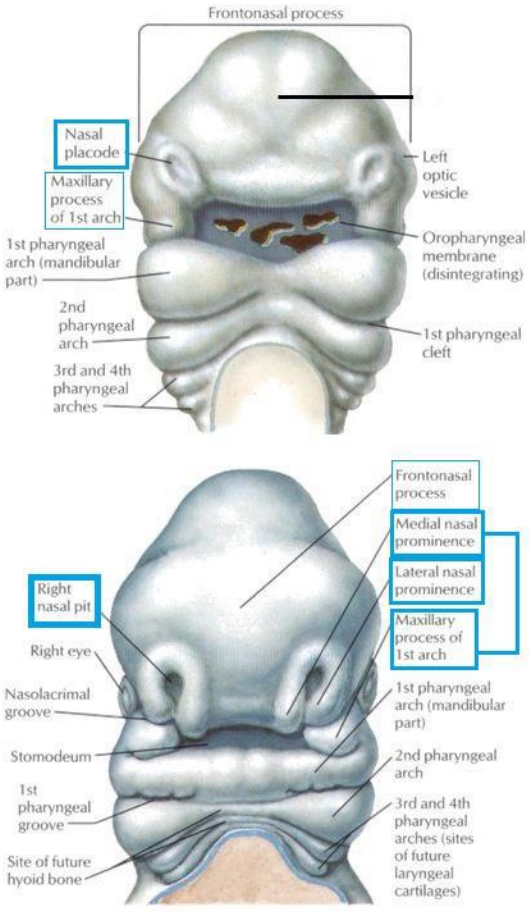


Figure 2

The embryonic structures involved in the formation of the nose:

1. Frontonasal Prominence: Gives rise to the **Nasal Septum**
2. Medial Nasal Prominences: After merging they form the **tip of the nose**
3. Lateral Nasal Prominences: Form the **Alae** of the nose
4. Olfactory pit: Initially forms the **Nostril** and with further invagination leads to the formation of the **Vestibule**

A summary of each prominence and its contribution to the nose or face:

Prominence	Contribution to the structures of nose and face
Frontonasal	1) Forehead 2) Bridge of the nose 3) **Nasal Septum** 4) Medial Nasal Prominence 5) Lateral Nasal Prominence
Lateral Nasal	**Alae of the nose**
Medial Nasal	1) Nasal Crest 2) **Tip of the nose** 3) Philtrum 4) ***Medial* portion of the upper lip**
Maxillary	1. Cheeks **2. *Lateral* portion of the upper lip**
Mandibular	**Lower lip**

*All the previous prominences are paired the only exception is the **Frontonasal prominence** which is single and unpaired.

Development of Nasal Cavities:

During the sixth week, the nasal pits deepen considerably (canalize), partly because of the growth of the surrounding nasal prominences and partly because of their penetration into the **underlying mesenchyme** (due to signaling by a group of proteins known as Fibroblast Growth Factors *the doctor stated here family factors but I'm pretty sure he means Fibroblast Growth Factors). The cavities formed from this process are still separated from the primitive oral cavity by what is known as the **oronasal membrane**. This membrane separates the nasal pits from the primitive oral cavity by way of the newly formed foramina known as the **primitive choanae.**

These Choana lie on each side of the midline and posterior to the primary palate. We will see later on that the development of the palate consists of the formation of a primary and a secondary palate that will fuse.

Following the previously described processes, the secondary palate is formed, further separating the nasal cavity from the oral cavity, and the definitive choanae will lie at the junction of the nasal cavity and the pharynx (opens into the nasopharynx). At this moment walls of the nasal cavity are taking their final shape and choncae appear at the lateral wall.

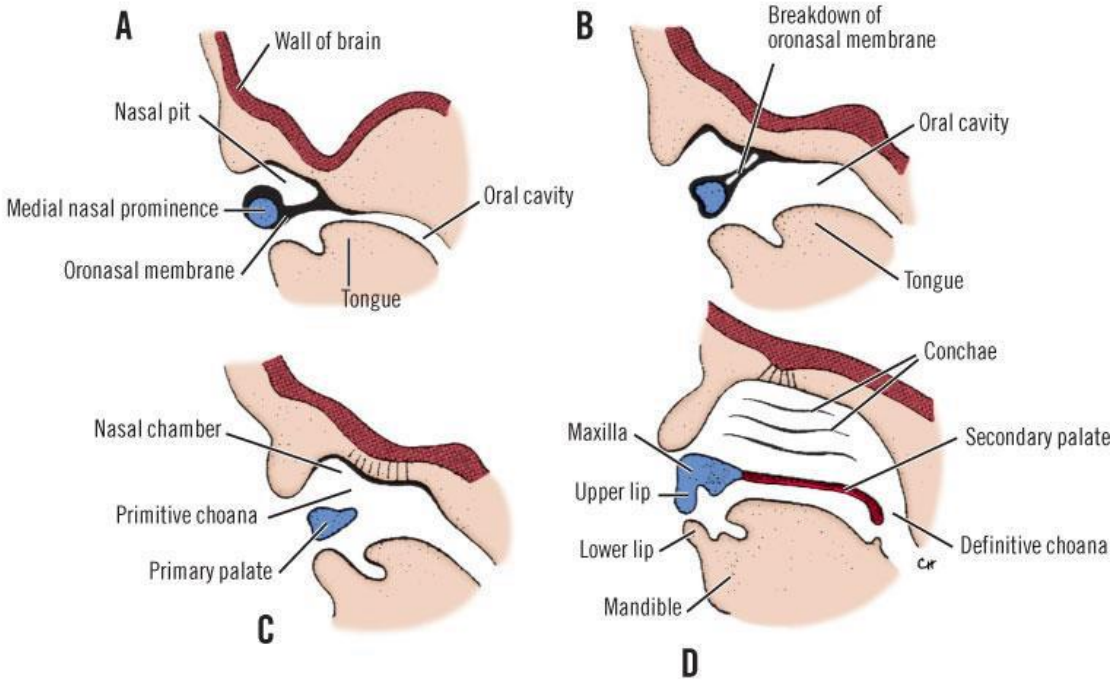


Figure 3

Development of the Paranasal Sinuses:

Paranasal air sinuses develop as diverticula from the lateral nasal wall and extend into the associated skull bone forming cavities which are located in the Maxilla, Ethmoid, Frontal, and Sphenoid bones. As we know each sinus has an opening in the lateral nasal wall. These opening form invaginations/diverticula (some books name this process canalization) which form ducts until they reach their respectful sinus.

As we took previously in the Gross Anatomy lectures these sinuses are rudimentary and birth, and they reach their maximum size at the time of puberty and contribute to the definitive shape of the face.

Development of the Primary and Secondary Palates:

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**, it's contains:

1. Labial component, which forms the **philtrum** of the upper lip
2. Upper jaw component, which carries the **four incisor teeth**
3. Palatal component, which forms the **triangular primary palate**

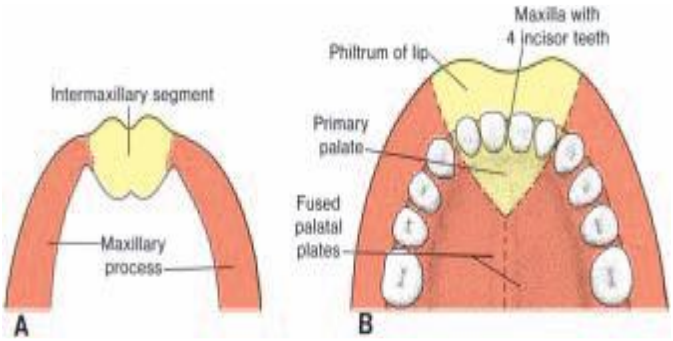


Figure 4

Secondary Palate:

In the **sixth week** of development the Palatine Shelves appear as two shelf-like outgrowths from the Maxillary Prominences. Theses shelves are directed obliquely and downwards on each side of the tongue. Then during the **seventh week**, the palatine shelves ascend to attain a horizontal position above the tongue and a group of fusions thus proceeds:

1. The two shelves meet medially and fuse **together** forming the secondary palate
2. Simultaneously as the palatine shelves fuse, **the nasal septum** grows down and joins with the cephalic aspect of the newly formed palate
3. Anteriorly, the shelves fuse **with the triangular primary palate**, and the **incisive foramen** is the midline landmark between the primary and secondary palates.

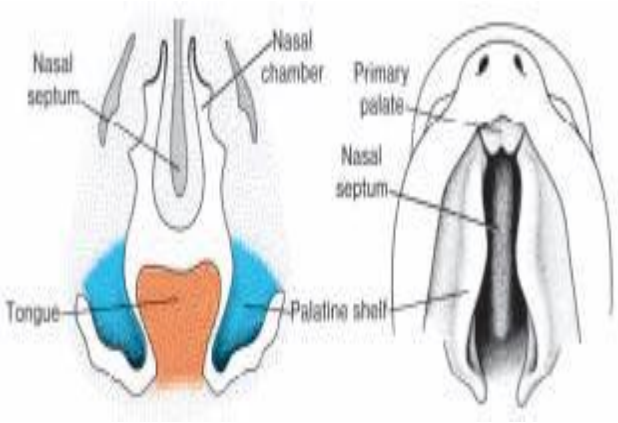


Figure 5

Two folds grow posteriorly from the edge of the palatine process to form the soft palate and the uvula, the union of the two folds of the soft palate occurs during the **eighth week**, while the two parts of the uvula fuse in the midline during the **eleventh week**.

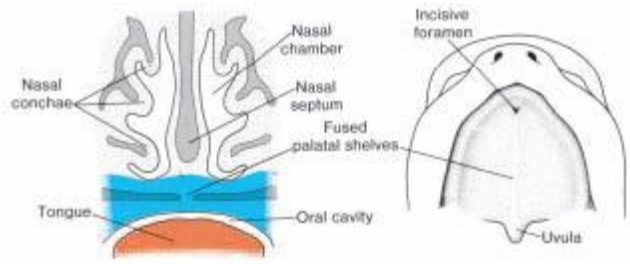


Figure 6

Once again and similar to cleft lip which occurs due to failure of fusion between the Maxillary Prominences and the Medial Nasal Prominences. In the case of the palate, if there is failure of fusion between the primary and secondary palates another developmental anomaly known as **Cleft Palate** will arise. Cleft Palate has the following characteristics:

1. It could be unilateral or bilateral
2. Unilateral cleft lip and palate can extend to the nose and nasal cavity
3. In cleft soft palate cleft uvula can also occur

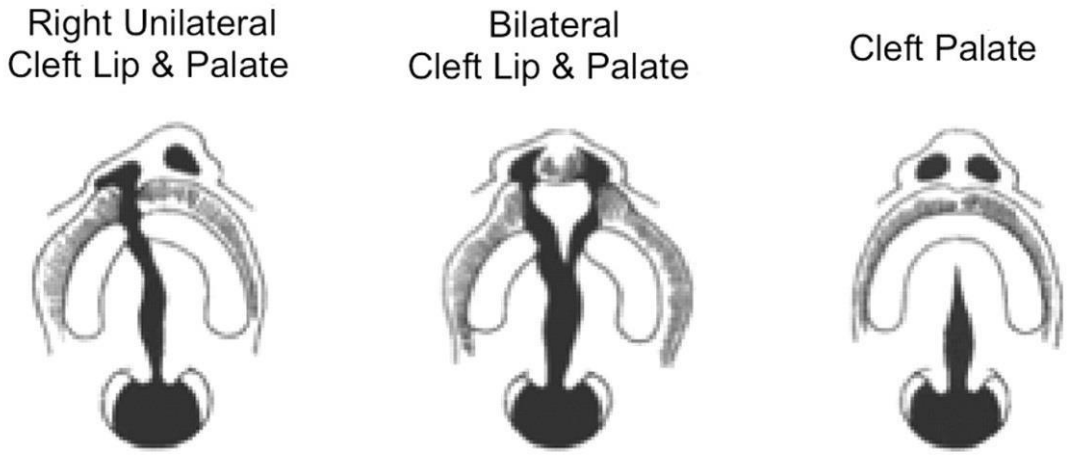


Figure 7

Development of the Respiratory Tract:

The respiratory tract consists of:

1. The larynx
2. Trachea
3. Bronchi
4. Alveoli

As you know from previous embryology courses, we have three layers in the embryo:

1. Endoderm: turns into the inner lining of some systems, and some organs such as the liver and pancreas
2. Mesoderm: gives rise to bones, muscles, the heart and circulatory system, and internal sex organs.
3. Ectoderm: develops into parts of the skin, the brain and the nervous system

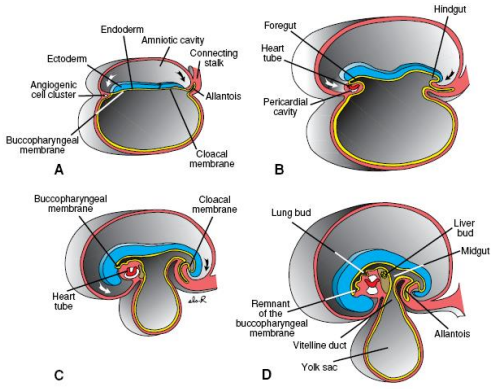


Figure 8

The Primitive Gut:

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

1. The pharyngeal gut, or pharynx, extends from the buccopharyngeal membrane to the tracheobronchial diverticulum
2. The foregut lies caudal to the pharyngeal tube and extends as far caudally as the liver outgrowth.
3. The midgut begins caudal to the liver bud and extends to the junction of the right two-thirds and left third of the transverse colon in the adult.
4. The hindgut extends from the left third of the transverse colon to the cloacal membrane

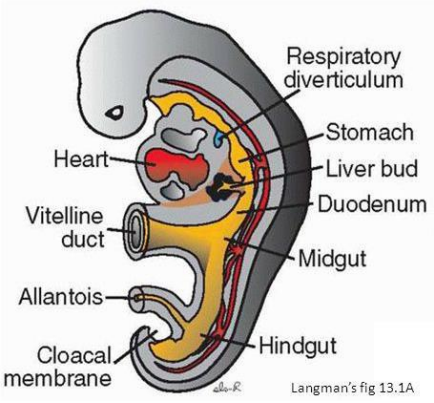


Figure 9

When the embryo is approximately **four weeks old**, the respiratory diverticulum (lung bud) appears as an outgrowth from the ventral wall of the foregut. This happens under the influence of **fibroblast growth factors (FGFs)**, which are secreted at a specific time inducing growth of

lung bud at a certain spot on the foregut. This is due to the fact that the embryo has what is known as a "gene box" that is in charge of controlling the signals for growth of the several systems of the embryo.

Therefore, each layer of the embryo has a specific contribution to the respiratory tract:

- The lining epithelium for the whole respiratory system is **endodermal** in origin
- All cartilage (ex. The cartilage of the Larynx), muscle, and connective tissue are derived from the **splanchnic mesoderm**
- The outer surface is derived from the **ectoderm**

Initially the lung bud has an open communication with the foregut.

When the diverticulum expands caudally, two longitudinal ridges appear at the beginning of the associated diverticulum known as **the tracheoesophageal ridges**, which separate it from the foregut. Subsequently, these ridges grow medially until they **fuse and separate** to form the tracheoesophageal **septum**, thus separating the foregut into a dorsal portion (the esophagus) and a ventral portion (the trachea and right and left lung buds).

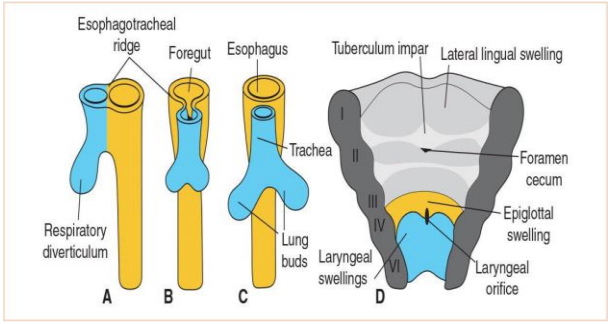


Figure 10

However, this does not mean that the respiratory tract and the digestive tract are now completely separated, as the respiratory tract maintains some communication with the Laryngopharynx through the Laryngeal orifice which is evident in Figure 9. The Laryngeal Orifice begins as a slit-like opening, then further develops into a T-shape opening, and finally into the laryngeal orifice.

Development of the Esophagus:

At the beginning of its development, the Esophagus is very short. However, due to the descent of the heart and lungs it elongates rapidly. As we know from the Digestive System, the Esophagus is a muscular tube. Its beginning/upper portion is innervated by the **Vagus Nerve,** followed by its lower portion that is innervated by the **Splanchnic Plexus**.

Anomalies of the Trachea and Esophagus:

These defects result from an abnormality in portioning of the esophagus and trachea by the tracheoesophageal septum. These anomalies are more **predominant in males** comparing with their female counterpart.

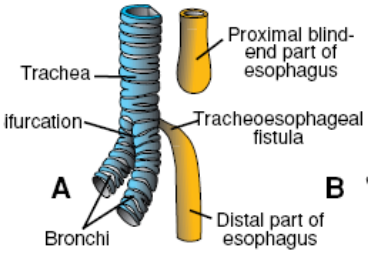


Figure 11

1. **Tracheoesophageal Fistula**
    a. **Proximal Esophageal Atresia with Tracheoesophageal Fistula (TEF)** (Figure 11)**:** The most common anomaly, this defect occurs in approximately 1/3000 births (accounts for approximately 90% of the cases).
    b. **Double Atresia** (Figure 12)**:** Also known as Isolated Atresia and accounts for approximately 4% of the cases.
    c. **H-type Tracheoesophageal Fistula Without Esophageal Atresia** (Figure 13): also accounts for 4% of the cases.
    d. **Double Atresia and Double Tracheoesophageal Fistula** (Figure 14)**:** accounts for 1% of the cases
    e. **Distal Esophageal Atresia and Proximal Tracheoesophageal Fistula** (Figure 15): accounts for 1% of the cases

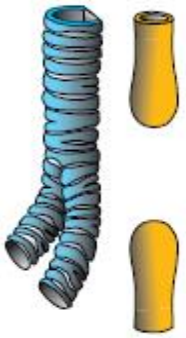


Figure 12

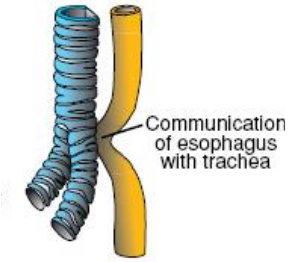


Figure 13

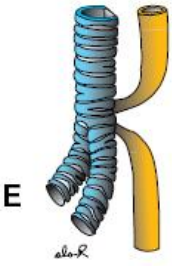


Figure 14

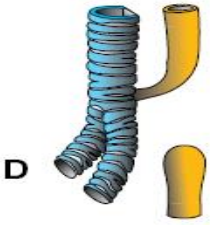


Figure 15

When infants with common type TEF and esophageal atresia try to swallow milk it rapidly fills the esophageal pouch and is **regurgitated**. A complication of some TEFs is **polyhydramnios** (excess amniotic fluid around the baby), since in some types of TEF amniotic fluid does not pass to the stomach and intestines as what should normally happen. Also, gastric contents and/or amniotic fluid may enter the trachea through a fistula, causing **pneumonitis and pneumonia**.

These abnormalities are associated with other birth defects, including cardiac developmental anomalies which occur in 33% of these cases. The most common Cardiac abnormalities are Atrial Septal defects, Ventricular Septal

defects, and Tetralogy of Fallot. 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 occur more frequently than predicted by chance alone. In other cases, air may enter from the lungs into the stomach causing the infant to have a distended abdomen while crying.

2. **Tracheal atresia and stenosis:** Are uncommon anomalies and usually associated with one of the varieties of TEF
3. **Incomplete Tracheal Atresia:** In some case a web tissue may obstructs the airflow

Development of the Larynx:

The internal lining of the larynx originates from the **endoderm**, but the cartilages and muscles originate from **mesenchyme** of **the fourth and sixth** pharyngeal arches. If you look back at Figure 9 you could see that the Laryngeal Orifice was a slit like opening and is now a T-like opening (Figure 16) due to rapid proliferation of the mesenchyme.

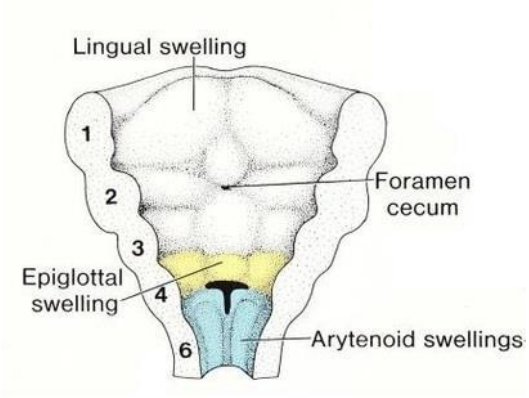


Figure 16

The mesenchyme of the fourth and sixth arches then transforms into the Thyroid, Cricoid, and Arytenoid cartilages. Thus, giving rise to the characteristic shape of the adult Laryngeal cavity/orifice this orifice is bound anteriorly by the epiglottis and by the aryepiglottic folds on each side.

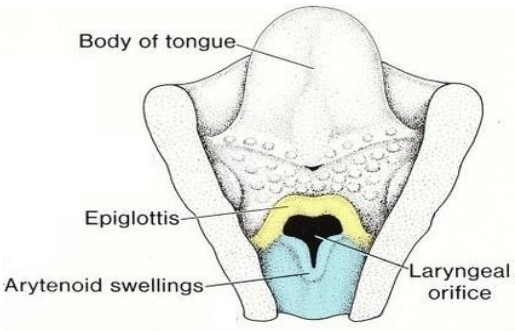


Figure 17

Simultaneously to the formation of the cartilages the Laryngeal epithelium proliferates rapidly resulting in a temporary **occlusion** of the lumen. Following this proliferation, **recanalization and vacuolization** produces a pair of lateral recesses known as the laryngeal ventricles which will be located in the Glottic area of the Larynx between the False Vocal Cord (superiorly) and True Vocal Cord (inferiorly).

Since all the muscles of the Larynx are derived from the mesenchyme of the fourth and sixth pharyngeal arches (as we stated previously), their innervation is by branches of the tenth cranial nerve, the **Vagus Nerve.** The **Superior Laryngeal Nerve (External Laryngeal Nerve)** innervates the structures that are derived from the **fourth pharyngeal arch** and the **Recurrent Laryngeal Nerve** innervates those derived from the **sixth**. Now we can deduct the reason why all muscles of the Larynx are innervated by the Recurrent Laryngeal Nerve except the Cricothyroid which is innervated by the External Laryngeal Nerve. This is due to the fact that the Cricothyroid muscle is derived from the fourth pharyngeal arch and all others are derived from the Sixth.

Laryngeal Developmental Anomalies:

Laryngeal Atresia is a rare anomaly and may cause obstruction of the upper fetal airway, it is more commonly known as Congenital High Airway Obstruction Syndrome (CHAOS). This syndrome causes lung enlargement distal to the atresia or stenosis and the lung can produce echoes. In addition, other anomalies may accompany CHAOS such as anomalies of the diaphragm and fetal ascites and hydrops, which are due to an accumulation of serous fluid. The gold standard for diagnosis of this anomaly is Prenatal ultra-sonography.

Development of the Lungs and Bronchial Tree

As we know the Lung Bud forms the trachea and it descends to the Intervertebral disc between T4 and T5 (Angle of Louis), where it bifurcates into to lateral outpocketings known as **Bronchial Buds.** At the beginning of the fifth week, each bud enlarges forming the right and left main bronchi. Furthermore, they continue growing giving us Lobar or Secondary Bronchi in association with each lobe (3 on the right and 2 on the left). They then continue growing into what are known as segmental or tertiary bronchi (10 on the right and 8 on the left). Finally, we reach the Alveoli.

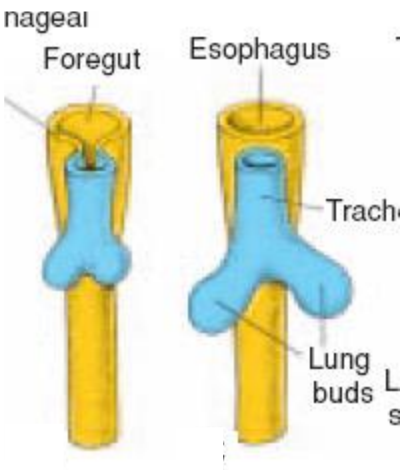


Figure 18

As the bronchi grow distally, structures known as the **Pericardioperitoneal canals** are developing, which will be separated into

a peritoneal cavity in the abdomen and a pericardial cavity in the thorax. Later on, the pleuroperitoneal and pleuropericardial folds separates the pericardioperitoneal canals from the peritoneal cavity and the pericardial cavities. Thus, the remaining spaces form the primitive pleural cavities. Then the formation of the parietal and visceral pleura occurs with the pleural space between them.

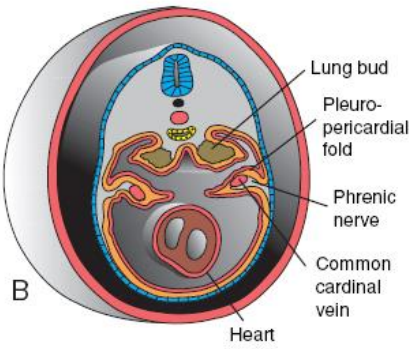


Figure 19

As we stated previously the lobar bronchi separate into segmental bronchi (bronchopulmonary segments) with 10 on the right and 8 on the left. Now at the end of the **sixth month** we have approximately 17 generations which are growing in a dichotomous fashion. Following birth or what is known as the postnatal period an additional 6 generations form. Thus, as an adult we have a total of 23 generations in the respiratory tract.

This process of branching is regulated by epithelial-mesenchymal interactions between the ectoderm of the lung buds and the splanchnic mesoderm that surrounds them. Similar to the lung bud development this is also signalled by the Fibroblast Growth Factor family.

While all 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