

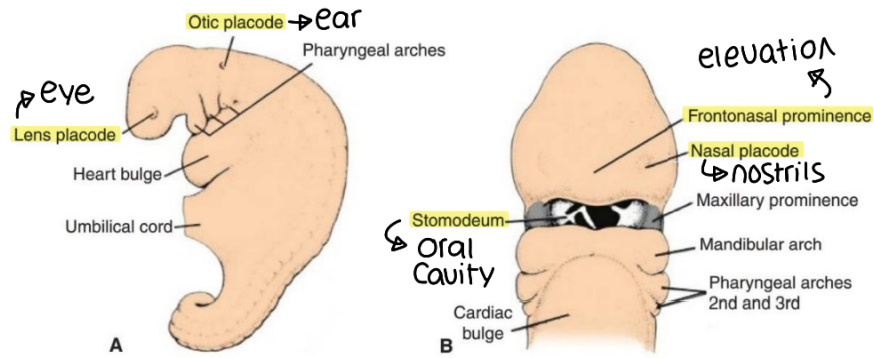
# RS EMBRYOLOGY

## NOSE AND PALATE

\* At the end of 4th week

facial prominences begin to develop (mainly of neural crest mesenchyme & first pair of Pharyngeal Arches)

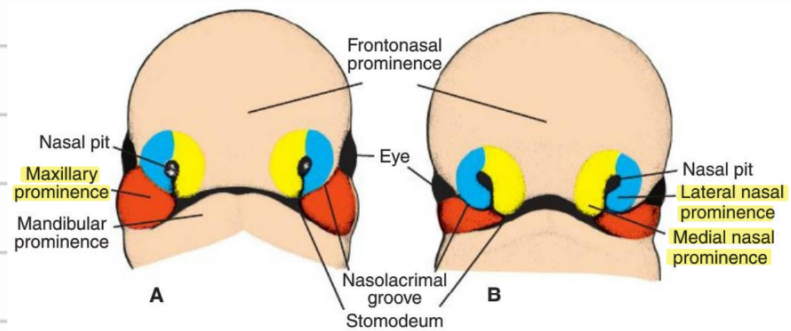
- prominence: an elevation that happens due to increased proliferation in a certain area



Prominence	direction of proliferation	involves in forming:
① frontonasal	ventral to brain vesicle (bony)	Upper part of Stomedeum & nasal septum
	on both sides ectoderm cells proliferate (induced by ventral fore brain)	Olfactory placodes (nasal)
② maxillary	internally	jaw, upper lip, nose
③ mandibular		mandible, lower lip

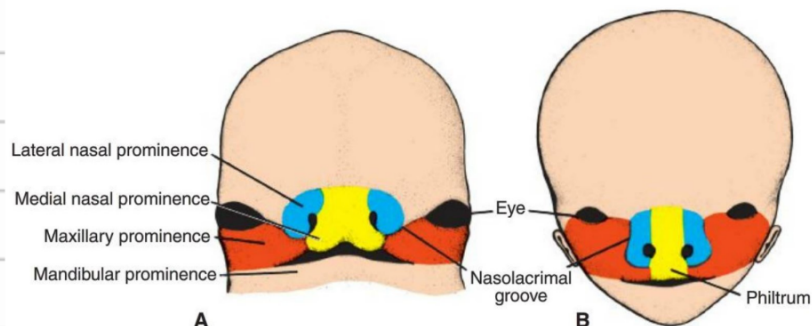
\* during 5th week:

nasal placodes invaginate inwards → form nasal pits (nostril) & nasal prominences (lateral & medial) → dilation of structure forms vestibule



\* during the following 2 weeks:

maxillary prominence grows medially → pushes medial nasal prominences → fusion of maxillary & nasal prominences



**TABLE 17.3** Structures Contributing to Formation of the Face

Prominence	Structures Formed
Frontonasal <sup>a</sup> + Septum	Forehead, <b>bridge of nose</b> , and medial and lateral <b>nasal prominences</b>
Maxillary	Cheeks, lateral portion of upper lip
Medial nasal	Philtrum of upper lip, crest, and <b>tip</b> of nose
Lateral nasal	<b>Alae</b> of nose
Mandibular	Lower lip

<sup>a</sup>The frontonasal prominence is a single unpaired structure; the other prominences are paired.

## \* Structures that form Nose

- ① frontonasal → Septum
  - ② medial nasal (x2) → tip
  - ③ lateral nasal (x2) → alae
  - ④ olfactory pit → Nostril & vestibule
- } → **5 Prominences**

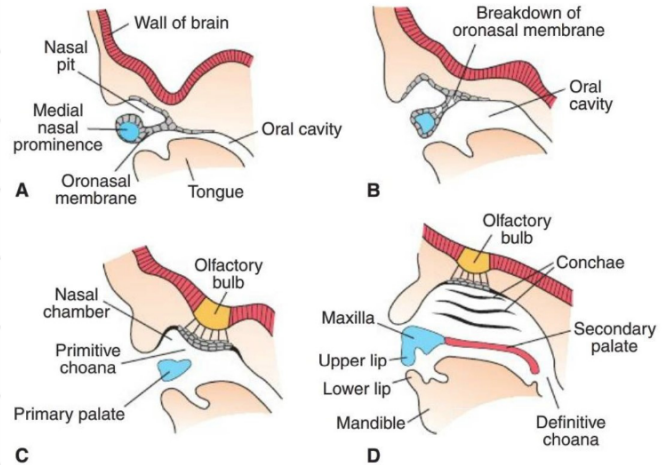
## \* during 6th week

### A) Nasal pits canalize due to:

- ① growth of nasal prominences
- ② their penetration into underlying mesenchyme (due to signaling of fibroblast growth factors)

B) Nasal pits are separated from oral cavity by oronasal membrane by way of forming primitive choanae (foramina) which lie on each side of midline & behind 1° palate

D) then 2° palate forms & development of nasal chambers (further separation of oral & nasal cavities → definitive choanae lie at junction of nasal cavity & pharynx (lateral wall))

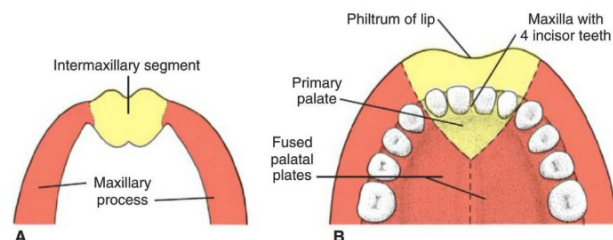


\* **paranasal sinuses** → develop as diverticula (canalization) from lateral wall to target skull bone (frontal, maxillary, ethmoidal, sphenoidal) / max size at puberty

## \* 1° palate

medial growth of maxillary prominence → merge & form intermaxillary segment (continuous with rostral portion of nasal septum (formed by frontal prominence) / the segment has:

- ① **labial component** → forms philtrum /
- ② **upper jaw** → carries 4 incisors /
- ③ **palatal component** → forms triangular 1° palate



## \* 2° palate

. at 6th week palatine shelves appear as oblique & downward directed outgrowths from maxillary prominences (on sides of tongue)

. during 7th week

① palatine shelves ascend horizontally above tongue & fuse medially forming 2° palate

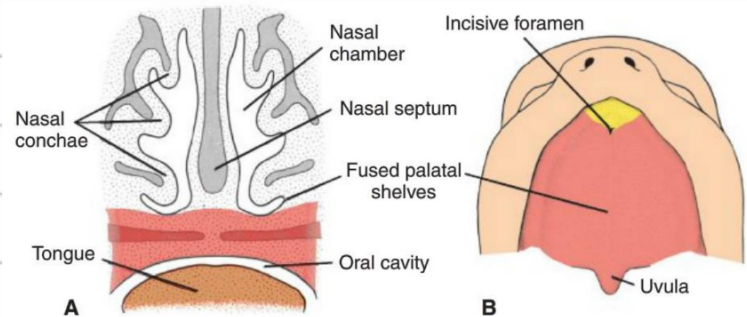
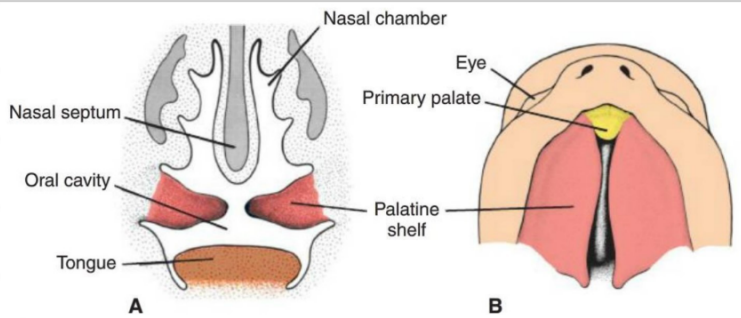
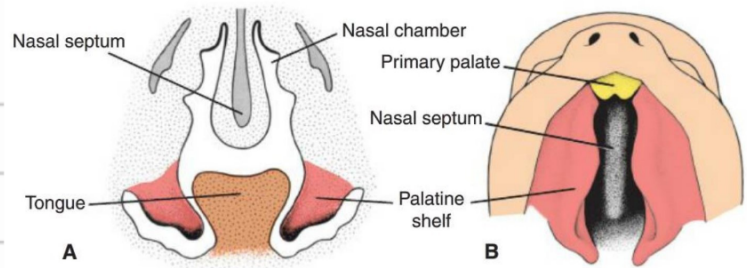
② anteriorly, the shelves fuse with triangular 1° palate (midline is incisive foramen)

③ nasal septum grows & joins cephalic aspect of 2° palate

. the 2 folds grow posterior from edge of palatine process to form soft palate & uvula:

① soft palate folds unite → during 8th week

② uvula folds unite → during 11th week



## \* developmental anomalies

① no fusion of maxillary & medial nasal prominences →

uni/bilateral cleft lip (unilateral cleft can reach nose)

② no fusion of 1° & 2° palate → uni/bilateral cleft palate

(can involve soft palate & uvula)

## \* embryo layers:

① endoderm → inner lining

② mesoderm → bone, muscle, CVS, internal sexual organs

③ ectoderm → skin, nervous system

# PRIMITIVE GUT

\* 4 sections:

## ① pharyngeal gut

from buccopharyngeal membrane (between primitive mouth & pharynx / will rupture later) to tracheobronchial diverticulum

## ② foregut

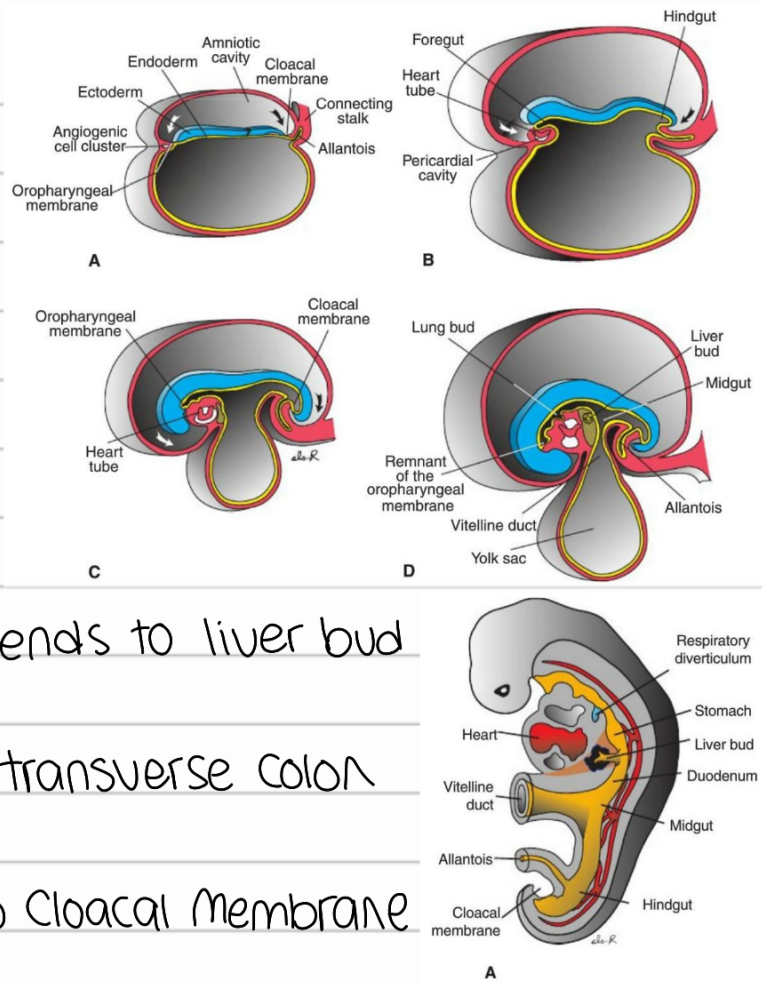
caudal to pharyngeal tube & extends to liver bud

## ③ midgut

caudal to liver & extends to 2/3 transverse colon

## ④ hind gut

from left 1/3 transverse colon to cloacal membrane



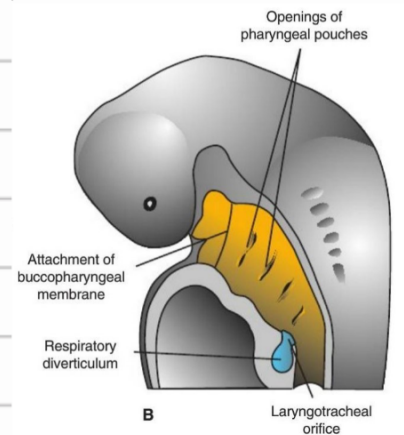
\* during 4<sup>th</sup> week: appearance of respiratory diverticulum (lung bud) from ventral wall of foregut induced by fibroblast growth factor (FGFs) because the embryo has a gene box that controls signals of growth of several systems.

\* respiratory tract embryonic origin:

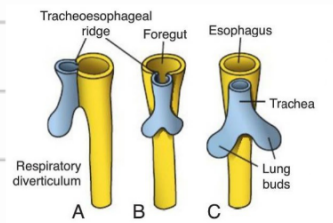
① endoderm → lining epithelium

② mesoderm → cartilage, muscle, CT  
(splanchnic mesoderm surrounding foregut)

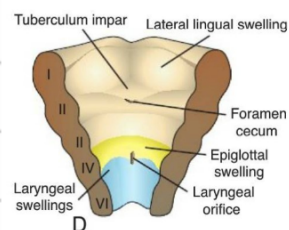
③ ectoderm → outer surface



\* initially lung bud has open communication with foregut → when bud expands caudally it's separated from foregut by tracheoesophageal ridges → ridges fuse into a septum

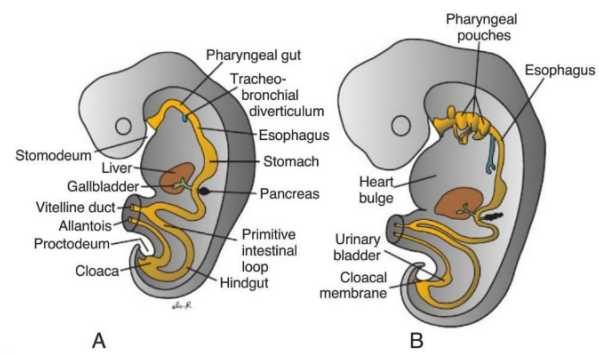


\* respiratory primordium maintains communication with pharynx by laryngeal slit → T-shaped → opening



# ESOPHAGUS

- at beginning it's very short → elongates rapidly with descending heart
- Upper 1/3 → Striated / Vagus
- Lower 2/3 → Smooth / Splanchnic plexus



## \* anomalies in trachea & esophagus:

### 1 tracheoesophageal fistula (TEF)

A → proximal atresia / distal fistula / most common

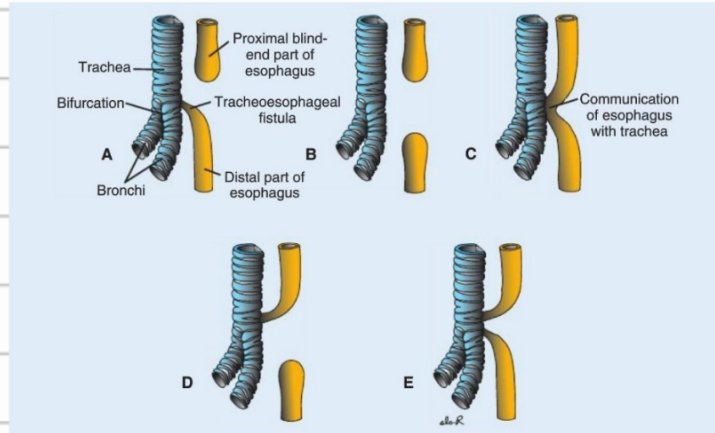
(1/3000) / 90% of cases

B → double atresia (not TEF) (isolated / 4%)

C → H type fistula without atresia (4%)

D → distal atresia & proximal fistula (1%)

E → atresia & double tracheoesophageal fistula (1%)



• TEF is most common anomaly in lower respiratory tract & causes:

① infants cough & choke due to ↑ saliva in mouth

② can't swallow milk

polyhydramnios (↑ amniotic fluid around baby) /

③ food enters trachea → pneumonitis & pneumonia

• TEF is associated with other abnormalities (VACTERL)

V → vertebral / A → anal / C → cardiac (33%) / T → TEF /

E → esophageal atresia / R → renal / L → limb

• the cause of these abnormalities is unknown / ♂ > ♀

• most common associated cardiac abnormalities: ASD, USD, fallot

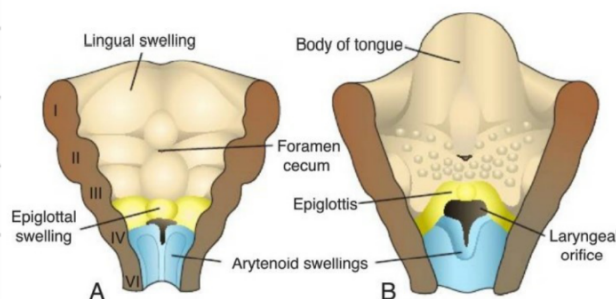
2 tracheal atresia & stenosis → usually associated with TEF

3 incomplete tracheal atresia → obstruction of airways by web tissue

# LARYNX

## \* origin:

- ① endoderm → lining epithelium
- ② mesoderm → cartilage, muscle  
(mesenchyme of 4<sup>th</sup> & 6<sup>th</sup> arches)



## \* formation:

- 4<sup>th</sup> & 6<sup>th</sup> arches form thyroid, arytenoid, cricoid cartilages giving characteristic shape of laryngeal orifice which is bound anteriorly by epiglottis & laterally by aryepiglottic folds
- rapid proliferation growth → occlusion of lumen → recanalization & vacuolization → forming lateral recesses (laryngeal ventricles) in glottic area of larynx between true & false vocal cords.

## \* innervation:

Vagus branches:

- superior laryngeal (external) → 4<sup>th</sup> arch structures (cricothyroid muscle)
- recurrent laryngeal → 6<sup>th</sup> arch structures (other intrinsic muscles)

## \* anomalies:

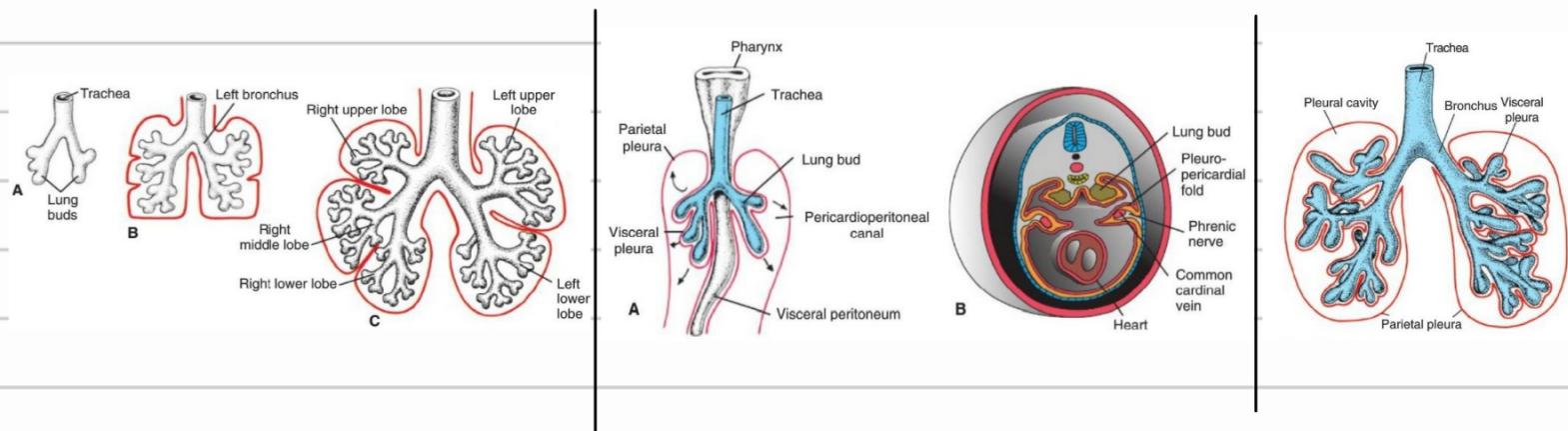
- **laryngeal atresia** → rare, may cause **CHAOS** (congenital high airway obstruction syndrome) → lung enlargement & echoes
- anomalies that accompany CHAOS:
  - ① diaphragm (flattened/inverted)
  - ② fetal ascitis & hydrops (↑ serous fluid / diagnosed by prenatal ultrasonography)

# LUNGS AND BRONCHIAL TREE

- lung bud  $\rightarrow$  forms trachea  $\rightarrow$  elongates till T<sub>4</sub>, T<sub>5</sub> (angle of Louis)  
 $\rightarrow$  bifurcates to bronchial buds  $\rightarrow$  at beginning of 5<sup>th</sup> wk: buds enlarge into rt & lt main bronchi  $\rightarrow$  give lobar bronchi (3 rt, 2 lt)  $\rightarrow$  give segmental bronchi (10 rt & 8 lt)  $\rightarrow$  then reach alveoli
- as bronchi grow distally pericardioperitoneal canals are developing  
 $\rightarrow$  later on, pleuroperitoneal & pleuropericardial folds separate pericardioperitoneal canals from peritoneal & pericardial cavities & the remaining spaces form primitive pleural cavities  $\rightarrow$  forming of parietal & visceral pleura surrounding pleural cavity

## \* bronchial tree :

- trachea  $\rightarrow$  1<sup>o</sup> bronchi  $\rightarrow$  2<sup>o</sup> bronchi  $\rightarrow$  3<sup>o</sup> bronchi  $\rightarrow$  + 14 generations of dichotomous divisions (each one divides to 2)  $\rightarrow$  at end of 6<sup>th</sup> month we have 17 generations  $\rightarrow$  + 6 gens after birth (adult has 23 gens)
- branching is regulated by epithelial mesenchymal interactions between endoderm of lung buds & surrounding splanchnic mesoderm (signalled by fibroblast growth factor)
- branching is associated with caudal descending of trachea to reach 4<sup>th</sup> thoracic vertebrae at birth
- branching of 3<sup>o</sup> bronchi forms terminal & respiratory bronchioles marks the beginning of maturation of alveolar ducts, sacs & alveoli



# MATURATION AND DEVELOPMENT OF LUNGS

## \* development of respiratory bronchioles

### Stage 1: pseudo glandular period

- in weeks 5-16 (half of 4<sup>th</sup> mo.) → terminal bronchioles ONLY (conducting) / simple cuboidal epithelium

### Stage 2: Canalicular Period (pic A)

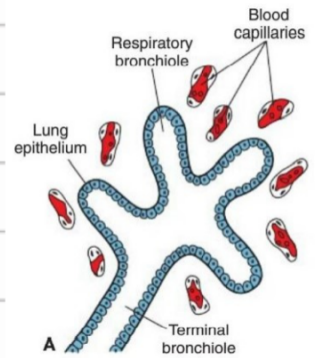
- in weeks 16-26 (6 & half mo.) → alveolar ducts (canaliculi)
- 1 terminal bronchiole → 2 respiratory bronchioles → 3-6 ducts (x2)

#### • Changes:

① Simple cuboidal epithelium → simple squamous

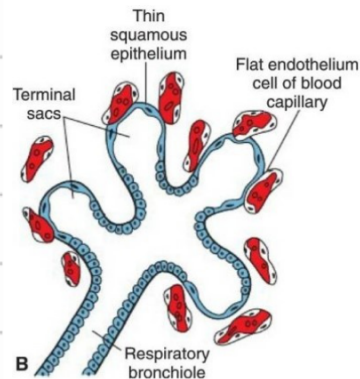
② ↑ vascular supply (formation of alveolar capillaries) but no gas exchange (no connection)

→ baby born in this stage (≥ 7<sup>th</sup> mo.) can survive (with adequate treatment to enhance alveoli & capillary growth + O<sub>2</sub> & surfactant)



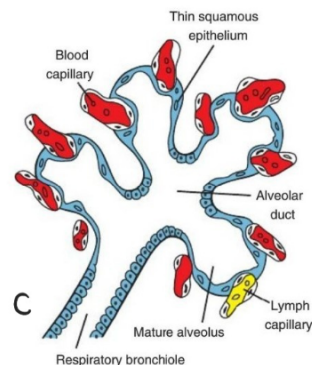
### Stage 3: terminal sac period (pic B)

- in weeks 26 - birth → terminal sacs or primitive alveoli (immature) / from respiratory bronchioles
- connection between squamous epithelium & blood capillaries → gas exchange is possible → baby born at >7 mo. can survive without support



### Stage 4: alveolar period

- from 8<sup>th</sup> mo. to 10<sup>th</sup> year of age → mature alveoli
- thinning of type I alveolar cells (sac lining) allowing capillaries to protrude into alveolar sacs → fusion → complete contact (respiratory memb./blood-air barrier)
- connection of lymph to walls





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.

## \* Notes:

- Only 1/6 of total adult alveoli are present at birth / increase in number of alveoli & bronchioles is more important than increase in size
- type II surfactant alveolar cells (from end of 6<sup>th</sup> to 8<sup>th</sup> mo.) → peak surfactant production (9<sup>th</sup> mo. / 2 wks before delivery) / importance: less pressure needed to keep alveoli open after expiration / missing → atelectasis / collapse (next inspiration is hard)

## \* lungs

### • before birth

lungs filled with fluid (↑ Cr, ↓ protein, some mucus of bronchial glands, surfactant) / breathing (aspiration) of amniotic fluid stimulates growth of respiratory muscles needed after birth

### • at/after birth

blood & lymph resorb lung fluid, a small amount of fluid leaves through trachea during delivery → lungs are left with liquid-air interface at sacs + phospholipid surfactant

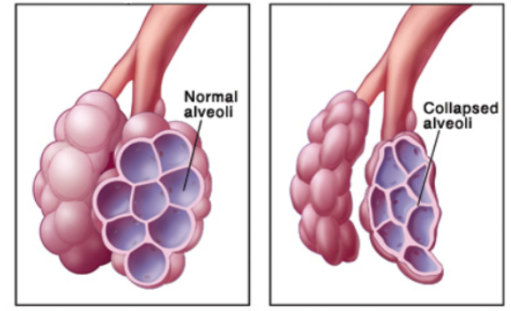
### • after birth

Dr. Slaps baby's back to stimulate skin receptors → nerve impulses to respiratory centers → brain sends impulses (phrenic motor nerve) → stimulate diaphragm to contract → air flow from nose to lung → breathing starts & baby cries

\*anomalies:

## ① RDS (respiratory distress Syndrome)

- missing surfactant at birth (premature birth) → loss of compliance → collapse of alveoli → need high pressure to open
- 30% of neonatal diseases / 20% of neonatal deaths
- Common complication: **intrauterine asphyxia** (suffocation due to deprivation of  $O_2$ ) → irreversible damage of type II cells → no survival even with treatment)
- treatment: ⊕ surfactant production by:
  - ↳ **glucocorticoids** (betamethazone)
  - ↳ **thyroxine** (most important stimulator / for mothers with hypothyroidism)
- RDS can also be called: **hyaline membrane disease** (↑ protein content & lamellar bodies derived from surfactant layer)

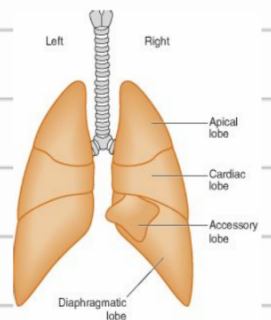


## ② blind ending trachea (atresia) + agenesis of one of lungs

- rare / if led to ↓  $O_2$  → death / can be caused by a **teratogenic drug** the mother used.

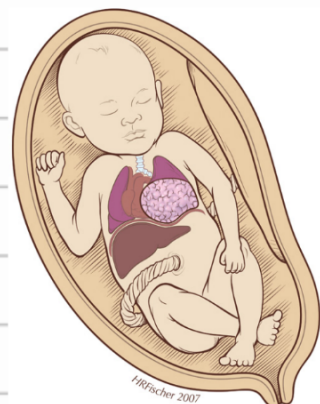
## ③ supernumerary lobules & ectopic (accessory) lobes

- **excessive branching** of bronchial tree → 3-4 lobes in left lung / no functional significance
- **additional respiratory buds** by foregut → lobes from trachea, esophagus or in mediastinum independent on respiratory system



## ④ congenital cysts of lung

- **most important clinically**
- formed by dilation of large terminal bronchi (uni/multi) → restrict inflation → ↓  $O_2$
- honey comb appearance in radiograph
- cysts drain poorly → chronic infxns
- treat by surgical removal (can be intrauterine)



# ⑤ lung hypoplasia



- most common cause: **congenital diaphragmatic hernia (CDH)** → hernia pushes some abdominal structures to thoracic cavity → lung is unable to develop normally (compressed by abdominal viscera) → ↓ lung volume (left side more common)
- infants with CDH usually die of pulmonary insufficiency
- **oligohydramnios** (↓ amniotic fluid) → severe lung hypoplasia

\* if the newborn was found dead after delivery → possibilities:

- ① air filled lung → float on water (slipped from dr's hands)
- ② fluid filled lung → sink in water (baby is already dead in womb/stillborn)

### Embryo of Lungs

**EMBRYOLOGY of the Lungs**  
BUDDING & DEVELOPMENT  
SWIPE TO REVIEW

### Gastrulation

**GASTRULATION**  
ECTODERM  
MESODERM  
ENDODERM

Notochord, Neural groove, Somatic mesoderm, Paraxial (muscle), Intermediate (gonad & kidneys), Lateral plate (heart, limbs, spleen, blood, adipose, lymph, smooth muscle & endothelium), Splanchnic mesoderm, Endoderm (epithelium from gut tube and glands of the trachea, bronchi, & alveoli of the lung).

### The Fetus

**SAGITTAL SECTION**  
ENDODERM (GIT): Pharynx, Foregut, Respiratory diverticulum (outpouching of the GIT (foregut)), Stomach, Septum transversum, Liver bud, Midgut, Hindgut, Cloaca.

Heart, Vitello-intestinal duct, Allantois.

**Fetus at 4 weeks**

### Budding of Lungs

**BEGINNING OF 4TH WEEK**  
1 Tracheoesophageal ridges, 2 Tracheal buds, Respiratory diverticulum, LARYNGO, TRACHEAL GROOVE, Splanchnic mesoderm, FOREGUT, Outpouching, 3 Trachea, Bronchial buds.

### Budding of Lungs

**BEGINNING OF 5TH WEEK**  
4 Trachea, 5 Bronchial buds, 6 Trachea bifurcates, Right main bronchus, Left main bronchus, Secondary bronchial buds, Splanchnic mesoderm.

### Pseudoglandular period

**BEGINNING OF 6TH - 8 WEEKS**  
7 Superior lobe, Middle lobe, Inferior lobe, Superior lobe, Inferior lobe, Secondary bronchial buds, Right, Left, THREE SECONDARY BRONCHI ON THE RIGHT & TWO SECONDARY BRONCHI ON THE LEFT, Trachea, Left primary bronchus, Tertiary bronchial buds, Parietal pleura from somatic mesoderm, Visceral pleura from splanchnic mesoderm, Superior lobe, Secondary bronchi, Middle lobe, Inferior lobe.

### Canalicular to Saccular

**CANALICULAR PERIOD** 16-24 weeks  
Terminal bronchiole, Cuboidal epithelium, Respiratory bronchiole, Blood capillaries, Future respiratory bronchiole, Terminal sacs.

**SACCULAR PERIOD** 36 weeks to birth  
Capillaries are now in direct contact with cells, Alveolar Type 1 cells (SITE OF GAS EXCHANGE), Alveolar Type 2 cells (PRODUCE SURFACTANT).

### Lung Stages Table

Stage of Maturation	Fetal Time period
<b>EMBRYONIC</b>	<b>3 - 7 WEEKS</b>
EVENTS Respiratory bud forms. Initial branching. Trachea and larynx forms.	
<b>PSEUDOGLANDULAR</b>	<b>6-16 WEEKS</b>
EVENTS Branching continues. Terminal bronchioli. Closure of pleuroperitoneal folds.	
<b>CANALICULAR</b>	<b>16-28 WEEKS</b>
EVENTS Development of respiratory bronchioli + some alveolar ducts Terminal sacs. Lung tissue vascularized. Gas exchange at 24 weeks.	
<b>SACCULAR (TERMINAL SAC)</b>	<b>24 - 38 WEEKS</b>
EVENTS Many terminal sacs. Epithelium thins. Type 1 & 2 pneumocytes.	
<b>ALVEOLAR</b>	<b>36 WEEKS - 3 YEARS</b>