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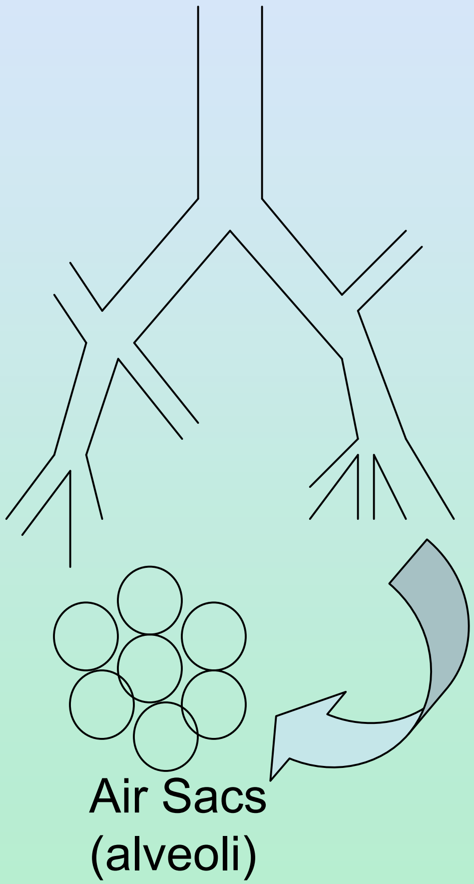
Function of Breathing



Ventilation-air conduction

Moving gas in and out of the chest

Gas Exchange

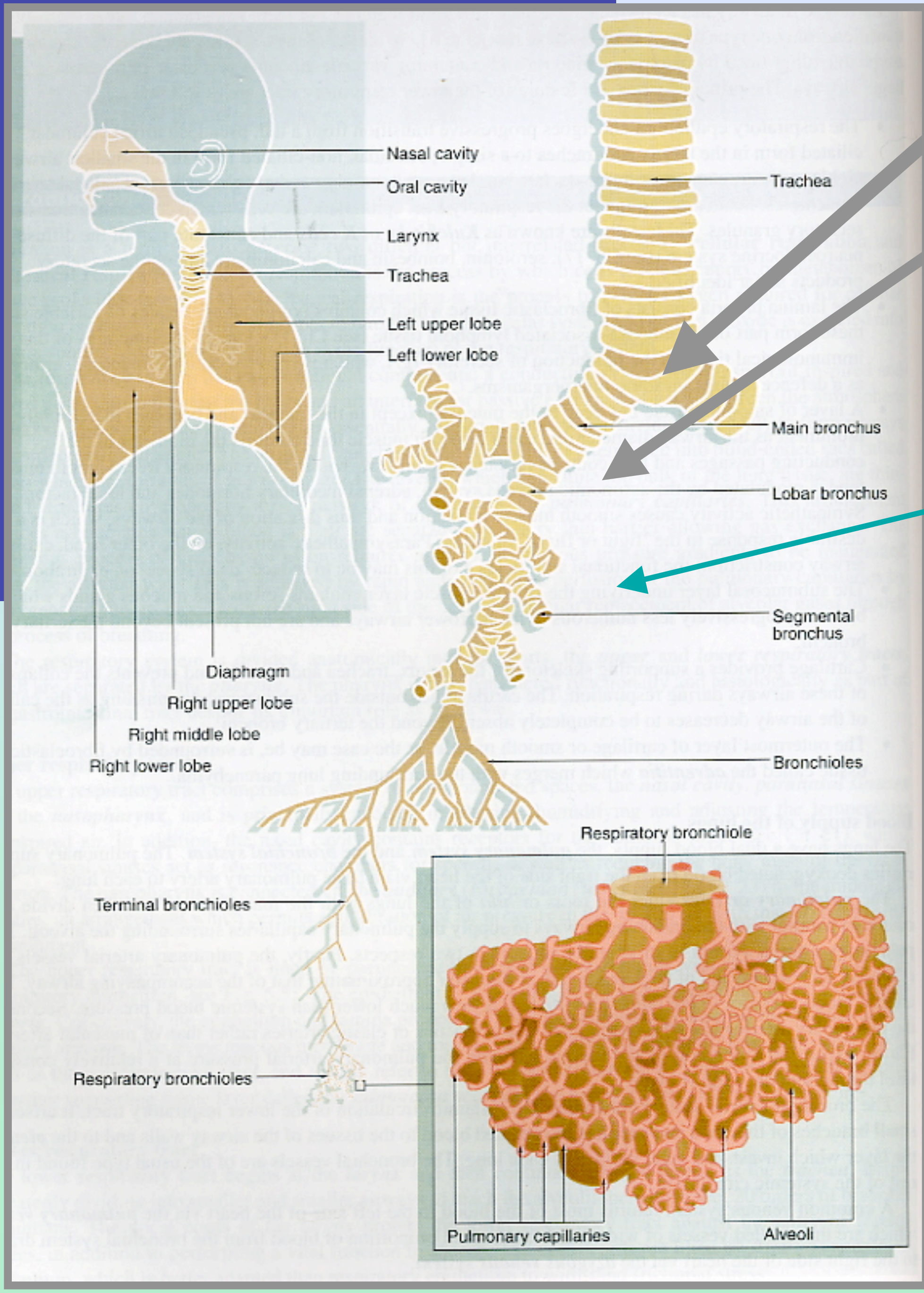
Moving gas Oxygen and carbon dioxide in and out of the blood

oxygen from air to blood

carbon dioxide from blood to air

Critical to the Development of the Lung

- Need a branched respiratory tree with a mucociliary cleaning mechanism
- A complex gas-exchange region with efficient diffusion and short diffusion distance
- Network of capillaries in close contact with the airspaces
- A surface film to reduce the surface tension of the alveoli and prevent collapse



Main stem bronchus

Lobar bronchus (5 lung lobes)

Segmental bronchus (10 bronchopulmonary segments on right, 9 on left

Branching continues as airways become bronchioles, then at terminal bronchioles airways transition into respiratory bronchioles

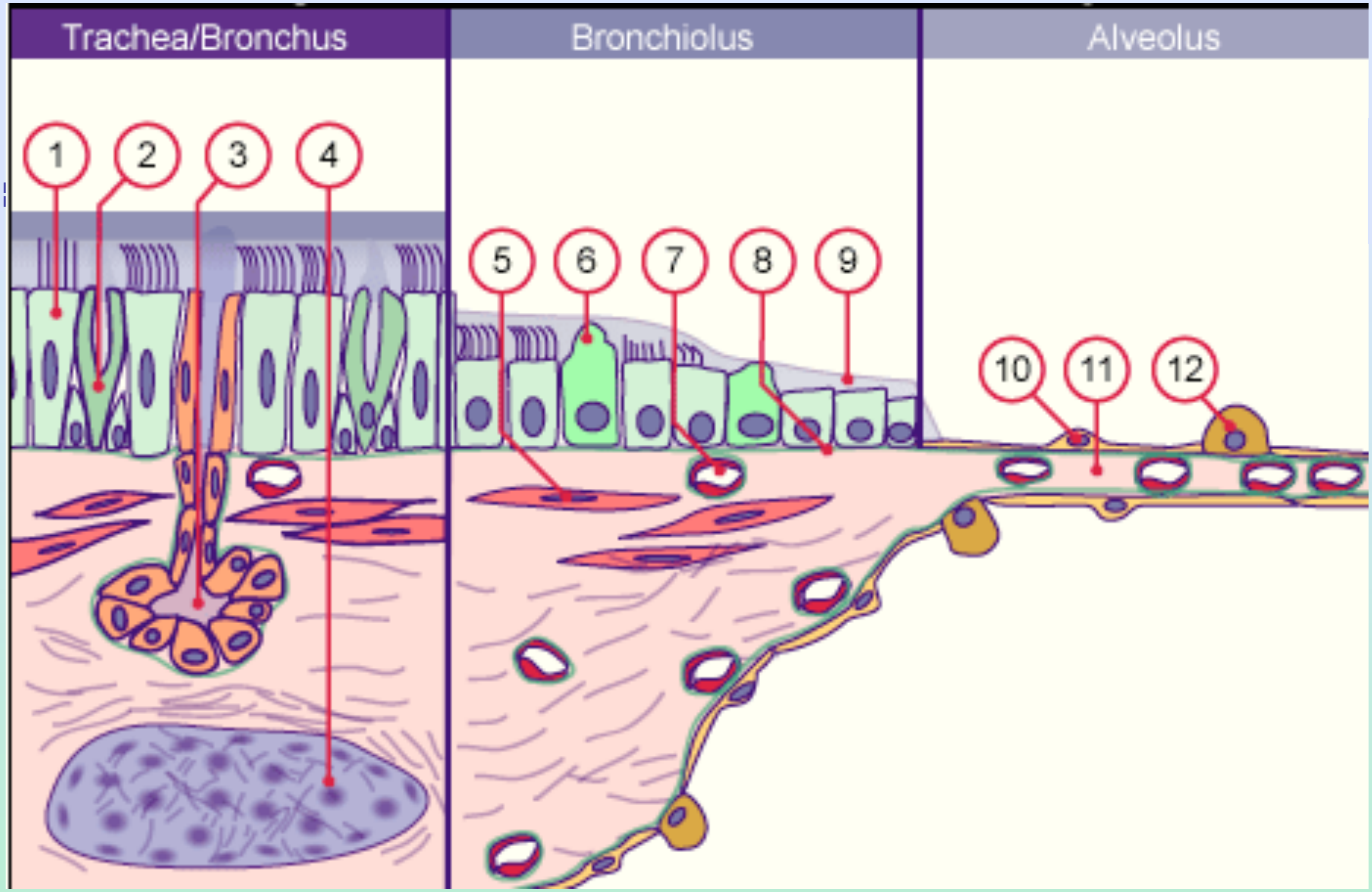
About 20 branch generations from beginning to end

Conducting Portion

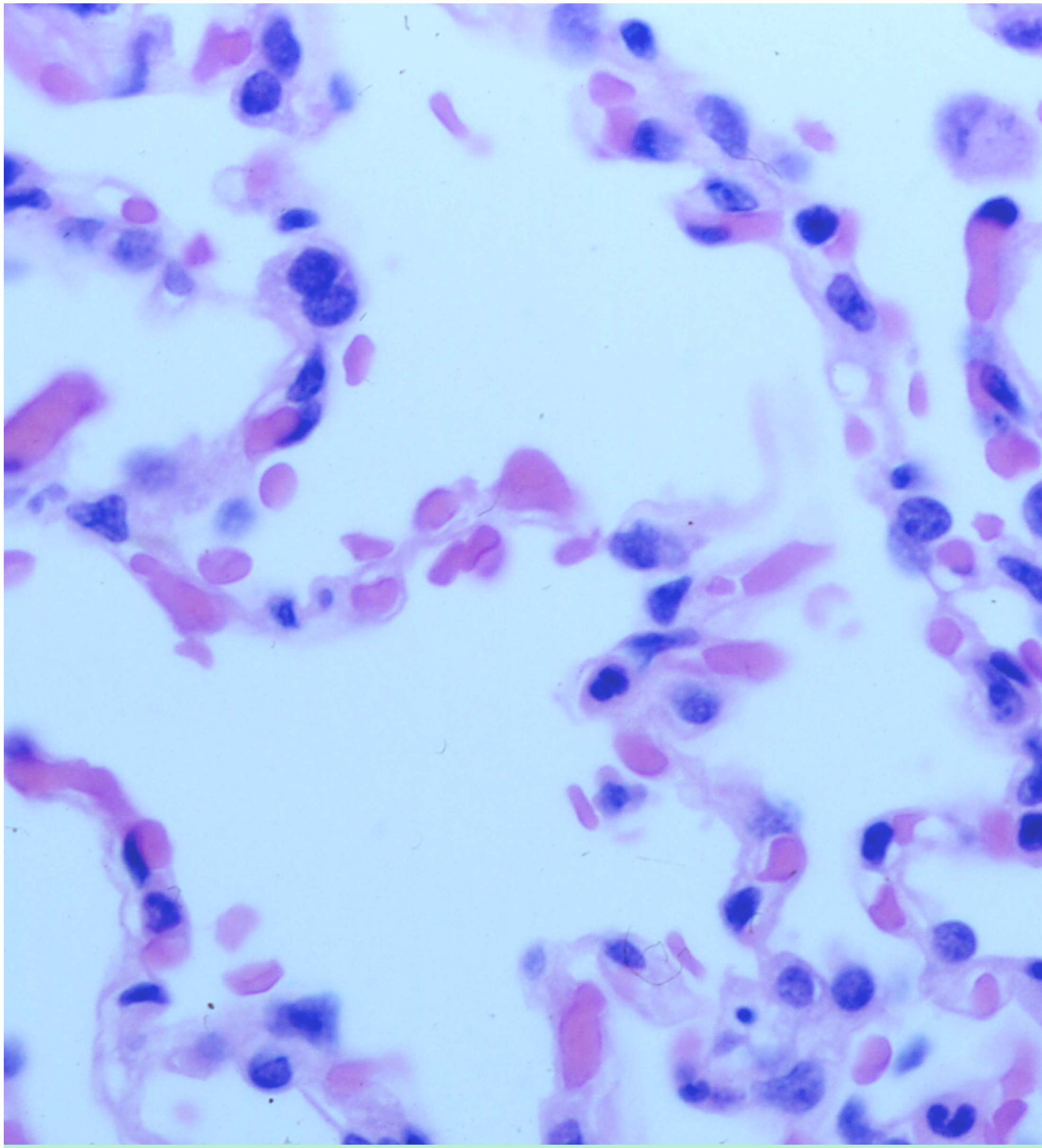
- Naval Cavity-hairs for filter, olfactory mucosa for smell
- Pharynx-cavity for speech and part of alimentary tract
- Larynx-vocal cords
- Trachea-Flexible connection between lungs and more rigid structures of upper respiratory tract
- Bronchi-Trachea divides into 2 primary bronchi which lead to left and right lung
- Bronchioles-final Conducting portions. Devoid of cartilage, undergo more branching and final segments are called terminal bronchioles.

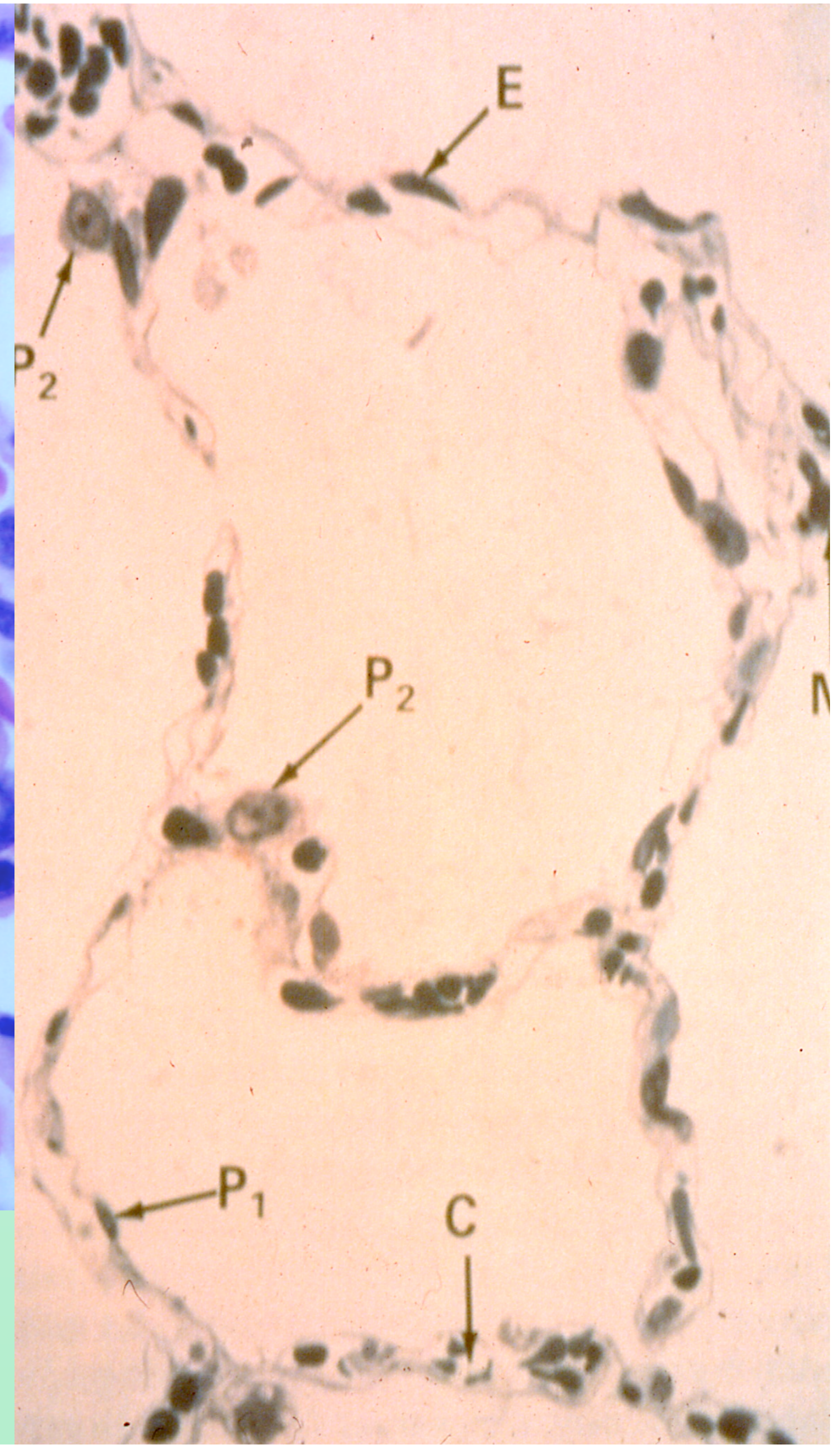
Respiratory Portion

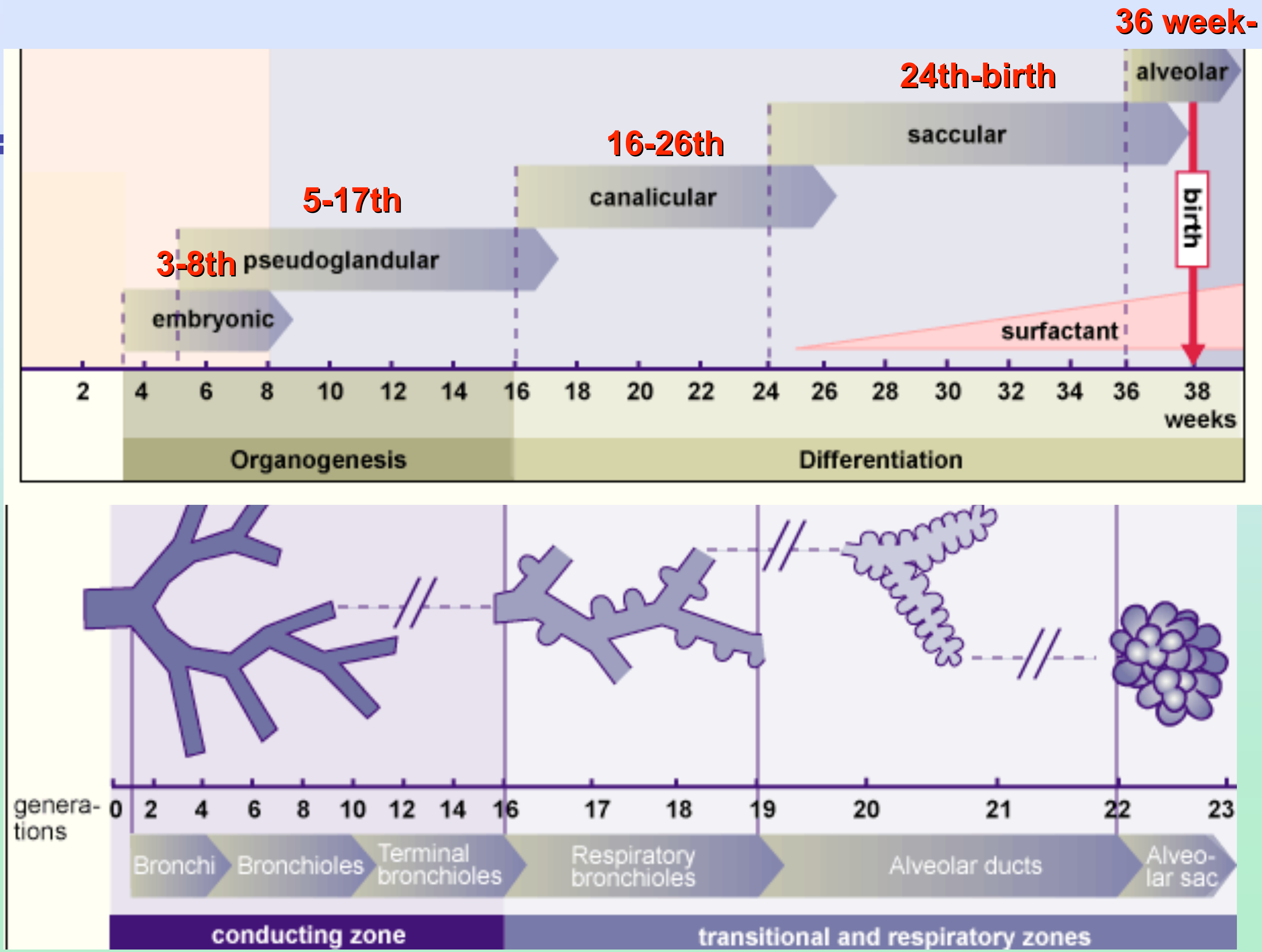
- Respiratory bronchioles-lead to alveolar component
- Alveolar Ducts-proportion of interspersed alveoli increases such that they occupy the majority of the airway surface
- Alveolar Sacs-end of alveolar ducts (cluster of alveoli)
- Alveolus-Unit of gas exchange



1. Ciliated Epithelium
2. Goblet Cell
3. Gland
4. Cartilage
5. Smooth Muscle Cell
6. Clara Cell
7. Capillary
8. Basal Membrane
9. Surfactant
10. Type I pneumocyte
11. Alveolar Septum
12. Type II pneumocyte




E
P2
P2
P1
C



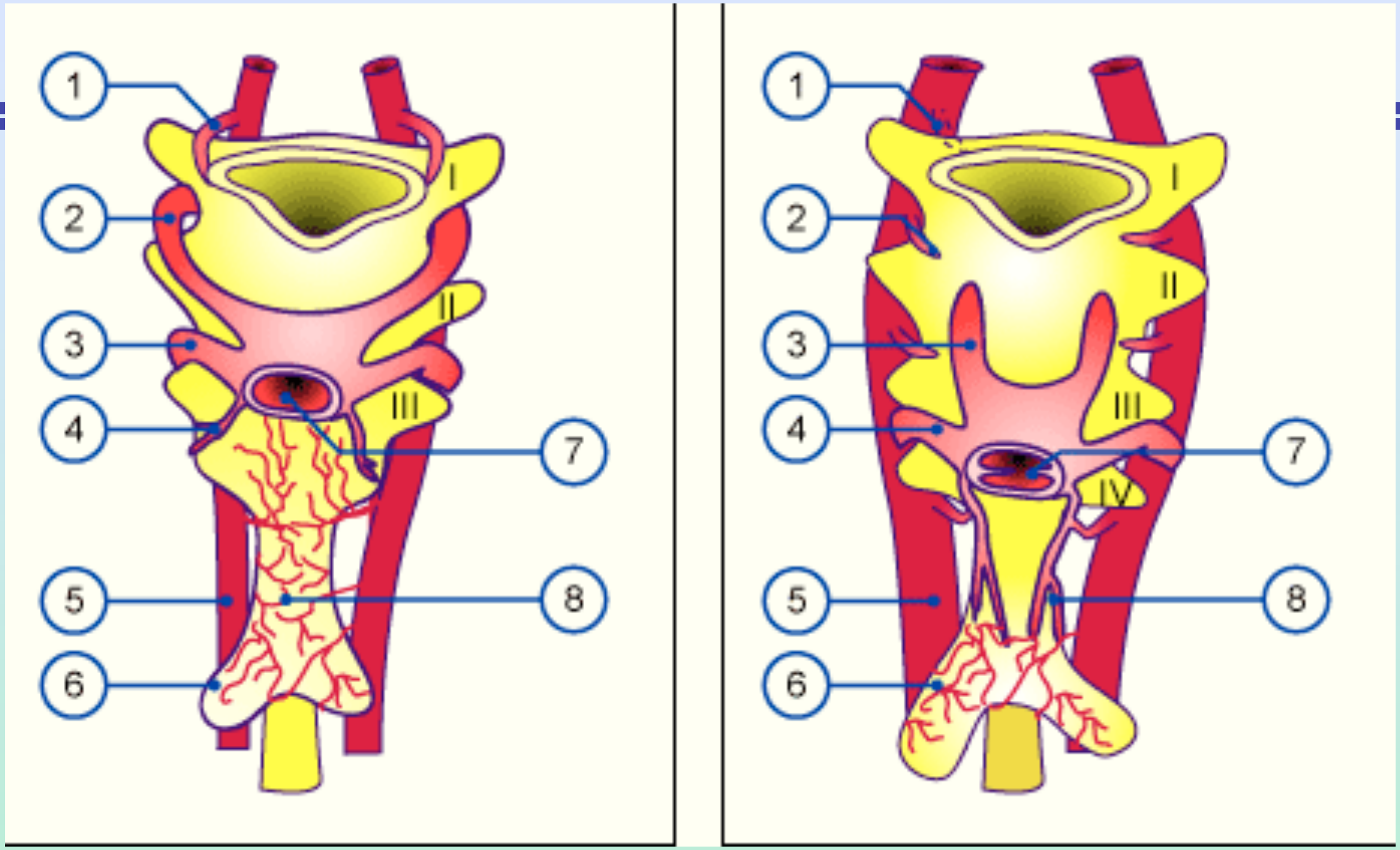
36 week-
24th-birth
16-26th
5-17th
3-8th
alveolar
saccular
canalicular
pseudoglandular
embryonic
birth
surfactant
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
weeks
Organogenesis
Differentiation
genera-
tions
0 2 4 6 8 10 12 14 16 17 18 19 20 21 22 23
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveo-
lar sac
conducting zone
transitional and respiratory zones

Embryonic Phase

3-7 Weeks

Initial budding and branching of lung buds from primitive foregut

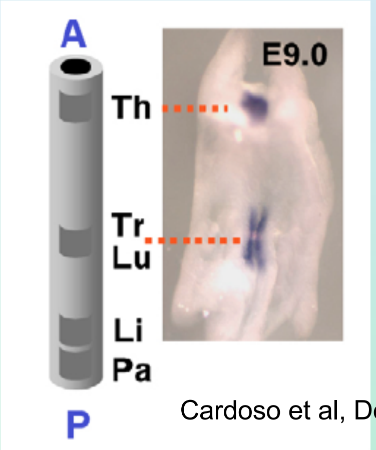
Pulmonary Circulation



1. First aortic arch
2. Second aortic arch
3. Third aortic arch
4. Fourth aortic arch
5. Dorsal Aorta
6. Lung buds
7. Aortic Sac
8. Pulmonary Plexus

Laryngeal development

- Week 4
  - Respiratory primordium arises from distal/caudal pharynx
    - Laryngo-tracheal groove



Cardoso et al, Dev. 133:(2006)

    - Proximal portion gives rise to larynx and trachea, distal portion gives rise to left and right mainstem bronchial buds.
    - Connective tissue, smooth muscle and cartilage from splanchnic mesenchyme surrounding the foregut

Laryngeal development

- LT groove evaginates and forms LT diverticulum
- This becomes invested with splanchnic mesoderm to form lung bud
- This maintains a laryngeal inlet

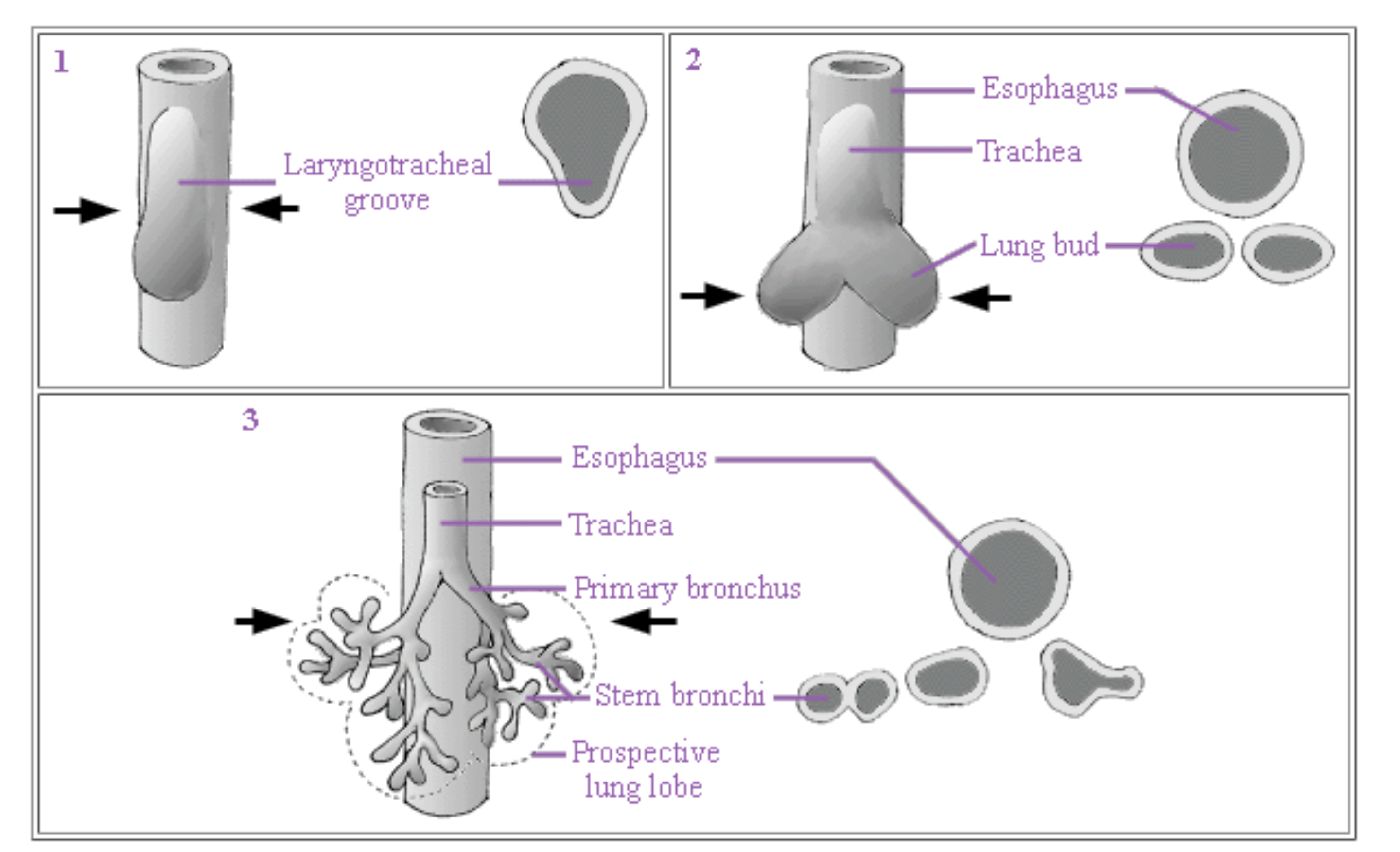
The septum that forms by folds and fusion keeps a septate inlet that becomes trachea and esophagus

Epithelium of the larynx

- Endoderm of proximal/cranial end of LT tube and cartilage from neural crest origin
- Formation of proximal larynx – cranial tube
  - Arytenoid swellings grow towards tongue
  - Airway gets closed off, eventually recanalizes
- Laryngeal webs – Incomplete recanalization
- Laryngeal atresia – ascites, hydrops and lungs do not properly form.

Trachea

- Endoderm of distal LT tube
  - Epithelium of trachea and lung
- Splanchnic mesenchyme
  - Connective tissue
- 4th week
  - If esopahgeal separation from LT tube is incomplete, develops into TE fistula



This page shows ventral views of the esophagus and developing lungs, accompanied by cross-sectional views through the area between the black arrows. Note how the lung starts as an evagination, from the esophogeal endoderm, called the larygotracheal groove (1). As the the larygotracheal groove grows, it develops two outcroppings at its caudal end, the lung buds (2). As the lung buds grow, they branch repeatedly forming the primary bronchi and stem bronchi (3) which branch further to form bronchioles, which will eventually develop terminal air sacs (alveoli) to complete the adult lung. Also, note how the trachea, once attached as a ventral groove on the esophagus, has separated to become a distinct tube (3).

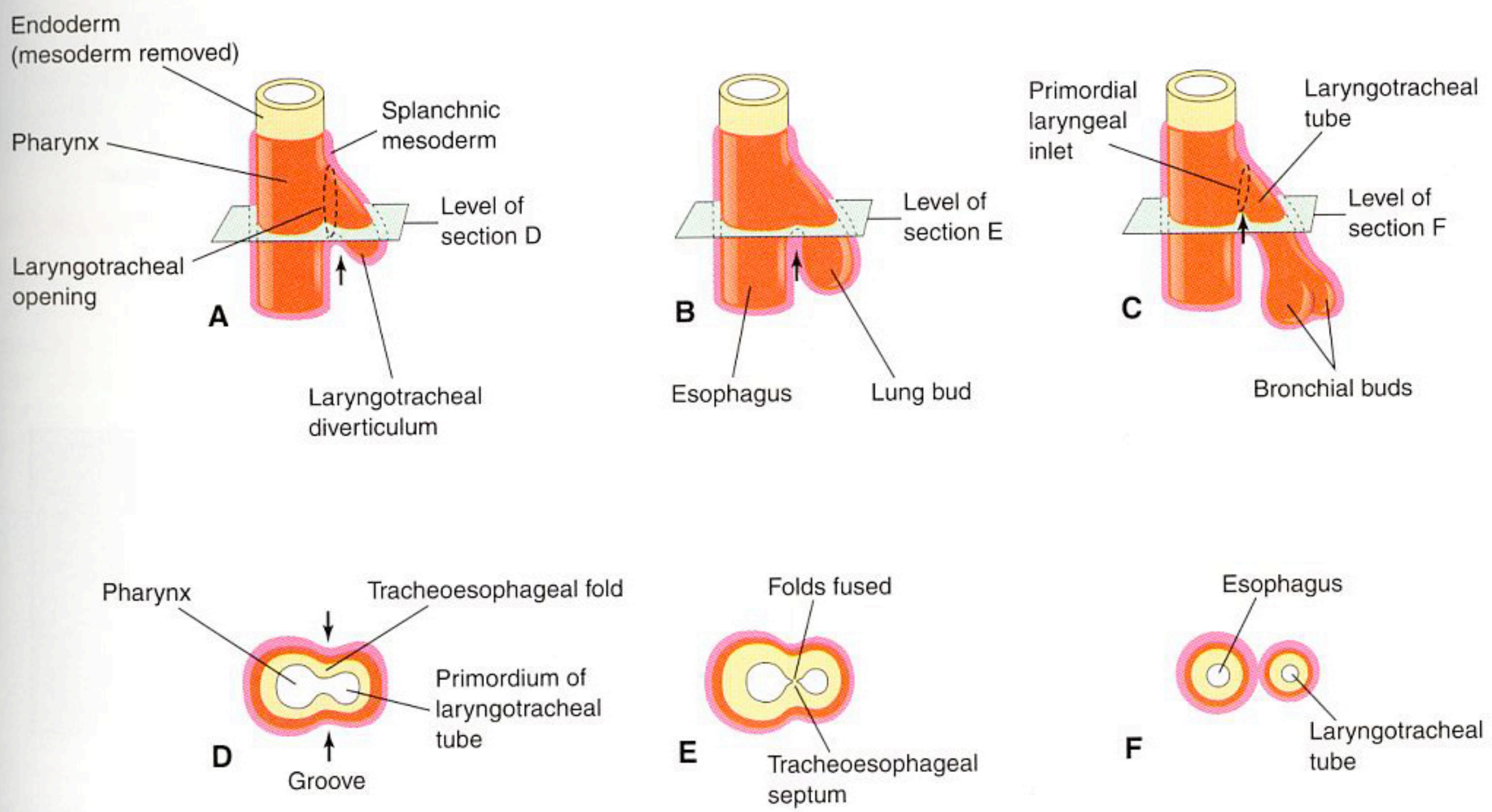
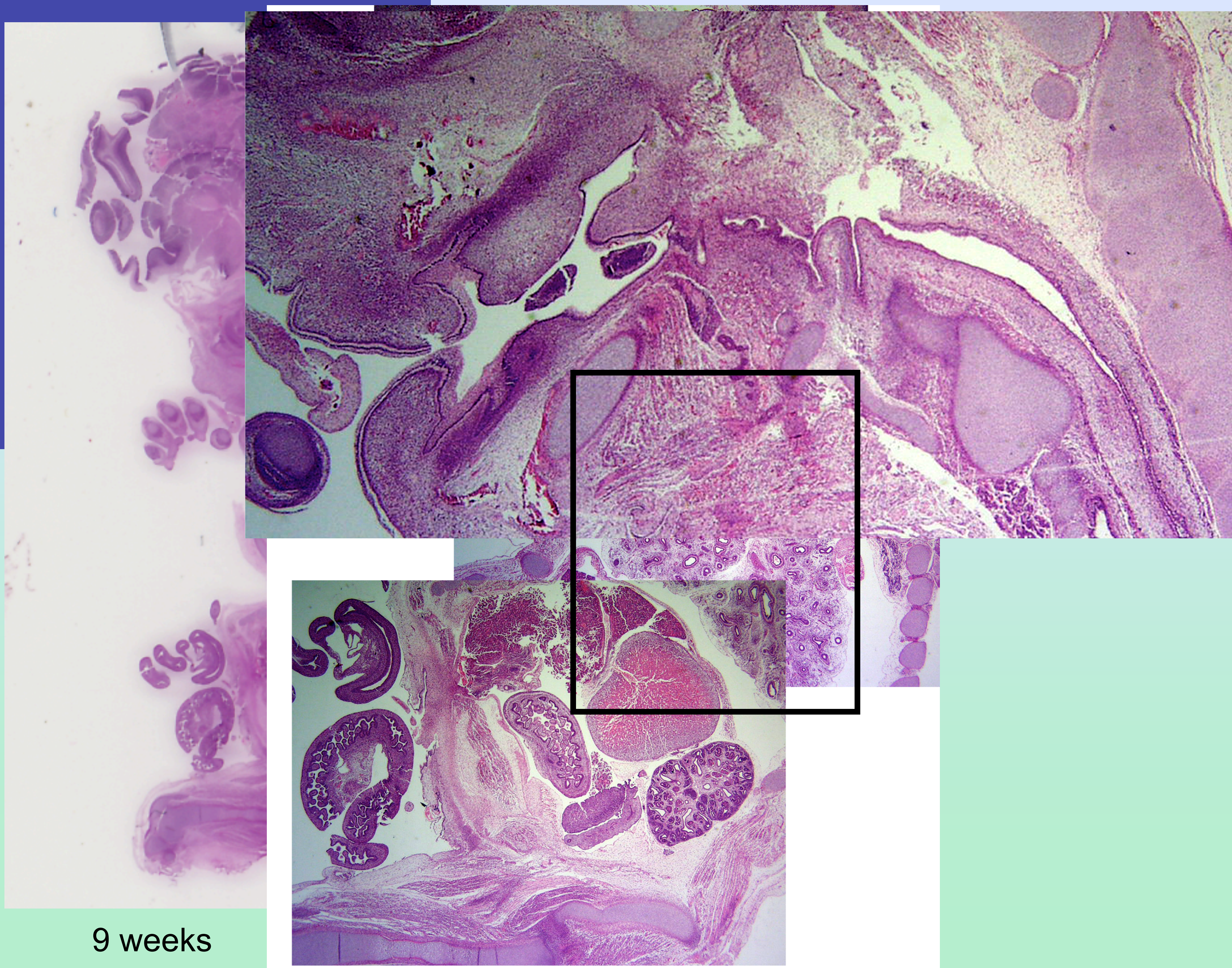


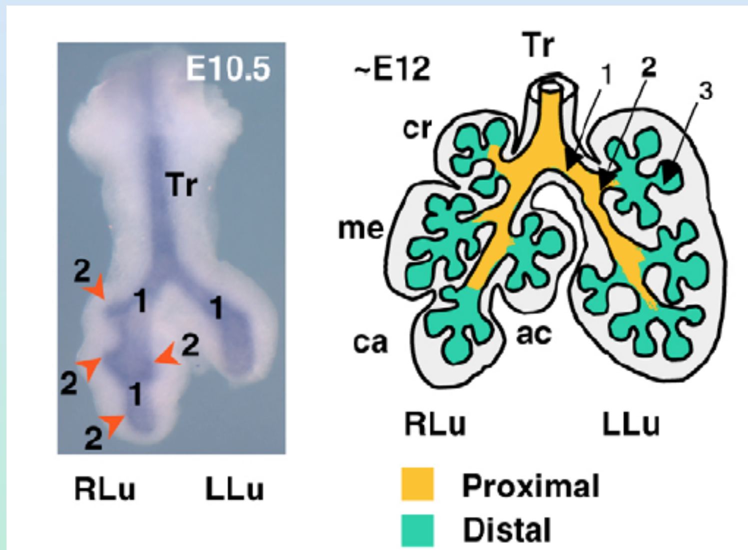
Figure 11–2. Drawings illustrating successive stages in the development of the tracheoesophageal septum during the fourth and fifth weeks. *A, B,* and *C,* Lateral views of the caudal part of the primordial pharynx showing the laryngotracheal diverticulum and partitioning of the foregut into the esophagus and laryngotracheal tube. *D, E,* and *F,* Transverse sections illustrating formation of the tracheoesophageal septum and showing how it separates the foregut into the laryngotracheal tube and esophagus.



9 weeks

Bronchi/lungs

– Secondary Bud Formation

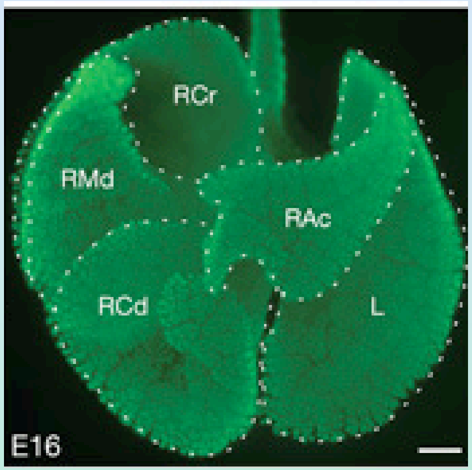


Cardoso et al, Dev. 133:(2006)

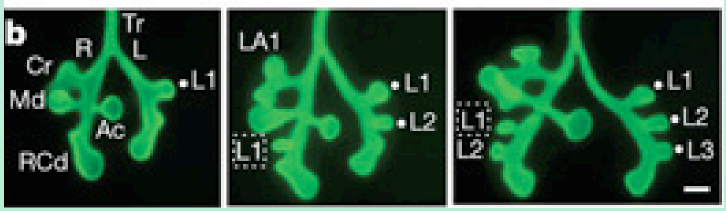
– By 28 days – endodermal buds grow along with splanchnic mesenchyme
– By 35 days – Second degree bronchi, upper middle and lower on right, upper and lower on left
– By 42 days – Tertiary bronchopulmonary segments, 10 on the right and 8-9 on the left.

The branching programme of mouse lung development

- Bronchial tree of human lung consists of more than 10^5 conducting and 10^7 respiratory airways generating an excellent system for oxygen flow.



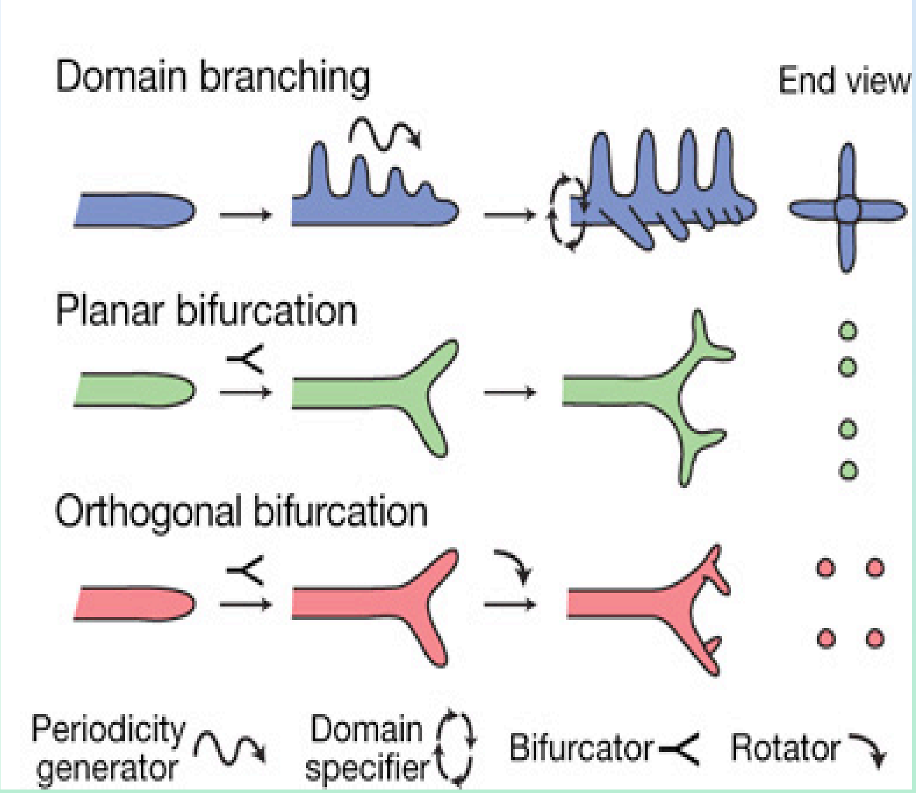
- There are three geometrically distinct branching modes used repeatedly throughout the lung.



(Krasnow et al., Nature 2008)

Three branching modes

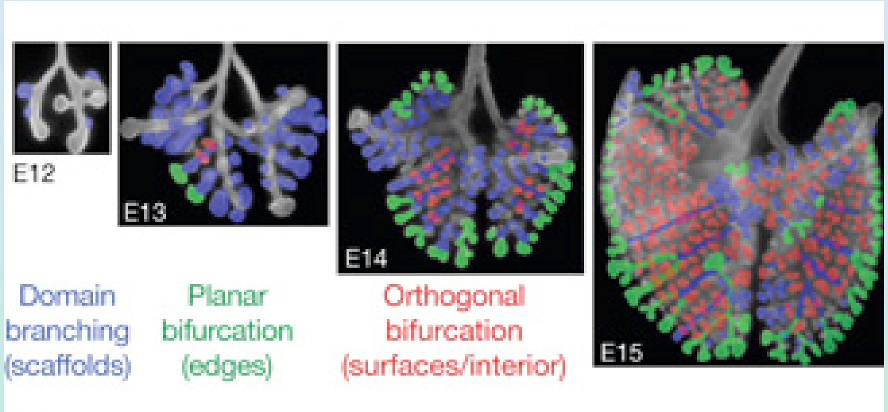
- **Domain branching** daughter branches form in rows at different positions around the circumference of the parent branch
- **Planar bifurcation** the tips of branches expand and bifurcate in the same plane
- **Orthogonal bifurcation** branches bifurcate at their tips and between each round of branching there is a 90^0 rotation in the bifurcation plane



(Krasnow et al., Nature 2008)

Deployment of branching modes

- **Domain branching** generates central scaffold of each lobe, setting its overall shape
- **Planar bifurcation** forms the edges of lobes
- **Orthogonal bifurcation** creates lobe surfaces and fills the interior



(Krasnow et al., Nature 2008)

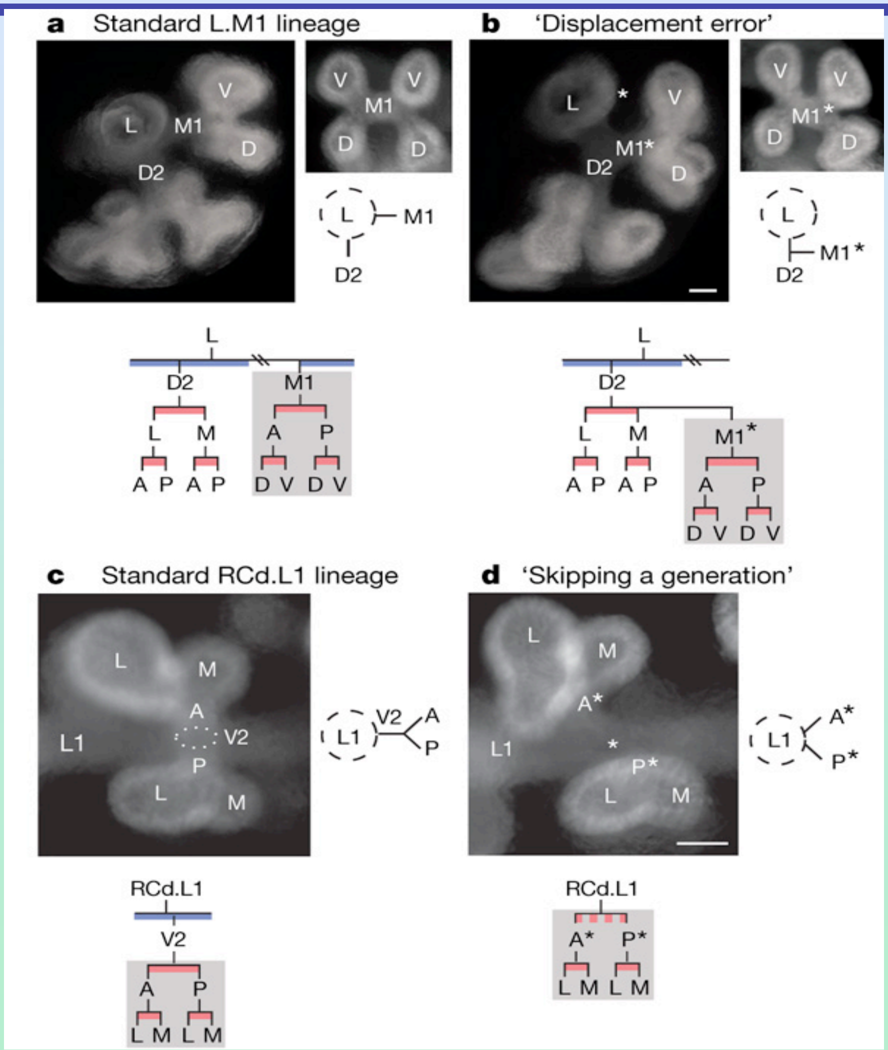
Branching 'errors'

- **Branch displacement**

  branch originates off the wrong parent branch

- **Skipping a generation**

  branch is missing and daughter branches spring directly from the grandparent



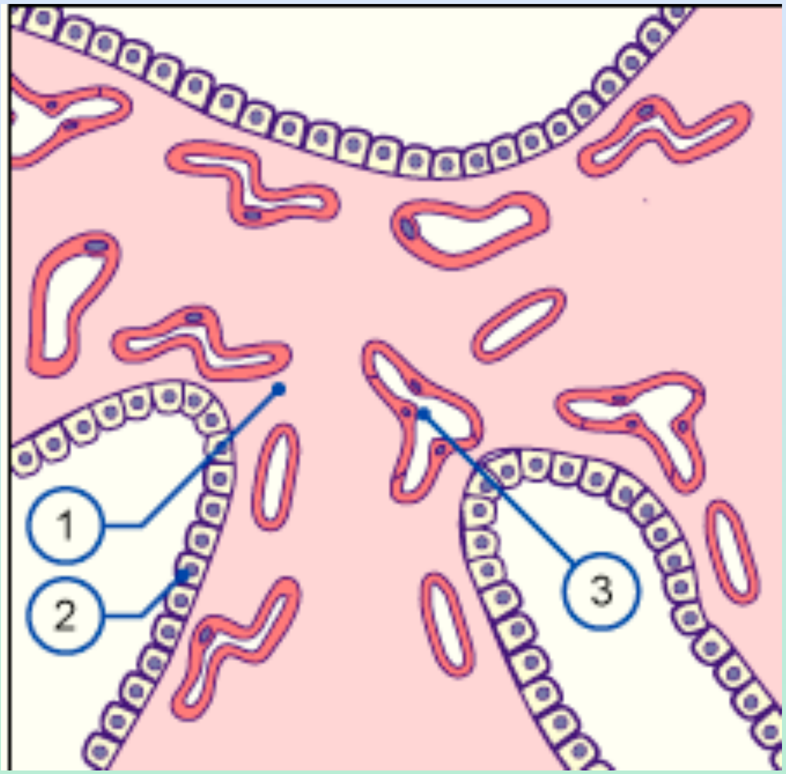
(Krasnow et al., Nature 2008)

Pseudoglandular

5-17 Weeks

Formation of bronchial tree up to a preacinar level

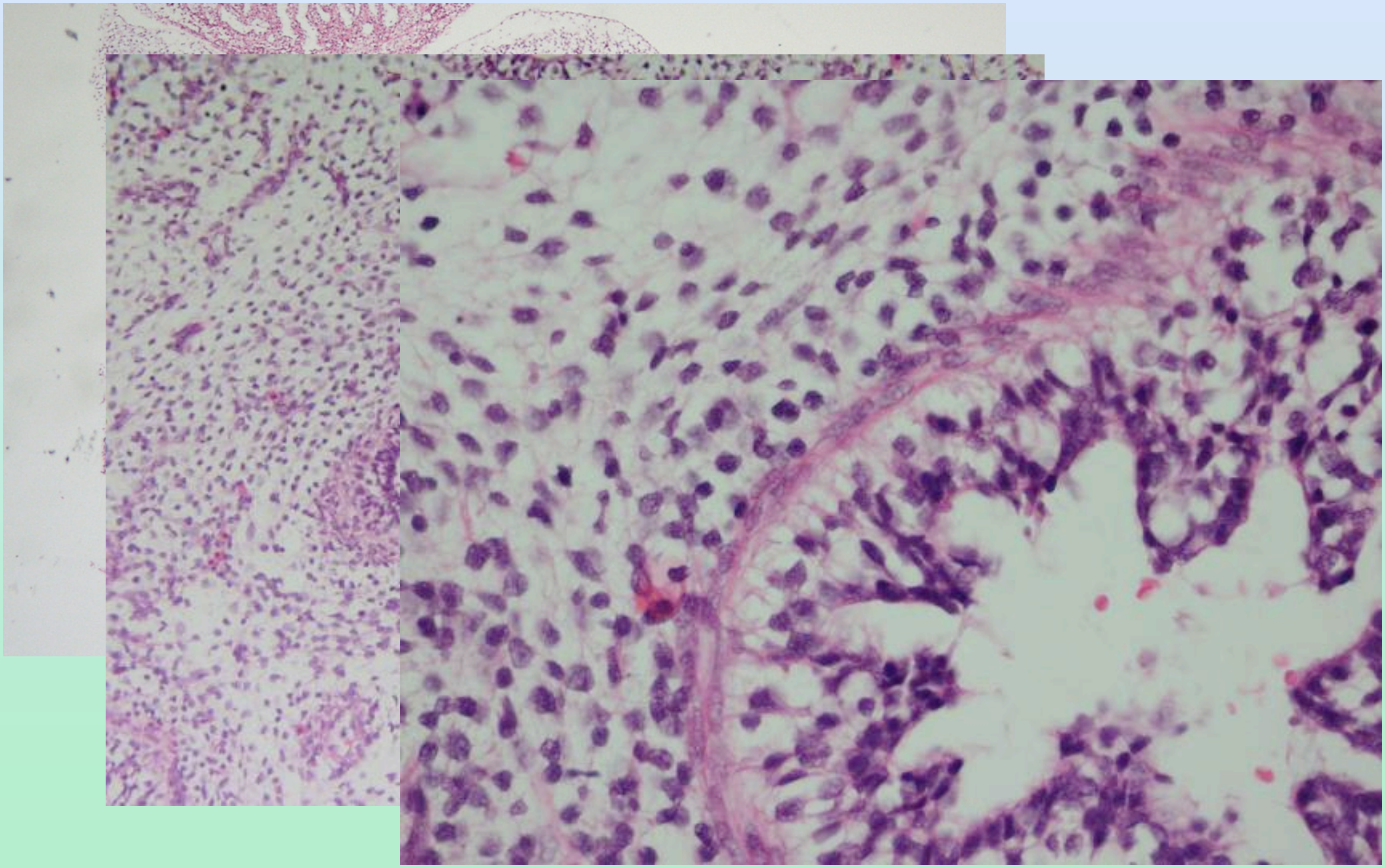
Pseudoglandular



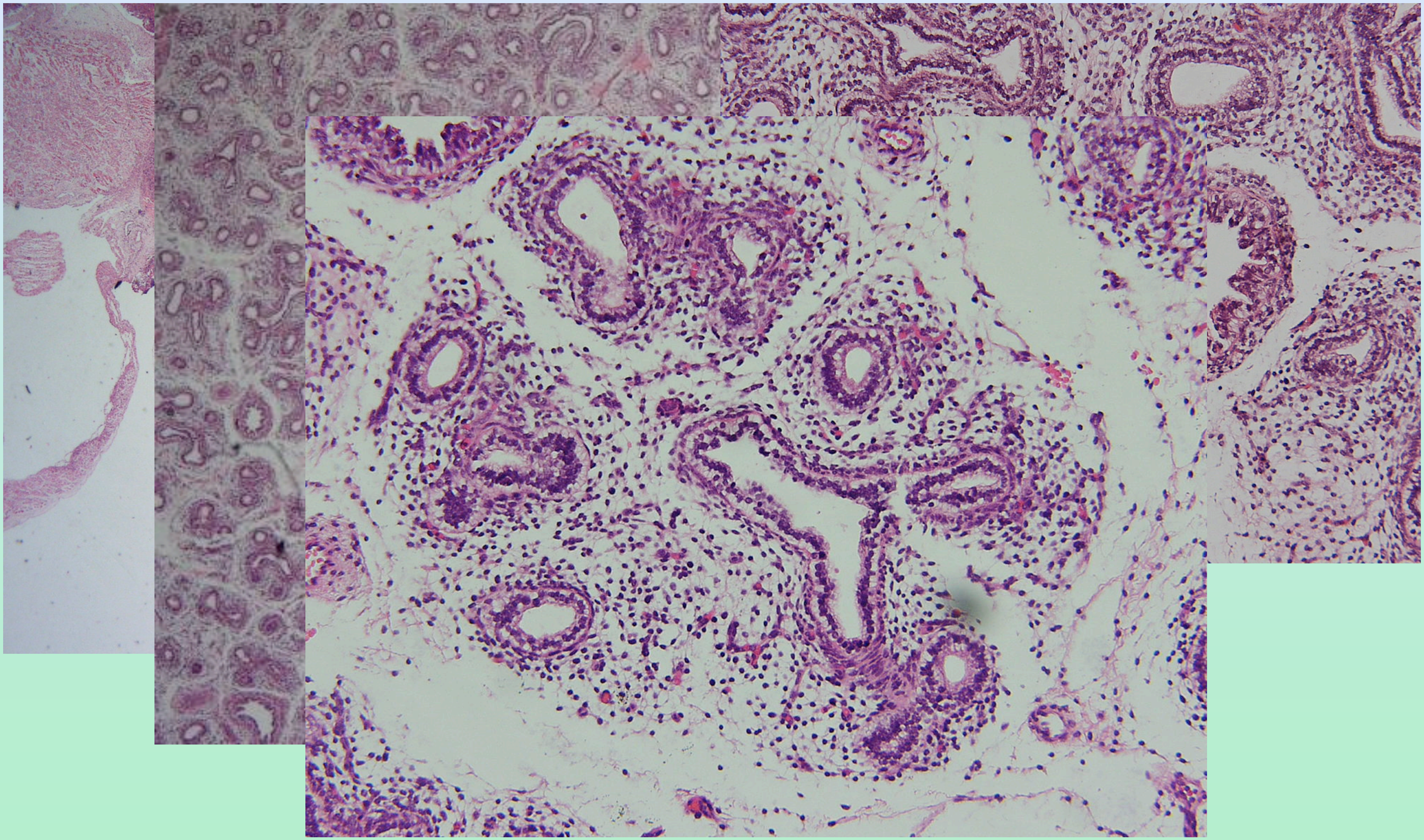
In the pseudoglandular phase the lungs resemble a gland. At the end of this phase the precursors of the pneumocytes can be discerned in the respiratory sections as cubic epithelium

1. Lung mesenchyme
2. Type II pneumocytes
3. Capillaries

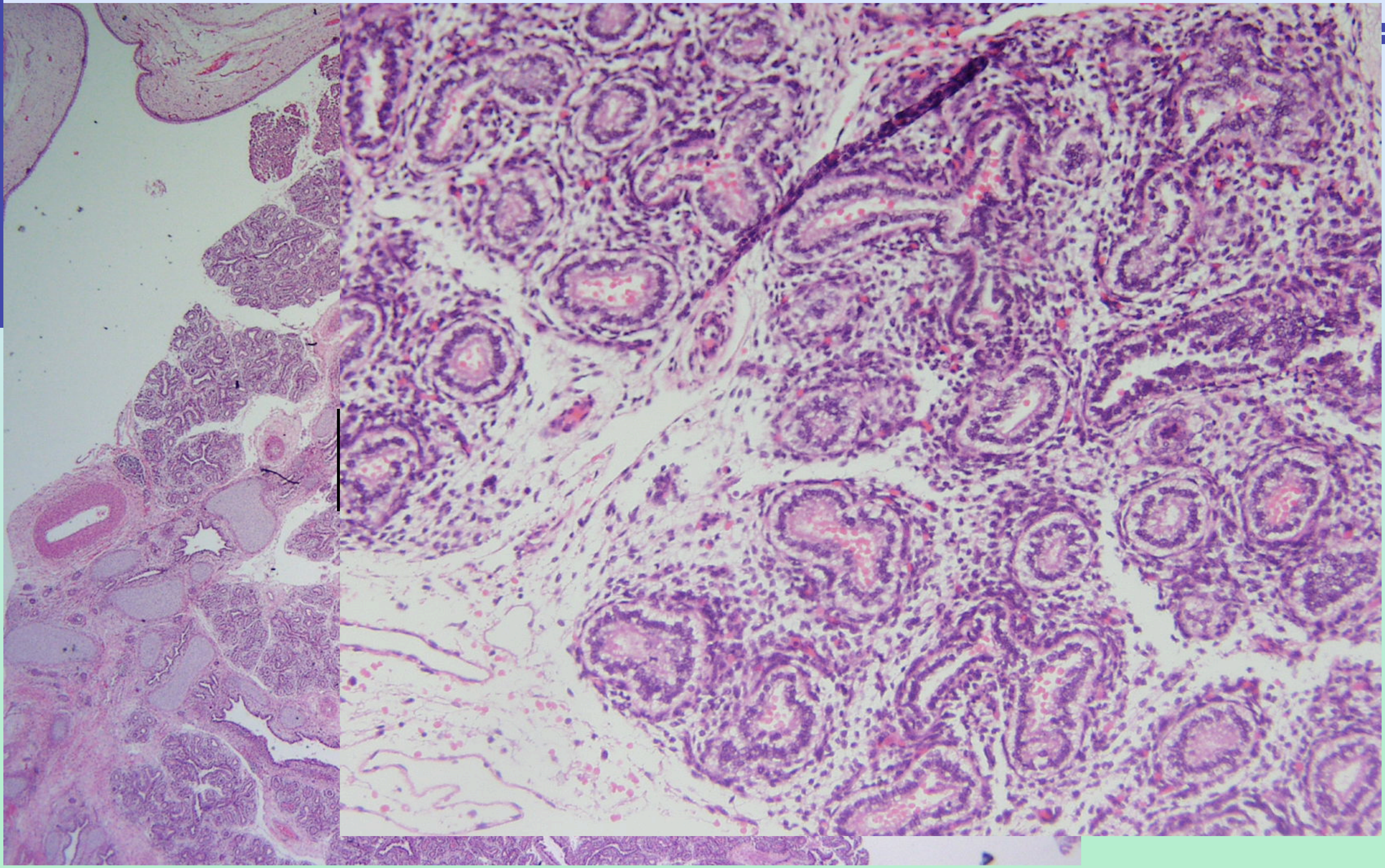
Early pseudoglandular 8 wk



Mid Pseudoglandular 13 wk



Late pseudoglandular-16 weeks

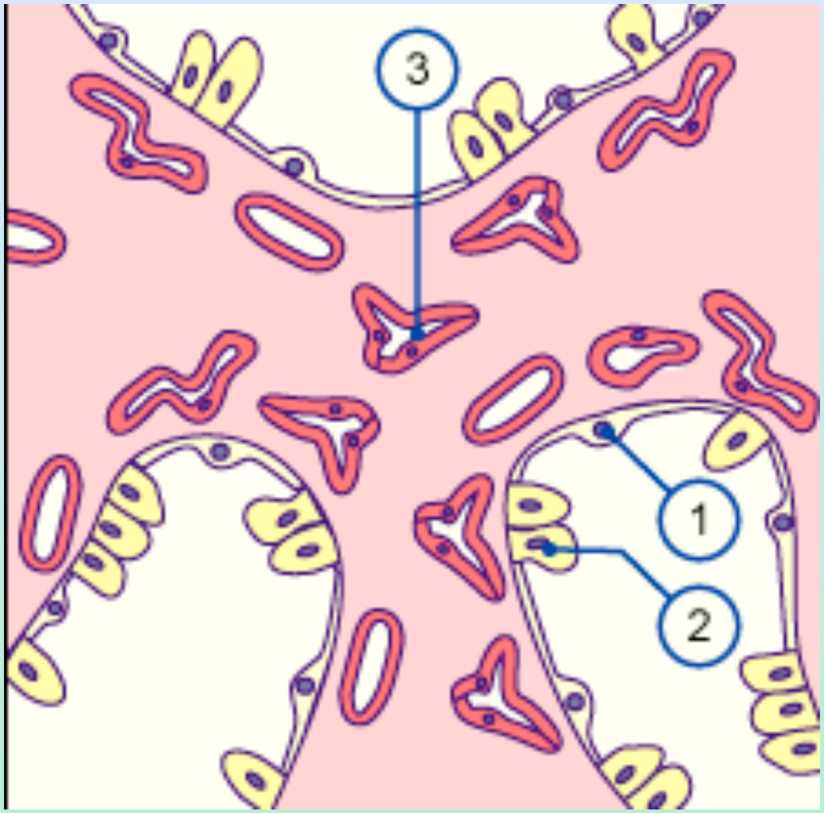


Canalicular

16-26 weeks

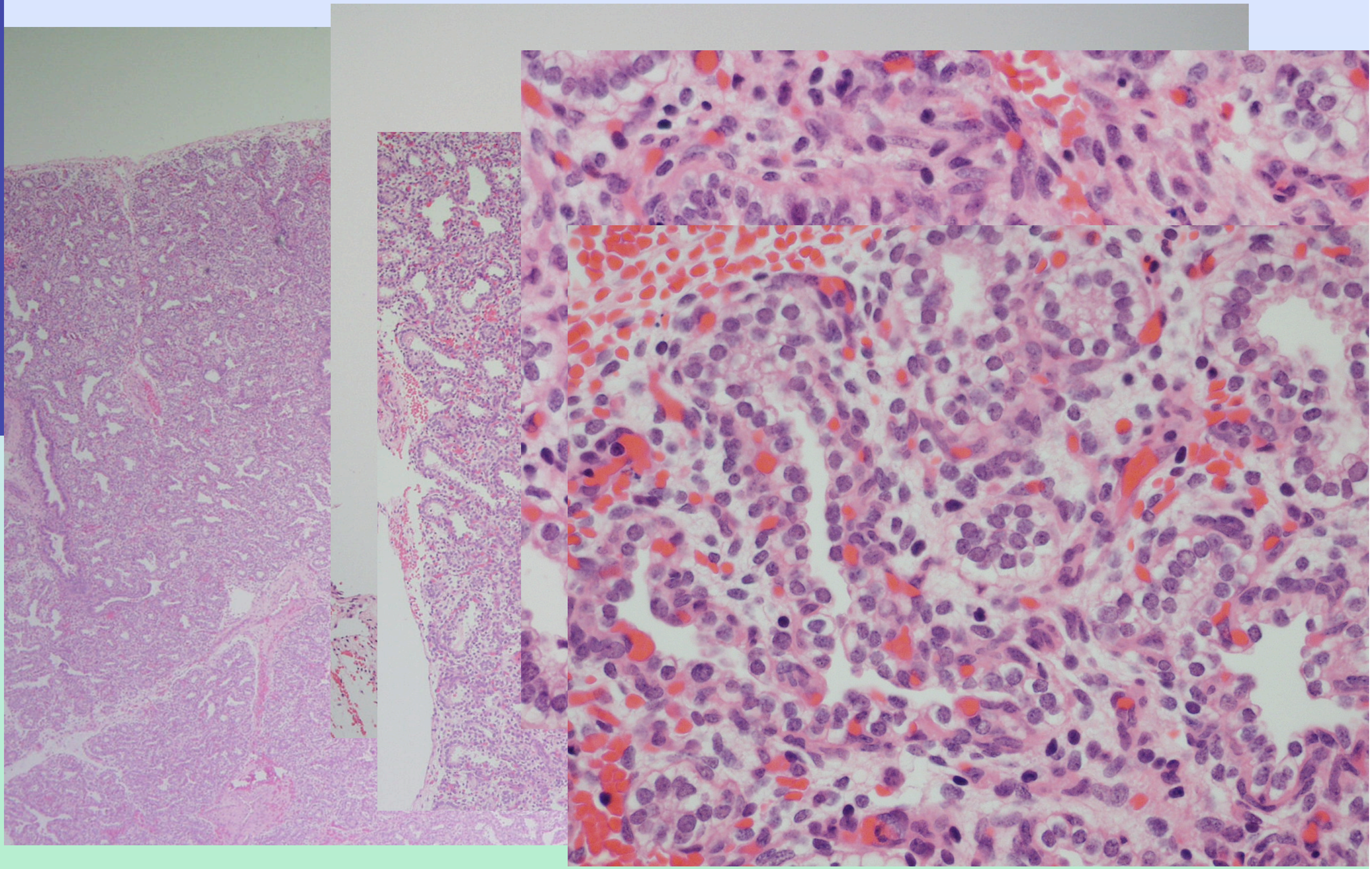
Formation of the pulmonary acinus and of the future air-blood barrier, increased capillary bed, epithelial differentiation and first appearance of surfactant

Canalicular



1. Type I pneumocytes
2. Type II pneumocytes
3. Capillaries

In the canalicular phase the type I pneumocytes differentiate out of the type II pneumocytes.
The capillaries approach the walls of the acini.
Large amount of amnionic fluid is produced by lung epithelium

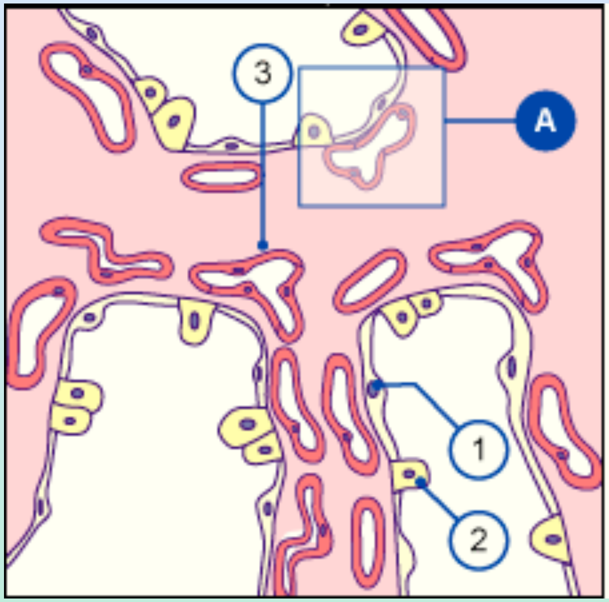


Mid-canalicular - 22 weeks

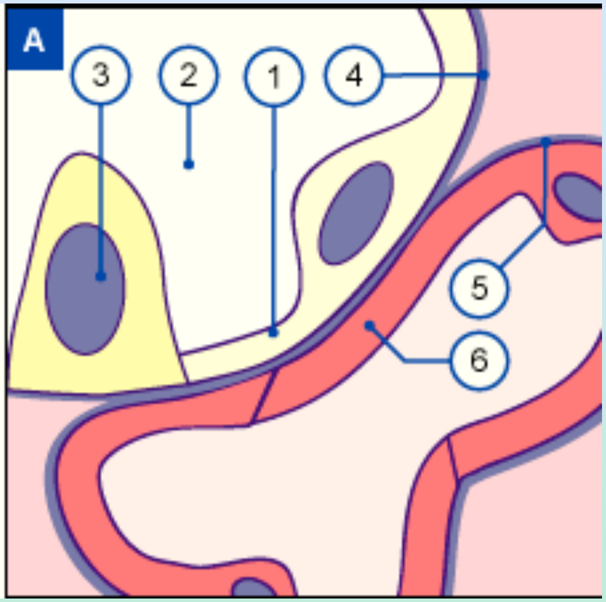
Saccular

24-38 weeks

Formation of transitory air spaces



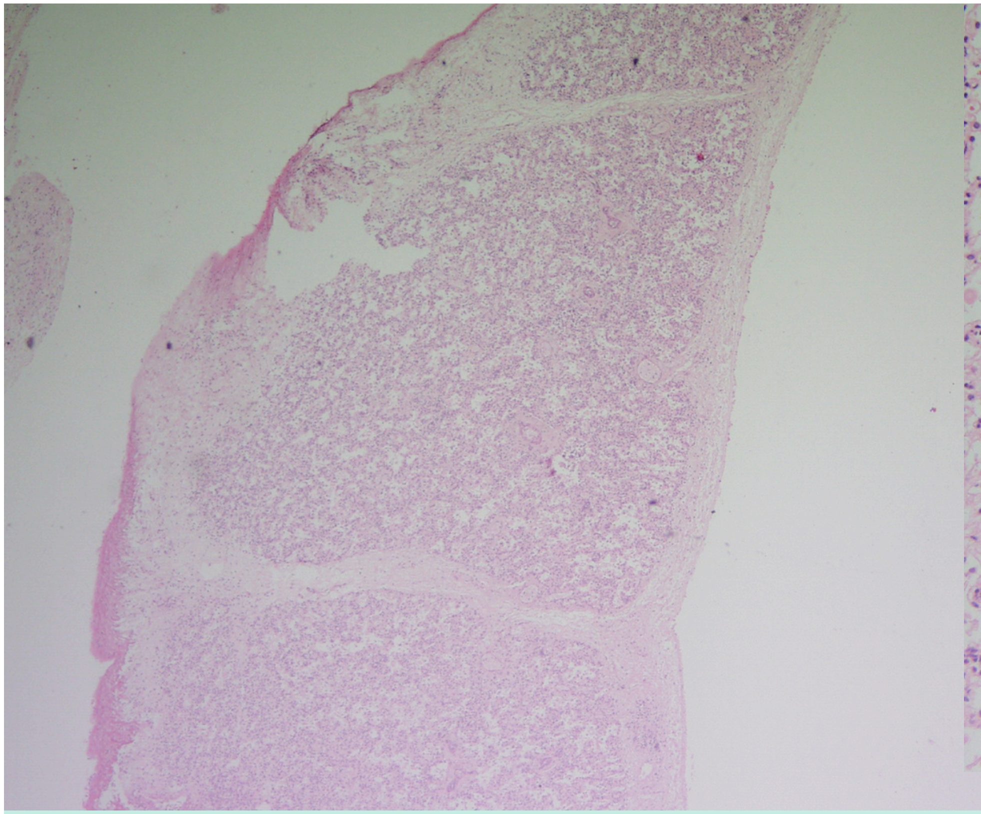
1. Type I pneumocyte
2. Type II pneumocyte
3. Capillaries

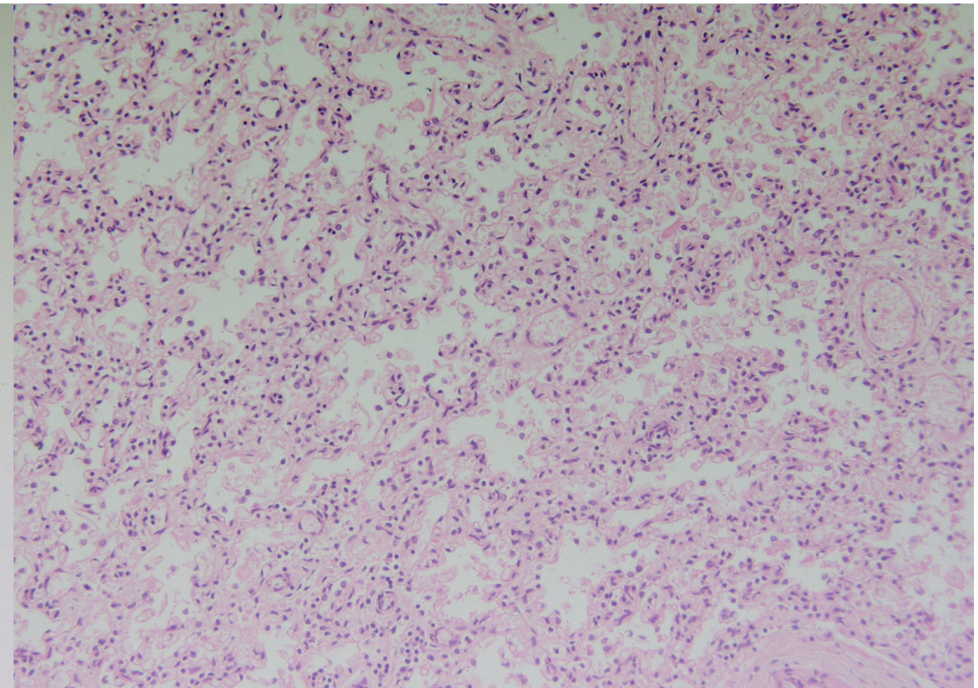


1. Type I pneumocyte
2. Saccular space
3. Type II pneumocyte
4. Basal membrane of the air passage
5. Basal membrane of the capillaries
6. Endothelium of the capillaries

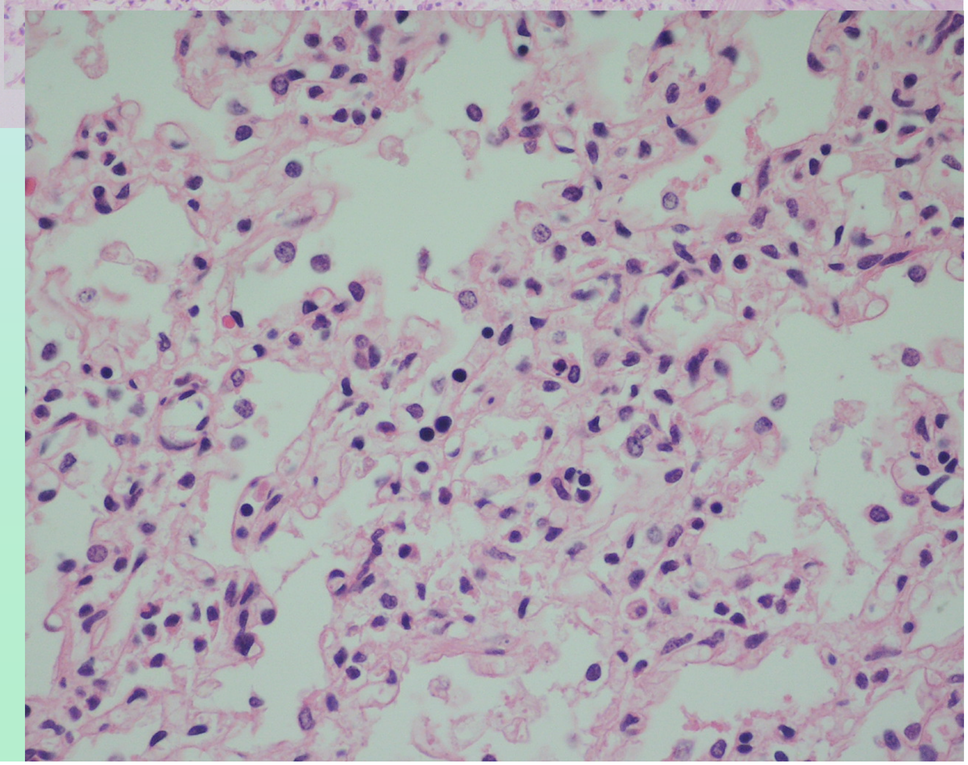
The capillaries multiply around the acini and push close to the surface and form a common basal membrane with that of the epithelium

The blood-air barrier in the lungs is reduced to three, thin layers: type I pneumocyte, fusioned basal membrane, and endothelium of the capillary





SACCULAR 31 weeks

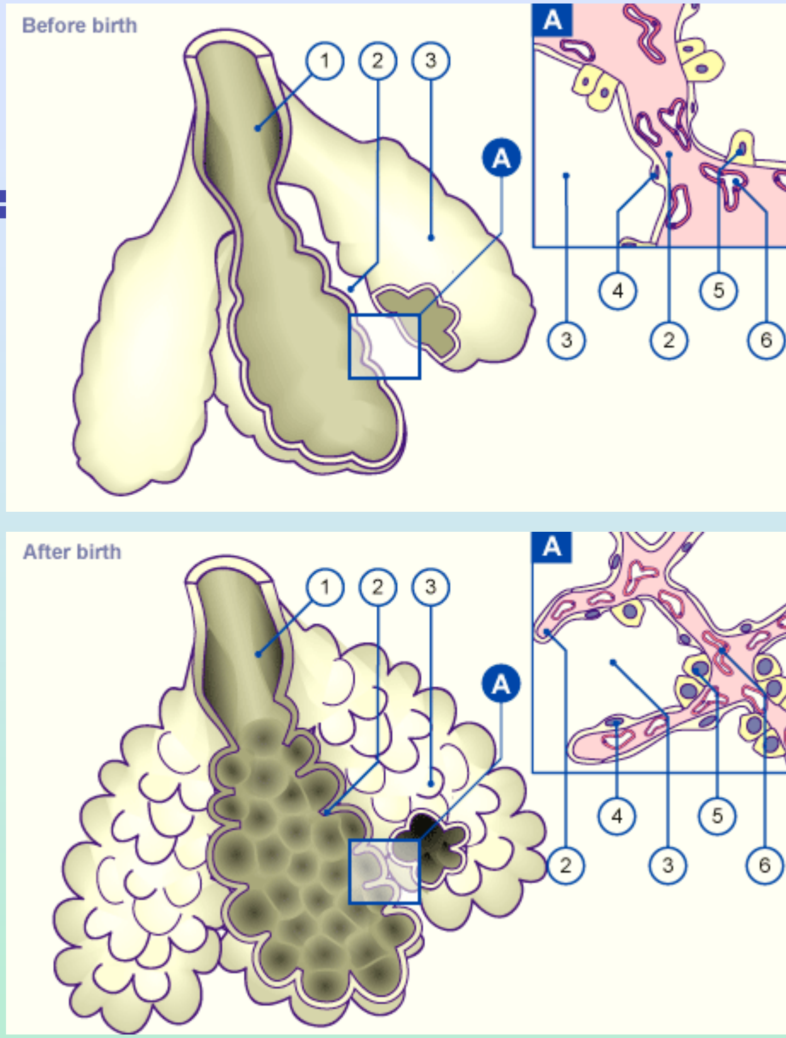


Alveolar

36 weeks to 2 years postnatal

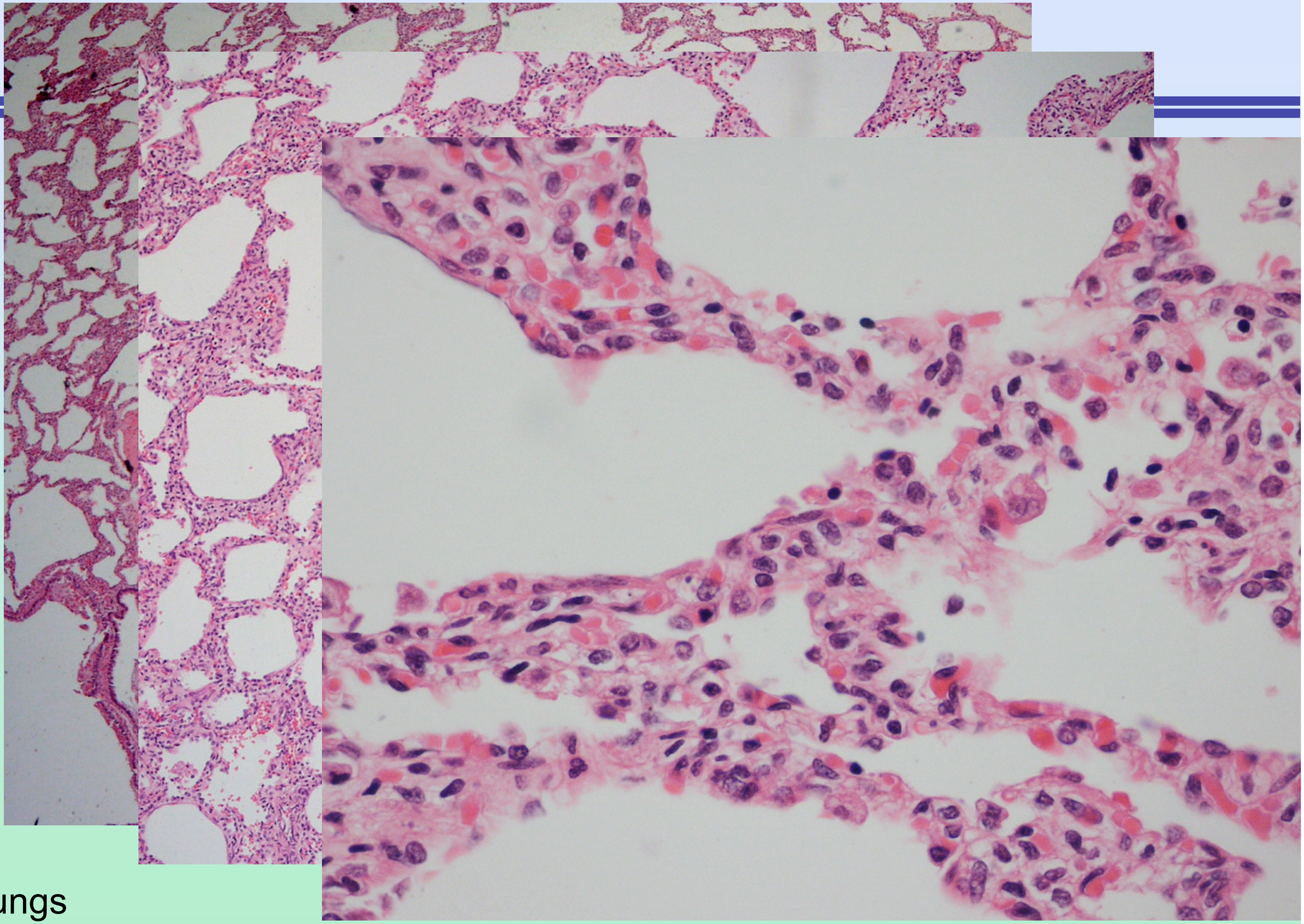
Alveolarization by forming of secondary septa

Alveolar

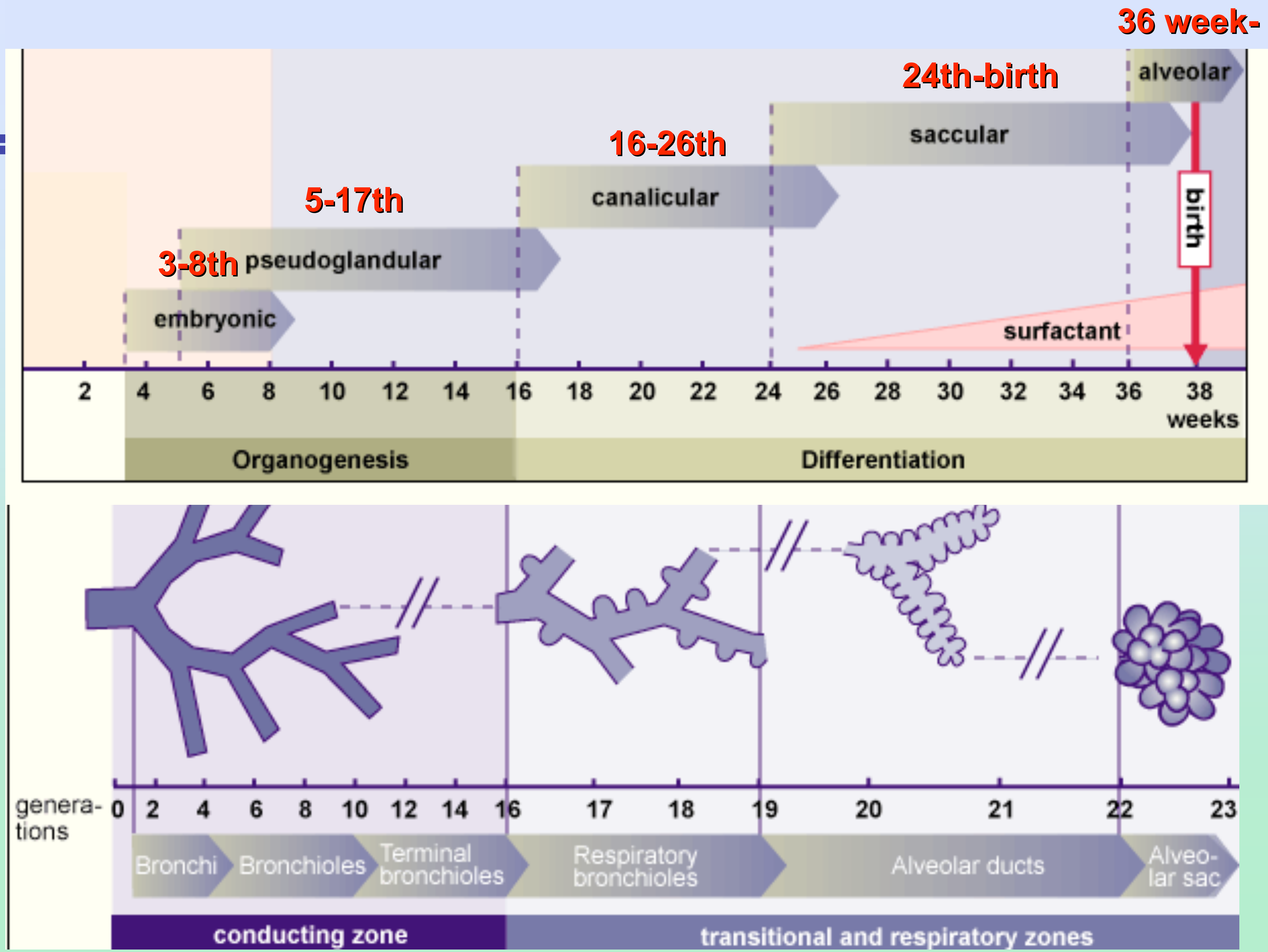


1. Alveolar duct
2. Primary septum
3. Alveolar sac
4. Type I pneumocyte
5. Type II pneumocyte
6. Capillaries

The alveoli form from the terminal endings of the alveolar sacculi and with time increase their diameter. After birth more and more alveoli form from the terminal endings of the alveolar and increase in diameter. They are delimited by secondary septa.



Term lungs


36 week-
24th-birth
16-26th
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weeks
Organogenesis
Differentiation
generations
0 2 4 6 8 10 12 14 16 17 18 19 20 21 22 23
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sac
conducting zone
transitional and respiratory zones

Molecular Determinants of Lung Development

- Production of laryngotracheal groove correlates with the appearance of retinoic acid in the ventral mesoderm. If RA is blocked, foregut will not produce the lung bud (Desai, 2004).
- Regional specificity of the mesenchyme determines differentiation of the developing respiratory tube (Wessels, 1970)
  - Neck-grows straight forming trachea
  - Thorax-branches
- Retinoic acid induces formation of Fgf10 by activating Tbx4 in the splanchnic mesoderm adjacent to the ventral foregut (Sakiyama, 2003).

Lung hypoplasia – diminished lung development

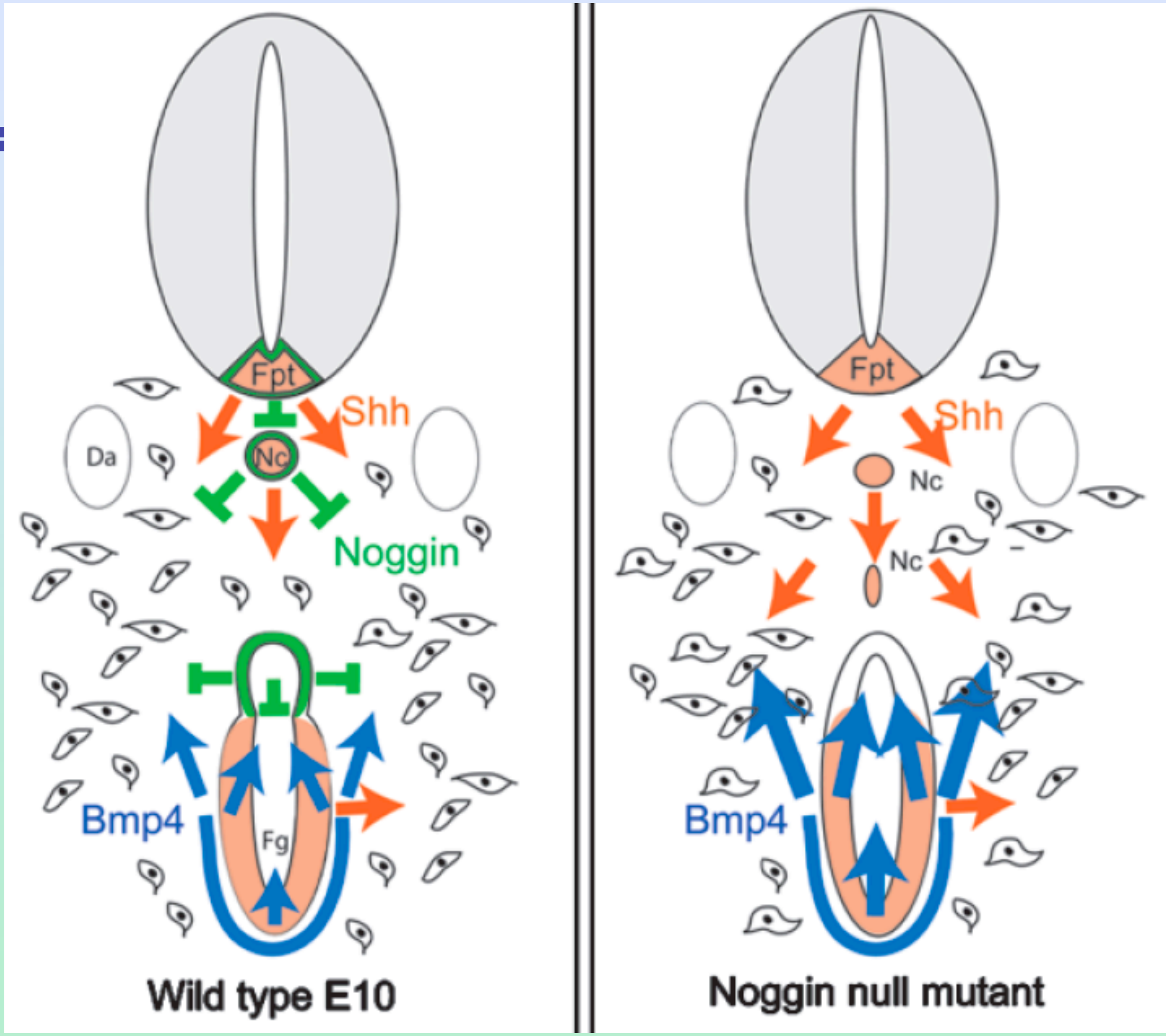
- Oligohydramnios – insufficient amniotic fluid
- Compression
  - Congenital diaphragmatic hernia – intestinal contents compress left hemithorax (usually)
  - Intrathoracic fluid or thoracic wall abnormality

Branching morphogenesis

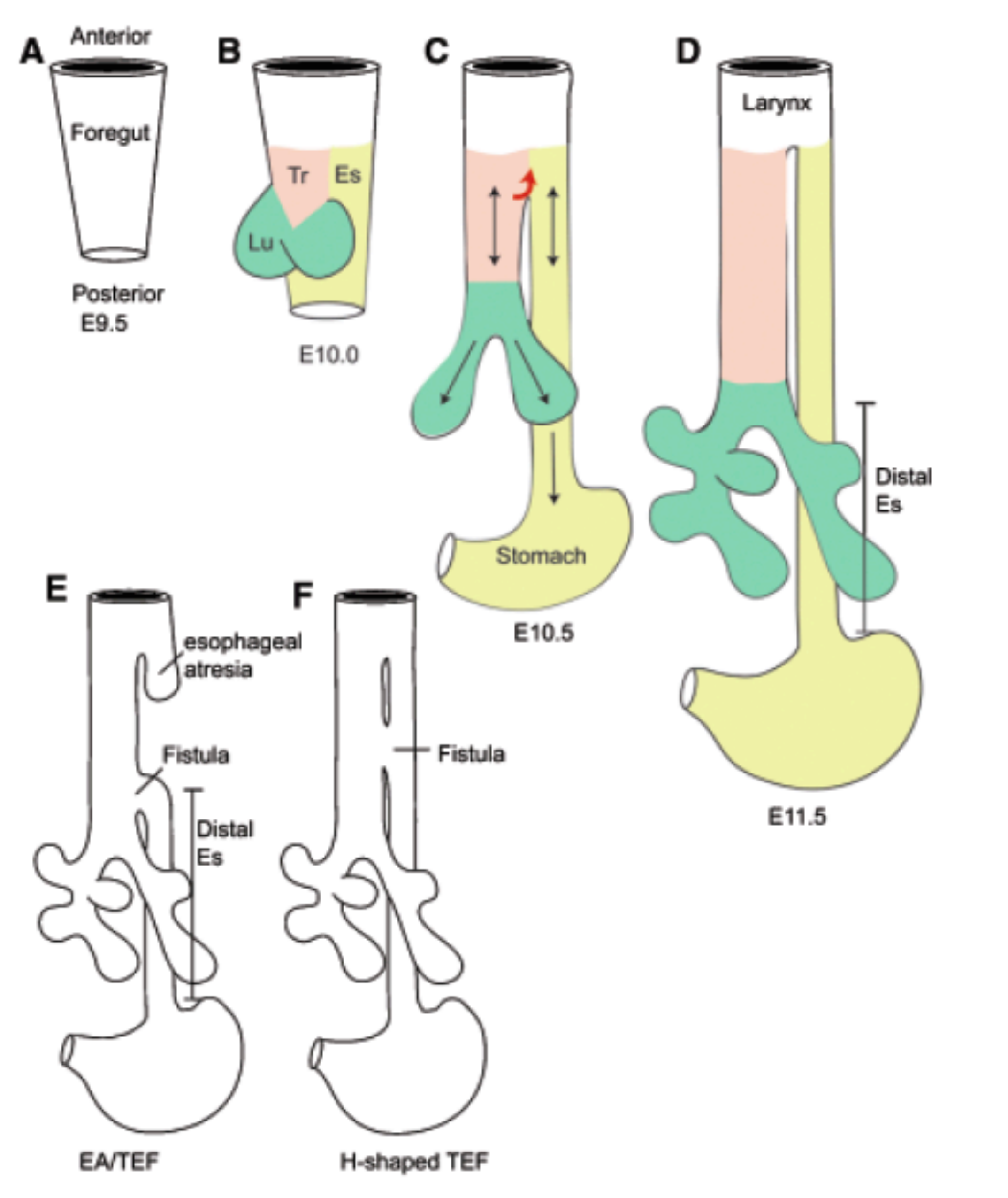
- By 24 weeks, 17 orders of bronchi and respiratory bronchioles (7 more after birth)
- Lungs grow to pleura – visceral pleura from splanchnic mesenchyme and parietal pleura from somatic mesoderm.

Defect in Embryonic Phase

- Shh null embryos delay lung bud emergence and no separation of a trachea and esophagus (Littingtung, 1998).
- Nkx2.1 null mice develop severe defects in separation of trachea and esophagus (Minoo, 1999).
- RAR a1-/-/b2-/- mutant embryos fail to separate. Nkx2.1 is regulated by RA signaling (Mendelsohn, 1994)
- Disruption of Bmp4-noggin antagonism (Que, et al, 2006)



(Que, et al, Differentiation 2006)


A
Anterior
Foregut
Posterior
E9.5
B
Tr
Es
Lu
E10.0
C
Stomach
E10.5
D
Larynx
Distal
Es
E11.5
E
esophageal
atresia
Fistula
Distal
Es
EA/TEF
F
Fistula
H-shaped TEF

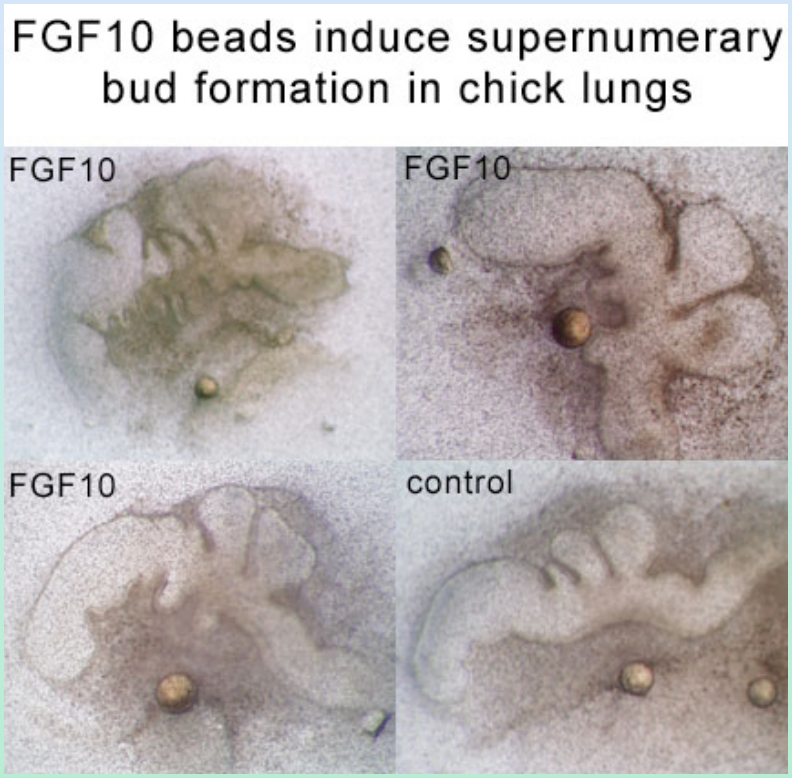
Defects early development

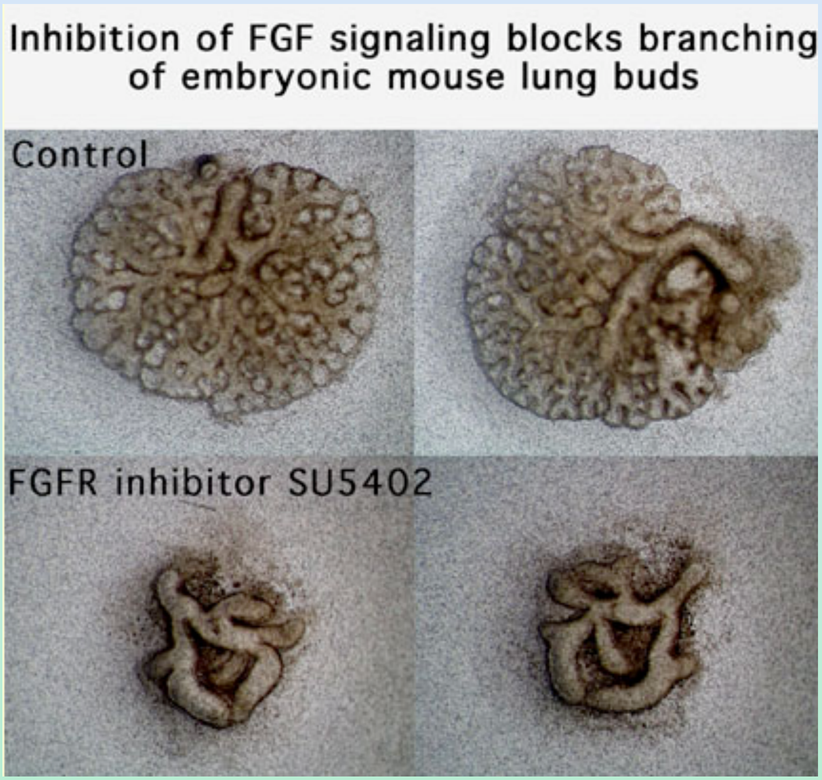
Mouse gene	Molecular function	Foregut phenotypes	References
Foxf1	Forkhead family transcription factor	Hets have narrow esophagus or TEF, abnormal lungs	Mahlapuu et al. (2001)
Gil2 &Gli3	Hedgehog pathway transcription factors	EA/TEF, abnormal lung development	Motoyama et al. (1998)
Nkx2.1	Homeodomain-containing transcription factor	Es and Tr do not separate, abnormal lung development	Minoo et al. (1999)
Noggin	Secreted BMP antogonist	EA/TEF in about 60% of heterozygotes	This work
RAR α & β2	Retinoic Acid Receptors, nuclear hormone receptor superfamily	Failure of foregut separation and abnormal cartilage development in some compound	Mendelsohn et al. (1994)
Shh	Secreted hedgehog family ligand	EA/TEF, abnormal lung development	Litingtung et al. (1998)

FGF Ligands and Receptors Direct Epithelial Migration and Differentiation

- FGF10 promotes directed growth of the lung epithelium and induces both proliferation and chemotaxis of isolated endoderm.

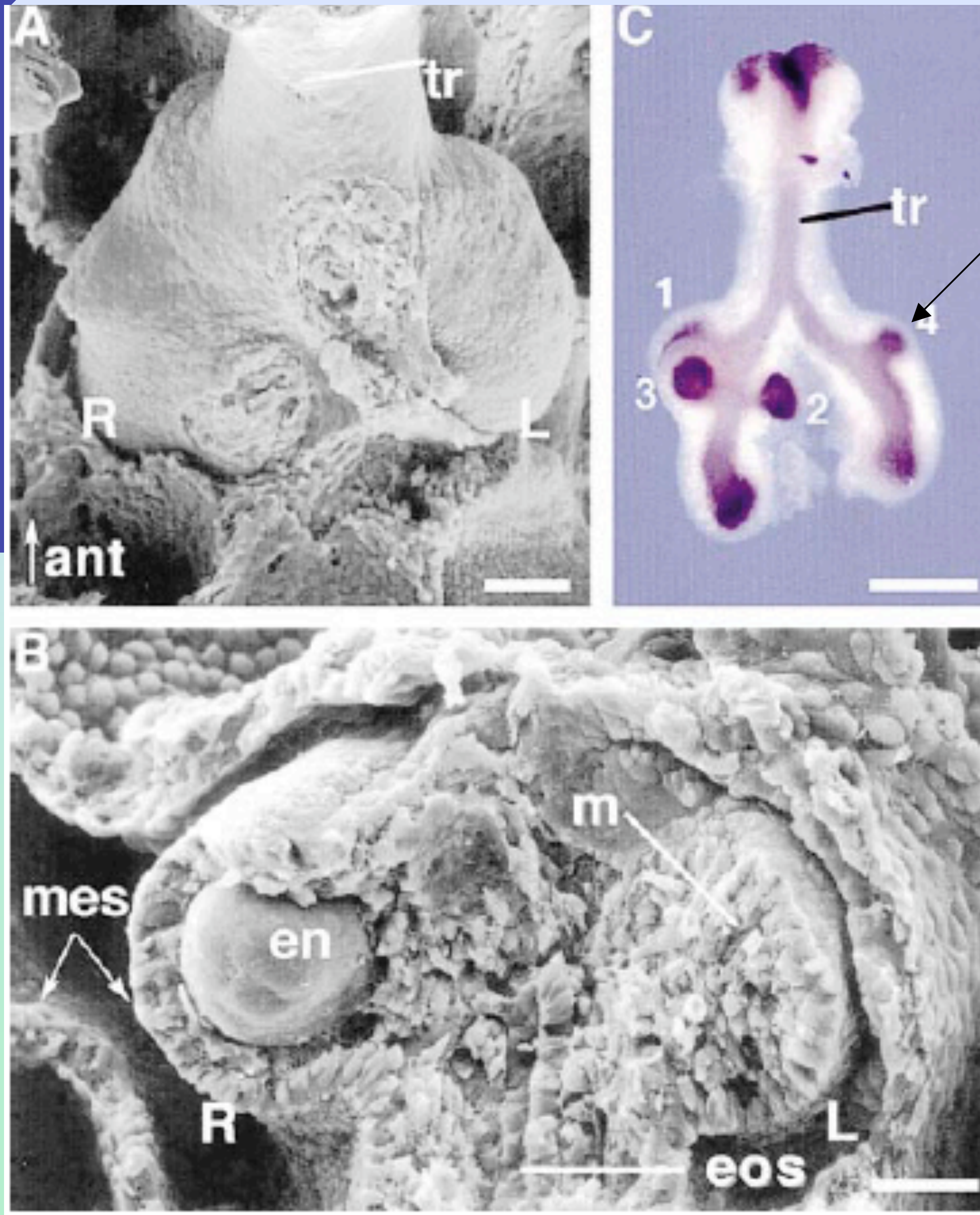
- The chemotaxis response of the lung endoderm to FGF10 induces the coordinated movement of the entire epithelial tip towards an FGF10 source.

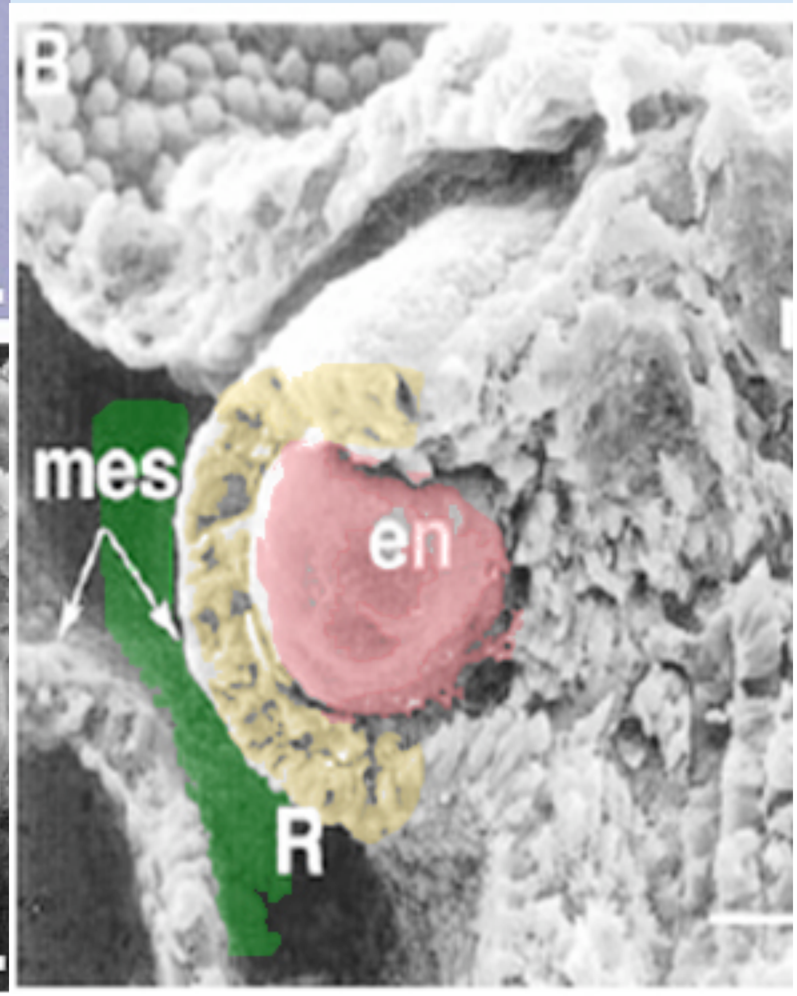




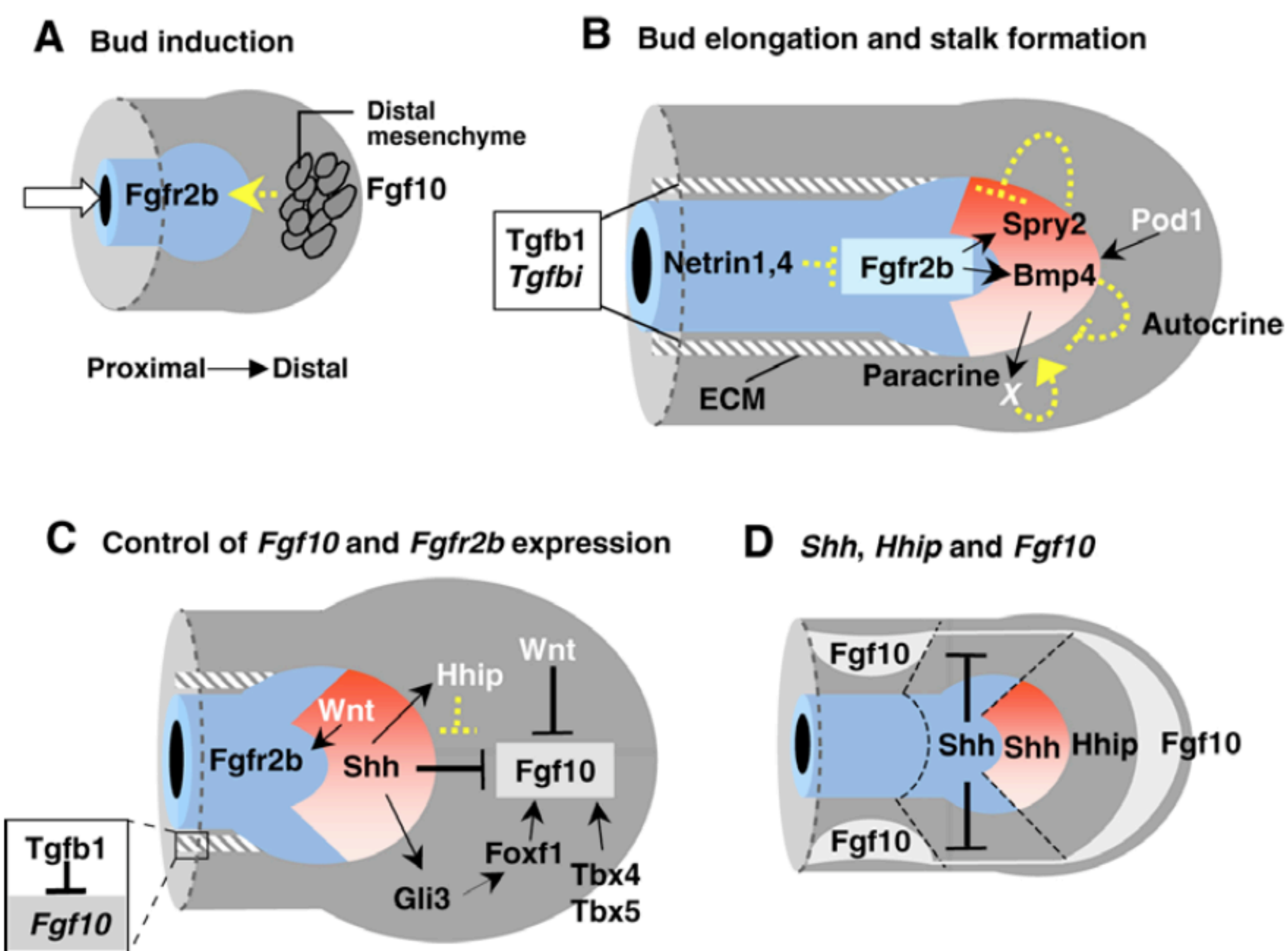
Cebra-Thomas, J.A. 2003

Localization of Shh





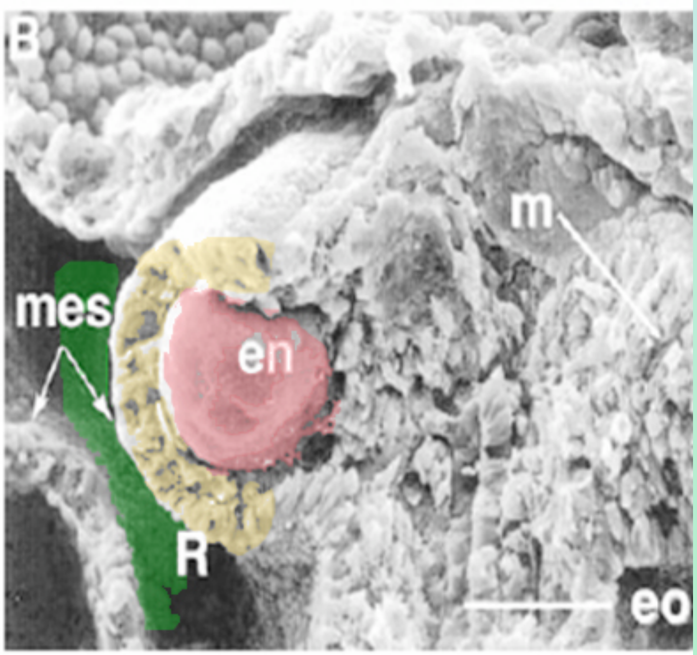
Lung Bud-Branching Morphogenesis

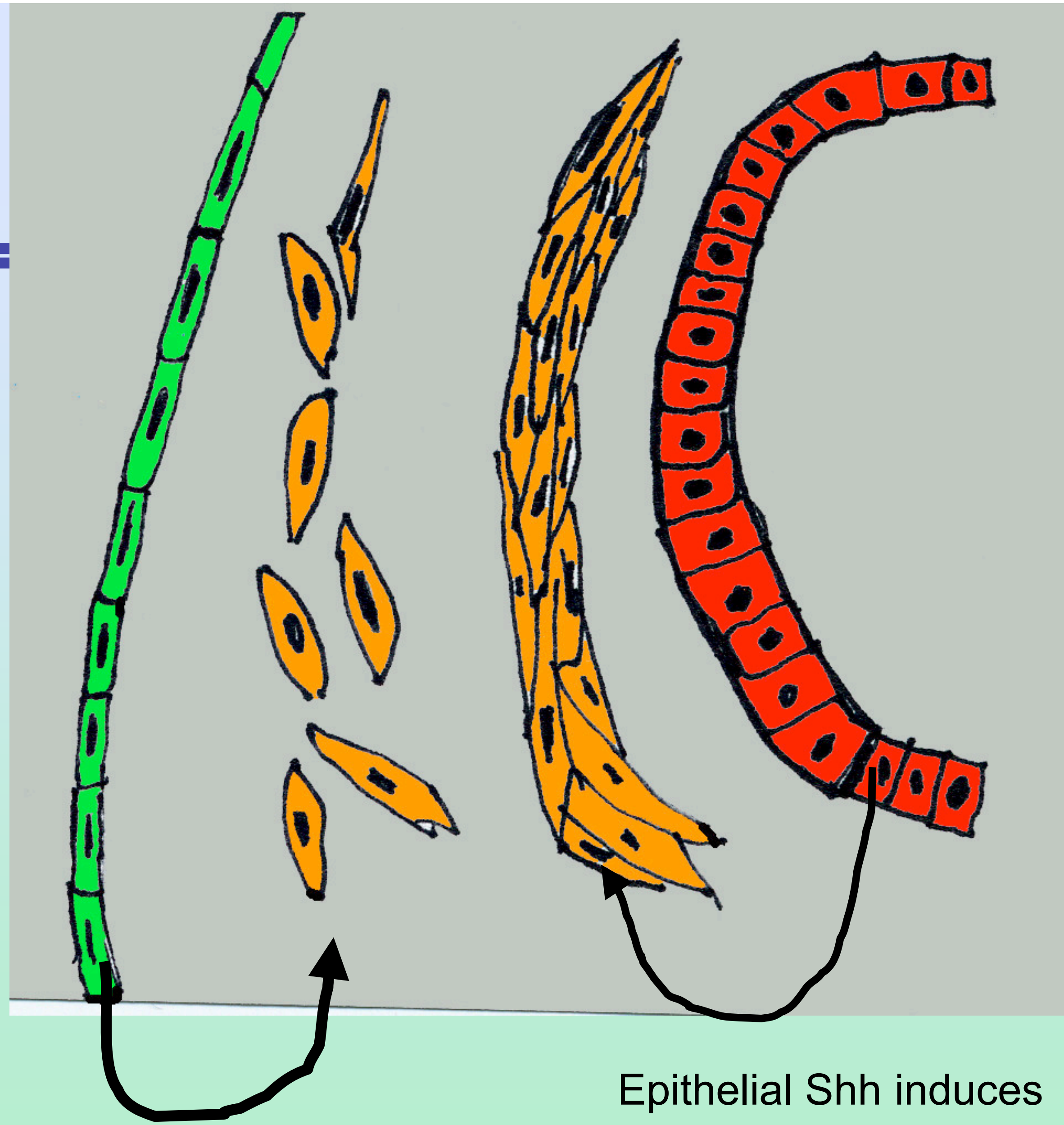


Cardoso and Lu, Dev. 133: 1611-1624 (2006)

When is it done?

This allows for continued
Differentiation and growth
Towards mesothelium
until balanced effect
between FGF9 and Shh
is reached.





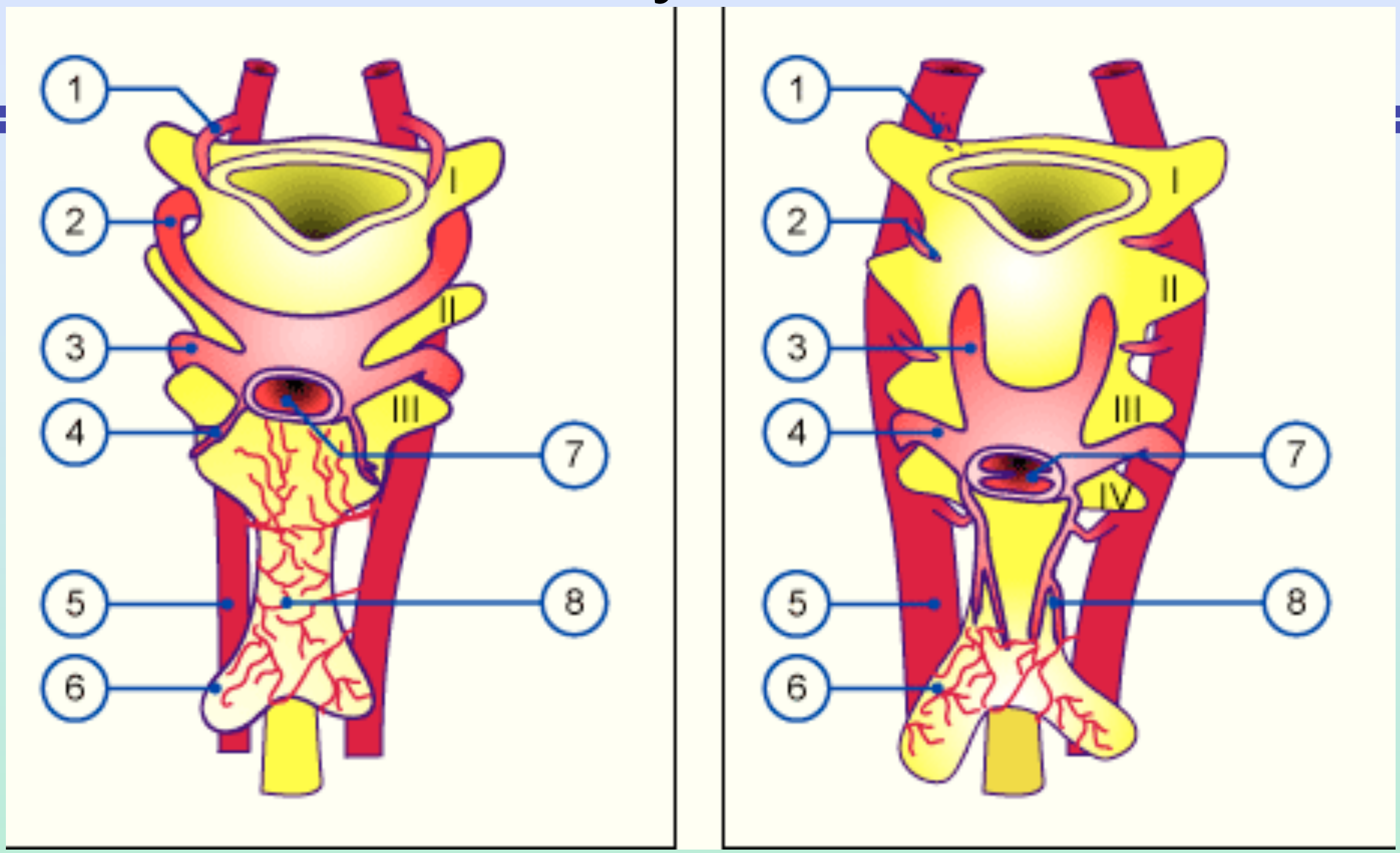
FGF9 from mesothelium
Supports mesenchymal
pluripotency

Epithelial Shh induces
Mesenchyme
proliferation
And differentiation

Pulmonary vasculature

- At birth, fetal lung circulation is a high pressure that must convert to a low pressure circulation.
- As air enters the lung with the first breath, oxygen tension rises.
  - Increased nitric oxide production increases arterial vasodilation, reducing pulmonary arterial pressure.

Pulmonary Circulation

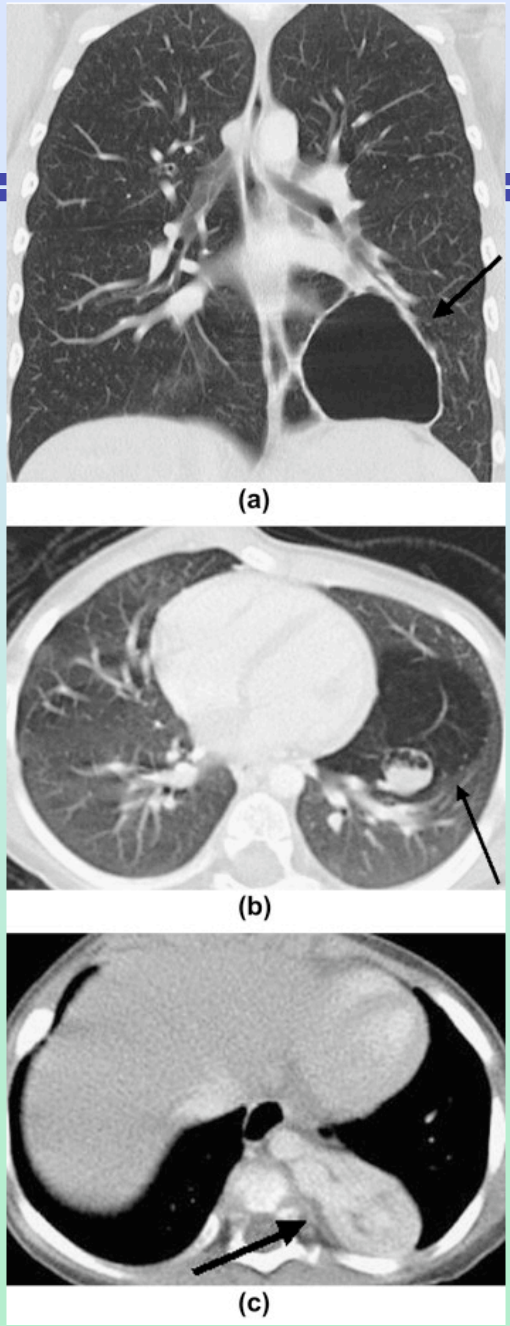


1. First aortic arch
2. Second aortic arch
3. Third aortic arch
4. Fourth aortic arch
5. Dorsal Aorta
6. Lung buds
7. Aortic Sac
8. Pulmonary Plexus

Congenital malformations

- Cystic adenomatoid malformations
  - Maturation arrest in lung segments
- Azyous lobe
  - Superior apical bronchus grows medially instead of laterally; vein is at bottom of superior lobe fissure
- Sequestration –
  - Accessory piece of lung that becomes disconnected from tracheobronchial tree and parasitizes systemic circulation from diaphragm.

Pulmonary Sequestration

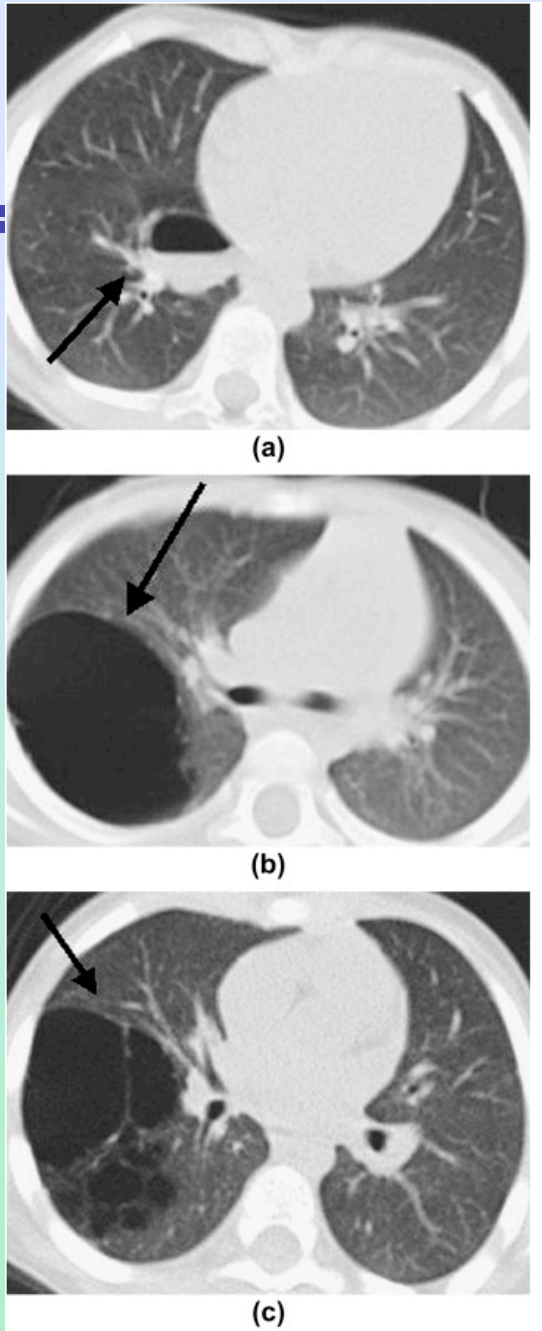


(a) 20-year-old man

(b) Cyst with an air–fluid level with surrounding low attenuation (arrow) in a 2-year-old male patient

(c) Extralobar sequestration appearing as an enhancing mass (arrow) of soft-tissue attenuation with arterial supply and venous drainage in a 2-year-old male patient

Congenital Cystic Adenomatoid Malformations

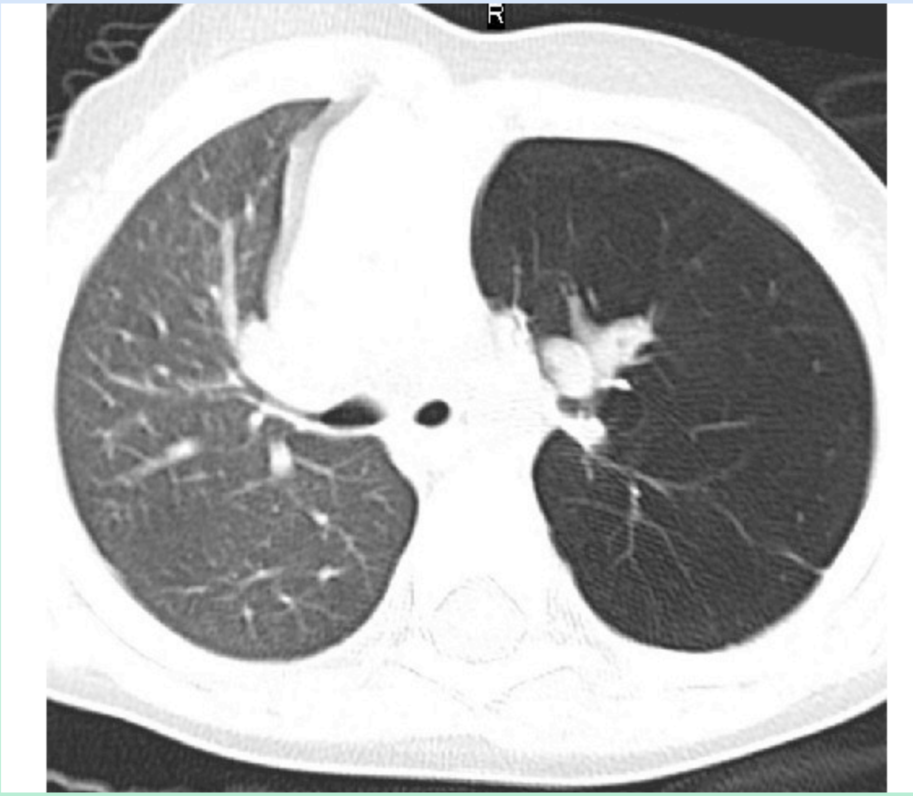


(a) Unilocular cyst (arrow) with air–fluid level in a 5-year-old female patient

(b) Unilocular air filled cyst (arrow) causing mass effect in a 2-year-old male patient

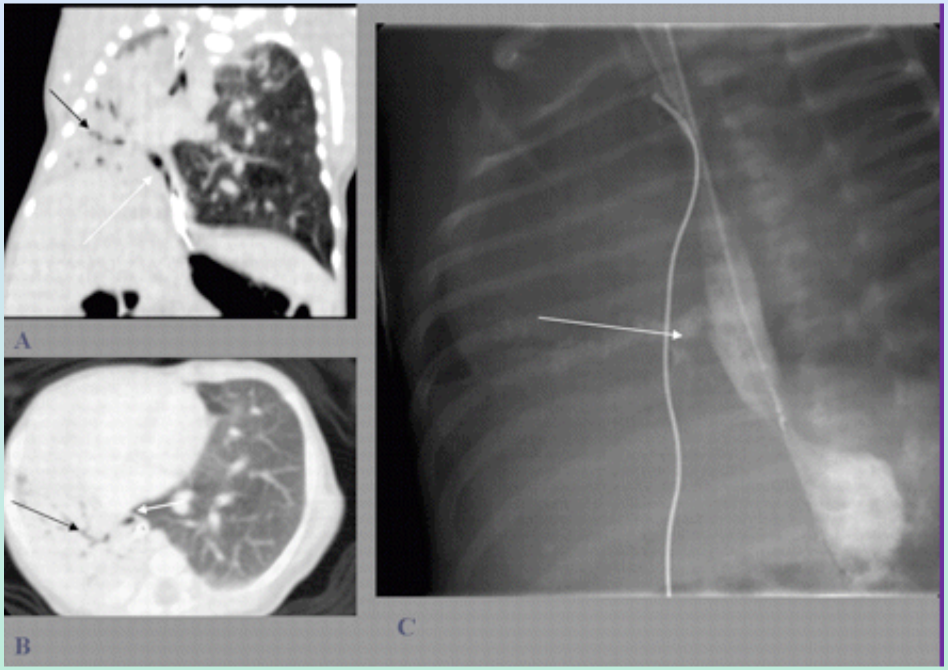
(c) Multilocular cysts (arrow) in a 2-year-old male patient

Bronchial Atresia



2 year old with respiratory symptoms in the past, asymptomatic at this time

Esophageal Bronchus

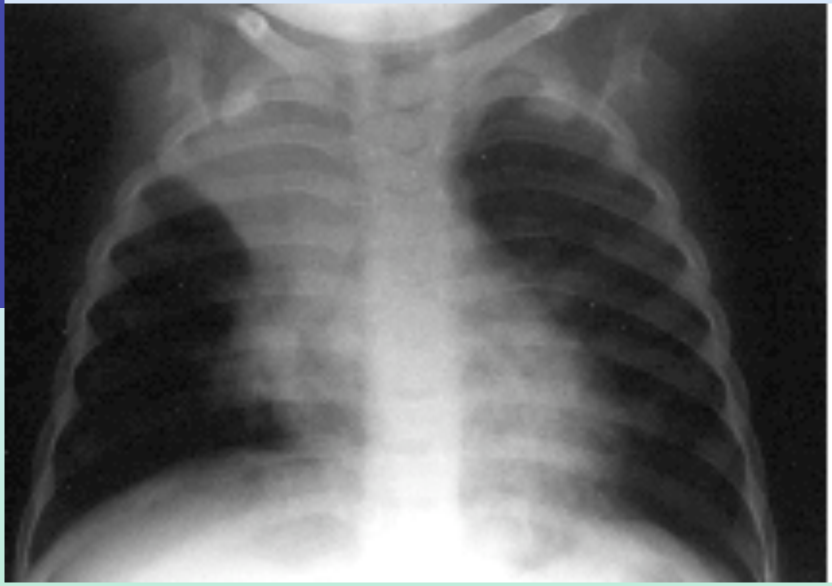


Esophageal bronchus in a neonate with respiratory distress.

(A) Coronal and (B) axial CT images in lung windows show an esophageal bronchus (white arrows) associated with the right lower lung. The right lung is small and almost completely opacified, (black arrows).

(C) Esophagogram confirms the presence of the esophageal bronchus (arrow). At surgery, the right middle lobe and lower lobe were noted to communicate with the esophageal bronchus as part of a bronchopulmonary foregut malformation.

Supranumerary Right Tracheal Bronchus



13-month-old female with hemoptosis and pertussoid illness (fever, cough,).

Tracheal bronchus is a bronchial branch arising directly from the lateral wall of the trachea at any point above the carina.

RDS-Respiratory distress syndrome

- Low surfactant – Respiratory distress syndrome – usually due to pre-maturity, rarely due to surfactant protein deficiency (genetic cause)
  - Surfactant is critical to reduce surface tension and allow lung expansion at the air fluid interface.
    - Inadequate surfactant leads to alveolar collapse on expiration of air, and difficulty re-inflating
    - Damage to the alveolus leads to cellular injury and exudation of proteins known as hyaline membranes (Hyaline membrane disease)
      - Continued injury from ventilation of immature lungs can lead to chronic injury known as bronchopulmonary dysplasia.
  - Steroids accelerate lung development and surfactant production
    - Surfactant can also be administered