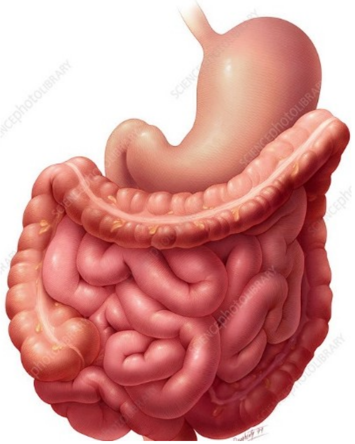
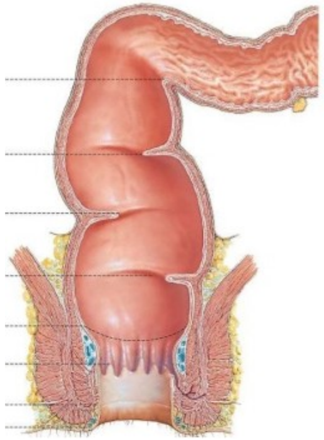
DEVELOPMENT OF GASTROINTESTINAL SYSTEM

FUNCTION OF GASTROINTESTINAL SYSTEM

- food intake and processing



- absorption of nutrients



- excretion of waste products

DEVELOPMENT OF GASTROINTESTINAL SYSTEM IN VERTEBRATES

- sources of precursor cells of gastrointestinal

- Endoderm:
  - pharynx
  - esophagus
  - stomach
  - intestine

- Mesoderm:
  - vessels
  - muscles

- Ectoderm:
  - oral cavity
  - glands
  - teeth
  - anus

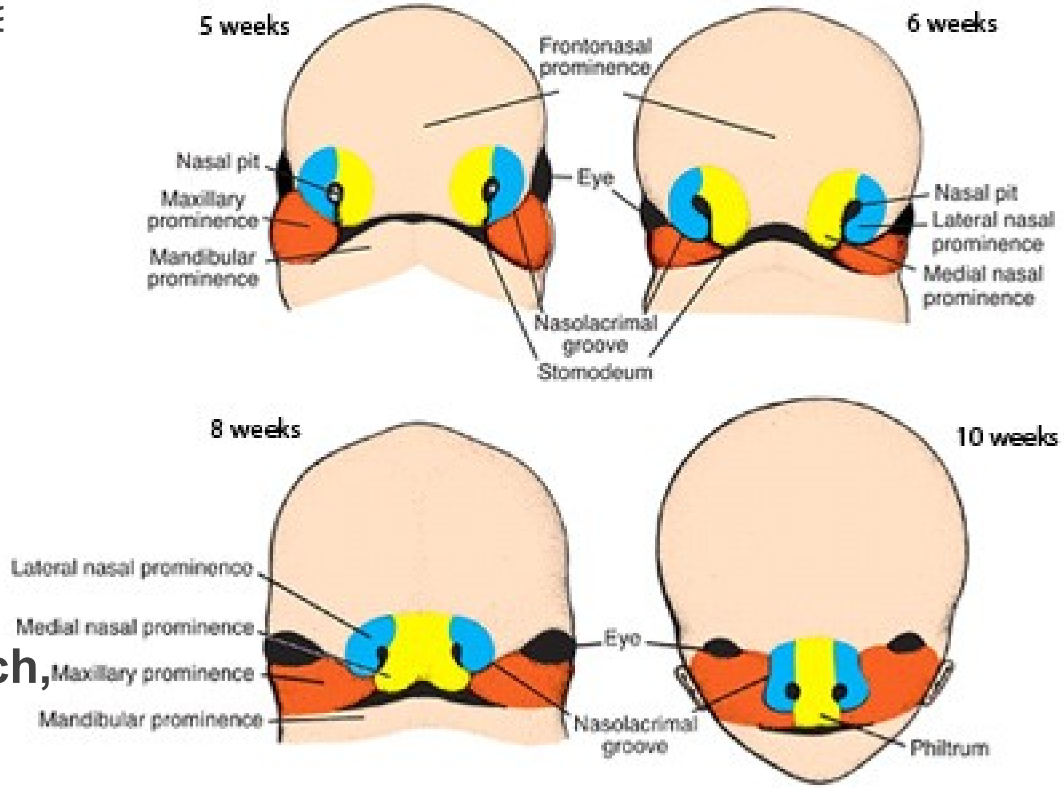
- Neural crest:
  - teeth
  - muscles
  - upper and lower jaws
  - nerves

DEVELOPMENT OF ORAL CAVITY

- formation of **facial prominences – mesenchyma** swellings

- **Cranial neural crest cells** migrate to forebrain region, surface **facial ectoderm**
  - **Middle part – frontonasal prominence**
  - **lateral – lateral nasal prominences**
  - **medial – medial nasal prominences**

- **Neural crest cells** migrate to **1. pharyngeal arch,** surface **pharyngeal arches ectoderm**
  - **cranially – maxillary part** (upper jaw, palate)
  - **caudally – mandibular part** (lower jaw)



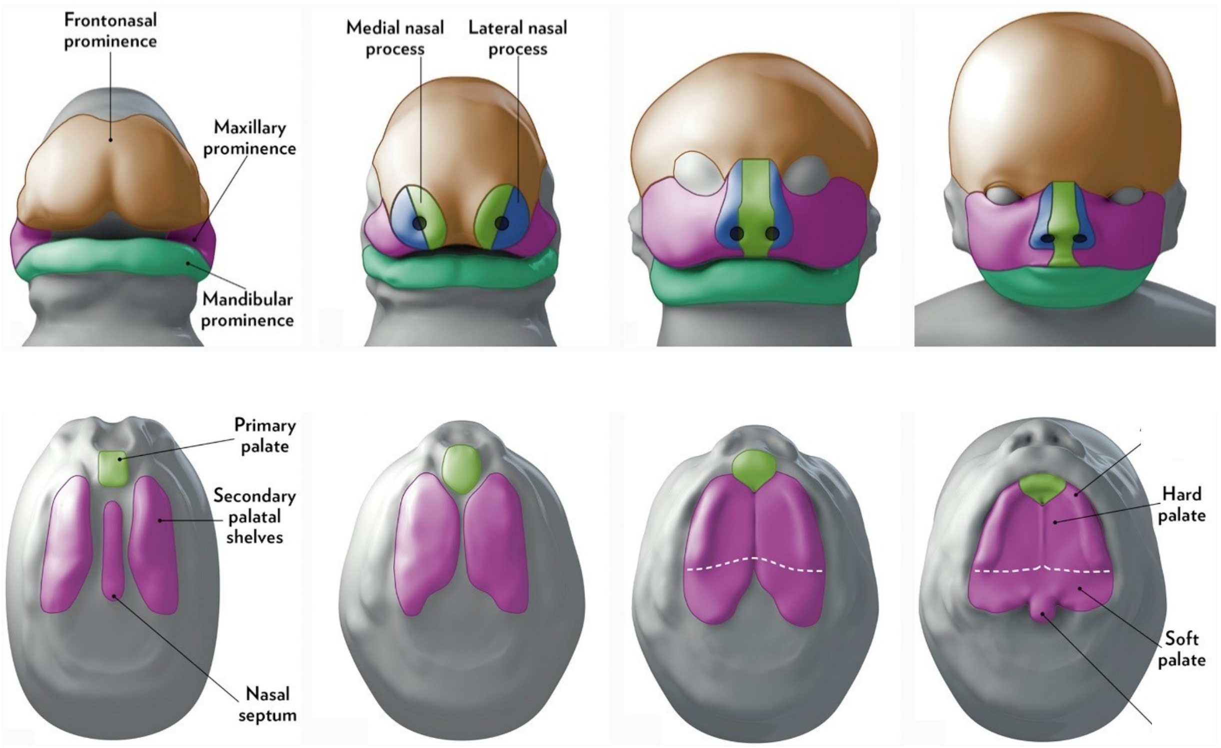
Duke Embryology

DEVELOPMENT OF THE PALATE

- Palate composes of two parts:
  - **Primary palate – anterior, frontonasal prominence**
  - **Secondary palate – lateral palatal shelves, maxillary prominence**

- **medial nasal prominences** pushed **medially** by **maxillary prominences**
  - **Intermaxillary segment** formation – formation of **primary palate**, philtrum, parts of nose

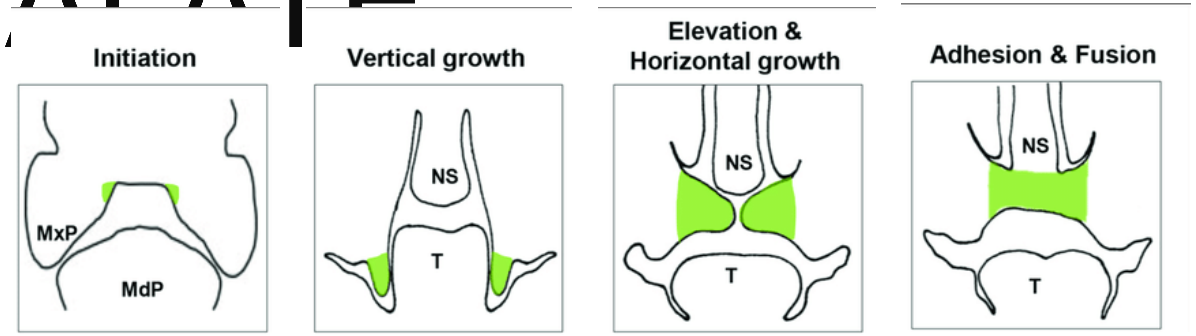
- Maxillary prominences grow **medially**
  - gradual **separation** of **oral** and **nasal** cavivites
  - **medial fusion** in some species
  - **anterior - hard** palate
  - **posterior – soft** palate
  - interspecies **variability**



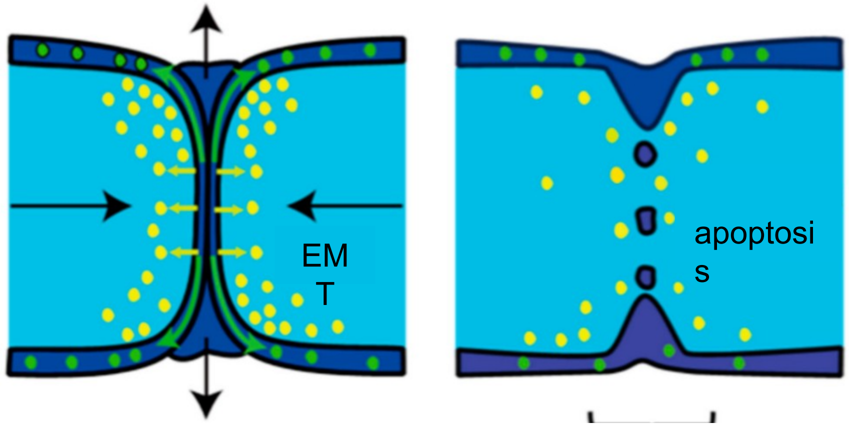
Worley et al. 2018. Clin Perinat

DEVELOPMENT OF THE PALATAL SHELVES AND SECONDARY PALATE

- **palatal shelves medially** outgrow from **maxillary** prominences (mesenchyme from **neural crest**, stomodeal epithelium from **ectoderm**)
- tongue prevents horizontal growth – **vertical growth** along the tongue
- vertical head elongation, **tongue** recedes **ventrally**, palatal shelves **reorient** into **horizontal** plane
- **connection** of opposite palatal shelves, formation of **epithelial seam**
- **epithelial cells** undergo **apoptosis** and **epithelial-mesenchymal transition** → **fusion** and complete palate formation

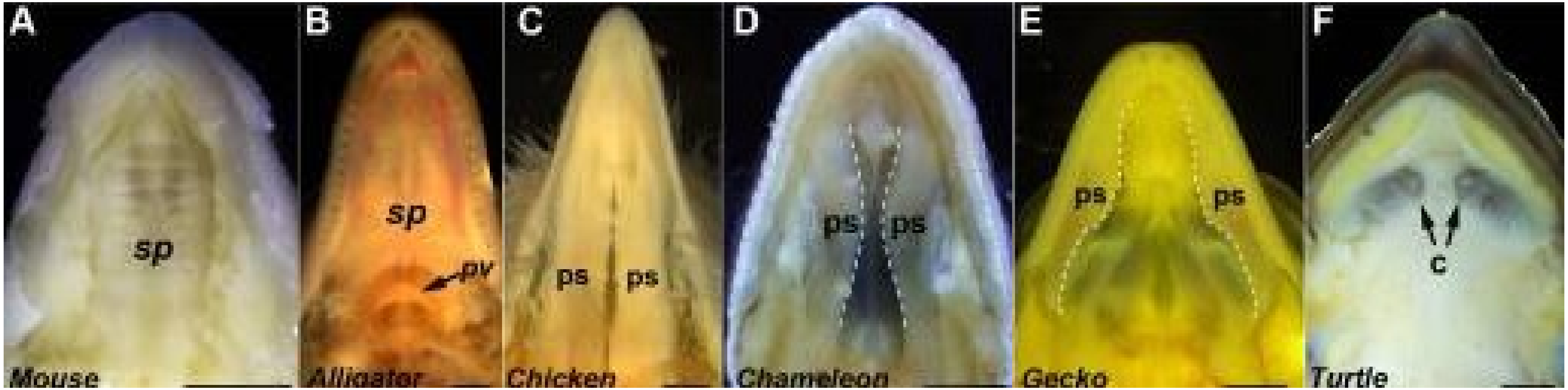


Schoen et al. 2017. Front Physiol



Nakajima et al. 2018. Int J Mol Sci

SECONDARY PALATE VARIABILITY

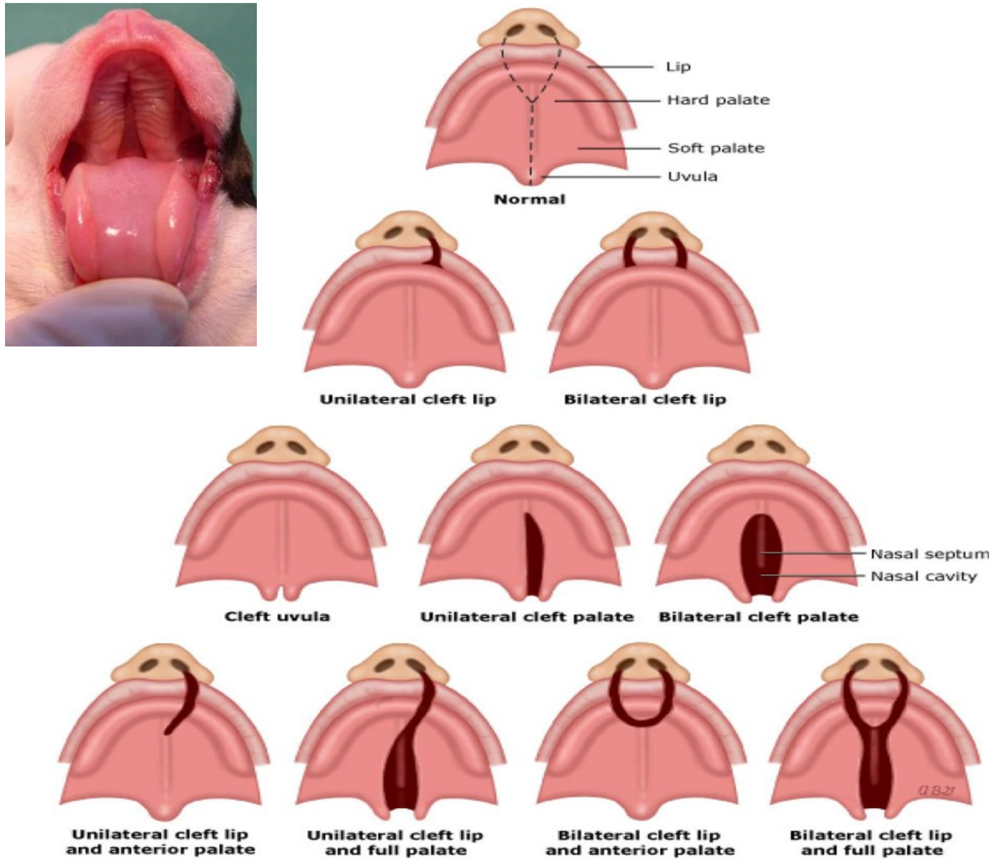


fusion of palatal shelves – complete palate (mouse)	fusion of palatal shelves – complete palate (alligator)	palatal shelves in contact – keratinization, physiological cleft (birds)	palatal shelves not in contact, great variability (chameleon)	rudimentary palatal protrusions (gecko)	palatal shelves not formed (turtle)

Abramyan and Richman, 2015. Dev Dyn

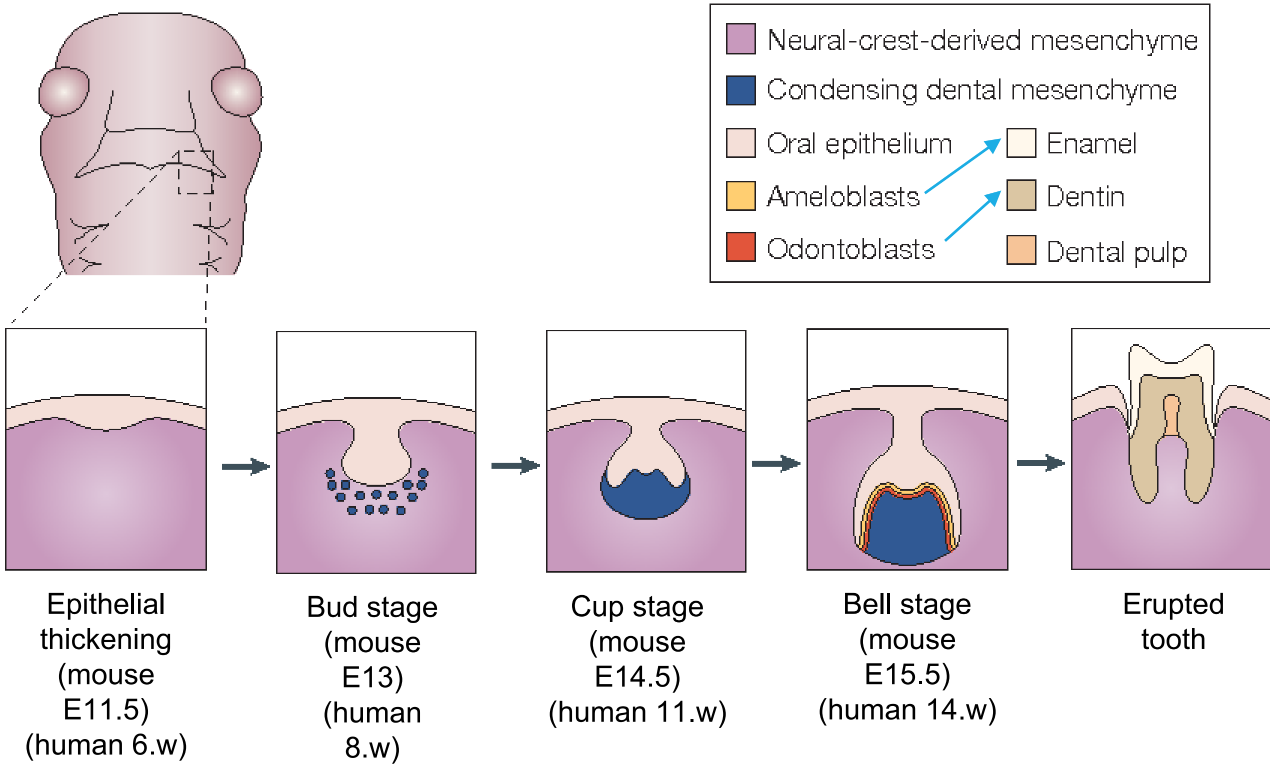
DEVELOPMENTAL DEFECTS OF LIP AND PALATE

- **Cleft lip and/or palate** – the most often developmental defects of head and neck (1:500/700)
- 3 % of all the developmental defects
- combined and isolated
- unilateral and bilateral
- syndromic and non-syndromic clefts



TOOTH DEVELOPMENT

- Cooperation between cells of different origin:
  - oral cavity ectoderm
  - Neural crest mesenchyme
  - **vessels from mesoderm**
- oral epithelium (ectoderm)
  - **ameloblasts**
  - **enamel**
- mesenchyme (neural crest)
  - **odontoblasts**
  - **dentin**
  - **cement**
  - **dental pulp**



Tucker and Sharpe, 2004. Nat Rev Genet

1. EPITHELIAL THICKENING

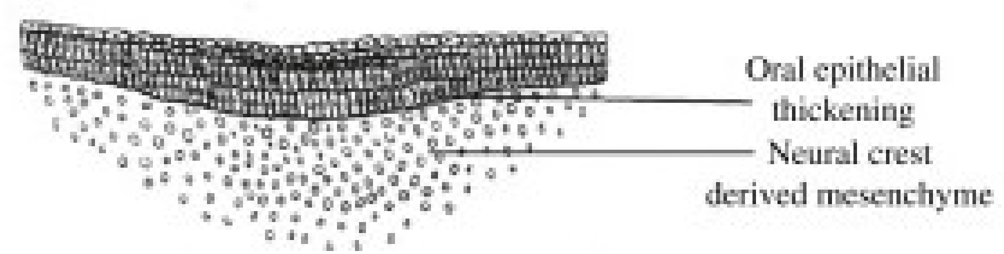
- in the region of future tooth are proliferating **oral epithelial** cells – **epithelial thickening**

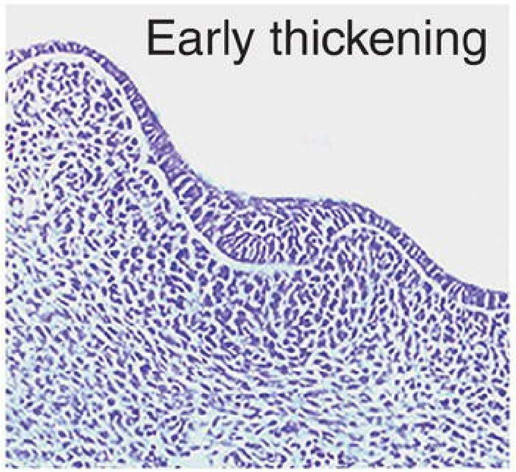
- epithelial thickening – **dental placode**

- **placodal** cells proliferate and **invaginate** into underlying **mesenchyme** originating in **neural crest**

oral

aboral





Cobourne and Sharpe. Tooth development. Pocket dentistry

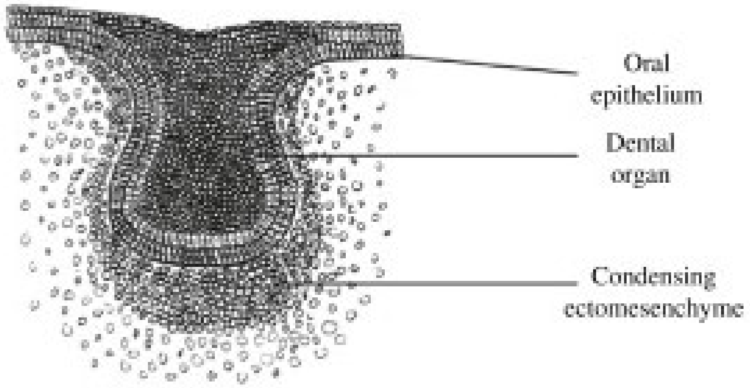
2. BUD STAGE

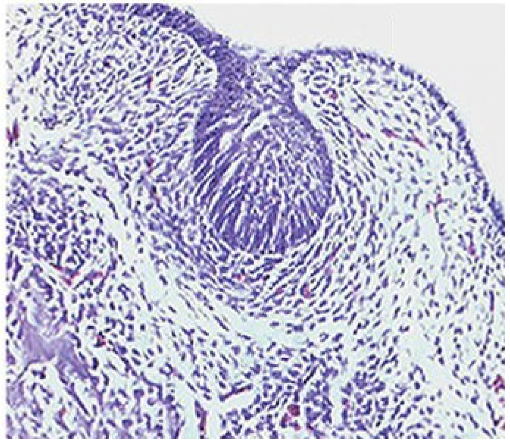
- **epithelium** invaginates into **mesenchyme**, formation of **dental organ** (epithelium) – epithelial cells are **proliferating**

- **mesenchyme** starts to **condensate** around forming epithelial bud – **bud stage**

oral

aboral

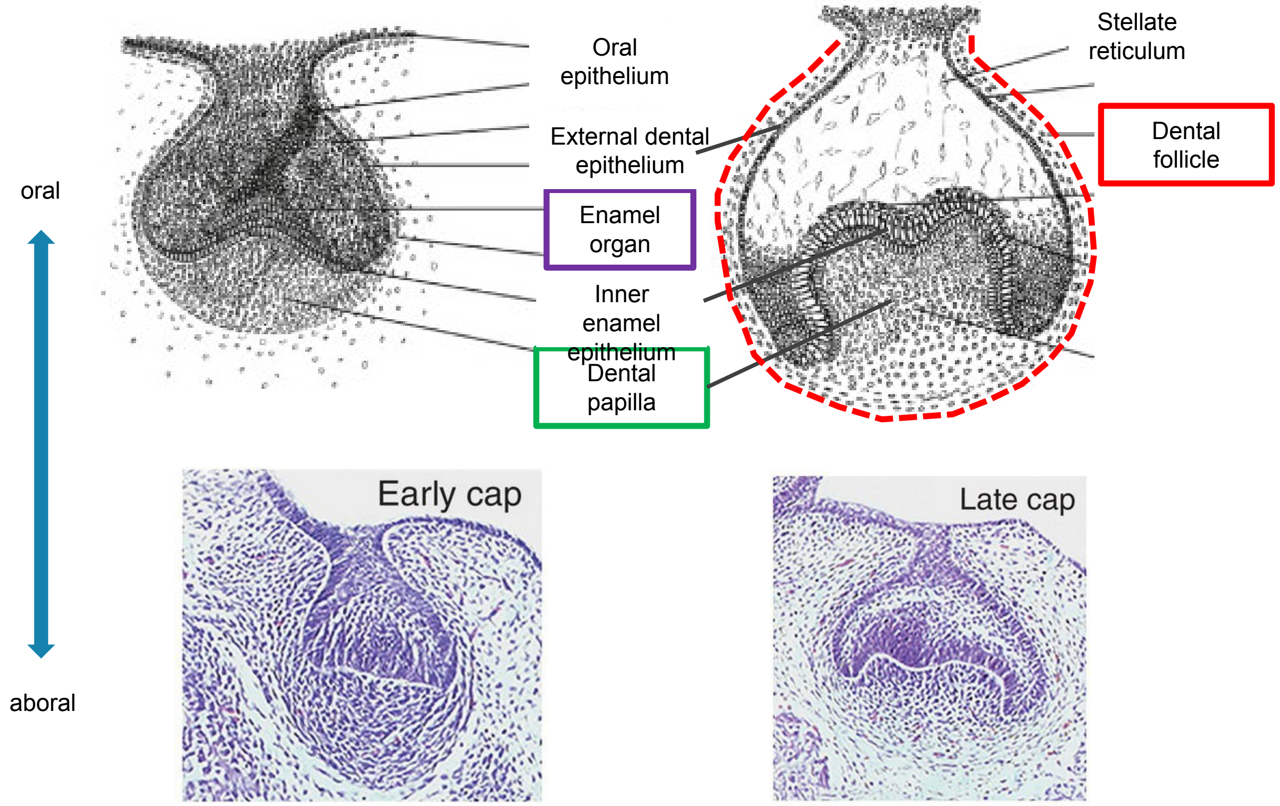




Cobourne and Sharpe. Tooth development. Pocket dentistry

3. CUP STAGE

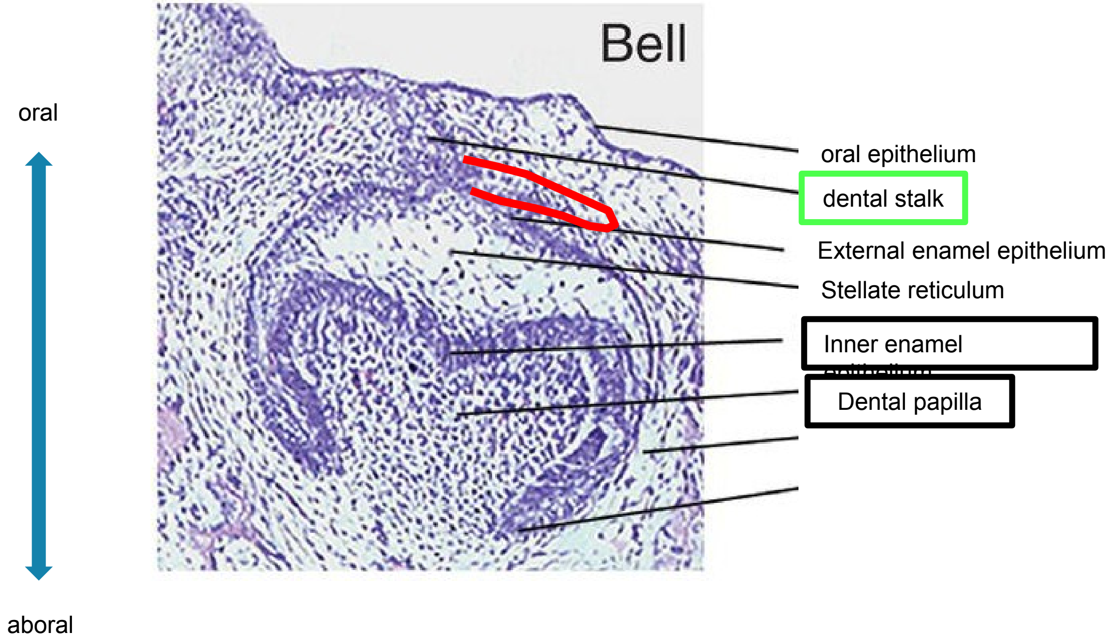
- epithelial **bud** growth into **mesenchyme**, formation of **epithelial** (enamel) **knots**
- **inner** and **external** epithelial cells distinguished, layer of loose **reticular** cells (**stellate reticulum)** form layer between them
- **enamel organ** formed from **inner** enamel epithelium, **dental papilla** formed from **mesenchyme – cup stage**
- **mesenchymal cells** form **Dental follicle** around forming tooth



Cobourne and Sharpe. Tooth development. Pocket dentistry

4. BELL STAGE (EARLY BELL)

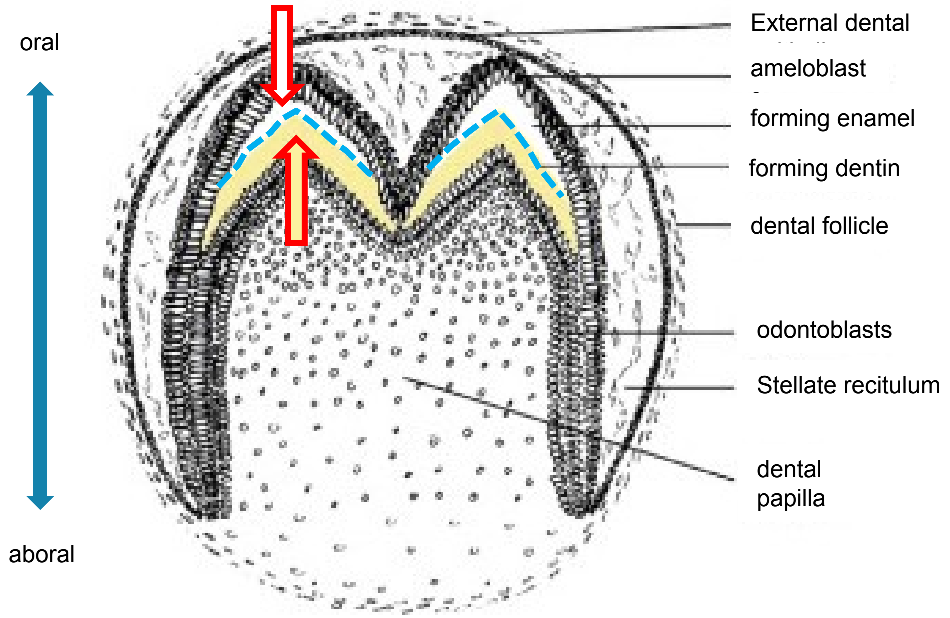
- Tooth cup grows further into jaw mesenchyme, **connection** with oral epithelium preserved via „string“ of epithelial cells – **dental stalk**
- diphyodont and polyphyodont species – outgrow of so called **dental lamina** (next generation teeth source) from dental stalk
- stellate reticulum cells induce **differentiation** of **inner enamel ep** cells – formation of **ameloblasts**
- **mesenchymal** cells of **dental papilla** in contact with differentiating **ameloblasts** – differentiation into cylindrical cells - **odontoblasts**



Cobourne and Sharpe. Tooth development. Pocket dentistry

5. APPOSITION STAGE (LATE BELL)

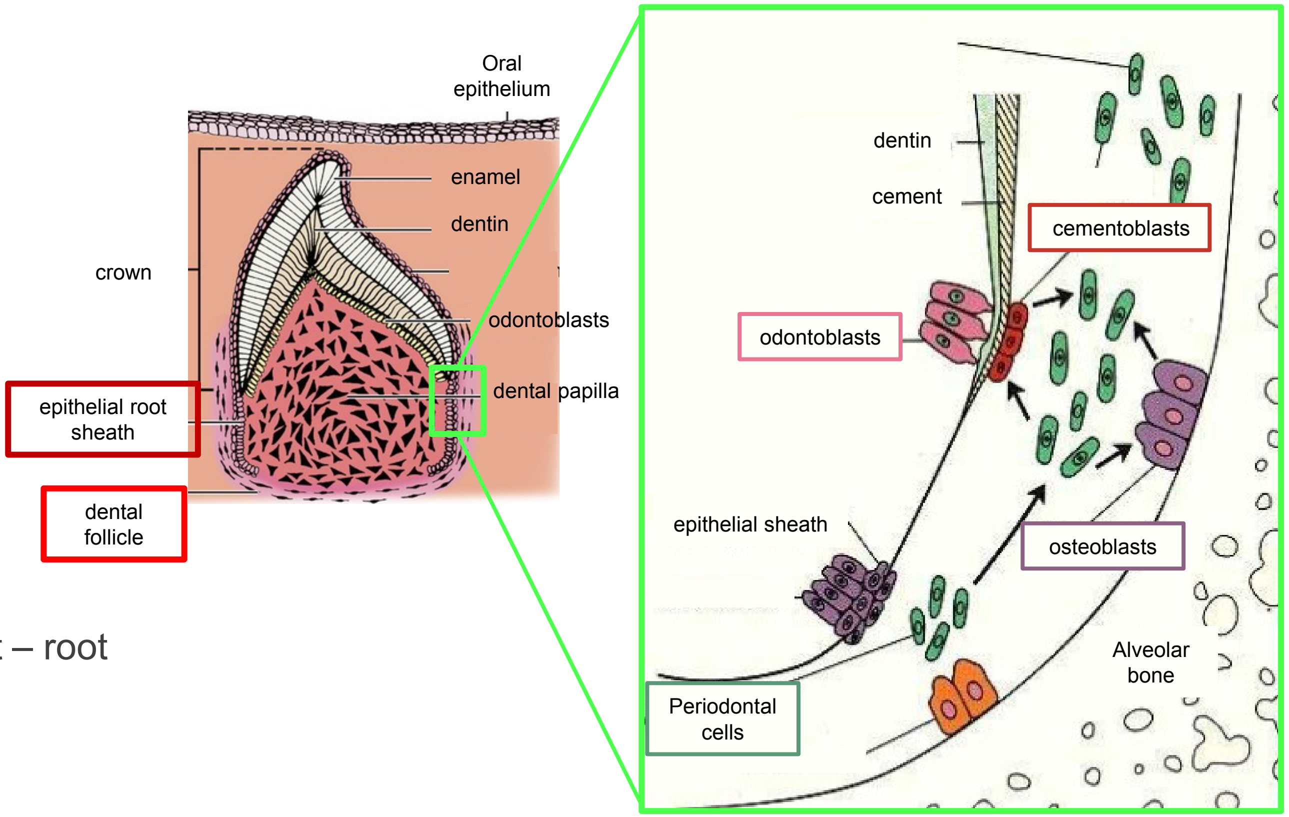
- ameloblasts form enamel
- odontoblasts form dentin
- **ameloblasts** produce **enamel** into space towards odontoblasts, **ameoblasts transfered** to the tooth **surface**
- **odontoblasts** produce **dentin** into space towards ameloblasts, **odontoblasts transfered** to the **dental cavity**
- enamel and dentin in direct **contact**
- dental **crown** base formed



Cobourne and Sharpe. Tooth development. Pocket dentistry

DEVELOPMENT OF TOOTH ROOT

- enamel organ **base** – crown and root **interface**
- enamel organ **base** – direct contact of inner and external enamel epithelium, proliferation and migration into mesenchyme → **epithelial root sheath** (root base)
- **sheath induces** dental papilla mesenchymal cells to form **odontoblasts** → **connection** of **crown dentin** to **root dentin**
- stellate recitulum **absence**→ epithelial cells **do not** differentiate into ameloblasts
- **dental follicle inner** cells – **cementoblasts** (cement – root surface)
- **outer** cells – **osteoblasts** (alveolar bone)
- **middle** layer – **mesenchymal** cells of **periodontium**, collagen fibers (periodontal ligaments)



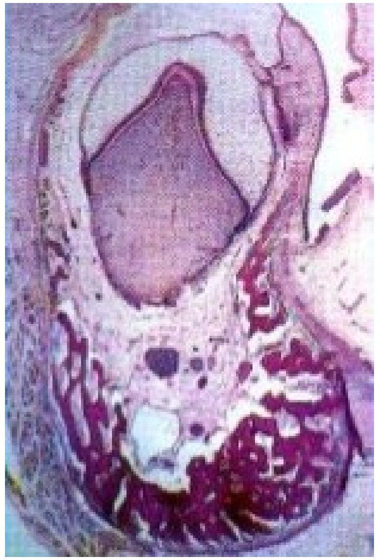
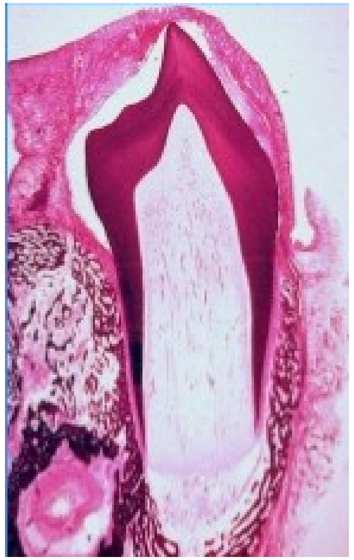
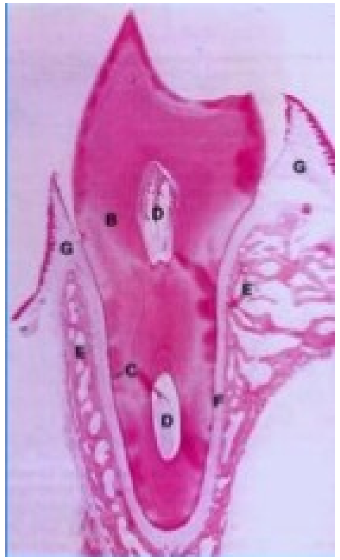
1994. Curr Top Periodontol

6. TOOTH ERUPTION

- **Pre-eruption** phase – preparation for tooth eruption, **begins** in early **bell stage**, **terminates** at the **begining** of the **root** formation

- **Eruption** phase – intensive growth of root, tooth supported by formed **alveolar** bone, oral epithelium **rupture**, tooth **enters** oral cavity

- **Post-eruption** phase – further growth of tooth into oral cavity

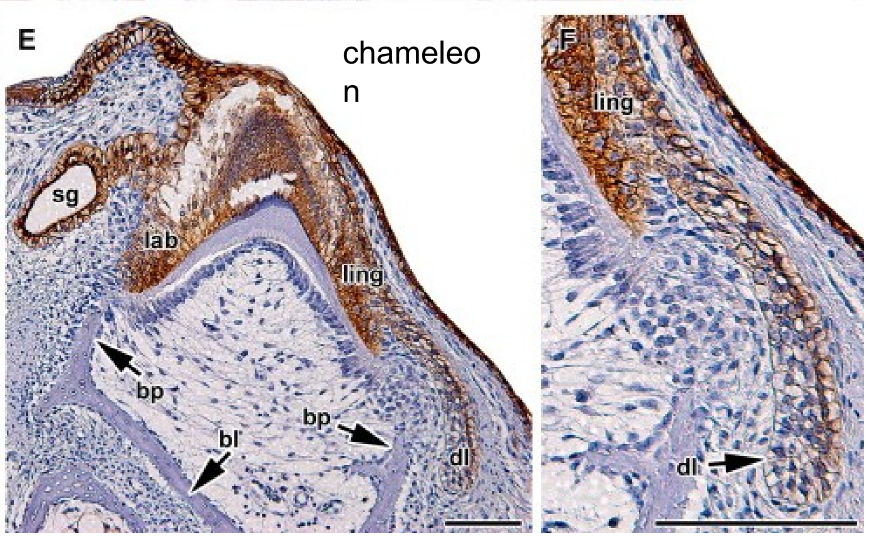
Bleahid, 2017. Health and Medicine

NEXT GENERATION TEETH DEVELOPMENT

- monophyodont species (chameleon, mouse, marsupials, whales, moles) – **one** generation, dental lamina **do not** develop

Buchtova et al. 2012. JDR

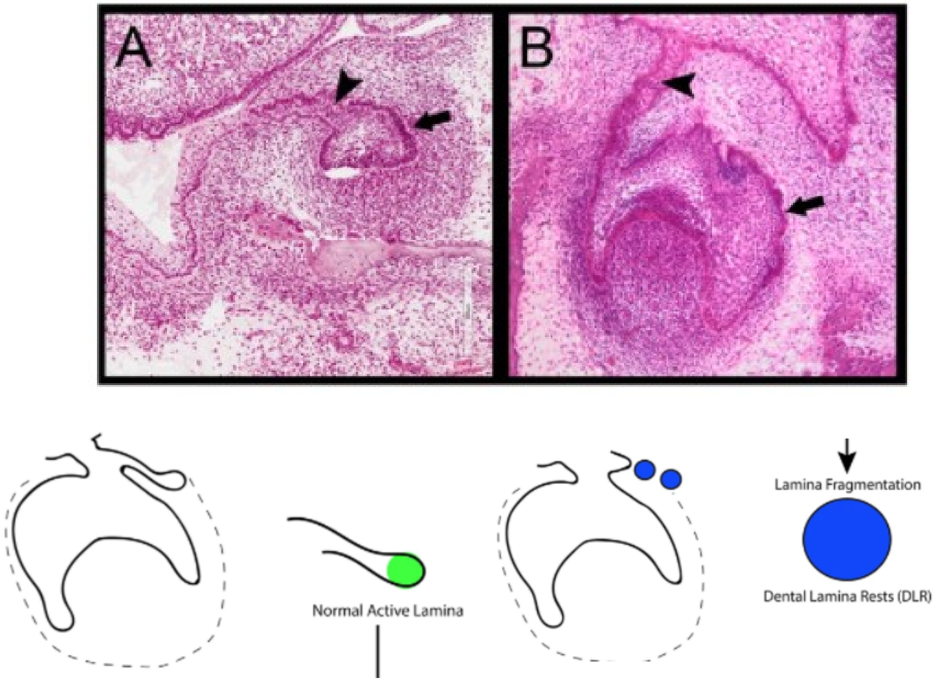
- Dental lamina **is formed** in chameleon – next tooth generation **is not formed**



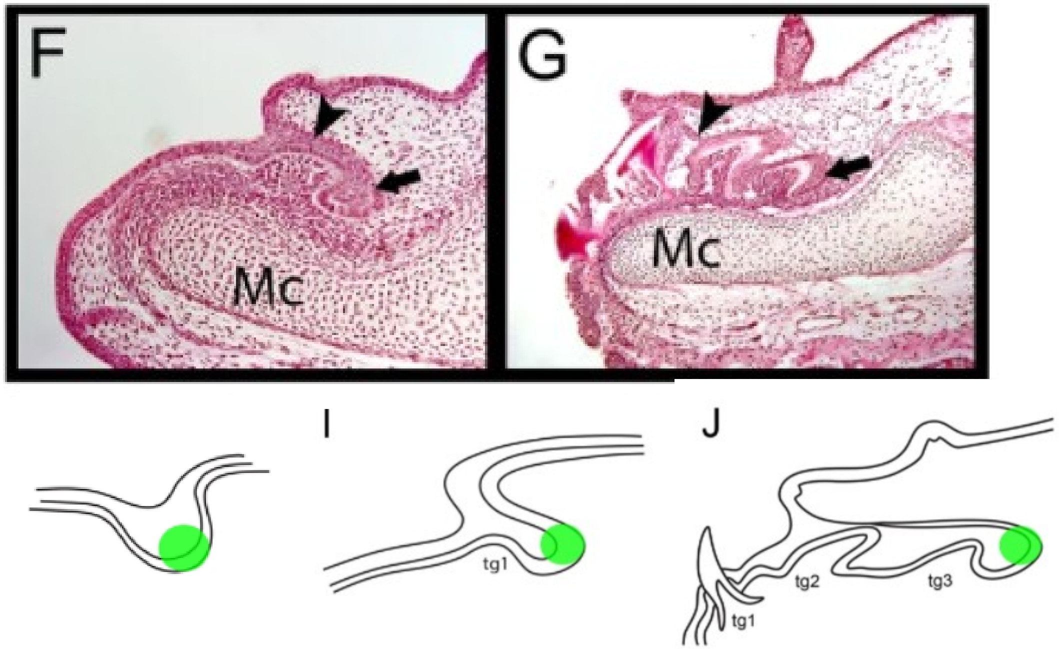
Buchtova et al. 2013. Arch Oral Biol

NEXT GENERATION TEETH DEVELOPMENT

- **diphyodont** species (majority of mammals, human) – **second** teeth generation, **secondary** or **successional** dental lamina



- polyphyodont species (sharks, snakes) – more than **two** teeth generations, **lifelong** teeth replacement, **active** dental lamina



Fraser et al. 2019. Sci Rep

DEVELOPMENTAL DEFECTS OF TEETH

- Hypodontia – missing one or more teeth

- Hyperdontia – excessive teeth

- microdontia – smaller teeth

- malposition – teeth in atypical positions

DEVELOPMENTAL DEFECTS OF TEETH

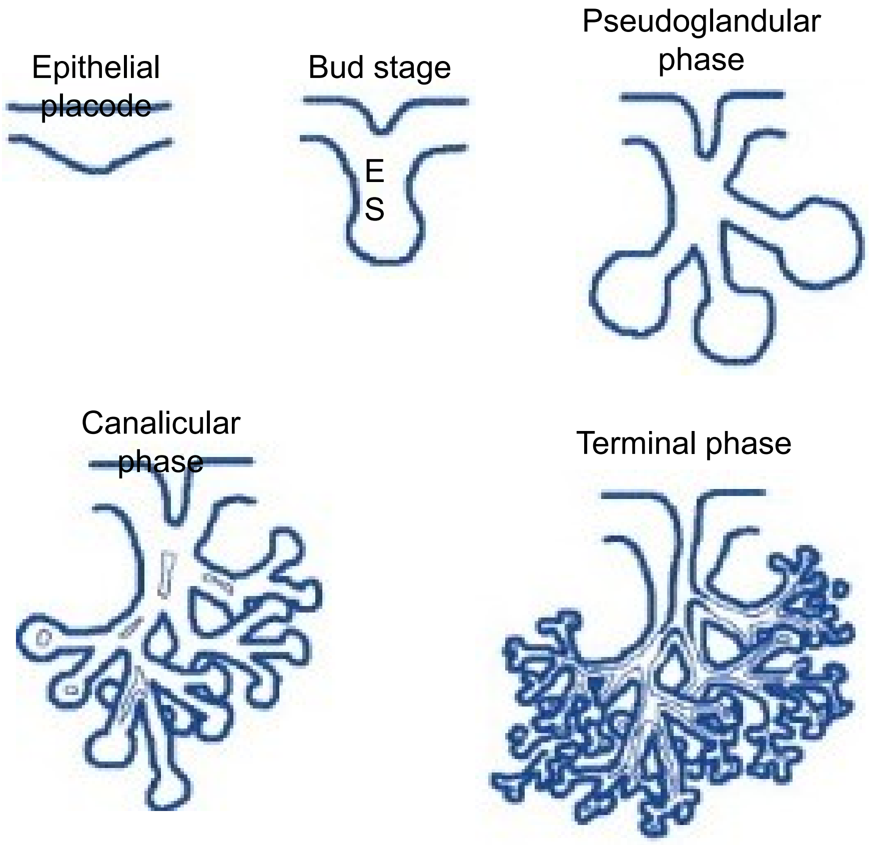
- Enamel hypoplasia
  - insufficient or abnormal enamel development
  - **Amelogenesis imperfecta** – congenital defect, insufficient enamel development

- Dentin dysplasia
  - Dentin development affected
  - **1. type –** crown dentin not disturbed**, missing** or **rudimentary roots**
  - **2. type – crown** dentin development **disturbed,** altered crown color

DEVELOPMENT OF SALIVARY GLANDS

Major salivary glands – ectoderm; minor mucuous glands of the tongue – endoderm; palatal glands – mixed origin

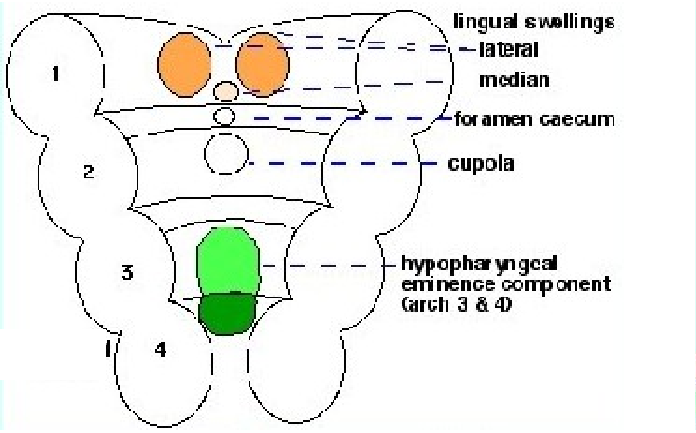
- proliferation → **oral epithelium** thickening – formation of **epithelial placode** (pre-bud stage)
- invagination of epithelial cells into **mesenchyme of 1. pharyngeal** arch (**neural crest**) – formation of **bud** and **epithelial stalk (ES)**, **condensation** of mesenchyme
- other buds formed from main by branching, onset of **cavitation** from oral cavity, mesenchymal **capsule** – **pseudoglandular** phase
- Following **branching**, **cavitation** via **apoptosis** of the **inner epithelial** cells, luminisation from **proximal** to **distal** parts, formation of glandular **acini** (lobes) – **canalicular** phase
- **cavitation** ended, **differentiation** of **epithelial** cells in **ducts (excretory** cells) and **acini** (**secretory** cells) – **terminal** phase

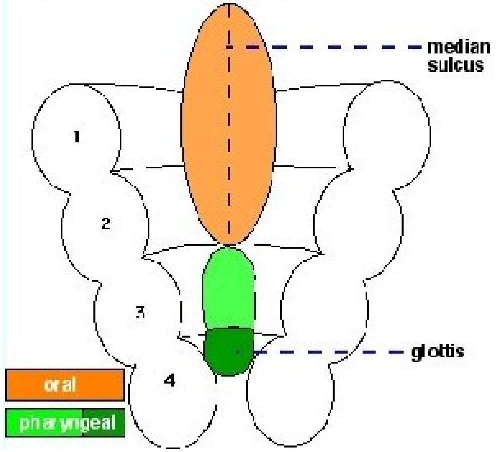


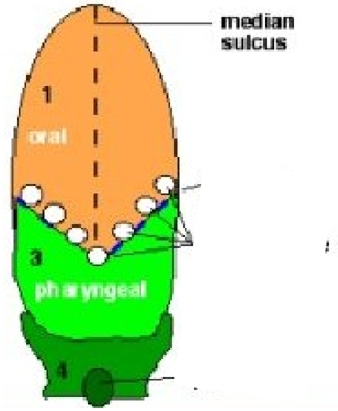
Tucker, 2007. Sem Cell Dev Biol

TONGUE DEVELOPMENT

- Interaction of cells from two sources:
  - **connective** tissue from **neural crest mesenchyme**
  - **muscles** from **occipital segments (mesoderm**
- **1. pharyngeal** arch – **paired lateral** and **unpaired medial** swellings (**tubercle**), **lateral** grow and **overgrow medial** swelling → formation of **medial tongue sulcus, covered with epithelium from ectoderm** (2/3 anterior part, **body** of tongue)
- **2. and 3. pharyngeal** arches – formation of **ventromedial swelling,** called **cupola**
- **3. and 4. pharyngeal** arch – **hypopharyngeal eminence** from mesenchyme
- **Fusion** of cupola and hypopharyngeal eminence – **root** of tongue, covered with epithelium from **endoderm**
- **fusion** of tongue root and body







Gallatz Katallin

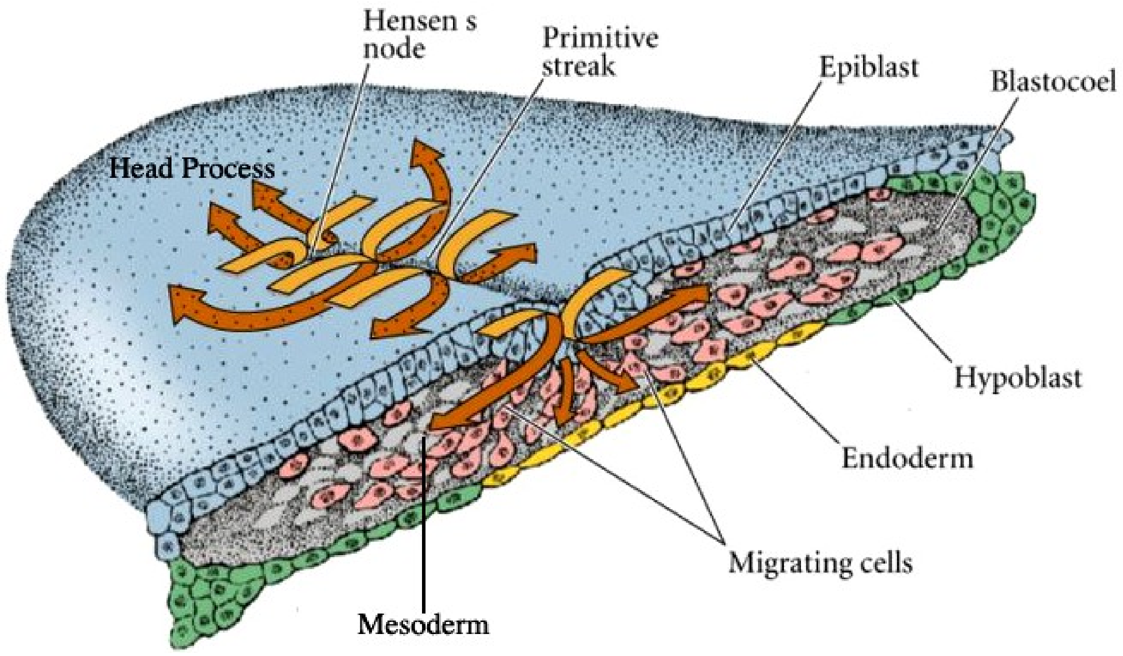
DEVELOPMENTAL DEFECTS OF TONGUE

- **Cleft tongue** (bifid tongue)
  - deffective interaction between medial and lateral swellings
  - formation of longitudinal cleft
  - surgery
  - Mostly syndromic

Fleming and Flood, 2005. British Dental Journal

ENDODERM FORMATION

- **Epiblast cells invaginate** in **primitive streak** and **Hensen`s node** regions
- **First epiblast** cells **invaginating** through **Hensens node** – migrate cranially, forming future **pharyngeal cells** of the **primitive gut**
- **hypoblast** cells **replaced by endoderm** cells
- **Attachment** of **digestive tube** – formation of dorsal and ventral mesentery (hinge) from **splanchnic mesoderm**

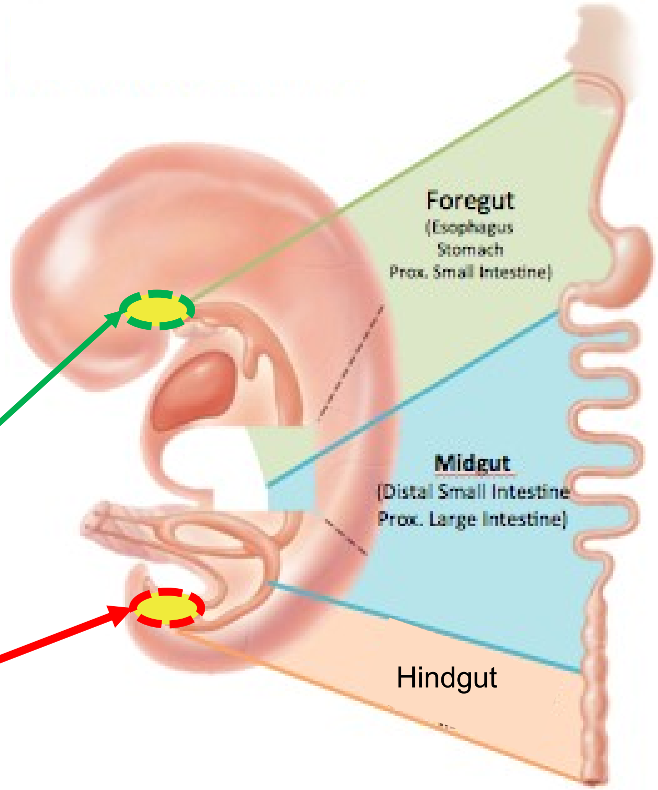


Balinsky, 1975

FORMATION AND DEVELOPMENT OF PRIMITIVE GUT

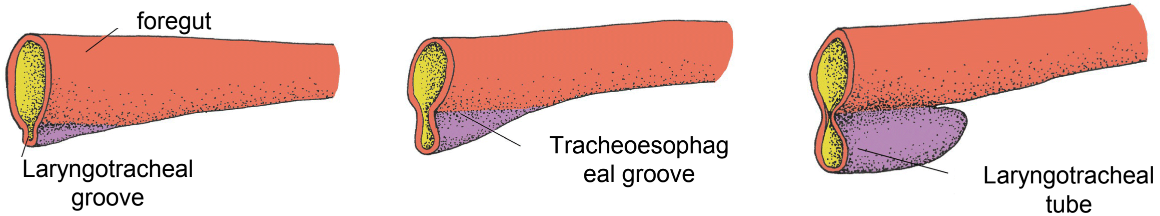
- blindly terminated tube of primitive gut connects cranial and caudal parts of the developing individual
- Primitive gut divided into three parts:
  - **foregut** – pharynx, esophagus, stomach, cranial part of duodenum
  - **midgut** – from liver bud to transversal colon
  - **Hindgut** – from transversal colon to cloacal membrane

- Gut endoderm connected with ectoderm on both sides, formation of two membranes:
  - **cranial** – connection with **primitive oral** cavity (stomodeum) – **oropharyngeal membrane**
  - **caudal** – connection with primitive anal opening (proctodeum) **– cloacal membrane**

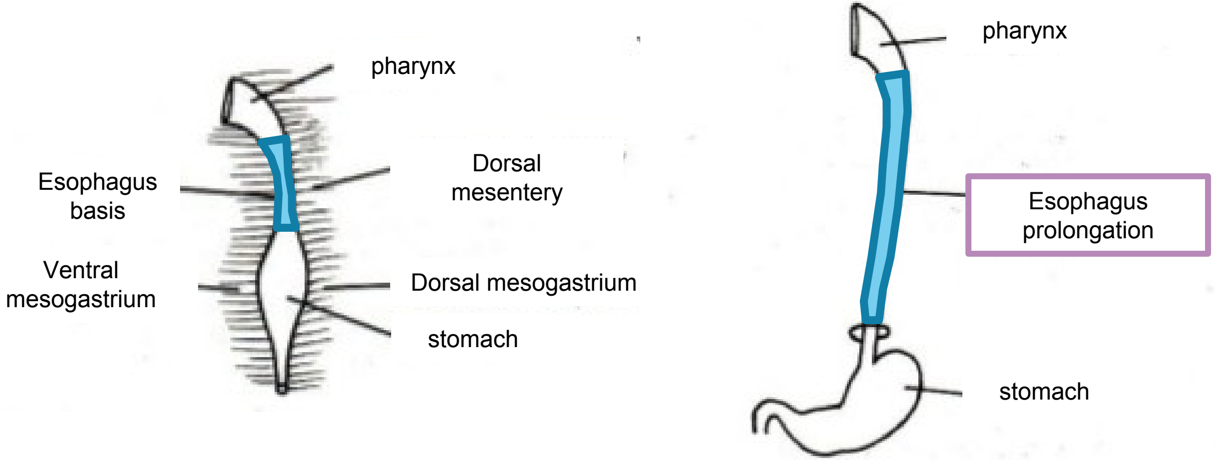


DEVELOPMENT OF ESOPHAGUS

- Separation of **laryngotracheal** tube in pharynx region, **dorsaly** basis of **esophagus**, **ventraly** basis of **trachea** and **lung**
- **Embryo** grows along **cranio-caudal** axis – separation of head and neck from thoracic cavity – **prolongation** of **esophagus**
- **Primitive esophagus** – multilayered cylindrical epithelium, prolongation, number of layers **lovered** → **proliferation** leads to narrowing of **esophagus** (no temporary encloser) in region of **tracheal biffurcation** → **recanalization**
- **Epithelial** cells start to form **cilia** → gradual **replacement with multilayered squamous** epithelium, **ciliary epithelium** preserved only in **cranial** region of esophagus
- **finally** – **cylindrical** epithelium only in **initial** and **final** regions of esophagus



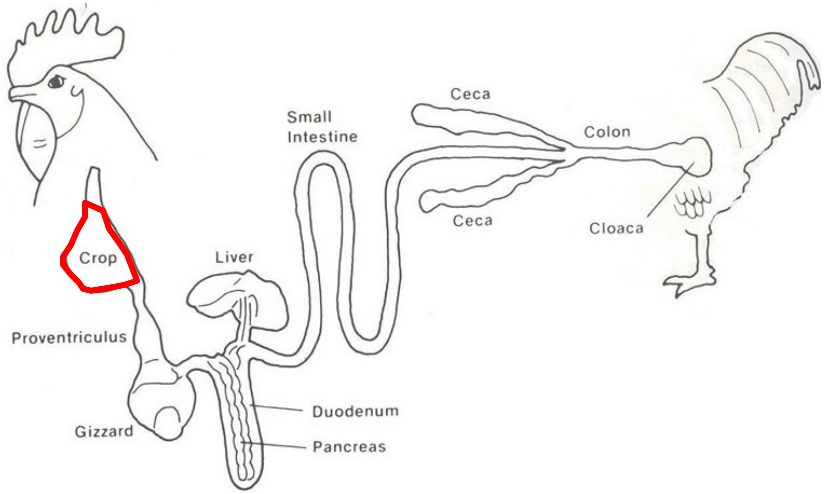
Veterian Key

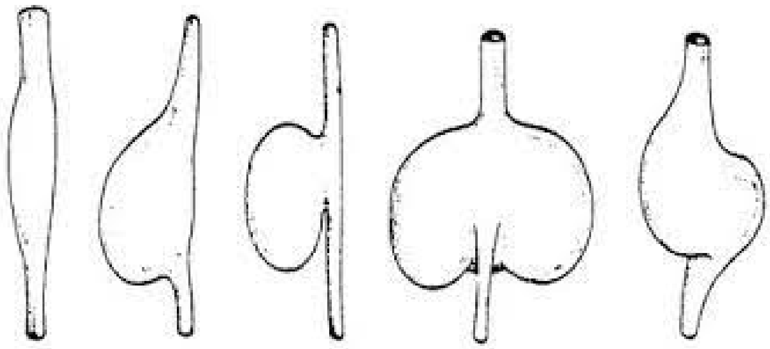


Sahar Hafeez

DEVELOPMENT OF CROP IN BIRDS

- Formation of **bag-like** extension from **ventral** side of **esophagus** in neck region
- Extended part of esophagus for food **storage**
- **morfology** based on species according to **type** of **food**



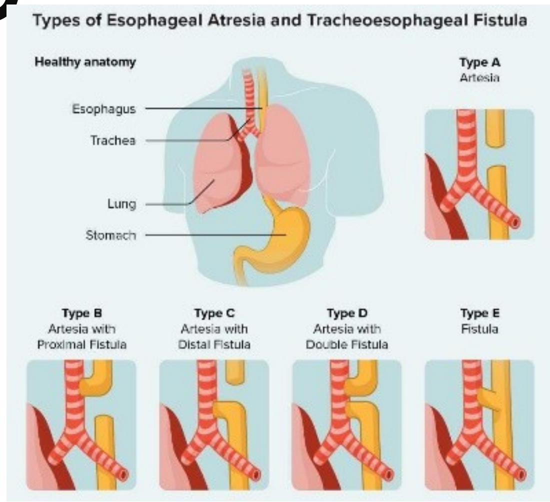


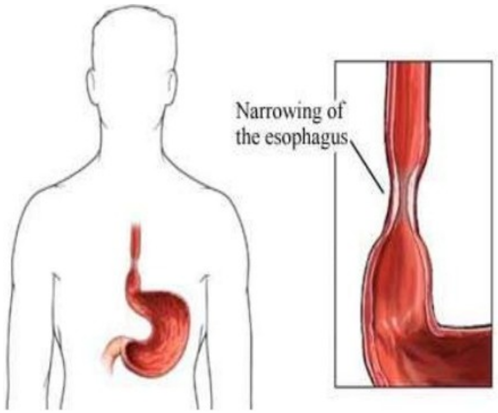
DEVELOPMENTAL DEFECTS OF ESOPHAGUS

- **Tracheoesophageal fistula**
  - Improper division of basis of trachea and esophagus
  - Persistent communication between them

- **Esophageal atresia**
  - Blindly ended termination of esophagus
  - Often connected with tracheoesophageal fistula

- **Congenital esophageal stenosis**
  - Narrowing of esophagus
  - Insufficient recanalization of esophagus
  - Problems in movement of food to stomach

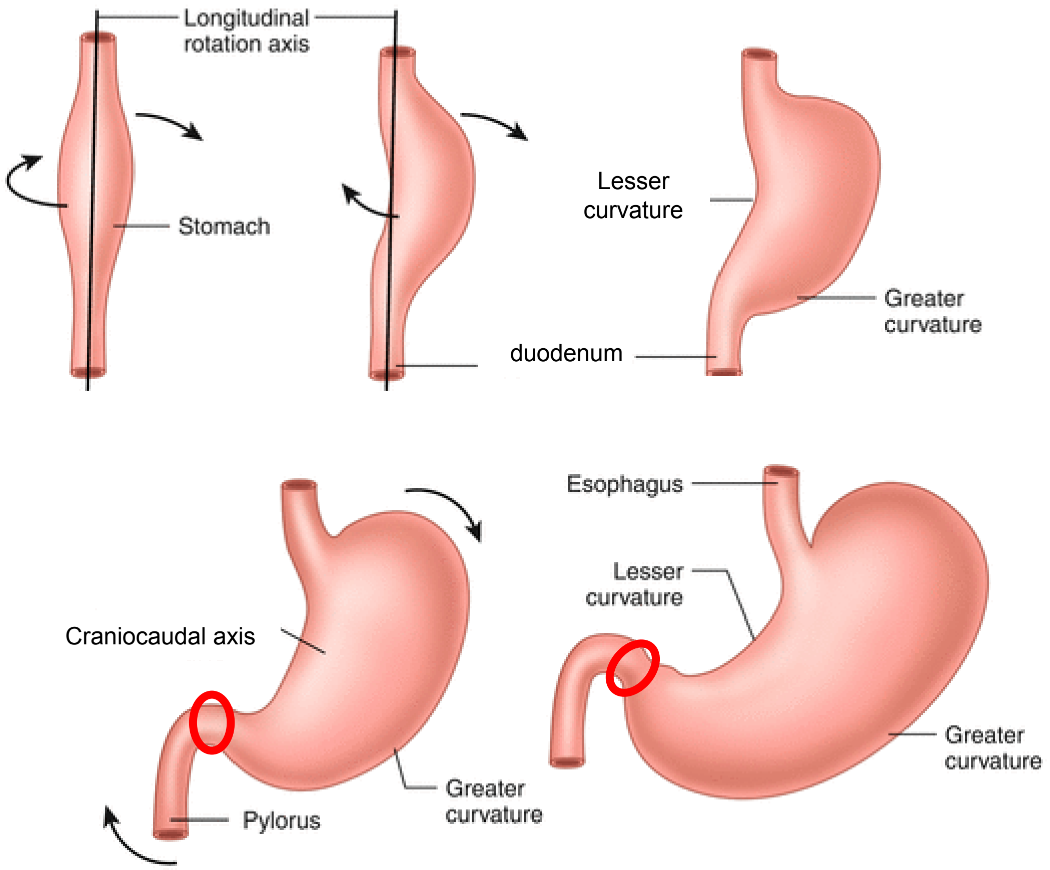




https://www.healthline.com/health/tracheoesophageal-fistula#types

DEVELOPMENT OF STOMACH

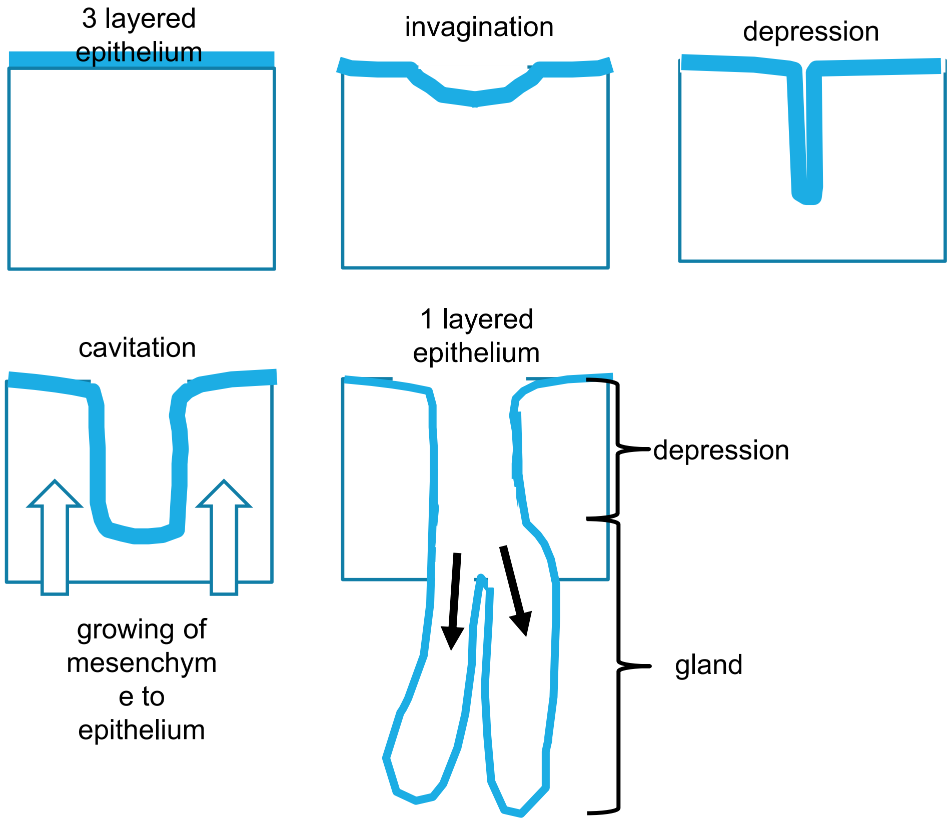
- Develops from **front** region of primitive gut
- **Expansion** of primitive gut endoderm, formation of larger cavity
- Rotation around **longitudinal** axis:
  - **left** side displaced **ventraly**
  - **right** side displaced **dorsaly**
- **left** cranial side grow **faster** than the **right** side → basis for **greater** curvature on **left** side, **lesser** curvature on **right** side
- Further growth results in **displacement** of former **cranial** part to the **left** and **caudal** to the **right**
- **proliferation** of **smooth muscle** cells **precursors** (mesoderm) on the **interface** of stomach and small gut – **pyloric sphincter**



Thomson, 2017. Embryology of the Stomach

FORMATION OF GASTRIC GLANDS

- Formation of **depressions** in epithelium (**invagination**) – basis of **gastric depressions,** 3 layered epithelium
- Epithelium further **invaginates** (grow) into underlying **mesenchyme**, formation of **cavities** in depressions, concurrent growth of **mesenchyme** to epithelium
- Rearrangement of cells, from **3** to **1** layered epithelium
- Invagination and proliferation of epithelial cells at the bottom of depressions → basis of **glands**

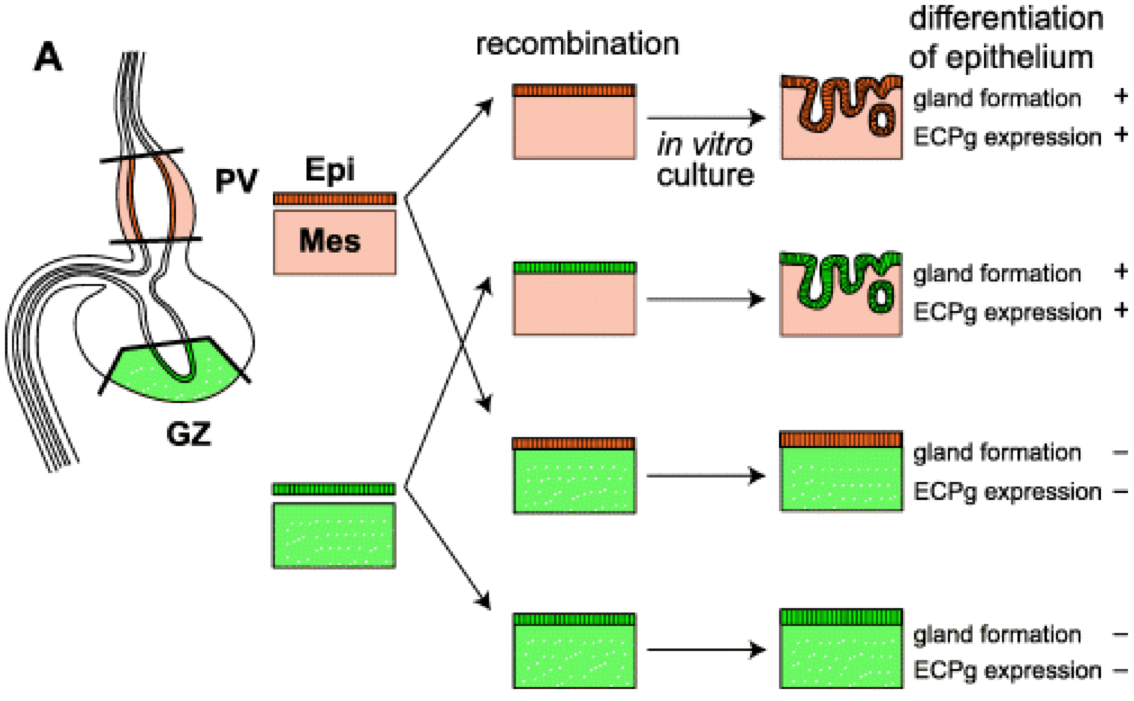


DEVELOPMENT OF TWO TYPES OF STOMACH IN BIRDS

- Two types of stomach:
  - cranialy – proventricle (**glandular**)
  - caudaly – **muscular** stomach

- **Glandular stomach** – **invagination** of epithelial cells into underlying mesenchyme, onset of **glands** developemnt, epithelium divided into **glandular** and **covering**, production of digestive **enzymes**
- **Muscular stomach** – formation of **thick smooth muscle layer** from underlying **mesenchyme**, **epithelial** cells differentiate and **keratinize**

- **Determining role of mesenchyme** – stomach epithelium specifically differentiate based on **factors** produced in underlying **mesenchyme**

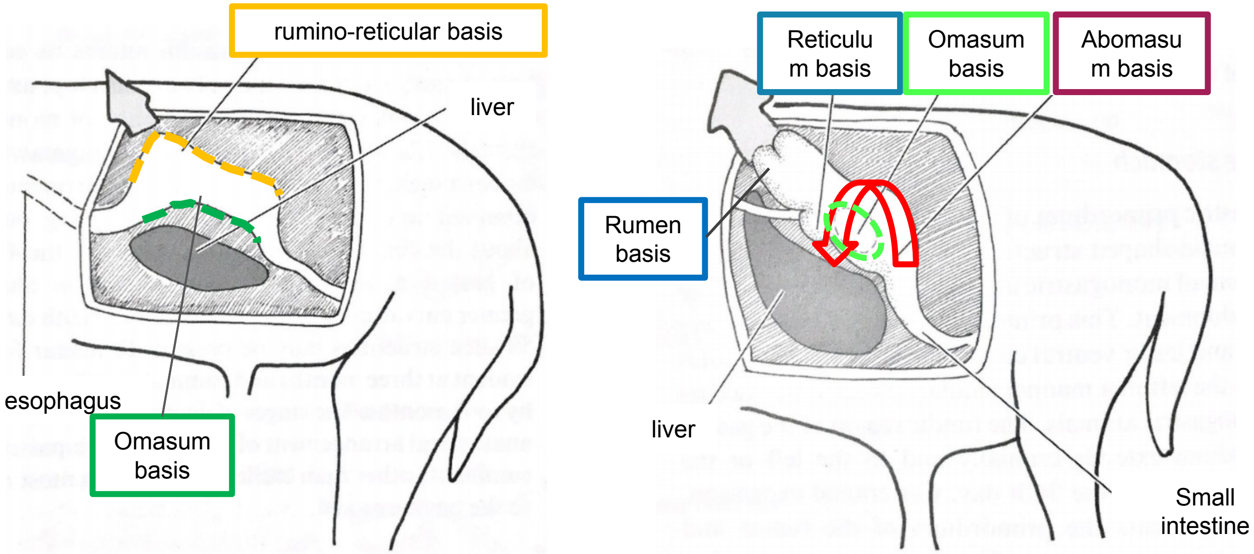


Takiguchi-Hayashi and Yasugi, 1986 – 1996, experiments

DEVELOPMENT OF STOMACHS IN RUMINANTS

- Three parts of prestomach, one main stomach:
  - rumen, reticulum, omasum
  - abomasum (stomach glands)
- Formation of spindle-shaped dilatation of the caudal region of foregut, **dorsaly** **greater** curvature, **ventraly** **lesser** curvature

- **greater** curvature – basis for **rumen** and **reticulum**
- **lesser** curvature – basis for **omasum**



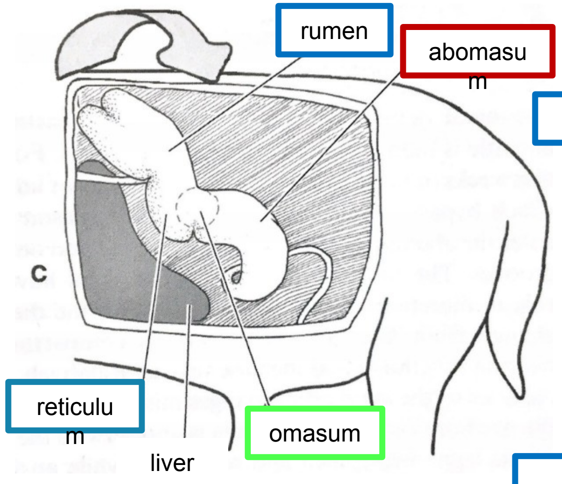
Edited: McGeady et al. Veterinary Embryology. 2009

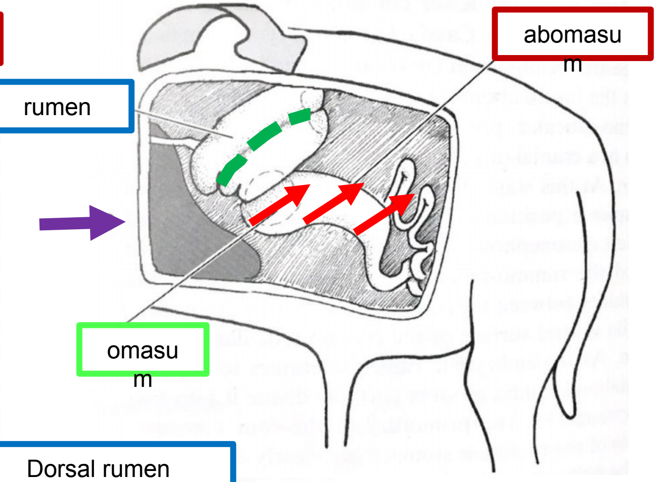
- Rotation around **longitudinal** axis:
  - **Dorsal** side displaced to the **left**
  - **ventral** side displaced to the **right**

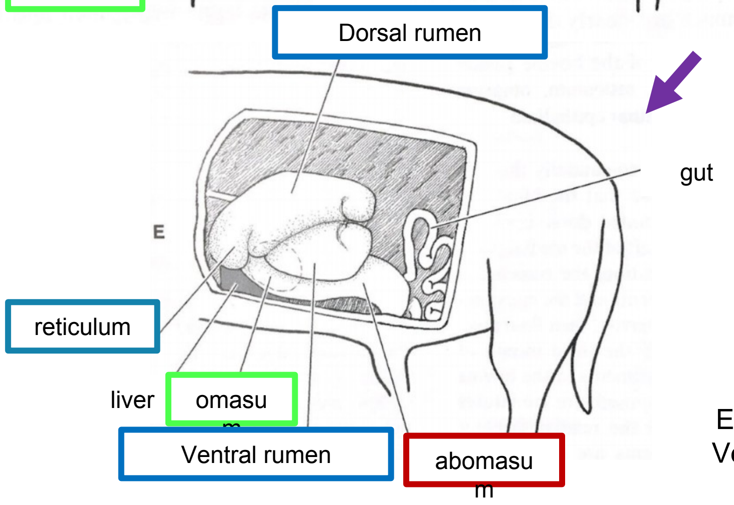
- **left** and **cranialy** – formation of **rumen** and **reticulum** basis
- **right** formation of **omasum** basis
- **right** and **caudaly** basis of **abomasum**

DEVELOPMENT OF STOMACHS IN RUMINANTS

- **Growth of rumen** and **reticulum** in **cranial** direction and **to the left**, stomach lining formed of **cylindrical** epithelium
- **groove** divides **rumen** into two parts and undergo **dorsocaudal rotation**
  - **former dorsocranial** direction, **now caudal** and **left direction**
- **rotation** of **rumen** causes **displacement** of other parts of stomach and gut to the **right**
- accelerated **growth** of **abomasum**, other parts grow slowly → **doubling** the **volume** compared to other parts
- lining:
  - **rumen**, **reticulum**, **omasum** – **replaced** with multilayered squamous epithelium
  - **abomasum** – cylindrical epithelium **preserved**, formation of **glands**



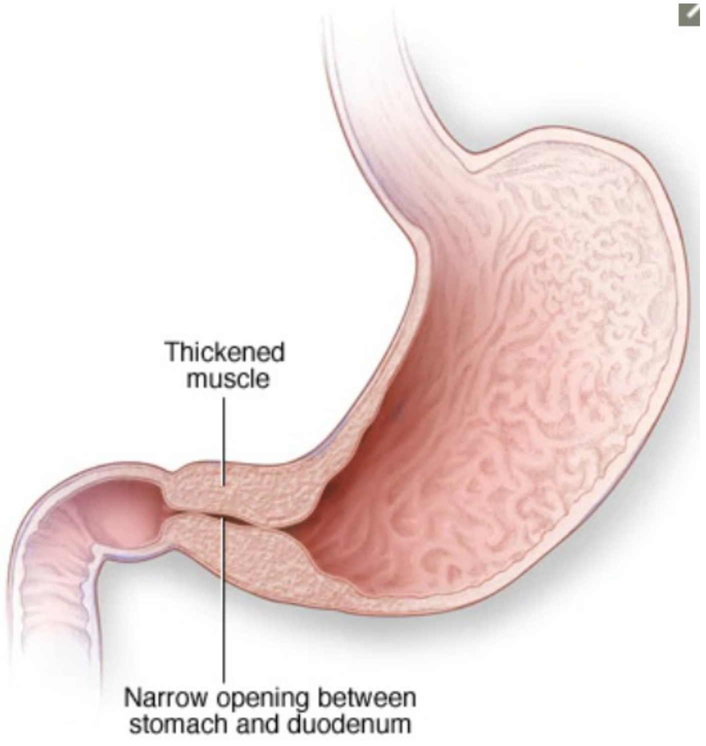




Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENTAL DEFECTS OF STOMACH

- **Hypertrophic pyloric stenosis**
  - Partial pyloric blocking of stomach
  - Hypertrophy of the pyloric sphincter muscle
  - Blockade of digested food transition from stomach to duodenum

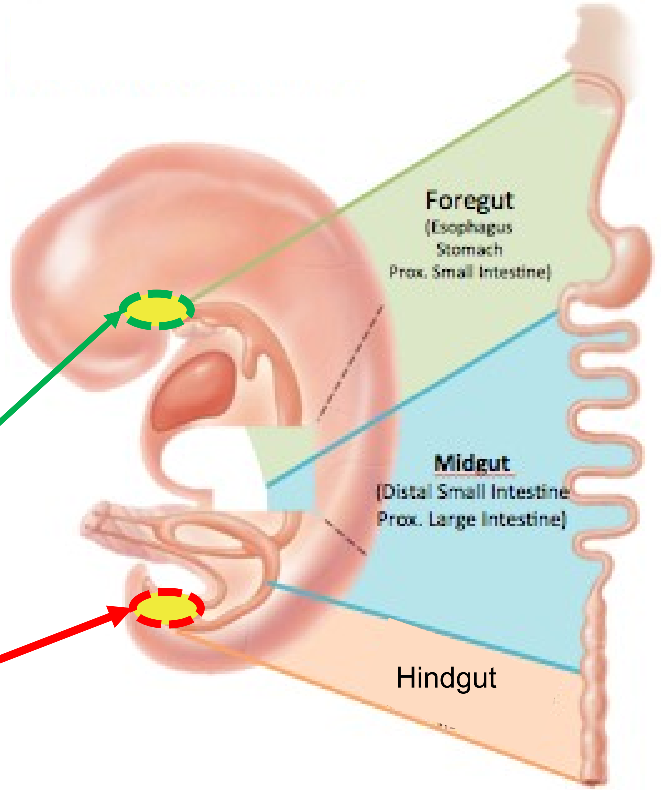


Mayo Clinic

FORMATION AND DEVELOPMENT OF PRIMITIVE GUT

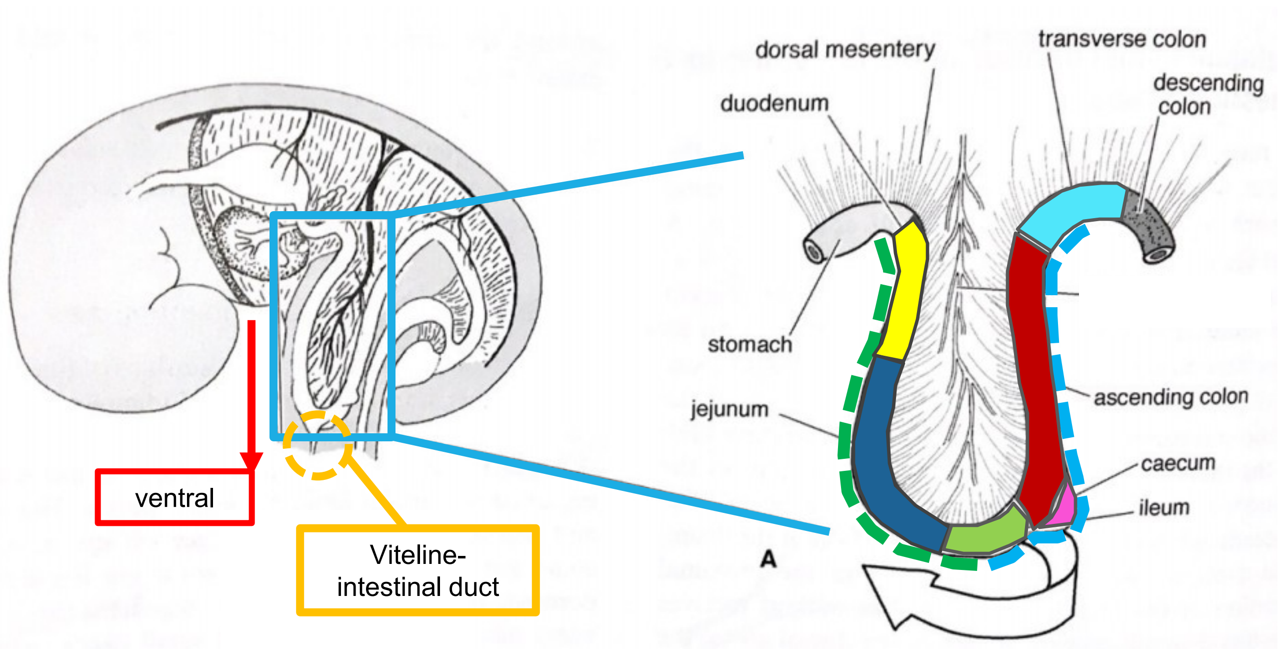
- blindly terminated tube of primitive gut connects cranial and caudal parts of the developing individual
- Primitive gut divided into three parts:
  - **foregut** – pharynx, esophagus, stomach, cranial part of duodenum
  - **midgut** – from liver bud to transversal colon
  - **Hindgut** – from transversal colon to cloacal membrane

- Gut endoderm connected with ectoderm on both sides, formation of two membranes:
  - **cranial** – connection with **primitive oral** cavity (stomodeum) – **oropharyngeal membrane**
  - **caudal** – connection with primitive anal opening (proctodeum) **– cloacal membrane**



INTESTINE DEVELOPMENT

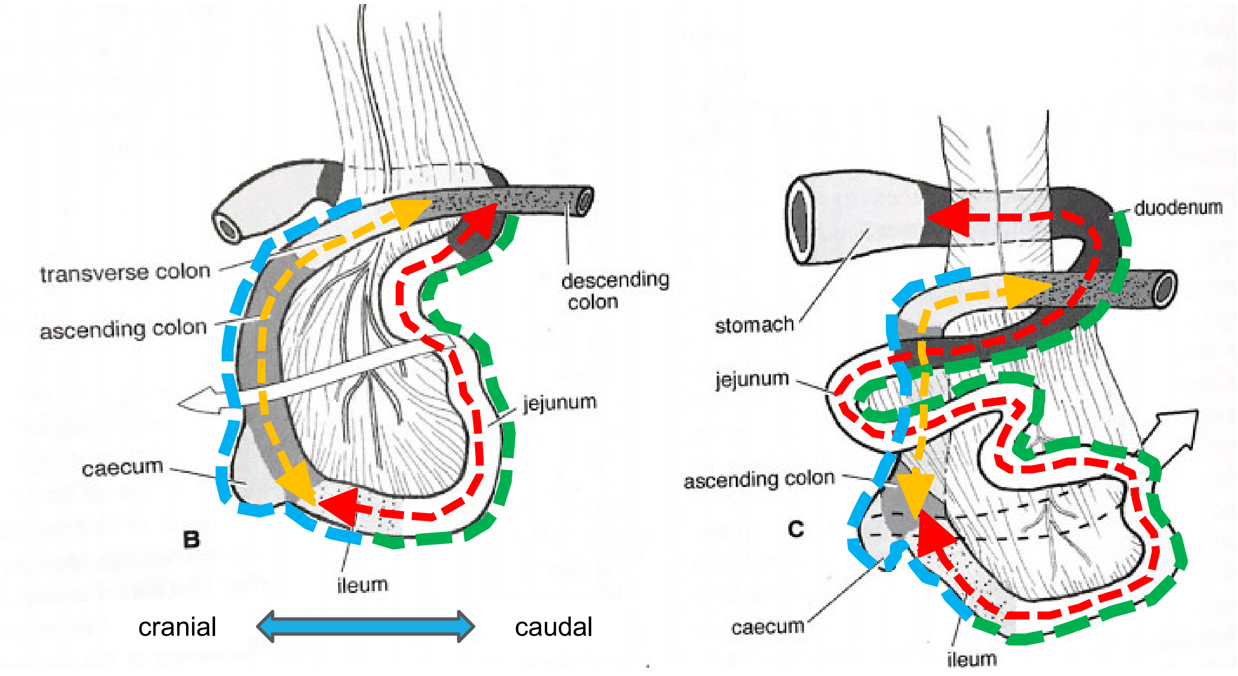
- Develops from caudal foregut, midgut and hindgut
- Prolongation of midgut – midgut loop formation **ventraly** (remnants of **viteline-intestinal duct** in the loop)
- **descending** loop– distal **duodenum**, **jejunum** and **ileum**
- **ascending** loop – distal **ileum**, **caecum**, **ascending colon**, part of **transverse colon**
- Prolongation of loop – temporary leave of abdominal cavity, located in extraembryonic cavity – **physiological umbilical hernia**
- Onset of dorso-ventral rotation



Edited: McGeady et al. Veterinary Embryology. 2009

INTESTINE DEVELOPMENT

- Dorso-ventral rotation –180^{O} transfer of structures
- **descending** loop structures→ **caudal**
- **ascending** loop structures→ **cranial**
- **Prolongation of descending** part – formation of coiled loops –**small intestine** basis
- **ascending** part, basis of **colon** and **caecum**, **slower growth**
- Further growth– **not enough space** in extraembryonic cavity – **return of** descending and ascending parts to abdominal cavity



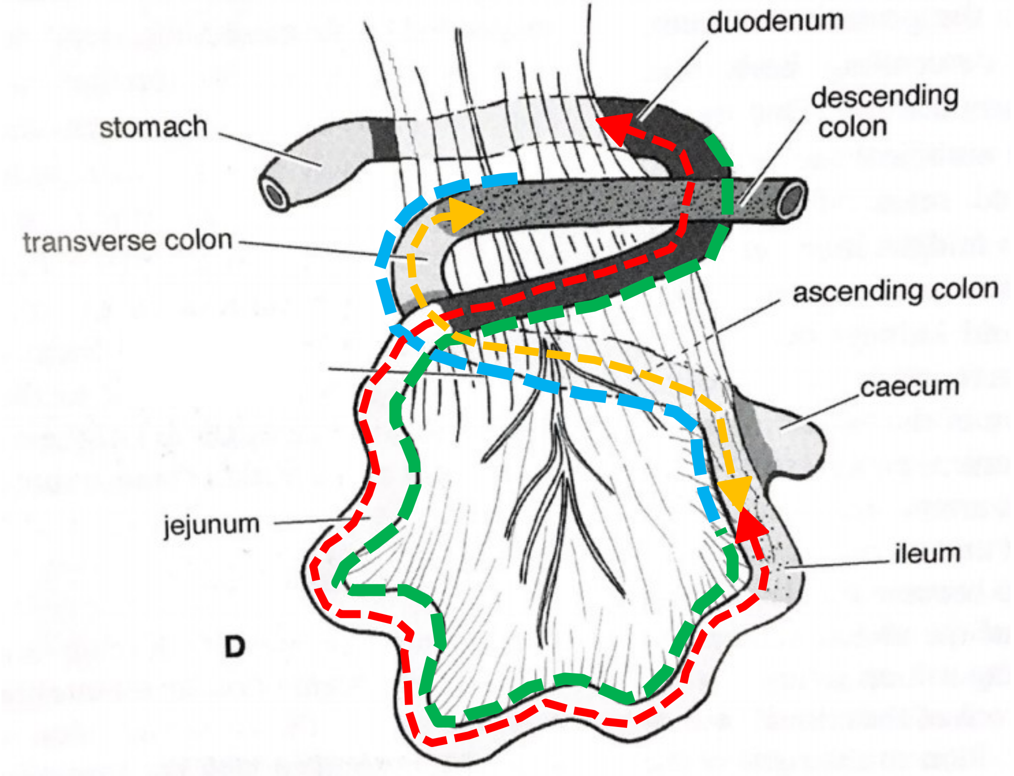
Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF INTESTINE

- **return** of intestine to cavity causes further rotations

- Further **prolongation** of coiled loops in forming **small intestine** and **colon**

- Structures movement:
  - originally **descending** moved left
  - originally **ascending** moved right
  - basis of descending **colon** left

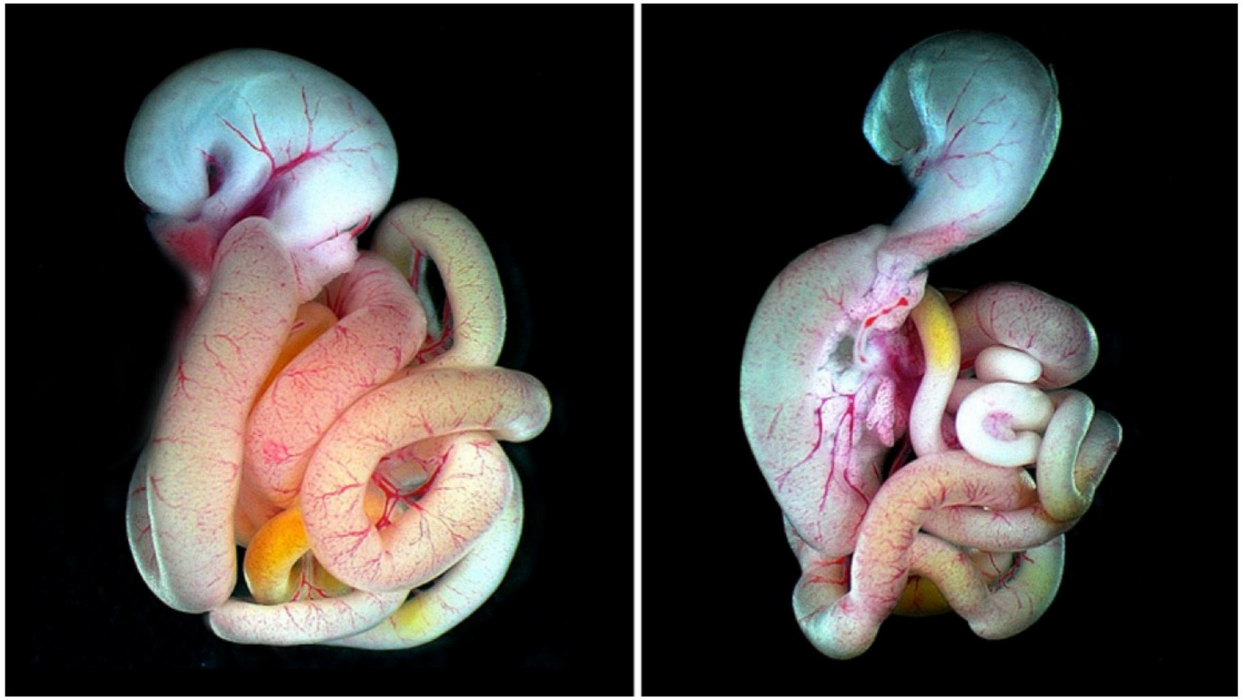


Edited: McGeady et al. Veterinary Embryology. 2009

Video: https://www.news-medical.net/health/Malrotation-of-the-Gastrointestinal-Tract.aspx

INTESTINE TWISTING

- **Bowl of spaghetti** look**?**
- **What molecule is responsible for this twisting?**
- connective tissue molecule **hyaluronan**
- **decorated** with **amino acids** chains – only on **right side** of the **gut**
- **accumulation** of **modified hyaluronan** on **right side**
  - **right side expansion**
  - **tilting the intestine leftward**
  - **triggering rotation**



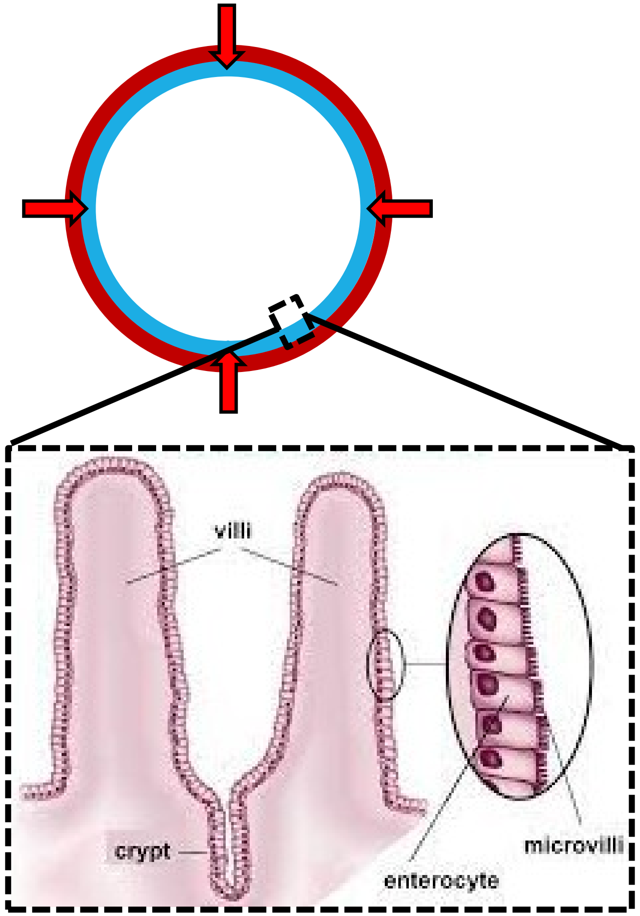
WT embryo

Embyro mut

Kurpios et al. 2018. Nature

INTESTINE DEVELOPMENT

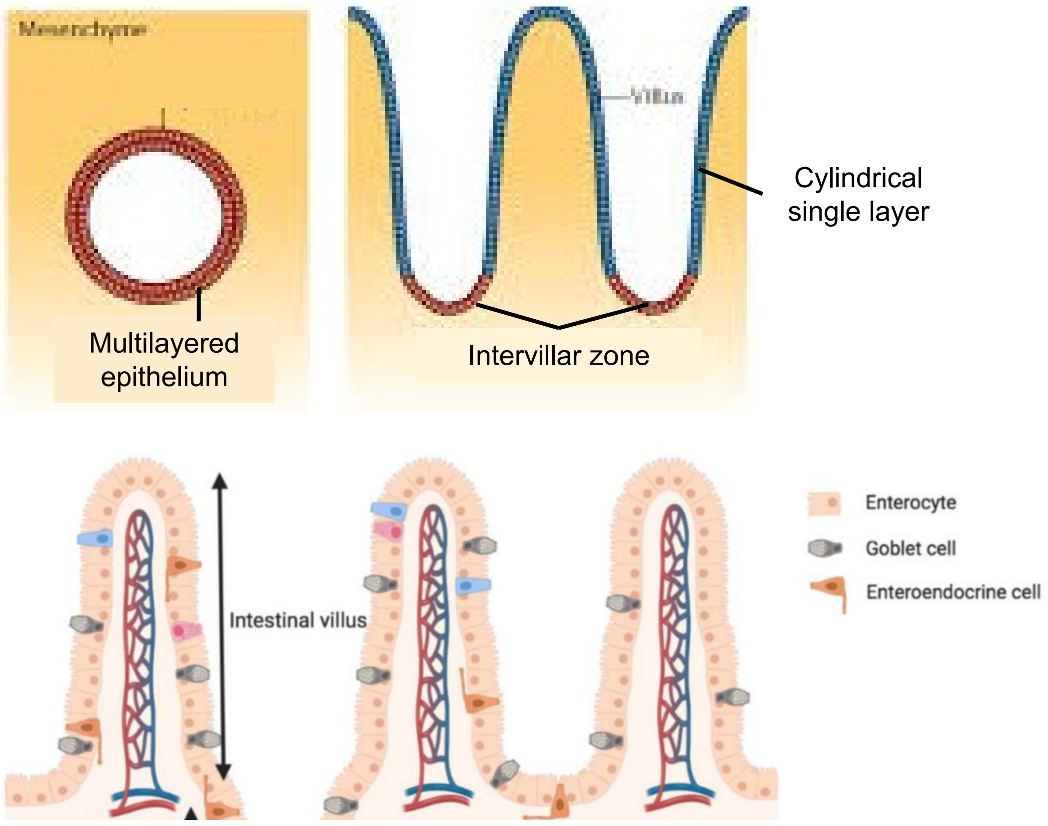
- **endoderm** – intestine lining
- **mesoderm** – vessels, muscular layer, connective layer
- **endodermal** cells **differentiate** → growth, thickening and **diffentiation of mesoderm** to **smooth muscle** cells
- Formation of specific intestinal mucosa – **crypts** and **villi**



Teach me Physiology

SMALL INTESTINE DEVELOPMENT

- intensive **proliferation** leads to partial or complete **blocking** of intestinal **lumen**–**recanalization** via vacuoli formation and their fusion
- First **villi** formed in **duodenum** – **proliferation** and **infiltration of mesenchymal cells** into multilayered epithelium, villi **start** to form in **duodenum** and follow to ileum
- Epithelium transformed from **multilayered** into **single** layered
- formation of **intervillar zone** –intensively proliferating cells
- Epithelium of villus – differentiation to **enterocytes**, **Goblet** cells, **enteroendocrine** cells



Zhang et al. 2019. MDPI Animals

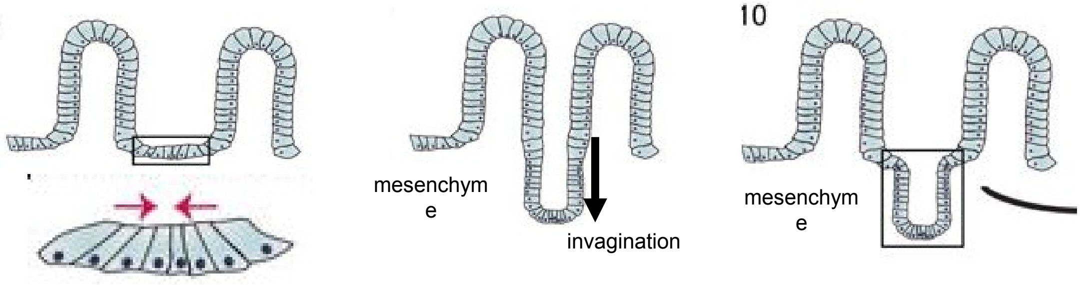
CRYPT FORMATION

- **Intervillar zone** – onset of **invagination**, so called **apical constriction**

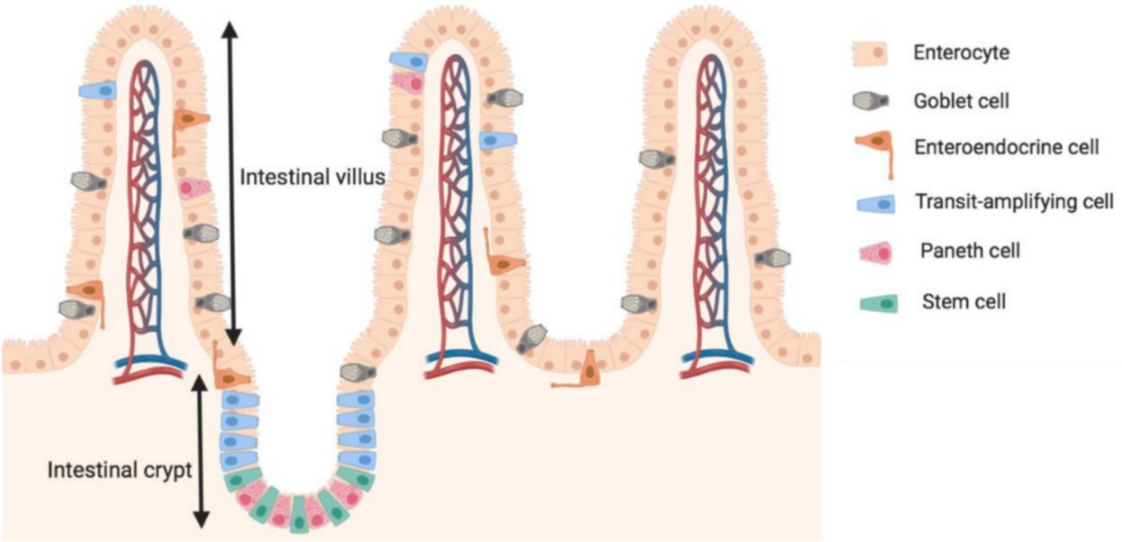
- cells **proliferate** and **invaginate** into underlying mesenchyme

- Formation of **crypts** – **progenitor** cells supply

- Three cell types:
  - **Stem cells** – source of immature progenitors
  - **Transit-amplifying cells**
  - **Paneth cells**



Sumigray et al. 2018. Dev Biol



Zhang et al. 2019. MDPI Animals

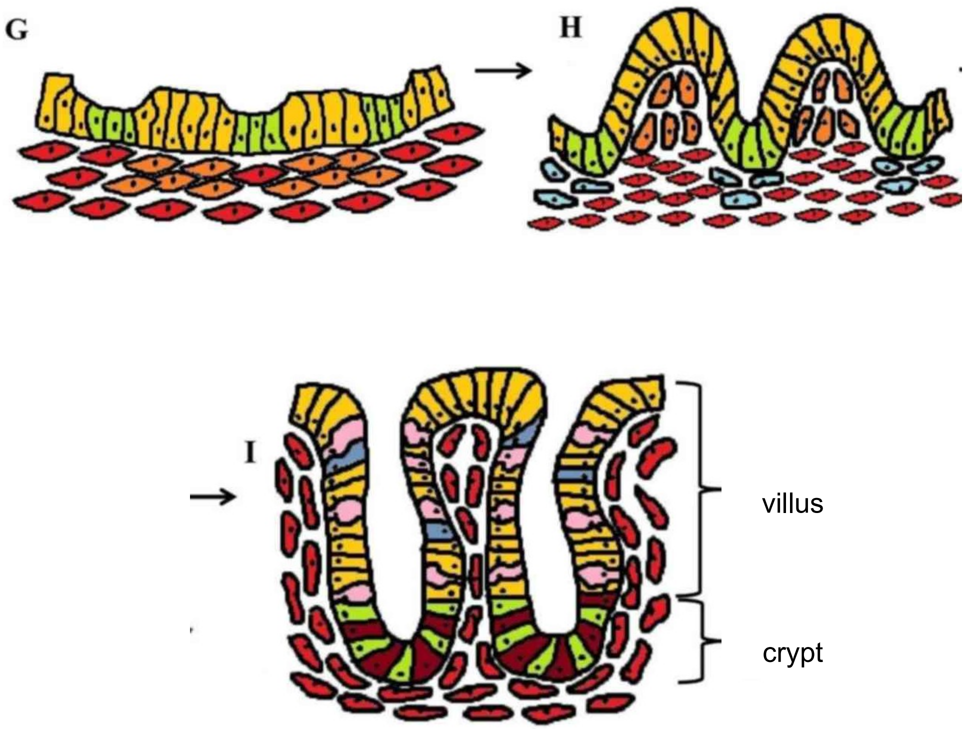
DEVELOPMENT OF COLON

- Develops from **mid** and **hindgut**

- **villi** and **crypts** form at the same time (compared to small intestine) from **endoderm**, **migration** of mesenchymal cells to forming villi

- Thickening of **apical** parts of villi during development
- **flattening** and transformation of villi **in width** – villi specific for small intestine disappear
  - **Enterocytes**
  - **Enteroendocrine** cell
  - **Goblet** cells

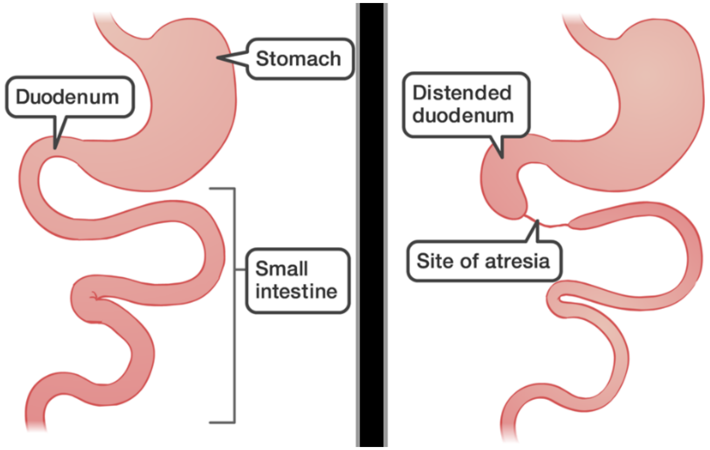
- Spaces between villi spaces develop into permanent crypts
  - **Stem** cell
  - **Paneth** cells



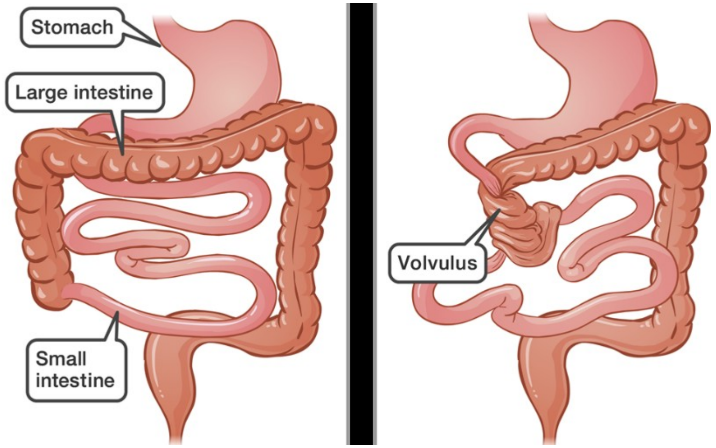
Kostorous et al. 2020. Int J Mol Med

DEVELOPMENTAL DEFECTS OF INTESTINE

- **Intestinal atresia**
  - Insufficient growth or recanalization
  - Often in duodenum
  - Results in vomiting, intestinal obstruction
  - Surgery



- **Altered intestinal rotation with volvulus**
  - often connected with missing mesentery
  - Caused by mislocalization of intestine during migration back to abdominal cavity and altered rotation
  - Knotting of intestinal mesentery and obstruction
  - surgery

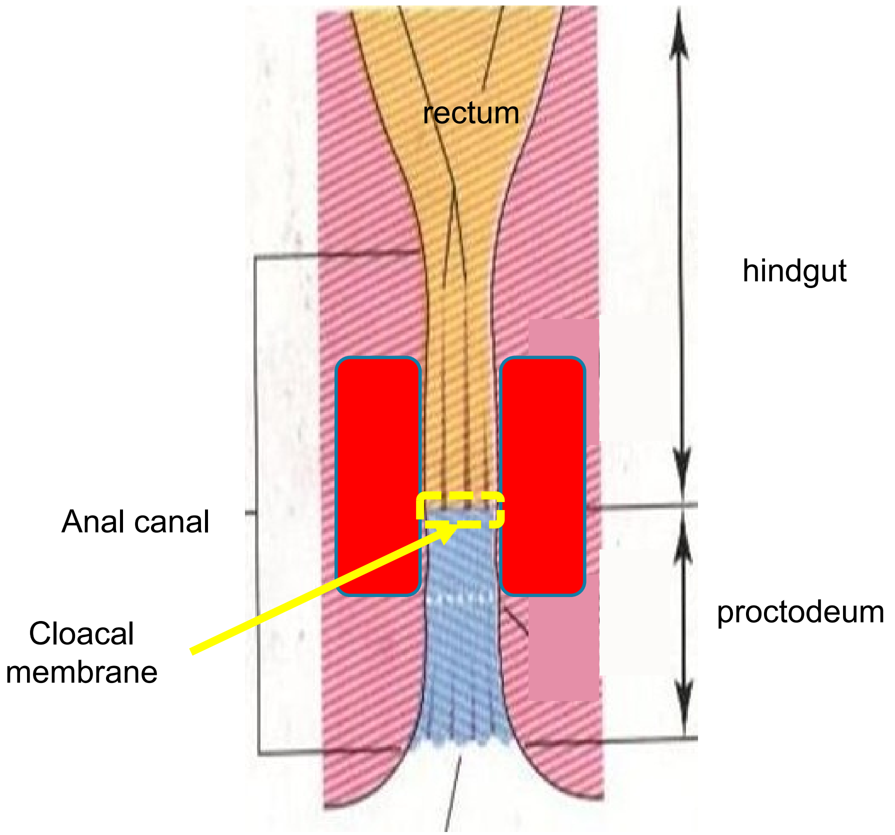


DEVELOPMENT OF RECTUM AND ANAL CANAL

- **terminal** part of digestive tube

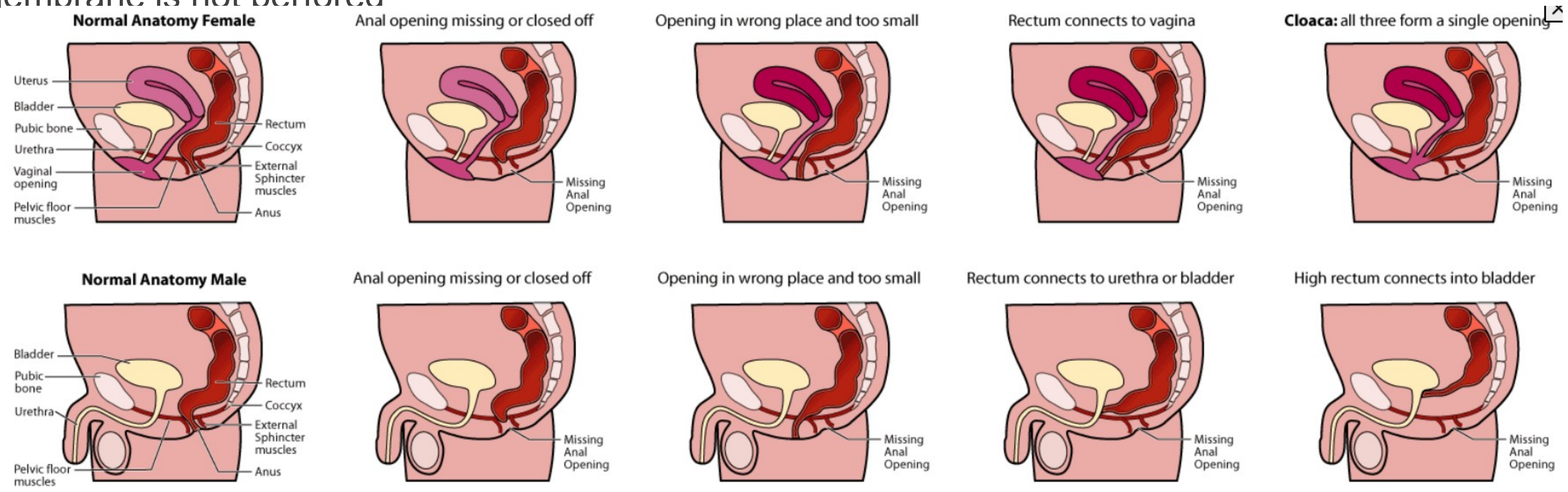
- Partly from **endoderm** of hindgut
- Partly from **ectoderm,** so called **proctodeum** (primitive anal opening)

- Connection between endoderm and ectoderm – **cloacal membrane**, rupture and formation of opening between digestive system and external environment
- Anal sphincters develop from **mesoderm**



DEVELOPMENTAL DEFECTS OF RECTUM AND ANAL CANAL

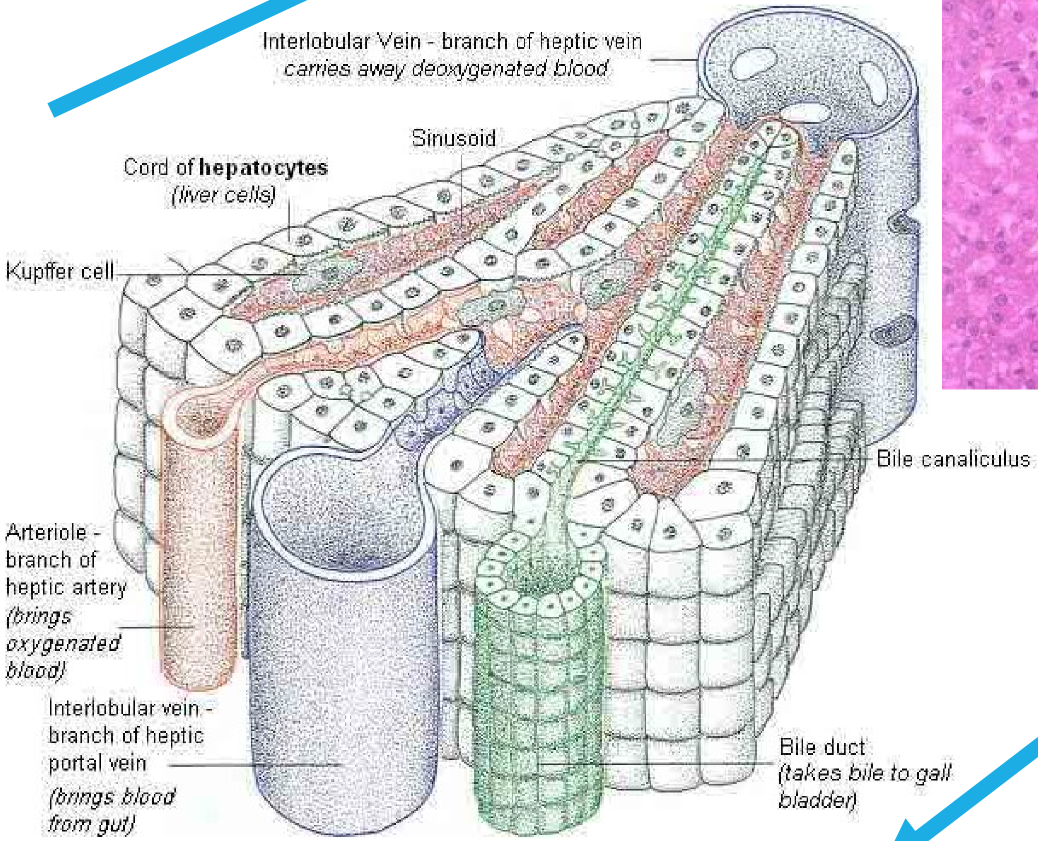
- **Displaced development of anus**
  - Insufficient development and blindly terminated rectum
  - Formation of fistula to other developing structures (urethra, bladder, penis, vagina)
  - Anus developed ectopically
  - Narrowing of anal canal
  - Cloacal membrane is not perfored

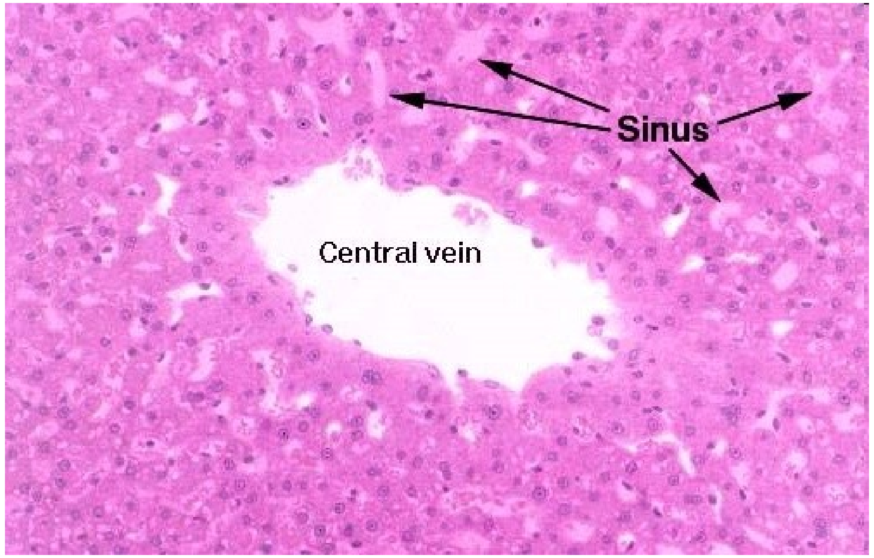


UCSF. Dep Surgery

LIVER – STRUCTURE OVERVIEW

Blood

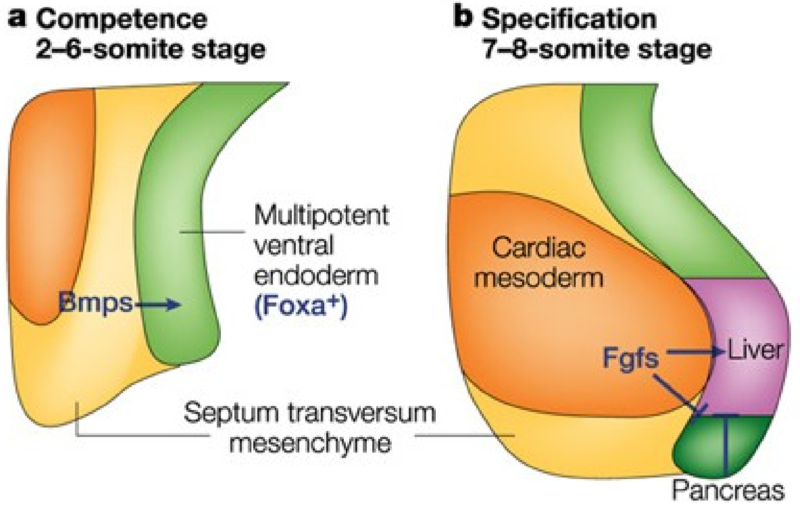


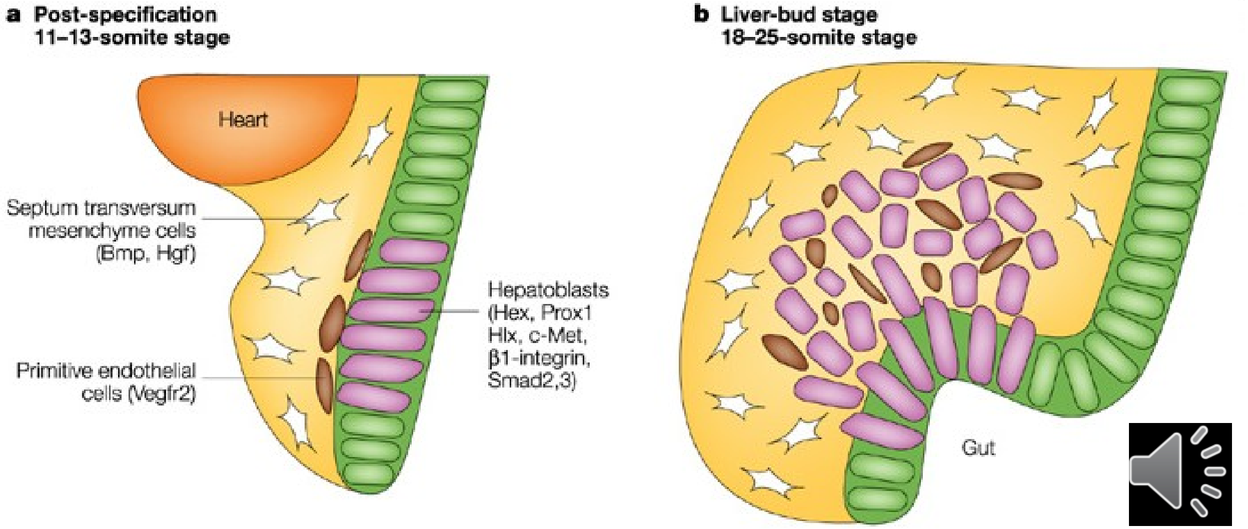


Bile

http://www.biologymad.com

LIVER LOCATION INDUCED BY CARDIAC MESODERM

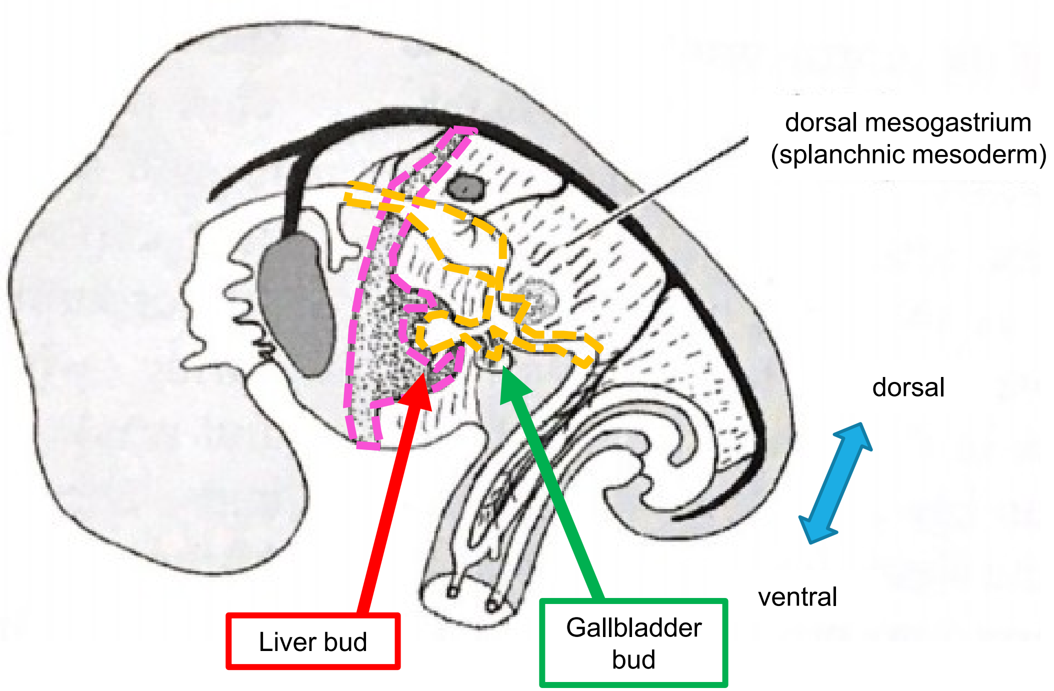




K.S. Zaret, Nature Reviews Genetics 3, 499-512, 2002

DEVELOPMENT OF LIVER

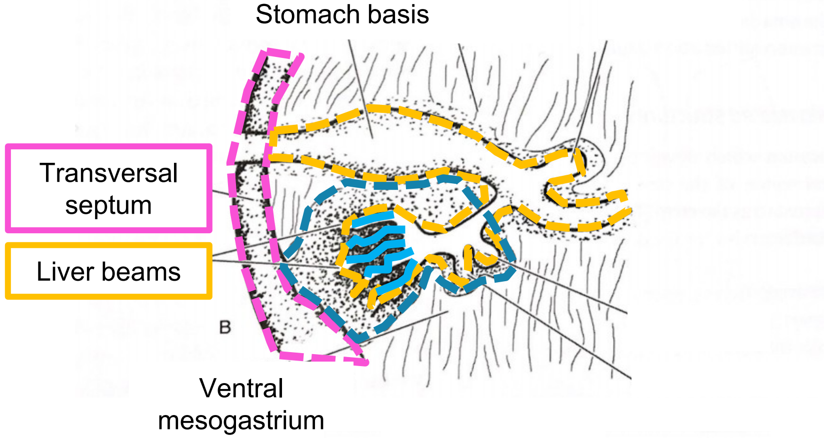
- Interface between **foregut** and **midgut**
- **Yolk sac** detaches from intestine
- **transversal septum** region (basis for diphragma)
- Interaction between **endoderm** of primitive **gut** and **mesenchyme** from **splanchnic** mesoderm
- **ventral** side of caudal area of **foregut** – formation of **liver diverticle** → basis for **liver** and **gallbladder**
- Basis for **liver** – **pars hepatica** (larger part cranialy)
- Basis for **gallbladder** – **pars cystica** (smaller part caudally)

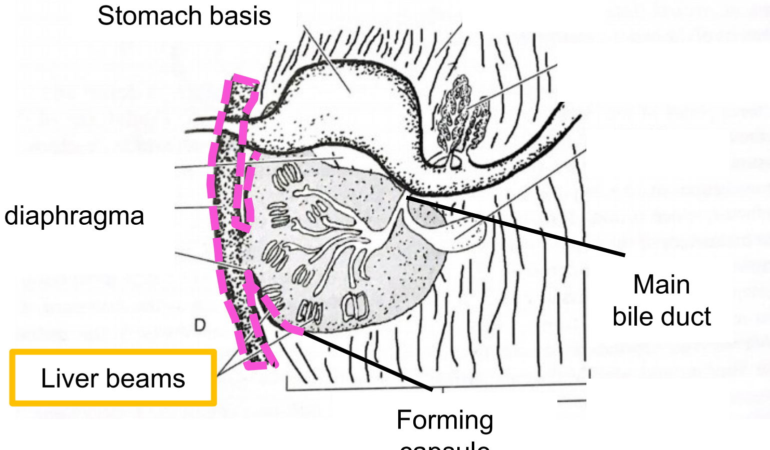


Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF LIVER

- **endodermal** liver basis grow cranio-ventraly into **ventral mesogastrium** (splanch. mesoderm) and reaches the **transversal septum**
- Epithelial cells proliferate (endoderm) – differentiate into **hepatoblasts** (liver cells) – furter growth into mesenchyme of **transversal septum**
- **hepatoblasts** form **liver beams**
- Formation of liver **sinusoids** (capillaries) from **mesoderm**
- Part of former diverticle between basis of liver and primitive gut – **main bile duct**
- From septum mesenchyme **capsule** is **formed**

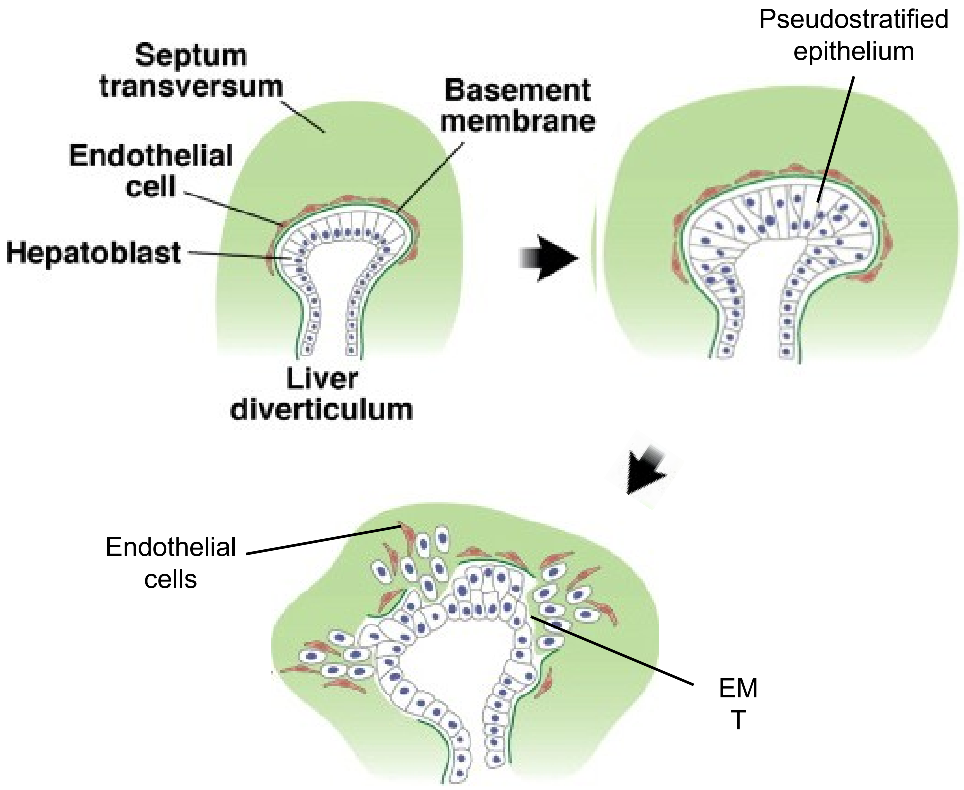




Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF LIVER

- Lining of bud formed from endodermal cells - **hepatoblasts**
- Condensation of **endothelial** cells – vessels formation
- Transformation from **cylindrical** cells to **pseudostratified** epithelium
- **Epithelio-mesenchymal transition (EMT)** – hepatoblasts leave liver beams, **migrate** and settle **mesenchyme** of transversal septum
- **endothelial** cells intercalate to migrating hepatoblasts – formation of **liver sinusoids** (exchange of metabolites between capilaries and hepatoblasts)



Lemaigre, 2009. Rev Basic Clinic Gastroenter

DEVELOPMENTAL DEFECTS OF LIVER

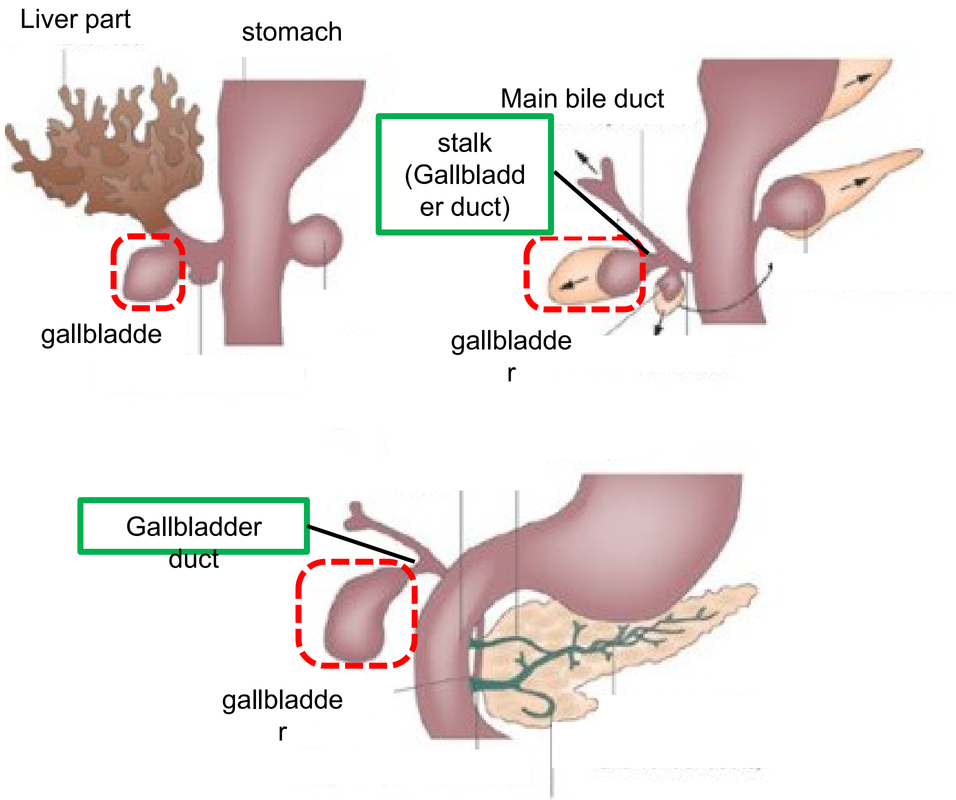
- **Liver agenesis**
  - Complete liver absence
  - lethal

- **Absence or liver lobes hypoplasia**
  - One or more parts of liver do not develop
  - Insufficient development of liver
  - Often connected with free gallbladder

- **Main bile duct agenesis**
  - Excretion directly to gallbladder
  - Excretion through gallbladder to duodenum
  - Very rare

DEVELOPMENT OF GALLBLADDER

- **ventral** of the caudal **foregut** – formation of **liver diverticle** → basis for **liver** and **gallbladder**
- Gallbladder basis is getting bigger and **prolonged**, formation of **gallbladder duct** (**stalk)**
- **Gallbladder duct** first hollow tube – **proliferation** leads to **solid structure**– **recanalization** by formation of vacuoles in endodermal cells
- Embryonic atrophy of gallbladder – horse, rat, whale



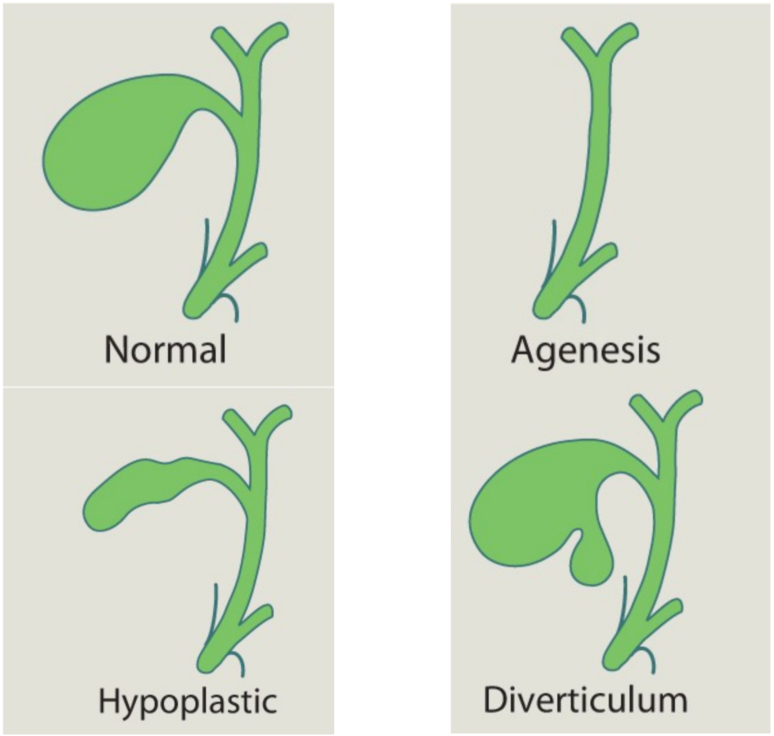
Cardinale et al. 2012. Nat Rev Gastroenterol Hepatol

DEVELOPMENTAL DEFECTS OF GALLBLADDER

- **Gallbladder agenesis**
  - Complete absence of gallbladder
  - Gallbladder does not outgrow from liver diverticle (pars cystica)

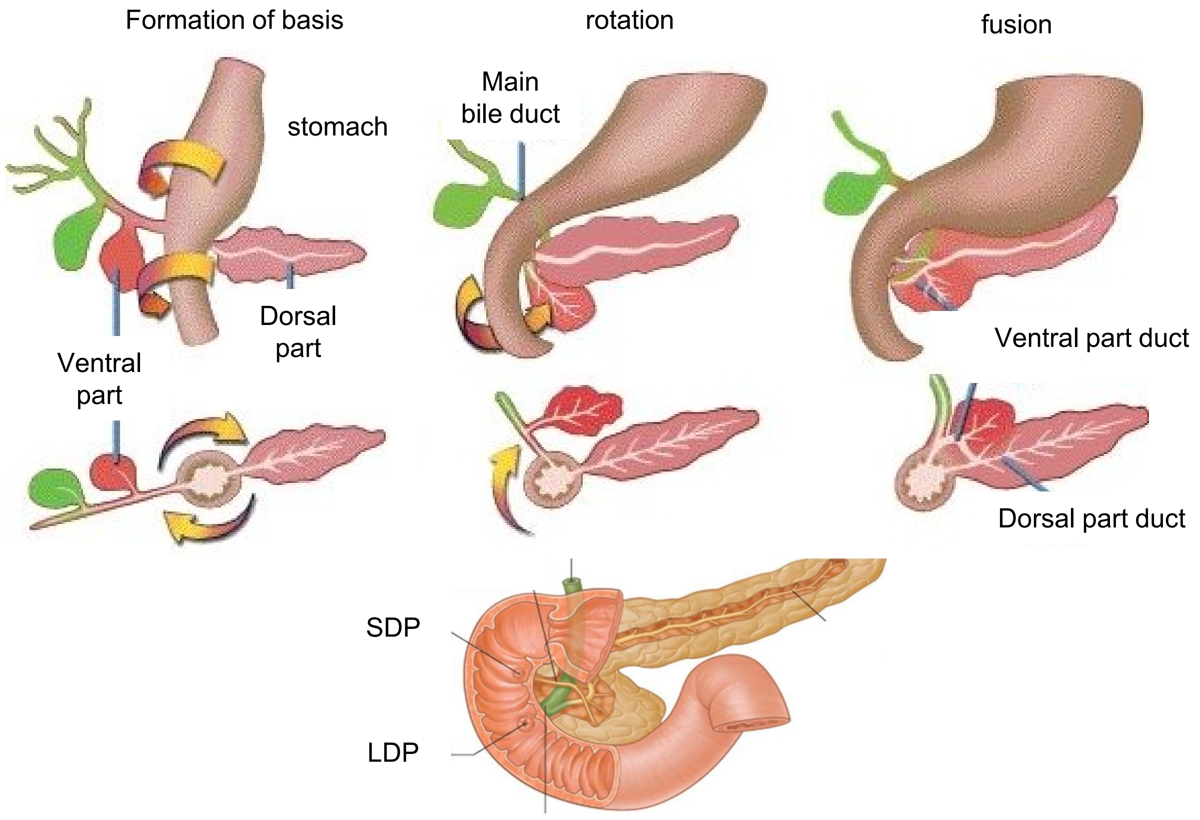
- **Gallbladder hypoplasia**
  - Insufficient growth of gallbladder
  - Only small basis of gallbladder

- **Gallbladder cleft**
  - Gallbladder basis split into two basis during development (diverticulum)



DEVELOPMENT OF PANCREAS

- **Two basis** from foregut **endoderm**:
  - **dorsal** – develops earlier
  - **ventral** – later from liver diverticle
- **rotation** of stomach and intestine – ventral part **moves** and contacts dorsal part
- **fusion** of parts **–** formation of one structure
- **ventral part duct** – main pancreatic duct conects to main bile duct, together form **larger duodenal papilla (LDP)**
- **dorsal part duct** – additional pancreatic duct, forms **smaller duodenal papilla (SDP)**

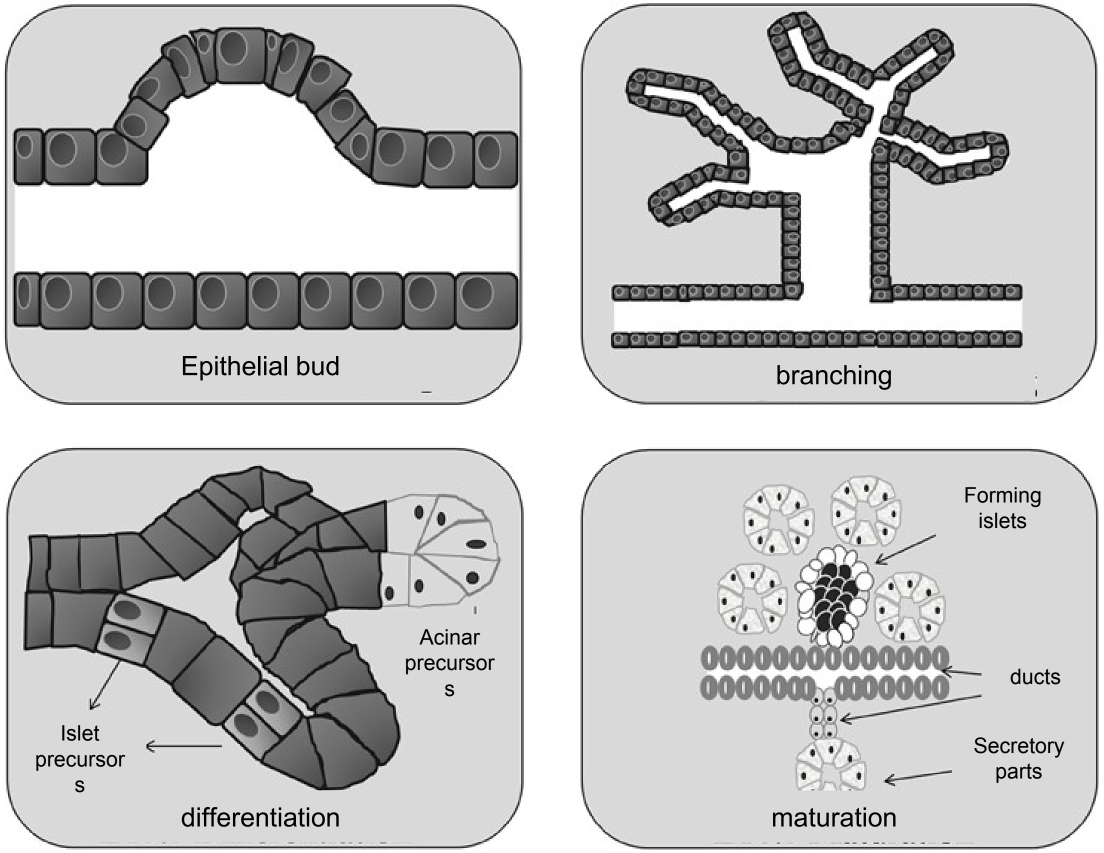


Gorelick et al. 2003. Gastrointestinal Teaching Project

DEVELOPMENT OF PANCREAS

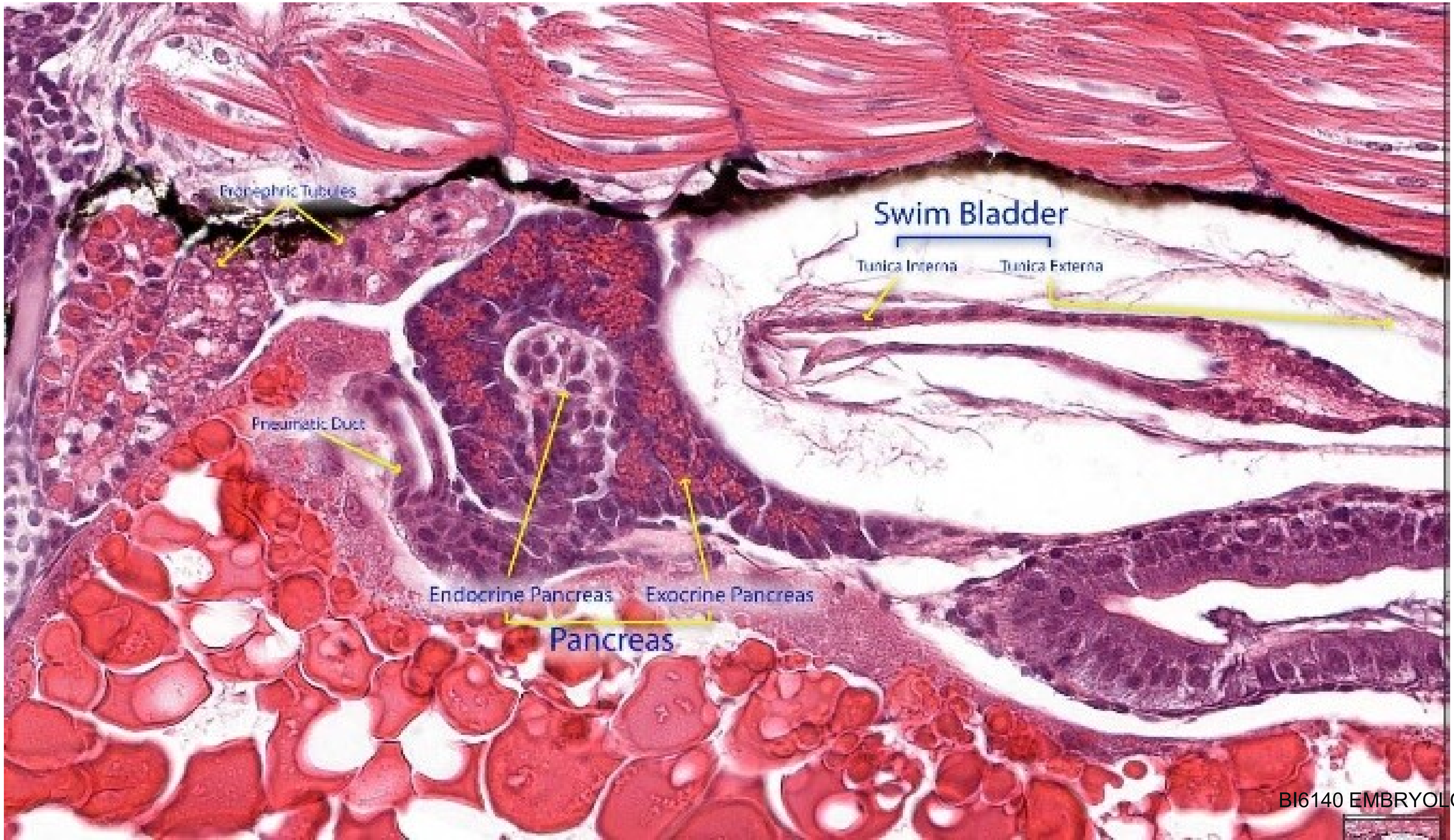
- **invagination** of epithelial (endoderm) bud into surrounding mesenchyme (splanchnic mesoderm)
- Epithelial cells proliferate, **branching** to mesenchyme
- Onset of **differentiation** of cells
  - Cells of **ducts** – form excretory canals
  - **acinar** cells – exocrine pancreas
  - Cells of **islets** – endocrine pancreas

- **acinar cells** – formation of **secretory parts** connected to ducts leading to duodenum, **exocrine** cells
- Cells of **islets** – **epithelial-mesenchymal** transition, migration into mesenchyme, differentiation to **endocrine** cells, vesseles formation

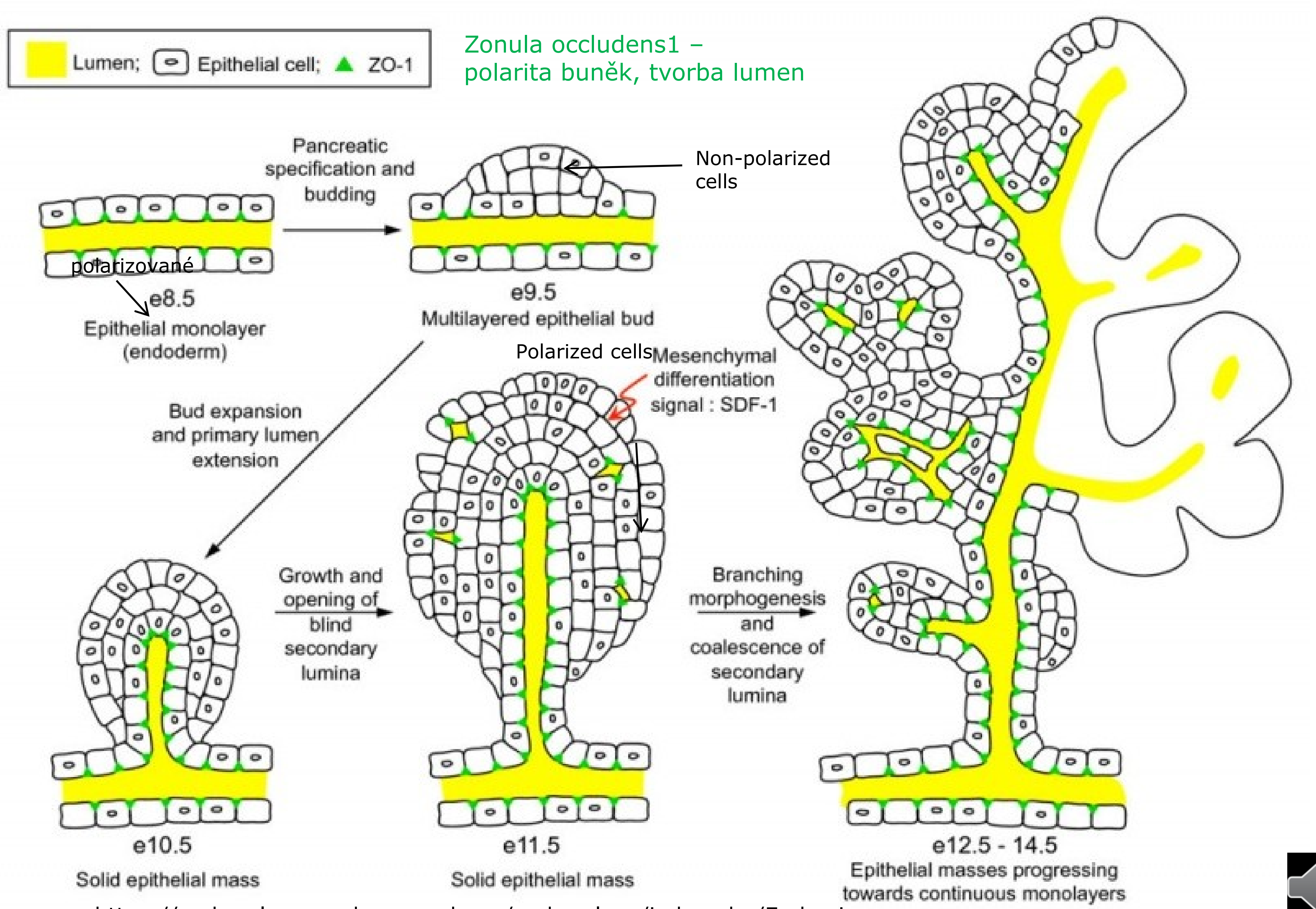


O´Dowd and Stocker, 2013. Front Physiol

ZEBRAFISH DIFFUSE PANKREAS



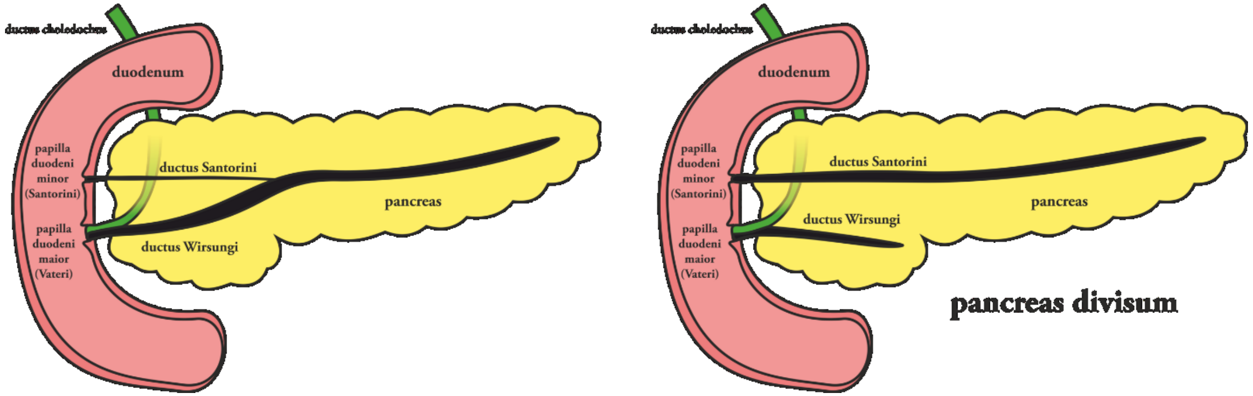
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2990215



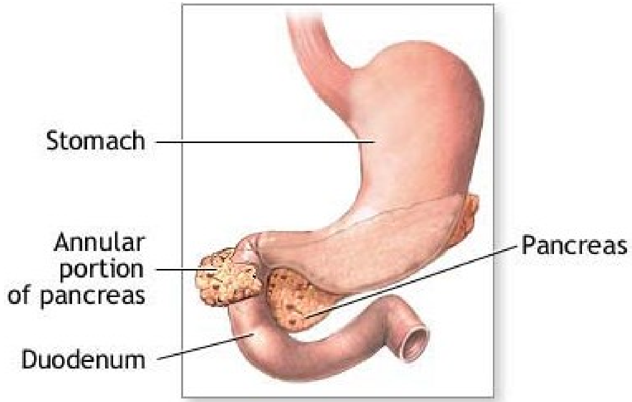
https://embryology.med.unsw.edu.au/embryology/index.php/Endocrine_-_Pancreas_Development#Developing_Pancreatic_Islets

DEVELOPMENTAL DEFECTS OF PANCREAS

- **Pancreas divisum**
  - Dorsal duct do not fuse with bile duct
  - Larger dorsal part drain pancreatic products through smaller duct
  - smaller ventral part drain to main bile duct
  - Insufficient drainage – inflammation of pancreas
  - 4 – 14 % population

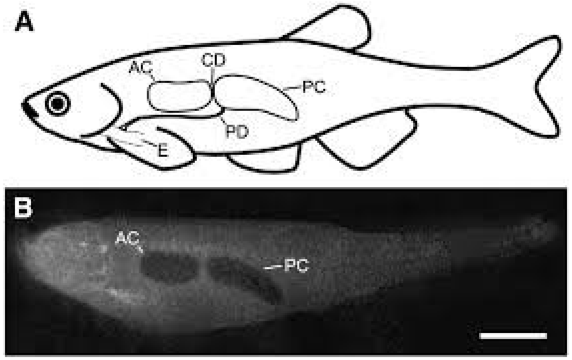


- **Anular pancreas**
  - The most often congenital defect of pancreas
  - Defect in rotation of ventral part
  - Formation of ring of panreatic tissue around duodenum
  - In majority of patients leads to partial or complete blockade of duodenum



https://www.sciencedirect.com/science/article/pii/S1566070210001840?via%3Dihub

GIT IN DANIO RERIO



- **Swimbladder**
- Functions – buoyanc (in teleosts), secretion of ions
- Dorsal outgrowth of foregut
- pneumatic duct degenerates in teleosts (inflating by oxygen from the circulation)

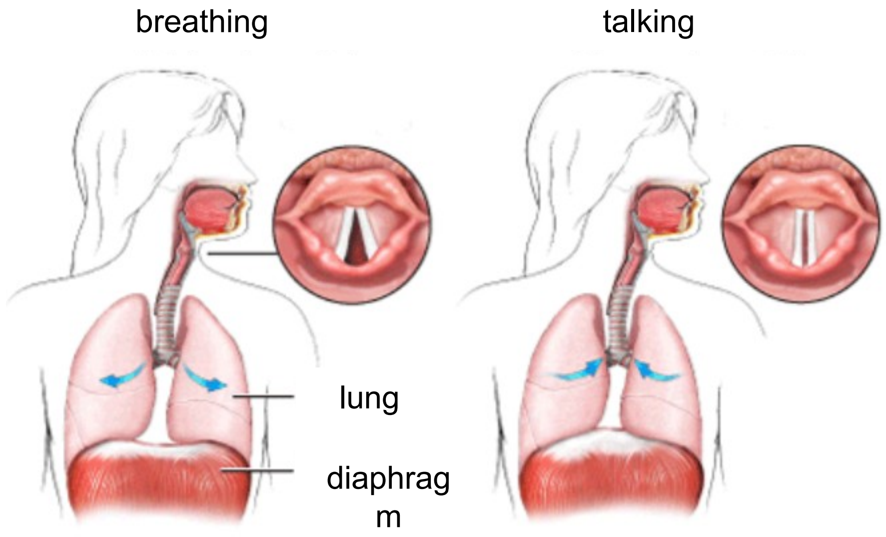
Typical features of GIT:

- cannot distinguish esophagus and pharynx
- doesn´t have stomach and acidification of chyme
- has anterior intestinal bulb, midle intesine, posterior intestine.

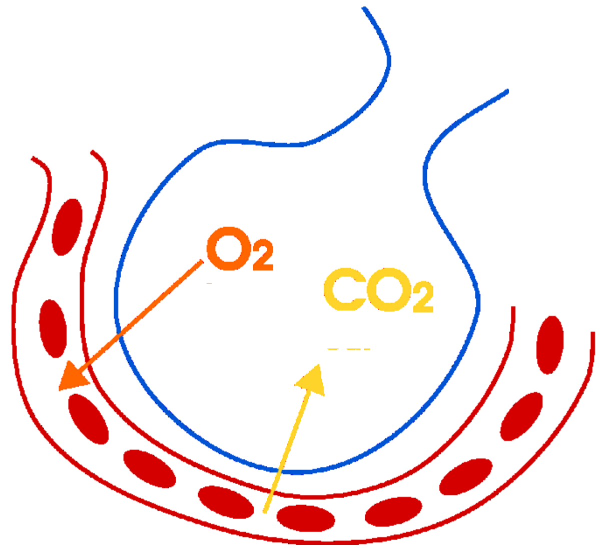
DEVELOPMENT OF RESPIRATORY SYSTEM

FUNCTIONS OF RESPIRATORY SYSTEM

- sounds creation

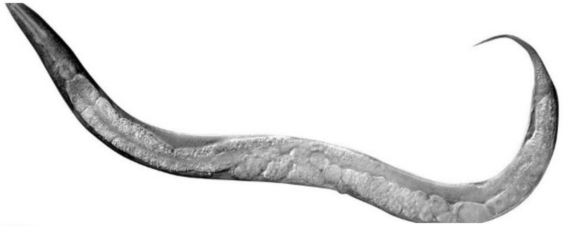


- gas exchange between individual and external environment

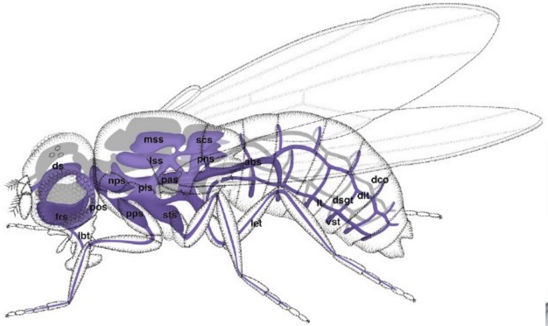


VARIOUS RESPIRATORY SYSTEMS

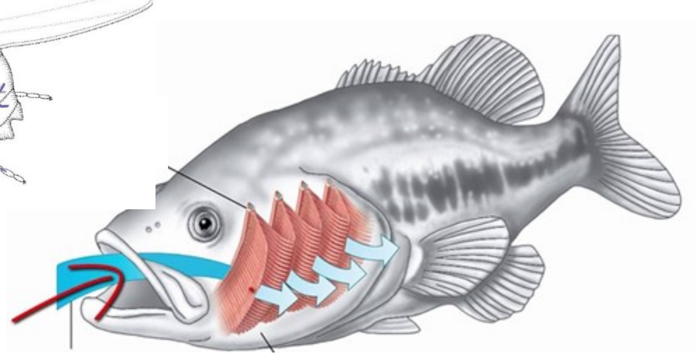
- **difussion** – gas exchange not dependent on specialized organ, through cuticle or skin



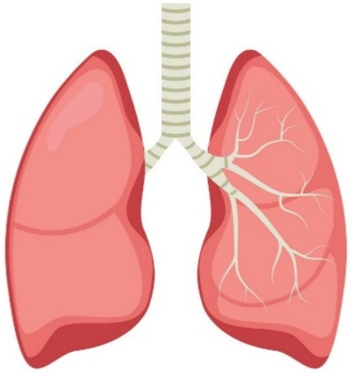
- **Tracheal system** – system of piping leading to terminal tissues



- **gills** – gas exchange in aquatic environment

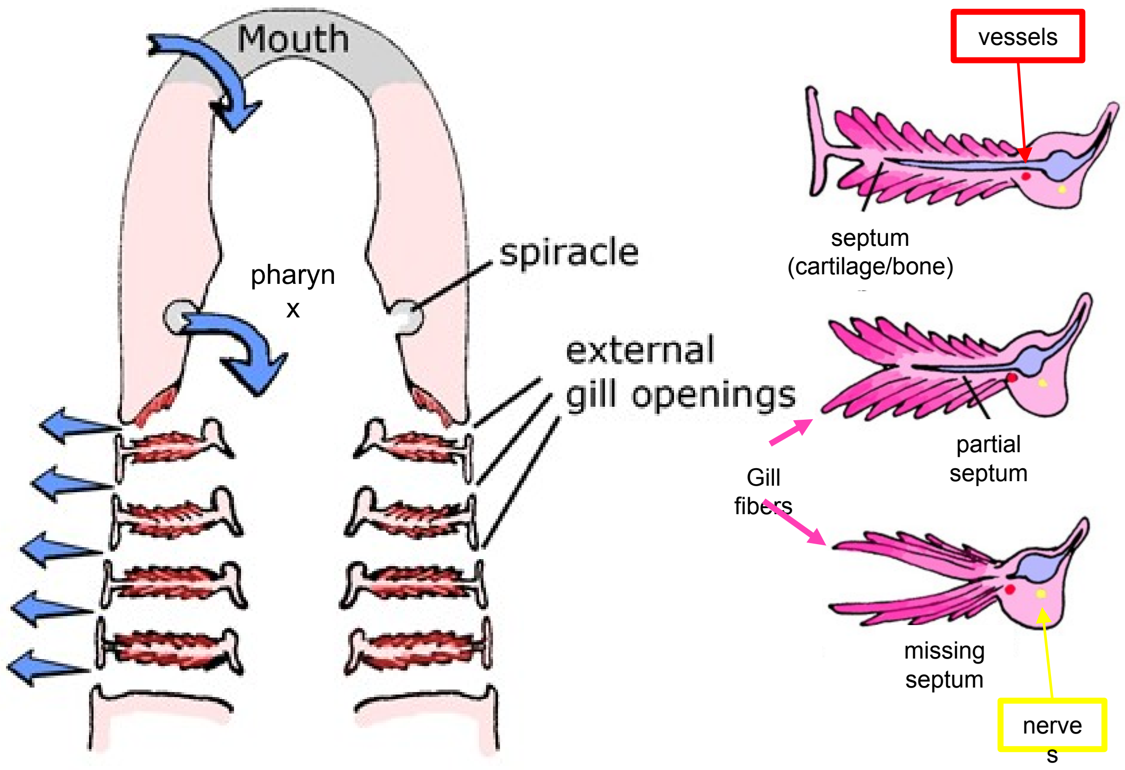


- **lung** – system of bronchi, bronchioles and alveoli, gas exchange in terrestrial and aquatic environments



DEVELOPMENT OF RESPIRATORY SYSTEM IN AQUATIC VERTEBRATES

- pharynx and gills
- oxygenated water enters the pharynx
  - **mouth**
  - **spiracle**
- mouth or spiracle is **closed**
- **pharynx pumps** water through **gills** via **gill openings** outside



Comparative Anatomy. University of the Cumberlands

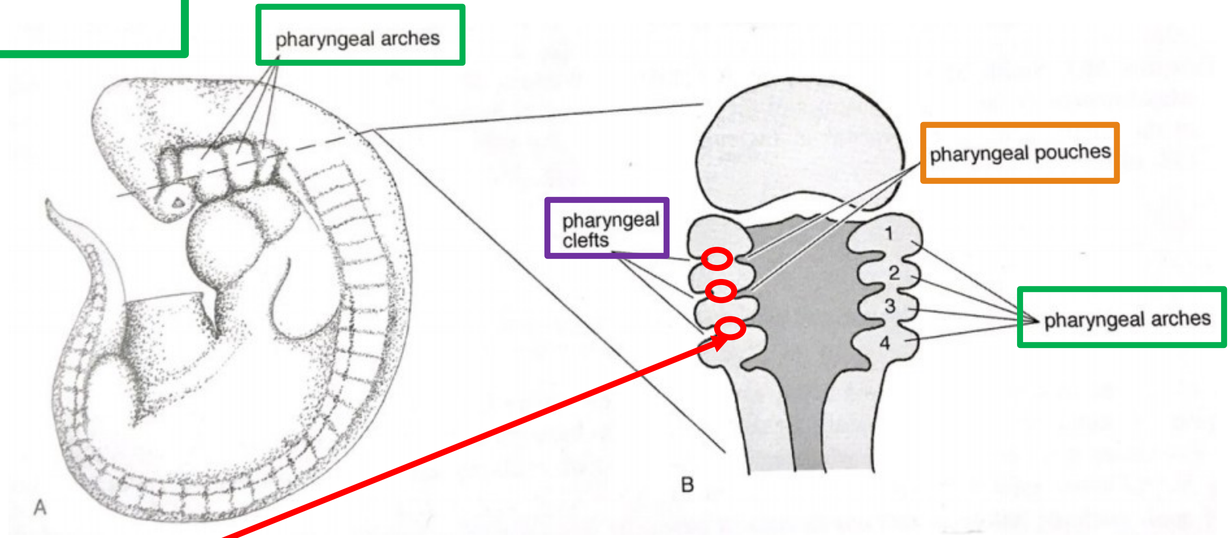
DEVELOPMENT OF GILLS – PHARYNGEAL ARCHES

- Neural crest cells migrating to region of developing head and neck into the space between surface ectoderm and gut endoderm → 6 pairs of **pharyngeal arches**

- **Pharyngeal clefts**
  - surface depression of ectoderm

- **Pharyngeal pouches**
  - primitive gut endodermal protrusions

- **Pharyngeal membrane** – connection of primitive gut endoderm with surface ectoderm

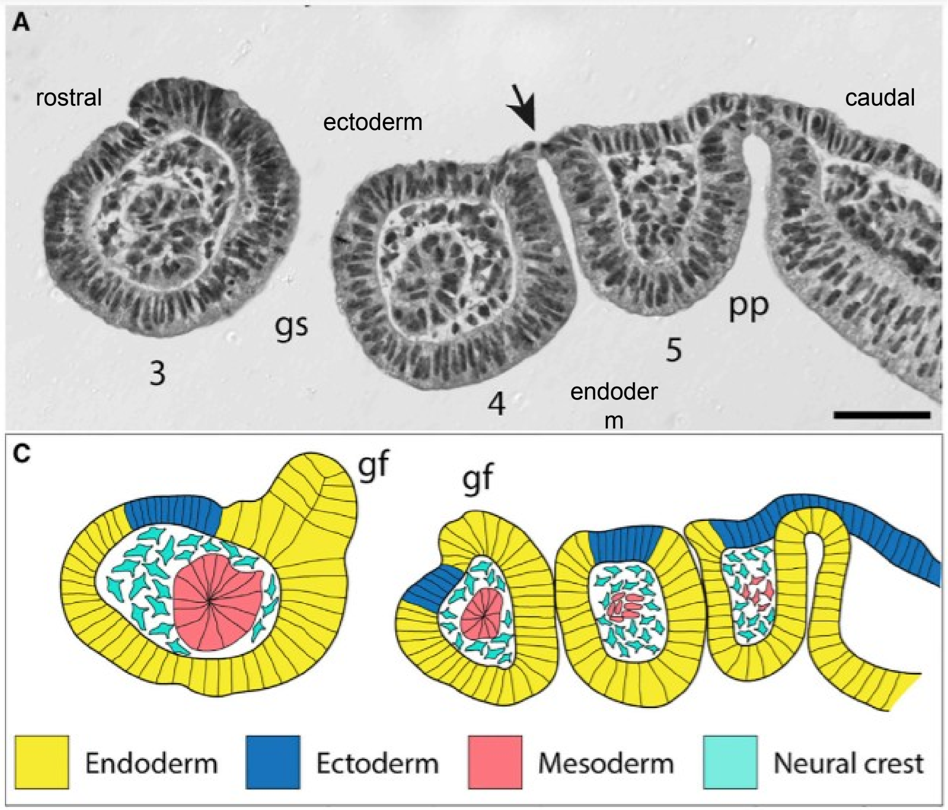


- **Pharyngeal slits –** pharyngeal **membrane broken,** formation of **gills opening**

McGeady et al. Veterinary Embryology. 2009

FORMATION OF THE GILL (PHARYNGEAL) SLITS

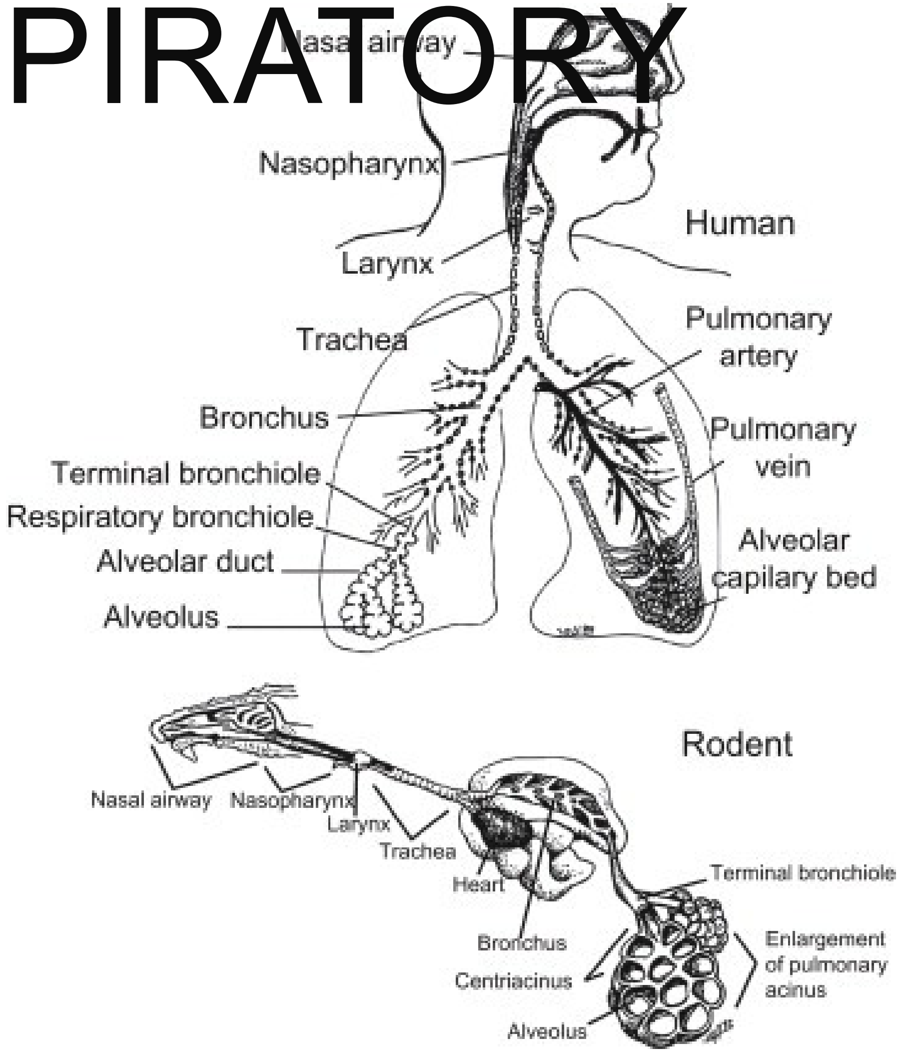
- **Pharyngeal pouches** endoderm (**pp**) reaches the surface **ectoderm** (**arrow**), fusion → **gill slit**
- **Endodermal** cells gradually **cover** majority of the pharyngeal arches surface
- Pharygeal arches give rise to:
  - **Gill fibers (gf) –** contain **vessels** (**mesoderm**) for **gas exchange,** both **anterior** and **posterior** sides
  - **cartilage** or **bone –** gill **support** (**neural crest**)
- **Internal gills** – majority of fish and cartilaginous fish
- **External gills** – some amphibians, larval stages of amphibians, some larval stages of fish



Gillis and Tidswell, 2017. Current Biol

PARTS OF THE RESPIRATORY SYSTEM

- **Conductive**
  - **nasal cavity and nasopharynx**
  - **larynx, trachea, bronchi**
- **Respiratory**
  - **bronchioles**
  - **alveolar ducts, alveolar sacs, alveoli**



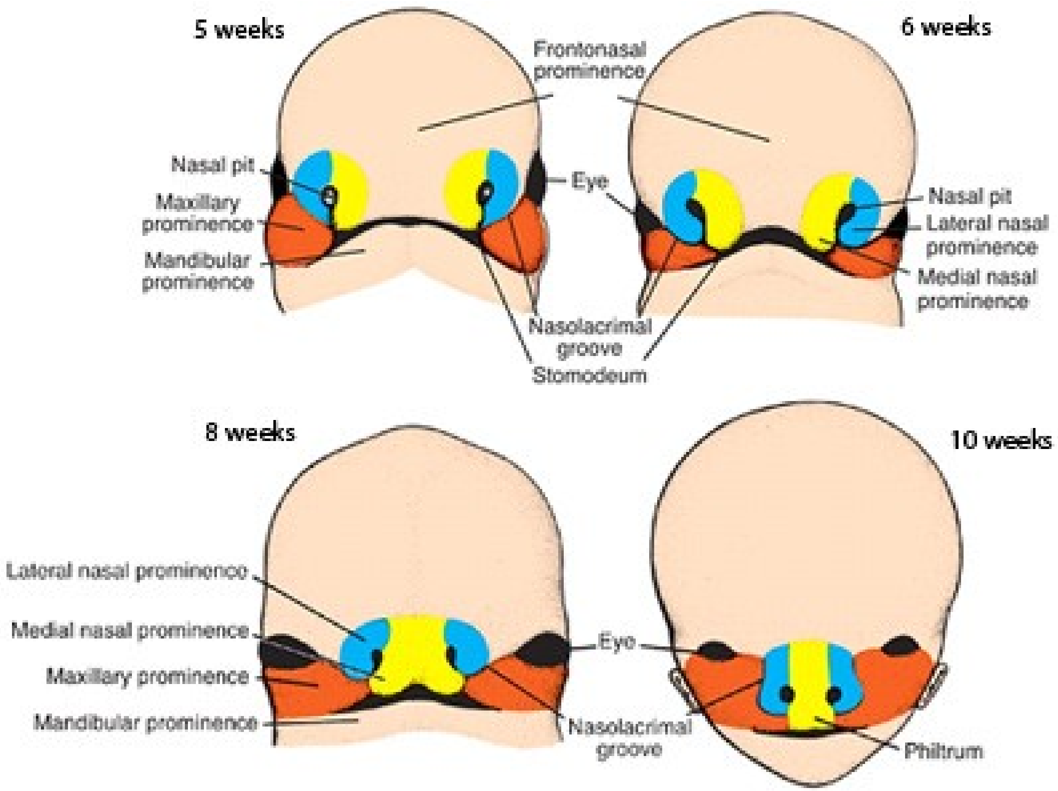
Harkema, Nikula and Haschek. Respiratory System. Hanbook of Tox and Path

DEVELOPMENT OF THE CONDUCTIVE RESPIRATORY SYSTEM

- formation of the **facial prominences**

- **Neural crest cells migrate** to **forebrain** region, covered by **facial ectoderm**
  - **Middle part – frontonasal prominence**
  - **laterally – lateral nasal prominences**
  - **medially – medial nasal prominences**

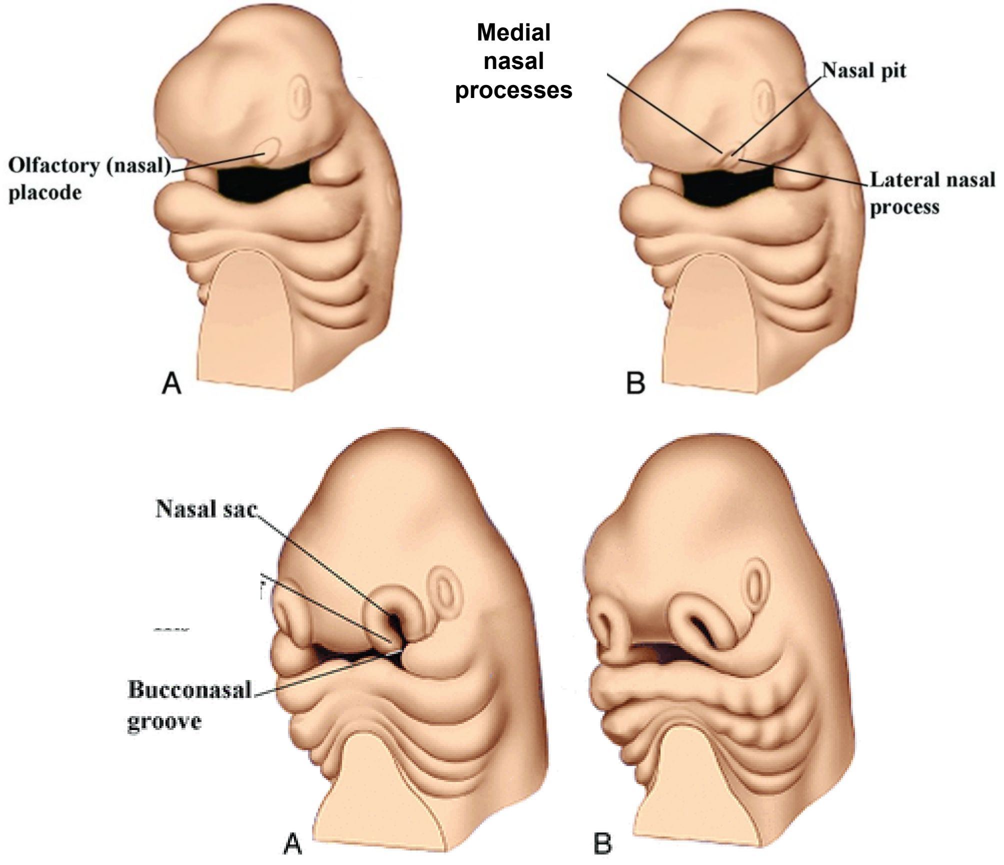
- **Neural crest cells migrate** to **1. pharyngeal arch,** covered by **pharyngeal arches ectoderm**
  - **cranially – maxillary part** (upper jaw, palate)
  - **caudally – mandibular part** (lower jaw)



Duke Embryology

DEVELOPMENT OF NASAL CAVITY

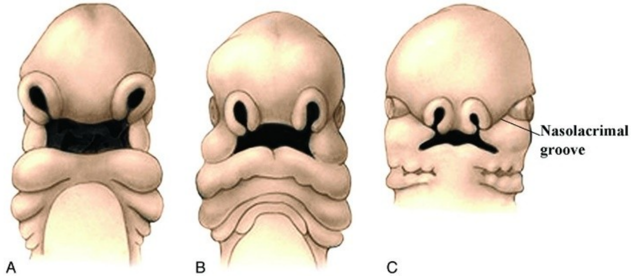
- formation of **nasal placodes** – **ectodermal thickening**, epithelium growth and mesenchymal proliferation around placodes
- Placode **deepening** – formation of **nasal pit**, **lateral nasal processes** on sides, **medial nasal processes** are formed **later**
- deepening and extension of nasal pit – **nasal groove**
- deepening of nasal groove, approaching stomodeum – formation of **nasal sac**

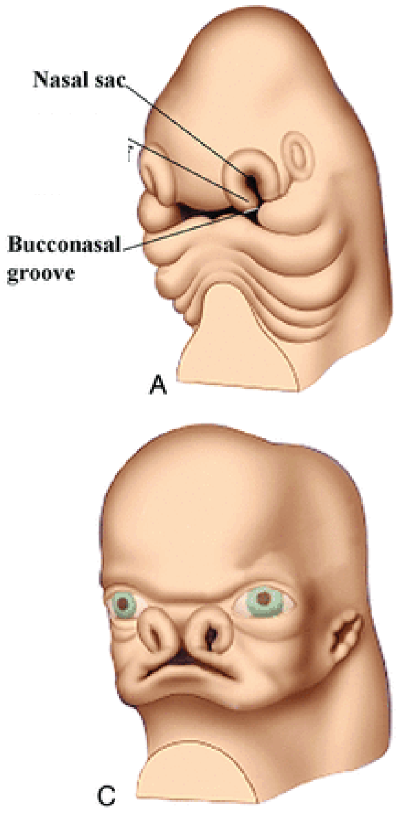


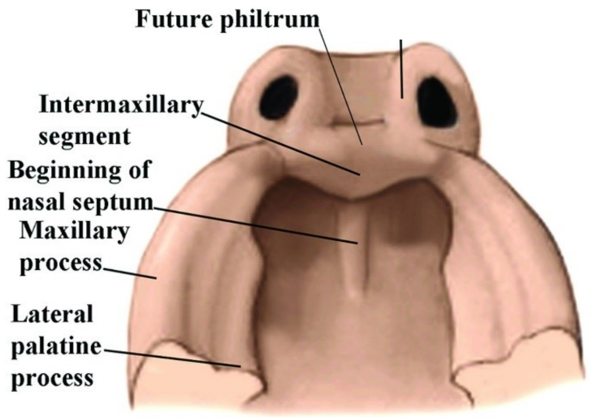
Som and Naidich, 2013. Am J Neurorad

SEPARATION OF PRIMITIVE NASAL AND ORAL CAVITIES

- **maxillary** prominences grow **medially** – nasal **sacs** are pushed **medially**
- medial nasal prominence form **intermaxillary segment**
- **closing** space between **maxillary** and **medial nasal prominences** – **buconasal groove** disappears → **closing** of the **nasal sac** lower part
- primitive nasal and oral cavities **separated**



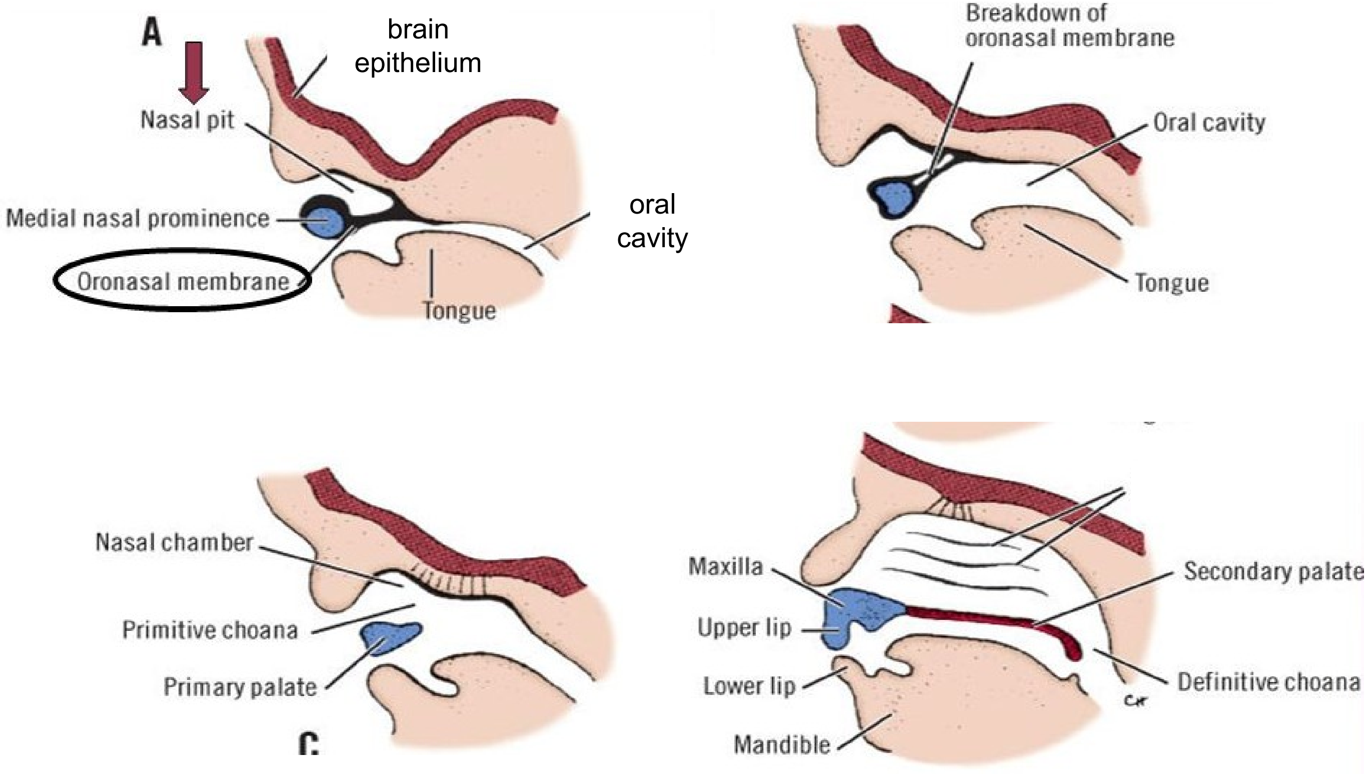




Som and Naidich, 2013. Am J Neurorad

FORMATION OF NASAL AND ORAL CAVITIES

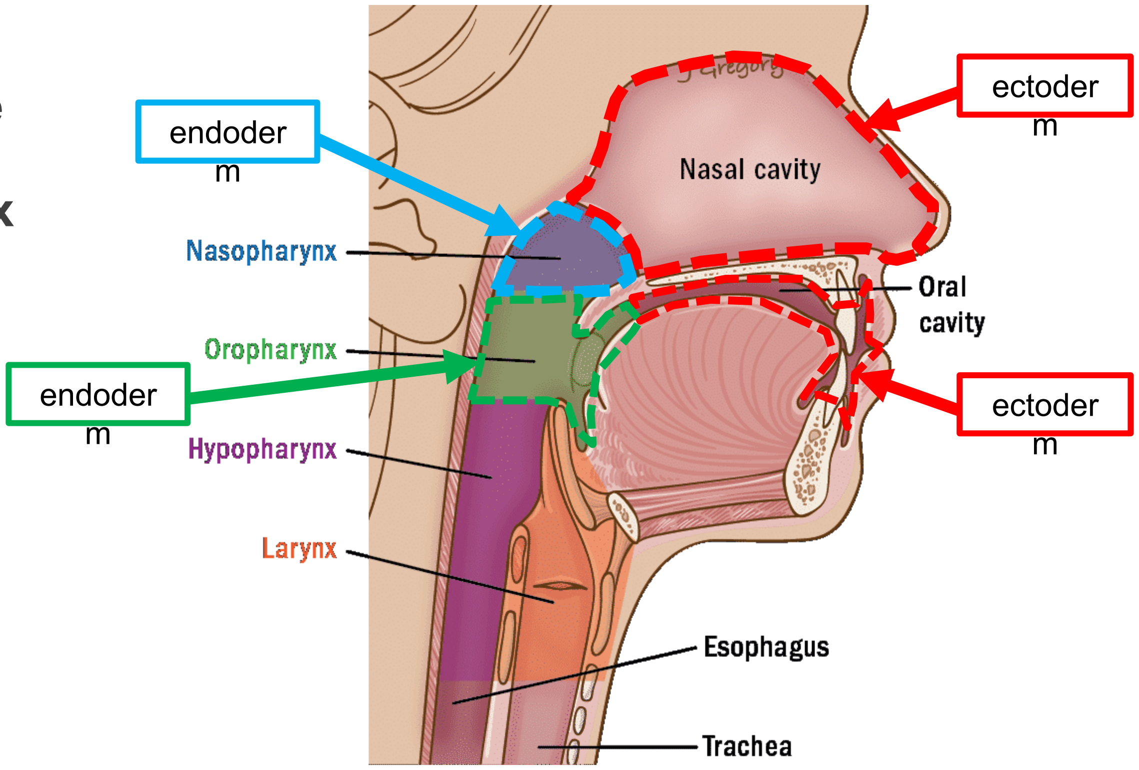
- primitive nasal cavity epithelium **grows to** underlying **mesenchyme** – formation of **oronasal membrane** (connection of primitive nasal and oral epithelium)
- **differentiation** of the **olfactory epithelium** dorsally
- **oronasal membrane breakdown**
- **communication** between oral and nasal cavitites through **primitive choana**
- **secondary palate** formed from **maxillary prominences**, **definitive choana** formed caudally



McGraw-Hill, 2006

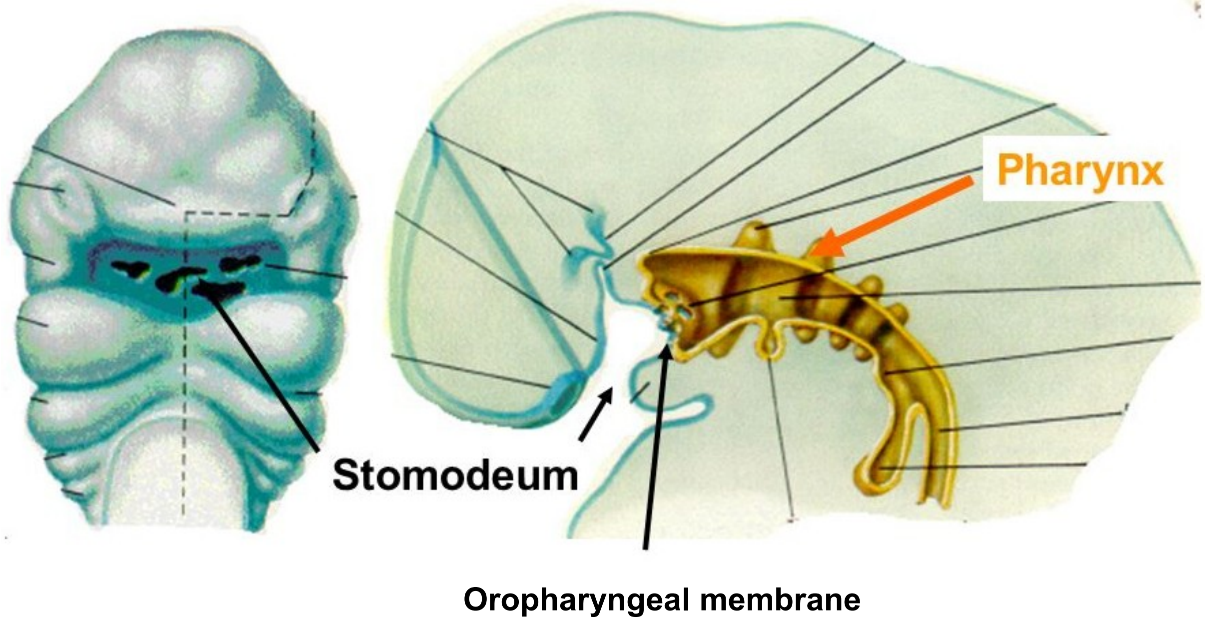
DEVELOPMENT OF NASOPHARYNX (NASAL PART OF PHARYNX)

- nasopharynx **connects** nasal cavity with larynx and trachea through oropharynx
- formation – breakdown of **oronasal membrane** and **secondary palate** formation→ connection between **nasal cavity (ectoderm)** and **pharynx (endoderm)**
- **Eustachean tube** opening – from the **1. pharyngeal arch pouch**
- **Anterior – extension of the nasal cavity**
  - similar microscopic anatomy to nasal cavity
  - pseudostratified cylindrical epithelium
  - vascularized tissue with lymphatic tissue
- **Posterior – extension of pharynx**
  - similar microscopic anatomy to oropharynx
  - stratified squamous epithelium



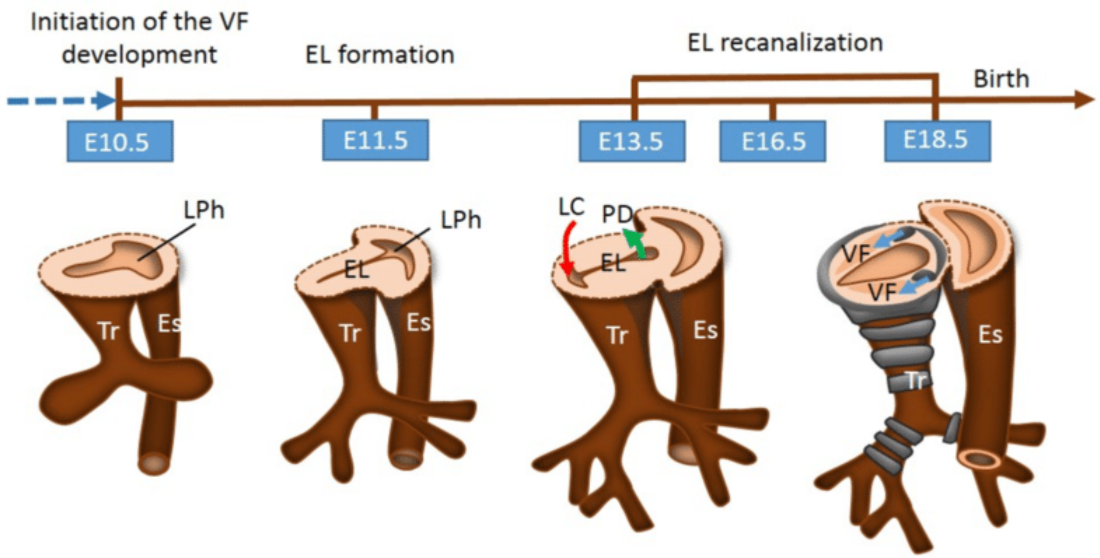
DEVELOPMENT OF OROPHARYNX (ORAL PART OF PHARYNX)

- connects **oral cavity** with **larynx**
- **caudally** from oral cavity
- **formation** – connects oral cavity (**ectoderm**) with pharynx (**endoderm**)
- region of **oropharyngeal** (**buccopharyngeal**) membrane breakdown – **separation** of **primitive oral cavity** (stomodeum) from **pharynx**
- **Anterior –** extension of the oral cavity
- **Posterior –** extends to larynx



DEVELOPMENT OF LARYNX

- connection of pharynx and trachea
- Epiglottis (laryngeal flap) located in larynx
- sounds creation – **vocal cords** (**vocal folds, VF**)
- epithelial lining and glands from **endoderm**
- Endoderm **proliferation** – **transitional** closure of larynx (epithelial lamina, EL) → **growth** and **expansion** laryngeal walls, **epithelial** cells **apoptosis** → **recanalization**
- cartilage and muscles
  - mesenchyme of **4. a 6. pharyngeal arches**
  - **cartilage – neural crest/mesoderm (somites)**
  - **muscles - somites**

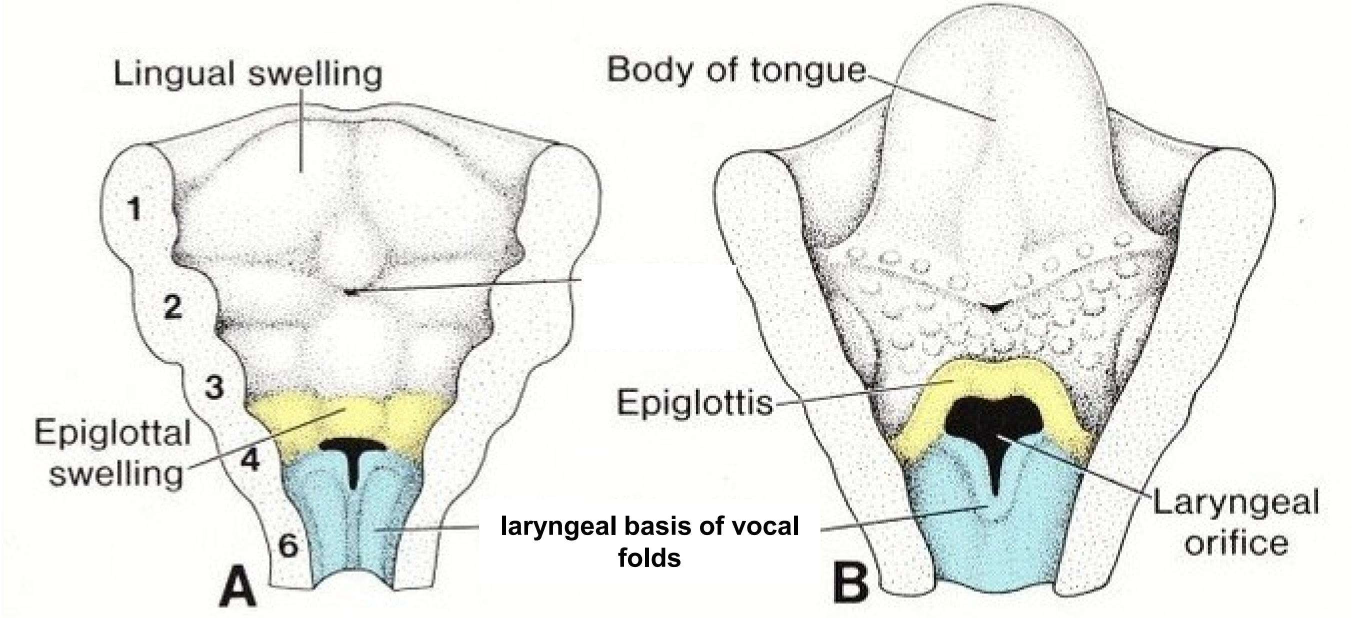


Lungova et al. 2018. Dev

EPIGLOTTIS DEVELOPMENT

- **separates** respiratory and digestive systems

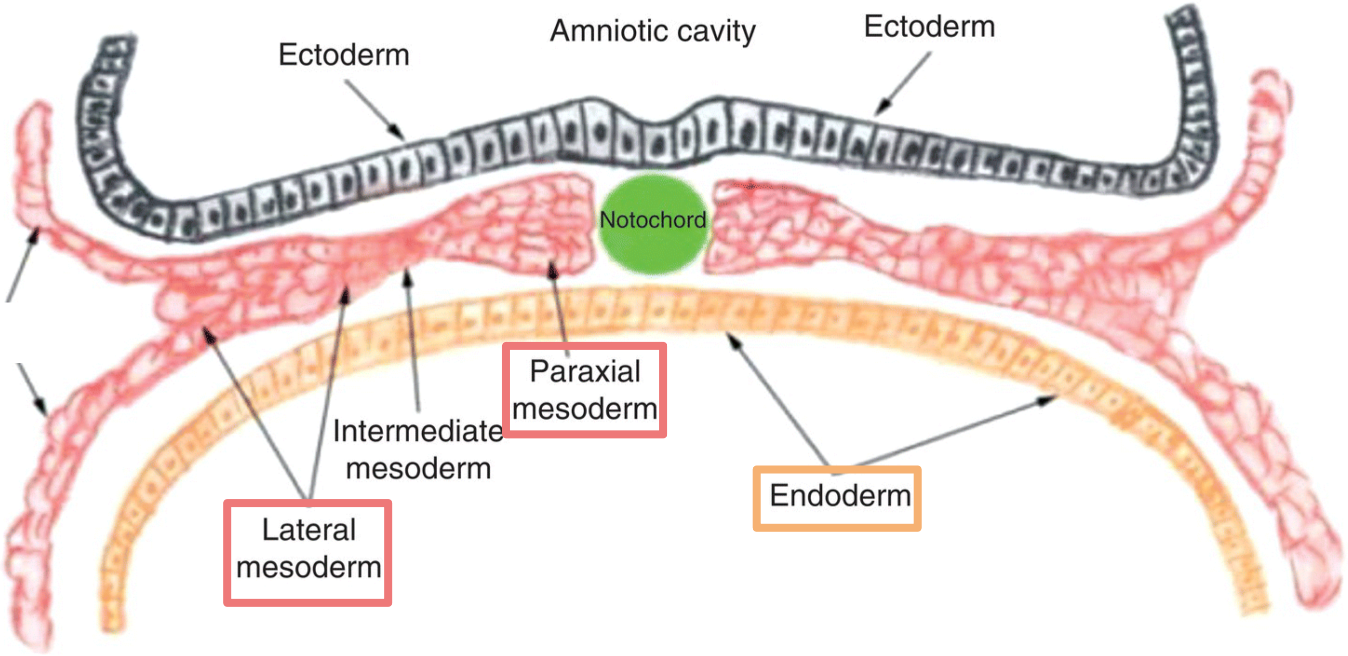
- Epiglottis swelling (basis) develops on ventral laryngeal side:
  - epithelial lining from cranial **endoderm**
  - mesenchyme and cartilage from **3. a 4. pharyngeal arches**



ORIGIN OF LUNG TISSUE

- Endoderm
  - basis for laryngotracheal (respiratory) tu
  - lung epithelial lining

- Paraxial mesoderm and lateral plate mesoderm
  - mesenchyme of lung buds
  - smooth muscle cells
  - fibroblasts
  - cartilage
  - vessels
  - lymphatic system



LUNG DEVELOPMENT

5 stages:

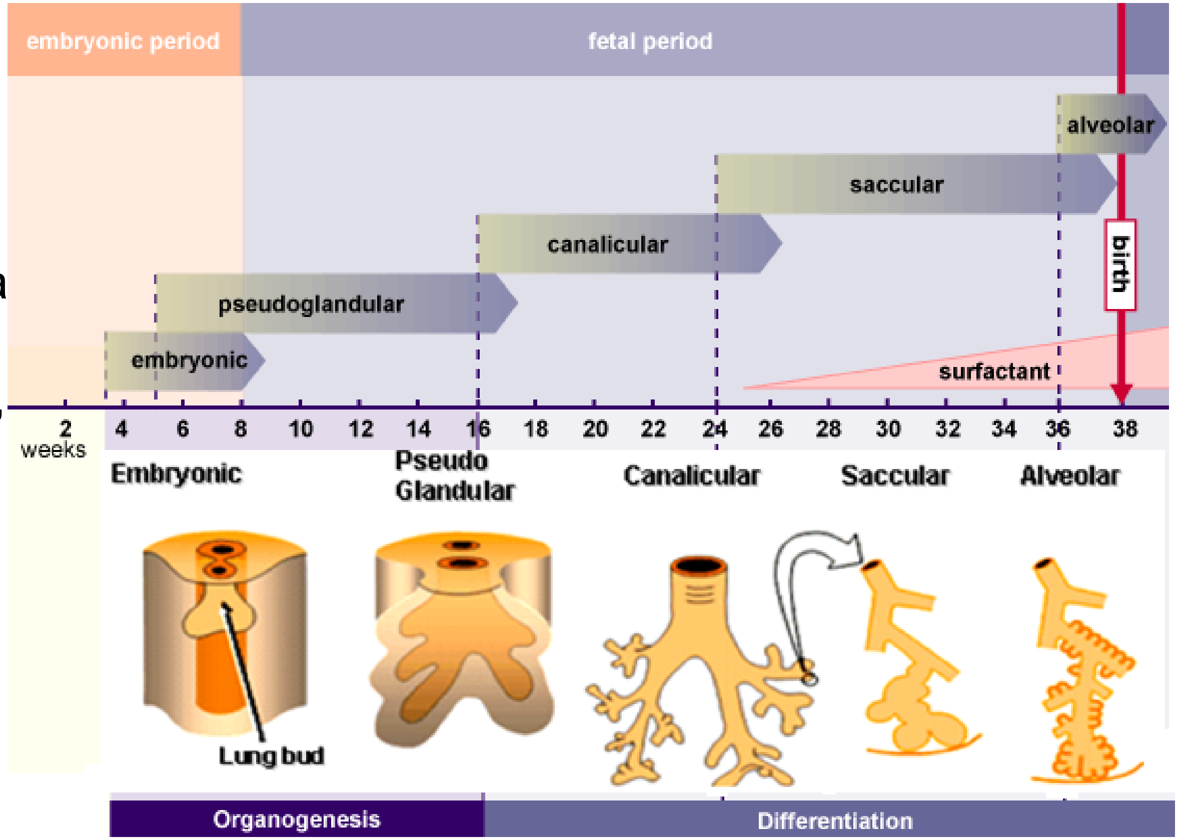
1. Embryonic – separation from primitive gut

2. Pseudoglandular – branching, onset of differentia

3. Canalicular – onset of pneumocyte differentiation, expansion of vessels

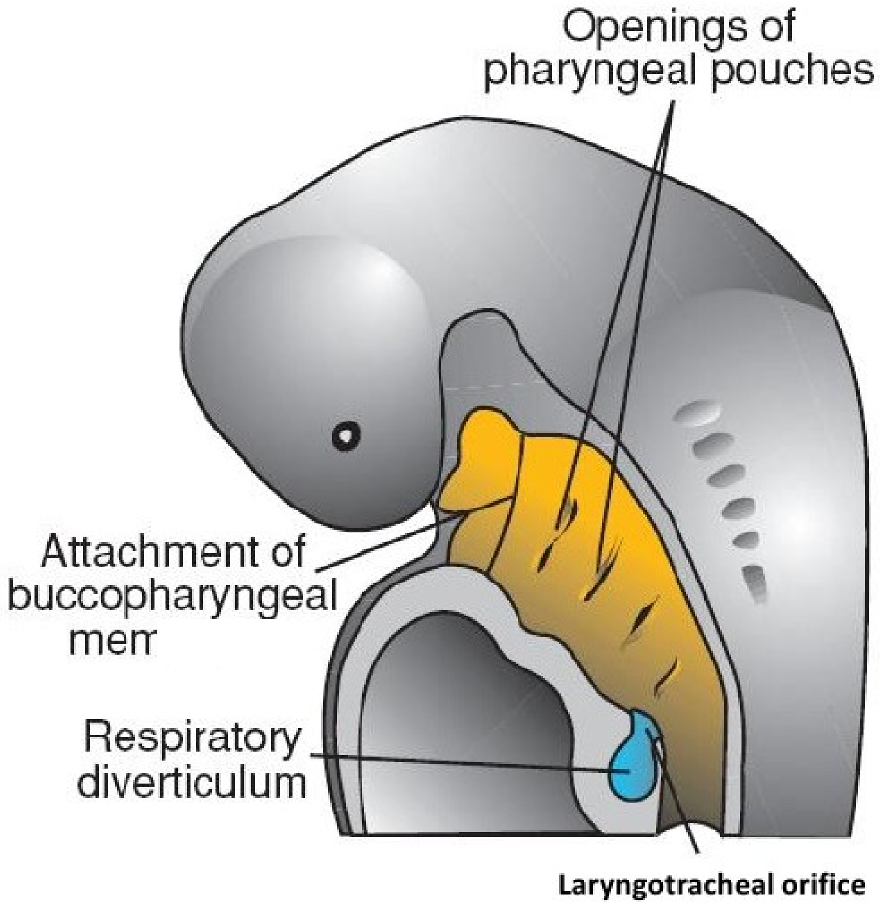
4. Sacular – functional pneumocytes, expansion of vessels

5. Alveolar – formation of alveoli



1. EMBRYONIC – SEPARATION OF RESPIRATORY ENDODERM FROM FOREGUT E

- **digestive tube** goes along the **whole body**
- **buds** formation – development of **liver, gallbladder, pancreas**
- **onset** of **respiratory** system **development – outgrowth** from the **digestive tube** in the primitive foregut
- place of separation **– caudally from pharynx**
- human: 3. – 7. week



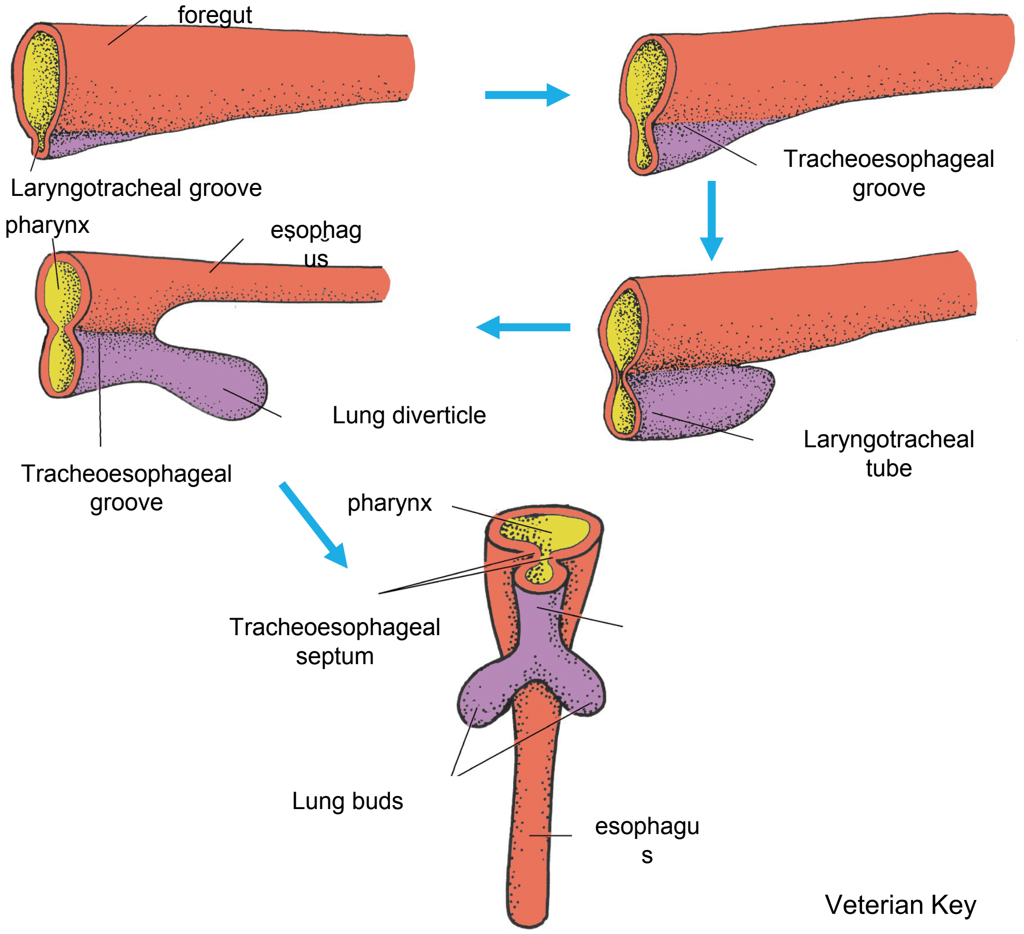
LUNG BUD FORMATION

- **Laryngotracheal groove**
  - **ventral foregut side**
  - 4. pharyngeal arch **region**
- **Deepening of groove**
  - formation of **tracheoesophageal groove** on both sides
  - **separation** from **foregut**
- growth in **caudal** direction **–** formation of basis of **laryngotracheal tube**

- **dorsally** – esophageal base

- **ventrally –** basis of laryngotracheal tube

- **cranially** from **tracheoesophageal septum** – **pharynx** develops from foregut



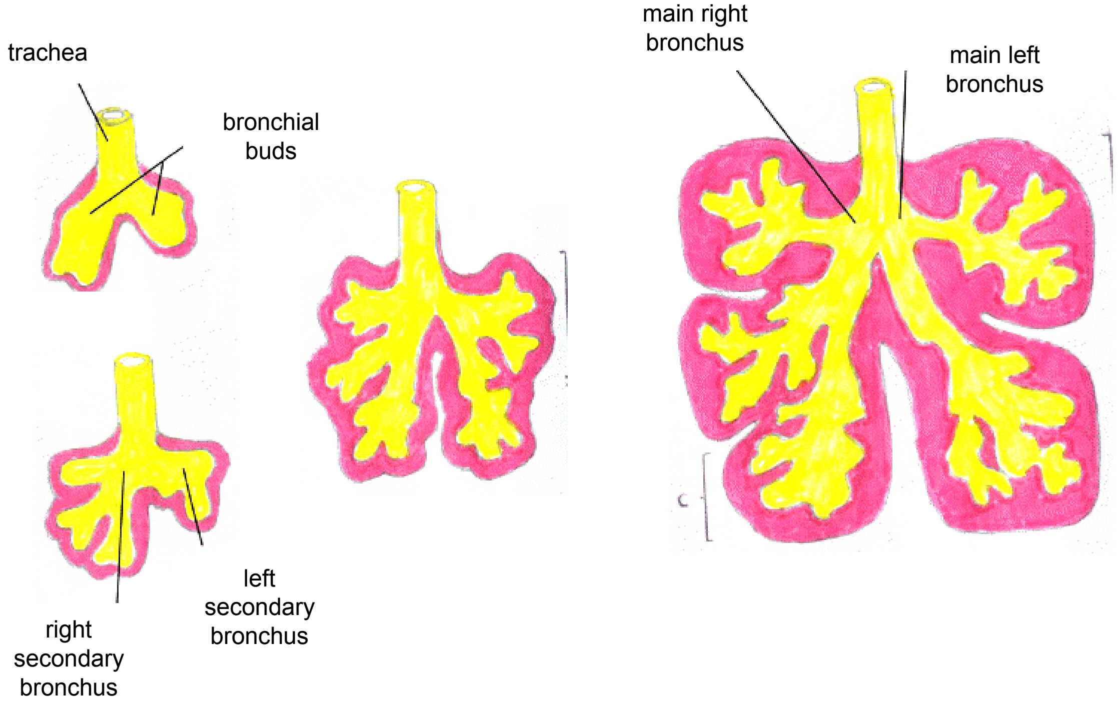
Veterian Key

2. PSEUDOGLANDULAR PHASE

- **Bronchial buds** start to grow into **mesenchyme** (6. – 16. week in human)

- penetration of epithelial organ to mesenchyme **reminds** exocrine gland formation – **pseudoglandular**
- all main **bronchial branches** are **formed** – epithelial **lining** originates in **endoderm**

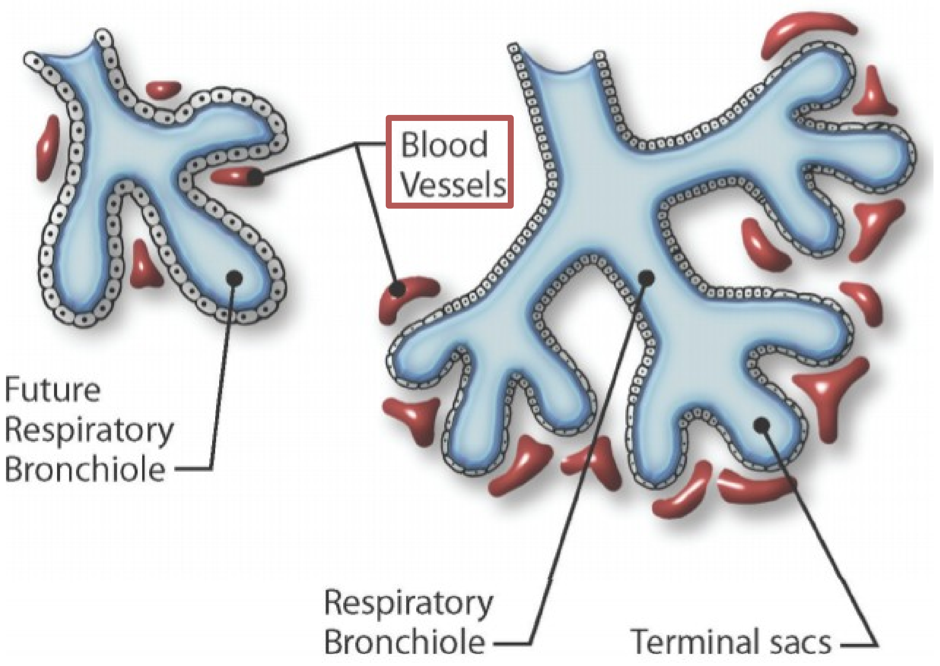
- Differentiation
  - ciliated epithelial cells (endoderm)
  - cartilage (mesoderm)
  - submucosal glands (endoderm)
  - smooth muscles (mesoderm)
  - endothelium – onset of vascularization (mesoderm)
  - lymphatic cells (mesoderm)



Moore and Persaud, 2008. The Developing Human

3. CANALICULAR PHASE

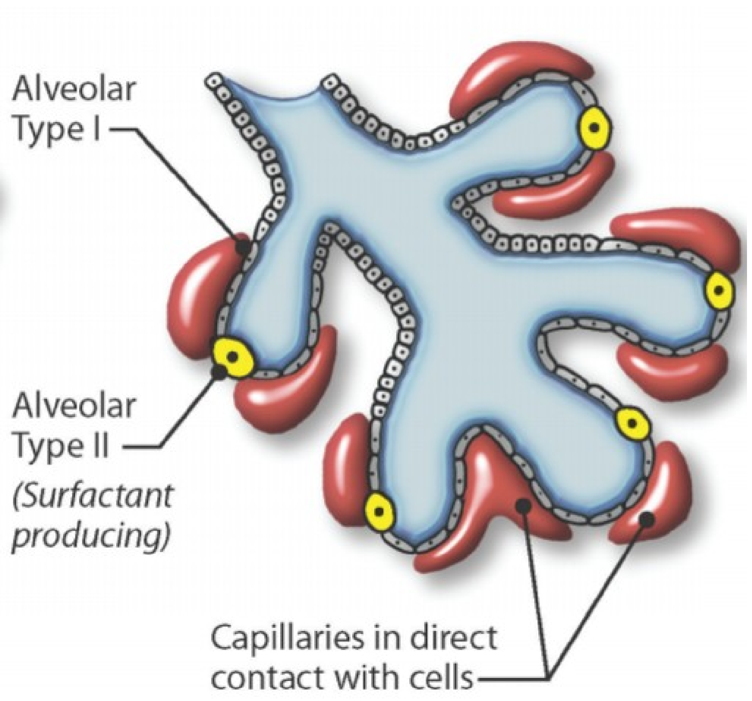
- **cavities** of bronchi and bronchioles **enlarged**
- **respiratory bronchioles** formed from **terminal bronchioles** – cubic epithelium
- from respiratory bronchioles – **alveolar tube with terminal sacs** – epithelial flattening
- around bronchiolar branching - **formation** of **vessels –** close surrounding of epithelial cells
- onset of epithelial cells differentiation in **respiratory bronchioles:**
  - **1. type Pneumocytes**
  - **2. type Pneumocytes**
- human: 16. – 28. week



Rubarth and Quinn, 2015. Neonat Net, Springer.

4. SACULAR PHASE

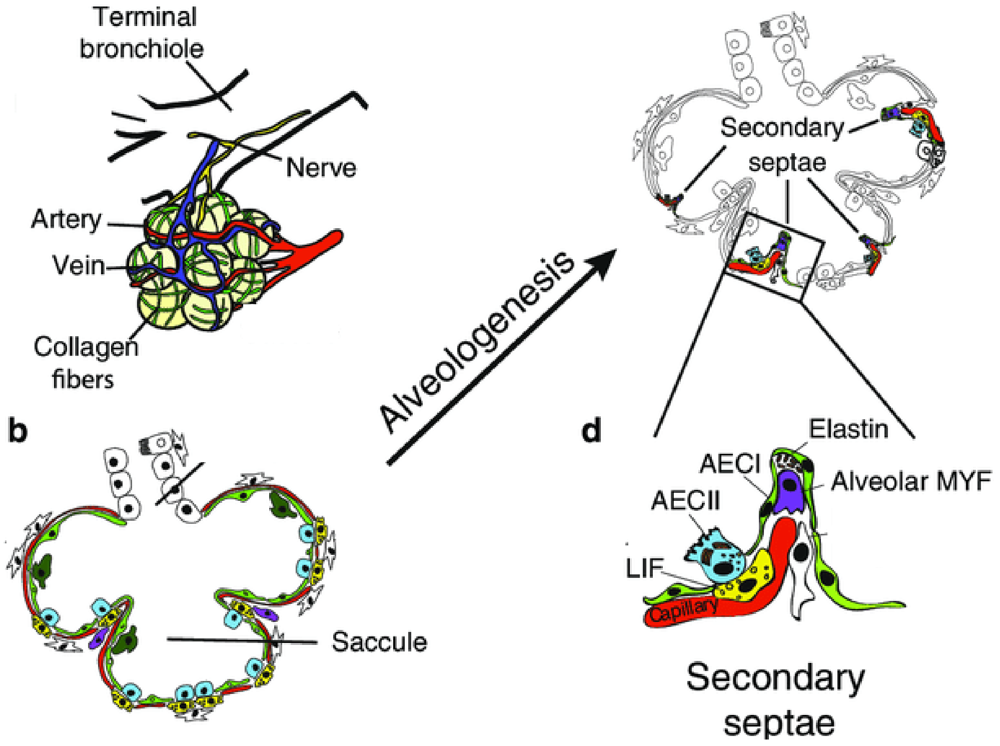
- differentiating pneumocytes partly functional
  - **1. type pneumocytes** – structural alveolar cells, „membrane“ for **gas exchange**
  - **2. type pneumocytes** – formation of lamelar bodies, **surfactant production**
- immature sacs
- **gas exchange** can tak place **(1. type P)**
- **surfactant** is slightly produced (**2. type P**)
- web of **blood** and **lymphatic** vessels **enlarged**
- human: 24. – 38. week



Rubarth and Quinn, 2015. Neonat Net, Springer.

5. ALVEOLAR PHASE

- **Alveologenesis** – alveoli development (36. w. - 3 years in human)
- formation of **secondary septae** → higher number of alveolar tubes and alveoli
- **more effective** gas exchange by formation of **septae (larger surface)**
- induced from **mesenchyme – septae formation by alveolal myofibroblasts and lipofibroblasts**
- **pneumocytes** on the **surface, vessels** and **mesenchyme inside**
- Alveologenesis
  - **human – prenatal** and **postanal** development
  - **mouse – postnatal** development



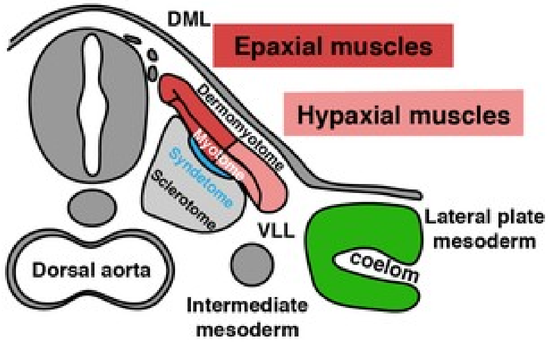
Chao et al., 2016. Mol Cell Pediatr

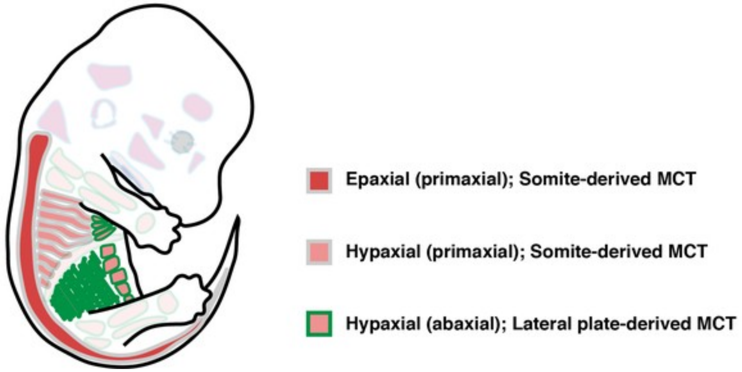
DEVELOPMENT OF RESPIRATORY SYSTEM MUSCLES

- intercostal muscles

- proliferation and migration of myotomal cells – muscle progenitor cells formed - **myoblasts**

- **Hypaxial** muscles:
  - **intercostal** muscles – muscle connective tissue originates in **somites**
    - intercostal muscles **don`t fuse**

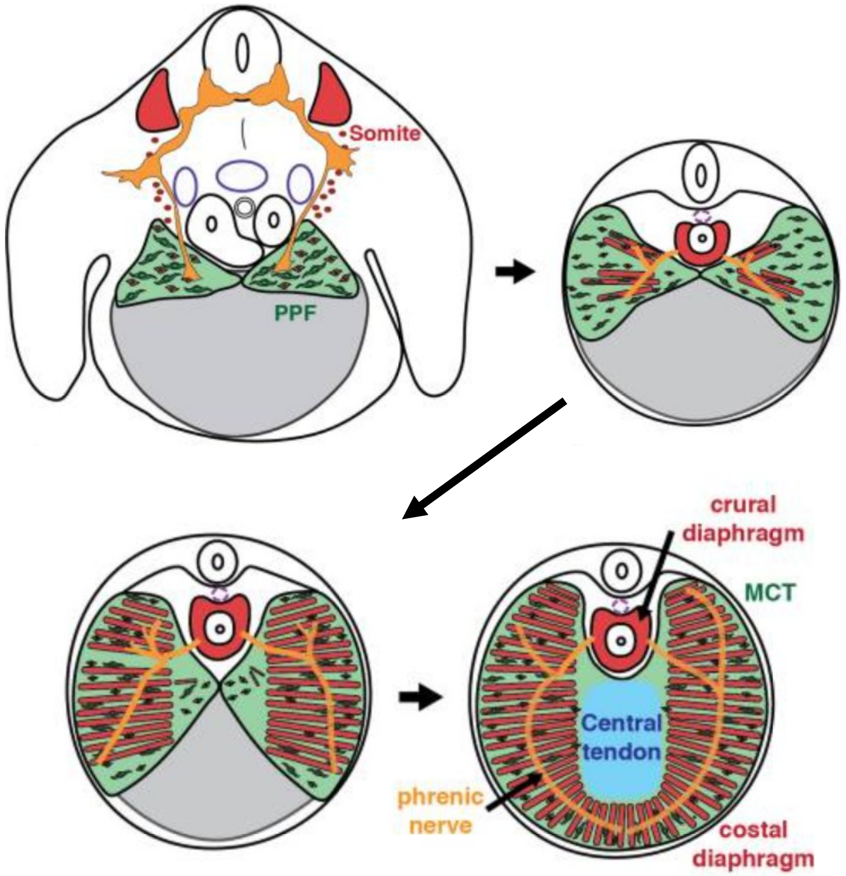




Sefton and Kardon, 2019. Curr Top Dev Biol

DEVELOPMENT OF RESPIRATORY SYSTEM MUSCLES

- diaphragm
- main muscle for **inspiration** phase, separating thoracal and abdominal cavity
- **diaphragm**:
  - myoblasts – **somites (cervical area)**
  - muscle connective tissue (MCT) – **lateral plate mesoderm**
- **migration** of **precursor cells** from lateral plate mesoderm to **pleuroperitoneal fold (PPF)** region
- **myoblasts** from somites **migrate** to **pleuroperitoneal** region – **asociation** with **MCT**
- **crural** diaphragm – **respiration, esophageal sphincter**
- **costal** diaphragm - **respiration**



Sefton and Kardon, 2019. Curr Top Dev Biol

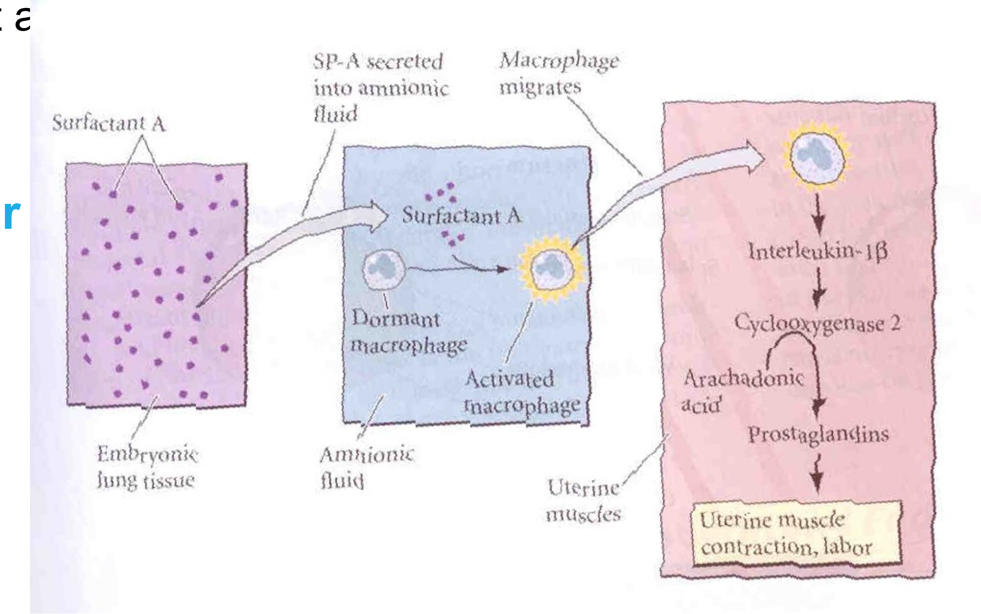
FBMS = FETAL BREATHING-LIKE MOVEMENTS

- movements resembling the breathing – crucial for lung development
- stimulation of production of PDGFs, IGFs, TTF1
- affect development a

pneumocytes typeI: – no FBMS = non-efective gasses exchange

pneumocytes type II: – no FBMS = no surfactant

Induction of labor



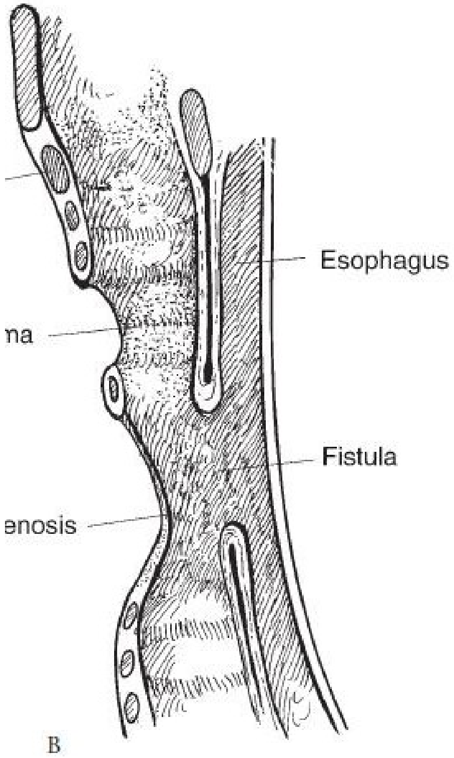
S.F. Gilbert, Developmental biology 2006

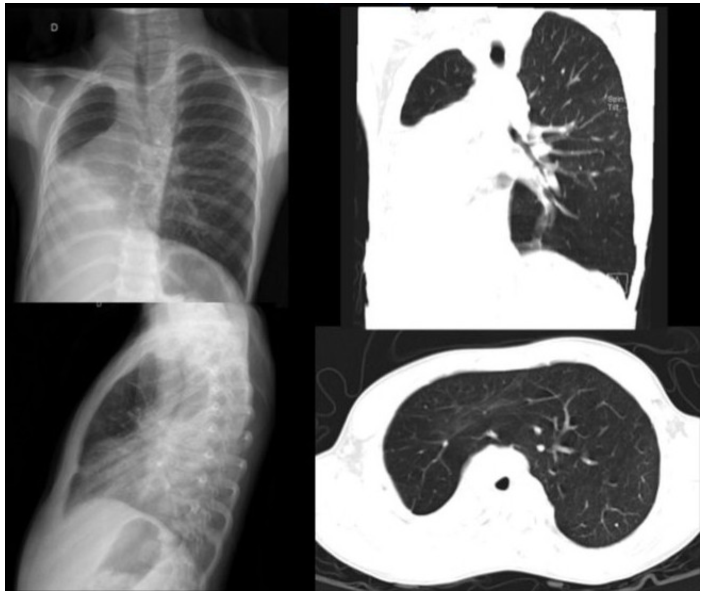
DEVELOPMENTAL DEFECTS OF RESPIRATORY SYSTEM

- **developmental defects – specific for developmental stages of lung**
- **1. embryonic**

- **Tracheoesophageal fistula**
  - **incomplete separation** of **trachea** and **esophagus**
  - **communication** between respiratory and digestive systems
  - surgery soon after delivery

- **Pulmonary agenesis**
  - lung development stopped at primitive stage
  - unilateral or bilateral defects
  - rare defect, often lethal

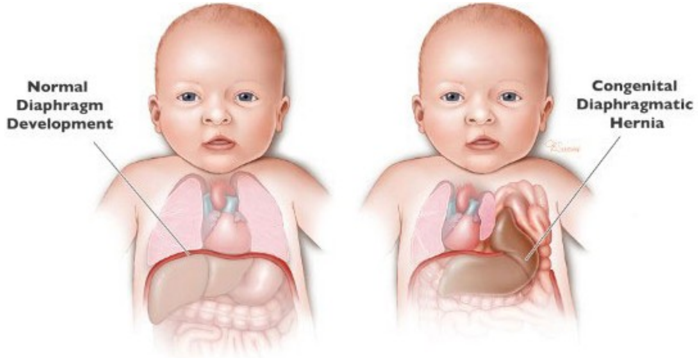




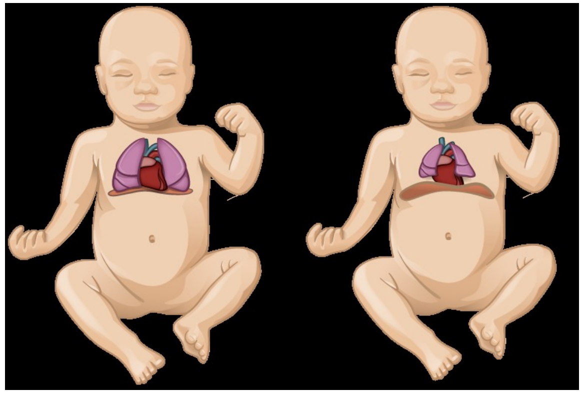
Serrado et al. 2016. ECR 2016

DEVELOPMENTAL DEFECTS OF RESPIRATORY SYSTEM

- **2. pseudoglandular phase**
- **Congenital diaphragmatic hernia**
  - insufficient development of diaphragm
  - organs from abdominal cavity **move** to thoracal cavity
  - defective lung development – **lung hypoplasia**, high lethality (50%)
- **Tracheal atresia**
  - congenital absence of trachea
  - mostly lethal
- **Pulmonary hypoplasia**
  - **insufficient development of lung**
  - small number of bronchopulmonary and alveoli segments
  - often **secondary** phenotype manifestation to other defects



Texas Children Fetal Center


St. Louis Fetal Care Institute

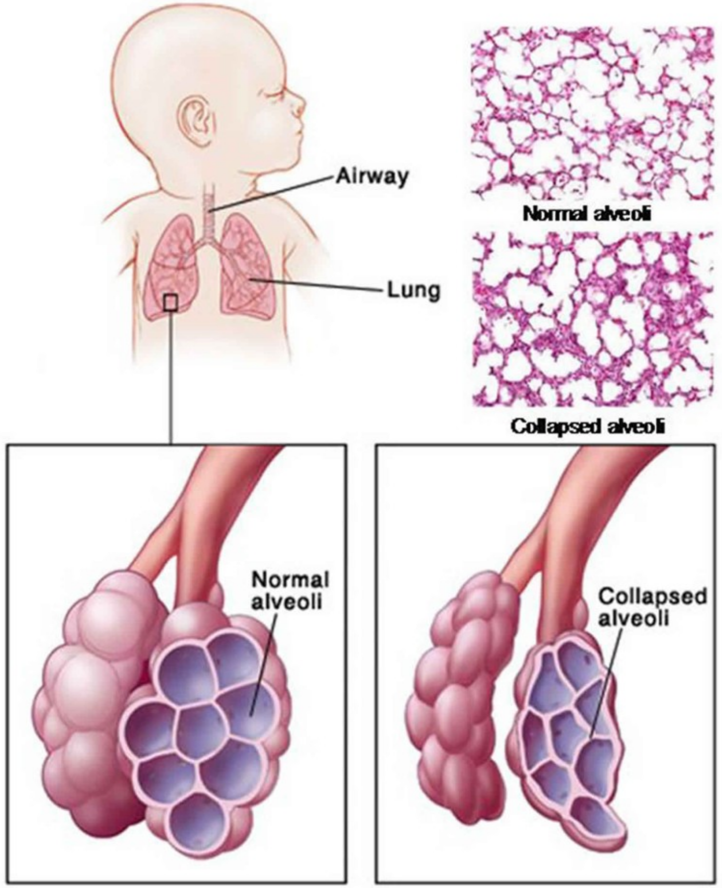
DEVELOPMENTAL DEFECTS OF RESPIRATORY SYSTEM

- **3. canalicular phase**

- **Respiratory insufficiency**
  - insufficient gas exchange
  - not enough bronchioles
  - insufficient vascularization of lung

- **4. sacular phase**

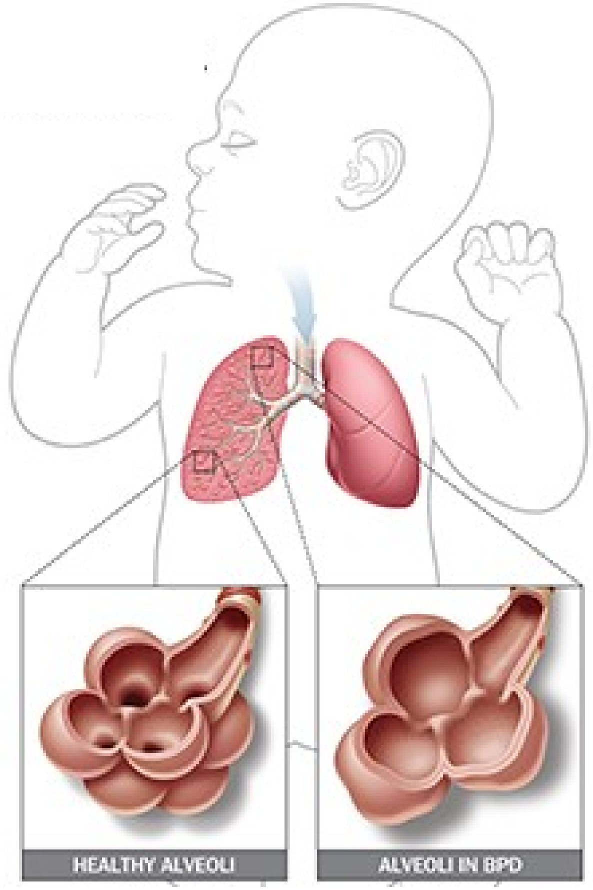
- **Acute respiratory distress syndrome**
  - lung not well developed
  - lung produce not enough surfactant
  - blue lips, fingers, toes
  - rapid breathing



DEVELOPMENTAL DEFECTS OF RESPIRATORY SYSTEM

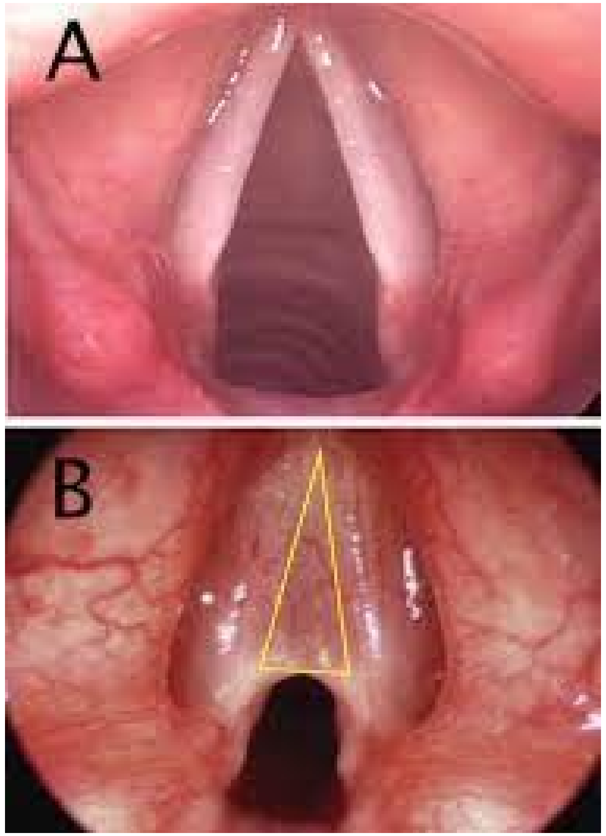
- **5. alveolar phase**

- **Bronchopulmonary dysplasia**
  - insufficiently or abnormally developed lung
  - **less** alveoli with **thicker** walls
  - insufficient gas exchange
  - may be caused by **premature birth**
  - insufficient development of lung lymphatic tissue - **inflammation**



DEVELOPMENTAL DEFECTS OF RESPIRATORY SYSTEM

- **Laryngeal atresia**
  - complete or partial blockage of laryngeal tube
  - caused by insufficient recanalization
  - dilatation of the lower respiratory truct
  - surgical removal



FUN FACTS

1. How long is the small intestine?
2. How many bacteria live in the colon?
3. What is the area of the whole intestine?
4. How many cells comprises the Langerhanz island in one pankreas?