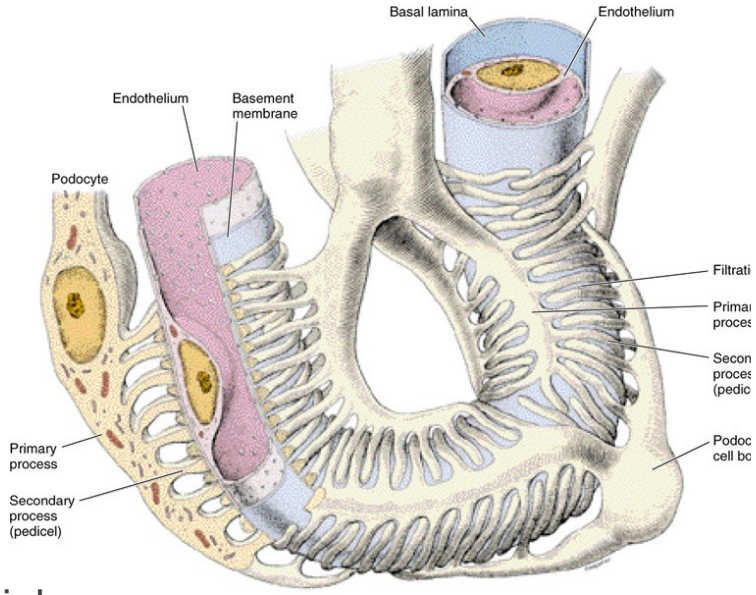
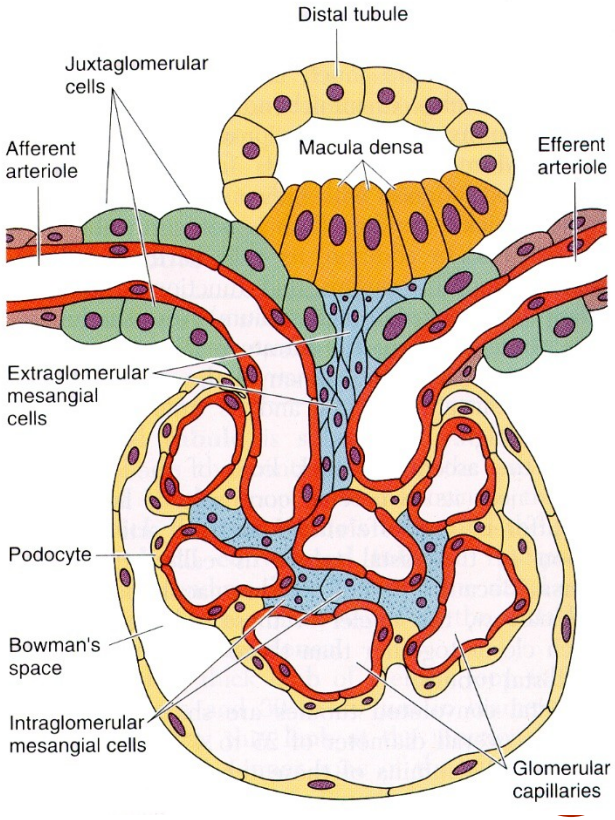
DEVELOPMENT OF UROGENITAL SYSTEM

1. Excretory system
2. Reproductive system

EXCRETORY SYSTEM FUNCTIONS

- Excretion of metabolites via filtration
- Regulation of electrolyte amounts in body
- Water reabsorption
- Renin production by juxtaglomerulac cells – regulation of blood pressure
- Production of erytropoetin by kidney intersticial fibroblasts – regulation of erytrocytes number





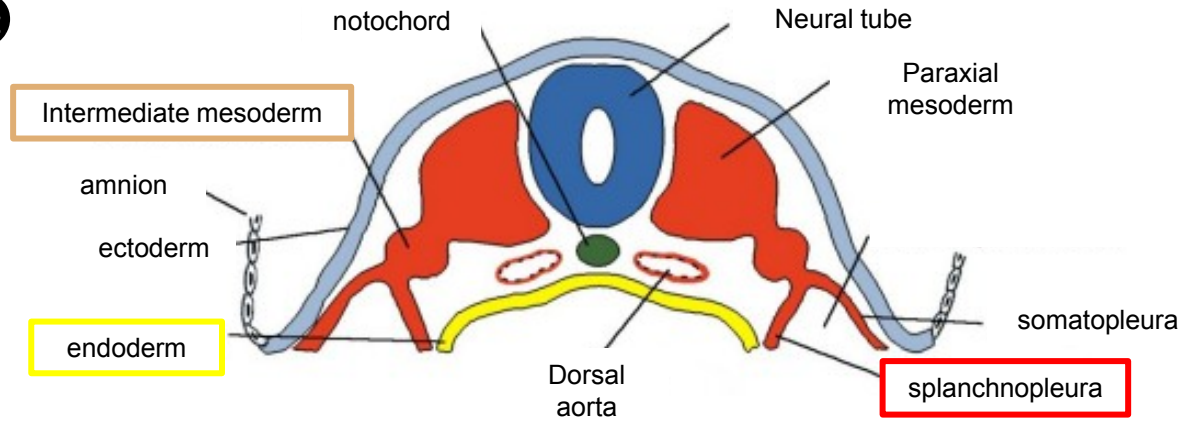
ORIGIN AND DEVELOPMENT OF EXCRETORY SYSTEM IN VERTEBRATES

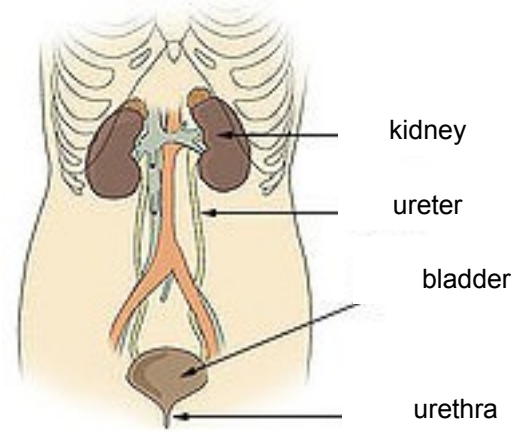
- Main source for excretory system – **intermediate mesoderm**
  - **endoderm** – epithelial basis of bladder and urethra
  - **splanchnic mesoderm** – vessels, connective tissue, muscle cells
  - **Ectoderm** – distal part of urethra (males)

- development of excretory system tightly connected with development of reproductive system (intermediate mesoderm)

- Excretory system developes earlier than reproductive

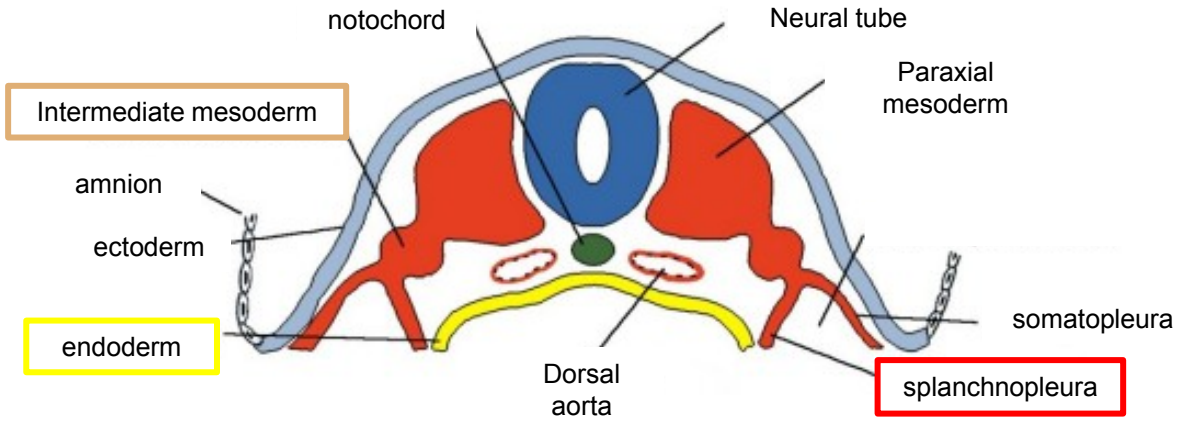
- Excretory system is composed of:
  - **kidney**
  - **ureter**
  - **bladder**
  - **urethra**





DEVELOPMENT OF INTERMEDIATE MESODERM

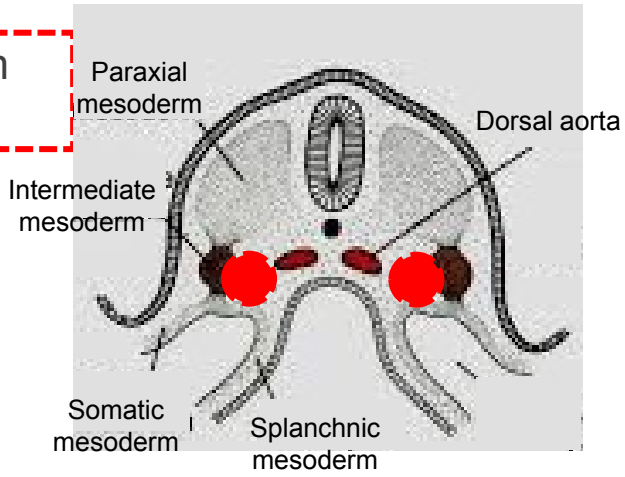
- mesoderm localized **intermediary** – between paraxial mesoderm and lateral plate mesoderm
- epiblast cells invaginate to space between newly formed endoderm (originally hypoblast) and forming ectoderm (originally epiblast)
- migration of mesodermal cells cranialy, caudaly, lateraly
- Three mesodermal zones:
  - **Paraxial mesoderm** – closest to developing neural tube
  - **Lateral plate mesoderm** – mesoderm localized on sides
  - **Intermediate mesoderm** – between paraxial m. and lateral plate m.



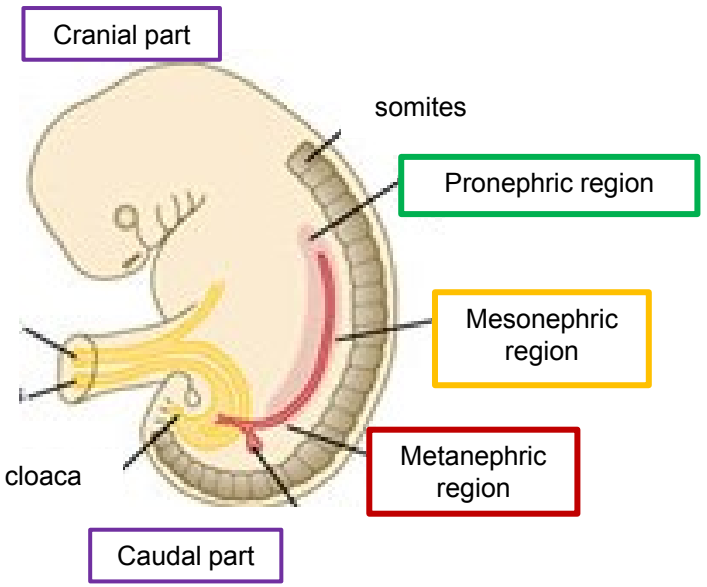
FORMATION OF NEPHROGENIC CORDS

- from **intermediate** mesoderm differentiate pairs of nephrotomes – **nephrogenic cords**

- Cords formed by migration of cells from mesoderm **lateraly** from developing dorsal aorta



- Cells of nephrogenic cords **migrate** and form three nephrogenic segments along craniocaudal body axis:
  - **pronephric** region - cranially
  - **mesonephric** region - caudally from pronephric region
  - **metanephric** region - caudally

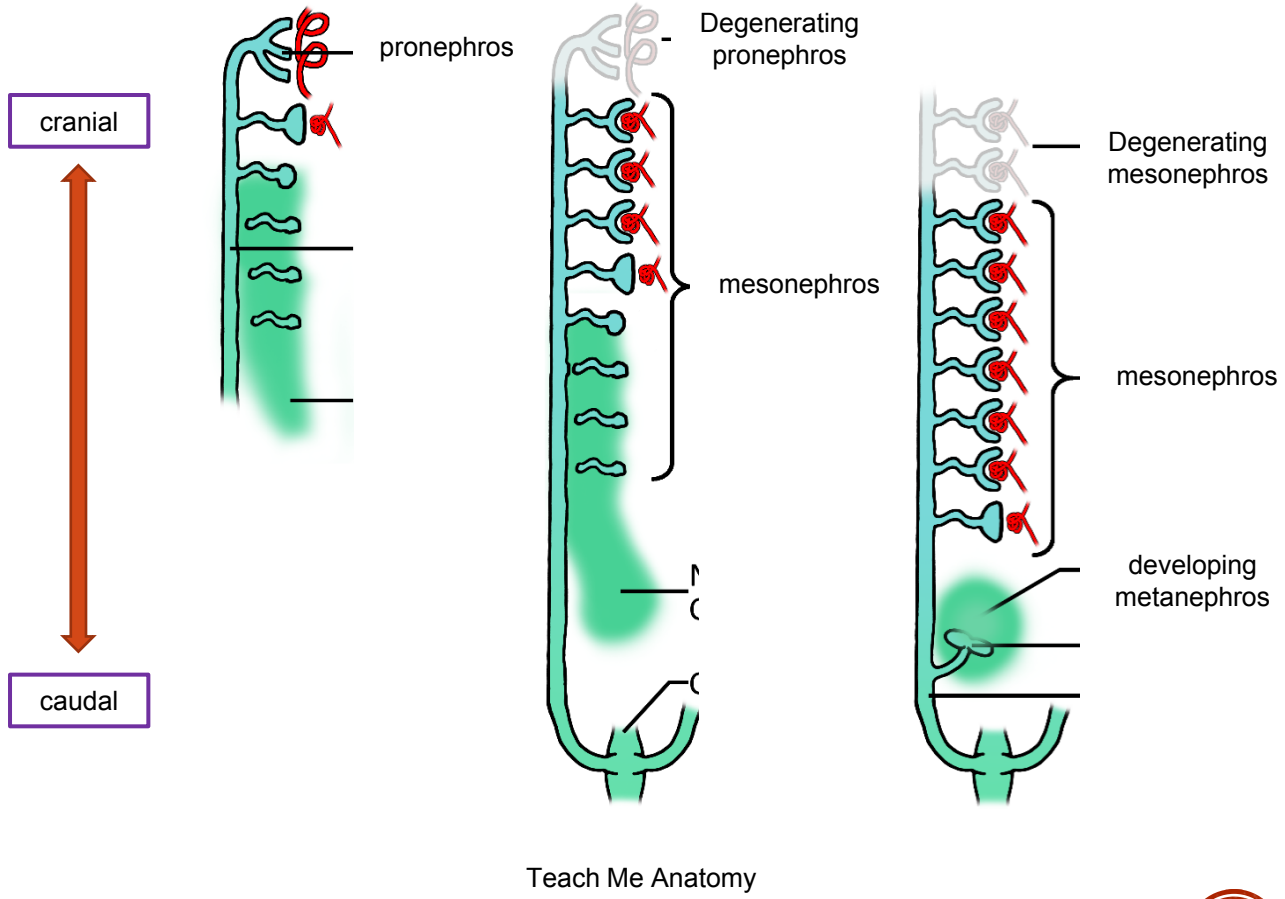


- Three paired basis of „kidney“ developmental stages

Duke embryology

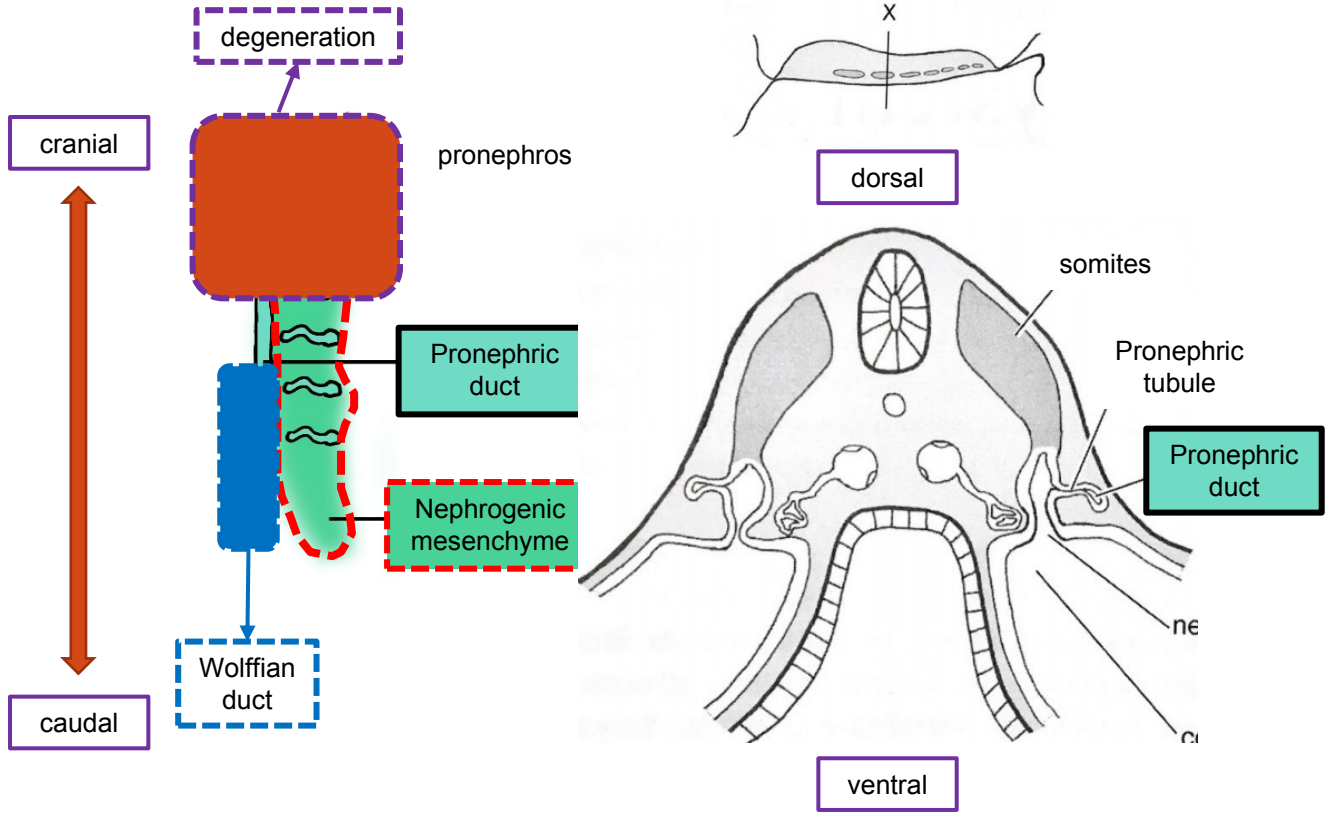
DEVELOPMENT OF KIDNEY

- Kidney develop in **two transitional** stages, **third** stage is **definitive**:
  - **Transitional** – pronephros a mesonephros
  - **Definitive** - metanephros
- **Pronephros** (pre-kidney) – **first** kidney tissue, gradual degradation
- **Mesonephros** (primary kidney) – **second** developmental stage, partial degradation, part is transformed
- **Metanephros** (definitive kidney) – last stage, **definitive** kidney



DEVELOPMENT OF PRONEPHROS

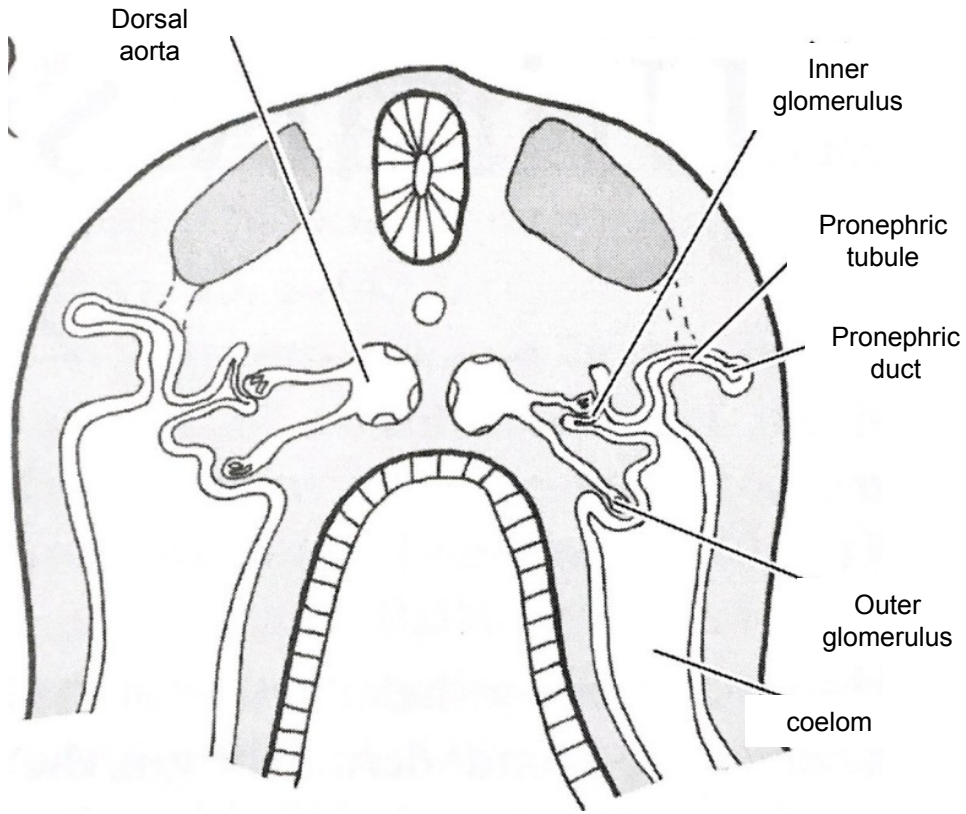
- Rudimentary, non-functional kidney
- formed **ventraly** from developing **cranial** somites
- Mesodermal cells form **pronephric duct** (tube) lateraly
- Cells of ducts **migrate** caudaly, cranial part of ducts induce formation of **pronephric tubules** from surrounding **nephrogenic mesenchyme**
- Pronephric tubules **functional** only in **fish** and **larva** of **amphibians**, **non-functional** in reptiles, birds and mammals
- **Cranial** part of ducts and tubules **degenerate**
- **caudal** part of **pronephric ducts** preserve excretory function during development - formation of **Wolffian** duct from caudal part of pronephric duct



Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF PRONEPHRIC BODY

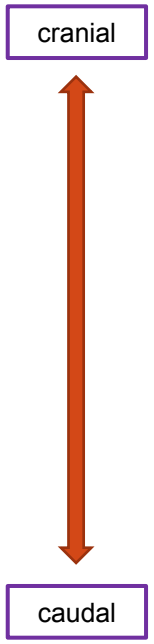
- Pronephric tubules formed on level of each cranial somite
- Each developing tubule is connected with nephrocoel cavity which opens to coelomic cavity through **nephrostome**
- **branching** of capillary loops (**glomerulus**) from **dorsal aorta**, invaginate to:
  - **Epithelium of coelom** – **outer glomeruli**, filtration from coelom
  - **Walls of tubule** – **inner glomeruli**, separated from coelom
- **epithelium** forming around loop of capillaries forms **Bowmans** capsule
- **Outer glomeruli**
  - Formation in **lower vertebrates**, less effective filtration
  - Filtration of fluid is allowed thanks to activity of ciliated cells from coelomic cavity to pronephric tubules close to nephrostome

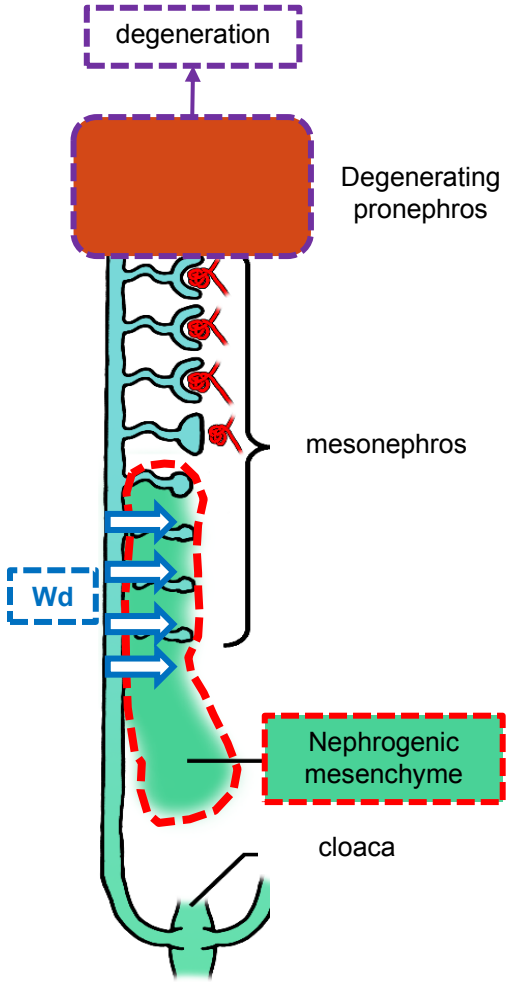


Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF MESONEPHROS

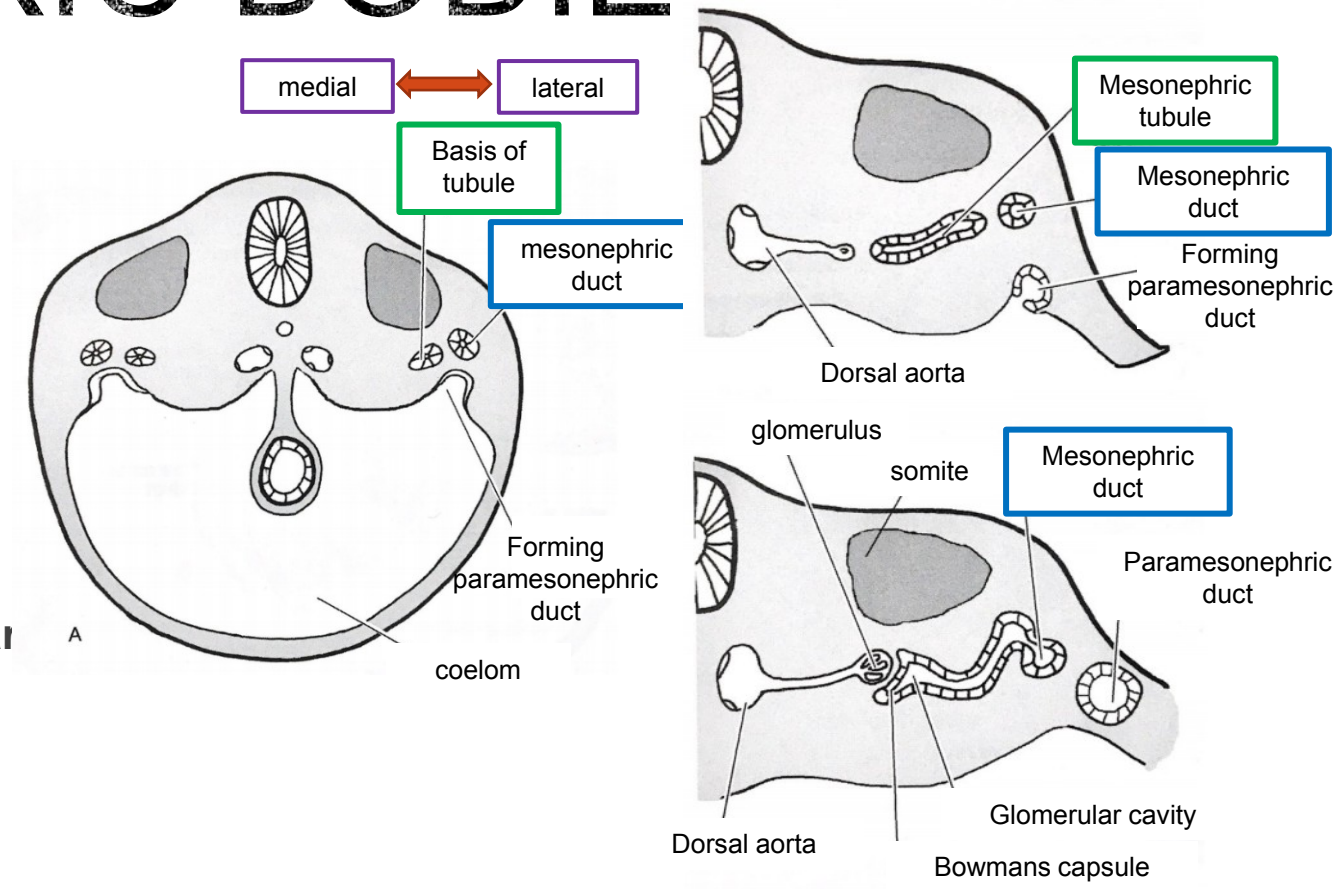
- **Wolffian duct** induces development of tubules from adjacent nephrogenic mesenchyme
- Formation of **mesonephros** – in some mammals (human) filtration is functional
- Induction of tubule formation more caudaly
- **degeneration** of pronephros cranialy
- male – **Wolffian duct** as basis for epididymis and ductus deferens development





DEVELOPMENT OF MESONEPHRIC BODIES

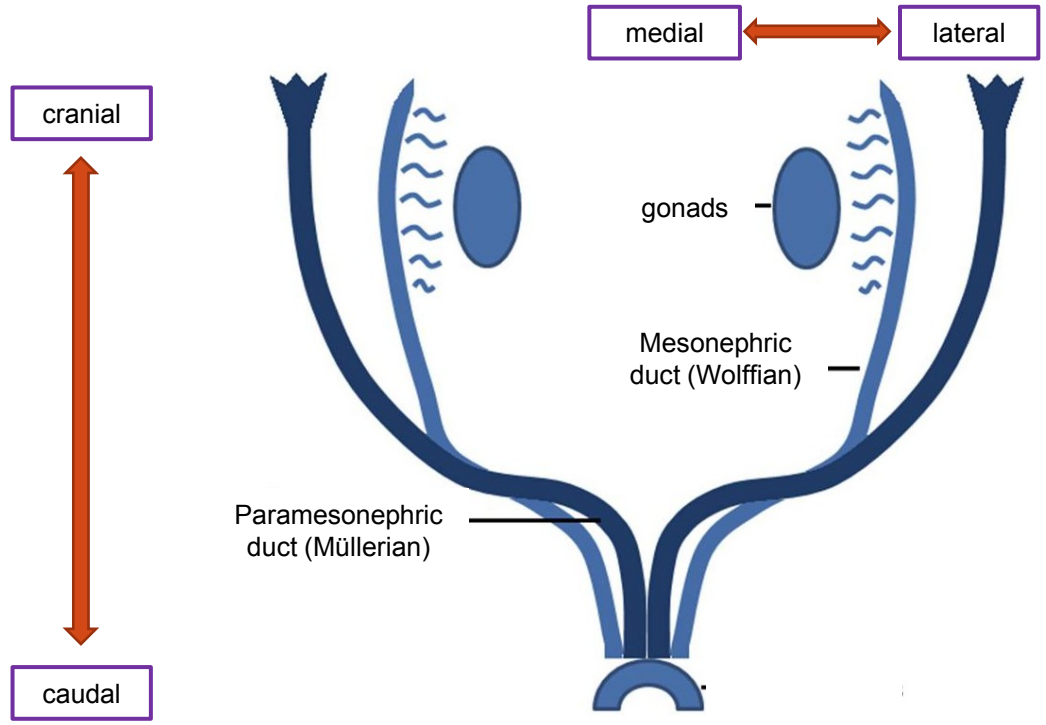
- **lateraly** development of **mesonephric** ducts
- Induction of **mesonephric tubule** formation medialy from **nephrogenic mesenchyme**
- **mesonephric tubules connect** laterally to **mesonephric** (**Wolffian**) **duct**
- **tubules** grow **medialy** and start to form **Bowmans capsule**
- Bowmans capsule **enclose** developing **capillar loops** of glomerulus from **mesonephric arteries**
- mesonephric arteries develop through **branching** directly from **dorsal aorta**



Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF PARAMESONEPHRIC DUCTS

- basis for **Müllerian** duct development
- **females** – basis for development of fallopian tubes, uterus, cervix and upper third of vagina
- **males** - atrophies
- Develop **lateraly** of Wolffian duct from coelomic epithelium, so called Müllerian ridge
- parallel development with Wolffian ducts in cranial region
- transition of Müllerian ducts to ventral side in caudal region



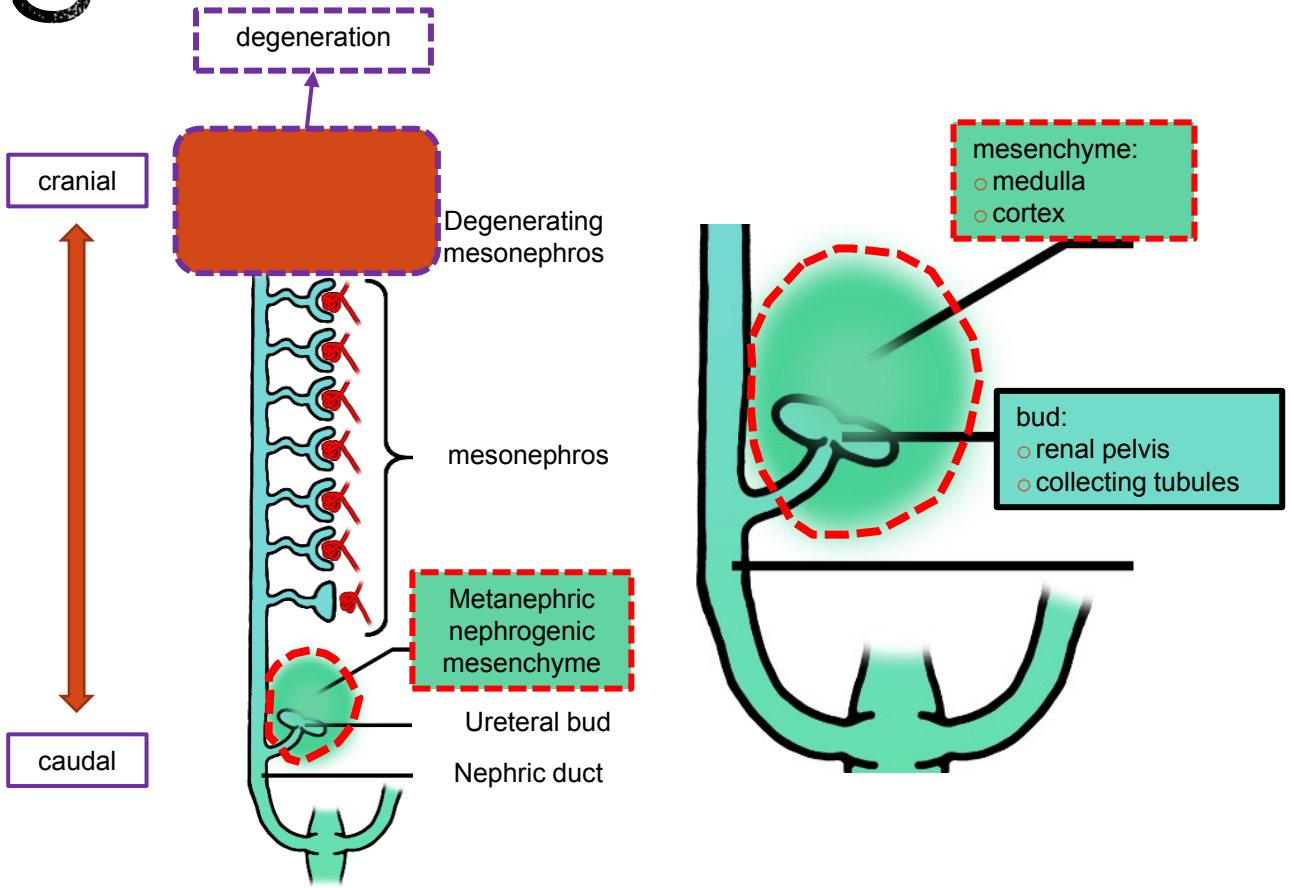
Corsoginho et al. 2016. ECR

DEVELOPMENT OF METANEPHROS

- Formation of definitive kidney (**metanephros**) **caudaly** from mesonephros
- Formed from paired primordial structures – **ureteral buds** – outgrowths of mesonephric ducts
- Buds grow into **nephrogenic mesenchyme** (caudal region of nephrogenic basis)

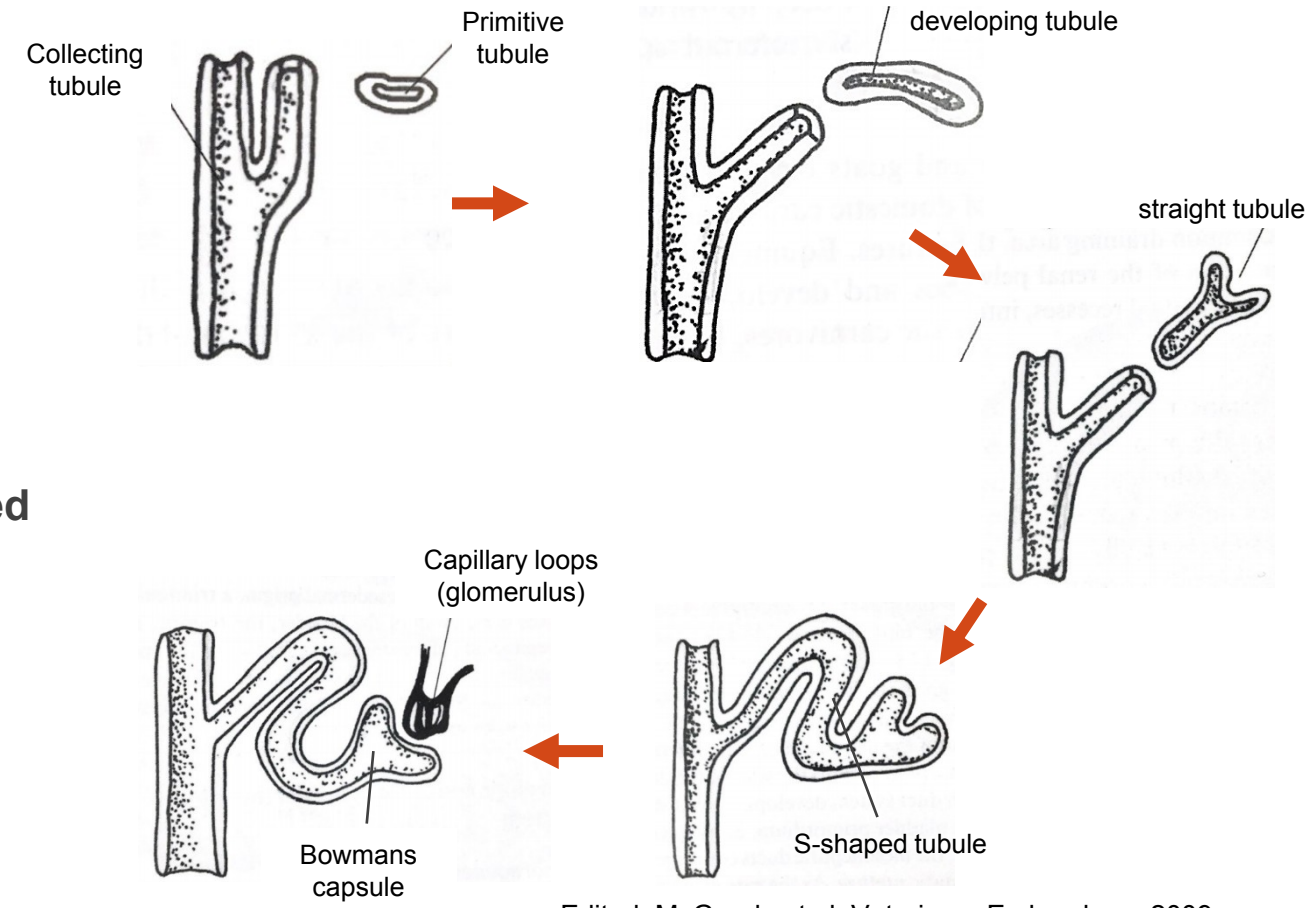
- from **buds** are developed:
  - renal pelvis
  - collecting tubules

- collecting tubules induce formation of **mesenchymal structures**:
  - medulla
  - cortex



DEVELOPMENT OF KIDNEY

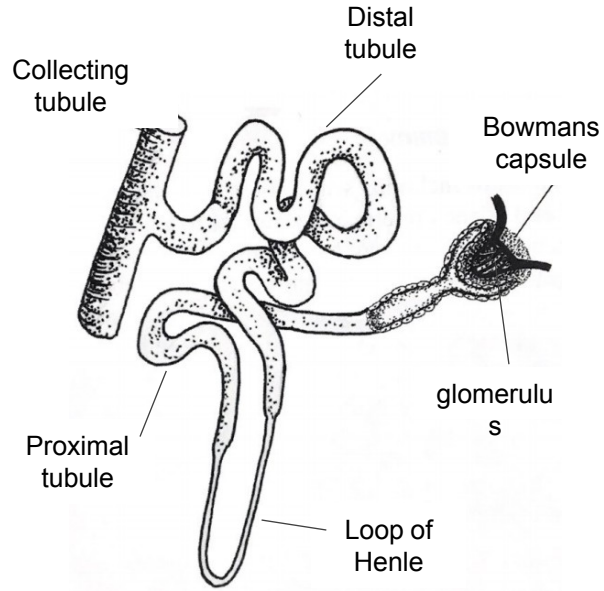
- branching of renal pelvis – formation of **collecting tubules**
- collecting tubules induce formation of **primitive tubules** from metanephric mesenchyme
- **Primitive tubules** connect with collecting tubules and change their shape from **straight** to **S-shaped** (basis for proximal, medial and distal segment of **nephron**)
- the other side of tubule forms **cup** (**Bowmans capsule**) surrounding **capillary loops** (**glomerulus**) – together form **renal body**

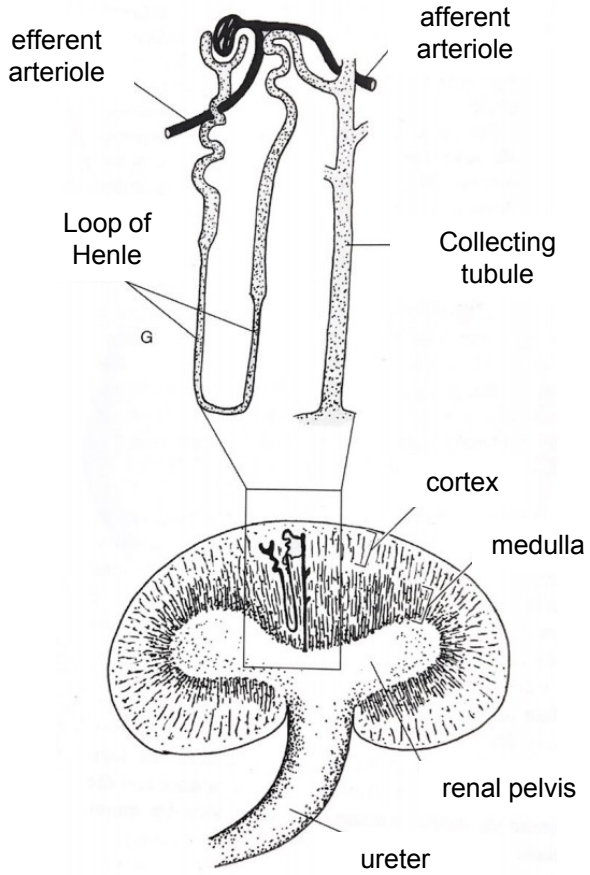


Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF KIDNEY

- tubules develop, U-shaped prolongation – formation of **Loop of Henle** (passage towards renal pelvis)
- Tubules withdrawing from Bowmans capsule – **proximal convoluted tubules**
- collecting tubules connects to **distal convoluted tubules**
- renal body, Loop of Henle, proximal and distal convoluted tubules - **nephron**
- **cortex** – renal bodies, proximal and distal tubules
- **medulla** – Loops of Henle, collecting tubules

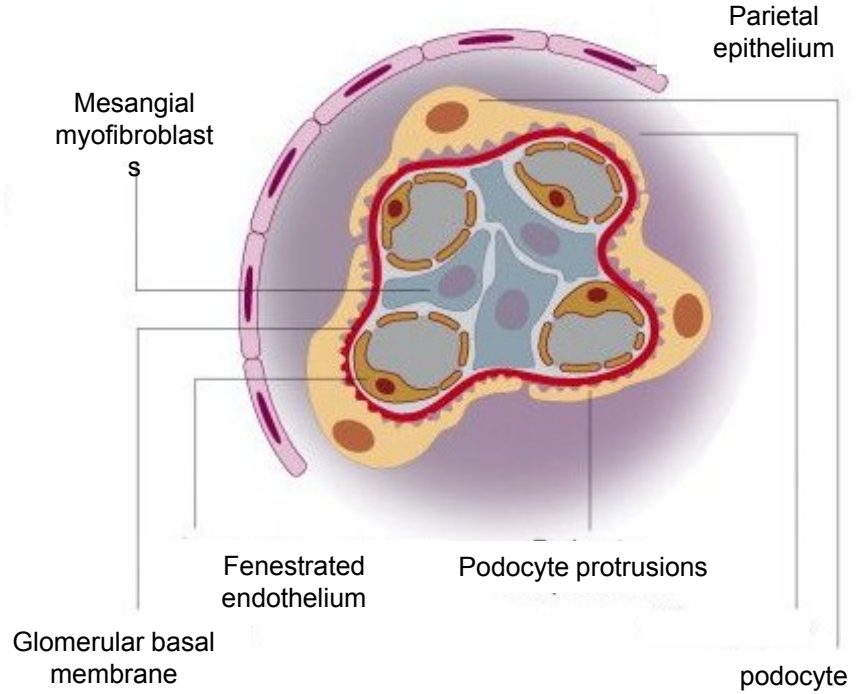




Edited: McGeady et al. Veterinary Embryology. 2009

CELLS FORMING RENAL BODY

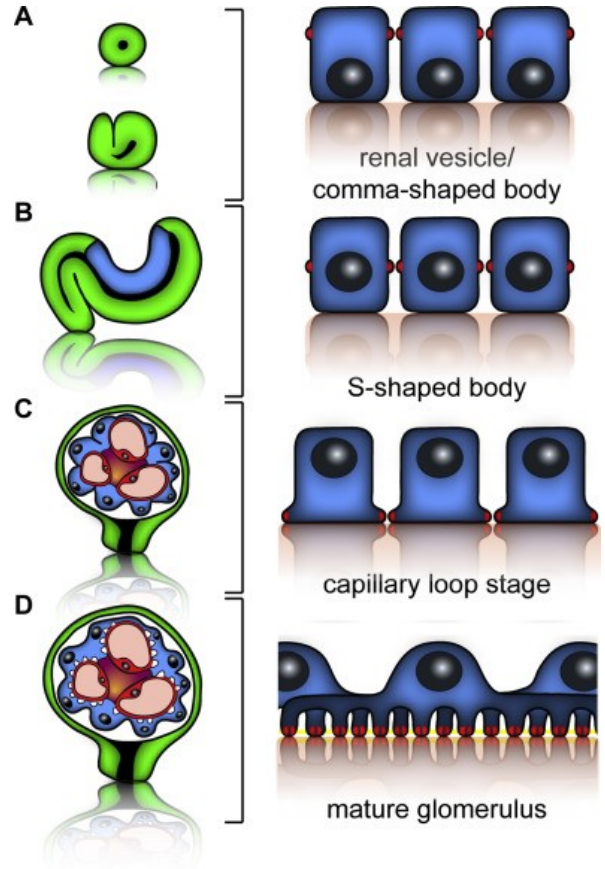
- **fenestrated endothelium** – endothelium of glomerular capillaries with pores for filtration of bigger molecules
- Glomerular capillaries surrounded by **podocytes** – formation of glomerular membrane
- **Mesangial myofibroblasts** – smooth muscle cells of vessels, induce invagination and thus segmentation of capillary loops
- **Parietal epithelium** of Bowmans capsule – epithelial cells form capsule of glomerulus, potential role in regeneration (not clear yet)



Trends in Genetics

DEVELOPMENT OF SLIT MEMBRANE

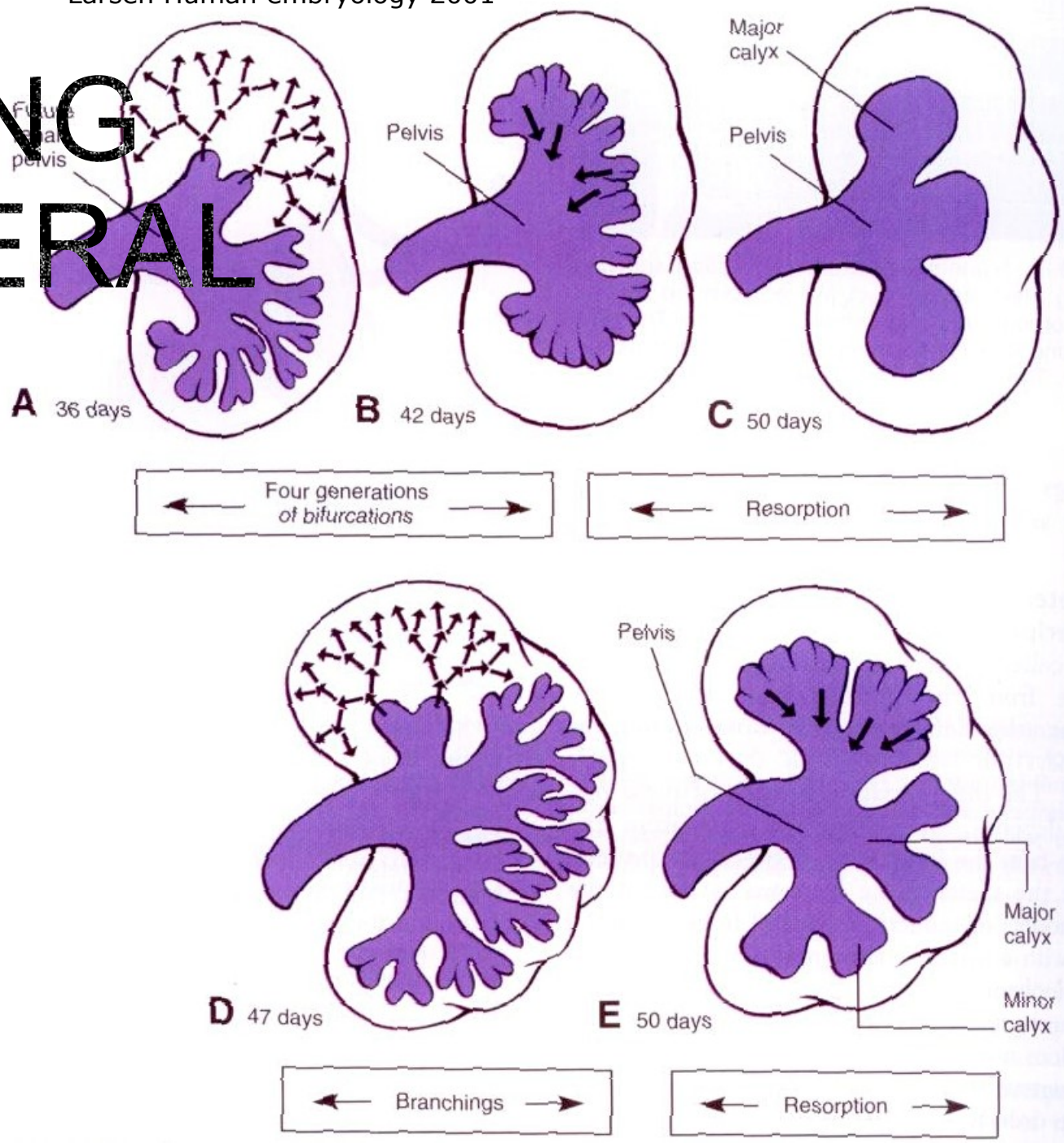
- **comma-shaped** (straight) tubules – pre-podocytes with cylindrical shape, apical intercellular connections
- **S-shaped** tubules – extension of apical sides of podocytes, intercellular connections moved to basal sides
- Formation of **capillary loops** – induction of apical side **expansion of podocytes around capillaries**, formation of intercellular connections on basal side
- **mature glumeruli** – intercellular connections moved to spaces between podocytes protrusions and basal membrane, **fusion of podocytes and endothelial cells basal membranes**, formation of one **glomerulal basal membrane**



Schell et al. 2014. Sem Cell Dev Biol

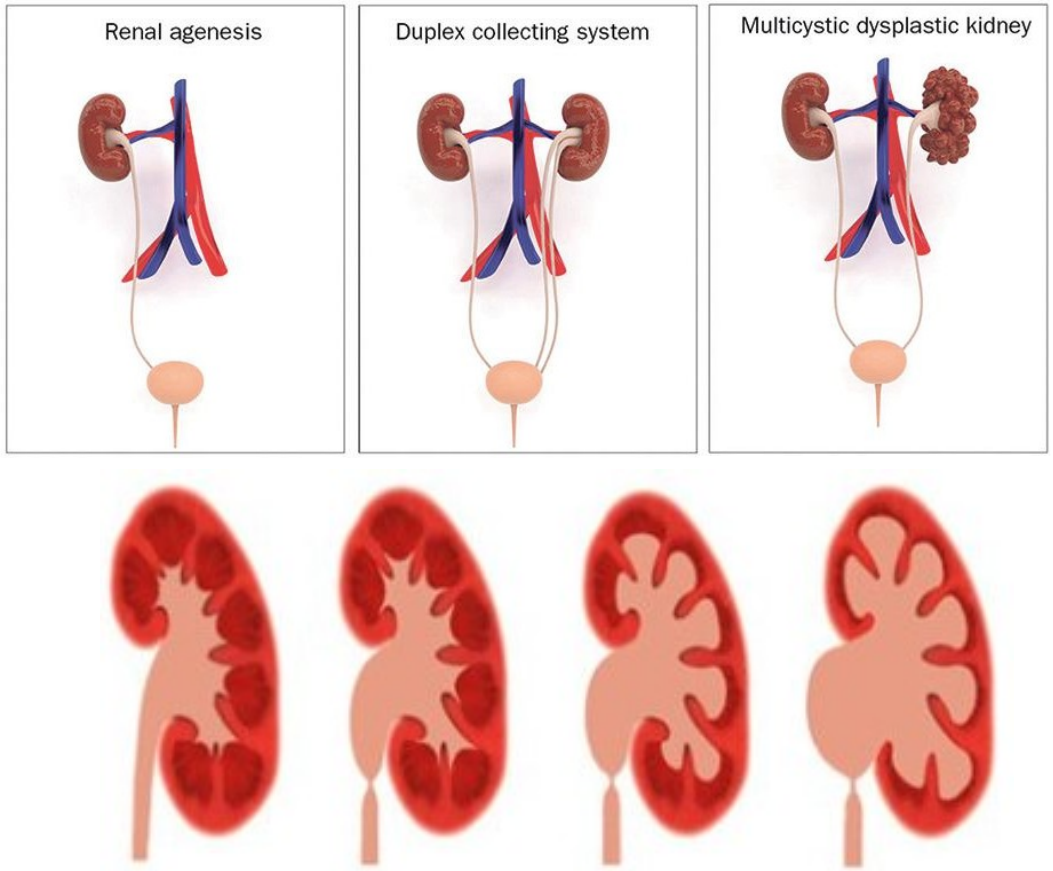
Larsen Human embryology 2001

BRANCHING OF URETERAL BUD



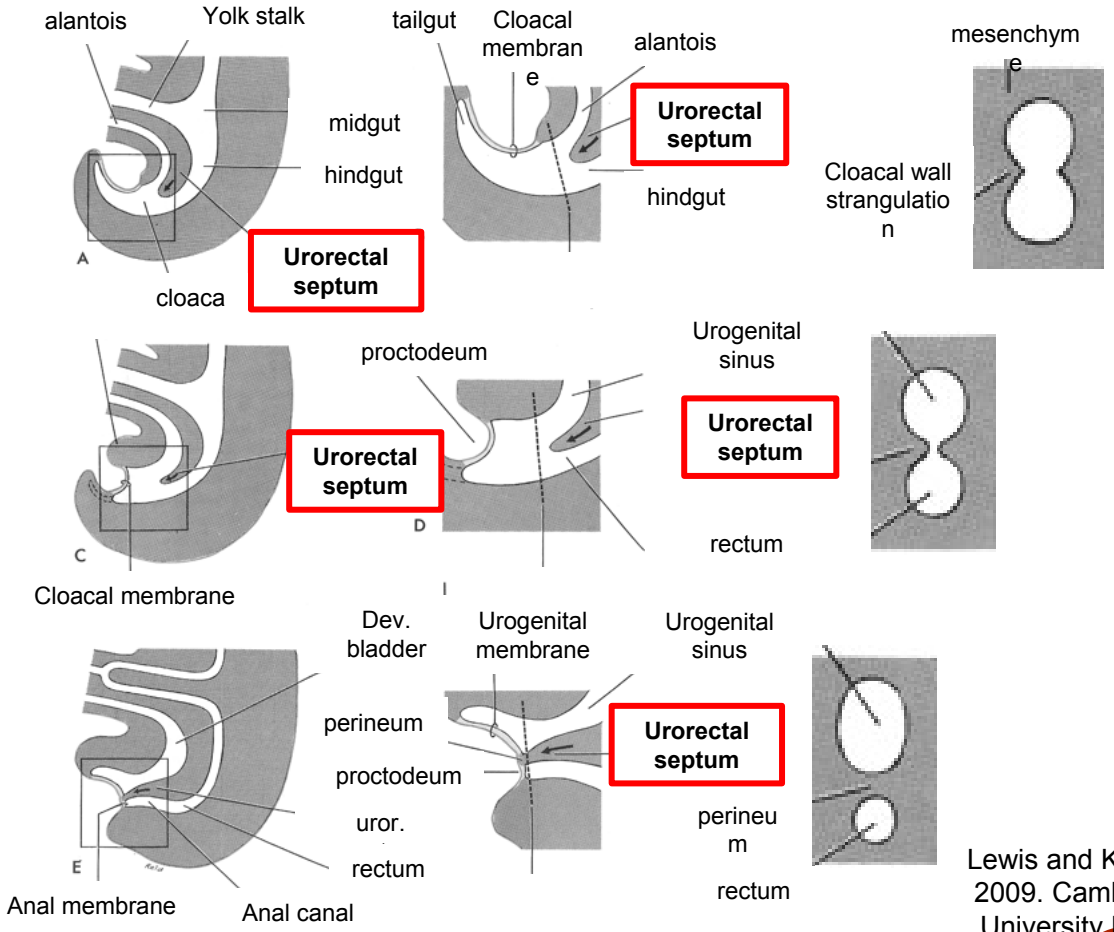
DEVELOPMENTAL DEFECTS OF KIDNEYS

- **Renal agenesis/dysgenesis**
  - Development of metanephric bud is altered or not developed at all, on one or both sides
  - Patients can live without one kidney
  - Missing both kidneys lethal perinataly
- **Multicystic kidney dysplasia**
  - Nephron not developed, ureteral bud is not branched
  - Renal tubules surrounded by non differentiated cells
  - Often bifid (cleft) ureter
- **Hydronephrosis**
  - narrowed connection between renal pelvic and ureter (stenosis) – altered drainage
  - Extension of renal pelvis
  - Higher preasure in cortex – loss of function
  - surgery



CLOACA DEVELOPMENT

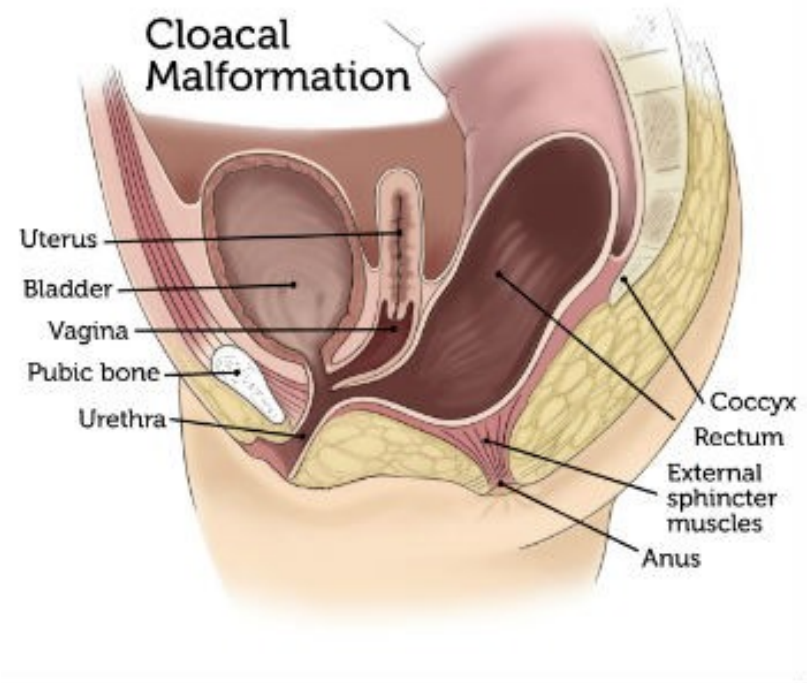
- origin – **hindgut endoderm**
- Later divided by **urorectal septum** into:
  - **dorsal** – part of colon, rectum
  - **ventral** – urogenital sinus (ureter, bladder)
- Caudal part connected with external environment by cloacal membrane, ventraly connected to alantois
- **mammals** – transitional structure
- **reptiles, birds** – permanent structure



Lewis and Kaplan, 2009. Cambridge University Press

DEVELOPMENTAL DEFECTS OF CLOACA

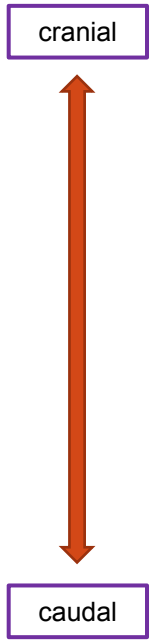
- **Persistent cloaca**
  - Cloaca is not divided
  - rectum, vagina and urethra connected into one canal
  - Mostly in place of developing urethra
  - surgery

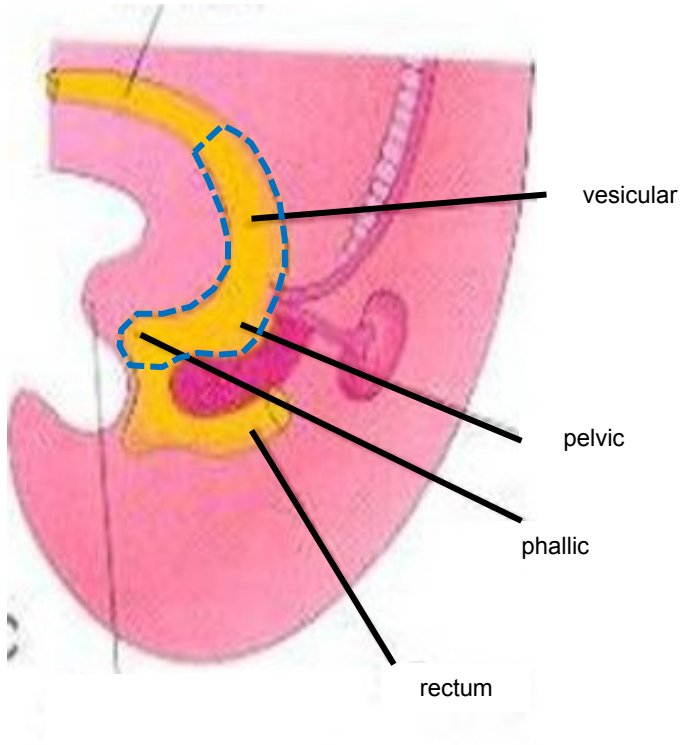


Boston Children`s Hospital

UROGENITAL SINUS

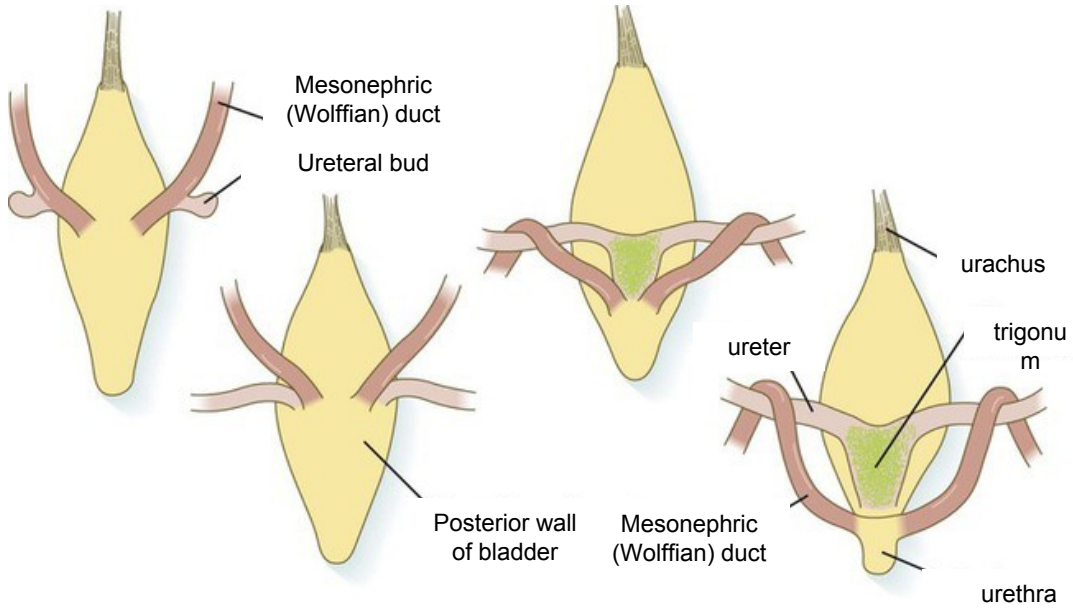
- Ventral part of cloaca – **urogenital sinus** – divided into:
- **vesicular** segment – cranial part, development of urinary bladder
- **pelvic** segment – middle narrower part
  - males – main part of urethra
  - females – whole urethra
- **phallic** segment – caudal wider part
  - males – part of urethra in penis
  - females – vaginal vestible





DEVELOPMENT OF URETERS

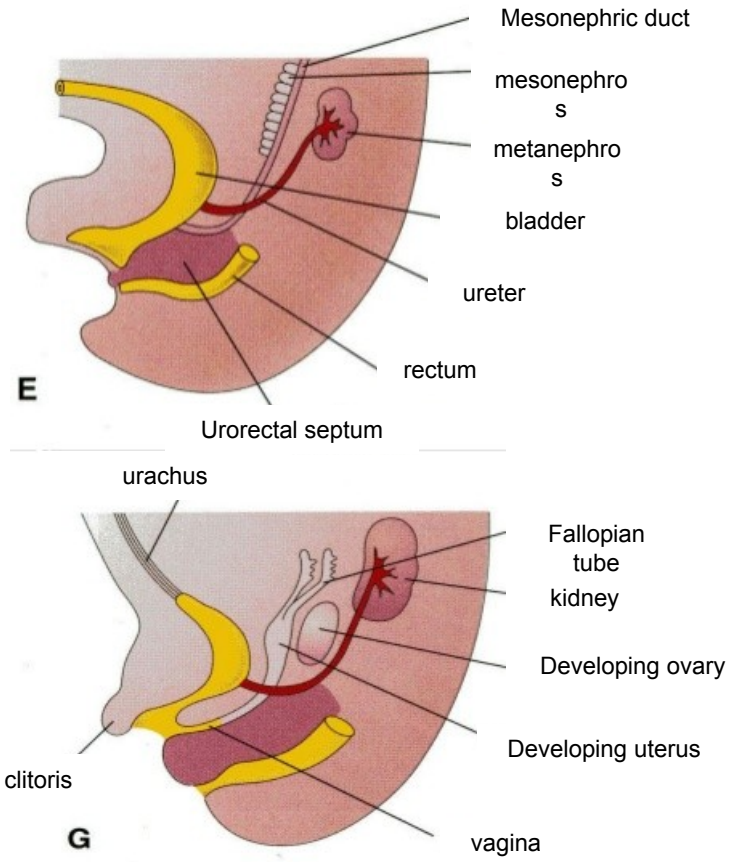
- **Muscular tube** important for active drainage of filtrate from kidney
- ureters form by **invagination of wall** of Wolffian duct (ureteral bud) **towards** the nephrogenic mesenchyme (kidney development)
- Wolffian duct and developing ureter connect to developing bladder from cloaca
- Kidney migrate cranially, **prolongation** of developing ureters
- formation of bladder **trigonum**
- **Ureters** connected to **cranial** regions of **bladder**
  - **males** – Wolffian duct moved caudally, connected to urethra
  - **females** – Wolffian duct degrades



Liaw et al. 2018. Differentiation

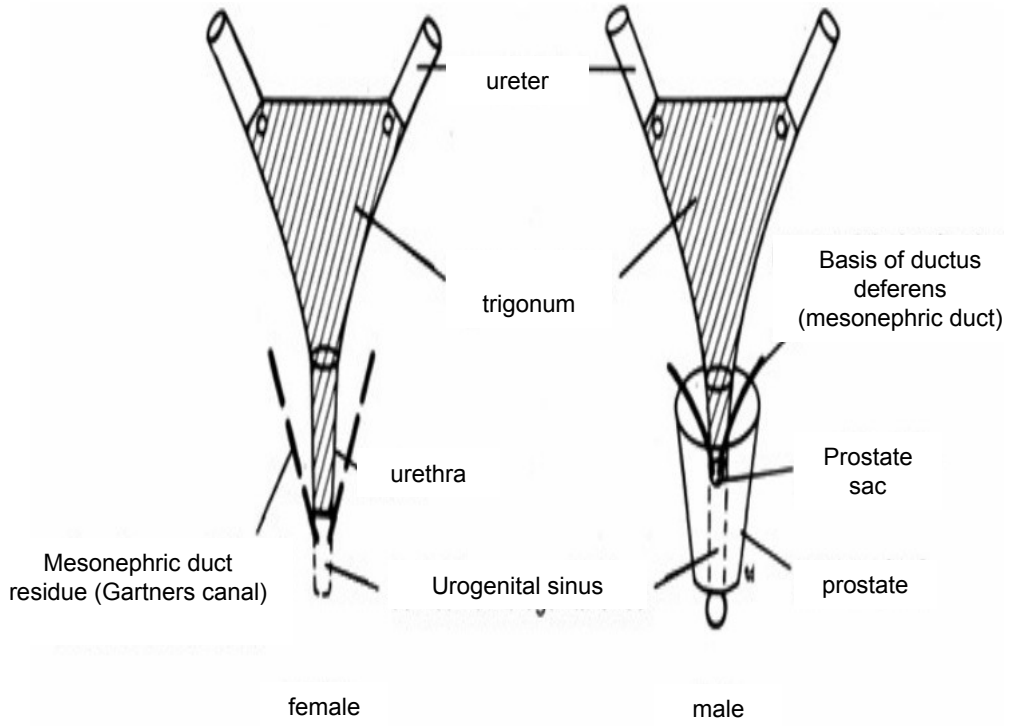
DEVELOPMENT OF URINARY BLADDER

- origin – **ventral side of hindgut endoderm**, so called **urogenital sinus**
- Ventral side of cloaca – divided by **urorectal septum**
- Urogenital sinus connected to **allantois cranially**, later **degrades**
- Rest is connected to allantois – bladder - **urachus** (bladder mesentery on ventral side)
- **Bladder develops from vesicular** segments (cranial part) of **urogenital sinus** cranially from ureters connection



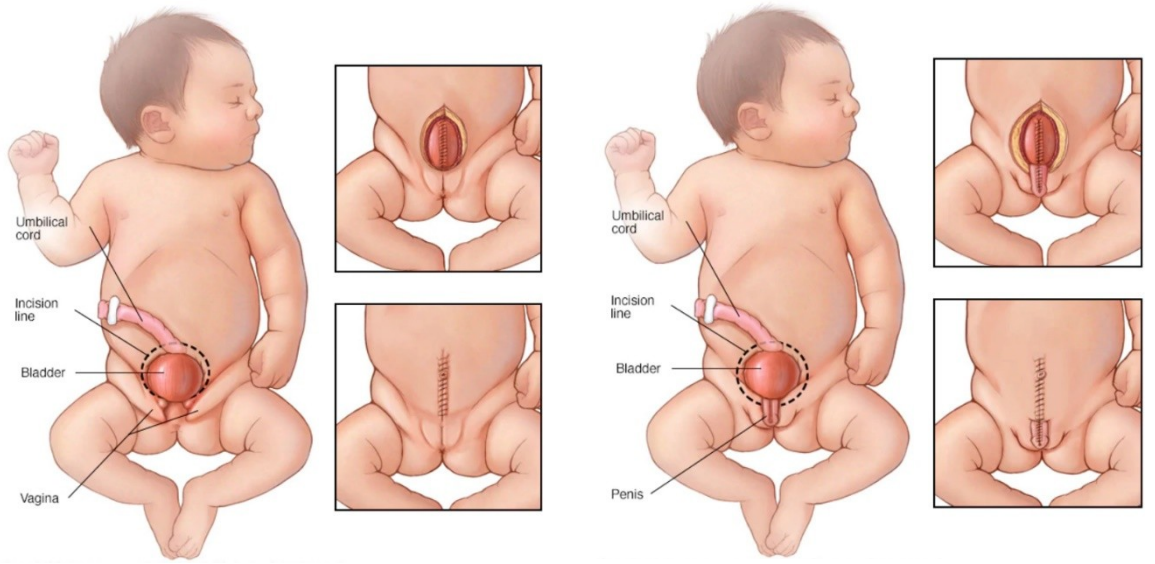
FORMATION OF URINARY BLADDER TRIGONUM

- region of **connection** between **ureter** and **Wolffian duct** (future deferens duct in males)
- region of connection – **urinary bladder trigonum**
- **trigonum** formed of urinary bladder **smooth muscles**, partly of smooth muscles from **ureters**
- basis for formation of **valves preventing return** of **urine** back from bladder through ureters to kidneys – kidney damage



DEVELOPMENTAL DEFECTS OF URINARY BLADDER

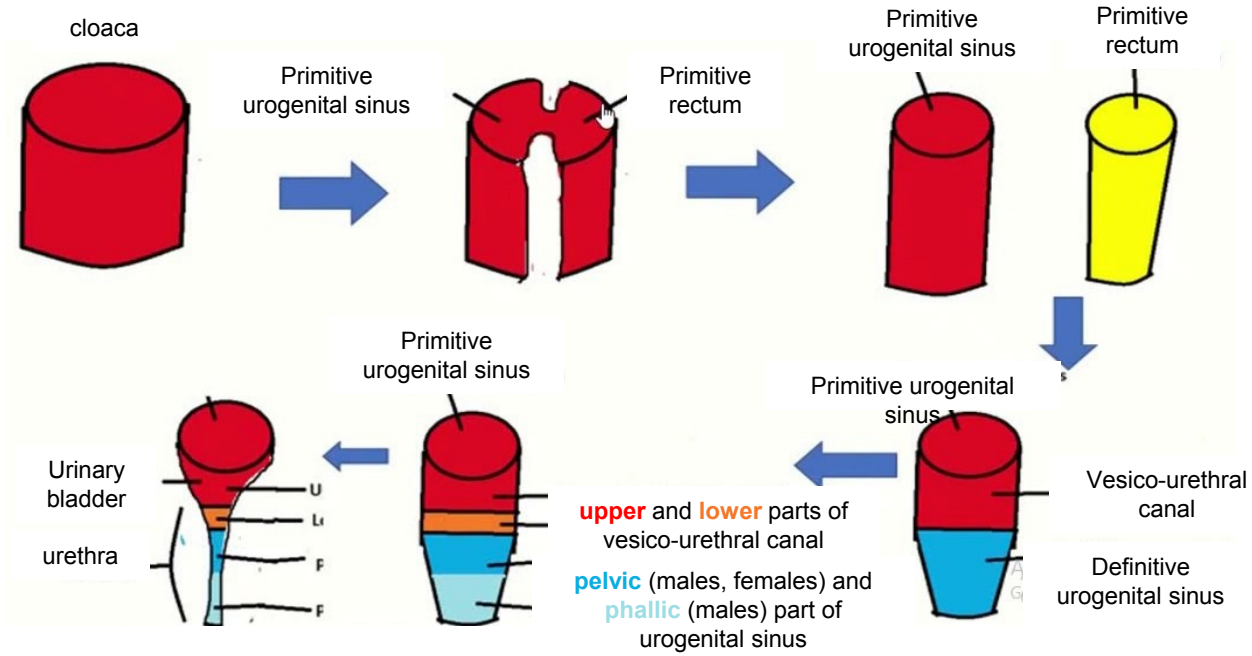
- **Urinary bladder extrophy**
  - Urinary bladder develops outside the body
  - bladder cant keep urine inside - incontinence
  - surgery



Mayo Foundation for Medical Education and Research

DEVELOPMENT OF URETHRA

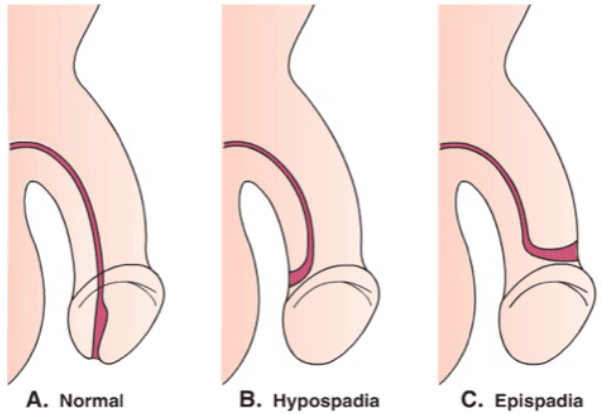
- origin – hindgut **endoderm**, forms together with urinary bladder by division of **urogenital sinus** from ventral side of **cloaca**
- urethra develops from **pelvic** and **phallic** parts of **urogenital sinus**
- **males** – **pelvic** and **phallic** regions of sinus, **distal part** of **phallic** region formed from **ectoderm**, connection of Wolffian duct (deferens duct) to urethra, **connection** of **excretory** and **reproductive** systems
- **females** – **pelvic** region of sinus, Wolffian ducts degrade, **ducts** of **excretory** and **reproductive** systems **separated**

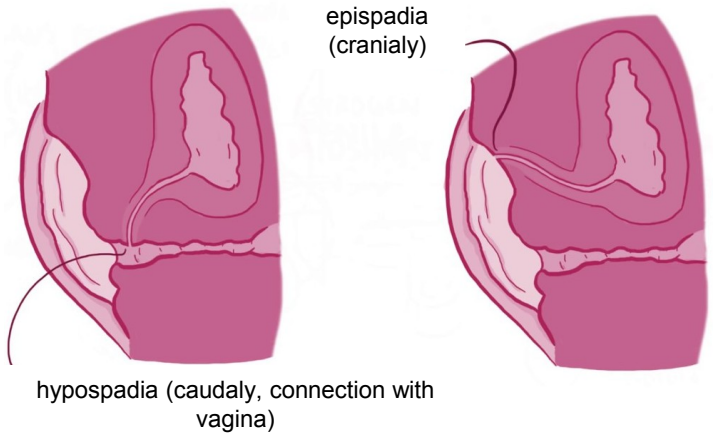


DEVELOPMENTAL DEFECTS OF URETHRA

- **Epispadia**
  - Displaced opening of urethra
  - Opening on dorsal side of genitals
  - More often in males

- **Hypospadia**
  - Displaced opening of urethra
  - Opening on ventral side of genitals
  - More often in males



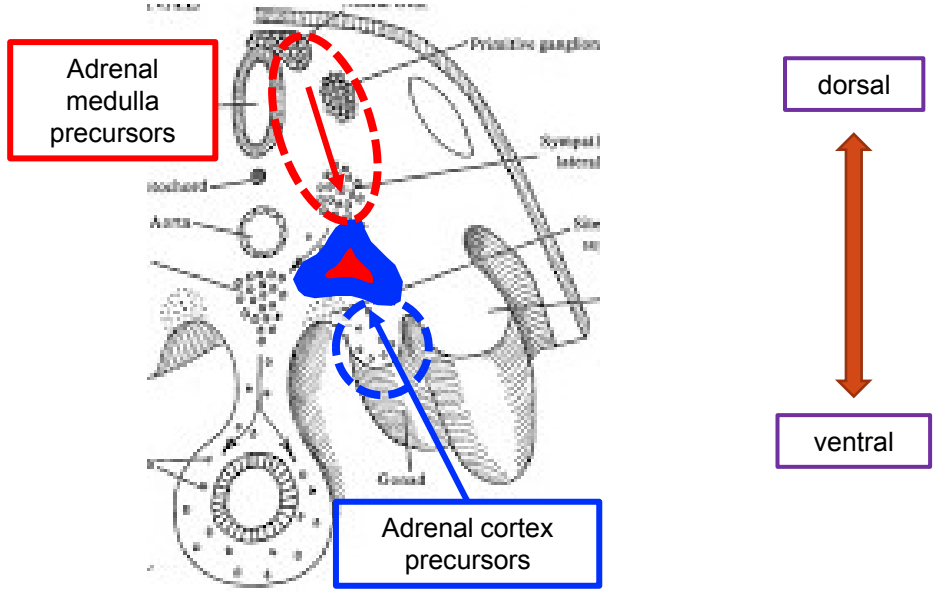


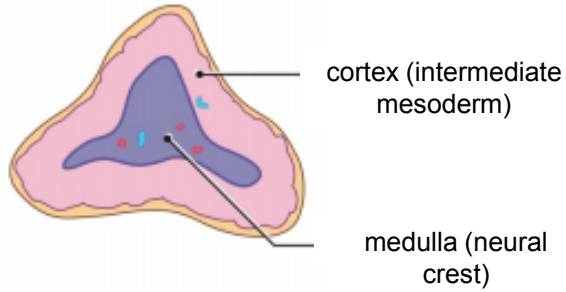
DEVELOPMENT OF ADRENAL GLANDS

- **Adrenal cortex** develops from **intermediate mesoderm**
- **Adrenal medulla** develops from **neural crest** cells

- **cortex** – develops from **epithelium** of **coelom** in urogenital cord region
- **medulla** –**neural crest cells migrate** to urogenital cord region

- medullary cells covered by cortical cells

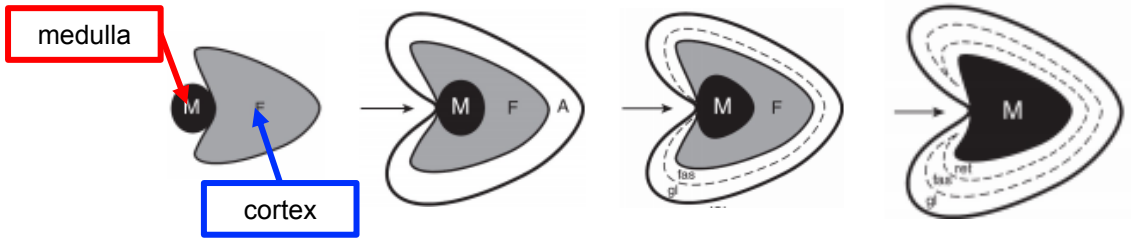


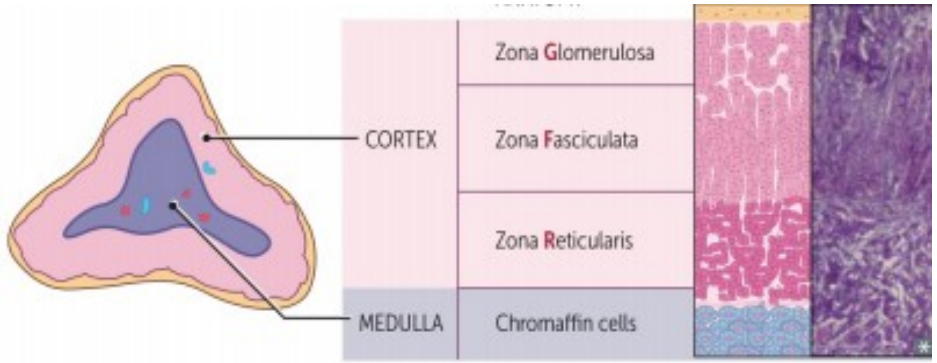


Pansky. Review of Medical Embryology

DEVELOPMENT OF ADRENAL GLANDS

- **Adrenal cortex** develops from **intermediate mesoderm**
- **Adrenal medulla** develops from **neural crest** cells
- **Neural crest** cells **migrate** to the region of developing **cortex**, cortical cells **cover** medullary cells
- Cortical cells differentiate and form layers:
  - Zona reticularis (androgens)
  - Zona fasciculata (glucocorticoids – cortisol, corticosterone)
  - Zona glomerulosa (mineralcorticoids - aldosterone)
- Adrenal medulla
  - Chromaffin cells (catecholamines – adrenaline, noradrenaline)



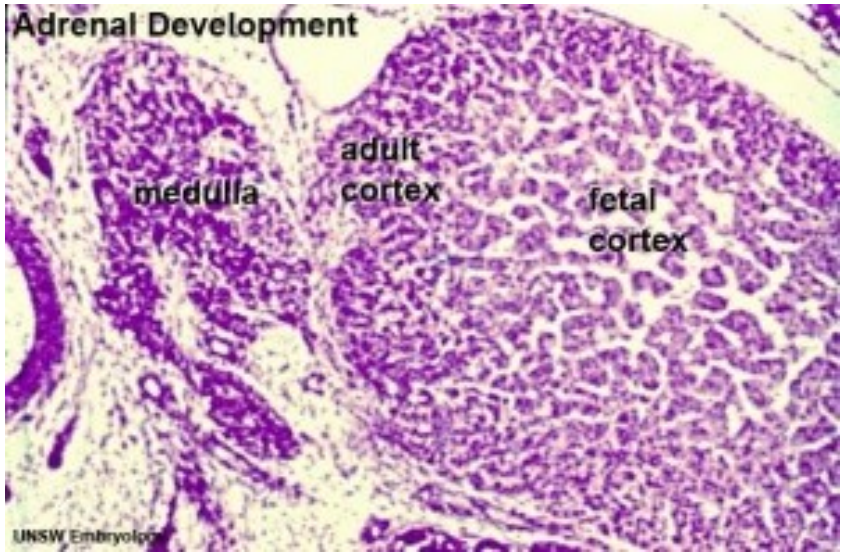


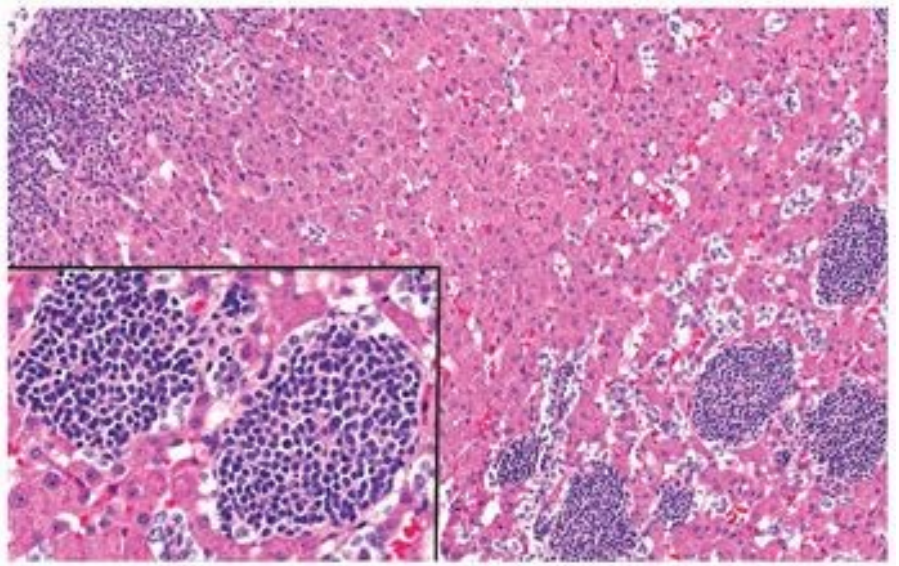
Pansky. Review of Medical Embryology

DOUBLE ORIGIN OF ADRENALS

- Medulla – neuroectoderm
  - Neural crest cells form sympathetic ganglion in solar plexus = chromafinne cells + primitive sympathetic cells (noduli)
  - Travel to cortex (7th week iud) and along main vein get to its center
- Cortex - intermediate mezoderm
  - Cluster of cells in urogenital ridge (5th week iud) – primitive cortex
  - Second wave of differentiation of mesotel cells (6th w iud) – definitive cortex
  - 8th w iud – separaconnective tissue
  - Zona reticulata appears after 3rd year of life
  - Proliferation and apopttion from other organs by osis reshape primitive cortex in definitive c.

8 w iud

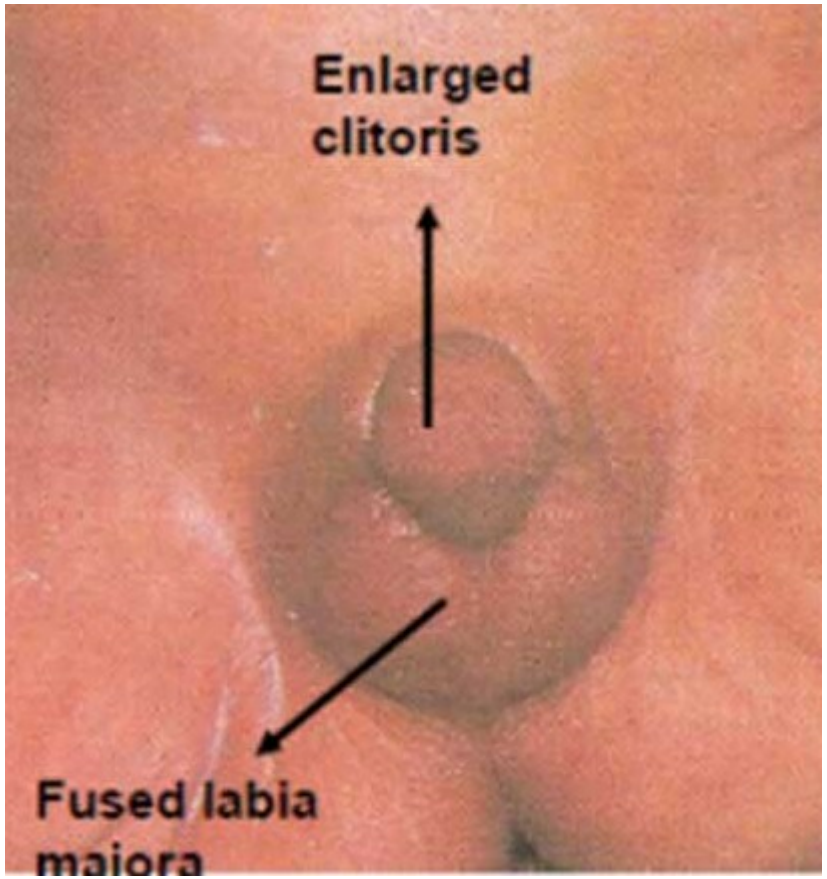




14 w iud

DEVELOPMENTAL DEFECTS OF ADRENAL GLANDS

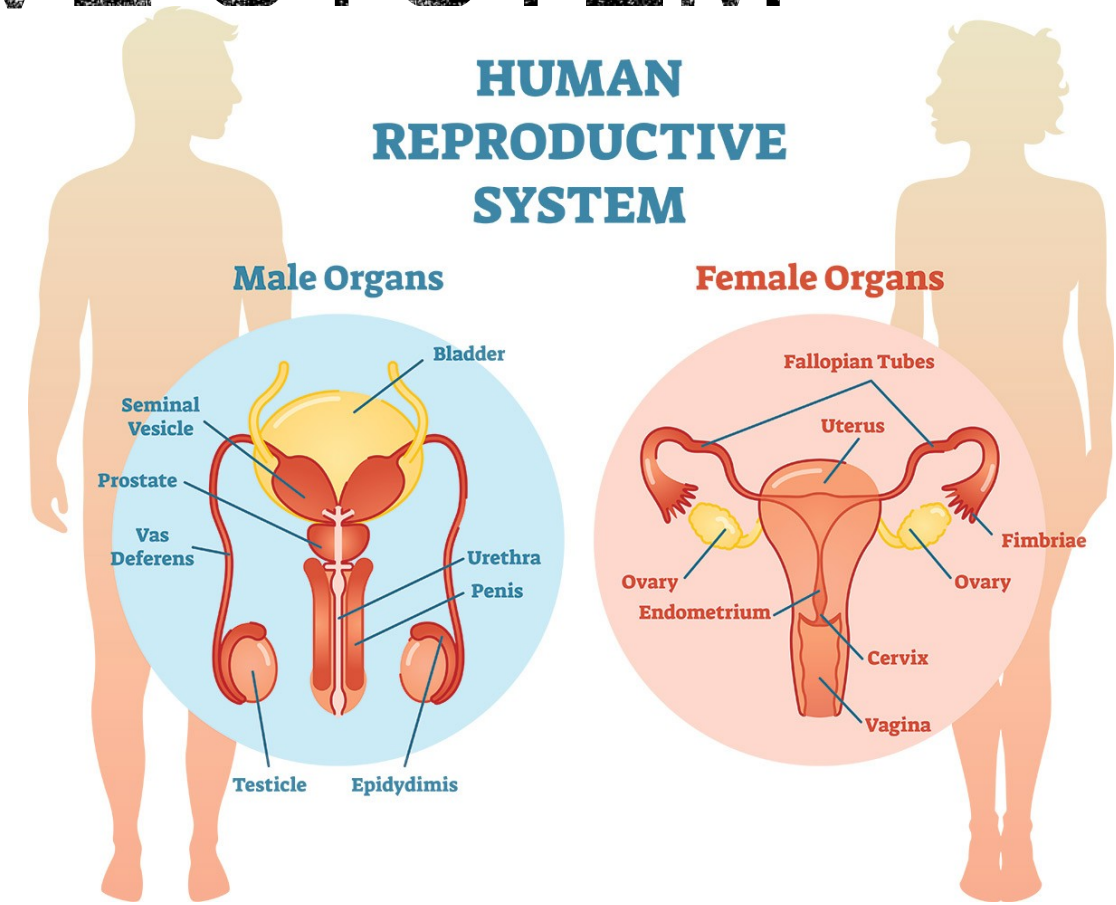
- **Congenital adrenal hyperplasia**
  - altered production of cortisol in zona fasciculata
  - higher production of adrenocorticotropic hormone
  - hyperstimulation of adrenal cortex to produce hormone precursors
  - hyperplasia caused by storage of more precursors
  - overproduction of androgens – formation of male sexual characteristics in females



DEVELOPMENT OF REPRODUCTIVE SYSTEM

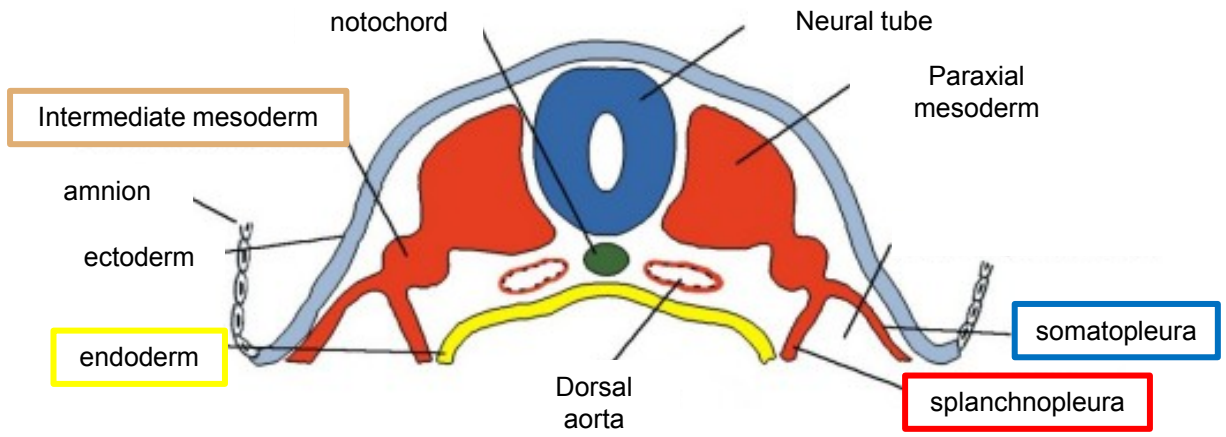
FUNCTION OF REPRODUCTIVE SYSTEM

- production of germ cells (oocytes, sperms)
- storage, maturation and transport of germ cells
- fertilization and development of new individuals of a given species



ORIGIN AND DEVELOPMENT OF REPRODUCTIVE SYSTEM IN VERTEBRATES

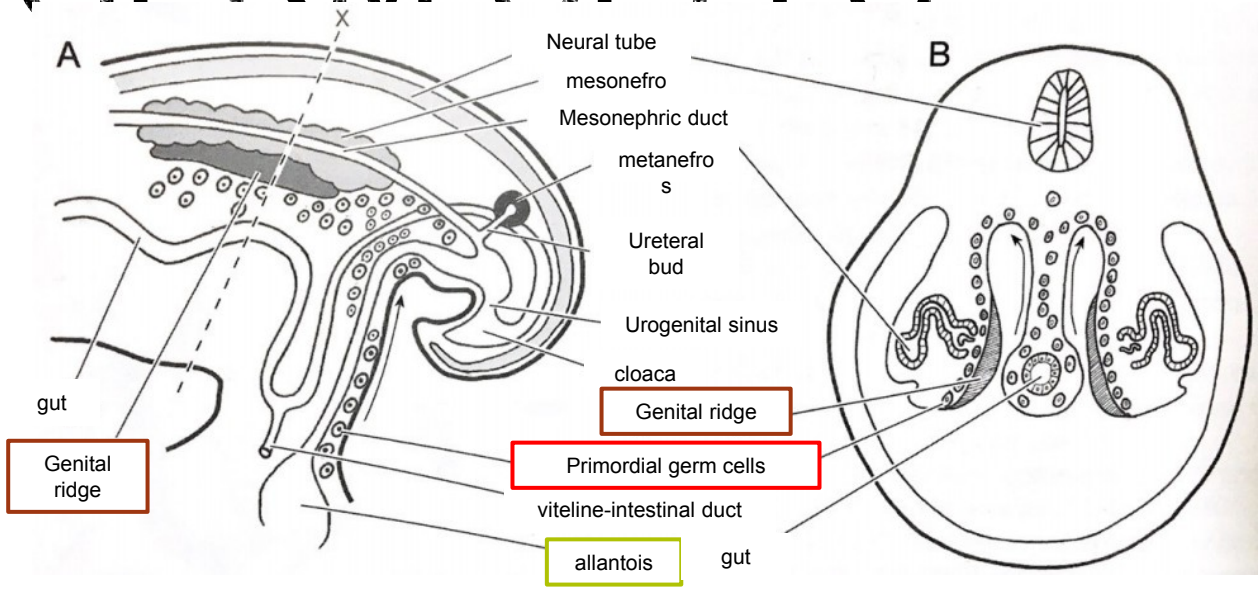
- Main source for reproductive system – **intermediate mesoderm**
  - **endoderm** – urethra and prostate males, vagina females
  - **splanchnic mesoderm** – vessels, connective tissue, muscles
  - **somatic mesoderm** – stroma of external genitals



- Reproductive system:
  - **female –** ovaries, oviducts, uterus, vagina
  - **male** – testes, epididymis, ductus deferens, glands, urethra, penis

FORMATION AND DEVELOPMENT OF PRIMORDIAL GERM CELLS

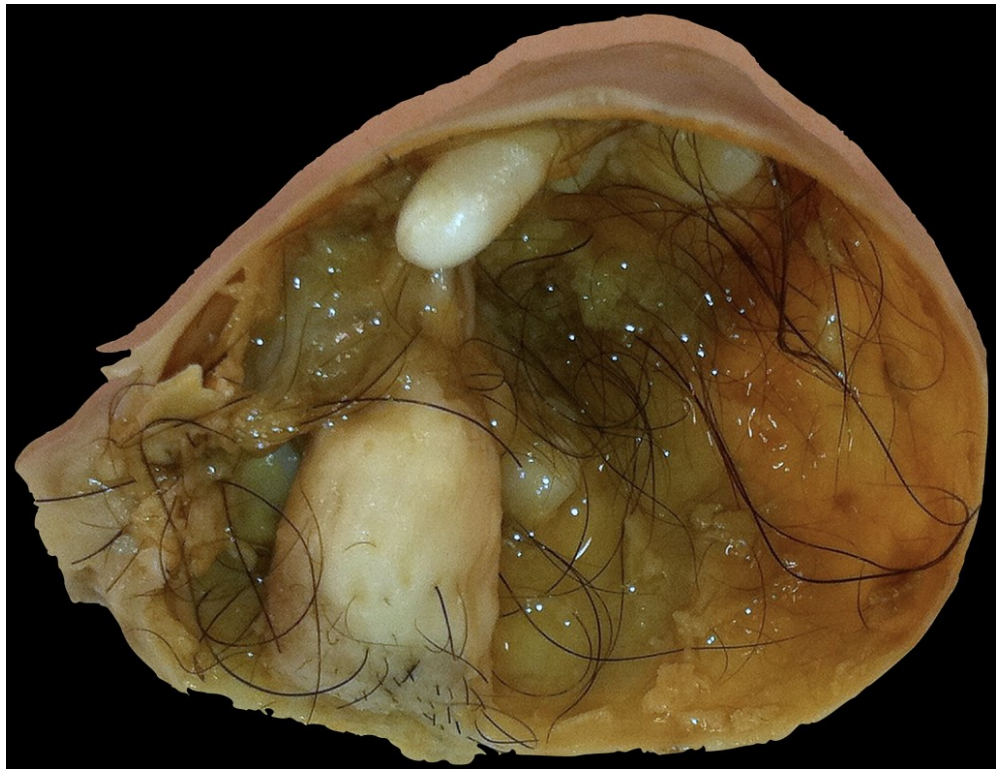
- **epiblast** cells migrate through primitive streak to yolk sac and **alantois** region
- Cells further migrate along the hindgut wall to **genital ridge** – region of developing gonads
- **Primordial germ cells** settle undifferentiated gonads (testes, ovaries)
  - mammals – **active migration** of cells through surrounding tissues
  - birds – germ cells **migrate** via **bloodstream**
  - maturation in gonads – cells outside gonads die, preserved germ cells outside gonads can form **teratomas**

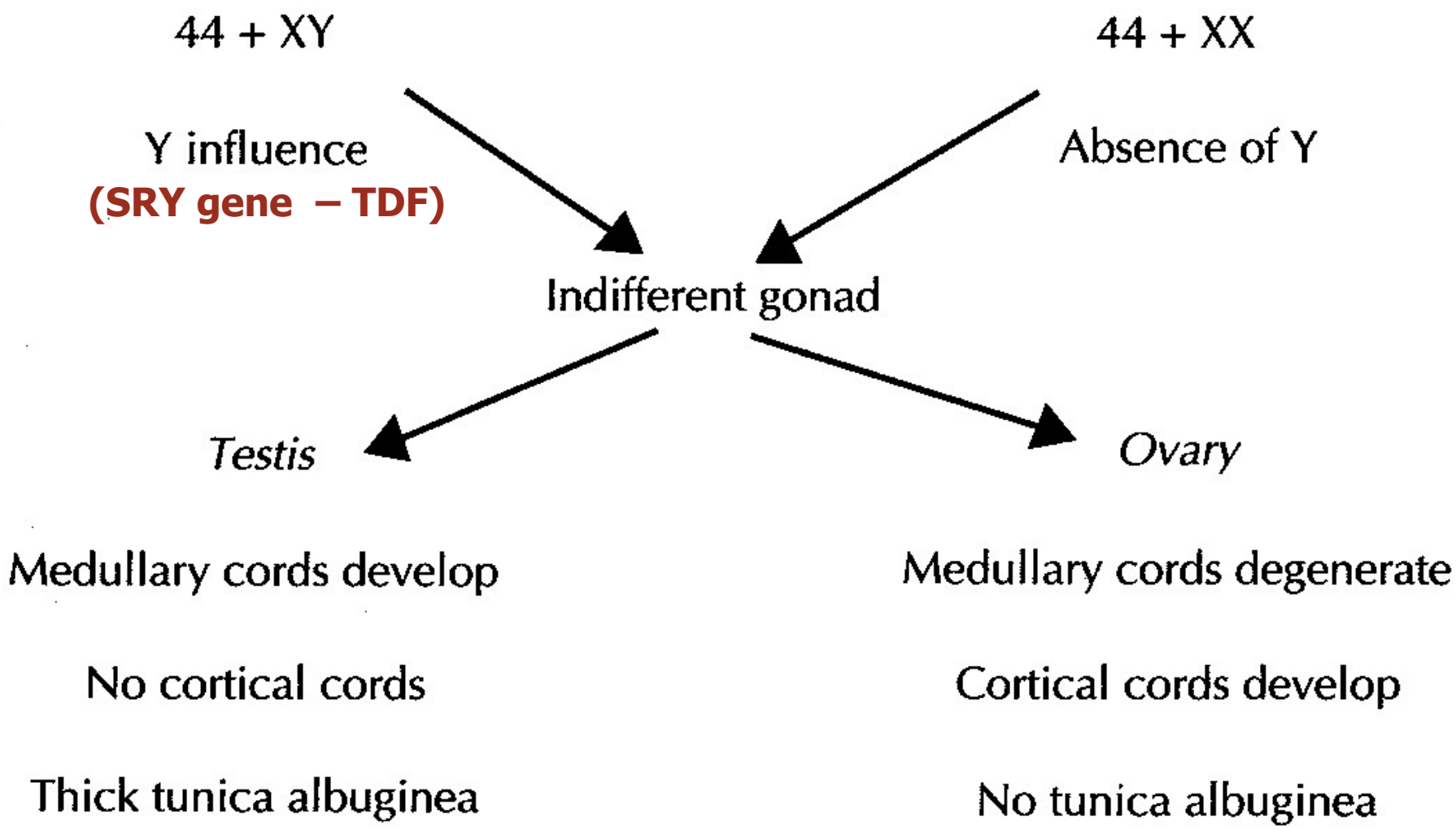


Edited: McGeady et al. Veterinary Embryology. 2009

FORMATION OF TERATOMAS

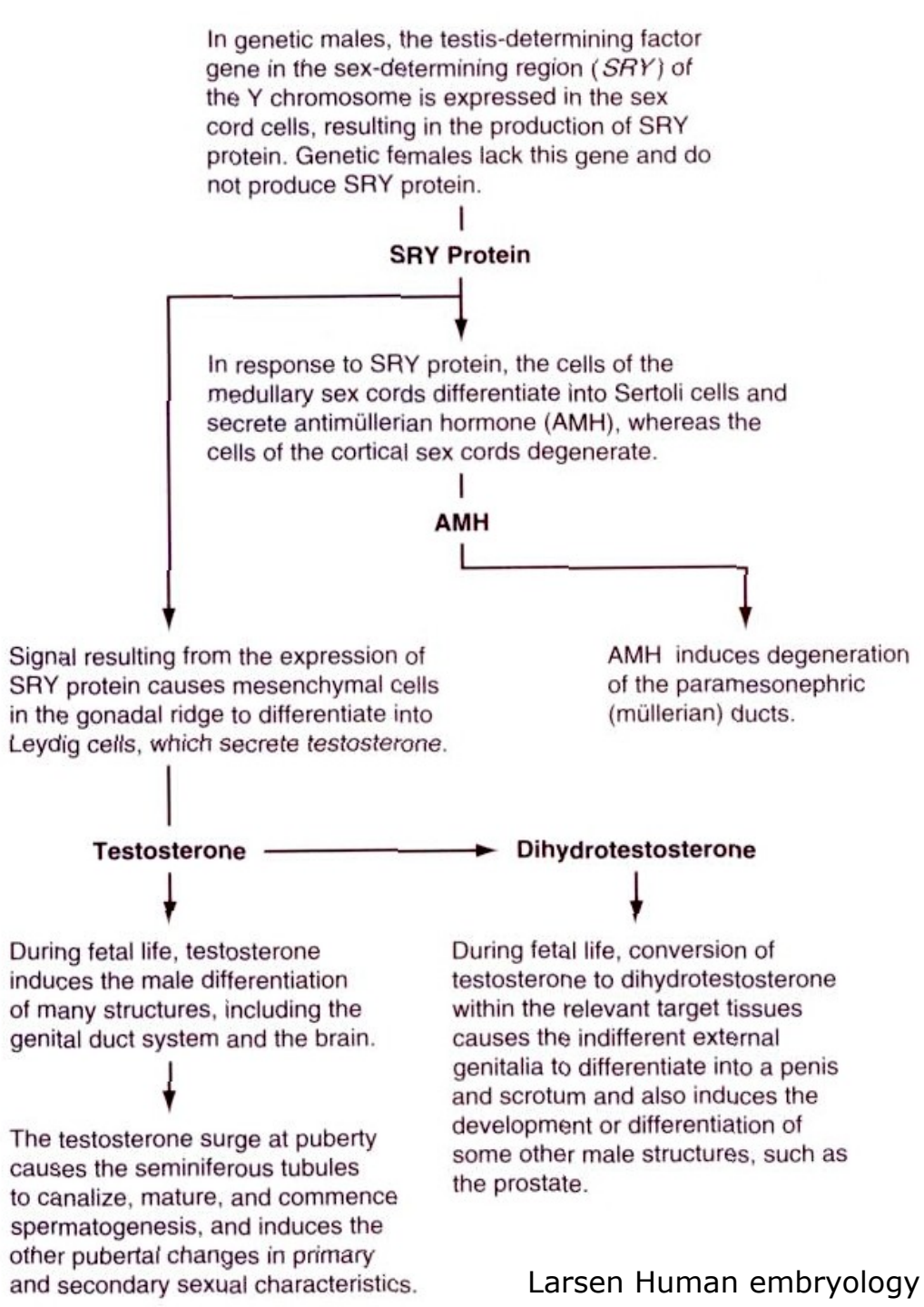
- **tumors** developed from **germ** cells
- formed from germ cells that did **not reach** gonads but did **not die**
- originates in **epiblast** → tumor formed of tissues of **all** germ layers (ectoderm, endoderm, mesoderm)





Primary female sexual differentiation is not hormone dependent – it occurs even if the ovaries are absent.

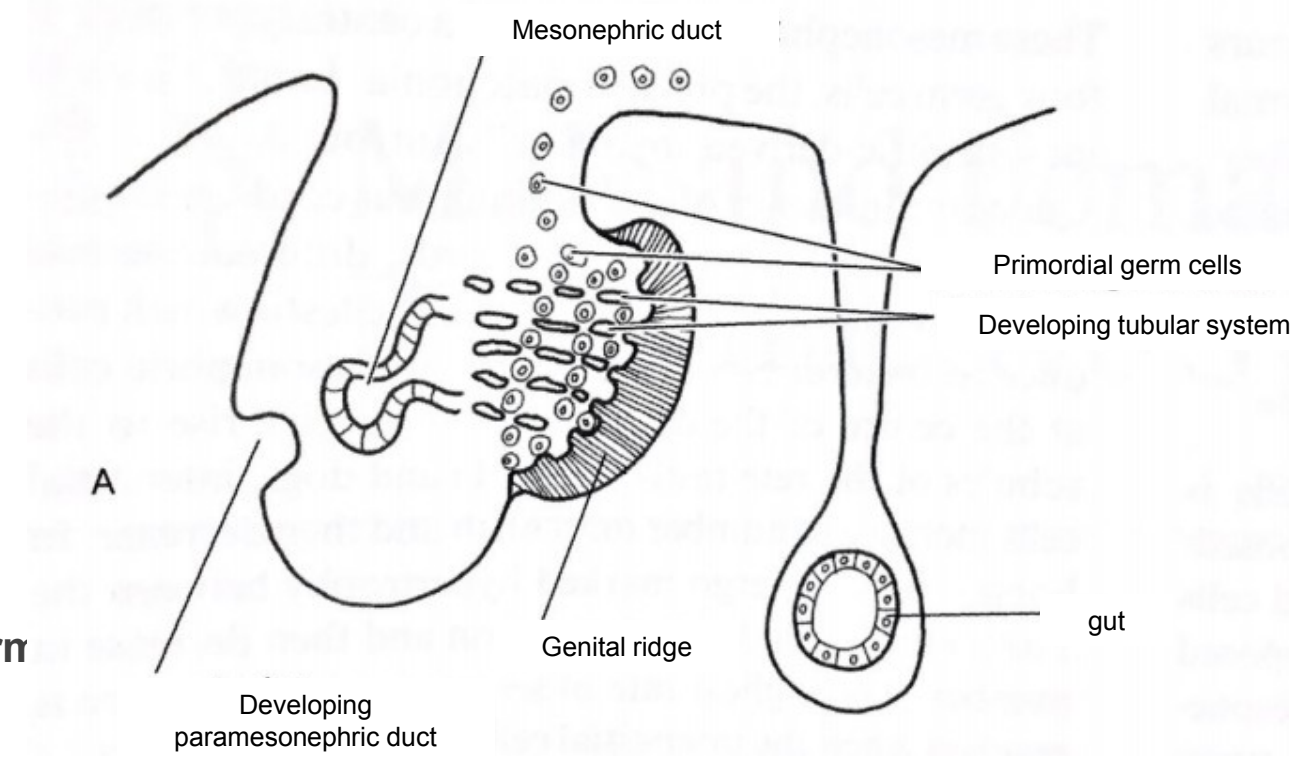
ROLE OF SRY GENE



Larsen Human embryology 2001

DEVELOPMENT OF GONADS AND DUCTS

- development of **undifferentiated** stage of gonads from 3 sources::
  - **Intermediate mesoderm mesenchymal cells**
  - **Epithelium of coelom**
  - **Cells of mesonephric tubules**
- development – **genital ridges** – on both sides medially from mesonephros
- Protrusions into coelom covered by **coelom epithelium**
- **Prolongation** along craniocaudal axis (from thoracic to lumbar region)
- **Undifferentiated** gonads **settled** by primordial **germ** cells
- cells of mesonephros and mesonephric tubules – formation of **rete** tubular system

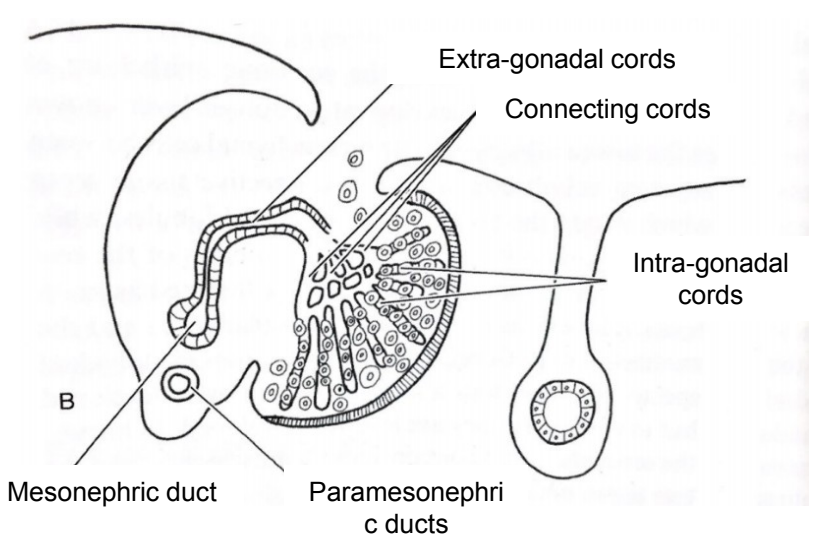


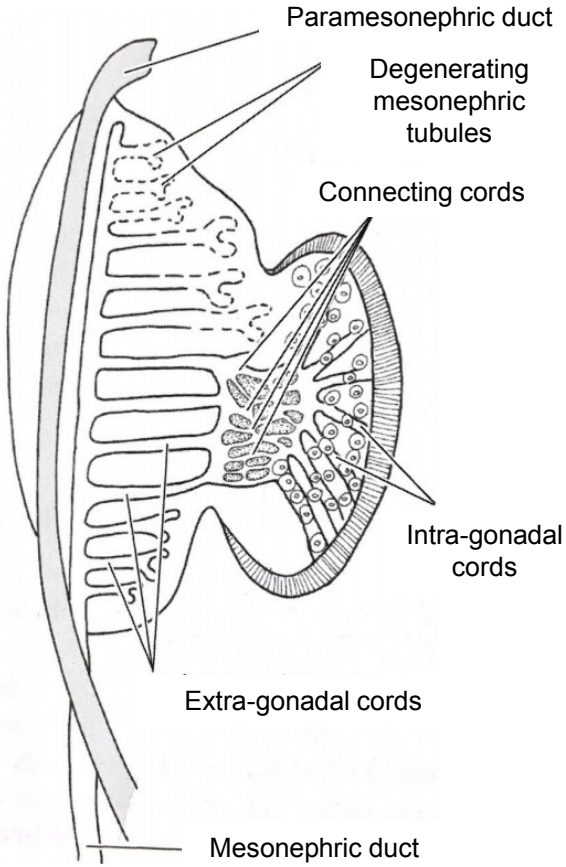
Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF GONADS AND DUCTS

- Tubular rete system divided to 3 parts:
  - **extra-**gonadal cords
  - **connecting** cords
  - **intra-**gonadal cords

- **proliferation** of inner part of gonads – genital ridge **getting rounded**
- **connection** with adjacent mesonephros preserved
- Formation of **ducts**:
  - **Wolffian** ducts – from mesonephric ducts (**male** ducts)
  - **Mullerian** ducts – from paramesonephric ducts (**female** ducts)





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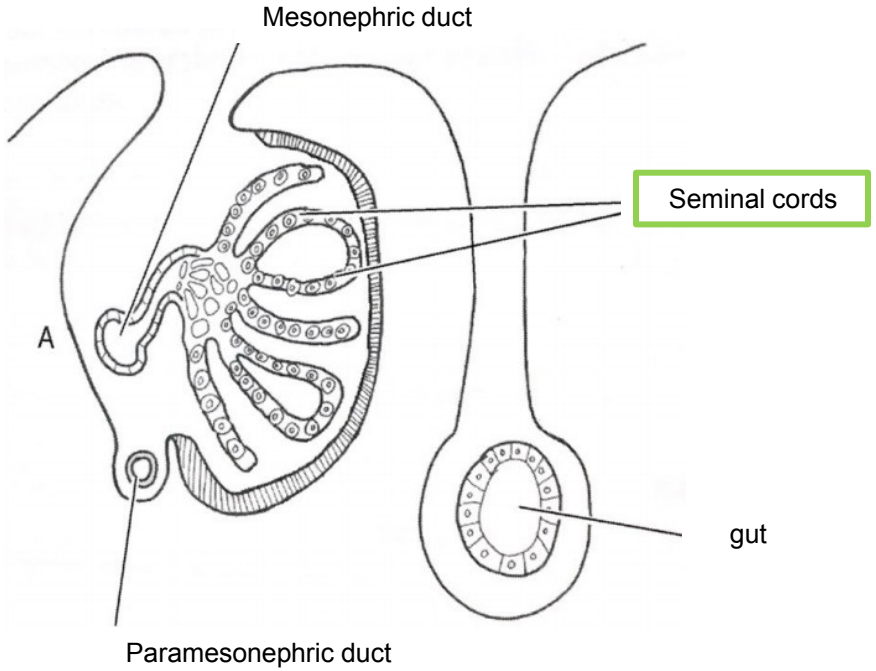
DEVELOPMENT AND MATURATION OF TESTES

- Formation of **seminal cords** from mesonephric cells on **periphery** → **incorporation** of **germ** cells

- Seminal cords connect with mesonephric cells in **center** of **gonads** – onset of convolution of seminal cords – formation of **seminiferous tubules**

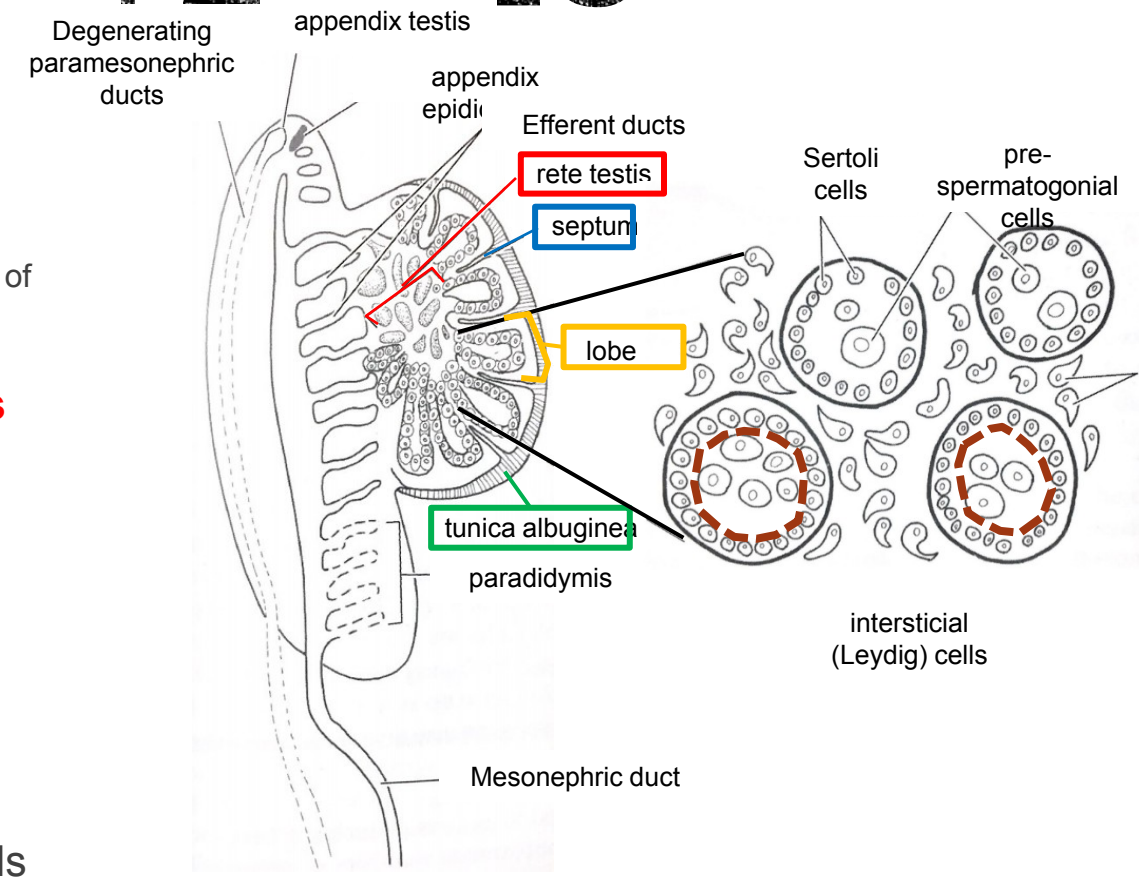
- **Seminal cords** – solid (not hollow) structures formed of 2 cell types:
  - **periphery** – precursors of **Sertoli** cells
  - **centraly** –precursors of **sperms** (pre-spermatogonial cells)



Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT AND MATURATION OF TESTES

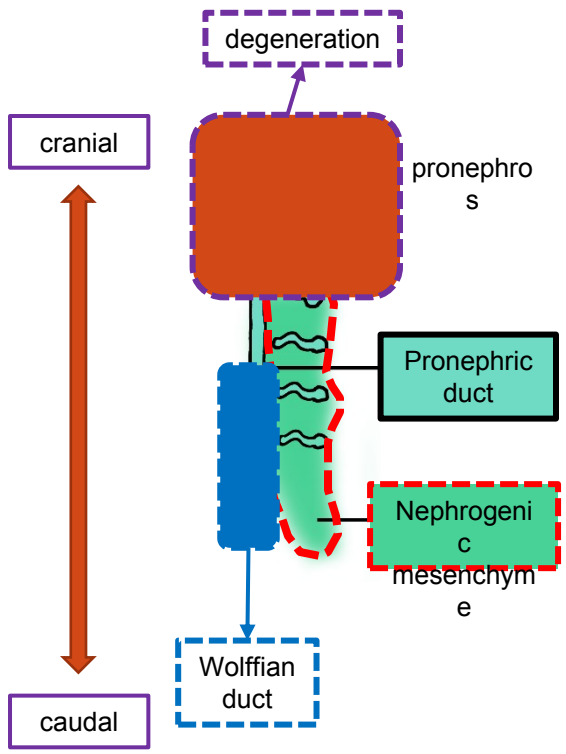
- **Seminiferous parts** finally formed of:
  - **wall** – **Sertoli** cells (support sperms development)
  - **center** – development of **sperm** precursors
- **Interstitial** cells between **seminiferous tubules** parts:
  - **Interstitial** (**Leydig**) cells – mesodermal cells differentiate under influence of seminiferous tubules, **testosterone** production
- **mesonephric cells in the center** – formation of **rete testis** canals (web of tubules between seminiferous tubules and efferent ducts)
- Mesenchymal cells **under** the epithelium of **coelom** – formation of connective tissue - **tunica albuginea**
- subsequent **septa** connected to tunica albuginea from **mesenchymal cells** between developing canals – **lobe** formation
- **canalization** – formation of **tubules** from seminiferous cords (adolescence)

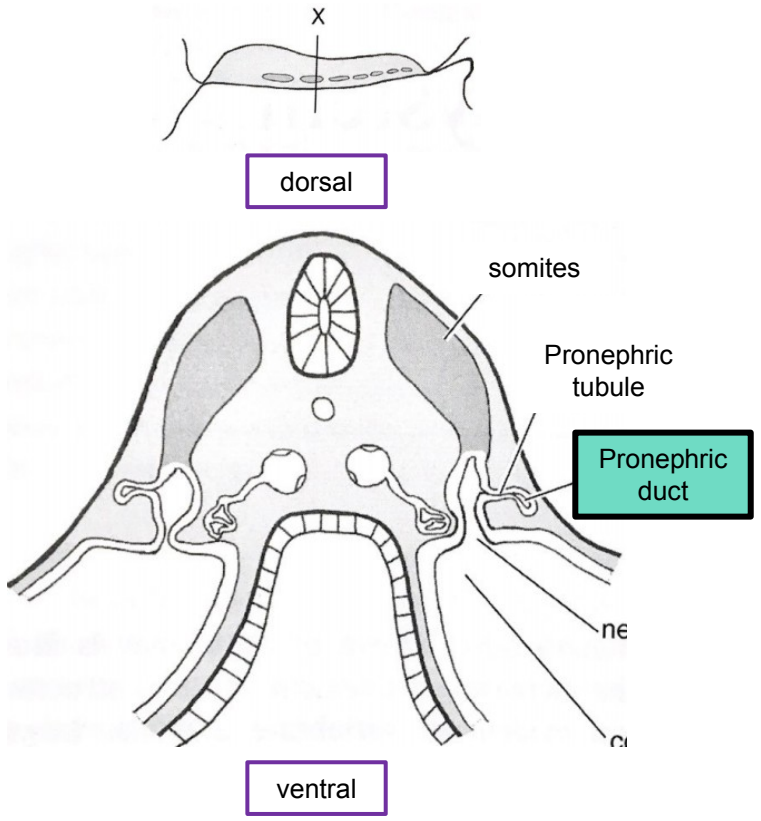


Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF MALE DUCTS

- Pronephros form **ventraly** from developing **cranial** somites
- mesodermal cells form **pronephric ducts** lateraly
- **cranial** part of ducts and tubules **degenerate**
- **caudal** part of **pronephric ducts** preserve its excretory function during development, formation of **Wolffian** (mesonephric) duct from caudal part of pronephric duct
- males – **Wolffian ducts** serve for formation of epididymis, ductus deferens, ejaculatory ducts and seminal vesicles
- females – Wolffian ducts gradually degrade (no production of testosterone)

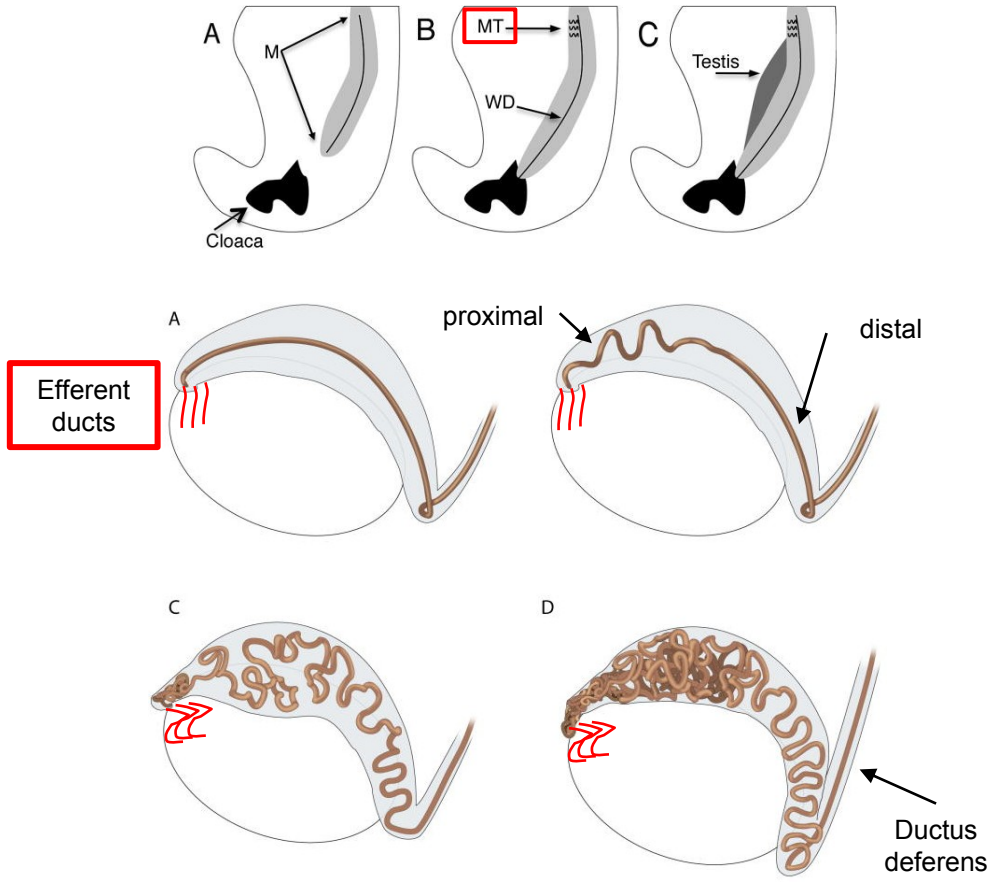




Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF EPIDIDYMIS

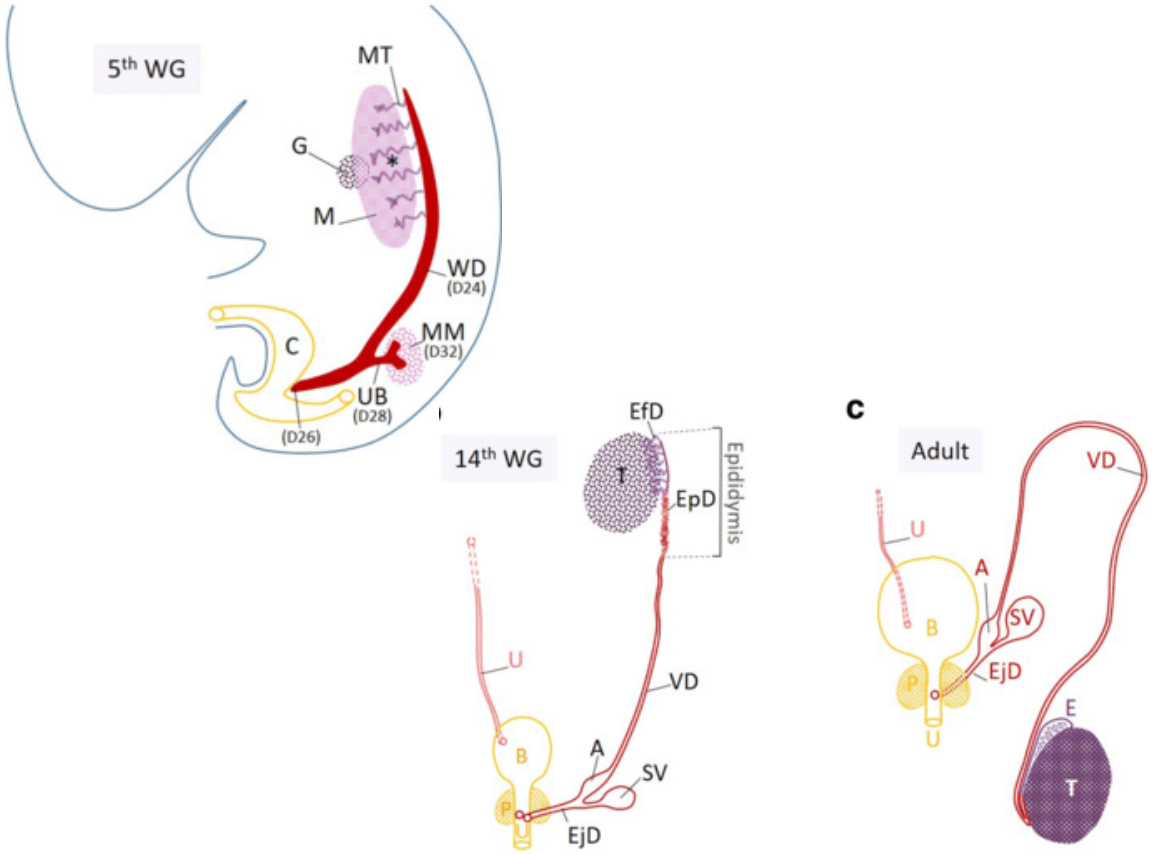
- **Wolffian ducts** grow towards cloaca, formation of **mesonephric tubules** from nephrogenic mesenchyme
- Luminization of Wolffian ducts, development of **efferent ducts** from mesonephric tubules (**MT** – connection between rete testis with epididymis)
- Intensive cell **proliferation** leads to **prolongation** and formation of **loops** – onset of convoluting in **proximal** region, onset of **convoluting efferent** ducts
- **distal** starts to convolute **later** – formation of loops in whole epididymis
- **Ductus deferens** is **not convoluted**



Joseph et al. 2010. Dev Biol

DEVELOPMENT OF DUCTUS DEFERENS

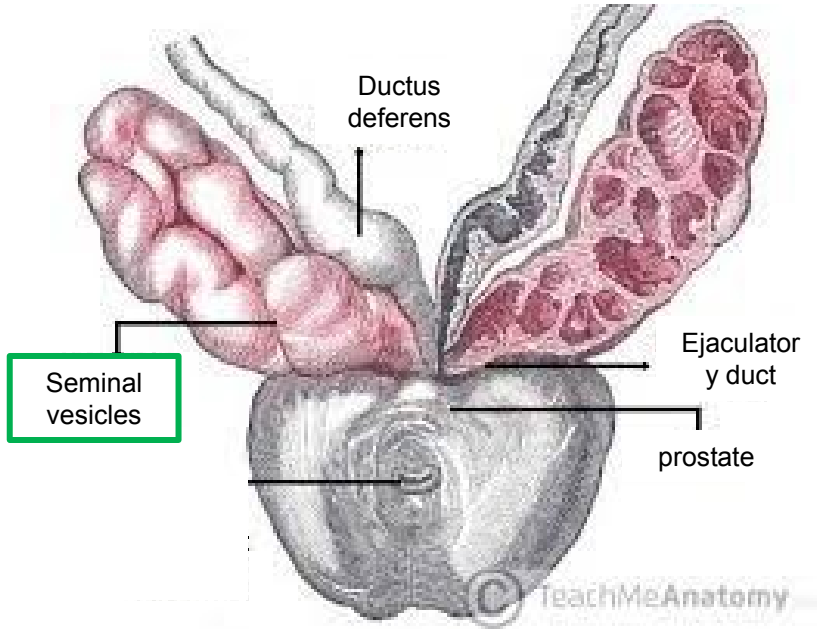
- basis – middle part of **Wolffian** duct
- **connection** of epididymis (EpD) and ejaculatory ducts (EjD)
- **prolongation** of duct, formation of cells with cilia and development of thick smooth muscle layer – **active** transport of sperms
- from **distal** part of **Wolffian duct ejaculatory** ducts develops - connected to urethra
- **Ductus deferens – ejaculatory ducts interface** region - development of **seminal vesicles**



Bieth et al. 2021. Hum Genet

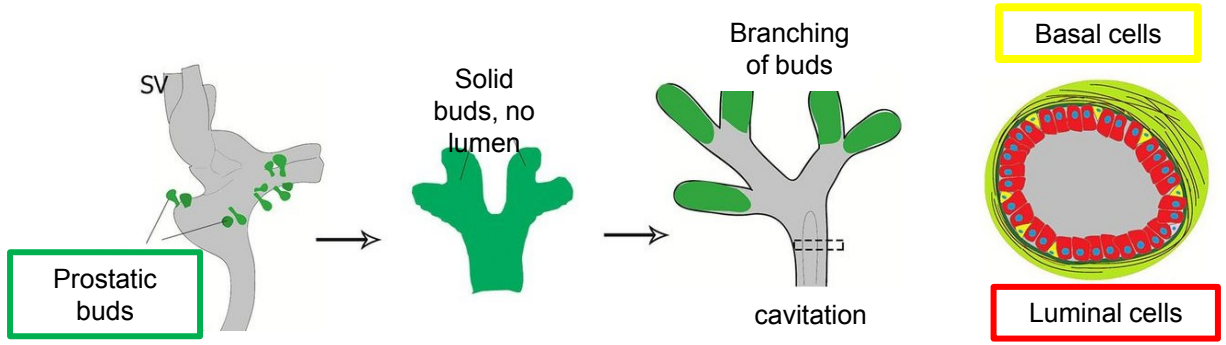
FORMATION OF SEMINAL VESICLES

- **Seminal vesicles** – supporting glands of male reproductive system
- Formation of paired **evaginations** (buds) from distal Wolffian duct into surrounding mesenchyme regulated by testosterone production
- Further growth and development – formation of prolonged vesicular structures
- Secretory cells **porduce supporting** components of ejaculate:
  - fructose, proteins, enzymes, vitamine C
  - semenogelin – protein forming gell matrix

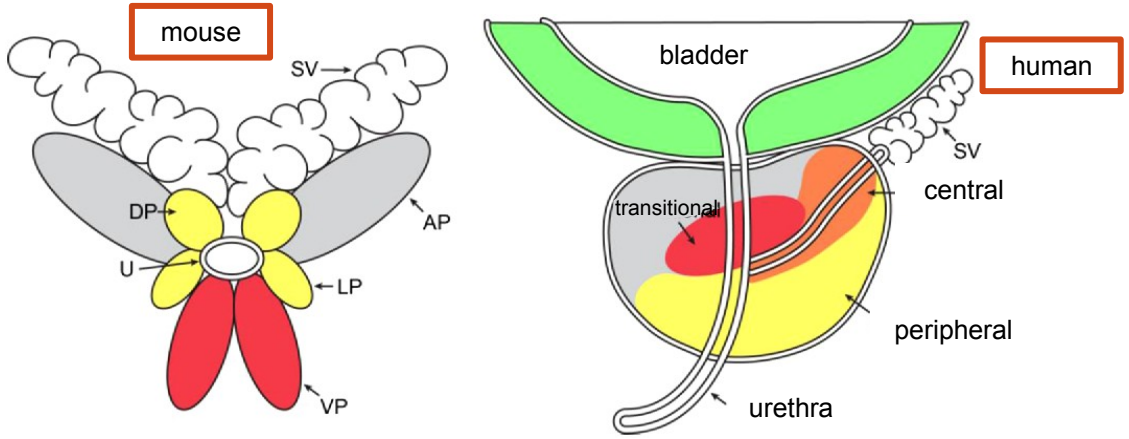


DEVELOPMENT OF PROSTATE

- Develops from **urogenital sinus** – ventral part after splitting cloaca
- Formation of **prostatic epithelial** buds (4 pairs in mouse, compact gland in human) from urogenital sinus
- Proliferation cause growth and branching of buds, differentiation of epithelial cells to **luminal** (production and secretion of supporting components, part of seminal fluid) and **basal** cells (keep integrity and diferentiation of luminal cells)
- **Canalization** from proximal part of bud - formation of ductal cavity
- **Urogenital mesenchyme** – stroma formation – smooth muscle and connective tissue cells



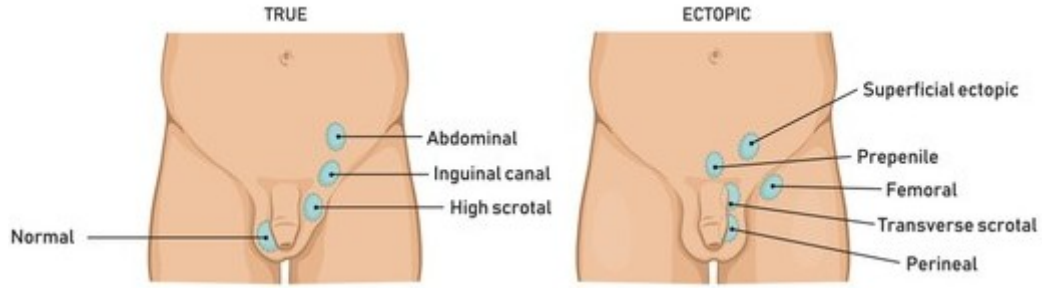
Kumari and Sinha, 2021.



Peng and Joyner, 2015.

DEVELOPMENTAL DEFECTS OF TESTES

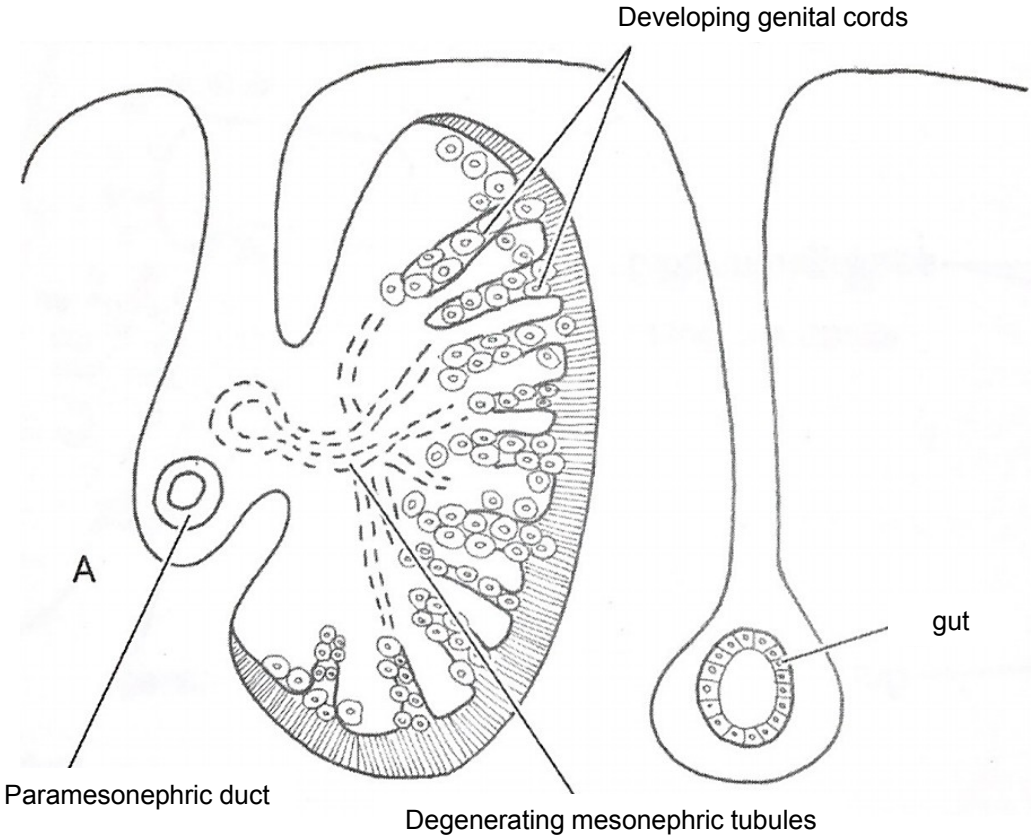
- Cryptorchidism (undescended testiscle)
  - The most often congenital defect of male reproductive system (25 %)
  - Absence of at least one testes in scrotum
  - Testicle ofeten descend after the born (within 3 months)
  - Surgery if not



- Anorchia
  - Complete missing of one or both testicles
  - Rare (1:20000)
  - unknown origin

DEVELOPMENT AND MATURATION OF OVARIES

- **genital cords** form from epithelium of coelom – incorporation of germ cells
- **mesonephric** tubules start to degenerate and **disintegrate**
- **genital cords** then **degenerate** – followed by intensive **mitotic activity** of **germ** cells



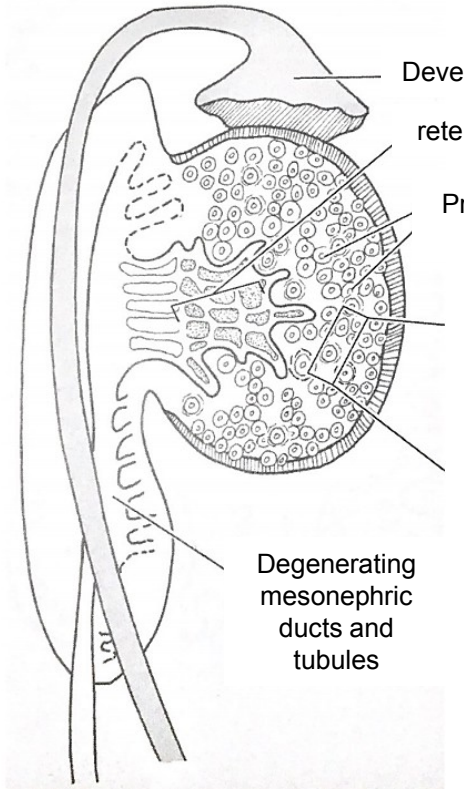
Edited: McGeady et al. Veterinary Embryology. 2009

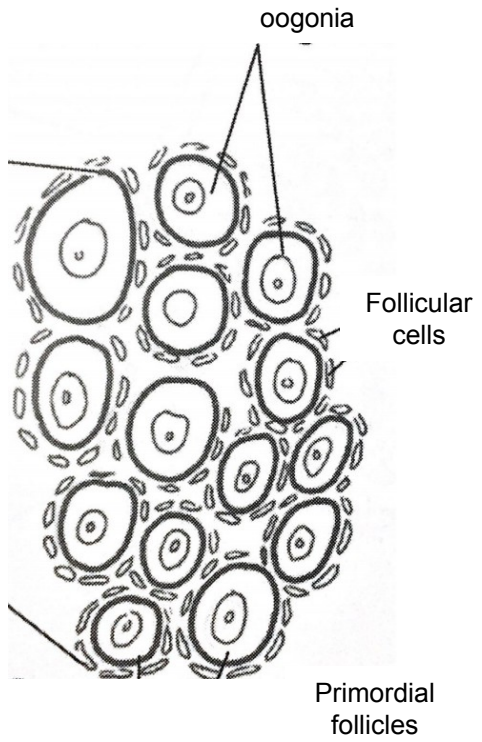
DEVELOPMENT AND MATURATION OF OVARIES

- **Mitotic** activity of **oocytes precursor** cells **terminated** (perinataly in mammals)

- **Primordial oocytes** after the **last mitosis** – **oogonia** – surrounded by cells originated in epithelium of coelom – **follicular** cells

- formation of **primordial folicles** – **germ** cell enclosed with **basal membrane** surrounded by **follicular** cells





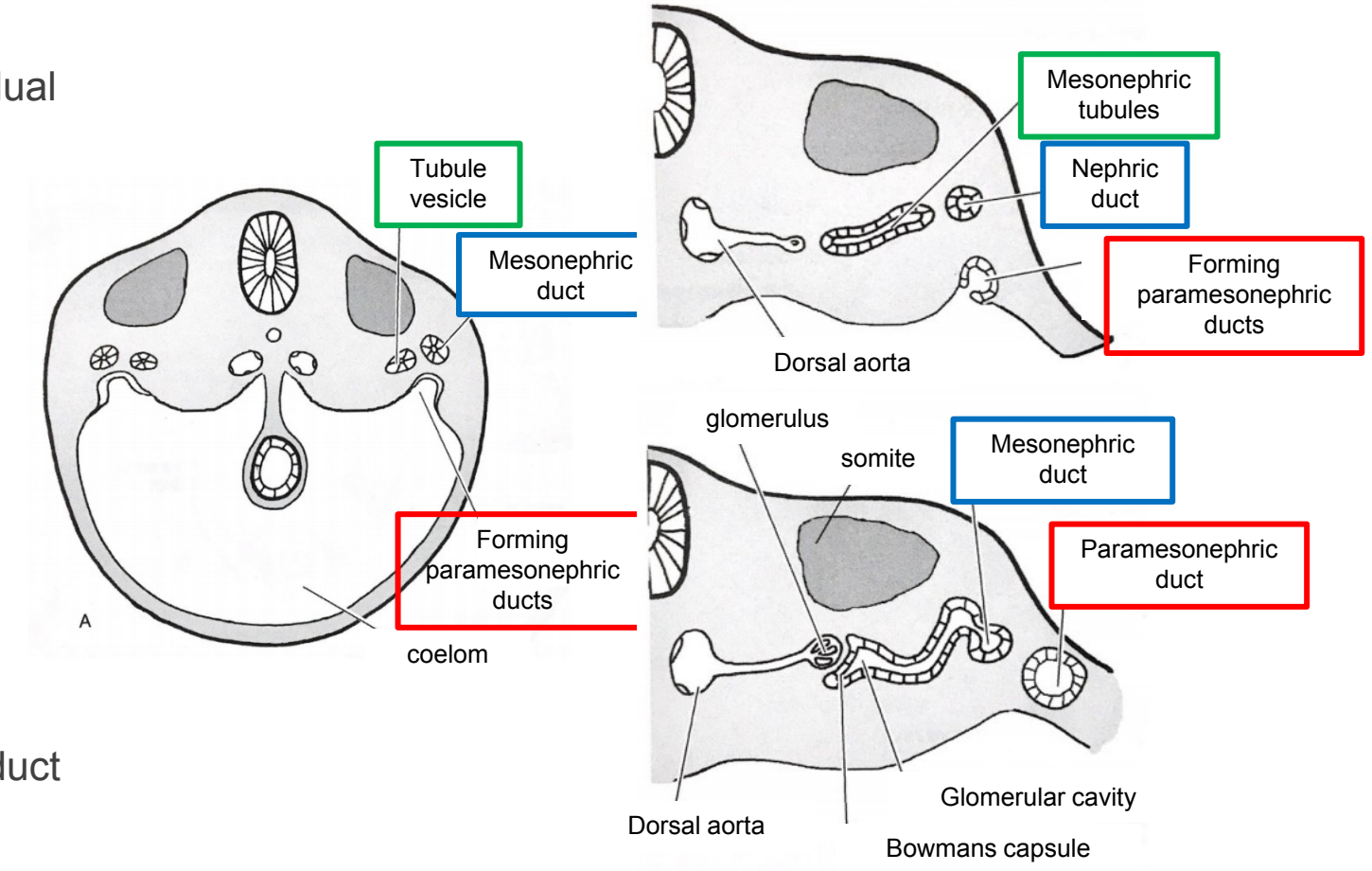
Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF FEMALE DUCTS

- **Mesonephric ducts** formed **lateraly**, gradual **degradation** in **females**

- **Lateraly** from mesonephric ducts fortmation of **paramesonephric ducts**

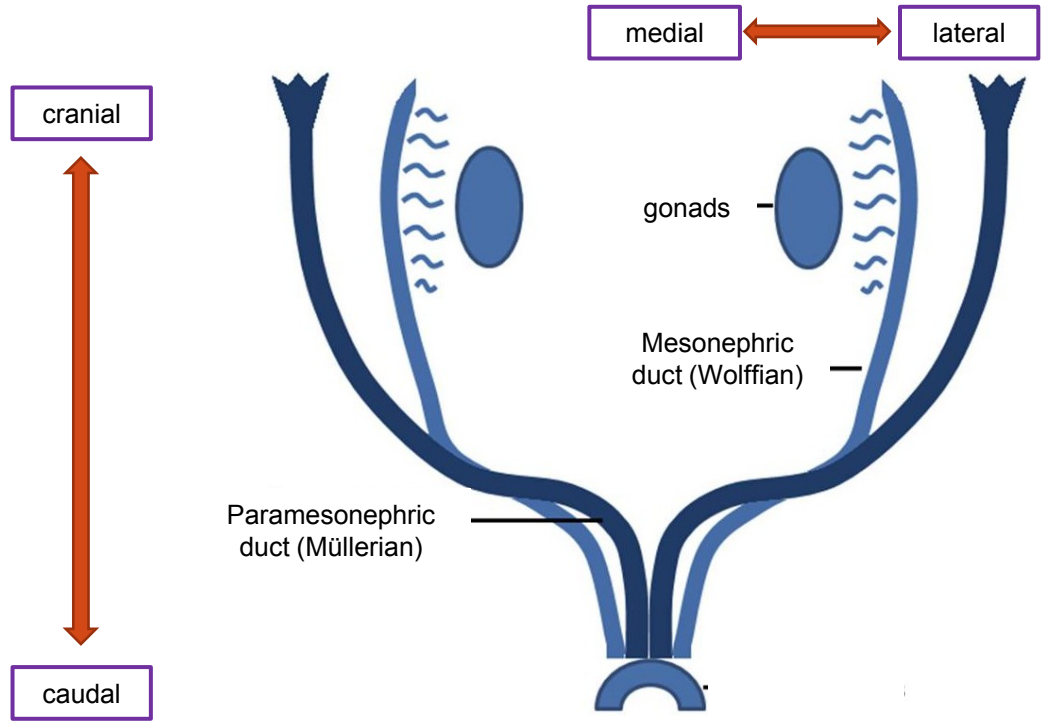
- **Paramezonephric duct** – future Müllerian duct



Edited: McGeady et al. Veterinary Embryology. 2009

DEVELOPMENT OF PARAMESONEPHRIC DUCT

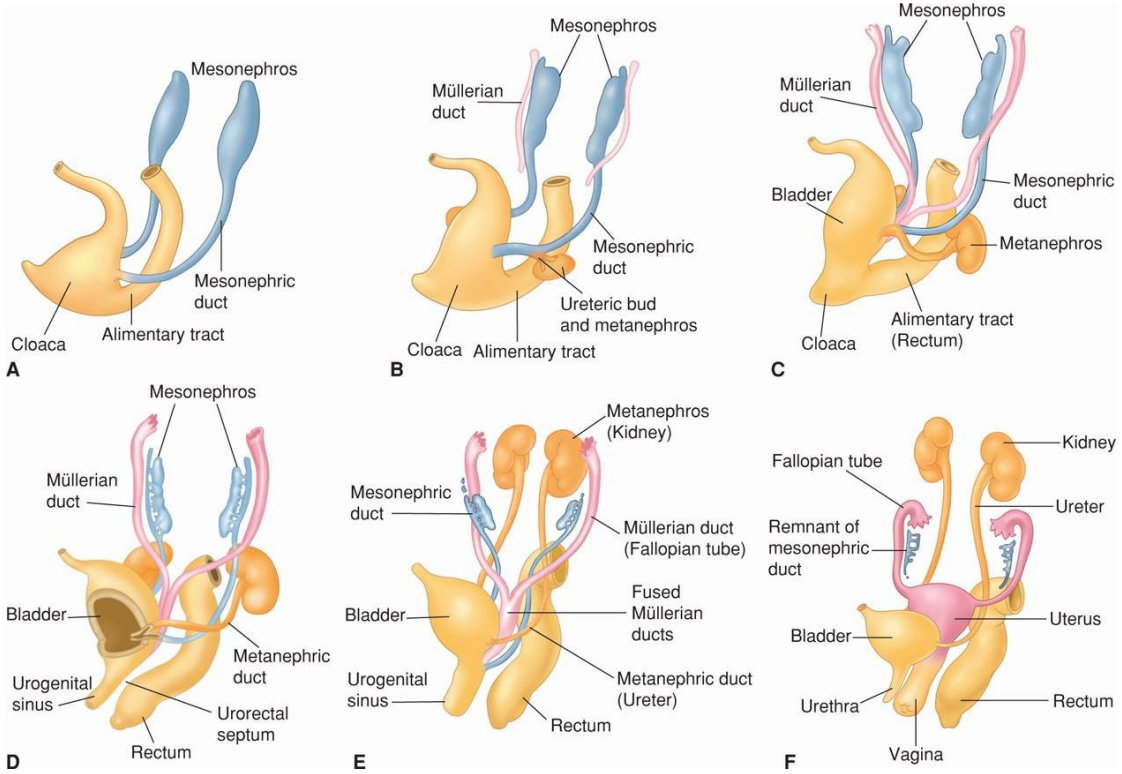
- Basis for Müllerian duct formation
- **females** – formation of oviducts, uterus and upper third of vagina
- **Male** – atrophies (Antimüllerian hormone, Sertoli cells)
- development **lateraly** from Wolffian duct, develop from **epithelium** of **coelom**, so called **Müllerian ridge**
- In cranial region, parallel development with Wolffian duct
- In caudal region, transition of Müllerian ducts ventrally



Corsoginho et al. 2016. ECR

DEVELOPMENT OF OVIDUCTS AND UTERUS

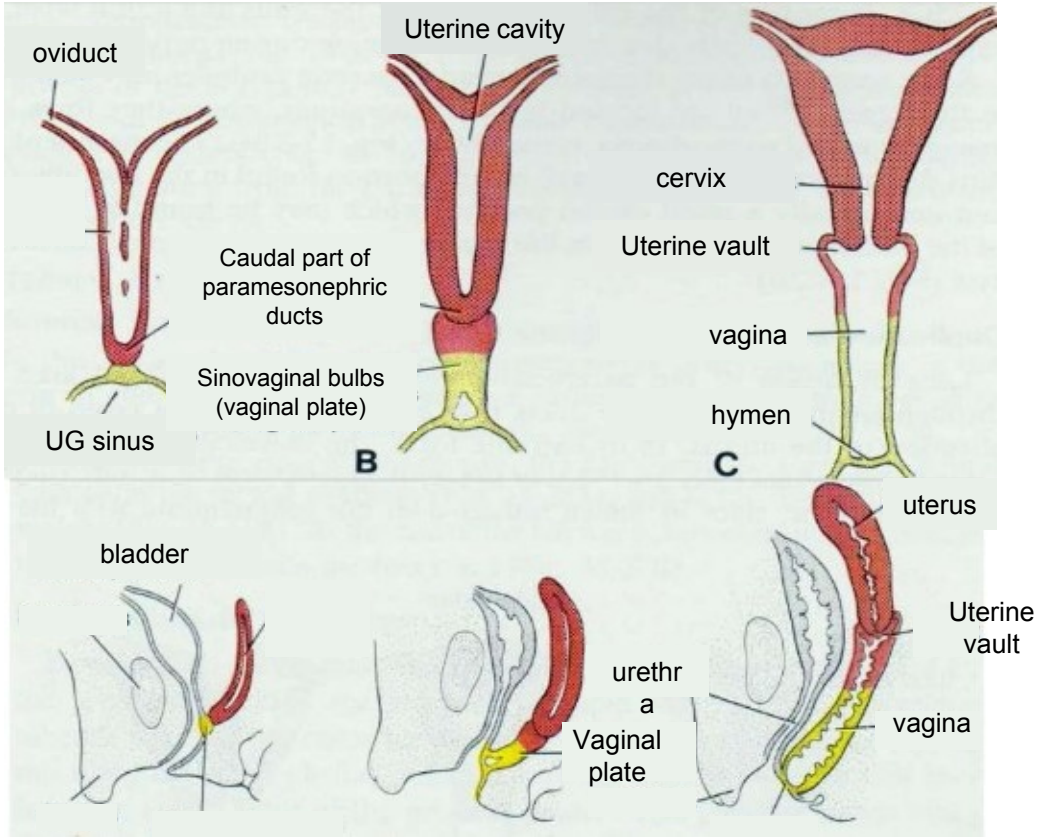
- develop from **Müllerian duct**, grow caudaly
- development of **paired oviducts cranialy**, oviducts connected caudaly – basis of **uterus** (proliferation in cranial region, extension)
- Connection of oviducts – formation of **uterine septum** – **degradation** of septum results in **cavity** of uterus
- **Oviducts: cranialy** open to **peritoneal cavity** (contact with ovaries), **caudaly** connect to **uterine horns**
- Developing uterus caudaly connected to endodermal **sinovaginal bulbs** – part of **urogenital sinus** close to uterus (originaly ventral side of cloaca)
- **Ventral** part of urogenital sinus divided into:
  - ventral - urethra and bladder
  - dorsal - **vagina**



Bradshaw, 2012.

DEVELOPMENT OF VAGINA

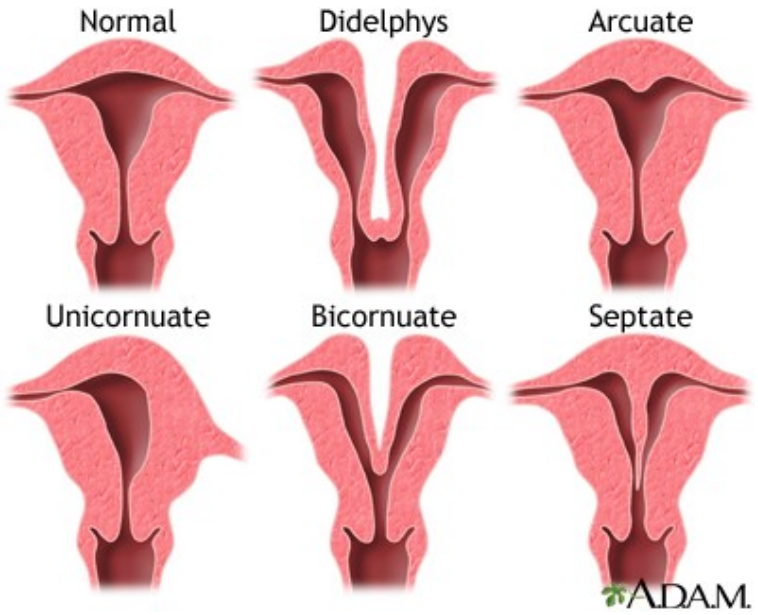
- 2 sources:
  - Upper 1/3 – **Müllerian** duct (**mesoderm**)
  - Lower 2/3 – **Urogenital sinus** (**endoderm**)
- Separation of ventral urogenital sinus:
  - ventral – urethra and bladder
  - dorsal - **vagina**
- Connection between uterus and **sinovaginal bulbs** (**vaginal plate**), proliferation and fusion → formation of compact structure (no cavity)
- later **resorption** of **vaginal plate** and **canalization** (apoptosis) – formation of vaginal cavity
- **vaginal** cavity separated from **urogenital sinus** cavity by transversal membrane - **hymen**



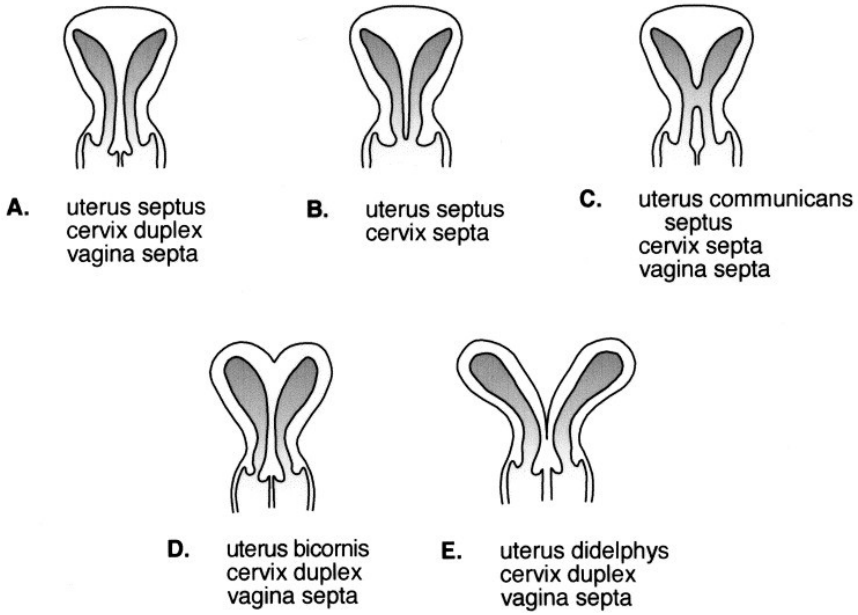
Sahar Hafeez

DEVELOPMENTAL DEFECTS OF FEMALE DUCTS

- developmental defects of uterus
  - Altered fusion of Müllerian ducts
  - Defects caused by insufficient degradation of septum
  - Often connected with defects of oviducts
  - Can lead to infertility and problems during pregnancy

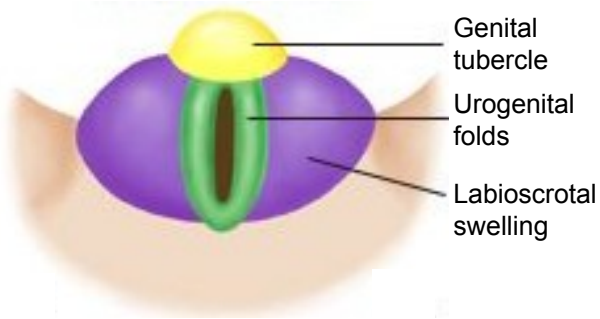


- Developmental defects of vagina
  - Often connected with defects of uterus and cervix
  - Vaginal septum – no fusion, split vagina



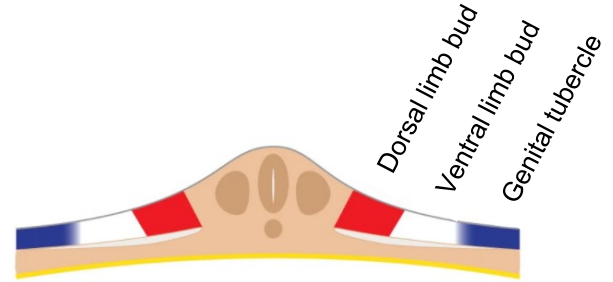
DEVELOPMENT OF EXTERNAL GENITALS

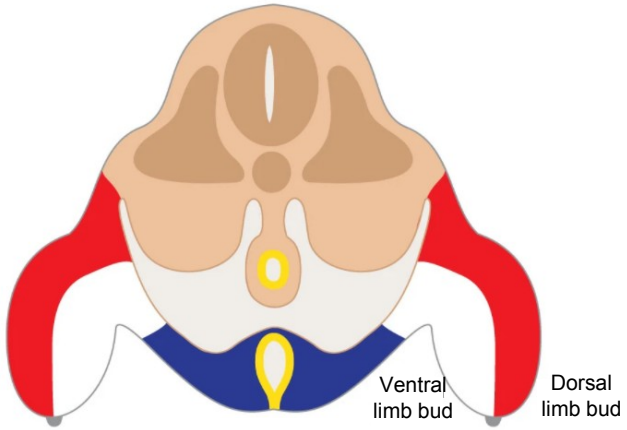
- basis – **indifferent** stage composed of **3** parts:
  - **Genital (phallic) tubercle** (penis, clitoris)
  - **urogenital (cloacal) folds** (urethra, labia minora)
  - **labioscrotal swelling** (scrotum, labia majora)



Development External Genitalia, 2011.

- External genitals form from all 3 germinal layers:
  - **Lateral plate mesoderm** – stroma (clitoris, penis)
  - **endoderm** – urethra
  - **ectoderm** – external cover by skin and its derivatives (hair)





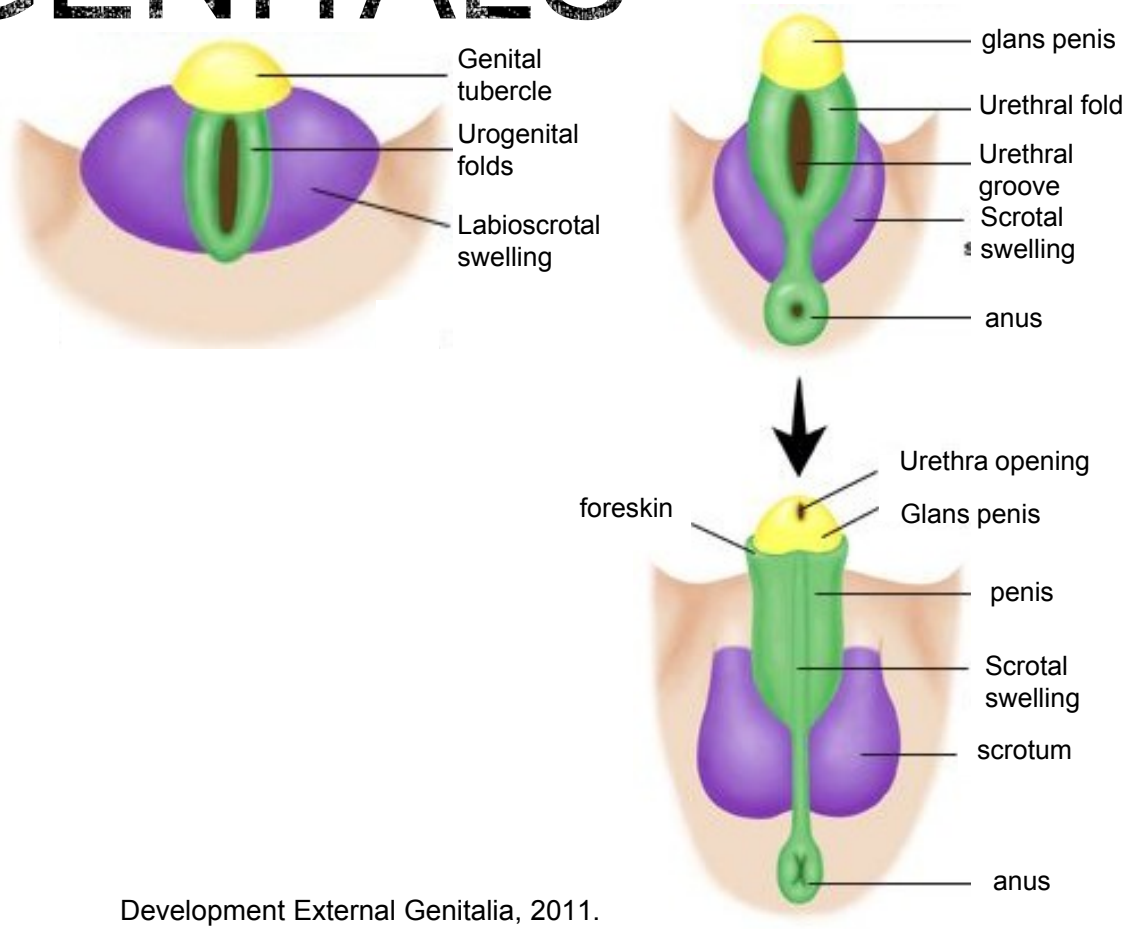
Herrera and Cohn, 2014. Sci Rep

DEVELOPMENT OF MALE EXTERNAL GENITALS

- **Genital tubercle**
  - Development of penis

- **Urogenital folds**
  - Fusion along the midline
  - Formation of enclosed urethra

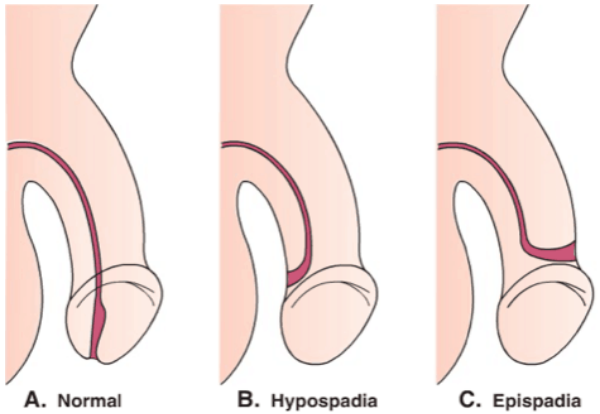
- **Labioscrotal swelling**
  - Grow towards the midline
  - Fusion in along the midline
  - Formation of scrotum



Development External Genitalia, 2011.

DEVELOPMENTAL DEFECTS OF MALE EXTERNAL GENITALS

- **Hypospadia/Epispadia**
  - Displaced opening of urethra
  - Opening on ventral/dorsal sides
  - More often in boys



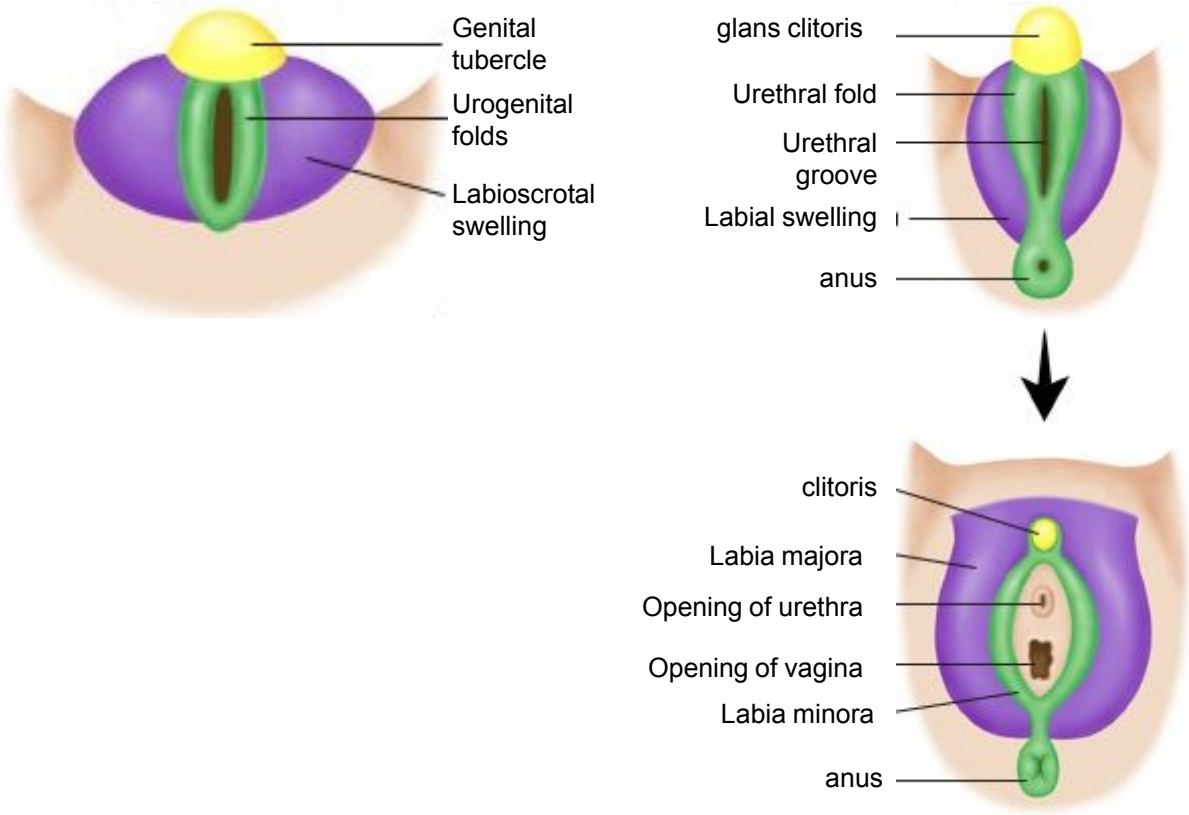
- **scrotum bifidum**
  - Labioscrotal swellings not fused along the midline
  - Testicles placed in two scrota

DEVELOPMENT OF FEMALE EXTERNAL GENITALS

- **Genital tubercle**
  - Slow growth
  - Formation of clitoris

- **Urogenital folds**
  - No fusion in the medial plane
  - Paired labia minora

- **Labioscrotal swelling**
  - No fusion in the medial plane
  - Paired labia majora



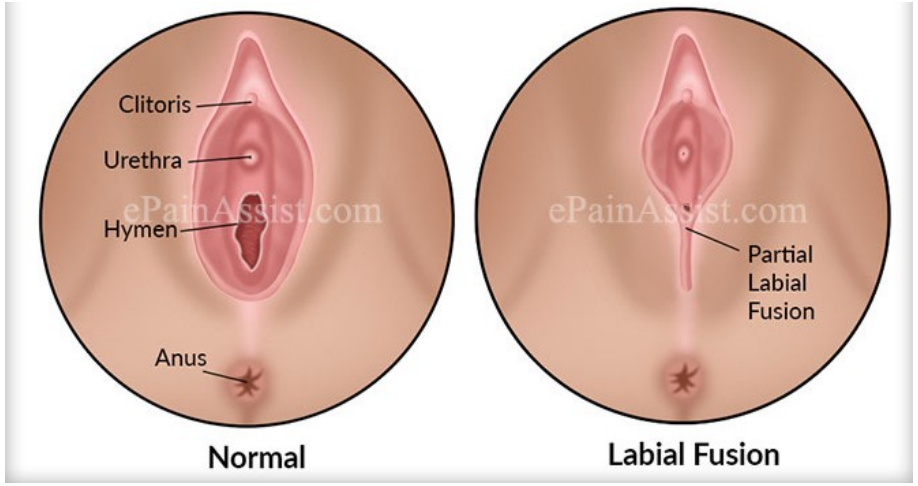
Development External Genitalia, 2011.

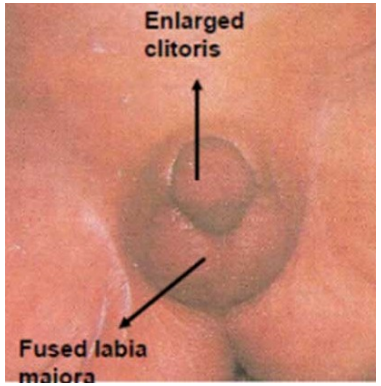
DEVELOPMENTAL DEFECTS OF FEMALE EXTERNAL GENITALS

- **Labial fusion**
  - Abnormal labial fusion
  - Vaginal opening is blocked

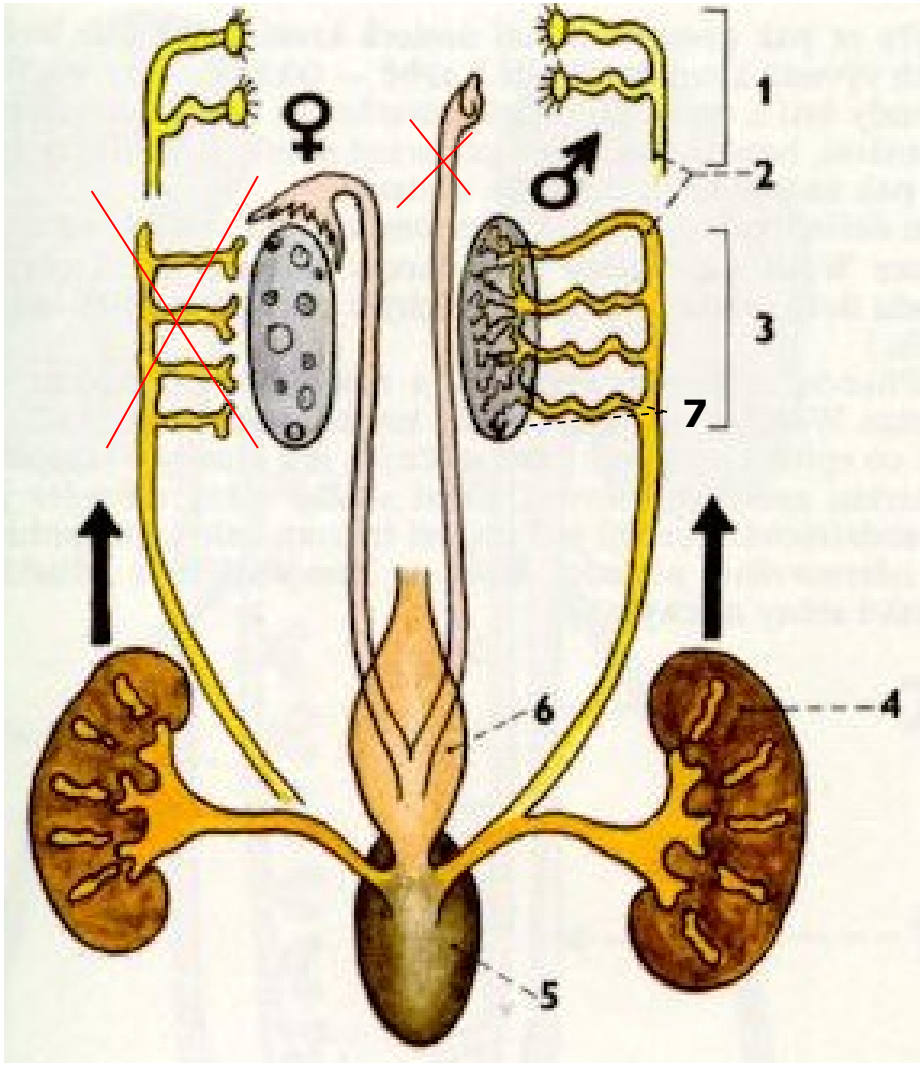
- **Hypertrophy of labia majora**
  - Abnormally enlarged labia majora
  - Cause – congenital adrenal hyperplasia

- **Clitoral defects**
  - Very rare
  - Bifid or duplex clitoris
  - Hypertrophy – caused by adrenal hyperplasia





SUMMARY



1) Degenerating pronephros

2) Wolffian duct

3) Degrading mesonephros

4) Metanephros

5) Urogenital sinus

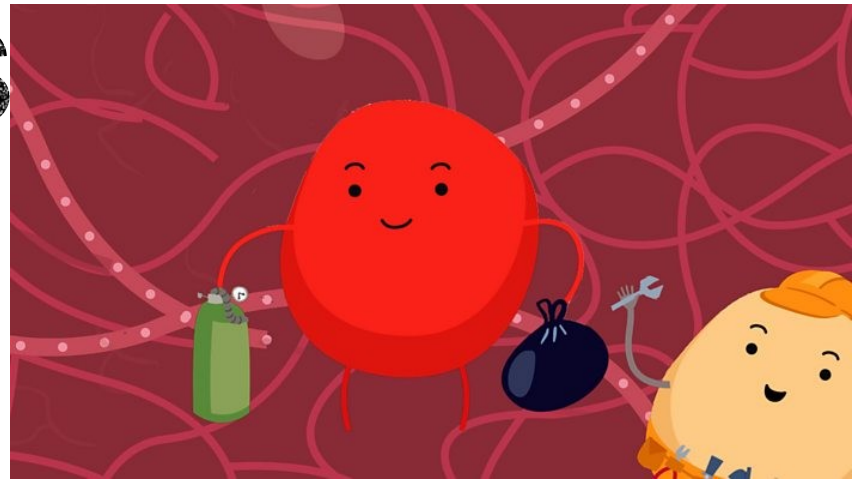
6) Urinal Bladder anlage

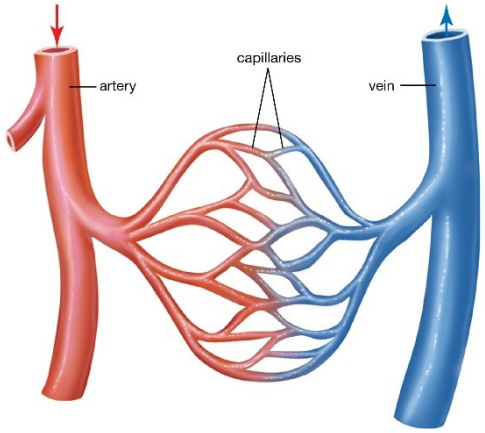
7) Müller´s duct

DEVELOPMENT OF CARDIOVASCULAR AND LYMPHATIC SYSTEMS

WHAT IS THE REASON OF DEVELOPING CARDIOVASCULAR AND LYMPHATIC S

- supply tissues with neccesary molecules
- disposal of waste products
- one of the first functional systems during development:
  - embryo is growing →
  - Exchange of nutrients and metabolites on long distances is no more effective →
  - development of **heart** and **vessels**





CARDIOVASCULAR SYSTEM - COMPARISON

- **Open** cardiovascular system
  - blood and tissue fluids are not separated - **hemolymph**
  - **Not involved** in gas exchange
  - energetically less demanding
  - **invertebrates**

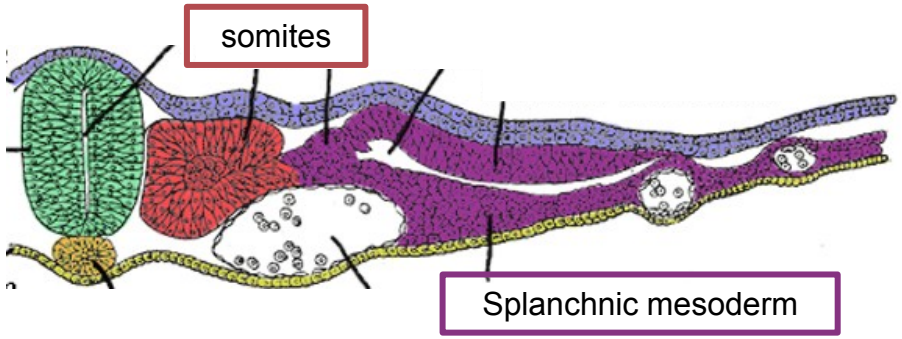
Enclosed cardiovascular system

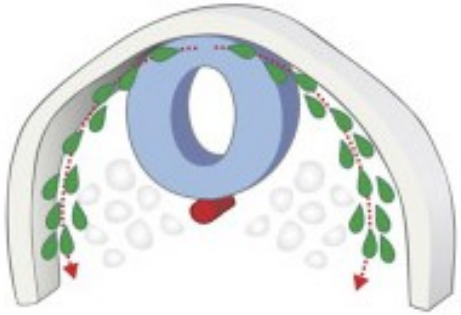
- blood and lymph separated in vessels
- blood is separated from tissue fluids
- **gas** and **nutrients** exchange
- **transport** of nutrients and metabolites on **long distances**
- **vertebrates**

DEVELOPMENT OF HEART AND VESSELS

- Develop from 3 sources:
  - Lateral plate mesoderm – **splanchnic** part
  - Paraxial mesoderm - **somites**
  - **Cardial** neural crest

- Dorsal aorta development
- Heart development
- Development of vessels
- Lymphatic organs and vessels development



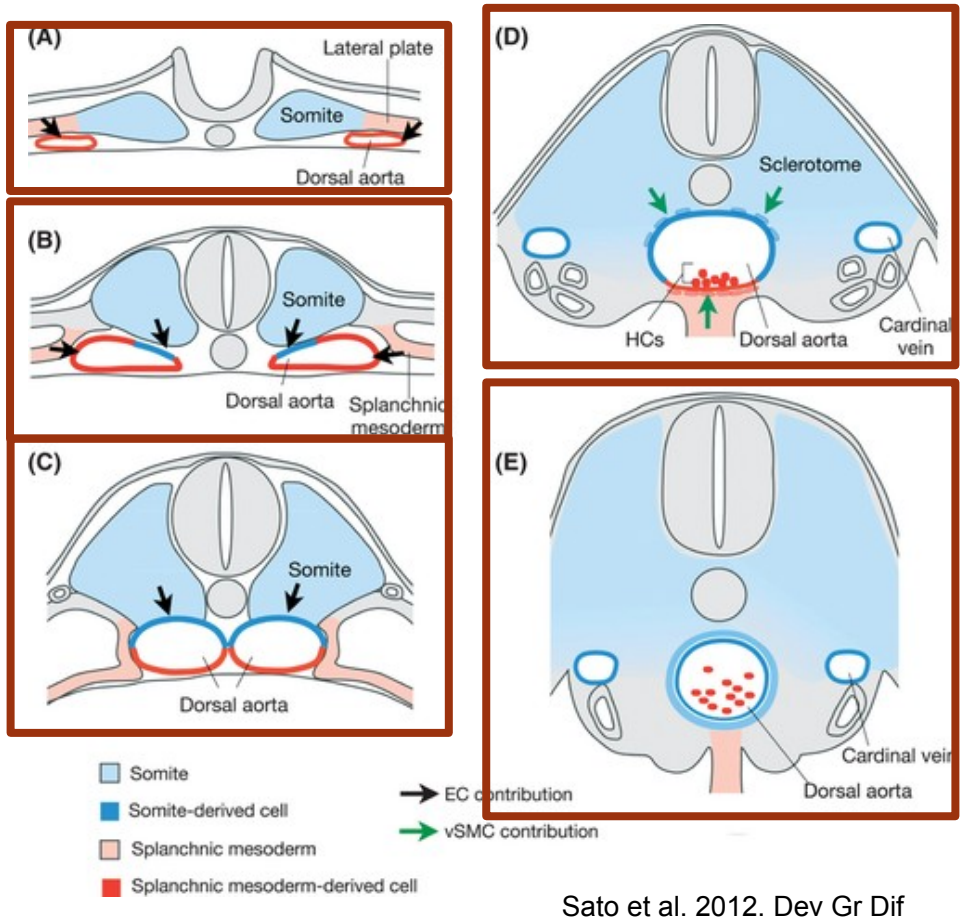


Rothstein et al. 2018. Dev Biol

DORSAL AORTA DEVELOPMENT

- agregation of endothelial precursor cells from **lateral plate mesoderm - endothelium**
- **somites** – endothelium, smooth muscle cells

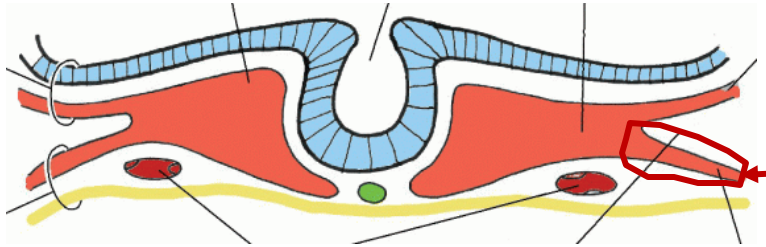
- **paired** basis in **cranial** part of embryo, **lateral** from embryonic **midline**
- **Lateral** embryo **bending** – paired aorta basis approach in the midline and **fuse**
- **endothelial** cells **transit** into **hematopoietic** cells
- mammals, birds, reptiles – paired dorsal aorta basis
- fish – single dorsal aorta basis



Sato et al. 2012. Dev Gr Dif

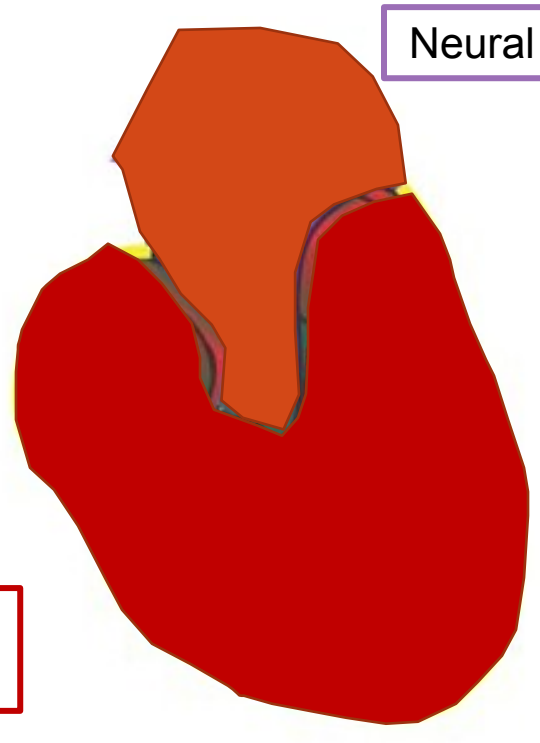
HEART DEVELOPMENT IN VERTEBRATES

- Heart develops from 2 sources:
  - Lateral plate mesoderm – splanchnic part
  - Cardiac neural crest



Dorsal aorta

splanchnic mesoderm



Neural crest

Santini et al. 2016. Dev

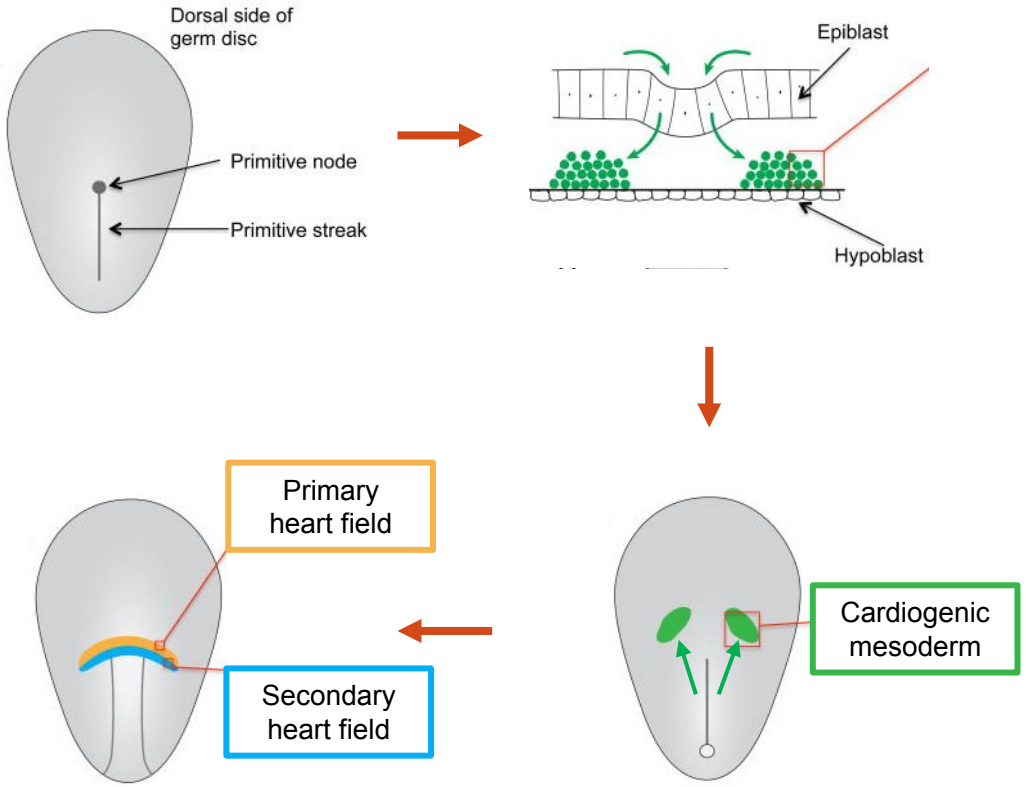
FORMATION OF HEART FIELDS

- Progenitor cells in epiblast – invaginate through primitive streak, formation of two groups of cells in **splanchnic lateral plate mesoderm**

- **Migration** in cranial and lateral direction → **cardiogenic mesoderm**

- **lateral** cardiogenic mesoderm → **primary heart field**

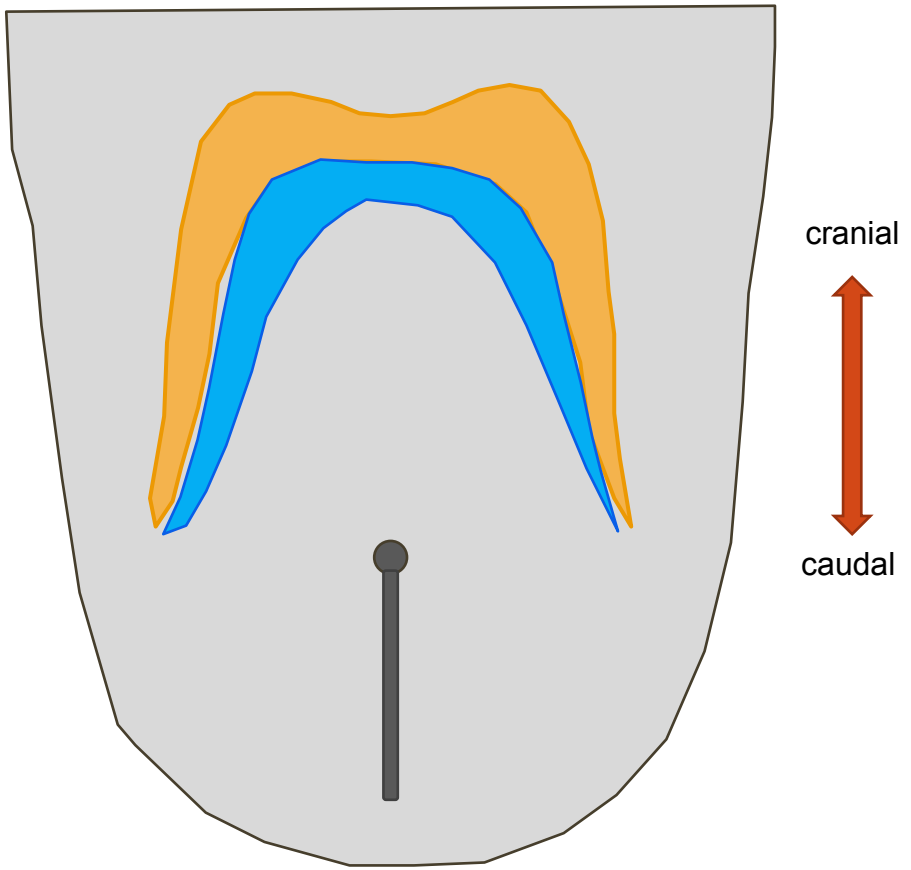
- **medial** cardiogenic mesoderm → **secondary heart field**



Kloesel et al. 2016. Anesthesia and Analgesia

DERIVATIVES OF HEART FIELD MESODERM

- Primary heart field
  - partly ventricles
  - left atrium
  - part of right atrium
- Cranial part of secondary heart field
  - part of right atrium
  - region of the receding heart vessels
- Caudal part of secondary heart field
  - atrial myocytes
  - myocardium between atriums
  - myocardium of the venous heart side



HEART TUBES DEVELOPMENT - TRANSVERSAL

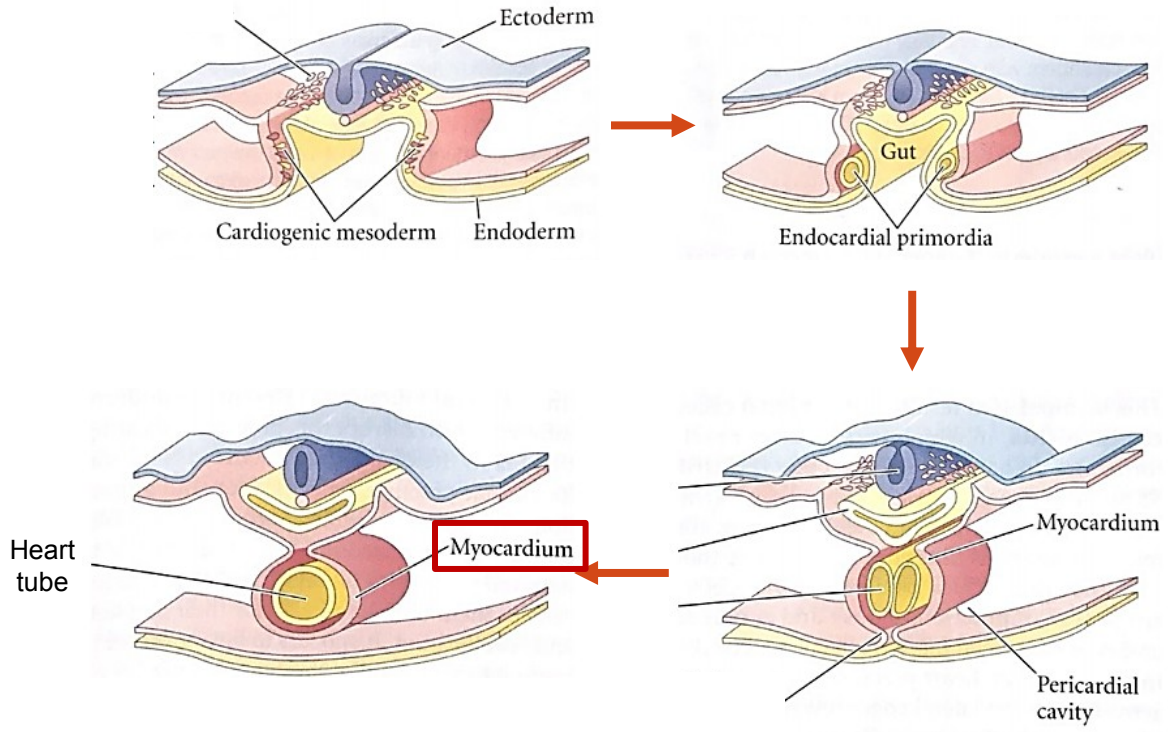
- paired heart tube basis – formation from cells of the **primary heart field mesoderm**

- **Lateral** embryo **bending** – paired endocardial primordia approach each other

- primordia **fuse** in the embryonic midline

- formation of left ventricle, **parts of atria** and **parts of right ventricle**

- **myocardium** forms from cells of the **secondary heart field mesoderm**



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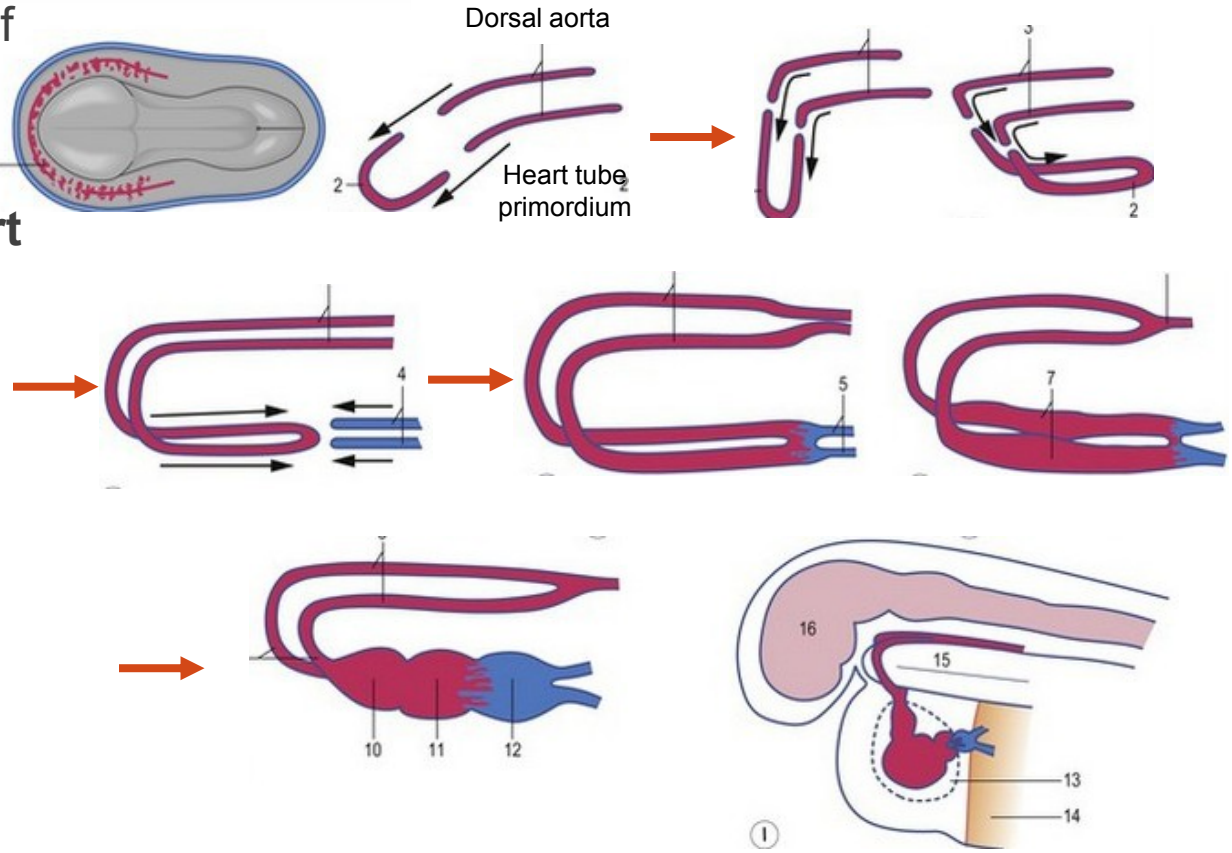
HEART TUBES DEVELOPMENT – LATERAL

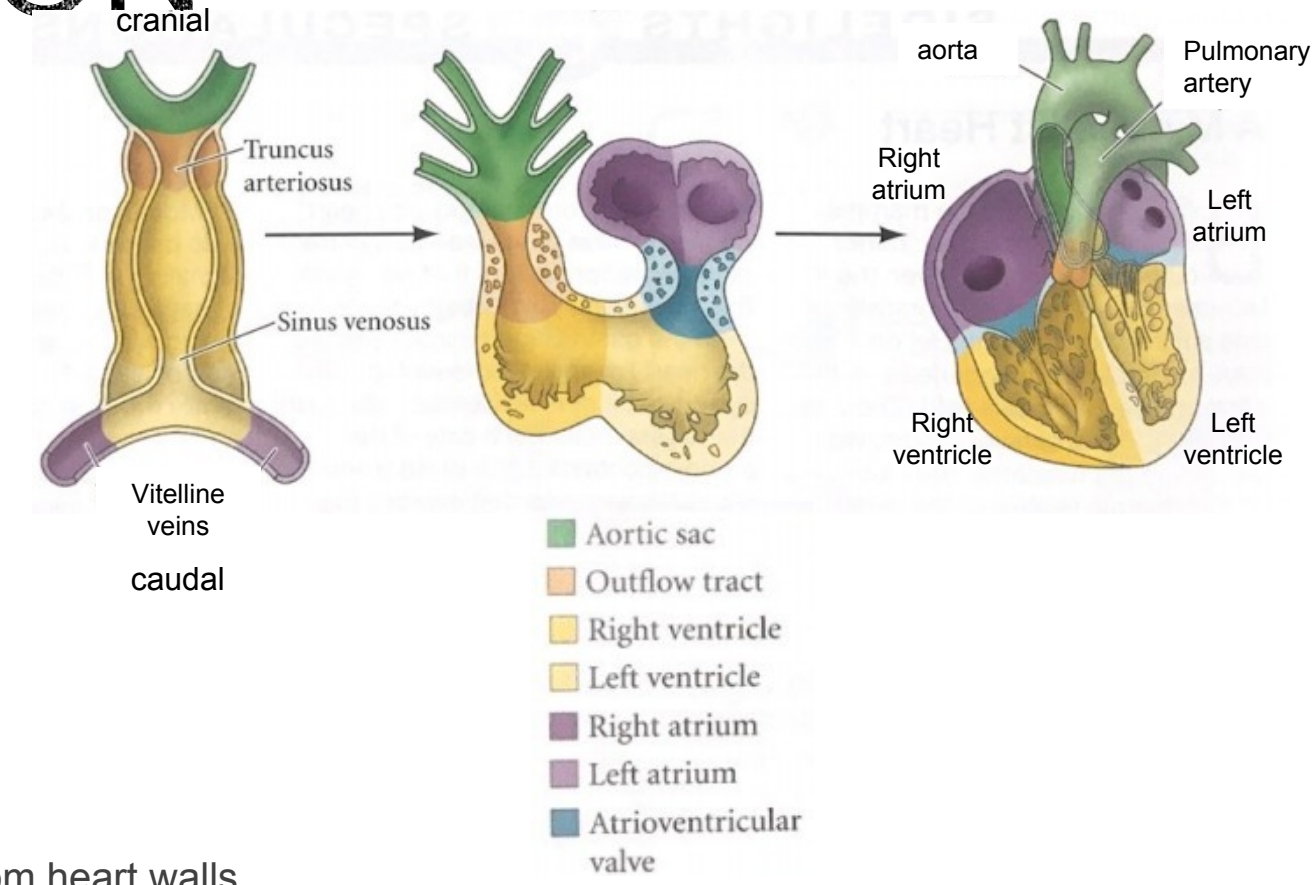
- paired heart tube basis – formation from cells of the **primary heart field mesoderm**
- **Craniocaudal** embryo **bending** – forming **heart tubes** (endocardium) translocates from **cranial** part of embryo to **ventral**
- tubes contact **dorsal aorta** and **vitelline veins** (from yolk sac)
- **Lateral** embryo **bending** – medial approach of paired endocardial primordia, beginning of **fusion**
- after the fusion – **segmentation of heart tube**



McGaedy et al. 2006

HEART TUBE SEGMENTATION

- Formation of first segments:
  - single chamber heart connects with **vitelline veins** (blood enters the heart) caudally and **aortic sac** cranially (blood exits the heart)
- Tube bending:
  - originally - cranio-caudal direction
  - now – right-left polarity
- Segmentation into two parts:
  - **atrium** (blood enters the heart)
  - **ventricle** (blood exits the heart)
- Bending completion:
  - cranially – **atria**
  - caudally - **ventricles**
- septation of atria and ventricles – formation of septa from heart walls



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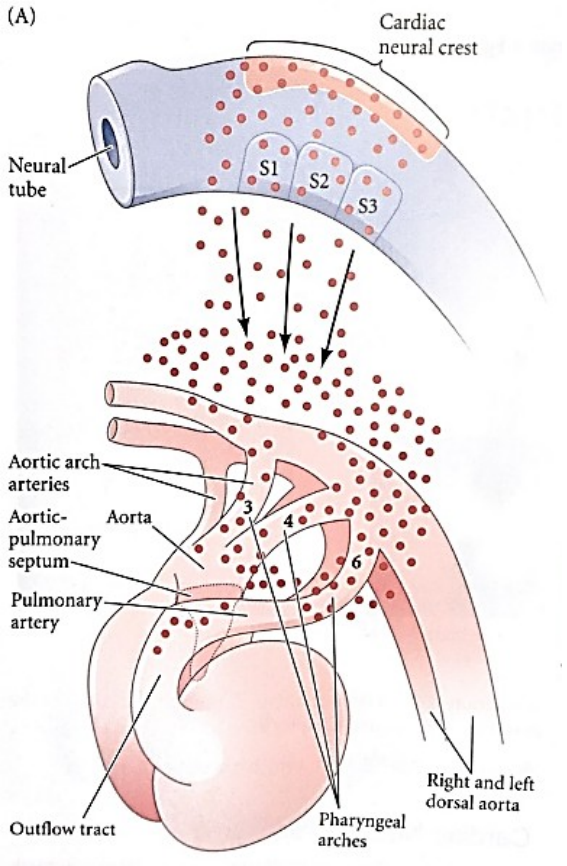
CARDIAC NEURAL CREST

- **Caudal** region of the cranial neural crest
- localized between otic placode and 3. somite
- **endothelium** of the **aortic** arch arteries
- Neural crest cells migrate into 3., 4., 6. pharyngeal arches → migration to region of the developing **aortic-pulmonary septum**



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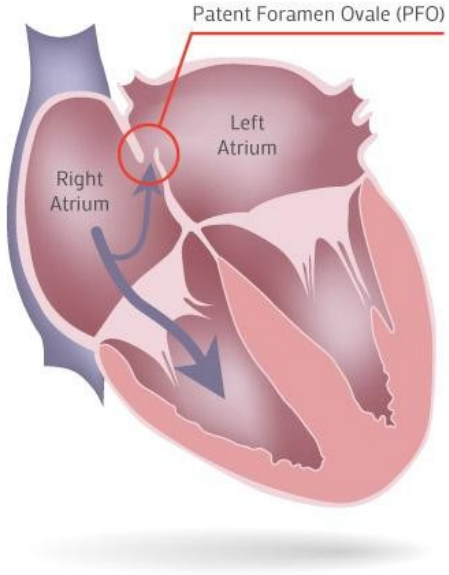
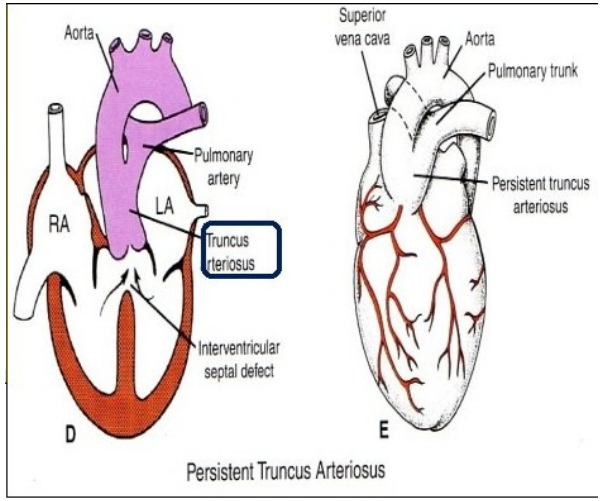
DEVELOPMENTAL HEART DEFECTS

- **Foramen ovale patens**
  - permanent opening in septum between atria
  - very often defect, people are mostly not even diagnosed – functional problems are not common

- **Truncus arteriosus persistens**
  - failure in division of pulmonary trunk and aorta
  - mixing of oxygenated and deoxygenated blood
  - manifests as blue skin (insufficient blood oxygenation) and heart failure
  - surgery is necessary

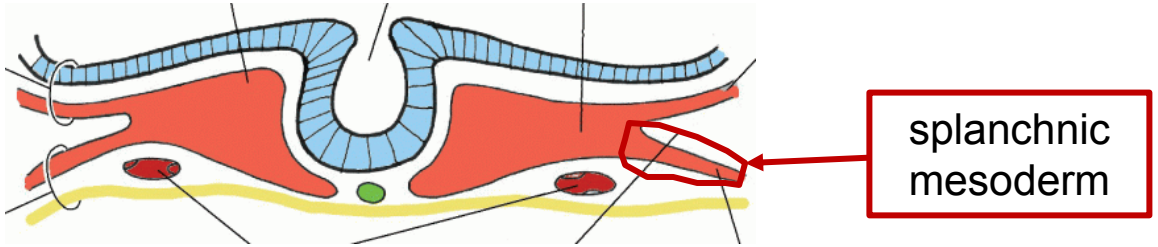




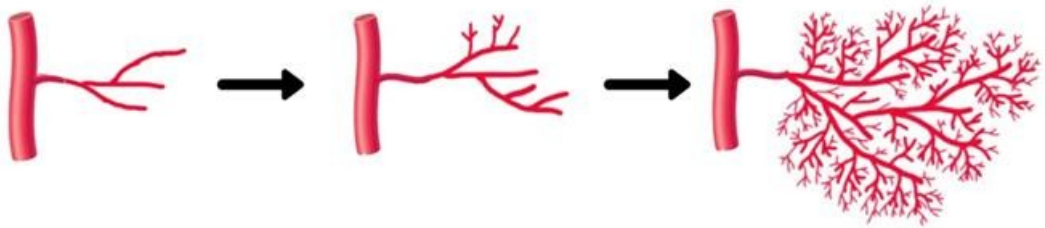
BLOOD VESSELS DEVELOPMENT

- Vessels develop by two different processes:

- **vasculogenesis** – vessels develop from **blood islands - splanchnic** lateral plate mesoderm
  - embryonic development only

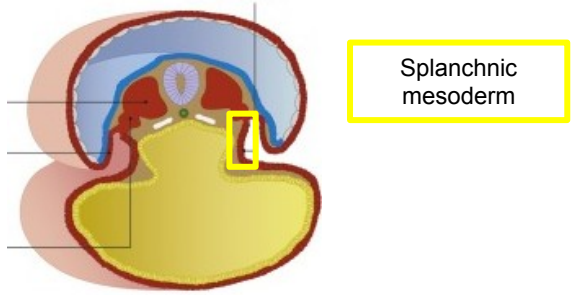


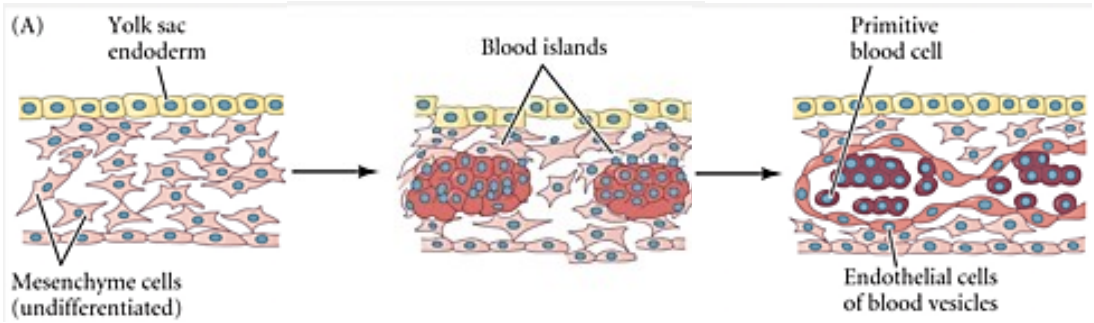
- **angiogenesis** – „budding“ and development of new vessels from **existing vessels**
  - both embryonic and postnatal development



VASCULOGENESIS

- Differentiation of mesodermal cells into **hemangioblast** precursors:
  - blood cells (**hematopoietic** precursors)
  - vascular cells (**endothelial** precursors)
- hemangioblasts condensate forming **blood islands**
- **Blood islands** have two parts:
  - **inner** – **blood cells** precursors
  - **outer** – **angioblasts**, vascular cells precursors
- **intraembryonic** and **extraembryonic** mesoderm





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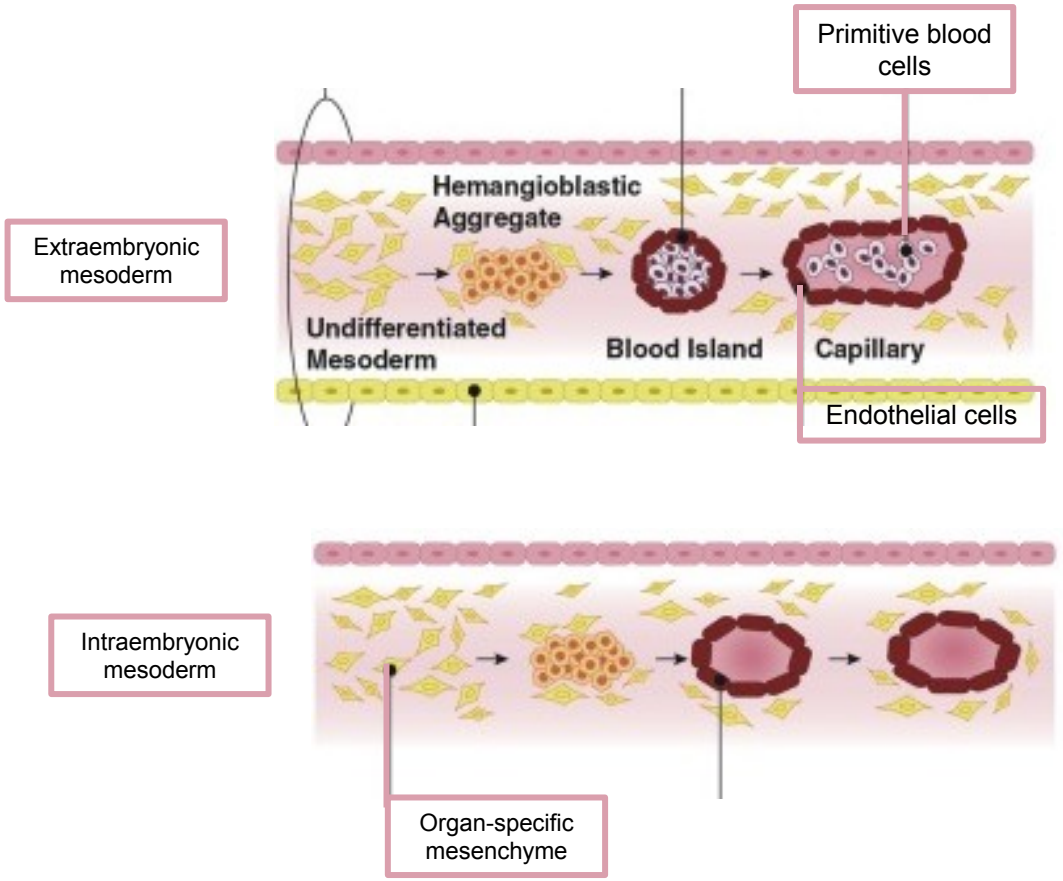
VASCULOGENESIS

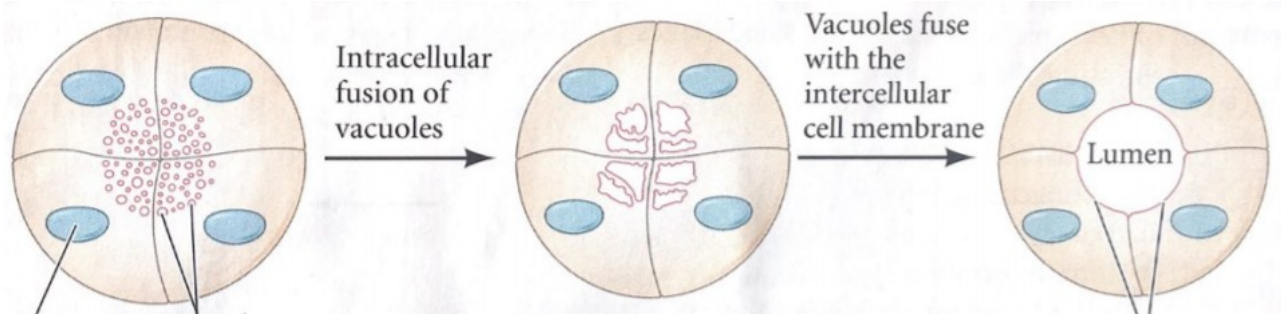
- **extraembryonic** vasculogenesis
  - blood islands of the **yolk sac**
  - important for **embryo nourishment**
  - **embryonic vessels** formation
  - formation of **hematopoietic cells** for **early embryonic stages**
- **intraembryonic** vasculogenesis
  - formation of **dorsal aorta**
  - **mesoderm** of individual **organs**
  - vessels form from **mesodermal angioblasts** in **organs**
- **outer** layers of vessels (smooth muscle cells) partly formed from **neural crest**



DeSesso, 2017. Rep Tox

HOLLOWING OF BLOOD VESSELS

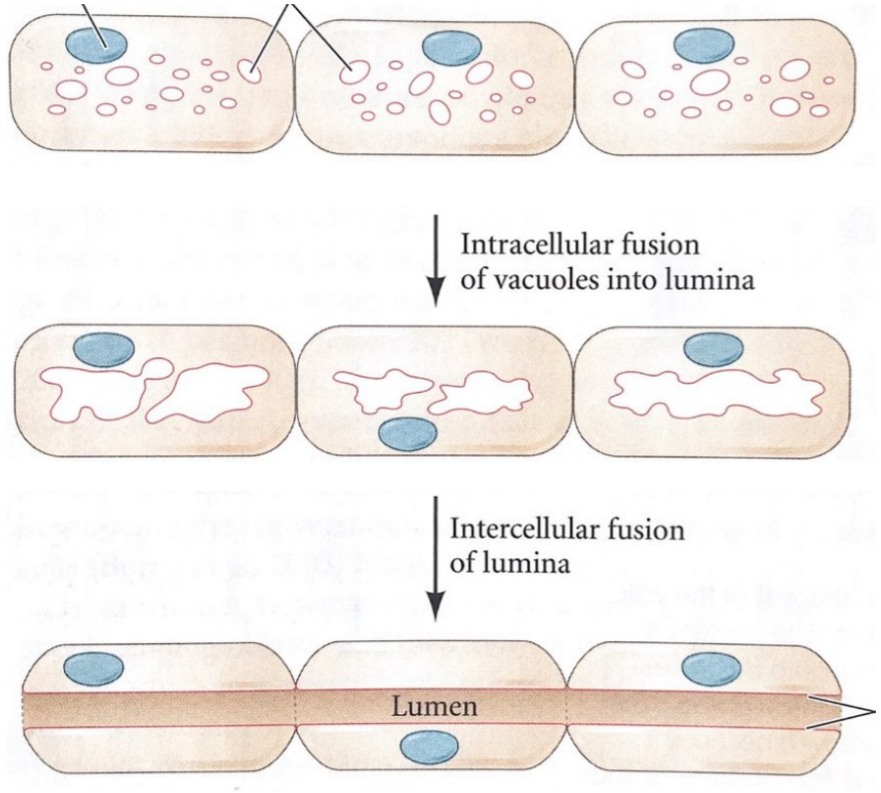
- **endothelial** cells **aggregation**
- small **vacuoles** are formed in individual cells
- **small** vacuoles **fuse** and form **larger** vacuoles
- large vacuoles **fuse** with **cellular membrane**
- formation of **lumen**



Scott Gilbert. Developmental Biology 10th edition

HOLLOWING OF BLOOD VESSELS

- formation of **intracellular vacuoles**
- formation of **cavity/channel** within **one** cell
- **fusion** of cells on their **ends**
- wall of vessel is formed by **membrane** of **one cell**

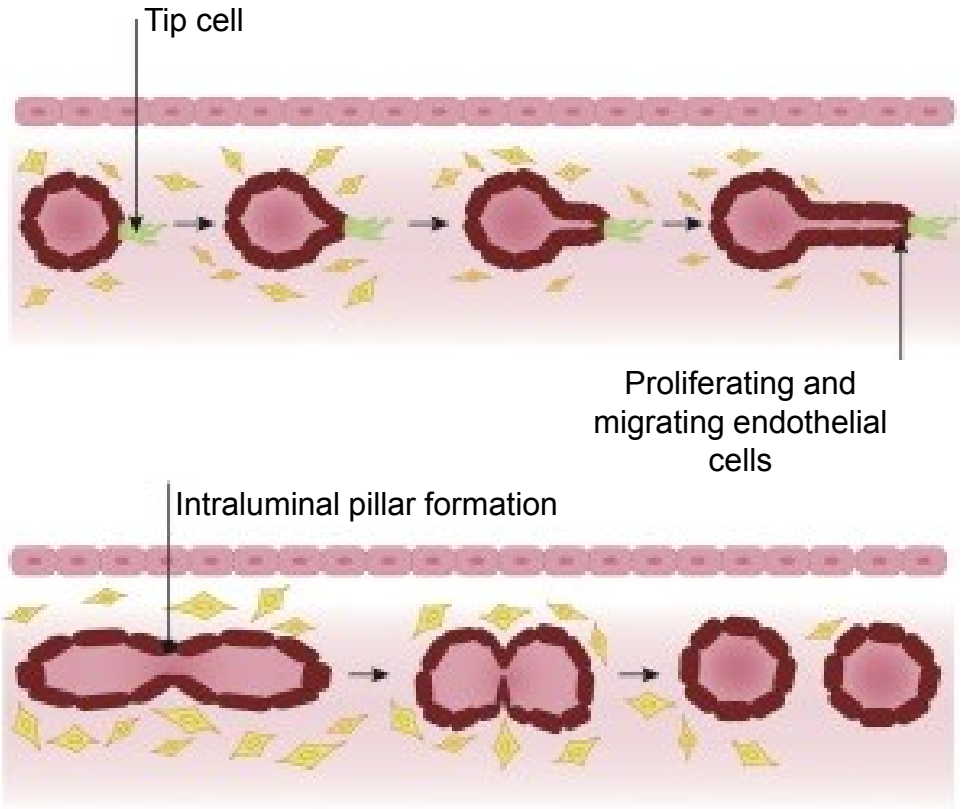


Scott Gilbert. Developmental Biology 10th edition

ANGIOGENESIS – BUDDING AND LONGITUDINAL SPLITTING

- **Budding**
  - formation of **tip** cell from endothelial cell
  - **migration** of tip cell into surrounding **mesenchyme**
  - another endothelial cells follow**, cavity** of vessel is **maintained**

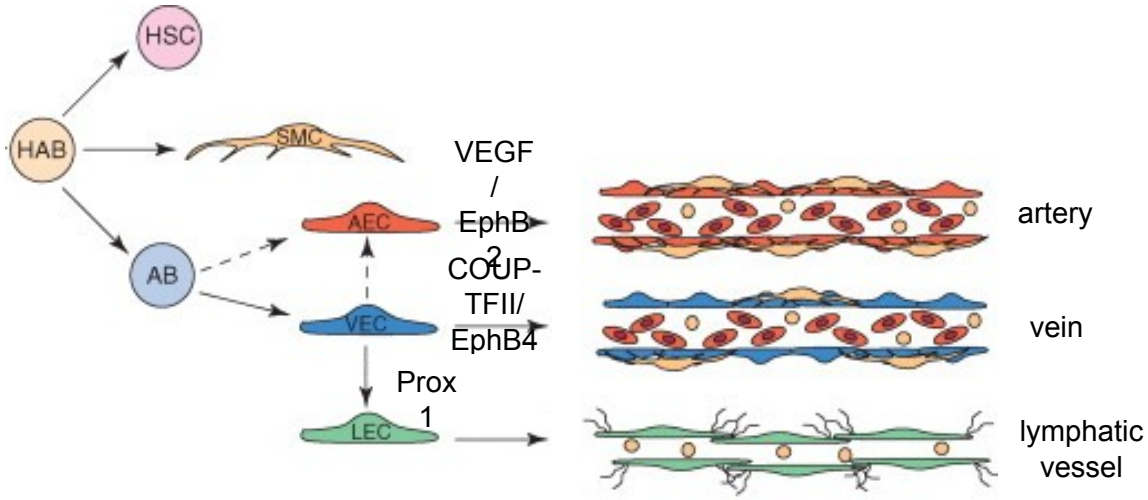
- **Longitudinal splitting**:
  - formation of the **intraluminal pillar** (walls of vessels **invaginate** into cavity), migration of the opposite endothelial cells into center of cavity
  - **enlargement** and **fusion** of pillars
  - splitting vessel into two vessels



DeSesso, 2017. Rep Tox

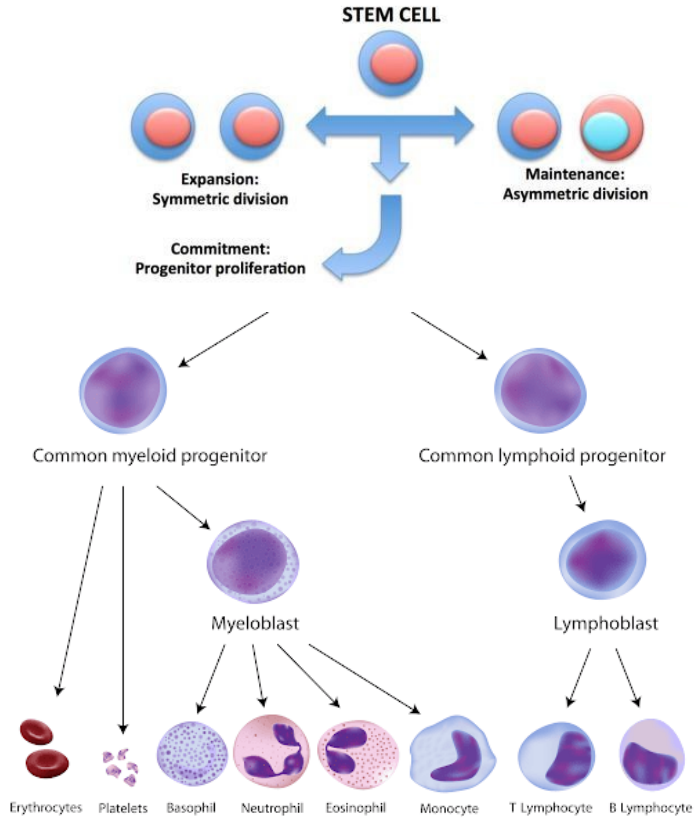
ARTERY, VEIN, OR LYMPHATIC VESSEL?

- precursors of **arteries** – endothelium formation dependent on **vascular endothelial growth factor** (VEGF)
  - specification – **Ephrin B2**
  - **arteries** are formed **earlier** than **veins**
- precursors of **veins** – artery specification is blocked by presence of **COUP-TFII** receptor
  - specification – **Ephrin B4**
  - veins are formed later
- **lymphatic** precursors – from venous endothelial cells
  - specification – **Prox1**



HEMATOPOIESIS – PRODUCTION OF BLOOD CELLS

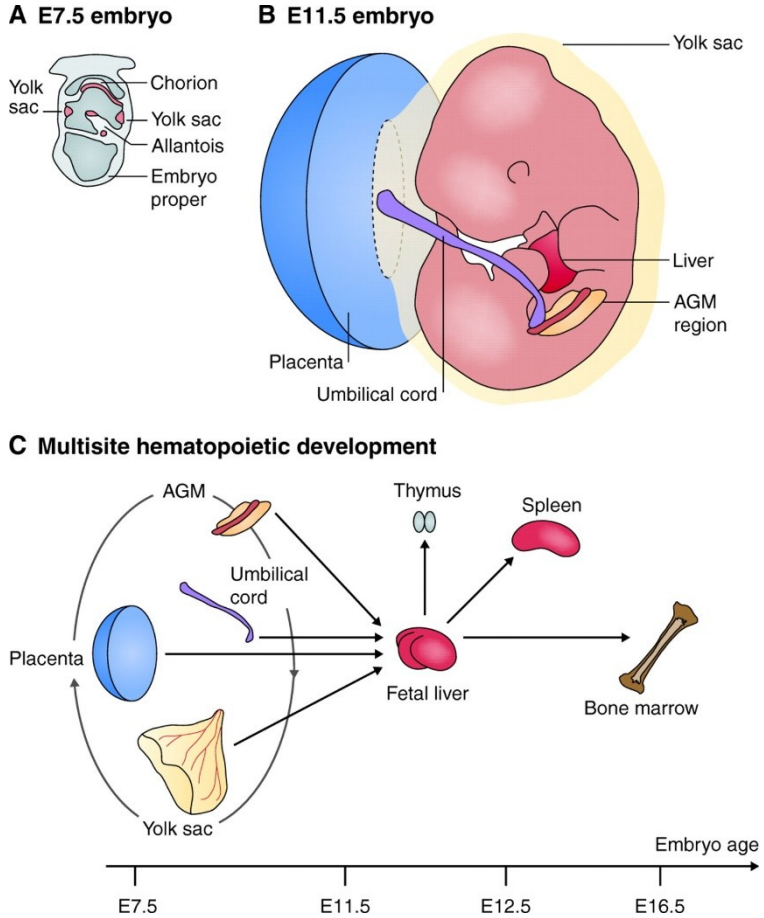
- Depends on existence of **hematopoietic stem cells** (HSC)
- HSC are able to:
  - **selfrenew** (stem cells production)
  - **differentiate** (production of hematopoietic precursors)
- Differentiate into **myeloid** and **lymphoid** progenitors
- production of specific blood cell types
- **Where and how are hematopoietic stem cells formed?**



Caocci and La Nasa, 2017. Med J Hem Inf Dis

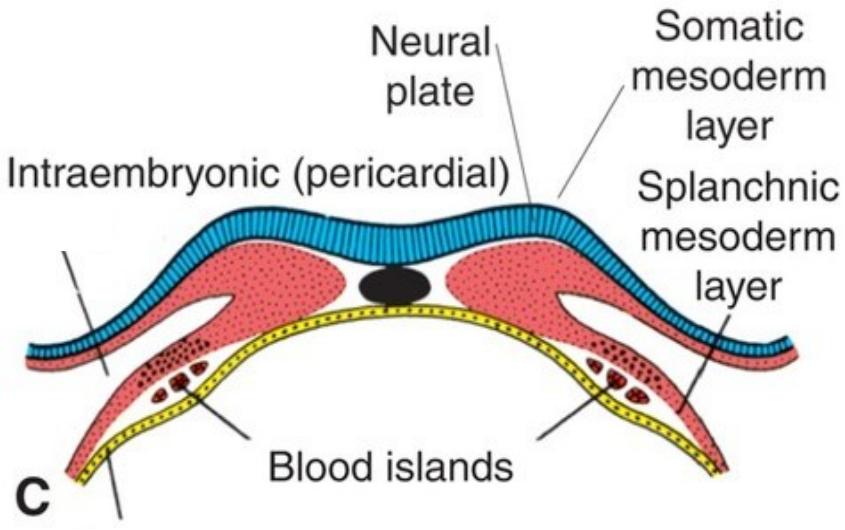
PLACES OF EMBRYONIC HEMATOPOIESIS

- Hematopoietic precursors are embryonically formed in:
- **yolk sac**
- **aorta-gonad-mesonefros**
- vessels of placenta, umbilical cord, liver, spleen, thymus, bone marrow



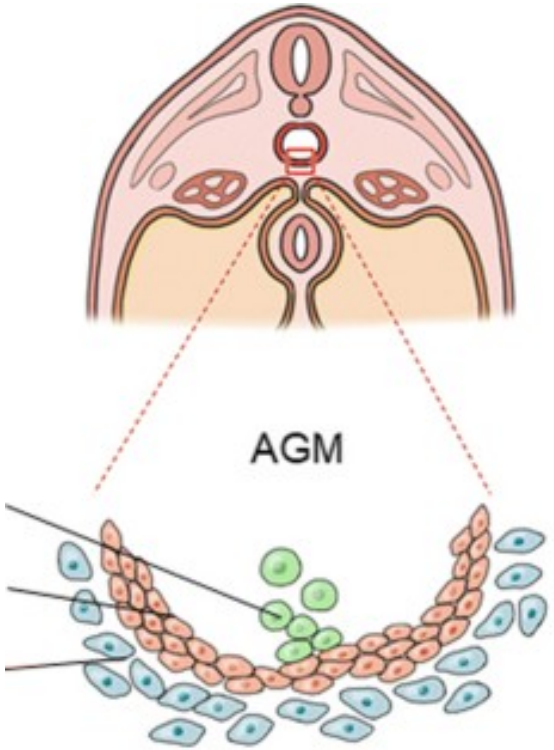
YOLK SAC

- **Extraembryonic** hematopoiesis phase
- develops from **splanchnic** lateral plate mesoderm
- blood islands are formed in **yolk sac wall**



AORTA-GONAD-MESONEFROS

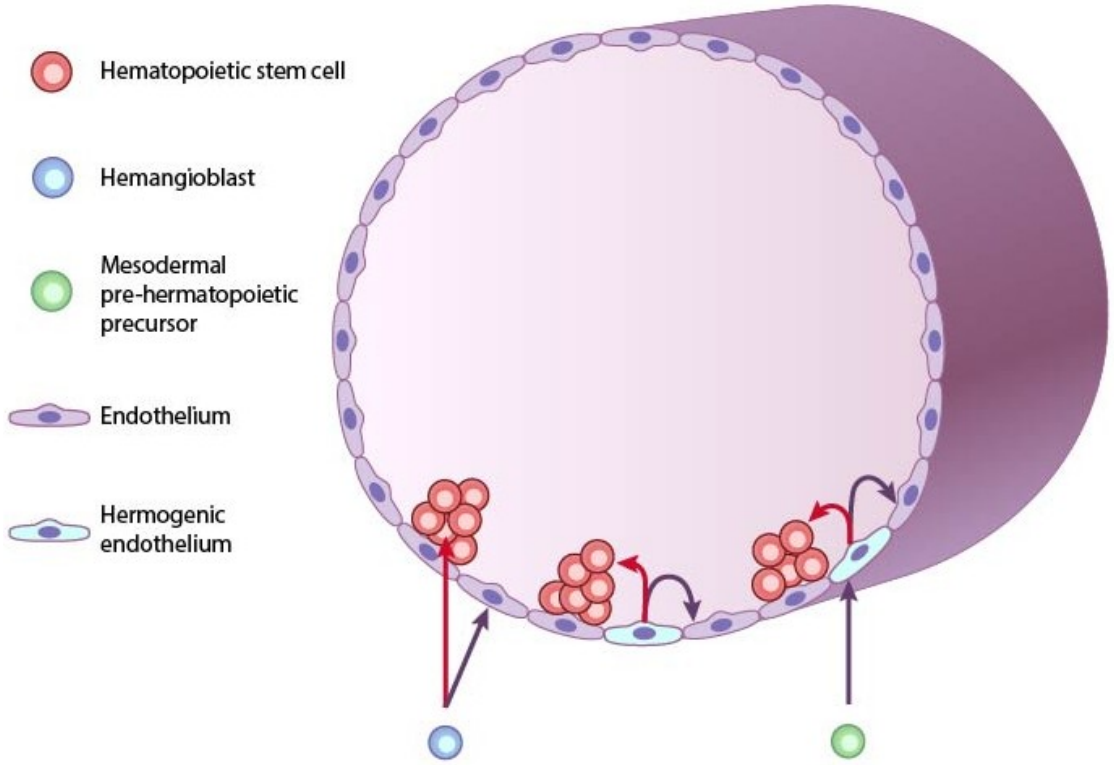
- **intraembryonic** development of hemetopoietic precursors
- mesoderm surrounding **aorta**, **developing urogenital system** and **adrenal cortex**
- hematopoietic precursors differentiate from **endothelium** of developing vessels



Sugimura et al., 2019. Biomed Microdev

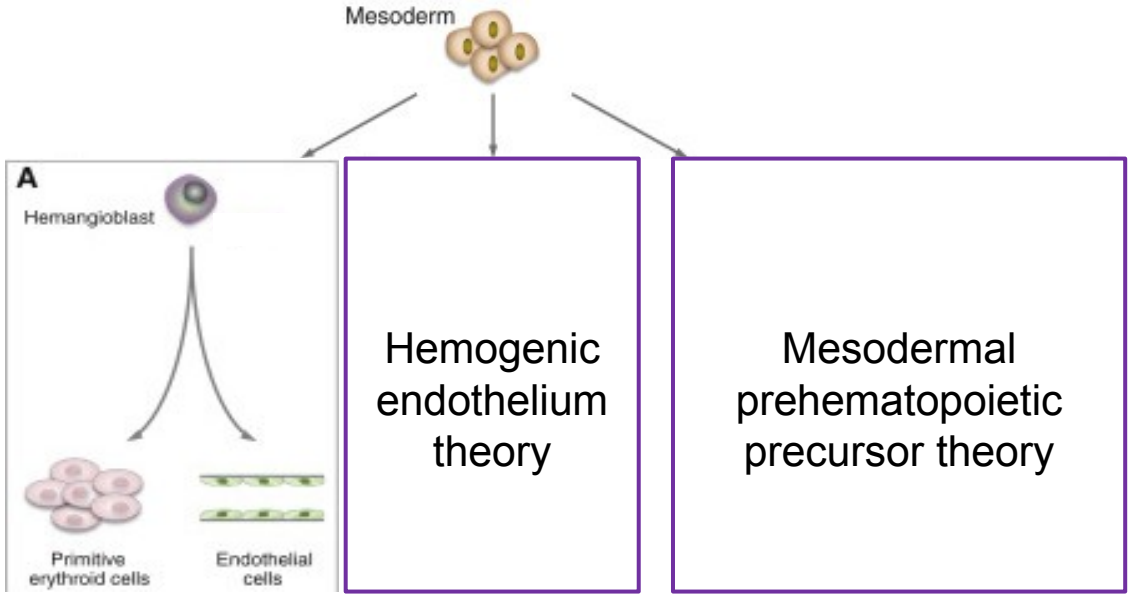
HOW ARE HEMATOPOIETIC STEM CELLS FORMED?

- More than one theory:
- **Hemangioblast** theory
- **Hemogenic** endothelium theory
- **Mesodermal prehematopoietic precursor** theory



HEMANGIOBLAST THEORY

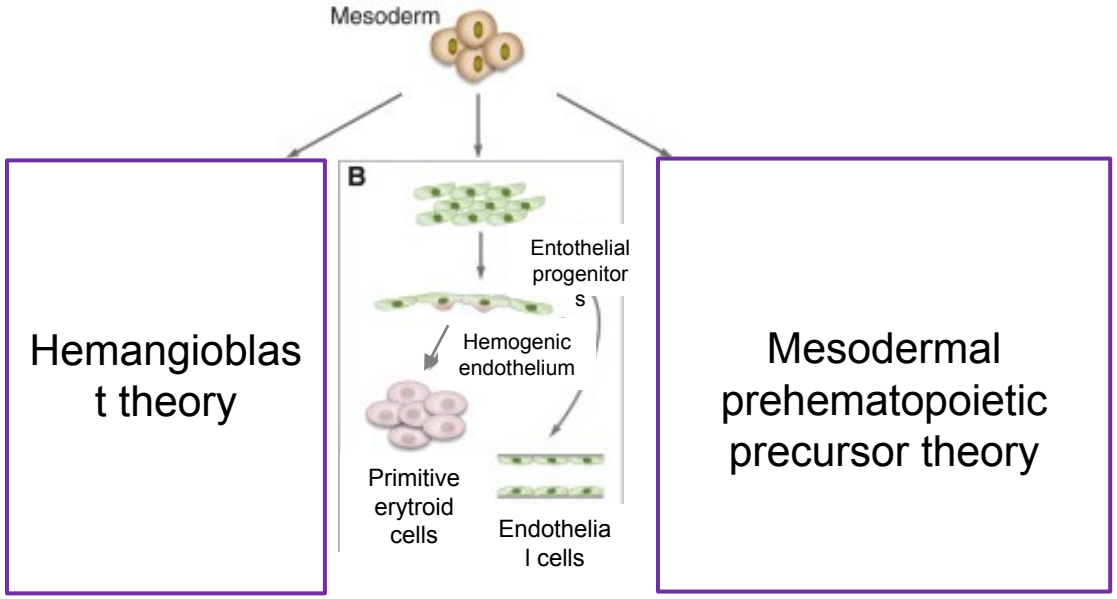
- **hemangioblast** is formed from mesoderm
- hemangioblast derivatives:
  - **hematopoietic** precursors
  - **endothelial** precursors
- hemagioblast precursors differentiate in **yolk sac**
- applicable theory for early hematopoiesis phases



Rossmann et al., 2016. Curr Biol

HEMOGENIC ENDOTHELIUM THEORY

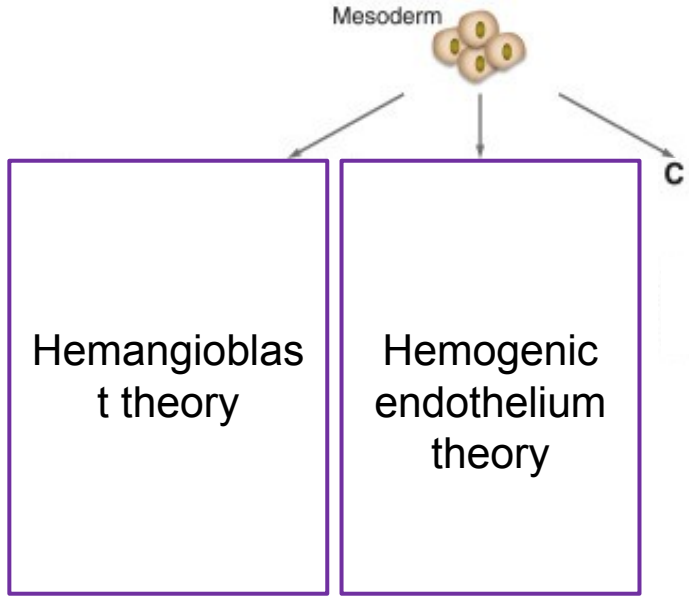
- **Hemogenic endothelium** forms from endothelial cells in **aorta-gonad-mesonephros** region
- Mesoderm from regions around developing **aorta**, **urogenital system** and **adrenal cortex**
- Hemogenic endothelium can differentiate into **lymphoid** and **myeloid** precursors
- applicable theory also for definitive **phases** of hematopoiesis

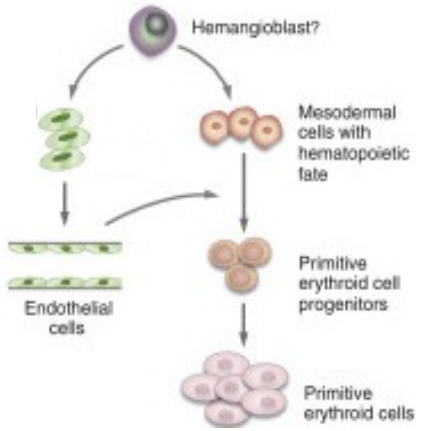


Rossmann et al., 2016. Curr Biol

MESODERMAL PREHEMATOPOIETIC PRECURSOR THEORY

- Theory combining previous theories:
- both theories are valid – consecutive parts of hematopoietic and endothelial cells development
- hemangioblast derivatives:
  - endothelial precursors
  - hematopoietic precursors
- hematopoietic precursors develop from endothelial cells
- **Endothelial-hematopoietic transition**:
  - endothelial cells loose their epithelial character
  - releasing from vessel walls
  - migration to lumen of vessel





Rossmann et al., 2016. Curr Biol

DEVELOPMENTAL DEFECTS OF VESSELS

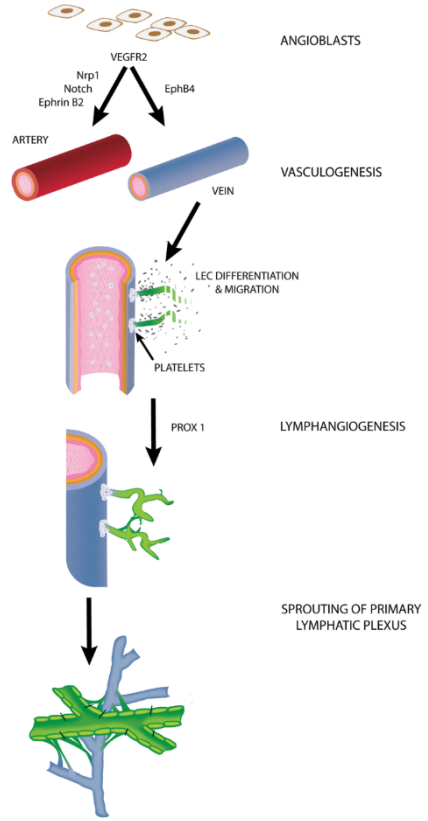
- **Hereditary hemorrhagic telangiectasia**
  - arterial-venous malformation
  - missing connecting cappilaries between arteries and veins
  - nose bleeding, bloody spots on skin

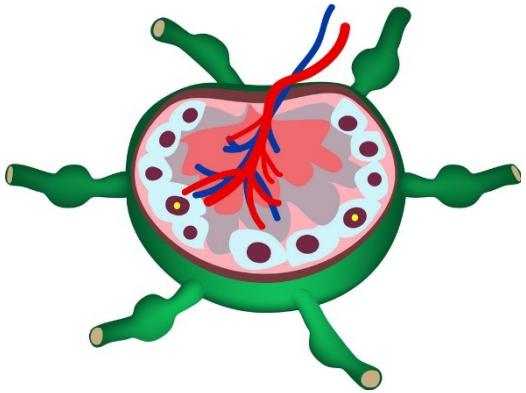
- **Cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL)**
  - defects in skin and brain arteries
  - degeneration of smooth muscle cells in vessels
  - accumulation of fibrous tissues around arteries
  - narrowed artery transit
  - migrains, dementia, stroke

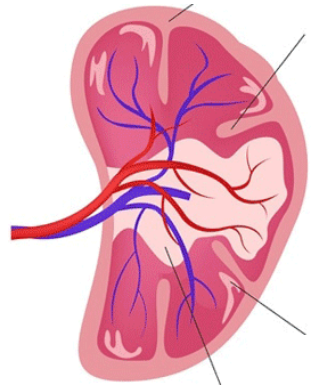
- **Alagile syndrome**
  - narrowing of big arteries including aorta
  - connected with defects in skeletogenesis and formation of face

LYMPHATIC SYSTEM DEVELOPMENT

- blindly-terminated system of tissue vessels
- **absorbtion** and **drainage of tissue fluid**
- enters venous system through **lymphatic vessels**
- transporting **antigens** and **antigen-presenting cells** to **lymphatic nodes** → immune response
- lymphatic vessels develop from **veins**
- development of lymphatic organs:
  - lymphatic nodes
  - spleen
  - thymus



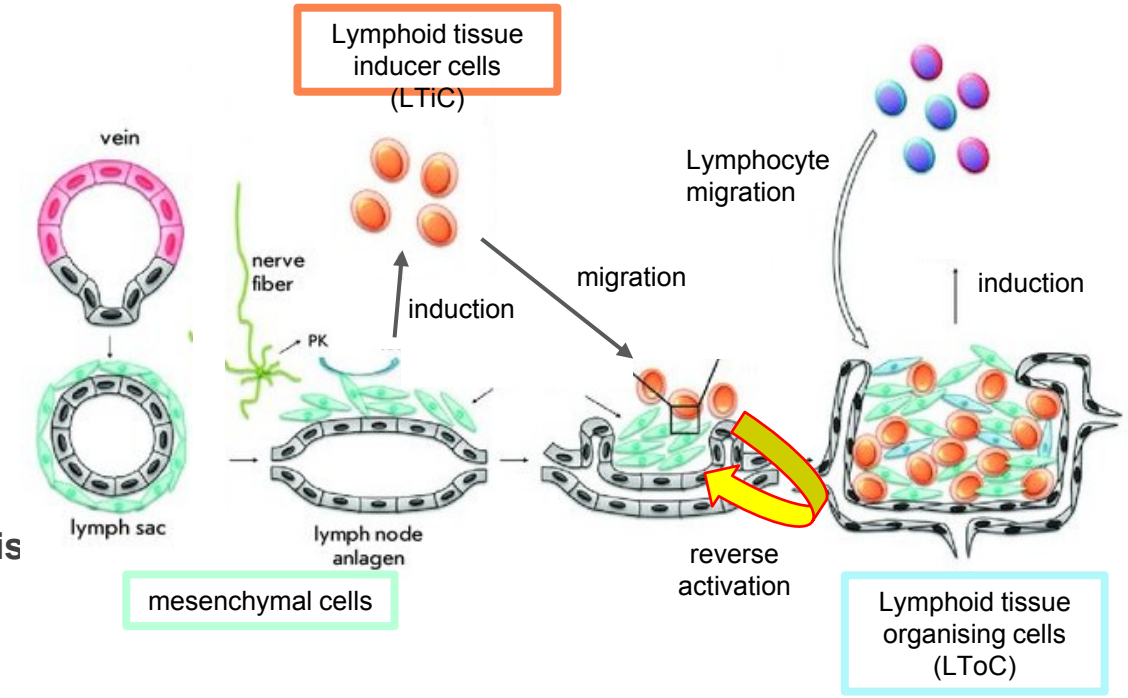




Alderfer et al., 2018. J Biol Eng

DEVELOPMENT OF LYMPH NODES

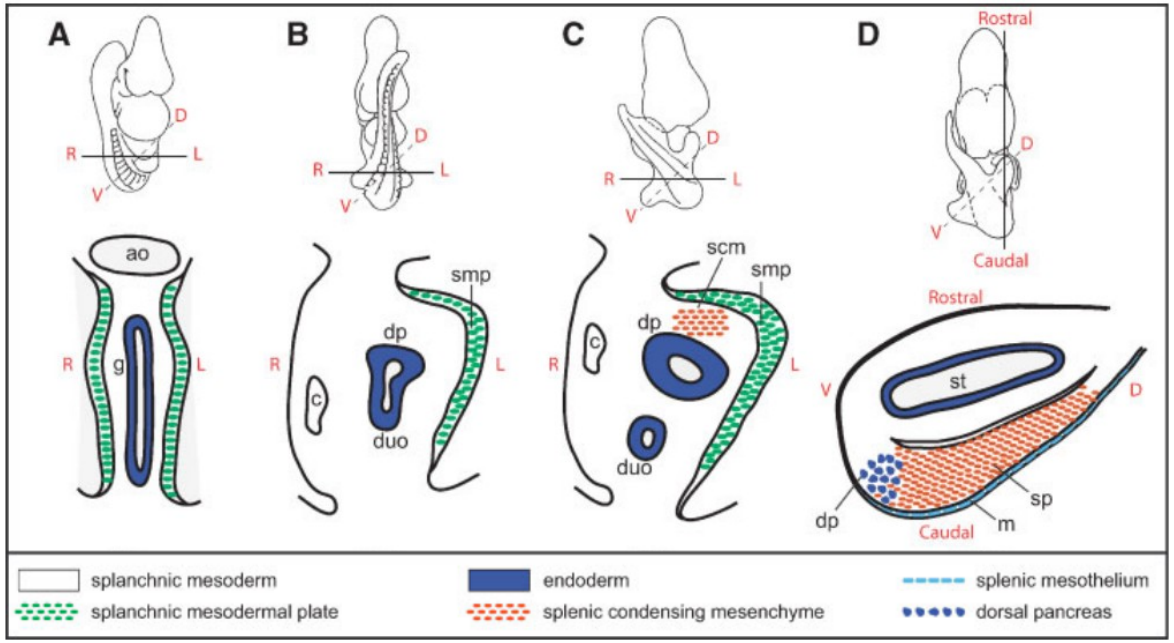
- Lymph nodes:
  - vessels in lymphatic sac
  - stroma and capsule
- initiation:
  - lymphatic vessels **branching** – **lymph sac** is produced
  - lymph sac is settled by **mesemchymal precursors of stroma**
- Lymphatic vessels
  - mesenchyme originates in **mesoderm –** from **vascular endothelium**
- stroma:
  - **mesenchyme** originates in **mesoderm**
  - mesenchyme induces **migration** of **LTiC** to sac surrounding – **basis of node** (LTiC originate in **hemogenic endothelium**)
  - **LTiC induces mesenchyme** in developing node – formation of **LToC**
  - **LToC differentiation** – formation of all stromal cell types of node
  - node induces migration of lymphocytes into node



Edited. Nosenko et al., 2016. Acta Natur

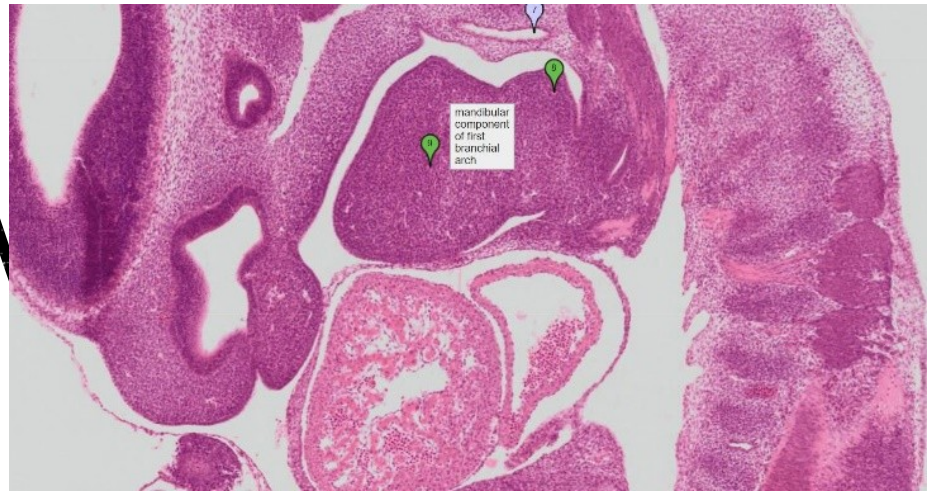
SPLEEN DEVELOPMENT

- **embryonically** – production of **hematopoietic** cells
- Immune organ, erythrocyte degradation
- Develops from **splanchnic lateral plate mesoderm** (mesenchyme surrounding stomach and pancreas)
- Spleen vessels – **branching** from **dorsal aorta**
- stroma:
  - ventral from aorta – **bilateral** splanchnic mesodermal plate (cylindrical epithelium), surrounded with splanchnic mesoderm
  - **right** – **plate replaced** by splanchnic mesoderm
  - **left** – **plate** cells **proliferate**, growth
  - mesenchymal cells under the plate **proliferate** and **differentiate**
  - Formation of spleen, mesothelial sheath on surface

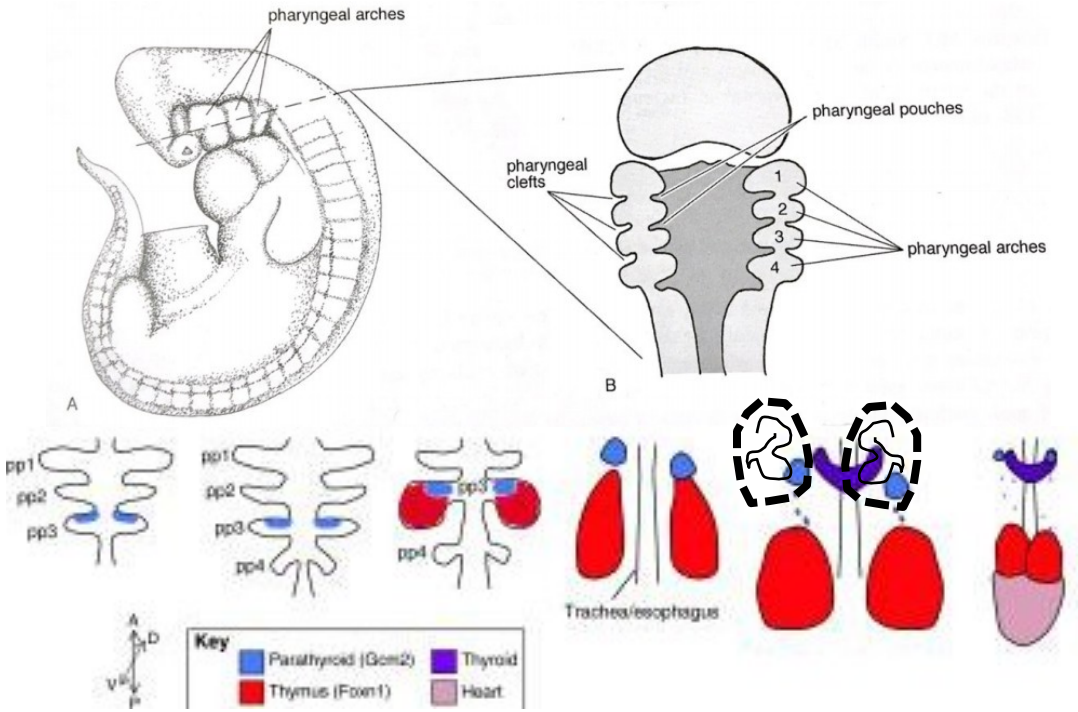


Brendolan et al. 2007. BioEssays

THYMUS DEVELOPM



- development of T-lymphocytes
- develops from 3 sources:
  - **Foregut endoderm**
  - **Neural crest**
  - **mesoderm** - vessels
- Foregut **endoderm** – 3. pharyngeal **pouch** of pharyngeal arch (gut epithelium)
- **Endodermal evagination** – formation of **epithelial sac** surrounded by **mesenchymal capsule**
- formation of primordial thymus and parathyroid gland
- Thymus **detaches** from endoderm and **migrate**
- **Neural crest** – mesenchymal capsule, partly **vessels**



Gordon and Manley, 2011. Dev

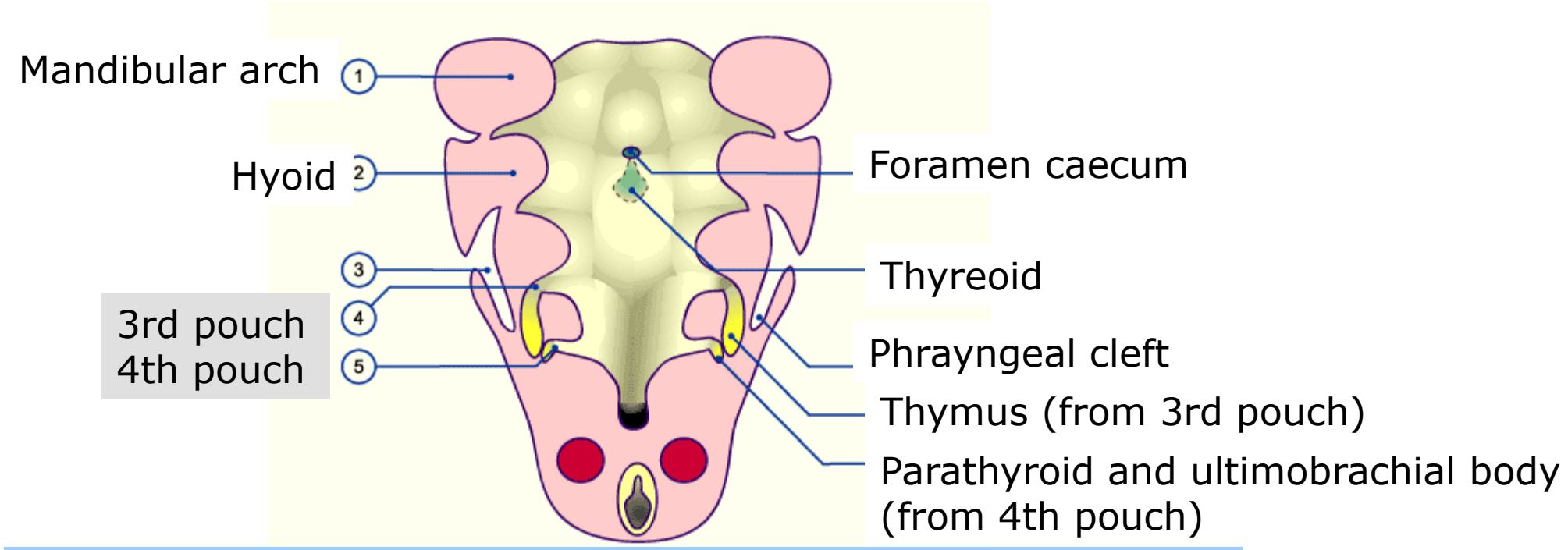
till 6th week iud – epithelial tissue
from 7th week – formation of mesenchymal septa
after 9th week – population with blood cells (T cell)

THYMUS

Ectoderm (neural crest)

Mezoderm

Endoderm (pouches)



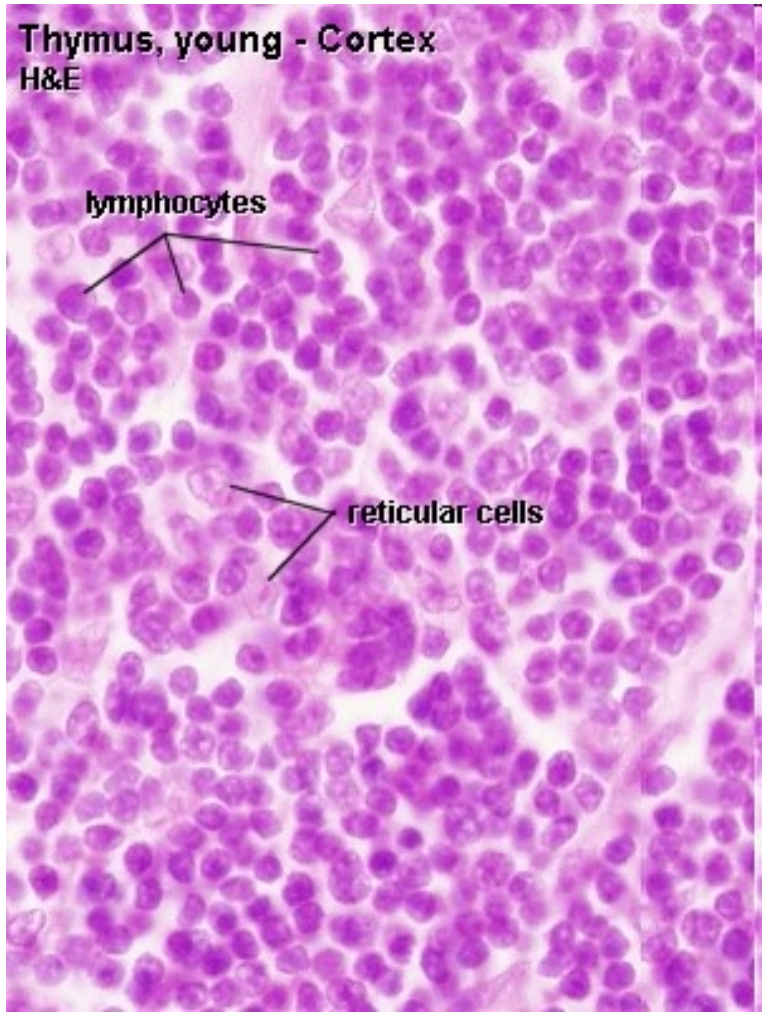
Neural crest – mezenchyme capsula, partially veins

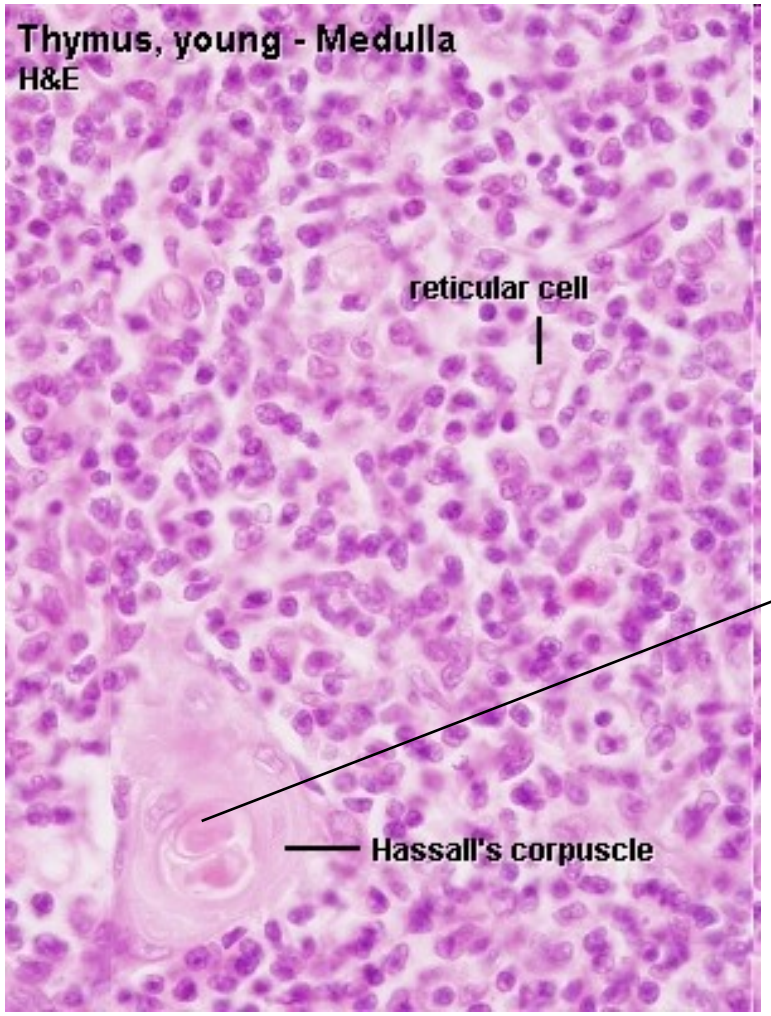
till 6th week iud – epithelial tissue
from 7th week – formation of mesenchymal septa
after 9th week – population with blood cells (T cell)

http://www.embryology.ch/anglais/qblood/lymphat03.html

THYMUS - CHILD

Maximal aktivity – puberty
T lymphocytes fate???

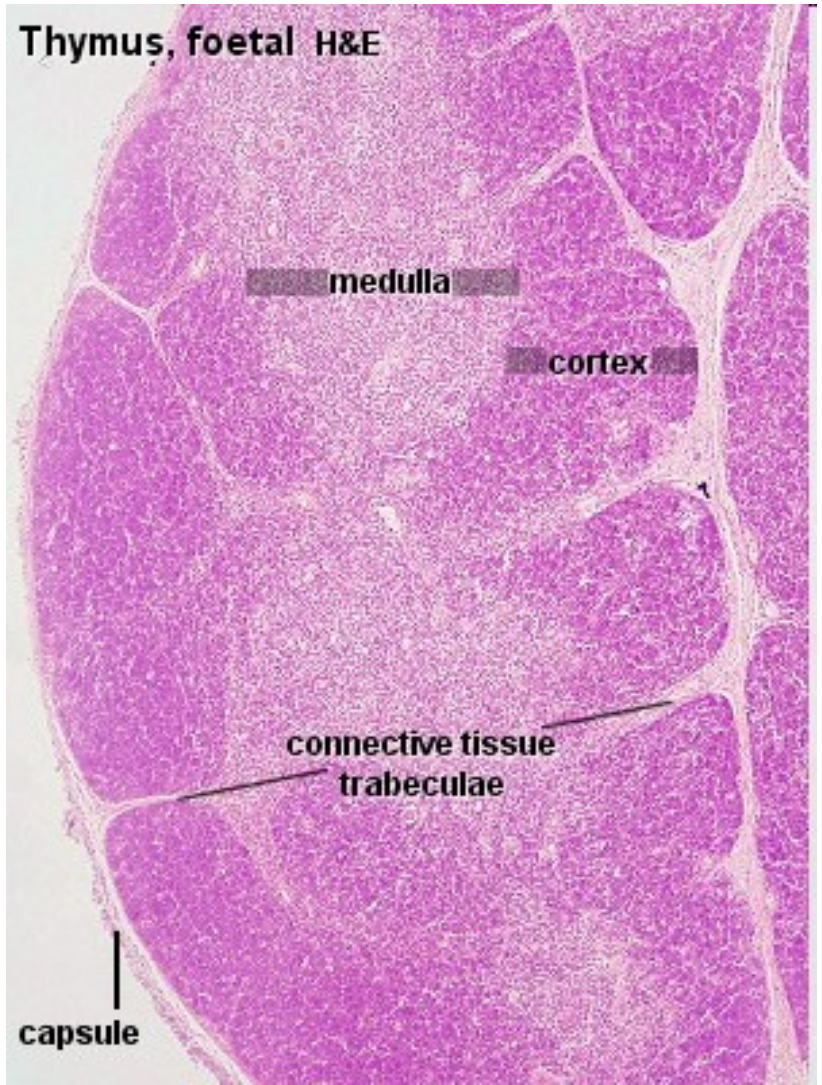




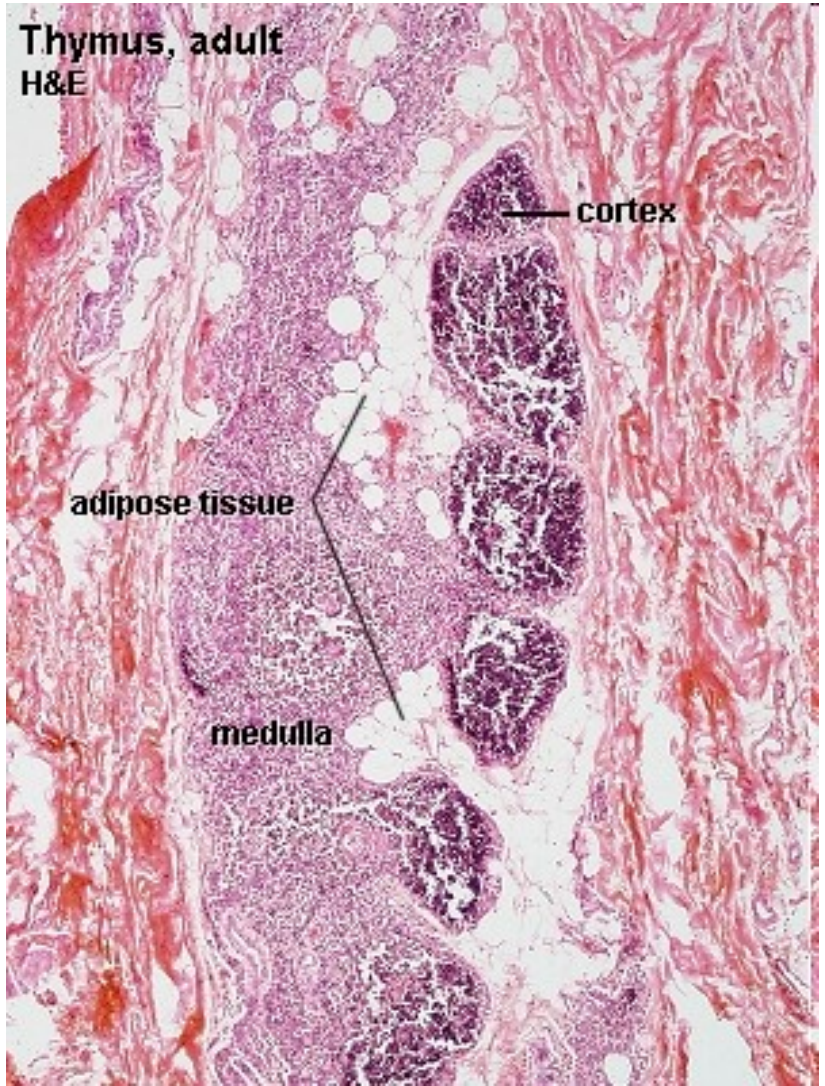
Cytokin TSLP
Thymic Stromal Lympho poietin

THYMUS - ADULT

Functional



Involution



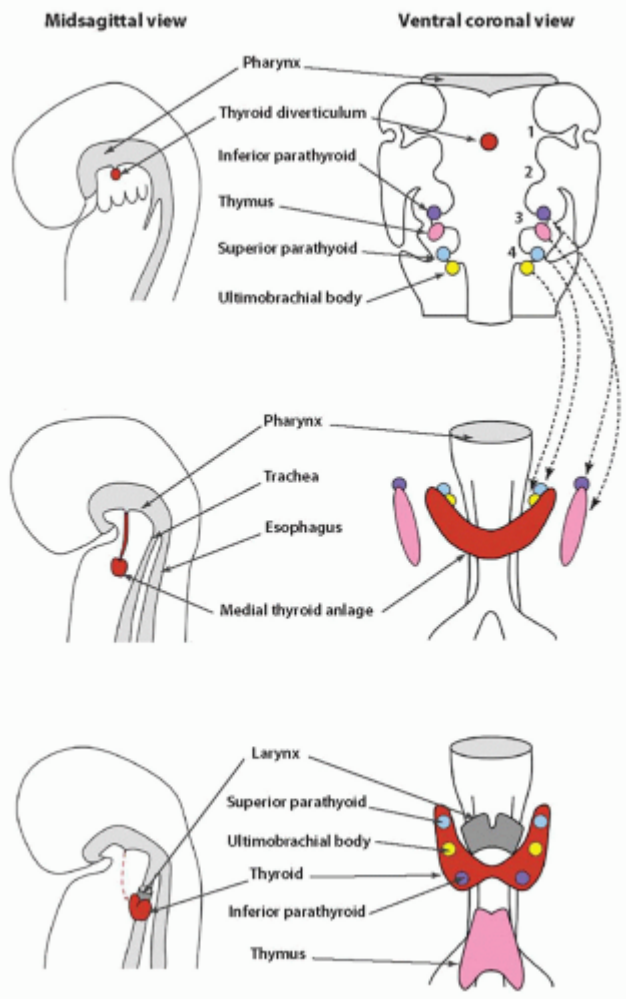
DEVELOPMENT OF THYROID GLAND

- 24th day of iud the endoderm on the floor of pharynx swells
- Formation of bud and its prolongation around the hyoid bone
- The anlage migrates toward the base of trachea
- Co-migration of superior parathyroid (dorsal part of 3rd pouch)

  thymus (ventral part of 3rd pouch)

  inferior parathyroid (dorsal part of 4th pouch)

  ultimobrachial body (ventral part of 4th pouch)
- 7th week – definitive location and shape



https://basicmedicalkey.com/embryology-and-developmental-lesions/

DEVELOPMENTAL DEFECTS OF LYMPHATIC SYSTEM

- **Lymphedema** – enlarged lymphatic vessels in tissues results in insufficient lymph drainage

- Spleen defects:
  - **Lobular** spleen – „clefts“ as remnants of defective development, no functional defects
  - **Wandering** spleen – missing fibrous spleen attachments in the abdominal cavity

- **Cystic hygroma** – cystic neck lymphangioma
  - polycystic
  - formation of cysts in lymphatic regions, endothelial lining
  - contains clear liquid
  - neck region – causing respiration problems and food intake problems