

# Urogenital Development

Intermediate Mesoderm

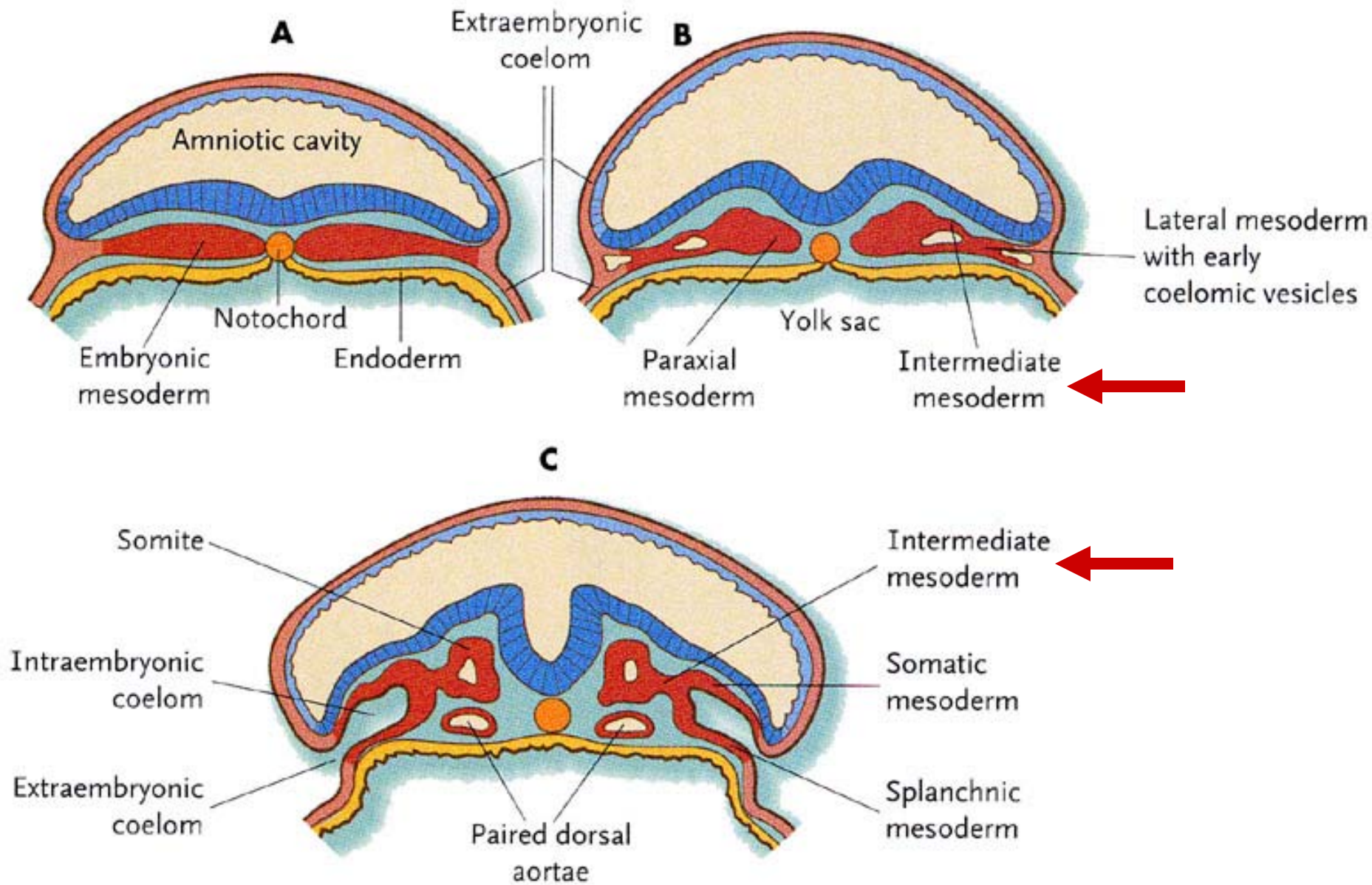
Interconnective - Urinary and Genital Systems

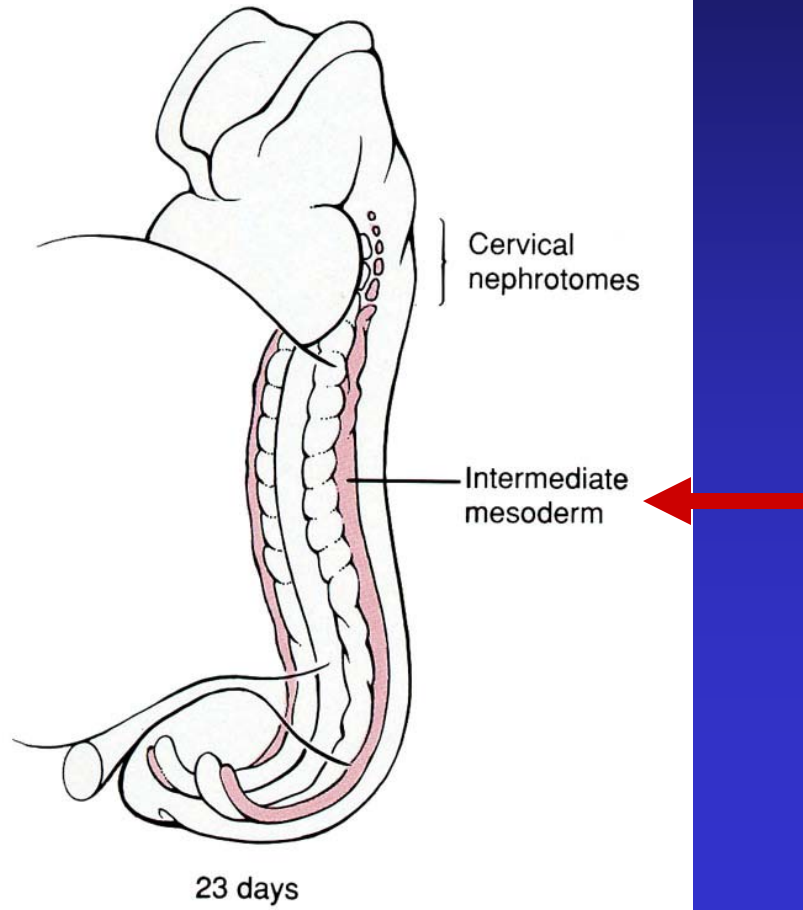
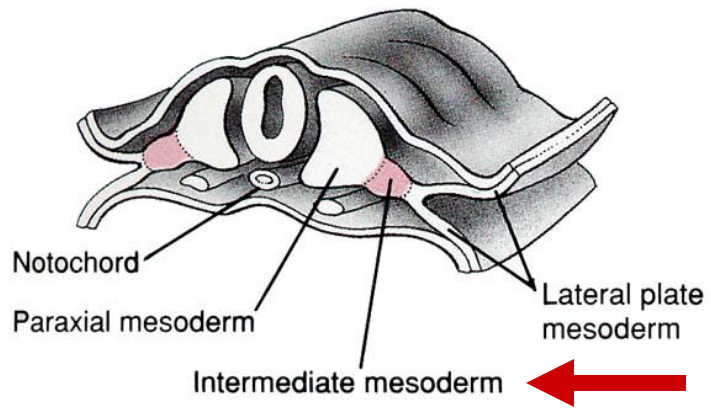
Recapitulation of Kidney Development

Epithelial-Mesenchymal Interactions

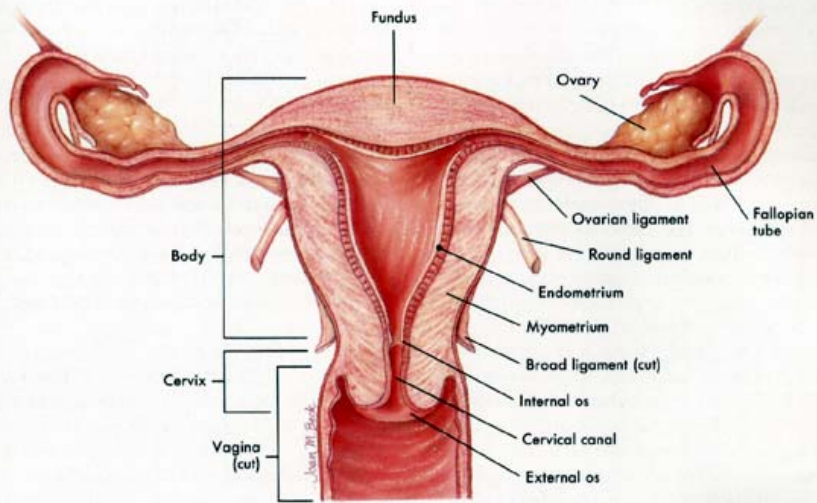
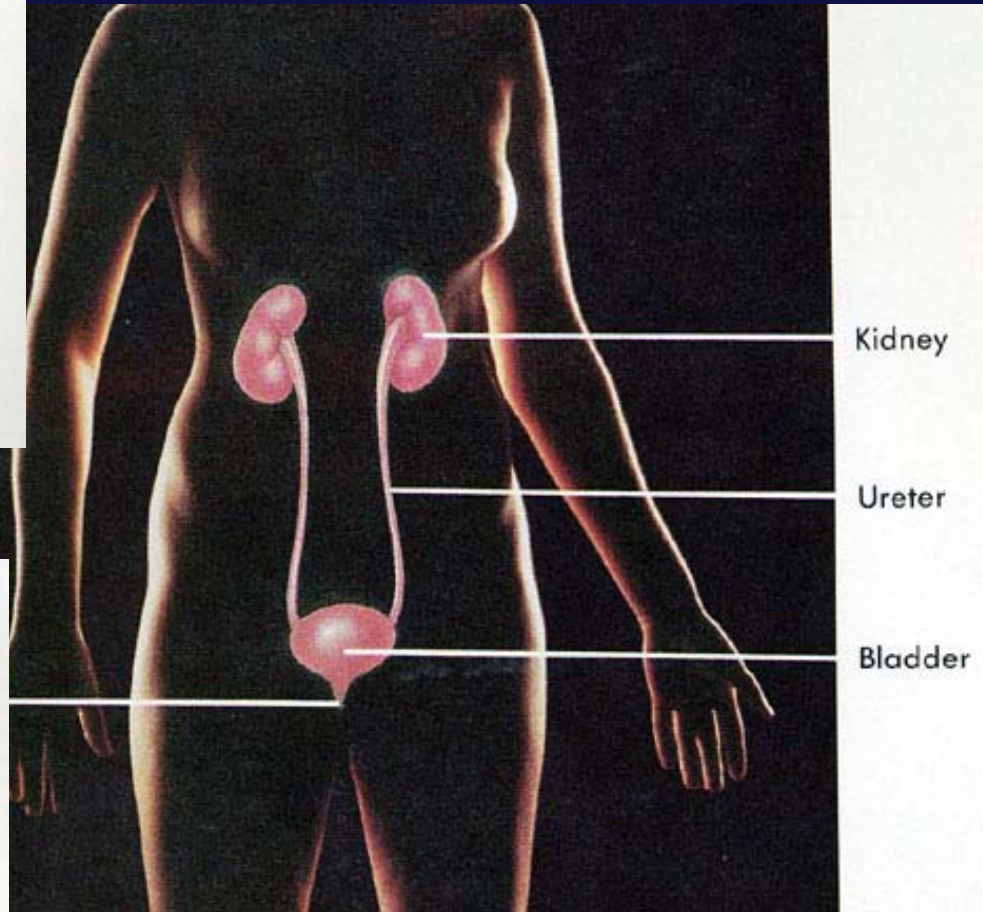
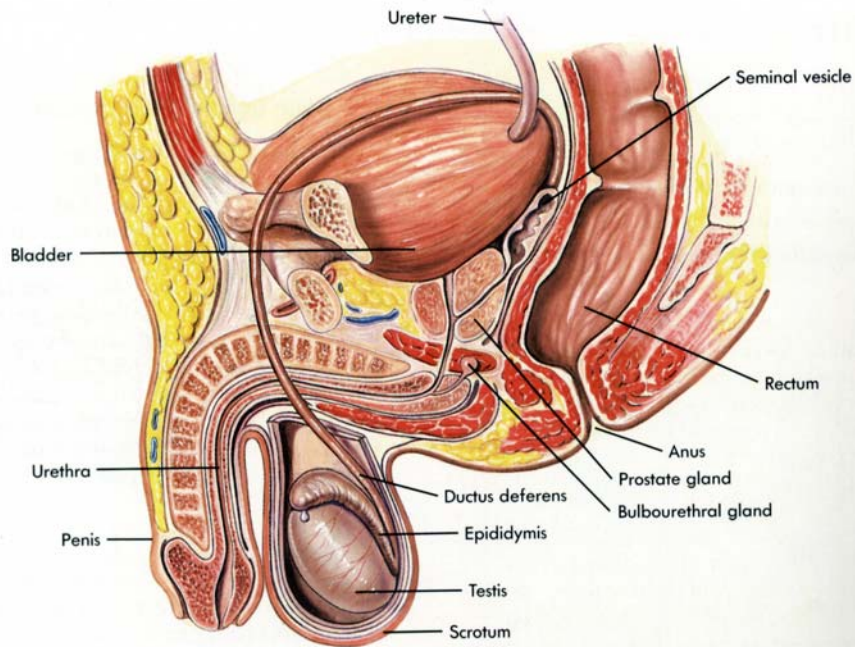
Indifferent Stage of Sexual Differentiation

Genetic vs. Environmental Factors



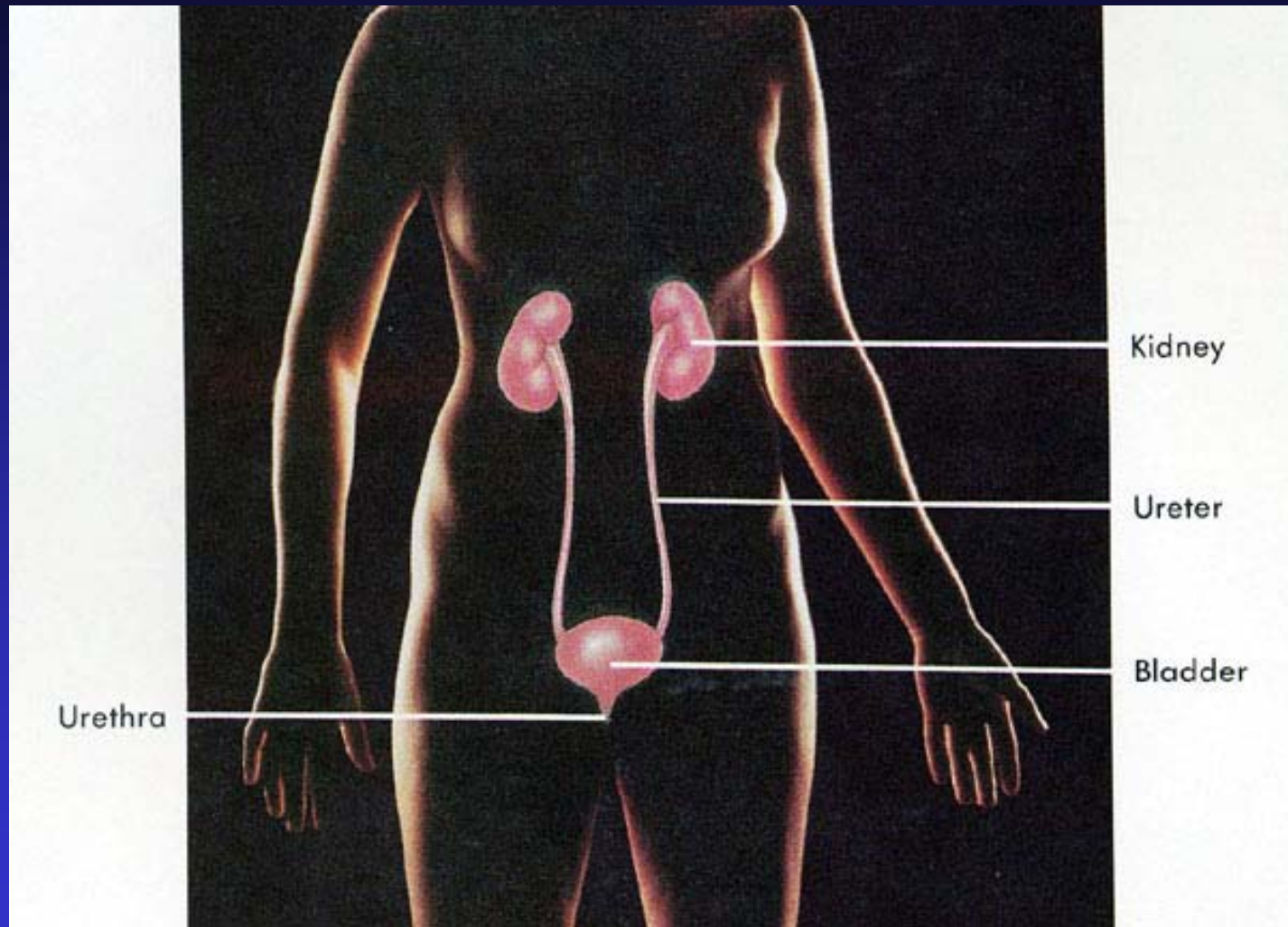








# Urinary System - Kidneys



Kidneys, Ureter, Bladder, Urethra

# Kidney Architecture

## Renal Cortex:

- Renal corpuscle

- Convoluted tubules

## Renal Medulla:

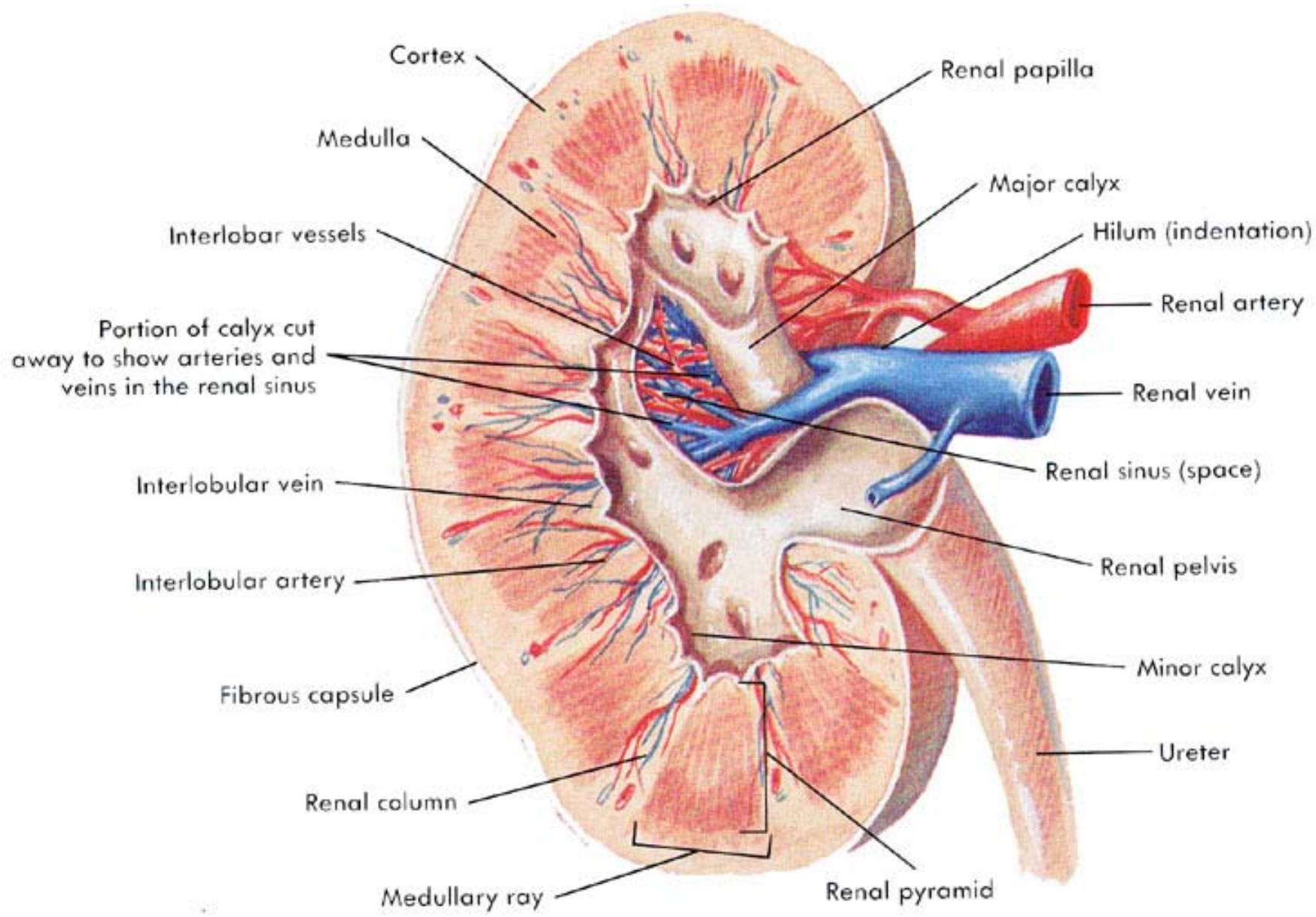
- Collecting ducts

- Loop of Henle

Each Minor calyx drains a tree of collecting ducts within a renal pyramid

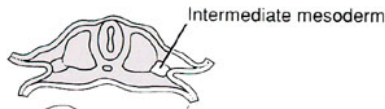
Pyramids are separated by columns of cortical tissues called renal columns

The Renal pyramids converge to form the renal papilla







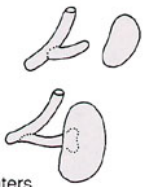


Intermediate mesoderm

At 24 days, cervical nephrotomes begin to appear; at 26 days, mesonephros and mesonephric duct begin to differentiate



By 28 days, the metanephric blastemas and ureteric buds appear



Ureteric bud enters metanephric blastema and bifurcates

Major calyces form



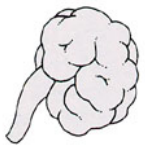
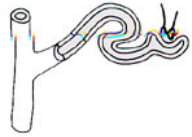
Metanephric tissue caps on terminal collecting ducts begin to form nephric vesicles



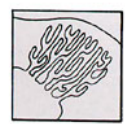
Minor calyces form



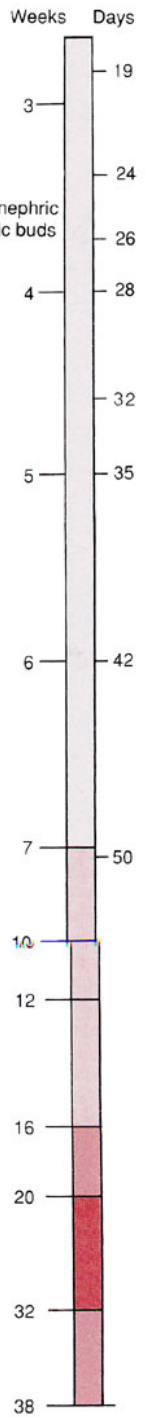
Nephric vesicles differentiate to form nephrons; each nephron becomes functional as its distal convoluted tubule joins with the collecting duct



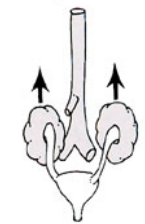
Surface of kidney exhibits lobes



Collecting duct system complete



Kidneys ascend



Mesonephric ducts exstrophy into the posterior wall of the bladder. Exstrophy replaces the ureters into the bladder wall, while the mesonephric ducts are carried down to the pelvic urethra. The region of exstrophied duct becomes the bladder trigone

# Intermediate Mesoderm

Early Development – 3 successive stages

Pronephros, Mesonephros, Metanephros

**Pronephros** - Most primitive Kidney

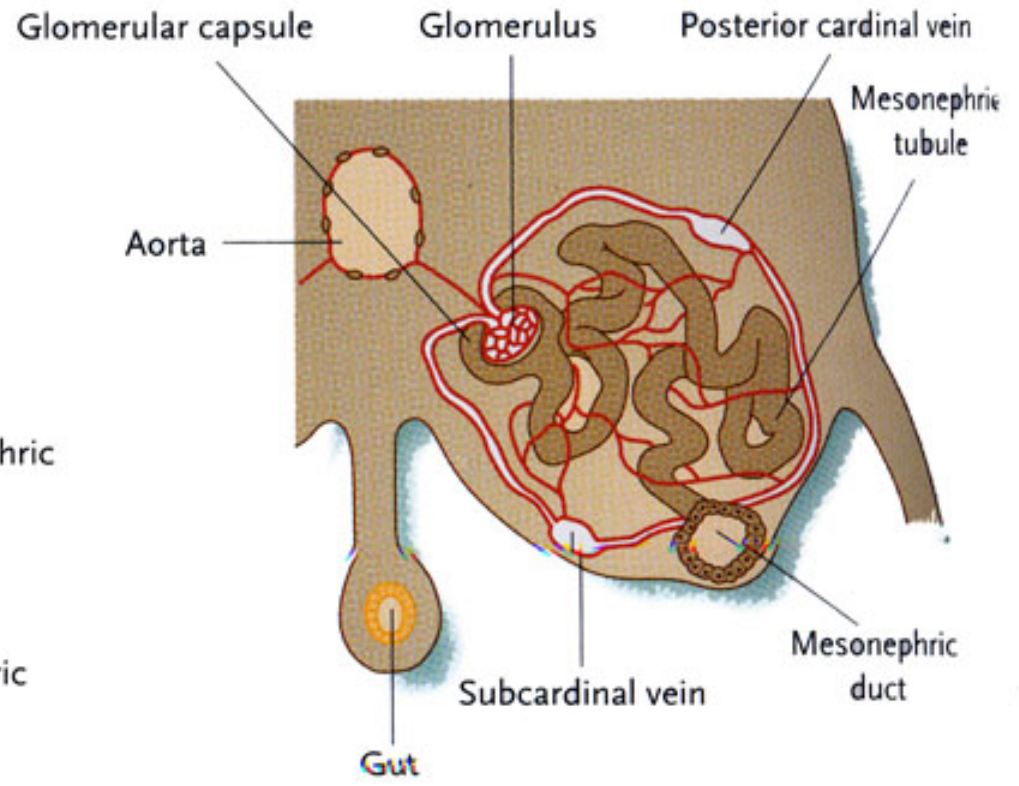
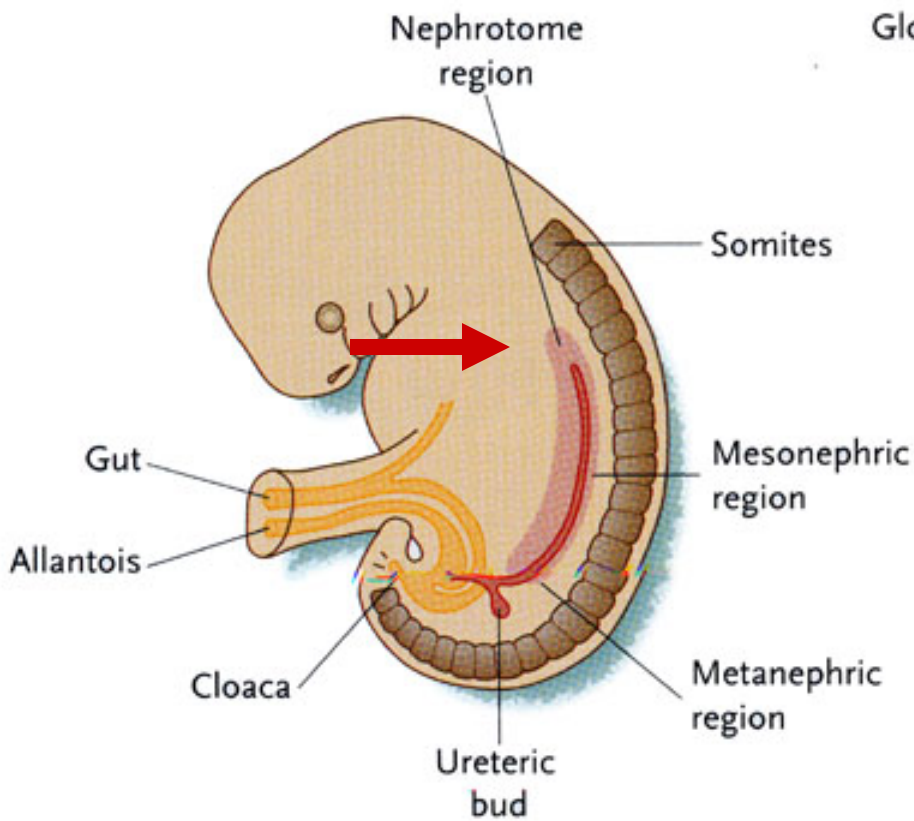
**Cervical nephrotomes** - 5-7 pairs of small hollow balls of epithelium – connected to the **primary nephric duct** (pronephric duct)

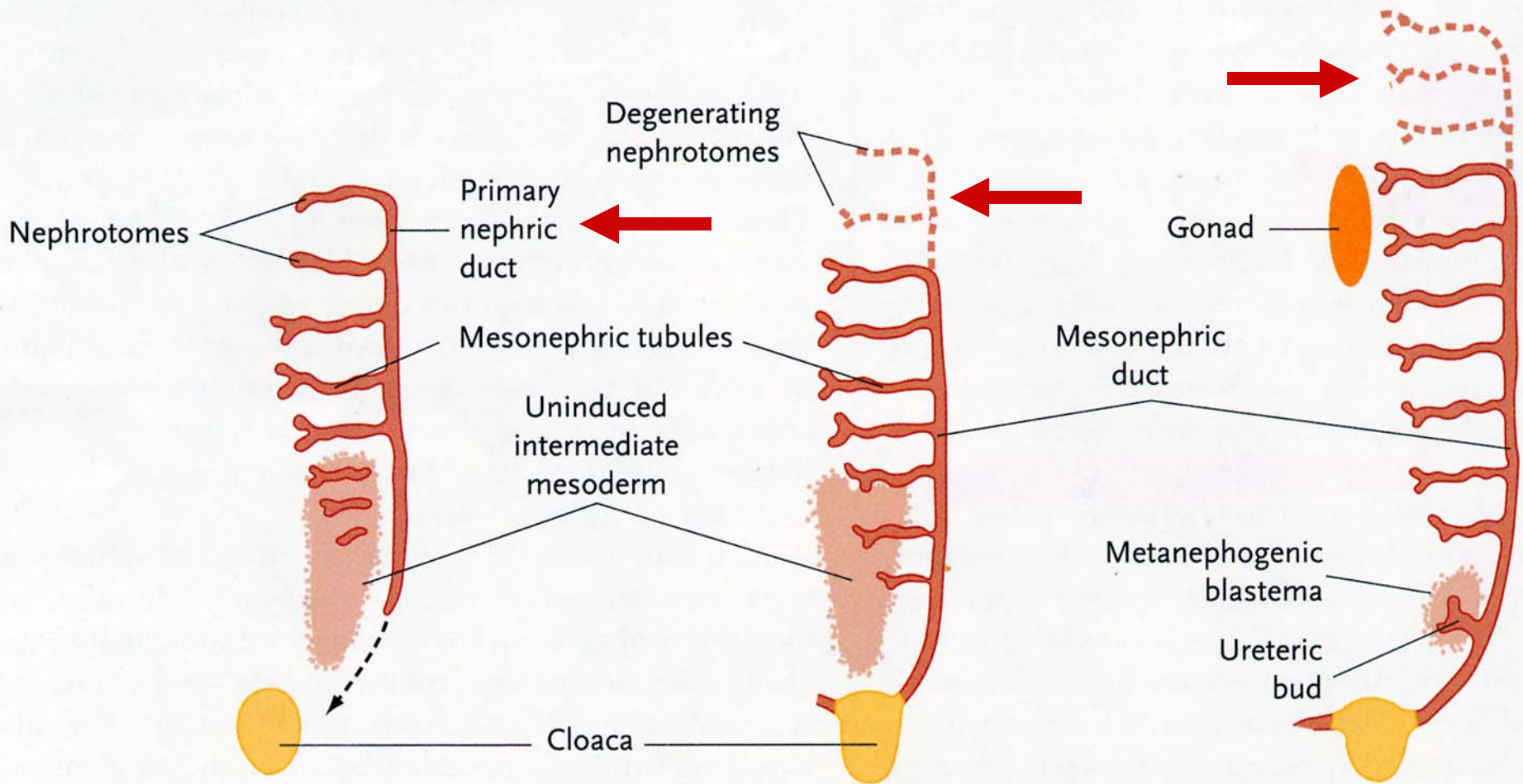
Non-functional in mammals

Transient – nephrotomes degenerates by 24-25 days

Primary nephric duct extends caudally to become the Mesonephric duct







# Mesonephros

Functional embryonic kidney

**Mesonephric tubules** form in each segment

Cranial to caudal sequence

First 4-6 bud out from the primary nephric duct

Remaining form in the intermediate mesoderm and connect with the Mesonephric duct

Mesonephric tubule differentiates a cup-shaped **Bowman's capsule** that wraps around the **Glomerulus**

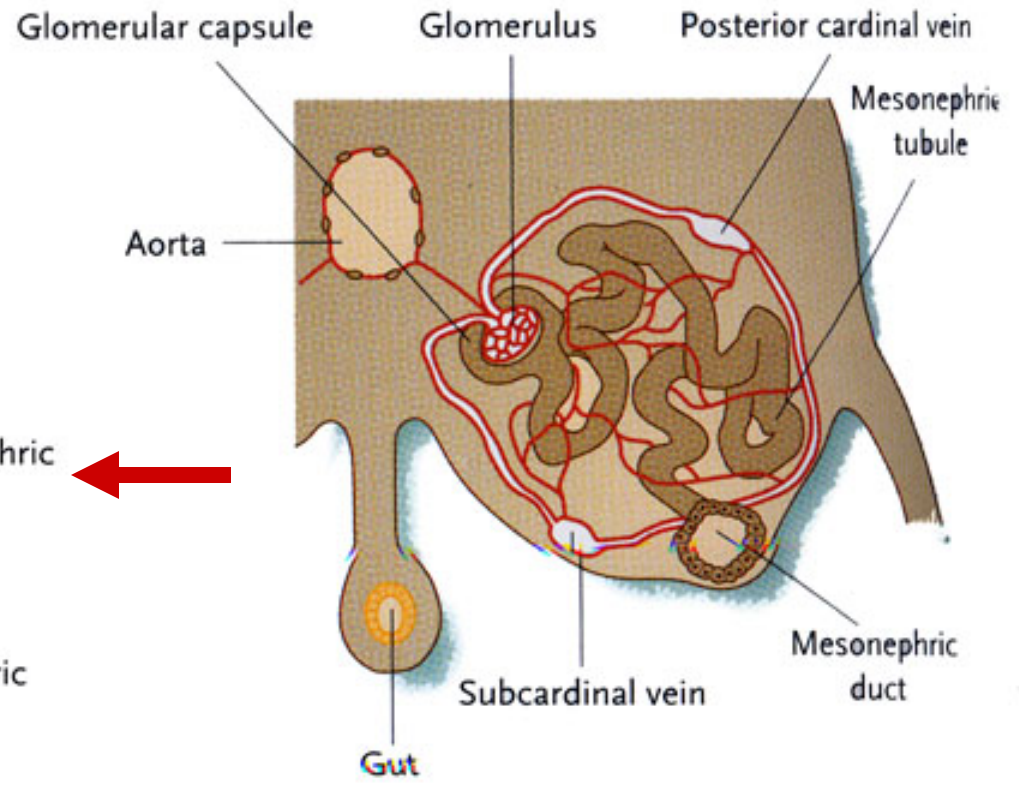
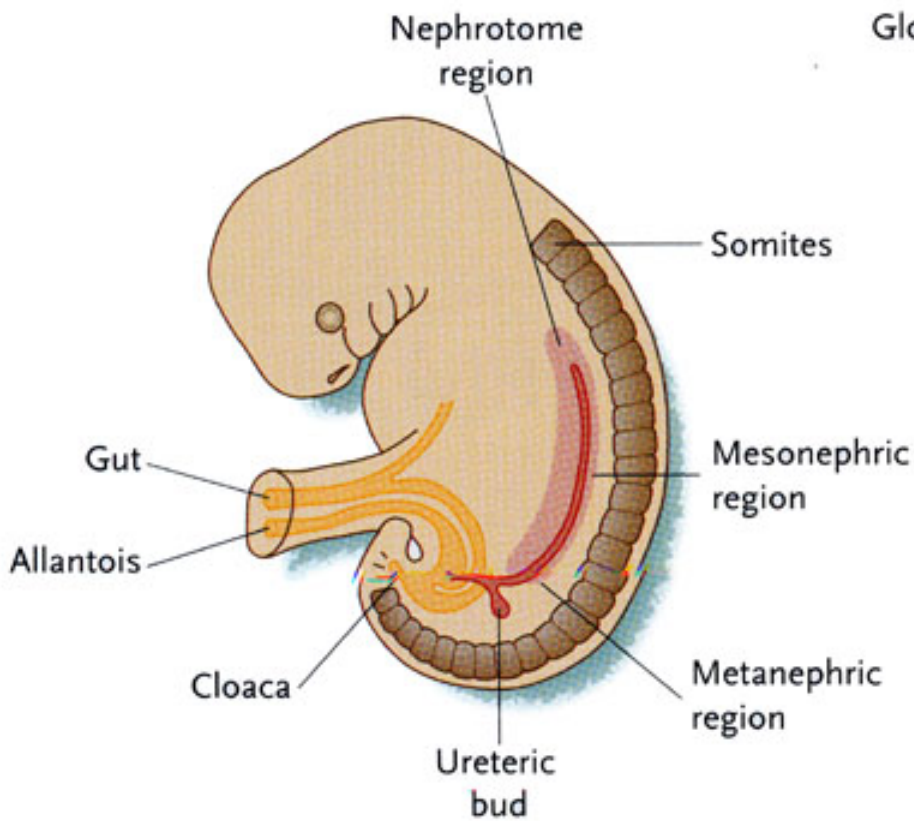
Glomerulus is a knot of capillaries

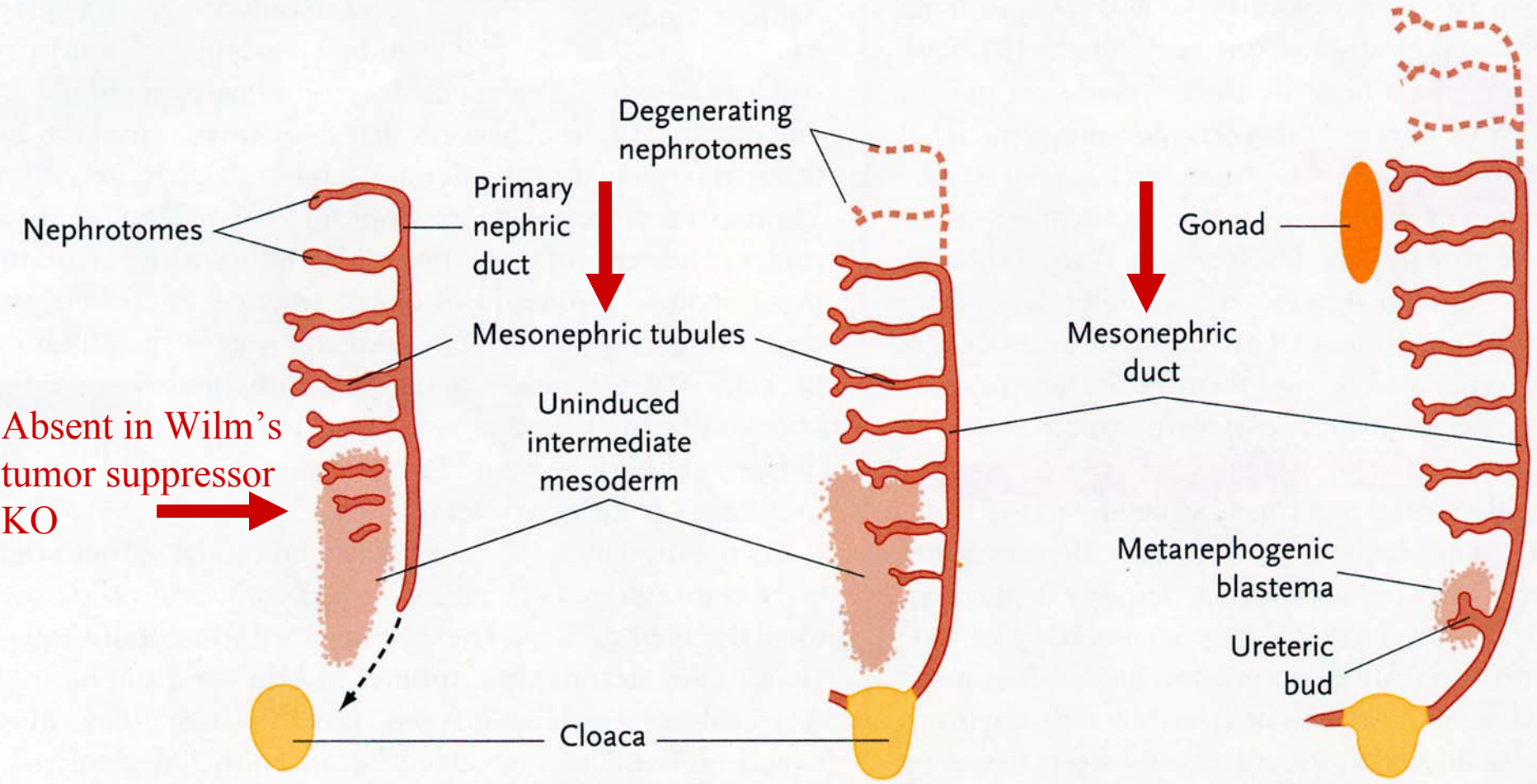
Bowman's capsule and Glomerulus make up the **Renal Corpuscle**

Mesonephric tubules connect to Mesonephric duct (Wolffian duct)

Mesonephric kidney is the functional adult kidney of fish and some amphibians







# Mesonephric Duct

Initially a solid rod that grows caudally

Diverges from intermediate mesoderm and fuses with the ventrolateral cloacal wall (future bladder)

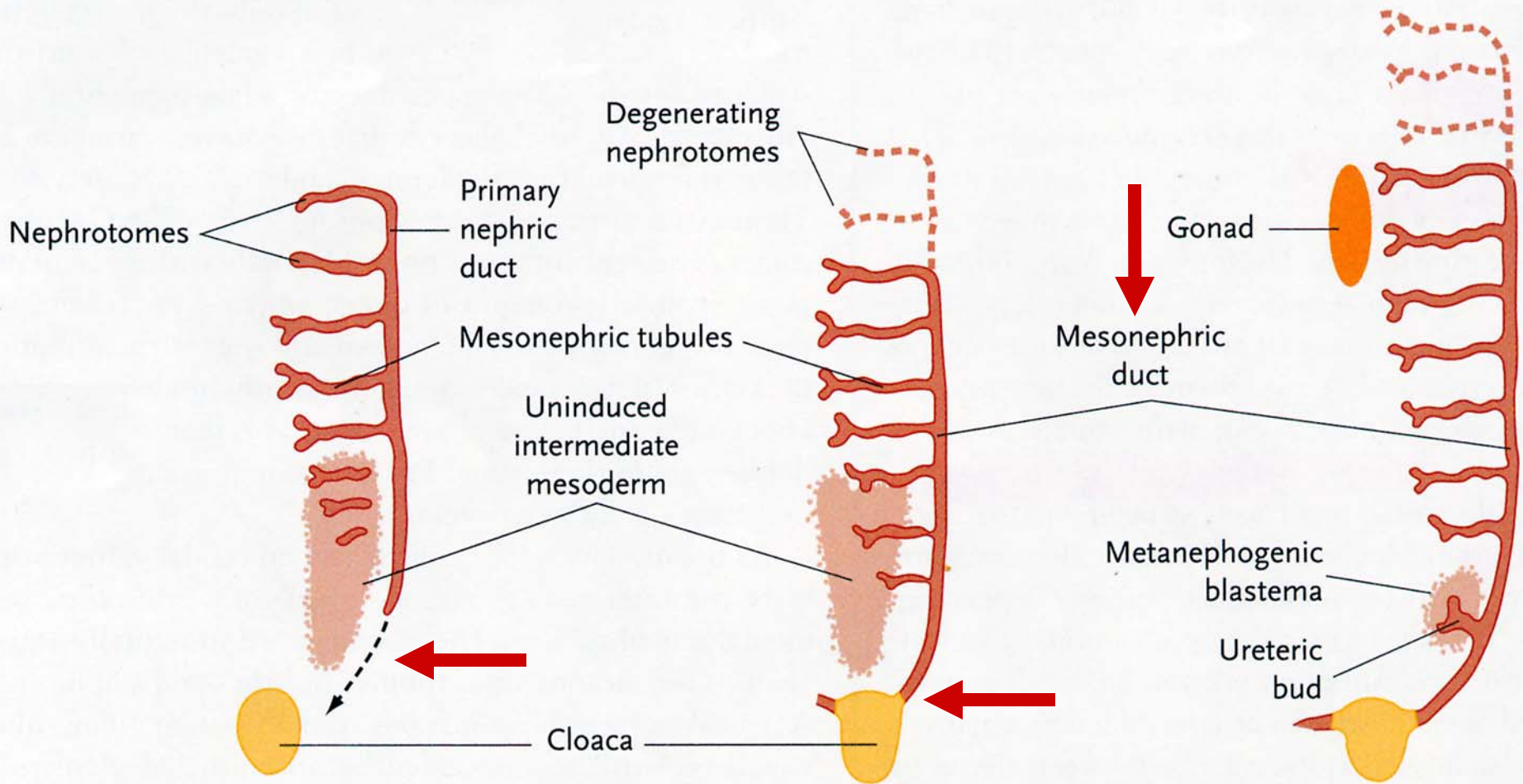
Mesonephric duct undergoes canalization – transformation from mesenchyme to epithelium

Mesonephros is functional until 10 weeks

Mesonephric Duct regression depends on sex (Genital Development)

Mesonephric is also called the Wolffian duct





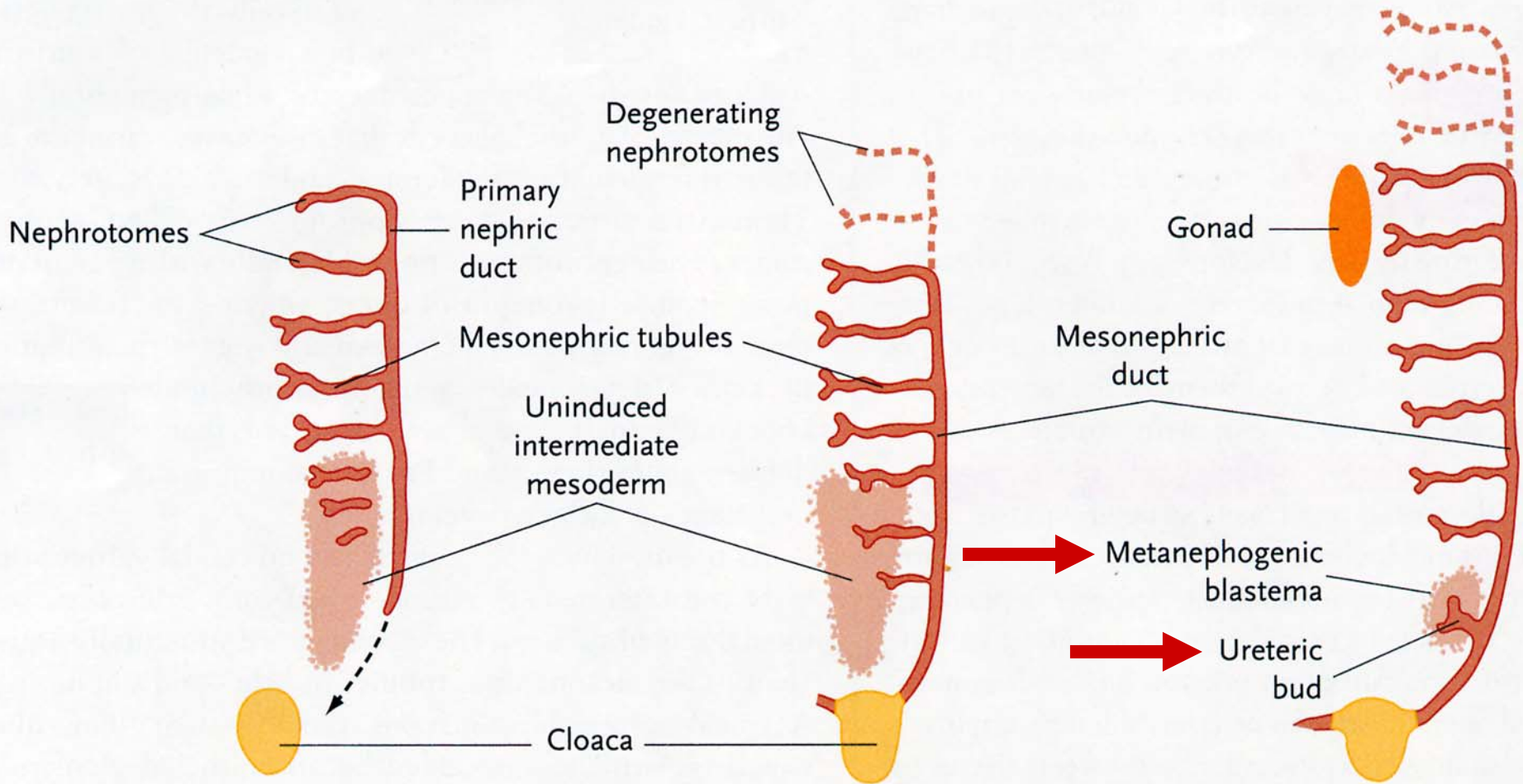
# Metanephros

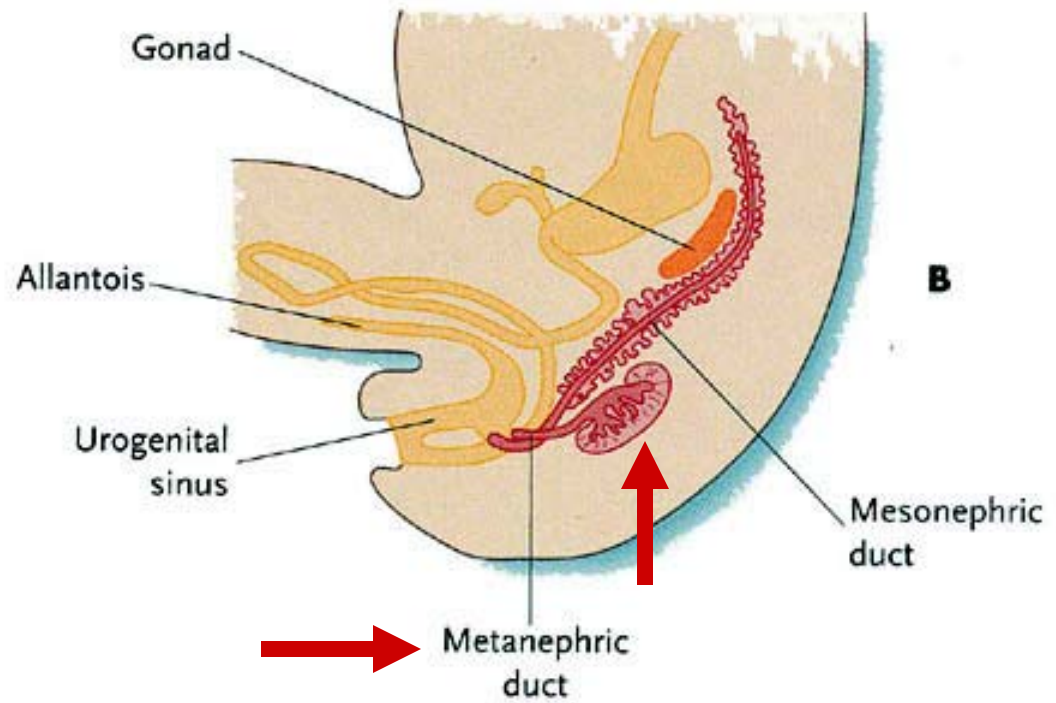
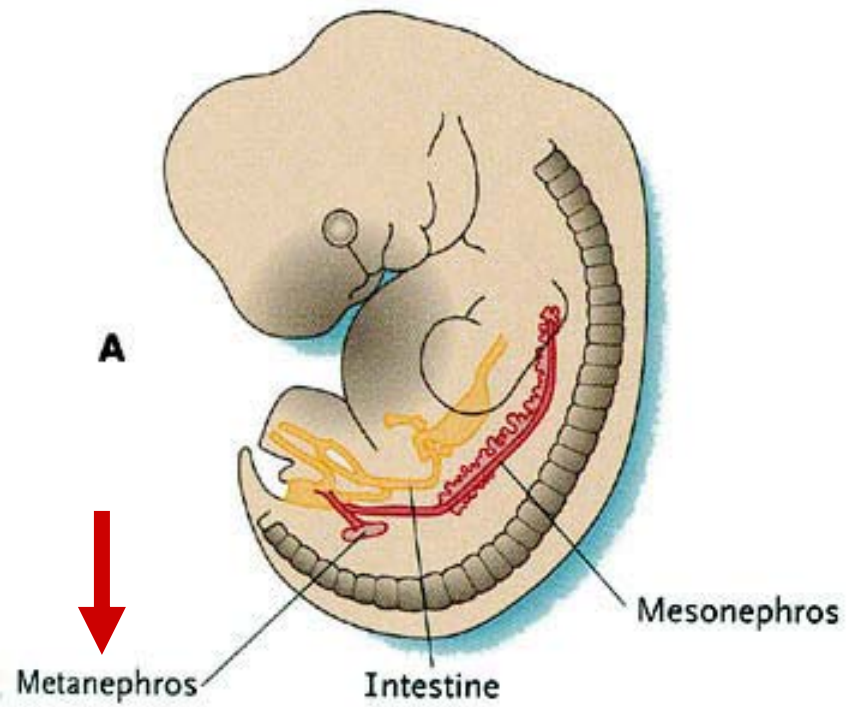
**Ureteric Bud** (Metanephric diverticulum) - outgrowth of the distal mesonephric duct

**Metanephric blastema** is the mesenchyme surrounding the ureteric bud

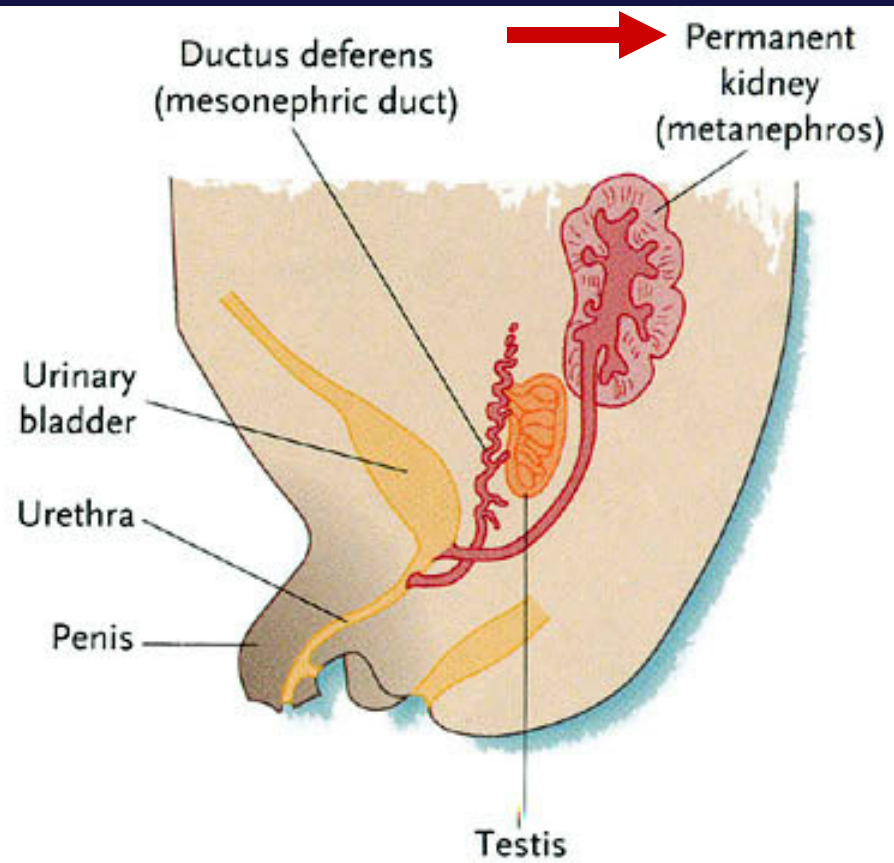
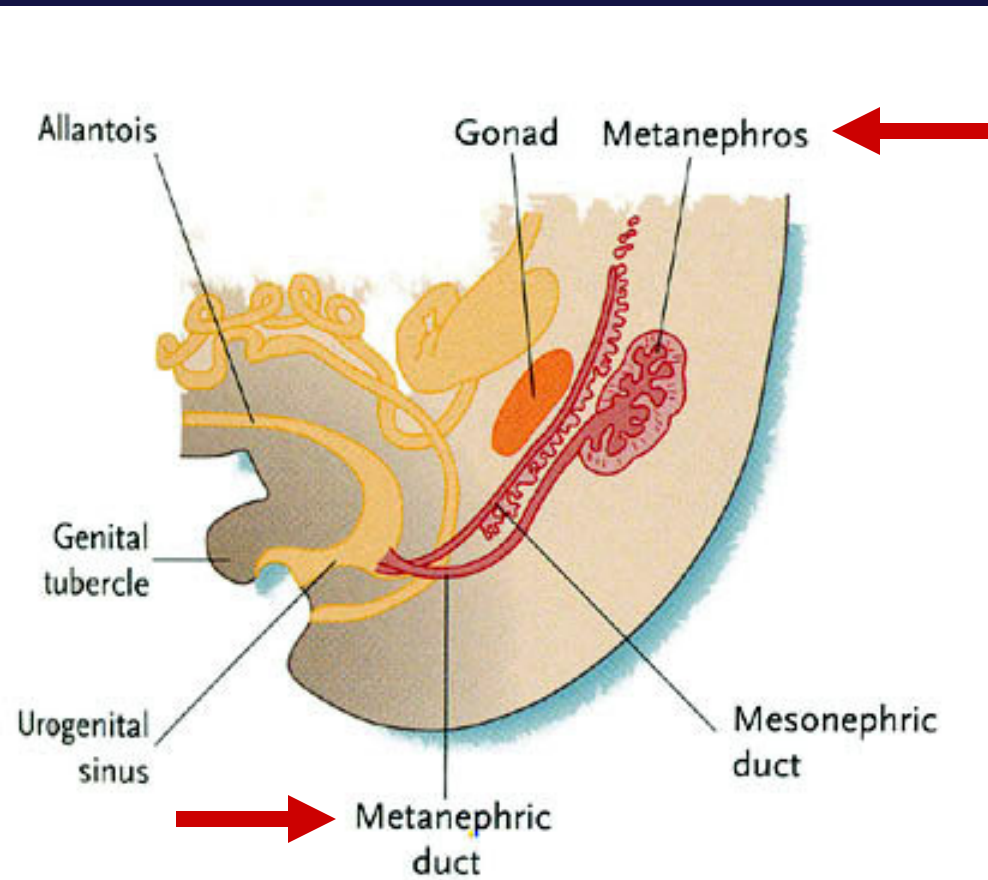
Ureteric bud – multiple events of **elongation** and **bifurcation**

Bifurcation results in two ampulla each with its blastema









# Ureteric Bud/Metanephric Blastema

Ureteric Bud is induced by surrounding mesenchyme

**GDNF** – Glial-Derived Neurotrophic Factor  
(metanephric blastema)

**C-ret** – Tyrosine kinase receptor family (mesonephric duct)

**WT-1** – Wilms tumor suppressor gene – controls GDNF

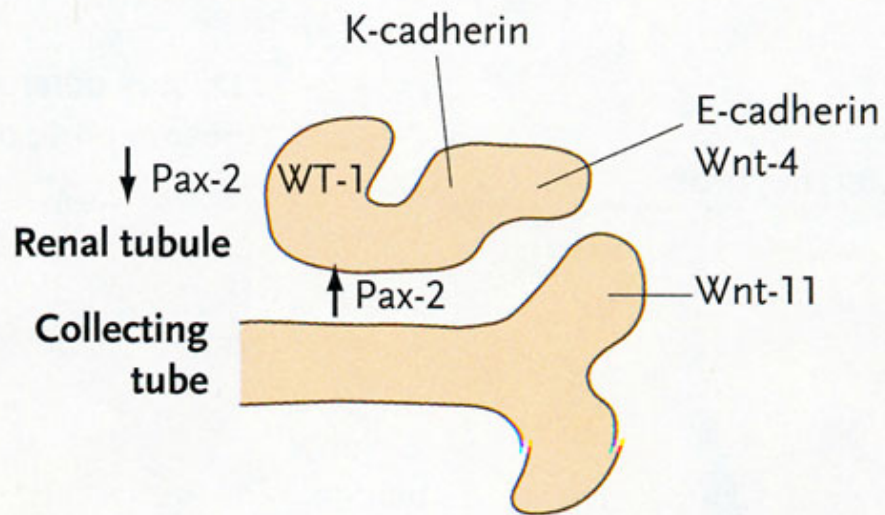
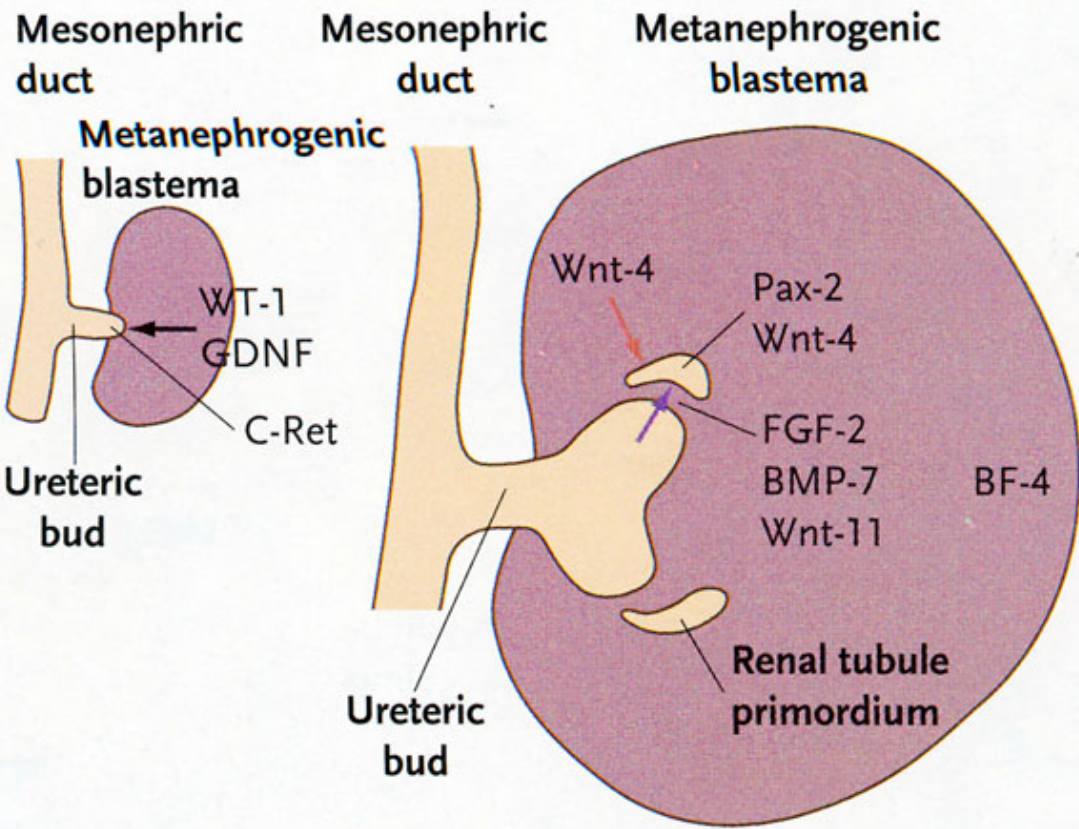
Elongation and Branching is controlled by cross-talk between the  
metanephric blastema and the tips of the branches

Ureteric buds produce FGF2, BMP7, Wnt11

Metanephric blastema produces Wnt4 and Pax2

Ureteric bud forms the collecting duct system

Metanephric blastema forms the renal tubules (note: mesenchyme to  
epithelium transition required)



# Ureteric Bud Branching

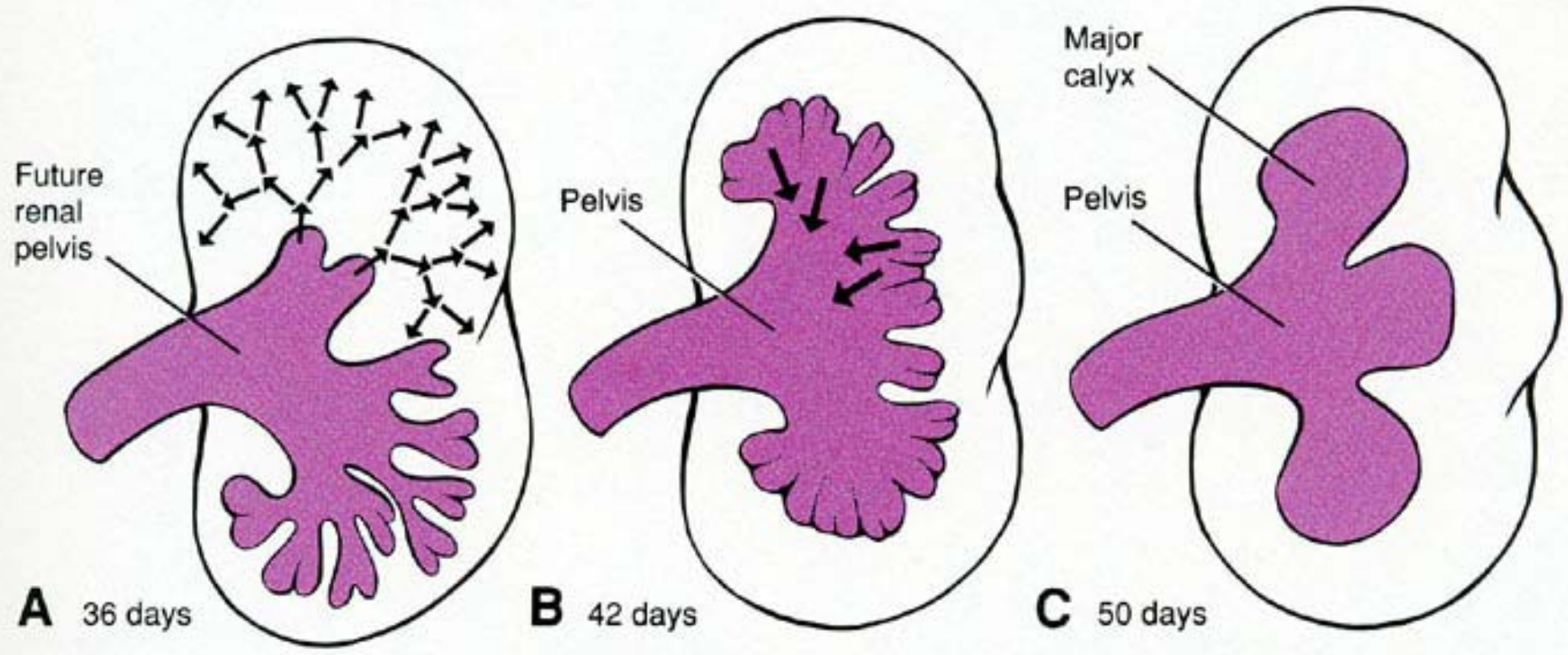
Branching of the Ureteric bud gives developing kidney a lobular appearance, Sulcus separates the lobes

First 4 bifurcations (16 branches) coalesce to form the Renal Pelvis and the Major Calyces

Next 4 bifurcations coalesce to form the Minor Calyces

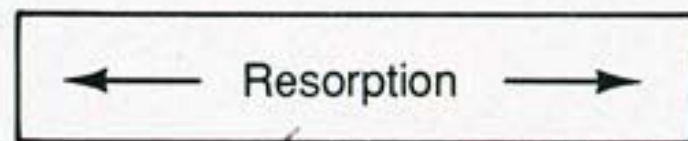
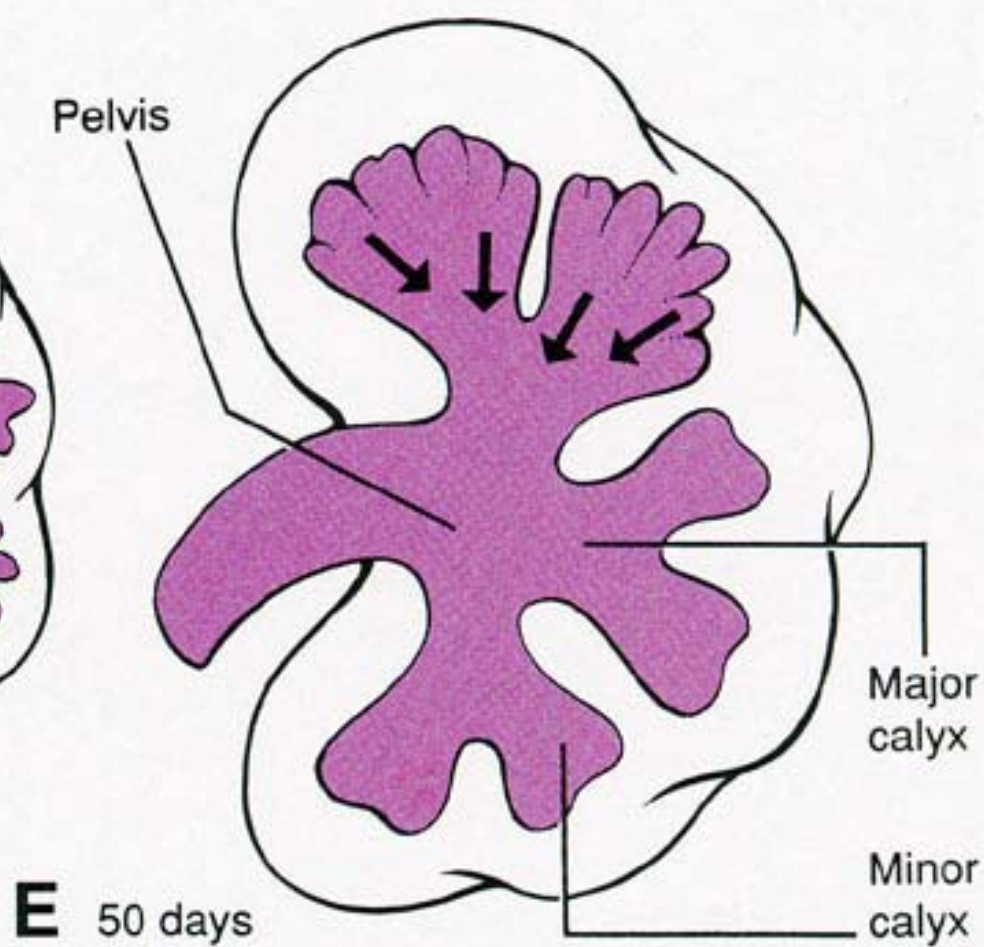
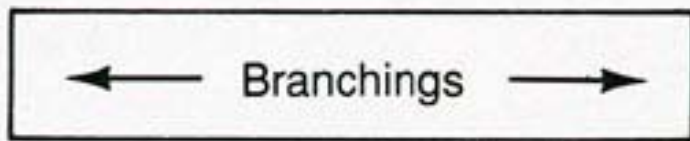
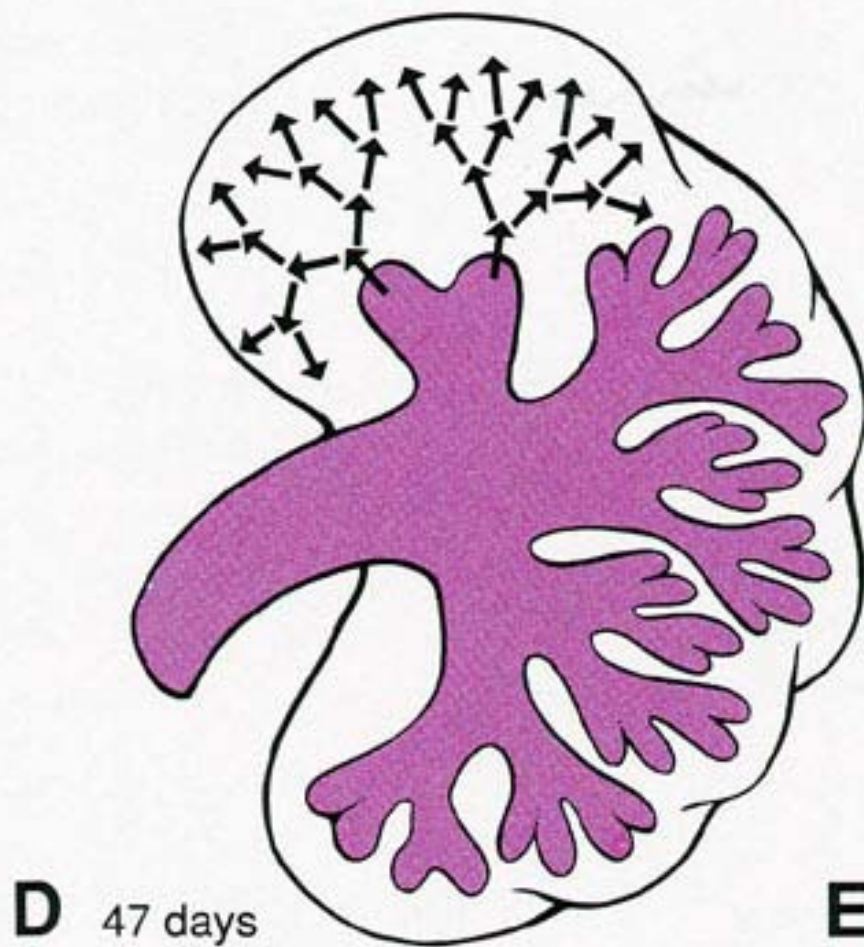
11 more branches forms 1-3 million collecting tubules





← Four generations of bifurcations →

← Resorption →



# Nephron

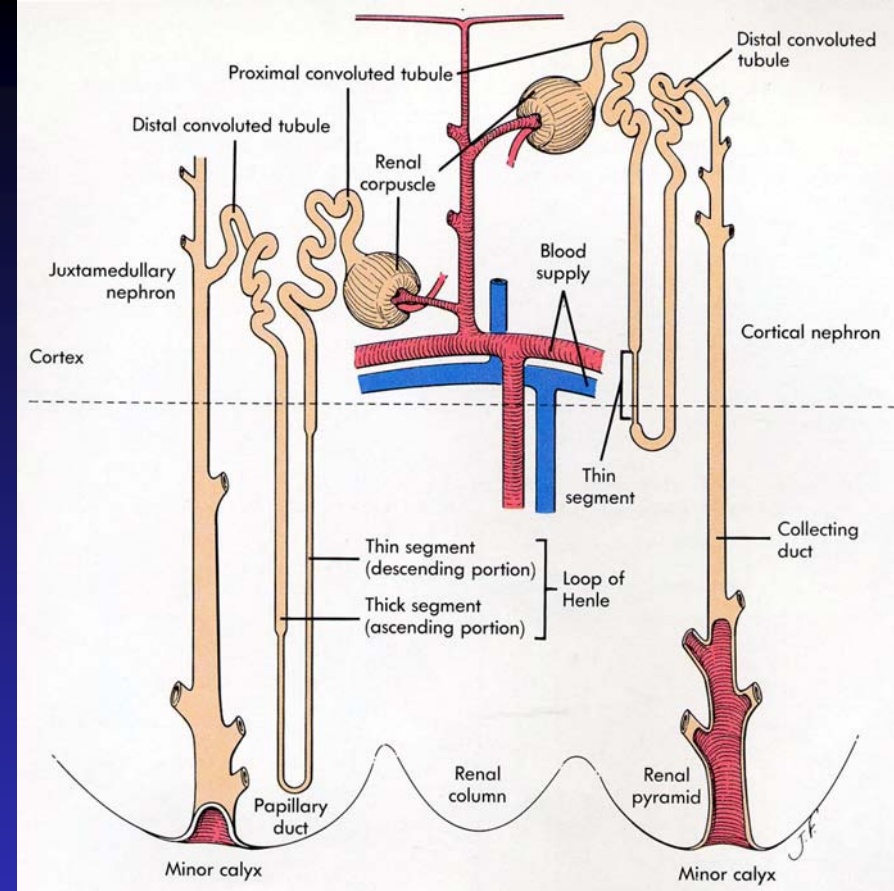
## Nephron formation

metanephrogenic blastema forms the nephric vesicle that elongates and associates with a glomerulus

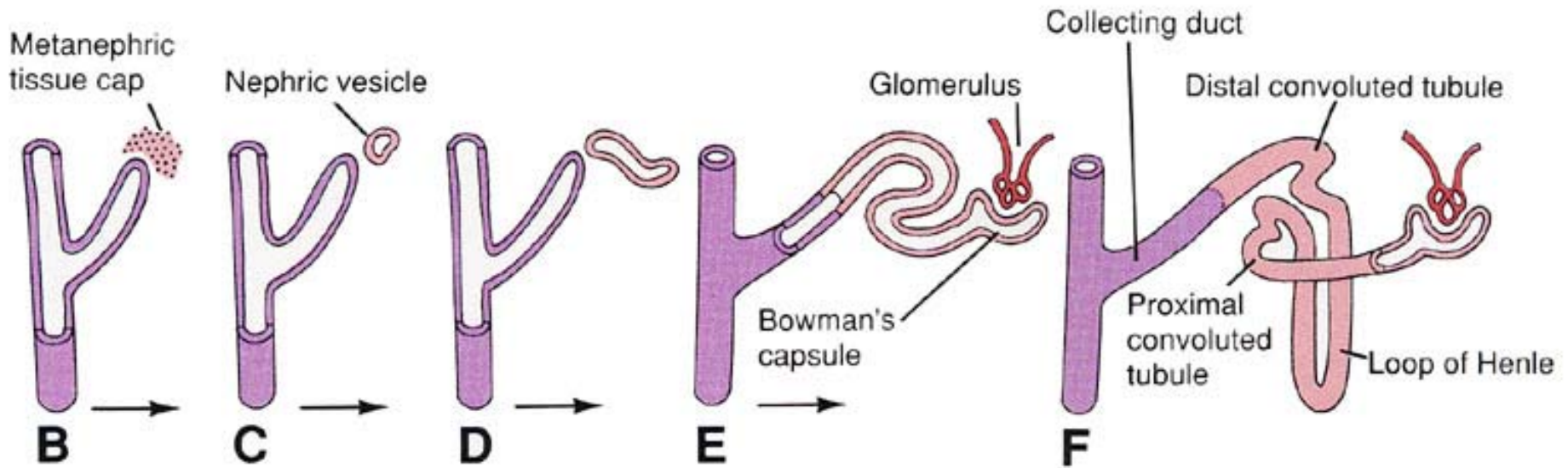
The tubules differentiates into the

- 1) Bowman's capsule
- 2) Proximal convoluted tubule
- 3) Loop of Henle
- 4) Distal convoluted tubule

The distal convoluted tubule fuses with the collecting duct.







Renal corpuscle = Bowman's capsule/glomerulus. The nephron is the metanephric excretory unit.

The origin of the Renal corpuscle and tubules is distinct from the collecting duct (Metanephric duct)

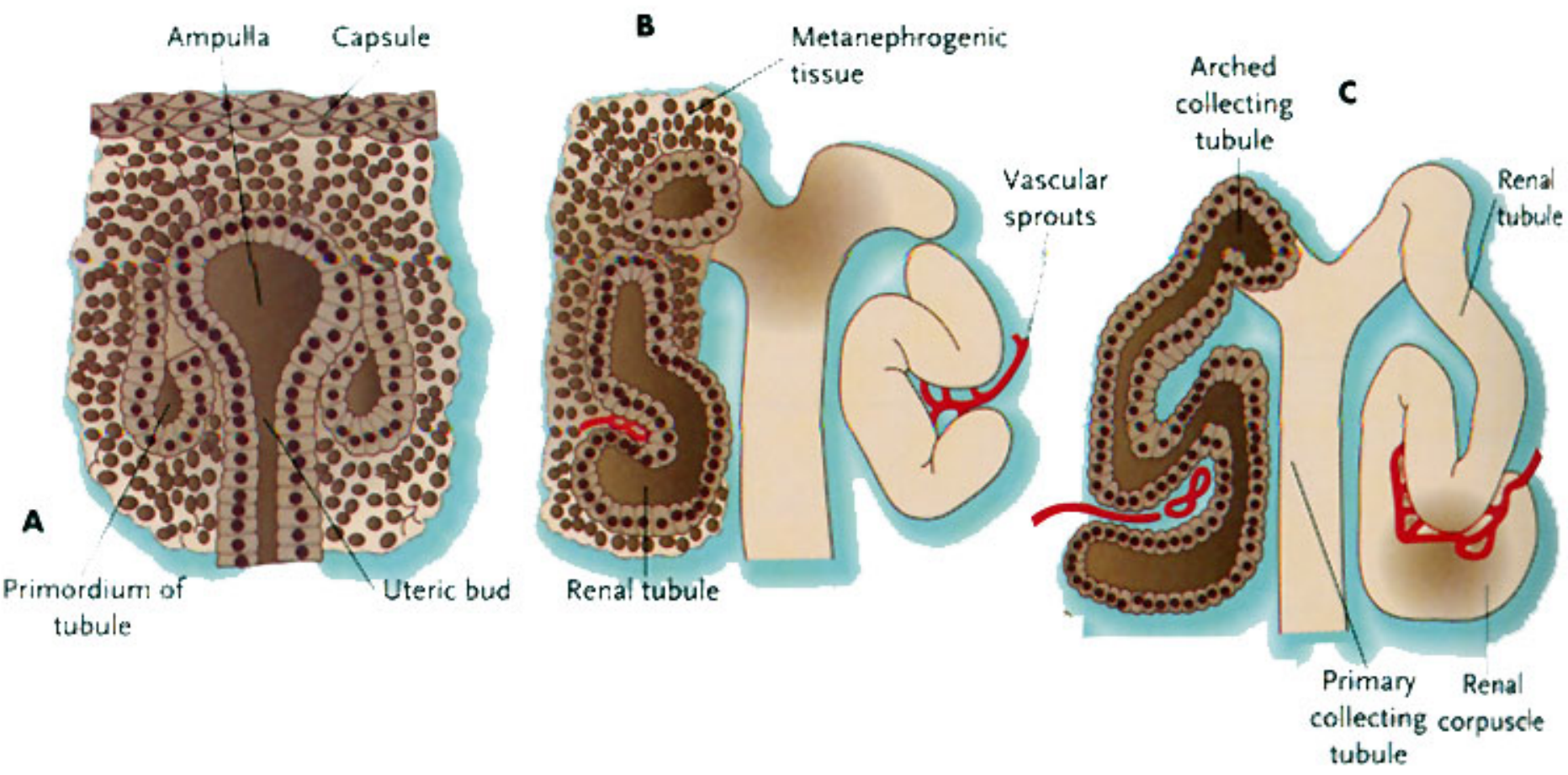
Duct systems merge

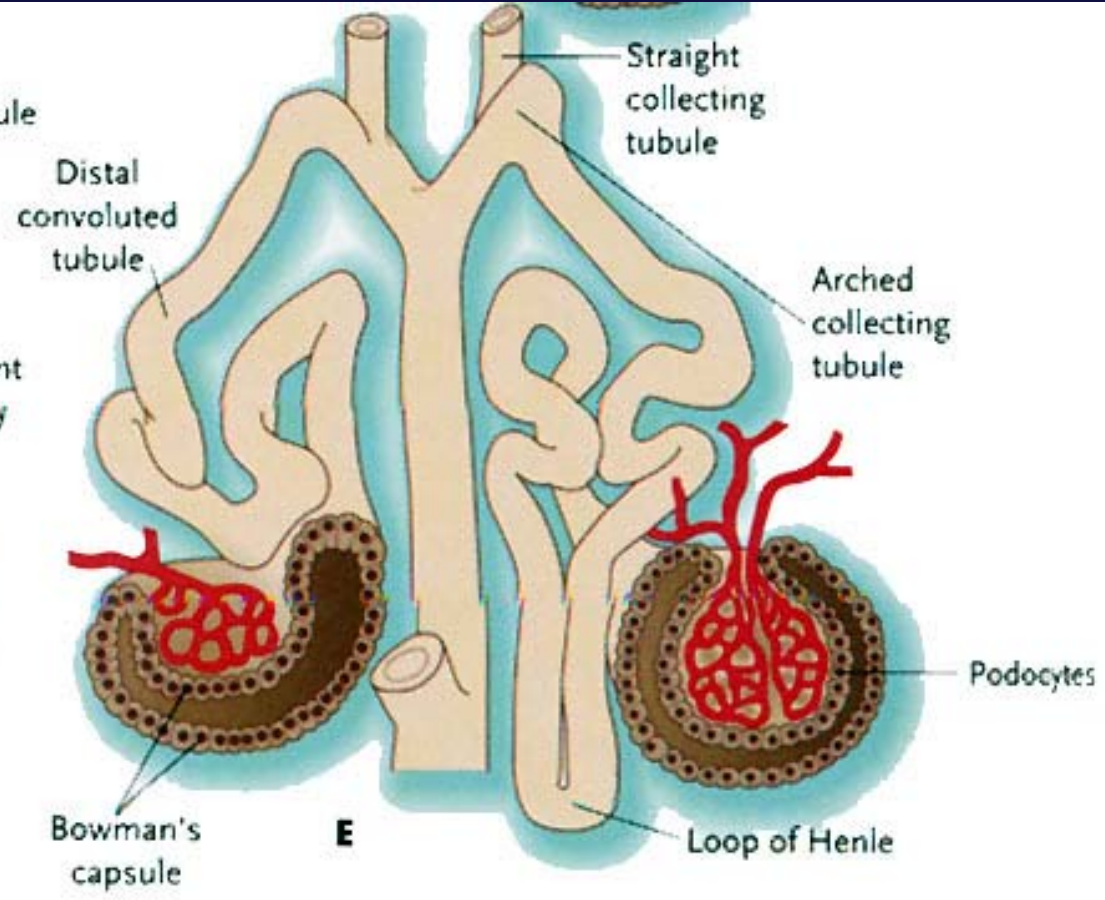
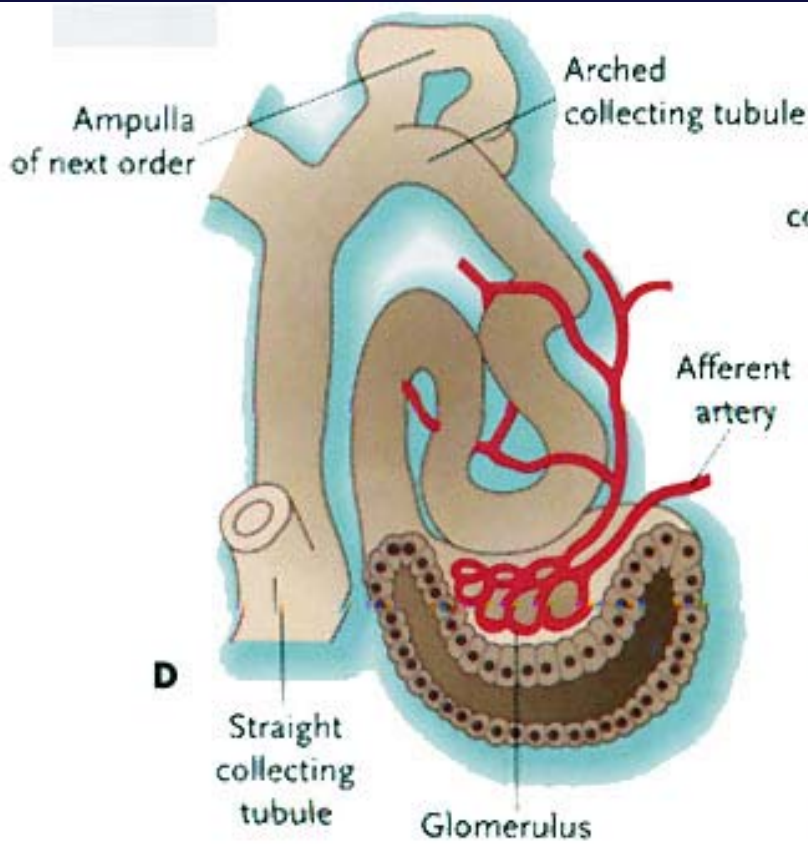
Renal duct – sequence of differentiation

renal corpuscle → proximal tubule → distal tubule

Loop of Henle elongates into the medulla







# Late Changes

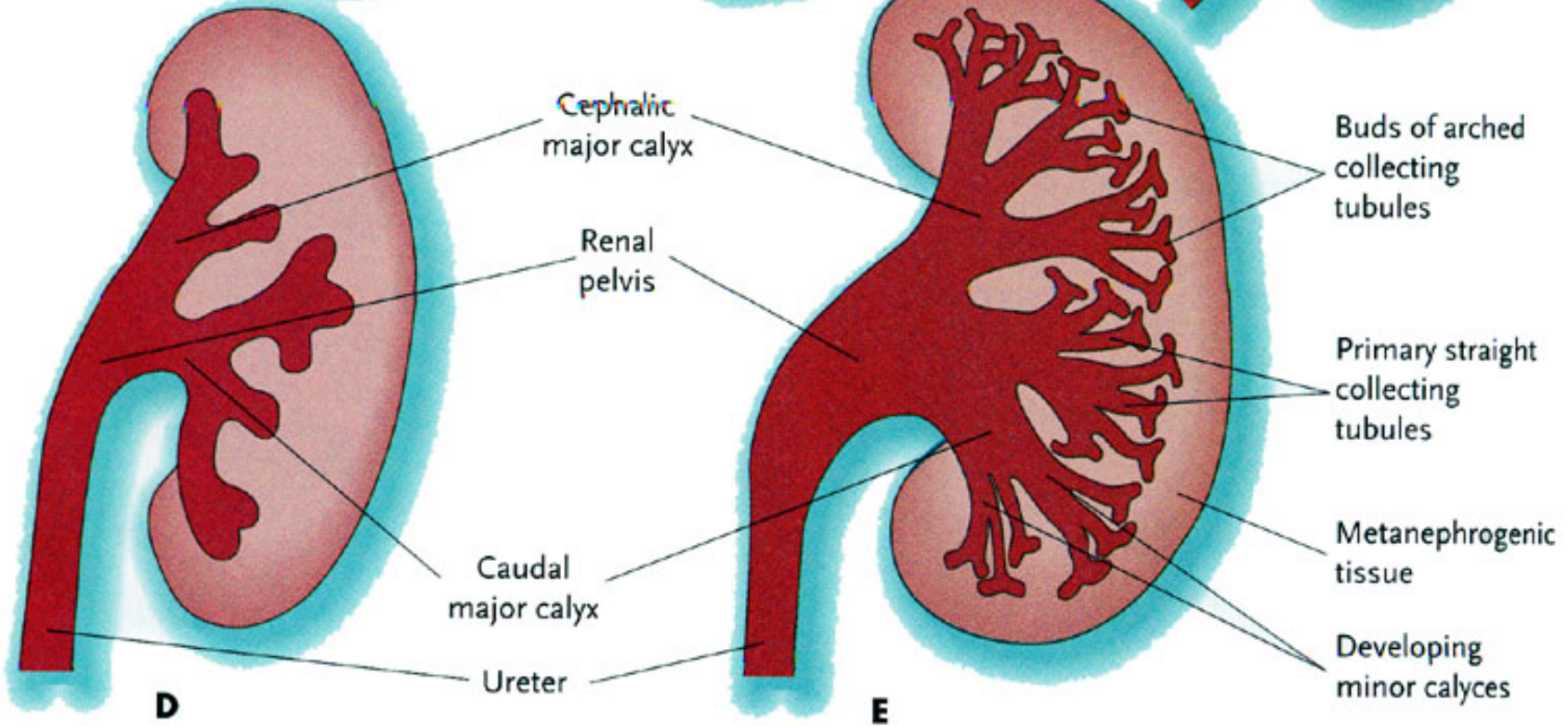
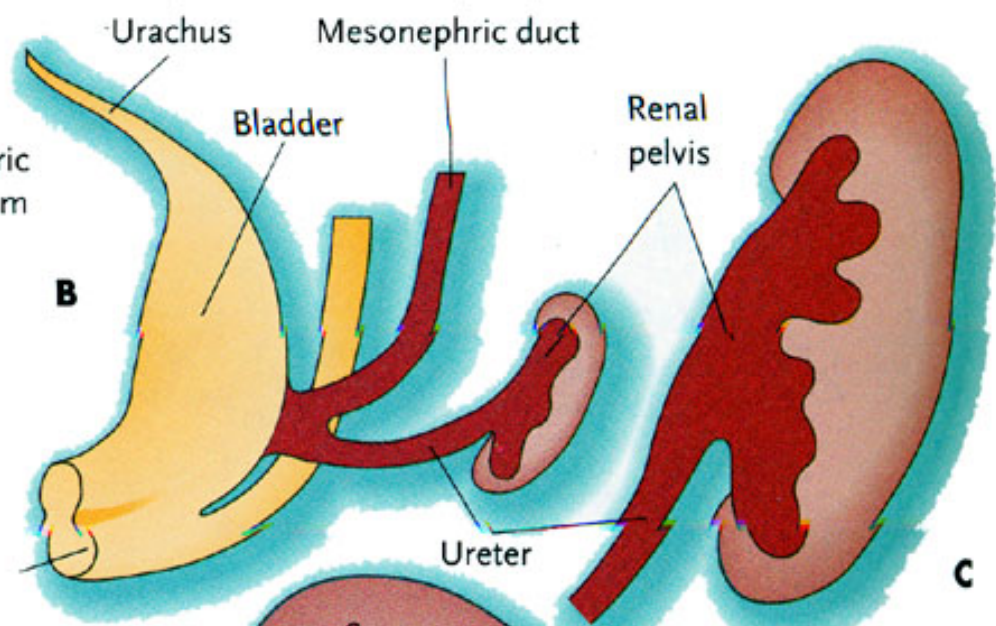
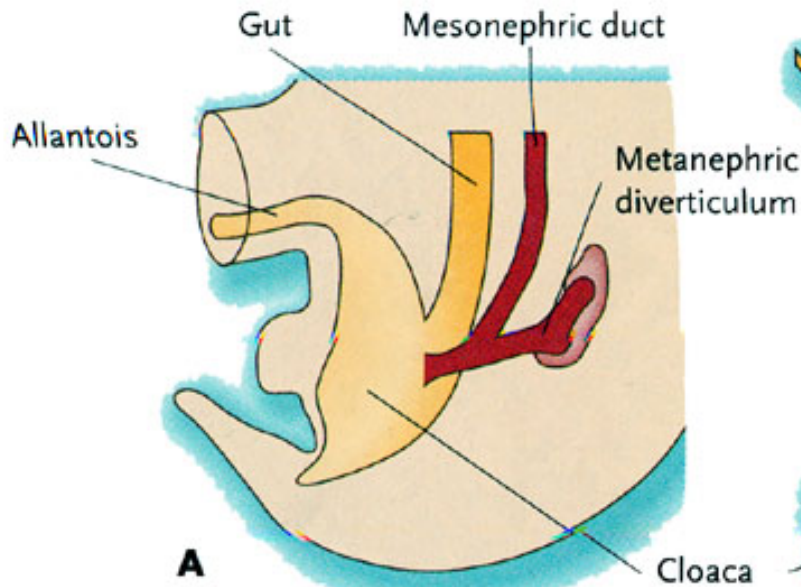
Branching system becomes larger forming the pelvis and calyces.

Kidneys undergo a cranial shift from the pelvic region to the abdominal region

Kidneys also undergo a lateral displacement that brings them in contact with the developing Adrenal glands that fuse to the cranial pole

Kidneys rotate 90° so that the renal pelvis is facing the midline

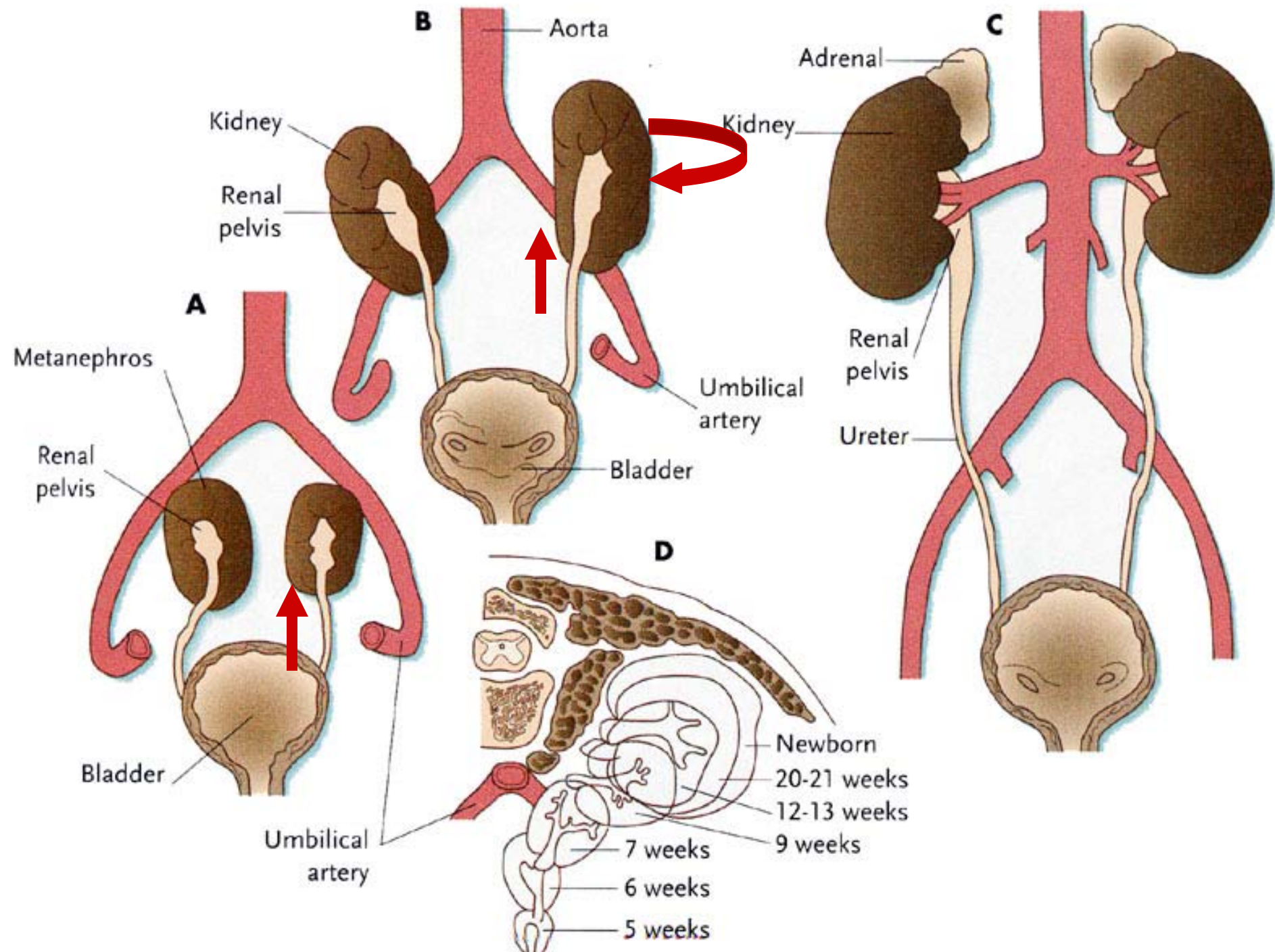




**D**

**E**





# Urogenital Sinus

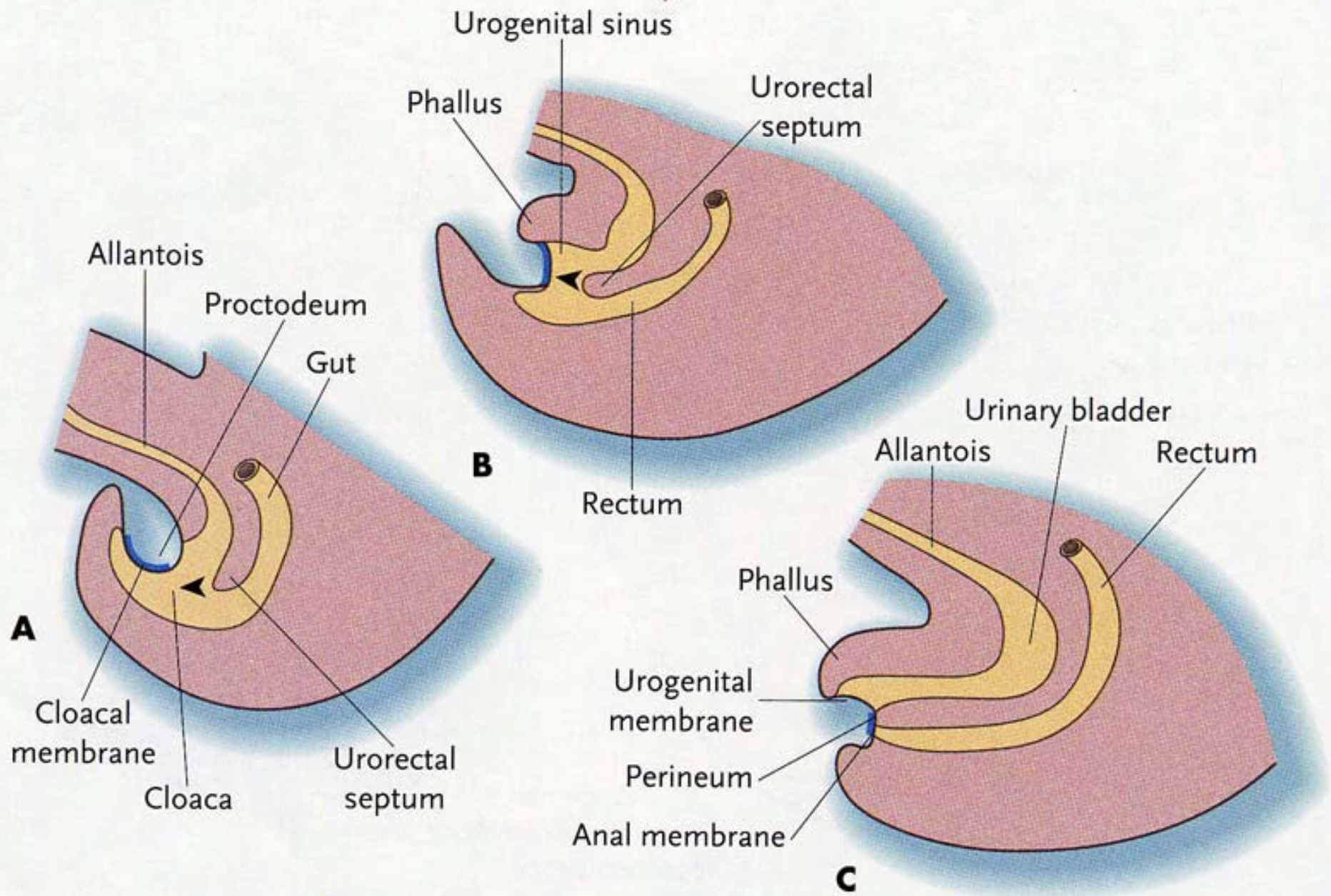
Urogenital sinus forms:

Bladder

Pelvic urethra

Definitive urogenital sinus

	<u>Males</u>	<u>Females</u>
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina





# Bladder Formation

The ureter drains into the mesonephric duct that drains into the bladder

The wall of the bladder expands and the mouth of mesonephric duct flares so the mesonephric duct blend into the bladder wall

The mesonephric duct contributes to the formation of the Trigone of the bladder.

The ureter gains a separate connection to the bladder.

The connections of the ureter to the bladder begins lateral to the mesonephric ducts and ends up at a superior position (the mesonephric duct migrates)



Mesonephric duct

Ureteric bud

Posterior wall of bladder

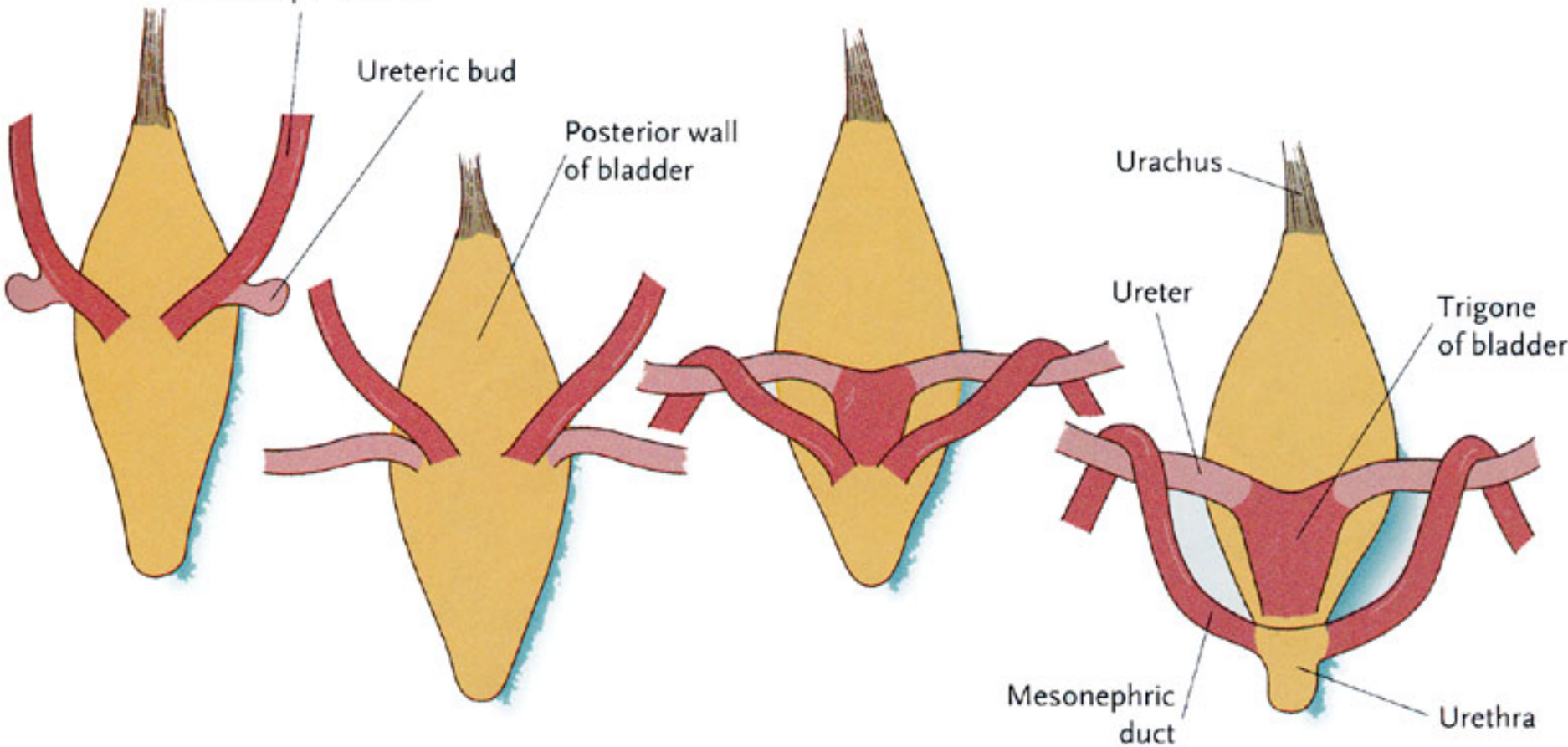
Urachus

Ureter

Trigone of bladder

Mesonephric duct

Urethra



# Urinary System Anomalies

3-4% of all newborns have a developmental abnormality of the urinary tract - most do not cause problems.

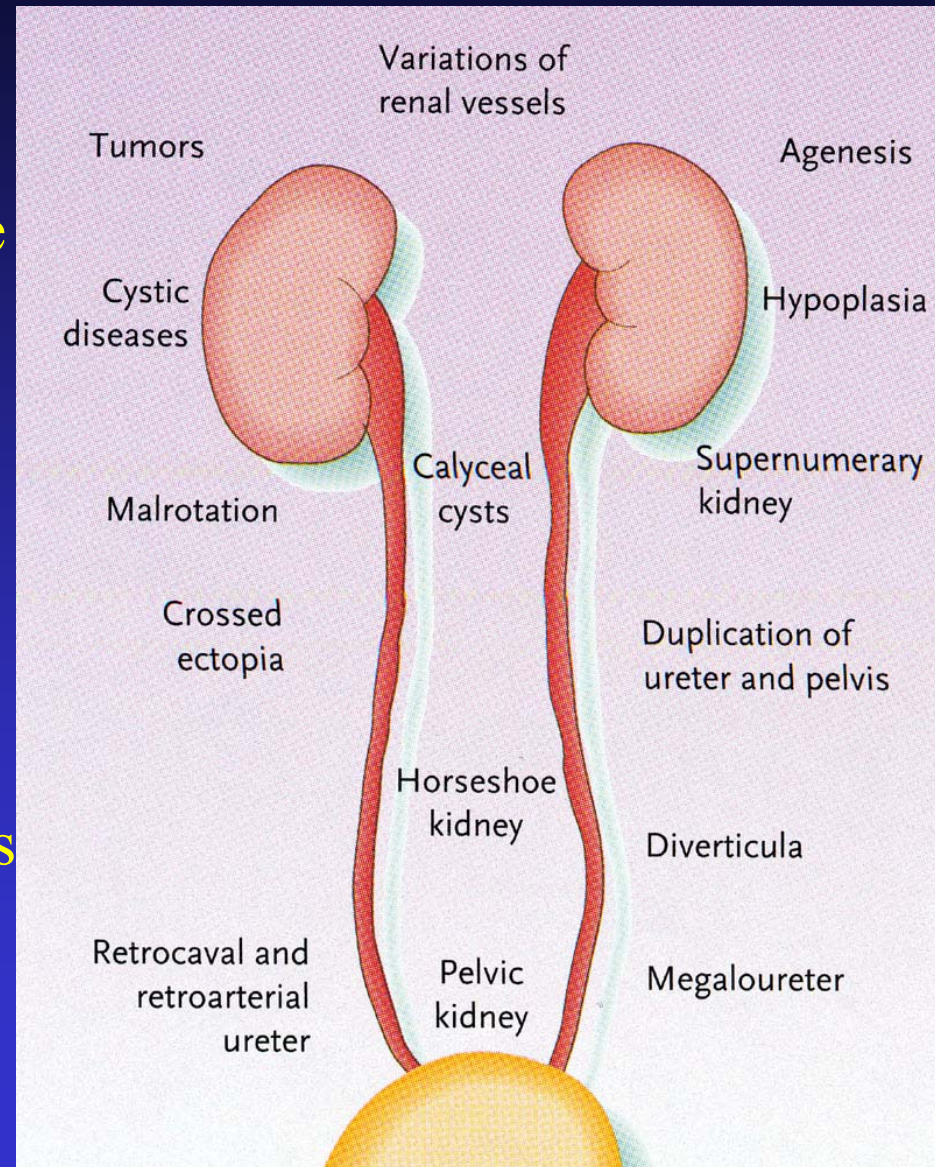
Renal agenesis – unilateral or bilateral

Supernumerary kidney

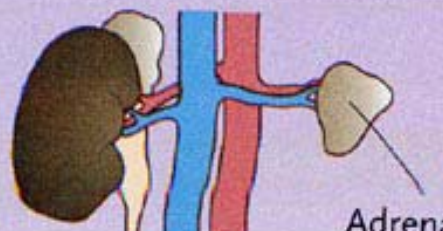
Crossed ectopia – migration problem

Horseshoe kidney – fusion of kidneys fails to ascend

Bifid ureter - bifurcation of the ureteric bud

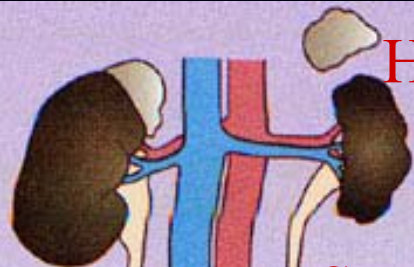






Adrenal  
**Agnesis**

**A**



**Hypoplasia**

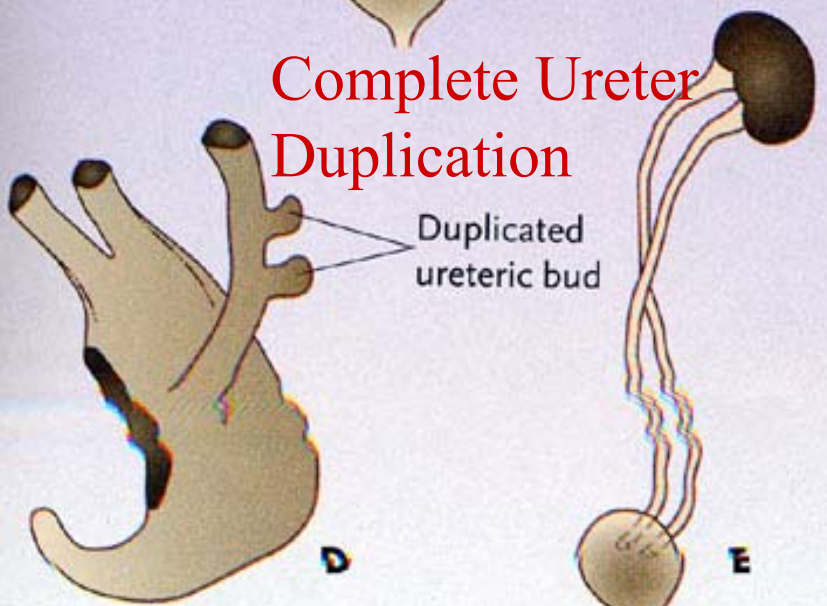
**B**



**Supernumerary  
Kidney**

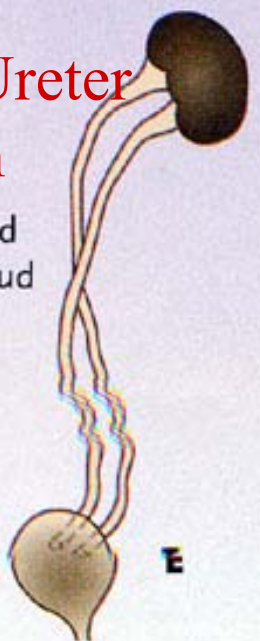
**C**

**Complete Ureter  
Duplication**



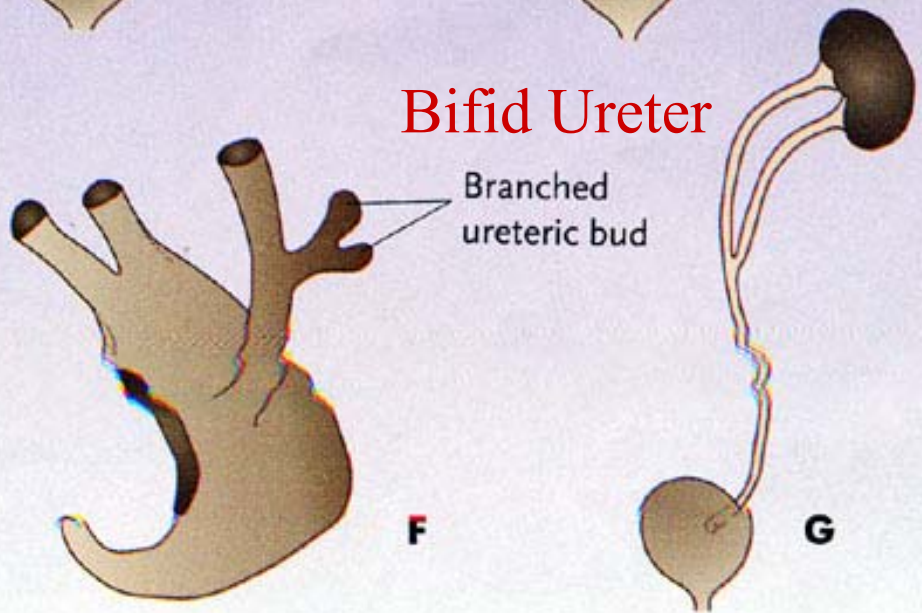
Duplicated  
ureteric bud

**D**



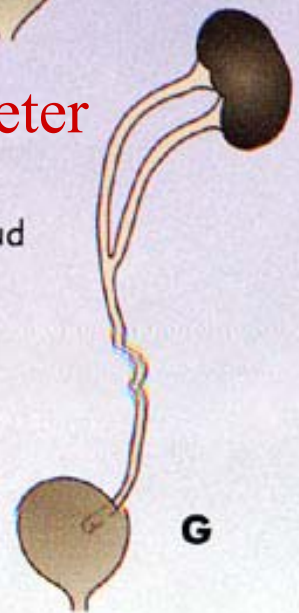
**E**

**Bifid Ureter**

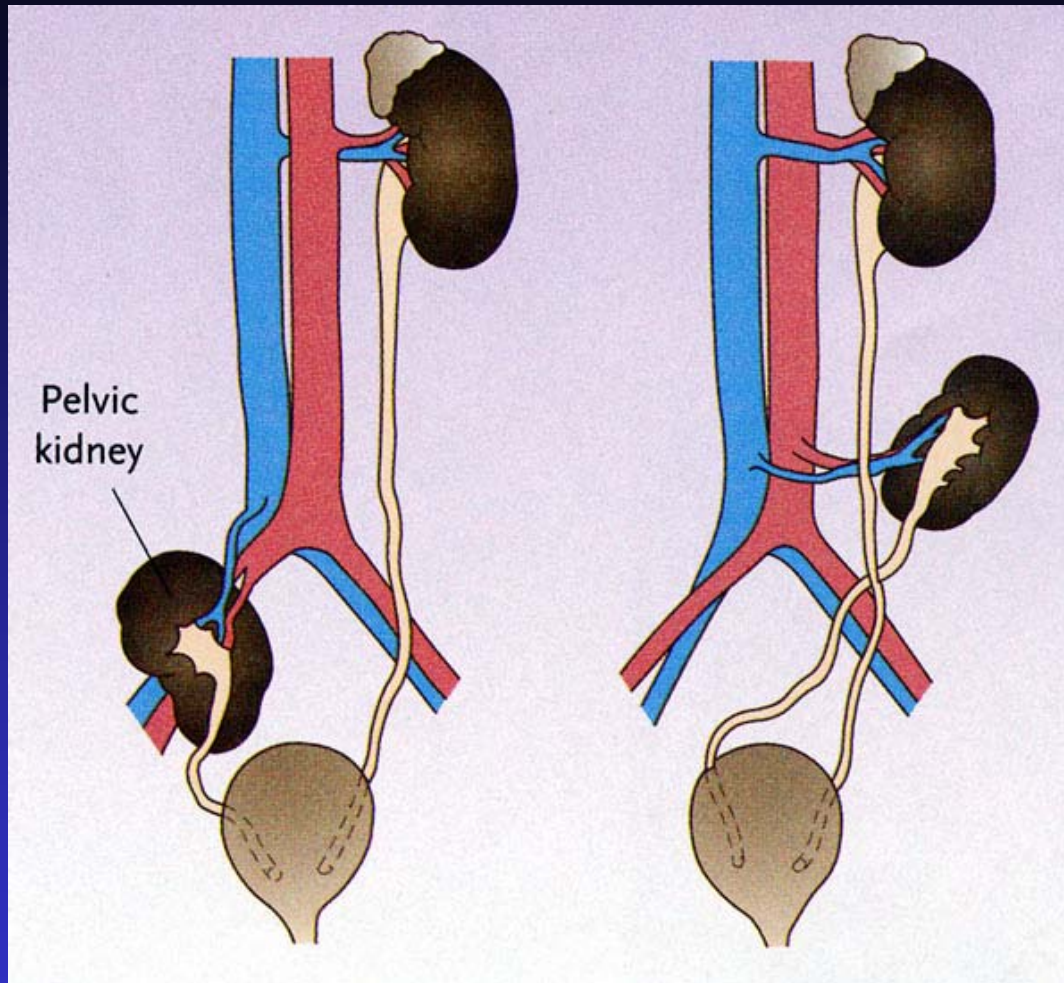


Branched  
ureteric bud

**F**

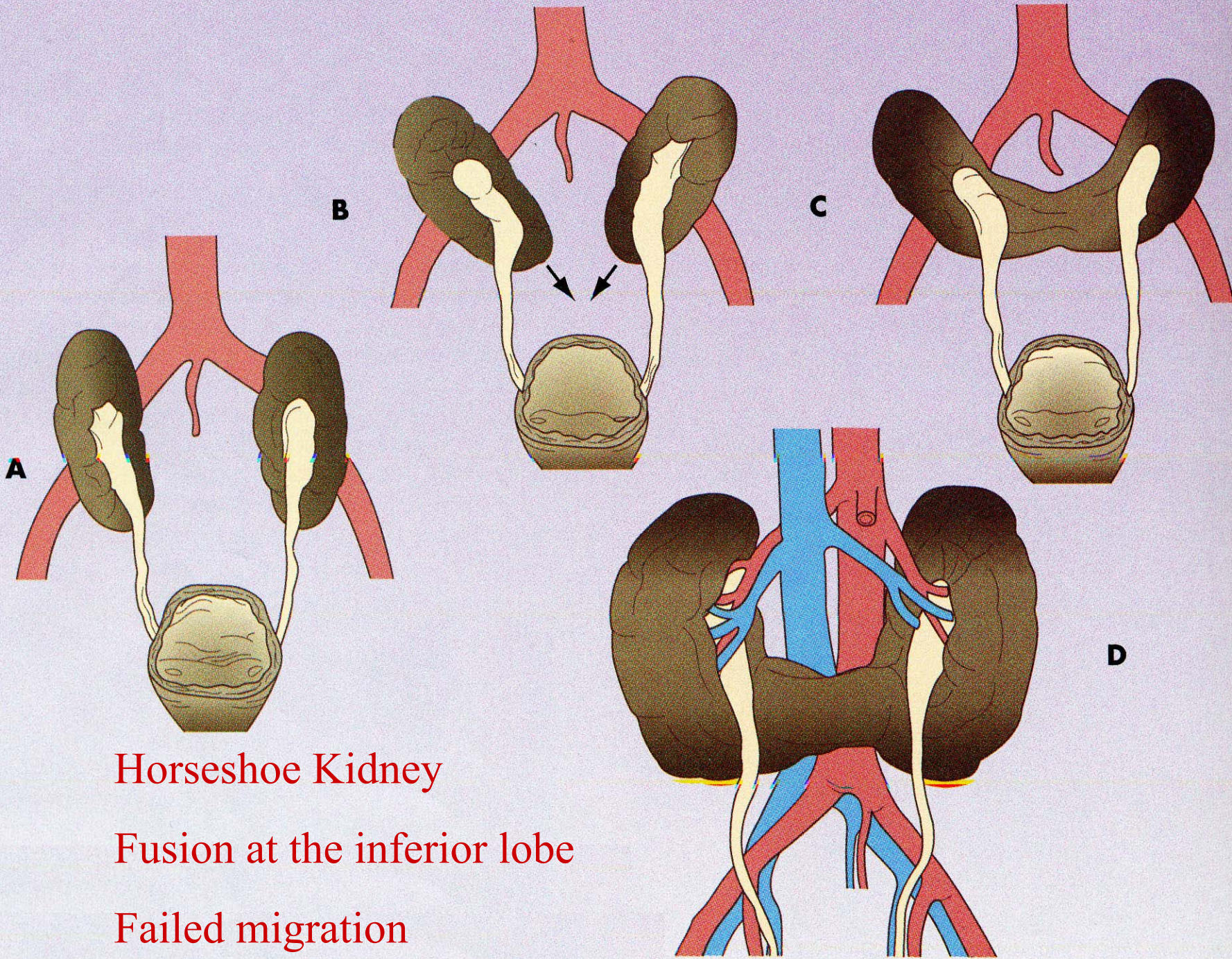


**G**



Migration Anomalies: Pelvic Kidney and Crossed Ectopia



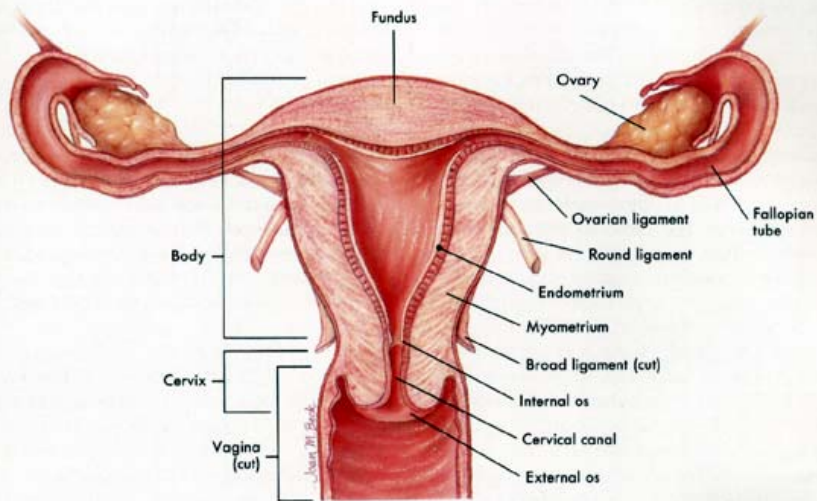
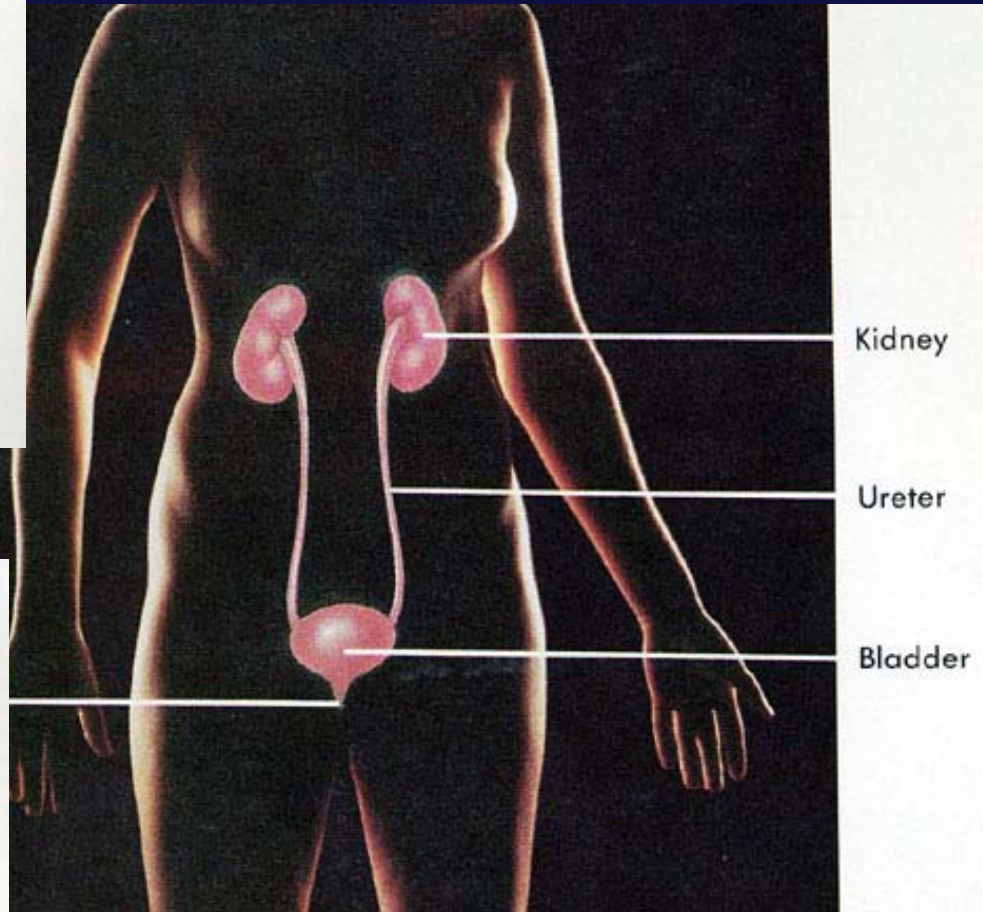
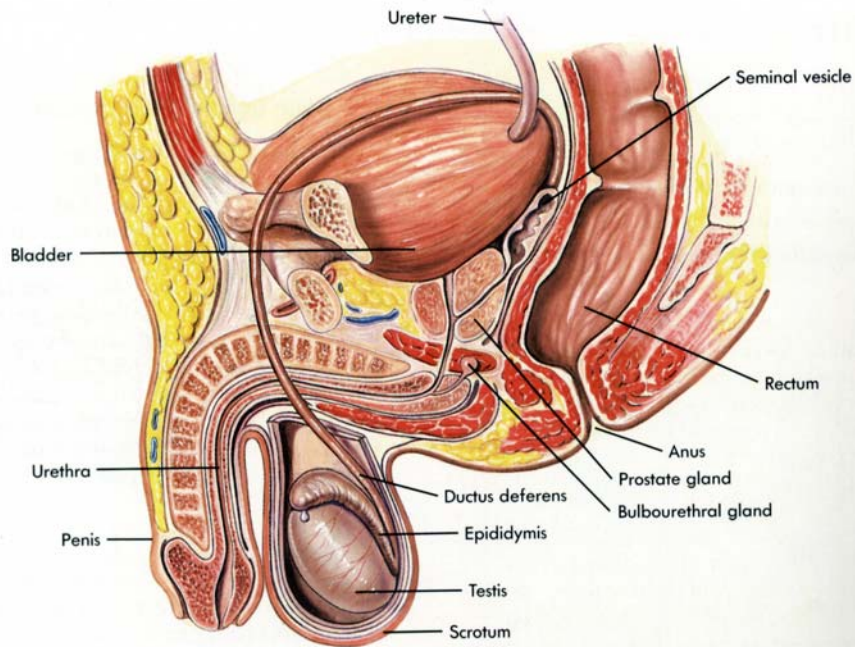


**Horseshoe Kidney**

Fusion at the inferior lobe

Failed migration





# Genital System

Develops in conjunction with urinary system

Germ cells migrate from yolk sac to intermediate mesoderm  
medial to the developing mesonephrose

The Genital ridge forms at the 10th thoracic level medial and  
ventral to the mesonephrose.

Early development of males and females are similar  
Indifferent Phase

# Gametogenesis

Spermatogenesis, oogenesis

Germ cells originate from yolk sac of embryo (parent)

Migration into genital ridge

Primary sex cords (compact strands of tissue)

Mitosis

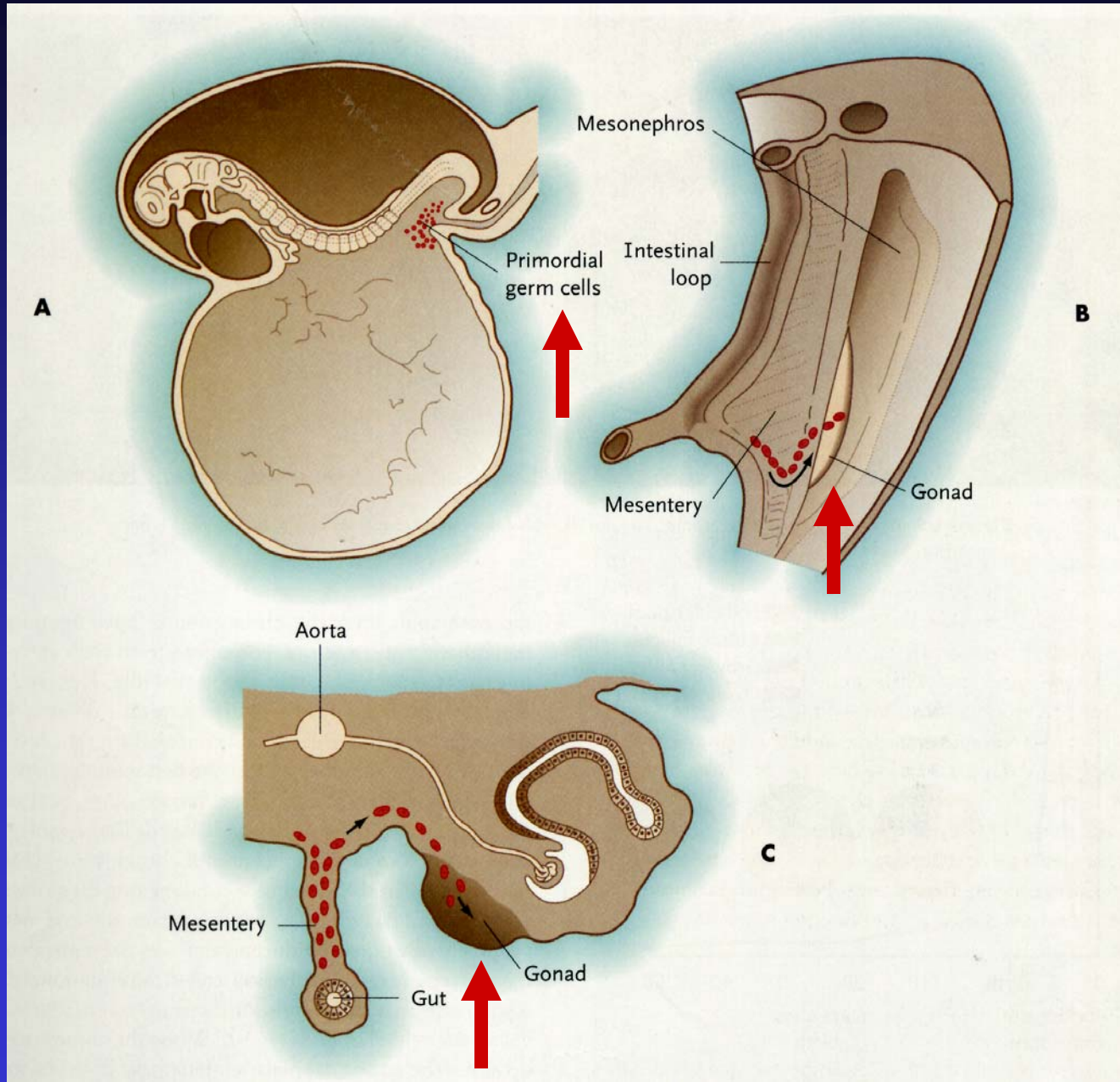
Female - ovary, sex cords cells → ovarian follicle

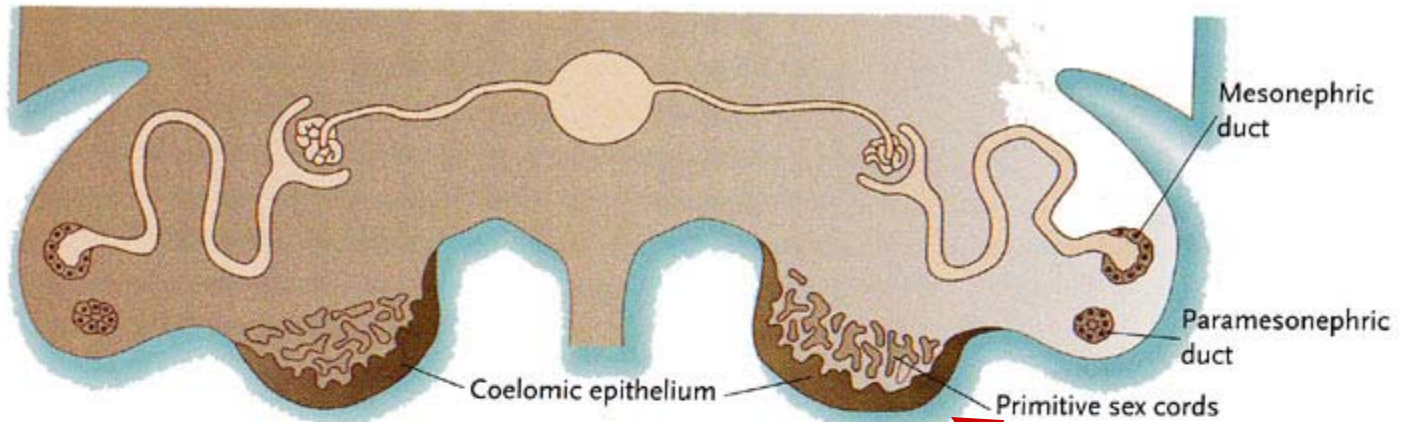
Male - testis, sex cord cells → Sertoli cells of the seminiferous tubules

Sex cord cells are essential for gametogenesis.

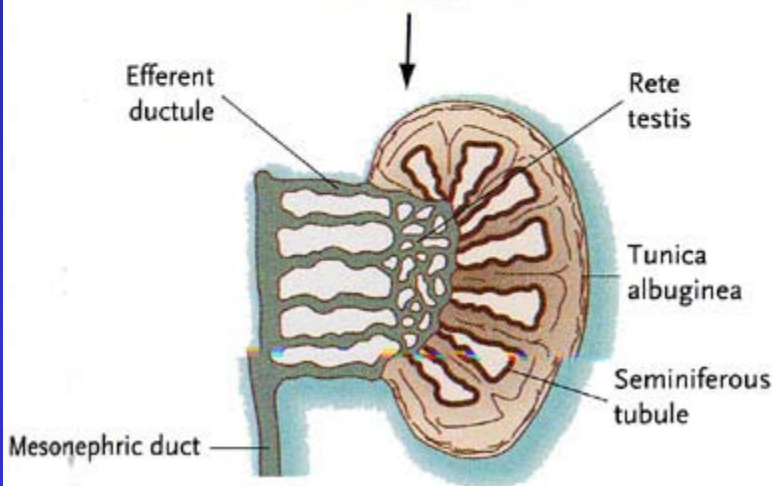
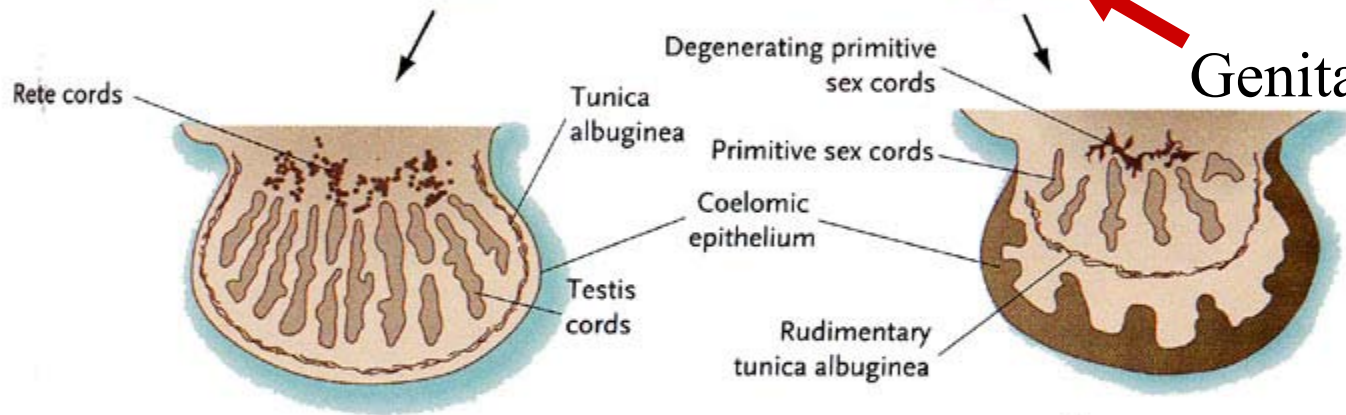


# Gametogenesis – Germ Cells

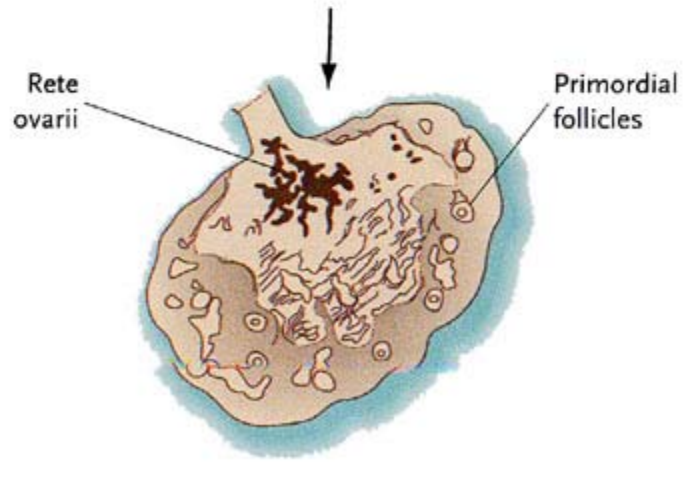




# Genital Ridge

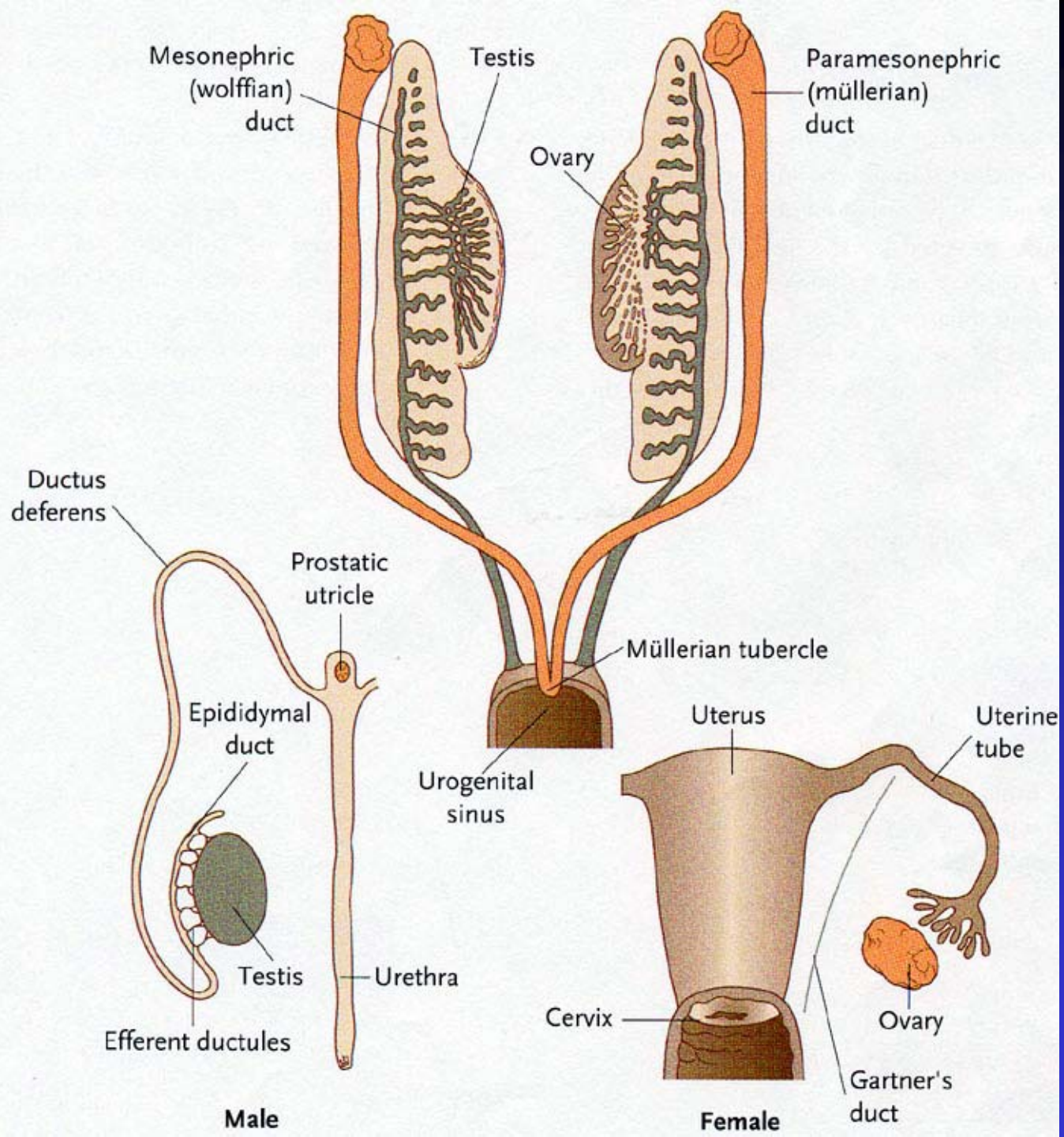


**Testis**



**Ovary**





# Genital Ridge

Supporting cells from the mesonephrose and coelomic epithelium invade the genital ridge and aggregate around the primordial germ cells to form the primary sex cords

Germ cells are required for invasion of supporting cells

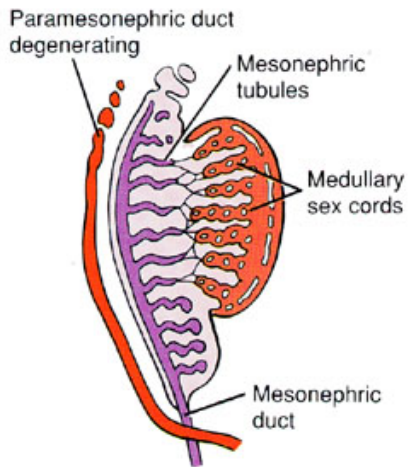
Supporting cells are required for survival of germ cells

Genital ridge enlarges and forms a cortex and medulla - these regions have different fates in males and females

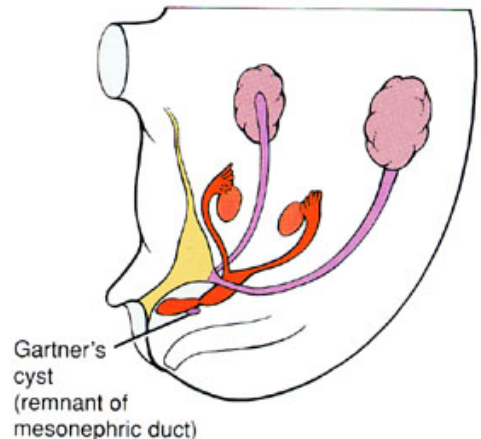
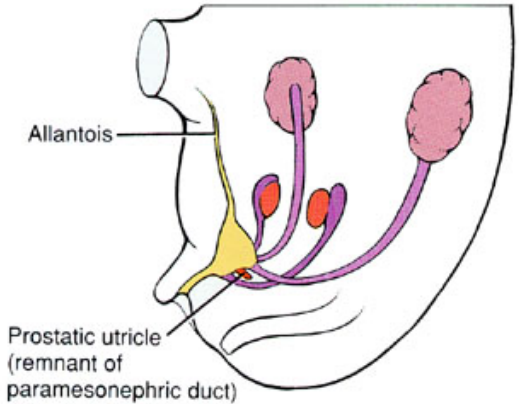
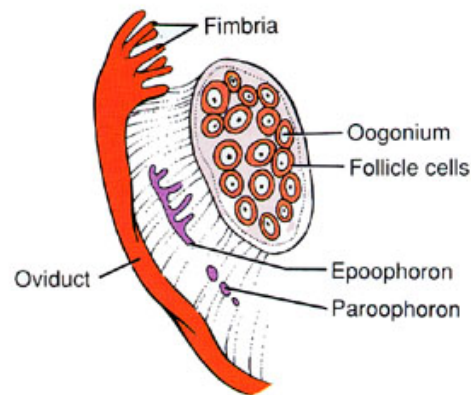
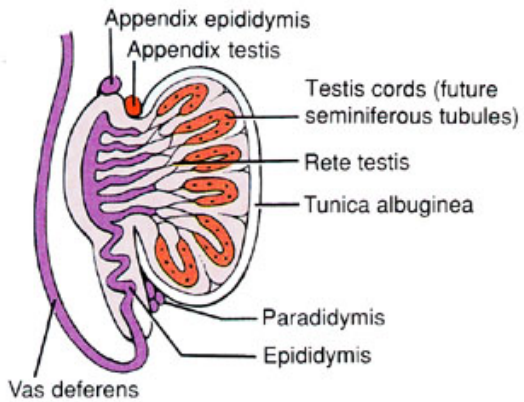
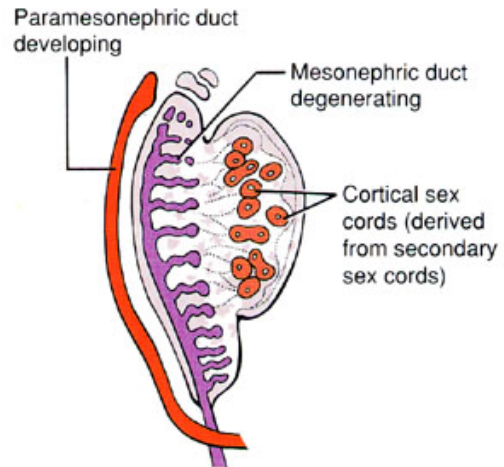
After 6 weeks - males and females diverge - prior to this is called the Indifferent phase of genital development



**Male**



**Female**



# Mullerian Duct

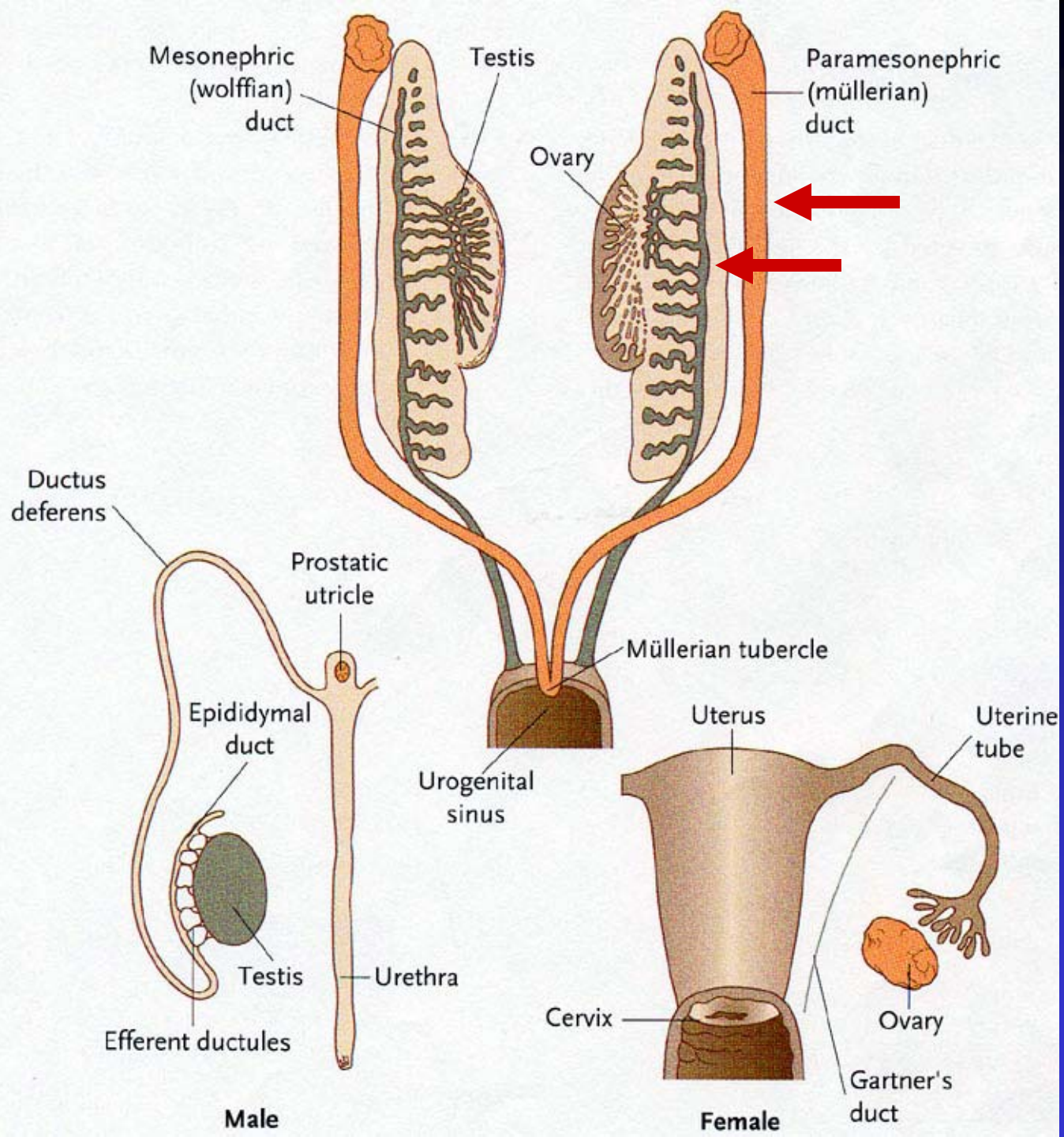
During week 6 - paramesonephric duct (Mullerian duct) forms lateral to the mesonephric duct

Mullerian ducts is an invagination of coelomic epithelium  
Cranially at the 3rd thoracic segment  
Caudally they elongate, join and fuse with the urogenital sinus (medial to the mesonephric ducts)

At this time the mesonephric duct opens into the pelvic urethra  
The site of fusion with the pelvic urethra is called the Mullerian tubercle

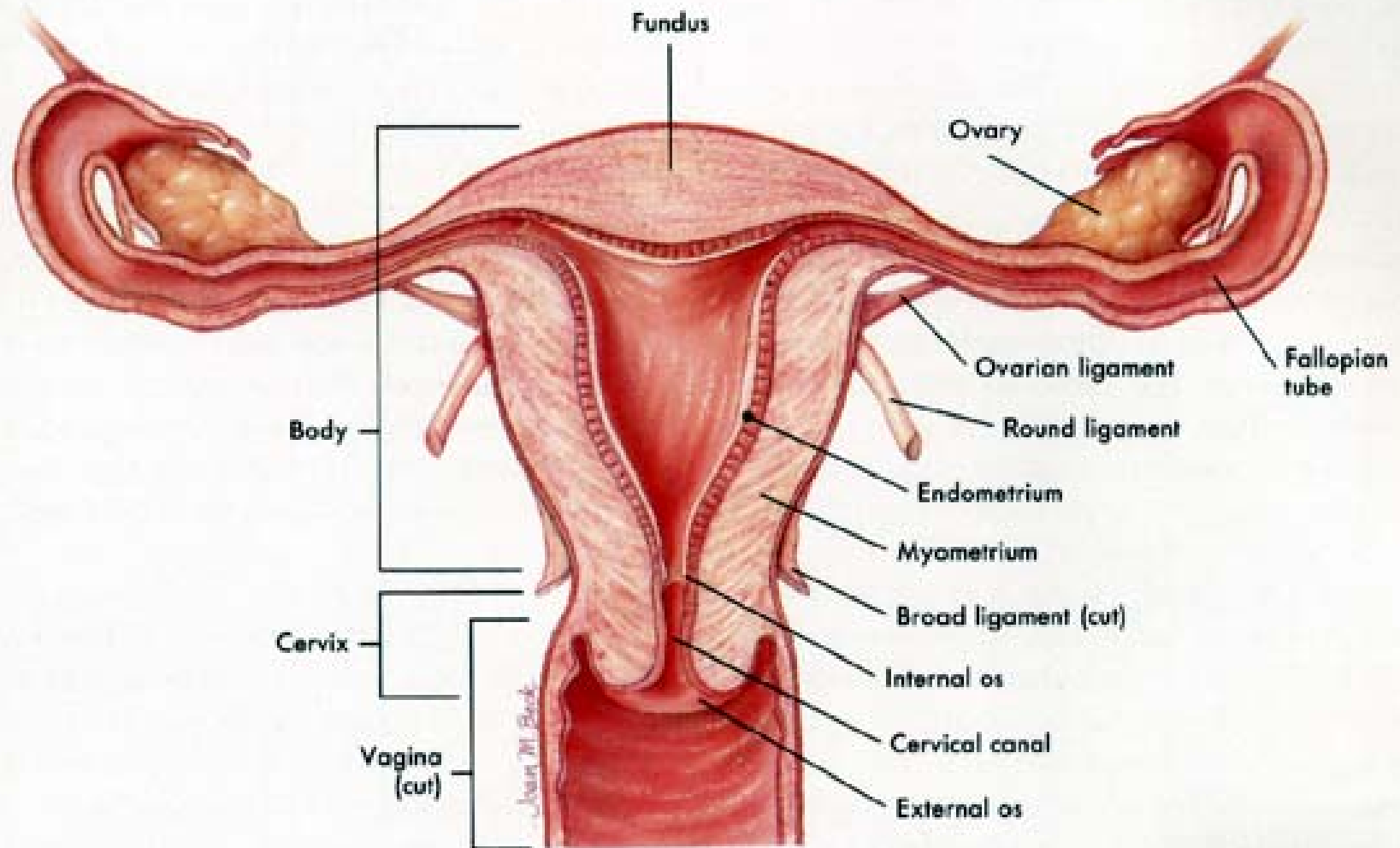
The bilaterally fused region of the duct is the Uterovaginal canal

At the cranial end there is an opening into the coelom that is funnel-shaped





# Female Reproductive Tract



# Female Reproductive Tract

Ovary - Oogenesis

Uterine (Fallopian) Tube

Fimbriae (finger like projections of Infundibulum)

Infundibulum

Ampulla – Fertilization

Isthmus

Uterus - endometrium, myometrium, perimetrium

Cervix

Vagina

# Ovary

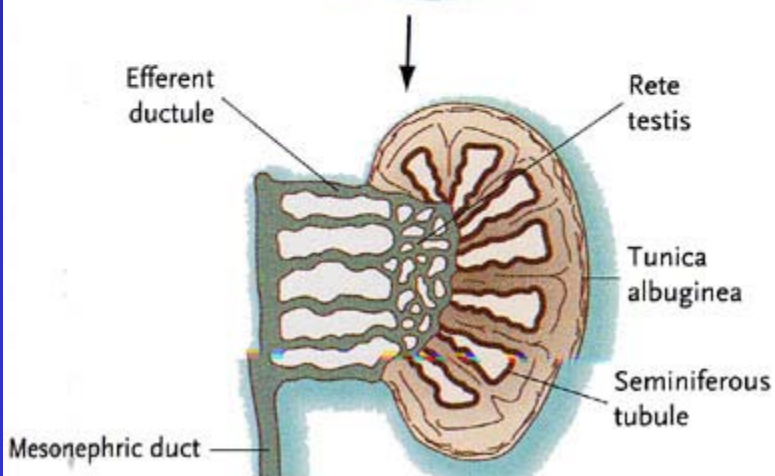
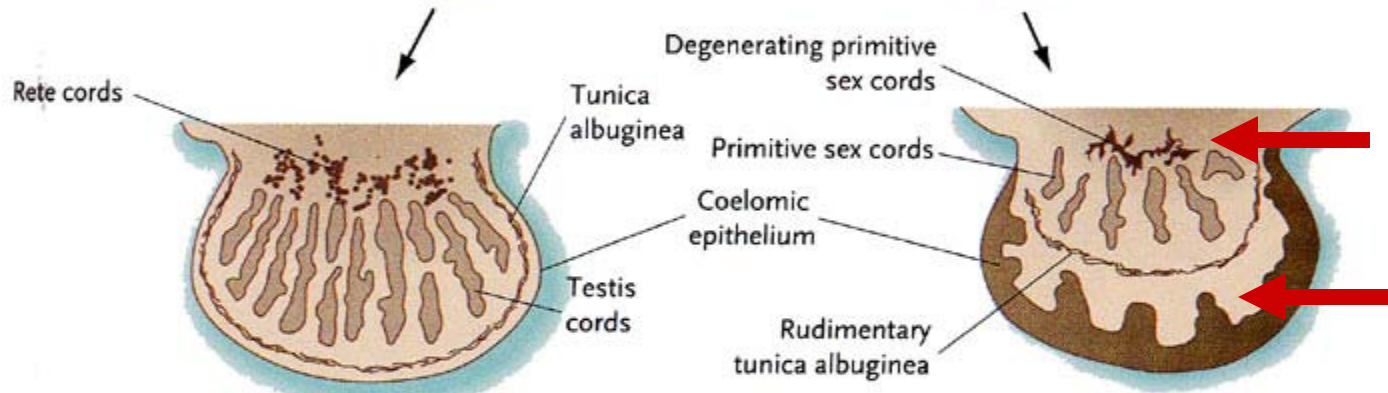
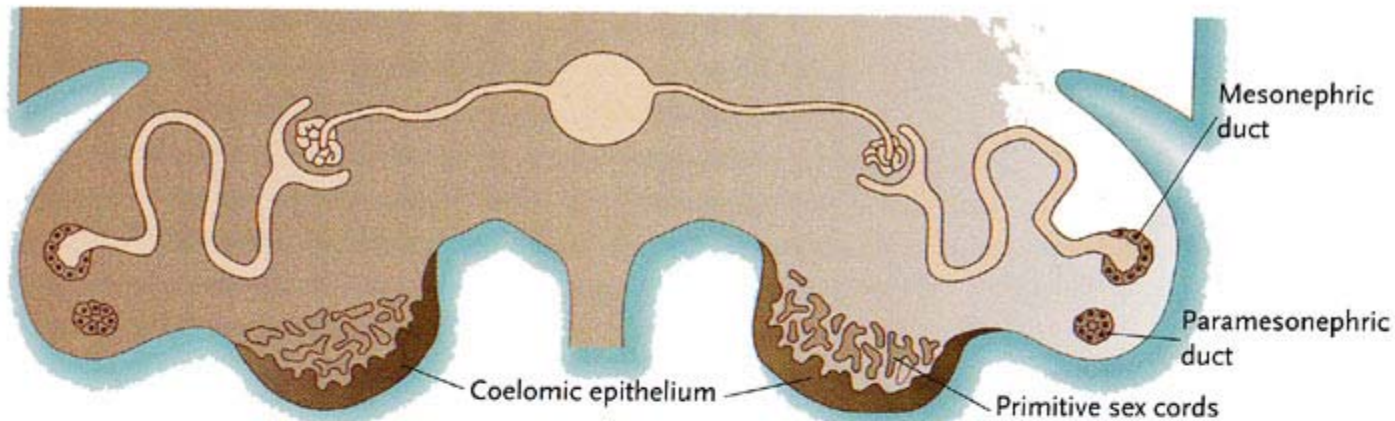
Primitive (medullary) sex cords degenerate and secondary sex cords form from cortical tissues - called Cortical sex cords

The germ cells in the degenerating medullary sex cords invade the cortical sex cords

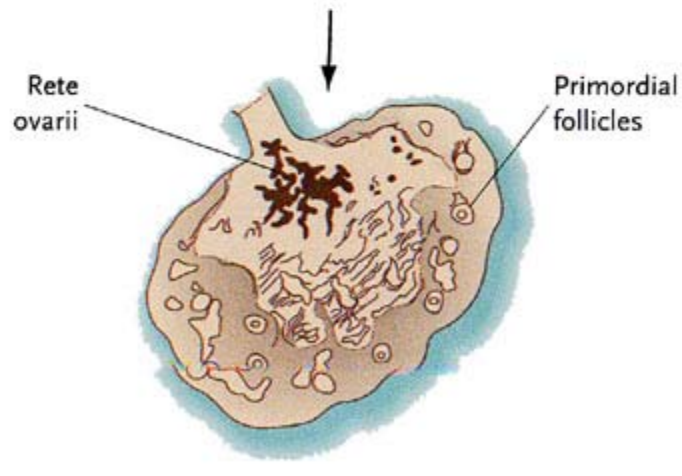
Germ cells differentiate into oogonia and enter 1st meiosis - then arrest

Cords break up into cell clusters = primitive follicles containing oogonia and follicle cells.





Testis



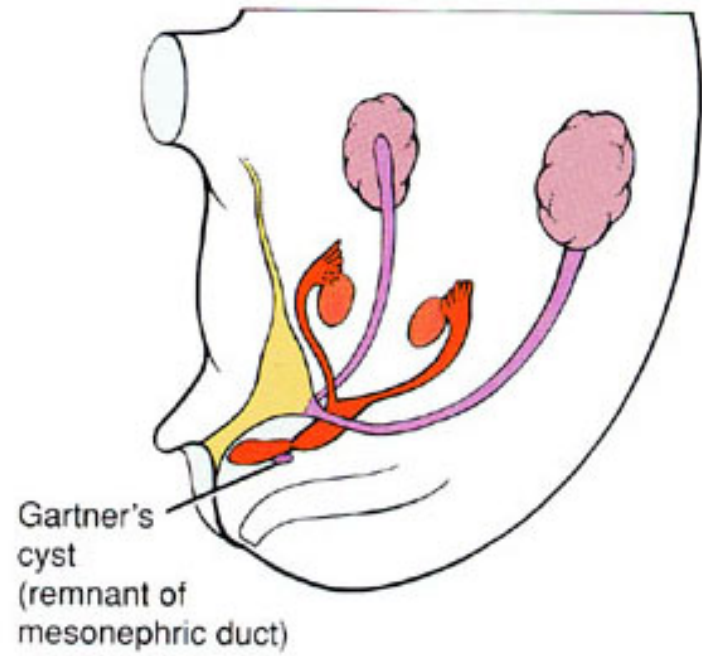
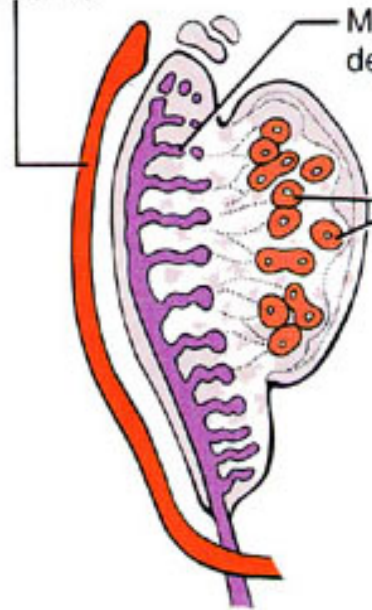
Ovary

# Female

Paramesonephric duct  
developing

Mesonephric duct  
degenerating

Cortical sex  
cords (derived  
from secondary  
sex cords)



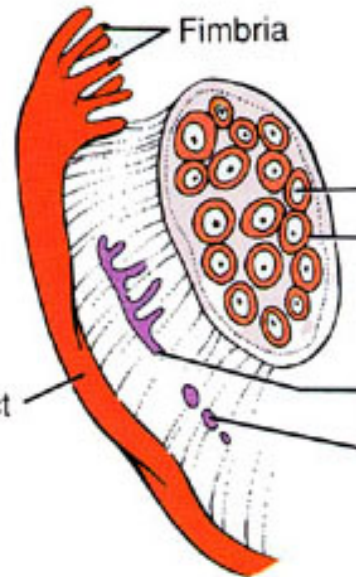
Gartner's  
cyst  
(remnant of  
mesonephric duct)

Fimbria

Oogonium  
Follicle cells

Epoophoron  
Paroophoron

Oviduct



# Mullerian Ducts Develop in Female

In the absence of testosterone:

- The mesonephric duct degenerates

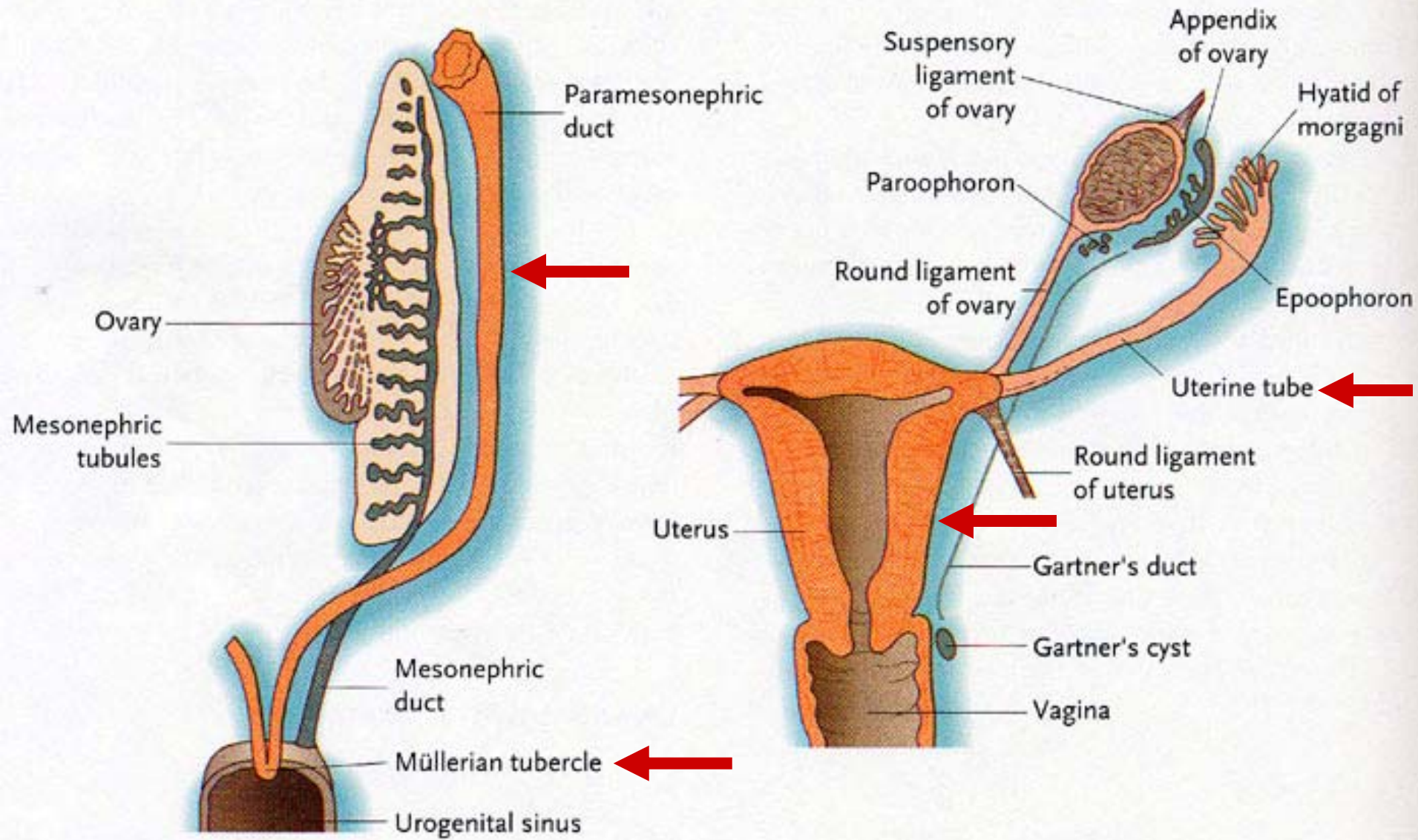
- The Mullerian duct develops uninhibited

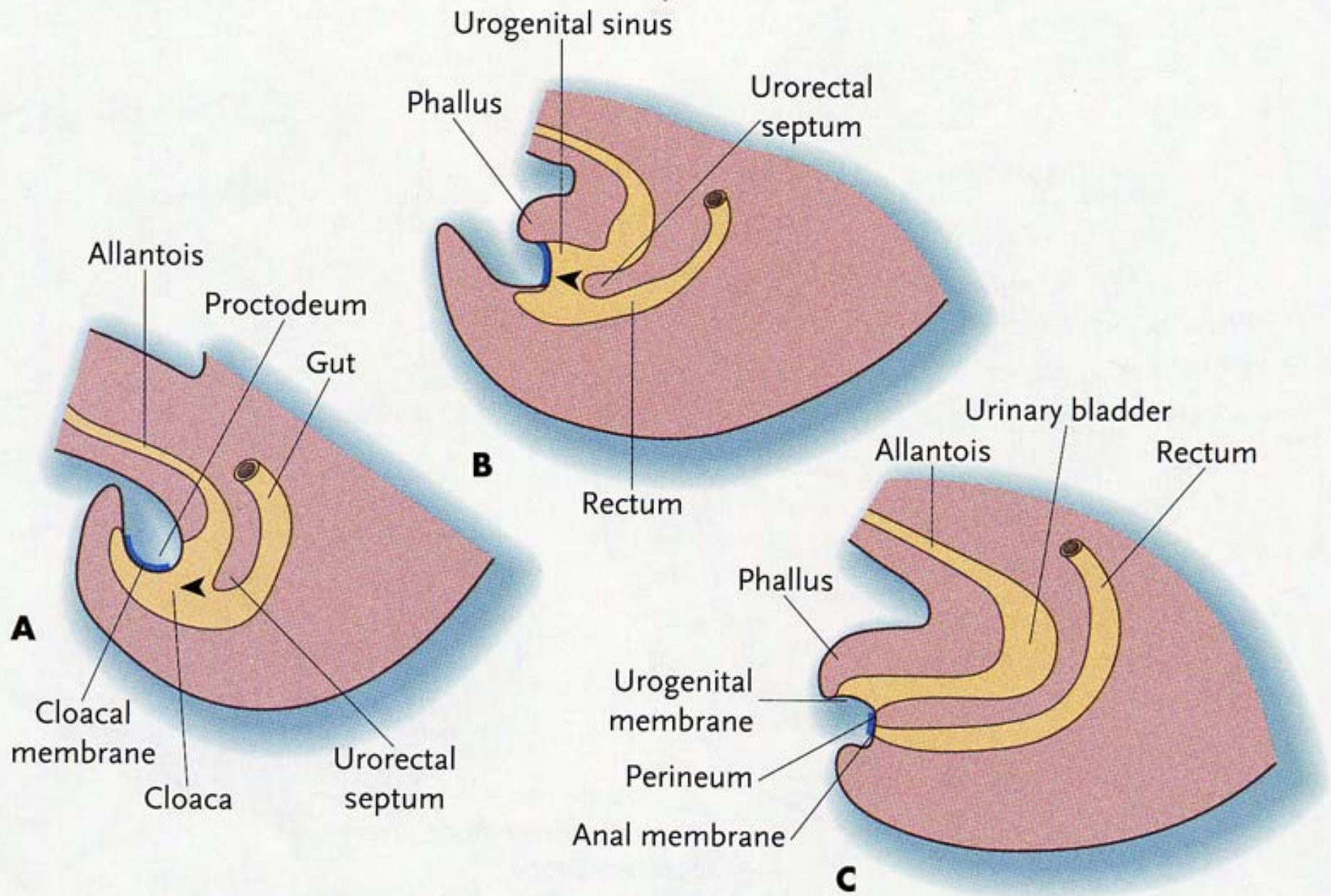
Mullerian duct - cranial funnel-shaped opening to the coelom forms the fimbriae of the infundibulum

The cranial Mullerian duct forms the uterine tubes

The caudal end of the Mullerian ducts fuse to form the uterovaginal canal that later forms the uterus and the superior vagina







# Urogenital Sinus

Urogenital sinus forms:

Bladder

Pelvic urethra

Definitive urogenital sinus

	<u>Males</u>	<u>Females</u>
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina



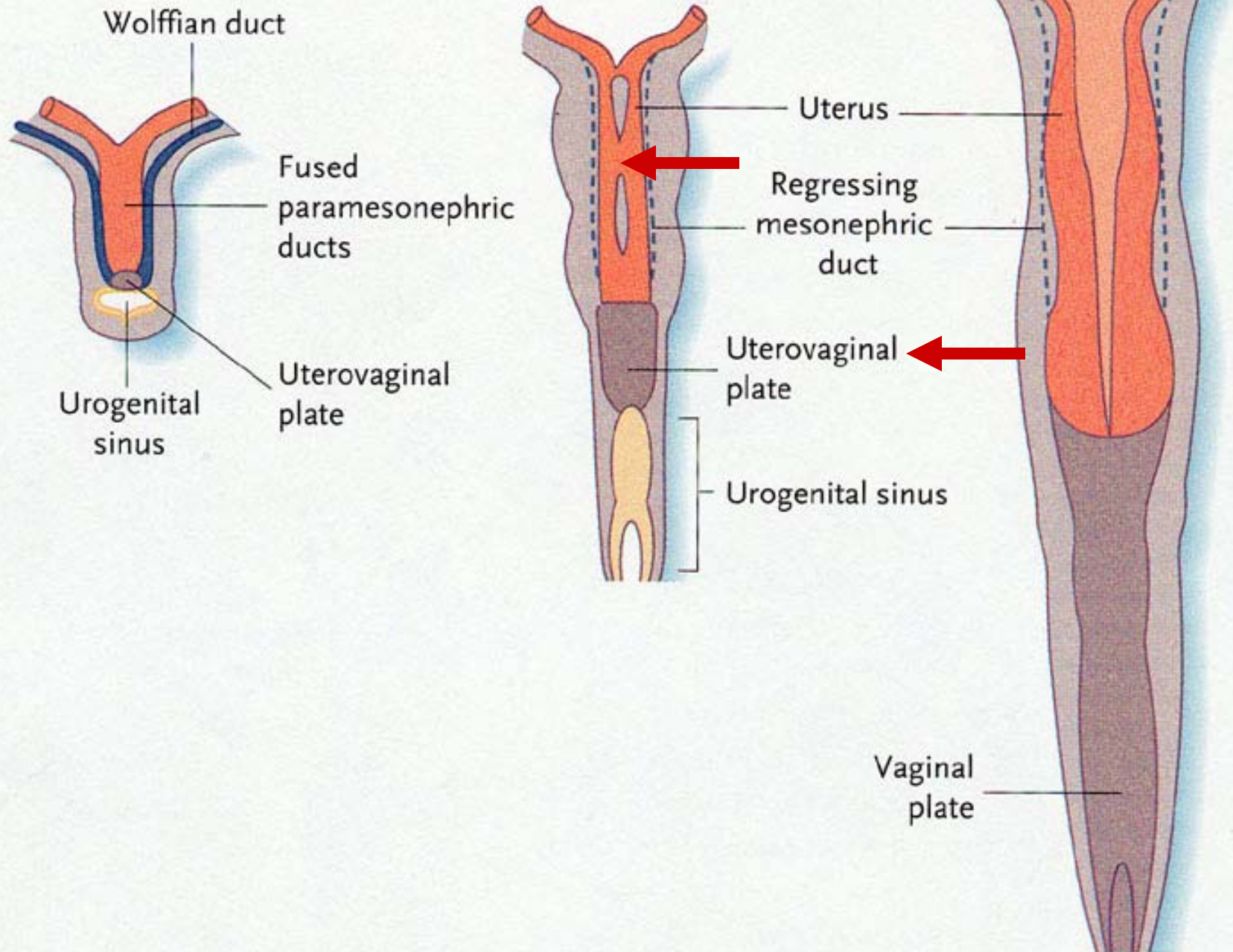
# Uterus and Vagina

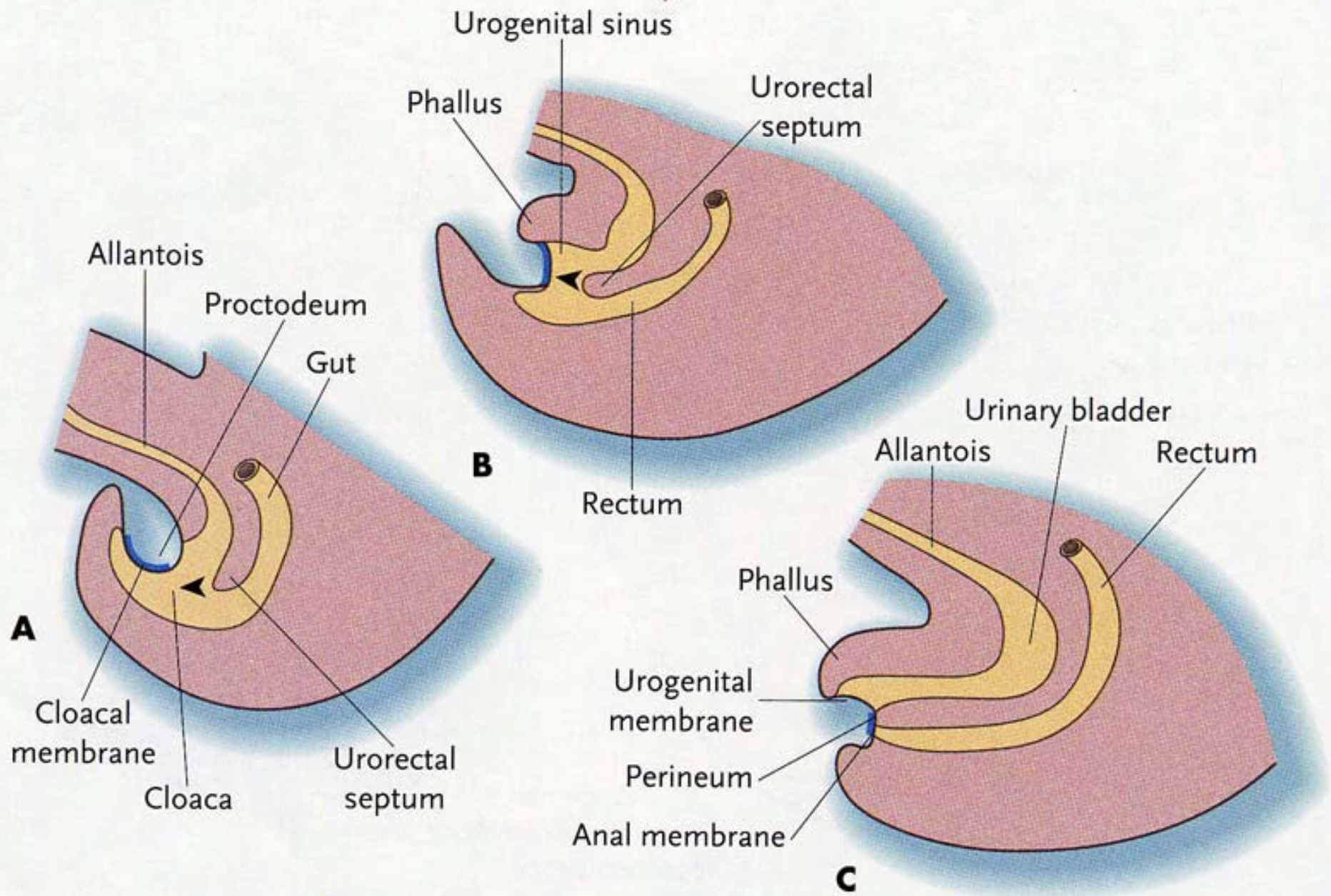
The cranial end of the uterovaginal canal forms the uterus

The caudal end of the uterovaginal canal forms the superior vagina

The inferior vagina forms from the definitive urogenital sinus

The uterus and vagina becomes occluded by tissue called the uterovaginal plate (forms from the Mullerian tubercle) that canalizes to form the lumen of the uterus and vagina







# External Genitalia

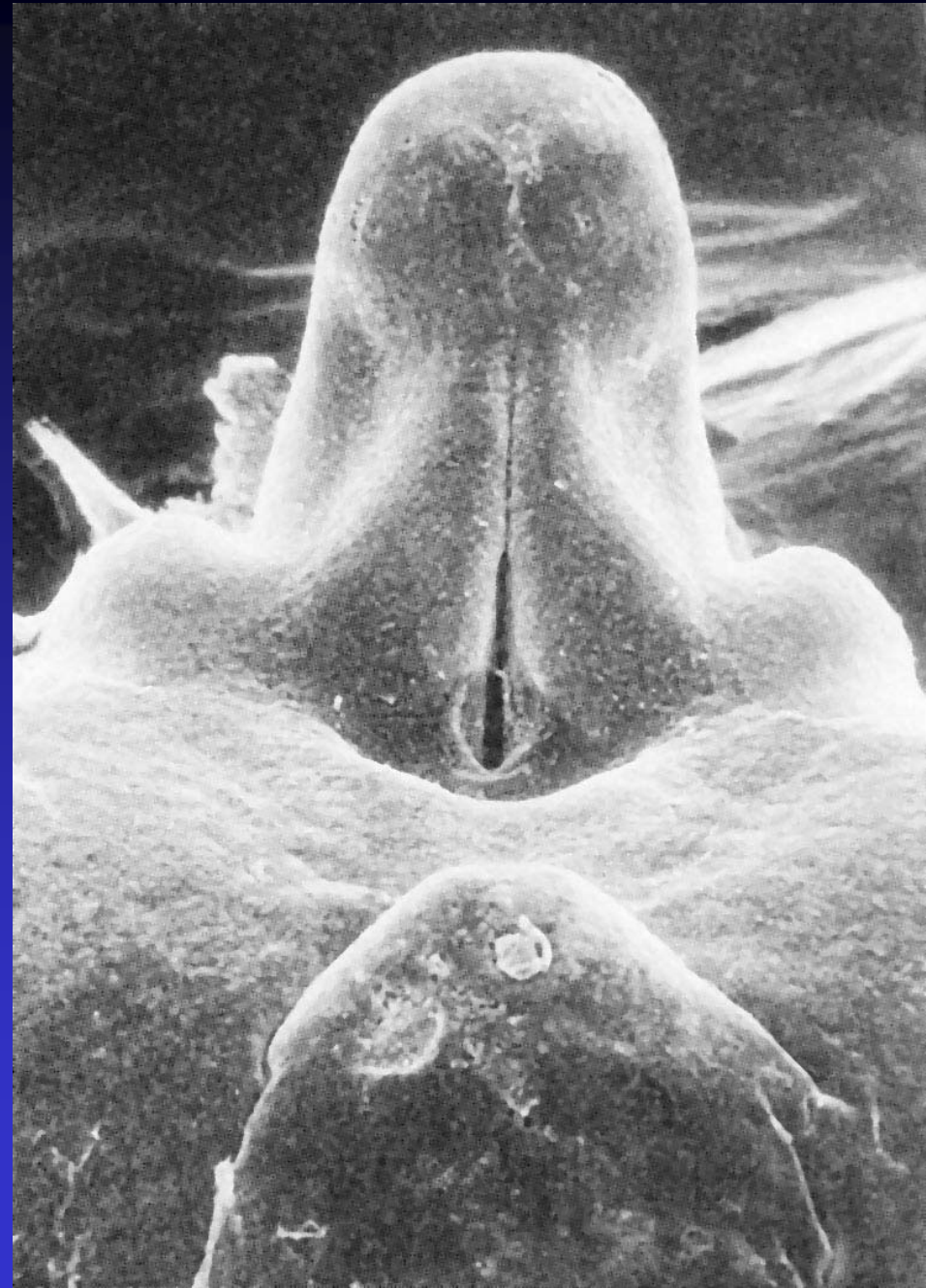
Initially the same in both sexes –  
**Indifferent stage**

**Genital folds** flank the urogenital membrane

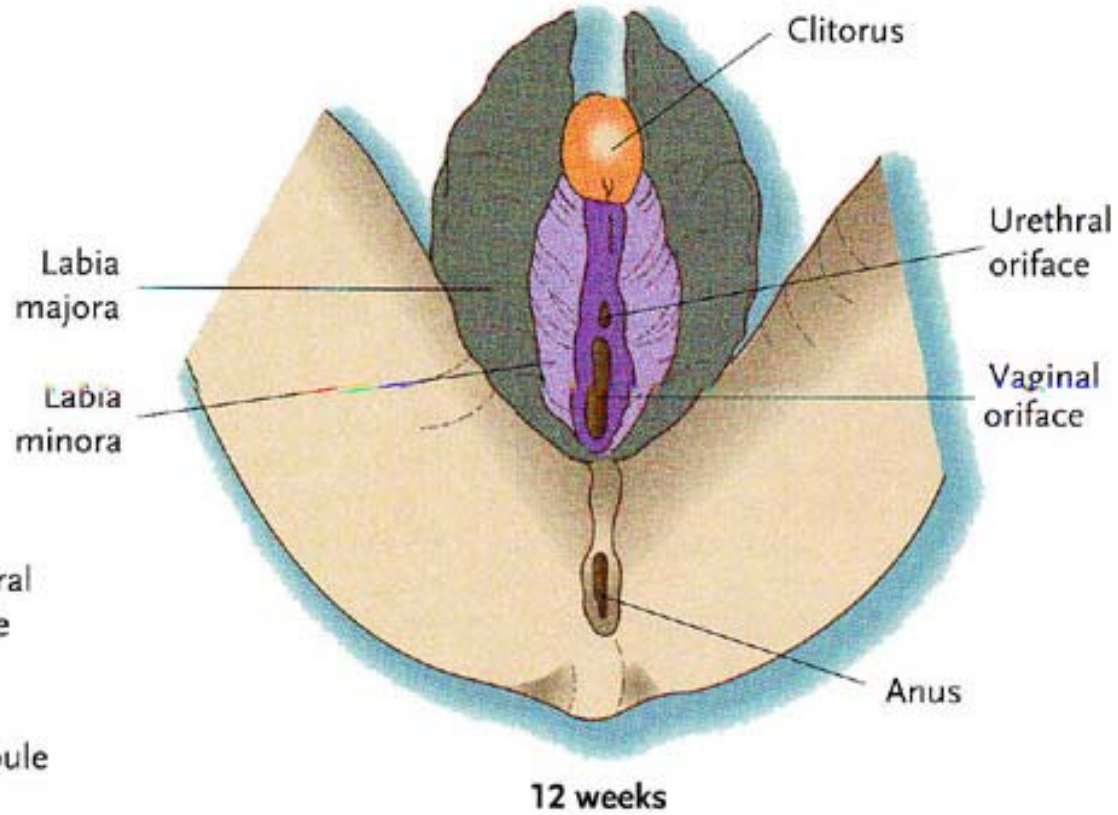
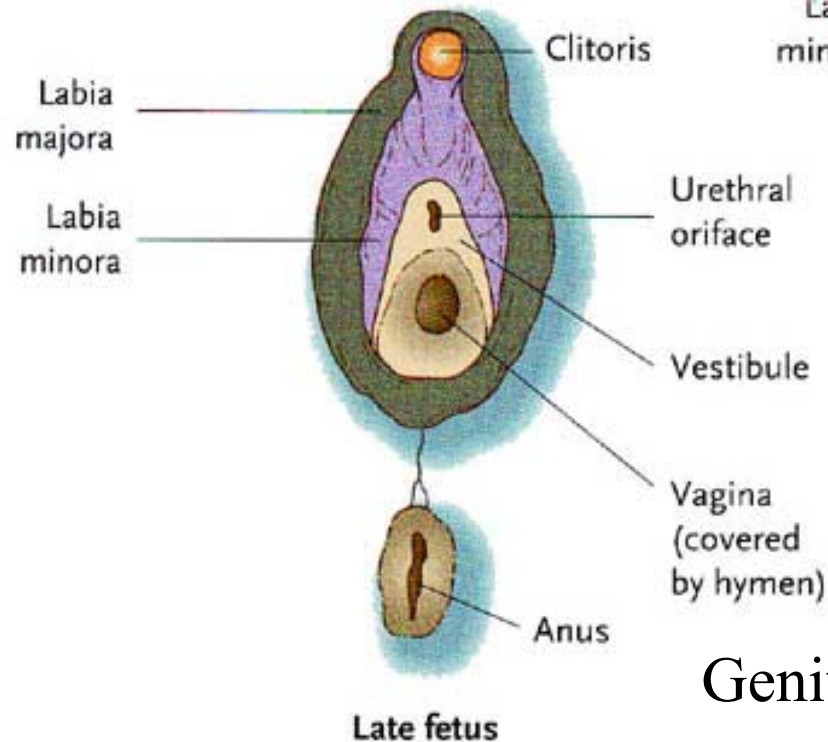
The anterior genital folds forms the  
**genital tubercle**

Lateral to the genital folds are the  
**genital swellings**

The genital tubercle elongates to  
form the **phallus**



Phallus becomes the clitoris

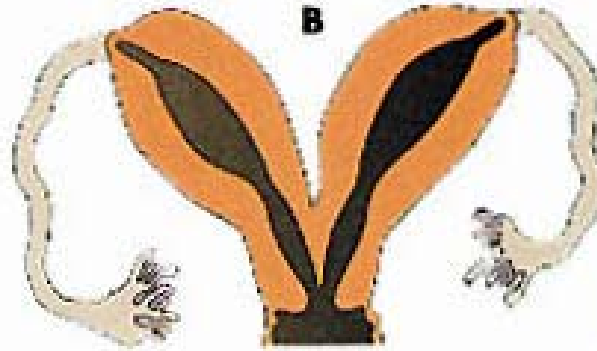
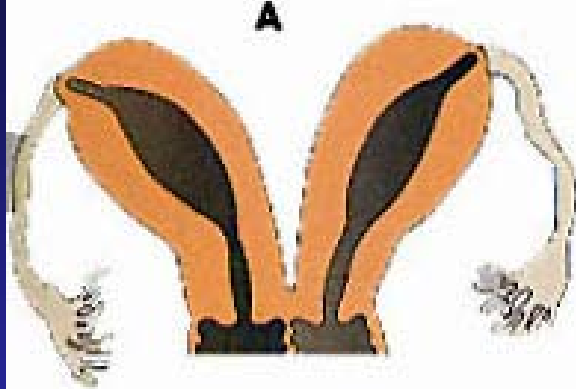


Genital folds become the labia minora

Genital swellings become the labia majora

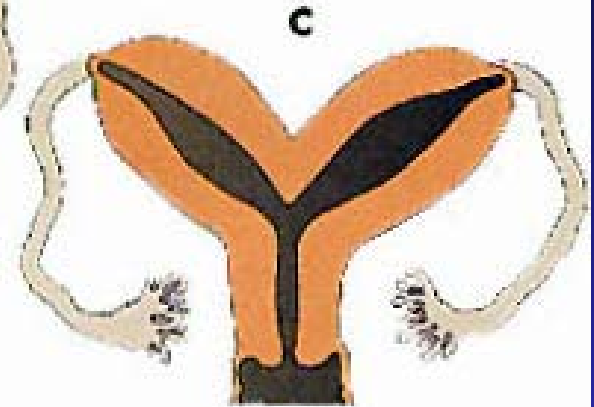
# Genital Anomalies - Females

Double Uterus  
Double Vagina

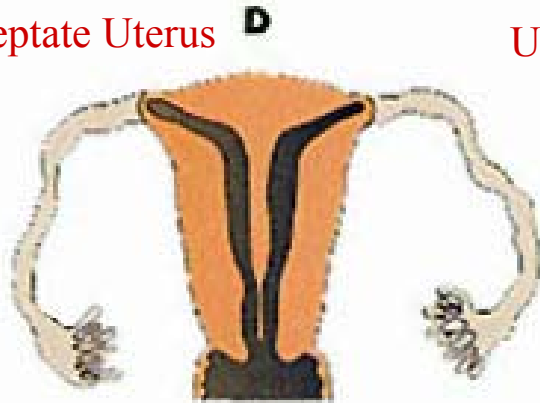


↑ Double Uterus  
Single Vagina

Bicornuate Uterus



Septate Uterus



Unicornuate Uterus



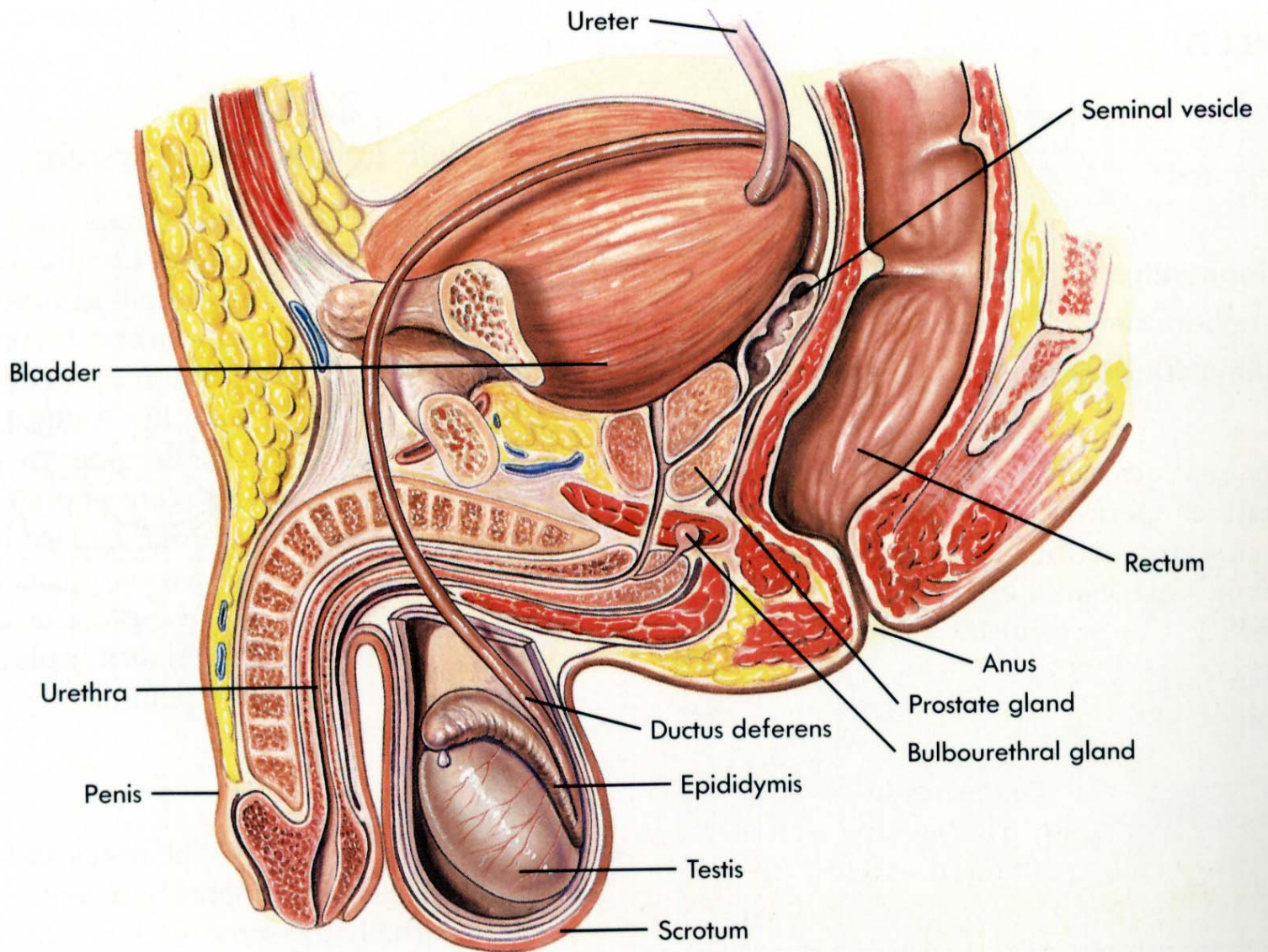
F Cervical Atresia



Uterus and Vaginal anomalies



# Male Reproductive Tract



# Male Reproductive Tract

Testis (seminiferous tubules) - Spermatogenesis

Epididymis – biochemical maturation

Ductus deferens (vas deferens)

Ejaculatory duct and inputs:

- seminal vesicle

- prostate gland

- bulbourethral gland

Urethra - out the penis

# Testis Development

With the expression of Testosterone:

Primitive (medullary) sex cords of the genital ridge are maintained and the cortical tissues degenerate.

The medullary sex cord cells form the testis cords that contain Sertoli cells

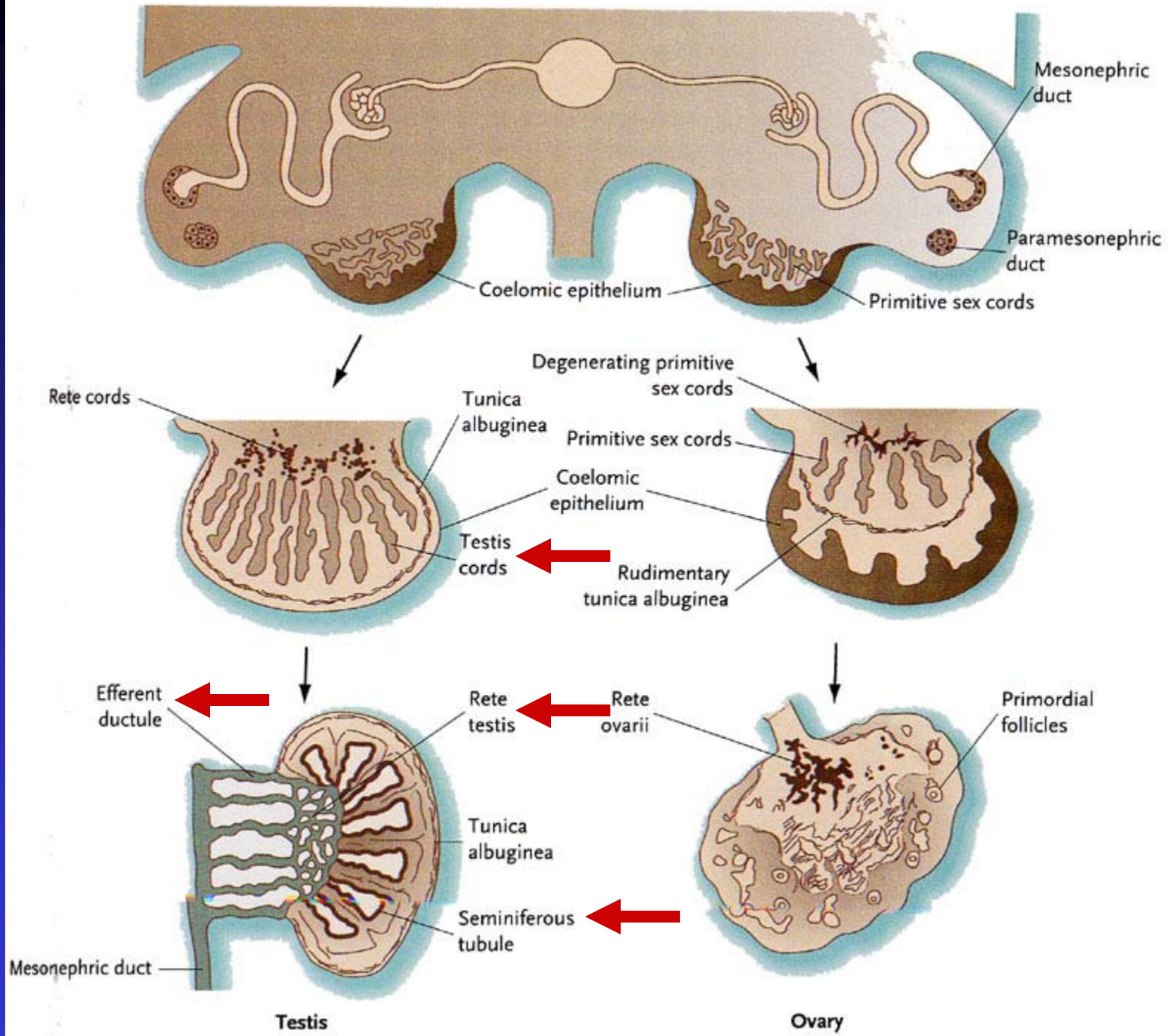
Regions of the testis cords that contain germ cells will canalize and form the seminiferous tubules of the mature testis.

The inner portion of the testis cords form the Rete testis

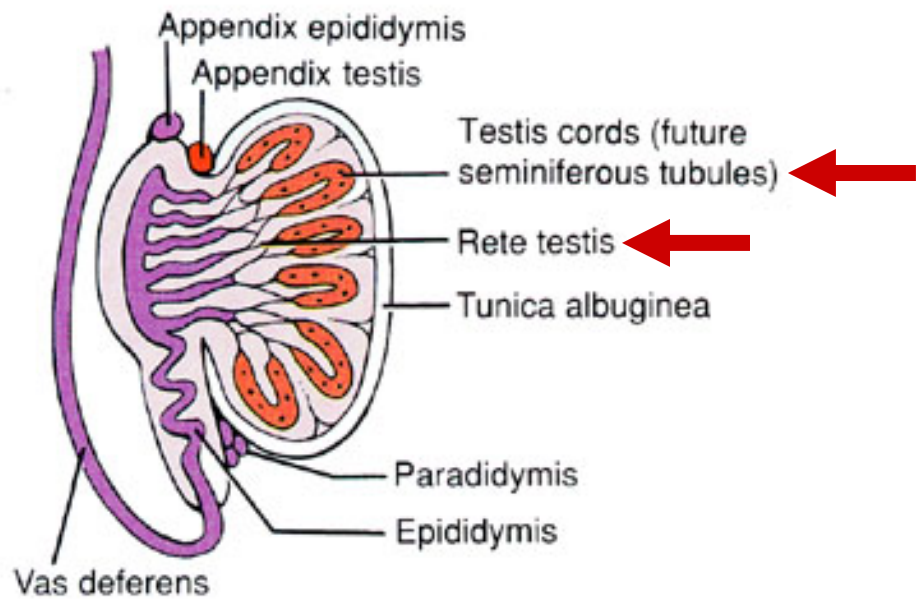
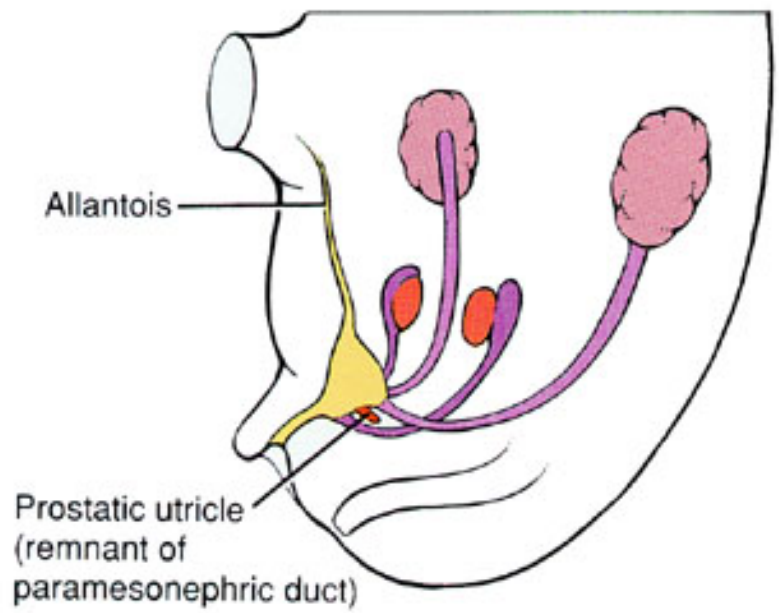
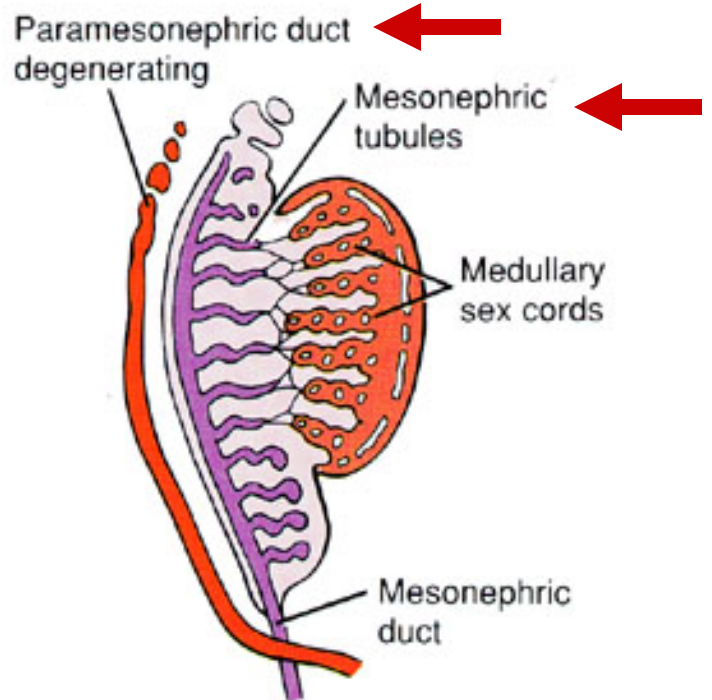
The Rete testis connects with the efferent ductules of the Mesonephric duct

Seminiferous tubules become separated by mesenchyme that forms the interstitial cells of Leydig

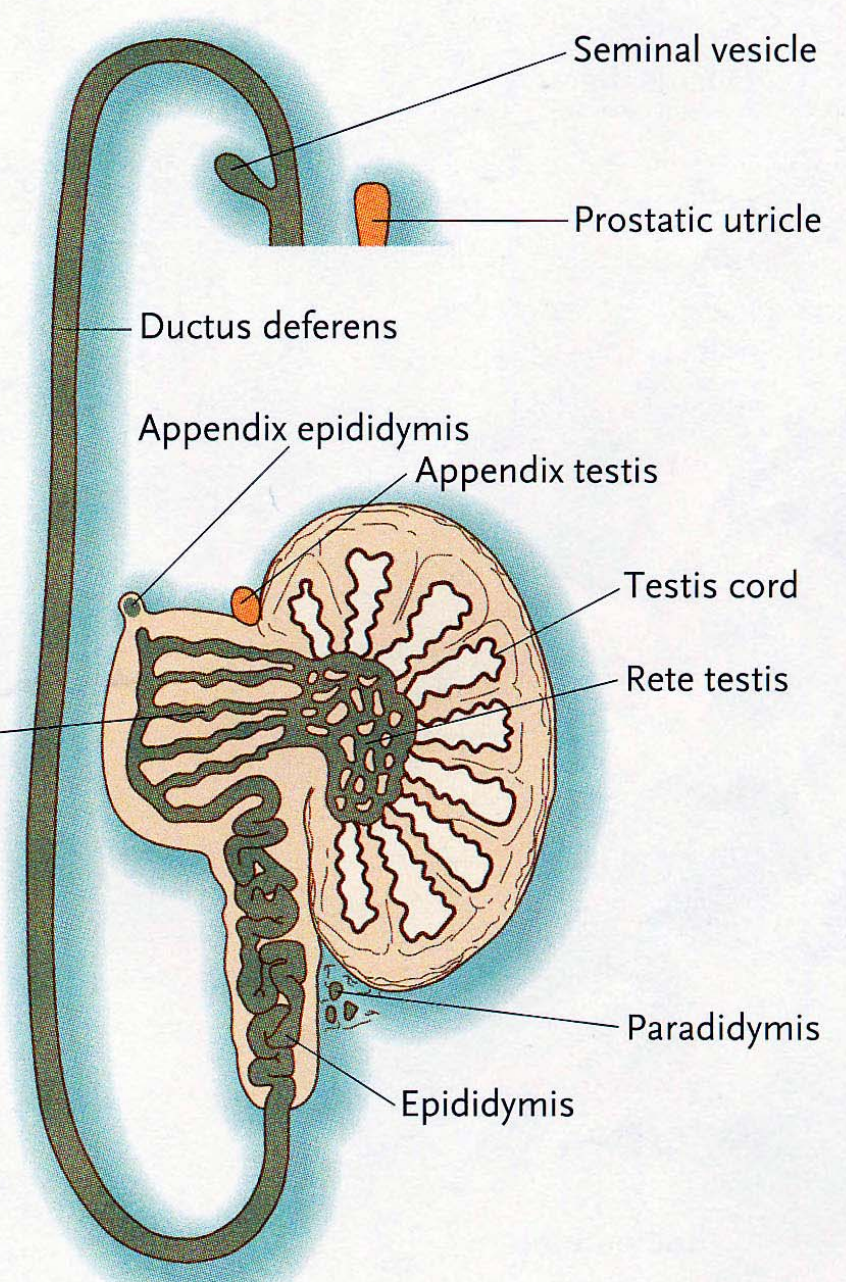
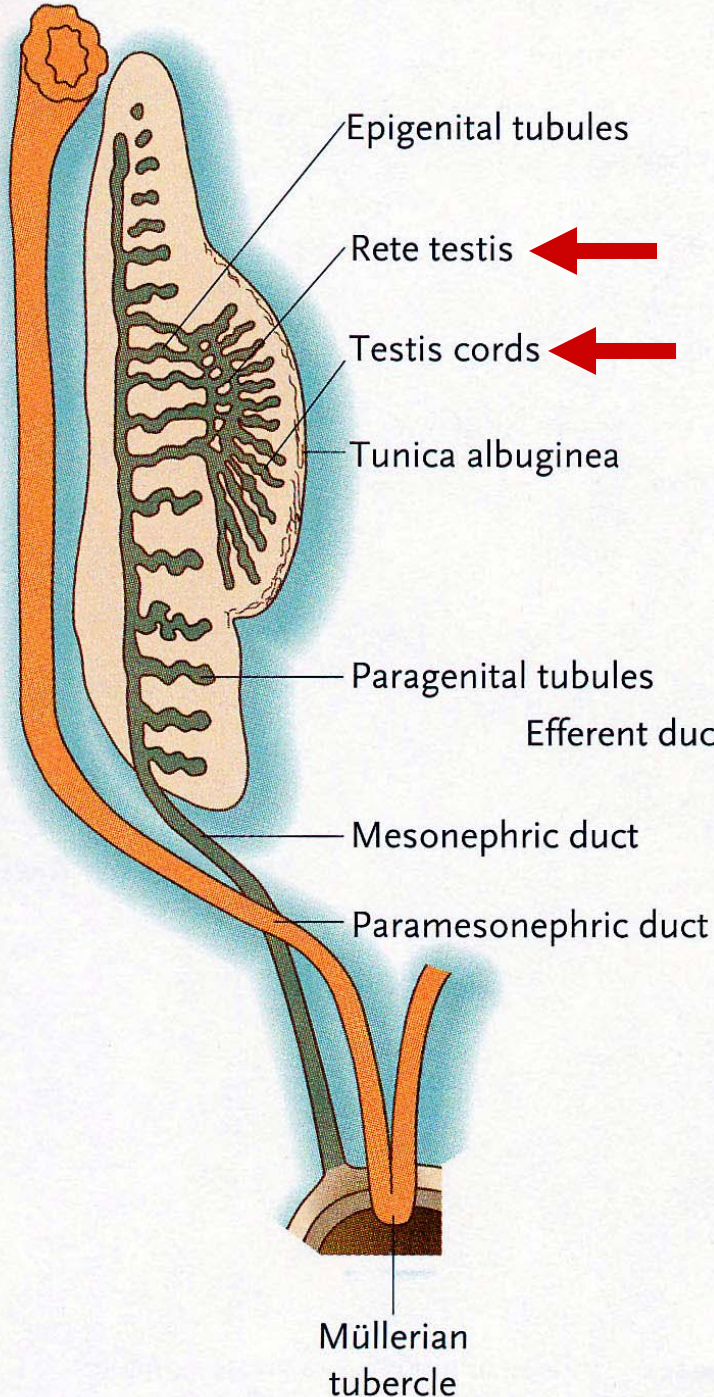




**Male**









# Mesonephric Duct Develops in Males

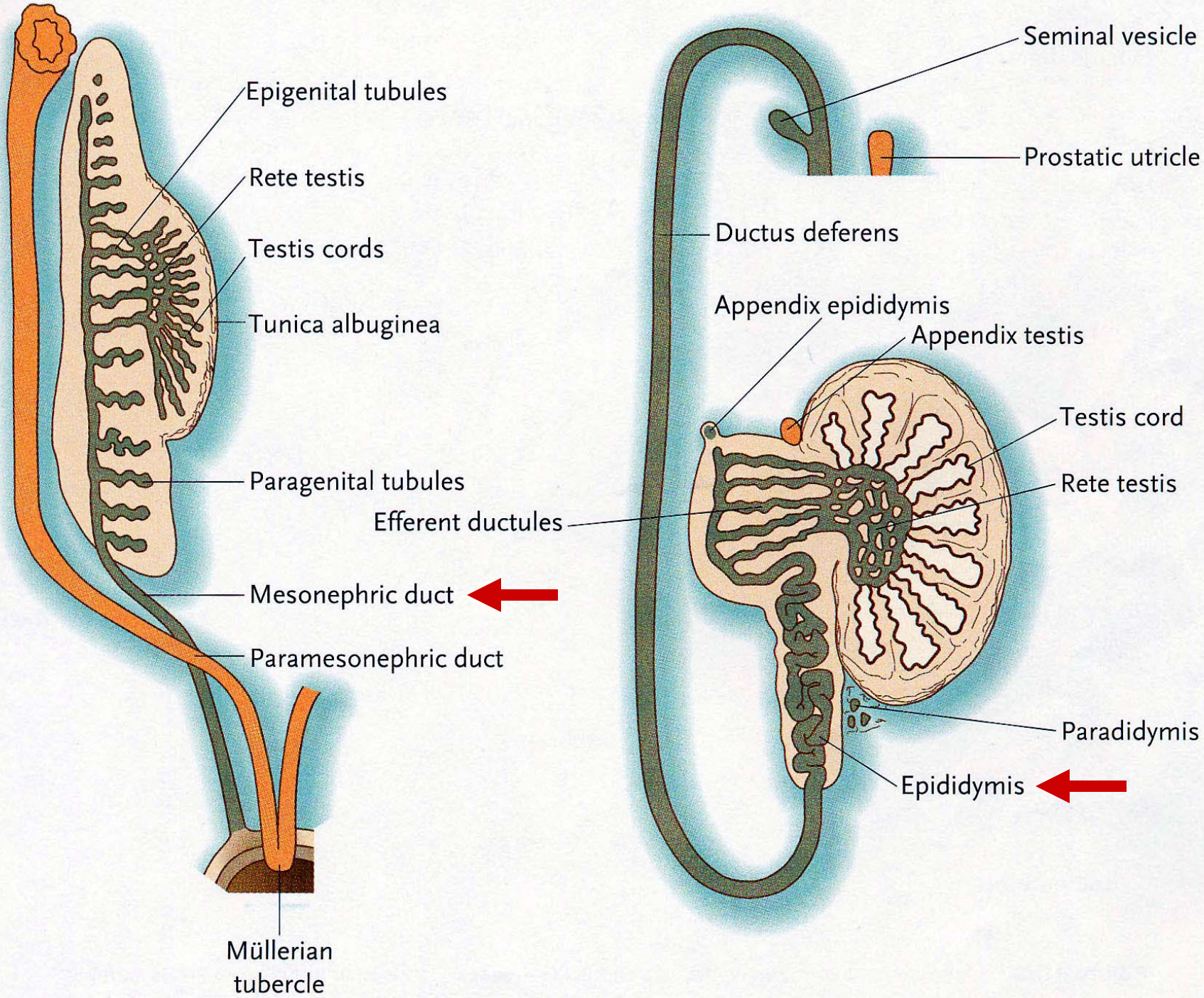
The male utilizes the mesonephric duct while the paramesonephric (Mullerian) duct degenerates.

Leydig cells produce testosterone and Mullerian-Inhibiting Substance (MIS)

MIS induces Mullerian duct regression

The Rete testis connects with 5-12 residual efferent mesonephric tubules which connects the testis to the mesonephric duct system

The mesonephric duct becomes the epididymis in this region.



# Male Duct System

Further caudally the mesonephric duct becomes the ductus deferens and drains into the urethra

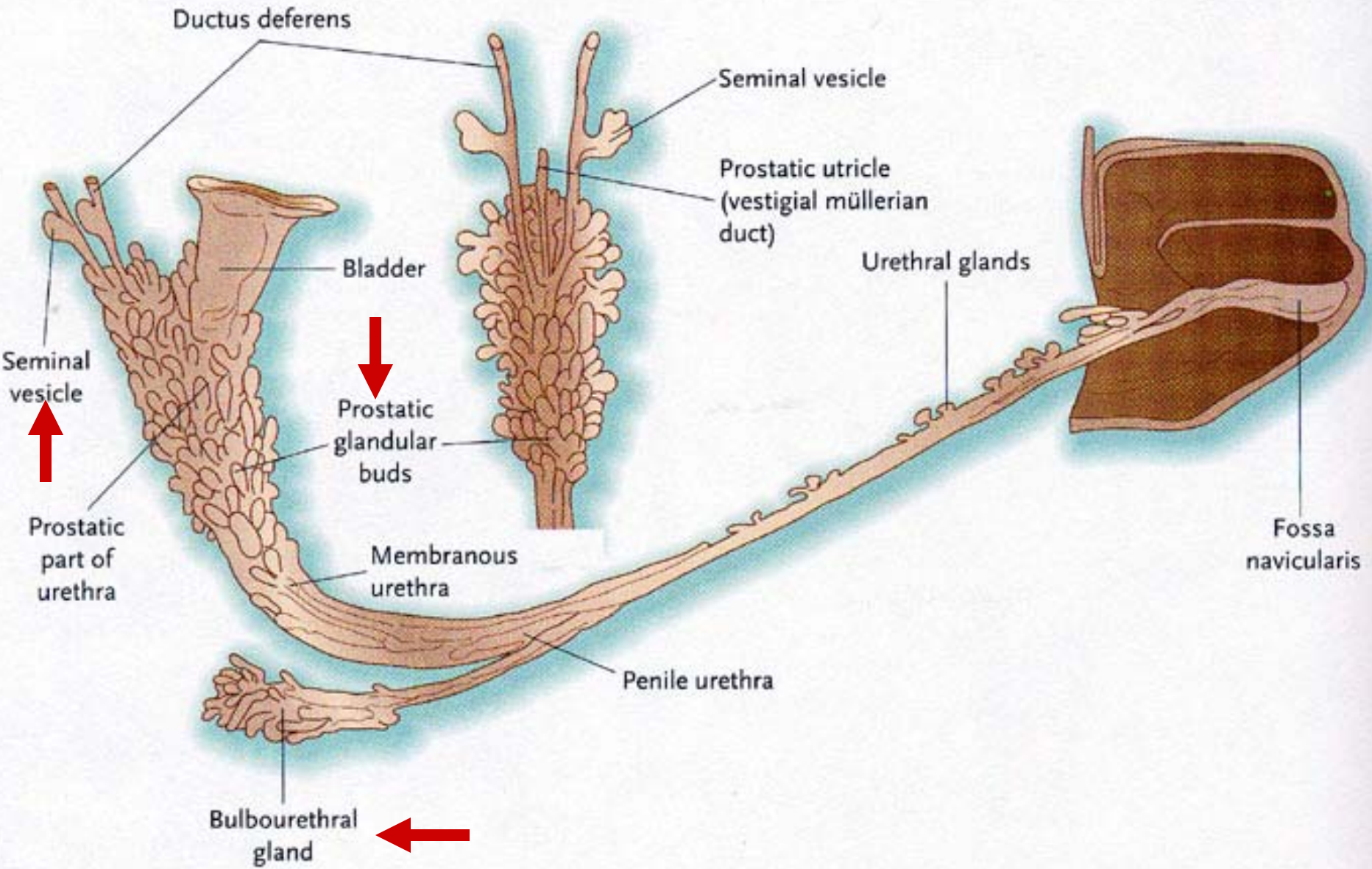
Near the caudal end of the mesonephric duct the seminal vesicle develops as a lateral outgrowth

Caudal to the seminal vesicle the mesonephric duct becomes the ejaculatory duct

Prostate Gland forms from endodermal cells of the urethra and the surrounding mesenchyme, the glandular epithelium is endodermal

Bulbourethral gland - pea sized - endodermal outgrowths from urethra





# Urogenital Sinus

Urogenital sinus forms:

Bladder

Pelvic urethra

Definitive urogenital sinus

	<u>Males</u>	<u>Females</u>
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina

# External Genitalia

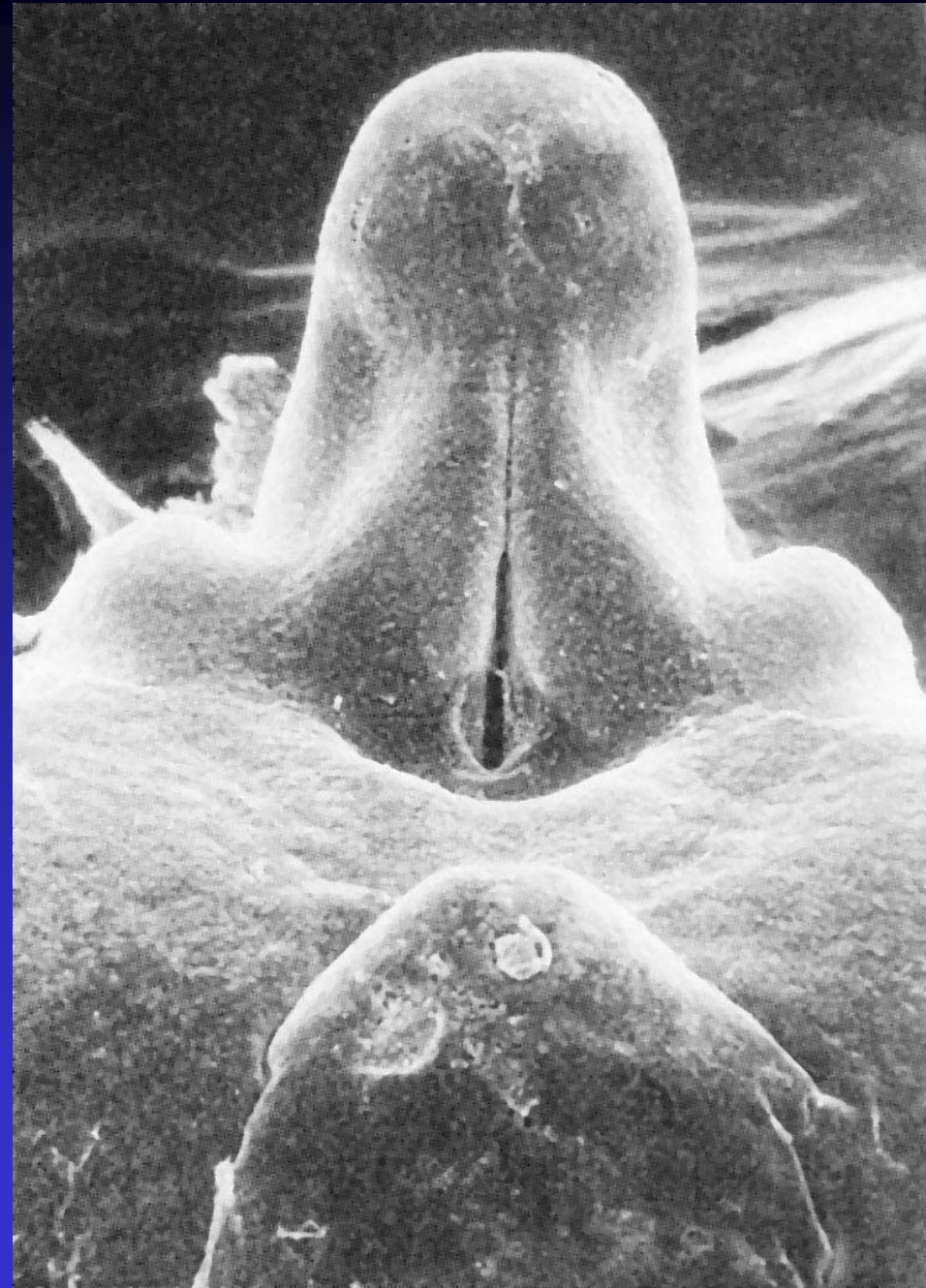
Initially the same in both sexes –  
**Indifferent stage**

**Genital folds** flank the urogenital membrane

The anterior genital folds forms the  
**genital tubercle**

Lateral to the genital folds are the  
**genital swellings**

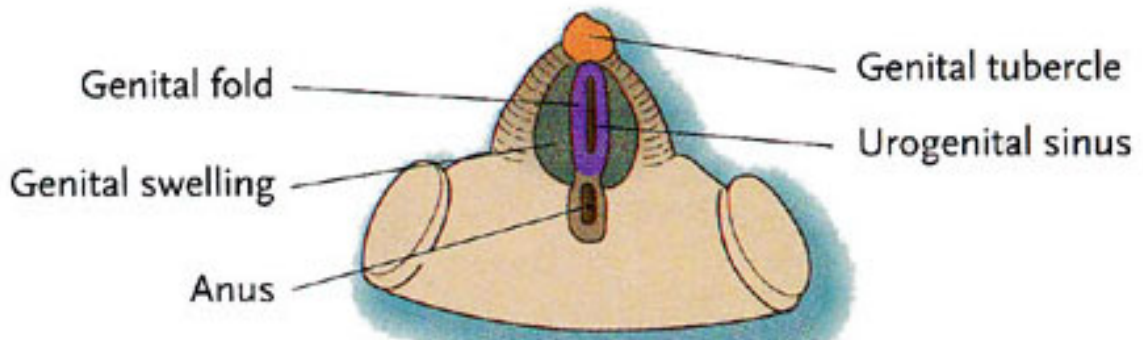
The genital tubercle elongates to  
form the **phallus**



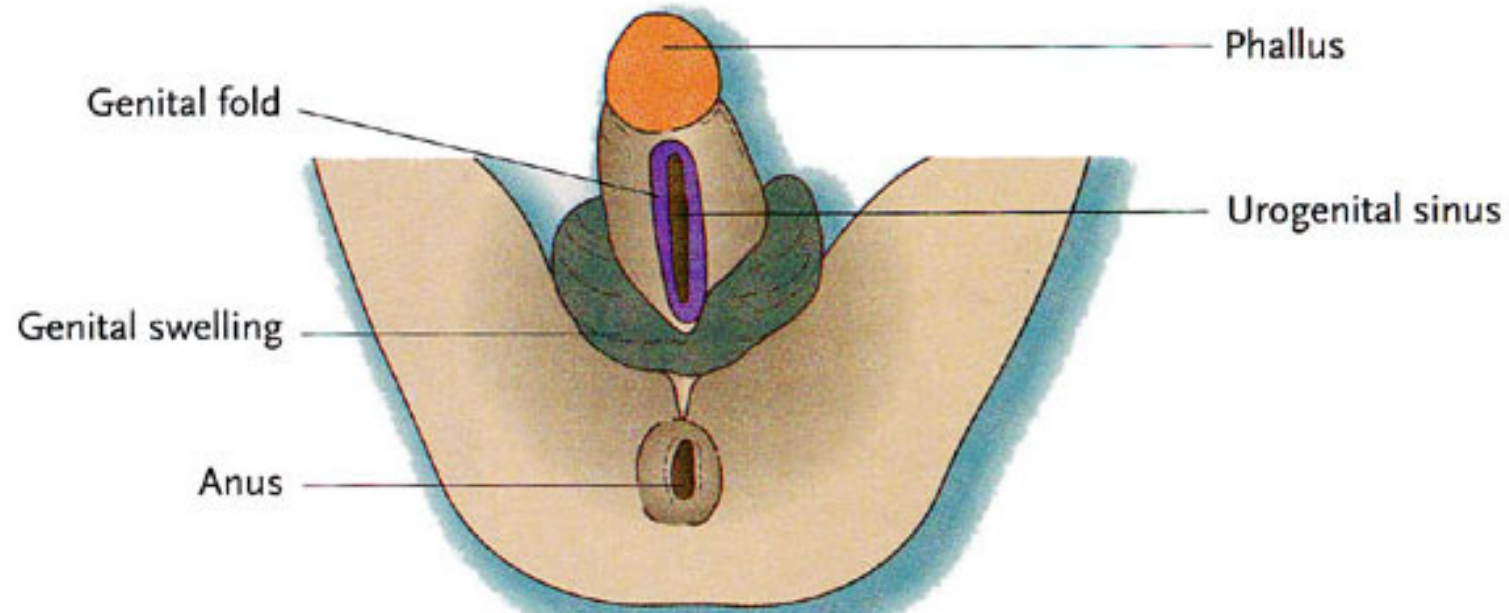


Indifferent stage

Male



7 weeks



9 weeks

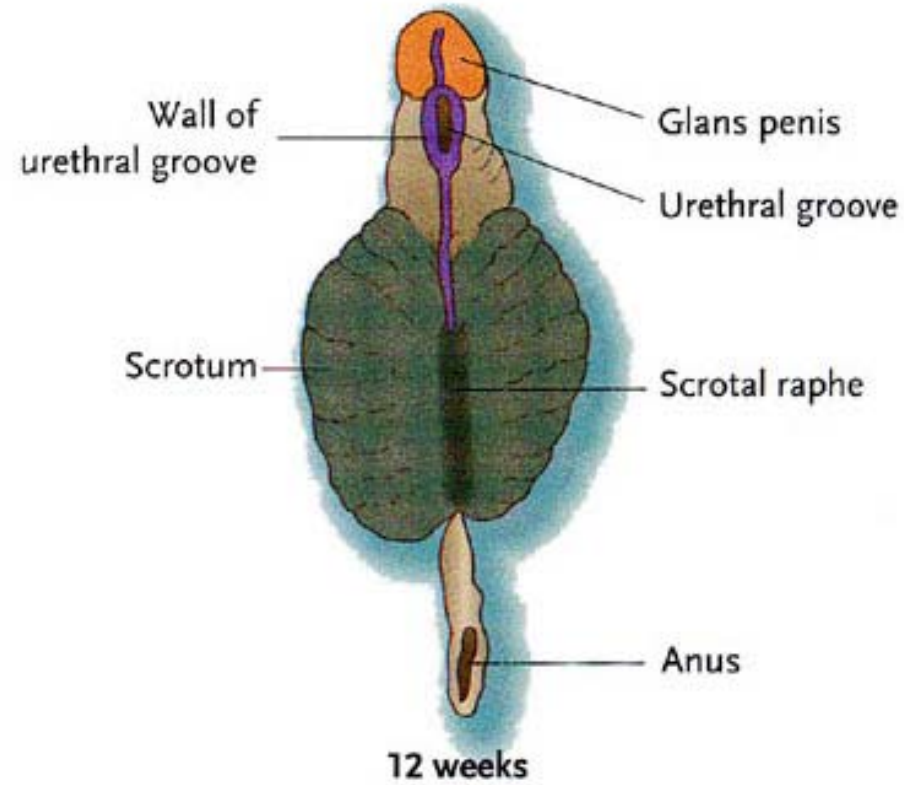
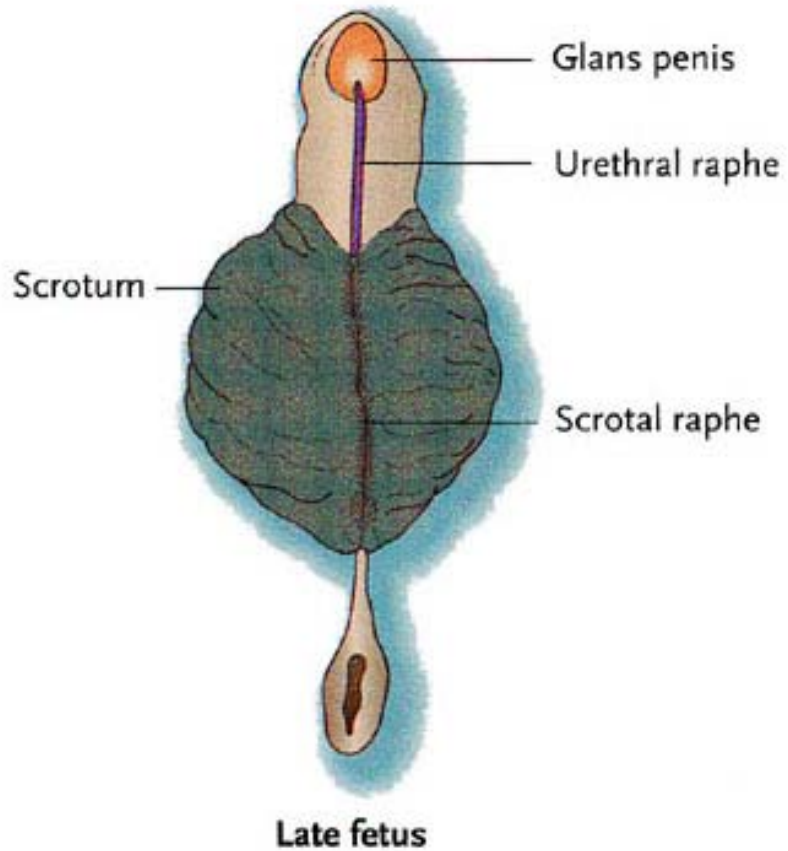
# Male Genitalia

Phallus elongates

Genital swellings enlarge and fuse to form the scrotum

Genital folds fuse to form the penile urethra - note: penile urethra does not extend to the tip of the penis

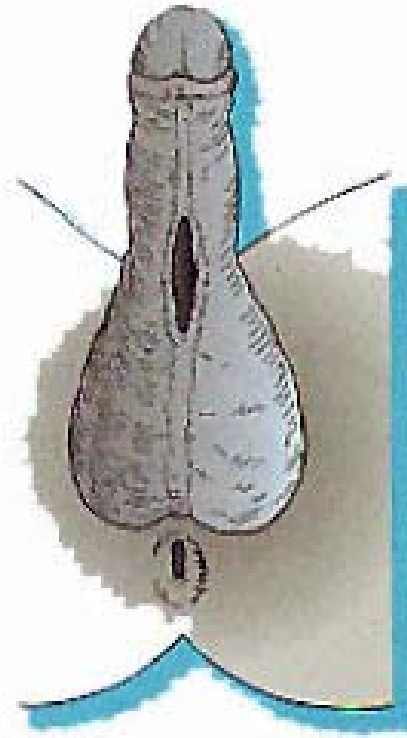
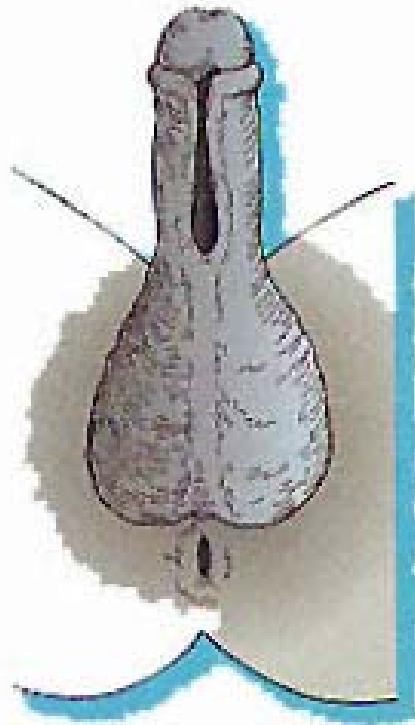
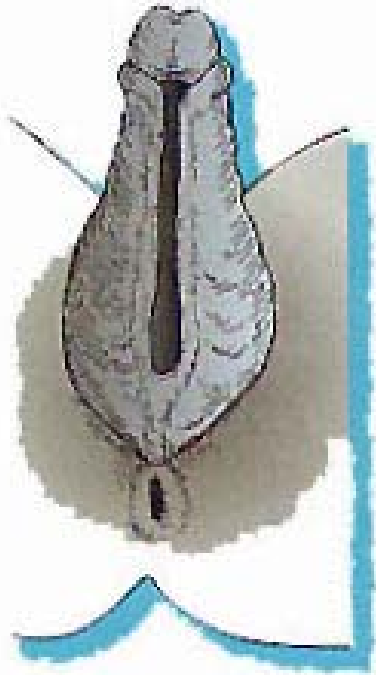
An ectodermal invagination at the tip of the penis fuses with the penile urethra.



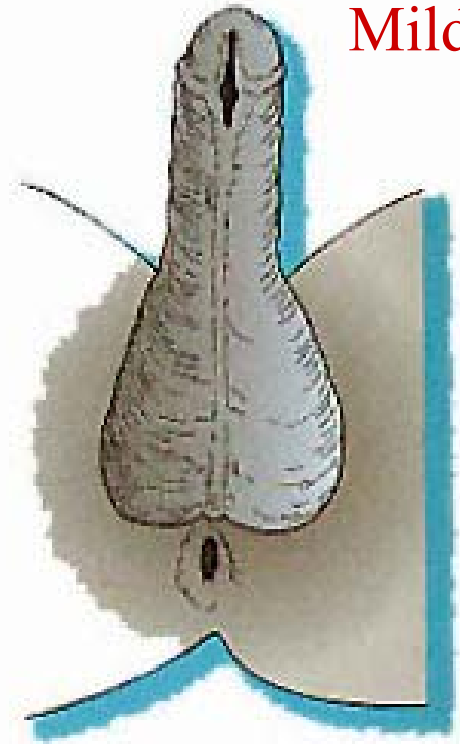


# Genital Anomalies - Males

Severe



Mild



Hypospadias – Ventral opening of urethra

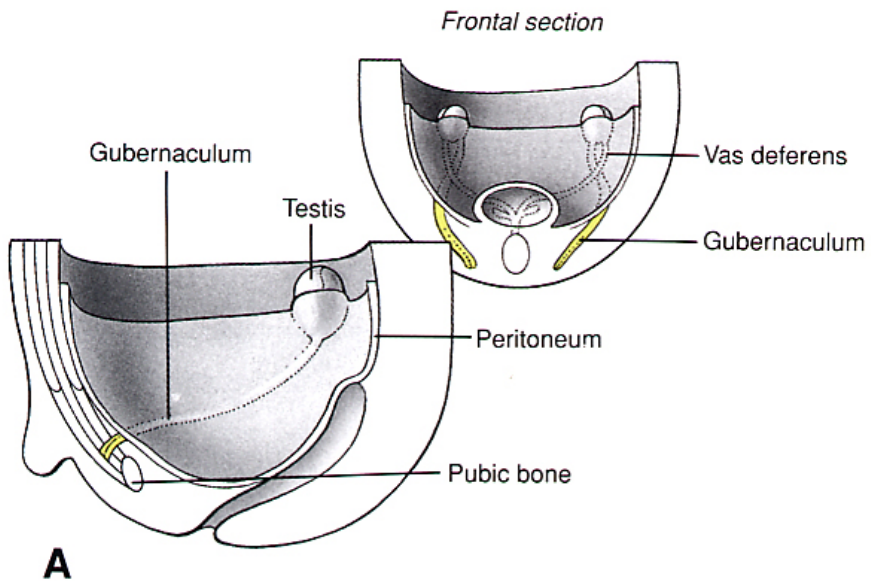
# Descent of the gonads

Both male and female gonads descend from the 10th thoracic level

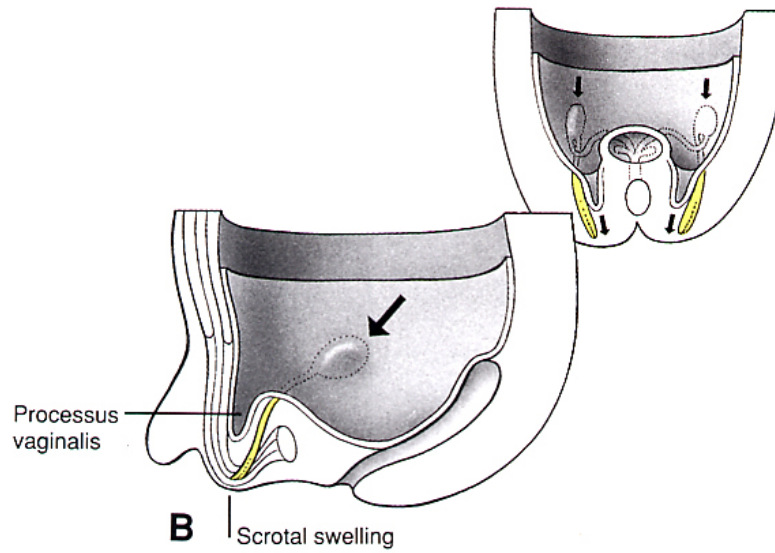
Females descend less than males

In Males there are 3 phases of the descent

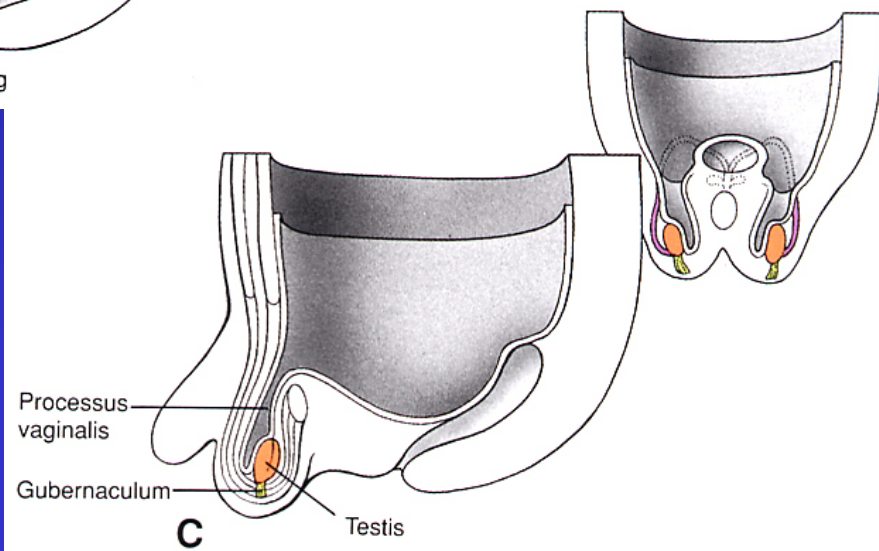
- 1) Caudal displacement due to regression of the mesonephic kidneys
- 2) Transabdominal descent to the Inguinal ring caused by regression of the Mullerian ducts (MIS activity)
- 3) Transinguinal descent into the scrotum guided by the gubernaculum into the vaginal process (evagination of the caudal abdominal wall)



**A**

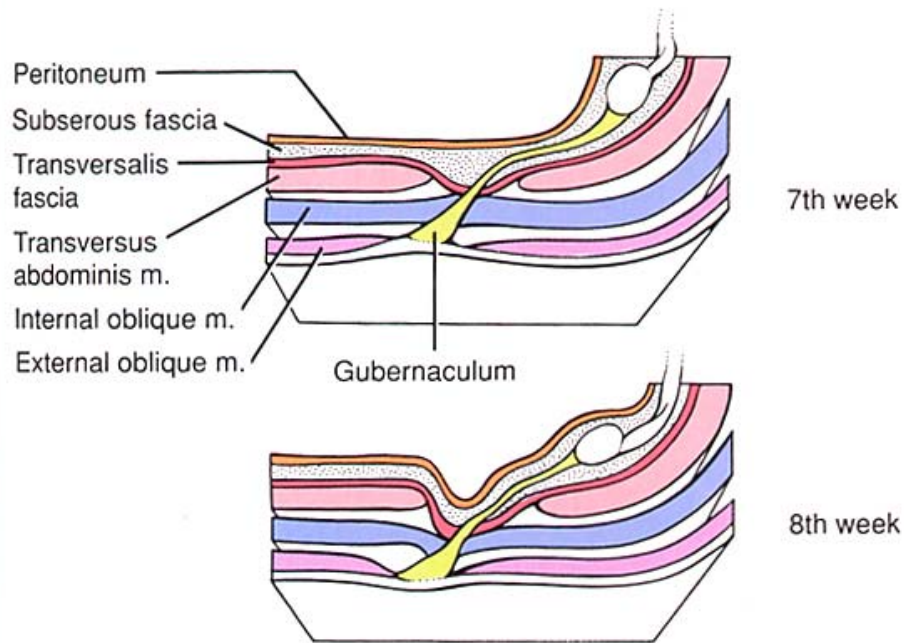


**B**

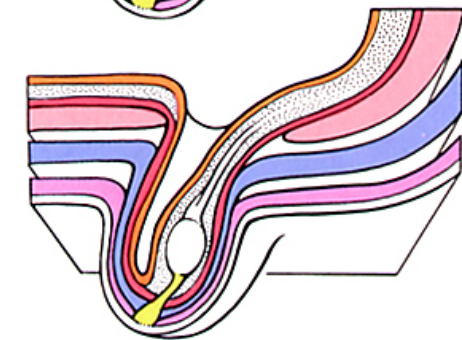
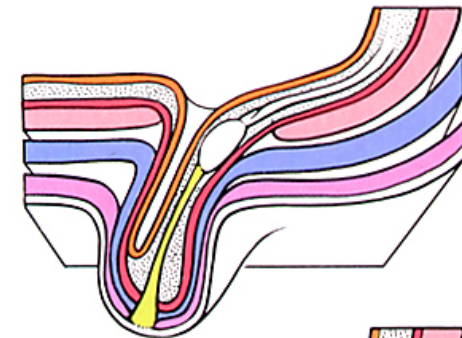
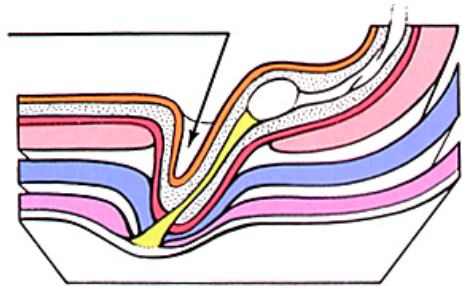


**C**



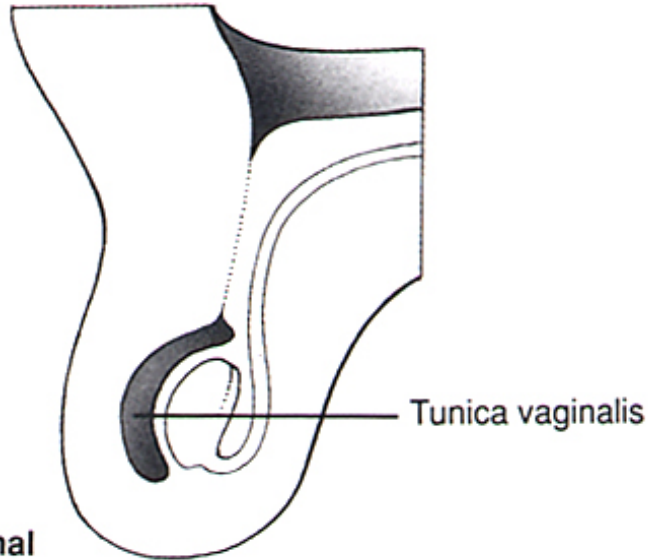


Processus vaginalis

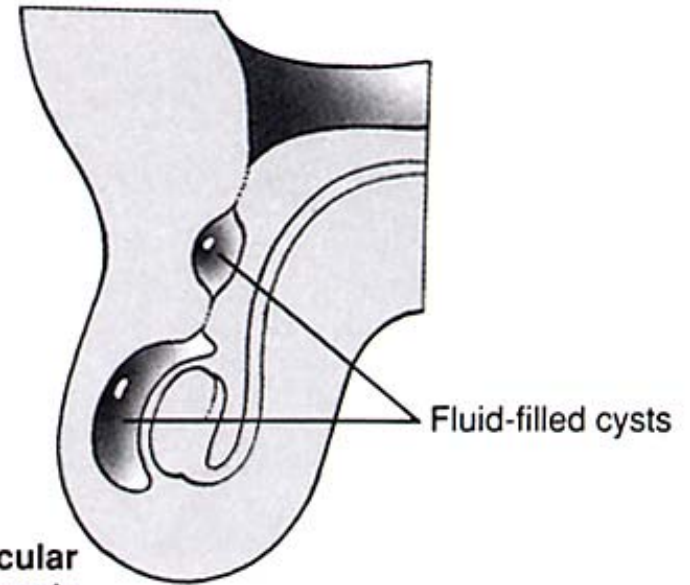


D

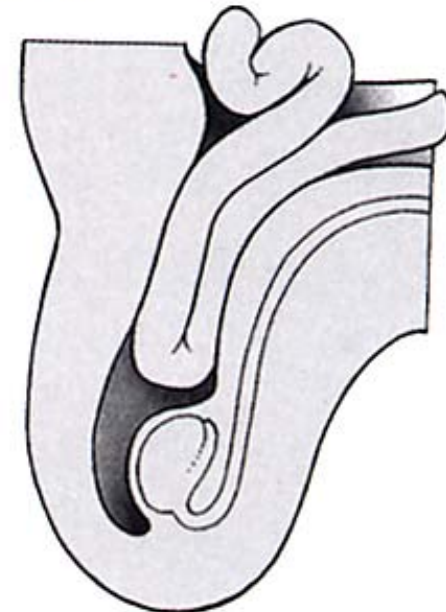
**A** Normal



**B** Testicular hydrocele

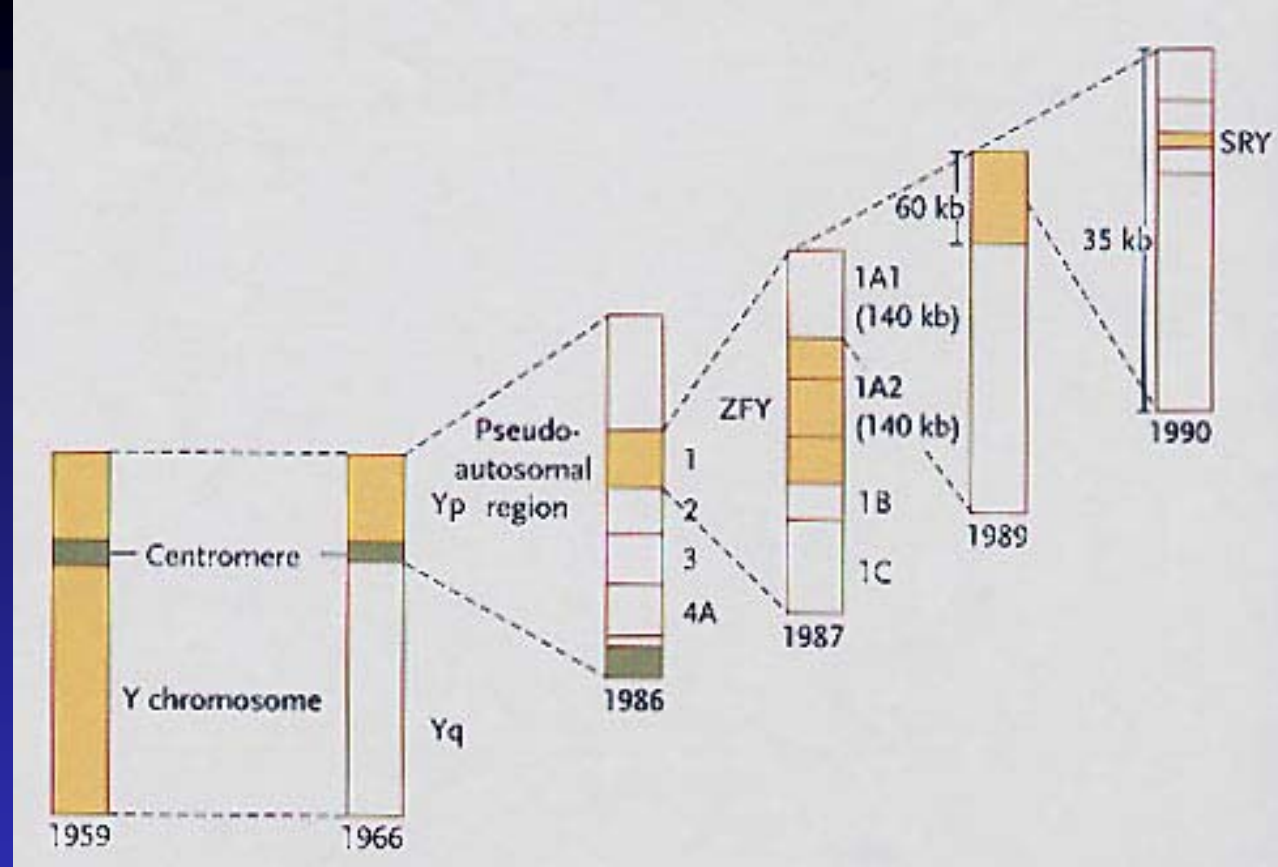


**C** Indirect inguinal hernia



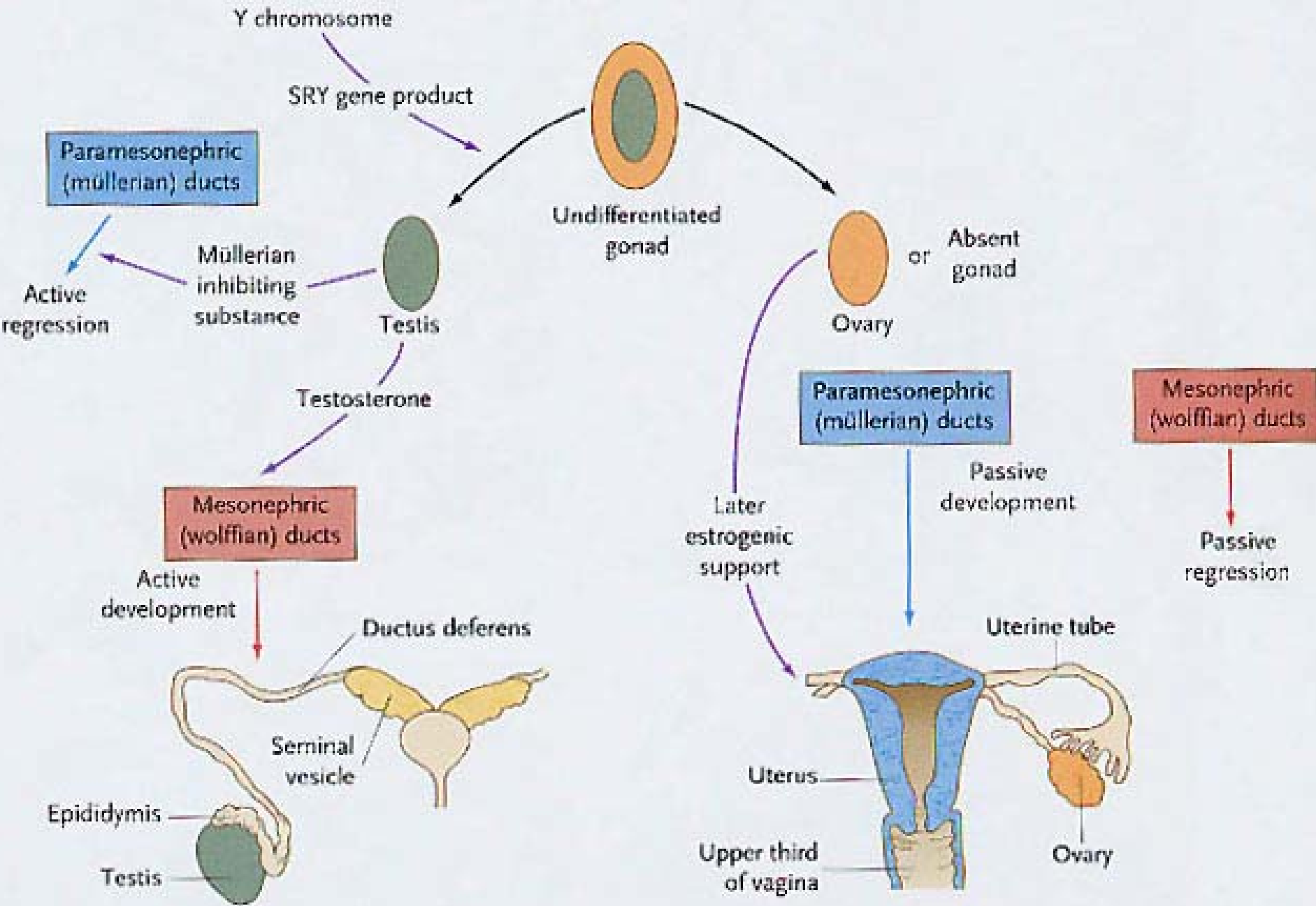
# Sex Determination

Genetic determination:  
female – XX  
male – XY



Y Chromosome - SRY – Sex-determining Region on the Y chromosome.  
Testis determination gene - DNA binding protein  
Expressed in Sertoli cells (not germ cells)  
Results in the induction of Leydig Cell differentiation  
Leydig Cell → Testosterone → Trigger male development (XX mice)





**Indifferent structure****Male derivative****Female derivative**

Genital ridge

Testis

Ovary

Primordial germ cells

Spermatozoa

Ova

Sex cords

Seminiferous tubules (Sertoli cells)

Follicular cells

Mesonephric tubules

Efferent ductules

Eoophoron

Paradidymis

Paroophoron

Mesonephric (wolffian) ducts

Appendix of epididymis

Appendix of ovary

Epididymal duct

Gartner's duct

Ductus deferens

Ejaculatory duct

Paramesonephric (müllerian) ducts

Appendix of testis

Uterine tubes

Prostate utricle

Uterus

Upper vagina

Definitive urogenital sinus (lower part)

Penile urethra

Lower vagina

Vaginal vestibule

Early urogenital sinus (upper part)

Urinary bladder

Urinary bladder

Prostatic urethra

Urethra

Genital tubercle

Penis

Clitoris

Genital folds

Floor of penile urethra

Labia minora

Genital swellings

Scrotum

Labia majora

# Genital Anomalies - Genetics

Hermaphroditism - ambiguous external genitalia

True hermaphrodite - both ovarian and testicular tissues

Generally 46,XX (crossing over, X with short arm of Y)

Ovotestes formation - medulla and cortex development

Male pseudohermaphroditism - 46,XY

External genitalia and ducts are intersex

Inadequate testosterone or abnormal MIS production

Female pseudohermaphroditism - 46,XX

Overproduction of androgens

Masculinization of genitalia - clitoral hypertrophy

Androgen insensitivity syndrome (Testicular feminization syndrome) - 46,XY - female in all ways but with testis - results from androgen receptor defects