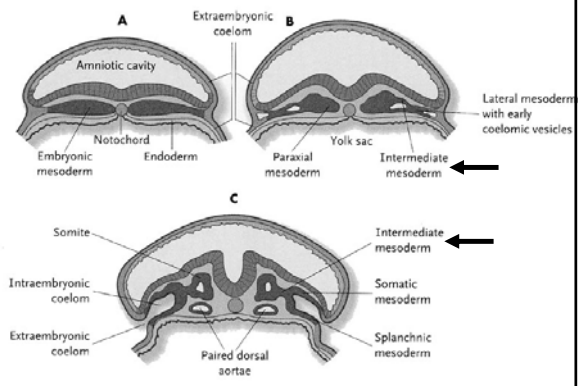
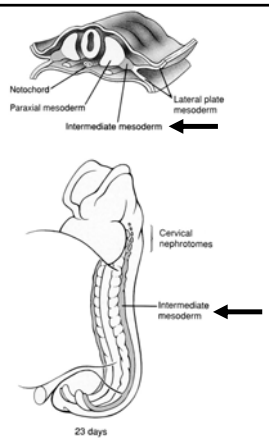
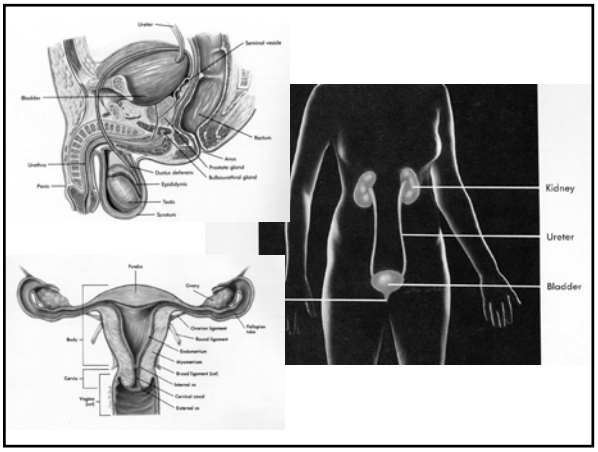
Urogenital Development

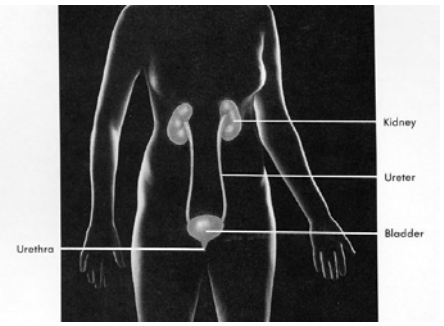
Intermediate Mesoderm
Interconnective - Urinary and Genital Systems
Recapitulation of Kidney Development
Epithelial-Mesenchymal Interactions
Indifferent Stage of Sexual Differention
Genetic vs. Environmental Factors







Urinary System - Kidneys



Kidneys, Ureter, Bladder, Urethra

Kidney Architecture

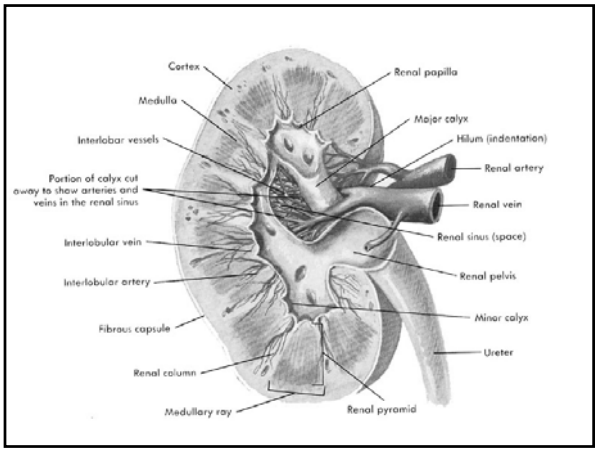
Renal Cortex:
- Renal corpuscle
- Convoluted tubules

Renal Medulla:
- Collecting ducts
- Loop of Henle

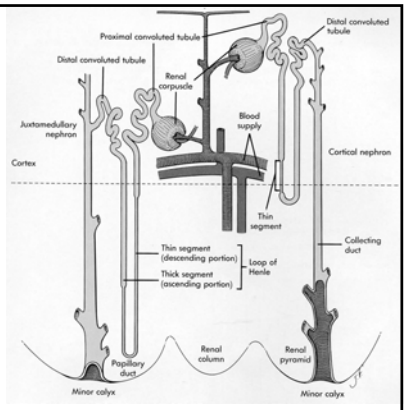
Each Minor calyx drains a tree of collecting ducts within a renal pyramid

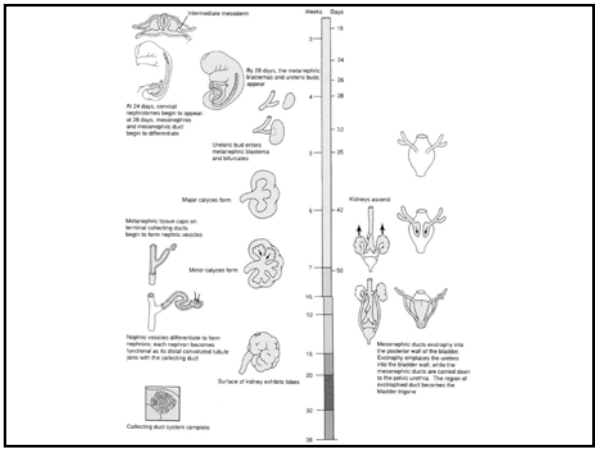
Pyramids are separated by columns of cortical tissues called renal columns

The Renal pyramids converge to form the renal papilla



Blood Renal artery
Glomerulus
Bowman's cap.
Proximal convoluted tubule
Loop of Henle
Distal convoluted tubule
Collecting duct
Minor calyx
Major calyx
Renal pelvis
Ureter
Bladder





Intermediate Mesoderm

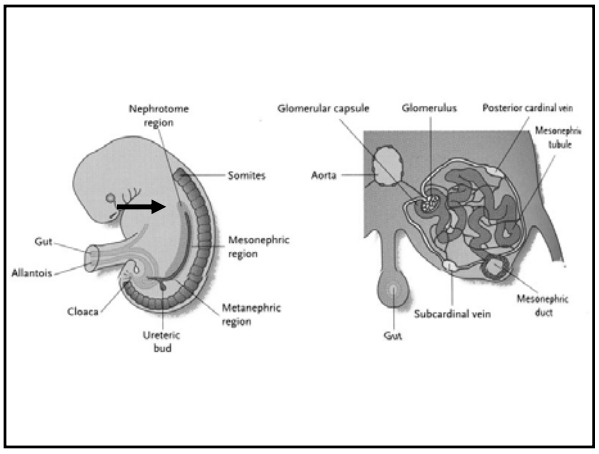
Early Development – 3 successive stages
Pronephros, Mesonephros, Metanephros

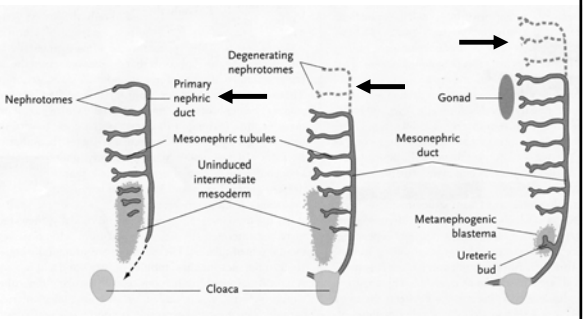
Pronephros- Most primitive Kidney
Cervical nephrotomes- 5–7 pairs of small hollow balls of epithelium – connected to the **primary nephric duct** (pronephric duct)

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

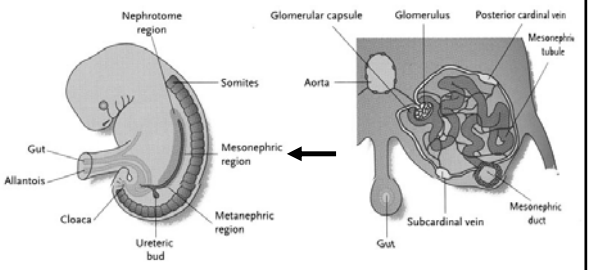
Mesonephric tubule differentiates a cup-shaped **Bowman's capsule** that wraps around the **Glomerulus**

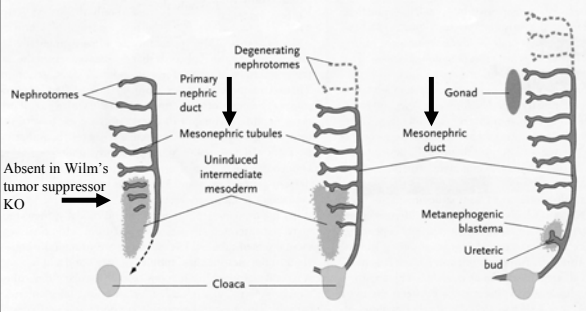
Glomerulus is a knot of capillaries

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

Mesonephic tubules connect to Mesonephric duct (Wolffian duct)

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





Mesonephric Duct

Initally a solid rod that grows caudally

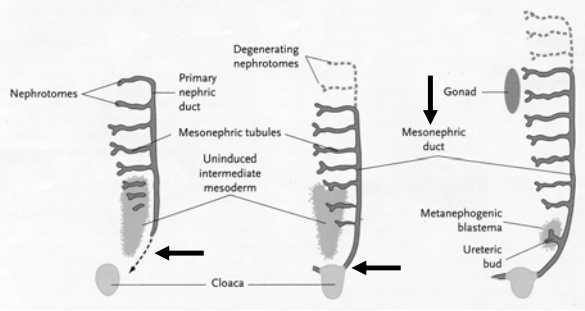
Diverges from intermediate mesoderm and fuses with the ventrolateral cloacal wall (future bladder)

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



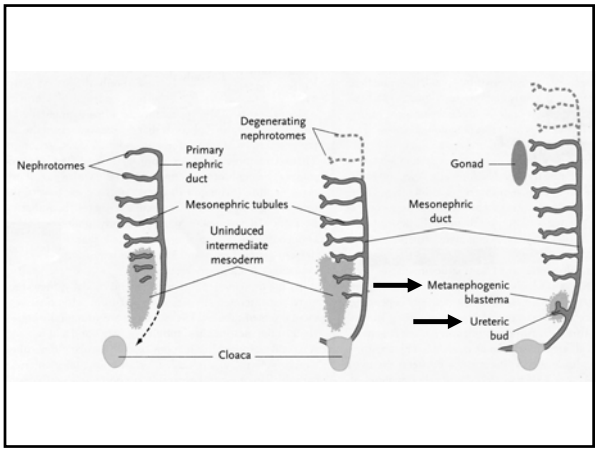
Metanephros

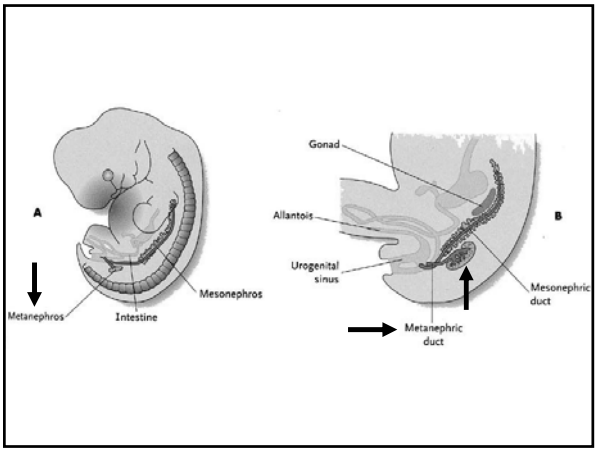
Ureteric Bud (Metanephric diverticulum)- outgrowth of the distal mesonephric duct

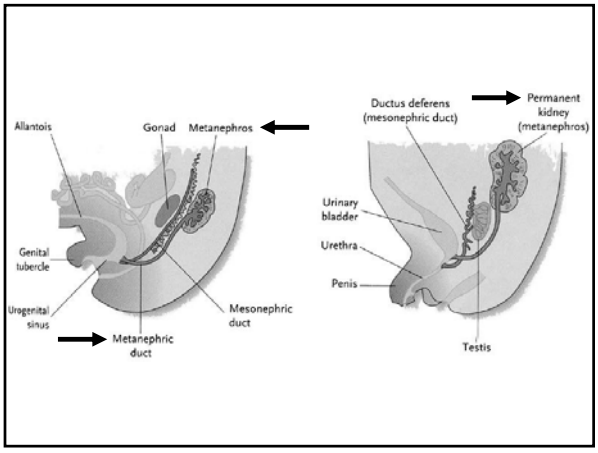
Metanephric blastema is the mesenchyme surrounding the ureteric bud

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

Bifurcation results in two ampulla each with its blastema







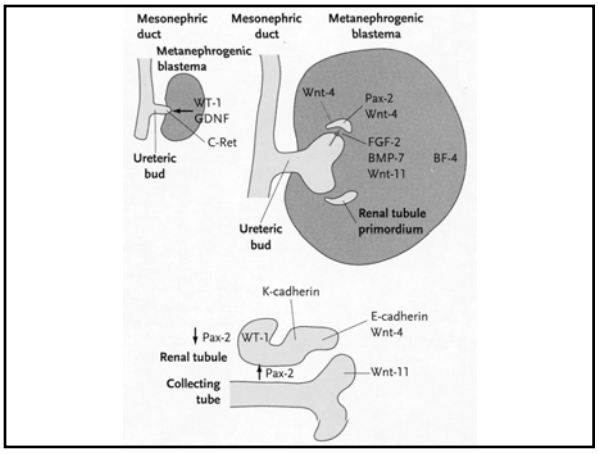
Ureteric Bud/Metanephric Blastema

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)



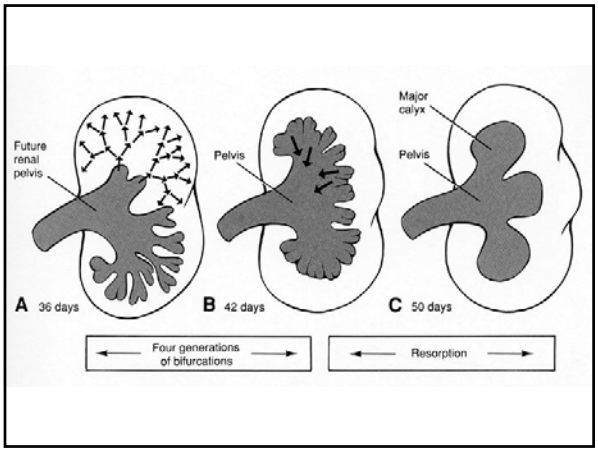
Ureteric Bud Branching

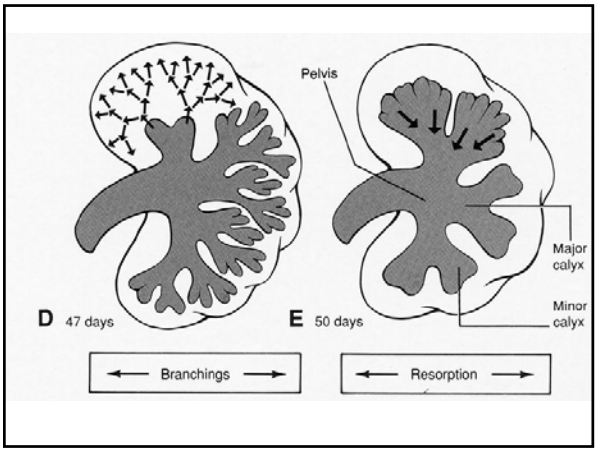
Branching of the Ureteric bud gives developing kidney a lobular appearance, Sulcus separates the lobes

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

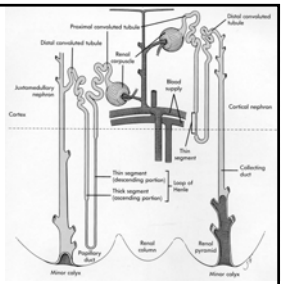
Next 4 bifurcations coalesce to form the Minor Calyces

11 more branches forms 1-3 million collecting tubules





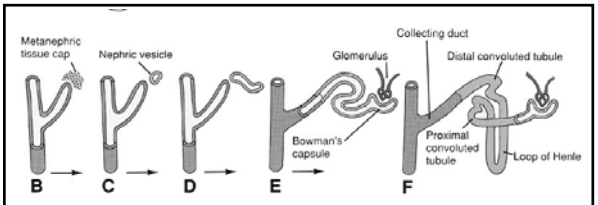
Nephron



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 convuluted tubule fuses with the collecting duct.



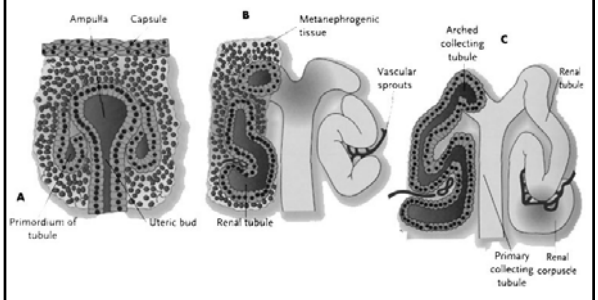
Renal corpuscle = Bowman's capsule/glomerulus. The nephron is the metanephric excretory unit.

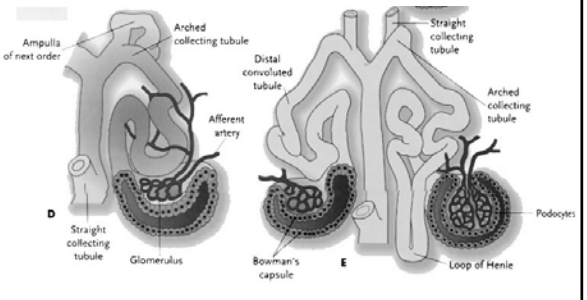
The origin of the Renal corpuscle and tubules is distinct from the collecting duct (Metanephric duct)

Duct systems merge

Renal duct – sequence of differentiation
renal corpuscle → proximal tubule → distal tubule

Loop of Henle elongates into the medulla





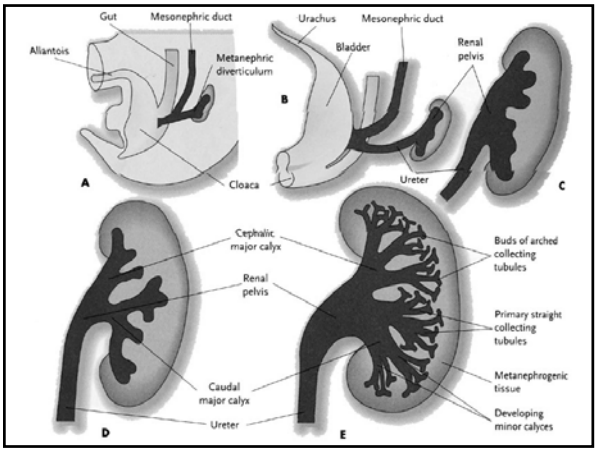
Late Changes

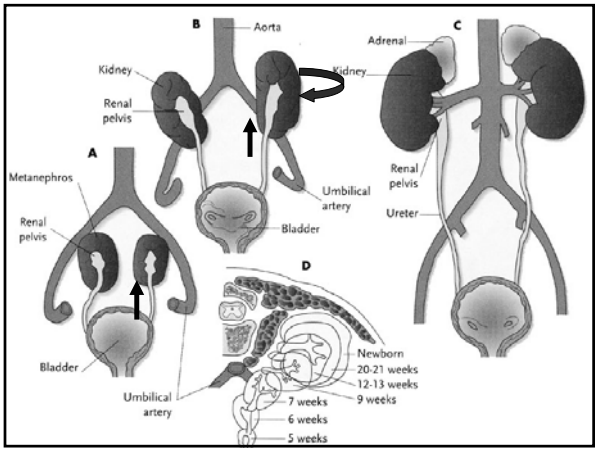
Branching system becomes larger forming the pelvis and calyces.

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 90º so that the renal pelvis is facing the midline

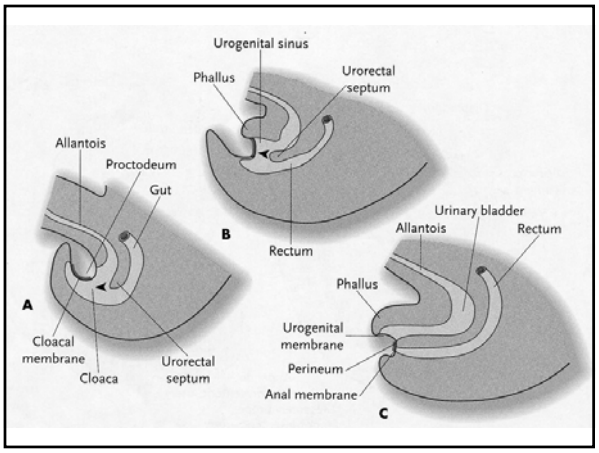




Urogenital Sinus

Urogenital sinus forms:
- Bladder
- Pelvic urethra
- Definitive urogenital sinus

	Males	**Females**
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina



Bladder Formation

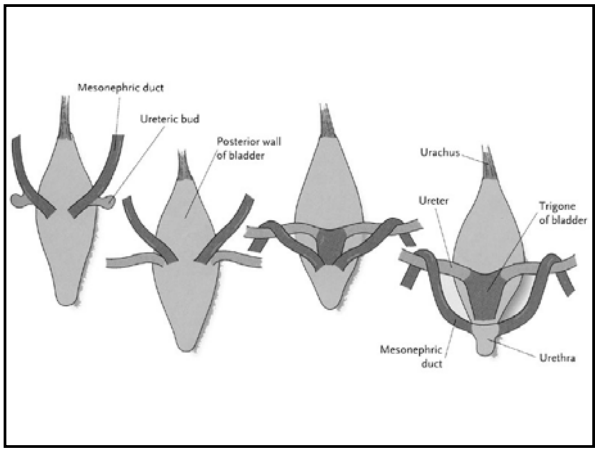
The ureter drains into the mesonephric duct that drains into the bladder

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 mesonephic duct migrates)



Urinary System Anomalies

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

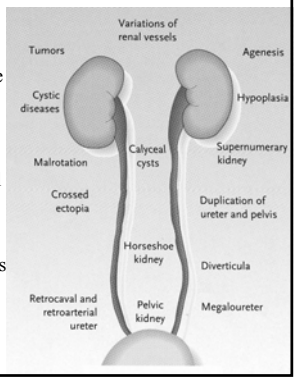
Renal agensis – unilateral or bilateral

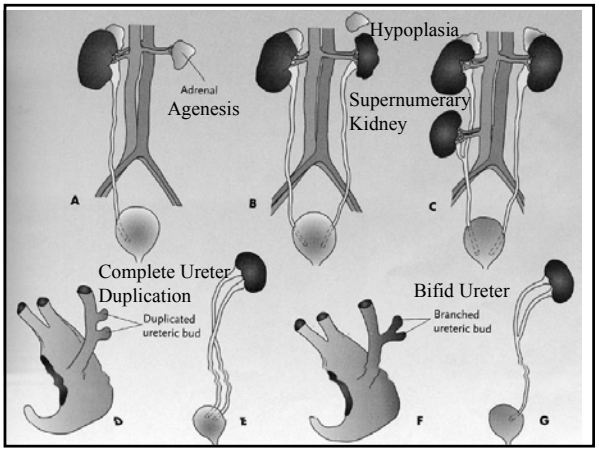
Supernumerary kidney

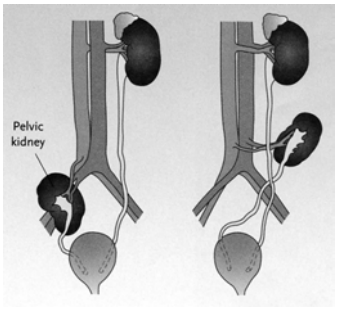
Crossed ectopia – migration problem

Horseshoe kidney – fusion of kidneys fails to ascend

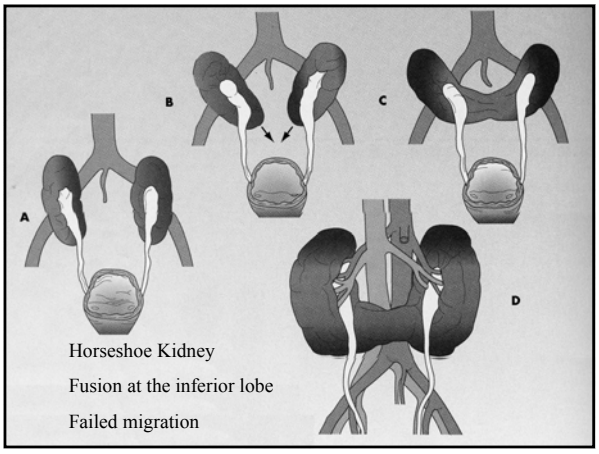
Bifid ureter - bifurcation of the ureteric bud







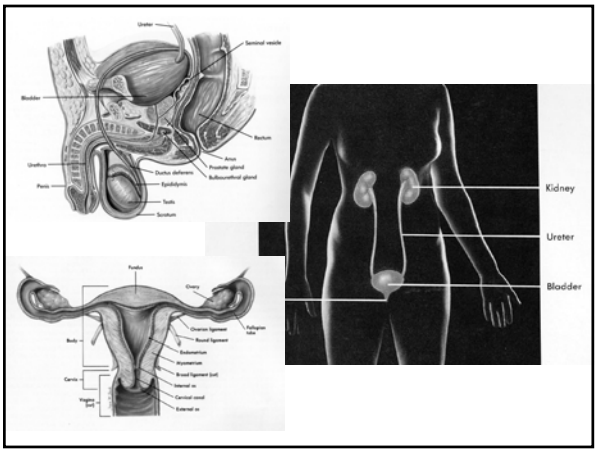
Migration Anomalies: Pelvic Kidney and Crossed Ectopia



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)

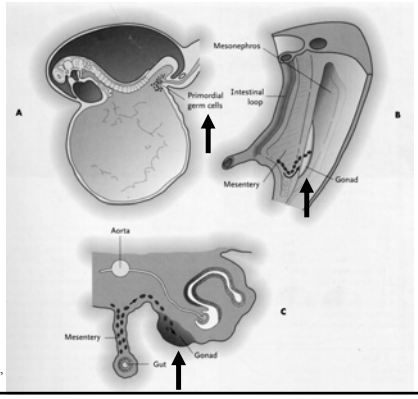
Mitosis

Female - ovary, sex cords cells → ovarian follicle

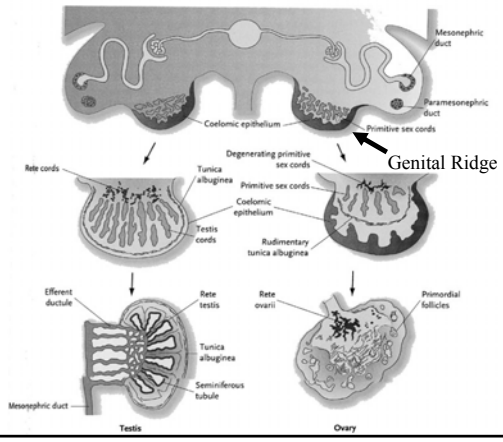
Male - testis, sex cord cells → Sertoli cells of the seminiferous tubules

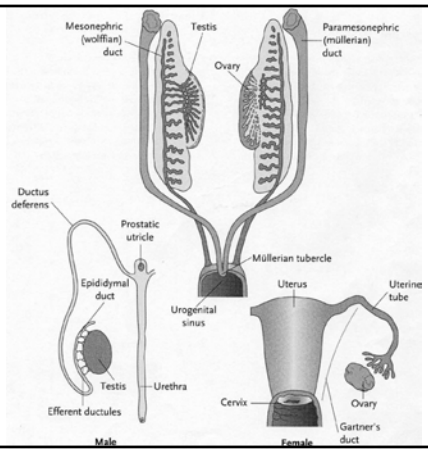
Sex cord cells are essential for gametogenesis.

Gametogenesis – Germ Cells



From BM Carlson, 1999





Genital Ridge

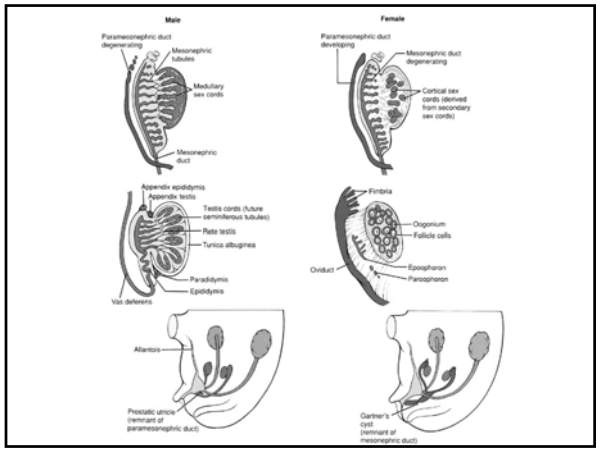
Supporting cells from the mesonephrose and coelomic epithelium invade the genital ridge and aggregate around the primordial germ cells to form the primary sex cords

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



Mullerian Duct

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

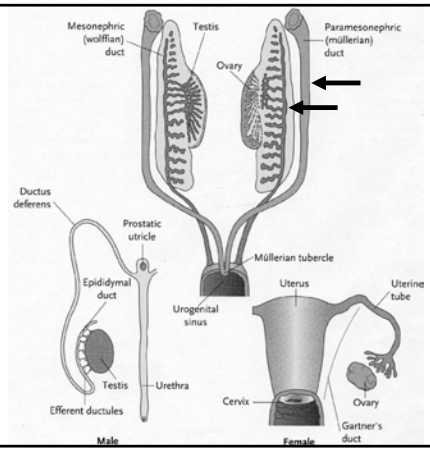
Mullerian ducts is an invagination of coelomic epithelium
- Cranially at the 3rd thoracic segment
- Caudally they elongate, join and fuse with the urogenital sinus (medial to the mesonephric ducts)

At this time the mesonephric duct opens into the pelvic urethra

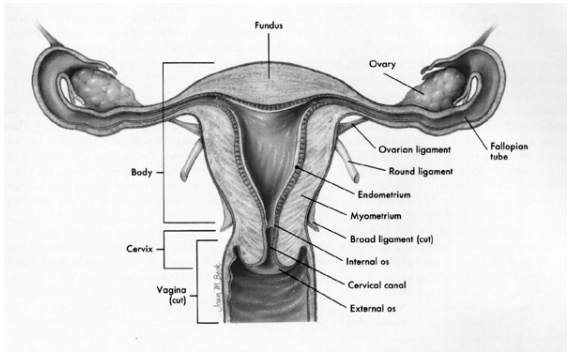
The site of fusion with the pelvic urethra is called the Mullerian tubercle

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



From Seeley, Stephens and Tate, 1989

Female Reproductive Tract

Ovary - Oogenesis

Uterine (Fallopian) Tube
- Fimbriare (finger like projections of Infundibulum)
- Infundibulum
- Ampulla – Fertilization
- Isthmus

Uterus - endometrium, myometrium, perimetrium

Cervix

Vagina

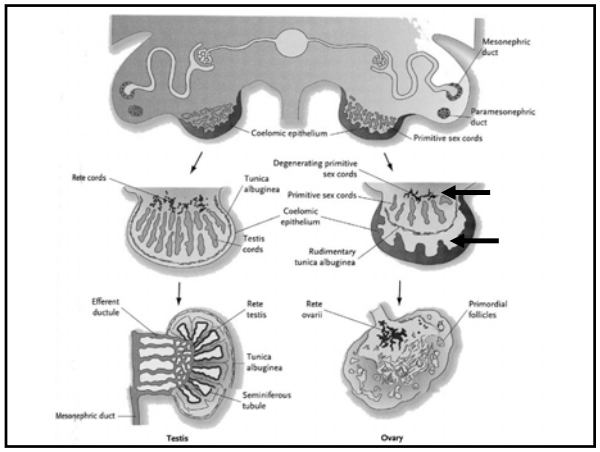
Ovary

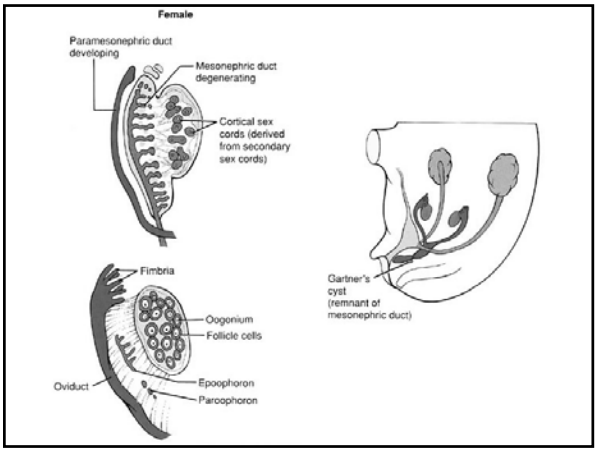
Primitive (medullary) sex cords degenerate and secondary sex cords form from cortical tissues - called Cortical sex cords

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.





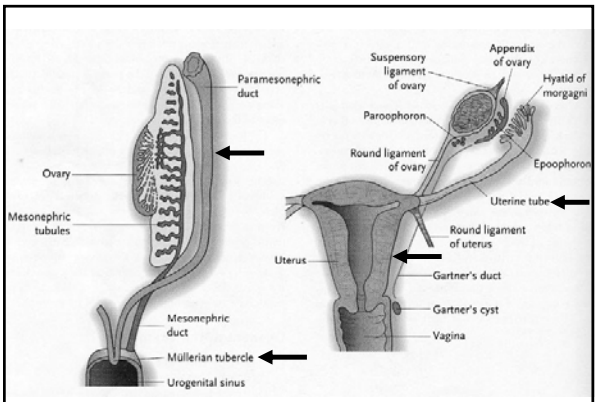
Mullerian Ducts Develop in Female

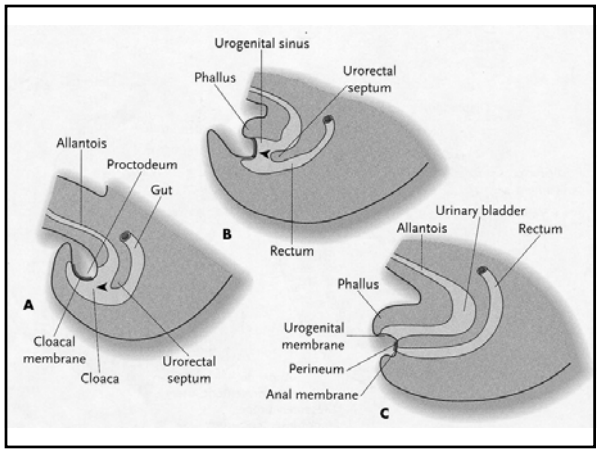
In the absence of testosterone:
- The mesonephric duct degenerates
- The Mullerian duct develops uninhibited

Mullerian duct- cranial funnel-shaped opening to the coelom forms the fimbriare 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

	Males	**Females**
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina

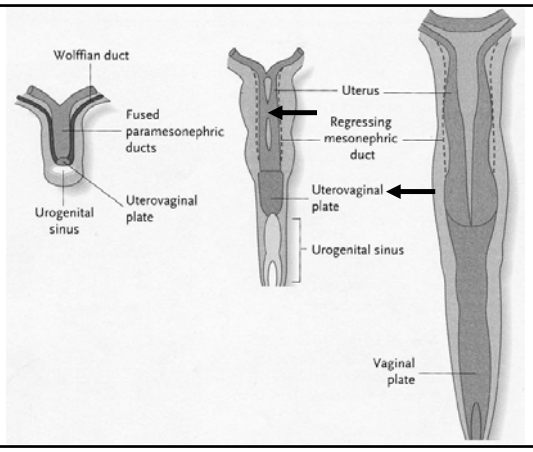
Uterus and Vagina

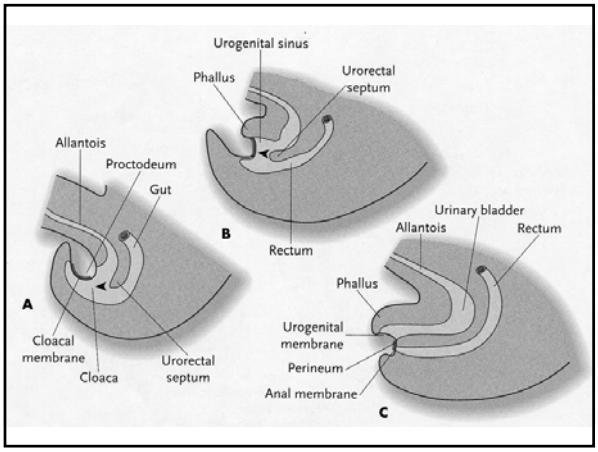
The cranial end of the uterovaginal canal forms the uterus

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

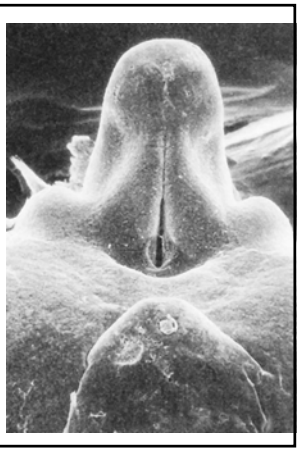
Initially the same in both sexes – **Indifferent stage**

Genital folds flank the urogenital membrane

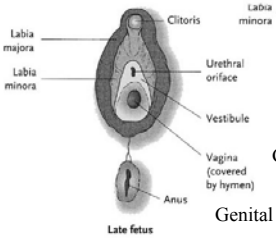
The anterior genital folds forms the **genital tubercle**

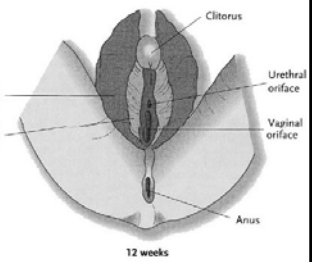
Lateral to the genital folds are the **genital swellings**

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



Phallus becomes the clitoris

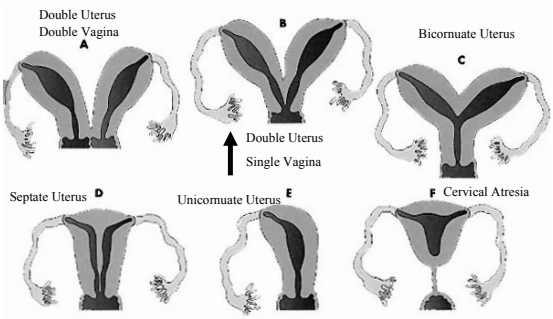




Genital folds become the labia minora

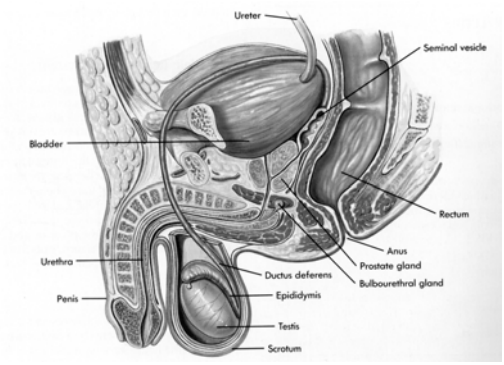
Genital swellings become the labia majora

Genital Anomalies - Females



Uterus and Vaginal anomalies

Male Reproductive Tract



From Seeley, Stephens and Tate, 1989

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.

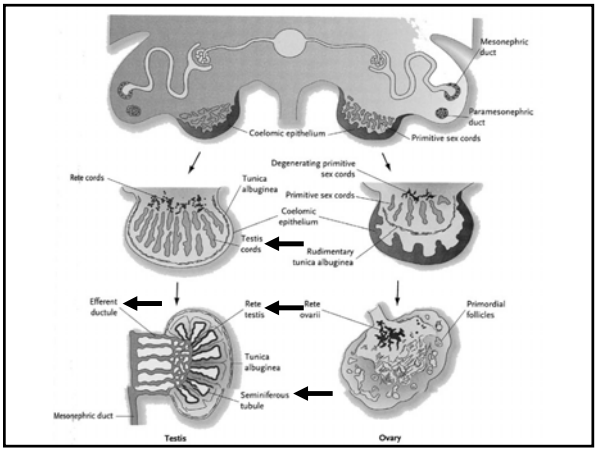
The medullary sex cord cells form the testis cords that contain Sertoli cells

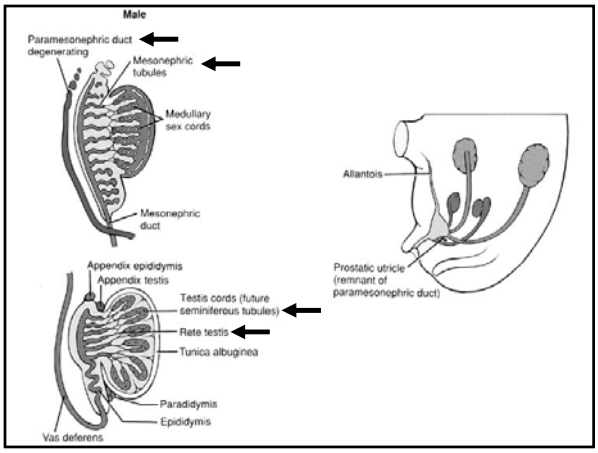
Regions of the testis cords that contain germ cells will canalize and form the seminiferous tubules of the mature testis.

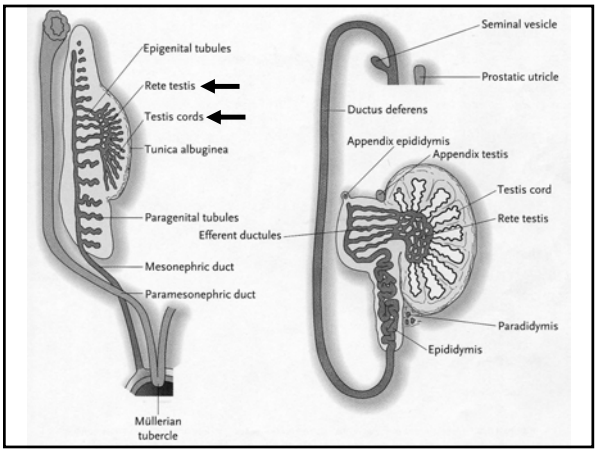
The inner portion of the testis cords form the Rete testis

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







Mesonephric Duct Develops in Males

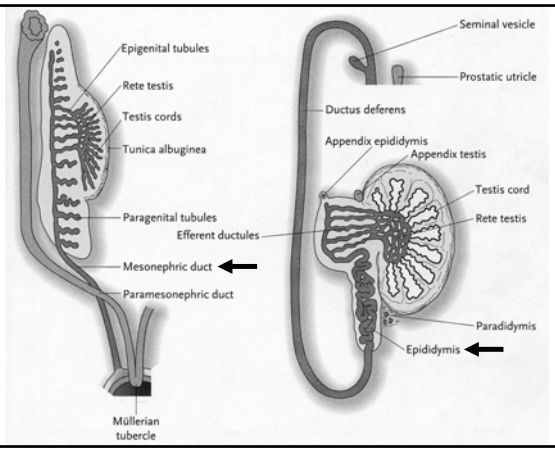
The male utilizes the mesonephric duct while the paramesonephric (Mullerian) duct degenerates.

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

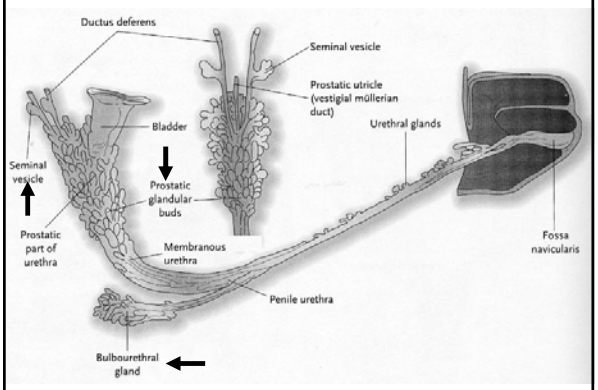
Futher caudally the mesonephric duct becomes the ductus deferens and drains into the urethra

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

	Males	**Females**
Pelvic Urethra	Membranous & Prostatic Urethra	Urethra
Definitive Urogenital Sinus	Penile Urethra	Vagina

External Genitalia

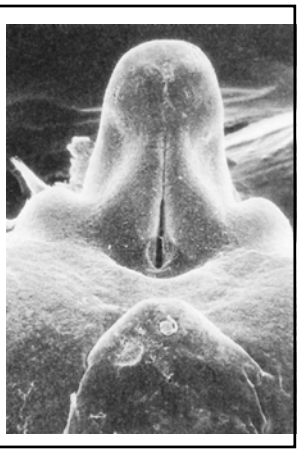
Initially the same in both sexes – **Indifferent stage**

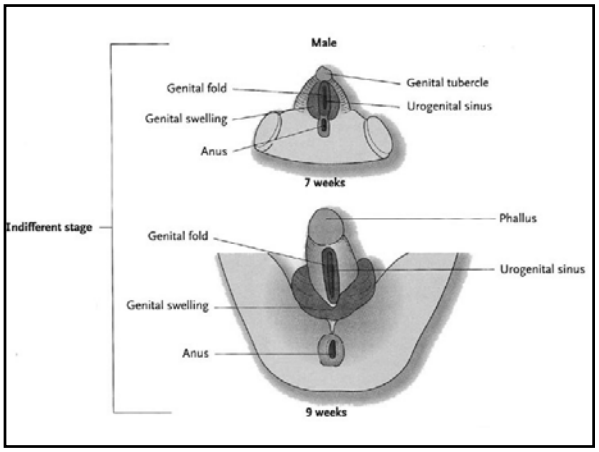
Genital folds flank the urogenital membrane

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**





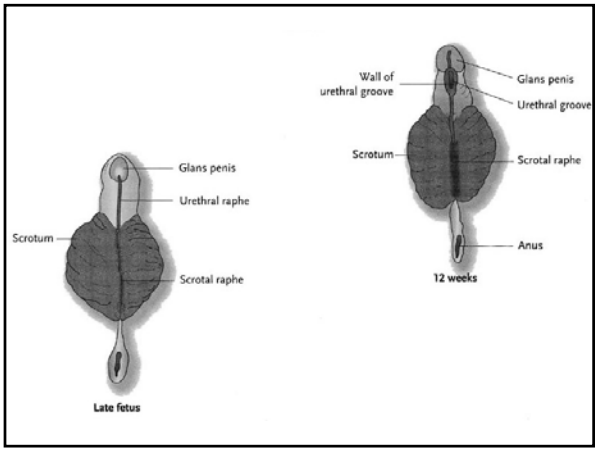
Male Genitalia

Phallus elongates

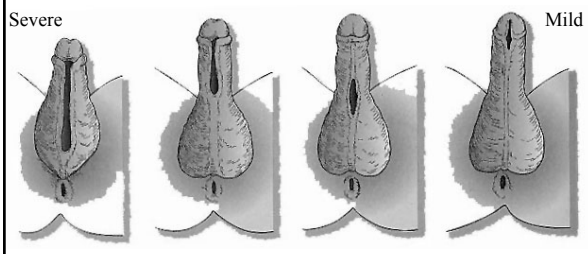
Genital swellings enlarge and fuse to form the scrotum

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



Hypospadia – Ventral opening of urethra

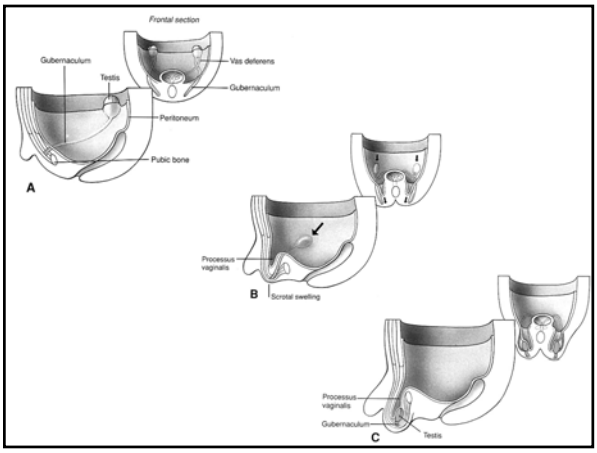
Descent of the gonads

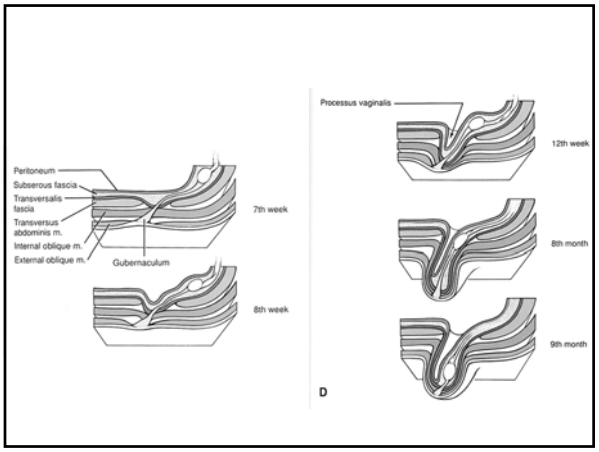
Both male and female gonads descend from the 10th thoracic level

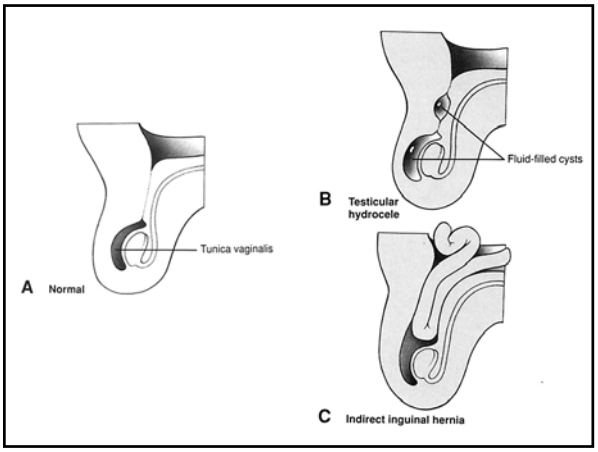
Females descend less than males

In Males there are 3 phases of the descent

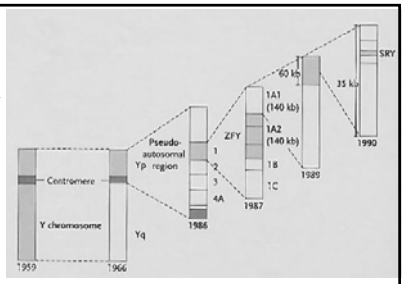
1) Caudal displacement due to regression of the mesonephic kidneys
2) Transabdominal descent to the Inguinal ring caused by regression of the Mullerian ducts (MIS activity)
3) Transinguinal descent into the scrotum guided by the gubernaculum into the vaginal process (evagination of the caudal abdominal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





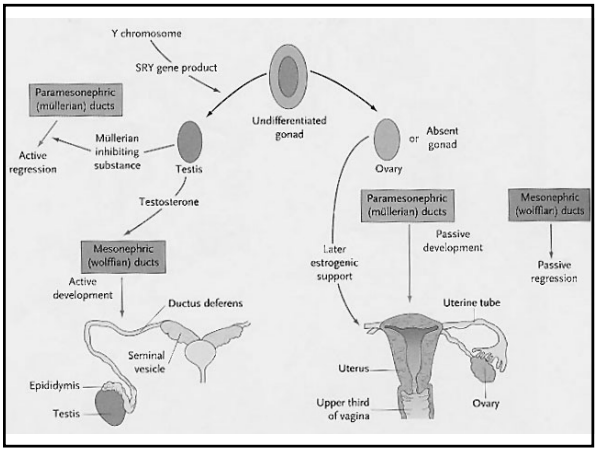


Sex Determination



Genetic determination:
female – XX
male – XY

Y Chromosome - SRY – **S**ex-determining **R**egion 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	Epoophoron
	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