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
Diagram A: Extraembryonic coelom
- Amniotic cavity
- Notochord
- Embryonic mesoderm
- Endoderm

Diagram B: Lateral mesoderm with early coelomic vesicles
- Paraxial mesoderm
- Yolk sac

Diagram C: Intermediate mesoderm
- Somite
- Intraembryonic coelom
- Extraembryonic coelom
- Paired dorsal aortae
- Somatic mesoderm
- Splanchnic mesoderm
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
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 extrophy into the posterior wall of the bladder. Extrophy emplaces the ureter into the bladder wall, while the mesonephric ducts are carried down to the pelvic urethra. The region of extrophied 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
Absent in Wilm’s tumor suppressor KO
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.
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
Urogenital Sinus

<table>
<thead>
<tr>
<th>Urogenital sinus forms:</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Urethra</td>
<td>Membranous &amp; Prostatic Urethra</td>
<td>Urethra</td>
</tr>
<tr>
<td>Definitive Urogenital Sinus</td>
<td>Penile Urethra</td>
<td>Vagina</td>
</tr>
</tbody>
</table>
Bladder Formation

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

The wall of the bladder expands and the mouth of the mesonephric duct flares so the mesonephric duct blends 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).
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
Agenesis

Hypoplasia

Supernumerary Kidney

Complete Ureter Duplication

Bifid Ureter
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.
Genital Ridge
Genital Ridge

Supporting cells from the mesonephroose 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

<table>
<thead>
<tr>
<th>Pelvic Urethra</th>
<th><strong>Males</strong></th>
<th><strong>Females</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Membranous &amp;</td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td>Prostatic Urethra</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitive Urogenital Sinus</th>
<th><strong>Males</strong></th>
<th><strong>Females</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penile Urethra</td>
<td></td>
<td>Vagina</td>
</tr>
</tbody>
</table>
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
- Bicornuate Uterus
- Septate Uterus
- Unicornuate Uterus
- Cervical Atresia

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

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

<table>
<thead>
<tr>
<th>Pelvic Urethra</th>
<th><strong>Males</strong></th>
<th><strong>Females</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Membranous &amp;</td>
<td>Urethra</td>
</tr>
<tr>
<td></td>
<td>Prostatic Urethra</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitive Urogenital Sinus</th>
<th>Penile Urethra</th>
<th>Vagina</th>
</tr>
</thead>
</table>
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

- Genital fold
- Genital swelling
- Genital tubercle
- Urogenital sinus
- Anus

7 weeks

Phallus

9 weeks

- Genital fold
- Genital swelling
- Urogenital sinus
- Anus
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

Hypospadias – Ventral opening of urethra

Severe

Mild
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 mesonephric 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 – 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 $\rightarrow$ Testosterone $\rightarrow$ Trigger male development (XX mice)
<table>
<thead>
<tr>
<th>Indifferent structure</th>
<th>Male derivative</th>
<th>Female derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital ridge</td>
<td>Testis</td>
<td>Ovary</td>
</tr>
<tr>
<td>Primordial germ cells</td>
<td>Spermatozoa</td>
<td>Ova</td>
</tr>
<tr>
<td>Sex cords</td>
<td>Seminiferous tubules (Sertoli cells)</td>
<td>Follicular cells</td>
</tr>
<tr>
<td>Mesonephric tubules</td>
<td>Efferent ductules</td>
<td>Eoophoron</td>
</tr>
<tr>
<td></td>
<td>Paradidymis</td>
<td>Paroophoron</td>
</tr>
<tr>
<td>Mesonephric (wolfian) ducts</td>
<td>Appendix of epididymis</td>
<td>Appendix of ovary</td>
</tr>
<tr>
<td></td>
<td>Epididymal duct</td>
<td>Gartner's duct</td>
</tr>
<tr>
<td></td>
<td>Ductus deferens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ejaculatory duct</td>
<td></td>
</tr>
<tr>
<td>Paramesonephric (müllerian) ducts</td>
<td>Appendix of testis</td>
<td>Uterine tubes</td>
</tr>
<tr>
<td></td>
<td>Prostate utricle</td>
<td>Uterus</td>
</tr>
<tr>
<td>Definitive urogenital sinus (lower part)</td>
<td>Penile urethra</td>
<td>Upper vagina</td>
</tr>
<tr>
<td>Early urogenital sinus (upper part)</td>
<td>Urinary bladder</td>
<td>Lower vagina</td>
</tr>
<tr>
<td></td>
<td>Prostatic urethra</td>
<td>Vaginal vestibule</td>
</tr>
<tr>
<td>Genital tubercle</td>
<td>Penis</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Genital folds</td>
<td>Floor of penile urethra</td>
<td>Urethra</td>
</tr>
<tr>
<td>Genital swellings</td>
<td>Scrotum</td>
<td>Clitoris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Labia minora</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Labia majora</td>
</tr>
</tbody>
</table>
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