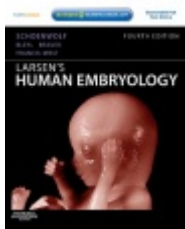
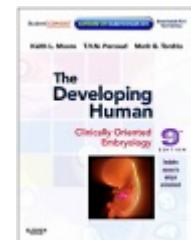


# Development of the Reproductive System



Resources:  
<http://php.med.unsw.edu.au/embryology/>  
Larsen's Human Embryology  
The Developing Human: Clinically Oriented Embryology



Dr Annemiek Beverdam – School of Medical Sciences, UNSW  
Wallace Wurth Building Room 234 – A.Beverdam@unsw.edu.au

# Lecture overview

Anatomy of the reproductive system

Sex determination

Embryonic origins of the reproductive system

Gonad development

Development of the reproductive tract

Development of the external genitalia

Development of secondary sex characteristics

Disorders of sexual development

# Lecture overview

## **Anatomy of the reproductive system**

### **Sex determination**

Embryonic origins of the reproductive system

Gonad development

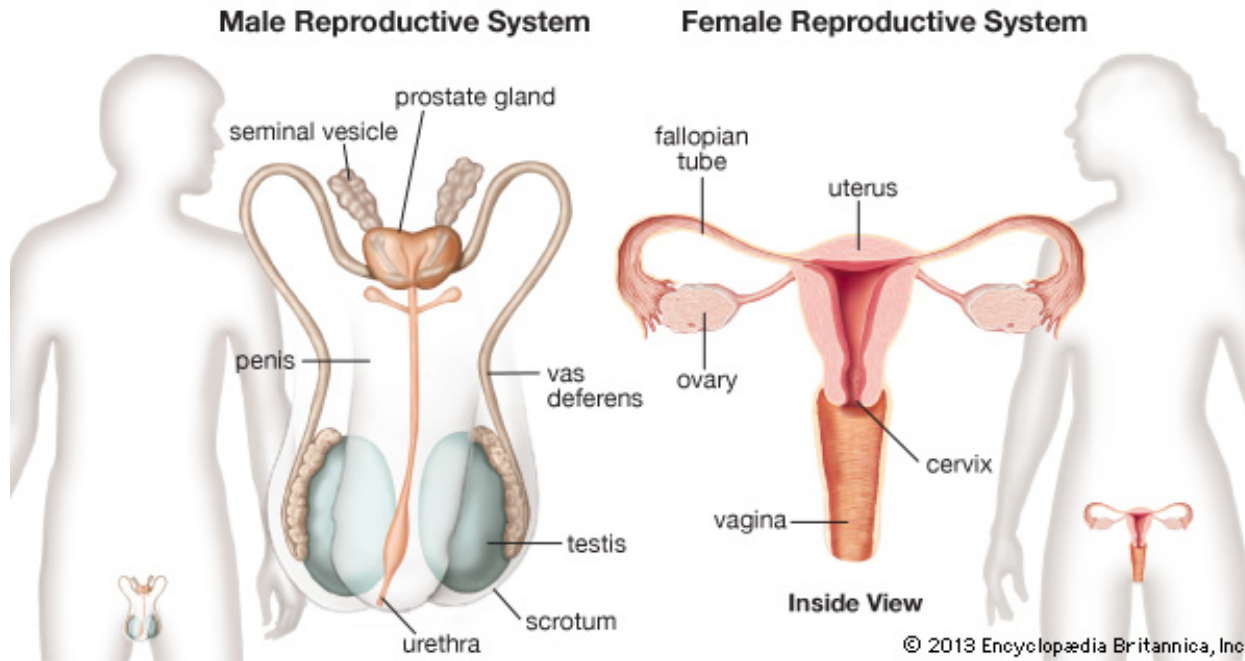
Development of the reproductive tract

Development of the external genitalia

Development of secondary sex characteristics

Disorders of sexual development

# Anatomy of the reproductive system



XY gonads: testes

XY reproductive tract:

- Epididymis
- Vas deferens
- Accessory glands:
  - prostate
  - bulbourethral gland
  - seminal vesicle
- Urethra

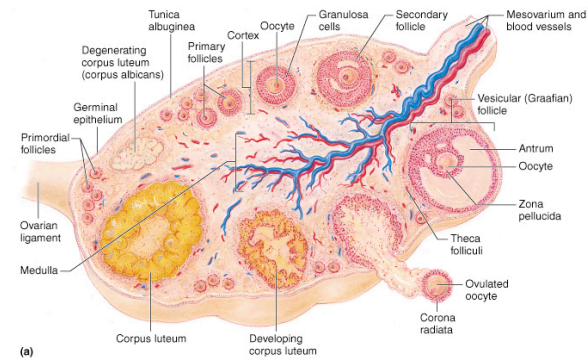
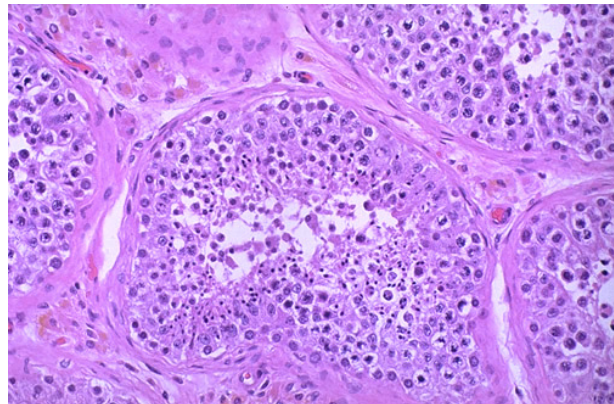
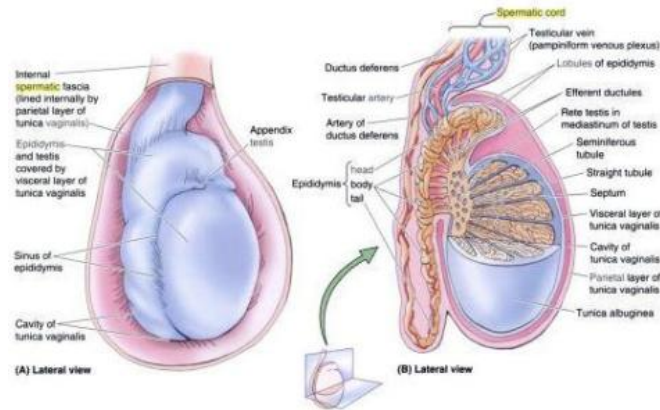
XX gonads: ovaries

XX reproductive tract:

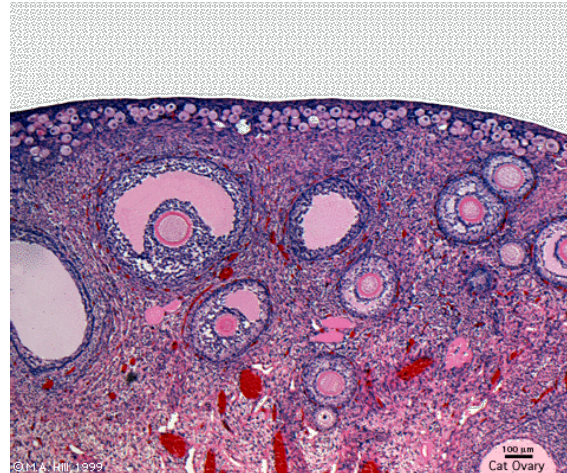
- Fallopian tubes
- Uterus
- Cervix
- Vagina

# Anatomy of the reproductive system

## Gonads



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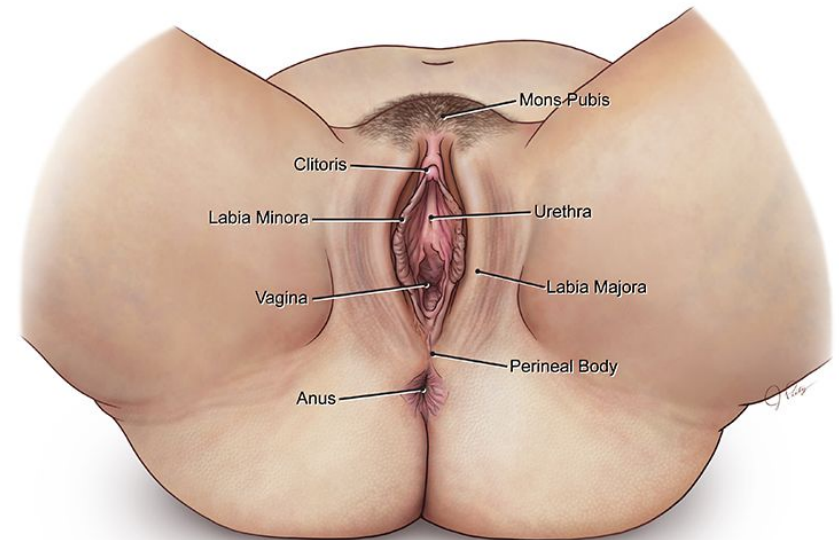
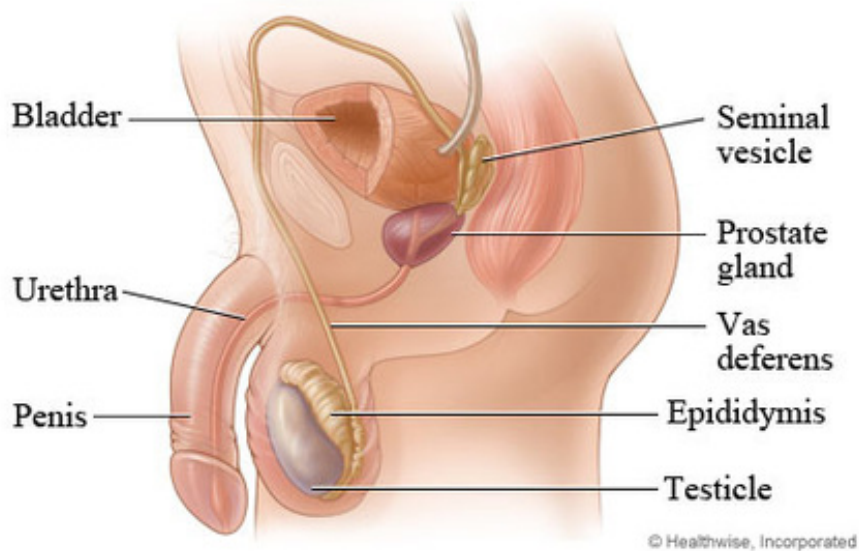


XY: Testes  
 Seminiferous tubules  
 Maturing sperm  
 Supporting cell type: Sertoli cells  
 Steroid producing cell type: Leydig cells

XX: Ovaries  
 Follicles  
 Maturing oocytes  
 Supporting cell type: Granulosa cells  
 Steroid producing cell type: Theca cells

# Anatomy of the reproductive system

## External genitalia



XY:

Glans penis  
Penis shaft  
Scrotum

XX:

Clitoris  
Labia minora  
Labia majora  
Vaginal opening

# Sex determination

Three factors determine gender phenotype:

## 1. Genetic sex

- Dependent on sex chromosomes: XX or XY
- Determined at conception

## 2. Development of the reproductive system (gonads, tracts, genitalia)

- Dependent on gonad development
- Occurs during embryonic development

## 3. Development of secondary sex characteristics

- Dependent on hormones
- Occurs during puberty

# Lecture overview

Anatomy of the reproductive system

Sex determination

## **Embryonic origins of the reproductive system**

Gonad development

Development of the reproductive tract

Development of the external genitalia

Development of secondary sex characteristics

Disorders of sexual development



# Embryonic origins of the reproductive system

## Trilaminar embryo

### Ectoderm (Neural crest)

brain, spinal cord, eyes, *peripheral nervous system*  
epidermis of skin and associated structures,  
*melanocytes, cranial connective tissues (dermis)*

### Mesoderm

musculo-skeletal system, limbs  
connective tissue of skin and organs  
urogenital system, heart, blood cells

### Endoderm

epithelial linings of gastrointestinal and respiratory tracts

### Germ cells

# Embryonic origins of the reproductive system

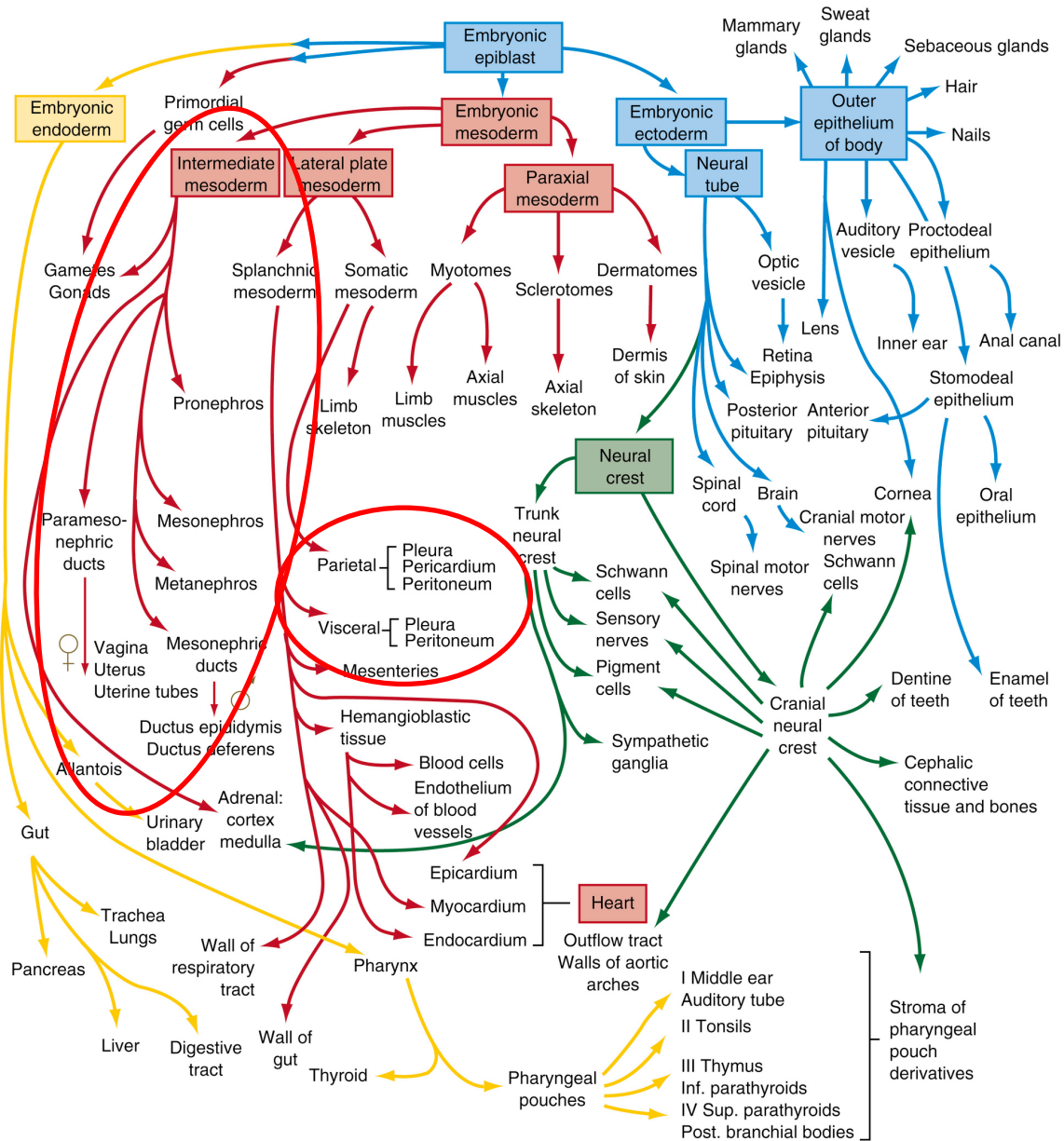
Intermediate Mesoderm  
Coelomic Epithelium (Lateral Plate Mesoderm)  
Primordial Germ Cells



Week 4 embryo

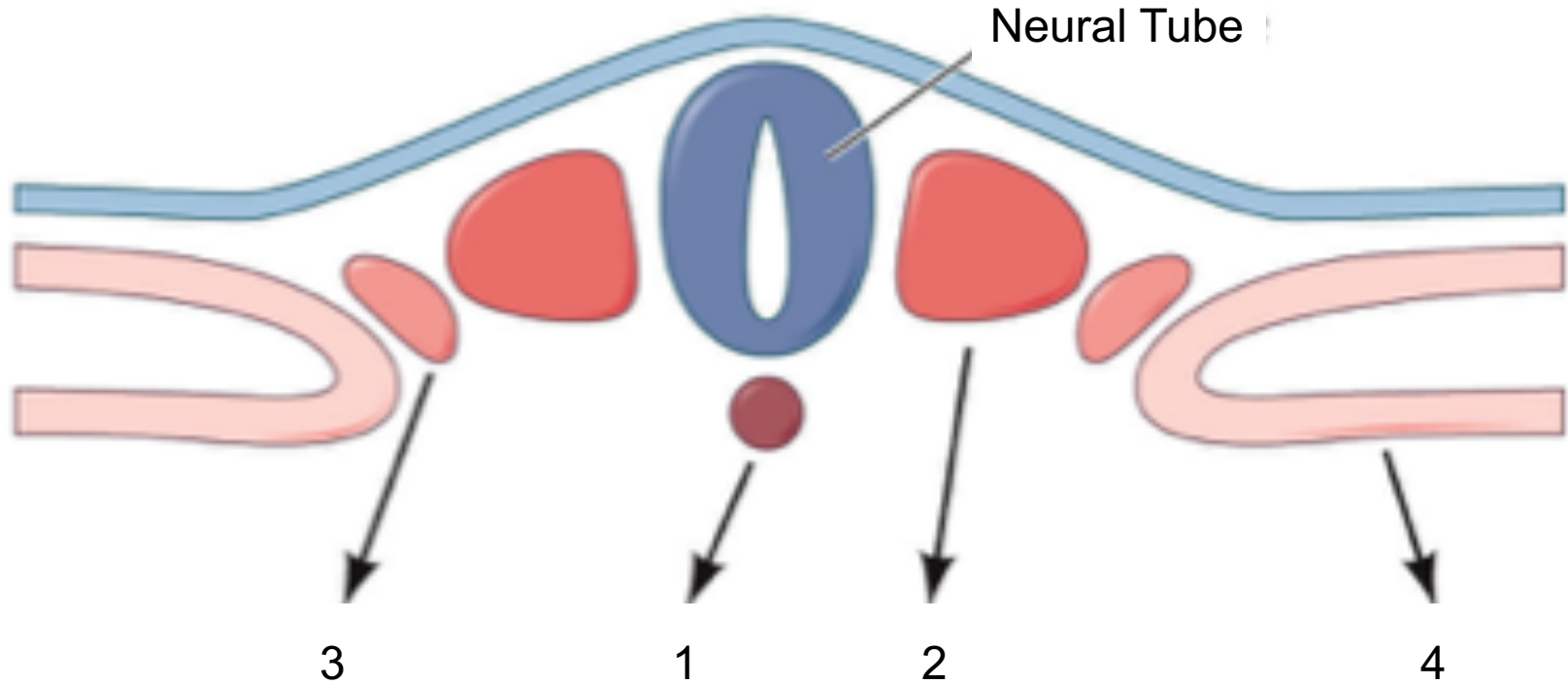
# Embryonic origins of the reproductive system

Primordial germ cells



# Embryonic origins of the reproductive system

## Intermediate Mesoderm



1: notochord

2: paraxial mesoderm

**3: intermediate mesoderm**

4: lateral plate mesoderm

# Embryonic origins of the reproductive system

## Intermediate mesoderm

### Mesonephros:

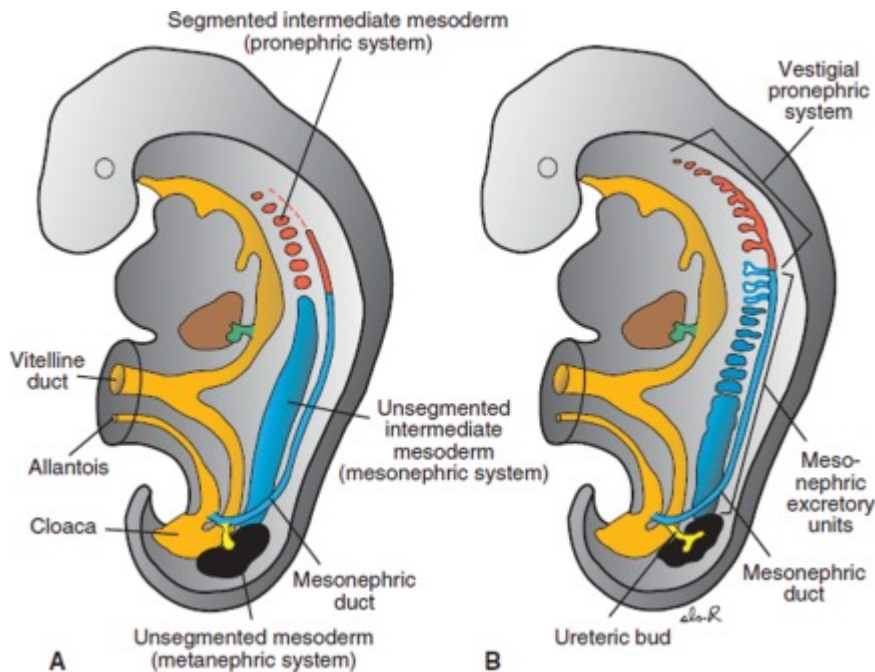
Mesonephric mesoderm

Mesonephric (Wolffian) duct (and tubules)

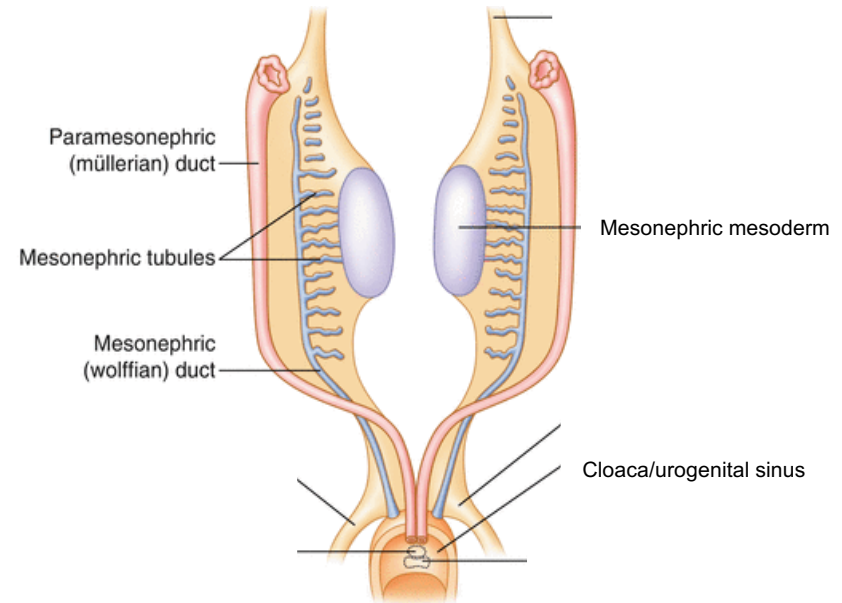
Paramesonephric (Müllerian) duct

Cloaca/urogenital sinus

Ureteric bud



### Bipotential reproductive system



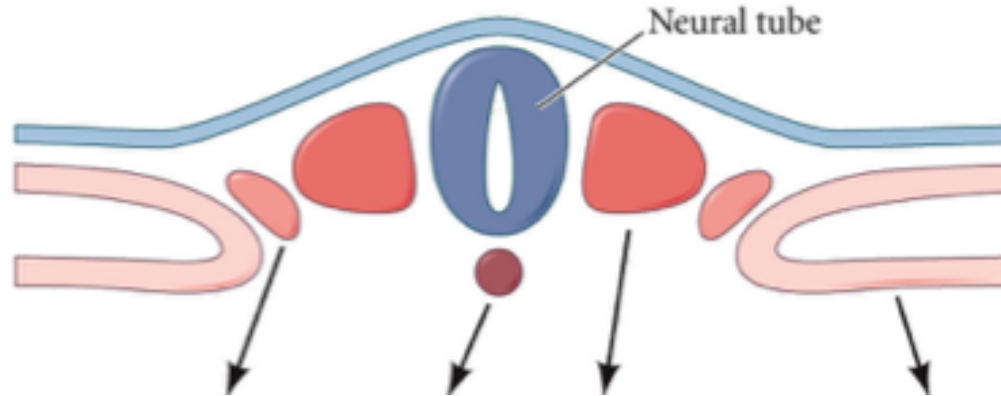
# Embryonic origins of the reproductive system

## Coelomic Epithelium

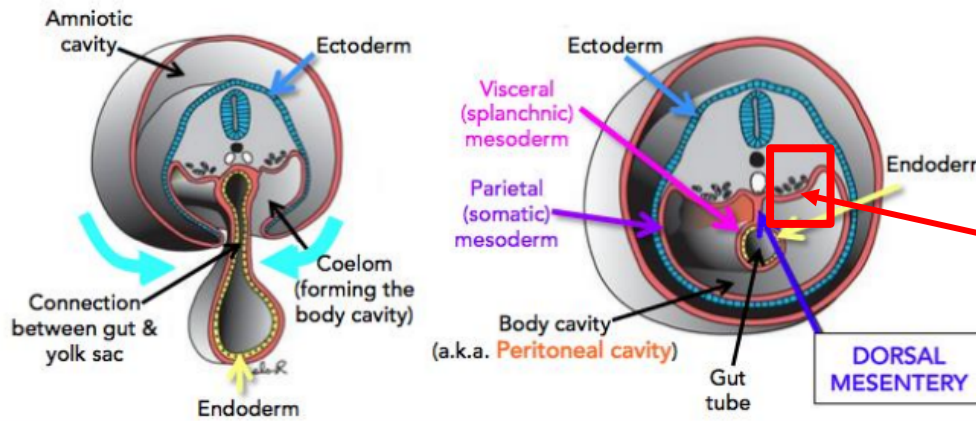
Mesothelium that lines body cavities and organs

Derived from lateral plate mesoderm

Somatopleure and splanchnopleure



Lateral plate mesoderm

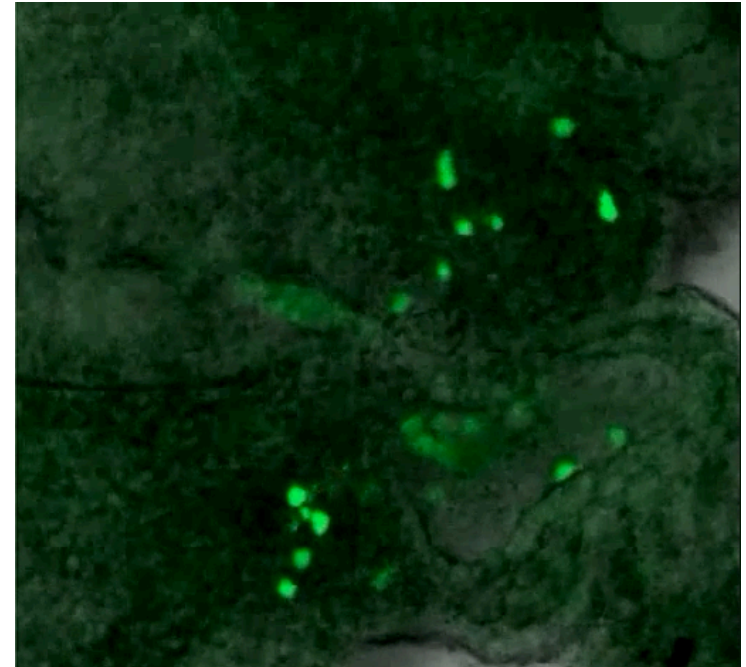
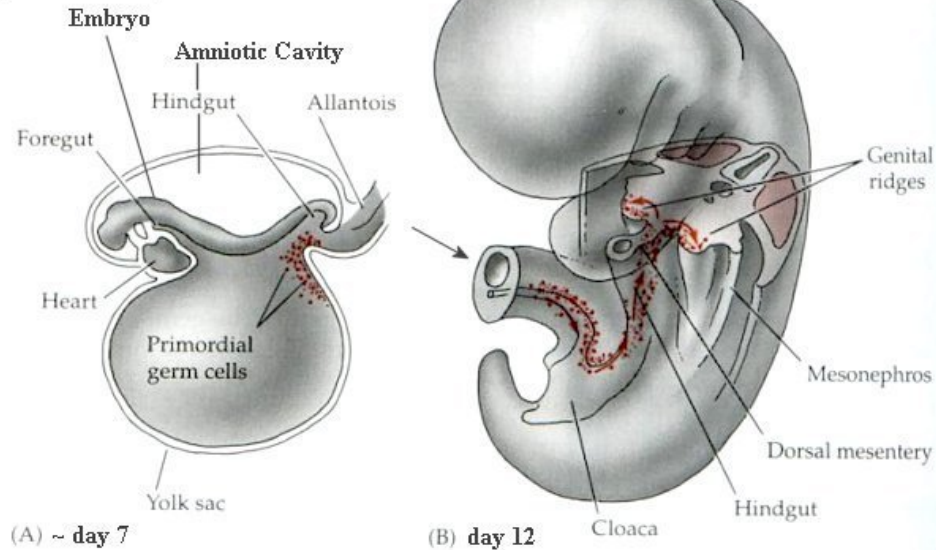


Coelomic epithelium:  
mesothelium lining  
the mesonephros

# Embryonic origins of the reproductive system

## Primordial Germ Cells (PGCs)

### Migration of mammalian primordial germ cells



PGCs arise during gastrulation

PGCs are initially set apart in hindgut/yolk sac/allantois

Later the PGCs migrate into the genital ridges through the gut into the genital ridges

# Lecture overview

Anatomy of the reproductive system

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Embryonic origins of the reproductive system

## **Gonad development**

Development of the reproductive tract

Development of the external genitalia

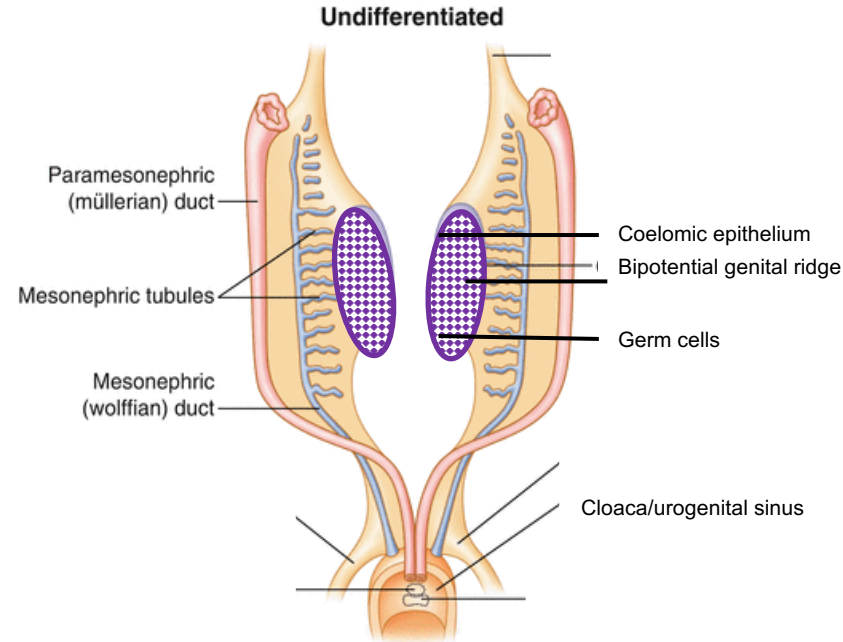
Development of secondary sex characteristics

Disorders of sexual development



# Gonad development

The bipotential embryonic reproductive system



XY and XX gonads develop from:

Mesonephric mesenchyme

Coelomic epithelium.

Germ cells

} Bipotential genital ridge

XX and XY reproductive tracts develop from:

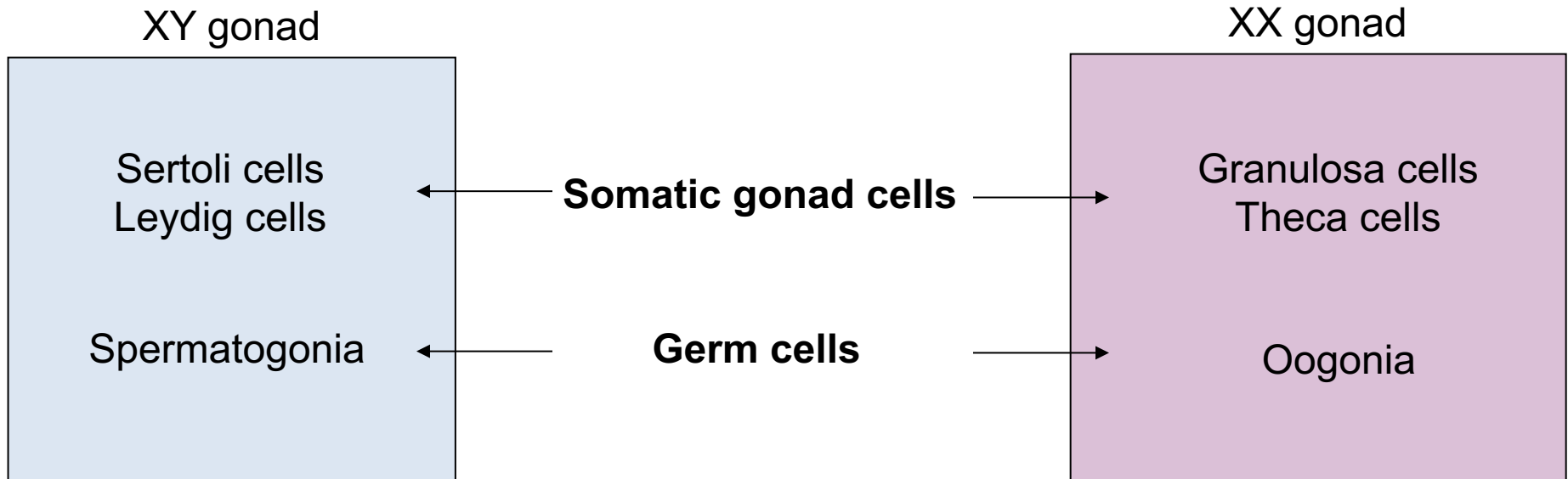
Mesonephric (Wolffian) duct

Paramesonephric (Mullerian) duct

Urogenital sinus

# Gonad Development

The bipotential embryonic reproductive system



# Gonad Development

## XY gonad development:

Coelomic epithelial cells proliferate and undergo EMT

Two waves: pre-Sertoli cells first, pre-Leydig cells later

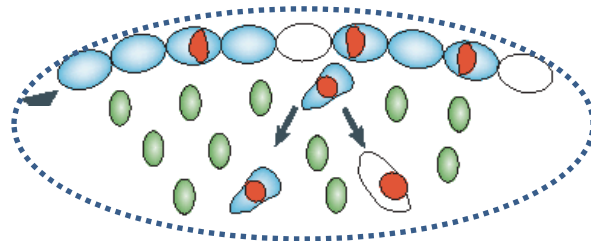
## Sertoli cells:

- supporting gonad cell type
- envelop germ cells to form sex/testicular cords (seminiferous tubules)
- produce anti-Mullerian Hormone (AMH)

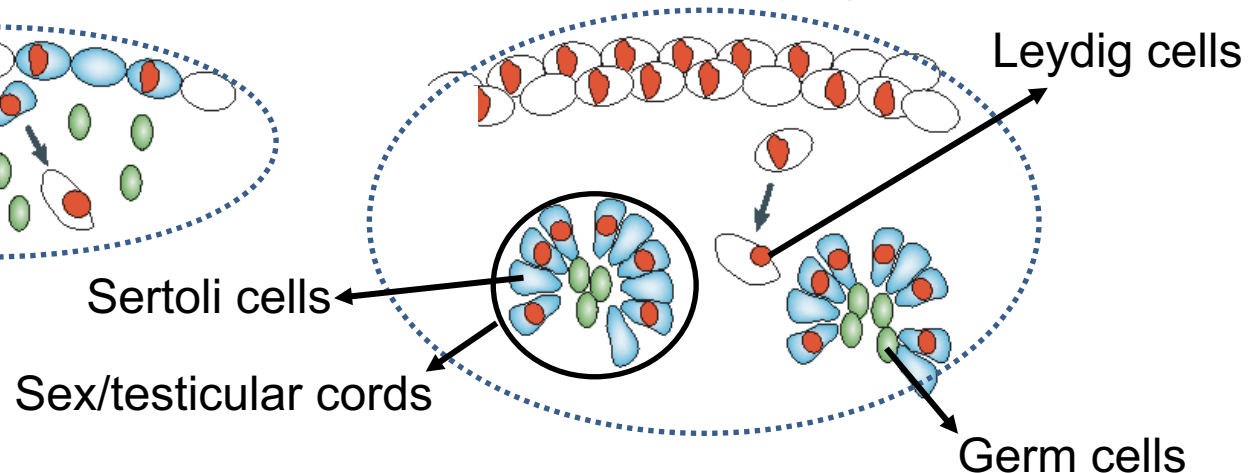
## Fetal Leydig cells:

- steroid-producing cell type: testosterone (masculinization)
- replaced after birth by adult Leydig cells

Wave 1: pre-Sertoli cell EMT



Wave 2: pre-Leydig cell EMT



# Gonad Development

## XX gonad development:

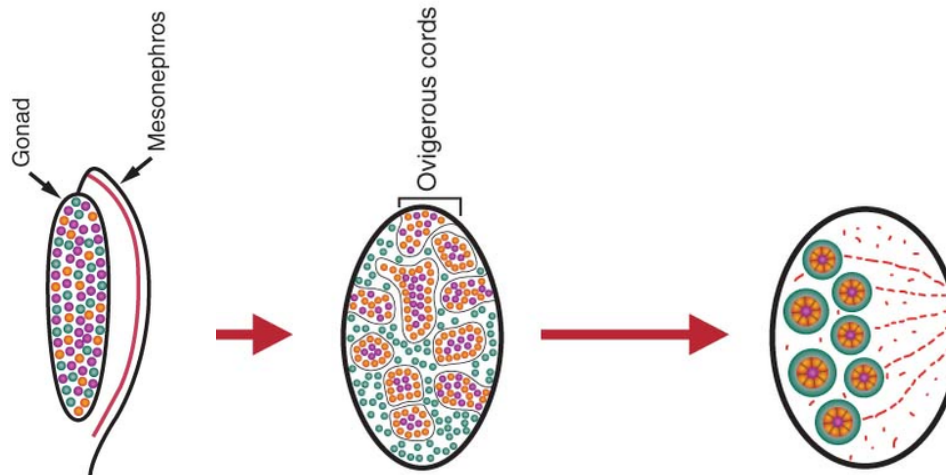
Coelomic epithelial cells proliferate, undergo EMT, and give rise to granulosa cells. (until after birth!)

## Granulosa cells:

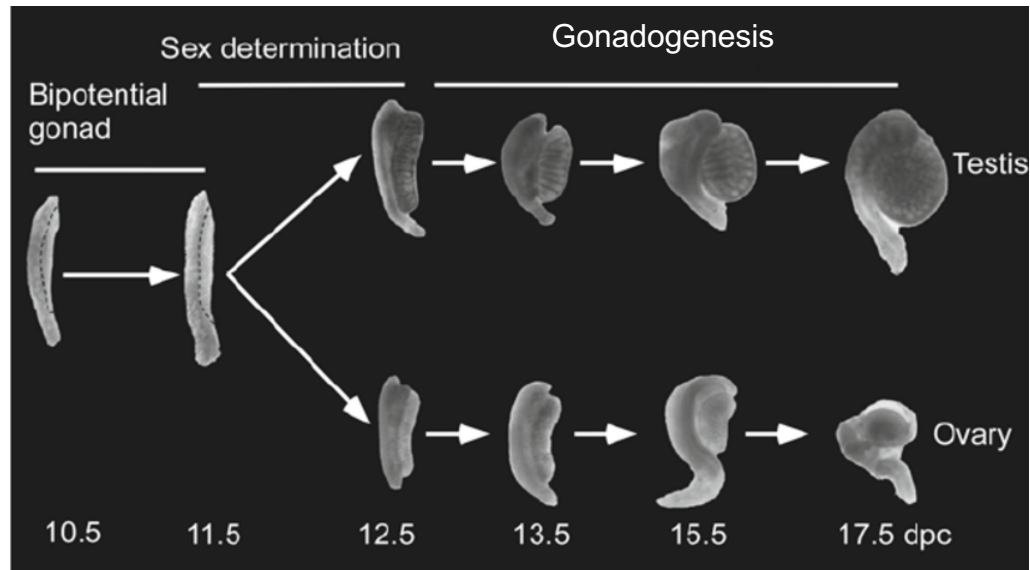
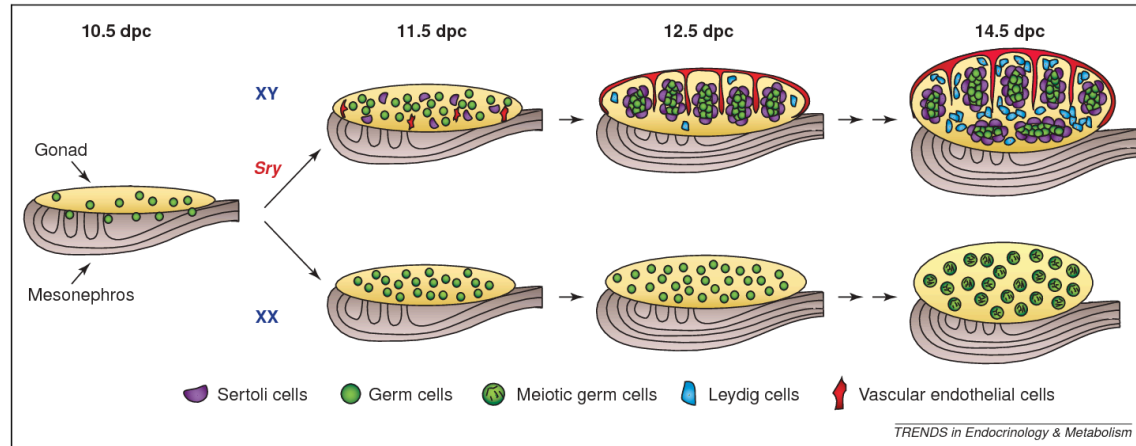
- supporting gonad cell type
- generate the ovigerous cords, which envelop germ cells, and fragment into follicles
- produce progesterone
- convert androstenedione (from Theca cells) to estrogen (feminization)

## Theca cells:

- derived from mesonephric mesoderm,
- steroid-producing cell type: androstenedione (estrogen precursor)



# Gonad Development

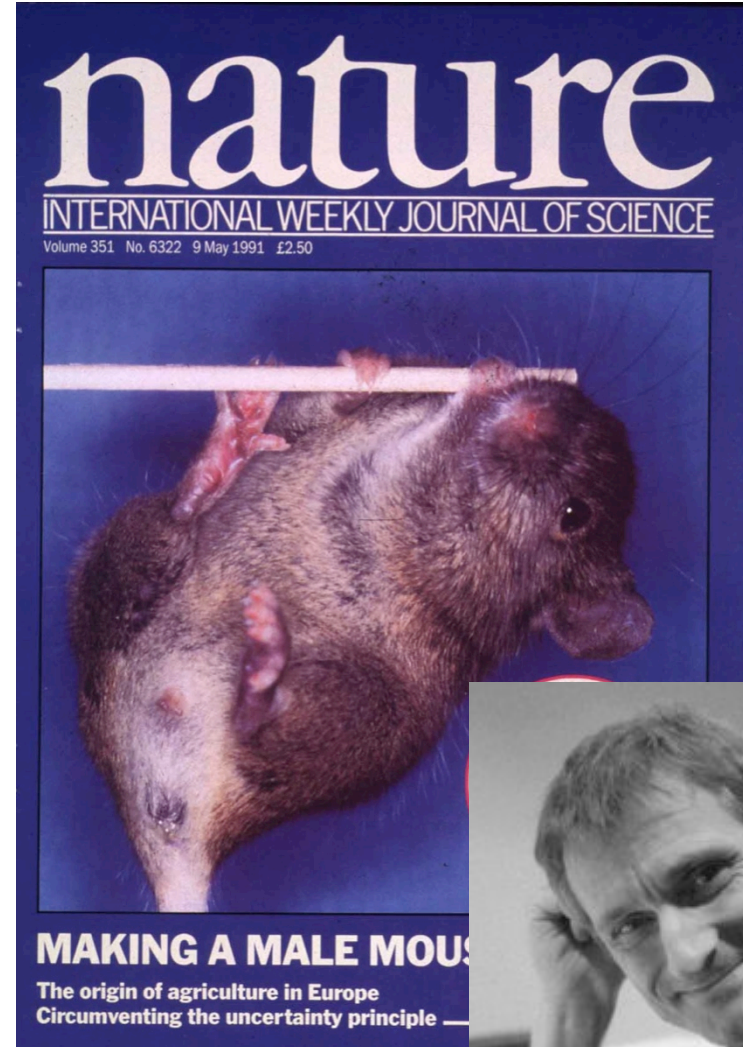
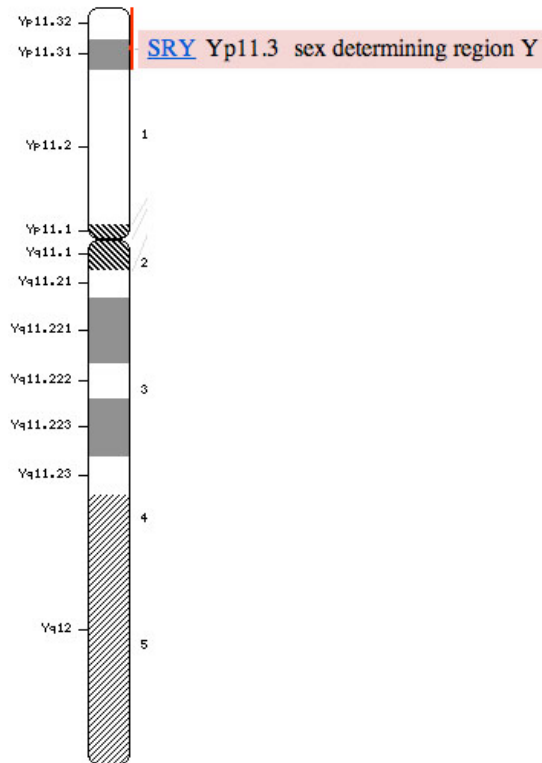


Mouse

# Gonad Development

*Sry*, the male sex determining gene

Y chromosome

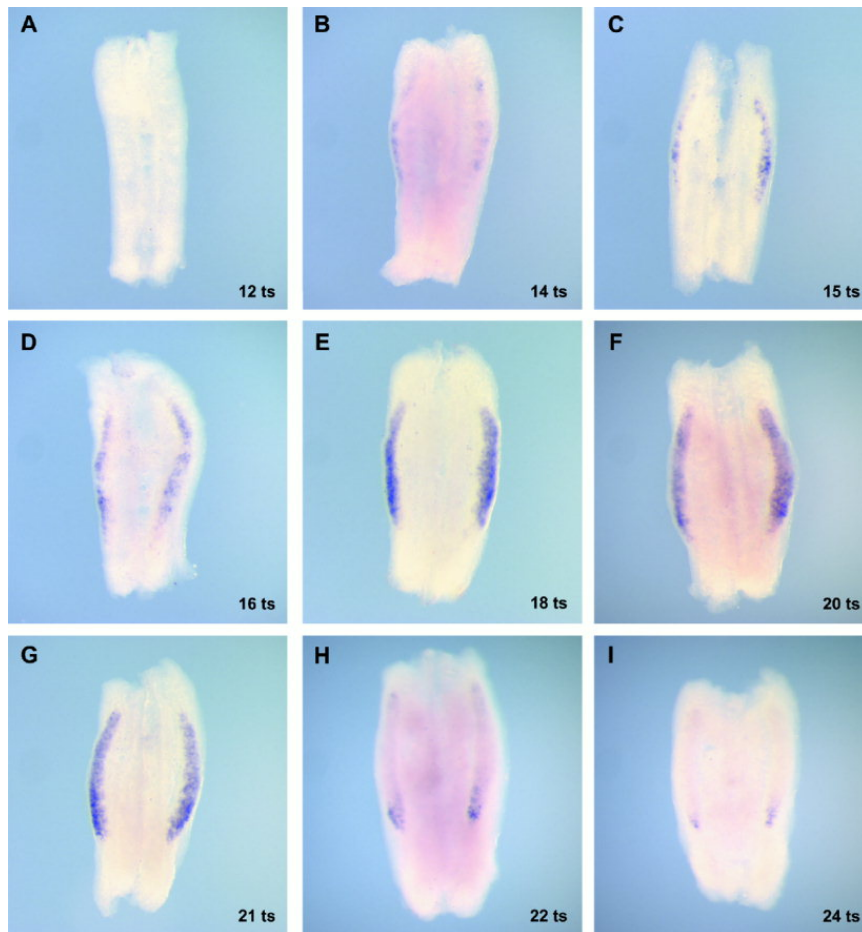


Peter Koopman

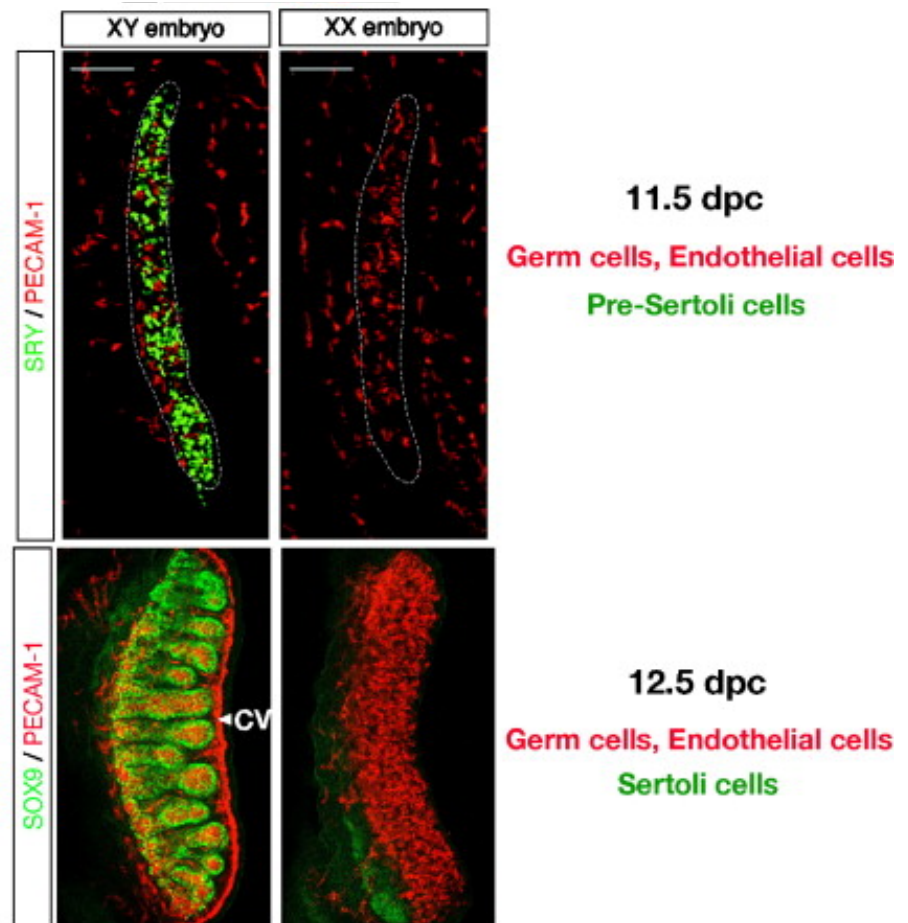
# Gonad Development

Sry -> Sox9 -> AMH/Testosterone -> Testicular development

Wave of *Sry* expression  
in pre-Sertoli cells

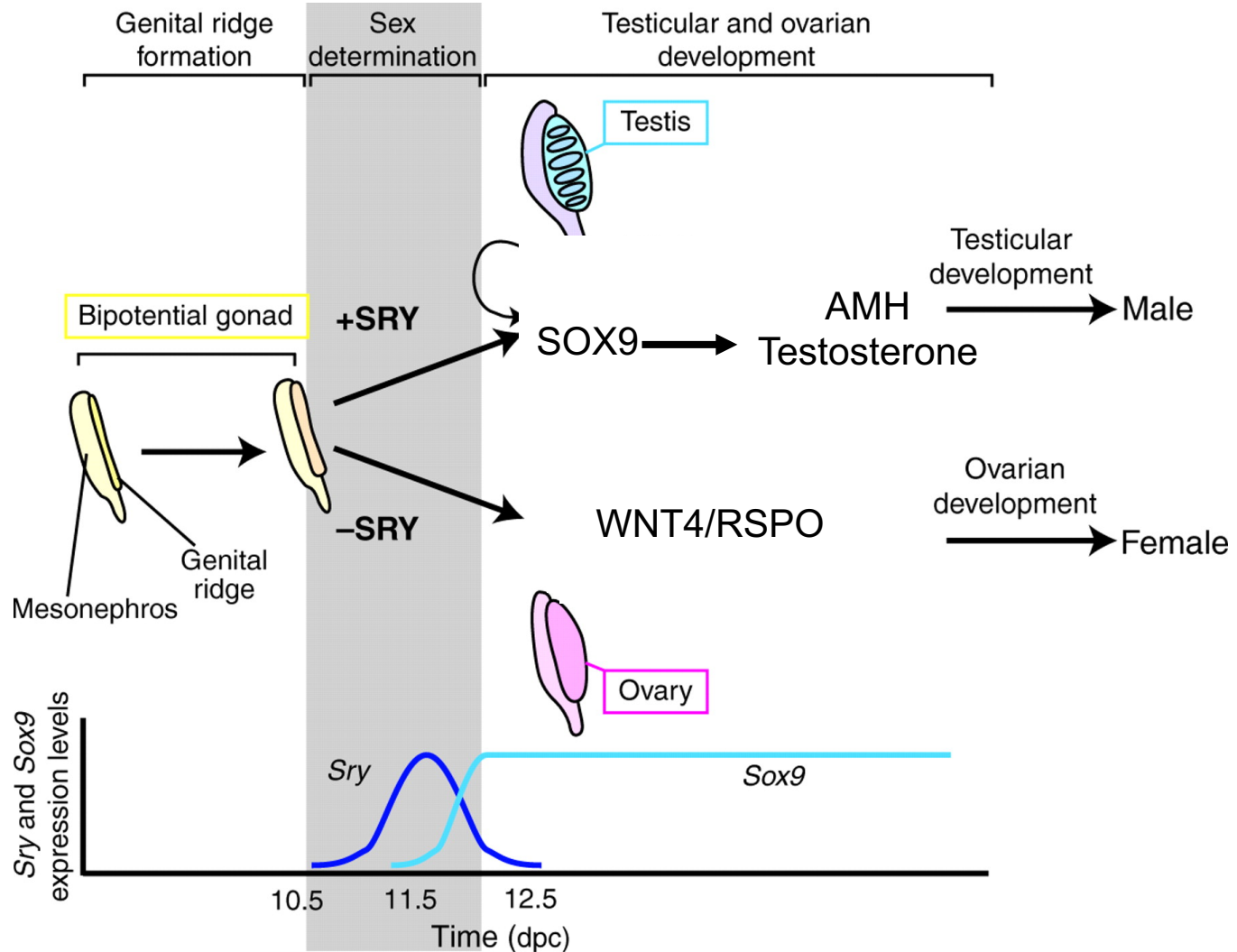


*Sry* is a transcription factor that activates  
SOX9 expression in Sertoli cells



# Gonad Development

Sry -> Sox9 -> AMH/Testosterone -> Testicular development





# Lecture overview

Anatomy of the reproductive system

Sex determination

Embryonic origins of the reproductive system

Gonad development

## **Development of the reproductive tract**

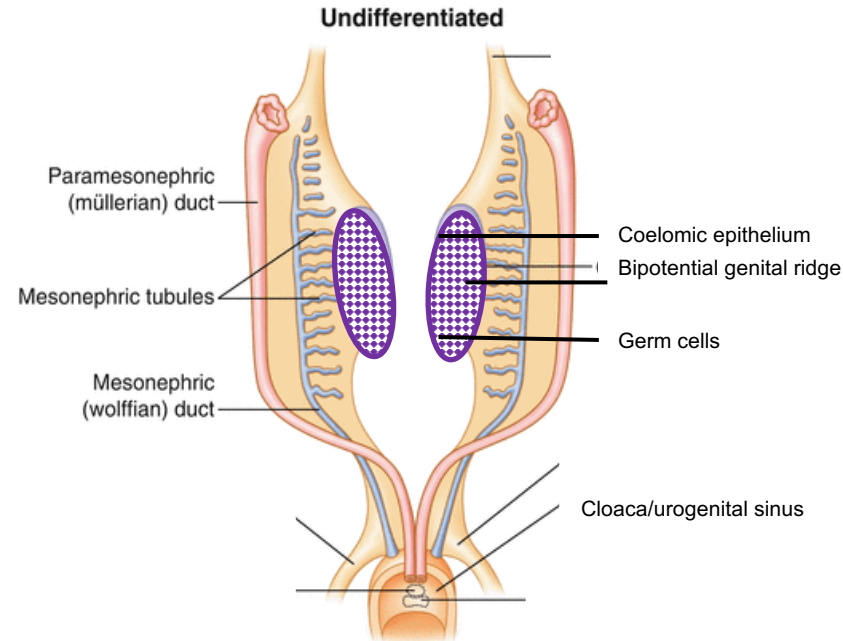
Development of the external genitalia

Development of secondary sex characteristics

Disorders of sexual development

# Development of the Reproductive Tract

The bipotential embryonic reproductive system



XY and XX gonads develop from:

Mesonephric mesenchyme

Coelomic epithelium.

Germ cells

} Bipotential genital ridge

XX and XY reproductive tracts develop from:

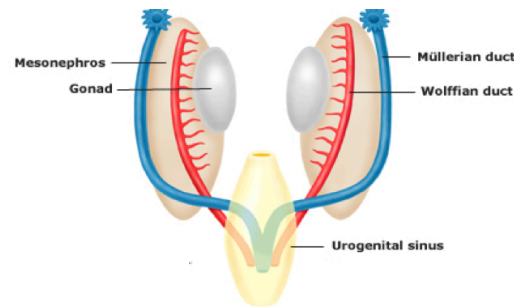
Mesonephric (Wolffian) duct

Paramesonephric (Müllerian) duct

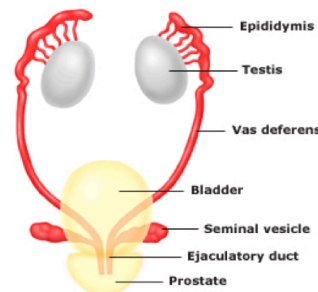
Urogenital sinus

# Development of XY Reproductive Tract

Sertoli cells produce anti-Müllerian hormone (AMH): Müllerian duct regression  
Leydig cells produce testosterone: Wolffian duct develops into male reproductive tract and seminal vesicles



AMH (Sertoli cells)  
Testosterone (Leydig cells)

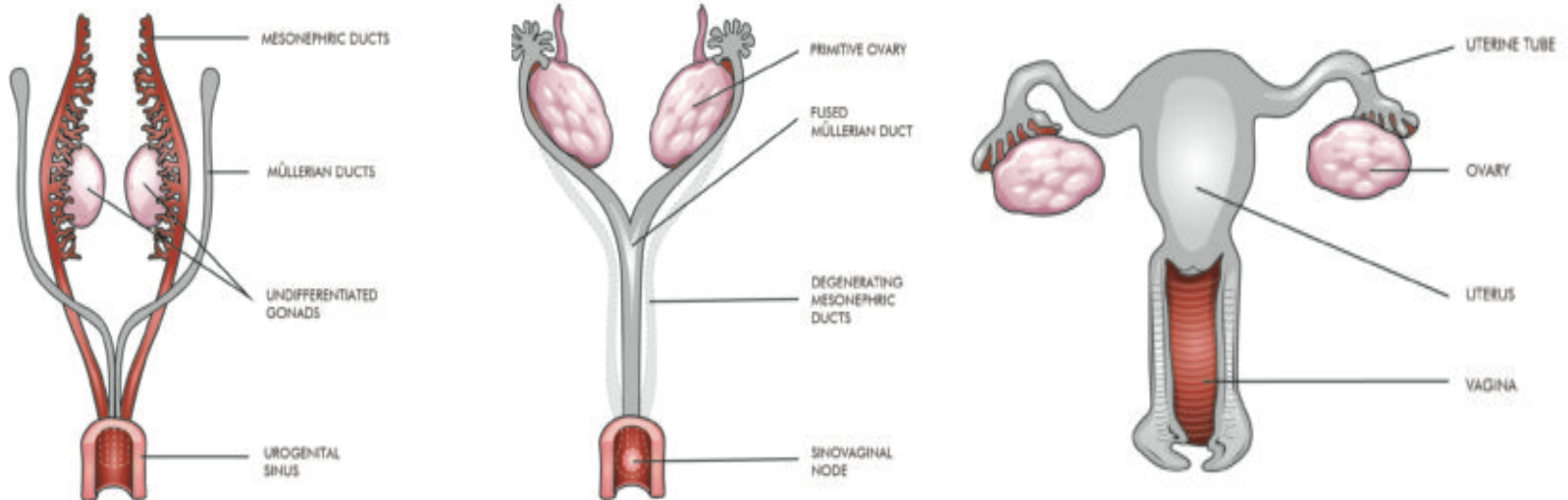


# Development of XX Reproductive Tract

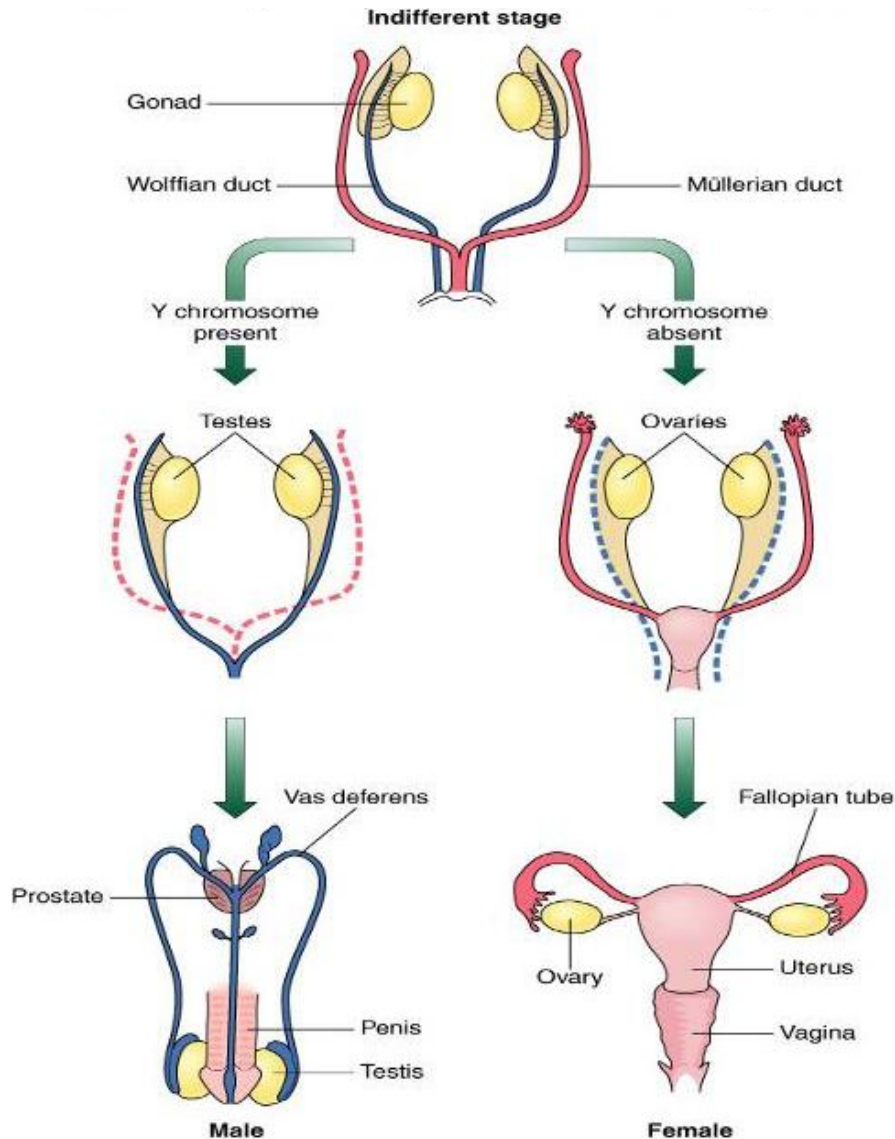
No testosterone: Mesonephric/Wolffian duct regresses

No AMH: Paramesonephric/Müllerian duct forms female reproductive tract

Bilateral paramesonephric/Müllerian tubes partially fuse to form uterus, cervix and vagina



# Development of the Reproductive Tract



**Male:**

Testes

**Wolffian Duct:**

Rete Testes

Epididymis

Vas deferens

Seminal vesicles

**Female:**

Ovary

**Müllerian Duct:**

Fallopian Tubes

Uterus

Cervix

Upper Vagina

# Development of the reproductive tract

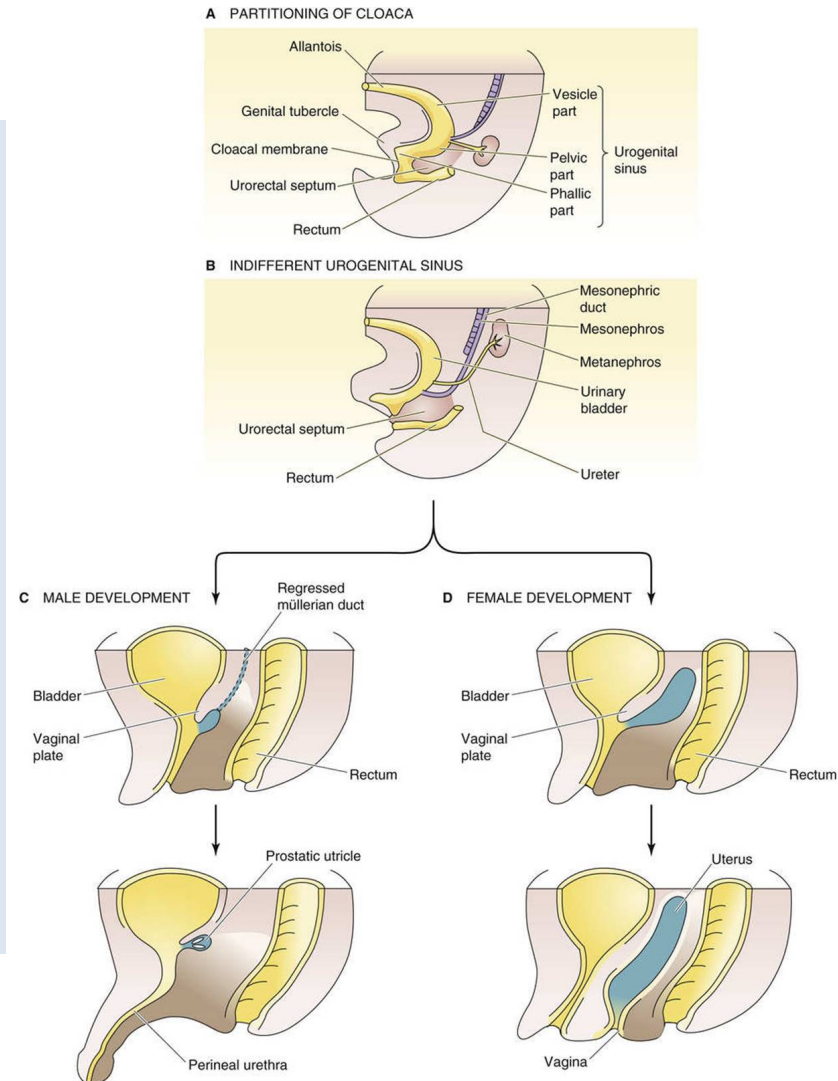
## XY Urogenital Sinus

Partitioning of the cloaca:  
Urorectal septum separates hindgut from urogenital sinus (continuous with allantois)

Wolffian ducts:  
Vas deferens ends in urogenital sinus

Mullerian ducts regress  
(except for caudally: prostate gland)

XY urogenital sinus:  
Bladder and urethra  
Prostate (Mullerian duct contribution)  
Bulbourethral glands



# Development of the XX Reproductive Tract

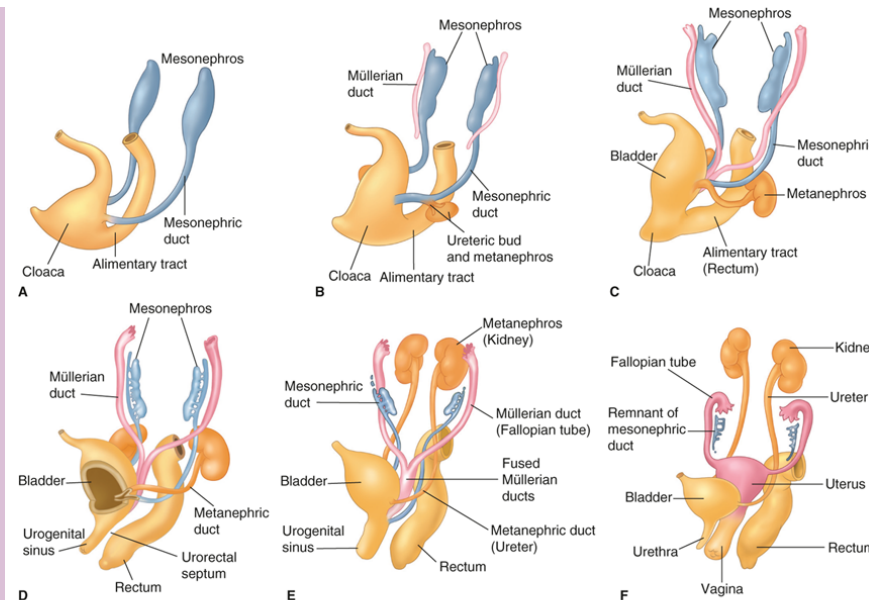
## XX Urogenital sinus

Partitioning of the cloaca:  
Urorectal septum separates hindgut from urogenital sinus

Wolffian ducts degenerate

Müllerian ducts:

- Rostrally: Fallopian tubes
- Caudally:
  - Fusion to form uterus, cervix and vagina
  - Separation from bladder and urethra



Source: Hoffman BL, Schorge JO, Schaffer JJ, Halvorson LM, Bradshaw KD, Cunningham FG: *Williams Gynecology, 2nd Edition*: www.accessmedicine.com  
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# Lecture overview

Anatomy of the reproductive system

Sex determination

Embryonic origins of the reproductive system

Gonad development

Development of the reproductive tract

**Development of the external genitalia**

Development of secondary sex characteristics

Disorders of sexual development



# Development of the external genitalia

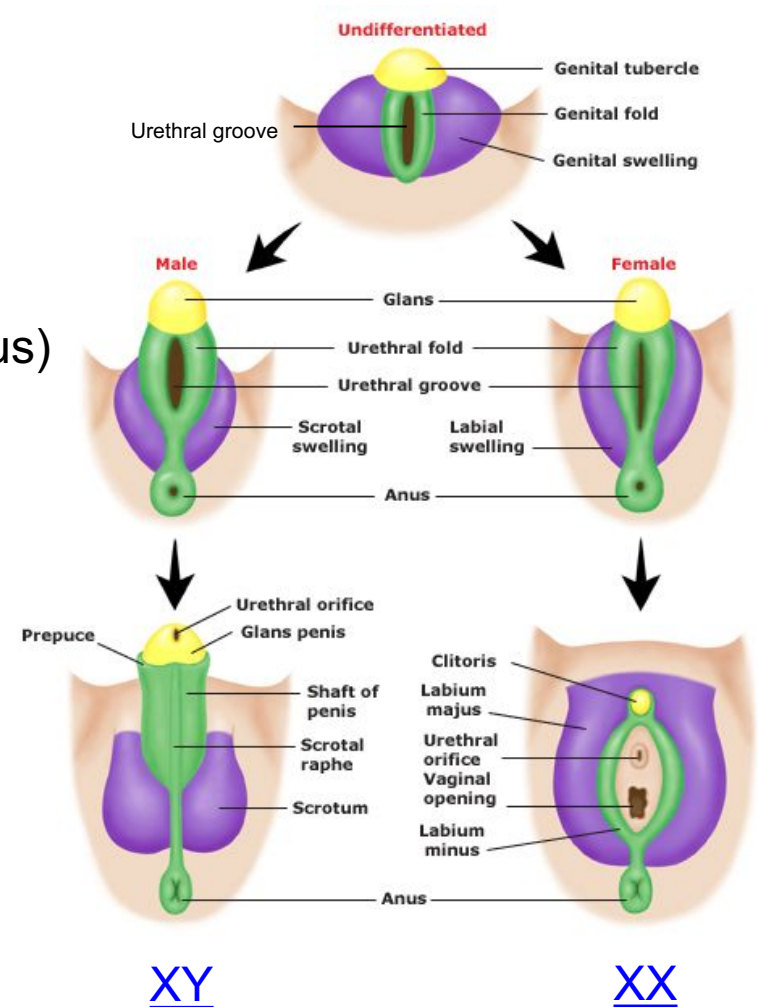
Embryonic genitalia are bipotential

Bipotential genitalia consist of:

- Genital tubercle
- Genital folds
- Genital swellings
- Urethral groove (access to cloaca/urogenital sinus)

XY: Dihydrotestosterone by fetal Leydig cells

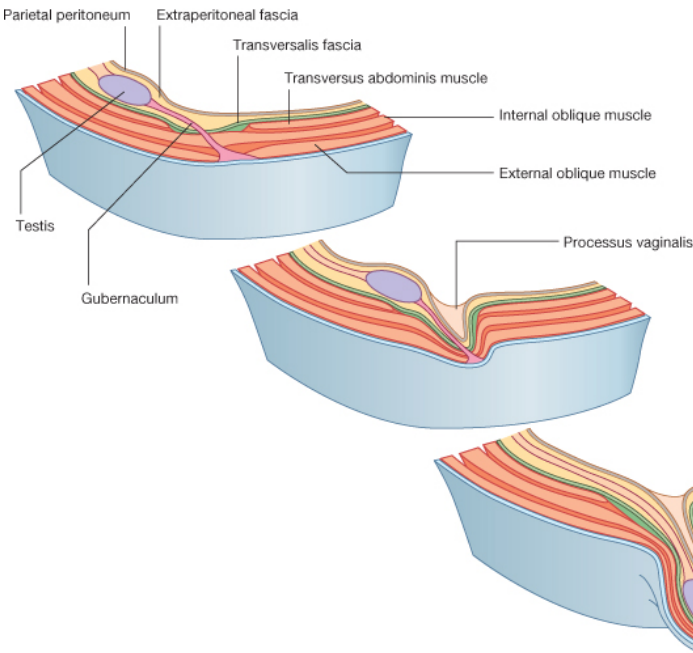
XX: Absence of dihydrotestosterone



Bipotential tissue	XY	XX
Genital Tubercle	Glans penis	Clitoris
Genital Folds	Penis shaft urethra	Labia minora
Genital swellings	Scrotum	Labia majora
Urethral groove	Disappears	Vaginal opening

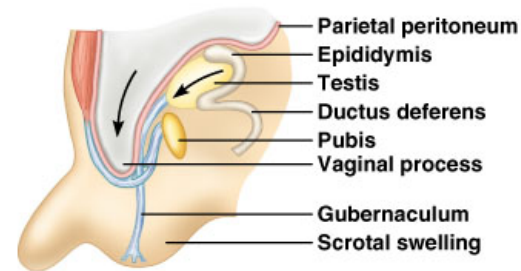
# Development of the external genitalia

## Descent of Testes

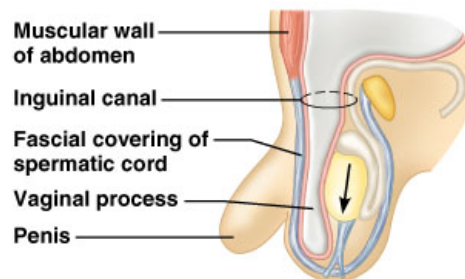


© Elsevier Ltd. Drake et al: Gray's Anatomy for Students www.studentconsult.com

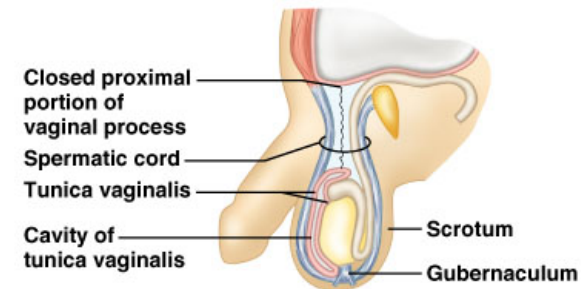
Late fetal event  
 Gubernaculum (connective tissue ligament)  
 Inguinal canal  
 Processus vaginalis: peritoneal fold ending in the scrotal sac



**(a) 7-month fetus**



**(b) 8-month fetus**



**(c) 1-month old infant**

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Development of the external genitalia

**Development of secondary sex characteristics**

Disorders of sexual development

# Development of secondary sex characteristics

## Sex Determination

Three factors determine gender phenotype:

### 1. Genetic sex

- Dependent on sex chromosomes: XX or XY
- Determined at conception

### 2. Development of the reproductive system (gonads, tracts, genitalia)

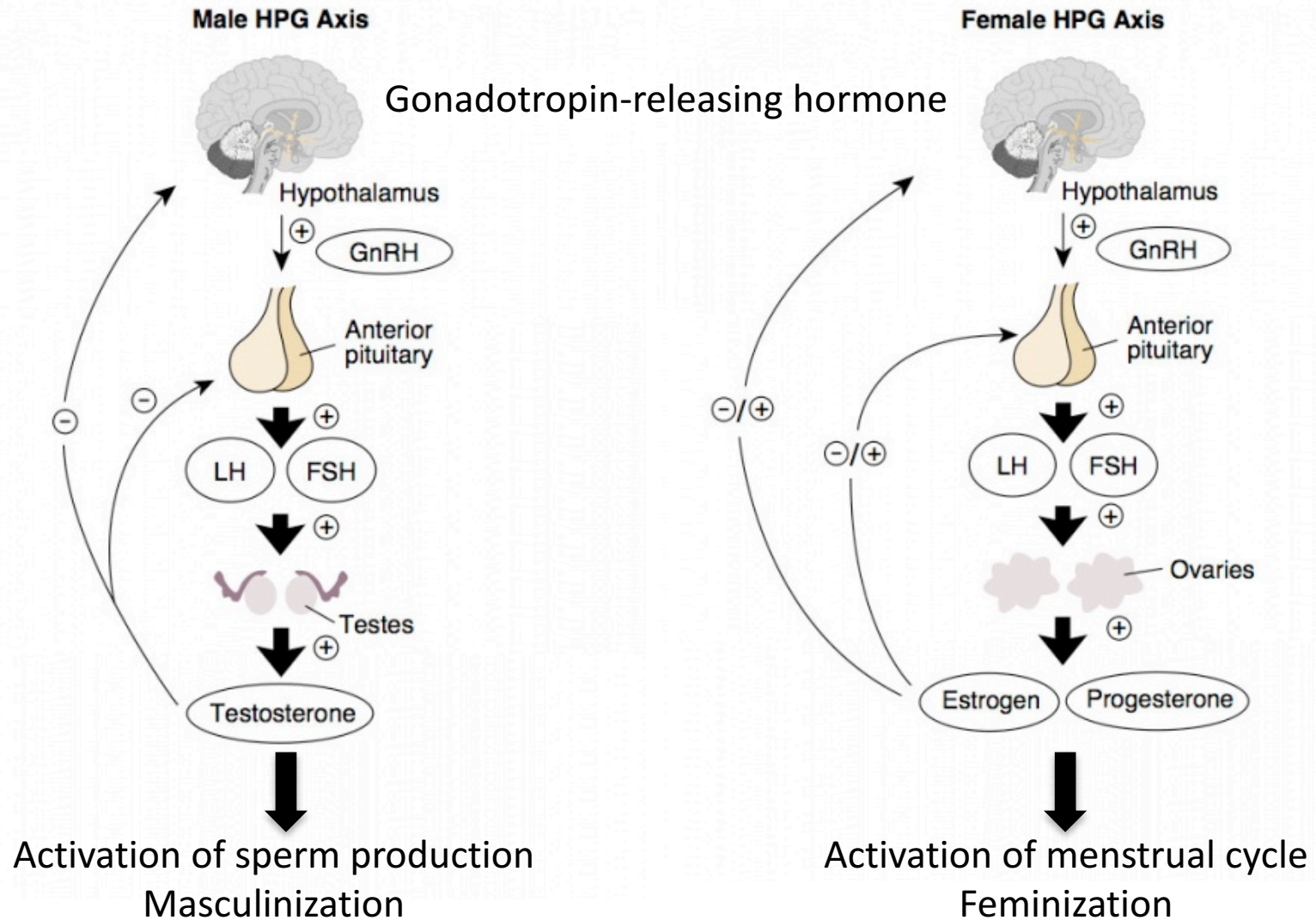
- Dependent on gonad development
- Occurs during embryonic development

### 3. **Development of secondary sex characteristics**

- **Dependent on hormones**
- **Occurs during puberty**

# Development of secondary sex characteristics

## Puberty



# Lecture overview

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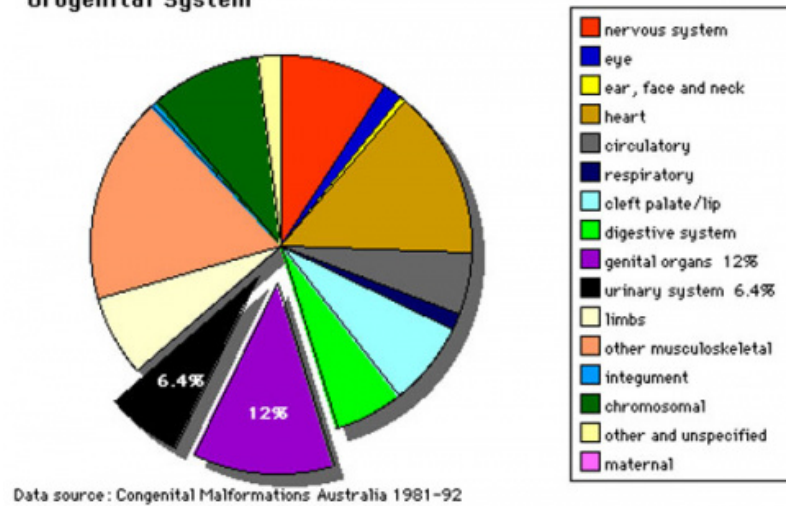
Development of the external genitalia

Development of secondary sex characteristics

**Disorders of sexual development**

# Disorders of Sexual Development

Congenital Malformations by System 81-92  
Urogenital System



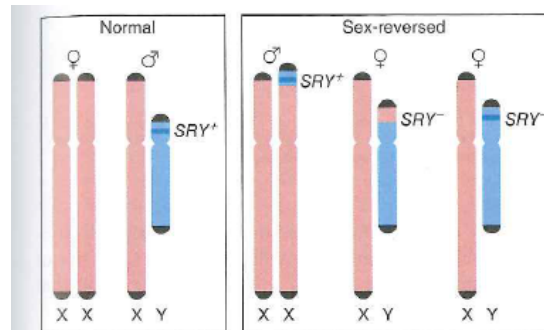
Very common: 12% of all congenital abnormalities!

# Disorders of Sexual Development

## Sex reversal syndromes

Chromosomal sex does not match phenotypic sex:

- XX males
  - Transfer of some Y chromosome DNA (incl *Sry*) onto X chromosome
  - Gonads develop as testes following *Sry* activation
  - Development male phenotype
  - Infertility
  
- XY females
  - Usually: steroidal origin:
    - Androgen insensitivity syndrome: mutations in androgen receptor
    - 5-alpha reductase deficiency: defective testosterone metabolism
  - Rarely: chromosome rearrangements or inactivating mutations in *Sry* gene

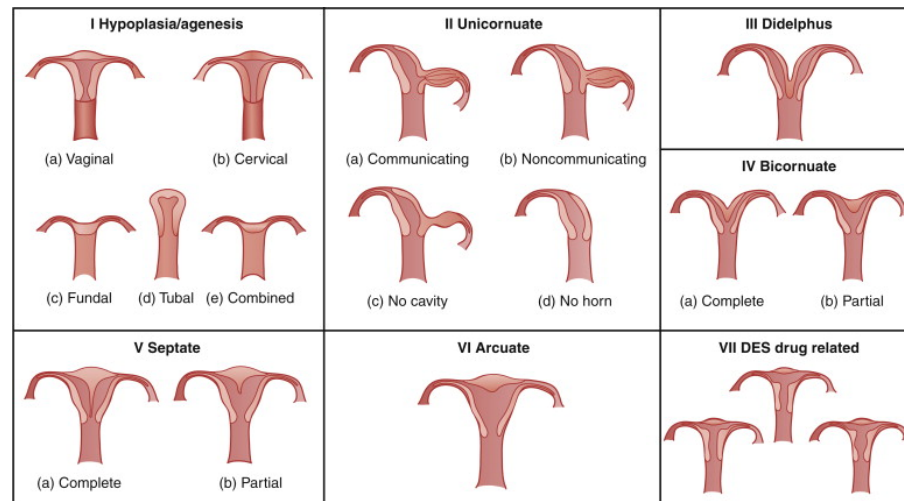
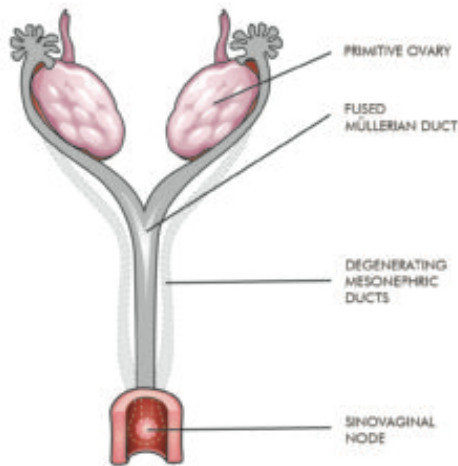




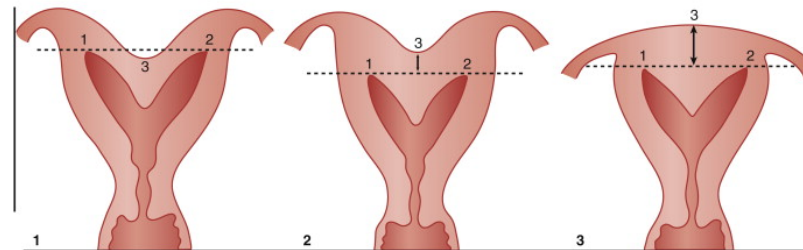
# Disorders of Sexual Development

## Female Reproductive Tract Abnormalities

Due to fusion failures of the paramesonephric/Mullerian duct



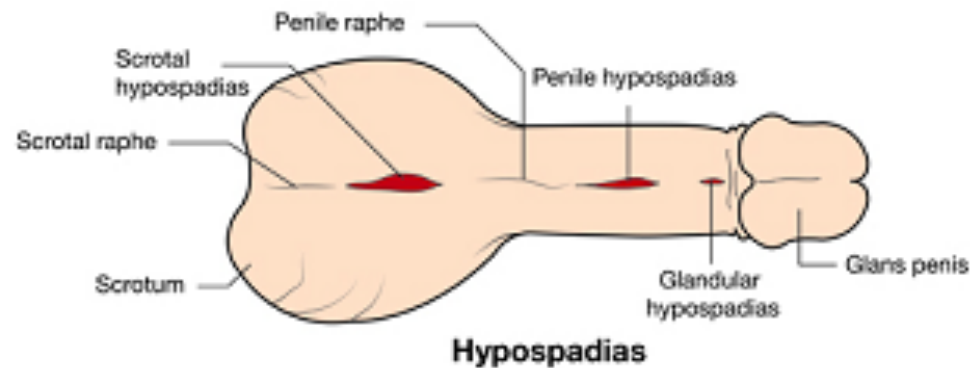
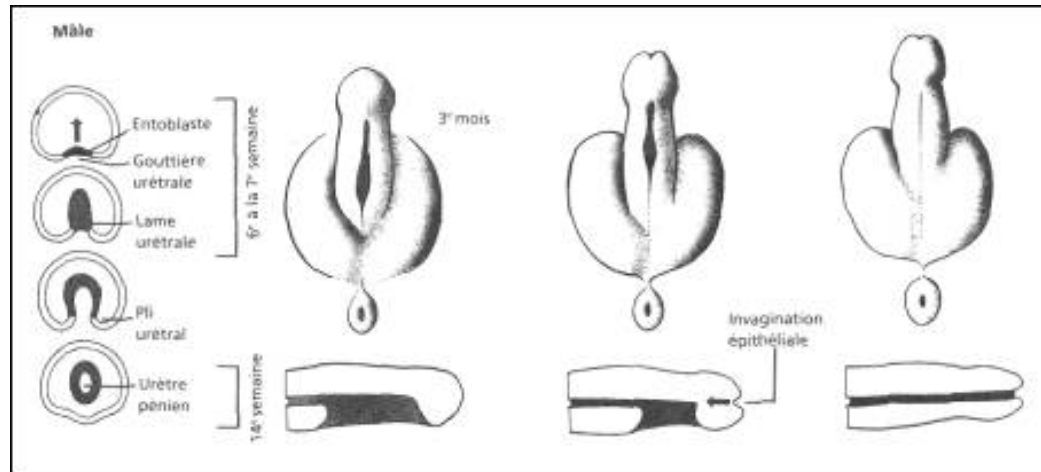
A



B

# Disorders of Sexual Development

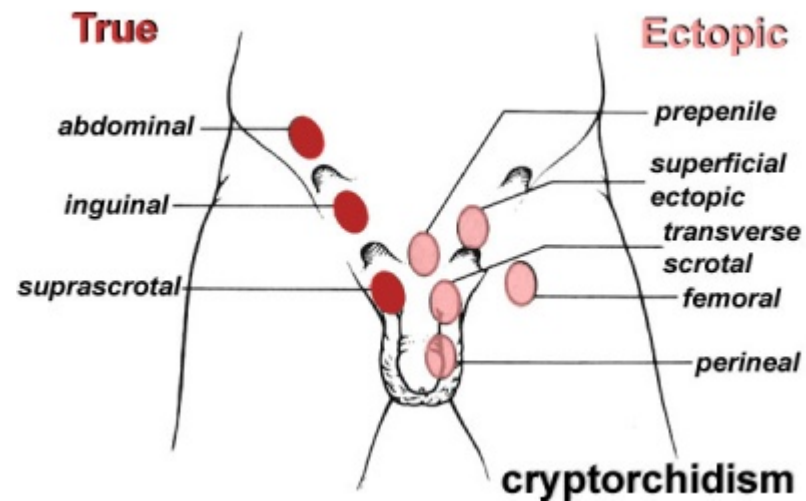
Hypospadias: incorrect closure of the genital folds



# Disorders of Sexual Development

## Cryptorchidism

Failure of correct gonad descent

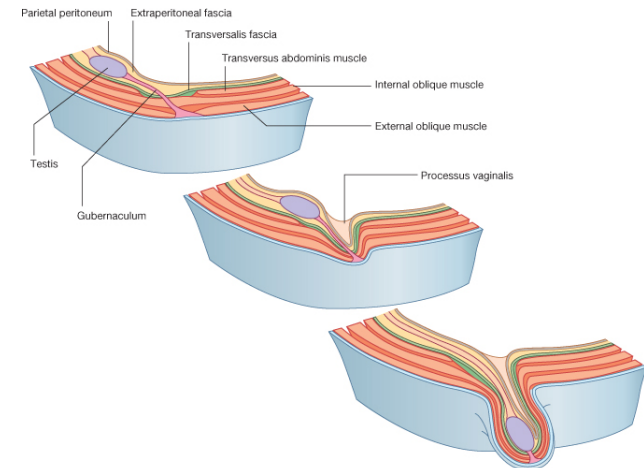
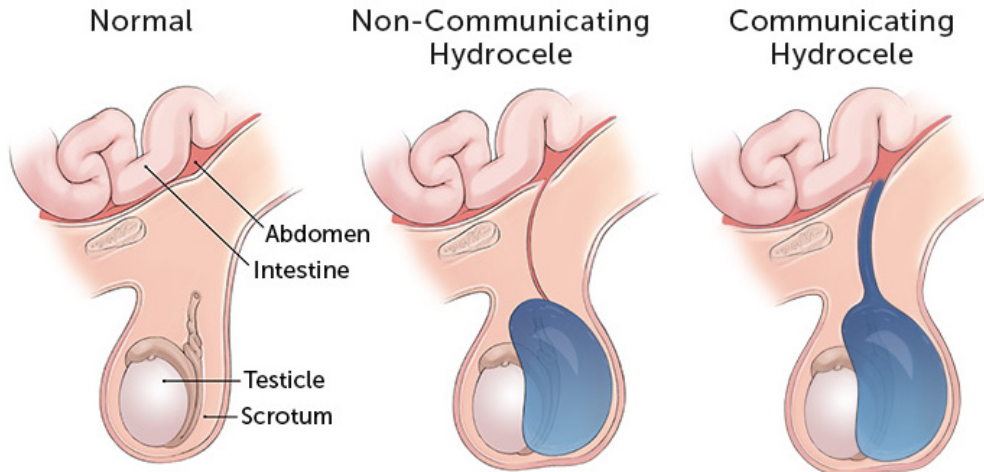


# Disorders of Sexual Development

## Hydrocele testes

Peritoneal fluid enters scrotal sac through processus vaginalis

Processus vaginalis: peritoneal fold ending in the scrotal sac



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