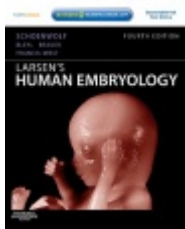
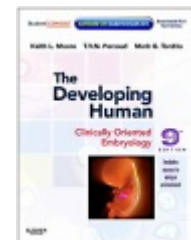


Development of the Reproductive System



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

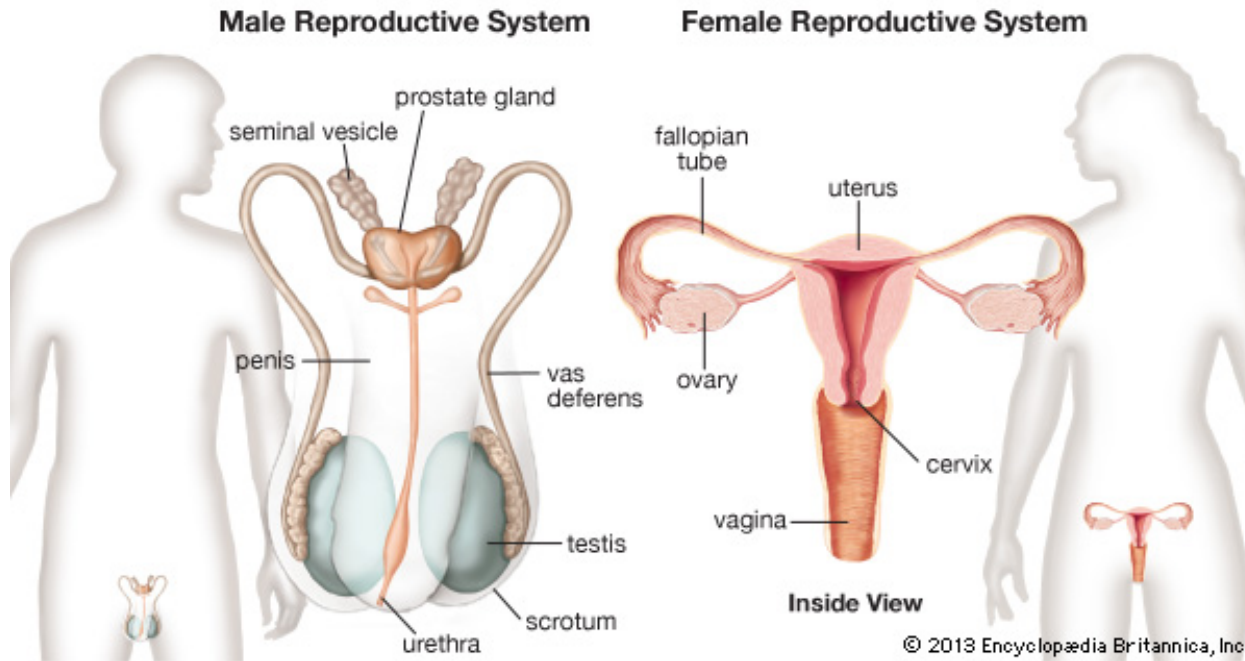
Development of the reproductive tract

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:

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

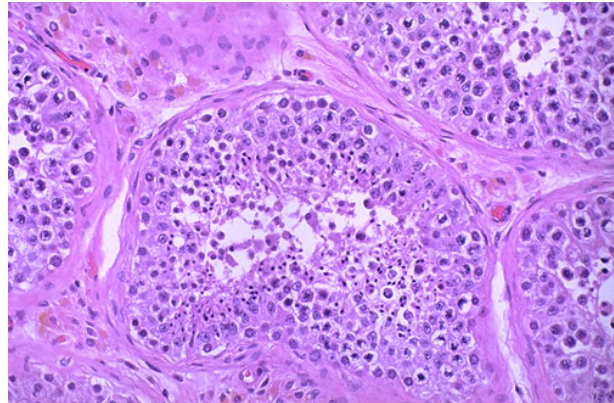
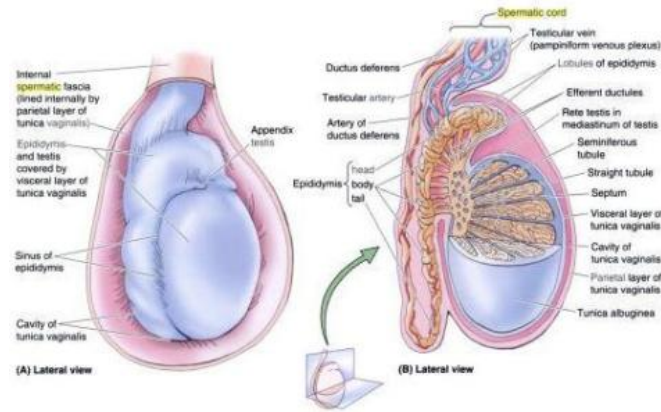
XX gonads: ovaries

XX reproductive tract:

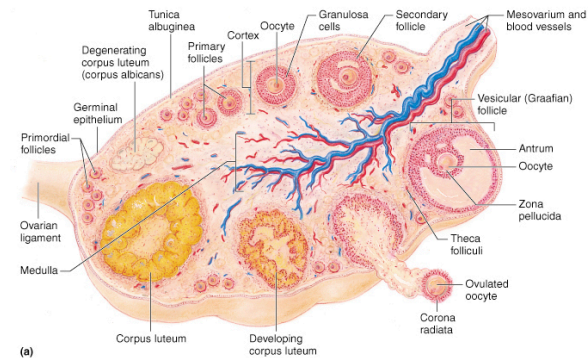
- Fallopian tubes
- Uterus
- Cervix
- Vagina

Anatomy of the reproductive system

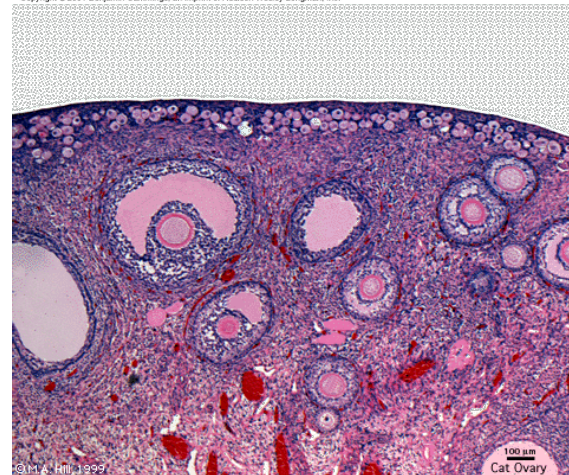
Gonads



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



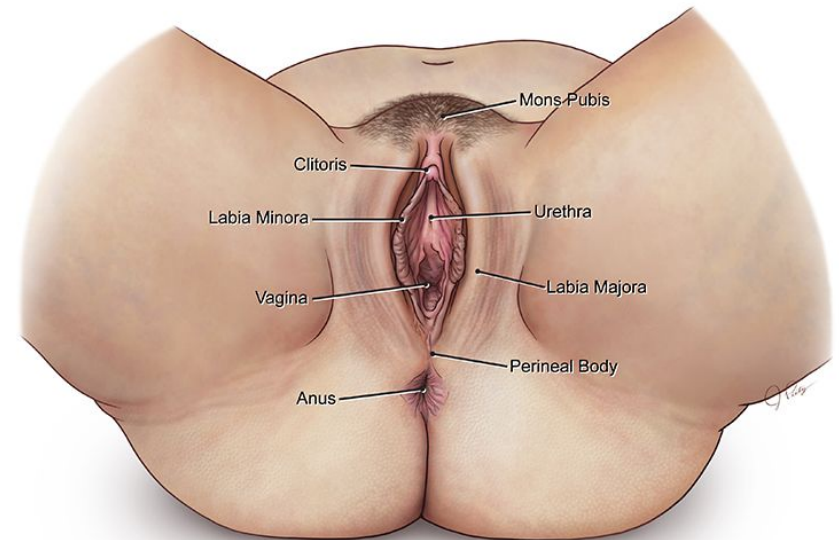
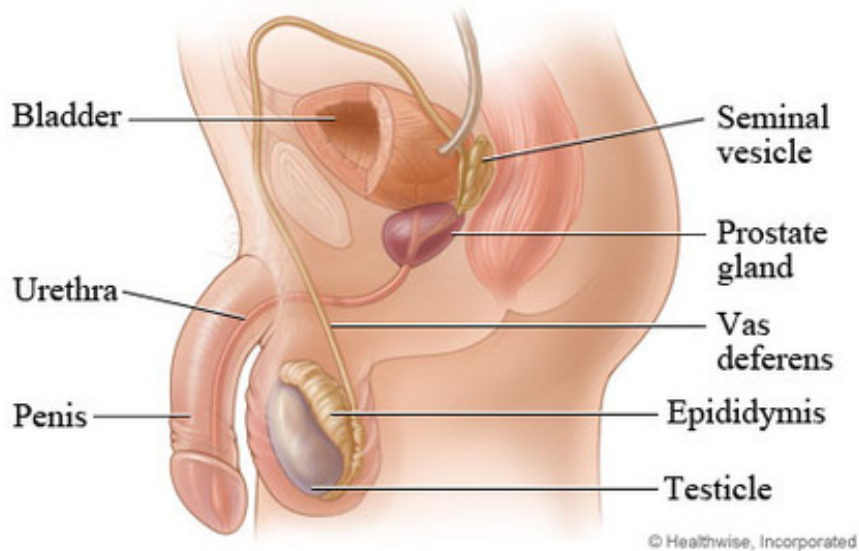
(a)
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XX: Ovaries
 Follicles
 Maturing oocytes
 Supporting cell type: Granulosa cells
 Steroid producing cell type: Theca cells

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

- Dependent on gonad development
- Occurs during embryonic development

3. Development of secondary sex characteristics

- Dependent on hormones
- Occurs during puberty

Lecture overview

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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

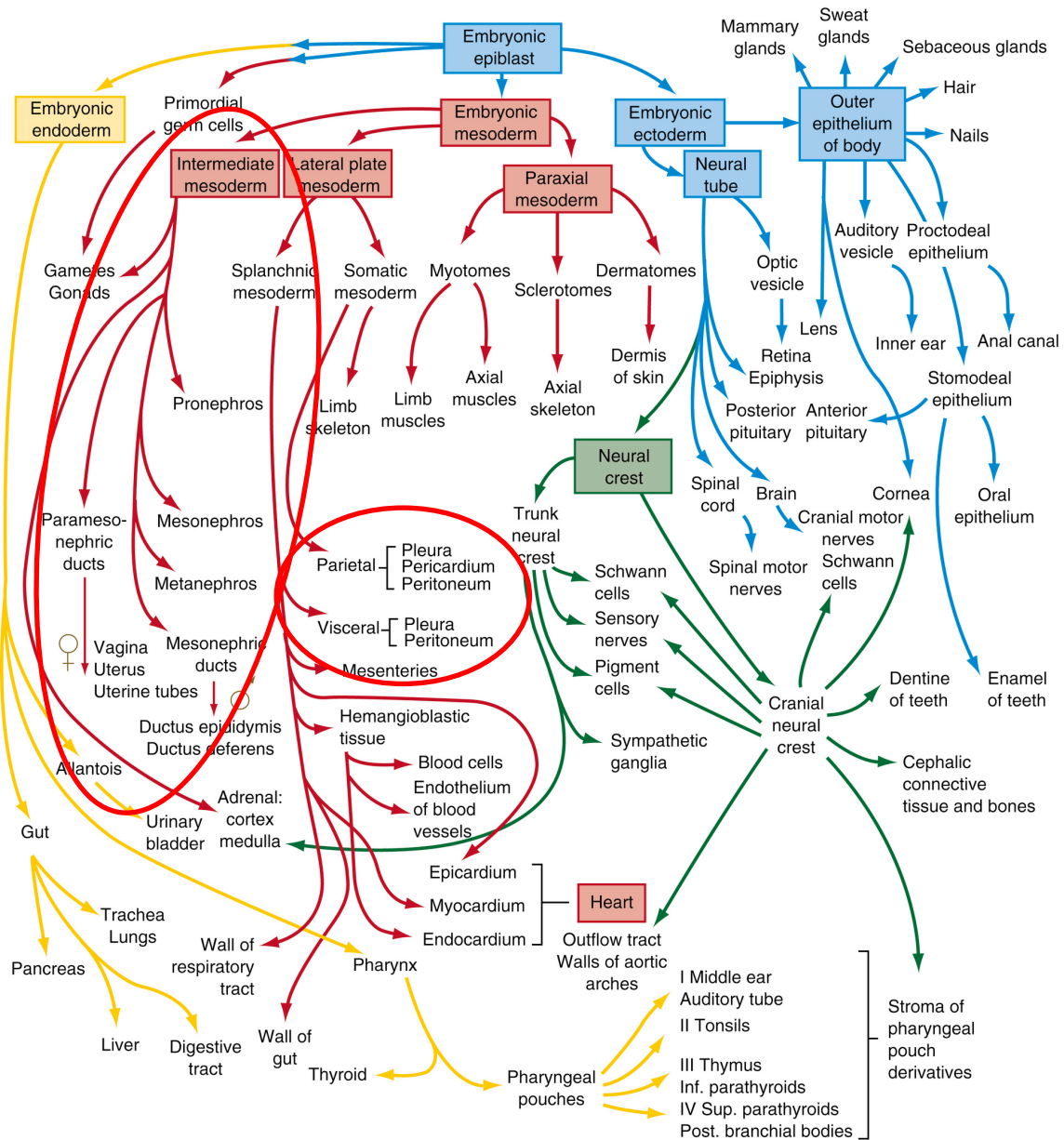
Intermediate Mesoderm
Coelomic Epithelium (Lateral Plate Mesoderm)
Primordial Germ Cells



Week 4 embryo

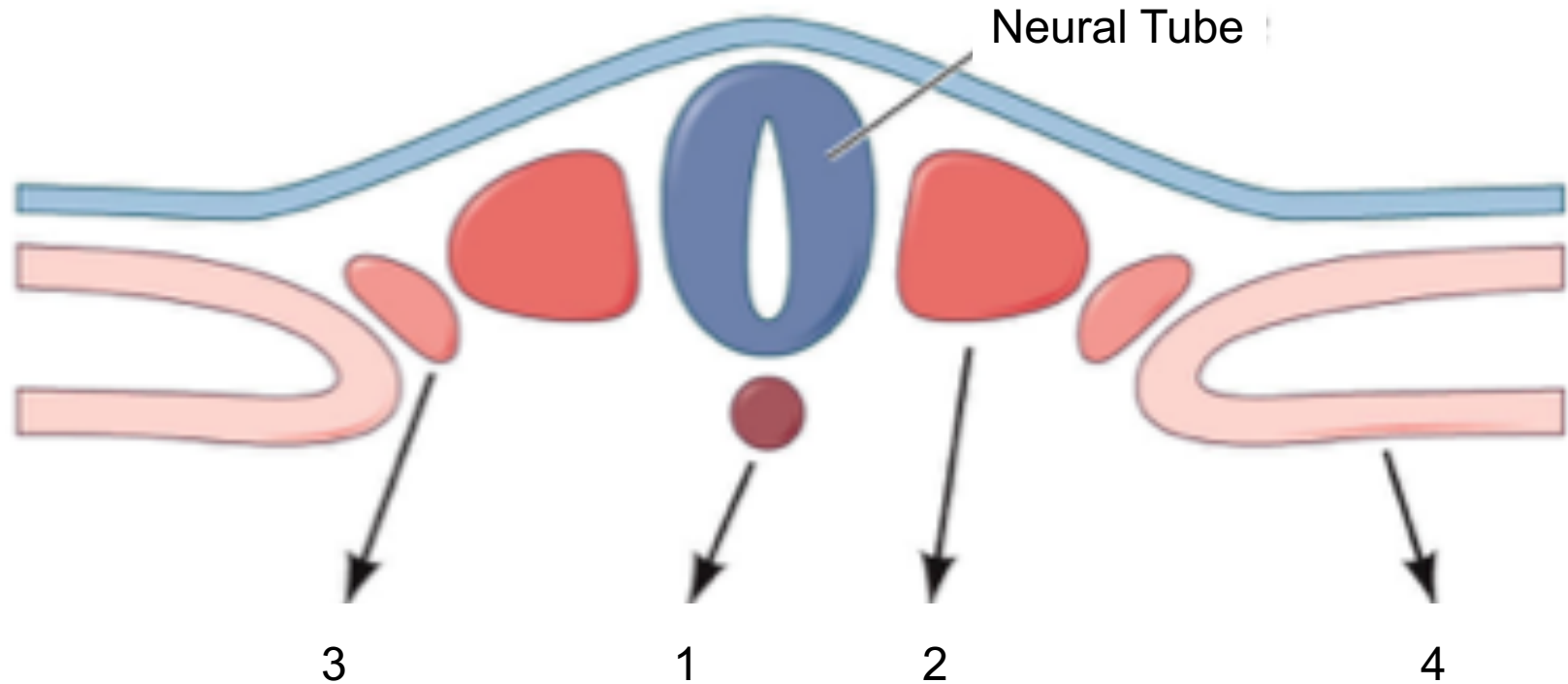
Embryonic origins of the reproductive system

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:

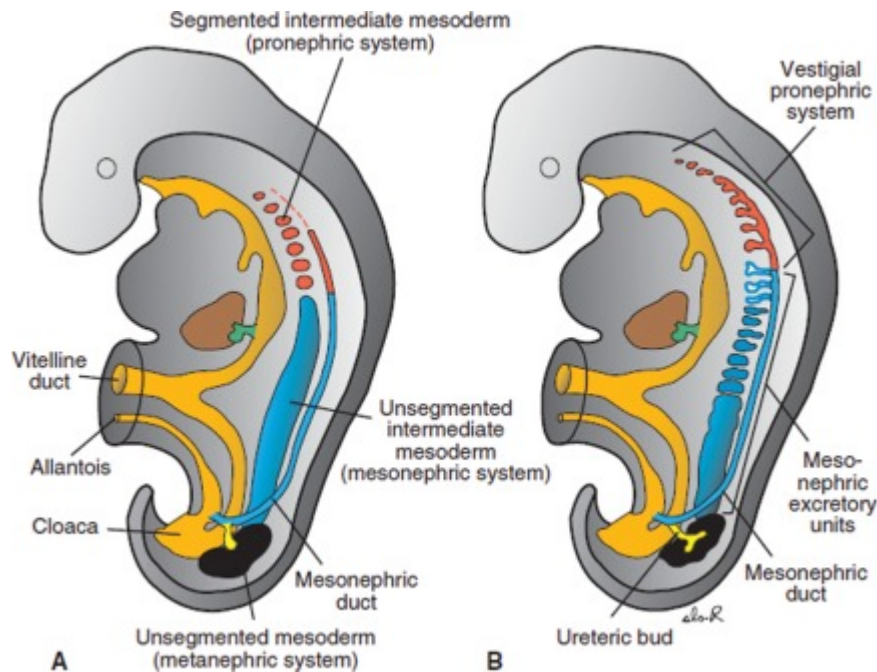
Mesonephric mesoderm

Mesonephric (Wolffian) duct (and tubules)

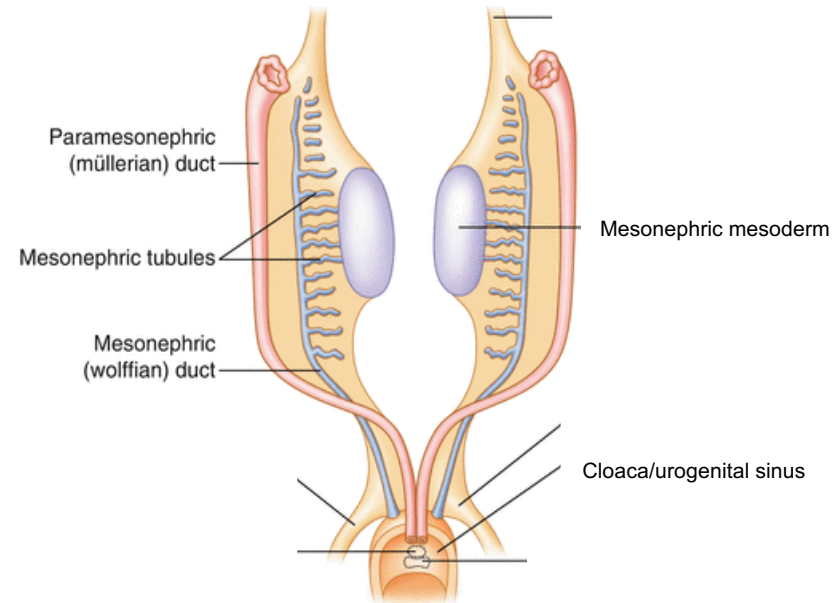
Paramesonephric (Müllerian) duct

Cloaca/urogenital sinus

Ureteric bud



Bipotential reproductive system



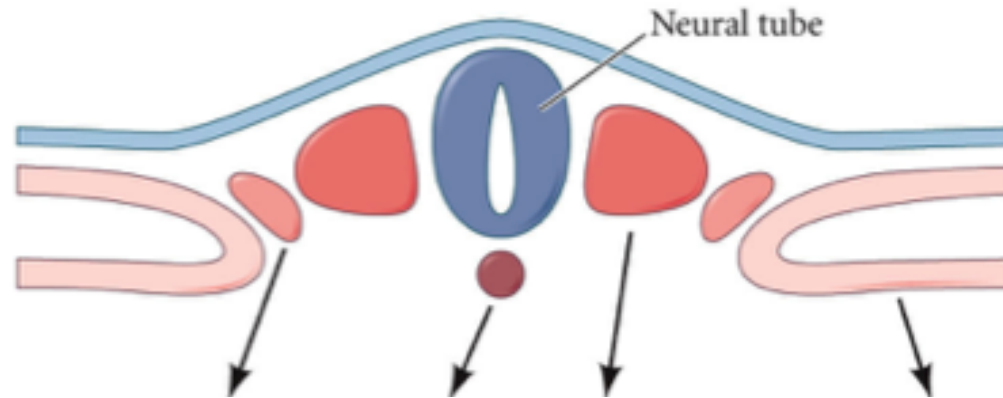
Embryonic origins of the reproductive system

Coelomic Epithelium

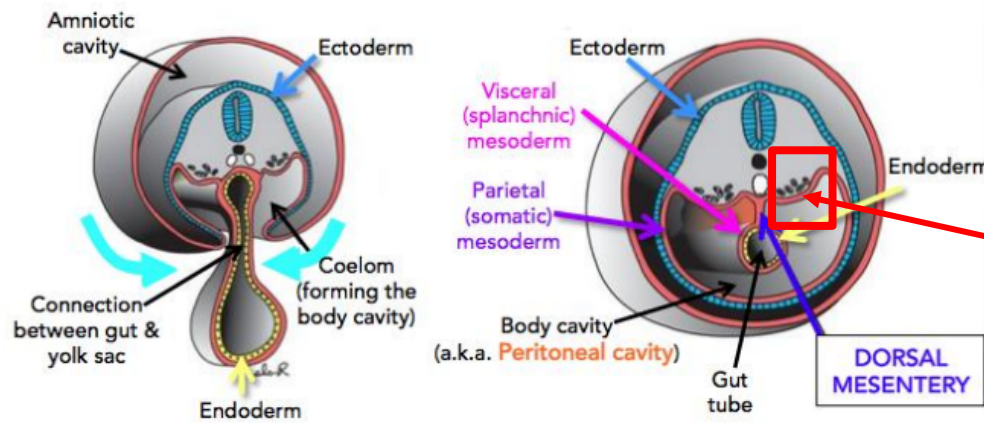
Mesothelium that lines body cavities and organs

Derived from lateral plate mesoderm

Somatopleure and splanchnopleure



Lateral plate mesoderm

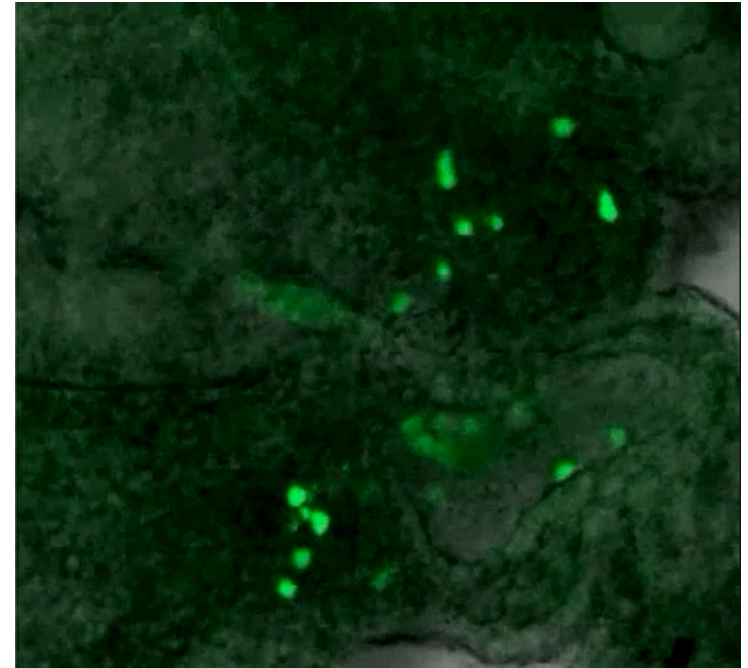
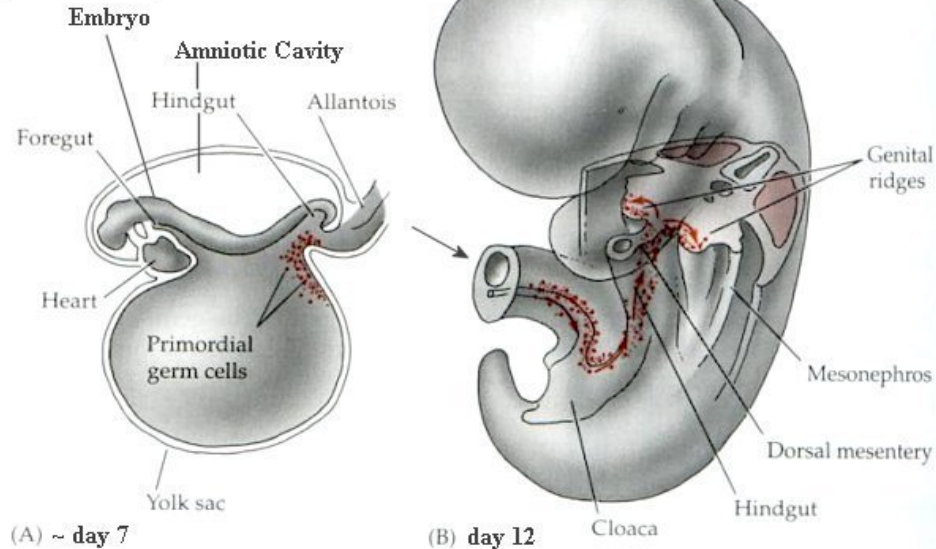


Coelomic epithelium:
mesothelium lining
the mesonephros

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 hindgut into the genital ridges

Envelopment by coelomic epithelial cells

Lecture overview

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Gonad development

Development of the reproductive tract

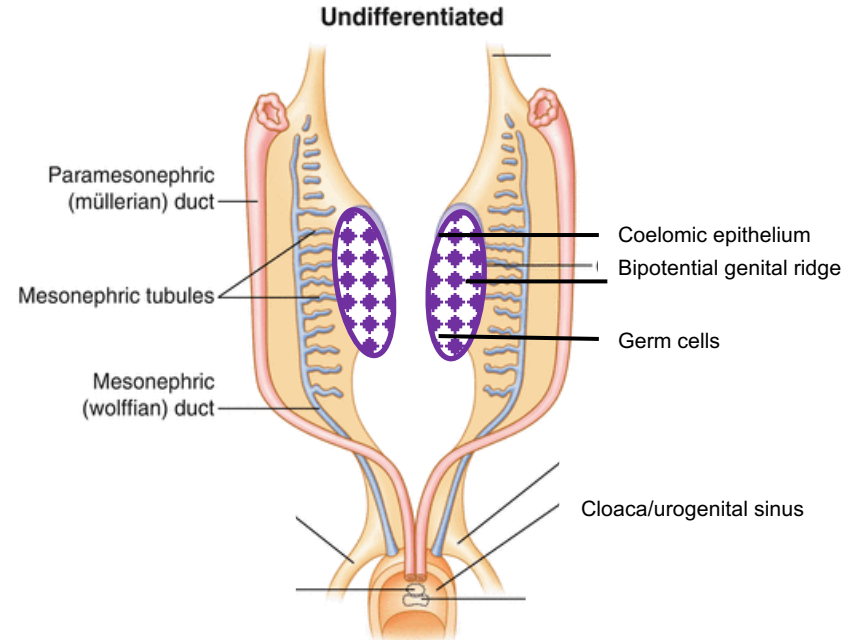
Development of the external genitalia

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:

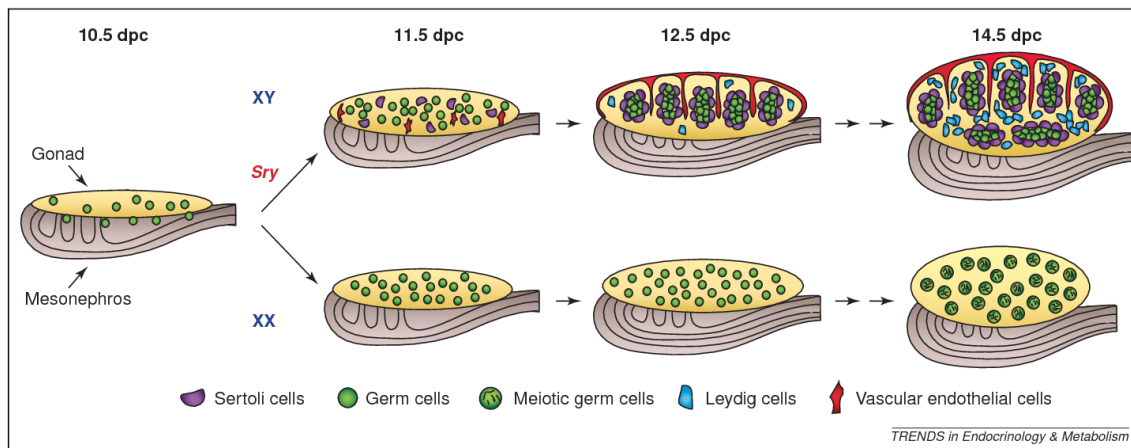
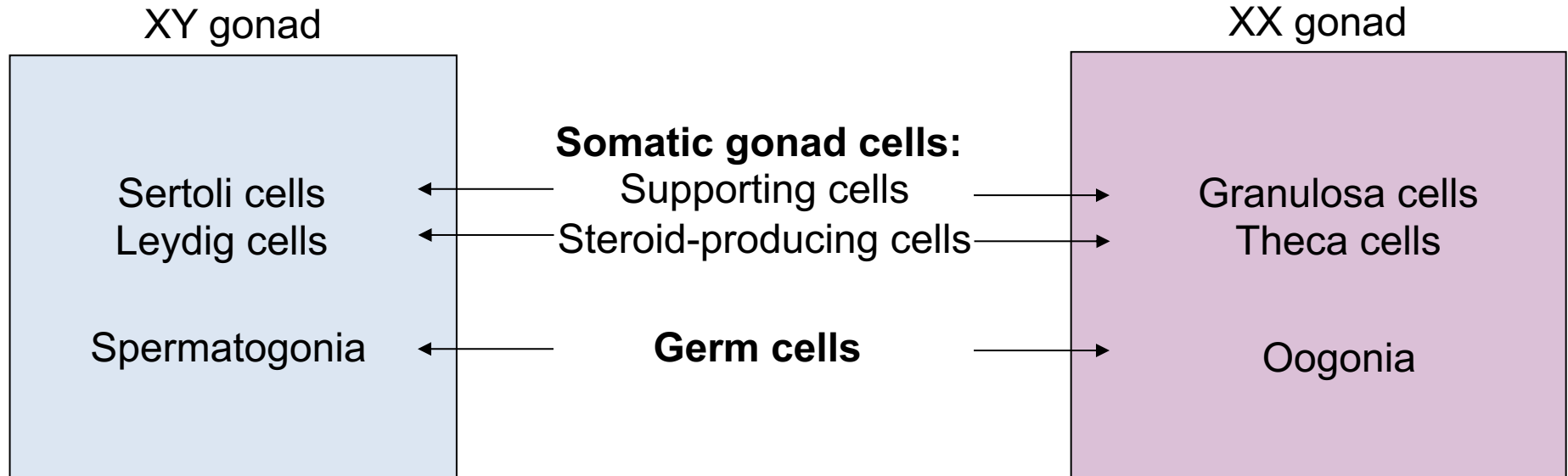
Mesonephric (Wolffian) duct

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

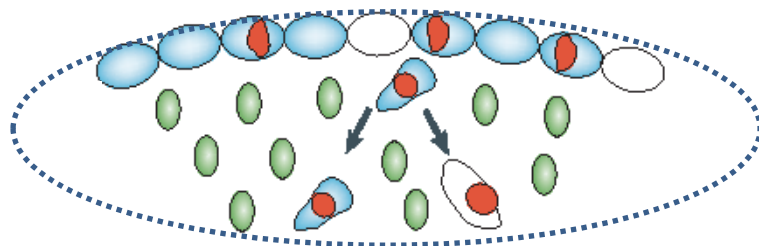
Sertoli cells envelop germ cells to form sex/testicular cords (seminiferous tubules)

Sertoli cells produce anti-Mullerian Hormone (AMH)

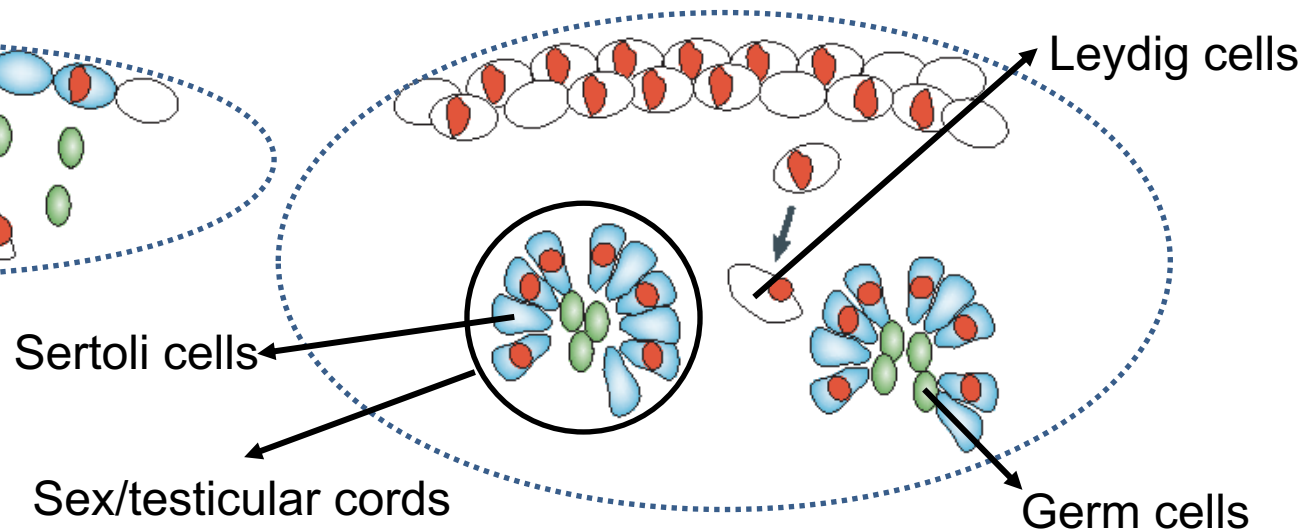
Fetal Leydig cells produce testosterone (masculinization)

Fetal Leydig cells 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 and undergo EMT (until after birth!)

Granulosa cells are derived from coelomic epithelium

Granulosa cells initially generate the ovigerous cords in ovarian cortex

Ovigerous cords envelop germ cells and fragment into ovarian follicles

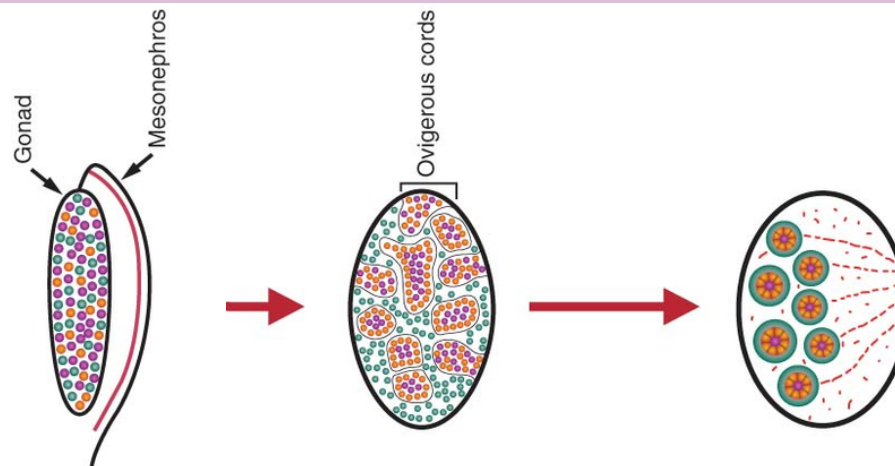
No clear follicles until later during fetal development

Granulosa cells:

- produce progesterone
- convert androstenedione (from Theca cells) to estrogen (feminization)

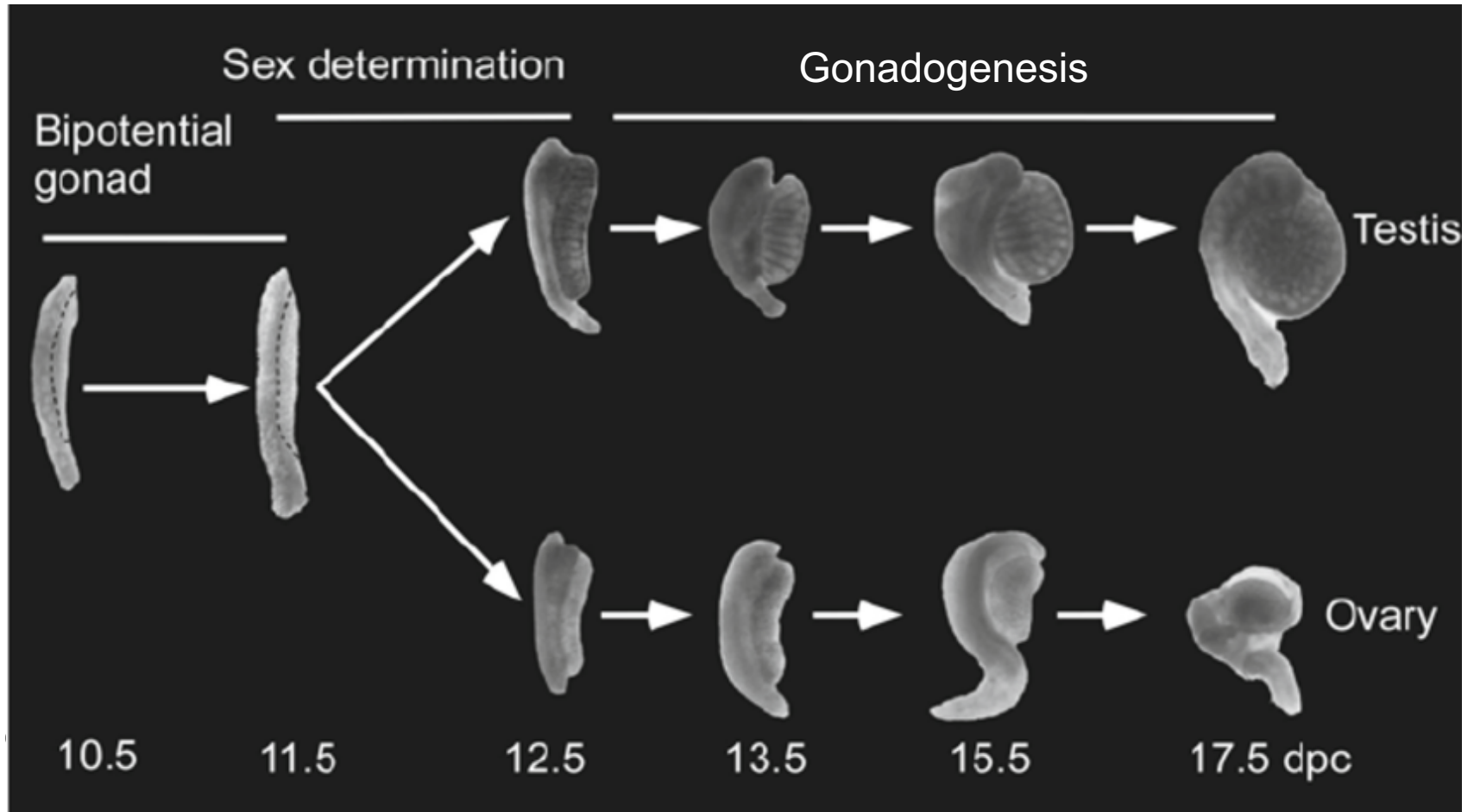
Theca cells are derived from mesonephric mesoderm,

They produce androstenedione (estrogen precursor)



Gonad Development

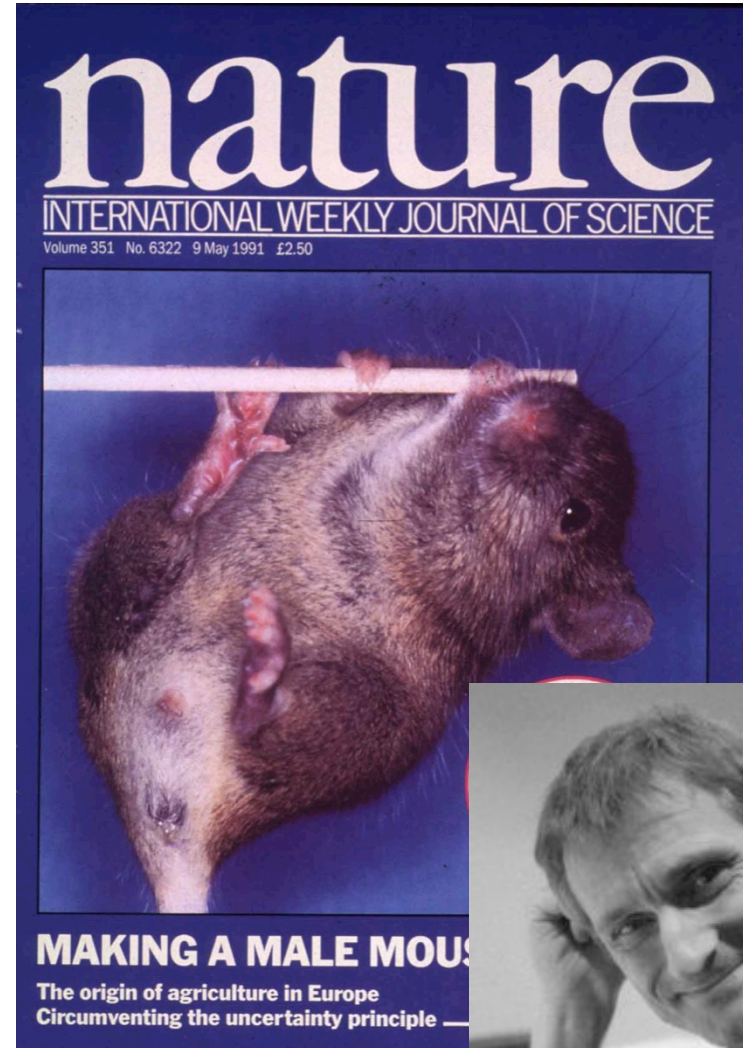
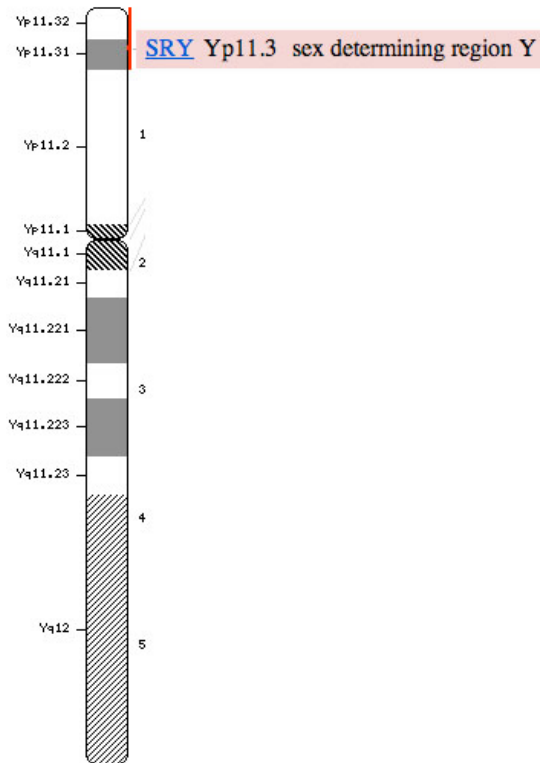
In mouse



Gonad Development

Sry, the male sex determining gene

Y chromosome

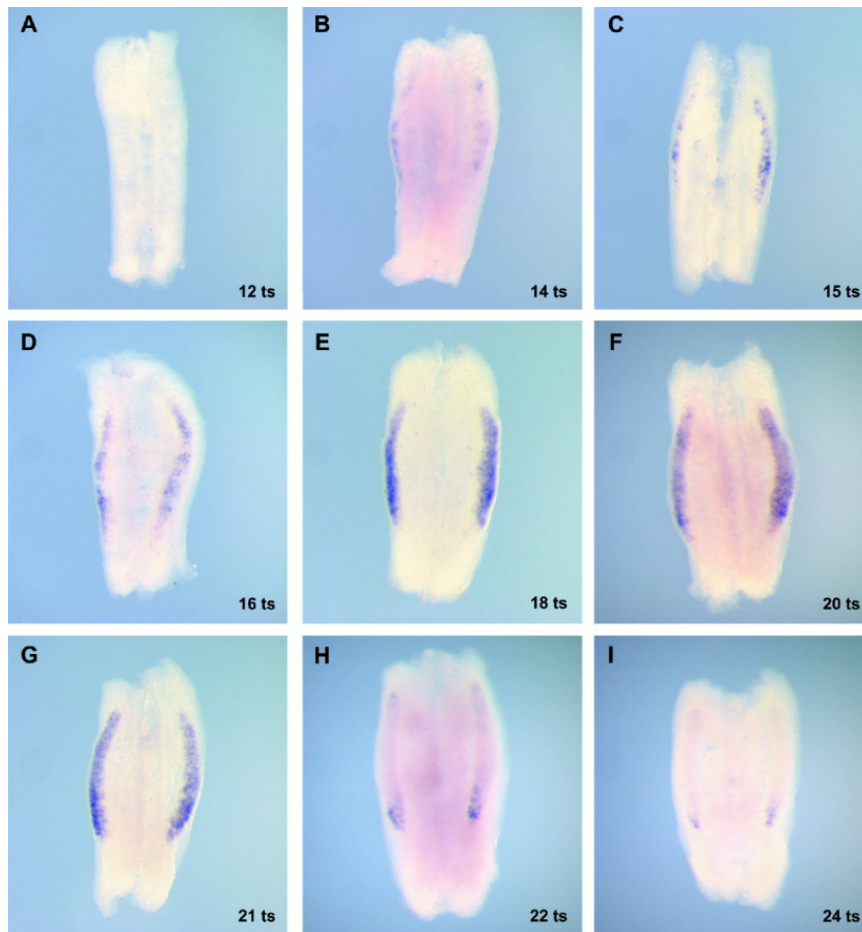


Peter Koopman

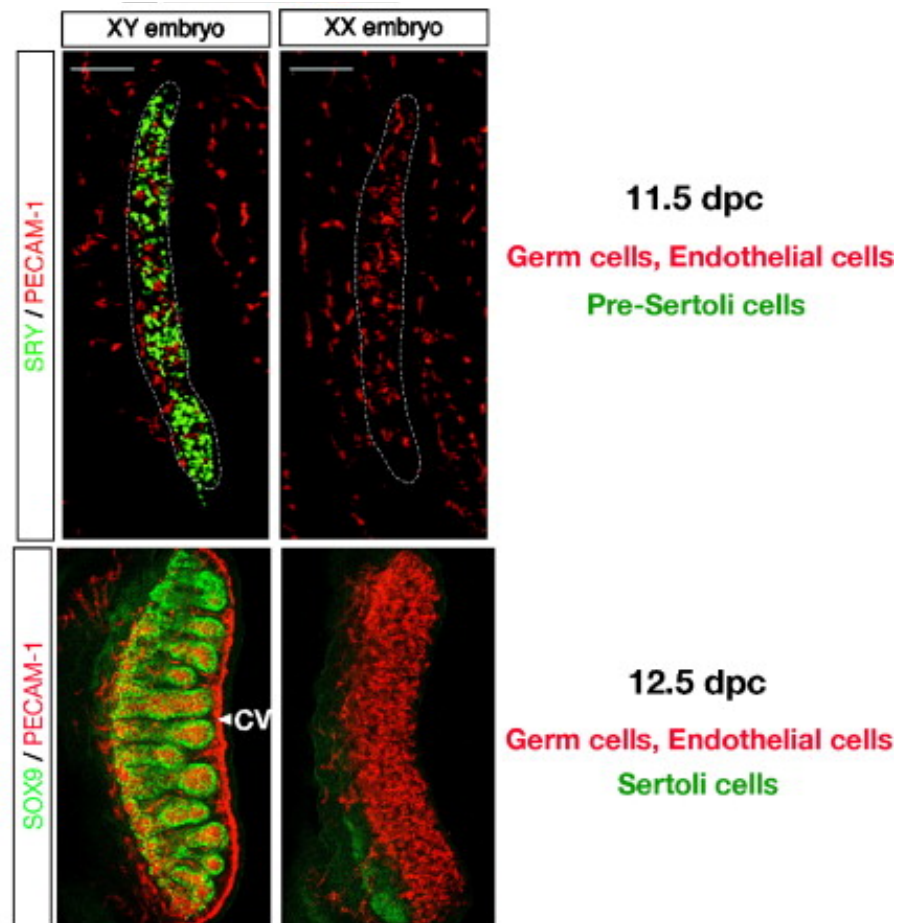
Gonad Development

Sry -> Sox9 -> Amh -> Testicular development

Wave of *Sry* expression
in pre-Sertoli cells

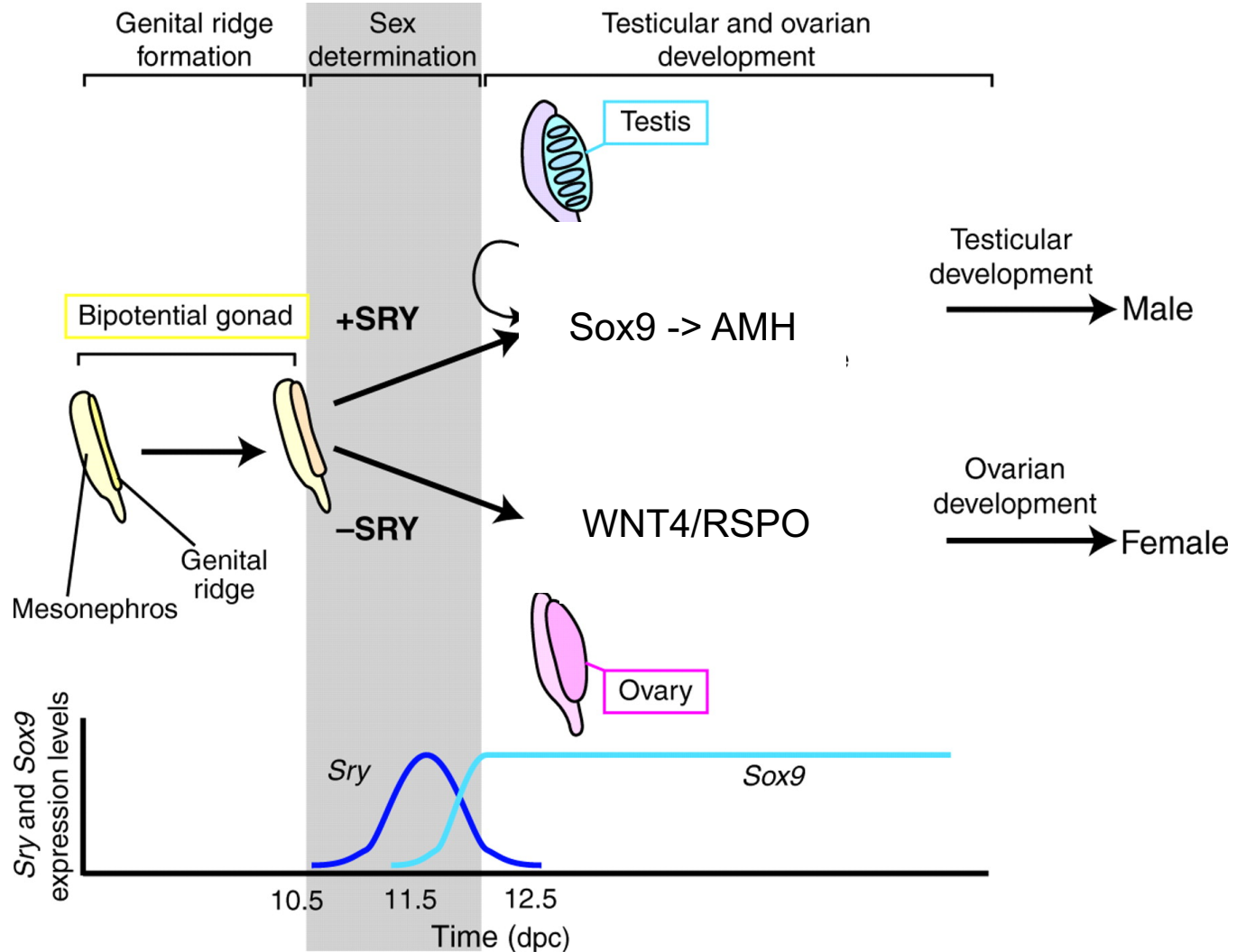


Sry is a transcription factor that activates
SOX9 expression in Sertoli cells



Gonad Development

Sry -> Sox9 -> Amh -> Testicular development



Lecture overview

Anatomy of the reproductive system

Sex determination

Embryonic origins of the reproductive system

Gonad development

Development of the reproductive tract

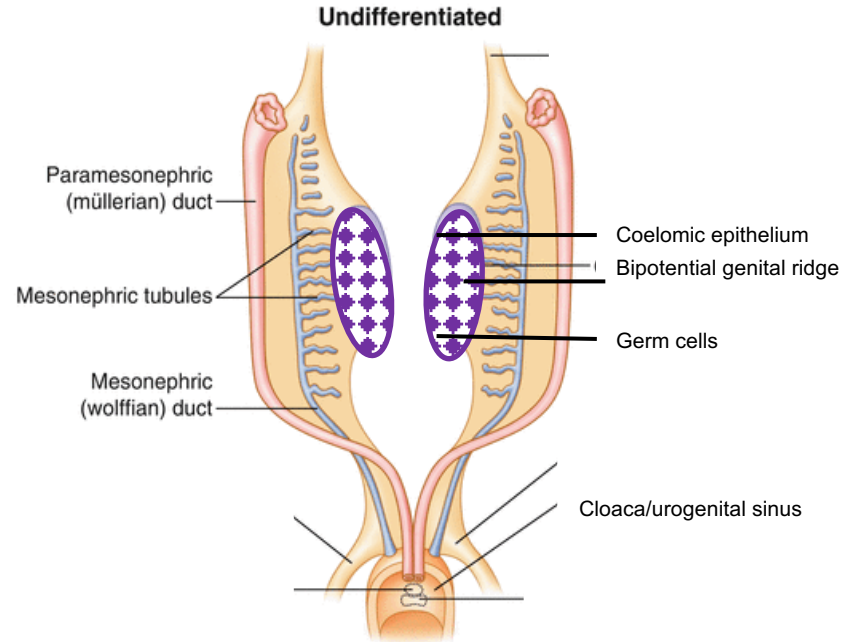
Development of the external genitalia

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:

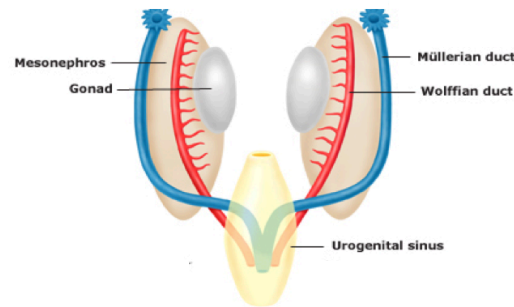
Mesonephric (Wolffian) duct

Paramesonephric (Müllerian) duct

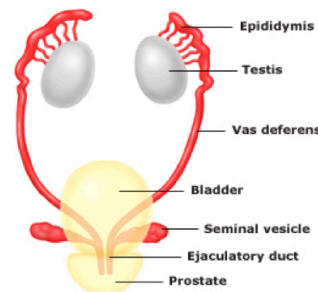
Urogenital sinus

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)

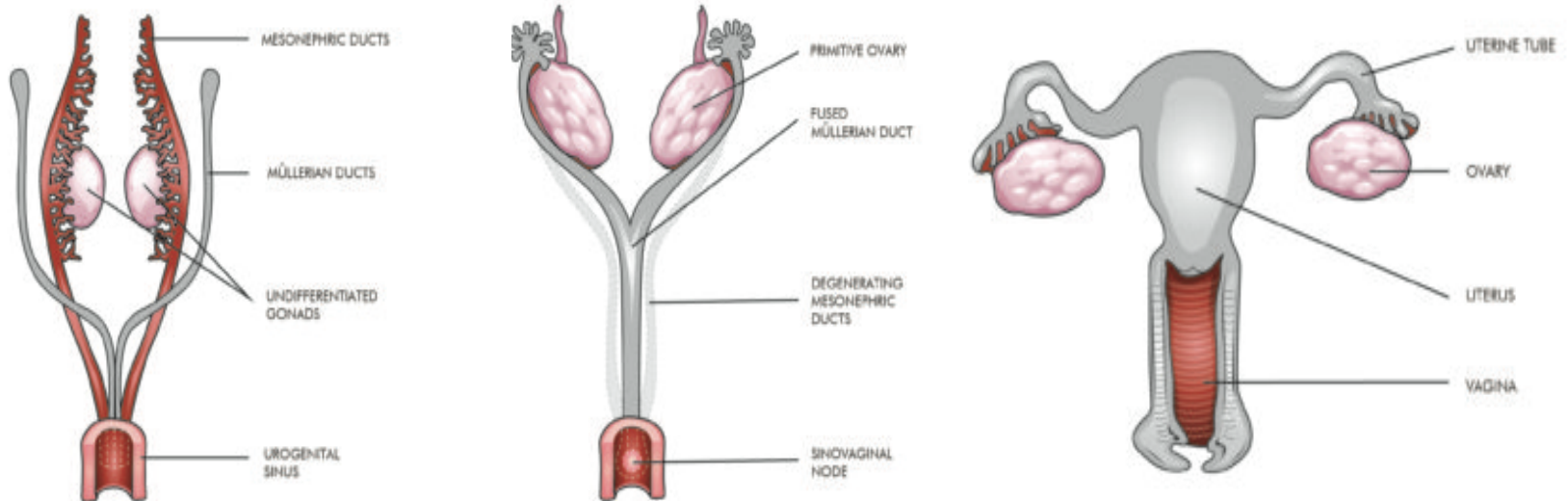


Development of XX Reproductive Tract

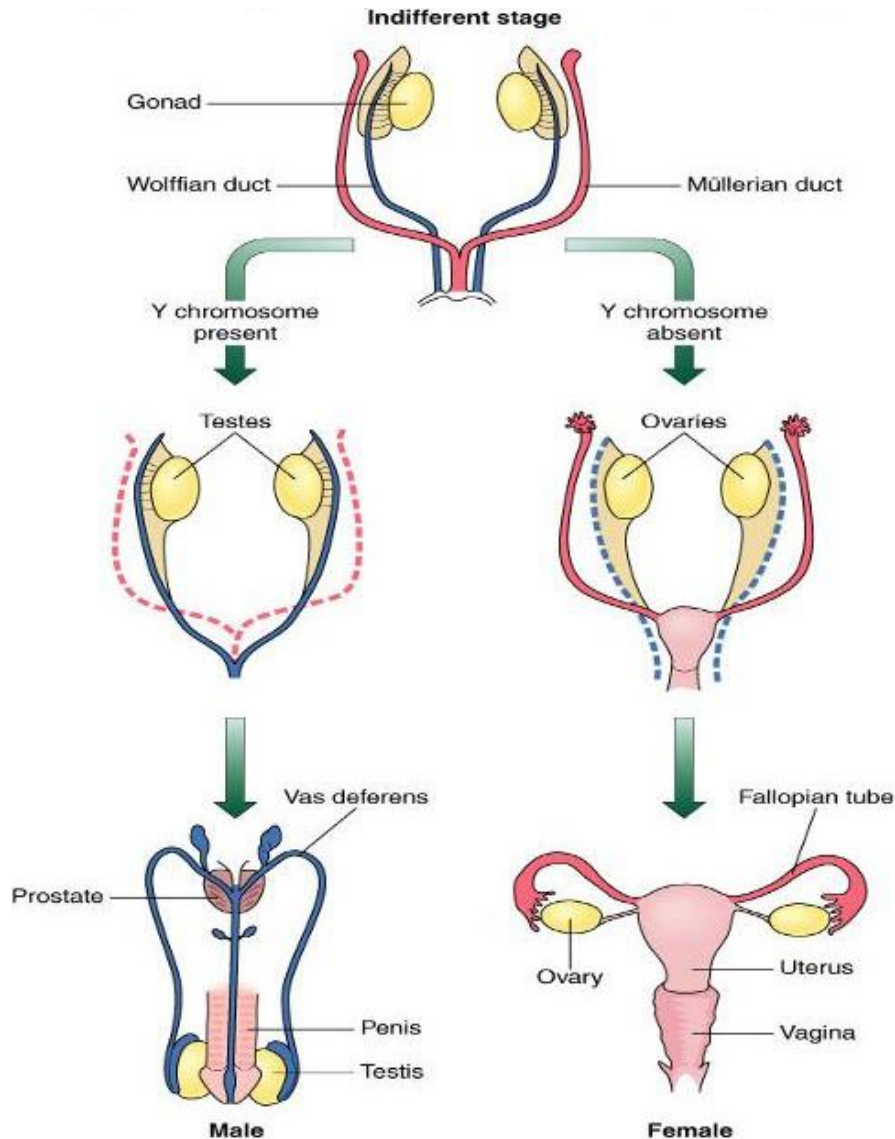
No testosterone: Mesonephric/Wolffian duct regresses

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

Epididymus

Vas deferens

Female:

Ovary

Müllerian Duct:

Fallopian Tubes

Uterus

Cervix

Upper Vagina

Development of the reproductive tract

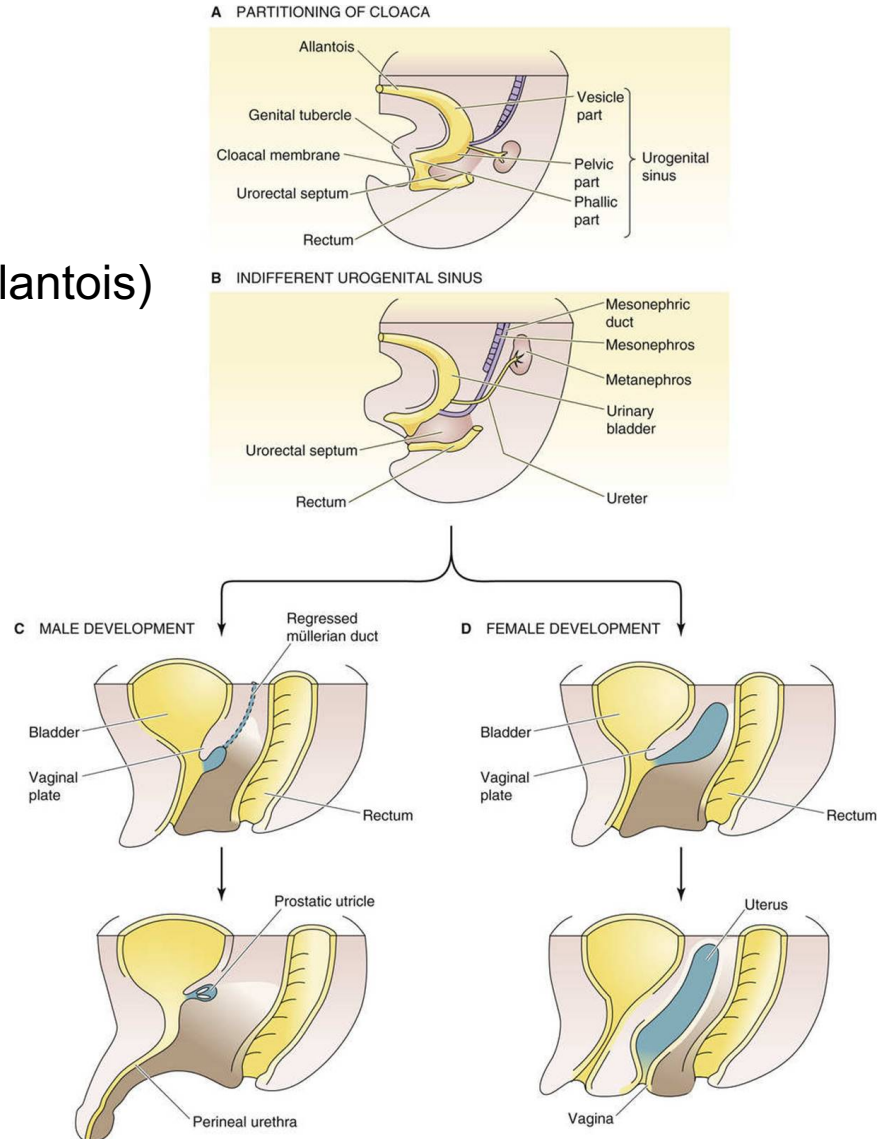
XY Urogenital Sinus

Urorectal septum separates hindgut from urogenital sinus (continuous with allantois)

Mullerian ducts regress (except for caudally: prostate gland)

Wolffian ducts:
Vas deferens ends in urogenital sinus

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



Development of the XX Reproductive Tract

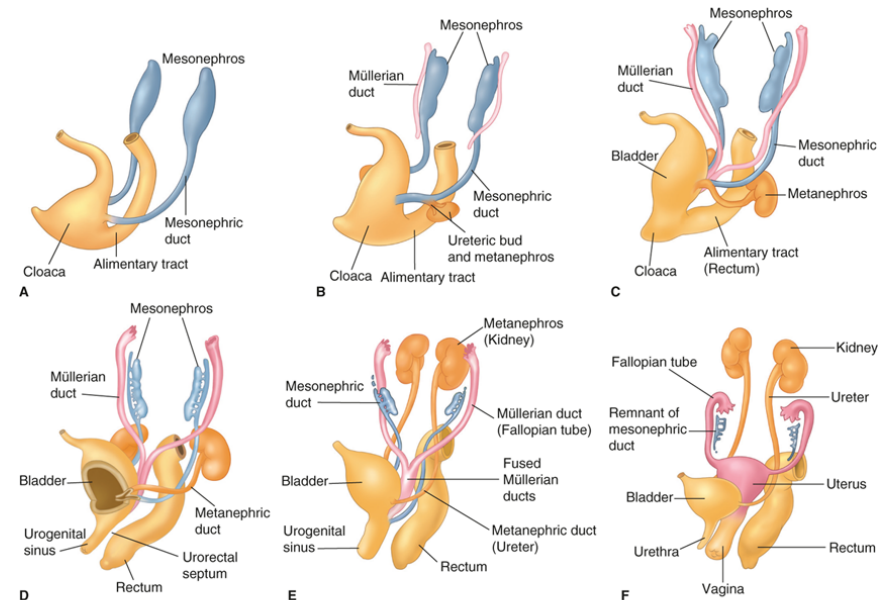
Urogenital sinus

Urorectal septum separates hindgut from urogenital sinus

Wolffian duct degenerates

Müllerian duct:

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



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

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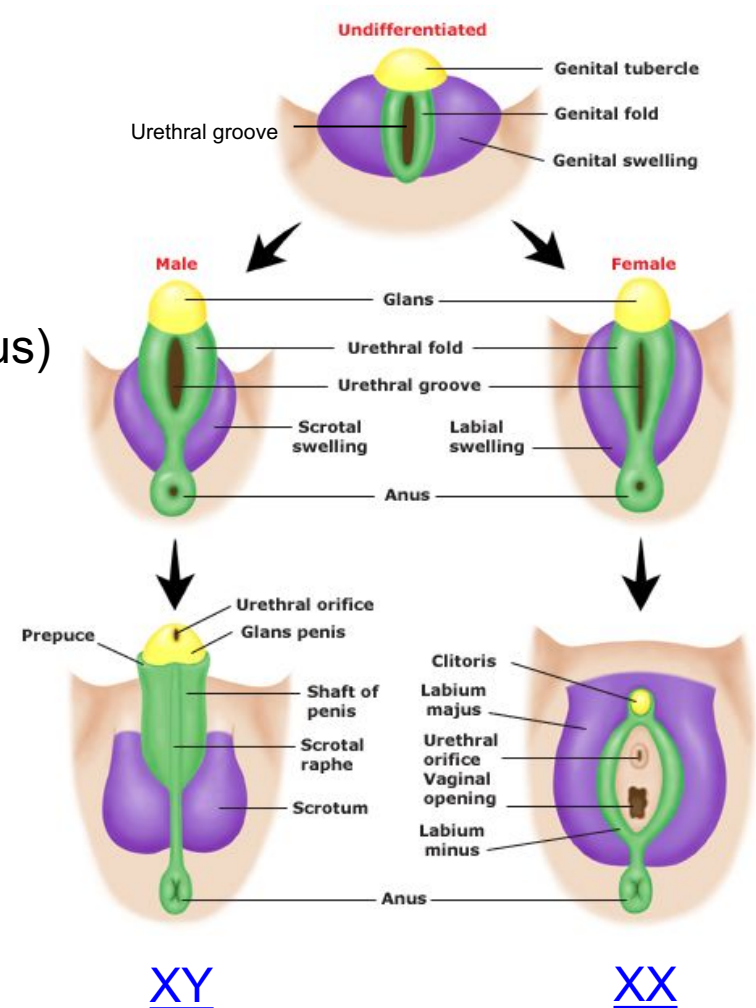
Development of the external genitalia

Embryonic genitalia are bipotential

Bipotential genitalia consist of:

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

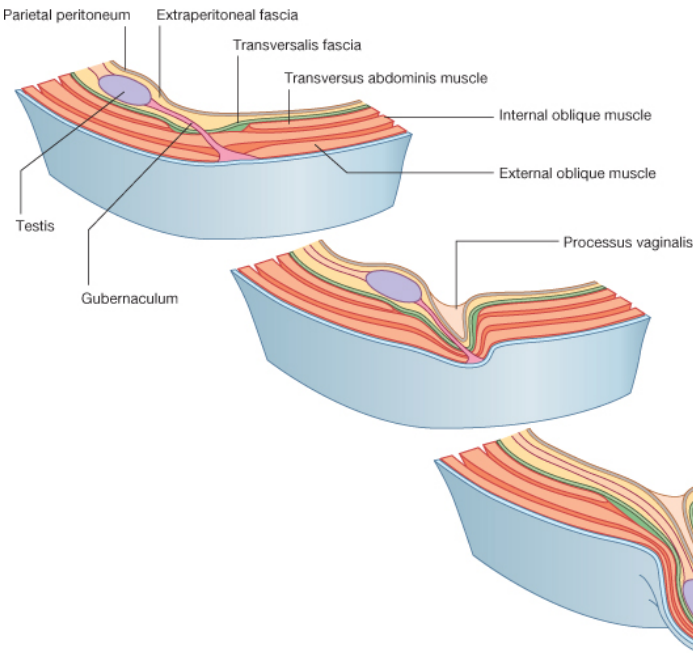
XY: Dihydrotestosterone by fetal Leydig cells



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

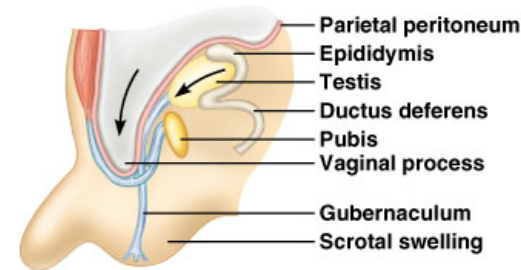
Development of the external genitalia

Descent of Testes

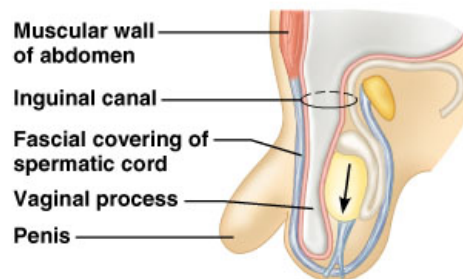


© Elsevier Ltd. Drake et al: Gray's Anatomy for Students www.studentconsult.com

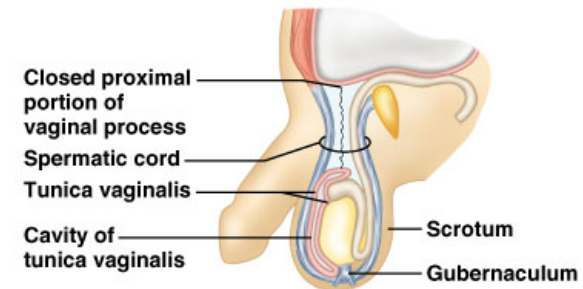
Late fetal event
 Gubernaculum (connective tissue ligament)
 Inguinal canal
 Processus vaginalis: peritoneal fold ending in the scrotal sac



(a) 7-month fetus



(b) 8-month fetus



(c) 1-month old infant

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Development of 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

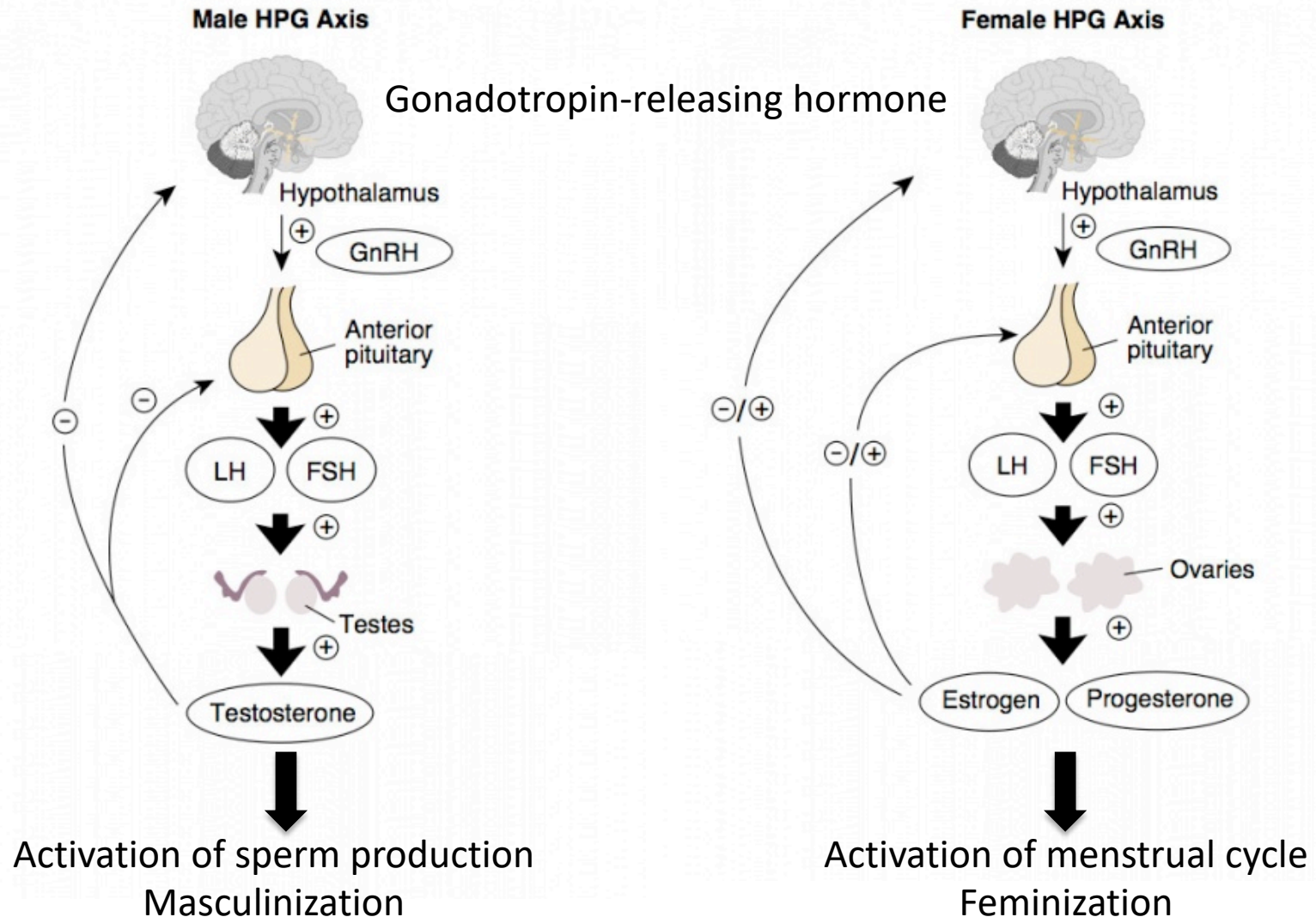
- Dependent on gonad development
- Occurs during embryonic development

3. **Development of secondary sex characteristics**

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

Development of secondary sex characteristics

Puberty



Lecture overview

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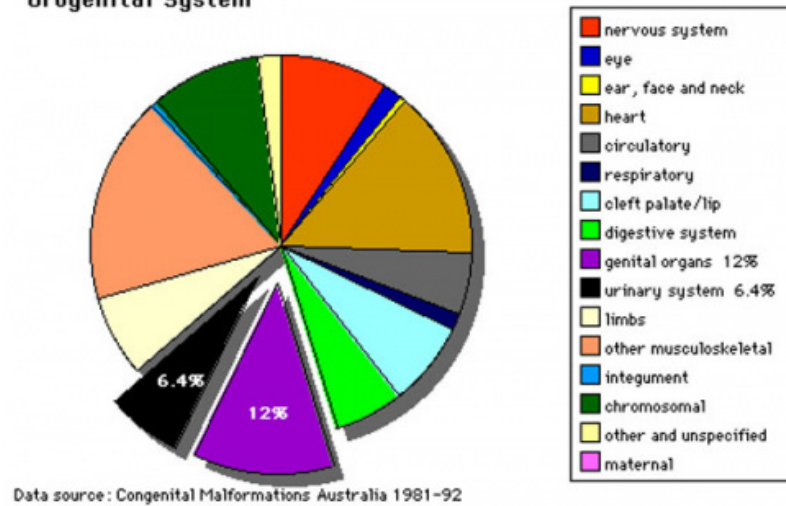
Development of the external genitalia

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!

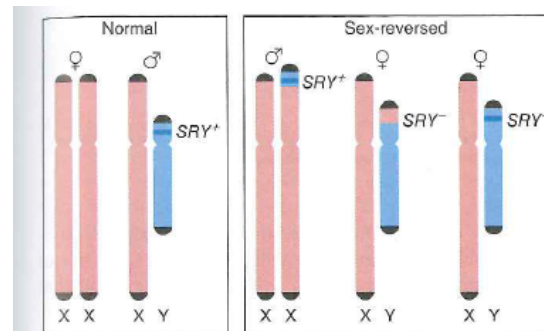
Disorders of Sexual Development

Sex reversal syndromes

Chromosomal sex does not match phenotypic sex:

- XX males
 - Transfer of some Y chromosome DNA onto X chromosome
 - Gonads develop as testes following *Sry* activation
 - Development as phenotypic male
 - Infertility

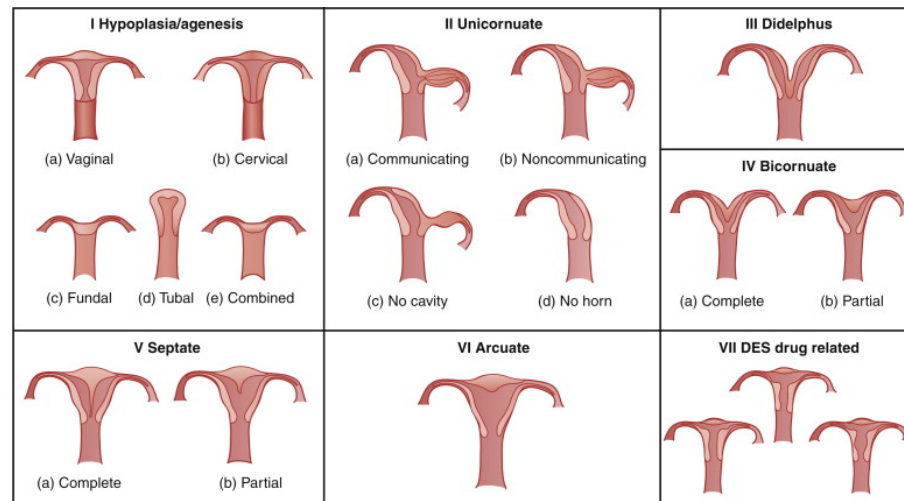
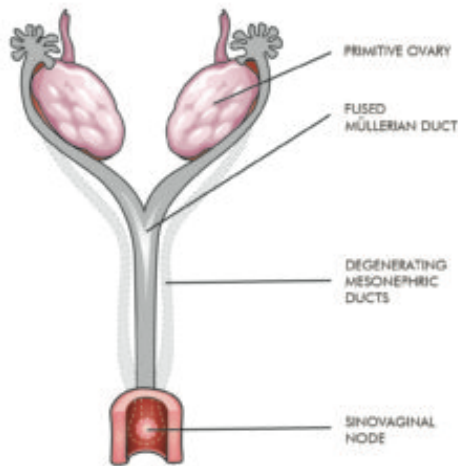
- XY females
 - Usually: steroidal origin:
 - Androgen insensitivity syndrome: mutations in androgen receptor
 - 5-alpha reductase deficiency: defective testosterone metabolism
 - Rarely: chromosome rearrangements or inactivating mutations in *Sry* gene



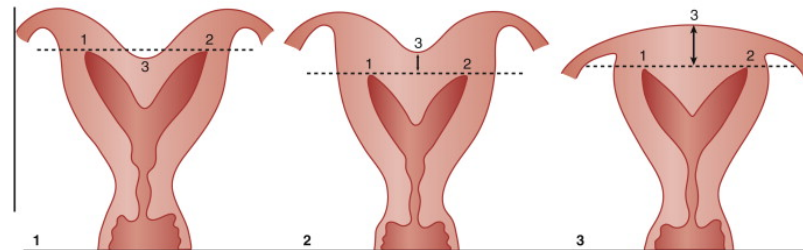
Disorders of Sexual Development

Female Reproductive Tract Abnormalities

Due to fusion failures of the paramesonephric/Mullerian duct



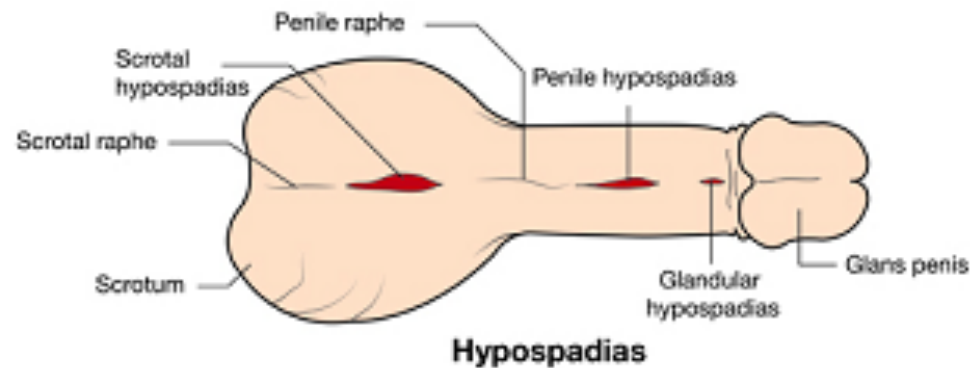
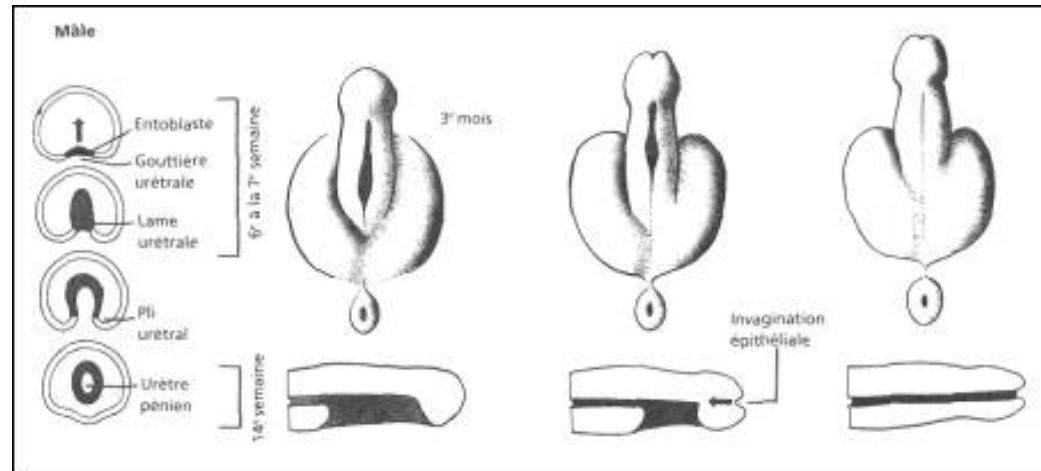
A



B

Disorders of Sexual Development

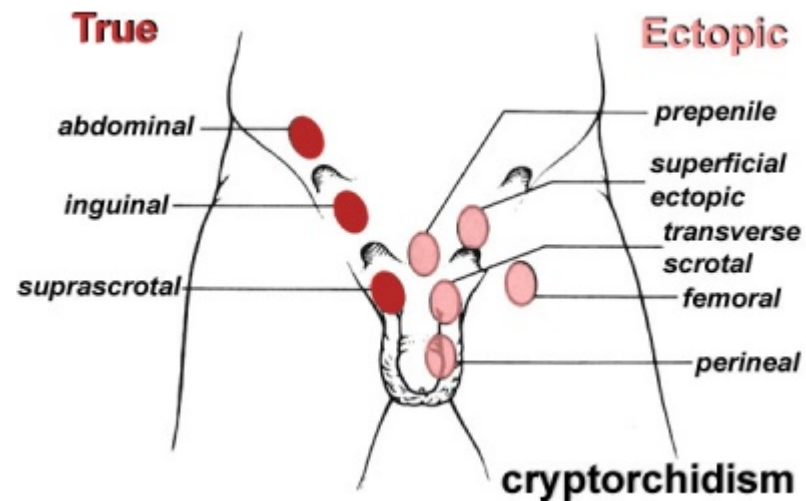
Hypospadias: incorrect closure of the genital folds



Disorders of Sexual Development

Cryptorchidism

Failure of correct gonad descent

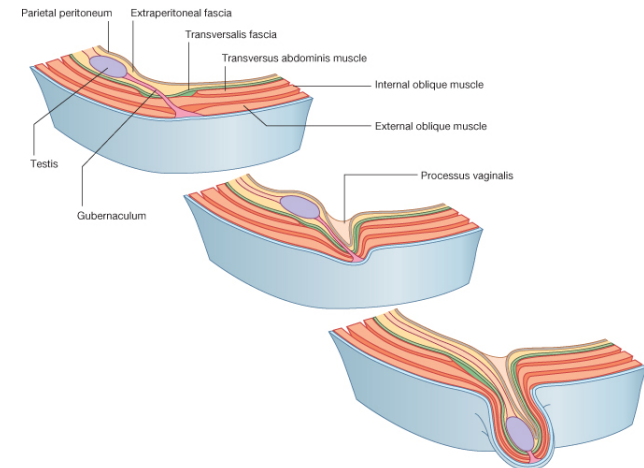
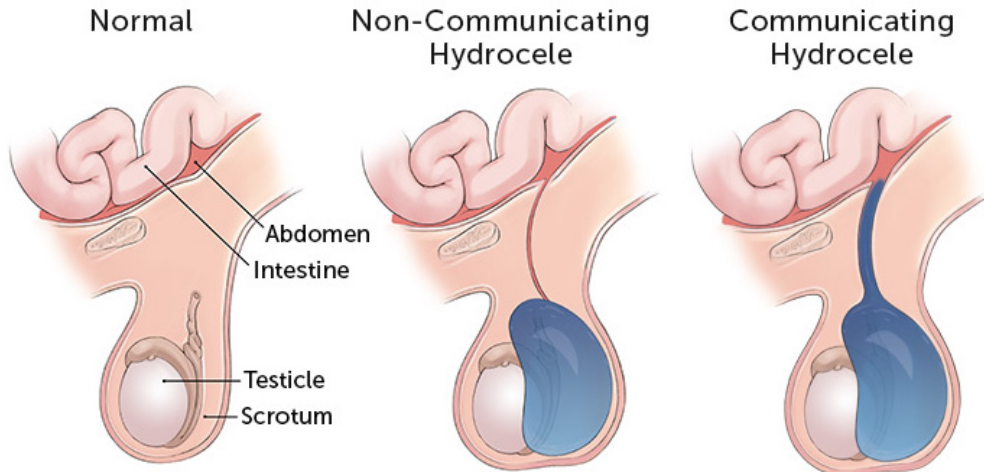


Disorders of Sexual Development

Hydrocele testes

Peritoneal fluid enters scrotal sac through processus vaginalis

Processus vaginalis: peritoneal fold ending in the scrotal sac



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