Sex Determination

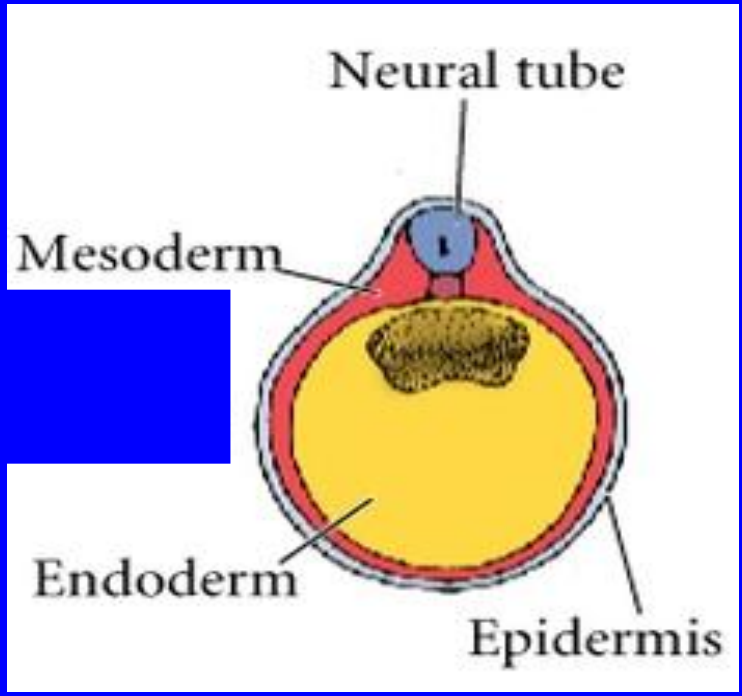
- Most animal species are *dioecious*
  - 2 sexes with different gonads
    - Females: produce eggs in ovaries
    - Males: produce sperm in testes
- Exception
    - Hermaphrodites: have both types of gonads
- Many animals also differ in secondary traits

What Determines Sex?

- Individual differentiates into male or female
- Causes
  - Genetic factors (sex chromosomes)
    - occur at fertilization
  - Environmental factors
    - occur after fertilization

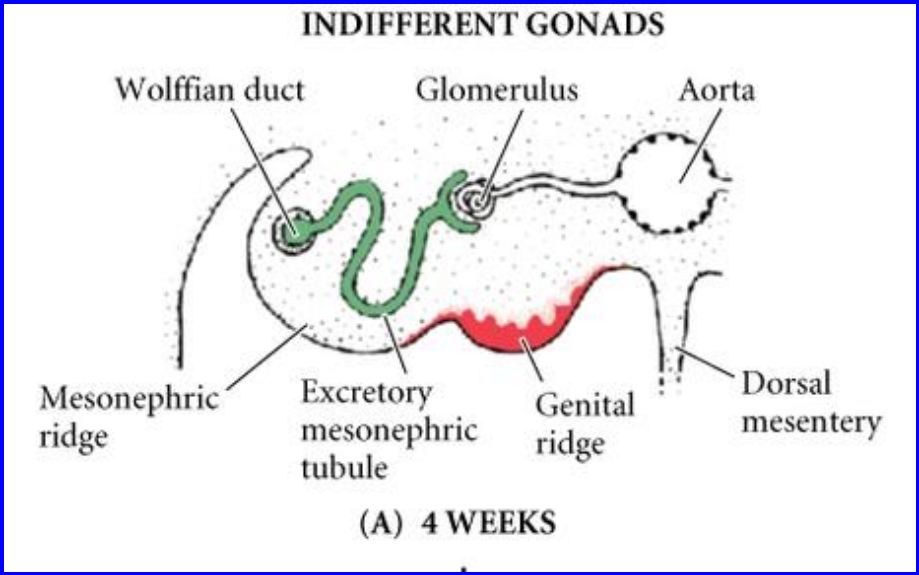
How Do Vertebrate Gonads Develop?

- Gonad differentiation
  - first morphological difference between males and females
- Gonads develop from intermediate mesoderm
- Paired structures



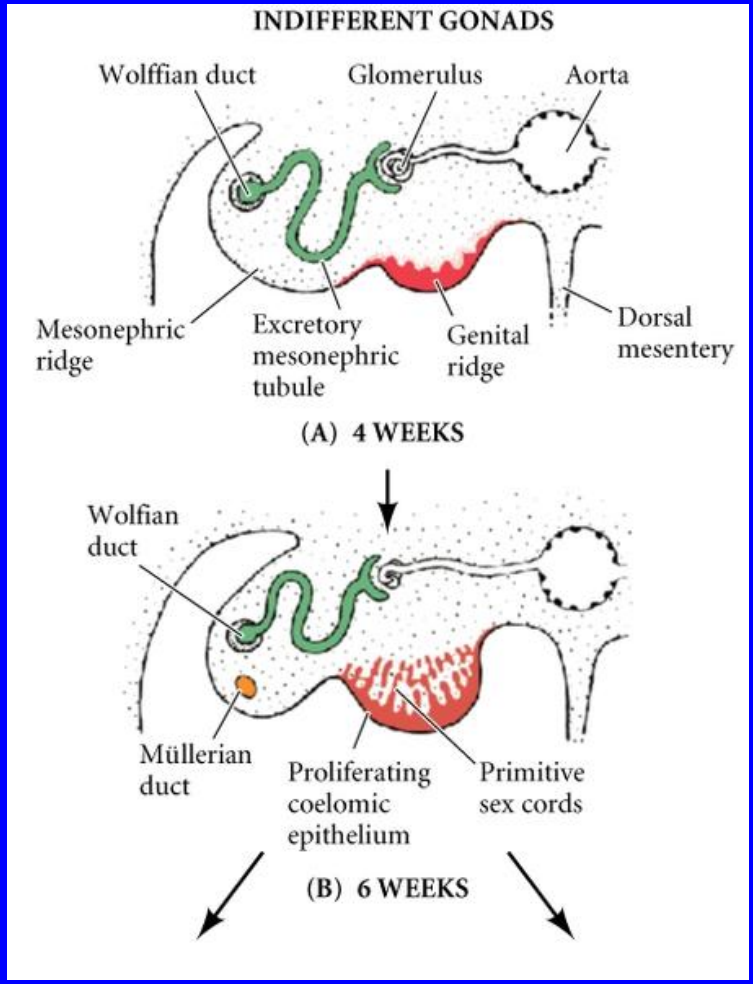
What is a Bipotential Gonad?

- Indifferent gonad develops
  - 4-6 wks in human = "bipotential stage"
  - genital ridge forms next to developing kidney (mesonephric ridge)



Structure of the Indifferent Gonad

- Sex cords form
  - Columns of epithelial cells penetrate mesenchyme
  - Primordial germ cells migrate from posterior endoderm
  - Become surrounded by sex cords

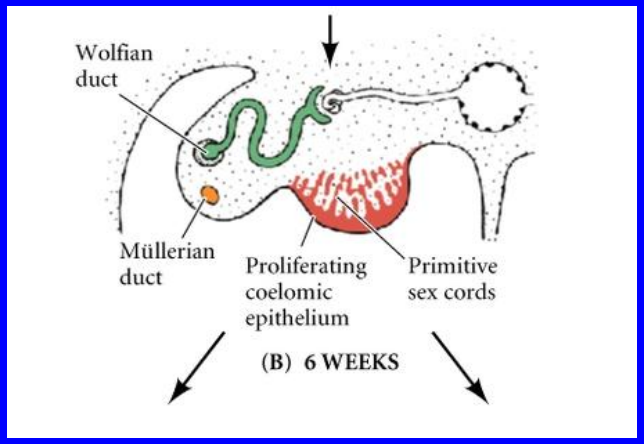


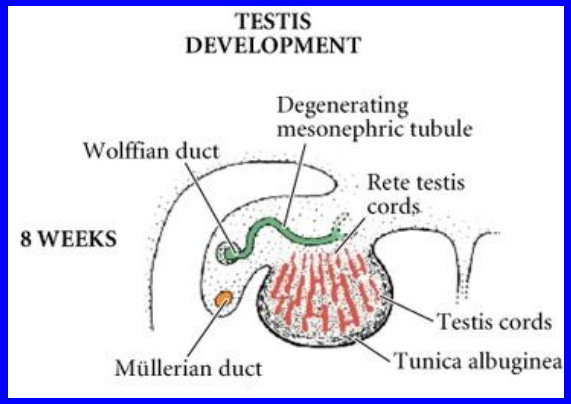
What is the Fate of the Sex Cords?

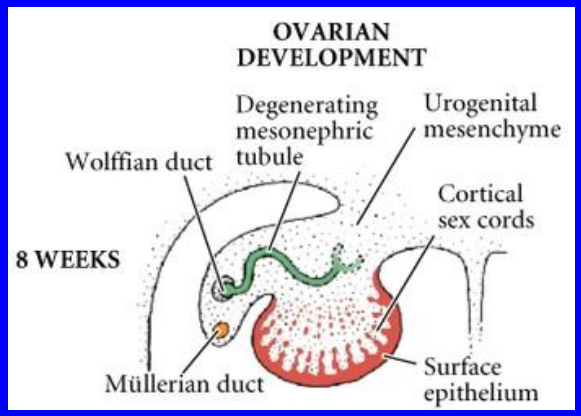
- Initially in central area (medulla, medullary)
  - Will develop in male
  - Proliferate
- In outer area (cortex, cortical)
  - Develop in female
- Normally binary choice

Differentiation of the Gonad

- Into testes or ovaries
  - primary sex determination
  - does not involve hormones





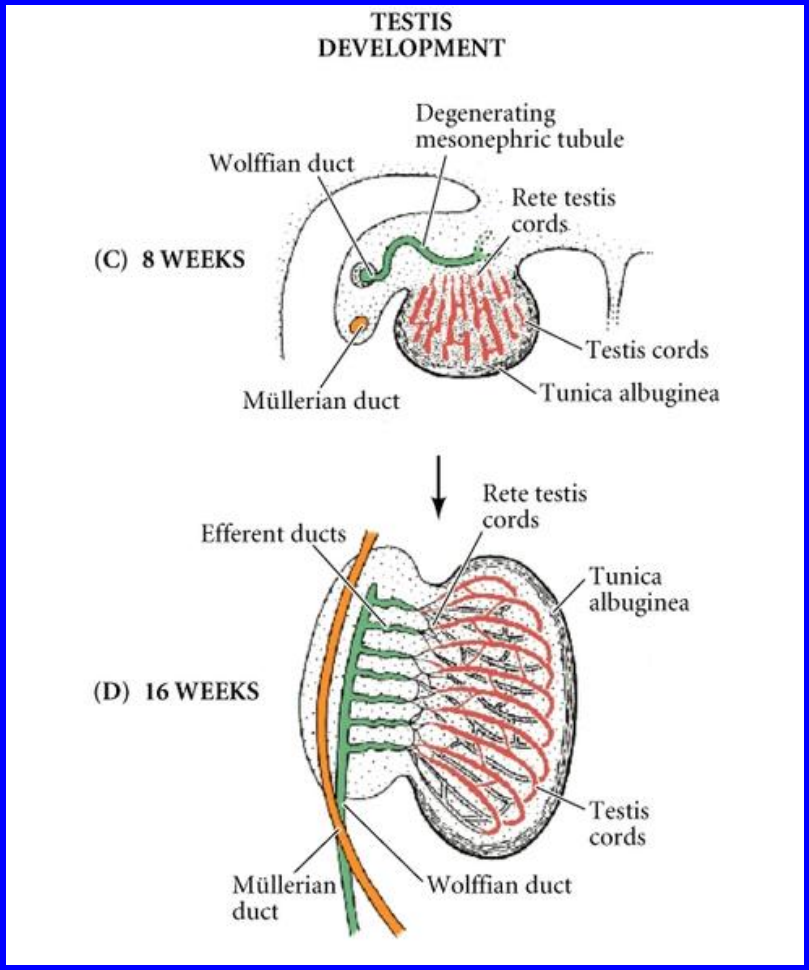


network of internal sex cords (at puberty: --> seminiferous tubules, Sertoli cells

new cortical sex cords cluster around each germ cell

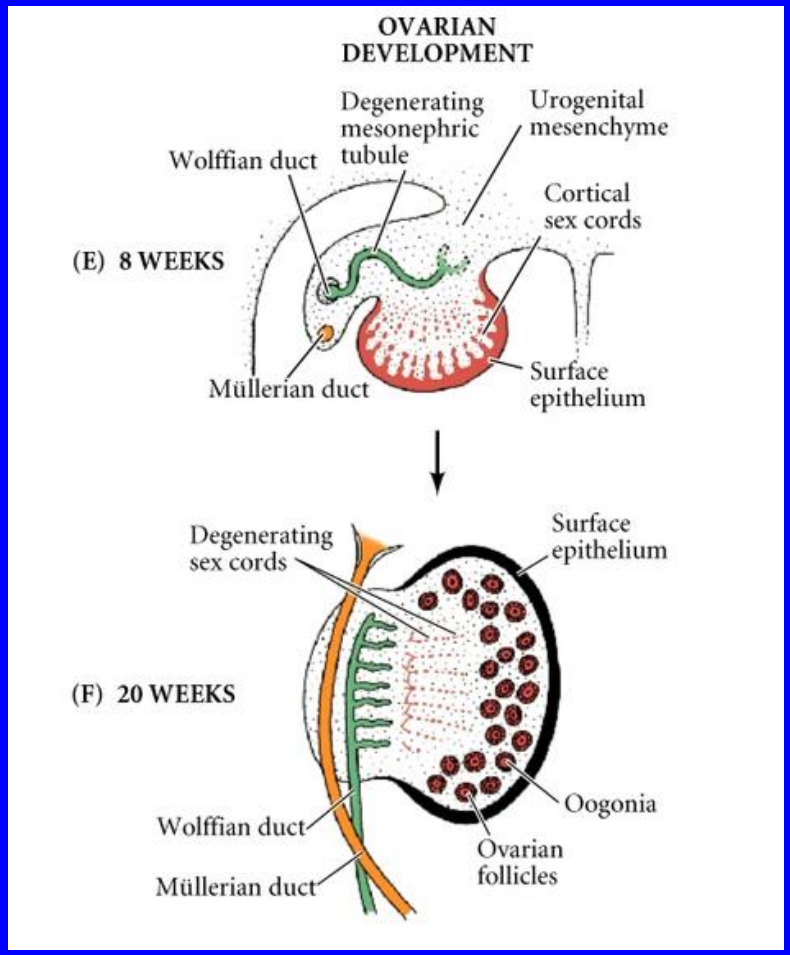
Male Differentiation

- Male sex cords or testis cords proliferate and cortex becomes thick layer of extracellular matrix
- Male germ cells inhibited from entering meiosis
- Secrete factors causing cord cells to become Sertoli cells



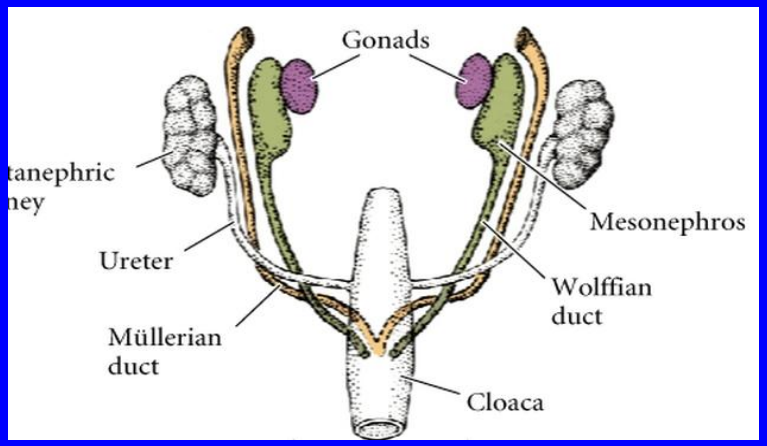
Female Differentiation

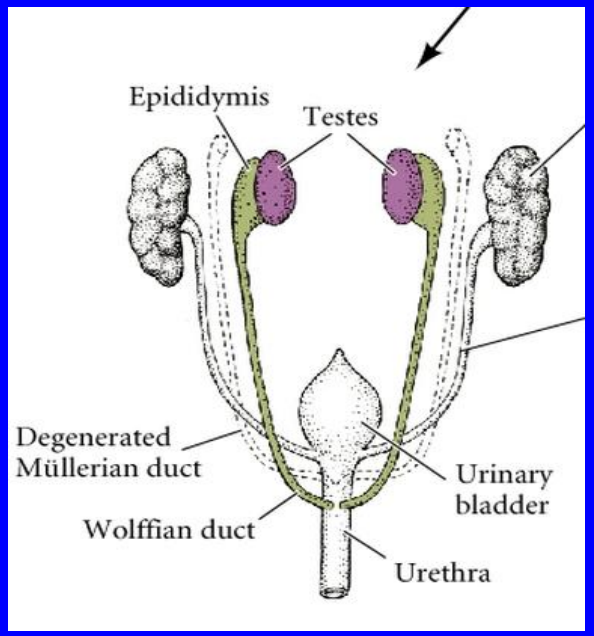
- Female germ cells in cortex enter meiosis
- New sex cords form there and form clusters
- Germ cell becomes egg
- Cord cells become granulosa cells
- Surrounnding mesenchyme cells become thecal cells
- Thecal + granulosa = follicle



Male Ducts

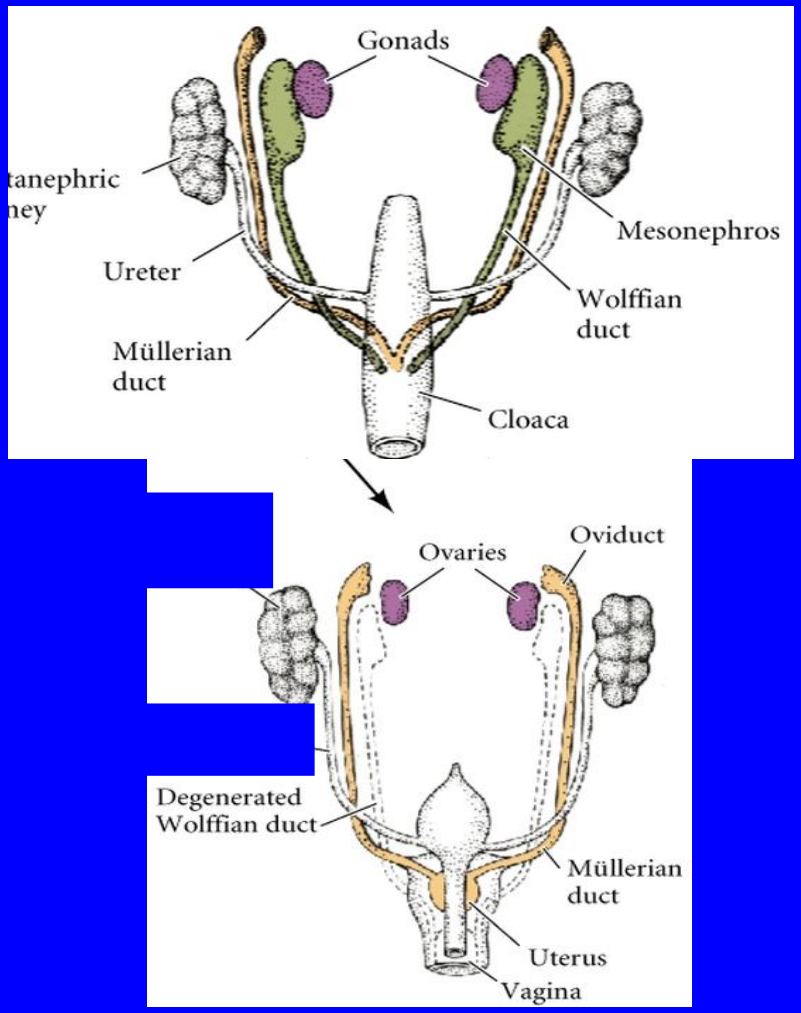
- Provide exit for gametes
  - In males remnants of mesonephric kidney called Wolffian ducts
  - Differentiates into *vas deferens* and *epididymis*
- Supported by testosterone
  - Made by Leydig cells
  - Leydig cells come from mesenchyme



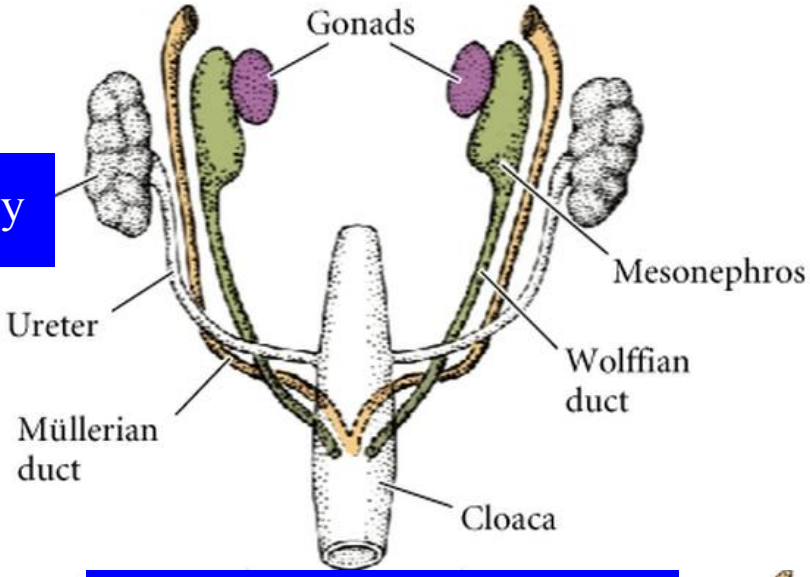


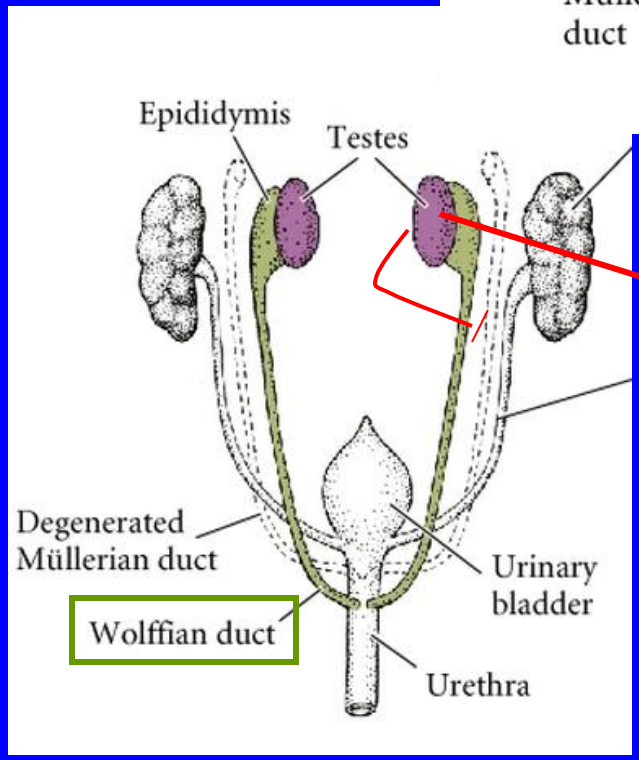
Female Ducts

- Also provide exit for gametes
  - In females, Mullerian duct part of gonad
  - Differentiates into *uterus, oviducts* and upper *vagina*
- Supported by estrogen
  - Destroyed in males by anti-Mullerian duct hormone



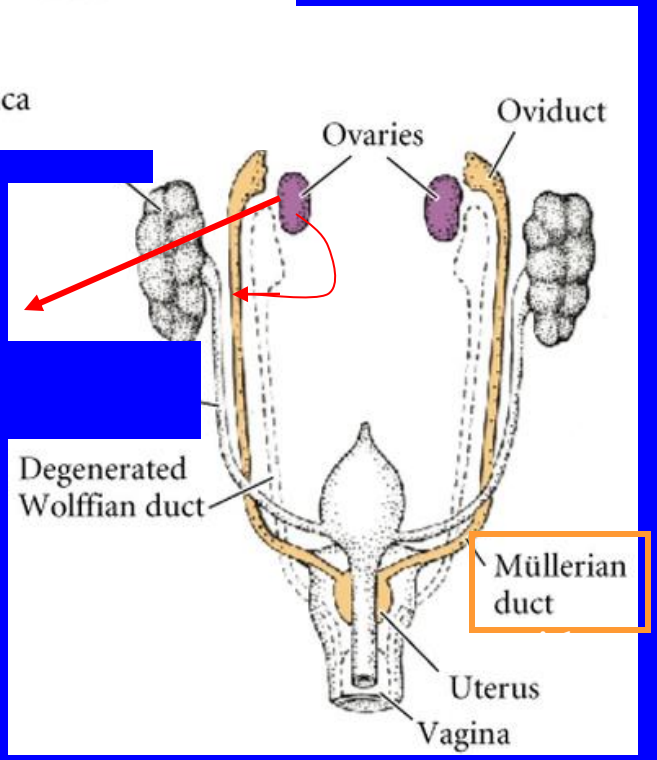
kidney





hormones

Secondary sex determination



Secondary Sex Determination

- Determination of *non-gonadal* differences
  - Females: oviduct, uterus, cervix, mammary glands
  - Males: vas deferens, seminal vesicle, penis, prostate glands
  - Also, non reproductive traits such as body size, vocal cords, musculature, etc.
- Usually depends on primary sex determination

Secondary Sex Determination

- Experiment:
- Remove gonad of young rabbit fetus before differentiation

  - XX Rabbit ----------> appears as female
  - XY Rabbit ----------> appears as female

  - Female = default path of secondary sex determination

How is Primary Sex Determination Triggered?

- Chromosomes: XX or XY?
  - What are the genes involved?
  - Compare to model systems (*Drosophila*, *C.elegans*)

Testis Determining Factor

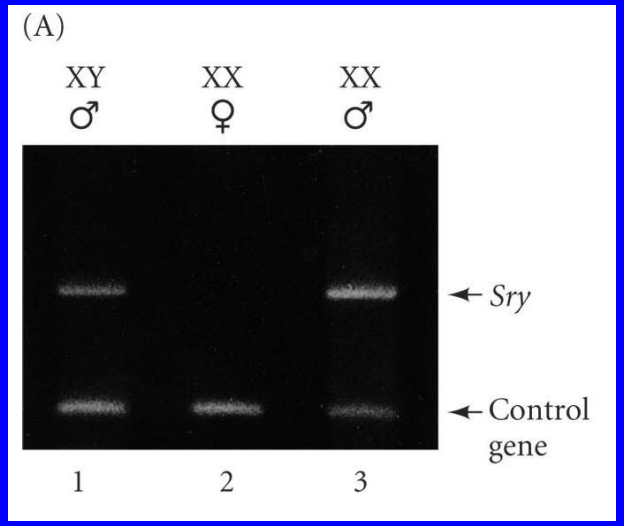
- XX and XXX are female
- XY and XXY are male
  - Must be a "testis determining factor on the Y chromosome"
  - Search for TDF
- Sex-reversed Females: XY
  - deletion of short arm of Y
- Sex-reversed Males: XX
  - addition of small piece from Y

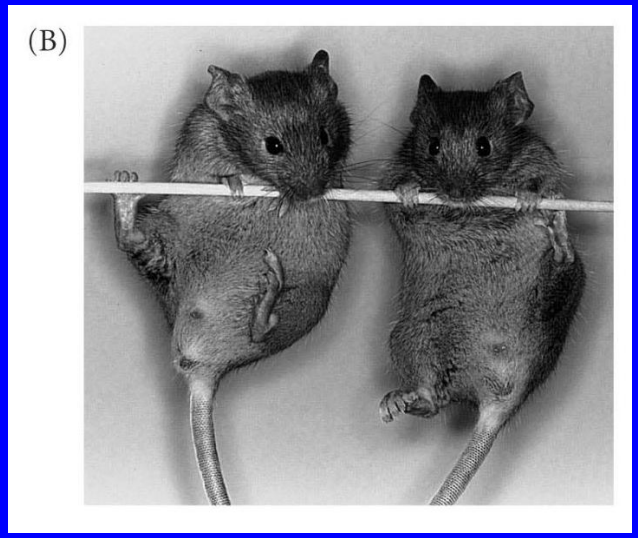
SRY

- SRY identified
  - SRY = sex-determining region of the Y chromosome
  - Encodes a 223 a.a. protein
  - Transcriptional regulator of testes-specific genes
    - possible splicing factor
  - Where is SRY expressed?

SRY Directs Male Development

- Experiments with mice and SRY:
  - Mouse Sry is expressed in the bipotential gonad of males
    - Disappears after testes differentiate
  - Transgenic mice
    - inject Sry into pronuclei of newly fertilized mice
    - find some "male" looking mice that are actually XX
  - Other genes are necessary for testes determining ability: even genes on autosomes!





Male Transgenic

Male Development Also Requires *Sox9*

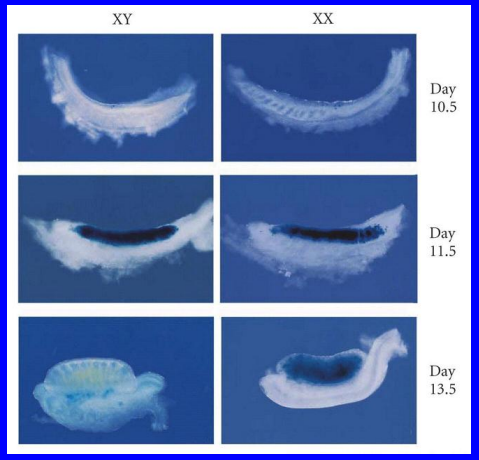
- *Sox9* = autosomal gene required for testicular development
- Expressed in genital ridges of males only, and in Sertoli cells throughout life
- Conserved throughout vertebrates
- Sex-reversed males:
  - XX lacking SRY
    - have extra copy of Sox9
  - XX transgenic for Sox9 form testis
- Transcriptional regulator
  - e.g. activates AMH gene (anti-Mullerian hormone)
- Splicing regulator also

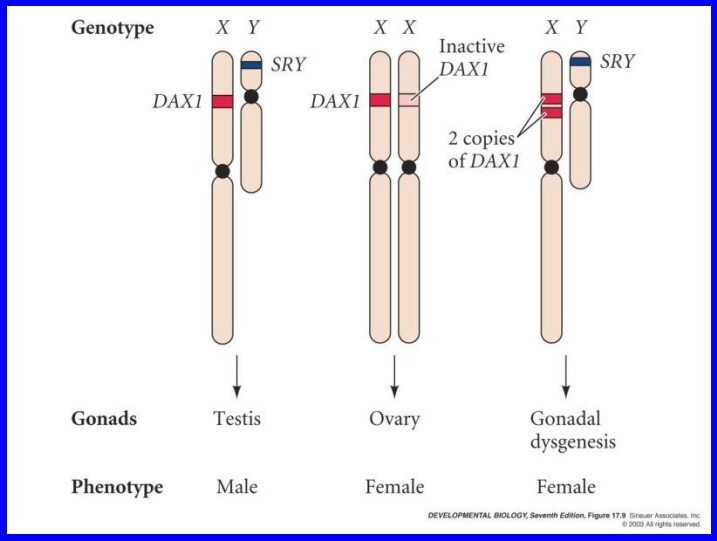
Male Development Also Requires SF1

- SF1 (steroidogenic factor 1)
  - Transcription factor
  - Necessary for bipotential gonad
  - Expression drops in XX gonad but persists in XY gonad
- Activates genes necessary for testosterone production (in Leydig cells) and AMH (in Sertoli cell)

Dax1 on X Antagonizes SRY and Sox9

- Expressed in genital ridges (in both sexes)
  - Stays on in developing ovary
  - Turned off in developing testes
- Gonadal dysgenesis female
  - XY but no deletion of Y
  - Instead an extra copy of Dax1 Dax1 acts as anti-testis gene in females

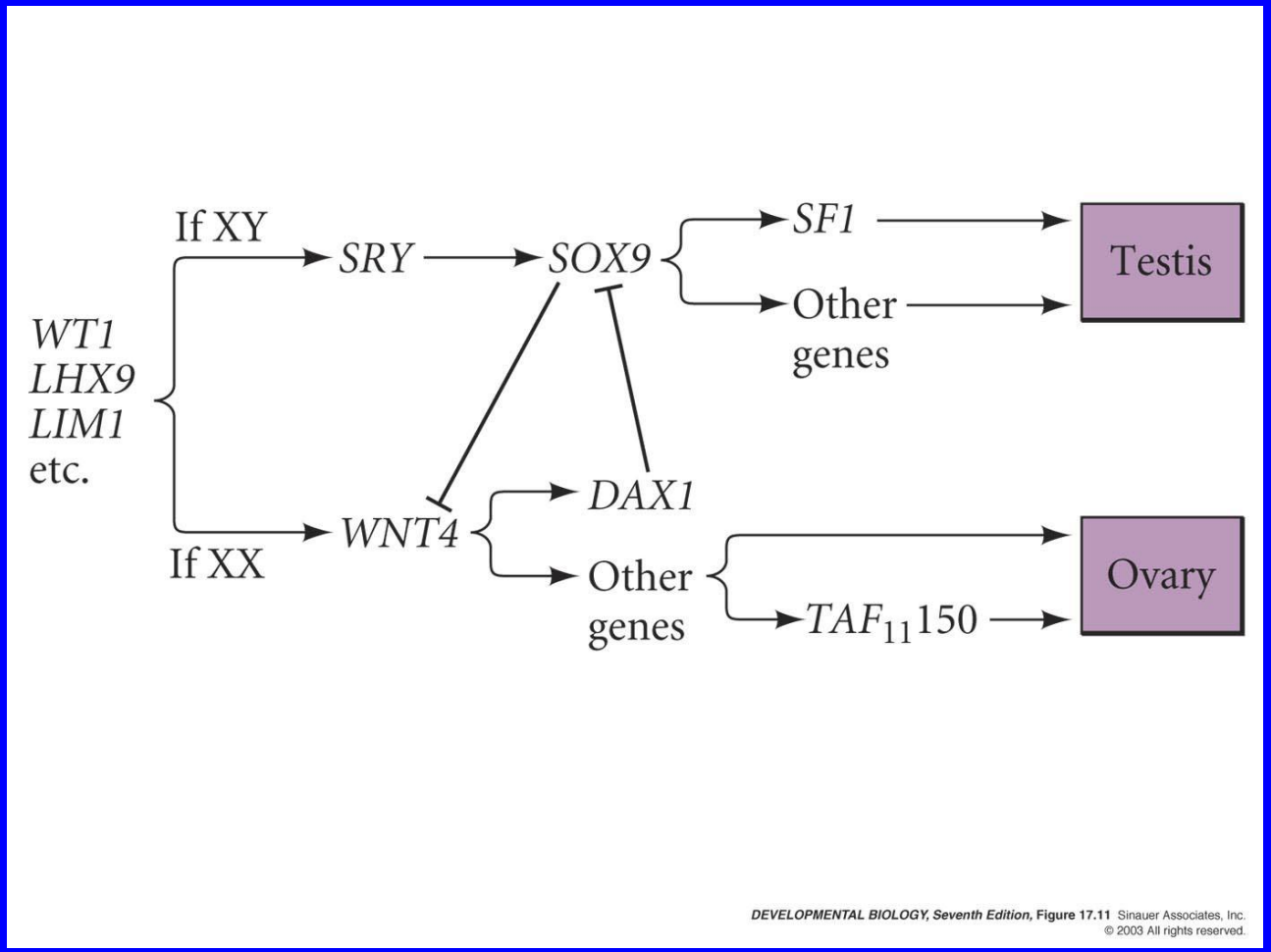




Wnt4 May Be an Ovary-Determining Gene

- Expressed in bipotential genital ridge
  - Expression lost in XY gonads, maintained in XX gonads
  - Activates Wnt4
- XX wnt4$^{-/-}$ mice fail to develop ovaries and instead gonads make AMH
- XY humans with double wnt4 make extra DAX1 and ovary

Partial Model of Vertebrate Sex Determination



DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 17.11 Sinauer Associates, Inc.