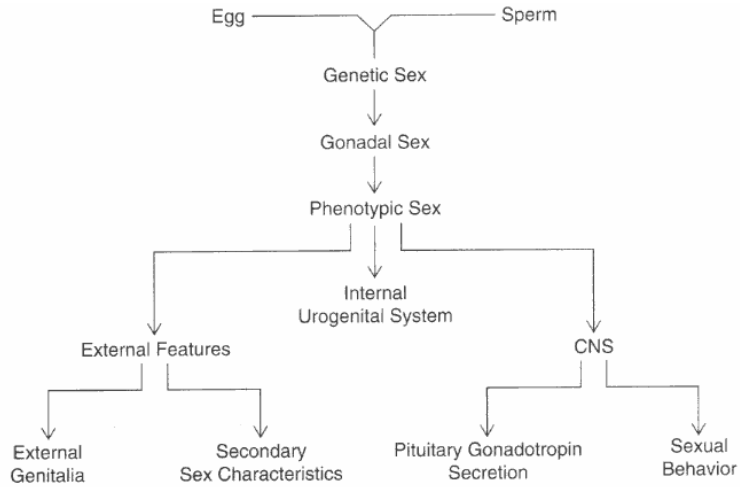
Chapter 16: Steroid Hormones
(Lecture 17)

A) 21 or fewer carbon atoms
B) Precursor: 27 carbon cholesterol
C) major classes of steroid hormones
1) **progestagens**
a) **progesterone- prepares lining of uterus for implantation of ovum**
- maintenance of pregnancy
b) site of synthesis: **corpus luteum**

2) **glucocorticoids**
a) **cortisol-promote gluconenogenesis /formation of glycogen**
-degradation of fat & protein
b) site of synthesis: **adrenal cortex**

3) **mineralocorticoids**
a) **aldosterone-increase kidney reabsorption of Na^+, Cl^-, & HCO_3^-**
-leading to increase blood volume & blood pressure
b) site of synthesis: **adrenal cortex**

4) **androgens**
a) **testosterone-development of male secondary sex characteristics**
b) site of synthesis: **testes**
5) **estrogens**
a) **estradiol-development of female secondary sex characteristics**
b) site of synthesis: ovary



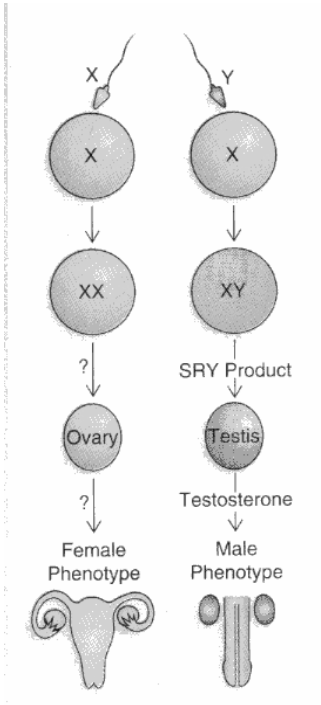
VERTEBRATE SEXUAL DIFFERENTIATION & DEVELOPMENT

1) genetic sex determined chromosomally of fertilized egg:
   a) governs development of gonadal sex of individual
   b) 23rd pair sex chromosomes XX or XY

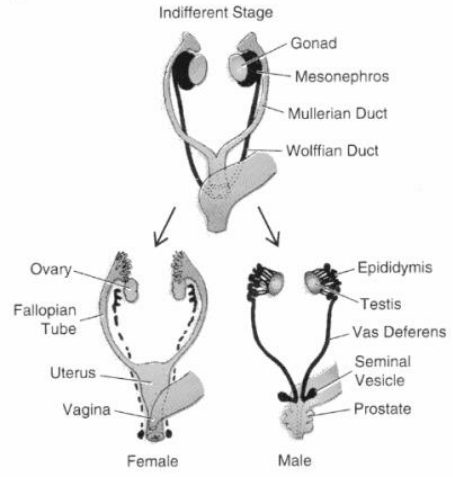
2) gonadal sex regulates phenotypic sex
   a) differentiation of internal & external sex organs
   b) attainment of adult secondary sexual characteristics
   c) gonadal hormones affect direction which gonads differentiate ovaries or testes
   d) development of brain into a female or male type dependent on gonadal hormone
   e) brain-affects pituitary gonadotropin secretions
      -regulate further development of gonads to produce mature gametes
   f) adult behavior dependent of both early/late effects of gonadal steroids on brain

3) human adult male **uncomplicated** reproductive system
   - >puberty reproductive system invariant its structural & functional characteristics

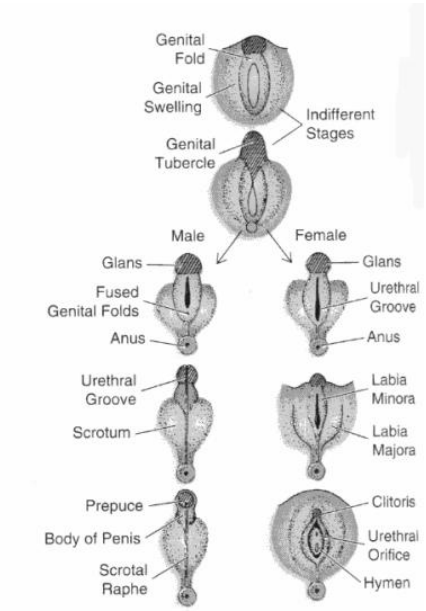
4) Human female **complicated**
   a) after puberty, cyclic hormonal output & gonadal function
   b) pregnancy-radical changes in reproductive organs
      to provide environment for fetal growth/development
         1. maintenance of pregnancy & parturition
         2. milk synthesis & secretion

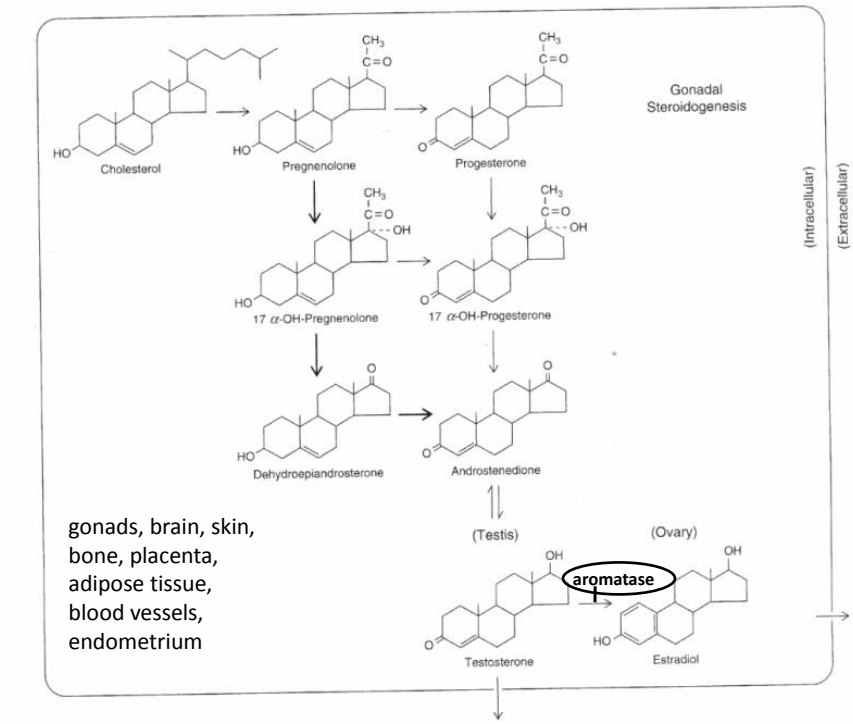


Internal Sexual Characteristics

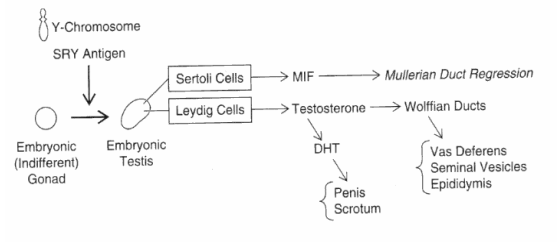


External Sexual Characteristics





Gonadal Sex



1) undifferentiated gonad
   cortical region
   medullary region
2) male sexual development
   suppression of cortex
   development of medullary region
3) female sexual development
   development of cortex
   suppression of medullary region
4) long held view that development of cortical/medullary regions
   related to corticomedullary inductive substances whose production
   related to either presence of XX or XY chromosomal complement
5) ***undifferentiated primordium normally tends to develop toward female in mammal unless influenced by genes located on the Y chromosome***
6) male testicular organogenesis -originally believed to be dependent on "H-Y antigen"
7) *dependent of product of **Sry gene** (sex determining Y gene on Y chromosome*

Female mice embryos (XX chromosome) injection of fragment with ***Sry gene***
- grow up to be males with testes & male behavior
- triggers genital ridges in embryo to develop into testes
- at 7th week gestation → testicular hormones

Sry gene-only a switch
- women (XX) testes development with no portion of Y chromosome
- cattle: genetic female develop testes
  - genes present in female turn embryonic genital ridge into testes
  - however gene *normally triggers this change present only in males*

- What turns on Sry gene??
  - women XY: no mutation in Sry gene
  - mutation "upstream" of the Sry regulates its activation??

Ovarian development begins 13-16 week gestation
- Two XX chromosomes needed
- Individuals: single X chromosome → only partially differentiated gonads

Freemartin Theory --Lillie (1916)

cattle breeders: term sterile female born co-twin to normal bull calf

twin pregnancy: result of fertilization of an ovum from each ovary
development proceeds separately in each horn of the uterus

elongating fetal membranes fuse & blood vessels from each side anastomose
result in constant interchange of blood between the two fetuses:

normal development if both fetuses either females or males:
- if one is male & other female reproductive system suppressed
  - some cases certain male organs may develop

Freemartin Theory: freemartin gonad mediated by circulating hormones of bull twin
unresolved: *Sry gene product lead masculinization of indifferent gonad in fetal cow?*

1) androgens do not alter development of fetal ovary when injected into pregnant cow

2) hormone-mediated sex reversal not yet shown in eutherian (placental) mammals

Heterogametic sex whether female or male important
bearing on role of hormones in gonadal & phenotypic development

Bear young outside body (e.g. egg) heterogametic sex may be either female or male

Most mammals grow/develop in maternal environment characterized by estrogens

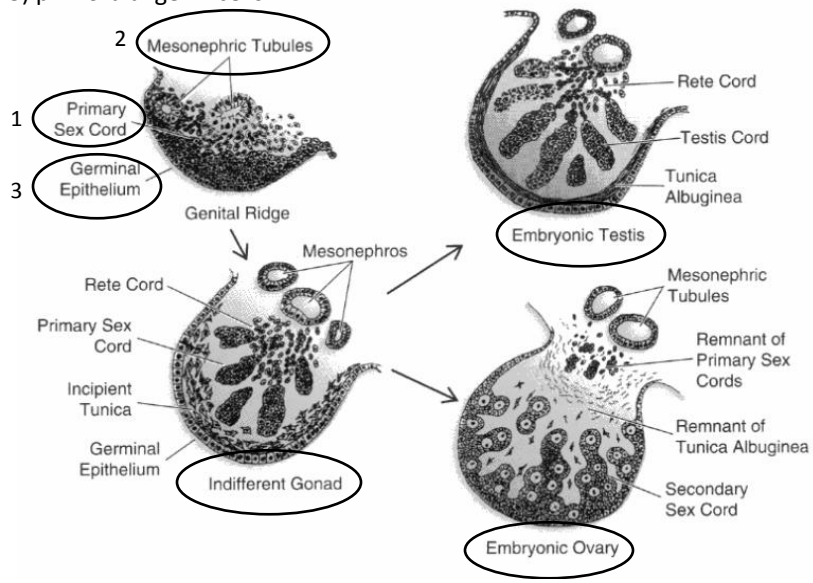
Evolution favored development of female:
neutral sex to protect the genetic male from influence of estrogens

Instead of protecting male from feminine influence differentiation toward
male gonadal & body phenotype requires inductive actions of gonadal androgens

Female development, ovarian & internal genital ducts & external genitalia
autonomous processes requiring no hormonally active inductive substances

Male mammal **"merely a female subjected to induction by testosterone"**

Presumptive gonadal primordia composed of
1) coelomic epithelia
2) underlying mesenchyme
3) primordial germ cells



Human Embryo

1) *gonadal anlagen (1st recognizable commencement of developing part* or organ in embryo) visible as pair of genital ridges after 4 weeks

2) primordial germ cells (*gonocytes)*
   a) arise from yolk sac endoderm
   b) move to mesoderm of gut
   c) seed the undifferentiated gonads by migration from hindgut

3) gonocyte migration may be due to substance?? from gonadal anlagen (genital ridge)

4) during migration of gonocytes; coelomic epithelium invades to varying degrees underlying mesenchyme of presumptive gonads to form ***primary sex cords*** this stage- gonads ***undifferentiated*** *or* ***bipotential****-depended on the genetic sex*

5) XX embryos early stage: germ cells remain in periphery away from central somatic blastema of gonad

6) XY embryos early stage: germ cells invade center of blastema

7) **Sry antigen** influences early organizational of gonadal differentiation d determine subsequent primordial germ cells →oogenesis or spermatogenesis

Nonmammalian vertebrates

germ cells become oocytes or spermatocytes
sex reversal: steroid injections

e.g. goldfish XY embryos → female phenotypes by estrogen injections
female phenotypes can be mated to normal males (XY)→ viable YY offsprings

e.g. medaka (*Oryzias latipes) XX female fish* → phenotypic male by androgens
male phenotypes can be mated to normal females (XX) → all female (XX) progeny

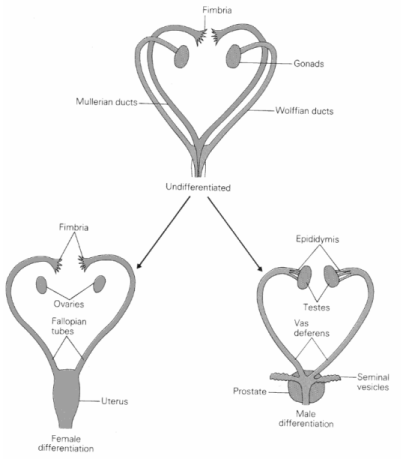
Prenatal Developmental Stages (following fertilization)

Gestation: carrying of embryo/fetus inside female viviparous animal

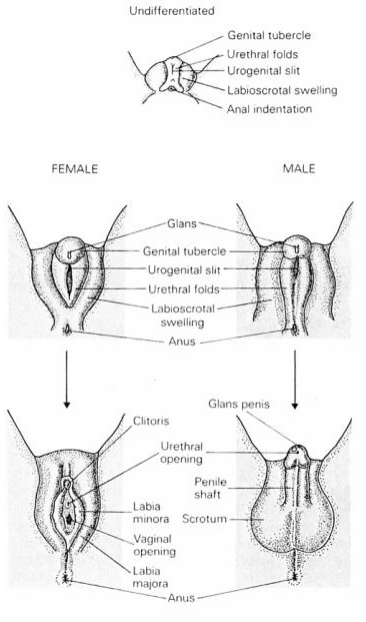
1) germinal stage weeks 0-2
2) embryonic stage weeks 2-8
3) fetal stage weeks 8-36 parturition (birth)
4) 0-6 weeks gonads of male/female embryos morphologically identical
5) 5-8 weeks (embryonic)-undifferentiated gonads differentiate into ovaries & testes

undifferentiated stage-Mullerian & Wolffian ducts present

Embryonic Ductal Systems



1) Ovarian differentiation of Mullerian duct system Week 12
   a) fallopian tubes
   b) uterus
   c) cervix
   d) vagina
   e) Mullerian ducts develop in absence of ovaries/testes
   f) atrophy of Wolffian ducts *progammed cell death @ week 12*
   g) Wolffian ducts atrophy in absence of ovaries/testes
   h) week 20-25 gonads can be structurally characterized as ovaries



2) Wolffian duct system: **Sry gene H-Y antigen** → testicular differentiation Weeks 6-7

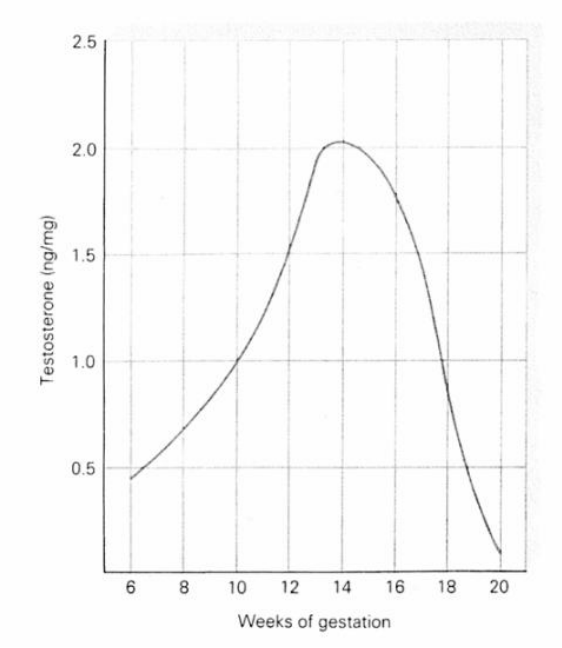
Leydig cells: testosterone: Weeks 7-9 → gonadal differentiation

a) epididymis (sperm transport/maturation/motility/fertility)
b) vas deferens (sperm storage)
c) seminal vesicles →seminal fluid (nutrients, fructose, prostaglandins)
d) prostate (production alkaline fluid with calcium & citric acid)
e) ejaculatory duct
f) fetal testes (Sertoli cells) → Mullerian Inhibiting Substance (MIS) glycoprotein (70,000 MW)

1) anti-Mullerian paracrine hormone → cells surrounding gonads
AMF (anti-Mullerian Hormone) = MIS/ MIF

2) induction of atrophy of Mullerian duct

3) maintenance/further development of Wolffian duct depended on testicular androgens & MIS?



4) MIS localized effect
castration fetal male rat/rabbit → female duct development

5) MIS gene expressed in ovary but function unknown

6) male infants born with normal testes but not synthesize androgens
a) Mullerian duct atrophy
b) MIS present but not androgens
c) persistent Mullerian duct syndrome
genetic/phenotypic males -have Fallopian tubes & uterus
Wolffian duct: no MIS production or tissue unresponsive to MIS

7)↑T effects ↓ MIF during normal/precocious puberty

8)↑T effects ↓ MIF in boys with gonadotropin-independent precocious development

GONADAL STEROID HORMONE SYNTHESIS/CHEMISTRY

1) produced by mesodermally derived tissues of ovaries & testes

2) nature of stimulus: activate testosterone biosynthesis fetal testis –unknown

3) rabbit testes or ovaries synthesize testosterone or estradiol media w/o hormones

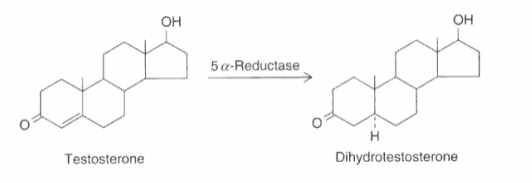
4) gonadal differentiation as endocrine organs controlled by factors intrinsic to gonads themselves

5) early development presence of C-21 steroids of placental origin
   not needed for gonadotropin as in adults
   control conversion of cholesterol to pregnenolone

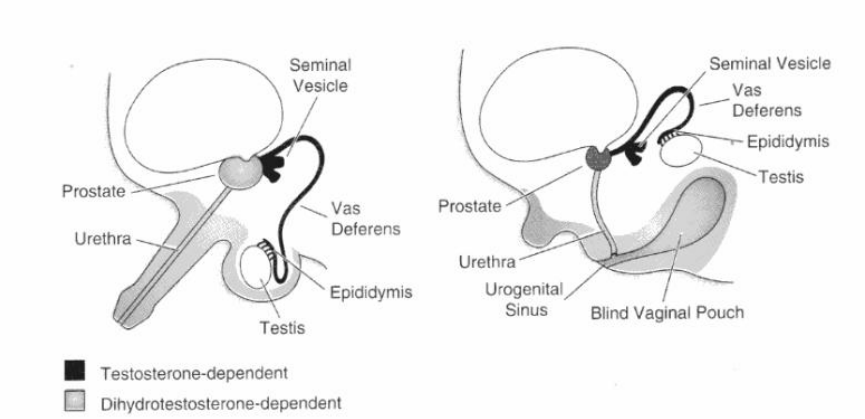
6) dihydrotestosterone (DHT) need enzyme **5 α-reductase**
   --rudiments of external genitalia & prostate
   convert testosterone to DHT for their development--needed for normal virilization-rare anomalies absence of 5 α-reductase activity

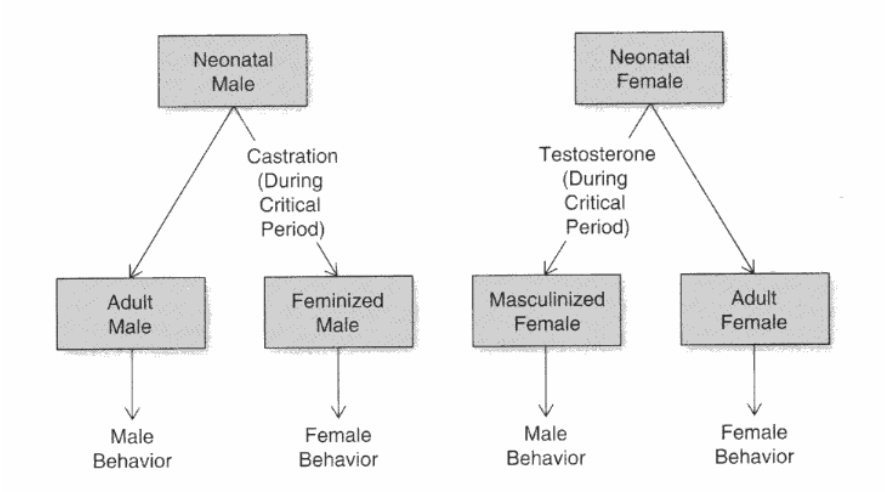
7) ovarian estradiol synthesis -precursors needed androstenedione & testosterone

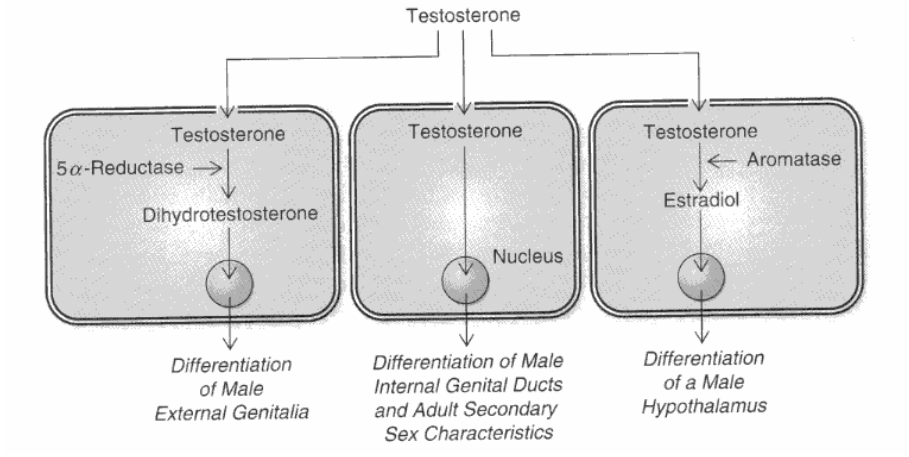
8) ovaries differentiate later than testes
   ? estrogens important in female fetal development: ? important ovarian maturation



DHT: necessary for development of male genitalia in utero




Neonatal Male
Castration (During Critical Period)
Adult Male
Feminized Male
Male Behavior
Female Behavior
Neonatal Female
Testosterone (During Critical Period)
Masculinized Female
Adult Female
Male Behavior
Female Behavior


Testosterone
Testosterone
5α-Reductase
Dihydrotestosterone
Differentiation of Male External Genitalia
Testosterone
Nucleus
Differentiation of Male Internal Genital Ducts and Adult Secondary Sex Characteristics
Testosterone
Aromatase
Estradiol
Differentiation of a Male Hypothalamus

Pathophysiology