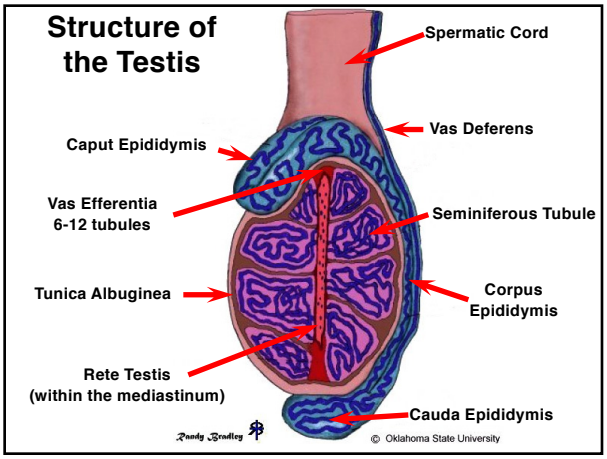
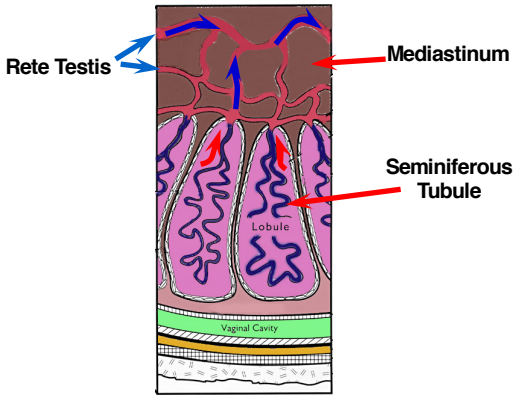
Endocrinology of the Testis

John Parrish

References: Williams Textbook of Endocrinology

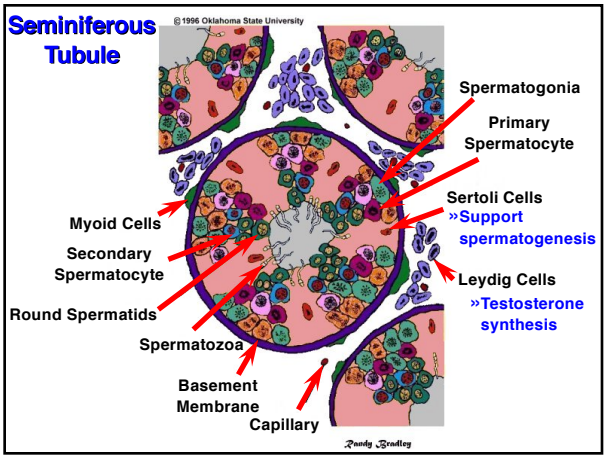
Structure of the Testis





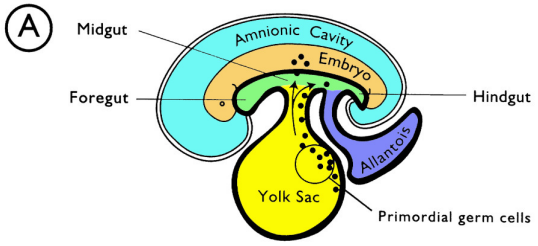
The Testis

Seminiferous Tubule

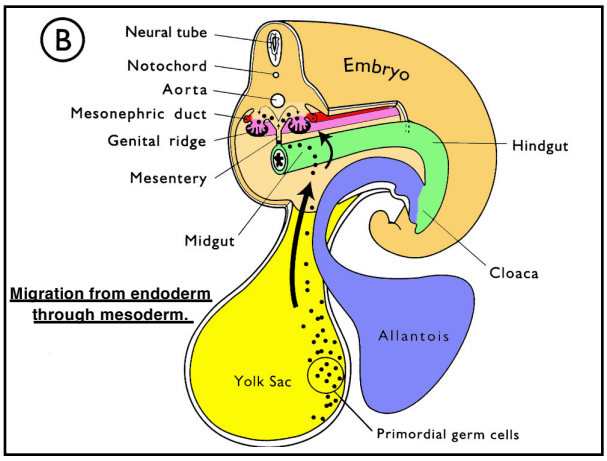


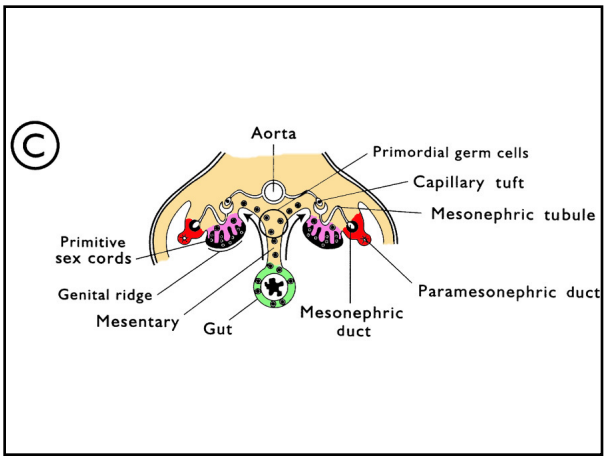
Sertoli Cell

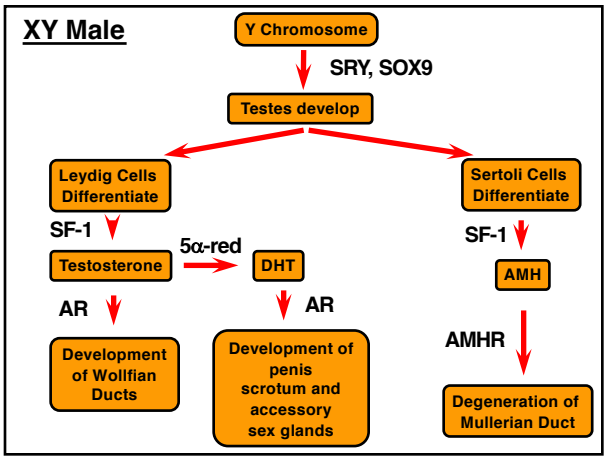
Germ Cell Migration



Migration begins by the 4 week of gestation in cow and human.







Circulating Androgen

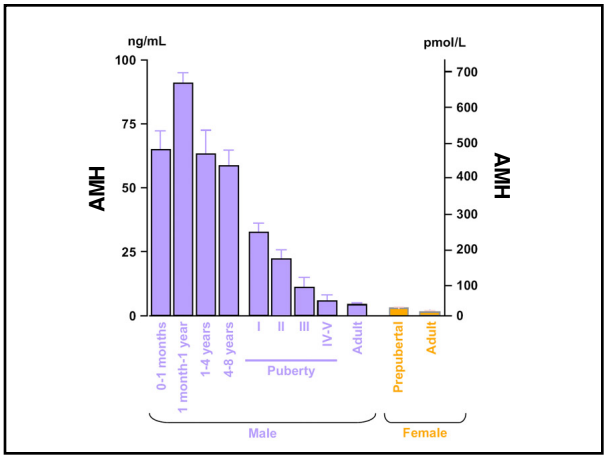
- Sex Hormone Binding Globulin - 44%
- Albumin - 54% (1000 fold less affinity than SHBG)
- Free - 2%

Bioavailable Testosterone = free + albumin bound

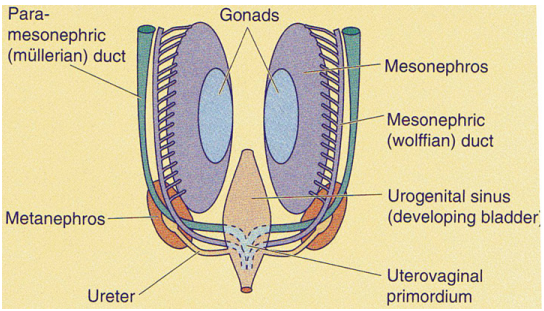
SHBG is made in Liver

ABP is made in Sertoli Cells

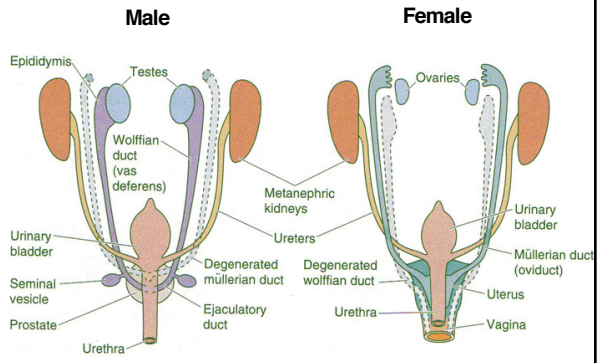
Both also bind estradiol



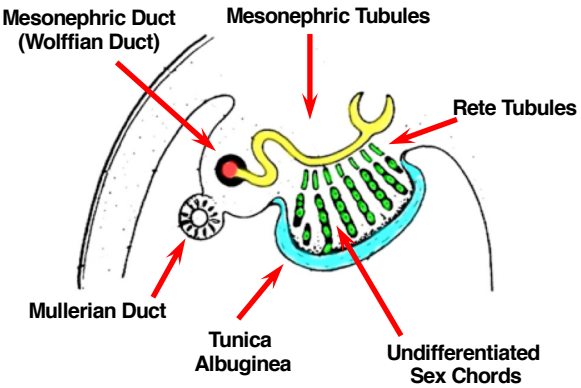
Undifferentiated Gonad

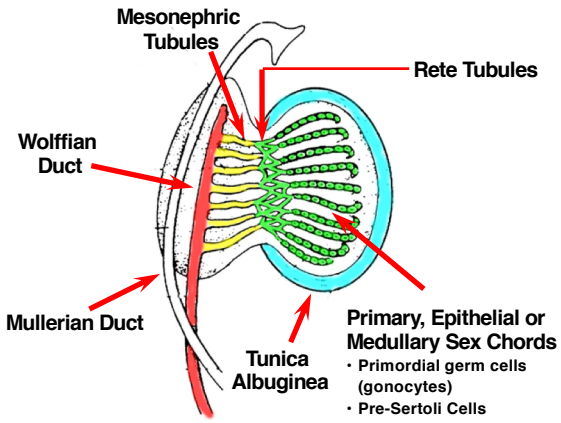


Differentiated Reproductive Tracts

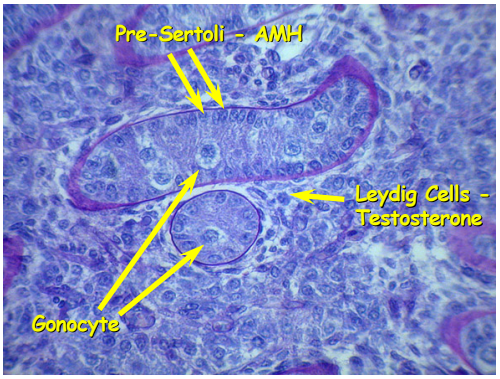


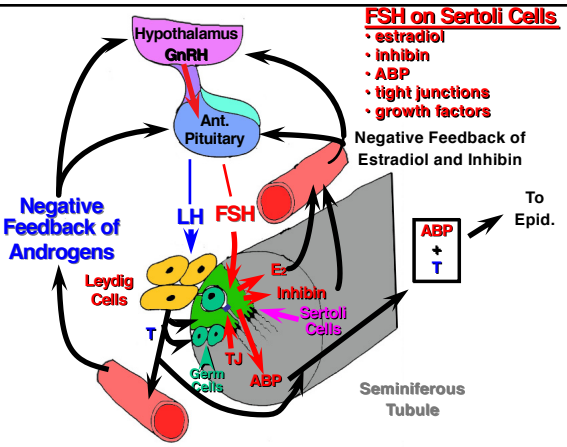
Testicular Development





Primary Sex Chords in Fetal Testis

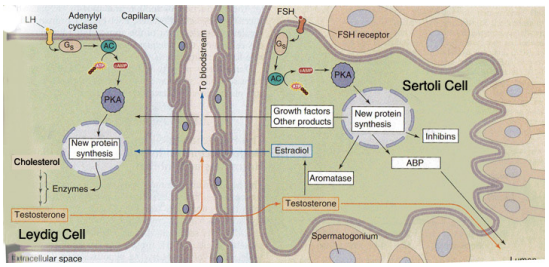


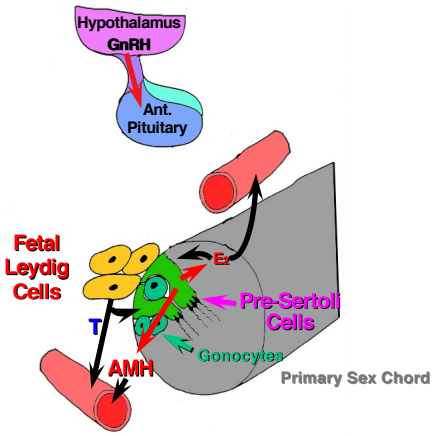


Negative Feedback

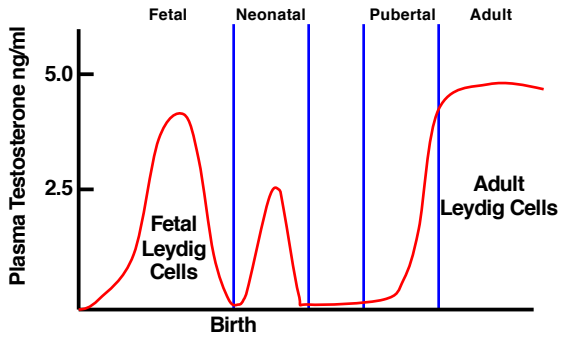
- Hypothalamus
  - » Testosterone conversion to Estradiol
  - » Androgen receptor is less important
- Anterior Pituitary
  - » Adrogen receptor involved because DHT has negative feedback as well testosterone
  - » Aromatization of testosterone to estradiol also occurs
  - » Inhibin

Leydig Cell and Sertoli Cell Interactions

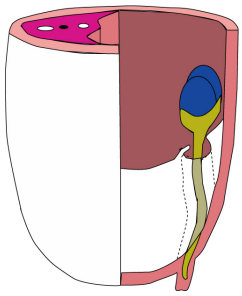




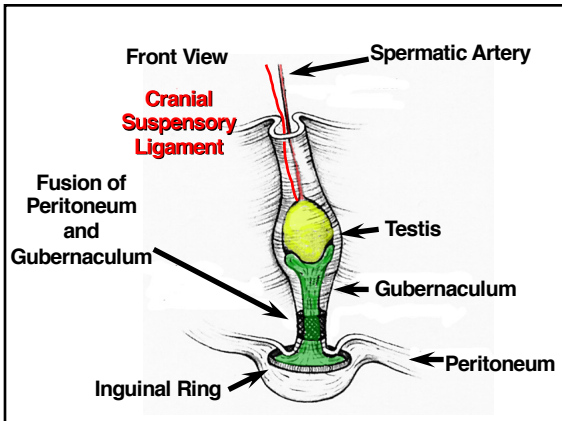
Testosterone Levels: Fetus - Adult

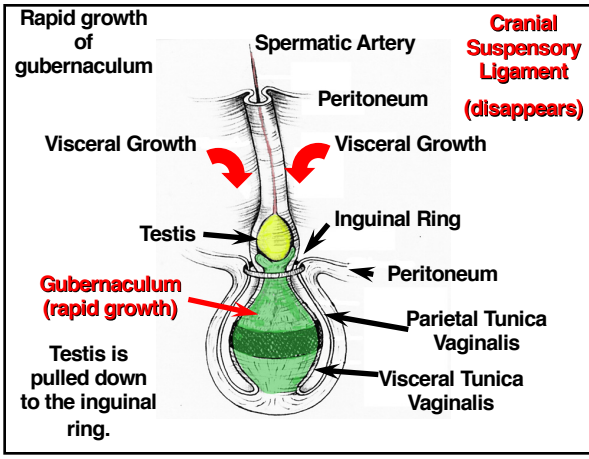


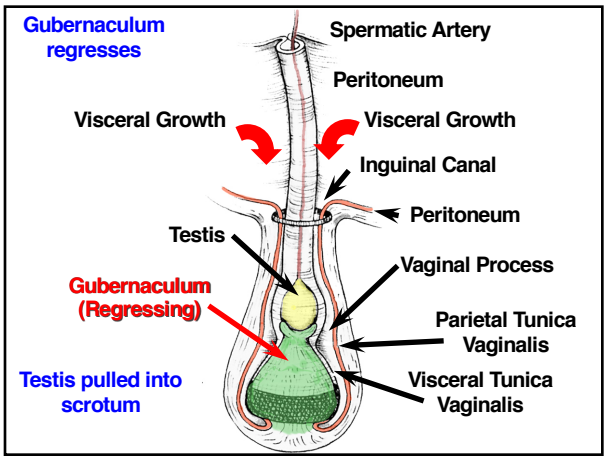
Testicular Descent

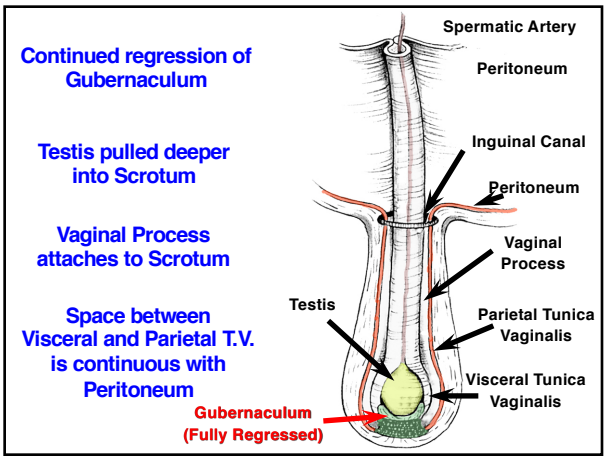


Fusion of the tunica albuginea and peritoneum to form the visceral tunica vaginalis





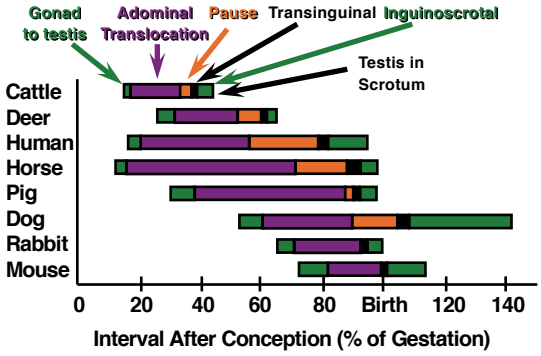




Testicular Descent

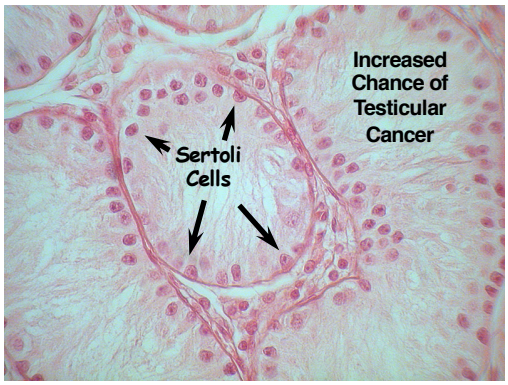
- Cryptorchid - failure of descent
- Controlling mechanisms
  - » Androgen dependent
  - » DHT supported
  - » Estrogen inhibits
- Gene Expression
  - » INSL3 - insulin like growth factor 3
    - From leydig cells
  - » Great/LGR8 - receptor for INSL3
    - In gubernaculum

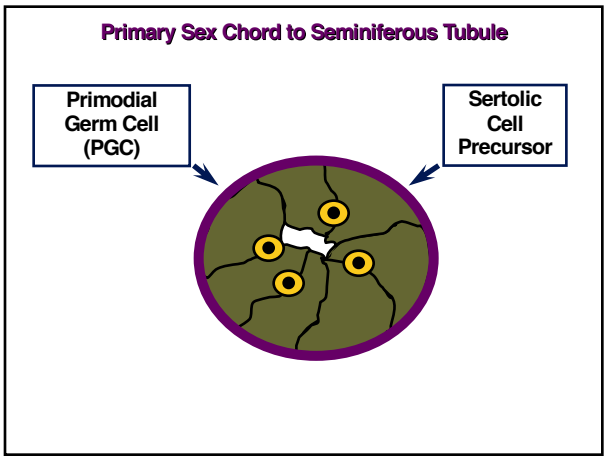
Timing of Testicular Descent in Mammals

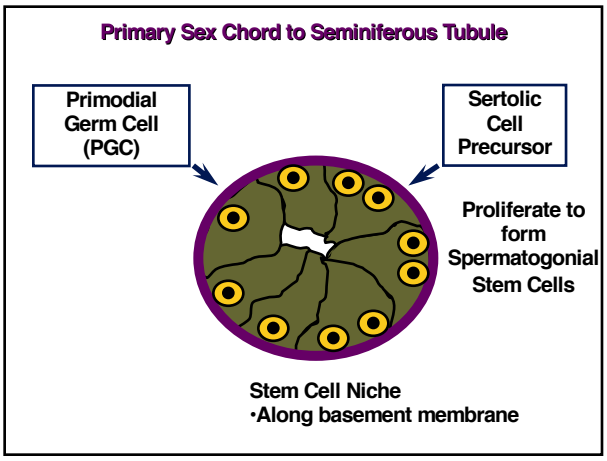


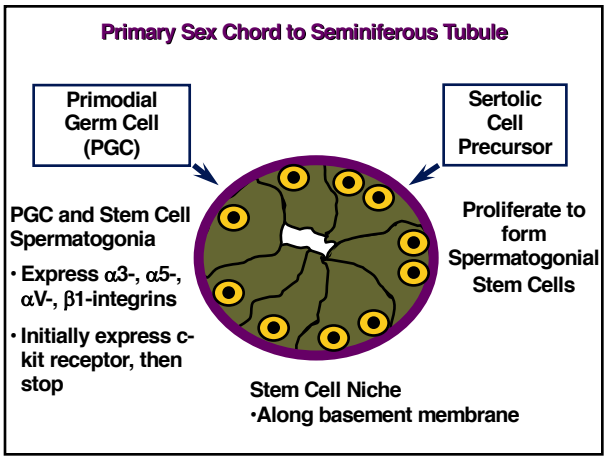
Normal Dog Seminiferous Tubule

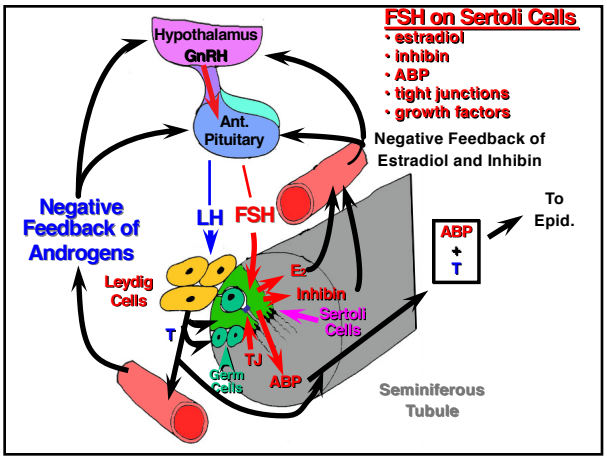
Cryptorchid Dog Seminiferous Tubule











Sertoli Cell Regulation

- Switch from FSH to Testosterone
  - » FSH causes increase in cAMP
  - » at puberty, phosphodiesterase increases
    - FSH less effective
  - » Testosterone takes over regulation
- Germ cells effect ability of Sertoli cell to respond to testosterone

Sertoli Cell Regulation (cont.)

- FSH causes Sertoli cells to secret factors that increase Leydig cell response to LH
  - » at puberty or start of breeding season
    - FSH increases first
    - Sertoli cells trigger the development of SER in Leydig cells

Hormonal Regulation of Spermatogenesis

- Level of Testosterone
  - » intratesticular testosterone is higher than in circulation
    - IF 600 nM (Leydig cells here)
    - TV 250 nM
    - SV 150 nM
    - PV 20 nM
    - It is usually 30 to 170 times that seen in PV
  - » Seminiferous Tubule Fluid (STF) testosterone
    - STF 170 nM
  - » Androgen receptor K_d for testosterone
    - 3 nM

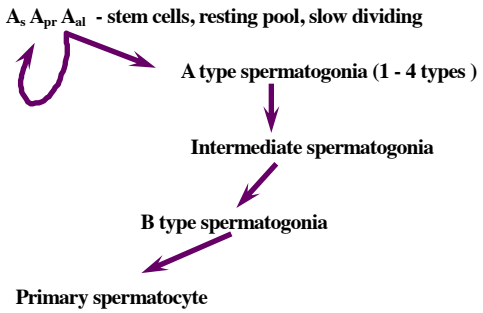
Hormonal Regulation of Spermatogenesis (Cont.)

- Why is testosterone so high in STF?
  - » Does testosterone work by androgen receptor?
    - – Yes, DHT is more effective than testosterone
  - » What is level of free testosterone in STF?
    - – Have not been able to measure
    - – ABP is produced by sertoli cells under influence of FSH and is present at 30 - 40 nM
      - · Certainly reduces free testosterone but there is still excess testosterone
  - » Artificial testosterone via implants found need 75 nM to maintain spermatogenesis

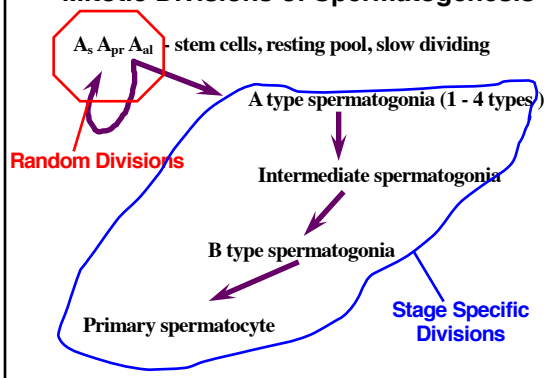
Hormonal Regulation of Spermatogenesis (Cont.)

- Level of testosterone in Sertoli cell
  - » Testosterone is converted to estrogen in sertoli cell
  - » Has not been addressed
- No good answer

Mitotic Divisions of Spermatogenesis



Mitotic Divisions of Spermatogenesis



Meiotic Divisions of Spermatogenesis

Primary spermatocyte - long interval

- **preleptotene -** DNA synthesis
- **leptotene -** condensation of the chromatin
- **zygotene -** thickening of chromosomes and pairing
- **pachytene -** RNA synthesis, thickening of chromosomes, crossing over
- **diplotene -** chromosomes separate but remain attached at chiasma
- **diakinesis -** cells separate and divide

Meiotic Divisions (cont.)

Primary spermatocyte

→ **Secondary spermatocyte** - short lived and undergoes reduction division

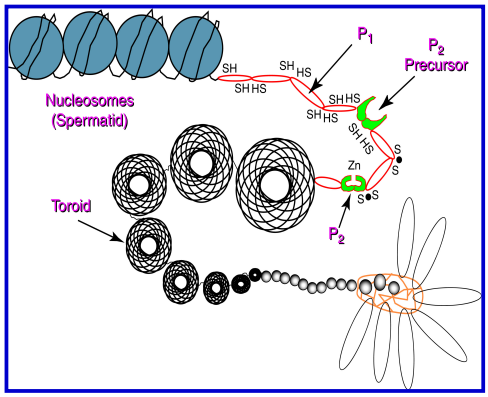
↓

Round spermatid

↓ spermiogenesis

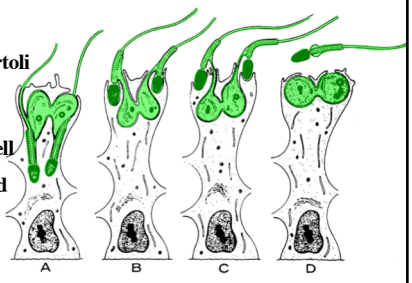
Spermiation

Sperm Chromatin Sturcture

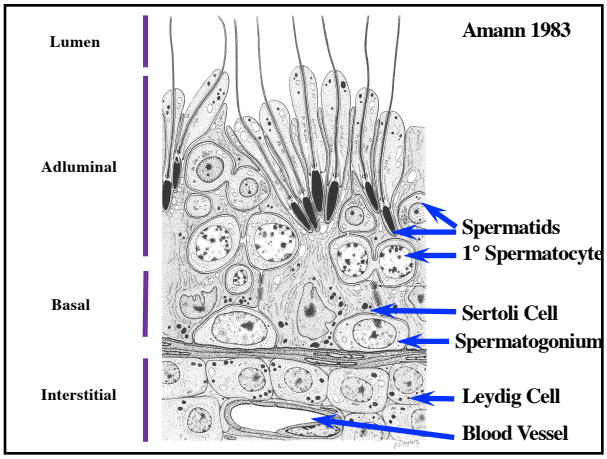


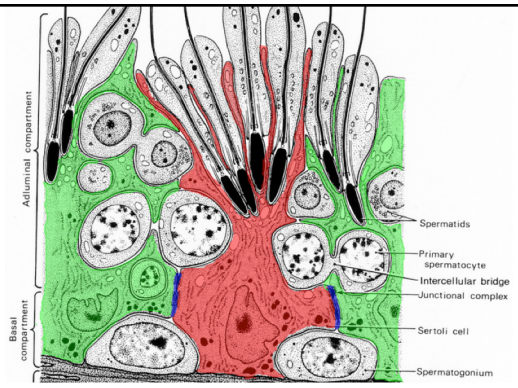
Cytoplasmic Elimination Phase and Spermiation

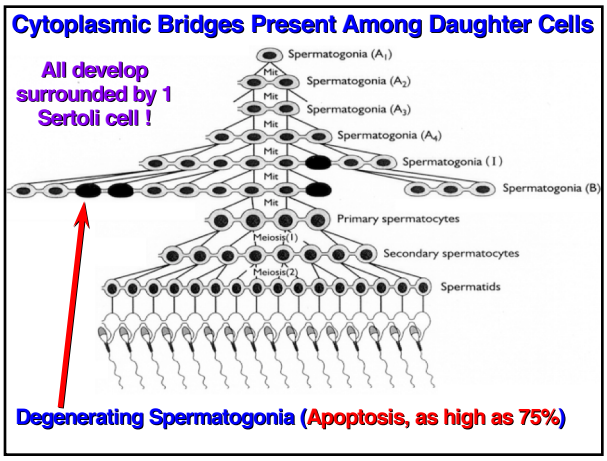
- residual body loss
- phagocytosis by sertoli cell
- elong. sperm. influences sertoli cell
  - –sem. tubual fluid
  - –ABP
  - –inhibin
  - –interleukin 1

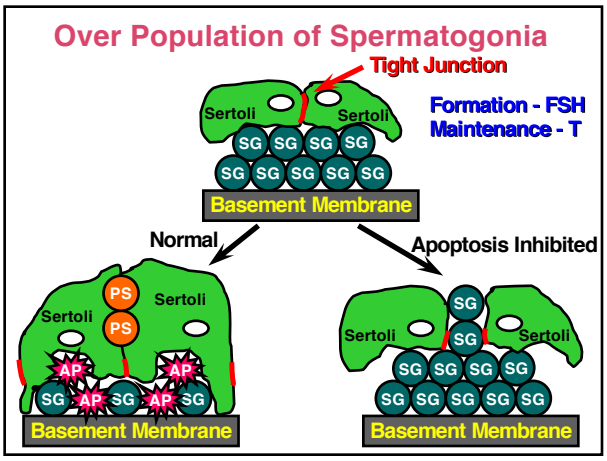


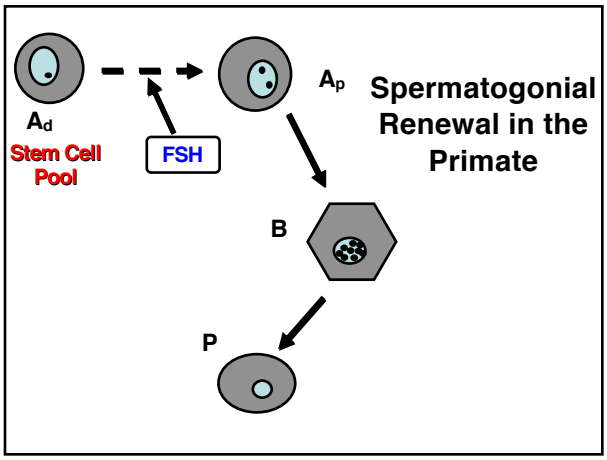
Seminiferous Tubule

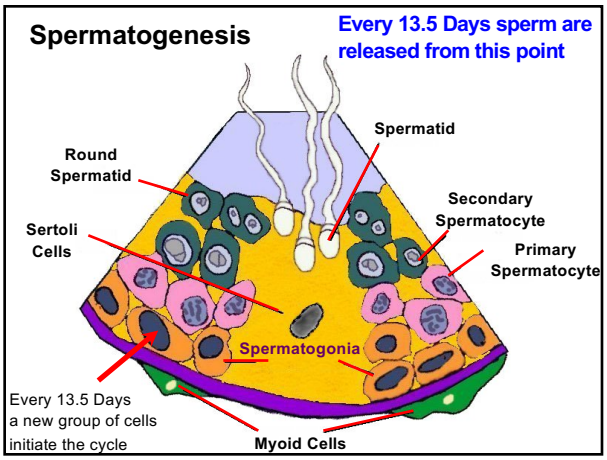










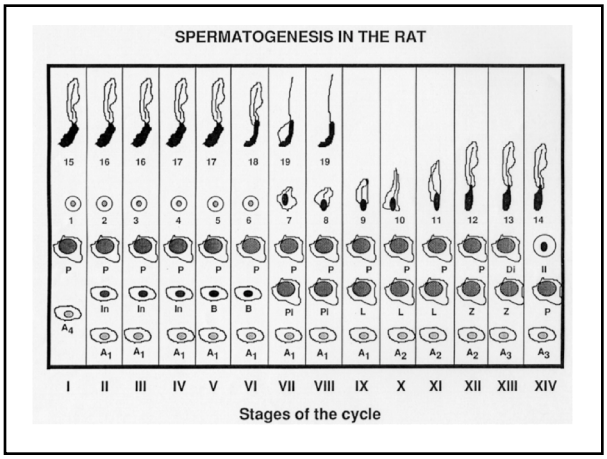


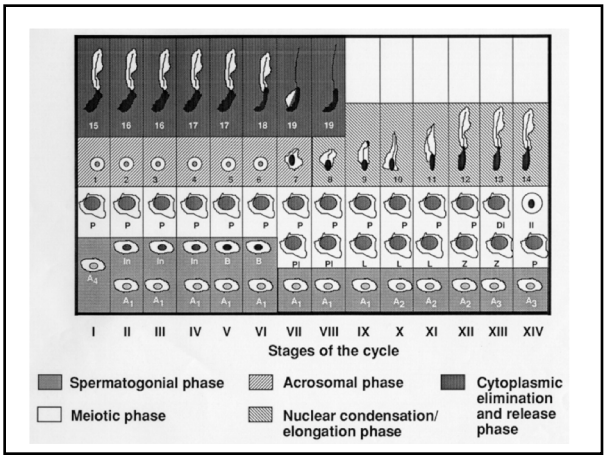
Stages

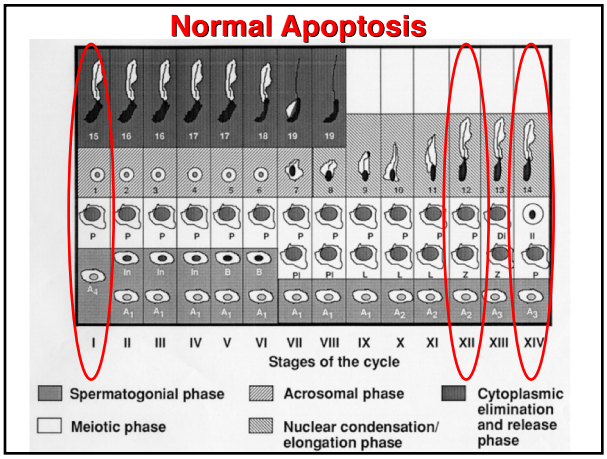
- Specific cellular associations within a small segment of a seminiferous tubule
- stages are not the same length in time

Cycle

- progression through sequence of all stages

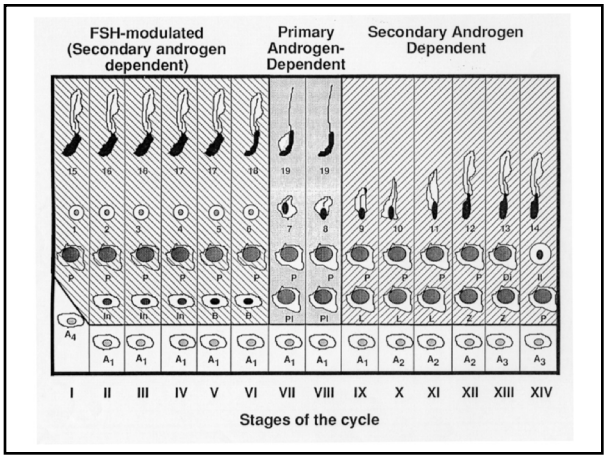


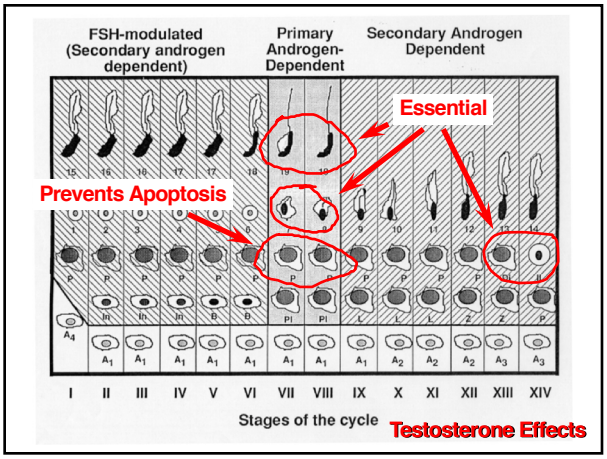


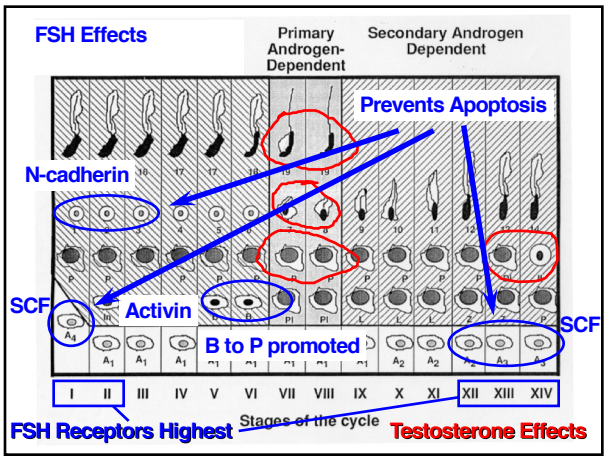


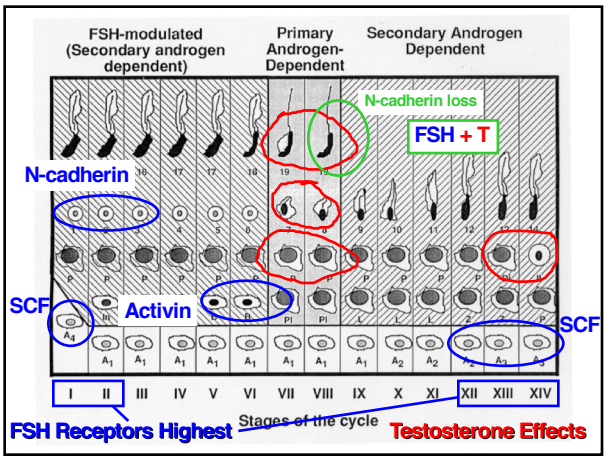
Effect of Hormone Withdrawal

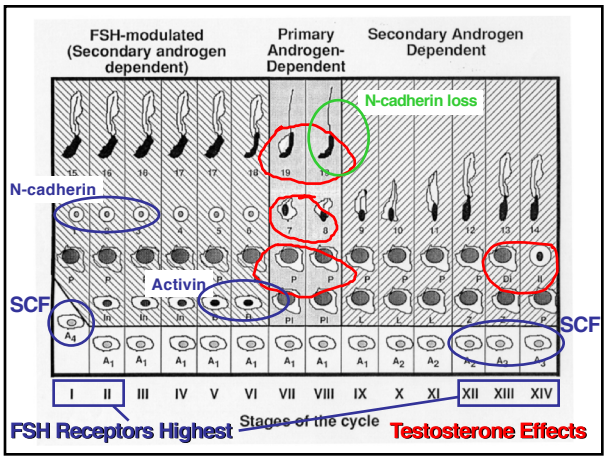
- Experimental Approaches
  - » Hypox.
    - can't restore with testosterone alone
  - » GnRH agonist
    - Decreased FSH and LH release
    - Requires both FSH and Testosterone to get normal spematogenesis
  - » Ethane dimethane sulfonate (destroys leydig cells)
    - get destruction of spermatogenesis
    - testosterone can overcome effects of EDS except does not prevent destruction of Leydig cells





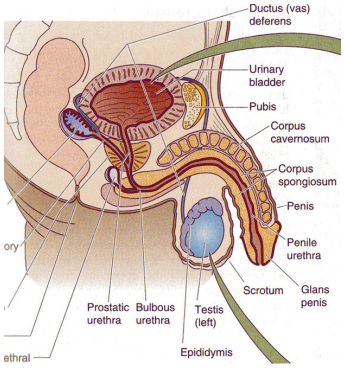






Normal Dog Seminiferous Tubule

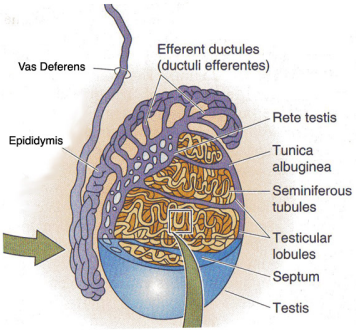
Human Male Reproductive Tract



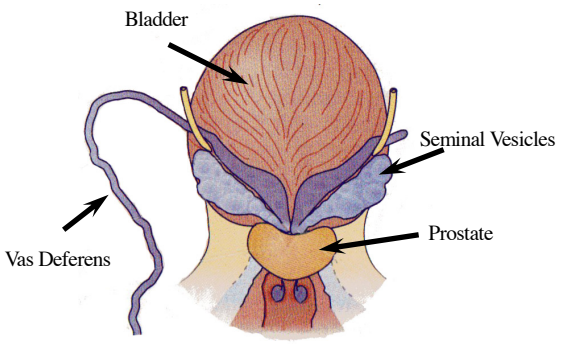
Hormonal Dependence

- •Testosterone
  - »Wolfian Duct
    - ▪Vas efferentia
    - ▪Epididymis
    - ▪Vas deferens
    - ▪Seminal Vesicles
- •DHT
  - »Rest of Male Structures
    - ▪Prostate
    - ▪Cowper's
    - ▪Penis

Human Testis



Human Male Reproductive Tract and Bladder

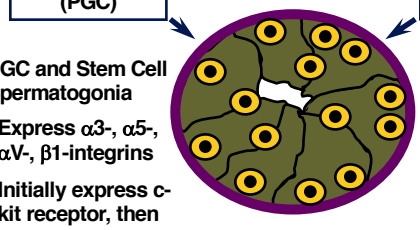


Hyperplasia of Human Prostate

- DHT driven via Androgen Receptor
- 5-α-reductase inhibitors common treatment
  - » Type 2 enzyme in prostate, hair follicle
    - No effect on libido
    - Hair follicles and other DHT dependent tissue affected
- Estradiol increases androgen receptor in prostate and estradiol increase with age

The End

Primary Sex Chord to Seminiferous Tubule



PGC and Stem Cell Spermatogonia

- Express α3-, α5-, αV-, β1-integrins
- Initially express c-kit receptor, then stop

Proliferate to form Spermatogonial Stem Cells

Stem Cell Niche
·Along basement membrane