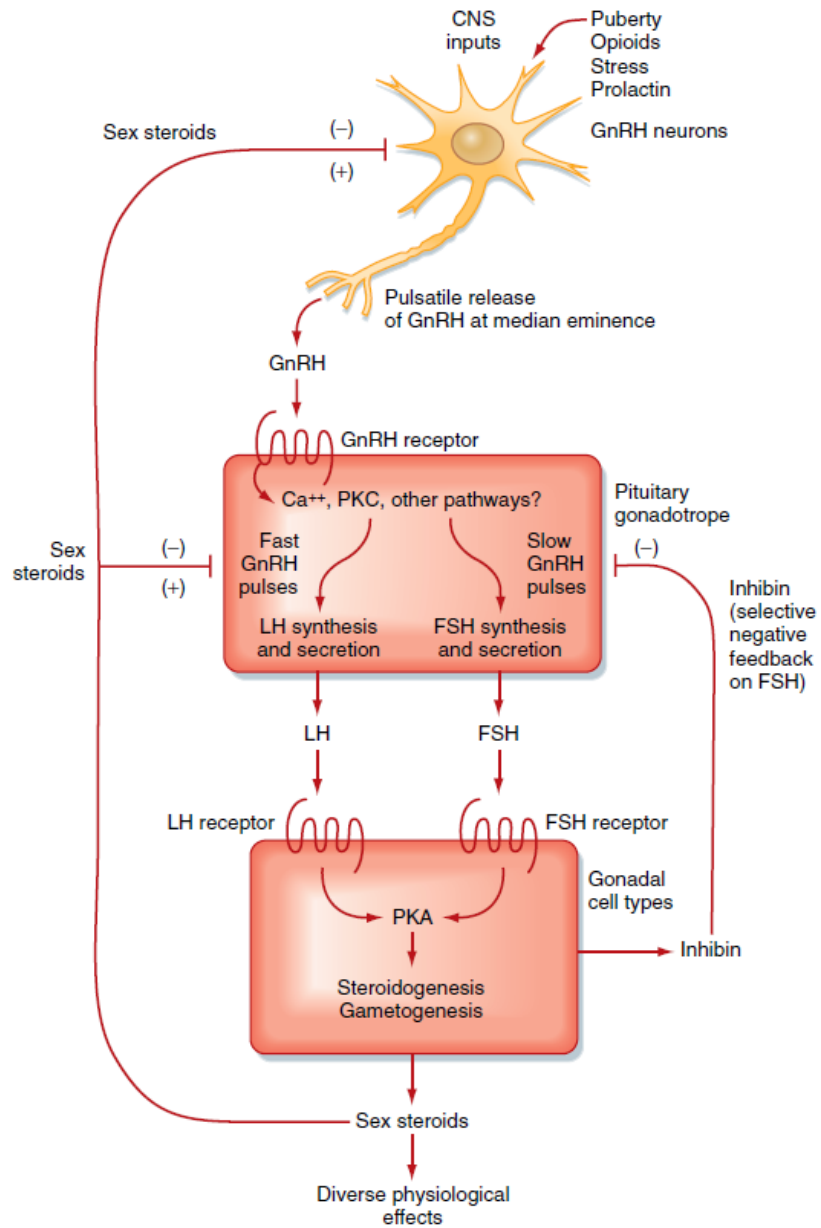


Reproductive Physiology

Hypothalamic-Pituitary- Gonadal-Axis

Dr. Khalid Alregaiey

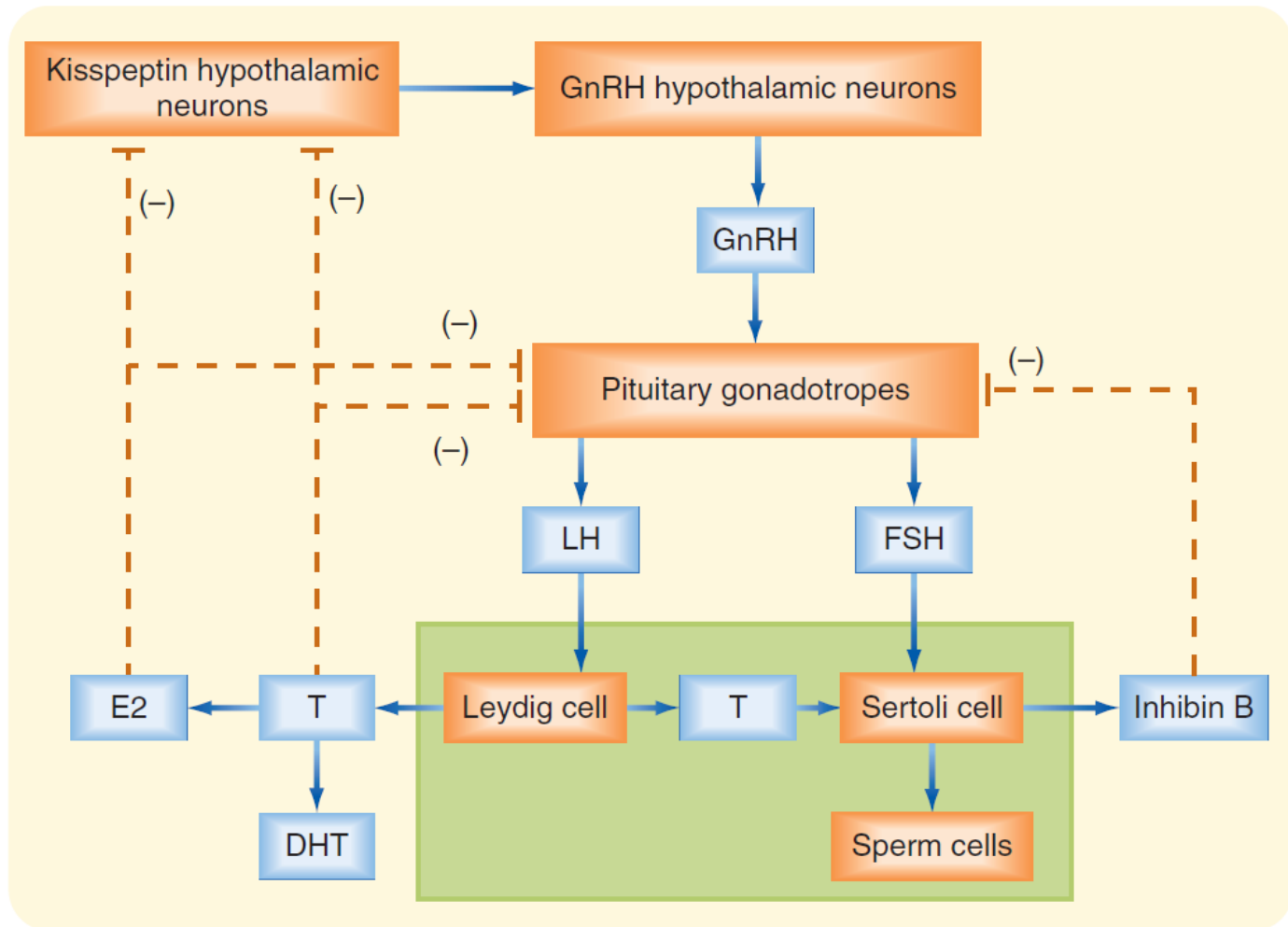
HPG



Regulation of Reproduction: General Pathways

- **Hypothalamus:** pulse generator
 - Gonadotropin releasing H (GnRH)
- **Anterior Pituitary**
 - Lutenizing H (LH)
 - Follicle stimulating H (FSH)
- **Ovary:**
 - Estrogen, progesterone, Inhibin
- **Testis:** testosterone

HPG



Control of male sexual functions by HPG:

GnRH :

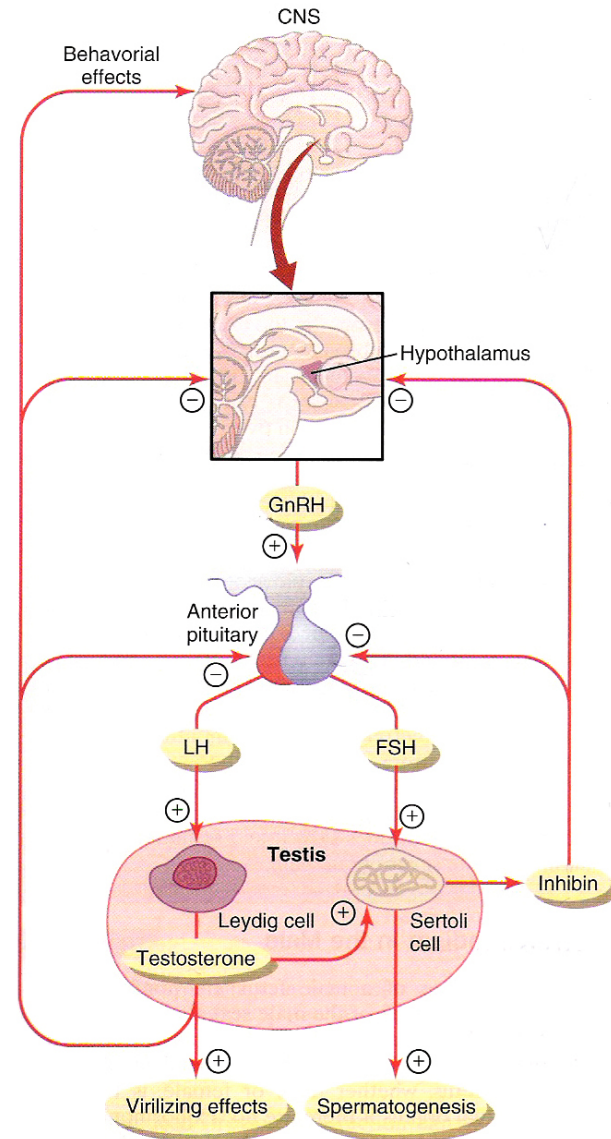
- A peptide secreted by the arcuate nuclei of the hypothalamus
- Stimulate anterior pituitary gland to release gonadotropins (LH and FSH).
- GnRH is secreted intermittently for few minutes every 1 to 3 hrs.
- Secretion of LH by the anterior pituitary is also cyclical following the **pulsatile** release of GnRH.

Regulation of Testosterone production by LH

- Testosterone is secreted by **leydig cells**, in the interstitium of the testis, by LH stimulation from the AP and
- Its release is directly proportional to the amount of LH.

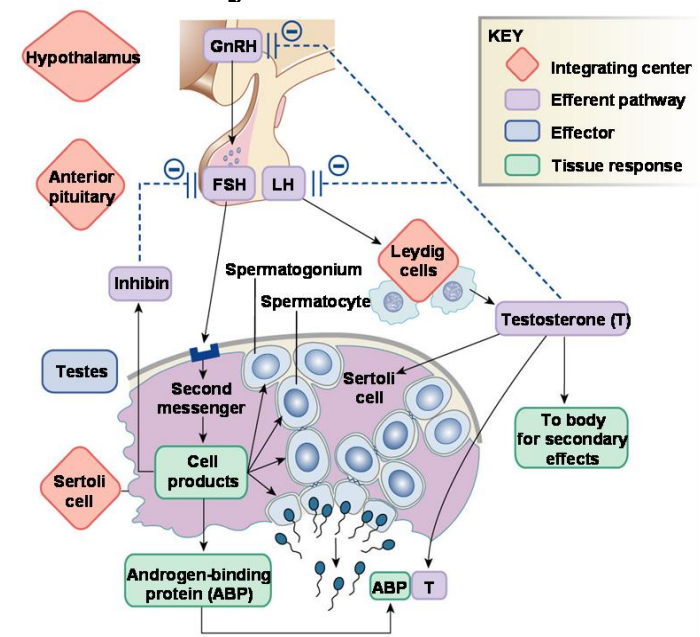
Negative feedback control of testosterone

- LH stimulate Testosterone secretion by the testis
- Testosterone inhibit the secretion of LH.
- Most of the inhibitory effect result from direct inhibition of GnRH release from the hypothalamus
- Inhibition of GnRH leads to decrease secretion of both LH & FSH.



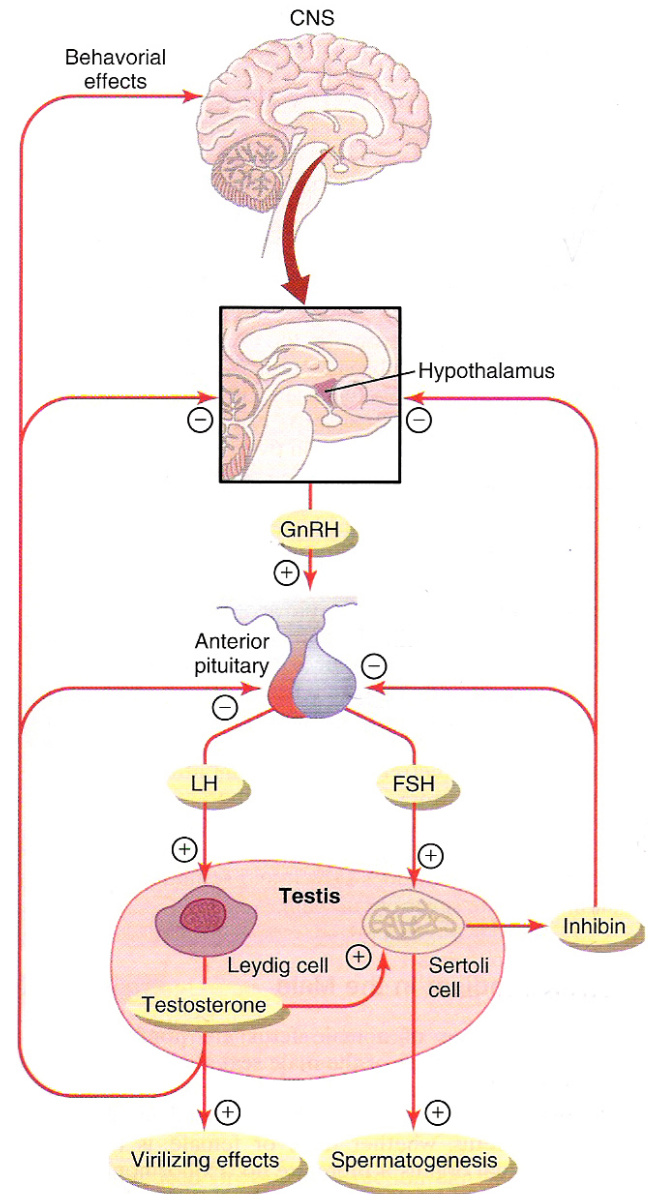
Regulation of spermatogenesis by FSH and testosterone

- **FSH** binds with specific FSH receptors attached to the sertoli cell in the seminiferous tubules, which causes these cells to grow & secrete spermatogenic substances.
- Also testosterone & dihydrotestosterone diffuses into the seminiferous tubules from the leydig cells affect the spermatogenesis,
- So both FSH & testosterone are necessary to initiate spermatogenesis.



Negative feedback control of seminiferous tubule activity: Role of inhibin:

- When the seminiferous tubules fail to produce sperm the secretion of FSH from the AP increases.
- Conversely, when spermatogenesis proceeds rapidly pituitary secretion of FSH diminishes.
- This is due to the secretion of inhibin hormone from the sertoli cells which strongly inhibit the AP- FSH
- Inhibin has slight inhibitory effect on the hypothalamus to inhibit GnRH secretion.

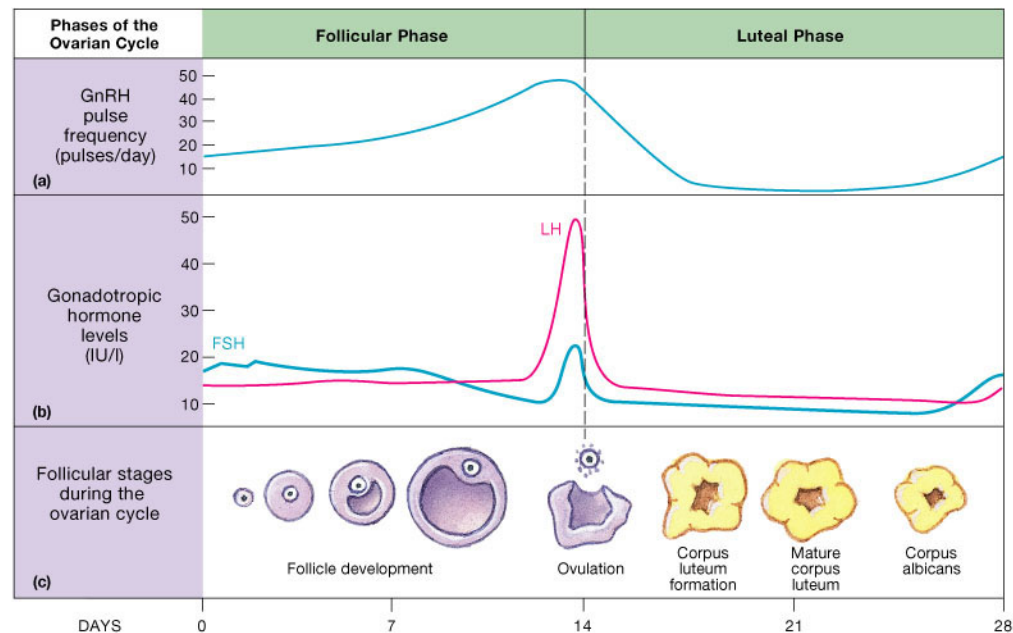


Regulation of the Female Monthly Rhythm: Interplay between the ovarian and hypothalamic-pituitary hormones:

- The neural activity that causes release of GnRH occurs in the mediobasal hypothalamus, in the arcuate nuclei which regulate most of the female sexual activity.
- GnRH is secreted in pulses lasting 5-25 minutes every 1-2 hrs.
- The pulsatile release of GnRH cause intermittent output of LH secretion about every 90 minutes.

Follicular phase

- After menstruation the level of FSH & LH increases
- Mainly FSH accelerates growth of few follicles (6-12 follicles).
- The growing follicle secretes increasing amounts of estrogen



Negative feedback effects of estrogen and progesterone

- Estrogen in small amounts has strong effect to inhibit the production of LH & FSH.
- This inhibitory effect of estrogen is increased when progesterone is available.
- This inhibitory effects more on the AP directly & to lesser extent on the hypothalamus to inhibit the secretion of GnRH.

Inhibin from the corpus luteum inhibits FSH secretion:

- The hormone inhibin secreted by the granulosa cells of the ovarian corpus luteum inhibit the secretion of FSH & to lesser extent LH.

Before Ovulation:

Positive feedback effect of estrogen before ovulation – the pre-ovulatory LH surge:

- AP secretes increased amount of LH for 1-2 days before ovulation.
- FSH surge is much smaller in the pre-ovulatory than LH surge.

The possible causes of LH secretion could be:

- Estrogen has special **positive feedback** effect of stimulating pituitary secretion of LH & to a lesser extent FSH
- The granulosa cells of the follicle begin to secrete small increasing amount of progesterone about 1 day before ovulation which stimulate LH secretion

After Ovulation:

Negative feedback:

- During the postovulatory phase the corpus luteum secrete large quantities of progesterone ,estrogen & inhibin
- Which all together cause negative feedback effect on AP & hypothalamus to inhibit both FSH & LH secretion.

(lowest level 3-4 days before the onset of menstruation)

Follicular growth phase

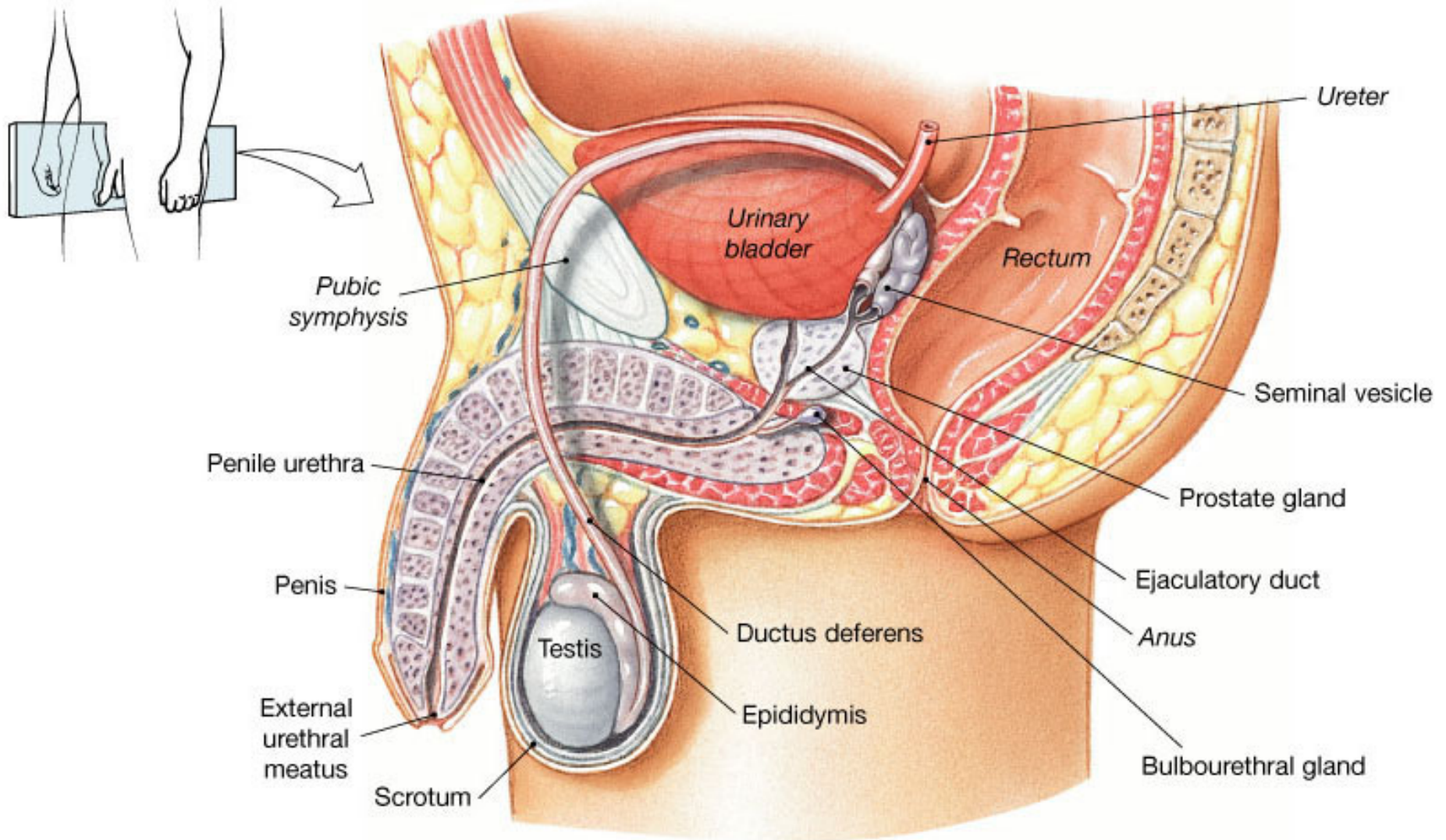
- 2 -3 days before menstruation, corpus luteum regress & secretion of estrogen, progesterone & inhibin decrease.
- This decrease remove the negative feedback effect on AP hormones.
- Therefore a day after menstruation FSH secretion begins to increase (2 folds) while LH secretion is low.
- These hormones causes growth of a new follicle.
- During the first 11 to 12 days of the follicular growth the rate of secretion of FSH & LH decrease due to the negative feedback effect of estrogen on the AP.

Physiology of Androgens and Control of Male Sexual Functions

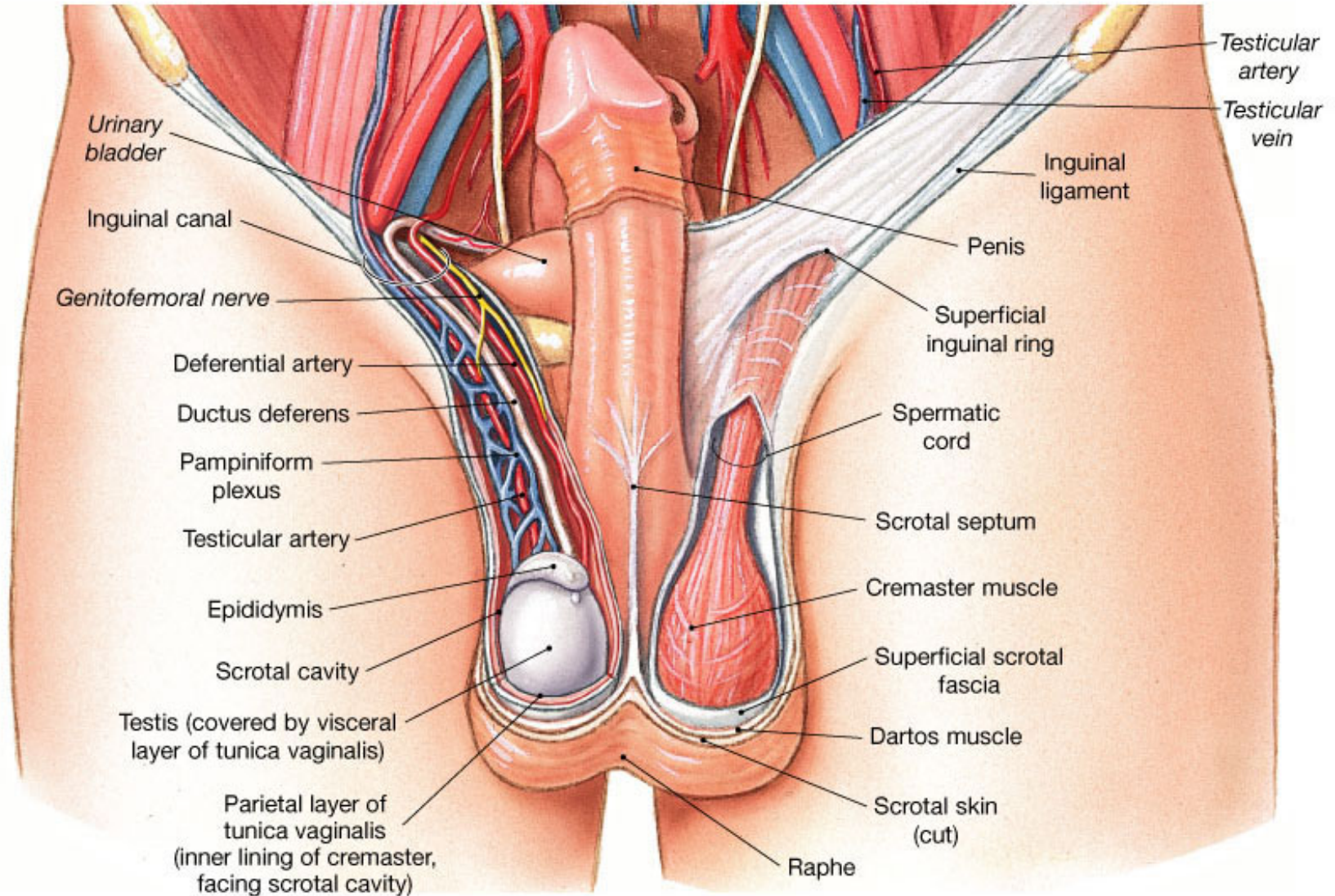
Male Reproductive Anatomy and Physiology

- Testis
- Epididymis
- Vas deferens
- Seminal vesicle
- Prostate
- Bulbourethral
- Ejaculatory duct
- Urethra
- Penis

Male Reproductive Anatomy



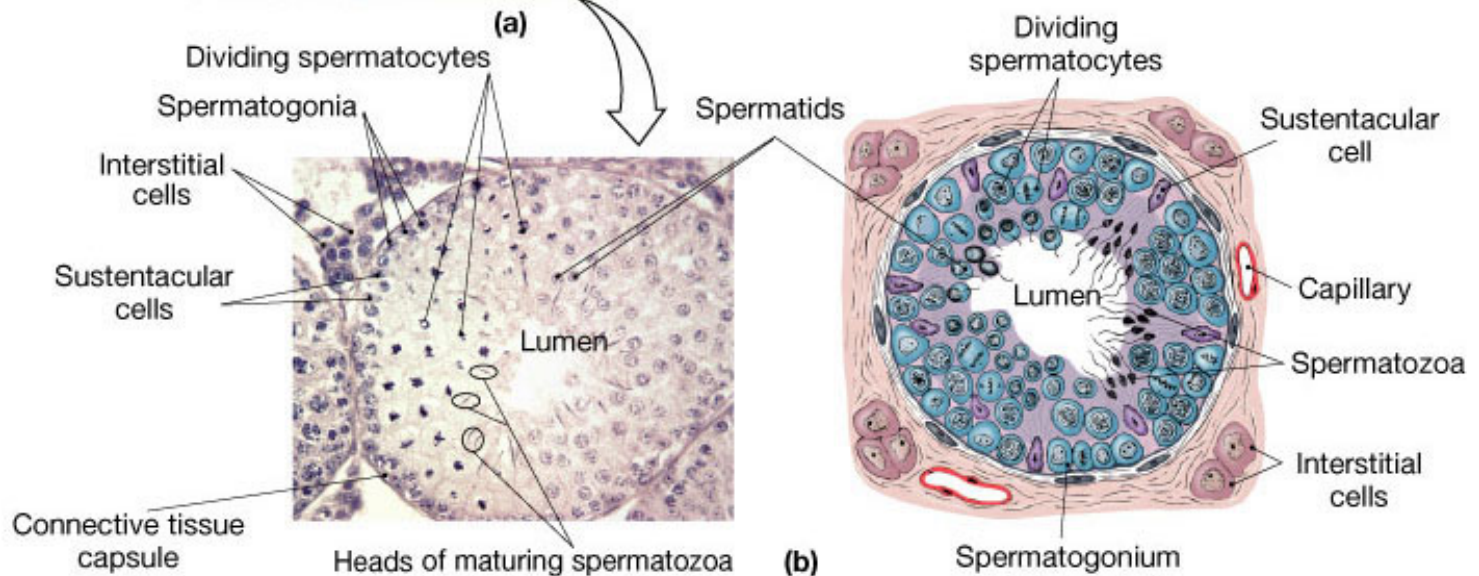
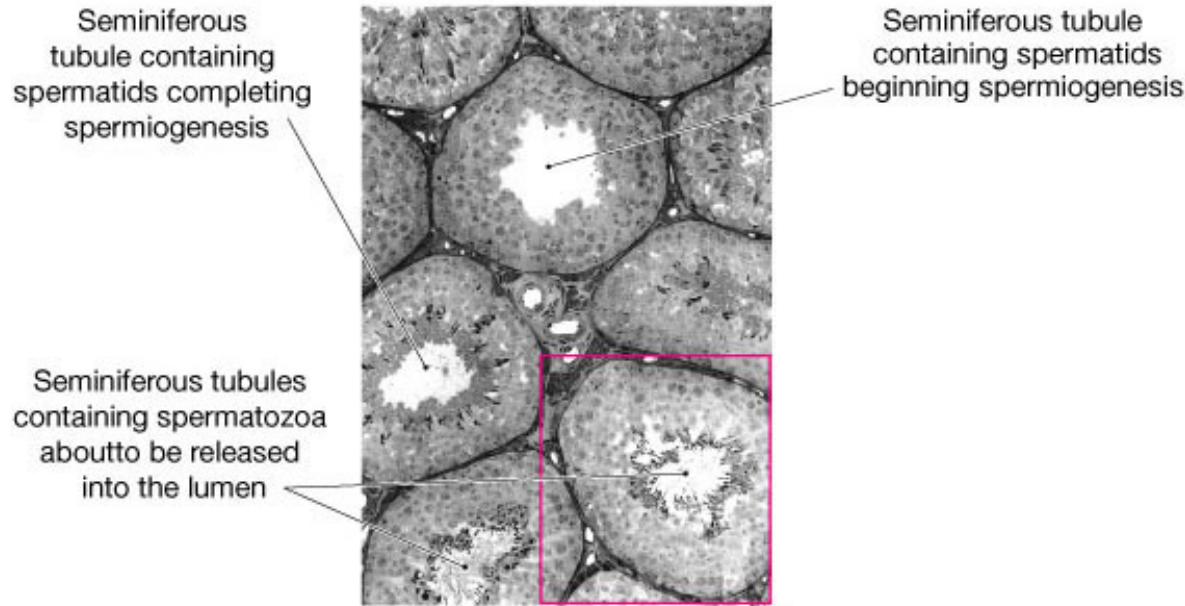
The Male Reproductive System in Anterior View



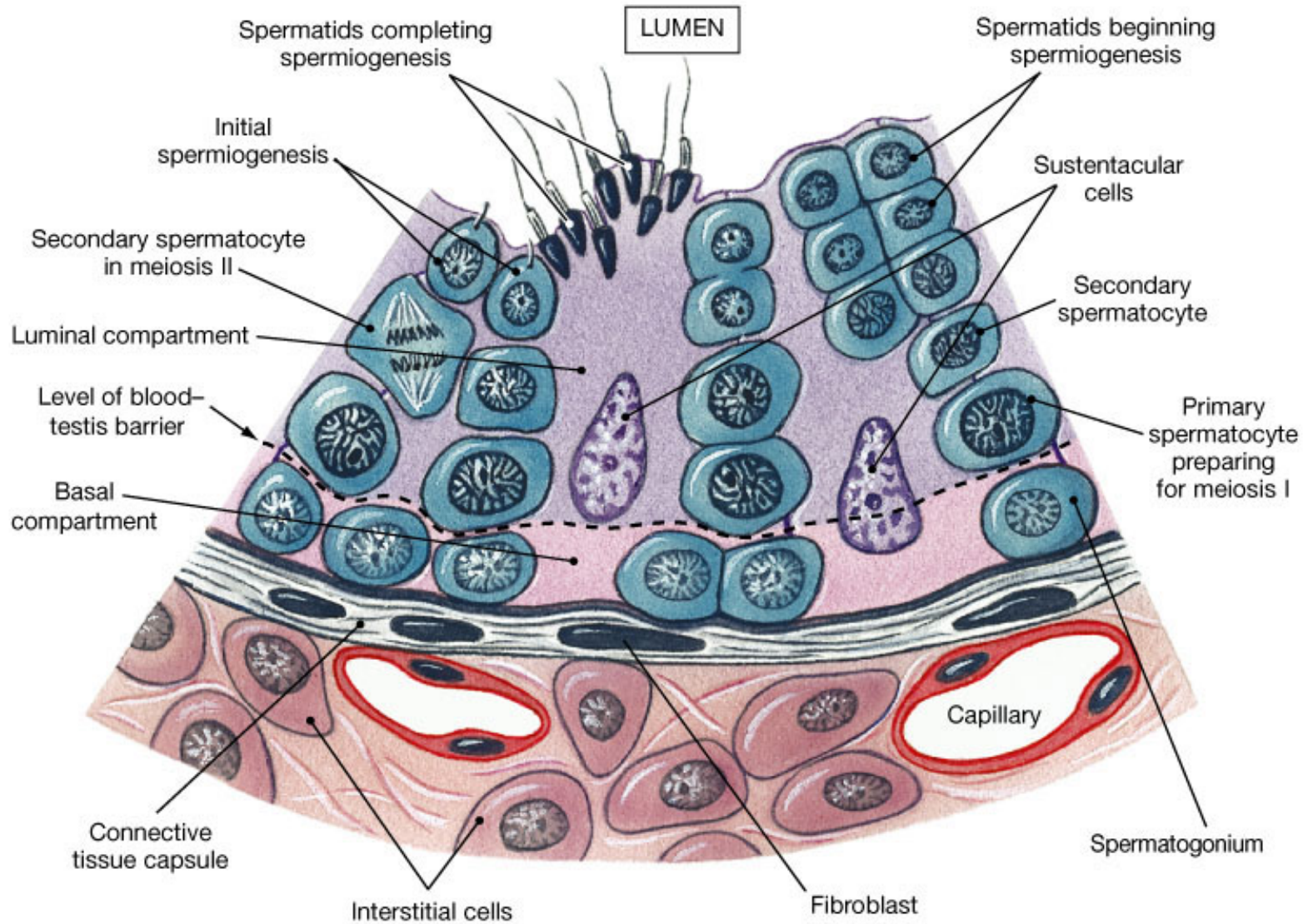
Testes

- The testes reside outside the abdominal cavity in the **scrotum**. This location maintains testicular temperature at about 2°C lower than body temperature.
- Each testis is composed of 300 lobules
- The seminiferous tubule is lined by a complex **seminiferous epithelium** composed of two cell types: 1. **sperm cells** in various stages of **spermatogenesis** and 2. the **Sertoli cell**, which is a “nurse cell” in intimate contact with all sperm cells

The Seminiferous Tubules



The Seminiferous Tubules



(c)

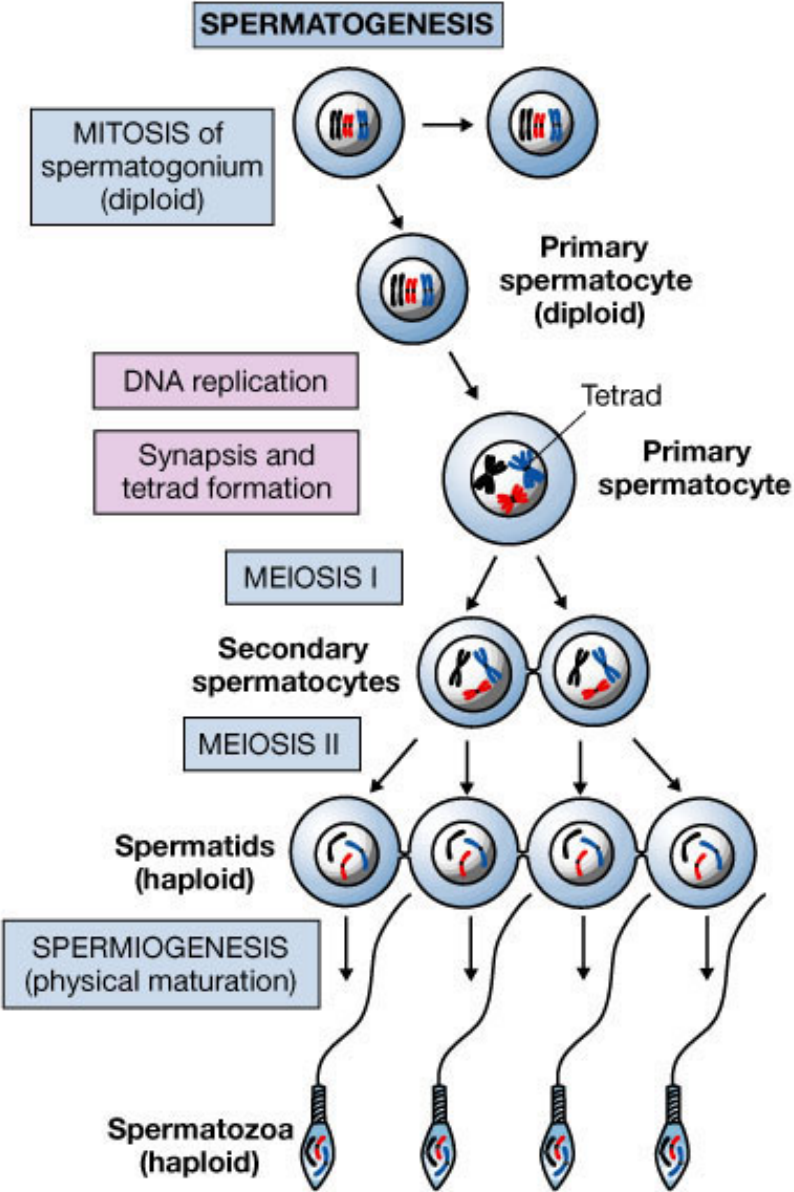
Sertoli Cells

- **Form blood-testes barrier:**
 - Prevents autoimmune destruction of sperm.
 - Produce FAS ligand which binds to the FAS receptor on surface to T lymphocytes, triggering apoptosis of T lymphocytes.
 - Prevents immune attack.
- **Secrete inhibin.**
- **Phagocytize residual bodies:**
 - May transmit information molecules from germ cells to Sertoli cells.
- **Secrete androgen-binding protein (ABP):**
 - Binds to testosterone and concentrates testosterone in the tubules.

Spermatogenesis

- Seminiferous tubules
 - Contain **spermatogonia**
 - Stem cells involved in spermatogenesis
 - Contain **Sertoli** (sustentacular) cells
 - Sustain and promote development of sperm

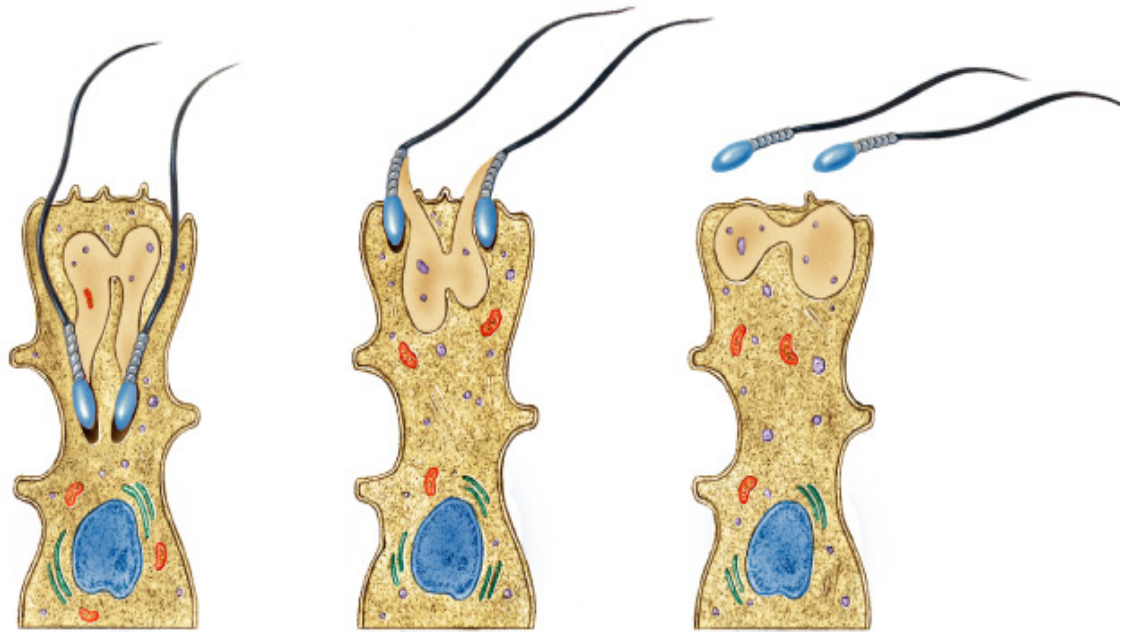
Spermatogenesis



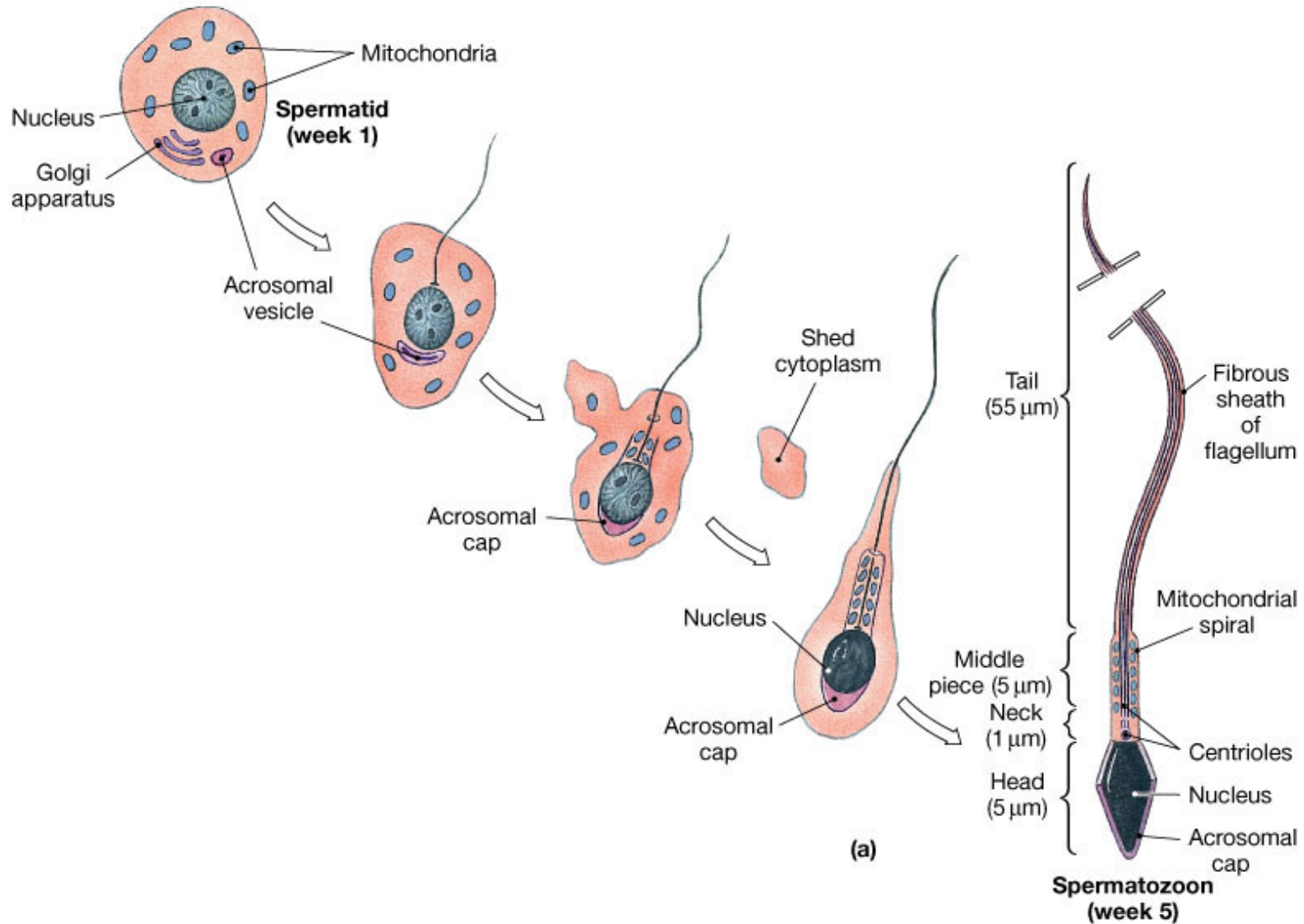
Spermiogenesis

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- Maturation of spermatozoa.
- Phagocytosis of cytoplasm by the Sertoli cells.



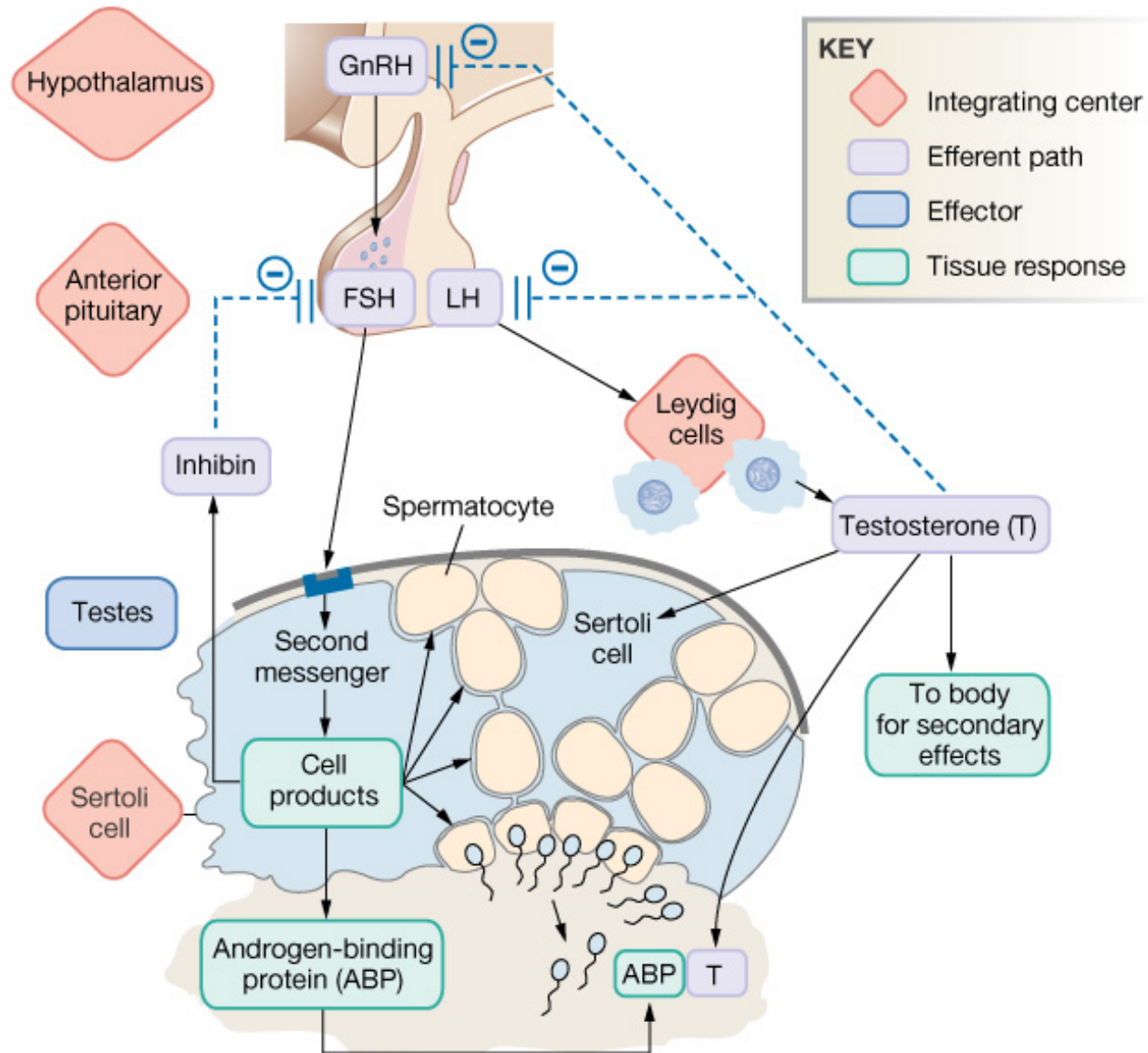
Spermiogenesis and Spermatozoon Structure



Regulation of Spermatogenesis

- GnRH → LH → Leydig cells → testosterone → growth and division of germ cells
- GnRH → FSH → Sertoli cells → spermatocyte maturation
- Inhibin feedback – FSH, testosterone – short & long loops
- Estrogen
- Growth hormone

Regulation of Spermatogenesis



Maturation of Sperm in Epididymis

- Sperms in the early portion of epididymis are nonmotile
- After 18-24 h they develop *capability of motility*
- Most of sperms are stored in epididymis
- After ejaculation they become motile
- Activity of a sperm is greatly enhanced in neutral to slightly alkaline medium
- The life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days

Prostate

- Slightly alkaline milky fluid that help in neutralizing other seminal fluids as well as the vaginal fluids
- Prostates fluids also contain clotting protein and profibrinolysin

Seminal Vesicles

- Secrete mucoid material containing fructose, citric acid & nutrient substances & large quantities of prostaglandins & fibrinogen.
- The prostaglandins are important help in fertilization:
 - By reacting with the female cervical mucus making it more receptive to sperm movement.
 - By causing backward reverse peristaltic contractions of the uterus & fallopian tubes to move the ejaculated sperm toward the ovaries.

Semen

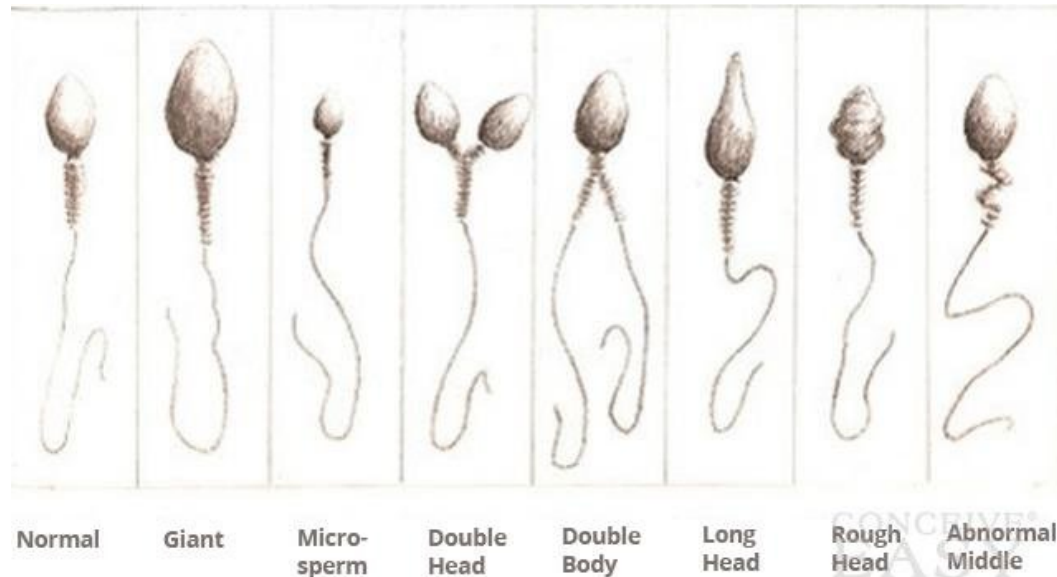
- Milky white, sticky mixture of sperm and accessory gland secretions (65% of semen is from seminal vesicle, 25% prostate)
- Provides a transport medium and nutrients (fructose), protects and activates sperm, and facilitates their movement
- pH is 7.5
- Prostaglandins in semen:
 - Decrease the viscosity of mucus in the cervix
 - Stimulate reverse peristalsis in the uterus
 - Facilitate the movement of sperm through the female reproductive tract

Semen

- Clotting factors coagulate semen immediately after ejaculation, then fibrinolysin liquefies the sticky mass during the next 15-30 minutes
- After ejaculation, sperms can live 24-48 h
- Freshly ejaculated semen undergoes a process called **capacitation**: 1. inhibitory factors are washed out by uterine and fallopian fluids, 2. the sperm swims away from cholesterol vesicles, 3. the membrane of the sperms becomes more permeable to Ca^{++}

Semen

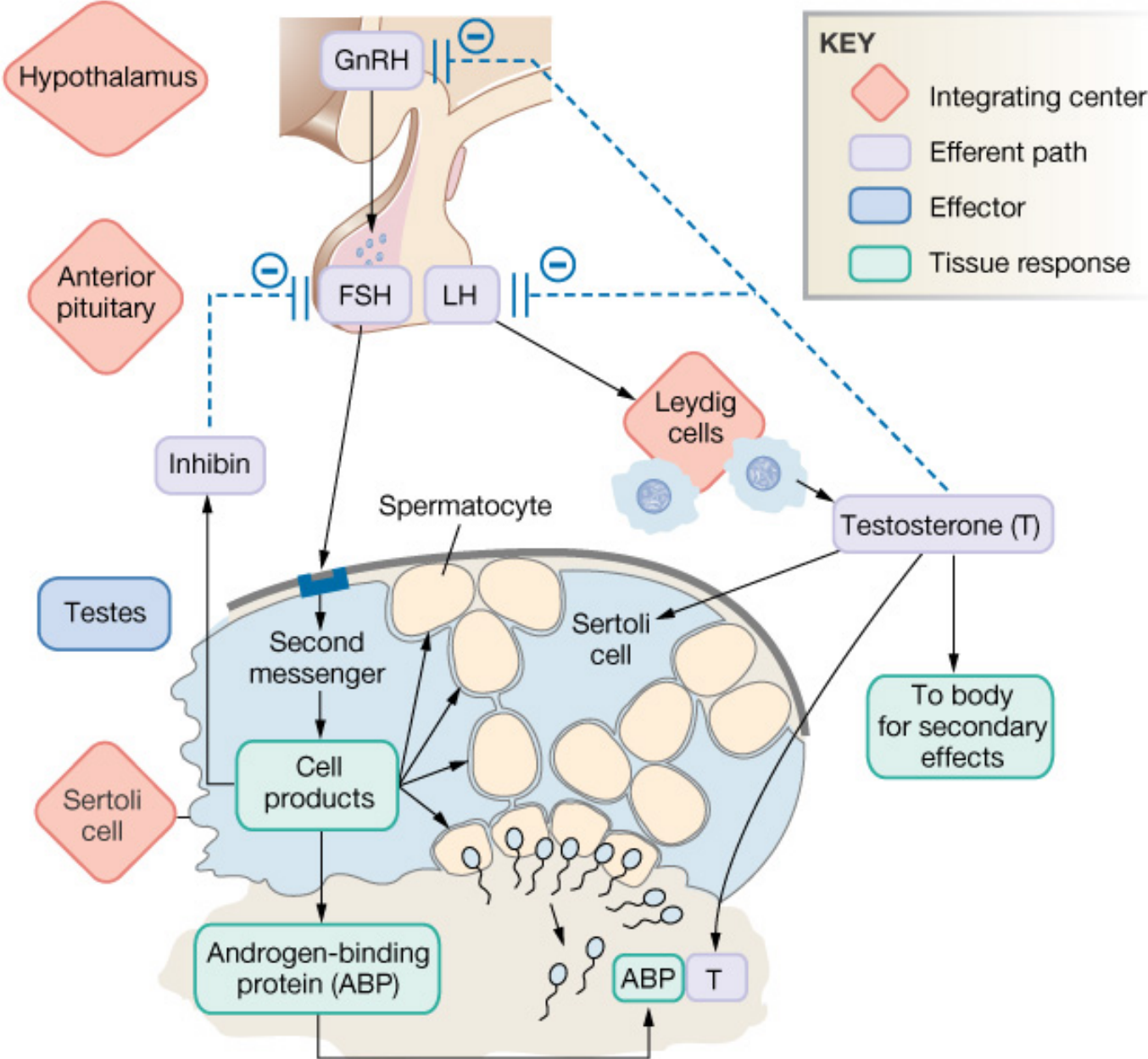
- Only 2-5 ml of semen are ejaculated, but it contains 35-200 million sperm/ml (<20 million infertile)
- When the majority of the sperm are morphologically abnormal or nonmotile, then person is likely to be infertile



Hormonal Regulation of Testicular Function

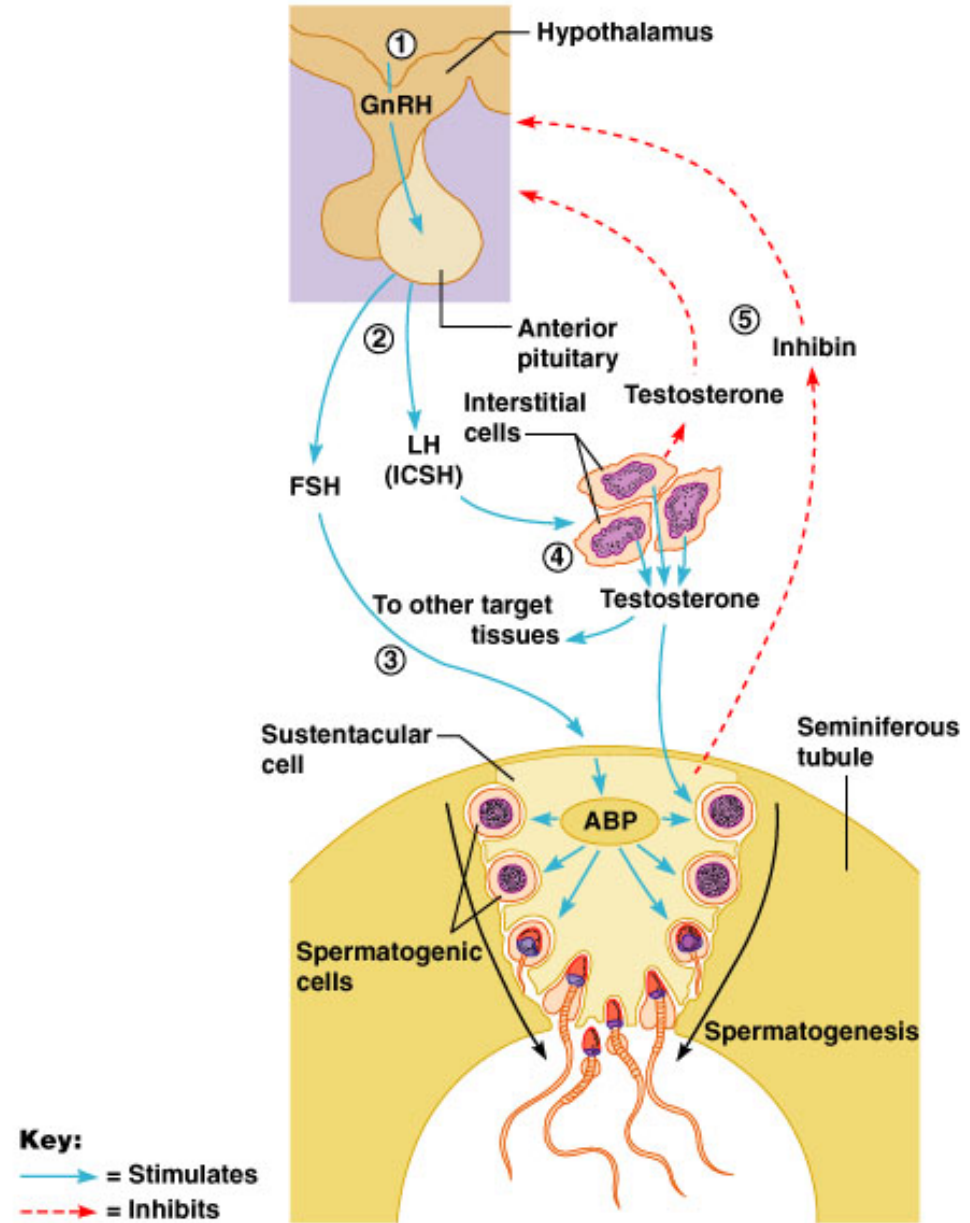
- The hypothalamus releases gonadotropin-releasing hormone (GnRH)
- GnRH stimulates the anterior pituitary to secrete FSH and LH
 - FSH causes Sertoli cells to release androgen-binding protein (ABP)
 - LH stimulates interstitial (Leydig) cells to release **testosterone**
- ABP binding of testosterone enhances spermatogenesis

HPG Axis



Hormonal Regulation of Testicular Function

- Feedback inhibition on the hypothalamus and pituitary results from:
 - Rising levels of testosterone
 - Increased inhibin



Mechanism and Effects of Testosterone Activity

- Testosterone is synthesized from cholesterol
- It binds to testosterone –binding globulin (TeBG), ABP, serum albumin, or to corticosterone-binding globulin (CBG)
- Once it diffuses to cells it either binds to androgen receptor or converted to DHT which then binds to the androgen receptor
- Testosterone targets all accessory organs, its deficiency causes these organs to atrophy
- It causes testes descent during the last 2-3 months of gestation.

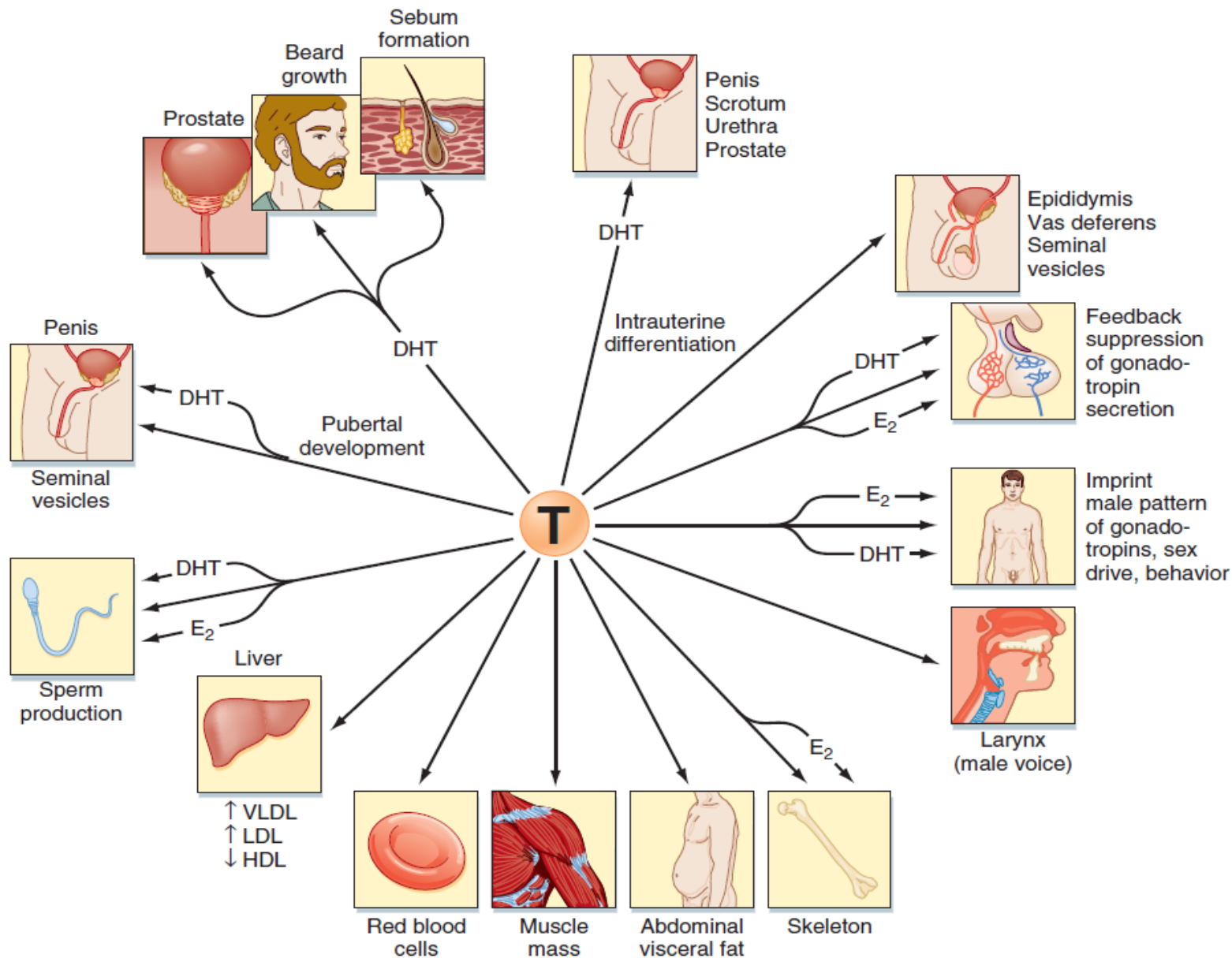
Testosterone Functions:

- Testosterone targets all male reproductive organs and accessory glands, its deficiency causes these organs to atrophy
- Causes the appearance of pubic, axillary, and facial hair
- Enhances growth of the chest and deepening of the voice
- Skin thickens and becomes oily
- Bones grow and increase in density and calcium retention. It is also responsible for the male pelvis shape (narrow, long, funnel-like shape).

Testosterone functions (continued)

- It increases basal metabolic rate
- Increases red blood cells
- It also causes hair growth (pubic, axillary) and libido in females.
- Spermatogenesis and erection.

Testosterone Functions:



Male Sexual Act

- Erection is initiated by sexual stimuli including:
 - Touch and mechanical stimulation of the glans penis and other parts
 - Erotic sights, sounds, and smells
- Erection can be induced or inhibited solely by emotional or higher mental activity
- Enlargement and stiffening of the penis from engorgement of erectile tissue with blood

-
- During sexual arousal, a parasympathetic reflex promotes the release of nitric oxide, VIP, and Acetylcholine.
 - Nitric oxide relaxes the penis arteries and causes erectile tissue to fill with blood
 - Expansion of the corpora cavernosa:
 - Compresses their drainage veins
 - Retards blood outflow and maintains engorgement

-
- When the sexual stimulus becomes extremely intense, spinal cord begins to send sympathetic impulses to initiate **emission**
 - Filling of the internal urethra with semen elicits signals that promotes **ejaculation**
 - After orgasm, the excitement disappears within 1-2 minutes (resolution)

The Erection Reflex

