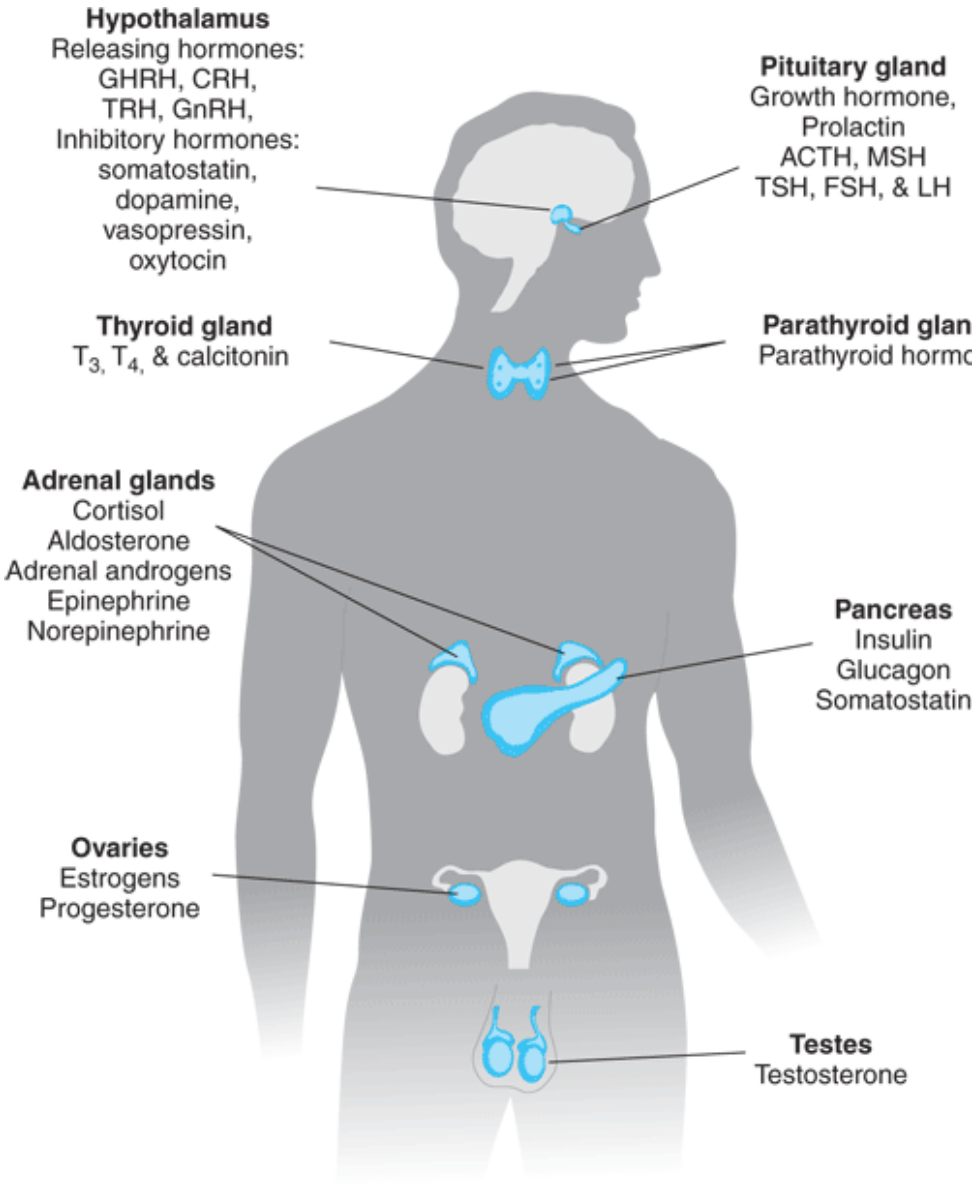
DISORDERS OF MALE IMAGE

Kenneth Alonso, MD, FACP



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Fig. 1-1 Accessed 02/01/2010

Hypothalamic control of pituitary hormones

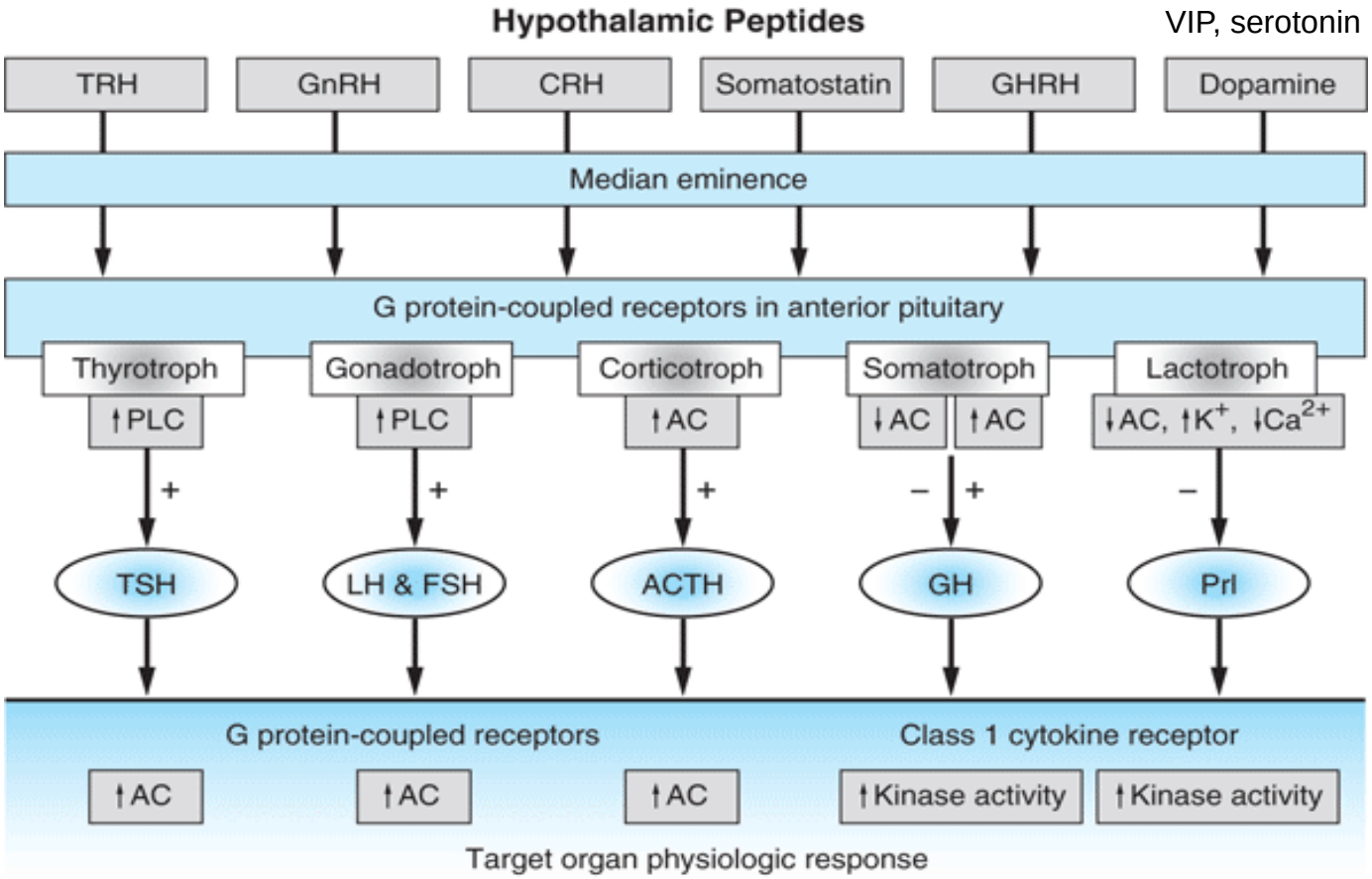
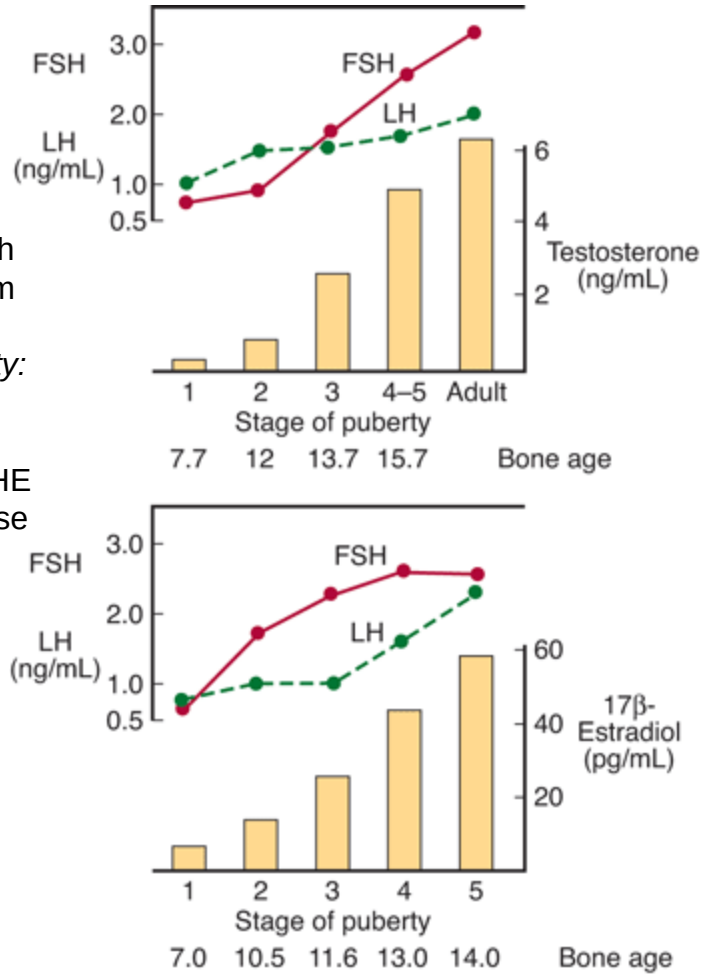


Fig. 3-3 Accessed 02/01/2010

Puberty

- Increased neuronal and hypothalamic expression of a peptide family (kisspeptins) and their receptor (G protein-coupled receptor GPR54), both at 19p3, may trigger gonadotropin releasing hormone production.
- The arcuate nucleus and anteroventral periventricular nucleus are thought to contain the kisspeptin secreting neurons.
- The arcuate nucleus (and medial preoptic area, MPOA) is linked into the olfactory system, through the vomeronasal organ.
- IRF2BPL (14q24.3) inhibits as well as facilitates gonadotropin production.

Puberty (boys)



(Modified and reproduced with permission from Berenberg SR (editor): *Puberty: Biologic and Psychosocial Components.* HE Stenfoert Kroese BV, 1975.)

Stage 1 of puberty is preadolescence.
Stage 2 is characterized by beginning enlargement of the testes.
Stage 3 is charactrized by penile enlargement.
Stage 4 is characterized by growth of the glans penis.
Stage 5 is characterized by adult genitalia.

Fig. 25-9
Accessed 02/01/2010

Precocious puberty (boys)

- Testicular enlargement suggests increased LH, FSH secretion.
- Determine HCG as well.
- Consider tumor (pituitary, pineal, testes).
- No testicular enlargement suggests an exogenous or adrenal source.
- Hypothyroid state can lead to precocious puberty. Check TSH.
- Gonadotropin analogs will suppress endogenous secretion in gonadotropin dependent disease.
- If independent, tamoxifen will suppress.

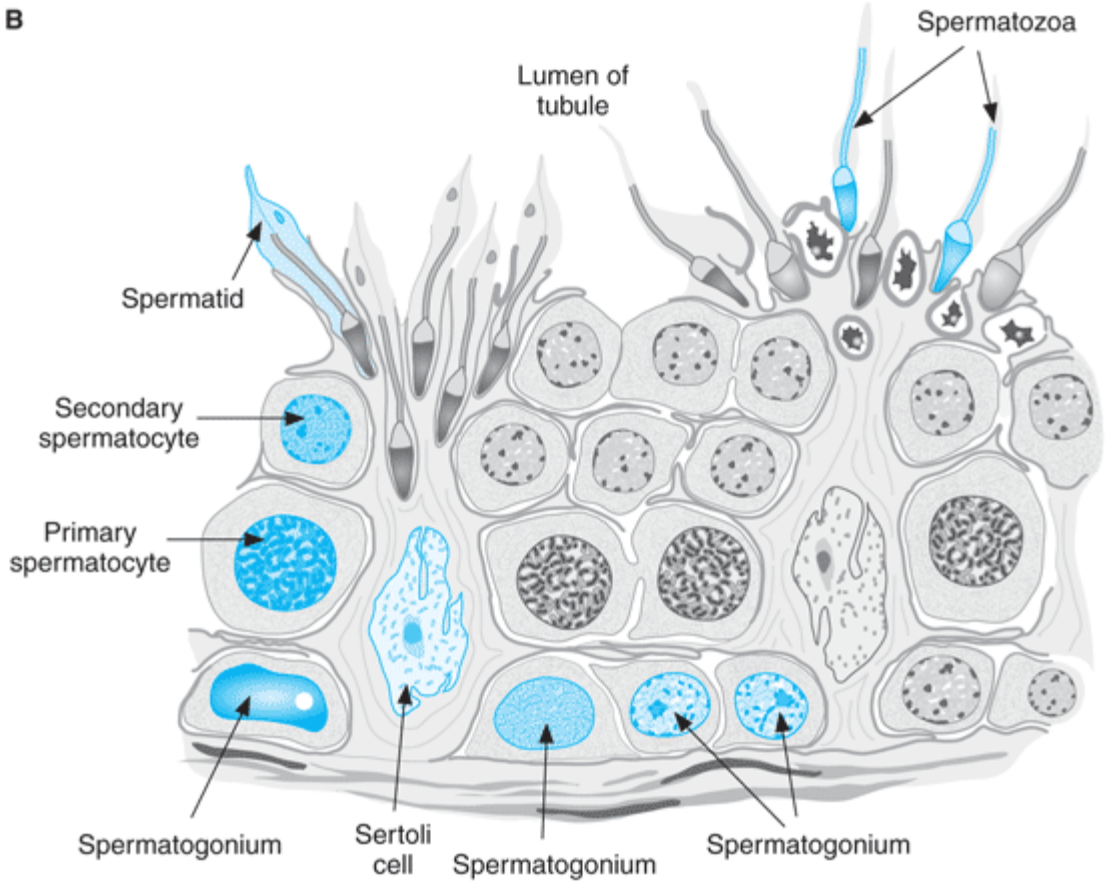
Testosterone

- Testosterone is principally produced in the Leydig cell of the testis.
- LH stimulates its production.
- Testosterone is transported to the Sertoli cell of the testis where it is converted to dihydrotestosterone (DHT)
- FSH stimulates this conversion.
- cAMP is the second messenger for both LH and FSH.
- 17βOH deficiency involves a failure to convert DHEA, androstenedione to testosterone.

Testosterone

- 5α-reductase deficiency involves a failure to convert testosterone to DHT in target organs
- A functional lack of testosterone at birth.
- Increased testosterone synthesis at puberty may be sufficient to masculinize.
- May show ambiguous genitalia.
- No breast tissue.

Spermatogenesis



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Male infertility

- 15% of couples are infertile
- 50% related to male abnormality.
- Is this a male?
- Do Müllerian elements (uterus) persist?
- Ultrasound evaluation
- Testicular feminization?
- Or a 17β hydroxylase or 5α-reductase deficiency
- Or loss of androgen receptors

Male infertility

- 20% azospermic
- 20-30% oligospermic (<1 million/mm^3) or with poor sperm motility.
- If LH, FSH normal with azoospermia, duct obstruction.
- Low semen fructose is noted.

  If no vas deferens, consider cystic fibrosis
- Vasectomy reversal does not guarantee fertility

Male infertility

- Y chromosome deletions common (SRY gene encodes for testes determining factor).
- LH normal, FSH elevated.
- Marijuana, anabolic steroid use contribute to infertility
- Testosterone administration has been used as a reversible contraceptive method
- Testicular torsion (abnormally high insertion of tunica vaginalis permits increased flexibility), trauma as possible causes
- If LH, FSH low, Prolactin normal, is a hypopituitary state.
- If Prolactin elevated, is a pituitary adenoma.

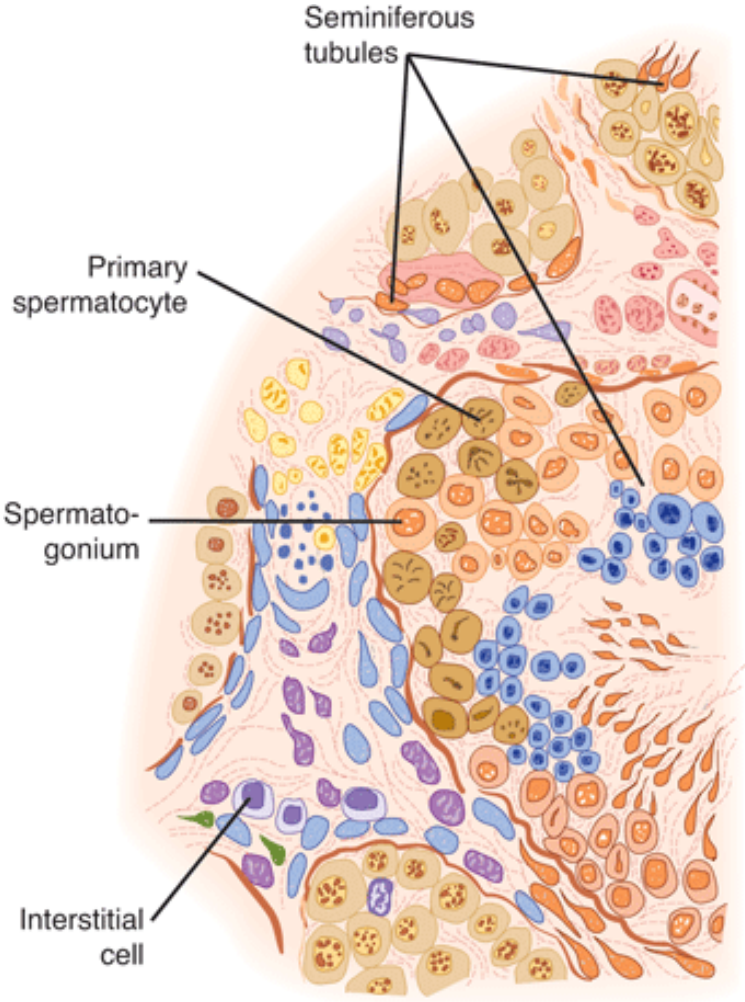
Gametogenesis

- Primary germ cells in the testis differentiate into spermatogonia.
- They are located at the basement membrane of the testis.
- They further divide and differentiate into primary spermatocytes.
- Further differentiation occurs into spermatids, and, then, spermatozoa.
- Immature spermatozoa pass into the epidydimis where they are modified by galactosyl-transferase.

Gametogenesis

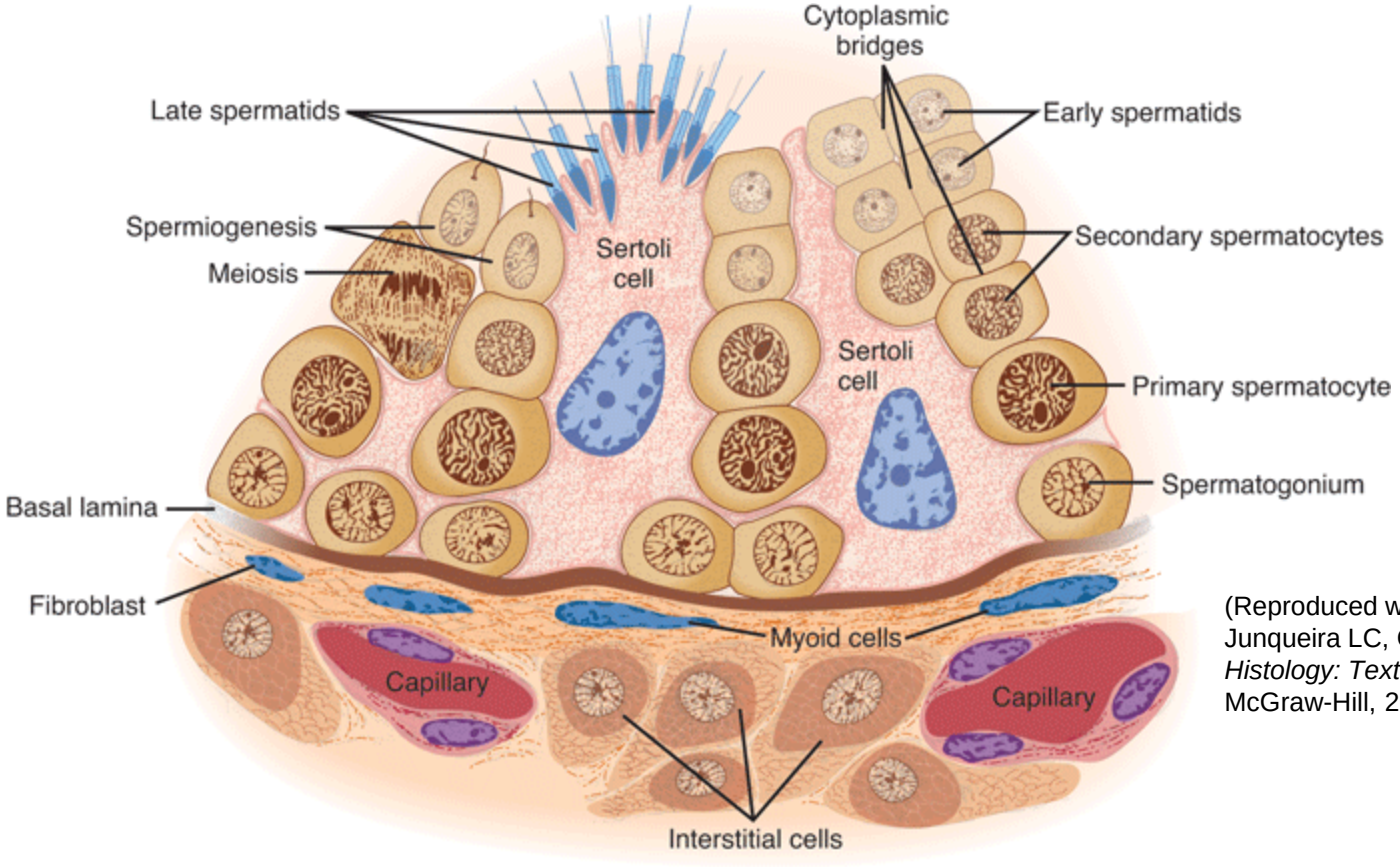
- Mature spermatozoa, when in the female genital tract, are capacitated.
- Galactosyl-transferase, acrosin activated.
- Motility increased.

Gametogenesis



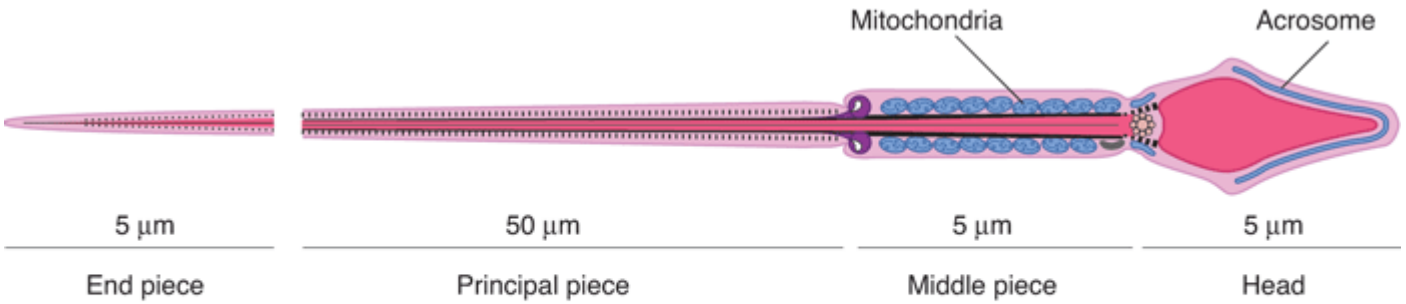
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Spermatogenesis



(Reproduced with permission from Junqueira LC, Carneiro J: *Basic Histology: Text & Atlas,* 10th ed. McGraw-Hill, 2003.)

Spermatozoon



(Reproduced with permission from Junqueira LC, Carneiro J: *Basic Histology: Text & Atlas,* 10th ed. McGraw-Hill, 2003.)

Testosterone

- Testosterone is a pro-hormone.
- 4% is altered by 5α-DHT reductase into the potent androgen, dihydrotestosterone.
- 2% is altered by 5α-DHT reductase and 3β-hydroxysteroid dehydrogenase into the weak androgen, androstenediol.
- 5% is aromatized to the potent estrogen, 17β-estradiol.
- The remainder is metabolized in the liver to produce 17-keto compounds (androsterones). Glucoronidation or sulfation occurs for elimination.

Testosterone

- Testosterone is produced in Leydig cells
- LH stimulates
- cAMP as second messenger.
- Testosterone is transported to the Sertoli cell of the testis where it is converted to DHT and binds to androgen binding protein (ABP) also produced in those cells
- FSH stimulates.
- cAMP as second messenger.
- Affects spermatogenesis.

Testosterone

- Testosterone from the liver binds to sex hormone binding globulin (SHBG).
- Only 1% is free and active.
- Affects sexual differentiation, anabolism, behavior.

Relative percentage contribution by tissues to plasma levels of sex steroids

Hormone	Testicular Secretion	Adrenal Secretion	Peripheral Conversion of Precursors
Testosterone	95	< 1	< 5
DHT	20	< 1	80
Estradiol	20	< 1	80
Estrone	2	< 1	98
DHEA sulfate	<10	90	---

Testosterone

- 17β-OH deficiency involves a failure to convert DHEA, androstenedione to testosterone.
- 5α-reductase deficiency involves a failure to convert testosterone to DHT in target organs
- A functional lack of testosterone at birth.
- Increased testosterone synthesis at puberty may be sufficient to masculinize.
- May show ambiguous genitalia.
- No breast tissue.

Steroid hormone receptor family

- Steroid hormone receptors belong to the steroid and thyroid hormone receptor super-family of proteins, that includes receptors for steroid hormones, thyroid hormones, vitamin D and vitamin A (retinoic acid).
- Receptors may be up-regulated or down-regulated with exposure to hormone or deprivation of hormone.
- Hormone receptors have multiple domains

Hormone receptors

- Peptide hormone receptors span the plasma membrane and bind ligand outside the cell.
- The hormone binding signal is transduced to the cell interior by binding to a series of G- proteins that lead to the production of the second messenger, principally cAMP.
- Steroid hormone receptors are ligand-activated proteins that regulate transcription of selected genes.
- Hormone receptors for glucocorticoids and aldosterone are found principally in the cytosol. When activated they translate to the nucleus.

Sex hormone action

- The sex steroid hormones bind to intracellular receptors that are members of the steroid-thyroid hormone receptor superfamily
- Hormone receptors are dimers that are stabilized in the cytosol by heat shock proteins, which dissociate after the hormone binds to the receptor.

Sex hormone action

- The hormone-receptor complex migrates to the nucleus and binds to a hormone response element (HRE) upstream of a gene and acts as a transacting factor that modulates the transcription frequency of RNA Pol II, which is bound to the promotor element (PE).
- Affects ribonucleoprotein synthesis.
- Binding of cytosolic mRNA to ribonucleoprotein particles stabilizes mRNA, limits degradation.

Loss of androgen receptor

- Testicular feminization.
- Affected individuals have ambiguous female external genitalia.
- Lack of response to androgens enhances female development, decreases body hair.
- Abdominal testes
- No uterus, primary amenorrhea.
- Androgen insensitivity due to mutation in androgen receptor
- Xq12

Gynecomastia

- Excess sex hormone binding globulin. May be a result of liver disease.
- Elevated estradiol, T_4 levels.
- However, free testosterone and free estradiol levels may be diminished.
- Leydig cell hyperplasia
- Cords of eosinophilic cells with bland nuclei
- Limited spermatocyte maturation

Male infertility

- LH normal, FSH elevation:
- Germ cell abnormality (Y chromosome deletions)
- LH, FSH normal with azospermia:
- Duct obstruction.
- Low semen fructose is noted.
- If no vas deferens, consider cystic fibrosis
- LH, FSH low, prolactin normal:
- Hypo-pituitary state.
- If prolactin elevated:
- Pituitary adenoma

Erection

- Psychic stimulation of the central parasympathetic pathway activates preganglionic neurons to pelvic ganglia supplying fibers to internal pudendal artery (muscarinic, VIP receptors).
- Cholinergic fibers also lead to nitrous oxide release.
- Glandular secretion (muscarinic receptors on acini of prostate and seminal vesicles).
- Psychic stimulation of the central sympathetic pathway activates pre-ganglionic neurons (α_1 receptors).
- Bladder β_2 receptors prevent detrusor contraction.

Erection

- Ejaculation through a reflex arc at S2-4.
- Motor fibers in the pudendal nerve cause rhythmic contractions of the bulbospongiosus muscles.
- Detumescence.
- Central sympathetic fibers activate preganglionic neurons to pelvic sympathetic ganglia supplying fibers to α_1 receptors on pudenal arterioles at entry into cavernous spaces.
- The cGMP phosphodiesterase inhibitors sildenafil, vardenafil, tadalafil are vasodilators, sustain an erection.

Erectile dysfunction

- Poor arterial filling and/or venous retention as mechanism.
- Psychogenic component as well.
- Check prolactin, testosterone, LH/FSH to exclude hormonal abnormalities.
- Neurogenic component if post radiotherapy or surgery to prostate.

Erectile dysfunction

- Disease prevalence in the US is 10-15%
- 21% of those aged 50-59.
- Diabetes, hypertension, coronary artery disease, low HDL, smoking as major risk factors.
- Thiazides, β-blockers, antidepressants, and spironolactone are common drug-related causes.
- Exclude long term anabolic steroid use

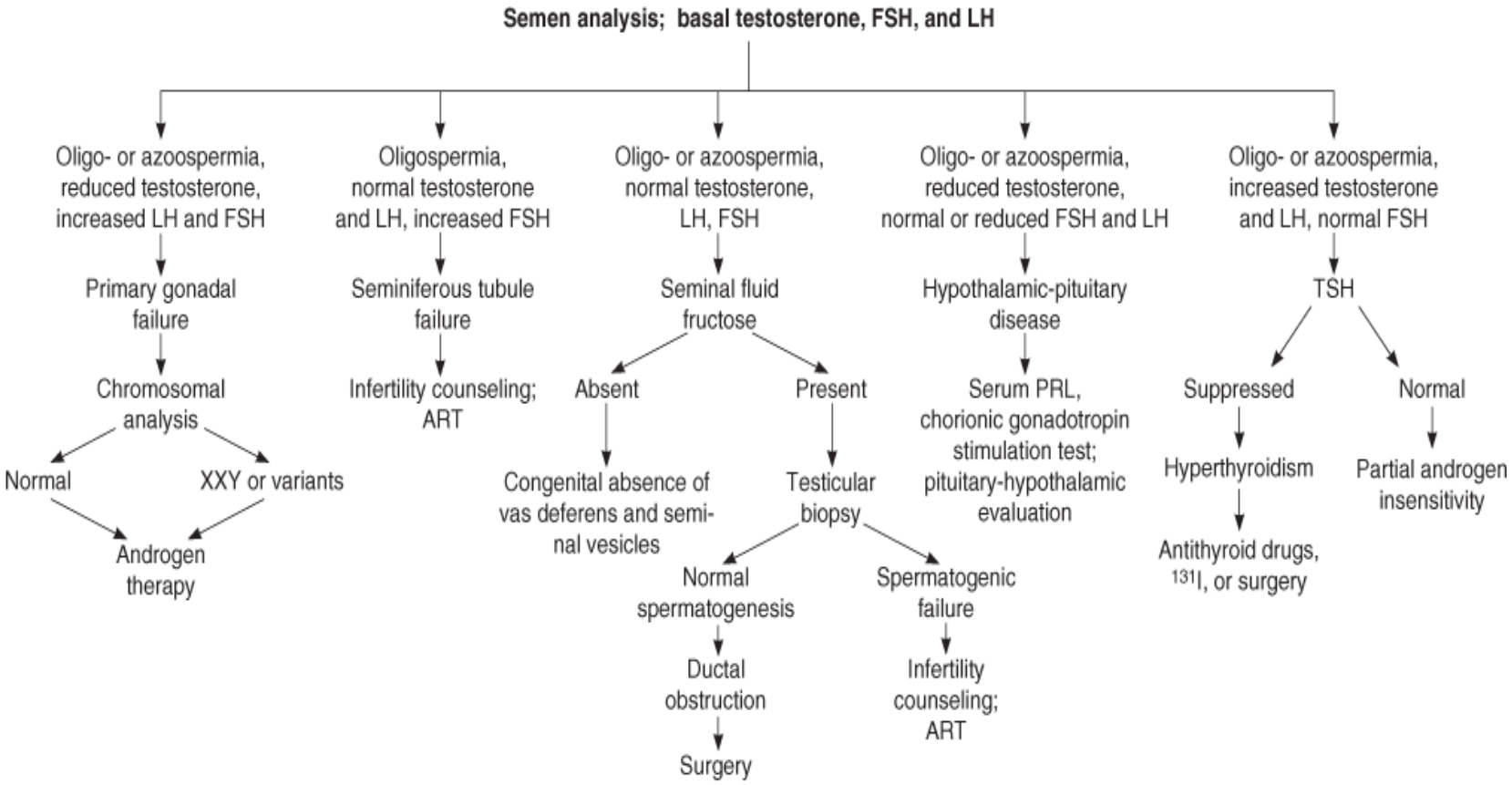
Treatment of erectile dysfunction

- Vacuum pump
- Urethral suppository

  Alprostadil

  Rapid onset and short duration
- Surgical Implants
- PDE-5 inhibitors (not to be used concomitantly with nitrates)
- α-blockers

Hypogonadism (males)



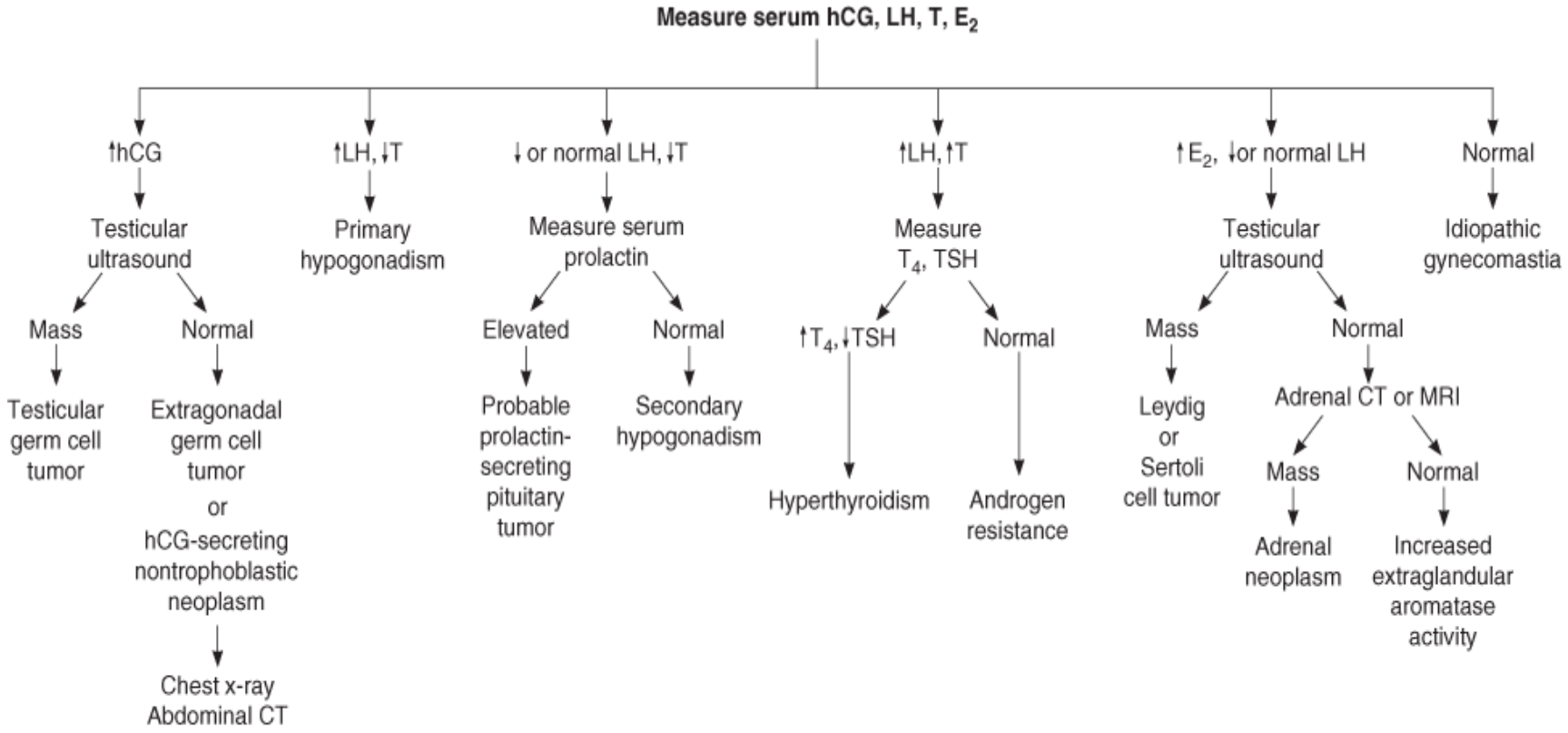
Source: Gardner DG, Shoback D: *Greenspan's Basic and Clinical Endocrinology*, 8th Edition: http://www.accessmedicine.com

Fig. 13-6
Accessed 02/01/2010

Gynecomastia

- Excess sex hormone binding globulin.
- May be a result of liver disease.
- Elevated estradiol, T_4 levels.
- However, free testosterone and free estradiol levels may be diminished.
- Leydig cell hyperplasia
- Limited spermatocyte maturation

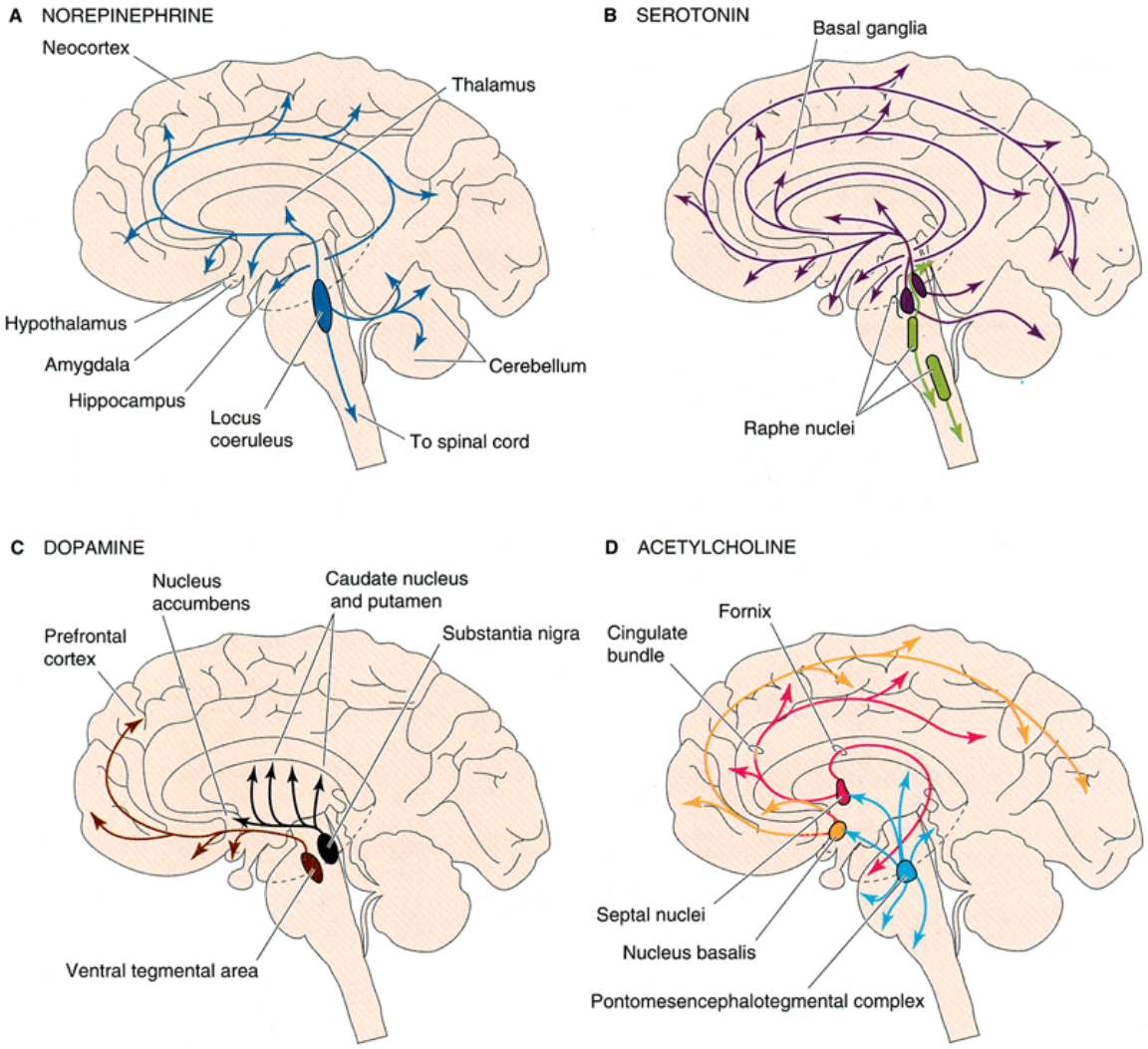
Gynecomastia



Source: Gardner DG, Shoback D: *Greenspan's Basic and Clinical Endocrinology*, 8th Edition: http://www.accessmedicine.com

Fig. 336-8
Accessed 02/01/2010

Neurotransmitters and pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Boron WF, Boulpaep EL: *Medical Physiology.* Elsevier, 2005.)

Acetylcholine

- Acetylcholine projections originate principally in the ventral tegmentum and project to the hypothalamus, thalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Regulate arousal, cognition, and memory, among other functions.
- REM promoting cholinergic pedunculopontine and lateral dorsal tegmental nuclei are counterbalance to the waking serotonergic dorsal raphé and the noradrenergic loci ceruleus nuclei (whose firing is related to state of attention).

Cholinergic cell groups

- Cholinergic cell groups in the basal forebrain include the medial septum, diagonal band, and the nuecleus basalis of Meynert.
- These topographicaly innervate the entire cerebral cortex and hippocampus and amygdala.
- Pontine cholnergic cellgroups innervate the brain stem reticular formation as well as the thalamus.
- The pedunculopointine nucleus is located ventrolaterally near the superior cerebellar peduncle
- Controls firing of glycinergic neurons in the lateral reticulospinal pathway.

Cholinergic cell groups

- The laterodorsal tegmental nucleus is a component of the periacqueductal gray matter just rostral to the locus ceruleus.
- VIP, substance P are neurotransmitters also found in cholinergic ganglia.

Sensory phenomena

- REM sleep is associated with pontogeniculate orbital activity (visual effects) and cortical activation coupled with atonia.
- Serotonin inhibits REM activity.
- Autoscopy (out of body activity) is related to dorsal prefrontal and temporal lobes.
- The ventrolateral periacqueductal gray is the switch between REM and awake states.
- Hypoxia and hypotension turn off locus ceruleus activity, leading to a cholinergic response.
- 85% of vagal efferents are in the neck. May be a protective response of inactivity (healing).