ACTIONS OF TESTOSTERONE & HORMONAL REGULATION OF TESTES

Testosterone (T) is the principal testicular hormone, secreted from the *interstitial cells of Leydig* at a rate of 10 mg per day. T is a steroid made from cholesterol and is the principal circulating androgen ("male maker" hormone). Other androgenic steroids are *di-hydroxy-testosterone* (DHT) and *de-hydro-epi-androsterone* (DHEA). DHEA is a precursor of T synthesis and is the main adrenal gland androgen. DHT is formed by conversion of T by the enzyme *α-reductase* and is present in plasma and in some body cells. Androgenic potency of T is less than DHT but much higher than DHEA.

TESTOSTERONE EXERTS THREE MAJOR TYPES OF ACTIONS
T has widespread effects in the body, which may be divided into three groups: (1) effects in adult male sexuality and reproduction; (2) actions on the development of the reproductive system and brain of the fetal male, as well orchestrating male puberty and body growth and behavior changes; and (3) non-reproductive, anabolic effects in the adult.

Stimulation and maintenance of the adult male reproductive system—In adult males, the steady secretion of testosterone (1) maintains spermatogenesis and the secretory functions of the accessory sex organs and glands—epididymis, prostate, and seminal vesicles; (2) maintains male secondary sex characteristics, including muscle and bone mass; and (3) promotes sex drive (libido) and other brain and mental effects.

Actions on the developing male & during puberty—The testes of the embryo, fetus, and neonate secrete T during these stages. In childhood, the testes remain inactive, only to start up again during puberty. The reproductive organs of the embryo initially are sexually indifferent and bipotential. In the male embryo, T promotes differentiation of the male-type genitalia. During fetal development, T promotes development of male-type hypothalamic systems, which regulate neural control of reproductive hormones and male sexual behavior.

During puberty, secretion of T in boys rises steadily from 10 years of age through adolescence, peaking in the early twenties. In adolescent boys, T promotes growth and maturation of the *primary sex organs* (e.g., testes, penis) and *accessory sex glands* (e.g., prostate, seminal vesicles), and development of *secondary sex characteristics* (low-pitched voice, dense facial and body hair, enhanced muscular and skeletal growth). T also acts on the brain to promote final maturation of the brain centers involved in regulating sexual activity and sexual behavior. Thus, immature boys transform into young men with fertile sperm and interest in the opposite sex, sexual activity, and procreation.

Anabolic and non-reproductive effects—T has widespread general anabolic effects on body cells and tissues that may or may not be related to maleness. Androgens enhance anabolism in many tissues by increasing synthesis of proteins and stimulating tissue growth. Increasing levels of T in adolescent boys increase bone growth and calcium deposition and enhance muscle mass by increasing protein synthesis. However, peak levels of T in post-adolescent boys induce the closure of epiphyseal plates of the bone, thereby terminating bone growth. Other non-reproductive effects include increasing the size of the kidneys and formation of red blood cells in the bone marrow. Large doses of T are used to stimulate tissue growth in emaciated patients and to enhance muscle mass in athletes. However, negative side effects of increased libido and decreased fertility (sperm production) discourage such uses.

Cellular mechanisms of T actions in target tissues—The cellular mechanism of action of T in its targets follows the general pathway for steroid hormones (plate 114). In the adult male reproductive tissue, T diffuses into a target cell nucleus to bind with nuclear androgen receptors possessing binding sites for T and DNA, initiating gene action and synthesis of mRNA and proteins that mediate T actions. In the developing brain, T is first converted to estrogen by neuronal aromatase before receptor binding. In certain body tissues during sexual maturation and puberty, T is first converted to DHT by the target cell α-reductase; DHT then binds to the androgen receptor. The affinity of DHT for androgen receptors is higher than that of T.

TESTICULAR FUNCTIONS REGULATED BY PITUITARY LH & FSH
The testes' functions are controlled by LH and FSH, two gonadotropin glycoprotein hormones from the anterior pituitary gland. LH controls T release by Leydig cells and FSH acts on Sertoli cells to control spermatogenesis. LH and FSH actions follow these steps: binding with plasma membrane receptors → activation of membrane G-proteins → activation of membrane adenylate cyclase → formation of cyclic AMP, which brings about the cellular effects of LH/FSH on target cells (plate 12, 114).

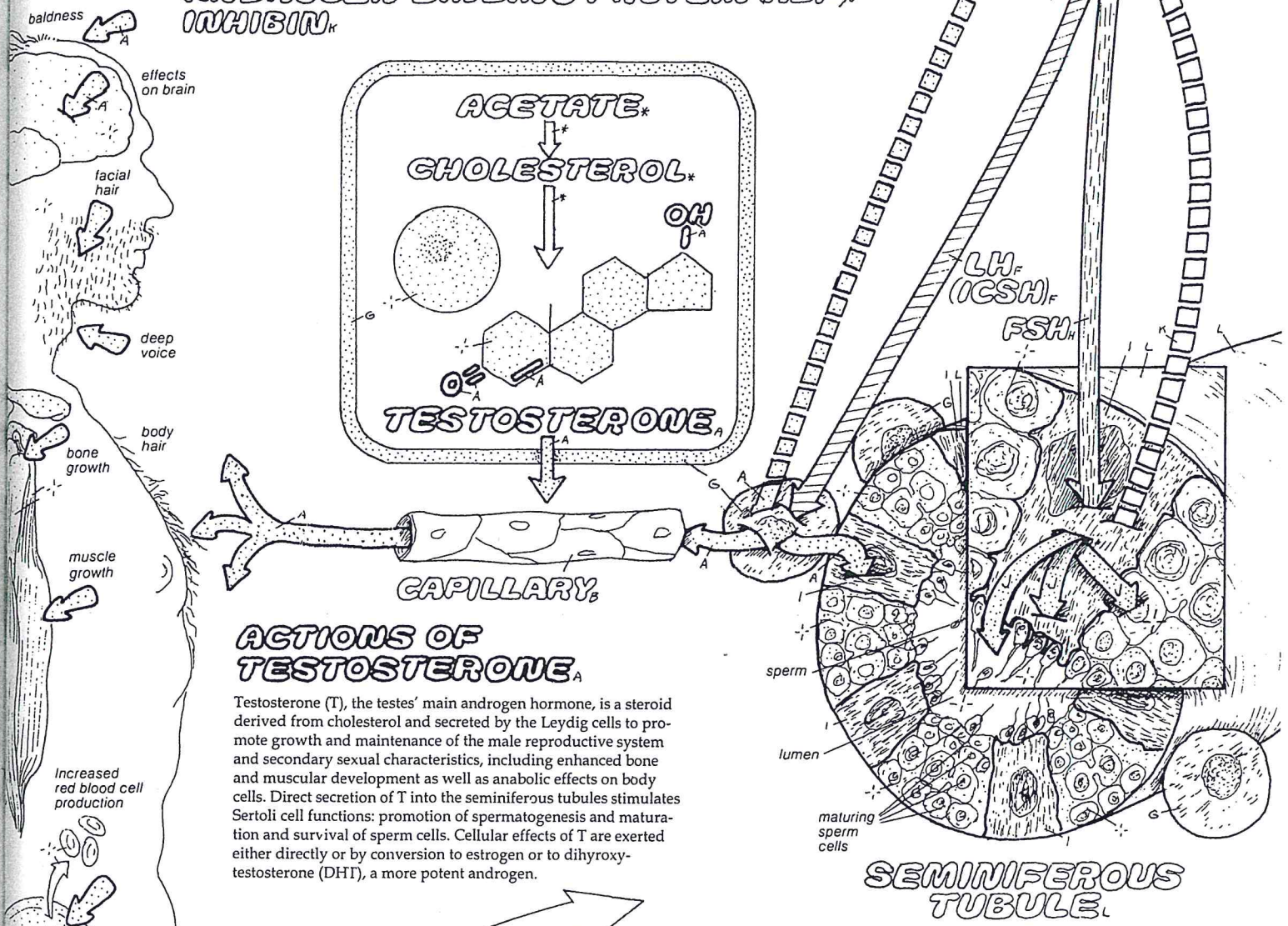
LH controls Leydig cells & T production—Steady plasma levels of T in mature males are achieved by the negative feedback effect of T on the *hypothalamus* and *anterior pituitary*. A decrease in T level stimulates the hypothalamus to release more *gonadotropin-releasing hormone* (GnRH), which stimulates the anterior pituitary to release LH into the blood. LH stimulates the Leydig cells to increase T release. If T levels increase above the normal set point, the same feedback mechanism will diminish GnRH and LH levels and restore the T level to normal. Release of GnRH occurs in *pulses* every 1–2 hours, each pulse lasting a few minutes. Changes in T levels change the frequency and intensity of GnRH pulses. Pulsatile secretion of LH is critical, since continuous secretion of GnRH desensitizes the pituitary, reducing plasma LH levels.

FSH controls Sertoli cells & spermatogenesis—Sperm formation in the testes is regulated mainly by the gonadotropin FSH from the anterior pituitary. FSH exerts tropin and trophic actions on the Sertoli cells, stimulating their various functions—chiefly, support of spermatogenesis and secretion of *androgen binding protein* (ABP). The Sertoli cells in turn secrete a peptide hormone, *inhibin*, which acts on the anterior pituitary to regulate FSH release by negative feedback. In fact, inhibin has the potential for use as a male contraceptive, because high doses of it cause reduced sperm production by reducing FSH secretion. LH is also important for spermatogenesis, but its effect is mediated by release of T, which in turn stimulates Sertoli cell function (plate 151).

CN: Use red for B and a dark color for A.
1. Begin with testosterone (A) functions as shown by the three arrows from an interstitial cell (G) in the right central portion of the page.
2. Go to the titles at the top of the page.

HORMONAL REGULATION OF TESTIS FUNCTION

HYPOTHALAMUS$_C$
GONADOTROPIN RELEASING HORMONE,
ANTERIOR PITUITARY$_E$
LUTEINIZING HORMONE (LH)$_F$
INTERSTITIAL CELL (OF LEYDIG)$_G$
FOLLICLE-STIMULATING HORMONE (FSH)$_H$
SERTOLI CELL$_I$
ANDROGEN-BINDING PROTEIN (ABP),
INHIBIN$_K$

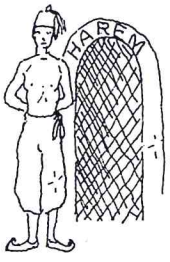


ACTIONS OF TESTOSTERONE$_A$

Testosterone (T), the testes' main androgen hormone, is a steroid derived from cholesterol and secreted by the Leydig cells to promote growth and maintenance of the male reproductive system and secondary sexual characteristics, including enhanced bone and muscular development as well as anabolic effects on body cells. Direct secretion of T into the seminiferous tubules stimulates Sertoli cell functions: promotion of spermatogenesis and maturation and survival of sperm cells. Cellular effects of T are exerted either directly or by conversion to estrogen or to dihyroxy-testosterone (DHT), a more potent androgen.

SPERMATOGENESIS

Secretion of T by Leydig cells is regulated by pituitary LH via negative feedback. High T inhibits LH secretion and low T stimulates it. Sperm formation is regulated by pituitary FSH. FSH stimulates Sertoli cells which support formation of sperm and androgen-binding protein (ABP). This protein provides high T levels in the tubules for sperm formation and maturation. FSH levels are regulated by the hormone inhibin from Sertoli cells. Low FSH decreases inhibin, which then increases FSH release by negative feedback effects, and vice versa. The hypothalamic peptide hormone GnRH regulates FSH and LH by a pulsatile release pattern. GnRH mediates the T negative feedback and other psychic and brain influences over the gonads.



Abnormally low T levels are caused by *hypogonadism*, mainly due to pituitary disorder. In *eunuchs*, testes or Leydig cell are absent or deficient from childhood. Low T levels prevents development of male secondary sexual characteristics. Eunuchs are femalelike but tend to be tall with long limbs due to delayed closure of epiphyseal plates in the long bones.

In rare cases, young male children show *precocious puberty*, usually because of hypothalamus or pituitary tumors; T levels are increased, leading to early sexual development and appearance of male secondary sexual characteristics as well as excessive muscle growth ("boy Hercules"); stature is stunted, due to premature closure of epiphyseal plates.