CPY 605:
CLINICAL ENDOCRINOLOGY

THE TESTES AND MALE SEXUAL FUNCTION
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HS09A182

INTRODUCTION:

- The testes is a bi-functional organ; i.e. site of sex steroid production, (testosterone synthesis) and site of sperm production, in the male.
- Controls both sexuality and fertility.
- Androgens and their metabolites, (estrogens), serve essential metabolic roles and maybe important inducers and effectors of brain function in men.

Male reproductive physiology (the reproductive axis)

- Consists of six main components: extra hypothalamic central nervous system, hypothalamus, pituitary, testes, sex steroid-sensitive end organs, sites of androgen transport and metabolism.
- Functions in an integrative fashion to control the concentration of circulating gonadal steroids required for normal male sexual development and function; for androgen and estrogen-mediated metabolic effects on critical end organs, (brain, bone, muscle, liver, skin, bone marrow), and for immune system.

Hypothalamic pituitary function

- The hypothalamus is the principal integrative unit, responsible for the normal pulsatile secretion of gonadotropin-releasing hormone, (GnRH)
- GnRH is delivered through the hypothalamic-hypophyseal portal blood system to the pituitary gland.
- GnRH is most concentrated in the medial basal arcuate and suprachiasmatic nuclei in the hypothalamus and travels by axonomic flow to the axon terminals of the median eminence.

- Pulsatile release of GnRH, (approx. 60-90mins), provides the signal for the timing of the release of luteinizing hormone, (LH), and follicle stimulating hormone, (FSH).
- GnRH is regulated by neuronal input from higher cognitive and sensory centers and by circulating levels of sex steroid and peptide hormones; (prolactin, activin, inhibin, and leptin).
- Local effectors of GnRH synthesis and release include: a number of neuropepetides, catecholamines, indolamines, neuropeptide Y, vasoactive intestinal peptide (VIP), corticotropion-releasing hormone (CRH), nitric acid, excitatory amino acids, gamma-amino

- Testosterone either directly or through its metabolic products (estradiol and dihydrotestosterone) has predominantly inhibitory effects on the secretion and release of GnRH, LH and FSH.
- Prolactin is a potent inhibitor of GnRH secretion, thus its role in inhibiting LH and testosterone secretion in conditions of hyperprolactinaemia.

- a second level of feedback regulation of LH and FSH secretion occurs at the pituitary, with testosterone, dihydrotestosterone (DHT), and estrogens inhibiting the synthesis and /or release of both gonadotropins
- Circulating testicular peptide products of the sertoli cell, (inhibin and activin), also produce selective inhibition or stimulation of FSH.
- LH and FSH circulate unbound to carrier proteins and act predominantly through specific cell surface receptors on the Leydig

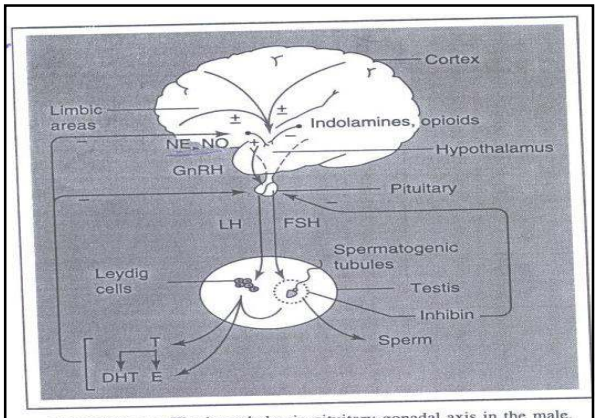


FIGURE 247–1 ■ The hypothalamic-pituitary-gonadal axis in the male.

Testis: structure and function

- **STRUCTURE**:
- A pair of ovoid structures about 5cm in length and 3cm in diameter, both testes are contained within the cavity of a saclike scrotum each suspended by a spermatic cord.
- A tough, white, fibrous capsule; tunica albginea, encloses each testes.
- Along its posterior border, the connective tissue thickens and extends into the organ, forming a mass called the mediastinum testis. From this structure, thin layers of connective tissues called septa pass into the testes and divide it into approximately 250 lobules.
- Each lobule contains 1-4 highly coiled convolated seminiferous tubules, which course posteriorly and unite to form a complex network of channels called the rete testis, which is located within the

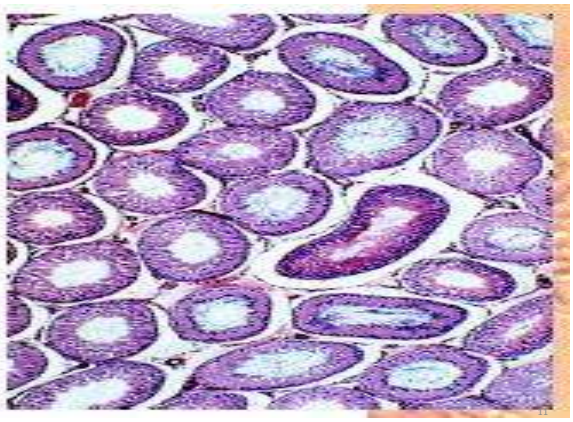
- The epididymis is coiled on the outer surface of the testes.
- Seminiferous tubules are lined with specialized stratified epithelium, which include spermatogenic cells that give rise to sperm cells.
- Interstitial cells (leydig cells) lies in the spaces between the seminiferous tubules and produce and secret male sex hormones.

In summary:

- Complex organ consisting of:

  1) seminiferous tubules containing sertoli cells and germ cells in various stages of maturation;

  2) the interstitium where the steroid-secreting cells (leydig cells), macrophages and blood vessels reside;



FUNCTIONS

- Serves as the site of sex steroid synthesis and sperm production, thus controls both sexuality and the perpetuity of species, (fertility).

❖SEX STEROID, (TESTOSTERONE__17ß-HYDROXY-ANDROST-4-ENE-3-ONE) SYNTHESIS.

- The leydig cells synthesize steroid hormones under the regulation of LH. Cholesterol is the parent compound from which synthesis starts.
- LH receptors on the cell surface these cells lead to G protein/cyclic adenosine monophosphate-mediated events, which involves a steroid acute regulatory protein essential for steroidogenesis in

- The enzymatic rate-limiting step in the process is the LH-inducible conversion of cholesterol to pregnenolone by cholesterol side-chain cleavage enzyme, (P450scc or 20,22 desmolase, or cholesterol desmolase)
- cholesterol

P450scc

pregnenolone — 3B-HSD → progesterone

P450c17 P450c17

17α-OH-pregnenolone — 3B-HSD → 17 α-OH-PROGESTERONE

P450c17 P450c17

DHEA — 3B-HSD → Androstenedione

17B-HSD 17B-HSD

Androstenediol — 3B-HSD → Testosterone

Testosterone transport in blood.

- Circulates mainly bound to two plasma proteins; sex hormone binding globulin (SHBG, or testosterone binding globulin) about 54%, and albumin about 44%.
- About 2-3% of the testosterone is unbound or free.
- SHBG-testosterone is tightly bound and serves a storage role.
- Bioavailable testosterone is the albumin bound and free testosterone and is measured by separating SHBG testosterone from the total

- Serum SHBG levels are increased in endogenous and exogenous hyperestrogenic states, hyperthyroidism, aging, anorexia nervosa, phenytoin treatment and prolonged stress.
- SHBG levels are lowered with androgen treatment, obesity, acromegaly, and hypothyroidism.
- Measurement of total testosterone will detect individuals with androgen deficiency, but in conditions with abnormal SHBG levels, total testosterone measurement may be misleading

Testosterone action

- Exerts its effect at different end organs either through direct action or after conversion to an active metabolite such as DHT (5 α-reductase) and estradiol (aromatase).
- Thus can act as an androgenic hormone or as a precursor for DHT with effect mediated by intracellular androgen receptor.
- Can also serve as precursor for estradiol in some tissues where it binds to estrogen receptors (α and beta) to induce estrogenic effects

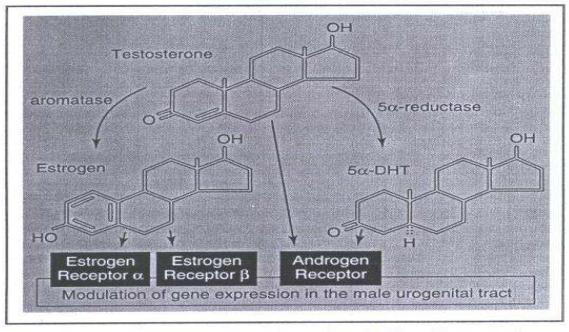


FIGURE 247–4 ■ Testosterone action is mediated either directly (androgen receptor), after conversion to estradiol (estrogen receptor α or β), or after conversion to DHT (androgen receptor). (From George GJ, Kuiper M, Carlquist M, Gustafson JA: Estrogen is a male and female hormone. Sci Med, July/August, 1998.)

❖Spermatogenesis

- Spermatogenic compartment consists of sertoli and germ cell and is interactive with the interstitial compartment.
- Sertoli cell bridge the entire space between the basement membrane and the lumen of the tubules and are the target of androgenic and FSH stimulation of spermatogenesis, and also the source of paracrine regulators of spermatogenesis and gonadotropin secretion (e.g inhibin, activin).

- Germ cell maturation depends on proper hormonal (FSH) and paracrine (testosterone) for proliferation to occur.
- Not all reach maturity, since spontaneous death of certain germ cells is a constant feature of germ cell homeostasis.
- Major effects of testosterone and FSH is to limit the amount of germ cell death (apoptosis)

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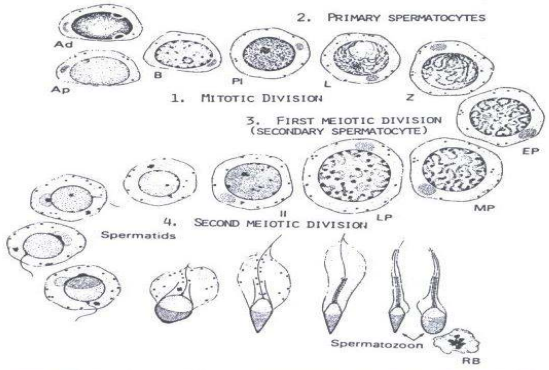

FIGURE 247–5 ■ Stages of human spermatogenesis. (From Hermo L, Clemont Y: How are germ cells produced and what factors control their production? *In* Robaine B, Pryor J, Trasler J [eds]: Handbook of Andrology. American Society of Andrology, 1995, pp 13–15.)

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Sperm transport

- Mature spermatozoa are released into the excretory system and travel through the rete testes and the epididymis, where they functionally mature before traversind the vas deferens.
- Semen gains constituents from the seminal vesicles, prostate and bulbouretthral glands before ejaculation

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Normal sexual function and erectile physiology

- Requires normal sexual desire (libido), and erectile and ejaculatory and orgasmic capacity.
- It's a complex process involving cognitive, sensory, hormonal,autonomic, neuronal and penile vascular integrative action for normal function
- Defects can occur at multiple levels thus an understanding of the normal physiology is essential for proper assessment and treatment of men with sexual dysfunction.

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- The brain, (the integrative center of the sexual response system), processes sensory input, stored fantasy information, purposeful thoughts, nocturnal reflex activity and hormonal signals;
- This create the hypothalamic neuronal message that traverses the spinal cord to the thoracic 9-12 sypathetic and sacral parasympathetic outflow tracts.
- The non-adrenergic, non-cholinergic (NANC) autonomic plexus nerve initiates vasodilation of the cavernosal arterial and corporal cavernosa sinusoids of the penis through release of local vasodilators (e.g nitric oxide NO, and VIP) from the vascular endothelium and the smooth muscle cells of the

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- Nitric oxide synthetases regulates NO synthesis which produces smooth muscle dilatation through activation of cGMP and modification of calcium flux. cGMP levels are rapidly reversible through inactivation by phosphodiesterase.
- All of these mechanisms lead to rapid increase in penile blood flow and expansion of the vascular channels which in turn inhibits venous return through compression of the venous channels against the tunica albuginea and limits drainage of the obliquely penetrating veins.
- Detumescence occurs after orgasm owing to less vasodilatation and greater vasoconstrictive signals

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- Testosterone seems to have its primary effect on erectile function by enhancing libido, (which is highly sensitive to testosterone) with secondary effects on penile NO synthase activity.
- The high sensitivity of libido to testosterone explains the preservation of erectile capacity in some men with partial androgen deficiency.
- Erectile dysfunction is common in older men despite normal serum testosterone levels, which appears to be the result of impaired penile vasodilatory capacity; but is often reversible through local administration of potent vasodilators (e.g protaglandins), or by oral administration of penile-specific phosphodiesterase inhibitors.

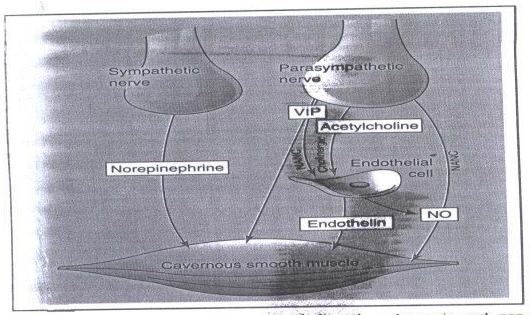

FIGURE 247–6 ■ The interaction among cholinergic, adrenergic and non-adrenergic, non-cholinergic (NANC) neuronal pathways and their contribution to penile smooth muscle contraction (patterned arrows) and dilation (open arrows). NO = nitric oxide; VIP = vasoactive intestinal polypeptide. (From Lue TF: Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. *In* Walsh P, Retick A, Vaughn E, Wein A (eds): Campbell's Urology, 7th ed. Philadelphia, WB Saunders, 1998, p 1164.)

Reproductive axis during foetal development, childhood and puberty

- Foetal sexual differentiation is complex and includes establishment of genetic and phenotypic sex.
- Adrenarche occurs at about 7-8yrs of age when the zona reticularis of the adrenal undergoes maturation thus secreting androgen precursors; androstenedione, dehydroepiandrosterone (DHEA), DHEA sulphate (DHEA-S).
- This process is probably under the control of ACTH and independent of the control of LH and FSH.
- Androstenedione and DHEA are technically androgenic prehormones and do not bind to the androgen receptor.
- In part prepubertal growth spurt and early development of pubic and axillary hair are mediated by conversion of these precursors to testosterone and

- Puberty occurs when a hypothalamic clock gets activated resulting in increased GnRH and gonadotropin secretion. This is determined by increase in the pulsatile pattern of hypothalamic GnRH secretion (every 60-90mins).
- As puberty progresses, feedback sensitivity of the hypothalamus and pituitary to circulating steroids lessens and increasing concentrations of both gonadal steroids and gonadotropins ensue.
- This increase in concentration of steroids (intratesticular testosterone and ciculating FSH), stimulates sertoli cells to produce factors leading to the maturation of spermatogenesis and inhibition of

Pubertal stages in boys

Stages	Pubic hair stage	Genital stages
Stage 1	Absence of pubic hair	Childlike penis, testes and scrotum (testes 2ml)
Stage 2	Sparse lightly pigmented hair mainly at the base of the penis	Scrotum enlarged with early rugation and pigmentation. Testes begin to enlarge (3-5ml)
Stage 3	Hair becomes coarse, darker, and more curled and more extensive	Penis has grown in length and diameter. Testes 8 to 10ml. Scrotum more rugated
Stage 4	Hair adult in quality but distribution does not include medial aspect of thighs.	Penis further enlarges with development of the glans. Scrotum and testes(10-13ml) further enlarged
Stage 5	Hair is adult and extends to thighs	Penis and scrotum fully

- The age range of these changes is from about 8yrs-17yrs
- Majority of the above extratesticular end organ events of puberty are secondary to the increased circulating levels of testosterone and its metabolites (DHT and estradiol).
- As spermatogenesis advances the testes increase in size

Aberration of timing of puberty

- Delayed puberty in boys is defined as a temporary form of hypothalamic hypogonadotropic hypogonadism, in which sexual development has not begun by age 13 1/2yrs.
- The majority of boys with delayed development have a constitutional delayed physiological clock and eventually attain full sexual adulthood, but careful documentation of changing physical findings and measurement of serum LH, FSH and testosterone may prove valuable clues of the

- Decision of how early to treat depends on the perceived degree of psychological stress associated with the maturation delay.
- Periodic withdrawal of treatment in adolescent boys with delayed puberty and low levels of gonadotropins, is used to determine if testosterone therapy should be begun if spontaneous puberty has occurred.
- Puberty should be completed within 4 1/2yrs once initiated.

- Precocious puberty in boys is the onset of pubertal development before 9yrs of age and two subcategories exist:

1. True isosexual precocious puberty:

- Is associated with increase in GnRH-stimulated LH and FSH secretion which is often associated with CNS disease, including hypothalamic tumours, cysts, inflammatory conditions and siezure disorders.

- Diagnosis is based on finding of sexual precosity, inappropriately elevated serum LH and associated elevation of serum testosterone. Lesions can be localised by CNS magnetic resonance imaging.

-Treatment is by removal of CNS lesion if possible and treatment with GnRH analogues.

2. Pseudo-precocious puberty:

- Is independent of GnRH stimulation of LH and FSH secretion.

- It is characterized by increased testosterone with suppressed LH levels.

- Diagnoses include; human chorionic gonadotrophin secretory tumours (testes, liver,hypothalamic and pineal), congenital virilizing adrenal hyperplasia (CAH), testiculaar testosterone-secreting neoplasm and constitutively active LH receptor mutation resulting in uncontrolled testosterone secretion.

- Treatment depends on the cause e.g glucocorticoids for CAH and ketoconazol (suppresses steroidogenesis) with or without adrenal antiandrogens.

Male senescence: decreased testosterone and other anabolic hormones

Testosterone deficiency in the elderly:

- Older men have significantly lower blood concentrations of testosterone, other anabolic hormones,(e.g GH), or pre-hormones, (e.g DHEA AND DHEA-S).
- aging in men involves a gradual decline in gonadal hormone secretion, beginning as a young adult and progressing throughout life.
- The effect of this low testosterone levels include decreases in muscle mass, muscle strength, bone mass, libido and erectile function and impaired mood and sense of well-being; there is increased body fat

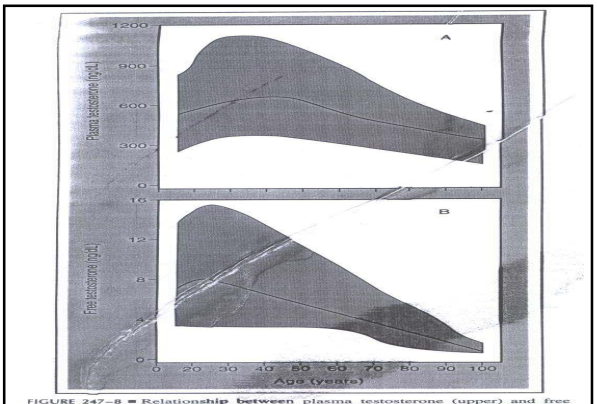

FIGURE 247–8 ■ Relationship between plasma testosterone (upper) and free testosterone (lower) levels and age in normal males. (From Baker HWG, Berger HG, DeKretser DM, et al: Changes in the pituitary-testicular system with age. Clin Endocrinol 5:349–372, 1976.)

- Testosterone replacement therapy in most cases decreases fat mass, increases lean body mass and improves strength, sense of wellbeing, increases energy level, enhances libido but not erectile dysfunction.
- Digital rectal examination should be performed and a prostate specifis antigen (PSA) level obtained to ensure there are no findings suggestive of severe benign prostatic hypertrophy or prostate cancer

Adrenal deficiency of androgen precursors in older men:

- Marked decline in the circulating levels of adrenal androgens (DHEA), and its sulphate, DHEA-S, also occur with age.
- This decline is not accompanied by a decreasse in ACTH.
- DHEA is a precursor to true androgens such as testosterone and DHT but does not bind to the androgen receptor itself. Thus how it functions is not clear.
- Administering oral dose (50mg/day) of DHEA

GH/IGF-I deficiency in older men:

- Hypothalamic GHRH mRNA, pituitary GHRH receptor concentration, pituitary secretion of GH,and serum IGF-I levels decrease with age.
- May be due in part to falling testosterone levels because testosterone is known to enhance GH secretion.
- Treatment with GH has side effects as oedema of lower extremities, hand stiffnessa and tiredness

MALE HYPOGONADISM

Definition:

- This refers to low circulating levels of testosterone, and most of such men are infertile.
- Could be primary, secondary or combined.
- **Primary hypogonadism;** originate in the testes,
- **Secondary hypogonadism;** a defect in the hypothalamus or pituitary, resulting in decreased gonadotropins and secondary impairment of testicular function
- **Combined primary and secondary hypogonadism;** occurs in aging and some of systemic diseases (alcoholism, liver disease, and sickle cell disease).
- **Decreased androgen action,** mimicking androgen deficiency occur in patients with androgen receptor defects, post-receptor signaling abnormalities and inability to convert

Etiology:

- Causes may be congenital, (e.g GnRH deficiency); acquired (e.g trauma, post surgery or post irradition); drug related (e.g cytotoxic agents) etc.

Clinical manifestation: clinical history and physical examination for hypothyroidism:

- Medical history, sexual history based on development of sexual organ and sexuality and also history of past systemic infections, medication and drug history, social history are taken.
- A generalized physical examination then follows including all body parts especially the genitals.

Laboratory test:

- Measurement of LH, FSH, and testosterone are determined from morning blood samples.
- Elevated levels of LH and FSH distinguishes primary from secondary hypogonadism.
- DHT should be measured in cases of abnormal differentiation of the genitalia and when DHT administration is suspected.

Hypogonadism and androgen resistance

- Primary testicular hypogonadism refers to a condition of anrogen deficiency with or without infertility in which the pathologic process lies at the testes level, and has several causes such as trauma, irradiations etc
- Secondary gonadal insufficiency (hypogonadotropic hypogonadism) represents a deficiency in the secretion of gonadotropins due to an intrinsic or functional abnormality in the hypothalamus or pituitary glands,which results

- **Acquired hypogonadotropic disorders, functional disorders**; occasionally seen in men but usually implies a variant of a more severe psychiatric disorder.
- Starvation from other than psychological basis, severe stress and systemic illness may reduce gonadotropin secretion.
- male patients with prolactin secretiing macroadenomas usually present with hypogonadism, erectile dysfunction, and visual manifestations from suprasellar extention.
- Large non-prolactin-secreting pituitary tumors may also produce gonadotropin insufficiency from damage of the adjacent normal pituitary gland resulting in decreased serum LH and testosterone levels.

- Androgen resistance (androgen-sensitive end organ deficiency); are either drug induced or congenital defects in the androgen receptor, postreceptor defects or 5alpha-reductase deficiency.

Treatment of androgen deficiency:

- Done by androgen replacement therapy. Testosterone esters are most widely used.

MALE INFERTILITY

- Definition: infertility is the failure of a couple to achieve a pregnancy after one year of frequent unprotected intercourse.
- Etiology: hypothalamic pituitary disorders, primarily testicular disorders.
- Diagnosis: examination of an ejaculate is the cornerstone for the investigation of an infertile man. In patients with abnormal semen analysis, measurement of serum FSH, LH and testosterone are indicated.
- Management: mostly by algorithmic

SEXUAL DYSFUNCTION

- Can be divided into four main categories:

1. Decreased libido; reduction in sexual interest, initiative and frequency, and intensity of response to internal or external erotic stimuli.
2. Ejaculatory failure and impaired orgasm; absence or reduced seminal emission and/or impaired ejaculatory contraction. Usually associated with neurologic conditions and medication therapy.
3. Anorgasmic state; distressing relatively uncommon condition, when the normal process of erection and ejaculation occurs in the absence of the subjective sensation of pleasure initiated at the time of emission and ejaculation

Erectile dysfunction

- Definition: the inability of a man to obtain rigidity sufficient to permit coitus of adequate duration to satisfy himself and his partner.
- Etiology: many causes which can be categorized as psychological, endocrine, systemic illness, neurologic, drug related, and aging.
- Clinical management: oral sildenafil is the most widely used drug, it is a competitive inhibitor of cGMP phosphodiesterase-5. inhibiton of phosphodiesterase-5 causes persistence of normally stimulated GMP in the corpora cavernosa, resulting in protracted cavernosal tumescence and rigidity. Also the intracavernosal injection of vasodilating drus such as

THANKS FOR LISTENING