



# MEDICAL AND NON-MEDICAL TESTOSTERONE AND STEROID HORMONE USAGE

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# DISCLOSURES

■ I have no relevant financial interests to disclose.

# LEARNING OBJECTIVES

- Explain the different effects of testosterone on men and women.
- Compare different steroid hormone testing options.
- Describe ways in which testing of hormones differs from testing for other analytes.
- Explain the ways in which anabolic steroid usage for athletic performance differs from medical usage of testosterone therapy.

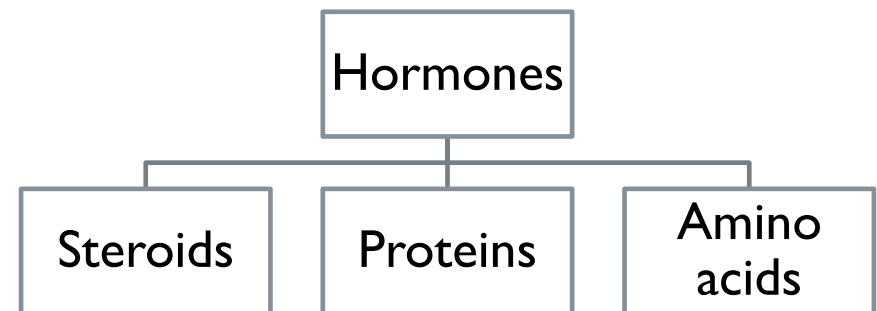


# TESTOSTERONE

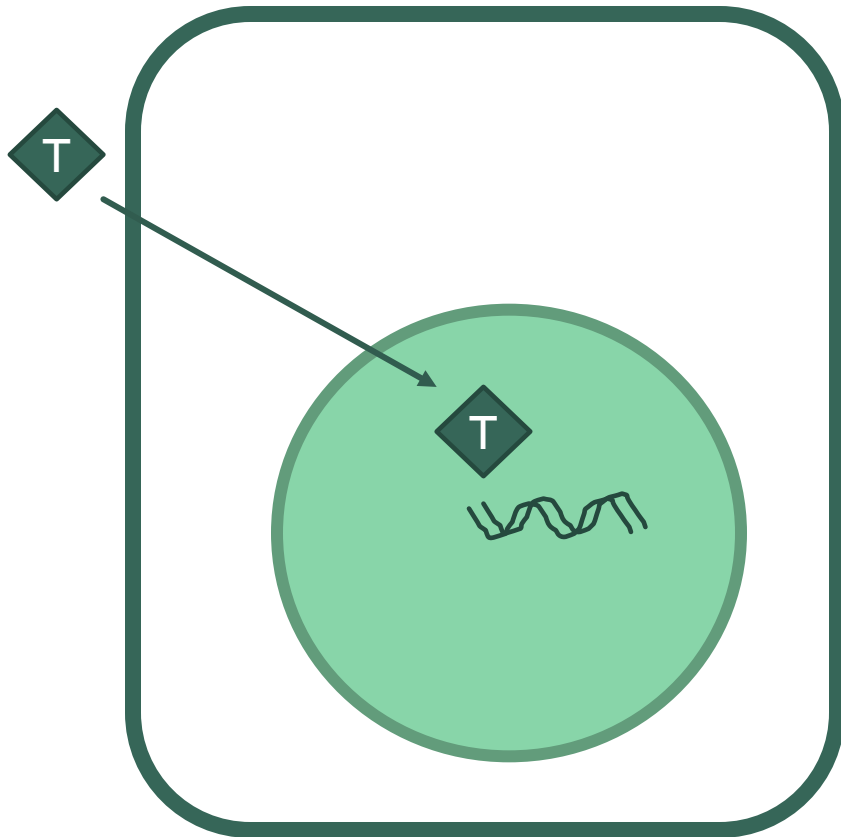


# DEFINITIONS

- **Hormone:** a small molecule produced by an endocrine gland that acts on other cells
  - Growth and development
  - Homeostasis
  - Energy usage
- **Steroid hormone:** a fat-soluble hormone with four fused rings in its structure
- **Other types of hormones:** proteins and amino acid derivatives

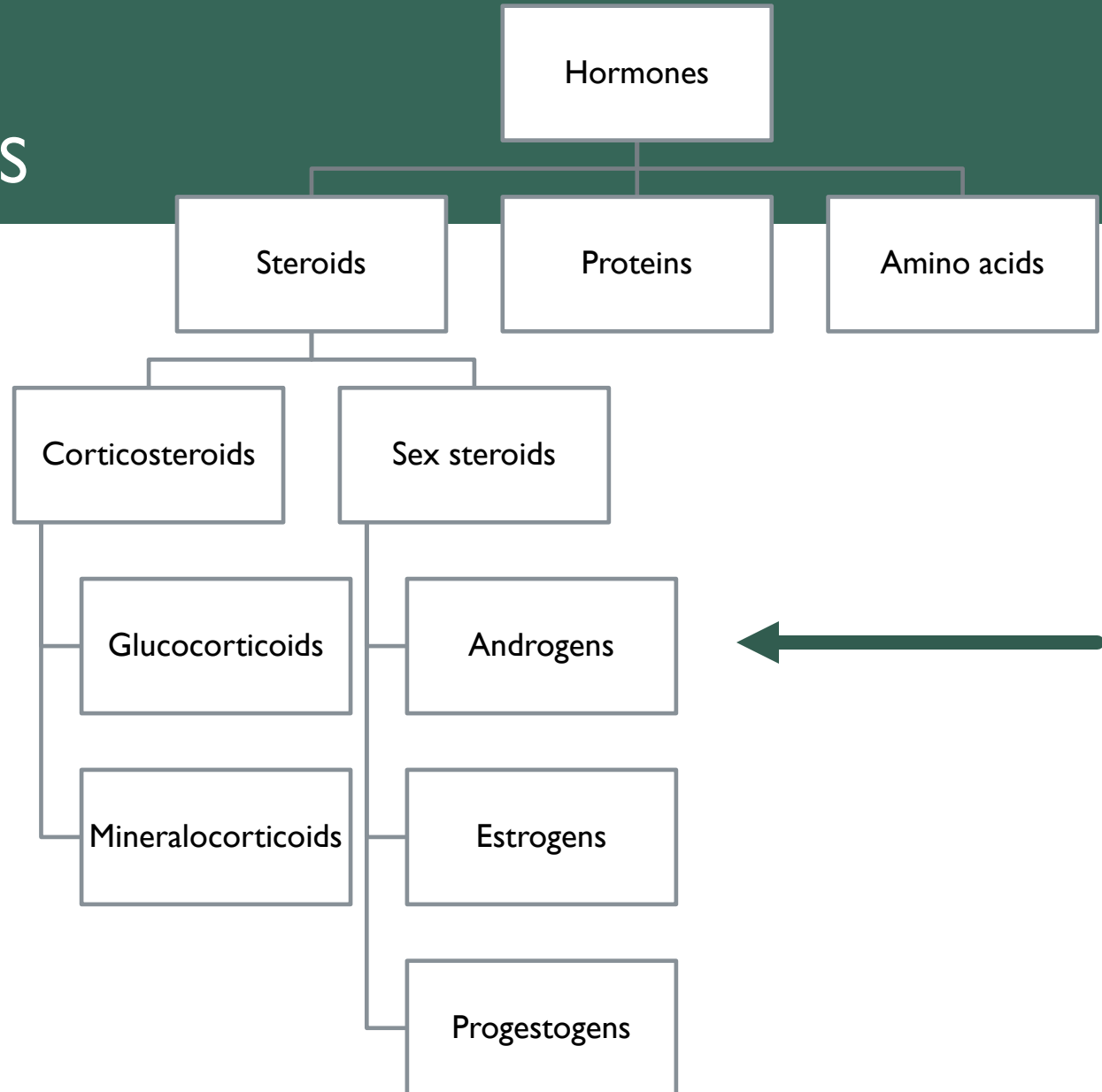


# STEROID HORMONES



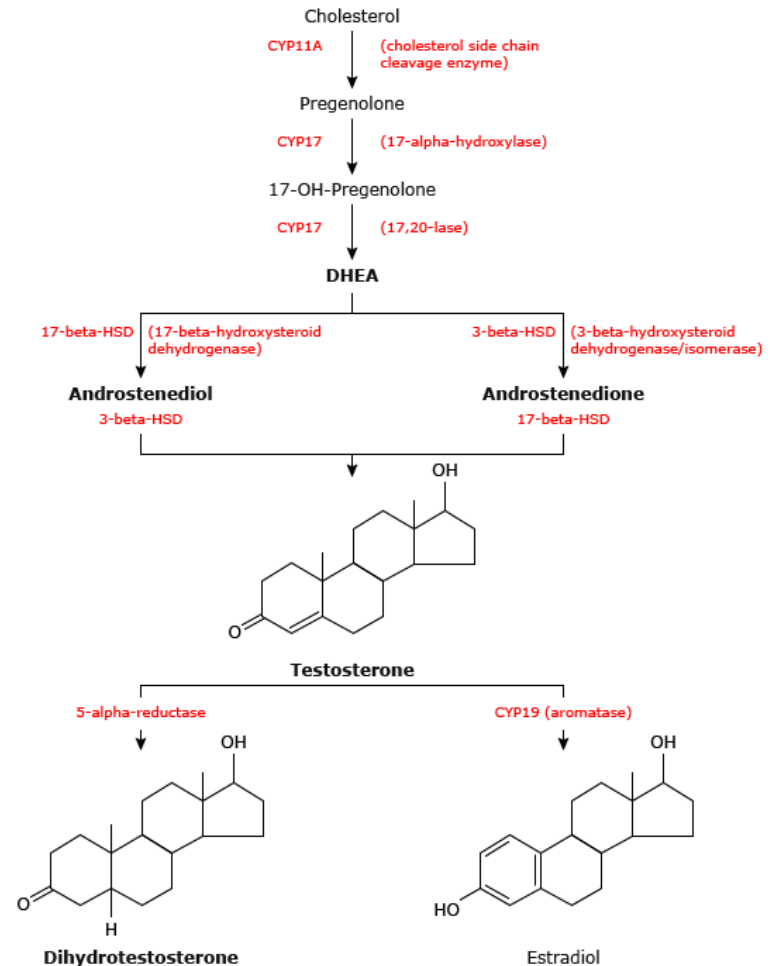
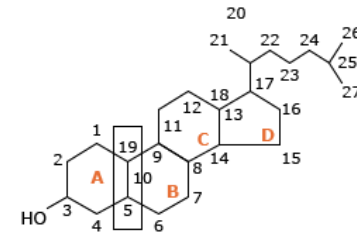
- Fat-soluble
- Can pass through cell membranes
- Act on nuclear receptors
- Affect gene expression
- Act more slowly than protein or amino acid hormones

# ANDROGENS



- Hormones that develop and maintain male secondary sexual characteristics

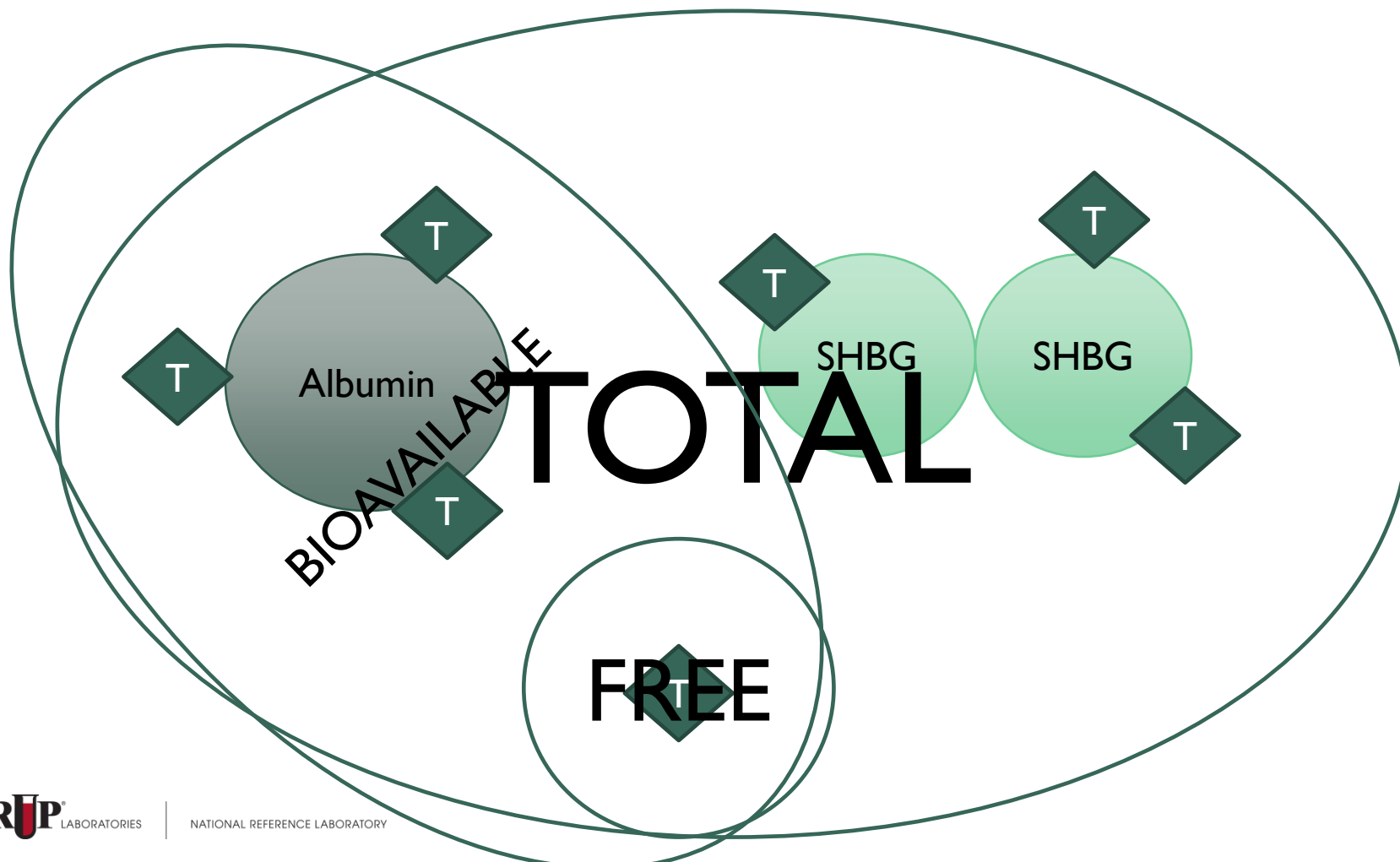
## Testosterone formation and metabolism



- Made out of cholesterol
- Precursors: DHEA, androstenedione
- 95% is made in Leydig cells in the testes
- Remaining 5% is made peripherally
- Circulate through the blood bound to transport proteins



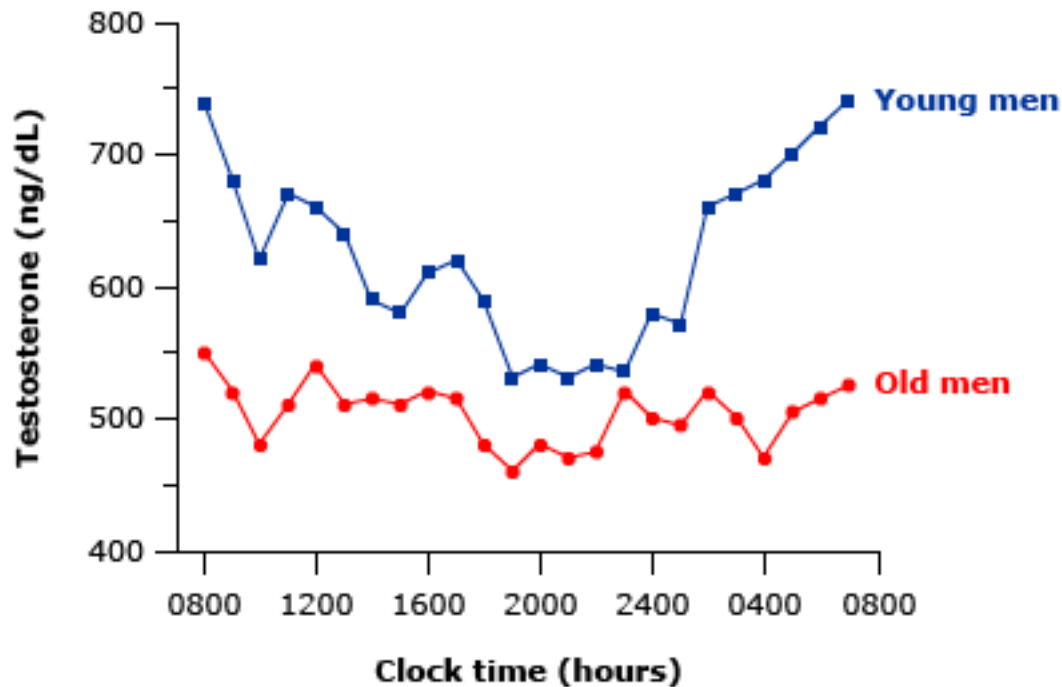
# TESTOSTERONE IN CIRCULATION



# CONCENTRATIONS - MALE

- Three peaks in the male life cycle:
  - 2<sup>nd</sup> trimester of fetal development
  - 2-3 months of age
  - Puberty (reaches a plateau) – 300-1080 ng/dL
- Starting around age 40, testosterone levels decline by 0.5-2%/year
  - Decrease in number of Leydig cells
  - Decrease in the GnRH pulse amplitude

## Diurnal pattern of testosterone secretion



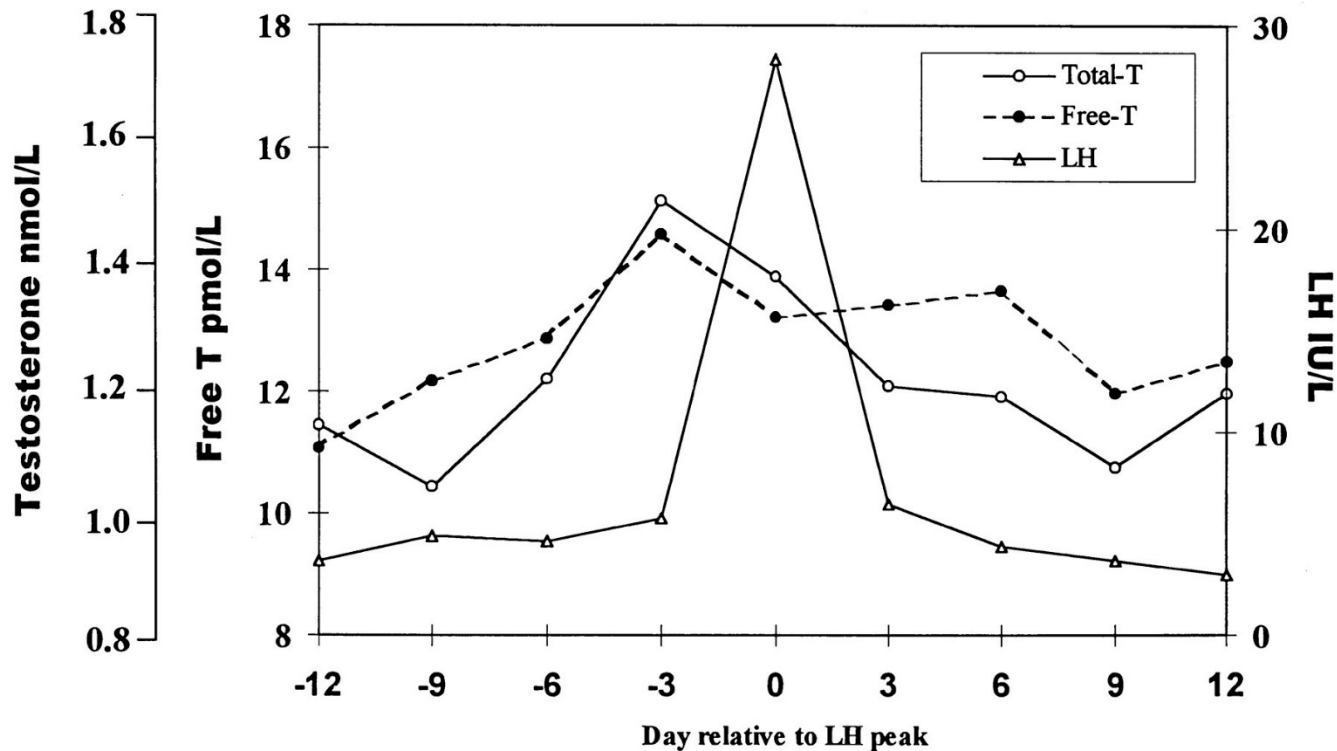
Hourly serum testosterone levels in normal young ( $n = 17$ ) and old ( $n = 12$ ) men. The circadian rhythm is lost in old men. Blood samples were obtained using an indwelling peripheral venous cannula, which allowed free movement and normal sleep.

*Data from: Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983; 56:1278.*

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# CONCENTRATIONS - FEMALE

- 9-55 ng/dL
- Made in the ovaries and the adrenal glands
- No fetal or neonatal peak
- Does increase at puberty
- Diurnal variation
- Total testosterone peaks slightly before ovulation
- Seems to decrease with menopause



**Figure 2.** Mean serum total and free testosterone and LH levels during the normal menstrual cycle in 34 healthy women. Data are the mean  $\pm$  sd.

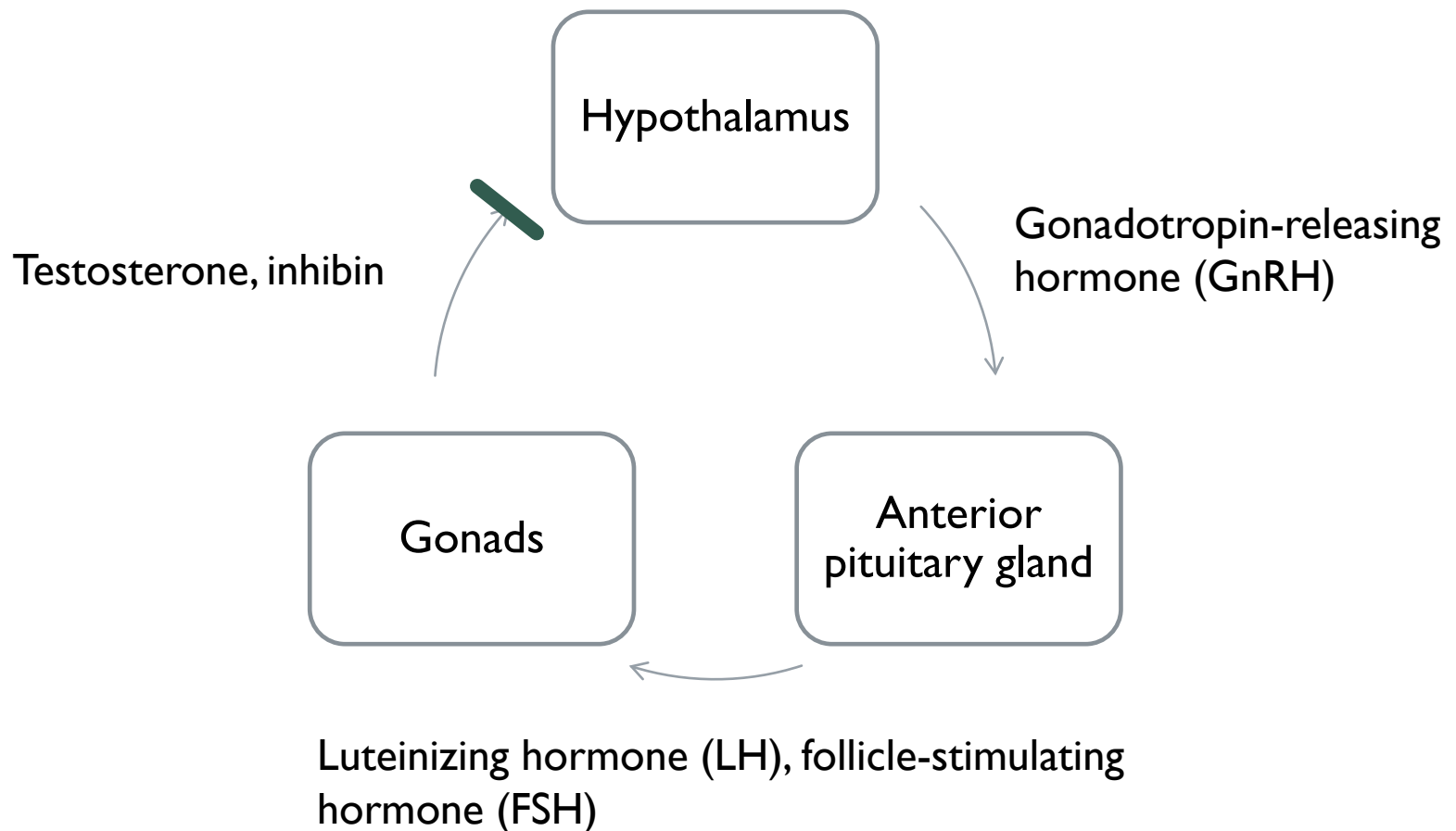
# CONCENTRATIONS

## Reference Interval ⓘ

Effective August 19, 2013

Age	Female	Male
Premature (26-28 weeks)	5-16 ng/dL	59-125 ng/dL
Premature (31-35 weeks)	5-22 ng/dL	37-198 ng/dL
Newborn	20-64 ng/dL	75-400 ng/dL
1-5 months	Less than 20 ng/dL	14-363 ng/dL
6-24 months	Less than 9 ng/dL	Less than 37 ng/dL
2-3 years	Less than 20 ng/dL	Less than 15 ng/dL
4-5 years	Less than 30 ng/dL	Less than 19 ng/dL
6-7 years	Less than 7 ng/dL	Less than 13 ng/dL
8-9 years	1-11ng/dL	2-8 ng/dL
10-11 years	3-32 ng/dL	2-165 ng/dL
12-13 years	6-50 ng/dL	3-619 ng/dL
14-15 years	6-52 ng/dL	31-733 ng/dL
16-17 years	9-58 ng/dL	158-826 ng/dL
18-39 years	9-55 ng/dL	300-1080 ng/dL
40-59 years	9-55 ng/dL	300-890 ng/dL
60 years and older	5-32 ng/dL	300-720 ng/dL
Premenopausal (Greater than 18 years)	9-55 ng/dL	Does Not Apply
Postmenopausal	5-32 ng/dL	Does Not Apply
Tanner Stage I	2-17 ng/dL	2-15 ng/dL
Tanner Stage II	5-40 ng/dL	3-303 ng/dL
Tanner Stage III	10-63 ng/dL	10-851 ng/dL
Tanner Stage IV-V	11-62 ng/dL	162-847 ng/dL

# REGULATION: HYPOTHALAMIC-PITUITARY-GONADAL AXIS



# EFFECTS ON THE BODY

- Affects cells that are sensitive to androgens
- Male sexual characteristics
- Acne
- Erythropoiesis
- Increased lean body mass
- Increased energy and libido





# HOW WE TEST FOR TESTOSTERONE



# CLIENT QUESTION

- My patient is receiving testosterone injections.
- What test do I order to measure testosterone?



# SOME OF THE QUESTIONS THAT NEED TO BE ANSWERED

- Man, woman, or child?
- Expected levels?
- Total, free, or bioavailable?

# MEN VS WOMEN AND CHILDREN

- Men: 300-1080 ng/dL
- Women and children: as low as 1 ng/dL
- Electrochemiluminescent immunoassay vs HPLC-MS/MS
- Analytical sensitivity:
  - Immunoassay: 3 ng/dL, but imprecise
  - HPLC-MS/MS: 1.0 ng/dL

# TOTAL, FREE, OR BIOAVAILABLE?

- Total: measures all testosterone
  - Free
  - Bound to SHBG
  - Bound to albumin
- Free: unbound, dissolved in blood
  - Either calculated or measured directly with equilibrium dialysis
- Bioavailable: free + albumin-bound
  - Calculated

# MEASURING SHBG

- Quantitative electrochemiluminescent immunoassay
- Helps to determine free vs bound testosterone
- Many conditions may affect SHBG and thus affect total testosterone

# FACTORS AFFECTING SHBG

## Decrease

- Obesity
- Hypothyroidism
- Diabetes
- Glucocorticoids and progestins
- Androgenic steroids

## Increase

- Aging
- Liver disease
- Hyperthyroidism
- HIV
- Estrogens
- Anti-seizure medications

# PITFALLS OF STEROID HORMONE TESTING

- Present in small amounts
- Bound to carrier molecules
- Diurnal variation



# TESTING CONSIDERATIONS

- Gender and age
- Expected levels – in concordance with patient's gender and age?
- Need more information than a total level?





# MEDICAL TESTOSTERONE THERAPY



## ACCORDING TO THE FDA...

- Testosterone replacement therapy should only be given to men with confirmed low levels of testosterone and symptoms of testosterone deficiency

# SYMPTOMS OF ANDROGEN DEFICIENCY

## Nonspecific

- Decreased energy
- Depression
- Anemia
- Reduced muscle bulk and strength
- Diminished performance

## Specific

- Decreased libido
- Loss of body hair
- Low bone mineral density or low-trauma fracture
- Hot flushes
- Infertility
- Small testicular size

# HYPOGONADISM

## Primary

- Disease of the testes
- High GnRH, FSH, LH
- Acquired or congenital

## Secondary

- Disease of the hypothalamus or pituitary
- Low GnRH, FSH, LH
- Acquired or congenital

# AGE-RELATED DECREASE IN TESTOSTERONE

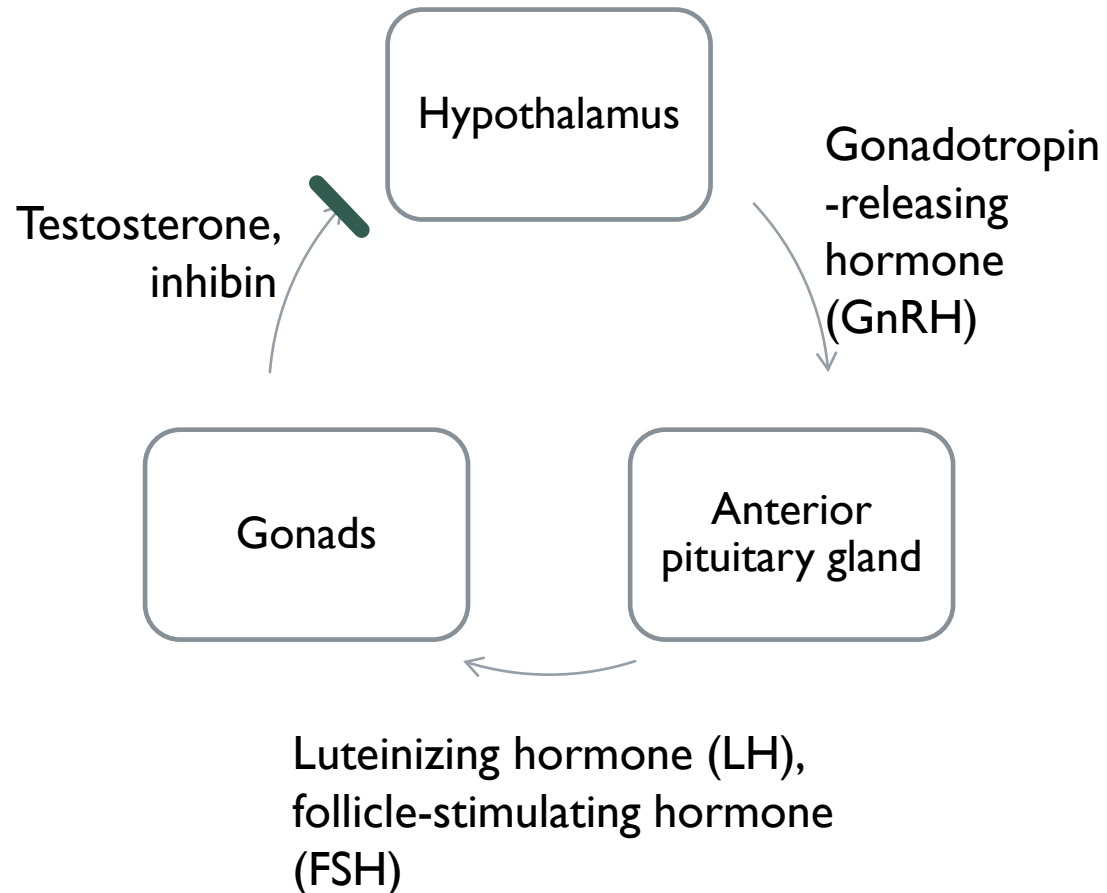
- Remember, testosterone decreases by 0.5-2%/year
- Only problematic when symptomatic
- Many names:
  - Testosterone deficiency syndrome (TDS)
  - Late-onset hypogonadism (LOH)
  - (Partial) androgen deficiency of the aging male ((P)ADAM)
- Goal: to improve signs and symptoms of deficiency

# LAB DIAGNOSIS

- **Endocrine Society Clinical Practice Guideline** (Bhasin S et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.):
  - Don't screen everybody
  - Measure morning testosterone levels twice
  - If borderline low, consider testing free or SHBG

# MALE CONTRACEPTION

- Testosterone inhibits production of LH and FSH
- The testes need FSH in order to produce sperm





# FEMALE TO MALE TRANSITION

- Hormone therapy is one part of the overall gender transition in transgender patients
- Two goals of hormone therapy in transitioning from female to male:
  - Suppress native (female) hormones
  - Induce and maintain male secondary sexual characteristics

# FEMALE TO MALE TRANSITION: EFFECTS OF TESTOSTERONE ADMINISTRATION

## What changes

- Facial hair growth
- Deepening of the voice
- Increase in lean body mass
- Acne
- Increased libido
- Breast changes
- Susceptibility to male pattern baldness
- Cessation of menstruation

## What stays the same

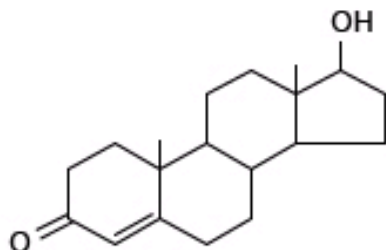
- Female bone structure
  - Shorter height
  - Broader hips
- Breast fat mass
- Genitalia

# FORMULATIONS

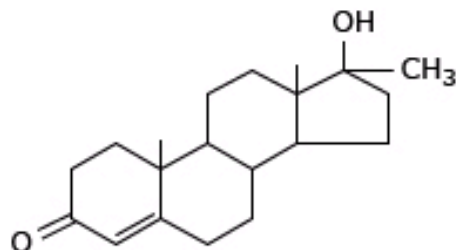
- Oral?
  - Almost completely metabolized in first pass
- Intramuscular injection
- Gel, cream, or patch
- Intradermal implant
- Nasal spray
- Buccal patch

# Structure of the different testosterone preparations

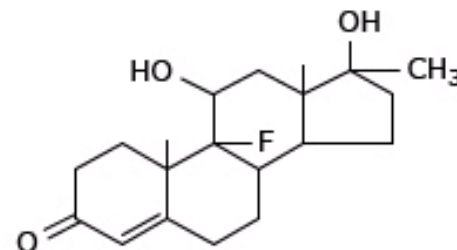
## Testosterone



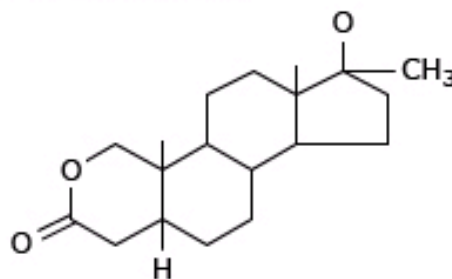
## Alkylated testosterone



Methyltestosterone

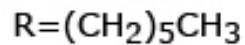
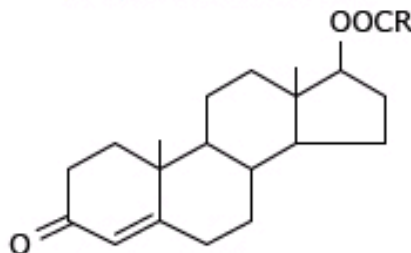


Fluoxymesterone

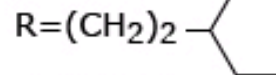


Oxandrolone

## Testosterone esters



Enanthate



Cypionate

Structure of the testosterone preparations available for the treatment of men with hypogonadism.

# MONITORING RECOMMENDATIONS

- **Endocrine Society Clinical Practice Guideline** (Bhasin S et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.):
  - Measure serum testosterone 3-6 months after starting supplementation and then annually
  - Goal is to achieve a total serum testosterone level in the middle of the normal range for a young, healthy adult male (300-1000 ng/dL)

# ADVERSE EFFECTS

- May increase risk of cardiovascular disease
- May worsen symptoms of BPH
- May increase risk of prostate cancer
- Probably increases hematocrit
- Acne
- Gynecomastia
- Suppression of spermatogenesis



# NON-MEDICAL TESTOSTERONE USAGE



# ANABOLIC STEROIDS





# ANDROGENIC ANABOLIC STEROIDS

- Hormones that have the same biological effects as testosterone
- We've discussed the androgenic (masculinizing) effects of testosterone
- Also anabolic (muscle-building) effects
- Synthetic hormones designed to have more anabolic than androgenic effects

# DO THEY WORK?

- Hard to determine, because often used in suprathreshold doses
- Lean body mass increase of 2-5kg
- Increase in circumference of shoulders, neck, upper arms
- Increase in muscle strength

# ADVERSE EFFECTS

- Hard to determine, because often used in supratherapeutic doses
- Suppression of HPG axis
  - Decreased sperm production and testicular atrophy
- Increased aggression and hostility
- Acne
- Gynecomastia

# REGULATION

- Over 630 sports agencies follow the guidelines of the World Anti-Doping Agency (WADA)
  - International Olympics Committee (IOC)
- Major US sports leagues have their own policies

# WADA DOCUMENTS

- Prohibited Substances
- Int'l Standard for Therapeutic Use Exemptions
- Int'l Standard for Protection of Privacy
- Int'l Standard for Testing and Investigation
- Int'l Standard for Laboratories

WORLD ANTI-DOPING CODE  
**INTERNATIONAL  
STANDARD**



# **PROHIBITED LIST**

JANUARY 2016

# BANNED AAS

- Exogenous AAS, and other substances with a similar chemical structure or similar biological effect(s).
- Endogenous AAS, when administered exogenously, and their metabolites and isomers.

# MEASURING ANABOLIC STEROIDS

- Tests available to measure many different anabolic steroids in the urine
- Testosterone to epitestosterone ratio
- Testosterone to LH ratio
- Creatinine
- Masking agents



# IN SUMMARY

- Testosterone is present in both men and women and exerts similar masculinizing effects on both
- Choosing a lab test to measure testosterone depends on the demographics of the patient and expected levels
- Steroid hormone levels change throughout the day and throughout the lifespan
- FDA recommends administration to a small group
- There are many possible side effects of exogenous administration
- Positive and negative effects of anabolic steroids are difficult to measure



THANK YOU!

