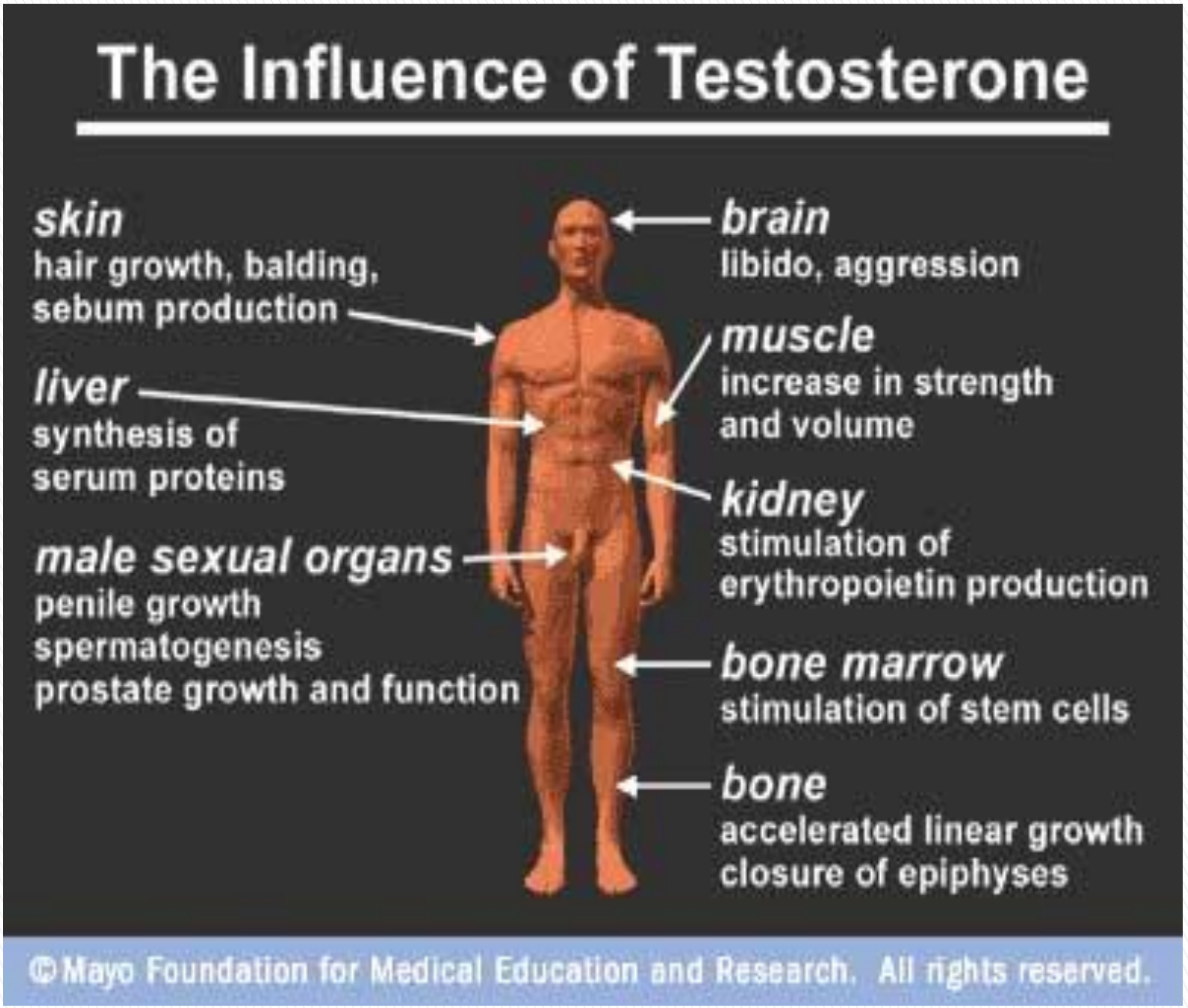
Testosterone Friend or Foe

Dr. Ken Cathcart FACE

The Influence of Testosterone



Definition of Male Hypogonadism

" … clinical syndrome that results from failure of the testes to produce physiological levels of testosterone … due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis."

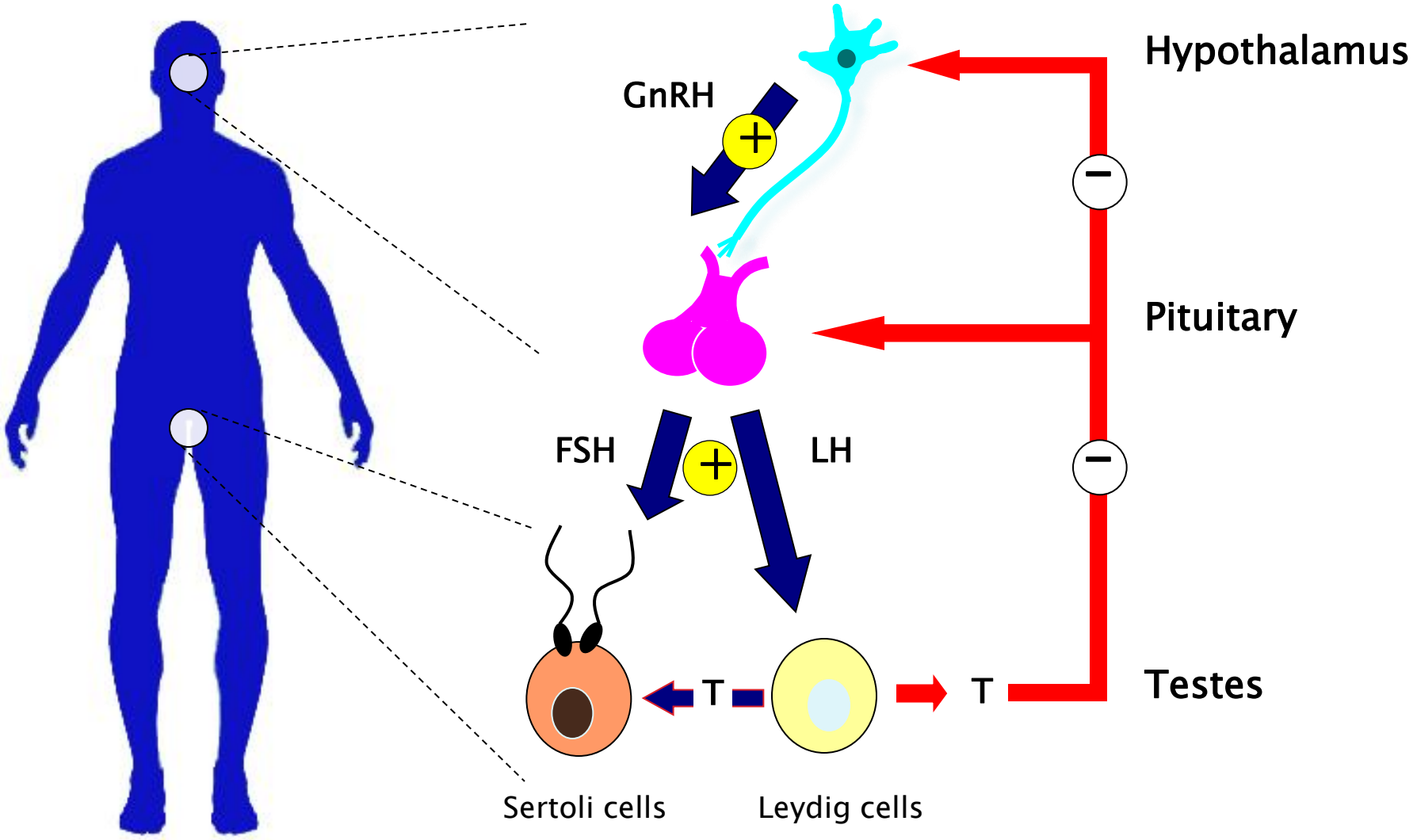
Endocrine Society Guideline (2006)

" … inadequate gonadal function, as manifested by deficiencies in …the secretion of gonadal hormones."

American Association of Clinical Endocrinologists Guidelines (2002)

Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.
Petak SM, et al. *Endocr Pract*. 2002; [illegible] 440-456.

Production and Regulation of Testosterone

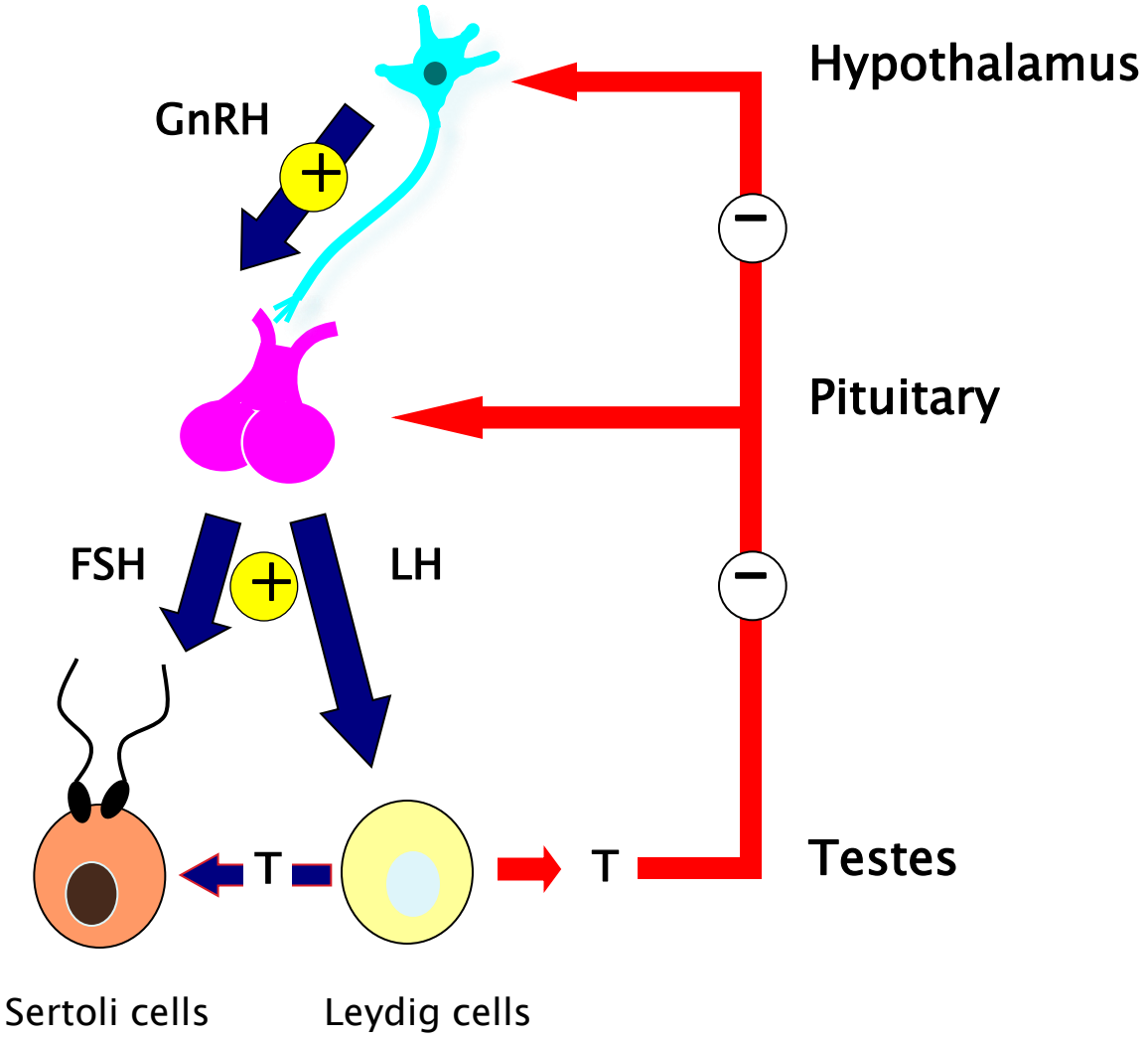


FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T = testosterone.

Costanzo LS. *Physiology*. 3rd ed. Saunders/Elsevier; 2006:449.

Regulation of Testosterone in the Eugonadal Male

- Normal – Eugonadal



FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T = testosterone.

Costanzo LS. *Physiology*. 3rd ed. Saunders/Elsevier; 2006:449.

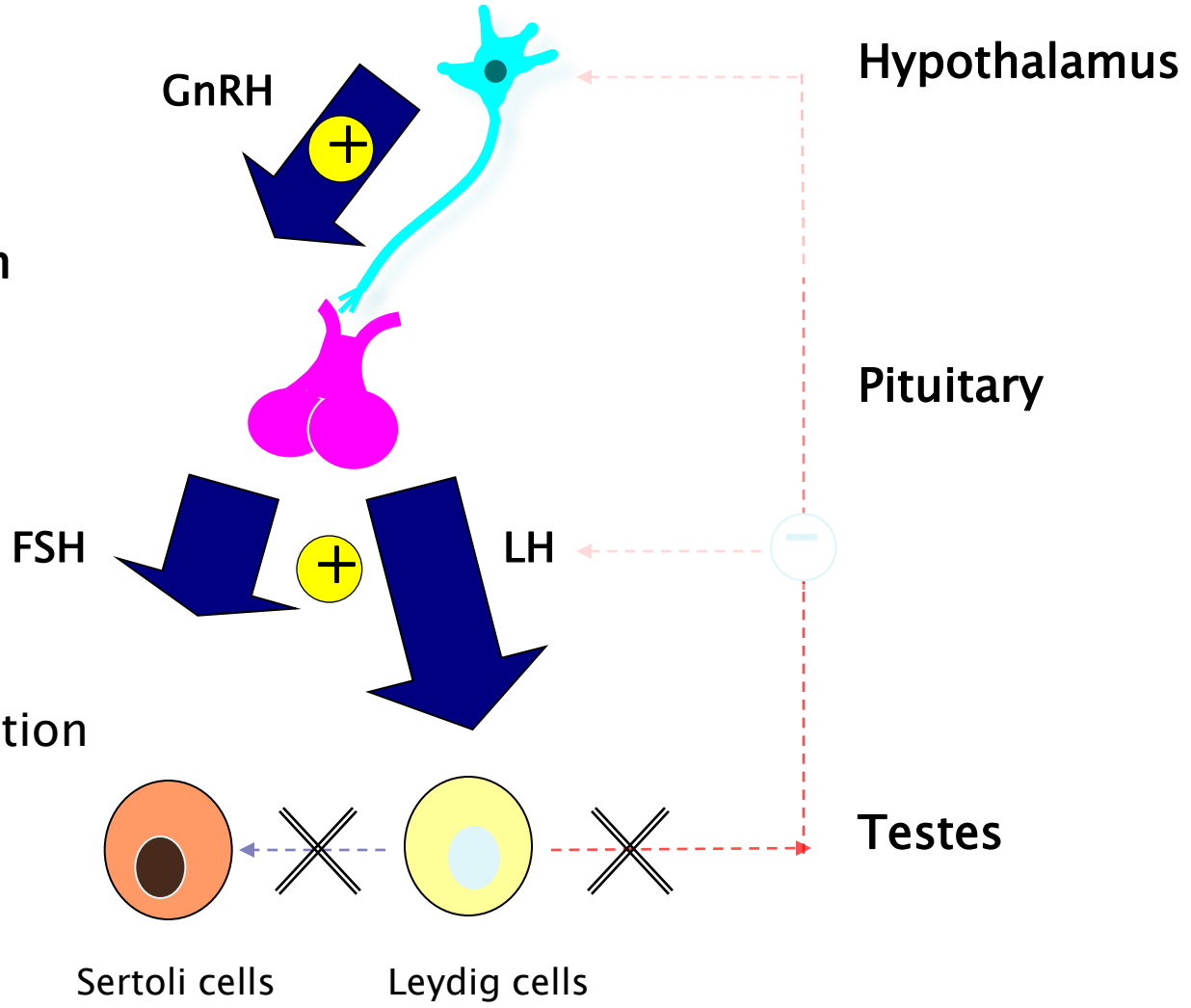
Primary Hypogonadism

*Hyper*gonadotropic Hypogonadism

- Testicular Dysfunction
- Normal Hypothalamic/ Pituitary Function

Results in

- Increased LH & FSH
- Low testosterone
- Impaired sperm production



FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

Seftel A. *Int J Impot Res*. 2006;18(3):22

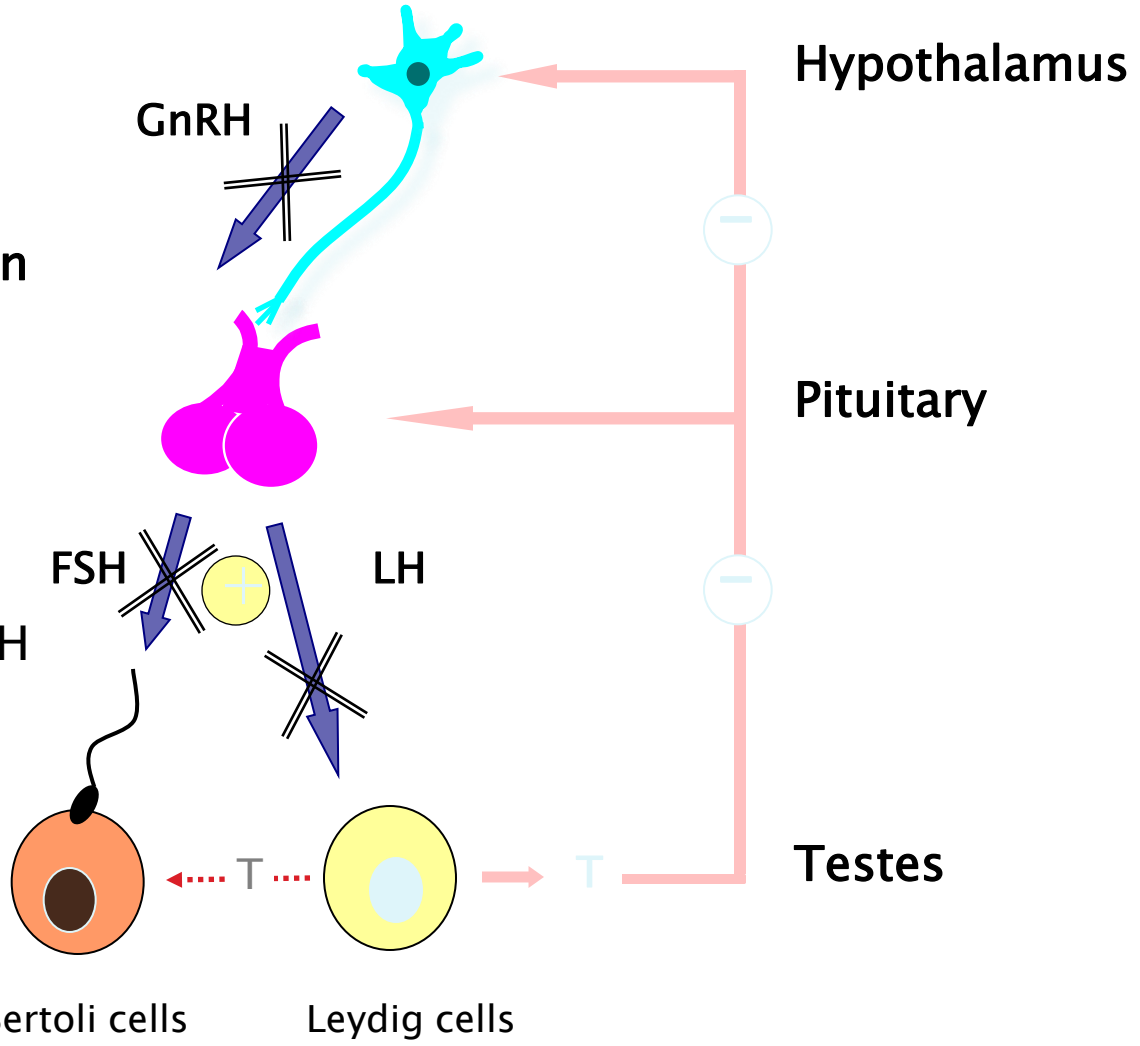
Secondary Hypogonadism

*Hypo*gonadotropic Hypogonadism

- Normal Testicular Function
- Hypothalamic/Pituitary Dysfunction

Results in

- Low or low-normal LH & FSH
- Low testosterone



FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; T = testosterone.

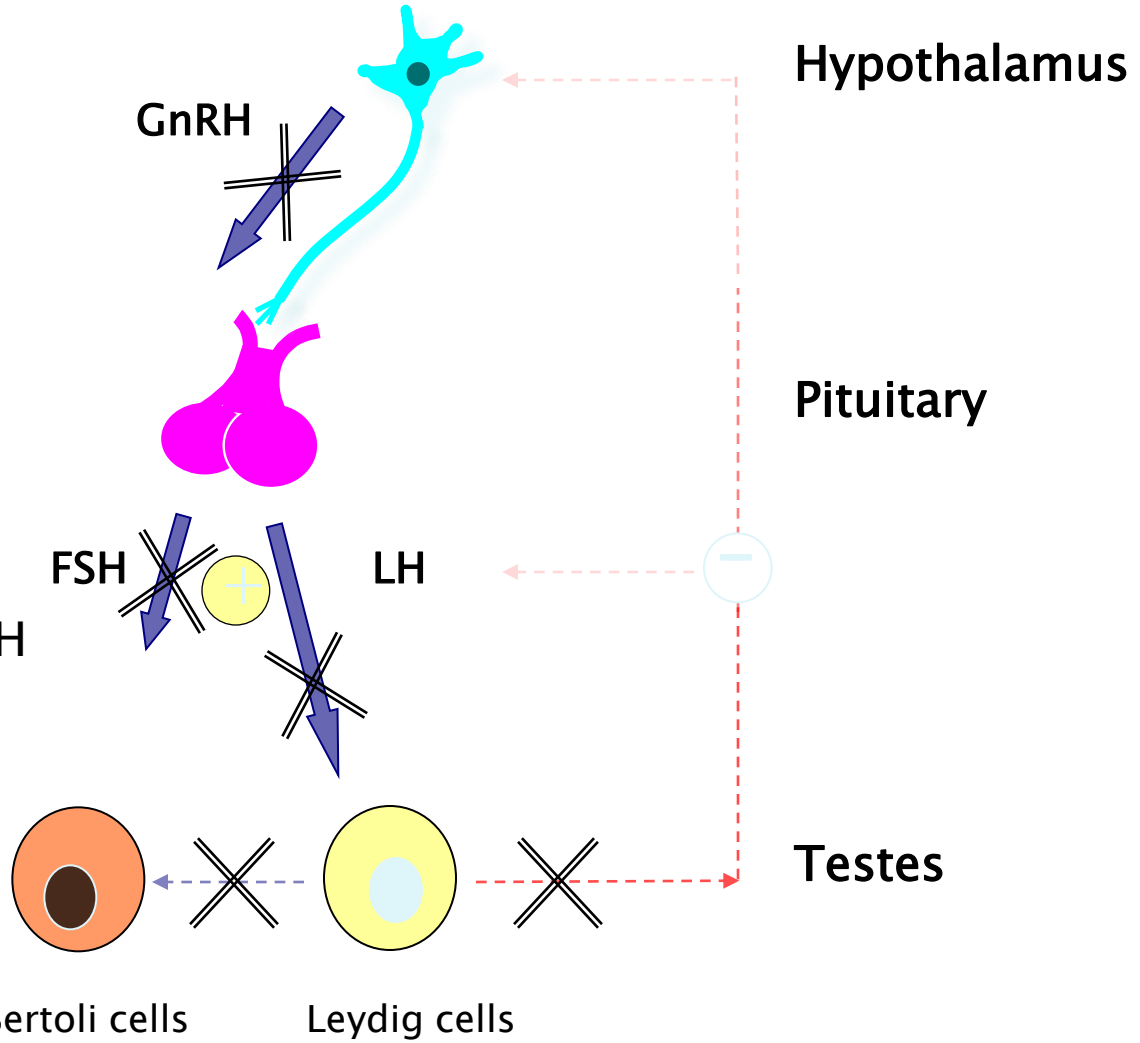
Seftel A. *Int J Impot Res*. 2006;18(3):22[illegible]

Mixed Primary and Secondary Hypogonadism

- Testicular Dysfunction
- Hypothalamic/Pituitary Dysfunction

Results in

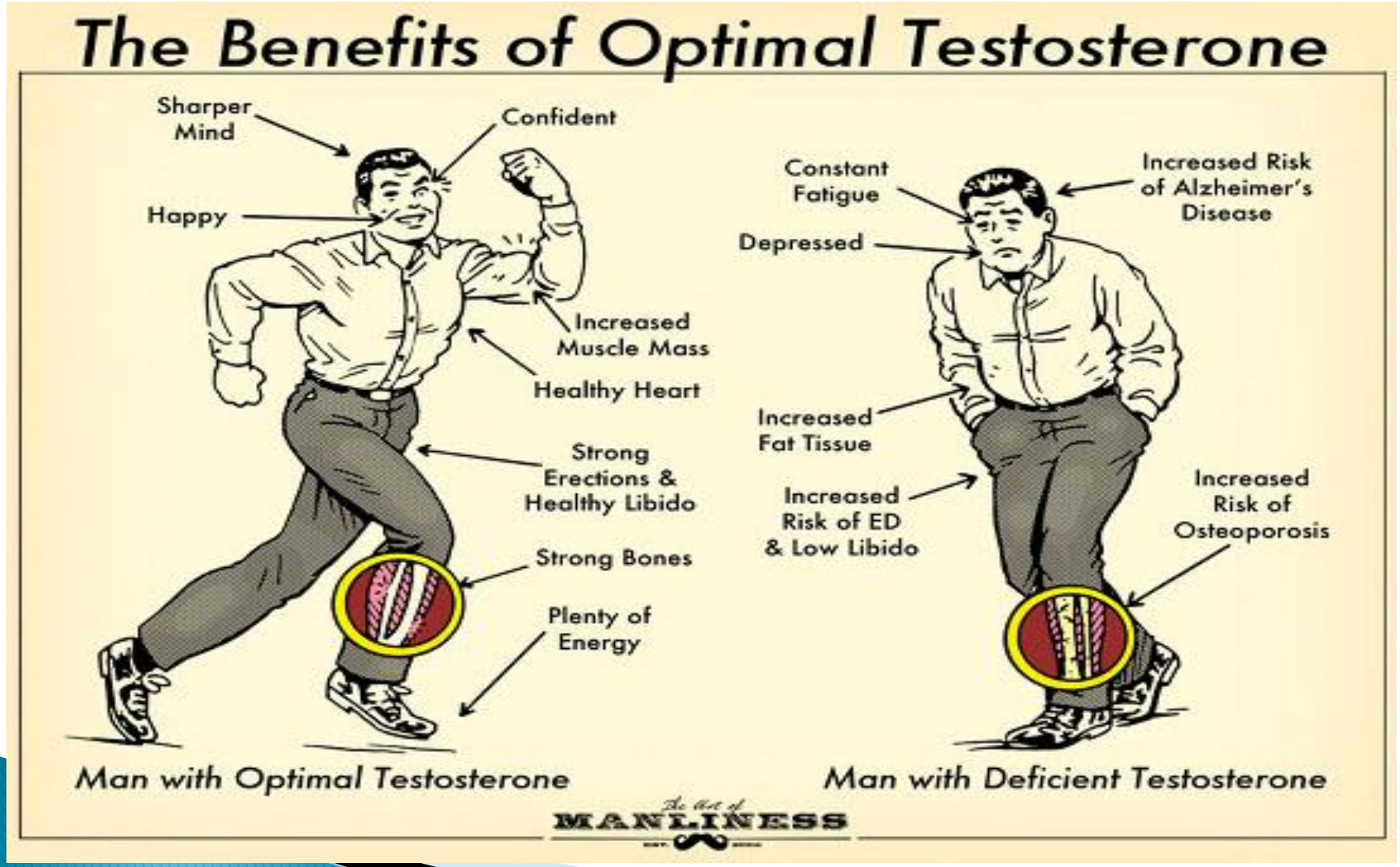
- Low or low-normal LH & FSH
- Low testosterone
- Impaired sperm production



FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

Bhasin S, et al. *J Clin Endocrinol Metab.* 2006;91(6):1995-2010.

Symptoms of low testosterone



Symptoms and Signs of Androgen Deficiency

- Reduced libido and sexual activity
- Lack of effect of PDE5 inhibitors for erectile dysfunction
- Reduced muscle mass and strength
- Depressed mood
- Decreased energy or vitality; increased fatigue
- Osteoporosis/low bone mass

Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995–2010.
Morelli A, et al. *J Endocrinol Invest*. 2[illegible]30(10):880–888.

Causes of Hypogonadism

Congenital

- Cryptorchidism (8/1000*)
- Klinefelter syndrome & variants (1/400*)
- Kallmann syndrome (1/10,000*)
- Sickle-cell disease
- Defects in androgen synthesis or action

Acquired

- Testicular trauma
- Mumps orchitis
- Severe systemic illness: HIV/AIDS
- Aging
- Pituitary disorder
- Obesity
- Medications
- Autoimmune syndromes

*** Incidence in the male population**

Kalyani RR, et al. *Endocrinol Metab Clin North Am*. 2007;36(2):333-348; Petak SM, et al. *Endocr Pract*. 2002;8(6):440-456; Seftel A. *Int J Impot Res*. 2006;18(3):223-228.

Other relationships to think about with low testosterone

Does TD Really Matter?

- **TD has been found to be associated with obesity, insulin resistance, cardiovascular disease, and all-cause mortality**
- **Assume that TD prevalence is 13.4% among men 45 - 74 years**
  - Over 20 years…
    - 1.1 million cases of diabetes
    - 1.3 million cases of CVD
    - 600,000 osteoporotic fractures
- **Cost of additional disease: $190 - $525 billion**

Medscape

Screening for Low T

Androgen Deficiency in Aging Males (ADAM) Questionnaire

1. Do you have a decrease in libido
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

If the answer is yes to question 1 or 7, or at least three of the other questions, low testosterone may be present.

Morley JE, et al. *Metabolism.* 200 49(9):1239-1242.

Testosterone measurements

- Testosterone should be measured between 0800 and 0830 to be most reproducible and representative of gonadal functions
- Recent data suggests that glucose loads can acutely lower total testosterone levels so that we now request the test be fasting from midnight on to the AM draw

Testosterone measurements

- For the most accurate and rigorous diagnosis of hypogonadism one should only use labs assays that have been standardized and certified by an accuracy based quality control program

- Use www.Cdc.gov/labstandards/hs_certified_participants.html

Testosterone measurements

- Serum testosterone levels demonstrate remarkable day-to-day variability
- Approximately30-35% of men who had a single low testosterone value were found to be normal on repeat sampling

Testosterone measurements

- In community dwelling middle-aged to older who had a single testosterone level measured appropriately less than 250 ng/dl initially had an average testosterone greater than 300 average if measured repeatedly over 6 months
- Can this get worse?

Testosterone measuremensts

- A College of American Pathologist study of serum from a hypogonadal man sent to 1133 laboratories using 14 different assays reproted values that ranged from 45-366ng/dl
- When that same sample was sent to 5 different labs that were certified using mass spectrometry based assay ranged from 60-72ng/dl

Testosterone in the Blood

Total Testosterone

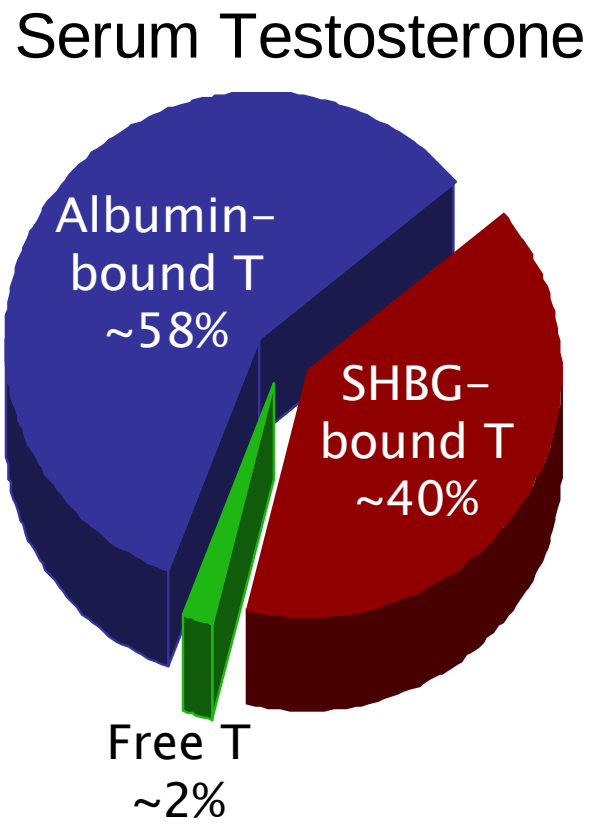
- Free and protein bound
- Normal range = 300–1000 ng/dL

Free Testosterone

- Normal range = 52–280 pg/mL*
- <50 pg/mL = hypogonadism

Bioavailable Testosterone

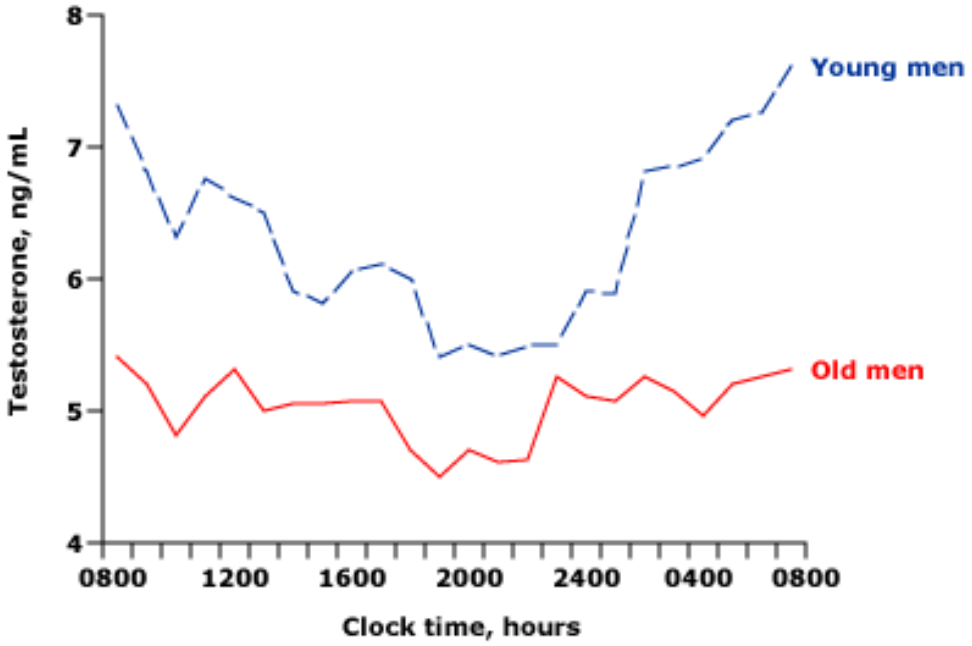
- Free and albumin bound
- Normal range = 70–320 ng/dL
- <70 ng/dL = hypogonadism



*Value by equilibrium dia[illegible]
SHBG = sex hormone-binding gl[illegible]

Morley JE, et al. *Metab*. 2002;51(5):554–559; An[illegible] [Prescribing Information]: Marietta, GA: Solvay Pharmaceuticals Inc; 2007.

Variation in serum total testosterone concentrations



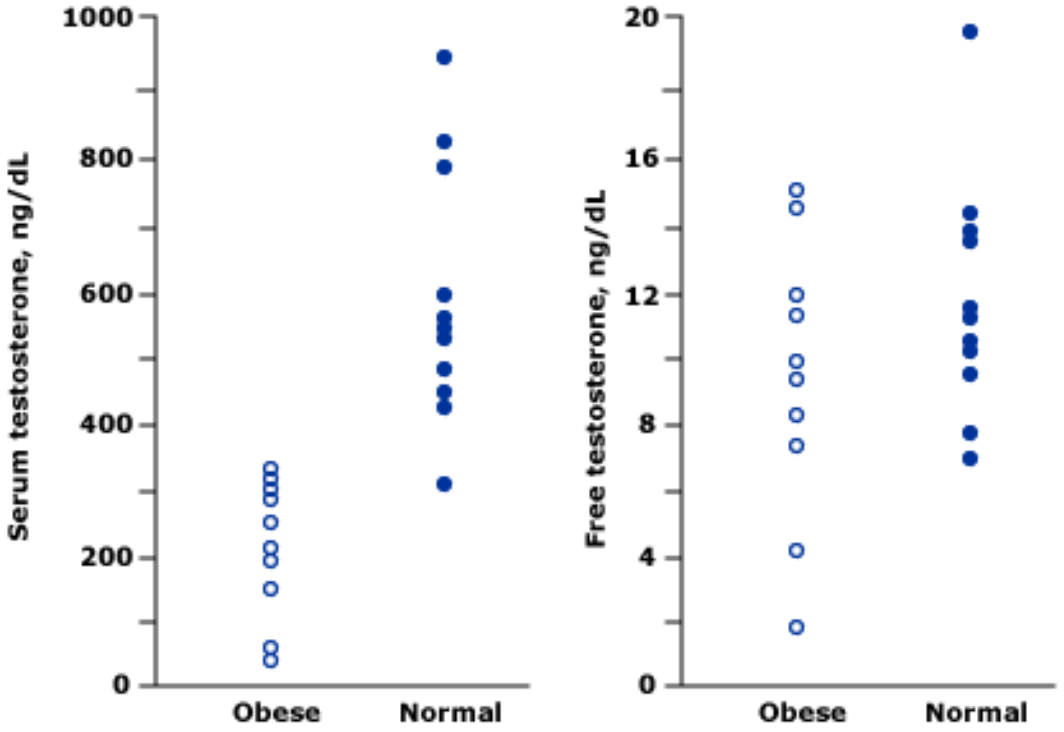
Serum total testosterone concentrations have a diurnal variation in young men (dashed line); concentrations are highest at 8 AM and lowest around 8 PM. In contrast, older men have little variation throughout the day (solid line). To convert serum testosterone values to nmol/L, multiply by 3.47.

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

Testosterone lab testing

- Situations that raise SHBG: aging, hyperthyroidism, high estrogen levels, liver disease, HIV, anti-seizure medications
- Situations that lower SHBG: obesity insulin resistance, type 2 diabetes, hypothyroidism, acromegaly, exogenous testosterone/androgen use, nephrotic syndrome, progesterone, glucocorticoids

Serum testosterone concentrations in obesity



Obesity is characterized by a reduction in serum total testosterone concentration (left panel) but a normal serum free testosterone concentration (right panel) due to decreased SHBG.

SHBG: sex hormone-binding globulin.

Data from Glass AR, Swerdloff RS, Bray GA, et al. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J Clin Endocrinol Metab 1977; 45:1211.

Testosterone measurements

- We currently recommend free testosterone measurements in obese males and men above the age 50 years of age
- If free testosterone levels are measured it should be done at a lab that uses equilibrium dialysis method

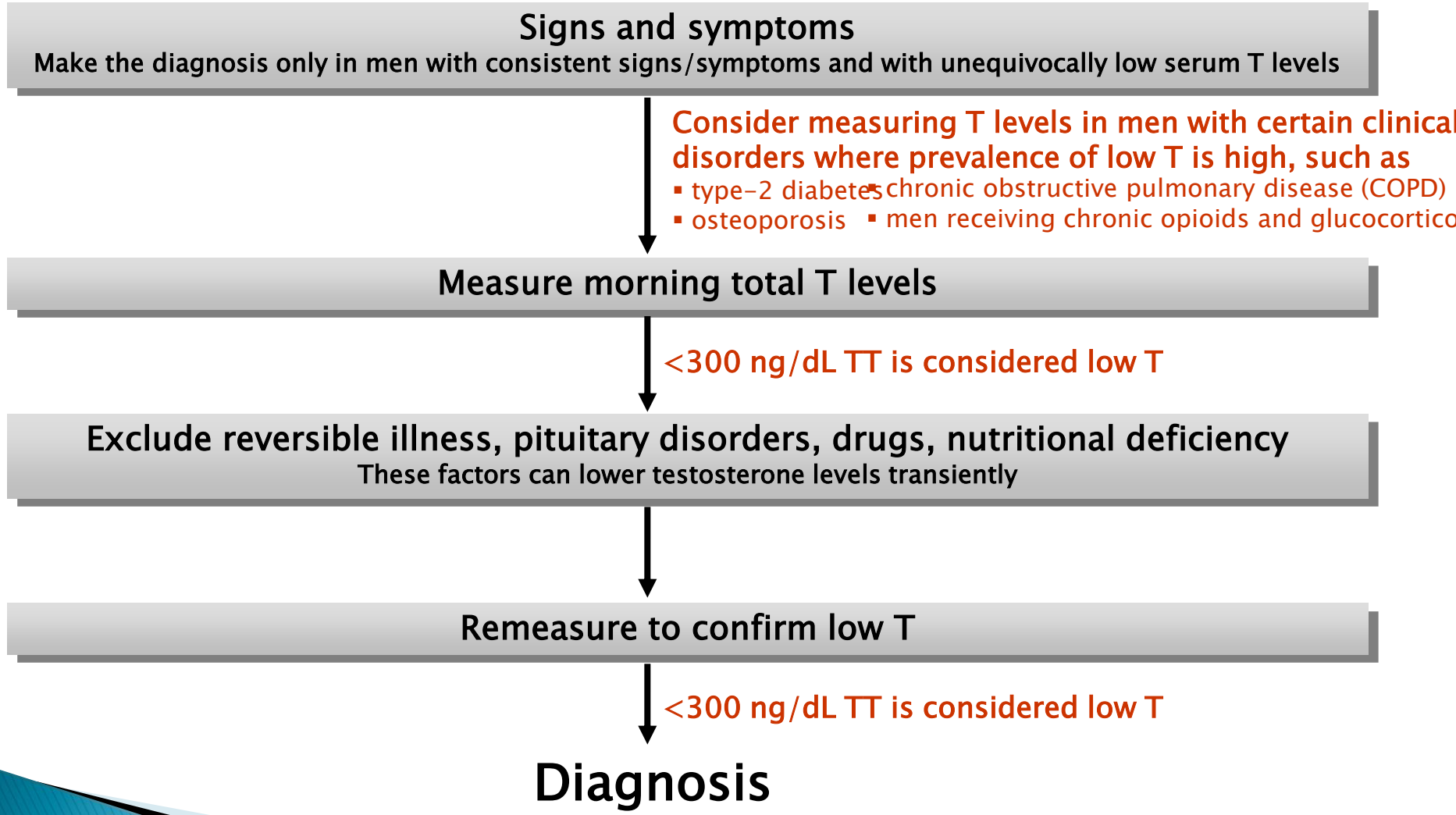
Testosterone measurements

- In a large VA trial (3672 males mean age 59.7 years) had a laboratory screen using total testosterone SHBG and albumin measurements to calculate free testosterone values in each man
- 61.7% of the men with a low total testosterone had a normal free testosterone and only 38.3% of the men with low total testosterone had a low free testosterone

Testosterone measurements

- The conclusion of the authors of the study and also the Endocrine society is that above the age of 50 total and free studies should be done to evaluate patients
- In addition in any patient only testosterone levels less than 150 could reliable predict low free testosterone levels consistently

Diagnosis



Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.

What is the workup?

- We now recommend that after a thorough history and ***exam*** and the use of Bayes' Theorum one should:
- Measure a fasting total testosterone between 0730-0900 weekly times 3 using free testosterone levels if indicated by age, weight etc

Further Diagnostic Recommendations

Primary Hypogonadism

- Karyotype to rule out Klinefelter syndrome

Secondary Hypogonadism

- Measure serum prolactin, iron saturation, and other pituitary hormones
- Obtain MRI if
  - Severe secondary hypogonadism (TT <150 ng/dL)
  - Hyperprolactinemia
  - Other pituitary-hormone deficiency (panhypopituitarism)
  - Symptoms/signs of tumor-mass effect (headache, visual-field defect, or impairment)

TT = total testosterone
MRI = magnetic resonance imag

Bhasin S, et al. *J Clin Endocrinol Metab*. 2 ;91(6):1995-2010.

Drug therapy

Testosterone-Replacement Therapy Dosing and Administration

Intramuscular Injection

- Testosterone enanthate or cypionate
- 75–100 mg weekly or 150–200 mg every 2 weeks

Transdermal Patches (Nonscrotal)

- 2.5–7.5 mg applied nightly for 24 hours*

Transdermal Gels 1%

- 5–10 g applied daily (5–10 mg testosterone systemically absorbed)

Buccal Tablets

- 30 mg tablet applied to the buccal mucosa every 12 hours

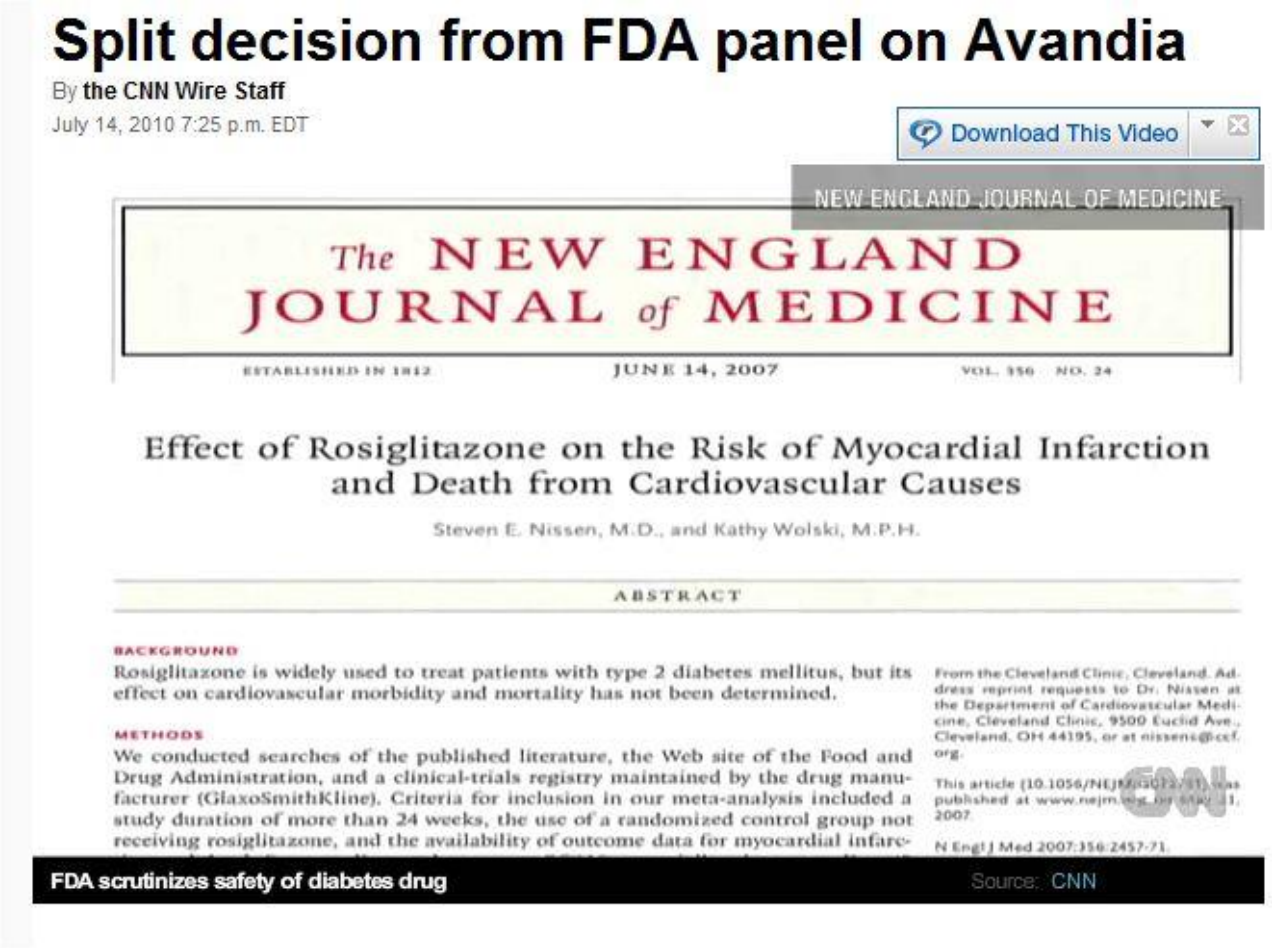
Pellets

- 150–450 mg implanted subcutaneously every 3–6 months†

*Androderm® [package insert]. Watson Pharma, Inc; 2005.
†Testopel® [prescribing information]. Slate Pharmaceuticals, Inc; 2007.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2006;91(6):1995–2010.

What are the risk of therapy?

What are the risk?



Split decision from FDA panel on Avandia

By **the CNN Wire Staff**

July 14, 2010 7:25 p.m. EDT

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarc-

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on June 11, 2007.

N Engl J Med 2007;356:2457-71.

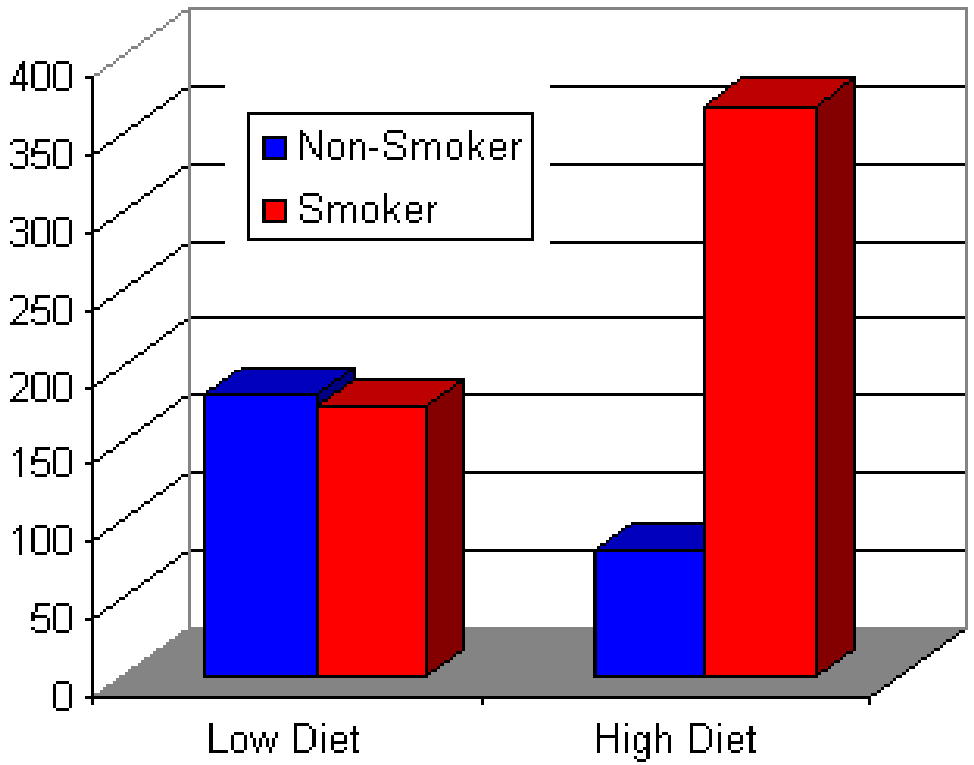
FDA scrutinizes safety of diabetes drug

Source: CNN

What are the risks?

- As many of you know this study was tragically flawed when published in 2007 yet the FDA did not rescind the final restrictions of rosiglitazone until December 16, 2015
- “The seeker of truth must, once in the course of his life, doubt everything as far as possible”. Rene Descartes

What are the risks?



What are the risks?

- Despite multiple epidemiology studies that suggested a protective effect of beta carotene a true double blind placebo controlled study actually shows the exact opposite as you just have witnessed
- Using ***Evidence Based Medicine*** is actually much harder in real practice than is often portrayed to the public

What are the risk?

- JAMA 310 (17) 1829-1836. Showed a 29% increase in cardiovascular events on VA patients (CI 1.04-1.58)
- However retrospective in nature any testosterone therapy was considered a treatment no matter how long the therapy lasted
- Only 60% of patients in the treatment group had any repeat testosterone levels

What are the risks?

- This study has had 2 official corrections including the shocking revelation that the data was not correct
- In an official correction from JAMA patients in the treatment arm actually had a 50% lower rate of CVD events in men receiving testosterone therapy
- In addition it was discovered that 100 women were actually among the patients included in the study. Thus 1 in 11 of the male patients the study were women

What are the risks?

- The actual rate of therapy group was 10.1% versus 21.2% in the control group
- This is an astonishing change taking a study which implicates testosterone as causing heart disease to a study which supports its safety

What are the risks?

- The study has been never been officially retracted by the editors of JAMA
- Unfortunately the study has been widely quoted in medical and more importantly non-medical sources of medical information including the NY Times editorial titled ***Overselling Testosterone***

What are the risks?

- The Cardiovascular Safety of testosterone-replacement therapy NEJM :2023;389:107-117
- The study took 5246 men age 45-80 with high risk for cardiovascular disease treated with testosterone gel vs placebo for mean 21.7 months showed no difference in events between placebo or therapy

What are the risks?

- The Testosterone Trials was a randomized double blind placebo controlled study that took 790 men half treated with gel and half with placebo gel
- The study screened 51,085 men to get the 790 for the study most of the the patients did not qualify as the first of second fasting testosterone levels

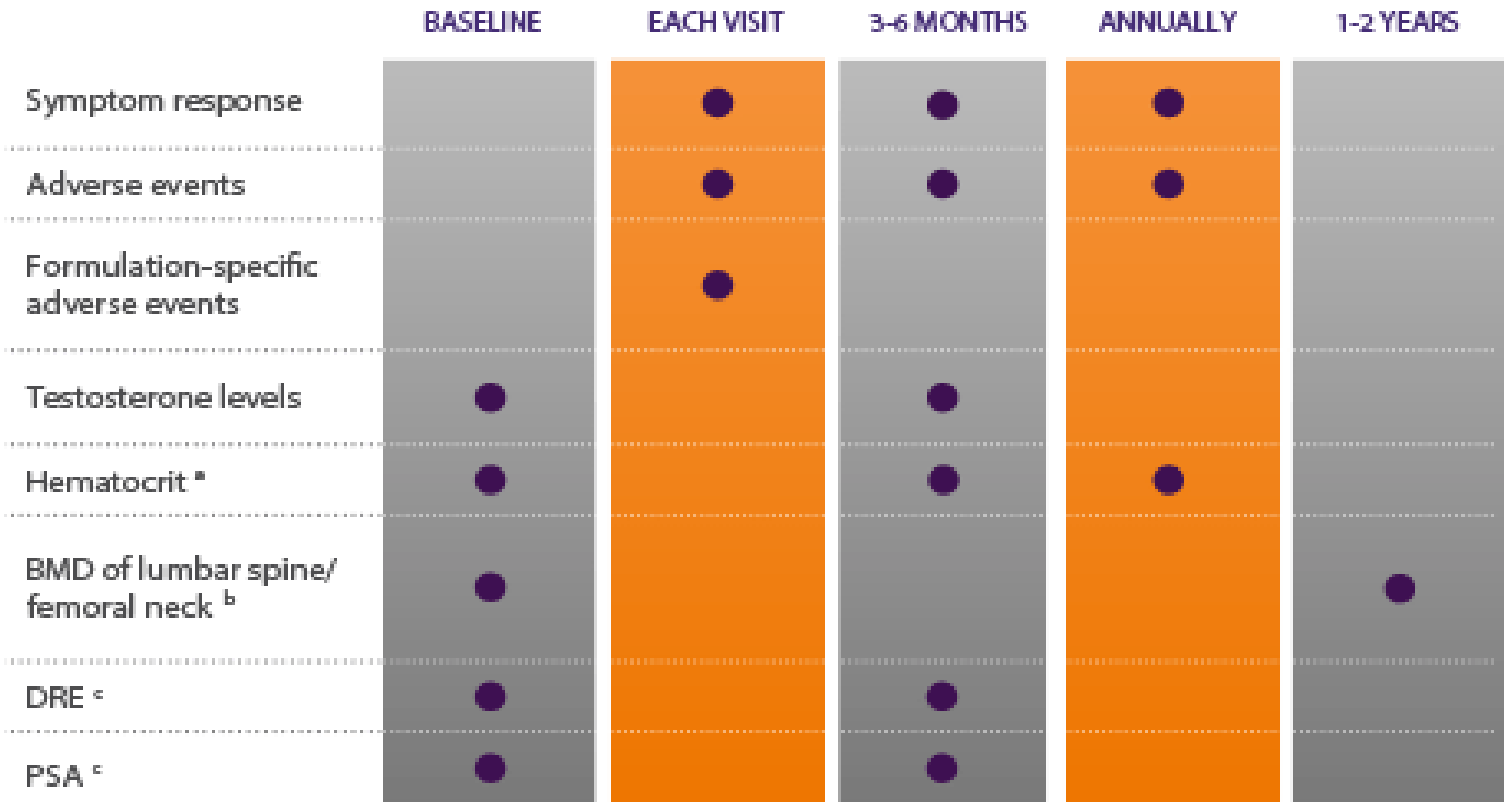
What are the risks?

Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N = 394)	Testosterone (N = 394)
	no. of participants	
Prostate-related event		
Increase in PSA level by ≥1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19†	26	27
Hemoglobin ≥17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

* PSA denotes prostate-specific antigen.
† The International Prostate Symptom Score (IPSS) questionnaire is used to identify symptoms of benign prostatic hyperplasia. Scores range from 0 to 35, with higher scores indicating more severe symptoms. A score of more than 19 indicates moderately severe lower urinary tract symptoms.
‡ Data on cardiovascular adverse events were collected with the use of a specific questionnaire administered at each visit and also identified from the adverse-event log and the form for reporting serious adverse events (see the protocol). Myocardial infarction, stroke, and death from cardiovascular causes were assessed by two adjudicators.
§ Other serious adverse events were defined as congenital anomaly, disability, a life-threatening event, or an event that may not be immediately life-threatening but is clearly of major clinical significance.

Endocrine Society Guideline
TRT Monitoring



*If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.

†For patients with osteoporosis or low trauma fracture, consistent with regional standard of care.

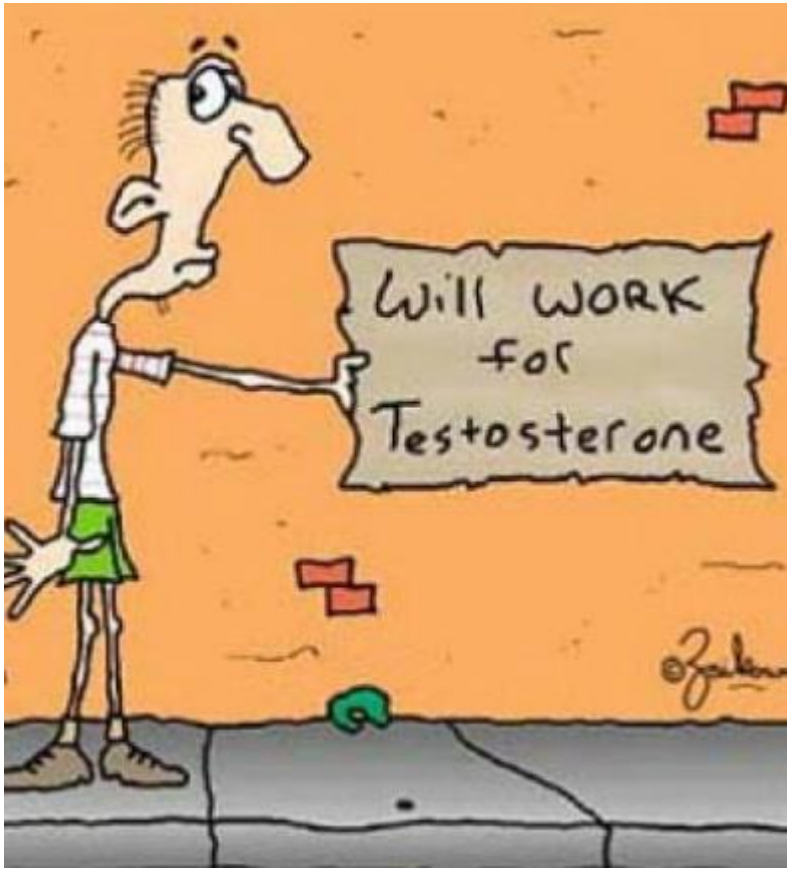
‡After 3 months, perform in accordance with guidelines for prostate cancer screening, depending on the age and race of the patient. Obtain urological consultation under certain conditions.

BMD = bone mineral densit[illegible]; DRE = digital rectal exam; PSA = prostate specific antigen; T = testosterone; TRT = testosterone-replacement t[illegible]

Bhasin S, et al. *J Clin Endocrinol Metab.* 2[illegible]1(16):1995-2010.

American Cancer Society Guidelines for the Early [illegible]n of Cancer. http://www.cancer.org/.

Questions?



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Elagizi, A et al. *Testosterone and Cardiovascular Health*, Mayo Clin Proc. January 2018:93(1) 83-100.

Snyder, P et al. *Effects of Testosterone Treatment in Older Men*, NEJM 2016; 374:611-624.

Snyder, P. *Testosterone treatment of male hypogonadism,* **Up to Date**: October 21,2022.

References

- Lincoff, A et al NEJM 2023; 389:107-117 DOI10.1056/NEJMoa2215025
- In addition I strongly recommend Endocrinology and Metabolism clinics Hypogonadism March 2022