THE HEART SUMMIT 2018

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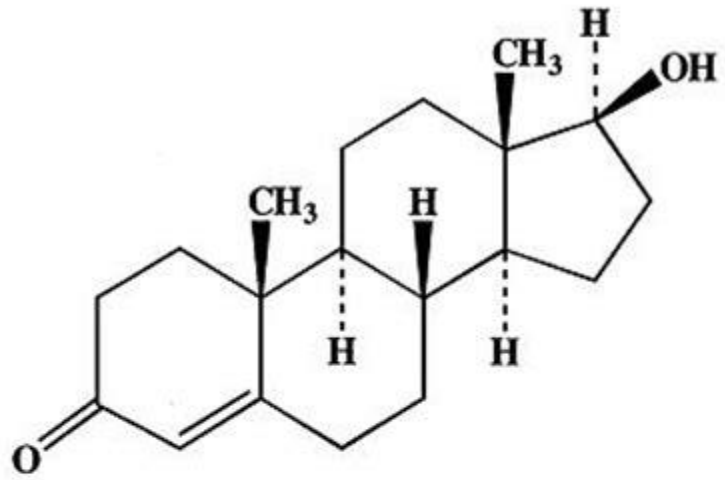
The Testosterone Quandary

Beth Crowder, PhD, APRN

Objectives

- Define testosterone, the hypothalamic-pituitary-gonadotrophic axis, and normal blood levels
- List functions of testosterone and symptoms of low testosterone
- Discuss low testosterone and fragility
- Break through the quandary, and define your treatment plan.

Testosterone



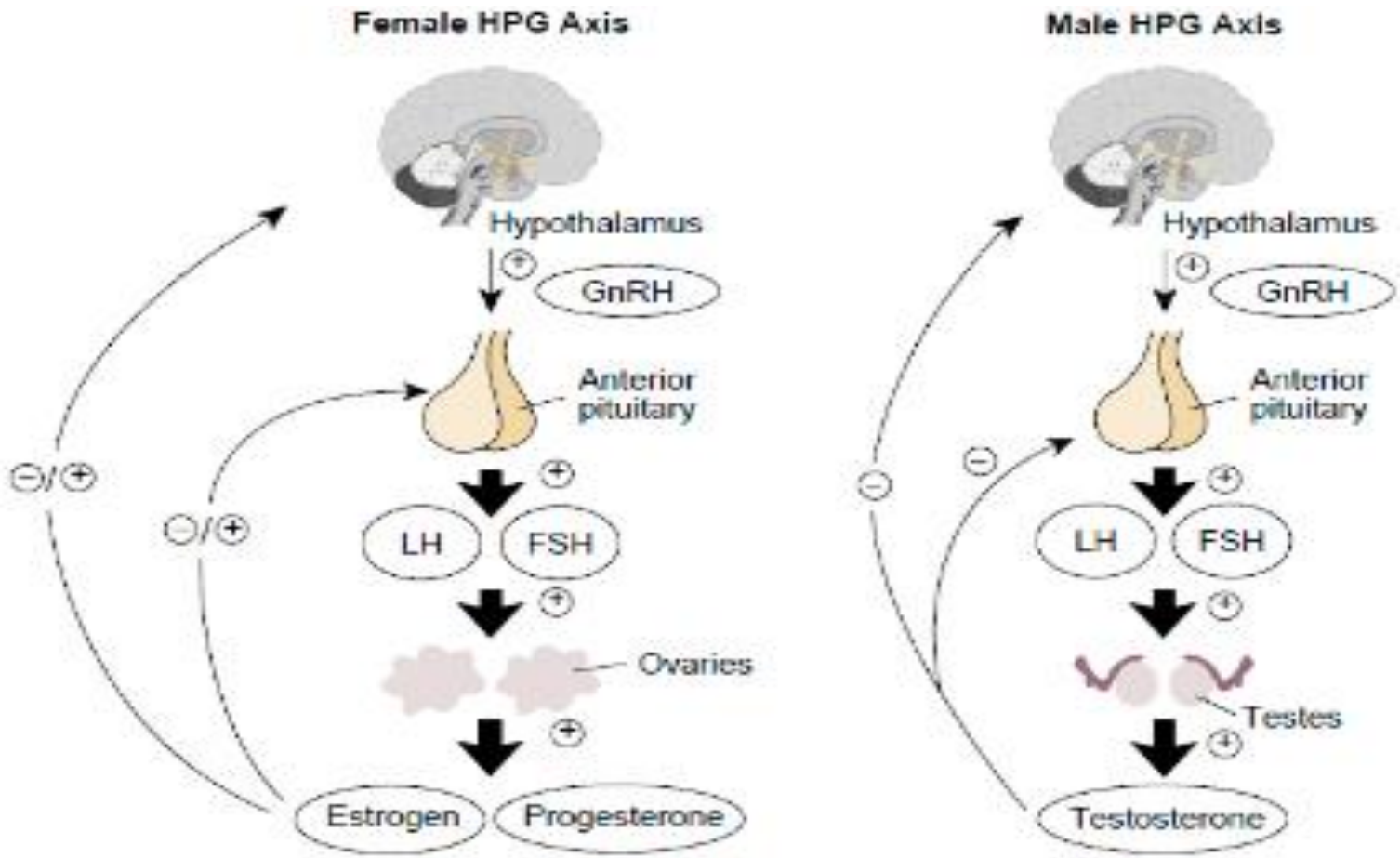
Testosterone

$C_{19}H_{28}O_2$ MW 288.42

What is Testosterone

- The most important male hormone
- Lower levels found in females
- Androgen, or anabolic steroid
- Men: produced mainly in the testes (small amount in adrenals)
- Women: produced mainly in the ovaries (small amount in adrenals)

Hypothalamic-Pituitary-Gonadotrophic Axis



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Primary Hypogonadism

- Primary
  - Testicular disorder
    - Klinefelter syndrome
    - Undescended testicles
    - Mumps orchitishemochromatosis
    - Injury to the testicles
    - Cancer treatment

Secondary Hypogonadism

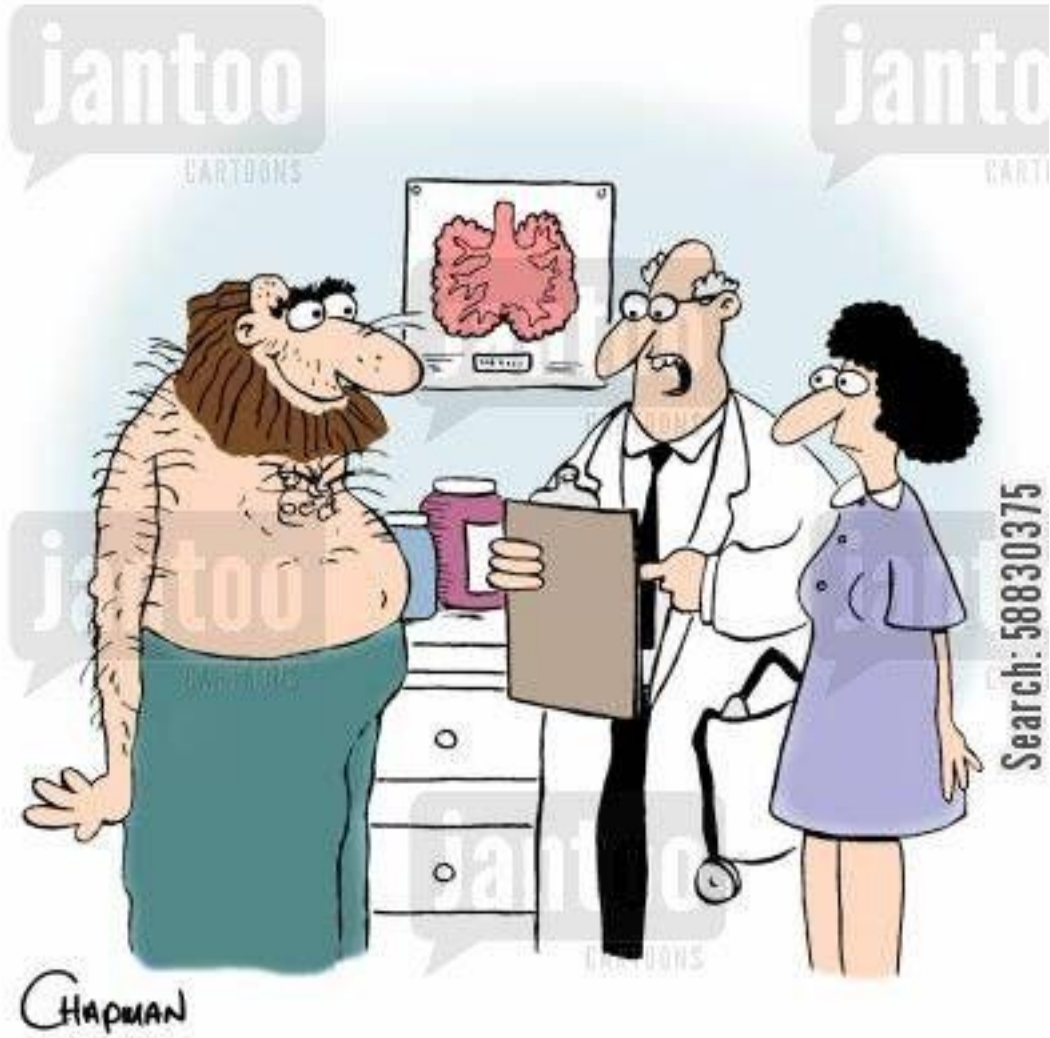
- Secondary
  - Testicular function is normal, but problem with the Hypothalamic-Pituitary-Gonadotrophic axis
    - Kallmann syndrome
    - Pituitary disorders
    - Inflammatory disease
    - HIV/AIDS
    - Medications (continuous opiate pain medications; chronic glucocorticosteroid treatment; hormone replacement)
    - Obesity
    - Normal aging
    - Concurrent illness (emotional/physical stress of an illness or surgery)

Normal Total Testosterone Levels

- Male: 300-1200 ng/dL (10.4-41.6 nmol/L)
- Female: 8-60 ng/dL (0.3-2.1 nmol/L)
    - Per the Endocrine Society

Physiological Effects of Testosterone in Males

- Maintains reproductive tissues
- Stimulates spermatogenesis
- Stimulates and maintains sexual function
- Increases body weight and nitrogen retention
- Increases lean body mass
- Promotes sebum production and axillary and body hair growth
- Promotes erythropoiesis



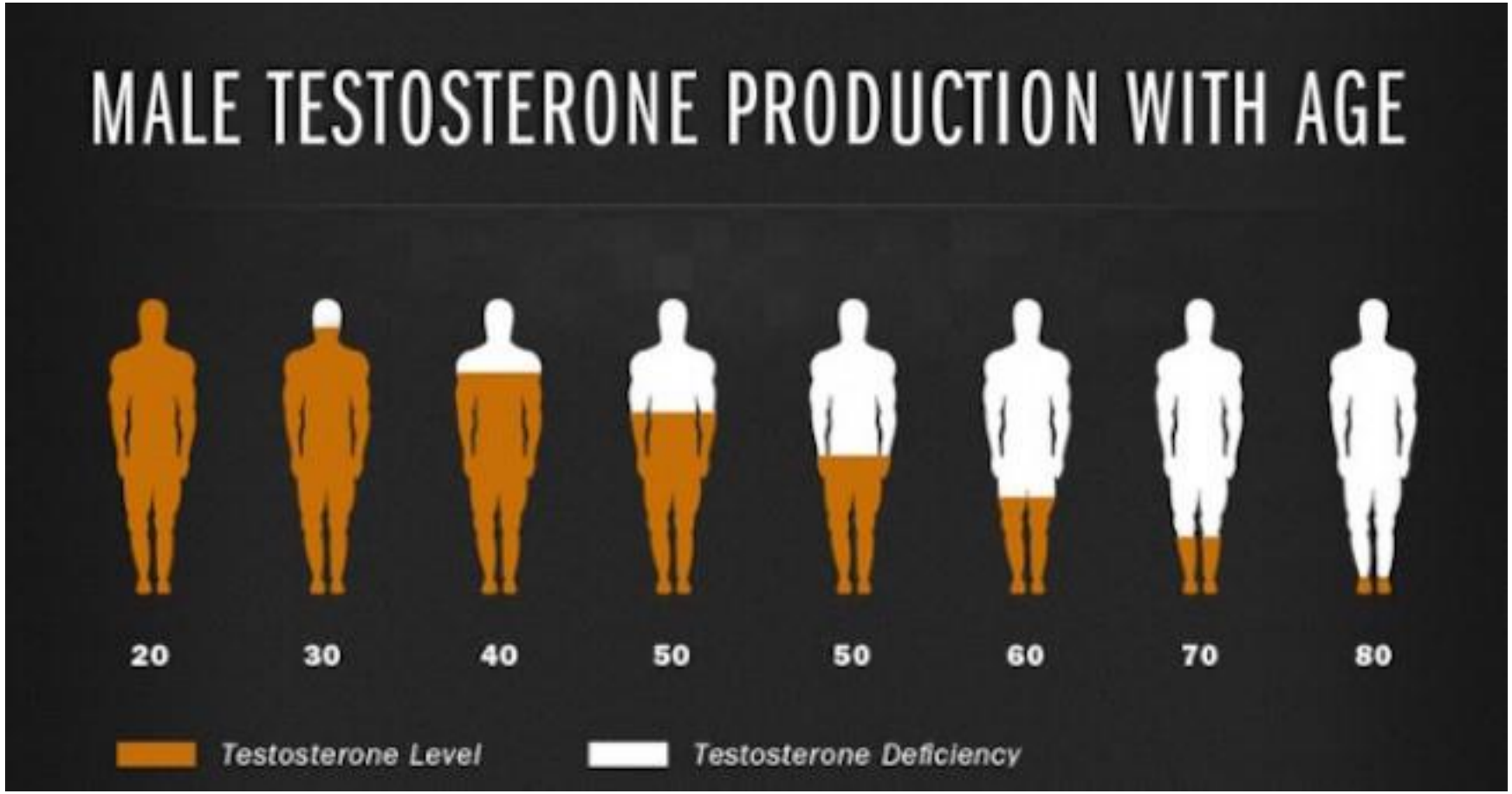
"Except for his testosterone level being out of whack, Frankie is a normal 7-year-old."

Low T or Hypogonadism

- Reduced sex drive
- Erectile dysfunction or impotence
- Increased breast size
- Lowered sperm count
- Hot flashes
- Less energy
- Depression, irritability and inability to concentrate
- Shrunken and softened testes
- Loss of muscle mass or hair
- Bones becoming prone to fracture
- Reduced physical performance
- Sleep disturbance

High Testosterone or Hypergonadism

- Irregular menstrual cycles
- Increased body hair and acne
- Polycystic ovarian syndrome



Timing of Serum Testosterone Level

- Involved in sleep-wake cycle
- Levels at peak between 0600-0800
  - Per Endocrine Society

Making the Diagnosis of Hypogonadism in Men

- Signs/symptoms c/w testosterone deficiency
- Two low fasting morning testosterone levels
- Serum luteinizing hormone and follicle-stimulating hormone
  - Per Endocrine Society

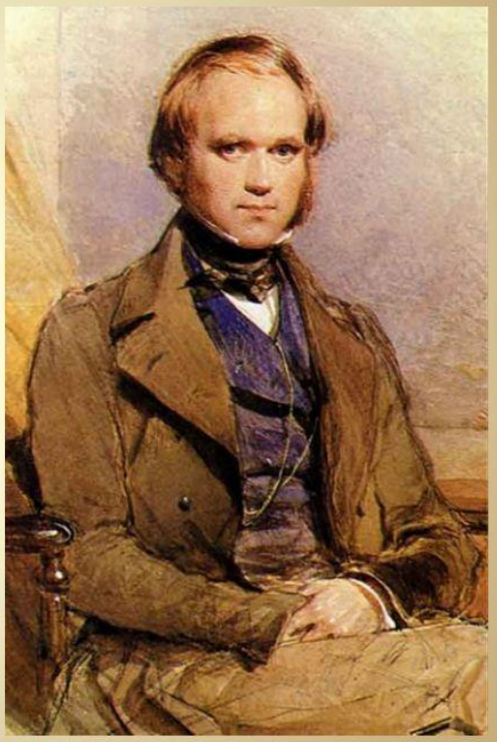
Frailty

- A clinical condition related to changes in metabolism, to saropenia, and to decline in muscle mass and strength, bone mineral density, and physical function with aging.
- The pathophysiology of frailty is multifactorial and associated with comorbidities.
- Testosterone is implicated in regulating metabolic function, maintenance of muscle and bone, and inhibition of adipogenesis

The Testosterone Quandary

History of Evolution

- Charles Darwin developed the THEORY OF EVOLUTION BY NATURAL SELECTION
- which explained how organisms changed over time (ADAPTED)



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Adaptation and Survival of the Fittest

- Frail organism
- Less energy
- Loss of muscle mass or hair
- Bones becoming prone to fracture
- Reduced physical performance

- All of above result from low testosterone levels leading to infertility……a bad thing?

Bottom Line

- Multiple systems in the body
- Reproductive system last system of importance when fighting illness
- When organism improves, testosterone levels improve……Coincidence?

So here we are today

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Testosterone……Yes sir!!
The story of two elderly men

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....”I believe there exists, & I feel within me, an instinct for the truth, or knowledge or discovery, of something of the same nature as the instinct of virtue, & that our having such an instinct is reason enough for scientific researches”…

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Metabolic Effects of Testosterone

- Increased protein synthesis
- Inhibition of adipocyte production in favor of satellite cells necessary for muscle repair
- Inhibition of muscle protein breakdown
- Enhanced amino acid reuse in muscle
- Erythropoiesis is promoted through stimulation of bone marrow
- Appetite is stimulated through action of increased ghrelin and decreased leptin

Low Testosterone Leads to Frailty

- Reduced circulating levels of sex steroid hormones
- Growth hormone deficiency
- Vitamin D deficiency
- Insulin resistance-related comorbidities
- Chronic inflammation
- Endocrine disruptions
- Oxidative stress
- Cardiovascular and metabolic dysfunction
- Nutritional deficiencies
- Mitochondrial dysfunction
- Subclinical multisystemic impairments

The Progression of Frailty

- Institutionalization
- Hospitalization
- Mortality

- Can testosterone impact the complex pathophysiology of frailty?

Effect of Testosterone Treatment on Body Composition, Scarcopenia, and Sarcopenic Obesity

- Testosterone treatment improved body composition, increases lean body mass, and reduces fat mass
  - O'Connell, et al., 2011
  - Svartberg, et al., 2008
  - Page, et al., 2005
  - Kenny, et al., 2010
  - Kvorning, et al., 2013
  - Srinivas-Shankar, et al., 2010
  - Bhasin, 2003

Effect of Testosterone Treatment on Muscle Strength and Physical Function

- Testosterone treatment improved muscle strength and physical function
  - Ferrando, et al., 2002
  - Page, et al., 2005
  - Sih R, et al., 1997
  - Ottenbacher, et al., 2006

Effect of Testosterone Treatment on Bone Mineral Density, Falls, and Fractures

- Testosterone treatment improved bone mineral density, leading to less falls, and less fractures
  - Orwoll, et al., 2006
  - Snyder, et al., 2000
  - Snyder, et al., 2017
  - Aminorroaya et al., 2005
  - T Trials, 2018

Effect of Testosterone Treatment on Anemia

- The prevalence of anemia increases from 5% at the age of 65 years, to over 20% at the age of 85 years
- Testosterone treatment improved anemia through erythropoiesis, improving energy and vitality
  - Ferrucci, et al., 2006
  - Zhang, et al., 2016
  - Dos Santos, et al., 2016

Effects of Testosterone Treatment on Frailty

- Testosterone treatment, with all of its aforementioned improvements, decreased the risk of mobility limitations, as well as increased quality of life
  - Krasnoff, et al., 2010
  - Srivivas-Shankar, et al., 2010
  - Snyder, et al., 2016

Conflicting Scientific Research

- Some studies reveal increased cardiovascular mortality and overall mortality with low testosterone levels
- Other studies revealed an increased risk in cardiovascular mortality and overall mortality with testosterone replacement

    - Ohlsson et al, 2011
    - Araujo et al, 2011
    - Srinath, et al., 2015
    - Corona, et al., 2011
    - Hyde, et al., 2010

***A large randomized, double blind placebo-controlled trial comparable to the Women's Health Initiative is warranted

Research Studies

- Low testosterone (androgen deficiency) is a risk factor for:
  - Diabetes
  - Metabolic syndrome
  - Inflammation and dyslipidemia
  - Diminished functional capacity
  - Diminished quality of life
  - Atherosclerosis, CV risk, and poor myocardial perfusion
  - All-cause mortality

    - Maggio & Basaria, 2009
    - Feeley, et al., 2009
    - Traish, et al., 2017
    - Mirdamadi, et al., 2014

Growing Evidence in Literature that Testosterone is Cardioprotective

- FDA published that the claim testosterone caused harm by increasing CVD risk lacked evidence of credibility
- Studies published supporting that testosterone treatment lowers cardiovascular risk are confounded by the short duration of treatment
  - Traish, 2016
  - Morgentaler, et al., 2015
  - Morgentaler, et al, 2016
  - Morgentaler, 2014
  - Morgentaler, 2016

Scientific Research

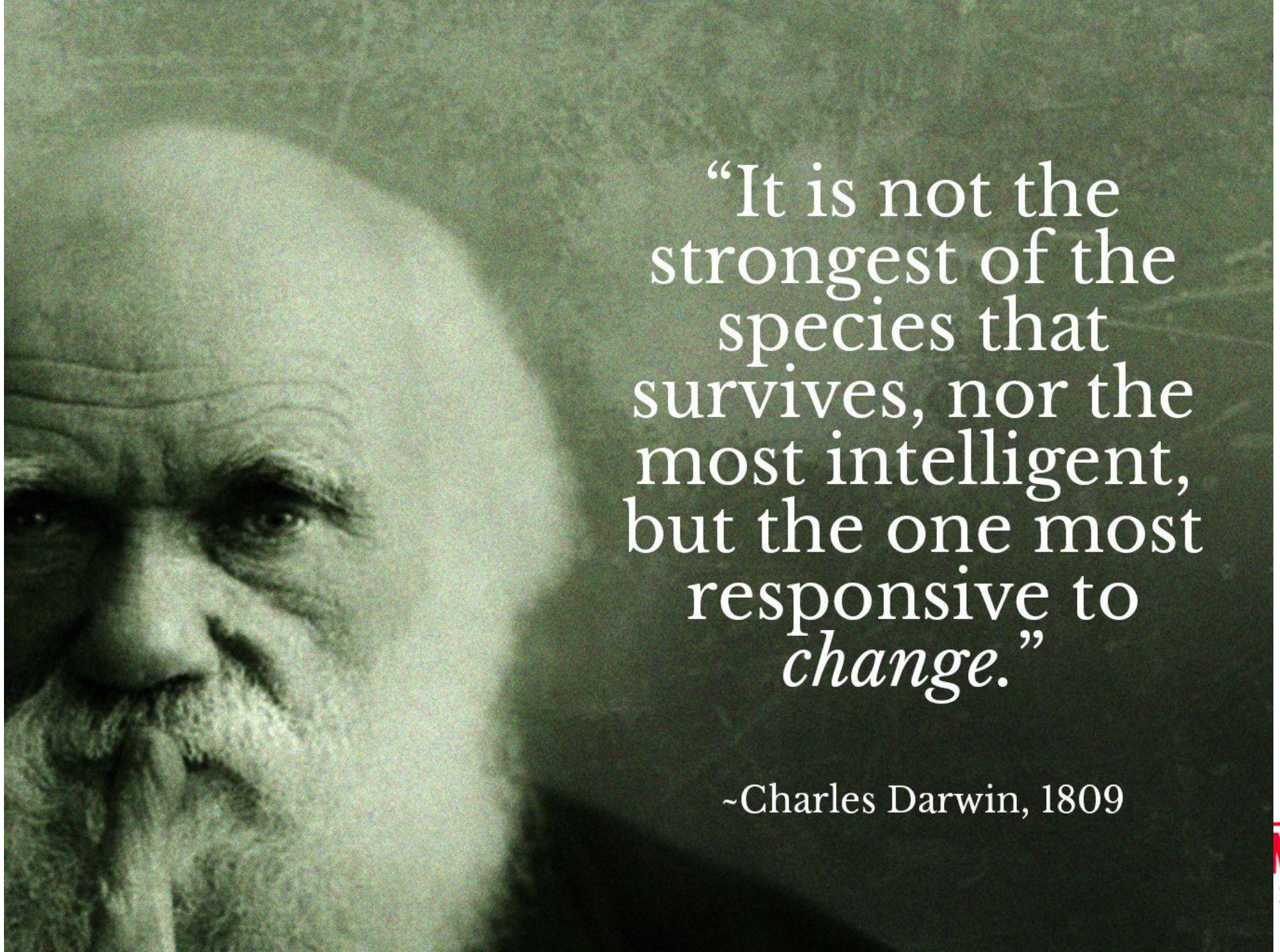
- Testosterone decreased hospital readmissions in men over 66 years:
  - 30 day readmission rate 9.8% for testosterone users vs 13% for non-users
    - University of Texas Medical Branch at Galveston, 2016

Testosterone for Women

- There are no FDA approved testosterone supplement products for women in the United States
- Testosterone is converted to estrogen in the blood
- Hence, testosterone products for women carry the same risks associated with long-term estrogen therapies (breast cancer, cardiovascular risk, thrombus risk) as per the Women's Health Initiative Study

The New Testosterone Quandary

- I have a few, or many patients in the hospital who fit this scenario, how should I treat them?
- What about men who need surgery, it may/may not be elective, should testosterone guide pre-habilitation, or be a predictor for prognosis?
- The Endocrine Society is a renowned and respected professional body, can we intermingle the Society's recommendations regarding who they are against starting therapy in, what lab tests to check before and after instituting therapy, necessary prostate evaluations, and devise a competent treatment plan leading to change?


"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*."
~Charles Darwin, 1809

References

- Available upon request

Testosterone Preparations

- Testosterone enanthate and cypionate (esters of testosterone), IM 50-100 mg weekly or 100-200 mg every 2 weeks
- Testosterone patch (Androderm) 1 or 2 patches q 24 hours
- Testosterone gels (Androgel, Testim, Fortesta, Axiron) 50-100 mg daily
- Other: buccal tablet, subcutaneous testosterone pellet (Testopel), nasal testosterone gel (Natesto), beta HCG, extra long acting injections)

Recommend AGAINST Starting Testosterone Therapy

- Men planning fertility
- Breast or prostate cancer
- Palpable prostate nodule or induration
- PSA level > 4, or >3 in men at increased prostate cancer risk
- Elevated hematocrit
- Untreated severe obstructive sleep apnea
- Uncontrolled congestive heart failure
- Myocardial infarction or stroke within last 6 months
- Severe lower urinary tract symptoms
  - Per Endocrine Society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