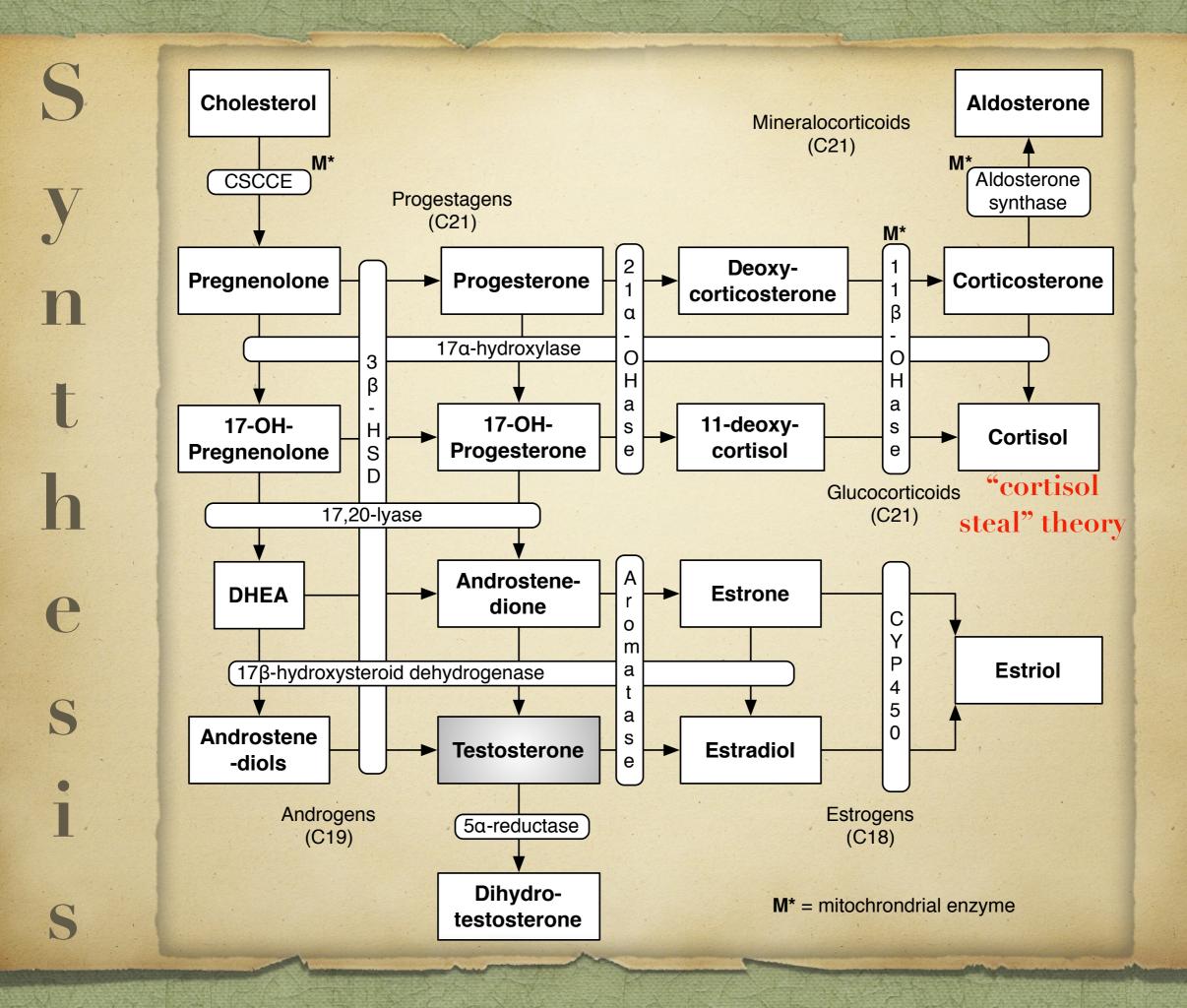
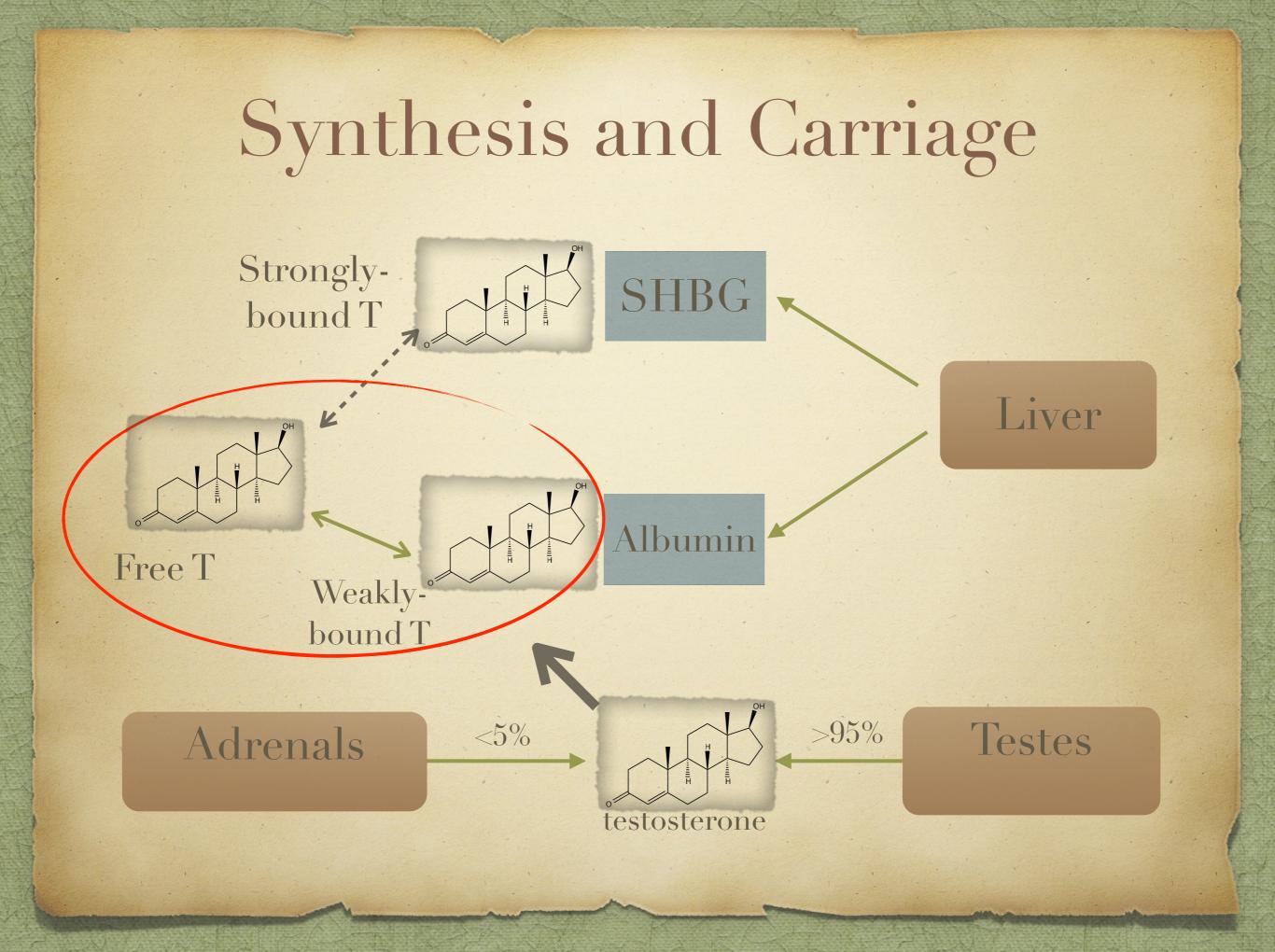
## (Mis-)Understanding Male Aging and "Low T" Syndrome Eric Yarnell, ND, RH(AHG)

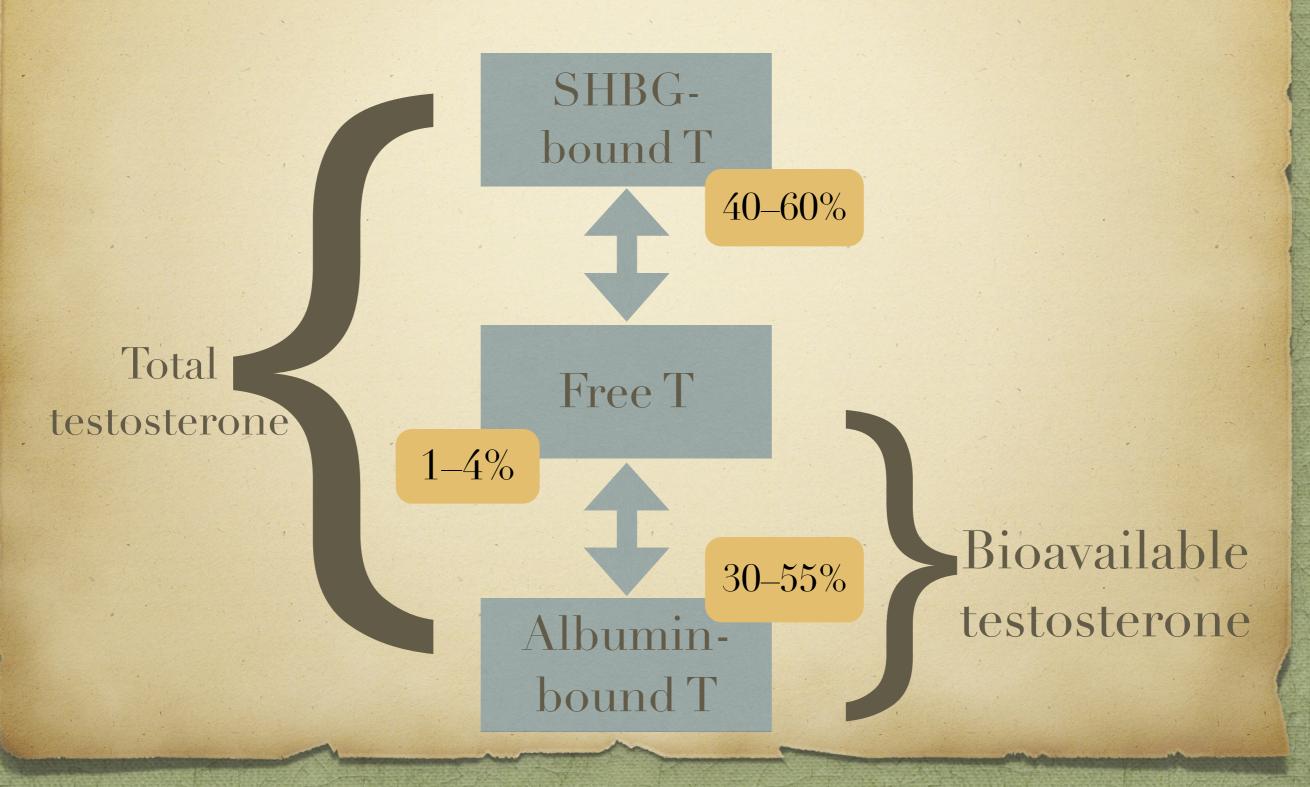
2015

Testosterone Physiology: Clarifying Misunderstandings





#### Three Pools of Testosterone



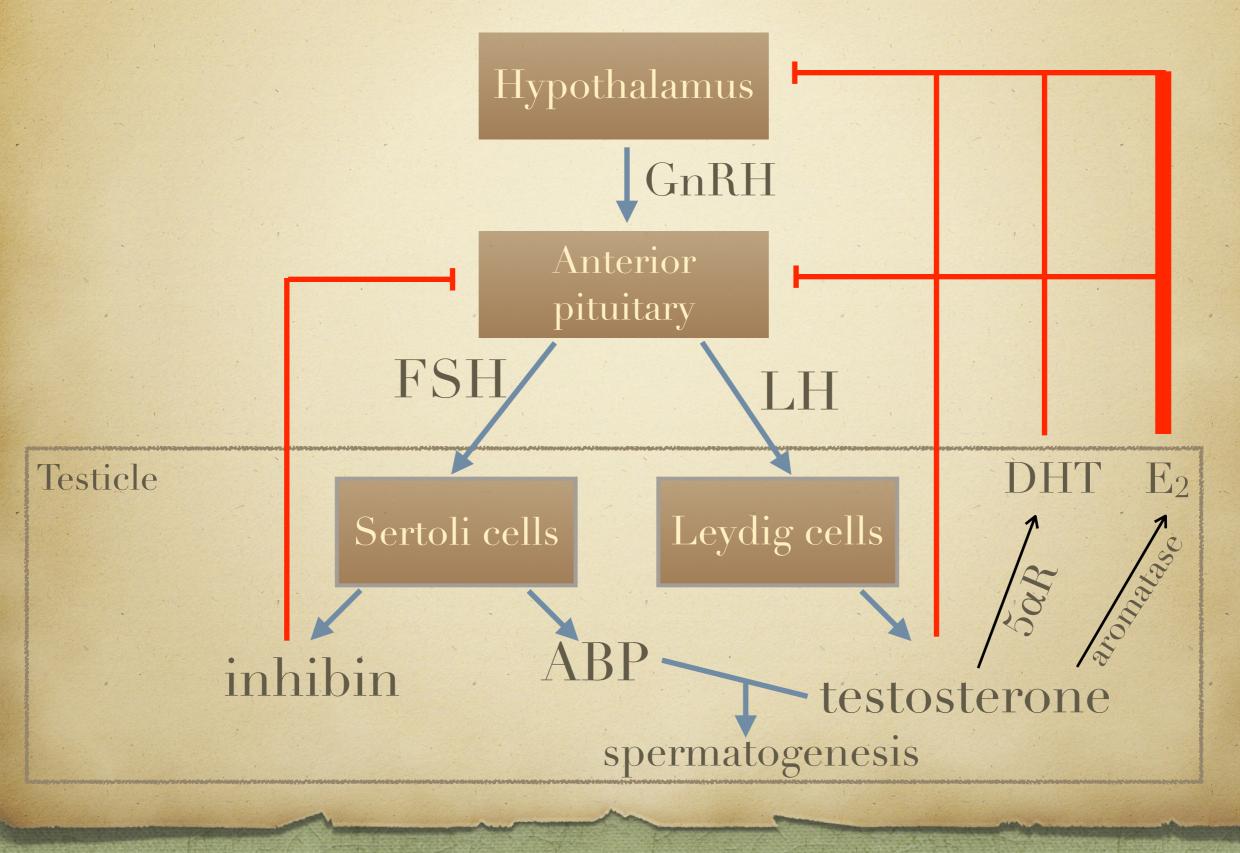
#### Size of the Pools 50-yr-old man example

Scenario 1: "Normal" Total T

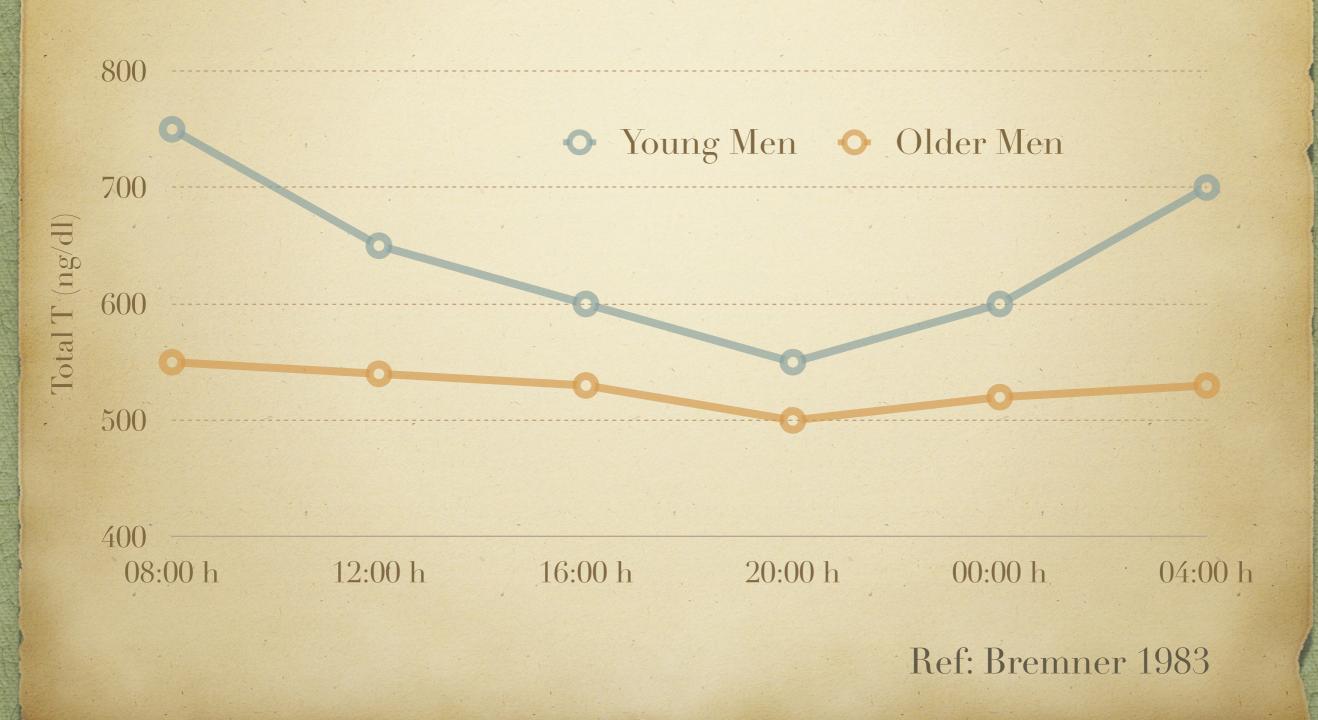
Scenario 2: "Low" Total T



## Regulatory Scheme



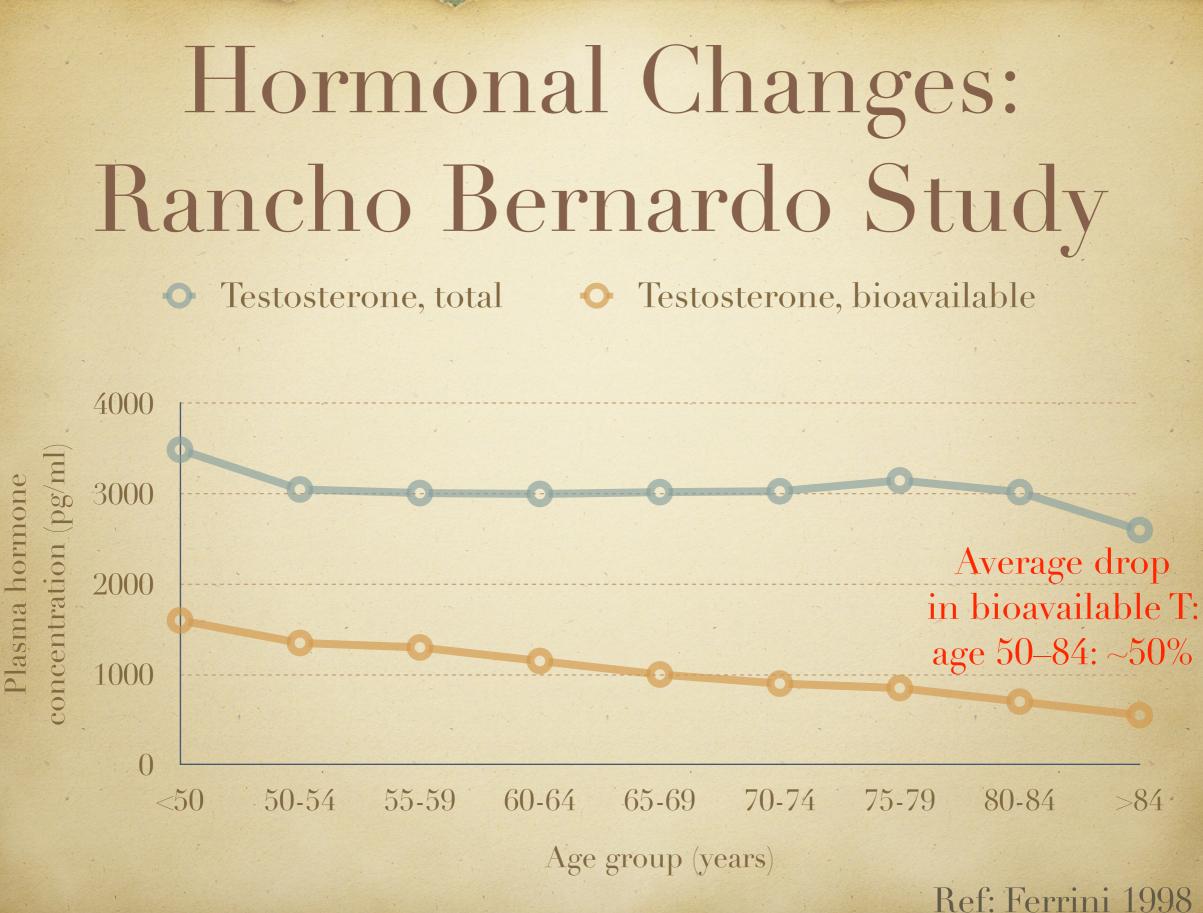
## **Diurnal Secretion**



# EMAS/MMAS Normal Aging

- > Typical pattern after age 30 yr in mostly white cohorts:
  - > Free and bioavailable T decreased 1–1.2%/year
  - > Total T decreased 0.4%/year
  - SHBG increased 1.2%/year
  - > DHEA-S decreased 2.2%/year
- Large inter-individual variability; subgroup analysis suggested obesity accounted for much of the decline in androgens
- Symptoms reach 35% in older men

Refs: Tajar 2010; Gray 1991



## Adrenal Aging

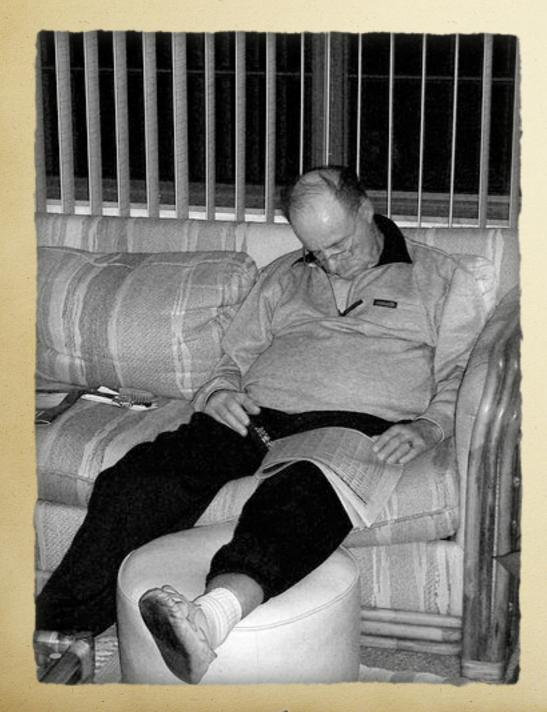
- Zona reticularis shrinks with age in men, by ~25% on average (Dharia 2005; Parker 1997)
  - > DHEA and DHEA-S production goes down measurably in most men as they age, likely as a result of this
- > However, percentage of androgens from adrenals may actually go up with age

#### Hypogonadism Syndromes

## "Low T" syndrome

- > Marketing hype anyone?
- > Have we learned anything from the female hormone replacement debacle related to menopause?
- > What "T" are they talking about?
- Total T >280 ng/dl are not sufficiently sensitive to rule out hypogonadism; levels >150 ng/dl are not specific (Anawalt 2012)

## Is andropause real?

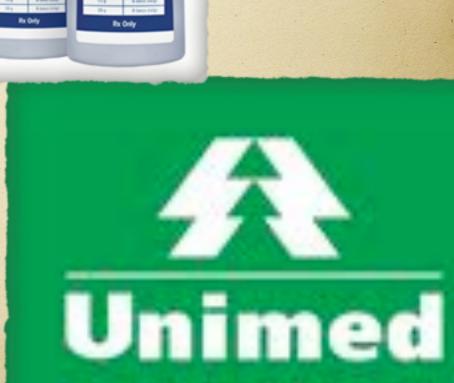


- > Aging is real...
- Are low androgens a problem? Which ones? Do their levels predict problems?
- > What androgens are being measured, in what form, and by what method?
- Is androgen supplementation necessary? safe? effective?

## Manufacturing Andropause

- Unimed is spending a lot to promote andropause and "low T"
- Drives off-label sales of AndroGel<sup>TM</sup> (FDA approved in 2000 for other uses)
- Expert panels, ads promoting the disease, ghost-written articles, the usual tricks

Ref: New Yorker 2002; July 29



AndroGe

Rx Only

AndroG

SOLVAY

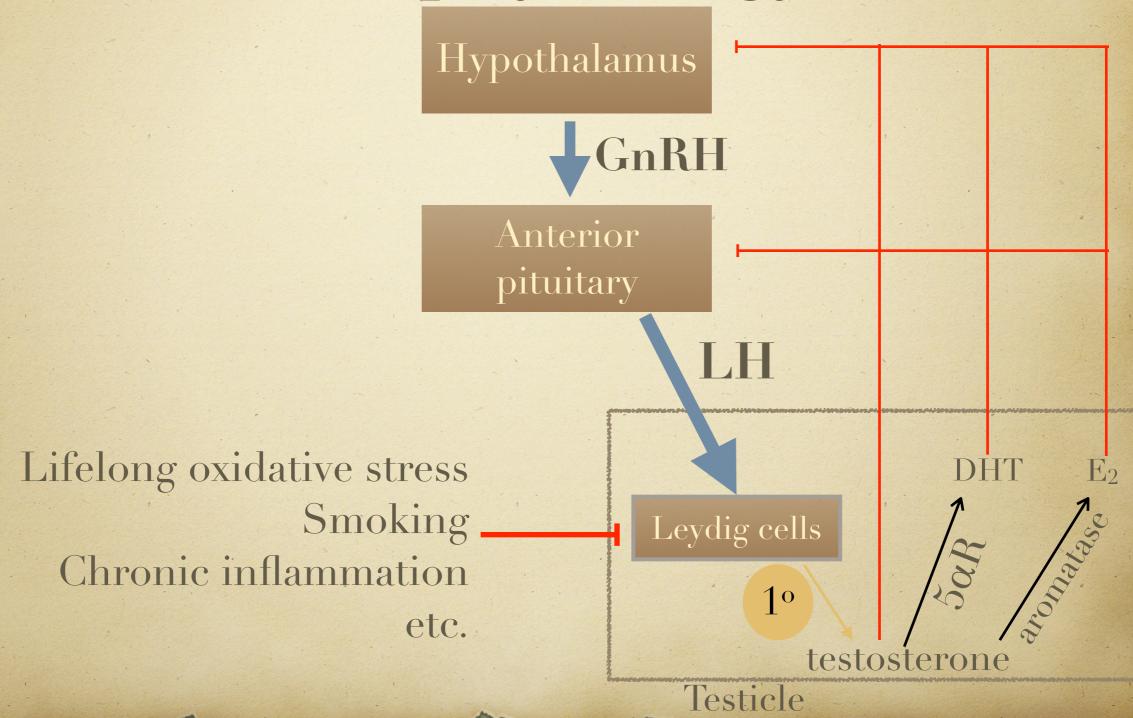
## MMAS: PADAM

- > PADAM definition they used: 3+ of 8 symptoms present (MMAS questionnaire), total T <400 ng/dl, FT <8.91 ng/dl (if total T 200–400 ng/dl)</p>
- N = 1691 men in Mass., mostly white, 102 cases (6%) PADAM at baseline
- N = 1087, 134 cases (12.3%) PADAM 8.8 yr later on average
- > Ref: Araujo 2004

#### Three Patterns of Hypogonadism

	Etiology	Total T	LH	Symptoms
Eugonadal	Normal state	Normal	Normal	Mild, common (!!)
Primary	Age-related Leydig cell failure	Low (<300 ng/dl)	Elevated (>9.4 U/L)	Moderate- to-Severe
Secondary	Obesity, metabolic syndrome	Low (<300 ng/dl)	Normal	Mild (particularly sexual)
Compensated	Unknown, age- related ("subclinical hypoandrogenism")	Normal	Elevated	Mild (mainly physical)

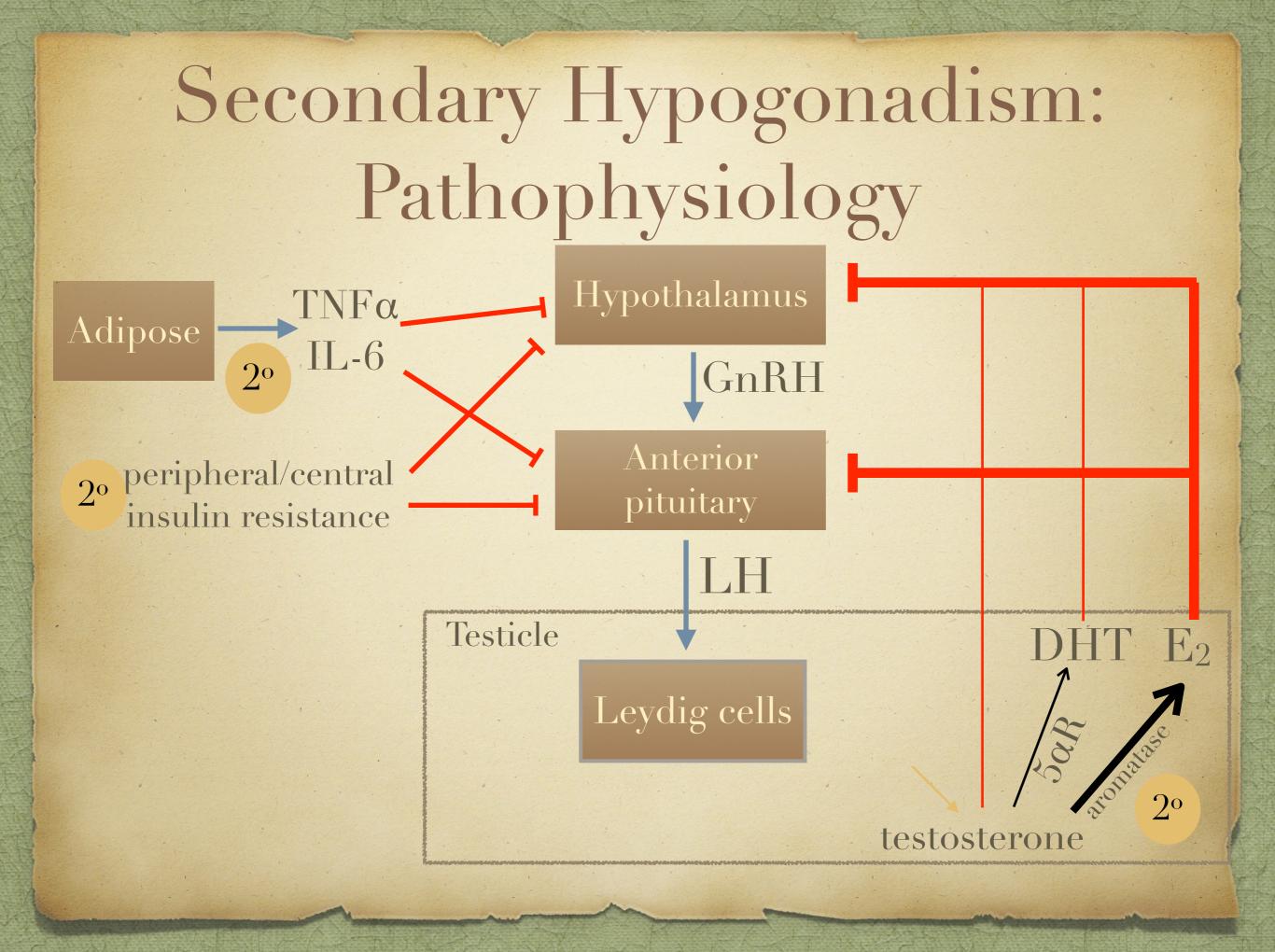
#### Primary Hypogonadism: Pathophysiology



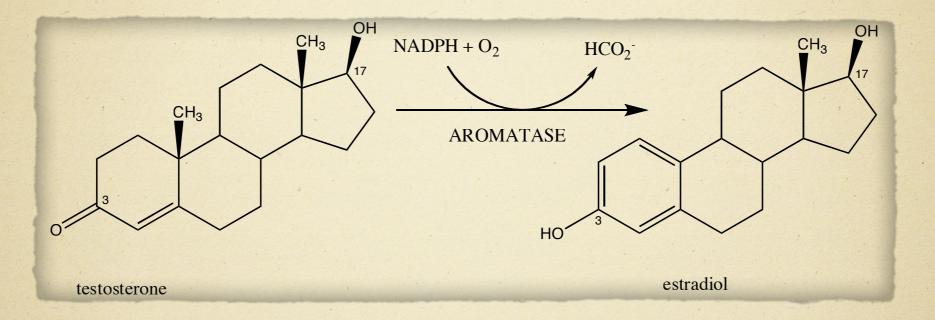
## Primary Hypogonadism

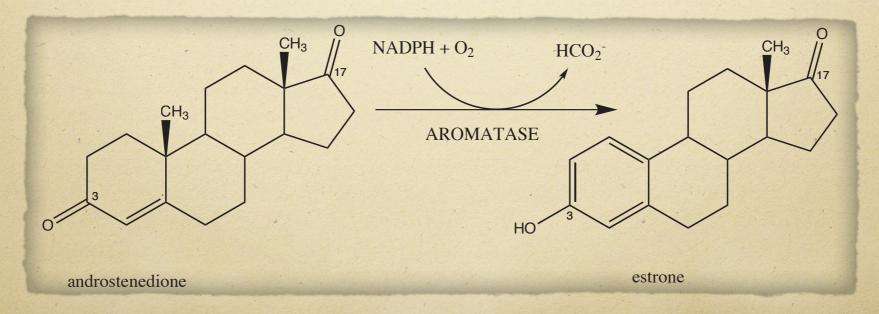
Decreased Leydig cell function
Decreased T synthesis and secretion
Increased FSH, LH and GnRH
Decreased estrogen! (Finkelstein 2013)

Etiologies: aging, medical castration, trauma, Klinefelter syndrome, chemo, alcoholism, heavy metals, orchitis



#### Aromatization





## Secondary Hypogonadism

- \* "Hypogonadotropic Hypogonadism"
  > Pituitary: serum FSH/LH low; GnRH normal
  > Hypothalamic (tertiary): serum FSH/LH and GnRH low
- > Etiologies: obesity, metabolic syndrome
  - Rare: trauma, metastatic cancer, radiation, other severe chronic diseases, tumors compressing pituitary/hypothalamus

# Compensated hypogonadism

> Relatively newly detected

Similar to "subclinical hypothyroidism"

> Big questions:

> Will it progress?

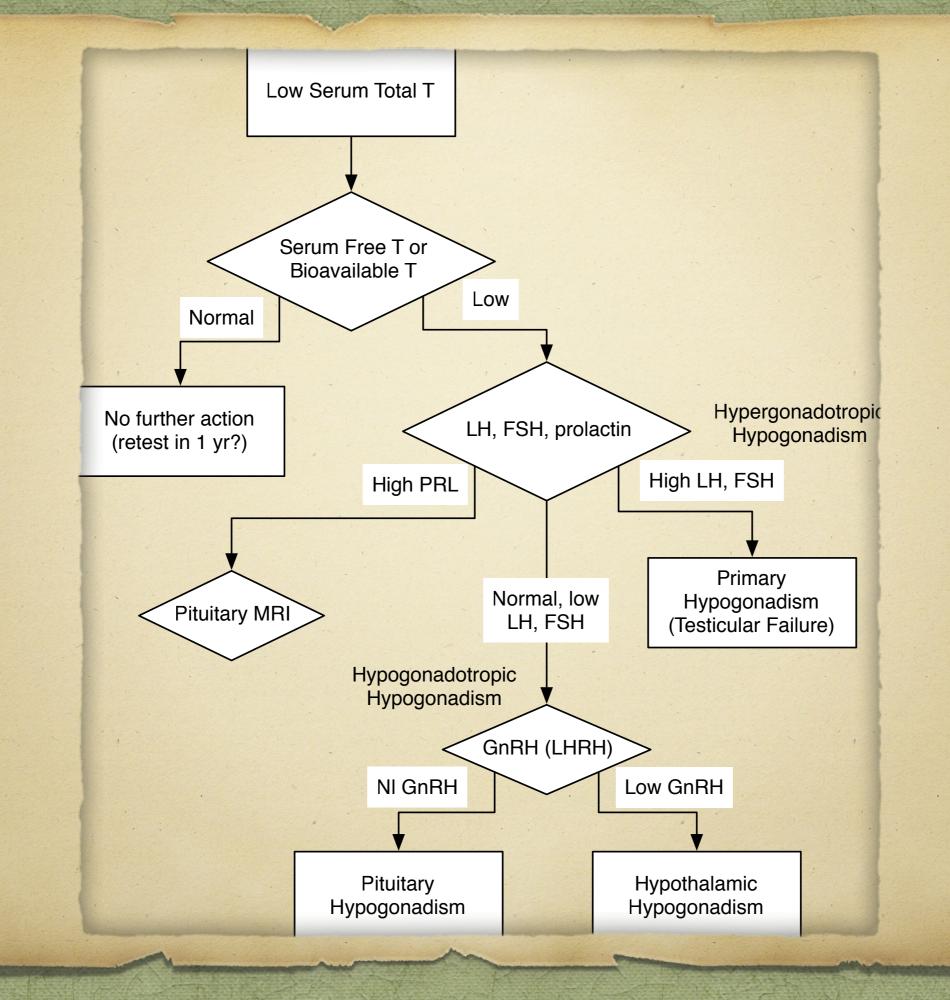
Should it be treated?

#### EMAS: Frequency of Problems

	%	Average T: Total (ng/dl), Free (pg/dl)	Average E <sub>2</sub> (ng/dl)
Eugonadal	76%	Normal	Normal
Primary	2%	Low (<300 ng/dl)	Elevated (>9.4 U/L)
Secondary	12%	Low	Normal
Compensated	10%	Normal	Elevated
			Ref: Taiar 2010

#### T Measurement Tips

- > Peak levels 7–10 am
- > Avoid carbs before test (high insulin -> low SHBG)
- > Heavy etoh use lowers T
- Smokers have 5–15% higher free, total T
- > Repeat all low levels (30% nl on repeat)
- Free T is hard to measure (~2% of total) but now feasible (using proper methodologies)



#### **Treatment and Prevention**

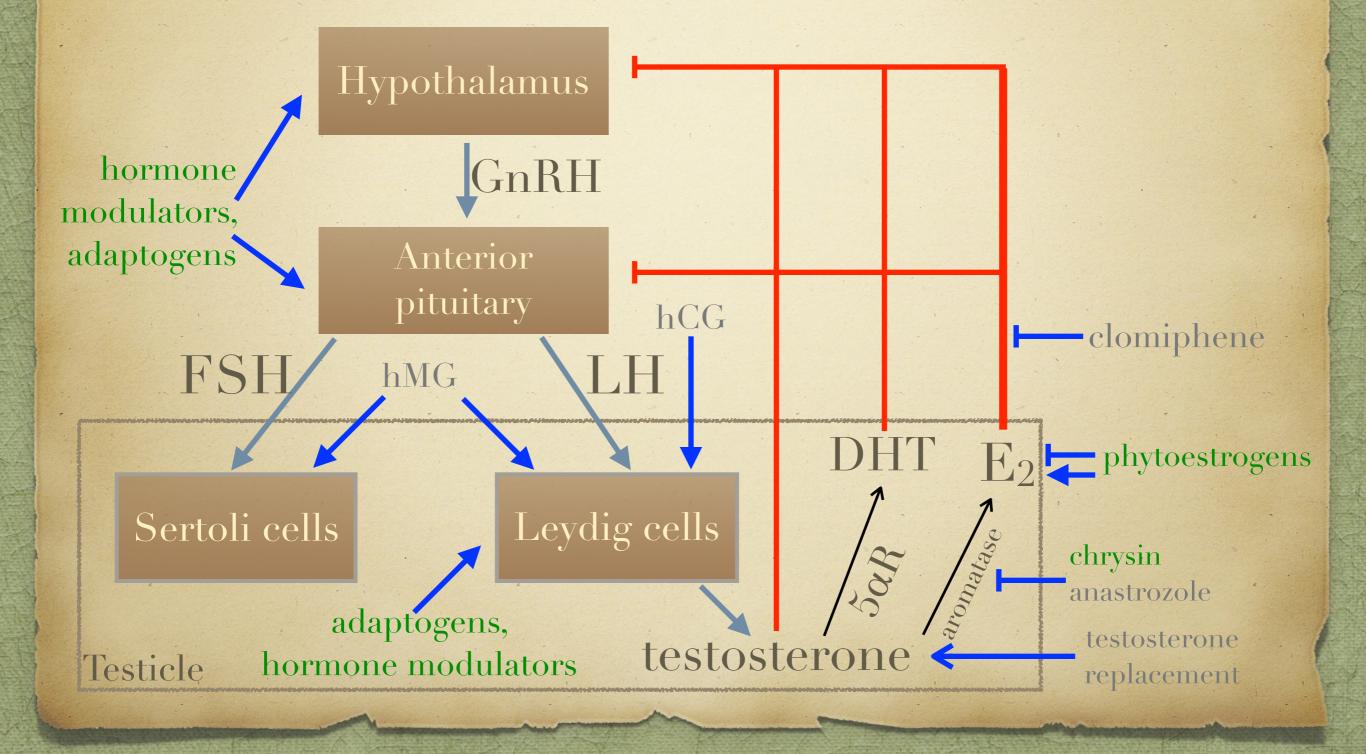
# Summary: Herbal

Form	Treatment	
Primary	Redox modulators; adaptogens; phytoestrogens	
Secondary	Insulin sensitizers; pituitary modulators; hormone modulators; phytoestrogens; adaptogens	
Tertiary	Pituitary modulators; hormone modulators; adaptogens	
Compensated	Insulin sensitizers; adaptogens	

## Summary: Non-Herbal

Form	Treatment	
Primary	Whole-foods diet, redox modulators Androgen replacement	
Secondary	Combat metabolic syndrome clomiphene, hCG, hMG, aromatase inhibitors	
Tertiary	Recombinant GnRH, hCG, hMG	
Compensated	Unknown (lifestyle change mostly)	

#### Mechanisms of Action



### Herbal Androgens?

- No herb has credibly been shown to elevate total T levels (and we probably don't want or need to)
- > Very little in the way of human trials showing free T elevation
- > Highly doubtful there are "phytoandrogens"

## Discredited Androgenic Herbs

> Epimedium spp (horny goat weed)—no human research

> Tribulus terrestris (caltrop vine)

> Trigonella foenum-graecum (fenugreek)

#### Tribulus terrestris

- > Negative trial in young men (Neychev 2005)
- > Negative trial in combo formula in young men (Brown 2000)
- Solution Not phytoestrogenic or 5α-reductase inhibiting in combo formula (Brown 2001)
- Did not increase urine testosterone/epitestosterone levels in athletes (Rogerson 2007); also didn't cause gains in strength or lean muscle mass
- > Negative ED trial (Santos 2014)
- Conclusion: Androgenic reputation of this herb is marketing hype
- > What it does help: low libido in older men and women (Iacono 2012; Postigo 2012)



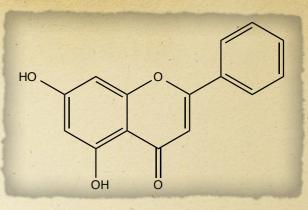
## Trigonella foenum-graecum

- Trial in 60 healthy men found no effect on serum T but did increase libido combined with Zn<sup>2+</sup>, caltrop vine (Steels 2011)
- 500 mg of extract increased total, bioavail T in one small study in men after 8 wk (Wilborn 2010)
- Recent trial in younger women found 600 mg/d extract increased free T, E2 and libido (Rao 2015)

## Natural Aromatase Inhibitors

- Chrysin\* 2–3 g bid
- *> Urtica dioica* root 1–2 g bid
- Zinc\*\* (elemental) 50 mg bid (decrease to 50 mg qd if it works)
- > Vit C\*\* 1 g qid and up
  - \* Efficacy poorly/minimally shown at lower doses \*\* No human research





> Low-dose (20 mg) trial in humans show no effect

> Higher doses (300 mg, 625 mg, combined with herbs) start to raise free T, definitely see aromatization so no increased total T (Brown 2001a and b)

Urtica dioica (stinging nettle) root

Photo (c) 2015 Yarnell

#### Pituitary Hormone Modulators

*Vitex agnuscastus* (chaste tree)

Photo (c) 2015 Yarnell

Paeonia californica (peony)





#### *racemosa* (black cohosh)



#### Nuphar polysepalum (yellow pond lily)



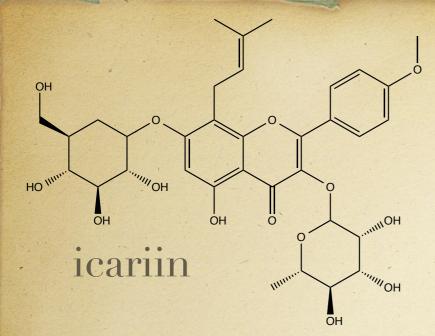
#### **General Hormone Modulators**

Smilax rotundifolia (sarsaparilla)

### Polygonum multiflorum

Photo (c) 2015 Yarnell

Epimedium grandiflorum (horny goat weed)



Epimedium spp

- > Lots of suggestive, intriguing research in rodents
- Icariin compound shows testosterone mimetic properties in rats (Zhang 2006)
- Extract and icariin decrease CRH and increases ACTH production during steroid therapy in rats, while increasing total T (An 2015)

### Male Adaptogens



## Withania somnifera

> No human research on androgenic effects

Classic example of lack of utility of rodent studies: rat study found ashwagandha extract decreased libido and increased ED (Ilayperuma 2002)

### Panax ginseng (Asian ginseng)

## Panax ginseng

- Extract didn't raise T in young men in a small trial (Kang 2002)
- Small increase in free and total T, DHT, and LH/ FSH in infertile men (Salvati 1996)

# Anti-Androgenic Herbs

- Solution Solution
- Serenoa repens (saw palmetto) fruit: very mild 5αreductase inhibitor

## Estrogen Metabolism

Soal: serum total estrogen level 10–30 ng/ml

Stassica vegetables and glucosinolates: promote estrogen metabolism down healthier 2hydroxylation pathway

> Reduce/eliminate alcohol

> Liver-stimulating herbs/bitters?

# Glossary

5αR = 5α-reductase DHT = dihydrotestosterone EMAS = European Male Aging Study FSH = follicle-stimulating hormone FT = free testosterone GH = growth hormone hCG = human chorionic gonatotropic hMG = human menopausal gonadotropins IGF = insulin-like growth factor LH = luteinizing hormone MMAS = Massachusetts Male Aging Study T = testosterone

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