Age-Related Endocrine Changes and the Role of Supplementation with GH, DHEA, and Melatonin

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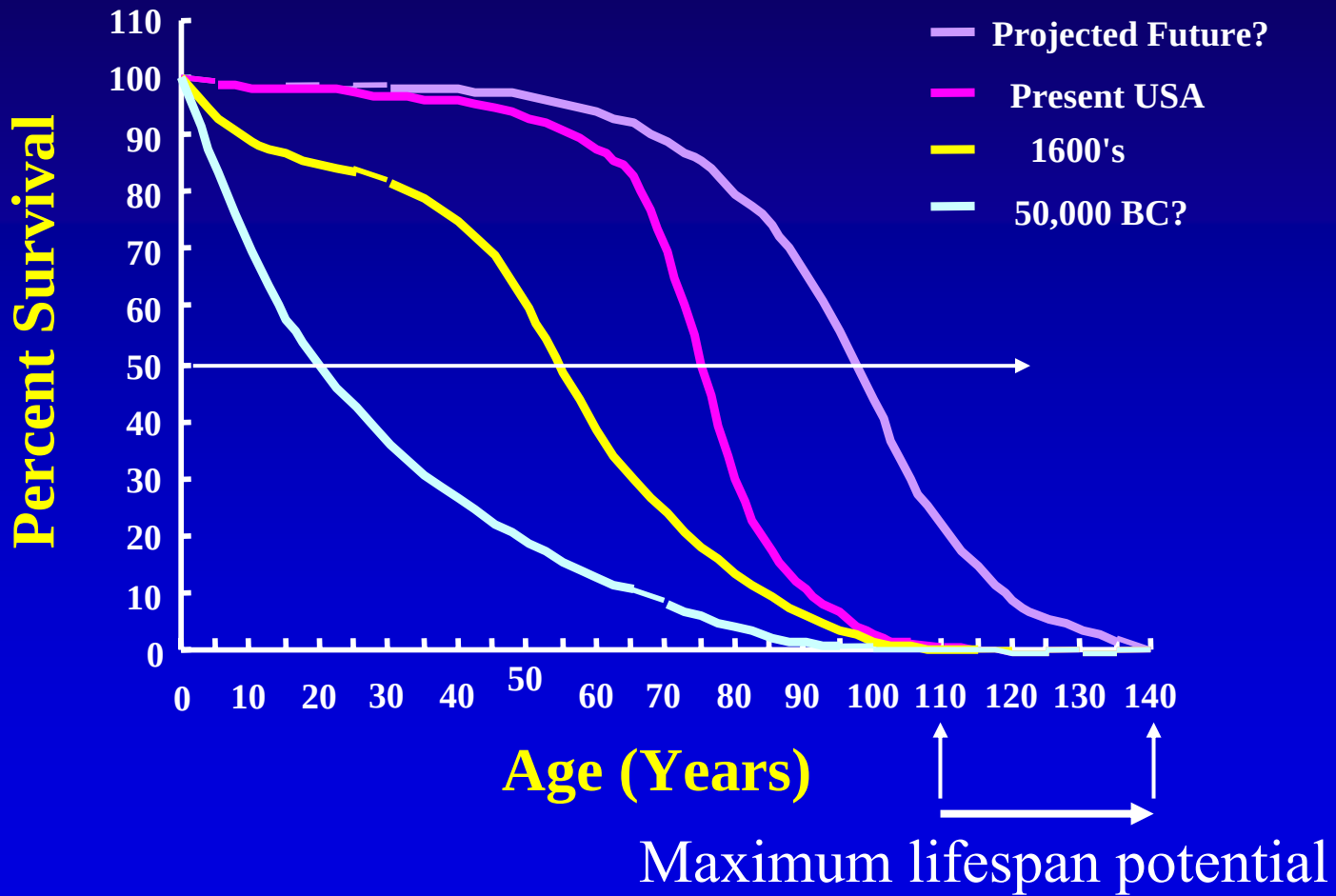
***Dietary Supplement Use in the Elderly*, 1/14/2003**

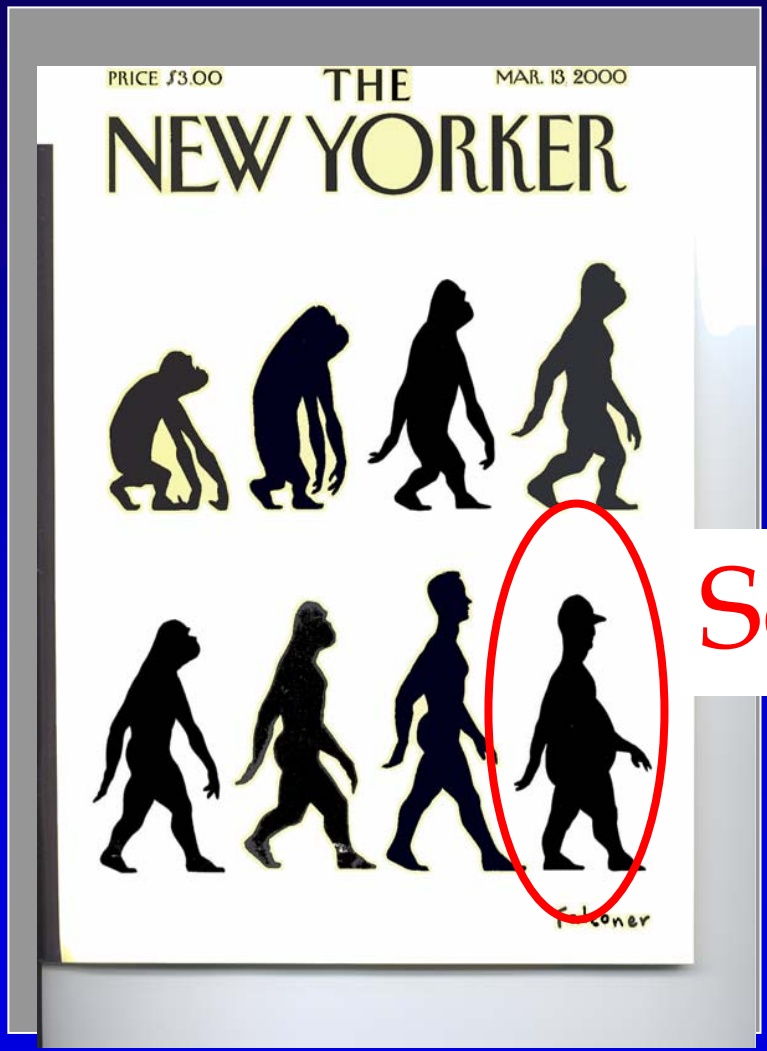
Dietary Supplements: DSHEA Definition

- Product intended to supplement the diet
- Contains one or more of the following:
  - A vitamin
  - A mineral
  - An herb or other botanical (not tobacco)
  - An amino acid
  - Any other dietary substance
- For oral intake as a concentrate, metabolite, extract, constituent, or combination

Rectangularization vs Extension of the Human Survival Curve



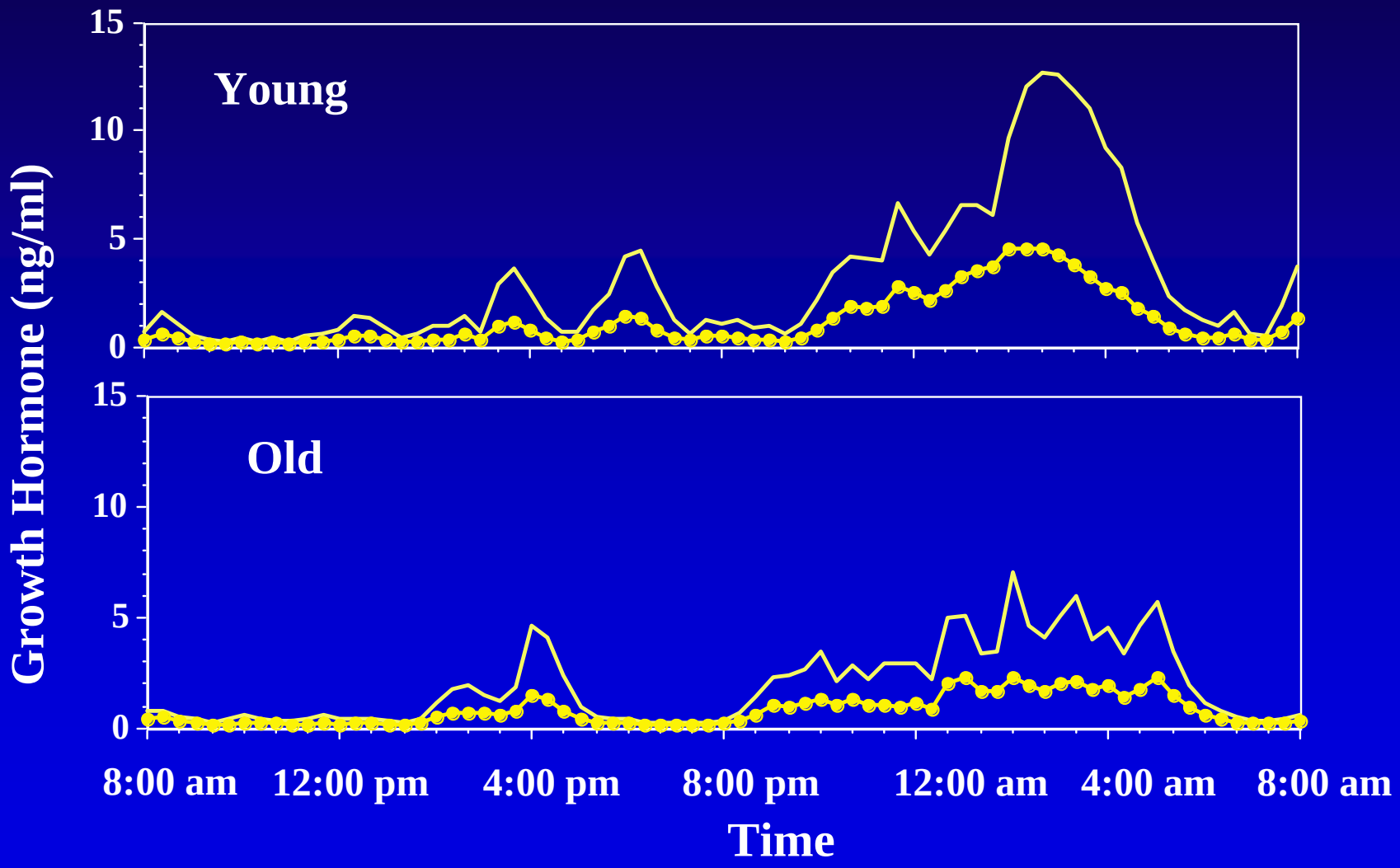
To What Extent are the Observed Changes in Body Composition and Function with Aging Due to Decreases in GH and IGF-I?



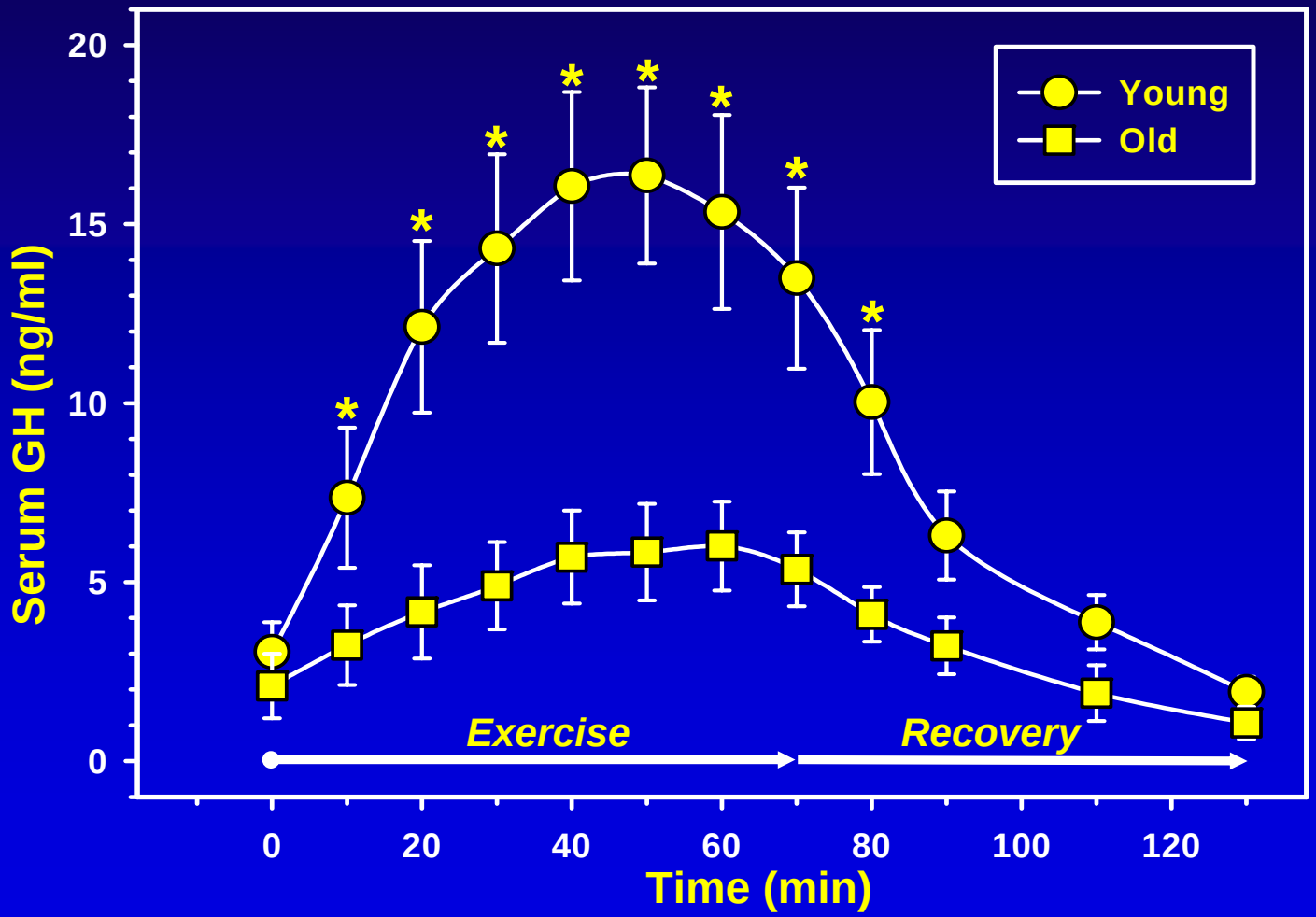
Somatopause?

Courtesy of Michael Thorner, MD

24 Hour GH Secretory Profiles: Means (+ SD's) at 20 min Intervals in 9 Young and 11 Healthy Old Men

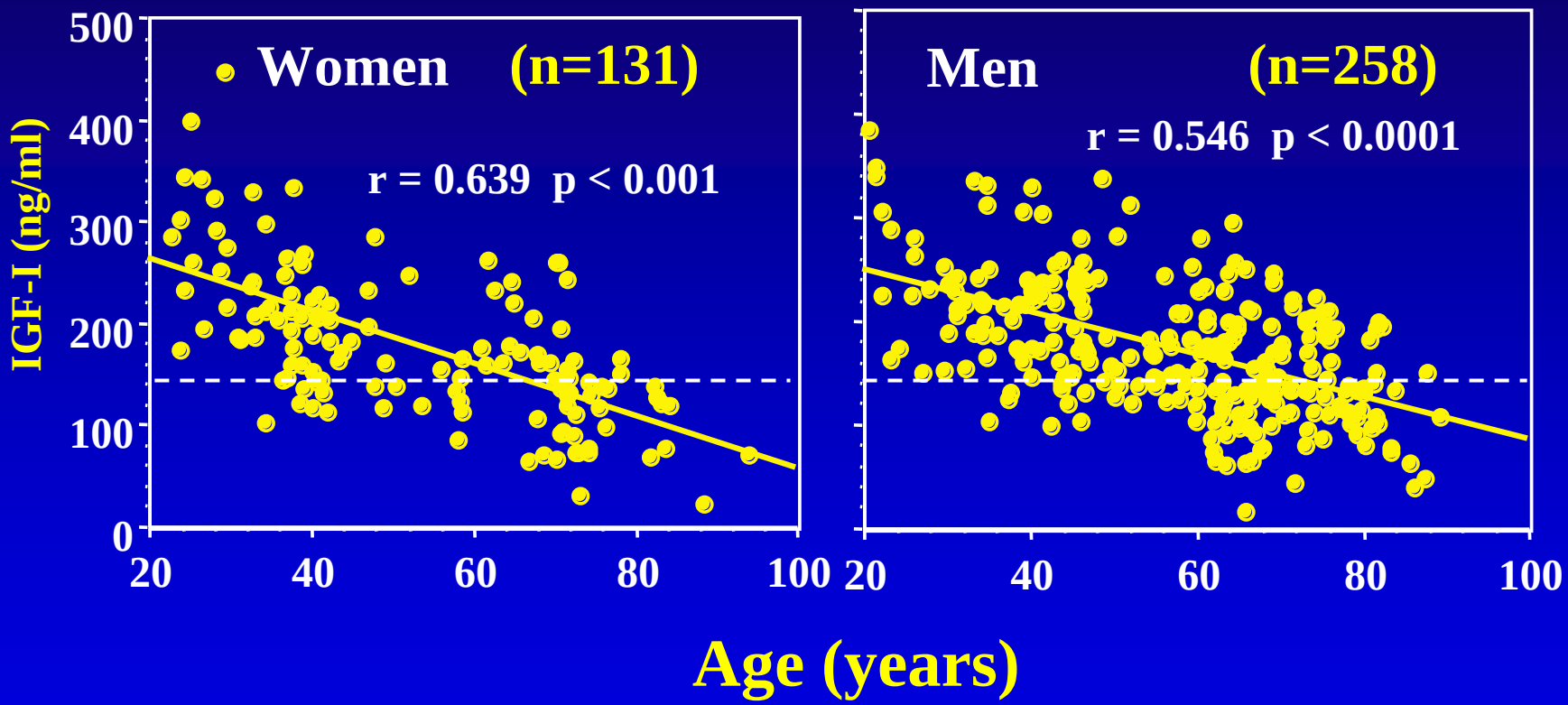


Age-Related Blunting of Serum GH in Response to a Single Bout of Resistive Exercise in Healthy Men

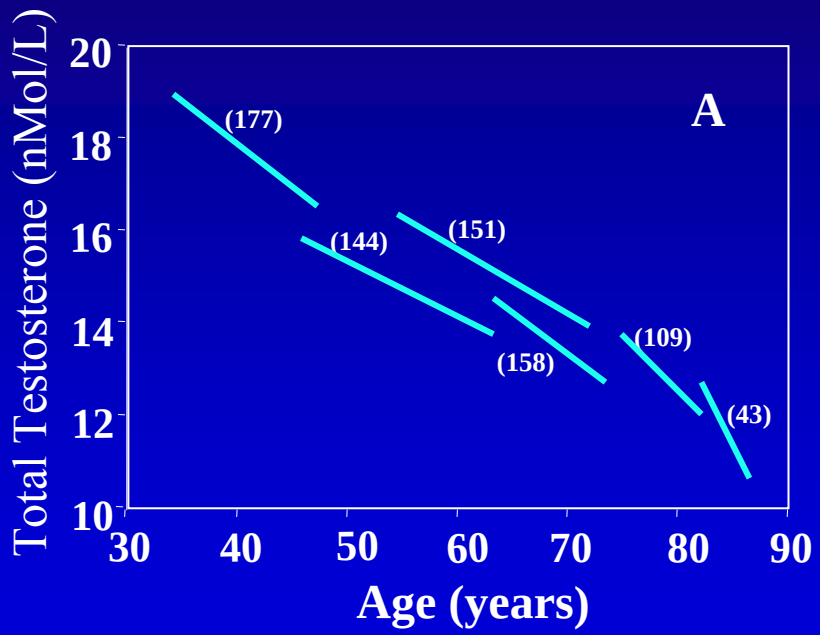


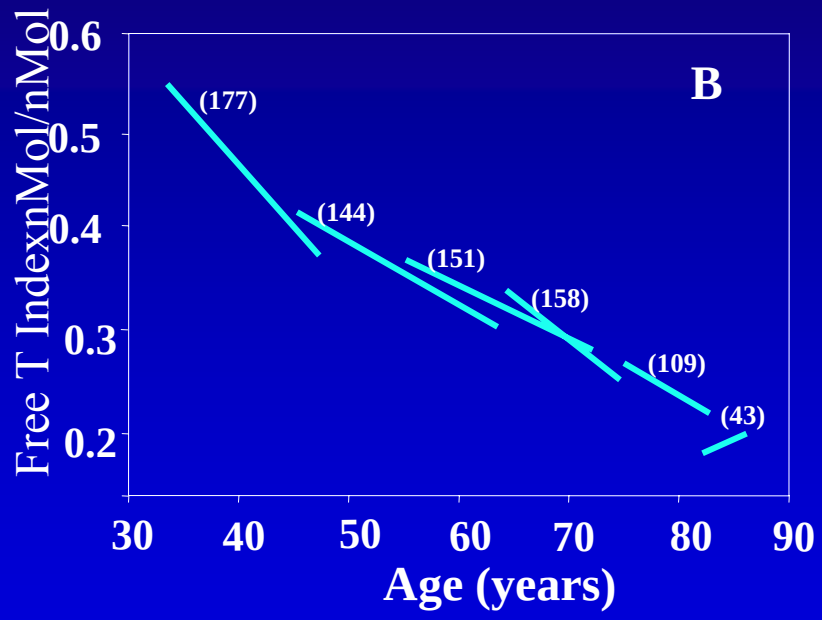
(Marcell, et al., 1999)

Serum IGF-I Levels vs. Age in Healthy Women and Men in the BLSA

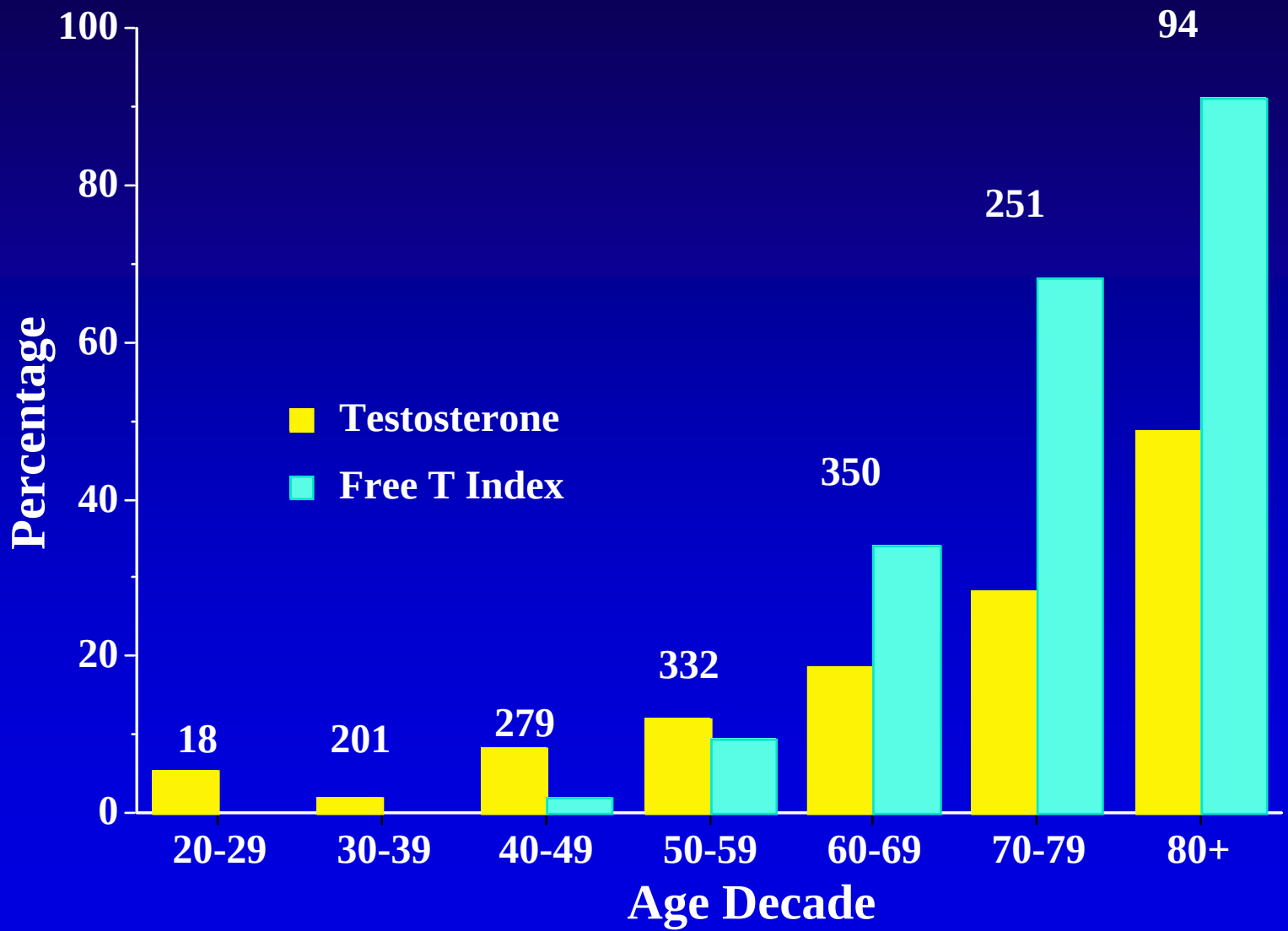


Linear Segment Plots by Decade; Longitudinal Effects of Aging on Date-adjusted T and Free T Index.





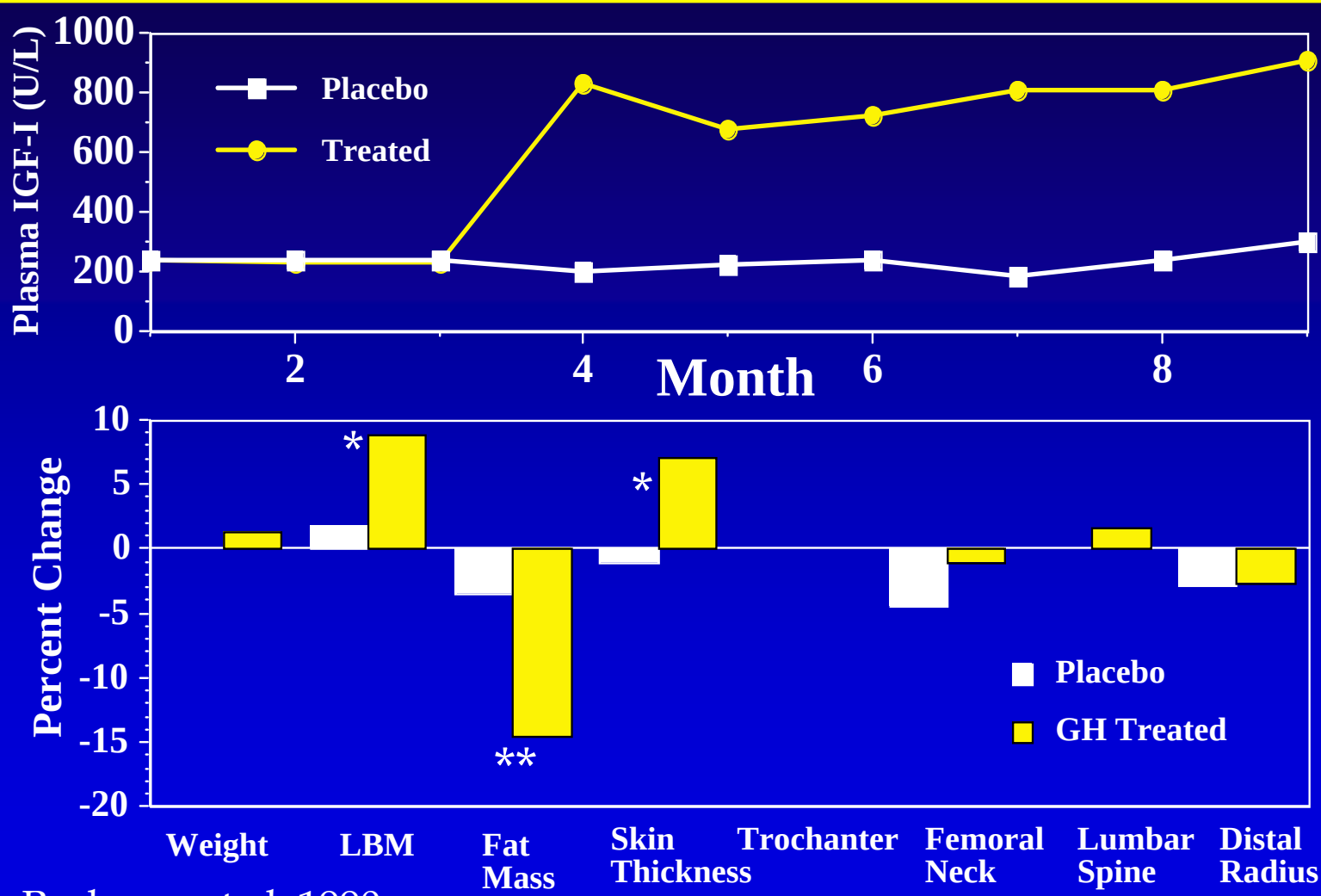
Percentage of Group Hypogonadal by Decade Using Total vs Free T Index Criteria (n in group above bars)



Similarities of Changes in Body Composition, Muscle Strength, Aerobic Capacity and Metabolic Variables with Aging and in Hormone Deficiency/Excess States

	Aging	Low GH	Low T or DHEA	High Cortisol	Low E2
Lean Body Mass Muscle Strength	↓	↓	↓	↓	–
Aerobic Capacity	↓	↓	↓	↓	–
Percent Body Fat	↑	↑	↑	↑	↑
Total and LDL Cholesterol	↑	↑	↑	↑	↑
Insulin sensitivity Glucose tolerance	↓	↓	↓	↓	–

Effects of hGH Treatment on Body Composition, Skin Thickness and BMD in Men >60 Years of Age



Rudman, et al, 1990

The plural of anecdote is not evidence

Study Design - Subjects and Interventions

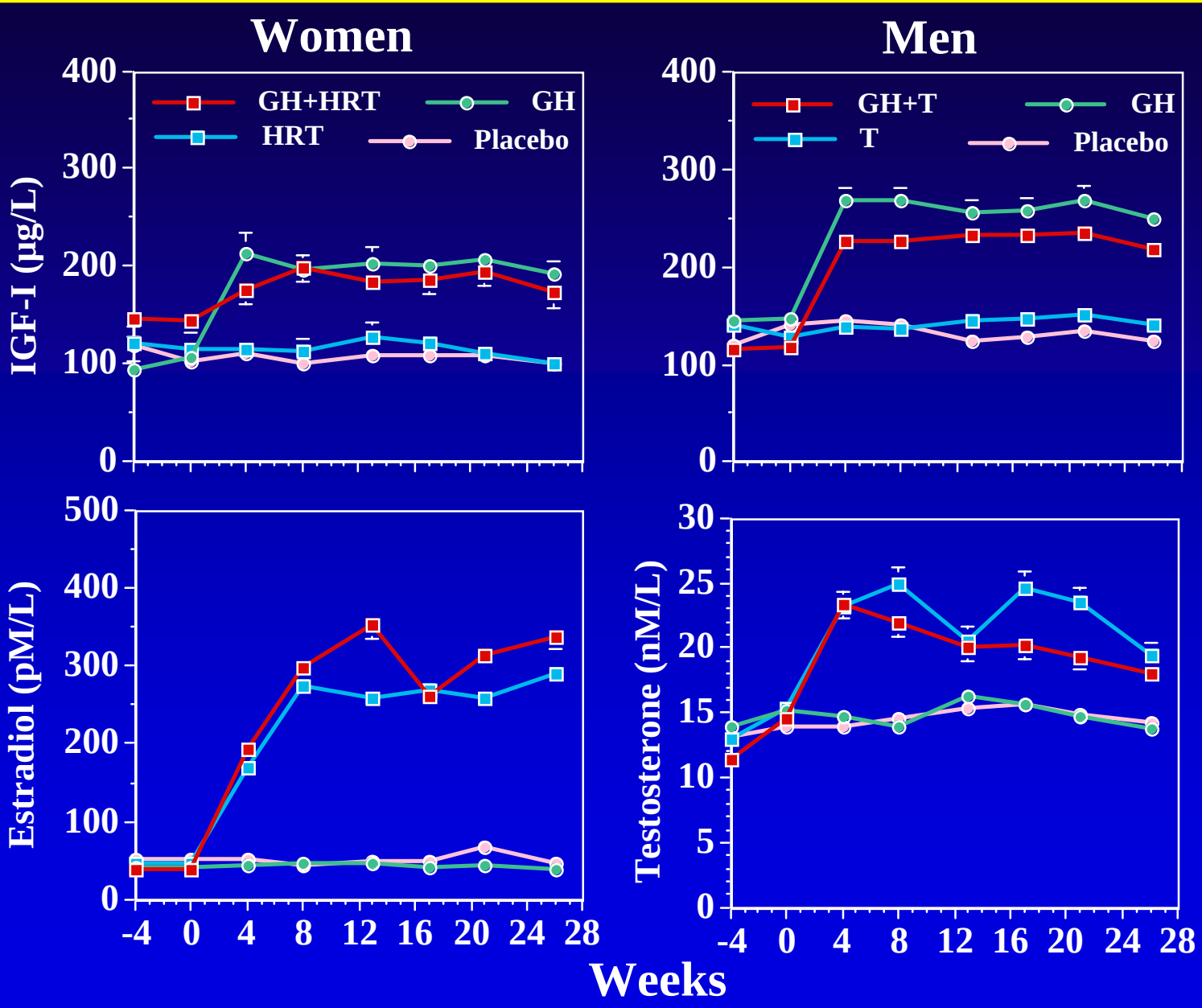
Subjects: Healthy women (n=53) and men (n=72), ages 65-88 y (mean, 72 y) with baseline age-related reductions in serum IGF-I (<230 ng/dl) and low to low normal gonadal steroid levels (women had had no exogenous estrogens for at least 3 months; men had total T levels < 470 ng/dl).

Study Design: Double-masked, placebo-controlled, randomized, non cross-over, 2x2 factorial

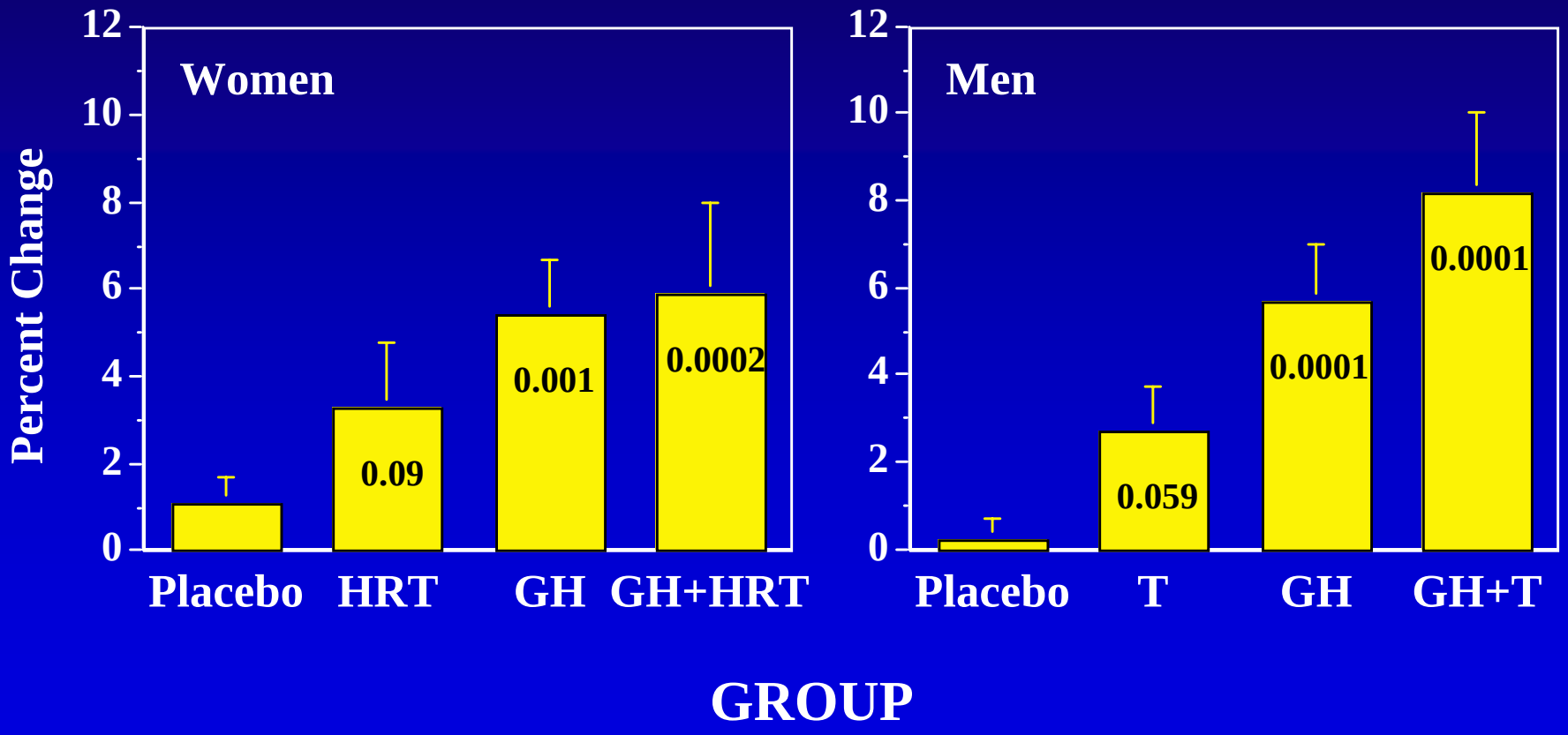
Women	Men
GH + HRT Placebo	GH + T Placebo
GH Placebo + HRT	GH Placebo + T
GH + HRT	GH + T
GH Placebo + HRT Placebo	GH Placebo + T Placebo

GH = rhGH 20 µg/kg s.c. 3x/wk in the p.m.
HRT = 100 µg/day E_2 patch + 2.5 mg/day MPA p.o.
T = 100 mg Testosterone enanthate i.m. every 2 wk

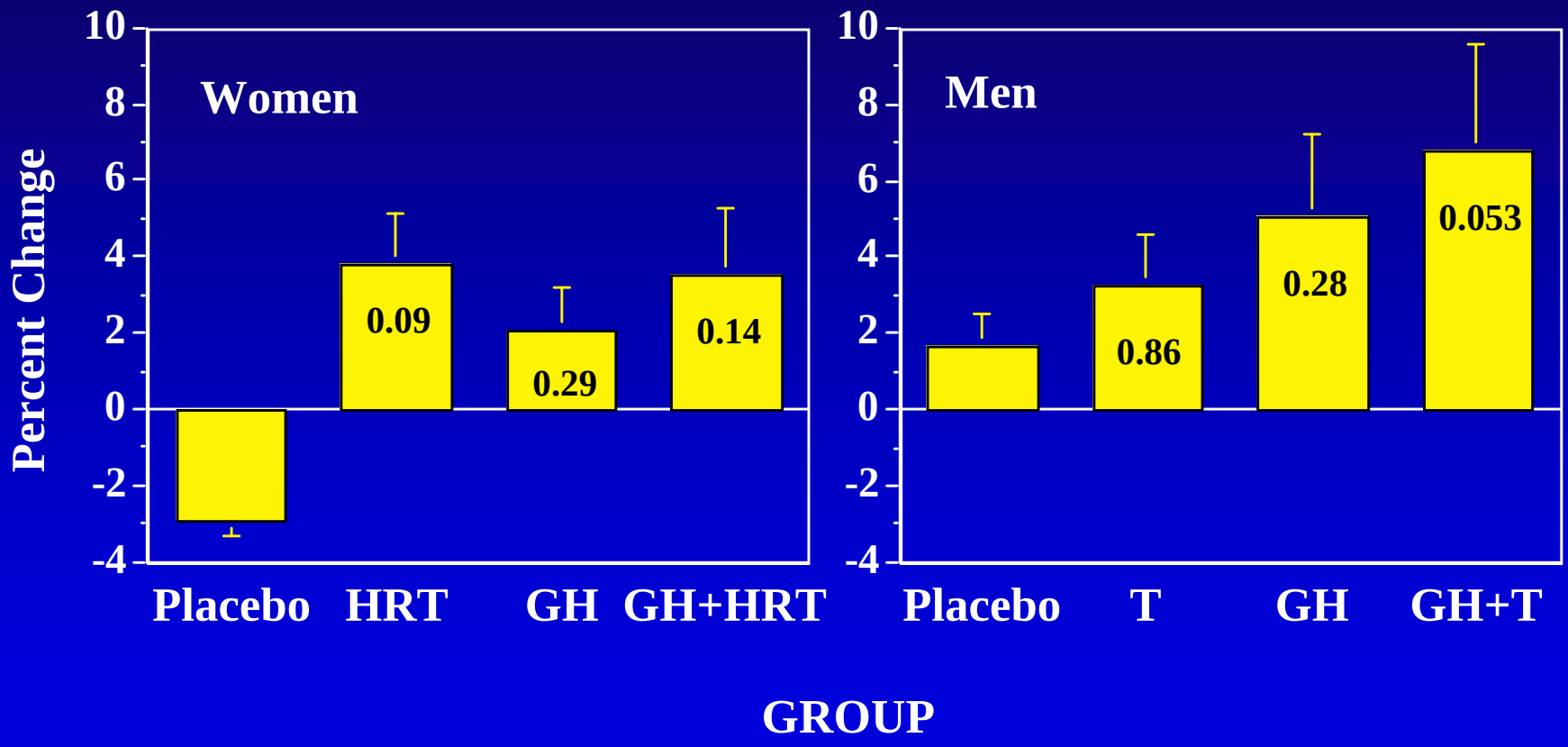
Hormone Levels in Men and Women Before and During Treatment



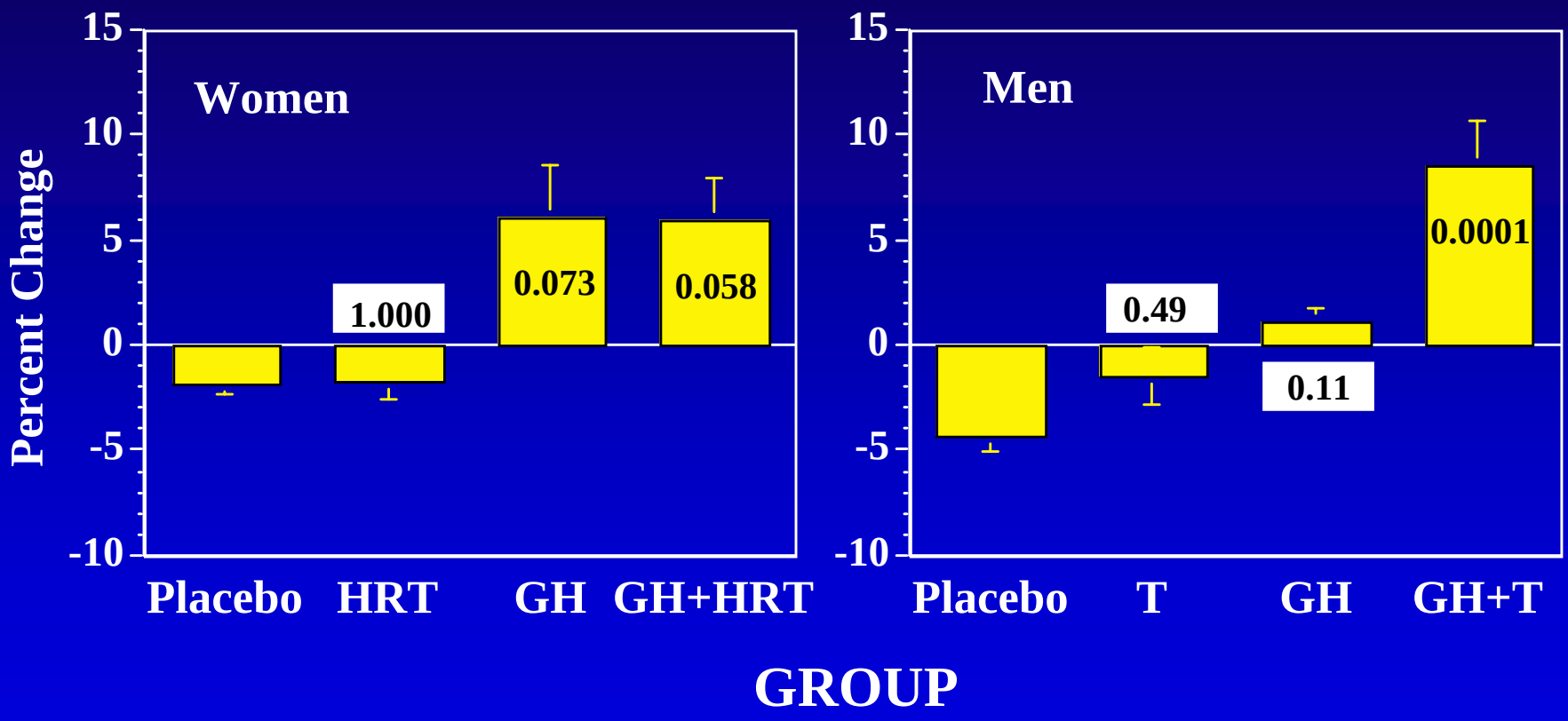
Effects of Hormone Administration on Lean Body Mass (DEXA) in Healthy Elderly Women and Men



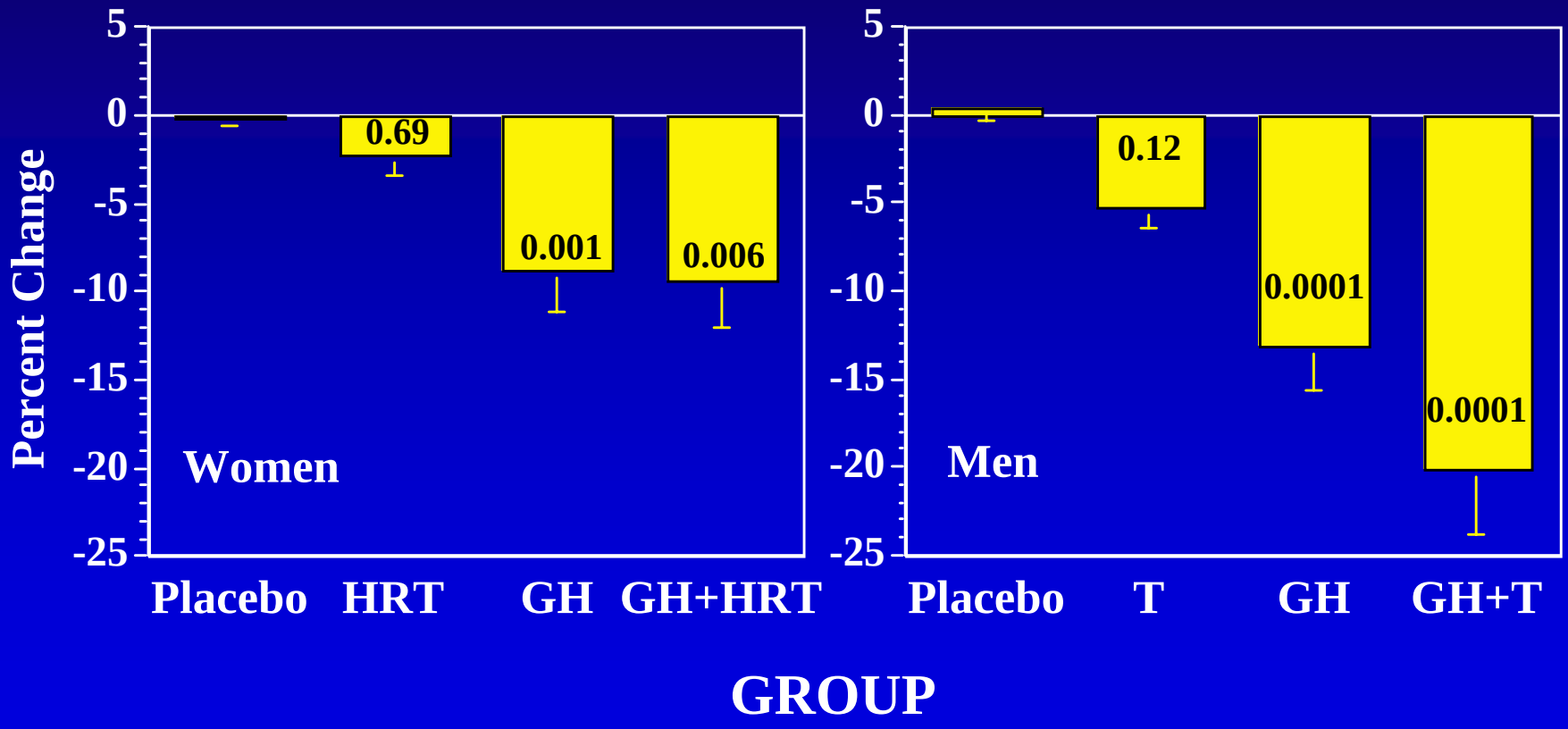
Effects of Hormone Administration on Total Body Strength in Healthy Elderly Women and Men



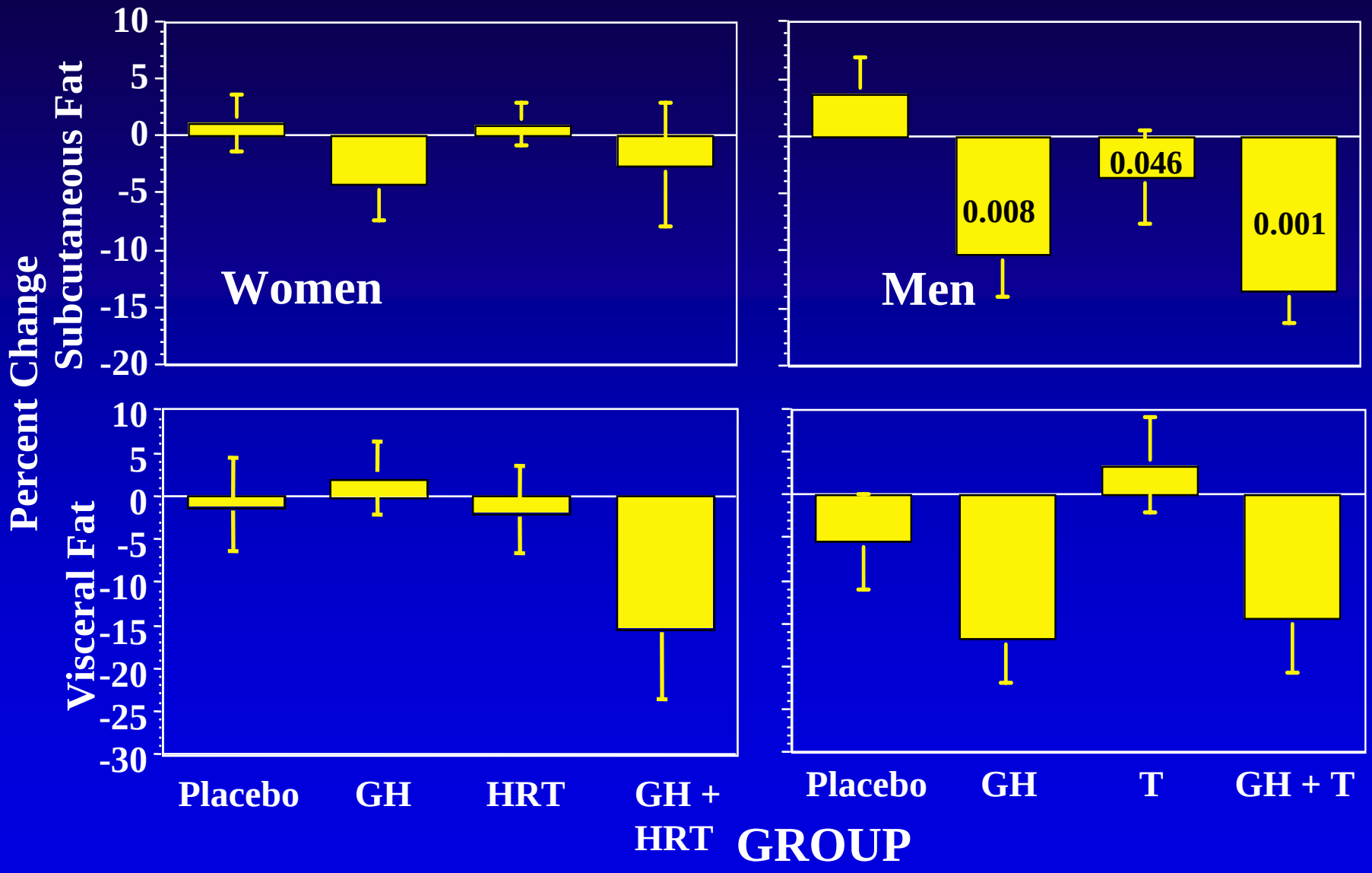
Effects of Hormones on Maximum Aerobic Capacity (ml O_2/min/kg BW) in Healthy Elderly Women and Men



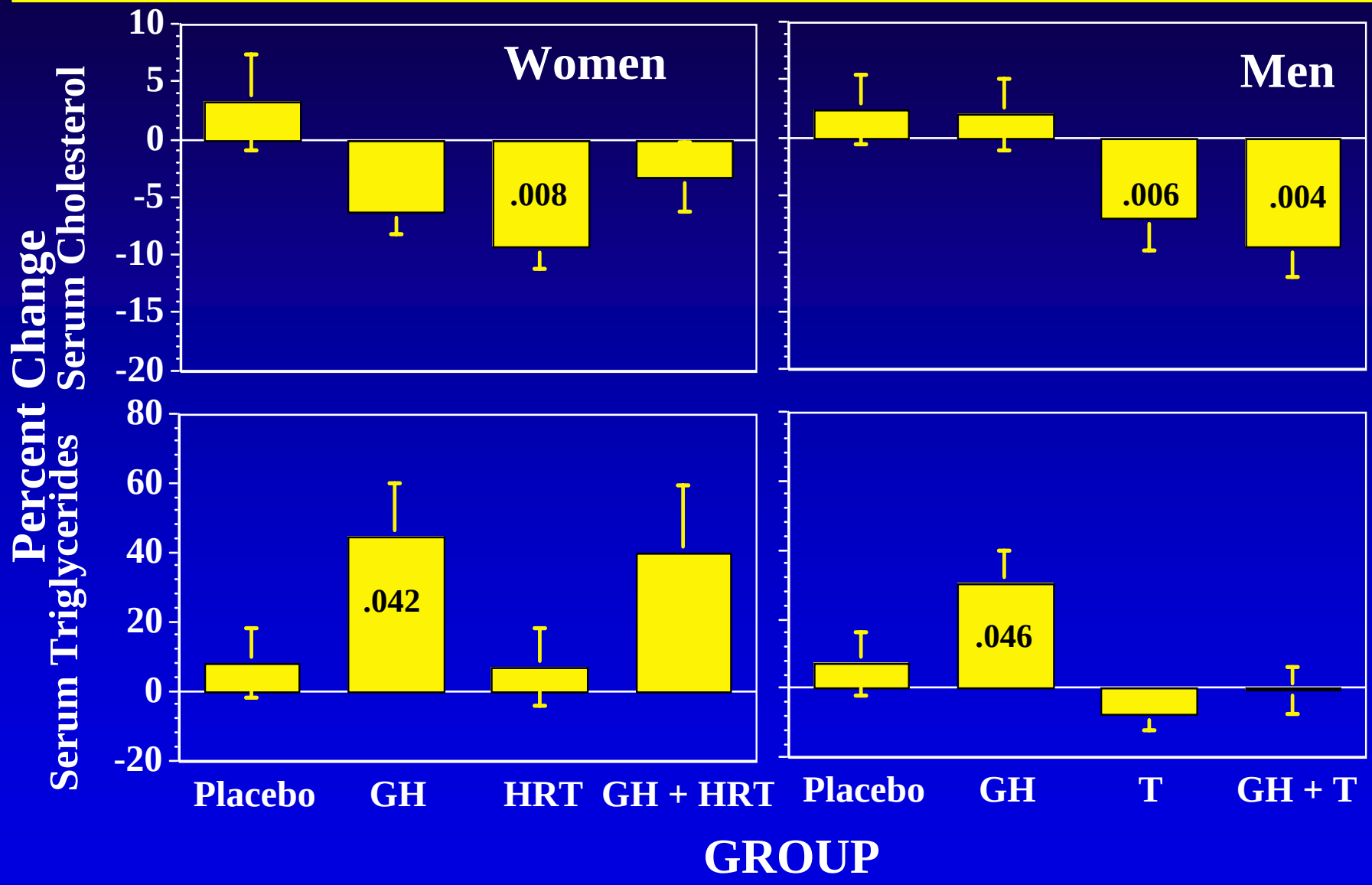
Effects of Hormone Administration on Body Fat (DEXA) in Healthy Elderly Women and Men



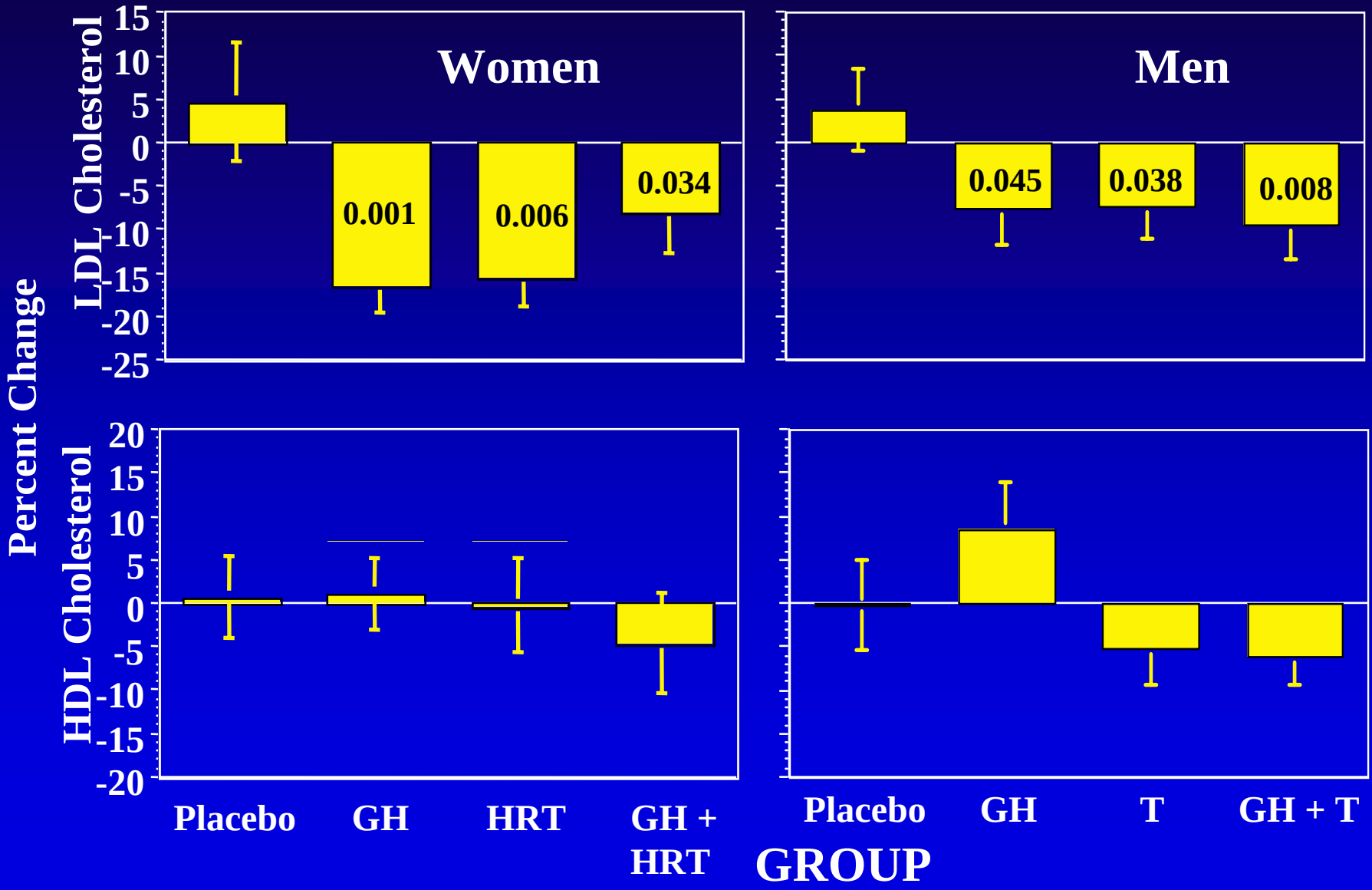
Effects of Hormone Administration on Change in Subcutaneous and Visceral Abdominal Fat (MRI) in Healthy Elderly Women and Men



Effects of Hormone Administration on Serum Levels of Total Cholesterol and Triglycerides in Healthy Elderly Women and Men



Effects of Hormone Administration on Serum Levels of LDL and HDL Cholesterol in Healthy Elderly Women and Men



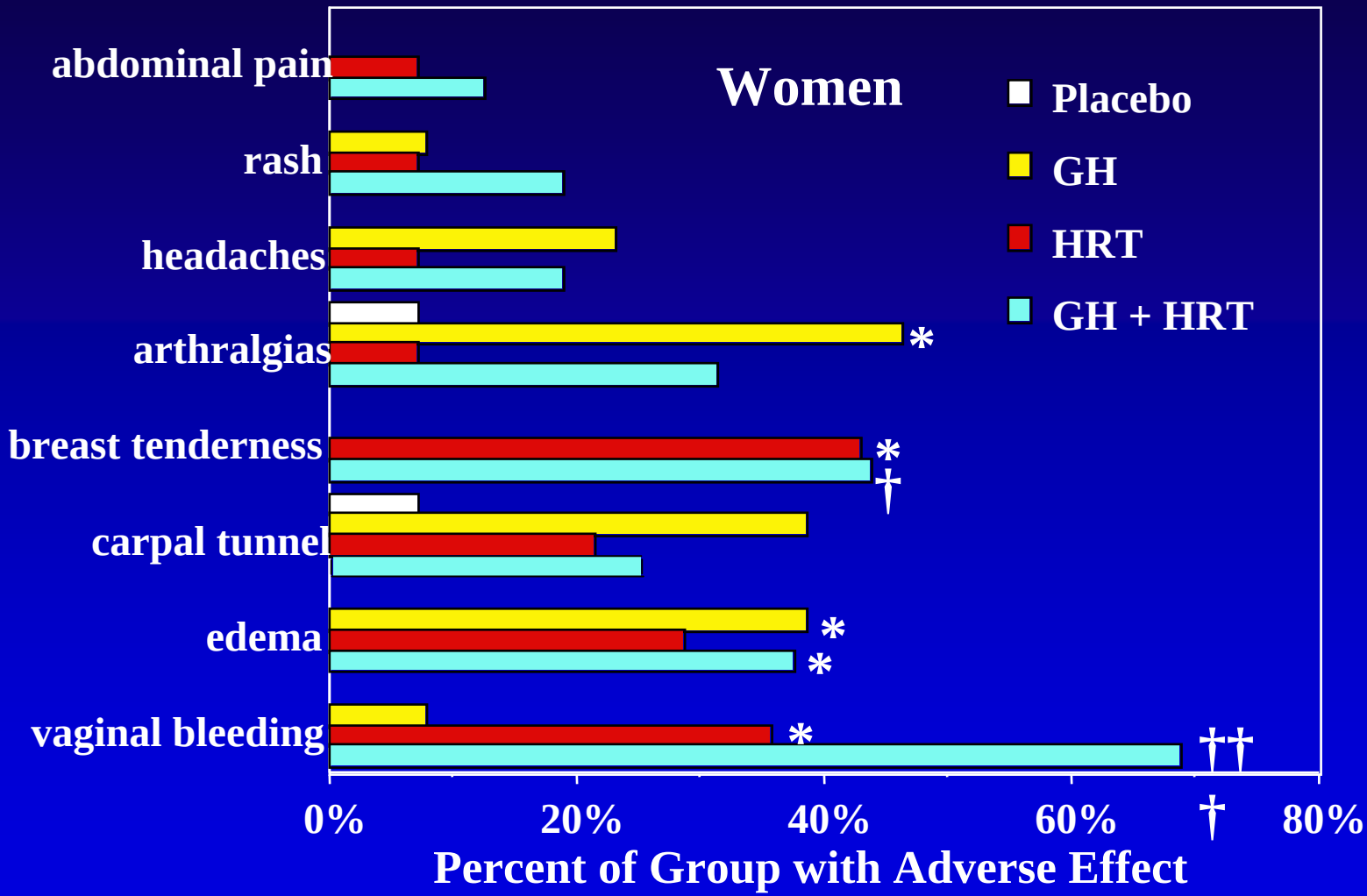
Summary I

- GH (and testosterone) can:
  - Increase lean body mass
  - Increase muscle strength
  - Increase exercise capacity
  - Decrease body fat
- Combination of GH and sex steroids
  - Effects of GH and testosterone tend to be additive
  - Female hormones (HRT) and GH are not additive

Potential Risks of Hormone Treatments

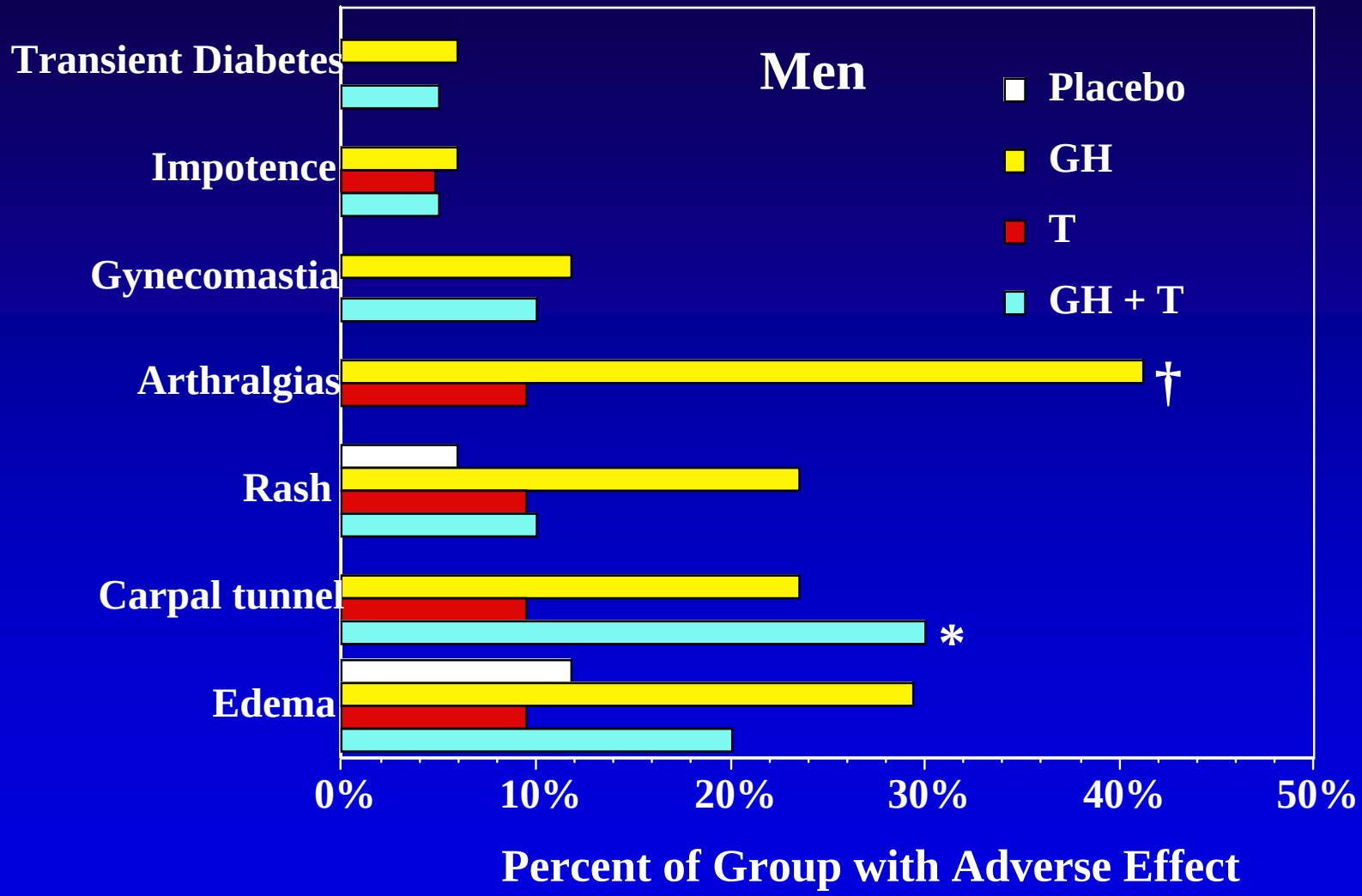
- Growth Hormone
  - Arthritis
  - Carpal tunnel syndrome
  - Fluid retention
  - Hypertension
  - Diabetes
  - Cancers (?)
  - Accelerated Aging (?)
- Female HRT
  - Mastodynia
  - Vaginal Bleeding
  - Thrombosis
  - Cholelithiasis
  - Breast Cancer
- Testosterone
  - Prostate
    - Hyperplasia (BPH)
    - Cancer
  - Coronary Heart Disease
    - Decreased HDL
    - Increased LDL
  - Polycythemia
  - Minor
    - Acne
    - Sleep apnea

Frequency of Adverse Effects During Hormone Administration in Healthy Elderly Women



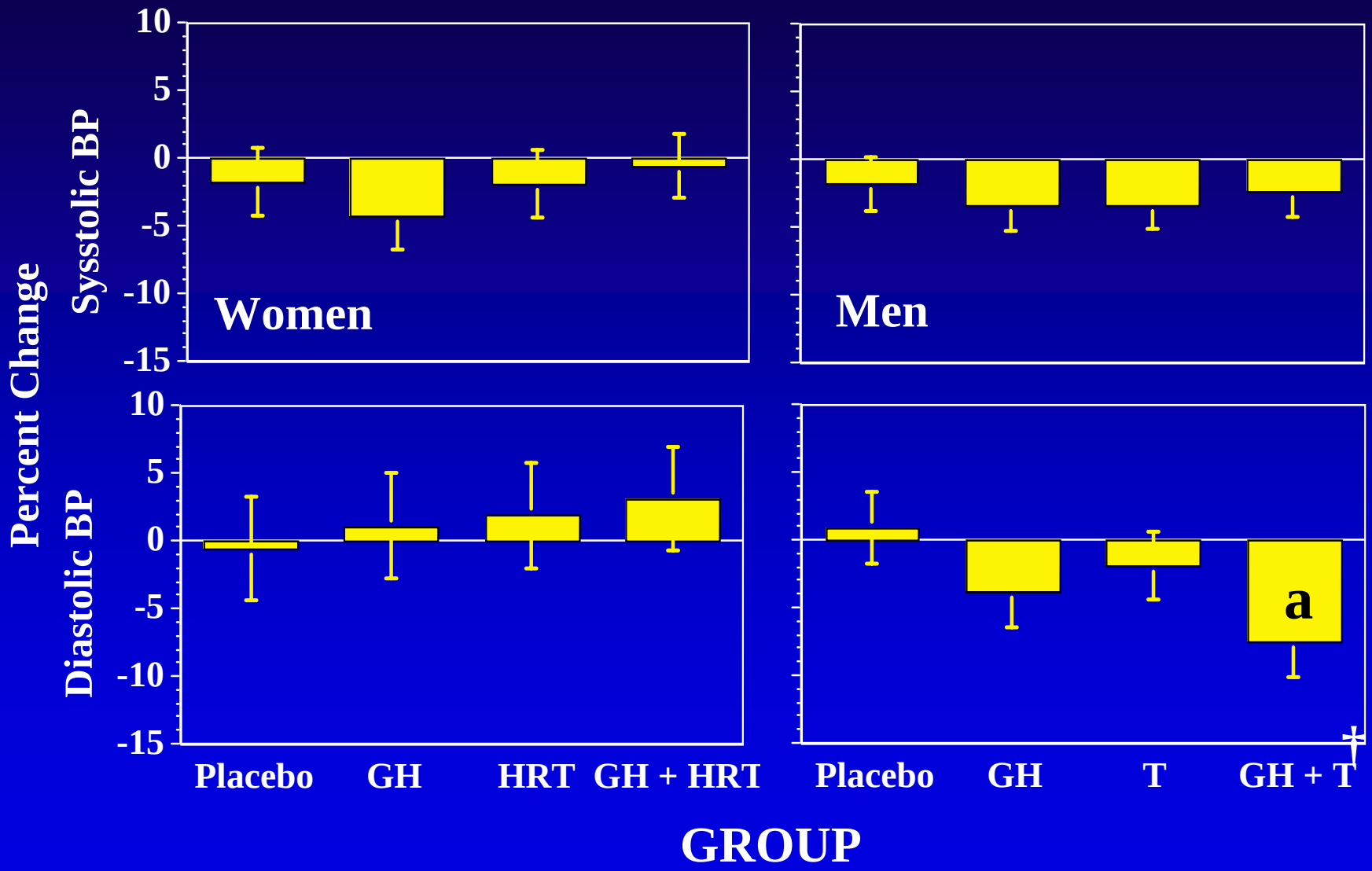
Fisher's exact test vs placebo: * $p < 0.05$; † $p < 0.01$; ††† $p < 0.0001$

Frequency of Adverse Effects During Hormone Administration in Healthy Elderly Men

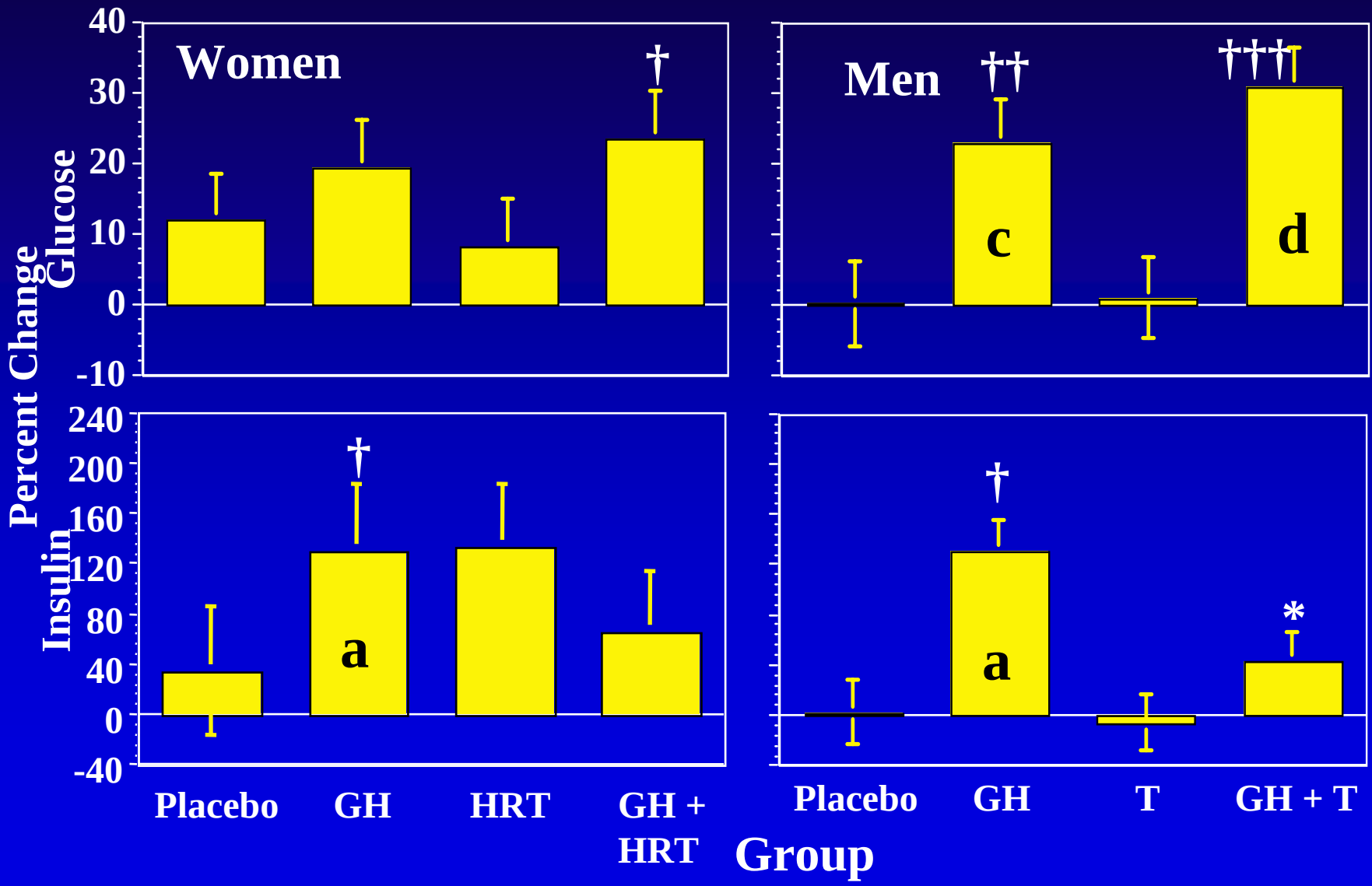


Fisher's exact test vs placebo: * $p < 0.05$; † $p < 0.01$

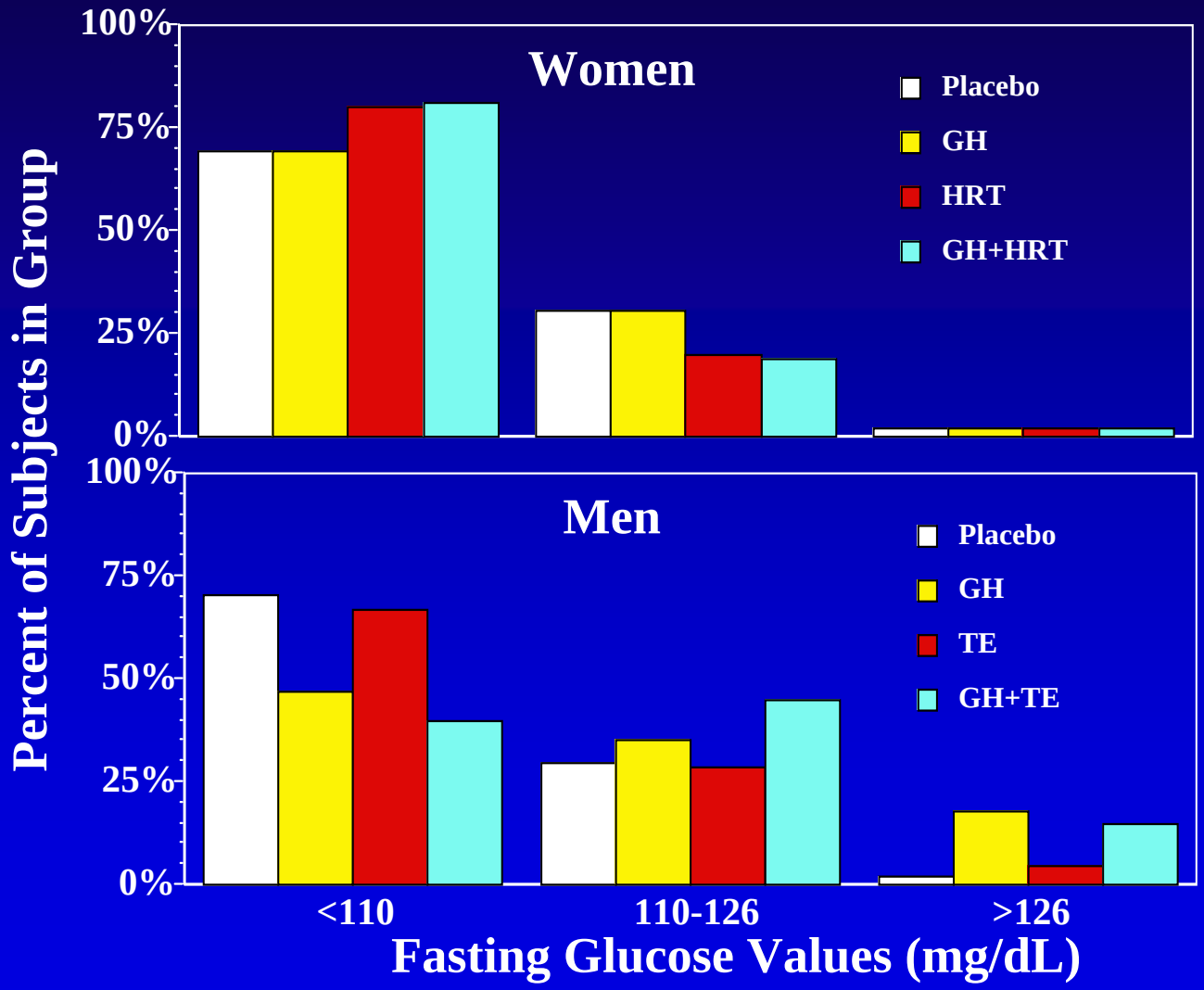
Effects of Hormone Administration on Systolic and Diastolic BP Levels in in Healthy Elderly Women and Men



Effects of Hormone Administration on Serum Glucose and Insulin Levels (GTT_{120}) in Healthy Elderly Women and Men



Percent of Women and Men by Group with Fasting Glucose Values During Treatment Indicating Glucose Intolerance or Diabetes



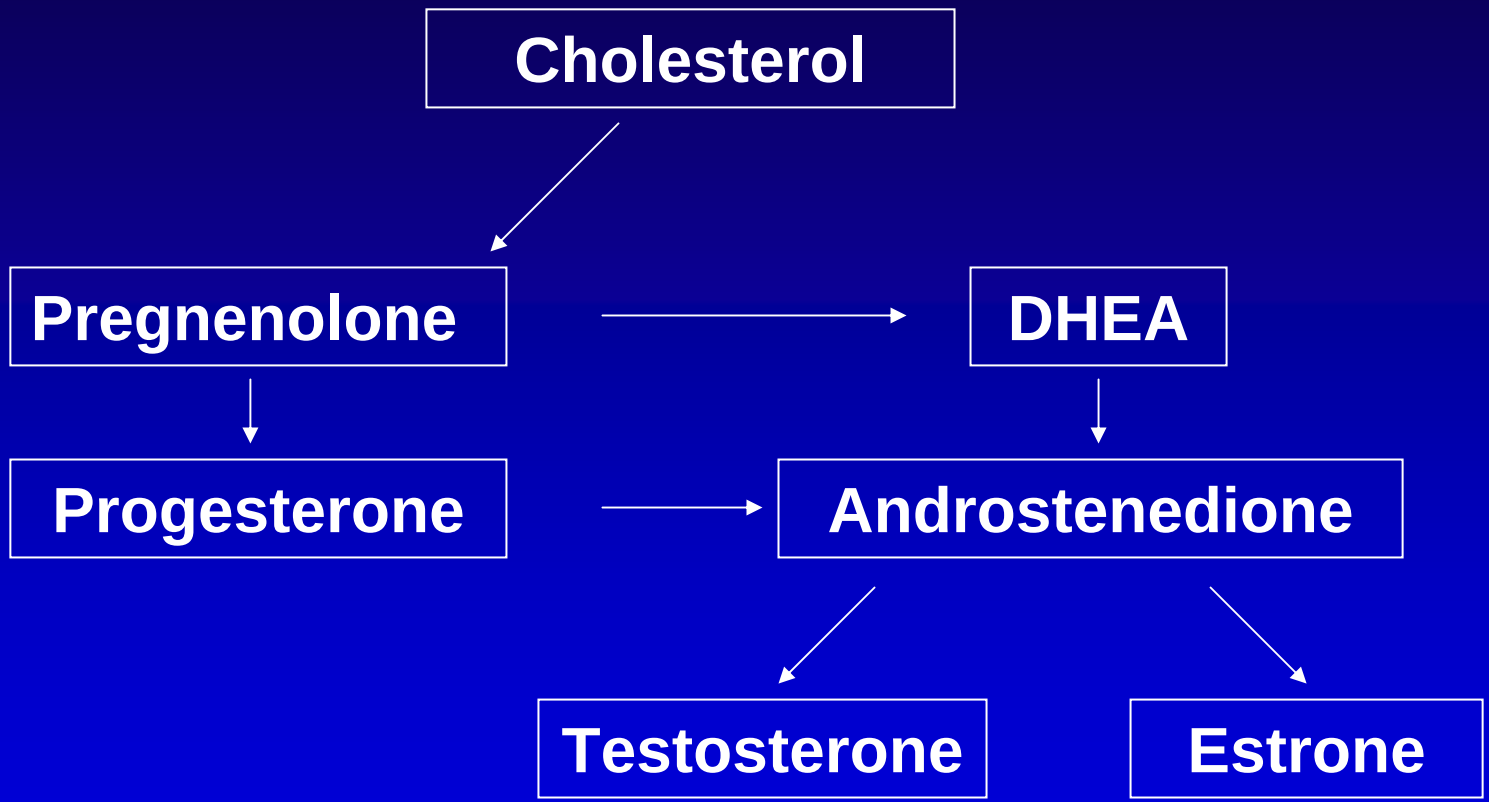
What Are the Gaps in Clinical Knowledge?

- Are the declines in GH and DHEA with aging adaptive or maladaptive?
- Whom to study and treat?
  - Healthy elderly
  - Frail elderly
  - Disease Groups - CAD/CHF, Hip Fracture, hip/knee replacement, cancer cachexia, etc.
- Patterns of treatment
  - Prevention vs therapy
  - When to initiate, how long to continue?
  - Pattern - continuous vs discontinuous
  - Route - oral vs parenteral agents
  - Mode of Rx - GH, GHRH, GH secretagogues, DHEA(S)

Summary and Conclusions

- Treatment of older adults with GH has significant adverse effects which need to be balanced against potential benefits
- GH may be a “pro-aging” hormone (mice)
  - Down-regulation of oxidative defense enzymes
  - Increase in oxidative tissue damage
- The true risk/benefit ratio and the treatment regimen to optimize this ratio are unknown

Adrenal Steroidogenesis



Legal Definition of Androgenic Anabolic Steroids (1990)

- Chemical structure like testosterone
- Not an estrogen, progestin, or corticosteroid
- Pharmacological activity like testosterone
- Must promote muscle growth

DHEA and Aging

- Weak adrenal androgen
- DHEA most abundant steroid in humans
- Levels decrease 80% with aging; may contribute to many age-related declines
- In animal models, DHEA reverses features of aging
- Widely used as dietary supplement
- Safety and efficacy not established

Adverse Effects of Androgenic Anabolic Steroids

- Feedback inhibition of testosterone and sperm function
- Acne, male pattern hair distribution
- Prostate enlargement
- Increases in blood pressure, red blood cells, and clotting
- Decreased HDL/LDL, liver and cardiac dysfunction
- Virilization (women)
- Increased libido, aggressiveness, and appetite

DHEA: Background

- DHEA levels decrease after birth, and increase dramatically during puberty. DHEA is the most abundant steroid in adults. Non human primates have less DHEA than do humans and non primates have little or none.
- DHEA-S is conjugated by the liver.

  DHEA t1/2 15-30 min, levels 2-4 ng/ml

  DHEAS t1/2 7-10 hr, levels 2-6 μg/ml
- DHEA is converted from Δ-4 to Δ-3 androstenedione and then to active androgens and estrogens in liver, fat, muscle, prostate, bone, skin, and brain
- No definite DHEA receptor has been identified, BUT a compelling candidate has recently been reported (J Biol Chem 277: 21379, 2002)

DHEA: Background

- A weak adrenal androgen that exerts its effects after conversion to androgen and/or estrogen
- Most abundant steroid in humans; receptor not defined
- Levels decrease by 80% with aging, and may contribute to age-related declines in body composition, endocrine-metabolic, immune, neuropsychological, and cardiovascular functions
- Administration to old rats reverses or attenuates many features of aging
- Widely used as a dietary supplement for anti-aging and athletic enhancement purposes, efficacy and safety not established

Melatonin: Background

- Melatonin, N-acetyl-5-methoxytryptamine, is synthesized from serotonin in many tissues, primarily the pineal gland
- Circulating melatonin is inactivated in the liver, and its conjugates are excreted by the kidney
- The pineal gland is regulated by a circadian rhythm-generating system located in the hypothalamic SCN
- Measurement of melatonin in plasma and saliva is a measure of the biological clock
- Capillary GC-MS is gold standard assay

Melatonin: Background

- Numerous prior reports suggest that melatonin is produced during the dark phase of the day-night cycle and that there is an age-related diminution in nocturnal melatonin secretion
- The bioavailability of melatonin in humans has not been well characterized
- Use of an improved GC-MS assay, and PK studies, suggest that melatonin secretion occurs at a constant rate rather than in peaks, with onset in the evening until pineal synthesis ends in the early AM, does not correlate with the duration of the dark phase, and does not differ by gender or with advanced age

(Fourtillan et al, Am J Physiol 280:E11, 2001)

Biological Research - It's All "Natural"…!

"People can be induced to swallow anything, provided it is sufficiently seasoned with praise."

Jean Moliere

Skepticism is the chastity of the intellect, and it is shameful to surrender it too soon or to the first comer.

G. Santayana (1923)

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