

Testosterone and Prostate Cancer



Dr. Ilan Z. Kafka



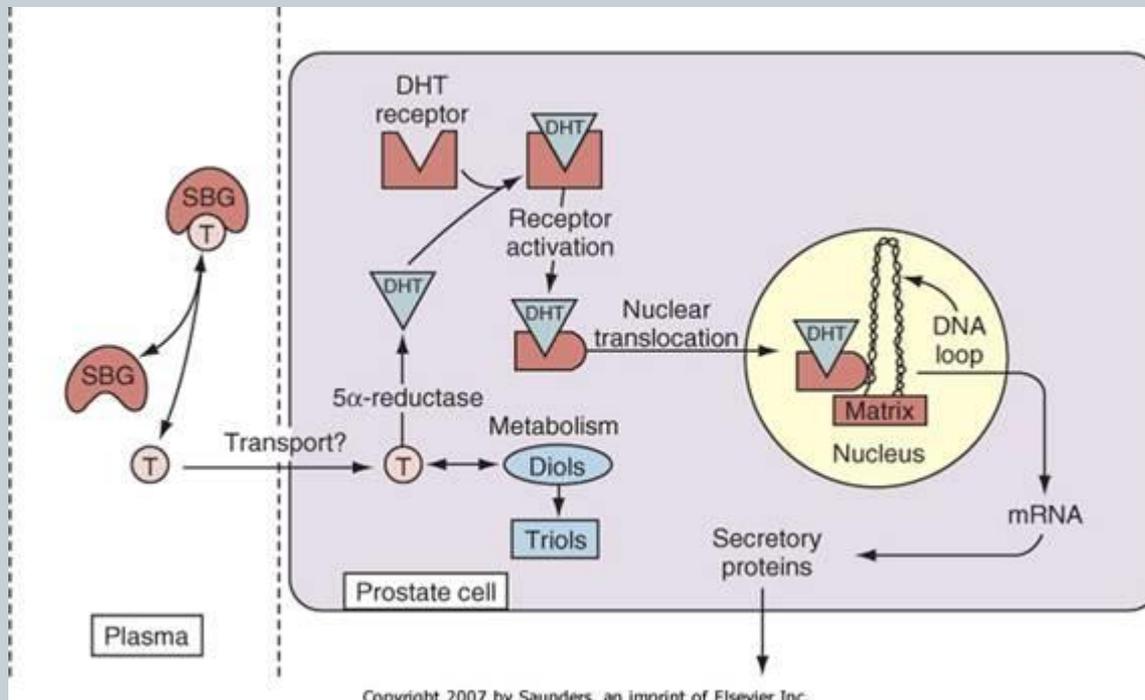
- “Prostate cancer is the most common of concerns among physicians recommending T therapy”

Gooren et al. *The Aging Male* 2007; 10:173-181

Introduction



- Testosterone
 - 90%-- Leydig Cells of Testes
 - 10%-- Adrenal Glands



Testosterone Deficiency in Men



Testosterone Deficiency in Men



- Hypogonadism-
 - AKA-
 - ✦ Androgen decline in the aging male (ADAM)
 - ✦ Late-onset hypogonadism (LOH)
 - ✦ Andropause
 - ✦ Testosterone deficiency syndrome (TDS)
- Annual incidence of TDS in the United States is as high as 500,000 new cases in men aged 40–69 /yr
- Low serum testosterone <300 ng/ml in men <50; <200 ng/ml in older men

| System/Function | Aging |
|------------------------------|-------|
| | |
| Erectile function | ↓ |
| Sexual desire | ↓ |
| Mood/cognition | ↓/→ |
| Tiredness/lack of motivation | ↓ |
| Sleep disturbances | ↑/→ |
| Spatial cognition | ↓ |
| Vasomotor (hot flashes) | ↑ |
| Quality of life | ↓ |
| Hematocrit | ↓ |
| Leptin production | ↑ |
| LDL and HDL cholesterol | → |
| Fat mass | ↑ |
| Muscle mass | ↓ |
| Bone mass | ↓ |
| Hair and skin changes | ↓ |

Serum Testosterone and Prostate Cancer incidence



- Do circulating sex hormones influence the risk of PCa?
 - Collaborative analysis of 18 longitudinal studies
 - 3886 men with PCa, 6438 controls
 - No association of PCa with serum androgens
 - Men with PCa have similar intraprostatic androgen concentrations as men without PCa
 - Men with highest T at no greater risk of PCa than men with lowest T

Roddam AW et al, JNCI 2008; 100:170-83

PCa in men receiving TT



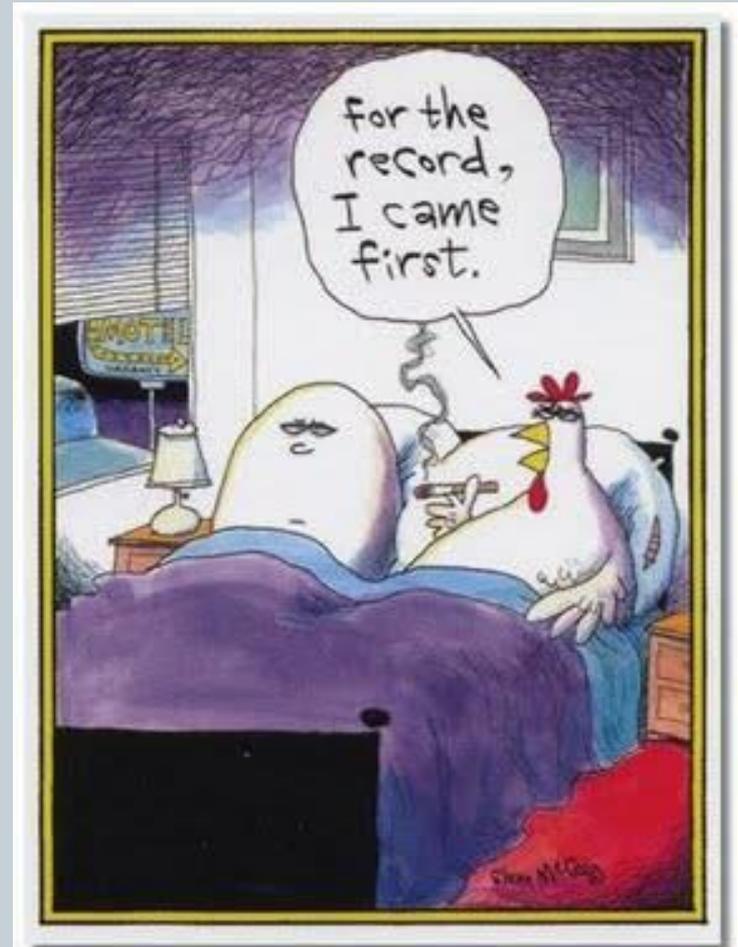
- TT does not exert a deleterious effect on prostate
 - ✦ 44 men, 44-78 years
 - ✦ testosterone levels <300 ng/dL and related symptoms
 - ✦ 150 mg of testosterone or placebo intramuscularly every 2 weeks for 6 months.
- TT increased serum testosterone levels to the midnormal with no significant change in serum testosterone levels in matched, placebo-treated men
- Median prostate tissue levels of testosterone did not change significantly in the TT group.
- No treatment-related change was observed in prostate histology, tissue biomarkers, gene expression, *or cancer incidence or severity*.
- In aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions

Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006;296:2351–61.

Testosterone and Prostate Cancer



- HOW IT ALL STARTED...

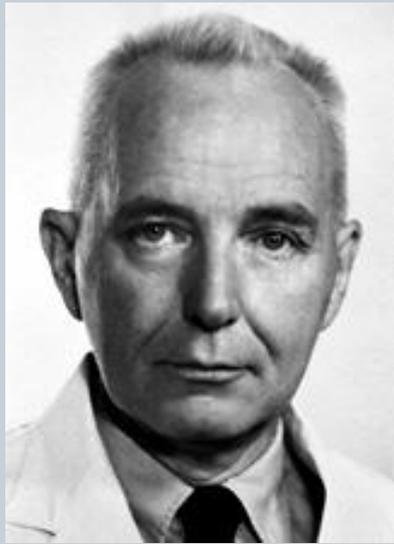


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Introduction



- Huggins and Hodges-



Charles B. Huggins, M.D

Huggins C, Hodges CV. **Studies on prostatic cancer, I: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate.**

Cancer Res 1941;1:293-7.

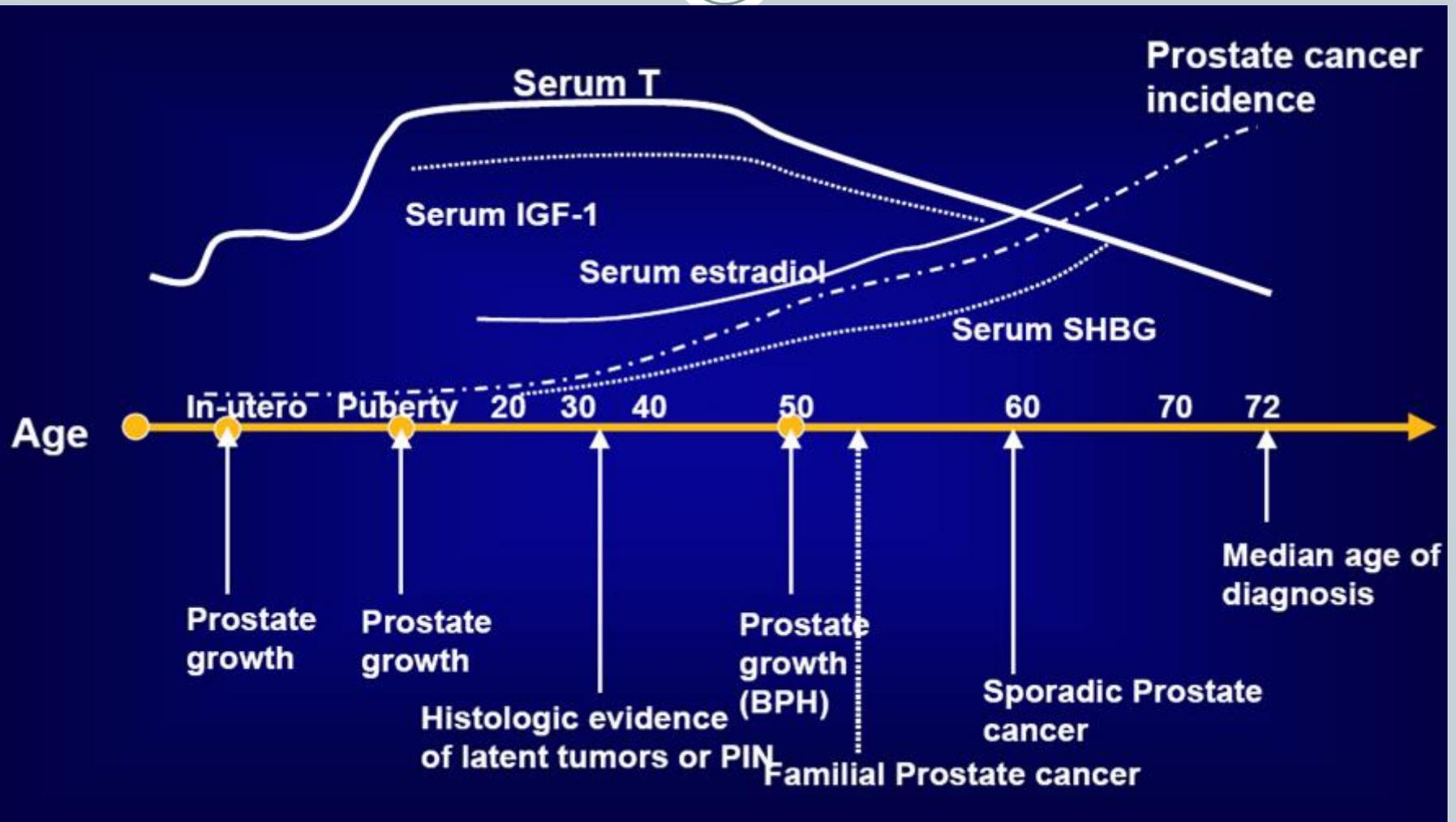
- Regression of metastatic Pca in 3 men after reduction in serum testosterone levels
- Progression of metastatic disease and symptoms in 1 man who received exogenous testosterone.

Won Nobel Prize 1966



- Is it justifiable to withhold TT, which is known to provide many benefits for symptomatic hypogonadal men, because of a “risk” that is unproven?

Age, Serum T and pCA



Effects of testosterone on prostate cancer growth



- **TT in hypogonadal men**
 - ↑in PSA , ↑prostate volume
- **TT in eugonadal men**
 - No changes

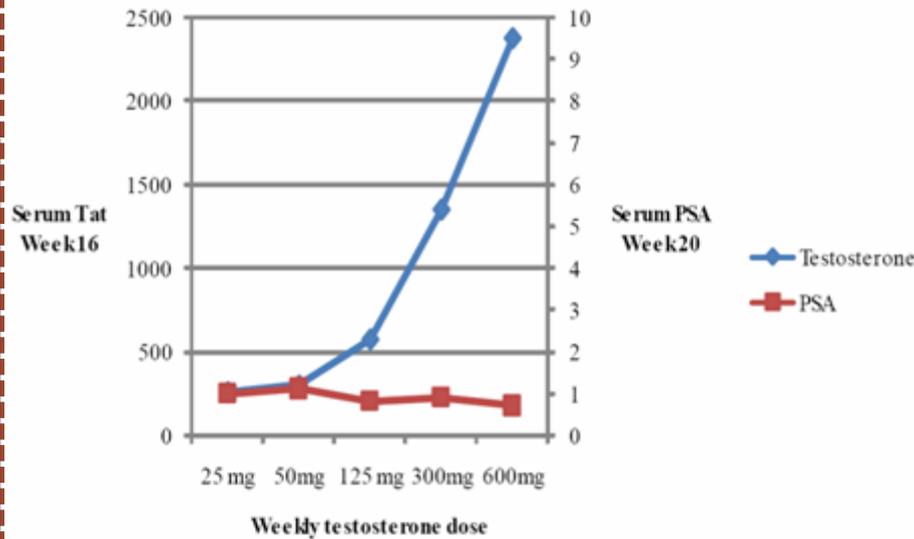
Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose–response relationships in healthy young men. *Am J Physiol Endocrinol Metab* 2001;281:E1172–81.

- **In men w/ low testosterone receiving TT**
 - ↑PGV- age matched eugonadal men

Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol* 1994;40:341–9.

Serum testosterone and PSA in young men

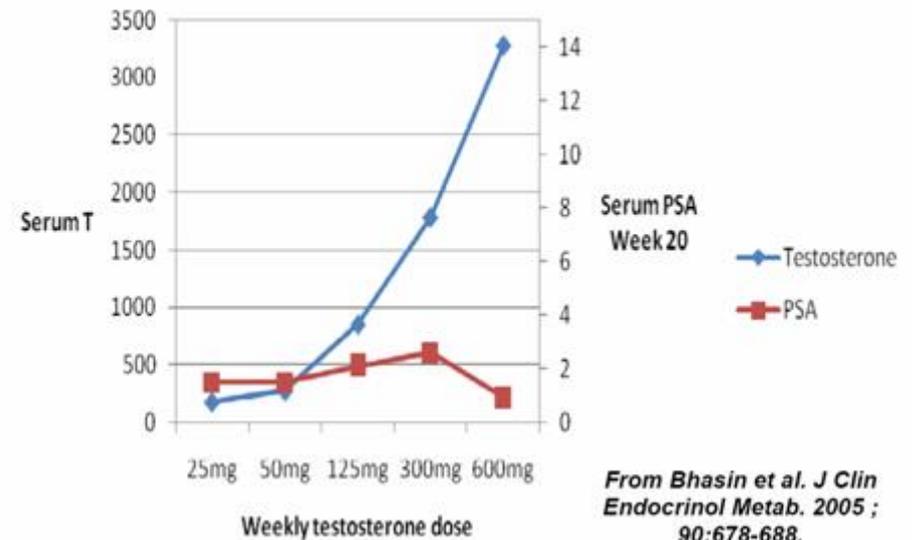
From Bhasin et al Am J Physiol Endocrin Metab 281:e1172,2001



- n=54
- 18-35 yo
- Long acting GnRH agonist

- n=60
- 60-75 yo
- Long acting GnRH agonist

Serum T and PSA in older men



From Bhasin et al. J Clin Endocrinol Metab. 2005 ; 90:678-688.

Effects of testosterone on prostate cancer growth



- Testosterone Administration to px with bone mets from PCa.
 - Previously untreated– beneficial response
 - Prior orchiectomy or estrogen exposure- unfavorable response
 - Response largely related to pre- tx testosterone levels

Fowler Jr JE, Whitmore Jr WF. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol
1981

Testosterone increases risk of PCa



- Serum Testosterone associated w/ aggressive Pca in older men.
 - 781 men in the BLSA – no cancer= 636
cancer not high risk= 109; cancer high risk=36
 - >65yo ↑ likelihood of high risk PCa w/ increase in free testosterone
 - ≤ 65yo likelihood inversely related to free testosterone
 - CONCLUSION -Higher levels of serum free testosterone are associated with an increased risk of aggressive prostate cancer among older men.

Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging

Phillip M. Pierorazio, Luigi Ferrucci, Anna Kettermann, Dan L. Longo, E. Jeffrey Metter, H. Ballentine Carter

BJU International October 2009



- Low Testosterone and PCa?

Serum Testosterone and Prostate Cancer incidence



- Association between low serum testosterone and PCa
 - 345 hypogonadal men
 - PSA level of 4.0 ng/mL or less
 - Testosterone 300 ng/dL or <
 - DRE and prostate biopsy before TRT
- Cancer was detected in **21%** of men with a testosterone level of **250 ng/dL or less** compared with **12%** of men with a testosterone level greater than **250 ng/dL**

Morgentaler A, Rhoden EL. Urology 2006

Serum Testosterone and Prostate Cancer incidence



- Low testosterone levels associated with:
 - Advanced Pathological State
 - High Gleason score
 - Biochemical recurrence after RP
 - %↑ positive-core rate at Bx.

- Imamoto T, Suzuki H, Fukasawa S, et al. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. *Eur Urol* 2005;
- Schatzl G, Madersbacher S, Thurnidl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate* 2001.
- Yano M, Imamoto T, Suzuki H, et al. The clinical potential of pretreatment serum testosterone level to improve the efficiency of prostate cancer screening. *Eur Urol* 2007
- Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 2003;
- Isom-Batz G, Bianco Jr FJ, KattanMW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *J Urol* 2005

Serum Testosterone and Prostate Cancer



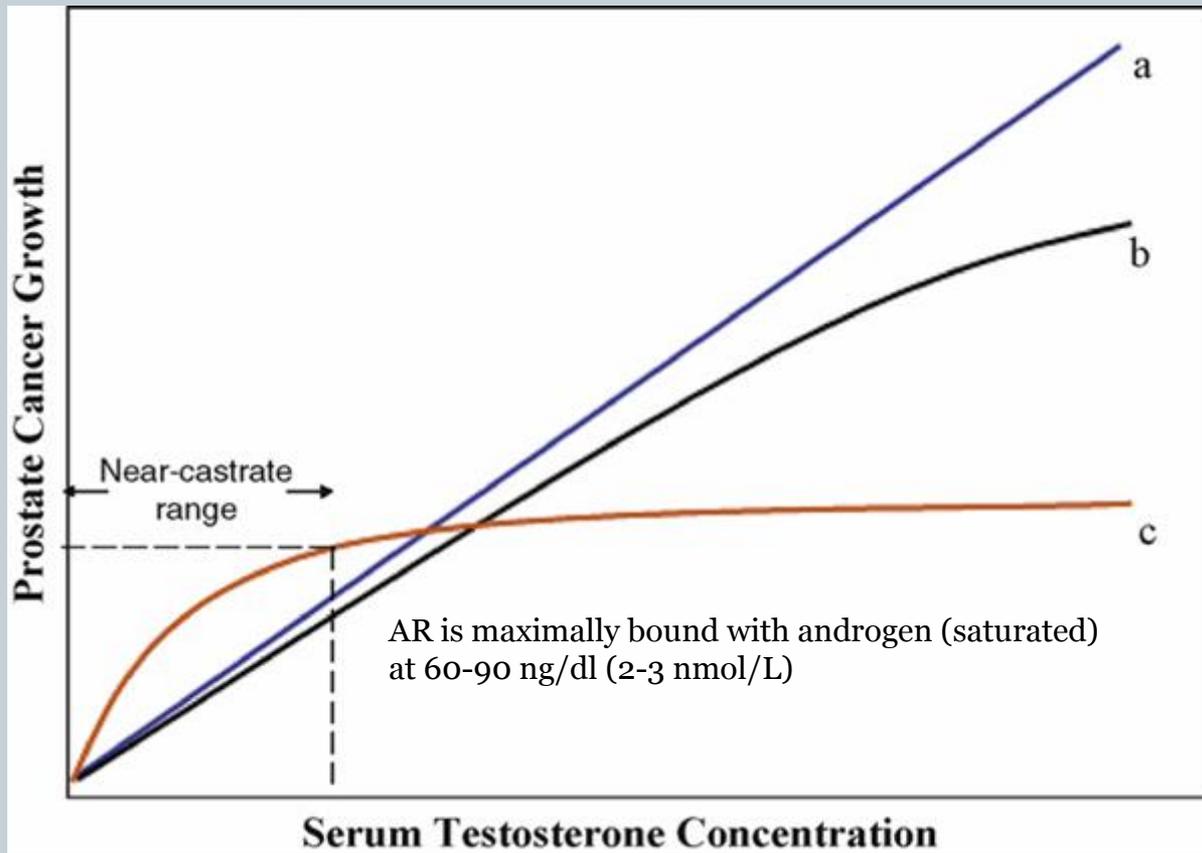
- **Saturation Theory**

Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009

- **Suppression Theory**

Miller LR, Partin AW, Chan Dw et al. Influence of Radical Prostatectomy on serum hormone levels. J. Urol 1998

Saturation Theory



Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009

Suppression Theory



- **63 healthy men 43 - 67 years-** clinically confined prostatic adenocarcinoma
- Blood for- testosterone, % free testosterone, DHT, estradiol, LH ,FSH, sex hormone binding, globulin and prolactin.
- Following radical prostatectomy -increase in serum testosterone, free testosterone, estradiol, LH and
-decrease in serum
- Does the normal prostate and/or prostate neoplasm could secrete a substance **or substances that give** negative feedback control to pituitary gonadotropin secretion?

Testosterone and PCa



- Prostatic changes in hypogonadal men with and without high grade prostatic intraepithelial neoplasia(PIN) after 1 year of TRT.
- 75 hypogonadal men -12 months of TRT
- 55 negative Bx. 20 PIN
- Prostate specific antigen (PSA), and total and free testosterone were determined prior to treatment and at 1 year. Repeat biopsy was performed for a change noted on digital rectal examination or for a PSA increase of 1 ng/l or greater.
- No significant differences in PSA responses were noted between these two groups, and in follow-up only a single PCa was detected (in the PIN group).

Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003;170:2348-51.

TT after definitive therapy for localized PCa



Table 1 – Reports addressing the effect of testosterone therapy in symptomatic hypogonadal men after definitive prostate cancer treatment

| Author | Sample size, <i>n</i> | PCa treatment | Start of TRT after PCa treatment | Follow-up | Cases of BCR |
|---------------------------|-----------------------|---|--|---|---|
| Kaufman and Graydon [29] | 7 | RP | Mean: 2.7 yr Range: 0–108 mo | Mean: NR Range: 1–12 years | None |
| Agarwal and Oefelein [28] | 10 | RP | Not reported | Mean: 19 mo Range: 9–29 mo | None |
| Khera et al [25] | 21 | RP | Mean: 54 mo Range: 1–181 mo | Median: 12 mo Range: 1–60 mo | None |
| Nabulsi et al [27] | 22 | RP | Mean: 26 mo Range: 2.5–11.8 mo | Mean: 24 mo Range: 14–30 mo | 1/22 |
| Davilla et al [24] | 20 | RP: 14 EBRT: 6 | Mean: 74 after RP; 57 mo after EBRT | Mean: 12 mo after RP; 9 mo after EBRT Range: NR | None after RP None after EBRT (according to ASTRO criteria) |
| Morales et al [69] | 5 | EBRT | Not reported | Mean 14.6 mo Range: 6–27 mo | None (according to ASTRO criteria) |
| Sarosdy [26] | 31 | Brachytherapy (with or without EBRT) | Median: 24 mo Range: 6–54 mo | Median: 60 mo Range: 18–108 mo | None (according to ASTRO criteria) PSA <0.1 in 74% PSA <1.0 in 100% |

ASTRO = American Society for Therapeutic Radiation Oncology; BCR = biochemical recurrence; EBRT = external beam radiotherapy; NR = not reported; PCa = prostate cancer; RP = radical prostatectomy; TT = testosterone therapy.

Current GL on TT



- American Society of Reproductive Medicine Practice Committee. Androgen deficiency in the aging male. *Fertil Steril* 2008;90:S83–7.
- Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *Eur J Endocrinol* 2008;159:507–14
- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91:1995–2010.

Current GL on TT



- All: No evidence that TT↑ risk of developing PCa, or converts subclinical PCa into clinically significant disease.
- EAU- TT relative contraindicated in men at high risk of dev. Pca – no def. of high risk Px.
- All: Literature on TT and PCa too sparse to draw a definitive conclusion on safety of TT.
- All: TT contraindicated in men w/ Dx. PCa.—Risk of PCa assessment
 - DRE+ PSA-----Bx.

Current GL on TT



- EAU- TT may be considered in symptomatic hypogonadal men s/p successful PCa Tx.
 - ✦ After a prudent interval -No clinical or laboratory evidence of recurrence
- Endocrine Society- no recommendation

Conclusions...



- Do men with PCa have higher T than men without PCa?
- Do men with higher T have greater risk of developing PCa than men with lower T?
- No evidence that TRT increases the risk of developing clinical prostate cancer

Future...



- **Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer**
Eur Urol. 2009 Aug
- **A Randomized Phase 1 Study of Testosterone Replacement for Patients with Low-Risk Castration-Resistant Prostate Cancer.**
Eur Urol. 2009 Feb



- Thank You...