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Goodbye Androgen Hypothesis, Hello Saturation Model

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It is worthy of remark that a belief constantly inculcated during the early years of life, while the brain is impressible, appears to acquire almost the nature of an instinct; and the very essence of an instinct is that it is followed independently of reason.

Charles Darwin, *The Descent of Man*

In this issue of *European Urology*, Muller et al [1] provide the final nail in the coffin for what had been a guiding principle of uro-oncology for >70 yr: the androgen hypothesis of prostate cancer (PCa). The androgen hypothesis originated with the Nobel-winning work of Charles Huggins, who, together with coauthor Clarence Hodges, reported in 1941 that castration caused PCa regression in men with metastatic disease, and that testosterone (T) administration caused PCa progression [2]. They concluded that T *activates* PCa, producing an *enhanced rate of growth*. Over the years, the androgen hypothesis came to include the following features: PCa is an androgen-dependent cancer; high T levels contribute to the development of PCa; high T causes rapid growth of PCa; and low T is protective against development of PCa and causes PCa to regress. Medical trainees were taught that the relationship between T and PCa was like *food for a hungry tumor* or like *pouring gasoline on a fire*. Conversely, men who developed severely depressed T early in life (eg, eunuchs) never developed PCa.

There was no reason to doubt the androgen hypothesis during my urology residency in the mid-1980s and in the period immediately afterward. Men who underwent castration for painful bony metastases experienced rapid relief, sometimes within hours. The newly available luteinizing hormone-releasing hormone (LHRH) agonists produced similar results, confirmed by dramatic declines in the new marker, prostate-specific antigen (PSA). However, one drawback of the LHRH agonists was the initial T flare, associated in some cases with sudden death and vertebral collapse, attributed to the transient rise in serum T. The introduction of finasteride in 1992 provided further confirmation, since this medication reduced PSA and prostate volume by depressing intraprostatic dihydrotestosterone (DHT) to castrate levels.

My first inkling that there was something wrong with the androgen hypothesis came when I began performing prostate biopsies in symptomatic T-deficient men to rule out the presence of cancer before offering T therapy. Although it was universally believed that low T should have been protective against PCa, our results revealed cancer in 11 of 77 men (14%) with normal PSA and digital rectal examination [3], a surprisingly high number similar to contemporaneous series in men with elevated PSA. A follow-up study in 345 men with low T and normal PSA revealed a similar cancer rate of 15%, with greatest risk for the most severely T deficient [4].

Clearly, low T was not protective, as one in seven men with low T had biopsy-detectable PCa. In 2004, while performing a review of the world literature, I was stunned to discover there was also no compelling evidence that high T was risky for PCa [5]. How was it possible that castration caused such dramatic effects on malignant and benign prostate tissue, yet higher T repeatedly appeared to have no relationship to PCa risk, prostate volume, or PSA? The androgen hypothesis that once seemed to explain everything was beginning to appear as if it explained nothing.

My curiosity took me to historical primary sources archived in the basement of the Harvard Medical School library, where I researched old texts like an archeologist seeking clues from a bygone era that might have relevance for those living and working today. I have described that research elsewhere [6], but it suffices here to say that I discovered there was never any basis for a broad androgen

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hypothesis. Anecdotal observations in small numbers of men with metastatic PCa were generalized beyond reason, findings were oversimplified, and contrary evidence was ignored. Huggins and Hodges, for example, based their conclusions that T activated PCa on the erratic and now-abandoned blood test, acid phosphatase, in only two men treated with T injections for no more than 18 d, one of whom was already castrated. Their results are uninterpretable. Remarkably, in other reports some men with metastatic PCa responded *positively* to T administration with an improved sense of well being and reduced pain. What I noticed in these historical series was that men who had already undergone androgen deprivation via castration or estrogen treatment demonstrated rapid PCa progression with T administration, whereas T administration in men who were still hormonally intact demonstrated no cancer progression.

This led to the saturation model [7,8] as a unifying conceptual framework, based on observations in humans, animals, and PCa cell lines. Those observations uniformly reveal that androgens have a *finite*, limited ability to stimulate prostate tissue, malignant or benign. This refinement is simple yet profound. Yes, prostate tissue requires androgens for optimal growth. However, it can only use a relatively small amount, beyond which additional androgen is merely excess. The saturation point is well below physiologic concentrations, which explains why manipulation of serum T into or out of the castrate range produces large changes in prostate biology, whereas normal prostate and PCa appear completely indifferent to variations in serum T from the near-physiologic to supraphysiologic range [8].

The study by Muller et al [1] provides the ultimate evidence disproving the androgen hypothesis and supporting the saturation model. The authors report on the relationship of serum T and DHT to prostate biopsy results in the placebo arm of the reduction by dutasteride of prostate cancer events (REDUCE) trial. Entry requirements included a PSA of 2.5–10.0 ng/ml and a prior negative prostate biopsy. Of 8122 men, 4073 were randomly assigned to placebo, and of these, 3255 underwent at least one of the planned biopsies at 2 yr and 4 yr. These 3255 men comprised the current study population, for whom biopsy results were analyzed with regard to baseline serum values for T and DHT.

The primary analysis revealed no significant association between PCa and serum T or DHT. Cancer rates were no different for men with normal T versus men with low T, defined as $<$10 nmol/l, or 288 ng/dl (25.5% vs 25.1%, respectively; $p = 0.831$). Interestingly, a subgroup analysis of men with low T presented a saturation-type curve, with lowest PCa rates at the lowest T values, increasing to a plateau value well below the normal range of T. The authors wrote, ''Our findings of the lowest testosterone levels being associated with the lowest PCa risk with no further changes with higher testosterone support a saturation model'' [1].

This last observation must be considered in light of multiple reports that suggest *increased* PCa risk with lower T [4,9]. Additionally, PCa rates declined at the upper end of serum T, an intriguing observation that must also be regarded cautiously due to the small cohort involved. Regardless, it is the primary findings of this study that merit serious attention.

This is the first large-scale study with mandatory, routine, prostate biopsies to investigate the relationship of serum androgens and PCa. Prior work had caused retrenchment of the androgen hypothesis, but until now it still could be argued that there was no definitive rejection of the general concept that higher serum T was somehow risky for PCa. In the 1980s, it was believed high T *caused* PCa. In the 1990s, the argument became that high T stimulated growth only of existing PCa. In the early 2000s, high T was proposed to affect risk only over a period of years. By 2010, a large longitudinal study [10] had rejected time exposure as a possibility. Adherents of the androgen hypothesis were left with the argument that systematic biopsies would be needed to exclude the possibility that high T might still cause an increased risk of androgen-stimulated PCa.

Enough! The biopsy results are now in, and it is time to face facts. Prostate cancer risk is unrelated to serum androgen concentrations. High T does not predispose to PCa and low T is not protective. The truth is there was never any credible evidence to support a generalized theory that high T was dangerous and low T protective. The androgen hypothesis was proposed and accepted before knowledge of hormone receptors, PSA, and prior to reliable measures of T. Indeed, the evidence against the androgen hypothesis was always obvious to anyone who wished to see: PCa occurs as men age and T declines; PCa never occurs in young men during the peak T years.

The importance of the article by Muller et al cannot be overemphasized. It finally lays to rest a false concept that has misinformed medical practice for decades. The failure to find increased PCa rates associated with higher serum androgens based on biopsies in a large at-risk population removes the last possible hope to those who wish to hold on to a disproved theoretical notion from a premodern era. There was never any basis for the assertion that eunuchs do not develop PCa. The reported tragic consequences from T flare consisted of anecdotal reports in a group of men with advanced disease, some of whom suffered the same complications without receiving LHRH agonists at all [6].

The persistence of the androgen hypothesis despite strong contradictory evidence teaches us how difficult it is to abandon ideas learned during our training, even in this age of evidence-based medicine. It is time now to move forward, with blinders removed. The sun is shining, the day is new, and the field of PCa is full of exciting research opportunities, including the possibility that T might actually be *beneficial* to men with PCa.

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References

[1] Muller RL, Gerber L, Moreira DM, Andriole G, Castro-Santamaria R, Freedland SJ. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2012.05.025.

[2] 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 Research 1941;1:293–7.
[3] Morgentaler A, Bruning III CO, DeWolf WC. Incidence of occult prostate cancer among men with low total or free serum testosterone. JAMA 1996;276:1904–6.
[4] Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen of 4.0 ng/ml or less. Urology 2006;68:1263–7.
[5] Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92.
[6] Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 2006;50:935–9.
[7] Morgentaler A. Testosterone replacement therapy and prostate cancer. Urol Clin NA 2007;34:555–63.
[8] 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;55:310–21.
[9] Garcia-Cruz E, Piqueras M, Huguet J, et al., Low testosterone levels are related to poor prognosis factors in men with prostate cancer prior to treatment. Brit J Urol Int. In press. http://dx.doi.org/10.1111/j.1464-410X.2012.11243.x.
[10] Endogenous Hormones Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170–83.

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