Guilt by Association: A Historical Perspective on Huggins, Testosterone Therapy, and Prostate Cancer

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ABSTRACT

Introduction. A long-standing belief is that higher testosterone (T) will increase the risk of prostate cancer (PCa), yet recent studies do not support this view.

Aim. To identify the key historical and scientific events leading to the establishment and persistence of the belief in a T-dependent model of PCa growth, despite evidence to the contrary.

Methods. Review of key historical scientific articles regarding T and PCa.

Results. The T-dependent model of PCa growth arose from the work of Huggins and coworkers, who in 1941 demonstrated dramatic responses to castration among men with advanced PCa. These authors and others also reported a rapid clinical progression with T administration. This led to the concept that T was like "food for a hungry tumor" for men with PCa. Fowler and Whitmore recognized in 1981 that the negative effect of T administration did not occur unless men had been previously castrated. However, this critical observation was either forgotten or dismissed amid major changes in PCa diagnosis and management during the 1980s. More recent studies have failed to provide clinical evidence supporting the belief that higher T represents a risk for PCa. Factors contributing to the persistence of the T-dependent model included dramatic effects of castration, continued use of androgen deprivation for treatment of PCa, an influential spokesperson (Huggins), groupthink (failure to acknowledge evidence inconsistent with the prevalent ideology), and an imprecise formulation of the model ("more T, more cancer growth"), making refutation difficult.

Conclusions. The fear that higher T will increase PCa growth stems from a theory of T-dependent PCa growth that originated with observations in a special population (castrated men) that is not particularly relevant to T therapy in hypogonadal men. The negative view of T with regard to PCa should be recognized for what it is—guilt by association. **Morgentaler A. Guilt by association: A historical perspective on Huggins, testosterone therapy, and prostate cancer. J Sex Med **;**:**–**.**

Key Words. Testosterone; Prostate Cancer; Risks

Introduction

Although testosterone (T) therapy provides important health benefits, there has been a long-standing fear that its use increases the risk of prostate cancer (PCa). This concern has had an enormous impact on the willingness of healthcare providers to consider treating hypogonadal men. A recent international study has indicated that the fear of inducing PCa is the most frequently cited physician concern regarding the use of T therapy [1]. No matter how much T therapy were to improve sexual function, body composition, mood, or sense of vitality in a given individual, none of this would be worthwhile if the treatment precipitated an aggressive PCa.

Remarkably, a review of the evidence strongly suggests that the proposition that higher T leads to increased PCa risk is without scientific support [2]. In particular, a recent collaborative worldwide pooled analysis of 18 longitudinal studies concluded decisively that PCa is unrelated to serum androgen concentrations [3], and an accompanying editorial exhorts the scientific community to finally move beyond the historical notion that PCa risk is governed by serum T [4].

It is rather shocking to discover that such a basic, axiomatic concept may not be true. Part of the shock is due to the fact that reduction of T to castrate levels continues to be a mainstay of treatment for advanced PCa, with rapid and easily observed beneficial results. Because lowering T causes PCa regression, it has always seemed reasonable to believe that raising T would increase PCa growth. Yet the predictions of a T-dependent model of PCa growth have all proved incorrect: PCa risk is unrelated to serum T [3]; high T concentrations have not been associated with worrisome PCa features [2]; low T is not protective against PCa [5]; and T therapy studies have not been associated with high cancer rates [6].

Huggins and coworkers provided the original evidence suggesting a T-dependent model of PCa growth ("more T, more PCa growth") in 1941 [7,8], and Huggins later was awarded the Nobel Prize in Medicine or Physiology for demonstrating the androgen-dependence of PCa in 1966. Two-thirds of a century later, the scientific community has continued to think about T and PCa as if the T-dependent model applied not only to castration, but also to T therapy, only to learn at this late date that the model fails to account for a number of important observations. The purpose of this review was to examine the historical and scientific factors that led to the establishment and persistence of the T-dependent model for so long without significant challenge, despite the absence of compelling scientific support.

The Origin of the T-Dependent Model of PCa Growth

The origin of the linkage between T and PCa came from the work of Huggins and co-workers, who in 1941 published two landmark articles. One reported that castration in men with metastatic PCa rapidly lowered the serum marker acid phosphatase, and T administration increased the acid phosphatase [7]. The second article reported prompt clinical benefits with castration, whereas T administration caused an increase in bone pain [8]. Huggins and coworkers concluded that T administration caused an "enhanced growth" of PCa.

The dramatic response to variations in T produced an immediate worldwide shift in the management of PCa. Castration represented the first effective treatment for metastatic PCa, and this procedure soon became a universal practice for men with advanced disease, even though it was quickly recognized that cancer eventually recurred in most men. The concept that PCa progressed or regressed depending on T concentration was clearly established, and this concept was reaffirmed on a regular basis as physicians saw the response to castration in men with advanced disease.

Confirming the Model: Tragic Consequences of T Administration in Men with PCa

Support for the T-dependent model of PCa growth came from additional reports that T administration in men with PCa caused rapid and even disastrous outcomes. Prout and Brewer reported that among 10 men in relapse after castration, the addition of T caused progression or death in five of them within several weeks [9]. Fowler and Whitmore reported that 45 of 52 men who received T administration experienced unfavorable responses, mostly within 30 days [10]. These experiences led to the well-known warnings that T administration in men with PCa would be like "pouring gasoline on a fire," or "feeding a hungry tumor" [2].

Well before the modern era of prostate cancer work began in the early to mid-1980s, there was a widely known set of experiences demonstrating an exquisite sensitivity of PCa to serum T concentrations: PCa regressed rapidly when T was lowered, and PCa grew, sometimes in dramatic and disastrous fashion, when T was increased.

Carrying the T-Dependent Model Forward into the Modern Era

The 1980s were a time of revolutionary change in the diagnosis and management of PCa, beginning with the introduction of the anatomic nerve-sparing radical prostatectomy by Walsh and Donker in 1982 [11]. The prostate-specific antigen (PSA) blood test was introduced and widely accepted shortly thereafter [12], and the use of luteinizing-hormone-releasing hormone (LHRH) agonist medications in place of surgical castration became popular around this same time. This period also introduced two new concepts that furthered the T-dependent model of PCa. One was the association of adverse events with the transient rise in serum T seen with LHRH agonists, termed "testosterone flare" [13]. These adverse events included reports of vertebral collapse with accompanying paralysis, or precipitation of acute urinary retention, or even sudden death [14].

The second new idea was the suggestion by Labrie et al. [15] as well as others [16] that it was

important in men with advanced PCa to block the effects of the small amount of residual androgen present after orchiectomy. Total androgen blockade, as it came to be known, as well as the worrisome experience with T flare, reinforced the idea that T was dangerous for PCa: short-term increases in T produced serious adverse events, and even tiny amounts of T could negatively impact survival.

Unraveling of the T-Dependent Model of PCa Growth

The model of T-dependent PCa growth was not seriously challenged until T therapy for hypogonadism became popular in the 1990s, coinciding with the introduction of topical T formulations. Although T therapy had existed for several decades, its use had been restricted almost exclusively to men with severe T deficiencies for whom T replacement was uncontroversial, such as in men with absent testes, central hypogonadism due to tumor, radiation, or surgery, or genetic abnormalities such as Klinefelters. The discovery that T therapy could improve sexual function and provide other clinical benefits in less severely affected men widened the indications for T therapy [17], and brought new attention to the potential risks of this therapy.

By the turn of this century, several inconsistencies in the T-dependent model became vexing, although not yet fatal. This model predicted that higher T should increase the risk of PCa, and a low T should be protective. Yet, a number of longitudinal studies failed to reveal any signal that men with PCa had higher T levels than men without PCa, or that men with high T were at any greater risk than men with low T [18]. And prostate biopsy in hypogonadal men with normal PSA revealed a substantial cancer rate of 14%, a value that was certainly no lower than the general male population [5]. In addition, T therapy trials were associated with a cancer rate of approximately 1%, a rate no greater than seen in prostate cancer screening trials [6], even though as many as one in seven hypogonadal men had biopsy-detectable PCa [5]. If T administration truly caused the "enhanced growth" of PCa, then it was hard to understand why T therapy trials did not result in high PCa rates given the substantial amount of undiagnosed, occult PCa in this population.

A recent study has arguably struck the death knell for the T-dependent model of PCa growth, particularly as it may apply to T therapy in hypogonadal men. In a collaborative worldwide analysis of pooled data from 18 longitudinal studies, the data clearly failed to provide any indication that PCa risk was associated with serum concentrations of T or any other sex hormone [3]. In stark contrast to the obvious effect of lowering T in men with PCa, the available evidence strongly indicates that changes in serum T within the physiologic range have little if any effect on the prostate, malignant or benign.

This apparent paradox has been resolved by recognition that PCa growth follows a saturation curve [19]: there is a steep PCa response to variation in T concentration at the castrate or near-castrate range, reaching a point of maximal prostatic stimulation beyond which further increases in serum T fail to produce any further effect. This biphasic relationship of T and PCa provides a window through which it can be understood how the T-dependent model seemed so plausible and came to be so widely accepted.

Reexamining the Evidence

The human and animal data supporting the saturation model demonstrate that variations in T occurring at or below the near-castrate range are associated with substantial changes in PCa growth, whereas variations in T above this range cause little or no prostatic effects [19]. This biphasic relationship between T and PCa provides a very different perspective on the published experiences of Huggins and others.

In the first publication by Huggins and coworkers demonstrating changes in acid phosphatase with castration or T administration, the authors indicated they had treated three men with T. However, the results were given only for two men, and one of these men had been previously castrated. Acid phosphatase results in this untreated man were erratic, and thus inconclusive [7]. In the second article, T was administered to three men, all of whom had already undergone castration [8]. Thus, the results reported by Huggins and coauthors with T administration referred almost exclusively to men who had been previously castrated. The response of the single individual without prior treatment did not support the "enhanced growth" concept proposed by Huggins. Huggins did not comment on the effect of prior castration on the response to T administration in these initial articles, or in subsequent comments [20].

As noted previously, Prout and Brewer had noted that 5 of 10 men in relapse after castration

experienced rapid progression or death with T administration [9]. However, a separate group of 26 men with advanced disease who were either untreated or recently castrated exhibited no negative effects or any rise in acid phosphatase with daily T injections over several weeks [9]. Moreover, the report by Fowler and Whitmore in which 45 of 52 men developed "unfavorable" responses with T administration consisted of a patient population that almost exclusively had already been hormonally treated with castration or estrogen [10]. Only four men in the study group were hormonally intact prior to T administration, and the authors clearly noted that this untreated group did not experience the same negative outcomes as the castrated group. In fact, these men continued to receive daily T injections for as long as 310 days [10].

The critical point, poorly appreciated even to this day, was that men with advanced disease who had been previously castrated responded to T administration with rapid PCa growth and negative outcomes, whereas T administration in untreated men appeared to have little negative impact. Fowler and Whitmore clearly were impressed by this point, concluding that naturally occurring T concentrations may be enough to provide near-maximal stimulation of PCa [10].

Addressing Other Concerns Regarding T and PCa

A number of additional observations have contributed to the acceptance of the T-dependent model of PCa growth. In retrospect, these observations did not directly address whether higher T leads to greater PCa growth, but appeared to provide confirmation of the T-dependent model by highlighting different facets of the importance of T to PCa growth. For instance, several of the adverse events reported in association with T flare occurred a month or more after the administration of LHRH agonists [13,14], when serum T would already have been at castrate levels for 2 weeks or more. In these uncontrolled studies, it is entirely possible that adverse events occurred as part of the natural history of the disease. However, because it was assumed that higher T led to greater PCa growth, any adverse event occurring at some point after an increase in T appeared to confirm a causal relationship ("higher T caused PCa progression").

Similarly, the argument that blocking the effects of adrenal androgens may provide some clinical advantage does suggest that androgens are important for PCa, but provides no information as to whether raising T in an untreated individual will increase PCa growth.

Factors Contributing to Persistence of the T-Dependent Model of PCa Growth

A review of the historical and scientific events that led to the establishment and persistence of the T-dependent model is illuminating, and reveals several important contributing factors.

The first is that the effects of castration in men with metastatic PCa were dramatic, and represented a true breakthrough in medicine. Moreover, T administration produced similar dramatic effects, often with tragic results [9,10]. It is easy to understand how such a revolutionary idea would generate enormous enthusiasm for the androgen-dependent model of PCa, and how this enthusiasm might lead to oversight of subtle distinctions, such as differences in response based on whether or not a man had been previously castrated.

A second key factor was the championing of the concept by a revered and influential figure. Charles Huggins was one of the most important scientists of his era, and he continued to reaffirm the concept that T administration caused the "enhanced growth" of PCa for several decades [20]. The influence of such a powerful spokesperson on the acceptance of a scientific idea within the medical community cannot be stressed enough.

A third factor was the plausibility of the concept. It seems logical that if lowering T causes PCa to regress, then raising T should cause PCa to grow more rapidly. The strength (and ultimate weakness) of the argument comes from its being so "obvious." In addition, the continued use of androgen deprivation to this day in the treatment of advanced PCa has allowed for the regular reinforcement of the idea that PCa responds rapidly and powerfully to changes in T concentration.

Timing was another important factor. Because T therapy was not widely offered until the last 15 years, this meant that the T-dependent PCa model had already been established for approximately 50 years before there was a much need or opportunity to evaluate whether raising T might be risky in men without known PCa or without prior hormonal manipulation.

Finally, it is critical to note that the T-dependent model has never been precisely formulated. Huggins had suggested that T administration caused an "enhanced rate of growth" of PCa, and this has generally been accepted to mean

that higher T leads to greater PCa growth while lower T leads to less (or negative) growth. However, there has never been a rigorous formulation of this concept, leading to a number of unanswered questions. Should a doubling of T result in a doubling of the PCa growth rate? More? Less? Is there some limit to this growth or does the "enhanced rate of growth" of PCa apply throughout the physiologic and even supraphysiologic range of T concentrations? Is T-dependent PCa growth immediate or delayed? It is unfair to pin any blame for this imprecision on Huggins himself, because he worked in a time when there were no accurate assays for measuring either serum T or PCa growth. Yet there should be no doubt that the lack of clarity regarding the details of the T-dependent model contributed to its longevity, for if an argument is never rigorously stated, it becomes nearly impossible to refute.

Discussion

The growing awareness that the traditional model of ever-greater PCa growth with increasing T is without clinical supporting evidence represents a remarkable change in the scientific landscape. This change has enormous implications for the future of T therapy, because it potentially removes a major hurdle for healthcare providers who have worried about the safety of T therapy in hypogonadal men [1]. More broadly, however, the persistence of this model represents a failure of the scientific process, in which hypotheses are routinely rejected if they fail to demonstrate fidelity to empirical evidence and accurately predict outcomes.

It seems clear that the long-standing belief in this traditional model was caused by a number of coincident factors working together to create a theoretical construct that seemed so plausible and solid that it became virtually unassailable for over three full generations. In the end, the T-dependent model became established because it seemed to explain the dramatic new phenomena associated with castration, because it was plausible, appealing, partly correct, vaguely worded, and because it had as its spokesperson one of the preeminent scientists of his time. The reasons for its lasting for so many years into the modern day are somewhat different.

It is much more difficult to challenge an idea once it has grown roots. In this case, the persistence of the Huggins model could be attributed in part to what sociologists call "groupthink," in which members of a community fail to recognize that some assumed principle or idea is erroneous because of shared ideology and the denigration, dismissal, or failure to acknowledge information that would support an alternative view [21]. In this regard, it is noteworthy that the failure of PSA to rise above baseline during T flare in men with metastatic PCa—suggesting that perhaps T flare may not cause increased PCa growth—did not merit a single comment in two major publications [22,23] or in reviews on the topic [13].

More recent social factors may have also played a role in furthering the concern that raising T will increase PCa risk. These include the current emphasis on medical risks, negative views of the pharmaceutical industry, parallels to experiences with hormone therapy and cancer in women, and a long-standing bias against hormone therapy in general, which stems in part from prejudices against sexuality [24].

The lessons of this experience with the T-dependent model are several. No theory or hypothesis should be immune to close examination; alternative theories should not be dismissed simply because they challenge conventional wisdom; a theory that makes correct predictions under certain conditions but not others cannot be accepted as a general principle; and a hypothesis that is inconsistent with the evidence must be discarded in favor of a new hypothesis that is consistent with the evidence.

For the field of T therapy, it is important to recognize and understand the genesis of the fear that raising T will increase the risk of PCa. This fear has been based entirely on an imprecisely formulated model of T-dependent PCa growth, and on the early experiences in which T administration in castrated men with metastatic disease resulted in disease progression. Not only is there no current or historical evidence to indicate that raising T in a noncastrated man will cause PCa growth, but the experience of Huggins himself, and others, actually suggests that no deleterious effects may occur with T administration in noncastrated men, even in the presence of a widespread disease. This radical idea gains support from the failure of PSA to increase during T flare [22,23], and clearly merits a careful study, but these experiences do place modern attempts to offer T therapy to men previously treated for PCa [25–27] in a new light. In fact, recent evidence suggests that androgens may have a beneficial effect on PCa by promoting a less aggressive phenotype via the androgen receptor, as shown using in vitro cell lines [28,29].

These new data are consistent with clinical evidence linking worrisome features of PCa to *low* serum T [30].

A review of the historical and modern literature clearly shows that the negative view of T therapy as a risk for PCa growth is due to a misunderstanding of the biology of the relationship between T and PCa. The fear of T-dependent PCa risk stems directly from historical experiences with the special case of T administration in androgen-deprived men with metastatic disease, yet it should be clear that a population of castrated men with metastatic PCa has no true relevance for T therapy in otherwise healthy hypogonadal men. It must be emphasized that no definitive assessment of the safety of T therapy can yet be made because of the absence of a long-term, large-scale placebo-controlled trial. However, the fear that T therapy will increase PCa risk should be recognized for what it is—guilt by association.

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