The History of Testosterone and the Evolution of its Therapeutic Potential

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ABSTRACT

Introduction: Testosterone therapy has been controversial since its synthesis in the 1930s to the present day. Testosterone's history provides depth and context for current controversies.

Aim: To review the history of testosterone therapy from its initial synthesis in the 1930s to the modern day.

Methods: Expert review of the literature.

Main Outcome Measures: Impactful events in the history of testosterone.

Results: By the 1940s there was already a fascinating literature that described the many symptomatic benefits of testosterone therapy that are recognized today. Numerous early reports suggested testosterone therapy improved angina pectoris and peripheral vascular disease. The assertion by Huggins and Hodges (Cancer Res 1941;1:293–297) in 1941 that testosterone activated prostate cancer (PCa) cast a pall for the next 70 years. The introduction of the radioimmunoassay in the 1970s shifted the diagnosis of testosterone deficiency from signs and symptoms to an undue emphasis on blood test results. The fear of PCa was the primary obstacle to the adoption of testosterone therapy for decades. Prescription rates increased as accumulated evidence showed testosterone therapy was not associated with increased PCa risks. The observation that androgenic stimulation of PCa reaches a maximum at relatively low testosterone concentrations—the saturation model—provided the theoretical framework for understanding the relation between androgens and PCa and led to multiple case series documenting reassuring results of testosterone therapy in men with PCa. Recent concerns regarding cardiovascular risks also have diminished because new evidence suggests testosterone therapy might actually be cardioprotective. In 2016 the Testosterone Trials provided high-quality evidence of multiple benefits of testosterone therapy, nearly all of which had been recognized by clinicians by 1940.

Conclusions: If the past has any lessons for the future, it is likely that research will continue to demonstrate health benefits of testosterone therapy, while it remains one of the most controversial topics in medicine. **Morgentaler A, Traish A. The History of Testosterone and the Evolution of its Therapeutic Potential. Sex Med Rev 2020;8:286–296.**

Key Words: Testosterone; Androgens; Hypogonadism; Deficiency; Saturation; Prostate Cancer

INTRODUCTION

Most modern readers will be aware of the prominent place of testosterone (T) therapy among the most controversial topics of the past decade. However, few will be aware of the rich history of T, which was 1st synthesized more than 80 years ago and has been used for medical and non-medical purposes since that time. We present a review of the history of T from the perspective of 2 individuals who have been involved in this field for many decades, one as a researcher and the other as a clinician-investigator.

We divided this review into 2 main sections. The 1st describes the discovery of T and the early years of its use as a therapeutic agent. This section is rich with observations and commentary that reflect the nature of science in that era, and we included several key passages from older articles and books to provide some flavor of those times and because many of these publications are not readily available to the modern reader. The 2nd section describes the modern history of T therapy through to the present day, noting key events and noteworthy publications and providing our perspectives on these events.

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PART 1. THE EARLY YEARS OF TESTOSTERONE

Discovery and Synthesis

One of the earliest experiments involving testicular hormones was carried out in 1849 by Arnold A. Berthold[1] of Gottingen. Berthold was curator of the local zoo and concluded that the rooster's comb must be an androgen-dependent structure, because castration results in atrophy of the comb, disappearance of aggressive male behavior, and loss of interest in hens. These castration-induced changes were reversed by the injection of a crude testicular extract or by transplantation of the testes. He concluded that "the testes act upon the blood, and the blood acts upon the whole organism."[1] However, from the beginning of human record, priests, saints, medicine men, farmers, and sultans had been demonstrating how clear-cut, sure, and simple it was to take away the vigor of animals and men by removing their testicles. Conversely, they lacked the power to restore virility once it was gone.[2]

In 1889, Charles-Édouard Brown-Séquard[3] (1817−1894), a renowned scientist at the prestigious French Academy of Sciences, reported results on self-injections of testicular extracts, stating that "his vigor and feeling of well-being were markedly restored but the effects were transient" *and* suggesting the extract contained a biochemical substance that promoted rejuvenation. Within a year, more than 12,000 physicians were administering the extract to their patients.[4]

A century later, scientists in Australia attempted to repeat the extraction of male hormones from dog testes according to the methods published by Brown-Séquard in his original work and concluded that insufficient amounts of T to elicit a biological response could be recovered from these testicular extracts.[5] They wrote, "… the placebo effect can be powerful, even in a highly-educated physician."[5] This conclusion fits neatly into a narrative that T therapy is a frivolous, vain attempt to restore youthful masculine vitality, yet, for reasons described below, the conclusion cannot be considered definitive.

A recent study by Coviello et al[6] determined intratesticular levels of T in healthy men and found mean T levels of 793 ± 96 nmol/L, a value approximately 40- to 50-fold higher than normal serum T levels. McGee[7] and Moore et al[8−10] demonstrated 90 years ago that injections of lipoid extracts of bull testes resulted in observable changes in the prostate and seminal vesicles of castrated male guinea pigs and rats. These studies coupled with the effect of testicular extracts on development of the coxcomb of capons indicate testicular extracts can elicit a biological response. So, it is not inconceivable that the daily 1-mL injections by Brown-Séquard consisting of 1 part testicular vein blood, 1 part semen, and 1 part testicular fluid from dog or guinea pig testes could have had sufficient T concentration to elicit an androgenic effect.

In 1927, T.F. Gallagher and Fred C. Koch[11] extracted 20 mg of a substance from 40 pounds of bovine testicles and then administered a specific dose of this purified material into castrated roosters, pigs, and rats, resulting in remasculinization. In 1932, Carl Heller[12] reported in the *American Journal of Anatomy* on the Cowper gland and its reaction to castration and to different sex hormone conditions. In 1934, Ernst Laqueur purified T from bovine testicles in a similar manner; however, isolation of the hormone in sufficient quantities to permit scientific experimentation in humans was not feasible.[13]

In the 1930s Schering (Berlin, Germany), Organon (Oss, Netherlands), and Ciba (Basel, Switzerland) began research and development toward full-scale steroid synthesis. In May 1935 the Organon group published "On Crystalline Male Hormone from Testicles (Testosterone)" and were the 1st to describe the isolation of the hormone, which was named *testosterone* from the stems of *testicle* and *sterol* and the suffix of *ketone*.[14] The structure of this newly synthesized hormone was elucidated by Schering's Adolf Butenandt at the Chemisches Institut of the Technical University in Gdansk. In 1935 Butenandt and Hanisch[15,16] were successful in the chemical synthesis of T from cholesterol followed by Leopold Ruzicka (1887−1976) and A. Wettstein,[17] from the Ciba group in Zurich, who published their synthesis of T.

Early Clinical Experience With Testosterone

Hypogonadism had been recognized for centuries as a condition that presented with pubertal delay or absence, decreased muscularity, and alterations in secondary sexual features such as sparse or absent body hair and beard. This diagnosis was largely made on clinical grounds and was known to be caused by a number of medical etiologies, including pituitary tumors and absent or atrophic testicles. However, soon after the availability of T products, there was already recognition that hypogonadism could exist without these major, identifiable causes.

In 1939 Arndt[18] wrote that a man might have the appearance of perfectly normal testicles that chemically might not be functioning optimally.

One of the earliest reports of the benefits of T administration in hypogonadal men was by Joseph Aub,[19] who wrote in *The New England Journal of Medicine* in 1940:

> "The best treatment for hypogonadism would be to stimulate the anterior pituitary gland to greater activity, and so indirectly stimulate the gonads. But a good technic for so stimulating the pituitary gland is not at hand." Upon administration of testosterone in these men, Dr. Aub observed, "Erections and enlargement of the penis rapidly occur, followed by the growth of hair, changing of the voice and a moderate change in body configuration. The prostate enlarges to normal size as judged by palpation, whereas before treatment the gland could not be felt. Greater psychologic vigor and assurance are obvious, though these may well be purely psychologic responses to the physical changes." He concluded, "From this report of the practical use of testosterone in clinical medicine it is obvious that the drug is a potent one, particularly in hypogonadism in males. In this condition, its effectiveness as substitution therapy is uniformly accepted."

In a subsequent report, Aub and Kety[20] elaborated on prior observations: "In view of the widespread physiologic effects of testosterone, which have been discussed in an earlier part of this paper, it is perfectly possible that the male sex hormone may exert a beneficial action on systems other than the urogenital tract."

In 1944 Carl Heller and Gordon Myers[21] reported that aging men develop symptoms attributable to hypogonadism. The symptoms included depression, impaired memory, easy fatigability, and loss of sexual vigor. Heller and Myers made the diagnosis of "male climacteric" by testicular biopsy and a bioassay showing increased urinary gonadotropin levels. Heller and Myers also showed that symptoms and gonadotropin levels reverted to normal with administration of T propionate.

In addition to addressing symptoms of hypogonadism, T therapy was investigated for a number of other medical conditions. Dobes et al[22] reported on the treatment of pruritus with T propionate. Others investigated the use of T therapy for the treatment of angina pectoris,[23,24] hypopituitarism and anemia,[25] depression,[26] renal failure,[27] various urologic disorders,[28–30] and the male climacteric.[31] These and other studies were brought to popular attention in a widely read book of that era by Paul De Kruif.[2]

Resistance to the Use of Testosterone

From the time of the very 1st reports of the benefits of T therapy, there also has been a countervailing negative reaction among some members of the medical community. This attitude persists to the present day. Many of the comments from decades ago persist today, almost unchanged despite decades of supporting clinical experience and research.

For example, in May 1939, a report regarding testosterone from the American Medical Association Council on Pharmacy and Chemistry stated:

> "Therapy has been attempted in the following conditions, and, while the treatment of all of them is still in the experimental stage, it appears that the results are promising in only a few." The report continues, "Reliable evaluations of benefits or dangers must await extensive experimentation over a period of years.… All other claims are either exaggerated or premature, and should be disregarded until substantial evidence become available on which to evaluate them." And, "Many pharmaceutical firms would have one believe that in the ampoule of testosterone propionate lies the 'Fountain of Youth.'"[32]

Another criticism familiar to today's readers is the assertion that treatment should be limited, even if effective. From the American Medical Association textbook of glandular physiology in 1942, the prevalence is described as follows: "the male climacterics is a relatively rare condition."[33] Some commentators then, as today, took a strong stance against the use of T therapy and demeaned the character of those who advocated for its use. In 1 such example from the *Journal of the American Medical Association* in May 1939, Morris Fishbein wrote, "This flamboyant exploitation obviously presupposes an extraordinary ignorance on the part of the physician."[2,34,35]

Responding to these criticisms in his landmark book, *The Male Hormone*, published in 1945, De Kruif[2] wrote: "… the vast majority of these medical reactionaries, if you stood them an examination in the rudiments of organic chemistry, could not draw you a simple diagram showing the structural differences between an open chain and a ring carbon compound." In discussing the results of several studies demonstrating cardiovascular (CV) benefits of T therapy, De Kruif commented: "Could our leading heart specialists, who are men of the highest medical dignity, break through a possible prejudice against testosterone because of its unfortunate sexual origin?"

Arguably the most important event in the history of T was the report in 1941 by Charles Huggins and Clarence Hodges[36] that castration caused metastatic prostate cancer (PCa) to regress and that T administration appeared to cause its growth. Huggins was awarded the Nobel Prize in Medicine and Physiology in 1966, and his work cast a pall over T therapy for more than 7 decades. However, De Kruif[2] in 1945 already provided a perspective that proved prescient: "Testosterone does not cause cancer in men, but it is an important factor in the continued growth of cancer cells in any part of the body, provided that the cancer originated in the prostate gland."

For a more comprehensive history of T, the reader is encouraged to refer to several reviews in the literature.[2,4,5,37–42]

Testosterone Therapy in Men With Vascular Disease

CV risk arose as a new item of concern for T therapy in 2013 (see Part 2), and therefore it will be surprising for readers to learn of an extensive published experience with T therapy for the treatment of cardiac and peripheral vascular disease during the early history of T therapy. We provide some extended commentary from studies of that era, because this chapter in T's history is not widely appreciated but has continued relevance today.

Peripheral Vascular Disease

In 1939 Arndt[18] suggested T treatment for the relief of intermittent claudication in men. Similarly, Edwards et al[43] reported that T treatment produced "marked improvement in the walking ability of all the patients, with delay or abolition of the intermittent claudication." Not all investigators agreed. Beaser and Massell[44] in 1943 reported that T therapy did not prevent intermittent claudication in 6 men occlusive vascular disease.

Here is a passage from Edwards et al[45]:

> Our attention was directed to the general vascular effect of testosterone propionate while studying the skin changes

> in human male castrates. With the recording spectrophotometer, we had noticed that the skin of these subjects showed a lack of arterial blood, although the more venous regions of the body contained an abnormally large amount of venous blood. After treatment, with testosterone propionate, there was an increase in arterialization and blood volume in those regions normally arterial, such as the head, palms of the hands and soles of the feet. Less constantly there was a diminution in volume of blood in the normally venous areas, such as the lower abdomen and the dorsum of the foot, attended by a shift in the contained blood to a more arterial type.

Based on such observation, the investigators treated 7 men with organic vascular disease with T propionate. There findings were summarized as follows:

> The ulceration in 1 patient with Buerger's disease has healed; the second has greatly improved. There was marked improvement in the walking ability of all the patients, with delay or abolition of intermittent claudication. Two patients were no longer subject to night pain, which had troubled them previously. Subjectively, the patients reported an increased activity and a feeling of optimism, results similar to those reported previously with male hormone treatment. We believe that this material deserves further trial in both organic and functional arterial disease in order to establish clearly its mode of action and to be sure of its harmlessness.

Angina Pectoris

In the early 1940s, a number of studies suggested T therapy might be of considerable therapeutic value in the treatment of angina pectoris.[24,46–53] Building on such observations, Waldman[54] investigated the effects of T treatments in a series of 10 cases with angina pectoris. Waldman reported that 7 of 10 cases showed significant improvement. Levine and Likoff[51] treated 19 patients (16 men and 3 women) with angina pectoris whose age ranged from 35 to 70 years. The duration of angina pectoris ranged from 1 month to 13 years (average = 6 years). They reported marked improvements in 5 patients and no changes in the other 11 patients. In another case series of 20 patients from Vancouver General Hospital, Strong and Wallace[53] reported that 3 showed no improvement, 6 showed marked improvement, and 11 showed slight to moderate improvement. 3 of 4 cases with peripheral vascular disease also showed slight improvement and 1 showed no improvement.

Walker[46,47] investigated the effects of T treatment in 82 individuals: 56 had essential hypertension, 12 had angina pectoris, and 14 had organic peripheral vascular disease. Walker noted improvements in blood pressure and lamented:

> While psychotherapy unquestionably has played an important role in this study, certain findings indicate that the sex hormones exert a definite and a sustained vasodilating action. The majority of the patients in this investigation were being treated by other methods when sex hormone therapy was initiated, and in many of these a further lowering of the blood pressure occurred. In the entire group of hypertensive individuals, sex hormone therapy has resulted in a more pronounced and more prolonged lowering of the blood pressure than I have usually obtained by other medical methods. Moreover, the effect of these substances in occlusive peripheral vascular disease and angina pectoris is further indicative of a pronounced vasodilating action.

Walker concluded that sex hormones appear to be valuable chemotherapeutic substances in essential hypertension, angina pectoris, and organic peripheral vascular disease.

Lesser[24] reported on 100 consecutive patients with angina pectoris who received T therapy, with follow-up ranging from a few months to 5 years. The group was composed of 92 men and 8 women whose age ranged from 34 to 77 years. Lesser reported that 91 patients showed moderate to marked improvements for periods of 2 to 34 months, with no appreciable improvement in patients treated with placebo, whereas 9 patients had no noticeable beneficial effects. Lesser classified the results as follows:

> A patient was classified as showing "marked improvement," if he was able to increase his physical activity without precipitating an anginal attack for a period of at least 2 months after testosterone therapy was discontinued. A patient was considered to have "moderate improvement" if the anginal attacks were reduced to less than half the number he had prior to treatment. Those patients in whom there was no noticeable reduction in the number of attacks following this form of therapy were considered failures.

Marked improvement was noted in 49 men and 2 women, moderate improvement was noted in 36 men and 4 women, and no improvement was observed in 7 men and 2 women.

Remarkably, Lesser also gave placebo injections.

> To eliminate the psychological effect of injection therapy per se, five patients were given six consecutive injections of sterile sesame oil prior to receiving testosterone propionate, and two were similarly controlled after a recurrence of anginal symptoms following the first course of the drug. None of the patients who had received sterile sesame oil alone showed any appreciable change in symptoms. On the other hand, progressive improvement was noted in these same patients following the use of testosterone propionate. The contrast was particularly striking in two patients who were first treated with testosterone propionate with marked improvement, and then had a recurrence of symptoms four and seven months respectively after the last injection. For these new attacks, they were given placebo injections of sterile sesame oil, without clinical improvement. Following a return to testosterone therapy, relief from anginal attacks was again obtained.

To illustrate the benefits, Lesser provided several case reports. One case is presented here:

> Case 2. W.W., a 64-year-old physician, had a history of angina pectoris of four years' duration. The pain, which was substernal and radiated down the left arm, was brought on by climbing one flight of stairs or by walking three or four city blocks, and was relieved by rest or nitroglycerin, of which from two to four tablets were required daily. After only three injections of testosterone propionate the patient reported that he was able to perform his usual duties without resorting to nitroglycerin. The exercise tolerance test, which prior to testosterone propionate therapy required from 32 to 43 trips to produce anginal pain lasting from 90 to 94 seconds, showed definite improvement after the eighth injection. At the end of twelve injections, the patient was able to perform 72 trips before precipitating an attack and the pain lasted only 23 seconds. To date, 34 months after the discontinuance of testosterone therapy, the patient has been able to take care of a busy medical practice without resorting to nitroglycerin except on rare occasions.

A number of other case series corroborated these results.[47,48,52–56] One that did not[51] was of short duration (4 weeks), which could have contributed to the lack of reported effect.

PART 2. RECENT HISTORY

The modern history of T deficiency and T therapy arguably begins with the introduction of the radioimmunoassay into clinical medicine in the 1970s. Indeed, this was the birth of modern endocrinology. For the 1st time, there was the ability to accurately, rapidly, and inexpensively measure minute concentrations of hormones in serum, an advance that permitted determination of concentrations from milligrams per milliliter to nanograms per milliliter—a 1,000-fold improvement.

This was an enormous advantage, one that coincided with improved objective capabilities in many areas of medicine, including imaging techniques and the use of computers. The overall effect of these changes for T deficiency was to shift diagnosis from clinical presentation to laboratory values. This emphasis on objective data spawned the prevailing current approach to clinical practice that discourages treatment for many men with classic symptoms based on test results categorized as normal.

The literature regarding T therapy in humans in the 1970s is scant; however, this was an active period for investigation of the effects of T deprivation and replacement in animals. Although it has been recognized for millennia that castration influences the behavior, appearance, and body composition of domesticated animals and even humans, the era of government-sponsored research showed that injections of radiolabeled T localized in muscle, bone, skin, liver, bone marrow, fat, and the genitalia. Within the brain, T was localized to several areas, most notably the preoptic area and the hypothalamus.[57] These regions are known to regulate sexual behavior.[58]

In the 1980s, the clinical use of T therapy was rare. There was no awareness at that time that otherwise healthy men could experience signs and symptoms of T deficiency that might be reversed with T therapy. Even if one believed T therapy might be helpful to a patient, the fear of precipitating PCa made consideration of T unthinkable. Many large medical centers had just 1 endocrinologist who treated a handful of these cases, consisting almost exclusively of men with pituitary tumors, brain resections that included the hypothalamus and/or pituitary, testicular atrophy or absence, and, occasionally, men with genetic issues, such as Klinefelter syndrome. Treatment was initiated in these men to progress through puberty, for sexual desire and function, and/or to promote secondary sexual characteristics such as beard, body hair, and muscularity.

Prostate Cancer

The history of T cannot be understood without appreciating events in the world of PCa. As noted earlier, by 1940, Aub[19] and Aub and Kety[20] had already published glowing reports on the benefits of T therapy. The very next year came a publication that made physicians believe T caused PCa, stopping T therapy in its tracks.

In 1941 Huggins and Hodges[36] published their initial experience with castration and estrogen treatment (which severely decrease serum T) in 8 men with metastatic PCa. These treatments caused the serum marker, acid phosphatase, to decrease in all these men, suggesting improvement in their cancer status. Huggins and Hodges also reported that daily injections of T propionate in 3 men for 14 days caused an increase in acid phosphatase. They concluded, "Cancer of the prostate is activated by androgen injections."

Androgen deprivation therapy (ADT) immediately became the mainstay of treatment for advanced PCa and remains so to this day. The primary form of ADT for decades was castration, until the introduction of luteinizing hormone-releasing hormone agonists in the 1980s provided a non-surgical, non-mutilating alternative for greatly lowering serum T.

In 1981 Fowler and Whitmore[59] reported on their experiences of administering T to men with advanced and metastatic PCa at Memorial Sloan Kettering Cancer Center in New York from 1949 to 1967, in which 45 of 52 evaluable men developed an "unfavorable response" within 30 days. This high rate confirmed the belief that increasing T in a man with PCa was like "pouring gasoline on a fire" or "feeding a hungry tumor," phrases that were widely taught to medical students around the world.

By this time, it was universally believed that high T, occurring naturally or by T therapy, was responsible for development of PCa and its rapid growth, and low T was protective against development of PCa. This set of beliefs was called the "androgen hypothesis." Given this widespread belief, it is not surprising that awareness of the benefits of T therapy noted in the early years, as

described earlier, was lost and T therapy was almost completely abandoned except for the most severe cases of T deficiency.

The 1st evidence against the androgen hypothesis came from results of sextant prostate biopsy series in men with low T, prostate-specific antigen (PSA) level lower than 4.0 ng/mL, and normal digital rectal examination findings, showing 11 cancers in 77 men (14%).[60] This cancer rate was similar to contemporaneous studies in men known to be at increased risk based on increased PSA levels of 4 to 10 ng/mL or abnormal digital rectal examination findings. A subsequent study of prostate biopsies in a larger group of 345 men with T deficiency confirmed the original results, with an overall cancer rate of 15%, including a 30% cancer rate in men with a PSA level of 2 to 4 ng/mL.[61] Clearly, low T was not protective against the development of PCa.

In 2004, a comprehensive review of the literature did not find compelling modern evidence that higher endogenous T or T therapy was associated with increased PCa risk.[62] Several years later, Roddam et al[63] published the results of a collaborative analysis of pooled worldwide data from 18 longitudinal studies involving 3,886 men with PCa and 6,438 controls, which found no association between PCa risk and serum concentrations of T or dihydrotestosterone. In particular, men with higher levels were found to be at no greater risk of developing PCa than men with lower androgen levels.

In 2006, the belief that high serum T was dangerous for PCa was directly challenged and described as an "historical myth."[64] Not only were there no modern data indicating increased risk of PCa with T therapy or higher endogenous T, but review of the old data had been misinterpreted. In the original report by Huggins and Hodges,[36] there was only 1 non-castrated man who received T injections, and his acid phosphatase curve did not show progression. In the report by Fowler and Whitmore,[59] all but 4 men were already on ADT when they received T. Of these 4 hormonally intact men, 3 received daily T injections for up to 355 days without an unfavorable response. It also was noted that men develop PCa when they are older and T levels are decreased, and that PCa is exceedingly rare during the peak T years of the late teens and early 20s.

The key to understanding the relation between testosterone and PCa comes from the following:

> The paradox of these data can be summarized as follows: Since lowering testosterone causes PCa to regress, why is it that raising testosterone fails to cause PCa to grow? The solution lies in the concept of saturation, in which maximal stimulation of PCa growth is achieved at some relatively low concentration of testosterone.[64]

This 2006 article was the foundation for the saturation model, which was refined and more thoroughly developed in 2009 and thereafter provided a theoretical framework supporting the use of T therapy in selected men with PCa.[65] The saturation model has since been confirmed by multiple observations, including prospective trials and registry data showing that the saturation point at which peak PSA is achieved is approximately 250 ng/dL. Groups of men with baseline serum T below this value demonstrate an increase in PSA with T therapy, whereas men with baseline T above 250 ng/dL do not.[66,67]

A moderate number of case series have been published showing that T therapy appears safe after various treatments for localized PCa, including radical prostatectomy, brachytherapy, and radiation therapy. Indeed, 3 series in men who received T therapy while on active surveillance have reported reassuring results regarding progression rates that appear no greater than in untreated men.[68–70] The T and PCa story has been further turned on its head by a report of high-dose T injections contributing to positive responses in men with castrate-resistant PCa.[71] This appears to be a radical new concept, but Morales et al[72] reported on beneficial effects of T propionate injections in 2 men with metastatic PCa in 1971.

The PCa and T story is worth noting, because the increase in T therapy coincided with the growing body of research that supplanted the androgen hypothesis with the saturation model.[65]

Rise of Testosterone Therapy

Despite the concerns regarding PCa, key figures in the early 1980s recognized the importance of T deficiency, with Alvaro Morales[73] advocating for T measurement in the evaluation men with erectile dysfunction and Eberhard Nieschlag[74] exploring T treatment options. However, this view would not be widely accepted for 20 years.

By the turn of the century there was growing interest in aging well among the lay public. Quality of life became a more common metric in research studies at this same time. The 1st topical formulation of T, a scrotal patch, was approved in the United States in 1998. Of greater consequence, the 1st topical gel, AndroGel (AbbVie, Inc, North Chicago, IL, USA), was approved in the United States in 2000. Soon after, a 2nd gel, Testim (Endo Pharmaceuticals, Malvern, PA, USA), was approved in the United States, and prescription rates began their impressive increase for the next 15 years. Multiple T products followed in the United States and elsewhere. Before this, the only widely available products in the United States were alkylated oral T, associated with serious liver toxicity, and the short-acting T esters, cypionate and enanthate. T propionate use had been largely discarded because of its short half-life.

An important advance in the global T market was the introduction of injectable T undecanoate in Europe and elsewhere. At a dose of 1,000 mg (Nebido, Bayer AG, Wuppertal, Germany), the drug achieved and maintained normal T levels with injections given every 3 months. The drug was later approved in the United States at a lower dose of 750 mg (Aveed, Endo Pharamceuticals), requiring injection every 10 weeks. Another long-acting formulation in the United States and some countries was an implantable T pellet, which lasts approximately 3 to 4

months. The convenience of these new formulations, coupled with rising interest in promoting health and well-being, resulted in a progressive rise in T prescriptions that has continued to the present day.

The Next Controversy: Overtreatment and a False Epidemic

Prescriptions for T therapy increased as fears eased regarding PCa. However, before too long, T therapy came under scrutiny for its increased use. T therapy became a surrogate in a proxy war by those who believed the pharmaceutical industry promoted unnecessary treatments for a false epidemic of non-existent medical conditions, which, according to adherents of this argument, would be better described as "normal aging." Some critics pointed to the rapid rise of T prescriptions to argue that, because there was no reason to believe the prevalence of T deficiency had increased, the increase in new prescriptions meant men were being overtreated. A related argument was that the widespread use of T therapy was a national uncontrolled experiment because no large, prospective, placebo-controlled study had been performed to definitively demonstrate the benefits or risks of T therapy.

The argument of overtreatment failed to acknowledge that diagnosis and treatment of T deficiency were suppressed for decades because of the fear of PCa, and its rare use in turn resulted in the lack of appreciation of the benefits of treatment. As with any treatment that is new or newly recognized, an increase in prescriptions is certain to follow. This cannot be logically argued to mean that there is overtreatment. In addition, there is an under-recognized "dark side" to T deficiency that goes far beyond its sexual symptoms.[75–77] Men with lower levels of T have been demonstrated to show increased mortality, greater incidence of atherosclerosis and coronary artery disease, and increased low-trauma fracture rates. Men with PCa who undergo ADT show rapid loss of lean mass with substantial gain in fat mass and decreased glycemic control. Simply put, T deficiency is associated with impaired health, and T therapy tends to cause improvements in these areas.

Publication of the results of the Testosterone Trials in a series of publications beginning in 2016 put to rest the criticism of inadequate evidentiary support for T therapy.[78] This coordinated set of studies was performed in 790 men at least 65 years old with serum T lower than 275 ng/dL who were assigned to 1 year of T gel or placebo gel. The results demonstrated that men who received T gel therapy compared with those who received placebo gel demonstrated greater libido, erectile function, sexual activity, physical activity, mood, bone density, and resolution of anemia.

By the end of 2017, T therapy was accepted as a reasonable treatment by many specialties, including urology, primary care, pain medicine, family medicine, and in some cases, endocrinology. However, suspicions persisted in many corners of the medical community.

Cardiovascular Risk

Late in the previous century there were concerns that T might be related to CV risk based on the fact that men are at greater risk than women for heart attacks, strokes, and CV deaths. However, this concern evaporated as studies in men showed that *low* levels of T were associated with increased risk and that higher T levels appeared cardioprotective.

Suddenly, in 2013 there was an urgent concern that T therapy was associated with increased CV risk. Vigen et al[79] reported that in a retrospective cohort of 8,507 men in the Veterans Administration system who underwent coronary angiography and had T levels lower than 300 ng/dL, those who subsequently received T had a greater absolute risk of myocardial infarction, stroke, and death than untreated men by 25.7% to 19.9%. The study was published in a prominent medical journal and precipitated a regulatory review of CV risk. The story of a frequently prescribed medication causing unexpected serious CV events generated considerable media attention and provided fuel for those who believed T therapy was largely unwarranted. However, the original study by Vigen et al[79] had from serious errors, including misreporting its primary results, which actually showed a lower absolute rate of events by half in the T-treated group—10.1% vs 21.2% in the untreated group—and contamination of the all-male study by nearly 10% women.[80]

Nonetheless, the damage was done. In the subsequent 4 years, approximately 1 dozen additional CV studies were performed, with nearly all showing that T therapy appears to be beneficial against CV risk. A notable study showed that mortality and myocardial infarction rates were decreased for men whose serum T levels normalized with treatment compared with men whose T levels continued to be persistently low despite T therapy and for men who were untreated.[81] Another study by Wallis et al[82] showed that mortality risk was lowered progressively with longer duration of T therapy.

Perhaps most importantly, the numbers of major adverse cardiovascular events in the Testosterone Trials were identical in the T and placebo arms in the 1st year (n = 7 in the 2 arms) and were greater in the placebo arm during a 2nd year of follow-up (9 in placebo arm and 2 in T arm). A large formal CV trial, mandated by the Food and Drug Administration, is scheduled to begin recruiting in the near future. It will take at least 5 years for the results of this study to be known. In the meantime, although the weight of evidence fails to support increased CV risk with T therapy, the public and many physicians remain wary.

General Health Benefits

A detailed review of the benefits of T therapy is beyond the scope of this article, yet there are key items that merit comment. The primary benefits were recognized by Aub[19] and Aub and Kety[20] in 1940, and since then countless physicians and patients have observed the positive results. Today, we have level 1 evidence that T therapy results in improvement in sexual desire, erection quality, and sexual activity. T therapy increases lean mass, decreases fat mass, and improves bone mineral density. Interestingly, observational data indicate that weight and waist circumference

improve progressively in obese men over periods of up to 8 years.[83] As the global population struggles with a rising rate of metabolic conditions, there are provocative data indicating that insulin resistance is decreased with T therapy.[84] Every clinician experienced with T therapy knows that one of the most important benefits of T therapy is what our patients tell us so often—they feel healthier, more vital, and with an improved sense of well-being.

TESTOSTERONE THERAPY TODAY AND IN THE FUTURE

T therapy has become a relatively common treatment for men with documented T deficiency. Clinicians observe a high rate of positive responses, often dramatic, in the areas of sexual desire, erectile function, energy, decreased fatigue, and improved mood. It is not unusual to hear a patient say he feels "younger" or "better than I've felt in years." From a research perspective, the benefits of T therapy are well documented in several areas.

Despite the clarity of clinical results and scientific research, T therapy remains controversial. Critics continue to claim it has been over-marketed, resulting in overuse and abuse. Fears of PCa and CV risk persist despite a wealth of data that fail to support these concerns.

The controversial nature of the topic makes it challenging to predict what will happen to T therapy in the future. Some concerns appear to be emotional rather than based on fact.[85] In addition, there are substantial differences in approach to treatment by medical specialties. Endocrinologists, for example, take a conservative approach to treatment, requiring strict adherence to biochemical thresholds before instituting treatment, whereas urologists are often more liberal with treatment, based on clinical presentation. The absence of consensus on basic questions, including who is a candidate for T therapy, represents a major hurdle for the field.

In the face of so much confusion and controversy, an International Expert Consensus Conference was held in Prague in 2015, involving 18 individuals from 12 countries, from endocrinology, urology, andrology, basic science, epidemiology, diabetology, and general medicine.[86] There was unanimous agreement on several key points: T deficiency was a serious global problem; the evidence failed to support increased risk of PCa or CV risk; total T was a useful but unreliable test to determine androgen status; and the possibility that T therapy is cardioprotective should be investigated, particularly in men with metabolic conditions such as diabetes and obesity.

An important detail was that the term "hypogonadism" should be replaced in most instances by "testosterone deficiency," as we use in this text, because of its greater clarity, and similarly, "testosterone therapy" was favored over "testosterone replacement therapy."[86]

What will the future look like? We anticipate the introduction of more convenient treatment modalities such as oral formulations that achieve solid serum T concentrations without hepatotoxicity. Another consideration is long-lasting treatments that are not associated with side effects such as infertility and testicular atrophy. One promising idea is a slow-release human chorionic gonadotropin formulation, currently in development, designed to boost endogenous serum T for at least 2 months.

Another set of possibilities relates to the known properties of T therapy separate from its indication in the treatment of men with T deficiency. It seems reasonable to investigate whether short-term T treatments might have useful benefits in the treatment of trauma, sepsis, and perioperatively for major surgical operations such as radical cystectomy, or even for routine orthopedic procedures in which they could have value in promoting muscular repair and strength.

If the past has any lessons for the future, T therapy research will continue to demonstrate new health benefits and continue to be one of the most controversial and fascinating topics in medicine.

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