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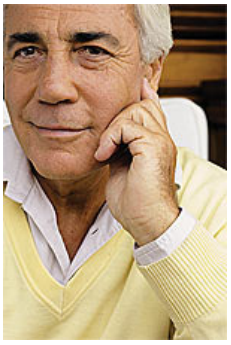
REPORT

Destroying the Myth About Testosterone Replacement and Prostate Cancer

By Abraham Morgentaler, MD, Facs Introduction By William Faloon



For decades, the medical establishment erroneously conjectured that testosterone replacementestosterone therapy increases one's risk of prostate cancer.

Harvard-based Abraham Morgentaler, MD, FACS, has demonstrated this theory to be mistaken. Contrary to the notion that restoring testosterone to youthful levels is somehow risky, Dr. Morgentaler meticulously shows an increased risk of prostate cancer in aging men with low testosterone. This same information about the dangers of low testosterone was long ago uncovered by the **Life Extension Foundation.**

In this exclusive excerpt from his book, *Testosterone for Life*, Dr. Morgentaler recounts how it takes years, even decades, to correct a medical myth. Inthis case, the medical establishment's misconception about testosterone and prostate cancer has condemned millions of aging men to suffer degenerative diseases caused by testosterone deficiency.

Until just a few years ago, it was almost universally believed that T [testosterone] therapy would lead to some degree of increased risk of prostate cancer. During that time testosterone therapy was seen to represent the proverbial pact with the devil, by trading short-term sexual and physical rewards for the ultimate development of a malignant cancer. Fortunately, this belief has been shown to be incorrect, and medical opinion has begun to shift quite dramatically, with good evidence that testosterone therapy is quite safe for the prostate. There is even now a growing concern that low testosterone is a risk for prostate cancer rather than high testosterone.

How the original fear about T and prostate cancer came to be is a fantastic story involving Nobel Prize winners, medical breakthroughs, and a critical paradox that took two-thirds of a century to solve. In the end, it is also a cautionary tale of how it may take years—even decades—to correct a medical "truth" once it has been established. I have taken great pleasure in participating myself in the evolution of attitudes regarding T and prostate cancer, and here describe how this all took place.

The relationship of testosterone to prostate cancer has undergone a significant reevaluation, and all recent evidence has reinforced the position that testosterone therapy is safe for the prostate. I've been fortunate to have participated in the evolution of this idea, which is of critical importance to anyone considering testosterone therapy.

Origins of the Concern

The basis for the fear that testosterone therapy increases the risk of prostate cancer originated with the work of Charles B. Huggins, a urologist at the University of Chicago. Huggins was initially interested in the medical condition called benign enlargement of the prostate, called benign prostatic hyperplasia (BPH), which causes frequent and urgent urination and also can occasionally cause complete obstruction of the urine passageway. Benjamin Franklin was reported to have suffered from BPH and was credited with inventing a tube he inserted through the urine channel to relieve the obstruction.

Curiously, dogs are the only species we know of other than humans that naturally develop prostate problems on a regular basis. At the turn of the twentieth century, there were reports that castration was successful in treating some men with severe obstruction from BPH, and Huggins began experimenting on the effects of castration on BPH in dogs. Not only did the dogs' prostates shrink after castration, but Huggins made an additional far-reaching observation.

Huggins noticed that the microscopic appearance of prostates of some of these dogs contained areas that were indistinguishable from human prostate cancers. Even more importantly, after castration, dogs with these cancerous-appearing areas also demonstrated shrinkage of their prostates. Indeed, when their prostates were removed, the dogs had no further evidence of the cancerous-appearing areas.

Huggins and his coworkers then applied his dog results to humans. By this time, it was known that the key effect of castration was to reduce testosterone levels in the bloodstream. He took a group of men who had prostate cancer that had already spread to their bones and lowered their testosterone levels, either by removing the testicles or by administering estrogen. A blood test called acid phosphatase was high in men with metastatic prostate cancer, and Huggins and his coworkers showed that acid phosphatase dropped substantially within days of lowering testosterone. Of even greater consequence for the future of testosterone therapy, Huggins also reported that administration of testosterone injections to men with prostate cancer caused acid phosphatase to rise. Huggins and his coworkers concluded that reducing testosterone levels caused prostate cancer to shrink and raising testosterone levels caused "enhanced growth" of prostate cancer.

This demonstration of the androgen dependence of prostate cancer was incredibly important, because until that time in the early 1940s prostate cancer was untreatable. From that point forward, lowering testosterone by castration or by estrogen became the standard treatment for advanced disease and remains a mainstay of treatment to this day. Because estrogen treatment caused heart attacks and blood clots in some men, and because most men did not care for the idea of having their testicles removed, a new type of medication—LHRH agonists—was introduced in the 1980s. Injections of this medication are now the usual way testosterone is lowered in men with prostate cancer.

Huggins was eventually awarded the Nobel Prize in 1966 for his work showing that prostate cancer grew or shrank depending on testosterone levels. Until recently, this prevailing wisdom regarding prostate cancer and testosterone had not been seriously questioned.

My Involvement in the Story

By the time I performed my urology training in the mid 1980s as a resident at the Harvard Program in Urology, based at the Brigham and Women's Hospital in Boston, one of the unassailable assumptions held by all the urologists I trained under was that prostate cancer shrunk with low testosterone and grew with high testosterone.

In my training, we learned that men who had been castrated early in life never developed prostate cancer. In the laboratory, prostate tumors could be placed under the skin on the back of mice, and the tumors would grow to a large size. Pieces of these tumors could then be transferred under the skin of another male animal and would again grow to a large size. If the males were castrated or given estrogen (which lowers testosterone), the tumor would shrink rapidly or not even take root.

The tumor would not grow at all, however, if it was transferred under the skin of a female. On the other hand, if the female were given testosterone, the tumor would grow just as well as if it had been placed in a male. All these studies indicated that testosterone was a critical element in allowing prostate cancer growth. There seemed to be good reason to believe that it would be dangerous to give testosterone supplementation to a man with prostate cancer. I believed that, and so did everyone around me.

My fellow residents and I thus learned to repeat the comments of our teachers to our patients in the clinics. Whenever issues of testosterone would come up, we would say the relationship of testosterone to prostate cancer was like "pouring gasoline on a fire" or providing "food for a hungry tumor." These phrases are still in use throughout the medical world.

In those days, we all spoke about testosterone and prostate cancer as if there were a simple, direct relationship, but the truth is not quite so simple.

A Fateful Interaction

Once I finished training, I began my specialization in the treatment of "guy stuff," primarily male infertility and sexual problems. I also began diagnosing and treating a large number of men with low testosterone. This was not a common practice at the time; in fact, I had very little experience with testosterone therapy during my training. This was because there was little research showing that testosterone treatment helped the symptoms seen in men with low testosterone. Indeed, one of the most bothersome symptoms—erectile dysfunction—was believed at the time not to improve with testosterone treatment (later research has shown this belief to be incorrect). Doctors also were reluctant to prescribe testosterone because of the fear of promoting a prostate cancer that might be lurking silently inside the man's prostate gland.

At the end of my second year of practice, I ran into one of my former teachers at the national meeting of the American Urological Association. He asked me if it were true that I was treating men with testosterone. I replied that I was and explained that I had been pleasantly surprised to find so many good responders despite my earlier training.

"I wouldn't do that anymore, if I were you," he said. "I just had a patient diagnosed with prostate cancer within a year after beginning testosterone treatment. If you're going to continue treating men with testosterone, and I recommend

you don't, you should at least do a prostate biopsy first to make sure they don't have cancer."

Naturally, this was a disconcerting conversation, especially coming from a former teacher of mine whom I respected greatly. So I followed his suggestion and began performing prostate biopsies before initiating testosterone therapy. At least with a biopsy, I could rule out the presence of cancer.

At the time, the only reasons to do a prostate biopsy were for an abnormal-feeling prostate, as determined by digital rectal exam (DRE), or for an abnormally high result for the prostate-specific antigen (PSA) blood test, which can indicate an increased risk of prostate cancer. Surprisingly, despite a normal DRE and PSA, one of the very first men I biopsied had cancer. This was very strange, because it was assumed at the time, as I've explained earlier, that a man with low testosterone should have been protected against prostate cancer. It didn't take long to find several more cancers in men with low testosterone despite normal DRE and PSA results. Indeed, of the first thirty-three men I biopsied, six had cancer. This was a very high cancer rate, especially for a group of men without known risk factors. After presenting these results at the national urology meeting, one of the academic chiefs, a well-respected man, declared in his trademark booming voice, "This is garbage! Everyone knows that high testosterone causes prostate cancer, not low testosterone. You guys just got unlucky. I bet if you biopsy the next 100 men, you won't find another cancer."

It was a dramatic moment—I was a young unknown being castigated on a national stage by a major figure in the field. And he was right—given what we knew about testosterone and prostate cancer, the results made no sense.

All I could do was to respond, "These are the results we obtained. We present them here because they do fly in the face of conventional wisdom, which is why we believe they may be of interest to this audience."

When the size of the group we had biopsied was fifty men and the cancer rate was unchanged, my colleagues and I submitted a manuscript to the *Journal of the American Medical Association*, one of the top medical journals in the world. The associate editor soon called me up to say, "Our editorial board finds your data very interesting, because it runs counter to what we would expect. But our concern is that your numbers are small, and perhaps you may have just had an unlucky run with your biopsies. If you gather additional men and your cancer rate holds up, we will seriously consider publishing your manuscript." Before long I submitted data on seventy-seven men, eleven of whom had cancer, and the paper was published.

At the time, in 1996, the 14 percent cancer rate we reported was several times greater than any previously reported cancer rate in men with normal PSA (4.0 ng/mL or less). Several studies had reported biopsy results in men with normal PSA with cancer rates of 0 percent or 2 percent, with the highest value reported being 4.5 percent. The much higher cancer rate in our population certainly seemed to suggest there was something different about prostate cancer risk in men with low testosterone.

Frankly, most experts just didn't know what to make of our results. A high cancer rate among men with low testosterone didn't fit into the existing way of thinking regarding testosterone and prostate cancer. And because we hadn't biopsied a control group of men (men with normal T and no other risk factors), it was impossible to say whether men with normal T would have had a different cancer rate than our patients with low testosterone.

In retrospect, though, that paper was the first direct evidence in a major medical journal that standard assumptions about testosterone and prostate cancer might not be correct. At a minimum, it was obvious that low testosterone could not be considered protective against the development of prostate cancer, as had been assumed for so long. And it made me wonder whether other assumptions about testosterone and prostate cancer were also incorrect.

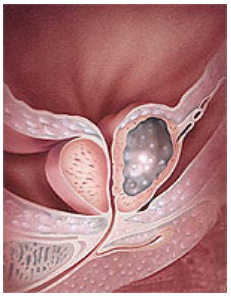
The New England Journal of Medicine

After publication of my article on prostate biopsies in men with low testosterone, I published a number of additional articles looking at the relationship between testosterone and the prostate. In one provocative study, a colleague and I looked at whether testosterone therapy posed special dangers for men who were already at high risk for developing prostate cancer.

In this study, we compared the results of testosterone therapy given for twelve months in two groups of men with low testosterone. The first group consisted of twenty men considered to be at high risk for prostate cancer based on biopsy results showing an allegedly precancerous condition called prostatic intraepithelial neoplasia (PIN). The second group consisted of fifty-five men with normal biopsy results. At the end of one year of treatment, both groups had a similar, modest increase in PSA. One man in the study, who was in the high-risk group, developed cancer.

So, overall testosterone therapy resulted in a one-year cancer rate of 1.3 percent (one of seventy-five men). More importantly, the one-year cancer rate among the high-risk men with PIN was 5 percent. This compared to the known cancer rate of 25 percent over three years in this population. While the two figures are not directly comparable, these results certainly did not seem to suggest that testosterone therapy had increased the cancer rate in this high-risk group. And the overall cancer rate was not very high at all.

Here was another piece of evidence that the old assumptions about testosterone and prostate cancer were incorrect, specifically the notion that testosterone therapy was like pouring gasoline on a fire. First, we had found that men with low testosterone did not seem to be protected against developing cancer. Now, at the other extreme, we found that men at high risk for prostate cancer did not seem to suffer any dramatic "explosion" of cancer when treated for a year with testosterone therapy. And when I looked back at my extensive experience of treating men with testosterone therapy, many for ten years or longer, precious few cases of cancer had developed.



Prostate tumor confined to prostate gland.

It was heresy, but I couldn't help thinking that the old stories linking testosterone levels to risk of prostate cancer might well be wrong. After all, if one looks at the natural progression of prostate cancer, it never occurs in men in their twenties when testosterone levels are at their lifetime peak, even though autopsy studies have shown that a significant percentage of these young men already harbor microscopic prostate cancers. Instead, prostate cancer becomes increasingly common as men age, when testosterone levels have declined.

I was coming to the conclusion that the average physician might be unduly fearful of the risk of prostate cancer with testosterone therapy. From my lectures to physicians around the country, it became clear to me that many physicians withheld testosterone therapy from their patients because they feared stimulating a sleeping cancer. I thought it might be time to write a review article that put the risks of testosterone in perspective, particularly the risk of prostate cancer. Fortunately for me, the *New England Journal of Medicine* was receptive to my proposal to consider such a publication.

The *New England Journal of Medicine* is arguably the most prestigious medical journal in the world, and its reputation stems in part from publishing only the best-researched articles. Together with Dr. Ernani Rhoden, a urology professor from Brazil who came to Boston to do a year-long research fellowship with me, we spent a year reviewing all the available scientific and medical literature on the risks of testosterone treatment to be able to provide a manuscript that lived up to such standards. Once we had written up the manuscript, our paper was subjected to multiple waves of reviews by physicians from various specialties—urology, oncology, endocrinology—to make sure that we had not left out any key studies or misrepresented any of the data.

The first thing we looked at was the rate of prostate cancer in men undergoing treatment with testosterone. Although many of the studies were small, the cumulative cancer rate in these trials was only slightly higher than 1 percent. This cancer rate was actually less than the cancer detection rate in men undergoing screening for prostate cancer. However, there was no large, long-term study looking at cancer rates in men receiving testosterone therapy and comparing them to men who did not receive testosterone therapy; thus, by themselves, these studies could not provide a definitive conclusion regarding risk.

There also were some large, sophisticated studies that indirectly addressed the risk of testosterone and prostate cancer. Unlike the studies I just mentioned, in which men given T treatment were monitored for the development of prostate cancer, these large studies simply looked to see if there was a connection between a man's own natural level of testosterone and his risk of developing prostate cancer. In these observational studies, blood samples were taken and frozen at the beginning of the study, and then the large study group was followed for long periods of time. At the end of the study period, often ten to twenty years later, a group of men would have developed prostate cancer. The blood samples obtained from these men at the beginning of the study would then be tested for testosterone and other hormones and compared to a similar group of men who were matched for age and other characteristics but who did not develop prostate cancer. What did they find?

In 2004, when my article in the *New England Journal of Medicine* was published, there were fifteen of these longitudinal studies examining the relationship of hormones and prostate cancer. Since 2004, there have been approximately a half-dozen more. Not one has shown any direct relationship between the level of total testosterone in a man's blood and the subsequent likelihood that he will develop prostate cancer. Specifically, average total testosterone levels were not higher in the cancer group compared to men without cancer, and men with the highest T values were at no greater risk for later developing prostate cancer than men with the lowest T values.

Among the dozens of additional calculations in each of these studies, an occasional minor correlation did show up, such as a connection with the minor androgen DHEA in one, a ratio of testosterone to SHBG in another, or a calculated free T in a third. But in all cases so far, attempts to confirm these minor connections have failed.

At the end of immersing ourselves into this literature for a full year, Rhoden and I were stunned by the fact that there was not a single study in human patients to suggest that raising testosterone increased the risk of prostate cancer. Although I was fairly convinced at this point that testosterone therapy was not a risk for prostate cancer, I had to admit that the evidence was not absolutely conclusive. And there was still a widespread belief that testosterone therapy was risky. And so our relatively sanitized conclusion appeared as follows:

"Thus, there appears to be no compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk."

Our article appeared in the *New England Journal of Medicine* in 2004. Whatever the truth may turn out to be regarding testosterone and prostate cancer, it was clear that raising testosterone did not appear to be like "food for a hungry tumor." Physicians who had been interested in offering testosterone therapy to their patients but were worried about the cancer risk now had a reference article that gave them some degree of comfort.

Later that same year, the Institute of Medicine, a branch of the National Academy of Sciences, published its recommendations regarding testosterone research in aging men, with an eye toward ensuring the safety of men participating in testosterone studies. Recognizing the disparity between the concern that testosterone stimulates prostate cancer and the lack of any strong supporting evidence, the report concluded: "In summary, the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined . . ." The unwillingness of the report's authors to identify testosterone as a definite risk for prostate cancer was a major departure from the standard story line that had colored earlier discussions of testosterone therapy and served as a nice bookend to our article on testosterone risks in the *New England Journal of Medicine*.

Discoveries in the Basement of the Countway Medical Library

As much as my year-long review of the scientific literature had given me confidence that testosterone therapy did not increase the risk of developing prostate cancer, there were still a few issues that disturbed me.

The first was the original observation by Huggins himself that administration of testosterone to men caused "enhanced growth" of prostate cancer in men with metastatic disease. A second was a well-known 1981 article from the Memorial Sloan Kettering Cancer Institute in New York, authored by the most prominent prostate cancer expert of his era, Dr. Willet Whitmore, that reported near-universal poor outcomes when men with metastatic prostate cancer received testosterone injections. And the third was the phenomenon known as testosterone flare. Testosterone flare refers to the temporary increase in testosterone caused by the use of medications called LHRH agonists in men with advanced prostate cancer. Testosterone flare has been associated with a variety of complications attributed to the sudden growth of prostate cancer.

All three of these issues applied only to men with known metastatic disease, and because no one was suggesting that testosterone therapy be offered to men with advanced prostate cancer, the existence of this literature wasn't terribly troubling. What was of concern to those of us prescribing testosterone therapy was the possibility that we might be putting our otherwise healthy patients at risk for prostate cancer, but so far all the data looked reassuring on this point. Metastatic disease was something quite different, and it would not have been shocking to learn that it responded differently to high levels of testosterone than localized disease within the prostate.

But I was still bothered. I had read all the relevant articles years ago during my training, but not with a critical eye toward the relationship of testosterone and prostate cancer. One day, I found myself with an unexpectedly free afternoon and decided to investigate. Everything changed for me the day I descended into the basement of the Countway Library, Harvard Medical School's incredible archive of medical literature. It was the most exciting day of my professional career, a day that changed my views on testosterone, prostate cancer, and, even more, on medicine itself.

The Original Huggins Article

The basement of Countway Library is where the old volumes of medical journals are kept. Some of these, from august journals such as The Lancet, go back to the 1800s. It is an amazing collection, open to any member of the Harvard community.

I found the original article by Huggins from 1941. It was in the very first published volume of what is now a highly respected journal called Cancer Research. I read how Dr. Huggins and his coinvestigator, Clarence Hodges, used the new blood test called acid phosphatase to show that lowering testosterone by castration or estrogen treatment caused prostate cancer to regress, and how T injections had caused "enhanced growth" of prostate cancer in these men. And then I noticed something that made my heart race.

Huggins and Hodges had written that three men had received T injections. But results were given for only two men. And one of these men had already been castrated. This meant that there were results for only a single man who had received T injections without prior hormonal manipulation. Dr. Huggins had based his "enhanced growth" conclusion on a single patient, using a test—acid phosphatase—that has since been abandoned because it provides such erratic results!

I sat there in the basement of the library, reading the same lines over and over to make sure I hadn't misread it. Later, I asked several colleagues to read it as well. Dr. Huggins's assertion that higher testosterone caused greater growth of prostate cancer, repeated for so long and accepted as gospel, was based on almost nothing at all!

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