

# 10. TIP:

## Testosterone Inactivating Pharmaceuticals

Excerpted from *INVASION OF THE PROSTATE SNATCHERS*

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Someday soon, a nontoxic treatment for prostate cancer is going to come along. Perhaps the new treatment will be straightforward, similar to the way we treat precancerous skin lesions by freezing them with liquid nitrogen. When that day comes, all the controversies and conflicts about treating prostate cancer will fade away. Everyone will know the best thing to do. Men will simply take the treatment and move on with their lives. The present reality, however, is that the potential side effects of surgery or radiation are intimidating. No one knows who will end up with irreversible impotence or incontinence. With surgery or radiation there is no going back. It's impossible to undo any harm that may have occurred.

### A MEDICINE TO TREAT PROSTATE CANCER?

What if there were a highly effective treatment with *reversible side* effects, a treatment that not only worked inside the prostate but also had anticancer effects covering the whole body? Believe it or not, there is such a treatment presently available – blockade of the male hormone testosterone, the type of treatment that Ralph describes in chapter 7.

Another of my patients, Max Leiber, a gentle, self-effacing accountant, first consulted me in May of 1997. He was sixty-four, with an elevated PSA of 12 detected during a routine insurance examination. He had intermediate grade disease in the right base of the prostate with areas of low grade disease in the right apex and right mid-gland. Endorectal MRI showed early spread of cancer a few millimeters outside the surface of the prostate. He started a one-year course of treatment with testosterone inactivating pharmaceuticals (TIP) in November 1997 and his PSA dropped to undetectable levels within five months. A biopsy in September 1998 showed no residual cancer. Five years later, in August 2003, a color Doppler ultrasound demonstrated a subtle, ill-defined lesion in the right mid-peripheral zone, and a biopsy showed recurrence of intermediate grade disease. A second cycle of TIP was started in September 2003. One year later, biopsy of the previously abnormal areas was clear and TIP was stopped. Max continued on observation, and as of 2009 had a stable PSA of 1.67.



***“Wars are not won  
by fighting battles:  
Wars are won by  
choosing battles.”  
— George Patton***

### The Essence of Mojo

Testosterone is the hormone that causes masculinization at puberty. Prior to puberty the prostate gland exists as a vestigial nubbin the size of your fingernail. When the teenage surge in testosterone occurs, the gland expands to the size of a walnut and begins producing semen. This remarkable transformation occurs because the cells of the prostate gland are uniquely sensitive to the presence or absence of testosterone. And because prostate cancer cells are derived from the prostate gland, the cancer cells retain the same dependency on testosterone for survival. Cancer cells can grow and proliferate when testosterone is present; they shrivel up and die when testosterone is absent. When testosterone levels in the blood drop, the cancer cells literally commit suicide through a cellular process called *apoptosis*.

Ever since Charles Huggins discovered the beneficial effects of surgical castration for treating prostate cancer, urologists have followed a policy of reserving anti-testosterone therapy until the development of metastatic bone cancer. Since irreversible castration was the only means for lowering testosterone, a hesitation to use such draconian means was understandable. As repugnant as castration is, the anticancer results are undeniable. Doctor Huggins was given the Nobel Prize for his discovery that castration could cause metastatic prostate cancer to go into remission. Today, thankfully, there are medications that achieve similar or better results.



### TIP Gets No Respect

When TIP was invented in the 1980s, doctors continued to adhere to the same old policy – they persisted in withholding treatment until the onset of bone metastasis. TIP for earlier-stage disease was scarcely considered. Bearing in mind that the main interest of urologists is surgery, this is hardly surprising. However, there is another reason the idea of TIP for newly diagnosed cancer has been very slow to catch on. The medical community has wrongly assumed that remission in men with early-stage disease will be just as brief as in men with bone metastasis, lasting only three to six years. This lack of understanding about TIP's effectiveness in early-stage disease might have been understandable in the 1990s, before studies using TIP in early-stage disease were published. Now, however, we know that men who start TIP before the onset of bone metastasis respond well for more than ten years before developing resistance to TIP.<sup>1</sup>

### Long-Term Results With TIP

Being medical oncologists rather than surgeons, and being more impressed by the toxicity of surgery than by its effectiveness, my partners and I hypothesized in the early 1990s that medications powerful enough to reverse metastatic disease should be even more effective against less entrenched, early-stage disease. Our initial experience bore out these suppositions. Jim Taylor, a podiatrist, came to our office in 1992 for his newly diagnosed prostate cancer. His PSA was substantially elevated to 34 and his prostate biopsy showed Gleason 6 disease. Even though his scans were clear, his high PSA made us concerned about possible microscopic cancer outside the gland. Using TIP as primary therapy in that era was highly unorthodox. Nevertheless we decided to proceed, encouraged by the knowledge that treatment could be stopped. (Continued on page 18)

After two months Jim's PSA was down to 0.3. A repeat prostate biopsy in June 1993 showed no evidence of any residual cancer! We decided to stop his TIP in February 1994 and by June of 1995 his testosterone blood levels were back to normal. As of 2009, Jim, now seventy-eight, continues to be under surveillance with periodic color Doppler ultrasound and PSA testing. He has never required any additional therapy and his PSA has been stable between 4 and 5.

Over the years we have seen hundreds of men with excellent responses to TIP. Larry McCoy is a professional musician diagnosed in May of 1996 at age seventy-five. His PSA was 14 with a doubling time of fourteen months. Endorectal MRI in August 1996 showed a small prostate with bilateral tumor in the mid-gland and possible early spread of cancer outside the capsule. At the end of a sixteen-month course of TIP, his PSA was undetectable. A year later, an endorectal MRI showed marked improvement. To this day, Mr. McCoy continues on Proscar as his sole form of therapy, with a stable PSA of 3 and a normal testosterone level of 381.

Tom Fox was first diagnosed with prostate cancer in January of 1997 at the age of seventy-eight. His initial PSA was 33. The prostate examination showed extensive palpable disease. He started an eighteen-month course of TIP in February of that year. After he stopped, his testosterone recovered quickly. He has never required any additional therapy other than Proscar. His last prostate ultrasound in September 2007 showed stable lesions in the left base and right

mid-gland. In mid-2008, at the age of ninety his PSA was only 0.6.

We recently submitted for publication a scientific article detailing the twelve-year outcome for seventy-three men who embarked on TIP as primary therapy in the mid 1990s. The average age of this group was sixty-seven. The average PSA was 9 with a Gleason score of 7 (intermediate grade). In most of the participants, the cancer was large enough to be felt by digital rectal examination prior to treatment. All the men were treated with TIP and all seventy-three of them recovered their testosterone when TIP was stopped. Twenty-one of these men (29%) never needed any further therapy; a single course of TIP kept their PSA low indefinitely. Twenty-four men (33%) required periodic retreatment with TIP to keep their PSA levels under 5. Twenty-eight men (38%), rather than continuing on intermittent TIP, decided to have local therapy such as surgery, seeds or radiation. Their local therapy was performed, on average, five and a half years after the first cycle of TIP. Of these twenty-eight men who had delayed local therapy, only three developed a cancer relapse and none have developed metastasis.

### **TIP, A Totally Unique Form Of Cancer Treatment**

Prostate cancer is the only type of cancer so exquisitely sensitive to hormone blockade. Although women with breast cancer also benefit from hormonal manipulation, TIP for prostate cancer is approximately *five times more effective* than the best breast cancer therapy. Compared to other medical treatments such as chemotherapy, TIP works much better and is far less toxic. Other

than breast cancer, all the other types of cancer, such as colon, lung or stomach cancer, are completely immune to hormonal treatments. Almost all men treated with TIP experience sharp declines in PSA down to undetectable levels.<sup>2</sup> If they have a palpable abnormality on digital rectal examination, the nodule usually disappears within three to four months.

We know that TIP does not completely eradicate every last prostate cancer cell. Microscopic evaluation of surgically removed prostate glands after eight months of TIP shows that total eradication of cancer occurs only in a small minority of cases.<sup>3</sup> However, studies done in our office show that after twelve months of TIP the amount of residual cancer is usually too small to be detected with a careful lesion-directed biopsy using color Doppler ultrasound.

Our belief is that using TIP as a primary therapy is eminently reasonable considering how well men with *Low-Risk* disease fare on active surveillance. If biopsy-positive *Low-Risk* disease can be safely monitored, why not use the same surveillance techniques to monitor men with TIP-induced, biopsy-negative disease? Criticisms of using TIP as primary therapy for *Intermediate-Risk* or *High-Risk* disease seem to be based more on an unwillingness to deviate from "the way things have always been done" than justifiable logic.

### **Some Basic Practicalities**

The medications that make up testosterone inactivating pharmaceuticals fall into three different chemical categories: LHRH agonists, anti-androgens and 5-alpha

reductase inhibitors. Medicines in the first category such as Lupron, Zoladex, Eilgard and Vantas are administered as quarterly or annual shots. They work by sending a false hormonal message to the testicles via the pituitary gland, which turns off testosterone production. The anti-androgens, pills such as Casodex, Eulexin and Nilutamide, work at the molecular level by interposing themselves between the testosterone molecule and the androgen receptor. This deactivates the androgen receptor and inhibits cell growth. The 5-alpha-reductase inhibitors, pills such as Proscar or Avodart, block the chemical conversion of testosterone into dihydrotestosterone, a substance five times more potent than testosterone.

Generally, a combination of these medications is used – one from each class – to attain the most potent anticancer results.

As you can tell, I have seen a lot of men benefit from TIP. One of the advantages is how easily the anticancer effects can be monitored with PSA. Within the first few months of starting treatment, the degree of PSA decline reveals how well treatment is progressing. More than 95% of men with newly diagnosed disease see a drop in their PSA to less than 0.05 within eight months of starting therapy.<sup>2</sup> Fortunately, it's a rare cancer that continues to produce PSA above a threshold of 0.05 after six months of TIP therapy. However, when that is the case, additional treatment with radiation is required. These unusual types of prostate cancer are known to be much more dangerous.<sup>4</sup> Even if the disease is not arrested altogether, TIPs usually delay cancer progression for many years.

### Reading The Fine Print

So what's the catch? Up to this point TIP sounds like a decidedly superior type of treatment. Basically, there are two problems. First is it may be hard to find a qualified doctor who is familiar with up-to-date methods for administering TIP. Second, even though the side effects of TIP are manageable, they are not trivial. Adverse side effects like Ralph's are all too common. Without attention to diet, notable weight gain occurs. Without regular resistance training and weight lifting, significant muscle weakness will ensue. And perhaps most impor-



tant of all, while on treatment, the majority of men have a total loss of sex drive.

A loss of sex drive is different than impotence. With medications such as Viagra and Cialis most men on TIP can have erections sufficient for intercourse.<sup>5</sup> The problem is apathy, a low libido. Sex can be enjoyed, but it is not sought with the usual male verve. Unfortunately, there is no known way to rejuvenate libido other than stopping TIP.

These issues – weight gain, muscle loss and low libido – are the biggest concerns. However, there is also the potential for additional side effects such as breast enlargement, osteoporosis, hot

flashes and anemia. As dire as these side effects sound, they are preventable with proper medical management (chapter 16).

### What About Heart Attacks?

Of even greater concern are claims from retrospective studies stating that TIP causes more heart attacks.<sup>6,7</sup> The weakness of these retrospective studies is their failure to account for the well-known fact that urologists generally reserve TIP for men who can't have surgery, those most likely to have preexisting heart problems. However, there is a single prospective study that also argues for an increased risk of heart attacks with TIP.<sup>8</sup> Offsetting this are higher quality prospective studies that either show no increased risk<sup>9,10,11</sup> or an actual reduction in the risk of heart attacks.<sup>12</sup> The question arises as to why researchers would be suspicious that TIP could induce heart attacks in the first place. The reason is the weight gain that so commonly accompanies treatment with TIP. Putting on weight exacerbates diabetes, a condition that is well known to be associated with an increased incidence of heart attacks.<sup>13,14</sup>

How then can we explain studies that report a *reduction* in heart attacks? The mechanism is the very same one that enables women to live five years longer than men. Women have fewer heart attacks because their blood is thinner and flows more freely, creating less trauma to the vasculature. Testosterone in men thickens the blood by increasing the number of red blood cells, putting a greater strain on their hearts and blood vessels. The advantage of having greater numbers (Continued on page 20)

of red cells is that physical performance and endurance are enhanced. Nevertheless, at the same time, this thicker blood creates excess wear and tear on the walls of the blood vessels, leading to hardening of the arteries and more heart attacks and strokes at a younger age. *When TIP lowers the testosterone levels, it thins the blood down into the female range.*<sup>15</sup> The controversies raging about TIP's potential cardiac effects are rooted in the undeniable fact that weight gain and secondary diabetes significantly increase the risk for heart problems. However, the best prospective study evaluating this question shows that the net effect of TIP is an overall *reduction* in heart attacks by about 10%. The beneficial effect of thinning the blood is apparently sufficient to offset the known increased risks from gaining weight.

### Final Thoughts

There has been no incentive among surgeons and radiation therapists to support research into the viability of TIP as a treatment option for men with newly diagnosed prostate cancer. After all, it competes directly with surgery, their preferred method of treatment. TIP is rarely presented or even discussed as a treatment alternative. Like all forms of prostate cancer treatment, it has undesirable side effects. However, at least men can “test the water” and determine its effectiveness and tolerability without risking irreversible lifelong impotence or incontinence. If after starting treatment, a man feels that the side effects are excessive, therapy can be stopped and another form of treatment implemented.

### The Patient's View By Ralph H. Blum

It amazes me that, even to this day, testosterone inactivating pharmaceuticals are still primarily utilized as a “salvage technique” for advanced cancers – meaning, you have been through surgery or radiation and the cancer has returned. Now, however, thanks in good measure to Mark's unwavering commitment, that is changing. TIP is slowly becoming recognized by physicians – and even more to the point, by patients – as a viable, noninvasive alternative to surgery or radiation.



Yes, there are the side effects we could do without, but that's small potatoes compared with the advantages. And almost all of those side effects are reversible. So TIP has been my treatment of choice. It has bought me and my tortoise of a cancer time to wait for less toxic treatments to become available. I ended TIP in May 2004. Since then I have been taking Avodart and monitoring the cancer. But if at any point I need to start treatment again, then I can revisit TIP if Mark and I agree that it's the best option.

### Resources

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