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Oncology Medical Group

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TESTOSTERONE LEVELS AND PROSTATE CANCER - THE HIGHER, THE BETTER?

An editorial appeared in the November 21, 2001 *Journal of the National Cancer Institute*, entitled the "Two Faces of Janus: Sex Steroids as Mediators of Both Cell Proliferation and Cell Death." Janus from Roman mythology is a god who guards portals, and is Patron of Beginnings and Endings. He is shown as having two faces, one in front, the other at the back of his head. The concept that sex hormones can both stimulate or suppress cancer has been known for more than 40 years. In the 1960's and 1970's, our standard approach to a premenopausal woman who presented with metastatic breast cancer was to remove the ovaries. This would remove estrogen, and there was an excellent chance that her metastatic breast cancer would go into remission. If theoretically the following week, her 72-year-old postmenopausal mother also presented with metastatic breast cancer, the treatment would be vastly different. In the example of the mother, assuming she was postmenopausal since age 50, it would have been 22 years since her body had seen any estrogen. The correct treatment for her would be the addition of estrogen. This would also result in the same remission rate as the example in premenopausal women, where you remove estrogen. Thus, the same hormone, namely estrogen, can stimulate breast cancer in a premenopausal woman, but cause it to go into remission in a postmenopausal woman.

In the 1970's, a hero of mine, Dr. Nick Bruchovsky, showed that androgens had three main actions in the rat prostate gland. They inhibited cell death; they induced cell proliferation, but they could also **inhibit** prostate cell proliferation. The human prostate carcinoma cell line, LNCaP, has a biphasic response to androgens. Low doses of androgens increase the percentage of these cells in S-phase (growth phase), and increase their proliferation rate, while **high physiologic doses** result in arrest of cell synthesis. Two other cell lines that contain the human androgen receptor frequently acquire the ability to respond to

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androgens by entering a prolonged dormant state. Ordinarily one assumes that when you add androgens to prostate cancer cells, you stimulate their growth. Here are two examples where the addition of androgens cause cells to either die or become dormant.

The inhibitory effect of androgens is mediated by the AS3 gene which encodes a particular transcription factor. This means we actually have identified a gene that can cause androgens to **inhibit** prostate cancer cell growth. Unfortunately, we do not yet have the methodology to determine who has this gene and/or whether this gene would function when androgens are given to a man with prostate cancer. LNCaP cells that had been exposed to androgen-free medium (such as in a man who had been on combined hormone blockade, Lupron, Zoladex or had been castrated), developed into variants that proliferated maximally in this androgen-free medium, but then responded to the addition of androgens by arresting their proliferation. Here we see an example where androgens inhibit cell proliferation and induce programmed cell death (apoptosis). The editorial goes on to state "these findings suggest that the inhibitory effect of androgens on tumor growth may have the potential to be used for prostate cancer treatment."

Androgen inhibition of cell proliferation and androgen induction of cell death, "provides the basis to support the administration of androgens to prostate cancer patients." Obviously, it would be ideal if we were able to find reliable markers to predict who would have the inhibitory and apoptotic response to androgens. "These data also provide additional support for intermittent androgen withdrawal treatment which was originally proposed to avoid the selection of androgen resistant phenotypes." I have used intermittent androgen deprivation for all patients since 1993 (except hormone resistant or refractory patients).

When a man goes off hormone blockade, recovering testosterone levels may preferentially stimulate hormone sensitive cells to regrow at the expense of hormone resistant cells. The "good cells" that regrow suppress the more aggressive cells and this allows a man to remain off hormone blockade for prolonged periods of time. Androgens

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allow a cell to enter a sequence called apoptosis, or programmed cell death. Normal prostate cells do this. Could it be that the addition of high physiologic levels of testosterone cause prostate cancer cells to enter apoptosis? That is my hope; it is pure speculation today. Others have speculated that if you could stay off hormone blockade long enough, eventually you might have an entire population of hormone sensitive cells and avoid the need for retreatment with hormone blockade. Although all of this is theoretical, it has already convinced me that in men I treat with testosterone replacement therapy, I believe it is incorrect to aim for low testosterone levels of 300 to 600. I have been utilizing testosterone replacement therapy in very select men since at least 1997. In January 2002, I decided to aim for "high physiologic levels of testosterone." I defined this as testosterone levels of 400 to 500.

As of January 2003, I have noted that when men are treated with testosterone replacement therapy, the best results are seen in men whose testosterone levels are rapidly elevated to over 1,000, and remain above 1,000. On the other hand, men who take many months to get their testosterone levels to rise seem to do much worse. In many of them, I have had to discontinue testosterone altogether. The good news is that when I have stopped testosterone for this type of patient, their PSA levels almost always decline quickly, and usually to pre-testosterone replacement therapy levels. Some men had to go back on hormone blockade but, to date, all are responding nicely.

An article in the *British Journal of Urology*, May 2002, Volume 89, pages 710-713, reports on "The Correlation Between Pretreatment Serum Hormone (Testosterone) Levels and Treatment Outcome for Patients with Prostate Cancer and Bony Metastases." This article is only referring to one type of population of prostate cancer patients. However, I believe that perhaps some of their findings may be applied to other stages of prostate cancer patients. They divided 96 patients into two groups. All 96 had received hormone treatment after a diagnosis of metastatic prostate cancer. The patients were divided according to their response to hormone blockade treatment. Group I had a good response with either stable bone scans or resolution of metastatic

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lesions on the bone scans, and a declining PSA. Group II had increased PSA or progression in number or size of metastases on bone scan. The mortality rate at 18 months was 19 percent in Group I and 83 percent in Group II. The major difference between Group I and Group II was the level of testosterone prior to treatment. The testosterone level in Group I was 4.6, while in Group II, it was 2.6. Normal testosterone from their lab is 3 to 10. The conclusion from this study is that higher testosterone levels are a good prognostic factor for patients with metastatic prostate cancer under hormone treatment, irrespective of Gleason score. An interesting reference cited comments "testosterone would **not** stimulate the development of subclinical prostatic carcinoma to become a clinical carcinoma." Another reference cited speculated that "low testosterone results in the growth of more androgen-independent carcinoma cells, which show a poor response to hormonal treatment."

An article appeared in the *Journal of Urology*, May 2002, Volume 167, pages 2025-2031. Some of the points from this article are that "previous investigators have suggested an association between low serum testosterone and high-grade disease in men diagnosed with prostate cancer." Since PSA production is known to be under the control of androgen, PSA levels can be **artificially lowered** in an androgen deficient state. In this study, there were approximately 4% of 2,254 patients who presented with a Gleason score of 7-10 and a PSA of 4 or less. Their outcome was significantly **worse** than the patients with Gleason scores 7 to 10, but PSA's higher than 4. The article states, "Our study provides evidence to support the previous hypothesis of other authors that low serum free testosterone may be a marker for more aggressive prostate cancer, particularly for patients with a PSA of 4 or less."

I believe that additional references in the future will appear and support my extremely controversial belief and opinion that high testosterone levels are beneficial for men with prostate cancer, either before or after appropriate treatment with triple hormone blockade.

A fascinating article appeared in the *International Journal*

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of *Andrology*, 2002, Volume 25, pages 119-125; 2002, by A.V. Puchersky. The title of the article is "Androgen Administration in Middle-Aged and Aging Men: Effects of Oral Testosterone Undecanoate on Dihydrotestosterone, Estradiol, and Prostate Volume." The article mentions that we are aware of the reduction of plasma testosterone in middle-aged and older men from midlife onwards. Testosterone levels decline 1-2% each year after age 40. Paradoxically, this is when there is progressive growth of the prostate, a highly androgen-dependent organ. The pituitary gland produces something called LH. LH stimulates the testicles to make testosterone. If testosterone levels are low, you would expect LH levels to be high, since the brain would sense low testosterone levels, and would send out more of this LH messenger to the testicles to try to get the testicles to produce more testosterone.

In order to be eligible for this study, men had to have an elevated LH level. This study examines prostate volume, PSA, and lower urinary tract symptoms in 207 men, aged 40 to 83 years. They were treated for six months with an oral testosterone preparation. The men were divided into three groups. Group 1 were men with a normal testosterone level. Group 2A were men with a reduced testosterone level, but following treatment with testosterone, their LH levels decreased to within normal range. Group 2B were those men who started with reduced testosterone levels, but following testosterone administration, their LH levels remained elevated. Patients in Group 1 received 80 mg of the testosterone preparation per day; in Groups 2A and 2B, 120 mg. The results may surprise you. In Groups 1 and 2A, prostate volume **decreased** by 35 and 33% (Group 2B by only 3%). What will surprise you even more is that PSA levels **decreased** by 45 and 38% in Groups 1 and 2A (only by 7% in Group 2B). Symptoms of urinary obstruction improved dramatically in Groups 1 and 2A (not in 2B). Plasma testosterone levels rose in Groups 1 and 2A, but not 2B. Plasma dihydrotestosterone (DHT) levels were significantly reduced in Groups 1 and 2A by 46 and 40% (Group 2B by only 14%). "This study suggests that administration of exogenous testosterone to middle-aged and older men with sexual and/or urinary dysfunction symptoms may retard or reverse age-related prostate growth." The authors go on to state, "These findings support the suggestion that late life

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prostate growth may be enhanced by either falling testosterone and/or the higher levels of bioactive testosterone metabolites such as dihydrotestosterone and estradiol." Elevated LH concentrations may be a useful indicator of more severe androgen deficiency. I use patients' LH levels to help guide my dosing recommendations for men on testosterone replacement therapy. It was nice finding an article to reassure me that this approach for dosing testosterone may be correct. The authors go on "despite administration of exogenous testosterone, plasma dihydrotestosterone concentrations are reduced in proportion to reduction in prostate volume and plasma PSA concentrations. This is consistent with the suggestion that most blood plasma DHT arises from the prostate gland where type 2 5-alpha-reductase is highly expressed, and most incoming testosterone is avidly converted to dihydrotestosterone." Proscar (finasteride) is a selective inhibitor of the type 2 5-alpha-reductase enzyme. 5-alpha-reductase inhibits the conversion of testosterone to dihydrotestosterone (DHT). Proscar inhibits type 2 5-alpha reductase and therefore raises testosterone levels. All men in our practice are currently on Proscar.

It is known that DHT is the most potent stimulant for prostate cancer cell growth. In the example above, testosterone therapy lowered DHT levels. Perhaps some of the benefit from utilizing Proscar may involve this phenomenon as well. Since there is such a low level of DHT, the brain sends out LH to the testicles and tells them to make more testosterone. As testosterone levels increase, at least according to this article, it would seem that DHT levels would further fall. This latter bit of speculation (or logic) is mine, not the authors of the paper. One other conclusion from the paper would be that if you are going to use testosterone replacement therapy, you must reduce elevated levels of LH in order to have the most benefit. This article shows us that administering testosterone caused PSA levels to fall by one-third, and caused prostate gland size to decrease by the same amount.

The reader is reminded that in this particular article, the men studied did **not** have prostate cancer. Therefore, the authors conclude with an appropriate caution that such hormonal treatment may contribute to retardation of the

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progression of BPH; however, its effects on incidence and severity of prostate cancer remains to be established.

In late 2002, a new 5-alpha-reductase inhibitor became commercially available -- dutasteride (trade name Avodart). It inhibits type 1 and type 2 5-alpha-reductase. Type 2 is exclusively found in intraprostatic tissue. Type 1 is also found in the liver and skin.

Studies have shown that Proscar lowers serum DHT levels by about 70%. Dutasteride lowers serum DHT by over 90%, with 85% of men achieving a 90% or greater reduction by 12 months. After just one month of dutasteride, 58% of men had already achieved this 90% reduction. However, what is most important to patients with prostate cancer is whether dutasteride lowers intraprostatic DHT better than Proscar. According to **unpublished** data on file with the manufacturer, dutasteride lowered intraprostatic DHT to lower levels than unpublished Proscar data. We need more reliable information before we can accept this as factual.

We know that men on Proscar have their testosterone levels increase. In our triple hormone blockade protocol, an average increase was about 10%. What excites me is that Avodart raises the serum testosterone levels by about 24% at two years. What really interests me further is that the greatest changes in testosterone were found in men who presented with subnormal baseline testosterone levels. I believe that for most men, the higher the testosterone, the better the prognosis. If dutasteride raises testosterone levels more than Proscar, it is certain that we will be investigating any possible antiprostata cancer benefit with dutasteride compared to Proscar.

The major take-home message in the paper you are reading is my belief that high testosterone levels are beneficial for men with prostate cancer.

In the same dutasteride article from *Urology*, 2002, 60 (30), pages 434-441, the authors, Claus Roehrborn et al., report that PSA levels fell about 52% on Avodart. This is a similar reduction in PSA that men on Proscar achieve.

The side effects for dutasteride were fairly similar to Proscar.

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After 24 months, 42 of 2,158 men on the placebo arm developed prostate cancer (incidence 1.9%). For men on dutasteride, 24 of 2,167 men (1.1%) developed prostate cancer during the 24-month trial. The study was not designed to see whether Avodart (dutasteride) could lower the risk of prostate cancer. Therefore, this reduction in prostate cancer incidence is an extremely intriguing observation, but not a conclusion. A recent article suggests that taking Proscar probably reduces the risk for developing prostate cancer.

We have had such wonderful results with Proscar that it makes it difficult to advise men that they should switch to Avodart. As of January 2003, we have begun to give Avodart to selected patients. Do not switch until or unless it can be shown that Avodart is superior to Proscar for men with prostate cancer. It is probable/possible that dutasteride will become our 5-alpha-reductase inhibitor of choice, but not quite yet.

Let us now look at the relationship between testosterone and prostate cancer. It has always fascinated me that we have known for more than 50 years that the incidence of prostate cancer increases with age. Eighty percent of men in their 80's have prostate cancer at autopsy, while prostate cancer is virtually unheard of in men in their 20's. You can chart the incidence of prostate cancer as men age from their 30's on up, and see the dramatic increase in incidence of prostate cancer with each decade of aging. Many of us, however, are not aware that the level of testosterone declines as we age. Therefore, the incidence of prostate cancer goes up as the level of testosterone goes down. Perhaps this helps to explain some of the background information that has influenced my opinions.

It has been reported many times in the past that low testosterone levels predict for a poor response to hormone blockade. I had always believed it was almost self-evident. Men whose prostate cancer evolves in an environment with low testosterone levels would not be expected to respond as well to hormone blockade, since their prostate cancer cells were already growing with low testosterone levels. In patients who present with prostate cancer and high testosterone levels, it has been my experience that their response to treatment is superb. Prior to April 2002, I did not want to

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push this concept too aggressively. Hence, I tried to keep testosterone levels below 500 for my patients on testosterone replacement therapy. With additional insight and experience, I believed in July 2002 that ideal testosterones were between 600 and 1,100. As of January 2003, I believe in order for men to have the best chance of doing well on testosterone replacement therapy, we need to quickly get their testosterone levels over 1,000, and maintain them over 1,000. When a man's testosterone level is 800 or higher, they almost invariably report an improved overall sense of well-being. They feel stronger; they feel better, and this is in addition to any positive effects regarding either libido (desire to have sex) and/or potency (ability to get and maintain an erection). Another "side effect" of testosterone replacement therapy is enhanced memory, concentration, and/or improved mental acuity.

An article entitled "Endogenous Sex Hormones and Cognitive Function in Older Men" appeared in the *Journal of Clinical Endocrinology and Metabolism*, Volume 84, Number 10, 1999. The object of the study was to determine whether endogenous testosterone levels predicted cognitive function in "older" men. They studied 547 men aged 59 to 89. None of them were using testosterone or estrogen. The study pointed out that the only clinical trial that tested testosterone supplementation and cognitive function found testosterone enhanced various measures of cognition. The article also points out that animal studies suggest sex hormones play a role in the organization of the nervous system and memory. An additional point was that administration of pharmacological doses of testosterone was associated with higher scores on tests of serial subtraction in healthy **young** men. This particular 1999 study was a prospective study which gives it even more credibility. The conclusions were that **low** estradiol levels were associated with better performance on two standard cognitive function tests, whereas high total or bioavailable testosterone levels predicted better performance on tests of verbal memory and mental control. In summary, in this prospective, longitudinal study, high testosterone levels predicted better performance on several tests of cognitive function. As the title of my article suggests, "Testosterone -- The Higher, The Better." (Stick with high **physiologic** levels, don't translate this literally.)

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This opinion of mine to aim for testosterone levels of 1,000 or higher is clearly extraordinarily controversial. More than 99% of doctors would strongly disagree with utilizing any testosterone in a patient with a prior history of prostate cancer. In fact, package inserts for testosterone state, "Do not use if you have prostate cancer." I cannot overemphasize the fact that testosterone replacement therapy is not indicated or appropriate for almost all men with prostate cancer. Almost all other doctors would simply say it is not indicated for any man with a history of prostate cancer. I would disagree with that. For some men, quality of life issues may lead them to consider testosterone.

You must not use this article to try to convince your own doctor to prescribe testosterone for you. You could literally shorten your life, and possibly risk getting spinal cord compression or other terrible, potentially irreversible complications.

In the 1940's a Nobel Prize Winner in Medicine demonstrated that removing the testicles caused metastatic prostate cancer to go into remission. This pioneering work won him the Nobel Prize in Medicine, and has been the basis for treating metastatic prostate cancer ever since. Urologists unanimously state that hormone blockade does not cure prostate cancer. (I don't necessarily agree with that, but would agree that hormone blockade does not cure metastatic prostate cancer.) For the past 60 years, the standard treatment for metastatic prostate cancer has been surgical or medical castration with permanent suppression of androgens. Urologists will further admit that blocking male hormone in men with metastatic prostate cancer invariably leads to hormone refractory prostate cancer. I do not believe that statement is controversial whatsoever. I believe that more than 99% of urologists believe that. I would like my readers to take a step back and consider what I have just written.

If you follow conventional treatment strategies that have been used for the past 60 years, that is permanent suppression of testosterone for treating metastatic prostate cancer, you always end up developing hormone refractory prostate cancer. In almost 100% of men this occurs. If you do it the way it has always been done, you are guaranteed to develop hormone refractory prostate cancer. Additionally,

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the average duration of response to hormone blockade for metastatic prostate cancer is only 18-20 months. Using conventional "gold standard" therapy means accepting 18-20 months remission. It is time to come up with better ideas and not accept such short remissions. I again state what I first wrote in 1995: "Intermittent androgen blockade, when administered in the way I recommend, will be proven to markedly prolong lives compared to continuous blockade."

If you are on continuous hormone blockade, you are also guaranteed to develop the symptoms of the so-called androgen deprivation syndrome. The symptoms of androgen deprivation include all or some of the following: loss of libido (desire to have sex), loss of potency (ability to get an erection), reduced mental acuity, intellectual impairment, anemia, osteoporosis, elevated cholesterol, reduced physical endurance, conversion of muscle to fat, possibly bringing out latent diabetes or worsening diabetes already present, emotional lability with mood swings, and at times, significant depression. Most men who are only treated with hormone blockade for 13 months do quite well and only suffer from some of the above symptoms, and to a relatively mild to moderate extent. However, for those men who are on permanent androgen blockade to have to suffer from the above symptoms the rest of their lives, and know that eventually you get hormone refractory is a terrible "punishment." This is the type of competition that my new ideas have to conquer. I believe that quality of life issues are vitally important to most men, especially a man with metastatic prostate cancer, since it is an incurable disease. Isn't it time that we at least consider changing the 60 year old approach for treating metastatic prostate cancer? To me, the answer not only is yes, it is emphatically yes. That is what I have been trying to do for the past nine years.

As of January 2003, Dr. Tucker and I have treated between 50 to 75 prostate cancer patients with testosterone replacement therapy. This series even includes men with metastatic, hormone refractory prostate cancer. I have additionally used high-dose testosterone replacement therapy on men with virtually any stage of prostate cancer, other than men who have never received hormone blockade.

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I have had three men with metastatic, hormone refractory prostate cancer respond poorly to testosterone. One of them only stayed on testosterone for several days; one for only two weeks, and one for only three weeks. In all of them, increased bone pain was noted, and as soon as it was noted, the men stopped testosterone. If their PSA's had risen, they promptly regressed back to their pre-testosterone replacement therapy levels. In those men with metastatic, hormone refractory prostate cancer who had to have testosterone discontinued, and who had to go back on hormone blockade, their PSA levels have declined so rapidly that the hardest decision I am now facing is whether to keep them off testosterone for three months, or closer to four to six months. As of January 2003, I have not yet decided.

I must emphasize that all of the men with hormone resistant or hormone refractory prostate cancer on testosterone replacement therapy are also being treated with my prostate cancer antiangiogenic cocktail. I have not had to re-treat any of these men with chemotherapy, although I have had to stop testosterone replacement therapy in some men and put them back on hormone blockade.

I continue to be extraordinarily impressed with the success of the antiangiogenic cocktail for treating men with advanced disease, including metastatic prostate cancer, hormone resistant and/or hormone refractory prostate cancer. I have had the "cocktail" fail to work in some men, particularly those with bulky metastatic disease and large total body tumor burdens. It seems that you have to first debulk the body of prostate cancer by utilizing effective chemotherapy. After men are successfully debulked, usually with weekly, low-dose Taxotere/ Emcyt/Decadron/carboplatinum chemotherapy, I then stop chemotherapy and switch them to the antiangiogenic cocktail. They continue on hormone blockade, and if their PSA is controlled or falling on antiangiogenic cocktail and hormone blockade, then after only one or two months of this, I consider stopping hormone blockade, and adding in high-dose testosterone. Men are then maintained on antiangiogenic cocktail plus testosterone replacement therapy.

As of January 2003, we have a number of patients who continue to be treated with high-dose testosterone replacement

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therapy, even though they had clearly documented metastatic, hormone refractory prostate cancer. Most of them now enjoy testosterone levels higher than 1,000. Some of these men have been on high-dose testosterone for close to one year. It still seems almost incomprehensible to me that any patient should be able to remain on high-dose testosterone replacement therapy when they have metastatic, hormone refractory prostate cancer. I believe that this type of experience and knowledge challenges virtually all prostate cancer treatment biases.

For men in this category who had to go back on hormone blockade, they were able to be treated with testosterone replacement therapy for an average of five to seven months. They have continued on their antiangiogenic cocktail, and were re-treated usually with Lupron and ketoconazole. Alternatively, men can be treated with Zoladex instead of Lupron, or aminoglutethimide instead of ketoconazole. When we utilize ketoconazole, we only give 200 mg three times per day and, of course, we also use hydrocortisone. Most of the men who have gone back on hormone blockade have had their PSA's fall to pre-testosterone replacement therapy levels within one to two months of restarting hormone blockade. With a number of these men, I have already discussed the possibility of putting them back on high-dose testosterone, and I suspect that in the near future, this will happen.

I gave a lecture in October 2002 that has much this information on it. It also has our five-year follow-up results for triple hormone blockade as sole treatment of clinically localized prostate cancer. There is also an update on chemotherapy. It is available on video or DVD. If you wish to order it, please call my office at (310) 229-3555. If you know somebody who has prostate cancer, and who believes they have been sentenced to a life of permanent hormone blockade, please share this paper with them, and allow them the possibility of hope.

In 1975, I co-founded the first oncology unit in the San Fernando Valley. I named it the Hope Unit. I have always believed that Hope is what patients need, are entitled to, and are so appreciative when they receive it. Providing hope, honest hope, is one of the most important things that any oncologist does for his patients. It is my prejudicial

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opinion, not anywhere near based yet on fact, that testosterone replacement therapy has the potential to markedly prolong the lives of men with many different stages of prostate cancer. On the other hand, if used incorrectly, it can cause death and/or paralysis. Handle with care, proceed with caution, but at least be informed that new approaches to prostate cancer can work. A number of our patients can testify to this. If you wish to speak to some of our volunteers who have been treated with testosterone replacement therapy, please call the office and we can give you a list of them.

Creating cancer cures and remissions, giving patients HOPE, and looking forward to my fourth grandchild is what nourishes and sustains me. My second son, Josh, and his wife, Andrea, are expecting their first child in March.

As always --

Be happy,

Be well,

Live long and prosper,

DR. BOB

January 25, 2003

** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician.