

PROSTATE CANCER COMMUNICATION

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CURRENT STRATEGIES FOR PROSTATE CANCER HORMONAL THERAPY

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**Atrix Laboratories, Inc., Fort Collins, CO

Hormonal therapy for prostate cancer now exists under many guises. First there are varieties of agents that can interfere either directly or indirectly with androgen-dependent growth.¹ Second there are a variety of schedules and combinations of agents that can be utilized. Despite the well documented activity of individual agents and combinations, comparative trials are few, and optimal regimens remain largely undefined. In this brief overview, we will first discuss broad options in the hormonal management of prostate cancer and then focus more intently on data now available from a new delivery system for leuprolide acetate (Eligard™).

Traditional hormonal agents can be broadly classified into those that interfere with synthesis of androgens and those that interfere with androgen action. Androgens can be classified in broad categories of testosterone and its highly active metabolite (dihydrotestosterone or DHT), and the adrenal androgens such as androstenedione or dehydroepiandrosterone. Androgens, though somewhat diverse in structure, bind to a single steroid (androgen) receptor. The androgen receptor gene resides on the X-chromosome.² Because each man has only one X-chromosome, each male expresses only one receptor. Several genetic polymorphisms are documented that can effect normal protein structure. These polymorphisms may play a role in stratification of prostate cancer risk.

Under normal (wild-type) androgen receptor structure, DHT is more potent than testosterone which is many-fold more potent than the adrenal androgens. If the androgen receptor is mutated, however, this hierarchy may not hold true. Mutant androgen receptors have been described in human prostate cancer specimens.³ Certain mutant receptors have been shown to

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be quite promiscuous in ligand recognition. These alterations can lead to altered ligand recognition. Even conventional androgen receptor antagonists (flutamide, nilutamide, bicalutamide) can increase tumor growth and PSA synthesis.⁴⁻⁵ For this reason, the antiandrogen should be discontinued when there is evidence of a PSA rise. Of note, all antiandrogens are not the same and it is possible for a patient to respond to one antiandrogen after failing another.⁶

Classic experiments performed in the 1940s by Dr. Huggins and colleagues established that androgen deprivation was effective in the treatment of advanced prostate cancer. Both surgical orchiectomy and estrogens were established to lower testosterone and improve patient symptoms. Today we know that a number of compounds exert estrogenic action. These compounds include the classic estrogens such as diethylstilbestrol (DES), diethylstilbestrol diphosphate (fosfestrol), and estradiol as well estramustine and “herbal” agents such as the now outlawed PC-SPES.⁷⁻¹¹ Compounds that interfere with normal androgen metabolism (such as dual 5 alpha-reductase inhibitors) may increase circulating estrogens.¹⁰ Estrogenic actions in men are characterized by lowered

testosterone as well as promotion of gynecomastia and thrombosis. Serum proteins such as thyroid binding globulin can be used to measure estrogenic action in serum. Transdermal estrogen delivery may diminish thrombotic action. Dose response curves were established long ago for DES in prostate cancer for hormone sensitive disease; however dose response curves for other compounds with estrogenic action are lacking. This is an important and often non-discussed point that prevents ready comparison of one estrogenic compound to another. Of note, estrogens also have activity in patients with previously castrate levels of testosterone.⁸ The mechanism of this activity is debated. Much work remains to be done in an effort to optimally understand the use of estrogens in patients with prostate cancer.

LHRH (luteinizing hormone releasing hormone) analogues have virtually replaced surgical orchiectomy and estrogens as the initial hormonal-treatment option of choice. Building upon the Nobel prize winning work of Dr. Andrew Schally^{12,13} (who isolated LHRH from pig brains), it was soon discovered that continuous LHRH administration down-regulated pituitary gonadotropin (luteinizing hor-

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In an effort to conserve space and be able to insert as much material as possible in the newsletter, references from various articles are intentionally omitted. If you would like to obtain those references, please contact PAACT, we keep all of the original articles and the references used on file.

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mone or LH) secreting cells and this action preceded a fall in serum testosterone. Creating potent LHRH agonists could potentiate these actions.¹⁴ Such agonists in various forms now dominate the market for hormonal treatment of prostate cancer and include agents such as Lupron (an injectable form of leuprolide acetate), Zoladex (injectable gosarelin acetate), Viadur (implantable pump form of leuprolide acetate), Eligard (an injectable leuprolide acetate), and Trelstar (an injectable triptorelin pamoate). Antagonists of LHRH also inhibit testosterone production but attempts to commercially develop LHRH antagonists have been ongoing for years without success to date.¹⁵

As noted above, testosterone is converted to dihydrotestosterone by the enzyme 5-alpha-reductase. Two isoforms of the reductase exist, type I and type II.¹⁶ Finasteride is commercially available as a type II inhibitor. It is not approved by the FDA for use in prostate cancer but is approved for treatment of benign prostate hyperplasia (BPH) and male pattern baldness. The FDA has recently approved newer dual 5-alpha reductase inhibitors. Their role in prostate cancer also remains to be determined.¹⁷

Decreasing testosterone synthesis can be reliably elicited by ketoconazole which, when given at higher doses, potently inhibits adrenal and testicular androgen synthesis.¹⁸ Ketoconazole can be used to induce a castration level of testosterone in a very short period (48-72 hours). This can be useful under certain conditions of urgency in patients with hormone-sensitive disease. Ketoconazole also has activity in patients who have failed surgical or medical orchiectomy;¹⁹ the mechanism is not clear.

Agents such as corticosteroids (prednisone, dexamethasone, etc.) decrease adrenal androgen synthesis by diminishing ACTH secretion.²⁰ Though inadequate to induce testosterone suppression, these agents have potential roles in the management of prostate cancer progression after initial hormonal therapy (for reasons perhaps unrelated to their adrenal androgen suppressive properties).²¹

It is also possible to interfere with androgen action by blocking androgen/receptor interactions. These compounds are termed and classified as anti-androgens. When given alone these agents increase circulating testosterone levels given that androgen feedback on

the hypothalamus and pituitary are minimized and LH secretion increased. Three androgen receptor blocking agents are now commercially available. These agents include flutamide (Eulexin), bicalutamide (Casodex), and nilutamide (Nilandron). The data on these compounds is extensive and will not be covered here other than to say that they are typically employed in combination with a LHRH agonist. Newer studies indicate that bicalutamide monotherapy may be feasible and reasonable in patients without evidence of metastatic disease.²²

In terms of hormonal therapy schedules, it has long been assumed that continuous therapy is most appropriate. This assumption has held since the initial studies of Huggins in the 1940s. Data to support the superiority of continuous versus intermittent therapy are lacking. It is clear that intermittent therapy is deemed acceptable by many men (and their physicians) and that time off therapy may provide benefit in terms of diminished bone loss and other sequelae of androgen deprivation.²³⁻²⁵ Suffice it to say that optimal schedules of hormonal therapy are yet to be established by mature clinical data.

Recently, the FDA approved a new delivery formulation of leuprolide acetate, Eligard™ (Sanofi-Synthelabo, Inc.). This formulation uses the unique patented Atrigel® technology made from polymers of d,l-lactide-co-glycolide.^{26,27} A patient friendly small 20 gauge, 1/2 inch hypodermic needle is used to subcutaneously administer the viscous liquid mixture containing leuprolide acetate. The Atrigel® forms a solid implant *in situ* holding the leuprolide acetate in the polymer matrix. Enzymes slowly degrade the polymer implant and release the leuprolide acetate over the currently available 1- or 3-month dosing intervals.

Two recently published clinical trials showed Eligard™ effectively reduced testosterone to levels observed in surgical castration.^{28,29} The first trial studied the Eligard™ 7.5 mg one-month formulation in a multicenter study.²⁸ One hundred and twenty patients with advanced prostate cancer were treated with six monthly subcutaneous injections of Eligard™ 7.5 mg. The results showed 94.1 percent (112/119) of the patients had serum testosterone effectively suppressed below 50 ng/dL by 3 weeks. The remaining 7 patients achieved castration levels within 7 weeks. In addition, 97% of the patients were suppressed below

20 ng/dL by 4 weeks of treatment. This lower level of testosterone (20 ng/dL) has been suggested by a panel of 17 leading physicians writing the prostate cancer treatment guidelines for the “National Comprehensive Cancer Network” to be the testosterone level advisable for monotherapy (that is to say no other treatments are necessary such as antiandrogens according to this panel). The second notable Eligard™ treatment attribute was absence of any testosterone breakthrough events. A breakthrough is defined as a rise in serum testosterone above the castration level (50 ng/dL) at any time after suppression has been established. No breakthrough events indicated that the Atrigel® delivery system releases leuprolide acetate in a way that is highly effective at suppressing testosterone levels. In agreement with this, at the conclusion of this 6-month trial all 117 patients who completed the study had testosterone levels at or below 50 ng/dL and had an average PSA reduction of 90%.

The second Eligard™ clinical trial was also a 6-month study of 117 patients diagnosed with adenocarcinoma of the prostate.²⁹ Eligard 22.5 mg was administered subcutaneously once every 3-months. Ninety-eight percent (111/117) of the enrolled patients completed the 6-month study. Five patients withdrew for non-treatment related events; one patient was withdrawn because he received less than a full dose of the study drug. After four weeks of treatment, 98% of the patients had serum testosterone below the castration level of 50 ng/dL and 84% of the patients were below 20 ng/dL. All the patients had achieved castration levels by 7 weeks. One patient had breakthrough response post testosterone suppression on Day 49 (112 ng/dL) but regained suppression (27.0 ng/dL) 14 days after the second injection. At the end of 6 months, all the patients were \leq 50 ng/dL with an average testosterone value of 10.1 ng/dL. The patient’s average PSA score decreased more than 98%. These clinical trials demonstrate the effectiveness of this new delivery system for leuprolide acetate and the suppression of serum testosterone. Additional randomized prospective studies will be necessary to evaluate the importance of achieving total serum testosterone below 20 ng/dL.

In summary, prostate cancer hormonal treatment has many forms. LHRH agonists remain the mainstay of treatment for advanced disease with several LHRH agonists and extended delivery systems now avail-

able. Only comparative clinical trials with clinically relevant endpoints can determine the best approach to therapy.¹ Comparative trials are lacking for many of the newer forms of hormonal therapy.

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MINIMALLY INVASIVE TREATMENT OPTIONS - Part I

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The traditional and accepted treatments for confined prostate cancer (cancer that has not spread outside of the gland) include radical prostatectomy (surgical removal) and radiation therapy. Unfortunately, these treatments can result in significant complications.

Specimens examined from radical prostatectomy often indicate that the cancer has already spread outside of the gland. The surgical procedure did not result in complete removal of the cancer from the patient. This is known as a positive surgical margin. It has been reported that 40-60% of all radical prostatectomy procedures demonstrates a positive surgical margin. This is usually the result of underestimating (understaging) the extent of the cancer prior to surgery.

Radiation therapy is associated with a 20-70% failure rate. This rate is based on biopsy-confirmed recurrent tumor following treatment. Due to the limited effectiveness of the traditional treatment modalities, new more effective and less invasive options for the treatment of prostate cancer are being investigated.

CRYOTHERAPY

Cryotherapy is an emerging alternative that shows great promise.

HISTORY

Cryoablation of the prostate involves the controlled freezing of the gland in order to destroy both cancerous and native prostatic cells. In 1968, Gonder and Soans introduced cryoablation of the prostate and achieved tissue necrosis (destruction). In the 1970s, Bonny reported his cryosurgical experience with an open-perineal approach on 229 patients. The report revealed that cryosurgery patients had a probability of long-term survival equal to that seen in radical prostatectomy patients in each cancer stage.

However, a high rate of complications resulting from a lack of precise monitoring of the freezing process forced the abandonment of this technique. In 1988, Dr. Gary Onik reported the feasibility of monitoring the freezing process using real-time ultrasound. In 1994, Dr. Fred Lee and I reported a further defined and tailored cryosurgical technique based on advanced transrectal ultrasound and advanced cryo technology, coupled with much improved interventional radiology skills.

CRYOABLATION OF PROSTATE

Pre-operative staging: Candidates for cryoablation therapy should have accurate cancer staging with a transrectal ultrasound and prostate biopsy (targeted, staging biopsy, not random biopsy) prior to the procedure. Knowledge of the exact location and size of

the tumor, as well as the status of nearby structures, such as neurovascular bundles and seminal vesicles, proves crucial to the success of the treatment.

To achieve a high level of accuracy in staging, one must use state-of-the-art ultrasound equipment with color-Doppler, tissue harmonic capability. Patients will also have a bone scan and CT scan of the pelvis to rule out the possibility of distant metastases (cancer spread). Lymph node sampling is also recommended in selected cases. If distant metastasis or lymph node involvement is confirmed, the patient is not a candidate for cryosurgery.

Pre-operative medication: Since current technology limits the amount of tissue that can be effectively frozen, the patient may be placed on three to six months of androgen ablation therapy (blockade of male hormone production). This therapy shrinks the prostate and cancer volume (downsize and downstage) prior to the cryoablation procedure.

Team Approach: Every patient is assigned to a team consisting of a board-certified radiologist and urologist for the cryosurgical ablation procedure and follow-up care.

Cryosurgery: Routine preoperative blood work and a chest x-ray are required on the day prior to cryosurgery.

Most patients will spend one night in the hospital following the procedure.

Cryosurgery is performed under either general or spinal anesthesia. We typically make four to eight needle punctures in the perineum (skin surface between the rectum and scrotum), and using ultrasound guidance, advance the needles to pre-selected locations in the prostate gland. The needle tracks will be dilated for insertion of the cryo probes used for the freezing. Precise temperature monitoring during the procedure is accomplished with multiple thermocouples placed at strategic locations surrounding the gland. After a warming device is placed to protect the urethra, the freezing process begins.

We apply a minimum of two freezes (two freeze and thaw cycles) for effective tissue destruction. The entire prostate, including the tumor and surrounding tissue, will be frozen.

The patient is discharged the next morning with a Foley catheter in place for drainage for two to three weeks.

Follow-up: Patients are required to have a PSA test three (3) months after cryosurgery. A PSA test is recommended every six- (6) months for three years and yearly thereafter. A biopsy is absolutely necessary at six (6) months, one (1) year, two (2) years and five (5) years after cryosurgery, or any time the PSA level rises over 0.5mg/ml.

CLINICAL STUDIES

Recently, my colleagues and I published a 7-year outcome study based on 590 consecutive patients who underwent cryoablation therapy for prostate cancer.

The overall biopsy proven disease free rate was 85.8%. If the stage of the cancer was T1-2 (cancer confined within the prostate), it was 88.7%, and if the stage was T3-4 (cancer already spread to outside of prostate capsule, but no distant metastasis), it was 74%. The overall biochemical disease free rate (PSA < 1.0 ng/ml) was 76% (Urology 60, Suppl 2A: 3-11, 2002).

Complications: Although cryoablation therapy of the prostate is subject to some of the same complications as radical prostatectomy and radiation therapy, the cryo-related complication rates are relatively low. The major complication recorded is a fistula (connection between rectum and prostatic urethra), which occurred in 0.5% of the patients. All patients except two who experienced this complication had failed radiation therapy prior to having cryosurgery.

Based on a patient questionnaire study, urinary incontinence (defined as the use of a pad) was seen in 4.3% of patients who had no prior treatments for prostate cancer. It was reported as 11% after radiation therapy¹ and 31% after radical prostatectomy.² In our study, most patients used one pad for a few drops per day as a protective measure. In the radiation failure group, the incontinence rate was significantly higher than in the virgin group.

Impotency is an expected side effect of this procedure. It is due to the intentional freezing of tissue outside of the prostate gland to kill cancer cells that may have already spread beyond the prostate capsule. Our

study showed only 15% of patients gained potency (defined as a firm erection enough for vaginal penetration) and an additional 23% of men claimed partial recovery. These numbers are essentially the same as the radiation and radical surgery reports.^{1,2}

There were other minor complications which included: outflow obstruction in 9%; pelvic pain in 11%; scrotal swelling in 17%; penile numbness or tingling sensation in 14%. These usually resolved within three months after the cryosurgery.

*96% of the patients surveyed stated that they would choose cryosurgery again if it became necessary.

Conclusions

1. Using every definition of biochemical failure, cryotherapy was shown to equal or surpass the outcome figures of conventional treatment.
2. Cryosurgery is a promising option in radiation failure patients, including seed implantation failure.
3. Complication rates are favorable compared with conventional treatment.
4. Cryotherapy is an efficacious modality for organ confined (T1-2) and especially locally advanced (T3-4) prostate cancer.
5. Cryotherapy is a minimally invasive procedure and cost-effective option with a high rate of patient acceptance.

- 1) *Jonler et al. Urology 1994*
- 2) *Fowler et al. Urology 1993*

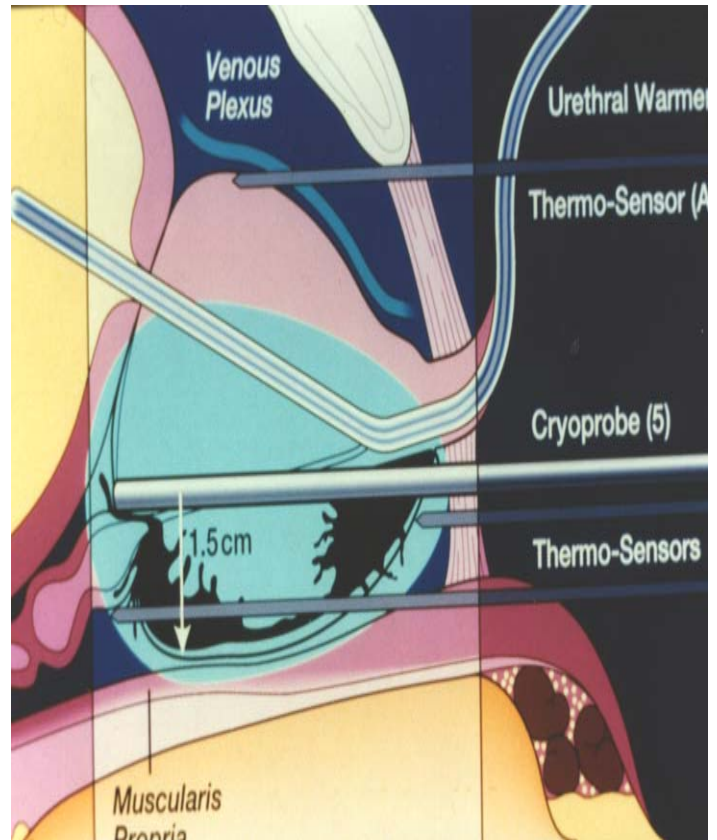
ADVANTAGES OF CRYOSURGERY

1. Minimally invasive: no blood loss, no surgical incision, and outpatient surgery.
2. Favorable success rate (based on seven year follow-up) & complication rates.
3. Short recuperation period.
4. Procedure can be repeated if first cryosurgery fails.
5. Radiation therapy (external beam or seed implantation) or radical surgery is still an option if first cryosurgery fails.
6. Costs less than half of traditional treatments.

DISADVANTAGES OF CRYOSURGERY

1. No long-term randomized multi-center studies.
2. The procedure is highly operator-dependent with a steep learning curve.

*Note: Part II - Brachytherapy will be published in June 2003.



Side view of prostate: Each cryoprobe creates an oval shape ice ball (blue color). We use up to 8 cryoprobes to cover the entire prostate.

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

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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 1960s and 1970s, 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 postmeno-

pausal 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 1970s, a hero of ours, 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 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 causes 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 an 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.” We 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 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 our 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 us that in men we treat with testosterone replacement therapy, we believe it is incorrect to aim for low testosterone levels of 300 to 600. We have been utilizing testosterone replacement therapy in very select men since at least 1997. In January 2002, we decided to aim for “high physiologic levels of testosterone.” We defined this as testosterone levels of 400 to 500.

As of January 2003, we 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, we have had to discontinue testosterone altogether. The good news is that when we have stopped testosterone for this type of patient, their PSA levels almost always decline quickly, and usually to pre-testosterone re-

placement 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, we 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 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 androgens, 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 Glea-

son 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."

We believe that additional references in the future will appear and support our 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 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 was men with a normal testosterone level. Group 2A was men with a reduced testosterone level, but following treatment with testosterone, their LH levels decreased to within normal range. Group 2B was 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 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. We use patients’ LH levels to help guide our dosing recommendations for men on testosterone replacement therapy. It was nice finding an article to reassure us 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 ours, 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 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 us is that Avodart raises the serum testosterone levels by 24% at two years. What really interests us further is that the greatest changes in testosterone were found in men who presented with subnormal baseline testosterone levels. We 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 antiprostate cancer benefit with dutasteride compared to Proscar.

The major take-home message in the paper you are reading is our 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.

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.

Now let us look at the relationship between testosterone and prostate cancer. It has always fascinated us that we have known for more than 50 years that the incidence of prostate cancer increases with age. Eighty percent of men in their 80s have prostate cancer at autopsy, while prostate cancer is virtually unheard of in men in their 20s. You can chart the incidence of prostate cancer as men age from their 30s 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 our opinions.

It has been reported many times in the past that low testosterone levels predict for a poor response to

hormone blockade. We 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 our experience that their response to treatment is superb. Prior to April 2002, we did not want to push this concept too aggressively. Hence, we tried to keep testosterone levels below 500 for our patients on testosterone replacement therapy. With additional insight and experience, we believed in July 2002 that ideal testosterone levels were between 600 and 1,100. As of January 2003, we 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 our article suggests, “Testosterone — The Higher, The Better.” (Stick with high **physiologic** levels, don’t translate this literally.)

This opinion of ours 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.” We cannot over emphasize 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. We 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 1940s 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. (We 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 hormones in men with metastatic prostate cancer invariably leads to hormone refractory prostate cancer. We do not believe that statement is controversial whatsoever. We believe that more than 99% of urologists believe that. We would like our readers to take a step back and consider what we 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, 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. We again state what we first wrote in 1995: “Intermittent androgen blockade, when administered in the way we 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 our new ideas have to conquer. We 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 us, the answer not only is yes, it is emphatically yes. That is what we have been trying to do for the past nine years.

As of January 2003, we have treated between 50 to 75 prostate cancer patients with testosterone replacement therapy. This series even includes men

with metastatic, hormone refractory prostate cancer. Additionally, we have used high-dose testosterone replacement therapy on men with virtually any stage of prostate cancer, other than only men who have never received hormone blockade.

We 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 we are now facing is whether to keep them off testosterone for three months, or closer to four to six months. As of January 2003, we have not yet decided.

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

We 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. We 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/ Emycyt/Decadron/carboplatinum chemotherapy, we 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, we consider stopping hormone blockade, and adding in high-dose testos-

terone. 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 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 us that any patient should be able to remain on high-dose testosterone replacement therapy when they have metastatic, hormone refractory prostate cancer. We 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, we have already discussed the possibility of putting them back on high-dose testosterone, and we suspect that in the near future, this will happen.

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.

** 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.

A Note From Dr. Leibowitz:

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 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.

**Men as Health Care Consumers:
Shop As If Your Life Depends On It!**

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When I was asked to write an article for PAACT, I was told to say anything I wanted— which forced me to think hard about exactly what *I* could offer to a population of men (and their families and friends) who have been diagnosed with prostate cancer. I am a woman – and an ovarian cancer survivor. No man could ever suffer my cancer and no woman could ever suffer yours. In my role as a patient advocate, however, I have met dozens of men diagnosed with a variety of cancers. As I reflected on my interactions with them, some interesting patterns emerged which I have tried to describe here. What follows are some of my thoughts, filtered through my experience – please take them in that spirit. This is not intended as a scholarly work, but a reflective one.

MY STORY:

In 1994, I was diagnosed with ovarian cancer that, in due course, spread to my liver. At that point, because I appeared to have at least a dozen tumors, a prominent cancer surgeon told me to “go home and think

about the quality and not the quantity of (my) remaining days.” My children were three and one. I did not go home and think about my remaining days – I went home and made appointments with five doctors in three states. My father and I embarked on an odyssey of sorts that landed me on a surgeon’s table for an experimental procedure that saved my life. It turned out that I only had one tumor – the rest were cysts, common in about 10% of the population. Had I not had a legal education, adequate insurance, some powerful luck and a ‘won’t-take-no-for-an-answer’ attitude, I would probably have died, although later than expected, with everyone’s remarking on what a testament the late dying was to my will to live. No one would have known that, instead, I *could* have lived – all would have thought my death an obvious and inevitable end to a horrible disease.

My experience as a health care consumer was so powerful that it changed the course of my career. In September of 2000, I became the first director of the brand new Center for Patient Partnerships – a multidisciplinary linking of the schools of Law, Medicine and Nursing at the University of Wisconsin, Madison. I felt called to work with patients with life threatening illnesses – to help them cope with their diagnoses and navigate the sometimes-treacherous waters of the health care system. It is from my experiences working with both men and women who seek help at the Center that these observations emanate.

For all of our sophisticated medical resources, ours is not an easily accessible or particularly welcoming health care system – for any ill human being. But, many men have distinct liabilities as health care consumers. Of course, I am generalizing and I know such generalizations can sometimes give offense. Please don’t take any, for none is intended. I offer these generalizations only because they provide the simplest and most direct way to help readers of this piece, particularly men with prostate cancer, examine their skills and maximize their effectiveness at the time when they are most needed. So, where you see the words “tend to,” expect a characterization to follow – if it applies to you, take note. If not, skip to the next one.

MEN AS SHOPPERS:

Men tend to do less of the day-to-day shopping than women, as any quick trip to the grocery store or the

drug store will likely confirm. Men typically shop for cars, tools, electronic equipment and jewelry at holiday time. Historically, women have done most of the shopping for the home, the family and themselves – often even buying their husband’s clothing.

While this may be a generally efficient distribution of labor, it results in a decrease in some men’s experience as consumers. On the other hand, women have evolved into shrewd consumers – shopping for bargains, insisting on value for their money and returning items that are defective, unsuitable or just not, in hindsight, what they wanted. Perhaps prehistory can cast some light on this dynamic – in ancient times men were the hunters and women the gatherers. The hunter’s task required a directed, time limited, goal oriented “one shot deal.” The gatherers, on the other hand, were always at it – constantly on the lookout for everyday things that might someday be of value, gathering and storing them for future use.

Not surprisingly, there is value to both skill sets – indeed, without both, we might not have survived as a species. Women tend to fuss about things, to “worry” them – they tend to keep mulling over, considering, and gathering more information, and questioning even after having made a decision. Men tend to be better filterers – better at narrowing their focus, making a decision, and not feeling the need to revisit it over and over again.

In my experience, women health care consumers tend to be better at taking in the options given, searching for others that may exist, weighing them carefully and choosing one that suits their needs and values. With less experience as day-to-day consumers, many men simply have not honed these skills.

MEN AND DOCTORS:

Even men who are experienced shoppers, however, must first leap other hurdles that encumber them, particularly as consumers of *health care*. For most women, a visit to the doctor is at least a yearly event. While some of these visits might be triggered by illness, many are simply annual “clean bill of health” events. And, many women are fortunate to have remarkably joyful health care experiences (or at least outcomes) related to birthing children.

For men, on the other hand, getting through the door

is a powerful initial hurdle. Men tend to visit the doctor only when there is something wrong. Many men are taught as boys that going to the doctor when you don’t feel well is for sissies, guys who can’t “tough it out” until they get better. Even those men who were not heckled for seeking medical attention usually only went to the doctor when something was wrong. When the doctor’s office is a place you go when something is wrong, then it is a place to avoid.

Further, boys are often taught, in not so subtle ways, that their bodies are “maintenance-free” and that visits to the doctor should not be necessary for them. Thus, men must overcome an aversion to *going* to the doctor and to seeking care for their bodies. Over and over again I have heard patients talk about agonizing months of symptoms and concerns, which they kept to themselves. My sense is that this is based partly on doctor aversion and partly on the “maintenance-free body” myth.

When you toss in the elements of prostate cancer, you add another powerful deterrent to men’s seeking medical attention; namely, it’s a problem “down there”... My own family’s experience is instructive here: all three of my father’s brothers are prostate cancer survivors. When my two aunts and I were fighting lymphoma, breast and ovarian cancer respectively, our progress was readily discussed among the members of both genders of both generations. When my uncles were diagnosed, however, their “privacy” was carefully guarded during their journeys with prostate cancer. It didn’t have to be said; we could just tell that we were not to discuss treatment options that could have a bearing on their virility – their “manhood.”

It goes without saying that no one’s manhood resides in any one body part. Yet, for a variety of reasons (probably not the least of which is our culture’s constant portrayal of the naked female and still extremely rare portrayal of the naked male) men tend to feel more strongly about the privacy of their “private parts.” When this value on privacy keeps them from seeking medical attention, it becomes counterproductive, even dangerous for men as health care consumers.

Finally, when men who never go to doctors finally do go, they tend to be in such discomfort just from being

there, leaving aside the pain of their illness, that they shut down emotionally and intellectually and just accept what they are told – “whatever you say, doc.” While this is better than not going to the doctor at all, it is still essentially a stiff-arm posture with respect to the realities of the problem. It is a medically unwise, ostrich-in-the-sand position that compromises information gathering and, thus, decision-making.

THE GOOD NEWS (MOSTLY):

All that said, men tend to embody several qualities that can make them very effective consumers.

- 1) Relative to women in nearly every race or culture, men have been empowered to expect the best for themselves. For this reason, some men are extraordinarily effective health care consumers because they do expect the very best and, when care is sub-standard, they insist on its improvement. It is this skill that I have seen enable men to overcome the experience deficit they may have as consumers. And it tends to be quite effective in an ‘iron fist in a velvet glove’ sort of way. It is almost as if the subtext is “we both know I deserve this and it is your job as a professional to see that I get it. Now, let’s get on with it”. Women tend to trust more at first, feel hurt when their care lacks a personal touch, worry about how to say how they feel and then distrust their health care practitioners thereafter. Suffice it to say, that isn’t optimal.
- 2) As descendants of the hunters, men tend to be able to focus on a problem, evaluate the possible solutions, choose one and move on. The up side of this is that they don’t experience the stress of always second guessing themselves and their health care practitioners. The down side is that they may not stay quite as flexible or open to other options during treatment.
- 3) Men also tend to obsess less than women on their fears about the future – ‘can’t control it, not gonna sweat it’. This makes for a better quality of life despite their diagnosis and during treatment. The down side is that they might also feel more devastated if the initial treatment modality is not effective because they haven’t been pondering the possibility of failure all along.
- 4) Men tend to be good at making data driven decisions, which, since they don’t second-guess and since medical science is hugely data driven, can work out to be better decisions for them. When

faced with the same data surrounding a treatment choice, women tend to incorporate a myriad of other factors into their decisions such as the timing of a family wedding, the place where treatments will occur, hair loss, etc. Men tend to simplify these decisions – filter out all but the data – and decide.

- 5) A large majority of oncologists are men. Thus, it would seem that male consumers might be well positioned to interact with these doctors. To the extent that we understand and relate better to those who share common life experiences, there would seem to be some potential for a more effective relationship between male patients and their male doctors. Of course I have seen the opposite – for instance, when a male doctor, having just told his patient that the radiation he was recommending could cause the patient to lose his ability to speak comforted him by saying “well, it’s better than pushing up daisies.” No comfort was felt.
- 6) My sense is that men tend to feel more positive about their bodies than women who are taught never to be satisfied with how they look. This is a pretty powerful advantage in treatment where in order to maintain a positive outlook; it helps to minimize feelings of betrayal by one’s body.

SOME FINAL THOUGHTS:

The single most significant skill for health care consumers is active participation in decision-making. The better we understand our diagnosis and treatment, the better equipped we are to give useful information to our health care practitioners, to make choices that “work” for our lives, and to head off medical errors before they occur.

A cancer diagnosis is never good news. Some of us will die regardless of our best efforts and some of us will survive without much ado. It is those of us on the margin – and we never know who we are – who might change the outcome of our disease because we have the courage and maturity to stay invested in the outcome even though we know we cannot control it. Sometimes, we can influence it enough to make all the difference – and, either way, we will make choices in the process that reflects who we are and how we want to live and die.

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**A NOTE OF THANKS
FROM THE STAFF AT PAACT**

We wish to acknowledge and thank all of you for your overwhelming support during 2002. The response to the December 2002 publication was incredible to say the least. December was the best single month for donations since July 2001. This says a great deal about the heart and core of PAACT, **its members**, especially during such difficult economic conditions. We have printed a 2002 year end financial report in this newsletter. Please note that 2002 did not finish in the red by \$30,000 as was the case in 2001, but just the opposite. Revenues exceeded expenditures by over \$43,000. This will now allow us to begin upgrading our computer system into the 21st century, which will allow us to improve our member services significantly.

BOOK INFORMATION

A Primer on Prostate Cancer

By Donna Pogliano and Stephen B. Strum, M.D.

For the warriors in this battle who have been newly diagnosed with prostate cancer, and for their families and loved ones, *A Primer on Prostate Cancer: The Empowered Patients Guide*, serves as a guidebook to the successful management of this epidemic disease. Many of the suggestions for topics in the *Primer* came from men who have experienced prostate cancer and from their partners.

This book is a comprehensive guide on the basics of prostate cancer, diagnosis and testing procedures, and the numerous treatment options. Also included: full color illustrations and photos, notes sections for readers, case studies, chapter summaries, and a list of additional resources.

Within the 268 pages of this full-color in-depth book on prostate cancer, newly diagnosed men have access to the vital information that those who have experienced prostate cancer consider indispensable. Armed with this education, the prostate cancer patient has the ammunition to become empowered and involved in intelligently managing his own care.

The suggested retail price is \$28.95. For more information, please call Rey Searles at Life Extension at 800-544-4440, or visit www.lefprostate.com.

VIDEO INFORMATION

"The Challenge for a Newly Diagnosed Prostate Cancer Patient to Choose His Initial Therapy"

Lecture given by Mark Scholz, M.D.

Healing Touch Oncology
Marina del Rey, California

This video is available on a 98 minute VHS tape as Video #302. It was made with a home video camera and is not studio quality, however it contains a lot of valuable information including a five-page handout and the Kattan Nomograph. To order please send a personal check or money order to Lew Pfeffer, 1250 Fieldgate Avenue, Hacienda Heights, CA 91745. The cost is \$15 per video including shipping by priority mail in a padded mailer anywhere in the 50 United States. For orders from other countries, please send an international money order for \$10.00 plus enough for air mailing a 10-ounce package. Payment to be in U.S. Dollars. Please specify Video #302 - Scholz.

**The Fullerton Prostate Forum in California has just started a website, www.prostateforum.org. It is primarily to provide information about their meetings. It also contains an up to date list of the best of the prostate cancer videos of their speakers and how to order them. A number of prostate support groups are now using these videos at their meetings when they do not have a speaker.

**"Challenging PC Treatment Biases -
Is Nothing Sacred???"**

Lecture given by Robert Leibowitz, M.D.
Compassionate Oncology Medical Group
Los Angeles, California

Topics Include:

1. Testosterone and CaP - The higher the better?
2. Treatment options for "localized prostate cancer."
3. Updated results of triple hormone blockade as sole treatment of Prostate Cancer.
4. Update on Antiangiogenic Cocktail.
5. Chemotherapy 2003 - highly effective with minimal side effects.

The lecture is available on VHS and DVD. If you wish to order it, please call Dr. Leibowitz's office at 310/229-3555.