

PROSTATE CANCER COMMUNICATION

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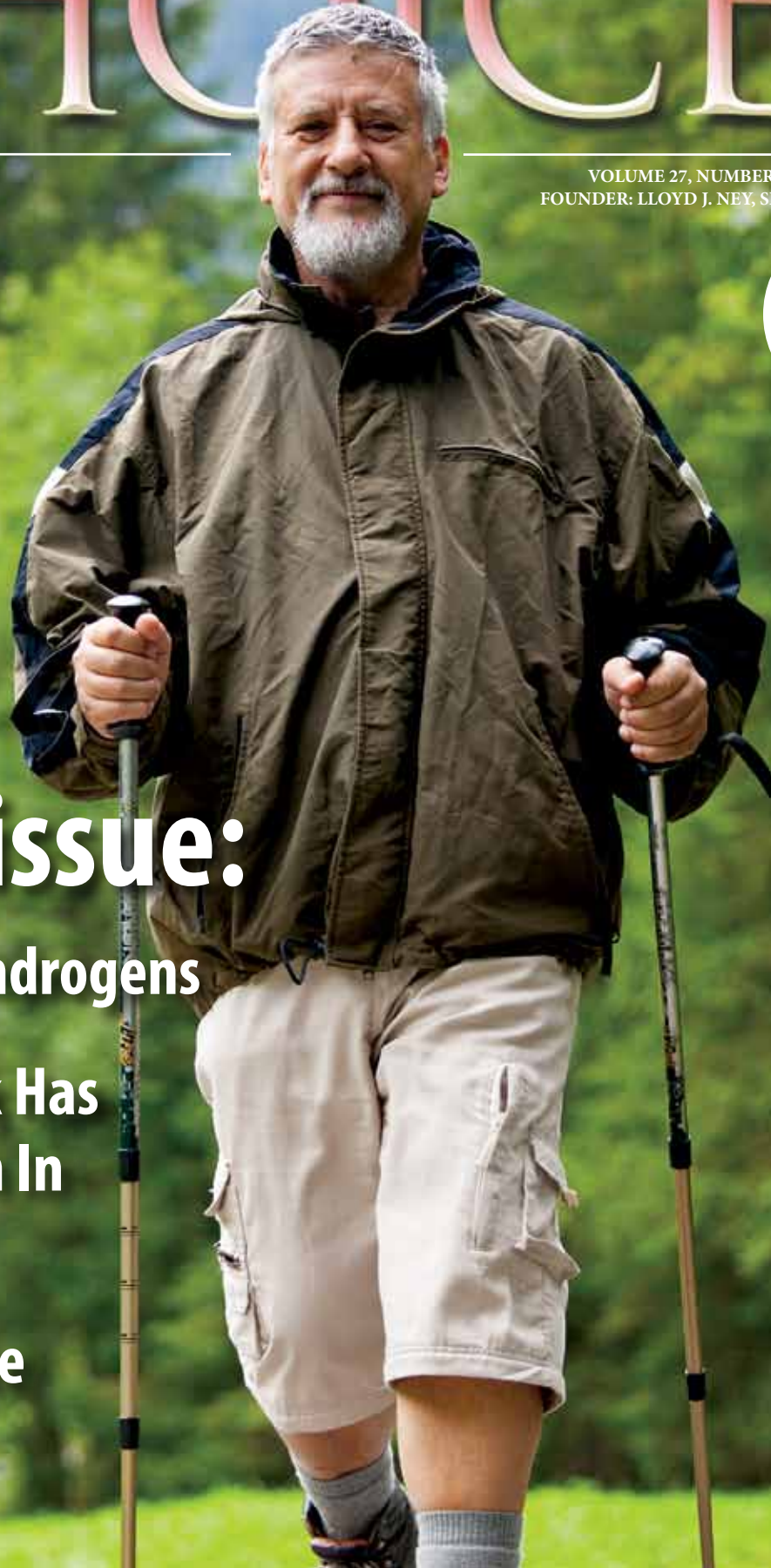


In this issue:

Blockade of Androgens

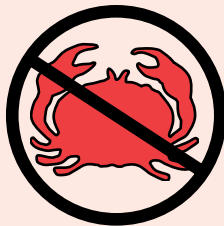
**What the Heck Has
Been Going On In
My World**

**A Strange Place
and More!**



Life Without Prostate Cancer:
Imagine The Possibilities!

P A A C T, INC.



PROSTATE CANCER COMMUNICATION
CHOICES

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BLOCKADE OF ALL SOURCES OF ANDROGENS IS KEY TO OPTIMAL TREATMENT AT ALL STAGES OF PROSTATE CANCER: OBSERVATIONS MADE IN THE 1980'S ARE THE BASIS OF CURRENT PROGRESS IN NEW DRUG DEVELOPMENT

BY FERNAND LABRIE, OC, OQ, MD, PhD

I - INTRODUCTION

Prostate cancer is the most responsive of all cancers to hormone therapy. Every effort should be made, therefore, to take advantage of this unique characteristic in order to develop and use drugs which have the optimal efficacy to block androgens of all sources. During the last 70 years, castration, first achieved by surgery ([Huggins and Hodges 1941](#)) followed by GnRH (gonadotropin-releasing hormone) agonists ([Labrie, Bélanger et al. 1980](#)) 30 years ago ([Labrie, Bélanger et al. 1980](#)), has been the most common androgen blockade used worldwide. As discussed later, castration, however, is only a partial androgen blockade and, accordingly, only a partial treatment for prostate cancer.

In 2010, 32,050 deaths from prostate cancer were estimated to occur in the US alone ([American Cancer Society 2010](#)). Most importantly, despite improvements in diagnosis and treatment, prostate cancer remains the second most common cause of death after lung cancer in American men. Although improvements in surgery and radiotherapy have also played a role, a study by Lichtenberg ([Lichtenberg 2002](#)) using National Cancer Institute data from 2.1 million patients with cancer in the USA from 1975-1995 concluded that "cancer-fighting drugs improved survival rates, especially for cancer of the prostate, where drug innovations have been the greatest." In prostate cancer, arguably the most important drugs have been GnRH agonists ([Labrie, Bélanger et al. 1980](#); [Labrie, Bélanger et al. 2005](#)) and antiandrogens permitting combined androgen blockade (CAB), which refers to the administration of a pure antiandrogen (a compound which has pure antagonistic activity at the androgen receptor, and does not act as an agonist) combined with medical or surgical castration ([Labrie, Dupont et al. 1982](#); [Labrie, Dupont et al. 1985](#); [Crawford, Eisenberger et al. 1989](#); [Labrie 2007](#)).

The main objective of physicians managing patients suffering from any type of cancer is to permanently free them from the disease. It is thus a major progress to see that androgen blockade is now increasingly recognized as curative, conditional to its use in localized (when it is curable) instead of advanced and metastatic (when it has become non-curable) disease. This news is particularly timely since more than 95% of patients can now be diagnosed by simple PSA (prostatic-specific antigen) screening and can thus be treated at the localized and only potentially curable stage ([Labrie, Candas et al. 1996](#)), thus providing an explanation for the important decrease in prostate cancer deaths observed since 1992 ([Jemal, Siegel et al. 2007](#)).

The extremely long delay in recognizing the curative potency of androgen blockade can be explained by two misinterpretations concerning androgen blockade which, unfortunately, are still at the basis of the official guidelines distributed to guide the clinical practice of members of some urological associations. These two common misinterpretations are as follows:

1. Application to localized prostate cancer of conclusions derived from advanced disease and which do not apply to localized disease. As well indicated by Professors Akaza and Namiki ([Akaza 2008](#); [Namiki, Kitagawa et al. 2008](#)), the erroneous belief of a temporary efficacy of androgen blockade due to the relatively rapid development of resistance to treatment is a characteristic typical and limited to advanced and metastatic disease. There have never been valid reasons to apply to localized prostate cancer these observations of resistance to treatment which exclusively belong to advanced disease. In fact, contrary to the situation in metastatic prostate cancer, a continuous and very long-term positive response with the high probability of a cure is observed in localized disease ([Labrie, Candas et al. 2002](#); [Akaza 2008](#); [Namiki, Kitagawa et al. 2008](#)) when optimal

androgen blockade or CAB is used. This possibility of cure is however conditional to the start of CAB sufficiently early at time of diagnosis (Labrie, Candas et al. 2002).

The conclusion that androgen blockade can be curative and does not simply delay progression has been reached in many studies including a meta-analysis of the controlled clinical trials performed as adjuvant hormonal treatment in non-metastatic prostate cancer (Fleshner, Keane et al. 2007). The author of this meta-analysis concluded that androgen blockade given as adjuvant to surgery or radiotherapy should be classified as a treatment of curative intent for patients with poor prognosis non-metastatic prostate cancer. It should be mentioned that such positive results could even be observed using a non-optimal androgen blockade, namely monotherapy, while much better results are achieved with CAB without additional negative effects (Labrie, Candas et al. 2002; Labrie 2004; Akaza, Labrie et al. 2007; Akaza 2008; Namiki, Kitagawa et al. 2008).

2. A second extremely common error, not to say generalized error, is the use of monotherapy as first treatment, a treatment much inferior to CAB even though a significant rate of cure (33%) can be obtained with monotherapy in localized prostate cancer (Peto and Dalesio 2003). However, a major limitation of monotherapy (castration alone or an antiandrogen alone) is that 40-50% of active androgens are left in the prostate with monotherapy (Labrie, Dupont et al. 1985; Labrie 2007; Labrie, Cusan et al. 2009a). These androgens made locally in the prostate continue to stimulate prostate cancer after any treatment limited to castration or an antiandrogen alone, thus permitting continued stimulation of cancer proliferation and metastasis at distance where resistance to treatment always develops and cure becomes impossible.

In localized disease, the simple addition of a pure anti-androgen to castration in order to block the action of the androgens made locally in the prostate increases the potential of cure from 33% observed with monotherapy (Prostate Cancer Triallists' Collaborative Group 2002; Peto and Dalesio 2003; Fleshner, Keane et al. 2007) (Figure 1-B.1) to more than 90% (Labrie, Candas et al. 2002; Labrie 2007) (Figure 1-B.2). It is very important to read Professor Akaza (2008) saying: "cure of prostate cancer is almost always possible with current androgen blockade...."

At the metastatic stage, on the other hand, while monotherapy first used by Huggins and Hodges (1941) has never been demonstrated to prolong survival, a 20%

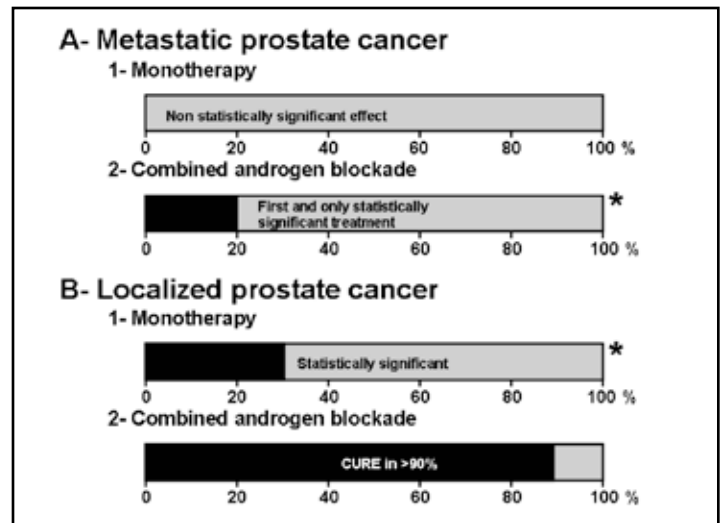


Figure 1: Comparison of the efficacy on prostate cancer specific survival of monotherapy (castration alone or antiandrogen alone at high dose) (1) and combined androgen blockade (castration + pure antiandrogen) (2) administered in metastatic (A) and localized (B) prostate cancer.

A1: No positive study available

A2: (Labrie, Dupont et al. 1985; Crawford, Eisenberger et al. 1989; Janknegt, Abbou et al. 1993; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Triallists' Collaborative Group 2000)

B1: (Prostate Cancer Triallists' Collaborative Group 2002; Peto and Dalesio 2003)

B2: (Labrie, Candas et al. 2002)

*Since the antiandrogen was added at time of progression following castration, these studies compare early versus late combined androgen blockade (CAB) and are not true comparisons between placebo and CAB.

prolongation of prostate cancer-specific survival can be obtained with CAB applied at start of treatment (Labrie, Dupont et al. 1982; Labrie, Dupont et al. 1985; Crawford, Eisenberger et al. 1989; Janknegt, Abbou et al. 1993; Labrie, Bélanger et al. 1996; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Triallists' Collaborative Group 2000). It is important to indicate that since, in all the randomized clinical trials mentioned above, the anti-androgen was added at time of progression in the groups of men who had castration alone as first treatment, comparison was in fact made between early and late CAB and no true comparison of placebo versus CAB has ever been made.

In other words, a greater difference in survival, even at the advanced metastatic stage, should have been obtained if a true comparison between placebo and CAB had been studied. It is, in fact, well recognized that a significant number of positive responses are observed when a pure anti-androgen is added at time of progression in patients who had castration as first treatment (Labrie, Dupont et al. 1988). The significant number of responses observed at time of addition of the anti-androgen when progression occurs after castration decreases the difference between the theoretical castration alone and CAB groups.

II - LOCAL FORMATION OF ANDROGENS IN THE PROSTATE CANCER (INTRACRINOLOGY) IMPLIES THAT LOCAL ANDROGEN BLOCKADE, IN ADDITION TO CASTRATION, IS NEEDED TO EXERT MAXIMAL INHIBITION OF PROSTATE CANCER GROWTH

An important advance in our understanding of the biology and endocrinology of prostate cancer is the observation that humans are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroids dehydroepiandrosterone (DHEA), and its sulfate DHEA-S, which are converted into active androgens in a large series of peripheral tissues, including the prostate (Figure 2).

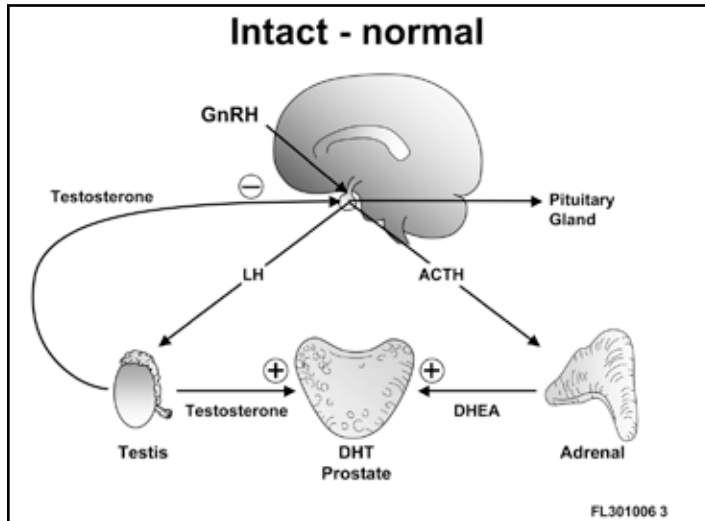


Figure 2: Schematic illustration of the two sources which provide approximately equal amounts of androgens to the normal prostate and prostate cancer.

- 1) The testicles secrete testosterone released in the blood stream from which it reaches the prostate while
- 2) the adrenals secrete dehydroepiandrosterone (DHEA) in the circulation, the inactive precursor which is converted into testosterone and then into DHT (dihydrotestosterone) in the prostate.

The local synthesis of active steroids in peripheral target tissues has been named intracrinology (Labrie, Simard et al. 1989b; Labrie 1991; Labrie, Luu-The et al. 2003; Labrie, Cusan et al. 2004). The active androgens made locally exert their action by binding to the prostatic androgen receptor (AR) without being released in significant amounts in the extracellular environment or general circulation. Most importantly, the active androgens made in peripheral tissues are inactivated locally as glucuronides before their elimination through the circulation. Contrary to the previous belief that the testes are responsible for 95% of total androgen production in men (as could be inferred from the 95–97% decrease in serum testosterone observed after castration) (Figure 3A), it is now well established that the prostate makes the androgens testosterone and dihydrotestosterone (DHT) locally in relatively large amounts.

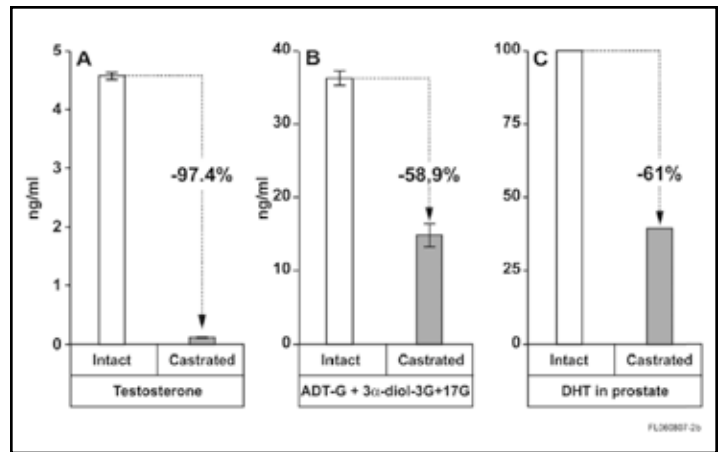


Figure 3: Effect of castration on the concentration of serum testo (A), total androgen pool (sum of serum ADT-G, 3 α -diol-3G and 3 α -diol-17G) (B) and intraprostatic DHT, the predominant androgen present in the prostate (C). Data in C are the average of values published in (Labrie, Dupont et al. 1985; Bélanger, Bélanger et al. 1989; Nishiyama, Hashimoto et al. 2004; Mostaghel, Page et al. 2007). Data are presented as means \pm SEM (Labrie, Cusan et al. 2009b).

III - CASTRATION ALONE IS AN INSUFFICIENT TREATMENT FOR PROSTATE CANCER

Local formation of androgens in the prostate cancer (intracrinology) implies that local androgen blockade, in addition to castration, is needed to exert maximal inhibition of prostate cancer growth. While the serum levels of testosterone are reduced by 97.4% following castration in 69 to 80-year old men (Figure 3A), the sum of the metabolites of androgens androsterone glucuronide (ADT-G), androstane-3 α ,17 β -diol-G (3 α -diol-3G) and 3 α -diol-17G, the only accurate and valid parameter of total androgenic activity measurable in the circulation (Labrie, Bélanger et al. 2006), is only reduced by 58.9% (Figure 3B), thus indicating that a very important amount (41.1%) of androgens are still present in the prostate after complete elimination of testicular androgens by medical or surgical castration. Such data are in close agreement with the concentration of intraprostatic DHT that shows that, on average, 39% of DHT is left in the prostate after castration in various studies, namely 45% (Labrie, Dupont et al. 1985), 51% (Bélanger, Bélanger et al. 1989), 25% (Nishiyama, Hashimoto et al. 2004) and 35% (Mostaghel, Page et al. 2007). In another study, it was observed that intraprostatic DHT levels remained at 50% of pre-treatment values after castration (Yoon, Gardner et al. 2008).

The observations based upon the best and validated parameters of androgenic activity, where all steroids are measured by the mass spectrometry technology show that approximately 40% of androgens are made in the prostate in 69 to 80-year-old men. Since serum DHEA decreases markedly with age starting in the thirties (Labrie, Luu-The et al. 2005), and testicular androgen secretion decreases only slightly, it is most likely that intraprostatic androgens of adrenal origin have an even greater relative and absolute importance at younger ages. The logical

conclusion from these data is that castration is an insufficient treatment for prostate cancer since, on average, it eliminates only 60% of androgens in the prostate.

IV - CLINICAL DATA IN FIRST LINE LOCALIZED DISEASE.

The simple addition of a pure anti-androgen to castration (Figure 1-B.2, CAB) can achieve long-term control or even cure in more than 90% of localized prostate cancers instead of the 33% decrease in deaths obtained by monotherapy (Figure 1-B.1).

As mentioned above, although GnRH agonist therapy in localized prostate cancer has shown important benefits in terms of survival in localized disease, the knowledge that 40-50% of androgens (Figure 3C) remain in the prostate after castration indicates that superior results should be expected from the use of CAB or the combination of an GnRH agonist with a pure anti-androgen.

The effect of CAB on long-term control or possible cure of prostate cancer was evaluated by the absence of biochemical failure or the absence of PSA rise for at least 5 years after cessation of continuous treatment (Figure 4). A total of 57

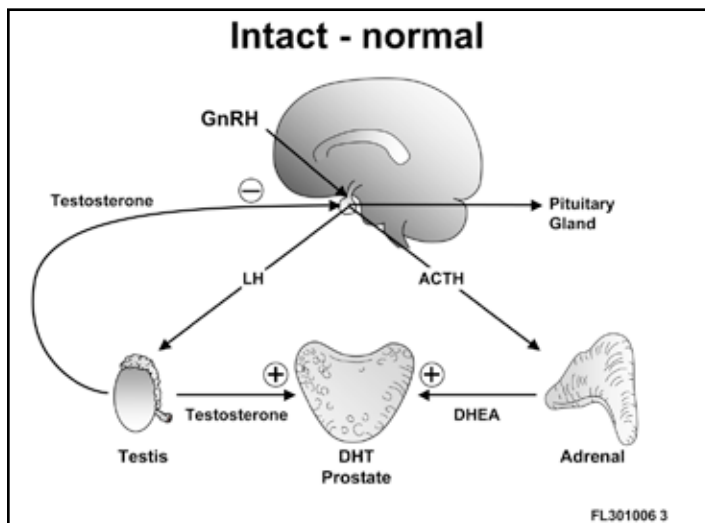


Figure 4: Effect of duration of treatment of localized prostate cancer with continuous combined androgen blockade (CAB) on the probability of long term control or "cure of the disease" illustrated by no recurrence of PSA rise for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the 3 patients treated with CAB for 3.5-5.0 years and followed for at least 5 years, while the point at 5.75 years refers to the 8 patients treated continuously with CAB for 5.0-6.5 years before cessation of treatment. The point at 8.25 years, on the other hand, refers to the 8 patients treated continuously for 6.5-9.0 years while the point at 11 years refers to the 13 patients treated for 10-11.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after cessation of continuous CAB or until PSA rise. Only 1 patient has died from prostate cancer while 18 have died from other causes (Labrie, Candas et al. 2002).

patients with localized or locally advanced disease received CAB for periods ranging from 1 to 11 years. With a minimum of 5 years of follow-up after cessation of long-term CAB, only two PSA rises occurred among 20 patients with Stage T2-T3 cancer who stopped treatment after continuous CAB for more

than 6.5 years, for a nonfailure rate of 90% (Figure 4). On the other hand, for the 11 patients who had received CAB for 3.5-6.5 years, the non-failure rate was only 36% while the serum PSA increased within 1 year in all 11 patients with Stage B2/T2 treated with CAB for only 1 year, thus indicating that active cancer remained present after short-term androgen blockade despite undetectable PSA levels. Most importantly, in all patients who had biochemical failure after stopping CAB, serum PSA rapidly decreased again to undetectable levels when CAB was restarted and PSA remained at such low levels afterward. Of these patients, only one patient had died of prostate cancer at last follow-up (Labrie, Candas et al. 2002).

A series of studies recently performed in Japan clearly illustrate the very high efficacy of CAB in localized disease (Egawa, Misaki et al. 2004; Akaza, Homma et al. 2006; Ueno, Namiki et al. 2006; Akaza 2008; Namiki, Kitagawa et al. 2008). In a prospective study performed in stage C and D prostate cancer patients (Akaza, Yamaguchi et al. 2004; Akaza 2006) comparing GnRH agonist monotherapy and CAB (GnRH agonist + bicalutamide 80 mg/day), the effect of CAB was more pronounced in patients with C than with D disease. In fact, only 5.8% (3/52) of patients progressed under CAB compared to 42.6% (20/47) with monotherapy, thus showing a marked superiority of CAB compared to monotherapy, especially in stage C or locally advanced disease. These data strongly support our results showing an even much greater advantage of CAB in stage B disease (Labrie, Candas et al. 2002).

Based upon the above-summarized data, at least for older men, primary hormone therapy is a valid therapeutic option for localized or locally advanced prostate cancer (Labrie, Candas et al. 2002; Akaza, Homma et al. 2006). A similar conclusion was reached in a retrospective study of 447 stage B prostate cancer patients who received androgen blockade alone or radical prostatectomy combined with androgen blockade. No difference in disease-specific survival was found at 9.2 years, thus indicating the predominant effect of androgen blockade and the absence of effect of prostatectomy in men receiving androgen blockade (Egawa, Misaki et al. 2004).

Data on the current treatment of prostate cancer in Japan show that primary androgen blockade is the treatment chosen for localized and locally advanced prostate cancer in a high proportion of cases. In the survey of the Japanese Urological Association published in 2005, androgen blockade alone was used as primary treatment in 40% of T1 patients and over 50% of T2 patients. Moreover, from the data collected in 2001-2003 by the Japanese Prostate Cancer Surveillance Group (J-CaP) (Akaza, Yamaguchi et al. 2004), about 60% of patients who receive androgen blockade receive CAB. In addition, about 70% of patients who receive androgen blockade receive hormone therapy as first treatment. A trend in the same direction is seen

in the US from the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) (Cooperberg, Grossfeld et al. 2003).

V - CLINICAL DATA IN FIRST-LINE METASTATIC DISEASE

No study has ever shown that medical or surgical castration alone has a statistically significant effect on survival in patients with metastatic prostate cancer. As mentioned above, early data have indicated that the benefits of CAB are greater for patients with minimal metastatic disease than for those with extensive metastatic disease (Crawford, Eisenberger et al. 1989; Denis, Keuppens et al. 1998) and clinical trials in patients with advanced prostate cancer have shown that CAB has several advantages over castration alone. These advantages include a higher proportion of patients with complete and partial responses to treatment, improved control of pain associated with metastatic disease, longer disease-free survival, and longer overall survival (Crawford, Eisenberger et al. 1989; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Trialists' Collaborative Group 2000).

In fact, the combination of a pure antiandrogen (flutamide) with an GnRH agonist was the first treatment shown to prolong life in patients with advanced prostate cancer (Labrie, Dupont et al. 1982; Crawford, Eisenberger et al. 1989). A large-scale study comparing castration and flutamide as initial treatment versus flutamide added later (when the cancer progressed following castration (Eisenberger, Blumenstein et al. 1998) did not reach a statistically significant difference ($P=0.14$). Unfortunately, that study has generally been misinterpreted and used to “say”, erroneously, that CAB had no benefit. In fact, the risk ratio observed of 0.91 (90% CI 0.81-1.01, $P=0.14$) in favor of CAB indicates a 86% probability that CAB administered at the start of treatment is superior to administering flutamide later at time of relapse. It should also be mentioned, as indicated earlier, that that study did not truly compare CAB to castration alone but compared, in two groups of castrated men, administration of flutamide at start of treatment versus delayed administration of the same drug at time of progression. It should be taken into account that adding flutamide in patients progressing after castration has been found to induce a positive response in 34.2% of patients (Labrie, Dupont et al. 1988). It is thus reasonable to believe that the addition of flutamide at time of progression in the group of men who initially had castration alone, had a beneficial effect sufficient to decrease the difference between the two groups, thus removing the statistical difference. In any case, a 86% probability that CAB administered at start of treatment is superior to the administration of the same drug at time of progression clearly suggests the superiority of CAB and should preclude using such data to say that there is no benefit....

In fact, CAB administered as first treatment increases overall survival by an average of 3–6 months compared to adding the antiandrogen at a later time (Figure 1-A.2) (Crawford,

Eisenberger et al. 1989; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Trialists' Collaborative Group 2000). This prolongation of life corresponds to an actual increase in life duration of 6-12 months, assuming that about half of these patients die from causes other than prostate cancer.

VI - NEW DEVELOPMENTS IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

The development of CRPC is the rule in patients with metastatic disease initially treated by castration. Most importantly, CRPC has generally been viewed as the end of the therapeutic role of androgen blockade. However, early preclinical (Labrie and Veilleux 1986) and clinical (Labrie, Dupont et al. 1988) data obtained in the 1980s indicated that androgen sensitivity remains at all stages, thus offering a major opportunity to improve our understanding of the mechanisms that lead to CRPC and to develop effective hormonal therapies for these patients.

a - Further androgen blockade

Most prostate cancers that continue to grow after castration, although generally considered androgen-insensitive, are in fact sensitive to androgens. In fact, these cancers are able to grow in the presence of the reduced level of androgens of adrenal origin left after castration (Labrie, Dupont et al. 1988). Evidence of the remaining presence of androgen-sensitive cancer cells was reported by Fowler and Whitmore in 1981, (Fowler Jr and Whitmore Jr 1981) who observed a rapid and severe exacerbation (relapse) of the disease in 33 of 34 patients within the first 3 days of testosterone administration, indicating that at least some prostate cancer cells remain androgen sensitive even at an advanced stage of progression after castration. Logically, control of the growth of these cancers could be achieved using further androgen blockade (Labrie, Dupont et al. 1988).

That CRPC patients can, in fact, respond to further androgen blockade, or to a change in the agent used, has been known for about 40 years. The benefits of additional androgen blockade are illustrated by the observation that disease progression is slowed in 30–60% of patients with metastatic CRPC originally treated by castration alone following hypophysectomy, adrenalectomy, treatment with aminoglutethimide or the addition of a pure antiandrogen (Maddy, Winternitz et al. 1971; Drago, Santen et al. 1984; Labrie, Dupont et al. 1985; Murray and Pitt 1985; Labrie, Dupont et al. 1988). In a study of 209 patients with metastatic CRPC who showed disease progression despite treatment with orchiectomy, high-dose estrogens or a GnRH agonist, the addition of flutamide led to complete, partial and stable responses for at least 6 months in 6.2%, 9.6% and 18.7% of patients, respectively (Labrie, Dupont et al. 1988). In total, 34.5% of patients derived a clinical benefit from the addition of flutamide treatment, and the mean duration of response in that study was 24 months (Labrie, Dupont et al. 1988).

b - Drugs that target the prostatic formation of androgens

As mentioned above, the prostate contains the enzymes that convert DHEA into active androgens (Labrie, Bélanger et al. 1988; El-Alfy, Luu-The et al. 1999; Nakamura, Suzuki et al. 2005; Luu-The, Bélanger et al. 2008; Pelletier 2008), and intraprostatic DHT remains at sufficiently high levels to activate the androgen receptor following castration (Labrie, Dupont et al. 1985; Bélanger, Bélanger et al. 1989; Mizokami, Koh et al. 2004; Nishiyama, Hashimoto et al. 2004). The enzymatic conversion of DHEA to DHT is essential for the activation of the androgen receptor in LNCaP prostate cancer cells (Evaul, Li et al. 2010), and *in vitro* studies have shown that prostate cancer stromal cells and human LNCaP prostatic cancer cells coordinate activation of the receptor via synthesis of testosterone and DHT from DHEA (Mizokami, Koh et al. 2009). In addition, increased expression of genes that code for the enzymes that convert DHEA into testosterone has been observed in CRPC (Stanbrough, Buble et al. 2006).

Interestingly, testosterone levels are higher in metastases of prostate cancer from anorchid men than they are in primary cancers obtained from untreated eugonadal men (Mizokami, Koh et al. 2004). Moreover, cancerous prostate tissue can synthesize more DHT than benign prostatic tissue (Nishiyama, Ikarashi et al. 2007). These findings could be explained by dysregulated expression of the genes that encode steroidogenic enzymes in cancer cells, a well-known phenomenon related to aberrant control of gene expression. In addition to increased androgen receptor levels, the local and autonomous synthesis of androgens could explain the observation that androgen deprivation in prostate cancer xenograft models results in only transient cell cycle arrest. Xenograft tumors show little evidence of apoptosis, and frequently grow rapidly, despite androgen deprivation (Agus, Cordon-Cardo et al. 1999).

VII - CURRENTLY DEVELOPED HORMONAL THERAPIES FOR PROSTATE CANCER

As for any type of cancer, treatment of prostate cancer should aim at an early treatment which precedes migration of the cancer to the bones or at other distant sites where cure is no more a reasonable possibility and where, at best, only a few months of life can be added (Labrie 2010; Labrie 2011).

a - Drugs that target the androgen receptor

More potent antiandrogens

Although antiandrogens are available that have pure antagonistic activity at the androgen receptor level (flutamide, bicalutamide and nilutamide), and have shown major benefits in prostate cancer therapy (Labrie, Dupont et al. 1982; Labrie, Dupont et al. 1985; Dupont, Labrie et al. 1988; Crawford, Eisenberger et al. 1989; Dupont, Cusan et al. 1993; Janknegt, Abbou et al. 1993; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998;

Eisenberger, Blumenstein et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Trialists' Collaborative Group 2000; Labrie, Candas et al. 2002; Akaza, Yamaguchi et al. 2004; Egawa, Misaki et al. 2004; Homma, Akaza et al. 2004; Akaza 2006; Akaza, Hinotsu et al. 2006; Ueno, Namiki et al. 2006), the actual affinity of these compounds for the androgen receptor is low (Luo, Martel et al. 1996; Labrie, Simard et al. 1997; Simard, Singh et al. 1997; Labrie, Simard et al. 1999). In fact, an estimated 5–10% of DHT activity remains in the presence of current antiandrogen treatment, a quantity of DHT which is sufficient to continue to stimulate the androgen receptor and increase prostate cancer growth (Labrie, Luthy et al. 1987). Consequently, the currently available antiandrogens cannot induce maximal apoptosis in prostate cancer tissue. In fact, CAB must be continued for at least 7 years to ensure long-term control (or potentially cure) of localized prostate cancer, even when treatment is started at the localized stage before the development of metastases (Labrie, Candas et al. 2002).

The need is obvious, therefore, for novel antiandrogens with higher affinity for the human androgen receptor in order to take full advantage of the particularly high sensitivity of prostate cancer to androgens. Highly potent antiandrogens should be able to neutralize the low levels of androgens which currently remain after treatment with the presently available agents, especially GnRH agonists combined with flutamide, bicalutamide or nilutamide. The new compounds could even block the activity of the androgen receptors having a mutated ligand-binding domain, which currently respond to low intracellular androgen levels (Debes and Tindall 2004). In this context, positive clinical data on serum PSA have been obtained in studies with the new antiandrogen MDV3100 in patients with CRPC where a decrease in serum PSA has been observed (Tran, Ouk et al. 2009; Jung, Sawyers et al. 2010). No other novel antiandrogen has so far shown efficacy in clinical trials.

b - Inhibitors of androgen biosynthesis

Promising data have been obtained with abiraterone, an inhibitor of 17 α -hydroxylase (CYP17A1) (Scher, Beer et al. ; O'Donnell, Judson et al. 2004; Attard, Reid et al. 2008; Attard, Reid et al. 2009; Attard 2010; Reid, Attard et al. 2010). The results obtained should be compared to the addition of flutamide to GnRH agonists in patients with CRPC, in whom a clinical response lasting on average 24 months was observed in one-third of patients (Labrie, Dupont et al. 1988).

When administered alone, abiraterone caused symptoms of mineralocorticoid excess, including hypertension, hyperkalemia and fluid retention, in two-thirds of patients in the study group. This observation led to the addition of oral glucocorticoids (dexamethasone or prednisone) to prevent the increase in mineralocorticoid secretion. Even with the addition

of prednisone, fluid retention, edema and hypokalemia were more frequent in patients who received abiraterone (de Bono, Logothetis et al. 2011), these effects being caused by excess adrenocorticotropin secretion (Attard 2010).

In a phase III study, 1195 patients who had previously been treated with docetaxel received abiraterone acetate plus prednisone (797 patients) or prednisone alone (398 patients) (de Bono, Logothetis et al. 2011). At a median follow-up of 28 months, 42% of patients had died in the abiraterone acetate group compared to 55% ($p < 0.001$) in the placebo group. The median overall survivals were 14.8 and 10.9 months in the abiraterone and placebo groups, respectively. Time to progression based upon radiographic evidence was improved from 3.6 to 5.6 months with abiraterone (de Bono, Logothetis et al. 2011). Such data, as mentioned above, should be compared to the addition of flutamide in CRPC patients where 34.5% of patients derived clinical benefit (Labrie, Dupont et al. 1988). In both cases where further androgen blockade is achieved, namely the use of an antiandrogen or treatment with an inhibitor of androgen biosynthesis, significant benefits are observed.

c- Nonhormonal treatment options

In patients with early stage prostate cancer who experience disease progression after castration, treatment with the cancer vaccine sipuleucel T (Provenge) has shown an overall survival benefit of about 4 months (SCRIP Intelligence 2010a). In addition, the chemotherapeutic agent cabazitaxel has been shown to prolong life by 2.4 months in clinical studies.

The 2.4-4 months of prolongation of life provided by these agents in patients who failed previous androgen blockade should be compared to the 3-6 months of life gained with the combination of a pure antiandrogen with castration at the start of treatment (Labrie and Veilleux 1986; Labrie, Dupont et al. 1988; Janknegt, Abbou et al. 1993; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Eisenberger, Blumenstein et al. 1998; Bennett, Tosteson et al. 1999; Prostate Cancer Trialists' Collaborative Group 2000). The 34.2% response rate observed by the addition of flutamide in CRPC patients should also be taken into account (Labrie and Veilleux 1986). Accordingly, prolongation of life using sipuleucel T and cabazitaxel is comparable to that observed when using CAB instead of monotherapy as first treatment (Labrie, Dupont et al. 1982; Janknegt, Abbou et al. 1993; Caubet, Tosteson et al. 1997; Denis, Keuppens et al. 1998; Bennett, Tosteson et al. 1999; Labrie, Bélanger et al. 2005). The importance of considering CAB at the localized stage (Labrie, Candas et al. 2002; Akaza, Yamaguchi et al. 2004; Egawa, Misaki et al. 2004; Homma, Akaza et al. 2004; Akaza 2006; Akaza, Hinotsu et al. 2006; Akaza, Homma et al. 2006; Ueno, Namiki et al. 2006; Akaza 2008; Namiki, Kitagawa et al. 2008), should also be considered.

Conclusions

In the past, clinicians and researchers did not appreciate that prostate cancer cells could make their own hormones, although the scientific evidence has been available for 25 years (Labrie, Dupont et al. 1985; Labrie, Simard et al. 1989a; Labrie, Simard et al. 1989c; Labrie 1991; Labrie 2010; SCRIP Intelligence 2010b). This 'blind spot' is no longer justifiable. Accordingly, the proposal that all patients with prostate cancer should receive CAB as the minimal degree of androgen blockade, regardless of the stage of their disease, seems scientifically sound. In fact, when androgen blockade is indicated as first-line treatment, CAB should be used instead of performing stepwise blockade of androgens namely castration followed by CAB, as is usually done today. Such an approach of castration alone generally leads to CRPC, a stage of the disease where only a few additional months of life can be offered to the patients. The management of patients with prostate cancer should take into account the need for an optimal blockade of the two main sources of androgens at start of treatment in order to delay, minimize or even avoid the development of androgen resistance, a phenomenon typically associated with metastatic disease. When resistance to CAB does occur, however, discontinuing or changing the antiandrogen can permit further significant clinical responses.

Even the few months of life added by currently available treatments for patients with CRPC are both medically and socially important, and real hope exists that development of more potent androgen receptor antagonists as well as more specific and potent inhibitors of androgen biosynthesis should further improve the survival and quality of life of patients with prostate cancer, especially by improving first line treatment, where the greatest benefit can be obtained. These new drugs, moreover, could well permit a series of successive positive responses—up to 4th and 5th line treatments, as observed in breast cancer—before the need to move to nonhormonal agents, such as the cancer vaccine sipuleucel T and chemotherapeutic agents such as docetaxel and cabazitaxel, which carry higher risks of toxicity.

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WHAT THE HECK HAS BEEN GOING ON IN MY WORLD-PART 54!

BY MARK A. MOYAD, MD, MPH, UNIVERSITY OF MICHIGAN

Note: A total of 54 times in a row (over 15 years) I have written and volunteered for this newsletter, and I have yet to receive any financial compensation or personalized gifts for my efforts except I recently saw that shake weight commercial on television and thought that I really do NOT need that from PAACT, or a member of the PAACT audience anytime soon! I am not just saying this because I believe I am already muscularly developed like Popeye, but I believe I would look silly shaking that weight for a variety of reasons, and decorum does not permit me to tell you what those reasons are right now!

**BREAKING NEWS STORY #1!-
DR. MOYAD'S NEW BOOK NOW AVAILABLE!
WOW! WOW! WOW! WOW! WOW! WOW SPELLED
BACKWARDS!!**

200) NEW DR. MOYAD BOOK "BEYOND HORMONAL THERAPY" WAS JUST RELEASED WITH ALMOST 300 PAGES OF THE LATEST TREATMENT INFORMATION FOR MEN WITH HRPC (HORMONE REFRACTORY PROSTATE CANCER), AND HOW TO PREVENT OR REDUCE MANY SIDE EFFECTS OF CANCER TREATMENT WITH LIFESTYLE CHANGES, SUPPLEMENTS, AND PRESCRIPTION MEDICATIONS!

(Reference: Me)

BOTTOM LINE:

Can you imagine a book for men with HRPC that is almost 300 pages! I can, because I wrote this gigantic guide and it is available now! We tried to make some copies available at no charge to advocacy groups like PAACT. Talk to them for more information or visit amazon.com if you want to pay for it, and help contribute to the Moyad Beer Fund (MBF) where our motto this month is "I will share anything I own with you except the beer in my refrigerator!"

201) SLEEP REDUCTION=TESTOSTERONE REDUCTION?!

(Reference: Leproult R, Van Cauter E. JAMA 2011;305:2173-2174)

BOTTOM LINE:

Small reductions in sleep can reduce your testosterone levels by 10-15% in just 1 week. Since testosterone has multiple positive roles for some men including energy, weight loss, muscle development, mood, bone health, sexual health, ... it would be wise to get 6-8 hours of sleep per night.

WHAT ELSE?

Getting enough sleep today is about as tough as convincing your local politician to do the right thing or getting Tiger Woods to win another golf tournament or preventing Coach Jim Tressel from opening a tattoo parlor (ouch—below the belt Moyad)! We are a society that has become sleep deprived for many reasons. And,

since most of the daily testosterone production occurs while you are supposed to be sleeping, researchers began to wonder what would happen to these levels if sleep restriction occurred even for a short period of time. It is already known that some men with sleep apnea (breathing issues during sleep that can wake a person many times a night) have lower testosterone levels. A group of 10 men received 8 hours of sleep for 1-week, and then basically spent 8 days getting only 5 hours of sleep (12:30 to 5:30 AM). Men felt less energetic with less sleep, and their daytime testosterone levels were reduced by 10-15% in this short period of time. The reason this is interesting is because most Americans report some difficulty with sleep. And, if you watch enough television like I do (love those reality shows!) there are plenty of commercials selling testosterone enhancement products that remind you that men lose 1-2% of their testosterone every year, but what about the 10-15% loss with sleep deprivation?! You never hear about this, or how about the fact that with weight gain men produce less testosterone! I understand that many men reading this column are on androgen deprivation therapy (ADT) for prostate cancer and probably wonder what this story has to do with them? Well, I am glad I asked myself this question. If a man goes on intermittent therapy or comes off ADT it is theoretically possible that it takes longer to enjoy the benefits of testosterone if you are not getting enough sleep and/or gaining weight. In addition, if your energy levels drop significantly with less sleep then it is easy to see how fatigue could get worse on ADT if you are not getting enough sleep. I am always amazed at how many individuals I have ever met with any kind of sleep problem have never had a sleep study. In other words, we try all sorts of expensive and crazy things to get more sleep. **The prices alone of some of the prescription sleep drugs probably keep some people up at night trying to figure out how they are going to pay for them!** And, many of the over the counter sleep medicines have the same ingredient in them as Benadryl (aka "diphenhydramine"), which means that the long term use of these things are not good for your sexual health, memory, and even sleep patterns. Melatonin is okay for helping you get to sleep but many folks do not respond to it. However, it really makes the most sense to talk to your doctor about getting a 1-night laboratory sleep test or having one done at home. It can tell you all about your sleep patterns and based on just 1 test the physician can recommend the most appropriate solution to your sleep problem. Why throw any pills at this problem, until you discover what the real source of the problem is with your sleep? I have seen so many men and women over 15 years get sleep studies and just a behavioral change or another simplistic change solved the problem without loading up on expensive pills.

202) WEIGHT LOSS=MORE INCREMENTAL INCREASES IN VITAMIN D! ANOTHER WAY TO SAVE MONEY! AND, DO NOT TAKE MASSIVE DOSES OF VITAMIN D!

(References: Mason C, Xiao L, Imayama I, et al. Am J Clin Nutr 2011; published ahead of print & Albanes D, Mondul AM, Yu K, et al. Cancer Epidemiol Biomarkers Prev, published online July 22, 2011.)

BOTTOM LINE:

Weight loss can increase vitamin D blood levels! In fact, multiple heart healthy lifestyle changes can improve vitamin D blood levels without the need for taking more vitamin D supplements. And, another study is suggesting that getting too much vitamin D can increase the risk of aggressive prostate cancer! Ouch!

WHAT ELSE?

It is well known that lower blood levels of vitamin D are generally found in obese compared to normal weight or waist men and women. Some researchers believe that this may be a partial explanation for the higher risk of certain diseases in obese individuals. However, what had not been adequately addressed in the past is the impact of weight or waist loss on blood levels of vitamin D, and if higher baseline blood levels could lead to more weight loss compared to those with lower initial blood levels. Researchers recently did a study of 439 overweight and obese individuals (average age of 58 years and BMI of 30 = obese) and allocated them to 1 of 4 groups: diet change, exercise, diet and exercise, or control. Diet change consisted of caloric reduction (consume 1200-2000 calories/day), and exercise consisted of 45 minutes of moderate to more high intense aerobic activity 5 days a week. Vitamin D levels were measured at the start of the study and after 12 months.

Individuals that lost <5%, 5-9.9%, 10-14.9%, or \geq 15% of their baseline weight experienced increases in vitamin D blood levels of 2.1, 2.7, 3.3, and 7.7 ng/ml (P trend=0.002) on average, but some individuals had even greater increases. Lower or higher blood levels of vitamin D did not have an impact on the effectiveness of the interventions for weight loss, which means that vitamin D did not appear to do much for weight loss but at least the blood levels increased with increasing weight loss. So, the researchers concluded that weight loss via reducing overall calories or exercising more could potentially increase vitamin D levels.

Vitamin D continues to receive more attention than a politician sending inappropriate half-naked personal photos to individuals around the U.S. (that is an old and lame joke by now, but it is still pretty darn funny so I had to say it). The problem is that as the vitamin D massive hype continues to increase, there needs to be some rational and calm person (that would be me—the guy that you want on your sinking ship) that reminds you that the big picture is getting completely missed when discussing this supplement. Vitamin D has now established itself as one of the best all-time blood markers of healthy behavior, and probably one of the most over-hyped dietary supplements since shark cartilage (remember how that stuff was going to cure cancer)!

In other words, if you lose weight, your vitamin D level will increase. If you reduce your bad (LDL) cholesterol, your vitamin D level could increase. If you increase your good (HDL) cholesterol, your vitamin D level could increase. If you exercise more, and/or exercise outside (wear sunscreen please), your vitamin D level will increase. If you eat more fish loaded with omega-3 fatty acids such as salmon, your vitamin D level will increase! If you just continue to eat or drink healthy food (not necessarily fortified with more vitamin D) then your vitamin D level will increase. Why don't we have more "experts" telling the public about these simple ways to increase vitamin D blood levels without having to take more pills or worship the sun?! Folks are running around trying to supplement with large doses of vitamin D to get diverse beneficial results that will not generally occur without other healthy lifestyle changes. Instead folks like you and I need to make a lifestyle change that will give them the result they want, with minimal initial supplementation. Individuals did not lose more weight in this study if they had a higher or lower vitamin D level as long as they either reduced their calories or moved more. Somehow the message continues to be twisted with vitamin D, and it is my job to fix it. In my opinion, too many health care professionals are vocally advocating high-dose vitamin D supplementation without a full understanding of the benefits and limitations of this product. Vitamin D is a hormone, not really a vitamin, which means too little is not good and too much is not good but lifestyle changes can increase your vitamin D level if you are willing to make them.

There is also recent research to suggest once again that excessively large intakes of vitamin D or larger blood levels of vitamin D could increase the risk of aggressive prostate cancer. Some researchers have argued that too much vitamin D can desensitize the body to this hormone and may stimulate more insulin production. Until someone can prove to me that getting mega-doses of vitamin D from supplements are better I would rather play it safe my friends! In fact, recent research from this study by Albanes, D, et. al, (see full reference above) concludes by stating "Our findings indicate that men with higher vitamin D blood levels are at an increased risk of developing prostate cancer." OUCH!

203) MAYBE A LITTLE MERCURY IN YOUR FISH IS NOT SUCH A BAD THING? YOU BET! (HOW MUCH HATE MAIL AM I GOING TO GET FOR THIS STORY?)

(References: Mozaffarian D, Shi P, Steven Morris J, et al. N Engl J Med 2011; 364:1116-1125.)

BOTTOM LINE:

Higher blood levels of mercury from fish are NOT associated with an increased risk of cardiovascular disease because the overall health benefits of fish consumption appear to outweigh the ongoing concern or risk over mercury levels.

WHAT ELSE?

Yesterday I was out with my son and we ordered a thin-sliced pizza with light cheese, green olives, mushrooms, and anchovies (it was almost as satisfying to me as hearing that the Ohio State Football

team might lose another top notch football recruit to Michigan). And, I also asked the waiter for a small cup loaded with extra anchovies that I could eat while consuming MY pizza (notice that I call it “my” pizza because I believe the rights of teenage kids should come second to the hunger of the adult that has raised and fed them for a lifetime and that is paying for their college tuition). Anyhow, I think the person at the restaurant seemed concerned because he commented that I would be getting my fill of mercury after this meal! However, I was too hungry to laugh at him and tell him that anchovies have little to no mercury and even if they did there is a new study that suggests that mercury may not be as concerning as we once thought. HA! HA!

Some past studies have suggested that higher intakes of fish that contain methyl-mercury may be bad for your health. However, there has been a lack of really good studies to prove any cause and effect. Recently, over 170,000 individuals from the Health Professionals Follow Up and Nurses’ Health Study were followed that filled out questionnaires every 2 years. Researchers measured mercury from stored toenail clippings (sounds gross, but actually a good way to measure mercury) in nearly 7,000 participants (average age 61 years for men and 54 years for women) that did and did not experience cardiovascular events. Over 3,400 cases were then matched to over 3,400 controls for comparison. The median follow-up was over 11 years. There was simply no association found in this study between exposure to mercury and a higher risk of cardiovascular disease. **There was an actual trend that was almost significant (p=0.06) that showed a reduced risk of cardiovascular disease with higher levels of mercury.** Fish consumption with higher or lower levels of selenium (thought to reduce the impact of mercury) was also not associated with risk of cardiovascular disease. So, there was NO EVIDENCE of harmful effects of mercury exposure on heart disease, stroke, or total cardiovascular disease.

The results of this study will probably surprise a lot of folks! There is a constant desire to focus on fascinating medical distractions in my world. In other words, hey let’s focus on the fact that healthy fish may contain higher levels of mercury that can damage the human body in some unproven way? Hey, your memory is not what it used to be; well it must be from the mercury in all the sushi you eat?! This has been the focus over the past decade and people get obsessed with this issue. Many individuals are now being told to get a mercury blood test every year! And, why even eat fish when you can just take a fish oil pill?! This kind of thinking is more damaging than any amount of mercury that hits the brain or the penis (can I use that word in this newsletter, you know, the word “brain”). Why do we ignore the fact that fish consumption tends to be associated with multiple other healthy behaviors? Fish are a fabulous source of high quality protein, vitamin D and multiple omega-3 fatty acids. Fish consumption, in general, is also associated with lower rates of certain cancers, cardiovascular disease, eye diseases, and even mental health issues such as depression and brain diseases such as Alzheimer’s. In other words, before deciding what is healthy or not, shouldn’t the sum of the health benefits generally outweigh one or several potential health

detriments? I really believe it should when it comes to consuming fatty oily fish high in omega-3 compounds. For example, I like to jog outside, but I do realize that this behavior increases my risk for inhaling pollutants from cars and buses, twisting or breaking an ankle, getting hit by a large or small car, and stepping in dog number 2 (also known as poop spelled backwards) land mines hidden in the grass because some lazy owner did not want to clean up after Old Yeller/Benji. Yet, somehow I still believe that the health benefits of jogging will always outweigh these multiple negatives. **And, in case you were wondering, I have never had a mercury blood test, but I will get one if I happen to swallow the family thermometer - because I thought it looked like beef jerky or because my friend that always liked to hit me on the back and say “atta boy” did this ridiculous ritual at a most unusual time.** Oh and by the way, I am about to jump on my treadmill but I am nervous that it might cause me to go flying into a wall if I am not paying attention! This could cause serious injury to me, and the wall, and I am sure that my insensitive health insurance company does NOT cover wall damage caused by a flying human being. Should I still use my treadmill (sarcasm alert)???

PS. Dr. Moyad’s favorite fish - again that are low in mercury, yummy to the tummy and high in omega-3 and protein include: Anchovies (bring on the pizza), Herring (mixed feelings about this fish in terms of taste), Mackerel (love to use the word “Holy” when describing this fish), Salmon (**love to order Captain Tim Berg’s Salmon rub/Dynamite Cajun Seasoning and salmon from Alaska, www.great-alaska-seafood.com**), Sardines (oily and fun), Trout (beautiful fish and tasty), and I also like tuna sushi (sorry, realize it is higher in mercury but who gives a hoot after this recent study). Also, never ever forget the poor old WHITEFISH (see story below).

204) DOES AN ANTI-CANCER LIFESTYLE AND DIET REDUCE THE RISK OF DYING FROM HEART DISEASE AND OTHER CAUSES? ABSOLUTELY!

(References: McCullough MK, Patel AV, Kushi LH, et al. Cancer Epidemiol Biomarkers Prev 2011;20:1089-1097)

BOTTOM LINE:

Healthy weight, diet, physical activity and alcohol in moderation reduced the risk of cancer, heart disease and early death from all causes. Heart Healthy = All Healthy!!!

WHAT ELSE?

Few studies have evaluated the combined impact of following healthy lifestyle changes on cancer, cardiovascular disease (CVD), and all-cause mortality. Since the majority of Americans are no longer smoking, it is important to determine what other lifestyle changes could have a profound impact on multiple diseases. In a recent and wonderful study, over 111,000 NON-SMOKING individuals from the Cancer Prevention Study-II nutrition cohort completed questionnaires on lifestyle. This prospective study utilizes data from 21 states and was started by the American Cancer Society in 1982. The average age of men and women at the beginning of the study was 64 and 62 years of age.

After 14-years of follow-up, over 10,000 men and 6600 women died. All-cause (any cause), CVD and cancer mortality were each favorably and significantly ($p < 0.0001$) reduced by 42%, 58%, and 24% in individuals that adhered regularly to healthy lifestyle changes compared to those that did not. **HOWEVER, ONLY a total of 3.5% of the men and 4.0% of the women followed healthy lifestyle changes optimally in this study (similar to what is going on today).**

Wow! Heart healthy lifestyle changes are tantamount to all-healthy lifestyle changes. Multiple international studies (the China Study...) have demonstrated over and over again that geographic regions of the world that follow the most simplistic healthy lifestyle behaviors not only have a reduced risk of dying from heart disease, but cancer and all-causes! Now, we have the evidence in the U.S. that this is also true for Americans! Yet, many of us still want to know about the latest supplement, drug or even health scare, but isn't it incredible that less than 5% of Americans were optimally following lifestyle behaviors that can help them live longer and better! In other words, we have become fixated with the tree over the forest, or the wheel over the car, or the egg over the carton, or the clown over the circus (new clichés-pass them on folks, but keep in mind I am trade marking them, so if you use any of my jokes at a party then you owe me money). Maintaining a healthy weight, getting 30 minutes a day of exercise (most days of the week), eating primarily a plant-based diet and not consuming or moderately consuming alcohol were the 4 primary and consistent factors that provided the most benefit. It takes a HECK (I could have used a stronger word there for emphasis like "Dang") of a lot of time to just follow these 4 healthy lifestyle behaviors, which is exactly why I (and you) do not have the time or energy to worry too much about mercury in fish, or who Justin Bieber or Justin Timberlake are dating this week. Oh, and please, please, please do not get me started about tweeting, which is the most conclusive evidence thus far that the world is going to end real soon.

205) MDV3100 IS AN INTERESTING DRUG IN PHASE 3 CLINICAL TRIALS.

(Reference: ME)

BOTTOM LINE:

MDV3100 is currently in two phase 3 trials for men with HRPC (and no, I do not own any stock or have any financial interest in this company)

WHAT ELSE?

I like to call this thing "Super Casodex," which sounds like an oil change place or a discount store, but in reality MDV3100 is a pill going through phase 3 clinical trials right now. Hopefully, we will hear about how well it is working in the next 6-12 months. It is one of the most potent anti-androgen drugs ever invented. There is a phase 3 trial in progress right now known as "AFFIRM" that has completed its enrollment so I hope there will be positive results soon. Men with advanced/HRPC/castrate resistant

prostate cancer (CRPC) that no longer respond to taxotere-based chemotherapy were candidates for this study. However, there is another phase 3 trial known as PREVAIL that is testing this drug for men with CRPC before receiving chemotherapy. Androgen receptors are increased in CRPC. Thus, if a drug could tightly bind to the androgen receptor, it would make it difficult for anything else to fit into that receptor and stimulate tumor growth. Anti-androgens pills available on the market today, such as bicalutamide, flutamide, and nilutamide, are not able to bind as tightly to the androgen receptor as MDV3100. So, this is definitely a drug to watch and I know the company is also going to test this drug for some men that are still sensitive to hormone therapy (neat stuff).

206) COREGONUS CLUPEIFORMIS OR WHITEFISH FROM THE GREAT LAKES GET NO RESPECT! (RODNEY DANGERFIELD, IN MY MIND CIRCA 2011)

(Reference: ME)

BOTTOM LINE:

Great Lakes Whitefish compete with most fish around the world when it comes to health benefits because they are high in omega-3 fatty acid levels and low in mercury.

Unfortunately, numerous bone-headed experts are not giving this fish the credit it deserves, so now I am going to shout out of my window in a lightning storm that "I'm as mad as hell, and I'm not going to take this anymore!" (Name the movie that famous line came from?...tick tock tick tock....The answer is "NETWORK," released in 1976).

WHAT ELSE?

What fish on planet earth could possibly have well over 1000 mg of omega-3 fatty acids in just a single 3-ounce serving? This is higher than several types of salmon!!! Yet, no one seems to give a hoot (sorry about that vulgar swear word) about whitefish. Why? I think this is an educational issue. It is my job to give this poor old fish the respect it deserves. There are also about 20 grams of high quality protein and 350 mg of potassium in a single serving of whitefish! How much carbohydrate? Zero! How much sodium? Only 2% of your daily intake! How many calories? Only 150 calories in 1 cooked fillet! Oh, and the Great Lakes Whitefish is not really white in color but has silver sides and a silver-white belly and a greenish-brown back. The point here is that it is really easy to tell folks to eat fish weekly and just recommend salmon, but in reality there are fish around the world that have just as many health benefits, and are also really low in mercury, but never get credit. The next time you order whitefish, please remember to thank me (not the restaurant).

THAT IS ALL FOLKS! See you in winter, when I will write about many other serious issues and give timeless advice in the next newsletter, such as why it is never smart to let an urologist with really gigantic swollen fingers that likes to wear big and thick gloves do your next prostate exam!

REBUTTAL TO DATTOLI URORAD EDITORIAL

BY JERROLD SHARKEY, MD FACS

My SHORT BIOGRAPHY summarizes my expertise in the diagnosis and treatment of Prostate Cancer.

The Urologist is the PRIMARY CARE DOCTOR for Men with respect to urinary tract and Prostate Conditions of all kinds. Specifically, BPH and Prostate Cancer.

Dr. Dattoli, a Radiation Therapist specializing in the treatment of Prostate Cancer for many years, attacks his Urological Colleagues in his editorial opinion. Most radiation therapists see new patients AFTER referral by a Urology colleague, not by direct patient marketing.

For years, he has provided care at his personally owned Radiation Center. He first consults with new patients (generally self-referred), with Prostate Cancer. He then refers and treats them in his personally owned center. I respectfully suggest there is financial gain for his center, just as there is in a jointly owned Urology-Radiation Oncology Center he seems to be universally deriding with one brush stroke. All of these centers are not of the SAME caliber. Yet, he does not clarify these centers by equipment or expertise of the Radiation Oncologist. Mr. Herbert seems to accept this opinion at face value without the facts of this editorial being substantiated.

The usual standard of proper Urological care for men is to see their PCP for Annual PSA starting at age 50 (Age 40 if Family History exists or African American where the incidence is much higher). In my 40 plus years of active practice experience, Urologists (like myself) and my Radiation Oncologists were NOT fierce competitors, but rather colleagues and allies in the fight to cure patients with Prostate Cancer. We still are respectful of each other's expertise and experience. I am unsure why Dr. Dattoli has not worked together in the same manner with any Urology colleagues in his long career.

When I did BRACHYTHERAPY procedures, it was always done together in the OR with my Radiation Therapy Colleague and his expert PhD Physicist. I believe Dr. Dattoli works alone during these procedures. Perhaps this can be clarified.

I believe patients are owed UNBIASED DISCUSSION of all treatment options by their diagnosing and treating Urologist.

Second Opinions and/or Referral to another specialist should be provided if needed. Either another Urologist, Radiation

BIO: JERROLD SHARKEY, MD FACS

Formerly, a Director and Principal Investigator at Advanced Research Institute for Urological Drugs and Devices until 2010, and has spent 40 years in the ACTIVE PRACTICE OF UROLOGY.

He is a Graduate of the City College of New York 1959 and the Albert Einstein College of Medicine 1963.

After 5 years of Residency in Surgery and Urology, Dr. Sharkey became Board Certified in Urology in 1972 and a Fellow of the American College of Surgeons (FACS).

He was the U.S. Army Chief of Urology from 1968-1971 at several military locations. Following that he was Chief of Surgery at Baptist Hospital, Miami from 1971-1982 and HCA New Port Richey Hospitals from 1982-2007.

He was a Clinical Assistant Professor on the Faculty at the University of MIAMI from 1971-1982 as well as in Private Practice in Miami, and then held a similar position at USF Departments of Urology along with his private group practice in New Port Richey until 2007. He was the managing partner of a 7 man group there.

He is a Past president of the Tampa Urological Society and A senior member of both the American Brachytherapy Society and the American Urological Society (AUA).

He has Published and lectured extensively on Prostate Cancer.

He was a Founder and Developer of the Bay Area Renal Stone Center for Lithotripsy for treatment of Kidney Stones) 1986-2006.

His latest publications and posters compare his group's results with 2500 patients using brachytherapy (Seed Implants) versus radical prostatectomy for the treatment of Prostate Cancer for 14 years.

Previously, he was a Prostate Cancer Educational Consultant providing patients with information on their TREATMENT OPTIONS for Prostate Cancer. In addition, he gave talks to the Public on Prostate Cancer Issues as well as Men's Health Issues.

He is working with Prostate Cancer Patients receiving care during their weekly Radiation Treatment visits in conjunction with Radiation Oncologist Dr. Charles Brooks at the USWF Prostate Cancer Center in Clearwater, Florida. June 2010-present.

Therapist, Brachytherapist or Medical Oncologist with a significant volume of experience.

The need for these referrals is usually determined over a series of visits after the diagnosis of Prostate Cancer is made. The patient and his significant other or relative are counseled during these visits and the patient's INDIVIDUAL CASE is considered. No one treatment is "best" for every patient diagnosed with Prostate Cancer.

The patient should have been given proper reading materials and the patient's wishes and fears for his individual and personalized treatment taken into account. All risks and complications of all the possible treatments should be explained simply and in detail. Only in that way can an informed decision result.

I believe most of my Urology colleagues do this now as I have done for over 43 years in practice.

If the patient and his family decide after this process to seek out Radiation Therapy, then the patient should be informed of all the Radiation facilities in the area and outside the immediate area. There is NO lack of ethics here. An Urologist is capable of making this referral to any high caliber Center, including one he may have ownership in. I believe Dr. Dattoli evaluates new patients and then refers them for treatment to HIS own facility. What is perplexing to me is that this seems to be his major finding of criticism with what the Urologist does for his patients!!

Is there something wrong with medical professionals (including Dr. Dattoli) earning a reasonable income like lawyers, accountants, and other professionals? I think not.

If Urologists and Radiation Therapists jointly own a center, then they must:

1. Disclose their ownership interest in the facility they refer the patient to and give the patient other optional facilities of equivalent excellence.
2. Stay closely involved through the treatment process and post-treatment months and years.
3. Be actively involved with the Radiation facility he might have ownership interest in and be certain the governing board has provided the following controls:
 - a. A Board Certified Radiation Oncologist with expertise and experience in the treatment of Prostate Cancer.
 - b. A facility that has its own in house Physicist, Dosimetrist and Technologists involved with treatment planning and administration.
 - c. The facility should have the latest Radiation Therapy machines and planning technology.

Urologists are still doing Radical Prostatectomy, Cryosurgery, Seed Implantation and Active Surveillance. They DO NOT refer ALL their patients for Radiation Therapy as implied by Dr. Dattoli. Also, only 70% of patients referred for Radiation actually choose radiation therapy. There is no coercion, nor hidden "scandal."

In the years past, Urologists did not "roundly Condemn Radiation" as a treatment option as Dr. Dattoli implies. Rather, Surgical and Brachytherapy options with or without Hormones were both, as effective, or more effective in select cases. This is even more so now with major improvements in the current Radiation Therapy Technology. The new machines are faster and more precise and I might add expensive to own.

As these newer improvements in Radiation technology came into effect in the last number of years - Urologists

have an improved additional option for their patients. This is especially so for those patients that are not candidates for Surgery (due to age, medical risks or those patients wishing to avoid the potential complications of surgery or Brachytherapy).

I have had and still have excellent relationships with multiple Radiation Therapy Colleagues and their centers, as has been the case in my entire practice career. I am sure it is and has been mutually respectful.

Dr. Dattoli refers to Stark "kickbacks." Is there a difference to his advertising and marketing DIRECTLY to patients and then treating them in the facility HE OWNS??

He competes directly with Urologists for patients and perhaps is impacted by these newer treatment facilities?

Urologists need not be trained in radiation therapy to partially own their own center. They need to hire the best Radiation Oncologist and purchase the latest and best equipment and staff.

What could possibly be better than a center owned jointly by Urologists and a Radiation Oncologist, that NOT ONLY TREATS, BUT BECOME EXPERTS IN THE TREATMENT OF PROSTATE CANCER?

Having a Staff that specializes in the treatment planning, dosimetry and physics, and then have technologists carry out that treatment of a SINGLE disease, provides the best Radiation Treatment I as a professional could imagine. The greater the volume of patients treated, the greater the experience of the center and the better the results. A well known fact in medical care.

I am personally consulting at such a facility here in Florida and have NO ownership interest. The care and results are superb, and I am proud to work there. The patients are comfortable, happy and confident in their treatment and have few side effects.

In addition to an outstanding and experienced Radiation Oncologist, there is an experienced and excellent Dosimetrist and Physicist. Their plan is given to a team of experienced and specialized Radiation Technologists. In addition we have an experienced RN who helps with patient weekly visits, new consults, and triages and comforts daily patient concerns.

In addition she is collecting clinical data to document our treatment results. A Clinical Research paper on those results, both short and long term will be forthcoming in a Peer Reviewed Journal. This will demonstrate that Urologists and Radiation Oncologists can "jointly" create Centers of Excellence.

A STRANGE PLACE - PART II

AN INFORMATION GUIDE TO PROSTATE CANCER

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This article is a booklet being printed in a multi-part series. The next series will begin with GETTING STARTED - THE PROCESS which will discuss PSA, Biopsy and additional tests and scan. It will also include staging and diagnosis.

Terry Herbert, the author of this booklet, has no medical training. He was diagnosed as having prostate cancer in August 1996 and has learned something about the subject since then. In 1998, with colleagues Gregg and Kerry Morrison he established a website - YANA- You Are Not Alone Now at www.yanaweb.net. The stated aim of the site, which is still active, is:

“To provide comfort to any man diagnosed with prostate cancer, to offer thoughtful support to him and his family and to help them to decide how best to deal with the diagnosis by providing them with and guiding them to suitable information, being mindful at all times that it is the individual's ultimate choice; that the path he decides to follow is his own and that of his family, based on his particular circumstances.”

Terry Herbert has produced this booklet. It represents a significant input of the knowledge, skills and time of Terry Herbert. It is regarded as intellectual property owned by Terry Herbert and is subject to copyright.

Acknowledgement is made, and thanks given, to Donna Pogliano; members of the Prostate Support Action (PSA) Group and the YANA - You Are Not Alone Now website and members of my family who assisted in the final editing of this booklet. And to members of the YANA site for their generous donations that made this edition possible.

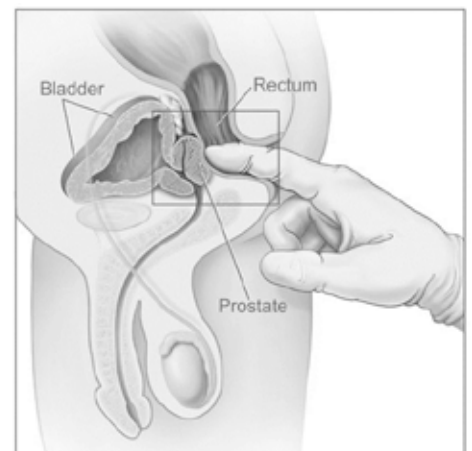
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GETTING STARTED – THE PROCESS

DRE - DIGITAL RECTAL EXAMINATION

The first step in the process of getting to the **Strange Place** is usually what is referred to as a DRE. This stands for Digital Rectal Examination and is dreaded by most men. Many refuse to even consider it. Most women cannot understand



In my previous Urology practice, we became experts in Brachytherapy as well as Radical prostatectomy over 15 years. Our results speak for themselves, and are in publications. This was truly “evidence based medicine” at its highest level. The very same is occurring in high caliber Urology and Radiation Oncology jointly owned centers.

Perhaps there are “UroRad” centers (as Dr. Dattoli is citing them in a derogatory tone), that don’t have the high standards that other Urology owned centers that I know have.

However, with that label, he condemns ALL Urology Owned Centers by looking through biased and narrowed lenses, with blinders on.

Who is to determine whether Dr. Dattoli’s center and other Radiation Therapy centers are giving proper care not linked to financial gains? Can he personally be objective about his motivations in his own center? I think not.

In addition, Patients must be “educated consumers” and ask the questions raised by Dr. Dattoli. They should not be scared off by words used by Dr. Dattoli that these Urology owned centers are “scandalous” and “motivated by financial greed,” without getting the facts.

I suggest Dr. Dattoli investigate which centers are providing substandard care and to prove which patients being referred for Radiation therapy in 2011, would not have been referred by these same Doctors in 2008, 2009 and 2010. Only then can he prove there is abuse. It should not be written about and by innuendo condemn all facilities other than his own and specifically those with Urologist owners. This scares and misleads patients and their families. Perhaps then he can write a more believable editorial based on fact.

His editorial does a disservice to patients comfortable with and confident in their treatment decision, and to the honest and ethical Urologists guiding their patients to obtain proper and effective treatment of this frightening disease diagnosis.

Urologists are not diagnosing Prostate Cancer excessively, simply to refer them for financial gains, but to save lives as they always have been. With the advent of the PSA test, properly interpreted, they are diagnosing the disease in its earliest stages. Then, by treating it promptly, this deadly disease can be prevented from spreading and killing men painfully and prematurely.

Respectfully submitted,

Jerrold Sharkey, MD FACS

BOARD CERTIFIED UROLOGY

Prostate Cancer Educational Consultant

what the fuss is about. It is a simple procedure and there is no discomfort when it is done well - and if the man is relaxed. The examination does not take very long - usually less than 30 seconds.

If you have an understanding of where the prostate is located, it is pretty obvious that the only way it can be reached practically is via the rectum. The doctor inserts a finger to feel the prostate. In doing so, the doctor is trying to establish whether there is anything unusual about the gland: a firmness perhaps, or nodules, or roughness on the surface. A biopsy may well be ordered if the DRE reveals any abnormal features.

In days gone by the DRE was one of the few ways in which prostate cancer was diagnosed - men with symptoms were often diagnosed after a TURP. The DRE is not a very accurate method of diagnosis because of the limits imposed by the examination. For one thing the doctor can only feel one side of the gland; for another, the examining finger is clad in a glove.

There are considerable differences of opinion in the recommendations of various authorities around the world, but broadly speaking, the DRE should be a standard item on an inclusive health checklist for men over 50 years old, or for men over 40 years of age if they are 'at risk' - for example if breast or prostate cancer has been diagnosed in parents, aunts, uncles or siblings. In the U.S. Afro-American men are seen to be at risk because of the high incidence of prostate cancer amongst these men.

PSA - PROSTATE SPECIFIC ANTIGEN

This is the most widely used test for detecting prostate cancer today. It is simple to do. A small sample of blood is taken, usually from a vein in the arm, and is tested for the presence of PSA (Prostate Specific Antigen). This is an enzyme initially thought to be formed only by the prostate gland - hence "prostate specific." It is now known that very small quantities of the enzyme are produced by other glands - and even by women.

The laboratory testing the blood will report a number, which reflects the level of PSA in the blood, usually in nanograms per milliliter (ng/ml). A nanogram is one billionth of a gram; a milliliter is one thousandth of a liter. The method used to measure these very small amounts differs between the manufacturers of the testing equipment and the results produced vary considerably. Although manufacturers agreed to calibrate their equipment to produce comparable results, this is often not done in practice. It is best if you can have all tests run by the same laboratory using the same equipment. Most laboratories will only guarantee accuracy to within 80%.

IMPORTANT INFORMATION ON PSA LEVELS

PSA is not a prostate cancer specific marker. PSA levels can be elevated by a number of causes, from infection to physical activities. So it is very important to investigate the cause of any elevated PSA reported and not to assume that it is prostate cancer. In one reported case, a man with a PSA of 362 ng/ml was found to have an infection that responded to treatment - it was NOT prostate cancer. Although a PSA of 4.0 ng/ml is regarded as "normal," only a minority of men - between 25% and 35% - with a reading higher than that will be diagnosed as having prostate cancer. Men with a PSA level lower than the "normal" were biopsied in one study - many had positive results.

The scale of measurement is unlimited and PSA readings of over 1,000 ng/ml are not unheard of. One man in the United States had a PSA reading of 3,552 ng/ml in 1991, which climbed to 12,600 ng/ml in 1992. In 1999 his PSA was down to 109 ng/ml after treatment and he was still working as a commercial pilot on a large American cargo airline, subsequently rising to Chief Pilot before retiring in 2009. It is unusual for a man to survive so long with such high levels of PSA - this level is usually associated with a very aggressive tumor. Just another example of the Golden Rule

When the PSA test was introduced as a diagnostic tool in 1990, a level of 10 ng/ml was considered "normal" and anything higher required further investigation. This figure was subsequently reduced to 4.0 ng/ml, which is regarded as "normal" in most countries. In the US there is a move to lower the measure to 2.6 ng/ml and there is even some pressure to go to 1.25 ng/ml as a "standard." Prostate cancer will **not** be found in roughly 65% of men with a PSA higher than 2.6 ng/ml. In many cases where prostate cancer is discovered after an "abnormal" PSA test, the tumor will be regarded as "insignificant" or "very low risk" and may not need immediate treatment.

There is another PSA test - the fPSA, PSA II or Free PSA test. This test refers to the amount of what is referred to as “unbound” or “free” PSA in a sample of blood and is discussed below.

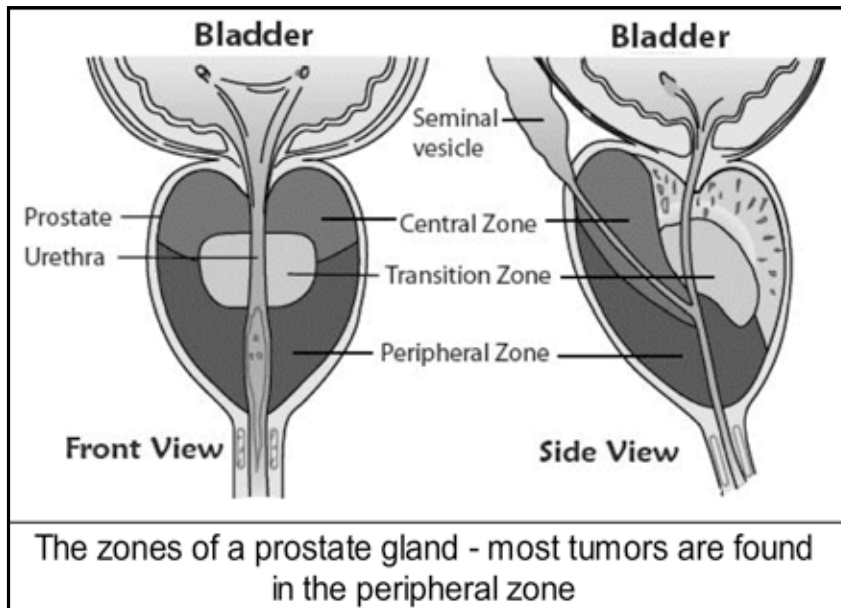
The most common causes of an elevated PSA are prostatitis (an infection of the prostate), a bladder infection, or BPH (Benign Prostate Hyperplasia). This last condition affects most men over 50 years of age and is not deadly. There is little which can be done to reduce the effect of BPH on the PSA level in the short term, but any infection should be treated before a second PSA test is carried out. Acute prostatitis can cause the PSA levels to rise up to five to seven times the normal level for up to six weeks. Infections of the bladder and prostate are often very difficult to deal with.

It is recommended that blood for PSA testing should be drawn as early in the day as is convenient and preferably before eating. Physical activities can affect the PSA level, and these should be avoided before drawing the blood. Examples of physical activities to avoid include:

- DRE (Digital Rectal Examination). Although doctors often carry out the DRE before drawing blood, they should reverse these procedures.
- Sexual activity: Ejaculation can elevate PSA levels for up to 48 hours after it has taken place.
- Cycling or motor cycling: This can increase levels up to three times for up to a week, depending on how strenuous the cycling is. This includes use of an exercise bicycle.
- Alcohol and coffee: Both can irritate the prostate and should be avoided for 48 hours prior to blood being drawn.

If any PSA result is between 4 and 10 ng/ml, a second test should be run - the so-called fPSA, PSA II or Free PSA test. Some laboratories will do this automatically, while others require a specific request since the cost of the fPSA test is higher than

the PSA test alone. The result of this test will usually be shown as a percentage of the total PSA measured and is a valuable part of the diagnostic process. The risk of cancer being present varies in inverse proportion to the percentage shown. So the higher the percentage, the less chance of the PSA being caused by prostate cancer. An fPSA of over 25% would mean that the most likely cause of the elevated PSA is not prostate cancer; an fPSA level of under 15% will point to prostate cancer as being potentially the main cause of the elevated PSA. If the fPSA level is high, alternative causes of the elevated total PSA level should be investigated before a biopsy is undertaken, since there are some risks associated with biopsy.



PSA levels can also vary significantly for no obvious reason. It is therefore usually important to have a series of PSA tests done to establish the average level before moving on to the next important test, which is the biopsy. Many men monitor their PSA levels for some years, watching for any upward trend in the numbers. There are two commonly used measures PSADT (PSA Doubling Time) and PSA

Velocity (PSAV). The first looks at the time the PSA takes to double or it projects an estimated doubling time. The more rapid the PSADT, the more likely it is that prostate cancer is the cause of the high PSA result. So, a PSADT measured in months certainly requires investigation; a PSADT measured in years may be watched closely for some time further without any further direct intervention. The second measure is PSAV (PSA Velocity) which looks sequential increases in values of the PSA levels - if the increases are greater than a target figure (usually 0.75 ng/ml per year) further investigation may be warranted. It is important to note that if PSA values fluctuate up and down, it is far more likely that the cause will be infection or BPH - PSA values associated with prostate cancer tend to increase consistently.

Finally there is a school of thought that PSA density should be considered. This is measured by taking the PSA level and dividing it by the volume of the gland. The result is expressed in ng/ml/gm and the lower the figure the better. As an example, if a man has a PSA of 5.6 ng/ml and has a large gland estimated at 65 gm, his PSA density would be 0.086 ng/ml/gm, indicating that much of the PSA is generated by the normal

cells in the large gland. A PSA density of over 0.15 ng/ml/gm may require further investigation.

BIOPSY

If the DRE (Digital Rectal Examination) and/or the PSA tests indicate the possibility of cancer cells being in the prostate, the next step is to biopsy the gland - taking samples to examine under a microscope. A spring loaded biopsy "gun" is inserted into the rectum and very fine needles are 'shot' into the gland to collect samples. In the past six needles were used, but twelve needles, or more, are more common now. Occasionally a higher number of needles are used and up to 100 needles may be used in what is termed a 'saturation' or 'mapping' procedure intended to establish the precise site of any tumor. This is an unusual procedure and would rarely be undertaken in an initial biopsy, but rather when a focused treatment such as Cryotherapy or HIFU is being planned.

The biopsy procedure is uncomfortable - the procedure has been described rather like being kicked hard in the backside. However some men have reported considerable pain, especially from procedures using 12 or more needles, and recommend asking for an anesthetic spray or other pain deadening methods - for some reason many doctors do not offer this, and some are even reluctant to do so when asked. An ultrasound device is often used to establish whether there are any specific areas to be investigated. If any are identified, the biopsy "gun" is guided to these areas. If there is no specific target, the samples are taken in a standard pattern. Before the biopsy is done, confirmation should be sought that the samples will be clearly identified by site when the biopsy report is completed. This is not always done.

One of the developments in biopsy procedures is the use of Color Doppler Ultrasound. Some manufacturers of this equipment claim it can identify tumors without the necessity of biopsy procedures, but the more general view is that the procedure can be used to identify potential tumor sites more clearly and to guide the biopsy needles to those sites. Regrettably very few establishments use this procedure, which produces more definitive results.

CAN BIOPSY PROCEDURES SPREAD THE CANCER?

Concerns are often expressed about side effects from the biopsy procedure. The most worrisome of these is the speculation that the entry of the needles might cause any cancer to spread. There

is no firm evidence of this happening, although there is a view that it is a possibility. It is clear that there can be an increase of cancer cells in circulation in the bloodstream after a biopsy. The unresolved argument concerns the possibility of these cells lodging in other parts of the body and establishing a metastasized disease.

Given the number of biopsy procedures carried out, especially in the United States, since the widespread use of PSA testing began there would be the expectation, if this concern was justified, that the incidence of prostate cancer would rise sharply. It has not but has in fact reduced.

There are usually some short-term side effects. The prostate bleeds after the procedure, so both urine and ejaculate will usually be bloody for some time. Initially the urine will often be the color of Cabernet Sauvignon, but will fade to Rose. The long-term side effects can include erectile dysfunction, but, as said previously, are very rarely reported. One study puts their incidence at less than 3%.

Because the biopsy needles pass through the lower bowel on their way to the prostate, there is a chance of infection so it is important to take the antibiotics, which will be prescribed before the procedure is carried out. Most samples taken by needle biopsy come from what is termed the peripheral zone of the gland

Samples are also submitted for analysis when men have the procedure known as a TURP (Transurethral Resection of the Prostate), the common way of dealing with BPH (Benign Prostatic Hyperplasia). This material is examined for cancer cells and if found these are graded in the same way as the samples from the biopsy procedure described above. If there is a positive diagnosis following a TURP, the material will have come from the transition zone of the gland. The majority of tumors in this area are very low risk and will probably not progress to become life threatening. This may make the man a candidate for what is termed Active Surveillance or watchful waiting.

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FINANCIAL SUMMARY REPORT (JANUARY 1, 2011 THROUGH JUNE 30, 2011)

	<u>GENERAL FUND</u>
BALANCE ON HAND DECEMBER 31, 2010	<u>1,680,280.68</u>
REVENUES RECEIVED -	
Membership Contributions	34,557.37
Memorial Income	4,510.00
Trusts & Bequests	0.00
Investment Income	22,825.38
Miscellaneous Income	<u>10.00</u>
TOTAL REVENUES	61,902.75
TOTAL BALANCE ON HAND AND REVENUES	<u>1,742,183.43</u>
EXPENDITURES-	
Investment Withholding	9.61
Employee Wages	51,634.06
Payroll Taxes	4,346.35
Insurance (Health, House, Workman's Compensation)	17,653.58
Outside Services, Labor	3,856.25
Rent	7,500.00
Meals, Motel, and Transportation	5,522.10
Auto Expense	430.00
Printing	23,405.77
Postage and Delivery	13,458.10
Telephone	2,652.68
Service Plans/Licenses & Permits	2,785.68
Program Expense-Conference Exhibit Fees	0.00
Office and Computer Supplies	1,134.62
Utilities - Refuse	76.00
Repairs (Building, Equipment)	919.87
Miscellaneous	417.73
TOTAL EXPENDITURES	<u>135,802.40</u>
BALANCE ON HAND JUNE 30, 2011	<u>1,606,381.03</u>
ASSETS:	
Checking Account	14,159.42
Petty Cash	50.00
Savings Account	29.63
Certificates of Deposit, Stocks, and Bonds	1,243,216.09
Money Market Funds	210,340.51
Equipment	13,338.06
NET ASSETS:	<u>1,481,133.71</u>
FOUNDATION FUND BALANCE:	<u>261,651.40</u>

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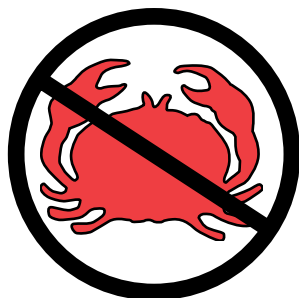
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