



## February Newsletter 2005

Prostate Cancer 101, Inc.  
Kingston, New York

The Newsletter of PCa101 Kingston - Prostate Cancer Information and Support Group

### A Message from Ron Koster

On Tuesday, February 15, 2005, Dr. Hugh Fisher will be the guest speaker at PC101's Distinguished Lecture Series. The topic of his talk will be "Prognosis Assessment of Prostate Cancer – Is My Cancer Life Threatening or a Bump in the Road of Life". Dr. Fisher is a Board Certified Surgeon specializing in Urology and has a wealth of experience he would like to share with us. Regarding his talk, he told us that he will include information on "What we know and what we hope to know regarding the aggressiveness of individual tumors using clinical and molecular information."

Dr. Fisher received his medical degree in 1973 from St. Louis University School of Medicine, St. Louis, Missouri and did a residency in surgery in Medical Center Hospital of Vermont and his urology residency at Albany Medical Center Hospital, Albany, NY

where he continues to practice. In 1981 he was a Special Fellow in Urologic Oncology, Memorial Sloan-Kettering Cancer Center, NY, NY.

In 1978 he started as an Instructor in the Department of Surgery, Division of Urological Surgery, Albany Medical College and Albany Medical Center Hospital. At present he is an Associate Professor of Surgery at Albany Medical Center along with being a consultant to Albany Veteran's Administration Medical Center.

Besides his busy practice with Community Care Physicians in Albany, NY he has participated and been the principal investigator in over fifteen clinical trials including A Randomized Prospective Study Comparing Radical Prostatectomy Alone vs. Radical Prostatectomy Preceded by Androgen Blockade in Clinical B2 Prostate Cancer, Tap Pharmaceuticals. His findings along with the co-authors of this trial were published in Journal Of Urology 154:424-428, 1995. From April 2002 to January 2003 he was the principal

investigator of An Open Label Study to Evaluate the Feasibility of Switching to Treatment with an LHRH Agonist Following 12 Weeks Treatment with Abarelix in Patients with Prostate Cancer.

Dr. Fisher is the co-founder of The Albany Medical Center Men's Cancer Prevention and Screening Clinic, Chairman of the Albany Medical Center Professional Advisory Committee and also a member of the American Cancer Society Prostate Cancer Advisory Committee, NY State. In addition, he is a reviewer for JAMA (Journal of American Medical Association) and he has either written or co-authored forty eight publications from 1978 to present.

We are privileged to have Dr. Fisher as our speaker and all are invited to attend. All of our DLS meetings are held at the Hurley Reformed Church, Hurley, NY at 4:30 p.m. A question and answer period will follow. Please plan on attending.

Please turn the page for our Distinguished Lecture Series for 2005

## **A Message from Ron Koster- Our Distinguished Lecturer Series 2005**

I am pleased to be able to announce this outstanding series of lecturers in our 2005 program and wish to invite you, your friends and acquaintances to plan for and attend as many of these presentations as possible. Write to me at rkoster@hvc.rr.com for directions to the Hurley, NY site (about 2 miles from Exit 19 on the NYS Thruway) where the presentations are held:

### **Distinguished Lecturer Series 2005 Prostate Cancer 101 Kingston, NY**

January 18, 2005

Drs. Yoram Beer (Urologist) and  
Arun Puranik (Radiation Oncologist)

February 15, 2005

Dr. Hugh Fisher  
(Urologist, Albany Medical College)

March 15, 2005

Dr. Howard Scher  
(MSKCC medical oncologist/researcher)

April 19, 2005

Dr. Daniel Petrylak  
(Columbia, medical oncologist/researcher)

May 17, 2005

Dr. T. Ming Chu  
(Roswell Park researcher, creator of the PSA assay)

June 21, 2005

Dr. Peter Scardino

(Chief of genitourinary oncology-MSKCC,  
Urologist)

July 19, 2005

Dr. Donald Sodee  
(Cleveland University Hospitals,  
Expert in Cytogen's Prostate test,  
and pioneer in fusion of Prostate w/other  
technologies)

August 16, 2005

Dr. Peter C. Albertsen  
(Urologist/researcher – University of Connecticut)

September 20, 2005

Dr. Ashutosh K. Tewari  
(pioneer in Robotic Prostatectomy, Cornell  
Weill Medical College)

October 18, 2005

Dr. Michael Dattoli  
(Sarasota, FL radiation oncologist,  
pioneer in Brachytherapy & IMRT techniques  
for PCa)

November 16, 2005

Dr. Kenneth Chu,  
(Chief radiation physicist, multiple radiation  
centers in the Hudson Valley)

December 20, 2005

Traditional Annual Sharing and Caring Session

## Atrasentan, renamed Xinlay™: Abbott seeks FDA Approval for Prostate Cancer Drug

Phase III results show "delay in time to disease progression" for advanced prostate cancer patients with bone disease

December 14, 2004. Abbott Laboratories Inc. said on Tuesday it is seeking U.S. regulatory approval for a drug to treat advanced prostate cancer that has spread through the body.

Previously known by its generic name atrasentan, now given the trade name Xinlay™, the drug is an oral, non-hormonal, non-chemotherapy anti-cancer agent.

Xinlay™ (atrasentan) has fast track review status at the U.S. Food and Drug Administration (FDA). Abbott will complete the NDA (new drug application) filing for Xinlay in metastatic hormone-refractory prostate cancer by year-end, ahead of the 2005 timetable predicted after its pivotal trial in the indication failed to reach statistical significance.

Abbott will continue to support studies of this drug in other cancers including kidney, ovarian, brain, and non-

small-cell lung cancers.

One factor influencing choice of prostate cancer for study is the prevalence of hormonal ablation therapy (or chemical castration) for men with advanced prostate cancer. Preclinical tests on dogs showed that castration produces a change in the ET receptor density in the prostate and brain.

Xinlay™ (atrasentan) appears to be a generally well-tolerated. Commonest side effects are headache, peripheral edema (swollen limbs) and rhinitis (nasal congestion, "stuffy nose"). The question has been, is the drug as effective as theory suggested it could be?

### How Xinlay™ came this far

In February 2003 atrasentan looked disappointing after Abbott disclosed that data from a late-stage trial showed a delay in progression of the disease that was not statistically significant.

However, last summer in New Orleans at the American Society of Clinical Oncology (ASCO) annual meeting, Michael A. Carducci, M.D., an associate professor in oncology and urology at Johns Hopkins Medical Institu-

tions, presented findings based on pooled data from two clinical studies. Analysis of this pooled data looked more promising. The data showed a statistically significant delay in time to disease progression in men with metastatic, hormone refractory prostate cancer who took atrasentan compared to those who took placebo.

Yet analyzed separately the studies still did not show statistical significance.

Abbott Labs said the results "trended towards" showing positive effect. Company representative Perry Nisen, M.D. Ph.D., a drug development vice president, said: "These meta-analysis results are encouraging and show that atrasentan holds promise for the treatment of metastatic, hormone-refractory prostate cancer."

Now in the December 2004 issue of the journal *Expert Opinion on Investigational Drugs*, Dr. Carducci has published his results with focus on a Phase III study of atrasentan for prostate cancer.

"Biological and clinical activity in patients with prostate cancer," Carducci writes, "has been demonstrated in a Phase III clinical

*(Continued from page 3)*

setting by the suppression of markers of biochemical and clinical prostate cancer progression, and by a delay in time to disease progression, especially in patients with bone disease."

More details about Xinlay™ (atrasentan)

Xinlay™ (atrasentan) belongs to a class of compounds known as selective endothelin-A receptor antagonists, or SERAs. SERAs antagonize the effect of endothelin (ET-1), one of the proteins thought to be involved in the stimulation of the spread of cancer cells.

Endothelin-1 is a small molecule that causes changes in blood vessels and helps regulate blood pressure. Researchers at the University of Pittsburgh explain that "the endothelins and their receptors--referred to as the endothelin (ET) axis- have key physiological functions in normal tissue, acting as modulators of vasomotor tone, tissue differentiation, development, cell proliferation and hormone production. Based on new data, the ET axis also functions in the growth and progression of various tumors.

By last June, atrasentan had been tested in Phase II and Phase III clinical trials in men with metastatic, hormone refractory prostate cancer. Another Phase III pivotal trial (M00-244) was test-

ing it on men with prostate cancer that had not spread (non-metastatic). Also it was being tested in a Phase II trial (M01-366) in men with rising prostate-specific antigen (PSA) following prostate cancer surgery.

To sum up the drug's overall treatment effect in men with metastatic, hormone refractory prostate cancer, Abbott conducted a simple retrospective pooling of its two large, randomized, well-controlled clinical trials (M96-594 & M00-211) with a total patient population of 1,097 men.

Results pooled from two different atrasentan doses (2.5mg and 10mg) demonstrated a statistically significant delay in time to disease progression in the "intent to treat" analysis for men taking atrasentan vs. placebo.

The two individual studies pooled for the meta-analysis tested the same patient population with similar baseline demographics, used the same endpoint of time to disease progression (radiographic progression was more explicitly defined in the M00-211 protocol) and were placebo-controlled and double blind. Abbott conducted statistical tests to make sure the studies were comparable and on the overall treatment effect to support the rigor of the meta-analysis.

## **Side Effects**

Atrasentan (10mg) was generally well tolerated in both studies among all patients. Comparing adverse events for atrasentan vs. placebo showed headache (21 percent vs. 13 percent), peripheral edema (39 percent vs. 13 percent), and rhinitis (34 vs. 14 percent) respectively.

Was this pooled data method a good way to study how the drug affects patients? According to Professor David Dearnaley, MD, FRCP, Institute of Cancer Research/Royal Marsden Hospital, "A meta-analysis is a useful tool in assessing modest but nevertheless clinically important treatment effects. The combined results from these studies are very encouraging and suggest atrasentan may be an exciting novel treatment option which targets the endothelin axis," he said.

About the overall outlook for this drug, Dearnaley added: "These are the first trials to explore the benefit of the endothelin-A receptor antagonists in hormone refractory prostate cancer and give rise to optimism than an entirely different class of agents may be valuable after failure of conventional treatments."

Today in the company press release, John Leonard, M.D., vice president for global pharmaceutical development at Abbott Laboratories, said: "We are very excited about the possibility to bring the

## Getting Cancer Therapy into the Bones

first of several Abbott --discovered oncology drugs to patients. We are looking at novel approaches to treat prostate cancer with the hope of providing additional treatment options to patients sooner."

### Sources and links

Company press release: ABBOTT LABORATORIES ANNOUNCES INTENT TO SUBMIT NEW DRUG APPLICATION FOR XINLAY™ (ATRASENTAN) IN THE U.S. Dec 14, 2004

Atrasentan clinical trials Abbott Labs site

Review: Endothelin receptors as novel targets in tumor therapy Anna Bagnato and Pier Giorgio Natali Journal of Translational Medicine 2004, 2 : 16 May 24, 2004 Full free text (open access)

Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of Atrasentan An Endothelin Receptor Antagonist for Refractory Prostate Cancer Bernard A. Zonnenberg , Gerard Groenewegen , Todd J. Janus , Terri W. Leahy , Rod A. Humerickhouse , Jeffrey D. Isaacson , Robert A. Carr and Emile Voest Department of Internal Medicine, University Hospital, 3584 CX Utrecht, the Netherlands [B. A. Z., G. G., E. V.], and Abbott Laboratories, Abbott Park, Illinois

This page reported by J. Strax, last updated December 14, 2004

Weizmann Institute scientists develop a new approach for directing treatment to metastasized prostate cancer in the bones.

When prostate cancer, one of the leading causes of cancer death among men, spreads in the body, it most often goes to the bone where it is particularly difficult to treat. Metastasis to the bone is implicated in over 70% of prostate cancer deaths. Prof. Zelig Eshhar, Head of the Immunology Department at the Weizmann Institute of Science, has now shown how a treatment that works on cancer in the prostate can be redirected to the bones.

The treatment, which was developed in Eshhar's lab a number of years ago, is based on cells that have been engineered to combine two different types of weapons used by the immune system to fight invaders. Antibodies are best at recognizing foreign or altered molecules such as antigens on the outer walls of bacteria, viruses or cancer cells. T cells are better at killing unwanted cells, but not as adept at identification, especially of tricky cancer cells that may already have developed methods of evading detection by the immune system. By attaching an antibody-based structure designed

to recognize specific cancer cells directly to a T cell receptor, Eshhar produced custom-modified cells, dubbed T bodies, which are proficient at both finding and killing cancer cells.

However, getting T bodies into the bone to treat metastasized cancer was another story. The cancer in this case is likely to be spread throughout the bone, in hard to reach places. When Eshhar's research team first injected T bodies into immunodeficient mice in which human prostate cancer developed in the leg bones, they saw no real improvement, indicating to them that the cells were not getting to the cancer in significant enough quantities to have an effect.

To address the problem, the Weizmann team, which included Dr. Jehonathan Pinthus of Sheba Medical Center, Tel Hashomer, "preconditioned" the mice using one of two strategies already in use in some forms of cancer therapy: low doses of radiation or a specific chemotherapy drug. Both treatments cause some disruption in the bone marrow, the intended target of the T

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bodies. In response, the bone marrow sends out a chemical distress signal to the immune system. This signal not only alerts immune cells such as T cells to the danger, but assists them in homing in on the problem area and in passing through barriers that might otherwise prevent them from getting into the bone marrow tissue.

Mice treated with either therapy 24 hours prior to being injected with T bodies showed a significant drop in the tumor marker, PSA (an indicator of cancer levels), a reduction in the tumor load and prolonged survival. Because the method holds promise for treating disseminated cancers that are resistant to other forms of therapy, Eshhar hopes to move it into clinical trials in the near future.

Prof. Zelig Eshhar's research is supported by the M.D. Moross Institute for Cancer Research and the Crown Endowment Fund for Immunological Research.

Prof. Eshhar is the incumbent of the Marshall & Renette Ezralow Professorial Chair of Chemical & Cellular Immunology.

Source: Weizmann Institute of Science

## February Birthdays

<u>Name</u>	<u>Date</u>
Alton Christiana	1-Feb
Frank W. Degenhardt	1-Feb
Frederick DeMayo	2-Feb
Burton Van Aken	3-Feb
Ronald Gjurovich	9-Feb
Ed Donnelly	10-Feb
Eugene C. Groelle	13-Feb
Jack D. Dockery	16-Feb
John Grant	17-Feb
Jerry Pappalardi	18-Feb
Stephen Josephs	19-Feb
Robert Stokrocki	19-Feb
Daniel Klinkenberg	20-Feb
Arthur P. Callaghan	21-Feb
Glen Hunter	23-Feb
Ron Koster	23-Feb
Fritz Beckert	24-Feb
George A. Kremer	24-Feb
Roy P. Anderson	25-Feb
Stanley C. Cruden	25-Feb
Stan Breite	29-Feb

Birthdays are announced on Kingston radio stations between 7:15 and 7:25 a.m. on WKNY (1490 am) and between 7:40 and 7:50 a.m. on WGHQ (920 am) each day on the early morning shows. Listen for Birthday Greetings from "The Gang".

Each station also draws a name from all the men, women, and children celebrating birthdays each day for the award of "special gifts" Many of our members have been selected as winners.

Celebrate your birthday at Mariner's Harbor at the Rondout, where you will receive a free Lobster or Prime Rib Dinner on your actual birth date. One of our members is an owner of Mariner's and they have lent us their support.

### *If You Want to Help:*

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# Lessons In Life: Reflections on "An Essay by Desire" *by Stephen B. Strum, MD* *Medical Oncologist Specializing In Prostate Cancer*

An article entitled "An Essay on Desire" by Harold Harrod, Ph.D., was published in the February 2003 issue of the Journal of the American Medical Association.<sup>1</sup> It is a very personal and poignant story of Dr. Harrod's odyssey with prostate cancer. It was clear to me that not only should his story be told but also that others could benefit from his experience. My responses to Dr. Harrod's essay are interspersed throughout this article and are designated as "SS". These constructive thoughts are made without the knowledge of what specifically was done in Dr. Harrod's case. The physicians caring for Dr. Harrod were able to provide him with ten years of survival beyond his diagnosis and the majority of this time was of high quality. Therefore, it is important to emphasize that I am using Dr. Harrod's personal story as a means to share what I have seen happen in many other men's lives, but that this is no reflection on what may have occurred in his actual care.

## An Essay on Desire

The fall and winter of 1993 were among the best times of my life. I was 62 years old and working on a book about Native American animal rituals; my wife, Annemarie, was preparing a paper in environmental sociology. Our intellectual lives were full. And since we were living in a remote area near the Canadian border and Glacier National Park, spectacular beauty surrounded us. During the fall, we laid in firewood, took long hikes, and fed our souls on the gorgeous crispness and soli-

tude that fall on the land in anticipation of winter. After the main range of the Rocky Mountains was covered with snow, we spent long evenings reading. During that part of the day not given over to writing and research, we ventured forth on cross-country skis.

SS: The author of this essay, Dr. Howard Harrod, and his wife Annemarie, clearly were leading full lives, sharing a wonderful relationship, and making meaningful contributions to society, while being mindful of the beauty of the creation.

We returned to Nashville in December to spend Christmas with our children, grandchildren, and extended families. On the drive back, I experienced an urgency to urinate that would not be denied. Fortunately, a deserted cornfield just off the freeway provided me with sufficient cover and blessed relief. Reassured by previously normal PSA tests, I was certain the possibility of infection was high and made an appointment with a urologist.

SS: In 1993, Dr. Harrod was 62 years old when he experienced the acute onset of urinary urgency. At that time, the PSA blood test had been commercially available since 1987—about 6 years.<sup>2,3</sup> Articles had

been published indicating that serial PSA testing provided value in assessing the biological activity of prostate cancer.<sup>4-6</sup> The determination that this important biomarker—PSA—was either stable or whether progressive increases in PSA were being noted was deemed to be of diagnostic and prognostic value.<sup>7,8</sup> Therefore, it is possible that Dr. Harrod had multiple PSA levels prior to 1993. If so, what we do not know is whether those levels were stable or if they had shown progressive elevation while still within the so-called normal range. The essential concept to be emphasized here and throughout all of medical practice is the value of observations over time to determine a trend. Laboratory values are presented to the doctor on lab reports as either "normal" or "abnormal". Yet, within the so-called normal range, if we evaluate the results paying attention to trend, we often see the blood levels of a test march from low- to mid-normal, then to high-normal and eventually to abnormal. This is, in essence, laboratory history. If we pay attention to relative changes in laboratory or any clinical test results, we diagnose illness earlier, at a time when it is more amenable to successful therapy. With a malignant process, this "lead" time is extremely valuable. The same concept could be invoked as regards Dr. Harrod's urinary symptoms or what we call LUTS (lower urinary tract symptoms). Was this totally new or had Dr. H. experienced lesser degrees of urgency but just did

not relate this to us? We do not know since this information was not related in the Essay on Desire.

Infection was not detected, but my PSA level had risen significantly. My urologist strongly suggested an ultra- sound biopsy. The results: a fast-growing, probably very aggressive cancer. I spent much of January anxiously reviewing options, spending as much time as possible in the medical school library at Vanderbilt. Alternatives were murky. I gradually became more deeply aware that significant risks and uncertain benefits accompanied each therapy and that alternate paths were contested.

SS: The expressions of biology are manifested in findings such as the clinical examination of the prostate or DRE (digital rectal examination), laboratory tests and in the pathology report. These provide a profile of the prostate cancer that allows the healthcare team to decide if they are dealing with a slow-moving or indolent variant of prostate cancer or a more rapidly aggressive subtype. Here is where the Gleason score, read by an expert in PC pathology, the clinical stage as per the DRE and the PSA prior to the biopsy diagnosis of PC can provide information that forecasts the findings if a radical prostatectomy is to be performed.<sup>9</sup> The best known and prototype of such predictive studies has been that of Partin et al from Johns Hopkins Medical Center. This analysis might have resulted in enough concern to influence the choice of Dr. Harrod's therapy.

After reviewing research, further

consultation with my physicians, long conversations with my wife, and listening to my own body, we decided that surgery was the best option for me at that time. So in early 1994 I entered Vanderbilt Medical Center and underwent surgery for the removal of my prostate. The cancer had spread to my lymph nodes but, thankfully, had not metastasized to my bones.

SS: The 1993 Partin Tables evaluates the probability of OCD (organ confined disease), CP (capsular penetration), SV (seminal vesicle involvement), and LN (lymph node involvement) in men undergoing RP. If we assume that Dr. Harrod had a Gleason Score of (4,4) or higher (his pathology was said to be aggressive) and his PSA was at least 8 if not higher, and his clinical stage was T2a, the Partin Tables would predict a 39% chance of OCD, a 59% chance of CP, 22% chance of SV, and a 15% chance of LN. If the PSA were over 10, then the likelihood of OCD drops to 29%, the chance for CP (capsular penetration) increases to 70%, SV to 29% and LN (lymph node involvement) to 17%. We do not have those values and can only speculate in this matter. We also do not know what lymph nodes or how many nodes were involved; this is relevant to the probability of systemic disease, despite the lack of overt clinical findings of such an occurrence such as a negative bone scan.

Hormone therapy was the recommended course of treatment, so I began monthly injections of Lupron. Every month upon entering

the Vanderbilt clinic, a flood of memories swept over me as I relived aspects of the operation and despaired of what had happened to me. Finally, after a year of treatment, I decided to give up my testicles.

SS: The therapy that Dr. Harrod received in 1995 is important to review. Monotherapy (single agent therapy) with Lupron had been initiated. The purpose of such therapy is to reduce the level of testosterone—the male hormone so critical to PC growth—to levels below 20 nanograms per deciliter (ng/dl). Lupron lowers testosterone levels by inhibiting the release of the pituitary hormone that stimulates the testicles; this hormone is called LH or luteinizing hormone. Lupron works as a Luteinizing Hormone Releasing Hormone agonist or LHRH-A. Prior to the discovery of LHRH agonists or LHRH-A, the reduction of testosterone was accomplished surgically by removal of the testicles. This procedure is called an orchiectomy or surgical castration. LHRH-A achieves the same physiologic effect and some have termed such therapy “medical castration”. The mechanism of LHRH-A is a repetitive stimulation of the anterior pituitary to release LH, which over the course of about two weeks results in shutting off of this hormonal switch. An initial release of LH from the pituitary does occur when the LHRH-A is first started, but this is followed by a turning down of LH production. This process is called downregu-

lation. What is ignored, however, is that for the first 10-14 days of monotherapy with an LHRH-A, the initial release of LH actually stimulates PC growth. This occurs because LH stimulates Leydig cells within the testicles to make testosterone. Although the importance of this biochemical surge in testosterone and the increase in PSA that follows is downplayed by most doctors, it is perhaps the only instance in the annals of oncology where we stimulate cancer growth and yet appear unconcerned about the consequence of this effect. This testosterone surge with its resulting biochemical flare in PSA should be avoided since we do not have a sense of what this means insofar as possible development of disease resistance over the long term. In addition, if there is tumor present in a critical location, such as near the spinal cord or ureters draining the kidney, this biochemical flare can result in clinical findings (clinical flare) that can be life endangering. We, as physicians, are asked to take an oath to "Do No Harm". In my opinion, we are not following this mandate when we do not protect the patient from either biochemical or clinical flare with simple measures to prevent this. One such measure is the use of an anti-androgen such as Flutamide or Casodex given for one week prior to the initiation of the LHRH-A. Although the testosterone level still rises, the ability of the testosterone or its metabolic product (dihydrotestosterone or DHT) to interact with the tumor cell at the site of the androgen receptor is markedly diminished.

After the orchiectomy, I was still

physically able to do almost all that I wanted. But I was impotent, and despite considering all the possibilities, from penile implants to pumps. I remained in a state of despair.

SS: The choice of an orchiectomy eliminated the use of an intermittent androgen deprivation (IAD) approach to the PC treatment. This assumes that the therapy being given, i.e. Lupron or another androgen lowering therapy, would have had a significant response with all indicators of disease activity disappearing. Given our limitations as to the details of Dr. Harrod's therapy, it is not clear whether the Lupron therapy had achieved its goal of lowering the testosterone level to less than 20 ng/dl. Clearly, if physicians intend to use ADT (androgen deprivation therapy), they have a responsibility to document that androgen deprivation has indeed been achieved. This is no different from a physician treating high blood pressure with an anti-hypertensive drug such as Procardia. We definitely would expect the physician in such a context to be monitoring the blood pressure. So, it is true with ADT. The urologist or oncologist must monitor the serum testosterone to be sure that a level of less than 20 ng/dl has been achieved.<sup>10,11</sup> Removing the testicles, as in Dr. Harrod's case, served no clear advantage but rather had the effect of demoralizing the patient.

As a consequence of trying to sort out this complex emotional tangle, I gradually became aware of how deep my gender socialization had been. Not only had I a sense of having been mutilated, I had also lost the very capacities that were symbolically associated with manhood in American society. I no longer had a prostate, I was incapable of an erection, and I had no testicles. More fundamentally, I had lost the capacity to experience desire.

SS: Dr. Harrod's reaction to the orchiectomy reinforces the positive contribution that LHRH agonist agents have made to the morale of the PC patient. The rationale for doing an orchiectomy in the context of PC that is progressive despite LHRH agonist monotherapy is for the most part related to failure of the latter therapy to achieve a testosterone less than 20 ng/dl. This can be medically accomplished by assessing the serum testosterone level to see if it is greater than 20 ng/dl and, if so, determining the source of this testosterone. Is it the testicles or the adrenals or both? If the LHRH-A has not reduced the LH level to less than 1.0, the failure is with the LHRH agonist. If the adrenal androgens such as DHEA-S and androstenedione are in the mid-normal range or higher, it is likely that the adrenal glands are contributing to the "excess" testosterone level. This process involves using a differential approach to assess the cause of an apparent therapeutic failure—and logically evaluating where the problem may lie. This is in contrast to switching to another therapy when there may be no rhyme or reason to

do so. Most importantly, it is highly possible that the prostate cancer that Dr. Harrod faced was comprised of clones that were androgen independent and that it was not the so-called garden variety of PC that is very sensitive to androgen deprivation. This is a critical distinction: is it Androgen Dependent PC (ADPC) or Androgen Independent PC (AIPC)? In other aspects of medicine, we do this all the time. In diabetes we ask: "Is the condition insulin-dependent diabetes or not?" In infectious disease we ask: "Is the pneumonia penicillin-resistant or not?" In the management of prostate cancer patients we must ask: "Is the PC androgen dependent or not?" If it is not, then LHRH agonists, orchiectomy and other agents that reduce male hormone are not going to put the patient into remission.

The sudden loss of libido produced forms of suffering I had not anticipated. The initial forms were stimulated by my context: I taught at a university each day; on campus and elsewhere, I encountered young people caught in the throes of raging hormones. Because I had lost the capacity to experience desire did not mean that I was not tormented by memories of desire. Surrounded by the presence of youthful Eros, expressed in forms of touching or longing looks, I began to feel a crushing weight of loss. Why was this happening? After all, mine was a mature sexuality fully integrated, I thought, into my personality.

But such experiences continued and they produced increased suffering. The sight of young males

walking across the campus tormented me. I began to envy their capacities and, most fundamentally, their possession of what I had lost. I hated these feelings; and sometimes I hated myself for having them. But they were difficult to suppress, and they continued to break into ugly blooms in my experience. As I endured the suffering produced by unwanted fantasies, I finally began to see what was producing them. Like a range of mountains that appears in the distance, those structures of meaning that had formed the capacities for my erotic responses came gradually into focus.

When these meanings became clearer, I confronted an idea that I had read about in literature by feminist scholars: male sexuality was excessively genital in its focus. Confronting this idea at a deep emotional level was shattering; and allowing it to have an affective impact on my experience began to deconstruct my previously taken-for-granted expressions of erotic pleasure. As a consequence of my male socialization, how restricted these "pleasures" now appeared, and, more painfully, I began to sense how much I had missed.

SS: This aspect of male sexuality is seldom discussed among men. Men are much more isolated in their nature than woman. Men do not get together for lunch or for coffee and discuss their innermost feelings. This emotional isolation makes whatever personal pain we go through even more intense. Importantly, and painfully, is the recognition that men sometimes

confuse intimacy with sexual arousal. It is clear that in a situation such as that faced by Dr. Harrod, experiencing a radical prostatectomy and then androgen deprivation via LHRH-A and subsequent orchiectomy, that personal counseling with sensitive discussions about his emotional and endocrinological turmoil may have been of value.

On a different note, we now are embarking in new approaches with the use of testosterone supplementation in men who have predominant Androgen Independent PC (AIPC). Studies by Liao, Kokontis and colleagues have shown that androgens inhibit the proliferation of AIPC tumor cells in human prostate cancer cell lines.<sup>12</sup> The mechanism involves the ability of androgen to up-regulate a protein called p27Kip1—a protein that inhibits the cell cycle through its antagonistic action on the enzyme cdk2 or cyclin-dependent kinase 2.13

All of this was not new to my wife. She had been saying many of these things for years, but I was not listening. The loss of capacities, body parts, and what I thought of as my essential maleness was less important to her than the intimacy that accompanied other forms of reciprocal communication: touching, holding, sharing feelings, and being deeply present to one another. As a consequence of these of these insights, a surprising disgust arose in me and now I began to hate my previous sexual responses: how insensitive, narrow, and compulsive they had been.

And, in a phrase that seemed to summarize all that I was feeling, how goatish!

SS: The feelings that Dr. Harrod was experiencing are understandable. Man is driven by the same hormonally-induced urges as every life form on this planet; the goal is to procreate. What makes humankind different from other life forms is their ability to think, and to reflect, and theoretically to learn from the past. Unfortunately, in all societies, both Western and Eastern, it is extremely uncommon for men to discuss their feelings in general, no less their feelings about the urgency of their sexual impulses, the nature of their sexual satisfaction, the emotions that occur just before and after orgasm and the immense swing in libido that contrasts the pre- and post-orgasmic state.

What I had not yet realized was the deeper significance of testosterone deprivation. It was clear that this manipulation of my body had probably postponed my death, and for that I was grateful. While I did not fully grasp what it would mean to live in a male body without potency, I had not begun to contemplate the meaning of continuing to live without the experience of desire. Desires are always directed toward a subject or an object, and erotic desires are no different. But when desire is radically extinguished, then the way it had been shaped as well as the objects and subjects of its focus still remained as memories. Without the urgency of desire, these memories stood out in ways that were both painful and instructive.

Male socialization had taught me to imagine the female body in a certain manner, to focus my erotic attention on particular body parts, to objectify and depersonalize these body parts, and to understand sexual pleasure as focused almost entirely on orgasm. These structures of the embodied imagination had shaped my experience of desire. The practices, language, and example of other males in my environment powerfully enforced them. I had been so deeply formed by that world that there was virtually no transcendence of it in my experience. Again, I was plunged into despair and, finally, into hatred of the structure of desire that was still alive in my memory and projected in my imagination.

SS: And here is the essence, I believe, of this essay. It is clear that men are driven by testosterone in hundreds of ways. The endocrine nature of man is not only evident on a social level but on a cellular level. It is manifested in the changes that are clearly evident as a boy goes through puberty and enters manhood. Changes in bone and muscle growth, production of red blood cells, skin, nail and hair changes, emotion, mentation and libido are but a few examples of the targets of testosterone and other androgens. But all of life has its cyclic nature. The tides of life also are seen in the tidal changes of the endocrine system. And, as we enter the tidal swing of puberty and manhood, in but a blink of the eye, we experience the ebb tide of the same cycle. Yet, with all of our technology and so-called sci-

entific advances, we have not yet evolved enough to discuss this rhythmic nature of our lives in a close-up and personal manner. Intimacy threatens us—at least it does most men. Not only do we not discuss male menopause, we are frightened to embark on discussions of the nature of love and intimacy. We can send spaceships to the moon, we can explore outer space, but we have not yet been able to venture into our inner space—our hearts and souls—when it comes to the nature of intimacy, of true love. What an incredible opportunity to take this poignant essay and memorialize it with curriculums on the nature of intimacy—throughout all of our formal education, and for that matter throughout our lives, as well as with cultivated commentaries via the media. Moreover, think about what we could learn by understanding more about the rhythmic nature of our health. Certainly, we have major clues to prolong health and prevent illness by understanding what our baseline endocrine status is, how to monitor it as we age, and how to preserve the link between our endocrine health and our mind-body health. The ramifications of this essay, of this discourse, are immeasurable.

I still struggle with these issues, but at least some feelings of acceptance and consent to my condition are beginning to be stronger than the more negative and destructive responses. At the same time, I am increasingly aware of several things that I consider invaluable. I have learned, first, that women are embodied in much

more complicated ways than I had ever imagined. Second, relationships between men and women are complicated—inevitably so—by Eros. But for me, there is a sense of transcendence and peace in being able to experience persons as the complex beings they are without being so completely captured by the undercurrent of desire. Third, there is richness and creative playfulness in human relationships that is distorted by patterns of male socialization. Fourth, the terrain of manhood is much richer and fuller of possibilities than I had ever imagined.

SS: Here we see an evolution from feelings of frustration, self-pity and anger to evolved perceptions that have been the subject of poetry, texts, novels, and philosophies. This altered perspective, transformed from occult or overt machismo is of critical relevance in our attempts to understand why men, time and time again, march into the horrors of war. I have witnessed such transcendence to a higher plane of sensitivity and spirituality in other men who have undergone androgen deprivation treatment for prostate cancer. Experience again teaches us that there are pros and cons in all of our life's passages; everything in life is a two-edged sword.

I have survived and, in many ways, flourished for almost 10 years. Six of these years have been characterized by excellent quality of life on many levels. But there have been other losses and some deepened suffering

connected with aggressive treatment. In the fall of 2000, for example, when I was again on leave in Montana, I experienced kidney failure as a consequence of lymph node swelling that blocked my ureters. I now have two nephrostomy tubes that require care but that are partially internal so that I urinate "normally." It became clear, however, that if my quality of life were to be sustained I would have to undergo further treatment.

After consultation with my oncologist, I endured 6 months of chemotherapy with Taxol, which gave me about 4 additional months of satisfactory quality of life. Then in the spring of 2002, I was diagnosed with cancer progression in my right femur and some involvement in my left hip. I underwent surgery and a pin was placed from the top of my femur to my knee. My left hip was radiated at the same time. My recovery was successful, and I went from a wheelchair to a walker to a cane and then to full mobility.

SS: As pointed out at the beginning of this article, it is easy to review what others have done and retrospectively criticize. It is worthwhile re-emphasizing that I am using Dr. Harrod's personal story as a means to share what I have seen happen in many other men's lives and that this is in no way reflects on what may have occurred in his actual care. The constructive criticisms presented below, therefore, are related in the context of experience being a great teacher.

The Importance of Baseline and Monitoring Dr. Harrod mentioned that his original pathology indicated

an aggressive form of prostate cancer. No mention of the Gleason score was given. We do know that high Gleason scores, such as 8 to 10, are associated with less PSA production and often elevations in other biologic markers that are expressions of the dedifferentiated or more primitive nature of the prostate cancer cell population. Such biomarkers include cell products such as PAP (Prostatic Acid Phosphatase), CEA (Carcino-Embryonic Antigen), CGA (Chromogranin A) and NSE (Neuron Specific Enolase).<sup>14-16</sup> We have no input whether these were ever tested or, if elevated, followed over the course of Dr. Harrod's illness. If they were tested, and were elevated or showed increasing values during serial testing, a change in strategy would have been indicated. Prostate cancers expressing such biomarkers most often are not androgen dependent; they reflect androgen-independent prostate cancer or AIPC.<sup>17-19</sup> Patients with AIPC can benefit from the use of therapies beyond LHRH agonist agents or orchiectomy. Such therapies include Ketoconazole plus Hydrocortisone or estrogens like Diethylstilbestrol (DES). Medical publications on the use of long-acting somatostatin inhibitors such as Lanreotide have shown efficacy in CGA-producing tumors.<sup>20</sup>

Supportive Care Monitoring of the patient's status over time is often discontinued, especially in patients who have failed first or second-line therapies. A consideration that the quality of life can be maintained even in the face of

such treatment failures seems not to be a top priority for many physicians. When this philosophy of caring for the patient all along the course of illness is abandoned, the important concept of crisis prevention falls by the wayside. Instead, the patient enters a nightmarish journey involving one difficult crossroad after another. As stated above, this often occurs in settings where physicians are not able to cure the patient. There is a strategy-missing unspoken defeatist attitude that surfaces. Since the cancer has not been cured, then major efforts to control the disease are not justified.

This nihilistic attitude is not at all uncommon. It is often associated with a lack of intensity on the part of the physician in regard to supportive care of the patient. This means preventative measures to minimize or eliminate potential adverse effects associated with the disease or with the treatment. An aggressive prostate cancer histology would be expected to be associated with lymph node and/or bone metastases. These sites of metastatic spread for the PC are the ones that lead to morbidity and to mortality. Monitoring laboratory tests to evaluate for progressive disease and obtaining periodic radiologic tests to exclude a mounting problem are critical tactics to maintain the welfare of the patient.

One such test that is underused in this setting is the ProstaScint scan, a monoclonal antibody scan used especially to evaluate lymph node involvement by prostate cancer. The ProstaScint image has now been improved by what is called

co-registration or fusion technology whereby the radiologic image of the ProstaScint is fused with the electronic outputs of a CT scan or PET scan or both. If spread of prostate cancer to lymph nodes was found through such testing, then a change in treatment strategy could have taken place. Therapy becomes forward-thinking rather than reactive. Patients that have documented lymph node involvement may be treated with various modalities with documentation to see if such treatments are effecting regression in lymph node size. Modalities such as neutron beam radiation may have a special role to play in such settings since the neutron particle can penetrate and destroy bulky prostate cancers.<sup>21</sup>

Another area representing preventative strategy involves assessing bone integrity by testing bone density and bone resorption by Quantitative Computerized Tomographic Bone Mineral Density (QCT BMD)<sup>22</sup> and Pencil-D (Dpd)<sup>23</sup>, respectively. Bone is a huge repository of growth factors such as transforming growth factor beta one (TGF-B1), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF).<sup>24</sup> Stabilizing the bone microenvironment with bisphosphonate drugs like Fosamax, Actonel, Aredia or Zometa has been associated with a decrease in bone metastases in some studies while in others in a decrease in major skele-

tal-related events such as fractures and spinal cord compression.<sup>25,26</sup> Bisphosphonates should be used in conjunction with bone-building supplements containing bioavailable calcium along with magnesium, boron and silica so that healthy bone is formed. The role of fluoride is still controversial among many doctors but this bone-seeking element attracts calcium to the bone and forms an incredibly tough bone structure.<sup>27</sup> Perhaps, such considerations were part of the strategy in the care of Dr. Harrod. However, I have seen far too many patients who first experience a fracture and then have studies done to assess bone integrity and receive treatment with a bisphosphonate compound and sometimes a bone supplement. We must learn to be proactive in our supportive care of the patient, not re-active.

The chemotherapy of prostate cancer also has evolved greatly in the last ten years. Taxotere, not Taxol, has emerged as the most active agent in prostate cancer. Weekly regimens of Taxotere are very well tolerated and allow the patient to maintain a high quality of life.

With the blessings of my surgeon and my oncologist, my wife and I left in July 2002 for another research trip to Montana. But after less than 2 weeks I lost bladder control as well as my ability to walk. An MRI revealed serious spinal cord compression, and we were immediately flown back to Nashville where I endured another surgery to decompress the spinal cord. This surgery was apparently

successful and I am now proceeding from the wheelchair to the walker; my hope is for full mobility.

These surgeries were defined as "palliative," but the last one had real authority. The pain was significant, and recovery has been slower than I would like. My condition is different now, and the sense of loss has a different quality and weight. I clearly anticipate the loss of my world. But I am not simply contemplating this possibility; it is a powerful sensibility that arises within me daily. Nurtured by a supportive network of friends, family, and groups like Gilda's Club and Alive Hospice in Nashville, I feel a strange peace descend on me. My life seems to have come full circle as meaning folds back upon itself and deepens in a manner that makes more and more sense.

SS: It is clear from the above that Dr. Harrod was or had come to grips with his own mortality. It is clear that all of our lives are so precious and so often we take our health for granted until we experience a loss of good health. We do not know enough about Dr. Harrod's findings prior to his pathology diagnosis of prostate cancer to know if an earlier diagnosis could have been made. We do know that physicians still debate the issue of such an early diagnosis and some physicians feel that we may harm the patient with our therapies when prostate cancer is diagnosed at a time when it may not be biologically significant. I believe that this confuses the mission with the man or the message with the messenger. An early diagnosis of

prostate cancer does not equate with forcing the patient into surgery, radiation or cryosurgery. Instead, it announces to the patient that a change in their lifestyle must be considered. Dietary changes, the use of anti-oxidants to reduce or prevent further excessive oxidative damage, the avoidance of toxins such as alcohol, cigarette smoking, and saturated fats, and taking the time to do moderate exercise, time to meditate and reflect on life and your priorities are important contributions to the health and welfare of all of us. A diagnosis of PC, made early, is a wake-up call to evaluate your total health. We know that prostate health is intertwined or integrated with cardiovascular and neurologic health as well as bone integrity.

Certainly my experience will not characterize all who read this description. In part, the quality of my experience is dependent on having had sufficient time to assimilate the meaning of what has happened to me. First I lost desire. Now I am gradually losing my body, and I will soon lose my life, my wife, my family, my friends, and the whole beautiful world. I hope that other readers in my situation will have sufficient time to integrate their experiences as I have, and I hope these reflections are helpful for their respective journeys.

Howard L. Harrod, PhD  
Nashville, Tennessee

SS: And here, Dr. Harrod poignantly but succinctly tells us the heart of not only his story, but all

of our stories. We need to stop and take the time, along the entire journey of our lives to assimilate the meaning of what is happening with us. His lessons were intensified by his loss of desire, followed by loss of physical function and then his life. We all need to be not only mindful of this completely beautiful world, but also of the beautiful world that resides within our minds and bodies. We are magnificent creations that need love and attention. Our challenge is do we wake up to the realization of how important this is now, or do we find ourselves on the slippery slope of failing health before we realize what we have lost and that it may be too late to recapture.

What distinguishes humankind is that we are a historical society. We have history to fall back on—to guide us in our choices of what we do in our lives on a personal level, as well as on a societal level. The great philosopher Santayana said, "Those who cannot remember the past are condemned to repeat it". So, it is also possible to use the history of others to guide us on what we should consider on our life's journey and what we should avoid.

Editor's Note: Professor Harrod died February 3, 2003.

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Source: Life Extension Foundation

## Wonderful Surprises

Very special thanks to our member, **Frank Guido**, of **Mariner's Harbor** at the Rondout in Kingston for sponsoring a 50/50 drawing to benefit Prostate Cancer 101 at the restaurant. Not only did Mariner's Harbor do something unique for us, but the winner of the drawing, **Joseph O'Connor** of **Mainetti, Mainetti & O'Connor** on Clinton Street, Kingston, donated all of his winnings back to Prostate Cancer 101. We received a check for \$400.00 due to the generosity of these fine people and firms.

As a small reminder, Mariner's Harbor honors everyone on their actual birthday with a free Lobster or Prime Rib Dinner, so go there to celebrate and take a friend or two!

We received a donation of \$1500.00 from **Thomas Struzzieri** of **Horse Shows In The Sun** in Saugerties. This is a perfect example of local enterprises supporting each other. Several of our members have mentioned going to HITS during the warmer months.

For those of you, who have not had that pleasure, be sure to go and have a wonderful time helping to support those who help support us.

TAP Pharmaceuticals, makers of

Lupron and other drugs, sent us a donation of \$1200.00 to enable us to send out additional hard copies of our newsletter. Many of our members have had treatment with Lupron, a rather costly drug, so it is especially nice to see a firm giving back to those who have had to use their product.

This donation will help us further educate our membership on treatments, modalities and ways to stay healthy.

What a great way to start the year!

Diane Sutkowski/Secretary Treasurer

"Experience is not what happens to a man; it is what a man does with what happens to him"  
*Aldous Huxley*

"I'm a firm believer in the theory that people only do their best at things they truly enjoy."  
*Jack Nicklaus*

"Everything has its beauty but not everyone sees it."  
*Confucius*

"We all have dreams. But in order to make dreams come into reality, it takes an awful lot of determination, dedication, self-discipline, and effort."  
*Jesse Owens*

Source: Dattoli Cancer Foundation -Calendar

## PSA Doubling Time

by Ralph Valle

“Hello Jerry,

PSA doubling time (PSADT) is defined as the time that it takes for a PSA value to double. Using your results, a PSA of 0.01 going to 0.02 took three months and therefore your PSADT is three months.

The shorter the PSADT the faster is the disease progressing, but your latest PSA results are very low and this should not be cause for concern at this point in time.

Your response to hormone deprivation was very fast (a drop from 1.6 to 0.029 in a month) and that is a sign that the residual tumor after RP was highly androgen-dependent. Another very good sign is that your PSA has remained very low after stopping HDT some 10 months ago.

You should get a testosterone measurement to see if your testosterone has increased back into the normal range.

The best way to track PSA and PSADT is by plotting your PSA results on semi-log paper displaying PSA on the y-axis

and time on the x-axis. The slope of the resulting line visually provides PSADT.

This requires at least three points, and the more the better. This formula for calculating PSADT is valid as long as values 1 and 2 truly lie on an exponential curve:

$$\text{PSADT} = \text{Log}2 \times t / (\text{LogPSA2} - \text{LogPSA1})$$

Where: t = time elapsed between PSA measurements

PSA2= final PSA value

PSA1= initial PSA value

At this point, it seems that continuing a close watch of PSA is in order. An increase in PSA would trigger a treatment action. Because you were diagnosed with aggressive disease and your primary treatment failed to reduce PSA it seems reasonable to resume HDT at a low preset PSA value of your choice.

Hope that your PSA remains low for a long, long time.

Godspeed,

Ralph V “

*Source: Ralph Valle  
rav33@MINDSPRING.COM*

### Donations Received

We are most grateful for the donations recently received from PCa101, Kingston Members:

Frank & Agnes Becker  
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The paid newspaper ads, notices to religious groups, and word of mouth keep our organization visible in the community and regularly bring us newly diagnosed men seeking information and support.

Those who are either active or retired employees from companies having matching grants programs should provide a filled out form along with their donations.

If you wish to contribute financially, mail your check (along with the matching grants form, if applicable) made payable to **PCa 101**, Kingston to:

**PCa 101**, Kingston  
c/o Diane Sutkowski,  
Secy/Treasurer  
8 Alcazar Avenue  
Kingston, NY 12401-4302

## Potentially fatal toxicities occur with off-label use of cancer drugs - example, thalidomide

December 21, 2004. /source: Northwestern University, CHICAGO/ -- Food and Drug Administration policies prevent pharmaceutical manufacturers from informing patients about potentially fatal toxicities that occur with some cancer drugs -- policies that should be revised immediately, according to Northwestern University researchers.

Andrew M. Evens, D.O., instructor in medicine, and Charles L. Bennett, M.D., professor of medicine, Northwestern University Feinberg School of Medicine, have called for an immediate revision of these FDA policies, particularly because the drug thalidomide, which was approved by the FDA as an off-label cancer treatment in 1998, has been reported to have caused potentially fatal blood clots in the legs and the lungs in over 190 cancer patients.

Virtually all patients who have received thalidomide over the past six years have received the drug for cancer, making this drug the only one in the country whose use is exclusively off label.

The FDA strictly restricts discussion or dissemination of information to physicians and patients to "on label" indications, which prevents the pharmaceutical manu-

facturer from advising cancer patients about the side effects of thalidomide when it is used to treat cancer.

Moreover, despite an FDA mandate that all health care personnel and patients involved with thalidomide treatments participate in the preventive System for Thalidomide Education and Prescribing Safety (STEPS), the program does not provide patients, pharmacists or health care providers with information on thromboembolisms.

Evens presented the RADAR (Research on Adverse Drug Events and Reports) data on the thalidomide-associated blood clots on at the 46th Annual Meeting of the American Society of Hematology in early December.

The Northwestern study identified the occurrence of potential fatal blood clots in the legs and the lungs in up to 20 percent or more of cancer patients who received thalidomide.

The highest rates of thromboembolism occurred in patients who received concurrent treatment with thalidomide plus chemotherapy (18 percent) versus blood

clots associated with thalidomide-corticosteroid combinations (13 percent) and single-drug treatment (5 percent).

Thalidomide, banned initially in 1962, has had a remarkable resurgence since 1998 for cancer, although its formal FDA approval is as a treatment of skin complication of the rare illness, leprosy.

"Given the current controversies about the FDA and pharmaceutical safety, our findings provide additional evidence that dramatic changes in the way the FDA address patient safety are needed," Evens said.

Evens and Bennett are faculty physicians in the department of medicine, division of hematology/oncology, at Northwestern University Feinberg School of Medicine and researchers at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The RADAR project, led by Bennett, is supported by a \$5 million grant from the National Cancer Institute.

This page reported by J. Strax, last updated December 21, 2004

*Source: psa rising*