

PCRI Insights

Produced by: The Prostate Cancer Research Institute

New Developments in Prostate Cancer Treatment **October 1998 vol. 1, no. 1**

Welcome To the Premier Issue of *Insights*

The premier issue of *Insights* has its inauguration at a time of promising activity in our understanding of prostate cancer (PC). In planning *Insights*, we encountered a serious dilemma. How could we share with you crucial concepts, results from landmark papers and so many new findings in PC without overwhelming you? At the same time how could we project to you a sense of order in what is being presented?

This is no easy task. In fact, just naming the newsletter was difficult. "*Insights*," "*Crossroads in Prostate Cancer*," "*Prostate Cancer: New Alternatives*," and "*PC and Applied Science*" were just a few of the suggested names. *Insights* seemed most appropriate. We want to share with you what we see to be valuable concepts. Therefore, in addition to presenting new information, *Insights* will re-present information of landmark importance. Articles will be fully referenced. Articles that are opinion or hypothesis will be labeled as such.

We realized that with the complex-

ity of these subjects we needed a format to organize the material that we present to you. We settled on the image of a "Monopoly" board as a structural framework. As shown, it has the sense of a beginning in topics such as "genetic history," "nutritional adjuncts," and "preclinical phase," and then moves on to topics that relate to PC progression as with "diagnostic phase," "local disease," and "systemic disease." Interwoven with these topics are "novel therapies" and "pain control" as well as "philosophical issues" and "political activism". Other related topics are also shown.

In each issue, key articles will have an identifying title that corresponds to one of the topics shown below. We suggest you photocopy these key articles and place them in a 3-ring binder with tabbed separators. In addition, since new "boxes" or topics may be added along the way, we have identified our board below as *Insights* version 1.0. Any suggestions from readers for new topics will be welcomed.

We will also share with you

computer software that will enhance your understanding of PC (that's prostate cancer, not personal computer). The reason for this software development relates to the concept of applied science. Medical writers too often present findings in a way that makes their utilization in the everyday care of the patient virtually impossible. We decided to change this. Therefore, our software allows your medical database to be analyzed simply and printed out to become part of your medical record. Much of this software is currently available for download from our homepage at www.prostate-cancer.org.

Three themes dominate this issue of *Insights*. They are: risk assessment of the PC patient, high-risk PC, and the importance of bone integrity in men with PC. These key topics are color-highlighted in the monopoly board and show the page numbers of the articles. We will attempt to bring you diversity in every issue of *Insights*. Whatever your primary interest in PC, we know you will find needed information here. ❖

Genetics	Philosophical Issues	Political Activism	Pain Control	PC Address Book	Novel Therapies
Nutritional Adjuncts					
Preclinical Phase	Schematic Approach to Topics in Prostate Cancer <i>Insights</i> Version 1.0				Treatment Side-effects
Diagnostic Phase					Systemic Disease
Risk Assessment (Page 3)	Staging or extent of disease	Local Disease	Hormone Blockade	Bone Integrity (Page 7)	High-risk PC (Page 8)

In This Issue:

Welcome to <i>Insights</i>	1
What's Happening at the PCRI? ..	2
Upcoming Events	2
Risk Assessment	3
The PC Digest.....	4
Bone Integrity	7
High-Risk PC.....	8
Website Worth Hitting	10
Gift from PAACT	12
Lloyd Ney	12

PCRI Insights®

Author: Stephen Strum, MD

Editor: Charles Bader

Review Board: Stephen Strum, MD

Harry Pinchot

Jon McDermed, PharmD

Publisher: The Prostate Cancer
Research Institute



PRINTED ON RECYCLED PAPER

Prostate Cancer Research Institute

4676 Admiralty Way, Suite 103

Marina del Rey, CA 90292

Helpline: (310) 827-2366

FAX: (310) 827-2686

Website: www.prostate-cancer.org

Executive Director: Jim Goyjer, MA

Phone: (310) 827-3866

FAX: (310) 827-1567

E-mail: pcri.goyjer@earthlink.net

**"It is the goal of PCRI
to see that
prostate cancer is
no longer a threat to
any man's life."**

If you wish to share in this goal and find this complimentary newsletter of value to you, please help us continue our work by sending a tax-deductible donation to PCRI c/o Freeman Hospitals Foundation, 333 North Prairie Avenue, Inglewood, CA 90301-4514.

What's Happening at the Prostate Cancer Research Institute?

The Prostate Cancer Research Institute (PCRI) was founded less than two years ago in November 1996 by Drs. Stephen Strum and Mark Scholz. In this short time, the PCRI described, for the first time, the Anemia Associated with Androgen Deprivation (AAAD) in men with PC¹, defined the constellation of signs and symptoms that may arise from androgen deprivation therapy as ADS or Androgen Deprivation Syndrome² and is currently ready to publish a series of articles on Intermittent Androgen Deprivation (IAD)³.

The PCRI last year presented data to the American Urologic Association on the treatment to correct AAAD using recombinant erythropoietin (Procrit, Epogen)⁴. This year, at the American Society of Clinical Oncology (ASCO), Dr. Strum presented data on optimal induction and maintenance approaches for IAD⁵. The PCRI is a study site for OncoVax, a new vaccine against PSA from Jenner Biotherapies, Inc., and is also soon to be approved as a study site for a new angiogenesis inhibitor, AG3340, from Agouron Pharmaceuticals, Inc. How can a little ma and pa institute accomplish so much? First, a little background on the PCRI.

Also An Educational Center

The PCRI is a not-for-profit educational and medical research center associated with the Freeman Hospitals Foundation and Daniel Freeman Marina Hospital. The PCRI has the stated mission of seeing that "prostate cancer is no longer a threat to any man's life". To this end, the PCRI is dedicated to educate the public about PC, to pursue research into the prevention and treatment of PC, and to improve the present level of care for men with the disease. In the months since

establishing the PCRI, Drs. Strum and Scholz and PCRI research assistants Jonathan McDermed and Harry Pinchot have increased their already extensive schedule of presenting new information and ideas at PC symposia, conferences, and support group meetings. McDermed and Pinchot have just spoken at a PC forum in Grants Pass, Oregon with Dr. Eric Small and Dr. Charles Myers.

Dr. Strum is scheduled to speak again at the 4th Annual PC Public Forum in San Diego with Drs. Tia Higano of the U of Washington and Eric Small of UCSE. Dr. Strum will also be speaking in November in Las Vegas at the Us Too chapter chaired by Don Swirnow and then is off to Phoenix to speak at the Metro PC Symposium with other PC experts. In March of 1999, Dr. Strum and Dr. Don Coffey of the Johns Hopkins Medical Center will co-moderate a meeting for professionals and for patients at the Pittsburgh Cancer Institute. We will give more details about these meetings open to the public in future issues of *Insights*.

Internet Communication

Already, PCRI has published over 30 papers on various aspects of PC research and treatment. In addition, Drs. Strum and Scholz are active participants on the Internet List called "Patients to Physicians" or "P2P". The PCRI Homepage has had over 30,000 visitors, receiving an average of 35 hits per day, with this number increasing steadily.

At its new center in Marina del Rey, California, PCRI has worked closely with the Daniel Freeman Marina Hospital to expand its PC treatment and research capabilities. Current accomplishments include successful lobbying of California

(Continued on bottom of page 3)

Risk Assessment in PC

A patient just diagnosed with prostate cancer is in a state of shock. He simply does not know what to do. If a urologist made the diagnosis, more often than not the patient will be told to have a radical prostatectomy. The patient may well seek additional opinions as to the “best” treatment. This often leads to consultations with a radiation therapist, a brachytherapist, or a cryosurgeon. These four consultations can result in four very different treatment recommendations. How does the patient sort this out?

In an article published in the January 1998 issue of *The Prostate Cancer Exchange*, Roy Berger, M.D. pointed out that physicians will respond to the question, “Is there a correct way to treat prostate cancer?” based on the biases inherent in their own specialties. Urologists will lean toward surgery, radiation therapists will favor external beam radiation or seed implantation, and cryosurgeons will prefer cryosurgery. The patient should be forgiven if he concludes that few agree on the correct way to treat prostate cancer.

Organ-confined or not?

We believe that there is a correct way to individually treat each man diagnosed with prostate cancer. The proper treatment should be based on an understanding of key concepts in the evaluation and treatment of prostate cancer. One such key concept we find most improperly dealt with is organ-confined disease versus non-organ confined disease. Over and over again, we see patients being treated with local therapy with the intent to cure when there is no significant probability that the prostate cancer is organ-confined. In what settings do we find this?

A prostate cancer patient with a PSA of 85, a Gleason score of 8, and a clinical stage of T2c certainly does not have organ-confined disease. His physician should not suggest that local therapies such as radical prostatectomy, external beam radiation, brachytherapy, or cryosurgery can effect a cure. The reflex use of radiation therapy when the PSA continues to rise after a radical prostatectomy (RP) is most often to no avail if evaluating the PSA velocity

post-RP and the findings at RP such as Gleason score, lymph node and seminal vesicle involvement indicate a high likelihood of systemic disease. We believe that the ProstaScint scan has a major role to play in this setting as well.

What is missing in both of these examples is the utilization of existing information, available in the medical literature, that is able to clarify the patient’s status in order to best serve that patient. With this information, we are in a better position to determine the extent of the disease and thereby select the best available treatment for it.

Risk Assessment Necessary for Proper Staging

Staging of the prostate cancer patient involves assessing the patient’s risk of having non-organ-confined disease, capsular penetration, seminal vesicle involvement, lymph node involvement or bone involvement. We can use the experiences of almost 12,000 patients to determine the risk of non-organ-confined

(Continued on bottom of page 4)

Continued from page 2... What's Happening at the Prostate Cancer Research Institute?

Medicare to approve the use of Cytogen’s Quadramet radioisotope for treating painful bone metastases from PC and the upgrade of the hospital’s ProstaScint scanning equipment to enable dual-isotope imaging. Current goals are the establishment of a world class radiation seed implant program, and the addition of an endorectal MRI and spectroscopy unit. General Electric and InSight are supporting the latter project.

Collaborations with the private sector include a clinical trial of fermented soy in association with Beso Pharmaceutical,

Inc. of mainland China, and the initiation of a protocol in association with Pharmacia Upjohn using Dostinex to lower prolactin levels in PC patients with high-normal to elevated levels. The PCRI is also working with UCLA’s Medical Oncology Department on novel PC protocols. Two of the studies which just closed included Sugem’s 101, a platelet receptor inhibitor, and Cell Pathway’s FGN-1, an inducer of apoptosis or programmed cell death.

The PCRI is collaborating with Amgen, the makers of Neupogen and Epopen, on a treatment protocol for high-

risk PC. Neupogen stimulates white blood cell precursors in the bone marrow and allows safer delivery of chemotherapy, and Epopen stimulates red blood cell precursors and corrects anemia associated with cancer as well as improving the anemia due to certain chemotherapy drugs. As mentioned, Epopen (Procrit) also corrects the anemia associated with androgen deprivation (AAD). We are optimistic in also working with Amgen on issues of PC patient empowerment.

A lot is going on at the PCRI.✚

disease as well as the most likely sites for metastases. These experiences are presented using predictive algorithms already published in peer-reviewed medical literature. They involve human experiences that correlate preoperative physical examination, laboratory, pathology and radiologic findings with the findings at RP and with prognosis after local therapy.

A predictive algorithm combines multiple variables and gives information that is statistically more significant than any individual variable. The most familiar algorithm is derived from the work of Partin et al from the Johns Hopkins Medical Center. We have called these the

Partin Tables. Multiple algorithms have been published in the peer-reviewed literature. Those that we find useful have been published by Partin, Narayan, Bluestein, D'Amico, Lerner, Scardino, and Kleer. Many of the algorithms have inputs in common because specific variables have been shown to be significant. Therefore, most algorithms include PSA and GS. Bluestein, Kleer and Partin also include the clinical stage. Lerner includes ploidy analysis.

These algorithms yield a risk assessment expressed as a probability but they do not define an exact number for an individual patient. They do, however, represent a powerful tool in guiding the

patient to the proper staging studies and possibly to identify disease which is not local. Today's predictive algorithms will soon yield to more informative neural net analyses. That subject is for a future issue of *Insights*. Most patients would benefit from a risk assessment using the currently available predictive algorithms. It is Dr. Strum's opinion that these algorithmic findings should be mandatory in the evaluation of the patient, both at diagnosis and at times of disease progression. The algorithm approach leads the physician towards objective reporting and away from simply "eyeballing" the patient. However, obtaining data from algorithms does involve work. ❖

The Prostate Cancer Digest (PCD)

To take full advantage of these predictive tools, the patient and the physician need data that will provide a baseline prior to initial therapy or any subsequent therapy. To provide data for this baseline in a consistent, organized, and complete form, we believe each patient should have what we call a PC Digest or PCD. It is simply a chronological file maintained on a personal computer or by hand to compile, maintain, and update a PC patient's history in an organized fashion. In doing so, it enables the patient and the physician to stay current with the patient's status.

What we suggest is a one-page form that includes all PCD essentials as well as the results of the available predictive algorithms. Computer software to facilitate the use of the predictive algorithms by Partin, Narayan, Bluestein, D'Amico, Kleer, as well as a tumor volume determination based on the work of D'Amico and Aihara, is available without charge from

our homepage.

Why should a patient compile this medical data? A newly diagnosed patient, or a patient with worsening disease, has to take a bearing. He has many questions. What is his status, where are his areas of risk, and what can be done to evaluate these potential problem areas? A baseline is needed prior to initial therapy or any subsequent therapy to gauge the success or failure of therapy. Without this, how do we know what is happening?

Since most physicians are not doing this, we are directing our efforts to empower the patient by teaching him this approach. In this reversed setting, the patient needs to convey to the physician the essential information necessary for a logical course of action. What does a PC Digest look like? It is a growing, evolving document that starts with just a few available clinical and laboratory findings. The following is an example of a PCD for a typical patient:

- **Tom Harrison, age 59,**
Dx 12/23/97, bPSA 5.1,
GS 6, CS T1c.

This is a start. There are abbreviations that are necessary for this to be a digest. We will be adding more as we go along in this issue and other issues.

- PC- prostate cancer
- bPSA- baseline PSA
- CS-clinical stage
- Dx- diagnosis
- GS- Gleason score

The definition and significance of GS and CS are discussed on our homepage in the papers, Early PC, parts I and II. We can build on the above PCD by asking for the gland volume obtained from the Transrectal Ultrasound of the Prostate (TRUSP). Also, how many biopsy cores were obtained at TRUSP and how many were positive? Was one side (lobe) of the gland involved with PC or both sides? We

(Continued on page 5)

have software that we wish to share with you based on the work of D'Amico et al^{6,7} and Aihara et al⁸. Using the TRUSP volume, the bPSA, the number of cores from the right side, the GS of those involved cores and the same from the left side, you can calculate tumor volume and probability of organ-confined PC and print out the results of this Microsoft Excel worksheet.

In Tom's case, the gland volume was 44 cubic centimeters (cm³) or cc's. This is also often expressed as grams (gms). For prostate tissue, grams and cubic centimeters are equivalent. The biopsies showed 1 of 3 cores on the right to be involved with PC with a GS of 6 (3+3) while 3 cores on the left showed benign prostatic hyperplasia (BPH). Therefore, one side of the gland was involved (TRUSP stage of Narayan B-1). The calculated tumor volume per D'Amico and Aihara is 0.55 cm³. Treatment considerations discussed with the patient included a radical prostatectomy (RP), brachytherapy or seed implantation, and external beam radiation therapy (EBRT).

Among other "Inputs" of data that are needed to help in the assessment is ploidy analysis or DNA analysis of the PC from the diagnostic biopsy. This is expressed as a normal amount of DNA (diploid DNA) or an abnormal amount (aneuploid or tetraploid DNA). Microvessel density also appears to be a significant prognostic variable that relates to extent of disease⁹. You know this as angiogenesis or blood vessel formation. Angiogenesis is expressed within the BioStage evaluation that also uses bPSA, and GS. Unfortunately, BioStage evaluation is not available at the present time. We found BioStage to be in harmony with the results of the algorithms as well as with findings at RP. In future issues of

Insights, we will discuss how microvessel density was statistically more significant than either Gleason score or PSA. We hope that we have not seen the demise of this analysis due to internal problems with the marketing company, Bard Diagnostics.

If we list the contents of the PCD that we find helpful, the list would look like this:

- Patient name, current age, and date of Dx
- bPSA
- TRUSP gland volume
- Cores involved / number of cores obtained from right, and GS
- Cores involved / number of cores obtained from left, and GS
- CS
- Prostatic acid phosphatase (PAP)
- Ploidy

The above data is individualized according to the specific concerns for the patient. For example, if PC is suspected but not diagnosed, then the dates and values of all PSA results would be helpful to determine PSA velocity (PSAV) and PSA doubling time (PSADT). The results of PSAV and PSADT are important clues in the diagnosis or Dx of PC. The free/total PSA result would also be helpful to determine a diagnosis of PC, as would results of a ProstaSure blood test¹⁰.

Do not be concerned if you have little or no idea what these items are; we will cover them in future issues. You may find that printing out the paper on Abbreviations or Acronyms from our Homepage and having it handy will make reading *Insights* easier. What we want you to understand is the need to have key information to allow for risk assessment anywhere along your course.

You are a sailor on an open sea, but now you have inputs that you can process to enable you to chart a course. How do you proceed? The input form for patient Tom Harrison is shown below. (Additional data such as pertinent chemistry results, CBC, radiology studies can also be included as can prior PSA values and dates to determine PSAV and PSADT.)

- **Tom Harrison PCD: age 59, Dx 12/23/97**
- **bPSA 5.1**
- **TRUSP volume 44 cc's**
- **1/3 cores + on R with GS (3,3)**
- **0/3 cores + on L**
- **Slides reviewed by expert (Dr. X)**
- **Pathology report available**
- **CS T1c**
- **PAP 3.0 (normal to 3.5)**
- **Ploidy diploid**

From the now expanded PC Digest, the predictive algorithm software processes Tom's data. The results are placed into a form that summarizes risk assessment and prognosticates about freedom from relapse post-RP. (See Table 1 on page 6.) When the data is portrayed in this fashion, it objectifies the evaluation of the patient with PC. In addition, it points to the areas of risk for spread of the disease. These are areas needing further evaluation before assuming that local therapy will be curative.

The blank template for this form is available off our homepage for you to print out and input your data derived from the predictive algorithm software that you have downloaded. If you have problems downloading the software, call the PCRI (310-827-2366) and ask Harry Pinchot to help you.

TABLE 1: Algorithm Template to Help the PC Patient

ALGORITHM	OCD	ECE or CP	SV	LN
Partin *	67	30	2	1
Narayan	81	17	3	3
Bluestein **				N
D'Amico †	70% OCD going to 84% since only 1/6 cores with PC. If erMRI is negative for ECE, then the chance of 3 YFFR after RP would be 85%. If erMRI is positive, then 3 YFFR would decrease to 32%.			
Lerner ††	If organ-confined at RP, the chance of 5 YFFR would be 85% if diploid DNA on diagnostic biopsy.			
PC volume	0.52 cc's. D'Amico's data would predict an 80% chance of organ-confined disease.			
<p>* Using the new Partin Tables published in JAMA 277:1445-51, 1997. ** Bluestein results are node involvement negligible (N) or not negligible (NN). † D'Amico applies to men undergoing a RP. †† Lerner applies to men who had apparent pathologically confirmed organ-confined disease at RP.</p> <p>ABBREVIATIONS OCD : Organ-Confined Disease ECE: Extra-capsular Extension (applies to Narayan). CP: Capsular Penetration (Applies to Partin). SV: Seminal Vesicle Involvement. LN: Lymph Node Involvement. 3 YFFR: 3-year Freedom From Relapse. 5 YFFR: 5-year Freedom From Relapse.</p>				

Inputting this data into Tom's PCD results in the following:

- **Tom Harrison PCD: age 59, Dx 12/23/97**
- **bPSA 5.1**
- **TRUSP volume 44 cc's**
- **1/3 cores + on R with GS (3,3)**
- **0/3 cores + on L**
- **Slides reviewed by expert (Dr. X)**
- **Pathology report available**
- **CS T1c**
- **PAP 3.0 (normal to 3.5)**
- **Ploidy diploid**
- **Partin: 67,30,2,1; Narayan: 81,17,3,3; Bluestein: N; D'Amico: 84% OCD, 3 YFFR pending erMRI**
- **Lerner: 5 YFFR if OCD at RP is 85%; PC calculated volume 0.52 cc's with 80% prediction of OCD.**

With this expanded PCD, based on almost 10,000 patient clinical experiences involving RP's, we can now more properly advise Tom about further studies to evaluate the stage of disease. Tom can be told that a bone scan is not necessary in his setting. Only 1 out of 200 men (0.5%) with these findings will have a bone scan consistent with PC. We can also advise him, based on the above findings, that CT scanning to look for lymph nodes will show abnormal results in 1% of all men so studied. Performing a CT scan of the pelvis and abdomen will therefore be a waste of money and time as well as needless exposure to radiation. We can also tell him, with fair certainty, that ProstaScint scanning is not indicated at this time given the negligible risk for lymph node involvement per findings of Partin¹¹, Narayan¹², and Bluestein¹³. Our focus should be on evaluating areas

of significant risk such as the capsule and peri-prostatic tissue.

Arriving at the above understandings is a lot more than we could do prior to

starting the PC digest, and it is by no means the limit. We will continue with Tom's case history in the next issue of *Insights*. ❖

Upcoming Events

• **4th Annual Prostate Cancer Public Forum**

October 17-18, 1998 • San Diego, California
 Town & Country Hotel & Resort
 Phone (619) 682-7413

• **Phoenix Metro Prostate Cancer Awareness Symposium**

November 14, 1998 • Phoenix, Arizona
 Crowne Plaza • 2532 W. Peoria Avenue
 Phone (602) 242-3131

Bone Integrity: A Critical Issue in PC Management

Since the bones are the structural framework of the body, maintenance of bone integrity is essential to good health. This is especially true in the case of PC, since the osseous tissue or bone is a favored place for the spread of PC. Bone metastases are a major part of the morbidity of advanced PC, resulting in bone pain, anemia due to bone marrow involvement, fracture, spinal cord and nerve root compression.

Why does PC so frequently spread to the bone? One explanation may be related to the observation that growth factors have been isolated from the bone marrow. These growth factors show preferential stimulation of PC whereas tumor cell lines not related to PC show little or no growth response to the same substance¹⁶.

The bone is in a constant state of growth, with bone formation and resorption occurring throughout life. In our early years, the balance is towards bone formation. At approximately age 25, we reach our peak bone mass. Depending on how high or low this peak bone mass is, we are at a lesser or greater risk for the development of osteoporosis as we lose bone during the aging process, or secondarily from illness or medications.

In essence then, the bone is essentially a bank account with a balance (bone density), deposits (bone growth), and withdrawals (bone loss). The endocrine environment is critical to building and maintaining bone. It is well established that androgens in men are stimulants towards positive bone balance the same way that estrogens favor bone growth in women. Other factors responsible for bone deposit or formation include exercise, ample supplies of trace elements such as calcium, boron and silica, as well as induction of osteoblastic cell growth by

fluoride. Vitamin D also enhances calcium absorption and may have other effects on bone formation as well.

On the opposite side of the coin, factors that deplete the bone bank balance by decreasing bone growth and increasing bone loss include: lack of exercise, decreasing hormone levels, increase in osteoclast activity, deficiency in calcium and the other trace elements, and vitamin D deficiency.

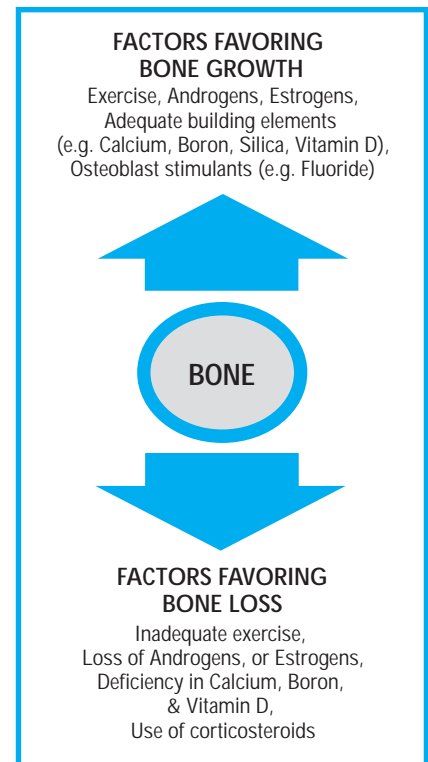
It has been shown that surgical or medical castration will induce osteoporosis^{17, 18}. This occurs immediately at a cellular level but may take months or years to manifest itself as changes in bone density or as clinical symptoms of bone pain or bone fracture. We commonly hear complaints of bone pain in the feet and hands within weeks of commencing androgen deprivation therapy. The measurement of bone degradation products in the urine (DPD, Pylrilinks-D, pyridinolinium cross-links) will enable us to determine if there is increased bone catabolism (destructive metabolism) indicative of a negative bone balance and on-going bone loss.

Our approach toward improving bone integrity involves (1) a graduated exercise program (read the Anti-Oxidant Revolution by Ken Cooper for examples of such programs); (2) the use of bisphosphonate compounds (Fosamax, Aredia or Zoledronate in increasing order of potency) that inhibit osteoclast cell activity; (3) supplementing with calcium in the form of calcium citrate (1000-1500 mg per day); (4) using synthetic vitamin D (Rocaltrol at a starting dose of 0.5 µg per day, best taken just before bedtime), and (5) taking oral Fluoride at a dose of 30-50 mg per day.

Currently, the commercially available bisphosphonates are Fosamax and

Aredia. Fosamax is poorly absorbed and must be taken on an empty stomach ideally one hour before breakfast. Aredia (also known as Pamidronate) is given intravenously, thus avoiding absorption issues. Patients on such compounds must supplement their diet with calcium citrate to facilitate bone formation. We also feel that Fluoride is a key substance that will make more bone and harder bone.

We regard bone integrity as a critical area of PC management. In future issues of *Insights* we will look at bone physiology in more detail. We will delve into the importance of the bisphosphonates that are vital to bone integrity and discuss their function to inhibit bone breakdown by blocking cells that chew up bone (osteoclasts). We will review the literature on fluoride and show how this inexpensive product can stimulate bone growth and help to decrease osteoporosis and bone fractures. ❖



High-Risk Prostate Cancer

The greatest problem we face today is how to prevent the emergence of androgen independent prostate cancer (AIPC), how to identify it, and how to effectively treat AIPC when it develops. A risk assessment that shows a high probability for systemic disease is highly correlated with AIPC.

This is true since AIPC represents aggressive disease that is, more often than

not, systemic. It also makes sense, since a risk assessment that indicates high probability of systemic disease results from inputs such as large tumor volume, high Gleason score, high PSA, abnormal ploidy analysis (DNA), and a high clinical stage. All of these adverse variables are part of the evolutionary changes that are seen as PC becomes androgen independent. In later issues, we will

continue to discuss AIPC. Herein, I will discuss two regimens that employ simultaneous chemotherapy along with androgen deprivation therapy to treat patients with either frankly metastatic disease (D₂), or high-risk patients with stage C, D₀ or D₁ disease. The first of these regimens is that of Servadio et al¹⁹ and the second approach is the work of Bagley et al²⁰. ❖

Metastatic Prostate Cancer Treatment: The Servadio Paper

The Servadio paper, published in 1987, relates the authors' experience in treating 36 men with metastatic prostate cancer. The Gleason scores were as follows:

Gleason Score	10	8	6	4	No score available
Patient Number (%)	6 (21%)	6 (21%)	13 (46%)	3 (11%)	8

Their treatment regimen over this 11-year study was:

- **INDUCTION:** Medical or surgical castration + diethylstilbestrol (DES) at 3 mg/day and radiation to the breasts to prevent gynecomastia (dose: 1,500 cGy).
- **FIRST 2 YEARS:** Weekly Cytosan & 5-FU at a dose of 10 mg/kg intravenously for each drug; the dose intensity (DI) for a 73 kg man, 68 inches tall, would be 730 mg/week for each drug.
- **3RD & 4TH YEARS:** Cytosan & 5-FU at a dose of 5 mg/kg i.v. for each drug given every 3 weeks.
- **5TH YEAR:** Same dose as above but every 4 weeks.

The survival pattern of patients

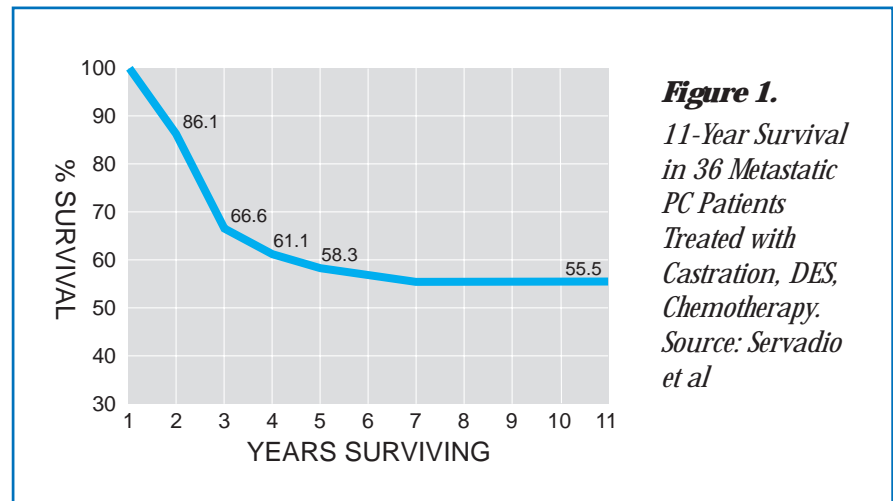
undergoing this regimen is graphically portrayed in Figure 1 below. As shown, the cumulative 5-year survival for the 36 patients was 58.3% and at 11 years, it was 55.5%. Repeat bone scans showed partial or complete response in 55.5% of patients. Hematological complications were transient thrombocytopenia and leukopenia in three patients. With results such as these, we speculated that perhaps we also should be using this approach in patients with metastatic disease.

Problems with the Servadio Approach

A problem with the Servadio approach relates to the over-treatment of

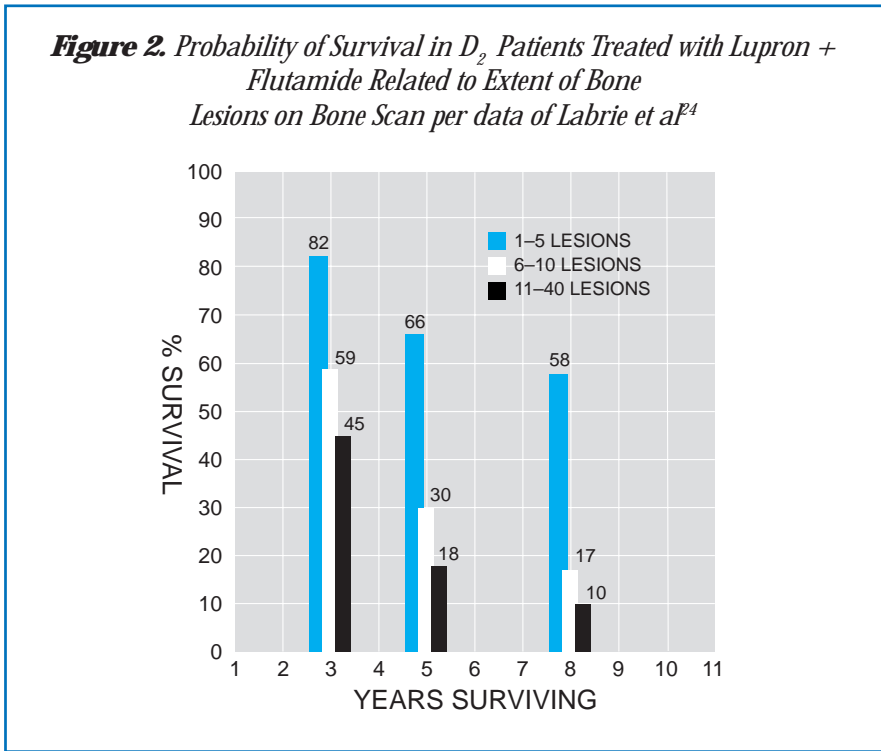
patients who would do well with castration alone. We have all seen patients with extensive bone metastases that have done spectacularly well with surgical castration (orchiectomy) or with medical castration alone. Whether the addition of DES would improve survival time over castration alone or castration plus the use of an anti-androgen has never been formally studied. The latter is further compounded by a recent NCI Intergroup trial -0105 that showed adding an anti-androgen (Flutamide) to orchiectomy does not provide a survival benefit

(Continued on page 9)



over orchiectomy plus placebo²¹. However, other studies refute these findings^{22, 23}.

These issues become particularly obvious if one looks at the 1993 results of Labrie's survival data on D₂ patients with 1-5 bone lesions being treated with Lupron and Flutamide only²⁴. As shown in Figure 2, their 5 year survival was 66% and their 8-year survival was 58%. Therefore, in Labrie's study, the 5-year 66% survival for patients with 1-5 bone lesions on bone scan compares favorably with the 58.3% reported by Servadio et al. Unfortunately however, Servadio did not detail the extent of bone disease. If Servadio had mostly extensive D₂ patients, then his results are better than Labrie's, but if he had a lot of patients with 1-5 bone metastases, then the therapeutic approach he used represented over-treatment. A comparison of the Labrie findings and those of Servadio are shown in the table below.



Comparison of Labrie vs. Servadio Data					
Study (patient number)	Probability of Survival (%)				
	At Year → → →	3	5	8	11
Labrie: 1-5 lesions (105)		82%	66%	58%	no data
Labrie: 6-10 lesions (45)		59%	30%	17%	
Labrie: 11-40 lesions (50)		45%	18%	10%	
Servadio: (36)		67%	58%	56%	55.5%

DES: The Forgotten Drug

What might be important in the 1987 Servadio paper is the use of DES in combination with medical or surgical castration. In 1994, Jazeih et al²⁵ reported on the efficacy of DES in post-orchiectomy patients with progressive PC. In this study, 14 patients with progressive increase in PSA post-orchiectomy were treated with DES +

Coumadin. Nine of the 14 (64%) patients experienced a > 75% decrease in PSA. Seven of these nine patients had symptomatic improvement. The median time to reach a PSA nadir with this treatment was 3 months (range 1-10 months). The median duration of response in this study was 8 months (range 2-24+ months).

The use of DES becomes more intriguing in the light of data showing that estrogens or estrogenic compounds increase sex-hormone binding globulin (SHBG). SHBG has a half-life of 9 days. It binds to dihydrotestosterone (DHT) four times more avidly than to testosterone (T) (5.5 vs. 1.6). The use of estrogen or estrogenic compounds amplifies the effects of SHBG since the affinity is so much greater for DHT and T than for estradiol or estrone, e.g. 5.5/1.6 vs. 0.68/0.1526.

Of course, one must weigh this against the effects of estrogens and estrogenic compounds on increasing the

prolactin levels. Advocates of estrogenic compounds will respond by stating that the increase in SHBG as a result of estrogenic compounds leads to more bound DHT and T and less free DHT and T, thus outweighing possible adverse effects of raised prolactin levels. Agents such as DES, Stilphosterol, Emcyt, and PC spes may have other mechanisms of action besides decreasing LH production and having a direct cytotoxic effect on the prostate cancer cell. Careful clinical research is needed to unravel these issues.

It would be of interest to try to reach Dr. Servadio and determine the number of bone lesions present in the D₂ patients in his study. If there are significant numbers of patients with more than 5 bone lesions, then the Servadio regimen becomes more intriguing in its use of combined orchiectomy plus DES as well as in the use of long-term chemotherapy. ❖

HIGH RISK PROSTATE CANCER: The Bagley Regimen

In the Bagley paper²⁰, patients with pathological stage C-D₁ comprised 20 of the 27 (74%) of the study population. Six more patients had clinical C-D₁ disease. Details of the study population are shown below:

NWTI Treatment of high-risk PC using chemo-hormonal + local RT Data from 8/86-8/93: Bagley et al		
	Patients Treated	Patients Refused
Patent Number	27	10
Median Age	65 (53-73)	67 (61-71)
GS (range)	6.9 (4-9)	7.1 (5-8)
PSA (range)	54 (7.6-358)	51 (6.3-128)
Increased PAP	6	3
D1 – Clinical	3	0
D1 – Pathological	14	5
C – Clinical	3	4
C – Pathological	6	0
Increased PAP only	patient w. PAP of 32	

The Bagley regimen and our modifications (*in color*) are as shown in Table 1.

Table 1. Bagley Regimen & Our Modifications (in color)	
Drugs	Schedule
Velban at 3 mg/m ²	Days 1 & 3
Adriamycin at 40 mg/m ² Novantrone at 8 mg/m ²	Day 1 only Day 1 only
Mitomycin C at 10 mg/m ²	Day 1 of every other cycle
RT given over cycles 2-3	Adriamycin dose Novantrone dose reduced by 50%
LH-RH agonist + Anti-Androgen + Proscar	Given after cycle 3; (Bagley used orchiectomy)

An evaluation of the chemotherapy dose intensity revealed that 93% of the intended chemotherapy was given. Bone marrow suppression was limited to the white blood cells with the median lowest neutrophil count being 200 (range 0-1500). No marrow growth factors such as Neupogen or Epogen were used in this study. Nausea and vomiting were minimal. Mitomycin-induced pneumonitis occurred in 2 patients.

In the treated group, there have been only four relapses for a 5-year relapse-free survival of 85%. Of the 10 patients who refused this approach, eight have relapsed with a median relapse-free survival of 27 months.

As shown in Table 2, a total of 22 of the 27 patients treated with the Bagley

regimen have undetectable PSA (UDPSA) levels after five years. Three others have PSA levels less than 2.0 and two patients have PSA levels of 33 and 13.

Table 2. Bagley Regimen 5-Year Results				
Treatment	Patient Number	Relapses Number	5-Year Relapse-free Survival	PSA@ 5 Years
Bagley Regimen	27	4	85%	22 with UDPSA
No Rx	10	8	20%	

Perhaps it would be reasonable to consider the following in light of these outstanding results:

1. The use of a luteinizing hormone-releasing hormone agonist or orchiectomy plus DES. The DES would also help in decreasing bone loss while increasing SHBG to lower the free androgen index. In addition, the cytotoxic effects of DES on the PC cells would add to cell kill and be independent of hormone dependency.

2. Prophylactic radiation treatment to the breasts to prevent gynecomastia (breast enlargement) or mastodynia (breast tenderness) as well as use of Coumadin to prevent blood clotting problems from DES.

3. Chemotherapy. This is more prob-

(Continued next page)

A Website Worth Hitting

A principal problem for most PC patients is the lack of objective, scientific information about the disease and its treatment. Faced with his initial Dx of PC, where can a man turn for the facts he needs to make informed decisions that will have such a major impact on the rest of his life? A good answer to that question is www.prostate-cancer.org. That's the address of the PCRI's website, which is packed with information that PC patients and their physicians can readily use. It has papers written by Drs. Strum and Scholz, with the assistance of PCRI research assistants Jonathon McDermed and Harry Pinchot. The website has a link

to P2P (Patients to Physicians). List members can get answers to their questions from physicians focused on PC. Dr. Strum has volunteered his time regularly on the Internet for 4 years. This last year he is joined by Dr. Scholz. Dr. Israel Barken also contributes his time on P2P.

On the PCRI website, new software can be downloaded free of charge. This software includes programs that will generate your Partin, Narayan, D'Amico data along with PSA velocity, PSA doubling times, tumor volume calculation and ways to monitor the man doing watchful waiting¹⁴. Software to predict local vs. systemic recurrence after RP

using PSA velocity and RP findings is also there¹⁵. These programs provide information that can really empower the patient in making informed decisions leading to optimal therapy.

A valuable feature of this website is its link to Prostate Pointers, which provides a super abundance of outstanding information on PC. We owe a great deal of thanks to Gary Huckabay for creating Prostate Pointers and for supporting our work on the Rattler server. We hope to establish links with other websites we believe to be of major importance to the PC patient. ✚

lematic. Certainly, Bagley's results are outstanding. Achieving 22/27 undetectable PSA levels at five years is unmatched by any other treatment regimen. Giving the Adriamycin or Novantrone on Day 1 only and the Velban on Days 1 and 3 allow us to use Neupogen on days 4-7, to check the white blood cell (WBC) count on day 8, and possibly to extend the Neupogen to days 8-12 and check the WBC on day 14 or 15.

The table at the right shows a modified Bagley regimen using the anti-emetic Kytril, the marrow growth factor Neupogen, and Novantrone in place of the more toxic Adriamycin. In addition, Dexamethasone, both an anti-emetic and an anti-prostate cancer agent, is also part of this regimen.

If there were no significant WBC depression, Dr. Strum would increase the dose of Novantrone to 10 mg/m². All patients should be on vitamin E and taking selenium (400-600 µg per day) as well as coenzyme Q10 to protect heart muscle.

If a pilot study shows good results, he would consider using this approach in a cooperative group trial. Radiation therapy to the prostate primary would be given during cycles 2-3 and hormonal

therapy would not begin until after cycle 3. We will discuss other approaches for high-risk prostate cancer in future issues of Insights since this is our most challenging area in PC treatment today. ❖

Modified Bagley Regimen: After Strum et al									
Drug Name	mg or mg/m ²	Route	Day on Study						
			1	2	3	4	5	6	22/1
Kytril	1 mg	i.v.	X		0.3 mg				X
Dexamethasone	10 mg	i.v.	X						X
Novantrone	8 mg/m ²	i.v.	X						X
Velban	3 mg/m ²	i.v.	X		X				X
Mitomycin C	10 mg/m ²	i.v.	X	Given only on Cycles 1,3 and 5					
Neupogen	300 µg	sq					Given on days 5-12		
New Cycle			Begin new cycle every 22 days for 6 courses						
Notes	On 1st cycle check CBC days 8 & 15 to adjust Neupogen dosing. Epopen as per CBC Baseline calculated creatinine clearance and checked monthly. Watch for platelet nadir from Mitomycin C on Days 30-35.								

References:

- Strum SB, McDermed JE, Scholz MC, et al: Anemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. *Br J Urol* 79(6): 933-41, 1997.
- Strum SB, Scholz MC & McDermed JE: The Androgen Deprivation Syndrome: the incidence and severity in prostate cancer patients receiving hormone blockade. Accepted for poster presentation at the ASCO meeting May 19th, 1998, Los Angeles, CA. *Proc Amer Soc Clin Oncol*. 17: 316A, 1998.
- Strum SB, Scholz MC & Strum M: Prolonged non-detectable PSA (NDPSA) in PC patients treated with androgen deprivation may allow for discontinuation of hormone blockade. International Symposium on Recent Advances in Diagnosis & Treatment of Prostate Cancer, Quebec City, September 21-23, 1995 (Poster Presentation).
- Strum SB, McDermed JE, Scholz MC, et al: Anemia associated with androgen deprivation (AAAD) due to combination hormone blockade (CHB) responds to recombinant human erythropoietin (r hu-EPO). *J Urol* 157:232 1997. (Abstract).
- Strum SB & Scholz MC: Intermittent Hormone Blockade: optimal induction duration and predictive factors for prolonged time off hormone blockade. Accepted for oral presentation at the ASCO meeting May 19th 1998, Los Angeles, CA *Proc Amer Soc Clin Oncol*. 17: 313A, 1998.
- D'Amico A, Chang H, Holupka E, et al: Calculated prostate cancer volume: the optimal predictor of actual cancer volume. *Urology*. 49:385-391, 1997.
- D'Amico A & Propert K: Prostate cancer volume adds significantly to prostate-specific antigen in the prediction of early biochemical failure after external beam radiation therapy. *Int. J. Radiation Oncology Biol. Phys.* 35:273-279, 1996.
- Aihara M, Lebovitz R, Wheeler T, et al: Prostate specific antigen and Gleason grade: an immunohistochemical study of prostate cancer. *J. Urol.* 151:1558-1564, 1994.
- Bostwick DG, Wheeler TM, Blute M, et al: Optimized microvessel density analysis improves prediction of cancer stage from prostate needle biopsies. *Urology* 48:47-57, 1996.
- Babaian RJ, Fritsche HA, Zhang Z, et al: Evaluation of ProstaSure index in the detection of prostate cancer: a preliminary report. *Urology* 51:132-136, 1998.
- Partin AW, Kattan MW, Subong ENP, et al: Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. *JAMA* 277:1445-1451, 1997.
- Narayan P, Gajendran V, Taylor SP, et al: The role of transrectal ultrasound-guided biopsy-based staging, preoperative serum prostate-specific antigen, and biopsy Gleason score in prediction of final pathologic diagnosis in prostate cancer. *Urology* 46:205-212, 1995.
- Bluestein DL, Bostwick DG, Bergstralh EJ, et al: Eliminating the need for bilateral pelvic lymphadenectomy in select patients with prostate cancer. *J. Urol.* 151:1315-1320, 1994.
- Dugan JA, Bostwick DG, Myers RP, et al: The definition and preoperative prediction of clinically insignificant prostate cancer. *JAMA* 275:288-294, 1996.
- Partin AW, Mohler JL, Walsh PC, et al: Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology* 45:831-838, 1995.
- Chackal-Roy M, Niemeyer C, Moore M, et al: Stimulation of human prostatic carcinoma cell growth by factors present in human bone marrow. *Endocrinol Metab* 76:288-290, 1993.
- Clarke NW, McClure J, & George NJR: The effects of orchiectomy on skeletal metabolism in metastatic prostate cancer. *Scand J Urol Nephrol* 27: 475-483, 1993.
- Goldray D, Weisman Y, Jaccard N, et al: Decreased bone density in elderly men treated with the gonadotrophin-releasing hormone agonist decapeptyl (D-Trp- GnRH). *J Clin J. Clin. Invest.* 84:43-50, 1989.
- Servadio C, Savion M & Mukamel E: Combined hormone-chemotherapy for metastatic prostate carcinoma. *Urology* 30:352-355, 1987.
- Bagley C, Lane R, Grimm P, et al: Adjuvant chemotherapy and hormonal therapy of high-risk prostate cancer. *Proc Amer Soc Clin Oncol*. 14:230, 1995.
- Crawford ED, Eisenberger MA, McLeod DG, et al: Comparison of bilateral orchiectomy with or without flutamide for the treatment of patients with stage D2 adenocarcinoma of the prostate: Results of NCI Intergroup Study 0105 (SWOG and ECOG) (Abstract). *J Urol* 157(suppl):336, 1997.
- Labrie F, Dupont A, Belanger A, et al: Combination therapy with flutamide and castration (LH-RH agonist or orchiectomy) in advanced prostate cancer: a marked improvement in survival. *J. Steroid Biochem Mol Biol* 23:833-841, 1985.
- Janknegt RA, Abbou CC, Bartoletti R, et al: Orchiectomy and Nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 149:77-83, 1993.
- Labrie F, Dupont A, Cusan L, et al: Major advantages of "early" administration of endocrine combination therapy in advanced prostate cancer. *Clin. Invest. Med.* 16:6 493-498, 1993.
- Jazieh AR, Munshi NC, Muirhead M, et al: Clinical efficacy of Diethylstilbestrol treatment in post-orchietomy progressive prostate cancer. *Proc AACR*, 35:233, 1994.
- Dunn JF, Nisula BC & Rodbard D: Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J. Clin Endocrinol Metab.* 53:58-68, 1981.

A Generous Gift from PAACT

The work and accomplishments of the not-for-profit PCRI depend on continued support from the Daniel Freeman Marina Hospital and are greatly aided by generous donations from cancer patients and charitable organizations. The most recent of these was a \$10,000 gift from PAACT (Patient Advocates for Advanced Cancer Treatments). PAACT, its remarkable founder Lloyd Ney, and Dr. Strum have worked closely over the years. Now, Dr. Strum is hoping that PAACT will be more involved in supporting the efforts of the PCRI since the PCRI is essentially the medical evolution of the concepts (Communication, Clinical Trials, Compassion, Centers of Excellence, and Charity) embodied in PAACT's bylaws.

This significant contribution from PAACT enables PCRI to extend its work still further. What kind of work? Ideas recently discussed at the PCRI include establishing video conferencing between support groups along with a video library with internet access, developing a notebook for patients with instructions on how to develop and maintain a medical record, and establishing a financial support fund for young men with aggressive PC needing the expertise of medical oncologists who focus on chemo-hormonal-immuno therapy. Unfortunately, we are seeing a lot of these men mismanaged by medical organizations that do not offer optimal approaches for treating aggressive PC.

PCRI Insights

PROSTATE CANCER INSIGHTS®

is published by:

The Prostate Cancer Research Institute
4676 Admiralty Way, Suite 103
Marina del Rey, CA 90292

LLOYD NEY - A PIONEER IN PATIENT EMPOWERMENT

On August 19, 1998, a powerful voice for effective treatment of prostate cancer was stilled with the death of Lloyd Ney, the man who founded PAACT and really initiated and nurtured the empowerment movement of men with prostate cancer.

Lloyd Ney himself was diagnosed with prostate cancer in January, 1984. He received radiation therapy, but eight months later had metastatic prostate cancer that involved the thoracic spine, sacrum, and left ribs. He was informed that his prognosis was terminal and was advised to get his affairs in order.

Lloyd found this unacceptable, and proceeded to search the literature on prostate cancer. He came upon the little known pioneering work of Fernand Labrie in Quebec City, and went to Canada to commence combination hormone blockade treatment. The six months prognosis he had been given turned into 14 years.

When Lloyd Ney realized he was not going to die, he dedicated the rest of his life to helping men with prostate cancer. Over this time, he has helped so many people throughout the world, not only the men with prostate cancer, but also the family circles of these men. Through his empowerment movement, he touched the lives of millions. To quote the moving tribute Stephen Strum delivered at the Ney funeral:

“God bless you, Lloyd, for being so involved in mankind, for saving so many souls, for causing so many lives to breath easier, for being selfless and for finding ways to right the wrongs in the world. We will continue your cause, and soon, one day, we will see the time when prostate cancer will not be a threat to any man's life.”

Non Profit Org.
U.S. Postage
PAID
Inglewood, CA 90311
Permit No. 166