PCRInsights
August 2001 vol. 4, no. 3 New Developments in Prostate Cancer Treatment Patient and Physician in Co-Partnership
Prostate Cancer Research Institute
Working together for a cure

High-Dose Ketoconazole (HDK or Nizoral®) is Effective Against Androgen-Dependent and Androgen-Independent Prostate Cancer and is Synergistic With Chemotherapy

By Stephen B. Strum, M.D.

A review of the concepts involved with androgen dependency and a detailed discussion of this highly effective agent that is commonly forgotten in the management of prostate cancer.

CB was 55 years old when he developed pain in his right hip. *A routine x-ray showed* ***blastic*** *changes and a bone scan showed marked uptake of isotope in his right proximal femur, ischium and sacrum. He underwent biopsy of his prostate and was found to have adenocarcinoma with a Gleason score of 4,4. He had never had a prior PSA test before that time. His baseline PSA was 1,020.*

In April of 1992, he was started on Flutamide (Eulexin®) at the usual dose of 250 mg three times a day. A week later, he underwent orchiectomy. On 1/22/93, nine months later, the PSA declined to a nadir value of 0.3 and then steadily rose to 25 by 12/14/93, to 139 by 7/16/94, and then to 885 by 12/14/94. All during this time his physicians at his HMO observed the PSA increases without initiating any form of therapy.

I first saw CB in late 1994 in a second opinion consultation, and I advised him to stop Flutamide and to start high-dose ketoconazole (HDK) in conjunction with hydrocortisone (HC). His HMO physicians reluctantly began this treatment in mid-December 1994. By August of 1995, the PSA had dropped to 0.2, the nadir level achieved while on HDK + HC. The PSA continued to rise but the patient did clinically well until 12/96 at which time his PSA was 2.89. This excellent response was of two year's duration using an oral medication that the patient tolerated well. The patient remains alive as of this writing, more than nine years since his diagnosis with D-2 prostate cancer.

At the age of 71 in December of 1992, RK had his first PSA–a value of 168. *He was diagnosed with prostate cancer with a Gleason score of 3,3. A CT scan showed lymph node involvement; a bone scan showed uptake at T-11 and S-1. His PAP was 46.6. An MRI scan of his thoraco-lumbar spine showed possible disease at T-10 and L-5. RK underwent treatment with an orchiectomy plus Flutamide on 12/14/92. His bone scan became normal in 1/96 and his PSA reached a nadir value of 0.08. His PSA then began to progressively increase to 0.37.*

He stopped Flutamide and began HDK and HC on 6/2/97. His PSA dropped to undetectable on 9/1/97 using a hypersensitive PSA assay (DPC 3rd Generation Immulite) with values of less than 0.05 ng/ml, which were maintained for almost 3 1/2 years. RK has recently lowered his dose of HDK and currently is taking only 200 mg once a day. He is also taking Fosamax® and calcium to improve his bone integrity since he was found to be osteopenic on bone mineral density evaluation. RK, at age 81, continues to work and lectures worldwide. RK is the discoverer of the cataract operation. He has an outstanding quality of life. His major toxicity from HDK has been a peeling of the skin involving his lips. He applies an inexpensive over-the-counter ointment called Carmex® (Carma Labs, Franklin, WI) that has significantly helped him and other patients diminish this side-effect of HDK.

These are not isolated cases. We have found that HDK is an incredibly versatile drug with a broad spectrum of activity against PC cell populations that may be both androgen-dependent and androgen-independent. HDK is also synergistic with a number of chemotherapy drugs. Ketoconazole absorption is highly variable, but a simple blood Nizoral® level provides the physician-patient team with valuable biologic feed-back that allows tailoring of the HDK dose. Moreover, HDK and HC is a very affordable out-patient oral regimen.

The following review of the use of HDK for PC is divided into the following sections:

- Concepts essential to the use of broader spectrum agents against PC
- Necessity for castrate testosterone levels
- Androgen receptor mutation
- Androgen-independent prostate cancer (AIPC)
- HDK therapy in the setting of AIPC
- HDK and anti-androgen withdrawal response (AAWR)
- HDK Administration guidelines
- Side effects of HDK
- Cost of HDK
- Conclusions

The employment of HDK in PC management has been neglected. This article is intended to provide more physicians and PC patients with insights into HDK and to describe the proper contexts in which to use HDK in order to take advantage of the unique pharmacology of this versatile drug.

Concepts essential to the use of broader spectrum agents such as HDK, PC SPES and DES

Tumor cell heterogeneity

It is reasonable to assume that at the inception of malignancy prostate cancer (PC), like other malignancies, is comprised of an essentially homogeneous cell population. If the cancer goes

(continued on page 3)

In This Issue:

PCRInsights

Editor-in-Chief: Stephen B. Strum, MD
Editor: Charles Bader
Publisher: The Prostate Cancer Research Institute

Prostate Cancer Research Institute
5777 Century Boulevard, Suite 885
Los Angeles, CA 90045
Helpline: (310) 743-2110
Phone: (310) 743-2116
Fax: (310) 743-2113
E-mail: pcri@prostate-cancer.org
Web site: www.prostate-cancer.org

Medical Director: Stephen B. Strum, MD
E-mail: sbstrum@prostate-cancer.org

Executive Director: Glenn D. Weaver
E-mail: gdw@prostate-cancer.org

The cost of printing and mailing this newsletter is made possible through a generous grant from ***The Life Extension Foundation****, P.O. Box 229120, Hollywood, FL 33022; Phone: 1-800-544-4440; Web site:* www.lef.org

What You Should Get From the Article on Ketoconazole & Hydrocortisone

1. Prostate Cancer is highly dependent on male hormones for its growth.
2. Most patients will have a significant regression of PC by approaches that involve lowering of testosterone, i.e. androgen deprivation therapy or ADT.
3. You cannot optimize such results unless you know the blood level of testosterone. The goal should be a testosterone of less than 20 ng/dl.
4. Advanced prostate cancers involving lymph nodes and/or bones or PC with Gleason scores of 8-10 are more likely to have components of Androgen Independent PC (AIPC) compared to more localized PC and/or PC with lower Gleason scores.
5. Patients with unfavorable Gleason scores or those with extensive disease cannot be expected to have long and durable remissions with ADT alone.
6. A PSA drop to <0.05 ng/ml on ADT is indicative of a highly sensitive PC population that is more likely to represent Androgen Dependent PC (ADPC). This is especially true if the above PSA level is not only achieved but maintained for one year or more.
7. If the Gleason score is 8-10, other blood markers such as PAP, NSE, CEA and CGA are important to check to make sure you are not missing tumor growth reflected by a progressively rising level(s) of these biomarkers.
8. Patients who achieve a castrate testosterone of <20 ng/dl but who do not achieve and maintain a PSA of <0.05 ng/ml most likely have AIPC. They need a treatment that is broader in spectrum.
9. Broader spectrum therapies that have been mislabeled as "secondary hormonal manipulations" include high dose ketoconazole (with hydrocortisone), DES and PC SPES. These therapies involve mechanisms that include ADT but go beyond the lowering of testosterone.
10. High dose Ketoconazole with hydrocortisone (HDK with HC) is a very powerful approach in such a setting, especially when the treatment is initiated at a PSA of less than 10 and when a low nadir PSA is achieved on HDK therapy. Long durable responses are common in such settings.
11. The use of HDK with hydrocortisone mandates an understanding of the pharmacology of HDK including issues relating to absorption, measurement of ketoconazole blood levels as well as monitoring of liver function tests and being cognizant of potentially serious drug interactions.
12. HDK is synergistic with many kinds of chemotherapy and also diminishes the probability of drug resistance (MDR). This should stimulate clinical trials of HDK with various kinds of chemotherapy.

Wow! What a Response

PCRI and Life Extension printed 10,000 copies of **"What You Should Know About Prostate Cancer."** That supply only lasted a week!

As the requests for this pamphlet continued to pour in, we printed an additional 50,000 copies. As of today, we have sent out over 35,000 copies to individuals, support groups, doctor's offices, churches and cancer centers around the country and abroad.

We want to thank all of you who have taken this active role in helping to bring Prostate Cancer Awareness to your fellow man and for letting us know how much you value the information contained within this pamphlet.

If you haven't yet ordered your copies, please help us keep this effort going by ordering your supply today either by going to PCRI'S web site at **www.prostate-cancer.org** or by calling our office at **310-743-2116.** The cost is very low, only 10 cents a copy, to help defray printing costs, with a minimum order being 100.

It is our goal to end the threat of prostate cancer to any man's life. These pamphlets can be an important tool in ultimately achieving this goal.

undiagnosed, the chances of continued mutations in DNA are high and a change in the tumor cell population to that of a more heterogeneous or mixed population of cancer cells is likely.

This is called **tumor cell heterogeneity**. It appears that the older the tumor is, the more likely that tumor cell heterogeneity is present. Patients who present with advanced PC at diagnosis, or whose course of illness has led to manifestations of advanced PC, most commonly have a heterogeneous population of tumor cells. Clinical and pathological findings that manifest advanced PC include Gleason scores of 8 to10, PSA levels >20, clinical stages of T3 or T4, aneuploidy, short PSA doubling times (less than 6 months) and the finding of elevated serum tumor markers such as PAP, NSE, CGA and/or CEA.

In this setting of advanced PC, the first choice of treatment remains androgen deprivation therapy or ADT. PC growth, to an overwhelming extent, is mediated by androgens such as testosterone and dihydro-testosterone (DHT). A metabolite of testosterone, DHT is five times more potent than testosterone in stimulating PC growth. Medical or surgical manipulations that lower testosterone and DHT are therefore helpful in arresting tumor growth and/or causing programmed cell death or **apoptosis**. These very approaches using surgical castration (orchiectomy, orchidectomy) or medical castration (DES or diethylstilbestrol) in advanced PC, led to a Nobel Prize in Medicine for Charles Huggins in 1966 for work initiated in the 1930s.[1, 2]

However, although ADT is the treatment of choice for advanced PC, such patients are the ones most likely to exhibit tumor cell heterogeneity, i.e. have tumor cells that are both androgen-dependent and also androgen-independent.

Since ADT is directed at the tumor cell population that is androgen DEPENDENT, we cannot expect those clones of PC cells that are independent of androgen to respond to testosterone lowering therapies. Yet this is what is assumed in countless publications and presentations on the use of ADT in advanced PC. Moreover, patients who initially responded to ADT but who are now showing progressive disease are labeled "hormone refractory" when in fact they may have responded appropriately to ADT. It is the Androgen-INDEPENDENT PC (AIPC) that is not responding to ADT. It is the AIPC that is manifesting PC growth and giving us evidence of progressive disease. If we were to have used the same thinking in our approach to microbiology, we would never have considered the possibility of mixed populations of bacteria that require the use of multiple antibiotics or antibiotics with a broader spectrum. **We need to understand the nature of the tumor cell population before glibly labeling the patient's PC as "hormone refractory" when in fact that population of "resistant" cells may have been present at the start of treatment.**

Figure 1.

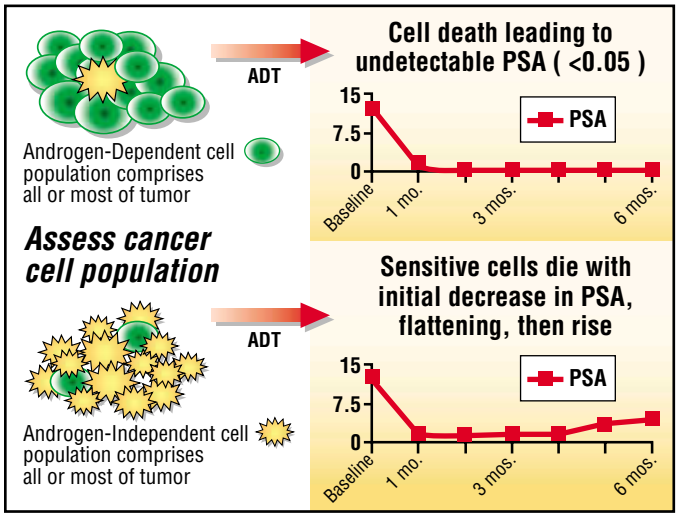


Table 1. Causes of a Rising PSA While on Androgen Deprivation Therapy

I. Suboptimal Lowering of Testosterone due to:	a) Inadequate Suppression of LH by the LHRH agonist
	b) Excessive Production of Adrenal Androgens
II. Presence of an Androgen Receptor Mutation **(ARM)**	
III. Androgen-Independent Prostate Cancer **(AIPC)**	

The top portion of **Figure 1** portrays what occurs in a patient with predominantly **androgen-dependent PC** when **ADT2** or **ADT3** is initiated. The PSA drops from its baseline value to low levels, and an undetectable PSA is achieved usually within the first four months of ADT. This undetectable PSA level (less than 0.05 ng/ml) is maintained while the patient is on ADT. In such a setting, we have found the use of a hypersensitive PSA (DPC 3rd Generation or Tosoh Hypersensitive) assay helpful in distinguishing Androgen-Dependent PC (ADPC) from AIPC.

The patient with AIPC shows an initial drop in PSA reflecting the component of ADPC that was present. However, after this element of the cell population has undergone **apoptosis** or **G1 arrest**, the remaining part of the PC, the AIPC portion, becomes manifest. As shown in the lower half of Figure 1, a rise in PSA and/or other markers follows.

The occurrence of a rising PSA while a patient is on ADT is a cause for alarm for both the patient and physician. Such patients are often immediately labeled as being "hormone refractory" and given a dire prognosis. In reality, however, the cause of a rising PSA may be due to one of a number of factors as shown in **Table 1**.

These underlying causes, or etiologies, have been described in the October 2000 issue of *Insights* (vol. 3, no. 3) on pages 3-5. Because this aspect of ADT is so critical throughout much of the management of the man with PC, an in-depth discussion follows.

Necessity for castrate testosterone levels

The use of ADT mandates that the treating physician confirm that the serum testosterone has at least reached **castrate levels** of testosterone. This is defined as a testosterone of less than 20 ng/dl (nanograms per deciliter) or less than 0.69 nM/L (nanomoles per liter). This should be an absolute requirement for any patient receiving therapy that has its basis in the lowering of testosterone. However, probably less than 5% of physicians take steps to confirm that ADT has indeed resulted in androgen suppression. **This ignores the biologic foundation of ADT and puts the patient at risk for a suboptimal outcome and, perhaps, heightens the risk of drug resistance during hormonal manipulations.**

(continued on page 4)

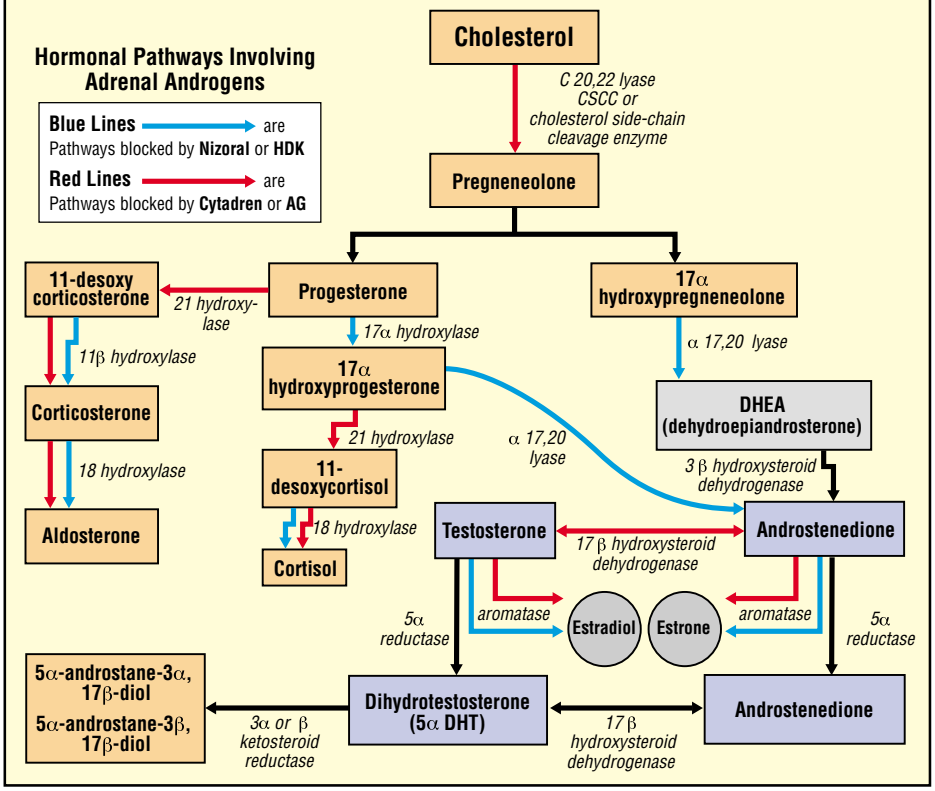
In the event that a castrate testosterone is not confirmed, differential testing should follow with measurements of the pituitary hormone **LH** and the **adrenal androgen precursors DHEA-S and Androstenedione.** An elevated testosterone in the context of ongoing treatment with ADT must result from either or both of these sources. If the LH is 1.0 or higher, it is quite possible that the LHRH agonist is not optimally blocking the LHRH receptor in the pituitary. This may be due to either:

- over-expression of LH in the individual patient or
- inadequacy of the dose or dosing frequency of the LHRH agonist drug, e.g. Lupron® or Zoladex®.

In my experience, the latter has been more common when using the longer-acting LHRH agonists (e.g. 112 day or "four-month" Lupron® or Zoladex®). We therefore advise that the dosing schedule of the LHRH agonist be on a 28-day schedule for the first six months of treatment. This also allows for "monthly" monitoring of the patient for changes in liver function that may be seen with either Eulexin®, Casodex® or Nilandron®, as well as signs or symptoms that may occur relating to the androgen deprivation syndrome or ADS.[3] The latter includes the anemia of androgen deprivation,[4] increased bone resorption, cognitive changes, emotional lability, decrease in libido and impotence, muscle loss, weight gain as well as skin, nail and hair changes. Not all of these findings necessarily occur; that is why this is termed a syndrome — it reflects a spectrum of possible findings. Most importantly, many, if not all of these changes can be either prevented or treated by the clinician experienced in the management of ADT and ADS.[5,6]

If the LH level is less than 1.0, adequate LH suppression is established and a non-castrate testosterone must be the result of contributions from the pituitary-adrenal axis. In such circumstances, the serum DHEA-S and/or androstenedione level(s) will be in the high normal range or elevated. This is our explanation for a PSA not falling to less than 0.05 ng/ml, or for a PSA that is rising. The adrenal androgen precursors are being converted to testosterone by the enzymes within the prostate cell population and peripheral tissues, and testosterone and its metabolite dihydrotestosterone (DHT) are stimulating PC growth. In such patients, treatment with HDK + HC will block the synthesis of these adrenal androgen precursors. **If an elevation of testosterone is due to such occurrences, HDK will lower the serum testosterone to castrate levels.** Follow-up serum measurements of testosterone as well as DHEA-S and androstenedione will confirm the efficacy of HDK and HC.

Figure 2: Endocrine Pathways Inhibited by Ketoconazole (HDK or Nizoral) and Aminoglutethemide (AG or Cytadren)



In **Figure 2**, the pathways involving various enzymes blocked by Nizoral® (HDK) are shown using blue arrows. HDK decreases DHEA by inhibiting the enzyme α-17,20 lyase, and also decreases androstenedione levels by blocking the conversion of 17-α hydroxyprogesterone to androstenedione via the same enzyme. Since DHEA is sulfated in the liver to DHEA-S, the levels of DHEA-S and androstenedione are lowered by HDK, assuming proper dosing and sufficient absorption of HDK through the stomach and small intestine. This will be discussed later. Of importance is the additional inhibition of the enzyme "aromatase" by HDK. This is important since therapies that result in increased amounts of testosterone (e.g. monotherapy with antiandrogens such as Casodex® or Flutamide or the use of combined Finasteride® with Casodex® or Flutamide) are associated with significant breast tenderness and enlargement. **The use of HDK could prevent that complication and add to the spectrum of activity seen with these other agents.** Unfortunately, the addition of HDK to such a combination of agents would also result in decreased serum testosterone levels, thereby reducing the beneficial effects of potency preservation currently attributed to such therapeutic approaches.

Androgen Receptor Mutation (ARM)

Receptors are docking sites on or within the cell that allow for interaction between chemical messengers (ligands) and the cell's central intelligence agency- the DNA. Receptors facilitate signaling to the DNA to turn on or turn off. Receptors are located within the nucleus of the cell or within the cytoplasm. Estrogen receptors have been shown to be critical to the management of breast cancer. Blocking estrogen receptors in breast cancer cells with drugs such as Tamoxifen® or Raloxifene® have improved the survival outlook for millions of women with breast cancer. We are able to quantitate the amount of estrogen receptors (ER) as well as progesterone receptors (PR). More recently, drugs have been created that selectively inhibit ER in one part of the body while allowing estrogen to still interact at other receptor sites. An agent that does this is called a selective estrogen receptor modulator (SERM). Current research is investi-

gating drugs that selectively modulate the androgen receptor. A drop with such properties is called a selective androgen receptor modulator (SARM).

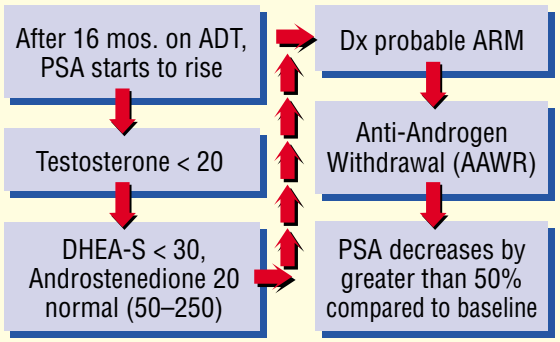
The androgen receptor (AR) involved with prostate growth is found within the nuclei of prostate cells. AR are not only within prostate cells but are found in virtually all tissues throughout the body e.g. brain, muscle, bone marrow, skin, hair follicles, etc. Wilding et al,[7] Wolf et al,[8] and Schuurmans et al[9] have shown point mutations in the hormone-binding domain of the androgen receptor. In the mouse LNCaP cell line, this mutation may lead to paradoxical stimulation of growth after incubation with hydroxyflutamide (a metabolite of Eulexin® or Flutamide), Nilutamide®, Cyproterone® acetate and progestins. In humans, PC cell mutation may result in the paradoxical stimulation of cancer cell growth by the anti-androgen, the very agent that is used to block the AR to decrease cell growth. Stopping the anti-androgen in patients with an ARM usually results in an anti-androgen withdrawal response (AAWR). Dupont et al,[10] noted an AAWR in 30/40 or 75% of patients (1 CR, 3 PR, 26 Stable). A decrease in serum PSA was seen in 34/40 or 85% of patients. The average duration of AAWR was 14.5 months ranging from 3.6–29.9 mos.

Scher and Kelly[11] documented an AAWR in only 10/35 (29%) of patients defined by a PSA decline of 50% or more. Their median response was 5+ months in contrast with Dupont's median response of 14.5 months. Of these ten patients who had an AAWR, all had received an anti-androgen combined with an LH-RH agonist as ***initial*** therapy. Therefore, in this subset (25 patients), the frequency of AAWR was 10/25 or 40%. None of the ten patients who initially received monotherapy with an LHRH agonist or orchiectomy and then showed progressive disease and were next treated with Flutamide monotherapy were found to have an AAWR.

In a preliminary report, Herrada et al[12] noted there is a high probability that patients with suppressed adrenal androgen levels have an AAWR. In other words, if the anti-androgen was causing an ARM and acting as an agonist or stimulator of PC cell growth, the pituitary gland and other receptors in the brain would be sensing the presence of androgen and signal a down-regulation of adrenocorticotrophic hormone (ACTH), thus decreasing adrenal androgen precursor production. This manifests as lower levels of androstenedione and DHEA-S. Please note that the above authors were checking DHEA and not the DHEA-S metabolite. DHEA-S is subject to less diurnal variation than DHEA and thus is considered to be a more reliable laboratory test. A subsequent publication by the same authors failed to show a statistically significant relationship between DHEA levels and AAWR but a trend in that direction was still apparent.[13] We believe that measurements of DHEA-S and androstenedione more accurately reflect the status of the adrenal androgen precursors and that suppression of one or both of these hormones helps to predict a positive response to AAWR.

AAWR should be at least part of the first step in patients progressing under ADT. Whether this should be done as a solitary maneuver or in conjunction with initiating a secondary "hormonal" manipulation such as HDK + HC or Cytadren® + HC is unknown. We have seen prolonged responses to such secondary treatments when these regimens are instituted simultaneously with discontinuation of the anti-androgen. In the report by Sartor et al, all patients had received Suramin®, hydrocortisone, Flutamide and either surgical or medical castration immediately prior to Flutamide withdrawal. Fourteen of 29 or 48% of patients had a PSA decrease of more than 80% for four or more weeks.[14] A schematic approach to ARM is shown in **Figure 3**.

Figure 3: Decision Tree in Suspecting, Evaluating and Confirming the Presence of an Androgen Receptor Mutation (ARM)



AIPC or Androgen-Independent Prostate Cancer

AIPC is said to be present if both of the following conditions are met:

1. Patients on ADT have achieved a castrate testosterone level defined as less than 20 ng/dl or less than 0.69 nM/L (units used in the United Kingdom & elsewhere).
2. There is evidence of a progressive rise in PSA despite anti-androgen withdrawal having occurred.

The term "hormone refractory" does not really define such patients. First, hormonal manipulations that lower testosterone would not be expected to be effective against androgen-independent tumor cells; we really can't define such clones of cells as refractory. Secondly, we have good reason to believe that AIPC clones are already present in most, but not all patients, who present with or progress to advanced PC. We have no evidence that the AR have become insensitive to testosterone. Clearly, these patients need a therapeutic approach that is not dependent on lowering of testosterone as the mechanism of action to activate tumor cell kill. **Table 2** shows examples of treatments active against AIPC.

Table 2. Treatments Active Against AIPC

High-dose ketoconazole: (HDK or high-dose Nizoral®) in combination with hydrocortisone (HC)

Estrogens: diethylstilbestrol (DES), Stilphosterol®, Honvan®, Fosfestrol®

PC SPES

Chemotherapeutic agents: Taxotere®, Adriamycin®, Carboplatin®, Cisplatin®, Novantrone®, Cytoxan®, Mitomycin C®, Velban®, Etoposide®, Vinorelbine®, Emcyt®, 5-FU®

Radiation therapy: external beam RT, brachytherapy, radioactive isotopes, monoclonal antibodies with radioactive payloads

Investigational therapies: Immunotherapies: Dendritic cell infusions (Provenge®); Oncolytic viruses (Calydon®); Receptor antagonists (Atrasentan®); Bisphosphonates (Zometa®, Aredia®, Fosamax®, Actonel®); Anti-angiogenesis agents (Endostatin®, Angiostatin®, Thalidomide®); Inducers of apoptosis (Exisulind®); Pro-drugs activated by PSA (Merck L-377202®); Antisense to bcl2 (Genasense®); Gene insertion treatments (p53); Other treatments.

All of these examples are therapies that have mechanisms of action ***unrelated in part or totally*** to manipulating the hormonal environment.

If AIPC is distinguished by its lack of dependency on the hormonal environment, it is reasonable to hypothesize that those cells remaining

(continued on page 6)

biologically active and able to secrete PSA and/or other biomarkers into the circulation after ADT must reflect the androgen-independent population. **We believe that ADT is a treatment that discerns these cell populations—androgen-dependent vs androgen-independent, based on a differential response to testosterone-lowering therapy.** In the above setting, it is the clones that have mutated to an androgen-independent state that show a suboptimal response to ADT when response criteria are defined using a hypersensitive PSA assay (Figure 1). At a genetic level, this has been shown to be the case in animal models of AIPC where the development of androgen independence was correlated with the acquisition of 3-7 genetic changes involving gains in chromosome 13 and losses in chromosomes 4, 6, 20 and 21. Hyytinen et al showed that such genetic changes were not only associated with AIPC but also correlated with biological aggressiveness and the frequency of metastasis.[15]

At a human level, it has been our experience that the failure to reach an undetectable PSA of less than 0.05 ng/ml using a hypersensitive assay is highly correlated with AIPC. A decision tree relating to this is shown in **Figure 4**.

A strategy to identify the underlying cause in a situation characterized by a rising PSA while on ADT is shown in **Table 3**. Decision making at Level 1 uses the serum testosterone level as the first cross-roads. If the testosterone is greater than 20, decision Level 2a uses the LH level as a differential test. Finally, if the testosterone is less than or equal to 20 ng/nl, the status of the adrenal androgens (AA) are used to decide on the probability of an ARM vs AIPC. The assessment of the nature of the PC present is therefore made using input relating to the patient's endocrine milieu in the setting of ongoing ADT. Some of the treatment options for each possible assessment are shown. Investigational therapies that could also be employed for AIPC are not shown but were described in **Table 2** on page 5.

Figure 4.
Decision Tree To Distinguish ADPC from AIPC

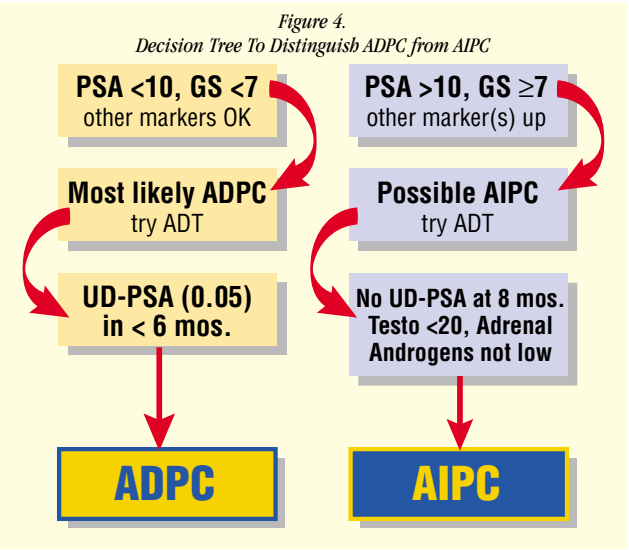


Table 3: Differential Diagnosis in the Cause of a Rising PSA in Patients on ADT and Suggested Treatment Options

PSA Rising on ADT: Differential Testing and Treatment Strategies				
Decision Making	**Laboratory Findings, Assessments & Treatment Options in the Setting of a Rising PSA on ADT**			
Level 1	**Testosterone ≤20**		**Testosterone >20**	
Level 2a			LH <1	LH >1
Level 2b	AA* decreased or low normal	AA* normal	AA normal or ↑	
Assessment	**ARM likely**	**AIPC**	**Excessive AA production**	**Inadequate LH suppression**
Treatment Options	1] Stop Anti-Androgen 2] Stop Anti-Androgen and start HDK + HC 3] Stop Anti-Androgen and start Cytadren + HC	1] HDK + HC 2] DES + coumadin 3] PC SPES + coumadin 4] ChemoRx †	Suppress AA with HDK + HC	↑ LHRH-A dose, decrease dosing interval or try different LHRH-A

***AA** = adrenal androgens DHEA-S and Androstenedione
† = Taxane regimen; Adriamycin + Cytoxan; Adriamycin + HDK; Cytoxan + HDK; Novantrone + Prednisone; Novel therapies.

Legend:
The treatment algorithm above is useful in the setting of a rising PSA in a patient on ADT(androgen deprivation therapy). The crossroads of therapeutic decision related to using the findings at Levels 1-2b to determine the most likely explanation for the rising PSA. The treatment options are not exhaustive but do list major Treatment Options based on the Assessment.

Given this discussion of AIPC and the endocrinology of PC, it is appropriate at this time to share with you the impressive characteristics of Ketoconazole as it relates to PC management.

High Dose Ketoconazole (HDK) Therapy in the Setting of AIPC

HDK is a broad-spectrum agent against PC

HDK is a broad-spectrum anti-PC agent that has testosterone lowering effects through its abilities to decrease both testicular and adrenal production of androgens by blocking various synthetic pathways.[16] These were shown in Figure 2. HDK is novel in that it also had direct cytotoxic effects on the PC cell, making it a valuable agent against AIPC.

HDK effects on the endocrine pathways

HDK acts on cytochrome P-450 dependent demethylation (an important enzyme activation pathway) and decreases conversion of lanosterol to cholesterol, thus lowering serum cholesterol. This lowering was selective for LDL cholesterol with a reduction of 38% noted without any lowering of the beneficial HDL cholesterol levels.[17] HDK blocks 17,20-lyase resulting in a decrease in serum testosterone, androstenedione, & dehydroepiandrosterone (DHEA).[18] 24-hour urinary free cortisol is reduced 25% but still remains within the range of normal.[19] Other studies indicate that HDK also blocks 17-α hydroxylase.[20]

HDK works rapidly

HDK has a rapid onset of action with a decline in serum testosterone. It starts 30 minutes after its administration and achieves a 90% reduction in serum testosterone by 48 hours[21] (see **Figure 5** on page 7).

HDK is synergistic with chemotherapy

In addition, HDK showed synergy in tissue cultures when used with the chemotherapy agents Velban and Etoposide (VP-16).[22]

HDK has direct cell-killing effects independent of its hormonal action

In addition to affecting testicular and adrenal androgen synthesis, HDK also has a direct cyto-

toxic effect on the prostate cancer cell. In two human cell lines of androgen-independent prostate cancer, PC-3 and Du-145, HDK had direct cell killing effects at serum values between 1.1 to 10.0 µg/ml; these levels are clinically attainable.[23] This is illustrated in **Figure 6**.

HDK bioavailability can be monitored by a commercial blood test

Serum Nizoral or Ketoconazole levels are commercially obtainable. HDK therapy is unique in enabling us to assess the blood level of HDK in patients on this therapy. Since there are many variables associated with absorption of HDK, a laboratory test of this nature is invaluable. Pont et al[19] and Heyns et al[24] reported on the value of serum HDK monitoring and their correlation with lowering androgen levels and clinical response. Trump et al reported a mean serum level of 28.8 µg/ml after 28 days of HDK therapy.[25]

We suggest that after a patient has been on HDK for three weeks or more, a blood Ketoconazole level be obtained at four hours after the morning dose of HDK. This test is available through Focus Technology (formerly called Microbiology Reference Laboratory), 1-800-445-4032, in Cypress, California. See the laboratory report form in **Figure 7** on page 10.

HDK increases intracellular accumulation of VP-16 (Etoposide), works to enhance cell kill with Velban® and blocks the Multi-Drug Resistance gene (MDR) when used with both Velban® and Adriamycin® (Doxorubicin)

HDK has other added benefits. Not only is it directly cytotoxic to androgen-independent PC, it also exhibits synergy with Velban® and VP-16. Rochlitz et al showed that ketoconazole increased the intracellular accumulation of VP-16 by 80%. In the same study, the sequence of VP-16 with the other agent studied (FUDR) was critical to the cytotoxicity of the combination. **VP-16 followed by FUDR was synergistic in contrast to the opposite sequence which was antagonistic.**[26] Ketoconazole also blocked recovery of multiple prostate cancer cell lines following 24-hour pulse treatment with vinblastine.[27]

In addition to this, HDK also blocks the gene that is largely responsible for the development of chemotherapy drug resistance (Multi-Drug Resistance gene). In one paper by Siegsmund et al, HDK overcame multi-drug resistance to Velban® and Adriamycin® in cell culture.[28]

We should consider the use of HDK in chemotherapy programs directed against PC and realize the importance of sequencing of agents. Recently, Ismael et al showed that dramatic improvement in the chemotherapeutic response to taxotere and gemcitabine (Gemzar®) occurred in a variety of tumors including prostate cancer when Gemzar® was given on week 1 and followed 7 days later by taxotere. If both agents were given at the same time, instead of the marked synergy seen with the above sequencing, the cytotoxic effects of taxotere were markedly diminished.[29]

HDK has significant clinical activity against PC

Published clinical trials of HDK involved studies in the pre-PSA era and in the current era of using PSA as a biomarker of disease response. In the pre-PSA era, Pont et al reported an 88% decrease or disappearance in pain in 17 *previously untreated* men receiving HDK. Two patients remained in complete remission with no manifestation of disease after 30 months of treatment.[30]

Muscato et al[31] reported on 21 patients who were considered to be hormone-refractory. The patients were treated with HDK and HC. Seven of 21, or 33%, had a greater than 90% drop in PSA with six of the seven having remissions lasting greater than 12 months (range: 14–35 or more months). The percentage of responders (30%) at one year was significantly different from other reports in the literature of over 260 patients treated with HDK. The authors attributed these excellent responses to the **detailed attention paid to the importance of maintaining an acid environment to facilitate absorption of HDK. This involves:**

- Avoiding food during HDK administration
- Avoiding acid-blocking drugs or agents
- Using acidifying agents

Attention to these factors is highly significant to the success of HDK therapy. However, patients with PC not only need to pay attention to the maintenance of proper acidity (pH) in their stomachs to enable HDK absorption, but they should have some idea of their baseline pH status prior to such therapy. Achlorhydria (the lack of stomach acid) is a common finding in an aging population and a lack of sufficient gastric acidity would be expected in the older patient population affected by PC.

(continued on page 10)

Figure 5.

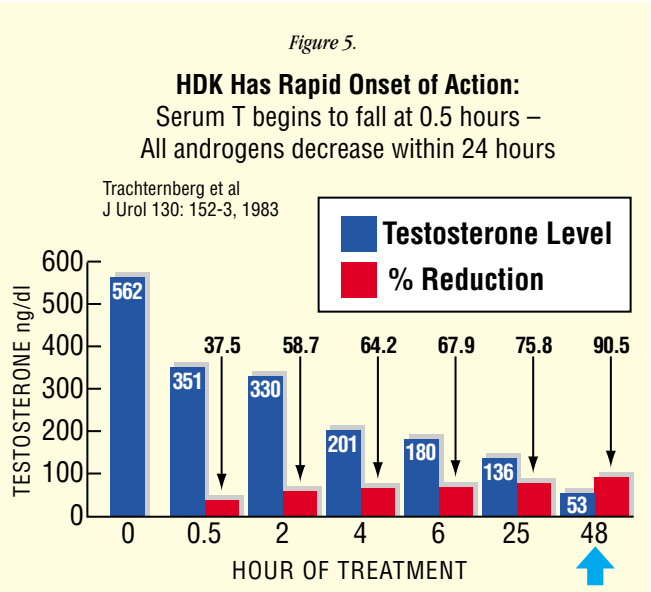
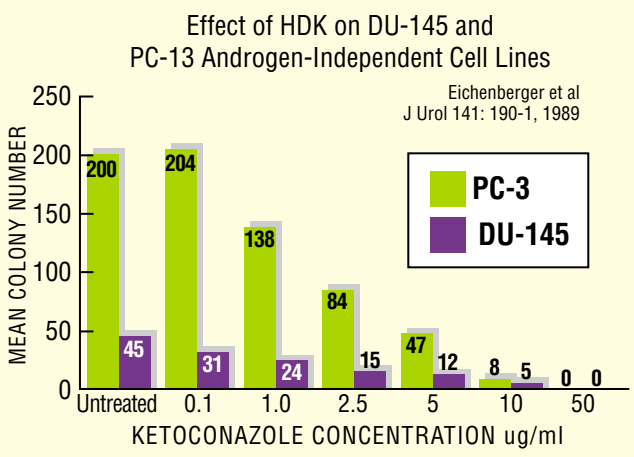


Figure 6.
Cytotoxic Effects of HDK on Two AIPC Cell Lines



The Concerns of an Oncologist

Mistakes and misinformation have long plagued the treatment of prostate cancer, resulting in needless suffering for men and their families afflicted with this disease. For many years, the absence of accurate diagnostic tools was the cause of mistreatment. Now such tools exist; and there is no reason for misdiagnosing and mistreating patients in contemporary times. I am exasperated when I receive communications from men describing treatment that falls far below acceptable standards. A good example is the e-mail I received in the last month involving a 46 year old man newly diagnosed with PC. His e-mailed information is shown in italicized text with some minor editing changes.

Patient just turning 46, Dx 11/96—large nodule noted during DRE; baseline PSA 24.4

I personally have interacted with hundreds of men with PC between the ages of 40 and 50 who were asking for guidance. Given such a sampling, it would seem to me that the use of screening PSAs, starting at age 40, would result in an earlier diagnosis of PC in such younger men resulting in a higher chance for cure. If there is a family history of prostate or breast cancer, or other high-risk factors, PSA screening should begin at age 35.

PC presenting at an earlier age may be similar to presentation of other malignancies in this fashion: the presentation may be earlier because the disease is more aggressive and has a more rapid doubling time along with a higher Gleason score. This is what I have seen, time and time again, despite published articles that insist the disease is no different in young men. The patient went on to write.

Biopsy Gleason (4, 5) in all 9 cores sampled

Diploid analysis verified by Oppenheimer

Stage $T3_cN_oM_x$

$T3_c$ means that seminal vesicle involvement was documented clinically by DRE and/or MRI and/or CT or by some other clinical examination. Nine of nine cores involved indicate significant tumor density. The DNA ploidy being normal (Diploid) is unusual for a Gleason Score (GS) of 9. As reported in the article on Gleason score in the January 2001 issue of *Insights*, **only 13% of men with GS of 9-10 will be diploid.** Perhaps a request for ploidy should be sent out again to a different lab or pathologist, (e.g. UroCor or Bostwick), just for confirmation. This does have therapeutic implications.

The patient continued…

1/97 RP done with nerve sparing margins involved at the urethra and bladder neck. Seminal vesicles involved, lymph nodes uninvolved

Doing an RP given the above findings, no matter whether the patient is 45 or 70, makes no sense to me without first **establishing baseline studies** to determine the extent of disease. In addition, you would think the patient would be presented other options; perhaps he was and we were just not told.

Let me elaborate on these suggestions. First, where are the results of the predictive algorithms? What is the result of the PAP? If the PAP is 3.0 or higher, the chances of PSA recurrence after RP are increased four-fold. What does the endorectal MRI (ideally with spectroscopy) show? Are the seminal vesicles or regional nodes involved? If so, this patient's chance of a successful RP is dramatically reduced. Where are the ProstaScint scan and the bone scan results? In a patient with a PSA of 24.4 and a Gleason score of 9, these studies should certainly be considered. I can't accept that this is a health cost issue when we subject a human being to an RP and then again to another local therapy such as RT when clearly the risk of systemic disease is overwhelmingly high.

What is the gland volume (GV)? Let's suppose the GV was 30 cubic centimeters (cc). Given the GS of 9, the GV of 30 and the bPSA of 24.4, the **calculated** tumor volume would be 16.44 cc. John McNeal, an outstanding pathologist from Stanford, states that a tumor volume that is greater than 12 cc invariably reflects systemic disease.

The PSA of 24.4 AND the GS of 9 equates to a much higher tumor volume since the PSA leak with high GS tumors is low. **Table 1** presents Gleason GRADES (half of the GS usually) and the associated amount of PSA Leak.

In the table, the Gleason Grade (GG) is weighted in the sense that if you had multiple biopsies showing various cores with differing Gleason scores, that would be taken into account in giving you an average Grade. If both the cores are (3,3), it makes no difference. The average GG would of course be 3.

Here is where the GS is very important in elaborating on the significance we give to the PSA during the initial evaluation of the patient. I have seen patients present with GSs of 9 and 10 with low levels of PSA and yet large tumor volumes.

In the case of this patient's calculated tumor volume, an RP would give him a 6% chance of cure on the assumption that the tumor volume calculations were close to reality.

The findings of positive (abnormal) margins and seminal vesicle involvement could have been predicted by the Partin and Narayan algorithms. For both nomograms, the percentage likelihood of OCD (organ confined disease), CP (capsular penetration), SV (seminal vesicle involvement) and LN (lymph node involvement), respectively, would be as follows:

Partin: 5, 37, 33, 24
Narayan 13, 66, 55, 65

Therefore, his "negative" node status would be in question. The number of nodes that were actually removed at RP should be ascertained to see if this represented a reasonable sampling.

In addition, obtaining a baseline Pyrilinks-D (Dpd) would suggest microscopic metastases to bone if the results were elevated. These are some issues of value in the counseling of patients. We can decrease the incidence of bone metastases with the use of bisphosphonates and bone supplements.

2/97 PSA rose to 1.37 at one-month post-RP and continued to rise despite EBRT radiation given from 4/97–6/97

How can we as physicians compound one bad judgment with another? Why have we not learned the basics of PC medicine? This man did not have

Table 1. PSA Leak in Relation to the Weighted Gleason Grade

Gleason Grade (Weighted)	PSA leak Rounded Off (exact)
5	1 (0.93)
4.5	1.5 (1.36)
4	2 (1.99)
3.5	3 (2.92)
3	4 (4.26)
2.5	6 (6.23)
2	10 (9.12)
1.5	15 (13.33)
1	20 (19.49)

By Stephen Strum, M.D.

OCD (organ-confined disease) at diagnosis. After the first approach with local therapy failed, the physicians treating him put him through another form of local therapy. If there were three or four more local therapies I wonder how many such therapies he would have received before the dawning of a realization that he did not have OCD.

Folks, you gotta do your homework when you are diagnosed with PC. Your involvement is critical to prevent the catastrophic outcomes associated with "fast-food" medicine. Cognitive function, logic and strategy must be encouraged if we are to improve the quantity and quality of life. Let us work together as part of our human responsibility to optimize medical care. This is a wonderful legacy for our children.

10/97 PSA 11.0

This PSA doubling time is less than six months, consistent with systemic disease (which we already knew after the first half dozen lines of this PC history).

11/97 Began 150 mg of Casodex® and 5 mg of Proscar® daily

5/98 PSA undetectable (less than 0.02)

5/99 Penile implant done

This surgery and any associated emotional and/or physical pain and suffering would have been totally unnecessary IF the focus had been more properly directed at issues of systemic disease along with the control of local disease. At most, it should have been limited to treatment with 3DCRT or IMRT after first staging the patient properly and getting his systemic treatment onboard. I still do NOT see any attention paid to risk of bone metastases and the use of agents to stabilize the bone environment and prevent the spread of disease to the bone.

9/99 PSA detectable (0.02). Slowly increased over next few months

Another area of medical deficiency involves the failure to realize that **high Gleason score lesions frequently make other proteins besides PSA and that PAP, CGA, NSE and CEA must be checked to rule out growing clones of tumor.** If these are normal, then there is no need to recheck them again and again. Perhaps once every 4-6 months if the clinical situation is not stable. Why wasn't a ProstScint scan ordered here? This is another tool that could have been employed, not just at diagnosis, but certainly when PSA progression was documented after the radical prostatectomy.

3/00 PSA 0.77

3/00 Withdrew Casodex® and Proscar® hoping for AAWR

4/00 PSA 3.71; Recheck three days later 4.71

There obviously was NOT an AAWR going on here and therefore not an Androgen Receptor Mutation (ARM). See October 2000 *Insights* and pages 4–5 of this issue for full discussions of ARM.

4/00 Began 84-day Zoladex® injections

How could docs put this patient on Zoladex® without **first restarting an anti-androgen to prevent flare or use Ketoconazole to do the same thing?** Until Abarelix® is finally approved by the FDA, this pre-treatment is essential. (Abarelix® is an LHRH ANTAGONIST (not an agonist) that does not cause testosterone surge upon initiation of therapy as does Lupron® or Zoladex.®) **Moreover, 84-day Zoladex® or 84-day Lupron® often does not last the full 84 days.** I would use a 28-day injection until the serum testosterone was documented to be below 20 ng/dl or 0.69 nM/L. After documentation of such levels, longer acting LHRH agonists could be used without jeopardizing PC control. Please read the article on flare in the May 1999 issue of *Insights*.

The **anti-androgen should be administered at least seven days prior to the LHRH agonist. This is done to prevent or diminish the effects of initiating the LHRH agonist which routinely triggers the release of LH, stimulates gonadal testosterone, and increases growth of PC with release of PSA.** The cell populations that are stimulated involve both benign and malignant prostate cells.

I use Flutamide to prevent flare since it has a SHORT half-life measured in hours (< 8 hours) as opposed to Casodex,® which has a half-life measured in days (six days). I want a short time to a steady state blood level (32 hours or four half lives with Flutamide) vs a long time (37 days or six half lives with Casodex®) if I am only going to have seven days to prevent flare. We need some scientific studies to confirm or refute these concerns about the optimal way to use such anti-androgens.

(continued on page 10)

Nine Concepts You Should Get Out of This Article

1. Prostate cancer screening should begin at age 40 if there are no high risk factors for PC. If there are, then age 35 would be appropriate.
2. Patients and physicians need to establish a discipline in assessing a patient regarding extent of disease.
3. This discipline results in a better understanding of extent of disease (Stage) and the appropriate treatment options for that particular stage.
4. You cannot cure a systemic disease with local therapy. If we bombard a patient with local therapies that are not needed, we switch the focus from systemic disease and end up spending valuable time on a medical front that is not as critical to the life of the patient as is controlling systemic or metastatic disease.
5. High Gleason score lesions don't leak out as much PSA into the blood stream. Therefore, patients having Gleason scores 8-10 may have low PSA values but still have significant PC volume. Therefore, evaluate other markers such as: PAP, CEA, CGA and NSE and consider staging studies such as the ProstaScint scan, ideally using new fusion technology combining the ProstaScint with CT and PET scans.
6. Patients at high risk should be placed on bisphosphonates such as Aredia®, Fosamax®, Actonel® or Zometa® (when FDA approved) to alter the bone environment and prevent the spread of PC to the bone.
7. Initiation of Lupron® or Zoladex® therapy should be with a 28-day injection and not the longer acting products. Some men will not achieve a castrate testosterone and maintain it smoothly throughout treatment using the longer acting LHRH agonists.
8. Flare is a real phenomenon; any patient treated with an LHRH agonist should be protected against testosterone surge and associated PSA elevation.
9. Testosterone levels are mandatory to evaluate the success of ADT (androgen deprivation therapy). Otherwise, how do you know if you have achieved a castrate testosterone?

Figure 7:
Laboratory Report for Nizoral ® or Ketoconazole (HDK) Blood Level

```
KETOCONAZOLE LEVEL: SERUM
   OR BODY FLUID LEVEL                    0.8

      Drug concentrations are expressed in ug/mL.

      INTERPRETATION:

      Normal Therapeutic Levels:

          Peak serum      1.0 - 4.0 ug/mL
          Trough serum    Not well established

   Specimens collected just before the next antibiotic
   dose represent the TROUGH levels. Those obtained
   within 15 minutes after the end of I.V. infusion or
   45 min. after an IM injection represent the PEAK
   levels.

   Note:  Any undisclosed antibiotics might affect
          the results.

'WD'  refers to site:   SBCL-LOS ANGELES (METRO)
                        7600 TYRONE AVENUE
                        VAN NUYS CA 91405
                        (818) 989-2520
                        PETER S. NOCE M.D., Ph.D.
'XE'  refers to site:   MICROBIOLOGY REFERENCE LABORATORY
                        5785 CORPORATE AVENUE
                        CYPRESS CA 90630
                        800-445-0185
                        RICHARD K PORSCHEN, PHD
                             >> END OF REPORT <<
```

We can bypass this problem or, at the very least, minimize its effect by enhancing absorption of HDK with a concurrent administration with diet Coke or diet Pepsi, grapefruit juice, or chewable Vitamin C. **One study showed a 65% enhanced absorption of Ketoconazole when given with Coca-Cola®.** The same study showed a dramatic reduction of Ketoconazole to 17% of baseline when gastric acidity was reduced by drugs such as Prilosec®. In the presence of Prilosec®, Coca-Cola® was said to enhance Ketoconazole absorption but not to the degree seen when sufficient acid was present in the stomach without Prilosec® onboard.[32] **This is another example of why we need to maximally utilize the drugs currently available to patients by understanding basic principles of pharmacologic absorption and bioavailability.**

Small et al[33] reported the results of HDK + HC therapy in men having progressive disease after previous treatment with combination hormone blockade and anti-androgen withdrawal. Of 48 evaluable patients, 30 (62%) had a PSA decrease of greater than 50% for at least eight weeks while 23 of these (48%) had a decrease in PSA of greater than 80% also for at least eight weeks. The PSA dropped to 0.3 ng/ml or less in 5 patients for 3+, 3.5+, 4.5+, 7+ and 10+ months. These patients had pre-HDK PSA values of 22, 47.4,15, 488 and 6.7 ng/ml respectively. **For all**

(continued at right)

The Concerns of an Oncologist continued from page 9

5/00-9/01 PSA bounced around never going below 0.70 and never above 0.90

2/01 PSA 0.78

5/01 PSA 1.44

I do not see a serum testosterone level. **Without measuring a serum testosterone, we have no idea if ADT (androgen deprivation therapy) has optimally been delivered.** Again, other markers such as PAP, NSE, etc. and the other staging tools should be done. **The use of prophylactic bisphosphonates after a baseline Pyrilinks-D (Dpd) and qCT bone density is also critical to a better outcome.**

This man's care could have been far better. His clinical course to date is what I would have expected 10 years ago, not today. I feel ashamed at being a physician hearing his story. The following recommendations were made to him:

1. Have Baseline Pyrilinks-D (Dpd) and quantitative CT (qCT) bone density evaluations, and get started on Aredia® 30 mg with increase to 60 after two weeks and then to 90 mg every two weeks. At the same time, add Life Extension'sBone Assure or Iprical®. Iprical® contains calcium, magnesium, zinc, boron and Ipriflavone. A total of 1000 mg of calcium taken mostly between dinner and bedtime is advisable.
2. Get a serum testosterone and all the other markers mentioned above.
3. Begin Ketoconazole with hydrocortisone per our paper in the current issue of ***Insights***. Use hydrocortisone with it. Note the need for monthly chemistry panels and also to use the blood levels of ketoconazole (Nizoral® is its brand name) four hours after the morning dose to see if you are absorbing it sufficiently.
4. Consider adding chemotherapy to the above, pending the full workup.
5. While the first few things are being done, also consider a ProstaScint-PET fusion study. You could get a ProstaScint combined with a CT or PET or all three (called a Fusion CT-ProstaScint or a Fusion CT-PET-ProstaScint, respectively) at a center of excellence such as University Hospitals of Cleveland with Dr. Bruce Sodee (216-844-8142) or the University of Illinois with Dr. Michael Blend (312-996-3970). Sodee & Blend have unusual talents and are doing this imaging prodcedure.
6. Stay on the Zoladex® or Lupron® but at shorter intervals i.e. 28 days as noted above.

Once hormones have stopped keeping the PSA from rising and bone mets have developed, does Quality of Life decrease rapidly?

I would believe that the actions detailed above would prevent this patient from having problems and lead him to a major improvement in the quantity and quality of his life. We have to go way beyond the bell-shaped curve in his care at this point. In my opinion, if we can find a team of healthcare professionals to work with him at a more advanced level of care, we can fulfill the philosophy PCRI shares with Ralph Waldo Emerson.

"To leave the world a bit better,
whether by a healthy child,
a garden patch
or a redeemed social condition;
To know even one life has
breathed easier because you lived.
That is to have succeeded."

patients, the median PSA decrease was 79% (range 0–99%). The median duration of response was 3.5 months with 23 of the 48 patients having ongoing responses (range 3.2+ months to 12.3+ months). No difference was seen in response rates despite the presence or absence of an anti-androgen withdrawal response (AAWR). The median survival of all patients had not been reached at 6+ months.

Scholz and Strum evaluated 80 patients with AIPC in a retrospective evaluation to determine factors that would predict for a longer response to HDK (**Table 4,** below). Duration of response was measured from start of HDK to PSA progression or last follow-up. PSA progression was defined as the first of two consecutive PSA levels 50% above the lowest PSA achieved i.e. the PSA nadir (PSAN), or above baseline PSA (bPSA) if no nadir occurred. At low PSA levels, progression was defined as a PSA rise of 2 ng/ml over PSAN or bPSA if no PSAN occurred (this definition was used whenever a 50% PSA rise would have been less than 2 ng/dl). The average bPSA was 108 (median 21). Sixty-one patients progressed. Eleven are still responding after a mean of 24 months (range 3-66). Four responders stopped HDK after two, 12, 17 and 25 months for visual problems, azotemia or lassitude (two patients). Two died of unrelated causes after three and 30 months. Two were lost to follow-up, both after 3 months. The average treatment time was 15 months (eight months median).

The median duration of response (in months) for PSA declines of >75%, 51-75% and less than 50% were: 17.5, 6.5 and 3, respectively. **Baseline PSA ≤10.0 was the only significant pre-therapy predictor of response duration in multivariate analysis (p<0.003). The PSA nadir on HDK was the best predictor of response duration overall (p< 0.0002).**

Table 4. Factors Relating to Response to HDK + HC Treatment[34]

	# of Patients	Median # months response
Baseline PSA ≤ 10	**25**	**25**
Baseline PSA > 10	55	4
PSA nadir < 0.2	**14**	**40**
PSA nadir 0.2 – 4.0	20	18
PSA nadir 4.1 – 10	11	8
PSA nadir > 10	35	4

The authors concluded that prolonged response with HDK is far more common in AIPC patients if treatment is initiated before the bPSA rises above 10 and if the PSA nadir on HDK falls to below 0.2.[34]

HDK and the AAWR

In a recent ASCO abstract, Small et al reported on 20 patients receiving simultaneous AAWR and HDK + HC. Of these, 14 (70%) had a greater than 70% drop in PSA and 10 had a greater than 80% drop in PSA. Six of 10 responders are still responding at 2+ to 9+ months.[35]

In the *Journal of Clinical Oncology*, Sella et al reported on the combination of HDK + Adriamycin® (Doxorubicin). The Adriamycin® was given as a 24-hour infusion once a week at a dose of 20 mg/m^2. Administration of Adriamycin® by infusion over 48–72 hours or more markedly lessens the cardiac toxicity of this treatment and allows for longer therapy (assuming response). A PSA decline greater than 50% was seen in 21 of the 39 men (55%) of the patients studied. **The median survival in those 21 patients was 17.3+ months with a median survival of 20 months if the PSA decrease was greater than 80%.**[36] These authors also reported an interesting skin toxicity secondary to HDK administration that they termed the "sticky skin" syndrome. This occurred in 29% of patients treated. We have seen this side effect as well in patients who have not received concomitant Adriamycin.® Hence, this is most likely an adverse effect of HDK or the HDK + HC combination.

HDK: Biologic Flare and Use in Oncologic Emergencies

In a small study of four patients, an initial surge of serum testosterone was seen after starting HDK. Wasil et al found mild increases of 11.5% and 17.7% in serum testosterone over baseline in two of the four patients.[37] However, in an earlier study by Trachtenberg, 13 patients were studied with levels of serum testosterone, androstenedione, DHEA, progesterone, and LH obtained at hours 0, 4, 8, 24, 32 and at weeks 1, 4 and 12. No patient exhibited an increase in serum testosterone after starting HDK. Levels of androstenedione, and DHEA decreased while levels of progesterone and LH rose by 4 weeks.[38] **Because of the reflex rise in LH during HDK therapy,**[39-41] **it is advisable to continue the LHRH agonist therapy or institute the use of agents like DES or PC SPES to inhibit LH and thus prevent testicular stimulation and possible over-ride of the effects of HDK.**

Initial increases in serum testosterone may be of greater magnitude and cause clinical symptoms (***clinical*** flare) such as bone pain, spinal cord compression or compression of the ureters after ***initiation*** of therapy with an LHRH agonist if such patients are not pretreated with HDK, DES or an anti-androgen.[42,43] The relatively small increase in testosterone reported by Wasil et al in two patients noted above does not deter us from using HDK to prevent flare or from the use of HDK in emergency situations that require rapid drops in serum testosterone in which surgical castration (orchiectomy) is not performed. However, we do need additional studies to clarify (1) whether or not there is any degree of testosterone increase when using HDK as sole therapy and (2) if any increase in testosterone translates to biologic evidence of an increasing tumor mass as evidenced by a rising PSA. The latter is the critical end-point that must be evaluated in all studies involving flare. A new agent that also inhibits testosterone dramatically while having no associated testosterone surge or PSA increase is Abarelix® or Plenaxis.®[44] This drug should be approved by the FDA sometime in 2001.

HDK Administration Guidelines

As stated earlier, an acid pH in the stomach is needed to enhance absorption. We advise patients to take HDK with Diet Coca-Cola® or Diet Pepsi® or other acid beverages like grapefruit juice. Chewable Vitamin C at 1000 mg should also work. Studies on bioavailability of HDK before and after ingesting such agents are needed. We suggest that HDK **not** be taken with food since food buffers the acid. H-2 blockers (Zantac®, Tagamet®, Pepcid®, Axid®) decrease absorption by 75%. Proton-pump inhibitors (Prilosec®, Prevacid®, Nexium®) reduce acid even more than the H-2 blockers and should be avoided. Antacids and Carafate also interfere with HDK bioavailability. **Monitoring the serum Nizoral® level will reveal if a therapeutic level of HDK has been achieved. We consider this a must in the optimal usage of HDK.**

Our starting dose of HDK is a 200 mg tablet every eight hours for the first week and then 400 mg (two tablets) every eight hours thereafter. In regard to hydrocortisone (HC), we recommend a

(continued on page 12)

20 mg dose with breakfast and an additional 20 mg with dinner. HC is used not only to compensate for the 25% reduction in urinary cortisol and consequent protection against adrenal insufficiency but also to block a compensatory rise in adrenocorticotrophic hormone (ACTH) that occurs with adrenal cortical suppression resulting from HDK administration.[45] If there are symptoms that suggest hydrocortisone excess, such as ankle edema or worsening diabetes, then we would suggest a decrease in dose to 20 mg with breakfast and 10 mg with dinner, or possibly 10 mg with breakfast and 10 mg with dinner. If HDK is discontinued, then HC is tapered off over 2 weeks and not stopped abruptly.

HDK affects the metabolism of many drugs

Drugs used therapeutically in the human body are metabolized by enzyme systems. One of the most important is the cytochrome P450 enzyme system that is involved in thousands of degradation pathways. This P450 pathway and its isoenzymes (e.g. CYP3A4), are involved in the metabolism of androgens from the parent compound cholesterol. **HDK blocks the P450 cytochrome pathway in a highly efficient manner; this property of HDK is one of the main reasons for the utility of this agent in PC.** Figure 2 showed some of these pathways. HDK inhibits cholesterol synthesis by a dose-dependent inhibition of 14 α-demethylase. HDK inhibits adrenal androgens via inhibition of α17,20 lyase as well as α20,22 lyase, the cholesterol side-chain cleavage enzyme and 17-α hydroxylase. HDK inhibits cortex-derived steroids (corticosteroids) via 21 hydroxylase, 11β hydroxylase and 18 hydroxylase enzymes. In gonads, HDK inhibits aromatase that converts testosterone to estradiol and androstenedione to estrone.[46] The critical issue with HDK is whether this profound effect on the P450 system will **enhance** "other" drug activity by preventing degradation into weaker metabolites or will **diminish** drug activity by preventing metabolism to more active break-down products. Since other chemotherapy agents are also affected by P450 enzymes and also directly affect P450 enzymes, this distinction becomes critical in our proper utilization of any therapeutic substance. As you will see in **Table 5**, **HDK appears to prevent the metabolic degradation of many compounds into weaker agents and therefore is a potentiating agent and not a weakening agent in most, but not all instances. Table 6** shows additional drugs that interfere with HDK absorption by reducing stomach acidity.

Table 5. HDK Drug Interactions, Precautions, & Side-Effects

DRUG	GENERIC	HDK SIDE-EFFECT OR WARNINGS!!!
Anti-histamine Class		
Hismanal	Astemizole	HDK enhances activity: possible serious heart toxicity
Seldane	Terfenadine	Same
Claritin	Loratadine	HDK increases Claritin levels by > 250%
Anti-diabetic agents		
Diabinese	Chlorpropamide	possible severe hypoglycemic effect
Glucotrol	Glipizide	possible severe hypoglycemic effect
DiaBeta	Glyburide	possible severe hypoglycemic effect
Glynase	Glyburide	possible severe hypoglycemic effect
Micronase	Glyburide	possible severe hypoglycemic effect
Glucophage	Metformin	possible severe hypoglycemic effect
Orinase	Tolbutamide	possible severe hypoglycemic effect
Miscellaneous agents		
Propulcid	Cisapride	HDK enhances activity; possible serious heart effects
Sandimmune	Cyclosporine	HDK increases blood levels; dose reductions of Sandimmune may be needed
Digoxin	Lanoxin	HDK increases blood levels
Dilantin	Phenytoin	HDK enhances blood levels; obtain Dilantin blood level
Halcion	Triazolam	HDK seriously increases blood levels
Versed	Midazolam	HDK seriously increases blood levels
Warfarin	Coumadin	HDK increases coumadin effect
Rimactane	Rifampin	HDK increases blood levels
Isoniazid	Rifamate	reduces blood levels of HDK
Medrol	Methylprednisolone	reduces blood levels of HDK

HDK should not be taken with alcohol. This may result in flushing, rash, peripheral edema, nausea and headache.

Side-Effects of HDK

The side-effects of HDK are related to gastric irritation leading to nausea and anorexia in at least 15% of patients.[47] The use of hydrocortisone appears to have diminished the frequency of this side-effect. Liver function abnormalities are usually mild to moderate. Elevations of SGOT and SGPT are the most common manifestations of altered liver function. This is usually not severe enough to warrant discontinuation. **Monthly chemistry panels that include these liver enzymes as well as bilirubin and alkaline phosphatase are mandated. The preventive use of anti-oxidants that are specific for liver (hepatic) cell protection such as silymarin, alpha lipoic acid and selenium would be reasonable to use in patients receiving HDK or any potentially hepatotoxic agent.**[48] There would be no reports of serious toxicities from HDK or from anti-androgens such as Flutamide or Casodex® if routine serum chemistries were part of the follow-up of men receiving such agents. **This is a critical part of the supportive care of the PC patient that is too often overlooked.**

Future applications for HDK or analogs include clinical trials which could compare an LHRH agonist + HDK vs an LHRH agonist + anti-androgen therapy. Consideration for analogs of Ketoconazole should be entertained. Analogs with a longer half life allowing for once-a-day dosage and with no requirements for an acid pH would significantly increase the therapeutic index beyond that of HDK.[49-54] Grigoryev et al have synthesized new agents that inhibit the key enzyme 17-α-hydroxylase/C(17,20)-lyase (see Figure 2). These agents appear to be more potent than HDK by a factor of 40-80 fold, have the ability to block testicular and adrenal androgens, and have inherent anti-androgen activity. Human clinical trials involving such agents would be very exciting and should be encouraged. This work was done by members of the Department of Pharmacology and Experimental Therapeutics at the University of Maryland, School of Medicine.[55]

(continued next column)

Table 6. Other drugs that decrease stomach acidity and lower HDK's absorption:

Artane	Cogentin	Levsinex	Transderm scopolamine
Atrovent	Cystospaz	Librax	Urised
Beelith	Ditropan	Lomotil	
Bellergal	Donnatal	Pro-banthine	
Bentyl	Levsin	Robinul	

Cost of HDK (Nizoral®)

Nizoral® tablets cost approximately $2.00 per 200 mg tablet. At six tablets a day, this is a reasonable cost for an anti-tumor therapy. Hydrocortisone 20 mg tablets are available as generic brands. Patients having access to pharmacies in Mexico can purchase Nizoral® 200 mg tablets for as little as 52 cents per tablet. We have checked blood levels using this Mexican formulation and were delighted to see blood excellent levels that were well within the therapeutic range. If Nizoral® is purchased in this fashion, it is mandatory that blood levels of Nizoral® confirm adequate absorption. One Internet site that may be of value in this respect is **http://www.overseasrx.net/index.htm.** The U.S. Congress has recently approved legislation allowing for the purchase of drugs from foreign countries.

Conclusions

HDK is one of the most active agents used in the treatment of PC and has an incredibly broad spectrum of pharmacologic activity. In addition, it has the potential to be synergistic with chemotherapy compounds and/or block the enzymatic degradation of multiple anti-cancer agents. HDK blood level monitoring is an excellent tool to evaluate absorption and hence bioavailability of this anti-cancer agent. These unique properties are of great value in the therapy of prostate cancer. Unfortunately, this agent has never been approved by the FDA for the treatment of PC. Many physicians are unaware of the efficacy of HDK or are afraid of its toxicity based on exaggerations of HDK's effect on the liver. Certainly, HDK should be considered for active therapy of PC and be evaluated in well-designed trials that take advantage of our better understanding of the pharmacology of anti-neoplastic agents. While this is being done, clinical trials exploring structurally similar agents that can be given less often, or that might have better bioavailability without issues of gastric acidity, should be undertaken.

HDK + HC is one of the most active regimens in the therapy of PC. ✣

References

1. Huggins C, Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1:293-297, 1941.
2. Huggins C, Hodges CV: Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 43:209-223, 1941.
3. 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.
4. Strum SB, McDermed JE, Scholz MC, et al: Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. Br J Urol 79:933-41, 1997.
5. Strum S, 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 157:232A 1997.
6. Strum, SB: The Androgen Deprivation Syndrome. Insights 2:8-9, 1999.
7. Wilding G, Chen M, Gelmann EP: Aberrant response in vitro of hormone-responsive prostate cancer cells to antiandrogens. Prostate 14:103-15, 1989.
8. Wolf DA, Schulz P, Fittler F: Synthetic androgens suppress the transformed phenotype in the human prostate carcinoma cell line LNCaP. Br J Cancer 64:47-53, 1991.
9. Schuurmans AL, Bolt J, Veldscholte J, et al: Stimulatory effects of antiandrogens on LNCaP human prostate tumor cell growth, EGF-receptor level and acid phosphatase secretion. J Steroid Biochem Mol Biol 37:849-53,1990.
10. Dupont A, Gomez JL, Cusan L, et al: Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 150:908-13, 1993.
11. Scher HI, Kelly WK: Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. J Clin Oncol 11:1566-72, 1993.
12. Herrada J, Hossan B, Amato R, et al: Adrenal androgens predict for early progression to flutamide withdrawal in patients (pts) with androgen independent prostate carcinoma (AIPCa). Proc Annu Meet Am Soc Clin Oncol 13:A734 1994.
13. Herrada J, Dieringer P, Logothetis CJ: Characterization of patients with androgen-independent prostatic carcinoma whose serum prostate specific antigen decreased following flutamide withdrawal. J Urol 155:620-3, 1996. Comment in: J Urol 158:552,1997.
14. Sartor O, Cooper M, Weinberger M, et al: Surprising activity of flutamide withdrawal, when combined with aminoglutethimide in treatment of "hormone refractory" prostate cancer. JNCI 86:222-227, 1994.
15. Hyytinen ER, Thalmann GN, Zhau HE, et al: Genetic changes associated with the acquisition of androgen-independent growth, tumorigenicity and metastatic potential in a prostate cancer model. Br J Cancer 75:190-5,1997.
16. Pont A, Williams PL, Azhar S, et al: Ketoconazole blocks testosterone synthesis. Arch Intern Med 142:2137-40, 1982.
17. Kraemer FB, Pont A: Inhibition of cholesterol synthesis by ketoconazole. Am J Med 80:616-22, 1986.
18. De Coster R, Caers I, Coene M-C, et al: Effects of high dose ketoconazole therapy on the main plasma testicular and adrenal steroids in previously untreated prostatic cancer patients. Clinical Endocrinology 24:657-664, 1986.
19. Pont A, Graybill JR, Craven PC, et al: High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med 144:2150-3, 1984.
20. De Coster R, Mahler C, Denis L, et al: Effects of high-dose ketoconazole and dexamethasone on ACTH-stimulated adrenal steroidogenesis in orchiectomized prostatic cancer patients. Acta Endocrinol 115:265-71, 1987.
21. Trachtenberg J, Halpern N, Pont A: Ketoconazole: a novel and rapid treatment for advanced prostatic cancer. J Urol 130:152-3, 1983.
22. Eichenberger T, Trachtenberg J, Chronis P, et al: Synergistic effect of ketoconazole and antineoplastic agents in hormone-independent prostatic cancer cells. Clin Invest Med 12:363-6, 1989.
23. Eichenberger T, Trachtenberg J, Toor P, et al: Ketoconazole: a possible direct cytotoxic effect on prostate carcinoma cells. J Urol 141:190-191,1989.
24. Heyns W, Drochmans A, van der Schueren E, et al: Endocrine effects of high-dose ketoconazole therapy in advanced prostatic cancer. Acta Endocrinol 110:276-83, 1985.
25. Trump DL, Havlin KH, Messing EM, et al: High-dose ketoconazole in advanced hormone-refractory prostate cancer: endocrinologic and clinical effects. J Clin Oncol 7:1093-8, 1989.
26. Rochlitz CF, Russi MB, Damon LE, et al: Cytotoxicity and effect of ketoconazole on VP-16 action and cellular uptake in malignant cells. Clin Res 35:168A, 1987.
27. Blagosklonny MV, Dixon SC, Figg WD: Efficacy of microtubule-active drugs followed by ketoconazole in human metastatic prostate cancer cell lines. J Urol 163:1022-6, 2000.
28. Siegsmund MJ, Cardanrelli C, Aksentijevich I, et al: Ketoconazole effectively reverses multi-drug resistance in highly resistant KB cells. J Urol 151:485-491, 1994.
29. Ishmael DR, Hamilton SA, Launey-Rodolf RM, et al: Phase VII trial of sequential docetaxel and gemcitabine--a new schedule based on preclinial testing with the BOT-2 human breast cancer cell line. Proc Amer Soc Clin Oncol 20:119a, 2001.
30. Pont A: Long-term experience with high dose ketoconazole therapy in patients with stage D2 prostatic carcinoma. J Urol 137:902-904,1987.
31. Muscato JJ, Ahmann TA, Johnson KM, et al: Optimal dosing of ketoconazole (Keto) and hydrocortisone (HC) leads to long responses in hormone refractory prostate cancer. Proc Amer Soc Clin Onco 13:229, 1994.
32. Chin T, Loeb M, Fong IW: Ketoconazole "goes better with Coke." Mycology Observer 12:5, 1994.
33. Small EJ, Baron AD, Fippin L, et al: Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. J Urol 157:1204-1207, 1997.
34. Scholz M, Strum S, Mittelman P: High-dose ketoconazole and hydrocortisone (Keto) for hormone refractory prostate cancer (HRPC). Proc Amer Soc Clin Oncol 19:370a, 2000.
35. Small EJ, Baron A & Apodaca D: Simultaneous anti-androgen withdrawal(AAWD) and treatment with ketoconazole and hydrocortisone in patients with advanced "hormone refractory" prostate cancer. Proc Am Soc Clin Oncol 16:13a, 1997.
36. Sella A, Kilbourn R, Amato R, et al: Phase II study of ketoconazole combined with weekly doxorubicin in patients with androgen-independent prostate cancer. JCO 12:683-688,1994.
37. Wasil T, Kreis W, Budman D et al: Rapid fall in serum testosterone levels with oral ketoconazole. Proc Am Soc Clin Oncol 16:347a, 1997.
38. Trachtenberg J: Ketoconazole therapy in advanced prostatic cancer. J Urol 132:61-64, 1984.
39. Veldhuis JD, Zwart AD, Iranmanesh A: Neuroendocrine mechanisms by which selective Leydig cell castration unleashes increased pulsatile LH release. Am J Physiol 272:R464-74, 1997.
40. Tapazoglou E, Subramanian MG, Al-Sarraf M, et al: High-dose ketoconazole therapy in patients with metastatic prostate cancer. Am J Clin Oncol 9:369-75,1986.
41. Glass AR: Ketoconazole-induced stimulation of gonadotropin output in men: basis for a potential test of gonadotropin reserve. J Clin Endocrinol Metab 63:1121-5, 1986.
42. Ohuchi H, Noguchi K, Kinoshita Y, et al: Inhibition of disease flare with diethylstilbestrol diphosphate and chlormadinone acetate administration for two weeks prior to slow-releasing leuprolide acetate in prostatic cancer patients. Hinyokika Kiyo 46:531-6, 2000.
43. Lacoste D, St-Arnaud R, Caron S, et al: The rise in testicular androgens during the first days of treatment with an LHRH agonist in the dog can be blocked by aminoglutethimide or ketoconazole. J Steroid Biochem 31:963-70, 1988.
44. Tomera K, Gleason D, Gittelman M, et al: The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: initial results of endocrinological and biochemical efficacies in patients with prostate cancer. J Urol 165:1585-9, 2001.
45. Lamberts SW, Uitterlinden P, de Jong FH: Rat prostatic weight regression in reaction to ketoconazole, cyproterone acetate and RU 23908 as adjuncts to a depot formulation of gonadotropin-releasing hormone analogue. Cancer Res 48:6063-8, 1988.
46. Miossec P, Archambeaud-Mouveroux F, Teissier MP: [Inhibition of steroidogenesis by ketoconazole. Therapeutic uses]. [Article in French] Ann Endocrinol 58:494-502, 1997.
47. Small EJ, Baron A, Bok R: Simultaneous antiandrogen withdrawal and treatment with ketoconazole and hydrocortisone in patients with advanced prostate carcinoma. Cancer 80:1755-9, 1997.
48. Berkson BM: A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin and selenium: three case histories. Med Klin 94:84-9, 1999.
49. Li J, Li Y, Son C, et al: 4-pregnene-3-one-20 beta-carboxaldehyde: a potent inhibitor of 17 alpha-hydroxylase/c17,20-lyase and of 5 alpha-reductase. J Steroid Biochem Mol Biol 42:313-20, 1992.
50. Rowlands MG, Barrie SE, Chan F, et al: Esters of 3-pyridylacetic acid that combine potent inhibition of 17 alpha-hydroxylase/C17,20-lyase (cytochrome P45017 alpha) with resistance to esterase hydrolysis. J Med Chem 38:4191-7, 1995.
51. Barrie SE, Potter GA, Goddard PM, et al: Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase).J Steroid Biochem Mol Biol 50:267-73, 1994.
52. Sergejew T, Hartmann RW: Pyridyl substituted benzocycloalkenes: new inhibitors of 17 alpha-hydroxylase/17,20-lyase (P450 17 alpha). J Enzym Inhib 8:113-22, 1994 .
53. Boccardo F, Cannata D, Guarneri D, et al: R75251 in prostate cancer patients in progression after first-line hormonal treatment. Tumori 80:276-9, 1994.
54. Wachall BG, Hector M, Zhuang Y, et al: Imidazole substituted biphenyls: a new class of highly potent and in vivo active inhibitors of P450 17 as potential therapeutics for treatment of prostate cancer. Bioorg Med Chem 7:1913-24, 1999.
55. Grigoryev DN, Long BJ, Nnane IP, et al: Effects of new 17alpha-hydroxylase/α(17,20)-lyase inhibitors on LNCaP prostate cancer cell growth in vitro and in vivo. Br J Cancer 81:622-30, 1999.

HONOR ROLL OF DONORS April 01 – June 30, 2001

$5,000 to $19,999

Robert and Martha Atherton Foundation
Botaniclab International Medical Research, Inc
California Community Foundation
Diagnostic Products Corporation

$2,000 to $4,999

Healing Touch Oncology
Mr. Gilberto Huber

$1,000 to $1,999

Mr. Bernard S. Appleton
Mr. Arthur L. Fagan, Jr.
J.C. Foltz
Erna and Dzago Kljajo
Lyons Lavey Nickel Swift, Inc.
Modern Assistance Programs Inc.
Mr. T's Family Foundation
Notsew Orm Sands Foundation
Mr. R. C. Quick-Croft
Mr. Jon N. Santemma

$500 to $999

Mr. Arthur W. Adams
Mr. Charles D. Agresti
Mr. and Mrs. Philip E. Arnold
Mr. and Mrs. Maherji N. Bilimoria
Mr. and Mrs. Clyde F. Czernek
Mr. Tom W. Gunby
Mr. Harry S. Meislahn
National Charity Support, Inc.
Mr. Robert C. Peace
Philip Morris Companies, Inc.
San Jose Prostate Cancer Support Group
Mr. and Mrs. Julian B. Snow
Mr. Richard W. Spaulding
Mr. Timothy W. Sullivan

$100 to $499

The Adventurers' Club
Mr. Russ Allan
Mr. David S. Allen
Mr. Peter W. Arney
Mr. Edward Balajewski
Mr. Donald H. Baldwin
Mr. William C. Ball
Mr. James M. Barrett III
Susan and Carl Benedict
Mr. Richard Berman
Mr. Michael Bevis
Mr. Jack Bivens
Carole and Frank Boucher
Friends of Breakheart Reservation
Mr. Franklin C. Brewster, Jr.
Mr. and Mrs. Joseph R. Brooks
Mr. James E. Brown, Jr.
Eloise W. Burnaford & Family
Mr. John C. Cassidy
Mr. Horace T. Caviness
Mr. Robert R. Chambers
Charitable Gift Fund
Mr. John C. Coe
Mr. James R. Cox
Mr. William J. Coyne
CTA Research
Mr. Scott Dahlberg
Mr. Scott Dally
Ms. Ione B. Dines and Dr. Charles E. Dines
Mr. Robert E. Doheny
Mr. Martin H.R. Donald
Mrs. Anne M. Drohan
Mr. and Mrs. Charles Edwards
Mr. Robert Ellis
Mr. Melvin Elward
Mr. John S. Escher
Mr. William R. Evitt
Mr. John A. Fanning
Mr. Don Fenton
Mr. Philip E. Fess
Mr. Willis Finlayson
Mr. Jack B. Fisher
Mr. Edward H. Fox
Mr. Rodney J. Fugate
Mr. William E. Garrison, Jr.
Mr. Robert J. Geary
The J. Paul Getty Trust
Mr. Konrad Goeldner
Ms. Sylvia Goldberg
George L. Graziadio, Jr.
Mr. Donald L. Greggs
Mr. Richard M. Gulbrandsen
Ms. Maryanne L. Hall
Mr. Brian K. Hamilton
Mr. D.O. O. Harton
Mr. and Mrs. Steven A. Helms
John F. Hensler, Jr.
Mr. Robert J. Herdin
Mr. Kenneth Hillderth
Mr. David Holmes
Mr. James L. Howell
Mr. Dennis Howlett
Mr. and Mrs. Jack D. Hutchison
Mr. Thomas J. Hutton
Mr. and Mrs. Franklin D. Johnson
Mr. and Mrs. Jeno F. Kalozdi
Mr. Richard A. Kauflin
Dr. Walter R. Kendall
Dennis S. Klos, Ph.D.
Mr. Michael Korek
Mr. and Mrs. Ralph H. Kotoski
Mr. and Mrs. Norbert J. Lapasinski
Jean and Bob Lawrence
Mr. Frank Levy
Mr. Olin L. Looker
Mr. Joseph P. Maguire
Ms. Sharon L. Maher
Mr. Joseph J. Mallini, Jr.
Mr. Fred R. Marburger
Mr. Leonard Morris
Mr. and Mrs. Peter L. Mullins
Mr. Myron H. Murley
Mrs. Patricia Myers
Mr. Vernon Neff
Mr. Brandi Noel
Mr. Robert E. Normandie
Havner H. Parish, Jr. M.D.
Walter and Alice Parks
Mr. Sydney Parlow
Mr. John W. Perkins
Mr. and Mrs. Joseph Peter, Jr.
Rex G. Pierce
Mr. Don Poole, Sr.
Mr. Christopher Priston
Mr. Thomas T. Putnam
Mr. Richard D. Quinn
Mr. Richard K. Reid
Richwood Farm
Mr. J.M. Robinson
Mr. Battagion Romano
Mr. Nathaniel Sack
Mr. Walter E. Sadlik
Mrs. Nora Schafer
Seamans Electric
Mr. Charles C. Seeber
Mr. Ronald F. Setina
Mr. John O. Shaline
Mr. Tom Short
Mr. Dennis C. Smith
Mr. Gregory Smith
Mr. John B. Squyres
Staff Depot, Inc.
Mr. E.A. Stafford
Mr. Stanley Stillman
Mr. Lee E. Strawbridge
Mr. Daniel L. Streimer
Mr. Clarence E. Takeuchi
Peter and Carole Taussig
Mr. David A. Taylor
Techniscribe, Inc.
Texas Urology, P.A.
Mr. Jerry Thompkins
Mr. Donald Thornton
Judy and Randy Thurman
Union Bank of California
Mr. James R. Van Sant
Mr. Edgar W. Wellbaum
Mrs. Niki Wenger
Jan Wennink
Mr. James S. Whitehead
Mr. Robert Widinski
Judge Ralph Yachnin
Mr. and Mrs. Joseph M. Youmans, Jr.
Mrs. Deborah A. Zeigler
Mr. Donald J. Zoeckler
Mrs. Judy Zoldowski

$1 to $99

Mr. John H. Abeles
Mr. Irving Abrams
AES NewEnergy, Inc.
Col. and Mrs. Charles G. Allen, USAF
Amgen Foundation
Mr. and Mrs. Terence J. Anderson
Mr. Earl E. Asbury
Mr. Clifford J. Astill
Mr. and Mrs. Gregory A. Banaszynski & Family
Bank of America
Mr. Hugh B. Barker III
Mr. George Z. Barth
Bethel Food Market
Mr. Carl Bloom
Mr. and Mrs. Bernard M. Bogdan
Mr. Richard L. Bourke
Mr. Ian Brett
Mr. Gerald O. Brown
Mr. & Mrs. Irving S. Bubes
Mr. David F. Butt
Alvaro and Martha Cadena
Mr. Jim Campione
Mr. Andrew J. Caplis
Pat and Bruce Carlson
Joseph F. Caron, ED.D., D.C.
Mr. Darrell D. Carpenter
Richard L. Chafey, ED.D.
Mr. and Mrs. James P. Christianson
Conejo Valley Friends
Mr. Howard E. Cook
Mr. R. Dale Crowell
Mr. and Mrs. William A. Crowther
Mr. and Mrs. Ismael G. Dambolena
Mr. and Mrs. Eugene De Bor
Mrs. Christine H. Deambrose
Mr. Arthur DeCastro
Mr. Maynard Deutschman
Mr. Ralph Diamond
Mr. William F. Dixson
Ms. Eleanor V. Eggers
Mr. Ed Eliot
ERC Communications
Mr. Jack M. Ercanbrack
Mr. and Mrs. Duane H. Ericson
Mr. Steve Ermenkov
Eron & Associates
Mrs. June A. Estlin
Mr. Norman L. Evans
Mr. Howard C. Fagley
Mr. David Farber
Mr. Arthur A. Fink
Mariehamn Finland
Fish & Neave
Mr. and Mrs. George L. Florman
Mr. Leon Friedman
Mr. Edward B. Fry
Mr. and Mrs. Todd J. Galucki
Mr. Jack E. Gardner
Mr. C.R. Gibson
Mr. and Mrs. L.H. Gindler
Ms. Alyce Mae Goodman
David and Sandra Goulet
Mr. Donald L. Graham
Mr. and Mrs. James C. Greer
Mr. Byron L. Gundlach
Mr. Ray Halpenny
Charles J. Hansen, Jr.
Mr. Walter S. Hanson
Mr. and Mrs. David R. Haun
Mr. Jerry A. Herfield
Mr. John F. Hessman
Mr. and Mrs. William D. Hightower
Mr. Jerry Hill
Mr. John E. Hillman
Mr. Jim Hockings

HONOR ROLL OF DONORS April 01 – June 30, 2001

$1 to $99 (cont'd)

Mr. Ronald F. Huber
Mr. John R. Hulme
Mr. Jerome Jacobson
Lucie and Manuel Joffe
Ms. Barb Johnson
Mr. Red Johnson
Mr. and Mrs. Eldon B. Johnson
Ms. Mary Ellen Johnson-Hermann
Mr. Richard B. Jones
Mr. Lewis E. Kaplan
Mr. Marvin D. Karp
Mr. and Mrs. Charles E. Kaufman
Mrs. Eva M. Keller
Mr. Charles H. Kerrigan
Mr. Roy T. Kniebbe
Mr. Charles E. Kohlhase
Mr. Anton E. Kruzic
Edwin A. Kuhn
Mr. Albert Kushner
Mr. Melvin E. Lapides
Mr. James A. Laughrey
Mr. Dan Lee
Wayne G. Legreve, Sr.
Mr. Frederick W. Link
Mr. Harry Lipka
Mr. Edwin R. Loder
Mr. Richard G. Longaker
Mr. Gary A. Loyd
Mr. Hans P. Luley
Mrs. Virginia B. Luthans
Benjamin L. Mackall III
Janice and Dominic Manarite
Norman and Jewel Martens
Oneida L. Mason and Lin Mason
Mr. Vincent J. Mazza
Mr. William J. McCoppin
Mr. Alexander A. McKenzie
Earl Graham McQuaide, Jr.
Mr. and Mrs. George Montgomery
Mr. Jeffrey A. Moore
Mr. and Mrs. Alan J. Napoliello
Mr. Robert B. Naramore
Mr. and Mrs. James F. Nasuti
Mr. and Mrs. Dean L. Nelson
Mr. Ronald J. Nelson
Mr. Richard D. Nielsen
Mr. Robert C. Nolte
Jackie Odom and Kevin Odom
Mr. Donald G. Olander
Mr. Robert C. Oliver
Mr. Gregory Oveson
Mr. Leo B. Packard
Mr. and Mrs. Fred Pearlstein
Mr. Arnold Pernick
Mr. Charles E. Pettingall
Mr. George A. Pfeifer
Mr. and Mrs. John F. Phillips
Mr. Paul Pink
Karen and Edward Poort
Mr. Andrew K. Porth
Mr. Jerry M. Quint
Mr. Jerry Rainey
Mr. Peter W. Rapelje
Mr. Derald E. Rasmussen
Mr. James J. Regan
Mr. Robert C. Reis
Mr. Leonard M. Renick
Mr. and Mrs. Edward G. Renzetti
Mr. Victor W. Richard
Mr. Milton E. Ricketts
Mr. Jim Riskowski
Dr. Eugene W. Rochester, Jr.
Mr. Reed L. Roger
Mr. Arnold J. Rosenthal
Mr. John T. Ross
Mrs. Mary R. Rowell
Mr. Maurice E. Salsbury
Mr. Joseph S. Sardegna
Mrs. Ellen G. Sathe
Mr. George Satterfield
Mr. Robert W. Schepf
Mr. Donald J. Schickler
Ms. Jane Ann Schildmeyer
Mr. Edward Schlaffer
Mr. Terrence M. Schumacher
Mr. Joseph Scialfa
Mr. Anthony H. Scofield
Mr. Robert Shapiro
Mr. and Mrs. Michael A. Sheets
Mr. Larry Simonsen
Mr. Larry Sloan
Mr. Gordon O. Smith
Mr. Horace Smith
Peggy and R.B. Smith
Mr. William B. Smith, Jr.
Edward F. Steinfeldt, M.D.
Mr. Joseph A. Strada
Mr. Robert N. Summers
Ms. Nancy L. Swanson
Mr. George J. Symes
Mr. and Mrs. Walter Szarko
Mrs. Lisa Tarantino
Mr. Conway Taylor
Dolores and Raymond Todtenhagen
Werner and Irmagard Traub
Mr. Mark P. Troseth
Mr. Robert C. Unetic
Mr. and Ms. James P. Waldenfels
Mr. Raymond M. Walsh
Mr. David M. Warren
Mr. William L. Warrick
Dr. Richard J. Wassersug
Mr. J.M. Wells, Jr.
Mr. and Mrs. Bob Whitney
Mr. Thomas A. Willson
Mr. David Winkler
Elise and Leo Wolcott
Mr. William Zmeko

"The goal of the PCRI is to end the threat of prostate cancer to any man's life and quality of life."

We are grateful to the many people who share our goals and are helping us to achieve them.

You can support the Prostate Cancer Research Institute (PCRI) in several ways:

- A direct donation of cash (check or credit card), stock or real estate
- Memorial and "Gift in Honor" Contributions: Honoring someone you care about with a memorial or commemorative gift
- Planned Giving: Naming the PCRI in your will or as beneficiary of a life insurance policy

Direct Donation

Your tax-deductible gift in the form of cash, stocks or real estate should be made payable to the Prostate Cancer Research Institute and sent to:

Prostate Cancer Research Institute
5777 W. Century Blvd., Suite 885
Los Angeles, CA 90045
Federal Tax ID Number: 95-4617875

Credit card donations can be made online at **www.prostate-cancer.org.**

Donation of Property

The PCRI accepts property donations from interested donors throughout the U.S. Those who wish to donate cars (in Southern California only), boats, jewelry, art, real estate or other property should call toll-free **1-800-203-2940**. Your donation is tax-deductible, and there is free towing for donated cars anywhere in Southern California. A free appraisal service is available.

"Gift in Honor" and Memorial Contributions

A gift to the Prostate Cancer Research Institute can be a special way to give tribute. These gifts are a gratifying way for individuals, organizations, businesses and groups to honor someone while supporting the Prostate Cancer Research Institute's mission to prevent and cure prostate cancer and to improve the lives of all men affected by the disease.

With each **"gift in honor"** contribution received, a letter is sent to the appropriate person named – please include the name and address of the person you would like to be notified of your contribution. The amount given is never indicated in the letter. The donor, however, will receive an acknowledgment letter. A "gift in honor" is a special way to recognize a friend or loved one's birthday, anniversary or other important event while also benefiting the Foundation.

A **memorial contribution** is a particularly meaningful way to remember deceased friends and loved ones while helping the Institute expand its important programs.

You can send your memorial or "gift in honor" of contributions to:

Prostate Cancer Research Institute
Attention: Memorials
5777 W. Century Blvd., Suite 885
Los Angeles, CA 90045

Planned Giving Opportunities

For information on Planned Giving Opportunities, or how to put PCRI in your will, please contact Brian Gauthier, (310) 419-8292, by fax: (310) 419-8248 or by e-mail at: **foundation@danielfreeman.org.**

The Prostate Cancer Research Institute is a non-profit corporation, exempt from federal income taxes under section 501(c)(3) of the Internal Revenue Code. It has been classified as an organization that is not a private foundation as defined in section 509(a) of the Code, and qualifies for a maximum charitable contribution by individual donors.

Meetings at the Web

We promised you web-based meetings and now we are delivering on that promise. Starting in August, we will begin to present full seminar sessions over the Internet to you whether you're a single patient or physician or a member of an entire support group in a local assembly hall – wherever you are in the world.

Presentations and documents can be shown in an image size to accommodate different size displays, so that an attendee with a laptop, an attendee using a 17" desktop monitor, or an entire group in a conference room will see the image fill their screens with no degradation in image quality or clarity. Presentations, including PowerPoint slides or other documents can be readily seen with just a 56K modem.

Dr. Strum will present three sessions to PC support groups in the Midwest in August. And you will be able to see and hear these sessions because they will be brought to you at your computer via the PCRI web site **www.prostate-cancer.org.**

The three sessions are:

- **Is There a Correct Way to Treat Prostate Cancer?** (2 hours)
- **PSA Recurrence After Initial Treatment** (1 hour, 15 minutes)
- **Your Bones and Prostate Cancer** (1 hour, 40 minutes)

As you can see from these subjects, these will be important sessions presenting the latest information on PC and its treatment. There will be a subscription cost for this service to defray the Internet charges to PCRI. To subscribe to a session, simply access the PCRI website and follow the cues displayed there.

This is a breakthrough in PCRI's goal to serve doctors, patients, and families worldwide. With this capability, PCRI will be able to disseminate crucial PC information when and where it is needed throughout each year. Unlimited by travel time and the costs of air or car travel, hotels, and restaurants, Web-based meetings will greatly extend our reach and increase our effectiveness for education and research. Be part of this evolving paradigm of patient empowerment. Take advantage of this new technology of the new millennium and stay current in the fight against prostate cancer. ✣

✣ ✣ ✣ Other Upcoming Events ✣ ✣ ✣

"Throw Cancer a Curve" • September 12, 2001

A Fundraiser for California and National Prostate Cancer Coalitions (CPCC and NPCC).

Come see the **Los Angeles Dodgers & San Diego Padres** on September 12 in San Diego!

Private Cocktail Reception 5:00–7:00 pm with special guest **Hall of Famer Dave Winfield**, followed by the baseball game at 7:05 pm.

Tickets are $500 and $1000, which include the party, raffle tickets for collector items, and premium grade seats.

For information call Merel Nissenberg at **(858) 459-0631** or e-mail at: **mgrey@ucsd.edu.**

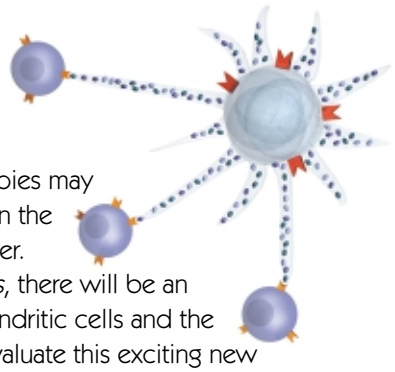
Second International Conference on Angiogenesis
October 6–9, 2001 • Paris, France

Program: http://www.esh.org/pgangio.html

Registration: http://www.esh.org/inangio.html

Comment: This is a highly technical program for physicians specially focused on angiogenesis or for patients who are particularly interested in advances in this area. Angiogenesis relates to the process of blood vessel development as it relates to tumor growth. If we can inhibit angiogenesis, we can prevent the growth of tumors.

Investigational Drug News Upcoming



Dendritic cell-based therapies may soon play a valuable role in the treatment of prostate cancer. In the next issue of *Insights*, there will be an overview of the role of dendritic cells and the research taking place to evaluate this exciting new technology in prostate cancer treatment. Want to learn more about the Phase 3 clinical trial currently enrolling patients?

Call 1-866-4-PROSTATE or visit **www.dendreon.com**

PCRInsights

is published by:

Prostate Cancer Research Institute
5777 W. Century Blvd., Suite 885
Los Angeles, CA 90045
Web site: www.prostate-cancer.org

BULK RATE
U.S. POSTAGE
PAID
LIFE EXTENSION FOUNDATION