

# PROSTATE CANCER COMMUNICATION

PROSTATE CANCER COMMUNICATION NEWSLETTER • VOLUME 19, NUMBER 2 • JUNE 2003

FOUNDER: LLOYD J. NEY, SR. – FOUNDED 1984

**President and Chairperson:**

Janet E. Ney

**Board of Directors:**

Edwin Kuberski  
Treasurer

Newton Dilley  
Helen Mellema  
Peter Noor Jr.  
Anthony Staicer  
Richard H. Profit Jr.

**Honorary Board Members:**

Donald F. Mellema  
Russell Osbun  
Frank Perry

**Medical Advisory Board:**

Richard Ablin, M.P.  
V. Elayne Arterbery, M.D.  
Robert A. Badalament, M.D.  
Duke K. Bahn, M.D.  
E. Roy Berger, M.D.  
Michael J. Dattoli, M.D.  
Fernand Labrie, M.D.  
Fred Lee Sr. M.D.  
Robert Leibowitz, M.D.  
Mark Moyad, M.P.H.  
Charles E. Myers Jr. M.D.  
Gary M. Onik, M.D.  
Haakon Ragde, M.D.  
Donald Trump, M.D.  
Steven J. Tucker, M.D.  
Ronald E. Wheeler, M.D.

**DIETARY SUPPLEMENTS/ALTERNATIVE MEDICINES FOR  
ERECTILE DYSFUNCTION. DO ANY OF THESE THINGS  
REALLY WORK?**

By Mark A. Moyad, M.P.H

Erectile dysfunction or E.D. is the persistent inability to achieve or maintain an erection necessary for sexual performance. It has numerous etiologies and is estimated to affect as many as 30 million men in the U.S. alone. This condition is associated with increasing age and a variety of other factors. Currently, numerous treatments exist for this condition, but which dietary supplements (if any) may help men with E.D.???

**Quality control-Does it exist?**

Currently supplements sold in the U.S. are not subject to specific standards or quality control testing. This is unlike the situation that exists currently in other parts of the world, including many European countries. For example, a saw palmetto product sold in France needs to demonstrate some quality control, but many of these so called "supplements" sold in the U.S. are actually prescription drugs in these other countries. In the U.S., a supplement label may report a specific amount or dosage of a compound, but the actual pills or capsules may contain significantly higher, lower or no amounts of this supplement. Therefore, without any adequate independent and universal randomized quality control studies, it is difficult to access the actual quality and quantity of any dietary supplement sold in the U.S. For example, a recent study of ginseng supplements (discussed for E.D. later in this article) found that out of 25 preparations examined, a concentration variability between products of 15 to 200 fold in the active ingredients existed. Another study of 16 different dehydroepiandrosterone (DHEA) dietary supplements (also discussed later in this article) found the actual range of content to be 0 to 150% of what was advertised on the label. Additionally, a journalist from the Newark Star Ledger purchased 10 over the counter (OTC) products, which claimed to enhance sexual function. The newspaper submitted these supplements to an independent laboratory for chemical analysis and found that 9 out of the 10 products contained at least one or more compounds that could not be detected or were detected in minimal quantities compared to what was actually advertised on the label

**Let's Conquer Cancer in OUR Lifetime**

The tenth product had less than 50% of the claimed amount of its only compound (yohimbine). Again, without any official and enforced standards the consumer must be reminded to expect the unexpected when purchasing some dietary supplement products.

### **Alternative procedures/therapies for E.D.-acupuncture**

The National Institutes of Health (NIH) issued a statement on acupuncture in November 1997, after a two and one-half day conference organized by the NIH Office of Alternative Medicine and the NIH Office of Medical Applications of Research. This conference gathered numerous experts in the fields of acupuncture, drug abuse, epidemiology and biostatistics, health policy, pain, physical medicine, physiology, primary care, and psychiatry. According to this NIH statement, the overall effectiveness of acupuncture can be appropriately considered because of the variety of clinical studies that have already been completed in this discipline. However, this report also mentioned that quality research of acupuncture versus placebo is severely limited. The vast majority of published data is on traditional needle acupuncture, and has not adequately involved other types of

additional and apparent synergistic acupuncture stimuli techniques, such as electro-stimulation (electroacupuncture), laser (laser acupuncture), external pressure (acupressure), or heat (moxibustion). Most of the research on acupuncture has centered on its use for acute and chronic pain relief or the management of pain. The consensus statement mentioned that the evidence does demonstrate needle acupuncture's effectiveness for relief from postoperative pain and chemotherapy-induced nausea.

The patient seeking acupuncture treatment and the health care professional recommending it should keep in mind a number of things before undergoing this type of therapy. There are virtually no sound randomized studies to date that have been published which demonstrate the possible role of this treatment in patients experiencing side effects such as E.D. from cancer treatment, or that experience E.D. from other etiologies. In general, side effects from this procedure itself have been minimal in the hands of a well-trained practitioner. In addition, patients have to assess whether or not adequate training in this discipline was completed by the practitioner before this type of treatment is initiated. Many states do not re-

#### **CANCER COMMUNICATION**

##### **Published Quarterly by: PAACT, Inc.**

Patient Advocates for Advanced Cancer Treatments  
1143 Parmelee NW  
Grand Rapids, MI 49504

**Director....Richard Profit**  
**Editor ...Richard Profit & Staff**  
**Webmaster...Art Schlefstein**

**Postmaster: Send address changes to:**

**Prostate Cancer Communication**

**P.O. Box 141695**  
**Grand Rapids, MI 49514**

**Phone: 616/453-1477**

**Fax: 616/453-1846**

**E-Mail: [paact@paactusa.org](mailto:paact@paactusa.org)**

**PAACT Web Page: <http://www.paactusa.org>**

**Newsletter: <http://www.paactusa.org>**

##### **Editor:**

Articles authored by other than the editor may not fully reflect the views of the corporation but are printed with the understanding that the patient has the right to make his own interpretation of the efficacy of the information provided.

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

#### **INDEX**

##### **Page**

1. Dietary Supplements/Alternative Medicines For Erectile Dysfunction. Do Any Of These Things Really Work? (*Mark A. Moyad, M.P.H.*)
6. Gynecomastia (*Charles E. Myers, Jr. M.D.*)
9. Minimally Invasive Treatment Options-Part II (*Duke K. Bahn, M.D.*)
12. Understanding Drug Development Processes: A Critical Issue When Evaluating The Efficacy Of Novel Therapeutic Compounds (*Oliver Sartor, M.D.*)
14. Notice From Mediplan Health Of Canada
15. Proven Therapy For The Palliative Treatment of Advanced Prostate Cancer ELIGARD® (leuprolide acetate for injectable suspension)
18. LAC-PAACT Update (*Gregory H. Teufel, Esq.*)
18. Media Release
20. Acknowledgements
23. Financial Summary Report

quire additional training in acupuncture to perform this procedure. A M.D. or D.O. degree is the only requirement, regardless of the clinical background of the practitioner.

A preliminary and recent pilot study of the effect of acupuncture in the treatment of E.D. was completed. A total of 10 patients (median age 41.8 years) were included in this crossover trial. Group 1 (n=7) received 10 weeks of acupuncture (two sessions per week) that specifically addressed E.D., while Group 2 (placebo group, n=3) was treated for 4 weeks with general acupuncture that did not specifically address E.D. The patients in group 2 were crossed over into group 1 in the case of placebo failure. It should be noted that before acupuncture treatment began all of these patients responded to 0.01 mg of Alprostadil (drug treatment) with a full and rigid erection. Overall, 7 patients reported "good results" with improvements noted in their sexual performance, and 6 patients did not require additional treatment and were self-defined as successfully cured. In 3 cases, acupuncture was not beneficial and these patients were successfully treated with 50 mg of oral sildenafil (Viagra). Again, this was a small and preliminary study that requires a larger randomized trial to validate these results. Currently, it is not possible to determine the true effectiveness of acupuncture for any type of E.D. However, these results were interesting and perhaps it is possible that acupuncture may have added benefits beyond a placebo response. However, again the possibility of a large placebo response with this procedure cannot be ignored. For example, acupuncture has recently gained some attention for the relief of hot flashes from prostate cancer treatment, but this study did not utilize a placebo group. Other supplements that have reported a dramatic benefit for hot flash reductions have been a disappointment when large placebo controlled trials were completed. In fact, a recent study of soy pills found that 36% of patients receiving placebo and only 24% receiving soy pills reported a hot flash reduction frequency of 50%. At the end of the study, more patients actually preferred the placebo compared to the soy pill for hot flash reductions. Results with vitamin E for hot flashes showed a somewhat similar story and fate. In addition, a recent preliminary randomized trial of acupuncture for lower urinary tract symptoms and prostate-specific antigen (PSA) reduction found that it was not superior to watchful waiting over the 12 week study period.

### **Amino Acid Supplements (precursors to nitric oxide)-L-arginine.**

Nitric oxide is most likely the primary compound that helps with penile erection. L-arginine is an amino acid that is a precursor to nitric oxide. Theoretically it would make some sense that adequate amounts of this precursor has the potential to improve E.D. in some men. It is important to mention that fairly large sources of dietary L-arginine exist in nature. For example, legumes, whole grains, and a variety of nuts may be a source of more than several grams of L-arginine per day, when consumed in moderate amounts.

Three small pilot clinical studies of L-arginine versus placebo have recently been conducted. The first study was a placebo-controlled clinical trial that used 2800 mg/day of L-arginine for 2 weeks, and reported that 40% of patients had improvement in their erections. The actual responders were younger and had better vascular function by hemodynamic investigation compared to the non-responders. The second pilot trial included 1500 mg/day of this amino acid versus placebo for 2 weeks. L-arginine given in these amounts did not demonstrate a benefit over placebo. In the third trial, patients (n=50) were given 5 grams/day of L-arginine or placebo for 6 weeks for E.D. Approximately 31% of the men in the L-arginine group reported a benefit versus 12% in the placebo group. The difference may not seem dramatic, but it was statistically significant. The primary side effect was a decrease in blood pressure of approximately 10% in the L-arginine group. Therefore, it seems possible that men willing to take large daily dosages of L-arginine may benefit. Further studies are needed in this area, but currently L-arginine seems to be one of several possible exceptions to the rule that dietary supplements provide little to no benefit currently for men with E.D.

### **Anabolic steroid supplements-Androstenedione (Andro) and Dehydroepiandrosterone (DHEA)**

The first question that needs to be addressed about these potentially dangerous supplements is why they are even available for purchase in the U.S. by individuals of any age? The answer to this question is a result of two rulings (federal laws) passed by congress in the past decade. The Dietary Supplement and Health Education Act was passed by congress in 1994. This act allows almost anything to become a dietary supplement as long as the manufacturer does

not make any health claims on the label of the supplement container. More specific to these supplements is the approval of the 1990 Anabolic Steroid Control Act. This act requires different criteria to be met for the removal of any anabolic type dietary supplement. These criteria include:

- A) Molecular structure related to testosterone
- B) Pharmacology related to testosterone
- C) Cannot be an estrogen, progestin, or corticosteroid
- D) The substance cannot promote muscle growth

Androstenedione and/or DHEA has a molecular structure and pharmacology similar to testosterone, and it is not an estrogen, progestin, or corticosteroid. The reason that these supplements are still available for purchase is because they have not yet clearly demonstrated muscle growth in past clinical trials utilizing smaller dosages. It is highly plausible that they promote this kind of growth when higher dosages are used but these trials have not been initiated. Therefore, under current federal law, companies are still permitted to sell these types of supplements. Basically, I would not recommend the use of either of these supplements without talking to your doctor and if you qualify, I would get a prescription from the doctor and not purchase these supplements over the counter.

**Circulatory enhancement supplements-Ginkgo biloba**  
There is some clinical evidence that demonstrates Ginkgo extracts can improve circulatory function; however, most of these studies have focused on its use in patients with dementia. It has been approved in Germany for this condition. No studies to date have been published on the use of Ginkgo for E.D. following localized prostate cancer treatment, but there have been other relevant studies.

In one study without a placebo group, 60 patients who did not respond to papaverine (drug therapy) injections (50 mg or less) were treated with 60 mg of an extract of Ginkgo biloba for 12 to 18 months. Ultrasound techniques detected an improved blood supply after 6 to 8 weeks in some patients, and after 6 months 50% of these patients regained erectile function, and in a smaller number papaverine injections were later successful. The authors concluded the study by mentioning that a randomized controlled trial was going to be initiated, and the results of their follow-up study were presented in 1998. This pla-

cebo-controlled double-blind randomized study used 240 mg daily of an extract of Ginkgo for 24 weeks versus placebo for E.D. from circulation problems. No significant difference was observed between the two groups, which emphasizes the ongoing need for these kinds of quality studies before recommendations can be made for patients. Although, Ginkgo still needs to be adequately tested alone or in combination with other drugs for patients who experience E.D. from prostate cancer treatment before a definitive conclusion can be made, it is important to emphasize that there is no current data to espouse its use for patients with this specific condition. In addition, several studies have suggested that Ginkgo may increase bleeding time and could be dangerous when combined with other blood thinners.

### **Drug copycats for E.D.-yohimbine**

This drug is extracted from the bark of West African yohim trees. It is a prescription drug that you can get from your doctor. Since this compound may cause blood vessel dilation and increased blood flow some researchers began to test its ability to improve erectile function. A meta-analysis of 7 randomized trials of over 400 men with E.D. from a variety of etiologies determined that yohimbine (15-43 mg/day) was better compared to placebo for all forms of E.D. combined, but since the approval of Viagra, this drug has little benefit for most individuals. The most common side effects are palpitations, fine tremor, elevation of diastolic blood pressure, anxiety, and nausea.

Yohimbe is also an over the counter supplement, but it is questionable whether or not they have any value or contain any of the active ingredient found in yohimbine. In 1995, the FDA found little or no yohimbine in the majority (11 of 18) of yohimbe supplements brands that were tested. None of the other seven brands contained amounts of yohimbine that were near to what has been used in past clinical trials. Thus, there seems no justification at this time for purchasing any supplement that claims to contain yohimbine. If a patient seems interested in this compound, the potential for using the prescription drug should be discussed.

### **Zinc**

Zinc is found in high concentrations in seminal fluid and in certain accessory sites such as the prostate. Zinc supplements have been touted as a potential

immune system booster and as a treatment for BPH and E.D. by numerous alternative medicine books, but the evidence to support these claims are lacking. For example, zinc supplements in higher quantities have the potential to induce immune-suppression and the few dietary studies of BPH have actually found an increased risk of this condition with greater quantities of zinc.

There is little evidence that zinc can impact sexual function for patients with E.D. Several older studies have tested zinc supplements on sexual function, but these only included men on kidney dialysis. Some investigations demonstrated a benefit and in the other studies no benefits were observed. Patients on dialysis may have a zinc deficiency with hyperprolactinemia and adding supplemental zinc may correct this deficiency and produce higher levels of male hormone. However, these studies cannot provide an adequate assessment of what role, if any, zinc has in general E.D. treatment.

#### **Other dietary supplements-Korean Red Ginseng**

Numerous other dietary supplements have limited clinical data, so it is difficult to evaluate their effect on E.D. at this time. A possible recent exception is Korean red ginseng (panax ginseng) that has been preliminarily investigated against HIV, and as a potential agent to reduce severe menopausal symptoms in post-menopausal women with some limited positive results. In addition, Ginseng can dramatically lower sugar levels in the blood (this can be very dangerous) so be careful-talk to your doctor before trying this supplement. Two clinical trials of Korean red ginseng have demonstrated some encouraging results. The older trial (published in 1995) utilized 90 patients with E.D. that were divided into 3 groups of 30 and were given Korean red ginseng, placebo, or a drug (trazodone). There were no significant changes in the frequency of intercourse, premature ejaculation, and morning erections after treatment in any group. The group taking Korean red ginseng experienced significant positive changes in a number of other erectile parameters such as: penile rigidity, penile girth, libido, and patient satisfaction compared to the other groups. Approximately 60% of the patients taking ginseng experienced a therapeutic benefit versus 30% for the placebo and drug groups. No complete remissions of erectile dysfunction, only partial responses were recorded. In addition, penile hemodynamic changes did not occur after the ad-

ministration of this specific type of ginseng. Therefore, it is difficult to conclude currently whether or not ginseng had a noticeable objective effect without further clinical trials. Other investigations are needed, but it's apparent ability to increase nitric oxide levels or reduce fatigue, insomnia, and/or depression demonstrates that a compound(s) from this herb may have some promise for some types of E.D. or sexual dysfunction. During the time of this articles preparation, a new preliminary trial of Korean red ginseng was published. A total of 45 patients with E.D. were enrolled in this placebo-controlled crossover study that consisted of 8 weeks of treatment, a 2 week washout period, and another 8 weeks of treatment. The dose of ginseng was 900 mg three times daily. The mean patient age was 54 years and organic comorbidities (hypertension, diabetes, dyslipidemia) were found in over 50% of the patients. Men excluded from the study included those with a history of radical prostatectomy, or neurological problems, or hormonal and chemotherapy treatment, or Peyronie's disease, or substance abuse and drugs that interfere with sexual function. This small trial offered some support for ginseng for some subjective symptoms of E.D. and an enhanced penile tip rigidity, but this supplement still needs a larger placebo trial to determine its overall role for E.D. treatment.

#### **Lifestyle Modifications**

No discussion on dietary supplements, prescribed agents, or any intervention for E.D. seems sufficient without at least mentioning lifestyle factors that may influence the risk of E.D. Approximately half of the men with chronic diabetes have E.D. Chronic renal failure has also been associated with decreased erectile function and libido. Men with heart disease, peripheral vascular disease, and stroke also have a greater risk of E.D. Other factors associated with E.D. include smoking, hypertension, obesity, high cholesterol, lack of physical activity, and chronic alcoholism. Studies seem to suggest that healthy lifestyle modifications initiated early in life may have the largest impact on reducing the risk of E.D. in elderly individuals.

Whether or not lifestyle changes initiated later in life have any effect on reducing E.D. itself remains to be determined from future studies. However, regardless of this answer it is more than obvious that implementing healthy changes at any age can affect the quality and quantity of an individual's life.

## Conclusions

Numerous supplements seem to be promoted by alternative medicine books, the Internet, and even media sources. These supplements not only lack adequate clinical trials, but also in some cases may actually provide the opposite result of what is touted in advertising. Other supplements may be enjoying the overall benefits of the placebo response. Since a general placebo response of 25% has been observed in past clinical trials with effective agents, it is not difficult to understand why some supplements continue to enjoy financial success despite the limited research espousing their actual use. In other words, if 1 to 2 out of 4 individuals who try a dietary supplement actually get some benefit for their E.D., the market for these supplements will still remain large. On a larger scale this means that of 100,000 men who try a supplement, approximately 25,000-50,000 will claim success with any particular agent in question. The challenge for clinicians is to adequately explain the placebo response and the need for good research before any intervention, especially when supplements can be advocated for general use. There seems little doubt that some supplements may in the future have some active ingredient or impact those with certain types of E.D. in a favorable manner. However, deciding which supplements have merit and which do not can only be determined from randomized clinical trials.

## GYNECOMASTIA

By Charles E. Myers, Jr. M.D.

American Institute for Diseases of the Prostate

Earlsville, VA

Phone: 434/964-0212

Gynecomastia or breast enlargement is a common side effect of prostate cancer treatment, especially hormonal therapy. While some men do not seem to be disturbed by this complication, others are devastated. Fortunately, we have a wide range of approaches to this problem. For example, there are now multiple ways to accomplish androgen withdrawal, some of which are much more likely than others to cause breast enlargement. Additionally, we have a growing list of drugs that are able to reduce or eliminate breast enlargement without compromising cancer control.

### What causes breast enlargement?

During puberty in women, blood levels of estradiol, the major female sex hormone, surge. This increase in estradiol causes a similar increase in blood levels of a hormone called prolactin. It is the combined effect of both of these hormones that cause normal female breast development. Later, during pregnancy, further increase in both estradiol and prolactin cause further breast development and prepare this organ for milk production. In fact prolactin gets its name for its role in promoting lactation. As you may be aware, some women either do not want to breast feed or may have medical conditions that make this not prudent. Drugs have been developed that shut off the production of prolactin in this situation.

When men go through puberty, testosterone levels surge. The presence of prolactin appears to play an important role promoting some of the actions of testosterone. For example, prostate tissue does not develop normally nor does it respond to testosterone normally during puberty. However, a portion of this testosterone is converted to estradiol and in some men sufficient estradiol and prolactin are present to cause significant breast tenderness and enlargement. This can even lead to secretion of fluid into the developing breast ducts, causing cysts to form. This process is usually self-limiting and disappears after age 18 when testosterone and estrogen levels attain their adult levels. A similar situation appears to develop in men who try to enhance their athletic performance through the use of anabolic steroids. One important point is that the glandular tissue in male gynecomastia produces PSA and will stain positive for this protein. This might lead to the erroneous diagnosis of prostate cancer metastatic to the breast.

Gynecomastia can also be caused by certain drugs that cause an increase in circulating prolactin levels. This is a relatively common problem with spironolactone, cimetidine, verapamil and cancer chemotherapy, especially alkylating agents and estramustine. Less commonly, this can also be caused by diazepam, tricyclic antidepressants, neuroleptics, calcium channel blockers, captopril, digitalis glycosides, and omeprazole. Some of these drugs are known to increase prolactin levels and others, like the anticancer drug estramustine, act like estradiol.

### Breast Enlargement During Hormonal Therapy

Any factor that increases estradiol, DES or other estrogenic compounds within the brain will cause a

drop in the release of leutinizing hormone (LH). Since LH is the major factor stimulating the production of testosterone from the testes, administration of estradiol and other estrogenic compounds cause a drop in testosterone production, causing a medical castration. This was one of the earliest forms of hormonal therapy used in the treatment of prostate cancer and remains attractive, largely because it is quite inexpensive compared to other forms of medical castration. As you might expect, this form of hormonal therapy typically causes an increase in circulating prolactin and the combined impact of estrogen and prolactin causes gynecomastia.

Administration of antiandrogens, such as Eulexin or Casodex, cause a steady increase in the release of LH, leading to steady increases in circulating testosterone. A portion of this testosterone is converted to estradiol, leading to increased prolactin and gynecomastia. This problem does not develop immediately, but appears gradually over the course of several months.

Administration of Lupron or Zoladex leads to an initial surge in LH followed by a dramatic decline. The fall in LH results in a parallel decline in testosterone. As testosterone levels decline, the conversion of this androgen to estradiol also declines. Prolactin levels also do not increase. Because breast tissue does not see elevated estradiol or prolactin, breast enlargement is not nearly as common as it is after the administration of either estrogenic drugs or antiandrogens. However, some patients do experience mild breast enlargement on Lupron or Zoladex and this presumably is the result of an elevation of estrogen level to that of testosterone.

In patients on intermittent hormonal therapy based on Lupron or Zoladex, the discontinuation of these drugs leads to a gradual increase in testosterone and estradiol that duplicates many of the aspects of puberty. As with puberty, this can lead to gynecomastia. Thus, ironically, treatment with Lupron or Zoladex often leads to greater gynecomastia when treatment is stopped rather than when it is continued.

There are a growing number of herbal preparations used to treat prostate cancer, most of which have phytoestrogens sufficiently powerful to cause gynecomastia. The best characterized of these was PC-SPEs. Unfortunately, it was also shown to be con-

taminated by variable amounts of DES, which may well have contributed to the gynecomastia seen with this preparation. While it seems likely that these herbal preparations also induced prolactin production, I can find no evidence that this has ever been studied.

Estramustine or Emcyt acts as a strong estrogenic stimulus and causes some degree of gynecomastia in nearly all men who are treated with it for any length of time. Emcyt is a component of many of the most active chemotherapy combinations used to treat hormone-refractory prostate cancer because it markedly enhances the activity of a wide range of other chemotherapy drugs.

### **Treatment options for gynecomastia**

Prophylactic breast radiation This approach has been widely used and is quite effective at reducing the severity of gynecomastia in men with prostate cancer. Unfortunately, this approach does not completely block gynecomastia and many men still get some enlargement. Additionally, the radiation dose is sufficient to cause breast inflammation and tenderness.

My major concern about this approach is that the combination of estrogenic stimulation and breast radiation is a well-established mechanism for inducing breast cancer. To judge from the information published on female breast cancer, breast cancers are likely to appear after a latent period of ten or more years. Prior to 1990, it was quite unusual for men on hormonal therapy to survive ten or more years on treatment. However, it is now quite common for men on hormonal therapy to survive and be in remission longer than ten years after initiation of hormonal therapy. The best-documented situation would be men with lymph node metastases who were subjected to radical prostatectomy followed by adjuvant hormonal therapy. In the series from the Mayo clinic, men with a single lymph node metastases would have close to a 90% chance of being in remission at 10 years. As a result, I now think we need to consider the risk of male breast cancer in patients who have received breast radiation therapy followed by estrogen-based hormonal therapy.

Reduction Mammoplasty Surgical removal of the excess breast tissue is another well-established treatment option. Several techniques have been developed. One common approach is to make an incision

around the areola, remove the excess skin, fat and glandular tissue and then reattach the skin to the areola. After surgery, the scar tissue that forms around the nipple will initially be quite prominent, but by the end of the first year or so, the scar will shrink to the point of near invisibility. Liposuction is another approach that has adherents. The few cases I have seen have been left with lumpy breasts – fine for clothes, but not great on the beach.

**Tamoxifen** Tamoxifen is a drug that blocks the action of estrogen on the breast. It is widely used to treat breast cancer in women. There is rather extensive literature documenting its ability to treat breast enlargement in men, including one randomized controlled clinical trial. The doses used have ranged between 10 to 30 mg a day. In women, this drug is a known carcinogen, causing an increase in the risk of liver and uterine cancers. This issue has not been examined in men.

**Raloxifene** Raloxifene is another drug, like tamoxifen, that blocks the action of estrogen in the breast. Unlike tamoxifen, it does not appear to be a carcinogen. However, it is not FDA approved for the treatment of breast cancer, but rather as a method for treating osteoporosis. While there are no clinical trials testing its ability to prevent male breast enlargement, there are a number of laboratory papers that document the ability of raloxifene to suppress the size of the normal prostate gland. Additionally, it has been shown to arrest the growth or kill human prostate cancer cells. Clinical trials are now in progress testing raloxifene in the treatment of human prostate cancer. I have used raloxifene to prevent osteoporosis in men who cannot tolerate Fosamax or other bisphosphonates and noted that gynecomastia is quite uncommon, suggesting a potential role for raloxifene in the prevention of gynecomastia. The standard dose range is 60-120 mg per day. The major disadvantages of this agent are that it can markedly worsen hot flashes and increase the risk of blood clots in the leg.

### **Future of Drugs that Block Estrogen Action**

Cells respond to estrogen because they have estrogen receptors. At present, we know of two forms of the estrogen receptor, the alpha and beta form. Estrogen receptor alpha is found in normal and malignant breast tissue, while estrogen receptor beta is found in prostate tissue. The alpha-receptor in the breast causes breast tissue to grow when exposed to estro-

gen. The beta form of the receptor found in the prostate gland causes growth arrest and death of prostate tissue, normal or cancerous. If one could block estrogen receptor alpha selectively, then it would be possible to block breast enlargement from estrogen while preserving the ability of estrogen-like drugs to treat prostate cancer. Another, more attractive option is to find a drug that selectively activates estrogen receptor beta: this would block the growth of prostate cancer without causing breast enlargement and would largely eliminate the need for problematic drugs like DES. The therapeutic potential of drugs able to selectively stimulate or suppress one form of the estrogen receptor has caused considerable excitement within the field of endocrinology and in the pharmaceutical industry. With raloxifene, you can get a sense of what all this is about: this drug stimulates bone formation, suppresses breast cancer and breast enlargement and may have useful activity against prostate cancer. From what I have seen published or presented by the pharmaceutical industry, it is very likely that selective estrogen receptor beta antagonists already exist and may well be in clinical testing.

**Arimidex** The major source of estrogen in men is the conversion of testosterone to estradiol by an enzyme called “aromatase.” Androstenedione is the immediate precursor to testosterone and aromatase can convert this to estrone, a weaker estrogen than estradiol. This drug is now widely used to treat metastatic breast cancer and is more effective than tamoxifen for this purpose. It is also a much safer drug that lacks the ability of tamoxifen to cause cancer and raloxifene to cause blood clots.

Arimidex has been tested in men, but not as a means of preventing breast enlargement in men with prostate cancer. In the adult male, the brain monitors circulating testosterone levels by converting the testosterone to estrogen in the brain: the higher the blood testosterone levels, the more estrogen the brain sees. If testosterone drops too low, the brain sees less estrogen and releases LH to stimulate the production of additional testosterone. Arimidex blocks the conversion of testosterone to estrogen in the brain. The brain then reacts to the low estrogen levels by increasing LH, stimulating the formation of testosterone. In aging men with low testosterone levels, Arimidex can increase the testosterone level by 20-50%. One theoretical danger of Arimidex in men is that it can also deprive the bone of the estrogen it needs to

prevent osteoporosis.

In a number of men on Zoladex or Lupron, I have found that coadministration of Arimidex has lessened breast tenderness and appeared to prevent additional breast enlargement. Men on intermittent hormonal therapy tend to develop breast tenderness and enlargement as their testosterone recovers. Arimidex also appears to be successful in this setting. However, I would point out that these are just anecdotal observations from my clinic and that there are no clinical trials that have formally tested Arimidex in the treatment or prevention of gynecomastia in these clinical settings.

### **Management Of Gynecomastia In Conjunction With Various Forms of Hormonal therapy**

#### **I. DES, Phytoestrogenic Herbal Products, Estradiol**

Breast radiation works, but is usually not completely effective, can cause the breasts to become inflamed from radiation damage and may increase the risk of breast cancer in men likely to survive greater than 10 years.

Surgical removal of breast tissue can also be effective, but is associated with the pain and other obvious risks of surgery.

Dostinex, and perhaps other prolactin inhibitors, appear to lessen the discomfort in most men and appear to reduce the amount of breast enlargement. Tamoxifen may also work, but might also block the therapeutic action of estrogen on the cancer.

Raloxifene, because of its impact on estrogen receptor beta, might lessen breast enlargement while preserving anticancer activity, but is has not yet been tested.

#### **II. Lupron, Zoladex, High dose Casodex**

While breast irradiation is commonly used, I think this is needlessly harmful. In these forms of treatment, circulating estrogen and prolactin levels are not thought to be essential for the hormonal response. Tamoxifen has a clearly established role in this situation. In practice, I find that Dostinex and/or Arimidex nearly always prevent gynecomastia and seem much less harmful than the other options. In a number of patients, I have used Raloxifene to prevent osteoporosis in men on hormonal therapy who could not tolerate bisphosphonates and found that the symptoms

of gynecomastia where reduced, but not eliminated.

### **III Emcyt-based Chemotherapy**

Breast irradiation or surgical treatment appear to be the only options. It is possible that blocking the interaction of Emcyt with the estrogen receptors might lessen its anticancer activity. We do not know if prolactin plays any role in the gynecomastia caused by this agent and prolactin inhibitors have not been tested.

### **Summary**

There are a wide range of options available to prevent, lessen or treat gynecomastia. Except for treatment with Emcyt, severe, symptomatic gynecomastia can nearly always be prevented by means that are tolerated better and more effective than breast radiation.

## **MINIMALLY INVASIVE TREATMENT OPTIONS - Part II**

Duke K. Bahn, M.D.

Medical Director, Prostate Institute of America  
& Department of Radiology  
Community Memorial Hospital  
Ventura, CA 93003  
Phone: 888/234-0004

## **BRACHYTHERAPY (Radioactive Seed Implantation)**

### **INTRODUCTION**

Brachytherapy is a form of radiation treatment in which tiny pellets containing radioactive material, such as Iodine-125 or Palladium-103, are implanted directly into the tumor-containing organ. This form of radiation therapy has long been used in other types of malignancies including cervical, breast, endometrial as well as head and neck cancers.

Brachytherapy offers the appealing concept of delivering high doses of radiation to the prostate while limiting the radiation dose to the adjacent organs.

### **HISTORY**

Brachytherapy of the prostate dates back to 1911, when Pasteau published the first case in medical literature.

Utilizing a technique rather crude by today's standards, Pasteau used a catheter to insert radium into the prostate urethra. Although the results showed

fairly good local control of the cancer, the complications were too high to be considered acceptable.

Dr. Flock an urologist in Iowa developed a technique using colloid gold, injecting it into the prostate for treatment. With the advent of high-energy linear accelerators, the interest in prostate brachytherapy waned.

Dr. Whitmore introduced an open brachytherapy method in 1972, using Iodine-125 or gold-198. Because the seeds were not always placed uniformly, the clinical results were less than satisfactory and the complication rates related to the surgical procedure were too high and unacceptable.

These early failures, to a large degree, were due to the fact that they were performed utilizing blind approaches. Imaging technologies, such as transrectal ultrasound, crucial for seed implantation, were not yet available. Some researchers tried temporary implantation with iridium-192 using an open surgical field, but they were still unable to visualize the internal structures of the gland. This technique was also burdened by the limitations of a blind approach. Precise placement of seeds is a crucial factor in the success of brachytherapy.

Without the benefit of modern day imaging techniques, accurate placement of the radioactive seeds was not attainable.

In the early 1980s, the old concept of brachytherapy was revisited. Improved imaging technologies made the procedure more feasible. The most important of these were transrectal ultrasound (TRUS) and computerized tomography (CT). These new technologies allowed a non-surgical, uniform seed distribution into the prostate through needle punctures. With recent developments in computer software, TRUS has become the most commonly used modality for seed implantation procedures. However, the results can be highly operator-dependent.

### **BRACHYTHERAPY RATIONALES**

1. Transrectal ultrasound imaging permits the radioactive seeds to be placed in a precise and predictable way.
2. Can deliver radiation to the gland at much higher doses than those achievable with external beam radiation (2X).

3. Optimal seed strength and locations are easily determined by computer based dosimetry system.
4. Short tissue penetration of radiation limits collateral damage to adjacent organs.
5. Outpatient procedure, low morbidity, and cost-effective

### **CANDIDATES FOR BRACHYTHERAPY (SEED IMPLANT)**

In determining who is a candidate for seed-implant therapy, there are several factors that must be considered.

The patient's general state of health is a very important factor in determining which form of therapy should be chosen. Since this procedure is only minimally invasive, it is better tolerated than the more aggressive surgical procedures. The age of the patient is also important for this same reason. Therefore, an older patient that requires treatment may consider brachytherapy as an option.

Accurate staging of the tumor is mandatory before considering brachytherapy. A good color Doppler Ultrasound examination with staging biopsy is key to accurate staging. Patients with early-stage, small-volume tumors are the best candidates for this procedure. Treatment with implants alone (either iodine-125 or palladium-103) is usually adequate for early stage small volume prostate cancer. For larger volume tumors, brachytherapy is usually performed in combination with additional external-beam radiation.

Younger patients with early small volume tumors may also choose brachytherapy because of the lower complication rates. This is especially true when impotency is a major consideration. Nevertheless, concerns over impotency should not allow the tumor treatment to be compromised. There are newer drug therapies that will allow impotent men to regain erections.

The treatment decision is a highly personal one that involves both medical, personal and life-style issues. The most important first step is that the patient needs to have his tumor accurately staged. Under staging (underestimating) a cancer is the most common reason for patients choosing inappropriate treatment options. This often leads to subsequent treatment failures.

## **IODINE-125 SEED IMPLANT ALONE CRITERIA**

Tumor stage: less than or equal to T2a

Gleason grade: less than or equal to 6

PSA: less than or equal to 10

If prostate volume is more than 40 cc, pre-operative Androgen Ablation (Hormone) Therapy is used (AAT) for a 3-6 month duration to downsize the prostate volume

## **PALLADIUM-103 OR IODINE-125 SEED IMPLANT WITH EXTERNAL BEAM TREATMENT CRITERIA**

Tumor Stage: T2b, or T3a

Gleason grade: equal or over 7

PSA: over 10, but less than 30

All patients get 3-6 months of Androgen Ablation Therapy

The gland volume after AAT must be less than 40 cc

## **PROCEDURES PRIOR TO SEED IMPLANT**

1. A precise prostate volume study: utilizing a dedicated transrectal ultrasound machine, this procedure is performed to create a road map for seed implantation. This is usually done 2-3 weeks before treatment. This study is transferred to a computer treatment program that determines the optimal number of seeds, needles and the distribution in the prostate in order to achieve the proper dose.

2. Routine pre-operative tests (Blood test, EKG, chest X-ray etc.) will be done a few days before the treatment. Specific instructions will be given to you regarding diet and bowel prep.

## **PROCEDURES DURING SEED IMPLANT**

1. Unless there are contraindications (preventing factors), the procedure is performed in the operating room under spinal or general anesthesia.

2. An ultrasound probe is inserted into the rectum to image the prostate. The prostate is continuously visualized during the course of the procedure.

3. Based on the planning map, an average of 60-120 seeds are placed in the prostate through a needle that is placed through the perineum (skin between the rectum and the scrotum). The ultrasound guidance provides for precise and accurate positioning of the seeds.

4. Intra-operative real time dosimetry programs identify a radiation field on the computer screen any time a seed is placed in the prostate during the procedure. If a cold spot (poor radiation field) is detected, an extra seed is placed to correct the radiation distribution.

Therefore, near perfect implantation is achieved.

5. At the end of the procedure, a catheter is temporarily inserted into the patient's bladder to assure adequate drainage of urine. The entire seed placement procedure takes about one hour.

## **PROCEDURE AFTER IMPLANT**

1. The patient is transferred to a recovery room and remains there approximately two hours with an ice bag placed at the needle entry site on the perineum. This is done to reduce local swelling. The Foley catheter is removed after the anesthesia has worn off and the patient has regained urinary control. Occasionally, the catheter may be left in overnight.

2. The patient is usually discharged that same day. However, it is strongly recommended that he not drive himself home. There are no diet restrictions. Heavy lifting and/or strenuous exercise are prohibited for approximately two weeks.

## **FOLLOW-UP SCHEDULE**

The patient is required to have a PSA test every 3 months for the 18 months after the procedure, followed by one test every 6 months for a period of five years.

Biopsies should also be performed at 24 and 60 months after the procedure, or any time the PSA level rises on two consecutive occasions.

## **RADIATION SAFETY**

Potential dangers of radiation to the family members are almost non-existent. Iodine-125 emits very low energy radiation, which is mostly contained in the region of the prostate. However, small amounts of radiation may escape from the prostate and travel a short distance. It is also possible for very small amounts of radiation to escape the body when a patient passes a radioactive pellet through the urine. For this reason, it might be prudent to avoid close contact with small children or pregnant women during the first two months following implantation.

## **CLINICAL OUTCOME AND COMPLICATIONS**

Recent data (Ragde, Cancer, July, 2000), 12 years follow-up data, shows 66% biochemical disease free rate (PSA < 0.5 ng/ml). My data, containing more advanced cancer patients than Ragde's study, also showed 67.5% biochemical disease free rate. When the PSA < 1.0 ng/ml is used as a criterion for disease free status, it was 86%. The results are very similar to

cryotherapy statistics. However, it should be noted that the patient selection process was more stringent in the seed implant group. Seed implantation therapy is only offered to a select group of patients who have small-volume, early-stage cancer.

Complication rates are generally lower in brachytherapy than with other modalities and comparable to cryotherapy.

Complications include proctitis, cystitis, incontinence and rectal bleeding. Current literature reports that significant rectal complications can occur in 5-10% of patients and urethral complications can occur in 10-14%.

It is common to experience problems with urination for a few months after seed implantation. Various degrees of impotency are also common after the procedure. The reported impotency rates are in the 20-30% range. However, there is also a correlation to the patient's age and general state of health.

As with cryotherapy, the brachytherapy procedure is highly operator-dependent. If a patient is considering brachytherapy, he should look for the following:

1. An institution that utilizes the highest quality color-Doppler ultrasound equipment.
2. Intra-operative real time dosimetry capability.
3. Physician experience of a minimum of 50 patients.

**UNDERSTANDING DRUG DEVELOPMENT  
PROCESSES: A CRITICAL ISSUE WHEN  
EVALUATING THE EFFICACY OF NOVEL  
THERAPEUTIC COMPOUNDS**

Oliver Sartor, M.D.  
Chief, Hematology/Oncology Section  
Director, Stanley S. Scott Center  
LSU Health Sciences Center  
New Orleans, LA  
Phone: 504/568-5148

Particularly with regards to human drug development, it is essential to understand that divergent types of potential data are available. Each category of data has particular strengths and weaknesses and it is important to recognize each when evaluating the activity of a potential compound. There is no substitute for mature multi-center clinical trials with end points that emphasize quality or quantity of life.

The four main categories of data that can be used to evaluate the activity of anti-cancer compounds include:

1. *in vitro* (test tube) models
2. Animal models
3. Human observational studies
4. Human interventional studies

Most anti-cancer drug testing begins with an *in vitro* model that uses cancer cells grown in a test tube. This typically involves growing a defined type of tumor without supporting cell elements such as blood vessels and supportive tissue. This has the advantage of providing a pure population of cancer cells as well as the advantage of being able to fully define drug dose response curves. Substances which might kill normal cells (as opposed to cancer cells) are not discriminated in this system. It is important to recognize that cells growing within a culture media can be perturbed by a wide variety of compounds including acids, salts, etc. that can also kill normal cells efficiently. It is also important to recognize that drugs undergo virtually no metabolism in an *in vitro* setting and issues such as protein binding (which may be problematic in the patient) are a relatively small issue *in vitro*. Drug delivery consists solely of adding a compound into the cancer cell culture media. Suffice it to say that agents that show anti-cancer activity *in vitro*, require many hurdles before successful clinical development can be achieved. Agents such as acid and salt have anti-cancer activity when tested in the test tube but obviously have no role in treating a cancer patient. The challenge is to kill the cancer, which is part of a patient, without harming the patient as a whole.

Animal models come in four basic varieties including xenografts (foreign tumors), transgenic models, chemically induced models, and naturally occurring tumors. Animal models allow drug testing to occur in a setting in which one can determine what dies first, the tumor or the animal. Agents that damage normal cells to the same extent that they damage cancer cells will fail in the animal model phase of drug development.

Xenografts can be derived from a variety of sources (including human tumors) and then grown in animals with suppressed immune systems so that rejection does not occur. A "nude" mouse carrying a tumor is a common model system. A significant limitation of

xenografts includes the fact that it is a relatively homogeneous population of tumor cells and often the therapy is extremely well timed according to the tumor implantation date. Humans are rarely treated in such a tidy manner. Transgenic models may utilize a variety of artificially introduced tumor inducing and tumor suppressing genes that may or may not reflect actual events in human biology. Thus treatment of the transgenic models, though sometimes productive, does not represent an ideal model for treating human spontaneous cancers. Animals can be induced to have tumors by exposure to carcinogenic agents in combination with growth factors. Perhaps the best model for animal model tumors are those that occur naturally. Veterinary hospitals can be canvassed to acquire animals with naturally occurring tumors. Veterinary oncologists typically have a relatively busy practice and certain animal species have predilection for certain tumors that at times may relatively mimic the human naturally occurring tumor population. Of note, occasional pharmaceutical companies have utilized naturally occurring animal tumors in veterinary populations as being a proof of principle necessary for a compound to reach human clinical trials.

Given the limitations of *in vitro* drug testing, it is critical to define toxicities in animal models. Animal model testing is critical because issues such as toxicity to normal cells as well as drug metabolism and drug delivery are critical elements for a drug to achieve success in human trials. Suffice it to say that compounds such as salts, which are highly toxic to cancer cells *in vitro*, are also toxic to normal cells with no differential cell kill. In all animal experiments (including those in humans) the goal is to kill the tumor without harming the animal and this is a difficult issue even with today's current technologies

Human data is derived from two distinct sources of data. These include both observational and interventional studies. In observational studies, cases and/or cohorts are observed and these types of studies are well described in the epidemiologic literature. Cohort analyses have contributed substantially to our knowledge but require verification in interventional studies. An important element is that the scientists make no attempt to intervene but only to assess. This is potentially a problematic issue, as many factors are not properly controlled within this study design. Observational studies may or may not translate into clinically relevant findings, but are excellent in terms

of generating hypothesis and in terms of creating ideas that may be new and/or unexpected. A classic example of a potential mismatch between observational and interventional studies have occurred with the beta carotene compounds which were found to be clearly linked to lower cancer incidence in a variety of observational studies, however in interventional studies beta carotene supplementation failed to yield clinical benefit. In fact beta-carotene was associated with an increase incidence of lung cancer in smokers.

Interventional studies can be categorized as either Phase I, II, or III. Phase I studies typically are the initial studies that evaluate dose and toxicity of a compound. Though end points may include how disease responds, more typically Phase I studies are performed in order to better understand toxicities, drug dosing, and drug metabolism in humans.

Phase II studies should utilize a previously well-characterized compound (or compounds), which have had initial dosing parameters as are described in Phase I studies and which are now ready to be evaluated in terms of disease responsiveness in humans, in discrete settings. In typical Phase II studies, a drug at a prescribed dose and schedule is given in a particular manner to a series of individuals in which both tumor assessment, as well as toxicity assessments are carried out under carefully controlled conditions. If successful in phase II studies, phase III studies will need to be performed. It is important to recognize that phase II single institution studies should be replicated in a multi-institutional setting.

The essence of good drug development data is that the initially reported results can be (and should be) verified by others. Good science is repeatable. Unfortunately there are many instances in which initial data from one source has not been able to be repeated by others. Do you remember the "cold fusion" hoopla that occurred several years back? Drug development has many similar stories and unfortunately people who are unscrupulous may attempt to profit from those who have desperate needs.

In Phase III studies, individuals with a characterized disease are included within a randomized study that compares current best treatment to an experimental intervention. It is noteworthy that at times the current best treatment arm may or may not represent standard of practice and this has been a significant

issue in some oncologic trials. Scrutiny is needed to determine that the group receiving conventional therapy has been optimally treated. In addition it is necessary to carefully examine the inclusion and exclusion criteria to ensure that the treated patient population is similar to that present in the community as a whole. Regardless, Phase III trials represent the most common mechanism for achieving FDA drug approval in the United States. Patient survival or quality of life endpoints are considered paramount in terms of FDA evaluation. Tumor shrinkage without an improvement in either quality or quantity of life is an unimpressive endpoint in terms of many FDA reviews and this has frequently been misunderstood. Unless the patient lives longer, and/or lives better, it is difficult to decide that a drug is truly useful. Bottom line, you cannot be certain that a patient has benefited by following biochemical parameters unless those biochemical parameters have been unequivocally linked to patient relevant outcomes.

Consecutive patient reviews provide another type of data, and a reputable investigator publishing his results may very well contribute to overall medical knowledge. There are many instances, however, in which consecutive patient's series are potentially problematic if careful follow-up is not part of the reporting process. Selective reporting may give biased results.

Single institution series are distinct from multi-institutional series. It is not uncommon for single institution experiences not to be able to be exactly replicated in a more general setting. Analysis of data should take into account the number and reputation of the investigators and institutions involved.

Trial maturity is a key factor in evaluating data. Many trials are reported at a time when the adverse events have occurred at a relatively low rate relative to the population that is being studied. Prostate cancer takes a long time to kill in most (but clearly not all) cases. If survival is being examined in a study, then a sufficient number of deaths must occur before conclusions can be drawn. If time to metastatic disease is being studied, then sufficient time must elapse for metastatic disease to have occurred. Recent drug approvals at the FDA level have failed in part be-

cause adequate duration of follow-up had not been reported.

Targeted therapies that require molecular alterations (such as Gleevec for certain types of leukemia) represent a new paradigm for cancer drug development for those tumors that bear well-characterized molecular lesions. Gene therapy also represents a targeted molecular approach. As understanding of cancer biology proceeds, detection of key structural lesions will provide the insights necessary for targeted drug development. It is critical to define the molecular lesion that causes the disease in order to appropriately develop target therapies. This is very difficult at times. We have known for many years the precise molecular cause of sickle cell anemia; we have yet to design therapies that can reverse this defect. It is problematic that the underlying molecular defects in prostate cancer, which are both necessary and sufficient for tumor formation and metastases, remain controversial.

### **Summary**

Drug development depends on a series of interrelated experiments that typically begin using cells grown in a test tube and then progresses on to testing in animal models. The ability to target tumors without harming the host is a critical element in drug development. Many compounds, which are equally toxic to tumor and non-tumor cells fall by the wayside during the drug development process. There is no substitute for prospective interventional trials with appropriate patient-relevant endpoints when evaluating drug activity. Whether or not one therapy is better than another often cannot be determined without appropriate comparative studies, in similar patient populations, using carefully optimized therapeutic regimens. Randomized trials often yield the highest quality data but these too may be imperfect.

### **NOTICE FROM MEDIPLAN HEALTH OF CANADA**

Customers sending a Money Order, for their prescriptions, purchased at the Post Office must be an INTERNATIONAL money order. Their bank is returning REGULAR U.S. money orders. Money Orders purchased through a BANK are fine. They can only accept Money Orders or Cashiers Checks made out to MEDIPLAN or MEDIPLAN PHARMACY.

### **Proven Therapy for the Palliative Treatment of Advanced Prostate Cancer ELIGARD®**

## **(leuprolide acetate for injectable suspension)**

When it comes to LHRH agonist therapy, there is more than one choice.

### **Prostate Cancer**

If you have been diagnosed with prostate cancer, your doctor has probably given you a prostate-specific antigen (PSA) blood test. This test measures the level of PSA in your blood. PSA is produced by both normal and cancerous prostate cells. As cancerous cells multiply, the level of PSA in your blood increases. It is possible; however, to have a high PSA score even if you do not have prostate cancer.

### **Hormonal Therapy**

Testosterone and other male hormones such as dihydrotestosterone, or DHT, are called androgens and help prostate cancer grow. ELIGARD (a luteinizing hormone-releasing hormone [LHRH] agonist therapy) offers hormonal therapy for the palliative treatment of your advanced prostate cancer. The goal of this hormonal therapy is to shrink prostate tumors or slow tumor growth by lowering the levels of these androgens in the body. Sometimes hormonal therapy is used after radiation therapy or surgery to help prevent prostate cancer from coming back.

LHRH agonist therapies, such as ELIGARD, are the most commonly used medications for lowering levels of androgens in the body. These medications are used to slow tumor growth.

### **ELIGARD is a smart choice**

Not all LHRH agonists are administered in the same way. ELIGARD uses a technology that allows it to be injected just under the skin with a ½" or 5/8", 20-gauge needle. The injection is subcutaneous, or under the skin.

ELIGARD is injected as a small volume (about one tenth of a teaspoon) of liquid under the skin with a small-gauge needle. After injection, the liquid solidifies into a small pellet that releases medication throughout the treatment period. You may feel a small bump when you first receive the injection. Over the next several months, the subcutaneous mass will disintegrate as the medicine is absorbed.

ELIGARD is designed to deliver its active ingredient (leuprolide acetate) continuously over a period of time. Depending on your lifestyle and medical con-

dition, you and your doctor can discuss and decide which dosage form is best for you. Three dosage forms can be given:

- ? Monthly (1-month depot, 7.5 mg)
- ? Every 3 months (3-month depot, 22.5 mg)
- ? Every 4 months (4-month depot, 30mg)

### **Benefits of ELIGARD**

Now let's discuss the important medical reasons why your doctor might choose ELIGARD when selecting a LHRH agonist.

#### **ELIGARD:**

- ? Reduces PSA levels in most patients who have elevated PSA at baseline
- ? Reduces and keeps testosterone levels low in most patients
- ? No worsening of bone pain, urinary pain, and urinary symptoms associated with advanced prostate cancer
- ? Is administered with a small needle under the skin
- ? Uses a unique delivery system that slowly releases a continuous supply of the active ingredient (leuprolide acetate)

#### **Contraindications**

ELIGARD contains a gonadotropin-releasing hormone (GnRH)-like substance. The hormone leads to the release of other hormones that stimulate the functioning of the testes and ovaries. ELIGARD is contraindicated in women, children, and patients with hypersensitivity to GnRH agonists or similar agents, or to any of the components of ELIGARD.

#### **Important information about LHRH agonists**

Like other LHRH agonists, ELIGARD 1-month, 3-month, and 4-month formulations cause a temporary increase in testosterone levels during the first week of treatment. Some patients may experience worsening of symptoms or notice new signs and symptoms during the first few weeks of treatment. Some of these signs and symptoms may include bone pain, nervous system disorders, blood in the urine, or difficulties with urination. Rare cases of urinary tract blockage and/or increased pressure on the spinal cord, which may contribute to paralysis with or without fatal complications, have occurred in patients who are on LHRH agonists for the palliative treatment of advanced prostate cancer. If you begin to experience increased pressure on the spinal cord or problems

with normal kidney function, your doctor will prescribe standard treatment for these complications.

Additionally, as recommended with other LHRH agonists, your health-care provider will periodically check your PSA and testosterone levels.

### Side Effects

The most common side effects with ELIGARD (leuprolide acetate for injectable suspension) 1-month and 3-month therapies are hot flashes/sweats, extreme tiredness, reduction of the size of the testes, dizziness, stomach or intestinal upset, joint pain, urinary frequency, and itching. The most common side effects with ELIGARD 4-month therapy are hot flashes, extreme tiredness, clamminess, dizziness, reduction of the size of the testes, decreased libido, night sweats, hair loss, breast enlargement, muscle pain, nausea, frequent need to urinate (especially at night), and testicular pain.

In clinical studies in men with advanced prostate cancer, the majority of men treated with any LHRH agonists experience hot flashes. However, the majority of the hot flashes were mild in men who used ELIGARD.

You may also experience skin reactions at the injection site, including burning or stinging, pain, redness, and bruising. In clinical studies, most of these skin reactions were described as mild and brief in duration.

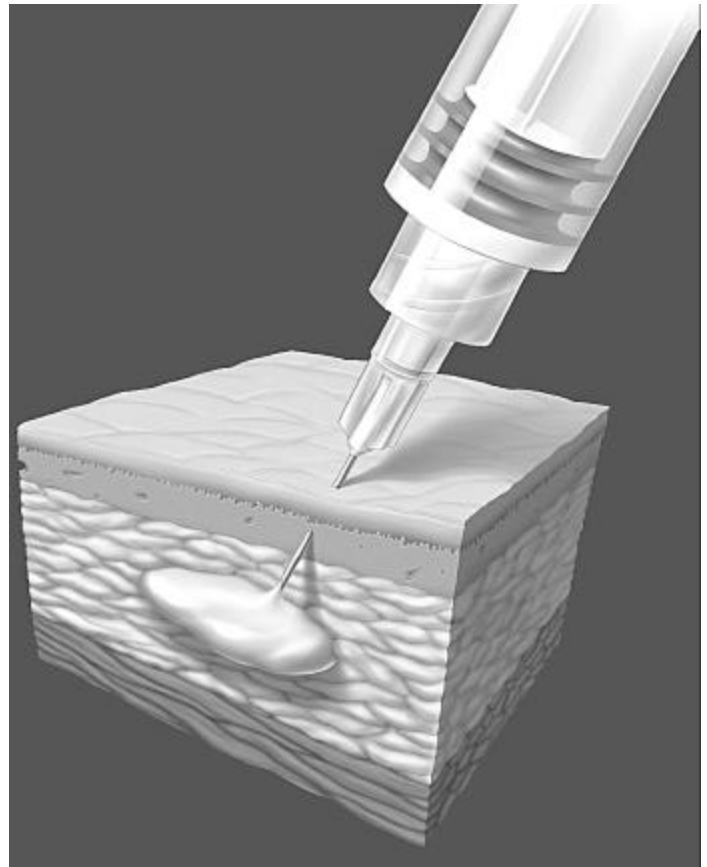
Be sure to tell your health-care provider about any side effects you experience, and ask about what you can do to minimize them.

Talk to your doctor about whether ELIGARD is right for you.

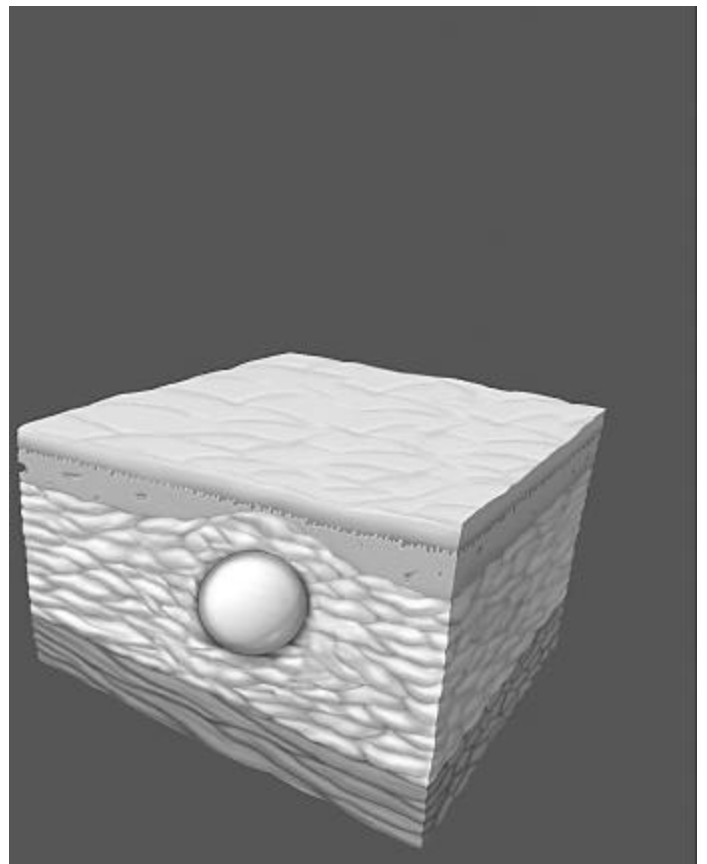
For full prescribing information, please ask your doctor or nurse.

If you have any questions about prostate cancer or therapy with ELIGARD, be sure to ask your health-care provider.

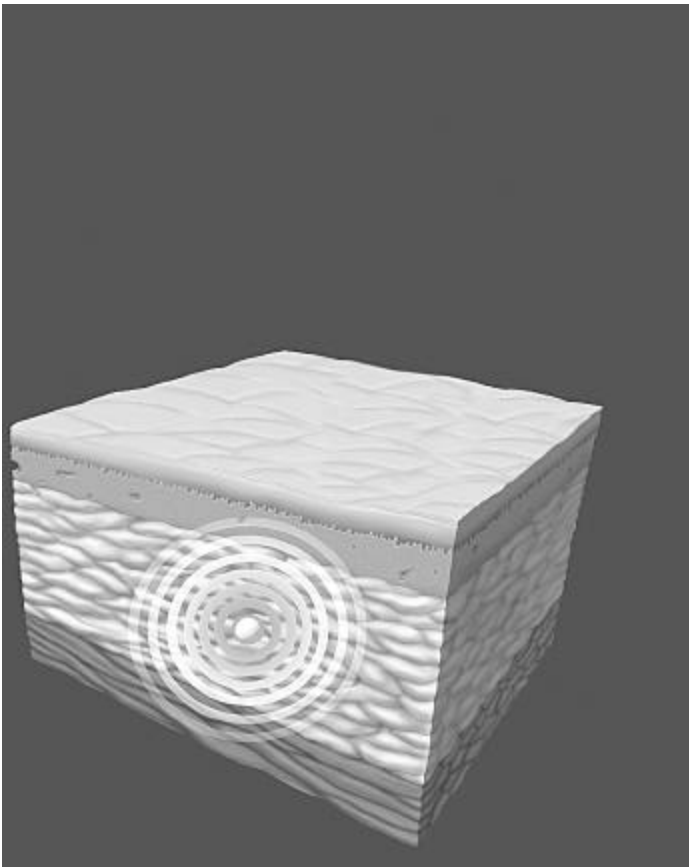
Please visit us at [www.ELIGARD.com](http://www.ELIGARD.com).



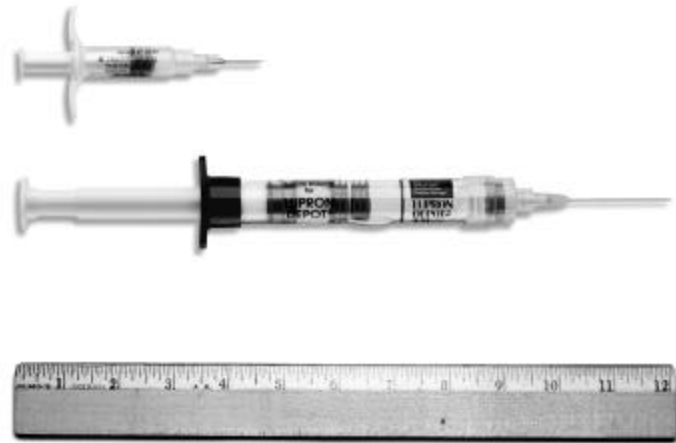
ELIGARD 30 mg is injected subcutaneously as a viscous liquid.



It solidifies in the body...



...then gradually dissolves to release a continuous supply of leuprolide acetate over 4 months.



Proven performance. Novel delivery.

**1-month depot**

 **Eligard<sup>®</sup>** 7.5mg  
(leuprolide acetate for injectable suspension)

**3-month depot**

 **Eligard<sup>®</sup>** 22.5mg  
(leuprolide acetate for injectable suspension)

**4-month depot**

 **Eligard<sup>®</sup>** 30mg  
(leuprolide acetate for injectable suspension)

**sanofi~synthelabo**

Sanofi-Synthelabo Inc. New York, NY 10016

© 2003 Sanofi-Synthelabo Inc.

## LAC-PAACT <sup>1</sup>UPDATE

By Gregory H. Teufel, Esq., Chairman<sup>2</sup>

I have nothing but bad news to report but we are helping fight to correct the unfortunate situations that have been reported to me.

One member informed me that, BCBS of Texas has begun denying laparoscopic node dissections apparently after many years of paying for the procedure. The member reports that they deem it experimental and he was forced to have an open node dissection, which was far more invasive. The cost difference did not appear, to the member, to be the issue. He believes that they deem the open procedure to be more accurate. The recovery time was 3 weeks versus a few days. The member noted that Medicare and other insurers pay for the procedure and he has no idea of the reason for the refusal by BCBS of Texas to cover the procedure. The member filed a complaint with the Texas Insurance Commission. We hope that this position will be reversed so that others with medical complications that make the laparoscopic procedure desirable can at least have the option.

Another member is fighting with Texas BCBS over denial of coverage for cryosurgical ablation of the prostate (CSAP). He has retained an attorney and is suing over it. He has obtained the LAC-PAACT kit for use with his case and his attorney feels they have a strong case.

Another member called from Southern California to report that a Kaiser Permanente health plan has told him it will not pay for his CSAP. It is a most unfortunate case because the gentleman really does not have the money to front the costs of the surgery and then chase after the insurance company for reimbursement. He has relatives that may be able to help him front the costs though. Meanwhile, we are help-

<sup>1</sup> LAC-PAACT is PAACT's legal advisory committee. Despite the name of the committee, for various reasons, we generally cannot give you legal advice or act as your personal attorney. Please do not consider anything in this article as legal advice. If you want legal advice, I encourage you to consult a lawyer in your state, so that your specific situation and local laws can be considered.

<sup>2</sup>Gregory H. Teufel, Esq. is an associate in the Litigation Department of Schnader Harrison Segal & Lewis LLP's Pittsburgh office. The views expressed are those of Mr. Teufel personally and not of the firm.

ing him find an attorney and pull together the information he will need to fight the denial of coverage.

In one of the few remaining Medicare appeals that I am aware of regarding CSAP, we had a terrible setback as the District Court ruled against the cancer victim. This was a case where the procedure had been performed after Medicare had announced it would start paying for CSAP but before the "effective date" of the national coverage decision. This is truly ridiculous, as Medicare has no excuse for refusing to pay for the procedure after it recognizes that the procedure is no longer considered experimental and is generally accepted as safe and effective. Last word from the member and his attorney is that they plan an appeal and I have contacted them for an update on the case. I will keep you posted on all of these situations as I learn more.

### Contact LAC-PAACT

If you have any questions or comments, or any suggestions about how LAC-PAACT can best serve your needs, please do not hesitate to contact me. The preferred method to contact me is via email at [gteufel@schnader.com](mailto:gteufel@schnader.com). You can also call me at work at (412) 577-5289, home (412) 421-7123, or on my cell phone (412) 596-6316, or send me a letter at Schnader Harrison Segal & Lewis LLP, Suite 2700, Fifth Avenue Place, 120 Fifth Ave., Pittsburgh, PA 15222. Please note that requests for the LAC-PAACT kit should be addressed to PAACT. Contact information for PAACT is on page 2 of this Newsletter. Please remember that this article is not legal advice and I cannot generally give you legal advice or become your personal attorney.

## MEDIA RELEASE

### Before You Join A Clinical Trial

By Denise Goodman

Printed in Parade Magazine

March 9, 2003

"WHEN YOU'RE POKING YOURSELF FOUR times a day, this sounded very good," says Larry Willis, a diabetic who had been injecting himself with insulin for 12 years. His physician had suggested that he volunteer for a drug trial for inhaled insulin. Nearly two years into the research project, the 55-year-old carpenter from Pembroke Pines, Fla.,

says his blood-sugar levels have stabilized. He feels much better, and he figures that accepting a "guinea pig" role will benefit millions of other diabetics.

Every prescription drug, from Vioxx to Viagra, has been subjected to clinical trials before receiving approval from the Food and Drug Administration (FDA). Last year, an estimated 8.3 million Americans participated in some 80,000 clinical trials to assess the safety and effectiveness of experimental drugs and medical procedures.

In order for a trial to be compliant with federal guidelines, an Institutional Review Board (IRB) must be present. This is a panel of physicians and scientists assembled by the National Institutes of Health or by the pharmaceutical company or university conducting the research. It formulates criteria and trial procedures, then monitors trial implementation and review. These boards are mandated by the FDA, which oversees industry-sponsored clinical trials, and by the U.S. Department of Health and Human Services which oversees government-sponsored trials. In both cases, the IRB can halt a study when trial protocols are not followed or when significant adverse reactions occur.

While there are many benefits to participating in a clinical trial, such as alleviating a long-term medical problem, people should be aware of the risks involved before volunteering. "One risk is not fully understanding what you're getting into," warns Dr. Clifford Scharke, former senior adviser for special projects in the Office of Human Research Protections of the U.S. Department of Health and Human Services. Here are some questions you should ask?

### **Who pays for the treatment?**

Drug companies finance many clinical trials, but routine costs often are borne by patients or their insurers. Insurers tend to be apprehensive about clinical trials but will pay for them on occasion. "Volunteers considering participating in a trial should speak with their primary-care physicians to determine how best to inform their health-insurance providers that they are taking part in a trial," says Kenneth Getz, president of CenterWatch, a Boston-based information-services company focusing on the clinical-trials industry.

### **What are the time commitments and costs? Will I be compensated?**

Commitments vary. Some require weekly clinic visits for a year. Others can last 10 years or longer.

The compensation should cover expenses incurred during the trial but should not be the reason to participate. "Incentives should not be so alluring that you would not consider the risks," Dr. Scharke says. It should also be noted that if subjects are told they will be paid at the completion of a trial, it would be considered coercion, since the subject should be free to withdraw at any time.

### **Who will pay for any complications?**

New drugs have to go through preliminary tests before they are administered to human beings in a clinical trial. Still, side effects are possible, as is death in a very few cases (1 in 10,000).

"Who pays for complications is a very murky issue, because sometimes conditions are present before the trial or they are exacerbated during the trial," says Kenneth Getz. However, if complications arise and are linked to the investigational drug or device, then typically the sponsor will pay.

### **Will the trial use a placebo?**

Volunteers must be told if there is a chance that a placebo will be used. Based on various government reports, Getz estimates that placebos are used in 30% to 40% of clinical trials. "Placebos are only used for novel drugs for which there is no basis for comparison," he says. Typically, placebos are not used in trials where the patients are suffering from a serious condition. In this case, they are given the best available treatment so their conditions do not worsen.

### **If it works, can I get the drug even if the FDA doesn't approve it?**

In some cases, FDA regulations allow subjects to continue to receive experimental drugs after the trials even if they have not been approved for general use. But production of the experimental drug is simply discontinued in most cases. Ultimately doctors will find alternative medications for the patients, but the replacement drugs may not be as effective as the drug involved in the trial. Check beforehand if you will have access to the new treatment after the trial.