WRAMC US TOO, Inc.
A PROSTRATE CANCER SUPPORT GROUP
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NEWSLETTER

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♦ HELPING TO DIRECT PROSTATE CANCER RESEARCH DOLLARS ♦
I DID IT, SO CAN YOU!
by Thomas Cox

Imagine sitting in conference with other prostate cancer survivors and an array of distinguished scientists to recommend the award of $85 million for promising prostate cancer research proposals. That's what I did last April as a participant in the Department of Defense Prostate Cancer Research Program (PCRP), a part of the Congressionally Directed Medical Research Programs. I was a consumer reviewer bringing my perspective as a prostate cancer survivor to represent the interests and concerns of the greater prostate cancer community.

Learning about this unique opportunity for service, I applied for nomination by my Us TOO chapter and I was pleased to be selected. I soon received the packet of research proposals assigned to me. Of course, the proposals were technical in nature, but that was not a concern. Evaluating the scientific aspects of the proposals was the responsibility of scientists on my panel who had been chosen for their expertise in the scientific areas under consideration. As a consumer reviewer, my job was to assess the relevance of the proposals for prostate cancer prevention, diagnosis, and treatment from the perspective of the prostate cancer community. I was assigned to the Clinical and Experimental Therapeutics Panel that reviewed research proposals in the areas of chemoprevention, diet regimens, lifestyle changes, surgical procedures, and chemotherapy. I spent about thirty hours at home reviewing and critiquing my assigned proposals, again not letting myself get bogged down in their scientific validity. Then I joined fellow prostate cancer survivors and scientists at a hotel in Fairfax, Virginia, for evaluation sessions over the course of two and one-half days.

The peer review sessions were a mind-expanding learning experience for me. I was an equal voting member with the scientists as we reviewed and voted on the merits of the research proposals assigned to our panel. The atmosphere was very collegial, and the scientists demonstrated by their remarks and demeanor that I was a welcomed resource for the deliberations. The scientific reviewers had no personal experience with prostate cancer, so they listened with interest to what we consumer reviewers had to say. They sincerely appreciated our efforts to bring out the "bottom line" for prostate cancer survivors and their families. **(Continued on page 7)**

♦ *INSIDE THIS ISSUE* ♦

WRAMC US TOO NEWSLETTER EDITOR
Write or Call
Vincent P. McDonald
8661 Chase Glen Circle
Fairfax Station, VA 22039
Telephone: (703) 643-2658
FAX: (703) 643-2658
E-Mail: vpmjam@aol.com

♦ FROM THE EDITOR'S DESK ♦

Our front page article recounts the experience of a WRAMC Us TOO member who got involved in the Congressionally Directed Medical Research Programs (CDMRP). The CDMRP provides a unique opportunity for the prostate cancer survivor to influence the direction of prostate cancer research. I encourage every reader to investigate the opportunity by contacting the CDMRP to learn more about the research programs. See page 7.

Our regular feature "The Doctor Is In" does not appear in this edition. It will resume in November.

Our speaker for the May meeting was Dr. Myron I. Murdock, a noted educator, surgeon, author, and authority on prostate health, impotence and incontinence. His topic was "Preventing and Treating Sexual Dysfunction in the Prostate Cancer Patient." His presentation gave encouragement to men challenged by impotence associated with their treatment for prostate cancer. A summary of Dr. Murdock's remarks begins on page 10.

♦ PROGRAM FOR WEDNESDAY, AUGUST 3, 2005 ♦

Our speaker for August 3 is James L. Gulley, MD, Ph.D., F.A.C.P. Dr. Gulley is a medical oncologist and the Director of the Clinical Immunotherapy Group at the National Cancer Institute (NCI). He received his medical training at Loma Linda University in its medical scientist training program where he obtained his medical degree and a Ph.D. in tumor immunology. He did his residency in Internal Medicine at Emory University, then joined the National Cancer Institute for a fellowship in Medical Oncology. At the NCI, he conducts clinical trials in prostate cancer and has a special interest in advanced prostate cancer. Dr. Gulley's topic is "Vaccines for Prostate Cancer - Science and Technology at the Cutting Edge." Join us at 7 PM on Wednesday, August 3, 2005, in Joel Auditorium, WRAMC, to learn about exciting new approaches to dealing with the disease. Plan now to attend and bring your spouse or a friend. They are always welcome.

Longer Screening Intervals Delay Prostate Cancer Detection. Extending the prostate cancer screening interval to between to 2 or 4 years would substantially delay the detection of advanced prostate cancer, according to Dr. William J. Catalona at Northwestern University. Catalona, et al., used data on 18,000 men who were screened for prostate cancer at 6-month and 1-year intervals to determine the potential delay in detection that could result from 2- and 4-year screening intervals. PSA level at time of detection was less than 2.6 ng/ml in 21 percent of the men; 2.6 ng/ml to 4.0 ng/ml in 57 percent; and over 4.0 ng/ml in only 20 percent of the men. Increasing the screening interval from one to two years would have resulted in at least a 4-month delay in prostate cancer detection in 62 percent of the men. The researchers noted that many of the diagnosed tumors had potentially aggressive characteristics. They said that the current widespread use of infrequent screening intervals could lead to delays in detection of potentially lethal cancers. (Source: *J of Urol* 2005;173:1116-1120 via Reuters Health Information, April 28, 2005)

Nerve Sparing and Incontinence. Nerve sparing during radical prostatectomy is acknowledged to be useful in preserving sexual potency after the procedure, but there is controversy over the role of the procedure in avoiding urinary incontinence. Arai, et al., Tohoku University School of Medicine, Senai, Japan, investigated this issue by studying 85 patients undergoing nerve sparing retropubic prostatectomy. Using electrophysiological testing to confirm the preservation of the neurovascular bundles, the researchers classified the patients as having bilateral nerve sparing, unilateral nerve sparing, or no nerve sparing. Patient assessments at six months showed that the bilateral group maintained urinary function significantly more than the other two groups. A second important outcome of the study was that electrophysiological testing of the degree of preservation during the operation provides useful information about postoperative urinary incontinence to the surgeon. Overall, the researchers concluded that bilateral nerve sparing helps recovery of urinary continence, and that electrophysiological testing during the operation is a useful method of predicting outcome. (Source: *J Urol* 2005; 173:1139-1142 via Reuters Health Information, April 12, 2005)

Internet Websites and Herbal Treatments for Erectile Dysfunction. Up to 62 percent of internet users seek health information from websites offering medical advice and products. It is also estimated that in 2001, over half of the US population were regularly taking herbal supplements. A recent study investigated the safety and reliability of internet websites selling herbal remedies for erectile dysfunction. The safety of herbal treatments purchased via the internet is uncertain, and the quality and reliability of the websites offering ED herbal products varies considerably. Most websites offered anecdotal evidence and third party testimonials instead of scientific data to support their claims of efficacy. Herbal products for ED often contain ingredients such as yohimbine, ginseng and ginko bilboa. There is some limited evidence that these ingredients improve erections, but they also may cause clinically significant adverse effects and contraindications. Yet only 24%

of the websites studied encouraged users to seek medical advice for treatment of ED. The study warns that patients relying on herbal products for ED obtained via the internet should exercise caution until more stringent regulations are in place. (Source: *Intern'l J Impot Research* 2005; 17(2): pp 196-200, via Medscape, April 19, 2005)

The Link Between Fruit and Vegetable Consumption and Cancer Risk - The Debate Continues. Recent authoritative studies of the benefits of diets high in fruits and vegetables conclude that higher consumption of fruit and vegetables decreases the risk of heart disease, but the benefit to cancer risk is less clear. According to Walter Willett, MD, at the Harvard School of Public Health, simply eating five servings of fruit and vegetables daily is not likely to have much benefit in reducing cancer risk. He cited three important recent studies. One involved over 100,000 participants that found that total fruit and vegetable intake was unrelated to cancer incidence. Another examined the risk of breast cancer among 285,526 women. After a median follow-up of 5.4 years, the authors found no association between fruit and vegetable intake and breast cancer risk; analysis of produce subgroups such as citrus fruits and green leafy vegetables also yielded no significant results. Finally, a long-term study of 9,506 adults by the Centers for Disease Control and Prevention found no relationship between produce consumption and cancer. These recent studies fly in the face of the earlier enthusiasm for fruits and vegetables to reduce cancer risk. For example, the World Cancer Research Fund had concluded that eating five servings of fruit and vegetables a day could reduce cancer rates by more than 20 percent. An internal evaluation by the National Cancer Institute in 2000 touted the role of fruit and vegetable consumption for protection against cancer. Observers often cite the differences in study methodology to explain the discrepancies between the older studies and the most recent ones. Both sides agree that a fruit and vegetable regimen has some overall beneficial effect on health, but the skeptics say that in reducing cancer risk, there should not be too much hope for fruits and vegetables. (Source: *J Nat'l Can Instit*, Vol. 97, No. 7: pp 474-476; April 6, 2005)

Green Tea is Back. Research had shown that green tea could inhibit prostate cancer cell growth in laboratory models. Now the research has been extended to humans. Bettuzzi, et al., University of Parma, Italy, recruited 62 men identified as being at high risk of developing prostate cancer. They ranged in age from 45 to 75. Thirty-two men were asked to take 200-mg pill supplement derived from green tea (green tea catechins) three times daily for a year. The other 30 men were given a placebo. Biopsies were performed at six months and twelve months. Only one man in the group taking green tea catechins developed prostate cancer compared to nine men in the group taking the placebo. The findings were presented at the recent meeting of the American Association for Cancer Research. Bettuzzi said the research had special implications for men at high risk for the disease, such as African Americans and those with a family history of prostate cancer. He does not recommend at this time that men start self-treatment with green tea or green tea supplements. To consume an amount equivalent to that used in the study, a man would have to consume 12 to 15 cups of tea daily. Furthermore, Bettuzzi said that the quality of commercially-available supplements cannot be assured because they may contain caffeine and other contaminants. A commentator noted that the conclusion of the study was interesting, but needed further study, saying that he would

not now recommend the green tea regimen to his patients. (Source: Forbes.com, HealthDay News, April 20, 2005)

Nerve-Sparing and Its Effect on Surgical Outcome. Surgical techniques that aim to preserve the neurovascular bundles during radical prostatectomy (RP) can minimize the risk of postoperative impotence, but there is concern that nerve-sparing procedures increase the risk of positive surgical margins, thereby compromising the primary purpose of the operation. Researchers conducted a retrospective study of men who underwent RP at the Mayo Clinic between 1990 and 2000. All the men were candidates for nerve-sparing. The decision to proceed with nerve-sparing or wide excision was made by the surgeons during the operation based on observation and frozen section analysis of the surgical margins. Nerve-sparing was performed on 3,741 men and wide excision was performed on 3,527. The men who had nerve-sparing were generally younger, with lower preoperative PSA, clinical stage, and biopsy grade, and a higher rate of preoperative potency. Analysis of the data showed that nerve-sparing techniques did not significantly increase the likelihood of positive surgical margins, nor did they significantly increase the risk of eventual biochemical recurrence. The study confirmed earlier analyses that nerve-sparing is a safe procedure in experienced hands. (Source: *Nat Clin Pract Urol.* 2005; 2 (3): 124-125)

Blindness Reported by Some Viagra Users. The Food and Drug Administration (FDA) has received 40 reports of a rare type of blindness in men taking impotence drugs. The reports involve the three popular products, Viagra, Levitra, and Cialis, but most come from Viagra users. The loss of vision is attributable to a rare condition known as non-arteritic anterior ischemic optic neuropathy (NAION). The FDA has not yet found a cause and effect relationship between the condition and the use of the drugs. NAION is not uncommon for men of the age who may rely on impotence drugs and who have health problems such diabetes and heart disease. Pfizer, maker of Viagra, said there is no evidence that NAION occurs more frequently in men using Viagra than men of similar age and health who do not take the drug. There were 103 clinical trials for Viagra involving 13,000 patients with no reports of NAION. About 27 million men have used Viagra since it became available in 1998. The manufacturers are expected to make their product labels more specific regarding possible effect on vision. To date, one man has filed suit against Pfizer alleging the company failed to provide adequate warning about NAION which restricts the flow of oxygenated blood to the optic nerve, causing irreversible vision loss. The FDA is evaluating the reports of NAION. (Source: *Reuters Health Information* via Medscape, May 27 and June 9, 2005)

Active Surveillance for Some Men With Prostate Cancer. Parker, et al., The Royal Marsden National Health Service Trust, Surrey, England, use a strategy they call "active surveillance" to manage favorable-risk, early prostate cancer patients. They say their method differs from "watchful waiting" because it applies radical treatment in the event of biochemical progression, rather than palliative treatment for symptomatic progression. They say that prostate cancer is the only human cancer which is curable, but which commonly does not need to be cured. The challenge of managing early prostate cancer is to distinguish between patients with clinically relevant cancers from those whose disease is destined to be an incidental histological phenomenon. The researchers followed 80

patients with early disease (clinical stage T1 and T2, initial PSA of 20 ng/ml or less, a Gleason score of 7 or less, and a mean age of 70.5 years. Surveillance included PSA testing and digital rectal examination (DRE) every 3 to 6 months for the first two years, then every 6 months thereafter. At a 42-month follow-up, 64 men were still under active surveillance, 11 underwent radical prostatectomy, and 5 had died from causes unrelated to prostate cancer. There was no evidence of metastatic disease. The researchers also evaluated outcomes for 32 other men with clinically localized disease (average age 77 years) who were considered unsuitable for the primary therapies of surgery or radiation. They also were enrolled in the active surveillance program with regular PSA tests and DREs. In this group, 20 remained in the program, eight were eventually treated with hormonal therapy, and four died, one from metastatic disease. The researchers said that the long-term prostate cancer mortality for younger, fit men in active surveillance is unknown. In the worst case, it will be as good as that associated with the older men placed in active surveilance in their study. (Source: *Brit J of Urol Int'l* 2005; 95: 956-960)

Exercise and Sexual Function After Radiotherapy. An article in a recent issue of *Urology* says that increased physical activity after external beam radiotherapy for prostate cancer leads to better sexual functioning. Dahn, et al., at the University of Miami, studied the association among treatment procedures, physical activity, and sexual functioning in 111 men who were treated with radiotherapy for localized prostate cancer. Physical activity was found to be independently related to sexual functioning. It was especially strong among men who had external beam radiation, but physical activity was not significantly related to sexual functioning among men who had brachytherapy or combination radiotherapy. The researchers agree that a randomized clinical trial with a larger sample is necessary to confirm their findings. (Source: *Urology* 2005; 65:953:958 via Reuters Health Information and Medscape, June 17, 2005)

Congressional Opposition to Erectile Dysfunction Drugs Continues. The House of Representatives recently passed legislation to ban the federal Medicare and Medicaid programs from paying for drugs that deal with erectile dysfunction. Proponents of the legislation said the law would save over $2 billion over the next decade. Treatment for erectile dysfunction was lumped with face lifts, weight-loss drugs, and hair growth treatments as examples of items that the federal programs should not be supporting. The legislation earlier had barred such drugs as Viagra, Cialis, and Levitra for known sex offenders after authorities discovered that 14 states had been providing impotence drugs to almost 800 registered sex offenders under Medicaid. The battle now moves to the Senate where it is likely to receive a more balanced review that will consider the reasonableness of providing these drugs under federal health programs for men whose impotence is disease-related. (Source: *Associated Press,* June 24, 2005, via Us TOO-News You Can Use)

(Directing Prostate Cancer Research Dollars -Continued from page 1)

Let me add that the PCRP logistics for the entire process, from my selection to the end of the peer review sessions, was outstanding. Travel arrangements, hotel accommodations, meals and other administrative arrangements were first-rate, and our time was well-managed.

The Congressionally Directed Medical Research Programs are administered by the U.S. Army Medical Research and Materiel Command. Colonel Kenneth Bertram, its director and an oncologist, was enthusiastic about the role of consumer reviewers. He cited the unique perspective we can bring to the funding decisions, at the same time that we broaden our own understanding of prostate cancer and the research efforts to cure the disease.

Finally, the enthusiasm and commitment to find the cure for prostate cancer were palpable throughout. And I greatly enjoyed the sense of camaraderie and achievement engendered by the entire peer review process. I was honored to represent the prostate cancer community and my Us TOO chapter. I hope to be selected again next year. Why not apply to be a consumer reviewer? Since 1977, 325 consumer reviewers have helped direct $650 million for prostate cancer research. Together we can make a difference. Come join us at the conference table.

♦ HOW TO BECOME A CONSUMER REVIEWER ♦

Get more information by going to the website of the Congressionally Directed Medical Research Programs. Go on-line to **http://cdmrp.army.mil/cwg** to learn more and to obtain the nomination form.

Tell the leader of your local prostate cancer advocacy group that you are interested in being a consumer reviewer and get him to complete and forward your nomination form.

OR

Request a nomination packet by contacting:

Congressionally Directed Medical Research Programs
ATTN: Consumer Recruitment
1077 Patchel Street
Fort Detrick, MD 21702-5024

Telephone: (301) 619-7079
Fax: (301) 619-7792
E-mail: cdmrp.consumers@det.amedd.army.mil

♦ VIRGINIA PROSTATE CANCER COALITION ♦

The Virginia Prostate Cancer Coalition is a non-profit corporation dedicated to eliminating prostate cancer. It strives to make prostate cancer an urgent priority for the medical, patient and legislative communities and the citizens of Virginia through education, outreach, advocacy, and fundraising programs.

The statistics in Virginia are telling:

- 4,900 new cases of prostate cancer are diagnosed annually.
- 800 Virginians will die from the disease this year.
- Two-third of the other states have a lower cancer mortality rate than Virginia.
- African-American men have the highest rate of prostate cancer in Virginia and double the mortality rate of white males.

Virginia needs to do better! Join the VPCC to make it happen!

Work with the VPCC to provide education and outreach; increase access to early diagnosis and treatment; increase public awareness of prostate cancer; increase research funding, encourage healthy lifestyles; and increase awareness of clinical trials.

Visit the VPCC website at www.vapcacoalition.org or call 1-703-339-0508 for more information

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PREVENTING AND TREATING ERECTILE DYSFUNCTION IN THE PROSTATE CANCER PATIENT

Myron I. Murdock, MD

Medical Director
hisandherhealth.com

(A summary of a presentation to WRAMC US TOO on May 4, 2005)

INTRODUCTION

Tonight we are going to talk about prostate cancer and its relationship to erectile dysfunction. Erectile dysfunction (ED) is a very important aspect of prostate cancer therapy and now we have more tools at our disposal to treat ED. Obviously, the most important goal in treating the prostate cancer patient is to cure his disease. Nevertheless, we cannot overlook related potential side effects like urinary control and ED. We cannot avoid the fact that the procedures used to treat prostate cancer, particularly localized prostate cancer, can affect sexual function. For instance, when a radical prostatectomy is done, the nerves that go to the penis literally wrap around the prostate gland. In the process of removing the prostate, those nerves may be injured or removed, so sexual function is impaired. The bilateral nerve-sparing radical prostatectomy was developed to try to preserve those nerves, while at the same time achieving the primary purpose of the therapy - curing the patient.

THE PRIMARY THERAPIES

The radical prostatectomy was the so-called "gold standard" for many years, but

improvements in technique and technology have made radiation therapy very attractive to the newly diagnosed patient. Now when you look at the comparative statistics, radiation therapy—whether in the form of radioactive seeds (brachytherapy) or external beam radiation therapy or combinations—is probably as good as surgery in terms of fifteen-year survival and fifteen-year PSA-controlled periods. Still, radiation therapy is not without potential side effects like incontinence and ED; and contrary to what many think, the incidence of ED is greater in patients who had radiation therapy than those patients who had a bilateral nerve-sparing prostatectomy. For example, more than sixty percent of under-sixty males who had bilateral nerve-sparing prostatectomy will regain potency, whereas more than sixty percent of under-60 males who had brachytherapy, external beam radiation or combinations thereof will have erectile dysfunction within two to five years.

Now let's consider cryosurgery or cryoablation of the prostate. It is mainly indicated for patients who had previous radiation therapy and who now have rising PSAs and local recurrence without metastases. One of the problems in evaluating cryosurgery is that we lack adequate data about the procedure regarding its long term efficacy. Cryoablation is where brachytherapy was about five to ten years ago. What statistics we do have indicate that in terms of cure and PSA-free period, cryoablation is almost as good, if not as good, as radiation therapy So at least for the short term, cryoablation is a reasonable form of treatment for prostate cancer for the carefully selected patient. Its problem is that one hundred percent of the patients who are cryoablated will become impotent. Even though warming techniques are being developed in an effort to preserve the nerves

and just freeze the main bulk of the prostate gland, it is a very difficult procedure with many questions of efficacy remaining to be answered. The surgeon performing cryoablation must be very certain that the prostate cancer is primarily located only at the base of the prostate, toward the bladder neck, and not at the apex, or the lateral apex, where the nerves are very close to the prostate. Any attempt to spare those nerves is likely to leave cancer cells behind. So, for all practical purposes, cryoablation always leads to ED.

No doubt many of you have had hormonal manipulation of some sort. Thirty or so years ago, the common hormonal manipulation was surgical castration which dropped testosterone levels down very quickly. You know that prostate cancer cells thrive on testosterone. If you give a prostate cancer patient testosterone, you will see a rise in his PSA, and eventually the spread of the disease. If you take away the testosterone, e.g., by surgical removal of the testes, lowering the testosterone will actually kill the hormone-sensitive prostate cancer cells. But somewhere in the body there is always a cluster of cells that either mutate or are more resistant to hormonal manipulation. They eventually will grow independent of hormonal manipulation.

TESTOSTERONE

Testosterone is the sex hormone, so low testosterone affects libido and sexual function. It is one of the reasons why men think about sex so frequently during a day. Testosterone affects women, too. Women have about one-twentieth as much testosterone as men. Studies have shown that about forty percent of all women who have sexual problems have them in the realm of low sexual desire, often stemming from low testosterone. The normal amount of testosterone in a man is over 300 ng/dl, and in a woman, over 30 ng/dl. Unlike men with prostate cancer, women could be helped with testosterone replacement therapy.

The male whose testosterone level is below fifty ng/dl is at the castration level. A level under fifty ng/dl is insufficient to sustain sexual desire or to maintain the endothelium (lining) of the blood vessels that is necessary for blood flow to the penis. A man at these levels will likely hear a term called "endothelial dysfunction," indicating that the lining of the blood vessels of the penis are not functioning properly. Diseases like diabetes, hypertension, dyslipydemia, and elevated cholesterol actually injure the lining of the blood vessels, preventing them from making enough nitric oxide to stimulate the whole process of increased blood flow to the penis. We find that about eighteen to twenty-five percent of men don't respond to drugs like Viagra, Levitra, or Cialis—the PDE-5 drugs now used for ED—because their testosterone is too low. A man needs a certain baseline level of testosterone for these drugs or other therapies to work. Testosterone gives a certain amount of nutrition to the lining of the blood vessels, the endothelium. Without that minimal level of testosterone, the endothelium can't function normally and can't produce enough nitric oxide. So the whole process of increasing blood flow to the penis is negated by the lack of testosterone.

Testosterone is an interesting hormone. As I have already noted, it is necessary for the lining of the blood vessels to function, and it is also necessary for sexual desire. As many of you are aware, when you don't have any desire, you don't even care about ED! This reminds me of the joke about the doctor who tells his patient, "I have some good news for you and I have some bad news. What do you want to hear first?" The patient says, "Give me the bad news first." The doctor tells

him, "The bad news is that you have AIDS, and you're going to be dead within three months. The good news is that you also have Alzheimer's disease. You won't remember that you have AIDS, so it won't make any difference to you." That is similar to what happens to people who have very low levels of testosterone. They no longer feel that sex is an important aspect of their lives, and therefore, their interest levels drop off dramatically. A patient who has prostate cancer cannot be given testosterone replacement therapy. We'll talk now about dealing with this major dilemma.

DEALING WITH ED

Here you see a diagram showing the nerves that come from the spinal cord. This is the bladder. Running right next to the prostate is a bundle of nerves that goes to the penis. In a radical prostatectomy, the surgeon excises the prostate at its apex with the urethra and at the bladder neck, and frequently the nerves are totally removed. This is important because the drugs that we have available to us, particularly the PDE-5 inhibitors—Viagra, Levitra, and Cialis—must have the connection between the brain and the penis intact in order to be effective. However, there are times when a radical non-nerve-sparing prostatectomy must be done to eliminate the cancer. Overall, the standard, old-fashioned radical prostatectomy is probably the better cancer operation. When these neurovascular bundles are removed, the connection between the brain and penis goes with them. If you are a patient who has had a standard, non-nerve-sparing radical prostatectomy, there is no way that those drugs are going to work unless you fall into a very rare category—maybe one to two percent of patients—who may have an auxiliary set of pudendal nerves that are outside the prostate. As you know, you don't need both neurovascular bundles intact, but the results with the PDE-5 inhibitors are much better if you have both nerve bundles intact compared to only one.

Here you see the penis. It is basically composed of two spongy rods surrounded by a very tense capsule. When the penis fills with blood, the pressure inside builds because the capsule is not very elastic. The build-up of blood in the penis presses against the venous outflow, holding the blood in the penis causing an erection. It is a combination of two processes: the engorgement with blood which we refer to as "tumescence," and the actual increased pressure and firmness of the penis which is termed "rigidity."

Now the question is, can we prevent ED in men who have prostate cancer and who are undergoing prostate cancer therapy? The answer is "yes," particularly for men who are younger, sexually active, functioning well, and without any significant co-morbidities, e.g., they are not diabetic, hypertensive, on Lipitor for their cholesterol, or already have minor ED. This younger, sexually active man without significant co-morbidities has—speaking statistically—a sixty percent chance of functioning spontaneously after therapy. It's probably closer to ninety percent when we consider the drugs that we could use as an adjunct to his spontaneous function.

I'm sure you are aware of the laparoscopic prostatectomy and how effective it is. Is a laparoscopic radical prostatectomy as good as an open retropubic, radical, nerve-sparing prostatectomy ? I don't think anyone knows the answer yet. It may be better or may not. We simply don't have definitive statistics to date. It appears that it is as good. From a sexual point of view, there may be reasons why it's a better procedure. For example, the surgeon gets a better visualization of the

neurovascular bundles. On the other hand, many of us who do open procedures use improved magnification to help sweep the neurovascular bundles off the prostate. Also, laparoscopic surgery takes a significant amount of training, and it has a very long learning curve. A good surgeon likely could do 25 open retropubic, radical nerve-sparing prostatectomies and become very proficient, but a surgeon doing 100 laparoscopic procedures could not say that he was as proficient as the surgeon doing 25 open procedures. So patients must carefully evaluate the two procedures, seeking second opinions, as they weigh the surgical options available to them.

We talked about radiation therapy which has a delayed, but high incidence of ED. At the outset, the patient won't have ED, but as the years go on—two to five years—sixty to seventy percent of patients will have significant ED requiring the assistance of ED therapy. Cryosurgery—expect 100% ED. Hormone therapy as we classically think of it depends mostly on LH-RH agonists—Lupron, Zolodex, among others. These drugs lower your testosterone and decrease your desire and your ability to function sexually. In Europe—and actually we've studied it in the United States—the antiandrogen Casodex, which is bicaludamide, has been used instead of LH-RH agonists as a form of the hormonal manipulation therapy. This drug works differently, but the outcome is the same—chemical castration, but instead of lowering the testosterone in the pituitary-testicular axis, Casodex lowers the testosterone by blocking the effect on the prostate cancer cell. Now, why is that so important? Using an antiandrogen like Casodex allows elevated testosterone levels. The serum testosterone is not affected. Therefore, men who use just antiandrogens like Casodex do not have decreased libido and do not have as much sexual dysfunction as men who are using LH-RH agonists or antagonists for the treatment of advanced prostate cancer. For advanced prostate cancer in Europe, they are now using triple-dose Casodex as a monotherapy. We've done studies on it in the United States, but the FDA has not yet approved it. It certainly is an off-label way of handling this particular problem. If you're an individual who needs hormonal manipulation and sexual activity is important to you, then you may want to consider monotherapy Casodex rather than one of the LH-RH agonists. I have many stories I could tell of patients on extended monotherapy Casodex who have done very, very well as far as their cancer control is concerned while maintaining their sexual function.

THE PDE-5 DRUGS

The question remains, how can we improve outcomes in patients who have had radiation therapy, surgery, or cryoablation, etc.? The answer may very well be the early and continuous use the PDE-5 drugs, perhaps even before the primary therapy. If we do so, we're likely to find that the time for spontaneous improvement in sexual function, post-therapy, will shorten dramatically. Studies have shown that using PDE-5 drugs (like Viagra, Levitra, and Cialis) soon after radical prostatectomy reduces the average time to achieve spontaneous erections from nine to twelve months down to three to six months. There is another related matter to consider. The fact is that over time the non-functioning penis becomes dysfunctional. The term, "Use it or lose it" is literally true! It is very important to get blood bringing oxygen to the penis on a regular basis. If you don't get blood and oxygen to the penis regularly, i.e., have erections or sex, you'll end up getting a fibrotic, scarred penis that loses its elasticity

and its capability of getting sufficient blood flow into it.

What we do nowadays is to start our patients very, very early, even before they have their primary therapy (surgery or radiation therapy), on a daily regimen of PDE-5 drugs to maximize their normal nocturnal erections, thereby preventing debilitating, non-reversible changes that may occur during the time that the patient is healing from his surgery and is becoming interested in sexual activity.

This brings up the advantages of the PDE-5 drugs. Most of you are aware that Viagra is a short-acting drug which lasts for about four to eight hours; Levitra lasts from about six hours up to twenty-four hours; and that Cialis is a thirty-six hour drug. In Europe, it is approved as a seventy-two hour drug. In reality, Cialis is a one hundred hour drug. For patients who desire ED therapy for prostate cancer, we give two doses of Cialis a week (20 milligrams every Tuesday and Wednesday). This will maximize their nocturnal sleep erections throughout the week with only two pills. To get the same effect with Viagra or Levitra, we have to give them the drugs every night, which becomes very costly. But with Cialis, two pills per week prophylactively helps prevent irreversible fibrosis of the penis which we otherwise may not be able to treat until ten to fifteen months later. Studies show that fifty-five percent of the patients respond to Cialis.

Viagra is an unusual drug. I did original studies on it more than thirteen years ago. It's a relatively short-acting drug. It's a great drug, but it doesn't have the advantages of some of the other drugs in terms of duration. Obviously duration facilitates spontaneity of sex, which is much more likely if you take a pill which lasts from thirty-six to one hundred hours instead of one that lasts only six to twenty-four hours.

We also do combination therapy with these drugs, i.e., we use combinations of these drugs and we can do so because of their remarkable safety. Among our patients with severe ED—many of them had a radical prostatectomy or radiation therapy—are men who don't respond to maximum doses of monotherapy, e.g., twenty milligrams of Cialis, twenty milligrams of Levitra, or one hundred milligrams of Viagra. A common combination is Cialis twice a week to maximize nocturnal sleep erections and improve the "nutrition and health" of the penis, so to speak, combined with a Levitra tablet or Viagra tablet one to four hours before sexual activity to give an added boost. The longer you take PDE-5s, the better they work and the lower their side effects. Patients relying on self-injection programs or penile implants also would respond well to combination therapy.

Why do these drugs help overcome ED? Because they cause better nocturnal erections and better nutrition to the penis. That alone will help as time goes on. As already noted, the nerves have to be intact in order for the drugs to work. There has to be a connection between the brain and the penis. The lining of the blood vessels has to be intact and functional. That's why twenty percent of patients who have poor response to these drugs have low levels of testosterone. You need testosterone to make the endothelium function. We've talked about the truism, "Use it or lose it."

ALTERNATIVES TO PDE-5 INHIBITORS

What are the alternatives to these oral drugs, the PDE-5 inhibitors, to combat ED? There are vacuum compression devices,

intraurethral and self-injection systems using prostaglandin E and other compounds like them; and we could consider a penile prosthesis for those patients who have tried the minimally invasive therapies, but continue to have significant sexual dysfunction. We can also use combined therapies of various sorts to avoid resort to a penile implant. For instance, we may use a PDE-5 drug that, in and of itself, would not cause an erection adequate for penetration, and combine it with self-injection therapy, which in some patients would not, in and of itself, cause a satisfactory erection for penetration. The combination is synergistic, not simply additive in effect. In short, you prime the system with the PDE-5 and then you add the prostaglandin E to enhance vascular dilation and blood flow.

There are other combination therapies to deal with ED. A penile prosthesis will always give you an erection when you want it for as long as you want it, but is not always a panacea. Everybody has a different concept of what sex should be. Some patients with penile prostheses complain that the head of the penis, the glans penis, does not get rigid. They can use the intraurethral drug MUSE or a vacuum device to complement the prosthesis to make the glans penis firmer. Resort to a PDE-5 also may be reasonable under certain circumstances. So we have these various combinations available to help the ED problem.

Let's talk about MUSE for a moment. Here is what it looks like. You can see MUSE. At one time it was very popular, particularly in patients who had radical prostatectomies. As you can see, it is a small, plastic inserter that holds a very small pellet that is very high dose of concentrated prostaglandin E. It is available in doses of 125, 250, 500, and 1000 micrograms with 500 or 1000 micrograms being the most common dose. A small pellet is pushed into the urethra. Only about ten percent of the pellet gets absorbed. Of the 1000 micrograms inserted, you may get 100 micrograms into the spongy rods of the penis. On the other hand, direct self-injection into the penis does not require nearly as much medicine as is needed in a intraurethral application.

Probably somewhere between one-third to half of ED patients rely solely on MUSE as their treatment of choice. A constriction band is also available to help retain the blood flowing to the penis after insertion of MUSE. The frequent side effect of MUSE is local pain; about three percent of patients who use MUSE report local pain sufficient to cause them to discontinue its use.

Here you can see a vacuum compression device. I know you are familiar with them and that many of you have used them. This method is conservative; it doesn't involve taking or injecting drugs or having surgery. It involves placing a plastic tube over the penis. The tube is attached to a vacuum device. The device causes suction into the plastic tube which actually increases the blood to the dermis (skin) and to the subdermal areas. It does not increase the blood to the spongy rods of the penis, but its effect is often adequate to give sufficient rigidity to the penis. That is all some men may need to achieve penetration. A caution—if you are on anticoagulants, you shouldn't use it because you run the risk of developing subdermal hemorrhages causing your penis to become swollen and turn purple! Also, the constriction band should be kept on for no more than thirty minutes; otherwise you may get serious congestion that could result in damage to the penis. My observation is that many vacuum devices end up on a closet shelf. Nevertheless, the vacuum device has a place as a single therapy alone or in combination with other therapies.

Let’s talk about penile prostheses. We generally reserve the penile prosthesis for patients who either don't respond to oral drugs or who prefer not to rely on injections or the vacuum device. There are two types, the malleable and the inflatable. Here is what they look like. The inflatable prosthesis is much more beneficial. Emplacement techniques have been improved; the complication rates have been greatly reduced; and patient satisfaction is high. Nowadays, surgeons who do penile prosthesis emplacements are getting excellent results. The infection rate in the non-diabetic population is down to 0.1 percent. The infection rate for diabetic men is less than 2 percent. The devices themselves have been greatly improved. The patient spends very little time in the hospital. The immediate post-operative period can be trying, but once healing occurs, the satisfaction rate of penile prostheses is exceptional—about 98-99 percent. The device also has exceptional acceptance from partners. In my experience, when a patient’s penile prosthesis becomes inoperative, he wants it fixed yesterday, not tomorrow! This is an indicator of how satisfied patients are with the inflatable penile prosthesis.

So the inflatable penile prosthesis is a very effective way of handling ED regardless of its severity. It's truly curative in the sense that you achieve an erection whenever you want, for as long as you want. It also enhances spontaneity. On the other hand, its disadvantages are obvious. It requires an invasive operative procedure; some patients sense that the erection feels unnatural; there is the potential for mechanical failure, infection and erosion. It is also likely to be irreversible; once in place, the other techniques such as oral drugs and injection therapy are not going to work. It's also costly, although—believe it or not!—Medicare pays for it, and the non-federal insurance policies in Maryland, the District of Columbia, and Virginia cover it. Unfortunately, the federal government-sponsored insurance plans do not pay for any treatment of sexual dysfunction, even after primary therapy for prostate cancer.

SUMMARY

Now let’s review. The first objective in treating a man with prostate cancer is to treat the disease, hopefully affecting a cure. Other considerations are secondary. Secondly, we want to minimize erectile dysfunction. We're going to do nerve sparing, if we can, as long as there are no contraindications. As appropriate, we can begin a regimen of PDE-5s before, at the time of, or soon after primary therapy to shorten the period until the resumption of spontaneous sexual function. We always start treatment of ED with the most minimally invasive techniques—the oral drugs or combinations of oral drugs. If that is not effective, then we move to more invasive techniques, such as self-injection programs with prostaglandin E and related drugs or a combination of them. And if that's still not good enough, we next consider combination therapies. Lastly, if all else fails, there is resort to maximally invasive therapy with penile prostheses. Keep in mind that erectile dysfunction is treatable. No one should have it if he doesn't want it. That is the message I want to leave with you. Unfortunately, many prostate cancer patients are on hormone manipulation and so their level of interest in sex is very low. That is why they don’t seek treatment. Assuming that men with prostate cancer and their partners have a reasonably normal desire for sex, patients should be able to be treated in some way, shape, or form, no matter what primary therapy they had for their prostate cancer.

I've enjoyed being with you this evening. I'm open to any questions that you may have.

QUESTIONS AND ANSWERS

Q: Would you clarify the term "spontaneous erection."

A: If a man requires assistance from the PDE-5s (Viagra, Levitra, or Cialis), the vacuum device, or any of the other interventions we discussed, in order to achieve an erection, then his erection is not spontaneous, i.e., it is not generated by natural processes. After a patient has had a radical prostatectomy, we must decide whether he should be put on drugs or not. The question is how long is it likely to take him to get spontaneous erections without medication? A successful bilateral nerve-sparing prostatectomy in a less-than-sixty-year-old gives a sixty percent chance that he will regain relatively adequate erections, provided he was sexually active prior to his surgery. It may take him nine to twelve months do so. But if I treat him early with PDE-5 inhibitors (Viagra, Levitra, Cialis), I could shorten that period to three to six months. Then instead of having a sixty percent success rate, he may achieve an eighty to eighty-five percent success rate. Men who fail to regain spontaneous erections or who get inadequate erections will need erection assistance using these drugs. When you read about various ED studies, you must understand how success is measured and how "success" is defined. Is success truly spontaneous erections without the drugs or other therapy, or is it with the assistance of the drugs?

Q: I have a comment and a question. My comment concerns a friend who is an advocate of the penile implant. He swears by it and speaks freely about his reliance on it. He's on his second one. Now what does it cost?

A: Your comment is easy to address. Once men have penile implants, many become cheerleaders for them. I suspect many of you may be saying, "Who in the heck wants to go through that? Fifteen days with a swollen penis and scrotum, walking with my legs apart, and dealing with ice packs and the like—is it really worth it? Like your friend, many men think it is worth it. In short, most men are pleased, and so are their partners.

Now for the cost. The device itself costs around six thousand dollars which includes the hospital's mark-up. Medicare pays the surgeon about eight hundred dollars for the operation. Add about 2,000 dollars for a one day hospital stay and anesthesia service. So expect a bill for about of about nine thousand dollars, maybe as high as ten thousand dollars. But put the cost in perspective. You can get fifteen years out of the device. What if you took two doses of Cialis a week at ten bucks a pop for fifteen years? You'd end up spending more than fifteen thousand dollars and have the uncertain long-range effect of placing a drug in your body. Finally, it has been shown that if men remain sexually active, they less likely to be depressed, they feel better about themselves, have a better quality of life, and probably live longer.

Q: Tell me about the concept of taking the PDE-5s on a regular basis apart from immediately prior to intercourse.

A: Right. It involves getting away from taking a drug on an "as needed basis" prior to sexual activity. Instead, a PDE-5 drug is taken on a regularly scheduled basis. This offers several advantages. First, it improves

spontaneity, making the sexual situation more "natural," so to speak. Even more important, the regularly scheduled basis helps prevent the deterioration of the endothelial function. Why not be on Cialis twice a week and increase your nocturnal erections every single night as well as improve your overall blood flow. For example, if you are a diabetic, you're likely going to be impotent sooner or later. The regularly scheduled basis will slow down the progression of your endothelial dysfunction, then maybe you won't need that penile implant at all in the next five to ten years. Perhaps you'll be able to rely on drugs throughout.

Q: I have a follow-on question. You mentioned that you consider putting men on a PDE-5 regimen prior to a radical prostatectomy. What kind of effect would the prophylactic use of the PDE-5s have on them?

A: It could only be positive. It wouldn't be negative, except perhaps for the expense. Many insurance companies are limiting the coverage for these drugs. To be effective as a prophylactic, a minimum of eight pills a month are necessary, so the patient will face an out-of-pocket expense. Patients with ED who have not been treated should start with an the oral drug as a monotherapy. I would probably recommend Levitra first. Now, why Levitra? In general, studies indicate that Levitra is the most efficacious of the three of the drugs for radical prostatectomy patients. Levitra is effective for seventy-two to seventy-five percent of the patients, providing an erection firm enough for penetration yielding sexual satisfaction. Cialis is right behind Levitra. About sixty-eight to seventy-two percent of the patients who had bilateral nerve-sparing radical prostatectomies had a satisfactory response with Cialis in terms of sexual satisfaction. On the other hand, Viagra was effective in about forty-three percent of the patients. Therefore, I would start with Levitra as a monotherapy. If that wasn't effective, I would use a combination therapy of Cialis twice a week and Levitra before sexual intercourse. Most men, regardless of the extent and duration of their ED, will get some kind of positive response from this combination therapy. And then, as time goes on, their responses will actually improve. So, the patient must decide how long to wait before moving to the next level of therapy if the oral drugs are unsatisfactory. The next step would be an injection program. And I can tell you, ninety-five percent of the men who directly inject prostaglandin E into the penis will get a good erection. You just have to push the doses high enough without pain. That should always work, but if it doesn't, or you don't like doing it, you can move to a penile implant.

Q: Why is the Federal Government so stingy in its coverage of prostate cancer-related therapies for ED?

A: First of all, there is the economic aspect—the government is trying to keep health costs down. It is also very concerned about female sexual dysfunction. Female sexual dysfunction is going to be a major health problem in the future. If the government provides ED therapies to males, denying appropriate sexual dysfunction therapies to women would be intolerable for social and political reasons. The resultant cost would be immense, particularly in the next three to five years when female sexual dysfunction becomes a major health issue.

In seeking coverage for ED, we're willing to limit it to the side effects of radical prostatectomy. We seek to equate the patient who has had a radical prostatectomy and now has severe ED to the woman who

has breast cancer and ends up with a procedure reconstructing her breast. If the federal government-sponsored health insurance programs allow insurance carriers to cover reconstruction of a woman's breast after mastectomy, why can't it provide coverage for the male who has morbidities associated with surgery for prostate cancer? The situations are very analogous. Who could possibly argue that sexual dysfunction for the male after radical prostatectomy is less psychologically difficult than mastectomy for the woman?

Q: Many of us have had a radical prostatectomy and now experience a slow rise in PSA, but not enough to trigger additional therapy. Is there any contraindication to drug therapy for ED for men in this situation??

A: No, your PSA level has no relationship to these drugs. They should be just as effective, and they will in no way be detrimental. The reaction should be positive. As you may know, Viagra is already being used as an anti-cancer drug.

Next, the May newsletter's first person account said that the radical prostatectomy can result in diminished penile length, an outcome one seldom hears about when considering a primary therapy. An authoritative source provided the most common explanation. After removing the prostate and while reattaching the urethra to the bladder, the surgeon often pulls the urethra "up to the bladder," instead of "pulling the bladder neck down to the urethra." In some cases, the bladder cannot be "stretched," resulting in the pulling up of the urethra. Hence the reduced penile length.

♦ READERS WRITE ♦

We received two interesting comments about the May newsletter. First, the newsletter had two items about the prostate biopsy, noting the pain that many men report while undergoing the procedure. A reader writes that he was so distressed by the procedure that when he got off the table, he told the urologist "If all doctors had to have this done to them before they could do it to someone else, you would quickly find a less painful procedure!"

♦ WRAMC US TOO COUNSELORS ♦ (AS OF AUGUST 1, 2005)

(These persons are willing to share their experiences with you. Feel free to call them.)

SURGERY

Tom Assenmacher	Kinsvale, VA	(804) 472-3853	
Jack Barnes	Oakton, VA	(703) 620-2818	
Jack Beaver	Falls Church, VA	(703) 533-0274	
Jerry Bussing	Laurel, MD	(301) 490-8512	
Gil Cohen	Baltimore, MD	(410) 367-9141	
Richard Dorwaldt	Burke, VA	(703) 455-8657	(Laparoscopic Surgery)
John Fellows	Annandale, VA	(703) 503-4944	
Tony French	Annandale, VA	(703) 750-9447	
Robert Gerard	Carlisle, PA	(717) 243-3331	
Ray Glass	Rockville, MD	(301) 460-4208	
Monroe Hatch	Clifton, VA	(703) 323-1038	
Bill Johnston	Berryville, VA	(540) 955-4169	
Dennis Kern	Reston, VA	(703) 391-9418	
Steve Laabs	Fayetteville, PA	(717) 352-8028	(Laparoscopic Surgery)
Don McFayden	Pinehurst, NC	(910) 235-4633	
James Padgett	Silver Spring, MD	(301) 622-0869	
George Savitske	Alexandria, VA	(703) 671-5469	
Artie Sheraton, MD	Olney, MD	(301) 523-4312	
Jay Tisserand	Carlisle, PA	(717) 243-3950	
Don Williford	Laurel, MD	(301) 317-6212	

RADIATION

John Barnes	Springfield, VA	(703) 354-0134	(Intensity-Modulated Radiation Therapy)
Leroy Beimel	Glen Burnie, MD	(410) 761-4476	(External Beam Radiation)
Philip Brach	Washington, DC	(202) 966-8924	(External Beam Radiation)
Ron Gabriel	Bethesda, MD	(301) 654-7155	(Brachytherapy)
Irv Hylton	Woodstock, VA	(540) 459-5561	(Brachytherapy)
Harvey Kramer	Silver Spring, MD	(301) 585-8080	(Brachytherapy)
Bill Melton	Rockville, MD	(301) 460-4677	(External Beam Radiation)
Oliver E. Vroom	Crofton, MD	(410) 721-2728	(Proton Radiation)
John Waller	Yorktown, VA	(757) 865-8732	(Brachytherapy)
Barry Walrath	McLean, VA	(703) 442-9577	(Brachytherapy)

INCONTINENCE

Larry Schindler	Silver Spring, MD	(301) 649-5946	
Ray Walsh	Annandale, VA	(703) 425-1474	

HORMONAL

"Mac" Showers	Arlington, VA	(703) 524-4857	
Tony Bicknell	Springfield, VA	(703) 451-7517	

WATCHFUL WAITING

Tom Baxter	Burke, VA	(703) 250-9676	

SPOUSE SUPPORT

Faye Lohmann	Kensington, MD	(301) 933-3678	

OTHER THERAPIES/MULTIPLE THERAPIES

Howard Bubel	Fairfax, VA	(703) 280-5765	(Cryosurgery, Hormonal, Sexual Function)
Arthur E. Clough	Kerryville, TX	(210) 896-8826	(Surgery and Radiation)
S.L. Guille	Sumerduck, VA	(540) 439-8066	(Surgery, Radiation, Hormonal)
Richard Leber	Chapel Hill, NC	(919) 942-3181	(Surgery, Radiation, Hormonal)
Glenn A. Leister	Lynchburg, VA	(434) 384-1661	(Surgery, Hormonal, Chemotherapy)
Hank Lohmann	Kensington, MD	(301) 933-3678	(Surgery and Radiation)
Charles Preble	Annandale, VA	(703) 560-8852	(Cryosurgery, Hormonal, Intermittent Hormonal)
Emerson Price	Absecon, NJ	(609) 652-7315	(Hormonal, Radiation, Cryosurgery)
S.L. Ross	Alexandria, VA	(703) 360-3310	(Brachytherapy, Radiation, Hormonal)
Ken Simmons	Alexandria, VA	(703) 823-9378	(Radiation and Hormonal)
Bill Stierman	Vienna, VA	(703) 573-0705	(Surgery and Hormonal)
Ray Walsh	Annandale, VA	(703) 425-1474	(Surgery and Hormonal)

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7 PM

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♦ SPEAKER ♦

JAMES L. GULLEY, MD, Ph.D., F.A.C.P.
Director, Clinical Immunotherapy Group
National Cancer Institute

♦ TOPIC ♦

"VACCINES FOR PROSTATE CANCER - SCIENCE AND TECHNOLOGY AT THE CUTTING EDGE"