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Hunt of a Lifetime **ONE MAN'S** **PURSUIT OF A CURE**

*By Howard Sheridan
Us TOO / The Outdoor Channel
Prostate Cancer Patient /Spokesperson*

The air is crisp and dewy and the hike up the mountain seems like a race in the dark, especially in the thin Colorado mountain air. We need to get above the elk before daylight's warming air drives them to higher, cooler altitudes. We split up and my partner begins to cow call; instantly there is a bugle from below. He calls only sparingly and the bull answers every call—seemingly closer each time. Then, unexpectedly, I feel the breeze coming down the mountain across the back of my neck and I never hear the bull again.

It's September 2002 and I'm experiencing my first Colorado elk hunt. This is truly what I believed to be the hunt of a lifetime. Everyday is filled with new experiences and challenges that exhaust me both mentally and physically as I find my way through foreign surroundings in search of elusive elk in a wilderness much different than the Michigan farm country with which I'm familiar.

It's hard to believe that just two Septembers ago I received the phone call that no man wants to get. My



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HOT SHEET

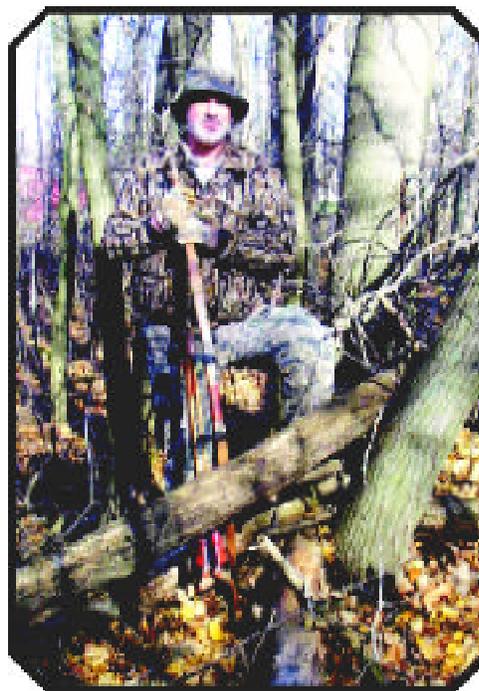
FEBRUARY 2004

urologist called to tell me that the biopsy confirmed what an elevated PSA reading had indicated. I had prostate cancer and I was only 45! My father's family propensity for the disease had crossed into the next generation. That phone call started quite a different kind of hunt for me, the REAL hunt of a lifetime—the battle to beat the enemy living inside of me.

Because of my family history with the disease, my doctor had been performing annual exams and checking my PSA each year since I was 40. As a result, we caught the disease early, and because we caught it early, the cancer had been confined to and localized in the prostate. It hadn't spread.

The initial shock, anger and fright are impossible to fully describe. You feel as if someone hit you in the stomach with a baseball bat, and while you

were doubled over, they socked you again with a sharp uppercut right between the eyes. Those initial feelings, for me however, were quickly replaced by a determination to make a treatment decision; little did I know what a daunting task that would be.



My partner for this 'hunt' would be the person I started bow hunting with 15 years earlier, my wife Judy. This was going to be the most intense experience of our lives, not exactly a pleasant October bow hunt or pheasant opener. We talked to doctors, read the books, researched the Internet, and read magazine articles until

our heads hurt. The amount of data that had to be sorted, analyzed, and comprehended was overwhelming. It amazed me how exhausting a one-hour consultation with a doctor could be.

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Us TOO PUBLICATIONS

In addition to the Hot Sheet, *Us TOO* also publishes a FREE e-mail based news service providing updates on the latest prostate cancer related news. To subscribe or link to the archives simply visit the *Us TOO* Website: www.ustoo.org

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TREATMENT UPDATE

LASER TEST FOR PROSTATE CANCER

Researchers are hoping that lasers could be used to help treat prostate cancer patients and prevent them experiencing the side effects of more invasive surgery.

A team at University College London is carrying out trials using photodynamic therapy (PDT) to safely treat prostate cancer - the most common form of male cancer.

The technique is already used to treat some cancers, including those in the head, neck, lungs and oesophagus.

It uses lasers or other light sources combined with light sensitive drugs which are injected into the patient's body to kill cancer cells.

The drugs circulate to all tissues but do not start to work until they are activated by the laser or another light source.

Caroline Moore, clinical research fellow at UCL's National Medical Laser Centre, said, 'If proved effective, photodynamic therapy could revolutionize the treatment of prostate cancer.'

'There are currently a number of effective treatments, and survival rates are high, but they can have significant effects on continence and erectile function, which negatively affect patients' quality of life.'

The project has been awarded a pounds 100,000 grant by the Bupa Foundation, a charitable organisation which funds medical research.

Mrs. Moore said men could eventually have photodynamic therapy as outpatient treatment, making it more convenient.

Mark Emberton, a senior lecturer in oncological urology at the Institute of Urology at UCL, added, 'This project will determine whether PDT has the characteristics that a future prostate cancer treatment needs to have.'

'We are particularly keen to establish whether we can achieve targeted destruction of tumour, whilst at the same time preserve both the anatomy of the prostate and the function of the important nerves to preserve potency and muscles

to preserve continence.'

Dr Andrew Vallance-Owen, governor of the Bupa Foundation and its medical director, said, 'We look forward to seeing the results of these studies over the coming years and hope they will benefit patients directly.'

DENDREON'S PROVENGE EXTENDS SURVIVAL IN ADVANCED PROSTATE CANCER

Dendreon Corporation announced updated survival data from patients with advanced prostate cancer with Gleason Scores of seven and less who participated in its completed and previously reported Phase 3 trial (D9901) of Provenge, the Company's investigational immunotherapy for the treatment of prostate cancer.

Patients with Gleason Scores of seven and less receiving Provenge had a significant survival advantage, having on average an 89 percent overall increase in their survival time as compared to placebo (log rank $p = 0.047$, hazard ratio = 1.89). This benefit is reflected by a prolongation in the median survival time in patients receiving Provenge by 8.4 months (30.7 months versus 22.3 months). At 30 months from randomization, the survival rate for Provenge-treated patients is 3.7 times higher than for patients receiving placebo (53 percent versus 14 percent, $p = 0.001$).

Consistent with previous reports, a majority of those patients in D9901 who are still alive have received treatment with Provenge and will continue to be followed according to the study protocol. The Company expects to present this as well as other updated data at major scientific meetings throughout the year.

Prostate cancer is the most common non-skin cancer in the United States. More than one million men in the United States have prostate cancer, with an estimated 220,000 cases diagnosed and 28,900 deaths in 2003.

'This is the longest survival benefit ever reported in a Phase 3 study in late stage prostate cancer,' said Dr. John M. Corman Director of the Virginia Mason Comprehensive Prostate Cancer Clinic and Assistant Clinical Professor of Urology at the University of Washington in Seattle. 'With the combination of this

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exciting new survival data and favorable side effect profile, Provenge has the potential to change the way we treat prostate cancer in the future.”

These updated survival data are consistent with other previously reported data from the D9901 trial that showed significant clinical benefit from Provenge treatment for men with a Gleason Score of seven and less. For these men, the average time to disease progression is more than two-fold longer than that for patients treated with placebo ($p = 0.001$) and the average time to experiencing cancer-related pain is more than 2.5 times longer than that for patients treated with placebo ($p = 0.016$). Treatment was well tolerated, with mild infusion-related fevers and chills the most common adverse events. As previously reported, no benefit has been seen in men with Gleason Scores of eight and higher.

Last year, Dendreon also released data confirming Provenge’s mechanism of action based on T-cell mediated immune response. These data showed that among men treated with Provenge, those with a Gleason Score of seven and less demonstrated a T-cell mediated immune response 7-fold greater than men with a Gleason Score of eight or more ($p = 0.0065$).

“Based on the strength of this survival data, which is consistent with all of the data gathered to date on our other endpoints in the trial for patients with Gleason Scores of seven and less, we are more enthusiastic than ever regarding the pivotal role that Provenge may play in providing a new and well tolerated targeted therapy for prostate cancer patients,” said Mitchell H. Gold, M.D., president and chief executive officer of Dendreon. “The results from this study represent an important milestone in the fight against prostate cancer and indicate that Provenge may provide for a well-tolerated treatment option that offers patients a potential survival advantage.”

The ongoing, pivotal D9902B Phase 3 trial of Provenge is based on the knowledge gained from the results of D9901. The study is being conducted under a Special Protocol Assessment (SPA) agreement with the FDA. Provenge also has Fast Track designation. The pivotal double blind, placebo-controlled D9902B trial is now underway at leading cancer centers around the country. To be eligible for the study, patients must have

metastatic prostate cancer that has progressed following hormone therapy and have a Gleason Score of seven and less. Patients must also be free of cancer-related pain. To learn more about the trial, go to www.dendreon.com or call 1-866-4-PROSTATE (1-866-477-6782).

INTERLEUKIN-24 GENE THERAPY SHOWS PROMISE IN THE FIGHT AGAINST PROSTATE CANCER

According to a study from the United States, “subtraction hybridization identified melanoma differentiation associated gene-7, mda-7, in the context of terminally differentiated human melanoma cells. Based on its structure, cytokine-like properties and proposed mode of action, mda-7 has now been classified as IL-24. When expressed by means of a replication-incompetent adenovirus, Ad.mda-7 induces apoptosis in a broad range of cancer cells, without inducing harmful effects in normal fibroblast or epithelial cells. These unique properties of mda-7/IL-24 suggest that this gene will prove beneficial for cancer gene therapy.”

“We now demonstrate that Ad.mda-7 decreases viability by induction of apoptosis in hormone-responsive (LNCaP) and hormone-independent (DU-145 and PC-3) human prostate carcinomas, without altering growth or survival in early-passage normal human prostate epithelial cells (HuPEC). Ad.mda-7 causes G(2)/M arrest and apoptosis in LNCaP (p53-wildtype), DU-145 (p53 mutant, Bax-negative) and PC-3 (p53-negative) prostate carcinomas, but not in HuPEC. Apoptosis induction correlated with changes in the ratio of pro- to antiapoptotic Bcl-2 protein family members,” reported I.V. Lebedeva and colleagues, Columbia University College of Physicians and Surgeons, Herbert Irving Comprehensive Cancer Center.

“A potential functional role for changes in bcl-2 family gene expression in Ad.mda-7-induced apoptosis was suggested by the finding that forced overexpression of bcl-xL or bcl-2 differentially diminished the apoptotic effect of Ad.mda-7 in prostate carcinomas. These results confirm that induction of apoptosis by the mda-7/IL-24 gene in prostate cancer cells is Bax- and p53-independent and is mediated by mitochondrial pathways involving bcl-2 family gene members.”

“The mda-7/IL-24 gene represents a new class of cancer-specific apoptosis-inducing genes with obvious potential for the targeted gene-based therapy of human prostate cancer,” investigators concluded.

Lebedeva, et al published the results of their research in *Oncogene* (Bcl-2 and Bcl-x(L) differentially protect human prostate cancer cells from induction of apoptosis by melanoma differentiation associated gene-7, mda-7/IL-24. *Oncogene*, 2003;22(54):8758-8773).

FOR CANCER PATIENTS, LAPAROSCOPIC PROSTATECTOMY OFFERS QUICK RECOVERY, FEWER COMPLICATIONS

Mike Erice was shocked when a biopsy determined that he was one of the more than 220,000 men diagnosed with prostate cancer each year. Just a year earlier, results of his annual prostate specific antigen test (PSA) had been excellent, giving the 60-year-old private investigator a sense of security.

This time, however, his doctor included a digital rectal exam and ordered the biopsy when he felt something suspicious. Because prostate cancer kills 28,000 men each year, Erice and his wife quickly researched their options, which included radiation therapy, watchful waiting and radical prostatectomy - major surgery to remove of the cancerous gland.

“If you have cancer, you just want it out. That is how I felt,” he said. “I just didn’t like the idea of major surgery that was painful and would keep me off the job for six weeks.”

Therefore, when they found out about a minimally invasive surgical procedure that removes the gland through small incisions with less pain, fewer days in the hospital and quicker recovery, they came to the Cedars-Sinai Medical Center Endourology Institute, one of about 50 centers nationwide offering the new approach.

“Using minimally invasive techniques to treat prostate cancer became a natural extension of my previous experience in laparoscopic surgery in other areas of urology,” said Gerhard Fuchs, M.D., director of the Institute and one of the world’s pioneers in endourology. “This application was adapted and improved

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HUNT OF A LIFETIME

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One solid month of research culminated with “the decision.” I was going to have daily radiation treatment, five days a week for six weeks, followed by a month of recuperation before receiving radioactive implants.

This was all too much to digest. I desperately needed to clear my head and make sure my attitude was in the right place before treatments started. Judy and I spent almost three weeks splitting our time between bow hunting and following our Brittanys through the pheasant cover. I’ve never found a better way to clear my head and sooth my soul than spending time in the field during the crisp, colorful days of October. My attitude adjustment must have worked because the treatments went quite well and I only missed two days of work.

It’s now October 4, 2003 and I’m sitting in a ground blind watching deer at the far end of a clover field. I can’t do it. This just isn’t going to work. I’m far too distracted by the pain I’m experiencing and my thoughts keep wandering back over everything that has happened since I came back from Colorado.

This past spring I found out that the radiation treatments had failed—the cancer was still alive. Once more though, we had options because we got the news early—we had stayed on top of it, and even though the cancer was more aggressive this time around, it was once again confined to my prostate.

Knowing all the risks involved, I decided to have surgery to remove my prostate and therefore, the cancer as well. In June, doctors tried their best but found that damage from the radiation treatments was so extensive that it prevented them from being able to remove my prostate. My surgery ended with six weeks of recovery and the knowledge that I still had cancer.

Now I’m sitting here only five days after my cryotherapy on September 29. This is crazy! I have a catheter

and a leg bag, I’m sitting on an ice bag in a full-size chair just because it’s opening week of bow season. I’m fidgeting and I’m sure I stick out like a sore thumb. But the woods are bright yellow, the does are gray and their fawns are still showing a bit of summer red. I guess I’ll enjoy this afternoon and just take the rest of the season one day at a time.

If my experience can be used to save just one life—oh what a gift that would be! Regardless of your family history, this can happen to you. If you’re 45 years of age (40 if you have a family history of prostate cancer or are African American), tell your doctor you want to “establish a PSA.” In fact, there is a good chance that I wouldn’t be here today had I not done so myself. One simple test makes all the difference in the world. Do it!

The more I think about this experience over that last three years, the more it seems like chasing those elk in Colorado. When you’re hunting elk, you can be complacent about the direction of the wind. You probably won’t be successful at bagging an elk, but it isn’t a fatal mistake. Don’t be complacent about your health. Establish a PSA today; that way you’ll be around next season to chase that bugling elk.

Meanwhile, Judy and I will continue this hunt for a cure. We’ve moved on them three times now, we’re approaching the top of the ridge and I think I heard the herd bull bugling down below. I guess we’ll check the map and the wind and take a slow walk to the top to see what’s over this next ridge.

Know Your PSA

Prostate Cancer is one of the most common men’s cancers. It is estimated that nearly a quarter million new cases appear per year throughout North America and the number will further rise in years to come. Prostate cancer is *not simply a disease of old men*. It can—and DOES—affect men at any age.

In its early stages, prostate cancer typically has no symptoms. But new diagnostic methods and changes in men’s attitudes due to increased awareness of the disease mean that more and more prostate cancers are found at an early stage, when treatment options are more effective.

Take the following six steps to monitor your prostate health:

1. Consider establishing a ‘baseline PSA’ value—even by age 35 when the likelihood of problems is very low— against which your future values can be compared.
2. Schedule an annual prostate examination with your doctor, starting by age 40 for African Americans and for men with a family history of prostate cancer, but not later than age 45 for all other men.
3. Get BOTH a PSA blood test AND a DRE (Digital Rectal Exam) as a part of your annual exam. Prostate cancer survivor (Retired) General H. Norman Schwarzkopf had a low PSA test result, but his doctor felt a lump during the DRE exam. Further testing confirmed the presence of prostate cancer, and his subsequent treatment was successful.
4. Schedule your annual exam on a memorable day such as your birthday, Father’s Day or during September, which is Prostate Cancer Awareness Month.
5. Keep a record of your exact PSA test result and know ‘the score,’ not just that it is “in the normal range.”
6. Track your PSA from year to year, so you will know if it has increased too much since last year. A rise of 0.75 or more in PSA within a year may require further investigation. The rate of change can be more significant than the number itself.

NUTRITION NEWS

RESEARCHERS STUDY BROCCOLI-DERIVED CHEMICALS TO PREVENT CANCER

Fruits and vegetables are good for overall health, and a newly funded study at the University of Pittsburgh Cancer Institute (UPCI) may show that certain vegetables, such as broccoli, also offer protection against prostate cancer.

UPCI researcher Shivendra Singh, PhD, professor of pharmacology and urology at the University of Pittsburgh School of Medicine, has received a \$1.7 million grant from the U.S. National Cancer Institute to study prostate cancer prevention by phytochemicals found in broccoli called isothiocyanates (ITCs).

“Clearly, what we eat has an effect on the development of diseases such as cancer,” said Singh, also co-leader of UPCI’s cancer biochemoprevention program. “However, we know little about the mechanisms by which certain edible plants like broccoli help our bodies fight prostate cancer and other diseases. Our goal with this study is to better understand the function and relationship of substances in broccoli that appear to be linked to inhibiting prostate cancer growth.”

ITCs are substances in vegetables that are generated when vegetables are either cut or chewed. Previous research has demonstrated that ITCs are highly effective in affording protection against cancer in animal models induced by carcinogens including those in tobacco smoke. Epidemiological research also has shown that increased consumption of vegetables that contain ITCs significantly reduces the risk for prostate cancer.

Singh’s laboratory has found that some naturally occurring ITCs are highly effective in suppressing the growth of human prostate cancer cells at concentrations that are achievable through dietary intake of cruciferous vegetables such as watercress and broccoli. In his current study, Singh seeks to further define the mechanisms by which ITCs induce apoptosis, or cancer cell death, to provide insights

into the key structural relationships between ITCs and cell processes and to identify potential biomarkers that could be useful for future intervention trials involving ITCs.

“The knowledge we gain from this study will help guide us in formulating practical and effective nutritional strategies for the prevention and treatment of prostate cancer,” said Singh. In addition to studies involving broccoli, Singh also is examining the effect of garlic on prostate cancer prevention.

In the United States, only 23% of adults eat five or more fruits and vegetables per day.

STUDY STRENGTHENS LINK BETWEEN ANIMAL PRODUCTS, CANCER RISK FACTORS

A new multicountry study strengthens the link between animal products as risk factors for prostate cancer, and vegetable products, especially onions, as risk reduction factors.

The study investigated links between national diets and prostate cancer mortality rates to identify major risk factors for prostate cancer. The indication that this might be a useful approach comes from comparing national prostate cancer mortality rates: prostate cancer mortality rates in the U.S. and northern Europe are approximately five times higher than in Hong Kong, Iran, Japan, and Turkey.

The findings were published online December 9, 2003, in *European Urology*, (Grant WB. A multicountry ecologic study of risk and risk reduction factors for prostate cancer mortality.),

The strongest risk factor for prostate cancer mortality was animal products, such as meat and dairy products; the strongest risk reduction factors were onions and other protective vegetable products (cereals/grains, beans, fruits, and vegetables, but excluding alcohol, oils, and added sugar (sweeteners)). Thus, fat and protein are risk factors, while complex carbohydrates and antioxidants are risk reduction factors.

This finding points to insulin-like

growth factor-I (IGF-I) being an important risk factor for prostate cancer. IGF-I is also increased by total energy consumption. This study supports earlier reports that allium family vegetables (e.g., garlic, leeks and onions) as important risk reduction factors for prostate cancer. This study also found that alcohol is a minor risk factor. No independent correlation was found for tomatoes, a source of lycopene, thought to reduce the risk of prostate cancer.

Prostate cancer mortality rates for 32 predominantly Caucasian countries for the late 1990s were obtained from the World Health Organization. Dietary supply data were obtained from the Food and Agriculture Organization. Linear and multiple linear regression analyses were conducted for all 32 countries as well as the 20 European countries. Dietary supply data for 1979-81 yielded the highest correlations, indicating that prostate cancer takes approximately 20 years to progress from initiation to death.

These results are similar to results reported by Grant in 2002 for breast cancer, although onions were not found to play a role for breast cancer. Animal products including animal fat and alcohol are now recognized risk factors for breast cancer, and vitamin D is recognized as an important risk reduction factor. UVB radiation, the primary source of vitamin D for many people, was inversely correlated with prostate cancer mortality rates but not in a multiple linear regression with the dietary factors.

These results should provide guidance for reducing the risk of prostate and other cancers.

LYCOPENE INHIBITS THE GROWTH OF NORMAL HUMAN PROSTATE EPITHELIAL CELLS IN VITRO

Researchers hypothesize that lycopene might inhibit the growth of prostatic epithelial cells in vivo.

According to a study from the United States, “Lycopene has repeatedly been shown to inhibit the growth of human prostate cells in vitro. However,

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TREATMENT UPDATE

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over time and became a viable option for men about five years ago.”

Endourologists use scopes and instruments to perform surgical procedures on organs and structures accessible through the urinary tract, without making an incision in a patient’s skin. In situations that do not permit the use of endourologic procedures, the least invasive approach - such as laparoscopic techniques that are accomplished with thin instruments inserted through tiny incisions - are employed. Dr. Fuchs has more than 20 years of experience in this specialty field.

The use of a laparoscope - a lighted tube with a tiny camera lens at the tip - provides a clear, magnified view of the prostate and surrounding nerves, resulting in greater precision, minimal blood loss, and greatly reduced risk of complications such as impairment of urinary continence and erectile function.

“An internal structure that the surgeon sees clearly can be better saved from damage during a procedure,” explained Dr. Fuchs, noting that he expects his patients to maintain functions that are considered essential to quality of life. At least 95 percent of them are fully continent within a year of surgery, for example.

Like most of Dr. Fuchs’ patients undergoing laparoscopic prostatectomy, Mike Erice was out of the hospital in two days, experienced little pain, and said he felt almost like normal within five days. His body continues to function as it did before surgery. “I went back to work after 12 days and was very pleased that my life could continue almost without interruption,” he said. He also recommended Dr. Fuchs and the Endourology Institute to a friend who was recently diagnosed with prostate cancer.

The PSA test, which measures a protein in the bloodstream produced by the cells of the prostate gland, is considered a fairly reliable indicator of the likelihood of prostate cancer, but Erice feels fortunate his physician was thorough.

“Don’t rely on your PSA results alone,” he said. “Get a digital rectal exam because you want to be sure. I am living proof that

prostate cancer can hit any man and surgery today is not what it used to be.”

OLDER PROSTATE CANCER PATIENTS MAY FACE AGE BIAS

When it comes to deciding what kind of treatment a man with prostate cancer receives, the person’s age trumps life expectancy, according to a new study from the University Health Network.

The findings, published in the January edition of the journal *Cancer*, run counter to the accepted medical practice of deciding treatment options based on the length of remaining time a patient is expected to live, rather than his age. The study showed that older men who are healthier and expected to live for at least another 10 years are more likely to receive inadequate cancer treatment than a younger prostate cancer patients who will probably die sooner.

“These are worrisome findings that suggests older prostate cancer patients may face a bias because of age,” said Dr. Shabbir Alibhai, lead author of the study, a physician with University Health Network, and Assistant Professor with the University of Toronto’s Departments of Medicine & Health Policy, Management, and Evaluation. “Even though an older prostate cancer patient’s prognosis may be better than a younger patient’s, they likely won’t receive important treatment that could significantly extend their life.”

Even after adjusting for the remaining life expectancy of a patient, researchers found that a prostate cancer patient younger than 60 years old was 25 times more likely to be treated with curative surgery than a man 70 years or older even if both were expected to have the same number of years left to live.

A study published earlier this year by Dr. Alibhai showed that healthy older men, particular those in their 70s, who have aggressive prostate cancer benefit significantly from surgery or radiation therapy. With appropriate treatment these patients can receive an extra year of life or more, with most having an improved quality of life as well, the earlier study showed.

“This new study is important because it is the strongest data so far to show that many

treating doctors are not sensitive to the issue of age,” said Dr. Neil Fleshner, a urologist and head of Princess Margaret Hospital’s Genitourinary site group. “Life expectancy, not age, should be the main factor in determining which prostate cancer patients receive appropriate treatment.”

The research was supported in part by the Department of Medicine, University of Toronto; the Physicians Services Incorporated Foundation; the Toronto Rehab Foundation; the Canadian Institutes for Health Research; and the Mary Trimmer Chair in Geriatric Medicine Research, University of Toronto.

OKAYAMA UNIVERSITY TO TEST NEW VACCINE FOR CANCER

Okayama University (Japan) will start clinical tests on a new vaccine for cancer next year in a joint project with the U.S.-based Ludwig Institute for Cancer Research, university officials said Tuesday.

At a meeting held the same day, the ethics committee of the university’s medical department approved a plan submitted by Eiichi Nakayama, professor of immunology, to test the new vaccine on prostate cancer patients.

The new vaccine is a combination of an immune-boosting adjuvant and protein with the same antigen as cancer cells. By injecting the mixture under the skin, the lymphocytes of immune cells are activated and it is hoped they will fight off cancer by attacking the protein.

Compared with the conventional vaccine treatment that uses peptides, the new vaccine can be used on a wider range of patients, and has the benefit of activating two types of lymphocytes, the officials said.

The Ludwig Institute of Research, a research body headquartered in the United States, has already started clinical tests at its branch in Melbourne using the same protein with a different adjuvant from that to be tested by Okayama University.

The university’s clinical tests will be conducted on patients aged over 18 who

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NUTRITION NEWS

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previous studies with lycopene have focused on cancer specimens, and it is still unclear whether this carotenoid affects the growth of normal human prostate cells as well.

"Therefore, we investigated the effects of lycopene on normal human prostate epithelial cells (PrEC) by treating them with synthetic all-E-lycopene (up to 5 micro mol/L) and assessing proliferation via [3H]thymidine incorporation," wrote U.C. Obermuller-Jevic and colleagues, University of Southern California, School of Pharmacy.

"The effects of lycopene on cell cycle progression were investigated via flow cytometry. To elucidate whether lycopene modulates cyclins involved in cell cycle progression, protein expressions of cyclins D1 and E were analyzed. The results show that lycopene significantly inhibited the growth of PrEC in a dose-dependent fashion," the researchers wrote.

"Flow cytometry revealed a significant cell cycle arrest in the G0/G1 phase. This effect was confirmed by inhibition of cyclin D, protein expression, whereas cyclin E levels remained unchanged. The results demonstrate that lycopene inhibits growth of nonneoplastic PrEC in vitro," they added.

The researchers concluded: "We hypothesize that lycopene might likewise inhibit the growth of prostatic epithelial cells in vivo. This might have an effect on prostate development and/or on enlargement of prostate tissue as found in benign prostate hyperplasia, a potential precursor of prostate cancer."

Obermuller-Jevic and colleagues published their study in the *Journal of Nutrition* (Lycopene inhibits the growth of normal human prostate epithelial cells in vitro. *J Nutr*, 2003;133(11):3356-3360).

PHASE II STUDY SHOWS CITRUS FRUIT NUTRIENT COMBATS PROSTATE CANCER

A new phase II study validates that men diagnosed with recurring prostate cancer in which conventional therapies have failed may benefit from modified citrus

pectin (MCP), a nutrient derived from citrus fruits.

The study tested 10 men on the rate of their prostate-specific antigen doubling time (PSADT) before and after taking PectaSol MCP. The patients, ages 57-79, had undergone prior conventional medical treatments including radical prostatectomy, external beam radiation, or cryosurgery and experienced a recurrence of cancer as determined by rising PSA levels. In this 12-month study, seven of the patients experienced a significant lengthening in their PSADT, which correlates to slower cancer progression and can lead to prolonged life.

"It is hoped that by slowing the PSADT with MCP we can delay the need for more aggressive therapy and perhaps enhance the quality of life of those patients exhibiting PSA recurrence after surgery or radiation therapy," said Stephen B. Strum, MD, FACP, a coauthor of the study, published in *Prostate Cancer and Prostatic Diseases Journal* (www.nature.com/pcan).

Modified citrus pectin is derived from the peels and pulps of fruits, such as oranges and grapefruits, which contain citrus pectin, a naturally occurring soluble fiber. Citrus pectin is processed or "modified" into shorter-chain molecules that are more easily absorbed from the digestive tract and into the bloodstream. This modified citrus pectin, once in the bloodstream, becomes a powerful cancer-fighting nutrient, binding to cancer cells and preventing growth and metastasis (Guess BW, Strum S, et al., Modified citrus pectin (MCP) increases the prostate-specific antigen doubling time in men with prostate cancer: a phase II pilot study. *Prostate Cancer and Prostatic Diseases Journal*, 2003;6(4):301-304).

"While MCP shows promise to treat a wide range of cancers, this study focused on prostate cancer, since disease progression is easily measured through PSA levels," said Isaac Eliaz, MD, formulator of Pecta-Sol MCP, which was used in the study. "This phase two study with MCP has clearly shown effectiveness. Now it's time to

expand the patient pool and move on to phase III research."

VITAMIN D SHOULD BE A PRIORITY FOR MEN OF ALL AGES

Adequate vitamin D nutrition should be a priority for men of all ages, researchers report.

According to a study from the United States, "Human prostate cells contain receptors for 1alpha, 25-dihydroxyvitamin D, the active form of vitamin D.

"Prostate cancer cells respond to vitamin D-3 with increases in differentiation and apoptosis, and decreases in proliferation, invasiveness and metastasis. These findings strongly support the use of vitamin D-based therapies for prostate cancer and/or as a second-line therapy if androgen deprivation fails," wrote T.C. Chen and colleagues, Boston University School of Medicine.

"The association between either decreased sun exposure or vitamin D deficiency and the increased risk of prostate cancer at an earlier age, and with a more aggressive progression, indicates that adequate vitamin D nutrition should be a priority for men of all ages," the researchers stated.

The researchers concluded: "Here we summarize recent advances in epidemiological and biochemical studies of the endocrine and autocrine systems associated with vitamin D and their implications for prostate cancer and in the evaluation of vitamin D-3 and its analogs in preventing and/or treating prostate cancer."

Chen and colleagues published their study in *Trends in Endocrinology and Metabolism* (Vitamin D and prostate cancer prevention and treatment. *Trends Endocrinol Metab*, 2003;14(9):423-430).

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TREATMENT UPDATE

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have progressive prostate cancer and who have shown no signs of improvement with conventional treatment.

A group of about 10 patients will be injected with the new vaccine four times every two weeks for about six months.

Nakayama said that if the safety and effectiveness of the vaccine can be confirmed, clinical tests will be made on other types of cancer patients.

RESEARCHERS IDENTIFY MOLECULAR CAUSE OF DRUG-RESISTANT DISEASE

Cancer researchers at the University of California Los Angeles (UCLA) have discovered a surprisingly straightforward mechanism that causes prostate cancer cells to develop resistance to cancer-fighting drugs. The studies also point to specific ways to improve drugs to prevent the problem of drug resistance in prostate tumors.

The researchers describe the molecular mechanism of resistance to anti-androgen therapy for prostate cancer in an advance online publication in the Dec 21, 2003, issue of the journal *Nature Medicine*.

Dr. Charles Sawyers at UCLA's Jonsson Cancer Center and a Howard Hughes Medical Institute (HHMI) investigator led the research. Sawyers and his colleagues were trying to understand why drug therapy for prostate cancer often fails despite early success. The current "gold standard" for treatment of prostate cancer consists of a drug regimen that lowers testosterone levels administered with "anti-androgen" drugs. These drugs compete for the binding site on the testosterone receptor proteins located in prostate cancer cells. When testosterone activates these receptors, they, in turn, switch on internal cellular machinery that drives the growth of the tumors.

"While drug therapy works in almost everyone for a period of time, usually measured in years, it stops working, despite the fact that patients continue to take the drugs," said Sawyers. "And that is why men die of this disease."

According to Sawyers, the tumor cells become "hormone-refractory," meaning they somehow "learn" to continue to

proliferate even in the absence of the hormone, androgen, which is their normal growth signal.

The scientists reasoned that one of the ways to get at the molecular signals driving drug resistance was to use DNA microarray technology to look for specific genes that are switched on only in drug-resistant prostate cancer cells. DNA microarrays measure the relative levels of gene expression in cells.

Before the researchers could look for genes that are switched on in drug-resistant cells, they first used a technique called xenografting to establish hormone-sensitive human prostate cancers in mice. After the human tumors were established in the mice, the scientists treated the mice so they had lower androgen levels, to cause the cancers to progress to a drug-resistant state.

"This process mimics what happens in patients," said Sawyers. "And the advantage for gene-profiling studies is that we end up with hormone-refractory cells that are directly derived from hormone-sensitive cells. So, they are otherwise genetically matched."

When the researchers used DNA microarrays, or "gene chips" to compare gene expression in seven different sets of the two genetically matched types of prostate cancers, they found a surprise.

"The microarray data pointed us to just one consistent change among all the xenografts," said Sawyers. "And that was a change in the expression of the gene for the androgen receptor itself." According to Sawyers, the identification of a single difference between hormone-sensitive and hormone-refractory cancers was entirely unexpected.

"We never really required that there even be one consistent change," said Sawyers. "We were fully prepared to find a signature of expression differences in some of the xenografts and another signature in others."

The researchers then performed additional experiments in which they established that the alteration in the androgen receptor gene produced functional changes in the cancer cells. Those studies showed that when the scientists engineered hormone-sensitive cells to overexpress genes for the androgen receptor, the cells behaved like hormone-refractory cells. Conversely,

when they reduced receptor gene expression in hormone-refractory cells, those cells began to behave like hormone-sensitive cells.

They also established that the overexpressed hormone receptor still required binding by the ligand androgen in order to become hormone-refractory. "This finding is perhaps the most important," said Sawyers. "Everyone, including me, would have thought that you did not need to have ligand binding if you overexpressed the receptor. The fact that it is still required is a surprise, and it is very important for drug discovery. The current anti-androgen drugs work by competing for this ligand-binding site, and this finding means that the site is still a key target for improved drugs."

According to the researchers, the fact that the receptors still require their hormone ligands means that receptor-overexpressing tumor cells are likely activated by even low levels of androgen in patients who are already being treated to reduce their testosterone levels. Other experiments by the researchers revealed that the normal cell-signaling machinery was still involved in the cancer cells' response to androgens.

Sawyers collaborated on the studies with HHMI investigator Michael G. Rosenfeld at the University of California, San Diego. Co-lead authors were Charlie Chen and Derek Welsbie of Sawyers' laboratory. Another co-author on the paper is from the University of Washington in Seattle.

The studies also revealed that higher levels of receptors somehow convert anti-androgen drugs into "agonist" drugs that activate receptors. "It's counterintuitive, and it's quite surprising," said Rosenfeld. "We now have only a few clues to how this conversion occurs. Our guess is that as the level of androgen receptor increases, they cannot recruit the apparatus in the cell that an antagonist needs to prevent the action of androgen. Also, the exquisite sensitivity of prostatic cells to androgen that drives their proliferation may be another part of the story."

Sawyers and Rosenfeld are now collaborating on studies to determine how this conversion arises. Their hope is that they can use information gleaned from their research to identify a new generation of androgen antagonists that will be more effective while avoiding the phenomenon of conversion.