

PROSTATE CANCER COMMUNICATION

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POTPOURRI OF PROSTATE PEARLS AND INSIGHTS

By Robert L Leibowitz, M.D.
Compassionate Oncology, Los Angeles, CA
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The Value of Scans For Staging Prostate Cancer (CaP):

The Absence of Proof is Not Proof of Absence - My office overlooks Beverly Hills High School, their athletic fields, basketball court, and running track. At any given time, we might see five or six people playing basketball. If we were flying in a plane at 32,000 feet and looked down, we would be unable to see anyone playing basketball; we would not be able to identify the basketball court, athletic field, or even the school. Carrying the analogy a step further, if we flew over the Rose Bowl on New Year's Day and looked down, we **would** be able to observe some activity. But, it takes a Rose Bowl full of cancer cells before you get an abnormal bone scan, CT scan, MRI scan, or any other type of scan.

Unfortunately, when a patient is told by their urologist and/or radiation therapist that their scans are normal and that there is no evidence of metastatic disease; patients logically conclude that their prostate cancer has not already spread (metastasized). However, since it takes a Rose Bowl full of cancer cells to cause an abnormal scan, it means that normal scans are absolutely **worthless** for trying **to exclude metastases**. But most patients do not understand the severe limitations of scans. They are not educated, and what is tragic is the fact that most patients place too much trust in the first prostate cancer doctor they see. Most patients tend to follow the recommendations of that first CaP doctor. Believing that the normal scans "prove" local disease only, and exclude the possibility of metastatic disease anywhere in the body, men then consent to radical prostatectomy, radiation therapy, seeds, or other local treatments. If patients truly understood that normal scans are meaningless to exclude metastatic disease, I believe that far fewer men would consent to undergo radical local procedures.

It is usually accepted that 50-70% of a vertebral (spinal) bone must be destroyed by cancer before you see an abnormal x-ray. Bone scans do not become abnormal until approximately 10-15% of the bone is replaced by cancer cells. Since there are two billion cancer cells in one inch of cancer,

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think of how many cells must be present before they cause an abnormal bone, CT and/or MRI scan. Lymph glands identified on CT or MRI scans are not considered abnormal until they are larger than 1 centimeter (10 millimeters). One centimeter equals approximately four-tenths of an inch; one inch, two billion cancer cells; therefore, 0.4 inches of tumor contains hundreds of millions of cancer cells.

Almost always doctors recommend the treatment that they administer. Urologists urge radical prostatectomy; radiation therapists advise radiation therapy and/or seeds. Some surgeons or radiation therapists may emphasize that their unique skills, techniques, or type of radiation therapy give better results with higher success rates compared to others in their field. This is not the case for men treated with Triple Hormone Blockade®/Leibowitz protocol because any doctor can prescribe and administer the same medicines that I pioneered. To be sure, it is essential to use the exact protocol we use, but that information has been published and is available at no charge. This means that you do not have to see us in order to be treated with Triple Hormone Blockade®.

The best advice anyone can give to a patient with newly diagnosed prostate cancer is to go to several different prostate cancer men's support group meet-

ings before deciding how to be treated. He will hear men lament, "If only I knew then what I know now, I never would have allowed radical prostatectomy or radiation therapy, seeds and/or cryotherapy." Talk to the men and/or their significant others who attend these support group meetings, and find out how their quality of life has been permanently affected. You will also learn that the frequency of side effects resulting from radical local therapies are far greater than the complication rates quoted to you, and that the chances for success are far lower.

In spite of failing to inform patients that normal scans do not by any means exclude the presence of metastases, patients are often told by their urologist and/or radiation therapist that **if** their prostate cancer cells have not spread beyond the prostate, then the **radical** local therapy should "cure" them. If there was a way to know for certain that all of your prostate cancer cells were limited to one of your fingernails, then removing the fingernail cures you. If, through Divine Intervention, you knew that all of your prostate cancer cells were confined to the prostate, and if surgery itself does not spread cancer cells (which it has been shown to do), then you could be cured with a radical prostatectomy. But this is a circular argument. The most important word in "If they are all in one place," is the word, "If." Prostate cancer cells have had ten

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

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

or more years to spread before a man is diagnosed. This gives cancer cells a long time to escape from your fingernail and/or your prostate gland before your diagnosis/treatment. Radical local therapies cannot cure you if significant numbers of prostate cancer cells have escaped from your prostate before or during surgery. Autopsy studies show that 27% of men in their 30's and 34% of men in their 40's already have prostate cancer. These are standard **invasive** prostate cancers, not some premalignant condition or noninvasive cancer. Each decade of life increases the incidence of prostate cancer in men by approximately 10%, so that ultimately 80% of men in their 70's and 80's have prostate cancer. Since invasive prostate cancer is already present in such a high percentage of men younger than 50, we can see that prostate cancer cells almost always have had one or more decades to grow, mutate, and even spread long before the disease is diagnosable. The next time you hear a doctor tell a patient that he has "early" prostate cancer, you know that the statement is essentially an oxymoron. Studies have been done where men with clinically localized prostate cancer have samples from their bone marrows obtained prior to the start of their radical prostatectomy. An amazing 74% of men believed to have "early" clinically localized prostate cancer already have PSA secreting cells in their bone marrow. Men with BPH do not have PSA secreting cells in their bone marrow. Urologists will not dispute these facts, but argue that not all of these cells will become viable islands of metastatic disease. But men with these cells have higher rates of recurrence.

Does Surgery Disseminate or Accelerate the Growth of Cancer?

In the journal, *Lancet*, 1996; 347:260, author Baum, M., asks the question, "Does surgery disseminate or accelerate cancer?" Here is an enormously profound statement with major implications for anyone considering radical prostatectomy, radiation therapy and/or seeds. An article reported in the *Scandinavian Journal of Urology and Nephrology*, 1995; 172:65-77, by Iversen, P., et al., found no survival benefit for radical prostatectomy versus **no** treatment for prostate cancer patients randomized to radical prostatectomy plus placebo versus placebo alone. Imagine that. Does it surprise you that treatment with a placebo pill is as effective as radical prostatectomy? This was a prospective randomized study that followed 111 patients for 23 years. If you previously had a radical prostatectomy, did your urologist inform you prior to surgery about this study that did not find any survival advantage to radical prostatectomy. In this study, radical prostatectomy did not even reduce the risk for developing metastatic disease compared to patients who were treated only with a placebo pill. What makes this study even more impressive is the fact that there was an average 23-year follow-up for these patients. Therefore, the study could not be criticized by claiming that if only patients were followed a little longer, the group treated by placebo would have been found to have an increased risk for developing metastatic disease.

The NCI today is conducting the PIVOT Trial, which stands for Prostate Intervention Versus Observation Therapy. This study is once again comparing radical prostatectomy to no treatment. If you have newly diagnosed clinically localized prostate cancer, and went to the NCI and asked to participate in one of their ongoing clinical trials to help determine the best treatment for men with so-called clinically localized prostate cancer, the computer would randomly assign you to one of two arms. In one arm, you would have a radical prostatectomy; in the other arm, your treatment would be observation therapy, which is another term that means no treatment. If you have newly diagnosed prostate cancer, and asked to enter their current high priority prostate cancer treatment trial, there is a 50% probability you would be told, "We are not going to treat you, we are only going to follow you."

If the value of radical prostatectomy, or radiation therapy, or seeds had already been proven to be both necessary and effective, the National Cancer Institute could not do a study in which 50% of men receive no treatment other than observation. This should convince our readers that the value of radical prostatectomy for improving overall survival for men with prostate cancer remains to be proven. To Compassionate Oncology, this means that radical prostatectomy as a treatment option for prostate cancer must still be considered experimental.

Why the Word “Cure” Does Not Appear in the Consultation From Your Radiation Therapist:

What are your chances for “cure” if you are treated with radiation therapy and/or seeds? Get a copy of your radiation therapy consultation. The word “cure” will not appear in the consult. The doctor will use terms such as “success,” “control,” “remission,” or other poorly defined adjectives. Ask him/her to write down in your medical record your chances for “cure,” and have him/her define the word cure in your records. Ask your urologist and radiation therapist:

1. Will your treatment prolong my life?
2. Will your treatment improve or worsen my quality of life?

Then ask him/her to give you a copy of your medical record with that information recorded. Ask him/her for the specific medical references that confirm his answers. If he/she cannot provide you with the references, it is because they do not exist. Do not accept anything less than the references that confirm the promised **cure** rates. By the way, in modern radiation therapy literature, there are over 55 different definitions for “cure.” For men treated by radical prostatectomy, there are approximately 50 different definitions of cure. By choosing a different definition of cure, you are able to markedly improve your reported “cure rates.” Were you aware of this “sleight of hand”; I mean, this interesting way to improve cure rates without changing anything except your definition of cure? Many radiation therapists do not even agree on what PSA level to use to define “success,” let alone cure. But all you as the prostate cancer patient really care about...is cure. Total and permanent cure. If it comes back, it was not cured. The burden of proof as to whether local therapy can cure you lies with the radiation therapist and urologist. If they cannot provide references that show radiation therapy or radical prostatectomy is both necessary and effective, why risk all of those side effects?

Hormone Blockade: Continuous, Intermittent, or?

I am certain that the most effective way to use hormone blockade is neither continuous, nor intermittent, since both of these methods hasten evolution to hormone resistant/refractory prostate cancer. The “best” way to use hormone blockade (opinion) is to treat with one 13-month cycle of Triple Hormone Blockade®/Leibowitz protocol for patients presenting with previously untreated, low-risk or intermediate-risk, clinically localized prostate cancer. For those who disagree with me, one of my original and favorite quotes is: “Everyone is entitled to their own (wrong) opinion” (even me). For men who have previously been treated with hormone blockade, my approach to controlling their prostate cancer is to use all effective medications to postpone, or hopefully prevent, the need to go back on another cycle of hormone blockade. You cannot develop hormone resistant or hormone refractory prostate cancer unless you are re-treated with another cycle of hormone blockade, since the definition of those conditions is a rising PSA while on hormone blockade. If we can find effective, non-hormone blocking medicines to control a rising PSA, then you can remain off hormone blockade. **I am certain that the longer you are off hormone blockade, the much longer you will live** (opinion, but the logic, to me, is essentially irrefutable, and the only possible interpretation). Every time you are treated with another cycle of hormone blockade, your time on hormone blockade lengthens, your time off hormone blockade shortens, and the PSA nadir on each subsequent cycle of hormone blockade is higher. This occurs because there are ever increasing numbers of hormone resistant cells remaining after each subsequent hormone blockade cycle; each cell makes PSA; therefore, the greater the number of these resistant cells, the higher the PSA nadir. You can recognize this pattern as evolving hormone resistant prostate cancer.

Continuous hormone blockade is the worst way to use hormone blockade since it essentially always evolves to hormone resistant/refractory prostate cancer (HRPC), and does so faster than IAB. Intermittent androgen blockade (IAB) is far superior to continuous androgen blockade (CAB), if for no other reason than the fact that when you are off hormone blockade, your quality of life markedly improves. This is fact, not opinion.

Beginning in 1992, I no longer used CAB on any patient except a minority of men with metastatic, hormone refractory prostate cancer. Our CaP experts review the same medical articles that I do, but their opinions almost always seem so distant and different from mine.

Since 1994, I have written that IAB will be found to be far more effective than CAB. At the Sixth Annual Massachusetts Prostate Cancer Symposium on May 21, 2003, I was one of two keynote speakers; the other was Dr. Phil Kantoff from Massachusetts General. The sponsors included Massachusetts General Hospital Cancer Center, Dana-Farber/ Harvard Cancer Center, Tufts-New England Cancer Center, Beth Israel Deaconess Medical Center (also a Harvard Hospital), the American Cancer Society, and others. I was the only doctor at the Symposium who expressed the opinion that intermittent androgen blockade was superior to continuous androgen blockade. A few years earlier, at the same conference, I was one of many prostate cancer specialists that participated in a panel discussion on IAB versus CAB. Some of the other participants included Dr. Philip Kantoff, moderator; Dr. Anthony D'Amico, a Harvard radiation therapist; Dr. Glen Bubly, a Harvard oncologist; Dr. Mark Garnick, a medical oncologist; at least one Harvard urologist, and a number of other nationally acknowledged prostate cancer experts. Dr. Kantoff, the moderator, asked the panelists whether they recommended IAB. Everyone said no, except for me. Dr. Kantoff then asked the panelists to predict whether ongoing or future studies would prove CAB or IAB superior. Not being shy, I spoke first, and stated that I was certain that treatment with IAB prolongs survival compared to CAB. When polled by Dr. Kantoff, every one of the other panelists stated that CAB would be found superior.

Ever since the term IAB was first used, CaP national and most international experts essentially had universal agreement that you should never recommend using IAB. They told us that CHB was the “standard of practice” and throughout the 1990's that was their final word on the subject. Beginning perhaps around 2003 or 2004, there was a slight change in their position. They still admonished us to only use CHB in our practices for all CaP patients except for patients registered in a clinical trial comparing CHB to IAB.

Like me, the reader might wonder how CHB became the standard of practice. How many studies were done before it was accepted as standard of practice? How many other methods of HB were tested against CHB? These latter questions are easy to answer – none and none!! How can I be so certain? Because the first hormone blockade used to treat metastatic CaP was orchiectomy (castration) and that procedure is not reversible surgically. Many years ago, I wrote that “castration should be outlawed.” Now, I feel that way more strongly than ever.

In February of 2007, at the Third International Symposium on Prostate Cancer jointly sponsored by ASCO, AUA, etc., I again had the opportunity to address a panel following some lectures. I asked about their use of CAB versus IAB. They each stated that they do not recommend IAB for any of their patients. I then asked their opinions regarding the outcomes of ongoing studies comparing continuous to intermittent HB. They all responded that they were convinced CHB would be proven to be more effective than IAB. Under my breath I mumbled: “Everyone is entitled to their own wrong opinion.”

To reiterate and re-emphasize their opinion, our CaP experts in April 2007, got together and published brand new joint guidelines by ASCO/AUA for using hormone blockade. Once again, they concluded that IAB should only be used in the context of a clinical trial. These practice guidelines, as they are called, are gradually becoming mandates. Insurance companies are already using some ASCO “guidelines” for other oncology conditions to determine whether to reimburse for certain treatments or not. I believe that we are losing the option to individualize treatments. “They” want us to use a one size fits all approach to treating cancer. Patients need to protest or we will not be able to treat them other than by “clinical guidelines.”

For the past 14 years, we have been “taught” not to use IAB. The correct and the only correct form of HB to use is continuous. Our experts have spoken the same message for the past 14 years. But in the August 10,

2007 issue of *Oncology Times*, Dr. Phil Kantoff stated that IAB “is at least as good as, if not better than CAB.” I first read this September 5, 2007, and sent a letter to Dr. Kantoff to confirm the facts in the article. Dr. Kantoff, being the true gentleman that I have always admired and respected (in spite of differences of opinion regarding certain CaP treatments) acknowledged that the information in the article was correct. There are some IAB exceptions that we both agree upon, especially for a patient whose PSA does not fall “low enough.” He went on to tell me that he was flattered that I agreed with his interpretation of the data.

More recently I believe that another expert, Dr. Ian Thompson, now agrees that IAB should be considered a “standard treatment.” But for the past 14 years, those of us who used IAB were criticized (loudly and continuously). It seems that we practiced “bad” medicine for 14 years, but then our experts decided that today it is good medicine. What is ironic is that “they still believe we were wrong for those 14 years and they were correct. I know my patients are happy they were treated the “wrong way” since it turned out to be the “right way.”

I am happy to be able to declare victory for IAB over CHB. This means that CHB moves from the #1 position to #2 according to the experts, and IAB from #2 to #1.

Now we need to “show off” our treatment results which prove that the best form of hormone blockade is a single cycle of Triple Hormone Blockade®/Leibowitz protocol followed by Proscar, 5 mg once a day, so-called finasteride maintenance® therapy.

In order to postpone and, hopefully, prevent the need to go back on another cycle of HB, in patients whose PSA rises too rapidly and/or too high, we have, fortunately, pioneered an extraordinarily successful treatment option that is not chemotherapy, is not hormone blockade, and enhances your immune system. Isn't this exactly what you are looking for? The name of this treatment option is prostate cancer antiangiogenic cocktail (AAC). Space permitting, and if the creek does not rise too high, we will elaborate on AAC in the next (exciting) edition of PAACT's Prostate Cancer Communication newsletter. Stay tuned.....

®Triple hormone blockade, triple androgen blockade, and finasteride maintenance therapy are registered trademarks of Robert L. Leibowitz, M.D.

WHAT THE HECK HAS BEEN GOING ON IN MY WORLD-PART 17

(When I think of the number 17, I think about the age I was when I was first allowed to go to an R-rated movie...oops I actually snuck into an R-rated movie when I was 15 years old---sorry mom and dad)!!!

By Mark A. Moyad, M.D., M.P.H.

(Note: You can now log on to www.seminarsprevaltmed.com and order the latest medical journal info, renew a subscription, and get past reprints of articles)

Michigan rules! Football prediction: Michigan 42 and Ohio State 14 (note: I came up with this prediction after drinking a few beers!)

92) American ginseng (also known as “panax quinquefolius”) at 1,000 to 2,000 mg per day may reduce fatigue and increase energy levels during and after cancer treatment. Finally, an herbal product that may work well in cancer patients!

(Reference: Barton DL, Soori GS, Bauer B, Sloan J, Johnson PA, Figueras C, Duane S, Dakhil S, Liu H, Loprinzi CL: A pilot, multi-dose, placebo-controlled evaluation of American ginseng (panax quinquefolius) to improve cancer-related fatigue: NCCTG trial NO3CA. *J Clin Oncol* 25(18S Part I of II), page 493S, abstract 9001, 2007.)

Herbal products in my opinion carry more hype than the Notre Dame Football team before the 2007 season started if you know what I mean. Remember Saw Palmetto or black cohosh!? However, once in a while you have to give credit where credit is due my friends and this herbal product impressed the heck out of me, so let's review the study, which has yet to be published.

Fatigue has become one of the most common side effects of cancer treatment, especially for those receiving chemotherapy, hormone suppressive therapy and other types of treatment including radiation therapy. The choices for reducing fatigue include: weight lifting and a variety of over the counter and prescription drugs that come with all sorts of catches and not much research. However, there may be another cost-effective treatment. Laboratory studies have suggested that American ginseng may reduce fatigue, but it needed to be tested in a well-done clinical trial. Researchers decided to test 3 doses of ginseng (750 mg, 1,000 mg, or 2,000 mg per day) compared to placebo for a period of 8 weeks. The ginseng and placebo were given in 2 divided doses a day to equal the total amount per day. For example in the 2,000 mg per day group, a total of 1,000 mg was given at two different times of the day.

Patients with a life expectancy of at least 6 months and a history of cancer-related fatigue for about 1 month were eligible for this randomized trial. Patients were not allowed in this study if they had used ginseng before, used steroid medication for a long period of time or had cancer in their brain tissue. Evaluation of patients was completed at the beginning of the study (baseline), 4 weeks and at 8 weeks. Researchers used a variety of measures to determine if ginseng worked better than placebo including:

- The Brief Fatigue Inventory (BFI)
- Vitality subscale of the SF-36
- Several analogue scales of perceived benefit

A total of 282 patients (that's right - an unusually high number for a dietary supplement trial which makes this trial wonderfully unique), which included approximately 69 to 72 patients per study group were enrolled in the study from October 21, 2005 to July 5, 2006. There were no significant side effects between the different groups of the study (including placebo), and an equal number of patients dropped out of the trial in each group.

The preliminary results were truly a big surprise that may have immediate application in patients with fatigue, especially from cancer or perhaps due to other scenarios. Does this study prove that ginseng works? Not necessarily, but to be honest if this was a prescription medication with such a low rate of side effects I believe it would be discussed with patients immediately. I think the authors summarized the results of this study the best by saying "This randomized pilot trial provided data to suggest that American Ginseng doses of 1,000-2,000 mg per day may be effective for alleviating cancer related fatigue. Therefore, further study of American Ginseng in cancer survivors appears warranted." This is exciting and it should be further mentioned that this trial was conducted at a variety of well-known and objective academic centers including the Mayo Clinic in Rochester, MN, which makes the results that much more impressive in my opinion. However, I have to believe that just because the researchers did not find a side effect does not mean it does not actually have one. For example, previous studies of ginseng have shown that it can be a blood thinner or it may significantly reduce blood sugar levels so I would still be careful before running out and buying this product without talking to your favorite doctor first and foremost.

93) Not enough younger and older individuals are getting the pertussis (DTaP or Tdap) vaccine for the prevention of this respiratory tract infection that is highly contagious.

(Reference: Landers SJ: "Outbreaks" show pertussis diagnosis not easy": the CDC seeks a better test to differentiate pertussis from other respiratory illnesses. American Medical News from the American Medical Association, 50(35), page 21, September 17, 2007.)

Pertussis is highly contagious, but especially so before the patient begins to cough, and it begins as a respiratory tract infection that seems similar to a simple cold. The best way to prevent this problem is through vaccination, and combined vaccines are used to prevent diphtheria, tetanus and pertussis (DTaP). It is given to young children and is known as "DTap" in older children and adults it is known as "Tdap." The uppercase letters are used to mention full-strength doses of diphtheria and pertussis and lowercase "d" and "p" stand for reduced doses, and the "a" stands for acellular.

Pertussis can be difficult to diagnose in a rapid manner and there have been 3 recent potential outbreaks of this disease in Massachusetts, New Hampshire, and Tennessee. Again, there is no simple and rapid test for it and it seems to initially resemble a cold. However, a test known as polymerase chain reaction (PCR) is the most popular and accurate test to see if one has the disease, but it is not cheap, and some people will be told they have the disease when they do not (false-positive test). Regardless, experts are agreeing that those with a cough and positive PCR test should be treated as if they have pertussis. Using a two-target PCR test has been more accurate than the single specificity test that is actually more common in the U.S. Still, the PCR test is more accurate the earlier it is given in the disease course, but after a few weeks of coughing the test becomes even more accurate, which is around the time the doctor may suspect pertussis in some individuals. Regardless, just getting the vaccine would prevent a lot of this mess.

Bottom Line

The Center for Disease Control (CDC) Advisory Committee on Immunization Practices recommends that individuals ages 11 to 64 receive the Tdap vaccine, which is predicted to be 85% to 92% effective in preventing pertussis.

94) The FDA approved orlistat, the weight loss drug, for over-the-counter use. But will very many people buy this lower dose version of a drug that never sold that well when it was first introduced into doctor's offices in 1999?

(Reference: FDA approves orlistat for over-the-counter use, accessed March 9, 2007, <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01557.html> P07-15, February 7, 2007.)

The FDA approved the over the counter (OTC) sale of orlistat (Xenical) for weight loss for adults and it is already at your local pharmacy and grocery store. The drug was initially approved in 1999 as a drug to treat obesity at a higher dose than the over the counter version. This form of OTC orlistat is produced by GlaxoSmithKline under the name "Alli" and will be indicated for adults age 18-years or older along with a low-calorie, low-fat diet, and exercise. The drug works by reducing the intestinal absorption of dietary fat. The 60 mg capsule can be ingested up to 3 times a day with each fat-containing meal, but the company also recommends taking a multivitamin in the evening because of the concern of additional loss of vitamin and mineral absorption. Bowel problems are the most common side effect, which include loose stools, but eating a reduced fat diet could reduce the risk of this side effect. Individuals that have had an organ transplant should not take the OTC medication because of potential drug interactions. Individuals on blood thinning medication or those being treated for diabetes and thyroid disease should also talk to their doctor about whether or not it is safe to take this medication.

This drug has not been without a lot of controversy. When the FDA panel originally agreed to allow the over the counter sale of this drug there was some concern by a number of advocacy groups. This pill as a prescription was not exactly a blockbuster selling drug and the results for weight loss were not very impressive, and the OTC amount is less than the prescription amount. Also, the side effects associated with this drug were well-known by many patients. Finally, the cost could be as much as 2 dollars a day. Also, is reducing fat intake healthy, or is it smarter to eat certain healthy fats as most nutrition experts recommend. Regardless, this drug has garnered a lot of attention and may help some individuals that need a little help to jump-start their weight loss program.

95) Deer hunting may be risky for men with poor heart health.

(Reference: Haapaniemi S: Am J Cardiology, July 15, 2007.)

Men with heart disease or risk factors for heart disease may be putting their health at risk by going deer hunting. A study of 25 middle-aged male deer hunters found that certain activities that hunters have to follow could be dangerous to their health. For example, walking over a rough terrain, and shooting an animal and dragging its remains increased men's heart rates significantly. In certain cases, these activities also led to potentially dangerous changes in the rhythm of the heart, or a reduced oxygen delivery to the heart.

Out of the 25 hunters, 17 had coronary heart disease, while the others had risk factors such as smoking, obesity, or high cholesterol and blood pressure. These findings suggest that in certain men hunting can increase the risk of a heart attack or going into cardiac arrest.

Men in this study were outfitted with a portable monitor that records the heart's electrical activity. They wore the heart monitor during a day of deer hunting. Then this information was compared to their heart being monitored while they were placed on a treadmill on a different day. In general, this preliminary research showed that hunting put men's hearts under more of a strain compared to a treadmill. A total of 10 men had their heart rate going beyond the maximum of safety seen on the treadmill while hunting and several had dangerous heart responses different from those seen on the treadmill. A total of 3 men had reduced flow to the heart not seen while on the treadmill, but only while hunting, and 3 men with heart disease had heart rhythm problems hunting, but not seen on the treadmill. Researchers believe that the combination of the physical demands of hunting along with an adrenaline rush, and the stress of rough walking terrain and cold weather may place extra strain or stress on the heart. What is also concerning is that most men in this study were already involved in regular exercise programs so these results could have been much worse for the hunter that hardly takes care of himself and his health, but likes to go hunting.

Bottom Line

Is this more like leveling of the playing field or is this really a health issue?! Is it possible that deer hunters and other hunters in general may be putting their health at risk because of the cardiovascular demands of hunting? This seems to be the case and I have never given this much thought, but hunting is physically demanding on the body and if a person (man or woman) is not in shape, this can increase the risk of injury and cardiac problems. I guess the message should be that staying in shape is important for all of us, including hunters.

96) Perhaps a blood test that has been used for decades in general medicine known as “C-reactive protein” (CRP), may be able to predict prognosis in prostate cancer patients, and may predict the risk of erectile dysfunction (ED) in other patients when using the “high-sensitivity-C-reactive protein” (hs-CRP) test.

(Reference: Nakashima J, Kikuchi E, Miyajima A, et al: Simple stratification of survival using bone scan and serum c-reactive protein in prostate cancer patients with metastases. *J Urol* 177(4):page 336-337, abstract 1020, 2007 & Rokkas K, Loakeimidis N, Vlachopoulos C, et al: Correlation between penile doppler find

ings and c-reactive protein levels in patients with erectile dysfunction of vascular origin. *J Urol* 177(4):page 231, abstract 689, 2007)

It is interesting that blood levels of IL-6 have been reported to be a significant prognostic factor in prostate cancer patients in some studies. However, determining the level of IL-6 is not always very easy in the clinic, but IL-6 does stimulate the production of CRP in the liver so perhaps CRP would be a cheaper and easier test? Researchers from Tokyo, Japan decided to study this issue. Serum PSA levels were measured in 126 prostate cancer patients (98 with cancer in the bone) with metastases. The blood level of IL-6 correlated with the CRP level ($r = 0.826$). The blood levels of CRP, PSA, and alkaline phosphatase (ALP) increased significantly and hemoglobin decreased significantly in men with advancing disease. However, in a closer statistical look at the research only CRP levels and bone scan disease amounts were correlated with survival of patients. Men with a CRP less than or equal to 0.15 mg/dl were considered low-risk, CRP of greater than 0.15 mg/dl were considered intermediate-risk and higher-risk if there was more extensive disease on the bone scan with a high CRP. The researchers suggested that men with prostate cancer should consider having a CRP test when they have advanced disease.

Another study from Greece looked at 120 consecutive men with erectile dysfunction (ED) and no evidence of heart disease. High-sensitivity C-reactive protein (hs-CRP), a more specific CRP test for the prediction of

heart disease, was used in this study. Penile arterial flow problems were associated with higher levels of hs-CRP. Thus, this potential cheap blood test for heart disease known as hs-CRP may not only predict the risk of heart disease but may also predict the risk of progressive ED in men.

97) Increasing the consumption of fruits and vegetables after cancer treatment had no impact on cancer recurrence rates. Unless a tangible marker is impacted through a proposed behavioral change, what is the point of making the actual behavioral change?

(Reference: Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer. *JAMA* 298; 289-298, 2007)

Despite laboratory and some epidemiologic data, there is very little research on whether or not increasing fruit, vegetable, or fiber intake, and reducing the intake of dietary fat has any impact on cancer recurrence rates after conventional therapy. So, the goal of this study was to evaluate the impact of a diet high in fruit, vegetable, and fiber and low in overall dietary fat on the risk of recurrent breast cancer and all-cause mortality. It is important to look at breast cancer to determine what may happen in prostate cancer.

This was a randomized controlled trial involving an intervention group (1,537 patients) that received telephone counseling program, personal cooking classes and newsletters that promoted 5 servings of vegetables plus 16 ounces of vegetable juice; 3 fruit servings; 30 grams of fiber and 15% to 20% of energy intake from fat per day. The control group (1,551 patients) was just provided with reading materials that explained the "5-A-Day" dietary guidelines.

The intervention group had the following significant differences over the control group: higher servings of fruits (25% higher), vegetables (65% higher) and fiber (30% higher), and a low caloric intake from fat (13% lower). Blood makers of nutrients validated these changes in dietary behaviors. Over a 7.3-year follow-up, approximately 17% of the women in the intervention group and 17% in the control group experienced a breast cancer recurrence, and approximately 10% of the women in each group died. No significant differences were found in any clinical parameters and changes in diet between the intervention and control groups.

Bottom Line: Survivors of breast cancer treated with conventional treatment, dietary changes that included higher intakes of fruits, vegetables, and fiber and lower intakes of dietary fat did not decrease the risk of cancer recurrence, or all-cause mortality over a 7.3-year follow-up period.

Please do not repeat this study in prostate, bladder, kidney, or any other cancer group, because there was enough learned in this trial to last a lifetime and save the taxpayers money. Cancer patients have enough to deal with during the course of their disease, and adding the burden of extreme dietary changes may seem initially helpful, but I feel it is also destructive, demoralizing, and has no scientific merit. It is interesting that in this trial there were no significant weight differences, overall caloric intake differences, or major heart healthy changes. Unless some heart healthy tangible marker of health is impacted then the diet should not be advocated.

98) ALA, an omega-3 fatty acid from plants, is heart and prostate healthy. Omega-3 fatty acids from plants may be just as important as the omega-3 fatty acids from fish.

(Reference: Zhao G, Etherton KR, Martin KR, et al. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. *Am J Clin Nutr* 85: 385-391, 2007)

Heart disease and various urologic conditions are both based partially on a chronic inflammatory process. Previous laboratory and epidemiologic studies have suggested that an omega-3 fatty acid unique to plants known as alpha-linoleic acid (ALA) may reduce lipids and inflammatory risk factors in individuals with high cholesterol.

The goal of this study was to evaluate the impact of a diet high in ALA on pro-inflammatory markers in individuals with high cholesterol.

The study was a randomized, controlled, 3-diet, 3-period crossover study that utilized a diet high in ALA (6.5% of energy, or ALA diet), a diet high in an omega-6 fatty acid (linoleic acid; 12.6% of energy, or LA diet), and an average American diet (AAD) for 6 weeks each, with a break of approximately 3 weeks between diets.

A total of 23 overweight or obese subjects with high cholesterol, including 20 men (36 to 69 years) and 3 postmenopausal women (55-65 years) were utilized. Serum IL-6, IL-1Beta (IL-1B), and tumor necrosis factor-alpha (TNF-a) and IL-6, IL-1B, and TNF-a production by peripheral blood mononuclear cells (PBMCs) were measured.

Serum TNF-a, and PBMCs production of IL-6, IL-1B, and TNF-a were significantly lower with the ALA diet compared to the other two diets. PBMC production of TNF-a was inversely related to the ALA intake. Participants achieved the following omega-6 to omega-3 ratios in their 2,400 kcal/d diet, 2:1 with the ALA diet, 4:1 with the LA diet, and 10:1 with the AAD diet. Walnuts, walnut oil, and flaxseed oil were the primary products used to increase the amount of plant ALA in the omega-3 diet.

Bottom Line: Greater intakes of the omega-3 fatty acid, ALA, may reduce the risk and progression of inflammatory diseases by reducing the production of pro-inflammatory compounds in the blood and from white blood cells.

Flaxseed is a wonderful heart healthy, urologic healthy and cheap food, which is why it probably does not receive enough attention. Fish oil omega-3 fatty acids known as EPA and DHA are indeed heart healthy and prostate healthy. However, it is time to also give credit to the plant sources of omega-3 fatty acids, in which ALA is the primary plant omega-3, and is found mainly in flaxseed, canola oil, and walnuts.

99) Vitamin C, multivitamins and other supplements for healthy men to prevent cancer, cardiovascular disease (CVD), and eye disease---do they really work...well we will know very soon!

The Physicians' Health Study I (PHS I) was simply one of the most famous and groundbreaking randomized trials for CVD prevention ever completed. Researchers found an almost 50% reduction in the risk of a first heart attack when taking the equivalent of a regular aspirin every other day compared to a placebo. The trial was stopped early to inform the men in the placebo part of the study of the benefits of aspirin for some individuals.

Currently, the Physicians' Health Study II (PHS II) will be completed in the next few months! It is a randomized trial of beta-carotene, vitamins C and E, and multivitamins in an attempt to prevent cancer (more specifically prostate cancer), CVD, and eye disease. The trial has enrolled about 15,000 doctors aged 55 years and older and includes physicians from PHS I that were willing to be a part of this new study. An estimated 7,500 doctors from the PHS I are expected to be a part of the total number of doctors from the PHS II. The other 7,500 healthy doctors were recruited in the U.S. from the American Medical Association (AMA) beginning in the summer of 1999. These physicians also had to be enrolled in a 12-week (3-month) trial period to see who could take their pills regularly (defined as two-thirds of the time) before being allowed to be a part of this study. If the doctor was not able to take the pills regularly then this individual was simply not allowed in this trial.

Doctors in the PHS II had to be completely healthy and could not have any of the following conditions:

- Skin cancer (except non-melanoma skin cancer or basal and squamous cell cancer)
- CVD (heart attack or stroke)
- Liver disease in the past 6 months
- Kidney disease
- Ulcer

-Gout

The PHS II will attempt to answer several important questions, which are listed in the table. PHS II is the first randomized trial in the history of medicine to determine whether or not vitamin C by itself may reduce the risk of cancer.

Doctors in the PHS II will take 3 PILLS PER DAY, either:

- Vitamin E or placebo every other day with beta-carotene or placebo every other alternate day (1 pill per day)
- Vitamin C or placebo daily (1 pill per day)
- Multivitamin or placebo daily

Currently, it is very difficult to discuss the possibility of whether or not vitamin C supplements prevent cancer or have any role in the treatment of cancer with conventional therapy, so the PHS II should provide more clarity on these issues.

Table. Some of the questions that may be answered by the time the PHS II is complete.

Dietary Supplement	Clinical Question that the PHS II will help to answer, especially in men
Vitamin C (500 mg daily)	Does it reduce the risk of: -Cancer? -Prostate cancer? -Cardiovascular disease or CVD? -Eye diseases?
Beta-carotene (50 mg every other day)	Does it reduce the risk of: -Cancer? -Prostate cancer (in men with low levels of beta-carotene in their blood)? -CVD (in men at high risk for this disease)?
Multivitamin (Centrum Silver®) (Moderate dosage or recommended daily allowance to be taken daily)	Does it reduce the risk of: -Cancer? -Prostate cancer? -CVD? -Eye disease?
Vitamin E (400 IU every other day)	Does it reduce the risk of: -Cancer? -Prostate cancer? -CVD? -Eye disease?

Bottom Line: The largest study in human history of men taking various supplements, including vitamin C will soon be completed. What will happen?! Stay tuned!

100) OH MY GOSH!!!! I HIT 100 DIFFERENT REVIEWS IN PAACT. I AM THE MAN! PLEASE SEND ME MONEY TO BUY ME DINNER---I DESERVE IT!

Never forget that most readers of PAACT should have received their influenza vaccine and if not please, please go get one right now!

Influenza is a respiratory disease caused by a virus and an average of 36,000 deaths and more than 200,000 people are hospitalized yearly because of it! Approximately 5-20% of the U.S. population gets infected with

the virus. The flu vaccine is usually 70-90% effective in preventing influenza in healthy children and adults, and those that still get infected usually have a more mild illness if they were vaccinated. A big problem not usually discussed about why you should also get vaccinated is that unvaccinated healthy individuals can spread the infection to others who are more vulnerable to the influenza virus.

The Centers for Disease Control (CDC) suggests that the following people receive the influenza vaccine now:

- Anyone, including school-aged children that want to reduce their risk of becoming ill with influenza or of spreading it to other people
- All children 6 months to 5 years of age
- All individuals age 50 years of age or older
- All women who will be pregnant during the influenza season
- Adults and children with any of the following conditions: a chronic disorder of the cardiovascular or respiratory system; a chronic disease of the blood, liver, or kidneys, immunosuppression (for example from medications, HIV...), or diabetes; and a reduced ability to handle respiratory secretions or those that have an increased risk of choking on their own body secretions (for example, cognitive dysfunction, spinal cord injury, seizure problems, or other neuromuscular problems)
- All individuals in nursing homes or other long-term health facilities
- All healthcare workers
- All household contacts, including children and caregivers of children ages 0 to 5 years (especially younger than 6 months), adults 50 years and older, and individuals having high-risk medical conditions
- Individuals planning to travel to an area of the world with influenza activity (for example to the tropics at any time of the year)
- All children and teenagers receiving long-term aspirin therapy

The influenza vaccine should NOT be given to an individual that has an allergic reaction to eggs, a previous influenza vaccine, or to one of its components.

WELL, THIS IS ALL THAT I CAN COVER FOR NOW. HOPE YOUR WINTER HOLIDAY IS FILLED WITH HIGH FIBER FOODS AND PLENTY OF READING MATERIAL!

AVAILABILITY OF NOSCAPINE IN THE U.S.

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On Feb 15th this year in Vail, Colorado, a scientific presentation to physicians generated great enthusiasm among patients about Noscapine. For the first time, a study demonstrated Noscapine's activity against prostate cancer. It is very understandable that when a natural substance that has anti-prostate cancer properties is discovered in an animal model, many patients immediately become interested in trying that substance.

In the last issue of PAACT, I wrote an article explaining the basics about Noscapine and that generated a lot of interest which translated into phone calls and e mails. It is very understandable why patients became frustrated when they discovered that Noscapine is not readily available in the U.S or in Canada or Mexico. This is in contrast to the information posted in our article that Noscapine as a cough medicine component is over the counter in many countries around the world.

Starting to investigate the issue, it became frustrating because sometimes the information I obtained was not the same information given to the callers who had contacted the same resources. So it was hard for me to know whether different answers were given or whether the people who called had their own interpretation of the information. I came to the following findings that I would like to share with you in this article. The intention is to help you cope with the situation and point out some solutions.

The Decision Makers and their Influence on Availability of Noscapine:

1. The FDA:

I contacted the FDA numerous times and was able to get some verbal information and e-mail correspondence. Verbally I was told that Noscapine is not allowed to be manufactured in this country for human consumption and that Noscapine was removed from the list of drugs when the last and only American company making Noscapine as an ingredient for cough medicine closed its doors and stopped producing the drug in the mid 1980s.

I pointed out to the FDA that on their web site it is clearly posted that Noscapine is an approved drug, over the counter or by prescription, in the U.S at this time. Currently, Noscapine does still appear on the FDA site as an over the counter ingredient. If you click on the Search button on the home page of the FDA site, you will find the following link: [OTC Ingredient List Updated August 2006 Ingredient Review Panel](#). On this Ingredient List, Noscapine appears on page 60 and Noscapine HCL appears on page 61 of the FDA document as an over the counter component.

Furthermore, under the link: [Maximum Recommended Therapeutic Dose \(MRTD\) Database](#), Noscapine appears in the list related to the maximum recommended therapeutic dose of 2.5 mg per Kg per day. Noscapine and the chemical structure are posted.

The information from the FDA web site was the source for the statement in our previous article that Noscapine is an over the counter substance. I want to add that Noscapine is also on the formulary of the World Health Organization.

Here is the information provided by e-mail from the Division of Drug Information, Center for Drug Evaluation and Research of the Food and Drug Administration. I was told in the e-mail that the final rule for Noscapine as an antitussive on the over-the-counter monograph is cited in the Federal Register link (52FR30054). Since Noscapine is considered an unapproved drug in the United States, it therefore does not have any approved indication.

The other possibility for obtaining Noscapine is to request a single patient treatment IND (Investigational New Drug) for compassionate use, <http://www.fda.gov/cder/cancer/singleIND.htm>. I myself was able to use this route to obtain Noscapine under compassionate use for a few patients, some 12 years ago. I am sure that any physician can do it for their patient today. He will have to follow the FDA instructions and fill out their forms.

As to questions about doing clinical studies, here is the e-mail response that I received from the FDA:

“If you are making a therapeutic labeling claim, I believe Noscapine would fall under the definition of a drug. If your IRB wants an official notice from the FDA, you must submit your IND and then the review division has 30 days to respond. I recommend submitting this information, since the answers to many of your questions would be answered by the FDA Review Division itself, for which you would have to submit Form 1571 and a brief protocol as mentioned above.”

The IND forms can be found at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm#IND Forms

The e-mail above was sent by Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration. The FDA e-mail did not answer my questions, but it ended with this disclaimer. "This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed."

In addition, the FDA official recommended that the best way to get answers to my questions was to come to Washington, DC and try to meet with the proper officials, since I couldn't get answers to my questions by phone or by e-mail.

2. U.S. Pharmacies:

All the pharmacies that I called told me that they do not have a supply of materials to compound the medication. There were a few patients who claimed that certain pharmacies had or could compound Noscapine, but when I inquired, the pharmacies denied this.

3. Industry:

The large suppliers of chemicals for drug companies denied supplying materials to local pharmacies for compounding. I was told by one company that they are studying the matter and for the time being, they will supply it only for animal research. They confirmed that they do send Noscapine to companies abroad.

4. Biotech Companies:

There is one company in the U.S. conducting studies using Brominated Noscapine under the auspices of the FDA and they have their own patent for this form of Noscapine. A multiple myeloma study will probably begin by the time this newsletter is published. I asked when we can expect studies on prostate cancer and Noscapine and the answer was that this will probably not be immediately, but some time in the future after more research is conducted. The same company is also examining other derivatives of Noscapine.

5. Academia:

Some prominent oncologists from prestigious universities stated that they would love to conduct studies, but they need funds and the price tag mentioned was in the millions of dollars.

So what can American patients do meanwhile? Here is what is available:

1. Compassionate use as prescribed by the FDA - See the link mentioned above.
2. Wait for studies sponsored by American drug companies.
3. Import their own Noscapine from outside of the United States, and use under guidance by their physicians.

The question would then be: What is the FDA's policy on patients getting the drug from abroad?

Here is a quote from the FDA web site: http://www.fda.gov/ora/compliance_ref/rpm/chapter9/ch9-2.html

“FDA personnel may use their discretion to allow entry of shipments of violative FDA regulated products when the quantity and purpose are clearly for personal use, and the product does not present an unreasonable risk to the user. Even though all products that appear to be in violation of statutes administered by the FDA are subject to refusal, FDA personnel may use their discretion to examine the background, risk, and purpose of the product before making a final decision. Although the FDA may use discretion to allow admission of certain violative items, this should *not* be interpreted as a license to individuals to bring in such shipments.”

I am aware of patients who ordered Noscapine from abroad. It appears to be quite expensive, and the hunt is still going on to find less expensive sources. The problem is that the source has to be reliable. We posted information on our web site www.noscapine.org for patients outside of the U.S to share information about the sources of Noscapine in their own countries. If anyone decides to order Noscapine on their own, you should always use a prescription from your doctor. This probably will convince any custom authorities that you are not importing the drugs for commercial use. This will also protect your health by having your own doctor involved.

To stay in touch with us and to learn about issues of Noscapine and learn about ongoing developments, please check the www.noscapine.org web site. www.noscapine.org is the central clearing house for all Noscapine information shared among patients. The site is maintained by the Prostate Cancer Research and Education Foundation (PC-REF), 619/461-8181. We do not sell Noscapine nor do we have any financial interest or benefit from the sale of Noscapine from any source. The site also provides articles and literature that you can browse for educational purposes.

Among other links on the home page at www.noscapine.org, it contains an e-mail list for people who have questions about Noscapine. The e-mail list, Noscapine@pcref.org, is all about sharing information about Noscapine. Potential users and patients who are taking it are posting their e-mails and their experiences. It encompasses people around the world.

When you get on the Noscapine web site, you also get access to the Medical Smart Chart. We hope that people from all over the world will post their medical data in general and about Noscapine in particular. Those that take Noscapine will help us learn whether it really works and, perhaps more important, whether there is any harm in taking it. A **sample copy** of the Medical Smart Chart is available through PAACT, but you would need computer access to enter your own data.

One important issue to bear in mind is that Noscapine for cough medicine is given at the maximum allowed dose of up to 200 mg a day. Please don't even consider buying cough syrups in large quantities, as one patient's e-mail to me suggested. The human studies with Noscapine for cancer used much larger doses, up to 2.5 grams in oral tablet form. It is absolutely crucial that any decision to use these high doses has to involve a doctor to monitor and to ensure safety to the patient. The one study on humans at Johns Hopkins used 1 to 6 grams and the conclusion was that up to 3 grams was safe for the patients in the study.

It is obvious that there is excitement among patients and researchers about Noscapine and that companies are looking at the economical potential. We need to move cautiously and do the appropriate studies. Some patients feel that they can buy the substance and prepare their own capsules; they should be warned that they may cause harm to themselves. Let's not ruin the opportunity to bring to clinical use an oral drug which has an anti-tubulin effect (a chemotherapy like activity) and which appears to be safe. We need patience, and we need to use precautions to make the Noscapine Project successful.

Join our effort and fill out a Medical Smart Chart. Anyone can do that; it is free. Participate in the e-mail discussion about Noscapine. Share your experiences. And most important - Help us to find funds to support

clinical research and collect clinical data from those using it. If we can raise \$500,000, the Noscapine Project will be a reality.

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COGNITIVE CHANGES DURING ANDROGEN DEPRIVATION THERAPY

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One of the most frustrating and potentially life-altering complications men may experience while receiving androgen deprivation therapy (ADT) is cognitive dysfunction. Changes in memory and declining function in other cognitive domains can be associated with aging, making it harder to isolate a specific effect of ADT. However our daily clinical experience with prostate cancer patients suggests there are ADT-associated changes in memory, and this is supported by scientific studies of the effects of androgen deprivation on the brain, even if clinical studies have only just begun to confirm our suspicion. As an example, a group of physicians searched the SEER-Medicare linked database (which includes over 50,000 men with prostate cancer and 50,000 men without) for diagnoses of cognitive disorders, and found that while men receiving ADT were much more likely to be diagnosed with this type of problem, they were also older and had more general health issues (Shahinian). Specifically, 9.5% of men with prostate cancer had cognitive decline, while 12.1% of men with prostate cancer **and on androgen deprivation therapy** had cognitive decline. As prostate cancer specialists we know it happens, and it can be severe, but how can we diagnose and quantify it, let alone intervene effectively? Let's review...

Testosterone affects the brain (no question).

Aging is associated with loss of nerve cells in the frontal and temporal lobes, and increased deposits of protein known as amyloid (Hof, Salat, Sunderland). However, the extent of these changes varies between individuals of the same age, suggesting that factors other than age play a role in declining cognition. In animal studies, lowering the testosterone level was found to result in higher levels of amyloid deposits in the brain and decreased density of neurons in the region of the brain known as the hippocampus; these changes reversed when testosterone was restored (Leranth, Ramsden).

Clinically, the decline seen with aging, and to a greater extent seen in Alzheimer's disease, are a loss of working memory and difficulty with the creation or "consolidation" of new memories (Howieson, Light). In animals, changes in memory were inducible by castration, which again links decline in testosterone with cognitive loss associated with aging; suggesting that as we get older, our brains may be more and more dependent on testosterone for optimal function.

Giving testosterone to elderly men has been shown to improve some areas of cognitive function (Janowsky), but there has been some question whether estrogen, specifically estradiol, is the key player (recall that testosterone is converted by the enzyme aromatase to become estradiol in the brain). In one recent study, inhibiting the aromatase enzyme blocked the cognitive benefits that were otherwise seen in men receiving testosterone therapy. (Cherrier 2005). Scientists translated this clinical finding back in the laboratory and designed the following additional evaluations. Subsequent set of animal studies found that, while estradiol supplementation did improve performance on memory tasks in elderly male and female mice, it did not reverse the

neurological effects of castration in the male mice. (Kriter). In a final set of experiments, scientists discovered that nerve tissue in castrated rats was found to only improve with testosterone supplementation, and not with estradiol (Leranth).

What types or forms of cognitive decline occur during ADT, and to what extent?

Multiple studies have detected cognitive changes, albeit in varying domains, and with varying severity. These are summarized in Table 1 and discussed further below. One study from Finland, involving 23 men with prostate cancer on ADT followed cognition serially over time, and correlated changes with the changes in testosterone level. In this report, significant differences in cognitive function were seen, but only after 12 months. Men showed worsening in several domains, specifically subtraction, recognition of letters, and sustained attention. Interestingly, delayed recall of objects improved in men with castrate levels of testosterone. All of these changes correlated with decline in testosterone (Salminen). This study’s conclusions are however limited by not only the small sample size, but also a lack of documentation of clinical significance of the changes observed. Additionally, the study lacked a control group, which further limits interpretation. The importance of a control group is exemplified by a study from the UK, which found declines in at least one area of cognition in 47% of men receiving ADT for 9 months, but also in 17% of healthy males (Jenkins). Without the denominator, the true amount of change cannot be determined.

The study by Beer and colleagues was also small, including only 18 prostate cancer patients on ADT, 18 receiving estradiol, and 18 controls. Strengths of trial design included baseline intelligence testing, addressing an important potential source of bias, and repeat testing after 4 weeks, for intra-subject consistency. This study used immediate and delayed paragraph recall tests and working memory tests aimed at evaluating temporal and prefrontal function. ADT was associated with impaired verbal memory, and high dose estradiol showed some capacity to reverse this (Beer).

The most recent addition to the body of literature on this topic; an abstract from the ASCO Prostate Cancer Symposium 2007, states “Use of ADT does not affect cognitive function in prostate cancer.” This was based on 141 men; 41 on ADT, 59 with prostate cancer but not receiving ADT, and 41 healthy controls. Complex testing was performed to measure various domains of cognitive function, including IQ, COWAT (controlled oral word association test), CVLT (California verbal learning test), and D-KEFS (Delis-Kaplan executive function system). Testing was repeated after 6 months. Only two men (one on ADT and one with prostate cancer but not on ADT) lost function during that time. The authors concluded that no statistically significant association was detected between men with normal and castrate levels of testosterone; however the study’s power to detect a difference is questionable (Breunis).

In all, with at least 7 high quality trials published, no consistent global cognitive deterioration has been documented during ADT, with the caveat that the studies are all small, use different ADT regimens, and test cognitive function using different techniques. The parameters which deteriorate on ADT most consistently are visuospatial performance and attention. Corroborative evidence comes from trials of testosterone supplementation, in which spatial cognition has been shown to significantly improve (Janowsky 1994), and there is lesser evidence for improvement in memory tasks with normalization of testosterone: estradiol ratios (Janowsky 2000). These domains, therefore, may be the most promising measurement parameters in future supportive care trials designed to alleviate cognitive changes associated with ADT.

Table 1: Studies of cognition during ADT.

Study	N	Domains Tested	Conclusion
Breunis (Indiana)	141	Intellect Word association Verbal learning Executive function	·No worsening attributable to ADT in any domain.
Salminen	23	Verbal fluency →	·No Change

(Finland)		Visuomotor → Memory → Speed → Attention →	·Worsened with lower testosterone ·Improved with lower testosterone ·Worsened with lower testosterone ·Worsened with lower testosterone
Jenkins (UK)	50	Intellect Verbal memory → Visual memory Speed Attention	·Worsening occurred, but was not associated with testosterone level
Cherrier (Washington)	34	Verbal memory → Visual memory → Spatial ability → Executive function→ Language →	·Improved ·No change ·69% of ADT pts significantly worsened ·No change ·No change
Almeida (Australia)	40	CAMCOG → Verbal memory → Word Association → Visual memory → Spatial ability →	·Improved off ADT, statistically ·Improved off ADT ·Improved off ADT ·No change ·No change
Beer (Oregon)	53	Intellect Verbal memory → Working memory →	·Worse in men on ADT ·Slower processing in men on ADT
Green		Memory → Information Processing →	·Worse with ADT ·Slower with ADT

CAMCOG – various aspects of cognitive function, including orientation, language, memory, attention, concentration, perception, calculation, executive function.

Assuming cognitive deterioration occurs, does it reverse after ADT is stopped?

Unfortunately, few studies have thoroughly evaluated what happens to cognitive function after discontinuation of ADT. In the paper by Cherrier and colleagues, continued decline in performance on spatial tasks was seen in only 15% of men after stopping ADT, which is hardly reassuring. The Australian study did seem to

show gains of function after completion of ADT. Although the lack of documentation that testosterone had recovered in men who improved, improvements could have been due to the learning which occurs with repeat testing. In our anecdotal experience, cognitive changes do seem to get better, typically lagging a few months behind testosterone recovery to normal levels, although return to baseline cognitive function has not been universal.

What can we do about this?

Surprisingly few interventional trials have been completed to address this question. This is likely due, in large part, to the difficulty in documenting the potential changes, the conflicting available data, and the various forms of cognition testing that have been employed by researchers. While testosterone replacement is clearly contraindicated in men actively being treated with ADT, perhaps estradiol or a non-hormonal intervention would be helpful. To date, only estradiol has been specifically tested for cognitive benefit in men on ADT for prostate cancer.

The good news is that estradiol may be helpful. Recall the Beer study cited above; the 18 men on estradiol patches performed better at paragraph recall after just 1 month of therapy, although working memory was not significantly improved (Beer). However, a similar trial of estradiol in 27 men, using a placebo-controlled design, failed to demonstrate improvement in any of the cognitive domains tested (Taxel). Clearly additional studies are needed to better answer the question of estrogen supplementation and cognitions.

Vitamin E has been a source of hope, in that scientists have documented its involvement in memory retention (Eidi). In animals, inability to process vitamin E results in aberrant behavior that worsens with age (Gohil). In dietary supplementation experiments, vitamin E protected female mice from the impairment in spatial navigation that was otherwise induced by removal of their ovaries (Monteiro). Sadly, in the Women's Health Initiative, long-term vitamin E supplementation did not reduce the risk of cognitive decline (Kang). More encouraging was a retrospective study of patients with early Alzheimer's disease who took vitamin E in addition to donepezil, and showed 1/3 as much disease progression compared to patients who took neither (Klatte). Specific data isolating the effect of vitamin E, as well as clarifying timing and dose required for benefit, are underway.

What can we learn from the parallel syndrome, "Chemo brain"?

"Chemo brain" describes a syndrome of cognitive changes in people who receive chemotherapy ("lupron brain" for men on ADT), with difficulty concentrating or memory lapses, which can lead to problems with job performance or management of household functions. One of the major obstacles to research in this area is uniform testing, and the question of how performance on a neurocognitive test translates into "real-world" function (Tannock). Imaging may provide more uniform, objective evidence of changes, and provide an excellent tool for further study. For instance, when researchers at UCLA analyzed brain activity using PET scans in women who had received chemotherapy for breast cancer and healthy controls, they found that the brains of women who had received chemo had to work much harder than controls when faced with a task. In addition, there was less frontal cortex activity at rest (Silverman).

Preliminary data were presented at the American Society of Clinical Oncology annual meeting in 2003 regarding the use of dexamethamphetamine (Focalin, Novartis) in breast cancer survivors complaining of fatigue or "chemo-brain." This drug is a mild stimulant, similar to those used in treating attention deficit disorder. Fatigue, overall quality of life, and memory improved over a period of 6 weeks in the breast cancer patients, then a plateau was reached, or in some cases regression was noted (Hanna). Extrapolating this experience to cognitive changes related to ADT is an enormous stretch, but it is a question which merits study.

What about the drugs used to treat Alzheimer's? Donepezil (Aricept, Pfizer) won approval for mild-to-moderate Alzheimer's disease, based on significant (on the order of 25%) improvements in broad tests of

cognition on a disease-specific scale, the ADAS-cog. This drug is now in clinical trials for pediatric brain cancer survivors, to see if any of the clearly documented cognitive losses in this population can be prevented. No testing has yet been performed specifically in prostate cancer patients for hormone-induced cognitive dysfunction. However, a study in elderly men with early signs of generic cognitive dysfunction did find a delay in development of frank Alzheimer's symptoms. Although it is intriguing, this is a prescription drug, with serious potential side effects, and without more specific evidence of benefit, requires a lengthy and intense discussion with your physician before considering its use. Ideally, one would use it in the setting of a clinical trial, so that benefit could be assessed for the good of all those suffering from "Lupron-brain."

No, really, what can we do about this?

Various natural and non-pharmacologic interventions have been touted for keeping the brain healthy with aging. While their effect specifically for ADT-induced cognitive changes is unknown, they may be worth trying in someone who is exasperated by their deterioration in function:

1. **Exercise** – this has been shown to stimulate brain-derived neurotrophic factor, similar to estrogen's effect on the brain. A study of post-menopausal women found that those who exercised and were more physically fit had less brain tissue loss in the frontal lobe and hippocampus over a period of 10 years.
2. **Exercise PLUS** - a small trial of physical exercise in conjunction with a comprehensive program of dietary changes (5 small meals daily, high in omega-3 fats and whole grains), stress reduction, and mental exercise showed improved cognitive function subjectively, as well as by scans evaluating brain metabolism. Sound overwhelming? These changes were seen in just 14 days. Worth a try...
3. **Brain Exercise** – crosswords or other puzzles, playing musical instruments, doing artwork and participating in a variety of activities involving different aspects of brain function were found to correlate with a lower risk of developing Alzheimer's. For those of us in the video-game era, Nintendo has developed specific programs to exercise the brain, called Brain Age. This program has everything from Sudoku to memorization of words to complex tasks of tracking and interconnecting objects.
4. **Green (or black) Tea** – studies have found that tea blocks the activity of 2 enzymes in the brain linked with development of Alzheimer's disease. Given the similarity of changes induced by lack of testosterone and Alzheimer's, this seems a reasonable option.
5. **Folate** – an observational study of aging men found that those who ate diets higher in folate (leafy green vegetables, citrus fruits) lost less verbal fluency and less spatial function than men with lower folate intake. Additional studies have shown that for men with normal vitamin B12 levels, having higher folate levels was shown to correspond to better cognitive function. **WARNING:** cognitive function was worse for those with low vitamin B12 levels and high folate levels. Do this only in concert with your physician to make sure you get benefit and not harm.
6. **Nootropics** ("smart drugs" and "smart nutrients") – this includes a wide range of substances, from caffeine to herbs to prescription drugs (including dexamethylphenidate, see "chemo brain" section above). Many have largely unsubstantiated efficacy, or just animal data, and certainly none have been tried specifically for ADT-induced cognitive dysfunction. Nevertheless, here is a short list, of notable nootropes:
 - a. **Piracetam** and its derivatives are the oldest and most commonly used nootropics. Available in prescription form in Europe, piracetam increases brain metabolism, improves concentration and memory, and has neuroprotective effects. It has been shown to minimize damage done during cardiac bypass surgery (Uebelhack) and to slow cognitive decline in a population of Alzheimer's patients (Croisile).
 - b. **Acetyl-L-carnitine** is an amino acid, purported to slow progression of Alzheimer's via antioxidant properties and keeping mitochondria functional by clearing fatty acid metabolites.
 - c. **Inositol** - a form of this is currently in phase I testing for Alzheimer's (AZD-103). Stay tuned for more.

- d. **Hydergine** – an ergot, derived from the same Rye fungus as LSD. Widely used despite minimal evidence.
- e. **Idebenone** – an Alzheimer’s drug, thought to stimulate nerve growth, with properties similar to CoQ10.
- f. **Milacemide** – a modulator of the brain’s NMDA type receptors, this failed to show benefit in Alzheimer’s patients, but did improve word retrieval (accuracy and speed) in healthy subjects.
- g. **Bacopa monnieri** – an ayurvedic medicine, with some clinical studies of neuroprotection following electroconvulsive shock therapy.

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****There is a DVD available of the Dr. Mark Scholz lecture entitled “Staging and Treatment of Newly Diagnosed Prostate Cancer” given at the Fullerton Prostate Forum in August 2007.**

This is pure gold information for any newly diagnosed man. It could also be used as the main part of a support group meeting.

To obtain a copy, please send a check for \$15.00 payable to:

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It will be mailed first class to any U.S. addresses.

For orders from outside the U.S., please send a check in U.S. Dollars for \$10 plus the cost of International mail for a 5 ounce package.

Support groups have permission to make copies for their members.

****There is a new videotaped lecture available by Dr. Bob Leibowitz from his March 2007 Fullerton Support Group Lecture.**

“Conquering/Controlling/Taming Advanced Prostate Cancer & Proving How to Successfully Live with Advanced Prostate Cancer”

The lecture is available on VHS and DVD.

If you wish to order a copy, please call Dr. Leibowitz’s office at 310-229-3555.

There are also a limited number of Video’s/DVD’s available for loan from PAACT at no charge (616-453-1477).

These Video's/DVD's should be returned
within 2 weeks, in original working order and
in the original case, so that they are made available for others to view.

CHARITY RIDE AROUND THE WORLD

Simon Buckley is planning a charity ride around the world for next year. His plan is to ride overland on motorbike from Melbourne to London, via SE Asia, China, Mongolia, Russia, Kazakhstan, and Eastern Europe; then on to the U.S. down through South America and home via New Zealand. He has aligned himself with the Association of International Cancer Research (AICR – www.aicr.org.uk/) to raise funds and awareness during his trip.

The goal of his trip are awareness and early detection, as well as to generate a greater network of support for those affected by Prostate Cancer. He is looking for advice and help with generating publicity, to help make his trip a success. He intends to leave in May 2008.

Simon Buckley
City Ambassador Supervisor
Tourism Melbourne

Phone: 03 9658 9071
Mobile: 0409 699 200
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January 1st 2007 through September 30 2007

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Balance on Hand December 31, 2006	1,486,821.96
REVENUES RECEIVED -	
Membership Contributions	112,134.95
Memorial Income	3,459.66
Trusts & Bequests	14,042.75
Investment Income	29,244.25
Total Revenues	<u>158,881.61</u>
Total Balance on Hand and Revenues	<u>1,645,703.57</u>
EXPENDITURES-	
Employee Wages	66,421.79
Payroll Taxes	6,935.26
Medical Insurance	18,140.31
Outside Services, Labor	3,745.50
Rent	11,250.00
Meals, Motel, and Transportation	4,746.76
Auto Expense	1,486.98
Printing	20,353.11
Postage and Delivery	18,952.35
Telephone	2,071.91
Service Fees	1,983.79
Program Expense-Conference Exhibit Fees	1,100.00
Office and Computer Supplies	1,877.05
Miscellaneous	1,443.43
Total Expenditures	<u>160,508.24</u>
 Balance on Hand September 30, 2007	 <u>1,485,195.33</u>
 Assets:	
Checking Account	3,829.15
Petty Cash	50.00
Savings Account	29.63
Certificates of Deposit, Stocks, and Bonds	1,893,863.19
Money Market Funds	116,535.59
Equipment	12,295.17
 Net Assets:	 <u>2,026,602.73</u>
Foundation Fund Balance	<u><u>323,151.40</u></u>