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Treating the whole man: Dr. Larry Goldenberg to speak at the 2008 National Conference

Dr. Larry Goldenberg, founding director of the Prostate Centre at the Vancouver General Hospital, is not one to rest on his laurels. This 2008 recipient of the Order of British Columbia will be a key speaker at the upcoming CPCN national conference in August. And he is currently championing a new cause---the foundation of a men's health centre at VGH.

Goldenberg explains that, although there are women's hospitals or women's health centres in many Canadian cities, organizations focussing on men's health are few and far between in Canada. "Men are 20 years behind women in terms of gender-specific health centres," he says. Of course, there are centres devoted to prostate health. "But," as Goldenberg quips, "there's more to men's health than penises, prostates, vasectomies, and circumcisions."



Wise words coming from a dedicated urologic surgeon with an international reputation for excellence in prostate cancer research and treatment!

But then, Goldenberg has always had a broad perspective. Even his clinical research demonstrates an interest in the health of the whole man, focussing, as it often does, on quality of life issues and on men's experience of prostate cancer and its treatment.

In 2007, for example, he co-authored a study on what factors patients with prostate cancer believed were important determinants in their decisions about whether to participate in clinical trials. (See [an abstract](#) of this article.) Some interesting trends emerged. Men reported that they were motivated more by their concern to help future patients with prostate cancer than by their belief that the study treatment would affect their survival. Also, it appears that good and open communication between a man and his medical team was rated as having a very significant effect on clinical trial participation.

This study is only one of many indicating Goldenberg's long-term interest in helping men and the medical profession cooperate to achieve premium health care. (See the CPCN article "Dr. Larry Goldenberg: Helping men take an active role in their prostate cancer treatment.")

Dr. Goldenberg is also a pioneer in the use of intermittent hormone therapy for the management of prostate cancer. And he continues to be an active researcher in this field. He is particularly interested in the potential of intermittent androgen suppression to improve the quality of life for men who rely on hormone therapy and on the possibility that this treatment will preserve the hormone-dependent state of tumours so that prostate cancer can be controlled longer. Intermittent hormone therapy, also known as

intermittent androgen suppression (IAS), is a treatment protocol in which the drugs blocking the production or effects of male hormones are periodically stopped and restarted.

A March 2008 article co-authored by Goldenberg concludes that "intermittent androgen suppression is a potentially useful treatment for locally recurrent prostate cancer after radiation therapy with quality of life benefits in the off-treatment interval and no apparent deleterious effects on short- to medium-term survival." ([See the abstract.](#))

Goldenberg's other areas of research include evaluating the role of molecular imagery in targeted therapy for prostate cancer, the use of robotic surgery in prostate cancer treatment, and investigating safety issues related to androgen replacement therapy for men. (See the related CPCN article on dietary supplements containing male hormones.)

CPCN reached Dr. Goldenberg to ask him four questions of import to our membership:

QUESTION: You seem to be very aware of the effects of treatment on a man's quality of life, always considering, primarily, which treatment offers the best chance for a "cure," of course. *What innovations do you think are the best bets, in terms of offering men newly diagnosed with localized prostate cancer both a cancer-free future and minimal negative quality of life effects?*

ANSWER: There are many "innovations" which reach a level of popularity and then fade away as results do not withstand the test of time or the rigours of scientific evaluation. The ultimate test of a new treatment for localized cancer is the ability to eradicate the disease, or to set back its biologic clock in such a way as to minimize the threat to a man's longevity --- all the while minimizing negative impact on quality of life. This is a huge challenge, which physicians around the world are facing. In the midst of the milieu are several technologic advancements that are promising. These include HIFU, photodynamic therapy, intraprostatic injection therapy, and focal therapy or "male lumpectomy" using various sources of energy. All of these are interesting approaches that deserve to be studied in a thoughtful manner, and all continue to be debated by experts worldwide.

QUESTION: *What about when cancer comes back? What are the current "gold standard" treatments and the most promising areas of research for men in this situation?*

ANSWER: When cancer comes back it may not be a life-threatening situation. My best advice is to monitor the situation for a while to determine the characteristics of "the beast" prior to deciding on treatment. Many clinical trials of experimental drugs are available for different types and degrees of "recurrence."

QUESTION: *How about prevention? What are your thoughts on the newly published findings regarding the use of androgen suppression in the prevention of prostate cancer?*

ANSWER: I am personally convinced that a significant number of men, with the appropriate genetic makeup, can decrease their risks of developing prostate cancer by taking finasteride. There continue to be conflicting reports on micronutrients, diet, and environmental influences.

QUESTION: *And finally, if you could wave a magic wand, how would you improve the way the Canadian health sector and Canadian men manage prostate health?*

ANSWER: Awareness is the key and appreciation that not every prostate cancer needs to be treated, at least not immediately. However, there is a subtype of cancer that can kill, and in order to find these we have to look for, and uncover, all types including the benign actors. We need a means of separating the "tigers" from the "pussycats." This will be a blood biomarker (or a combination) or an imaging method (perhaps a form of contrast enhanced ultrasound or MRI) or a genetic test on the biopsy material itself.

Intermittent hormone therapy: What's new?

When Norm Oman was diagnosed with prostate cancer, he asked his doctor about intermittent hormone therapy --- a treatment protocol known to the medical profession as intermittent androgen suppression (IAS) or intermittent androgen deprivation (IAD). "It was very experimental at the time," says Norm. "I knew I wanted enough treatment, but hormone therapy can be really rough on the body --- low energy levels, weight gain, sometimes ED." So the opportunity to have the benefits of hormone therapy while enjoying breaks from this treatment was very attractive to Norm. "We decided to go for it and monitor the situation carefully." Norm's situation then was similar to that of many men whose doctors have recommended intermittent androgen suppression therapy today.



What is this protocol, which is currently undergoing phase III trials? To understand, we need to know a little general information about hormone therapy. First, the medical profession has known for a long time that male hormones, such as testosterone, drive the growth of prostate cancer. Take away these hormones, known as androgens, and you take away the environment that prostate cancer needs to grow and flourish. (See the CPCN web page on hormone therapy.)

Increasingly, drugs that interfere with the production of androgens or that block the effects of androgens are prescribed to men whose prostate cancer has spread outside the prostate gland, whose cancer appears to have returned after they have undergone surgery or radiation treatment, or who are at a high for recurrence. And, most often, their cancers are controlled well by this hormone therapy, at least initially.

But there are complications. Hormone therapy can have side effects, such as loss of libido, erectile dysfunction, hot flashes, night sweats, osteoporosis, anaemia, fatigue, and loss of muscle mass. But more important, although hormone therapy works well to control prostate cancer (often for many years), eventually, in almost all men undergoing this therapy, the prostate cancer cells discover a way to grow without the presence of male hormones. They become "androgen independent," and a man's cancer begins to grow, his prostate-specific antigen (PSA) level increases, and he experiences worsening symptoms.

Medical researchers and physicians, among them Dr. Larry Goldenberg, developed intermittent androgen suppression (IAS) as a response to these two problems: the side effects sometimes experienced by men on hormone therapy and the fact that, over time, hormone therapy no longer controls prostate cancer growth. The thinking was that stopping hormone therapy periodically and then restarting it would enable men to enjoy a better quality of life during off-treatment times and might postpone the day when the drugs

no longer worked to control their cancer.

In the 1990s, studies conducted in the lab using mice were promising. One reported that IAS prolonged threefold the time that it took cells to reach androgen independence, from 50 to 150 days. (See abstract of "[Effects of intermittent androgen suppression on androgen-dependent tumours.](#)")

These studies sparked a number of clinical trials exploring how effective IAS was outside the lab --- as a treatment protocol for men with prostate cancer. Goldenberg and fellow researchers at the University of British Columbia helped to define the optimal time to stop and restart hormone therapy by observing the responses of 47 men to IAS. The study concluded that intermittent androgen suppression works to control prostate cancer, affords "improved quality of life when the patient is off therapy," and "results in reduced toxicity and cost of treatment." (See an abstract of "[Intermittent androgen suppression in the treatment of prostate cancer.](#)")

This and numerous other studies taught some valuable lessons. Restarting hormone therapy after it was stopped worked. In other words, if a man's cancer responded to hormone therapy initially, it still responded after a "time out." Most men experienced a 6- to 9-month off-treatment phase after their first treatment, which usually lasted from 9 to 12 months. A few men, especially those with localized disease, had treatment holidays lasting 3 years or longer. Norm reports that his first treatment break lasted from between 18 months to two years. "We didn't know much about when to begin treatment again in those days," he states. "It became a matter of at what time do you loose your nerve."

"But I did feel fine, very healthy," Norm reports. The research concurs. Although some phase II trials suggested that regular, continuous hormone therapy improved men's quality of life in terms of controlling pain and urinary symptoms, most men reported an improved overall sense of well-being during the off-treatment phase of IAS. Significantly, men on IAS reported less psychological distress, fewer hot flashes, and more energy, as well as improvements in libido and sexual function, during the off-treatment phase.

The most important question is awaiting the results of further phase III clinical trials. How do survival times of men on IAS compare with those of men on traditional hormone therapy? One such trial, headed up in Canada by Dr. Laurence Klotz, is comparing continuous androgen suppression with intermittent androgen suppression as a treatment for patients whose rising PSA levels indicate that their cancer has come back after radiation therapy but who show no clinical signs of metastatic disease. (The official title is equally a mouthful: *A Phase III Randomized Trial Comparing Intermittent Versus Continuous Androgen Suppression for Patients With Prostate-Specific-Antigen Progression in the Clinical Absence of Distant Metastases Following Radiotherapy for Prostate Cancer.* Click [here](#) for more information.)

Still, most conclude that intermittent androgen suppression can ameliorate the short- and long-term side effects associated with continuous androgen suppression and is a reasonable alternative, as long as men are fully informed that the therapy is still being investigated and that mature research results are not yet available from some significant clinical trials.

And what about Norm? How is he doing? "Healthy and going strong" is the verdict, and still interested in innovations in prostate cancer research.

Prostate cancer prevention with finasteride: New research

A review of data from the 2003 Prostate Cancer Prevention Trial (PCPT) concludes that finasteride, a drug known to reduce a man's risk of developing prostate cancer, is safer than was once supposed. The drug is a 5-alpha-reductase inhibitor, which, by blocking production of the enzyme 5-alpha-reductase, modifies the effects of the male hormone testosterone on the prostate. Finasteride has long been used in the treatment of benign prostatic hyperplasia (BPH) because it can reduce the size of the prostate. (See the section "5-Alpha-Reductase Inhibitors" of CPCN's web page on BPH.)

Finasteride has been a drug of interest to men at risk for prostate cancer since the Prostate Cancer Prevention Trial. That trial, which involved 18,882 men, found that those taking finasteride had an overall 25 per cent relative risk reduction in prostate cancer incidence



On the down side, the trial detected a greater incidence of high-grade, advanced tumours among the men taking finasteride who did happen to develop prostate cancer. So, as often happens in the wake of clinical trials, medical professionals and researchers, while optimistic, urged caution and more study.

In May 2008, researchers reported the results of further study --- a careful and comprehensive re-examination and re-interpretation of data from the 2003 PCPT. Their findings suggest that finasteride not only reduces prostate cancer incidence overall but also does not cause more aggressive tumours among the men who develop the disease in spite of taking the drug. (See the [press release](#) about this study from Weill Cornell Medical College.)

The original finding, "that men taking finasteride had fewer prostate cancers overall, but a higher incidence of grades 7, 8, 9, and 10 cancers," was a "methodological artefact," suggests Dr. Steven Kaplan of Weill Cornell Medical College. According to Dr. Laurence Klotz (Sunnybrook Health Sciences Centre, Toronto) and Dr. Fred Saad (Director of Urologic Oncology at the University of Montreal Hospital Centre), various new analyses of the PCPT results strongly suggest that *better detection* as opposed to an *increased prevalence* of high-grade tumours resulted from finasteride use and may have skewed the earlier findings of the Prostate Cancer Prevention Trial.

To simplify, finasteride, because it shrinks the prostate, probably makes these aggressive tumours easier to find rather than encouraging their growth. Dr. Kaplan puts it graphically in a CBC interview: "It's easier to find a cherry pit in a cherry than it is in a watermelon. So from the perspective of finding a tumour, it's much easier to find in a smaller prostate."

After the researchers re-examined the data on biopsies taken from men in the PCPT study, they adjusted this data statistically to account for factors such as baseline prostate-specific antigen (PSA) levels and prostate volume. (The thinking was that finasteride may have reduced PSA to a lesser extent in men with high-grade cancer than in men with low-grade cancer, which might also have contributed to detection bias during the trial.) For men taking finasteride versus the placebo, they found

- a significant reduction in the incidence of prostate cancers;
- a significant decline in tumours with Gleason scores 5, 6, and 7;
- and, when they adjusted for prostate volume, no higher incidence of tumours with Gleason scores of 8, 9, and 10.

Other researchers agree that finasteride does not increase the risk of high-grade prostate cancer. A recent article published in the June 2008 issue of *Cancer Prevention Research* concludes that "the observed, unadjusted higher risk of high-grade disease with finasteride seems to have been due to facilitated diagnosis resulting primarily from increased biopsy sensitivity with finasteride." These researchers go on to recommend that men undergoing prostate cancer screening or those expressing an interest in prostate cancer prevention be made aware of "the opportunity to take finasteride for preventing prostate cancer." (See [an abstract](#) of this article.)

Dr. Fred Saad is already prescribing the drug to his high-risk patients and is considering its use in older men who have less risk.

Nevertheless, finasteride use can cause negative side effects, and, as always in prostate cancer prevention and therapy, one approach is not the answer for every man. It takes a skilled medical team and experts to advise men of the risks and benefits of using any drug.

Some of the potential side effects of finasteride use include

- decreased sex drive,
- erectile dysfunction,
- decreased ejaculate amount,
- and breast enlargement.

However, several recent studies suggest that the drug does not impact sexual function in most men. A double blind placebo-controlled study assessing sexual dysfunction in 17,313 men over a 7-year period found that finasteride "increased sexual dysfunction only slightly and its impact diminished over time." (See [an abstract](#) of this article from the *Journal of the National Cancer Institute*.)

As always, further research on 5-alpha-reductase inhibitors is either planned or underway. Dutasteride, another drug in this class, is currently being investigated for its efficacy in reducing the risk of prostate cancer among men at high risk for the disease. The 4-year REDUCE study (Reduction by Dutasteride of Prostate Cancer Events) should have preliminary results sometime next year. And the 3-year REDEEM trial (Reduction by Dutasteride of Clinical Progression Events in Expectant Management) should be completed in 2010. REDEEM will assess the same drug as a treatment to extend the time to progression in men with low-risk localized prostate cancer who would otherwise undergo active surveillance.

Currently, however, finasteride remains the only agent proven to reduce the risk of prostate cancer.

For more information:

["Androgens and prevention of prostate cancer,"](#) *Current opinion in endocrinology, diabetes, and obesity*, June 2008.

["PCPT, MTOPS and the use of 5ARIs: a Canadian consensus regarding implications for clinical practice,"](#) *Canadian Urological Association Journal*, March 2007.

["A review of phase III clinical trials of prostate cancer chemoprevention,"](#) *Annals of the Royal College of Surgeons of England*, April 2007.

CPCN executives welcomed in Ottawa

Recently, executives of the Canadian Prostate Cancer Network (CPCN) met with Health Minister Tony Clement and Minister of National Defence Peter McKay. CPCN took this opportunity to acquaint the ministers with the work CPCN and the Canadian support groups are doing across the country, and with the need for financial support similar to that being accorded the Canadian Breast Cancer Network.

With one employee and the dedicated work and enormous energy and goodwill of a number of survivors and volunteers, as well as the help of internationally renowned doctors and medical researchers and the support of corporate and individual sponsors, CPCN



- operates a prostate cancer helpline that is accessible 24-hours a day, 7 days a week
- publishes a handbook for those newly diagnosed with prostate cancer
- maintains and updates monthly a highly respected website, offering general information and the latest news about prostate cancer as well as vital access to support groups across Canada
- publishes an electronic newsletter, which informs men, their friends and families, and support groups about survivorship, treatment, and awareness issues.
- hosts an annual conference that builds crucial connections between men who have experienced prostate cancer, professionals involved in caring for these men, and prostate cancer researchers
- conducts national prostate cancer awareness campaigns
- assists Canadian support groups by providing informational and awareness material, advice, and an umbrella organization that connects their efforts
- raises funds to ensure that CPCN services are free to those who need them

As well as this impressive catalogue of accomplishments, CPCN detailed for the ministers its structure and mandate:

- CPCN has a management board that represents every region of Canada
- CPCN is dedicated to creating and sustaining prostate cancer support groups, continuous efforts to raise awareness of the disease, and advocating for increased funding and better treatment modalities.

Some of CPCN's past and present special initiatives were also highlighted in the meeting. CPCN was an organizing member of the 1997 National Prostate Cancer Forum and the co-founder of the Canadian Prostate Cancer Initiative. More recently, the organization has become a founding member of the World Wide Prostate Cancer Coalition.

Although nothing final was decided at the meeting, the CPCN members attending were encouraged by the ministers' responses and look forward to further dialogue with federal officials.

CPCN wishes to thank all those who have contributed to its efforts in the past by donating time and funds.