

INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 162

NOVEMBER 2005

14th YEAR



In this issue we continue William Ware's excellent series of articles concerning the prostate and its problems. Part II deals with the subject of prostate biopsies, their effectiveness in detecting prostate cancer, and the potential serious adverse effects associated with the procedure.

This month we report that high homocysteine levels may be implicated in dementia and cognitive decline; testosterone therapy may be linked to prostate cancer; vitamin D may help protect against gum disease; and fish or fish oils may help reduce heart disease associated with systemic inflammation.

I have just completed a major renovation of my web vitamin "store" with lots of new products for you to consider and, as a subscriber, you receive a 10% discount on already bargain prices. You can find the "store" at <http://www.yourhealthbase.com/vitamins.htm>. Please keep in mind that when you order, it is very important to begin the ordering process from this web page every time you place an order, rather than directly from the iHerb site. This way you will be sure to get your proper discount and I will be sure to get my commission which, as you know, makes it possible to continue publishing the newsletter.

*Wishing you good health,
Hans*

November Highlights

High homocysteine and cognitive decline	p. 2
Fitness reduces risk of metabolic syndrome	p. 3
Testosterone therapy and prostate cancer	p. 4
Depression and IBS in chronic cystitis	p. 4
Fish oil helps with inflammation	p. 5
NEWSBRIEFS	p. 5
RESEARCH REPORT	
<i>Diagnosis & Staging of Prostate Cancer</i>	
<i>- Part II: The Prostate Biopsy</i>	p. 7

LETTERS TO THE EDITOR

My friend has a son who has suffered with acid reflux since he was 16 years old. He is now 21 and takes 4 prilosec per day. He has been to many doctors. His condition has affected his gums, which has resulted in no enamel left on his teeth and he must now have implants.

I checked with a health food expert and she recommended high doses of folic acid and digestive

enzymes. Do you agree? Or do you have any other ideas?

AB, USA

Editor: *Sorry to hear about your friend's son's gastroesophageal reflux disorder (GERD). I agree that taking digestive enzymes with each meal may be quite helpful, but have not come across anything indicating that folic acid supplementation would be of benefit. It is possible that deglycyrrhizinated licorice (DGL) taken between meals may be helpful as well. Finally, it may be worthwhile to give the natural remedy "Digest RC" (available from Life Extension Foundation) a try.*

If the GERD occurs when lying down to sleep elevating the upper part of the body with pillows or raising the head of the bed may also be beneficial.

Long-term use of prilosec may lead to vitamin B12 depletion so he should be checked for a possible deficiency and supplement if necessary.

My sister who has just turned 67 years old has been diagnosed with early vascular dementia. What supplements could help prevent further deterioration and perhaps even improve her present condition? Memory and awareness seem to be problems now, according to her oldest daughter who lives with her. Hopefully there is still help for this dreadful condition.

LP, USA

Editor: Sorry to hear about your sister's vascular dementia. There are several supplements that may help.

- Vitamin C (3 x 500 mg/day)
- Vitamin E (400-600 IU/day)
- Ginkgo biloba (3 x 60 mg/day)
- Phosphatidylserine (3 x 100 mg/day)
- Zylflamend (2 soft gels/day)
- Coenzyme Q10 (100 mg/day)

Your sister should be tested for a vitamin B12 level and if low, should consider supplementing with 1 mg/day of sublingual methylcobalamin. She should also take a daily, high-quality multivitamin containing at least 400 mcg of folic acid, 50 mg of vitamin B6 and 500 mcg of vitamin B12.

ABSTRACTS

High homocysteine levels predict cognitive decline

BOLOGNA, ITALY. Elevated homocysteine in blood plasma is now a recognized risk factor for vascular dementia, and may also be linked to Alzheimer's disease (AD) and milder cognitive decline. Homocysteine is an amino acid, used in protein metabolism and other essential processes. Elevated homocysteine is usually due to inadequate folate, vitamin B-12, or vitamin B-6 intake.

AD and elevated plasma homocysteine have been linked in many studies, but the two long-term studies so far have shown conflicting results, so a research team from the University of Bologna carried out another large, long-term study. They followed 382 men and 434 women with an average age of 74, for four years. Results suggested that high homocysteine (greater than 15 micromoles per liter) is associated with a 2-fold rise in the risk of AD and dementia. Low serum folate was also an independent predictor of the development of dementia and AD. Note: Foods in Italy are not fortified with folate.

Another recent study from Tufts University adds to the evidence by showing that homocysteine, folate, vitamin B12, and vitamin B6 are independently linked to cognitive decline and AD. The Tufts researchers measured plasma homocysteine and took dietary data from 321 men with an average age of 67 years. Cognitive ability was measured 3 years apart. Low folate, in particular, was linked to a decline in cognitive ability even when all other factors were statistically accounted for. The data

suggest that elevated homocysteine is toxic to the nervous system and directly involved in cognitive function, although it may instead be a marker for deficiencies in folate or an underlying neurodegenerative process.

In a commentary, experts from the University of Texas Southwestern Medical Center note that multiple mechanisms, perhaps interacting, may account for the consequences of elevated homocysteine and B vitamin deficiency. They state that clinical studies are necessary so that we can understand whether lowering plasma homocysteine can produce cognitive improvement or protection against cognitive decline.

*Ravaglia G, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. **American Journal of Clinical Nutrition**, Vol. 82, September 2005, pp. 636-43*

*Tucker KL, et al. High homocysteine and low B vitamins predict cognitive decline in aging men: the VA Normative Aging Study. **American Journal of Clinical Nutrition**, Vol. 82, September 2005, pp. 627-35*

*Bottiglieri, T. and Diaz-Arrastia, R. Hyperhomocysteinemia and cognitive function: more than just a casual link? **American Journal of Clinical Nutrition**, Vol. 82, September 2005, pp. 493-494*

Editor's comment: Whilst awaiting the results of additional research it would seem prudent to ensure an adequate daily intake of folate (minimum of 400 mcg/day), vitamin B12 (minimum of 1000 mcg/day), and vitamin B6 (minimum of 10-50 mg/day).

Vitamin D may protect against gingivitis

BOSTON, MASSACHUSETTS. Vitamin D may reduce the risk of periodontal disease and tooth loss, but there is currently limited evidence of whether it could reduce chronic marginal gingivitis. A study based at Boston University investigated the link between body stores of vitamin D and gingivitis, a common inflammation of gum tissues due to bacterial plaque build-up.

The study involved 6,700 non-smokers between 13 and 90 years of age taking part in the 3rd National Health and Nutrition Examination Survey. Participants gave blood samples, and vitamin D status in blood serum was measured with a radioimmunoassay kit. Levels ranged from 25 to 125 nanomols of 25-hydroxyvitaminD(25(OH)D) per liter (nmol/L). Study participants then underwent an assessment of their gums in which examiners used a periodontal probe to examine the health of the gums, as bleeding on probing is a typical symptom of gingivitis.

The researchers found a significant inverse association between serum vitamin D concentration and chronic gingivitis in all participants, meaning that the higher the vitamin D status of the individual, the less gingivitis they showed. Men and women in

the highest fifth for vitamin D status were 20 per cent less likely to bleed on gingival probing than those in the lowest fifth. The link appeared to be linear, and was independent of age, sex, ethnicity, income, body mass index, diabetes, use of oral contraceptives and hormone replacement therapy. It was also unconnected to use of vitamin and mineral supplements. Although vitamin D is essential for bone growth, gingivitis is usually not related to the health of the jawbone, so the researchers conclude that vitamin D reduces vulnerability to gingivitis through an anti-inflammatory and immune system enhancing effect. They also believe that marginal gingivitis could be used to further study vitamin D's anti-inflammatory effects on the human body.

Dietrich, T. et al. Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. American Journal of Clinical Nutrition, Vol. 82, Sept 2005, pp. 575-80

Editor's comment: It is becoming increasingly clear that vitamin D deficiency is a huge problem and linked to an increased risk of many diseases including breast and prostate cancer. Daily supplementation with 1000 IU of vitamin D3 is generally safe and a prudent measure to protect your overall health.

Greater fitness reduces risk of metabolic syndrome

DALLAS, TEXAS. Detecting metabolic syndrome in people with no overt symptoms would enable doctors to identify those individuals who would benefit from intensive preventive therapy. Metabolic syndrome is increasingly viewed as an important precursor of type 2 diabetes and cardiovascular disease. It consists of a cluster of risk factors including insulin resistance, high blood pressure, low levels of "good" cholesterol (HDL cholesterol), and abdominal obesity. Abdominal obesity is clearly linked to physical fitness and exercise but so far, few of the studies on predictors of metabolic syndrome have looked at this area. Researchers at the Cooper Aerobic Center have however shown that low cardiorespiratory fitness is among the strongest risk factors for cardiovascular disease and related mortality.

Now a team from the same center has confirmed that cardiorespiratory fitness (the most reliable index of physical activity) independently predicts risk of developing metabolic syndrome. They

followed 9,007 men and 1,491 women with an average age of 44 years, participating in the Aerobics Center Longitudinal Study. During follow-up of about six years, 1,346 men (16%) and 56 women (4%) developed metabolic syndrome. For men, the risk of metabolic syndrome was 26 per cent lower for those who were moderately fit and 53 per cent lower for those who were highly fit, compared to those in the lowest fitness category. In women, the risk was 20 per cent lower with a moderate fitness level and 63 per cent lower for a high fitness level.

The researchers say the new data suggests higher fitness levels provide substantial protection against metabolic syndrome even in individuals with existing metabolic risk factors. Most people can achieve moderate levels of cardiorespiratory fitness by 30 to 40 minutes of brisk walking about five days per week. A high fitness level requires a similar frequency and duration of more vigorous exercise.

In an accompanying commentary, an expert from the Quebec Heart Institute says the study emphasizes further the relevance in clinical practice of gathering information on the physical fitness status of patients, and he concludes that reshaping our sedentary habits will be a huge challenge.

*LaMonte, M. J., et al. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: A prospective study of men and women. **Circulation**, Vol. 112, July 2005, pp. 505-12*
*Despres, J. P. Our passive lifestyle, our toxic diet, and the atherogenic/diabetogenic metabolic syndrome: Can we afford to be sedentary and unfit? **Circulation**, Vol. 112, July 2005, pp. 453-55*

Testosterone therapy may be linked to prostate cancer

SAN DIEGO, CALIFORNIA. The recent increase in the use of testosterone therapy has led to concern over prostate cancer, which is linked to high testosterone levels. A team of researchers from the University of California at San Diego Medical Center report on 20 cases of prostate cancer developing in men a few months to a few years after they began testosterone supplementation for sexual dysfunction or "rejuvenation". The average PSA (prostate-specific antigen) level of the 17 men tested before treatment was 3 nanograms per milliliter, although the range was 1 to 15. The threshold for further evaluation is usually 4. The researchers say that in these 20 patients, clinically significant prostate cancer was presumed to be related to testosterone therapy. Although the authors state that there is no conclusive evidence yet, they add that, in their opinion, men should not receive a prescription for testosterone supplementation without careful, informed consultation regarding the risks and benefits of such treatment. This is particularly relevant for those with a family history of prostate cancer.

Furthermore, the authors are concerned about the high prevalence of subclinical prostate cancer and how testosterone supplementation might affect such tumors. They hope that expert guidelines will be drawn up to aid doctors in appropriately and carefully prescribing testosterone replacement to men who need it, monitoring them for potential adverse outcomes.

The article appears alongside an editorial by a urologist from Cornell University who points out "serious flaws" in the study. For example, it does not show how common the risk of prostate cancer is in men on testosterone therapy. If results from a previous study are accurate, it may be no higher than in the general population. Moreover, in this study there is a lack of pre-treatment data for many of the patients on PSA or DRE (digital rectal examination). Nevertheless, doctors need to be extremely careful before beginning testosterone therapy, he writes, and PSA and DRE testing should be performed frequently during treatment.
*Gaylis, F. D. et al. Prostate cancer in men using testosterone supplementation. **The Journal of Urology**, Vol. 174, August 2005, pp. 534-38*

Depression and bowel problems linked to chronic cystitis

PHILADELPHIA, PENNSYLVANIA. Recent studies have found an association between bladder problems and irritable bowel syndrome in women, and both conditions may be linked to depression. Now a research team from the University of Pennsylvania have examined the rates of irritable bowel syndrome and depression in women with interstitial cystitis - a chronic disorder characterized by an inflamed or irritated bladder wall and leading to severe pain and a frequent need to urinate.

using reliable questionnaires. Of the women with interstitial cystitis, 43 per cent had been diagnosed with irritable bowel syndrome, compared to 11 per cent of the comparison group. This indicates that women with interstitial cystitis are several times more likely to also have irritable bowel syndrome. Severity of cystitis was not linked to presence of irritable bowel syndrome.

The researchers compared 46 women with newly diagnosed interstitial cystitis and 46 comparable women seen at their annual gynecologic exam. Information on the women's health was gathered

Concerning depression, 41 per cent of women with interstitial cystitis met the criteria for depression, compared with 11 per cent of the comparison group - a four-fold increased risk. Depression risk, however, was affected by cystitis severity. Women with severe cystitis had a 10-fold higher risk than

those with mild cystitis. Among women with cystitis, those with depression were significantly more likely to complain of bladder pain, needing to urinate in the night, abdominal pain and bowel symptoms.

The authors hypothesize that there may be a common underlying source for the inflammation and pain, based on nervous system inflammation or defective serotonin receptors. They add that both may be a causal factor in depression, at least before interstitial cystitis treatment has become effective, or the women have developed coping

strategies. As pain has often been linked to depression, pain management techniques may improve depression symptoms in women with interstitial cystitis, the authors suggest. They believe that women with interstitial cystitis should be screened for irritable bowel syndrome and depression.

Novi, J. M. et al. Risk of irritable bowel syndrome and depression in women with interstitial cystitis: a case-control study. The Journal of Urology, Vol. 174, September 2005, pp. 937-940

Eating fish may lower inflammation in the blood vessels

ATHENS, GREECE. Consuming fish has long been thought to help protect against heart disease, possibly through reducing inflammation in blood vessels. However, study results on the effects of fish on inflammatory markers are mixed, so a team of researchers from Harokopio University set out to examine the relationship in a population-based group of men and women free of heart disease.

They gathered data on 1,514 men and 1,528 women aged 18 to 89, taking part in the ongoing ATTICA study into the benefits of a Mediterranean diet on heart health. Compared to those who did not eat fish, those who ate the most (10.5 ounces per week or more) had an average 33 per cent lower level of C-reactive protein, a widely-used marker for inflammation. They also had a 33 per cent lower level of interleukin-6, another inflammatory marker found in the plasma. This group had 21 per cent lower tumor necrosis factor-alpha, which affects lipid metabolism, coagulation, and insulin resistance, and 28 per cent lower serum amyloid A, a blood protein increased by inflammation. Significantly lower levels of these markers were also found in people who ate about 5 to 10 ounces of fish per week.

This clear and strong inverse association between fish consumption and inflammatory markers may help explain why people who eat fish tend to have lower rates of heart disease, say the authors. The benefits remained once many risk factors were taken into account and were observed even in people with high blood pressure or diabetes, but not high cholesterol. Nevertheless, it was a cross-sectional study which did not follow people over time, so cannot prove causation.

These results support recommendations that people eat more fish, the authors write, particularly oily fish with their high levels of omega-3 fatty acids. One or two portions per week may be sufficient, but the fish should not be fried. In some cases, omega-3 fatty acid supplements may be appropriate to achieve an optimal intake of 0.6 grams of omega-3 fatty acids per day.

Zampelas, A. et al. Fish consumption among healthy adults is associated with decreased levels of inflammatory markers related to cardiovascular disease: The ATTICA Study. Journal of the American College of Cardiology, Vol. 46, July 2005, pp. 120-24

NEWSBRIEFS

New NSAID combination avoids ulcers. The main drawback of nonsteroidal antiinflammatory drugs (NSAIDs) is that they can cause stomach and duodenal ulcers. NSAIDs such as indomethacin act by blocking both the COX 1 and COX 2 enzymes. However, since COX 1 actually protects the gut lining, blocking it is not really that great an idea. Researchers at the University of Sydney have now discovered that adding copper ions to indomethacin

prevents the drug from blocking COX 1 and, according to recent animal tests, reduces stomach ulcers by 80% and completely eliminates intestinal ulcers. A new drug combining indomethacin with copper is already being used in dogs and has been found very safe and effective. Human trials are planned to begin within the next year.

New Scientist, July 9, 2005, p. 17

Possible defense against bird flu. Acute respiratory distress syndrome (ARDS) is a serious and often fatal condition resulting from an infection of the lungs. The infection can be triggered by the SARS virus and, most likely, by the bird flu virus as well. A team of Austrian and Chinese researchers now reports that ARDS is caused by a runaway immune response in the lungs triggered by an over-production of angiotensin II. Animal experiments have shown that Losartan, a drug used to control high blood pressure, prevents ARDS by blocking angiotensin receptors. They speculate that drugs like Losartan or perhaps even regular ACE inhibitors might save many lives during a flu pandemic, since vaccines and anti-flu drugs will likely be unavailable or in short supply.

New Scientist, July 16, 2005, p. 12

Is big Pharma bribing its way to success?

The Washington DC Center for Public Integrity (CPI) recently reported that the pharmaceutical industry now employs an army of 1300 lobbyists (at a cost of \$128 million/year) to influence the administration and lawmakers on Capital Hill. Campaign donations to candidates in Congress and presidential elections totaled \$87 million over the last 7 years – of which, President Bush received almost \$800,000. All told, the pharmaceutical industry has spent at least \$800 million over the past 7 years buying influence – way more than any other industry group. This expenditure, according to the CPI, has paid off handsomely. During the period studied, federal oversight of the pharmaceutical industry was weakened, more tax credits were granted, cheaper generic drugs were squeezed out of the market, and patent protection was strengthened.

New Scientist, July 16, 2005, p. 4

Obesity weighs heavily on healthcare. The cost of health insurance in the US has risen by 60% since 1987. Dr. Kenneth Thorpe and colleagues at Emory University believe that the increase is being fuelled by the explosive growth in the number of overweight and obese people. Spending on diseases related to obesity has increased 10-fold since 1987 and now accounts for 12% of the healthcare budget in the US. Diabetes, high cholesterol, high blood pressure, and depression are just some of the disorders with a clear link to obesity. Says Dr. Thorpe, "Taxpayers, employers and workers are all affected by this and will have to

tackle the problem together, as they have tackled smoking in the past."

New Scientist, July 2, 2005, p. 6

Prevention of deep vein thrombosis. It is becoming increasingly clear that deep vein thrombosis (formation of blood clots in a vein deep inside the leg) is a serious problem associated with long distance air travel. At least one clinical trial has found pinokinase (a blend of the enzyme nattokinase and the antioxidant pycnogenol) to be highly effective in preventing deep vein thrombosis (DVT). Now Taiwanese researchers report that wearing below-knee, graduated compression stockings during the flight is also very effective in preventing DVT. Their meta-analysis covered 9 randomized controlled trials involving almost 2500 airline passengers. The researchers conclude that passengers wearing compression stockings (flight socks) have a 20-times lower risk of developing DVT than do passengers not wearing the stocking.

Journal of Advanced Nursing, Vol. 51, No. 1, July 2005, pp. 83-98

Cancer linked to combat trauma. Many veterans develop post-traumatic stress disorder (PTSD) after participating in combat operations. The disorder, previously known as shell shock, involves harrowing flashbacks and outbursts of rage, guilt and depression. While there is little doubt that PTSD can be emotionally devastating, there is now also mounting evidence that it can take a heavy physical toll as well. Joseph Boscarino of the New York Academy of Medicine has reviewed medical data for more than 18,000 Vietnam veterans who underwent a detailed health survey in 1985. Veterans with PTSD were more likely to die from accidents, drugs, and suicide. However, PTSD sufferers who had seen active combat were also more likely to die of heart disease and various kinds of cancer. Israeli researchers have found that veterans of the 1982 Lebanon fighting who developed PTSD are twice as likely to have high blood pressure, ulcers and diabetes, and 5 times as likely to have heart disease and headaches. It is estimated that 60,000 Iraq veterans, so far, have developed PTSD.

New Scientist, August 27, 2005, pp. 6-7

Please Visit Our Vitamin Store



<http://www.yourhealthbase.com/vitamins.htm>

RESEARCH REPORT

Diagnosis and Staging of Prostate Cancer

Part II – The Prostate Biopsy

William R. Ware, Ph.D., Emeritus Professor of Chemistry, University of Western Ontario

The ultrasound guided hollow needle biopsy is the so-called *gold standard* for the diagnosis of PC. In the US, according to 2002 cancer statistics, about 1,300,000 prostate biopsies were performed annually and detected 189,000 new cases of PC (15%) [82]. However, if the gold were “24 carat” for a single biopsy, it would never be necessary to repeat the procedure to “find” a suspected tumor or tumors. Unfortunately, this is not the case. The reason is that the procedure may miss the tumor or tumors because either they are small or in a part of the prostate that is not biopsied. Consider a small blueberry muffin containing only one or two blueberries and imagine trying to see if there are any at all with a few random thrusts of a hollow needle. Once a biopsy has identified the characteristic cells associated with PC, the diagnosis takes on a fairly high level of certainty. In fact, the nature, distribution and quantity of cells recovered that are suggestive or indicative of cancer are the basis of a scoring system, although the resultant scores are frequently changed (mostly upward) if a pathological study of the removed prostate is carried out. This is always done after a radical prostatectomy (RP), but those who elect radiation therapy do not have the opportunity for this definitive check on the information provided by their biopsy.

The importance of a correct diagnosis, including a correct assessment of the significance or seriousness of the disease if present, cannot be understated. The diagnosis of prostate cancer judged significant will most certainly lead to a discussion of treatment, and the two common treatments for localized cancers both have side effects that may profoundly alter an individual's quality of life. To have a radical prostatectomy or radiation therapy when in fact there is only insignificant or indolent cancer present is obviously something to avoid, although there are no doubt some who would debate this point. Likewise, to have a false negative diagnosis when an aggressive cancer is present is also highly undesirable unless the individual has a very short life expectancy. Thus the imperfections inherent in the standard diagnostic method are disturbing.

The prostate is relatively inaccessible and to acquire tissue sample requires an invasive procedure. Since sampling needles are used, the two most direct routes are through the wall of the rectum or through the perineum, which is the area between the anus and the scrotum. Almost all biopsies employ the former approach. The first reported needle biopsy occurred in 1930 and the first transrectal procedure was reported in 1937. The procedure was revolutionized in the mid 1980s with the advent of both a transrectal ultrasound device of adequate imaging resolution and its combination with a needle device which allowed the operator to direct needles under ultrasound guidance into the targeted sections of the prostate. Shortly thereafter a spring-loaded core biopsy device (a so-called gun) was developed that operated in conjunction with the ultrasound probe. Continued improvements in the resolution of the probe and the design of the needle gun have resulted in the present day instruments which provide both a satisfactory level of visualization coupled with the ability to direct the biopsy needle into a variety of regions of interest. The procedure can be done in an urologist's office, generally requires less than an hour, and is generally accompanied by minimal or at worst tolerable pain, especially if local anesthetic is used.

Some tumors can be imaged by the ultrasound device used in biopsy, and this can prompt targeting these areas for sampling. However, many tumors, especially early ones, are effectively invisible on the current grey-scale ultrasound [83]. Thus using ultrasound alone is not a solution to the diagnostic problem. While the ability to visualize and study the prostate gland has increased greatly with modern transrectal ultrasound, this has not resulted in substantially improved cancer detection without biopsy confirmation [83].

Since a biopsy is at present the *only* means of PC diagnosis, it is difficult to test its false negative rate since there is no "standard" for comparison. One can obviously not recruit a group of men who agree to radical prostatectomies after a negative biopsy to see if PC was missed! The solution to this dilemma is repeating the biopsy in cases where there is a high risk or a suspicious DRE, since repeating such an invasive procedure can be justified on medical grounds, and if enough biopsies are done, it turns out that a limiting and reasonably accurate estimate is achieved regarding the presence or absence of cancer. Men should be aware that repeat biopsies following a negative result in patients with high risk or suspicious DRE represent normal practice. The repeat procedures are done six to twelve weeks apart in order that the trauma associated with the previous test has resolved.

BIOPSY TECHNIQUE AND THE OPTIMUM NUMBER OF CORES

When ultrasound guided biopsies became routine, they initially involved taking six samples in the peripheral zone, the so-called sextant biopsy. In a sense this was a random biopsy since no attempt was made to target selected spots. It soon became apparent that the sextant procedure missed a significant number of cancers, the percentage frequently quoted being around 25%. Thus protocols that used a single sextant biopsy to determine the presence or absence of cancer in, for example, studies of the success of screening with PSA, were in fact using a rather imperfect diagnostic tool. That is, in general more subjects below a given PSA cut-off had PC than the biopsy data indicated. Also a single biopsy, when used to define a "cancer free" population for the purposes of a study, was in fact quite unsatisfactory. The situation is even more serious in subjects with large prostates where even a higher percentage of cancers are missed with the sextant protocol.

A recent study reported in 2005 provides an example of the problem of missed tumors. Djavan *et al* [84] studied 1051 men with risk defined by a PSA between 4 and 10 and compared the results of multiple biopsies with those obtained at the initial biopsy. A random sextant set plus two additional transition zone samples were used in all the biopsies. The first biopsy revealed an incidence of 22% PC. A second biopsy on those who were negative found 10% had PC giving an overall incidence for the two procedures of 30%. The third biopsy on the remaining "negatives" found 5% PC for an overall incidence of 33.3%. The fourth biopsy increased the incidence to only 33.6% overall. If one assumes that the fourth biopsy found most of the remaining cancer, the first biopsy missed 12% of the tumors present. A subset of patients had an RP. Organ-confined disease was present in 58% of cancer found in the first biopsy, 60.9% in the second, 86.3% in the third and 100% in the fourth. As might have been expected, cancers detected in the fourth biopsy had lower grade, stage and tumor volume as compared to those found in the first or second biopsy, i.e. the smaller the tumor or tumors, the harder they are to find. The third and fourth biopsies were accompanied by slightly higher level of morbidity than the first two. Thus an initial so-called extended biopsy protocol involving 8 cores still had a false negative rate of approximately 12%.

In a large serial biopsy study (2526 subjects), Roehl *et al* [85] found cancer detection rates of 29%, 17%, 14%, 11% 9% and 7% for one to six procedures. In this study the number of cores was variable but frequently the sextant scheme was used. In agreement with Djavan *et al* [84], there was a trend toward more organ confined cancers detected in subsequent biopsies as compared to the initial biopsy. Nearly 25% of the cancers ultimately detected were missed in the initial biopsy. Viewed another way, 77% of cancers were detected on first biopsy, 91% after two, 97% after three and 99% after four.

Both of these studies indicate the need for improving the first biopsy to decrease the number of repeats. Ochiai *et al* [86] have recently reviewed the current status of this problem. This review of the recent literature makes it clear that both altering and increasing the regions sampled and increasing the number of cores from 6 to 10 or 12 significantly increases the rate of cancer detection on first biopsy. This improvement is in part due to directing sampling to regions of the prostate with high probability of harboring tumors. For example, Presti *et al* [87] found that a more judicious use of even the sextant protocol yielded an 83% detection rate as compared to

78% with the random standard sextant approach, while a 10-core scheme which included high probability regions yielded 97% detection. The reference standard in this study was the 12-core biopsy which was not validated with repeat biopsies. Thus the number of missed cancers, while probably small, was in fact unknown, as it was also in the technique comparison studies reviewed by Ochiai. It in fact appears that the optimum number of cores and the core location strategy remains unknown if the ultimate concern is how many cancers were missed. Studies that compare two or more protocols employed during a single biopsy are relatively easy to accomplish since the protocols are combined in a single procedure, but to test several different protocols where three or four identical repeat biopsies are used to approximate the cancers missed in each protocol represents a much more complex study, both to organize and implement.

In what is called a saturation biopsy, a large number of cores, even over 40, are taken! General anesthetic is generally required and the procedure is accompanied by higher morbidity than observed in normal biopsy procedures. Scardino recommends against this protocol [2].

Current practice involves taking more cores than in the traditional sextant protocol, typically, 8, 10, 12 or 13. In addition, when a negative first biopsy is obtained with a patient judged at high risk because of a suspicious DRE, a very high PSA, or a family history of PC, one or more additional biopsies are generally recommended. After three or four negative results, the probability of cancer being present is low, typically less than 5%, but still finite and, unless the specific biopsy protocol has been studied locally with repeat biopsies, it is unknown. Coming back to the individual who wants to know for sure whether he has cancer, it appears from what is currently known that not only is a biopsy required, but one would not be enough unless a highly reproducible protocol was used that had been validated locally by repeat biopsies to establish the false negative rate and the initial biopsy was found to give a very low rate. One 12-core protocol yielding 2.3% false negatives on first biopsy has been reported, but the group studied was very small [64]. Thus journal articles can be misleading when a high detection rate is quoted for a particular protocol. For example, Philip *et al* [88] report that their 10-core biopsy technique found 98.6% of cancers in the group studied, but this was based on the reference standard of the number found with a 12 core protocol, not on repeat biopsies until there was a negligible increase in the discovery rate. It is also now fairly clear that men with large prostates require a larger number of cores to achieve the same detection rate as a man with a small prostate [86].

The ultrasound guided needle biopsy can also be used to investigate such questions as whether or not the cancer has spread to the surrounding fatty tissue, the seminal vesicles, or the prostate nerves. Information from such targeted sampling can be of great help in assessing the probable extent of the cancer. Thus a positive biopsy can sometimes prompt a repeat biopsy, the object being to obtain more information about the tumor or the presence of cancer in adjacent areas accessible in the transrectal biopsy. Such information may impact treatment decisions.

BIOPSY PAIN

The pain associated with the biopsy procedure arises mainly from the prostate itself rather than from the needle puncture of the wall of the rectum. In the past it has been generally considered that pain was not an issue. However, discomfort associated with the procedure is indeed experienced with 60-80% of men reporting mild to moderate pain and 6% of patients judging the pain so uncomfortable that they considered general anesthetic indicated [89]. In unusual cases, the pain may be so severe as to limit the number of cores that can be taken [90]. The current practice of taking up to 12 cores aggravates the problem [89]. Several approaches can be used to minimize this pain. One involves "conscious sedation" such as is used in colonoscopy. Complications from sedation are extremely rare. With sedation, one is awake, feels little pain, and generally does not recall the details of the procedure [37].

Another approach involves a local anesthetic gel (lidocaine gel) used to lubricate the ultrasonic probe, while a more direct approach involves injecting (infiltrating) lidocaine directly into the vicinity of the nerves leading into the prostate, a procedure done under ultrasound guidance. This latter technique is reminiscent of the dental nerve block used for work on the lower jaw. Studies that have either compared the use of lidocaine gel with infiltration or simply evaluated the infiltration method in a randomized fashion find the infiltration protocol superior to the gel and very effective in pain reduction [89-92]. However, lidocaine, even when used as a nerve block, is effective only for a few hours, and patients frequently report rebound pain by the evening of the biopsy. This can

be relieved by the use of a long-lasting anti-inflammatory (diclofenac) administered via a suppository about an hour prior to the procedure [93]. The lidocaine nerve block became popular after the study of Soloway and Obek was published in 2000 [94].

If pain can be controlled, what else is there to worry about in connection with having a prostate biopsy? Two things come to mind. One is dealing with positive results that require a decision regarding treatment or watchful waiting but also may induce psychological stress, perhaps severe, associated with the knowledge that cancer is present. The other involves the potential for complications associated with the needle biopsy. The incidence of biopsy-related complications has received considerable study. Complications include blood in the urine and semen (hematuria and hematospermia), prostate or urinary infection, a serious or even life-threatening systemic infection, an acute urinary retention episode, temporary erectile dysfunction, and finally rectal bleeding, which if severe can require immediate intervention including surgery. Also, moderate to severe so-called vasovagal responses can occur with drops in systolic blood pressure requiring intravenous fluid administration and in severe cases, with neurological events such as seizure or loss of consciousness. The complications of the prostate biopsy merit further discussion.

BIOPSY COMPLICATIONS

Since the rectum is not sterile there is risk of the needle puncture carrying intestinal bacterial into the prostate with the resultant possibility of infection. To guard against this eventuality, it is now standard practice to prescribe antibiotics both before and after the procedure, with the fluoroquinolone class the most popular (e.g. ciprofloxacin, levofloxacin or ofloxacin). However, even with antibiotic prophylaxis, there is still a small risk of post-biopsy infection. In rare instances the fluoroquinolone class of antibiotic can cause very serious side effects.

It is difficult to quote meaningful combined statistics from studies of complications due to a variation in definitions, the failure to distinguish early from delayed morbidity, mild from severe complications and the lack of stratification with regard to antibiotic use. Reviews of large numbers of studies produce huge ranges in percent incidence. For example, Ghani et al [95] give the following ranges:

- Hospitalization 0-4%
- Hematuria 12.5-80%
- Hematospermia 1.3-58%
- Urinary retention 0.2-10%

It is perhaps more meaningful to look at a study where early and delayed as well as mild vs. severe complications were distinguished. Djavan et al [96] examined the complication rate associated with 1051 initial biopsies which were all done with fluoroquinolone antibiotic prophylaxis preoperatively and for 4 days thereafter. For early morbidity, between 97.2 and 98.2% of patients had no or mild complications with the exception of mild hematuria, which was seen in 38% of cases. For moderate to severe early complications, they found rectal bleeding 2.1%, hematuria 62%, vasovagal episodes 2.8%, and urinary retention 1.8%. Delayed morbidity was as follows:

- Urinary tract infections 10.9%
- Fever 2.9%
- Urinary tract infections with fever 2.1%
- Urinary retention 0.9%
- Hematospermia 9.8%
- Recurrent mild hematuria 15.9%
- Persistent dysuria (difficulty or pain during urination) 7.2%

The authors also present a review of eleven studies. In all but two cases antibiotic prophylaxis was used. The range of incidence was smaller than reported by Ghani et al [95] but still rather large.

Rectal bleeding can be serious. Scardino [2] gives a rate of 1 in 1000 patients that required hospitalization for transfusion, cauterization or sutures to resolve biopsy induced severe rectal bleeding. He also quotes a rate of about 3% for urinary tract infections or prostatitis if antibiotic prophylaxis is used, with 6-10% otherwise. He makes a very strong point as does Walsh [37] that patients must be very vigilant after a biopsy for symptoms of complications that can quickly become severe. The warning signs are a fever of 101°F (38.3° C) or higher, chills, muscle aches, or urinary problems such as abnormal frequency, urgency or burning. In his opinion, immediate action is indicated, at an emergency room if necessary, in order that the infection apparently present can be cultured and treated. Patients should inform the ER staff or attending physician of the recent transrectal biopsy. Failure to take immediate action (even a 6-12 hour delay is serious) can in some cases result in an overwhelming septic condition with attendant long hospitalization, serious health risks and even death. Scardino gives a risk of 1 in 200 of this scenario. Because of the risk of delayed infection or bleeding, Scardino suggests avoiding long air trips or travel to remote areas where immediate medical attention is unavailable until the risk of these complications is very low.

Biopsy candidates who have previously undergone total joint replacements are at increased risk of hematogenous prosthetic joint infections. The American Academy of Orthopedic Surgeons (AAOS) and the American Urological Association (AUA) have issued a joint advisory statement regarding this potential problem (<http://aaos.org/wordhtml/papers/advistmt/1023.htm>). Those at increased risk include all patients during the first two years after joint replacement, patients immuno-compromised or immuno-suppressed, and patients with previous prosthetic joint infections, malnourishment, hemophilia, HIV infections, diabetes and malignancy. Patients corresponding to one or more of these criteria should inform their urologist of the situation prior to a biopsy. The AAOS/AUA recommendations provide a suggested special antibiotic prophylaxis regimen.

It is important to realize that most of the complications of the transrectal ultrasound guided biopsy are mild and short lived. The use of anesthetic, especially the prostatic nerve block, should reduce the procedural pain to a minimum, and while severe complications are unpleasant to contemplate and of finite but low probability, it is hard to see that they should be a deterrent to having a medically justified biopsy. However, as has been discussed at length above, what is medically justified is sometimes far from clear and subject to debate.

The biopsy generates a set of tissue samples (cores) approximately 0.4 mm in diameter and 15 mm in length which are then examined by a pathologist who will look for cells characteristic of PC and characterize the type and extent in each core. The number of cores yielding positive results is reported and in most studies is correlated with the risk of non-organ confined disease. Finally, a score, called the *Gleason Score* is calculated and forms part of the basis of clinical judgments as regards treatment and prognosis. While this is the now a widely accepted protocol for the analysis of biopsy cores, it turns out to be somewhat less than perfect in either identifying the seriousness of the cancer or the prognosis. It is, however, all that there is available aside from PSA levels and DRE observations to guide the urologist down the path to treatment or watchful waiting unless the patient presents with symptoms of advanced disease or distant metastasis. These scores are also used to judge prognosis. Pathologists also grade the cancer with the Gleason system when it is found in tissue samples recovered during the TURP surgical procedure for BPH. Gleason Scores can also be calculated from an examination of the prostate after an RP.

Part III of this report will discuss the significance of the Gleason score, the staging of the cancer and the ultimate prognosis.

Please see Part I for references



<http://www.yourhealthbase.com/prostatesupps.htm>

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: <http://www.yourhealthbase.com>
ISSN 1203-1933 Copyright 2005 by Hans R. Larsen

INTERNATIONAL HEALTH NEWS does not provide medical advice. Do not attempt self-diagnosis or self-medication based on our reports. Please consult your healthcare provider if you are interested in following up on the information presented.