INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 163 **DECEMBER 2005 – JANUARY 2006** **14th YEAR**

In this issue we conclude William Ware's excellent 3-part article on the prostate and its problems. Part III deals with grading and staging of prostate cancer.

With today's trend toward assembly line medicine it is of utmost importance to take a very active role in decisions regarding your treatment. There is a growing consensus that prostate cancer is vastly overtreated with a commensurate increase in the number of patients ending up incontinent and impotent for no good reason. Thus, the explanations and methods provided by Bill for determining your treatment alternatives from Gleason score and staging information are vital and an absolute necessity when it comes to making the crucial decisions together with your physician. Don't miss this article!

Also in this issue we report on such topics as the tanning bed controversy, a natural supplement for reducing the pain of diabetic neuropathy, omega-3 fatty acids can reduce mortality from cardiovascular disease, calcium helps protect against colon cancer, and will hypnotherapy prove a viable alternative to general anesthesia?

Don't forget, if you need to restock your supplements, by ordering from our web "store" you, as a subscriber, will 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 makes it possible to continue publishing the newsletter.

Since this is a combined issue for the end of a year, I will take this opportunity to wish you and your family a Happy Holiday Season and good health in the coming year.

All the best,
Hans

Highlights

LETTERS TO THE EDITOR

My son is diabetic. His feet tingle, burn, and are numb and cause him extreme pain. Do you know of any vitamins that can help him?

VH, USA

Editor: *There are a couple of natural supplements that have been found to be helpful for diabetic neuropathy. Alpha-lipoic acid is perhaps the most powerful at an adult dose of 200 mg three times a day. If your son has a low blood level of vitamin B12 then weekly or monthly injections or*

supplementation with 1000 micrograms/day of sublingual vitamin B12 may also be helpful.

****

I have read your entire article about the benefits of taking a B-12 supplement and I think it's a good thing to do. I take 1000 mcg daily. I know I feel better when I take it except for one thing. I can't sleep. Three of my friends are also taking it and we realized we are all having the same problem after taking the supplement for 2 - 3 months. We walk the floor all night ..... getting up and down from the bed several times during the night because we can't sleep. Could this be a side effect of the B-12? I have read many articles about this vitamin, but there is nothing about sleeplessness. I would appreciate any information you know about this.

JG, USA

Editor: *Thank you for sharing your observation concerning sleep difficulties and vitamin B12 supplementation. I am aware that vitamin B12 has been used to treat certain sleep/wake disorders, but have not seen any data indicating that it might cause insomnia. However, I will certainly look out for anything that may confirm this.*

ABSTRACTS

Disagreement over health benefit from tanning beds

PROVIDENCE, RHODE ISLAND. The benefits of vitamin D for bone health have been long known. Vitamin D is manufactured in the skin on exposure to ultraviolet (UV) rays in sunlight. In December 2004, the possibility that indoor tanning beds may improve a person's vitamin D status was raised by a study in the *American Journal of Clinical Nutrition.*

Vitamin D status was measured in 50 participants who regularly used a tanning bed, and 106 who did not. The researchers claimed to show that regular use of a tanning bed that emits UVB radiation is associated with a 90 per cent higher concentration of serum vitamin D, and thus may benefit bone health. It later emerged that some of the authors were linked with the US Indoor Tanning Association (ITA), a professional society representing the indoor tanning industry.

Now, experts from Brown University and the University of Minnesota take up the argument in a letter to the editor of the journal. They state their concerns over the original research suggesting that tanning beds may provide a medical benefit. Firstly they point out that the methods of recruitment into the study do not make the results applicable to the general population. Many relevant characteristics of the participants were not measured, they add, so could not be taken into account. People who visit tanning centers will not be able to tell whether they are under UVA or UVA/UVB lamps, or have a measurement of their exposure to radiation, they write. The study authors also fail to acknowledge the possible skin cancer-causing effects of artificial tanning lamps, or recognize that oral vitamin supplements are much safer and less expensive. If the readers were aware of the researchers' links to the commercial tanning industry, they may have reached a different conclusion, they write.

In a response published alongside the letter, one of the original researchers calls attention to the 'epidemic' of vitamin D deficiency in the US population, and states that vitamin D requirements cannot be met through diet alone. The researcher defends his study against criticisms of its methodology and conflicts of interest, and restates his belief that UVB-emitting lamps are very effective at producing vitamin D in the skin and increasing serum concentrations of the vitamin.

Tangpricha, V., et al. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. American Journal of Clinical Nutrition, Vol. 80, December 2004, p. 1645-49

Weinstock, M. A., Lazovich, D. Tanning and vitamin D status. American Journal of Clinical Nutrition, Vol. 82, September 2005, p. 707

Holick, M. F. Reply to MA Weinstock and D Lazovich. American Journal of Clinical Nutrition, Vol. 82, September 2005, p. 707

Editor's comment: There is no question that vitamin D deficiency is rampant. However, in my opinion, supplementing with 1000 IU or more per day of vitamin D3 (cholecalciferol) is far safer and substantially less expensive than using a tanning bed.

Natural supplement reduces diabetes-related pain

DETROIT, MICHIGAN. Researchers studying pain in advanced diabetes have found good results in two large trials. Diabetic polyneuropathy (DPN) is a complication of diabetes causing deterioration of the nerves. It often leads to pain, although the mechanisms behind this pain are not fully understood.

One possibility is treatment with acetyl-L-carnitine (ALC), an amino acid which is often lacking in diabetics. Studies using diabetic rats indicate that giving ALC has preventative and therapeutic effects on nerve function. Early studies on humans suggested that ALC can reduce the pain of DPN, so two larger trials were undertaken. The findings are presented by researchers from Wayne State University. Both trials were multicenter, double-blind, placebo-controlled and randomized. They both lasted for a year and took place in the US and Canada (US-Canadian Study, UCS) and the US, Canada, and Europe (UCES). Together they included 1,257 patients of between 18 and 70 years of age, who had been diabetic for over a year. In both trials, patients received either 500 or 1,000mg per day of ALC and underwent physical and neurological tests at the beginning and end of the trials.

The results were analysed both separately and together. Pain was examined in the 342 (27 per cent) of patients who rated it as their 'most bothersome symptom'. The combined results showed that ALC at 500 and 1,000mg was significantly associated with regeneration of nerves. ALC at 1,000mg was significantly linked to improved vibration perception (a measure of sensation). Pain was significantly reduced among those taking ALC at 1,000mg, both at 6 months and a year, in a combined analysis of both trials. This was particularly evident in those with type 2 diabetes, those with greater compliance to the treatment, and those at an earlier stage of diabetes. The patients whose pain improved the most also showed the most nerve regeneration.

The researchers state that ALC at 1,000mg per day shows beneficial effects on pain in patients with DPN. They conclude that ALC is efficacious in alleviating many symptoms of DPN, but longer trials must be carried out on patients at an earlier stage of the disease.

Sima, A. A. F., et al. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy. Diabetes Care, Vol. 28, January 2005, pp. 89-94

B12 deficiency requires high supplement doses

WAGENINGEN, THE NETHERLANDS. Vitamin B12 deficiency is fairly common among older people and can cause anemia, pain and depression. Supplementation with cobalamin may reverse the deficiency, however, the ideal dose when given orally is yet to be determined.

A team from the University of Wageningen undertook a study in which 120 participants were given either 2.5, 100, 250, 500 or 1,000ug (micrograms) of cyanocobalamin in capsules per day. These doses cover the full range from recommended dietary allowance in the Netherlands to the normal dose used in injections for B12 deficiency. The participants were aged 70 to 94, with an average age of 80. They were all mildly deficient in vitamin B12, with serum concentrations of 100 to 300 picomoles per liter. Their levels of methylmalonic acid (MMA, a marker for vitamin B12 deficiency) were above 0.26umol per liter, showing a deficiency. All of the participants received each of the experimental doses for 16 weeks, in a random order.

Compliance with the medication was very high, at 98 per cent. Overall, levels of MMA and serum vitamin B12 improved with increasing doses of cobalamin. Elevated MMA was significantly reduced after 8 weeks, and remained so after 16 weeks. The percentages of participants whose MMA reduced to below 0.26umol per liter when taking 2.5, 100, 250, 500 or 1,000ug cobalamin were 21, 38, 52, 62 and 76 per cent respectively.

The researchers explain that a major knowledge gap existed over the lowest oral cobalamin dose required to normalize elevated MMA. They state that in this study, a daily dose of 647-1032ug was the lowest dose to give 80-90 per cent of the maximum reduction in MMA. These doses led to an average reduction in MMA of 33 per cent. However, they add that diagnosing vitamin B12 deficiency is

complicated due to the limitations of current techniques. The authors conclude that the lowest dose needed to normalize vitamin B12 deficiency is more than 200 times higher than the recommended dietary allowance. They add that the relevance of treating vitamin B12 deficiency in older people could be substantial, were further trials able to show benefits to cognitive functioning and depression.

Eussen, S. J. P. M., et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency. Archives of Internal Medicine, Vol. 165, May 2005, pp.1167-1172

Editor's comment: It is odd that the researchers used cyanocobalamin in their trials since methylcobalamin is known to be better absorbed and more effective.

Omega-3 fatty acids may reduce mortality from heart disease

BASEL, SWITZERLAND. Hyperlipidemia, or excess levels of fats in the blood, is associated with increased risk of cardiovascular disease. Many lipid-lowering agents exist for both primary and secondary prevention of cardiovascular disease.

To determine the overall benefit of these agents on mortality, a group of researchers at the University Hospital Basel reviewed the most reliable published studies. They searched for good-quality randomized, controlled trials between 1965 and 2003, comparing lipid-lowering drugs or dietary interventions against placebo. This process left them with 35 trials on statins, 17 on fibrates, 8 on resins, 2 on niacin, 14 on omega-3 fatty acids, and 17 on other dietary interventions. This produced a total of 137,140 participants in treatments groups and 138,976 in control groups.

A combined analysis showed that treatment with omega-3 fatty acids (fish and flaxseed oils) reduced overall risk of death by 23 per cent as compared to placebo. Treatment with statin drugs, on the other hand, only reduced overall mortality by 13 per cent as compared to placebo. Fibrates (gemfibrozil, fenofibrates), bile acid resins (cholestyramine, colestipol), niacin and dietary interventions showed no statistically significant differences from results obtained in the control groups.

Deaths from cardiovascular causes were 32 per cent lower in the omega-3 fatty acid groups than in control (placebo) groups. Statin drugs reduced cardiovascular mortality by 22 per cent and the use of bile acid resins were associated with a 30 per cent decline in cardiovascular mortality. When death from non-cardiovascular causes was considered, none of the interventions were significantly linked to reduced mortality. However, fibrates were linked to a 13 per cent increased risk of death.

The effects on mortality tended to be more pronounced in longer studies and those with patients whose cardiovascular disease was well established, say the authors. Regarding n-3 fatty acids, they speculate that the reduction in mortality risk does not occur through a reduction in cholesterol but by other means, possibly antiarrhythmic, antithrombotic or anti-inflammatory effects.

The trials of n-3 fatty acids used different dietary and supplement sources; nevertheless, the authors conclude that this study adds to the positive evidence for n-3 fatty acids. They suggest that further trials be carried out to examine the effects of combined treatment with n-3 fatty acids and statins.
Studer, M., et al. Effect of different antilipidemic agents and diets on mortality. Archives of Internal Medicine, Vol. 165, April 2005, pp. 725-30

Dietary linolenic acid may reduce atherosclerosis

BOSTON, MASSACHUSETTS. A reduced risk of death from cardiovascular disease has been found in study participants with higher dietary intakes of linolenic acid, a polyunsaturated fatty acid. The mechanism is unclear, but may occur through prevention of atherosclerosis (narrowing and hardening of the arteries). In the early development of atherosclerosis, calcium is deposited in the artery walls. This process can be measured using a computed tomography (CT) scan.

A team of researchers from the University of Boston set out to determine whether linolenic acid intake is linked to coronary artery atherosclerotic plaque build-up. They gathered data from 2,004 male and female participants in the National Heart, Lung, and

Blood Institute (NHLBI) Family Heart Study, aged 32 to 93 years. Medical and lifestyle history was taken and food questionnaires were given, together with CT scans, and repeated on average 7 years later. Participants were selected either at random or because they were at higher risk for coronary artery disease. Results from both groups were combined. Linolenic acid intake ranged from 0.23g to 3.48g per day (average 0.82g) for men and 0.17g to 2.29g (average 0.69g) for women, the main sources being salad dressing and canola oil. Linolenic acid is also present in flaxseed oil.

There was an inverse, linear association between calcified atherosclerotic plaque and intake of linolenic acid, for both sexes. Those in the top fifth for linolenic acid consumption were 65 per cent less likely to have this type of plaque than those in the bottom fifth. This result took into account many relevant factors such as age, gender, smoking and illness history, and remained significant after taking into account body mass index, cholesterol levels and several other factors.

The authors say that linolenic acid may have anti-inflammatory properties, but this is unconfirmed. They conclude that each additional gram of linolenic acid per day was linked to a 62 per cent lower chance of calcified atherosclerotic plaque.

In a commentary, an expert from the Mid America Heart Institute at Saint Luke's Health System describes the finding as an important advance. He explains that linolenic acid is a precursor to the n-3 fatty acids EPA and DHA, but there are doubts over the extent to which it converts to these forms. Clear results from randomized, controlled studies which also take into account trans and saturated fats are needed, he believes, before we can confirm a benefit for linolenic acid on heart health, especially considering evidence linking it to advanced prostate cancer.

Djousse, L., et al. Dietary linolenic acid is inversely associated with calcified atherosclerotic plaque in the coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. Circulation, Vol. 111, June 2005, pp. 2921-26

Harris, W. S. Alpha-linolenic acid: A gift from the land? Circulation, Vol. 111, June 2005, pp. 2872-4

Further evidence that calcium may prevent colorectal cancer

BUFFALO, NEW YORK. It is suggested that calcium may help prevent colorectal cancer, as it seems to reduce the incidence of colorectal adenomas – benign, pre-cancerous growths which are present in 70 to 90 per cent of colorectal cancers. Efforts to prevent colorectal cancer currently focus on detecting and removing adenomas, but their rate of recurrence is high. Ideally a chemopreventative agent would be discovered. Calcium is cheap and safe, but is it effective?

Observational studies suggest that it is, and now randomized controlled trials of calcium and adenomas have been examined by researchers from the State University of New York. Their criteria for inclusion were very strict, so only three trials out of 2,053 were included. The three trials randomly gave either calcium supplements or placebo and used endoscopy to examine the participants for recurrence of adenomas after either 3 or 4 years. They all included men and women, with an age range of 35 to 76 years, and participants in the treatment groups took 1,200-2,000mg of calcium per day. Using data from a total of 1,279 participants, the researchers calculated that the recurrence of adenomas was 20 per cent lower with calcium supplementation, a significant result.

They conclude that calcium supplementation can help prevent recurrent colorectal adenomas. This study has important implications for clinical practice, they write, despite being based on a small number of trials. They add that colorectal cancer would have been a more appropriate 'endpoint', but this would require decades of follow-up.

In an accompanying editorial, a professor from the University of North Carolina at Chapel Hill agrees that these results support a preventative role for calcium supplements. He also highlights the apparent safety of calcium as a chemopreventative agent, but points out that using adenomas as a surrogate endpoint for cancer has pitfalls which may overstate the case. Overall, he believes, there is little doubt that calcium supplements decrease the risk of colorectal adenomas.

Shaukat, A., Scouras, N. and Schunemann, H.J. Role of supplemental calcium in the recurrence of colorectal adenomas: a metaanalysis of randomized controlled trials. American Journal of Gastroenterology, Vol. 100, February 2005, pp. 390-94

Sabdler, R.S. Calcium supplements to prevent colorectal adenomas. American Journal of Gastroenterology, Vol. 100, February 2005, pp. 395-96

Editor's comment: Another large, recently completed clinical trial found that the protective effect of calcium was only evident in participants who had high blood levels of vitamin D. Thus, calcium supplementation with the aim of preventing colon cancer should always be accompanied by an adequate intake of vitamin D3.

NEWSBRIEFS

Keep olive oil in the dark. Researchers at the University of Bari in Southern Italy warn that olive oil packaged in clear glass or plastic containers gradually lose the effect of its beneficial antioxidants, notably tocopherols and carotenoids. Even after just 2 months exposure to light the oil becomes oxidized to such an extent that it can no longer be classified as extra virgin. Food scientist Lisa Mauer of Purdue University in Indiana recommends buying and storing olive oil in coated, non-reactive metal containers. Tinted glass containers are the second best choice and should be stored in the dark.
New Scientist, August 27, 2005, p. 15

Smoking is distinctly "uncool" in Australia. In 1983 the Australian government began a big push to eliminate cigarette smoking. This effort now seems to be paying off. In 1983 about 40 per cent of Australian men and 32 per cent of women were regular smokers. By 2004 only 17 per cent of Australians smoked every day. If the trend continues there will be no more women smokers by 2029 and the last male smoker will light up in 2030. The US has a larger proportion of smokers than does Australia, but the weed's popularity is declining there as well. Among American doctors, who know the devastating effects of smoking first hand, the percentage of regular smokers has declined to 1.5 per cent.
New Scientist, August 6, 2005, p. 4

Hypnotherapy – an effective alternative to general anesthesia? There is mounting evidence that general anesthesia (GA) is not as benign as most anesthetists would have us believe. Several studies have shown that GA seriously suppresses the immune system and that people who have had GA are more likely to develop Parkinson's and Alzheimer's disease later in life. Now British and Belgian doctors report that hypnotherapy may be a viable alternative to GA. Anesthetists in Liege Hospital routinely use a procedure they call "hypnosedation". This involves combining hypnosis with local anesthesia and a small dose of painkiller. They have found hypnosedation to be an effective alternative to GA and so far, have used it in over 4800 major and minor surgical operations. Hypnosedation is also associated with much shorter recovery times. The Liege team compared the recovery times for 20 patients undergoing thyroid surgery under hypnosedation with the same number of patients undergoing the same procedure using GA. Whereas the hypnosedation patients returned to work an average of 10 days after their surgery, it took the GA patients 36 days to fully recover. Neuroscientists who have studied the effects of hypnosedation on the brain estimate that the technique would be effective in as many as 80% of surgical patients.
New Scientist, August 6, 2005, pp. 34-37

Passive smoking induces addiction. It is well established that passive smoking (breathing secondhand smoke) can result in the development of lung cancer and other smoking-related diseases. Researchers at McGill University in Montreal now report that children exposed to secondhand smoke are more likely to become smokers themselves than are children brought up in smoke-free homes. The study involved 191 9-year-old boys and girls. The researchers ascertained how many people smoked in the children's home, how much they smoked, income levels, and other pertinent factors. They also measured the children's lung capacity and took samples of their saliva which were analyzed for cotinine, a breakdown product of nicotine. Four years later, the children were contacted again, by which time 44 per cent of them had taken up smoking. The researchers found a strong, clear association between the saliva level of cotinine (a measure of the amount of smoke exposure) in children at 9 years of age and the probability that they would be smokers at 13 years of age. This correlation was independent of other factors, which might influence the decision to take up smoking.
New Scientist, August 27, 2005, p. 7

Chronic fatigue syndrome finally recognized. Chronic fatigue syndrome (CFS) is a devastating condition involving unrelieved fatigue, extreme weakness, inability to think straight, disrupted sleep, and headache. CFS is often initiated by a flu-like illness that never goes away. Up until recently, the medical community has dismissed CFS as "all in the mind" and has treated it with tranquilizers and antidepressants. This may now change. A team of British researchers compared levels of gene expression in the white blood cells of 25 healthy individuals with 25 patients diagnosed with CFS. They found significant differences in 35 of the 9522 genes analyzed and are now repeating their study in 1000 CFS patients and healthy controls, this time looking for differences in 47000 genes. The researchers hope that their findings will lead to the development of definitive blood tests for the diagnosis of CFS and ultimately to pharmaceutical drugs that will help alleviate the condition.
New Scientist, July 23, 2005, p. 9

Weather and heart attacks. American researchers have found an interesting correlation between rapid decreases in barometric pressure and the incidence of acute myocardial infarction (heart attack) on the day after the change, specifically during the autumn and winter seasons. The researchers found that for every 0.01 inches of mercury pressure drop per hour during a given day the incidence of heart attacks on the following day increased by 10 per cent. They speculate that the rapid decrease in atmospheric pressure might contribute to plaque rupture, the main cause of heart attack. The researchers found no correlation between the incidence of stroke and changes in atmospheric pressure.
American Journal of Cardiology, Vol. 96, July 1, 2005, pp. 45-51

RESEARCH REPORT

Diagnosis and Staging of Prostate Cancer

Part III – Grading and Staging

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

THE GLEASON SCORE

The Gleason score is derived from low-power microscopic examination of cells on slides prepared from the core samples. Normal cells, also called *well differentiated*, are characterized by distinct clearly defined borders and clear centers. Johns Hopkins pathologist Jonathan Epstein describes them as "little round doughnuts" [37]. As differentiation is lost, cell borders become irregular, cells appear to clump together, and highly irregular shapes become more and more common until at the highest grade, the cells bear little or no resemblance to normal cells. Gleason divided this transition from normal to poorly differentiated into five patterns which generate the numbers one to five used in the pattern grading system.

Gleason dealt with the problem of more than one malignant pattern in a biopsy sample by having the pathologist characterize what is termed a primary or dominant and a secondary pattern, the latter representing at least 5%

of the cancer. The dominant and secondary patterns are graded according to the Gleason 1-5 system, and then the two grades added to give the Gleason Score, with the first number the primary grade and the second the secondary. Thus the score runs from 2 to 10. When there is no secondary pattern, the primary pattern score is simply doubled. Some doctors will give the patient just the sum, whereas the individual numbers are also of interest. A description of each core provides the best information. A Gleason score of 6 could be 4+2 with the predominant finding being poorly differentiated cells, whereas 2+4 indicates that the poorly differentiated cells were present in smaller amounts. Patients with high Gleason scores are more likely to have cancer that has penetrated the prostate wall to the point where it perhaps cannot be removed surgically as well as cancer that is more likely to have spread to the seminal vesicles or lymph nodes, and even to other organs. Also, the presence of poorly differentiated cells that yield a high Gleason score suggests an aggressive cancer. Thus high Gleason score cancers may be less likely to respond to standard curative treatment.

At the opposite end of the Gleason scale is the 2 to 4 score. According to Hopkins pathologist Jonathan Epstein [97], most 2-4 scores obtained from needle biopsy are graded 5-6 when reviewed by experts in prostate pathology. In a study at Johns Hopkins Hospital, it was found that their pathologists agreed as to the 2-4 scoring in only 4 of 87 reviews of slides graded initially at other institutions. Sixty-eight were regraded as 5-6, thirteen as 7, and two as 8-10. He also remarks that the few cases actually graded 2-4 at Hopkins showed higher-grade tumor at RP radical prostatectomy). Epstein points out that in a study involving 10 expert pathologists, no agreement was found on what a 2-4 score looked like in a slide review. This is a serious matter since a true grade of 2-4 from a needle biopsy suggests that there is no need for immediate definitive therapy where in fact, the real score is probably higher and indicates the need for treatment. In a series of cases with Gleason scores of 2-4 from outside institutions who underwent RPs at Hopkins, 55% of the patients showed extraprostatic extension, including four cases with either lymph node or seminal vesicle invasion. Epstein quotes his experience with 2-4 grades at Hopkins [97]. He assigned a Gleason grade of 2-4 in only 1.1% of 2285 needle biopsies, whereas 24% of 83 pathological examinations of TURP tissue sent to Hopkins for consultation were given grades in this range. The low-grade cancers typically seen in TURP samples reflect the fact that cancers tend to be small when located anteriorly in the prostate within the TZ (transition zone) where tissue is removed during the TURP procedure.

Dr. Peter Scardino expands on the validity of the 2-4 grade in his recent book [2]. He points out that today many pathologists believe that Gleason patterns 1 and 2 may not be cancer at all, and thus it is rare to have a Gleason score of less than 6, i.e. 3 + 3. He suggests for anyone having a score of 5 or lower that a review of the slides by a pathologist considered an expert in prostate cancer is advisable. Another reason why it is wise to get a second opinion in any case is that pathologists in general differ in their interpretation of what they see through the microscope, and there is a variation in expertise as regards the Gleason grading system. He mentions three so-called referee centers where a second opinion can be obtained: the Armed Forcers Institute for Pathology, Memorial Sloan-Kettering, and Johns Hopkins, all of which have pathologists whose sole occupation is examining prostate tissue. If a man has a Gleason 2-4 result confirmed by expert review, he should raise the question of the merits of proceeding with treatment. The issue is confused by studies in the literature that include the 2-4 score in RP or RT series when in fact, the probability is high that an expert review of the slides would have upgraded these cases into a range where there would be less debate about treatment.

After Gleason score 6, a score of 7 is as the most common found with needle biopsy [98]. There are two ways to get this score, i.e. 3 + 4 or 4 + 3. In the former the lower grade Gleason pattern predominates, whereas in the latter it is the higher grade. Thus the patient should ask to see a breakdown of a score of 7. The score 4 + 3 is generally considered more ominous than 3 + 4, although the evidence is as yet not compelling [99]. Scardino points out that the real issue is the presence or absence of poorly differentiated cancer (patterns 4 and 5), and if so, how much, since poorly differentiated cancer should be treated promptly [2].

Both the Gleason scores of 2-4 and 8-10 are relatively rare in current needle biopsies. The former have an incidence of about 2%, the latter about 8% [37,99]. *Authentic* scores of 2-4 are generally considered harmless, but as discussed above, they may actually be of higher grade. Many experts feel that scores of 2-4 should not be reported. Grade 5-6 tumors are considered slow-growing, whereas 7 is considerably more dangerous and 8-10 very dangerous. Scores of 7 or greater are more likely to involve extra capsular extensions, seminal vesicle involvement, and lymph node infiltration. The higher the score, the poorer the expected outcome of treatment [99]. But the score is rarely used in isolation, but rather combined in the calculation of prognostic factors using

the number of cores containing cancer and how much, tumor stage (see below) and PSA at the time of biopsy. Examples are given below.

An obvious question relates to the correlation in general between the Gleason score derived from needle biopsy and the corresponding score found upon pathological examination of the prostate itself after a RP is performed. Sved *et al* [100] investigated this question for men with a biopsy score of 6. Out of 451 patients, 41% had a score of 7 or greater when the prostate itself was examined, whereas 8% had a lower score and 51% retained the same score. Those who were undergraded at biopsy were more likely to have extraprostatic extension, seminal vesicle invasion and recurrence post-RP. Lattouf and Saad [101] also found significant undergrading in a study of 390 patients with biopsies who went on to have a RP. Undergrading was found in 38.2%, and overgrading in 32.6%. The discrepancies were somewhat smaller when the patients were grouped into categories (Gleason score 2-4, 5-6, 7 and 8-10) with 48.5% of the patients remaining in the same group after pathologic grading. There was also an improvement when only a subset was considered where a single pathologist examined both the cores and the RP pathology. Nevertheless, it is clear that the Gleason score is only an approximation, if it is assumed that the histological examination of the sectioned prostate is really a gold standard. Perhaps this is not surprising considering that the tissue collected in the needle biopsy represents only 0.04% of the average prostate volume.

Finally, there is a problem with both intra-observer and inter-observer variability. For the former, studies find only 43-78% exact agreement on blinded reexamination of slides, whereas the disagreement between observers of plus or minus one score unit has been reported to range from 72-87% [99]. Perhaps more confidence and reliance is placed on the Gleason numbers than is actually deserved.

ATYPICAL RESULTS, INTRAEPITHELIAL PROSTATIC NEOPLASIA

Aside from the unfortunate fact that the initial biopsy may fail to detect a cancer present in the prostate, the results of the needle biopsy may not be clear-cut (i.e., benign or PC). The report may come back with terms such as “inconclusive” or “atypical hyperplasia” or prostatic intraepithelial neoplasia (PIN). PIN is sub-classified as low- or high-grade. The low-grade is generally considered clinically insignificant. High-grade PIN (HGPIN) is thought to be the earliest stage in prostate carcinogenesis and is regarded as a premalignant lesion that has the potential of progressing to adenocarcinoma [102]. Thus HGPIN is viewed as an early warning sign. The incidence of a HGPIN diagnosis in needle biopsies averages 9% (range 4-16%). Thus somewhat over 100,000 new cases of HGPIN are diagnosed each year in the US. Low-grade PIN is sufficiently hard to distinguish form normal cells that Epstein, for example, suggests it not be included on pathology reports [103].

Studies of PC risk subsequent to or associated with the observation of HGPIN have produced widely variable results. When both PC and PIN are found at the initial biopsy, the classification is PC because for diagnostic purposes the presence of PIN is now irrelevant. However, until recently the sextant biopsy was the standard protocol and missed approximately 20-25% of cancers in the initial biopsy. Finding HGPIN but not PC generally indicates one or more repeat (immediate) biopsies, and a number of large studies [104] found the repeat biopsy yielded 23 and 35% PC. This range is close enough to that for normally missed cancer in the sextant biopsy that the risk of PC being present in newly diagnosed cases of PIN was not clear. However, Lefkowitz *et al* [105] reported in 2001 that when HGPIN but no cancer was found in an initial 12-core biopsy, the cancer yield of a repeat 12-core biopsy within one year was only 2.3%. However, this result was inconsistent with that of Rosser *et al* [106] who also used an extended biopsy protocol. The reason is not clear. Nevertheless, in a subsequent study, Lefkowitz *et al* [107] used the observation that only 2.3% of patients undergoing repeat 12-core biopsy within 1 year had cancer as validating their particular 12-core protocol and they then examined the incidence of PC after three years in 31 men who had only HGPIN initially and no cancer as determined by this initial 12 core biopsy. They found 25.8 % had developed PC.

Scardino quotes [2] the statistic that 50% of men with high grade PIN will be found to have prostate cancer on a subsequent biopsy over a 5-year period, but it is not clear how effectively undiagnosed cancer at baseline was excluded. Only additional studies will resolve the important question of the real risk of progression of HGPIN to PC if one has HGPIN but no cancer present initially. HGPIN and cancer frequently coexist. For example, 85% of patients diagnosed with PC will also have areas of high grade PIN on examination of the prostate itself [2].

There is no consensus on when a repeat biopsy should be done when HGPIN is found, with some experts recommending six month, others recommending as soon as possible [103]. As regards atypical needle biopsy results in general, Epstein recommends a repeat biopsy within 3 months [103]

STAGING OF PROSTATE CANCER

There are two types of "stage" of prostate cancer, the *clinical* and the *pathological* stage. The first is an estimated stage based on what the physician believes the patient's cancer to represent, which in turn is based on the DRE (digital rectal examination) and needle biopsy. It is to some extent an educated guess. The pathological stage is determined after surgery when reliable information is available regarding the extent, not only of the cancer within or outside the gland, but also whether or not it has spread to the lymph nodes, seminal vesicles or regions adjacent to the prostate. In cases where advanced disease is suspected, the information available for the clinical staging can be enhanced by bone scans or knowledge of metastasis found in distant sites. Staging information can be obtained when an operation is performed to examine the lymph nodes. Information gathered from the DRE is of necessity incomplete since only part of the prostate can be explored. Nevertheless, staging based just on the DRE and the biopsy is commonly done and is a very important guide with regard to treatment. It is however important to realize that all the information required might be unavailable when the cancer is not organ confined. The 1997 so-called TNM staging system is given by the following (after Walsh [37]).

TNM Staging

T1a: Not Palpable with DRE. Cancer found incidentally during TURP; 5% or less of removed tissue cancerous.

T1b: Not Palpable with DRE. Cancer found incidentally during TURP; more than 5% of tissue cancerous.

T1c: Not Palpable with DRE. Cancer found with needle biopsy prompted by elevated PSA. Most common stage presently.

T2a: Palpable with DRE. Involves one lobe.

T2b: Palpable with DRE. Involves both lobes.

T3: Palpable with DRE and penetrates the wall of the prostate and/or involves seminal vesicles.

T4: Spread to adjacent muscles, bladder neck,
external sphincter and/or rectum.

N+: Spread to lymph nodes.
M+: Spread to other sites including bone

The TNM stage is central to therapy decisions [37]. T1 and T2 cancers are viewed as favorable for treatment with RP or RT (radiation treatment) with the intent to cure, whereas T4 cancers have traditionally been considered suitable only for systemic treatment, e.g. hormone therapy, as are M+ and N+ stages, although the prognosis associated with positive lymph nodes and the merits of surgery in this case are debatable and changing with time [108]. T3 tumors are in the gray area. However, there is growing evidence that for clinically staged T3 tumors, RP offers a number of advantages over other forms of treatment [109,110].

As indicated in the table, individuals with a non-suspicious DRE and an elevated PSA who have a positive biopsy are staged as T1c. Approximately 25% of the radical prostatectomies performed for this stage disease reveal potentially insignificant tumors [51]. Epstein *et al* [51] and Walsh [37] provide guidance regarding the prediction of tumor significance in T1c grade disease (adapted from [37]).

T1c cancer significant if *any one* of the following characteristics is present:

- Cancer found in three needle cores or is present in greater than half of any one needle core

- Gleason score ≥ 7
- PSA density > 0.1-0.15 ng/mL/cc (volume should be available from ultrasound directed biopsy)
- %fPSA < 15%
-

T1c cancer *probably* insignificant if *all* of the following characteristics are present:

- Cancer found only in one or two needle cores and makes up less than half of each needle core.
- Gleason score ≤6
- PSA density < 0.1-0.15 ng/mL/cc
- %fPSA > 15%

Walsh states that the above guidelines are only about 75% predictive [37]. If one is in the low risk group, gambles with watchful waiting (more recently called expectant management) and suffers progression, the cancer *may* still have a high probability of being curable [37]. The challenge is acting before it is too late.

DIAGNOSING ADVANCED PROSTATE CANCER

The needle biopsy can reveal spreading outside the gland, but only into areas accessible during the transrectal procedure. In particular, no information is obtained regarding lymph-node or bone metastasis aside from the enhanced probability of advanced disease inferred from a high Gleason score. Pelvic lymph-node metastasis has significant adverse prognostic implications and it presence impacts treatment decisions. While modeling techniques such as nomograms (see below) or probability tables are used to estimate the chances of lymph-node metastasis, surgical removal followed by histological examination has been the only satisfactory way to obtain a dependable answer. Traditionally, one common protocol was for an examination of the question of lymph-node (LN) metastasis to be done at the start of the RP operation. If lymph-node involvement was found upon frozen section analysis, some surgeons would not proceed with the RP but simply close the incision. This approach is now less common, partly because it is evident that surgery can benefit some patients even if there is lymph-node metastasis [37,111].

Nevertheless, it is generally desirable to know the LN status. The performance of a lymphadenectomy to obtain lymph nodes for pathological examination as a stand alone procedure, as would be required if RT was the planned mode of treatment, is only justifiable if the results are going to significantly impact treatment. If hormone therapy is planned anyway as an adjunct to RT, knowledge of the LN status is unnecessary. The removal of the lymph nodes associated with the prostate at present appears to have no therapeutic value even if metastasis is present, but knowledge of its presence is important in both judging prognosis and, in some cases, in treatment decisions. If a patient is of very low risk of LN metastasis, as determined from tables or nomograms, some surgeons will omit the removal of these nodes. A recent study [112] justifies this approach for low-risk patients, but merits of omitting pelvic lymph node dissection have also recently been questioned by Weckermann *et al* [113] who suggest not dispensing with surgical LN staging even in apparently low-risk disease. Some surgeons routinely remove the easily accessible nodes, while some remove all the relevant ones in a so-called extended pelvic node dissection. There is no doubt that patients with LN metastasis are at high risk of not remaining progression free, and the more extensive the LN involvement, the poorer the prognosis [114].

Non-invasive procedures such as CT scans and traditional MRI would be attractive as procedures to acquire information on lymph node status, but both lack the sensitivity, especially for clinically occult disease where there has not been as yet an enlargement of the infiltrated nodes. In what appears to be a major diagnostic breakthrough, Harisinghani *et al* [115] have recently reported the results of a study using a special imaging agent which collects in lymph nodes but does not image areas where metastasis has occurred. MRI with superparamagnetic nanoparticles correctly identified all patients with nodal metastases, and node-by-node analysis had a significantly higher sensitivity than conventional MRI or nomograms. Only in the case of nodes measuring less than 5 mm was there a decrease in sensitivity. This approach has the advantage of being non-invasive, does not require hospitalization for surgery, is free of side effects, and has 100% sensitivity. The reference standard for the presence of metastasis was based on surgical lymph-node resection or a biopsy.

Metastasis frequently involves the spread of the cancer to bones, and thus if this is suspected, a bone scan may be offered or recommended prior to treatment decisions. There have been a number of studies that attempt to

establish guidelines for when a bone scan is appropriate. The most recent appears to be that of Lee *et al* [116] from Columbia University. They studied 631 patients with bone scans for whom they had a Gleason score, PSA value and DRE based clinical staging. From this study they developed a guideline for identifying patients for whom a bone scan would have a low probability of being positive. The guidelines were a Gleason score of 2-7, a PSA of 50 or less, and a clinical stage of T2b or less. For patients with clinical stage ≤ T2b and Gleason score 2-7, and PSA ≤ 15, zero out of 237 patients had a positive bone scan. Raising the limit to PSA ≤ 50 resulted in 3 out of 545 patients with a positive bone scan. Positive bone scans were obtained in 49.5% of patients with PSA > 50. They recommend a bone scan in all patients not meeting the above criteria and especially those with a PSA > 50. The authors review the literature up to 1999-2000 and find similar but not identical results. The studies reviewed looked only at a PSA cut-off. Patients with a PSA of ≤ 10 always had negative bone scans, whereas ≤ 20 produced a small percentage of positive results. The guidelines presented by the authors are similar to that given by Scardino [2] where he states that a bone scan may provide useful information if the Gleason score is 8-10, PSA > 20 , and the clinical stage is T3 or greater. For those who do not meet these criteria, he suggests that the scan offers little value and has considerable potential to generate unnecessary problems due to false positives and possible recommendation of a bone biopsy, which itself is not necessarily conclusive.

CRUNCHING THE NUMBERS - EVALUATING THE PRE-TREATMENT PICTURE

At the time of diagnosis the patient generally has a PSA value, a Gleason Score, and a stage based on the T1, T2 etc. system. In the last few years considerable effort has gone into developing mathematical models that allow predictions based on these clinical diagnostic results [16,117-120]. These models are based on pathological and medical outcomes from large databases, but to some extent contain institutional bias (the institutions specializing in PC may get the best treatment results). The results are presented in the form of tables (Partin Tables, http://www.urology.jhu.edu) or so-called nomograms (a diagram where points can be assigned to the various predictive factors and then summed to yield a total which is used to predict outcome). The pencil and paper analysis using nomograms or tables can now be avoided by using the internet based nomogram from the Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/mskcc/html/10088.cfm), which does all the calculations The patient inputs the PSA, Gleason score and tumor stage and the program calculates and displays the *probabilities* of organ confined disease, extra capsular penetration, seminal vesicle involvement, LN involvement, and the 5-year progression-free probability after RP or RT. This provides the patient with an easy to understand analysis of the *probable* significance of the set of parameters that characterize their diagnosis. The probabilities are based on databases that use clinical rather than pathological (post surgical) input, and thus the problem of under-grading is presumably taken into account. It is nomograms such as these that are used by some surgeons to decide if looking for LN metastasis can be omitted during surgery because the probability is very low.

As an example of the application of nomograms, the online Memorial Sloan-Kettering calculator, will be used to examine various outcomes for exceeding the two commonly suggested PSA thresholds for biopsy, 2.5 and 4.0. In this example, it will be assumed that the cancer stage is T1c, the most common situation today (T2a and T2b are next in incidence [38]). The results are given in the table below. The second, third and fourth items stratify the non-organ confined disease. Note that on the basis of the databases used to construct this model, Stage T1c and a “low” PSA did not completely rule out non-organ confined disease. The low biochemical failure rate (high % progression free) for these two typical screening scenarios for a Gleason score of 6, a common score with screened patients, is consistent with the view that early detection is highly curative. This table also illustrates that the lower cut-off for triggering a biopsy had a negligible influence on 5-year disease-free outcome as compared to the traditional cut-off. This was one of the principal arguments presented by H. Ballentine Carter from Johns Hopkins in an editorial discussing lowering the cut-off [43]. In fact, in a 1999 study by Carter *et al* [39] it was found that the probability of curable cancer was only slightly different within the range of PSA values from 2.5 to 6.0 for men with clinical T1c cancer. Increasing the PSA to 4.5 for a Gleason score of 6 does not change the figures in the above table. From these results it would appear that, for example, a PSA of 4.5 is not a crisis situation. In fact it can be argued that there is merit in repeated measurements at this point to determine the PSA velocity. It is even possible that the value would come back down below 4.0. However, recovery from PSA spiking above a cut-off does not rule out PC [121].

Results from the Memorial Sloan-Kettering online calculator

	PSA = 2.6 ng/mL			PSA = 4.1 ng/mL		
Gleason score	6	7	8-10	6	7	8-10
Organ confined disease (%)	78	63	52	67	49	37
Extra-capsular Penetration (%)	21	31	34	30	40	40
Seminal Vesicle Involvement (%)	1	4	9	2	8	15
Lymph Node Involvement (%)	<1	1	4	1	3	8
5-year % Progression Free (After A Radical Prostatectomy)	93	86	86	92	85	84

SUMMARY

One of the characteristic features of prostate cancer is the uncertainty surrounding practically every important aspect. Screening is a probability game, to some extent like handicapping horse races. Both the total PSA test and the modern variations have significant false positive and false negative rates. What is now quite clear is that *while PSA testing can indicate the risk of PC, it cannot be used to rule out the presence of the disease.* Intra-individual PSA variations from day to day and year to year are significant and confuse the issue of decision making with regard to biopsy advice. Drugs used to treat BPH (5-α-reductase inhibitors) and perhaps elevated cholesterol (statins) significantly lower PSA levels, the accuracy of corrections required before applying diagnostic benchmarks is unknown, and other drugs that influence PSA levels may turn up any time. The transrectal ultrasound guided needle biopsy only *approaches* 100% diagnostic accuracy when biopsies, if negative, are repeated several times. Pathologists reading needle biopsy generated slides exhibit alarming intra- and inter-observer variations when establishing Gleason scores. The DRE is notorious for false positives and false negatives. Imaging techniques still fail to provide definitive diagnosis. These are all complex issues. It is not for lack of research that these uncertainties exist. At present, nothing better appears available. A vast amount of careful and thoughtful research has brought us to this point. Clearly there are great challenges ahead. Knowledge of this rather unsatisfactory state of affairs is no doubt limited among the general public unless they have made a considerable effort at self-education.

However, it is also true that PSA screening has revolutionized the diagnosis of PC. The disease is being identified and treated at a much earlier stage than was possible before the PSA era. The PSA test offers the *only* approach to early diagnosis in general and routine use today. PSA screening is gaining popularity worldwide and is well established in the practices of urologists, internists and general practitioners. The problems and uncertainties are clearly not compelling enough to discourage this widespread use.

This review is concerned mainly with two issues. The first involves the PSA test—what does one need to know to decide whether or not to have the test or if variations in the PSA test should also be requested if not offered, especially the %fPSA, and the PSAV. The second issue concerns the basic knowledge deemed desirable prior to agreeing to proceed with the biopsy phase of diagnosis.

The pros and cons of getting the PSA test are those elaborated above in connection with the screening debate. To these must be added age, life expectancy, race and family history. It is not possible to resolve this debate since it depends not so much on disputing the facts as how each argument is weighted. The arguments of those opposed to screening are to some extent weakened by the studies that suggest that the %fPSA and the PSAV enhance the specificity of the tPSA test. There is still no escaping the fact that all three tests have their gray areas. At the extremes the indication of high or low risk has fairly high probability of being correct, and this supports either feeling good about the low risk of having PC or being forced to consider the merits of a biopsy if the risk is high.

It is the gray area that causes the most anguish. However, being in the gray area or at high risk also brings up the question of the merits of treatment vs. watchful waiting (WW), since there is little point is getting a biopsy or even worrying about screening if the decision has been made to reject conventional treatments, at least until the

cancer, if present, causes major problems requiring palliative treatment. Such a rejection might be motivated by what the individual views as unacceptable adverse effects associated with either the radical prostatectomy (RP) or radiation treatment (RT) coupled with what the individual perceives as only marginal benefits of treatment over WW when it comes to prostate cancer specific mortality. As discussed above, such a rejection ignorers or rejects a considerable body of evidence supporting the advocates of screening which suggests a definite shift to favorable probabilities associated with having a PSA test and a DRE.

A compromise between the extreme options of aggressive treatment such as RP or RT or WW followed if necessary by palliation involves WW until evidence for progression suggest it is now or never for treatment with the intent to cure. This protocol is currently under study [122] and offers an approach which may be attractive to some men. It requires PSA and DRE monitoring and more biopsies. For men with diagnosed but possibly indolent cancers, such a compromise would have merit. It will be a number of years before long-term survival data associated with this protocol are available.

The discussion of the prostate biopsy in this review makes it clear that a single biopsy is by no means a gold standard for the presence or absence of PC. Quite the contrary, it misses a substantial percentage of cancers. Men should be aware that once one has agreed to a biopsy, one or more repeats may be suggested for good reason. Also men should be aware that the "classical" sextant biopsy is in general inferior to the so-called extended biopsies which utilize more needles, some directed to higher probability zones, with 12 or 13 needles now being common. While the biopsy is far from perfect, with all due respect neither are the pathologists who read the slides, and men should be aware of the advisability in some cases of a second opinion, preferably from someone with no potential conflict of interest (e.g. avoid having slides reviewed by an office or department associate). Also, if one elects to have a biopsy, there appears no reason to hesitate in asking for local anesthetic and in particular the nerve block, especially if the extended protocol is used. Being aware of the potential complications, their signs and symptoms, and what action is indicated is extremely important. Serious complications associated with the needle biopsy are rare but some can develop very rapidly and can be life-threatening. Finally, one probably should not have a biopsy unless the decision has been made beforehand as to what the next step will be if the result is positive or negative. However, some men who have no intention of being treated may still want to know in detail the nature of what they have decided not to treat, just for future reference.

Please see Part I for references

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