INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 160 **SEPTEMBER 2005** **14th YEAR**

I hope you enjoyed a great summer. In this issue we continue with the second part of Bill Ware's excellent article on benign prostatic hyperplasia (enlarged prostate). Most men over the age of 60 years are probably, at least somewhat, familiar with the symptoms of BPH and most of us will eventually be searching for ways to alleviate the condition. Well, look no further. Bill discusses both conventional and alternative approaches to dealing with BPH. Alpha-blockers, finasteride, saw palmetto, pygeum, beta-sitosterol, stinging nettle, and other herbal remedies are covered in detail, as are both conventional and minimally invasive surgical procedures such as TURP, TUIP, TUMT, TUVP, TUNA, et al. This is a must-read indeed!

Also in this issue – Even people living in southern Florida are vitamin D deficient, design of the SELECT trial is revealed, the dangers of secondhand smoke, and the serious shortcomings of computerized medication dispensing systems – all this and more.

I have completed a major overhaul of my web vitamin "store", so there are lots of new products for you to consider and, as a subscriber to our newsletter, you receive a 12% discount on already bargain prices. You can find the "store" at 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.

Wishing you good health,
Hans

September Highlights

LETTER TO THE EDITOR

I have read with great interest your website but cannot find what I am looking for. Far from having a deficiency of vitamin B12, I have been told my reading is "very high". What does that mean please? Even my GP did not know and could find no reference in her UK medical books.

JH, UK

Editor: I am not surprised that your GP could find no reference to high vitamin B12 levels in her medical textbooks. I have not been able to find any information either about the causes and possible consequences of high vitamin B12 levels. It seems that there is a huge "black hole" in regards to information on this subject. I even checked with two MDs who have written articles about vitamin B12. Neither one was able to offer any explanation for high levels other than the use of B12-containing vitamin supplements. They were not aware of any proven consequences of high levels, but suggested avoiding vitamin B12 supplementation.

ABSTRACTS

Vitamin D deficiency in southern Florida

MIAMI, FLORIDA. A vitamin D deficiency is widespread in northern latitudes and has been associated with an increased risk of osteoporosis and certain cancers, notably breast, colon and prostate. The main sources of vitamin D are sunlight exposure and supplementation with dietary sources playing a minor role. Since sunlight is capable of synthesizing large amounts of vitamin D, it has generally been assumed that people living in southern latitudes would be fairly immune to a vitamin D deficiency. Researchers at the University of Miami School of Medicine now dispute this assumption.

Their study included 77 men and 135 women with an average age of 55 years (18-88 years). The participants completed food frequency and sun exposure questionnaires at the end of winter (March 2000) and at the end of summer (September 2000) and had blood samples drawn and tested for 25-hydroxyvitamin D [25(OH) D], 1,25-dihydroxyvitamin D, and parathyroid hormone (PTH). Vitamin D deficiency was defined as a blood level of 25(OH)D below 20 ng/mL (50 nmol/L); this is the point at which PTH levels begin to rise.

The researchers found that 38% of men and 40% of women were deficient in vitamin D at the end of winter and that 10% of men and 28% of women were deficient at the end of summer. Actual average concentrations of 25(OH)D were 23.3 ng/mL (58.3 nmol/L) at end of winter and 26.8 ng/mL (67.0 nmol/L) at end of summer. A higher intake of supplemental vitamin D (800 IU/day or more) and greater sun exposure were associated with higher levels of 25(OH)D, but there was no association between 25(OH)D level and age. The researchers suggest that the higher than expected prevalence of vitamin D deficiency in southern Florida can be explained by sun avoidance and the use of sunscreens because of the heat and increased awareness of the risk of developing skin cancer.

Levis, S, et al. Vitamin D deficiency and seasonal variation in an adult south Florida population. **Journal of Clinical Endocrinology & Metabolism**, *Vol. 90, March 2005, pp. 1557-62*

Design of the SELECT trial

HOUSTON, TEXAS. It is estimated that 230,000 American men will be diagnosed with prostate cancer and that 30,000 men will die from the disease in 2004. There are currently no pharmaceutical drugs that have been proven effective in preventing prostate cancer. Finasteride (Proscar) showed some promise in reducing overall cancer incidence but was, unfortunately, associated with a significant increase in advanced cancers. Finasteride is therefore no longer considered suitable for prostate cancer prevention.

In contrast, two natural agents, selenium and vitamin E, have been found effective in prostate cancer prevention. The Nutritional Prevention of Cancer (NPC) study concluded that supplementing with 200 micrograms/day of elemental selenium (in the form of high-selenium yeast) reduced prostate cancer risk by 63%. The large Finnish ATBC study concluded that supplementing with 50 mg/day (50 IU/day) of synthetic alpha-tocopheryl-acetate reduced prostate cancer risk and mortality by 32% and 41% respectively.

Based on these and other findings, the National Cancer Institute has embarked upon a major trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The trial, opened for recruitment in July 2001, now has a total enrollment of 35,534 men with a median age of 62 years (range of 50-93 years) who were free of prostate cancer. The expected follow-up time is 7-12 years. After much deliberation and a thorough review of the literature, the SELECT Steering Committee decided that the supplements to be evaluated would be 200 micrograms/day of elemental selenium in the form of L-selenomethionine and 400 IU/day of synthetic alpha-tocopheryl acetate. The trial design will involve 5 pair-wise comparisons of prostate cancer incidence, in association with – vitamin E vs placebo, selenium vs placebo, vitamin E plus selenium (combination) vs placebo, combination vs vitamin E, and combination vs selenium. The Steering Committee points out that there is strong evidence that 200 micrograms/day of elemental selenium is entirely safe, as is up to 1000 mg/day of

vitamin E. They acknowledge that natural alpha-tocopherol is significantly more effective than synthetic alpha-tocopheryl acetate and that gamma-tocopherol may be even more effective than either as far as prostate cancer prevention is concerned. However, due to the fact that more clinical trial data is available on synthetic alpha-tocopheryl acetate they decided to go ahead with this form. All study participants will also receive a daily multivitamin devoid of selenium and vitamin E, but including 400 IU of vitamin D3.

Lippman, SM, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). **Journal of the National Cancer Institute**, *Vol. 97, January 19, 2005, pp. 94-102*

Editor's comment: It is indeed gratifying to see such a massive undertaking by the National Cancer Institute aimed at evaluating natural supplements in the prevention of prostate cancer. Personally, I would have liked to see the vitamin E component consist of a 50:50 mixture of natural alpha- and gamma-tocopherols, but the Steering Committee obviously decided that there was not enough evidence to support this. In any case, involving over 35,000 men in a 7- to 12-year trial of selenium and vitamin E clearly shows that hopes are high that these two natural compounds will prove effective in prostate cancer prevention and that they are entirely safe. In view of this, I see no reason to wait 10 or more years for the results to be published. All men should supplement with selenomethionine and natural vitamin E (preferably a 50:50 mixture of alpha- and gamma-tocopherols).

Vegetarians less likely to be overweight

BOSTON, MASSACHUSETTS. Observational studies suggest that a plant-based diet rich in high-fiber foods such as vegetables, fruits, cereals, whole grains, and legumes is inversely related to body mass index (BMI). Other studies highlight the benefits of dairy products, but it is not yet clear whether animal products are beneficial in controlling weight.

A team of researchers from Tufts University has now examined whether vegetarian diets are linked to lower rates of obesity and being overweight. Taking data from healthy women in the Swedish Mammography Cohort, they compared 960 semivegetarians, 159 lactovegetarians, and 83 vegans against 54,257 omnivores. Just over two per cent of women fell into one of the vegetarian categories. All participants provided their height and weight, and completed a food questionnaire. For the study, vegan was defined as no meat, poultry, fish, eggs, or dairy products, lactovegetarian as the same but with dairy products, and semivegetarian as the same but with dairy products, fish and eggs. The results showed that average weight, BMI, and rate of overweight and obesity were highest among omnivores. In each of the vegetarian groups, average BMI was approximately one point lower than in omnivores. Forty per cent of omnivores were overweight or obese compared with 29 per cent of semivegetarians and vegans, and 25 per cent of lactovegetarians. Further analysis showed that lactovegetarians and semivegetarians had half the risk of being overweight or obesity as omnivores, and vegans had a third of the risk. The vegetarian groups had a lower energy intake and ate less protein, more carbohydrate and more fiber than omnivores.

The researchers conclude that women who are semivegetarian, lactovegetarian, or vegan are less likely to be obese or overweight than women who are omnivores, even if they eat some animal products. They suggest that it would help individuals control their weight if they were given advice to consume more plant foods and fewer animal foods, and add that future studies should examine the effects of single nutrients and different types of vegetarian diet.

Newby, P.K., Tucker, P.L. and Wolk, A. Risk of overweight and obesity among semivegetarian, lactovegetarian, and vegan women. **American Journal of Clinical Nutrition**, *Vol. 81, June 2005, pp. 1267-74*

Possible prostate cancer link to low-fat milk

PHILADELPHIA, PENNSYLVANIA. Several previous studies have linked dairy foods with risk of prostate cancer. The cause of the link was initially attributed to the fat content of these foods, but it may be that their calcium content suppresses the body's production of vitamin D, a potential protective factor against prostate cancer. As dairy products are widely promoted and have certain

health benefits, researchers from the Fox Chase Cancer Center investigated the link to prostate cancer using a group of men from the first National Health and Nutrition Examination Epidemiologic Follow-up Study.

They followed 3,612 men from across the US for about eight years, during which time 131 were diagnosed with prostate cancer. Food questionnaires were given at the start of the study, when the participants were, on average, 58 years of age. The men consumed an average of 13 portions per week of dairy products, varying from three to 23 portions. Calcium intake was 730 mg on average and vitamin D intake was 172 IU on average (well below the recommended daily intake of 400 IU). Analysis showed that men in the highest third for dairy intake were 2.2 times more likely to develop prostate cancer than those in the lowest third. When each food was studied separately, risk was increased with low-fat milk but not whole milk or any other dairy food. Calcium intake also increased risk by the same amount, but in further analyses only calcium from milk was significant. Calcium supplements did not increase risk.

The authors suggest that their findings support the vitamin D suppression hypothesis. They explain that the suppressive effects of the calcium from whole milk may be countered by fortification with vitamin D, but low-fat milk has a lower vitamin D content, as it is a fat-soluble vitamin. On the other hand, prostate cancer may simply be diagnosed more in the higher social groups which tend to drink low-fat milk and are more likely to attend screening. In conclusion, the authors state that the increased risk from dairy may occur through a calcium-related pathway. They add that the link must be clarified, as both calcium and low-fat milk may be important in avoiding osteoporosis and colon cancer.

Tseng, M. et al. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. **American Journal of Clinical Nutrition***, Vol. 81, May 2005, pp. 1147-54*

Second-hand smoke nearly as damaging as smoking itself

SAN FRANCISCO, CALIFORNIA. Evidence suggests that exposure to second-hand smoke (passive smoking) increases the risk of heart disease and accounts for thousands of deaths each year. The cardiovascular system is sensitive to tobacco smoke in many ways – smoke can impair the function of blood cells and blood vessel linings, increase hardening of the arteries, and produce oxidative stress, inflammation, and abnormal heart rhythm.

In response to the accumulating evidence about the considerable impact of exposure to second-hand smoke, researchers from the University of California have conducted a review of the evidence of its biological effects compared with the effects of active smoking. They concentrated on low doses of exposure and placed greater emphasis on research published since 1995. Through analyzing 29 studies, the researchers found that the dose of smoke received by an active smoker is at least 100 times the dose received by a passive smoker. However, passive smoking has much larger cardiovascular effects than would be expected by comparing the doses delivered to active and passive smokers. In many cases, the effects of even brief passive smoking are often nearly as large as long-term active smoking. They report that the impact of second-hand smoke on the cardiovascular system is similar to, but larger than, the effects of outdoor air pollution. The effects of second-hand smoke are substantial and rapid, they write, which explains the relatively large risks that have been reported in population-based studies and earlier reviews of the evidence.

In conclusion, the authors state that there is consistent evidence that passive smoking has a much larger effect than would be expected from the dose of toxins received. The effects of even brief exposures are 80-90 per cent as large as from active smoking, and the means by which they occur are numerous and impact on each other. They support the implementation of smoke-free policies, particularly in the workplace, in order to reduce passive smoking and encouraging current smokers to quit.

Barnoya, J and Glantz, S.A. Cardiovascular Effects of Secondhand Smoke. Nearly as Large as Smoking. **Circulation,** *Vol. 111, May 2005, pp. 2684-2698*

Supplementary vitamin D may prevent fractures

BOSTON, MASSACHUSETTS. Bone fractures in older people are a significant cause of mortality and ill-health, with rates set to increase with the aging population. Hip fractures are particularly widespread, and lead to permanent disability in approximately 50 per cent of patients.

One prevention strategy, which has been suggested, is supplementing with vitamin D. It has been examined in several studies and a team from Harvard School of Public Health has analyzed the findings so far. They used rigid rules to select 14 reliable studies of oral vitamin D supplement (using cholecalciferol [vitamin D3]) against placebo on hip and non-vertebral fractures in people over 60 years of age. In total, this included 9,294 participants in hip fracture studies and 9,820 in studies of non-vertebral fractures. The average age of participants was 79 years, and two-thirds were female. The trials using low-dose (400 IU/d) and higher-dose vitamin D (700-800 IU/d) were analyzed separately. The higher dose lowered hip fracture risk by 26 per cent and overall non-vertebral fracture by 23 per cent. No benefit was found for the lower dose. Results suggest that for every 45 people taking the higher dose, one hip fracture could be avoided, and for every 27 people one non-vertebral fracture could be avoided. The duration of supplementation did not alter fracture rates, possibly due to the rapid effects of vitamin D found previously. The mechanisms which lie behind the benefit may be reductions in bone loss and increases in muscle strength and balance, all of which reduce fall risk. However, calcium was also given in many of the trials and may have influenced fracture rates.

The authors conclude that vitamin D at 700-800 IU per day should reduce fracture rates by about a quarter. They believe that a compelling case has been made for general vitamin D supplementation in older people. They also conclude that the currently recommended daily intake of 400 IU is inadequate to prevent fractures. A high intake of calcium may also be necessary and should be investigated further, as should even higher doses of vitamin D and the interaction between the two nutrients.

Bischoff-Ferrari, H.A. et al. Fracture Prevention with Vitamin D Supplementation A Meta-analysis of Randomized Controlled Trials. **Journal of the American Medical Association***, Vol. 293, May 2005, pp. 2257-2264*

Computerized medication dispensing systems do not improve safety

SALT LAKE CITY, UTAH. Adverse drug events - injuries resulting from the use of a drug - are a significant problem, leading to an estimated 41 per cent of all hospital admissions. Computerized systems have been widely installed in an attempt to reduce the rate of adverse drug events (ADEs) occurring in hospitals. Researchers from the Veterans Administration Salt Lake City Health Care System have examined the effects on ADEs of each stage of their computerized medication ordering and administration process.

ADEs which necessitated additional or altered treatment were recorded from medical records over 20 weeks of admissions to the Salt Lake City VA hospital, following the adoption of computerized systems including computerized physician order entry (CPOE). The team found that 483 clinically significant ADEs occurred during 937 hospital admissions - a rate of 51 per cent. A quarter of the hospitalizations had at least one adverse drug event. Almost all (93 per cent) were for adverse reactions to the drugs. Most (61 per cent) of these ADEs occurred during drug ordering, a quarter during monitoring, and 13 per cent during administration. Nine per cent of the ADEs led to serious harm. Many necessitated additional monitoring and interventions. Of particular interest is the finding that only one per cent of all ADEs were actually documented on the patient's medical record.

The authors report that the most common errors were: failing to anticipate common adverse drug reactions, failing to monitor for such reactions, providing incorrect doses, and giving inappropriate drugs. They explain that certain problems were avoided with the computerized systems, such as reading physicians' orders, however many others were not.

They conclude that ADEs may still occur at high rates when hospitals use CPOE and similar computerized medication systems. They believe that decision support for drug selection, dosing, and monitoring would help lower ADE rates, and add

that CPOE systems should not be relied upon to improve medication safety. Simple modifications to the computer program may vastly improve the utility and safety of CPOEs. For example, at the time a physician enters an order for a loop diuretic, CPOE should suggest an order for a potassium supplement and orders for monitoring serum creatinine and potassium levels.

Nebeker, J.R. et al. High Rates of Adverse Drug Events in a Highly Computerized Hospital. **Archives of Internal Medicine***, Vol.165, May 2005, pp. 1111-1116*

Editor's comment: The finding that over 50 per cent of patients admitted to hospital experience an adverse event from drugs dispensed in the hospital is indeed sobering and clearly underscores the need for vigilance on part of the patient and their advocate.

Nutty alternative benefits heart health

NEW YORK, NY. In the quest for the 'ideal' diet, fats have often been viewed in a negative light. But could certain fats actually help prevent disease? A recent review article by experts at SUNY Upstate Medical University discusses the potential benefits of consuming nuts, particularly as a partial replacement for sugars and saturated fats from meat and dairy foods. Although nearly 80 per cent of the energy in nuts derives from fat, the fats they contain are mainly monosaturated. Nuts are consumed in significant quantities in the Mediterranean diet, the authors explain, a diet which is linked to improved heart health.

The basis for the health benefits of nuts may be their effects on serum lipids - fats circulating in the blood. Macadamia nuts, for example, contain plant sterols which are believed to improve serum lipids. In one study, a diet high in macadamia nuts improved cholesterol levels compared with the typical American diet, and benefited serum lipids more than an American Heart Association diet in both healthy volunteers and those with elevated cholesterol.

The authors give details of further cholesterol and serum lipid-reducing effects in studies on walnuts, almonds, pecans and pistachio nuts. Billions of dollars each year are spent on lipid-lowering medications such as statin drugs, the authors write, and often these medications do not achieve target levels. Use of these drugs is likely to increase over time. However, by substituting nuts into the diet, their favourable effect on lipids may act as a useful addition to treatment. One ounce per day of nuts may be sufficient to lower fatal heart disease risk by 30-45 per cent, depending on the food they replace.

The authors conclude that, in an era of rapidly increasing medical costs, concerns over drug safety, and "low-fat" or "low-carb" fad diets, it is reassuring to have a nutty alternative.

Nash, S.D. and Westpfal, M. Cardiovascular benefits of nuts. **American Journal of Cardiology***, Vol. 95, April 2005, pp. 963-65*

NEWSBRIEFS

Daycare and childhood leukemia. Leukemia is the most common childhood cancer in the industrialized world. British researchers have followed 11,000 children for 15 years in order to determine the risk factors for leukemia. They found that one in 20 children have a mutant gene (DNA break) that predisposes them to the disease. Out of these, only 1% develops leukemia, perhaps triggered by an infection later in life. Mel Greaves and colleagues at the Institute of Cancer Research in London, UK compared 6300 leukemia-free children with 3100 children with leukemia and found that the incidence of the cancer was lower in children who attended formal daycare before they were 3 months old. Says Greaves, "One explanation for this link is that infections early in life establish an appropriate immune response."

New Scientist, April 30, 2005, p. 14

Capsaicin helps swallowing. Capsaicin is what gives red chili peppers their "hot" taste. Japanese researchers now report that supplementation with a capsaicin troche (containing 1.5 micrograms capsaicin) prior to each meal significantly improved the swallowing and cough reflexes in a group of elderly (average age of 82

years), institutionalized people. An improvement in these upper respiratory protective reflexes has been associated with a significantly reduced risk of aspiration pneumonia.
Journal of the American Geriatrics Society, Vol. 53, May 2005, pp. 824-28

An effective treatment for shingles. Shingles (herpes zoster) is an extremely painful skin condition that can take a long time to heal. It is an acute infection caused by reactivation of the chickenpox virus. Orthomolecular physicians now report that large doses of vitamin C are highly effective in curing the condition. They suggest starting out in the morning with 3000 mg of vitamin C (ascorbic acid) and repeating this does every 30 minutes until you have a single episode of loose stool (not quite diarrhea). Then reduce the dosage to 2000 mg every hour and gradually adjust to a dosage that will relieve shingles symptoms, but not cause loose stools. For a massive shingles outbreak intravenous injections (infusions) of vitamin C may be required. High stress levels deplete vitamin C and can be a precipitating factor for a shingles outbreak.
Orthomolecular Medicine News Service, June 15, 2005 (www.orthomolecular.org)

Polio makes a comeback. Indian medical authorities have confirmed that an 18-month-old boy from a village in West Java has polio. This pretty well wipes out the goal of the World Health Organization to have the disease declared extinct by December 2005. Cases have now been reported in 16 countries and involve a strain originating in northern Nigeria. Officials there apparently blocked polio immunization efforts for a year claiming that the vaccinations were a Western plot to make Muslim girls infertile.
New Scientist, May 7, 2005, p. 7

Beware of oysters and liver disease. Septicemia (blood poisoning) caused by the bacterium *Vibrio vulnificus* is the leading cause of fatalities related to seafood consumption in the US. Although the overall incidence of *V. vulnificus* poisoning is low at 0.6 per million, it is particularly dangerous for people with chronic liver disease. Other high-risk conditions include hemochromatosis, AIDS, achlorhydria (lack of stomach acid), cancer and generally, a poorly functioning immune system. Almost all recorded cases of the disease were preceded by the consumption of raw oysters.
American Journal of Gastroenterology, Vol. 100, May 2005, pp. 1195-99

Update on bird flu. The H5N1 strain of bird flu is now infecting people in Vietnam and it is likely only a matter of time before the disease will appear in other countries. Last month the World Health Organization reported that a patient in Vietnam had been found to be resistant to Tamiflu (oseltamivir), the only antiviral drug thought capable of preventing bird flu. Fortunately, it appears that the Tamiflu-resistant strain is considerably less contagious than other strains. The best hope for preventing a bird flu epidemic is still the early use of Tamiflu. However, the drug is difficult to make and in very short supply. Rich Western countries are stockpiling Tamiflu leaving little for poorer countries like Vietnam where a pandemic is most likely to begin. It is now clear that Chinese farmers have been fighting bird flu outbreaks prior to 2003 and have been using amantadine, another powerful antiviral drug, in their chicken feed prior to 2003. This has resulted in the H5N1 strain becoming resistant to this potentially useful drug. Frequent hand washing and the avoidance of crowded places are probably the best approaches to prevent becoming infected for those who do not have access to Tamiflu.
New Scientist, June 4, 2005, p. 10

Cancer now the leading cause of death. Up until 1999 heart disease was the number one killer of Americans. This has now changed, at least for people under the age of 85 years. The latest statistics show that cancer killed 478,082 Americans in this age group in 2002; this compares to 446,727 deaths from heart disease. Among people over the age of 85 years heart disease is still the number one killer accounting for 3 times as many deaths as is attributable to cancer (250,000 versus 80,000). Death rates from cancer have essentially stayed unchanged since 1975, whereas death rates from heart disease have dropped by half over the same period. It is estimated that about 70% of all cancers are preventable by avoiding smoking, poor diet, obesity, and lack of exercise. Unfortunately, few Americans have taken this message to heart.
Journal of the National Center Institute, Vol. 97, March 2, 2005, pp. 330-31

RESEARCH REPORT

Benign Prostatic Hyperplasia: A Not So Benign Condition

Part II – Conventional and Alternative Treatment

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

MEDICAL TREATMENT OF BPH

The two obvious goals of medical treatment for BPH are a reduction in the severity of symptoms and the delay or elimination of progression which can ultimately lead to intolerable symptoms, acute urinary retention (AUR) and surgery. That BPH is a progressive disease now appears well established, as is the observation that progression is associated with increasing prostate volume, in particular in the transition zone [2]. There are two standard types of prescription medication in use for the treatment of BPH, α_1-adrenoreceptor antagonists (alpha-blockers) and 5-α-reductase inhibitors (5-ARIs). They differ totally in their biological function and are used both as monotherapy and together in combined therapy. Both classes of drug have been rather extensively studied and the comparative side effects both within each class and between classes appear reasonably well documented. These drugs offer the potential for a conservative, non-surgical approach with minimal serious side effects that appear well tolerated. Alpha-blockers are commonly the first-choice option for the treatment of BPH.

α_1-ADRENORECEPTOR ANTAGONISTS (ALPHA-BLOCKERS)

Historically, alpha-blockers were developed for the treatment of hypertension, and their use in blood pressure treatment goes back some 30 years. Their effect on blood pressure resides in their ability to relax the smooth muscles in blood vessel walls. But it was more recently found that they also relaxed muscle tension in the prostate, bladder neck and urethra, which allowed urine to flow more freely. The older drugs, i.e. Cardura (doxazosin) and Hytrin (terazosin) act on both the prostate and the vascular system in general with associated blood pressure effects. Both must be "titrated" starting with a low initial dose which is then increased to achieve a compromise between adverse side effects and the reduction of BPH symptoms. These adverse effects include postural (orthostatic) hypotension (a sharp drop in blood pressure upon changing position such as standing up) as well as dizziness, fainting, and actual loss of consciousness due to diminished cerebral blood flow. These cardiovascular related side effects are a serious consideration since they can result in falls, fractures and head injuries. There are two newer drugs, Flomax (tamsulosin) and Uroxatral (alfuzosin) that are specific in relaxing only the prostate and not only do they not need to be titrated to ascertain the appropriate dose, but their use is in general associated with a lower level of side effects. Because titration to find the best dose is unnecessary, these newer specific alpha-blockers also result in a more rapid symptom improvement, although over the long term, most studies indicate that all four of these drugs are approximately equivalent in effectiveness.

Milani and Djavan [51] have recently provided a comprehensive review of studies on alpha-blocker use in treating BPH with special reference to relative effectiveness, cardiovascular side effects, and the effect of alpha-blockers on blood pressure management and abnormal ejaculation. The following points are of interest.

- With regard to cardiovascular adverse events, a review of the literature indicated that the newer alpha-blockers were superior to the traditional ones when dizziness, orthostatic hypotension, and discontinuation of drug use were considered. When tamsulosin (0.4 mg) and alfuzosin (10 mg) were directly compared, tamsulosin caused less dizziness but the incidence of syncope (unconsciousness), hypotension and discontinuations were similar. However, in elderly patients, tamsulosin caused less symptomatic orthostatic hypotension during orthostatic stress testing than did alfuzosin. Also, a comparison of studies indicated that alfuzosin might be less well tolerated in elderly patients and patients with cardiovascular comorbidity or comedication.
- An issue with using alpha-blockers for the treatment of BPH concerns the effect on blood pressure regulation. One study

indicated that tamsulosin can be administered along with several antihypertensives such as calcium antagonists, beta-blockers, and ACE inhibitors.

- Another side effect associated with alpha-blockers involves abnormal ejaculation which can take the form of retrograde ejaculation (ejaculation partially or totally into the bladder), or reduced or total absence of ejaculate volume. In placebo controlled trials, abnormal ejaculation has been reported mainly with tamsulosin. In European trials, the incidence was 4-5% whereas in US trials it was 6-11%. A direct comparison study between alfuzosin and tamsulosin, however, found similar percentages of patients with ejaculation failure with these two drugs, although overall, tamsulosin resulted in slightly greater incidence of abnormal ejaculation. Interestingly, tamsulosin has also been shown to slightly improve overall sexual function vs. a placebo. Studies also find that less than 1% of patients discontinue usage because of abnormal ejaculation.

The authors [51] conclude that an alpha-blocker that has a low potential to interfere with blood pressure regulation, induce cardiovascular adverse effects, or interfere with commonly used blood pressure medication should be considered a first-choice treatment option for LUTS/BPH.

5-α-REDUCTASE INHIBITORS

The enzyme 5-α-reductase converts testosterone into dihydrotestosterone (DHT), the form thought to be involved in prostate enlargement. Inhibiting the action of this enzyme reduces the level of DHT and in fact generally significantly reduces prostate volume as well as LUTS/BPH symptoms. While alpha-blockers influence the *dynamic* aspect of BPH, inhibiting this enzyme is thought to influence the *static* component. Inhibition improves symptoms and flow rate in part by shrinking the transition zone of the prostate [52]. At present there are only two α-reductase inhibitors (5-ARIs) on the North American market, finasteride (Proscar) and dutasteride (Avodart). Both have now been rather extensively studied. A 1996 study by Lepor *et al* [53] indicated that finasteride failed to alleviate BPH symptoms, and a second placebo-controlled randomized trial also found no benefit of finasteride [54]. It has been suggested that the these studies failed because of low prostate volume in the subjects and that as well, insufficient time was allowed for finasteride to reach complete effectiveness [52,55]. The Lepor *et al* study is the only one cited with regard to Proscar in a book on prostate health [56] published in 2005, where the position is taken that Proscar "does not relieve any symptoms." In fact, both earlier and recent studies have found this drug to be effective. Indeed, the landmark Proscar Long-term Efficacy and Safety Study (PLESS) which involved 3000 men and extended over a four-year period, found that finasteride was as effective as alpha-blockers for symptom relief and was more effective than alpha-blockers in preventing acute urinary retention and the need for surgery [57]. Evaluation of data from this trial over an additional two years confirmed the earlier results and indicated that the use of finasteride led to a sustained decrease in the risk of acute urinary retention and/or BPH surgery in men with BPH and enlarged prostates. Patients who switched from placebo to finasteride in the two-year extension had similar results to those in the continuous finasteride arm [58].

Optimal conditions for finasteride to be effective were present in another large study [59], the Medical Therapy of Prostatic Symptoms (MTOPS), where the effectiveness of finasteride alone, the alpha-blocker doxazosin alone, or both drugs in combination was investigated. The duration of the trial was five years. It was found that the combination therapy was superior in halting the progression of the disease and reducing symptoms, but finasteride was more effective than the alpha-blocker in reducing the risk of acute urinary retention or the need for surgery. The total risk of progression was reduced by 39% for doxazosin, 34% for finasteride, and 67% for the combination therapy. The risk of AUR was reduced by 35% by the alpha-blocker, 68% by finasteride and 81% by the combination, while the risk of surgery was reduced by 64% for finasteride and 67% for the combination therapy with no significant effect found with the alpha-blocker. Treatment with doxazosin alone only slightly delayed the time to acute urinary retention and did not significantly reduce the risk of invasive therapy. The authors suggest that the continued growth of the prostate during doxazosin mono-therapy overcame the reduction of prostatic urethral obstruction achieved by smooth muscle tone relaxation due to the action of the alpha-blocker alone. However, as emphasized by Desgrandcamps in a recent paper [52] which asks the question "Who will benefit from combination therapy?" the adverse effects observed in MTOPS were found to be more or less additive in combination therapy. Desgrandchamps suggests

that combination therapy be used only for patients in whom the baseline risk is high. These are generally patients with larger prostates and higher PSA values. MTOPS involved one of the older alpha-blockers. In an uncontrolled trial of 1000 patients the ALFIN study [60] compared the newer alpha-blocker alfuzosin (slow release) with finasteride, either along or in combination. Those taking either the combination therapy or alfuzosin had significantly better symptom scores, but the combination offered no additional benefit. There do not appear to be any published studies of combination therapy using finasteride and tamsulosin. Patients offered a choice between mono- and combination therapy may wish to consider the potential downside of combination therapy due to increased side effects. Randomized placebo-controlled trials do not appear to have been done for the newer alpha-blockers in combination with dutasteride (Avodart).

The α-reductase enzyme exists in two isoforms. Type I has been reported to be located predominantly in the skin, liver, prostate and kidney, whereas type II is found in the male genitalia and prostate. Finasteride is a type II inhibitor and typically reduces DHT by about 70%. Dutasteride, the other 5-ARI currently approved by the FDA for the treatment of BPH, inhibits both isoforms. Studies have shown that dutasteride (0.4 mg) decreases DHT by over 90% [61]. Controlled studies on the efficacy and safety of long-term use of dutasteride are currently limited to three randomized, placebo-controlled phase- III clinical studies carried out over 2 years. Debruyne *et al* [62] have recently reported on these studies along with a 2-year open-label extension aimed at assessing the long-term safety and efficacy of dutasteride. In a comparison between the 2-year and 4-year results, it was observed that there were continuing improvements in urinary symptoms and flow rate and a further reduction in total prostate volume in men with symptomatic BPH. In addition, the reduction in risk of AUR and BPH-related surgery, which was found in the 2-year study, was durable over the 4-year treatment. The three most common side effects, impotence, decreased libido and ejaculation disorders occurred in 6.0%, 3.7% and 1.6% respectively in patients during the first year, but the incidence dropped off rapidly and dramatically after the first year to 0.4%, 0.1% and 0.1% respectively by the fourth year. Breast/nipple tenderness and breast enlargement remained more or less constant at 1% of patients (range 1.3-0.7%). The low percentages of adverse effects after the first year suggest that dutasteride is well tolerated in long-term use. Long-term incidence of these four adverse reactions was similar in the PLESS trial of finasteride involving the open-label 2-year extension, which covered years 4 to 6. Also, for those switched from placebo to finasteride, the rate of these four side effects was similar to that seen in the first year of dutasteride use.

In a recent study the use of finasteride was also found [63] to statistically significantly reduce the risk of surgery in BPH patients as compared to patients on alpha-blockers only. The study covered 8 years and involved 1430 men, and all five alpha-blockers commonly in use from 1994 to date were involved. These results are consistent with those reported for the MTOPS study by McConnell *et al* [59].

While both finasteride and dutasteride are obviously intended for male patients, both drugs carry warnings that women who are pregnant or may potentially be pregnant should not handle crushed or broken Proscar tablets, or handle dutasteride soft-gel capsules because of the possibility of absorption of the drug through the skin. The resultant exposure even to minute amounts carries a potential risk of a serious abnormality in the male fetus. The seriousness of the problem is made clear by the warning in *The Physicians Desk Reference* (2005 Edition) that men treated with dutasteride should refrain from donating blood for at least six months following their last dose to prevent pregnant women from receiving the drug via blood transfusion.

Both finasteride and dutasteride have a profound effect on PSA levels with approximately a 50 % reduction. This becomes an issue for those whose PSA levels are being followed for diagnostic purposes. It is now standard practice to correct PSA levels for patients taking either of these drugs in order to normalize the results with pre-treatment values or interpret absolute values. Since this is only approximate, there will be a problem for those with corrected values near a cut-off.

A study published in 2003 which received considerable media attention suggested a potential new use for finasteride—the prevention of prostate cancer [64]. In a seven-year study, over 18,000 men over 55 years of age with a normal DRE and a PSA level of 3.0 or lower were randomized to 5 mg/d of Proscar or a placebo. The primary endpoint was prostate cancer during the seven-year period of study. A 24.8% reduction in prostate cancer over the seven years (confidence limits 18.6-30.6%, $P<0.001$) was found in men who had data for the

final analysis. However, high-grade tumors were more prevalent in the finasteride group than in the placebo group (37.0% vs. 22.2%, P<0.001). This latter aspect has put a damper on what might otherwise be enthusiasm for the use of Proscar in the primary prevention of PC. However, Proscar may not actually "cause" high-grade or aggressive cancer. The authors point out that Proscar might select for high-grade tumors by selectively inhibiting low-grade tumors. The observed decrease in low-grade cancer in the Proscar group would support this explanation. A similar study does not appear to have been conducted for dutasteride, but tissue studies suggest that treatment with this 5-ARI may cause regression in some prostate cancers. One can view these results in two ways. Individuals taking Proscar for LUTS/BPH symptoms and to reduce the risk of AUR and BPH-related surgery may receive an added benefit of a lower risk of developing PC, but the risk of developing aggressive PC can be added to the "side effects" list, although it may in fact be an artifact and thus a non-issue. Life is never simple!

The 5-ARIs have the merit of reducing the prostate size, which it can be argued, represents treatment of the disease rather than treatment of symptoms. The 5-ARIs also significantly retard the progression of BPH and thus delay or avoid invasive treatments for AUR or severe BPH symptoms. These characteristics distinguish the 5-ARIs from the alpha-blockers which do not reduce the risk of invasive therapy. The cardiovascular side effects associated with the older alpha-blockers are absent in the 5-ARIs.

The AUA considers the four alpha-blockers discussed above to offer appropriate treatment options for patients with LUTS secondary to BPH. The 5-ARIs and combination therapy are considered appropriate for patients with demonstrable prostatic enlargement [41]. This latter recommendation is based on the observation that the 5-ARIs are not effective if the prostate is not enlarged.

NATURAL TREATMENTS FOR BPH

While the modern prostate-specific alpha-blockers and the 5-ARIs have a rather low incidence of side effects when used long-term, there will always be interest in so called alternative or "natural" treatments with lower or no side effects. These come under the general category of *phytotherapy* or herbal treatments. Mainstream medicine does not acknowledge the extent to which the use of some phytochemicals is in fact evidence based [1]. The American Urology Association (AUA) guidelines of 2003 state that phytotherapeutic agents and other dietary supplements cannot be recommended for treatment of BPH [41]. The EAU take a similar position—more studies are required [42]. This EAU position is surprising since the vast majority of patients in Europe with BPH are treated with phytotherapeutic agents *by physicians and by prescription.* As will be discussed below, two substances commonly used in the treatment of BPH in Europe and used as over the counter herbal remedies in North America are in fact backed by a number of randomized, placebo-controlled studies.

SERENOA REPENS (SAW PALMETTO)

The extract derived from the American dwarf palm *Serenoa repens* (saw palmetto) is unquestionably one of the most widely used phytochemicals for the treatment of the symptoms of BPH. The plant is found in swampy areas along the southeastern coast of the US and inland as far as Texas and as well in the West Indies. The ripe berries are the raw material for the extract. Historically, the dwarf palm berries were used by American Indians for genitourinary problems. Today, the extract is licensed in Germany, France and other European countries where it has the status of a prescription drug. In Germany and Austria, phytotherapy is the first line treatment for mild to moderate LUTS/BPH and represents > 90% of all drugs prescribed for BPH [65]. In the US the popularity of saw palmetto has increased in recent years and it is readily available in health food stores. A recent survey found that one-third of US men choosing non-surgical treatment for BPH used herbal preparations alone or in combination with prescription drugs [66].

A large number of studies aimed at evaluating the effectiveness and side effects of saw palmetto have appeared in peer-reviewed literature. One problem with these studies is that not all saw palmetto preparations were equal in terms of the composition of the extract, which makes comparison of results difficult. However, in Europe saw palmetto is a prescription drug (Permixon) which is standardized and subject to quality controls normally applied to such drugs. Thus of special significance are studies

that used this extract of *Serenoa repens*. Three reviews of clinical trials are of particular interest:

- Boyle *et al* [67] examined all the clinical trials involving Permixon, comprising 14 randomized clinical trials and three open-label trials, involving 4280 patients. They concluded from a combined analysis that all available published trials of Permixon for treating BPH showed a significant improvement in flow rate and a reduction in nocturia as compared to a placebo.
- Gerber *et al* [68] also restricted their review of studies to those using Permixon. They reviewed both placebo-controlled studies and comparison studies with alpha-blockers and finasteride. Eighteen studies were examined. The authors summarize their results as follows: "S. repens extract significantly reduces the symptoms of BPH, increases urinary flow, improves the quality of life and is well tolerated. Analysis of the overall clinical database indicates that extract of S. repens may be considered a viable first-line therapy for treating LUTS." Comparison between Permixon and the alpha-blocker tamsulosin indicated both drugs were equally effective in treating urinary symptoms. A similar conclusion was reached regarding the comparison of Permixon and finasteride. In addition, evidence was presented that indicated the course of prostatic disease may be delayed by Permixon, especially in patients of high risk of progression. The lowest level of adverse side effects was associated with Permixon when compared to alpha-blockers and finasteride. The authors point out that the lack of Permixon induced sexual dysfunction may have important implications among those who prefer natural products rather than the prescription drugs.
- A comprehensive review was published in 2002 in *The Cochrane Database of Systematic Reviews* [69]. Trials were eligible for inclusion if randomized with men with BPH receiving preparations of *Serenoa repens* (alone or in combination) compared with a placebo or other BPH medication. The studies had to include clinical outcomes such as urologic symptom scales, symptoms or urodynamic measurements. Twenty-one trials involving 3139 men were assessed. Eighteen were double-blinded. All were randomized. The researchers conclude: "The evidence suggests that *Serenoa repens* provides mild to moderate improvement in urinary symptoms and flow measures. *Serenoa repens* produced similar improvement in urinary symptoms and flow compared to finasteride and is associated with fewer adverse treatment effects. The long term effectiveness, safety and ability to prevent BPH complications are not known."
- Djavan *et al* [70] found in a 4-year study that *Serenoa repens* reduced the incidence of symptomatic progression and AUR in BPH patients. Patients were minimally symptomatic.

Thus, contrary to popular belief in the medical community, there is considerable evidence supporting the effectiveness and lack of side effects associated with the extract of *Serenoa repens.* The frequently seen objection based on the absence of really long-term studies can also be advanced for many prescription drugs, and in the case of saw palmetto, its use as a prescription drug for decades in Europe suggests an acceptable level of safety.

While the biological mechanism of the action of saw palmetto is not well understood, there have been a number of studies addressing this subject which have produced several hypotheses [71]. Saw palmetto appears to have 5-α-reductase inhibitory properties, as judged by the decrease in DHT and the increase in testosterone seen in prostate tissue samples when individuals taking the extract are compared to controls [72]. The results were similar to those produced by finasteride. A number of cell and tissue culture studies also suggest this [71]. Most of the components of the extract have been isolated and identified. The extract is predominantly composed of fatty acids. When these were tested in cell culture for 5-α-reductase inhibitory activity, the oleic, linolenic, lauric and myristic acid fractions were all found to have this property [73]. Saw palmetto also appears to preferentially reduce DHT in the transition zone [74] and studies of gene expression suggest that saw palmetto shifts the balance between proliferation and programmed cell death (apoptosis) with resultant tissue growth inhibition [75].

The possible connection between inflammation, BPH and Permixon treatment has been investigated. In a recent study, Vavarrete *et al* [76] examined prostate tissue obtained during surgery from patients given either Permixon or no treatment for three months prior to the operation. Two

biological markers for inflammation, Tumor Necrosis Factor-alpha and Interlukin-1-beta were both dramatically lower in the tissue of the treated group. Treatment was accompanied by a significant reduction in the IPSS score in the three months prior to surgery. These results are consistent with the commonly observed presence of inflammation related mono-nuclear cells in BPH tissue that are absent in normal prostate tissue. The authors speculate that Permixon modifies the inflammatory status of the prostate through cytokine regulation.

Finally, studies consistently report that saw palmetto has little or no influence on prostate volume nor does it decrease the PSA level [71,72]. Thus, while 5-α-reductase inhibition appears to be part of the action of this extract, there are mechanistic differences as compared to the synthetic 5-α-reductase inhibitors such as finasteride. Thus while saw palmetto does not interfere with the use of PSA in the context of PC, it may be less successful in the long term in halting progression of BPH than the synthetic 5-α-reductase inhibitors because it fails to reduce the prostate volume. Saw palmetto also does not act as fast as the new specific alpha-blockers in relieving symptoms of BPH. In addition, adding saw palmetto to alpha-blocker therapy does not appear to provide any additional benefit, at least in the first year [77].

Acquiring saw palmetto that has the amount of extract indicated on the label may be a problem in North America where Promixon is not available. The label should indicate that the capsule contains an extract that is at least 80% fatty acids, but there is no guarantee that the capsule contains the indicated amount. The dose used in many studies was 160 mg twice a day of an 80-85% preparation. Saw palmetto is frequently found combined with other phytochemicals in what are sometimes called *prostate formulas* or *prostate health* capsules.

PYGEUM AFRICANUM (AFRICAN PYGEUM)

An extract derived from *P. africanum* (African prune tree) is probably the second most popular phytochemical after saw palmetto for the treatment of the symptoms of BPH. Active ingredients are extracted from the bark of this evergreen species, which is found throughout Africa at altitudes above 3000 feet. Interest in its therapeutic value can be traced back to the 1700s when European travelers learned from African tribes that the bark extract could be used to treat bladder discomfort and “old man’s disease” as BPH was called then. Widespread use in Europe began in the mid 1960’s and it is the most commonly used remedy in France for BPH [78].

In 2000 Ishani *et al* [79] published a review of clinical studies of P*. africanum* extract. They examined 18 randomized, controlled trials published between 1996 and 2000 and involving over 1500 men. The reviewers found that *P. africanum* extract yielded significant improvement in the combined outcome of urological symptoms and flow measures. Also, subjects taking pygeum extract were more than twice as likely to report improvement in overall symptoms as compared to those taking a placebo. Nocturia was reduced by 19% and residual urine volume by 24% while peak urine flow increased by 23%. This review covers essentially the same set of studies as that reviewed in *The Cochrane Database of Systematic Reviews* in 1998, which arrived at similar conclusions [80]. Compared to saw palmetto, pygeum does not have as extensive a set of clinical studies to substantiate effectiveness, nor are the studies as large or as uniform in endpoint measures, but the studies that have been reported are consistent and those reviewed were randomized and placebo controlled. The popularity mentioned above in Europe and especially in France also anecdotally attests to significant effectiveness. In addition, the majority of studies report an absence of any significant adverse effects [78,79].

There has been very little research involving human subjects that has investigated possible mechanisms whereby *P. africanum* extract influences the prostate gland. However, several hypothetical mechanisms have been suggested. These have been reviewed by Levin and Das [81]. Included are (a) inhibition of various growth factors known to operate in prostate tissue; (b) a weak anti-estrogenic effect; (c) inhibition of the enzyme 5-α-reductase; (d) anti-inflammatory effects. A number of other mechanisms have been investigated, mostly in an animal model of BPH, but these have emphasized effects on the bladder rather than the prostate. While a number of constituents of the pygeum extract have been isolated and identified, including the polysterol beta-sitosterol, a known anti-inflammatory agent also used in BPH phytotherapy, and alcohols that reduce the prolactin levels which might inhibit testosterone uptake by the prostate, in fact little is really known about whether one or more of the isolated constituents is in fact an active ingredient.

African pygeum is frequently found in prostate formulations. The typical dose is 40 mg twice a day

of an extract containing 13% beta sitosterol. Preparations that fail to give the percentage of sitosterol should be viewed with suspicion.

BETA-SITOSTEROL (PHYTOSTEROL)

Three randomized, placebo-controlled clinical studies conducted between 1986 and 1997 which examined the effect of β-sitosterol on the symptoms of BPH have been reviewed by Wilt *et al* [82]. It was consistently found that β-sitosterol improved urologic symptoms and flow measures. In two studies, IPSS scores improved significantly as did residual urine volumes. One of the studies reviewed [83] was continued with 18 months of additional open label treatment and follow-up. It was found that the beneficial effects observed in the initial 6-month study were maintained for the additional 18 months, and patients who had been on the placebo but were switched to the β-sitosterol improved to the same extent as the treatment group. No change is prostate size was observed. These appear to be the only randomized clinical trials. However, they were of short duration and there was a lack of a standardized β-sitosterol preparation. This plant sterol is now being added to prostate formulations. The Life Extension *Enhanced Natural Prostate Formula* contains 90 mg. β-sitosterol per soft gel and the recommended dose is two a day (available at http://store.yahoo.com/cgi-bin/clink?iherb+7VEBu7+natpros1.html+ihn). The Whitaker formulation *Prostate Health* contains a similar amount with a comparable suggested daily dose.

URTICA DIOICA (STINGING NETTLE)

This herbal drug has been used for many years in Germany where it is believed that it is effective. However, there are no studies that appear to meet reasonable standards of acceptability that shed light on the question of how effective this herbal extract really is. When it is used in combination with saw palmetto, encouraging results are obtained but it is not possible to isolate the effects due to urtica dioica [84,85]. Thus in using stinging nettle, one is essentially depending on anecdotal or weak clinical evidence.

CERNILTON (CERNITIN, FLOWER POLLEN or RYE-GRASS POLLEN)

Cernilton (also called Cernitin, a proprietary preparation) is made from rye-grass pollen. It is used by millions of men worldwide for BPH and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina [86]. *In vitro* studies suggest that Cernilton has anti-androgenic effects, may relax urethral smooth muscle tone and increase bladder muscle contraction [86]. In reviews of clinical studies, Macdonald *et al* [86] and Wilt *et al* [87] point out that Cernilton trials were limited by their short duration, small number of participants, omissions in reported outcomes, and the unknown quality of the preparations used. However, the available evidence does suggest that Cernilton is well tolerated and modestly improves overall urological symptoms including nocturia. It does not appear to improve urinary flow measures [87]. It is clear that additional randomized controlled studies with large numbers of enrollees and significant duration are needed to evaluate the clinical effectiveness and safety of this product. Nevertheless, it is included in prostate formulations such as Dr. Julian Whitaker's *Prostate Health* with a recommended dose of 200-400 mg/day. The Life Extension *Enhanced Natural Prostate Formula* also contains Cernitin with 2 capsules a day providing 250 mg and is available at http://store.yahoo.com/cgi-bin/clink?iherb+7VEBu7+natpros1.html+ihn .

OTHER PHYTOTHERAPY

The phytoestrogens daidzein and genistein found in soy are commonly promoted for the prevention or treatment of BPH, but these substances exert estrogenic effects that may pose risks by disturbing the hormonal balance [88]. An herbal tea made from the small-flowered willow herb also has a following based on anecdotal evidence http://www.swedishbitters.com/prostate_health.htm

INVASIVE TREATMENTS FOR BPH

Historically, surgery was the most common treatment for BPH, but surgery is on the decline because of the increased use of medications and the use of less invasive therapy. However, when drug therapy fails or if symptoms worsen to the point where they severely affect normal living, invasive treatments become an important or even necessary option. Repeated acute urinary retention episodes, repeated bleeding in the urine, bladder stones, or recurrent urinary tract infections may prompt the consideration of an invasive or surgical solution to the problem. These procedures are designed to either physically remove, "vaporize", or kill prostate tissue which then sloughs off over a

period of time. The following descriptions of surgical procedures for relieving the severe results and complications of BPH should stimulate a strong interest in prevention!

Minimally invasive procedures for treating BPH are of fairly recent origin. Comparison studies both within this group and between these procedures and conventional surgery are limited. Comparisons are also difficult because of variations of technique and equipment and the level of training and skill of those doing the operations, important variables which are difficult to quantify and take into account.

TRANSURETHRAL RESECTION OF THE PROSTATE (TURP)

This surgical procedure is also colloquially known at the "Roto-Rooter" operation. It accounts for 95% of the surgical procedures done to relieve the symptoms of BPH. Increased use of medical therapy has reduced the number of TURPs by 60% in the past decade, but it is still one of the most commonly performed operations in the US [1]. The operation is done under general anesthesia or a spinal block. The surgeon threads a narrow instrument up through the penis and into the urethra. The instrument employs small cutting tools to remove excess prostate tissue and a small electrical loop to cauterize the wound. The so-called internal urinary sphincter at the base of the bladder is generally removed in this operation, leaving only the external urinary sphincter at the exit end of the prostate for urinary control. The tissue recovered is normally examined by a pathologist and it is not uncommon to discover histological evidence of prostate cancer. In his recent book [1], Dr. Peter Scardino provides the following statistics regarding side effects and complications, statistics presumably based in part on the experiences at Memorial Sloan-Kettering Cancer Center, where he is presently chair of urology. Bleeding that may require transfusion—4% of cases; acute urinary retention—6 to 7% of cases, infections—2%, urinary stricture—5%, incontinence—1%. Erectile dysfunction is reported in about 13% of cases, but Scardino claims that a properly performed TURP should not cause this side effect. Over 50% of men develop retrograde ejaculation (ejaculation partially or totally into the bladder due to the absence of the internal urinary sphincter) with resultant partial or complete infertility. One percent per year experience recurrence requiring additional treatment. There is also what is known as TURP syndrome caused by the irrigant solution being absorbed into the blood stream, which can result in symptoms of mental confusion, visual and digestive disturbances and cardiac symptoms. Presumably, the risk of complications and side effects increases when the surgery is performed by a less experienced or less skilled surgeon. Scardino suggests that it is "always wise to put yourself in the best possible hands" but many, even perhaps most patients do not have the option or the opportunity of searching out and selecting the best possible surgeon and hospital.

OPEN PROSTATECTOMY

Performed through an abdominal incision, this operation involves removal of the inner portion of the prostate while leaving the outer or peripheral portion intact. Men with very large prostates or with medical or physical problems that preclude the physical positioning required for a TURP are may be offered this option. The open prostatectomy is as effective as TURP in symptom relief, but the hospital stay is generally longer and the risk of bleeding requiring transfusion greater. The risk of subsequent retrograde ejaculation is greater than in TURP. and there is a small risk of more serious surgical complications such as deep vein thrombosis, pulmonary embolism, heart attack or stroke [1].

TRANSURETHRAL INCISION OF THE PROSTATE (TUIP)

This transurethral procedure involves making one or two small incisions in the prostate near the bladder neck with an electric current or laser. This reduces the constriction. General or a spinal anesthetic is used and the procedure is sometimes done on an outpatient basis. TUIP results in less improvement in urinary flow and other symptoms and there is greater risk of recurrence and the need for additional treatment than with TURP. However, blood loss, the incidence or retrograde ejaculation, erectile dysfunction and incontinence are low [1]. The AUA guidelines [41] indicate that it should be used in cases where the prostate is only somewhat enlarged with a volume of less than 30 mL.

MINIMALLY INVASIVE THERAPIES

TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT)

In TUMT excess prostate tissue is killed by microwave "cooking" which is more properly called

coagulative necrosis. TUMT is done by inserting into the urethra a microwave antenna. The urethra is protected by a jacket through which a coolant is circulated. The probe has a balloon that inflates to close off the bladder outlet and anchor the probe. Local anesthetic is used to control pain. Urinary retention is a common temporary side effect and about 30% of TUMT treated patients need to use a urinary catheter for several days to a week and sometimes longer [89]. Other immediate complications include urgency and urinary infections. Full effects are obtained after the dead tissue sloughs off, and this can take from three to six months. Several microwave devices are currently in use in North America. The Prostatron, TherMatrx and Targis devices do not monitor the prostate tissue temperature whereas CoreTherm, made by Prostalund, a Swedish firm, which also uses a cooled trans urethral microwave antenna, inserts a temperature probe into the prostate and monitors tissue temperature at three locations. Penile and rectal sensors are also employed to guard against unwanted tissue damage. CoreTherm uses a software-based feedback system to monitor and control in real time the temperature to which the tissue is heated which customizes the treatment to each individual patient and prevents either under- treatment or excessive tissue damage. This feedback system stands out as the most distinctive treatment modality [90]. The CoreTherm procedure requires from 10 to 70 minutes, which is similar to other TUMT devices. Procedures done without actually monitoring the tissue temperature are in a sense being done blind.

Studies of the effectiveness and adverse effects compare TUMT to TURP, the so-called gold standard of non-medical treatment. There do not appear to be studies that compare heat-to-head the individual devices. Hoffman *et al* [91] have reviewed six studies with a maximum follow-up of one year which compared TUMT with TURP. Five involved the Prostatron device and one employed CoreTherm. From these studies, which the authors regard as the best available clinical data at the time (most recent study examined was published in 2001) TUMT was an effective treatment for BPH that could be delivered on an outpatient basis and had fewer adverse events than TURP. But TURP produced greater improvements in symptom scores and peak urine flow and fewer men required re-treatment. The CoreTherm based study reviewed by Hoffman *et al* has been extended with two additional years of follow-up [92]. The degree of improvement was similar to that found in the 12 month study. A small but significant difference was found for IPSS in favor of TURP, but contrary to the results of the analysis of Hoffman *et al,* there were no statistically significant differences in peak urine flow. There were also no differences in the quality of life between the two groups. The safety profile which favored TUMT after 12 months was preserved after 36 months. Two other recently published studies also found the CoreTherm device effective and safe in treating BPH with TUMT [93,94]. In one, prostate volume changes were measured in 33 patients and it was found that six months after TUMT, volumes dropped from an average of about 64 mL to 36 mL and after twelve months the average was 35 mL [93].

In spite of the cooling of the urethra during TUMT, a recent study found extensive urethral necrosis. This observation was made on prostates available after a prostatectomy which occurred three to six weeks post-treatment (some of the patients studied had PC and were scheduled for a radical prostatectomy after TUMT). Significant necrosis was found in the bladder neck. In this study, patients were treated with the CoreTherm device. The authors comment that “this study challenges the myth that the prostatic urethra should be preserved to have effective treatment” [95].

TUMT offers a number of advantages over TURP. It can be done on an outpatient basis, transfusions are not required, retrograde ejaculation is rare, and risks associated with hospitalization are avoided. In the 3-year CoreTherm study [92], impotence, urination urgency, incontinence, and urethral disorders were all significantly and dramatically lower in the TUMT group as compared to those who had a TURP. It is also an attractive option for patients with comorbidities such as uncontrolled diabetes, cirrhosis of the liver, or kidney or heart disease, patients who may not be good candidates for surgery [89]. The CoreTherm device would appear to be superior to devices that do not control the tissue destruction based on actual tissue temperature measurements, but this will remain theoretical until studies involving a direct comparison are conducted.

There have been a limited number of unexpected procedure-related injuries associated with the use of TUMT, which have prompted the FDA to issue special safety recommendations (see http://www.fda.gov/cdrh/pdf/P000043b.pdf).

Compared to other minimally invasive procedures, TUMT appears to offer the soundest basis for management of BPH, since it has the longest term

follow-up and the largest number of studies completed to date [96,97]. In the 2003 AUA Guidelines [41], TUMT using Prostatron, Targis, CoreTherm or TherMatrx devices was included in treatment options. The EAU guidelines [42] recommend that TUMT should be reserved for patients who prefer to avoid surgery and for high-risk patients presenting with recurrent urinary retention.

TRANSURETHRAL ELECTROVAPORIZATION (TUVP)

This is a modified TURP where a high-frequency electrical current is used to vaporize excess tissue while simultaneously cauterizing. The hospital stay is generally shorter than for TURP with less postoperative catheterization time [89]. The frequency of retrograde ejaculation and incontinence are similar to the TURP operation. About 12% of patients have blood in the urine for a few weeks after surgery [1]. In a 7-year follow-up reported by van Melick *et al* [98], no significant differences were found in subjective or objective results for patients with BPH when TUVP was compared with TURP. This is a relatively new procedure, but the operation offers the advantage of low blood loss and shorter hospitalization. Lasers can also be used as the source of energy for the tissue vaporization process. The AUA guidelines [41] take the position that long-term comparative trials are needed to determine if TUVP is superior to TURP.

TRANSURETHRAL NEEDLE ABLATION (TUNA)

Prostate tissue is heated and killed by microwave needles placed in the BPH nodules. Transrectal ultrasound is needed to insure precise needle placement. The dead tissue sloughs off slowly over days or weeks and symptom improvement is only seen after one to two months. Urine retention is common after the operation and thus a catheter must remain in place for up to a week. One-third of men develop retrograde ejaculation and there is a small risk of erectile dysfunction, but less than 1% of patients develop incontinence [1]. TUNA is regarded by the AUA as an effective treatment in partially relieving symptoms of BPH [41].

LASER-BASED PROCEDURES

The laser is merely a source of energy which can be used to coagulate, incise, vaporize, resect and dissect, all fundamentally different procedures. There are also a number of different types of lasers with different wavelengths, differences in the depth of tissue penetration of the light energy, power, and the mode of energy delivery, i.e. pulsed, continuous wave, etc. Lasers are generally more complex to maintain and operate than for example, a microwave based device. Randomized comparative studies thus far have been of short duration, have involved a very limited number of subjects and are highly dependent on the equipment employed. It is not in keeping with the general goal of this review to examine the various laser based procedures and how they compare with TURP or TUMT since it may be some time before laser techniques are employed on a routine basis in a large number of centers. Even then, the results will no doubt depend on the experience and skill of those doing the procedures, the specific procedure being used, and in particular the type of laser system employed. At this point, generalizations are not particularly meaningful or useful. However, in the next decade it would be reasonable to expect that laser treatments will become well established and popular since they offer some unique advantages.

EMERGING THERAPIES

The emerging therapies interstitial laser coagulation and water-induced thermotherapy are considered by the AUA as having uncertain outcomes which should be discussed with the patient, whereas they recommend that high-intensity focused ultrasound and ethanol injections are sufficiently investigational that they should not be offered outside of the framework of clinical trials.

SUMMARY

It is an understatement to say that invasive procedures are not pleasant to contemplate, nor is the required encounter with a hospital with the associated risks of antibiotic resistant infections, an overworked and perhaps stressed-out staff, and the well documented propensity to errors, sometimes fatal, associated with patient care. In addition, the presence of comorbidity can dramatically increase the risk of adverse events associated with any surgical procedure. Nevertheless, there are circumstances where this is the only alternative if BPH has progressed to the point where life is no longer bearable and medical or alternative treatments are no longer effective. There are a number of minimally invasive options, but most are relatively new and lack long-term data regarding effectiveness and side effects. The exception appears to be TUMT. Also, if one seeks out a center where a particular minimally invasive procedure is frequently carried out with a known local track record and skill developed through experience, then some of the concerns disappear. For example, the Mayo Clinic has pioneered the use of one of the latest laser techniques which uses the

KTP laser [89], and thus would merit consideration as a potential center if one desired this particular approach.

MEDICAL VS. MINIMALLY INVASIVE TREATMENT

Finally, there is the question of the relative merits of drug treatment vs. the minimally invasive approach. Djavan *et al* have addressed this question, using TUMT as the preferred invasive treatment, partly because it is the most extensively characterized. They point out that the improvement in symptoms and voiding function is greater with TUMT than with drug therapy and the associated morbidity is low. TUMT offers long-term improvement, whereas medical treatment must be continued indefinitely. Patients with small prostates and severe baseline symptoms can be treated successfully with TUMT, whereas finasteride for example is relatively ineffective in this situation. However, they also point out that approximately one-third of patients treated with the Targis or Prostatron TUMT devices required either TURP or another intervention two to three years after TUMT [99]. Similar data for CoreTherm does not appear available, but this feedback-controlled procedure with tissue temperature monitoring might be expected to decrease the incidence of under-treatment. Retreatment rates for TURP are by comparison about 6% over three years [90].

WATCHFUL WAITING

Watchful waiting generally implies no medical treatment. The American Urology Association (AUA) "Standard" is as follows: "Patients with mild symptoms of BPH (AUA Symptom Index ≤ 7 and patients with moderate to severe symptoms (AUA Symptom Index ≥ 8) who are not bothered by their symptoms (i.e. they do not interfere with daily activities of living) should be managed using a strategy of watchful waiting." It is also suggested that information regarding the benefits and harms of BPH treatment options should be explained to patients with moderate to severe symptoms who are bothered enough to consider therapy. This "Standard" highlights the dilemma associated with the natural progression of BPH and thus the question of whether to initiate medical treatment rather than watchful waiting, since it does not give guidance in the decision making process with respect to predictors of risk of progression. They are not explicitly introduced into the criteria for the option of watchful waiting. Rather, the "bothersome" nature of the symptoms is clearly the primary factor. Some would argue that there may be advantages to considering the risk of progression in selecting therapy to alter the long-term clinical outcome of the disease [100].

Watchful waiting has been the subject of a few studies. In one type, the primary object was to determine the risk of clinical progression. In the other, the watchful waiting study was actually the placebo arm of an intervention study with either an alpha-blocker or a 5-α-reductase inhibitor or both. Djavan *et al* [101] recently published as study where about 400 men were followed with examinations every 3 months for four years. All had mild LUT symptoms at baseline and were on watchful waiting. Clinical progression was defined as worsening of the IPSS with migration to the moderate or severe symptom group and an increase in IPSS of more than two points. Progression was observed in 13%, 24%, 28% and 31% of patients at 1, 2, 3, and 4 years, respectively. Of these, 19 (4.9%) developed acute urinary retention (AUR) during the four-year follow-up, but only 2 patients required a TURP. The study found that baseline PSA, transition zone volume (TZV) and obstructive symptom score all significantly predicted clinical progression. A baseline PSA cut-off of 1.5 ng/mL and a TZV of 20mL accurately predicted clinical progression in 82% of the cohort.

In a study that reported in 1995 [102] with an extended follow-up report in 1998, Flanigan *et al* [103] used the crossover from watchful waiting to TRUP as a measure of failure of watchful waiting. Patients were randomly assigned to either a TRUP or a watchful waiting group. The failure rate for the watchful waiting group at 5 years was 36%. Men with low baseline peak flow rates who were randomized to TURP had an 85% greater improvement in peak flow as compared to men randomized to watchful waiting who eventually crossed over and had surgery. No difference, however, was seen in adverse outcomes. The authors also note that the symptoms of some watchful waiting patients actually stabilized or regressed without treatment. It is also possible that those who regressed did not have BPH.

In a landmark study, McConnell *et al* [59] examined the long-term effect of doxazosin (alpha-blocker),

finasteride (5-α-reductdase inhibitor), or both on the clinical progression of BPH. The placebo arm, which was equivalent to watchful waiting, revealed the following: at 4 years, 17% experienced clinical progression, including 14 % that had a greater than 4 point increase in AUA Symptom Index score, and 2% experienced AUR. A mean increase of 2.7 points in the AUA Index was perceived by patients as a worsening of their condition, although patients with high baseline scores required only 1.2 points and those in the lowest score level needed 3.3 points to have the same perceived level of worsening. Thus the 4-point change was a significant marker. Invasive therapy due to BPH was required by 5% of the placebo group. The men were at least 50 years old, had AUA Symptom scores of 8 to 30 (moderate to severe). In this placebo group, baseline prostate volume, PSA, maximum urinary flow rate, and severity of symptoms individually predicted the risk of clinical progression.

Watchful waiting can involve so-called self-management which may improve the effectiveness of this strategy [104]. Self-management interventions include education, reassurance, fluid management, caffeine restriction, bladder retraining and avoiding if possible medication, both prescription and over-the-counter, that aggravates BPH. The principal component of reassurance involves the question of the presence or absence of prostate cancer. As pointed out above, a high level of certainty would require one or more biopsies with their attendant low but finite morbidity. Fluid management mainly involves both the quantity of fluid intake and the timing relative to daily activities and as well minimizing nocturia. Caffeine is known to aggravate the symptoms, thus it should be minimized or eliminated by avoiding coffee, tea, and caffeine containing soft drinks. A large number of medications are implicated, including diuretics, antidepressants, anti-spasmodics, anti-parkinsonism drugs, calcium channel blockers and finally, decongestants and anti-histamines which are widely available over-the-counter [104]. Consultation with a health care professional is of course essential when attempting to minimize the effects of prescription drugs on BPH. Bladder retraining involves attempting to increase the tolerance for the urgent need to urinate and this can ultimately increase the bladder capacity as well as the inter-void time. Bladder training has been shown in many studies to improve urgency, and reduce frequency and nocturia in BPH patients and as well in men and women with so-called overactive bladder [104]

From these and other studies it is clear that BPH is a progressive disease that can result in acute urinary retention episodes and eventually require invasive procedures such as TURP. However, not all individuals with mild to even moderately severe LUTS or PSA and prostate volume values suggesting high risk actually exhibit progression, and as indicated above, reversal or disappearance of symptoms has been observed. Thus the dilemma and the associated probability really is a "numbers game." In the absence of evidence of progression, watchful waiting is obviously a winning strategy. When there is a high risk or actual evidence of progression deemed worrisome, the risk-reward question comes up since the medical treatments are not without side effect, although they appear rather low and appear to decrease with treatment time. This is a problem that must be sorted out between the patient and his health-care provider. Since phytotherapy is generally associated with minimal or no side effects, the fact that *Serenoa repens* has been found to reduce the incidence of symptomatic progression and AUR is of particularly interest in this context [68,70].

Finally, buying time by either watchful waiting, medical therapy or phytotherapy will also delay when action might be necessary that involves an invasive procedure. This carries the potential benefit that over time there should be continued progress and improvement in minimally invasive procedures, which may have increased effectiveness and a lower level of morbidity than present day methods.

CONCLUSIONS

BPH develops slowly starting at about 40 years of age. A clinical trial aimed at testing a true primary preventive protocol would have to start at age 35-40 years and run for 20 to 40 years with periodic physical exams and questioning regarding LUTS. Half the participants would be randomized to a placebo. Such a study would be very expensive and difficult to administer over such a long period and will probably never be implemented. Even some of the investigators might not survive for the duration of the study! Thus guidance must come from shorter-term studies which rely on examining the relief of symptoms and the slowing or halting of progression. Extrapolation to long-term prevention

is speculative. Thus in the end, one is left with some difficult questions and related decisions. These include:

- Should phytotherapy with its presumably minimal side effects be initiated at the age of 40-50 as a preventive measure in *asymptomatic men* in the hope of slowing or stopping the renewed growth of the prostate that occurs in many men in this age group? At present, the use of phytotherapy is generally initiated when symptoms appear. In North America, it is almost always initiated by the individual; whereas in Europe it is by the physician. This intervention would be based on extrapolating backward the results of phytotherapy in treating symptoms and decreasing already ongoing progression. Studies are very limited that address the question of whether or not saw palmetto, for example, actually slows or stops progression. It might turn out that additional studies would not support the observed positive result. This is an unavoidable risk at this point in time.
- When symptoms are present which do not immediately demand invasive intervention, there are really only four options, watchful waiting, phytotherapy, alpha-blockers and 5-ARIs. Watchful waiting is a numbers game—there is a certain probability of progression for the population of individuals with a given level of risk of progression. Not everyone will progress, but any given individual has no way of knowing what will happen, only the probabilities. What does one do? The answer will depend on the individual, his tolerance for risk, his reaction to the probabilities of side effects, and in the case alpha-blockers or 5-ARIs, the advice of his physician who must write the prescription. There appears to be no simple answer.
- When medical treatment fails, one is faced with the decision regarding either surgery or the so-called minimally invasive treatments. Here what ultimately happens will be strongly influenced by the local urology scene, the types of treatment and equipment available, and the attitude, beliefs and ultimately the advice of the patient's urologist, who will probably be someone acquired by referral rather than selected. Some patients will have the option of shopping around at the major urology centers in search of "the best" but most will not have that luxury. Asking for a TUMT rather than a TURP will probably produce a wide spectrum of reactions from one urologist to another, but the patient should keep focused on the basic principle that it is his body that is about to be subjected to the procedure and he should have a voice in the matter.

As suggested above, life is never simple, especially when it comes to medical problems. However, the studies discussed above also indicate lifestyle changes that might prove effective in preventing BPH. These include exercise, taking steps to attempt to avoid developing the metabolic syndrome or adult-onset diabetes, and as well considering limited alcohol consumption. The evidence that supplementation with vitamin E, selenium and lycopene might enhance a prevention program should also be considered.

Please see Part I for references

INTERNATIONAL HEALTH NEWS is published 10 times a year by:

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E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com
ISSN 1203-1933