INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 159 **JULY/AUGUST 2005** **14th YEAR**

Welcome to our summer issue – and what a banner issue this is! Bill Ware contributes the next segment in our new series on prostate problems. In his article Bill provides a thorough discussion of benign prostate hyperplasia (BPH or enlarged prostate) with particular emphasis on its causes, diagnosis, and prevention. In the next issue Bill will cover conventional and alternative treatment of this very common ailment among older men.

Our New Zealand correspondent, Maurice McKeown, contributes a thought-provoking article on the latest findings regarding travellers' DVT (deep vein thrombosis) with specific emphasis on the role of aspirin and natural supplements in the prevention of thrombosis in general and DVT in particular.

Also in this issue we report that some polyunsaturated fatty acids can increase cataract risk; breast cancer has been linked to depression; the recommended daily intake of selenium may need an upward revision; vitamin C requirement increases during pregnancy; kidney stone risk can be reduced through diet; and much, much more.

I have just 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 and a great summer,
Hans

July/August Highlights

Breast cancer linked to depression

TEHRAN, IRAN. Many women believe that stress and depression increase the risk of breast cancer. Iranian researchers have now confirmed this belief. Their study involved 3000 women attending a breast cancer screening clinic in Tehran during the period 1997-1999. Data were collected regarding age, education, marital status, age at first menstruation, age at first full-term pregnancy, family history of breast cancer, menopausal status, oral contraceptive use, presence of depression and anxiety, and overall health. A diagnosis of breast cancer was made for 243 patients. The data for these patients were combined with that from 486 cancer-free controls and analyzed.

The researchers confirmed that early age at first menstruation (menarche) and a family history of breast cancer are potent risk factors for breast cancer. However, they also found a strong association between depression, anxiety, a feeling

of hopelessness, and loss of interest and pleasures and the risk of breast cancer. Women who were depressed and hopeless had almost twice the risk of developing breast cancer than did more cheerful and upbeat women even after allowing for other known risk factors.

Montazeri, A, et al. The role of depression in the development of breast cancer: analysis of registry data from a single institute. **Asian Pacific Journal of Cancer Prevention**, *Vol. 5, No. 3, July-Sept. 2004, pp. 316-19*

Mediterranean diet adds years to your life

ATHENS, GREECE. A large European study has concluded that the 'Mediterranean diet' can reduce mortality among the elderly. A total of 74,607 healthy participants aged 60 or over were assessed by researchers at the University of Athens Medical School. The participants came from nine European countries, and were taking part in the ongoing European Prospective Investigation into Cancer and Nutrition (EPIC) study. They were assessed for lifestyle, medical history, smoking, physical activity levels, and other relevant factors. Adherence to the Mediterranean diet was rated on a ten-point scale.

After an average 89 months of follow-up 4047 of the participants had died with most deaths occurring in the Danish, Swedish and UK cohorts. The researchers found that a higher intake of vegetables, legumes, fruits, cereals, fish, olive oil, and a moderate intake of wine, together with a lower intake of saturated fats, dairy products and meat were linked with longer life expectancy. Specifically, a two-point increase on the Mediterranean diet scale was linked to an 8 per cent reduction in risk of death, and four points were associated with a 14 per cent reduction.

In countries with a low intake of olive oil, total unsaturated fat intake was measured instead, which may explain why the links were stronger in Greece and Spain where olive oil use is more common. The Mediterranean diet has been the focus of many studies, as many of its components have been linked to improvements in chronic diseases, including heart disease. The new study adds to the evidence of a health benefit by showing an effect in a large and varied population. The researchers conclude that adherence to a Mediterranean type diet may be particularly appropriate for elderly people, who represent a rapidly growing group in Europe.

Trichopoulou, A et al. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. ***British Medical Journal,*** *Vol. 330, April 2005, pp. 799-805*

PUFAs can increase cataract risk

BOSTON, MASSACHUSETTS. Age-related cataracts are very common in elderly people and are the leading cause of blindness in the world. They cause cloudiness in the lens of the eye, which can be corrected surgically, but at a large social and medical cost.

A team of researchers at Tufts University has investigated some of the ways in which dietary fat is related to lens cell membrane composition and function. They gathered data from 440 women aged 53 to 73 years. The participants were recruited from the Nurses' Health Study in 1976. Over the next 10 to 15 years, the women's intake of polyunsaturated fats (PUFAs) was measured five times. PUFAs consist of omega-6 and omega-3 fats; both generally considered healthy elements of the diet. Omega-3 fats are present in flax seed and canola oils, and fish oils. Omega-6 fats are found in most common vegetable oils such as safflower, sunflower, corn and soy oils. Of all the fatty acids found in foods, only two, linoleic acid (LA) and alpha-linolenic acid (ALA), cannot be made in the body and thus are essential. However, small amounts are adequate to avoid deficiency. LA and ALA are present in the lens membrane, and may become oxidized, so high concentrations could lead to free radical damage and cloudiness in the lens.

The researchers found an increased risk of developing cataracts when long-term intake of either LA or ALA was increased. Women in the highest quartile for LA and ALA intake were at more than double the risk of developing a cataract. This link applied to age-related nuclear cataracts, the most common type, but not to cortical or subcapsular cataracts. The researchers noted that the average intake of linoleic acid was almost 10

times the intake of alpha-linolenic acid; they surmise that linoleic acid may be the major culprit in cataract formation, but suggest that further study is needed to clarify the relation between dietary fat and cataract risk. Previous findings also indicate that a high intake of omega-6 fats can be damaging to health, and suggest that the ratio of omega-6 to omega-3 fats needs to be kept low. Experts also point out that early humans would not have had access to the liquid vegetable oils that are so widely available today.

Lu, M et al. Dietary fat intake and early age-related lens opacities. ***American Journal of Clinical Nutrition****, Vol. 81, April 2005, pp. 773-779*

RDA for selenium may need revision

BEIJING, CHINA. Deficiency of the micronutrient selenium is common in many developing countries. Selenium is of fundamental importance to human health, as it is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defence systems, and immune function. An intake consistently below the recommended dietary allowance (RDA) for adults of 55 micrograms per day could therefore have several potential public health implications.

Researchers from the Chinese Academy of Preventive Medicine measured the effects of selenium supplementation in two forms: selenite, an inorganic salt, and selenomethionine, an organic form of selenium. Selenomethionine is the major form of selenium found in food. They recruited 120 men and women in China who were deficient in selenium, and monitored their selenium status by measuring plasma levels of glutathione peroxidase and selenoprotein P. Before the study, the participants had an average selenium intake of 10 mcg per day. They were randomized and given supplements for 20 weeks at various doses from zero to 66 mcg per day, or placebo. Results showed that optimum levels of glutathione peroxidase were reached with 37 mcg when given as selenomethionine, and with 66 mcg as selenite. However, optimum levels of selenoprotein P were not reached at all, leading the researchers to conclude that this is a better indicator of selenium nutritional status. Optimization of selenoprotein P would require either a longer period of supplementation or higher doses, they suggest. They also point out that the RDA was set based on studies using glutathione peroxidase, so propose that the recommendation should be revised on the basis of selenoprotein P. Regarding the form of supplementation, the study demonstrates that selenomethionine has nearly double the bioavailability of selenite and is thus superior for increasing selenium status. This work supports previous studies which have demonstrated superior absorption rates with selenomethionine as compared to selenite.

Xia, Y et al. Effectiveness of selenium supplements in a low-selenium area of China. ***American Journal of Clinical Nutrition****, Vol. 81, April 2005, pp. 829-834*

Vitamin C requirement increases during pregnancy

MEXICO CITY, MEXICO. Premature rupture of the chorioamniotic membranes (PROM) affects up to 20 per cent of all pregnancies. If these membranes, which enclose the fetus and amniotic fluid, rupture too soon, and the waters break, the fetus can be put at risk of premature birth. Because vitamin C plays an important role in maintaining these membranes, inadequate availability of vitamin C during pregnancy may be a risk factor for PROM.

Previous studies have linked low maternal levels of vitamin C with an increased risk of PROM, but it is not known whether supplementation could help reduce this risk. Researchers from Mexico's National Institute of Perinatology investigated the effects of vitamin C supplements. They recruited 120 women who were halfway through their pregnancy. Half were given 100 mg vitamin C per day and the other half received a placebo until week 36 of pregnancy. Vitamin C concentrations were measured in plasma and leukocytes (white blood cells) every four weeks. All of the women's plasma levels of vitamin C dropped during the study, but leukocyte levels of vitamin C, a measure of stored vitamin C, increased in the supplement group. PROM occurred in 25 per cent of pregnancies in the placebo group and 8 per cent in the supplement group. This equates to a protective effect of 74 per cent. However, supplementation did not affect the incidence of preterm delivery.

The researchers conclude that daily supplementation with 100 mg vitamin C after 20 weeks of gestation is effective at reducing the

incidence of PROM. Because PROM may be responsible for 40 per cent or more of all cases of preterm delivery, vitamin C supplements may be a valuable tool in sustaining pregnancy to term, they report. They add that it would be worthwhile to develop educational programs to promote adequate intakes of vitamin C through diet rather than reliance on supplements during pregnancy, and suggest that it might be necessary to adjust the current recommended dietary allowance for pregnant women.

Casanueva, E et al. Vitamin C supplementation to prevent premature rupture of the chorioamniotic membranes: a randomized trial. ***American Journal of Clinical Nutrition****, Vol. 81, April 2005, pp. 859-863*

Editor's comment: Extensive research has shown that it takes at least 400 mg/day of vitamin C to saturate blood plasma. It is possible that the incidence of PROM could be even further reduced by supplementing with higher doses.

HRT increases risk and severity of stroke

NOTTINGHAM, UNITED KINGDOM. It is widely believed that estrogen is a protective agent that may reduce stroke risk. This is thought to explain the relatively low risk of stroke in premenopausal women which rapidly increases following menopause. Hormone replacement therapy (HRT) supplies the body with synthetic or artificial estrogen alone or estrogen and progesterone combined with the aim of reducing menopausal symptoms and bone loss. Early studies suggested that women on HRT have less heart and blood vessel disease, but these studies were observational and open to bias. On the other hand, some trials have indicated that there is a possible link between HRT and an increased risk of stroke.

Researchers at the University of Nottingham reviewed the results of 28 reliable HRT trials including a total of 39,769 participants. Using a well-established analysis tool they found HRT to be associated with a 29 per cent increase in overall risk of stroke. This increased risk was particularly strong for ischemic stroke, in which part of the brain does not get sufficient blood for a period of time. Stroke severity was also greater in women on HRT, who were 56 per cent more likely to have a stroke leading to death or disability. HRT did not significantly increase the risk of hemorrhagic stroke (caused by bleeding in the brain) or transient ischemic attack ('mini-stroke'), but in none of the studies did HRT reduce stroke risk.

The authors report that it remains unclear why HRT should increase rates of ischemic stroke and its severity. They speculated that progesterone might be the likely cause, since progestogens can promote atherogenesis and vasoconstriction (restriction of the blood flow in blood vessels), but further analysis of the studies did not support this theory. Given these findings, HRT cannot be recommended for the primary or secondary prevention of stroke, and it may not be safe for women at high risk of stroke, they conclude.

Bath, P M W and Gray, L J. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. ***British Medical Journal****, Vol. 330, February 2005, pp. 342-345*

Kidney stone risk can be reduced through diet

BONN, GERMANY. Kidney stones affect up to 10 per cent of adults in developed countries at some point in their lifetime. They develop in the urinary system, usually due to an increase in dissolved solids in the urine. Crystals begin to stick together and slowly form a stone which may grow for months or years before it causes symptoms. Nutrition is widely believed to play a role in calcium oxalate stones, the most common type of kidney stone. Earlier studies have focused on individual dietary constituents, so researchers from the University of Bonn undertook a study of a specially-designed diet to prevent recurrence in patients with previous calcium oxalate stones.

They recruited 107 men and women and compared their urine composition while on their normal diet and after a week spent on a diet incorporating food advised for the prevention of stone recurrence. This consisted of increased intake of water (to 2.5 liters per day), fiber, potassium and vitamin B6, and a decreased intake of protein, sodium, fat and cholesterol, and no alcohol. Results showed high levels of metabolic abnormalities linked to stone formation on their normal diets, but a significant

reduction on the study diet. This manifested through an increase in volume of urine, increased pH (reduced acidity) and increased levels of citrate, a key inhibitor of stone formation. Calcium and uric acid levels in the urine were reduced on the stone-preventing diet. Analysis of the participants' usual diet identified low fluid intake, excretion of less than two liters of urine per day, and increased intake of protein and alcohol as the most important risk factors. These have also been highlighted in previous studies. The shift to a nutritionally balanced diet according to the recommendations for kidney stone formers reduced the risk of further stones by 42 per cent, the researchers conclude.

Siener, R et al. The efficacy of dietary intervention on urinary risk factors for stone formation in recurrent calcium oxalate stone patients. ***Journal of Urology****, Vol. 173, May 2005, pp. 1601-1605*

Daily treatment may be unnecessary for mild asthma patients

SAN FRANCISCO, CALIFORNIA. Millions of people take asthma medication regularly to alleviate their wheezing, coughing, and chest tightness. Standard treatment usually comprises two drugs: a bronchodilator medication for immediate relief through the stimulation of beta-receptors in the autonomic nervous system, and daily use of inhaled corticosteroids to reduce airway inflammation and minimize risk of severe asthma attacks and airway scarring that might permanently reduce lung capacity.

Now researchers from the University of California, San Francisco have questioned the recommendation for daily therapy, especially as many patients use it irregularly. They monitored 225 adults with mild persistent asthma for a year. The patients were all instructed to take medication for several days when they felt symptoms come on. They were then randomized to twice daily treatment with either a budesonide inhaler (a corticosteroid known as Pulmicort) and placebo pills, or zafirlukast pills (an anti-leukotriene known as Zyflo or Singulair) and a placebo inhaler, or placebo pills and a placebo inhaler. At the end of the study, there was no significant difference between the groups regarding peak expiratory flow (PEF), which measures how well a person can expel air from their lungs. Average PEF increased by eight per cent in each group. Comparable rates of asthma exacerbations were also found. Daily budesonide led to a greater number of symptom-free days and less bronchial inflammation, but did not significantly reduce the risk of severe attacks or prevent loss of pulmonary function. Daily zafirlukast showed no benefit over medication taken only in response to symptoms.

The researchers conclude that short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen may be the best approach for mild persistent asthma. However, they encourage further studies to support this approach, which could reduce medical costs and decrease the adverse effects of medication. Around a quarter of all people with asthma have mild persistent asthma, defined as symptoms on two to six days of the week, or waking in the night due to asthma two or three times a month. It is well established that patients with moderate or severe asthma require anti-inflammatory drugs every day.

Boushey, H A et al. Daily versus as-needed corticosteroids for mild persistent asthma. ***The New England Journal of Medicine****, Vol. 352, April 2005, pp. 1519-1528*

NEWSBRIEFS

Herbal medicines regulated in Europe. Herbal medicines are immensely popular in Germany, France and Italy, but considerably less so in the UK. Sales (at wholesale level) exceeded $2 billion in 2003 in Germany alone. German health insurance covers such products as ginkgo biloba, St. John's wort, mistletoe, saw palmetto, ivy, hawthorn, stinging nettle root, myrtol (a highly effective remedy against bronchitis), phytosterols, and cucurbita (pumpkin seeds). A drive, presumably by the pharmaceutical companies, to make herbs undergo the same clinical trials as specified for new drugs would seem to have lost out within the European Union. Herbal products can now be approved and marketed if the producer can demonstrate, through detailed references to published scientific literature, that the product is safe and effective. It must also have been used medicinally for at least 30 years, including at least 15 years within the European Community. The EU

has established a committee to develop standard indications, specified strength and dose, and any other information necessary for the safe use of herbs.
New England Journal of Medicine, Vol. 352, March 24, 2005, pp. 1176-78

Oysters really do make you feel sexy. Researchers at Barry University in Florida have found high levels of the amino acid N-methyl-d-aspartate in Mediterranean clams. Previous studies have found that this compound increases sex drive by raising testosterone production. The researchers point out that Mediterranean clams are very close cousins to oysters, so it is likely that the presence of N-methyl-d-aspartate is behind the claims that oysters are a powerful aphrodisiac.
New Scientist, March 26, 2005, p. 21

Aircraft are a potent breeding ground for infections. Researchers at the Lahey Clinic Medical Center in Massachusetts have confirmed that one single passenger with SARS infected 18 other passengers on a 3-hour flight from Hong Kong to Beijing in March 2003. Some of the infected passengers were as much as 7 rows away from the source. The researchers recommend that airlines double their ventilation rates during disease outbreaks and point out that passengers can help protect themselves by turning their air blowers so as to deflect stale air from where they are sitting. Frequent hand washing is also important to avoid infection.
New Scientist, March 19, p. 15

Atkins diet does work. The Atkins diet emphasizes protein and limits the intake of carbohydrates. It is effective in promoting weight loss. Its inventor, Dr. Robert Atkins, claimed that the weight loss came about because the digestion of protein requires more energy than the digestion of carbohydrates. A new study carried out at Temple University in Philadelphia suggests that the diet works, not for the reason suggested by Dr. Atkins, but for the simple reason that people on the diet tend to eat less than they otherwise would. The study involved 10 obese, diabetic volunteers who were put on a low-carb diet for 2 weeks while being closely monitored. The researchers found that the volunteers tended to consume about 1000 calories less per day when they were allowed to eat as much low-carb food as they wished. Their insulin sensitivity and blood glucose levels also improved dramatically.
New Scientist, March 19, 2005, p. 12

Travellers' Thrombosis – An Update

by Maurice McKeown

In March last year I presented an article on the risk of deep vein thrombosis (DVT) in travellers. I think it is now appropriate to provide an update. The problem has not disappeared and little has emerged to suggest that official health sources have been able to provide more appropriate advice on preventive measures.

Is aspirin the answer?
Mainstream medicine continues to advocate aspirin as the main (possibly only) suggested preventative anti-thrombosis compound which does not require comprehensive control by doctors. Modern medicine has potent anti-thrombotic agents such as warfarin (Coumadin), but they need to be very carefully controlled and monitored. Aspirin has proved to be a wonderful asset to the human race over the last 100 years. Yet it is well known to have serious side effects. Gastric irritation and even severe hemorrhage are not uncommon. One recent European study claimed that for every Euro spent on aspirin another 75 cents had to be spent on treating its side effects. A new Australian investigation involving 10,000 men and 10,000 women aged 70-74 on low dose aspirin, has concluded that 389 heart attacks and 19 strokes in men and 321 heart attacks and 35 strokes in the women, could be prevented by regular aspirin consumption. (It should be emphasized that this was a theoretical analysis using data from many different investigations.) Unfortunately, it also concluded that 499 men and 572 women, would experience excessive bleeding and 76 men and 54 women would experience brain hemorrhages[1].

Other recent research suggests that aspirin, for some people, may be less effective than previously realised. US researchers have discovered that aspirin's antiplatelet properties, in which the drug stops blood platelets sticking together to form clots,

may be compromised. It seems that more than 30% of recipients may have a genetic make up which results in no beneficial result from aspirin therapy. More recent research has found that aspirin resistance occurred in 32% of a group of patients with stable ischaemic heart disease[2]. Tests are now available to identify individuals suffering from the problem, but they are not widely used[3].

New evidence also suggests that those who take aspirin on a long-term prophylactic basis may also be at risk, as the anti-blood clotting virtues of aspirin may wear off after a relatively short period of regular use. A 2004 Italian study found that aspirin therapy resulted in a decline in the ability of platelets to aggregate after the first two months of therapy. Unfortunately this benefit was short lived. Continuing treatment lead to progressive decreases in the anti-aggregation effect over the following two years[4].

Clearly a sizeable proportion of long-term aspirin users may have a false sense of security if they believe they are getting valuable anti-clotting protection; without a test – they can only hope that they have not developed resistance.

Who is at risk for DVT?
Air travel is associated with a definite risk of DVT. The extent of that risk is largely determined by the health of the individual and the presence of known risk factors.

Some of those personal risk factors are:

- Oral contraceptive or HRT use
- Advanced age
- Diabetes
- Cancer (particularly blood cancers and those of lung and GI tract)
- Unfavourable genes
- Recent surgery (particularly to the lower limbs)
- Circulatory problems
- History of blood clotting
- **Perhaps we might add – a dreadful diet!**

In this age of global everything, travel is a fact of daily life and health tourism is becoming ever more common. People are seeking medical treatment in far off lands where the treatment may be better or cheaper. It is well known that air travel after surgery carries with it a greater risk of thrombosis. After orthopedic surgery, particularly to the lower limb, the risks are particularly high. Now new research suggests that the risk is not confined to post operative situations; it is present in those who travel long distances by air to obtain surgical treatment. Researchers at the Mayo clinic have discovered that patients who traveled more than 5000 miles to receive surgery were 30 times as likely to develop blood clots in the 28 days after surgery as were local patients[5]. Another study in the same issue concluded that the duration of the surgery (longer than 3.5 hours) was a critical increased risk factor.

How can one prevent DVT?
There appear to be four key pillars to the DVT prevention edifice – nutrients, therapeutic agents, exercise, and venous support. Exercise and venous support are not contentious issues. It is widely accepted that regular exercise during travel, particularly of the lower limbs is beneficial if not always practical in the confines of today's economy travel. Suitable flight hose have also been shown to provide substantial protection, as they encourage sluggish blood to flow back to the heart.

Nutrients, in the liquid sense, are a much more contentious issue. The conventional wisdom is that dehydration is to be avoided. Unfortunately there appears to be little evidence to suggest that tea and coffee contribute to it, as widely claimed. Last year a small study at Mount Everest base camp concluded, "*that even when drunk at high altitude where fluid balance is stressed, there is no evidence that tea acts as a diuretic when consumed through natural routes of ingestion by regular tea drinkers, but that it does have a positive effect on mood."[6]* A review of caffeine consumption by athletes in 2002 came to similar conclusions. The study reviewed ten major investigations. It concluded that, *"There is no evidence of a fluid-electrolyte imbalance that is detrimental to exercise performance or health."* **It noted that consumption of identical volumes of water and caffeinated beverages resulted in fluid retention of 81% in the case of water and 84% in the case of the caffeinated beverage**.

Alcohol is also on the hit list of conventional advice. Red wine reduces platelet stickiness and is more likely to be beneficial than detrimental, if consumed in moderation. Consumption of beer and spirits also results in beneficial reduction of platelet stickiness. The key difference is that there is a rebound effect after beer and spirit consumption, which results in increased platelet adhesiveness that may be significant if larger quantities of alcohol are consumed.

The commonest fluid myth is of course the advice to drink copious amounts of water. This seems to be logical advice to combat dehydration. Yet I have been unable to find any supporting research. I should elaborate on the Japanese study I mentioned in my previous article. It was carried out by Japan Airlines Medical Services in 2002. Forty healthy men were placed in a pressure chamber to simulate a nine hour long-haul flight. The 40 male participants received either plain water or an electrolyte solution at regular intervals. The electrolyte beverage, called *Pocari*, contained sodium and potassium (roughly in the ratio 4:1) and carbohydrate. Regular urine samples were taken. The researchers concluded that those who drank the electrolyte fluid had a greater net fluid balance at the end of the simulated flight than those who were drinking plain water. The electrolyte subjects were "*also less likely to show an increased thickness in blood from their legs."*

Can nutrition provide protection?

It seems that some societies are less prone to DVT than others. It has been noted that in Japan DVT after major surgery may be half that experienced in western countries[7]. It has also been reported that in Thailand DVT is very uncommon. An interesting investigation done in 1982 in Thailand concluded that fibrinolytic activity differed dramatically between local Thai people and white Americans living in Thailand. The authors attributed the differences to the consumption of capsicum, which the authors pointed out rapidly results in hypocoagulability of blood[8]. The virtues of the Japanese diet might just be the result of eating Natto regularly. The natto enzyme nattokinase is now being used as an anti-thrombotic agent in pills to prevent DVT in air travellers.

It seems that it may be possible to minimise thrombosis risk with diet. Adherence to a prudent diet seems advisable. There is widespread acceptance that diets high in fruit and vegetables and low in saturated and trans fats are beneficial. But can specific additional items be recommended?

Asian style diets, which contain a variety of spices, appear best. Substances such as chili, ginger, garlic and turmeric (known to inhibit the formation of fibrinogen) seems the best bet. The Japanese food Natto may also provide valuable protection but it is not widely available (or appreciated) outside Japan. The enzyme nattokinase is now a widely available alternative.

Proprietary products for DVT prevention

I have identified two currently available anti-DVT supplements. (A third is in the pipeline; a tomato based anti-coagulant '*Cardioflo*' containing a substance P3 which is present in the yellow jelly-like substance surrounding the pip of the tomato.)

Zinopin is a supplement developed by UK surgeon John Scurr, containing 100 mg of pycnogenol and 150mg of ginger (www.zinopinusa.com)

Pinokinase was developed by Neil Riordan, a DVT victim, and contains pycnogenol and nattokinase (www.flitetabs.com)

There are other natural clot inhibiting compounds available, but they do not seem to have been targeted to prevent travellers' thrombosis – e.g. lumbrokinase (***Boluoke***) (http://canadarna.com)

Readers may intuitively presume that nature may have more to offer than big Pharma. Perhaps it is the ultimate irony that the ultimate natural medicine aspirin has become the ultimate recourse of mainstream medicine in the treatment and prevention of so much, in spite of its limitations.

Most commercial anti-thrombosis products are relatively expensive and concerned travellers may wish to consider a combination of grape seed extract (equal to or better than pine bark products) and nattokinase as a DVT therapy. Both are available through the IHN web store (www.yourhealthbase.com/vitamins.htm).

Dr Johnson did say, "It is better to travel hopefully than it is to have arrived." Perhaps he was right!

On my next brain-bending trip from New Zealand to Europe I shall be consuming a grape seed/nattokinase combination washed down with an electrolyte drink.

References

1. Nelson, MR, et al. Epidemiological modeling of routine use of low-dose aspirin for the primary prevention of coronary heart disease and stroke in those aged 70 years or older. British Medical Journal, Vol. 330, June 4, 2005, p. 1306
2. Coma-Canella, I, et al. Prevalence of aspirin resistance measured by PFA-100. International Journal of Cardiology, Vol. 101, May 11, 2005, pp. 71-76
3. www.accumetrics.com

4. Pulcinelli, FM, et al. Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients. Journal of the American College of Cardiology, Vol. 43, March 17, 2004, pp. 979-84
5. Gajic, O, et al. Long-haul air travel before major surgery: a prescription for thromboembolism? Mayo Clinic Proceedings, Vol. 80, June 2005, pp. 728-31
6. Scott, D, et al. The effect of drinking tea at high altitude on hydration status and mood. European Journal of Applied Physiology, Vol. 91, April 2004, pp. 493-98
7. Seo, N. Postoperative pulmonary thromboembolism. Nippon Rinsho, Vol. 61, October 2003, pp. 1713-19 (article in Japanese – English abstract only)
8. Visudhiphan, S, et al. The relationship between high fibrinolytic activity and daily capsicum ingestion in Thais. American Journal of Clinical Nutrition, Vol. 35, June 1982, pp. 1452-58

RESEARCH REPORT

Benign Prostatic Hyperplasia: A Not So Benign Condition

Part I – Causes, Diagnosis, and Prevention

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

INTRODUCTION

Benign prostatic hyperplasia (BPH) or enlarged prostate refers to changes in the prostate that involve an overgrowth of cells (hyperplasia), which results in nodules that enlarge the gland. It is a disorder that afflicts only humans and dogs. The term benign in this context means no cancer, although general usage, according to the Oxford Dictionary, benign describes a gentle, mild or kindly condition. BPH frequently causes problems that are far from gentle or mild and in fact can be responsible for a number of *Lower Urinary Tract Symptoms* (LUTS) that range from merely bothersome to critical emergency situations involving urinary blockage. In simple terms, the urinary problems arise from the tissue of the enlarged prostate pressing against the urethra and limiting or even completely cutting off the flow. But what is taking place as BPH develops is somewhat more complex. First the bladder tries to overcome the flow restriction by building more muscle, which over time thickens the bladder wall that influences its capacity to expand and store urine. The result is more frequent urination. Eventually the bladder becomes worn out and weak, a condition known as bladder decompensation [1]. Symptoms now include increased urinary urge and frequency, decreased voiding volume and flow rate, nocturia (frequent need to urinate at night), post-voiding dribbling and urine retention. This is an important concern for men as they age because the disorder is highly prevalent and its incidence and severity generally increases with age, ultimately requiring surgery or other invasive interventions in a significant number of older individuals. BPH also has a negative psychological impact associated with worry over urinary symptoms, prostate cancer, and the possibility of total blockage [2]. Preventing or slowing its progression so as to avoid surgery is thus a topic of great interest.

Recorded accounts of men's urinary problems can be traced back to the fifteenth century BC. Hippocrates (fifth century BC) described the urinary obstruction as a condition with poor prognosis and no hope for permanent relief. No significant progress in treating BPH occurred prior to the twentieth century [3]. In Victorian times men with severe urinary symptoms were known to carry catheters in hollow shafts of their walking sticks or umbrellas in order to be able to quickly deal with what has become known as A*cute Urinary Retention* (AUR). Even some cowboys were said to carry catheters in their hats [3]. By the turn of the last century surgical techniques were being used to open the urinary channel but these procedures were crude compared to modern invasive therapy, and no doubt accompanied by a high incidence of morbidity since postoperative infections were common in that era. As will be discussed below, rapid and significant progress has been made in the last few decades with regard to both surgical and non-surgical treatments of BPH. Much of what has been learned regarding the natural history of this disease has in fact come from the placebo arm of drug

intervention studies which allowed the close observation of untreated individuals over a number of years.

BPH is a highly prevalent disease. According to autopsy studies tissue evidence of BPH is present in 20% of men age forty, 60% of age 60 and 90% of men in their 80s [4], although some studies find lower percentages [5]. Disease progression appears to slow after age of 80 [6]. The severity of the problem can be judged by the observation [1] that in about 25% of all men, BPH causes urinary symptoms that are sufficiently disturbing to seek medical advice. In a recent study it was found that there is a 45% risk of developing LUTS/BPH in a symptom-free 45 year-old man over a period of 30 years [7]. It is estimated that by 2020 over 11 million American men each year will require treatment for the symptoms of BPH and the annual cost just in the US now exceeds $8 billion [8]. An aging population is driving a rapid increase in prevalence and underlines the importance of the challenge to diagnose the disease and slow its progression at an early stage and prevent or postpone the situation where surgical intervention is required.

CAUSES OF BPH

It is a commonly held view that BPH is in part a hormone dependent disease, but the details remain unclear. In fact, the etiology of BPH is not well understood and appears multifactorial [1]. Prostate growth occurs during childhood development, but the size of the prostate remains relatively stable from puberty to middle age, after which the growth frequently resumes. Men castrated before puberty never develop BPH. Three hormones (the so-called sex steroids), testosterone (T), dihydrotestosterone (DHT) and the estrogen hormone estradiol (E2) are thought to play a role in the etiology of BPH [9]. Both T and DHT are so-called *androgens* which are hormones that stimulate the activity of male sex organs or control the development of male sex characteristics. All three of these hormones appear to be involved in cell growth within the prostate. Testosterone is converted into the more powerful and active form DHT by the action of the enzyme 5-α-reductase (there are actually two enzyme isoforms). Individuals lacking this enzyme fail to develop male sexual characteristics including a normal prostate gland, an observation which has focused attention on DHT, as has the success of the 5-α-reductase inhibitors in reducing prostate size and improving symptoms. However, studies to date seem merely to underscore the complexity of the relationship of the androgens and estrogen to the etiology of BPH.

Neuhouser *et al* [10] recently reviewed six studies examining the connection between serum steroid hormones with BPH. The results from these studies failed to present a clear or consistent picture of a relationship with comparisons between the lowest and highest quintiles generally not achieving statistical significance. However, one result was of statistical significance—a 3-fold increase in BPH risk for men in the highest vs. the lowest quintile of serum estradiol concentration. Unfortunately, serum levels are not directly correlatable to prostate tissue levels.

Shibata *et al* [9] found from prostate tissue analysis as a function of increasing age that intraprostatic DHT decreased with age. Intraprostatic tissue levels of T and E2 tissue levels remained constant. However, Walsh *et al* earlier found no decrease of DHT prostate tissue levels with age, merely a large scatter of results, and in addition, they found that the DHT levels were the same in BPH and non-BPH tissue [11]. The BPH model of Shibata *et al* involves the decreasing DHT and constant E2 tissue levels producing a "relatively estrogen-dominant status" which induces cell proliferation by some mechanism and thus yields BPH. In a recent study Roberts *et al* [12] found that in older men, there is an association between serum E2 and surrogate measures of BPH that depend on serum levels of bioavailable T. Among men with serum bioavailable T at levels above the median, E2 levels had a dose dependent positive relationship with prostate size. They point out, however, that while androgens and estrogens may act synergistically in BPH as it relates to prostate size, the precise mechanisms that underlie their effects on the maximum flow rate and other symptoms are neither simple nor clear.

Studies that implicate estradiol in the etiology of BPH have stimulated interest in intervening with aromatase enzyme inhibition which decreases the production of E2. The results have been reviewed by Sciarra and Toscano [13]. The drug Atamestane was used in both an open label and randomized, controlled studies. This drug has demonstrated ability to dramatically reduce estradiol levels (40-60%). No improvement in obstructive symptoms was found in one open label and two randomized trials. A possible explanation is that the estrogen reduction is counterbalanced by the observed parallel increase in T and DHT.

This short summary of the hormone connection underscores the present uncertain state of knowledge, the probable complexity of the hormone related mechanisms, and the need for additional research, especially studies that examine the complex biochemistry in the prostate itself rather than attempting to make associations with serum levels. However, this in no way decreases the importance of the observation that 5-α-reductase inhibitors decrease the prostate volume and have beneficial effects on the symptoms of BPH. Finally, as will be discussed below, there is evidence that a damaged prostate vascular system may play an important role in the development of BPH [14].

POSITIVE AND NEGATIVE RISK FACTORS FOR BPH

In this context, reduction of risk is akin to protective or preventive intervention. Risk factors over which one has no control include ethnic background, age and family history. Studies conducted in a number of countries find a high prevalence of moderate to severe urinary problems and while the absolute prevalence varies widely among countries, there are remarkably consistent age-related increases found in prostate volume at autopsy [5]. Based on data collected in the US, a recent study found that Asian men had the lowest risks for nocturia, physician-diagnosed BPH and surgical treatment for severe BPH. The risks for Caucasians and African Americans were similar for most measures of BPH [15]. These results are consistent with an earlier study of the influence of race and ethnicity on BPH in the Health Professionals Follow-Up [16]. The much lower incidence found for those of Asian background is not clear, but may be due to dietary habits such as the consumption of low-fat high-fiber diets which provide an enhanced supply of weak phytoestrogens [17].

Evidence for a genetic contribution to BPH appears quite consistent. Previous family history of either an enlarged prostate or early-onset BPH increases the risk of this disease in descendents by two to four times [18]. However, a family history of prostate cancer does not appear to confer an enhanced risk of BPH, although a family history of bladder cancer was found in to increase the risk by a factor of over two [19]. The connection with bladder cancer may in part be an artifact, since surgery for this cancer can reveal unsuspected prostate cancer.

DIET

Although limited in number, recent studies support a role, albeit relatively minor, of diet in the risk of BPH. In a recent large study, Suzuki *et al* [20] report the results of examining the intake of energy and macronutrients (protein, carbohydrate and various fats) on the risk of BPH based on food frequency questionnaires. Cases were drawn from a cohort of over 51,000 individuals in the Health Professionals Follow-up Study. Four categories of BPH were used: (1) surgery for BPH; (2) high to moderate LUT symptoms; (3) total BPH consisting of the above two categories; and (4) enlarged prostate as detected by DRE. Non-cases were defined as men who had no BPH surgery and those with a low score in a test of urinary tract symptoms. Risk, as measured by odds ratios, rose with increasing total energy intake and in a comparison of highest to lowest quintiles yielded ORs of 1.29 for category (3) and 1.43 for category (2). Total protein intake (energy-adjusted) was positively associated with total BPH (OR = 1.18) and BPH surgery (OR = 1.26). Moderate increased risk was found for eicosapentaenoic (EPA), docosahexaenoic (DHA), and arachidonic (AA) polyunsaturated fatty acids (PUFAs). All other macronutrients failed to show statistically significant associations. Food groups were not studied. The authors comment that the association with the fatty acids should be explored further (the ORs were only marginally above 1.00) because these polyunsaturated fatty acids (PUFA) have been found beneficial in preventing heart disease. The n-3 fatty acids are also implicated in preventing sudden death during a heart attack. The authors also suggest that since these PUFAs are easily oxidized, the findings also suggest a possible role of oxidative stress in the etiology of BPH. The association with total calorie intake was not found in another large study reported in 2001, and in that study there was also no connection between total fat intake and BPH [21]. Additional research will be necessary to resolve these inconsistencies.

In 1999, Yang *et al* [22] reported a comparison between normal controls and patients with BPH, where the parameters studied included serum levels of omega-3 (n-3) and omega-6 (n-6) PUFAs. They found that the n-3 levels were significantly decreased and the n-3/n-6 PUFA ratio was lower for BPH patients relative to controls. This would be consistent with an inflammatory component to the etiology of BPH, but is inconsistent with the results of Suzuki *et al* [20] discussed above which was based on the PUFA content of foods reported in a food frequency questionnaire. The use of serum levels would appear to be a more direct approach to

the question, but blood samples were either not available or not studied by Suzuki *et al*.

In a case control study of BPH patients in Athens, Greece, Lagiou *et al* [23] examined both food groups and some individual foods. They found that among the food groups, only fruits were significantly inversely associated with BPH risk. Increased consumption of both butter and margarine was positively associated with risk, but olive oil was neutral. Among the micronutrients studied, only zinc consumption was found to be associated with BPH risk, in this case increased risk. This is important because of the frequently seen recommendation to take zinc supplements for prostate health.

The connection between alcohol consumption and BPH has been the subject of several recent studies, and in one the combined effect of alcohol and coffee was examined. Neuhouser *et al* [10] have summarized the alcohol consumption studies that occurred between 1992 and 2001. Four studies found significant inverse associations with odds ratios or relative risks ranging from 0.46 to 0.72, i.e. significant protection. One study reported an OR of 0.86 that was not significant, and one found no association. In a study reported in 2004 [24], a significant beneficial trend with alcohol consumption was found with an OR of 0.71 for 3-4 drinks/day, 0.79 for 5-6, and 0.65 for ≥ 7 drinks/day. When the results were stratified according to wine, beer or liquor, the patterns of risk were similar but only marginally significant. The authors also found that the inverse relationship between alcohol and BPH was stronger in subjects with lower body mass index. They suggest an interaction between androgen levels and alcohol.

In a very recently published case control study [15] involving approximately 35,000 male participants ranging in age from 55 to 74, it was also found that alcohol consumption offered significant protection from BPH. Three levels of BPH were used: (1) nocturia—10756 cases; (2) physician diagnosed BPH—526 cases; (3) surgery for BPH—973 cases. Alcohol consumption ranged from < 20 g/day (reference) to ≥ 60 g/day (a glass of table wine contains between 17 and 20 g of alcohol). ORs for low to high consumption for categories (2) and (3) were from 0.8 to 0.6 and 0.7 to 0.4 respectively, with highly significant trends and individual ORs. These ORs indicate a moderate protective effect. Stratification by type of alcoholic beverage produced similar results, but not all ORs were statistically significant.

In one of the studies included in the summary of Neuhouser *et al* [10], the combined effects of coffee and alcohol were examined [25]. Coffee consumption was found to be rather strongly and significantly positively associated with BPH risk. When controls having no BPH were used, the ORs for BPH among coffee users was 2.20 for 1-4 cups and 2.74 for > 4 cups/day. The combined intake of one or more glasses of an alcoholic drink and 1,2 or 3 cups of coffee/day resulted in ORs will below 1.00, but only the results for one cup of coffee/day were statistically significant (OR = 0.13). Other studies that have examined the connection between coffee and BPH are inconsistent and the mechanism whereby coffee increases the BPH risk is unknown. Also, filtered coffee has a different lipid composition than non-filtered coffee, which confuses the issue. The authors suggest that men drinking more than four cups of unfiltered coffee daily should also drink some alcohol. However, no data in this context appears available regarding the relative risks of filtered vs. unfiltered coffee.

In connection with cardiovascular disease risk, it is common to see the recommendation of up to three glasses of wine or the equivalent per day as a preventive measure for men. In fact, a recently published study found that the risk of extensive coronary calcification, a measure of atherosclerosis, was 50% lower in individuals who consumed one to two alcoholic drinks per day as compared to non-drinkers [26]. However, more than two drinks a day eliminated the benefit. Although “more than three” was not included in the data workup, three drinks a day may still be protective in this context. The studies discussed above would appear indicate that two or three alcoholic drinks such as beer or wine might also reduce the risk of BPH by around 30-50%.

MICRONUTRIENTS

The relationship between micronutrient intake and BPH risk has been the subject of only a limited number of studies. One of the most recent [27], which examined the connection with a number of micronutrients, involved men who participated in the Third National Health and Nutrition Examination Survey. In this case control study the cases had three of the following four LUT symptoms, as ascertained by an interview: nocturia, hesitancy, incomplete emptying of the bladder and a weak stream. Controls were men without symptoms. Serum levels of vitamins A, C and E, α- and β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene and selenium were determined and compared in cases and controls. The only

statistically significant lower serum levels in cases vs. controls were found for vitamin E, lycopene and selenium. When the data was examined in terms of quintiles of micronutrient concentration, there were no statistically significant trends with serum level but the odds ratios for these three micronutrients clustered around 0.5 to 0.75, suggesting that men with higher levels of circulating vitamin E, selenium and lycopene had a reduced risk of LUTS and thus presumably BPH. High serum levels of vitamin C appeared to be highly protective for current smokers (OR = 0.1, 95% confidence limits 0.02-0.67). On the other hand, for individuals who had never smoked, comparison of the highest with the lowest vitamin C quintile yielded an OR of 3.61 with 95% confidence limits of 1.10 and 11.85. No significant associations were found with the other micronutrients studies. The authors suggest that the mechanism of action of lycopene may be associated with its ability to quench singlet oxygen and thus reduce oxidative damage. They hypothesized that the inverse association with selenium may be due to its being a constituent of glutathione peroxidase, which is a potent free radical quencher and is also know to inhibit cell growth. The positive association in non-smokers with high intakes of vitamin C was attributed to the possibility of this vitamin becoming pro-oxidative at high concentrations. No theory was offered for the protective effect observed for current smokers. It is interesting that the three micronutrients identified as possibly important in the context of LUTS and BPH have also been implicated as protective for prostate cancer.

A number of epidemiologic, clinical and *in vitro* data suggest that phytoestrogens are involved in the pathogenesis of BPH [28]. Dietary sources include tea, fruits and vegetables and in particular soy and soy products. High phytoestrogen intake has been suggested by many observers as an explanation for the difference in incidence of BPH between Far East and Western countries. The results of a recent study [28] address this matter. Prostate tissue levels of two phytoestrogens, enterolactone and genistein, were determined in a series of men undergoing surgery to relieve the symptoms of BPH. It was found that genistein tissue levels were significantly greater in men with small prostate volumes as compared to those with large volumes. No significant correlation was found for enterolactone. Genistein is thought to be biologically the most active isoflavone in soy products. The authors suggest that a possible mechanism for the influence of genistein on the incidence of BPH is that it inhibits the degradation of vitamin D which is implicated in prostate health. While these results do not prove a cause and effect relationship, they carry an implication of benefit in the context of BPH. A number of mechanisms have been proposed for the action of phytoestrogens in the prostate but what is clear is that there is still a lack of detained knowledge regarding the interplay of hormones, enzymes and weak estrogen-like compounds in this gland [29]. There may also be a risks associated with disturbing the hormone balance with substances having estrogenic properties.

A natural conclusion based on the above results would be that supplementation with vitamin E, selenium and lycopene and perhaps consuming modest quantities of soy containing foods might be worth considering. Unfortunately, there appear to be no randomized intervention studies that address this issue, and it may be decades before such studies are conducted, if ever. Furthermore the amounts in the form of supplements that might be effective are unknown and the doses safety of some supplemental forms has never been investigated. Lycopene can be obtained from cooked tomato products, the best being tomato paste, whereas raw tomatoes are a poor source. Genistein can of course be obtained by eating soy products such as tofu (bean curd). For these two phytochemicals, food sources appear attractive and may in fact contain other beneficial substances. The selenium content of foods is highly variable since it depends on soil concentrations. Only small amounts of vitamin E are available in food compared to the amounts many individuals take in the form of supplements. Guidance regarding supplementation with these two micronutrients can perhaps be obtained from the fact that an ongoing, multicenter clinical study of vitamin E and selenium as protective agents for prostate cancer is using supplementation of 200 micrograms of selenomethionine and 400 IU of synthetic vitamin E a day, amounts deemed safe for a study involving over 30,000 participants.

A recent review concerning the safety of vitamins E and C should reassure individuals worried by recent media coverage of the “dangers” of taking these supplements. In this review of the scientific literature, no consistent evidence was found for adverse events among healthy individuals or those with a range of diseases for daily intakes of up to 1600 IU (equivalent to about 1000 mg of natural vitamin E) or up to 2000 mg of vitamin C [30].

BPH, DIABETES, CARDIOVASCULAR DISEASE AND THE METABOLIC SYNDROME

The hypothesis that there is an association between BPH and diabetes has been around for over 30 years but still no consensus exists. Diabetes can eventually produce bladder dysfunction which involves neuropathy. Impaired detrusor (muscle involved in bladder emptying) function results in lower flow rates and can increase residual (postvoid) urine. But BPH can also cause the same lower urinary tract symptoms even though the underlying pathology is different since BPH does not directly impair detrusor function but rather enhances bladder outlet resistance by mechanisms that are both static and dynamic. In addition, both diabetes and BPH increase with age and a fraction of patients with BPH also suffer from diabetes and vice versa. The question then is whether the incidence of comorbidity of these two diseases is greater than would be expected by chance, i.e. is diabetes an independent risk factor for BPH.

Hammarsten and Högstedt have examined this question in a direct manner by examining the correlation between the rate of prostate volume change in both non-insulin dependent diabetes mellitus (NIDDM) and in individuals with the metabolic syndrome, a condition closely related to diabetes, and also in individuals with elevated insulin levels [31,32]. Since gland growth in BPH occurs in the transition zone (TZ), the authors used transrectal ultrasound to determine the TZ volume. They established that there was a linear and highly significant correlation between the total prostate volume and the TZ volume, and thus the former was a valid measure of BPH. Prostate growth rates were calculated assuming that the prostate had a volume of 20 mL at age 40. Prostate growth rates were obtained for 307 patients. Those with metabolic disease, NIDDM, treated-hypertension, obesity and dyslipidemia all had prostate growth rates significantly greater than controls. When the fasting insulin was stratified by quartiles, those in the first quartile (< 7 mU/L) had an annual growth rate of 0.84 mL whereas in the highest quartile of plasma insulin (>13 mU/L), the growth rate was 1.49 mL/year, and this difference was statistically significant. The authors regard these results as supporting the hypothesis of a relationship between BPH and diabetes, the metabolic syndrome, and hyperinsulinemia. This hypothesis is further supported by the observation that diabetes is associated with greater BPH symptom severity even after age adjustment [33]. It is also clear from these and other studies [34] that BPH and cardiovascular disease(CVD) share a common set of risk factors, it also appears that CVD is a risk factor for BPH [21,35]. In fact, when studies segregated age-matched patient populations according to clinical signs of CVD, atherosclerosis and hypertension vs. those without [35] , patients with overt vascular pathology were at a much higher risk for BPH than those where this pathology was absent, independent of age.

The question of the mechanism involved in the observed connection between diabetes, vascular disease and BPH was recently examined by Berger *et al* [14] using a novel approach. They employed computer-assisted quantification of color Doppler ultrasound to examine the patterns of blood flow in normal prostates and prostates in patients with NIDDM. The hypothesis was that diabetes-related vascular damage, a well-established phenomenon, might extent to the prostate. Such damage is known to reduce the available oxygen (hypoxia) and in prostate cell culture studies, hypoxia caused increased growth factor production [36,37] which could trigger prostate growth. The ultrasound technique permitted the examination of circulation in both the peripheral zone (PZ) and the transition zone (TZ). Significant reduced circulation was observed in the TZ of diabetic patients as compared to non-diabetic patients, whereas there were no differences in the circulation in the PZ. It will be recalled that the prostate growth in BPH occurs in the TZ. TZ circulation of patients with non-diabetic BPH as well as those with diabetes was significantly lower than controls, but no differences were found for the PZ. The authors conclude that these results indicate considerable vascular damage in the TZ of diabetic patients and this may contribute to the pathogenesis of BPH, perhaps via hypoxia. Thus action aimed at decreasing the risk of metabolic syndrome or adult-onset diabetes may be effective in reducing the risk of BPH. Obviously other health benefits would also accrue from such action.

Moyad [38] has recently reviewed the connection between obesity, physical activity and BPH. The strongest connection is with the waist-to-hip ratio (incidentally a metabolic syndrome factor), which is an indication of abdominal obesity. Abdominal fat may increase estrogen levels, providing the link to BPH. Hammarsten and Högsten in fact also observed a significant correlation between the waist-to-hip ratio and prostate growth rates [31], and Dahle *et al* [39] found that abdominal obesity was associated with a higher risk of BPH. In all the studies reviewed by Moyad, physical activity had a strong and significant impact on the risk of developing BPH. Even walking two to three hours a

week resulted in a 25% reduction in the risk of BPH and in one study, men with the highest level of physical activity compared to the lowest had a 50% reduction in risk.

DIAGNOSIS OF BPH

The lower urinary tract symptoms (LUTS) characteristic of BPH may not in fact be due to this disease. Thus the diagnostic challenge is to differentiate between BPH and other causes of LUTS. Other causes include diabetes (LUTS by a non-BPH mechanism), Parkinson's disease, stroke, urethral stricture caused by scar tissue from catheterization or from a sexually transmitted disease such as gonorrhea, urinary tract infections, prostatitis, bladder cancer, advanced prostate cancer, and bladder stones. A recent study from the Mayo Clinic and Merck in fact identifies seventeen conditions that should be distinguished from BPH as causing LUTS. These include back surgery and stroke, as well as the conditions listed above. This study also found the following percentages of men with LUTS unrelated to BPH: age 50-59, 5.4%; age 60-69, 8.5%, and age > 70, 32.8% [40]. Thus older individuals present a significant diagnostic challenge, and an oversight during the initial evaluation would result in incorrect treatment and even misclassification of subjects in clinical trials. While mild symptoms are easy to ignore, severe symptoms of LUTS such as blood in the urine, recurrent urinary tract infections, bladder stones, or trouble emptying the bladder should not be ignored, since the risk of acute urinary retention or bladder or kidney damage is elevated [1]. Correct diagnosis is critical since it determines treatment.

The American Urology Association (AUA) recommends [41] that for all patients presenting with LUTS suggestive of BPH the initial evaluation should involve a medical history, physical exam including a digital rectal exam (DRE), and a urinalysis to screen for blood and urinary tract infection. It is further recommended that symptoms be assessed with either the AUA Symptom Index or the equivalent International Prostate Symptom Score (IPSS). More extensive testing may be suggested by the results. Similar recommendations have been recently made by the European Association of Urology (EAU) [42]. The success in eliminating non-BPH causes of LUTS will depend on the skill of the diagnostician.

The AUA Symptom Index [41] questionnaire is scored according to the following answers: not at all = 0; less than one time in five = 1; less than half the time = 2; about half the time = 3; more than half the time = 4; almost always = 5. The questions, which all relate to a one month period, are:

1. How often have you had a sensation of not emptying your bladder completely after you finish urinating?
2. How often have you had to urinate again less than two hours after you finished urinating:
3. How often have you found you stopped and started several times when you urinated?
4. How often have you found it difficult to postpone urination?
5. How often have you had a weak urinary stream?
6. How often have you had to push or strain to begin urination?
7. How many times did you most typically get up to urinated from the time you went to bed until the time you got up in the morning? Score according to the number of times with five for five or more.

Symptoms are classified as MILD if the total score is 0-7; MODERATE for 8-18, and SEVERE from 19-35. The IPSS uses the same questions and scoring system. This score is not necessarily diagnostic of BPH but merely indicates severity of LUTS.

The AUA also recommends [41] that the serum prostate-specific antigen (PSA) test be *offered* under the following circumstances: (1) those with at least a 10-year life expectancy and for whom knowledge of the presence of prostate cancer would change the management; or (2) those for whom the PSA measurement may change the management of their voiding symptoms. This brings up the subject of PSA testing, an area of great controversy in urology, even in the context of BPH. The use of the word *offered* in the AUA recommendation speaks volumes.

At issue is the detection of prostate cancer (PC) in patients presenting with LUTS and the use of PSA levels in managing the treatment of BPH. The above recommendation implies that this test will provide an answer to the question of the presence of prostate cancer. Research in the last several years has cast serious doubt on this simple view of the PSA test and highlights the difficulties associated with the exclusion of PC when evaluating patients presenting with LUTS. Most prostate cancers occur in the peripheral zone of the gland and some are palpable, but only a portion of

the surface area of the prostate is accessible via the DRE. When this exam reveals abnormalities, it is normal to pursue further the question of PC. However, the common situation is a non-suspicious DRE, and a normal or elevated PSA. But "elevated" is based on a somewhat arbitrary cut-off. A lengthy discussion of the PSA debate is not appropriate for this review, but the following appears important.

If the offer of a PSA test is accepted, the result will be a number ranging from the lower limit of sensitivity of the test (≈0.2 ng/ mL) to possibly a number over 100 ng/mL. Values above 20 ng/mL are cause for alarm. The "normal" cut-off is 4 ng/mL, above which it is usual practice to suggest a biopsy. But this cut-off is not age-adjusted. However, it is now known that PC, including high-grade cancers, is not rare among men with PSA levels of less than 4.0 ng/mL. Furthermore, PSA levels between 4 and 10 ng/mL occur in men with BPH, and prostate cancer is present in only 25% of patients with PSA in this range [43]. The magnitude of the problem is illustrated by recent results reported by Thompson *et al* published in *The New England Journal of Medicine* [44]. A cohort of 2050 men with normal DRE and PSA that that had been below 4 ng/mL for seven years were enrolled and underwent biopsy at the end of the study. PC was diagnosed in 15.2% of the men and of these, 14.9% had high-grade cancer. Among those with PC, the prevalence of cancer was 6.6% for the group with PSA up to 0.5 ng/ml, 10.1% for those with values between 0.6 and 1.0, 17% for those with values from 1.1 to 2.0, 23.9% for those between 2.1 and 3.0, and 26.9% for those with values between 3.1 and 4.0 ng/mL. The prevalence of high-grade cancer was 12.5% of those with PC for PSA ≤ 0.5 and 25% for PSA in the range 3.1-4.0. Tumor grade is important because if one is old enough, low-grade cancer found in the majority of these cases may not pose a threat. It is well known that most men die with rather than from PC. These results point to the folly of the view that a cut-off of 4 can be used to answer the question, does this patient have cancer, and this cut-off also fails to discriminate low- from high-grade tumors. In fact, if a cut-off of 2.1 had been used, it would have, on the basis of this data, missed 33% of the cancers.

Another problem involves intra-individual variations. A recent study examined this question over four years of annual check-ups. Among men with an abnormal PSA finding, a high proportion had a normal PSA finding at one or more subsequent visits. For those with a PSA greater than 4 ng/mL, i.e. a value that would trigger the recommendation of a biopsy, 44% had at least one normal value on subsequent visits. When a cutoff of 2.5 ng/mL was used similar results were obtained. Thus significant intra-individual variations must be added to the lack of specificity that characterizes this test. The authors suggest that an isolated elevated PSA level should be confirmed several weeks later before proceeding with other tests or to a biopsy [45].

Given that men with BPH have elevated PSA and that PSA tends to increase with age even among the cancer free, and that as Thompson *et al* [44] demonstrated, even a PSA cut-off of 2.1 ng/mL would miss a third of cancers, it would seem that if a definitive answer regarding PC is the goal, the only solution appears to be a biopsy, *or more than one*, as some urologists suggest [1]. This appears to be the position of Dr. P. C. Walsh, the well-known urologist from Johns Hopkins Medical School who is responsible for the development of the nerve-sparing radical prostatectomy procedure [46]. Commenting on the paper by Thompson *et al,* he states, "…if a patient really wants to know whether or not he had cancer, I guess we have to do a biopsy." In fact, based on the experience of Stanford University Urologists, Stamey *et al* [47] have recently taken the position that PSA is only useful in the context of estimating the size of the prostate! However, it is almost inconceivable that the recommendation would be put forward that everyone presenting with LUTS have a biopsy for PC. The term "offered" implies a discussion between patient and physician where the pros and cons and probabilities are considered, and especially what would be the next step if a certain PSA value were found. Such a discussion involves the age, health, life expectancy and attitudes of the patient and perhaps his spouse, and as well, the attitude and knowledge of the physician as regards PSA. It is important to remember that PSA is organ specific but not cancer specific.

There are other more sophisticated PSA tests that show promise for use in the differential diagnosis of BPH vs. PC. These are not routinely done and are not part of either the AUA or EAU general recommendations, but appear definitely worth considering when one is confronted with the problem of the lack of specificity of the PSA test. For example, in a recent study [48] aimed at reducing the number of biopsies in men with non-suspicious DRE and PSA between 4 and 10 ng/mL, it was found that by measuring the free PSA rather than the total PSA, and using a cut-off of ≤ 23% as a criterion for biopsy, 94.4% of cancers would have been detected and 18% of biopsies yielding benign

results would have been avoided. The researchers also found that PSA density, calculated from the prostate volume and total PSA, gave a similar specificity. However, PSA density requires the gland volume, which can only be reliably estimated from transrectal ultrasound or other more expensive imaging techniques. DRE generally underestimates the volume [49]. In the next few years these alternative PSA tests as well as others now under development will no doubt become better characterized and more commonly performed.

It appears well established that PSA has its place in the management of BPH treatment and in particular in assessing the probability of progression, an acute urinary retention episode, or the future need for surgery. A very recent consensus statement at the end of a series of papers on this subject in the *British Journal of Urology International* [50] outlines the current status of this application of PSA levels. The following points are of interest.

- Prostate volume (PV) consistently increases with age and in studies higher baseline PVs were associated with greater growth rates of the prostate. Men with a PV of ≥ 30 ml are 3.5 times more likely to have moderate to severe symptoms, 2.5 times more likely to have decreased flow rates and 3 to 4 times more likely to an AUR episode than men with lower PVs. However, the accuracy of the DRE in determining PV is limited, and MRI in general too expensive. Transrectal ultrasound provides a more accurate measure of PV, but the specialized equipment is not normally used in the physician's office environment. Thus another marker would be useful.
- PSA levels have been shown to be closely related to PV in benign glands, and even low PSA is indicative of an enlarged prostate. Eighty-nine percent of a patient group studied in Holland with PSA of at least 1.5 ng/mL had PV of > 30 mL.
- When a group of patients in the placebo arm of a drug study were examined for a correlation between PSA levels, symptom severity, and risk of AUR or surgery, those in the highest PSA quartile vs. the lowest had greater symptom severity and a higher risk for surgery to treat BPH and also higher risk of an AUR episode.
- Thus PSA appears to be a satisfactory surrogate for PV and to have utility in identifying patients with higher risk of BPH progression. The consensus group [50] concluded that men with a PSA ≥ 1.5 ng/mL should be considered at increased risk of clinically significant BPH progression and therefore should be considered for more aggressive therapy than those with PSA below this limit. For the latter, they suggest symptomatic treatment.

The suggested PSA threshold for aggressive treatment is low and would probably include many older men with BPH. But is must be acknowledged that the consensus group recognizes a pharmaceutical treatment protocol is available which can reduce the size of the prostate and slow or even halt progression, and presumably the view is the earlier the better.

References

1. Scardino PTKJ. Dr. Peter Scardino's Prostate Book. New York: Avery/Penguin Group, 2005.
2. Djavan B, Waldert M, Ghawidel C, Marberger M. Benign prostatic hyperplasia progression and its impact on treatment. Curr.Opin.Urol. 2004;14:45-50.
3. Murphy LJT. The History of Urology. Springfield, Ill: Charles C. Thomas, 1972.
4. Carter HB, Coffey DS. The prostate: an increasing medical problem. Prostate 1990;16:39-48.
5. Jacobsen SJ, Girman CJ, Lieber MM. Natural history of benign prostatic hyperplasia. Urology 2001;58:5-16.
6. Naderi N, Mochtar CA, de la Rosette JJ. Real life practice in the management of benign prostatic hyperplasia. Curr.Opin.Urol. 2004;14:41-4.
7. Bhargava S, Canda AE, Chapple CR. A rational approach to benign prostatic hyperplasia evaluation: recent advances. Curr.Opin.Urol. 2004;14:1-6.
8. Lanes SF, Sulsky S, Walker AM et al. A cost density analysis of benign prostatic hyperplasia. Clin.Ther. 1996;18:993-1004.
9. Shibata Y, Ito K, Suzuki K et al. Changes in the endocrine environment of the human prostate transition zone with aging: simultaneous quantitative analysis of prostatic sex steroids and comparison with human prostatic histological composition. Prostate 2000;42:45-55.
10. Neuhouser ML, Kristal AR, Penson DF. Steroid hormones and hormone-related genetic and lifestyle characteristics as risk factors for benign prostatic hyperplasia: review of epidemiologic literature. Urology 2004;64:201-11.
11. Walsh PC, Hutchins GM, Ewing LL. Tissue content of dihydrotestosterone in human prostatic hyperplasis is not supranormal. J Clin.Invest 1983;72:1772-7.

12. Roberts RO, Jacobson DJ, Rhodes T, Klee GG, Leiber MM, Jacobsen SJ. Serum sex hormones and measures of benign prostatic hyperplasia. Prostate 2004;61:124-31.
13. Sciarra F, Toscano V. Role of estrogens in human benign prostatic hyperplasia. Arch.Androl 2000;44:213-20.
14. Berger AP, Deibl M, Halpern EJ et al. Vascular damage induced by type 2 diabetes mellitus as a risk factor for benign prostatic hyperplasia. Diabetologia 2005;48:784-9.
15. Kang D, Andriole GL, Van De Vooren RC et al. Risk behaviours and benign prostatic hyperplasia. BJU.Int. 2004;93:1241-5.
16. Platz EA, Kawachi I, Rimm EB, Willett WC, Giovannucci E. Race, ethnicity and benign prostatic hyperplasia in the health professionals follow-up study. J Urol. 2000;163:490-5.
17. Denis L, Morton MS, Griffiths K. Diet and its preventive role in prostatic disease. Eur.Urol. 1999;35:377-87.
18. Pearson JD, Lei HH, Beaty TH et al. Familial aggregation of bothersome benign prostatic hyperplasia symptoms. Urology 2003;61:781-5.
19. Negri E, Pelucchi C, Talamini R et al. Family history of cancer and the risk of prostate cancer and benign prostatic hyperplasia. Int.J Cancer 2005;114:648-52.
20. Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. Am.J Clin.Nutr. 2002;75:689-97.
21. Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J.Clin.Epidemiol. 2001;54:935-44.
22. Yang YJ, Lee SH, Hong SJ, Chung BC. Comparison of fatty acid profiles in the serum of patients with prostate cancer and benign prostatic hyperplasia. Clin.Biochem. 1999;32:405-9.
23. Lagiou P, Wuu J, Trichopoulou A, Hsieh CC, Adami HO, Trichopoulos D. Diet and benign prostatic hyperplasia: a study in Greece. Urology 1999;54:284-90.
24. Crispo A, Talamini R, Gallus S et al. Alcohol and the risk of prostate cancer and benign prostatic hyperplasia. Urology 2004;64:717-22.
25. Gass R. Benign prostatic hyperplasia: the opposite effects of alcohol and coffee intake. BJU.Int. 2002;90:649-54.
26. Vliegenthart R, Oei HH, van den Elzen AP et al. Alcohol consumption and coronary calcification in a general population. Arch.Intern.Med 2004;164:2355-60.
27. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. Urology 2004;64:504-9.
28. Brossner C, Petritsch K, Fink K et al. Phytoestrogen tissue levels in benign prostatic hyperplasia and prostate cancer and their association with prostatic diseases. Urology 2004;64:707-11.
29. Morton MS, Turkes A, Denis L, Griffiths K. Can dietary factors influence prostatic disease? BJU.Int. 1999;84:549-54.
30. Hathcock JN, Azzi A, Blumberg J et al. Vitamins E and C are safe across a broad range of intakes. Am.J Clin.Nutr. 2005;81:736-45.
31. Hammarsten J, Hogstedt B. Clinical, anthropometric, metabolic and insulin profile of men with fast annual growth rates of benign prostatic hyperplasia. Blood Press 1999;8:29-36.
32. Hammarsten J, Hogstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur.Urol. 2001;39:151-8.
33. Michel MC, Mehlburger L, Schumacher H, Bressel HU, Goepel M. Effect of diabetes on lower urinary tract symptoms in patients with benign prostatic hyperplasia. J.Urol. 2000;163:1725-9.
34. Sandfeldt L, Hahn RG. Cardiovascular risk factors correlate with prostate size in men with bladder outlet obstruction. BJU.Int. 2003;92:64-8.
35. Weisman KM, Larijani GE, Goldstein MR, Goldberg ME. Relationship between benign prostatic hyperplasia and history of coronary artery disease in elderly men. Pharmacotherapy 2000;20:383-6.
36. Berger AP, Kofler K, Bektic J et al. Increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia. Prostate 2003;57:57-65.
37. Ghafar MA, Puchner PJ, Anastasiadis AG, Cabelin MA, Buttyan R. Does the prostatic vascular system contribute to the development of benign prostatic hyperplasia? Curr.Urol.Rep. 2002;3:292-6.
38. Moyad MA. Lifestyle changes to prevent BPH: heart healthy = prostate healthy. Urol.Nurs. 2003;23:439-41.
39. Dahle SE, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. J Urol. 2002;168:599-604.
40. Gades NM, Jacobson DJ, Girman CJ, Roberts RO, Lieber MM, Jacobsen SJ. Prevalence of conditions potentially associated with lower urinary tract symptoms in men. BJU Int. 2005;95:549-53.
41. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. J.Urol. 2003;170:530-47.
42. Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms

suggestive of benign prostatic obstruction (BPH guidelines). Eur.Urol. 2004;46:547-54.
43. Denmeade SR, Isaacs JT. The role of prostate-specific antigen in the clinical evaluation of prostatic disease. BJU.Int. 2004;93 Suppl 1:10-5.
44. Thompson IM, Pauler DK, Goodman PJ et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N.Engl.J Med. 2004;350:2239-46.
45. Eastham JA, Riedel E, Scardino PT et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003;289:2695-700.
46. Walsch P. Editorial comment on N Eng J Med,2004; 350:2239. J Urol 2004;172:550.
47. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? J.Urol. 2004;172:1297-301.
48. Martinez-Pineiro L, Garcia Mediero JM, Gonzalez GP et al. Probability of prostate cancer as a function of the percentage of free prostate-specific antigen in patients with a non-suspicious rectal examination and total prostate-specific antigen of 4-10 ng/ml. World J Urol. 2004;22:124-31.
49. Roehrborn CG, Girman CJ, Rhodes T et al. Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. Urology 1997;49:548-57.
50. Bartsch G, Fitzpatrick JM, Schalken JA, Isaacs J, Nordling J, Roehrborn CG. Consensus statement: the role of prostate-specific antigen in managing the patient with benign prostatic hyperplasia. BJU.Int. 2004;93 Suppl 1:27-9.
51. Milani S, Djavan B. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: latest update on alpha-adrenoceptor antagonists. BJU.Int. 2005;95 Suppl 4:29-36.
52. Desgrandchamps F. Who will benefit from combination therapy? The role of 5 alpha reductase inhibitors and alpha blockade: a reflection from MTOPS. Curr.Opin.Urol. 2004;14:17-20.
53. Lepor H, Williford WO, Barry MJ et al. The Efficacy of Terazosin, Finasteride, or Both in Benign Prostatic Hyperplasia. N Engl J Med 1996;335:533-40.
54. Kirby RS, Roehrborn C, Boyle P et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 2003;61:119-26.
55. Sandhu JS, Te AE. The role of 5-alpha-reductase inhibition as monotherapy in view of the MTOPS data. Curr.Urol.Rep. 2004;5:274-9.
56. Simone CB. The Truth About Prostate Health, Prostate Cancer. Princeton, NJ: Princeton Institute, 2005.
57. McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N.Engl.J.Med. 1998;338:557-63.
58. Roehrborn CG, Bruskewitz R, Nickel JC et al. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. J.Urol. 2004;171:1194-8.
59. McConnell JD, Roehrborn CG, Bautista OM et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. N Engl J Med 2003;349:2387-98.
60. Debruyne FM, Jardin A, Colloi D et al. Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. Eur.Urol. 1998;34:169-75.
61. Clark RV, Hermann DJ, Cunningham GR, Wilson TH, Morrill BB, Hobbs S. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin.Endocrinol Metab 2004;89:2179-84.
62. Debruyne F, Barkin J, van Erps P, Reis M, Tammela TL, Roehrborn C. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. Eur.Urol. 2004;46:488-94.
63. Souverein PC, van Riemsdijk MM, de la Rosette JJ, Opdam PC, Leufkens HG. Treatment of benign prostatic hyperplasia and occurrence of prostatic surgery and acute urinary retention: a population-based cohort study in the Netherlands. Eur.Urol 2005;47:505-10.
64. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. N.Engl.J.Med. 2003;349:215-24.
65. Buck AC. Phytotherapy for the prostate. Br.J Urol. 1996;78:325-36.
66. Bales GT, Christiano AP, Kirsh EJ, Gerber GS. Phytotherapeutic agents in the treatment of lower urinary tract symptoms: a demographic analysis of awareness and use at the University of Chicago. Urology 1999;54:86-9.
67. Boyle P, Robertson C, Lowe F, Roehrborn C. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. BJU.Int. 2004;93:751-6.
68. Gerber GS, Fitzpatrick JM. The role of a lipido-sterolic extract of Serenoa repens in the management of lower urinary tract symptoms

associated with benign prostatic hyperplasia. BJU.Int. 2004;94:338-44.
69. Wilt, T, Ishani, A, and MacDonald, R. Serenoa repens for benign prostatic hyperplasia. The Cochrane Library (1). 2005.
70. Djavan, B, Seitz, C, Dobrovits, M, and et al. Multicenter European prospectdive comparative study of phytotherapy and watchfuyl waiting in men with mild symptoms of bladder outle obstruction. Can progression be delayed or prevented. J Urol 171, 244. 2005.
71. Buck AC. Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action. J.Urol. 2004;172:1792-9.
72. Marks LS, Hess DL, Dorey FJ, Luz MM, Cruz Santos PB, Tyler VE. Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens. Urology 2001;57:999-1005.
73. Raynaud JP, Cousse H, Martin PM. Inhibition of type 1 and type 2 5alpha-reductase activity by free fatty acids, active ingredients of Permixon. J.Steroid Biochem.Mol.Biol. 2002;82:233-9.
74. Di Silverio F, Monti S, Sciarra A et al. Effects of long-term treatment with Serenoa repens (Permixon) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia. Prostate 1998;37:77-83.
75. Tunuguntla HS, Evans CP. Minimally invasive therapies for benign prostatic hyperplasia. World J.Urol. 2002;20:197-206.
76. Vela NR, Garcia Cardoso JV, Barat A, Manzarbeitia F, Lopez FA. BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers. Results of a double blind pilot clinical assay. Eur.Urol. 2003;44:549-55.
77. Djavan B. Lower urinary tract symptoms/benign prostatic hyperplasia: fast control of the patient's quality of life. Urology 2003;62:6-14.
78. Pygeum africanum (Prunus africanus) (African plum tree). Monograph. Altern.Med Rev. 2002;7:71-4.
79. Ishani A, MacDonald R, Nelson D, Rutks I, Wilt TJ. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. Am.J Med 2000;109:654-64.
80. Wilt.T, Ishani, A, MacDonald, R, Rutks, I, and Strark, G. Pygeum africanujm for benign prostatic hyperplasia. The Cochrane Library (1). 2005.
81. Levin RM, Das AK. A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. Urol.Res. 2000;28:201-9.
82. Wilt TJ, MacDonald R, Ishani A. beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. BJU Int. 1999;83:976-83.
83. Berges RR, Windeler J, Trampisch HJ, Senge T. Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Beta-sitosterol Study Group. Lancet 1995;345:1529-32.
84. Sokeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. BJU International 2000;86:439-42.
85. Koch E. Extracts from fruits of saw palmetto (Sabal serrulata) and roots of stinging nettle (Urtica dioica): viable alternatives in the medical treatment of benign prostatic hyperplasia and associated lower urinary tracts symptoms. Planta Med. 2001;67:489-500.
86. MacDonald R, Ishani A, Rutks I, Wilt TJ. A systematic review of Cernilton for the treatment of benign prostatic hyperplasia. BJU Int. 2000;85:836-41.
87. Wilt TJ, Ishani A, Rutks I, MacDonald R. Phytotherapy for benign prostatic hyperplasia. Public Health Nutr. 2000;3:459-72.
88. Comhaire F, Mahmoud A. Preventing diseases of the prostate in the elderly using hormones and nutriceuticals. Aging Male. 2004;7:155-69.
89. Mayo Clinic On Prostate Health. Rochester, MN: Mayo Clinic Health Information, 2003.
90. Djavan B. Benign prostatic hyperplasia in the new millennium. Curr Opin.Urol 2005;15:33-4.
91. Hoffman RM, MacDonald R, Monga M, Wilt TJ. Transurethral microwave thermotherapy vs transurethral resection for treating benign prostatic hyperplasia: a systematic review. BJU Int. 2004;94:1031-6.
92. Wagrell L, Schelin S, Nordling J et al. Three-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. Urology 2004;64:698-702.
93. Alivizatos G, Ferakis N, Mitropoulos D, Skolarikos A, Livadas K, Kastriotis I. Feedback microwave thermotherapy with the ProstaLund Compact Device for obstructive benign prostatic hyperplasia: 12-month response rates and complications. J Endourol. 2005;19:72-8.
94. David RD, Grunberger I, Shore N, Swierzewski SJ, III. Multicenter initial U.S. experience with CoreTherm-monitored feedback transurethral microwave thermotherapy for individualized treatment of patients with symptomatic benign prostatic hyperplasia. J Endourol. 2004;18:682-5.
95. Huidobro C, Bolmsjo M, Larson T et al. Evaluation of microwave thermotherapy with histopathology, magnetic resonance imaging and temperature mapping. J Urol 2004;171:672-8.
96. Naspro R, Salonia A, Colombo R et al. Update of the minimally invasive therapies for benign prostatic hyperplasia. Curr Opin.Urol 2005;15:49-53.

97. Naderi N, Mochtar CA, de la Rosette JJ. Real life practice in the management of benign prostatic hyperplasia. Curr Opin.Urol 2004;14:41-4.
98. van Melick HH, van Venrooij GE, Boon TA. Long-term follow-up after transurethral resection of the prostate, contact laser prostatectomy, and electrovaporization. Urology 2003;62:1029-34.
99. Djavan B, Seitz C, Marberger M. Heat versus drugs in the treatment of benign prostatic hyperplasia. BJU.Int. 2003;91:131-7.
100. Fong YK, Milani S, Djavan B. Natural history and clinical predictors of clinical progression in benign prostatic hyperplasia. Curr.Opin.Urol. 2005;15:35-8.
101. Djavan B, Fong YK, Harik M et al. Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. Urology 2004;64:1144-8.
102. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. N.Engl.J.Med. 1995;332:75-9.
103. Flanigan RC, Reda DJ, Wasson JH, Anderson RJ, Abdellatif M, Bruskewitz RC. 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J.Urol. 1998;160:12-6.
104. Brown CT, Emberton M. Could self-management challenge pharmacotherapy as a long-term treatment for uncomplicated lower urinary tract symptoms? Curr.Opin.Urol. 2004;14:7-12.

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