INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 178 **JUNE 2007** **16th YEAR**

This issue begins with a discussion of the latest diet trial, in this case pitting the Atkins diet against the Zone, Ornish, and an establishment diet. If Dr. Robert Atkins were still alive, he would be pleased with this study and delighted to see it in the JAMA. This is followed by a discussion of the role of triglycerides as a risk factor for cardiovascular disease, based in part on a report of a large meta-analysis.

Vitamin D continues to be featured. Three studies are discussed that concern the evidence for widespread deficiency around the world, and even in newborns. This is followed by a highly significant and important study of vitamin D and breast cancer. This paper leaves little doubt as to the merits of maintaining high serum levels of 25-hydroxyvitamin D, and may even encourage readers to have this marker of vitamin D status measured, especially in the spring. Also, the breast cancer results are remarkably similar to the colorectal cancer results presented in the May newsletter.

Cognitive decline is an important issue as one ages. Also, readers may have parents or relatives entering old age whose quality of life will be determined in part by maintaining a high level of cognitive ability. Two studies are presented that deal with the relationship between folate status and cognitive decline, one involving the risk encountered at low levels and one dealing with the effects of supplementation.

Other features this month include a review of a new book on heart disease and the monthly Prostate Monitor.

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Wishing you continuing good health,

William R. Ware, PhD, Editor

Highlights

ATKINS FINALLY VINDICATED

THE A TO Z WEIGHT LOSS STUDY: A RANDOMIZED TRIAL

A study, which has just been reported in the *Journal of the American Medical Association,* provides a head-to -head comparison between four diets where the outcomes of interest were not only weight loss but also metabolic and coronary risk factors. To the Atkins, Zone and Ornish diets the researchers added what is called the LEARN diet which represented current mainstream recommendations. Thus the study examined more or less the full range of diet philosophies from very low carbohydrate (Atkins) to very high carbohydrate. (Ornish). Those who followed the Atkins diet went through the 2-3 month "induction" period and were instructed to keep carbs to at or below 20g/day, after which there was a transition to the "ongoing weight loss" protocol with a maximum of 50 g/day or less of carbs. Participants were randomly assigned to one of the four diet groups. Members of each group were given a diet book and attended eight weekly

classes during which the details of the diet in question were discussed in detail. The books were *Dr. Atkins' New Diet Revolution, Enter the Zone, Eat More, Weigh Less* (Ornish), and *The LEARN Manual for Weight Management*. Energy intake at baseline was between 1850 and 1975 kcal/day and declined over the year to between 1500 and 1650 kcal/day (kilocalorie is equivalent to the layman's "calorie"). Frequent contact between the study staff and the participants was used to maintain maximum adherence. Data was collected at the beginning of the study (baseline) and at 2, 6 and 12 months. The participants were premenopausal women, mean age about 40, mostly white and with about 16 years of education. The mean weight was 85-86 kg (187-189 lbs) with body mass indices indicating low-level obesity (31-32 kg/m^2). At baseline and during follow-up body mass index, body fat, waist-to-hip ratio, blood lipids (HDL and LDL cholesterol, triglycerides), insulin, glucose and blood pressure were determined.

A total of 249 participants completed the full 12-month protocol. Women assigned to the Atkins diet had more weight loss and more favorable changes in related metabolic factors at 2 and 6 months. The finding of greater weight loss for the Atkins diet continued through 12 months and the difference between the Atkins and Zone weight loss was statistically significant. But there was no statistically significant difference in weight loss among the Zone, LEARN or Ornish diets. Those on the Atkins diet lost a mean of 4.7 kg (10.3 lbs) during the 12-month period. The Atkins diet also resulted in the largest decrease in blood pressure, blood insulin and glucose, and the largest increase in HDL cholesterol found with the four diets. The increase in HDL was almost 5 mg/dL – from a baseline mean of 53 mg/dL.

One of the major objections to low-carb diets from mainstream medicine has been the high level of total fat and saturated fat intake, which according to the hypothesis that fat was bad for the heart rendered these diets dangerous. Consistent with recent trials, at 12 months this study found that the Atkins diet raised the HDL cholesterol levels (the so-called good cholesterol), decreased triglycerides (also viewed as a beneficial change), had no effect on LDL cholesterol and lowered blood pressure. The magnitude of these favorable changes was larger for the low-carbohydrate groups (Atkins and Zone) and largest for the Atkins diet. Thus the Atkins diet not only produced the largest weight loss, but also there was evidence of benefit, not risk in the context of coronary heart disease.

Gardner, C. D. et al. Comparison of the Atkins, Zone, Ornish and LEARN Diets for Changes in Weight and Related Risk Factors Among Overweight Premenopausal Women. ***Journal of the American Medical Association****, 2007, Vol. 297, No. 9, po.969-77.*

Editor's comment: The Atkins diet is the flagship diet of the low-carbohydrate school. Developed by the late Robert Atkins, M.D., it was immediately and vigorously condemned by mainstream medicine and professional nutritionists. Patients wishing to try the diet were told that it would surely kill them. The reasons given centered on the high fat and protein content and the perceived lack of fruits and vegetables. This was the low-fat era when all fats were labeled by the establishment as dangerous and low-fat foods and low-fat, high carbohydrate diets were advocated by the experts. The high triglyceride levels and low HDL cholesterol levels that were a natural result of the recommended diet, especially because of the type of carbohydrate substituted for fat, were ignored by most, as were the deteriorating glucose metabolism markers. Extremists even suggested that no one should eat any fish and especially fatty fish! Fine points of the diet such as the emphasis on the selection of so-called complex carbohydrates and the avoidance of refined carbohydrates, advice that today is accepted, were ignored. Also ignored was the claim by Atkins that the diet changed blood lipid profiles in a heart friendly manner and that metabolic abnormalities involving insulin and blood glucose were reduced or eliminated. These latter aspects in fact were objectives of the diet that were as important as weight loss for many patients. Atkins and his colleagues treated thousands of patients and developed an international following. His diet books were record-breaking best sellers. With apparently intentional disrespect, mainstream medicine called his diet a fad diet and viewed the advocates as cult members. In the past decade, similar low-carb diets also became popular, and were also labeled fad diets. Yet there were studies appearing in the peer-reviewed literature, also ignored, that largely answered the objections of the critics. The critics used the convenient fallback position that randomized trials were required. As the authors of this study point out, over the past several years there have in fact been a number of randomized trials comparing one or another aspect of the low-carb vs. high-carb debate which have not confirmed the views of the low-carb critics. This randomized study adds significantly to that body of data. The participants appear to have been very well instructed and monitored, the dropout rate was low compared to similar studies, and the number of

parameters studied was such that a fairly comprehensive picture was obtained of the blood lipid and metabolic parameters as well as weight loss. The results of this latest study are entirely consistent with what Dr. Robert Atkins said repeatedly in his books and on TV interviews. It is unfortunate that his accidental death prevented him from seeing his diet philosophy vindicated. However, as discussed in last month's Newsletter in the mini-review concerning the French Paradox, mainstream medicine is still holding fast to the dogma that saturated fat is bad for the heart and ideally should be kept to 7% and certainly no more than 10% of total energy intake. But the Atkins diet in the study discussed above had about 15% of total calories in saturated fat and at the end of the study, 44% from total fat. This strengthens the arguments given in the French Paradox review concerning the lack of evidence that saturated fat is bad, although of course this was a short study and heart attacks or overall mortality were not endpoints. The reader is also referred to the archives of the IHN Research Reports for a review on popular diets including the Atkins diet (The *Diet Zoo*, in the December 2003-March 2004 issues).

TRIGLYCERIDES AND HEART DISEASE

The 2002 National Cholesterol Education Program-Adult Treatment Panel report which established guidelines in the U.S. (and elsewhere) for blood lipids and coronary heart disease (CHD) risk took the position that there was insufficient evidence to justify regarding triglycerides as an independent risk factor for CHD. In a paper in the journal *Circulation,* Sarwar *et al* address this issue with a report on two new studies and an updated meta-analysis of 27 additional prospective follow-up studies in Western populations. Triglycerides are routinely determined as part of the blood lipid profile, and in fact the LDL cholesterol level is calculated with a formula that requires this triglyceride value, a formula that incidentally fails if the triglycerides are too high (> 400 mg/dL). The first of the new studies, the so-called Reykjavik Study, found that when the top third was compared with the bottom third stratified by triglyceride levels (actually log-triglyceride levels), the increase in CHD risk was about a factor of 2 for both men and women. This relationship was weakened by adjusting for age, gender, period, smoking and other established risk factors, with a 51% increase in risk for men. However, a 24% increase in risk for women failed to reach statistical significance. In the second study, called the EPIC-Norfolk Study, results adjusted the same way gave 33% and 88% increase in CHD risk for men and women, respectively. Further adjustment of the results from this second trial for HDL cholesterol gave a 59% increase in risk for women, but the 16% increase in risk for men failed to achieve statistical significance. Nevertheless, for all individuals, a significant 31% increase in risk was found. For the EPIC-Norfolk study, the threshold for the top third of triglyceride levels was 2.0 mmol/L (177 mg/dL) whereas for the Reykjavik Study it was 1.28 mmol/L (113 mg/dL). The higher threshold in the EPIC study may have been partly responsible for the higher relative risks found.

In the pooled analysis of 29 studies, an overall 72% increase in CHD risk was found which was statistically significant. The total number of participants in this meta-analysis was over 250,000 with over 10,000 CHD cases. This result was close to that found for a meta-analysis of Asian and Pacific populations. Also, the impact of triglycerides on CHD risk was found to be similar in men and women, in contrast to earlier studies that frequently found greater risk in women. In addition, the presence or absence of fasting prior to sample collection did not influence the results of the analysis. The authors conclude that these data indicate consistent, moderate and significant associations between triglyceride levels and CHD risk.

Sarwar, N. et al. Triglycerides and the Risk of Coronary Heart Disease. ***Circulation,*** *2007. e-published ahead of print.*

Editor's comment: Mainstream medicine maintains its fixation on LDL cholesterol, and tends to relegate triglycerides to a secondary role as a risk factor. This paper may help to enhance the position of triglycerides in the hierarchy of risk factors. In fact, some cardiologists already give considerable weight to this lipid fraction. For example, two cardiologists, Dr. Stephen Sinatra and Dr. J. C. Roberts, in their new book *Reverse Heart Disease Now* (reviewed in this Newsletter) go so far as to present what they term *The New Cardiology Risk Assessment,* a table of factors for scoring risk, which includes HDL cholesterol and triglycerides but ignores LDL cholesterol altogether. Their emphasis is on the triglyceride to HDL ratio, which they believe should be lower than 4:1. In their opinion the

threshold for an unfavorable level of triglycerides is >150 mg/dL. This value is consistent with the threshold used in the popular definitions of metabolic syndrome (see the April Newsletter). It is also consistent with the "top third" threshold used in the EPIC study of 177 mg/dL. But one can have a high triglyceride level but not have the metabolic syndrome, and the condition may be ignored. In the diet comparison study discussed above, the Atkins diet produced the largest change in triglycerides at all measuring times, with a 12-month mean decrease of 29.3 mg/dL (from a mean at baseline mean of 125 mg/dL. (to get mmol/L, divide by 88.6). Sinatra and Roberts suggest weight reduction, exercise, carbohydrate restriction, fish oil (2-3g), L-carnitine (1-2g) and reduction in alcohol intake as interventions that work for them for reducing serum triglycerides in their patients

VITAMIN D DEFICIENCIES

EVIDENCE FOR WIDESPREAD VITAMIN D DEFICIENCY

A paper just published in the *American Journal of Clinical Nutrition* adds to the evidence that vitamin D deficiency in the temperate zones is widespread. The researchers measured 25-hydroxyvitamin D levels (25(OH) D), the now well-accepted marker for vitamin D status, in 7437 British white-skinned individuals of age 45. The prevalence of vitamin D deficiency was greatest in the winter and spring when 25(OH)D levels of <25, <40, and <75 nmol/L were found in 15.5%, 46.6% and 87.1% of the subjects, respectively. The equivalent numbers for summer and fall were 3.2%, 15.4% and 60.9% respectively. As the authors point out, the *threshold* for optimal bone health is ≥ 75 nmol/L (>80 nmol/L has also been proposed) and thus the prevalence of vitamin D deficiency is, in their words, "alarmingly high" and they suggest that this situation requires action at a population level rather than a risk group level. The threshold is based on achieving optimal bone mineral density and calcium absorption. A study of the monthly changes revealed a smooth variation with a minimum mean 25(OH)D level in February and a maximum in September, a variation which of course clearly reflects sun exposure. This was also beautifully illustrated by the variation from north to south in Great Britain which was maintained throughout the seasons. Men tended to have slightly higher levels than women throughout the year, but the differences were small. Also, the expected variations with supplements and oily fish intake were observed. The authors conclude that since vitamin D deficiency is also implicated in the development of various types of cancer, cardiovascular diseases, and diabetes the high rates of deficiency suggest immediate action is needed.

Hypponen, E. et al. Hypovitaminosis D in British Adults at Age 45 y: Nationwide Cohort Study of Dietary and Lifestyle Predictors. ***American Journal of Clinical Nutrition****, 2007, Vol. 85, pp.860-8.*

Editor's comment: This paper prompted an editorial in the same issue (pp. 649) with an author list that reads like a *Who's Who* in vitamin D research and nutritional epidemiology. They point out that 30-40 years ago, these same low levels of 25(OH)D were considered indicative of healthy white adults in the UK, a judgment based on levels that just prevented rickets, a crippling disease characterized by the softening and bending of bones. The authors of this editorial reiterate the position that the *threshold* for a desirable 25(OH)D level is 75 nmol/L. Statements indicating the merits of this threshold and as well the widespread prevalence of vitamin D deficiency have repeatedly appeared in the medical literature and in the media, but the authors point out that media reports also frequently repeat what they term outdated and misleading guidelines from such organizations as the Institute of Medicine, and the impression is frequently given that it is not wise to exceed the amounts recommended by accepted guidelines for daily intake, amounts that are in general inadequate to raise 25(OH)D levels to a minimum of 75 nmol/L. They also point out that a recent study of toxicity concluded that a safe upper limit for adults should be raised to 10,000 IU/day (Am J Clin Nutr, 2007;85:6-18), whereas the conventional guidelines for daily intake for those aged 51-70 is a mere 600 IU/day and the currently accepted safe upper limit is 2000 IU/day. Finally, they recommend that action be taken with regard to more food fortification and increasing the amounts of vitamin D in supplement products (such as multivitamins), actions they suggest that could well bring about "rapid and important reductions in morbidity" associated with the current state of affairs as regards low vitamin D status.

VITAMIN D INTAKES IN NORTH AMERICA AND ASIA-PACIFIC COUNTRIES INSUFFICIENT

This study from Canada, New Zealand and the U.S. presents essentially the same picture as the British

study discussed above. In the U.S. there have been only minor changes in vitamin D intake from foods and supplements over the periods 1988-94 and 1999-2000. The amounts based on national surveys range from about 200 to 400 IU/day with most clustered between 200 and 300 IU/day. The figures they present for Canada for intakes from food and supplements range from 350 to 730 IU/day. with the latter figure applying mainly to older adults with osteoporosis and presumably taking heavier doses via supplements. In New Zealand, the prevalence of vitamin D deficiency as determined by 25(OH)D levels ranges from 43% to 79% of the population, and this is using 50 nmol/L as a cut-off. They conclude that the mean requirement for vitamin D needed in the absence of ultraviolet exposure cannot be reached except by aggressive supplementation.

Whiting, S. J. et al. Vitamin D Intakes in North America and Asia-Pacific Countries Are Not Sufficient to Prevent Vitamin D Insufficiency. ***Steroid Biochemistry & Molecular Biology****, 2007, e-published ahead of print.*

VITAMIN D DEFICIENCY IN PREGNANT WOMEN

Bodnar *et al* have just reported a study in *the Journal of Nutrition* concerning the vitamin D status of pregnant black and white women and their newborn children living in the Northern U.S. All the subjects resided in Pittsburgh, PA (latitude 40º N) where the sun provides only negligible vitamin D generation in the winter. Vitamin D deficiency was defined as < 37.5, insufficiency as 37.5-80, and sufficiency as > 80 nmol/L of 25-hydroxyvitamin D. For newborns the assay was done on cord blood. At the time of delivery, deficiency and insufficiency occurred in 29.2% and 54.1 % of black women and 45.6% and 46.8% of black newborns, respectively. For white women and their babies, the comparable figures were 5% and 42.1% at delivery and 9.7% and 56.4% for newborns. The results were similar at < 22 weeks gestation. This study also looked at seasonal variation adjusted for body weight and preconceptional multivitamin use. Black women had smaller increases in 25-hydroxyvitamin D from spring to summer than white women (changes of 13.2 vs. 27.6 nmol/L). The authors conclude that both black and white pregnant women and their babies residing in the northern U.S. are at high risk of vitamin D insufficiency. Data collected on vitamin D intake from prenatal vitamin use suggested that the above prevalence of deficiency or insufficiency persisted even when the mothers were compliant with regard to taking prenatal vitamins. This is a significant problem, according to the authors, since *in utero* and early-life vitamin D deficiency is associated with skeletal problems, type 1 diabetes, schizophrenia, autoimmune diseases, cancer, and heart disease, and that high dose supplementation is needed to improve maternal and neonatal vitamin D status.

Bodnar et al. High Prevalence of Vitamin D Insufficiency in Black and White Women Residing in the Northern United States and Their Neonates. ***The Journal of Nutrition****, 2007, Vol. 137, pp.447-52.*

Editor's comment: The skin color dependence of vitamin D status from spring to summer simply reflects the well-known effect of skin pigments in attenuating the photosynthesis of vitamin D by solar UV light. Also, in this study, white women were much heavier users of multivitamin supplements than black women. Nevertheless, even though white women on average regularly took a multivitamin both before conception and in the last 3 months of pregnancy (66.5% and 94.3%, respectively), vitamin D insufficiency was still observed, a result which reinforces the view held by vitamin D experts that the amount of vitamin D in commonly used multivitamin preparations is too low.

VITAMIN D AND BREAST CANCER

A report has just appeared in the *Journal of Steroid Biochemistry & Molecular Biology* by Garland *et al* that addresses the issue of vitamin D and breast cancer risk with a pooled analysis of studies that determined the vitamin D status from serum 25-hydroxyvitamin D (25(OH)D) levels. The list of authors includes both well-known vitamin D experts and nutritional epidemiologists. The authors were only able to find two studies that met their requirements for inclusion in their pooled analysis, but together they involved 1760 individuals. Both studies covered a wide range of 25(OH)D levels and exhibited a high level of inverse correlation between breast cancer risk and the serum level of this vitamin D marker. When pooled analysis was carried out, the odds ratios for the lowest to highest quintile of 25(OH)D levels were 1.00, 0.90, 0.70, 0.70 and 0.50, i.e. the highest vitamin D status provided a 50% reduction in risk. The authors present a graph of risk (odds ratio) against serum 25(OH)D levels with an amazing correlation coefficient of 0.94 (a statistical measure of the goodness of fit to the model, in this case a straight line, and 1.00 represents a perfect fit), a correlation

coefficient that would please those trained in the physical sciences and in fact a correlation very rarely seen in plots presented in the medical literature.

The authors discuss the level of intake that would accomplish the 50% level of risk reduction. If a person were to start at a serum level of 24 nmol/L (10 ng/mL) it would require supplementation of 4000 IU/day to achieve the required level of 120 nmol/L. This exceeds the current upper limit of 2000 IU/day. However, as they point out, a proposal has been made to raise this limit to 4000 IU/day. As discussed in this Newsletter, levels of 24 nmol/L are not uncommon among US women in the winter months. An alternative they explore is to take 2000 IU/day orally and make up the balance by judicious sun exposure. They estimate that 12 minutes of sun exposure for 50% of the skin would produce the missing 2000 IU. However, this would not happen in the northern latitudes in the winter months.

The authors hammer home their point regarding the importance of vitamin D by calculating that, based on their data, an intake of 4000 IU of vitamin D per day would, in the U.S., prevent over 100,000 cases of breast cancer per year. Intake of 2000 IU/day was estimated to prevent 66,000 cases. In this paper, vitamin D refers to vitamin D_3.

Garland, C. F. et al. Vitamin D and the Prevention of Breast Cancer; Pooled Analysis. ***Journal of Steroid Biochemistry & Molecular Biology,*** *2007, Vol. 103, pp. 708-711.*

Editor's comment: A preliminary report of this analysis was presented in the Research Review concerning the primary prevention of breast cancer which appeared starting in the October 2006 issue of the Newsletter. The reductions in risk seem very impressive. No doubt Big Pharma would love to have a patent drug that would accomplish this result. But 1000 IU capsules of vitamin D_3 are widely available in health food stores, drugstores and online. It is noteworthy how little summer sun exposure, albeit to a significant skin area, that is necessary to generate the equivalent of 2000 IU of vitamin D. Working outside or sunbathing in the summer can quickly generate 10,000 or more IU of vitamin D, but the body as a mechanism for limiting the effect of prolonged exposure so toxicity is never a problem. After all, if one believes modern theories, our human biochemistry goes back virtually unchanged to times when our distant ancestors were exposed to intense tropical sunlight daily throughout the year. The real issues here are the winter months in the temperate zone and the modern tendency to severely limit sun exposure at all times with clothing, hats and sun screen and as well, for some, severely limited sun exposure due to lifestyle or disability. The net result is discussed in this Newsletter where papers are presented which deal with the near epidemic level of vitamin D deficiency. Because mainstream medicine tends to identify deficiency of vitamin D with rickets which is rare today (but still seen), if one judges by the conservative guidelines, it is concluded that all is well, especially since there is some food fortification. Including a 25(OH)D measurement along with the normal blood tests in a routine physical would be an extraordinary event, probably not covered by many insurance plans and government health care programs, and some physicians may not even be aware of the strong variation of vitamin D status from summer to winter in the northern latitudes. Also interpreting the results might be a problem if the laboratory reference range is used rather than what one finds in the modern literature. One Canadian medical laboratory a couple of years ago was giving 25-100 nmol/L as the reference range and > 250 nmol/L as potentially toxic, so 25 nmol/L is viewed as OK (divide by 2.4 to get mg/dL). Finally, the paper by Garland *et al* is not in the public domain. Even doctors cannot read it unless they subscribe (highly unlikely at $400 a year for a very highly specialized publication) or have privileges at a medical library, something generally restricted to academic physicians, other academics (like your Editor) and researchers. In fact, many physicians will probably never hear about this paper. Drug company reps will certainly not be promoting vitamin D during their frequent visits to doctor's offices!

PREVENTING OR DELAYING TYPE 2 DIABETES

In the year 2000 an estimated 170 million people worldwide had diabetes, and the number is expected to double by 2030. Thus delaying or preventing type 2 diabetes (so-called adult onset diabetes) should be of great interest both to individuals at risk and the public health establishment in general. In a study just published in the *British Medical Journal*, Gillies *et al* have carried out a systematic review and pooled study analysis (meta-analysis) of both lifestyle and

pharmacological interventions designed to prevent or delay type 2 diabetes. A total of 17 studies with 8084 participants qualified for inclusion in the meta analysis. Participants in all studies had impaired glucose tolerance at baseline. Most studies used the World Health Organization (WHO) definition of a fasting blood glucose of less than 140 mg/dL and a glucose level between 140 and 200 mg/dL two hours after consuming a drink containing 75 g of glucose—called the oral glucose tolerance test. The trend has been to replace this with the American Diabetes Association (ADA) so-called impaired fasting glucose (values between 100 and 125 mg/dL) and some studies used this definition as an inclusion criterion. Divide glucose values by 18 to get mmol/L, the unit used in Canada and Europe. Lifestyle interventions involved exercise and/or diet whereas pharmaceutical intervention involved drugs such as metformin, acarbose and orlistat. Follow-up in the lifestyle studies ranged from 1.8 to 4.6 years and in the pharmacological studies from 0.92 to 4.4 years.

For the lifestyle intervention, 12 studies were included of which 8 achieved statistical significance as independent studies. The pooled reduction in risk of progression to or development of type 2 diabetes was 49%. For the pooled analysis of pharmacological studies, 11 were used but only 6 independently achieved statistical significance. Pooled analysis of the pharmaceutical drug benefits yielded a 30% risk reduction whereas the pharmaceutical implemented anti-obesity studies when pooled (two studies) gave 56% reduction in risk of progression or development of type 2 diabetes. All the pooled results were statistically significant. The authors conclude that either intervention has the potential to reduce the risk of type 2 diabetes and lifestyle changes "seem to be at least as effective as pharmacological interventions." As regards the use of drugs, it was pointed out that once the treatment stopped, the risk reduction was not sustained. Furthermore the drug interventions were associated with adverse effects such as gastrointestinal side effects, and the authors point out that these take on greater importance if lifelong intervention is involved. It was also found that lifestyle interventions may have had a greater impact for individuals with higher baseline body mass index. Finally, they raise the question "....should what is fundamentally a lifestyle issue really be treated with a lifelong course of medication?"

Gillies, C. L. et al. Pharmacological and Lifestyle Interventions to Prevent or Delay Type 2 Diabetes in People with Impaired Glucose Tolerance: Systematic Review and Meta-Analysis. ***British Medical Journal****, 2007, e-published ahead of print Jan 19.*

Editor's comments: This study was not sponsored by the drug industry and only one author reported a minor conflict of interest. The risk reductions found in both the drug and lifestyle pooled analysis are large and significant and the latter approach appears to be somewhat better at reducing risk and of course comes with no or very limited side effects. The lifestyle approach is obviously better for those who can maintain an exercise program and reduce weight and then maintain weight loss. The great benefit of this approach over drug intervention, aside from adverse side effects, is, as the authors note, avoiding lifelong drug use. Nevertheless, the appeal of drug intervention is understandable given its convenience and the magnitude of the problems associated with diabetes that an individual is trying to avoid.

FOLIC ACID STATUS AND COGNITIVE FUNCTION

LOW FOLATE AND COGNITIVE IMPAIRMENT IN THE VERY OLD

In an Italian study just published, Tettamanti *et al* investigated the association between serum B12 and folate levels and cognitive and functional deficits in the very old. Blood analysis data were available for 471 individuals with a mean age of 87.4 years. Three tests were used to assess cognitive and functional status. This cohort had very low serum folate. No significant association was found with B12 status, but large and significant associations were found for dementia and serum folate. Compared to those with levels in excess of 6.1 ng/mL of folate, those in the 6.1—4.0 and < 4.0 tertiles had increased risks of dementia that were enhanced 5.4 and 6.6 fold. These results were adjusted for age, gender, education, smoking, hypertension, diabetes, heart attack, stroke and B12 levels. The authors point out that these results are consistent with an earlier study where the mean age was 75-80. In that study, various measures of cognitive impairment and dementia were also strongly and significantly associated with serum folate levels with risk enhancements of 3.1 to 3.8 fold. In this study, the results were also adjusted for the influence of homocysteine levels, which were

also found to be independently and positively associated with cognitive and dementia risks. The authors conclude that studies of the very old suggest that a folate deficiency may represent a risk factor for the cognitive decline associated with aging that could contribute to Alzheimer's disease as well as other aspects of dementia.

Tettamanti, M. et al. Low folate and the Risk of Cognitive and Functional Deficits in the Very Old. ***Journal of the American College of Nutrition,*** *2007, Vol. 25, No. 6, pp. 502-8.*

Quadria, P, et al. Homocysteine, Folate, and Vitamin B12 in Mild Cognitive Impairment, Alzheimer's Disease and Vascular Dementia. ***American Journal of Clinical Nutrition****, 2004, Vol. 80, pp. 114-22.*

FOLIC ACID SUPPLEMENTATION AND COGNITIVE FUNCTION

The paper discussed above raises the obvious question—does supplementation with folic acid influence the development of cognitive malfunction? In a paper just published in the journal *Lancet*, Durga *et al* report the results of a randomized, placebo-controlled intervention trial where 818 participants were given either a placebo or 800 micrograms of folic acid for three years. The subjects were chosen for having high homocysteine levels. Changes in various measures in cognitive function were measured and comparisons made between the intervention and placebo groups. At baseline, the placebo and folic acid groups has similar serum folate levels of about 5.3 ng/mL. For the placebo group the levels remained unchanged over the three-year period, but for the folic acid group they increased to a mean value of 33.4 with a range of 22 to 45 ng/mL. Significant improvements were found in test scores for memory, information processing speed, and sensorimotor speed when the folic acid group was compared with the placebo group. All of these functions tend to decline with age. The authors indicated awareness of other studies that failed to find beneficial effects of folic acid supplementation. They offered several explanations. First, the population in this study had high homocysteine levels, which the authors assumed was a causal risk factor for cognitive decline, and folic acid significantly reduced these levels. Second, the cohort was large and supplemented for a long period. Third, the population was unlikely to have had dementia at baseline since one of the tests used gave scores indicating otherwise for all participants at the start of the study. Thus this study attempted to look at the impact of folic acid early in the development of cognitive problems whereas some other studies treated individuals who had already advanced beyond the initial stages. They suggest that folic acid is most effective at the early stages. Finally, they used sensitive cognitive tests which were more likely to reveal subtle aspects associated with aging. The authors conclude that folic acid improves performance on tests that measure information processing speed and memory, domains that are known to decline with age, especially in older adults with elevated homocysteine levels. They remark that additional trials are needed to clarify the clinical relevance of folic acid supplementation on populations with mild cognitive impairment and dementia.

Durga, J. et al. Effect of 3-Year Folic Acid Supplementation on Cognitive Function in Older Adults in the FACIT Trial. ***Lancet****, 2007, Vol. 369, pp 208-16.*

Editor's comments: As the authors point out, trials with folic acid supplementation have been inconsistent. However, the above studies of both risk and intervention suggest that folic acid status is something that should not be ignored, and the level of supplementation needed to achieve high levels is similar to that which would be obtained from common multivitamins. As well, in certain countries where fortification is mandated, some intake will be from food. The added effect on homocysteine would also presumably be advantageous. A recent study in fact indicated that homocysteine levels were not only inversely associated with various cognitive performance scores, but that the association remained statistically significant after adjusting for a number of potential confounders including cardiovascular disease (*Psychosomatic Medicine* 2006;68:547-54).

BOOK REVIEW

Reverse Heart Disease Now. Stop Deadly Cardiovascular Plaque Before It's Too Late

Stephen T. Sinatra, M. D. and James C. Roberts, M. D.

John Wiley & Sons, New York, 2007

The title and subtitle of this book make a bold statement. However, this book draws on over forty years of collective clinical experience of two cardiologists. Stephen Sinatra was formerly chief of cardiology and director of medical education at Manchester Memorial Hospital in Connecticut, and has specialized in preventive cardiology for the last twenty years. He has written a number of popular books and writes the widely read newsletter *Heart, Health and Nutrition*. Sinatra has also held a position in academic medicine at the University of the Connecticut School of Medicine. James Roberts has practiced invasive and integrative cardiology for twenty years and is Medical Director of the EECP Center and Advanced Magnetic Research Institute of Northwest Ohio. Both practice what is called integrative cardiology—a combination of conventional medical therapy and alternative therapy designed for each patient individually to provide the maximum benefit. The authors term their viewpoint the *New Cardiology.*

The introductory chapter provides an outline of this New Cardiology, including a discussion of the question—are you at risk? The authors include a risk assessment one can carry out at home, given the required data. However, the blood tests and other diagnostic data include components and screening results not generally measured in routine physical exams. This is in fact, in this reviewer's opinion, a strength since it alerts the reader to what may be significant deficiencies in how cardiovascular risk is judged in current practice. It also provides a list one can take to the next physical exam, but at the risk of causing annoyance. It is generally true that an individual does not see a cardiologist until there are significant problems. Those who lack problems that justify such a referral depend on general practitioners and internists for cardiovascular assessment and these practitioners may consider such extensive testing as suggested by the authors to be excessive. Many would probably consider an assessment of the presence or absence of high blood pressure, the metabolic syndrome, diabetes, and elevated cholesterol as all that is needed in the context of coronary heart disease risk. The reader may be surprised at what else is on the list and that, in the view of the authors, it applies in general to apparently health individuals as well as those presenting with symptoms. In fact, in chapter 4 an even longer list of blood tests is presented and justified.

Part One of the book titled *How We Get Clogged* deals with the role of inflammation in heart disease, what the authors term the obsession mainstream medicine has with cholesterol, and finally twelve risk factors called the "Dirty Dozen." First there is a fairly detained discussion of how inflammation ultimately results in atherosclerotic plaques and the role of stable and unstable plaque in the symptoms and adverse events associated with coronary heart disease. This section establishes the critical importance of inflammation. With regard to cholesterol, they view as detrimental only oxidized LDL cholesterol, the form that contributes to the inflammatory cascade. They appear to regard dealing with the risk factors that are associated with the inflammation—plaque process as more important than reducing cholesterol per se. They also present a good review of the research that leads to a balanced view of cholesterol as partly beneficial, in some cases irrelevant, and under some circumstances a promoter of coronary heart disease. Incidentally, the New Cardiology Risk Assessment presented in the introduction does not include LDL cholesterol levels, only triglycerides and HDL! The establishment, which regards LDL levels as central to cardiovascular risk, will no doubt have a big problem with this.

The Dirty Dozen starts with the dangers associated with too much insulin, and then what is termed toxic blood (high levels of homocysteine, lipoprotein(a), C-reactive protein, fibrinogen, and ferritin, a marker of iron load). Next come oxidative stress, poor bioenergetics, infection, in particular gum disease, toxic metals, emotional stress, gender factors, trans-fatty acids, high blood pressure, genetics and finally radiation, especially

therapeutic radiation. Each is discussed in enough detail for the reader to understand the origin and nature of the risk.

Part Two is titled "*How To Get Unclogged*." Chapter 4 deals at length with the tests one needs, expanding on the risk assessment presented in the introduction. The authors are careful to explain for each test those who are deemed appropriate candidates, depending on the clinical picture. This chapter is followed by one on medication—what is needed and what is not needed. Included is a lengthy discussion of the pros and cons of statin therapy, and when, based on the collective clinical experience of the authors, it is appropriate. Other medications discussed include those in common use for treating hypertension, and as well, aspirin and non-steroidal anti-inflammatory drugs. They take the position that low-dose aspirin is not indicated for primary cardiovascular prevention among healthy people due to its side effects. The authors point out that it is one of the leading causes of gastrointestinal bleeding.

There follow two chapters that provide a comprehensive discussion of supplements in the context of cardiovascular disease. Central to their integrative approach is the use of supplements, and they provide for each a detailed justification, and as well their recommendation on dose and how and when the supplement should be taken. After a short chapter on detoxification, which mainly deals with chelation therapy, they present a chapter on what they view as an anti-inflammatory diet. Here there are strong similarities with the Zone Diet of Barry Sears.

The authors' favorite supplements for individuals with coronary heart disease and heart failure are coenzyme Q-10, L-carnitine and D-ribose. The book provides considerable justification for each. However, readers desiring a more comprehensive and technical discussion of these three supplements are referred to another recently published book by Dr. Sinatra titled *The Sinatra Solution. Metabolic Cardiology* (Basic Health Publications, New Jersey, 2005).

Finally, the book ends with a discussion of exercise and how selected supplements can energize one to get off the couch, and a chapter on stress, which is rather short considering the case the authors make for its critical role in both the development of heart disease and in triggering acute events.

In the final chapter, titled *Putting It All Together*, the authors include a valuable section on what interventions work for them when the New Cardiology Risk Assessment pinpoints a risk factor that needs modification. Included are the author's views concerning primary prevention for healthy individuals and the supplements they suggest, something that should be of considerable interest to readers of this Newsletter.

This book should appeal to anyone who does not want to sit back and wait for cardiovascular disease to become symptomatic. The book should also appeal to anyone who is at any stage of symptomatic coronary heart disease or cardiovascular disease or heart failure. The book discusses the whole spectrum of clinical presentations from angina to inoperable blockage and how these two cardiologists view the treatment options and what has, over the years, worked for them. The book should also appeal to those who feel that the best approach to patient care integrates conventional and alternative medicine. Throughout the book there are case histories which underscore the success the authors have had with this approach.

Editor: William R. Ware, PhD
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

The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 4 **June 2007** **1st Year**

In this issue we first review recent results regarding the use of intermittent hormone therapy for advanced or recurrent prostate cancer. As will be seen, research so far has yielded indications of significant benefit when comparison is made between intermittent and continuous treatment. In addition, a very important study is reviewed which deals with the use of 5α-reductase inhibitors (e.g. the BPH drug Proscar) during the off-period of intermittent therapy. The new results are very encouraging and may lead to wider acceptance of this protocol with attendant benefits for the patients.

As promised in the last Prostate Monitor, chemotherapy is reviewed in this issue. Unfortunately, not much has changed since this topic was discussed in our book. The reader will have to judge for himself if the enthusiasm of the oncology community is justified.

As readers of this newsletter are aware, vitamin D is the current hero in the alternative cancer prevention field. In fact, anyone who reads the national newspapers, at least in Canada, is now, to some extent, informed on the importance of vitamin D and health. The status of vitamin D and prostate cancer is briefly reviewed, but the results are only suggestive and certainly not as remarkable as those reported in the newsletter for breast and colorectal cancer.

Finally, risk factors and prevention for benign prostatic hyperplasia (BPH), including both diet and metabolic factors, are discussed in the light of recent research.

Wishing you continuing good health,

William R. Ware, PhD, Editor

INTERMITTENT HORMONE THERAPY

Hormone therapy is widely employed in the treatment of prostate cancer. Uses include therapy prior to radiation or surgical removal of the prostate (radical prostatectomy) and the treatment of recurrent or advanced prostate cancer. Its use for advanced cancer can in fact be monotherapy when the decision is made not to pursue surgical or radiation options. The other common scenario involves the treatment of recurrence after surgical and radiation options have been exhausted and a rising PSA indicates that the cancer has not been eradicated. Hormone therapy works by either cutting off the generation of testosterone or blocking its action in the prostate,

or both. The first is generally termed androgen deprivation therapy or the use of so-called androgen agonists or LHRH agonists; the second involves the use of antiandrogens. Cutting of the supply of testosterone from the testes with a drug is more or less equivalent to surgical castration, but has the merit of being reversible. Antiandrogen therapy does not significantly disturb the circulating testosterone levels which translate into fewer side effects, since most to the adverse effects of hormone therapy are the result of very low levels of this hormone. Androgen deprivation therapy and antiandrogen therapy are also frequently combined with more or less additive side effects, although the antiandrogen may be discontinued after a short period. See Chapter 7 of our book *The Prostate and Its Problems* for more information about the action and applications of hormone therapy.

While these hormone related protocols have been around for some time, there is currently uncertainty concerning two aspects: (1) when should hormone therapy be initiated after recurrence or as monotherapy for advanced cancer, and (2) should hormone therapy be given continuously or intermittently. This month we will examine the current status of intermittent hormone therapy. With intermittent hormone therapy involving androgen deprivation and low testosterone levels, during the off-treatment period the testosterone levels recover and the side effects associated with the deprivation subside. In general, PSA levels which have dropped dramatically during the initial hormone treatment phase will start to increase once therapy is stopped, and at some point treatment is resumed to initiate a second cycle. Several cycles are common before there is evidence of that the growth of the prostate cancer cells has become independent of testosterone, i.e. the so-called hormone refractory or hormone resistant stage in the process which has either already or will eventually become metastatic disease. At issue here are questions regarding side effects, quality of life, prostate cancer-specific survival and overall survival when a comparison is made between continuous and intermittent therapy.

Ulf Tunn has recently provided an update of the status of intermittent hormone therapy (IHT) which includes an examination of preliminary reports recently presented at meetings [1]. His discussion provides the following information:

- Phase II trials: Phase II trials examine such questions as effectiveness and side effects of an intervention. They are not randomized or placebo controlled. The results of a number of phase II trials of IHT are available. Tunn reported that there was good acceptance and feasibility. Quality of life was found to improve during the off-treatment interval (OTI); there was reduced toxicity and also a positive affect on bone density. An important result was that the studies reviewed showed no negative effects on cancer progression or survival. The duration of the OTI was also a predictor of clinical outcome. In a study which directly addressed quality of life issues, Spry *et al* [2] found that declines in quality of life during of the off-treatment period were slower than during treatment, but that the testosterone recovery was slower and less complete in older men and resulted in a concomitant poorer quality of life recovery. The maximum recovery of quality of life occurred most frequently by 9-12 months.

- Phase III trials: Phase III trials are generally randomized, although in the case of hormone treatment, placebo control is frequently not possible or unethical, and thus a comparison between two protocols is common. Phase III trials are underway in both North America and Europe which in general provide a randomized comparison between IHT and continuous therapy, either with or without antiandrogens. Preliminary reports discussed by Tunn were as follows. In one European study, there were no differences in overall survival between those on IHT and continuous combined therapy (LHRH agonist plus antiandrogen). In another European study, an interim analysis showed that the OTI, expressed as a percentage of the duration of a whole treatment cycle, appeared to decrease with each subsequent cycle, but in an Canadian study when the duration of the OTI was expressed as a percentage of the duration of the first OTI, the OTI appeared fairly stable over several cycles. One study also looked at the rate and extent of recovery of testosterone levels during the OTI and found normalization after about 3 months with 90% recovery during the first OTI and less in second cycle. Bone degradation was found to be worse in those receiving continuous treatment. The European investigators concluded that intermittent and continuous therapies are equally effective in terms of progression-free survival times.

Tunn remarks that the final answer regarding the potential benefits of IHT vs. continuous therapy must await the completion of these randomized phase III trials. However it appears that the above preliminary results should

prompt men to discuss the intermittent option vs. continuous therapy with their oncologist or urologist, since thus far, the advantages appear considerable and any unfavorable comparative aspects do not appear to have been found to date.

The guidelines discussed in last month's Prostate Monitor included the suggestion that for intermittent hormone treatment the 5α-reductase inhibitor (5ARI) finasteride (Proscar) might be considered for use during the off-treatment period. The authors associated with those guidelines list a number of reasons why the hypothesis that 5ARIs might confer benefit. These include evidence that finasteride has activity against prostate cancer, delays by 1 to 2 years the PSA increase associated with recurrence after surgery, enhances hormone therapy, and results in deeper PSA minimums when added to antiandrogen treatment alone. This approach was discussed in our book *The Prostate and Its Problems* but studies addressing this protocol were limited. Now there is additional evidence of the potential benefits from this option. A study which recently appeared in the *Journal of Urology* looked at two questions: (a) does finasteride prolong the off-treatment interval (OTI) and (b) does it influence the development of androgen independent prostate cancer, i.e. prostate cancer cells that do not respond to androgen deprivation [3]. This study was based on chart reviews which allowed the comparison between men who received finasteride (5 mg daily) during the OTI (60 men—group 1) and men who did not (41 men—group 2). All had biopsy proven prostate cancer, negative bone scans, combined hormone treatment with an LHRH agonist and antiandrogen, hormone sensitive disease as indicated by achieving and maintaining a PSA level of < 0.1 ng/mL during the treatment phase, a minimum of 5 years follow-up after initiation of hormone therapy, and finally testosterone recovery of > 150 ng/dL within 12 months of stopping hormone therapy. The results were as follows. The median OTI in groups 1 and 2 was 31 and 15 months respectively. Longer hormone therapy and increased age also predicted longer OTI. Predictors of a shorter OTI were a slow decrease in PSA while on hormone therapy, a higher baseline PSA and an increased Gleason score (see Chapter 4 of our book for a discussion of Gleason scores, clinical stage etc). Only higher clinical stage but not finasteride use predicted earlier onset of androgen independent prostate cancer—also termed hormone refractory cancer. The benefits this protocol was durable over almost 9 years of observation. During the follow-up, one patient in Group 1 died of prostate cancer whereas 4 died in Group 2.

Because finasteride reduces PSA generated from benign prostatic hyperplasia, allowance was made by using PSA threshold of 2.5 ng/mL rather than 5 ng/mL for ending the off-treatment period. The authors point out that his may have resulted in a shorter OTI that might have been warranted by cancer re-growth, i.e. even larger extensions of the off-treatment period might have been observed. About 70% of the men in this study had intact prostates.

This study addresses a very significant issue. Doubling the off-treatment time to two and a half years, even in cycle one, provides the patient with a significant extended period of relief from some of the side effects of hormone treatment, which incidentally include fatigue, weakness, reduced muscle mass, hot flashes, loss of libido, impotence, loss of bone mineral density, weight gain and anemia, and this is not a complete list! These adverse side effects are related to the profound reduction in testosterone during hormone treatment. And even if during additional cycles the off-time decreases, nevertheless the overall gain appears to be substantial and highly significant in terms of quality of life. The absence of an acceleration toward hormone refractory cancer found due to the use of 5ARIs in this study is of course very important.

CHEMOTHERAPY

Virtually all prostate cancer related deaths are attributable to the development of androgen deprivation resistance, i.e. hormone refractory cancer (HRPC). At this stage, if one ignores experimental drug trials, conventional oncology offers only chemotherapy as an option for attempting to influence the course of the disease. As of this writing, there still appear to be only two randomized Phase III trials reported in the literature, the so-called TAX 237 and SWOG 9916 studies. These were discussed in some detail in our book. It would seem very little has changed. Both of these studies used as a comparison, patients receiving the standard but ineffective treatment involving the drug mitoxantrone plus prednisone or hydrocortisone, a treatment used for palliation but one which does not improve survival. Both trials were based on the chemotherapeutic drug docetaxel. In SWOG, median survival was increased by 57 days from 15.6 months to 17.5 months. In TAX, the median survival time increased by 72 days from 16.5 months to 18.9 months. Adverse cardiovascular and gastrointestinal events were more frequent among patients in this trial receiving the chemotherapy. The

response from the oncology community appears to by and large be one of considerable enthusiasm. One recent editorial [4] used the title "Advanced Prostate Cancer: At Last a Role for Medical Oncologists." Another oncologist in a recent editorial wrote in reference to the TAS and SWOG trials [5]: "These trials have altered our perception about chemo-responsiveness of prostate cancer and have dramatically changed the standard of care in HRPC. We now have definitive evidence of a survival benefit with docetaxel based chemotherapy, which can be considered a new standard of care for the treatment of HRPC." A cynic or non-believer might simply observe that the success of chemotherapy with solid adult tumors is not that impressive in general and that small successes assume a significance entirely out of proportion to the actual benefit and in addition, there is no other treatment backed by randomized trials that can be offered to the patient. But one must be careful, because there are certain types of cancer that respond very well. The reader is referred to the *Perspective* in last month's Newsletter for the different ways these clinical results can be presented.

Men considering accepting the suggestion of chemotherapy should discuss with their oncologist or urologist the side effects of the specific protocol being promoted and decide for themselves if an increase in survival time, which still appears to be around 60-70 days, balances in their own minds the side effects and changes in the effectiveness of palliation that derive from this "new standard of care" as compared to the old protocol of palliation.

VITAMIN D AND PROSTATE CANCER

The reader of the Newsletter will recall that recent studies have provided strong evidence for a significant and large inverse association between the vitamin D serum marker 25-hydroxyvitamin D [25(OH)D] and both breast and colorectal cancer. It is therefore surprising that such a direct and evidentially easily observed relationship is not seen with prostate cancer. Epidemiological data is far from meager and yet has been characterized by inconsistencies and results that lacked statistical significance. Also, a metabolite of 25(OH)D, namely 1,25dihydroxyvitamin D [1,25(OH)D] has been strongly implicated as an inhibitor of the development of prostate cancer to the extent that safe ways of getting this metabolite into the prostate are currently under investigation. While 1,25(OH)D is made by an enzyme mediated reaction from 25(OH)D, the serum levels of the former are rather tightly controlled. However, 1,25(OH)D can also be made from its precursor within the cells of various organs. Thus one has a complex situation. The reader is referred to the Research Report on vitamin D that appeared in IHN for more detail (issues 147 and 148, May and June 2004).

A recently reported study attempts to address the issue of the role of vitamin D in prostate cancer using data from the Physicians Health Study, including serum levels of both 25(OH)D and 1,25(OH)D. This study found that a large proportion of US men had suboptimal vitamin D status, especially during the winter/spring season, An inverse association between 1,25(OH)D alone or together with 25(OH)D and aggressive prostate cancer was found which provided evidence that both of these metabolites may play a role in preventing the progression of prostate cancer, especially among older men. However, the results were not as compelling and seemingly straightforward as those presented in this Newsletter for breast and colorectal cancer.

These results are surprising because of several recent studies that connect sun exposure to reduced risk of prostate cancer. In one 528 prostate cancer patients and 442 basal cell carcinoma cases (a UV induced cancer) were examined for a correlation between cancer and sun exposure. Both groups were measured the same way as regards sun exposure. For those with the highest sun exposure, the risk of basal cell carcinoma was the highest, and for those with prostate cancer it was the lowest [6]. In another study, increased sun exposure decreased prostate cancer mortality [7] . In a study that looked at geographical distributions of UV intensity and prostate cancer mortality in the US, the expected variation with latitude was observed [8], i.e. those living in the higher latitudes had higher risk. Why this is not reflected in a more dramatic correlation between serum 25(OH)D and prostate cancer is not clear.

FRUITS, VEGETABLES AND BENIGN PROSTATIC HYPERPLASIA (BPH)

Two studies have recently appeared that address this issue. The first recruited a large prospective cohort of over 51,000 men from participants in the Health Professionals Follow-up Study [9]. The age range was 40-75 years of age. Macronutrient intake was determined by food frequency questionnaires. In 1992, six years after recruitment and as well in 1994, 1998 and 2000, an assessment by questionnaire was made of the presence

and nature of lower urinary tract symptoms (LUTS), the use of drugs for BPH, and surgery for BPH. LUTS were evaluated with the American Urologic Association Symptom Index (AUA Symptom Index). Readers are referred to Chapter 2 of our book for a discussion of BPH and this index. Incidentally, our book includes information for performing a self-administered evaluation of LUTS status. Total BPH was defined in this study as the combined endpoint of either surgery for or symptoms of BPH. The statistical analysis was organized by quintiles of intake measured in servings per day.

When the upper fifth in consumption was compared with the lower fifth, vegetable intake but not fruit was found to provide significant protection (an 11% reduction in risk of total BPH). Fruits and vegetables rich in beta-carotene, however, also offered benefit with a 13% reduction in risk when the first and fifth quintiles were compared. In this study, the vegetables and fruit regarded as rich in beta-carotene were carrots, yellow squash, yams, cooked spinach, raw spinach, cantaloupe, kale, romaine lettuce and peaches. Fruits and vegetables rich in vitamin C were also found to be beneficial. All these results were statistically significant, but only at the highest compared to the lowest intake, with the highest being 5 servings per day. When the results were broken down in terms of intake of micronutrients contained in the food consumed, beneficial results were obtained for only vitamin C, beta-cryptoxanthin and the combination of lutein and zeaxanthin. Incidentally, this latter combination is commonly used for supplementation in the context of macular degeneration prevention. Neither alpha- or gamma-tocopherol (vitamin E) intake was associated with BPH. The analysis was adjusted for confounding by age, race or ethnicity, smoking, body mass index, physical activity, alcohol consumption, energy and protein intake and intake of polyunsaturated fatty acids, The authors conclude that a diet rich in vegetables and in fruits and vegetables rich in beta-carotene, lutein and vitamin C may reduce the occurrence of BPH. However, significant benefit generally occurred only with heavy consumption (5 servings per day), although in the categories found beneficial, the trend in reduced risk with increased consumption was always statistically significant ($P \leq 5\%$). As readers of this newsletter are no doubt aware, there are numerous good reasons aside from BPH for consuming large amounts of fruits and vegetables.

The second study was of the case-control design using as cases patients surgically treated BPH [10]. A food frequency questionnaire was used to evaluate micronutrient intake. Consistent with the results of the Health Professionals Study, beta-carotene was found to confer an 18% risk reduction when the highest vs. the lowest quintiles of intake were used. Lowered risks were also found for alpha-carotene, and vitamin C with the vitamin C result just missing statistical significance. Also consistent with the above study, no protective effect was found for vitamin E. This study also found an adverse effect of high intakes of sodium and zinc. As an editorialist pointed out [11] the case of zinc may be understood because its intracellular level is increased in BPH and zinc is known to modulate 5α-reductase activity, an enzyme activity though to be directly related to prostate enlargement. The role of zinc in BPH is discussed in our book.

METABOLIC FACTORS AND BPH

Two recent studies have examined the relationship between the metabolic syndrome or its component in connection with the risk for BPH. In one study [12], 78 patients with BPH were divided into two groups depending on whether or not they had the Metabolic Syndrome (MBS as determined by the NCEP definition—see the April 2007 Newsletter). In patients with the MBS significantly higher prostate growth rates in two prostate zones were found as compared to those without the MBS. Thus the risk of progression of BPH can apparently be added to the rather long list of undesirable results of the MBS.

The second study [13] followed a group of men from 1993 to 2002. Prostate volume measurements were made with MRI and data on metabolic parameters and diabetic status were also collected. The primary outcome measure was MRI determined prostate volume whereas the secondary outcome was the severity of lower urinary tract symptoms as measured by the AUA Symptom Index. It was found that obesity, elevated fasting plasma glucose and diabetes were risk factors for BPH. For the fasting glucose, a significant tripling of risk of prostate enlargement was found when glucose levels $\geq$ 110 mg/dL were compared with $\leq$ 110 mg/dL, the former being the old American Diabetes Association cut-off for impaired fasting glucose. If the analysis was restricted to those without diabetes, the increased risk was 70% rather than 200 %. The authors comment on the impact this connection between metabolic factors and BPH will have on public health issues, given that there is a rising prevalence of obesity and diabetes and an aging population. However, they point out that physical activity and a healthy diet may help alter the natural history of BPH or prevent or attenuate its clinical manifestations.

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The Prostate Monitor is published 10 times a year by
International Health News, 1320 Point Street, Victoria, BC, Canada, V8s 1A5
Editor: William R. Ware, PhD
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