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William R. Ware, PhD - Editor

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This issue features colorectal cancer with three studies related to primary prevention. One study involves vitamin B6 and is of particular interest because of the low doses and large risk reductions obtained. This study should encourage readers to estimate their B6 intake. The second study presents some surprising results on the interaction between folic acid and selenium which has a significant bearing on taking supplemental selenium and also illustrates how poorly human biochemistry is really understood. Finally, the latest study on the fat-cancer hypothesis, this time in connection with colorectal cancer, is reviewed.

In previous issues the notion of the polypill was introduced. Now we have from the inventors of the polypill a huge meta-analysis which they use to promote the argument that everyone over some, as yet to be determined, age should be on three hypertension drugs. While the science turns out to be questionable, the proposal reflects a philosophy which will strike some readers as so absurd as to be amusing.

This issue also updates readers on activities at the FDA which provides insight as to the inner workings of that organization. One involves what is said on Cheerios cereal boxes, the other the declaration that a natural form of vitamin B6 which occurs in a number of food items is now classified as a new but untested drug and can not be sold as a supplement. That privilege is being reserved for a pharmaceutical company.

The remainder of this issue includes some of topics of general interest involving vitamin K and coronary calcium progression, alcohol and pancreatic cancer, and the age-old problem of the relative importance of overeating and exercise and the obesity problem.

In keeping with past tradition, a list of suggested summer reading is included in this issue. The books are all available from either amazon.com or affiliated book dealers.

The Prostate Monitor is also included with this issue.

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Wishing you good health and a safe summer,

William R. Ware, PhD, Editor

Highlights

MORE EVIDENCE—VITAMIN B6 REDUCES RISK OF COLORECTAL CANCER

A study just published appears to complete the picture on the association between vitamin B6 and colorectal cancer (CRC).[1] This investigation was part of the Physicians' Health Study and involved almost 15000 men who provided blood samples between 1982 and 1884. Through 2000 the researchers identified 197 incident colorectal cancer cases and individually matched them to 371 controls by age and smoking status. The vitamin B6 status was determined from a plasma marker PLP (pyridoxal 5'-phosphate) which when stratified by quartile had a range of medians from 43 to 144 nmol/L. Below 20 is apparently considered quite deficient. In the case-control comparison of the lowest to the highest quartile, the reduced risk of CRC was about 50%, a reduction that was statistically significant.

This protective benefit is consistent with the results reported in 2005 which were based on the Nurses' Health Study cohort which was also of case-control design.[2] PLP was used as the status marker and statistically significant associations were found for both colon cancer and colorectal cancer with risk reductions of 52% and 62% respectively. Total vitamin B6 intake was also estimated and a significant inverse association was found with a relative risk of 0.5. In this study, the total B6 intake ranged from 1.6 mg/day to 8.6 mg/day (quartile medians. The association between dietary and supplement intake of B6 and CRC was confirmed in a study published in 2008[3] although the risk reduction was less and the B6 intake less. In this study the authors also conducted a meta-analysis using 6 case-control studies of the association between CRC risk and dietary and total B6 intake which supported a statistical significant association with 33% risk reduction.

Thus there is strong evidence not only from studies were intake was estimated, but where B6 status was measured in plasma samples, that what appear to be modest amounts of vitamin B6 provide very significant protection against CRC. The range of total B6 intake was approximately 1 to 10 mg/day. Dietary Reference Intakes are generally stratified by age but to not exceed 2 mg/day. One popular multivitamin contains 3 mg per recommended daily dose, and at the opposite extreme, the formulation of another well-known firm in the US contains 75 mg in the recommended two pills per day. The popular "B-50" B complex formulation typically contains 50 mg of B6. Many drugs reduce the effectiveness of B6, especially antibiotics, blood pressure medications and estrogen containing drugs. Among the richest sources are sunflower seeds, wheat germ, beef liver, tuna and soybeans. Green vegetables are also good sources. Abram Hoffer, MD and Andrew Saul, PhD, in their new book *Orthomolecular Medicine for Everyone* (Basic Health Publications, Inc, 2008, Chapters 6 and 15) provide a good discussion of the use of high doses of B6 for children with learning and behavioural disorders and for schizophrenics. They comment that very few persons report negative symptoms with an intake of 1000 mg/day and when taken as part of a B complex supplement, side effects are virtually unknown. Incidentally, in your editor's opinion, this basic book on orthomolecular medicine should be on the bookshelf of everyone concerned about maintaining optimum health.

SELENIUM, FOLIC ACID AND COLORECTAL CANCER

A number of studies have reported lower mean selenium levels in colorectal cancer (CRC) cases vs. control, but overall the studies addressing this issue have been somewhat inconsistent. A recent study by Connelly-Frost *et al* has attempted to address some of the potential sources of inconsistency and they have discovered an interesting new confounding factor.[4] This was part of the North Carolina Colon Cancer Study which was a large case-control study of almost 1700 patients. Selenium status was measured from blood samples and dietary and lifestyle factors including folate intake obtained by interview. When three groups were compared, i.e. high selenium and high

folate, high selenium and low folate and low selenium and low folate, the reduced relative risk of colon cancer for those with high selenium and high folate was 50%, whereas the there was no benefit from high selenium levels if folate was low or for those with low selenium and low folate. High selenium was defined as > 140 micrograms/L (mcg/L) and high folate as > 354 mcg/day. Folate levels were estimated from dietary and supplement intake. Folate intake ranged from 45 to > 625 mcg/day. In the US, the average serum level of selenium is 123 mcg/L, a number derived from the NHANES national survey. Thus high selenium levels that were found associated with reduced risk were considerably above this average. In the famous SELECT trial of selenium and vitamin E for prostate cancer prevention, the baseline selenium median was 135 mcg/L and supplementation of 200 mcg/day raised this to around 225-250 mcg/L.[5] SELECT also looked at colorectal cancer incidence and mortality and found no significant association when the comparison was with a placebo. In this study, folate status was not considered, which might help account for the null CRC result. As discussed in *The Prostate Monitor* this month, there have been questions raised as to the suitability of the selenium source used in SELECT. But the data from SELECT clearly show that 200 mcg/day elevates the serum selenium level to well above that found protective in the above study, provided there was adequate folate.

In the discussion, the authors comment that to their knowledge this is the first report of an interaction between selenium and folate in connection with colon cancer risk. Studies of folate and colon cancer have ignored selenium and vice versa. Also, it is difficult to assess selenium intake from questionnaires or interviews. In fact, there is a significant geographical variation in the selenium content of soils and thus the food produced.

As has been discussed several times in this Newsletter, the role of folate in colon cancer appears complex with low status conferring risk which returns at high levels from supplementation, suggesting high intake of folic acid as a possible promoter of existing neoplastic processes. This complicates the study of the effectiveness of high levels of both micronutrients in reducing cancer risk. The folate levels reported in the study of Connelly-Frost *et al* are similar to those found in the NHANES database for the period 1999-2000 for individuals not taking supplements.[6] Mandatory folic acid fortification occurred halfway through their study at the start of 1998. The daily intake of 345 mcg/day, which was the threshold used for high folate intake, is around the 50th percentile in the US male population for the same age group (≥ 50 years), but for women, only 25% were in the high-folate group. Thus even with a high selenium status, low folate status is far from unlikely in the absence of supplementation. However, a single multivitamin pill per day containing 400 mcg of folic acid would bring the level of intake well above the cut-off for benefit, and this level would be mostly metabolized, whereas for higher levels of intake, as has been discussed in the Newsletters, this is not the case.

The study of Connelly-Frost *et al* is important because it illustrates a level of complexity in human biochemistry that is frequently ignored. The advances in biochemistry and microbiology appear to have generated the notion that studies carry great credibility simply because they are based on modern science. This ignores the high probability that the level of ignorance still vastly exceeds the level of knowledge.

ANIMAL FAT OR PROTEIN INTAKE AND RISK OF COLORECTAL CANCER

The notion that eating fat causes cancer has been around for some time. It was an integral part of the war on fat which, as it turns out, appears to have been somewhat misguided. A meta-analysis of data related to the association between colorectal cancer and animal fat or protein has recently been published in the *American Journal of Clinical Nutrition*.[7] While the study was financially supported by national pork and beef associations, the assertion is made in the paper that they did not contribute to the writing, analysis or interpretation of the research findings.

Six prospective cohort studies were identified which contributed 1070 cases of colorectal cancer in over 1.5 million person years follow-up. In the summary relative risk estimates, no evidence was found for enhanced risk associated with animal fat. Similar null results were obtained from the analysis of case-control studies and dose-response analysis for associations between 20-g/day increments in animal fat intake and colorectal cancer. In an analysis of a smaller number of studies reporting animal protein intake, similar null results were obtained. Only one out of the six prospective

studies on animal fat was in strong disagreement with this conclusion. This was based on the Nurses' Health Study and reported in 1990 a two-fold increase in risk for the highest intake vs. the lowest. The authors of the meta-analysis do not offer an explanation, but it seems clear that the weight of evidence is in favour of animal fat and protein being benign in the context of colorectal cancer.

BLOOD PRESSURE MEDICATION FOR ALL

In the June issue of the Newsletter, the progression toward the so-called polypill was documented with a discussion of a variant called the Polycap which combined a statin, three antihypertensive drugs and aspirin. The Polycap was intended for use with individuals independent of the presence or absence of hypertension or hypercholesteremia. In the latest issue of the *British Medical Journal* (BMJ), Law *et al* [8] present a meta-analysis of 147 randomized trials regarding the use of blood pressure lowering drugs for the prevention of cardiovascular disease. Two of the three authors (Wald and Law) were the "inventors" of the polypill and hold or have applied for patents on the combination and a copyright on the term. The conclusion from this huge lumping together of diverse studies was that blood pressure lowering is important for everyone over a certain age and that it is unnecessary to measure blood pressure, but rather just lower it. Dr. Law was quoted making the following statement to *the heart.*org, a daily newsletter for cardiologists. "Whatever your blood pressure, it is concluded that you will benefit from lowering it further. Everyone benefits from taking blood-pressure-lowering drugs. There is no one who does not benefit because their blood pressure is normal." This position is justified by the meta-analysis which showed that in people aged 60-69 with a diastolic blood pressure before treatment of 90 mm Hg or a systolic pressure of 150 mm Hg, three drugs at half the standard dose in combination (as in the polypill) was calculated to reduce the risk of CHD by approximately 46% and stroke by 62%, and that the five main classes of blood-pressure-lowering drugs were equally effective with the exception of calcium channel blockers, which had a greater preventive effect on stroke. The researchers also found that individuals with and without CVD benefited equally from the indiscriminate anti-hypertensive treatment. In anticipation of the accusation that they favour "medicalising" a population, the authors offer for the reader's consideration the following examples: anti-malarials, vaccines, and contraceptive pills.

Editorial comment in the same issue of the BMJ was favourable to this notion, but *theheart.org* (May 22, 2009 online) quoted two experts from the US that took issue with what amounts to a new concept in the practice of medicine. Dr. James Elliott (Rush Medical College, Chicago) suggested abandoning blood pressure measuring was like throwing the baby out with the bathwater. Furthermore, he was critical of the meta-analysis which he claimed included 37 studies of beta-blockers used after a heart attack which should never have been included. He called the meta-analysis simple and old fashioned and the investigators "the ultimate lumpers." Dr. Franz Messerli (St. Luke's-Roosevelt Hospital Center, New York City) was quoted as saying that the authors had to make numerous assumptions in their analysis, "some possibly valid, others clearly not." He also points out that "it is a little surprising that now beta blockers look better than in any review ever done, and that numerous meta-analyses have clearly demonstrated that beta blockers do not reduce the risk of coronary heart disease in hypertension, despite the fact that they lower blood pressure." *The heart.org* summarized Dr. Messerli's views with the following quote, "A meta-analysis is like a sausage; only God and the butcher know what goes in, and neither would ever eat any."

It would seem unlikely that what one BMJ editorialist describes *as a new era for blood pressure management* will replace the well established practice of measurement and if necessary, treatment with one or more drugs at doses appropriate to the individual in question. But in the world apparently favored by Law and colleagues, the next step would seem to be a drive-through window for drug stores where one can quickly get their polypill or their combo blood pressure pill, perhaps at a discount with a coupon. If everyone over a certain age should take the blood pressure combo, then probably a prescription will be unnecessary, just ID. However, the notion of treating everyone including individuals with low blood pressure with three drugs because a questionable meta-analysis suggests benefit in terms of CHD and/or CVD indicates a trend in medicine which some may find troubling. Nevertheless, the notion that the salvation of humans beset by health problems lies mainly in

prescription drugs is probably here to stay, and true primary prevention through non-pharmaceutical interventions will require a long time to be come a routine aspect of primary care that is aggressively promoted.

FDA DECLARES CHEERIOS® AS A NEW DRUG WHICH HAS NOT BEEN APPROVED

On Wednesday, May 13, 2009, it was reported in the media (e.g. the *Minneapolis St. Paul Business Journal*) that in a letter to General Mills, the FDA took the position that "Based on claims made on your product's label, we have determined that your Cheerios Toasted Whole Grain Oat Cereal is promoted for conditions that cause it to be a drug." The claim is that eating the cereal can help lower bad cholesterol by 4% in six weeks. It is because of this promoted benefit that the product is deemed a drug. In addition, the FDA pointed out that this new drug has not been recognized as safe and effective for use in the prevention of hypercholesterolemia or coronary heart disease. General Mills cannot legally market Cheerios unless they apply for approval of Cheerios as a new drug or change the way the product is labelled. If General Mills does not correct this violation of the law, the product could be pulled from shelves by government agents and legal action initiated. In the words of a famous humorist, I'm not making this up.

For many readers this will remind them of Cheerios TV ads which are currently running. It is also reminiscent of the FDA attack some time ago on farmers who were making health claims about cherries and were presented with the same arguments as given above. But another issue with Cheerios seems to be the clinical significance of what appears to be a rather small if not negligible impact on LDL cholesterol, even assuming that LDL is as important as mainstream medicine would have us believe (see the Research Report in the last Newsletter). There is also the false sense of security implied by the TV ads that if one eats this breakfast cereal, then all their worries about heart disease are over.

The FDA has also moved to prevent the use of a natural form of vitamin B6. It is called pyridoxamine and is found in food. It leads to the same end product metabolite as the two other forms of B6. The FDA decision is in response to a petition from a drug company which wants to use this natural product as a prescription drug for diabetes-related kidney disease. Organizations that are fighting this ruling point out that pyridoxamine is protected by a grandfather clause in the law which the FDA is using as justification for its actions. This clause in simple terms states that a natural product that was marketed as a supplement before being authorized for investigation as a "new drug" is exempt. The FDA, at the request of a drug company, is instituting a ban on the sale of a natural product found in fish, chicken, walnuts, carrots, eggs and other foods simply because it is isolated and included in multivitamins or sold as a separate supplement. Individuals take enhanced amounts of this particular form of B6 for a number of reasons related not only to kidney disease prevention but also related to atherosclerosis, chronic inflammation, cataract formation, and Alzheimer's disease.

Historically, drug companies created some drugs by making small modifications to the chemical structure of natural products to facilitate patent protection. It now appears that this is no longer necessary. As has been discussed in previous newsletters, there is even an omega-3 supplement that is a prescription drug which costs substantially more than approximately equivalent preparations widely available in health food stores. But in this case, the FDA has not attempted to prevent us from purchasing the over-the-counter product. And there is certainly no problem finding fish oil supplements that are highly purified and termed pharmaceutical grade. The creation of a very expensive prescription equivalent was no doubt partly motivated by the belief that some physicians feel more comfortable writing a prescription than sending a patient to the health food store, and in addition, some patients feel they are getting better treatment from a prescription "drug."

PREDICTING RISK OF DEMENTIA IN OLDER ADULTS

This study which was just published online in the journal *Neurology*[9] is interesting because of the factors selected in the process of constructing a risk score or index for the purpose of making predications of the development of dementia. The subjects used for the collection of data had a mean age of 76 with recruitment between 1991 and 1994 and follow-up through 1998-1999. The score was based on 480 out of 3375 individuals who developed dementia within 6 years of baseline evaluation. The score consisted of 12 measures or factors. Those modifiable factors of interest in the context of prevention because of associated increased risk were body mass index (BMI) < 18.5 (Wt in kg divided by the square of height in meters), history of coronary heart bypass surgery, and lack of alcohol consumption. The BMI value represents being quite underweight. Someone 65 inches in height with a weight of 114 pounds would have a BMI of 19. The connection with bypass surgery is complicated because it implies cardiovascular disease and it is well known that dementia can have a vascular component. But it also takes into account the well-known but not much discussed risk of cognitive impairment caused by the procedure. In the parlance of the trade, it is called "pump head" in recognition of the adverse cognitive effect of the heart-lung machine hook-up during the procedure. The alcohol connection is no doubt complex, but recognizes the cardiovascular benefits of moderate alcohol consumption discussed on a number of occasions in this Newsletter. The remainder of the factors are of more interest to those directly involved in the evaluation process since they require mental status tests, genetic information and the results of MRI studies of the brain and carotid artery ultrasound estimation of atherosclerosis.

HIGH CARB VS. HIGH FAT DIETS FOR TYPE 2 DIABETICS

This is a topic that will no doubt continue to be debated. The philosophy of "covering" carbohydrates with added insulin injections appears to be popular. A meta-analysis has just been published of a large number of studies that examined head to head or cross-over studies of the impact of low fat-high carb vs. high carb-low fat diets on parameters of glucose metabolism and blood lipids.[10] Nineteen studies involving 306 subjects met the inclusion criteria which included the requirement that only the amount, not the nature of the carbohydrate was changed and the total energy and protein intake remained the same. Excluded were trials with type 1 diabetics. The median diet carbohydrate/fat ratio in the low-fat high-carb (LFHC) and high-fat low carb (HFLC) diets were 58%/24% and 40%/40%, respectively. There were no significant changes observed between the two diets in glycated haemoglobin (HbA1c), fasting plasma glucose, and total or LDL cholesterol. However, the LFHC type diet significantly increased fasting insulin and triglycerides and lowered HDL cholesterol when compared to the HFLC diets. The authors conclude that replacing fat with carbohydrate, the general result of going on a low fat diet, could deteriorate insulin resistance and have an adverse impact on triglycerides. The triglyceride/HDL ratio also changed in a direction indicating increased dyslipidemia which is generally accompanied by an increase in small, dense LDL particles which may be the only LDL fraction with any atherogenic potential. The authors comment that the increase in triglycerides can be avoided by calorie restriction sufficient to produce weight loss. The triglyceride/HDL ratio is frequently used to estimate insulin resistance, and a ratio of 3.5 is a common threshold. Insulin resistance is of course bad news since it is the gateway to type 2 diabetes.

VITAMIN K AND PROGRESSION OF CORONARY CALCIUM

The progression of coronary calcium is a serious matter since it implies increasing silent atherosclerosis and correlates very well with an increase in future risk of acute coronary events. The failure of silent atherosclerosis to correlate with total or LDL cholesterol was discussed at length in a Research Review in the last Newsletter and is the subject of a paper by your editor which is in press in the journal *Medical Hypotheses*.[11] Intervention studies aimed at slowing or reversing the progression of coronary atherosclerosis are rare and mostly based on statin drugs, which incidentally

do not work in this application for individuals free of symptomatic heart disease. Thus the study of Shea *et al*[12] is of particular interest because it involves a micronutrient, not a prescription drug.

In this randomized intervention trial, coronary artery calcium (CAC) was measured at baseline and after 3 years of follow-up in 388 health men and postmenopausal women. A daily multivitamin with 500 micrograms of vitamin K1 (phylloquinone) per day was taken by 200 subjects whereas 188 received a multivitamin alone and thus acted as the control. In the subgroup that was ≥ 85% adherent to the study protocol, those who received vitamin K1 had 6% less progression than did those who received the multivitamin alone. This effect was seen only with those with pre-existing CAC. In both the treatment and control groups the baseline CAC was low (vitamin K group, 19 Agatston units, control group 34 Agatston units). If one uses the observed increases in CAC score in the vitamin K and controls groups over the 3 years, if both had started at 20 CAC units, then at the end of 12 years the control group CAC score would have quadrupled whereas the vitamin K group CAC score would have doubled.

As the authors point out, the rate of progression of CAC has not yet been established as a surrogate marker for therapy success in the context of cardiovascular event risk. Thus the justification for increasing the intake of vitamin K1 would be based simply on the established increase in risk of acute events ultimately associated with progression. Foods that contain over 500 mcg of vitamin K1 per normal serving include kale, collards, spinach, turnip greens, cooked beet greens, and cooked turnip greens. Avocado and kiwifruit are also high in vitamin K. The vitamin is also available as a supplement. Individuals on anticoagulants such as warfarin (coumadin) should consult with their physician before increasing their vitamin K intake since this vitamin interacts with the action of anticoagulants.

ALCOHOL AND PANCREATIC CANCER

Amid all the good news about moderate alcohol consumption, two studies just published in the *American Journal of Epidemiology* suggest that moderation may be even more important than realized.[13,14] Both studies find an approximately 50-60% increase in risk of pancreatic cancer relative to light drinkers (< 1 drink per day) or abstainers when alcohol consumption exceeds moderate levels. The threshold for enhanced risk was between 30 and 40 grams of alcohol per day, which translates to 2 to 3 drinks. Both studies attempted to adjust for smoking as a cofounder, and on also found the increased risk was not influenced by folate intake. Both studies had long follow-up times and the results were statistically significant.

Pancreatic cancer is among the most rapidly fatal cancers with a dismal 5-year survival rate of 6% or less. There is no effective way to screen for this cancer and thus prevention becomes of paramount importance. Current smoking, diabetes and body fatness have so far been identified as risk factors.

HYPOTHESIS: OBESITY RESULTS MOSTLY FROM EATING TOO MUCH

This of course is not a novel idea, but new research recently reported does not contradict this notion. The research, which was reported at the 2009 European Congress on Obesity held in Amsterdam in May, used an innovative approach to study, for the first time, the relative contributions of food and exercise habits to the development of the obesity epidemic. The work, presented by Professor Boyd Swinburn from Deaken University in Australia, concluded that the rise in obesity in the United States since the 1970s was virtually all due to increased energy intake. The study is the first to examine the question of the proportional contributions to the obesity epidemic from food consumption and lack of exercise by combining metabolic relationships, conservation of energy, epidemiological data and agricultural data.

Professor Swinburn was quoted as saying that “this study demonstrates that the weight gain in the American population seems to be virtually all explained by eating more calories. It appears that changes in physical activity played a minimal role.” The scientists started by testing 1,399 adults and 963 children to determine how many calories their bodies burn in total under free-living conditions. Once they had determined each person's calorie burning rate, Swinburn and his colleagues were

able to calculate how much adults needed to eat in order to maintain a stable weight and how much children needed to eat in order to maintain a normal growth curve. They then determined how much Americans were actually eating, using national food supply data (the amount of food produced and imported, minus the amount exported, thrown away and used for animals or other non-human uses) from the 1970s and the early 2000s.

The researchers used their findings to predict how much weight they would expect Americans to have gained over the 30-year period studied if food intake were the only influence. They used data from a nationally representative survey (NHANES) that recorded the weight of Americans in the 1970s and early 2000s to determine the actual weight gain over that period. The researchers found that in children, the predicted and actual weight increase matched exactly, indicating that the increases in energy intake alone over the 30 years studied could explain the weight increase. "For adults, we predicted that they would be 10.8 kg heavier, but in fact they were 8.6 kg heavier. That suggests that excess food intake still explains the weight gain, but that there may have been increases in physical activity over the 30 years that have blunted what would otherwise have been a higher weight gain," Swinburn said. "To return to the average weights of the 1970s, we would need to reverse the increased food intake of about 350 calories a day for children (about one can of ordinary soda pop and a small portion of French fries) and 500 calories a day for adults (about one large hamburger)". "Alternatively, we could achieve similar results by increasing physical activity by about 150 minutes a day of extra walking for children and 110 minutes for adults, but realistically, although a combination of both is needed, the focus would have to be on reducing calorie intake." This type of study is easily confounded and the thesis will no doubt continue to be examined and debated before there is general agreement as to whether or not it is correct.

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

BOOK SUGGESTIONS FOR SUMMER READING

1. ***Slow Death by Rubber Duck*** by Rick Smith and Bruce Lourie with Sarah Dopp (Knopf Canada, 2008). This book carries the more informative subtitle *How the toxic chemistry of everyday life affects our health.* Rick Smith holds a doctorate in biology from the University of Guelph in Ontario, Canada, and is one of Canada's leading environmentalists. Bruce Lourie started one of Canada's largest environmental consultancies and is also President of the Ivey Foundation, a major supporter of education and medicine. Their book deals with the major pollutants that we encounter every day in food, fabrics, food and beverage containers, air, water, toys, cosmetics, personal care products, out-gassing from TV sets and computers, and this is just a limited list. The authors use as introductions to some of the chapters the results of experiments they conducted on themselves, intentionally undergoing exposure to toxins in order to see how much showed up in urine and blood samples. The results were interesting but hardly of much scientific merit. Toxins are discussed in detail both historically and from the point of view of toxicology and politics. But this is a complex area. The studies that need to be done are impossible because human subjects would be necessary, large ranges of chronic and periodic intake required, and unreasonably long follow-ups needed to produce convincing evidence. Circumstantial evidence is regarded by some as junk science and the chemical industry normally will contend that exposure to small amounts of their chemicals is harmless, that no danger has ever been "scientifically" demonstrated and that the millions of tons of chemicals spread around the world are harmless and provide great benefit to mankind. This book represents the position of those who promote playing it safe and aiming at zero exposure in the belief that the introduction of chemicals foreign to human biochemistry into a system of incredible and not well-understood complexity is in general not a good idea. This book obviously sides with the conservative approach and may inspire some readers to attempt to achieve a more chemical free home and stop using a variety of consumer products that appear to contain potentially toxic chemicals with totally unknown long-term consequences. After all, there appear to be large differences in chemical sensitivity and it is well known that there is a large variation in the ability to naturally detoxify. This book is also a good source of websites relevant to both US and Canadian consumers who are seeking help in navigating what the authors describe as a toxic world the chemical companies have created. But it appears important to recognize that expert opinion is of necessity based on inadequate knowledge, studies will generally be of debatable value, and expert opinion is really just opinion, in some cases strongly biased. Better things for better living trough chemistry, a phrase coined by a major chemical company many years ago, may turn out to be one of the most cynical and deceiving promotional statements ever made. But we may never know.

2. ***Gut and Psychology Syndrome*** by Dr. Natasha Campbell-McBride, MD. The cover indicates a subtitle--*Natural treatment for dyspraxia, autism, ADD, dyslexia, ADHD, depression and schizophrenia* (Medinform Publishing, 2004). Clearly a tall order. Dr. Campbell-McBride has postgraduate degrees in neurology and nutrition to augment her MD. In 2002 she opened the Cambridge Nutrition Clinic. As a parent of a child diagnosed as autistic, she is acutely aware of the difficulties facing other parents with similar problems, and she has devoted much of her practice to helping these families. The thesis of this book is that many neurological disorders have their origin in gut dysfunction. She believes that there is a strong link between learning disabilities and other psychological problems, the food and drink we consume, and the condition of our digestive systems, and the results of her work and research worldwide have supported her position on this subject. This book summarizes the nutritional and biochemical connections between psychiatric and neurological disorders seen in both children and

adults and gastrointestinal dysfunction. The biomedical approach to autism discussed in a recent Newsletter illustrates this principle. This is not a connection mainstream medicine normally makes, which this book makes clear is a profound mistake. The gut is normally considered the domain of the gastroenterologist. Individuals with problems listed in the subtitle are presumably rarely referred to this specialty, and if they were, it is not clear that it would be beneficial. This book presents evidence that the gut-brain connection and well as the gut-general health connection is strong, important, and is ignored at the risk of poor health and the failure of therapy. The connection between gut dysfunction and immunity, the proper digestion of proteins and carbohydrates and the ability to naturally detoxify are critical aspects of this subject. Your editor recently heard Dr. Campbell-McBride give a compelling talk on this subject at a recent international conference in Montréal billed *Orthomolecular Medicine Today*, and immediately purchased and read her book. It is probably one of the most important books anyone can read who is concerned with not just mental health but health in general. A major focal point must be the gut.

Part One of the book describes what goes on in the gut and what can go wrong. Part 2 provides a guide to treating the Gut and Psychology Syndrome (GPS), i.e. treating what goes wrong. It features diet and supplementation, including probiotics, digestive enzymes and vitamin and mineral supplementation. Part 3 deals with other issues including immunity and constipation. This book is a must-read for anyone interested in their health and essential for anyone confronted with psychological problems, either their own or in a family member or relative or friend.

3. ***Fruitless Fall*** by Rowan Jacobsen with the subtitle *The collapse of the honey bee and the coming agricultural crisis* (Bloomsbury, New York, 2008). This book was mentioned in an earlier Newsletter. It addresses a problem that the politicians have apparently not clued in on. Once the honey bees are gone, many aspects of modern agriculture collapse. No bees, no pollination, no fruit and nuts. It is that simple. One would think that there would be a crash program akin to the Manhattan project (development of the atom bomb) to find out why honey bee colonies are collapsing and what to do about it. Rowan's book represents a comprehensive treatment of this critical subject of bees at risk and reads like a mystery novel. The book also includes an excellent discussion of the life cycle and behaviour of honey bees. Unfortunately, Rowan is unable to provide an answer to the fascinating mystery of the disappearing bee colonies, but he does an excellent job in bringing the reader up to date regarding the various theories and the research that is ongoing. The book includes many interviews with leading bee researchers and environmentalists. This book should be required reading in schools simply because it provides valuable background for understanding the complexity of our biological environment and the amazing organization of the beehive and what amazing things bees do. It has been referred to as a squeal to the famous book *Silent Spring* by Rachel Carson.

4. ***Worried Sick*** by Nortin M. Hadler, MD. The subtitle is *A prescription for health in an overtreated America* (University of North Carolina Press, 2008). Dr. Hadler is a professor of medicine and microbiology and immunology at the University of North Carolina at Chapel Hill. This book is sort of a sequel or companion to his earlier book *The Last Well Person, How to Stay Wells Despite the Health-Care System.* He is clearly not someone Big Pharma would recruit to propagate their philosophy and message. He introduces two interesting concepts, Type I Medical Malpractice and Type II Medical Malpractice. Type I is what keeps malpractice lawyers in business. Type II involves doing the unnecessary but doing it superbly, and represents practices of mainstream medicine which are counter-productive for both the patient and those who provide health care dollars. It is an interesting concept that for sure is not popular in the corridors of power of mainstream medicine. This is an very relevant, interesting and entertaining book that is highly recommended for those interested in insight into how modern mainstream medicine really works and what can be done to fix its manifold problems. However, some will find his final solution to the US health care crisis somewhat idealistic, especially given its heavy reliance on hard evidence of benefit and small numbers needed to treat to justify spending public funds.

5. ***Catching Fire. How cooking made us human*** by Richard Wrangham (Basic Books, 2009). The author is the Ruth Moore Professor of Biological Anthropology at Harvard and curator of Primate Behavioural Biology at the Peabody Museum. His book presents a groundbreaking new theory that the advent of cooking was responsible for our evolutionary success, and that this transformation took place

quite early in the process starting with the immediate predecessors of *Homo erectus* and approaching completion with *Homo sapiens.* The theory is mostly based on evidence of the advent of the ability to make a fire at will and the fossil evidence concerning brain size and the size of the digestive system. The author provides a fascinating proposal concerning the impact of cooking and what we today would call a campfire on the shift from raw to cooked foods and suggests that this was a central turning point in the evolution of humanity. Once the practice of cooking food started, the human digestive tract shrank, the brain considerably and significantly enlarged, time and energy spent on spent chewing, especially raw meat, decreased dramatically, and cooking became the basis of pair bonding, greatly expanded social structures, and ultimately led to the creation of the household. Being able to build fires also allowed early man to deter predators, which reduced the risk of living on the ground, and allowed eating after dark. The change to eating many foods in cooked form had a huge impact on many aspects of life and the evolution of modern man, as did the fire as a heat source, and some of these are addressed in the final chapters of the book. In Wrangham's view, "Cooking was a great discovery not merely because it gave us better food, or even because it made us physically human. It did something even more important: it helped make our brains uniquely large, providing a dull human body with a brilliant human mind." The book should fascinate anyone interested in our ancient origins and the evolution of our modern eating habits. Much of the evidence presented in this book should also motivate those who believe humans evolved only as vegetarians and that this is the natural lifestyle to reconsider their views.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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This issue reviews the use of MRI for prostate cancer diagnosis, the possible reasons for the failure of the SELECT trial, and chemotherapy for prostate cancer. In addition, a number of studies reported at the 2009 American Urological Association meeting are presented on the basis of information available in the meeting abstracts.

The shortcomings of the current methods available for diagnosing prostate cancer are well known among urologists but might come as a surprise to patients. Imaging theoretically offers an opportunity for improvement and MRI, being readily available except where health care is rationed, continues to be investigated. Not only is it non-invasive, but even if it is never able to provide definitive results, there is the potential for offering guidance in the standard biopsy procedure.

The SELECT trial which was a multicenter randomized clinical trial of vitamin E and selenium for the primary prevention of prostate cancer turned out to be a big disappointment. However, questions continue to be raised as to the design of the study and the validity of the results. Even as the trial was being launched, there were questions concerning the choice of the form of vitamin E. Now serious questions are being asked about the selenium compound used.

Presumably, the goal of oncology is to have a chemotherapy drug for every cancer, and indeed, one that works. However, judging whether or not a particular protocol works can be based on tumor size regression which may be meaningless, or increased survival time, which for many adult solid tumor cancers appears, at least to those not confronted with the decision to say yes or no, to be very short. Prostate cancer appears to fall in that category. An update of the Cochran Collaboration meta-analysis of chemotherapy for prostate cancer will be discussed.

Finally, some interesting papers from the annual meeting of the American Urological Association held in Chicago in April will be discussed.

Wishing you continuing good health,

William R. Ware, PhD, Editor

DOES MRI HAVE A ROLE IN PROSTATE CANCER DIAGNOSIS

While there has probably been more research on prostate cancer than any other malignancy all this effort has not resolved several outstanding issues. These include: when are the indications strong enough to justify recommending a biopsy, how to improve the biopsy technique in order that fewer cancers are missed, how to decide when a diagnosed cancer is insignificant, indolent and appears to present no immediate risk to the patient and therefore does not need immediate treatment, and finally, what is the best action to take when the first biopsy is negative and PSA remains elevated.

MRI technology is emerging as a very important imaging tool for identifying low-volume prostate cancers, characterizing tumors, helping in patient-risk stratification and aiding the focused use of the standard biopsy procedure. MRI also has utility in improving the targeting of treatments and verifying treatment success.[1] Those interested in perfecting and introducing MRI procedures into prostate cancer diagnosis are partly motivated by the often quoted statistic that first biopsies miss up to 20-25% of cancers. Nevertheless, the prevailing view is that MRI has a limited role in the management of prostate cancer.[2]

One problem with prostate MRI derives from artefacts when the scan is done after a biopsy. This situation could arise after a negative biopsy when cancer was strongly suspected. The artefact is caused by biopsy-generated hemorrhages. These artefacts take 2 to 4 months to resolve, introducing an unacceptable waiting time. The simple solution is obviously to do the scan prior to the biopsy, a sequence which makes sense for a number of reasons.

But the central problem has to do with the ability of imaging to correctly identify those with disease and also correctly identify those without disease. This has to do with true and false positives and true and false negatives, i.e. sensitivity and specificity. Proposed techniques need to offer rather large improvements in these measures. The classical MRI has evolved and continues to evolve. There are currently four protocols: T1 weighted imaging (T1-WI) T2 weighted imaging (T2-WI), dynamic contrast enhanced MRI (DCE-MRI), and magnetic resonance spectroscopy imaging (MRSI). There are also options regarding the placement of radiofrequency coils including pelvic and rectal. Given all these possibilities, researchers are now attempting to examine the specificity and sensitivity of various combinations, and there are obviously a number of them.

But in the final analysis there is a need for a gold standard of comparison for the existence or absence of the disease so one can separate true from false positives and true from false negatives. This requires, ideally, a large number of individuals who have had MRI work done before biopsy and then undergo surgery to yield a prostate for pathological examination. It also requires a set of pathological standards for deciding whether or not cancer is present and when existing cancer is insignificant, the latter call being somewhat arbitrary.

Where we stand today appears to be that there have been a number of small studies using various combinations of the MRI protocols listed above. The overall impression is that MRI improves the diagnostic accuracy, and the more sophisticated the protocol, the better the sensitivity and specificity.[3,4] There is also growing evidence that MRI has a significant role in the case where a negative biopsy comes as a surprise due to perceived elevated risk.[5] But it also appears that there is a long way to go before MRI will be used routinely prior to biopsy, either in the hope of avoiding the biopsy or assisting in identifying patients who are candidates for active surveillance. Cost will also be an issue with many health care providers.

POSSIBLE REASONS FOR FAILURE OF THE SELECT TRIAL OF VITAMIN E AND SELENIUM

The failure and early termination of the SELECT trial received extensive coverage in the print and TV media. In a recent issue of the journal *Molecular Interventions* Hatfield and Gladyshev [6] have examined what appear to be design flaws in the SELECT trial which may have biased the results toward the observed null. They examine the differences between the SELECT trial and earlier selenium trials which produced significant reductions in the risk of various cancers.

First, the form of selenium used, L-selenomethionine, can be diverted away from the synthesis of selenium containing proteins because of the methionine moiety. Earlier studies used selenite and selenium-enriched bakers yeast, and while the latter also contains selenomethionine, it also contains other selenium containing

compounds as well which cannot be diverted and are therefore converted into the presumed anti-tumor metabolites.

The second problem they discuss relates to the baseline selenium status of the study group which was higher than that in earlier human trials. In fact, in earlier trials patients were selected for low serum selenium levels and treatment benefits were found to be restricted to those with low baseline selenium levels. They point out that serum selenium levels in most Europeans, even those supplementing with selenium, are lower than Americans not taking supplements. Thus Europe might have been a better place to stage the SELECT trial. While they do not comment on this, the use of study subjects in supplement trials that already have significant and perhaps adequate baseline serum levels is a common practice.

Finally, they point out that the understanding of how selenium acts at the molecular level is not well understood, and argue that given this, such a large-scale study was perhaps not justified. Nevertheless, it would appear to be a mistake to view selenium as useless since it is in fact a very important micronutrient.

CHEMOTHERAPY FOR PROSTATE CANCER

One frequently sees statements in papers indicating that improvements in survival for hormone resistant prostate cancer are primarily seen with docetaxel-based therapies. In our book this subject was discussed and it was pointed out that enthusiasm depends strongly on how one regards very small increases in survival, given that such treatments have serious side effects. Not much appears to have changed since that chapter was written. The well known and respected Cochrane Collaboration has just updated their 2006 analysis[4] which included 47 randomized trials. The studies involved 5-fluorouracil, cyclophosphamide, doxorubicin, mitoxantrone and docetaxel. The found that only studies using docetaxel reported significant improvement in overall survival compared to the best standard care. But, and this seems like a big issue, *the increase in survival was less than 2.5 months*. The major plus seems to be pain relief which was reported in 35-76% of patients. Reported toxicity included gastrointestinal toxicity, cardiac toxicity, neuropathy and myelosuppression and hair loss. Docetaxel used alone compared to its combination with mitoxantrone plus prednisone had a superior quality of life profile. But the < 2.5 months overall survival needs to be weighed against these toxic effects, since the figure of < 2.5 months is an average and thus some individuals experienced even less if any benefit but still had the side effects.

Life extension benefits of this magnitude resulting from chemotherapy are not uncommon, as has been pointed out before in this newsletter in the context of solid adult tumors, but there appears to be an attitude that something must be done, and that providing hope, even if in fact insignificant, is needed. There is patient pressure and an expectation of treatment and the picture can be brightened artificially by expressing the benefits in relative rather than absolute terms. All this must be put in the context of the much higher level of success achieved with some blood related cancers, especially in young patients. Patients being advised to undergo chemotherapy should always inquire regarding the absolute life extension found in the most recent studies. Survival information is also available on the Internet and abstracts of chemotherapy studies are always free at PubMed (just Google PubMed and go to PubMed Home) and sometimes full text is also free.

Attempts to find new approaches to hormone-resistant prostate cancer are ongoing. A recent update indicated disappointing results in phase III tests of three agents, but that researchers in this field still indicated high expectations.[7]

HIGHLIGHTS FROM THE RECENT AMERICAN UROLOGICAL ASSOCIATION MEETING

Also included in this issue are highlights from the 2009 American Urological Association (AUA) meeting held in April in Chicago. What follows is based on information derived from the meeting abstracts.

INTERPRETING ELEVATED PSA

One of the shortcomings of the PSA test is that in some patients its elevation can be explained by bacterial infection of the prostate. The obvious way to rule out this possibility is with a course of antibiotics and a repeat PSA measurement. Hannah H. Alphs *et al* reported on a study of 179 consecutive patients with PSA > 2.5 ng/mL, a negative digital rectal exam, and urinanalysis and/or culture findings negative for a bacterial infection

that underwent a prostate biopsy. Of these, 127 were treated with a 2-week course of empiric antibiotics followed by another PSA measurement. For comparison, a group of 52 patients who had not received antibiotic treatment were used. Those with a 25% decrease in PSA were offered the option to defer the biopsy. All other patients had a 12-core transrectal ultrasound guided biopsy, and some of the antibiotic responders also agreed to the procedure. This generated four groups with biopsy results, the complete responders, partial responders, the non-responders, and the controls. Biopsies were positive for 47% of the non-responders, 36% of the partial responders and 14% of the complete responders. In the comparison group, 32% had positive biopsies which seems a bit high. Thus the antibiotic challenge appears to have merit and is simple to implement.

WHICH IS BETTER, SURGERY OR RADIATION FOR TREATING PROSTATE CANCER WITH CURATIVE INTENT?

The answer of course depends on to whom the question is addressed. In a recent study German urologists were asked which treatment they would elect if diagnosed with prostate cancer. The surgeons answered surgery, and the radiation oncologists answered radiation. At the AUA meeting, Adam S. Kibel *et al* examined which worked better in a group of over 6000 patients diagnosed with PC at their institution between 1995 and 2007. The analysis was restricted to patients with localized disease and no other medical problems who underwent a radical prostatectomy (RP) or radiation therapy (RT). Patient variables examined included age, race, clinical stage, Gleason score, and initial PSA.

Of the 6460 patients initially reviewed, 2552 received local therapy with curative intent, with 84.5% treated with RP and 15.5% given RT. RT was associated with a 69% worse overall survival compared to RP. Survival analysis controlling for age, ethnicity, tumor grade and PSA also indicated that surgery was associated with an improved survival.

IS RADICAL PROSTATECTOMY INDICATED FOR HIGH-RISK PATIENTS?

This has been an ongoing debate. At the meeting, Edward M. Schaeffer *et al* reported on the outcomes for a series of high-risk patients. High risk was defined as a clinical stage of > T2c (palpable tumor extending through the prostate capsule), a very high biopsy Gleason score of 8-10, or a PSA > 20 ng/mL. 94% of the men involved had just one of these three high-risk factors. At RP 36% had organ confined disease, 45% had extracapsular extension and seminal vesicle invasion was present in 8%. Positive surgical margins were reported in 18% and lymph node metastasis in 14%. At 10 years, the biochemical recurrence-free survival (PSA increase) was 68%, metastasis free survival 84% and prostate cancer specific survival was 92%. At 10 years, 71% were not receiving any hormonal therapy. This indicates the absence of an indication of metastasis or patient reluctance. Of the high-risk criteria, a biopsy Gleason score of 8-10 was the strongest predictor of all outcomes. Given the high-risk nature of this cohort, these results appear to justify the intervention, although the abstract gives no comparative results for untreated individuals selected with the same protocol.

SHOULD INTERMITTENT HORMONE THERAPY BE THE STANDARD OF CARE FOR ADVANCED PROSTATE CANCER?

This is an issue that continues to be debated. At the AUA meeting, three experts provided the following overview.

With intermittent androgen ablation (IAB), i.e. intermittent hormone therapy, the treatment is stopped when the testosterone level has decreased to a low level, and then resumed after it has increased to some arbitrary threshold and the cycle is continued. Hormone therapy is also termed *androgen deprivation therapy* (ADT) and is frequently started when other therapeutic options have been exhausted and the PSA is > 3 ng/mL, although this cut-off is also debated with some using a much higher level due to the morbidity of ADT. This subject is discussed in our book *The Prostate and Its Problems.* One of the problems with continuous ADT is that after 2 years, many men over 60 do not recover the production of testosterone upon termination of the treatment. However, after 6 month of ADT, most men regain their testosterone production with the concomitant decline in morbidity when treatment is stopped. Also, the adverse effects of ADT with regard to developing the characteristics of the metabolic syndrome reverse after short term ADT.

Dr. Anthony Zietman pointed out IAB resulted in repeated PSA reduction compared to continuous ADT that had an overall earlier rise in PSA suggesting so-called castration resistance (hormone therapy ceases to work). He also commented that men who eventually needed salvage ADT responded with equivalent survival whether or not they had previous IAB.

Dr James Montie commented that it is still unknown which patients should be treated and how to cycle ADT, but that IAB is proposed to be less likely to result in castration resistant prostate cancer and to diminish the side effects and cost. However, it should be initiated prior to symptomatic metastases, but how long before is also unknown. With regard to the connection with the metabolic syndrome, whether IAB decreased the risk of metabolic syndrome also was unknown.

Dr. Maha Hussain pointed out that in many trials, using continuous ADT has not led to sizable increases in survival and that in most phase II trials on IAB, the study groups were small and heterogeneous. In one phase III trial she cited, a PSA decline of > 80% after 12-14 weeks was followed by randomization to IAB or continuous ADT. Men on IAB were found to have a longer time to progression and better sexual function but no difference in overall survival.

SALVAGE HORMONE THERAPY FOR BIOCHEMICAL RECURRENCE AFTER PROSTATE SURGERY

Hormone therapy termed androgen deprivation therapy (ADT) is occasionally used as a salvage option after biochemical recurrence (increasing PSA but no other indication) post radical prostatectomy (RP). In a study by Bruce J. Trock *et al* the impact of salvage androgen deprivation (SAD) on overall survival was compared with no salvage. In no patient was salvage RT used. Men who received SAD were more likely to have RP Gleason score of 8-10 and seminal vesicle and lymph node involvement. That is, they would be considered at high risk of eventual symptomatic metastasis. In a multivariable model which adjusted for PSA doubling time, pathological stage, RP Gleason score, time from RP to recurrence and year of RP, SAD strongly improved overall survival in men with a PSA doubling time of < 6 months but failed to increase the overall survival time for those with a doubling time of > 6 months.

The investigators concluded that compared to no salvage therapy, SAD provided an important increase in overall survival for men with PSA recurrence after surgery who have a short doubling time, regardless of other adverse prognostic features. Short doubling times after a radical prostatectomy suggests residual aggressive cancer.

IMPACT OF THE METABOLIC SYNDROME FACTORS ON DEVELOPMENT OF PROSTATE CANCER. A 15-YEAR FOLLOW-UP STUDY

This study was conducted in Olmsted County, MN on Caucasian men ages 40-79 and reported by Dr. Lauren P. Wallner. Baseline characteristics were obtained by clinical examination and a questionnaire. Biopsy confirmed prostate cancer was identified from medical records during the 15-year follow-up. The metabolic syndrome characteristics of interest were hypertension, obesity and diabetes. It was found that men with hypertension alone were more likely to develop prostate cancer, and the combination of hypertension and diabetes was significantly associated with the development of this disease. But having all three of the characteristics together was not found to be associated with the development of prostate cancer. Thus obesity appears protective.

CLINICAL PREDICTORS OF INSIGNIFICANT PROSTATE CANCER

So-called active surveillance is a protocol that allows the judgment call that a diagnosed prostate cancer is sufficiently insignificant or indolent that nothing needs to be done other than periodic assessment, which if suggestive of a change to more serious picture, can prompt treatment without loss of the opportunity for a cure. The key is of course the set of criteria for the pronouncement of insignificance. This subject has come up repeatedly in the Prostate Monitor and is discussed in our book. It is an exceedingly important subject since at issue here is the avoidance of unnecessary treatment and the associated side effects which can have a profound effect on the quality of life.

One of the common sets of criteria is due to Epstein and judges a cancer insignificant if it meets the following conditions: PSA density of less than 0.15 ng/mL per ml of prostate volume, less than 3 positive biopsy cores with 50% or less of any core involved and a Gleason score of 6 or lower. These criteria can be tested by looking at the tumor characteristics after surgical removal of the prostate. This involves a second set of criteria which one might call the pathological criteria for insignificance. At the AUA meeting, Dr. Michael C. Lee *et al* presented such a study. At the Cleveland Clinic between 1999 and 2007, 268 men with a biopsy Gleason score of 6 underwent both a prostate biopsy and a radical prostatectomy which provided sufficient data to examine the ability of Epstein's criteria to provide an accurate means of predicting insignificant prostate cancer. Pathologically

insignificant cancer as judged after surgery was defined two ways; (a) a specimen Gleason score of ≤ 6 and a low tumor volume (<0.5 mL) and (b) organ confined tumors with a Gleason score of≤ 6.

In this group of participants, the positive predictive power of the Epstein's criteria for insignificant disease was 36.8% for definition (a) and 58.1% for definition (b). For just organ-confined disease, the positive predictive value was 92.6%. It was concluded that Epstein's criteria did not provide an accurate means to predict insignificant prostate cancer and thus identify patients suitable for active surveillance. Incidentally, Epstein's criteria are used in the Johns Hopkins program of active surveillance. The criteria may still provide a very adequate approach, as is suggested by a several studies reviewed in the Prostate Monitor in the past.

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