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This issue begins with a discussion of recent research results concerning the role of vitamin D in respiratory infections, a particularly relevant subject given the flu season and the so-called H1N1 pandemic. The multiplicity of positive results concerning the protective nature of adequate vitamin D status in the context of respiratory infections seems impressive.

A second interesting aspect of vitamin D concerns the considerable and remarkable elevation of serum 25-hydroxyvitamin D by statins and in particular rosuvastatin (Crestor). The reduction of heart attack risk in the JUPITER trial, which was unusually large for a statin and attributed to the selected participants who had elevated C-reactive protein (CRP), can be explained entirely by the elevation of serum levels of 25-hydroxyvitamin D, suggesting that the decline in LDL cholesterol and CRP levels may not have been the principal reason why there was a decrease in the risk of heart attack. Thus vitamin D has become a new, important and still apparently unrecognized confounding factor in statin studies and this fact may provide critics of the cholesterol hypothesis with additional evidence for their position.

Still on the vitamin D subject, a study of benefits found in a nursing home population are described and as well, studies providing guidance as to the elevation in 25-hydroxyvitamn D that can be expected from D3 supplementation are discussed.

Other topics discussed include the risk to children associated with taking antipsychotic drugs; the possibility that the pigments in egg yokes as well as melatonin can delay or prevent age-related macular degeneration; and the possible role of elevated triglycerides in diabetic neuropathy.

Finally, an attempt is made to summarize the highlights of this year's Newsletters in the form of suggestions for healthy living.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at *http://www.yourhealthbase.com/vitamins.htm*.

Wishing you and your family a Happy Holiday Season and good health in the coming year,

William R. Ware, PhD, Editor

Highlights

H1N1 VIRUS

The general public naturally relies strongly on the media for information and advice during crises or national emergencies. In the case of the H1N1 flu, by now it must be widely recognized that hand washing, avoiding contact with infected individuals and getting vaccinated are the mainstream recommendations for avoiding the flu. The pros and cons of the vaccination with or without adjuvants are

the subject of worldwide controversy, articles in such popular magazines as the *Atlantic* (November, 2009 issue) examining the evidence for a number of inconvenient questions concerning efficacy in general, a lawsuit in New York by the nursing profession and strong rejection in Germany of adjuvant-containing H1N1 vaccines. The president of the German College of General Practitioners and Family Physicians told the British Medical Journal (24 Oct, 2009 News section) that the adjuvant vaccine approved for use in Germany has not been sufficiently tested to be declared safe for millions of people, especially small children and pregnant women. His main concern was the adjuvant. As mentioned in the last Newsletter, the vaccines approved in the U.S. are free of adjuvants. In Canada, adjuvant-free preparations are being given to pregnant women.

What is interesting is the total absence of any mention whatsoever in the print and TV media of the role that vitamin D plays in infectious diseases in general and influenza in particular. Lack of professional awareness may be due to the fact that the key literature is not in any of the very few high-profile journals (but nevertheless is in important peer-reviewed specialty journals). It may be due to the fact that a major source of medical information is the drug rep, and drug reps obviously do not discuss vitamin D or hand out appropriate reprints. Furthermore, the high levels of evidence "required" today combined with the general distaste for vitamin therapy may combine to encourage many professionals simply to dismiss vitamin D, thus ignoring both our evolution and a huge body of evidence related not just to the flu but to infectious diseases in general, heart disease, multiple sclerosis, diabetes and cancer. Whatever the reason, the general public is not being told about the one simple, cheap and potentially effective step they can take to reduce the risk of flu in themselves and their children. And in fact this information should have been provided months ago in order that vitamin D levels could be enhanced. Measurement of vitamin D status appears rare, although the two reports in the November issue of the Newsletter http://www.yourhealthbase.com/ihn_november2009.pdf suggest that when it is done and corrective measures taken, the dividends appear large in the context of influenza.

The H1N1 virus appears to be particularly dangerous for children, young people and pregnant women. Thus the question, what is known about the role of vitamin D in respiratory infections in newborns and children? The answer appears to be quite a lot. A recent review of the vitamin D connection with pediatric infections and immune function makes a number of important observations.[1]

- Several recent epidemiologic studies have observed the association between inadequate vitamin D concentrations and hospitalization and/or respiratory infection among children.
- Children who have contracted TB typically have inadequate vitamin D stores.
- Vitamin D deficiency manifest by rickets is strongly correlated with respiratory diseases.
- Subclinical vitamin D deficiency was associated with acute lower respiratory tract infections (ALRIs) in children without rickets admitted to a private hospital in India.
- A study found that newborns with acute lower respiratory infections had lower serum 25-hydroxyvitamin D levels than healthy controls. Infants with ALRIs spent an average of eight days in the neonatal ICU.
- In contrast to data from adults, infections observed in children with inadequate vitamin D stores were more frequently of viral origin.
- Susceptibility to infections in children appears before the overt manifestations of nutritional rickets are apparent.
- Vitamin D insufficiency among pregnant women places newborns at greater risk for vitamin D deficiency which is dependent on and correlated with maternal 25-hydroxyvitamin D levels with the neonates exhibiting lower levels than the mother. Those born to marginally vitamin D sufficient women will still be at risk of significant deficiency, and those born to women who are deficient will almost certainly be deficient if not severely deficient themselves.

A study just published supports this general view. Twenty-five newborns with ALRIs who were admitted to a neonatal ICU were compared with 15 health newborns of the same age who acted as controls. The mean 25-hydroxyvitamin D (25(OH)D) levels were significantly lower in the ALRI group than the control group and as well, so were the levels of the mothers in the case group as compared to the control mothers. It was concluded that this strong correlation between vitamin D status

and ALRIs shows that adequate vitamin D supplementation should be emphasized during pregnancy and especially in the winter months.[2]

In this connection, it is of interest that in 2008 the American Academy of Pediatrics changed their 2005 recommendation regarding vitamin D from 200 IU/day to 400 IU/day with supplementation to begin in the first few days after birth and continue through childhood and adolescence. The consensus committee involved in these recommendations also acknowledged the possibility that studies might indicate the merits of higher doses (1000-4000IU/day). It is clear that there is a critical need for clinical data that directly connects maternal and neonatal 25(OH)D levels and the risk of infectious diseases, including influenza and ALRIs.[1]

The connection between serum 25-hydroxyvitamin D levels and adolescent and adult upper respiratory tract infections based on a study published in the February 23 issue of the *Archives of Internal Medicine*[3] was briefly reviewed in the April, 2009 issue of the Newsletter. Contrary to the impressive results reported in this large study, recently a small randomized trial running only 12 weeks found no benefit from 2000 IU/day of vitamin D3 as regards the incidence of upper respiratory infections in adults. But this study was limited by short duration, the relatively high baseline levels of 25(OH)D, the lack of optimum power because of the small sample size and the limited number of self-reported cases and the fact that the subjects were not taking vitamin D before the influenza season started. Furthermore, this was not a trial to determine the impact of supplementation on a vitamin D deficient population. It would be unfortunate if this study was used to discredit vitamin D in the context of influenza or respiratory infections.[4]

VITAMIN D AND JUPITER TRIAL

As discussed in the February issue http://www.yourhealthbase.com/ihn194jn.pdf, in the JUPITER trial the statin rosuvastatin (Crestor) reduced non-fatal heart attacks (MIs) by about 50% in individuals with normal LDL cholesterol and quite elevated C-reactive protein (CRP).[5] This was a primary prevention trial of subjects free of symptomatic heart disease although a significant number of subjects had the characteristics of the metabolic syndrome. It now turns out that there may have been more going on than just the reduction of LDL and CRP. In a just published study by Yavuz *et al*,[6] rosuvastatin was found to dramatically increase levels of 25(OH)D. Doses of 10-20 mg per day of rosuvastatin caused the 25(OH)D levels to increase from a mean of 14.0 (3.7—67) to 36.3 (3.8—117) ng/mL. Thus many individuals who would be considered deficient or insufficient achieved sufficiency or even optimum levels under the statin treatment. If one looks at the inverse association between the relative risk of MI according to 25(OH)D levels, for ≤ 15 ng/mL vs. ≥ 30 ng/mL, the relative risk of 2.42 was found in a recent prospective study of subjects free at baseline of cardiovascular disease.[7] In Jupiter the subjects quite probably experienced a similar increase in vitamin D status as Yavuz *et al* found since the dose was the same. In JUPITER the relative risk of an MI for no statin vs. statin therapy was about 2.2. Thus there arises the question, was JUPITER seriously confounded by changes in vitamin D status? The change in 25(OH)D was large enough to explain the entire effect! In addition, the benefit in terms of MI was larger in JUPITER than, for example, in studies with atorvastatin which causes a much smaller increase in vitamin D status.[8] While the decrease in the risk of an MI was attributed to the impact of rosuvastatin on LDL and CRP in the JUPITER trial, it seems clear that this may be only part of the story, and how big a part can be debated. The most recent subgroup analysis of the JUPITER trial did not discuss this potential confounder.[9]

The results of Yavuz *et al* are curious in that statins inhibit the synthesis of 7-dehydrocholesterol which is both the precursor of cholesterol and the compound upon which UV light acts to produce vitamin D3 in the skin which then yields the metabolite 25(OH)D. It was expected that statins would reduce the levels of vitamin D3, but this effect was looked for some time ago but never observed. Now it appears that statins in fact increase at least the metabolites of vitamin D3 including 25(OH)D. In an editorial concerning the paper by Yavuz and colleagues, David Grimes discusses the possibility that the effect of the statin on 25(OH)D levels may be due to an interference with some mechanism which reduces the consumption of this metabolite. He suggests a mechanism involving the anti-inflammatory action of statins. He concludes that the ability of statins to lower cholesterol may be

their least important clinical effect and reminds readers of the Framingham result that a significant relationship between life expectancy and high serum cholesterol is seen only in young men.

BENEFITS OF HIGH DOSE VITAMIN D IN NURSING HOMES

The latitude common to European countries is such that little or no vitamin D is obtained from sun exposure in the winter. The problem becomes acute for individuals who spend most of their time indoors with nursing home residents the prime examples. The consensus among experts appears to be that to prevent fractures in the elderly a serum concentration of 25-hydroxyvitamin D (25(OH)D) should exceed 30 ng/mL (75 nmol/L). Even though deficient individuals typically have levels of 10 ng/mL or less and 400 IU/day is expected to raise serum levels by only 4 ng/mL, studies have typically used 400 IU to 800 IU when looking for benefits in highly deficient individuals. The negative results should have been predictable, but such studies generate the conclusion that supplementation does not work. However, real progress has recently been reported in a study involving European nursing home residents where finally a realistic supplementation program was tested.[10] The location was Lasi, Romania at a latitude of 47ºN which is far enough north for the sun to be ineffective in the winter. Residents were given 5000 IU/day in bread along with 350 mg of calcium. After 12 months, the 25(OH)D levels increased on average from 11.4 to 50.2 ng/mL and 92% had levels exceeding 30 ng/mL. Bone mineral density at 12 months was increased significantly and no adverse effects were observed. No cases of hypercalcemia were observed. Also, the 5000 IU daily dose did not result in the subjects exceeding the so-called physiologic range (96 ng/mL), a value achieved through sun exposure. Humans, incidentally, have a mechanism whereby prolonged exposure to sunlight does not produce unlimited amounts of vitamin D and its metabolites such as 25(OH)D, but rather a steady state is reached.

This study illustrates that simple supplementation is all that is necessary to correct potentially dangerous vitamin D deficiencies, not only in nursing home residents, but also in the general public where similar deficiencies as seen above are widespread. It also highlights the impossibility of achieving adequate levels using small doses such as 400-800 IU/day, the amounts typically found in multivitamins, or even eating oily fish which typically contain 200-400 IU per serving. Capsules containing 5000 IU of vitamin D3 are readily available at http://www.yourhealthbase.com/vitamins/vitamin16.htm and in health food stores. The current recommendation for optimum health is typically a 25(OH)D level of 50-70 ng/mL. One can only hope that sometime in the future, the failure to measure this vitamin D metabolite during physical examinations or when a patient presents with practically any complaint will be considered malpractice. There is probably no other micronutrient where deficiency is so strongly related to such a multiplicity of disorders and there is probably no micronutrient so underappreciated.

D3 DOSE DEPENDENCE OF SERUM 25-HYDROXYVITAMIN D

In a letter commenting on a recent study[11] which attempted to establish the vitamin D requirements for free-living adults age ≥ 65, Reinhold Vieth criticizes the extrapolations used and comments that empirical data on the topic already exists. If one examines the publications from Vieth's laboratory over the last decade which address the question of the connection between vitamin D intake and serum levels of 25(OH)D, it is clear that there is considerable inter-individual variation and that there is a distinct plateau effect that occurs within 3 months of initiation supplementation.[12-14] Furthermore, the final 25(OH)D concentration is not significantly correlated with the initial value nor with body weight.[13] For example, supplementation for more than 6 months produced the following results in one study[14]

Dose IU	Initial ng/mL	Final ng/mL
600	19.2±3 .6	31.6±12.0
4000	19.2±3.6	44.8±16.4

The ± values represent one standard deviation and illustrate the inter-individual variation in a group totaling 64 individuals, but based on an earlier study, the final numbers were probably reached within 3 months.[13] Data from the above table was derived from a study involving individuals much younger than the nursing home cohort discussed above whose initial levels were much lower but 5000 IU brought the levels to about 50 ng/mL, again with considerable inter-individual variation, and the plateau was reached within 6 months.

These results suggest that once one has their baseline 25(OH)D value, something everyone no matter what age should have, then it is only possible to roughly estimate the dose required to achieve, say, 50 to 70 ng/mL. If it is assumed that all the studies on toxicity are correct, then starting with 4000-5000 IU per day appears safe, and after a few months another blood test is indicated and the dose adjusted accordingly.

USE OF ANTIPSYCHOTIC MEDICATIONS IN CHILDREN AND ADOLESCENTS

A recent study concerns the impact of so-called atypical or second-generation antipsychotics on weight and heart disease risk factors observed in children and adolescents. Atypical antipsychotic drugs have become popular because in general they appear associated with a lower level of side effects. They are commonly and increasingly being prescribed to children and adolescents in the U.S. for treatment of bipolar and both psychotic and nonpsychotic disorders. But there are concerns regarding cardiometabolic adverse effects such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities during this developmental phase of life and the fact that these abnormalities predict adult obesity, the metabolic syndrome, cardiovascular problems and cancer. A recent study has examined this problem in first-time, second-generation users of this class of medication.[15] Large and rapid weight gain was a common outcome even over a short period of use. After about 11 weeks of treatment, olanzapine increased weight by a mean of 8.5 kg, 6.1 kg with quetiapine (Seroquel), and 5.6 kg with risperidone and 4.4 kg with aripiprazole (Abilify). A control group gained only 0.2 kg. Quetiapine was associated with a large and unfavourable increase in the ratio of triglycerides to HDL cholesterol, i.e., a large increase in the dyslipidemia associated with both diabetes and the metabolic syndrome. Patients receiving olanzapine (Zyprexa) experienced the highest incidence of hyperglycemia and the metabolic syndrome. A diagnosis of disruptive or aggressive behaviour spectrum disorder was present in 22% of the patients in the study. The authors suggest that the benefits of second-generation antipsychotic medication must be balanced against cardiometabolic risks and consideration given to lower risk alternatives and proactive adverse effects monitoring. The fact that these adverse effects on children's health could last well into adulthood should give those who prescribe these drugs cause for reflection on the possibility of overmedication. It is interesting that antipsychotic drugs are not as widely used for children in the UK as in the US.

The March 2009 issue of the Newsletter http://www.yourhealthbase.com/ihn195hi.pdf contains a discussion of the association of atypical antipsychotic drugs and sudden cardiac death in adults.

EGGS MAY PREVENT AGE-RELATED MACULAR DEGENERATION

Age related macular degeneration (AMD) is a leading cause of vision loss in the elderly. Dry AMD is a progressive disease in many individuals and at present there are no standard so-called medical treatments, but lutein and/or antioxidant supplements are now prescribed. Dry AMD is thought to be caused by a breakdown of cells in a small region in the posterior of the retina (the macula) which results in loss of central vision. Light-induced oxidation is thought to cause the breakdown in retinal epithelial cells beneath the macula. The macular pigments include lutein, zeaxanthin and meso-zeaxanthin and these pigments act as a light filter to prevent the photooxidation in the underlying retinal cells. The pigments are also powerful antioxidants. Thus intervention to increase the concentration of these pigments is indicated. While the pigments are

available as supplements, food sources appear to be equally if not more bioavailable, and this appears especially true for eggs.

A recent study[16] of an elderly population (mean age 69) examined the impact of egg consumption on the concentration of lutein and zeaxanthin pigments by measuring macular pigment optical density (MPOD) which should be proportional to concentration. The intervention involved eating 2 or 4 egg yolks per day. The MPOD increased significantly with greater increases seen with 4 yolks per day.

With the advent of the diet-heart hypothesis a number of years ago and the associated advice to severely limit the consumption of cholesterol, eggs were not viewed with favour by either the medical or nutritional establishments. But as has been discussed on a number of occasions in this Newsletter, studies have for the most part found that neither the heart-diet hypothesis nor concern with eating eggs are justified and in fact eggs confer benefit, being excellent sources of a number of nutrients. In the study under discussion, the researchers were of course aware of the "egg problem" and examined the effect of their intervention on LDL and HDL cholesterol. Neither the 2- or 4-yoke intervention increased HDL but also did not change the levels of either LDL or the triglycerides. Incidentally, the subjects in this study were on statin drugs since this was a selection criterion. Presumably it was not considered ethical to feed people eggs if they were not on statins although presumably statins inhibit the synthesis of cholesterol, not its absorption from food.

AMERICAN HEART ASSOCIATION RECOMMENDS DRASTIC SUGAR REDUCTION

In a "Scientific Statement" just published in the journal *Circulation*, the American Heart Association has taken a position regarding the high if not almost unbelievable sugar consumption in the U.S.[17] During the period 2001 to 2004, the usual intake of added sugars for Americans was 22.2 teaspoons per day which is equivalent to 355 calories. Taking one teaspoon as equivalent to 4 grams of table sugar, this yields 87 pounds of sugar per year as an average intake which can be visualized by imagining a pile of 44 two-pound bags or roughly a bag per week. The intake of 22 teaspoons represents about 18% of a 2000-calorie diet which would be a common daily energy intake. Actually, one sees estimates of the annual intake that considerably exceed 87 pounds per year and thus the AHA is perhaps using a conservative value.

After discussing briefly the literature on the impact of dietary sugars on blood pressure, inflammation, elevated triglycerides, obesity, the glucose-insulin response, and the fact that refined sugar represents so-called empty calories, the ADA recommends a reduction in intake of added sugars such that they represent no more than 100 calories per day for most women and 150 calories per day for men. This represents a decrease from 22 teaspoons to about 6 to 7 teaspoons. By added sugar they mean sugars and syrups added to foods during processing or preparation and includes sugars and syrups added at the table. For individuals who eat a lot of processed foods, candy, baked goods, add sugar to their drinks and fruits, and drink sugar-sweetened soft drinks, the limitation of 6 teaspoons will no doubt be viewed as a severe hardship if not an almost unbearable deprivation. In fact, whole books have been written about refined carbohydrate addiction. But it is worth recalling that our genetic makeup is that of the Stone Age or Late Paleolithic people and they ate "raw" sugar only occasionally when honey was available, albeit at some risk. It appears safe to say that our biochemistry never evolved to accommodate almost 100 pounds of refined sugar a year. It is also worth pointing out that the sugar intake that is the basis of concern in the AHA recommendation is an average with many exceeding this amount by a significant margin. The food industry can be thankful that only a negligible fraction of the population reads the journal *Circulation* and that many individuals, when advised to drastically reduce sugar intake, will fail to do so.

ANTI-INFLAMMATORY DRUGS, DEMENTIA AND ALZHEIMER'S

The relationship between nonsteroidal anti-inflammatory drugs (NSAIDs) and the incidence or progression of Alzheimer's disease (AD) is not clear with inconsistent results and indications of

considerable complexity from a variety of studies. In well-designed studies, NSAIDs are not found helpful for people with established AD dementia and selective COX-2 inhibitors have not been found effective in halting the progression of milder cognitive symptoms of AD. NSAIDs also do not appear to provide benefit to people whose preclinical AD pathology is sufficiently advanced that they develop the symptoms of dementia over a very few years.

In view of the above, a recent study of NSAID-use and incident dementia and AD is of interest.[18] Participants were members of a group health organization which maintained computerized pharmacy-dispensing records. Over 2700 dementia-free enrollees with extensive prior pharmacy data were followed for up to 12 years starting in 1997. The endpoint was dementia and AD. The pharmacy records identified 351 individuals with heavy use of NSAIDS at enrolment and another 107 became heavy users during follow-up. Contrary to the hypothesis that NSAIDs protect against AD, the heavy users showed an increased incidence of dementia and AD with a significant 66% increase in risk of dementia and a 57% increased risk of AD. Addition of self-reported exposure did not alter these results. These results apply to an elderly cohort with a median onset age of about 84 years.

The authors discuss the fact that these results are in direct conflict with a number of prospective studies and meta-analyses which in general showed that anti-inflammatory treatments including NSAIDs could delay or prevent the onset of AD, although as mentioned above, NSAIDS do not appear helpful for individuals with established AD. Thus the question, why the discordant results with respect to the incidence of AD with NSAID exposure? The authors discuss the possibility that their study provides a correct picture because of the rigorous prior exposure data from pharmacy records (17 years prior to enrolment), a community based sample, biennial assessment for dementia and AD, and a consideration of self-reported additional exposure. Another explanation offered involved the difference in participant ages across the studies in question. In fact, two studies that involved substantially older cohorts failed to show reduced risk of AD with the use of NSAIDs. Finally, they suggest as an explanation the possibility that NSAID exposure, if it defers the onset of AD, would then enrich older cohorts for cases that otherwise would have appeared earlier. Clearly, more studies are called for to investigate the observed discordance, but one must not loose sight of the fact that this study did not find a protective effect. NSAID consumption is not risk free with respect to gastric complications, and in fact such complications are a major cause of hospitalization among elderly individuals.

ELEVATED TRIGLYCERIDES AND PROGRESSION OF DIABETIC NEUROPATHY

Peripheral neuropathy occurs in about 60% of all diabetic patients, is a leading cause of diabetes-related hospital admissions and non-traumatic amputations, and obviously seriously impacts the quality of life. Since peripheral neuropathy correlates with myelinated fiber densities (MFD) in the sural (calf) nerve, this can be used to examine the correlation with various risk factors. In a study just reported, during a year-long period a group showing progression in MFD was compared to one with no progression. MFD was not affected by drug treatment, diabetes duration, age or body mass index. However, elevated triglycerides at baseline were significantly associated with both a loss of MFD and as well, measured nerve conduction velocities. At baseline, both groups had a similar degree of neuropathy. These results support the emerging notion that dyslipidemia defined in terms of elevated triglycerides and depressed HDL is a contributing factor for diabetic neuropathy. The results are also consistent with the observation that diabetic neuropathy develops later in the course of type 1 diabetes and a delayed development of dyslipidemia coincides with the delayed onset of neuropathy. In this study, triglycerides were significantly elevated in participants exhibiting progression of diabetic neuropathy independent of diabetes type or insulin treatment.[19]

It should be noted that a common and reproducible consequence of a diet high in refined carbohydrates is elevated triglycerides, in some cases to extreme levels. Individuals encouraged to follow a low-fat diet need to be aware of the critical nature of their choices with regard to the source of calories to replace those derived from fat and also to recognize that many low-fat prepared foods are heavily enriched in undesirable sources of carbohydrate. Carbohydrates from fruits, vegetables and whole grains (not refined) generally do not have this

adverse effect on triglycerides and HDL. The reader is referred to the Research Review in the September 2009 issue of the Newsletter http://www.yourhealthbase.com/ihn200sg.pdf that discusses the alternative approach to diabetes and pre-diabetes, i.e. carbohydrate restriction, and presents evidence for the lack of risk associated with the consumption of fat.

NEWS BRIEFS

MID-LIFE WEIGHT GAIN IN WOMEN AND HEALTHY SURVIVAL AFTER 70

This issue has been addressed in a prospective cohort study which was part of the Nurses' Health Study.[20] Healthy survivors were participants who reached 70 or older and were free of cancer (ignoring non-melanoma skin cancer!!), diabetes, cardiovascular disease, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis or amyotrophic lateral sclerosis, and had no major cognitive impairment, no major limitation of physical functions, and good mental health. Out of 17,065 women who met the survival criterion, only 9.9% were actually healthy survivors. Compared to lean women (BMI between 18.5 and 22.9) in midlife, obese women (BMI > 30) had a 79% lower odds of healthy survival and the more weight gained from age 18 until midlife, the less likely was healthy survival after 70. The lowest odds of healthy survival were among women who were overweight (BMI ≥ 25) at age 18 who then gained ≥ 10 kg when the comparison was with lean women who maintained a stable weight. These results emphasize the critical importance of maintaining a healthy, stable weight from early adulthood.

OMEGA-3 FATTY ACIDS AND HEART FAILURE

At the Heart Failure Society of America 2009 Scientific Meeting held in September it is reported that a common concern was the absence of new heart failure agents (translation—pharmaceuticals) that show clinical benefit when given on top of the current treatment protocol. But on the last day of the meeting in a roundtable discussion, four academic physicians made the case that part of the answer resides simply in long chain omega-3 fatty acids such as are found in dark oily fish and fish oil, but that the evidence that they confer benefit is ignored.

BREASTFEEDING AND PREMENOPAUSAL BREAST CANCER

As part of the Nurses' Health Study II, information from over 60,000 participants who had given birth was collected from 1997 to 2005. The primary outcome examined was the incidence of premenopausal breast cancer. Overall, for women who had breastfed there was a 25% reduction in the incidence of breast cancer, but this result just barely missed being statistically significant. However, for the subgroup with a first-degree relative with breast cancer, a statistically significant 59% reduction in risk accompanied breastfeeding as compared to those who never breastfed.[21]

MACULAR DEGENERATION AND MELATONIN

A recent study using a metabolite of melatonin in first morning urine as a marker, investigators found an association between circulating melatonin and age-related macular degeneration (AMD).[22] In a case-control setting, it was found that patients with AMD had significantly lower levels of the metabolite than controls both before and after adjusting for a variety of confounders. The authors discuss various possibilities for this association and indicate preference for some unknown protective mechanism, perhaps involving the antioxidant properties of melatonin. They also mention a clinical trial which found that supplementation with melatonin appeared to protect the retina and delay progression of AMD.

While the authors do not mention this, it appears evident that this study provides one more reason for sleeping in a totally dark room and avoiding exposure to bright lights if it is necessary to leave the dark room. Melatonin production has a marked circadian rhythm and is strongly inhibited by exposure to light in the blue end of the visible spectrum. Readers will recall that various diseases and especially cancer have been associated with shift work which disturbs this circadian rhythm.

YEAR-END SUMMARY

If one looks at the material covered this year and attempts to distill the essence related to healthy living, it might look some thing like this.

- Get a reading on serum 25-hydroxyvitamin D and act accordingly. Take vitamin D as necessary to keep levels of 25-hydroxyvitamin D at 50-70 ng/mL (125-175 nmol/L) year round. Get adequate sun exposure in the summer but never burn.
- Take a simple multivitamin with for men no iron and for everyone no more than 800 mg of folic acid. If the supplementary intake is 800 micrograms, examine dietary intake from fortified foods and if present, limit supplementary intake to keep daily total intake around 800 micrograms.
- Be sure to get enough long-chain omega-3 fatty acids from fish, or capsules containing highly purified fish oil.
- Take 100-200 mg of highly absorbable coenzyme Q-10 daily.
- Eat a Mediterranean-style diet. Avoid sugars, refined grains, processed meat and as much processed faux food as possible. Emphasize fish, poultry and limited amounts of very lean red meat. Focus on organically grown foods and free-range meat and eggs.
- Try to make one meal each day a family affair that is relaxed, protracted, characterized by pleasant conversation, and has limited portion sizes and variety.
- Enjoy but limit alcohol to no more than 2-3 drinks per day for men and 1 for women.
- Actively attempt to minimize psychological stress. Avoid social isolation if at all possible.
- Breastfeed babies for as long as possible.
- Exercise, e.g. by walking 30 minutes 5 times a week.
- Avoid taking prescription drugs unless absolutely necessary.
- Have triglycerides and HDL cholesterol measured and if dyslipidemia is present, attempt with diet and supplements to lower triglycerides and raise HDL.
- If prediabetic, consider carbohydrate restriction *and* exercise.
- Always follow a course of antibiotics with probiotics to restore friendly gut flora. This may require expert advice on which probiotics are best.
- Follow the philosophy found in societies characterized by longevity by stopping eating when 80% full. Perhaps even a lower percentage would be better. Eat slowly if possible.
- Avoid man-made chemicals applied to the skin, ingested, or inhaled. This is a much bigger challenge than generally appreciated.
- Take oral hygiene and regular dental check-ups seriously. May be as important as physical check-ups.
- Take with a grain of salt the claims that have their origin in the pharmaceutical industry or are based on studies they fund and control. Likewise, view in the same way the claims that chemicals to which we are exposed are harmless. Be careful with regard to media coverage of health issues. The same networks make vast sums on advertising revenue from Big Pharma and in addition, the science and medical correspondents (experts) may not be trained to uncover junk science even if they actually read the full text of studies rather than abstracts and press releases. Bottom line—be careful when entering the jungle.

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Reviews of recent studies from the peer-reviewed literature

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The main theme in this issue is PSA screening and the debate that just will not go away. Most readers are no doubt familiar with the recent task force recommendation against mammography screening below a certain age and the quite considerable polarization among "experts" paraded on prime time evening TV news. Almost an exact parallel exists with PSA for essentially the same reasons. In both cases, the debate and controversy will no doubt continue unabated until new screening tests are found, tested and validated that do not suffer from a high rate of false positives and the attendant unnecessary additional diagnostic procedures and in some cases unnecessary treatment. In the case of PSA the situation seems even worse than the false positive for breast cancer since the end result is treatment that in general seems somewhat more devastating than a lumpectomy and can result in a lifelong and significant alteration in quality of life, mainly through incontinence and impotence and, for radiation therapy, additional problems with bowel and rectal function. All in all, a dismal picture where the unfortunate patient is confronted, in the process of informed consent, with probabilities from fancy statistical considerations which in fact are more akin to race horse handicapping, casino gambling or stock market predictions based on so-called technical analysis, all presented under the guise of scientific evidence or what "science" predicts.

We are told repeatedly in ads on the evening news that "only your doctor can tell if you have a more serious problem such as prostate cancer." True, but this ignores the fact that such a determination requires a rather unpleasant biopsy which can miss up to 25% of cancers, and that no doctor is presumably going to suggest a biopsy before prescribing a drug for BPH (enlarged prostate) unless there are significant reasons to think prostate cancer is present. Some would say that this is an oversimplification of the differential diagnostic procedure when a patient presents with lower urinary tract problems, but the fact remains, for the most part only a biopsy involving at least six and preferably more samples is definitive, and definitive must be qualified with the term "more or less." In addition, even in the best institutions, some patients (5% at one institution) have a radical prostatectomy, but the pathologist can't find any tumors in the removed gland. However, these very negative comments are not in any way intended to downplay the value and importance of PSA levels after definitive treatment, where they indeed assume a key role.

Once a screening test becomes established, dressed up in studies and guidelines even if the rate of false positives and false negatives is high, it seems to take on a life of its own. There is a profound impact on how the associated medical speciality is practiced and the income it generates. One unfortunate result is that this may discourage extensive research aimed at finding a good screening test. In the case of mammography, there is even the issue of the lawsuits generated by angry women who have a second mammogram that "proves" the radiologist who read the previous one was guilty of malpractice by missing what in retrospect was "obviously" there.

In this issue we discuss the commentary associated with the study of Welch and Albertsen which presents data suggesting considerable overdiagnosis and overtreatment due to the advent of the PSA test, and we revisit the

major aspects of the test and the additional controversy surrounding the use of so-called PSA dynamics and PSA density in an attempt to improve screening.

*The remainder of this issue is devoted to recent results in what is called active surveillance, deferred treatment, or more loosely, watchful waiting. If one accepts that overtreatment is rampant, then many men would benefit from active surveillance and many would for life avoid the adverse effects of definitive interventions, an nice term for surgery and radiation treatment. They would join the ranks of those who die **with** rather than **from** prostate cancer. This already describes a very large number of men, given the large percentage of elderly men who have latent prostate cancer and as well the results of post-mortem prostate examinations in cases where the cause of death was not prostate cancer.*

Wishing you a Happy Holiday Season and all the best in the New Year,

William R. Ware, PhD, Editor

SCREENING FOR PROSTATE CANCER—THE DEBATE CONTINUES

The May issue of *The Prostate Monitor* http://www.yourhealthbase.com/197df.pdf contains a discussion of three PSA screening trials and the editorial and other comments they precipitated. As was indicated at that time, opinion, both from individuals and professional organizations was highly polarized. This continues to be the case and recognition of the complexity of the both diagnostic and therapeutic issues and of prostate cancer itself continues to develop.

Screening is done by measuring serum PSA, generally along with a digital rectal exam. Prior to the advent of PSA, only the latter plus clinical evidence of metastatic cancer and lower urinary tract symptoms were available. Early asymptomatic cancer was missed. Thus it is argued that failure to do a PSA test at the appropriate time in life can lead to undetected cancer which may be aggressive and potentially life threatening. But since PSA is not specific, the test can also yield a false positive *indication* and lead to an invasive diagnostic procedure, over-treatment and unnecessary interventions which in turn can seriously, and in some cases needlessly, impact the quality of life. These issues are dealt with by probability considerations (nomograms, algorithms, online calculators etc.) to which many individuals have trouble relating or even understanding. An even smaller fraction would appreciate the meaning of the number needed to screen or treat to produce one favourable result as a way of looking at study results, especially when the overall benefit is small. The clinician has many options as to the spin that can be put on a PSA of 4.5 or a Gleason score of ≤6. PSA elevated to some arbitrary level may prompt a biopsy and if the biopsy is positive, it may prompt intervention although the biopsy clinical characterises responsible for the suggestion for surgery, radiation or some other intervention are again somewhat arbitrary in the sense that there are a range of responses to any given set of biopsy observations when coupled with the PSA level and the results of a digital rectal exam. These options include no immediate intervention with perhaps more observations at a future date.

Once there has been a positive biopsy strong psychological factors enter in with some patients unable to live with the thought of cancer growing in their prostate even if there is convincing evidence that it may pose no threat to them during their remaining lifetime and that if this picture changes, the matter can be reconsidered. They elect definitive treatment and the associated potentially severe alteration in their quality of life. Even spousal pressure can be a deciding factor in favour of treatment (I don't care about the side effects, I don't want to loose my husband). Thus we have a complex matter which over the years since PSA use became common (late 1980s) has generated an ongoing debate and controversy in the urologic community. In fact it is probable that it will continue until there is a definitive test for prostate cancer which is widely regarded as suitable for mass screening.

The flow of commentary regarding two of the three studies discussed in May continues[1,2] and now we have a recent study by Welch and Albertsen which attempts to establish the total extent of overdiagnosis in the PSA era.[3] They begin by commenting on the evidence that overdiagnosis in cancer screening is probably the rule, not the exception. They cite neuroblastoma, melanoma, thyroid, breast and lung cancers. Chest X-rays for lung cancer screening are frequently cited as an example where the practice was popular in the 1960s but abandoned in the 1970s after trials showed it to be ineffective.[4] Welch and Albertsen found that since PSA testing was introduced around 1986 an estimated 1,305,600 additional men were diagnosed with prostate cancer, of whom 1,004,800 were definitively treated. They then made the most optimistic assumption that the entire decline in prostate cancer during this period was attributable to this additional diagnosis and from this conclude for each man that experienced presumed benefit, more than 20 had to be diagnosed with prostate cancer. They conclude that most of the excess diagnosis brought about by the introduction of PSA must represent overdiagnosis.

In an editorial accompanying the paper by Welch and Albertsen, Otis Brawley from the American Cancer society made the following points.[4]

- Does prostate cancer screening save lives? In the two randomized trials discussed in the May issue, one from Europe found a benefit (20% decline), the other, an American study, found none,

but the latter was widely criticized as essentially meaningless. The European study leads to an estimate that screening caused about half the decline in mortality, but some countries which do not have widespread screening have also seen declines in prostate cancer mortality. After it is determined who needs treatment and who does not, there arises the question of how good the treatments are, and there are about a dozen from which to choose. According to Brawley, little has been done to figure out which therapies are most effective and "…every treatment looks good when more than 90% of the men getting it do not need it."

- In the past there has been a lack of appreciation for the need for scientific evidence. He cites a number of procedures and screening techniques which were withdrawn or substantially modified after scientific assessment examined what was merely based on "expert opinion."
- "Know what is known, know what is not known, and know what is believed. Label them accordingly."

Brawley concludes that prevention trials, the randomized screening trials plus the study of Welch and Albertsen indicate that prostate cancer is a highly complicated disease, screening a complicated intervention, and the benefits of the latter still open to question. Another editorial commenting on the randomized European trial of screening found the number needed to screen to save one life was "alarmingly high."[5]

In response to recent studies the American Urological Association (AUA) has just issued a statement clarifying their cancer screening recommendations. (a) Prostate cancer is most treatable when detected early. Men ages 40 and older should be offered a baseline PSA test and DRE for early detection and to enable risk assessment. The future risk of prostate cancer is closely related to a man's PSA score; men who are screened at age 40 establish a baseline PSA score, which can be tracked over time. The AUA strongly supports informed consent before screening is undertaken, including a discussion about the benefits and risks of testing. (b)Test results should influence the decision to treat and the controversies should not influence this aspect. The decision to have a prostate biopsy should be based not only on elevated PSA and/or abnormal DRE results, but should take into account multiple factors including prior biopsy history, free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, and comorbidities. (c) Not all prostate cancers require immediate treatment but cancer cannot be treated if it is not detected. An option that should be considered for some men is active surveillance in lieu of immediate treatment. The information required to make an informed decision is important for both patients and their urologists and partly arises from testing.[6]

In sharp contrast, the position statement just released by the European Association of Urology, also in response to the new randomized studies, states that current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy because of the significant overtreatment that would result. Overdiagnosis leads to significant overtreatment. In addition, current screening algorithms are insufficient because of their lack of specificity and selectivity for aggressive cancers that require treatment.[7] The extreme divergence of "official opinion" represented by this position vs. that of the AUA illustrates the huge gap between those who favour screening all men over some arbitrary age and those who strongly disagree.

It is clear from the AUA position that they view such parameters as PSA density and velocity as important input into the assessment and decision-making process. A recent commentary by Loeb and Carter from the Brady Urological Institute at Johns Hopkins takes a similar position.[8] They point out that screening as it is being studied in an attempt to determine the impact on such outcomes as prostate cancer specific mortality and overall mortality looks just at the total PSA. They advance the notion that it is not a matter of screening or not screening, but rather an attempt needs to be made to increase the specificity of screening. This they believe can be done by using PSA velocity and density. Both complicate and increase the cost of the screening process since the former requires two or more serial measurements and a consideration of the statistical significance of the derived velocity. The latter requires a reasonably accurate measurement of the prostate volume which is generally done by transrectal ultrasound. However, with regard to the use

of PSA velocity or the related doubling time, it is not generally agreed that this adds significantly to the decision-making. Vickers *et al* [9] conducted a systematic review of the literature and found that there was little evidence that PSA velocity or doubling time in untreated patients provides predictive information beyond that provided simply by the PSA test alone and they found no evidence-based justification for the use of these so-called PSA dynamic parameters in decision-making in early-stage prostate cancer. Ulmert *et al* [10] also concluded that PSA velocity does not aid in long-term prediction of the risk of prostate cancer diagnosis.

Attempts to quantify overdiagnosis of prostate cancer frequently involve models and to some extent are model dependent. A recent study found overdiagnosis after PSA screening came into use in the U.S. ranged from 23% to 42% depending on the model used.[11] These results were compared to earlier studies which found 66% and 42%. Since overdiagnosis implies the discovery of cancers followed by a high probability of treatment when the tumors would have presented no risk during the lifetime of the patient, even 23% seems large and numbers in the 40-70% range alarming. In addition, a recent commentary on breast and prostate cancer screening estimated from U.S. and European randomized trials, screening 1410 patients for 9 years was required to prevent one death.[12] The comparable number for breast cancer was 838 screened to prevent one death.

This summary of the current state of the debate is far from complete but seems adequate to suggest that it becomes essentially a personal and emotional rather than an evidence-based choice as to agreeing to or declining a PSA test since the evidence for the balance between benefit and harm is still very unclear no matter how it is presented to the patient. Furthermore, using the popular online prostate cancer risk calculators such as the one based on the famous Prostate Cancer Prevention Trial (PCPT) simply provides one with the percentage risk of biopsy-detectable prostate cancer and the risk of biopsy-detectable high-grade prostate cancer.[13] But this seems little different than calculating gambling odds, handicapping horses or using so-called technical stock market analysis to make predictions, and in fact the European Association of Urology does not favourably view the use of these algorithms. In contrast, we have the comments of one well-known clinician in a highly respected American institution. He finds the PCPT algorithm to be very useful in his practice, with any man having a 10% or higher risk of high-grade cancer being encouraged to undergo a biopsy.[1] This algorithm uses age, PSA, ethnic background, family history, digital rectal exam results and whether or not the individual has had a prior negative biopsy. The problem is that the threshold of 10% is arbitrary.

An essential feature of this debate and controversy and the one that causes the most anguish is that the issue here is not whether one wins at the casino, the race track or in the stock market, it is an issue that concerns life and death and the quality of that life. The need for a non-invasive screening test for prostate cancer that really “works” is obviously urgent, and in fact the subject of very active research.

DEFERRED TREATMENT OR WATCHFUL WAITING OR ACTIVE SURVEILLANCE

These terms are essentially equivalent and the basic notion has been discussed repeatedly in the Prostate Monitor and was given extensive treatment in our book *The Prostate and Its Problems.* As time goes on, more and more data are being collected concerning the success of this approach to prostate cancer treatment. Its benefits appear clear. Its downside will only be fully known after a number of years but progress is being made.

If one studies a group who elect deferred treatment (DT), then over the years some will elect one of a variety of available treatments and some will remain on the program. But at this point studies become difficult. There can be a criteria-based variation in the number who give evidence of needing treatment before it is too late but refuse it. Between studies and within a study there can be a variation of the criteria for enrolment, i.e. the criteria for a cancer which presents little immediate risk, and the criteria indicating it is time for definitive treatment. Endpoints in studies

examining the success of various protocols vary but typically include time to treatment, number still untreated, disease related mortality, overall mortality, progression to advanced disease, etc. In some or all of these endpoints, age and comorbidities are an issue. Furthermore, the patient generally can have treatment whenever desired and thus relatively strong psychological factors enter in and some will be treated who still meet the criteria for deferred treatment. Thus comparing studies becomes difficult as does reaching conclusions that can be generalized to larger populations.

An example is the recently reported prospective study based on the Health Professionals Follow-up Study cohort of over 51,000 men.[14] There were 3331 subjects diagnosed with prostate cancer from 1986 to 2007 but only 342 elected deferred treatment. Over half of these men remained without treatment during follow up of almost 8 years. Also prostate cancer mortality and metastasis did not differ between the deferred treatment and active treatment patients. However, there was no uniformity in criteria for deferred treatment such as is imposed in formal programs, nor were there uniform criteria for triggering intervention.

In the above study, the small percentage (10.3%) of men electing deferred treatment probably reflects under-use of this option. In an editorial accompanying the above paper, Anthony Zietman from Harvard Medical School comments that the culture of early detection coupled with early treatment is deeply ingrained. Results of deferred treatment are presented at major meetings and receive favourable comment in editorials, and yet "in the daily reality of the clinic," the results are not being applied to patients. In fact, as Zietman points out, the percentage of men being managed conservatively has been declining. He points out that this is a complex issue rooted in a conflict between knowledge and belief with "disturbing undertones of economic self-interest." He calls for "conscience-based medicine."[5] Zietman goes on to comment that "tens of thousands of men in their 70s and 80s are being diagnosed with early prostate cancer, men who have relatively little, if anything, to gain from either knowledge of the diagnosis or treatment."

Another study which also obtained positive support for deferred treatment, termed active surveillance in this case, was a multi-center investigation involving four North American tertiary care academic institutions. Uniform criteria for inclusion in the active surveillance cohort were applied, but the criteria for recommending subsequent treatment were non-standardized and physician specific. Inclusion criteria were selected to mirror patients who would otherwise be considered for surgery or radiation due to life expectancy greater than 10 years. They were age 75 or younger, clinical stage T1-T2a (see our book for a discussion of T-staging), PSA 10 ng/mL or less, 3 or less positive cores in diagnostic biopsy, biopsy Gleason score 6 or less, and a restaging biopsy before commencing active surveillance to confirm the clinical pathology. The active surveillance group consisted of 262 men. A median follow-up of 29 months, 43 ultimately received active treatment. The 2 and 5-year probabilities of remaining on active surveillance were 91% and 75%, respectively. Of the 43 patients undergoing delayed treatment, 41 were without disease progression at a median of 23 months after treatment. It was concluded that based on the follow-up of 29 months, active surveillance for select patients appears to be safe and associated with a low risk of systemic progression.[15]

OBSERVATIONS WHEN ACTIVE SURVEILLANCE FAILS

At Johns Hopkins Medical School a program of active surveillance has been in existence since 1995 and as of November, 2006, approximately 60% of those enrolled were still deferring treatment, 25% had undergone curative interventions, 10% had withdrawn from the program, and 5% had been lost to follow-up or died from other causes. The November *Journal of Urology*[16] contains a report on the pathological findings in patients on active surveillance who eventually underwent radical prostatectomy. The inclusion criteria for the Hopkins program are as follows: negative digital rectal exam, PSA density of less than 0.15 ng/mL/cc prostate volume, the absence of all of the following results from a 12 core biopsy: Gleason score of 7 or more, any Gleason pattern of 4 or 5, 3 or more cores involved or more than 50% involvement found in any one core. The recommendation for intervention is based on an annual repeat biopsy rather than PSA values or dynamics, something many other protocols do not follow. The average time between the first

biopsy and radical prostatectomy was about 30 months with a range of 13 to 70 and 44% and 75% of the patients showing progression failed the second or third biopsy, respectively. These results suggested that there was an initial under-sampling of more aggressive tumors rather than progression of indolent tumors. It was found that 27% of the tumors found after surgery were potentially clinically insignificant and all tumors with a large dominant nodule (> 1 cc) where located predominantly anteriorly (anterior/transition zone), a result that indicated more attention needs to be paid during biopsy to the anterior region of the prostate. Hopkins has now modified their protocol in recognition of this result. The authors point out that in routine practice transition zone biopsies are rarely positive and thus have limited usefulness. In this study, the large tumors that were missed in the biopsy protocol tended to be primarily in the transition zone.

In response to criticism of active surveillance in an editorial comment at the end of the paper, the authors point out that their experience at Hopkins as of 1997 was that that 26% to 29% of all prostate cancers treated by surgery were in fact found on pathological examination of the removed prostate to be potentially insignificant, organ confined cancers of less than 0.5 cc volume with no Gleason pattern (as distinguished from score) of 4. They also mention that in 5% of their radical prostatectomy cases, their pathologists had difficulty identifying (finding?) the tumor! Nevertheless in the main text they state their policy of recommending curative intervention for healthy young men with low risk prostate cancers “to avoid harm.” If this suggestion is declined, they recommend their active surveillance protocol with its repeated biopsies. They also cite a recent study which found that prostate surgery vs. watchful waiting in men with non-screen detected cancer, the benefit was restricted to men under 65 years of age. Thus they suggest that there is evidence of the safety of surveillance (presumably not active) for carefully selected older men with cancers detected by screening in the PSA era.

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