INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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In the last issue of the Newsletter, there was a discussion of zinc and the common cold. We start this issue with some additional information since it appears that the lozenge formulation found most effective is not readily available. Even the product sold by one of the leading online supplement suppliers is only partly zinc gluconate (amount not given), with no zinc acetate, and contains vitamin C which, as will be discussed, decreases significantly it's effectiveness as a cold therapy. However, a source with international shipping has been found.

The main theme of this issue involves the question of salt and cardiovascular risk and mortality. On several occasions, the media has given significant coverage to studies with what must have resulted in considerable confusion among listeners who pick up on the inconsistencies from study to study. The American Heart Association has just published a call for salt intake reduction which for many would be difficult without giving up eating large amounts of processed foods. They appear to view the science as settled, a notion that used to be popular in climate science. One also reads of dire population-wide predictions based on a linear no-threshold model for the cardiovascular risk of hypertension which is then translated directly into salt intake, as it turns out, with the use of dubious and highly inconsistent data. Furthermore, the guidelines and viewpoint of many experts focus exclusively on sodium and ignore both potassium and magnesium in spite of evidence that, at least for potassium, there is a strong interrelationship with sodium intake and potassium is critical in the control of blood pressure, something frequently disregarded by mainstream medicine. Your editor calls his the Single Factor Obsession-Fixation Syndrome with, at present, no known psychopharmaceutical treatment.

This issue also contains a review of two studies that concern the use of antidepressants (SSRIs) during pregnancy and point to the heightened risks of having a child with autism or certain so-called congenital heart defects. The greatest risk occurs during the first trimester. These studies add to a very limited literature on this subject. In fact, there are no significant reproductive safety data available for atypical antipsychotic drugs although it appears well known that lithium can cause birth defects including heart malformations, and suppress the brain of the fetus or nursing baby leading to flaccidity and lethargy. This brings up the standard problem that there is frequently a time lag between conception and awareness of the presence of pregnancy. Furthermore, the lag time can involve a significant part of the first trimester if, for example, a woman waits for a second missed period or is slow to do or get a pregnancy test. Thus even if the intention is to stop all or most medication upon getting pregnant, this may be delayed for as much as half the first trimester. In addition, if we are talking about antidepressants or other psychiatric drugs, only someone who is foolish or uninformed will abruptly stop taking these drugs, a factor that adds more time on medication during the critical period. Discontinuation of antidepressants presents such serious risks that new FDA warnings specifically address the need for physicians to carefully monitor patients, especially for signs for suicidal ideation. Other symptoms associated with SSRI withdrawal include impulsivity, aggression, anxiety, depression, crying spells, insomnia, dizziness, vertigo, nausea, vomiting, headaches and tremors. At the upper end of the severity scale, patients are temporarily but completely disabled during withdrawal. Even stopping cold-turkey a drug such as Xanax can cause severe withdrawal symptoms. A good description based on personal experience can be found in Confessions of an Rx Drug Pusher by Gwen Olsen, an ex-drug company rep (p. 55, paperback

edition). Time lag is of course the reason for the universal recommendation today that women who even may become pregnant take folic acid to prevent spina bifida.

This issue also contains the latest issue of the Prostate Monitor.

Finally, 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 the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

ZINC AND THE COMMON COLD. FINDING AN ACTIVE AND SATISFACTORY LOZENGE

The last Newsletter reported that that according to George Eby in a recent paper in the journal *Medical Hypotheses,* when one is trying to cure or limit the common cold and associated problems the best choice for a source of zinc in lozenges was zinc acetate. Zinc gluconate comes in second [1]. He also makes a very strong case for the beneficial action being restricted to the free, doubly ionized zinc atom. In the cited studies that used zinc acetate, there was a large and significant reduction in cold duration.[2-4] These were all randomized, double blind, placebo controlled trials. Subjects started treatment within 24 hours of the appearance of symptoms. Prasad *et al,* who conducted the most recent study suggests that the beneficial effects of zinc may relate to its anti-inflammatory and antioxidant properties and its effect on a major cellular receptor for the rhinovirus (intercellular adhesion molecule (ICAM-1).[2]

The optimum lozenge does not appear to be readily available. Issues include additives such as citric acid, vitamin C, and glycine, all of which tie up zinc ions in the saliva. Also, because of viral turnover rates, a lozenge that dissolves over 30 minutes is needed to achieve optimum effectiveness. In addition, the heating for of making hard-candy like lozenges can cause reactions with additives which render the zinc totally ineffective.[5,6]

Three of the clinical trials of zinc acetate reported in the literature and cited above where the treatment "really worked" used a lozenge prepared approximately or exactly according to the specifications of Eby. He recommends looking for a zinc acetate lozenge that yields about 18 mg of zinc and contains only the additives dextrose, glycerol mono-stearate and flavouring. The recommended dose is one lozenge every 2 hours while awake. Your editor is unable to purchase *any* zinc acetate lozenges where he lives (London, Ontario), nor do they appear to be available from well known supplement vendors. However, Eby's Cold Cure, as it is called, is available online from the Tahoma Clinic Dispensary (425-264-0051). They ship to most countries including Canada.

THE SALT HEART AND STROKE DEBATE

The American Heart Association (AHA) has just published a call for action regarding sodium reduction to prevent cardiovascular disease (CVD) and stroke.[7] The recommendation is to limit salt to < 1.5 g (1500 mg) of sodium per day which translates into about < 3.75 g of salt. The simple view is that salt raises blood pressure and elevated

blood pressure is a risk factor for cardiovascular disease. Since a number of recent papers have raised important questions, it seems important to examine the evidence concerning the risks and association of salt intake and both blood pressure (BP) and cardiovascular disease (CVD).

CARDIOVASCULAR AND MORTALITY ISSUES

Early in May 2011 the *Journal of the American Medical Association* published a paper which stirred up a lot of controversy.[8] The study followed almost 3700 individuals for about 8 years. Blood pressure and 24-hour urine sodium levels (a good indicator of salt intake) were measured at baseline. The main outcomes examined were the incidence of all cause, cardiovascular and non-cardiovascular mortality and fatal and non-fatal cardiovascular (all), coronary and stroke events, and their association with BP and sodium excretion. Repeated measurements were made on a much smaller subset during 1-3 follow-up visits. Urinary sodium excretion over 24 hours is approximately equal to daily sodium intake and for interpreting this paper, they were assumed equal.[9] In this study low intake had a mean ingestion of about 6 g/day of salt (2400 mg/day of elemental sodium) and high was about 14 g/day (5600 mg/day of elemental sodium). It was found that systolic pressure changes over time correlated with the change in sodium excretion, but the effect was minor. For an approximate 10 g/day increase in salt intake, systolic blood pressure (SPB) changed by less than 2 mm Hg. Contrary to the conventional wisdom, low sodium excretion was associated with *higher* cardiovascular mortality (adjusted odds ration 1.56—statistically significant, and this was the only outcome studied to show any significant association with salt intake, low or high. Furthermore, changes in blood pressure associated with large changes in urinary sodium excretion at follow-up were so small that most would consider them of no significance. This study met with criticism which was expected, given the results. Several recently published studies will be summarized which relate to this matter.

In a study just published, Yang *et al*[10] studied the correlation of both sodium and potassium intake with the risk of death associated with either any cause, cardiovascular disease (CVD) and ischemic heart disease (IHD). They obtained data from the Third National Health and Nutrition Examination Survey (NHANES). This prospective cohort study involved over 12,000 US adults considered representative of the population and examined the above endpoints as they related to sodium intake, potassium intake, and perhaps most importantly, the sodium to potassium intake ratio. Sodium intake varied from an average of 2.18 g/day (1st quartile) to 5.14 g/day (4th quartile) corresponding to salt intakes of 5.4 g/day and 12.8 g/day. The intake of elemental potassium varied from 1.8 g/day to 4.1 g/day; well below the recommended daily intake of 4.7g/day. During a follow-up of 14.8 years, 2270 deaths (1.28%/person year) were observed - 825 from CVD (0.46%/person year) and 443 (0.25%/person year) from IHD. The researchers found no correlation between sodium intake and deaths from CVD and IHD, but did observe a strong correlation between a high sodium intake and overall mortality (73% increased risk from 1st to 4th quartile). A high potassium intake was found to be associated with lower risk of CVD (61% risk reduction from 1st to 4th quartile), IHD (74% risk reduction from 1st to 4th quartile), and overall mortality (39% risk reduction from 1st to 4th quartile). A low sodium:potassium ratio (on a g/g basis, not molar) was also associated with reduced mortality with risk reduction from 1st quartile (average ratio = 0.98) to 4th quartile (average ratio = 1.57) of 46% for CVD, 115% for IHD, and 46% for overall mortality.

The authors cite a number of other studies addressing the role of sodium which obtained moderately inverse, moderately positive or non-significant associations. As will be discussed below, highly inconsistent results across a number of studies generally support the conclusion that there is no effect or a J-shaped relationship. However, the importance of adequate potassium intake is clear, and as the authors point out, low potassium intake is common and public health recommendations should emphasize the simultaneous reduction of sodium and increase in potassium intake. These results were consistent with another study published in 2009 which also highlighted the importance of the sodium/potassium ratio.[11] As will now be discussed, these studies join a large number of other recent studies which raise serious questions about the issues under discussion.

A just-published Cochrane review has just been published examined randomized controlled trials of reduced dietary salt consumption for the prevention of cardiovascular disease.[12,13] The researchers found that there was insufficient evidence to form an evidence-based conclusion regarding this question. Critics attacked the study claiming the analyses were not rigorous and the conclusion not reliable. But the Cochrane organization has a sterling reputation of unbiased and realistic reviews. Incidentally, they found that salt restriction increased the risk of all cause death in those with congestive heart failure by 159%, a result that was statistically significant.

In an editorial strongly supportive of the Cochrane review,[14] Alderman, expanded on the suggestion put forward in a 2007 paper by Cohen and Alderman that the inconsistencies that led to the Cochrane finding of null results can be explained by a J-shaped association between salt intake and CVD events.[15] As of 2011, he points out that there are seven studies in low-sodium settings which indicated an inverse relationship with outcome and four in high-sodium setting which yielded a positive association. Risk increased both below 2 g/day and above 5g/day of elemental sodium (5 and 12.5 g salt). Thus there is considerable evidence that a broad intermediate range of intake exists which presented no evidence of enhanced risk and which encompasses the consumption representative of most of the world's population. The AHA recommendation of < 3.75 g salt/day (1500 mg/day of elemental sodium) is at the level of intake where risk may start to increase significantly if the intake is reduced below this value.

SALT-BLOOD PRESSURE ISSUE

The standard syllogism is simply that salt raises blood pressure and increases in blood pressure increase the risk of cardiovascular mortality and morbidity. Ergo, increased salt consumption increases the risk of CVD problems. Thus it is of interest to examine recent studies that relate to this notion.

In 2009, the Cochrane Collaboration attempted to determine if lower BP targets (≤ 135/85 mm Hg) were associated with a reduction in mortality and morbidity as compared to standard BP targets (≤140-160/90-100 mm Hg). They concluded that treating patients to lower than standard targets does not reduce mortality or morbidity.[16] This is contrary to the widely held view and one of the basic premises of the AHA call for action, i.e. there is a continuous and increasing risk as BP increases above 135/85 mm Hg. Instead, there may be a threshold around 160 for SPB. The presence of a threshold makes a huge difference in public health projections. The AHA paper fails to mention this study.

In 2005 Townsend and colleagues, mostly from the University of California, examined the relationship between BP and a number of factors using the National Health and Nutrition Examination Survey data from NHANES III and IV, a survey covering 1989 to 2000.[17] The resultant cohort consisted of 11,000 individuals representative of a cross section of the U.S. population. The remarkable result was that dietary sodium intake was *significantly lower* in both NHANES III and IV for persons with isolated systolic hypertension compared to those with normal BP. Isolated systolic hypertension is considered a risk factor for cardiovascular risk. Furthermore, for individuals with both elevated systolic and diastolic BP (SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg), there was no difference in sodium intake when compared to those with normal BP. The fact that higher sodium intake is not associated with higher BP was already noted in the first NHANES study published in 1984. Perhaps the most important observation from this recent analysis was that inadequate mineral intake (calcium, magnesium and potassium) was related to higher BP, confirming earlier observations over two decades.

The famous Dietary Approaches to Stop Hypertension (DASH) studies also provide an interesting perspective and are widely viewed as definitive evidence for the importance of sodium reduction. The original study compared three diets called a control diet low in potassium, magnesium and calcium, a DASH diet (rich fruits and vegetables), and combination DASH diet which included low-fat dairy products to also give higher calcium. The latter two were also rich in potassium and magnesium. Calorie content was constant. It was found a dietary impact of the combination diet on SBP about a large as seen in the most successful sodium restriction studies (-11.2 mm Hg for hypertensives, -3.5 mm Hg for non-

hypertensives), *but note that sodium was held constant at 3 g/day (7.5 g salt) in all three diets,* but potassium, magnesium, and for the combination diet, calcium were dramatically increased compared to the control diet.[18] In a later intervention study, a DASH diet with 3.5 g of sodium/day was compared with the same diet with a much lower level of 1.1 g/day.[19] For this particular comparison, the potassium, magnesium and calcium were high and held constant. The change in SBP was -1.7 mm Hg for non-hypertensives and -4.9 mm Hg for hypertensives. Unless one is impressed with a change of about 2 Hg in SBP, then for non-hypertensive individuals sodium appears to be a non-issue. If one has high blood pressure with a SBP of 160 or more, a drop of 4.9 does not appear that impressive either. The main conclusion from DASH would seem to be that one must focus more on minerals rather than on sodium.

A subgroup analysis of the DASH data was published in 2004 which examined age and ethnic factors. [20] A control diet representing the typical American diet was compared to the DASH diet and for both, sodium was reduced to 3.45, 2.3 and 1.2 g/day for a feeding period of 30 days after which BP changes were compared for the two diets and the three levels of sodium intake. Larger effects on BP were found for hypertensives compared to non-hypertensives, the impact increased with age and for African Americans. The largest SPB decreases were found for the control group and ranged from 4.1 to 9.3 mm Hg SBP. However, those on the DASH diet of any age who were non-hypertensive exhibited small changes in SBP (1.5-2.8 mm Hg). Those on the DASH diet ≥ 45 years of age who were hypertensive had a decrease upon salt restriction of 6.7 mm Hg SBP. Hypertension was defined as ≥ 140/90 mm Hg. Hypertensives on the control diet with the high sodium content all had SBP below 145 mm Hg. Thus this study did not look at the effect of diet on hypertensives with SPB above 160, mm Hg, the value where the Cochrane study identified a threshold for potential mortality and morbidity.

Thus a reasonable conclusion from all the analyses of the DASH data might be that if one is on the this diet with its high potassium, calcium and magnesium content, whether hypertensive or not (by the conventional criteria), neither the sodium intake level nor lowering it have more than a small impact of SPB unless one is convinced that several mm Hg change for non-hypertensives, or up to 9 mm Hg for older hypertensives has clinical significance. The studies discussed above suggest that these changes may not be clinically significant. It would seem that the emphasis on sodium and the focus only on sodium are misplaced, and the focus instead should be on increasing potassium, magnesium and calcium provided by a diet high in fruits and vegetables. The DASH diet provided 4.7 g potassium, 423 mg magnesium, and 1.27g of calcium daily. Amounts of these magnitudes can of course also be provided partially or totally by supplementation.

Also, it is noteworthy that when scientists examine the impact of intra-individual blood pressure variability on study results (over a period of days for the same individual), they typically use a standard deviation of 6-8 mm Hg.[21] This standard deviation (32% of expected results are statistically predicted to be either above or below one standard deviation from the mean provided the distribution is normal) is near the upper limit of the effect of salt intake on blood pressure as "measured" in a very large number of trials. To confuse the issue even more, it is well known that frequently office BP is higher, sometimes significantly, than home measurements. It has recently been suggested on the basis of a systematic review and meta-analysis that neither is satisfactory for identifying hypertension if ambulatory monitoring is taken as the reference standard.[22] This impacts the stratification many studies make between hypertensive and non-hypertensive patients and thus the conclusions drawn.

SALT AND RISK OF STROKE

A component of CVD is stroke, an event of great concern since if non-fatal the impact on quality of subsequent life is in general vastly more severe than the aftermath of a survived heart attack. Studies that combine coronary events and stroke as a single outcome may underestimate the importance of sodium and potassium in connection with stroke risk. There have been a number of studies examining the association between potassium intake and adverse events where the outcomes are stratified to isolate stroke

incidence. A recent meta-analysis of prospective studies is thus of interest.[23] Fifteen cohort studies involving about a quarter million subjects with a 5 to 19 year follow-up were examined. For a 1.64 g/day increase in potassium intake, the risk of stroke was 21% lower. The authors note that in all the populations studied, the potassium intake was far lower than recommended by current guidelines. They cite a meta-analysis published in 2009[24] by the same group which found a significant 23% increase in stroke associated with higher compared to lower salt intake, but the result for cardiovascular disease in general failed to achieve statistical significance unless one study was omitted. The pool included over 177,000 individuals in 13 studies.

At the February 2011 International Stroke Conference, Gardener and coworkers reported on a study of the association of high dietary salt intake and ischemic strokes. The risk of stroke increased 16% for every half-gram increase in sodium intake (1.3 g salt) after adjusting for a large number of confounding factors. Those consuming 4 g/day of sodium (10 g/day salt) had more than double the stroke risk compared to those consuming less than 1.5 g/day (3.75 g salt).

Finally, the reader is referred to the book by David Brownstein, M.D. titled *Salt Your Way To Health* (Medical Alternatives Press, Second Edition, 2010). He discusses the problems that may arise on low or very low sodium diets and as well the merits of natural, unrefined salt sources due to the presence of a variety of minerals (e.g. Celtic sea salt). If one uses very little salt at home and avoids all commercially prepared foods, it is easy to develop a severe deficiency in sodium. He describes several case histories where he has seen very significant therapeutic benefits from natural salt supplementation. He also provides a number of examples where conventional therapeutic interventions for a variety of problems have not been successful until a sodium-mineral deficiency was addressed. For hypertensive patients he recommends 3-7 g unrefined salt per day. This is somewhat less than suggested from the J-shaped relationship which estimated the safe range in general was 5-13 g/day of salt. However, he regards the optimum intake as related to water consumption and suggests 0.5 g unrefined salt per quart of total water consumed, but this seems a difficult guideline to follow.

SUMMARY

To summarize, it appears that the evidence for the benefits of salt reduction in the context of cardiovascular disease is weak, inconsistent and there is some evidence suggesting risk in severe sodium restriction. However, the evidence for stroke appears stronger, highlights the critical importance of both sodium and potassium and does strengthen the argument that it might be prudent to target the lower end of what appears to be a J-shaped risk relationship, i.e. 4 to 5 g /day of salt. But high potassium and magnesium status appear equally if not more important and the ratio of sodium to potassium should be the important feature of recommendations, not just sodium alone. The mainstream focus is just on sodium and even the real meaning of the DASH results appears to have escaped notice. The AHA call for action does not even mention guidelines for potassium and magnesium nor entertain the notion that very low-sodium diets could be dangerous. In addition, the connection between salt and blood pressure does not appear as strong as mainstream medicine would lead us to believe, although salt sensitive individuals are an important exception but this enhanced sensitivity is apparently not prevalent enough to influence the studies suggesting only a weak or very weak relationship between salt intake and hypertension, especially when the decreases in SBP brought about by salt restriction are of the same size as typical intra-individual variations from day to day.

The salt saga, which now has a history of over two decades with the origin actually going back to the turn of the century, represents a good example of the Single Factor Fixation-Obsession Syndrome. We have seen examples of this syndrome in connection with dietary fat, saturated fat, cholesterol, serotonin, dopamine, beta amyloid, etc. Who knows, this may be one of the approximately 200 new disorders in the expanded psychiatry handbook of mental disorders, the famous DSM, the fifth edition of which is due out in 2013. Many scientists, and not just in medical science exhibit well defined symptoms of this syndrome. It appears to be a manifestation of a huge flaw in training, philosophical outlook

and a disregard or lack of knowledge of the history of science.

There is danger that the above discussion will be taken as indicating that there are no health risks in high salt intake. For a small fraction of populations, there is significant if not high sensitivity to salt intake in the context of blood pressure. For them the weak associations discussed above do not apply. There are other health risks of high levels of salt intake including kidney disease, left ventricular hypertrophy, kidney stones, osteoporosis and stomach cancer.[25] There is also the special case of the small fraction of some populations that consumes 20-25 g/day of salt, vastly in excess of the AHA recommendation and is well up on the risk arm of the J-shaped curve. It does not appear that they have been singled out for intensive study. Thus there may be merit in trying to keep daily salt intake at or a bit below the low end of Cohen and Alderman's 5-13 g/day range and then concentrate on adequate levels of magnesium and potassium such as were in the DASH diet, with both fruit and vegetable consumption and supplementation. A sodium/potassium ratio of one, the ratio in the lowest quartile (reference quartile) in the study discussed above,[10] would for example be achieved at intakes of 4 g of sodium (10 g salt) and 4 g of potassium (7.6 g of potassium chloride). The DASH diet had about 4 g of potassium, all from food and thus when sodium was held at 3 g, the sodium/potassium ration was highly favorable. Potassium content of common foods is readily available on the internet. But it needs to be emphasized that at present it appears the risk of stroke should be driving concern, not the other presentations of cardiovascular disease.

Note also that salt restriction reduces the non-elective supplementation with iodine that comes with mandated fortification as does the use of unrefined salt. See the September 2010 issue of the Newsletter for a research report on iodine and cancer and health in general which contains information about iodine deficiency, its importance and how to address it.

AUTISM AND PRENATAL ANTIDEPRESSANT USE

The use of prescription drugs either prior to or during pregnancy is frequently debated. Furthermore, if a drug is contraindicated during pregnancy it may still be taken for the first month or so of pregnancy due to the lag time in recognizing the condition. The conservative view is not to take any drug during pregnancy unless absolutely necessary, the argument being that embryonic development is highly complex, no one can predict the impact of synthetic chemicals, few if any women would enroll in clinical studies that address adverse effects during pregnancy, and the only evidence pro or con is either anecdotal, experimental (animal or mutagenic), or based on extremely sparse data. The exceptions are drugs that are considered too important to terminate and where the use is widespread and has gone on for so long that reasonable evidence of safety or the risk of adverse side effects associated with pregnancy is fairly clear. For new drugs, one must never forget the thalidomide saga. Incidentally, there is evidence that thalidomide increased the risk of autism only during the early part of the first trimester.

Depression is widespread and is diagnosed (over-diagnosed?) in many women who are pregnant or about to become pregnant. Estimates run as high as 6%. Even though numerous studies indicate that antidepressant drugs have little or no beneficial effect except in cases of severe depression, many women are in fact prescribed antidepressants during pregnancy or continue to take them after they become pregnant. Thus a just reported study which connects a large increase in risk of autism with the use of some antidepressants during pregnancy, and in particular, the very popular selective serotonin reuptake inhibitors (SSRIs), is of particular interest.[26]

This study was based on data available from the Kaiser Permanente Medical Care Program in Northern California where prescription information can be tied to data concerning the occurrence of pregnancy and to the health of the resultant child. The issue was maternal antidepressant use and the incidence of childhood autism spectrum disorders (ASD). Population-based studies find that ASD affects 1% to 2% of the US. Using a case-control design, the researchers found a statistically

significant 2-fold increase in the risk of ASD associated with the use of SSRIs during the year before delivery. The strongest effect occurred with treatment that included the first trimester—almost a 4 fold increase in risk. No increase in ASD risk was found when mothers with a history of mental health treatment did not experience prenatal exposure to SSRIs.

Building properly functioning brain architecture as well as other development aspects during gestation is generally viewed as exquisitely sensitive to both genetic and environmental factors, and serotonin is clearly implicated in the very early development of forebrain circuitry strongly related to ASD and mood disorders.[27] In addition, for antidepressants taken during pregnancy, there is some evidence of an association with congenital malformations, spontaneous abortion, preterm birth, abnormal birth weight and persistent pulmonary hypertension. While the relevant studies are inconsistent, they are suggestive that SSRIs can potentially influence many pathways and processes during fetal development. In addition, it is clear that there is substantial transfer of SSRIs across the placenta and some neonates whose mothers were on SSRIs develop mild or even severe behavioral symptoms in the early perinatal period (i.e. withdrawal symptoms), but these are self limiting.[28] This is also called neonatal abstinence syndrome. The mild to severe symptoms can be put into four groups: central nervous system (depression followed by excitation), gastrointestinal, autonomic and respiratory.[29]

When one considers that psychotherapy (so-called talk therapy) is a viable if not preferable option to drugs for mild and moderate depression, and it is hard to imagine that talk therapy is accompanied by any of the large number of adverse side effects just described, the obvious question arises. Why do not guidelines and current practice put drug treatment as a last resort or even proscribe it for pregnant women or women at high risk of becoming pregnant who carry the diagnosis of depression? One answer is that psychotherapy is more expensive and for the patient more time consuming than just taking a pill. One can also ask about the care exercised in differential diagnosis in the situation under consideration since there are many causes of depression that are treatable, but not by psychopharmacy or even psychotherapy. Psychiatric drugs such as antidepressants are frequently prescribed after a rather short consultation and in the majority of instances, the consultation is not with a psychiatrist (current estimate—only 20%) For example, is hypothyroidism properly ruled out? Probably not since current practice misses most cases anyway due to a totally misinformed trust in TSH ranges and the common failure to measure all the thyroid hormones and look for other telltale signs of this disorder. Thus women with depression due to hypothyroidism are treated with the wrong drugs, become pregnant, and put their unborn child at unnecessary risk, and are not even aware of doing this or its absurdity.

ANTIDEPRESSANTS AND RISK OF MAJOR CONGENITAL ABNORMALITIES

Finland appears to be an ideal place to conduct epidemiological studies. The government maintains a Medical Birth Register, a Register of Congenital Malformations and a Drug Reimbursement register. All citizens have a unique personal ID number and coverage is very close to 100%. In a study just reported, these three registries were linked to provide data on the question of the association between selective serotonin reuptake inhibitor (SSRI) intake during the first trimester and major congenital anomalies.[30] First trimester exposure was defined as at least one purchase of a SSRI during the first month before pregnancy and during the first trimester. While some women may have discontinued SSRI medication when they discovered they were pregnant, the designers of the study considered that normally there is a tapering-off period to prevent severe adverse effects of abrupt termination and thus their fetuses were exposed during embryogenesis. The study was large enough that it was possible to investigate risk associated with a number of SSRIs. The association between fetal alcohol spectrum

disorders was included in the study. The Register of Congenital Malformations also contains information on the incidence of fetal alcohol spectrum disorders, and the inclusion in the register requires information provided by a clinician concerning the evidence of substantial alcohol consumption during pregnancy. The results were as follows:

- The SSRI Fluoxetine was associated with an increased risk of isolated ventricular septal defects. Odds ratio (OR) 2.03 (95% Confidence interval 1.28-3.21). Absolute risk 0.5%.
- The SSRI Paroxetine was associated with an increased risk of right ventricular outflow (obstruction) defects with an OR 4.68 (CI 1.48-14.74). Absolute risk 0.2%
- The SSRI Citalopram was associated with neural tube defects with an OR of 2.46 (CI 1.20-5.07).
- Fetal alcohol spectrum disorders were 10-times more common in SSRI exposed offspring than in unexposed referent offspring.

Ventricular septal defect is a defect in the wall dividing the left and right ventricles of the heart. In the US about 80% of cases are corrected by surgical intervention. The first three results were adjusted for a number of potential confounders and were consistent with several earlier studies which increase the credibility of the observations.

While the absolute risk were small in this study, increases in relative risk by factors of 2, 4 and 10 should not be taken lightly when they appear to be related to drug treatment which in some and perhaps many cases has been shown to be ineffective or inappropriate. The results also reinforce the conservative view that all synthetic chemicals including both prescription and over-the counter drugs, chemicals in household products, personal care products, pesticides, etc., should be avoided unless there are strong reasons for use. One can not maintain that human development during gestation is well enough understood and drug actions so well defined that the real studies, which are of course unethical and will never happen, are unnecessary when it come to reassuring patients that risk is minimal.

The reader is referred to the March 2011 issue of the Newsletter for a review of psychiatric drugs and recommended sources of information. Since probably most of the world's population in developed countries will be offered antidepressants, stimulants or antipsychotics during their lifetime, starting around age 2, self-education is indicated. Especially recommended for general audiences are: *Medication Madness*. *The role of psychiatric drugs in cases of violence, suicide and crime*. Peter Breggin, M.D. St. Martin's Griffin, New York. This was recommended in the review but worth repeating. Also recommended:

- *Listening to Prozac.* Robert D. Kramer, M.D. Published in 1993, and subsequently revised, it is one of the classics in the field and widely viewed as a landmark book.
- *Suffer the Children*. *The case against labelling and medicating and an effective alternative.* Marilyn Wedge, Ph.D. Norton and Co., New York, 2011. A just published discussion of the use of family psychotherapy in addressing psychological problems in children and teenagers. By a practicing family psychologist.
- *Your Drug May be Your Problem. How and why to stop taking psychiatric medications*. Peter Breggin, M.D, and David Cohen, Ph.D. Da Capo Press, Revised edition, 2007. Another classic in this field.

While a personal library containing all the important books on this subject, including those dealing with the flaws, faults and misbehaviour of the pharmaceutical industry , even when restricted to authorship by recognized experts, would take up a fair-sized book case, this is a start. Reading these books puts one at risk of depression and probably significant anger!!

While the information and point of view in these books may help some avoid psychiatric drugs in favour of alternatives, help some avoid medicating their children, and help some avoid having psychiatric drugs in their system when they conceive, for a huge number of individuals, the damage is already done, mostly unrecognized and constitutes a hopeless and tragic situation.

NEWS BRIEFS

VITAMIN D AND DIABETES RISK

In a presentation at the American Diabetes Association 2011 Scientific Sessions in June, Pittas *et al* reported on a study which found that participants in the highest tertile of vitamin-D levels (mean level 30 ng/mL) had a 26% reduction in risk of incident diabetes (corrected for body weight). A dose dependence was also evident with even more benefit for levels > 50 ng/mL.

VITAMIN D AND PANCREATIC FUNCTION IN PRE-DIABETICS

A study just reported in the American Journal of Clinical Nutrition found that 2000 IU/day of vitamin D given for 12 weeks significantly improved pancreatic function in mildly overweight adults. In spite of the very positive results, it is noteworthy that the dose was low and raised D levels only from 24 to 30 ng/mL, and thus leaves unanswered the benefits of an elevation to, for example, 50 ng/mL.[31]

LIFESTYLE AND SUDDEN CARDIAC DEATH AMONG WOMEN

In July a study led by a group from Harvard reported on the beneficial impact of a low-risk, healthy lifestyle on sudden cardiac death (SCD) in a cohort of about 82,000 women of mean age 72 at the time of the SCD. Four lifestyle factors were evaluated and quantified: smoking, exercise, diet and weight. The low-risk diet approximated the Mediterranean diet. For exercise, low-risk was associated with moderate or vigorous activity for 30 minutes/day or longer. For body weight, low risk was defined as a BMI < 25. It was found that the proportion of SCD attributable to smoking, inactivity, overweight and poor diet was 81%. Adherence to a healthy lifestyle by meeting all four criteria reduced the risk of SCD by over 90%.[32] Over 50% of cardiac-related deaths qualify as SCD.

OLIVE OIL AND STROKE INCIDENCE

A cohort follow-up study of about 5 years duration just published in the journal *Neurology* examined the association between olive oil and stroke in a French study of a cohort drawn from Bordeaux, Dijon and Montpellier.[33] Over 7600 participants (mean age 74, 38% male) were involved and in a secondary sample, 1250 subjects underwent plasma oleic acid determinations. Intensive use of olive oil was defined a use in both cooking and salad dressings. Intensive use was found associated with a 41% reduction in stroke risk compared to non-use when adjusted for a large number of confounding variables. In the subgroup study, it was found that compared to the first tertile, participants in the third tertile of plasma oleic acid had a 73% reduction in stroke risk. Olive oil contains 80% monounsaturated oleic acid and plasma oleic acid is a marker, although non-specific, for olive oil consumption. Butter and goose or duck fat are also sources of this fatty acid. The authors note that consumption of olive oil, a major component of the Mediterranean diet, has also been associated with a decreased risk of heart attack, lower risk of all-cause mortality after heart attack, and lower carotid intima-media thickness, a crude measure of coronary atherosclerosis. The authors conclude that within the context of the Mediterranean diet, olive oil may be a major protective component independent of other dietary components. They also point to the protective association of olive oil and the Mediterranean diet with cognitive decline, blood pressure reduction, and reduction of low-density lipoprotein susceptibility to oxidation, and improvement in endothelial function. These effects have been primarily attributed to oleic acid.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 30 **SEPTEMBER 2011** **5th YEAR**

This issue starts with what is probably the most controversial subject covered by the Prostate Monitor since its inception. Put simply, is there benefit in treating men who have prostate cancer for low testosterone, and what is the real story on prostate cancer and testosterone? After all, a classical treatment for metastatic prostate cancer is to reduce testosterone levels to near zero and before drugs were available that accomplished this, surgical castration was the standard of practice. But there is growing evidence that the current view which regards to giving testosterone to prostate cancer patients is insane. It appears that this is in fact a serious oversimplification of complex biochemistry. This issue includes a discussion of three studies along with some of the accompanying editorial comment which will surprise many readers.

Every month there seems to be a study that finds coffee consumption either beneficial or harmless. In this issue research based on the famous Health Professional's Follow-up Study is discussed which addresses this question in the context of prostate cancer. The results should please those who are heavy coffee drinkers.

Finally, a study of supplements and prostate cancer has appeared which looked at a large number of so-called speciality supplements, as distinguished from vitamin and mineral supplements, and found only one that offered significant benefit, but the risk reduction was substantial.

Wishing you good health,

William R. Ware, PhD, Editor

TESTOSTERONE, HYPOGONADISM AND THE PROSTATE

The conventional wisdom, with a long history, holds as axiomatic that high testosterone (T) is risky for prostate cancer and low T is preventive. Men with metastatic prostate cancer who undergo castration, either surgically or the equivalent accomplished by drugs, obtain rapid pain relief and a dramatic reduction in their PSA. A picturesque description of the matter is that giving T to an individual with prostate cancer was like "pouring fuel on a fire" or "feeding a hungry tumor."[1] But over the years there has been growing evidence that low T may be a risk factor for prostate cancer. Thus there appears to be a paradox, summarized as follows by Abraham Morgentaler, a Harvard Urologist, and recently published in the journal *Cancer*.[1] Morgentaler is by far the leading advocate for a rational view of testosterone based on the body of existing literature, but has been a voice crying in the wilderness. Consider:

- There appears to be no compelling evidence in the PSA-era that men with higher T or who had undergone T therapy had enhanced risk of prostate cancer. Multiple longitudinal studies failed to show any significant association either.
- Serum PSA did not correlate with serum T.
- Men undergoing T therapy were found to be at no greater risk of developing prostate cancer than men who received a placebo.
- Very high doses of T for up to 9 months cause no increase in prostate volume or PSA in healthy men.
- PSA goes down rapidly with androgen deprivation and cessation results in increased PSA as T increases.
- Administration of T produces rapid cancer progression in androgen deprived men with metastatic prostate cancer but when T is administered to hormonally intact men, there are no negative effects.
- A number of studies suggest that at any given PSA level, a lower T concentration confers an increased risk of prostate cancer.
- In studies of individuals undergoing radical prostatectomy, most but not all have reported low T is associated with increase stage, higher rate of surgical margins, increased risk of biochemical failure (increasing PSA after surgery), and worse survival.

Thus the paradox as summarized by Morgentaler. How can prostate cancer be so sensitive to androgen deprivation and yet appear to be indifferent to variations in serum androgens, e.g. T, under other circumstances. Morgentaler's solution to this paradox is that there is a limit to the ability of androgens to stimulate prostate cancer growth, and this limit is achieved at low concentrations, after which there is no effect. He calls this the *Saturation Model*. Put another way, there is a finite ability of the androgen receptor to bind androgen, with the maximum binding, i.e. saturation, occurring at a low level. Thus changes in serum T that pushes the patient in and out of the castrate range of very low T levels produces large changes in PSA, whereas changes in serum T within the naturally occurring range produces no effects. In this context, a study just published by Morgentaler *et al* is of considerable interest.[2]

The study, very recently published in the *Journal of Urology* recruited 13 symptomatic men, mean age 59 years, with T deficiency that had untreated prostate cancer. Gleason score was 6 in 12 of the men and 7 in one. The mean T level was 238 ng/dL with a range of 64-413 ng/dL. They were given testosterone therapy for a median of 2.5 years (range 1.0 to 8.1). Mean T increased to 664 ng/dL with a range of 308-969 ng/dL. Surveillance involved PSA and digital rectal examination at 3 month intervals and yearly follow-up biopsies which also provided prostate volume data. Testosterone treatment during the course of this study did not result in changes in PSA or prostate volume. The mean number of follow-up biopsies was two. No cancer was found in 54% of these biopsies. No biopsies were triggered by clinical concerns. In two men, biopsies suggested upgrading but in both cases a subsequent biopsy or post radical prostatectomy evidence indicated no progression. In fact, no local prostate cancer progression or distant metastasis was observed.

The authors remark that to the best of their knowledge this is the first study to provide direct evidence regarding the effects of T administration to a group of men with untreated prostate cancer who presented with testosterone deficiency. All men experienced symptomatic improvement in sexual performance, libido, mood or energy. Thus it was concluded that T therapy to correct a deficiency does not cause cancer progression during 1 to 8 years even though the conventional wisdom would have predicted activation or more accelerated progression of the disease. The results are consistent instead with a substantial literature in which prostate growth, malignant and benign, appears to be independent of serum T from near physiologic to the supra-physiologic range. The results are consistent with the saturation model and the belief that most men with T deficiency have androgen concentrations sufficient to produce maximal androgen mediated cancer growth, and additional T elicits little, if any additional growth. The results suggest that even 64 ng/dL, the lower limit of the baseline T range, is above the saturation threshold.

In an editorial, Martin Miner from Brown University School of Medicine comments favourably on this validation of the saturation theory and suggests that further studies might reveal that treatment of T deficiency might even improve prostate cancer outcomes.[3] Quite a switch from the fuel on the fire view universally believed. Another editorialist, a prominent urologist at the famous Vattikuti Urology Institute, Henry Ford Hospital, Detroit, comments that while this paper adds to the body of literature that restoration of patient to a normal Testosterone state may not stimulate prostate cancer growth, the approach is “experimental” at this point and patients should be appropriately cautioned.[4]

The reader is referred to a recent book by Morgentaler, *Testosterone for Life*, McGraw Hill, 2009, for a comprehensive discussion of the role of adequate testosterone levels in human health.

ANOTHER TESTOSTERONE AND PROSTATE CANCER STUDY

Salonia *et al* have just published a paper on the association of preoperative hypogonadism (low serum T) and high-risk prostate cancer in patients undergoing radical prostatectomy.[5] Low T was defined as < 300 ng/dL, just as in Morgentaler’s research. The cohort had a mean T of 450 ng/dL, range 2-1360 ng/dL. It was found that the risk of high-grade disease was increased by > 50% in men with low T compared to normal T levels (33% vs. 19.8%), seminal vesicle invasion was about double (21% vs. 11%) and for men with severe deficiency, the risk nearly trebled (59.5% vs. 19.8%). In an editorial, Morgentaler comments that these are impressive differences in pathological findings that matter, features known to predict a worse prognosis. However, he was concerned that multivariate analysis failed to find age as an independent variable.[1]

In the same editorial he comments that after 7 decades of circumstantial evidence pointing in the wrong direction, it is perhaps time to consider the unthinkable, a trial of T therapy of sufficient duration and size to settle the question of the merits of normalizing serum T in older men in the hope of reducing the risk of prostate cancer, and in particular, high-risk prostate cancer.

ADVERSE EVENTS FROM TESTOSTERONE THERAPY

The other side of the coin! A placebo controlled study published in the *New England Journal of Medicine* in July 2010 received wide publicity because it was terminated early due to the observed rate of adverse events.[6] The study group consisted of 209 elderly men (mean age 74) with limitations on mobility, although they were still dwelling in their communities. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity. When compared to the placebo group, the testosterone group had significantly greater improvements in muscle strength as exhibited in leg-press and chest press tests and stair climbing while carrying a load. Out of the 209 participants, 23 in the testosterone group as compared to 5 in the placebo group had cardiovascular related adverse events. But the relative risk of cardiovascular related adverse events remained constant throughout the 6-month follow-up period.

Morgentaler’s commentary on this study, published in the *European Urology* is of interest.[7] He claims that there was no rigorous cardiovascular assessment and the cardiovascular events consisted of a wide variety of symptoms and findings that are not specific to this disease. Also, serious adverse

events were infrequent with only two heart attacks, both in the T group, occurring in this frail study population containing a significant number of hypertensive diabetics. He also points out that there is a substantial literature on T and cardiovascular disease which consistently demonstrated a neutral or even beneficial effect of higher T. Also, a very similar European trial[8] of elderly men failed to identify any increased cardiovascular risk in men on T therapy and a recent study involving almost 1000 men referred for diagnostic coronary angiography found that men with low T were at increased risk of mortality during a 7-year follow-up as compared to men with normal serum T (21% vs 12%).[9] He underscores his view by saying that this study will not alter his clinical practice and he will continue prescribing T for symptomatic men with T deficiency, especially since the existing literature, from his point of view, even suggests that normalization of T may provide cardiovascular benefits.

COFFEE AND PROSTATE CANCER RISK AND PROGRESSION

A study has just been published which examines the association between coffee consumption and both the risk of incident prostate cancer and its progression.[10] According to the authors, previous epidemiological studies have generally found no association between coffee consumption and the risk of prostate cancer, but they regard all such studies as having limitations and none included examining the risk of advanced disease. This was a prospective cohort study based on the Health Professionals Follow-up Study data collected every 4 years since 1986. The analysis included almost 48,000 men. Between 1986 and 2006, 5035 patients with prostate cancer were identified including 642 with lethal prostate cancers. For this cohort data was available regarding the intake of regular and decaffeinated coffee along with information concerning potential confounders such as smoking, obesity and other variables. At baseline, 7890 men drank no coffee and at the upper end, 2492 drank ≥ 6 cups/day. Slightly less than half drank 1-3 cups/day.

When compared to non-drinkers, men who consumed ≥ 6 cups/day had a lower adjusted relative risk of overall prostate cancer representing a reduced risk of 18%. For lethal prostate cancer, consumers of ≥ 6 cups/day had a 60% risk reduction. Both results were statistically significant. Coffee consumption was not associated with the risk of non-advanced or low-grade cancer and only weakly associated with high-grade disease. There were no significant differences seen when regular coffee was compared to decaffeinated coffee. The authors provide a number of arguments regarding the absence of bias and the adequate adjustment for confounding. With regard to a comparison with other studies, the authors comment that previous studies have not reported the striking inverse association that they observed and attribute this mostly to reporting findings only for overall prostate cancer which overlooked the inverse association with advanced disease. Several studies were limited by too narrow a range of intakes, small numbers of subjects, and lack of adjustment for smoking, The latter is important since smoking is associated with prostate cancer specific mortality an strongly and positively associated with coffee intake.

While it appears clear that caffeine is not involved, the authors discuss a number of components in coffee that could impact the incidence or progression of the disease. Coffee improves glucose metabolism, has antioxidant and anti-inflammatory effects, affects sex hormone levels and increases insulin sensitivity.

Overall, this study provides reassurance to coffee drinkers that even high intakes appear safe in general and potentially very protective against lethal prostate cancer.

SUPPLEMENTS AND RISK REDUCTION OF PROSTATE CANCER

The VITAL study (VITamins And Lifestyle) has been investigating the association of the use of vitamin, minerals and speciality supplements and cancer risk. The researchers have recently reported on a set of so-called speciality supplements and prostate cancer risk,[11] including chondroitin, coenzyme Q-10, fish oil, garlic, ginkgo biloba, ginseng, glucosamine, saw palmetto and grapeseed supplements such as grapeseed extract. The 35,000 participants' were 50-70 years of age who lived in western Washington State. They were covered by the Surveillance, Epidemiology and End Results (SEER) cancer registry. Data was collected concerning the use of these speciality supplements as well as vitamin and mineral supplements over a 10-year period prior to baseline. Frequency and

duration of use but not dose were obtained. Tests of the validity of the data collection via questionnaire indicated a satisfactory degree of accuracy. Participants also reported known or suspected risk factors for prostate cancer including height, weight, family history of prostate cancer, medical history, history of prostate cancer screening, history of enlarged prostate and lifestyle characteristics including alcohol consumption.

When compared to non-cases, prostate cancer cases were observed to be older at baseline, more likely to be of Black race, consume more alcohol, take multivitamins, report recent PSA testing and benign prostate biopsy or prostate enlargement, or family history of prostate cancer. Cases were less likely to be obese.

Among all the speciality supplements listed above, only grapeseed supplements had any impact on prostrate cancer risk. Compared to non-users, men who used this supplement had a statistically significant lower prostate cancer risk (Hazard ratio 0.59) or a 41% risk reduction. High ten-year use was associated with a 62% risk reduction. Grapeseed supplement use was inversely associated with both low-grade (42% risk reduction) and high-grade (18% risk reduction) compared to non-users, although both these results failed to achieve statistical significance. However, high 10-year use was associated with a statistically significant and large reduction of low-grade (79% risk reduction) but not high grade prostate cancer.

The authors discuss potential constituents of grapeseed extract, the common form of the supplement, but find little guidance in existing human studies. However, in prostate cell culture studies, grapeseed extract has been found to induce cell death and reduce proliferation. Since grapeseed extract contains a number of phenolic compounds, it is possible that one or more might be metabolized by the CYP1B1 enzyme present only in cancer cells and produce a cytotoxic substance. This is the mechanism by which Salvestrols operate, as has been discussed on several occasions in this Newsletter.

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