INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 216 **APRIL 2011** **20th YEAR**

The principal theme of this issue was inspired by the recent events in Japan and in particular with the nuclear reactor disaster that is unfolding as this is written. There seems to be considerable panic and people as far away as the eastern U.S. are buying up and perhaps even taking very high-dose potassium iodide pills, presumably based on the assumption that huge clouds of radioactive fallout is soon to arrive. Fallout will no doubt arrive, but the levels and thus the potential exposure will probably be low.

Nevertheless, this new development brings up the old question of the risk of cancer associated with radiation exposure, especially from fission products from a failed reactor. Those who believe in the linear-no-threshold hypothesis (some lovingly call it a model) will sharpen up their pencils and busily calculate the increased cancer risk. There are hundreds of academics who more or less make a profession of this sort of calculation. As discussed in a Research Review in the November 2008 Newsletter, this hypothesis is far from universally accepted and there is strong contrary evidence. One can even pay several hundred dollars and purchase a recent medical monograph on hormesis—the beneficial effects of low-dose radiation. Thus it is of interest to look at what actually happened after the Chernobyl accident. There were well over 5 million individuals involved who were exposed to radiation, in some cases at high doses, and there has been extensive follow-up over more than 20 years. In addition, for large numbers there were good estimates of the dose received. There is a considerable peer-reviewed literature describing many studies on those exposed after Chernobyl. This is surely a better approach than using an unproven and disputed hypothesis and making speculative calculations. Thus the discussion that leads off this issue.

Other subjects discussed include the recent observation of the apparently strong connection between triglycerides and the risk of stroke. The focus on LDL cholesterol as the ultimate evil and one of the most profound threats to all of mankind has for decades limited interest in triglycerides while at the same time, mainstream advice, again for decades, has led people to change their lifestyle in a direction that can strongly increase triglycerides, and incidentally decrease HDL cholesterol. There is clearly something wrong with the system that operates in this fashion.

Insomnia in the elderly is also addressed. This is a serious problem since it appears to lead to inappropriate use of pharmaceuticals such as sedative-hypnotic drugs and psychiatric drugs. Both carry risks of adverse effects that suggest they are inappropriate for solving the problem of insomnia in the elderly. The risks of the latter were discussed in detail in Part I of the Research Review on psychiatric drugs in the February 2011 Newsletter. The study discussed in this issue represents a "return to nature" approach involving melatonin enhanced by small amounts of zinc and magnesium.

This issue also contains the latest ***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

RADIATION AND CANCER. WHAT CAN WE LEARN FROM CHERNOBYL?

In April, 1986, the Chernobyl nuclear power plant in what is now the northern Ukraine suffered a series of explosions and total destruction of the nuclear reactor. There was a massive release of radioactive material into the atmosphere that contaminated large surrounding areas. The most heavily contaminated areas were in Belarus, Russia and the Ukraine. Heavy rainfalls exacerbated the fallout and resulted in contamination of groundwater and soil. The initial ionizing radiation exposure came mostly from iodine-131 (half-life 8 days) whereas the later exposure was mostly due to cesium-137 (half-life 30 years), cesium-134 (2 years) and strontium-90 (29 years). In fact, iodine-131 represents about 3% of uranium fission products. These were mostly ingested, partly through contaminated milk. Other elements represented among the radionuclides deposited on the ground which contributed mostly to external radiation exposure included isotopes of zirconium, niobium, ruthenium, tellurium, barium, lanthanum and cerium. These radionuclides were of course products of the fission of uranium as well as the subsequent decay processes.

Three groups were exposed to significantly elevated levels of radiation: (1) Liquidators, i.e. recovery operation workers. They were involved in emergency response, containment and clean up at the Chernobyl site. It is estimated that 600,000 were involved of whom about 240,000 worked during 1986-7 when the radiation levels were the highest at the site and surrounding 30 km zone; (2) inhabitants who were relocated or evacuated. In the months following the accident about 220,000 people were relocated and 116,000 evacuated; (3) Inhabitants of contaminated areas who remained. About 5 million continued to live in contaminated areas of Belarus, Ukraine and Russia. The average doses estimated were (1) liquidators—100-185 mSv; (2) Evacuees—30 mSv; (3) those remaining—10-50 mSv with over 250,000 in areas of high contamination.[1,2] Note that these are averages with maximum exposure considerably higher. Incidentally, the issue with very high doses associated with nuclear disasters or atomic bombs is not cancer but immediate radiation sickness which becomes apparent above 1000 mSv with doses above 10,000 mSv frequently fatal.

For perspective in terms of the unit being used (the millisievert—mSv, i.e. 1/1000th of a Sievert), typical natural radiation exposure per year is 2-3 mSv, a chest x-ray 0.1 mSv, a mammogram—3 mSv, and a full-body CT scan—10 mSv. Angiography and lengthy interventional procedures can involve exposures up to 20 mSv. The average effective cumulative dose from natural background radiation over an average lifetime is about 160-240 mSv.[3] The Sievert unit attempts to evaluate quantitatively the cumulative biological effects of ionizing radiation. It is equivalent to the Gy (gray) for beta, gamma and x-ray radiation but not for alpha particles.

Awareness of the potential risk of cancer following the Chernobyl disaster prompted the follow-up of large populations which became an international effort, and now we have 10-20-year results. However, these studies have not been straightforward. Rather they have been confounded by vastly increased screening in countries where screening was minimal. In addition, radiation-induced cancer generally has a rather long latent period, typically 10 years, although leukemia and pediatric thyroid cancer appear to have shorter latent periods. The recovery operation workers, a large group with the highest dose levels, provide a significant insight into the risks of cancer as do the huge numbers of individuals who were exposed over a number of years to doses much greater than the annual dose from natural sources. In addition, exposure to radioactive iodine provided short-term high thyroid levels of radiation for many individuals including children who are particularly sensitive to radiation-induced

thyroid cancer. Thus Chernobyl should provide highly significant insights into the potential cancer risks now facing the Japanese and those living in other countries who may experience airborne contamination.

The general picture that has emerged is as follows. Higher than national rates of leukemia were found for some but not all recovery operation workers who were exposed to high levels of radiation, but the results are subject to question.[4] Aside from this subgroup, three studies found no evidence of any meaningful association between Chernobyl exposure and leukemia in adult or pediatric populations.[2,4] For pediatric thyroid cancer but not adult thyroid cancer, the evidence is strong that there is enhanced risk which appears dose dependent. For the three major groups exposed to elevated radiation levels, incidence for all other cancers were in general either not elevated or less than predicted from the rates in the unexposed populations.[1,2] Adult residents who elected to continue living in contaminated areas experienced no increased risk of cancer. In addition, for those living in the most contaminated areas and those relocated after some delay, the observed number of cancers was *less* than the expected number based on unexposed individuals.[1] Some details are provided below.

A study published in 2006 involved men who came from Estonia and Latvia to work on the clean-up at the Chernobyl reactor.[5] The study followed over 10,000 workers with a mean exposure of 110 mSv for a mean of 11 years. More than 12 years after the accident, there was no statistically significant increase in overall cancer risk, but there was some indication of excess leukemia, brain and thyroid cancer cases in the combined cohort. The researchers found that the excess thyroid cancer rate disappeared if corrected for the screening effect by a factor suggested by the National Council on Radiation Protection and Measurement. Furthermore, there was no indication of a dose-response relationship, and workers with the highest whole-body exposure did not have increased incidence of cancer, an observation that raises questions about the suspected increase in leukemia and brain cancer. Of those with documented dose data, 47% received doses > 100 mSv and 31% doses > 150 mSv. Thus, workers who received considerably higher doses than those who elected to remain in highly contaminated areas in general exhibited no significant increase in cancer incidence other than perhaps leukemia.

Therapeutic levels of radiation exposure appear to increase the risk of breast cancer. In a study that covered from the accident to 2001, using as a reference a cumulative dose of < 5 mSv, only after 1992 was a statistically significant increase in breast cancer incidence found, and this only in the 1992-1996 period for doses between 20 and 39 mSv with no significant increase for exposures > 40 mSv, and in the period 1997-2001, only for doses in excess of 40 mSv. These increases appeared about 10 years after exposure. The authors regard these excess cases to be greater than one would expect from increased diagnostic activity. However, this appears debatable given the well-known impact of aggressive screening on incidence. Another study compared areas in Belarus where there was maximal or minimal exposure and examined breast cancer incidence. The data provided no convincing evidence for Chernobyl-induced breast cancer in this country over the period 1978 to 2003.[6]

Leukemia has been associated with exposure to ionizing radiation. Increases appear within 2 to 5 years. As regards adults, studies have been done for both the general exposed population and the clean-up workers. For the period 1986 to 2003, there was an excess of leukemia among emergency workers who had received doses in excess of 150 mSv in comparison to less exposed workers.[7]. Another study found increased risk for cleanup workers who worked during the year of the accident as compared to those who worked in later years. However, these studies have serious limitations, especially with regard to ascertaining exposure.[2,4] Other studies find no association with dose and the overall picture is regarded as inconclusive.[2] For adults not involved in the recovery and clean-up, there is no evidence of any association between leukemia and the Chernobyl radiation exposusre.[4] For children, a recent case-control study found that there was a significant increase in leukemia at exposure doses higher than 10 mSv.[8] However, other studies have found no evidence of radiation-related increases in the incidence of leukemia in Belarus and Russia in the first five years after

the accident.[2] However, it has been pointed out that none of these studies was sensitive enough to detect small changes in the incidence of this disease and all had methodological problems.[2] Also two other case-control studies involving children have reported. One done after 14 years with a median exposure of 10 mSv (range 3 to 390 mSv) was unable to find convincing evidence of an increase in risk of leukemia in Belarus or Russia. This called into question their results for the Ukraine where there appeared to be a dose dependent increase in risk.[9] A second case-control study found evidence of increased risk in the Ukraine. This study has been criticized for the inappropriate selection of controls and the risk estimates appear far too high to be realistic.[10] Such inconsistent results suggest reserving judgment, especially since the evidence of enhanced risk generally appears in the first 5-10 years of exposure for individuals under 20 years of age. A recent review concluded that at this time, no meaningful conclusion can be reached concerning Chernobyl and pediatric leukemia.[4]

Thyroid cancer represents a special situation. If one searches Medline (PubMed) using cancer and Chernobyl as key words for any date, almost all of the many papers that come up are concerned with pediatric thyroid cancer. This in itself tells one something about the impact on adult cancer incidence even with long follow-up. As of 2007, pediatric thyroid cancer has been the most important medical consequence associated with the Chernobyl accident. Children in particular are at very high risk and after the Chernobyl accident were exposed to radioactive iodine from inhalation and ingestion, the latter principally via milk. They were also exposed to external whole-body radiation and internal radiation from other radioactive isotopes either ingested or inhaled. Iodine--131, the isotope of greatest concern, has a half-life of about 8 days. In the aftermath of the accident, it is estimated that about 90% of the thyroid dose was from this isotope and less than 10 % from the three shorter-lived iodine isotopes. Children and adolescents received higher doses than adults did because a higher percentage of the iodine concentrates in the thyroid as compared to adults and children drink much larger amounts of milk. Individual doses in children varied over a wide range from a few mSv to several thousand mSv! The relative risk associated with an exposure of 1000 mSv is in the range of 5.5 to 8.4 when the comparison is with unexposed children.[11]

The observed latent period for pediatric thyroid cancer of about 4 years turned out to be surprisingly short and in conflict with the conventional wisdom. This caused a period of official denial, which has now disappeared. The most recent data indicates that between 1986 and 2002, about 4000 cases of thyroid cancer occurred among exposed children when under the age of 15 years. Another 1000 cases have been identified in those between the ages of 15 and 17. The cure rate for this cancer is very high. The number of reported thyroid cancer deaths following the accident is less than 1%. As of 2005-06 only 15 persons have died from Chernobyl-related cancer of the thyroid.

The connection between pediatric thyroid cancer risk and thyroid iodine status is inconsistent and the status difficult to establish. However, studies that correlated incidence with the soil levels of iodine found that in areas where one would expect iodine deficiency, the incidence of thyroid cancer attributable to the accident was significantly higher.[12] Also immediate saturation of the thyroid with stable iodine when the threat has become apparent can reduce the incidence. But this may be difficult if the population is not prepared since ideally iodine (or iodate) must be taken before or within a few hours of the beginning of exposure. After Chernobyl, information about the accident was delayed. If fact for political reasons it was some time before the population became fully aware of the serious nature of the accident or the risk to children.[13] The population continued to drink local milk, which resulted in high doses of radioactive iodine. Studies where stable iodine was given to children evacuated after the accident indicated that this intervention strongly reduced cancer incidence.[14,15] The amounts given were very small, ranging from 0.5 mg/15 days for children aged 1-3 years to 1 mg/week for children 7 years or older. The odds of developing thyroid cancer after a 1000 mSv exposure in subjects who consumed potassium iodide were about 3 times less than those who did not.[15] An even better result might have occurred with higher iodine doses.

Information about thyroid cancer in adults exposed during and after the Chernobyl accident is minimal and inconclusive. The current opinion appears to be that the small increases found in some studies merely reflect increased screening, and as mentioned above, attempts have even been made to quantitatively correct for this. These findings are consistent with the general lack of an observed association of statistical significance between thyroid cancer and adult exposure to either external radiation from atomic bombing or internal radioiodine used for medical reasons.[12]

The Chernobyl experience provided large cohorts containing many individuals with known or estimated exposures who were subjected to numerous follow-up studies. After all, there were 5 million individuals who did not relocate and continued to live in contaminated areas. Over 250,000 individuals were living in contaminated areas where the *mean* dose was 50 mSv, about 5 times that of one whole body CT scan. People were not only exposed to external radiation but to that associated with ingestion and inhalation of fission products and radioisotopes that resulted from decay of these primary products, some very long-lived. It was possible to study the impact of chronic moderate levels of exposure and shorter-term very high exposures. Only for pediatric thyroid cancer were significant increases in cancer incidence observed even when studies extended 10 or 20 years from the time of the accident. Furthermore, the thyroid cancers were almost completely curable. Increased risk of leukemia in heavily exposed recovery and clean-up workers may have been present. The breast cancer data is inconsistent and has problems with confounding from aggressive screening. This leaves only pediatric thyroid cancer as a well-established cancer threat for populations exposed to ionizing radiation as a result of the Chernobyl accident.

These results undermine the conventional wisdom represented by the widely, in fact almost universally held belief that the risk of radiation-induced cancer has no threshold and increases linearly with dose. This hypothesis in no way accommodates observations of decrease in risk with abnormal exposure to radiation such as was observed not only in Chernobyl but elsewhere. The reader is directed to the Research Review published in the November 2008 issue of *International Health News* where this subject is examined critically. Note especially the episode of the apartment houses in Taiwan where a large number of residents were exposed to ionizing gamma radiation (Cobalt-60) for 10-20 years. More than 1600 persons lived in apartments that were highly or moderately radioactive and 2400 in apartments with low levels. The mean cumulative exposure was about 40 mSv with a range of < 1 to 2300 mSv). Occupants were subsequently forced to move and then followed-up for cancer incidence. The exposure was found to be significantly *protective* (hormesis*)* when measured by either mortality or the incidence of cancer (only 3% of the expected cancer mortality rate after 19 years follow-up).[16,17] Hormesis has also been found in a number of studies of atom bomb survivors.[18] These and many other results discussed in that review predict what has been observed after Chernobyl, i.e. a very high and in fact unknown threshold below which there was hormesis or negligible risk.

The Chernobyl results are in general agreement with a 2005 joint report from the French National Academy of Medicine and the Academy of Science where it was concluded that epidemiological studies have been unable to detect in humans (adults!) a significant increase in cancer incidence for doses below 100 mSv nor provide any evidence for the validity of the linear-no-threshold model. The French report also discusses the possibility of benefit from low doses.[19,20] Judging by the data discussed above, 100 mSv may be conservative. To this can be added a new report from the United Nations Scientific Committee on the Effects of Atomic Radiation released February 28, 2011, concerning the Chernobyl accident. They concluded; “Although several hundred thousand people, as well as emergency workers, were involved in recovery operations, there is no consistent evidence of health effects that can be attributed to radiation exposure, apart from indications of increased incidence of leukemia and cataracts among those who received higher doses.” The same conclusion was stated in a 2007 keynote address by a member of the International Atomic Energy Agency in Vienna concerning a retrospective analysis of the impacts of the Chernobyl accident.[21]

Panic over the Japanese situation may be unwarranted, although it could evolve into a disaster much greater than Chernobyl. But for those in North America and Europe exposed to airborne contamination, the Chernobyl results appear to offer an upper limit on risk, and it appears to be minimal or even non-existent, especially when one considers the short half-life of iodine-131. Levels from airborne fission products, especially in Europe and North America, will surely be much lower than in the contaminated areas after the Chernobyl accident. The same may be true for areas in Japan remote from the site of the damaged reactors. Children are obviously at risk, and some probably at very high risk of thyroid cancer. However, the reactors are not producing iodine-131 or the precursor fission product for the shorter-lived iodine radioactive isotopes. Those reactors that were operating have been shut down since March 11.

Individuals living near nuclear reactors obviously should keep on hand a source of iodine in case of an emergency. As discussed above, the principal concern is children and teenagers. Several companies sell high-dose potassium iodide pills formulated for emergency saturation of the thyroid. If there is significant fallout from the Japan disaster in areas where readers live, then iodine prophylaxis appears indicated, especially for children and teenagers. Time after the termination of fission is an important factor since iodine-131 is a fission product with a half-life of 8 days. Levels drop to 10% after about 27 days and to 1% after about 53 days. The radioiodine threat clearly depends on the actual amounts released, when they were released relative to the termination of fission, and the fallout transit time. The reader is referred to the CDC webpage for dose and cautionary information.[22] Maintaining optimal iodine status should require lower doses for successful radioiodine prophylaxis. The reader is referred to a recent Research Review concerning iodine (not radioactive) and cancer, which appeared in the September 2010 issue of the Newsletter, and in particular the section on how to develop and maintain optimal iodine status.

TRIGLYCERIDES AND STROKE

Serum triglyceride levels have been measured for ages. Since LDL cholesterol is not measured directly, triglycerides are a necessary component in the calculation. As the fat is bad dogma took root and flourished, the common reaction was to substitute carbohydrates for fat, a practice strongly encouraged by the food industry and more or less ignored by mainstream medicine. The net result was, among other things, elevated triglycerides and depressed HDL cholesterol levels. Some people went so far as to eat almost no fat, and one famous authority strongly argued against fish because they contained fat. Some individuals managed to get their HDL down to a point where it was surprising they were still alive, especially when viewed in the context of sky-high triglycerides. Now Big Pharma is looking for a pill to raise HDL! Yet there was never any real evidence that fat was bad.

There does not appear to be a connection between cholesterol levels and ischemic (occlusive) stroke. Some view it as a paradox that statins in some studies have reduced the risk of ischemic stroke. JUPITER is cited even though that study was probably confounded by the strong elevation of vitamin D levels, a unique aspect of the statin used.[23] Considering the large number of non-lipid lowering effects of statins that have been discovered and studied, it is amazing that the conventional wisdom still looks at any statin effect as a lipid lowering effect, a naïve and simplistic view which in most cases is self-serving. A recent study of triglycerides and stroke was in fact partly motivated by the notion that since statins reduce triglycerides and triglycerides had been associated with increased risk of stroke, the paradox disappears.

The Danish study in question just appeared in the Annals of Neurology.[24] Baseline data was collected in late 70s and follow-up examinations carried out periodically up to 2001-2003. The cohort was viewed as representative of the general Danish population. The median follow-up was 26

years during which 837 out of 7579 women and 837 out of 6352 men developed ischemic stroke. The issue was the association between non-fasting triglycerides and cholesterol and the stroke risk. Using < 1 mmol/L as reference, women with triglycerides between 1 and 1.99 had a non-significant increase risk of 20%, but for levels >5 mmole/L, the risk was increased to nearly four-fold with statistical significance. For men the pattern was similar except that for levels > 5 mmole/L, the risk increased only 2.3 times. Total cholesterol was irrelevant for stroke risk in women and appeared only between total cholesterol levels of 4 and 9 mmol/L for men (to convert to mg/dL, multiply triglycerides by 88.6 and cholesterol by 38.7). A cholesterol level of 9 would be typical of someone with familial hypercholesterolemia.

The authors offer as a mechanism the increased level of LDL remnants present in cases of elevated triglycerides and argue that these particles penetrate into the arterial wall and eventually cause atherosclerosis. But they cite only three references, a general discussion of atherosclerosis being a post-meal phenomenon written in 1979, a study on carotid arteries and a rabbit study—i.e. no real evidence at all.

This study was based on non-fasting numbers and thus casual triglyceride measurements and must have ranged from valleys prior to and long after a meal to peaks soon after eating. But the fluctuations would have been from a fasting level which in the high stroke risk group was no doubt elevated. Triglyceride levels can be kept low or near normal by careful control of the quantity and quality of carbohydrate intake. Judging by that faithful indicator, the drug ads on the evening U.S. national news, the drug companies are getting interested in triglycerides and HDL to the point of aggressively promoting slow-release niacin. The ads do not mention triglycerides.

INSOMNIA AMONG THE ELDERLY

Insomnia appears to be an underappreciated problem, especially in the elderly. Studies find that about half of older individuals are dissatisfied with the quality of their sleep and over 40% of community dwelling elderly report failing to stay asleep. More than two-thirds of insomnia cases are undiagnosed, there is a lack of treatment guidelines, and poor sleep correlates with elderly morbidity and mortality. Insomnia also impacts daytime quality of life and individuals with sleep disturbances require more healthcare and are subject to more slips and falls. There is some evidence that insomnia is a major risk factor for depression and is also a common comorbidity.

Short-term use of prescription sedative-hypnotic drugs is common. Long-term use is not evidence-based and there are serious concerns about adverse effects including cognitive impairment, daytime carry-over sedation, risk of accidents, and falls and slips. There is also no data on long-term safety and there is the issue of addiction.

One of the most popular alternative approaches simply augments the human hormone melatonin with oral or sublingual supplementation. Since both zinc and magnesium also play a role in facilitating sleep, a recent study published in the *Journal of the American Geriatric Society* has examined combination therapy involving all three.[25] Forty-three elderly participants living in a long-term care facility were enrolled in a double-blind placebo-controlled randomized clinical trial which in the intervention arm involved 5 mg of melatonin, 225 mg of magnesium and 11.25 mg of zinc in 100 g of peach pulp or a peach pulp placebo one hour before bedtime. Compared to the placebo group, the treatment group had considerably better sleep by a number of measures including alertness and behavioral integrity the following morning and the data indicated a beneficial effect on the restorative value of the resultant sleep.

The dose of melatonin used is readily available in capsule form and the zinc and magnesium amounts are similar to those found in many multivitamins. The approach obviously does not involve chemicals foreign to humans. Readers should be aware that natural melatonin secretion can be inhibited by

light, especially bright light, and that sleeping in a totally dark room in indicated.

NEWS BRIEFS

BERRIES AND PARKINSON'S DISEASE

A study presented at the 63rd Annual meeting of the American Academy of Neurology described a study of about 50,000 men and 80,000 women. At issue was the impact of flavonoid consumption on the risk of developing Parkinson's disease during a 20-22 year follow-up. During that time, 805 people developed this disease. Men who consumed the largest amount of berries (top 20%) were 40% less likely to develop Parkinson's than those in the bottom 20% of consumption. Interestingly, no association was found for women. However when subclasses of flavonoids were examined, regular consumption of anthocyanins, which are mainly obtained from berries, were found to be associated with lower risk of Parkinson's in both men and women, The authors commented that if confirmed, this may prove to be a safe and natural way to reduce the risk of this serious disorder.

Flavonoids are found in plants and fruits. They are found in berry fruits, chocolate and citrus. Organizations such as Life Extension sell formulations of flavonoids, polyphenols and berry extracts.

IBUPROFEN AND PARKINSON'S DISEASE

Neuro-inflammation is thought to contribute to the pathogenesis of Parkinson's disease (PD). The mechanism may involve progressive dopaminergic neuronal loss. Early studies suggested that nonsteroidal anti-inflammatory drugs (NSAIDS but not aspirin) were associated with decreased PD risk. A recent study follows earlier results suggesting that this is not a class action but due to ibuprofen.

The study reported by Gao *et al* from Harvard Medical School made use of the data available from the Nurses' Health Study and the Health Professional's Follow-up Study and followed over 135,000 subjects for 6 years starting in 1998-2000.[26] It was found that ibuprofen users had a significantly lower risk of PD compared to nonusers (35% relative risk reduction which was dose dependent). In addition, other NSAIDS, aspirin, and acetaminophen failed to provide risk reduction. The results were adjusted for age, smoking status, body mass index, caffeine intake, and as well lactose and alcohol consumption.

The authors cite studies that lend biological plausibility to the unique action of ibuprofen and as well point out that among the most commonly used NSAIDs, ibuprofen is most strongly associated with reduced risk of Alzheimer's disease. They also consider it unlikely that the study was confounded by the use of ibuprofen for indications that themselves when treated lowered the risk of PD.

The results of this study will no doubt prompt important clinical trials. However, as discussed in an earlier Newsletter, there are safety issues with ibuprofen as well as with all NSAIDs which involve both enhanced cardiovascular risk and the risk of gastric bleeding. Some would put the risk of PD in a different category!

SALT AND STROKE RISK

At the International Stroke Conference sponsored by the American Stroke Association, Dr Hannah Gardener from the University of Miami, FL, reported on a study of the association between high salt intake and ischemic stroke (stroke caused by an occlusion rather than a bleed). The study involved over 2600 subjects from a multiethnic cohort who were followed for about 10 years. There were 187 strokes. The risk of stroke increased 16% for every 500 mg of sodium consumed after adjusting for age, gender, race ethnicity, education, alcohol use, exercise, daily caloric intake, smoking, diabetes, cholesterol, blood pressure and previous heart disease. Those consuming 4000 mg or more had an increased ischemic stroke risk of almost 129%, a result which was statistically significant and appears clinically significant.

The author pointed out that an overwhelming majority (88%) of the subjects consumed more sodium than the maximum recommended by the American Heart Association (1500 mg/day). However, US dietary guidelines give their blessing to 2300 mg/day as an upper limit, or about a teaspoon per day of salt.

This study suggests an important and powerful intervention for reducing stroke risk but the consumer is confronted with many hidden sources, especially if they do not prepare their meals from scratch but eat a lot of foods of industrial origin.

RICKETS IS ON THE RISE IN THE UK

In a news item on the BBC, Dr. Joe Reed from Southampton Hospital alerted listeners that rickets is making a comeback after decades of absence as a childhood disease. The explanation is very simple. Children are becoming more and more vitamin D deficient. At Southampton Hospital they have looked for and found a resurgence of vitamin D deficiency among children. One of the causes is that parents have been lectured constantly to keep their children away from the sun, religiously cover them up, and regard sunlight as one of the major dangers confronting mankind. This is of course nonsense. Now the chickens come home to roost, to use the well-worn phrase, and children are being seen in clinics with bone deformities, knock-knees, bowed legs and non-specific musculoskeletal pain. Fortunately, there are attending physicians who recognize this, can acquaint residents and interns regarding this ancient scourge and are able to suggest that vitamin D supplementation is necessary in the winter in the UK and some sun exposure in the late spring to early fall is highly beneficial.

In fact, rickets is on the rise elsewhere as well, driven not only by the strong belief that the sun is bad, but also by the modern lifestyle which has children only rarely venturing outdoors and away from TV, video games, cell phones and computers.

VITAMIN D AND CANCER

This is no longer news, but what is new is a recent study reported in a news release from the University of California, San Diego Health System and Creighton University School of Medicine in Omaha. The report has also been published in the February 21 issue of *Anticancer Research*. Two well known vitamin D researchers, Cedric Garland and Robert Heaney, examined the issue of the optimum vitamin D status necessary to prevent the various cancers implicated in vitamin D deficiency. They set an appropriate serum target of 40 to 60 ng/mL and found that 4000 to 8000 IU/day are needed to reach these blood levels. They point out that national studies find that only 10% of the U.S. population have levels in this range. Incidentally, about 400 IU/day is necessary to prevent rickets and the Institute of Medicine, as reported in this Newsletter, likes 600 IU/day for the general population. Heaney and Garland appear confident that the message will get through and that 4000 to 8000 IU/day will become common and point out that the IOM, in spite of its recommendation for trivial supplementation, could find no problems with 10,000 IU/day.

Incidentally, it is important to realize that vitamin D does not generally work in isolation in biochemical pathways. According to the Vitamin D Council, important cofactors include magnesium, zinc, vitamin K2 and a small amount of vitamin A. A diet rich in vegetables and a simple multivitamin would take care of this problem. Large amounts of vitamin A such as found in cod liver oil neutralize many of the benefits of vitamin D.

Caucasian skin produces approximately 10,000 IU vitamin D after exposure to 20–30 minutes summer sun, even if one is decently dressed. This is over 16 times higher than the US government's recommendation of 600 IU per day! In the winter in northern latitudes, sun exposure produces almost zero vitamin D. In North America, this includes the upper third of the U.S. and all of Canada.

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Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com

ISSN 1203-1933

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 28 **APRIL 2011** **5th YEAR**

While readers of "The Prostate Monitor" may be tired of the subject of PSA screening, it remains probably the most important aspect of the prostate and its problems for most men. When a man reaches around 40, in some countries it is more or less routine for his physician to suggest a PSA test during an office visit for either a check-up or some other problem. It is far from clear the extent to which the pros and cons of this step are discussed and understood by the patient, especially in a short visit and where the office waiting room may contain a sign—"We deal with only one problem per visit."

The controversy and debate concerning PSA screening just goes on and on. Some academic urologists have devoted a substantial fraction of their career to studies and the debate. There is a continuing effort to find some way, any way, to mitigate the fundamental problems that make this test so far from ideal that some urology organizations and government agencies actually officially advise against the test.

In this issue evidence is provided that one of the pillars associated with this test, the PSA velocity, has collapsed. It is an interesting story since the guideline regarding velocity is well established in practice and in the minds of many urologists. What we appear to be seeing in medical science is a process akin to the functioning of living organisms—the operation of a mechanisms that gets rid of waste products. For example, randomized trials demolish long held beliefs, many of which were the basis of pharmaceutical riches. Organizations like the Cochrane Collaboration conduct meta-analyses based on studies selected for high quality and integrity and come up with results that frequently go against current practice.

Finally, a discussion of screening and mortality emphasizes the complexity of prostate cancer and the long period over which it evolves from insignificant to metastatic.

Wishing you good health,

William R. Ware, PhD, Editor

PSA VELOCITY AND OVERDIAGNOSIS

The guideline from the National comprehensive Cancer Network, a respected source for clinical guidance, states that men with a high PSA velocity—greater than 0.35 ng/mL per year should consider prostate biopsy even if the absolute PSA level is very low. The citation for this is a paper by a well known urologist, H. Ballentine Carter, who reported an association between PSA velocity and the diagnosis of fatal cancer approximately 10-15 years later. Other professional organizations such as the American Urological Association also cite PSA velocity in their guidelines but regard it as adding predictive value.

In a recent paper, Andrew Vickers, Ian Thompson and coworkers point out that it is unclear why a marker that predicts aggressive prostate cancer many years in the future would be used to indicate an immediate need for a biopsy, especially when attempts to demonstrate that PSA velocity adds predictive accuracy to PSA alone have failed.[1] They suggest that PSA and PSA velocity are closely correlated and that it is PSA itself that is predictive of advanced cancer. They also point out that to evaluate the recommendation it is required to have a dataset that involves men with low PSA and high PSA velocity who have been subjected to a biopsy. It turns out that there is indeed one database, that associated with the Prostate Cancer Prevention Trial (PCPT). Ian Thompson was the principal investigator for this unique trial. Men 55 or older with no previous prostate cancer diagnosis and a normal digital rectal examination and a baseline PSA of ≤ 3.0 ng/mL were randomized to a placebo or the drug finasteride (Proscar, used to treat benign prostate enlargement). Yearly PSA tests were done with biopsy recommended for men with PSA > 4.0 ng/mL (adjusted in the drug arm to account for the approximate 50% drop in PSA due the effect of the drug). The unique source of data came from the end of study request that all men not diagnosed with prostate cancer submit to an additional biopsy as a "definitive" assessment of the development of prostate cancer over the 7-year study period. Since PSA velocity data were obviously available, this data base turns out to provide a perfect test for Carter's recommendation.

The results of the analysis of the PCPT data did not support using PSA velocity. The incorporation of PSA velocity led to a very small improvement as measured by the area under a type of curve used extensively in clinical biostatistics. The change was barely detectable. Adding PSA velocity did not enhance outcomes for improve detection of more aggressive cancers. The authors concluded that PSA velocity did not add predictive accuracy beyond PSA alone and that if one was trying to accomplish this, it would be better to lower the threshold for biopsy rather than add PSA velocity. In fact, using as a threshold a velocity of > 0.35 ng/mL pr year would lead to a large number of additional biopsies (one in seven men vs one in 20 for simply a 4.0 ng/mL PSA cut-off).

An accompanying editorial raises some important issues.[2] First, it was pointed out that two recent studies provided only inconsistent results regarding the association between screening and mortality, one finding a 20% reduction, the other none (see below—the story is more complex than they assume). As regards overdiagnosis and overtreatment, the editorialists estimate that one-third to one-half of PSA screened patients may be over-diagnosed (finding cancer that would not have caused clinical symptoms during the patient's lifetime) but what is more important, most would have proceeded to aggressive local therapy with surgery or radiation.

The editorialists comment on the magnitude of the overdiagnosis problem as illustrated by estimates from Welch and Albertsen who calculate that since the introduction of PSA screening, more than 1 million additional men have been diagnosed and treated for prostate cancer just in the U.S. They comment that most of this excess incidence represents overdiagnosis.

One of the most frequently quoted statistics in this context is from U.S. data where PSA screening has been used for the longest duration. In the pre-PSA era (pre 1985), the lifetime risk of prostate cancer was 8.7% and well into the post-PSA era (2005) it was 17%. However, the lifetime risk of prostate cancer related death has been largely unaffected with pre-PSA rate of 2.5% and a rate in 2005 of 3%. Thus the suspicion of both overdiagnosis and overtreatment. However, it is not that simple. Critics point to autopsy results that most older men have evidence of the presence of prostate

cancer, but most prostate cancer detected on the basis of PSA screening turned out to be potentially clinically important. Several studies suggest that moderately differentiated or Gleason score 5-7 predominate the PSA era.[3]

A paper in the journal *Cancer* adds to the debate. It was found that a single PSA test before 50 predicts advanced prostate cancer diagnosis up to 30 years later. The authors regard this result as providing a way of stratifying this age group into low and high risk, with the latter eligible for increase frequency of testing and the low-risk group left almost but not quite free from concern. These conclusions come from comparing cases with a mean PSA of between 1.01 and 1.15 ng/mL and controls at about 0.62 ng/mL.[4] Should men younger than 50 with a PSA around 1.0 be told they are high-risk?

The waters are further muddied by the impact of obesity on PSA levels. In a study of men in the age range 45 to 75, the mean PSA was 1.43 ng/mL in men of normal weight, 1.4 in overweight patients, 1.05 in those who were obese and 0.85 in the morbidly obese. The main mechanism was thought to be dilution due to blood volume.[5] One more thing to add to prostatitis, enlarged prostate, and drug treatment for enlarged prostate when trying to interpret PSA results, and why exact cut-offs like 4.0 ng/dL are unrealistic, simplistic and dangerous.

Finally, the issue of overdiagnosis and treatment must include the impact on quality lf life. Treatment is well known to produce significant urinary and sexual impairment, but there is also a strong psychological component, which among other things, makes delayed treatment during surveillance a challenge. For the under 50 group described in the above report, a PSA of 1.15 provides the potential for years of worry and anguish and the fear of this dreadful disease.

The PSA test is widely recognized as imperfect. The literature is replete with studies trying to improve it, but with little success. It still reduces to a statistical game and the numbers are never overwhelming. Thus, some professional organizations and government agencies do not favour PSA screening, considering the uncertainties and imperfections to outweigh the as yet to be clearly defined benefits. Critics of this position would tell men that to pass up the opportunity of a PSA test may be a life or death decision. Are patients also told that the biopsy is far from perfect, misses a significant number of cancers, and reduces again to statistical considerations and debates such as the interpretation of Gleason scores less than 4 and if they should even be reported?

PSA LEVELS AND RISK OF FINDING CANCER AT BIOPSY

In spite of years of prostate cancer research, hundreds of impressive careers and tens of thousands of papers in the peer review literature, nagging questions remain. Included are (a) does risk increase as PSA increases above a biopsy threshold and (b) is there a substantive risk of cancer at low PSAs. Since these are non-trivial questions with answers that require endless qualification, the tendency is to turn to statistics, models, nomograms, or online calculators to generate probabilities, which may apply to restricted cohorts but not necessarily to general populations. Furthermore, many patients find probabilities confusing or at worst meaningless and their advisors have little to add since the numbers reflect not a state of knowledge but a state of ignorance, which is of course not their fault. In the context of PSA as an indicator of risk and the need for a biopsy, the problem is aggravated by the more or less continuous relationship between this serum marker and the probability of cancer being found at biopsy and as well the fact that an elevated PSA can reflect not only cancer but simply an enlarged or inflamed prostate. Furthermore, the biopsy is not completely free of complications, is viewed as extraordinarily unpleasant by some, and fails in a shockingly large number of cases to find cancer that is there. When cancer is suspected but not found, the frequently suggested next step is another biopsy, perhaps with more samples, a suggestion that makes some run the other way. The patient might as well be told that “if we keep looking, eventually we will find it and then treat you.”

Vickers *et al*[6] have recently looked at the question of the relationship between PSA level and prostate cancer risk, a study driven by fundamental disagreements in study results. They hypothesized that

the risk of cancer on biopsy for a given level of PSA was affected by characteristics of the cohort under study. Their final data set included almost 26,000 biopsies which found 8500 cancers. Put one way, about 33% of those biopsied had cancer. Put the other way, about 67% of the biopsies might be described as unnecessary if there had been a better tool for discriminating probable cases. The cohorts were drawn from Sweden, the Netherlands, France, the U.K., Austria and the U.S. There was a substantial variation in the indication for biopsy with PSA≥ 3ng/mL being common but higher and lower numbers also used as well as, in some cases an abnormal digital rectal examination (DRE), another test notorious for false positives and false negatives.

This study found "gross disparities" between cohorts for prostate cancer risk at a given PSA level. For example there was a 2.5-fold difference in risk between cohorts at the commonly used PSA threshold of 4 ng/mL. The main determinants of the discordant results were the number of biopsy cores used and prior PSA tests, the latter used in part to differentiate benign prostate disease risk from cancer risk. They found that U.S. cohorts generally had a higher risk of positive biopsy than European cohorts. Explanations offered include the almost exclusive use of biopsies involving ≥ 8 cores in the U.S. whereas many European studies used 6 cores. While they suggest the possibility that U.S. urologists and their pathologists were less likely to miss cancer, they comment that there is no evidence to support this notion. Another explanation involved the difference is cohort selection. European populations tended to represent the population as a whole whereas in the U.S. the study cohorts included selected groups. Finally, they suggest that in U.S. cohorts the decision of the attending physician had more influence and was based on considerations that are more extensive.

The authors list several implications of these results:

- They cast doubt on the simplistic use of cut-offs to determine biopsy. They show that a threshold of 4 ng/mL is associated with risk of prostate cancer diagnosis ranging from 15% to 40%. They view as unsound practice giving patients the same recommendation across such a wide spectrum of probabilities.
- Rather, they suggest risk calculators, which bring us back to confusing the patient with statistics. However, they emphasize that the models and their calculators are far from perfect and can be strongly cohort dependent.[7] For example they suggest that it is far from clear that the Prostate Cancer Prevention Trial risk calculator, developed for and based on intensely screened U.S. men, is applicable to European men. In fact, this calculator has been tested on European men and found wanting.
- Single cohort studies also can be misleading. They quote a study by Schwartz and colleagues based on single institution data which indicated essentially no correlation between PSA and biopsy outcome in men with PSA ≥ 2 ng/mL and a negative digital rectal examination result.

SCREENING AND MORTALITY

Three recent studies with drastically different results concerning the impact of PSA screening on mortality continue to generate interest, comment and extended analysis. The three studies were as follows:

- The Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO). This study found that in a U.S. cohort the risk of prostate cancer-specific mortality at 7 to 10 years did not differ between screened and unscreened men. The same results where seen at 10 years in two-thirds of the men that were followed for this period.[8]
- The European Randomized Study of Screening for Prostate Cancer (ERSPC).[9] This trial found a 20% relative risk reduction in prostate cancer-specific mortality. The median follow-up time was 9 years. When adjusted for non-compliance in the screening arm and contamination in the control arm, the mortality reduction increased to 31%.[10] Their model yielded 1401 as the number needed to screen (NNS) and 48 as the number needed to treat (NNT) to prevent one death.

- The Göteborg randomized population-based prostate cancer screening trial.[11] This trial had a follow-up of 14 years and the relative risk reduction for death from prostate cancer was 50% in the screening group compared to the non-screening group. The NNS and NNT in this study were 239 and 12. In this trial not all men in whom cancer was detected were treated. This suggests that screening can reduce mortality without all diagnosed patients being treated.

Thus the question—why the discordant trial results. Carrol *et al* have recently discussed some of the possibilities.[12] They raise the issue of comorbidity in the PLCO trial. According to study by Crawford *et al*[13] minimal comorbidity was present in over 35% of those in the trial and current practice was that healthier men were more likely to receive curative rather than non-curative treatment. When they took this into account there was a significant decrease in prostate cancer-specific mortality in the screened group (44%) with the NNS and NNT being 723 and 5. For men with more comorbidities, the prostate cancer-specific mortality actually increased.

Carrol *et* al also cite the work of Loeb *et al* who re-examined the ERSPC data taking into account the follow-up time evolution of the NNS.[14] According to their model it was 1254 at 9 years and decreased to 837 at 10 years and 503 at 12 years. The corresponding NNT were 43, 29 and 18. They emphasize that because of the long natural history of prostate cancer, follow-up of more than 10 years is necessary to evaluate cancer-specific mortality. The 12-year result compares favourably with the Göteborg study result at 14 years.

Carroll *et al* conclude the following: (a) PSA screening leads to reduced risk of death from prostate cancer among selected men; (b) men who are healthy and have along life expectancy may benefit most from screening because the benefits accrue over time; (c) screening in any patient is associated with a significant risk of over-detection; (d) the impact of over-detection can by mitigated by deferment of treatment in those with low-risk disease and treating only those who are at risk of cancer related morbidity and mortality as defined by tumor characteristics and competing risks. They also comment that despite what they view as mounting evidence in support of screening, men must realize that even those with high-risk disease ultimately die as a result of other causes.

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