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William R. Ware, PhD - Editor

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We start the new year with an update on vitamin D. In 2011 Medline (PubMed) listed over 3500 publications concerning this vitamin with reviews, commentaries, meta-analyses, and studies ranging from cell culture and animal studies to reports concerning studies conducted on humans. The interest in vitamin D has stimulated the activity of the so-called deniers. There are those who cannot accept that a simple vitamin available at low cost from a health food store can have widespread and strong preventive and therapeutic benefits which they associate only with pharmaceuticals. The deniers are busy looking for evidence to support this view and to show that those advocating significant supplementation are encouraging the general population to waste their money and take risks of serious side effects. Furthermore, we are seeing summaries of studies and meta-analyses that include research on vitamin D initiated before it was suggested that the common recommended intake of 200-400 IU per day was totally inadequate and that supplementation with 400-800 IU/day was of little significance in the context of therapeutic or preventive benefit. The recommendations of daily intake now range from the official and conservative ≤ 800 IU to 2000 to 5000 IU. The conservative recommendations, accepted by mainstream medicine, set the stage for null study results supporting the position of the deniers.

The consequences of the widespread vitamin D deficiency are not fully acknowledged and the supplementation required to achieve optimum levels strongly opposed by many experts. According to some authorities, large, long-term randomized intervention trials with placebo control are absolutely necessary before anyone should even consider taking vitamin D supplements. What is also amazing is the frequency with which one sees the suggestion that sufficiency should be achieved in the "natural way" by eating vitamin D-rich foods. Such foods do not exist if one is attempting to bring vitamin D status up from deficient to optimum, unless one is willing to eat phenomenal, mind-boggling amounts of one or two of the few foods that contain small amounts of vitamin D. It is of course a given that sun exposure is bad. The general public is not acquainted with the research regarding optimum levels or most other vitamin D research. Nor is there an appreciation of the strong latitude dependence of vitamin D generation from sunlight in the winter. There seems to be a serious misunderstanding of our evolution as a species that involved the generation of very large amounts of vitamin D through exposure to sunlight and created a dependence on a vitamin D status for overall health. What some researchers now regard as the optimum vitamin D status is far from common in most populations, at least in the developed part of the world. Rickets, the classical vitamin D deficiency disease, is now making a comeback and appears to go undiagnosed until it is at an advanced stage. It is in fact perhaps unfortunate that calciferol was called a vitamin.

Highlights

Vitamin D – Here come the attackers p. 2
Vitamin D, PTH and sudden death p. 3
Lung function and vitamin D status p. 5
Sodium intake and cardiovascular risk p. 6
Aspirin for primary prevention p. 7
Aspirin, macular disorders and SSRIs p. 9
THE PROSTATE MONITOR p. 11

Sodium intake and cardiovascular risk is revisited in this issue with a discussion of recent evidence reinforcing the notion discussed in earlier issues of IHN that there is a J-shaped relationship between risk and benefit. This is a serious matter since a strong movement is underway which may result in dangerous deficiencies of sodium, something the advocates of "the lower the better" fail to acknowledge.

Finally, the latest research on the risk—benefit aspects of the use of aspirin for primary prevention of cardiovascular events is examined since there is growing evidence that prophylactic aspirin therapy carries considerably more risk than benefit. In addition, the absolute cardiovascular risk reductions are extremely small, something that has been known for over a decade but never emphasized.

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

VITAMIN D UPDATE – HERE COME THE ATTACKERS

It is quite predictable**.** If evidence continues to increase that a cheap simple dietary supplement is highly effective in preventive medicine, anyone who claims to prove the absence of effectiveness or that the supplement is in fact is dangerous becomes a hero with all the associated benefits since such results confirm what mainstream medicine firmly and strongly believes, i.e. with few but noteworthy exceptions, supplements do not work, are probably dangerous and definitely a waste of money. The same attitude is present with regard to alternative medicine in general. The study and trials playbook for attacking oral supplements, if it existed in print, would probably list as very important the use of suboptimal doses, careful selection of subjects to shift the results in the desired direction, and deemphasizing the uncontrolled use of the supplement in control groups. The classical example is the famous vitamin C and cancer study from the Mayo Clinic, which was widely accepted by mainstream medicine as proving that the IV vitamin C therapy proposed and extensively test by Pauling and Cameron in fact did not work in the palliative setting for cancer. But the Mayo Clinic study used oral administration whereas Pauling and Cameron used IV administration. Thus as a comparison study, it was fundamentally flawed, and as it turns outs, strongly biased in favour of a null result because oral use of vitamin C has limited ability to raise serum levels compared to the IV route.

For vitamin D, the first playbook point is very important since guidelines give very low levels of supplementation as recommendations, mainstream medicine has a built-in terror of excessive supplement doses, and thus exceeding guideline doses by 50 or 100% in a study will be accepted by most as a very good test of efficacy. Enough is known about the connection between oral doses of vitamin D3 and serum levels of 25(OH)D that it is not difficult to judge studies on this basis and offer criticism based on the use of inadequate doses which fail to provide a hypothesis test. But negative supplement study results, even if based on this defective design, make great headlines and valid criticism is simply ignored.

The RECORD study is a good example.[1] *Theheart.org* carries the headline "Vitamin D fails again to affect CV mortality." The intervention used 800 IU. The study population was elderly, mostly female, had a previous history of low-trauma bone fractures and were attending fracture clinics or orthopaedic wards. Subgroup analysis suggested most were vitamin D deficient. The 800 IU/day would not come close to rectifying this problem. In fact, subgroup analysis where 25(OH)D levels were known suggests that the intervention still appears to have left everyone either a deficient or inadequate vitamin D status.

Another example involves a systematic review and meta-analysis published in July, 2011.[2] The researchers used 51 randomized intervention trials and included a tabulation of the vitamin D doses used. Meta-analyses were done for mortality, heart attack and stroke endpoints. If one looks at the studies included for each endpoint, those that used more than 800 IU/day were 4 for mortality, none for heart attack and one for stroke. Studies were also identified as involving either deficient, not deficient or "not recorded/not clear," but a number of criteria were used and 25(OH)D levels were available only in some studies (not indicated). In addition, it is

unlikely, given what is known today about widespread deficiency, that cohorts can be described as either deficient or not deficient. If the events and total subject numbers are examined in the higher dose group, it is clear that these were all very small studies with intervention and control groups of around 50 participants except for one study with around 300. All but one of these higher-dose studies had event numbers in the treated and control groups of < 10 and thus very poor statistics. Thus this analysis really concerns intervention doses (200-800 IU) that are very small relative to that needed to correct deficiency or insufficiency. It is thus not surprising that a null result was obtained. The results were put forward as indicating that recommending vitamin D to patients to reduce cardiovascular risk is not consistent with current evidence. The alternative interpretation is that this meta-analysis shows what is already known; small increases in vitamin D status produced by small doses are generally not clinically significant simply because the dose is too small. After all, short exposure to the noonday sun in the summer can provide a dose of 10,000-15,000 IU and typical recommendations from vitamin D researchers is a daily dose of at least 2000 IU.

In the "too much is bad" category, a study in press suggests a threshold of 21 ng/mL for 25(OH)D, below which vitamin D is beneficial, but above which circulating 25(OH)D is associated with increased C-reactive protein and therefore dangerous because this may neutralize heart benefits. As well, the researchers point to a significant positive association of 25(OH)D levels and cholesterol with those having higher vitamin D levels at baseline having *significantly* (clinically, realistically??) higher total cholesterol (201.6 vs. 198.6 mg/dL, P = 0.001).[3] One can only conclude that the researchers are challenging the optimum 25(OH)D values and offering "evidence" of the importance of avoiding overdoses. Readers are left to judge these results for themselves.

The campaign against what vitamin D researchers consider to be adequate or optimum vitamin D status will no doubt continue since it has already been significantly strengthened by high profile guidelines recommending totally inadequate levels and supplement intake. These low levels being recommended also have a tendency to refocus the attention of the nutritional community on food sources, which while offering the potential for meeting these unrealistic guidelines, are a totally inadequate if not impossible approach to achieving what many believe is an optimum status.

VITAMIN D, PARATHYROID HORMONE AND SUDDEN CARDIAC DEATH

A study just published in the journal *Hypertension* examined the hypothesis that individuals deficient in vitamin D as indicated by serum 25-hydroxyvitamin D levels (25(OH)D, and who also had elevated parathyroid hormone (PTH) levels would be at elevated risk for sudden cardiac death (SCD) compared to those with high vitamin D coupled with low PTH. Both of these factors had already been associated with the risk of SCD.[4] In addition, PTH serum levels represent, in part, inadequate vitamin D activity. Deo *et al* examined a cohort of 23,132 participants free of cardiovascular disease at baseline who were followed for a median of 14 years. They used 25(OH)D levels of < 25 vs. ≥ 25 ng/mL and PTH levels of 65 vs. ≤ 65 pg/mL as the criteria for high or low values of these two serum markers. It was found that the risk of SCD was double for those with combined low 25(OH)D and high PTH levels after multivariate analysis which adjusted for age, sex, race, season, clinic, education, physical activity, smoking, body mass index, hypertension, diabetes, and evidence of chronic kidney disease. This same comparison found a statistically significant 26% enhanced risk for total mortality, and a 39% enhanced risk for cardiovascular mortality including SCD. For the high vitamin D status--low PTH status group, the mean values for 25(OH)D and PHT were 31 ng/mL and 43 pg/mL respectively. In the opinion of many vitamin D researchers the optimum 25(OH)D level should be between 50 and 89 ng/mL. Thus those who were found to have a

lower risk of SCD were not even at the minimum of the optimal range. Incidentally, readers will recall that cholesterol has never been found to be associated with the risk of SCD, and it is reassuring that it did not appear in the factors used for data adjustment in this study.

The authors speculate that these results suggest deregulation of the mineral metabolism axis which may increase the risk of alterations in the electrophysical properties of the myocardium, which then elevates the risk of SCD.

A high level of serum PTH is termed hyperparathyroidism. If the problem has its origin in the parathyroid gland it is termed primary and may be caused by parathyroid adenoma, cancer or hyperplasia. If the cause is outside the gland, its can be due to kidney problems. Vitamin D deficiency is more common in patients with primary hyperparathyroidism than in the general population, and initiation of vitamin D therapy is indicated in patients with serum levels of 25(OH)D < 20 ng/mL.[5]

VITAMIN D – THE AHA MEETING IN ORLANDO

A number of studies regarding vitamin D and cardiovascular issues were reported at the American Heart Association Scientific Sessions 2011 in Orlando, FL in November. MedPageToday (November 17, 2011), provides a summary of 5 studies.

- The association between sufficient 25(OH)D levels and lower all-cause and cardiovascular mortality in healthy adults was found to be consistently independent of gender or racial group. Data came from the National Health and Nutrition Examination Survey.
- Decreased risks of both vascular and non-vascular disease were found in the Whitehall cohort when male civil servants in the top quartile of serum 25(OH)D levels were compared with those in the lowest. The relative risk reductions were 17% and 24% respectively. The researchers also conducted a meta-analysis which included new results (19 studies altogether) and which found individuals in the top vitamin D quartile were 30% less likely to die from any cause.
- Healthy postmenopausal Danish women with sufficient 25(OH)D levels had a 65% lower risk of overall mortality, heart failure, stroke or MI over 16 years of follow up.
- A study from Argentina examined the risk of overall and cardiovascular mortality among a cohort presenting with chest pain and suspected acute cardiac problems. Those in the highest 25(OH)D quintile compared to the lowest had a 62% lower risk of overall mortality and an 80% lower risk of cardio vascular disease mortality during two years follow-up.
- In a study of children and teens attending a clinic for high-risk cardiac issues, individuals with 25(OH)D levels < 20 ng/mL had a significant reduction in carotid artery distensibility. This serves as a marker for vascular function. This association had been observed in adults but never before in children. Deficiency in vitamin D was also accompanied by higher cardiometabolic risk.

This is rather a different picture than that provided by the null results of the systematic review and meta-analysis discussed above, and it should be noted that now much more frequently results are being judged on the basis of measured vitamin D status. The reader is referred to a commentary by William Grant, a well known vitamin D researcher, which appeared on the Vitamin D Council website under Member's Blogs, December 31, 2011. He discusses five studies published in 2010 and 2011, which provide additional strong evidence for the beneficial role of vitamin D in reducing the risk of cardiovascular disease. Grant's commentary is partly in response to a recent review by McGreevy and Williams[6] which, while finding strong evidence for the beneficial effect of this vitamin in reducing cardiovascular risk, stated that evidence must be considered insufficient for a firm conclusion. Also, Grant responded to McGreevy and Williams's comment that it is unlikely that a single hormone could play such

an important role in human health by pointing out that every cell in the body has vitamin D receptors and when activated by the 25(OH)D metabolite 1,25-dihydroxyvitamin D, can influence the expression of about 1000 different genes.

VITAMIN D STATUS, SEASONAL INFECTION AND LUNG FUNCTION

Seasonal variation of the incidence of respiratory infections and influenza as been recognized for decades and the connection with vitamin D status suggested as an important factor.[7,8] The mechanism may involve a dependence on adequate 25(OH)D levels and the immune response in the lung itself.

A study published recently in the *British Journal of Nutrition* examined the relationship between vitamin D status and both the prevalence of respiratory infections and lung function (measured by forced expiratory volume and forced vital capacity).[9] Suitable data were available for 6800 British adults age ≥ 45. The researchers found that each 4 ng/mL increase in serum 25(OH)D was associated with a 7% lower risk of respiratory infection. When 25(OH)D levels < 10 ng/L were compared with levels of 40 ng/mL and up, a statistically significant 43% decrease in incidence was found. Between these two limits, for levels of 20-30 ng/L and 30-40 ng/L the risk reductions were 26% and 34%, both statistically significant. This was consistent with the strong seasonal pattern of this type of infection. The authors display a striking bar graph by month showing a U shape for respiratory infections in a British cohort with a prevalence minimum in August and a maximum in serum 25(OH)D in September. Furthermore, lung function was positively associated with vitamin D status.

The authors suggest that these results indicate that randomized controlled trials are warranted to investigate the role of vitamin D supplementation on respiratory health and in addition establish the underlying biological mechanisms. They point out what vitamin D researchers have been saying for some time, i.e. vitamin D deficiency is a known avoidable health hazard and it is important to take action to reduce its prevalence even while waiting for additional evidence to accumulate for any specific vitamin D intervention influencing health outcome. In the context of respiratory health, achieving adequate vitamin D status could have a very significant population level impact.

EROSION OF FAITH IN EVIDENCE-BASED MEDICINE

Last year the *British Medical Journal* put out a call for papers concerning extent, causes and consequences of unpublished evidence from clinical trials (not infrequently with negative or null results or showing too many adverse side effects). On January 3 and 4 of this year the results were published online, accompanied by editorials. Lehman and Loder in their editorial [10] review the highlights of this cluster of papers, prefacing their remarks by the comment that it may come as a shock to clinicians that the evidence from clinical trials they depend on for guidance is not necessarily relevant, reliable or properly disseminated. In fact, a large proportion of evidence from human trials is unreported and much of what is reported is done so inadequately. One study incorporated unpublished data into existing meta-analyses of nine drugs approved by the FDA between 2001 and 2002. Reanalysis produced identical results of efficacy in only 7% of studies and the remainder were equally split between showing greater or lesser benefit.[11] Lehman and Loder comment that most of the interventions currently in use are based on trials carried out before mandatory registration, and they describe the reported difficulties investigators have in acquiring a complete set of data, where searching for and obtaining data from unpublished trials can take several years.

Another paper examined the impact of the requirement that as of 2005, prior trial

registration became a condition of later publication and the additional requirement for publicly funded studies in the US that a summary report must be published within 30 months of study completion. Ross *et al*[12] found that for publicly funded studies between 2005 and 2008, more than half of completed trials failed to report within the required time. Another study found compliance to be a dismal 22% with a regulation of 2007 that changed the time to 12 months for a summary of completed studies.[13]

The editorialists also comment on the interesting phenomenon that using the search item "randomized controlled trial" misses a large number of papers indexed by Medline (PubMed) which adds to the difficulties of searching for trials when doing systematic reviews and meta-analyses. Their overall conclusion: "What is clear from the linked studies (this BMJ set) is that past failures to ensure proper regulation and registration of clinical trials, and a current culture of haphazard publication and incomplete data disclosure, make proper analysis of the harms and benefits of common interventions almost impossible for systematic reviewers. Our patients will have to live with the consequences of these failures for many years to come….The evidence we publish shows that the current situation is a disservice to research participants, patients, health systems, and the whole endeavour of clinical medicine." Not a good report card but consistent with a considerable body of earlier critical literature.

SODIUM INTAKE AND CARDIOVASCULAR RISK. A J-SHAPED RELATIONSHIP

Readers will perhaps recall an earlier discussion in the Newsletter (September 2011) of salt and cardiovascular (CV) disease where the recommendation by the American Heart Association of limiting sodium intake to 1.5 g/day was questioned. Current maximum intake recommendations, including one from the World Health Organization, in fact range from < 1.5 to < 2.3 g/day. Note this is elemental sodium. To convert to grams of sodium chloride, the common table salt, multiply by 2.5. In addition, the salt-blood pressure connection, which is essential to the salt-heart hypothesis was discussed in detail. More evidence has just been published supporting those concerns. O'Donnell *et al* [14] have just reported on a very large observational study involving 28,880 individuals where it was possible to investigate the association between sodium and potassium intake (from a morning fasting urine sample) and the risk of cardiovascular events and mortality. The study cohort included participants in two large trials of anti-hypertensive drugs. All participants were at high risk of CV disease with established CV disease or high-risk diabetes and age ≥ 55 years. Median follow-up was 56 months with endpoints which included overall mortality, heart attack (MI), stroke and congestive heart failure (CHF). The 24 hour sodium and potassium intakes were estimated from a formula based on the sodium and potassium content of a fasting morning urine sample. The authors assert that this approach has been validated, used in previous studies and avoids collecting a 24 hour sample which would severely limit the recruitment of a large study cohort.

This study revealed a "window" of sodium intake that appeared innocuous, ranging from 3 g/day to 7 g/day. Above and below these limits, there was a significant risk for the various endpoints. For the composite endpoint of CV mortality, MI, stroke and hospitalization for CHD, when an excretion (intake) of 4-6 g/day was used as reference, < 2 g/day carried a 21% increase in risk whereas > 8 the increase was about 70%. The risk curve was thus J-shaped and the hazard ratios yielded a smooth curve. The choice of the reference was not arbitrary but could be seen from the raw data of percentage of events on follow-up. In addition, sodium excretion of < 3 g/day was associated with an increased risk of CV mortality and hospitalization for congestive heart failure. Higher estimated potassium excretion was associated with reduced risk of stroke. This study was published shortly after two other studies appeared which also questioned the conventional wisdom and

stirred up a lot of controversy.[15,16] They are discussed in the September Newsletter.

The study by O'Donnell *et* al can be criticized because of its failure to use 24-hour urine samples, failure to actually measure sodium intake, and in addition, the study cohort was made up of high-risk individuals. Nevertheless, these results would appear to call into question the recommendation, which appears to gaining momentum and has received wide media coverage, suggesting that it is beneficial and in fact necessary to reduce sodium intake to about < 2 g/day. Yet over 3 times this amount appears quite safe and the recommended action of very low sodium intake appears risky! Additional evidence for this conclusion and as well the vital role of potassium was discussed in the September Newsletter.

In the view of O'Donnell *et al* the recommendation for an intake of < 2 g/day was based largely on projections made from relatively small and short-term clinical studies which evaluated the effects of sodium restriction on blood pressure in primary prevention populations. However, these studies conflicted with prospective cohort studies. It would appear that the new recommendations targeted at worldwide populations may not result in benefit and have the real potential for harm. This is exactly the scenario which eventually destroys public faith in the credibility of organizations whose principal *raison d'êtr*e is public health and prevention of illness. Furthermore, it seems clear that mainstream medical myths have a very long lifetime for both professionals and the public. Very effective media coverage and publication in prestigious journals plant these myths and they frequently enjoy a long and vigorous lifetime. Contradictory studies tend to be ignored and not publicized. Furthermore, the producers of so-called industrial food pick up on such recommendations and use them as highly effective marketing tools. Low-fat is a perfect example.

ASPIRIN FOR PRIMARY PREVENTION. A TURNING POINT?

There are two aspirin issues currently in the news. One involves the use of aspirin for the primary prevention of cardiovascular events, whereas the other involves the question of aspirin preventing cancer. Most people are more familiar with the former and many may take aspirin daily without ever discussing this with their doctor and are unaware of the reservations and qualifications of the recommendations in guidelines.

First, aspirin and cardiovascular disease (CVD) risk. There are three recent meta-analyses published in 2006, 2009, and 2012. Subsequent to the 2006 study, only a few small, randomized controlled trials were added and in all three the total number of participants was around 95,000 to 100,000. As expected, all three have similar results. These analyses also examined the risk of bleeds. Consider the odds ratios given below for three meta-analyses involving primary prevention.

Study		CV Events	MI	Bleeds
Berger (2006) [17]				
	M	0.86	0.68	1.72
	F	0.88	1.01 NS	1.68
ATT* (2009)[18]		0.88	0.77	1.54
Seshasia (2012)[19]		0.90	0.80	1.31

*Antithrombic Trialists' Collaboration. NS = nonsignificant

Berger *et al* stratify by gender. For the ATT study, direct gender comparison is not possible for all the above endpoints, but for major coronary events, the ORs (odds ratios) for men and women were 0.77 and 0.95 respectively, the latter nonsignificant, and as well, nonsignificant results for serious vascular events in women were found. In ATT, the result for stroke was null for men and for women the OR was 0.77. Seshasia *et al* failed to find any material differences in aspirin treatment by gender and claim this is consistent with the ATT trial which is obviously arguable.

All studies provided total events per group for treatment and placebo, which allows the reader to calculate absolute results. It was consistently found that the absolute risk reduction from aspirin treatment vs. placebo is between 0.26% and 0.35% for the vascular related endpoints in the above table. Thus about 3 per 1000 treated benefit. The trial periods were 5-6 years.

There is general agreement that the risk—benefit analysis must include enhanced bleeding risk. This is not a clear-cut endpoint because it can be argued that trivial bleeds should be ignored. The OR cited above from the study of Seshasia *et al* is for non-trivial bleeds. For this category, the absolute increase in risk was about 1% or about 3 times the absolute risk reduction for MI or CVD events. Seshasia also calculate numbers needed to treat (NNT) and numbers needed to harm (NNH) to prevent or cause one event. For CVD events, the NNT was 120 for CV events and for MI it was 162. They also point out that in their analysis, aspirin was no better than a placebo for reducing non-fatal MI events in any trials published after 2000, and this corresponded to about half the participants in all of the recent studies included in the above analyses. Thus, one can speculate that there is no effect at all. For bleeds, the NNH was 73. They derive these numbers from sophisticated statistical considerations rather than a simple reciprocal of absolutes risk reduction or increase based on total events. Seshasia also found that aspirin treatment did not reduce the risk of CV death, a result consistent with the ATT and Berger studies. Thus on the basis of CVD events vs. bleeds, they do not recommend aspirin therapy. For women, an even stronger position can be proposed on the basis of Berger' stratification and the ATT results.

In connection with the cancer issue, Seshasia *et al* were only able to assess the relationship between aspirin treatment and cancer mortality and found no association. They point out that estimates based on incidence are affected by ascertainment bias. Thus they do not regard potential cancer prevention benefits as significant in the risk—benefit problem and conclude that the risk of induced bleeding outweigh the cardiovascular benefits. This is a stronger position than that contained in the U.S. Preventive Services Task Force guidelines, based mostly on the Berger *et al* meta-analysis, in which they suggest an individualized approach where aspirin is recommended when the risk of bleeding is less than the risk of MI, but only for men. For women, aspirin is only recommended if the risk of stroke outweighs the risk of bleeds. The USPSTF provides rather general guidance on assessing bleeding risk. They point out that the risk is strongly enhanced by the concomitant use of non-steroidal anti-inflammatory drugs. Furthermore, a history of gastrointestinal ulcers also strongly increases the risk of aspirin induced bleeding. What is not clear is the extent to which the above ORs for bleeding are influenced by these factors. Some would consider the bottom line to involve absolute risk reduction and view 3/1000 as too small a benefit to even merit consideration in the context of primary prevention and daily dosing.

The finding of Seshasia *et al* is inconsistent with a recent meta-analysis of four randomized trials concerning the association of aspirin intake and the incidence and mortality of colorectal cancer. A 20-year follow-up by Rothwell and coworkers was involved and it was found that aspirin taken for several years at doses of at least 75 mg/day reduced long-term incidence and mortality due to colorectal cancer.[20] In a very recent paper coauthored by Rothwell found daily aspirin reduced mortality for several common cancers (during and after trials). Benefit increased with duration of treatment and was consistent across difference study population. However, for a 0-20 year follow-up, statistically significant results were obtained, with the exception of esophagus, colorectal and lung, only by combining either gastrointestinal or

non-gastrointestinal cancers.[21] This seems like a somewhat arbitrary approach. Furthermore, bleeding data, if available, was not discussed. Thus the risk—benefit issue central to the aspirin-cardiovascular problem discussed above has not been fully resolved when cancer prevention rather than mortality is included.

ASPIRIN, MACULAR DISORDERS, AND SSRIs

Related to the above discussion, two recent studies contradict the widely held view among the general population that aspirin is innocuous. One study found that daily aspirin use was associated with early aging macular disorder (early AMD) and late onset AMD and the risk increased with frequency of consumption. Participants were 65 years of age or older and were selected at random.[22]

A second study found that patients taking a selective serotonin reuptake inhibitor (SSRI) to treat depression, when combined with aspirin or aspirin and the antiplatelet drug clopidogrel for prevention of recurrent acute myocardial infarction, experienced increased risk of bleeding when the comparison with aspirin use alone. Bleeding was defined as gastrointestinal bleeding, hemorrhagic stroke or other bleeding that either necessitated hospital admission or occurred in hospital. Compared with aspirin alone, the combined use with a SSRI was accompanied by a 42% increase in bleeding episodes. With an SSRI, aspirin and clopidogrel together the risk increase was 135% as compared to aspirin alone. These results were all statistically significant.[23] Adding aspirin to clopidogrel in the absence of SSRI therapy increased the risk of bleeding by 49% compared to aspirin, whereas for clopidogrel vs. aspirin the increase in risk was not significant. The observations in this paper are important because the use of SSRIs post MI is common as is antiplatelet therapy. In addition, the use of SSRIs is widespread. Also, aspirin is frequently taken *ad lib* with no concern for side effects.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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One of the constants that permeates medicine is that when a foreign chemical substance (medication) is introduced into the human system, its intended action such as the inhibition of an enzyme or pathway or the blocking of a receptor is accompanied by unintended consequences, some anticipated, many not. This simply reflects the incredible complexity of human biochemistry, immunology, endocrinology, genetics, neurologic process, metabolic process, etc. One can imagine a publication titled "The Journal of Unintended Consequences". Maybe it already exists. Many controversies of modern medicine involve these unintended consequences since they enter into the inevitable balancing of risk and benefit that must accompany passing judgement on therapies which have non-benign side effects. Examples abound, including statins, aspirin, non-steroidal anti-inflammatory drugs, psychiatric drugs, to name just a random sample.

In this issue we examine the standard therapeutic approach to advanced or metastatic prostate cancer, the so called androgen deprivation therapy (ADT). Traditionally, the goal of this therapy, the reduction of testosterone to near zero levels, was accomplished by surgical castration. Today, it is almost always done by drugs—so-called non-surgical castration. This subject is discussed in detail in our book "The Prostate and Its Problems", which is available online on our website. Readers of the Prostate Monitor may recall a recent discussion of therapy to increase levels of testosterone for prostate cancer patients with low but not very low levels of this important hormone. Benefits were described with no apparent documented arguments or evidence against this highly counterintuitive therapy.

While probably no physician would advise against ADT for someone with symptomatic metastatic prostate cancer even though there were side-effect issues, for less serious situations including simply failed definitive therapy with an increasing PSA level, the considerations become more complex. For example age, degree of disease advancement, assessment of aggressiveness of the cancer, and comorbidities now enter the picture. In this issue we examine recent research concerning side effects of androgen deprivation therapy related to adverse cardiovascular events and associated morbidity and mortality.

Another area of great concern in the context of prostate cancer is overdiagnosis and overtreatment in the so-called PSA era where many cancers found with biopsy are in their early stages of development and may not present a risk for the anticipated lifetime of the patient (or might even go away!) The typical finding is a Gleason Score of 6 cancer. In this issue we examine the arguments some researchers are making that Gleason 6 biopsy results, under some circumstances, should not be called cancer at all, and in addition, merely followed rather than aggressively treated. The latter is the norm today. Readers need to be aware of the distinction between clinical and pathological staging and grading of prostate cancer. The former involves a PSA test and digital rectal exam which then may lead to a biopsy. The information obtained is termed "clinical." The most important finding comes

from a histological examination of the tissue recovered in the hollow needles used in the biopsy. This process of biopsy and evaluation is far from an exact science. If the prostate is removed, then the actual state of affairs can be determined by a pathologist and yields the "pathological" staging and grading of the disease. On rare occasions, no cancer at all is found, the ultimate in overtreatment. Obviously, pathological staging and grading cannot be done if radiation therapy is used. When the uncertainties in the clinical phase of the diagnosis are considered, it is not surprising that controversy exists concerning how risky the cancer is, and this centers around the Gleason 6 cases since this score is in that grey area between clearly a precancerous situation and clearly the real thing. There are in fact similarities with the controversy concerning ductal carcinoma in situ in breast cancer.

Wishing you good health,

William R. Ware, PhD, Editor

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THE DEVIL AND THE DEEP BLUE SEA. ANDROGEN DEPRIVATION THERAPY

Androgen deprivation therapy (ADT) is a major issue in urology since there is an aging population, which generates increasing numbers of men with advanced or metastatic prostate cancer, and there is also a growing tendency for urologists to prescribe this therapy to younger men, in some cases as a prophylactic measure. While there are a number of issues with this therapy, two have received considerable attention. One involves increased risk of non-fatal cardiovascular events, the other increased risk of cardiovascular and all-cause mortality. These must be weighed against cancer-specific benefits of ADT.

Bourke *et al*[1] have recently presented a perspective on these issues. They present the following evidence regarding the increase in CVD risk associated with ADT:

- A pooled analysis of three randomized controlled trials suggested that ADT is linked to an earlier onset of fatal heart attack in men over 65.
- A study based on about 31,000 Swedish men found that the incidence of heart attack in men without prior CVD undergoing ADT was 40% higher than controls.
- In an observational study of 15,000 men, ADT with gonadotropin releasing hormone agonists (GnRH) was associated with a significantly higher incidence of diabetes, coronary heart disease (CHD), heart attack, sudden cardiac death (SCD) and stroke when the reference was men not subjected to this therapy. The rates per 1000 person years for ADT vs. GnRH therapy were for diabetes, 159 vs. 88, CHD, 144 vs. 81, heart attack, 12.8 vs. 7.3, SCD, 21.6 vs. 11.5 and stroke 18.5 vs. 10.8.

Whether androgen deprivation therapy (ADT) causes excess cardiovascular mortality is controversial. A recent meta-analysis addresses this issue.[2] The study involved 8 randomized trials with over 4000 patients. Inclusion required non-metastatic disease and GnRH based ADT. The median follow-up was more than 12 year. Incidence of CV death was similar among ADT recipients and controls (11.0% vs. 11.3%) and the risk was similar for short course (≤6 months) and longer course treatment (≥ 3 years). The incidence of prostate cancer-specific mortality was lower among ADT recipients than controls (13.5% vs. 22.1% with a relative risk reduction of 31%, a result that was statistically significant. Likewise, the incidence of all-cause mortality was lower in the treated group (37.7% vs. 44.4% with a

relative risk reduction of 14%, again significant. The 8.6% absolute risk reduction for disease-specific mortality represents roughly a number needed to treat of 11, although this is only approximate given the range of durations represented in the meta-analysis. Nevertheless, mainstream medicine will treat when this number is 100, and thus a number around 10 would appear to be quite convincing.

Consistent with the above, a study reported at a recent annual meeting of the American Society for Radiation Oncology found in a multivariate analysis of data from a large randomized trial with about 2000 participants that men receiving hormonal therapy with radiation had no increase in death from cardiac causes. The median age was 71 and the patients had clinically localized stage T1 or T2 prostate cancer. Comparison was between radiation alone and radiation plus ADT. The study recovered the expected associations between conventional risk factors and cardiovascular death.

As discussed above, if one excludes SCD, these results are in sharp contrast to studies with endpoints, both cardiovascular and otherwise, which did not involve mortality. In an editorial accompanying the above meta-analysis, Kelly and Gomella discuss this issue, and point to the fact that the evidence available prompted the FDA to issue a safety warning for GnRH agonists regarding increased risk of not only heart attack, sudden cardiac death and stroke, but also diabetes.[3] These concerns were echoed in a commentary in the *British Journal of Urology International*[4] which included a discussion of increased risks of insulin resistance, the metabolic syndrome, diabetes and dyslipidemia. The authors also expressed considerable concern about the impact of artificially induced very low testosterone levels on coronary heart disease, although they did not emphasize the impact on quality of life. It was suggested that physicians should carefully assess patients for risk of these disorders in the context of ADT recommendations and suggest risk reduction measures if risk factors were present. However, if cardiovascular disease was the issue, it is not clear that statin therapy is sufficient or even has any clinical utility, given that in the context of primary prevention, the number needed to treat is about between 75 and 100 to prevent one event.

In addition, as a commentary in *JournalWatch Oncology* (December 7, 2011) pointed out, the meta-analysis discussed above involved highly selected patients who were likely to have a low burden of comorbidities, were clearly at high risk in the non-metastatic setting, and likely were not representative of the larger group of patients with rising PSA after definitive therapy.

Bourke *et al* also discussed potential mechanisms. They point out that while the evidence suggests a link between ADT and CVD, a causal relationship is still open to question. However, they point out that there are multiple links between low androgen levels and CVD. In particular, low levels of androgens are commonly observed in patients with established CHD and heart failure, and testosterone supplementation in hypogonadal males improves lipid profiles. Furthermore, in older men higher levels of bioavailable testosterone is associated with a 26% reduction in CVD risk. This and other evidence (ADT increases body fat, reduces lean mass, induces change fasting glucose and insulin levels) recently led to a joint advisory by the American Cancer Society and the American Urological Association suggesting that it is plausible that ADT could increase cardiovascular risk simply on the basis of an impact on risk factors. Finally, they comment that for obvious reasons prospective randomized trials addressing effect of ADT vs. no ADT on CVD outcomes in men with advanced prostate cancer are unlikely to ever be carried out. Therefore, risk/benefit considerations must depend on existing data.

Bourke *et al* go on to discuss the problem faced by the urologist managing prostate cancer patients. The beneficial effects of ADT need to be weighed against the risks and there is no clear algorithm available which includes both the adverse effects of ADT combined with or aggravated by pre-existing co-morbidities. While they admit that in the case of symptomatic metastatic disease, the imperative is treating the cancer, the case of locally progressive disease or high-risk disease in men with existing co-morbidities presents a situation where the best therapeutic approach is far from clear. The situation is further complicated in that prostate cancer is generally managed by urologists, but CVD and other comorbidities are managed by cardiologists, internists or general practitioners. Added to the problem faced by the urologist is the set of side effects of ADT which impact the quality of life.

Thus it would appear from the above considerations that both patients and their physicians should analyze carefully the pros and cons of ADT in situations where the indications are less than compelling and in particular delaying ADT intervention when there is only early evidence of treatment failure. The multiple consequences of inducing the totally unnatural state of near zero testosterone should not be taken lightly. Previous issues of the *Prostate Monitor* have discussed intermittent ADT and a viable alternative, but the impact on CVD risks appears unknown.

For a detailed discussion of the combination of ADT and radiation therapy the reader is referred to a review by Hans Larsen which appeared in the May and July 2010 issues of the *Prostate Monitor*.

THE GLEASON 6 CONUNDRUM

A common scenario: Doctor—"The bad news is that you have prostate cancer. The good news is that it a low-grade which we judge from what is called a Gleason score. You have a Gleason score of 6. We can offer you curative treatment with a very high chance of getting rid of this cancer for good." But what may not be discussed in sufficient detail: "What we can also offer you is a significant probability of side effects such incontinence and sexual dysfunction that will impact your quality of life for many years to come. If you elect radiation treatment there may also be serious tissue involving damage impacting your bowel or bladder function." Some patients might, if given the whole story in its rather gruesome detail, respond: "Gee doc, I can't win, can I." Some men may even be concerned because the only source of advice and recommendations is coming from someone who makes a living doing the treatment and needs a constant stream of patients to support his or her lifestyle. The patient may wonder if recommendations for radical treatment based on borderline or debatable indications are biased, but this assumes the patient is aware of the borderline nature of the evidence. Actually, the problem is more complex. Once a patient is told they have cancer, the natural reaction is a strong desire to get rid of it, a view frequently supported by family members. Thus, as research shows, many patients are not receptive to suggestion of active surveillance until definitive treatment is clearly indicated to have benefits that exceed risks. Patients also abandon active surveillance when there is no good reason to do so, either because of anxiety or because they are given very conservative advice at the first sign of change in clinical parameters.

The hypothetical patient described above would probably be shocked to learn that experts are debating the question "Should we really consider Gleason 6 prostate cancer?" Your editor will never forget what a surgeon told a friend after his radical prostatectomy. He said "your really did have prostate cancer." Nor for that matter will he ever forget the encounter another friend had with his urologist who told him after inspecting his bone scan results that he had metastasis, and then noted in passing his hip joint replacement. Problem is, he never had hip surgery. One wonders how often biopsy results, scans, blood test results etc. do not have the correct names attached. Humans are prone to mistakes, surgeons remove the wrong kidney, amputate the wrong leg, etc.

The debate about what really constitutes an appropriate threshold for the diagnosis of prostate cancer is heating up. It is being suggested that a Gleason score of 7 upon biopsy should be the determinant, not 6, and that individuals with a score of 6 should not be told they have cancer. Avoiding this label is significant from a psychological perspective and is especially important in the PSA era where the majority of patients are found to have a Gleason score of 6 are given radical, so called definitive treatment. Critics claim that this represents overdiagnosis and overtreatment with concomitant side effects that are far from trivial or rare and may strongly impact quality of life.

In a recent commentary in the *British Journal of Urology International*, Nickel *et al* discuss various aspects of this problem.[5] They suggest that a Gleason 6 scores is frequently considered as indication of lethal cancer because most pathologists will be able to find a strong association between Gleason 7-10 cancers along with Gleason 6 cancers in radical prostatectomy specimens. Gleason 6 patterns are usually multicentric as are patterns of aggressive cancer and are intermediate between aggressive cancer and benign pre-cancer patterns. Thus if a Gleason 6 cancer is regarded as not really cancer, it cannot be considered truly benign.

Nickel *et al* suggest that clinical arguments can be advanced to support the hypothesis that a Gleason 6 biopsy result might indicate a benign condition. They point out that it is extremely hard to find any evidence that very many patients suffering fatal prostate cancer have Gleason 6 pathology at the time of death, although of course Gleason 6 can progress to higher Gleason scores after the initial diagnosis. They point out two reasons why patients originally diagnosed with Gleason 6 cancer die from prostate cancer. One is that the diagnosis missed more aggressive or even metastatic cancer and the other is the obvious scenario where the original Gleason 6 diagnosis was correct but the cancer progressed and became lethal. Thus it appears that the issue is not whether Gleason 6 is benign or not, but that the diagnosis from biopsy only of Gleason 6 prostate cancer fails to differentiate significant from insignificant cancer. This is not surprising given how the biopsy is done and underscores the critical need for better diagnostic procedures or much more reliable biomarkers than are currently available. But the Gleason 6 diagnosis is also part of the basis for advising some patients to consider active surveillance rather than immediate radical treatment (surgery or radiation). This judgment call is based on the number of needles with cancer-bearing tissue and the fraction of each sample that has the suspicious cells. If the cancer is really benign, then the probability may be very low that it will ever be a problem, especially in older men or men with serious comorbidities and a limited life expectancy.

Related to this last issue is a study from Korea which examined the pathological outcomes for a single very small Gleason 6 prostate cancer detected by contemporary multicore (≥ 12) biopsy, in this case in a cohort with PSA ≤ 10 ng/mL. Hong *et al* [6] retrospectively analysed the clinical and pathological data available for 119 patients selected out of a cohort of 1214 men who underwent radical prostatectomy. The inclusion criteria were pre-biopsy PSA ≤ 10 ng/mL, Gleason score of 6 with just one core out of 12 or more positive and this having ≤ 3 mm of Gleason tissue. Digital rectal exam information was also available. The mean age was 65, 86% had clinical stage T1c (PSA only indicator). Pathological examination of the removed prostate indicated 76% with Gleason 6, 21.8% with Gleason 7 (3 + 4) and 2% with Gleason 7 (4 + 3). The first number in these sums is the primary finding. Overall rates of insignificant and unfavourable cancers were 44.5% and 24.4% respectively. Unfavourable was defined as a Gleason score of 7-10 and/or extraprostatic extension of the tumor. Only a low PSA density (< 0.15 ng/mL/mL) was an independent predictor of insignificant prostate cancer. Correlations with postsurgical PSA failure were not possible since this occurred in only one of the 119 men during follow-up

Thus 24.4% of patients had what could be described as insignificant prostrate cancer based on contemporary biopsy techniques and highly favourable clinical features, and yet harboured pathologically unfavourable tumor. But then 44.5% ended up with insignificant tumors after surgery and pathological examination of the prostate. That is the problem. It is interesting that the PSA density found to be predictive of insignificant cancer is commonly used as one criterion for the recommendation to consider active surveillance rather than radical treatment for men with Gleason 6 scores.

NIH CONSENSUS PANEL ENDORSES ACTIVE SURVEILLANCE

A consensus panel of 14 researchers and clinicians convened by the National Institutes of Health has endorsed active surveillance in place of immediate surgery or radiation therapy for patients with low-risk prostate tumors. A principal concern addressed was that 90% of patients with localized prostate cancer deemed not aggressive at diagnosis and unlikely to become life threatening are aggressively treated with radiation or surgery. Treatment is accompanied by substantial short- and long-term side effects without evidence of clear benefits such as improved survival. The panel concluded that “It’s clear that many men would benefit from delaying treatment, but there is no consensus on what constitutes observational strategies and what criteria should be used to determine when treatment might ultimately be needed among closely-monitored men.” Considering the idea of active surveillance was put forward in some detail more than a decade ago both by Johns Hopkins and Sloan Kettering urologists, it is quite remarkable that the urology community has yet to get their act together and have enough data to reach a consensus on the details of active surveillance.
http://www.nih.gov/news/health/dec2011/od-07.htm

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