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William R. Ware, PhD - Editor

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The flow of important and significant papers on vitamin D and health continues unabated. Thus vitamin D will be the feature topic of this issue. Health problems associated with vitamin D deficiency are presumably easily and inexpensively modifiable and possibly avoidable, something that cannot be said of many health problems. Dr. Cedric Garland, professor of preventive medicine at the University of California, San Diego, one of the vitamin D research pioneers, was quoted recently (The Globe and Mail, Toronto, March 8, pp. F6) as saying, "I think vitamin D is introducing a golden age in medicine. We will be preventing an extremely broad range of diseases in a single, inexpensive way with virtually no complications. It will affect every branch of medicine and public health favourably." The feature article in the Globe and Mail also quoted a vitamin D expert who commented that most if not all researchers in this field take significant amounts of vitamin D daily with one very prominent scientist taking 8000 IU.

I apologize to readers who are tired of this subject and are already addressing the problem of vitamin D deficiency with intelligent sun exposure and supplements. However, judging by reports from the vitamin companies, the small increase in vitamin D sales suggests that the general public has not as yet reacted significantly to the steady flow of vitamin D reports in the media. In this issue we discuss vitamin D in the context of hypertension, autism, aging, breast cancer and influenza.

Three studies in this issue relate directly or indirectly to cardiovascular risk. One, which concerns a phenomenon that may be unfamiliar to readers, involves the so-called circadian variation of acute cardiovascular events where a significant majority of such events occur within about two hours of rising in the morning. Another study discussed involves an amazing beneficial effect of egg consumption combined with a low-carbohydrate diet which produced dramatic changes in both triglycerides and HDL. This study is particularly interesting because of the persistent fixation of mainstream medicine on dietary cholesterol even though the majority of individuals experience only small increases in serum levels even when they consume significant amounts in their diet. From the point of view of human biochemistry, it is a "controlled substance" where the endogenous production adjusts to dietary consumption. The study discussed provides a convincing example of this.

In our News Briefs, the floppy-iris syndrome, cataract prevention, soft drinks and gout, and more on the benefits of moderate alcohol consumption.

Last, but not least, is a fascinating report on A2 milk by our New Zealand correspondent Dr. Maurice Mckeown. Although the A2 story has received very little press in North America, it is a hot topic "down under" and should be required reading.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

VITAMIN D AND HYPERTENSION

Calcium metabolism is known to influence blood pressure (BP) and thus vitamin D may play a role in BP regulation. In fact, a receptor is present in smooth muscle tissue for the metabolite of vitamin D downstream from 25-hydroxyvitamin D (25-OH)D, suggesting a potential role of vitamin D in the regulation of smooth muscle contraction and therefore blood pressure. In addition, blood pressure is known to show a summer-winter variation in the northern hemisphere where vitamin D production during the winter is low. A study related to this subject has recently reported [1] that made use of data from the Third National Health and Nutrition Examination Survey, a gold mine of data for investigators attempting to examine important health related questions. The researchers made use of both serum 25-hydroxyvitamin D data and blood pressure data for a total of over 7600 individuals, a cohort representing white and black men and women. Sixty-three percent were between 18 and 49 years of age and 53% were women. Black individuals constituted about half of the cohort. It was found that a statistically significant inverse association was observed between circulating 25-(OH)D levels and six categories of systolic blood pressure (SBP) ranging from normal (< 120 mm Hg through the various stages to serious hypertension (≥ 160 mm Hg). In white participants, the age-associated risk of elevated SBP was 20% less in those who had 25-(OH)D levels > 80 nmol/L compared to their deficient counterparts with levels < 50 nmol/L. The researchers found that in the cohort examined, if a cut-off for deficiency of < 80 mmol/L was used, 61% of whites and 92% of blacks were deficient. In fact, the analysis for the black segment of the cohort was limited because so few black individuals had sufficient levels of vitamin D by this definition.

These results are consistent with another recently reported study that used the same database. When participants were divided into 25(OH)D quintiles, the mean systolic BP was 3.0 mm Hg lower and the diastolic BP 1.6 mm Hg lower for participants in the highest vs. the lowest quintile (≥ 86 vs. ≤ 40 nmol/L. This result was adjusted for confounding. The inverse association was stronger in participants ≥ 50 years of age compared to younger individuals.[2]

These studies looked at 25(OH)D levels at the time of blood pressure measurements. In a prospective study of middle-aged and older women with a follow-up of 10 years, the risk of developing hypertension was examined as a function of the dietary intake of dairy products, calcium and vitamin D, all of which were ascertained by a food frequency questionnaire. It was found that low-fat dairy products, calcium and vitamin D were each inversely associated with the risk of developing hypertension, an observation the authors suggest should prompt consideration of their potential roles in primary prevention both of hypertension and cardiovascular complications.[3]

These results suggest that supplementation with vitamin D should reduce BP, but intervention studies are very limited – one randomized, placebo-controlled study of 145 elderly women showed that 400 IU of vitamin D3 and 600 mg of calcium significantly reduced systolic BP by over 9% after 8 weeks, whereas 600 mg of calcium alone produced only a 4% reduction. Serum 25(OH)D levels increased by 72% in the calcium plus vitamin D group.[4] Also, a study that used UV light in a small group obtained a reduction in systolic BP of 6 mm Hg after 6 weeks which accompanied an average increase in serum 25(OH)D level from 50 to 152 nmol/L.[5]

AUTISM AND VITAMIN D

Your editor prefers to discuss research results rather than hypotheses, but recently Dr. John Cannell published a paper in the peer reviewed journal *Medical Hypotheses* advancing the theory that autism and vitamin D deficiency were related.[6]

Autism is a disorder that has a profound impact not only on the affected individual but also the entire family and prevalence figures for the period 1992 to 2003 suggest an increase in cases in the US and Puerto Rico from about 15,000 to 140,000. In

Britain, according to Cannell, the prevalence is 1 in 86 children! This is an astounding and shocking figure. Some readers may recall Cannell's name as one of the coauthors of the paper discussed a few months ago that addressed the question of why there was a strong and consistent seasonal variation in influenza in the northern latitudes of North America, mirrored by a similar variation in the southern hemisphere shifted by six months, and presented a considerable body of evidence in favour of vitamin D deficiency as a principal factor. In the paper in question, Cannell presents evidence that there is an association between autism and vitamin D deficiency, both maternal and when it occurs in offspring. The arguments in essence are:

- The strong increase in autism over the last 20 years corresponds with increasing medical advice to avoid the sun. This would theoretically greatly lower vitamin D metabolite levels in developing brains.
- Animal data consistently shows that vitamin D deficiency during gestation dysregulates a large number of proteins involved in brain development and leads to rat pups with abnormalities similar to those found in autistic children.
- Children with the vitamin D deficiency disease rickets have several autistic markers that apparently disappear with high dose vitamin D therapy.
- Estrogens and testosterone have very different effects on the metabolism of vitamin D metabolites, difference which may explain the strong gender differences seen in the incidence of autism.
- The principal metabolite of vitamin D, calcitriol, down-regulates the production of inflammatory cytokines in the brain, cytokines that have been associated with autism.
- Autism is more prevalent in areas where there is reduced UV light penetration.
- Autism is more common in dark-skinned persons and severe maternal vitamin deficiency is very common in dark-skinned individuals.

In the author's opinion, these add up to strong evidence of a connection between vitamin D deficiency and autism. The journal article justifies this hypothesis in considerable detail.

VITAMIN D, AGING AND TELOMERE LENGTH

Telomeres are the ends of chromosomes and they undergo shortening with each replication. Telomere shortening has been associated with chronic inflammation, autoimmune diseases such as arthritis, smoking, lupus, oxidative stress in general, and recently telomere shortening has been found to be a risk factor for coronary heart disease. Thus telomere shortening has been regarded as a marker for age related diseases and conditions associated with increasing burden of oxidative stress and inflammation. A recent study [7] has found that higher vitamin D concentrations, which the authors point out are easily obtained through supplementation, are associated with longer telomeres and that this underscores the potentially beneficial effects of this hormone on aging and age-related diseases.

MORE EVIDENCE OF VITAMIN D'S IMPACT ON BREAST CANCER

A recent study from Stanford University, Wake Forest University and the University of Southern California has examined the connection between sun exposure and breast cancer.[8] The study involved Hispanic, African-American, and non-Hispanic white women aged 35-79. A sun exposure index was created based on skin reflectance of light. In addition, tissue samples were obtained for genetic typing. A high sun exposure index based on reflectometry was associated with a reduced risk of advanced breast cancer among women with light skin pigmentation with a risk reduction of 49% that was statistically significant. The association did not depend on the vitamin D receptor gene variations. No protection was found for women with medium or dark skin pigmentation, nor was localized breast cancer associated with either sun exposure or gene types. The author concludes that this study supports the hypothesis that sunlight exposure reduces the risk of advanced breast cancer among women with light skin pigmentation.

VITAMIN D AND INFLUENZA

A short report presenting a *post hoc* analysis of the incidence of influenza and common colds has recently been published. The data was derived from a prospective double blind trial of supplemental vitamin D for the prevention of bone disease in 208 African-American postmenopausal women of approximately 60 years of age. The dose was 800 IU per day in the first two years and 2000 IU per day in the third, with half given a placebo. Twenty-six women taking the placebo reported at least on cold or influenza compared to 7 taking 800 IU and only one taking 2000 IU per day.[9]

Editor's comments: It seems the following quote from a paper that discusses the pros and cons of sun exposure is appropriate: "Although diseases caused by excessive UVR [ultraviolet radiation] exposure are extremely common, they tend to occur in older age groups (due to the long lag between exposure and tumor development or a requirement for cumulative exposure) and be relatively benign, thus incurring a relatively low burden of disease in spite of their high prevalence."[10] The reader can contrast this observation with the serious nature of the diseases impacted by vitamin D and should reflect on the fact that aside from malignant melanoma, the skin cancers associated with sun exposure rarely metastasize and are generally cured by local treatment in the doctors office, which is something that most certainly can not be said for breast cancer or colorectal cancer!

VITAMIN B6 AND RISK OF COLORECTAL CANCER

A large case-control study from Scotland of the relationship between dietary vitamin B6 intake and the risk of colorectal cancer (CRC) has just reported. One of the objectives was to attempt to sort out the question of the modification of B6 effects by dietary folate, which frequently accompanies B6 in foods, and as well the influence of alcohol.[11] Over 2000 cases and 2700 controls were involved. B6 intake was ascertained by a food frequency questionnaire looking back for a year. In this study, the main sources of dietary B6 were beans, legumes, nuts, eggs, meats, fish, breads, cereals, potatoes and bananas, and data was collected regarding supplements. A moderately strong inverse and dose dependent association was found for the whole case group between CRC risk and the dietary B6 intake (23% risk reduction) but total intake, while also protective, failed to reach statistical significance. In this study, high dietary intake category was ≥ 3.39 mg/day. These associations persisted after correcting for energy, fiber and folate intake and the dose dependent trends observed were significant. The B6 inverse association was of similar strength for subjects with low and high folate intake. The inverse association with both colon and rectal cancer was stronger in the younger age group of cases. No alcohol effect was found. The authors also conducted a meta-analysis of all prospective follow-up studies and case-control studies published that compared high with low B6 intake. For the former this comparison yielded 19% risk reduction for CRC whereas in the case-control studies the figure was 33%, with both being statistically significant. The authors also point to a study that examined B6 blood levels in nurses using a metabolite as a marker and found strong and significant protective effect (highest vs. lowest quartiles) of 52% for CRC and 62% for colon cancer after taking into account potential confounding by folates and multivitamins. In this cohort only a small percentage were taking B6 supplements and the strong inverse association remained after controlling for supplement use. [12]

Editor's comments: The Scottish study emphasized dietary sources of B6 and leaves open the question of the effect of supplementation. In this study and all the studies they reviewed, average intake was in the range of 2 mg/day. Typical multivitamin preparations provide 3-6 mg per recommended daily dose, and high-potency preparations such as the so-called B-50 contain 50 mg per tablet. Given the results of the serum level study, it would appear that if one consumes a diet rich in B6 containing foods, the serum level of B6 is adequate to provide significant protection, a conclusion supported by the Scottish study as well.

EGGS WIN ANOTHER ROUND

When the dogma that "fat and dietary cholesterol cause heart disease" was at its height of popularity, eggs were regarded as poison and egg sales plummeted. But a number of subsequent studies were unable to find anything wrong with consuming one or two eggs a day provided one did not use powdered egg, a source of oxidized cholesterol, to make omelets. The reader is referred to Dr. Walter Willett's book *Eat, Drink and be Healthy—The Harvard Medical School Guide to Healthy Eating* for a summary of the history of the fall and rise of the egg. Now a study has appeared that involved a carbohydrate-restricted diet and examined the effect of adding 3 eggs per day in a randomized intervention trial. Involved were 28 overweight or obese men aged 40-70 years. They were counseled to consume a carbohydrate-restricted diet containing only 10-15% energy from carbohydrates. Half ate eggs adding over 600 mg of extra cholesterol to their diet (the EGG group), and half ate an egg substitute with zero cholesterol (the SUB group). The object was to determine changes in blood lipids and metabolic syndrome criteria.

After 12 weeks, all subjects independent of the assigned group had reduced weight and waist circumference compared to baseline. In spite of the large increase in dietary cholesterol (approximately 300 to over 800 mg/day), the mean serum total cholesterol level increased only from 198.3 to 202.2 mg/dL. Mean plasma triglycerides were reduced from 119 mg/dL to 74 mg/dL in all subjects. LDL levels and the LDL/HDL ratio did not change significantly during the intervention. But in the EGG group HDL changed from a mean of 47.6 to 56.9 mg/dL whereas there was no change in HDL in the SUB group. At the start, 18 subjects were classified as having the metabolic syndrome whereas only 3 had this classification at the end. The authors conclude that the challenge of dietary cholesterol during a weight loss intervention involving carbohydrate restriction does not alter the positive effects of such an intervention on the features of the metabolic syndrome and in addition plays a major role in the beneficial effects on plasma HDL and triglyceride levels.[13]

This same research group has also recently shown that the carbohydrate-restricted diet plus a daily intake of eggs caused a greater increases in insulin sensitivity in the EGG group compared to the SUB group, and the inflammation marker C-reactive protein decreased only in the EGG group. [14]

Editor's comments: These studies directly challenge the National Cholesterol Education Guidelines which have always regarded dietary cholesterol as bad. In the above study, LDL cholesterol increased somewhat in both the EGG and SUB groups with no significant difference in the increase between groups, and the LDL/HDL ratio, which some regard as more significant, remained unchanged. The low-carb diet also produced the expected and dramatic favorable change in the TG/HDL ratio which is a measure of not only insulin resistance but also, when the ratio is high, the prevalence of small, atherogenic LDL particles is elevated. In the EGG group, the TG/HDL ratio went from 2.4 to 1.2 whereas in the SUB group the change was from 2.5 to 1.6. Both changes would be considered very favourable. It should be pointed out, however, that heavy consumption of eggs increases the dietary intake of omega-6 fatty acids which may increase silent inflammation, although some brands have enhanced omega-3 content which would counteract this.

VARIATION OF HEART ATTACKS WITH TIME OF DAY

There is a so-called circadian variation of when acute cardiovascular events (stroke and heart attack) take place. When one graphs the average incidence rate over a 24-hour period for samples of several hundred or more incidents a double humped plot results. A recent small study looked at this two-peaked circadian variation in order to examine the impact of the siesta or post-lunch nap on the occurrence and time of this second peak since much of the data regarding this circadian phenomenon was collected where the siesta was a cultural characteristic. In the group of 217 male heart attack patients (MI) studied, 152 were accustomed to taking an afternoon nap after lunch. Those who did not served as a comparison. The maximum number of MIs occurred at about 8 AM and the second peak occurred at about 4 PM for those who took a siesta and about 8 PM for those who did not. Since in the country where the study was carried out (Greece) lunch is at 2PM and dinner at 6 PM, the authors suggest that the shift in the second peak in the MI distribution curve could

simply reflect the timing of a heavy meal followed by inactivity. They cite evidence from other studies that are consistent with their observation of a siesta related shift in the second peak and suggest that interpretation is made complicated by confounding factors.[15] They also cite an earlier paper, also from Greece, which examined the circadian variation of the onset of stroke and compared this variation to that of systolic and diastolic blood pressure, pulse rate and physical activity. In this study, 75% of the participants were in the habit of taking a siesta, and it is thus interesting that the second peak occurs at close to the same time as that for the siesta group in the MI study. In the stroke study, all of the above mentioned variables correlated very well with the circadian variation of stroke incidence.[16]

Editor's comments: This study brings to mind what has been called the "Merry Christmas Coronary" and the "Happy New Year Heart Attack" which are facetious names for the two very pronounced peaks in MIs that occurs on these two days and which some have attributed to an extra heavy meal.[17] However, a number of explanations have been put forward, not only for this highly reproducible phenomenon, but also for the observation that siestas may influence mortality. Dealing with confounding in this area is a big problem. Nevertheless, the above studies provide an incentive for not overeating, being active after a big meal and resisting the "super size" or "all you can eat" culture that appears to be growing in popularity.

VITAMIN AND TRACE MINERAL INTAKE AND C-REACTIVE PROTEIN LEVELS

At issue here is the impact of micronutrient intake on inflammation, an important question since the inflammatory process underlies the pathogenesis of atherosclerosis, and primary prevention of cardiovascular disease and vascular disease in general needs to focus on this potent causative factor. A recent study from Germany has examined this question in a large group of men and women aged 25 to 75. It was found that intake of dietary supplements containing vitamins and trace elements was associated with lower C-reactive protein (CRP) levels. In particular, vitamin E in combination with vitamin C, vitamin B1, B2, B6, niacin, folic acid, pantothenic acid and selenium were significantly associated with lower CRP levels. Odds ratios for having a CRP level > 3.0 mg/L were 0.57 for the intake of vitamin E and also 0.57 for the intake of multivitamins (three or more different vitamins) and the results were statistically significant. These associations were seen only for women. The authors suggest that more research is needed to determine dose response relationships and the best combination for maximum benefit in this context.[18]

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)—IS IT RELATED TO AN OMEGA-3 DEFICIENCY?

The development of an assay for EPA and DHA in red blood cell fatty acids has made possible a number of interesting studies from sudden cardiac death to ADHD. In a just published study from the University of Guelph in Ontario, researchers examined the association between both dietary intake and red blood cell fatty acid status in a group of adolescents diagnosed with ADHD as compared to an age-matched control group. Both groups had similar anthropometric measurements such as weight, height, % fat mass, etc. Both groups consumed equivalent amounts of omega-3 and omega-6 fatty acids but the ADHD group consumed more energy and fat even though they had similar anthropometry. The ADHD children had significantly lower red blood cell levels of DHA and total omega-3 fatty acids, higher omega-6 fatty acids and a lower omega-3 to omega-6 ratio. In addition, this lower omega-3 status correlated with scores obtained with a standard behaviour measurement scale (the Conners' Parent Rating Scale or CPRS). The authors point out that these abnormal fatty acid profiles are also observed in younger ADHD children and again are distinctly different from controls of a similar age. Given that the dietary intakes in this study were similar, the results suggest that there are metabolic differences in fatty acid handling between ADHD adolescents and normal controls. Finally, they provide evidence from other studies that it may be possible to improve behaviour patterns with omega-3 supplements, but

the successful studies have used rather large doses (up to 16 g fish oil per day).[19]

The above described study is consistent with recent open-label pilot study of high-dose EPA/DHA concentrates on plasma phospholipids and behaviour in ADHD children.[20] Nine children were supplemented with 16.2/day of EPA/DHA. The dosage was adjusted depending on the arachidonic acid (AA) to EPA ratio in blood phospholipids. At the end of eight weeks there was not only a significant reduction in AA/EPA ratio from about 21 to about 6, but psychiatric assessment indicated significant improvements in inattention, hyperactivity, oppositional/defiant behaviour and conduct disorder. The AA/EPA ratio also correlated with a measure of the global severity of the ADHD. No significant side effects were observed. This was a short pilot study so there were no controls.[20]

These two studies are encouraging and one can hope that larger and longer studies will be done. Important issues are obviously the levels of EPA and DHA intake needed to maintain the improvement in ADHD patterns and the combined effects of supplementation and aggressive modification of the omeng-6 to omega-3 dietary intake once a low AA/EPA status has been achieved. It is perhaps worth pointing out that the very high AA/EPA ratio is a characteristic of modern and especially Western diets high in omega-6 fatty acids and low in omega-3 fatty acids, a situation that is at variance, it is thought, with our evolutionary biochemistry and was absent prior to the widespread use of vegetable and seed oils containing high levels of omega-6 fatty acids.

NEWS BRIEFS

THE FLOPPY-IRIS SYNDROME

While this is a rather rare problem that occurs during cataract surgery, it appears to be strongly associated with a drug commonly prescribed for the treatment of benign prostatic hyperplasia (BPH). A recent report adds to the evidence.[21] In a case report from the UK, two patients had the features of intraoperative floppy-iris syndrome in both eyes during bilateral cataract surgery. Both were taking oral finasteride (Proscar) for BPH. The message is simple. Men scheduled for cataract surgery who are taking Proscar (and perhaps Avodart which belongs to the same family) should inform the surgeon regarding this and, if necessary, mention the connection described above. While unlikely, some cataract surgeons may not be familiar with the association or the steps necessary to minimize the risk during cataract operations.

PREVENTING CATARACTS

Cataracts are very common in older individuals, and in countries where the health care philosophy is based on rationing, waiting times can be considerable. Interestingly, in some countries hospitals have been set up where the opposite extreme is seen and where the cataract operation has been reduced to an assembly-line process with an amazing daily throughput. Clearly, decreasing the risk is highly desirable. In a recent study from Harvard and Brigham and Woman's Hospital, researchers examined prospective data for almost 40,000 female health care professionals based on a food frequency questionnaire. Approximately 2000 cases of incident cataract were confirmed during a mean follow-up of 10 years. Lutein/zeaxanthin and vitamin E from both food and supplements were found to provide significant cataract protection in this large cohort. For the former, there was an 18% risk reduction whereas for vitamin E it was 14%. Lutein/zeaxanthin is readily available in health food stores and is also promoted for the prevention of age-related macular degeneration.[22]

SOFT DRINKS AND GOUT

While it is probably not generally realized, gout is the most common inflammatory joint disease in men. Its prevalence and incidence has doubled over the past few decades in the U.S. coincident with the increase in soft drink consumption with the associated increased intake of fructose. A recently reported prospective study in men has found that sugar sweetened soft drinks are strongly associated with the risk of gout with twice the risk at the highest intake compared to the lowest (by quintiles). In addition, intake of fruit juice or fructose rich fruits (apples and oranges) were also associated with higher risk of gout. This is important information not only of general interests to men but also of particular relevance for those who have already experienced one or more episodes of this very painful problem.[23]

TOP CULPRITS IN EMERGENCY DEPARTMENT VISITS FOR ADVERSE DRUG EVENTS IN OLDER INDIVIDUALS

There is a list, called the Beers criteria medication list, which contains drugs always potentially inappropriate. A recent study of older individuals has found that three drugs not on this list are in fact responsible for a substantial number of emergency department visits for adverse events. These are warfarin, insulin and digoxin. When normalized for prescription frequency, ED visits due to these three drugs were 35 times greater than any medication on the Beers list. Individuals taking one or more of these three medications should be aware of the enhanced possibility of an adverse reaction, ask their physician about warning signs, and act accordingly.[24]

ALCOHOL AND ARTERY DISEASE OF THE LEGS AND FEET

This is called lower-extremity arterial disease (LEAD) and affects approximately 10 million adults in the U.S. alone. A study has recently reported that assessed the association between alcohol and LEAD in a cohort of community-dwelling adults. It was found that 1-14 drinks a week in older adults may be associated with lower risk of LEAD, but the benefits are lost with heavier drinking. The authors found a similar relationship with the ankle-brachial index, a measure of peripheral artery disease which is measured in physical exams that look at more than the common risk factors and signs of atherosclerosis.[25]

ALCOHOL AND VENOUS THROMBOSIS

In a large case control study from the Netherlands, it has been found that 2-4 glasses per day of an alcoholic drink resulted in a 33% reduction in risk of venous blood clots. The benefit was more pronounced for women than men and more striking for pulmonary embolism (44 % risk reduction) than for deep vein thrombosis (26% risk reduction). Also, compared to abstainers, individuals who consumed alcohol had decreased fibrinogen levels which may partially mediate the protection against thrombosis.[26]

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Milk - The Devil in Disguise?

Maurice Mckeown, BDS, PhD
(our New Zealand correspondent)

Milk is a controversial food. Some believe it is unnatural for any species that has been weaned to continue to consume the milk of another species. Others believe that milk causes allergies or contains a microbacterium which wreaks havoc with our immune system.

Diabetes

The controversy which is the focus of this article all began back in 1993 when Professor Bob Elliott - a diabetes researcher at Auckland University in New Zealand became interested in the wide disparity in the rates of type 1 diabetes around the world. The incidence of the disease varies enormously. He initially observed that the incidence in Samoan children in New Zealand was dramatically higher (10 fold) than that occurring in their home islands. He also knew that casein - a protein present in milk was a diabetogenic agent in lab rats.

If milk is a cause of type 1 diabetes the disease ought to be very prevalent in societies where a lot of milk is drunk. The obvious focus would be the Masai people of Kenya who consume very large quantities. The problem is that they do not seem to get type 1 diabetes. Professor Elliott decided to ask New Zealand milk scientists whether the milk drunk in Kenya was in any way different from that drunk here in New Zealand. The scientists revealed that there was a difference in a protein component of the Masai milk which involved the structure of the casein molecules. *That type of milk is now designated A2, while the variety commonly consumed in New Zealand is designated A1. (Milk is made up of carbohydrates, fats and proteins. The precise nature of the protein content is determined by the genetic makeup of the animal producing the milk. Milk protein is made up of approximately 5% whey protein and 21% casein protein. It is the nature of the casein which can vary among different animals, breeds and species.*)

These observations lead to epidemiological and lab research. The most significant epidemiological study was published in 2003 in the *NZ Medical Journal*. (1) It examined the relationship between type 1 diabetes, ischaemic heart disease and cows' milk containing A1 beta casein - the type of milk commonly available in New Zealand and many other western countries. The twenty-country study reported very high correlations between A1 milk casein consumption and type 1 diabetes - in the order of 0.92 - a remarkable association in the

biological field. There was a 300-fold variation in the incidence of type 1 diabetes in the countries involved which is notable in itself!

Other research at the University of Iceland has compared milk consumption in Iceland with that of other Scandinavian countries. Most Icelandic milk comes from A2-producing cows and the incidence of Type 1 diabetes there is substantially lower than the other northern countries. Milk in Iceland comes from an ancient Norse breed of cow, which produces A2 milk. The studies have confirmed that Icelandic milk is indeed low in beta casein A1 (2) and also that consumption of milk is much higher in Iceland than the other Scandinavian countries.(3) This suggests that the nature of milk may be a risk factor for type 1 diabetes.

Further Evidence

Professor Elliott also conducted studies in which he gave rats susceptible to diabetes, the suspect A1 milk product, which contains a protein fragment now designated BCM-7, and casein derived from A2 milk which does not contain the protein in question. Sure enough none of the mice fed the A2 diet developed diabetes while 47% of those fed regular milk succumbed to the disease. (4)

Research by Boales and associates published in 2002 (5), involving rats and mice, only weakly support Professor Elliott's earlier work. It has, up until recently, formed the main rebuttal to his findings. It has now been revealed however that the feed used in that study was incorrectly formulated and the milk, supposedly free of the A1 protein, was contaminated with the key casein protein from A1 milk. Unfortunately it has now been alleged that those associated with the study failed to make this information public; indeed, that they may have deliberately withheld the information - thus leading to intense controversy in New Zealand over the role of Fonterra, New Zealand's major milk export corporation.

Heart Disease

In 2001 the link between A1 milk consumption and heart disease was explored by Corran McLachan who was startled to note the links between diabetes incidence and that of heart disease. He established a correlation of 0.86 between A1 casein consumption and ischaemic heart disease in a group of countries.(6)

A University of Queensland study in 2003 determined that rabbits fed A1 milk developed arterial plaque while those fed A2 milk did not (7). Note: There is also some evidence that the responsible component in A1 milk may lead to oxidation of LDL cholesterol.

Research by the Elliott group has found that A1 beta casein per capita consumption in the milk and cream supply was significantly and positively correlated with IHD (ischaemic heart disease) in 20 affluent countries. The study used a five-year time lag, over a 20-year period – thus providing an alternative hypothesis to explain the high IHD mortality rates in northern compared to those of southern Europe. In Crete for example where heart disease is the lowest in Europe, the locals drink only small amounts of milk, about 40% of which is reported to be from sheep and goats who do not produce A1 casein. In 1995, A1 milk per capita intake varied greatly among many countries, from about 0.3 g/day in Guernsey, to 3.0 g/day in Finland. (Consumption is even lower in Japan). Comparison has also been drawn between Ireland and France. The French have much lower heart attack rates in spite of similar total fat consumption levels. The research concluded that the Irish/French IHD rate of 3.8:1 was in line with the milk protein type ratios (total milk protein per capita ratio 3.1:1; A1 per capita ratio 4.1:1) Overall it was noted that countries with the highest IHD rates all consume more than 2 grams of A1 milk per capita per day in their diet.

Other Diseases

It has been shown that BCM-7, the key casein peptide in A1 milk, is biologically active (beta casein A2 cannot give rise to BCM-7), exhibiting amongst other things opiate-like properties. Independent research has also shown rats injected with BCM-7 exhibit symptoms similar to schizophrenia. BCM-7 has been shown to affect factors involved in heart disease, such as platelet aggregation and LDL oxidation.

A potential link between milk consumption and autism was postulated many years ago. A University of Florida

researcher Robert Cade reported in 1999 that beta-casomorphin-7 is found in high concentrations in the blood and urine of patients with either schizophrenia or autism. It is believed that in some children fragments of casein can leak through the gut wall into the blood, and from there into the brain causing significant behavioural problems. A2 Corporation, a NZ company involved in the testing and production of A2 milk, say that comments on the University of Florida website have stated that preliminary research findings have shown that 95% of autistic children have 100 times the normal level of milk protein in their blood. They go on to state that at least 8 out of 10 patients no longer had symptoms of autism or schizophrenia when put on a milk-free diet. Unfortunately the work does not appear to have been published to date and thus cannot be scientifically assessed.

How could some milk be much safer than others?

Milk is regarded by many as a natural food with many beneficial nutrients. How could it cause disease? The supporters of the A2 hypothesis believe that some thousands of years ago a natural mutation occurred in a few cows, which resulted in a change in a protein molecule in their milk. That molecule beta-casomorphin-7 (BCM-7) is the result of a variant of the casein molecule in which histidine is substituted for proline at one point in its structure. This interpretation does not appear to be in dispute.

It is however unclear how we have arrived at a situation today where some breeds produce the original milk and others produce A1 milk which by definition is now the most common variety in many parts of the western world.

How could a molecular change in a component of milk lead to disastrous results for human health?

The concept of "cross-reactivity" between antigens in cows' milk and antigens on the pancreatic ß-cell is appealing and has been proposed by several investigators. More recently, a more elaborate potential mechanism has been proposed. It is hypothesized that the BCM-7 cleaved from A1 beta-casein, has opioid characteristics which suppress the body's immune surveillance, or responses, to antigenic agents such as enteroviruses or endogenous retroviruses which then damage the pancreatic ß-cells. It is reported that it takes 10 times as much naloxone, an opioid antagonist, to counteract BCM-7 as it does to suppress morphine. *(Information from Bob Elliott's 1993 rat studies in which animals consuming A1 milk products and given naloxone, also failed to develop diabetes.)*

A2 researchers also believe that gut permeability in some individuals, particularly young children, leads to abnormal protein ingestion into the blood and probably the brain. It has been shown that type 1 diabetics have specifically higher levels of antibodies to A1 beta casein than non-diabetics.

Health Friendly Cows

Is your cow's milk healthy? If you have one in your back yard you could use the A2 Corporation's test kit to alleviate your fears. I suspect that this may not be an option for most readers!

The mutation which occurred in cows in the past has lead to a situation in which some breeds of cows appear to have changed little and still produce purely A2 milk. Examples are native Icelandic cows, Jersey and Guernsey animals together with many French cows. Asian and African cows and other milk producing species like camels and goats all produce A2 milk. In Western countries dairy herds are a genetic mixture. Thus in New Zealand approximately one third of animals produce A2 milk, one third produce A1 milk and the rest produce a mixture. The A2 Corporation produces these testing kits so that individual animals from mixed producing breeds like Red Danish, Holstein/Friesian and Ayrshires can be assessed to determine what type of milk individual animals produce. It is thus possible to create herds producing the desired type of milk. In New Zealand it has been estimated that in ideal circumstances the entire national dairy herd could be converted to A2 production in eight years.

A2 milk is available in supermarkets and health shops in New Zealand and Australia. Over 1000 US health stores are now reported to stock it. In New Zealand A2 milk is only guaranteed to contain 95% A2 beta casein.

Feeding Infants and Young Children

Cow's milk contains up to 3 grams per 100 ml of casein. Opponents of cow's milk consumption say that the problem with it is not simply its casein content - that's the part that may produce the casomorphin opiates. The nutrient "package" in milk - loads of sugar (lactose), animal protein and fats, can trigger the production of pro-inflammatory IGF-I in the body, and that may be the reason it is linked to a variety of diseases.

The milk of cows varies from that of humans in a large number of ways. The minerals sodium, potassium, calcium, magnesium and chloride are present in much larger quantities in cow's milk. Carbohydrate levels are also much higher (notably lactose). The most dramatic difference however lies in the casein content. Human milk contains very little. (It is also rich in whey protein of a different type to that present in the cow.)

The possible role of A1 milk in precipitating type 1 diabetes in susceptible children, and possibly laying the foundations for heart disease and other diseases in later life, creates some problems for prudent new parents. There doesn't appear to be any A2 baby milk food products currently available. *(Some studies have identified high levels of BCM-7 in infant formulas.)* No doubt A2-derived formulas will become available in the foreseeable future. Until they become available, it may be prudent for new mothers to breast-feed for as long as practicable. Some believe that the digestive and immune systems of infants may be better able to tolerate A1 milk products as they grow older.

Until there are more answers, it seems that a prudent approach, regarding the consumption of regular A1 milk products, should be applied to babies and young children. Those who are not breast-fed might consume A2-based products, including goat's milk, if available. Failing that they could consume baby formulas containing only whey protein, thus avoiding the possible offending casein derivative of A1 milk.

Adult Milk Products

There is some good news for concerned adults. Butter contains negligible amounts of protein, and beta casein is degraded during cheese making, so A1 milk can be safely used in the production of cheeses. It is not currently known whether yogurts derived from A1 milk are devoid of BCM-7. The role of pasteurization in providing protection from BCM-7 is controversial and a complex technical subject. It is discussed in Keith Woodford's book. The fascinating possibility that pasteurization methods common in the earlier part of the 20th century may have favoured the retention of BCM-7 and thus encouraged heart disease, is discussed in Woodford's book.

Speculations

The A2 hypothesis alleges that consumption of regular milk may lead to a wide variety of diseases. The A1 disease list includes type 1 diabetes, MS, autism, other neurological conditions and cardiovascular disease. Health science is now presented with a serious challenge. The possible association between milk consumption and a wide variety of human diseases will require specific studies designed to address possible associations on a case-specific basis. Unfortunately A2 milk has not hit the worldwide health radar to date.

Red wine has now become a health imperative believed to be responsible for the French cardiovascular advantage. What if the real advantage was A2 milk drunk by the French and few others? As a result of the unresolved controversy the author is hedging his bets and drinking A2 milk plus a glass or two of red wine daily!

The extensive publicity surrounding the A2 (or is it A1) issue here in New Zealand has lead to the government announcing an investigation into the safety of A1 milk. Subsequent to that it has now been announced that the investigation will not proceed as the European Food Safety Authority is taking over the investigations. Hopefully the regulatory authorities in Canada and the US will finally become aware of the issues involved. Until that happens the onus lies with the educated consumer. Will we eventually see health warnings on regular A1 milk? I suspect that the A2 Corporation hopes so.

Readers who would like to explore this fascinating controversy further are recommended to read "Devil in the Milk" by Keith Woodford Craig Potton Publishing Nelson New Zealand ISBN 978-1-877333-70-5 http://www.craigpotton.co.nz

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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This issue features comments and observations of three urologists from the Glickman Urological and Kidney Institute of the Cleveland Clinic which recently appeared in two papers in the Cleveland Clinic Journal of Medicine. The author of the first paper discussed is also Chairman of the Taussig Cancer Institute of the same clinic. These physicians attempt to put various aspects of prostate cancer in a realistic and modern perspective which emphasizes not only what is known but what is not. In spite of the fact that prostate cancer is one of the most thoroughly researched malignant diseases, its complexity makes huge demands on the machinery of evidence-based medicine.

Other topics covered include the prostate cancer risk associated with dietary trans-fatty acids which provide one more reason for aggressively avoiding these particular man-made fats, a review of a study comparing cryoablation with radiation therapy, and two important adverse effects of hormone therapy that have only recently been recognized. Finally, a study concerning prostate cancer surgery in men over 70 is discussed. This latter subject is of growing concern given the rapidly increasing over-70 population, and the high incidence of prostate cancer and as well the increased life expectancy in this age group.

Wishing you continuing good health,

William R. Ware, PhD, Editor

PROSTATE CANCER – A REALITY CHECK FROM THE CLEVELAND CLINIC

In the January 2008 issue of the *Cleveland Clinic Journal of Medicine,* Dr. Derek Raghavan from that institute attempts to put the present state of affairs in prostate cancer into perspective.[1] The title of the article is *Prostate Cancer: Too Much Dogma, Not Enough Data.* His arguments are interesting but no doubt clash with the views of some urologists.

Dogma #1; PSA ≤ 4 is normal and PSA > 4 is abnormal. It is probably generally appreciated that a single PSA value does not necessarily indicate cancer is present or absent, although Raghavan points out that there is an upper point where the suspicion become strong (e.g. 10 ng/dL.). But he points out that if a patient presented with a PSA of 100 ng/dL and a complaint of spinal cord compression from sclerotic bone metastases he would be inclined to assume prostate cancer was present and treat the patient in an urgent setting without a biopsy. In other words a markedly raised PSA is in a class by itself, but a problem concerns what cut-off makes tissue diagnosis unnecessary.

Dogma # 2. Prostate screening is beneficial. Raghavan points out that it seems intuitively sensible and logical that screening healthy, symptom free men for prostate cancer is a good idea and should lead to earlier diagnosis and an increased probability of a cure. He cites as evidence "first principles," common sense, the belief that death rates from prostate cancer have fallen in countries that have wide-spread screening, and the observation that prostate cancer is being diagnosed at a much earlier stage. However, there are no completed well-designed randomized trials that demonstrate improved survival attributable to screening with either PSA or the digital rectal exam. One trial is in progress in Europe. Otherwise, no data.

Dogma #3. Prostate screening is working. Uncorrected rates of prostate cancer related deaths have changed little since the advent of PSA testing in the 1980s. But the analysis is complicated by too many factors working in opposite directions such as changes in the incidence of prostate cancer and aging, improved diagnosis and treatment, better staging and pathological classification, advances in surgery and radiotherapy, the use of hormonal adjuvant therapy for locally advanced tumors, and better support technologies. Thus Raghavan points out that it is difficult to attribute any perceived major improvements only to screening.

Dogma # 4. Surgery is better…or…radiotherapy is better. To quote the author "One of the tantalizing dogmas of prostate cancer management is the myth that surgery is vastly superior to radiotherapy or vice versa." He points out many problems associated with the comparison between these two treatments such as surgical staging vs. clinical staging, case selection, single-center vs. collaborative group outcomes, and historical comparisons. As with Dogma #2, few well-constructed randomized trials have attempted to address this question, and most have closed prematurely because of poor participant accrual. To make a case one must consider long-term outcomes, balance inaccuracies of definition and documentation of side effects of treatment and deal with the variables outlined above and in addition deal with the heterogeneity of salvage therapy. This, he feels, makes it hard to construct a strong case that only one therapeutic option is best.

Dogma #5. Chemotherapy never works. Here the issue is the use of chemotherapy in the management of hormone-refractory prostate cancer, i.e. nothing now works but palliation. Raghavan takes the position that large randomized trials have made it clear that chemotherapy improves the quality of life and that survival can be prolonged. He appears to favour testing chemotherapy as an adjuvant to hormone therapy.

Raghavan concludes with a call for well-designed and well supported randomized clinical trials in order that the approach to prostate cancer can be more firmly based on the foundation of evidence-based medicine. Given the nature of the problems he outlines, this may be somewhat of a fantasy.

The reader is referred to our book *The Prostate and Its Problems* for a discussion of Raghavan's view concerning Dogma #5. The reference he cites[2] for prolonged survival is a recent study that found the improvement of mean survival of about 2 months (17.5 vs. 15.5), which some would regard as insignificant, especially considering that this is an average, some derived less benefit, and there were side effects that impacted quality of life.

In the same issue of the *Cleveland Clinic Journal of Medicine*, Jones and Klein also address the PSA problem.[3] They comment that during the first decade after PSA screening was approved, the "dogma" prevailed that the cut-off was 4.0 ng/dL. Patients below this level were reassured that all was OK—they did not have prostate cancer. Above this cut-off, the perceived risk generally prompted the recommendation of a biopsy. However, a number of recent studies have clarified this matter in a somewhat distressing manner. As Jones and Klein point out, there is no PSA level below which prostate cancer can be ruled out and no level above which prostate cancer is certain. Depending on other risk factors such as age, race, family history prostate size, percent free PSA, etc, men with identical PSA levels can have very different risks of prostate cancer. Also, if all other risk factors are the same, a man with a PSA of 3.9 will have essentially the same risk as one with a value of 4.1. Furthermore, they take the position that there is no PSA level; at which a biopsy is mandated and the decision should be based on a much broader assessment of risk. The characterization of patients as either normal or abnormal in this context makes no sense and yet laboratories around the world continue to promote this false division by printing a PSA reference ranges that use 4.0 as a cut-off.

Jones and Klein comment that the Cleveland Clinic Glickman Urological and Kidney Institute has now eliminated from their laboratory reports the 4.0 ng/dL value as the upper limit for normal and replaced it with a probability derived from large studies. This is reminiscent of the Framingham Risk Score philosophy. An online calculator has been developed that they believe will be useful not only to physicians but also to patients. It can be found at

http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp

But replacing a threshold approach with a probability approach simply admits that there is no either simple or satisfactory answer, aside from a 10 or more core biopsy, to the question, doctor do I have prostate cancer? A new era will dawn when there is a scanning protocol that will identify the presence, extent, size and exact location of prostate tumors, and while this is likely to happen eventually and perhaps sooner, it will still leave open the question of aggressiveness. Serial scans, however, if they are able to accomplish the above goals, would also presumably provide an answer to how aggressive the cancer is. To approach perfection, such a scan would also have a low or non-existent exposure to ionizing radiation (e.g. a MRI based protocol). For screening, the cost must be reasonable and the availability very high, two characteristics of the PSA test which may be hard to match with expensive, complex, high-tech machines, especially in jurisdictions where health care is rationed in order to control costs.

TRANS-FATTY ACIDS AND RISK OF PROSTATE CANCER

It is unlikely that any reader of this Newsletter is unaware of the adverse connection between *trans*-fat consumption and health. Recognition has reached federal and local government levels with unprecedented moves in the direction of making them illegal under certain circumstances. Those who have studied chemistry will recall that the *cis* and *trans* involve different geometrical arrangements around the carbon-carbon double bond. The *trans*-fatty acids are for the most part foreign molecules to human biochemistry and when incorporated into cell membranes have many adverse effects. Their origin as a significant component of human food was purely commercial—longer shelf life and the option of manufacturing a solid fat such as the classical margarine. They were in fact an inadvertent product of the hydrogenation process. Thus over a short period, people in the developed countries went from eating only traces of such molecules to embracing them in large amounts as part of what they were led to believe was a healthy diet, a view actively encouraged by practically any so-called health authority one cares to mention. After all, this was the ideal way to avoid saturated fats and margarine which, while high in *trans*-fats, was viewed as a heart-healthy butter substitute. The realization that this was all dangerous nonsense must have come a somewhat of a shock to those who had or have implicit faith in expert opinion.

A recent study from Harvard Medical School and Brigham and Woman's Hospital has examined the hypothesis that *trans*-fats are related to prostate cancer risk.[4] This hypothesis was in part based on studies indicating that the *trans*-fats increase systemic inflammation and insulin resistance, both of which may play a role in prostate carcinogenesis. These fatty acids also interfere with transcription genes that may be important in prostate cancer initiation and progression. They conducted a prospective case-control study nested within the Physicians' Health

Study. A 13-year follow-up was involved. It was found that blood levels of two *trans*-fatty acids were associated with an increased risk of non-aggressive prostate tumors. When the top and bottom quintiles of intake were compared, the relative risk was more than double for total *trans*-fatty acid intake and approximately double for each of the two acids that were implicated (oleic and linoleic). The authors point out that this type of tumor represents a large proportion of prostate cancer detected using PSA screening and that these finding may have implications for prostate cancer prevention.

CRYOABLATION VS. EXTERNAL BEAM RADIOTHERAPY

Cryoablation involves freezing the prostate and kills both normal and cancer cells. It was first introduced in the 1960s but was found to be associated with unacceptable complications. Improvements in the technique resulted in its reintroduction in 1998 and it has gained a considerable following. An introduction to this therapy is included in our book. A Canadian study has just reported on a randomized comparison between radiation (RT) and cryoablation therapy (CRYO). Patients in the study had biopsy confirmed disease, were clinically T2c or T3 (tumor involved both lobes or the tumor extended beyond the prostatic capsule), with a negative abdominal and pelvic CT scan, a negative bone scan, and a PSA of less than 25 ng/dL. Neoadjuvant (pre-treatment) hormone therapy was given to both groups followed by either CRYO or RT (dose of 68 Gy). This was followed by 3 additional months of hormone therapy. For the CRYO group, the treatment was repeated if a positive biopsy was found at 6, 12, 18, or 24 months. For the radiation group, salvage cryoablation was used if there was a positive biopsy at 24 months. The mean biochemical disease-free survival (based on PSA) was 41 months for the RT group and 28 months for the CRYO group. However, prostate cancer specific survival and overall survival were very similar for both groups and serious complications were uncommon in either group. Nevertheless, the authors conclude that the results of this prospective randomized trial indicate that CRYO was less favourable as compared to RT and is thus a suboptimal therapy for locally advanced prostate cancer.[5]

RISKS OF ANDROGEN DEPRIVATION THERAPY (ADT)

This therapy is also called hormone therapy. Readers wishing to acquire a background in this important and widely used therapy are referred to our book. Two recent studies emphasize that hormone therapy has serious side effects which must be balanced against the benefits derived in terms of prostate cancer control. One study found that newly diagnosed prostate cancer patients who received ADT for at least a year had a 20% higher risk of serious cardiovascular morbidity compared to men not receiving ADT. The researchers comment that this result has particular relevance to the decision to use ADT in men in settings in which the benefit has not been clearly established. For men with metastatic disease, they suggest that ADT be accompanied by aggressive efforts to reduce cardiac risk through diet, exercise or the use of lipid lowering drugs.[6] The second study concerned the risk of diabetes associated with ADT. The elevated risk associated with developing incident diabetes within one year was found to be 36% in men initiating ADT. This result was corrected for a number of potential confounding factors. The authors comment that this finding supports previous work that established a relationship between ADT and the metabolic syndrome.[7] Taken together, the results of these two studies clearly complicate the risk-benefit analysis regarding ADT. However, additional studies are needed to examine the importance of the duration of treatment since neoadjuvant and adjuvant treatment can be for relatively short term, but very long term when used to deal with recurrence.

RADICAL PROSTATECTOMY IN MEN OVER 70 YEARS OF AGE

Data on survival and recurrence after a radical prostatectomy (RP) in men ≥ 70 years of age has been limited due to the infrequency of such surgery and the long follow-up times required. A multicenter study has just reported which examined the effect of age on upgrading, upstaging and subsequent cancer control in men of this age group undergoing prostate surgery. This is an important subject due to the rapidly changing demographics. Between 2000 and 2050 it is expected that the number of men over 65 years will quadruple. In addition, life expectancy is expected to increase and there may be a decrease in the extent of comorbidities as more is learned about prevention of the major diseases that afflict that age group and more preventive measures are

adopted. In addition, > 70% of prostate cancer is diagnosed in men over 65. Also, prostate cancer is not a benign disease in the elderly. Albertsen et al in a study of over 750 men with localized prostate cancer treated expectantly or with hormone therapy showed that prostate cancer continued to cause significant mortality in men aged ≥ 70 and for those with Gleason scores of 6, 7 and 8-10, 32%, 40% and 60% respectively, died of prostate cancer.[8]

Richstone et al [9] have analysed data from a large series of men who had a RP, including over 250 who were of age ≥ 70. This allowed a comparison of the clinical and pathological features in older vs. younger men. They found that as a group, those ≥ 70 were more likely to be upstaged after surgery than the younger group, but the nomograms (Memorial Slone-Kettering nomograms—see our book) retained their validity. The upstaging did not affect cancer control. There was no difference in cancer specific survival in the older vs. the younger age groups (96% at 10 years) or PSA detected progression free probability (74% vs. 75%) at 10 years. This was in spite of the fact that men aged ≥ 70 tended to have cancers of higher clinical and pathological stage or grade. The authors conclude that with careful attention to patient selection the RP is a viable treatment option for men aged ≥ 70, but more research is need to address questions of morbidity and quality of life.

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