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This issue discusses a view of autism and its treatment that, while outside mainstream medicine, is being tried by physicians who apparently have considerable experience in this field. The new therapeutic paradigm is called the Biomedical approach. This is being featured in the Newsletter because of the belief that while most readers do not themselves have an autistic child, they probably know someone who does. This is certainly true of your editor and his wife. The results that are being obtained are dramatic, especially when compared to the dismal results achieved with brain-targeted drugs. The subject of the connection with vaccination is also briefly discussed.

The second subject this month involves the connection between night-shift work and breast cancer and the role of melatonin and our normal circadian hormone rhythms. The discussion includes some recent evidence in favour of the so-called melatonin cancer hypothesis, some interesting results regarding what shift workers might do to reduce the risk, and a surprising decision in Denmark to compensate selected women for work-related breast cancer.

Considerable space is devoted to the recent American Heart Association recommendation regarding omega-6 fatty acids. At attempt is made to sort out what appear to be the shortcoming of the recommendations and to recognize that the basic notion of a balance of omega-3 and omega-6 fatty acids may not be as important as having adequate omega-3 intake.

Also, there is more on vitamin D! This time the issue is cognitive impairment in those over 65. As each month goes by, it becomes more apparent that our human biochemistry, which probably was more or less fixed while our ancestors were running around half naked in the full sun, still has a strong dependence on a supply of vitamin D that cannot be provided by the combination of our modern lifestyle of indoor living and the impact of the dermatology community with their advice to avoid the sun at all costs. Furthermore, the popular notion of mainstream medicine that we get all the vitamins we need from food unfortunately does not hold for this particular vitamin. But the rumor has it that physicians who realize all of this are popping vitamin D pills in doses quite high.

Finally, some bad news for those who think the solution to their need for sweetened drinks lies in the chemicals that come out of factories.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

CAN AUTISM BE REVERSED OR CURED?

Autism is actually a spectrum of neurodevelopmental disorders without a clearly defined cause. This spectrum of disorders is characterized by a variety of neurobehavioral and neurological dysfunctions often occurring prior to age 36 months. Disorders include loss of eye contact, deficiencies in socialization, language dysfunction, abnormal mind function, and repetitive behaviours. The central mechanism that accounts for these disorders has not been proposed in the major scientific literature.[1] While most Newsletter readers do not have children with autism, they probably are acquainted with one or more families that do. As discussed in the last Newsletter, the incidence is rising dramatically and the question of what causes autism is still in the investigational stage with much debate and concern, especially among parents and would-be parents.

There are two ways of viewing autism. One, the conventional view, holds that it is a genetically determined brain-based disorder. That genetic propensity is involved is based in part on twin studies which suggest hereditability of over 90%.[1] The more recent view is that it is a reversible systemic disorder that is influenced by genetics and that affects the brain. These two are fundamentally different and which one is the working hypothesis profoundly influences the approach to treatment since the conventional view admits to few therapeutic approaches and leads to the opinion that autism is for the most part untreatable. The second view appears to be slowly revolutionizing the therapeutic approach this complex disorder. The new philosophy is that the broken brain of autism is due to a broken body and if one fixes the broken body, the brain can recover.[2] Obviously this profound paradigm shift has dramatically changed the therapeutic approach among those who believe it has merit. It also emphasizes the potential complexity of the problem of the primary cause since what is happening in the brain is secondary. Now accounts of success based on the new view are now beginning to appear in the peer-reviewed literature. This is called the *Biomedical* approach. Two recently published cases will be presented.

Case History No. 1. This case history was published by Dr. Mark A. Hyman, MD, editor of *Alternative Therapies in Health and Medicine* and presumably taken from his private practice.[2] Involved is a 2 ½ year old male just diagnosed with autism. The only aspect of his history prior to diagnosis that is mentioned is vaccination to guard against 13 disorders. The mother was told by the "best doctors" in a major city that there was nothing to do but minimally effective behavioural and occupational therapy and that she would keep her expectations low. A number of tests and clinical observations suggested impaired glutathione metabolism, impaired methylation in biochemistry that leads to folic acid, allergy to 28 foods, an indication of the leaky gut syndrome, profound digestive dysfunction, a wide range of suspected nutritional deficiencies, evidence of oxidative stress, and heavy metal toxicity and impaired detoxification. Treatment involved eliminating food sensitivities, treating small bowel overgrowth with a non-absorbable antibiotic, treating intestinal yeast with antifungals, and re-inoculating the gut with beneficial bacteria using a broad-spectrum probiotic and *S. boulardii.* Nutritional deficiencies were treated with a multivitamin, topical zinc, magnesium, methyl folate, and vitamin B6. In addition cod liver oil and vitamin D were given along with coenzyme Q-10. The detoxification and oxidative stress problem was treated with high dose B12 injections, topical glutathione, and chelating medication to remove mercury and lead. Ten months later he no longer qualified for the autism diagnosis.

Case History No. 2. This case history was presented by a board certified pediatrician and a board certified internist specializing in the care of children with neurodevelopmental disorders and autism.[3] The 3-year-old patient presented with a number of characteristics typical of autism. His history had a significant component of multiple toxic exposures. Like the child in case No. 1, he had chronic constipation, a hallmark of digestive dysfunction. Treatment extended over 6 months and involved treatment of the constipation with oral vitamin C and magnesium, a probiotic and antifungal medication, dietary restriction and diet that included only specific carbohydrates. At 6 months the specific carbohydrate diet, the probiotics, vitamin C and a bicarbonate alkalizing

supplement were continued and oil of oregano and *S. boulardii* were started as natural anti-yeast therapies. At one year he was no longer diagnosed as autistic and was continued on Vitamin C, cod liver oil, a multivitamin, a probiotic, an alkalinizing supplement and zinc, and a digestive enzyme that was specific for combating *Candida* organisms. At 2 years he was in a typical school and his mother was liberalizing his diet without observing regression, and he was taking *S. boulardii,* vitamin C and magnesium.

These two case histories have a number of interesting aspects. They represent a whole-body approach to treatment, an emphasis on non-pharmaceuticals, and the recognition of the non-brain origin of many of the symptoms of autism, and treating problems that appear to originate in the digestive system. But most of all, they worked! The contrast between this approach and the prognosis given to the mother in Case History No. 1 could not be more extreme. The physician involved in the treatment in Case History No. 1 appears to have engaged in a more extensive pre-treatment battery of tests, but the two treatment protocols have many similarities. An informative website with lists of practitioners who apparently treat autism with a biomedical approach is available along with much information and resources is the Defeat Autism Now website which can be found at www.autism.com/index.asp.

Dr. Mark Hyman, the author of the first case history asks the question "Is it possible to point to any one gene, biomarker or biological dysfunction, and say Aha!, this is the cause of autism and this is what we should treat?" His answer is an unequivocal no. None of the areas of dysfunction, he contends, is the cause of autism but all of them exist in varying degrees and patterns in each individual. He points to genetic predispositions, toxic environment and nutrient deficiency as insults which in the case of autism, are magnified by overuse of medications such as antibiotics and vaccination, which increase susceptibility to infections and promote allergy and autoimmunity. Thus in his view, autism is a complex, multi-system disorder rooted in toxic insults, infections, and allergic reactions. Incidentally, some of the toxic insults are now though to come from not only mercury, the traditional suspect, but from dietary excitotoxins such as monosodium glutamate, the Chinese food flavour enhancer, aspartame, fluoride, and aluminum, and mechanisms have very recently been proposed to describe how these individual chemicals act on the brain and the rest of the body to produce the autism spectrum of disorders.[1]

A final comment. In case history No. 1, cod liver oil was used. As was pointed out in a recent Newsletter, this can result in such high intakes of vitamin A that the benefits of vitamin D are destroyed.

VACCINE-AUTISM CONTROVERSY

In the above-cited article containing one of the case histories, Dr. Mark Hyman also comments on this issue. He points to studies that have linked the live measles virus from vaccination to the inflamed gut. If the immune system cannot manage the inactivated live virus, then it persists and produces low-grade inflammation both in the gut and brain. In a study he cites, 75 of 91 autistic patients with inflamed bowels had live measles virus in their intestinal tissues compared to 7 out of 70 controls. In addition, 95% of autistic children have intestinal problems and 90% have bowel inflammation on biopsy compared to 30% of controls. Also, he suggests that autistic children appear to be more susceptible to allergy and gut inflammation triggered by certain foods such as gluten and casein. The extreme inflammation of the guts of autistic children contributes, according to Hyman, to their inflamed brains. The connection between the residual inactivated but live measles virus in autistic children and the virus in vaccines was established by DNA analysis which excluded the wild types.

Dr, Hyman points out that autistic children have low levels of glutathione and because of this, have impaired ability to excrete metals. For example, autistic children have low levels of mercury in their hair but higher levels in their baby teeth. Chelation therapy causes the excretion of much more mercury and other metal than is found in normal children. He also comments critically on the recent study published in the New England Journal of Medicine that was accepted as proof that thimerosal (ethyl mercury) used as a preservative in vaccines had no link to autism. He points out that the study excluded all children with autism and ADHD, i.e. the children with genetic susceptibilities to heavy metal toxicity. They also did not measure total body burden, only exposure, and they ignored the genetic aspect of mercury detoxification. Also, the vaccine

manufactures employed or funded the authors of the study as well as the accompanying editorial. Finally, they did not explain why it could be safe for babies to receive over 187 micrograms of mercury by the time they were 6 months old and yet the safe level was 0.5 microgram at any one time. Thimerosal is still used in some vaccines given to children, including the flu vaccine. In fact, in the above study the children were followed for 7 years, but mercury intake was measured only for the first 6-7 months, after which all presumably underwent periodic flu vaccination which would should have rendered the whole group essentially equally exposed throughout most of the study. It is not surprising that no effect was seen.

Thus vaccines may play a role in autism, but the hypothesis that it is the causative agent is an oversimplification of a complex etiological problem and it is not surprising that epidemiological studies fail to consistently demonstrate a connection. For an interesting, recent and well-documented debate see http://www.thoughtfulhouse.org/pr/dr-ari-brown-response.pdf. The complexity of the question is illustrated by the 173 references cited in this debate.

DRUG TREATMENT FOR AUTISM—A DISMAL PICTURE

In sharp contrast to the biomedical therapy described above, the pharmacologic approach to the problem of autism does not appear to work. A recent review in the Journal of *Journal of* Pediatric *Health Care* reviews 20 recent studies involving 12 drugs.[4] Meta-analyses, randomized clinical trials, and prospective experimental studies of pharmacotherapy conducted in the U.S. over the past 10 years in children between 5 and 15 years were examined. The results indicted minimal success in treating core deficits across all drug classes. Core deficits involve impaired social interaction, impaired communication and interests and imagination, and restrictive, repetitive activities. Only moderate success was observed for the so-called associated behaviours such as hyperactivity, inattention, aggression and obsessive-compulsive disorders, sleep disorders and tics. Every drug had some adverse effects including weight gain, sedation, drowsiness, fatigue, dizziness, constipation, agitation, irritability, hyperactivity, insomnia, gastrointestinal symptoms, aggression, and behaviour reflecting a dull, sad and unhappy child.

This review confirms the commonly stated view that there is little conventional medicine has to offer if one thinks in terms of a drug intervention. In fact, the FDA has approved only one of the 12 drugs for the treatment of autism. Furthermore, the biggest challenge is treating the core deficits, and here pharmacologic therapy failed miserably. This simply underscores the importance of a new approach that stops regarding autism as “all in the head” and needing brain targeted drugs, and looks at the whole dysfunctional system. This is the approach of biomedical therapy discussed above.

MELATONIN, NIGHT-SHIFT WORK AND BREAST CANCER

Melatonin is a naturally occurring hormone found in most animals and humans. Its circulating levels vary over the 24-hour cycle and are important in regulating the circadian rhythms of several biological functions. Melatonin is mainly produced in the pineal gland located in the brain and the secretion is in part under the control of the light-dark cycle of day and night. Furthermore, the normal increase in secretion at night can be acutely suppressed by light exposure. The active wavelengths range from 420 to 520 nm (violet-blue to blue-green) with maximum suppression at 446-477 nm. Fluorescent lights have emission in the melatonin suppression range. Thus night-shift work has the potential for disrupting the circadian rhythm of melatonin secretion. After all, shift work and artificial lighting at night are very recent on the time scale of the evolution of our human biochemistry, light from wood fires or even candles is concentrated in the yellow orange and red regions of the visible spectrum, wavelengths that do not suppress melatonin, and genetic adaptation does not occur over short time periods. In humans, melatonin acts as an antioxidant, is involved in the immune system, and there is considerable literature dealing with its association with the incidence of various cancers and the treatment of cancer.[5] Epidemiological studies have found an association between night shift work and the incidence of breast cancer and colorectal cancer,[5] which has prompted

the "Melatonin Hypothesis" of cancer. A recent meta-analysis of eight observational studies of breast cancer risk and night work indicated a 40% enhanced risk which was similar to a meta-analysis of seven studies of flight attendants which found a 44% increased occupational risk. Of the fifteen studies included in these two meta-analyses only three failed to find a statistically significant effect, and this has been attributed to exposure misclassification.[6]

A just-published study, part of the Nurses' Health Study from Harvard, provides additional evidence for the Melatonin Hypothesis.[7] First-morning urine was collected from over 18,000 women between 2000 and 2002. A major metabolite of melatonin, 6-sulfatoxymelatonin (6sMT), was used as a marker of nocturnal melatonin secretion and levels. Some earlier studies had used a 24-hour urine sample which may not be as definitive. During the follow-up through May of 2006, 357 postmenopausal women developed incident breast cancer. Melatonin levels were compared with 533 matched controls. In an analysis that took into account confounding variables, when those in the highest quartile of 6sMT were compared to those in the lowest quartile, a statistically significant 38% risk reduction was found, i.e. enhanced risk was associated with low nocturnal levels of melatonin. No modification of risk by hormone receptor status, age, body mass index or smoking status was found. This study also found that circulating melatonin may be more strongly related to *in situ* rather than invasive cancers.

The authors compare these results with a study reported in 2005 based on the Nurses' Health Study II where first morning urine levels of 6sMT was associated with a 41% lower risk of breast cancer in premenopausal women when the top vs. bottom quartiles were compared, and with a very recent study which used 6sMT levels a 12-hour overnight urine sample and found a 44% risk reduction in postmenopausal women in a similar comparison. A third prospective study which used 24-hour urine specimens found no association which raised questions regarding how appropriate the 24-hour sample was in capturing the nocturnal peak in melatonin secretion.

An interesting development has just occurred that relates to this subject. The Danish government has compensated 38 women through their employer's insurance schemes for breast cancer the recipients claimed was associated with night shift work. They had worked a night shift pattern for at least 20 years but were otherwise judged at low risk for the disease. The Danish decision was based on a ruling by the International Agency for Research in Cancer, part of the World Health Organization, which placed night shift work just below the highest cancer risk category, even though the group involved in the ranking admitted that the evidence was subject to confounding, inconsistent definitions, and in some cases focused on a single profession.[8] In a commentary from the BBC (March 15) it was pointed out that about 20% of the national work force in the UK is involved in night shifts. This decision by Denmark is thought to have the potential for stimulating considerable worldwide demand for compensation.

Nocturnal levels of melatonin can be suppressed by light which points to the potential significance of sleeping in a totally dark room. If light is needed at night it should be yellow or red since this minimizes or eliminates the melatonin secretion suppression. Night shift work presents a more difficult problem. Advice commonly seen is wear dark glasses on the commute home in the morning and sleep in a totally dark room. Bright light exposure at work has also been suggested mimic daytime.

A novel solution for shift workers is to wear glasses at work that block the spectral region associated with melatonin suppression (mostly the violet and blue regions). Interesting results associated with this approach have been reported in a 2009 press release by Mount Sinai Hospital in Toronto, Ontario, which is available on their website. Dr. Robert Casper has been leading a research study aimed at developing and testing suitably tinted glasses which are coated with a filter to eliminate the active spectral region. He had already demonstrated that selective filtering of blue light (450-480 nm) attenuates the disruptive effects of nocturnal light on circadian phase markers in rodents.[9] The glasses have a yellowish tint. The researchers tested their glasses on 13 participants who wore them under simulated night shift working conditions. It was found that the tinted glasses prevented hormone disruptions and improved alertness, performance and mood during simulated shift work. Actual data on melatonin levels do not appear to have been published as yet. Dr. Casper was quoted in a report in the Toronto Globe and Mail (January 9, 2009) as indicating that while those wearing the glasses initially see things with a slight yellowish hue, they quickly become accustomed to them and may even find an increased contrast at night. This research group is planning studies of both autoworkers and nurses. Endpoints include alertness and mood and

whether or not the glasses will ease the transition to normal nighttime sleeping during weekends or when there is a change to day work. An anecdotal report from a shift-worker quoted in the Globe and Mail story provided strong endorsement. All her coworkers now want the glasses. Studies to determine if these glasses decrease the risk of breast cancer may have to depend on melatonin levels as a surrogate endpoint since actual intervention studies, if ever done, would require a long follow-up. Also, melatonin cannot be patented so probably if a clinical trial is done, it will require government or private funding.

Melatonin as a supplement has been available for a number of years and has been popular for dealing with jet lag and sleep disorders. Its potential in cancer prevention and treatment are areas of active research. So far, research in its use in cancer prevention and treatment has concentrated on mechanistic studies and studies such as described above rather than interventional studies where melatonin was administered.[5]

OMEGA-6 FATS AND RISK OF CARDIOVASCULAR DISEASE. AMERICAN HEART ASSOCIATION TAKES A POSITION

Omega-6 (n-6) polyunsaturated fatty acids (PUFAs) are common in our diet and occur in cooking oils, prepared foods and nuts. The level of n-6 fats in our diet is vastly in excess of what it was tens of thousands of years ago when the present genetic makeup which determines our biochemistry was more or less set. The ratio of dietary omega-6 to omega-3 dietary fatty acids for Paleolithic humans has been estimated at about 1 to 1 whereas it is now about 18-20 to 1. One popular theory is that n-6 PUFAs are inflammatory and n-3 PUFAs are anti-inflammatory and this has encouraged the recommendation frequently heard that one should decrease the intake of n-6 containing foods. This turns out to be a rather large oversimplification and there is growing evidence that the n-6 PUFAs may have beneficial aspects, in particular in the context of coronary heart disease (CHD). The evidence for this has now been more or less assembled by the authors of an American Heart Association Science Advisory just published in the journal *Circulation.*[10] The lead author, incidentally, has significant financial connections with Monsanto, and a less significant relationship with Unilever. Both companies are involved in various aspects of the editable oil business including oils which are good sources of n-6 PUFAs.

The AHA suggests that to reduce the risk of CHD, intakes of n-6 PUFAs of at least 5% to 10% of total energy are indicated and that these intakes appear safe. The arguments and evidence in favour of their position are based on the following assertions and interpretation of the literature

- The principal source of n-6 PUFAs is linoleic acid (LA). There is little evidence to support the contention that LA is net proinflammatory or pro atherogenic.
- Increasing n-6 PUFAs at the expense of carbohydrate or saturated fat reduces CHD risk as judged by changes in markers such as LDL, HDL and triglycerides and may improve insulin sensitivity. However, the authors admit that not all studies agree with this assertion.
- Benefits with regard to CHD events resulting from high levels of n-6 PUFAs are seen in observational studies such as case-control and prospective cohort studies. However, the authors indicate that many of the studies have serious faults and in addition, the results overall are inconsistent with some showing benefit, some none.
- Randomized controlled intervention trials are presented as evidence. These involved substituting saturated fats with PUFAs. While a reduction in CHD risk was found in some studies, in others none was found.

If one looks carefully at the evidence cited for the absence of inflammatory effects, one of the studies is not really relevant since the population had very low LA levels and was not representative of North American populations. The study group was from a small area in Tuscany, Italy, with a lower intake of n-6 PUFAs than even the rest of Italy. In addition, the results support the contention that it is the balance between n-3 and n-6 fatty acids that is important.[11] The second study cited also examined the joint effects of n-3 and n-6 PUFAs rather than LA in isolation.[12] The AHA authors state that higher n-6 consumption was associated with unaltered or lowered levels of inflammatory markers. This is not an accurate description of the results in the cited

paper. In fact, when the n-3 status was low, as it is in many North Americans, increasing LA caused two forms of tumor necrosis factor (TNF), an inflammation marker, to increase when LA intake of 3.4% of total energy was increased to 6.2%. It was only when both the n-3 and the n-6 status were high that the TNF markers were low and LA showed anti-inflammatory behaviour. In fact, the authors of the inflammation study state explicitly that "…at low levels of n-3 fatty acid intake, n-6 fatty acids are associated with high levels of inflammatory markers…" Thus the evidence provided by the AHA advisory is misleading since they fail to mention the strong and important connection between inflammation caused by LA and the n-3 PUFA status. From reading the advisory, one would never guess that this was a critical and strongly related aspect. How many physicians who read *Circulation* actually examine the key citations to see if the whole story is being told? The number is probably very small, and yet the history of guidelines and advisories is replete with examples of the whole story not being told. Extreme examples include guidelines giving citations that have no relevance at all to the proposals being promoted.[13]

The evidence presented which is based on observational and randomized studies appears weak and inconsistent and suffers, as do many dietary studies, from uncertainties associated with substitution where two or more variables are changed at the same time and it becomes arbitrary to assign the benefit to only of the changes. While arguments can and are be made that one of the changes was the important one, to convert this to a quantitative result is open to serious questions. To replace dietary saturated fat with PUFAs and see positive results from some marker or clinical endpoint can then be interpreted as (a) saturated fat is bad or (b) PUFAs are good or (c) both statements are true or (d) neither statement is true because something else changed which caused the benefit. This provides the opportunity to select a result that agrees with a preconceived notion.

The AHA advisory states that in the US, LA consumption currently averages about 15 g/day which in terms of percentage of total energy would be 6.7% of a 2000-calorie (kcal actually) diet. Thus Americans are already in the middle of the recommended beneficial range and many are at the upper end. The message from the AHA is that 10% would be good and an even higher intake might be beneficial. At an LA intake of 10% of total energy, if one has a low intake of n-3 PUFAs, this would be highly inflammatory and might have consequences in other areas of disease, a subject not discussed in the advisory. In fact, it seems that the greatest problem with the advisory is in fact that it almost completely ignores the role n-3 PUFAs in inflammation and CHD risk. Based on the current n-6 status quoted above, it would appear in fact that the n-3 status is a much more pressing and urgent problem. That such an important point was not emphasized in the AHA advisory is surprising. In fact the last AHA advisory on n-3s was in 2002 and in the current advisory this is cited, but the important role of n-3s and in particular the long chain EPA and DHA was underplayed. However, the AHA guidelines of 2006 did recommend two servings of fish per week.

This matter has been the subject to two commentaries, one by Walter Willett in 2008[14] and by Frank Hu in 2001[15], both from Harvard School of Public Health. Both are consistent with the position taken by the AHA that decreasing n-6 intake to improve the n-6/n-3 ratio may not be beneficial and might be harmful. But they make it clear that one must consider both the n-3 and n-6 intake, both must be adequate, and to look at the ratio is more or less meaningless and instead it is the absolute amounts of these two classes of fatty acid in the diet that are important.

The AHA advisory also suggests that increasing n-6 intake has no risk. While this may be true in the context of CHD, perhaps readers should have been cautioned that there may be exceptions in the area of other diseases. For example, women with a certain genetic makeup appear to have a n-6 related increased risk for breast cancer.[16] While this particular genetic makeup did not in itself increase the risk, there was a significant interaction between breast cancer risk and dietary LA with > 17.4 grams per day almost doubling the risk. That intake of LA is close to the U.S. national average. While the number at risk may be small, the point is that human biochemistry and disease is a complex matter and the possibility of problems outside the main focus of the recommendations should be recognized.

Additional problems with the AHA advisory include the failure to stratify their target, cardiovascular disease, into the incidence and progression of atherosclerosis, sudden cardiac death, acute cardiac problems such as a heart attack which is survived at least long enough so it is not considered a sudden cardiac death, etc. The impact of the n-3 and n-6 fatty acids on these various aspects are at the heart of the prevention question, and may well

be different for the different scenarios enumerated. This is certainly true for sudden cardiac death where the long-chain n-3 fatty acids appear to play a key role—probably a reason many cardiologists are now taking fish oil themselves. Furthermore, arguments made regarding the impact of n-6 fatty acids on cholesterol markers ignore the absence of correlation between serum cholesterol or LDL and the extent of coronary calcium or even total plaque burden, important if not major aspects of cardiovascular disease in the primary prevention setting. This was discussed last month in a Research Review.

It is unlikely that many individuals eating the modern Western diet are deficient in n-6 PUFAs. Common sources include poultry, eggs, cereals, whole-grain bread, baked goods, nuts, salad dressing and most vegetable oil. But the deficiency of n-3 PUFAs appears widespread. The best source is oily fish. Many people hate fish. The amount of n-3s in meat depends on what the cattle or fowl are fed, and the modern agricultural methods do not favour high n-3 PUFAs in animal food. The same applies to eggs, although some of which are advertised as omega-3 eggs have enhanced n-3 content. An important point with regard to the n-3 class of fats is that those derived from plants such as flax, from meat or from omega-3 eggs contain alpha-linolenic acid (ALA) whereas fish contain n-3 fatty acids where the chain length of the molecule has been extended (EPA and DHA for example). These are considered the important n-3s. The efficiency with which ALA is converted to the long-chain n-3 fatty acids is low. There is a huge variation in the n-3 content of fish with the oily fish such as salmon, herring, mackerel, lake trout and tuna having relatively high values, and perch, walleye, halibut, grouper, haddock and cod for example contain much lower levels. One has to eat three times the amount of halibut and six time as much perch to get the same amount of n-3 fatty acids as is in the equivalent weight of salmon. Fish oil capsules are widely available which provide in 2 or 3 capsules an amount of EPA and DHA considered desirable (combined, 1-1.5 g/day). Mainstream medicine recommends eating at least 2 serving of fish per day but this only makes sense in this context if it is fish rich in n-3 PUFAs.

VITAMIN D AND COGNITIVE IMPAIRMENT

The aim of this study was to examine the association between vitamin D status as measured by 25-hydroxyvitamin D (25(OH)D) levels and the presence of cognitive impairment in a large population- based sample of elderly adults, living independently and in institutions who were 65 years of age or older.[17] A total of 1766 individuals participated (708 men and 1058 women) who were evaluated for cognitive status and had valid serum 25(OH)D data. Cognitive impairment was quantified by a mental test score. The risk of cognitive impairment increased as the vitamin D status decreased. The ranges of the four 25(OH)D quartiles were 8-30, 31-44, 45-65 and 66-170 nmol/L (to get ng/mL, divide by 2.5). Compared to the highest quartile, the increased risk of cognitive impairment was 10%, 40% and 130% for decreasing quartiles, respectively. These results were adjusted for age, gender, education, ethnicity, season of testing, and additional risk factors for cognitive impairment. This study underscores the importance of having a high vitamin D status. According to the vitamin D experts, a good level to aim for is to be above 125 nmol/L (50 mg/dL). According to the newsletter of the Vitamin D Council, it is important to be aware that sometimes the wrong vitamin D test is ordered. It is for 1,25-dihydroxyvitamin D and does not directly indicate the 25(OH)D levels. Readers are encouraged to ask for copies of the lab reports and check the test and the units and judge for themselves if they are deficient.

DIET SODA, DIABETES AND METABOLIC SYNDROME. SURPRISING RESULTS

A study by Nettleton *et al*[18] just published online in the journal *Diabetes Care* has found that diet soda is positively associated with the risk of developing type 2 diabetes and selected components of the metabolic syndrome (MBS). This was part of the MESA study and involved almost 7000 individuals with a baseline examination in 2000-2002 and three follow-up examinations ending in 2005-2007. Dietary intake was determined by questionnaire. Daily consumers of diet soda had a 67% elevated risk of type 2 diabetes compared with non-consumers when the data were adjusted for

demographics and lifestyle factors. Adjustment for other dietary factors did not change the results, and adjustment for waist circumference and/or body mass index, the risk was only slightly attenuated and remained statistically significant. Consumers of diet soda also had an enhanced risk of MBS of 36% compared to non-consumers, and while adjustment for other dietary factors did not change the results, taking into account baseline measures of adiposity (waist circumference and/or BMI) rendered the association insignificant. Also, adjustment for the change in adiposity between baseline and exam 4 strongly attenuated the association between diet soda and MBS. In sharp contrast, the data showed no significant associations between sugar-sweetened soda and the risk of either MBS or type 2 diabetes.

These results appear counterintuitive. This appears to be the first prospective study that examined the association of diet beverages and type 2 diabetes. However, it is consistent with two recent studies which, while not focused on the question of diet soda drinks, also found an association between developing MBS and these beverages.[19, 20] However, only one of these studies also found no association with sugar-sweetened beverages[20] with the other finding enhanced risk of MBS with both classes of beverage.[19] The authors considered several explanations such as changes in body weight and composition, the possibility that diet soda could be a marker for unhealthy lifestyle and/or a dietary pattern that is associated with metabolic dysfunction, or a direct impact of the artificial sweetener on biological processes related to insulin resistance, glucose regulation and adiposity. The results of the adjustment to the data described above for body weight or fat distribution indicate that these factors do not mediate the association between diet drinks and type 2 diabetes but that the impact of these confounders on the risk of components of the MBS suggest that the adverse effect of diet soda in this context may be mediated by changes by adiposity and fasting glucose, i.e. prediabetic or diabetic conditions that comprise part of the MBS.

Attempts to explain the results by examining diet patterns revealed that diet soda consumption was associated with protective behavioral patterns and if it was possible to fully correct for these protective factors the result would be to make the adverse effect on metabolic dysfunction greater, not explain it. The question of the impact of specific sweeteners could not be addressed since several sweeteners were involved and they changed during the follow-up. However, it has been found that there is a correlation between drinking diet soda and glucose control in adults with diabetes, but this could easily be the result of confounding.[21] Thus the explanation for the results of Nettleton et *al* remain obscure and will no doubt motivate additional research, especially considering the popularity of artificially sweetened beverages.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 19	MAY 2009	3rd YEAR

This issue features some new research regarding both the screening for prostate cancer and its diagnosis by ultrasound guided needle biopsy. The debate on the merits of PSA screening goes on and on. The reason seems simple. There does not appear to be a solution based on any PSA measurement protocol that provides one with more than a nearly useless probability of having the disease. The problem involves the large number of false positives and false negatives.

On the diagnostic front, the gold standard is the ultrasound-guided needle biopsy. The fact that this procedure misses a significant number of cancers is contrary to what is implied on TV ads where we are told that "only your doctor can tell if you have a more serious problem such as prostate cancer." While this is true, what they don't tell one is that you will need a biopsy, which some find quite unpleasant, but that it will not provide a definitive answer. If the suspicion is high that cancer is present, it is frequently suggested that if the first biopsy is negative, a second is indicated. In this issue we look at a new study that still found cancer after 4 negative biopsies.

Finally, one of your editor's favourite topics, the risk of cancer associated with high doses of folic acid, is discussed in the context of prostate cancer. It is hoped that this discussion will motivate label reading and some simple arithmetic since it seems clear that many individuals may have folic acid intakes that put them at considerable risk. The differences between the synthetic chemical folic acid and its close cousin dietary folate provide a good example of why whenever possible, micronutrients should be obtained from food or bio-identical compounds in supplements rather than from unnatural synthetic chemicals.

Wishing you continuing good health,

William R. Ware, PhD, Editor

DEBATE OVER PSA SCREENING—SOME NEW RESULTS

The use of serum levels of prostate-specific antigen (PSA) was introduced in the late 1980s as a screening tool viewed as providing an indication of the presence of prostate cancer. However, its ability to do this is widely misunderstood. If one watches TV ads for drugs which are contraindicated if prostate cancer is present, the statement is generally made that "only your physician can determine if you have prostate cancer." This is true, but what the listener does not realize is that the only way to accomplish this with a reasonable level of certainty is with a biopsy involving generally more than 6 cores obtained by firing hollow needles through the rectal wall into the prostate under ultrasonic guidance, hopefully with local anaesthetic. The morbidity, while low, is not zero and up to 25% of biopsies come up negative when cancer is in fact present. Nevertheless, the first step the physician will take is to suggest a total PSA test. But the interpretation of the number that comes back from the lab must be based on probabilities since the distressing fact appears to be that 17% of patients with a PSA level of 1-2 ng/mL and 24% of those with levels from 2-3 ng/mL have biopsy proven prostate cancer, and these numbers may be low. For men with PSA between 2.5 and 4.0, the two popular cut-offs for triggering a biopsy, the cancer rate is approximately 20%. Furthermore, for a man with a PSA between 4 and 10 ng/mL, 60% will have a negative biopsy. In large populations, the median PSA levels for men in their 40s, 50s, 60, and 70s are 0.7, 0.9, 1.3 and 1.7 ng/mL, respectively.

PSA levels depend on a number of factors other than prostate cancer including the extent of benign prostatic hyperplasia (BPH—enlarged prostate), and inflammation due to prostatitis. High body mass can cause a deceptively low value. Thus there arises a significant problem of setting the cut-off for recommending a biopsy on the basis of a PSA test. By lowering the cut-off more cancers will be detected, but more unnecessary biopsies will be performed. Thus cut-offs are arbitrary.

In spite of these shortcomings, the American Cancer Society and the American Urological Association recommend annual screening beginning in the 40s for high risk and in the 50s for average risk men. In contrast, the U.S. Preventive Services Task force states that the risk to benefit balance cannot be determined for men younger than 75, i.e. there is no evidence of net benefit. For those over 75 years, they take the position that harms outweigh benefits.[1] The Task Force position has been criticized for being based on a set of studies, some of which were deemed of poor quality, but that seems to be what the Task Force is saying. With regard to the issue of age, the American Cancer Society takes the position that screening is appropriate for men with at least a 10-year life expectancy. But determining life expectancy for any given individual is a challenging and non-trivial undertaking subject to large uncertainties. Nevertheless, in the U.S. most men over the age of 50 have had a PSA test. Moreover, about 95% of male urologists and 78% of primary care physicians over the age of 50 report having had the test themselves. It is encouraging that they practice what they preach and some may well be influenced by the fact that death rates from prostate cancer have fallen about 4% per year since 1992, five years after the introduction of PSA testing. Nevertheless, for men older than 50 years, the lifetime risk of death from prostate cancer is only 3% and the median age at death is 80. This should be compared with estimates of prevalence, including insignificant tumors, which is 40% a 40 year old man and 80% for someone 80. Thus the common summary view that most men die with, not from prostate cancer.

The debate over the use of the PSA test for prostate cancer screening just will not go away. Opinions range from viewing the test as useless in the context of screening to being an essential feature of preventive medicine. But in some jurisdictions, where presumably the negative view is held by authorities, the cost is not covered. The reason opinion is divided is simply due to the weight one gives the one hand perceived benefits such as early detection, better prognosis, lower prostate cancer mortality, and on the other hand the perceived negative factors such as overtreatment, morbidity of unnecessary diagnosis and treatment, and anxiety associated with elevated values. One school of thought maintains that for screening to make sense, it must impact prostate cancer specific mortality. Screening results in more biopsies and more treatment and theoretically should decrease prostate cancer mortality. Two studies have just reported in the *New England Journal of Medicine* which can be viewed as merely confusing the issue.

The first study,[2] the PLCO cancer screening trial, randomly assigned over 38,000 men age 55-74 to screening or usual care. They were offered annual PSA tests for 6 years and a digital rectal exam for 4 years. The control was usual care, but as was expected, some controls also received screening. The quaint term for this is contamination. This study had high compliance in the screening group but rates of screening in the control group increased from 40% in the first year to 52% in the sixth year. After 7 to 10 years of follow-up, death from prostate

cancer was very low and did not differ significantly between the screened and control groups. The issues addressed by the study were further confused by the fact that 44% of the men in each study group had had one or more PSA tests by the beginning of the study. The reader is left to decide the extent to which this represented a definitive examination of the target question and even merited publication.

The second study was multicenter, based in Europe and involved over 182,000 men who were randomized into the screening and control groups with over 162,000 in the age group 55-69.[3] In contrast to the above study, the screened group was offered a PSA test once every 4 years. In the methods section of the report it is revealed the cut-offs for advising a biopsy varied substantially from center to center and country-to-country. In addition, not all centers adhered to the once in 4 years protocol which ranged from every other year to every 7 years. The biopsy procedures also varied from center to center with differences which could well influence the percentage of actual cancers detected. Treatment also depended on local policies and guidelines. No mention is made of actual attempts to ascertain contamination in the control group, nor was there any mention of the number of individuals with prior screening. The prostate cancer specific mortality rate ratio for all subjects 50 to 75 years of age represented a 15% benefit from screening but the result was not statistically significant. Stratification by age produced no significant differences between the control and screening group. When the calculations were restricted to the age range of 55 to 69, a 20% benefit was found which achieved statistical significance. This will be taken by many as proof that screening is beneficial. Some will view the results as meaningless.

In a roundtable perspective on these trials published in the same issue,[4] it was pointed out by Dr. McNaughton-Collins that there were serious limitation to the European study: (a) it was not a uniform trial but combined results that used different protocols; (b) the paper was only an interim report and the mortality reduction only marginally statistically significant; (c) the number of individuals needed to screen to prevent one prostate cancer death was 1400. She also commented that once it becomes possible to differentiate between indolent cancers that do not need treatment from aggressive cancer that does, the screening controversy will diminish.

Another study, also just published, deals specifically with the issue at what age should PSA testing be stopped.[5] This study was based on a long-term data from the Baltimore Longitudinal Study of Aging. The investigators identified 727 subjects with no cancer diagnosis and 122 diagnosed with cancer, some of which were considered to have high-risk disease. The objective was to evaluate the relationship between PSA and the risk of aggressive prostate cancer developing in men of various ages. It was found that no participants between 78 and 80 years old with a PSA < 3.0 ng/mL died from prostate cancer, whereas men of all ages with a PSA > 3.0 ng/mL had a continually increasing probability of death from prostate cancer. The time to death or diagnosis of aggressive cancer after age 75 years was not significantly different for ranges 3 to 3.9 and 4 to 9.9 ng/mL. However, the time to death or diagnosis of high-risk prostate cancer was significantly longer for those with PSA < 3 vs. ≥ 3 ng/mL. This led the investigators to conclude that for men aged 75 to 80 years, a cut-off of < 3 ng/mL identified men unlikely to die or experience aggressive prostate cancer during their remaining lifetime. It was suggested that the results of this study should help to inform regarding the age at which PSA screening might safely be discontinued. But the conclusion implies that screening should be continued for those with PSA over 3 ng/mL. This of course is contrary to the Task Force recommendation. In editorial comments at the end of the article, Albertson points out that the Scandinavian Prostate Cancer Group-4 trial found no survival benefit associated with radical prostatectomy after age 65. Furthermore, it has been estimated that for men 75 years of age, prostate cancer is overdiagnosed 56% of the time. Thus while screening may prevent a few deaths in patients older than 75, this comes with an enormous cost in testing and treatment.

The debate will for sure continue with more studies reporting. However, as Dubben points out in a perspective on screening trials,[6] the problems encountered in the two mortality trials suggest that to get a more definitive answer regarding the issues involved, methodologically valid mega-trials of long duration would be required and the evidence acquired would be out of date by the time it was available. This seems like a very important point, given that the real problem here involves the inadequacy of the PSA test itself and this has stimulated considerable research to find a practical alternative that is really prostate cancer specific. It is more likely than not that this research will sooner or later result in a new test long before meaningful long-term mega-trials can be organized, financed and executed.

One example of the new generation of prostate cancer diagnostic tools is the *prostate cancer gene 3* (PCA3). A urine test after a digital rectal examination, based on this gene and its messenger RNA, Is currently attracting

considerable interest. There seems little doubt that it results in an improvement in detecting prostate cancer and minimizing unnecessary biopsies. Nevertheless when on looks at the improvement in its ability to detect existing disease and identify individuals who are free from the disease, the improvements offered by PCA3 appear marginal if one is trying to achieve a major impact on the problems posed by the poor performance of PSA.[7] This test was discussed in our book *The Prostate and Its Problems.* Earlier studies appeared more promising than the one cited.

MULTIPLE BIOPSIES EXPOSE LIMITATIONS OF PROCEDURE

The biopsy procedure can be likened to trying to answer the question—does this blueberry muffin really contain blueberries? The muffin is wrapped in opaque plastic and one proceeds probe with hollow needles looking for blueberry pulp in the cores. The probability of getting a positive answer when there are in fact blueberries present depends upon the number of needles used or the number of cores taken, the number of blueberries and their distribution and size. In the case of prostate biopsies, only a limited number of needles are used, typically 6 to 18, and zones which statistically are favored for tumors are given more attention.

It is not uncommon that an individual will be considered at high risk, for example with a persistent elevated PSA, and yet the first biopsy is negative. A recent single center study from Spain[8] examined the yield of positive cancer diagnosis with a third, fourth and fifth biopsy on patients who came up negative after two. Indications for performing a biopsy on this subgroup included persistent elevated PSA (>4.0 ng/mL, persistent suspicious DRE, PSA velocity > 0.75 ng/mL/year, or the finding of precancerous pathology in prior biopsy. The results are interesting. On the third biopsy 15 cancers were found in 61 patients. The fourth biopsy found 5 cancers in 14 patients, and the fifth found 1 cancer in 2 patients. The classical six-needle biopsy was used on 25 patients and an extended 18-needle protocol was used for the balance. Thus out of 61 patients undergoing 3 to 5 biopsies, 21 were diagnosed with prostate cancer (34%). In other words, this group of 61 patients had had two negative biopsies and for those went on to have additional biopsies, over a third had prostate cancer. For those who went on to have a radical prostatectomy, examination of the prostate revealed that all had clinically significant disease. The authors comment that performance of the third, fourth and fifth biopsies were in fact unnecessary in retrospect in 29% of the patients, based on a Gleason score of ≤ 5 observed at biopsy. The patients undergoing the third biopsy had a range of PSA from 5.2 to 120 ng/mL. A suspicious DRE suggested the presence of only 4 out of 15 cases where tumors were found.

A limitation with this study is that not all those with a negative first biopsy went on to have additional procedures until either cancer is detected or four or five have been performed. In this study, out of 2457 first biopsies, 810 were positive but of the remaining 1647, only 306 went on to the second biopsy which incidentally had a 29% yield of positive diagnosis. Those encouraged having repeat biopsies presented with risk patterns suggesting that cancer had been missed. This pattern repeated with the majority of individuals having negative results not having additional biopsies. On the third round, only 61 out of 220 had biopsies, with 15 positive results. For the fourth round, only 14 out 146 had biopsies, with 5 positive results, and finally in the fifth round, only 2 had biopsies with one positive result. No information was provided on the prevalence of strong indications in those with a negative biopsy at each stage in the series. Nevertheless, the results are suggestive of large numbers of cancers being missed even in repeat biopsies. As discussed in our book, *The Prostate and Its Problems*, the design of this study is quite different from a study reported in 2001, where all participants had agreed to up to 4 biopsies if no cancer was found after the first.[9] The first biopsy yielded 22% positives, the second 10%, the third 5% and the fourth 4%. This study used an 8-needle protocol. Thus in the Spanish study, presumably there was some selection for high-risk candidates for each additional biopsy since they found much higher percentages of positive results.

Presumably, when a patient is told that his first biopsy is negative, he is also told that while it is unlikely that he has cancer, the probability is still significant. When a second biopsy is suggested, it is because there are clinical indications that there is a high probability cancer is present, frequently because of a persistently elevated PSA. It is nevertheless interesting that it can be missed in multiple biopsies. Thus what is held up as the gold standard in prostate cancer diagnosis is not quite 24 caret. We all, including the urology community, eagerly await both screening and diagnosis protocols that come closer to perfection. What is unfortunate is that so many individuals think that perfection has already been attained,

FOLIC ACID AND RISK OF PROSTATE CANCER

A recent study has found that there may be an enhanced risk of prostate cancer associated with folic acid supplementation.[10] This was a so-called secondary study associated with the Aspirin/Folate Polyp Prevention Study, which involved the prevention of colorectal cancer. During this study it was possible to follow a cohort for a median of almost 11 years while they were randomized to either a placebo or 1 mg/day of folic acid. Folic acid is a synthetic chemical used in supplements and must be distinguished from natural folate that occurs in food. While folic acid is more bioavailable, only a fraction of a dose such as 1 mg is metabolized, the balanced circulating as unmetabolized folic acid. The amount taken as a supplement must be added to that obtained from food fortification which also employed the synthetic chemical. The intake from fortified food can be substantial if heavily fortified foods are regularly featured in a diet. Taking extra strength B vitamins provides a large dose, and large amounts of folic acid are even hidden in some sublingual B12 preparations. In this study, the secondary endpoint was diagnosed prostate cancer. Folic acid supplementation used in the study was associated with a 2.6 fold increase in the risk of developing prostate cancer as compared to the placebo group. There was a suggestion that dietary folate was protective, but the results were not statistically significant.

These results are quite similar to those found in the colorectal cancer study where 1 mg/day of supplemental folic acid was associated with an elevated risk of having 3 or more new adenomas when the comparison was with the placebo group, and that result was consistent with observational studies where adenoma risk was inversely associated with folate levels only among individuals not taking multivitamins. In fact, the colorectal cancer study suggested that dietary folate was protective but that high levels of folic acid enhanced the progression of established cancer, i.e. a dual effect. The enhanced risk has also been seen in breast cancer where intake of folic acid ≥ 400 micrograms/day was associated with a 20% increase in risk. In addition, high doses of folic acid have been associated with advanced and fatal prostate cancer in men reporting multivitamin use of greater than 7 times per week. These adverse aspects of folic acid supplementation have been recently reviewed.[11,12]

The so-called B-50 high potency vitamin B supplement contains 1 mg/pill. North American multivitamins typically contain 400 micrograms of folic acid per pill. But high potency multivitamins will contain more, and common doses run around 800 mg if one follows the suggested intake. Food fortification, government mandated in some countries including the U.S. for the purpose of reducing birth defects was expected to provide 100-200 micrograms of folic acid but it now appears that the intake may be considerably higher. Fortified breakfast cereals contain 400 micrograms per serving, as do fortified drinks and nutritional bars. Thus just from fortified food and multivitamins it is easily possible to have an intake of 1200 to 1500 micrograms which exceeds the supplement dose used in the trial.

In 1997 it was already pointed out in the peer review literature that there was a problem with unmetabolized folic acid. This was in the context of breast cancer risk. But it has only been in the last few years that one is starting to see this pointed out in connection with a potential mechanism for folic acid mediated elevated cancer risk. This is partly due to the research connecting unmetabolized folic acid with a decrease in natural killer cell activity. This suppression could adversely impact natural cancer cell surveillance which is part of job of the immune system and could lead to higher incidences of tumor initiation. It is of interest that a number of studies directed at reducing homocysteine levels have in fact employed up to 5 mg/day of folic acid over extended periods, incidentally with no effect whatsoever on the risk of cardiovascular incidents. Such a high level of folic acid intake would produce large concentrations of circulating unmetabolized folic acid. And the interest in food fortification grows internationally. There is the potential here for providing benefit for a small number of individuals but increasing the risk of disease in a large number. This seems like a beautiful example of the risks associated with eating modified micronutrients which are not identical to those occurring naturally. The metabolism of folic acid is in fact different from naturally occurring folate. The message seems clear, not only from this example but from a number of others, that it is a good idea to eat man-made chemicals only when the reward and need appear very large. Fighting a severe infection with an antibiotic appears to be a good example. Our knowledge of human biochemistry and microbiology is large and growing, but unfortunately what needs to be understood to state that a given chemical is harmless is just not there yet, and large and unknown risks attend the consumption of these chemicals. Folic acid, available in large doses per pill at the corner health food store, appears to be an example.

FINASTERIDE (PROSCAR) AND PREVENTION OF PROSTATE CANCER

The American Society of Clinical Oncology and the American Urological Association (ASCO and AUA) have issued a new guideline on the use of 5-alpha reductase inhibitors (5-ARI) for cancer chemoprevention.[13] They found 15 randomized clinical trials that met their inclusion criteria. The main conclusion was that 5-ARI therapy during a 7-year period reduces the relative risk of developing prostate cancer by 25%. The absolute risk reduction however was only 1.4% which leads to about 71 persons needed to treat to prevent one cancer. Another way of looking at this result is that if 1000 men were followed over a period of 7 years, 59 would be expected to develop prostate cancer, and if they all took the 5-ARI, 45 would still develop cancer. This risk reduction is consistent with the result from the Prostate Cancer Prevention Trial which started in 1993 and was stopped in 2004 because of this same risk reduction. However, enthusiasm that should have arisen from this trial result, based on the 25% figure, was dramatically dampened by the suggestion that finasteride increased the risk of high-grade cancer. A majority (8 of 10) of members of the ASCO-AUA panel judged this higher observed incidence of high-grade cancer in the finasteride group to be due to confounding and thus not real. Finasteride is prescribed to relieve the symptoms of benign prostate hyperplasia (BPH—enlarged prostate) and 11 to 40 men experience side effects for every 1000 taking the drug. These include decreased sex drive and erectile dysfunction.

The position taken by the ASCO-AUA is that men who are asymptomatic with a PSA ≤ 3.0 ng/mL may benefit from a discussion of the benefits of 5-ARIs vs. the risk of side effects. For men taking the drug for symptoms associated with BPH, the guidelines suggest that a discussion is in order to acquaint them with the possibility of increased risk of high-grade cancer, but as pointed out, the panel considered this risk unlikely, and thus given the need for the drug in the context of BPH, the potential cancer prevention is an added bonus. An additional problem with 5-ARI therapy is an approximate 50% drop in PSA which must then adjusted when applying cut-offs for triggering a biopsy. The panel did not take a position or a revised cut-off.

While obtaining a 25% risk reduction seems very appealing merely by popping a pill daily, individuals who would otherwise not take 5-ARIs need to seriously consider the very high number needed to treat to prevent one cancer. It is not hard to find physicians who regard 71 as too high to justify an intervention that is not totally risk free. There is also cost to consider. Finasteride can cost up to $60 U.S. per month.

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