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William R. Ware, PhD - Editor

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This issue emphasizes subjects of particular interest to women. The feature article concerns ductal carcinoma in situ. Since this is commonly diagnosed after suspicion is raised by an abnormality in a mammogram, it is important that women are aware of the nature of this early stage breast cancer, especially since prior to 1970 it was not even considered to be cancer. This brief review is followed by a discussion of recent studies concerning vitamin D deficiency in infants and their mothers, and the propensity of artificially sweetened soft drinks to increase the risk of preterm delivery. In the News Briefs section a study of vitamin D and the risk of preterm birth and pregnancy-related infection is discussed, as well as a study of the increased risks of miscarriage associated with the intake of antidepressants.

In this issue we also update the report on the impact of coconut oil on Alzheimer's disease, take a critical look at the evidence supporting the seasonal flu shot, and examine the latest clinical results showing the power of vitamin D to prevent the flu. If vitamin D were a so-called patent medicine, it is not hard to imagine the intensity of the advertising campaign that would be underway.

This issue also includes The Prostate Monitor, which contains a discussion that should be of general interest rather than specifically directed at those interested in prostate problems. See "Misplaced Trust. Radiation therapy. Proceed at your own risk."

Finally, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

UPDATE ON COCONUT OIL AND ALZHEIMER'S DISEASE

In the September issue of Dr. Stephen Sinatra's *Heart, Health and Nutrition*, he has a short piece on a suggestion he made to Dr. Mary Newport whose husband was the subject of the case history in last month's Newsletter. He suggested she try coenzyme Q-10 (100 mg twice daily), acetyl-L-carnitine (1 g twice daily), magnesium (200 mg twice daily), and the sugar ribose (5 g two to three times daily). While he uses this combination in his cardiology practice (with L-carnitine rather than the acetyl derivative) with great success[1,2], he also has found it improves patients with early onset dementia. Dr. Newport reported back to Dr. Sinatra with the news that her husband's speech had become more fluent, and that this was one of his primary symptoms. She also told Dr. Sinatra, "He is now able to find the words easier and more consistently initiate conversation. He can

now pull his thoughts together, find the appropriate words, and complete sentences, rather than losing the thought midway through, and then go on to engage in a lengthy conversation. This improvement happened within a few days of putting him on this regimen."

WHAT WOMEN SHOULD KNOW ABOUT STAGE ZERO BREAST CANCER (DCIS)

Recently (September 4) a major news network (CNN) carried a half-hour segment at prime time (in Eastern North America) describing the personal story of a high profile athlete diagnosed with breast cancer who underwent a lumpectomy and radiation therapy (RT). The main take home messages were that the diagnosis is psychologically devastating, the lumpectomy (small) not a big deal, and the immediate side effects of the RT only temporarily bothersome after the 5th and 6th treatments. The story ended with a strong endorsement by this very well known sports personality for the benefits of mammography. In this case the diagnosis was ductal carcinoma *in situ* (DCIS) but no details were provided other than it was a small lesion.

As mammography has become more widespread, the diagnosis of DCIS has dramatically increased, and today over 20% of all breast cancer carries this designation with 90% of these arising from abnormalities found in mammograms.[3] It is identified by a biopsy. If DCIS is properly described to patients, they will be told that it is not an immediately life-threatening condition, is not generally rapidly invasive, traditionally it has been debated as to whether or not it was even cancer, and by the way, it is highly recommended that it be treated as if it were invasive breast cancer presenting significant risk. Prior to the acceptance of conservative surgery and lumpectomies, mastectomy was the end result. Today in the US, approximately 30% of DCIS cases are treated with mastectomy, 30 % with conservative surgery alone and 40% with conservative surgery plus radiotherapy. Ten-year recurrence rate for these three groups was 1%, 30% and 10%, respectively.[3] The option of watchful waiting is not generally offered nor studied. DCIS has a number of interesting features and presents some significant problems not only to patients but to oncologists, surgeons, pathologists and lawyers.

The rationale for this aggressive approach to a small growth in a breast duct which would almost never have been found without mammography and which shows signs of cancer-like cell types is that DCIS is widely believed to have a significant and perhaps even high probability of becoming an invasive cancer. It is of interest to look at the evidence. To collect meaningful data, women with DCIS which is established to be non-invasive would be left untreated and followed for a number of years to see if and when they progressed to invasive cancer *in the same location biopsied*. To be relevant to modern times, these DCIS lesions would be discovered by mammography since this is the main source of cases today. In the parlance of the trade, such studies would involve an examination of the *natural history* of DCIS. Given the current view regarding the risks of DCIS, ethics make it unlikely such a study will be conducted. Thus where did the evidence for the conventional wisdom come from? It was developed from studies now mostly decades old involving patients with biopsies viewed as benign which were motivated by breast lumps or other non-mammographic generators of concern. A few later developed invasive cancer. There are 4 studies described in a recent review by Erbas.[4] On the basis of these studies it was possible to follow up 136 patients with DCIS of which 34 subsequently developed invasive breast cancer. The motivation for almost all the initial biopsies predates the use of mammography. Thus the conclusion from this small set of studies was that 14% to 53% of DCIS progresses to invasive cancer. This is based on tumors which were initially palpable and much larger than the tumors represented by modern DCIS diagnosis. In many cases it might take years for palpable tumors to develop from the much smaller non-palpable abnormalities diagnosed today that represent the majority of DCIS. It is also interesting but worrisome that one study which was able to classify the stage of the

DCIS found no correlation between high vs. low risk pathology at biopsy and subsequent invasive cancer. Furthermore, the impact of the biopsy and the variable amount of tissue removed or disturbed for these palpable lumps on the future development of invasive cancer is unknown. It has been suggested that false positive sentinel node biopsy results could be caused by benign mechanical transport after biopsy.[5] These studies do not adequately address the issue of the natural history of DCIS in the mammography era.

One of the major errors turned up in modern studies of second opinions of breast biopsy slides is the upgrading from DCIS to invasive cancer. One wonders how probable this type of error was in the 1950s to 1980s when the early pre-mammography studies were conducted, i.e. some of the DCIS cases identified were already invasive cancer. In view of all of the above, the direct evidence for the conventional wisdom regarding DCIS appears virtually non-existent by any standard. Yet this appears to be the body of evidence that is propelling tens of thousands of women into the OR each year, and not all escape with a simple lumpectomy.

In sharp contrast to lack of information on the natural history of DCIS, there is considerable information about atypical ductal hyperplasia (ADH), also called simply atypia, still believed to be a benign breast disease but which some consider to be a precursor to DCIS. ADH can be difficult to distinguish from low grade DCIS and the mechanical aspects of the biopsy can add to the confusion. Thus some recommend excision for treatment even of ADH, although it is regarded as a benign condition.[6] The natural history of ADH is easier to study because there are ample potential untreated subjects. A recent study from the Mayo Clinic actually had an almost 14 year follow-up.[7] In a group of 331 women with atypia, the risk of breast cancer was increased 4 fold, the risk remained elevated over 20 years, and family history added no significant risk. The reasons for the biopsy identifying ADH included palpable mass (lump) or a mammographic abnormality (at a ratio of about 1:1). In the Mayo Clinic study, the cumulative incidence was 21% at 20 years follow-up. To the extent that ADH progresses to invasive cancer through a DCIS stage, these results add credence to the belief that DCIS indeed presents a risk for invasive cancer which may not be trivial. The problem is to identify those who need treatment and those who have indolent disease. The parallel with prostate cancer is remarkable.

This is not to say that it is unwise to play it safe, it is just that there appears to be not much evidence regarding the actual magnitude of the risk of diagnosed DCIS progressing to invasive cancer, and especially the time window over which indolent behaviour might prevail. It is for example recognized that not all DCIS may progress, but at present there is no protocol for distinguishing the two scenarios.

What if the pathology report is wrong? DCIS is not a medical emergency. There should be no urgency to rush to the OR. There are a number of centers which offer second opinions given by pathologists who examine hundreds of slides per year and are experts in cancer histopathology including DCIS. Not recommending a second opinion is probably a common response to a diagnosis of DCIS and is perhaps not surprising. There are insurance and financial issues (the hospital may have to pay) and there is the tacit admission that the diagnostic procedure which is about to result in the recommendation of a very invasive procedure perhaps followed by radiation or chemotherapy or both might in fact be wrong. But in addition to the original biopsy slides, the lumpectomy or mastectomy provides a second opportunity for a pathological examination which may invalidate the diagnosis based on the biopsy. In a *New York Times* feature (by Stephanie Saul, July 19, 2010), the stories of several women are provided which illustrate the lifelong psychological consequences of having a lumpectomy or a mastectomy and perhaps radiation and chemotherapy and then a few years later being told that no cancer was present, a final opinion generally confirmed by several experts when the end result was litigation. This reversal of opinion is based on the post surgical pathology, but also includes a re-examination of the biopsy slides. This is where the lawyers and the expert witnesses come in. Saul's article is highly recommended.

An interesting aspect of the legal side is when no liability is the verdict on the grounds that the pathologist can not be blamed if the procedures used conformed to standard care.

This seems to translate into the view that the pathology report is just an educated guess and that the problem is black at one end, white at the other and in the middle is a lot of grey where honest differences of opinion exist. But the lawyers for the plaintiff in the cases discussed by Saul apparently had no trouble finding a number of high profile pathologists who found no cancer, and generally the pathologists that found cancer saw only a limited number of cases a year and were far from being experts in the subject. The whole point is that there appears to be lots of time to get more than one opinion, and all women should demand this unless they are attending a clinic well known for expertise in this area, in which case the slides were probably reviewed by several pathologists highly experienced in diagnosing DCIS and differentiating it from an invasive cancer or benign disease. But a substantial fraction of all DCIS is diagnosed and then treated in small hospitals.

There is of course no guarantee that the second opinion is *a priori* the correct one. Only a limited number of studies have even compared first and second opinions for DCIS. Clinically important discordance is observed, but while the percentages vary considerably they are generally low. But if one is among those where a major change in indicated therapy, this is obviously important. Also, even low percentages yield a large number of patients misdiagnosed when one considers, for example, the current incidence of diagnosed DCIS in North America. It appears more common to see DCSI upgraded to invasive cancer than downgraded. Large studies where two or more opinions are followed up with an examination of the post-surgical pathology do not have appear to have been carried out for DCIS, and this is the only type of study that would be really informative.

There is evidentially also a strong incentive to treat in the presence of a merely suggestive diagnosis in order to “play it safe.” Patients’ fears regarding cancer mortality contribute to this approach as does the ever present threat of litigation, especially in jurisdictions where litigation is rampant. If the only issue were a simple lumpectomy that was either mildly or not even disfiguring, then aside for the ever present risk of acquiring an antibiotic resistant infection which could be fatal, one can understand why surgery would trump diagnostic uncertainty. But a mastectomy or adding radiation and/or chemotherapy introduces a whole new set of issues.

Post-operative radiotherapy for DCIS has recently been reviewed by the Cochrane Collaboration.[8] They find strong and significant evidence for benefit related to all recurrence, invasive recurrence and DCIS recurrence. In three studies, recurrence free survival was 95% 98-96%, and 86-87%, respectively. However, they were unable to reach any conclusions regarding long-term toxicity from this adjuvant radiotherapy. These figures should reassure women undergoing breast conserving surgery plus RT for DCIS that their outlook appears excellent. However, there appear to be no studies demonstrating overall survival or distant metastasis benefit for patients treated with surgery plus RT vs. surgery only, nor are there studies yielding protocols for distinguishing those who would benefit from RT from those who do not need it. The merits of adjuvant endocrine therapy (tamoxifen or raloxifene) appear debatable.[3]

The use of endocrine therapy may be dictated by the results of receptor typing. Errors in testing for the type of estrogen receptor (ER) or human epidermal growth factor receptor 2 (HER2) can have an impact on therapeutic decisions. Errors do occur and repeat tests are advisable if possible. Some large centers will examine and perhaps repeat the whole diagnostic procedure again prior to settling on a treatment plan to recommend to a patient referred from a smaller hospital or practice.

One source of error involves incorrect patient identification. Your editor knows someone who was listening to the results of a scan for bone cancer secondary to prostate cancer when the physician commented on his hip joint replacement, an operation he had never had.

VITAMIN D DEFICIENCY IN INFANTS

Human breast milk contains < 25 to 78 IU/L of vitamin D and a liter is a typical daily intake. The current recommendation from the American Academy of Pediatrics (AAP) for infants is 400 IU/day, just recently raised from 200 IU/day.[9] The (AAP) also advised that children younger than 6 months be kept out of the sun altogether and that those age 6 months or greater wear protective clothing and sunscreen to minimize UV skin exposure. Sunlight exposure in general is strongly discouraged during childhood and adolescence, generally without the qualification in particular of avoiding serious sunburn. If one looks at the few studies cited by the 2008 AAP recommendations, nowhere is there evidence pointing to 6 months being a critical point. These few studies, all before 2000, involve adult melanoma, depend on recall of childhood experience, and appear to offer weak if any evidence of risk associated with normal exposure not resulting in serious sunburn. The AAP position was strongly influenced by studies on the recall of adolescent sunburn and the incidence of adult onset melanoma, and thus represents a huge extrapolation from adults to adolescents or to infants, especially during their first 6 months.

We evolved to get our vitamin D from the sun. If our stone age ancestors living in equatorial regions also had inadequate levels of vitamin D in their breast milk, which is highly unlikely, this was surely not an issue since it is quite impossible to believe that they kept their children out of the sun for the first 6 months or at any time or that they were concerned about protective clothing. However, it would be natural to avoid painful sunburn. Also, it appears that any kind of skin cancer is almost never seen in pediatric practice. It is noteworthy that the AAP is focused on sun exposure in general whereas they perhaps should be focused on severe sunburn.

There appears to be only one mainstream rationale for maximizing the protection of babies, young children and adolescents from the sun. It is malignant melanoma, which is very dangerous if not caught early. However, it represents an extremely small fraction of skin cancers in adults. In contrast with most cancers, non-melanoma skin cancer (NMSC) is not considered dangerous, does not spread (metastasize) and is easily cured. But there is another problem with the AAP recommendations and that is the paradox associated with the very poor correlation between melanoma and sun exposure, and the evidence that high levels of vitamin D are in fact highly protective. This was discussed in the June 2009 Newsletter. Readers are referred to the online IHN archives for this discussion, as well as to the April 2010 issue where a paper was discussed which concerned the observation that incidence of NMSC is a poor surrogate for sun exposure or adequate vitamin D status with a strong *inverse* relationship between the risk of NMSC and vitamin D status. The information presented in these earlier Newsletters should provide grounds for seriously questioning the conventional wisdom propagated by the dermatology community and underscores the simplistic nature of the current viewpoint.

Over the past decade the incidence of childhood rickets has increased. This follows a long period where it was virtually eliminated by vitamin D supplementation but before the highly restrictive recommendations of the dermatology community started to influence pediatric practice. Cod liver oil was commonly given to children. Today this oil frequently contains much less vitamin D, and the high levels of vitamin A render it an unacceptable source of the sunshine vitamin. It also appears to have long since become unpopular as a supplement. It is quite likely that the antagonistic association between vitamin A and D is almost totally unknown in mainstream medicine.

Two recent studies relate to these issues in infants. The first reports widespread vitamin D deficiency in urban newborns and their mothers in Massachusetts.[10] The researchers used < 25 ng/mL (63 nmol/L) for deficiency and severe deficiency as < 15 ng/mL (38 nmol/L). It was found that 58% of infants and 35% of their mothers were deficient whereas 38% of infants and 23%of mothers were severely deficient. In addition, > 30% of women who took prenatal vitamins presumably did not take enough since they were still vitamin D deficient. Sun exposure

was found to reduce vitamin D deficiency in mothers, but this protective effect was not always transferred to their infants. While maternal vitamin D status was an important factor in predicting infant status, the correlation was not 1:1 with 18% of infants born to vitamin D deficient mothers were not deficient and 44% of infants born to vitamin D-replete mothers were deficient. Maternal obesity and in particular severe obesity (BMI ≥ 35) was a risk factor for vitamin D deficiency both mothers and infants.

The second study examined the adherence to vitamin D recommendations as reflected in levels in US infants.[11] It was found that most US infants were not consuming adequate amounts of vitamin D according to the 2008 AAP recommendation of 400 IU/day. Among infants who consumed formula but no breast milk, only 20-37% met the 2008 recommendation, and this group represented those with the highest intake. The authors take the position that infants who are either breastfed or consuming < 1 L/day of fortified formula be given oral vitamin D supplements.

In is interesting in this context that in August, two major British newspapers carried feature articles warning readers that by taking "a lunchtime stroll" they could end up with skin cancer (*Mail Online* August 18, and the *Express,* August 31). But in addition, just a bit earlier there was an article in the *Guardian* by Dr. Sam Shuster (July 21) with the title *Don't let the phoney melanoma scare keep you out of the sun.* Schuster is from the University of Newcastle-upon-Tyne and a few months earlier published a relevant paper in the *British Journal of Dermatology*. In this article Shuster discusses the paradox that if as claimed the incidence of melanoma in the UK has quadrupled in the past 30 years, how does one explain the absence of any increase in melanoma related mortality. He advances and discusses the explanation that the increase in tumors reported include those that are not true malignant melanoma but actually benign and describes what he terms error amplification by screening which causes spurious disease.[12] The driving force is defensive medicine. He also discusses points raised in our earlier Newsletters, i.e. there is a poor relationship between melanoma and cumulative UV dose, that melanomas do not predominate in sun-exposed skin and that melanoma mortality actually decreases with UV exposure.

As has been stated earlier in this Newsletter, someday it will be considered malpractice not to measure 25(OH)D in newborns and periodically during childhood and adolescence. The same applies to adults. Instead, everyone seems focused on cholesterol, blood pressure, blood sugar and body mass index in individuals of all ages. Calling vitamin D a hormone, not a vitamin has been suggested since vitamin supplements are held in low regard in mainstream medicine.

MATERNAL INTAKE OF DIET SOFT DRINKS—BAD NEWS FOR BABIES

A Danish study has just been published that reveals the risk of preterm delivery among women who consume artificially sweetened soft drinks.[13] Preterm delivery (< 37 weeks) is a major complication of pregnancy and the leading cause of perinatal morbidity and mortality. Long-term impairment and social inequality as an adult are also common consequences. Preterm delivery is also a well-established although minor risk factor for cerebral palsy.[14]

This study involved over 59,000 women. Soft drink intake was assessed with a food frequency questionnaire at mid pregnancy. It was found that for the intake of both carbonated and non-carbonated artificially sweetened beverages, there was a significant increase in preterm deliveries. Consumption of ≥ 1 drink per day was associated with a 38% increase in preterm deliveries, and for ≥ 4 drinks a day it was 78%. The comparison was with women with no intake of artificially sweetened soft drinks. Risk was somewhat attenuated for non-carbonated beverage intake. Furthermore, there was no connection observed for sugar-sweetened carbonated or non-carbonated drinks. These results were adjusted for confounding and were statistically significant. According to the researchers,

these results are suggestive that the artificial sweeteners represent a causal factor.

In Denmark artificially sweetened sodas contain a mixture of sweeteners, but aspartame (NutraSweet, Equal) and acesulfame-K (Sunett, Sweet One) were primarily used in products from major international companies and the average concentration of these two chemicals was 2-3 fold higher in carbonated vs. non-carbonated beverages which may account for the lower risk associated with the latter. Acesulfame-K is used in conjunction with aspartame to reduce the bitter aftertaste of the latter. The authors focus on aspartame in their attempt to provide a biological mechanism. After ingestion aspartame is broken down into aspartic acid, phenylalanine and methanol (methyl alcohol or wood alcohol). Methanol is then oxidized to formaldehyde and then to formic acid, the latter being considered as responsible for the toxicity. Animal studies have reported the accumulation of adducts of formaldehyde derived from aspartame in tissues and this has been suggested as an explanation for the association of aspartame with headaches. Methanol exposure has been shown to decrease the gestation period in non-human primates compared with control animals and this effect was seen at remarkably low serum methanol levels. Furthermore, methanol exposure resulted in increased need for C-sections in these experimental animals. Little more appears to be known about how aspartame might impact gestation. Also toxicology data regarding acesulfame-K appears remarkably limited. The major issue seems to be genetic damage to DNA at higher doses found in animal studies. In addition, this sweetener has been associated with thyroid tumors in rats. Aspartame has been associated with lymphomas and leukemia, again in rats, as well a reduced seizure threshold and headache in humans.[15] The study of the adverse side effects of artificial sweeteners in humans is not a popular research area! The above study on preterm delivery may be one of the most well conceived, designed and conducted studies to date.

Readers interested in the subject of the potential toxicity of artificial sweeteners are referred to the recent book *Sweet Deception*, by Dr. Joseph Mercola and Dr. Kendra Pearsall. Earlier books by Dr. H. J. Roberts, a well known critic of aspartame, may also be of interest. The history associated with FDA approval is quite revealing. For a complete list, search Amazon.com for “NutraSweet.”

SEASONAL FLU SHOT. IS IT EVIDENCE BASED?

By the time this issue goes online, the flu vaccination campaign will be in full swing and millions of doses administered. Thus it is of interest to examine the evidence regarding efficacy. One of the most respected organizations doing meta-analyses and systemic reviews is the Cochrane Collaboration. Their most recent review of the above question appeared June 2, 2010.[16] This study reviewed 50 reports of randomized controlled trials of influenza vaccines involving 70,000 individuals. Comparison was with a placebo or no intervention in naturally occurring influenza in healthy individuals 16 to 65 years of age. They found that in the relatively uncommon circumstance of the vaccine matching the circulating strain and high circulation of the strain, 4% of unvaccinated people vs 1% of vaccinated people developed flu symptoms. For the usual situation where there was a partial match between the vaccine and the seasonal strains of virus, the corresponding figure were 2% and 1%. Thus, for what they term the normal situation, i.e. a partial match, one needs to vaccinate 100 individuals to prevent on case of the flu. If by some accident, there is a very good match, then 33 individuals need to be vaccinated to prevent one case.

The Cochrane investigators warn that 15 of the trials included in the analysis were industry funded. Thus the actual efficacy may be somewhat less, given the well known problems with industry sponsorship and the fact that studies funded from public sources are significantly less likely to report conclusions favourable to vaccines.

Additional observations from the researchers:

- Vaccine use did not affect the number of people hospitalized.
- There is no evidence that vaccination for the flu affects the rate of complications such as pneumonia or transmission.
- One case of Guillian-Barré syndrome (a very serious neurological condition leading to paralysis) occurred for every million vaccinations.
- The "harms" evidence base was limited and did not allow significant conclusions.

Most readers probably realize that the make-up of the vaccine used each year involves merely an "educated guess" which due to the logistics of the operation must be done months before the wild strains in action are identified. But it seems that the merits of the vaccination are oversold with a widespread belief that getting the shot will prevent the flu. Even if the number needed to treat of 100 to prevent one case is not corrupted by industry sponsored trial data, to view the vaccine as working is stretching things quite a bit. The near absence of data on side effects means that to get this one-in-a-hundred benefit one is gambling on not having a serious side effect that is ignored or missed in studies. The alternative to the flu shot is Vitamin D, as has been discussed in previous Newsletters and as well in the studies described below.

VITAMIN D VS. INFLUENZA. THE LATEST STUDIES

The reader will also no doubt recall reports in this Newsletter concerning vitamin D and influenza, and in particular the experiment in a nursing home where vitamin D status was assessed and every resident brought up to sufficiency with supplementation prior to the flu season. The flu rate in this susceptible group was very low compared to that among the staff which had the not been supplemented with vitamin D (Dec 09-Jan 10 issue). Two more sophisticated studies related to this issue have appeared recently, one a randomized trial, the other a blinded cohort follow-up study.

The cohort study looked at the association between serum 25-hydroxyvitamin D (25(OH)D) and the incidence of acute viral respiratory tract infections in healthy adults.[17] Participants were blinded as to what was being assayed in their blood samples, and the incidence of infections was monitored by physicians blinded to the vitamin D status. Serial monthly 25(OH)D determinations were made over the fall and winter of 2009-2010 in 198 healthy adults. It was found that those with concentrations above 38 ng/ml (95 nmol/L) experienced a two-fold reduction in the risk of developing acute respiratory tract infections and a marked reduction in the percentages of days ill. As the season progressed through the Fall and into the Winter, the number of subjects having levels ≥ 38 ng/mL decreased and those below the cut-off increased. Another way of stating the results is that of the 18 who had levels above 38 ng/mL throughout the study, 3 (16.7%) became ill, whereas for the 180 below this cut-off, 81 (45%) became ill.

The second study of school children involved a randomized intervention trial employing 1200 IU/day of vitamin D3 or a placebo. The primary outcome was the incidence of influenza A, diagnosed with antigen testing. Influenza A occurred in 10.8% of the children in the intervention group vs. 18.6% in the placebo group (relative risk 0.58). The reduction was more marked in treated and untreated children who had not been taking other vitamin D supplements and was 0.36, i.e. a 64% risk reduction. Asthma attacks were reduced with 2 occurring in children in the intervention group and 12 occurring in the placebo group. It seems likely that more dramatic results might have been achieved if a somewhat higher dose of vitamin D had been employed. No 25(OH)D levels were reported.

When these studies are compared with the Cochrane study, one can not help notice the huge discrepancy between the incidence rates they found for either the vaccinated, placebo or untreated groups and those in the two studies just discussed. It would appear that vaccine studies either recruit participants much less susceptible to influenza or the bar is set much higher for identifying cases.

NEWS BRIEFS

VITAMIN D AND RISK OF INFECTION AND PRETERM BIRTH

A paper presented at the annual meeting of the Pediatric Academic Societies recently held in Vancouver, B.C. presented new information of this topic. About 500 women were given 2000 or 4000 IU of vitamin D3 per day between their 12th and 16th weeks of pregnancy. Higher levels of vitamin D were found to be significantly associated with lower risk of infection, preterm labor and preterm birth. Comparison was with a group taking a commonly recommended dose of 400 IU/day (e.g. Society of Obstetricians and Gynaecologists of Canada). Even though the study took place in sunny South Carolina, 85% of the participants had insufficient vitamin D levels at the start of the study. The higher levels found in the mothers was also reflected in the newborns. Dr. Carol Wagner, the lead author, took the position that pregnant women should be taking 4000 IU of vitamin D per day. She also commented that for 30-plus years it was dogma that vitamin D in pregnancy was dangerous! Odd notion when one considers that we evolved in an environment replete with sun exposure. Incidentally, the Canadian Pediatric Society began recommending that pregnant and breastfeeding women "talk to their doctor" about taking 2000 IU of vitamin D per day but Health Canada is still at 200 IU. (Source of the conference report, *Vancouver Sun*, May 3, 2010.

OBITUARY FOR A GREAT JOURNAL. *MEDICAL HYPOTHESES*, 1973-2010, RIP

For a number of years, Elsevier has published a journal called *Medical Hypotheses (MH)*. Submissions were reviewed only by editor or occasionally by members of the board. Its purpose was to provide a forum for new ideas, critical commentary, and unconventional views concerning existing conventional wisdom and dogma. Its most recent editor, Professor Bruce Charlton, felt passionately about the mission and the fact that the absence of peer review enabled this journal to fulfil its mission. Then they published a paper that irritated a lot of people, presumably some of whom were what is called important. At any rate, Elsevier came under intense pressure to convert this unique journal to a conventional format with peer reviewing, which of course would destroy its place in the medical literature as a forum for ideas, some radical, but rarely if ever absurd or unscientific. The objections to Elsevier's proposal were strong, including Charlton's. In the end, Elsevier won, Charlton was sacked, and we no longer presumably have an open forum for new ideas in medicine. Peer review is almost certain to stifle that. It is a pity, since this journal over the years has published a number of papers by high profile medical scientists which were thought-provoking and inspired additional thinking and research and the generation of new ideas. Elsevier has little to be proud of since it also a few years ago sold out to the pharmaceutical industry by creating a number of fake journals with sophisticated titles intended to give the industry a place to publish papers which might not have gotten into mainstream journals. Now every month we find papers and other evidence, published in highly respected peer reviewed journals, suggesting that intellectual freedom and scientific honesty in medical science are being eroded and replaced by dogma driven by special interests and individuals that have achieved the position of specialists in thought control. This will benefit some, but for the consumer of medical science, i.e. patients, it is a sad time corrupted by conflict of interest, bias, dishonest so-called science, and the manifestation of the power of money over the principles. This era of enlightenment regarding what really goes on came with the ability to the courts to obtain detailed data including internal emails from drug companies, and this forced transfer of this information, some of which was sensationally damming to say the least, into then the public domain. The result was critical papers in journals such as the *JAMA* and the *Annals of Internal Medicine*.

MH was uniquely successful in avoiding the bias associated with thought moulders and served a unique role in stimulating the thinking of many medical scientists. Its passing as it becomes a journal under the influence of the peer review system is sad and significant. This comes at a time when major universities and journals are struggling with the profoundly serious problem of conflict of interest between faculty and Big Pharma, as well as in that minefield called continuing medical education where it is suspected that on occasion, biased studies are discussed by biased presenters.

JOHNS HOPKINS MEDICAL PROFESSOR SPEAKS OUT ABOUT PREVENTABLE DEATHS

In a recent issue of the JAMA, Dr. Peter Pronovost, MD, PhD, professor of anaesthesiology and critical care medicine at Hopkins presented a commentary concerning preventable deaths.[18] He points out that in the US about 100,000 people die from health-care associated infections, another 44,000 to 98,000 die from preventable mistakes, and tens of thousands die from diagnostic errors or failure to receive recommended therapy. He cites one example close to his own interest—the 30,000 or more deaths each year in the US due to bloodstream infections associated with the use of so-called central lines, temporary fixed ports in the hospital setting for the introduction of drugs. He is responsible for developing a checklist which has been proven to reduce these infections to near zero but aside from Hopkins and hospitals in Michigan, the acceptance of this protocol has been negligible. He cites the difficulty of changing the established culture, especially when one adds the impediment of arrogance and he points out that despite a decade-long effort to improve safety, there is limited empirical evidence of improved patient outcomes. A strong and interesting critique of the health care system in the US. Readers who are amused by simple arithmetic comparisons might calculate the number of 747s that would have to crash each year or even each week with all lost to produce the death toll Dr. Pronovost enumerates, and then contemplate the governmental and public reaction.

VITAMIN D DEFICIENCY AND RISK OF COGNITIVE DECLINE IN THE ELDERLY

The abstract to the paper with the above title starts with the amazing assertion that, to the author's knowledge, this is the first prospective study that has examined the association between vitamin D and cognitive decline and dementia. The Italian population-based study was conducted between 1998 and 2006 with follow-up assessments every three years. A total of 858 adults 65 or older were involved. Vitamin D status was assessed with direct measurement of 25-hydroxyvitamin D levels and standard tests (e.g. the Mini-Mental State Examination—MMSE) were used to identify cognitive decline.[19]

When individuals who were severely deficient (< 25 nmol/L—10 ng/mL) were compared to those with sufficient levels (≥ 75 nmol/L—30 ng/mL), it was found that this level of vitamin deficiency resulted in a statistically significant 61% increased risk of substantial cognitive decline on the MMSM test and that the rate of decline was also impacted. This is an important result since the elderly are in particular at risk for vitamin D deficiency, especially those housebound or in nursing homes.

ANTIDEPRESSANTS AND MISCARRIAGES

In the September issue we discussed the association between some antidepressants and the risk of cataract and a study showing that certain antidepressants interacted with tamoxifen to reduce its effectiveness in breast cancer prevention and therapy. Now there is evidence that some members of this class of drug also increase the risk of miscarriage (spontaneous abortion).[20] In a case-control study in the province of Quebec, Canada, over 5000 women were identified as having experienced a spontaneous abortion. Each case was matched with 10 controls and the connection with antidepressants investigated. In general, after adjusting for confounders, antidepressants increased the risk by a statistically significant 68%. When stratified by type, selective serotonin reuptake inhibitors increased the risk by 61%, serotonin-norepinephrine uptake inhibitors by 110% and combined use of ≥ 2 classes by 251%. In terms of individual drugs, paroxetine and venlafaxine increased the risk of spontaneous abortion by 75% and 147% respectively.

This represents a serious problem since, as the authors point our, antidepressants are widely used during pregnancy for the treatment of anxiety, depression, bipolar disorder and pain. However, discontinuation of medication during pregnancy can result in relapse which puts both mother and fetus at risk. It should be recalled that antidepressants have been found in general to be no better than a placebo in mild or moderate depression.

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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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The merits of active surveillance, also known as watchful waiting or delayed treatment, continue to be debated. In this issue we examine the pro and con arguments presented in a panel discussion at the latest American Urological Association meeting. The con side is interesting because it takes an extreme position that all men with low risk cancer should be treated. This continuing debate underscores the highly imperfect nature of the procedures whereby an attempt is made to determine what exactly is going on in a man's prostate without removing the gland and subjecting it to detailed pathological examination. A black box indeed.

Men taking statin drugs will find one of the items in this issue of some interest since it deals with the association of statin intake and the risk of various endpoints associated with prostate cancer. The study deserves careful examination since it come from the Mayo Clinic in collaboration with the Southern California Permanente Medical Group.

Another major item in this issue is actually of general interest to all readers of both the PM and INH. It concerns just how wrong radiation therapy can go. While based on investigative reporting rather than a journal article, the report clearly made an impression on the American Society for Radiation Oncology.

Other subjects discussed include long-term follow up for recurrence after prostate surgery, the imperfections in the protocol for selecting candidates for the treatment of only one side of the prostate, and an analysis of a just-published study on the immunotherapy protocol recently approved by the FDA for hormone resistant prostate cancer.

Wishing you good health,

William R. Ware, PhD, Editor

MERITS OF ACTIVE SURVEILLANCE, A.K.A. WATCHFUL WAITING OR DELAYED THERAPY

At the latest American Urological Association annual meeting a panel discussion on active surveillance (AS) was held with pro and con positions presented by two distinguished urologists. Readers will recall that AS involves deferring treatment on the basis of a judgment call that the prostate cancer may present no threat now and perhaps never. A protocol is established to follow the patient and recommend action if the outlook changes. The subject is rendered a bit confusing because there is significant variation in criteria for eligibility for AS and as well for the signs indicating that it is dangerous to delay treatment any longer. This important subject is discussed at length in our book *The Prostate and Its Problems* as are the T1-T4 staging system and Gleason scores, both of which come up repeatedly in any discussion of prostate cancer.

Dr. H. Ballantine Carter from Johns Hopkins argued the pro side. He reviewed the Hopkins criteria: stage T1c (prompted by PSA) or T2a (evidence of a localized tumor from digital rectal exam), PSA < 10 ng/ml, PSA density < 0.15 ng/mL/cc, Gleason Score ≤ 6 with < 3 cores showing cancer with each having less than 50% per core. He estimates that the general group of men with low-risk prostate cancer have a 1.6 fold greater risk of high-risk disease than this AS subgroup. He also claimed that an upgrading to a Gleason score of 7 was a satisfactory indicator for the high-risk disease. For men under AS according to the Hopkins protocol, at 5 and 10 years 82% and 66% remained with no Gleason score ≥7. Overall, at 10 years, 30% of the AS group would have progressed to a Gleason score of 4+3. It is important to note that the Hopkins protocol requires an annual biopsy for the determination of progression. Treatment is recommended if the Gleason is ≥ 7 or > 2 cores are positive, or there is > 50% core involvement. Not all AS programs require biopsy data for abandoning AS.

The con side was taken by Dr. William Catalona from Northwestern University. Dr Catalona believes that all very low risk men should be treated with a radical prostatectomy. He quotes the latest numbers needed to treat (NNT) to prevent one death as 48 but suggests that this number will come down with longer follow-up and correction for data contamination. He points to an Irish study where the NNT was 15. He also argued the following points:

- Not every tumor that appears to be low risk grows slowly.
- In the Scandinavian Trial of AS vs. radical prostatectomy, there was a lower rate of metastases in the surgery group. Note that this study had vastly different eligibility criteria than Hopkins.
- In AS, the good news comes early, the bad news comes late. The latter arises from understaging and undergrading. In a Toronto trial 50% of AS patients had PSA failure. Note the Hopkins protocol does not use PSA failure as a criterion for abandoning AS.
- It is not possible to correctly identify very low-risk patients who have aggressive tumors and the Hopkins criteria is inaccurate in one-third of cases.

This sort of disagreement is not surprising. No set of criteria is perfect. It is well known that there will always be discordance between biopsy results and those obtained from a pathological examination of the removed prostate. In fact hundreds of urologists and pathologists around the world with variable expertise and experience are trying every day to figure out what is going on with patient's prostates by feeling one side of the prostate, doing a blood test involving a non-specific marker even though it is called specific, and trying to find tumors with hollow needles. The latter is like using a half dozen to dozen thrusts of a hollow needle to see if a blueberry muffin has any blueberries. If the number of blueberries is low or the blueberries small, the false negative rate is high.

According to the report of his talk available at *Urology Today*, Catalona also does not factor in treatment side effects which are far from trivial and focuses only on mortality and undergrading and understaging.

A recent review provides some perspective.[1] Over 2500 men on AS have been followed, 200 for over 10 years. To date, prostate cancer specific survival is over 99%. About 25% enrolled in such programs switch to treatment because of concerns regarding progression which can come from the patient or the attending physician. However, these concerns include PSA doubling times or PSA velocity. A recent study from Hopkins finds that these so-called post-diagnostic PSA kinetics do not reliably predict adverse pathology and should not replace annual surveillance biopsy as an essential component for monitoring men on active surveillance.[2] The bottom line appears to be that actions based on probabilities are always going to have exceptions, and it is hard to judge the exception rate when different criteria are used to set the protocols. Surgery or radiation has very high rate of prostate cancer cure in low-risk individuals, but it is convincingly argued by AS advocates that it represents over-treatment in a significant number of men with associated side effects that in some severely impact the quality of life. The absence of a worldwide uniform set of criteria for AS eligibility and for the recommendation of termination and definitive treatment significantly decreases the power of studies that attempt to answer critical questions about AS.

An example of the criteria problem is the Scandinavian Prostate Cancer Group-4 Trial which when updated in 2008 had been in progress for 12 years with a mean follow-up of 10.8 years.[3] Eligibility was < 75 years age, T1 to T3 tumors (i.e. tumors invading the surrounding tissue were included), PSA < 50 ng/mL and a negative bone scan. For watchful waiting vs. prostatectomy, disease specific mortality was 13% vs 18%, overall mortality 33% vs. 40%, local progression 22% vs. 46% and distant metastasis 19% vs. 26%. Aside from overall mortality, all these results statistically significantly favoured prostatectomy. At 6 years follow-up, there was no difference for the endpoint overall mortality. This cohort was significantly different than the AS cohorts discussed above, and the contrast with the Hopkins criteria substantial. In fact, it seems surprising that the differences were not much greater, especially with the inclusion of T3 cancers and very high PSA values.

STATIN USE AND SUBSEQUENT DIAGNOSIS OF PROSTATE CANCER

A study from the Mayo Clinic has just appeared which examines the association between statin use and increased risk of exceeding a specific PSA reference range, having a prostate biopsy, being diagnosed with prostate cancer, or being diagnosed with high grade prostate cancer (Gleason ≥ 7). The cohort was drawn from the Olmstead County Study of Urinary Symptoms among Men which is a long-term, population based cohort study of residents in Olmsted County, Minnesota. The study started in 1990, enrolled men between 40 and 79, and involved a follow-up of about 15 years. Participants had a biennial urological examination. Statin use was self-reported and information on prostate biopsy and cancer diagnosis was obtained from community medical records.

Statin use reduced the risk of prostate biopsy by 69%, the diagnosis of prostate cancer by 64% and the diagnosis of a high-grade cancer by 75%. All these results were statistically significant with upper 95% confidence intervals not exceeding 0.53, which increase the confidence one can place in these results as being both statistically and clinically significant.

Prior to this report, there had been a number of investigations addressing this subject and several failed to find the associations observed by the Mayo Clinic study. The researchers attribute this to their much longer follow-up and point to one study with a follow-up of five or more years which found a 15% in prostate cancer incidence reductions which just missed being statistically significant. They also point out that while statin users experience a small decrease in PSA (about 4% within one year), and this could delay biopsy and result in ultimately a higher risk of more advanced stage cancers, in the Mayo Clinic study just the reverse was found.[4]

In an editorial Getzenberg examines the question of biological plausibility. He mainly dwells on the anti-inflammatory properties of statins but is unable to reach a conclusion due to conflicting data, both *in vitro*, animal and clinical. He also discusses other mechanisms involving various pathways, but it is clear that the mechanism whereby statins achieved the above risk reductions is quite obscure.[5]

Statins provide only small or negligible benefit (depending on gender and age) in true primary prevention of coronary heart disease (except for that found in the JUPITER study which has a special cohort and in addition, which may be seriously confounded[6] by the statin dramatically increasing vitamin D). These results should be of great interest to men who have been talked into taking statins, and as well men who take statins to prevent an additional acute coronary event.

MISPLACED TRUST. RADIATION THERAPY. PROCEED AT YOUR OWN RISK

In a recent series based on investigative reporting, the *New York* Times has published an expose of serious cases of gross negligence involving radiation therapy that suggests that some radiation therapy technicians and their supervisors can only be described as both incompetent and indifferent. This expose was considered sufficiently important to be featured in *Journal Watch*, a high profile publication of the Massachusetts Medical Society which also publishes the *New England Journal of Medicine. Journal Watch* online and in print is read by physicians and medical scientists worldwide and other interested individuals (including your editor). The reports document the horrific harm incorrect radiation treatment is capable of inflicting. The January 24 issue of the *New York Times* carried a report by Walt Bogdanich of the problem of serious or fatal overdoses associated with radiation therapy, in this case when done with a linear accelerator type source. Also discussed were cases where the target was missed or the wrong organ treated. In some cases overdoses were repeatedly delivered to a single patient. Malfunctioning or maladjusted machines were also used repeatedly before the problem was observed, in spite of the fact that manufacturers have built in multiple features to provide warning of a problem. The report centers around two cases where the injury proved to be rapidly fatal. Both cases were attributed to technician error although the details suggest that more was involved than a simple error.

High dose, concentrated radiation can produce tissue damage which does not heal and can rapidly become fatal. The article quotes a statement from a company that specializes is treating wounds that will not heal or fail to respond but rather progress. In 2009 just this one company treated 3000 radiation therapy injuries, most of them serious enough to require the use of a hyperbaric oxygen chamber. This is probably only the tip of the iceberg, given the culture of denial which is systemic, the skill in cover-up, and the ever present threat of serious legal action from those injured. Out-of-court settlements generally carry the requirement of absolute silence. Patients probably do not realize the extent to which the success or failure of their radiation treatment depends on the skill of the technician in performing non-trivial programming and adjustments to the machine delivering the radiation. Nor would it occur to them that the computer involved may be malfunctioning or that they may be helping debug the machine's new operating software. The notion that the technician would miss the target completely would probably never occur to them. But as the article details, these things happen. There appears to be a considerable variation in technician competence in this speciality, as well as technician fatigue, and there is a heavy burden of cases and pressure to get on with the treatment. Rather than describe the horrible details of the two cases described, readers are referred to the original article which is available free online.[7]

The story is continued in two additional issues and the picture simply becomes more depressing. An individual is described who is now condemned for life to carry two bags, one for urine and one for stool, and a patient whose suicide over a ruined life is described by her daughter. Both highlight the magnitude of potential risks. These are the fruits of highly complex modern technological medicine combined with a shortage of talent, inadequate licensing and oversight, division of responsibility, inadequate operating funds, lack of concern from hospital supervisors and finally the casual approach of some radiation oncologists who design and customize the treatments and appear to have blind faith that the program will be carried out with an adequate level of competence.

These articles make it clear that in fact almost nobody cares. Hospitals and radiation clinics are forced to settle out of court to suppress publicity, and the patients are sworn to secrecy. These articles are highly recommended reading for an insight into how wrong things can go when technology overwhelms the overworked, technologically challenged who are supervised by the indifferent. *If it is really true, as claimed by the author of this series, that 30% of major radiation*

treatment centers in the U.S. fail to quality for participation in multi-center studies because they are independently judged incompetent, one begins to wonder what is really going on. The sad thing is that it is probably in the best interest of the general public that this sort of material is suppressed. They have no way of finding out how high the risk is of being killed or maimed in the process of cancer treatment at the only center to which they have access, anymore than they can evaluate fraudulent clinical studies or vastly exaggerated benefits that form the basis of the prescriptions they may be given but which in fact carry frequently serious risk with negligible benefits. The set of articles can be found in the NYT archives online. Use the advanced search for Bogdanich starting January 1, 2010.

The New York Times series did not go unnoticed by the radiology community. The American Society for Radiation Oncology issued a six-point plan that it claimed would improve safety and quality and reduce the probability of errors and radiation treatment and also started pushing for federal standards concerning training of technicians (*New York Times*, February 5, 2010).

LONG-TERM FOLLOW-UP FOR RECURRENCE AFTER RADICAL PROSTATECTOMY

A study has just reported from Brigham and Woman's Hospital in Boston which involved 505 men who had undergone radical prostatectomy between 1985 and 2000.[8] The object was to determine the PSA failure-free survival using ≥0.2 mg/mL as the indicator. The median follow-up was 10.7 years. The pathological characteristics of the group covered a wide range from low- to high-risk of treatment failure.

No patient had a PSA failure at year 5. At year 10, rate was 88% and at year 13 it was 82%. The factors found associated with failure after year 5 were Gleason score of 7 (88% increase in risk) and Gleason score 8-10 (381% increase), and extracapsular extension (137% increase), and seminal vescular invasion (52% increase). The authors point out that patients with a Gleason score of 6 were very unlikely to develop late recurrence and might be candidates for less-intense follow-up after 5 years, but those with the above risk factors for late progression need constant follow-up. The standard response to PSA recurrence post surgery is so-called salvage radiation therapy. Our book discusses this subject.

This study result emphasizes the length of time associated with the appearance of the first signs of evidence for recurrence after surgery. However, if these patients had all been left untreated, it is clear from the natural history of the disease that by 10 years a significant number would have shown clinical evidence of actual metastasis rather than just the initial warning that it probably was on the way.

PROBLEMS WITH SELECTING CANDIDATES FOR FOCAL THERAPY

Focal therapy is an attractive alternative approach for patients with localized prostate cancer. This protocol has been discussed in previous issues of the Prostate Monitor. A recent study from the University of Wisconsin addresses the issue of using pre-treatment assessment to determine eligibility for treating only one side of the prostate.[9] The researchers identified 158 patients with low-risk cancer (PSA ≤ 10 ng/mL, evidence of unilateral, low tumor volume ≤ 5%, and a Gleason score of ≤6) on first positive biopsy. These patients all underwent surgery and the so-called pathological status was determined from the removed prostates. Out of the 158 patients, 117 in fact had bilateral rather than unilateral cancer, 49 had increased tumor volume (≥ 10%), and 46 were upgraded to a Gleason score of ≥ 7. In addition, some patients had extended biopsy core protocols, and this was not found to be more reliable in identifying unilateral vs. bilateral disease, and one core positive was not significantly superior to > 2 cores positive in regard to the same problem.

These results suggest that there is a serious problem in identifying candidates for focal therapy using the above criteria. In particular, about three-quarters of those judged having unilateral disease in fact had bilateral disease. The authors comment that the current standard prostate biopsy protocols have

limited accuracy in identified candidates for this attractive alternative therapy. This is obviously a serious issue.

IS CLINICAL STAGE USEFUL IN THE MODERN ERA?

Clinical staging involves PSA and the digital rectal exam to identify patients in the T1 and T2 categories. A recent study from the University of California San Francisco examined the relevance of the T1-T2 clinical stage in predicting biochemical recurrence (PSA failure) after surgery by comparing staging with PSA levels, biopsy Gleason score, and percent of positive biopsy cores. A study cohort of almost 5000 men was involved. In a multivariable analysis of the results, including serum PSA, biopsy Gleason and percent of positive cores and T1 or T2 stage, the clinical stage offered no independent predictive benefit for biochemical recurrence.[10]

The authors point out that the current clinical staging system predates the widespread adoption of PSA screening and has not been significantly updated. The finding of a palpable nodule on DRE is taken as an indication of larger volume tumor but this may well not be the case at all. The majority of tumors today are detected before they become palpable and this increases the probability that abnormalities found on DRE are benign lesions and not cancer. It also appears that the percent of positive biopsy cores is a better indicator of potential tumor volume than DRE findings.

It was concluded that clinical stage should not be emphasized in counselling men with prostate cancer who plan to undergo prostatectomy, and this also should be taken into account in developing risk stratification systems, e.g. nomograms or algorithms.

NEW THERAPY FOR HORMONE RESISTANT PROSTATE CANCER APPROVED BY FDA

Normally the PM does not feature chemotherapy but this new approach represents a deviation from the standard systemic cytotoxic therapy. The drug is called sipuleucel-T (Provenge), was approved for use this spring by the FDA, and involves immunotherapy with an agent that is produced externally from the patients' blood cells and then used as an IV therapeutic agent. In the future it is certain that we will see more examples of immunological approaches since a number of agents are under development. A small randomized placebo controlled trial has just reported in the *New England Journal of Medicine* concerning Provenge.[11] Patients had exhausted all options but chemotherapy or immunotherapy since their cancer had become hormone resistant. The bottom line was a 4.1 month improvement in median survival (25.8 months for the therapy, 21.7 months for the placebo). But these are means and there is a spread of values about these survival times. At 36 months follow-up, the cumulative survival probability for the therapy was 0.317 vs. 0.23 months for the placebo. Assuming normal distributions, one can calculate the uncertainties in these survival probabilities from the data given in the paper. The value 0.23 plus one standard deviation was essentially equal to 0.317 minus one standard deviation. In other words, the distributions overlap to the point where a significant percentage of the population taking the therapy would be no better off than those taking the placebo. Approximately 16% of the treated group will have survival probabilities at 36 months that fall within plus or minus one standard deviation of the mean survival time of the placebo group and 16% of the placebo group will have survival times that fall within plus or minus one standard deviation of the mean survival time of treated group. Nevertheless, one can calculate from the data in the paper that probability of the two means actually being identical is < 1/1000. Patients given take-home information that the treatment will provide life extension should be warned that this may or may not happen to them because the effect is small and the distributions of survival, if normal, overlap strongly. Thus while the results in this study achieve statistical significance which is a precondition to clinical significance, the latter can be debated.

In an editorial, Dr. Dan Longo calls attention to the fact that this study found no measurable anti-tumor effect, either tumor shrinkage or at least disease stabilization reflected in reduced tumor progression. He comments that "This lack of tumor effect raises concern that the results could have been influenced by an unmeasured prognostic variable that was accidentally imbalanced in the study

group assignments." He also pointed out that the study design did not really allow one to conclude that the tumor antigen is the key agent for the therapy.[12] Incidentally the study was designed, conducted and analyzed by representatives of the sponsor, the company responsible for the therapy, in collaboration with the study investigators.

The result of the cost benefit analysis depends on the patients reaction to the uncertainty in the benefit and to taking the chance that the therapy might provide a few months life extension over a couple of years by spending somewhere between $75,000 and $95,000 for the treatment (the estimated cost available on the internet). It is disappointing that this immunological approach seems cursed with the same problem as more conventional chemotherapy, very small improvements in life expectancy and in some cases, high if not astronomical costs.

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