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In this issue we begin a two-part series by William Ware on the very difficult decision faced by a man just diagnosed with prostate cancer. Should he accept or reject radical treatment, or should he wait and see? Bill meticulously outlines the pros and cons of each approach and provides an impressive amount of scientific data to back up his discussion. This is a MUST READ for a man diagnosed with prostate cancer and for those who may have to face the decision sometime in the future.

Also in this issue we report that lycopene may help prevent atherosclerosis, breast cancer risk may be linked to weight gain in adulthood, a vitamin E derivative has been found effective in killing cancer cells, and depression correlates strongly with poor physical fitness.

Just a reminder, there have been some major changes to our on-line vitamin store. iHerb, our supplier, has moved to new expanded quarters and set up a new division, www.papanature.com which will handle its on-line sales. Coinciding with the move iHerb has changed their discount structure and instituted new (very low) shipping charges. I believe papanature.com now offers the best prices, freshest products, and best delivery service on the Internet and hope that you will continue to patronize the IHN vitamin store. Please keep in mind that when you order through my store I will receive a commission, which enables me to continue the publication of IHN.

Your continuing support is very much appreciated,
Hans

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Folate and dairy products linked to multiple births

NEW YORK, NY/ABERDEEN, UK. Recent research sheds some light on the dietary factors which may alter the chance of multiple-birth pregnancies. It is important to understand the factors that can lead to multiple births, as they have risen since assisted reproductive technologies (ART) were introduced in the 1970s, and continue to rise, as they are more common in older mothers.

In the first study, based at Long Island Jewish Medical Center, the twinning rates of women who ate a regular diet, vegetarian diet with dairy, and vegan diet were compared. The vegan women had twins only one-fifth as often as women who ate dairy products. The researcher suggests that the underlying cause is a protein called insulin-like growth factor (IGF). It is made in the liver, and is linked to a higher rate of ovulation. Once a woman becomes pregnant, IGF may help the embryos to survive. Levels of IGF in the blood are 13 per cent lower in vegan women than in women who consume dairy products. This may be because IGF is present in cows' milk - more so in recent years, as growth-hormone treatment is often given to cows to enhance their milk and beef production.

The second study examined the effects of maternal folate on the multiple birth rate of UK women undergoing in vitro fertilization (IVF). In the UK, it is standard for two embryos to be implanted in each cycle of IVF, in an attempt to increase pregnancy rates. Twins are born in a quarter of successful IVF

procedures. The researchers, from Aberdeen University, followed 602 women through their IVF treatment, and found that twin births were linked to high folate levels in the blood plasma. High folate did not increase the rate of IVF success. In the US, flour fortification with folic acid, to avoid neural-tube abnormalities such as spina bifida, has led to an 11-13 per cent rise in multiple births after fertility treatment. These results are consistent with the present study, say the researchers, who add that the high incidence of twins associated with fertility treatment could be reduced by encouraging women not to exceed the recommended daily intake of folic acid prior to or during pregnancy (600 micrograms a day).

Steinman G. Mechanisms of twinning. VII. Effect of diet and heredity on human twinning rate. Journal of Reproductive Medicine, Vol. 51, May 2006, pp. 405-10.
Haggarty, P. et al. Effect of B vitamins and genetics on success of in-vitro fertilization: prospective cohort study. The Lancet, Vol. 367, May 6, 2006, pp. 1513-19.

Hope for cholesterol benefit from cooked tomatoes

LIVERPOOL, UNITED KINGDOM. The humble tomato is currently under examination in the prevention of cardiovascular disease. Researchers at Liverpool John Moores University are investigating the health giving properties of cooked tomatoes, which contain a substance called lycopene. The team believes lycopene may help reduce high cholesterol, a major risk factor for coronary heart disease.

Cholesterol is transported in human blood by carriers called lipoproteins, of which low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are the most important. Too much LDL cholesterol in the blood can slowly build up on the walls of the arteries to the heart and brain. Together with other substances it can form a hard deposit that can clog these arteries - known as atherosclerosis. Lycopene and other carotenoids are incorporated into lipoproteins in the bloodstream. Most are associated with LDLs, where they may act as antioxidants delaying the onset of atherosclerosis. The team believes that lycopene could play a vital role in preventing atherosclerosis by stopping the lipoproteins from becoming oxidized. The oxidation of low-density lipoproteins can lead to 'fatty streaks' being deposited in the arteries. However, for the lycopene to become available to the human body, tomatoes must be cooked, preferably in some form of oil. The researchers will investigate which are the most effective cooking methods in terms of maximizing lycopene availability. They already recommend that one portion of fruit and vegetables consumed each day should be cooked tomatoes.
The research is supported by a recent 420,000 Euro award from the European Union. It forms part of a major initiative involving experts from fifteen institutions in six different European countries. The ways in which smoking affects the body's ability to harness the benefits of lycopene will also be examined.

El-Agamey, A, et al. Carotenoid radical chemistry and antioxidant/pro-oxidant properties. Archives of Biochemistry and Biophysics, Vol. 430, October 1, 2004, pp. 37-48.

Weight gain during adulthood increases breast cancer risk

ATLANTA, GEORGIA. Breast cancer in postmenopausal women has previously been linked to carrying excess weight. However, questions remain over the links between weight gain and breast cancer, and the specific types of breast cancer which may be involved. Researchers from the American Cancer Society set out to answer these questions by analyzing data from a group of 44,161 postmenopausal women enrolled in the society's Cancer Prevention Study II Nutrition Cohort. The women, none of whom were on hormone therapy, were divided into categories by weight gain since the age of 18. Of the women, 1,200 had been diagnosed with invasive breast cancer.

Overall, the women who gained weight in adulthood faced a higher lifetime risk of all types of breast cancer after menopause. The greater the amount of weight gained, the greater the risk of breast cancer of all types, stages, and grades. Specifically, women who gained over 60 pounds had an 89 per cent higher risk of ductal type tumors than women who gained 20 pounds or less during adulthood, and 54 per cent higher risk of lobular type cancers. The likelihood of metastatic disease (cancer which

spreads to other organs) was more than three times higher among women who gained over 60 pounds. When hormone receptors in the breast cancer cells were examined, it was found that weight gain was linked exclusively to tumors with estrogen receptors present (ER-positive). This is predicted by earlier findings that breast cancer risk is linked to increased lifetime levels of circulating estrogen. Fat tissue increases estrogen levels, contributing to the risk.

Obese women may have the chance of mitigating their breast cancer risk by taking hormone replacement therapy, the researchers explain. They add that current weight is not as important as weight gained since the age of 18. These data underline the importance of maintaining a healthy body weight throughout adulthood, they conclude.

Feigelson, H. S. et al. Adult Weight Gain and Histopathologic Characteristics of Breast Cancer among Postmenopausal Women. Cancer, published online May 22, 2006.

Improved version of vitamin E kills cancer cells

COLUMBUS, OHIO. The antioxidant vitamin E is widely used as a nutritional supplement for its health-giving properties. Evidence suggests it may have potent anti-cancer properties, so a team of researchers from Ohio State University investigated how this may occur. They looked at a derivative of vitamin E called vitamin E succinate, or alpha tocopheryl succinate. It is known to kill cancer cells by triggering the natural process of cell death (apoptosis). The team found that part of the reason it works is by blocking a protein called Bcl-xL, which is found in higher than normal levels in cancer cells, where it prevents the cell from dying. Computer modelling showed that vitamin E succinate disables Bcl-xL by lodging within its structure, causing the cell to die as normal. This action is independent of vitamin E's antioxidant effect, the team showed.

The researchers saw that the vitamin E molecule would fit better inside the protein, and therefore be more effective, if it was slightly adapted and made shorter. Again using computer modelling, they investigated a range of possible changes which could be made to the molecule to anchor it and stabilize it in position. They produced two improved versions and tested them in the laboratory, where they found that the improved molecules were able to kill cancer cells five to ten times more efficiently than the original. Replication among prostate cancer cells was also suppressed, and the new molecules left healthy cells almost completely unaffected. These findings could lead to a potent chemopreventive agent that has both strong anticancer and antioxidant properties, report the team. They hope that in future it could be used to help reduce the risk of prostate, colon and other cancers.

Shiau, C.W. et al. Tocopheryl Succinate Induces Apoptosis in Prostate Cancer Cells in Part through Inhibition of Bcl-xL/Bcl-2 Function. The Journal of Biological Chemistry, Vol. 281, April 28, 2006, pp. 11819-25.

Depression linked to death from heart disease via lower fitness levels

KENT, OHIO. The mortality among patients with heart disease appears to be greater for those who score more highly for depression. This has been shown in coronary artery disease, heart attack, and after coronary artery bypass graft surgery. Depression may even double the risk of death, the figures suggest, so many researchers have put forward possible mechanisms. One theory focuses on disruption of the autonomic nervous system (ANS), leading to a lack of variability in the heart rate, causing impaired recovery after exercise. This has now been investigated further by a team from Kent State University.

The team aimed to discover whether depression symptoms are associated with reduced heart rate recovery. They recruited 260 cardiac patients at the beginning of cardiac rehabilitation, and measured their heart rate recovery after a treadmill exercise test. Participants also completed the Beck Depression Inventory. They were aged between 28 to 98 years, and consisted of 192 men and 68 women. Results showed that patients with higher depression scores showed slower heart rate recovery after exercise, even once age, sex, and beta-blocker usage were taken into account. Depression scores were also associated with reduced exercise capacity, in other words, poorer physical fitness. Analysis showed that poorer physical fitness was likely the crucial element in the relationship between depression and heart rate recovery.

The researchers say these findings confirm that depression is associated with dysregulation of the ANS, and impaired physical fitness is implicated as a potential mechanism. This is not surprising, they write, as depression has previously been linked to physical inactivity among patients at risk for heart disease. Interventions focused on improving physical fitness may be particularly beneficial for depressed cardiac patients, they conclude.

Hughes, J. W. et al. Depression symptoms predict heart rate recovery after treadmill stress testing. The American Heart Journal, Vol. 151, May 2006, pp. 1122.e1-1122.e6.

A daily drink reduces heart disease, but only for men

COPENHAGEN, DENMARK/ LONDON, UNITED KINGDOM. A new study is adding to the evidence about the potential health benefits, or otherwise, of a daily alcoholic drink. Previous findings, showing that moderate drinkers have lower rates of heart disease than abstainers, have been criticized for not taking into account the effect of ex-alcoholics and the long-term sick among the abstainers. Furthermore, most research in the area has focused exclusively on men.

The new research comes from the Danish National Institute for Public Health where experts analyzed data on 28,448 healthy women and 25,052 healthy men aged 50 to 65 years. They are participating in an ongoing national study into diet and health, and regularly provide details of their food and drink consumption and state of health. Each week, the women drank an average of 5.5 alcoholic drinks, and the men 11.3. Over an average follow-up of 5.7 years, 749 of the women and 1,283 of the men developed coronary heart disease. Among women, analysis showed that the risk of coronary heart disease was similar for those drinking on one day a week (36 per cent lower than less frequent drinkers), and seven days a week (35 cent lower). However, men who drank on one day a week had a 7 per cent lower risk than less frequent drinkers, but men who drank every day had a 41 lower risk.

The researchers say these results indicate that the amount of alcohol consumed is more important than drinking frequency among women, but drinking frequency is more important among men. They add that this study raises important questions about drinking patterns and heart health among men and women. However, in an accompanying editorial an expert from University College London, UK points out that the results should be interpreted cautiously. She writes that it would clearly be unwise for physicians to advise non-drinkers to start drinking, when many other factors could reduce heart disease risk, without the side-effects of alcohol. She warns that this type of research may encourage the general public to justify unhealthy levels of alcohol consumption, but concludes that the findings raise interesting possibilities about gender-specific alcohol metabolism.

Tolstrup, J. et al. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. British Medical Journal, Vol. 332, May 27, 2006, pp. 1244-47.

Britton, A. How much and how often should we drink? British Medical Journal, Vol. 332, May 27, 2006, pp. 1224-25.

NEWSBRIEFS

How drugs cause bones to soften

Certain drugs can increase risk of a bone-softening condition called osteomalacia, or "adult rickets", researchers warned recently. The condition is usually caused by vitamin D and calcium deficiency, but can be brought on by long-term treatment with some antiepileptic drugs and antibiotics, say experts from the University of Washington, Seattle. These drugs can affect bone mineral density by converting vitamin D into a substance the body cannot use. Specifically, the drugs activate a receptor called SXR, which in turn activates an enzyme called CYP3A4 that breaks down vitamin D. Because of this, the bones cannot benefit from vitamin D in the normal way. The team made their discovery during experiments on both mice and humans using an antibiotic which activates SXR, called rifampicin. They report that SXR is now confirmed as a potential target for treatment or prevention of osteomalacia.

Zhou, C. et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. Journal of Clinical Investigation, published online May 11, 2006.

Happier mealtimes mean healthier nursing home residents

Nursing home residents benefit in many ways from 'family style' mealtimes, new research has found. Such mealtimes improve quality of life and physical performance; say researchers from Wageningen University, The Netherlands. Life in nursing homes can mean a loss of independence, privacy, and a familiar environment, leading to loneliness and depression. But mealtimes can be made more enjoyable and sociable by using proper plates and cutlery, tablecloths and flowers, and having staff sitting down and chatting with residents. Data on 282 dementia-free residents of five Dutch nursing homes showed that those in wards with this type of family-style mealtimes have significantly higher quality of life scores, improved motor function, more stable body weight, and greater energy intake than those who eat alone. The researchers believe that food and nutrition are essential components of 'the good life', and conclude that, with motivated staff, enjoyable mealtimes are easy to achieve on a low budget.

Nijs, K. et al. Effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents: cluster randomised controlled trial. British Medical Journal, Vol. 332, May 5, 2006, pp. 1180-84.

Internal bleeding risk with chamomile and blood-thinners

Using chamomile products may be risky for patients on blood-thinning medication for heart conditions. This warning comes after a Canadian woman experienced severe internal hemorrhaging when she drank chamomile tea and used chamomile lotion while taking the blood-thinning drug warfarin. Researchers at McGill University in Montreal explain that the 70-year old patient was admitted to hospital with multiple internal hemorrhages, which later healed safely. The doctors believe the incident was due to chamomile products. Several herbal products, such as garlic, onion and ginger, should not be taken with warfarin, and now chamomile may be added to the list. It potentially compounds the anti-coagulant effects of warfarin as it contains the same chemical compound, coumarin. Although this is a rare case, it highlights the potential dangers of mixing herbal remedies with physician-prescribed medications, say the researchers, adding that patient education may be necessary for those on warfarin.

Segal, R. and Pilote, L. Warfarin interaction with Matricaria chamomilla. The Canadian Medical Association Journal, Vol. 174, April 25, 2006, pp. 1281-82.

Common painkillers again linked to heart failure

Further research has added to the evidence that certain widely-used non-steroidal anti-inflammatory drugs (NSAIDs) may increase the chance of heart failure. A team from the Centro Espanol de Investigacion Farmacoepidemiologica in Spain analyzed UK data on NSAIDs. Osteoarthritis was the most common reason for taking the drugs. They found a 30 per cent increased risk of first hospital admission for heart failure among those currently taking NSAIDs. The drug indomethacin appeared to cause the greatest increase in risk - a three-fold increase compared with those not taking the drug. The researchers calculate that there would be one extra heart failure-related first hospital admission for every 1,000 people aged between 60 and 84 taking NSAIDs. Although this risk is small, they believe it could have a considerable impact on public health, particularly as it could give rise to three additional cases per 1000 patients aged 70 and older with diabetes, high blood pressure, or kidney failure.

Huerta, C. et al Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. Heart, published online May 22, 2006.

Metabolic syndrome associated with heart failure in long-term study

New findings on the metabolic syndrome suggest it significantly boosts the risk of heart failure in middle age. Metabolic syndrome is a set of conditions that often occur together, including obesity, high blood sugar, high blood pressure and high triglycerides. More than 2,300 men were followed for 20 years from the age of 50 by researchers from the University of Uppsala, Sweden. Having the metabolic syndrome at age 50 led to nearly twice the risk of heart failure by age 70. This calculation took into account several other risk factors including coronary artery disease, heart attack, smoking, and defective heart valves. This finding suggests that the metabolic syndrome may directly affect the heart as well as contributing to the build up of fatty deposits in the arteries, the researchers believe. They point to insulin resistance and excess insulin in the blood as the causative factors, as these may impair the working of the myocardium (heart muscle).

Ingelsson, E. et al. Metabolic syndrome and risk for heart failure in middle aged men. Heart, published online May 22, 2006.

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RESEARCH REPORT

PROSTATE CANCER

To Accept Or Reject Treatment, Or Compromise? – Part I

By William R. Ware, Ph.D.
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"Is cure necessary in those in whom it is possible, and is cure possible in those in whom it is necessary?" W. F. Whitmore, Jr., 1990 [1]

Subsequent to the diagnosis of prostate cancer, not all patients elect or receive treatment. Some patients are judged to have cancer that has advanced to the point where palliation is the only option offered. For others, it may be recommended that the course of their disease be followed closely and treatment initiated when progression is observed but before it is too late for the treatment to be potentially curative (active surveillance). Some men reject treatment even when advised that it would be beneficial if not in fact strongly indicated. Some of these men may change their minds later on while others will hold out until palliative measures are forced on them by end-stage disease or they die of some unrelated cause. It is of interest to first examine some of the reasons why treatment might be rejected.

- Belief that treatment will not influence overall survival, and thus there is no point in undergoing procedures which may impact the present quality of life. Some men may feel that their chances of dying of PC are less than from some other health problem, and they are willing to take the risk of a decrease in quality of life associated with palliative treatment if eventually necessary, or perhaps they just choose to ignore this possibility.

- Fear of surgery and the belief that the side effects and complications associated with surgery or any form of radiation therapy or other treatment are unacceptable.

- Some men who have examined the matter carefully may have concluded that the decision making process is merely a probability game where the probabilities are uncertain, and unlike other games, the game of life is played through only once which prevents taking advantage of probabilities through repeated trials, as would for example happen in a casino or in the game of baseball.

- Some men will fail to understand or appreciate the significance of the physician's arguments for the desirability of treatment; others will simply give different weights to the factors being discussed.

- The decision not to accept treatment may be merely based on an irrational gut reaction to the prospect of treatment options, may be based on very limited data such as the bad experience related by the fellow who lives down the street, or may even be the perceived result of seeking divine direction.

Many of these reasons obviously can not be addressed through evidence-based arguments, but it is of interest to examine what is known about the impact of treatment on overall survival, and in addition, the impact on PC-specific survival, the risk of metastasis and local progression.

Of greatest interest in the context of treatment and overall survival is a study from Scandinavia given landmark status that was first reported by Holmberg *et al* in 2002 [2] with a sequel reported by Bill-Axelson *et al* extending the data analysis period from 8 to 10 years [3]. This study is very important because the designers randomized individuals to either surgery (radical prostatectomy--RP) or watchful waiting (WW). Men in the watchful waiting group received no initial treatment other than the transurethral resection for urinary obstruction some had already undergone. For both the surgery and WW groups, hormone therapy was recommended for all men who developed disseminated disease, and as well, for RP patients who experienced local progression. Table 1 summarizes the results.

Table 1. Causes of death for the radical prostatectomy (RP) and watchful-waiting (WW) groups during 8.2 years (median) follow-up after diagnosis.

Cause of death	RP Group (N = 347)	WW Group (N = 348)
	Number of Patients	
Prostate Cancer	30	50
Other Causes	53	56
Any Cause	83	106

In the WW group, close to 50% of the deaths within 10 years were from PC. Treatment with surgery reduced mortality from prostate cancer by 40%. Radical prostatectomy resulted in a 10-year estimated 26% relative reduction in overall mortality. This appears to be the only long-term randomized study to indicate improved overall survival attributable to treatment (in this case radical prostatectomy) as compared to watchful waiting. However, as the table indicates, the number of patients in each mortality category was rather small, and as the authors point out, the absolute reduction in mortality due to treatment was moderate and "clinical decision making and patient counseling will remain difficult." The study also found treatment resulted in a 40% reduction in the risk of distant metastasis and a 67% reduction in local progression. Taken together, these results indicate positive benefits from surgical treatment and the authors predict the benefits will increase during longer follow-up. However, the reduction in PC-specific mortality as a result of surgery was limited to patients younger than 65 years of age, although the study lacked power to fully investigate this aspect. Interestingly enough, the earlier report from this same study covering a shorter follow-up showed no significant effect on overall survival [2].

In the follow-up period, the Scandinavian study found substantial absolute differences between the two groups in terms of local progression which can cause problems with urination, pain and anxiety. The WW group had a greater need for hormone treatment and palliative radiation for pain relief. Both these interventions are accompanied by side effects that influence the quality of life. The authors point out that the more immediate but stable side effects associated with surgery must be weighed against the increasing incidence of symptoms and use of various treatments after progression in the WW group. The point is that there are more factors to consider than overall or PC-specific survival and that the decision making process is multifactorial and complex.

However, the results of the Scandinavian study are not that clear-cut. As Chodak and Warren point out in a recent review [4], the mean prostate-specific antigen (PSA) at randomization was 12.9 ng/mL (see International Health News, October 2005 to December-January 2006 for a review that includes an extensive discussion of PSA). Today, that average would be closer to 6 ng/mL. This could reduce the overall relative survival benefit and illustrates one of the problems with studies of this type being currently reported, i.e. to have the long follow-up, the cohort will generally include a higher percentage of men with more advanced disease than would be the case if the study had been initiated recently and the effect of PSA screening on lead-time well established in the study population [5]. Thus it is not clear how applicable these results are to men diagnosed with PC today.

The issue is further confused by a recent study from Columbia University which revealed a significant dependence of the outcome for radical prostatectomy on the year of surgery [6]. Three periods were identified, 1988-1993, 1994-1998, and 1999-2003. The rate of cancer recurrence after surgery (also called biochemical

failure or recurrence when it is detected by a rising PSA) expressed as a percentage of patients in each group, was 40.0%, 17.8% and 8.1% for these three periods, respectively (median follow-up 54 months). The authors were unable to account for this dramatic improvement in outcome even after correcting for all obvious confounders. The Scandinavian study started in 1989 and follow-up lasted through 2003. If the phenomenon found in the Columbia University study was also present in the Scandinavian study, this complicates the application of these results to today's population of PC patients, and in fact the benefits of surgery might be greater than reported by Bill-Axelson *et al*.

When overall survival is the issue, there is a race, so to speak, between the prostate cancer and other causes of death, and what becomes significant is which cause crosses the finish line first. Making the decision to have surgery only on the basis of the results of Bill-Axelson *et al* ignores a number of factors including the individual's age and other diseases competing in the race to death. Also, since the time frame can be 15-30 years from today, there are bound to be changes in the prevention, diagnosis and treatment of not only PC but also the competing major causes of death. No one can predict the net result of this continuously changing picture on the overall survival question. The point is that of necessity, trying to use overall survival as the critical factor in the decision to accept or reject treatment is simply a probability game, but the data one has to work with is uncertain, changing with time, and the game is played only once!

A man may elect RP over WW merely because studies suggest a large decrease in the probability of metastasis and local progression. Also, RP does indeed offer the chance, and in many cases a very good one, of a permanent cure, while classical WW does not. If the cancer is organ confined and not aggressive, the probability of recurrence 10 years after RP can be less than 10%, i.e. a high probability of a "permanent" cure. Also, recurrence is not the end of the game since so-called salvage radiation therapy can also be highly curative. In addition, the RP, because it involves the removal of the gland, eliminates most cancer related causes of urinary obstruction which in the WW case would require treatment. The RP also provides much more prognostic information than was available prior to surgery since the removed prostate is subjected to detailed pathological examination. This can be an advantage in planning additional treatment if indicated. In rejecting surgical treatment, a man elects to forgo these potential advantages.

However, a man over 65 may point to the Scandinavian study and conclude that there is no benefit from surgery if the criterion is PC-specific survival. This ignores the low power of the subgroup analysis in that study, but more importantly, he is taking an average result and applying it to himself. This in fact is at the root of the problem of decision-making based on studies or probabilities, and it why, ideally, as many factors as possible need to be considered by both the patient and his physician.

In the end, however, it seems inevitable that attempts at rational analysis will fail to provide a really clear-cut answer to the treatment dilemma. The pessimist would simply argue that there are too many variables, too many uncertainties, and besides, an integral part of the decision making process involves predicting the future which at best is a tricky business.

It is widely recognized that a small but significant percentage of patients receiving a RP will be found to have tumors deemed insignificant or indolent. The surgery may well have been unnecessary. While these tumors may never have posed a threat during the lifetime of the patient, the word *may* is important. Again, no one really knows, especially if the time frame is 15 or 20 years or more. One solution is active surveillance (AS), which represents a compromise between immediate treatment and the classical WW described above. The essential features are as follows. If the probability is high that a man's cancer is not aggressive and may never present a problem during his lifetime, then the option is to closely follow the case with periodic PSA tests, digital rectal exams, and biopsies. If no progression is seen, nothing is done. Treatment may never be necessary. If progression suggesting a threat to the patient's life expectancy is observed, he is offered treatment. Patients are initially selected so that if the decision to treat is made, the chances of a cure are high and have not been significantly influenced by the waiting period.

Active surveillance reduces the uncertainties associated with the initial assessment because the repeated follow-ups provide more reliable information on the nature of the cancer than was available from the initial clinical assessment based on PSA, Gleason score and Tumor stage (see the above cited IHN newsletter for a discussion of Gleason scores and tumor stage). It can be argued that this is a much more intelligent approach to

the question to treat or not to treat than simply accepting or rejecting treatment on the basis a number of considerations, many of which were elaborated above. Active surveillance allows the decision not to treat to be reconsidered periodically, which makes more sense than the black and white options, to treat or not to treat. In particular, it reduces considerably the uncertainty in the educated guess made after the initial biopsy as to the true nature of the cancer present in what is really somewhat of a black box.

The AS program at Johns Hopkins is particularly interesting [7,8]. It is called the "Expectant Management with Curative Intent Program." The admission criteria are: stage T1c (non-palpable tumor, discovered by biopsy prompted by elevated PSA), PSA density ≤ 0.15 ng/mL/cc *and absence of all of the following results from a biopsy involving at least 12 cores*: Gleason score of 7 or more, any Gleason pattern of 4 or 5, three or more cores involved or more than 50% involvement found in any one core. Strict follow-up includes digital rectal examinations (DRE), a PSA measurement every 6 months and a biopsy every year. Disease progression was defined as a Gleason score of 7 or more, any Gleason pattern of 4, more than 2 cores involved with cancer or more than 50% involvement of any core with cancer. Thus the biopsy provides the only trigger for recommending treatment. For the purpose of evaluating results of a follow-up study**,** "curable cancer" was defined as greater than an estimated value of 70% for the disease free progression *probability* at 10 years after surgery, which in turn was based on the pathological Gleason score and individual core patterns, whether or not the cancer was organ confined, and as well as seminal vesicle and lymph node status.

Thus far results have been reported for only 81 (median age 65, range 52-72) men involved in the Hopkins program, but a number of interesting observations have already been forthcoming. The follow-up period ranged 12 to 58 months. Some patients exhibited progression after only one or two years, but the authors suggest that this was not real progression since the time interval is too short as judged by the natural history of this disease. Thus men who experienced treatment triggers during the first two years were viewed as under-diagnosed at the first biopsy. Of the 81 participants, 25 showed progression, but only 7 may have experienced true progression. It can thus be argued that 18 may not in retrospect have really met the admission criteria, but this was missed in the first biopsy. Of the 63 who apparently actually met the admission criteria, the observed number that experienced true progression and triggered a treatment recommendation was thus 7 (11.1%), or about 89% of this smaller group remained on AS during the follow-up period. Of the 25 men with progression, 13 underwent RP, and 92% had cancers judged curable according to the above criteria. Unfortunately, the follow-up time was short, and additional results over a longer period will be of great interest. The authors conclude that expectant management with curative intent may be a reasonable alternative for carefully selected men who are older and thought to have small volume cancers. This study [8] also looked at other potential ways to predict progression. An important result was that neither the percent free PSA nor the PSA density (see IHN newsletter cited above for details) was satisfactory because of extensive overlap in both measures for men with and without progression. This result has a bearing on the interpretation of other studies of AS which used only various PSA measurements as triggers, and also is relevant in regard to the practice where physicians used only PSA changes as a trigger to terminate active surveillance.

The Hopkins study also highlights the problem of biopsies missing cancer. A recent study from this same institution [9] addresses this issue. A total of 103 men were studied who were predicted to have insignificant cancer. However, at RP 71% were classified as insignificant whereas 29% were misclassified, i.e. the cancer was not insignificant. The study showed that by using so-called saturation biopsy techniques, the misclassification rate could be reduced to about 11%. This approach used on average 44 cores (range 24-54) but a modified protocol using half the number of cores produced similar results. The authors conclude that saturation biopsy provides an accurate prediction of tumor volume and grade for the selection of candidates for AS therapy. While 44 cores may not be very appealing to some men, the merits of avoiding or delaying radical treatment should be weighed against the small potential added discomfort and increased morbidity of the saturation biopsy.

Active surveillance may also be elected by individuals at higher risk of post-treatment failure than those currently considered ideal for this option. These men may want confirmation of the clinical assessment by experiencing progression before taking action, or they may simply hope to buy some time before undergoing treatment by taking advantage of what they hope is a slowly developing disease.

The reader will probably have observed that the only treatment modality discussed so far has been surgery. This is because there is no equivalent long-term overall survival data from randomized studies for radiation therapy or other treatments vs. WW.

NOTE: This review is based in part on the introduction to Chapter 6 of the book *The Prostate and Its Problems* by Hans R. Larsen and William R. Ware which is currently in press and will be available shortly from International Health News (http://www.yourhealthbase.com).

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