Omega-3 Fatty Acids and Risk of an Acute Coronary Event

We have reached a historic point when the American Heart Association actually recommends a supplement for cardio-protection, in this case long-chain omega-3 fatty acids derived from fish oil for those who don’t eat enough oily fish. Related to this, research recently published in the American Journal of Cardiology by Harris, et al report on a study that examined the relationship between a blood marker of omega-3 status and the risk of hospital admission for what is called an acute coronary syndrome (ACS) which translates into a heart attack (MI---myocardial infarction) or severe chest pains (severe angina pectoris). At issue here is just the incidence of ACS, not the outcome, i.e. no stratification was presented for sudden death from an MI vs. survival or if severe angina was followed by an MI. Mean age for the patients and controls was about 46 years, a group selected because the authors consider this age range to potentially have the highest association between ACS and serum fatty acids. About half
were women. In this study, the omega-3 status was determined by a blood test and expressed as the amount of EPA + DHA as a % of total blood fatty acids. As most Newsletter readers know, the essential long-chain fatty acids EPA and DHA are found mostly in oily fish and in fish oil. In this study, relative risk was established by comparison of cases with controls matched for age, race and gender.

When the risk was analyzed in terms of quintiles of omega-3 status (dividing omega-3 status into fifths), a comparison using the lowest level (< 1.2% of total blood fatty acids) as a reference revealed a dramatic drop in risk such that at 1.5-1.8% the risk reduction for ACS was approximately 60% and for > 2.6% is was 80%. This strong protective relationship persisted when the results were corrected for confounding by age, gender, race, body mass index, smoking, diabetes, alcohol consumption, blood lipids and history of an MI or balloon angioplasty. The only significant confounder was, interestingly enough, college education. The authors suggest that those with lower education might have been less able to afford fish and that a college education might be protective against non-omega-3 CHD related risks due to increased health awareness and the ability to follow a healthy lifestyle and as well this group may have had a higher consumption of omega-3 supplements. While high omega-3 status can also favorably influence both triglyceride and high-density lipoprotein (HDL) levels, the authors indicate that in their analysis, the EPA + DHA level was found to be an independent factor in ACS risk. The authors claim that the amounts of omega-3 fatty acids required to achieve cardio-protective blood levels have not yet been established, but intakes of 500-1000 mg/day of EPA + DHA have been suggested and are consistent with the current American Heart Association guidelines. Finally, the authors point out that not all studies provide results that agree with theirs and that answers to important questions must await further trials. They also remark that their study was done in the setting of the U.S. diet.


Editor's comments: The study of Harris et al adds to the already strong and convincing evidence of the importance of omega-3 status in preventing sudden death from an adverse coronary event, which incidentally is the unfortunate outcome in a very significant number of heart attacks. The victim is either clearly dead by the time help arrives or attempts to resuscitate fail. Two key studies by Albert et al (N Engl J Med 2002;346:1113-9) and Siscovick et al (Am J Clin Nutr 2000;71 (suppl):208S-12S) address this issue. Both studies involved individuals with no prior cardiovascular disease and the study of Albert et al involved only men. Rupp et al (Herz 2004;29:673-85) have examined these two studies using the same scales for risk and for EPA + DHA status (blood levels) and found almost complete agreement with the risk of sudden cardiac death decreasing by over 90% when the highest to the lowest omega-3 status groups were compared. One current hypothesis is that the omega-3 fatty acids are somehow associated with preventing arrhythmia associated with MI. These results compare favorably with those discussed in the featured study and further underscore evidence for the role of the long-chain omega-3 fatty acids in cardio-protection. Rupp et al point out that the EPA + DHA levels that yielded this remarkable risk reduction can be obtained by supplementation with 1-2 g/day of EPA + DHA. Typical commercial supplements sold either as fish oil or EPA/DHA supplements have a ratio of EPA to DHA of about 2:1 or 3:2 and are readily available from drug stores, health food stores, and from online vendors. Some of the EPA/DHA preparations are highly purified and probably contain a minimum of mercury and other contaminants. Of course, these fatty acids can also be obtained by eating the right kind of fish. See the April 2007 Newsletter for a discussion of a study dealing with the risk vs. benefit of fish consumption. According to that study among the commonly available fish, both wild and farmed salmon provide the highest EPA + DHA content (2 to 6 g per 100g of fish—about 3.5 oz) with the lowest mercury content (< 0.05 ppm). Incidentally, a recent study found that alpha-linolenic acid, a popular omega-3 source found, for example, in flax seeds, does not offer benefit in prevention of cardiovascular diseases in both primary and secondary prevention trials. The body only inefficiently converts this omega-3 fatty acid into the long-chain acids found to be protective.

It is not uncommon that the first indication of CHD is a heart attack and a not insignificant number of victims have few if any conventional risk factors or any warning signs. While many survive and many go on to die of something else, for some the initial MI is immediately fatal. It appears that having a
protective omega-3 status is not only associated with a substantial reduction in the risk of this initial heart attack, but also vastly increases the probability of surviving it. In fact a recent review of the literature concluded “Evidence suggests that increased consumption of n-3 FAs [omega-3 fatty acids] from fish or fish-oil supplements reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke” (Am J Clin Nutr 2006;84:5-17). The study of Harris et al adds additional evidence to support this position.

Are there precautions? The conventional concern has to do with blood thinning. In the book by the cardiologists Sinatra and Roberts reviewed in the last Newsletter, evidence is presented that even 10 grams of fish oil per day does not interfere with the action of Coumadin or other anticoagulants. They suggest that individuals taking Coumadin simply have their physician monitor their clotting status. They do suggest not taking fish oil prior to surgery. They also recommend taking the antioxidant astaxanthin (a natural concentrate of marine algae), which protects fish oil from oxidation in the body. It has been their experience that this antioxidant is of special benefit for diabetics taking fish oil. In general, it would seem that if it is safe to eat a 7oz farmed salmon steak which provides up to 12 grams of EPA + DHA, then there is not much to worry about. A recent review in the American Journal of Cardiology also indicates that bleeding concerns are “unfounded” (Am J Cardiol 2007;99 [suppl]:44C-46C).

A blood test is available for EPA + DHA status. This test was discussed in the IHN Research Review titled “Inflammation, A Double Edged Sword” in the section devoted to assessing inflammation status (IHN, March-May 2005).

**FISH, OMEGA -3 FATTY ACIDS AND COGNITIVE PROBLEMS**

Two papers in a recent issue of the American Journal of Clinical Nutrition and one in the Archives of Neurology have address the relationship between fish consumption, omega-3 status and the risk of cognitive decline in the elderly. In a 5-year follow-up study from the Netherlands, Gelder et al examined the relationship between fish consumption and a decline in cognitive function in a cohort of men aged 70-89 years. Fish consumption was ascertained by food frequency questionnaires. It was found that those with a daily intake of EPA + DHA of approximately 400 mg had less cognitive decline than those consuming 20 mg/day. An intake of approximately 400 mg of these two fatty acids can be accomplished by eating 6 servings of lean fish per week or 1 serving of fatty fish such as salmon, mackerel or herring per week. The authors point out that the consumption of 2 serving of fatty fish a week is recommended by the American Heart Association for the prevention of cardiovascular disease.

In the second study, Beydoun et al examined the relationship between cognitive decline and omega-3 status determined from the fatty acid content of blood plasma phospholipids and cholesterol esters, concentrations that are related to dietary intake. In the 2251 study subjects, the risk of verbal fluency decline was lower in subjects with high omega-3 status, especially in those with hypertension or elevated blood lipids. However, in tests of psychomotor speed or delayed word recall, there was no significant effect of a higher omega-3 status. The authors conclude that subjects under increased oxidative stress, particularly hypertensive and dyslipidemic subjects, may benefit from a diet enriched in omega-3 fatty acids such as found in cold-water fish (salmon, tuna and mackerel and other food of marine origin.

The third study prospectively followed 899 men and women who were free of dementia at baseline and had a median age of 76 years. The mean follow up was 9.1 years. Fatty acid levels were measured in the blood plasma and for a sub-group and fish consumption was determined by questionnaire. The study was part of the Framingham Heart Study. It was found that individuals with plasma levels of DHA in the highest quartile (upper fourth) compared to the other three quartiles had a decreased risk of all-cause dementia of 47%. Protection associated with DHA was also indicated for Alzheimer’s disease but did not achieve statistical significance. Also, the plasma levels of DHA correlated closely with levels of fish intake. No other significant associations were found.

Editor’s comment: A role of DHA in brain function is quite plausible given that it is the most abundant fatty acid in the cerebral gray matter. DHA is concentrated in neurons of the cerebral cortex, synaptosomes and mitochondrial areas of the brain, and these are the areas of greatest metabolic activity. Actually, DHA is found in significant concentrations only in the brain, retina and testes. The results of these studies are consistent with a number of earlier studies where the endpoint was either cognitive decline or Alzheimer’s disease, and while there have been studies that showed little or no effect, this may reflect imprecise estimates of DHA intake from dietary sources, especially since some studies simply noted fish intake but did not stratify according to DHA content or differentiate oily from non-oily fish.

There is also the question of the impact of very high doses of omega-3 fatty acids on severe Alzheimer’s disease. The reader is referred to Dr. Barry Sears’ book *The Omega RX Zone,* (pp. 110-111) for two fascinating case histories of individuals with terminal Alzheimer’s disease who recovered significant physical and mental capabilities after high-dose fish oil accompanied by nutritional therapy. In fact, one patient went from being totally unresponsive, unable to walk and confined to a nursing home to actually returning to live full-time at home and experiencing a more or less normal life. It will be interesting to see if eventually there are studies involving significant numbers of patients to test this therapy.

**STATINS FOR CHILDREN ??**

The American Heart Association has just published its latest guidelines regarding drug therapy for high-risk lipid abnormalities in children and adolescents. These represent modifications of the 1992 National Cholesterol Education Program guidelines. The main features of the older guidelines have been preserved, and merely modified on the basis of what the committee regards as the current situation with regard to other risk factors that might influence the decision for drug intervention. Thus the current guidelines are as follows.

1. Consider drug intervention in children age ≥ 10 (usually wait until menarche for females and after a 6-12 month trial of diet and exercise).
2. Consider drug therapy if LDL remains ≥ 190 mg/dL (4.90 mmol/L). If LDL remains > 160 mg/mL (4.1 mmol/L) and (a) there is a positive family history of premature cardiovascular disease or (b) ≥ 2 other risk factors are present after vigorous attempts to control these factors, then drug intervention is also indicated.
3. Treatment goal: Minimal, LDL < 130 mg/mL (3.35 mmol/L; ideal < 110 mg/mL (2.85 mmol/L)

Risk factors and high-risk conditions: male gender, low HDL, high triglycerides, small dense LDL, overweight or obese and other aspects of the metabolic syndrome, hypertension, smoking or exposure to passive smoke, and elevated lipoprotein(a), elevated homocysteine, or c-reactive protein. Finally, there are medical conditions that increase the risk such as diabetes, HIV infection, systemic lupus erythematosus, organ transplantation or surviving childhood cancer which also count as risk factors.

The authors comment that the evidence base underlying these recommendations is supported by indirect evidence, evidence extrapolated from studies in adults, studies performed in the context of familial hypercholesterolemia (which is associated with premature cardiovascular disease) and expert consensus. Furthermore, they caution that direct evidence of an impact of interventions during childhood and adolescence on later cardiovascular morbidity and mortality will likely always be lacking and that drug therapy should only be targeted toward individuals with high-risk lipid abnormalities or high risk conditions who have not reached the target lipid levels with lifestyle modification.


Editor’s comment: First, how common are levels of 190 or 160 mg/dL? A recent study
For the age group from 12 to 20 years, mean LDL values were about 100 nmol/mL. For boys, the 98th percentile came in at about 155 mg/dL and for girls the 95th percentile was about 135 mg/dL. Thus for this age group, LDL > 160 or especially ≥ 190 is rare and appears to truly represent an abnormality. But in the group of children with LDL > than 160 mg/dL, if only two of the above listed risk factors are necessary for triggering drug intervention, then this no doubt expands the eligible group considerably. Second, how successful are dietary interventions in correcting elevated LDL. In a study published in 2001, a conventional intervention involving reductions in total fat, saturated fat and cholesterol over 5-8 years produced a 2.0 mg/dL drop in LDL when comparison was made with a control group. Furthermore, for this group which was initially 8-10 years old, both the intervention and control groups experienced a drop in mean LDL from about 130 to 110 mg/dL on 5-8 years follow-up (Pediatrics. 2001;107:256-64). Obviously, a 2 mg/dL decrease in LDL would seem to have little clinical significance if one has an LDL over 160 and measurements in this age group may have little value anyway, given that they change significantly.

However, there are fundamental questions. We are dealing here with recommendations that are by and large not based on studies relevant to the age group in question nor to the intended long-term use of drug intervention. In a special article for the journal Pediatrics (2007;119:370-80) Belay et al address these and related issues. They make the following points: (a) Randomized clinical trials of statins in adults have been mostly for secondary prevention in older adults, and because even children considered at the highest risk rarely experience a cardiovascular event, the results of secondary prevention trials in adults should be cautiously applied to children; (b) the translation of aggressive treatment targets based on secondary prevention trials from adults to children and adolescents is not justified for primary prevention; (c) primary prevention studies using statins with adults have not demonstrated any reduction in absolute risk for total mortality and the reductions in coronary and cardiovascular mortality are modest in comparison with those observed in the secondary prevention studies. They regard this as a crucial aspect since before statins are used for primary prevention in children and adolescents, they consider it critical to demonstrate that both coronary and total mortality are reduced in later life with childhood statin therapy; (d) the anti-inflammatory benefits of statins on advanced atherosclerotic plaques may not be seen in children whose plaques are at a much different stage of development. They go so far as to suggest that the effect of statins seen in primary prevention relates to the subgroups of individuals who already have unstable plaques; (e) with regard to the safety issue, the AHA position which incidentally seems to downplay side effects and safety issues, is based on trials with children that have lasted only from 6 months to 2 years and these clinical trials have been underpowered (too few subjects) to detect infrequent or rare adverse effects. They also point to the problem that the intervention is during cognitive and endocrinologic maturation, skeletal growth, and bone mineral accretion and that there are no studies that directly address statin safety issues in this age group.

Other problems need to be mentioned. Statins may be associated with central nervous system and limb anomalies in a significant percentage of exposed first-trimester pregnancies (N Engl J Med 2004;350:1579). Therefore, statin therapy among female teenagers capable of reproduction may carry a very significant danger unless contraceptives are used. Also, girls have lower risk of developing cardiovascular disease than boys, and this must be taken into account in decisions about who to treat. There are also issues associated with breast cancer risk associated with use of oral contraceptives prior to about age 20.

Finally, a study published in 1990 (JAMA 1990;264:3034-8) looked at cholesterol levels in children 8 to 18 years of age and then followed them for 20-30 years to see how many as adults developed cholesterol levels that would have merited continued surveillance and intervention. They found that screening for total cholesterol resulted in significant numbers of individuals being incorrectly classified with respect to future cholesterol level elevations. They point out that based on their results, many children with high cholesterol levels have normal levels in young adulthood without intervention.

While the above considerations seem to make it clear that the AHA recommendations are not, as the authors admit, really evidence based and that there are many important issues, it is however almost impossible to implement studies that start
with very young children, put half of them on statins, and follow the cohort for 30-40 years to see if the childhood LDL levels and risk factors that would trigger this drug intervention in childhood really lead significantly to cardiovascular problems in much later life which are significantly decreased in the treatment group. Early treatment vs. treatment of adult disease if it occurs has never been carefully investigated. Thus the bottom line in the case of children deemed at risk appears to be very aggressive lifestyle intervention to correct childhood obesity and poor dietary habits. But the guidelines talk about diets low in cholesterol and saturated fat, and yet the studies they quote found this intervention had almost no effect on LDL levels. Other studies cited in the guidelines paper also were impractical (no meat or dairy products) or produced only small effects and these on children with normal LDL levels. The guidelines also are inconsistent in that they reference the AHA pediatric diet strategies which do not mention avoiding cholesterol containing foods and which appear more in tune with reality (Circulation, 2005; 112:2061-75. Free at journal website www.circulationaha.org). To get the diet plus exercise approach to really work will, it would seem, present a severe but obviously highly worthwhile challenge to parents with children who are overweight or have the metabolic syndrome.

Given that the indications for statin use in children are far from securely evidence-based and in fact mostly based on evidence from adult studies on individuals with heart disease, that we are presumably talking about very long-term therapy, that the long-term safety is not and may never be directly established for this age group and that the optimum age for pharmaceutical intervention has not been established, it would seem that parents need to be very concerned regarding the recommendation to proceed with childhood statin therapy. But it must also be acknowledged that children with a strong family history of premature heart disease are a special case for which some of the objections and cautions enumerated above may perhaps assume somewhat less importance. However, as will be discussed in an upcoming Research Review, the evidence that high LDL is a direct cause of CHD in young individuals is very controversial.

### HDL CHOLESTEROL AND RISK OF STROKE

In the U.S. the risk of stroke ranges from 35 per 100,000 people of age 35 to 1,100 per 100,000 in the age group 75-80. Among cardiovascular adverse events, it produces some of the most devastating non-fatal outcomes. The strong relationship to age and the aging population highlights the importance of stroke prevention. A paper just published in the journal *Stroke* endeavors to call attention to the role of HDL cholesterol in stroke risk. The authors list studies comprising over 60,000 participants published between 1994 and 2004. Five of the 7 large to very large cohort follow-up studies found significant benefits from elevated HDL levels with risk reductions of between 32% and 66%. With one exception the studies were restricted to so-called ischemic strokes rather than hemorrhagic (bleeding) strokes. The authors point out that case-control studies also showed this inverse relationship. They also point out that in a study of plaque in the carotid arteries (arteries in the neck running up into the brain) low HDL was related to high plaque volume as determined by ultrasound, a result found to be an independent effect. Also, in the very old (≥ 85 years), one study found that low serum HDL was associated with increased risk of stroke, cardiovascular disease and mortality, but LDL and total cholesterol had no such association, and in another study of young individuals it was shown that low HDL was the only serum lipid marker associated with an increase in stroke risk.

The authors also comment on interventions that raise HDL. In a study by Rubins, et al reported in 2001 in the journal *Circulation*, a total of 2531 men with heart disease and low HDL levels were randomized to the non-statin drug gemfibrozil, a drug that increases HDL, or a placebo and followed for 5 years. A significant 48% risk reduction for confirmed strokes was found for the intervention group, whereas there were no significant changes associated with risk vs. LDL or triglyceride levels. Other options discussed include niacin and statins. For the former there are no studies to date addressing the impact on stroke. However, while there appears to be no association between cholesterol levels and stroke risk, statins have been shown to reduce the risk of ischemic stroke.

Editor’s comment: Concerns about cholesterol levels, whether justified or not, are generally associated with coronary heart disease rather than stroke. In fact, repeated attempts to show a cholesterol/stroke relationship have almost always failed unless stratified for HDL. Those who claim there is an association ignore a large number of studies and invoke the ad hoc hypothesis that lowering LDL reduces the risk of ischemic stroke but its failure to influence hemorrhagic strokes masks the overall effect. But ischemic strokes constitute the vast majority of strokes. Some studies have failed to confirm an increase risk of hemorrhagic strokes at low levels of LDL although this is still be an open question since some studies conclude the opposite. Also, studies with statins, which reduce the risk of stroke in heart disease patients, do not show a dose dependence of LDL levels on stroke risk reduction, suggesting that the mechanism involved does not depend on LDL lowering but on other actions of statins, although in some cases there might be a weak effect of increased HDL due to the statin treatment.

NEWS BRIEFS

VITAMIN D AND NURSING HOME FALLS
Fall-related fractures and injury represent a serious problem affecting the quality of life of elderly nursing home residents. In a just-published paper by Broe et al. in the Journal of the American Geriatric Society, a randomized dose study was reported which investigated the role of vitamin D in the risk of nursing home falls. Supplement doses ranged from 200 to 800 IU/day. Participants in the 800 IU group (mean total intake 1026 IU, range 800-1200) had a 72% lower rate ratio of falls than those given a placebo and no significant differences were observed between the placebo and supplement groups at any of the lower doses (600, 400, and 200 IU/day). This threshold for effectiveness was associated with a serum 25-hydroxyvitamin D mean level of about 75 nmol/L. Those taking the standard multivitamin given regularly in the residence studied received 400 IU and 57% of the participants had levels below 50 nmol/L. The authors discuss the possibility that vitamin D supplementation provided both muscle and bone benefits which accounted for the decrease in falls for those above the threshold intake for benefit.


Editor’s comment: Readers with parents or friends confined to nursing homes should be concerned about the problem of vitamin D deficiency. While a blood test would settle the question of deficiency (if judged against standards such as > 75 nmol/L of 25-hydroxyvitamin D) a simpler expedient would be to attempt to implement supplementation at level such as used in this study or perhaps even higher. As discussed...
in other issues of the Newsletter, with the elderly and especially those confined to nursing homes, several thousand IU/d may be necessary to eliminate deficiency.

**VITAMIN E AND ALZHEIMER’S DISEASE**

There have been reports in the literature that vitamin E intake was only associated with Alzheimer’s disease when the source was food, and in particular not with supplements. While there are 4 different tocopherols called vitamin E, supplements only generally contain the alpha form. A study has now looked at the influence of vitamin E and the incidence of Alzheimer’s disease taking into account the intake of all four forms. During a four-year follow-up only gamma- and delta-tocopherol intakes were found to provide statistically significant protection, with a 40% decrease in incidence of AD for the former per 5mg/day increment and a 25% decrease for the latter per a 1 mg/day increment. In a model involving the rate of cognitive decline, alpha- and gamma-tocopherol were found to have the largest benefit.


**Editor’s comment:** Many vitamin E supplements and multivitamin preparations contain only alpha-tocopherol. However, vitamin E preparations containing all four forms are readily available and as well, alpha-tocopherol can be purchased separately if one wishes to simply augment their multivitamin.

**RED WINE AND POST MI OUTLOOK IN DIABETICS**

Red wine has been implicated in decreased cardiovascular disease risk. Some aspects were discussed in the Mini-Review *The French Paradox* in the April Newsletter. Marfella et al have recently reported on a study that examined the impact of moderate red wine intake on cardiac prognosis after a heart attack (MI) in subjects with type 2 diabetes. The outcomes studied were markers of inflammation, oxidative stress and cardiac function. One hundred and fifteen diabetic subjects who had experienced a first MI were randomized and data at 12 months compared to baseline values. In the intervention group, red wine intake was 118 ml (4-oz, a small glass) per day taken with meals. It was found that this intervention significantly reduced oxidative stress and the levels of pro-inflammatory markers and as well, there were fewer post-MI complications. The authors discuss at some length the evidence that there is benefit in this context associated with the observed decrease in inflammatory markers and measures of oxidative stress. They conclude that moderate red wine consumption may help prevent cardiovascular complications after MI in diabetics.


**AGING GRACEFULLY**

Researchers from several U.S. institutions have jointly examined the question of what characterizes women who maintained optimal cognitive function into old age. A cohort of almost 10,000 older women was followed for 15 years. Cognitive status was evaluated with a standard test at baseline and at 6, 8, 10 and 15 years. Participants were classified as cognitive maintainers, minor decliners and major decliners. The women were of mean age of 72 at the start of the study and 85 at the end of follow-up. Only 9% maintained optimal cognitive function until the end of the study period or death. The comparable figures for minor and major declines were 58% and 33%. Both the optimal and minor decliners would be considered cognitive normal to the casual observer. The factors most predictive of maintaining optimal cognitive function were lack of diabetes, hypertension and smoking, moderate alcohol consumption, no difficulty in daily living and the presence of a good social network. All of these factors carried significant positive benefits when the comparison was made between those maintaining optimum cognitive function and those with just minor cognitive decline. For example, when the optimal maintainers and minor decliners were compared the optimal group had almost twice the probability of not having diabetes. The authors point out that these factors have been associated in other studies with overall health status and risk of mortality.


**WHO PAYS FOR U.S. GOVERNMENT APPROVAL OF NEW DRUGS?**

Some readers may be unfamiliar with how the U.S. system works. In a perspective in the April 26 issue of the New England Journal of Medicine, Jerry Avorn, author of one of the books listed below, reviews the current status which apparently is about to be reaffirmed by Congress.
Based on 1992 legislation, the funding of the FDA was adjusted such that the drug industry paid the salaries of agency employees who reviewed the companies’ new drug submissions (the wolf guarding the henhouse model). Furthermore, the legislation forbid the use of company fees to evaluate drug side effects after approval, which resulted in a downsizing of that aspect of the agency operation. The industry payments per drug amount to about half a million dollars, and it is estimated that by 2008 the industry’s share of running the regulatory body will amount to over $400 million. This has resulted in the drug industry being in a sense a client of the agency that oversees it, whereas one might have naively thought that the clients of the agency were the citizens of the country. According to Avorn, four former FDA commissioners all hold the opinion that the new drug approval operation should be financed entirely by the government rather than industry.


**DRUG-POMEGRANATE JUICE INTERACTIONS**

A small study just reported in the *Journal of Clinical Pharmacology* appears to be the first to directly address this question in human subjects. Pomegranate juice is hypothesized to inhibit an important enzyme involved in the clearance of some prescription drugs. In this study the clearance process was challenged by a probe for the activity of this enzyme in human volunteers. Both oral and intravenous administration was employed and the comparison was with grapefruit juice. It was found that pomegranate juice did not alter the clearance of either intravenous or oral doses of this probe whereas grapefruit juice inhibited clearance after oral administration.


**Editor’s comment:** In the February newsletter work was reported indicating pomegranate juice might be very effective in dealing with PSA-only recurrence after radical prostatectomy or radiation therapy for prostate cancer. In the May issue of the Prostate Monitor this topic was given additional coverage and that discussion included mention of the potential interaction of pomegranate juice with prescription drugs by a mechanism identical to grapefruit juice. The basis of this concern is almost entirely based on cell culture experiments and studies in rats. Human evidence prior to the publication of the above report appears to be only one anecdotal case of statin-associated rhabdomyolysis (severe muscle problems) which occurred after ingestion of pomegranate juice. The authors of that report used the fact that grapefruit juice has been associated with rhabdomyolysis to implicate pomegranate juice. However, the above study of Farkas et al, which appears to be the first human study to look directly at the drug-pomegranate juice interaction hypothesis, was unable to provide evidence of that would support either the implications of the anecdotal rhabdomyolysis case or the cell-culture or rat studies.

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BOOKS FOR SUMMER READING

Interaction of the Medical Profession and Drug Companies

The list of books presented below was prompted by the following study which in turn was in part motivated by a publication in 2002 by the American College of Physicians and the American Society of Internal Medicine of two position papers on ethics associated with physician-drug industry relations. Concern was triggered by studies that demonstrated that commercial influence could compromise judgment about medical information and subsequent decisions about patient care. In addition, concern was expressed over bias introduced into educational activities sponsored by the industry. Several U.S. states are taking an active role in monitoring payments made by the drug industry to physicians and currently 5 states and the District of Columbia have laws mandating disclosure.

In the March 21 issue of the Journal of the American Medical Association, a paper by Ross et al describes some of the data they were able to collect as a result of these laws. They examined data from Minnesota and Vermont, but were unable to get a complete picture because, as they describe the problem, the disclosure laws had significant loopholes and industry compliance was only partial. Also, when the investigators attempted to acquire the required data, it turned out to be operationally difficult. In Minnesota they were required to photocopy each company disclosure form by hand and pay a fee.

In Minnesota, for the period January 1, 2002 to December 31, 2004, the investigators found a total of almost 22.4 million in disclosed payments to physicians, of which only 15.7% were for research grants. Other categories were education at 4.6 million, consulting at 1.05 million, speakers at 2.7 million, and “unspecified” at 9.4 million. They also provided the ranges of individual payments. The highest total payments to a single individual for consulting was over $330,000, for speaker services $154,188, and there was one unspecified payment of over $330,000. These represent lower limits since the researchers were only able to use publicly disclosed payments and it was clear that this represented only a fraction of the payments. Also, in Minnesota, while 60 companies disclosed payments overall, only 15 companies disclosed payments in all three years. As might be expected, the numbers for Vermont were much smaller, totaling only about 1 million dollars.


Editor’s comment: Consider how huge the payments, even if only partially disclosed, must be in New York or California where the number of medical schools and special high-profile institutes is much greater than in Minnesota, where there are essentially only the University of Minnesota and the Mayo Clinic. But this is just one aspect of a much greater problem. The interactions of drug companies, Wall Street, European bureaucrats, North American governments, medical academics, the medical profession and the regulatory agencies such as the United States Federal Drug Administration (FDA) in the area of so-called health care are complex, varied, and to some observers, quite alarming. It can be argued that most people might perhaps be better off not knowing what really goes on. Nevertheless, as a service to readers, your editor has prepared a list of recent volumes that probe into these matters, some reaching considerable depth. A quite comprehensive view of the whole matter can be had even by restricting attention mostly to books authored by medical doctors. As will be noticed, the authors of the books listed below have impressive credentials that permit them to speak with authority and, in some cases, they have held important positions offering unique observational opportunities. It may surprise some that they have spoken out at all on subjects as sensitive as those. All the books were published in the last several years by respected publishing houses. However, some may not find them amusing and entertaining books ideally suited to take to the cottage. But one thing is for sure, these books deal with very important current issues in modern medicine and so-called health care.

of Medicine and at the writing of this book was a member of Harvard Medical School’s Department of Social Medicine.

2. **On the Take. How Medicine’s Complicity with Big Business Can Endanger Your Health.** By Jerome P. Kassirer, MD, Oxford University Press, 2005. Dr. Kassirer was also an editor and chief of the *New England Journal of Medicine*, in fact for eight years, and when this book was written he was Distinguished Professor of Medicine at Tufts University School of Medicine.


4. **Powerful Medicines. The Benefits, Risks and Costs of Prescription Drugs.** By Jerry Avorn, M. D., Alfred A. Knopf, 2004. Dr. Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Bingham and Woman’s Hospital.

5. **The $800 Million Pill. The Truth Behind the Cost of New Drugs.** Merrill Goozner. University of California Press, 2004. The only non-M. D. author in this list, Merrill Goozner is former Chief Economics Correspondent at the Chicago Tribune, a background appropriate to this topic. He is a well-known investigative journalist.

6. **How Doctors Think.** By Jerome Groopman, M. D., Houghton Mifflin, 2007. Dr. Groopman holds the Dina and Raphael Recanati Chair of Medicine at Harvard Medical School and is chief of experimental medicine at Beth Israel Deaconess Medical Center in Boston. A hematologist, he has published over 150 scientific papers. This just published book covers a much broader area than those covered in the above books, but it also includes some of the topics that are central to the main theme of this list.

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**Pandemonium. Bird Flu, Mad Cow Disease, and Other Biological Plagues of the 21st Century**

by Andrew Nikiforuk

Penguin Group—Viking Canada, Toronto, 2006

This book provides a frightening view of the consequences, both present and future, of unrestricted trade and globalization of international traffic in living things that are potentially dangerous and which the author terms biological bombs and highly undesirable hitchhikers. Nikiforuk describes how our health and habitat are threatened by biological invaders—bacteria, viruses, fungi, prions, non-native insects and aquatic species—invaders that take up residence far away from “home” and possess the potential to produce health and economic disasters, in some cases of unparallel magnitude. We await the advent of a flu pandemic while having already gotten a glimpse through the SARS incident of the speed with which such a phenomenon can develop and the havoc it can cause. In this book, Nikiforuk explores the mechanisms associated with the development of potentially devastating strains of pathogens, how the structure and nature of our societies and governments contribute to a profound vulnerability leading to what he views as an impending crisis, and what might be done to prevent the ultimate disaster from occurring. The author is an award-winning journalist. His earlier book *The Four Horsemen: A Short History of Plagues, Scourges, and Emerging Viruses* won critical acclaim in Canada, the US and Britain. According to the author, *Pandemonium* took three years to write and is based on more than 3000 books and articles.

The tone and philosophy of the book is already set in the first chapter where the author describes in detail how the seeds of a pandemic can be sown and nurtured by profit driven practices as exemplified by the huge high-density chicken factories in Asia populated by stressed-out birds lacking genetic diversity that are immuno-compromised and thus highly susceptible to avian epidemics—epidemics that are promoted by inattention to risk factors and the need on the part of governments and owners to suppress information regarding any problems that might impact business while ignoring the fundamental causes. As many readers know, this is “serious stuff” since presumably if the H5N1 poultry virus mutates such that it is easily transmitted from human to human, we are all in potentially deep trouble. As we have heard repeatedly from the media, experts say this is inevitable—just a matter of time, and if it isn’t H5N1 it will be some other virus or pathogen. Prepare to stay home for months and eat your stockpiled emergency rations, we are told. This chapter provides many insights into just
how the present state of civilization has allowed, in the view of the author and the experts he cites, such a situation to develop. As the reader will find, solutions are far from simple, given that many governments are involved and we are all connected by air travel which can disseminate contagious pathogens with an efficiency and speed unique in human history. Migratory birds can also play a critical role in intercontinental spreading of avian pathogens.

Chapter 1 includes a lot of history of not only H5N1 bird flu but of other avian diseases. By 2004 H5N1 bird flu was of pandemic proportions among chickens in 10 Asian countries and resulted in the deaths of millions of birds, both from disease and culling, and as well a number of people. The author argues that these major epidemics all came from China, and the most important reason for the spread was trade and smuggling of agricultural and livestock products, including exotic birds. But the problem was not restricted to Asia, and when a relative of the H5N1 virus invaded the Fraser Valley of British Columbia, the government ended up culling 19 million birds. The author ends the chapter by quoting a French microbiologist “It is impossible to separate infectious diseases from our life style or from the structure of our societies, and above all, from venal considerations. Our infections mirror our primary interests and our way of life.”

Chapter 2 discusses how various invaders such as viruses, bacteria, fungi, ticks, rats, a huge assortment of aquatic species, etc., move around the world virtually unimpeded thanks to truly global commerce. People who live near the Great Lakes are familiar with one such example, the Zebra mussel. The author recounts numerous other examples and the amazing multiplicity of modes of transport. This chapter is followed by seven chapters dealing with such topics as livestock plagues, prion caused diseases such as mad-cow, rusts and blights that impact crops, anthrax, and a chapter about diseases that develop mainly in hospital populations and are resistant to antibiotics. Reading about this last topic will no doubt raise the bar considerably for many when considering whether or not to visit someone in a hospital, and it is a topic bound to be in the news and discussed in the pages of medical journals with ever increasing frequency. There is even an appendix giving “14 steps you can take to reduce your risk of a hospital infection.”

The contents of the chapter titled “Rusts, Blights and the Invaded Larder” will probably surprise and even shock most readers since knowledge of the worldwide situation with regard to food-crop pathogens is probably limited to plant pathologists, concerned government agencies, and the impacted farmers. Historical perspective is provided by descriptions of the almost total destruction of the thriving coffee business in Ceylon in the late 1800s due to the coffee rust fungus and then its spread to other countries, the Great Potato Famine in Ireland caused by the potato blight, a fungus-like infestation that is still very active today where in some farmers must spray toxic fungicides every three days, and the demise of the popular commercial banana variety Gros Michel and the distinct possibility that someday there will be no bananas that taste like those we know and fancy. Problems like these are occurring in many places with many food crops and obviously causing havoc. The author points out that half of the world’s crops are now destroyed each year by plant diseases despite the use of $35 billion worth of pesticides. He discusses how the vastly diminished genetic diversity of most food crops worldwide as well as the uncontrolled movement of pathogens and plant material in international commerce have combined to create a situation where the world now teeters, in his opinion, at the brink of worldwide disaster and famine.

In a chapter titled “Nemesis” the author describes what might be the scenario associated with a true human pandemic, how it would develop and play out, and what the ultimate effect might be on globalization, free trade, and the structure and functioning of modern civilization, especially if the death toll was enormous. This is a scenario that many have described in one way or another, but apparently the only plausible approach is to prevent it in the first place. Vaccines would probably take too long to design and produce, drugs probably would not be adequately effective and certainly in short supply, health care systems would certainly be overwhelmed, and in the end, it would be everyone for himself.

The mechanisms whereby contagious diseases are nurtured and spread, whether they involve humans, animals, fish, trees, agricultural crops, etc., contain the guidelines for prevention. Unfortunately, most of the solutions that might work are politically unpalatable, costly, and inconsistent with economic reality based on the current world economic and political structure. To limit free international commerce in birds, animals, food, feed, agricultural products, forest products, packing materials, etc., etc., and to impose rigorous inspections of most items at all ports of entry theoretically would provide protection and prevention, but on a global scale, the economic disruption would be catastrophic and the problems of implementation mind boggling. The only alternative that
may be at all realistic is responding to crises and doing only what is expedient even in the face of undeniable threats from every corner. In the long-run we may all suffer from the failure to address the many important issues raised and explored in *Pandemonium*. But readers of this book will at least have a good grasp of what probably went wrong. Some may even start stockpiling food and buying high-quality face masks!
In a break with tradition, this issue of The Prostate Monitor starts with a case study of a man who experienced recurrence both after a radical prostatectomy and subsequent salvage radiation therapy. His recent experience treating PSA-only recurrence with pomegranate juice should be of both general interest and as well, great interest to individuals with this type of recurrence either after surgery or radiation therapy. Readers will recall that this alternative therapy, based on a study from the University of California at Los Angeles, has been discussed already in both IHN and in The Prostate Monitor.

Other topics covered include alcohol (the beverage type) injections into the prostate to reduce the symptoms of prostate enlargement (BPH) and even reduce prostate volume, and as well a discussion of a recent study that compared minimally invasive therapies for BPH. This study is particularly interesting because of the rather high rate of treatment failure found for three popular minimally invasive protocols. Finally a study is presented which addresses the very important matter of treatment vs. watchful waiting for older men diagnosed with prostate cancer in the PSA era.

Wishing you continuing good health,

William R. Ware, PhD, Editor


POMEGRANATE JUICE AND PSA-ONLY RECURRENCE: A CASE HISTORY

While case histories are perhaps not entirely appropriate for this Newsletter, your editor would like to share with readers the following. An acquaintance had a radical prostatectomy in June of 1997 at age 65. His preoperative PSA was 12.0 ng/L. Postoperative pathology confirmed the biopsy result that he had prostate cancer. Within a month his PSA had become undetectable but by May 1998 it was up to 0.10 and over the period from then until February 2004 it slowly increased to 0.95 for a doubling time over most of this period of less than 2 years, not a good sign. At this point his urologist recommended salvage radiation therapy which was carried out using modern, three-dimensional conformal radiation therapy. By December 2004 his PSA had dropped to 0.1 but by December 2005 it was 0.12 and then took off, increasing exponentially with a doubling time of about 8 months. By Jan 3, 2007 it had reached 0.37. The failure to maintain a nadir after salvage radiation therapy normally indicates that the radiation had failed to reach and kill all the cancer cells, and a doubling time of 8 months is intermediate between indications of an aggressive recurrence and one that can be merely watched. In this case, there was no clinical manifestation of metastasis, just PSA-only recurrence.
After his PSA reached 0.37 ng/L, he became aware of the University of California at Los Angeles (UCLA) study where pomegranate juice was found for some men with PSA-only recurrence to slow, arrest or reverse the progression of PSA. He started a program of 8 oz of pure pomegranate juice per day, taking mostly the brand used in the UCLA study (POM Wonderful Company, Los Angeles, CA). By late April 2007, instead of his PSA being higher (projected value 0.55), it had dropped to 0.20. Needless to say, this individual was elated since an 8-month doubling time is not a good omen (see the May Prostate Monitor) and if the same rate had been maintained, then in less than 4 years his PSA would have been over 10 and he would probably have been encouraged to start hormone therapy. It is not known if the pomegranate juice effect, where there is a slowed increase or a reversal of PSA, really indicates a delay or halt of progression to clinically evident metastasis or the potential for complete remission, but one cannot argue with what appears to be a very good result. In fact, not only work done at UCLA but elsewhere strongly suggests that chemicals in pomegranate juice are acting as sort of natural chemotherapeutic agents. It will be a number of years before long-term survival data become available, if ever. The UCLA study did not involve a placebo arm, but the researchers did examine the question of the action of pomegranate juice on PSA levels in normal individuals and found no effect.

If this individual had been given a prescription drug (other than a 5-alpha reductase inhibitor such as Proscar) that accomplished in three months a 64% drop in PSA from that expected for this latest reading on the basis of the 8 month doubling time, it would have been regarded as a triumph of modern medicine. In the terminology commonly used, he showed an outstanding "response" to treatment. But he got his “drug” from the grocery store and in fact, it tastes quite good. The trouble is, probably most urologists, internists and GPs have never heard of this approach to dealing with PSA-only recurrence and if they have, prescribing a remedy obtained at the grocery store might seem just a bit unprofessional, especially since there are no multi-center, randomized placebo controlled intervention studies of long duration to satisfy the requirements of evidence based medicine. The article describing the UCLA research was discussed in the February Newsletter and in more detail in the May Prostate Monitor. Obviously, a case history involving one individual does not carry much weight, but your editor thought that men who are dealing with PSA-only recurrence might find it interesting. The reporting of this case history does not imply any therapeutic recommendation and is merely presented to provide information related to the possible therapeutic potential of pomegranate juice. Also, a recent human study on the potential for interaction between pomegranate juice and prescription drugs is discussed in the News Briefs section of this newsletter.

**PROSTATE ENLARGEMENT (BENIGN PROSTATIC HYPERPLASIA—BPH)**

**ALCOHOL INJECTIONS FOR SYMPTOMATIC BPH**

The idea that there might be some chemical that could simply be injected into the prostate and counteract enlargement, i.e. shrink the prostate and reduce the urinary problems of BPH, is in fact not new. As discussed in earlier issues of the Prostate Monitor and in our book *The Prostate and Its Problems*, one substance being studied is the neurotoxin Botox and early results are encouraging. Another substance that has been suggested is ethanol (ethyl alcohol—the alcohol in alcoholic beverages).

A phase I/II study has just been reported which has evaluated the safety and efficacy of alcohol (ethanol) injected directly into the prostate for the purpose of relieving lower urinary tract symptoms (LUTS) and examining the effect on prostate volume and PSA [1]. The transurethral injections were carried out under direct observation using a special retractable needle device (ProstaJet) which allowed a maximum of 2 cm penetration into the prostate. All procedures were done under anesthesia and oral sedation, e.g. a local block or regional anesthesia. All patients received antibiotics and were temporarily catheterized following the procedure.

The authors report the following. Adverse events were generally mild or moderate and no serious adverse events were reported. Statistically significant improvements were observed in the International Prostate Symptom Score, quality of life, maximum flow rate and the prostate volume decreased. Improvements were observed for the full range of prostate volumes present in the study and there was no apparent dose effect. For
patients with pre and 6-month post treatment PSA values, the mean was reduced from 3.47 to 2.70. Changes in prostate volume ranged from 12.6% to 24.8% [1]. This procedure qualifies for being called minimally invasive. Side effects resolved within a month.

COMPARISON OF MINIMALLY INVASIVE THERAPIES FOR BPH

In our book we discuss a number of options for treating BPH once the problems it causes have become intolerable or there is acute urinary retention, i.e. one can’t pee at all. The so-called gold standard treatment is still the transurethral resection of the prostate (TURP) better known to the layman as the roto-rooter operation. This procedure removes tissue from the inner part of the prostate and eliminates the constriction of the flow of urine. In the past decade or so a number of procedures considered less invasive have been developed, tested, and promoted as alternatives to the TURP.

In a recent study by Ohigashi et al three such minimally invasive therapies were compared with a 5-year follow-up [2]. The procedures studied were transurethral microwave thermotherapy (TUMT), transurethral needle ablation (TUNA) and transrectal high intensity focused ultrasound (HIFU). The details of these procedures can be found in our book. Urinary symptom scores, quality of life measures, maximum flow rates and post-void residual volumes were examined over a period of 24 months. No statistically significant differences in these parameters were found between the three minimally invasive procedures. However, those requiring re-treatment represent treatment failure; this study found that all three protocols resulted in high treatment failure. This study found that up to 62% of all patients initially treated with minimally invasive procedures required either medical or surgical secondary treatment within 5 years, but the risk of having additional treatment did not significantly differ between the three tested therapies. The authors point out that other studies have found re-treatment rates were significant but somewhat lower than they found in this study. However, Zani et al in a recent meta analysis, found only 5% re-treatment rates for the more invasive TURP procedure [3]. Unfortunately, in the study by Ohigashi et al the TURP procedure was not included for direct comparison, but they comment that the high treatment failure rate they observed should be taken into account when selecting among treatment options for BPH related lower urinary tract symptoms.

The success and durability of minimally invasive therapy for BPH may depend on the type of equipment employed and the skill of the operators, and men considering one of these approaches should consider investigating the success rates, if available, experienced in local and nearby facilities. However, this information may be hard to get or limited.

WATCHFUL WAITING FOR ELDERLY MEN WITH LOCALIZED PROSTATE CANCER

For men with localized prostate cancer, the option exists to either treat with surgery or radiation or merely to observe, an approach frequently called watchful waiting or expectant management. This very important topic received considerable attention in our book The Prostate and Its Problems at the beginning of Chapter 6. The issue is of course to avoid the side effects of treatment if radical or definitive therapy is unnecessary, but the matter is made complex by different proposed approaches to selecting individuals for watchful waiting and by the lack of adequate long-term data concerning relevant endpoints such as overall mortality and prostate cancer specific mortality, especially data that applies to the post PSA era where prostate cancer is in general diagnosed at a much earlier and more readily curable. Another very important issue, even with localized cancer, is the patient’s age and the so-called comorbidities, factors that come into play when an attempt is made to answer the question of estimated life expectancy.

Wong et al have recently published a study which addresses some aspects of this problem for patients in the age range of 65 to 80 years [4]. Previous studies had suggested that better survival among treated patients was only seen in younger men, i.e. < 65 years of age. This present study was based solely on U.S. Medicare data regarding claims for treatment. Individuals with claims for a radical prostatectomy or radiation treatment during the first 6 months after diagnosis were considered to have been treated, whereas if there was no such claim, they were deemed to have been merely observed. Those receiving only hormone therapy were excluded. The
main outcome measured was overall survival, thus addressing the question, does treatment influence actual lifespan in this older cohort? The average duration of follow-up was 12 years.

In this study, a 30% lower mortality risk was found over the study period for treated patients. In a subgroup analysis, there was a 27% mortality risk reduction for men between 75 and 80 years, a 35% reduction for black men, a 38% reduction for those diagnosed in the PSA era, a 29% reduction for men with no comorbidities, and a 21% reduction for men with tumors of the lowest stage and grade. These results will no doubt have an impact on advice provided by clinicians when men in this age group are agonizing over treatment options and the decision to treat or not to treat.

In an editorial, Litwin and Miller [5] provide arguments that might temper rampant enthusiasm, at least among patients. In the study of Wong et al, there were over 44,500 men in the sample studied, but death attributed to prostate cancer was seen in only 2.1% of the total sample. In addition, prostate cancer was found to be responsible for only 6.8% of deaths in the observational group and 8.0% of the deaths in the treatment group. Thus the absolute difference was only 1.2%. As they point out, “many more men die with prostate cancer than of it.” Furthermore, the editorialists remark that this was not a randomized study but rather an observational one, and that the potential for residual bias and confounding remains. For example, a Medicare claims based analysis fails to take fully into account the nature or severity of concurrent medical conditions nor the general impression of the clinician regarding life expectancy, and in fact in their opinion, and they claim most urologists and radiation oncologists would agree, older men who receive surgery or radiation therapy are “inherently different from those managed expectantly.” Also, they suggest that in the studied cohort, there might be an imbalance with respect to frailty, cognitive function and other important but unmeasured confounders.

Litwin and Miller also remark on the fact that this study contradicts the Scandinavian trial which was randomized, and found that men under 65 experienced the greatest survival benefit from treatment. They conclude that improvement in the quality of care for men with prostate cancer may be best achieved by treating patients more discerningly rather than just treating more patients. They quote the often seen comment of Whitmore that “for men in whom cure is possible it may not be necessary, and for men in whom a cure is necessary it may not be possible.”

Many men in the age group at issue are diagnosed with localized prostate cancer each year worldwide. Many men also have fathers or relatives who are or will find themselves in this situation. In keeping with modern practice, presumably the options of treatment and watchful waiting will be discussed during consultation with the clinician involved. As men and in fact also their wives and partners will find, this is a complex matter and it will be recognized that an informed decision requires knowledge of the factors involved. One source of evidence-based information is our book. Chapter 6 was written expressly to satisfy this need for information either by newly diagnosed men or vitally interested wives, children and relatives. Younger men also should be offered the option of watchful waiting. One of the modern variations is watchful waiting until the point is reached where further delay will diminish the chances of a definitive cure. In the PSA era, this option appears to be attractive even for older patients. Some men may be able to avoid treatment altogether under one of these special protocols and yet not compromise either prostate-specific or overall survival. This approach has growing support and men need to become familiar with the criteria employed by at least two of the major U.S. prostate cancer centers. Studies will no doubt shortly extend the age limit justified by evidence-based data. This option, called Expectant Management is discussed at length in Chapter 6 and is an area with which newly diagnosed men of all ages most need to be thoroughly informed. Quality of life is at stake. The Prostate Monitor will endeavor to update this area as more studies report.

REFERENCES