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This issue features two "emerging risk factors" for stroke and coronary heart disease. The term emerging risk factor generally refers to a factor or blood marker that appears from studies to offer significant predictive power but is not as yet accepted for general use. Skepticism generally is associated with such markers and purists demand large randomized trials. Such trials are very expensive and if primary prevention is an issue, then huge cohorts are required due to the low incidence of events or symptoms in so-called healthy populations. Furthermore, there is frequently no interest from the pharmaceutical industry in financing such studies since the emerging markers generally offer no opportunity for drug intervention. Nevertheless there appears to be growing interest in and utilization of emerging risk factors, especially in executive physical exams, a deluxe high-end one or two day version of the routine exam. One of the strong proponents of emerging risk factors for the assessment of cardiovascular risk and its reduction is the cardiologist Stephen Sinatra. Readers are referred to the book by Sinatra and Roberts, ***Reverse Heart Disease Now*** *(John Wiley, 2007) for a comprehensive discussion of what Sinatra calls "The New Cardiology."*

Other studies in this issue also relate to heart disease and stroke. In addition, several papers concerning cancer are discussed. Also, readers attention is directed to a study showing a remarkable risk reduction for Parkinson's disease simply with one cup of black tea a day. These results need to be confirmed, but they are of considerable interest.

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Wishing you good health,

William R. Ware, PhD, Editor

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EMERGING RISK FACTORS FOR STROKE AND CORONARY HEART DISEASE

Those who have read the last two research reviews in this Newsletter will be aware of the limitations of the traditional blood lipid levels in connection with estimating coronary heart disease (CHD) risk and the assessment of the probability of future adverse events. This issue features recent results concerning the emerging risk factors apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1) and their

ratio and their superiority over other blood lipid risk factors for predicting CHD and stroke risk.

An excessive number of ApoB containing particles is considered to be a trigger in the atherogenic process since it appears that the ApoB molecule in each LDL particle leads to the entrapment of the atherogenic lipoprotein in the arterial wall. Thus the total ApoB value represents the total number of potentially atherogenic lipoproteins whereas the non-HDL cholesterol, a marker of growing popularity, is thought to represent the concentration of all atherogenic lipoproteins. Non-HDL cholesterol provides the concentrations of LDL, intermediate density lipoprotein (IDL) and very low-density lipoprotein (VLDL) and is calculated by subtracting the HDL concentration from the total cholesterol and includes the lipoproteins lumped together under the term triglycerides which are primarily found in the VLDL fraction of the total cholesterol. Apolipoprotein A1 is the primary protein component of HDL and is involved in reverse cholesterol transport and anti-inflammatory and antioxidant effects. It is thought to reflect the concentration of anti-atherogenic HDL. Early studies suggested that the ApoB/ApoA1 ratio (Apo ratio) is superior to traditional blood lipid parameters in providing meaningful CHD risk assessment. There is now growing support for this view.[1]

A number of studies have been reported in the last few months that have examined the power of either ApoB or ApoA1 or the ratio in providing risk assessment for cardiovascular events or mortality. There have also been studies which examined the correlation with the presence and extent of atherosclerosis. The following appear to be of particular interest:

- Researchers involved in the INTERHEART study discussed in recent research reviews in this Newsletter have presented a detailed analysis of the relationship between the ApoB/ApoA1 ratio and the risk of having a myocardial infarction (MI—heart attack) based on an international case-control study of over 12,000 cases and 14,000 age- and gender-matched controls from 52 countries. The non-fasting ApoB/ApoA1 ratio was superior to any of the cholesterol ratios for the estimation of the risk of an acute MI in all ethnic groups, both genders and all ages. The total cholesterol to HDL ratio was the closest competitor and while inferior, it became insignificant after age 65. The authors of the report state that this ratio should be introduced into worldwide clinical practice.[2]

- A study which included researchers from the Mayo Clinic examined the association of ApoB and the ApoB/ApoA1 ratio in predicting CHD mortality. This prospective cohort follow-up study which was multiethnic and U.S. based involved an analysis based on the third National Health and Nutrition Examination Survey (NHANES III) database. After adjusting for cardiovascular risk factors, only ApoB and Apo ratio remained significantly associated with CHD mortality. The predicative ability of ApoB alone to assess CHD mortality risk was better than any of the routine clinical lipid measurements. The authors comment that these results are consistent with a study suggesting that LDL was not the best target for lipid lowering strategies since it was not significantly correlated with the history of atherosclerotic disease.[3] In addition, they cite a recent Framingham study where LDL was not found to be a significant risk factor for CHD.[4] The authors recommend the inclusion of apolipoprotein measurements in future clinical guidelines.[5]

- The metabolic syndrome is a condition that promotes atherosclerosis and is an established risk factor for CHD. A recently published study examined the association of the apolipoproteins with the prevalence of the metabolic syndrome in a large random sample of cardiovascular disease-free adults aged 18-87. In this group, the prevalence of the metabolic syndrome was 25% in men and 15% in women. The Apo ratio was the best diagnostic marker of the metabolic syndrome and if the ratio was greater than 0.72, there was over 3 times the risk after for adjusting for potential confounding factors including age, gender, physical activity status, smoking and dietary habits.[6]

- A recently reported study examined the association of ApoB and ApoA1 with the risk of stroke in patients with pre-existing documented coronary heart disease. It was found that the incidence of ischemic cerebrovascular events (stroke due to occlusion) was positively and significantly associated with ApoB, negatively associated with ApoA1, and when the

highest vs. the lowest quartiles for the Apo ratio were compared, the risk was cut roughly in half. This ratio remained an independent risk factor after adjustment for traditional risk factors. It is important to note that the subjects in this study all had pre-existing CHD.[7]

- In a study from McMaster University in Ontario, Canada, the presence and prevalence of subclinical atherosclerosis (SCA) was examined in a low-risk population and independent risk factors determined. SCA was determined by carotid artery ultrasound and defined as an intima media thickness (ITM) of ≥ 75th percentile adjusted for age, gender and ethnicity. Among the 752 participants classified as low risk by the Framingham Risk Score, 23% had evidence of SCA. Independent predictors of SCA in this low-risk group were female sex, systolic blood pressure and ApoB. LDL cholesterol was not a significant risk factor in this study with an odds ratio of 1.00 (a null result). Even the unadjusted odds ratio for LDL failed to reach statistical significance.[8]

- In a study published in the journal *Atherosclerosis* the risk factors for the development of atherosclerosis as measured by coronary artery calcium (CAC) were determined among post-menopausal women over a 6-year period. Baseline pre-menopausal data was available as well as changes during the study period. Baseline premenopausal age, ApoB levels, body mass index (BMI) and triglycerides were significant predictors for future incident CAC. In those with zero CAC at baseline, significant predictors of having CAC present at approximately 6 years were ApoB, BMI and triglycerides. LDL failed to show a significant association. The authors comment that if it were possible to prevent the development of new CAC during pre- to post-menopause then the incidence of CHD among post-menopausal women would be substantially reduced, even to a very old age. But they also point out that there is little evidence that lipid lowering therapies slow the progression of CAC, at least in the short term.[9] In this context, an earlier study that focused on men looked at the same question of risk predictors for CAC as well as extra-coronary subclinical atherosclerosis. Again, ApoB was the best predictor, non-HDL cholesterol the second best, and LDL the poorest predictor of high cardiovascular risk and subclinical atherosclerosis, and triglyceride levels were implicated in these differences.[10]

- The role of Apolipoproteins as risk factors in predicting cardiovascular events in statin-treated patients with established CHD has been examined in two recent studies. In one, subsequent major coronary events were most strongly correlated with the APO ratio and LDL was less predictive than either non-HDL cholesterol or ApoB.[11] Another study also found that the on-treatment levels of non—HDL cholesterol and ApoB were more closely associated with the cardiovascular outcome than levels of LDL. The authors comment, however, that the recommendation to use these superior markers seems premature given the absence of interventions that have been proven to consistently reduce cardiovascular risk through raising HDL or ApoA1 levels.[12]

Measurements of ApoB and ApoA1 are rarely included in physical exams. The assay is not available in many areas and there is no approved pharmaceutical approach to dealing with abnormal values. Thus readers might wonder at the decision to feature this topic in the Newsletter. The reason is simply that it highlights the fact that they are markers of presumably highly atherogenic lipids in the circulation and their presence is not adequately indicated by elevated LDL and in fact, the focus on LDL and its lowering distracts from the challenge of identifying and dealing with this more significant factor associated with atherosclerosis and the risk of adverse CHD events. But there were other reasons as well.

While the comment from researchers cited above concerning the absence of proven interventions is consistent with modern medicine's devotion to evidence based therapy and as well the absence of approved pharmaceutical approaches, nevertheless, the comment ignores some steps that can be taken. It has been shown that the ApoB/ApoA1 ratio is tightly linked to the metabolic syndrome and each of its components, with the most important association being with low HDL and high triglycerides.[13] Thus the low HDL-high

triglyceride pattern is in a sense a surrogate for an unfavourable Apo ratio. Furthermore, switching from a high-carbohydrate diet to one higher in protein has been found to reduce the ApoB in the very low density lipoprotein fraction, supporting the hypothesis that dietary carbohydrate reduction will reduce levels of atherogenic lipoproteins.[14] These observations point to the importance of addressing the dyslipidemia associated with the metabolic syndrome or the results of any blood lipid test that indicates high triglycerides and/or low HDL. The evidence presented above suggests that focusing on the Apo ratio or TG/HDL ratio may be more important than focusing on LDL. The various approaches to reducing the TG/HDL ratio were discussed in the last Research Review on heart disease published in this Newsletter. The dietary aspect of the approach was carbohydrate restriction and the elimination of all refined starches and sugars. There is also evidence of the benefits of exercise in the form of brisk walking on ApoB levels and TGs in middle-aged overweight or obese women (Korean). The brisk walking consisted of walking for 20 to 50 minutes/day for 3 to 6 weeks at an intensity that elevated the heart rate. Both ApoB and triglycerides decreased significantly.[15]

Newsletter readers may encounter the situation where their doctor will comment, "your blood work indicates elevated cholesterol and LDL. I suggest we put you on a cholesterol lowering drug." It is important to know that the blood work report almost invariably includes triglycerides. The value is needed to calculate the LDL level which is not generally measured directly. Thus if a reader is presented with the above scenario, or even just on general principles, it seems appropriate to inquire about the triglyceride and HDL levels and even ask for a copy of the lab report. There may be some physicians that are not impressed with the risk of high triglycerides or the so-called dyslipidemia that accompanies overweight, obesity and the metabolic syndrome. They will likely focus on lowering LDL and may be unsure as to how to approach the situation where the TG/HDL ratio is elevated. The standard dietary approach of reducing fat and saturated fat and dietary cholesterol is not the answer, and carbohydrate restriction and selection may not be viewed favourably. After all, low-carbohydrate diets have their highly vocal critics who like the label "fad diet."

Nevertheless, it is indeed true that studies on interventions directed at normalizing the ApoB/ApoA1 ratio and the impact of such interventions on cardiovascular events and mortality is almost non-existent, but there is growing interest. The Apo ratio is indeed an emerging risk factor. But in a recent review, Sniderman and Faraj make a case for including the Apo ratio or the individual components in the definition of the dyslipidemia of the metabolic syndrome.[13]

MEDITERRANEAN DIET AND RISK OF ADULT-ONSET DIABETES

Reducing ones risk of coronary heart disease (CHD) includes avoiding adult-onset (type 2 diabetes) which carries a huge increase in CHD risk and as well, a number of highly unpleasant morbidities including vision problems, impaired peripheral circulation, severely reduced mobility and the risk of amputation of extremities. The concern over heart disease, stimulated by the nightly prime-time TV ads for cholesterol lowering drugs, and the emphasis on cholesterol may well have pushed diabetes prevention off the radar screen for many individuals, and yet prevention of this common disease should be one of the main focus points of their "staying healthy" program. A recent Spanish study provides additional strong evidence that diet plays a central role and that a good choice is the Mediterranean diet. Over 13,000 Spanish university graduates without diabetes were followed for over 4 years. Diagnosis of diabetes was the endpoint and at issue was the degree to which a Mediterranean type diet was followed. An adherence score was used that gave equal weight to the following features of this diet: high ratio of mono to saturated fatty acids, moderate intake of alcohol, high intake of grains (presumably whole grains), high intake of fruit and nuts, high intake of vegetables, low intake of meat and meat products, and moderate intake of milk and dairy products. To this was added high intake of fish. When those with the highest vs. the lowest adherence score were compared, those with the highest score had an 83% reduction in the

risk of developing diabetes. Moderate adherence produced a 61% risk reduction. When the results were fully adjusted for confounding, the outcomes were similar.[16] If a drug was available that could produce similar results, there is little doubt one would hear about on prime-time TV and physicians would be handing out free samples.

VITAMIN C AND RISK OF ADULT-ONSET DIABETES

A 12-year follow-up study of over 21,000 healthy individuals has just reported which examined the association between baseline vitamin C and fruit and vegetable consumption and the incidence of new cases of diabetes. Vitamin C blood levels were determined at baseline and the consumption of fruits and vegetables was determined at the same time by a questionnaire. While the correlation between the vitamin C levels and the fruit and vegetable intake was poor, a strong association between the risk of developing type 2 diabetes and baseline vitamin C levels was observed. When the results were adjusted for a variety of potential confounders including multivitamin supplement use, a comparison of the lowest vs. the highest quintile of plasma vitamin C yield a decreased risk of 62%. The failure of vitamin C levels to correlate with fruit and vegetable intake was surprising given that in this European population it was estimated that 90% of the vitamin C was derived from fruits and vegetables. The authors suggest measurement error in determining dietary intake may have attenuated the association substantially. They also suggest that a biologically plausible mechanism for the impact of vitamin C on the development of diabetes may be associated with the prevention of oxidative stress which tends to accompany this disease.[17]

SUCCESS OF SMOKING BAN IN SCOTLAND

Smoking was prohibited in Scotland in all enclosed public spaces and workplaces after March of 2006. According to a study just published in the *New England Journal of Medicine*, in just 10 months since the implementation of the legislation, there was a 14% decrease in the number of hospital admissions for acute coronary syndrome, a 19% reduction among former smokers and a 21% reduction among never-smokers. Among the latter, there was a reduction in exposure to second-hand smoke, which while self-reported, was confirmed by blood tests. The principal investigator commented that the ban appears to be working in two ways, not only protecting non-smokers but also encouraging smokers to quit or reduce smoking. The authors remark that more studies will be needed to determine if these early changes are sustained.[18]

PERCUTANEOUS CORONARY INTERVENTION. SLIM EARLY GAINS SOON DISAPPEAR

Percutaneous coronary intervention (PCI) involves opening coronary occlusions with a balloon like device and frequently inserting a stent to keep the passage open. It is wildly popular with some hospitals directing individuals with acute coronary syndrome symptoms directly to the so-called cath lab, thus bypassing the emergency department and providing more rapid evaluation (an angiogram) and intervention (e.g. PCI or coronary bypass). This system is not without its critics, and the issues embrace both risk-benefit questions and the influence of financial incentives. A recent study relates to the first of these issues. For some readers of this Newsletter, risk-benefit is an important issue since the incidence of acute symptoms of a heart attack (MI) is unfortunately far from rare. This paper follows an earlier report from the same study that ignited a significant controversy when it reported similar rates of mortality or MI over 4 to 5 years when the PCI was compared with optimal medical therapy (OMT) only, but was better than first-line OMT in relieving coronary occlusions. The

report just published deals with quality-of-life issues and provided similar results to the earlier trial. It was concluded that patients will not be put at additional risk if PCI is deferred while the effectiveness of OMT is assessed. The study found that the quality-of-life benefits of PCI were dependent on the severity of angina. In general, the health-status advantages of PCI were found to persist for only 36 months. One of the issues voiced by critics was that while the benefits of PCI over OMT were statistically significant, they were likely too small to be considered clinically important. OMT involved aspirin, a beta-blocker and calcium channel blocker for blood pressure control, a nitrate based vasodilator and a statin. The report does not mention diet or exercise or weight reduction being included in the OMT.[19,20]

BLOOD LIPIDS AND STROKE

The role of blood lipids in the incidence of stroke is unclear and controversial. In this context, a recent paper in the journal *Neurology* is of interest. It involved data collected from over 1000 patients admitted to hospital for an ischemic (occlusive) stroke or transient ischemic attack (TIA). At issue were differences in fasting blood lipid profile for those with large artery atherosclerosis as compared to those presenting with TIAs. Extensive imaging was employed to differentiate these two groups. After adjusting the results for age, hypertension, diabetes, smoking, body mass index and preadmission statin use, the only blood lipids associated with significant risk of large artery atherosclerosis compared to all other stroke types were elevated triglycerides and non-HDL cholesterol. LDL cholesterol was not associated with large artery atherosclerosis in this study. The authors comment that these results are in accord with several studies of individuals with or without known vascular disease which found that LDL may not be the best predictor of atherosclerotic vascular risk and that clinicians may wish to consider focusing additional attention on other aspects of the lipid panel of patients with or at risk of an atherosclerotic stroke.[21] It should be noted that elevated triglycerides are common in individuals with poorly controlled diabetes and the metabolic syndrome and are a common finding in those who eat a diet high in refined carbohydrates and low in fat. This study can also be added to the ever-growing list of studies where the importance of LDL, the primary focus and target of mainstream medicine, is called into question.

BLACK TEA AND PREVENTION OF PARKINSON'S DISEASE

A follow-up study involving over 63,000 Singapore Chinese has examined the association between tea consumption and the risk of developing Parkinson's disease. For black tea consumption, when the highest vs. the lowest tertiles of intake were compared, high consumption resulted in a 71% decrease in risk. It is interesting that green tea consumption carried no decrease in risk nor did diet. Caffeine also reduced the risk as did smoking, but the above benefit observed from black tea was adjusted for these confounders. Thus ingredients of black tea other than caffeine appear responsible for the inverse association. For green tea, the benefit disappeared when the results were corrected for caffeine intake. For black tea, the benefit increased with intake, and the 71% decrease was found for intake of ≥ 23 cups/month which suggests that modest intake of a bit less than one cup per day provides a high level of protection.[22]

CANCER OF THE ESOPHAGUS AND DIETARY SUPPLEMENTS

The incidence of cancer of the esophagus and its precursor, Barrett's esophagus has rapidly risen in the U.S. to become the 7th leading cause of cancer death among men. The reasons are not fully understood although Barrett's esophagus is associated with acid reflux. Esophageal cancer has a dismal 5-year survival rate of only about 15%. A recent multicenter study has examined the association between vitamin supplementation and this form

of cancer and its precursor cellular abnormalities. In a prospective study with a mean follow-up of 5 years, it was found that after controlling potential confounding, participants who took one or more multivitamin pills/day had a decreased risk of abnormal cells in the lower esophagus of 81% and a decreased risk of esophageal cancer of 62% compared to those not taking multivitamins. As regards individual supplements, a 75% reduction in cancer risk was found for both vitamin C (≥ 250 mg/day) and E ≥ (260 IU) with benefit also seen at doses lower than those indicated. Selenium and beta-carotene did not appear to be protective.[23]

ASPIRIN AND RECURRENCE OF COLORECTAL ADENOMAS

Adenomas are benign growths which can form in many sites including the colon, and the adrenal, pituitary and thyroid glands. They have the potential to become malignant at which point they are called adenocarcinomas. In the colon they are quite prevalent and are frequently found by colonoscopy and removed. One issue is the risk of recurrence and how it can be modified. A recent study examined both folic acid and aspirin as preventive agents. In a randomized double blind study it was found that 500 micrograms/day of folic acid was ineffective but 300 mg/day of aspirin provided protection from recurrence. This dose of aspirin was found to reduce the risk by 37%, a result that was statistically significant. The authors regard benefit of this magnitude to suggest that aspirin could have a significant role in preventing the development of colon cancer in high-risk groups but the dose found effective (approximately one standard dose tablet) is too high to justify recommendation for general prevention due to the potential adverse gastric side effects. While not all studies dealing the this question have shown benefit, the authors point out that their trial along with 3 similar trials provide strong evidence for the effectiveness of aspirin in this context but there remains the question of the effective dose.[24] The failure to find a beneficial effect of folic acid is consistent with other studies that either found a null effect or an enhanced rate of cancer with folate supplementation.

ALCOHOL CONSUMPTION AND COLORECTAL CANCER RISK

A recent study from Japan has attempted to resolve with a meta-analysis the alcohol dose dependence for the risk of developing colorectal cancer. Five Japanese prospective cohort studies were included involving approximately 98,000 men and 112,000 women. For men, statistically significant risk appeared at intakes of > 23 g/day (one drink is generally contains 12-15 g of alcohol). Compared to non-drinkers, the increased risk for intakes of 23-45.9, 46-91.9 and > 92 g/day were 42%, 95% and 196%. These results were adjusted for confounding. For women, significant risk appeared for intakes ≥ 23 g/day (57%) but higher intakes were not stratified. The results for men were compared with other studies using pooled results. For a Western population, statistically significant enhanced risk (41%) appeared only for intakes ≥ 45 g/day whereas in a European study the first quintile of intake to show statistically significant enhanced risk of 26% was for 30-60g/day when results for men and women were combined. An intake of > 60 g/day produced a 64% increase in risk which was considerably lower than that found for the Japanese. These differences are attributed by the authors to the possible impact of higher levels of acetaldehyde, a metabolite of ethyl alcohol, which in Asians may be due to differences in enzyme activity. Nevertheless, there is a very consistent picture across these different populations in that high intake increases the risk. Japanese have a lower threshold and the increased risk of colorectal cancer is much larger for heavy alcohol consumption than in other populations studied. For Western and European populations, the threshold for risk among men appears to be somewhere between 2 and 3 drinks per day.[25]

MIXING A STATIN AND AN ANTI-ARRHYTHMIC DRUG MAY BE DANGEROUS

On August 8, 2008, the FDA issued an alert about the increased risk of a statin related serious and potentially fatal muscle disorder (rhabdomyolysis) for patients taking more than 20 mg./day of simvastatin (Zocor) along with the anti-arrhythmic drug amiodarone. The problem appears to be that amiodarone inhibits one of the cytochrome P450 enzymes that is involved in the metabolism of the statin, thus providing for increased levels to persist and therefore increasing the risk of side effects. The FDA recommendation is that consideration should be given to another statin for patients taking amiodarone who require doses of Zocor greater than 20 mg/day to meet their lipid goals.[26]

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BOOK REVIEW

Hippocrates' Shadow. Secrets from the House of Medicine

David H. Newman, M.D.
Simon & Schuster, New York, 2008

This just published book carries an additional subtitle on the dust jacket—"What doctors don't know, don't tell you, and how truth can repair the doctor-patient breach." David Newman teaches at Columbia University where he runs a clinical research program, and in addition is associated with the Department of Emergency Medicine at St. Luke's—Roosevelt Hospital Center. He was also deployed to Iraq where he received the Army Commendation Medal. He is widely published in biomedical journals.

This book discusses what Newman believes is a growing disconnection between doctors and patients brought about by profound changes in the way medicine is practiced and by the huge impact of the media and direct-to-customer pharmaceutical advertising on patient expectations. In his view, medicine focuses narrowly on the rewards of technology and science, exaggerating their benefits while ignoring or minimizing the associated perils.

A recurrent theme is this book is that there are many critical questions and problems for which medical science has no answer. These span a wide spectrum from diseases where the cause is simply unknown to situations where there is no treatment that works and yet treatments are demanded by patients and provided. The problem explored in the book is that the patient is unaware of the truth in many situations and the culture in the House of Medicine tends to conceal it—a culture of secrecy. The inevitable result is loss of confidence and as well dissatisfaction which occurs not only among patients but also their physicians. The secrets promised in the subtitle include:

"Our knowledge is far more limited than most believe; we advocate and utilize interventions we know don't work; we disagree on seemingly fundamental issues of science; at system levels, we care nothing about communication; we choose technology over touch; we openly defy established evidence; we deny and decry a

placebo effect while we tacitly accept and enlist it; and we know precisely how likely each patent is to benefit from an intervention, but seldom tell them."

This is strong stuff, and certainly debatable, but Newman provides justification, case histories which give the book a human touch, and all the critical points he makes are clearly referenced so readers with journal access can check out the sources that go beyond his own clinical experience and observations. Some of the examples may disturb readers. For example:

- Sudden cardiac death. Newman discusses resuscitation which he describes as a powerful symbol of modern medicine's success. The well-documented failure rate will shock some, especially when they read about the evolution Advanced Cardiac Life Support (ACLS) as a more comprehensive substitute for CPR. He discusses the 38% survival rate achieved in a casino where when people "went down" the response was almost instantaneous and by trained personnel and compares this success rate with what happens when the cases arise in the general population. He maintains that the casino provided a selected population of functionally active and relatively healthy people. This success rate he compared with studies of ACLS in large cities, where the rate of successful resuscitation is a dismal few percent, a result he attributes to a preponderance of individuals suffering sudden cardiac death who have comorbidities. He views all those suffering sudden cardiac death as in fact dead, and differentiates the "healthy dead" from the "unhealthy dead." It is only the former that has much of chance of being resuscitated. TV programs and the promotion of CPR suggest higher overall success rates than 1% or 2%.

- Interpretation of imaging results. Newman presents the reading of imaging results such as x-rays as an example where the general public is unaware of the well documented uncertainties. He discusses several clever studies where groups of experienced radiologists were given x-rays to analyze. In some cases the same groups participated in what they thought was a second study but which in fact involved the original set of images. In one study, a group was given what they thought was a set of 30 images, but in fact it consisted of only 10 images in triplicate. The diagnostic inconsistencies found in these studies were significant and clearly something that it has been deemed undesirable for patients to learn.

- Sore throats and antibiotics. This subject is used to illustrate the interaction between patient expectations, the prudent practice of medicine and what happens in real life. Newman discusses why antibiotics are almost always unnecessary but frequently prescribed and why this is dangerous.

- Patient-doctor interaction. Newman states that a pattern of patient avoidance is an integral part of the modern medical system and a key contributor to decreasing patient satisfaction and increasing alienation. This phenomenon is highlighted by the growing importance placed on impersonal tests and the time spend dealing with this aspect of health care in the hospital setting which competes with patient communication, contact and interaction. He cites studies that indicate that a major component in physician dissatisfaction with their work is the dearth of time spent interacting with patients. The skills of physical examination have been devalued and basic skills such as communication and observation have been shunned in favour of testing blood and taking x-rays.

- Causes of disease. Newman cites a number of diseases where the cause is totally unknown. Even if the cause is understood, in many cases no known treatment is available that has been demonstrated to work. But the pressure to do something is immense and in some cases answered by the use of treatment known to ineffective. This deception has its consequences which Newman explores.

Many other fascinating examples are examined in this book. Newman recognizes and balances modern medicine's undeniable successes against what he perceives as its failures. But most of all, he attempts to establish the thesis that patients and their families, under many circumstances, need to be aware of the limitations of patient care and treatment. These limitations are mostly due to weakness, inadequacies and lack of knowledge that are in no way attributable to or the fault of those who practice this profession, but are inherent in the present stage of development of the science and evolution of the art of medicine and all that this implies. Nevertheless, exceptions to this generalization can have a high profile and may be the most amenable to correction.

The book gives very little attention to the other side of some issues discussed. For example, there are probably situations where it is better that patients not be given all the facts or to know what goes on behind the scenes. There are huge "English as a second language" barriers to doctor-patient communication and many patients are ill equipped from the language or educational standpoint to understand many elementary aspects of modern medicine, even if the physician is careful not to use the specialized "foreign language" common to the world of medicine. Finally, from the patient's point of view, what are the *current* alternatives to the present system? But one should not underestimate the value of a good dose of realism.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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In this issue we update an important topic, active surveillance as a response option to the diagnosis of prostate cancer. It is generally recognized that the advent of PSA screening has been accompanied with a greatly increased discovery of indolent, low-grade and clinically insignificant tumors and that many of these cases are receiving radical treatment. If surgery or radiation therapy were free from adverse side effects there would be little concern, but this is unfortunately not the case and some men undergoing therapy experience post-treatment problems that have a profound impact on their quality of life (impotence, incontinence, need to wear a diaper, radiation damaged rectum, etc). Thus the quite justified concern in the urologic community regarding the treatment of cancers of the prostate that present no immediate threat and may never cause any problems during the lifetime of the patient. This is not a trivial problem because to address the issues requires determining beyond reasonable doubt the nature of the disease, and the standard procedures are far from perfect with a wide range of failures including missing advanced disease and misjudging the grade. Active surveillance addresses some of these issues by first making a judgment call regarding the nature of the disease and if it is thought to have a high probability of being indolent and not threatening, to then closely observe how the clinical picture evolves with time as a way of checking the validity of the initial assessment. If the assessment was wrong, then definitive treatment is advised.

In this issue of there is also an important update on the use of finasteride (Proscar) for the primary prevention of prostate cancer. One of the major concerns raised by the Prostate Cancer Prevention Trial, which first reported in 2003, was that the use of Proscar, a drug for treating prostate enlargement, increased by a small amount the risk of advanced prostate cancer. As is discussed in this issue, this concern now appears to have been based on an artefact, and the recommendation to use Proscar in this context may become more common.

Wishing you continuing good health,

William R. Ware, PhD, Editor

WATCHFUL WAITING AND ACTIVE SURVEILLANCE—AN UPDATE

In the U.S. over 200,000 new cases of prostate cancer were diagnosed in 2007 and the lifetime probability of developing prostate cancer is 1 in 6. This translates into about 600 men each day being confronted with this diagnosis and the treatment options. The existence of treatment options in itself makes for a stressful situation, and if a man is not knowledgeable regarding the uncertainties of diagnosis and the judgment call regarding the magnitude of the perceived threat, as well as the complexities of the potential benefit vs. side effects of the various treatment modalities, he may feel like he is wandering in a strange and unfamiliar wilderness of probabilities. As has been repeatedly pointed out in *The Prostate Monitor*, men need to be prepared with knowledge in order to intelligently deal with this common crisis and even with the decision to agree to a PSA test. We have attempted to provide assistance with our book *The Prostate and Its Problems*. In this issue we feature one of the treatment options which is called active surveillance which translates into no treatment right away. An older and different version is watchful waiting.

Watchful waiting essentially involves doing nothing until palliation is required. It is most commonly found among prostate cancer patients who are deemed unsuitable for radical treatment such as surgery or radiation. It is also a voluntary choice among some diagnosed with prostate cancer who prefer to take their chances and at least initially do nothing that impacts their quality of life. There are of course those who simply do not believe that what modern medicine has to offer them is positive on a risk—benefit scale, or simply reject treatment for a variety of reasons. Studies comparing watchful waiting vs. radical intervention generally involve individuals diagnosed prior to the PSA era who in general have more advanced cancer discovered by a digital rectal exam (DRE) or symptoms followed by a biopsy. Prior to the PSA test, there was no way to observe indications of elevated risk of prostate cancer in men presenting with no signs of tumor on a DRE and no indications aside from lower urinary tract symptoms typical of older men (benign prostatic hyperplasia). In the pre-PSA era, studies of the natural history of prostate cancer were also incomplete since observations started at a fairly advanced stage of the disease. The advent of the PSA test changed all of this.

Active surveillance (AS) essentially attempts to select patients where two conditions are met: (a) there is a high probability of the cancer being either indolent or insignificant in terms of cancer specific mortality or morbidity, and (b) There is a high probability that if this picture changes, definitive intervention (e.g. surgery or radiation) will have a high probability of providing a cure. The second point can also be stated in terms of a low probability that delaying treatment will decrease the chances of successful treatment if it later becomes evident that it is indicated. Widespread PSA testing has introduced a significant lead-time and the disease is well known in some cases to follow a protracted course. AS is initiated after a biopsy which indicates the presence of cancerous cells and, in most protocols, requires a repeat biopsy every 1-2 years and PSA tests every 3 months and clinical examinations every 6 months. There is considerable variation in the criteria used for advising AS and as well, for recommending abandoning it in favour of definitive treatment.

Active surveillance is a much more recent phenomenon than watchful waiting. It evolved not only after the use of the PSA test became popular, but also because of a vastly greater understanding of the prognostic information available from the biopsy cores and various derivatives of the simple PSA level such as PSA density. In addition, the development of active surveillance protocols was in response to evidence that indolent and insignificant tumors were receiving radical treatment, a situation which resulted in an unnecessary exposure to the risk of serious side effects such as impotence, incontinence and bowel problems impacting the quality of life. While the hypothesis of unnecessary and unjustified treatment of diagnosed prostate cancer in some individuals has been hotly debated in the urologic literature, the idea of active surveillance has slowly gained popularity. Unfortunately, a number of somewhat different protocols were developed for selecting suitable candidates for inclusion in surveillance programs which when combined with the relatively small numbers of participants and the short follow-up has made the analysis of benefits more difficult and uncertain. Nevertheless, a general picture has emerged.

Thus the question is—does AS really work? There have been a number of centers where AS programs have been initiated and results are being reported. However, as mentioned above, there is no consistency in the criteria for candidacy, the triggers of recommending radical intervention vary among the centers, and there has not as yet been sufficient time for the evaluation of the really critical endpoints. These endpoints would involve

comparison between immediate treatment and AS delayed treatment as regards failure of primary treatment, time to failure, time to clinically evident metastatic disease, and prostate cancer specific mortality. Rather, data has been collected regarding the frequency of conversion from AS to treatment, motivated in fact by several factors, and the percentage with a post-treatment disease or recurrence.

Results of the so-called first biopsy are almost always a critical component of AS eligibility criteria. In some protocols, additional biopsies are the central or even required procedure in predicting progression which triggers the recommendation for treatment. The common requirement is a Gleason sum of ≤6 with no pattern of 4 or 5, which means that the sum is achieved by patterns indicative of low-grade cancer, i.e. 3+3. But as discussed at length in our book *The Prostate and Its Problems*, the biopsy is an imperfect tool. It can miss cancer altogether and it can miss higher grade cancer providing a false picture of the nature of the disease. It is not unknown that the follow-up biopsy reveals no cancer at all even though there had been no therapy! Also, when a study is made of false negatives, three or four consecutive biopsies a few weeks apart may be required before a positive result is obtained. Thus the trend for using more samples (needles) in the attempt to reduce false negatives, and this has been suggested in the context of AS. Finally, decisions are of course being made on the basis of so-called clinical features of the biopsy cores. It is also well known that when clinical assessments of biopsy results are compared with assessments made on the prostate itself after surgical removal, there is considerable up-grading and down-grading, again suggesting that the biopsy is a rather imperfect tool. There is also interest in innovative imaging modalities in predicting meaningful tumors or disease progression for men with suspected low-risk disease but this is not relevant to the question of how successful AS is at present.

It is still too early in the use of AS for there to be meaningful randomized studies that compare head-to-head several of the common sets of criteria for candidacy or the various sets of criteria used to determine if progression has increased the risk of missing the "window of high curative probability." This is not to say that the various sets lack considerable justification based on post-surgical validation, but significant differences of opinion exist, as exemplified by the use or non-use of PSA limits such as ≤ 10 ng/mL as a criterion, or the use by some centers of PSA density or kinetics but not by others. These uncertainties regarding criteria should not detract from the reader's recognition of the importance of AS since the goal is to avoid unnecessary treatment and side effects which can strongly impact the quality of life. There is growing evidence of the merits of this approach. Men should also realize that the temporary discomfort of a biopsy and the associated very small risk of morbidity are minor compared to surgery or radiation therapy and that the requirement of an additional biopsy every one or two years should not be a deterrent to entering an AS program. The following recent studies appear of considerable interest.

OUTCOMES IN UNIVERSITY OF CONNECTICUT HEALTH CENTER PROGRAM

At the time the report was prepared, a total of 40 men had elected AS between 1990 and 2006. The entrance criteria were a PSA ≤ 10 ng.mL, Gleason score ≤6, 1 to 2 biopsy cores positive with less than 50% tumor per core, stage T1c (elevated PSA only) or T2a (small growth on one lobe found by DRE), and age < 75. Follow-up included PSA every 6 months or more frequently if the level was changing. DRE every 6-12 months, and repeat biopsy at 2 years or if there was an increase in PSA > 0.75 ng/mL. Definitive treatment was recommended on the basis of an increase in the number or percent of cores positive, progression in the Gleason score, onset of urinary symptoms, change in DRE or patient request due to anxiety.

Among 40 patients who started the AS program, 31 (77.5%) remained on AS for a median of 48 months (range 12-168). The diagnostic characteristics of those remaining on AS were indistinguishable from those requesting treatment. At 5 years, 74% of the patients remained on AS. As of July 2007, there had been no PSA failure in the patients who elected prostatectomy and 1 of 3 who elected radiation therapy had a post-treatment rise in PSA which continued. Two patients elected hormone therapy and exhibit no evidence of biochemical failure. There were no deaths from prostate cancer. The authors conclude that their study indicates that men with low-grade disease can have excellent long-term outcomes on AS.[1]

UNIVERSITY OF CALIFORNIA AT SAN FRANCISCO EXPERIENCE

The department of urology of the University of California (San Francisco) medical school has been accruing patients for their active surveillance program since 1990 with a big increase in enrolment starting in 2001. Three hundred and twenty one men, for whom there was data suitable for analysis, were available as a study cohort of AS as the initial management modality. While the mean follow-up has been only 3.6 years, the range was 1-17

years. The entrance diagnostic criteria were a PSA < 10 ng/mL, Gleason sum ≤ 6, absence of a Gleason grade of 4 or 5, cancer involvement in < 33% of biopsy cores, and clinical T1 or T2a (T2a means evidence was found on DRE of a small growth on one lobe). The surveillance protocol consisted of PSA measurements and a DRE, generally every 3 months and starting in 2003, repeat biopsies were recommended at 12-24 month intervals. There was also frequent phone contact from nurse practitioners. Data was collected on the switch or need for active treatment or progression. The later was defined as an increase in Gleason grade on rebiopsy or an increase in PSA with a velocity > 0.75 ng/mL per year. The mean PSA at enrolment was 6.5 ± 3.9 ng/mL At least one criterion for progression was met by 37% of the participants and 38% has a higher grade on repeat biopsy and 26% had a PSA velocity suggesting progression. At a median of 3 years follow-up, 24% received treatment but approximately 13% elected treatment with no progression. The prostrate-cancer specific survival rate in the entire group was 100%. Not all patients with progression elected treatment and a Gleason grade change on rebiopsy was the most important driver for electing treatment. It was also observed that most men in this cohort were able to tolerate the anxiety of living with prostate cancer diagnosis.[2]

UNIVERSITY OF MIAMI EXPERIENCE

For the subjects included in the reported study, the inclusion criteria were Gleason sum ≤ 6, PSA ≤ 15 ng/mL, stage ≤ T2 (evidentially T2b) and ≤ 50% cancer in no more than two biopsy cores. The age limit was ≤ 80 years at diagnosis. In all, 99 men met these criteria. Their mean PSA was 5.77ng/mL and the mean follow-up was 45months. Follow-up involved PSA and DRE every 3 months for 2 years and every 6 months subsequently. Repeat biopsies were done 6-12 months after the initial diagnosis and afterward when clinically indicated. The decision to continue AS was based on the rate of increase in PSA or its doubling time, the results of the rebiopsy, the tumor volume in the cores, stage progression and patient preference.

It is interesting that on repeat biopsy 63% had no cancer. Eight patients were treated, five with curative intent. It was estimated that 85% would remain treatment-free for 5 years and were judged as likely to have indolent cancer. No patient died from prostate cancer. The PSA doubling time, DRE and clinical stage at diagnosis were predictive of progression.[3]

EARLIER STUDIES

The results of these three recently reported studies are consistent with earlier reports. Two studies that reported in 2006 and 2007 which used very similar criteria to those described above and involved over 400 individuals on AS with follow-ups of 5.3 and 3.4 years found 34% and 25% rates of delayed intervention respectively.[4] Brewster has reviewed this subject and provides a favorable picture associated with this option.[4] However, it must be realized that there are many uncertainties due to the relatively brief experience in various institutions when inclusion criteria such as described above have been used. Some earlier studies enrolled a substantial fraction of men with less favourable indications and the results are not particularly relevant. But there appears to be no evidence which contradicts the basic philosophy of AS, i.e. avoiding radical treatment until there are indications that further delay will compromise the chances of a cure. Furthermore, the present criteria being employed for entrance to programs and for triggering treatment appear to be in keeping with the aims and goals of AS. The somewhat simplistic position that “you have cancer, lets get rid of it” is challenged by the AS philosophy, but it will be a number of years before sufficient evidence is accumulated to satisfy those desiring randomized trials with long follow-up. Many men, realizing the potential benefits of AS, will not want to wait.

FINASTERIDE (PROSCAR) AND PREVENTION OF PROSTATE CANCER

Three papers have recently appeared in the new journal *Cancer Prevention Research* (open access, not yet covered by PubMed) concerning the use of finasteride for the primary prevention of prostate cancer. The observation that finasteride reduced the incidence of prostate cancer was first demonstrated in 2003 in the Prostate Cancer Prevention Trial (PCPT). A 25% reduction was found but there appeared to be a small increase in advanced disease. This increase profoundly dampened enthusiasm for using finasteride, a well-known drug used for a number of years to treat the symptoms of benign prostatic hyperplasia, for preventing the incidence of prostate cancer. Subsequent to the 2003 report, there has been considerable research concerning the question of bias or confounding influencing the results associated with advanced cancer. These examined the impact of the decrease in prostate volume that accompanied the use of this drug and the possibility of detection bias

associated with improved sensitivity of PSA for overall and high-grade cancer detection, improved sensitivity of the DRE for cancer detection, and more accurate grading of high-grade cancer. In the new analysis from the same group responsible for the PCPT study. Redman *et al* [5], taking into account the increased sensitivity for detecting high-grade cancer in the finasteride arm of the trial presents a revised estimate of rates for high grade cancer of 8.2% in the placebo group and 6.0% in the finasteride group, a 27% reduction in risk and a reversal of the indications from the initial analysis of the PCPT. This conclusion is supported by studies of prostates removed during radical prostatectomy in the PCPT trial.[6,7] The PCPT researchers conclude that men who express interest in prostate cancer prevention should be informed of the opportunity to take finasteride for preventing prostate cancer. The implication is that now the only impediment to this recommendation has been removed.

In a perspective on the recent results associated with re-examining the PCPT results, Logothetis and Schellhammer[8] suggest three central questions:

1. Does finasteride preferentially suppress cancer with no lethal potential, and is therefore an unnecessary intervention?
2. Does finasteride accelerate adaptation that leads to early progression of prostate cancer to a lethal form?
3. Do we now have sufficient evidence about the efficacy and safety to change the perspective of physicians and overcome the reluctance to use it?

With regard to the first question, their answer is no. They find that the data currently available provide convincing evidence that the reduced frequency of detected cancer is clinically significant. Their answer to the second question is that the analyses of Lucia *et al*[6] and of Redman *et al*[5] effectively eliminate concern that finasteride caused an increased in aggressive cancers within the study period (7 years) of PCPT. With regard to the third question, they view the effectiveness of finasteride in reducing the frequency of detected meaningful cancer and the paucity of evidence of irreversible toxicity induced by the drug as supporting the recommendation that this drug should be offered to men at risk for prostate cancer.

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