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In this issue we examine the problem of evidence-based medicine and the extent to which therapies and procedures commonly used today can be characterized by this term. This is an important problem because if one applies the highest standards available, many therapies and procedures do not qualify, and in some cases it is impossible or unethical to even attempt to meet the modern criteria as exemplified by the randomized, double blind, placebo controlled trial. A requirement that all therapies and procedures meet the highest standards of evidence-based medicine would in fact cripple modern medicine. Yet when mainstream medicine for one reason or another does not like some therapy or procedure, it is often condemned as not being evidence-based. In connection with this problem, of particular interest are the views of Dr. Erich Loewy, who looks at this issue from the point of view of a bioethicist who is also a physician who believes that the practice of medicine is much more than just the mechanical following of sanctioned guidelines dictated by evidence-based medicine.

Other topics include lifestyle and dietary aspects of cardiovascular disease prevention, and as well diabetes diagnosis and breast cancer detection. In addition, some suggestions are included regarding books, some in fact unrelated to health issues, which might be interesting candidates for summer reading.

This issue contains the second and last part of the Research Review on coronary heart disease risk and its reduction. The theme of Part II concerns the role of diet in reducing inflammation and insulin resistance, the principal intervention suggested as potentially beneficial in Part I. The reader may be surprised at the large number of studies that have found significant and at times sensational risk reduction associated with certain dietary choices and as well, the consistency of the picture that emerges.

And finally, as many of you will know, International Health News has an affiliate agreement with Xtend-Life, a highly respected New Zealand manufacturer of unique, well-formulated supplements not available from manufacturers in the US and Canada. Xtend-Life recently announced the release of a line of exceptionally well-priced skin care products based on natural ingredients. I am not into skin care products myself (Nivea will do just fine for me), but Judi raves about these new products, so you may wish to give them a try. Xtend-Life has a 100% guarantee of satisfaction and provides quick and inexpensive shipping worldwide. For more information go to http://www.afibbers.org/vitamins/skincare.htm

Wishing you a safe and enjoyable summer,

William R. Ware, PhD, Editor

GAINING PERSPECTIVE ON EVIDENCE-BASED MEDICINE

The *British Medical Journal* has an on-line resource called *BMJ Clinical Evidence* (http://clinicalevidence.bmj.com) and a publishing company, both devoted to evaluating and publicizing of the strengths and weaknesses of the foundation on which so-called evidence-based medicine rests. They claim to be one of the world's

most authoritative medical resources for informing treatment decisions and improving patient care. The source of their information is the medical literature. Their reviews are conducted by appropriate clinical experts, subjected to peer review and periodically updated. They also publish guidelines for clinical practice. In Italy, *Clinical* E*vidence* is being used as the basis for a nationwide continuing medical education program.[1] A recent note on their website contains some interesting data. They have thus far evaluated about 2500 treatments and the following observations provide a fascinating picture of the status of this subject. They ranked treatments from "beneficial" to "of unknown effectiveness."

- Beneficial, 13%
- Likely to be beneficial, 23%
- Trade off between benefits and harms, 8%
- Unlikely to be beneficial, 6%
- Likely to be ineffective or harmful, 4%
- Unknown effectiveness, 46%

Thus about a third were judged clearly or likely beneficial, but almost half were characterized as of unknown effectiveness. The gray area in the middle represents only 18%. However, these figures suggest that what we are lead to believe is evidence-based medicine is at least to some extent a fantasy, and those who reject out of hand all treatments that are not clearly known to be beneficial or likely to be beneficial should reject 64% of all therapies, at least among those studied so far by the investigators involved with *Clinical Evidence*. And we are not talking about snake oil but rather treatments used worldwide in mainstream medicine. Their comment—"…the figures above suggest that the research community has a large task ahead and that most decisions about treatments still rest on the individual judgments of clinicians and patients." Patients take note! There are no doubt many therapies categorized as of unknown effectiveness that nevertheless may be highly beneficial—it is just that no one knows or no one has done the sort of studies that meet the criteria used by *Clinical Evidence.* A subscription or access to a subscribing library is required to obtain reports but BMJ offers individual reports on an online pay-for-view basis that seems very reasonably priced and could provide patients involved in difficult decisions with valuable, authoritative information that should be more acceptable for use in discussions with their physicians than a lot of what appears on the internet. The website is cited above, or just Google "BMJ Clinical Evidence." A link to the complete list of reviews is on their home page with a tab called "full review list."

CONFLICT OF ETHICS, PROFESSIONAL RESPONSIBILITY AND EVIDENCE-BASED MEDICINE

The above discussion of the BMJ's *Clinical Evidence* omits many issues of great importance, some of which have recently been explored by Dr. Erich Loewy, M.D., professor emeritus of medicine and a bioethicist, University of California, Davis, in a paper in the journal *Medscape General Medicine* which is "open access" after registration.[2] Loewy uses as a definition of evidence-based medicine (EBM) a statistically valid conclusion about a rigorously defined cohort. He makes the following points:

- EMB protocols can be helpful and sometimes necessary to a particular patient provided they are applied properly to an individual who belongs to the particular cohort to which the EBM applies. But he questions the need in the case of a well-trained and thoughtful physician.
- EBM provides a useful check-sheet that helps avoid overlooking something vital. Some point out that it saves time and the necessity of thinking.
- The development of EBM can be useful in the educative process but if an EBM therapy becomes a protocol into which a patient with a given disease can simply be plugged, any educational value associated with developing such an instrument is lost.
- EBM is basically anti-intellectual in the sense that it promotes a "mindless algorithm." The check-sheet nature of many EBM protocols rarely teach attending physicians and students to think, and in fact may discourage thinking. Thus EBM protocols become obstacles to thinking that ultimately interfere with the patient-physician relationship.
- EBM protocols, while initially viewed as serving as guideposts, can become straightjackets and institutions with the bottom line in view may in fact look at them as useful straightjackets rather than

guidelines, and physicians who do not follow the guidelines can be reprimanded, not to protect patients but because cash flow was at issue.

- When an official EBM is proclaimed, physicians are frequently afraid to insist on what might be called elbowroom in their treatment approach. Loewy regards this as "demeaning and disparaging to the profession where political, national or financial circumstances should not enter into therapeutic decisions".
- EBM can lead to regimented protocols without regard for the nature of the individual patient and in fact coverage for treatment and thus in some cases treatment itself can be denied in some systems by someone without a license to practice medicine mindlessly applying rules rather than a physician acting on the basis of his or her best judgment. Thus the EBM view of medicine provides a tool for reigning in costs, both by private health care organizations and governments.

But Loewy does not discuss specifically that EBM has also allowed local physician governing bodies such as Colleges of Physicians and Surgeons powerful arguments for punishing physicians who depart significantly from EBM into areas of controversy, especially in alternative and complementary medicine, even if the protocols they are using have worked for them over a number of years with countless patients with no evident harm and instead great benefit.

When one reflects on the data presented by *BMJ Clinical Evidence* that almost 50% of all treatments are of unknown effectiveness but nevertheless in common use, this also raises questions about the inherent hypocrisy of elevating certain protocols to EBM status and then looking the other way when it is convenient to use non-EBM protocols. But if medical practice was restricted to treatments that satisfied the criteria used to isolate the BMJ's 36% beneficial or likely to be beneficial protocols, this would almost certainly do a disservice to patients and physicians alike.

There are many other issues such as the difference between statistically significant benefit and clinically significant benefit, the huge role of biostatistics in establishing EBM, the failure to publish negative results and the impact of negative results on an investigators ability to attract research funds, the fact that randomized controlled trials sometimes fail to confirm case-control and prospective trials even though statistical and even clinical significance is not an issue, etc, etc. Space limitations dictate that a discussion of such issues be postponed for now. *BMJ Clinical Evidence* is trying to solve some of the serious problems associated with screening for study quality, something in which the Cochrane Collaboration has also very effectively been involved for some time.

AN EXAMPLE JUST PUBLISHED IN *THE LANCET*

The perioperative (around the time of an operation) use of drugs such as beta-blockers to lower blood pressure and control heart rate has a fairly long history which started with two studies in 1996 and 1999. The objective was to reduce perioperative cardiac mortality and morbidity in non-cardiac surgery. The end result was widespread enthusiasm for perioperative beta-blockage and equally widespread implementation of this therapy. Nevertheless, the two studies on which this action was based were openly challenged and serious reservations and problems discussed in the literature. Furthermore, additional studies proved inconsistent.[3] The 2007 guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA) state "Although many of the randomized controlled trials of beta blockage therapy are small, the weight of evidence--especially in aggregate—suggests a benefit to perioperative beta blockage during non-cardiac surgery in high-risk patients."[4] This guideline seems to significantly down play three studies that reported in 2004-2005 which failed to support the protocol. The *BMJ Clinical Evidence* organization does not appear to have as yet taken a position on this therapy, but from what has been outlined above, the evidence of benefit does not appear overwhelmingly conclusive. Some readers of this Newsletter or a family member or friend may well have had perioperative beta blockage. Failure to utilize this protocol has been considered as a black mark against an institution, a failure to provide an adequate level of quality of care.

Now a new study has reported which raises additional concerns. This was the multinational POISE trial which compared an extended release beta-blocker with a placebo for patients with or at risk of atherosclerotic disease undergoing non-cardiac surgery. Patients were given high doses just prior to and again after surgery. While there was a reduction in non-fatal heart attacks, these benefits were at the cost of an increased incidence of total

mortality and stroke. This was a large study involving 190 hospitals in 23 countries which randomized over 8300 patients to the intervention or a placebo. The authors suggest that patients are unlikely to accept the risks associated with the perioperative extended-release beta-blocker, in this case metoprolol (Toprol SR).[5]

In an editorial which appeared before POISE reported, but which took into account the three recent trials mentioned above, McCullough asks the question "Where did the evidence-based guidelines process go wrong?"[6] His answer was the reliance on small and in some cases unblinded trials which had low absolute differences in event rates. In an editorial which accompanied the report of the POISE study, attention was called to the high dose of beta-blocker used and the failure to increase (titrate) the dose slowly over a week or so prior to surgery while monitoring blood pressure and heart rate, which incidentally is part of the ACC/AHA protocol. They suggest that overall benefit may derive from such a protocol, but this view is based only on one of the early studies and its more recent extension.[7]

This example underscores the need now being addressed by *BMJ Clinical Evidence* which adds to the ongoing and highly respected work of the Cochrane Collaboration.

LOWERING SERUM TRIGLYCERIDES WITH OMEGA-3 FATTY ACIDS

The Research Review of risk factors for coronary heart disease (CHD) and their reduction, which concludes in this issue, discusses the risks associated with high triglycerides and the frequently accompanying low levels of HDL. Thus an important aspect of CHD of CHD prevention is the control of triglyceride levels and lowering them if elevated. While there do not appear to be randomized placebo controlled intervention trials that demonstrated reduced risk of adverse CHD events risk specifically associated with triglyceride reduction, it can be argued that it is probably safe and may provide benefit. Since the 1970s, epidemiologic, clinical and experimental evidence have all indicated that omega-3 fatty acids provide protective benefits against CHD and this may in part be due to their triglyceride lowering power. For a number of years, a pharmaceutical grade preparation called Omacor which contains the long-chain omega-3 fatty acids EPA and DHA has been used in Europe both for intervention trials and as a prescription drug. Recently the FDA approved essentially the same product which sells in the US under the different name of Laovza and is also called P-OM3. This prescription form of the pharmaceutical grade EPA + DHA sold in health food stores was featured in a recent review of the use of omega-3 fatty acids for the treatment of moderately elevated triglycerides (150-500 mg/dL). The pharmaceutical product is promoted on the basis of a high concentration of EPA + DHA per one gram capsule, guaranteed purity that is *a priori* assumed with prescription drugs and, while not emphasized, the fact that the patient is provided with a prescription which may be covered by insurance rather than being told to go to the local health food store and acquire the vastly less expensive pharmaceutical grade also available there.[8,9] Patients feel good about getting a real prescription, doctors may feel good about writing it, and as long as someone else pays, everybody is happy. While there may well be differences in the standards of purity between the over-the-counter highly purified pharmaceutical grade EPA + DHA and Laovza, the two products do not appear to have been compared directly in this context. But it is of interest to examine the claim that taking the prescription product considerably reduces the number of capsules required daily.

The prescription preparation involves what are called ethyl esters of the free fatty acids, whereas the over-the-counter product is generally the free acid. Thus when the grams of EPA and DHA are compared, one must correct for this which means reducing the EPA and DHA content of the prescription drug by about 10% in order to compare with the free acid. The recommended dose of Laovza is 4 capsules which provides about 1.7 g of EPA and 1.32 g of DHA for a total of about 3 g. Natural factors makes a pharmaceutical grade and 5 capsules will provide 3 g of EPA + DHA with slightly less EPA and slightly more DHA. Life Extension also sells a highly purified preparation with 5 capsules containing 3 g of EPA + DHA with almost the same ratio of EPA top DHA as the prescription drug. Thus the prescription drug does not drastically reduce the number of capsules required per day but rather simply reduces it from 5 to 4 and appears to be identical with regard to the active ingredient unless one is concerned that the acids are esterified.

The just published review of randomized placebo controlled intervention trials for the lowering of TGs with omega-3 fatty acids allows a comparison of the prescription preparation and ordinary fish-oil preparations.[8] The TG lowering is roughly dose dependent and ordinary fish oil products produced declines ranging from 39% for 4.5 g/d of EPA + DHA to around 26% for intakes of 2.2 to 2.5 g/day. Correcting the prescription intake to account for the fact that it is the ester, one gets an average TG lowering of 28% ± 5% for a dose equivalent to about 3 g/d of EPA + DHA free acid. This falls nicely on the dose depend curve and agrees well with the lowering obtained from an equivalent amount of the non-prescription preparation.

The bottom line appears clear. If one can be confident of the claims of certain over-the-counter suppliers of EPA + DHA regarding purity, then there is no apparent significant difference between the health store product and the vastly more expensive prescription drug, even when the comparison involves TG lowering.

ADOPTING MODERATE ALCOHOL CONSUMPTION IN MIDDLE AGE

The suggestion that there are benefits that accrue due to moderate alcohol consumption in the context of cardiovascular disease is probably common knowledge. The one or two glasses of wine is part of the food pyramid advocated by Harvard's Walter Willett and the recommendation is frequently seen in the media and even in this Newsletter. Now a group of researchers have managed to investigate the impact of initiating moderate alcohol consumption on fatal and non-fatal cardiovascular events for middle-aged men and women. These investigators from the Medical University of South Carolina managed to recruit almost 8000 participants with no history of CVD who were not drinkers at baseline, and follow the cohort for up to 6 years during which time 6% began moderate alcohol consumption (2 drinks per day for men and one for women) and 0.4% began heavy drinking—the risk many physicians rightly feel is a real problem associated with this recommendation.[10] It was found that after 4 years of follow-up, the moderate drinkers had a 38% lower risk of developing CVD than did the persistently non-drinking controls. This difference persisted after adjustment for confounding by demographics and the usual cardiovascular risk factors (Risk reduction 28% which was statistically significant) However, the benefits did not carry over to all-cause mortality which was unchanged, but the follow-up period was rather short, and the mortality at least did not increase.[10] This study adds to the overwhelming evidence that small amounts of alcoholic beverages reduce the risk of CVD. The mechanism is no doubt complex but may in part involve resveratrol, one of the phytochemicals (polyphenols) also implicated in cancer prevention, as discussed in the June issue.

PHYSICAL ACTIVITY AND BMI IN CORONARY HEART DISEASE RISK

In a prospective study of almost 39,000 women free of CVD, cancer and diabetes at enrolment, a follow-up of over 10 years was used to investigate the connection between being overweight or obese as measured by the body mass index and the benefits of physical exercise. This study had the merit of including individuals with a high level of physical activity. The endpoint was incident coronary heart disease as indicated by a non-fatal heart attack, bypass surgery, balloon angioplasty, or CHD death. Categories included normal weight, overweight and obese combined with active or inactive. When the active-normal weight group was used for comparison, the increased risk of incident CHD was 54% for overweight-active, 87% for obese-inactive, 8% for normal weight-inactive, 88% for overweight-inactive, and 153% for obese-inactive. Increasing levels of walking was found to result in significant reductions in CHD risk for overweight and obese individuals. Thus physical activity, while not completely eliminating the CHD risk associated with elevated BMI, nevertheless produced significant risk reductions. The bottom line remains, however, that the ideal is being both lean and physically active. The CVD risk associated with being overweight or obese was not eliminated by physical activity but merely reduced.

The researchers regard these results as consistent with the present understanding of the pathophysiologic processes associated with CHD. Adipocytes (a particular type of fat cell) release free fatty acids, and inflammatory molecules such as interleukins and cytokines which are known to play

a part in inflammation and coagulability, accelerating atherosclerosis and increasing endothelial dysfunction. Physical exercise favourably impacts coagulability through its influence on fibrinogen and platelet aggregation and in addition, is known to improve endothelial function and decease vascular resistance. However, the main effect according to their hypothesis is the impact of physical activity on pro-thrombotic factors released by adipocytes.[11]

COMPLEMENTARY AND ALTERNATIVE TREATMENT OF METABOLIC SYNDROME

In a recent issue of the *Journal of the American Dietetic Association*, Hollander and Mechanick have examined a number of non-pharmaceutical approaches to treating the metabolic syndrome and in particular have attempted to classify them according to the quality of the supporting evidence. Only four interventions were found to have strong evidence-based support. These were omega-3 supplementation at 4g/day, soy protein containing products at 20-40 g/day, psyllium at > 7 g/day, and adhering to the Dash diet (Dietary Approaches to Stop Hypertension). The risk factor addressed in the first three interventions was unfavourable blood lipids whereas the DASH diet addresses the problem of hypertension. The DASH diet involves high-fiber foods including fruits, vegetables and whole grains, and limited meat, poultry and fish consumption. Variations include salt restriction. Psyllium is a so-called soluble fiber which passes to the colon where it is fermented by the gut bacteria yielding short chain fatty acids which ultimately suppress cholesterol production by the liver. Psyllium is now added to some all-bran breakfast cereals in amounts that could approach the above intake. The omega-3 fatty acid supplements were discussed above.[12]

DO STATIN DRUGS INCREASE RISK OF CANCER?

The short answer appears to be no. In fact, experimental studies demonstrate that many malignant cell lines demonstrate a relatively high activity of the enzyme that the statins inhibit in order to accomplish cholesterol lowering. A recent meta-analysis of case-control studies has addressed this issue for a number of cancer sites. When all cancers were considered together, statin use reduced the risk by 29% but when the results were stratified by site, only colon cancer risk was significantly reduced (11%). While it is unlikely that statins will be promoted as cancer preventive drugs, the importance of this study is that no enhanced risk was found for any cancer including breast, lung, colon and prostate cancer.[13]

It is interesting to compare this study with that of Dale *et al* [14] which examined the risk of statins and cancer in 27 randomized clinical trials where cancer incidence was only a secondary endpoint. It was found that statins had a neutral effect on cancer incidence and cancer related mortality across all types of cancer and subtypes of statin. Thus there is an inconsistency regarding protective effect for colon cancer. More research is needed.

SCREENING FOR BREAST CANCER. COMBINING MAMMOGRAPHY WITH ULTRASOUND

Mammography is a classical example of a screening procedure that is plagued by false positives and false negatives which translate into unnecessary anxiety and ultimately a negative biopsy or on the other hand a cancer that is missed. Radiologists are sued for malpractice over false negatives where the so-called oversight becomes apparent only after comparison of two mammograms taken one or more years apart. Some radiologists have abandoned this sub-specialty. Nevertheless, there appears compelling evidence that the early detection and treatment of breast cancer confers substantial and significant advantages in terms of morbidity and mortality.

A study has just reported that compared mammography and ultrasound screening as compared to combining both techniques to reach an

assessment.[15] Approximately 2700 high-risk women participated in the study. Participants were women presenting for routine annual mammography who also submitted to a physician-administered ultrasound examination. If either was suspicious, then an integrated ultrasound plus mammography interpretation was recorded by a qualified site investigator radiologist. If both were negative, no integrated analysis was performed. The decision regarding the presence or absence of breast cancer was based on a combination of biopsy within 365 days and clinical follow-up at 1 year. To be considered disease negative, it was required that no cancer was confirmed during the one year follow-up. Biopsy results showing cancer (in situ or infiltrating ductal carcinoma), or infiltrating lobular carcinoma in the breast or auxiliary lymph nodes were taken as disease positive. Of the 40 cancer cases identified during the trial, 8 were so-called interval cancers which did not show up on either mammography or ultrasound at the initial screening. Of the 40 cancer cases identified, 19 had a positive mammography and positive integrated result, 12 had a negative mammography but positive integrated result, one had a positive mammography but negative integrated result, and 8, the interval cancers, were negative for both assessments. Put a different way, mammography identified 7.6 cancers per 1000, and mammography combined with ultrasound 11.8 per 1000 thus yielding a gain of 4.2 cases per 1000 identified by the integrated protocol. Sensitivity is defined as the % of the total cancers actually found by the screening. For the integrated protocol, the sensitivity was 77.5% whereas for mammography alone it was 49%. The low sensitivity of mammography is well known with one large trial yielding 55% and numbers as low as 25% have been observed. Looking just at those screened who did not have BC positively diagnosed during the study; mammography found 4.4% false positives, ultrasound 8.1% and the combined protocol 10.4%. Thus while the diagnostic yield was higher for the combined protocol, there were more screening positive results what were in fact false alarms but prompted further diagnostic procedures. This is the essence of the trade-off. But an editorialist suggested that what high-risk women fear most is a late diagnosis and that this is the real threat they desire protection from, not a false positive diagnosis.[16]

As discussed by the study investigators, mammography combined with MRI offers much higher sensitivity than mammography combined with ultrasound and in addition, unlike ultrasound, MRI readily depicts ductal carcinoma in situ, but the importance of this is debated as is the use of MRI in general for breast cancer screening. MRIs are expensive, but the editorialist points out that ultrasound may be about as expensive because the ultrasound procedure is time consuming, taking about 20 minutes of physician time whereas a breast radiologist involved in batch reading of screening mammograms can read about 50 per hour and similar numbers are possible with screening MRI. Also, it appears that a negative MRI yields a more definite answer than a negative ultrasound.[15] If mammography plus MRI became the standard for breast cancer screening, this would also put great stress on health care systems where limiting access to MRI scans with long waiting times is a common result of cost control.

BREAST CANCER AND CARBOHYDRATE INTAKE

Elevated circulating insulin in response to carbohydrate intake may affect breast cancer risk either by stimulating insulin receptors in breast tissue or through mitogenic effects of the insulin-like growth factor. This potential association may be particularly relevant in populations with a high prevalence of insulin resistance, a hypothesis suggested by a study where dietary carbohydrate was associated with increased breast cancer risk only among overweight women. A study has recently reported that addresses this issue by examining the relationship between breast cancer risk and dietary glycemic index (GI) glycemic load (GL), fiber intake and in addition was able to take into account the hormone receptor status of the cancers diagnosed. The prospective study involved over 62,000 women with a follow-up of 9 years. A direct association between carbohydrate intake, GI, and GL and overall postmenopausal breast cancer was not found. However, an association was found between dietary GI and breast cancer in overweight women, and both high GI and GL diets appeared to increase breast cancer among women with a large waist circumference. For the subset of women with ER negative breast cancer, it was observed that there was a direct association between both carbohydrate intake and GL and the risk of this disease. Fiber was not implicated. [17] These results add to the quite considerable data suggesting that there are widespread adverse health aspects

associated with consuming more than very modest amounts of refined grain products, potatoes, rice and sugars, the principal culprits in creating diets with high GI and GL.

PROBLEM OF UNDIAGNOSED DIABETES

Approximately 30% of individuals with diabetes in the U.S. are undiagnosed. Estimates run as high as over 6 million. The microvascular and macrovascular complications of diabetes are sometimes present even in pre-diabetics. The earlier diabetes is detected and treated, the greater the probability of minimizing or avoiding these and other problems that are associated with this disease. However, screening for diabetes is made difficult by virtue to the fact that many individuals undergoing routine physicals are not fasting nor do they eventually provide a fasting blood sample. In the absence of fasting, the plasma glucose level is a poor tool for detecting diabetes. Even the diabetes criterion of ≥ 200 mg/dL is very insensitive, requiring the diabetes to be in poor glycemic control. It has recently been proposed that the use of hemoglobin AIc (HbA1C) should now be routinely used for this purpose. Historically there were many objections to the use of HbA1C but now the assay is well standardized, the measurement provides a long-time average blood glucose level and thus examines the question of long-term glycemia, fasting is not required, nor is the level affected by short-term lifestyle changes. Their proposal for a diagnostic protocol is that the following should prompt follow-up: (1) Fasting plasma glucose of ≥ 100 mg/dL or a random plasma glucose of ≥ 130 mg/dL; (2) HbA1C ≥ 6.5-6.9% subsequently confirmed by a fasting glucose or oral glucose tolerance test: (3) HbA1C ≥ 7% confirmed by a second HbA1C test or a fasting glucose or oral glucose tolerance test. The message for readers is that they need to be concerned about surveillance for diabetes, and that this concern centers around their fasting status when blood tests are done and if HbA1C is included in the tests ordered. If only a random (non-fasting) blood glucose is measured, then they should request further investigation if the value exceeds 130 mg/dL, but should recognize that even this is not an ideal screening tool although it does appear to minimize false positives. The prudent approach would appear to be the addition of the HbA1C test and readers should consider requesting it. The estimate of over 6 million individuals in the U.S. with undiagnosed diabetes should provide a strong incentive for being extra vigilant.

While diagnosing diabetes is obviously very important, true preventive medicine should focus on so-called pre-diabetes, the hallmark of which is insulin resistance.[18] This has been discussed in some detail in the Research Report which appeared in the June issue and this issue. Thus any signs of abnormal glucose metabolism should be investigated. A comprehensive physical in some clinics includes a 2-hour oral glucose tolerance test just as a matter of routine simply because even fasting glucose is not a good indicator of insulin resistance. It is rarely done in general practice. The HOMA-IR test, which just uses fasting insulin and fasting glucose, two results frequently available from a routine blood work-up, also provides a good indication of the presence of insulin resistance. All that is required is plugging the numbers into a simple formula. Readers who have fasting blood work done should request the inclusion of serum insulin and the HOMA-IR calculation. The equation is provided in Part I of the current research report.

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Some Suggestions For Summer Reading

THE DENIERS
by Lawrence Solomon
Richard Vigilant Books, 2008

Lawrence Solomon will be familiar to many Canadian readers of the *National Post* as this book represents a significant expansion of the series he contributed on the world-renowned scientists who have stood up against the global warming hypothesis. The official view of global warming is that the science is settled beyond all reasonable doubt, that man has made a significant contribution to the problem, and that worldwide disaster looms in the not too distant future, unless drastic action with huge economic implications is immediately undertaken. Those who suggest that the matter is far from settled and that serious debate and research is needed regarding alternative hypotheses are by and large ridiculed, or even worse, treated as kooks and crooks in the pay of the oil companies who are hired to confuse the issue. Yet these skeptics in general admit that some global warming appears to be taking place. But they dispute the evidence that man is responsible for all or even most of this warming, that global climate or its changes are understood well enough to justify predictions, and that there is evidence of a need to reduce the use of fossil fuel now. The leading evangelist for the crisis school is Al Gore who describes these skeptics as so-called deniers, a calculated derogatory term usually reserved for those who deny the Holocaust, and is responsible for the following statement; “Fifteen percent of the people believe the moon landing was staged on some movie lot and a somewhat small number still believe the Earth is flat. They all get together on a Saturday night and party with the global warming deniers” (Seattle times, October 25, 2006). Solomon’s approach to this important debate was to locate a number of scientists with impeccable credentials and worldwide reputations and interview them in order to get a clear picture of the basis of the deniers’ position. This book is an account of this project and makes for fascinating reading. Solomon

presents what seems to be an unbiased account of the opinions these deniers hold and why they hold them. The book is also an interesting study in what Christopher Essex and Ross McKitrick call "Official Science" in their book on global warming titled *Taken By Storm* (Key Porter Books, 2007). Official science involves the artificial elevation of a mere hypothesis to the status of an established, evidence-based fact of science on a par with the natural laws which is not to be questioned by anyone who expects the respect of the scientific community. But this does not change the fact that it is still based merely on a hypothesis. Unfortunately, as many readers of this newsletter will recognize, climatology is not the only discipline where this phenomenon has run amok.

Becoming informed regarding this debate is not just an intellectually entertaining pastime for curious readers. Strong forces are at work to implement changes based on what the skeptics regard as mere hypotheses, and these changes will, if implemented, have a profound impact on developing countries and the economies of the developed world. Witness the huge effect of the corn to ethanol program on the use of corn for non-food applications. Yet, the benefits to the environment, according to studies published in peer-reviewed journals, suggest they are close to negligible aside from decreasing dependence on fossil fuels.

CLIMATE CONFUSION. How Global Warming Hysteria Leads to Bad Science, Pandering Politicians and Misguided Policies That Hurt the Poor
by Roy Spence
Encounter Books, 2008

Spencer is a principal research scientist at the University of Alabama in Huntsville where he directs a variety of climate research projects. A former senior scientist for Climate Studies at NASA, he is co-developer of the original satellite method for monitoring global temperatures. The author of numerous weather and climate research articles in scientific journals, he speaks with authority on this subject. This book is an excellent companion to Solomon's book reviewed above. From the two, the reader should achieve a balanced view of where science really stands in connection with the possibility that significant changes, both good and bad, in the global climate are really occurring and what the evidence is, if any, that man is responsible and what, if anything, needs to be done.

THE BLUE ZONE. Lessons for Living Longer from the People Who've Lived the Longest
by Dan Buettner
National Geographic, 2008

This book describes projects supported in part by the National Geographic that has been going on for some time. The studies not only involved the active participation of the author, but also important assistance and contributions from a number of experts in demographics, longevity and related disciplines. The goal of the research reported in this fascinating book is to attempt to obtain a generalized picture of the lifestyle of those who live the longest, the centenarians, and what contributes to their extraordinary longevity. The title derives from a demographer's term that identifies geographical areas of exceptional longevity where the number of centenarians per 1000 population is extraordinary. The Blue Zones examined in Buettner's book are remote or mountainous areas in Sardinia and Costa Rica, areas of Okinawa and Seventh Day Adventists enclaves in California. Beuttner and his colleagues studied diet and other lifestyle factors associated with extreme longevity and as well investigated such questions as philosophy of life and social and family interactions. The book includes interviews with some extraordinary centenarians.

The people studied in both Sardinia and Costa Rica had lifestyles that had remained essentially unchanged for centuries, grew almost all their own food, lived in a climate where year-long gardening was normal, and had strong family traditions where the elderly and very old were invariably cared for by their children. It was not uncommon for a centenarian to be cared for in the family home by children in their seventies and grandchildren in their forties. All the groups that lived in these four so-called Blue Zones consumed mostly if not exclusively what we would term genuine organically grown produce, ate sparingly of meat from animals that only grazed, and consumed eggs from chickens which were "free range." Duplicating some of the

dietary practices and family traditions in North America, for instance, would seem to be difficult. Climate in a large part of the continent prohibits year-around fruit and vegetable cultivation and most modern families would have trouble adapting to the practice of "extended care" of elderly parents at home. Nevertheless, it is interesting to examine the factors that appeared associated with both very low levels of the common non-infectors diseases and the significantly enhanced longevity. The common patterns Beuttner and his colleagues observed and documented are summarized in the last chapter of the book. Some merit close attention since they can be implemented in the North American food and lifestyle culture.

BEST CARE ANYWHERE. Why VA Health Care Is Better Than Yours
by Phillip Longman
Polipoint Press, 2007

A few decades ago the notion that a Veteran's Administration hospital run by the U.S. government was a great place to receive care would have been greeted with ridicule embellished with horror stories. Phillip Longman's recent book documents the metamorphosis that has taken place in the last 30-40 years such that today the VA hospitals rank among the best in the world by almost any measure. This remarkable phenomenon is of interest in its own right but also because it provides a model for hospital reform that is backed by solid evidence of achievement. Longman's book provides evidence against the widely held belief that governments are incapable of running anything as intrinsically complex as a health care system and furthermore, demonstrates that the particular brand of socialized medicine practiced at the VA hospitals works splendidly, an outcome not in keeping with mainstream medicine's fundamental distrust of this form of health care.

When the transformation of the VA hospitals began, they suffered from many of the problems that afflict the hospital system today—lack of electronic patient records, failure to coordinate care among specialists involved, a significant rate of incorrect medication, including both incorrect doses and wrong recipients, illegible records and doctor's orders, lack of attention to staff caused infections, dirty facilities etc., etc. Longman's book provides the fascinating story of how these problems were overcome. Of particular interest was the initial aggressive and nearly successful attempt by the VA administration to prevent the development and implementation of electronic patient records and drug orders which today is the centerpiece of the VA success story. The software was named Vista long before Microsoft used this name for an operating system. It is responsible among other things for solving the problem of coordinated treatment which has resulted in better outcomes and fewer treatment blunders. The VA patient record and management software, which is free, is widely used outside the U.S and is highly regarded has, interestingly enough, not been widely accepted or used in the U.S. except at the VA hospitals.

The VA hospital story is also the subject of a chapter in Shannon Brownlee's new book *Overtreated: Why Too Much Medicine Is Making Us Sicker and Poorer*, a book which is also highly recommended for the insight it provides on the downside of high-tech cutting-edge medicine when it gets out of control.

ENDING THE FOOD FIGHT. Guide Your Child to a Healthy Weight in a Fast Food/Fake Food World
by David Ludwig, MD, PhD
Houghton Miffen, 2007

Dr. Ludwig is director of the Optimal Weight for Life Program, Children's Hospital, Boston, MA. He is an endocrinologist and an associate professor of pediatrics at Harvard Medical School. The coauthor, Suzanne Rostsler is a clinical nutritionist. For this book, it seems sufficient to quote several of the testimonials provided on the jacket.

- "Dr. Ludiwig has brought together the best available scientific evidence on weight control and has personal insights from years of clinical experience working with overweight children. Anyone caring for children will want to read this book." Dr. Walter Willett, Chair of the Department of Nutrition, Harvard School of Public Health.

- "This book comes from a wise and caring physician and nutritionist whose compassion and devotion to children's health shines through every page. What they say should give hope and courage to any parent wondering how to best help an overweight child." Dr. Marion Nestle, Professor of Nutrition, New York University.
- "This road map will enable not just overweight children, but all children and their families, to understand how to be healthy and well. It is all the information needed to know how to navigate our complex and often toxic world and win." Dr. Francine Kaufman, past president of the American Diabetes Association.
- "I consider David Ludwig to be one of the most knowledgeable and compassionate physicians in the world of childhood nutrition. This book is an extremely valuable resource for any parent, as it contains very practical and clinically proven advice. If you care about having your child avoid the consequences of the growing epidemic of childhood obesity, this is a must-have book in your home." Dr. Barry Sears, author of the Zone books.

One of the great strengths of this book is that it deals not only with diet issues but also with the psychological issues that operate at the interface between parent and child when it comes to nutrition. Thus the title. It is of interest that Dr. Ludwig and his team believe in a low-glycemic approach to diets for children.

SPARK: The Revolutionary New Science of Exercise And The Brain
by John J. Ratey, MD
Little, Brown and Company, 2008

Dr. Ratey is a clinical associate professor of psychiatry at Harvard Medical School and is a bestselling author and renowned psychiatrist. This book describes the connection between the many functions of the brain and physical exercise. In it he discusses the role of exercise in stress, mood, memory loss, and intellectual power. He advances arguments and evidence that exercise is the best defence against depression, attention deficit disorder, aggression, problems associated with menopause and even Alzheimer's disease. This book should have a profound impact on the way one regards exercise and the role it plays in our wellbeing.

RESEARCH REVIEW

CORONARY HEART DISEASE RISK AND ITS REDUCTION PART II

REDUCING INFLAMMATION AND INSULIN RESISTANCE

William R. Ware, Ph.D.

INTRODUCTION

Part I provided a basis for the view that chronic, systemic low-level inflammation is an important risk factor associated with the development of insulin resistance, diabetes, atherosclerosis and coronary heart disease (CHD). Furthermore, the presence of the metabolic syndrome is a risk factor for all of the above. Thus it seems reasonable that primary prevention of CHD should focus on inflammation and the various aspects of the metabolic syndrome and this was systemized in Part I with a list of risk factors, their thresholds and potential interventions. If one has diagnosed metabolic syndrome, then the challenge is reversing it or in a broader context, normalizing as many of the criteria as possible. If one does not qualify for this diagnosis, then preventing the metabolic syndrome is the challenge along with maintaining all the criteria in the normal range. In addition, attention must be paid to the other risk factors discussed in Part I. The goal of the suggested prevention program is the normalization of risk factors discussed in Part I and this is strongly associated with the goal of preventing insulin resistance, type 2 diabetes, and vascular disease including CHD.

In the context of primary prevention of CHD, non-pharmaceutical interventions appear limited to diet, exercise, supplements and the minimization of psychological stress and depression. Diet is highly controversial and political, but the importance of exercise not even debatable, and dealing with psychological stress and depression is clearly challenging, given that its root causes frequently are not easily eliminated.

Part II will mostly deal with the issue of diet since strong arguments can be advanced that dietary factors play a key role in that they are associated with unfavourable levels of many of the risk factors discussed in Part I. The question of what is the best diet for 21st century *homo sapiens* is highly controversial with a wide range of distinctly different options along with their proponents and detractors. Government agencies have their recommendations as do a number of medically related organizations such as the American Heart Association, the various diabetes associations, the National Cholesterol Education Program (NECP), etc. The diversity of approaches to diet is evident to anyone browsing the diet section of a large bookstore. Some view diets as a weight loss tool; others take a boarder view that encompasses overall nutrition and disease prevention. In the context of this review, the central issue is the relationship between diet and inflammation. Are there diets or food patterns that raise inflammatory markers? Are there specific macronutrients that alter the inflammation balance? Since inflammation leads to insulin resistance which leads to diabetes which leads to cardiovascular disease (CVD) in general and CHD in particular, a lifestyle including diet that reduces the risk of type 2 diabetes is also of considerable interest. Such a diet will also be strongly associated with reducing the risk of acquiring the characteristic manifestations of the metabolic syndrome. In fact, it can be argued that the focus on cholesterol as the major risk factor for CHD and the primary target for therapy has provided a serious distraction from the real challenge in the primary prevention of CHD, i.e. the prevention of low-level systemic inflammation, insulin resistance and type 2 diabetes.

The connection between diet and heart disease has been the subject of countless studies, many of which were poorly designed and yielded meaningless results, and vast controversy has simmered for more than 30 years. The fat-heart disease hypothesis, which was initially advanced on the basis of selected data, became official science, an article of faith in medical and nutritional science, even though it remained a mere hypothesis under constant attack and under ordinary circumstances would have been relegated to the status of a weak and perhaps insignificant association of little importance. That this did not happen is a long story told most convincingly by Gary Taubes in his recent magnum opus titled *Good Calories, Bad Calories. Challenging the Conventional Wisdom on Diet, Weight Control and Disease* (Knopf, 2007).

Diet studies that try to sort out the impact of the individual macronutrients, i.e. fat, protein and carbohydrate, can be classified roughly into two groups. In one, the total number of calories remains constant whereas in the other, the energy intake is decreased. In the former, if the energy from one macronutrient category is decreased, this deficit must be made up by increasing the intake of another category. Thus more than one variable is always being changed. Within the major categories of fat, and carbohydrate, the composition of each can be changed by substitution while maintaining a fixed energy intake, or substitutions can be made along with a decrease in intake and thus energy. Studies that change the distribution of calories between fat, carbohydrate and protein and at the same time reduce energy intake are hard to interpret because of the two or more factors are changed at the same time. In some studies, exercise and even meditation and stress reduction are added to dietary changes which add significantly to the confusion. Randomized dietary intervention studies suffer from an unknown extent of compliance and those that are highly controlled are of necessity very short-term, and observation (follow-up) studies require multiple assessments with validated questionnaires in order to make sure that changes over time in diet patterns are taken into account. One of the most realistic approaches to dietary questions involves looking at patterns rather than the three macronutrients, since people eat meals, and in addition, alcohol in general and wine in particular, occupies a unique position in diet and lifestyle and is not normally considered part of one of the three macronutrients.

This review will focus on dietary patterns, inflammation and the risk of the metabolic syndrome, type 2 diabetes and CHD. It will be seen that there are dietary patterns and a certain lifestyle that have been found to provide dramatic risk reductions, reductions that in some cases are greater than anything that has been accomplished with pharmaceutical intervention. Furthermore, these diet patterns and lifestyle features also are associated with low levels of inflammation, insulin resistance, and favourable levels of the risk factors discussed in Part I.

DIETARY PATTERNS, AND THE RISK OF DIABETES AND CHD

Two large and important prospective follow-up studies from Harvard reported in 2000 and 2001.[1,2] They endeavoured to determine the optimum dietary pattern for the prevention of CHD in men and women in the age group 38-63. These studies were part of the men's Health Professional Follow-up (44,875 men) and the Nurses' Health Study (69,047 women). The least favourable and the most favourable dietary patterns were termed "Western" and "prudent." The former was characterized by higher intake of red meat, processed meat, refined grains, sweets and deserts, French fries and high-fat dairy products. The prudent diet pattern consisted of higher intakes of vegetables, fruit, legumes, whole grains, fish and poultry. Fatal or nonfatal heart attack was the endpoint indicating CHD. At the end of the follow-up period, the highest adherence to the prudent pattern combined with the lowest adherence to the Western pattern showed a 50% reduction in CHD as compared to the combined lowest prudent patter and highest Western pattern group. A similar comparison for women found a 36% % reduction.

Data from the Nurses' Health study was also used to investigate the proportion of coronary events that could potentially be prevented by adherence to a set of dietary and behavioral guidelines.[3] The low-risk diet was high in cereal fiber, marine omega-3 fatty acids and folate, had a high ratio of polyunsaturated fat to saturated fat, was low in *trans*-fats, and had a low glycemic load. Behavioral guidelines required a body mass index of < 25 (not overweight) no smoking, moderate to vigorous exercise for at least one hour a day, and at least ½ of an alcoholic drink per day. During fourteen years of follow-up, women who adhered to the low-risk guidelines had an 83% reduction in the risk of CHD and 82% of the coronary events in the total study cohort could be attributed to lack of adherence to this low-risk diet and lifestyle pattern.

Diabetes is a major risk factor for CHD. Thus diet and lifestyle factors that are effective in preventing CHD would be expected to impact the risk of diabetes. Put another way, preventing type 2 diabetes should be an important component of CHD prevention. In a study from the Nurses' Health Study, closely related to that described above which used essentially the same low-risk behavioural pattern (folate and fish omitted), a remarkable 91% reduction was found in the risk of developing type 2 diabetes over the 16 year follow-up.[4] On the other hand, for men in the Health Professionals Follow-up Study, a high score for the Western dietary pattern combined with low physical activity almost doubled the risk of developing type 2 diabetes. Obesity carried an eleven-fold increase in risk.[5]

A new study that relates to the issue of diet patterns and the risk of CVD has just reported.[6] The cohort was again from the Nurses' Health Study, and the follow-up was over 24 years with diet assessment carried out 7 times during this period with food frequency questionnaires. The main outcomes measured were nonfatal MI, CHD death and stroke, and the study examined the impact of adherence to the DASH diet pattern on these endpoints. Historically the DASH diet (Dietary Approaches to Stop Hypertension) was designed to examine the hypothesis that blood pressure lowering would result from a diet high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein but with substantial plant protein from legumes and nuts. Subsequent variations included sodium restriction and substituting part of the carbohydrate content with either plant protein or unsaturated fat.

In this study, adherence to the DASH diet was established by a score that depended on the intake of fruits, vegetables except potatoes, nuts and legumes, and whole grains. Negative points were given for the intake of sodium, red and processed meats and sweetened beverages. When the fifth vs. the first quintile for the adherence score were compared, there was a 27% relative risk reduction in total CHD, a 22% reduction in nonfatal MI, and a 34% reduction in fatal CHD events. These results were adjusted for a large number of confounders and were all statistically significant as were the trends for risk reduction across the quintiles. The DASH pattern differs somewhat from the patterns discussed above in that women with high scores consumed more fiber, and the intake of polyunsaturated and monosaturated fat was lower. Nevertheless the similarities with the prudent diet are noteworthy and highlight the importance of high fruit, vegetable, legume and nut intake.

It is interesting to compare the above results with those from the Woman's Health Initiative Randomized Controlled Dietary Modification Trial.[7] In this trial, the dietary intervention involved reducing fat intake to 20% of calories by increasing the intake of fruits and vegetables to 5 serving per day and grains to at least 6 servings per day. It was assumed that the reduction of fat intake would be accompanied by a reduction in saturated fat intake, which in fact did occur (12.4% to 9.5% of total energy). Weight loss was not a goal, and there appears to have been no emphasis on whole grains vs. refined grains if one judges from the indicated intakes for the intervention and comparison groups. In fact, after three years, the intervention resulted in small increases in triglycerides and small reductions in HDL. This highlights the magnitude of the emphasis on fat reduction in this study. The comparison group was given a copy of *Dietary Guidelines for Americans*. After a mean of 8.1 years of follow-up, this intervention did not reduce the risk of CHD, stroke or CVD in postmenopausal women. Nevertheless, the reduction of dietary fat in general and saturated fat in particular is one of the pillars of mainstream medicine's approach to reducing the risk of CHD and the changes that occurred during this study were in keeping with the mainstream guidelines.

CHD AND THE MEDITERRANEAN DIET

The diets which exhibited significant risk reduction for CHD and diabetes resemble the Mediterranean diet. The Mediterranean diet is generally characterized as having a high intake of vegetables, legumes, fruits, nuts and cereals (that traditionally were largely unrefined) and a high intake of olive oil but a low intake of saturated fats, a moderately high intake of fish, a low-to-moderate intake of locally produced dairy products, mostly cheese and yogurt, a low intake of meat and poultry and regular but moderate intake of alcohol, mostly in the form of wine with meals. Interest focused on this diet when it was observed that in countries like Greece, and in particular Crete, when the traditional diet was consumed, the incidence of heart disease was very low as compared to European countries or the U.S. Interest was further stimulated by several randomized, controlled trials of Mediterranean style diets for secondary prevention of cardiac events. One of the most famous, the Lyon Diet Heart Study, found a 68% decrease in cardiac death and non-fatal MI over four years of follow-up when the comparison was with the Step I NCEP control diet. The Mediterranean diet had augmented omega-3 fats in the form of alpha-linolenic acid. This large secondary protective effect was found in spite of little or no change in cholesterol levels among the intervention diet participants, an observation that surprised those committed to the LDL hypothesis. In the GISSI-Prevention Study of over 11,000 post-MI patients, 1g/day of omega-3 fish-oil supplementation was added to the Mediterranean diet. A 30% decrease in CV deaths and a 46% decrease in sudden deaths were found. While these secondary prevention results are of great importance to individuals with CHD, this review is concerned with primary prevention.

With regard to the issue of dietary omega-3 fatty acids, there do not appear to be any randomized clinical trials, and with one exception, prospective cohort studies have only indirectly provided information. For example, in the

Nurses' study, eating fish five times a week cut the risk of CHD mortality by 45% and in the Physicians Health Study, the relative risk of sudden death was lower among men with higher blood levels of omega-3 fatty acids.[8]

There have been two large prospective studies that directly addressed the connection between the Mediterranean diet and mortality. Both used a 9- or 10-point adherence scale for the Mediterranean diet. In one study involving a Greek population the risk of total mortality was reduced by 25% for a two-point increase in this score. The authors point out that magnitude in the reduction of mortality with greater adherence to a Mediterranean diet was compatible with the reported survival advantage of adult Mediterranean populations over North American and northern European populations.[9] Another large prospective study of a U.S. population of average age 62 years examined the association between adherence to a Mediterranean diet and mortality. The decrease in all cause and CVD mortality for those with the highest conformity as compared to the lowest was 20-25%.[10]

A case-control study from Spain also found that the degree of adherence to a Mediterranean diet was as important factor associated with significantly decreasing the risk of a first MI. This study also supported the exclusion of high glycemic load foods.[11]

DIETARY PATTERNS AND THE METABOLIC SYNDROME

Dietary strategy that eliminates or reduces the risk of the metabolic syndrome not only addresses non-traditional risk factors but also the etiology of CHD at an early stage in its natural history. The following studies are of interest.

- In a study from Greece that used a national health and nutrition survey, it was found that individuals who consumed a Mediterranean diet had a 19% risk reduction of the risk of having the metabolic syndrome and if even a little or moderate physical activity was present, the risk reduction improved to 25%.[12]
- In another study from Greece, a dietary pattern characterized by cereals, fish, legumes, vegetables and fruits was inversely associated with waist circumference, systolic blood pressure, triglycerides and positively associated with HDL levels and resulted in a 13% risk reduction for the metabolic syndrome.[13]
- In a study of women 40-60 years of age in Tehran, Iran, a diet pattern characterized by high intake of fruit, vegetables, poultry, and legumes was associated with reduced risk of insulin resistance and the metabolic syndrome whereas a diet high in refined grains, red meat, butter, processed meat, and high-fat dairy products and low amounts of vegetables and low-fat dairy products was associated with a greater risk of this syndrome. This study was jointly carried out by nutritional epidemiologists from Harvard and Isfahan University in Iran.[14]

DIET, INFLAMMATION AND INSULIN RESISTANCE

Diets considered beneficial in the context of CHD should not only decrease the risk of hard events (fatal and non-fatal MI), but also decrease the risk of atherosclerosis or its progression, since this, after all, impacts directly on the origins of the problem. The primary prevention of hard events is a common and convenient endpoint for studies, but the prevention of diabetes, the metabolic syndrome, insulin resistance, and inflammation which may be the root cause of it all, seems essential. Thus the impact of diet on markers of CHD risk, and in particular the non-traditional risk factors, is of considerable interest and has been the subject of a number of studies.

In a review published in the *Journal of the American College of Cardiology* in 2006, dietary strategies were examined in connection with inflammation reduction.[15] A highly inflammatory diet was high in refined starches, sugar and saturated and trans-fats, and poor in natural antioxidants and fiber from fruits, vegetables, whole grains, and poor in omega-3 fatty acids. Such a diet pattern may cause the activation of the innate immune system, most likely by an excessive production of pro-inflammatory cytokines associated with the reduced production of anti-inflammatory cytokines. It was concluded that the Western dietary patterns "warm up inflammation" and the prudent dietary patterns "cool it down." A number of studies support this view. For example

- A Mediterranean diet supplemented with olive oil was found to have beneficial effects on cardiovascular risk factors. When compared to a low-fat diet, significant beneficial changes over 3 months were found

for insulin resistance (decrease in the HOMA index), fasting insulin, fasting glucose, HDL, C-reactive3 protein (CRP) and interleukin-6 (a cytokine with associated with inflammation).[16]

- In a study of the Mediterranean-style diet on markers of vascular inflammation in a cohort with the metabolic syndrome, compared to those on a control diet, patients consuming the intervention diet experienced significantly reduced levels of CRP and several inflammatory interleukins, and as well reduced insulin resistance and improved endothelial function. Adherence to this diet also resulted in a significant number of patients being reclassified as not having the metabolic syndrome.[17]
- In a study of 5 dietary patterns, the Mediterranean pattern and one called the Alternate Healthy Eating Index which was similar to the prudent diets discussed above, both produced lower concentrations of biomarkers of inflammation and endothelial dysfunction as compared to diets similar to the Western pattern. For the Mediterranean and Alternate Healthy Eating Index patterns, the decreases from baseline in CRP were 24% and 30% whereas for interleukin-6 they were 16% and 31%.[18]
- In a study of the prudent diet pattern and insulin resistance, it was found that in comparison with a traditional Western or a northern European diet pattern, the prevalence of insulin resistance as indicated by the HOMA score was 47% lower.[19]
- A comparison of high to low adherence to a Mediterranean diet pattern found that high adherence resulted in a decrease in the HOMA Index of insulin resistance from 2.7 to 2.3 units, a change which reflected improved insulin sensitivity.[20]
- The traditional Mediterranean diet augmented with either extra olive oil or nuts was found in a randomized trial to significantly reduce LDL oxidation. The authors considered this additional evidence for recommending this diet pattern for the prevention of CHD.[21]

Other examples and a detailed discussion can be found in recent reviews.[15,22,23] The bottom line appears to be that if one is seeking an anti-inflammatory diet which also increases or maintains insulin sensitivity, evidence points to the Mediterranean diet or the prudent diet, both of which were also strongly implicated in the reduction of CHD risk in the studies discussed above.

METABOLIC AND INFLAMMATORY EVENTS AFTER A MEAL ARE ALSO IMPORTANT

The medical term for the period in time after a meal is called *post-prandial*. While derived from the Latin word for breakfast, it applies to any meal. The American culture currently favors a diet high in extensively processed, calorie dense, nutrient depleted foods which frequently results in exaggerated supra-physiological post-prandial spikes in blood glucose and lipids. This result, called post-prandial *dysmetabolism,* induces immediate oxidative stress, inflammation, endothelial dysfunction and an enhanced tendency toward clot formation. The oxidative stress is in direct proportion to the post-prandial increases in serum glucose and triglycerides. This is an important phenomenon since post-prandial dysmetabolism is an independent predictor of future CV events even in non-diabetic individuals. Epidemiologic studies indicate that eating patterns such as characterize the traditional Mediterranean diet will blunt the post-prandial increase in glucose, triglycerides and inflammation and this provides additional support for this diet pattern in the context of the primary prevention of CHD.[24]

LOW-FAT, HIGH-FAT, LOW-CARB, HIGH-CARB????

This discussion has so far avoided for the most part the question of the macronutrient balance reflected by the four diet types described in the heading to this section. In fact, the diets thus far discussed place emphasis on the selection of fats and carbohydrates rather than the percentages of energy derived from carbohydrates, fats and proteins. This approach in fact addresses a serious defect in some dietary recommendations which do not differentiate the types of fat nor do they take into account different carbohydrate sources such as refined grains and sugar in comparison with low glycemic vegetables and fruits. Furthermore, there is a large range in total fat content in so-called low-fat diets, and likewise, “low-carbohydrate” to one group of researchers can be high-carbohydrate to another. It appears that the types of fat and carbohydrate appear to play a key role in the cardio-protective nature of both the prudent and Mediterranean diet patterns.

It is also noteworthy that the prudent diet that produced a significant decrease in the risk of CHD and diabetes also highlighted only the nature of carbohydrates and fats, not the relative contributions to energy intake. In addition, the Mediterranean diet cannot be characterized as low or high in either of these macronutrient classes. In fact, the traditional Mediterranean diet typically contains 30-40% fat and 15% protein, which means the energy

input from carbohydrates is approximately 45-55%. At 55% carbohydrate, it would actually approach a high-carbohydrate diet. But if one compares the modern Western diet with the Mediterranean diet, the former is high in carbohydrates derived from refined grains, sucrose and fructose and low in fiber, just the opposite of the cardioprotective diets. In addition, the fats in the Mediterranean diet will be higher in monounsaturated and polyunsaturated fat and also higher in omega-3 fatty acids derived both from plant and marine sources. Studies discussed above suggest that the cardioprotection of these diet patterns derives in part from being less inflammatory, less likely to induce insulin resistance, and less likely to cause postprandial dysmetabolism, and as well, less likely to lead to type 2 diabetes.

This then sums up the dietary guidance provided by the studies discussed above and provides the incentive for thinking in terms of dietary patterns rather than high and low fat or carbohydrate and rather concentrating on selecting the types of each that appear to provide the greatest benefit.

CARBOHYDRATE RESTRICTION

The discussion thus far in this review concerning diet and the risk factors for CHD has concentrated on dietary patterns and in particular the merits of the prudent and Mediterranean diets. However, in Part I, carbohydrate restriction was suggested by Dr. Stephen Sinatra as the appropriate intervention for unfavourable TG/HDL ratio and/or the presence of insulin resistance. A high TG/HDL ratio and the frequent presence of small LDL particles have been termed *atherogenic dyslipidemia* and is part of the clinical picture generally presented by those with the metabolic syndrome. While dietary measures demonstrated to reverse or reduce the risk of the metabolic syndrome were discussed above, individuals with very high TG and very low HDL perhaps need to take more aggressive action and this appears to be the restriction of carbohydrate intake as well as the selection of sources in keeping with the prudent or Mediterranean diet principles.

However, a recent comprehensive review of this subject by Volek *et al*[25] points out that discussion or even acknowledgement of carbohydrate restriction as an effective lifestyle modification to treat atherogenic dyslipidemia is absent from much of the current literature and researchers examining the cellular mechanisms of strongly elevated TGs generally disregard carbohydrate restriction as a potent modulator of TG levels. Volek *et al* take the position that progress in dealing with elevated TG levels and atherogenic dyslipidemia will depend on putting the historical controversies aside. One is also reminded of the Atkins Diet, which in spite of a number of favourable studies which have shown that the major concerns voiced by nutritional experts are unfounded and the diet in fact provides a significant improvement in CV risk factors, it is still is considered an insignificant if not potentially dangerous fad diet. Recent studies however suggest that it is in fact a satisfactory and safe diet for inducing weight loss and a diet that significantly improves the TG/HDL: ratio.[26-28]

This subject will be explored more fully in the upcoming review on weight reduction. However, individuals with the metabolic syndrome or even just an unfavourable TG/HDL ratio of > 3 to 3.5 might consider not only the Mediterranean diet approach but also restricting carbohydrates and especially those associated with sugars, refined starches, rice and potatoes.

DIETARY OMEGA-3 AND OMEGA-6 FATTY ACIDS AND CVD

A popular notion has been that omega-6 fatty acids (n-6 FAs) are inflammatory and omega-3 fatty acids (n-3 FAs) are anti-inflammatory. The arguments in favour of this involve the metabolic products of the two classes of fatty acid and the competition for enzymatic pathways. Since the typical Western diet tends to be heavy in n-6 FAs and light to very light in n-3 FAs, this aspect of modern diets has been postulated as contributing to the incidence of CVD. A recent paper by Harvard's Walter Willett provides a modern perspective concerning the importance of both of these fatty acids in the prevention of CVD.[29]

The principal actors in these two classes of polyunsaturated fatty acid are linoleic acid (LA), alpha-linolenic (ALA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). LA and AA are n-6 FAs and ALA, EPA and DHA belong to the n-3 class. Aside from marine sources, dietary intake of these two classes of FA is mostly through LA and ALA. LA is metabolized to AA and ALA to EPA and DHA, the latter two FAs also being supplied directly by fish and fish oils. In connection with risk factors of interest in this review, Willett makes the following points with regard to the n-6 FAs.

- Compared to all other classes of fatty acid, intake of LA produces the most favourable blood lipid changes as reflected by the lowest ratio of LDL to HDL and by the fact that LA increases HDL levels.
- While there have been relatively few studies regarding n-6 FAs and inflammation in humans, nevertheless, they show that consumption of n-6 FAs does not appear to increase inflammatory factors and may reduce some indicators of systemic inflammation.
- There is strong evidence that LA consumption improves insulin resistance and decreases the incidence to type 2 diabetes.

Thus studies of the intakes of n-6 and n-3 FAs and CHD events assume great interest, given that it is the balance of risk and benefit that is important. Willett points out that studies do not find a positive association between LA consumption and the risk of CHD. In addition, both ALA and LA consumption were associated with lower incidence of fatal CHD and the ratio of dietary ALA to LA was also not associated with the risk of fatal CHD. Finally, a higher intake of LA did not reduce the strong inverse relation between the consumption of n-3 FAs derived from fish (EPA and DHA) and the risk of sudden death.

Willett concludes that it is better to consider the intake of n-3 and n-6 FAs individually rather than worry about the ratio, and that the reduction of n-6 intake to alter the n-6/n-3 ratio in a direction thought beneficial may actually increase the incidence and mortality rates of CHD and type 2 diabetes. In North America, the n-6 FA intake is generally high, and thus this advice translates into the importance of concentrating on an adequate n-3 FA intake.

THE PROBLEM OF BEING OVERWEIGHT OR OBESE

There is no doubt that being overweight or obese adds very significantly to the risk of CHD. The waist-to-hip ratio or the waist circumference attempts to quantify the problem and these measures in fact appear better than the body mass index (BMI--height in inches times 703 divided by the weight in pounds squared). The overweight individual has a BMI between 25 and 30 and obesity is generally defined as a BMI > 30.

There have been countless studies that have examined various diets in the context of weight loss. Typically the results have been modest and difficult to sustain. There are complex metabolic, genetic and psycho-physiologic factors at work here. But it must be recognized that in selecting a diet, the goals should include not only weight control or loss, but also address the issues of inflammation, insulin resistance and the classical dyslipidemia that is characterized by elevated triglycerides and low HDL and as well exaggerated postprandial elevations of blood glucose and triglycerides. Diets that normalize these factors should confer benefit independent of weight loss.

The diet-weight loss problem will be the subject of a Research Review in the near future.

CONCLUSIONS

The current emphasis on LDL cholesterol as the primary risk factor and the primary target for intervention may well have had the unintended result that taking statin drugs provides a false sense of security and the notion that the problem of prevention has now been solved with a pill. But as discussed in Part III of the Cholesterol Review (INH February 2008), in the context of primary prevention for individuals free of CHD the impact of statins is small for younger men and negligible for women and the elderly.[30,31] Also, the connection between CHD risk and cholesterol in younger men may be partly due to confounding by the presence of exaggerated blood pressure response to stress.[32] Only industry supported studies have found any benefit at all, and the numbers need to treat to prevent one adverse event are very high. On the other hand, the dietary and lifestyle approach indicated by a considerable body of research should produce significant if not sensational risk reduction for both CHD and diabetes. The NCEP approach is to recommend diet changes (reduce saturated fat to < 7% of calories, cholesterol to < 200 mg/day, increase the intake of soluble fiber and plant stanols/sterols), manage weight and exercise and after three months see if LDL goals are met. If not, institute drug therapy. But drug therapy in fact will be almost always the ultimate result since the recommended lifestyle interventions will frequently not produce the large changes in LDL necessary to meet the goals set by NCEP, especially the most recent goals.

Almost all the enthusiasm for LDL lowering derives from statin trials that involve individuals with established CHD or those at very high risk such as diabetics. The fact that there is a small absolute benefit and a large relative risk reduction has been accepted by an amazing number of medical and nutritional scientists as proof that it is the level of LDL that is the important and causative factor and the candidate to be the prime target for intervention. This view (actually an error in logic) ignores the multitude of beneficial actions of these drugs that have nothing to do with LDL lowering and these benefits would also be dose dependent and thus create an illusion of the lower the LDL the better. This has been discussed in the Cholesterol Research Review and in Part I of this review. The recent highly publicized failure of the trial involving a combination of two cholesterol lowering drugs has brought a number of critics of the LDL hypotheses out of the woodwork and has heated up the debate (see the June, 2008 issue of the Newsletter and as well Business Week, January 17, 2008, which presents a number of interesting comments from respected academic physicians. Google cholesterol Business Week).

In Part II the case has been made for specific dietary measures and exercise as an approach most likely to produce large and significant risk reduction not only for CHD but also for diabetes and the metabolic syndrome. In addition, this offers an approach the problem of preventing, reversing or retarding atherosclerosis as the major goal of the intervention in the context of primary prevention in asymptomatic individuals, especially younger individuals where atherosclerosis is in its early stages. Evidence provided in Part I based on coronary calcium scans suggests that measuring LDL cholesterol is not very successful in identifying asymptomatic individuals at risk which is of course why there is an ever increasing call for expanding the calcium scan to lower and lower risk individuals.

Finally, in Part I an approach to identifying chronic stress was discussed. The reduction or elimination of chronic psychological stress and/or depression is an important component of any CHD prevention program, but this is a complex issue and is beyond the scope of this review. Individuals with significant depression or chronic stress should seek professional help. However, it is not clear that the pharmaceutical approach to depression will impact the CHD risk.

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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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Featured in this month's Prostate Monitor is an update on chemoprevention of prostate cancer—in this case by pharmaceutical means. The class of drugs called 5-alpha reductase inhibitors, while widely used to treat the symptoms associated with benign prostatic hyperplasia (enlarged prostate), has also been observed to reduce the risk of developing prostate cancer. However, in the largest and most significant trial to date, it was observed that this benefit was restricted to localized cancer and that there appeared to be an increase in risk for advanced cancer, a result that profoundly dampened enthusiasm for this intervention as a preventive measure. This issue reviews the evidence that the connection with advanced cancer may not be nearly as significant as first thought and that the use of the trial drug, in this case Proscar, may well confer more benefit than risk in this context. It addition, Avodart, the other member of this class of drug, has been found in preliminary studies to also provide an impressive and significant risk reduction for both local and advanced prostate cancer and a large trial is ongoing.

Some perspective on this issue is provided by the results and discussion from a very recent meta-analysis of all the studies that examined the use of 5-alpha reductase inhibitors in prostate cancer prevention.

Finally, the latest round in the debate concerning PSA screening in older men, in this case men over 65 years, is described with a review of the pro and con positions presented in two back-to-back articles in the journal "Nature Clinical Practice Urology".

Wishing you continuing good health,

William R. Ware, PhD, Editor

ARE PROSTATE CANCER TREATMENTS EVIDENCE-BASED?

This month's newsletter contains a discussion of evidence-based medicine and the absence of evidence concerning benefits and harms for a surprisingly high percentage of commonly employed treatment protocols. A recent comprehensive review published in the *Annals of Internal Medicine* addresses this question in the context of treatments for clinically localized prostate cancer.[1] The authors are from various health and medical departments of the University of Minnesota. Eighteen randomized controlled trials and 473 observational studies met the inclusion criteria. However, the authors conclude that little high-quality evidence is available to guide patients, their families and health care providers on the comparative effectiveness and harms of treatment for clinically localized PC, especially in men with cancer detected by PSA screening. The lack of sufficient clinically important information from high quality randomized trials, in their opinion, remains the main barrier to well-informed decision-making. They were unable to evaluate many clinically important outcomes and point out that all treatments cause adverse events that occur soon after therapy and that the frequency, severity and duration vary among treatments. Primary androgen deprivation, cryotherapy, brachytherapy, intensity-modulated radiation therapy, proton-beam radiation therapy, and laparoscopic and robot-assisted prostatectomy have not been evaluated in randomized trials even though their use is widespread. The authors also conclude that observational studies failed to adequately control for important confounding factors and reporting and definitions of outcomes varied widely.

On a more positive note, they did conclude that data from RTCs indicate that men with Gleason Scores of 8-10 were more likely than men with scores from 2-6 to have evidence of biochemical (PSA) recurrence regardless of whether the treatment was radical prostatectomy alone or combined with androgen deprivation. Also, high-dose external beam radiation therapy was more effective than conventional-dose therapy in controlling biochemical failure in both low-risk and higher-risk disease.

Many of the important questions concerning PC treatment involve results or outcomes such as recurrence that occur over long periods of time and this makes studies difficult and expensive, especially if it is desired to studied a number of clinical or pathological factors and thus recruit a large cohort. Furthermore, many men do not want to be randomized into one of two distinctly different therapies but rather want to make an informed and guided decision as to which is best for them. Thus while the observations of Wilt *et al* are a bit disconcerting, they represent the reality of the world of randomized clinical trials.

PROSTATE CANCER PREVENTION

An important event in the chemoprevention of prostate cancer occurred with the publication in 2003 of the results of the Prostate Cancer Prevention Trial (PCPT), a landmark trial of unique design and execution. Over 18,000 men 55 years of age or older with PAS ≤ 3 ng/mL and a normal digital rectal exam (DRE) were randomly assigned to receive either 5 mg/day of finasteride (Proscar) or a placebo. Proscar, a 5-alpha reductase inhibitor (5ARI) was and still is widely used to treat benign prostatic hyperplasia. Follow-up over a 7-year period involved an annual DRE and PSA test. Men underwent a biopsy and if indicated, could elect treatment. What was unique about this clinical trial was that at the end a large number of participants in both the intervention and placebo groups agreed to undergo a biopsy in the absence of indications in order to make the judgment of the presence or absence of cancer much more definitive. It is hard to imagine improving on such a design except to also have a biopsy at enrolment. The placebo arm of the study provided considerable insight into questions such as the prevalence of PC as a function of PSA level in untreated individuals (see our book—Chapter 5--for a discussion of the surprising results of this trial regarding the prevalence of PC even in men with low PSA.) It was found that Proscar reduced the incidence of non-invasive cancer dramatically but there was an increase in the incidence of advanced cancer. This latter result profoundly dampened enthusiasm for the intervention although at the time it was suggested that this adverse aspect might be an artefact. Subsequent to the original publication, the data from this study has continued to undergo analysis and additional studies have reported. This issue will update some of the research that has appeared since the original publication of the PCPT results.

Three of the investigators in the PCPT, including the lead investigator Ian M. Thompson from the Department of Urology, University of Texas Health Sciences Center, have recently brought the status of the study up to date with the following observations.[2]

- The increase in incidence of high-grade cancers is now understood to be influenced by three factors. (1) Finasteride significantly improves the sensitivity of PSA for detecting not only cancer but also high-grade cancer. (2) Finasteride increases significantly the sensitivity of the DRE for cancer detection. (3) Finasteride significantly increases the sensitivity of the prostate biopsy for detecting high-grade prostate cancers. These factors, when examined by statistical modelling, appear to contribute to the observed increase in detecting high-grade disease in the finasteride arm of the PCPT.
- Finasteride significantly reduced the study subject's risk of a diagnosis of high-grade prostatic intraepithelial neoplasia which is considered to be a pre-malignant condition. This provides one mechanistic explanation for the observed chemoprevention of finasteride.
- The impact of this 5ARI on sexual function turned out to be clinically insignificant.
- The facilitation of detection of advanced cancer can be regarded as a benefit, given that outcomes are likely to be better with early detection.
- The observed 24.8% reduction in the risk of PC observed in PCPT must be viewed in light of the associated greater sensitivity of PSA and DRE for cancer detection. Thus the observed reduction may represent a significant underestimation of the real risk reduction.
- The enhanced detection of high-grade cancers appears to be related to the drugs impact on detection rather than an involvement in the induction of this lesion.

The authors also discuss the impact of the 2003 trial results on the attitude of the medical community toward chemoprevention with finasteride. Many physicians continue to regard it as a relatively benign agent for treating BPH which also may cause high-grade cancer. The three years of additional findings and analysis have rendered the concern regarding the promotion of advanced cancer highly questionable, but first impressions are exceedingly hard to correct.

In a recent publication, Thompson *et al* examined the question: "Does the level of prostate cancer risk affect cancer prevention with finasteride?" Based on the PCPT data, they concluded that finasteride significantly reduced prostate cancer risk regardless of the level of risk, estimated either by multivariable risk analysis or by PSA levels. They suggest that this result may indicate that finasteride exerts both treatment and preventive effects. They take the position that all men undergoing PSA screening should be informed of the potential for finasteride to reduce their risk of prostate cancer.[3]

In an analysis of pathology results that accompanied the PCPT, Lucia *et al* [4] make the interesting observation that among patients who had surgery, the finasteride-associated increase in high-grade disease (Gleason score ≥ 7) at biopsy (42.7% finasteride vs. 25.4% placebo) was diminished after pathological examination of the removed prostates to 46.4% for the finasteride group vs. 38.6% for the placebo. This evidence from the analysis of prostatectomies from PCPT indicates that the relative increase in high-grade tumors in the finasteride group compared to the placebo group was actually considerably less than originally believed.

During the year after the publication of the PCPT results, Merck's patent on finasteride expired and they never applied to the FDA for a chemoprevention indication which would have made the use of this drug as "on label" merely for PC prevention. However, there is an ongoing trial of the other 5ARI, dutasteride (Avodart), also widely used to treat BPH, which will report while its patent protection is still intact. This study follows a smaller study which reported in 2004 and found a 51% relative reduction in prostate cancers detected with an absolute risk reduction of 2.5% vs. 1.2% for those treated with dutasteride vs. a placebo. In contrast to PCPT, for patients having pathology data, the proportion of men with advanced disease, i.e. a Gleason Score of 7-10 was 30% in the dutasteride group and 41% in the placebo arm.[2] The results of this ongoing trial are awaited with interest and may lead to a FDA chemoprevention indication Dutasteride inhibits both forms of the 5-alpha reductase enzyme whereas finasteride influences only one. This difference may be important in the chemoprevention action of these drugs.

BPH will afflict most men sometime during their lifetime. As discussed at length in our book *The Prostate and Its Problems*, there are a number of non-pharmaceutical interventions that appear to work as well as the 5ARIs in

the early stages of this disorder. When this approach fails, many men will be advised to take alpha-blockers or 5ARIs or both. Those who elect 5ARIs or are already taking Avodart or Proscar should find the above information to be of considerable interest and relevance.

CHEMOPREVENTION OF PROSTATE CANCER WITH 5-ALPHA REDUCTASE INHIBITORS. A META-ANALYSIS

The Cochrane Collaboration which is well known for high quality meta-analyses directed at important clinical and therapeutic questions has just published an analysis of all qualifying studies that related to the question of the ability of 5ARIs to prevent prostate cancer.[5] The PCPT figured heavily in the analysis because it provided the largest number of cancer cases. In general, the overall conclusions and observed risk reduction were similar to that reported in PCPT. The authors emphasize the difference between relative risk reduction and absolute risk reduction by pointing out that 71 men aged 55 or older would need to be treated with a 5ARI for up to seven years in order to prevent detection of one case of prostate cancer. They also conclude that the relative reduction in prostate cancers detected would not differ based on race, family history or age, but the evidence is confined to men with baseline PSA levels < 4.0 ng/mL.

In this meta-analysis the investigators also examined the impact of 5ARIs on BPH and the associated adverse effects. The calculated that approximately two of 71 men would be prevented by 5ARI therapy from developing acute urinary retention and two would avoid the need for surgical intervention for benign urinary symptoms. But two to three out of the 71 would develop gynecomastia (enlarged and potentially painful breasts), four would develop decreased libido, and 13 would notice decreased or abnormal ejaculate volume.

DEBATE OVER PSA SCREENING CONTINUES

In the May issue of the journal Nature *Clinical Practice Urology*, the merits of PSA testing of men over 65 years of age are debated, continuing a debate that has endured for years. It is all about risk vs. benefit and is far from a simple matter.

Arguments in Favor, Whitson and Konety [6]

- First some statistics. Over 60% of PC diagnoses occur in men over 65 years and 71% of the most aggressive tumors (Gleason 8-10) occur in men over 65, corresponding to about 30,000 high-grade tumors in this age group per year. Screening produces a lead-time to clinical significant disease of 14 years for grade ≤ Gleason 6, 9 years for Gleason 7 and 5 years for Gleason grade 8-10 tumors. In the U.S., the life expectancy at 65 is 20 years and at 75 it is 10 years. For a 65-year old man with a Gleason 8-10, 7 or 6 score tumor, the estimated prostate cancer specific mortality at 20 years is estimated to be 70%, 40% and 10%, respectively. For a 75-year-old patient with a Gleason 8-10 tumor the estimated prostate cancer specific mortality at 10 years would still be 25%. Thus there is significant risk of prostate cancer related mortality even at age 75 and even low-grade tumor pose a mortality risk at 65, although for a Gleason 6 tumor, this risk is quite small (10%).
- Is treating patients over age 65 beneficial? Whitson and Konety argue partly on the basis of unpublished data from the CaPSURE study which indicated that for men receiving treatment for high-risk cancer the likelihood of prostate cancer specific mortality was no different between men < 65 and those ≥ 65 years of age. They also comment that while a randomized trial found a 5% benefit at 10 years for treatment vs. observation with this benefit mainly among younger patients, local progression of the disease occurred in 25% more patients in the observational group than the treated group.
- Whitson and Konety cite studies that suggest lower prostate cancer specific mortality among men undergoing surgery irrespective of cancer grade and even in patients 70-74 years of age as compared to untreated individuals and that models suggest survival benefit from locally curative treatment of high-grade cancers up to age 85.
- As regards PSA screening, the authors admit that the positive predictive value of PSA test for detecting prostate cancer is poor at 13-27% and they compare this to an even lower positive predictive value for

mammography, although the relevance of this argument does not seem clear. But they point out that a high degree of patient desire for PSA screening exists and many men find reassurance in a normal PSA value. Given the poor positive predictive value, this reassurance seems unjustified but then there is widespread belief among laymen that PSA actually diagnoses cancer, a notion that is constantly reinforced by TV ads suggesting that "your doctor can determine if you have prostate cancer" when in fact in the context of these ads, the required biopsy would by unthinkable.

The authors conclude that PSA screening should continue for men over 65 as long as they have a reasonable life expectancy of at least 10 years based on the assessment of their overall health and performance.

Arguments Against, P. C. Albertson [7]

The "con" side of the argument was written by Professor P. C. Albertson, Division of Urology, University of Connecticut Health Center. Albertson is well known for his contributions to the understanding of the natural history of prostate cancer. He makes the following points.

- The lifetime risk of prostate cancer death is 2.2%. PSA testing is associated with a long lead time before prostate cancer becomes clinically significant and thus men with a suspicious PSA at age 64 are unlikely to present with clinically significant disease before the age of 70-75. Most men diagnosed with PC in their med-seventies will have satisfactory outcomes with hormone therapy. If their cancers are of high risk (poorly differentiated disease) which have a short duration response to hormone therapy, they are unlikely to be cured by surgery or radiation therapy.
- After 65, the accuracy of PSA as a screening test declines, mainly due to BPH induced elevation of serum PSA. Unless physicians use age-specific cut-off points, there will be a high number of false positive PSA screening results in this age group. Albertson claims that not all physicians use age-adjusted cut-off data when deciding about recommending a biopsy.
- Albertson cited studies by his group and by Johansson *et al* that have demonstrated that the majority of men with well differentiated or moderately differentiated prostate cancer are unlikely to die of their disease and that this is particularly true for those over 65 years. Furthermore, based on the long-term outcomes of men aged 64 with normal PSA levels, the number expected to die from prostate cancer is small.
- In the last decade, there has been a change in Gleason scoring and pathologists in contemporary practice are reluctant to report Gleason 2-5 tumors. Thus the risk posed by small contemporary Gleason score 6 tumors or contemporary Gleason score 7 tumors is likely to be lower than indicated by natural history studies where these grades represented more advanced cancer. On the other hand. for men over 65 diagnosed with poorly differentiated disease, evidence suggests that aggressive intervention will not alter outcomes in a substantial number of these cases. He cites a Swedish randomized trial which showed benefit for surgical treatment of poorly differentiated disease to accrue only to men under 65 years of age.
- Screening results in the risk of men over 65 being subjected to a biopsy and being diagnosed with indolent cancer. It is estimated that the lead-time at age 55 for PSA testing is 12.3 years and the probability of detecting clinically insignificant disease on biopsy is 27%. By 75, the lead-time has decreased to 6 years but the likelihood of detecting clinically insignificant disease now is just above 56%.
- Most of the morbidity associated with PSA testing is related to the treatments that follow. The adverse effects are now known although probably not fully appreciated by the general public. They include impotence, incontinence, bowel problems related to radiation damage, and a number of adverse effects associated with the premature use of hormone therapy.
- The final answer awaits the results of two large randomized trials currently in progress.

Albertson concludes that public health policies that support PSA testing in men over 65 are not appropriate because the potential gains are limited and the potential losses are great.

This subject is discussed at length in our book with special reference to the problem of life expectancy.

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