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William R. Ware, PhD - Editor

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The focus of this issue is on cancer and heart disease, two of the major causes of mortality and morbidity worldwide. In a break from tradition, this issue contains a lengthy discussion of a potential cancer therapy that, thus far, is justified only by cell culture studies and five case histories. However, the biological plausibility seems compelling and the case histories reflect dramatic results and thus it seems important to alert readers to this research, and the therapeutic agent is an extract from selected fruits, which is commercially available. This is of course an "alternative medicine" approach and clinical trials take a long time or in most cases never occur. Nevertheless, in this case, a proprietary drug based on the same biological principles has been developed by the group responsible for the fruit extract work and is in the preliminary stages of clinical testing. Whether it will work better than the fruit extracts is unknown, but presumably it is patentable and thus easier to market to mainstream medicine as a pharmaceutical.

The second area of emphasis is coronary heart disease. The emphasis here is on cholesterol and triglycerides. In addition, in this issue, we start a two-part Research Review on coronary heart disease risk and prevention.

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Wishing you good health,

William R. Ware, PhD, Editor

SALVESTROLS—A NEW APPROACH TO CANCER THERAPY?

In a series of recent papers in *The Journal of Orthomolecular Medicine,* Professor Gerald Potter, Head of Cancer Drug Discovery Group, De Montfort University, Leicester UK, and Professor M.D. Burke and co-workers have introduced the concept of Salvestrols and in a paper in late 2007, presented case studies of the use of Salvestrols to treat five different cancers.[1-3] Salvestrols are what are called prodrugs which are substances administered in a non-active form. Once absorbed the prodrug is metabolized to produce an active compound. If the enzyme responsible for the metabolism resides only in a diseased cell, then this offers a unique mechanism for targeting these cells. If the metabolite is cytotoxic, then the target cell is destroyed. This seems to fit all the requirements of a magic bullet. Professor Potter and coworkers regard the discovery of a class of naturally occurring prodrugs that are uniquely cytotoxic to cancer cells to be one of the most important advances in cancer therapy in the past 25 years. While research in this area is new and limited, the results thus far seem sufficiently exciting and important to merit being featured in this newsletter.

Salvestrols are non-toxic dietary phytochemicals available from fruits and berries that are activated to toxic metabolites in tumor cells by a tumor specific enzyme, an enzyme that is essentially absent in normal cells. A new term, the name is derived from the Latin word *salve* a greeting which is derived from the verb *salvere* which means to be in good health. Salvestrols are present in our diet and have been consumed for millions of years. An example is the compound resveratrol which is found in red wine and is converted into the anticancer agent piceatannol by a particular enzyme of the P450 family called CYP1B1.[4] What is highly significant is that this particular enzyme is found almost exclusively in tumor cells. In the language of the field, it is *overexpressed*. In fact, this overexpression is well known. The enzyme is viewed by some as a "rescue enzyme."

The tumor specific enzyme CYP1B1 not only converts phytochemicals to chemicals capable of killing tumor cells, it also converts some chemicals into cancer promoters. For this reason, this enzyme has historically been associated with carcinogenesis. However, Potter and coworkers point out that while there is indisputable evidence that CYP1B1 does activate procarcinogens to their ultimate mutagenic metabolites, almost all of these procarcinogens are man made and thus the CYP1B1 enzyme could not have evolved to metabolize these so-called xenobiotics. They further speculate that the carcinogenic chemicals are activated by this enzyme because of their structural similarity to estradiol, the only endogenous substrate for the enzyme. Provided one does not consume the man-made procarcinogens, this aspect of the action of CYP1B1 does not appear to be an issue. The enzyme is already in cancer cells and the Salvestrols in fruit we normally eat, presumably for good reason. But as will be discussed below, the levels are in most cases too low.

Research in the early 1990s by Professor Burke found that the enzyme CYP1B1 was present in tumor cells of a wide variety of human cancers but undetectable in normal cells, and this has been confirmed in numerous additional studies in his and other laboratories. Potter and co-workers have in fact synthesized a range of novel anticancer drugs which become cytotoxic through the action of CYP1B1, one of which is currently undergoing preclinical studies. It was also observed that these drugs were very similar to natural compounds in our diet, and this resulted in the discovery regarding resveratrol mentioned above and in addition, other naturally occurring molecules that function the same way and are far more powerful. It is interesting that the concentrations of these prodrugs in food are strongly diminished by the use of fertilizers and pesticides. Thus the shift away from natural or "organic" crop management, the extreme contraction in the number of varieties cultivated, and the decline in the consumption of fruits and vegetables in favour of the so-called Western diet may have been partly responsible for a significant decrease in our natural defence mechanisms against cancer.

Some of these naturally occurring phytochemicals now constitute the proprietary ingredients of the commercial product Salvestrol which was used in the case reports [3] that prompted this discussion. While I generally restrict material in this newsletter to studies rather than case histories, these seem compelling and the paper describing them, while in a peer reviewed journal, is not available in full-text without a subscription. It must be understood that these are anecdotal reports, but at this stage in the development of Salvestrols, this is normal. In what follows, the authors quote the strength of the Salvestrol preparations in a somewhat odd unit they call "points."

Case #1. Stage 2-3 squamous-cell carcinoma of the lung in a 69-year-old male with an inoperable 7cm tumor adhering to the sternum and chest wall. The cancer was diagnosed after the patient presented coughing up blood. No chemo or radiation was recommended and life expectancy was estimated at 8 to 18 months. The patient immediately started a diet of fresh, organic fruits, vegetables and juices and avoided refined sugar and dairy products. He also took 6 Salvestrol Professional (350 point) and 6 Salvestrol Gold capsules (350 point) per day after meals for six weeks (the Gold" product is lipophilic whereas the Professional is hydrophilic). At the end of one week he was no longer coughing up blood. Six weeks after starting the program, a shrunken tumor and two lymph nodes (actually negative) were removed. The tumor was no longer adhering to the chest wall and sternum. The patient was later deemed cancer free.

Case#2. Stage 4 melanoma on the foot of a 94-year-old woman. The patient was unable to walk, had evidence of the spread of the cancer and life expectancy due to the cancer judged to be 2 weeks. Salvestrol Cream was applied topically and Salvestrol Gold (1000 point capsules, 4 per day) plus an anti-inflammatory diet constituted the program. After one year, the melanoma was gone,

the foot completely healed and the woman declared cancer free.

Case #3. Prostate cancer in a 74-year-old man. Stage and grade not given but surgery and radiation ruled out and hormone therapy prescribed. Patient started two capsules per day of Salvestrol Professional (350 point) along with hormone therapy (Lupron). This action was prompted by a relative who was a university professor and knew a student who recovered from "terminal" brain cancer after taking Salvestrols. Later the dose was changed to one Salvestrol Professional (1000 point) and three 350 point Professional capsule per day. At 12 months the patient's PSA had dropped to 0.2 ng/mL, a very low level that surprised the attending physician. Lupron was discontinued over 6 months and the PSA has remained at this low nadir.

Case #4. A 36-year-old woman with a 3-5 cm breast tumor (the size of a golf ball) and a large tumor in an underarm lymph node. Pre-surgical chemotherapy was started. Before her second chemo session she started with one Salvestrol Gold (1000 point) capsule per day. After her third chemo session, mammography and ultrasound suggested that the tumors were gone. Her medical team failed to conceal their surprise at her progress which shook her confidence since this indicated that they had not expected such progress from their therapeutic program. She had two more chemo sessions but refused radiotherapy and surgery even though strongly urged by her medical team to proceed.

Case #5. Bladder cancer in a 55-year-old male. Treatment consisted of removing some of the cancerous tissue by scraping, and this had continued for 6 years. At this point the patient started taking one Salvestrol Gold (1000 point) and three Salvestrol Professional (1000 point) per day. After five months, cystoscopic examination revealed no tumors or cancerous tissue and he was pronounced cancer free. A year later a kidney tumor was detected and he has resumed taking Salvestrols.

These case histories are of course anecdotal and no long term follow-up information was available. No side effects appear to have ever been reported. However, as is the case with many "alternative" or complimentary treatments, especially those that offer no hope of huge profits for the pharmaceutical industry, this is all one can hope for, at least initially and perhaps forever. Nevertheless, in all the cases described, the use of Salvestrols halted and reversed what otherwise would almost certainly been a steady or accelerated progression, probably ultimately fatal. Hopefully, a trial of significant size will be conducted but any trial will present problems because of the intolerance of the cancer treatment community toward "alternative" treatments even if they have a sound biological plausibility. However, such studies should meet with minimal resistance if they involve untreatable cases, and data on average life expectancy for purposes of comparison is generally good and spontaneous total regression is very rare in these situations. Randomized clinical trials would seem unethical and if the case studies were any indication, would be terminated early due to benefit in the treatment group.

These results seem to strongly support the hypothesis that there are phytochemicals in food that can enter many types of cells but only in tumor cells will they be chemically altered by the CYP1B1 enzyme and become effectively cytotoxic—indeed, a so-called magic bullet. This may eventually lead to the use of patented drugs which behave in this fashion, and if approved, could achieve acceptance by mainstream oncology. However, such drugs would almost certainly be vastly more expensive than formulations such as the plant derived Salvestrols and might not work any better. The specific preparations used in the cases described above are available without prescription. Google "Salvestrols" for information. The latest preparation, Salvestrol Platinum, which was not used in any of the above studies, is a mixture of the lipophilic and hydrophilic extracts in the Profession and Gold products plus a more selective newly discovered lipophilic Salvestrol. A low-dose formulation (100 point concentration) intended for primary prevention is currently available in the UK but the Platinum formulation currently available in North America may also be quite satisfactory. The company selling the products (Nature's Defence) indicates that the ingredients are 100% natural and include extracts of blackcurrants, blueberries, strawberries and tangerine peels. Potter and co-workers do not appear to have published the identity of the actual phytochemicals they have found as most active in this context. The authors of the papers cited strongly recommend Salvestrol therapy be accompanied by a diet based on organically grown fruits and vegetables in order to provide needed cofactors for the PYP1B1 enzyme and to avoid chemical residue contaminates in non-organic produce. They emphasize that this approach involves a food based rescue mechanism for an array of cancers regardless of oncogenic origin. This is of course in keeping with the well-

established presence of the CYP1B1 enzyme in many types of tumor cells.

The studies of Potter and coworkers are also of interest in connection with the frequently heard advice to eat lots of fruits and vegetables. While this is obviously important, it may well be that the difficulty in finding and affording authentic organically grown produce may be part of the reason for the somewhat inconsistent findings regarding cancer prevention from these foods. Furthermore, almost no one is eating so-called heritage varieties, but rather varieties that have been hybridized to the point where many of the cancer preventive agents are absent, if for no other reason than to improve flavour since Salvestrols are in general bitter. In fact, Potter's group is involved in resurrecting heritage varieties.[2]

The above information is provided as a service to readers and should not be considered a recommendation to take these products. No one involved with IHN has a financial interest in Salvestrol products. However, some or all of the authors of the papers cited may have a financial interest in the commercial fruit-based products.

BREAST CANCER AND ALCOHOL

A study concerning alcohol consumption and the risk of breast cancer has just been published and the results have been widely publicized by the print and TV media with the message that even one drink is dangerous.[5] Since it has usually been assumed that the threshold for significant risk was intake in excess of one drink, these new results merit some discussion. Studies of risk factors for breast cancer are complex because frequently the risk varies significantly with the type of tumor, i.e. estrogen receptor positive or negative and progesterone receptor positive or negative, and as well, menopausal status. About 75% of breast cancers are ER+ and 65% are ER+PR+. Positive means that a significant number of cells carry receptors for the hormone in question.

This study involved a meta-analysis of 4 prospective cohort studies and 16 case-control studies. The meta-analysis combines studies to get a new overall result with the hope of improving the statistics through a much larger number of cases. In this study, the estrogen positive cancers (EP+) and estrogen plus progesterone positive cancers (ER+PR+) had the highest risk associated with alcohol consumption. For the ER+PR+ tumors, among individual studies that compared highest to lowest intake, only 7/16 case control studies and 3/4 prospective studies yielded significant results. For ER+PR- tumors, 2/10 case control studies and 1/4 cohort studies found a significant association between highest vs. lowest intake. All the others provided null results, i.e. no significant risk could be detected. Such inconsistency between studies is disturbing to some and considered to suggest a weak effect that is easily confounded. Yet when combined in the meta-analysis, a 22% to 28% increase in risk was found which was now statistically significant. For example, for the ER+PR- tumors, this statistical manipulation converted a set of studies where only 3 out of 14 were significant into a statistically significant 28% risk.

The investigators also examined the dose vs. risk relationship. For a 10g/day increase in alcohol intake (less than one drink) they found a statistically significant 12% increase in risk of ER+PR+ tumors but no risk for the ER-PR- cancer. They present what is called a scatter plot of the results on which the 12% figure is based, and while the 95% confidence interval for this result was 8% to 15%, the correlation line that represented the 12% figure would not impress anyone in the physical sciences since the scatter plot appears very close to random with a huge scatter reminiscent of a target hit be a shotgun blast.

Thus while much was made in the media of the danger even of less than one drink per day (the 10 g/day of alcohol), the risk appears rather small and a result of a correlation calculation where there is huge scatter in the data. However, the agreement between the individual prospective cohort follow-up studies for ER+PR+ tumors with 3/4 being significant with an over 21% increase in risk in the meta-analysis for the highest vs. the lowest intake suggests that limiting consumption as is widely recommended is a very good idea. But the risk of one glass of wine a day, if it is small and in fact real needs to be balanced against the cardiovascular and psychosocial benefits. Furthermore, the intake of rather small amounts of folic acid such as is found in a simple multivitamin or in a diet replete with folate rich foods has been found to neutralize the risk associated with even several drinks per day (see the review concerning breast cancer

prevention, INH, October-November 2006 for details and documentation of the folic acid effect).

EXERCISE AND RISK OF COLORECTAL CANCER

A recent prospective study from Norway has examined the impact of recreational exercise and physical activity on the incidence colorectal cancer (CRC) stratified by the location of the cancer within the colon. Data was collected between 1984 and 1986 concerning a range of lifestyle and health-related factors. They used the ID number possessed by all Norwegian citizens to conduct follow-up from the Cancer Registry of Norway which provided the required clinical data. Overall, the researchers found an inverse association between recreational physical activity and CRC risk, but the association was confined to cancer in the transverse and sigmoid colon. For high vs. no physical activity the reduction in incidence was 56% and the reduction in cancer mortality was 67%, and these results achieved statistical significance with rather tight confidence intervals. For rectal cancer there was no association. An estimate of 28% was also made for the proportion of CRC deaths that could potentially be avoided if all participants in the study were at the highest level of physical activity. The authors suggest that the finding of reduced risk only in the transverse and sigmoid segments, i.e. the segments associated with slow transit times, may point to an increased colon motility and reduced transit time as possible underlying mechanisms. One weakness of the study was that only one evaluation of physical activity was made.[6]

A TALE OF TWO TRIALS

On March 30 of this year Merck and Schering-Plough announced the termination of a trial of Zetia and Vytorin which was examining the effect of using either a statin (Zetia) or a combination drug consisting of a statin plus a drug that interfered with dietary cholesterol absorption (Vytorin). Most readers have probably seen this idea promoted as an established, evidence based therapy in TV ads. While the addition of Vytorin to Zetia produced substantial additional LDL lowering, the end result as measured by progression of carotid artery atherosclerosis was the same. That is, the combined drug was no more effective in reducing progression than the statin used alone, in spite of the enhanced LDL lowering. The companies involved had delayed the announcement of this lack of effectiveness for over a year while the combined drug continued to be aggressively promoted, an action that triggered an ongoing congressional investigation in the U.S. The trial results have now been published.[7]

On March 31, AstraZeneca announced the termination of the Jupiter trial which tested the effectiveness of Crestor, a statin drug, on healthy individuals free of heart disease but with low or very low cholesterol and high levels of C-reactive protein (CRP), an inflammation marker. This study, launched by Dr. Paul Ridker, a world famous CRP researcher, was based on the hypothesis that inflammation might be a better indicator of risk than cholesterol levels, and one of the non-cholesterol-lowering actions of statins is to reduce inflammation. Cholesterol levels came down as did CRP levels, but shortly after the trial was started, the decrease in events such as heart attacks was sufficiently large that it was considered unethical to withhold the benefit from the placebo group and the trial was stopped. The results have not as yet been published.

These outcomes taken together have serious implications for the cholesterol hypothesis. In the second study the rapid occurrence of a large beneficial effect suggests that the action of the statin drug in CHD free individuals with high levels of inflammation was largely due to non-lipid-lowering action. This same rapid reaction has been seen in some secondary prevention trials. The results of the first study reinforce this notion since the statin and the anti-absorption drug both decreased LDL levels with the combination more effective than either drug alone, but Vytorin added nothing to the action of the statin in terms of the endpoint of the study, which would make sense if the action of the statin on the progression of carotid atherosclerosis was due to biological mechanism other than LDL lowering.

The results of these two studies have brought forth considerable commentary, mostly in the press, with the most informative pieces in *Business Week*,

where a number of respected academic researchers are quoted who feel that the non-lipid-lowering effects (pleiotropic effects) of statins may represent their major route of action.[8,9] While one does not generally turn to business magazines as a source of commentary by experts on medical research results, in this case this media venue provided a means of rapid publication of important comments. The articles cited, which are highly recommended, can be accessed through the online *Business Week* archives. Dr. James Liao, a researcher in vascular medicine at Brigham and Woman's Hospital in Cambridge, the lead research center for the first trial, commented, "It suggests a new paradigm. These drugs may be working in ways other than cholesterol lowering…..I think statins do work, but maybe not because they lower LDL." Dr. Liao has been very active in investigations of the pleiotropic effects of statin therapy, including other consequences associated with the enzyme inhibition whereby statins reduce cholesterol.

The outcome of these two trials has already added fuel to the controversy over the role of cholesterol in heart disease and the merits of making LDL the primary indicator of risk and the principal target for intervention. What seems hard to understand is the blind but almost universal acceptance of the notion that for individuals with heart disease, taking statins carries benefit and that therefore the benefit is due to LDL lowering when (a) there is a long and growing list of pleiotropic effects of these drugs, (b) many of these effects would be expected to be dose dependent just as the cholesterol lowering is dose dependent and (c) effects in some instances are seen to occur far too rapidly to be due to LDL lowering. What is involved here seems to be a *post hoc ergo propter hoc* fallacy of simple logic.

It can be argued that the time has come to consider shifting the emphasis away from LDL and cholesterol lowering and actively investigate and implement a different approach. Your Editor has discussed this matter in a recent paper in the journal *Medical Hypotheses*[10] and in the two-part Research Review that starts with this issue.

RISKS OF ELEVATED TRIGLYCERIDES. THE EVIDENCE ACCUMULATES

Two studies have recently presented data which adds significantly to the evidence that elevated triglyceride (TG) levels are associated with a high risk for CHD. The first, which was conducted in Taiwan, examined the triglyceride levels of 821 consecutive hypertensive men and women undergoing coronary angiography. The relationship between the extent of coronary artery disease (CAD) and TG levels was examined and the risk analysis adjusted for other CAD risk factors. Higher TG levels were found in subjects with severe CAD compared to those with no or minimal CAD. Two levels of adjustment were used. One corrected for age, gender, smoking, diabetes, BMI and total cholesterol. The other, called the lipid group, had an added adjustment for HDL. Using minimal CAD as a reference, the increased risk associated with high TG levels was 5.2 times which increased to 7.5 times after adjustment for the protective effect of HDL. What is interesting is that the criterion for high TG levels was ≥ 150 mg/dL, a threshold used by many experts but hardly a really high level. An additional interesting point is that when the patients were stratified according to no, mild, moderate or severe CAD, there was no correlation with LDL levels at baseline as judged by the so-called "P" value which attempts to quantify the probability that the result occurred by chance. However, there was a significant inverse correlation, as was expected, between the severity of CAD and HDL levels with those with no or minimal CAD having a mean value of about 50 mg/dL and those with severe CAD a value of about 42 mg/dL. Also, there was no correlation with systolic blood pressure but all the subjects had borderline or high values since this was a selection criterion for the study.[11]

The second study was part of a trial that compared two statin drugs in connection with the question of the merits of two different targets for lowering LDL. This study also collected data on TG levels and examined the impact of elevated levels on the risk of secondary events occurring in subjects hospitalized for acute coronary syndrome (unstable angina or a heart attack). Thus all patients were receiving a statin drug. On treatment TG < 150 mg/dL was independently associated with lower risk of recurrent CHD events and this was independent of the level of LDL. The mean follow-up time was 2 years.[12]

A study reported in late 2007 adds to the above evidence that high TG levels should be a matter of great concern.[13] In this study subjects had two TG

measurements 5 years apart. The association between both the absolute level and changes over 5 years and the incidence of an MI or angiography-proven CHD was investigated. The cohort consisted of untreated young men. The follow-up was over 5.5 years after the second TG measurement. For the association with baseline TG levels, the TG ranges were divided into quintiles and when the lowest vs. the highest were compared, the risk of CHD was increased four-fold. The highest of the TG ranges was 164-299 whereas the lowest was 30-66 mg/dL. This four-fold increase in risk represented a fully adjusted hazard ratio, but in the factors included in the statistical adjustment, LDL cholesterol is noteworthy by its absence, suggesting that its inclusion resulted in no significant change. In fact, there is no mention of LDL at all except a comment on the relationship between TGs and LDL particle size. When the impact of changing TG levels was studied, a significant risk persisted for those with a high initial level that decreased to a low level over 5 years and those with low levels initially who had intermediate or high levels after 5 years had significantly increased risk of CHD compared with the group that maintained low values. A change from the low to the high group over 5 years increased the risk of subsequent CHD by almost 7 fold.

In all three of these studies, the impact of TG levels on risk appears to be very high, and in fact considerably higher than the impact found for the traditional CHD risk factors. And these studies simply add to earlier ones that carried a similar message. Furthermore, the combination of high TGs and low HDL is a characteristic of the metabolic syndrome and the ratio is regarded by some as a stronger indicator or CHD risk than LDL, especially since an elevated ratio also implies the presence of small, atherogenic LDL particles which some consider the only dangerous form of LDL. A diet high in refined carbohydrates generally increased TGs and some consider that the advice to go on a low fat diet has increased rather than decreased the population risk of CHD through the elevation of TGs and a reduction in HDL. The natural action was to replace fat with carbohydrates, and when this was done by eating more refined carbohydrates from refined starches, potatoes, rice, and sweetened soft drinks, common components of the Western diet, up went the TG/HDL ratio, in some cases dramatically.

When blood lipids are measured during the course of a physical exam or other occasion for a doctor's office visit, TGs are almost always measured because the number is needed to calculate the LDL level which is not directly measured except in research settings. Thus not only the TG level, but also the TG/HDL ratio is always available. Perhaps it is time to focus on this rather than LDL, given the huge risk increases associated with TGs. TG levels are not considered in the Framingham Risk Score calculation which is widely used to judge the results of the standard blood lipid panel. Ignoring the TG level may be a huge mistake. Also, TGs can be lowered dramatically by diet and also by niacin. This subject is further examined in the Research Review that starts in this issue of the newsletter.

ASSESSING CHD RISK WITHOUT BLOOD WORK

Because the measurement of blood lipids is associated with cost and the inconvenience of a repeat visit to discuss results, researchers worried about risk assessment in developing countries have examined alternative protocols. In a study just published,[14] the National Health and Nutritional Examination Survey (NHANES) data base was used to examine the following question—what is the change in predictive power of CVD related events if cholesterol is removed from the risk factor list and replaced with a measure of overweight or obesity, i.e. the BMI? This was a follow-up study where the data was mined from the NHANES database and involved over 14,000 individuals between 27 and 74 years of age. Risk was assessed from first time cardiovascular events. When age, systolic blood pressure, smoking, history of diabetes, hypertension and BMI were used, the predictive power was essentially equivalent to that achieved when cholesterol levels were used instead of BMI. While this study did not consider low HDL levels, it nevertheless suggests that total cholesterol (TC) is not an essential factor of the risk picture. While probably no one is suggesting that in the developed countries the lipid panel be dropped from CHD risk assessment, it can be argued on the basis of this study and the studies discussed above that a risk assessment that included just TGs and HDL for the lipid component might prove more informative than the total cholesterol (TC) and TC/HDL ratio currently used. In fact, BMI should to some extent correlate with high TGs and low HDL.

LITHIUM AND AMYOTROPIC LATERAL SCLEROSIS (ALS)

ALS is also called Lou Gehrig's disease. Some call ALS the three letters that change people's lives—forever. ALS is incurable. A recently introduced drug riluzole (Rilutek) achieves only marginal life extension. The neurodegenerative disorder is devastating not only to those who have it but also for their families and friends. Thus a study just published in the prestigious *Proceeding of the National Academy of Science* is of great interest.[15] Forty-four patients who had diagnosed ALS for < 5 years were recruited. Eleven presented the bulbar form and the remainder the classical onset. The patients were divided into two treatment groups, one with lithium plus Rilutek, and the other with Rilutek alone. The lithium dose consisted of 150 mg of lithium carbonate twice daily and the dose was adjusted to produce a plasma range of 0.4 to 0.8 mEq/L. Subjects were assessed 6 times over a follow-up period of 15 months. At the end of the study, all the lithium patients were alive whereas for the control group 29% did not survive. This difference was statistically significant at both 12 and 15 months. When measures of progression such as the Norris scale or pulmonary function were examined, no significant progression was seen in the lithium group whereas those just receiving Rilutek progressed significantly. The researchers also conducted a parallel study on an ALS mouse model and obtained similar results and reported from a number of experiments which provided detailed mechanistic information.

Readers are cautioned that while lithium can be purchased over the counter and has been used for decades to treat psychiatric disorders, there is dose window beyond which toxicity occurs and thus should be used only under the supervision of a physician. The paper describing the above study is in the public domain and can be downloaded from the journal website (Google the journal name and go to archives for the Feb. 12 issue. The article is in the medical sciences section). Readers with partners or friends with ALS may want to download this paper so that it can be given to the physician managing the case. He or she may be unaware of this study which was done in Italy and published in a journal probably not scanned each month by doctors.

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RESEARCH REVIEW

CORONARY HEART DISEASE RISK AND ITS REDUCTION PART I

NON-TRADITIONAL CORONARY HEART DISEASE RISK FACTORS. THE TIME HAS COME TO TAKE THEM SERIOUSLY

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Coronary heart disease (CHD) assessment during a routine physical exam can be either cursory or comprehensive or somewhere in between. Several famous U.S. clinics offer executive physicals which take from one to three days and represent the ultimate physical exam experience. One clinic even has a branch in Toronto dedicated to such exams. Such exams are not available or affordable for most individuals but the merits of extensive use of scans in such physicals can be debated because of both false positives and radiation exposure. If the motivation for the physical includes primary prevention of CHD, then it should include assessment of the risk of or presence of atherosclerosis and the risk factors for its progression. Given the undesirable radiation exposure from the coronary calcium electron beam tomography (EBT) scan, a compromise appears to reside in the assessment of emerging and novel risk factors and a shift in emphasis away from LDL cholesterol as a primary indicator and target for therapy. In fact, the recent Cholesterol Review, which appeared in this Newsletter, detailed some of the shortcomings of the present assessment system and in particular the failure of the Framingham Risk Score (10-year risk of fatal or non-fatal heart attack) or total cholesterol (TC) or LDL cholesterol to correlate with the presence or progression of atherosclerosis. This seems like a serious flaw in the assessment protocol given that as atherosclerosis progresses, the risk of symptomatic heart disease or other serious vascular problems increases. Furthermore, as discussed in the above-mentioned Research Review, neither TC nor LDL correlates at all with the risk of sudden cardiac death which is responsible for about 50% of all fatal cardiac events. Also, approximately 50% of individuals who experience a heart attack have either normal or even low LDL.[1] Thus the interest seen in the recent literature concerning other methods of assessing risk that might provide better prediction of CHD, CHD related events and silent atherosclerosis and in addition provide guidance in interventions that provide an alternative to LDL lowering.

For the individual with no health complaints or concerns, the physical examination presumably has as its goal the primary prevention of chronic diseases such as cancer, diabetes and heart disease. Scheduling routine, periodic physical examinations is considered to be the sign of a prudent person. It is almost an article of faith that preventing the incidence of a disease or detecting signs of imminent incidence or signs of an early stage is preferable to treating the disease once it has become symptomatic, although the impact of early detection on mortality is often debated and there are those that maintain that for asymptomatic individuals, a too comprehensive examination runs the risk of false positives and unnecessary invasive diagnostic procedures and makes this conventional wisdom questionable. Nevertheless, the weight of evidence is probably on the side of early detection and aggressive primary prevention. In the context of this review, one reason is that there is considerable evidence that lifestyle including diet holds the key to the primary prevention of both CHD and type 2 diabetes and that the measures suggested by large prospective studies can reduce the risk by between 80% and 90%. These are huge reductions but this may not be generally appreciated or recognized in mainstream medicine even though the studies originate from premier U.S. institutions and were done by epidemiologists considered among the best in the world. The challenge then appears to be discovering risk factors present in an individual that are elevated but modifiable and convincing this individual to take them very seriously and act accordingly. The fear associated with not doing anything coupled with knowledge that the chances of more or less complete success are very high if action is taken may be enough to motivate some or most individuals. This

review in part is concerned with the selection of the risk factors to assess, bearing in mind that these factors must be easily evaluated in the office setting and must be associated with interventions that have been shown effective, practical and feasible.

During a routine physical examination, it is probably true that most patients are merely passive observers while the physician makes the choice of what to do and what tests to order. While this is entirely normal and appropriate, it can work to the patient's disadvantage if the assessment of CHD risk is traditional, i.e. blood pressure, TC, HDL and LDL, smoking, fasting blood sugar, and weight for a given build and height. Some physicians will use some of this data to calculate the 10-year Framingham Risk Score, and if it is low, pay little attention to a more comprehensive assessment of CHD risk. A much more complete picture would result from additional blood tests and a few questions about psychological stress and depression. The additional blood tests come under the heading of emerging or non-traditional risk factors and are viewed with suspicion by some physicians since they do not appear in the guidelines they have come to depend on. But the informed patient can attempt to insist on at least the additional blood tests and if necessary comparing the results at home with what are thought to be threshold values for significant risk. Threshold values are even available in books written by well-known cardiologists who believe there is merit in going well beyond the traditional assessment and treating individual risk factors independent of overall risk.[2]

Over 250 risk factors have been identified for CHD. Two recent attempts to reduce the list to manageable length have come up with either 10 or 30 factors that are suggested as potentially improving the predictive power of the assessment protocol and addressing the problem of the under-diagnosis of silent atherosclerosis.[3,4] But the evaluation of many of the factors in these lists is complex and more suited to the research rather than the primary care setting.

This review will examine emerging and non-traditional risk factors for CHD that could be added to a physical examination at no or minimal inconvenience and the commonly recommended reference values will be discussed along with interventions suggested by cardiologists to deal with elevated risk. Some of the material contained in this review is in an article by your editor which is in press in the journal *Medical Hypotheses.*[5] We will first look at non-traditional risk factors that meet the criteria outlined above.

INSULIN RESISTANCE AND COMPENSATORY HYPERINSULINEMIA

That insulin resistance and the associated compensatory hyperinsulinemia are directly involved in the development of atherosclerosis, obesity, type 2 diabetes and coronary heart disease does not appear to be in dispute. The association between insulin resistance and coronary artery disease has been found to be both highly significant and independent of the effects of blood lipids, hypertension and smoking, and in addition, insulin resistance correlates strongly with carotid intima-media thickness which is also a measure of the extent of atherosclerosis.[6] Much evidence supports insulin resistance and inflammation as fundamental hormonal and metabolic disturbances responsible for the cluster of disorders that the metabolic syndrome encompasses.[7-9] What is at issue here is the role given by the National Cholesterol Education Program (NCEP) ATP III guidelines[10,11] to the metabolic syndrome and insulin resistance. The metabolic syndrome is a secondary component of the NCEP ATP III CHD risk assessment. It is defined as having three of the following: fasting glucose ≥ 6.2 mmol/L (110 mg/L), waist circumference > 102 cm (40 in) for men and 88 cm (35 in) for women, triglycerides ≥ 1.7 mmol/L (150 mg/dL), blood pressure ≥ 130/85 mm Hg, and HDL < 1.036 mmol/L (40 mg/dL for men and <1.295 mmol/L (50 mg/dL) for women. The World Health Organization and the International Diabetes Federation have definitions which differ significantly with that given by ATP III.[12] But it appears important to distinguish between the metabolic syndrome and insulin resistance as a stand-alone factor. The problem is the inadequacy of fasting glucose for identifying those with insulin resistance and the fact that individuals with serious problems identified by one or more of the above criteria may still fail to be diagnosed as having the metabolic syndrome using the "any three" approach and perhaps fail to have their problem or problems adequately appreciated or treated. If LDL levels are not elevated and the 10-year risk is low, the question of the metabolic syndrome may not even be addressed since the question comes up in the guidelines after therapeutic lifestyle changes have been initiated, but this would be indicated only if LDL was above the goal set by the guidelines. Attention is first directed to triglyceride levels in connection with the question of the metabolic syndrome in spite of its relevance in connection with that aspect of dyslipidemia (high TG, low HDL) associated

not only with insulin resistance but also with enhanced risk of CHD.[13,14] Also, neither the metabolic syndrome nor high TGs are considered major risk factors in the ATP III guidelines.

Gerald Reaven, one of the world's leading metabolic syndrome researchers, has recently addressed these issues in several publications and takes the position that diagnosing the metabolic syndrome has neither pedagogical nor clinical utility.[12,15] In connection with identifying insulin resistance, Reaven points out that one study of about 500 apparently healthy individuals found that impaired fasting glucose had a very low sensitivity of about 10% for identifying those with insulin resistance. He also points out that impaired fasting glucose accounts for only 5-15% of the variance in insulin mediated glucose disposal in the population at large. Thus fasting glucose, even if it is embedded in the metabolic syndrome risk factor assessment and guideline design, cannot be regarded as a satisfactory surrogate for insulin resistance. Reaven also points out that the sensitivity for identifying insulin resistant individuals can be increased about threefold by measuring the plasma glucose after an oral glucose load and using the American Diabetic Association criterion for impaired glucose tolerance and recommends this approach.[15]

In the research setting, the gold standard for identifying insulin resistance is the euglycemic hyperinsulinemic clamp technique, a complicated procedure inappropriate in primary care. Approaches more suited to the office practice employ one of the following: (a) the 2-hour oral glucose tolerance test (OGTT) with either fasting and 2-hour blood glucose and insulin determinations, or a series of determinations that allow an average so-called steady state glucose value or the area under the glucose-time curve to be determined; (b) the use of the fasting insulin and glucose values in an simple equation (fasting insulin in µU/mL times the fasting glucose in mmol/L and divided by 22.5) to give the HOMA-IR measure which then has a cut-off for indicating insulin resistance; (c) the triglyceride (TG) to HDL ratio. The latter two approaches use just data normally collected in physical examinations although how widespread the knowledge is in the primary care community concerning currently favoured cut-offs or even the equation used to calculate the HOMA-IR, appears unknown. While not perfect, HOMA-IR correlates fairly well with the results from the euglycemic clamp technique,[16] and is in fact used in studies to identify individuals with insulin resistance.

INFLAMMATION IS OF SECONDARY IMPORTANCE IN CURRENT GUIDELINES

It appears to be generally accepted that inflammation is a cardiovascular risk factor and a cause of atherosclerosis.[17] The current protocol for judging CHD risk does not directly consider inflammation. This is compounded by the use of guidelines that tend to deemphasize or ignore insulin resistance and in addition completely ignore psychological stress, both of which also appear to operate on the cardiovascular system through an inflammatory mechanism.[18] C-reactive protein as a biomarker for inflammation was suggested a decade ago and numerous studies have shown that serum levels are related to cardiovascular risk.[19] In addition, data suggest that high-sensitivity CRP (hsCRP) is a stronger predictor of cardiovascular events than LDL.[20] Based on the consistency of prognostic data for hsCRP in connection with CHD and the practicality of its use in the primary care setting, it has recently been proposed that serious consideration be given to adding hsCRP to risk score algorithms for global risk assessment.[21] The debate concerning this has recently been reviewed by Ridker who takes the position that hsCRP screening should be used in primary prevention for those at 5% to 20% 10-year risk based the Framingham Risk Score.[22] The JUPITER trial which was examining the use of a statin drug which lowers hsCRP in a group of individuals with low LDL (< 130 mg/dL) who have elevated hsCRP levels (>2 mg/L) was recently prematurely terminated because the reduction in CHD events was sufficiently large to render continuing testing unethical. The fact that this occurred so soon after the intervention suggests that the benefit derived from inflammation reduction, not cholesterol lowering. The CRP lowering effect of statins is one of many non-cholesterol lowering aspect of these drugs. Part of the rationale for this study came from the observation that half of all heart attacks and strokes in the U.S. occur among those who have normal or even low levels of LDL.[1]

Diet, sedentary lifestyle, overweight and obesity, psychological stress and depression, and chronic infections such as mild gum disease are common causes of chronic low-level inflammation, frequently called silent inflammation since it is generally not accompanied by the classical inflammatory symptoms. This is type of inflammation that impacts long term primary prevention of CVD. Most of these causes are amenable to intervention as will be discussed in Part II. There are of course many causes of inflammation that are far from

silent such as physical injuries, respiratory and other symptomatic infections, allergies, arthritis etc., but many of these sources of inflammation are not also not chronic. The most common non-silent sources of chronic inflammation are arthritis and rheumatoid arthritis.

PSYCHOLOGICAL STRESS, DEPRESSION AND INFLAMMATION

It has been recognized for some time that psychological stress and depression increase the risk of atherosclerosis, CHD and adverse CHD events.[23-25] The INTERHEART study which recently reported has provided new and highly significant evidence of the importance of stress and depression as risk factors for first heart attack (myocardial infarct or MI) in a case-control study involving 52 countries and 10 geographical regions including North America.[26] It was found that the odds ratio (OR) for risk of first MI associated with psychosocial factors was 3.25 with smoking at 2.87, hypertension at 1.91, and diabetes at 2.37. A surrogate marker for cholesterol was used in the analysis which gave for the apolipoprotein B/apolipoprotein A-1 ratio (ApoB/ApoA-1) an OR of 2.87. These results applied with statistical significance to men and women, old and young and in all regions studied. It should be noted in connection with these results that other than age, no component of the Framingham Risk Score has an adjusted hazard ratio > 3.0 and most in fact are between 1.6 and 2.0.[22] The population attributable risk (PAR) is the relative risk weighted by the prevalence in the population being studied and provides an indication of the percentage of the population at risk. The PAR associated with psychosocial factors was 32.5% but varied considerably with gender and from country to country. In North America, the PAR associated with psychosocial factors was 63.7% for men and 32.7% for women. The factors included work stress, stress at home, general stress, financial stress, stressful life events, and depression. These were quantified by the use of a questionnaire professionally administered. Similar results were recently reported where a relative risk of 2.63 for incident CHD was found for patients with a high level of psychosocial stress when compared to those with low levels.[27]

In addition there is now some evidence from EBT and angiography studies that psychological stress and depression are implicated as risk factors for the presence and progression of atherosclerosis. While two recent cross-sectional studies found null results,[28,29] both looked only at the current situation and one was criticized as underpowered.[30] On balance the evidence from a number of studies appears to point to a significant association, especially as regards such characteristics as anger, hostility and major depression.[31-39]

There is also indirect evidence regarding the positive association between stress and coronary calcification from studies that revealed correlations between the CACS and the abnormal diurnal behaviour of cortisol levels.[40] Impaired cortisol response has been found to characterize individuals with coronary artery disease.[41] Thus there is evidence pointing to abnormal cortisol control (dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis) in connection with the adverse effects of psychological stress, and this in turn points to inflammation as a component of the biological mechanism.[42-44] An association between cardiac pathology, the acute phase response and the over-activity of the sympathetic limb of the autonomic nervous system with concomitant inflammation has also been observed and discussed.[7,45,46] The close connection between the inflammatory consequences of psychological stress and insulin resistance, obesity, atherosclerosis, and type 2 diabetes has recently been reviewed in considerable detail by Black.[47] The frequent parallel development of atherosclerosis and type 2 diabetes also suggests that primary prevention of the latter includes the former.

These results appear significant. Studies found psychosocial stress to have an odds ratio comparable to diabetes. Since diabetes is considered a CHD-equivalent risk factor in current protocols, this result underscores the potential importance of psychological factors in risk assessment and intervention.

FIBRINOGEN

Plasma fibrinogen is a vital component of the coagulation process and a major determinant of blood viscosity and flow. There is considerable evidence that elevated levels of this blood component are associated with increased risk of cardiovascular disorders including CHD, stroke and other incidents related to blood clots. The relationship between high levels of fibrinogen and atherosclerosis and thrombosis is complex but it is thought that fibrinogen also plays a key role in the process of atherosclerotic plaque formation. Epidemiologic studies

have established that elevated plasma fibrinogen levels are an independent and modifiable risk factor for coronary heart disease.[48,49] Individuals in the upper quintile of plasma fibrinogen as compared to the lowest quintile have a 1.5 fold greater odds of an adverse CHD event as compared to individuals judged by the lowest to the highest quintile of total cholesterol.[50] Thus fibrinogen is commonly included in the blood tests ordered by physicians who include emerging risk factors in their assessment of CHD risk.

THE OMEGA-3 INDEX

The Omega-3 Index is one of the latest emerging risk factors, in particular for sudden cardiac death (SCD). The common definition of SCD requires death to occur within an hour of the onset of the episode. SCD accounts for about half the deaths associated with adverse CHD events.[51] In this context, the omega-3 fatty acids are thought to be directly involved in the mechanism of arrhythmia which is the principal dysfunction associated with SCD. This index consists of the concentration of the long-chain omega-3 fatty acids EPA and DHA i.e. EPA + DHA, expressed as a percentage of the total phospholipids in the red blood cells. In prospective cohort and case-control studies, when ≤ 4% was used as a reference, an index value of ≥ 8% was associated with greatest sudden cardiac death (SCD) risk reduction with a remarkably low OR of approximately 0.1, i.e. a 90% lower risk, and an approximate inverse linear relationship of the OR and the Omega-3 Index between these two limits has been observed.[52-54] Since the blood or tissue omega-3 fatty acid content is considered an indication of inflammation status, this risk factor goes beyond simply introducing a measure of SCD risk related to arrhythmia.[55] Commercial laboratories offer this test and there is also a mail-in test available in the U.S. Nevertheless, the assay is not commonly done in routine physical exams and it is probably safe to state that knowledge of this risk factor and the existence of an assay is far from common among primary care physicians.

VISCERAL ADIPOSITY

This translates into excess abdominal fat, the apple shape or the beer-belly, and is one of the metabolic syndrome risk factors and a well-established risk factor for CHD. Some regard abdominal fat as organ-like in the sense that it is involved in the secretion of inflammatory substances. The best way to assess the risk associated with excess visceral adipose tissue appears controversial.[56] There is some evidence that the waist-to-hip ratio may be superior to waist circumference.[57,58] It has also been suggested that waist circumference be combined with triglyceride levels and there is evidence that when the former is enlarged and the latter elevated, the EWET factor or so-called hypertriglyceridemic waist, that this becomes a very good indicator of risk for coronary artery disease.[59]

OTHER RISK FACTORS

Two other emerging risk factors need mentioning. They are lipoprotein(a) and homocysteine. Homocysteine will not be discussed since while the evidence is strong that it is a risk factor, a number of intervention studies using folic acid alone or in combination with vitamin B6 and B12 have proved uniformly disappointing with a vast collection of statistically insignificant results for a variety of endpoints such as cardiovascular disease, CHD, stroke and all-cause mortality.[60]

Lipoprotein(a) is a cholesterol-rich lipoprotein similar in structure to LDL cholesterol but containing an additional molecular component thought to be involved in the mechanism of thrombosis. Thus some regard lipoprotein(a) as a risk factor for both CHD in general and as well clot formation. However, while lipoprotein(a) has been documented as a risk factor for CHD, there is no consensus as regards the mechanisms whereby this risk is conferred.[61]

A PROPOSED APPROACH TO CHD RISK ASSESSMENT

The risk factors and serum markers that are consistent with the theme of inflammation, insulin resistance and psychological stress are as follows.

- Psychological stress and depression
- Elevated TG/HDL ratio or the combination of high TGs and low HDL.
- Evidence of insulin resistance from an unfavourable HOMA-IR calculation based on fasting insulin and glucose, or a positive test for insulin resistance based on the oral glucose tolerance test.
- Omega-3 Index, a blood test based index that examines omega-3 status.
- Waist-to-hip ratio (WHR), or waist circumference (WC) and TG levels used together.
- C-Reactive protein (i.e. high sensitivity CRP or hsCRP)

To these can be added hypertension, elevated fibrinogen, current smoking and diagnosed diabetes, the latter normally considered a risk factor equivalent to existing CHD. Total and LDL cholesterol have been omitted for reasons set out above and because the TG/HDL ratio should provide a satisfactory measure of the blood lipid associated risk and is tied in with insulin resistance and the prevalence of small, dense LDL particles which are thought to be the dangerous LDL component. This set of factors is consistent with the primary care setting in that, aside from stress assessment, blood work and simple measurements are all that are required.

THRESHOLDS AND INTERVENTIONS

While the thresholds for elevated risk given below are mainly obtained from the literature, the interventions provided are mostly those suggested by the cardiologists Dr. Stephen Sinatra and James Roberts, who have been a strong advocate of using emerging risk factors in CHD assessment in what is termed "The New Cardiology Risk Assessment.[2] They call these "interventions that work for us."

Psychological Stress and Depression. The assessment of chronic stress and depression in non-pathological cases is a big problem but there is growing interest in the cardiology community regarding this aspect of the risk picture, which is termed *behavioural cardiology*, and which involves addressing both assessment and therapy.[25] This interest may accelerate the development of user-friendly questionnaires that can be administered by office or nursing staff. One of the serious problems associated with stress as a risk factor is that in many cases where the origin is work-related or domestic, the root cause may difficult or impossible to eliminate (changing jobs, avoiding toxic boss-worker relationships, solving marital problems, overcoming the stress of separation and divorce, etc, etc. may be next to impossible for many). Eliminating the root cause of depression may even be more difficult. While therapy is an obvious route to take, it may be that the only practical solution is to attempt to neutralize the inflammatory effects of stress and depression, an area that deserves research attention.

Psychological stress probably is never an issue during a physical exam unless the physician asks probing questions, something unlikely since this is somewhat outside the area of expertise of most in the primary care field. However, requests for tranquilizers or sedatives might prompt questions that would reveal a serious problem. It is probably more common that a patient will present with signs of depression or actually cite depression as an important problem or even the reason for the office visit. While one standard response is pharmaceutical based, it is far from clear that antidepressants will in general significantly reduce the depression induced chronic inflammation or diminish the adverse vascular effects of this inflammation. However, the selective serotonin uptake inhibitors (SSRIs) have been shown to have anti-inflammatory properties.[62] In fact, in one study, significant declines in CRP were found independent of the antidepressant action of standard doses of SSRIs.[63] However, there is some evidence that another class of antidepressant, the tricyclics, can increase ischemic heart disease.[64] Nevertheless, for both chronic psychological stress and depression, it appears important to get at the root causes and attempt to attenuate them through therapy or by directly eliminating them. But as pointed out above, the latter may be impossible if the root of the problem is work related or domestic stress. Obviously, this is a difficult but very important area. One should not forget that there is good evidenced that psychosocial stress is approximately equivalent to diabetes in terms of CHD risk. The following self-administered stress test may prove useful.

Psychological Stress—A Self-Administered Test

If the answers to the following questions are (a) quite a bit; (b) very much; or (c) extremely, the indication would be for evaluated stress. These are adapted from Lamyre and Tessier.[65]

1. I feel rushed and do not seem to have enough time.
2. I have chronic physical aches and pains such as a sore back, headache and stiff neck.
3. I feel overworked, preoccupied or tormented.
4. If feel confused. My thoughts are either muddled, not focused or I lack concentration.
5. I feel as if I had a great weight on my shoulders.
6. I experience difficulty in controlling my reactions, emotions, moods or gestures.
7. I feel stressed-out.

There is also an online stress test complete with analysis of the results that has been used in the medical resident-intern setting as well as in comprehensive physicals at Wellmax Center for Preventive Medicine, which offers about as complete a physical as one could ever want. It takes 3-4 days! This evaluation tool can be accessed for a nominal fee (ESSI Stress Map at www.essisystems.com).

An important and probably underappreciated approach to the treatment of depression is physical exercise. In fact, aerobic exercise has been shown to be as effective as antidepressants in some situations. This subject, along with many other exercise-brain benefits, has been treated in detail in a new book by John J. Ratey, M.D., a psychiatrist who is on the faculty of Harvard Medical school.[66]

The Fasting TG/HDL Ratio. Only a limited number of studies are available. This ratio is also sensitive to the units used. When the units mg/dL are used, Sinatra gives a ratio of 4 (1.7 in mmol/L) as the threshold for elevated risk. A recent study puts high risk at > 3 (1.3) and medium risk at 2.5-3 (1.1-1.3).[67] The ratio will always be available from the standard fasting blood lipid profile since triglyceride levels are needed to calculate LDL which is not directly measured. Interventions to lower TG levels include niacin (20-50% decrease), fibrates (20-50% decrease), and fish oil (20-50% decrease). Some statin drugs also reduce TGs. To raise HDL, niacin appears the provide benefit with a 15-35% elevation. Exercise and reduced carbohydrate diets influence the TG and HDL levels in the desired direction.[2,68]

Insulin Resistance. Given the inconvenience of the oral glucose tolerance test which requires a fasting blood sample and then another at 2 hours after glucose intake, the HOMA-IR seems like the most convenient approach. It uses the fasting blood insulin and glucose values. The equation is fasting insulin in µU/mL times the fasting glucose in mmol/L divided by 22.5. There does not appear to be a consensus regarding the threshold for identifying insulin resistance, but the value of the index of > 2-2.5 appears indicative. However, the use of the HOMA model for older men has been questioned and it has also been found that in Koreans, the model has limited validity for subjects with lower BMI and in lean type 2 diabetics with insulin secretion problems. An alternative is the oral glucose tolerance test. The American Diabetes Association definition of impaired glucose tolerance can be use to identify individuals with insulin resistance.[15] The definition requires a plasma glucose level of 140 to 199 mg/dL (7.8-11.0 mmol/L) two hours after a 75 g oral glucose challenge for an individual initially fasting. Sinatra uses a fasting insulin level > 17 µg/L as a threshold. Interventions that improve insulin sensitivity which include weight loss, exercise, and restricting carbohydrates, especially sugary or high-glycemic carbohydrates. Suggested supplements, according to Sinatra and Roberts, include alpha-lipoic acid, coenzyme Q-10, cinnamon, magnesium and chromium picolinate.

The Omega-3 Index. Oral EPA and DHA from either fish oil or from preparations containing the purified fatty acids have been repeatedly and consistently shown to increase this index. Typical daily doses for someone who has a low value are in the range of 1-3g/d of purified fish oil. Purified preparations typically contain more EPA than DHA in a ratio of around 2 to 1 and typical pharmaceutical grade preparations purified by molecular distillation will contain about 400 mg of EPA and 200 DHA per gram of oil. Cod liver oil provides somewhat less. Safety even at relatively high doses does not appear to be an issue.[69]

Waist-to-Hip Ratio (WHR) or Waist Circumference. The best way to assess risk associated with visceral adipose tissue appears controversial.[56] There is some evidence that the waist-to-hip ratio may be superior to waist circumference.[57,58] It has also been suggested that waist circumference be combined with triglyceride levels and there is evidence that when the former is enlarged and the latter elevated, the EWET factor or so-called hypertriglyceridemic waist, that this becomes a very good indicator of risk for coronary artery disease.[59,70] In the World Health Organisation (WHO) definition of metabolic syndrome, they use a risk threshold for the WHR

of > 0.9 for men and > 0.85 for women. For the waist circumference thresholds, the ATP III guidelines give > 102 cm (40 in) for men and > 88 cm (35 in) for women. The comparable numbers from the International Diabetes Federation are ≥ 94 cm (37 in) for men and ≥ 80 (31.5 in) cm for women. For the EWET, i.e. the combination of elevated waist circumference and triglycerides, one threshold suggested for men is ≥ 90 cm (35.5 in) and 177 mg/dL (2 mmol/L).[59] However, a common threshold recommended in general for triglycerides is ≥ 150 mg/dL (1.7 mmol/L) above which concern is appropriate. Interventions appear limited. Obviously, exercise and weight reduction are indicated.

High Sensitivity C-Reactive Protein. The reason for the designation "high sensitivity is that historically CRP was measured with a limit of sensitivity that rendered it useless in this context. A commonly quoted threshold for elevated risk is >1.5 mg/L. One problem with CRP is that it can be temporarily elevated by an infection. Thus elevated values call for one or more repeat measurements to attempt to eliminate this potential false alarm. The calls for CRP to be added to the standard risk profile become louder each year as the evidence accumulates regarding the value of this indicator of inflammation in the context of CHD risk. CRP can be lowered by statins, exercise, low dose aspirin, and fish oil. In addition, Sinatra and Roberts recommend nattokinase and coenzyme Q-10. Diets considered non-inflammatory or anti-inflammatory also reduce CRP.

Fibrinogen. Sinatra and Roberts give 180-350 mg/dL as the healthy range. To lower fibrinogen, they suggest fish oil, garlic, bromelain, ginger and/or green tea and nattokinase. Nattokinase is available from health food stores or by eating the Japanese preparation natto, which is made from fermented soybeans and sold in Asian food stores.

CONCLUSIONS

The basic philosophy underlying the above discussion is that it is more important to recognize and deal with individual risk factors, place less emphasis on global risk assessment such as APT III or the traditional Framingham Risk Score and focus on inflammation and insulin resistance. Such an approach seems to have a better chance of dealing with underlying causes such as inflammation and insulin resistance before they manifest their adverse effects in symptomatic heart disease or diabetes, the latter being in fact a pre-CHD disorder carrying a huge increase in risk of eventually developing and dying from CHD. A good general reference for the subject of emerging or novel risk factors is Sinatra and Robert's book.[2] Readers of the Newsletter will find this book reviewed in the June 2007 issue.

Part II of this review will address the question of the relationship between diet and inflammation and insulin resistance and as well the problem of weight loss and the maintenance of weight loss. This is a controversial area but of obvious importance since diet and exercise are prominent interventions for individuals when the above discussed risk factors exceed the risk threshold.

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The Prostate Monitor
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Reviews of recent studies from the peer-reviewed literature

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This issue features an update of prostate cancer prevention with vitamin E and selenium. While we all await the results of the SELECT trial of 400 IU/d of E and 200 micrograms of selenium, it is of interest to examine recent results that address the same issue being addressed in SELECT. Most of the studies have been with vitamin E.

This issue also discusses studies that examine the association between prostate cancer risk and diet. Included are studies of trans-fats, meat and prepared meats, and dietary fat in general.

Finally, recent results regarding the protective effects of physical activity and vitamin K are discussed and a mention is made of the possibility of secondary malignancy associated with prostate cancer chemotherapy.

Wishing you continuing good health,

William R. Ware, PhD, Editor

SELENIUM, VITAMIN E AND PROSTATE CANCER

By 2001 sufficient evidence had accumulated regarding the potential of vitamin E and selenium to reduce the incidence of prostate cancer that the large SELECT trial was undertaken. It is an intervention trial employing 400 IU/day of vitamin E and 200 micrograms (µg) of selenium and is expected to report in 2013. Many men, hearing about this trial and assuming that there was good reason for its existence, probably started taking these two supplements just on general principles. Some may already have been doing this even without knowing it if their multivitamin contained the required amount of selenium. Since then there have been a number of prospective follow-up studies and randomized clinical trials that have also addressed this issue. Four prospective follow-up studies are of interest.

- 2008. The VITAL prospective study with a 10-year follow-up of over 35,000 men from the state of Washington. Overall, there was no significant reduction in risk for ≥ 400 IU/d vs. non-use. However, for advanced cancer (regionally invasive or distant metastatic) the risk was significantly and strongly reduced by about 57% for this same dose over 10 years. Selenium was also investigated and it was found that there was no significant benefit from intakes > 50 µg/d compared to non-use. Smokers constituted about 40% of the cohort.[1]

- 2007. A 19-year prospective follow-up involving the cohort from the Finish study on smokers that prompted the SELECT study. A small but significant benefit was found overall with a 20% risk reduction when the high vs. the low quintile of vitamin E intake were compared. However, for advanced cancer, the risk reduction was 44%. All the participants were smokers with 35-36 mean smoking years and approximately 20 cigarettes/d.[2]

- 2007. An NIH supported study of men ages 50-71 prospectively examined the association of risk with the various forms of supplemental vitamin E. No overall benefit was found during 5 years of follow-up but for dietary γ-tocopherol, the most common form in food, the risk of advanced cancer was reduced by 32% when the highest vs. the lowest quintile were compared.[3] This is not the first time that γ-tocopherol has turned up as having stronger action than the standard supplement. In fact, the use of α-tocopherol in the SELECT trial has been questioned. Preparations of vitamin E containing the γ-isomer are readily available from health food stores and it can also be obtained as a separate supplement.

- 2006. A North American prospective study with a follow-up of about 8 years found no overall association between dietary or supplemental vitamin E intake, but found that among smokers, the decrease in risk of advanced cancer (Gleason score ≥ 7 or stage III or IV—see our book for details of staging) was 61% for intakes ≥ 400 IU/d and 70% for 10 years of use.[4]

- 2004. A U.S. based study of over 72,000 men 50-74 years of age employed 2 questionnaires to examine vitamin E intake, one in 1982 and one in 1992-3. Follow-up ended in 1999. Regular vitamin E supplement use (≥ 4 times per week) was not associated with overall prostate cancer risk or with the risk of advanced prostate cancer diagnosis. However, there was a suggestion of a benefit for smokers, although this did not achieve statistical significance. However, the number of advanced cancer cases was very small and thus this study would not have identified the risk reduction seen in the above studies for this subset.[5]

There was one randomized, placebo controlled clinical trial that reported in 2005 which used 400 IU/day as the intervention with a follow-up of 7 years. Prostate cancer was only one of many endpoints and an approximately equal number of cases were observed in the treatment and placebo groups. While this suggests no benefit, there was no adjustment for confounding and no stratification to examine advanced cancer. The number of prostate cancer cases was small. Thus this study appears to shed little light on the issues in question.[6]

Thus as regards vitamin E, a clear and large benefit for the prevention of advanced prostate cancer accrued to both smokers and non-smokers with the former appearing to receive greater benefit.

There is much less data for selenium. Aside from the 2008 prospective study, the most recent study appears to have reported in 2003. In this randomized, placebo controlled clinical study, the association between selenium and prostate cancer was secondary to the primary endpoint which consisted of the prevention of recurrence of non-melanoma skin cancer. Thus the group studied did not represent the general population. Nevertheless, in a follow-up of over 7 years, it was found that selenium supplementation of 200 µg/d of selenium from selenium yeast was beneficial. The protective effect of selenium was seen only in those with a PSA level below 4 ng/mL and represented a 65% risk reduction. However, the greatest risk reduction was seen with individuals with the lowest plasma selenium at baseline and represented an 86% risk reduction which was statistically significant. This latter result was adjusted for age and smoking status. The small number of cases precluded stratification to include advanced disease.[7]

Aside from the SELECT trial, there are two ongoing randomized clinical trials that also address this issue.[1,8] One involves men with high-grade prostatic intraepithelial neoplasia (see our book for a discussion of this important pre-prostate cancer condition) and the other is directed at men with diagnosed prostate cancer who have elected watchful waiting. The latter will report in 2009.

The above summary suggests that the SELECT trial will probably provide evidence of benefit given the long-term intervention and the use of both vitamin E and selenium. However, it is also possible that again, the principal benefit may involve preventing advanced prostate cancer. Nevertheless, there does not appear to be any reason for men taking the vitamin E-selenium combination not to continue this practice, but the possibility that it may not prevent localized or low-grade cancer should be recognized.

TRANS-FATTY ACIDS AND RISK OF PROSTATE CANCER

A study from Harvard has examined the association between *trans*-fatty acids in blood and the risk of prostate cancer. The researchers had almost 15,000 blood samples collected in 1982 and in a 13-year follow-up identified 476 cases of prostate cancer. These cases were matched with controls according to age and smoking status at baseline. Blood levels of all the *trans*-fatty acids taken together were found to be unrelated to total prostate cancer risk. When the results were stratified according to tumor aggressiveness, relative risks of about 2 were found for blood levels of *trans*- oleic and *trans*- linoleic acids when the top vs. bottom quintiles of blood levels were compared. None of the *trans*-fatty acids examined was associated with aggressive prostate cancer. The authors point out that the non-aggressive prostate tumor is the most common one found using PSA screening and that these funding have implications for the prevention of this disease.[9]

MEAT AND MEAT MUTAGENS AND RISK OF PROSTATE CANCER

The study of the connection between meat consumption and cancer is complicated by the large variety of meats commonly consumed, the method and degree of cooking, and the content of potentially mutagenic chemicals such as those introduced in the curing process as well as by cooking. For example, meats cooked at high temperatures, such as pan-frying or grilling, are a source of carcinogenic chemicals such as heterocyclic amines and polycyclic aromatic hydrocarbons. A study has just reported which involved almost 200,000 person-years of follow-up during which 613 prostate cancer cases were diagnosed after the first year and 140 were advanced cases. It was found that there was no association between meat type or specific cooking method and prostate cancer risk. However, intake of well done or very well done meat was associated with a 1.26-fold increase in risk and an almost 2-fold increase risk of advanced cancer when the highest tertile of consumption was compared with the lowest. The researchers also examined the risk associated with the two classes of mutagenic chemicals mentioned above and found associations that were only of borderline significance. The authors regard the connection with the extent and temperature of cooking to suggestive of the generation of mutagenic chemicals even though they were unable to make a positive connection, and they suggest more research is indicated.[10]

DIETARY FAT AND PROSTATE CANCER

The history of the fat-cancer connection has a long and troubled history with most associations disappearing as better studies were performed. A prospective study from Sweden has re-examined this question in connection with prostate cancer. Over 10,000 individuals initially cancer free were assessed by a diet history protocol and cases over the 11-year follow-up were ascertained from a national cancer registry. After adjustment of the results for age and energy intake there was no association between intake of any type of fat with the exception of the fatty acids EPA and DHA and the risk of prostate cancer, nor was there an association between fat intake and advanced disease occurring in persons < 65 years of age. For EPA and DHA, the association was weak and the authors suspect the result was confounded by significant levels of toxic contaminates present in the fish that were consumed by this population.[11]

OCCUPATIONAL PHYSICAL ACTIVITY AND RISK OF PROSTATE CANCER

While there is substantial evidence that regular physical activity decreases the incidence of certain cancers and especially breast and colon, the association with prostate cancer has been inconsistent. A recent study has reported results based on physical activity assessment in two groups of workers at a nuclear power systems and aerospace (rocket engine) testing facility in California. It was found that among the aerospace workers, high levels of work related physical activity were inversely and significantly associated with prostate cancer incidence with a risk reduction of 45% whereas for the nuclear systems workers no association was found. The authors suggest that the difference in the two results is associated with the continuous nature of the physical activity associated with the rocket testing work which was not the case with the nuclear testing workers. They conclude that jobs that are associated with continual high activity levels may be protective.[12]

PROSTATE CHEMOTHERAPY AND UNEXPECTED ACUTE LEUKEMIAS

During a phase III study of adjuvant chemotherapy with the drug mitoxantrone in individuals with high-risk prostate cancer, three cases of acute myelogenous leukemia were reported out of a total of 487 patients treated. This has prompted the organizers to close the trial to further accrual of subjects. To quote from the paper “The emergence of this possible pattern of secondary malignancy emphasizes the importance of randomized controlled trials in defining safety and efficacy of new approached for patients in the adjuvant setting.” This is an interesting problem since large randomized trials are very expensive, and in addition, the use of these highly cytotoxic chemicals frequently involves patients with a fairly short life expectancy which limits the opportunity to detect secondary malignancy. Secondary malignancy is clearly an issue in the risk-benefit analysis of chemotherapy in any case where there is an expectation of significant life extension.[13]

VITAMIN K AND PROSTATE CANCER PREVENTION

Vitamin K is found in many multivitamins and can also be obtained as a stand-alone supplement or as a combination of vitamin K2 and vitamin D for the prevention of osteoporosis. There are two forms of vitamin K that occur naturally in foods. These are phylloquinone (vitamin K1) and the menaquinones (vitamin K2) of which menaquinone-7 is the preferred form used in supplements. Vitamin K1 is abundant in green leafy vegetables and some vegetable oils whereas the components of vitamin K2 are synthesized by bacteria and therefore occur in fermented products such as cheese and natto. Meat and meat products are also a source of K2. There is cell culture evidence that vitamin K may have anti-cancer properties and in a randomized trial of 43 women with viral cirrhosis of the liver, mega doses of K2 reduced the risk of liver cancer by 80%. Now a follow-up study (8 years) has reported that examined dietary vitamin K intake in the context of prostate cancer prevention. It was

found that for a dietary intake of K2 but not K1, a statistically significant risk reduction of 35% was found for advanced prostate cancer when the highest vs. the lowest quartiles of intake were compared. A weaker association was found for total cancer and K2 intake. When the source of the K2 was examined, dairy products were found to be more important than meat in reducing the risk of advanced disease.[14]

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