INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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Vitamin C is featured in this issue with four reports covering terminal cancer, the common cold, problems in weight loss and cataracts. Eye problems also come up in a discussion of a study of the impact of high glycemic index diets on age-related macular degeneration, a huge problem facing the elderly. In addition, the significance of the newly proposed definition of impaired glucose tolerance is discussed in the light of a new study which examines predicting the progression to type 2 diabetes. The recurring theme in this Newsletter of conflicts of interest and questionable clinical studies is visited again, this time with a discussion of a short paper in the New England Journal of Medicine which describes the rapidly growing practice of drug companies contracting out clinical trials to private companies where the research can take place anywhere in the world, and in particular where it is cheap and regulatory oversight minimal. Heart disease is featured in two reviews, one regarding job-related stress, the other the importance of high HDL levels. Also a brief review is given of a study showing how women can dramatically reduce their risk of first heart attacks.

Included in this issue is Part II of the Cholesterol Review. In this part, the relationship between cholesterol levels in apparently healthy individuals and both coronary heart disease mortality and overall mortality in later life are examined for both genders and all ages. What is actually out there in the literature may surprise readers accustomed to the nightly blitz of cholesterol lowering drug advertising. However, it is very important to remember that most of the results in this review do not apply to individuals who already have heart disease, many of whom may benefit from cholesterol lowering drugs, but not necessarily because their cholesterol goes down. Cholesterol lowering will be discussed in Part III.

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Wishing you a Happy Holiday Season and good health in the coming New Year,

William R. Ware, PhD, Editor

Highlights

VITAMIN C—WHAT'S NEW?

"The medical profession itself took a very narrow and very wrong view. Lack of ascorbic acid caused scurvy, so if there was no scurvy there was no lack of ascorbic acid. Nothing could be clearer than this. The only trouble was that scurvy is not a first symptom of the lack but a final collapse, a premortal syndrome and there is a very wide gap between scurvy and full health." Albert Szent-Gyorgyi in his Nobel Prize acceptance lecture.

As is no doubt well known to readers of this Newsletter, man is one of the few mammals that lacks the ability to synthesize vitamin C—it must come from food or out of a bottle. This loss has been suggested as an adaptive trait in human evolution with selection on a population level. Many theories have been advanced regarding exactly what evolutionary advantages this loss conferred.

One hypothesis is that the inability to produce vitamin C may have been due to a selective mechanism against aging which allowed the re-distribution of foods for the young and fertile. As Li *et al* discuss in a paper in Medical Hypotheses (2007;68:1315-7), whatever the mechanism, what is clear is that adequate vitamin C intake is especially important among aging populations. They point out that there is growing evidence that many age-related diseases including heart disease, neural degeneration and cancer may have a contributing oxidative damage factor that might be reduced by antioxidants such as vitamin C. They hypothesize that high serum levels of vitamin C provide important, broad-ranging therapeutic benefits in treating age-related degenerative diseases. This issue will feature recent studies regarding vitamin C and various health issues.

VITAMIN C AND CATARACTS

A recently reported prospective study from Japan examined the association between dietary vitamin C and the incidence of cataract diagnosis or extraction. Over 30,000 men and women (aged 45-64) were involved in a 5-year follow-up. Dietary vitamin C intake was determined by a questionnaire and individuals taking supplemental vitamin C were excluded. Median intake when stratified into quintiles ranged from 55 to 212 mg/day for men and 76 to 259 mg/day for women. Significant risk reductions were found only at for those in the highest quintile of intake and fell in the range from 30 to 36% for either diagnosis or evidence from extraction. These results were adjusted for age, body mass index, hypertension, diabetes, alcohol intake and smoking. The authors comment that there have been a number of other studies that examined the association of dietary vitamin C and cataracts. Six found risk reduction but three did not. Also, they point out that most, but not all studies of the benefits of vitamin C supplements in this contexts found risk reduction.

Yoshida, M. et al. Prospective Study Showing that Dietary Vitamin C Reduces the Risk of Age-Related Cataracts in a Middle-Aged Japanese Population. ***European Journal of Nutrition****, 2007, Vol. 46, pp. 118-24.*

HIGH VITAMIN C AND TERMINAL CANCER

A recent study from Korea adds to the limited evidence associated with quality of life benefits derived from high doses of vitamin C in the case of terminal cancer. This study involved 39 patients with a variety of cancer sites. All patients were given 10 g of vitamin C intravenously (IV) plus 4 g/day of oral vitamin C over a period of a week. Changes in the quality of life one week later were assessed. All patients had metastatic cancer but only 28% had received chemotherapy and 2.6% radiotherapy. The most common cancers were stomach, lung and colorectal. A large number of quality of life parameters were evaluated including five that measured ability to function, three related to symptoms (pain, fatigue, and nausea/vomiting) and six additional items which included appetite loss and sleep disturbance. The assessment was quantified into what amounted to a score. Significant beneficial changes were found for global health, all functional parameters, fatigue, nausea/vomiting, pain, sleep disturbance, and appetite loss. The authors offer physiological explanations for some of these results.

Yeom, C. H. et al. Changes of Terminal Cancer Patient's Health-Related Quality of Life after High Dose Vitamin C Administration. ***Journal of Korean Medical Science****, 2007, Vol. 22, pp 7-11.*

Editor's comment: These results are particularly interesting because of the short duration and relatively low doses used, even though the authors viewed the doses as high. High-dose Vitamin C therapy, although only occasionally reported, employs much higher doses. In 2006, Padayatty *et al* (*Canadian Medical Association Journal, 2006;174:937-42)* reviewed three case histories where the IV doses used were 65 g twice a week for 10 months, 15 grams per week for two months followed by 15 g twice per week for 7 months, and finally 30g per week for 3 months, followed by the same dose at longer intervals. The cancers involved were kidney, bladder and large B-cell lymphoma. In all cases, while the cancers would have been expected to progress rapidly, this was not observed in the vitamin C treated patients. In addition, as regards dose and duration, in the ongoing Cancer Treatment Centers of America initiated FDA approved Phase I trial of IV vitamin C, the first cohort of patients are being treated with approximately 50 g infusions on 4 consecutive days per week for a period of 4 weeks and doses in future cohorts will be increased incrementally until the maximum tolerated dose is reached. This trial will evaluate quality of life during treatment as well at safety, tolerability optimum dose and the time dependence of serum vitamin C levels. Thus if the Korean researchers had used larger doses they might have observed greater changes, and if they treated for a longer period with a longer follow-up, then might have observed dramatic delays in progression.

Treatment with high IV doses of vitamin C for terminal cancer patients was discovered and studied a number of years ago by Linus Pauling and Ewan Cameron, who published two landmark papers in the *Proceedings of the National Academy of Science* in 1978. They found dramatic life extensions and improved quality of life from such treatments. Later, a paper from the Mayo clinic which used only oral doses and found null results was accepted by mainstream medicine as proof that the treatment had no merit. However, recently it has been demonstrated that there is a rather low upper limit to serum levels achievable with oral doses, but that very high serum levels can be reached with IV administration. Thus the above-mentioned FDA approved reexamination of the work of Pauling and Cameron.

VITAMIN C AND THE COMMON COLD

The suggestion by Linus Pauling that vitamin C could prevent the common cold or reduce its duration has inspired a number of trials over the years. The Cochrane organization, which has an excellent reputation for critical reviews and meta-analyses, has recently published a review and analysis of all randomized, placebo controlled trials they considered acceptable to determine if oral doses of 0.2 g/day or greater of vitamin C reduces the incidence, duration or severity of the cold when used either as a continuous preventive measure or after the onset of symptoms. The conclusions drawn from examining a large number of trials was that vitamin C supplementation failed to reduce the incidence of colds in the normal population. But they found justification for use in individuals exposed to brief periods of severe physical exercise or cold environments. Examples of the latter were marathon runners and skiers. No consistent benefit was found for the use of vitamin C after the onset of symptoms but there were only a few trials and some reported benefit.

Douglas, R.M. Vitamin C for Preventing and Treating the Common Cold. ***Cochrane Database of Systematic Reviews,*** *2007, Issue 3. Art. No. : CD000980.*

VITAMIN C AND PROBLEMS IN ACHIEVING WEIGHT LOSS

Vitamin C is a required cofactor in the biosynthesis of carnitine which is a molecule required for the oxidation fat, i.e. fatty acids. The possibility that this might explain the reported inverse association between vitamin C status and adiposity motivated Johnston *et al* to conduct a preliminary trial to evaluate the impact of vitamin C on fat oxidation during submaximal exercise. Fifteen sedentary non-smoking individuals from a campus population who had marginal vitamin C status and 7 with adequate status were recruited. Participants did not regularly use vitamin C supplements and were unaware of their vitamin status or the intent of the study. The study had two phases. In the first, fat oxidation was measured during a treadmill walk at 50% maximal oxygen consumption (determined earlier). Calculations were based on urinary nitrogen measurements and data based on oxygen and carbon dioxide measurements. In the second phase, an eight-week placebo controlled intervention was conducted on a subset of the participants which involved supplementation with vitamin C. The researchers found that individuals with marginal vitamin C status oxidized 25% less fat per kg of body weight during the treadmill test as compared to those with adequate status and the lower the fat oxidation, the higher the exercise related fatigue. Vitamin C repletion in depleted subjects (500 mg/day) raised the fat energy expenditure during exercise by a factor of 4 as compared to the depleted control subjects. The authors comment that these results may partially explain why some individuals are unsuccessful in their weight loss attempts.

Johnston, C.S. Marginal Vitamin C status is Associated with Reduced Fat Oxidation during Submaximal Exercise in Young Adults. ***Nutrition & Metabolism****, 2006, Vol. 3, PP. 35.*

COMMERCIALIZATION OF CLINICAL TRIALS

The medical literature regarding clinical trials gives a false impression that they are organized and carried out mostly by academic institutions. In the October 4 New England Journal of Medicine, Dr. Miriam Shuchman presents a perspective that clarifies the true state of affairs. This article describes the rise to dominance of contract research organizations (CROs) in the last few years. CROs are private companies that contract to carry out clinical trials for the pharmaceutical industry. One does not generally see the results in the peer-reviewed literature. In 1993 CROs played a substantial role in only about 28% of all phase I, II and III trials, whereas in 2003 the percentage was

64%. The clinical trial results end up in the ensemble of data presented to the FDA during the drug approval process in order to prove safety and efficacy. The four largest CROs each have annual revenues exceeding one billion dollars. By and large they are answerable only to their clients. It is pointed out by the author that while there is talk of certification of both researchers and sites, this is becoming more difficult since many of the trial sites are now in Eastern Europe, Russia, India and Asia where costs are lower, recruiting easier and there is less government oversight than in North America. The CROs compete directly and evidentially successfully with academic institutions although both, according to the perspective, generally comply with the industry requests and agree to conduct very conservative studies that leave important questions unasked rather than lose the contract in question. The perspective gives a number of examples to illustrate the point that in some cases there is insufficient concern regarding the wellbeing of participants and the failure of clients to use unfavorable results in their FDA presentations. In fact, CROs have been called data production sweatshops. All in all, an unsettling view of how the drugs in the U.S. are tested prior to being given the official blessing. Coupled with what appears to be a very lax post-approval adverse effects reporting system, the picture is even more alarming.

Shuchman, M. Commercializing Clinical Trials—Risks and Benefits of the CRO Boom. ***New England Journal of Medicine,*** *2007, Vol. 357, Oct. 4, pp. 1365-8.*

DIET AND AGE-RELATED MACULAR DEGENERATION

Two papers from the Age-Related Eye Disease Study have just appeared which address dietary issues related to the risk and progression of age-related macular degeneration (AMD). AMD is a neurodegenerative disease of the central retina (macula). While the macula comprises only about 4% of the human retina area, it is responsible for all of the high-acuity vision. AMD generally occurs after middle age and is the leading cause of irreversible vision loss in North America, Western Europe and Australia. With aging populations, AMD is emerging as a major public health issue. Two studies by Allen Taylor and co-workers examine the association between AMD and dietary glycemic index and the risk of AMD in non-diabetic subjects and the role of dietary carbohydrate in the progression of AMD. In the dietary glycemic index (dGI) study, there was a 49% increase in the risk of advanced AMD for persons with a dGI above the median, a result which indicated that 20% of the prevalent cases of AMD would have been eliminated if the study participants consumed diets with a dGI below the median. The dGI was calculated as the weighted average of the GI scores for each food item, based on the amount of carbohydrate consumed from each food item. Fiber content was subtracted from the carbohydrate content. The median dGI was about 80 and white bread was used as the reference food. In the second study, which involved a follow-up of over 8 years, the risk of progression was significantly higher in the high dGI group as compared to the low dGI group, high and low being defined as above or below the median dGI which again was about 80. The authors conclude that individuals at risk of AMD progression, especially those at high risk of advanced AMD, may benefit from consuming a smaller amount of refined carbohydrate. The same conclusion would apply to the risk of developing AMD.

Chiu, C-J. et al. Association between Dietary Glycemic Index and Age-Related Macular Degeneration in Nondiabetic Participants in the Age-Related Eye Disease Study. ***American Journal of Clinical Nutrition****, Vol. 86, pp. 180-8.*

Chiu, C-J. et al. Dietary Carbohydrate and the Progression of Age-Related Macular Degeneration: A Prospective Study from the Age-Related Eye Disease Study. ibid, pp. 1210-8

JOB STRAIN AND RISK OF ACUTE RECURRENT CORONARY EVENTS

Several but not all studies have shown that job-related psychological strain increases the risk of a coronary heart disease (CHD) event. However, only two studies have examined the impact of job strain on recurrent CHD events after a first MI (heart attack), and the findings were inconsistent. Limitations of these two studies were that they did not assess the duration of the psychosocial work-related stress exposure and involved only a small subject group. A study just reported was designed to overcome these two limitations. A prospective cohort of almost 1000 men and women aged 35-59

who returned to work after a first MI were followed from 1996 to 2005. Subjects were interviewed at baseline and then after 2 and 6 years. Job strain which involved a combination of high psychological demands and low decision latitude were evaluated. The outcome was a composite of a fatal or non-fatal CHD event or unstable angina, and was documented in approximately 20 % of the study group. It was found that chronic job stress approximately doubled the risk of a second adverse CHD event compared to those returning to a job without stress. This result persisted after adjustment for 26 potentially confounding factors. The authors comment that these results suggest that preventive interventions aimed at reducing job stress might have a significant impact on recurrent CHD events or symptoms and that these results should be made known to occupational health services. In an editorial, Orth-Gomer points out that these results really apply only to men since women comprised only 11% of the cohort, a proportion too small to allow separate analysis by sex. She also comments that knowledge is lacking as to how to prevent and manage job-related stress and psychosocial risk in general and that there is great need for research in this area, and that in addition, patients may benefit from having job stress evaluated as part of their post MI care.

Aboa-Eboule, C. Job Strain and Risk of Acute Recurrent Coronary Heart Disease Events. ***Journal of the American Medical Association****, Vol. 298, No. 14, pp. 1652-60.*

Orth-Gomer, K. Job Strain and the Risk of Recurrent Coronary Events. Ibid, pp. 1693-4.

IMPORTANCE OF HDL CHOLESTEROL AT LOW LDL LEVELS

In a post hoc analysis of a recent secondary prevention trial that examined the merits of high doses of a statin compared to low dose in connection with reducing the risk of cardiovascular events, an attempt was made to determine the effect of the HDL level on this outcome. Eligible subjects were men and women aged 35-75 with clinically evident heart disease defined as a previous heart attack, previous or current angina with objective evidence of coronary atherosclerosis, or previous coronary revascularization. The investigators concluded that low HDL levels were predictive of major cardiovascular events in patients treated with statins. Among study subjects with LDL cholesterol below 70 mg/dL, those in the highest quintile of HDL were at less risk for major cardiovascular events than those in the lowest quintile.

Barter, P, et al. HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular events. ***New England Journal of Medicine****, 2007, Vol. 357, No. 13, pp. 1301-10.*

Editor's comments: The results of this study are difficult for the reader to analyze because most are presented without any indication of statistical significance and the reader is expected to draw conclusions from the visual trends graphically illustrated without indications of statistical significance rather than from the usual tables with risk ratios or hazard ratios and 95% confidence intervals. However, there are several exceptions. When the 5-year risk of CV events for all patients was stratified by HDL quintile, compared to the lowest quintile (< 38 mg/dL HDL), only two of the four quintiles (2 and 5) showed statistically significant support for the assertion of benefit. When a similar analysis was done for patients in the lowest stratum of LDL (< 70 mg/dL), the upper three quintiles of HDL provided statistically significant evidence of benefit, but there was no trend with HDL level from 42 to > 55 mg/dL. When the ratio of LDL to HDL or total cholesterol to HDL was examined, comparison of the lowest vs. the highest quintiles produced significant results with increased risks of 1.82 and 1.72 respectively. However, if HDL was treated as a continuous variable, when the investigators used various models for adjusting the data, if one judges the results by the 95% confidence limits there was no significant relationship found for HDL levels and the risk of major CV events even though the event rate was about 10%. This was true for a model which adjusted for LDL levels at baseline and one that adjusted for LDL levels at 3 months, when most of the LDL lowering from statin treatment would have occurred. Thus, while this study provides some evidence to support the widely held view of the importance of high HDL levels, the casual reader of the abstract will not be aware that there is a noteworthy absence of statistical significance in some of the results, trend significance is by and large ignored, and for some reason a complete presentation of the data with accompanying statistics is absent from the report. This study was supported by Pfizer and 7 of the 9 authors report conflicts of interest involving Pfizer and as well, various other drug companies including major manufacturers of statins.

OMEGA-3 POLYUNSATURATED FATTY ACIDS AND RISK OF TYPE 1 DIABETES IN CHILDREN

Dietary factors have been implicated in the etiology of type 1 diabetes, a disease that frequently occurs during childhood. In a study from Norway, cod liver oil was implicated in preventing this type of diabetes, but it was unclear whether the effect was due to the omega-3 fatty acids, vitamin D or some other constituent. In a study just reported, Norris *et al* report on an observational study of dietary intake of omega-3 fatty acids and the incidence of pancreatic islet autoimmunity (IA) in a group of children judged at high risk of type 1 diabetes because of family history or the presence of an identified genetic predisposition. One group studied consisted of children recruited between birth and 8 years of age who had strong family history of type 1 diabetes. A second group consisted of newborns who tested positive for genetic markers of susceptibility. The association between intake of omega-3 and omega-6 fatty acids and the incidence of IA was examined during the follow-up. It was found that higher intake of omega-3 fatty acids was associated with a significant decrease in the risk of IA in the group identified by family history. For the newborn group, the risk of IA was inversely associated with the omega-3 status assessed by a blood test. These associations were relatively strong and statistically significant. Omega-6 fatty acids were not found to beneficial or harmful in this context. The authors comment that that if these results are confirmed in ongoing intervention study involving supplementation with DHA *in utero* and in infancy, then omega-3 fatty acids could become a mainstay for early intervention to safely prevent the development of type 1 diabetes in this high-risk group of children.

Norris, J.M. Omega-3 Polyunsaturated Fatty Acid Intake and Islet Autoimmunity in Children at Increased Risk for Type 1 Diabetes. ***Journal of the American Medical Association****, 2007, Vol. 298, No. 12, pp. 1420-28.*

IMPAIRED FASTING GLUCOSE—NEW GUIDELINES

In 2003 the American Diabetes Association revised their definition of impaired fasting glucose (IFG). The old definition was 110-125 mg/dL. The new definition significantly lowered this to 100-109 mg/dL which obviously now included many more individuals classified with a pre-diabetic condition (divide by 18 to get mmol/L, the unit used in Canada and Europe) The ADA clamed this optimized the predictive ability of serum glucose in the context of the risk of type 2 diabetes. The rates of diabetes development among IGF patients have been the subject of numerous studies based on the old definition, and the results showed a huge variation. This question has been examined in light of the new definition and reported recently in the journal *Diabetes Care.* In this paper, Nichols *et al* suggest that the large variations in progression times to diabetes were in part due to variable levels of the pre-diabetic state at the beginning of progression time assessment. In this study, an attempt was made to identify and follow patients who were carefully characterized as newly diagnosed pre-diabetics during follow-up. Progression based on both definitions was examined. This study utilized the database of a health maintenance organization (HMO) in Portland, Oregon. From a membership of almost half a million, they identified 5452 individuals who had no evidence of diabetes and who had a fasting glucose result of < 100 mg/dL prior to their first positive test, thus identifying them as newly diagnosed with IFG based on at least two glucose tests of ≥ 100 mg/dL. For those identified by the old definition, the rate of converting from newly diagnosed IFG to diabetes was on average 29 months, but for those who came under the new IFG definition, the time to diabetes was 41.4 months. Also, it was observed that a steeper rate of increase of fasting glucose, a higher body mass index (BMI), blood pressure and triglycerides, and lower the HDL level all predicted progression to diabetes. The authors point out that many patients newly identified as having IFG on the basis of the old definition progress to diabetes in < 3 years, which is the currently recommended screening interval, thus missing a potential window of opportunity for intervention. With the new definition, progression took longer on average, but was still less than 4 years. The paper makes the recommendation, on the basis of these results, that the screening interval should actually be shortened, especially for those who are obese or have a steeper glucose trajectory since this would allow more time for lifestyle interventions.

Nichols, G. A. Progression From Newly Acquired Impaired Fasting Glucose to Type 2 Diabetes. ***Diabetes Care****, 2007, Vol. 30, pp. 228-33.*

Editor's comment: Focusing attention on fasting glucose levels seems very important in view of these results which now highlight what has been considered only mildly elevated levels between 100 and 110 mg/dL. Early identification of impaired fasting glucose could enable some to successfully prevent progression to diabetes. The problem is that during routine physical examinations, the blood work may not represent the fasting state since this requires in many cases a very long fast (for an afternoon appointment) or a special trip to have blood drawn in the morning. Some individuals measure their own blood sugar periodically and then of course getting a fasting number is easy. However, those who do this should be warned that vitamin C intake, especially in amounts larger than a few hundred mg, can artificially elevate blood glucose results due to interference with the chemistry of the test. This in fact also seriously complicates acquiring data on pre- and post-meal levels if one takes large doses of vitamin C. The interference is easily tested by doing a control experiment, i.e. measuring a fasting level, taking vitamin C and a half-hour later retaking the fasting measurement.

NEWS BRIEFS

ALCOHOL AND POST-MEAL GLYCEMIA

An Australian study has found that an alcoholic beverage either before or with a high-carbohydrate meal favorably modulated the blood glucose response. Blood glucose was monitored over a two-hour period after consumption of a white bread meal which alone causes blood glucose to rise (glycemia) to a maximum in about 45-60 minutes and then to decline to near the pre-meal level by two hours. The lower the peak value and the faster the decline the better. The alcoholic beverages provided 20 g of alcohol which corresponds to between one and two drinks. Beer, wine and gin all produced similar beneficial effects by reducing the magnitude of the glycemic peak. Beer was effective in reducing glycemia despite having a higher carbohydrate content than wine or gin. The authors suggest that the physiologic mechanism may involve the ability of alcohol (ethanol) to inhibit new glucose formation and the glucose output of the liver. The authors suggest that this property of alcoholic beverages to moderate post-meal hyperglycemia may be an additional mechanism whereby moderate alcohol consumption with or before meals improves glucose metabolism and lowers the risk of developing glucose-related chronic diseases.

Brand-Miller, J.C. et al. Effect of Alcoholic Beverages on Postprandial Glycemia and Insulinemia in Lean, Young, Healthy Adults. ***American Journal of Clinical Nutrition****, 2007, Vol. 85, pp. 1545-51.*

ALCOHOL CONSUMPTION AND DIABETES AMONG OLDER ADULTS

A large population-based prospective follow-up study which was designed to examine whether self-reported moderate alcohol consumption was associated with lower incidence of type 2 diabetes has just reported in the journal *Obesity*. Alcohol consumption data was acquired at enrollment and during follow-up examination for over 4600 participants free of diabetes. Diabetes was defined as using diabetes medications or a fasting blood glucose of ≥ 126 mg/dL (7 mmol/L). The average follow-up was 6.3 years and the average age approximately 72. The percentage of males in the various categories of alcohol consumption ranged from 28 to 58%. Alcohol was found to be protective (approx. 40% risk reduction) only for current drinkers consuming up to 7 drinks per week compared with abstainers. The source of the alcohol did not influence the association. However, the number of cases observed was not large and attempts to investigate gender dependence mostly produced insignificant results.

Djousse, L. et al. Alcohol Consumption and Type 2 Diabetes Among Older Adults: The Cardiovascular Health Study. ***Obesity****, Vol. 15, No. 7, pp 1758-65.*

CARDIOVASCULAR RISKS OF HIGH NORMAL BLOOD PRESSURE

Hypertension (systolic ≥ 140, diastolic ≥90 mm Hg) is widely acknowledged as a risk factor for cardiovascular (CV) events. However, this risk is associated with blood pressure over a much wider spectrum of values and no evidence of a threshold exists down to at least 115/75 mm Hg. In a follow-up study from Harvard just published in the *British Medical Journal,* the CV risk associated with high normal blood pressure (systolic 130-9, diastolic 85-9) was investigated in a cohort of female health professionals. The study extended over an average of 10 years and the mean age was 53-57.

Compared with women with high normal blood pressure, those with normal blood pressure (systolic 120-9, diastolic 75-84) had a 39% reduced risk of a major cardiovascular event (stroke or heart attack). Women who remained normotensive during the follow-up had a 36% lower incidence of major CV events compared to those who progressed to actual hypertension. The authors comment that women with high normal blood pressure need close monitoring and lifestyle modifications.

Conen, D. et al. Risk of Cardiovascular Events Among Women with High Normal Blood Pressure or Blood Pressure Progression: A Prospective Cohort Study. ***British Medical Journal****, E-published ahead of print*.

HOW WOMEN CAN DRAMATICALLY REDUCE THEIR RISK OF A FIRST HEART ATTACK

In a study from the famous Karolinska Institute in Stockholm and the Boston University School of Medicine, which was based on a prospective Swedish cohort of over 24,000 postmenopausal women free of coronary heart disease at baseline, the investigators examined the impact of consuming a healthy diet and moderate alcohol consumption combined with being physically active, not smoking and maintaining a healthy weight on the risk of a heart attack. The follow-up was about 6 years. The low–risk diet was characterized by a high intake of vegetables, fruit, whole grains, fish, and legumes combined with ≥ 5 g of alcohol per day (approx. 1/3 of a drink). When this was combined with at least 40 minutes of daily walking or bicycling and one hour of weekly exercise and a waist/hip ratio of < 0.85, the result was a sensational 92% decrease in relative risk of a first heart attack as compared with women without any low-risk diet or lifestyle factors. This result was adjusted for age, education, family history of a heart attack, presence of high cholesterol, or hypertension, use of hormone therapy, aspirin use and total energy intake.

Akesson, A. et al. Combined Effect of Low-Risk Dietary and Lifestyle Behaviors in Primary Prevention of Myocardial Infarction in Women. ***Archives of Internal Medicine****, Vo. 167, No. 19, pp. 2122-27.*

Editor's comments: These results do not really constitute anything either new or unexpected, although the risk reduction is certainly noteworthy. It is of interest that the investigators used the waist/hip ratio as a surrogate for a healthy weight, with the so-called pear shape desirable (as compared to the apple shape). In other words, a healthy weight in this study meant low abdominal fat.

RESEARCH REPORT

Cholesterol – A Review: Part II

by William R. Ware, PhD

CHOLESTEROL AND MORTALITY

"To arrive at a contradiction is to confess an error in one's thinking; to maintain a contradiction is to abdicate one's mind and to evict oneself from the realm of reality" Ann Rand

As discussed in Part I, mainstream medicine regards the cholesterol-heart disease connection as an established fact. It has been elevated almost to a sacred belief. Anyone who questions the foundations of this hypothesis runs the risk of being branded a heretic or someone who is unable to appreciate the wisdom and beauty of one

of medical science's outstanding achievements. Many careers have been built on the Cholesterol Hypothesis, careers replete with high profile medical academic positions, drug company supported lectureships and consulting and financial support for research. Any medical professional who openly expresses serious doubts runs the risk of being ostracized by his or her peers. But there are indeed deniers and skeptics, and it seems important that Newsletter readers are aware of their views [1,2]. Avid readers of the British journals *The Lancet*, the *Quarterly Journal of Medicine* and the *British Journal of Medicine* are probably among those most keenly aware of these voices crying in the wilderness. Such criticism or questioning is rare in North American Journals. But science thrives and progresses on dissent, controversy and attempts to falsify hypotheses, a fact that seems underappreciated by those who guard the conventional wisdom. Some would argue that this does a profound disservice to the progress of medical science and the ultimate discovery of so-called truth.

Painting cholesterol and in particular LDL as demons, sort of on a par with toxic substances or even pathogenic bacteria, is unfortunate since this almost totally obscures the fact that cholesterol is essential for our wellbeing. It is involved in ensuring the integrity of cell walls and in the synthesis of testosterone, estrogen, dehydroepiandrosterone (DHEA), progesterone, cortisol, and last but not least, vitamin D by photosynthesis from the exposure to skin to ultraviolet light. We produce cholesterol in the liver, and in general, high dietary consumption results in lower endogenous production, and many feeding studies have found virtually no dependence of serum levels on dietary intake [3]. This is obviously inconsistent with the conventional wisdom which suggests limiting the dietary intake of cholesterol, a recommendation which the food industry picked up on and has played to the limit. Finally, the Cholesterol Hypothesis has resulted in widespread screening and a vast amount of anxiety, stress and pharmaceutical intervention over cholesterol levels labeled elevated and declared dangerous and even life-threatening.

What we will call the Cholesterol Hypothesis simply states that that high levels of total cholesterol, i.e. TC and LDL cholesterol (LDL), cause atherosclerosis and are associated with elevated risk of developing coronary heart disease. The word cause is important in this context because cause is relatively difficult to establish in many human disorders and CHD appears to be one of them. The reason in part is the extraordinary complexity of the sequence of events associated both with the development of atherosclerosis and the events leading to an acute coronary episode, e.g. a heart attack. One thing that appears clear is that the simplistic view of cholesterol clogging up ones arteries (the kitchen drain analogy) is just that—simplistic. The evidence against the Cholesterol Hypotheses as regards cholesterol-causing atherosclerosis was reviewed in Part I.

STUDIES CONCERNING CHOLESTEROL AND MORTALITY

Part II of this review series will deal with the question of cholesterol levels and both overall mortality and coronary heart disease mortality in men and women of all ages who are free of coronary heart disease as evidenced by the absence of chronic or acute angina, a history of a heart attack intervention to open an artery or insert a stent or coronary artery bypass. One frequently sees the concern put forward in the medical literature that some intervention or procedure has not been proven to favorably influence mortality and thus its value is questionable until this aspect is settled in randomized trials. In fact, critics of screening frequently use this as a "gold standard." Some consider the impact on mortality to be an important if not essential factor in the risk-benefit equation and in addition, there is always the possibility that an intervention or procedure actually increases mortality. In addition, impact on mortality is viewed by some as important in judging risk factors. Overall mortality is a relatively easily established endpoint because there is little room for debate since the patient is dead, but disease specific mortality is another matter since in may not always be clear as to what was actually the cause of death and death certificates can be inaccurate or even simply wrong about this.

One of the largest and most recent studies to address the mortality issue was published in 2004 and involved almost 150,000 Austrian men and women ages 20 to 95 years [4]. The study involved multiple evaluations of total cholesterol over a 15-year period between 1985 and 1999. Overall (all-cause) mortality and CHD mortality were evaluated by comparing the lowest and highest quartiles of TC with the middle quartiles used as reference. The following results are of particular interest.

- For men, there was no statistically significant association between all-cause mortality and high TC (> 248 mg/dL) for age > 50 years. For high TC, there was a weak association for ages < 49 years. For *low* TC (<187 mg/dL) there was an increase in the mortality rate.

- For women, there was no statistically significant association between high TC (> 244 mg/dL) and all-cause mortality at any age. For *low* TC (< 184 mg/dL), there was an *increased* risk of all-cause mortality for ages >49 years of age.
- For men, high TC was significantly associated with CHD mortality for the age group 20-49 years, and a weak positive association was also found for those ≥ 65 years.
- For women, high TC was associated with weakly elevated CHD risk only in the age group 20-49. However, some studies discussed below failed to find this enhanced risk.
- For both men and women, there was no association between either high or low TC and stroke mortality, but low TC was associated with increased risk of cancer mortality in men 50-64 years and women of >50 years of age.

Thus for overall mortality, high TC was not a significant issue for men over 50 or for women at any age, but in fact there was evidence of increased overall mortality associated with low cholesterol. For men under 50 years of age, overall mortality exhibited a U-shaped curve vs. TC. For women, the mortality rate curve which has been seen in many studies is more or less flat at high to intermediate TC levels and then slopes upward indicating increased mortality associated with low TC.

The weak positive association between CHD mortality and high TC for men over 65 is inconsistent with a large number of earlier studies. Ravnskov has summarized these studies in a recent commentary [5]. His review summarized 13 studies, the largest 4 of which involved over 12,000 men and women, where 7 studies found that the lower the TC or LDL, the higher the mortality, and all 13 studies found that high TC or LDL did not predict increased mortality in this age group. Seven of these studies had subjects in the age group 60-65 years and one exhibited an inverse relationship where increasing TC decreased coronary mortality (this was actually part of the famous Framingham Study).

Similar results related to elderly men were reported for the Honolulu Heart Program follow-up study which involved over 3500 men followed for a maximum of 20 years [6]. The age range was 71-93 years. Mean cholesterol levels for the quartiles were 149, 178, 199, and 231 mg/dL. When the lowest quartile for TC was used as reference, the relative risk for all-cause mortality decreased (0.72, 0.60 and 0.65) as TC levels increased. Thus there was benefit rather than risk associated with high TC as it relates to all-cause mortality. When results from the first year of follow-up were excluded, similar risk reduction with increasing TC were found. This argues against the low levels being due to preexisting illness. In addition, the long-term follow-up in this study, in the opinion of the authors, renders the hypothesis untenable that the low TC effect is due to undiagnosed preexisting conditions that reduced TC levels. The authors state that, "We have been unable to explain our results." This could be translated into a statement that the results are not in accord with the conventional wisdom.

In a U.S. study involving over 10,000 men and 8600 women, the relationship between TC and all-cause mortality was determined over a follow-up period of 22 years [7]. There was no stratification by age. For women, there was no significant association with overall mortality and TC. A third of the women had TC < 201 mg/dL and a third had TC > 240 mg/dL. For men, the only positive association was for TC > 240 mg/mL, but the relative risk was the lowest among all the risk factors that gave a positive association
(e.g. blood pressure and smoking).

In a large study of Korean men aged 30-65, it was found in a 6.4 year follow-up a low cholesterol level (< 165 mg/dL) was associated with increased risk of all-cause mortality [8]. The risk of CHD mortality was found only for men with the highest cholesterol levels (≥ 252) but there was no stratification by age. Thus this study also found a U-shaped relationship between overall mortality and TC. The strongest disease specific increase in mortality with decreasing TC levels was seen for cancer. The authors rule out the possibility that this was due to preexisting cancer since attempts were made to exclude patients with cancer or precancerous condition at baseline, and the increased risk of cancer with decreasing cholesterol levels remained significant throughout the 5-year follow-up period. This is an important point since the conventional explanation offered by mainstream medicine for the increased cancer mortality with decreasing cholesterol levels is that it is due to a preexisting condition that resulted in the low level. Also, the absence of increased cancer incidence in studies where cholesterol was aggressively lowered with statins in studies for secondary prevention or with very high risk

individuals does not appear relevant to the above issue since the patient population was different and there is the possibility that the statin drugs have anti-cancer properties unrelated to cholesterol lowering.

Studies published very recently present the same picture. Mortality was significantly correlated only with a low level of TC (≤ 160 mg/dL) in a small group of men and women 84 years or older [9]. In as study of over 300,000 Korean women age 40-64, no significant association was found with TC and CHD mortality for the 40-55 age group of pre- or postmenopausal women. For the 56-64 age group, the only significant association was for TC levels ≥ 236 mg/dL, i.e. the highest quartile. Given that all other associations were non-significant, this single result may be a fluctuation [10]. Finally, in a study of individuals presenting with ischemic stroke (from a blood clot) it was found that higher cholesterol levels favored minor strokes and thus post stroke mortality was inversely related to cholesterol [11]

Stamler *et al* examined the question of the relationship between TC and all-cause mortality and CHD mortality by an analysis of three prospective studies involving men 39 years or less of age [12]. One study had a mean age of about 30, another 32 the third study 37 years. In men in this age group, the overall and CHD mortality risk was elevated when those with elevated TC levels were compared to those with TC < 160 mg/dL but in the largest of the three studies which involved over 60,000 participants, significant increased in all-cause mortality was seen only for levels above 230 mg/dL when TC was stratified into quintiles. The two other studies revealed CHD mortality risks in all quintiles above the reference quintile (< 160 mg/dL). These results are consistent with studies discussed above where the data was stratified by age. The authors conclude that these results suggest a longer life expectancy for younger men with favorable cholesterol levels.

Thus there appears to be little data to indicate that elevated cholesterol levels are positively associated with CHD or overall mortality and in fact the opposite appears fairly well established, low cholesterol levels are accompanied by elevated mortality. Young men appear to be an exception. This will be discussed below.

CHOLESTEROL AND SUDDEN CARDIAC DEATH

In the U.S. population, about 65% of the cardiac related deaths in 1998 in adults aged > 35 were due to so-called sudden cardiac death (SCD) [13]. As de Lorgeril and Salen point out in a recent short paper in the journal *Nutrition, Metabolism and Cardiovascular Diseases* [13], two studies indicate that high cholesterol levels are not a risk factor for SCD. They point out that these findings are surprising given the widespread view that high cholesterol is a major risk factor for CHD death. In one study, over 121,000 women aged 30-55 with high cholesterol were followed [14]. The other study involved men with a mean age of about 60 (range 40-84) and a range of TC of 196-247 mg/dL [15].

Thus the picture emerges that if cholesterol levels are considered in the context of overall or CHD mortality high cholesterol is only an issue for young men and appears protective for women of all ages and men over 50 years of age. However, this applies to individuals who do not have coronary heart disease.

The current guidelines [16] of the National Cholesterol Education Program for TC (mg/dL) are:

Desirable	< 200
Borderline High	200-239
High	≥240

It seems noteworthy that these guidelines are not stratified by either age or gender. While the guidelines emphasize LDL, to a large extent TC is a surrogate for LDL in that high TC almost always implies high LDL. The guidelines also focus on risk of CHD rather than mortality, but the issue being discussed here is in fact mortality and whether or not serum cholesterol levels are related to either CHD mortality or all-cause mortality. However, the guidelines do introduce age and gender, but only when the estimation of risk is with the Framingham risk factor calculator. In one version of the Framingham data, risk for CHD includes fatal or non-fatal heart attack and unstable angina. In another version fatal and non-fatal heart attacks are the only endpoints.

HOW ABOUT THE ENHANCED RISK OF CHD IN YOUNG MEN WITH ELEVATED TC?

It seems obvious the there is an anomaly associated with young men and the risk of CHD mortality associated with elevated TC. Why for example, does the risk not persist in older individuals where the exposure to

circulating cholesterol is much longer? It does indeed appear to be true—high cholesterol predicts CHD in young and middle-aged men. But if cholesterol is merely a marker and plays no role in causative mechanisms, then the problem posed by young men can be resolved if some mechanisms unique to this age and gender group are responsible for cholesterol elevation. It has been suggested [5] that one factor may be stress which is well known to elevate serum cholesterol levels, and which would be expected to peak in age period prior to 50. Ravnskov [5] suggests a number of factors which can be expanded upon. This is the age where most men are in the midst of their professional careers, in many cases subject to great stress, even harassment. After all, it is well known that many individuals hate their jobs, their boss, the part of the country where they work, etc. There is the ever present risk of being fired, making mistakes that lead to bankruptcy, loosing ones job because of downsizing or failing to achieve or get promoted or get that much desired executive position, etc., etc., etc. There is the worry of loosing ones job at an age where it would prove difficult if not impossible to get an equivalent one. This is the age where marital break-ups are common and are generally highly stressful, where teenage children drive their parents mad or frantic with worry. It is when ones children may succumb to drugs and alcohol, and the age where parents sometimes have to contend with a child's unwanted pregnancy. One could go on indefinitely with the potential horrors that might confront the middle age man.

There have been a number of studies that examined the association between cholesterol levels and work-related stress. While it is true that the higher the stress the higher the serum levels, the magnitude of elevation is small and does not seem sufficient to support the idea that this is the mechanism giving rise to the anomalous effects seen in young men, which incidentally includes a weak but significant correlation between CHD in general and TC. Thus there is a problem with Ravnskov's suggestion. However, studies of cholesterol and CHD events or mortality that correct for confounding have of necessity failed to take into account at all one confounder, the magnitude of blood pressure changes due to stress. If resting blood pressure is measured and used as a variable in adjusting the association between CAD and cholesterol, this ignores the fact that higher levels of cholesterol appear to be associated with enhanced or exaggerated response to stress (hyper-response) and hyper-responders have enhanced CHD risk in response to stress. Thus in the population of young men, there will be these hyper-responders who will on average have considerably higher cholesterol levels, but it is the hyper-response of blood pressure to stress that increases the risk and thus the action of cholesterol is indirect. The impact of large fluctuations in blood pressure occurring on a daily basis in response to stress, either work related or domestic, would be the direct but unmeasured association with increased risk of CHD mortality or events. This could account for the modest correlations between CHD mortality or CHD events and cholesterol in young men who are exposed to a higher level of stress than older men and who may cope with stress less successfully than women. If studies had adjusted for the magnitude of blood pressure response to stress challenges it is suggested that the modest connection between cholesterol and CHD risk might disappear [17]. But operationally this appears impossible in studies large enough to provide adequate statistics since all that is practical to measure is resting blood pressure and it is obviously impossible to duplicate in a clinical examination or screening session the day- to-day stress of a toxic workplace or the stress associated with domestic problems.

In his recent book *The Myth of Cholesterol*, Dr Paul Dugliss, M.D. makes a case for stress being so important in the etiology of CHD that it renders cholesterol to a position of near irrelevance. He compares typical estimates of risk reduction due to stress reduction with risk reduction from cholesterol lowering drugs. The former can result in risk reductions of up to 540% for heart attacks, whereas typical risk reduction with lipid lowering is about 25% (but only in the subgroups where it works at all).

This view is strongly supported by results from the INTERHEART study, a case-control study involving subjects from 52 countries that examined the relative importance of risk factors for heart attacks [18]. It was found that psychosocial factors including stress at work and at home, general and financial stress, stressful life events, and depression resulted in risk of heart attack that was greater than diabetes or smoking, both of which are major traditional risk factors. Diabetes alone automatically confers a 10-year risk of CHD or CHD events of greater than 20%, i.e. high risk.

HOW ABOUT HDL, THE SO-CALLED GOOD CHOLESTEROL?

A rather small fraction of TC is due to HDL cholesterol, the so-called good cholesterol and TC is not a good surrogate for HDL. LDL according to the conventional wisdom is the bad guy, but some point out that this may only apply to the oxidized form, something that appears to be rarely measured in routine physical exams. Thus

the following question: are the protective properties of HDL borne out in the relationship between HDL levels and mortality? Several studies have addressed this issue.

A study from Finland [19] looked at CHD mortality and HDL. The variation of HDL levels with age over the total range from 25 to 64 was very small and thus the results without age stratification are of interest. For both men and women, the risk reduction for CHD mortality was about 10% per 4 mg/dL increase in HDL and was statistically significant. This appears to be clinically relevant since the difference between high and low HDL is about 20 mg/dL.

In a study of type 2 diabetics, cardiovascular mortality rates were independent of TC or LDL but significant protection was seen with HDL levels greater than about 53 mg/dL. The follow-up involved over 10,000 person-years and age did not influence the protective effect of HDL. However, adjustment for a large number of potential confounders reduced the benefit in all but those >70 years of age [20]. Thus there is nothing in these studies which contradicts the belief that high levels of HDL are protective.

CONCLUSIONS

Ravnskov points out that if high TC or LDL were an important cause of CHD or CVD, it should be a risk factor for both genders in all populations and in all age groups. But in many populations the association between TC and mortality is absent or even inverse, i.e. just the opposite, where increasing TC is associated with lower coronary and total mortality. In the elderly high TC is associated with longevity in most studies. The results with the elderly are especially significant because both the highest mortality and the greatest incidence of CVD are seen in the elderly. Ravnskov advances the hypothesis that the beneficial effects of high cholesterol on the immune system may explain why sometimes an inverse association is found between TC and mortality and as well inverse associations seen sometimes which contribute to the inconsistencies that characterize the angiographic studies which attempt to link TC or LDL and atherosclerosis [5].

It is also noteworthy that the vast majority of acute coronary events such as heart attacks occur after the age of 60, an age where the question of cholesterol and either CHD mortality or overall mortality becomes an issue only in that high TC appears either neutral or decreases rather than increases the risk of death. Thus, for a large fraction of the adult population, concern about high cholesterol amounts to worrying about something that appears to have no bearing on CHD mortality, and perhaps even increase life expectancy.

There are millions of individuals taking cholesterol-lowering drugs. The number worrying about their high cholesterol must be very large indeed. The total drug company income from statins is approximately $55 billion (not a misprint) per year. Today, recommendations are mainly based on LDL cholesterol, medical history and the presence of traditional risk factors, two of which (Framingham) depend on TC and HDL. But levels of LDL are closely tied to TC. Thus the studies that examined mortality as a function of TC are relevant. The evidence or lack thereof presented above would suggest that the recommendation of these drugs for women and the elderly who are free from symptomatic CHD and have not had a heart attack is not based on evidence involving risk of either CHD mortality or all-cause mortality, and some regard this as the most important consideration. If low TC indeed increases mortality, then this becomes an additional consideration, one that probably never comes up in consultations since mainstream medicine dismisses all the data regarding this problem with arguments given above. In addition, in younger men, high TC may lead to inappropriate therapy if the real problem has to do with high stress. Also, obsession with cholesterol levels may result in avoiding a number of potential actions associated with primary prevention. Since statin drugs have side effects, the above considerations assume added significance.

Thus we have now seen in the first two parts of this series that there does not appear to be a connection between CHD mortality or all cause mortality and circulating cholesterol. Nor are cholesterol levels associated with the extent of atherosclerosis. In connection with this second point, the British physician Malcolm Kendrick, a long-time student of the Cholesterol problem, poses three key questions in his book *The Great Cholesterol Con*:

- Why don't veins develop atherosclerosis?
- Why does atherosclerosis develop in discrete (separate) plaques?
- If high LDL level causes atherosclerosis, how can vast numbers of people with low LDL levels get the same disease?

When one thinks about it, it is remarkable that atherosclerosis does not develop in veins. They have the same cellular wall structure as arteries and they are exposed to identical levels of TC and LDL. If an artery is replaced by a vein, as in bypass surgery, the vein now acting as an artery can develop atherosclerosis as frequently seen in bypass restenosis, but replace a vein with an artery and the artery appears protected against atherosclerosis. Kendrick concludes that this has something to do either the position in the body or the function of arteries. But how can LDL be the culprit since it remains constant throughout the circulatory system?

For the discrete plaque patch puzzle, he likens this to sunbathing and getting burned only in patches in spite of uniform exposure, the analogy being with the uniform exposure to the hypothetical causative agent cholesterol. If plaques form in damaged areas and LDL does not itself damage the arterial walls, then something else causes heart disease.

Defenders of the Hypotheses respond to the third question by simply saying the low LDL levels that still result in atherosclerosis are not really low but are in fact high, and that almost everyone has the disease of hypercholesterolemia and clearly need aggressive therapy. Mankind has evolved, perhaps even over the past century, such that they now have a deficiency disease, where the deficiency is a prescription drug. Critics tend to view this explanation as total nonsense. This view will be examined and documented in Part III of this series.

A simple solution to the problems posed by these three questions is that the Cholesterol Hypothesis is false.

There are a number of other important issues associated with cholesterol and health. Some of these will be addressed in the final review of this series. They include the relationship of cholesterol levels and stroke, the various interpretations of the recent cholesterol lowering trials, and the suggestion that most of us should be taking the so-called polypill.

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

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In the context of prevention, risk factors for prostate cancer will always be of intense interest. In this issue, a new study is discussed which addresses this matter in a large prospective follow-up study with periodic updating of potential risk factors. Readers may find the results less than satisfying but nevertheless suggestive of positive actions than may help.

Robotic surgery to remove the prostate is in its 7th year and institutions continue to report their experiences with this interesting procedure which is minimally invasive by some definitions and certainly results in a much shorter hospital stay. In this issue we review a report from the Vattikuti Urology Institute at the Henry Ford Hospital in Detroit, MI, where data from over 2700 operations has been collected into a report concerning all aspects of the outcome. They have been obtaining very good results. This is of great interest because this Institute was one of the first to introduce the operation and today at that hospital it is the procedure of first choice for prostate removal among both surgeons and patients. In fact, there is concern that the urologic resident surgeons will not gain enough experience in open radical prostatectomies. While the Ford Hospital results make the robotic option appear very attractive, if one wishes to select this option it is still necessary to find a center where the technique is well established and the surgical staff well up on the learning curve. A good choice would seem to be a center which has actually published their track record and carried out a large number of procedures. Many individuals do not have the luxury of having such a center next door or being able to travel long distances to take advantage of the apparent expertise available at such institutions, but over the next few years there should be a large number of hospitals where the learning process is more or less over or at least well advanced. However, the paper reviewed suggests that it is never really over, since the authors report continual improvement is results.

Finally, prostate issues associated with green tea and zinc are discussed, and as well, the psychological barriers associated with active surveillance for men suspected of having low-grade or indolent cancers.

Wishing you continuing good health,

William R. Ware, PhD, Editor

RISK FACTORS FOR PROSTATE CANCER. NEW RESULTS FROM THE HEALTH PROFESSIONAL'S FOLLOW-UP STUDY

This study started in 1989 and the database has been updated every four years. Initially the cohort consisted of over 51,000 male health professionals ages 40-75. Giovannucci *et al* have recently reported the latest results on risk factors for prostate cancer derived from this study [1]. With regard to incidence of the disease, only family history of prostate cancer, being African- American, or consuming alpha-linolenic acid had positive associations. In addition, tomato sauce consumption was inversely related, i.e. low consumption was a positive risk factor (see the November issue for a discussion of recent studies on tomato sauce, lycopene, and prostate cancer risk). Only two or these risk factors are modifiable. The common source of alpha-linolenic acid is flax seeds or oil. Some consume one or the other of these for the purpose of increasing the omega-3 fatty acid intake, but the important 0mega-3 acids appear to be the longer chain acids such as EPA and DHA, and human biochemistry is very inefficient in the conversion. Thus fish oil or purified EPA and DHA appear to be better choices than alpha-linolenic acid quite apart from the apparent risk of prostate cancer. For fatal prostate cancer, the positive risk factors were cigarette smoking, excessive weight (BMI), family history, height, total energy consumption, and calcium intake. Physical activity was inversely related. Only for high calcium intake was there a close correspondence for positive associations between high-grade cancer (Gleason ≥ 7), and advanced or fatal cancer. Tomato sauce was protective for non-advanced and low-grade (Gleason ≤ 6) cancers. Thus the authors point out that reducing prostate cancer mortality through lifestyle and diet may generally more feasible than preventing its occurrence.

It is interesting that high intakes of calcium keep turning up in prostate risk studies. This is discussed in some detail in our book. Men need to worry about their total intake from supplements, diet and anti-acids containing calcium carbonate. In this latest study, the threshold for increased risk from calcium intake occurred around 1200 mg/day. Calcium carbonate, the active ingredient in popular anti-acids, contains 40% elemental calcium. Thus the extra-strength 750 mg tablet contains 300 mg of calcium.

ROBOTIC RADICAL PROSTATECTOMY—FIVE YEAR OUTCOME AFTER 2766 OPERATIONS

Robot-assisted radical prostatectomies were introduced into prostate surgical practice starting in 2000. Since then a number of centers have acquired the equipment and surgeons have learned and perfected the techniques required. In some institutions, the robotic approach, which is minimally invasive, generally accompanied by insignificant blood loss, has a time to discharge of only one or two days, and is the treatment of choice by both physicians and patients alike. As discussed in our book, there is definitely a learning curve and it varies from institution to institution. In general, those who are good at the robotic procedure achieve results that are comparable to the standard open prostatectomy. Now surgeons at the Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI report five-year outcomes after 2766 procedures using the da Vinci robotic system [2]. The mean surgical time was 154 minutes with 116 minutes of actual robotic console time. Estimated blood loss was 100 mL and 96.7% of patients were discharged within 24 yours of surgery. Only two patients were "converted" to open surgery and this was due to extensive adhesions from prior surgery. The procedure was aborted in eight patients, two because of visually obvious positive lymph nodes, two because the disease involved the bladder, and four for pulmonary comorbidity or obesity. In terms of a percentage of the total number of procedures done, these numbers are obviously very small.

Complete sexual function outcome data was available only for 910 patients. Of those without potency problems prior to surgery, almost 80% reported satisfactory resumption of sexual activity, although almost half used drugs such as Viagra. With regard to urinary function, the median time to complete urinary control was three weeks (range 1-120 weeks). The time to urinary control decreased as the surgeons gained experience. At the median follow-up of 22 months, 7.3% of men had PSA recurrence and the 5-year freedom from PSA recurrence was 84%. This figure must be viewed in the light of the fact that this cohort included a significant number of individuals with aggressive cancer. Also, throughout the period in question, the positive surgical margin rate decreased, which the surgeons attributed in part to the learning curve. Only 9 patients died during the 71 months follow-up and of these, only two died because of metastatic prostate cancer.

The patient characteristics with ranges were as follows:

- Mean age—59.9 years (39-80)
- Mean PSA—6.4 ng/mL(0.1-77.7).
- Pathological stage for the last 200 cases: T2a—9.5%, T2c—52.5%, T3a--30%, T3b—7.5%
- Pathological Gleason score, last 200 cases: 5—1%, 6—30%, 7—54%, 8—7.5%, 9—3.5%
- Number of positive surgical margins in the last 200 cases—4%.

Readers unfamiliar with the staging, Gleason score or the significance of positive surgical margins are referred to our book. The pathological Gleason score and stage are determined from the removed prostate and provide a more accurate assessment of the nature of the disease. It was concluded that robotic assisted prostatectomy remains a safe and reproducible treatment for men with clinically localized prostate cancer.

These results leave little doubt that robotic surgery has come of age. Any man contemplating prostate surgery will probably want to consider this option. The very short hospital stay, the presumably low risk of infection, and the low blood loss seem very attractive. Even if traveling a considerable distance is necessary, it may be worth it. The only problem is finding a center with a track record that is both long and good! This is a nontrivial problem because location and cost also enter in to the decision. If robotic surgery is being proposed, it is wise to ask the surgeon who would do the operation just how many he has done and how many the center as a whole has done. If the numbers are small, then obviously this puts one in what might be a not so great position on the learning curve. Some urologists may be able to provide a list of centers in the country or area in question where the technique is well established, but other may not have such information. Some centers publish their track records in the peer-review literature, and some also “advertise” on the Internet. The Henry Ford Hospital has done both.

ZINC INTAKE AND PROSTATE CANCER RISK

Zinc is an essential mineral in human biochemistry and acts as a cofactor for more than 70 enzymes. The recommended daily intake for men is 11 mg/day and high doses (> 150 mg/day) may reduce the immune function. Studies that found lower zinc concentrations in prostate cancer tissue as compared to normal prostate tissue have encouraged the notion that supplementation with zinc is beneficial in this context. A recent study from Italy does not support this notion and in fact finds increased risk. In a case control study based on assessment of dietary intake, the cut-point for low intake was 9.93 mg/day and for high intake, (fifth quintile) > 15.65 mg/day. For the comparison between the lowest and highest quintiles, a 56% increase in risk of prostate cancer was found after correcting for age, education, physical activity, family history of prostate cancer, BMI and total energy intake [3]. These results are consistent with those of Leitzmann *et al* [4] who found increased risk of prostate cancer associated with large doses (> 100 mg/day) over long periods (> 10 years).

Many popular multivitamin preparations contain approximately 15 mg per tablet or capsule and it is not uncommon for someone to take two a day. Thus in view of this recent study, there is the potential for increasing the risk of prostate cancer from this source alone.

GREEN TEA AND PROSTATE CANCER RISK

A large and long-term prospective follow-up study concerning the consumption of green tea and the risk of prostate cancer has just been reported. Over 49,000 Japanese men were included in two cohorts recruited in 1990 and 1993 and followed until the end of 2004. Green tea consumption was determined with a questionnaire. Green tea was not associated with the occurrence of localized prostate cancer but a significant protective result was observed for the risk of advanced cancer. When men drinking 5 or more cups a day were compared with those consuming less than one cup per day, a reduced relative risk of advanced cancer of approximately 50% was found that achieved statistical significance. This result was adjusted for confounding from intake of fruits, green and yellow vegetables, dairy food, soy food, and genistein consumption. The authors comment that these results are supported by many animal studies and suggest the next step should be a clinical trial in humans [5].

PSYCHOSOCIAL BARRIERS TO ACTIVE SURVEILLANCE FOR LOW-RISK EARLY PROSTATE CANCER

Active surveillance must be differentiated from watchful waiting. The latter generally refers to palliative care whereas the former involves postponing treatment with the hope that it will not be necessary, but using a surveillance protocol that will trigger a recommendation of treatment if further waiting significantly compromises the chance of a cure. Johns Hopkins and the Memorial Slone Kettering Cancer Center are two high-profile institutions that have championed active surveillance and developed and tested protocols and selection criteria. Justification for this approach involves the observation that a certain fraction of newly diagnosed men, especially in the PSA era, have indolent or very slowly progressing cancers that may never during their lifetimes cause significant problems. Those that are identified and agree to active surveillance are tested periodically in order to determine whether or not the criteria for selection are still being met. Generally this includes an annual biopsy as well as frequent PSA determinations. For a variety of reasons, active surveillance or even the decision as to whether or not to elect this option, places some men under considerable psychological stress. Pickles *et al* have recently reviewed what has been observed in this regard. The general picture they present is of interest even if it involves both patients under watchful waiting and active surveillance.

Some of the psychological forces present are as follows:

- Pressure from family and friends to do something positive about the cancer.
- The natural response that requires fighting the disease as if it were the enemy to be defeated.
- Lack of control implicit in doing nothing positive but instead monitoring possible progression.
- Knowledge that there may be a growing cancer that is asymptomatic, and that they are just letting it happen.
- Lack of confidence that selecting the option of active surveillance was the correct and wise move.
- Stress can be generated by reflecting on the merits of “cutting it out and being done with it” and ticking bomb anxiety.
- Anxiety caused by monitoring which is partly due to meaningless variations in PSA that are interpreted as bad news. Monitoring provides frequent reminders of the presence of the disease. Stress leading up to each PSA test has been termed PSA-itis and is seen in both active surveillance, watchful waiting and treated patients.
- Anxiety and stress can be generated by the knowledge that the physician in charge may not fully support anything but treatment or at least has reservations which the patient detects. Patients can also detect physician’s uncertainty and concern when, for example the PSA changes, even if the protocol specifically requires a biopsy to trigger treatment and downplays the importance of the PSA change.
- It is not uncommon for a man on active surveillance to change over to treatment even if the evidence available does not support this decision. This can be psychologically driven by how the individual feels at the moment or by a change of heart on the part of the physician. Physicians can also experience anxiety and feel the loss of control in active surveillance cases.

Clearly, these are serious problems. Some may be solved or moderated by strong physician support for the decision, much more effort to educate the patient regarding the merits of the option and the minimal nature of the risk of missing the window of opportunity for treatment. There is no question that support groups help and that partner attitudes are critical.

The authors close their review by commenting that it is currently estimated that half of all men with cancer detected by PSA screening receive unnecessary treatment and that the issues they review must be addressed if active surveillance is to become a widely accepted alternative [6]. In addition, a paper presented at the 2007 American Urological Association meeting in May, 2007 supports this view by reporting that out of over 7000 men studied where sufficient data was available, 16% met the criteria for low-risk disease and yet very few were being managed by active surveillance (Borocas, DA *et al*, Abstract 391)

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Editor: William R. Ware, PhD
e-mail: editor@yourhealthbase.com