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William R. Ware, PhD - Editor

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This issue highlights the Metabolic Syndrome, called by some Syndrome-X. A paper debating its utility as a diagnostic tool is discussed first, followed by a discussion of four studies that relate to the connection between cardiovascular disease and this syndrome. Two papers on fish are noted, one having to do with the risks of contaminants such as mercury vs. the benefits in connection with the heart and brain, and the other alerts readers to the fact that fish provide a very poor source of significant amounts of vitamin D. Coffee drinking continues to be featured with a discussion of two papers on its connection with heart disease and cognitive decline in the elderly.

Periodically this Newsletter has had Research Reviews which have generally been lengthy and comprehensive. This issue has a new feature—the Mini Review. This type of review aims at also being comprehensive, but is much shorter because, due to the nature of the topic, there is only limited significant literature. These will be a frequent feature of upcoming Newsletters. In this issue, a Mini-Review about the famous French Paradox is presented which, it is hoped, will provide some interesting and useful insights into one approach to a heart-healthy lifestyle.

This month's Newsletter continues the series The Prostate Monitor with an update of various aspects of prostate cancer. Included are issues related to risk reduction, diagnosis, prognosis and management. The Prostate Monitor is intended to supplement our book "The Prostate and Its Problems" with new and important information men need to know.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at <http://www.yourhealthbase.com/vitamins.htm>.

Wishing you continuing good health,

William R. Ware, PhD, Editor

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FISH INTAKE—RISKS AND BENEFITS

The benefits of eating fish are related to the content of the long-chain omega-3 fatty acids EPA and DHA. The risk is associated with a whole host of contaminants such as mercury, PCBs etc. Thus the question—do the benefits outweigh the risks? A detailed examination of this question appeared in the October 18th issue of the *Journal of the American Medical Association*. Mozaffarian and Rimm from Harvard Medical School first review the cardiovascular and neurological developmental benefits of fish and in particular the fatty acids EPA and DHA for which fish provide a significant dietary source. Numerous studies relating to the cardiovascular benefits of EPA and DHA are presented in tables and impressive graphs. DHA is also critical in the neurological development during gestation and the first 2 years of infancy. A number of studies are quoted to support the importance of maternal intake of DHA during pregnancy and while nursing. The other aspect of the question, i.e. the risks associated with contaminants, is much more difficult to address. Medical scientists obviously do not conduct experiments on humans where the dose dependence of toxicity from the contaminants in question is investigated by giving the participants toxic chemicals and observing the results. Thus data for high doses must come from accidental or occupational exposure but these levels are irrelevant in terms of the levels found in most fish. At the other end of the dose spectrum, making an association between the intake of traces of toxic materials and adverse health outcomes is very difficult and fraught with uncertainty and confounding.

This paper quotes a number of studies that relate to undesirable intakes of organic mercury for women of childbearing age, nursing mothers, and young children, but it is hard to believe that the limits are more than a rough estimate. The situation with regard to health effects of trace amounts of mercury on adults is even less clear-cut. There are reports of adverse effects of mercury on cardiovascular and neurologic health. As regards the former, the authors simply pose the question as to whether the expected benefits from fish consumption would merely be greater if mercury were not present. As regards the neurologic aspect, the evidence as to adverse effects is unclear but there is a growing body of evidence that fish consumption may favorably influence clinical neurologic outcomes in

adults, including benefits associated with ischemic stroke, cognitive decline and dementia, depression and other neuropsychiatric disorders. Translated into a useful guideline, the end result is advice not to eat shark, swordfish, golden bass and king mackerel since they typically contain more than 50 micrograms of organic mercury (methylmercury) per serving. Levels of dioxins and PCBs are low in fish and the authors take the position, based on what evidence is available, that any adverse effects from these contaminants are outweighed by the benefits of eating fish. Fish are also a rich dietary source of selenium and the authors mention evidence that some of the adverse effects of organic mercury may be mitigated by adequate intake of selenium, which incidentally is an essential dietary trace element. The bottom line is that the following fish pass muster as being good sources of EPA and DHA and are on average low in mercury: anchovies, Atlantic herring, wild and farmed salmon, sardines, and trout. These fish provide between 600 and 4500 mg per serving of EPA + DHA and contain on average 0.7 or less parts per million of mercury.

The authors also discuss plant sources of EPA and DHA. These two long-chain omega-3 fatty acids in fact do not occur in plants, but must be made in the body from alpha-linolenic acid which is present in flaxseed, canola, soybeans and walnuts. Only small amounts are converted to EPA and further conversion to DHA limited. Thus fish represent by far the best source, and the authors raise no objections to getting these fatty acids from fish oil capsules, which typically contain 20% DHA and 80% EPA with little or no mercury, and taking even 1-3 grams of fish oil, according to the authors, results in low intake of PCB and dioxins.

Mozaffarian, D and Rimm, E. B. Fish Intake, Contaminants, and Human Health. Evaluating the Risks and Benefits. Journal of the American Medical Association, 2006, Vol 296, No. 15, pp. 1885-99

Editor's comment: It is unfortunate that this article is not in the public domain since it contains an excellent summary of the cardiovascular and other health benefits of fish consumption as well as valuable data on the EPA/DHA, mercury, selenium, PCB and dioxin content of most commonly consumed fish. It can be purchased for online download from www.jama.com for \$15.00

GREEN TEA AND COLON CANCER

Studies continue to appear that examine the protective action of green tea in the context of cancer. Researchers at the University of Minnesota, Rutgers and the Shanghai Cancer Institute recently reported on what they claim is the first study to examine the association between specific biomarkers of tea polyphenols and the risk of colorectal cancer in humans. Subjects were drawn from the Shanghai Cohort Study who were between 45 and 65 years of age and had no history of cancer at recruitment. Dietary and lifestyle data was collected at enrollment and in addition, blood and urine samples were acquired and stored. The study involved 16 years of follow-up during which 162 incident colorectal cancer cases were identified and matched with 806 controls. Levels of green tea polyphenols and their metabolites (six in total) were determined in the urine samples of cases and controls. The results were stratified by quartiles or tertiles of polyphenol levels and colon, rectal and

the risks for colorectal cancer were determined. Significant results were obtained for two polyphenols, epigallocatechin (EGC) and 4'-O-methyl-epigallocatechin (4'-MeEGC) and only for colon cancer. For EGC, compared to undetectable levels, a 60% risk reduction was found for the highest urine level, and almost the same risk reduction was seen when the first vs. 4th quartile of 4'-MeEGC were compared or when the two polyphenol levels were combined. These results were consistent with epidemiologic data on green tea intake and colon cancer where a 26% risk reduction was found. The authors briefly discuss possible mechanisms including the potential for tea polyphenols to protect against the carcinogenic activity of heterocyclic aromatic amines.

Yuan, J.-M. Urinary Biomarkers of tea Polyphenols and Risk of Colorectal Cancer in the Shanghai Cohort Study. International Journal of Cancer, 2007, Vol. 120, pp. 1344-50.

RIBOSE AND CHRONIC FATIGUE SYNDROME AND FIBROMYALGIA

In a recent issue of *The Journal of Alternative and Complementary Medicine* Teitelbaum *et al* describe a small, pilot study of the use of oral D-ribose, a naturally occurring sugar, as a therapeutic measure in a group of patients with fibromyalgia (FMS) and chronic fatigue syndrome (CFS). This study was prompted by reports in the literature that ribose was effective in restoring tissue energy. Thirty-six patients completed the 1-2 month study. They received 15 grams of ribose per day in three doses and the effect was determined by before and after questionnaires concerning energy, sleep, mental clarity, pain and overall sense of well-being. A significant improvement in energy level was observed and in addition, the other outcomes all improved to a greater or lesser extent. For example, FMS patients and CFS patients reported 48% and 45% increase in energy and 39% and 37% increase in feeling of well-being. This was a very small study that was industry supported,

Teitelbaum, J.E. et al. The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study. The Journal of Alternative and Complementary Medicine, 2006, Vol. 12, No. 9, pp. 857-62.

Editor's comment: D-ribose is an inexpensive supplement which can be obtained for a little as about 10 cents a gram. There is little commercial

incentive that would prompt large clinical trials. However, in 2003 a feasibility study was done in Germany which concerned the ability of ribose to improve diastolic function and quality of life in congestive heart failure patients (CHF) (*European Journal of Heart Failure*. 2005; 5:615). A questionnaire, echocardiography and ergometer testing were used to assess benefit. The study indicated a beneficial effect on measured diastolic functional parameters and patients reported an enhanced quality of life. This is just what Dr. Stephen Sinatra has been claiming for some time. Sinatra is a board-certified cardiologist with a practice in Connecticut and is also well known for his newsletter *Heart, Health and Nutrition*. He is also an assistant clinical professor at the University of Connecticut School of Medicine. In a recent book *The Sinatra Solution—Metabolic Cardiology* he presents the basic science and the experimental and clinical evidence available up to 2005 in connection with the use of the trio of D-ribose, coenzyme Q10 and L-Carnitine to "help prevent and overcome heart disease, fibromyalgia, chronic fatigue and Syndrome X." In the book he documents remarkable success with this trio of supplements and provides detailed dose information according to the problem in question. Mainstream medicine of course rejects anecdotal evidence but unfortunately some individuals and in particular

CHF patients probably do not have time to wait for some non-profit organization to stage trials large

enough to satisfy the standards of modern evidence-based medicine.

MORE GOOD NEWS FOR COFFEE DRINKERS

COFFEE AND HEART DISEASE MORTALITY

In a study just reported in the *American Journal of Clinical Nutrition*, Greenberg *et al* report some interesting results of a prospective cohort study to test whether the consumption of caffeinated beverages exhibits a protective effect in the context of cardiovascular mortality. The study was motivated by previous studies which yielded conflicting results and by the hypothesis that caffeinated beverage consumption could ameliorate the effect of post-meal hypotension on the risk of coronary events and mortality, especially in the elderly. The analysis involved over 6500 participants aged 32-86 with no history of CVD at baseline. During an 8.8-year follow-up, there were 426 CVD deaths. Participants aged ≥ 65 with higher caffeinated beverage consumption had lower relative risk of CVD and heart disease related mortality than did those with lower consumption. For heart disease mortality, the relative risks were 1.00 (reference), 0.77, 0.68, and 0.47 for < 0.5 , 0.5-2, 2-4 and ≥ 4 servings per day. Only the result for < 0.5 servings/day was not statistically significant. The results were stronger when zero consumption was used as reference. This protective effect was found only in individuals who were not severely hypertensive and only for those > 65 years of age. No significant protective effect was found for those aged < 65 or in cerebrovascular diseases mortality for those aged ≥ 65 years. The protective effect was found only for two caffeinated beverages, ground caffeinated coffee and instant caffeinated coffee, and no protective effect from decaffeinated beverages, individually or when combined for analysis. The analysis also showed similar protective effects whether the participants with a history of CVD were excluded or included in the analysis. Adjusting for blood pressure, use of antihypertensive medication use, history of diabetes, and self-rated health gave similar results.

The authors discuss possible mechanisms that would explain these results, but they reached no conclusions. In particular, no conclusion was possible regarding the hypothesis that caffeine-induced post-meal increases in blood pressure provided protection, although they quote evidence that this effect is greater in the elderly and that diastolic and mean blood pressure tend to decrease

in persons > 70 years of age. The authors also discuss the possibility that their results were caused by one or more of the many known effects of caffeine on the cardiovascular system, some of which might be cumulative and thus offer more protection to the elderly, and they could not rule out other compounds in coffee that might explain the results. However, when the dose dependence was examined just on the basis of caffeine intake rather than beverage intake, the beneficial result and its dose dependence remained, suggesting but not proving that the active agent is indeed caffeine.

Greenberg, J.A. *et al*. *Caffeinated Beverage Intake and the Risk of Heart Disease Mortality in the Elderly: a Prospective Analysis*. *American Journal of Clinical Nutrition*, 2007, Vol 85, pp. 392-8.

Editor's comments: This study adds to the benefits of coffee consumption discussed in the February and March issues of the Newsletter. Since 80% of adults in the U.S. over 50 years of age consume coffee, one can imagine the potential disaster suggested by this study if for some reason many stopped. But this age group also represents $>80\%$ of all heart disease deaths in the U.S. in 2002. Does one conclude that this age group does not drink enough coffee??

COFFEE AND COGNITIVE DECLINE

This multinational prospective study investigated the relationship between coffee consumption and cognitive decline in elderly European men. Six hundred and seventy six men born between 1900 and 1920 were followed for 10 years. Participants at baseline who showed evidence of cognitive impairment, diabetes, history of heart attack, stroke or cancer were excluded. Coffee consumption was assessed by a questionnaire. The Mini-Mental State Examination score was used to evaluate cognitive status at baseline and during follow-up. Men who consumed coffee had a two-times smaller 10 year cognitive decline. While the results also suggested a J shaped risk curve with the maximum protection at 3 cups/day, the cognitive decline of men who drank 1, 2, 3, 4, or > 4 cups per day was not statistically different from each other. The mechanism is unknown, but the authors point to animal experiments that suggest coffee stimulates secretion of neurotransmitters which prevent beta-

amyloid-induced neurotoxicity. Beta-amyloid is strongly implicated in Alzheimer's disease. However, the authors also acknowledge that coffee contains many substances which might also be implicated in protective action in the brain.

Van Gelder, B.M. et al. *Coffee Consumption Is Inversely Associated with Cognitive Decline in Elderly European Men: The Fine Study. European Journal of Clinical Nutrition*, 2007, Vol. 61, pp. 226-32.

THE METABOLIC SYNDROME—ALIAS SYNDROME X

Studies indicate that in the U.S., one-third adults and an alarming proportion of children have the so-called Metabolic Syndrome. To many observers, it appears to represent a serious and challenging global public health problem. Nevertheless, fundamental uncertainties exist to the extent that national and international diabetes organizations have raised doubts regarding even its existence. This topic will be highlighted in this issue with inclusion of discussions of a number of recent studies.

DEFINITIONS AND CLINICAL UTILITY—TWO VIEWS

In a Perspective published recently in the *American Journal of Clinical Nutrition*, Gerald Reaven raises some interesting questions about the clinical utility of labeling someone as having the Metabolic Syndrome (MBS). Reaven is eminently qualified to raise such questions since he was the first to describe (in 1988) the set of metabolic abnormalities associated with increased cardiovascular risk, which he named Syndrome-X, and he has been active in this field ever since. In the same issue, Scott Grundy challenges some of the positions taken by Reaven.

Contrary to what some readers may assume, there are several definitions of the MBS which are not consistent in their details. They are from the World Health Organization (WHO), the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP), and the International Diabetes Federation (IDF). The NCEP and IDF definitions share four criteria with minor differences: Blood pressure $\geq 130/85$; HDL cholesterol < 40 (men) and < 50 (women); serum triglycerides ≥ 150 ; Fasting blood glucose ≥ 100 (IDF) or 110 (NCEP). While both IDF and NCEP use waist circumference as the fifth criteria, NCEP sets it at > 102 cm (men) and 88 cm (women) whereas IDF use 94 cm and 80 cm, respectively. But to have MBS by the NCEP criteria, three of the 5 criteria must be met, whereas for IDF, to have MBS one must fail the waist circumference test and meet two of the other criteria. The WHO definition requires that the

individual have type 2 diabetes, impaired glucose tolerance, impaired fasting glucose or documented insulin resistance. Reaven points out that when these three definitions are applied to a number of different clinical presentations, they are not unanimous in producing a yes or no verdict as the presence of MBS, and he further emphasizes that one can be judged free of MBS and still be at high risk for cardiovascular disease by other commonly accepted measures. In his opinion, diagnosing MBS had neither pedagogical nor clinical utility, that finding a major CVD risk factor should prompt the search for others, and suggests that the clinical emphasis should be on treating any CVD risk factor found. Grundy disagrees. In his view, the diagnostic classification of having or not having MBS is useful and should prompt strategies that will reduce all the risk factors simultaneously. This approach emphasized lifestyle changes (mainly weight reduction and exercise). He points out that the primary reason the NCEP introduced the MBS into its clinical guidelines was to emphasize the importance of lifestyle therapy in clinical practice.

Reaven, G.M. *The Metabolic Syndrome: Is This Diagnosis Necessary? American Journal of Clinical Nutrition*, 2006, Vol 83, pp.1237-47

Grundy, S. M. *Does a Diagnosis of Metabolic Syndrome Have Value in Clinical Practice? American Journal of Clinical Nutrition*, 2006, Vol. 83, pp. 1248-51

Editor's comment: Some aspects of the above debate were addressed by Stern *et al* several years ago (*Diabetes Care* 2004;27;2676-81). The authors used the NCEP definition and compared its predictive power to the Framingham 10-year Risk Score and the Diabetes Predicting Model. The latter estimates 7- to 8-year likelihood of type 2 diabetes based on age, gender, ethnicity, fasting glucose, systolic blood pressure, HDL levels, and family history. Framingham uses age, gender, smoking status, blood pressure, total and HDL cholesterol. This study found that the finding the presence of the MBS was inferior as a prediction tool as compared to the other two models for either type 2 diabetes or CVD. Moreover, combining the MBS with the other

two models did not improve the predictive performance. Kahn *et al* in a joint statement of the American Diabetes Association and the European Association for the Study of Diabetes reach a similar conclusion. They take the position that clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for MBS (*Diabetes Care* 2005;28;2289-2304). The take-home message seems to be that an individual should not be satisfied with a positive or negative MBS diagnosis but should suggest that his or her physician look at in addition least at the Framingham model, although some physicians may have trouble finding and applying the Diabetes Prediction Model. Being pronounced free of MBS does not, apparently mean that one is "home free." Also, having MBS is bad news, no matter which definition is used, but the degree of seriousness may depend on the definition used. In addition, there would seem little disagreement that lifestyle modification is an important intervention, no matter how risk is estimated. Finally, the MBS criteria have been used in a number of studies which have attempted to establish the extent of enhanced risk associated with this "diagnosis." There follow several examples.

THE METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE—A META ANALYSIS

Gami *et al* from the Mayo Clinic in Rochester, MN, have very recently reported the results of a huge meta-analysis of studies of the association of MBS and cardiovascular events and death. Included were 37 studies from 1971 to 1997 involving Over 170,000 subjects. The analysis showed that MBS had a relative risk of CVD events and death of 1.78 (95% confidence limits 1.58-2.00). For women the association was stronger and when the WHO definition was used, the relative risk was also stronger. This association remained after adjusting for traditional cardiovascular risk factors. Furthermore, the analysis revealed that the MBS confers cardiovascular risk beyond that which is associated with its component risk factors. The studies included in this meta-analysis included diverse populations including many rural and urban regions of the U.S., Norway, Sweden Finland, the Netherlands, Scotland, England, Spain, Italy, Poland, Turkey and Japan. The authors comment that given the cumulative results of these studies, investigators should design and conduct large randomized trials of aggressive dietary, lifestyle and pharmacologic interventions in individuals with MBS, and that trials should study interventions that address MBS as a single entity.

Gami, A.S. *et al*. *Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death*. **Journal of the American College of Cardiology**, 2007, Vol. 49, No. 4, pp. 403-14.

INFLUENCE OF AGE AND GENDER ON METABOLIC SYNDROME RELATED CORONARY HEART DISEASE

This study from Johns Hopkins examined the prevalence of coronary heart disease (CHD) in different age-gender groups in the U.S. as a function of the presence of MBS. MBS was defined according to the NCEP and data available from the Third National Health and Nutrition Examination Survey (NHANES III) was used. Four age-gender subpopulations were examined: age 35-54 and 55-74 for both men and women. Each subgroup had between 500 and 1000 subjects. For women the prevalence of MBS was 21 and 24% for the 35-54 and 55-74 age groups, respectively, whereas for men the corresponding figures were 39 and 38%. When the connection between MBS and CHD was investigated, there was no difference between those with MBS and the controls, whereas for women between 55 and 75 and in men over the entire age range, the enhanced risk due to MBS was about 2-fold. The authors comment that the lack of an association for younger women may be due to the fact that they were premenopausal since the transition to the postmenopausal state is known to be associated with the emergence of a profile of CVD factors similar to men and that many of these risk factors are MBS characteristics. The authors also point out that one potential explanation, i.e. that high levels of endogenous estrogen can block the pro-atherosclerotic effects of MBS, still represents an unresolved question.

Tong, W. *et al* *Age, Gender and Metabolic Syndrome-Related Coronary Heart Disease in U.S. Adults*. **International Journal of Cardiology**. 2005, Vol. 104, pp. 288-291.

LIFESTYLE AND METABOLIC CORONARY HEART DISEASE RISK FACTORS IN OLDER OBESE ADULTS

Lifestyle intervention is currently recommended by mainstream medicine for obese individuals with metabolic risk factors for coronary heart disease (CHD). The 27 subjects in this small randomized study consisted of obese (BMI \geq 30) older (age \geq y) men and women. Mild to moderate frailty was present. The intervention involved a diet that produced an energy intake deficit of about 750 kcal/day (kilocalorie is the diet world's "calorie"). Subjects also participated in exercise-training sessions three times a week which included

flexibility and endurance exercises. Waist circumference, blood pressure, serum lipids, free fatty acids, inflammatory markers fat mass and fat-free mass as well as a standard oral glucose tolerance test constituted the parameters followed. This data allowed the investigators to ascertain the presence of the MBS (NCEP definition). At the end of 6 months, body weight, waist circumference, plasma glucose, triglycerides, systolic and diastolic blood pressure all decreased. The number of subjects with MBS decreased by 59% and inflammatory serum markers such as CRP decreased. Thus this lifestyle intervention decreased multiple metabolic CHD factors simultaneously in this small group of obese adults and the decrease was significant when compared to the controls. At

baseline, 90% of the subjects had MBS. The fact that this is higher than the national average for this group was attributed by the authors to reflect selection according to combined obesity and inactivity. The authors also point out that these results refute the notion that it is difficult to achieve successful lifestyle induced weight loss in older persons because of lifelong activity and diet habits.

Villareal, D. T. Effect of Lifestyle Intervention on Metabolic Coronary Heart Disease Risk Factors in Obese Older Adults. American Journal of Clinical Nutrition., 2006, Vol 84, pp. 1317-23.

Editor's comments: The authors make an interesting comment in their introduction, i.e. that weight-loss therapy in obese older adults is controversial because of health risks associated with a decrease in BMI. They are apparently referring to studies that have to do with bone loss and bone mineral density. Also, obesity provides a

cushion that reduces the risk of fall related fractures. These issues were not investigated in the above study but appear to be minor compared to the benefits associated with the observed decline in adverse metabolic measures and the MBS.

FRUIT AND VEGETABLE INTAKES, C-REACTIVE PROTEIN AND THE METABOLIC SYNDROME

This recently published study represents a joint effort from Harvard and the Shaheed Beheshti University Medical School in Tehran, Iran. In Tehran, >30% of adults and 10% of adolescents are affected with MBS. In this study 486 women free of cardiovascular disease, diabetes, cancer or stroke were examined for evidence of the MBS (NCEP criteria) and their dietary habits assessed with a food-frequency questionnaire. When the lowest quintile of vegetable or fruit consumption was compared to the highest, significant reductions in both C-reactive protein (CRP) and the presence of the MBS were observed. The authors state that to their knowledge, this is the first study to directly relate fruit and vegetable consumption with MBS, although considerable indirect evidence exists. This protective effect persisted in multivariate models after potential confounders were taken into account. They also suggest that the lower MBS risk might be due to lower CRP levels, and that the findings support current dietary recommendations to increase intakes of fruit and vegetables as a primary preventive action against CVD. The results also support the hypothesis that high intakes of fruit and vegetables have are anti-inflammatory.

Esmailzadeh, A et al.. Fruit and Vegetable Intakes, C-Reactive Protein, and the Metabolic Syndrome. American Journal of Clinical Nutrition. 2006, Vol. 84, pp. 1489-97

NEWS BRIEFS

FISH A POOR SOURCE OF VITAMIN D

At issue here is how to get adequate amounts of vitamin D if sunlight exposure is avoided or sunscreen protection heavily used or if an individual's place of residence is above 40° latitude. One school of thought holds that the diet should be a major source of vitamin D. In a short paper recently published online in *Steroid Biochemistry and Molecular Biology*, Lu *et al* examined the vitamin D content of several commonly consumed fish and the influence of preparation on the final vitamin D content. They found about 1000 IU of vitamin D3 in a 3.5 oz portion of wild salmon (a typical dinner portion) but farmed salmon had only

25% of this amount. Blue fish is very oily but had only about 280 IU per 3.5 oz portion. White fish such as cod and sole were very low in vitamin D, farmed trout and Ahi tuna came in at 388 and 404 IU per 3.5 oz portion respectively. When farmed salmon was baked, almost all the vitamin D survived, but frying in vegetable oil resulted in a 50% loss. The authors also point out that fortified milk frequently does not contain as much vitamin D as is stated on the label and that food tables are highly inaccurate sources of information about the vitamin D content of foods. The authors point out that most experts agree that 1000 IU is required in the absence of sunlight-generated vitamin D.

These numbers suggest there is a real problem with the suggestion that individuals get all their vitamin D from food.

Lu, z. *An Evaluation of the Vitamin D3 Content in Fish: Is the Vitamin D Content Adequate to Satisfy the Dietary Requirements for Vitamin D?* **Steroid Biochemistry and Molecular Biology**, 2007. Published online ahead of print

CURRY AND COGNITIVE FUNCTION

A recent study from Singapore examined the relationship between curry consumption and cognitive function in a cohort of over 1000 non-demented elderly Asian subjects aged 60-93. Their curry consumption was found to be positively associated with their scores on the Mini-Mental State Examination, a standard tool used to assess cognitive function. Those who consumed curry occasionally or often or very often had significantly higher scores than those whose consumption was reported as never or rarely. Turmeric is widely used as a curry spice and curcumin and other products isolated from turmeric are known to possess very potent anti-inflammatory and antioxidant properties. The authors point out that curcumin inhibits lipid peroxidation in the brain, scavenges nitric oxide-based free radicals, and is several times more potent than vitamin E as a scavenger of free radicals. They also cite recent data that indicate that in healthy human subjects, 200 mg of curcumin lowers total blood lipid peroxides, promotes antioxidant-induced normalization of plasma levels of fibrinogen and the apolipoproteins B/A ratio, alterations which are associated with reduced cardiovascular risk. Both curcumin and turmeric are widely available as supplements.

Ng, T-P. et al. *Curry Consumption and Cognitive Function in the Elderly.* **American Journal of Epidemiology**, 2006, Vol. 64, No. 9, pp. 898-906.

ABANDONING HORMONE REPLACEMENT THERAPY VINDICATED?

In a paper presented at the annual San Antonio Breast Cancer Symposium, Ravdin *et al* presented the results of a multicenter study that used SEER (see above) data. Breast cancer incidence in the U.S. gradually increased by 1.7% per year from 1990 to 1998 and then decreased by 1% per year from 1998 to 2003. Then in 2003 there was a sharp decrease of 7% within a single year. The decrease was seen for both in situ cancers and malignant cancers. The decrease in 2003 started slowly but in the second half was 9% and the decline was greater in estrogen receptor positive than negative tumors. The decrease was even greater in women aged 50-69 where the decrease was mostly in estrogen

receptor positive cancer. In a news release from The University of Texas M.D. Anderson Cancer Center, Dr. Donald Berry is quoted as saying that "something went right in 2003, and it seems that it was the decrease in the use of hormone replacement therapy (HRT), but from the data we used we can only indirectly infer that this is the case."

Similar findings were reported in November by Clarke *et al* in the *Journal of Clinical Oncology*. They were able to track the decline in HRT and ET (estrogen therapy) among members of the Kaiser Permanente health maintenance organization (Northern California region-- KPNC). After the Women's Health Initiative results were announced, HRT and ET declined by 68% and 36% respectively, and between 2001 and 2003 there was a 10% decline in breast cancer among KPNC members and an 11% drop for the state of California, and for 2004, the rates in both the state and the regional population from which KPNC draws patients also declined further.

Ravdin *et al*, *A Sharpe Decrease in Breast Cancer Incidence in the United States in 2003.* Paper presented at the 29th annual San Antonio Breast Cancer Symposium, December 14, 2006.

Clarke, C.A. et al. *Recent Declines in Hormone Therapy Utilization and Breast Cancer Incidence. Clinical and Population Based Evidence.* **Journal of Clinical Oncology**, 2006, Vol. 224, No. 33, pp. 48-50

A WARNING FOR METFORMIN USERS

A recent study from Hong Kong appearing in the *Archives of Internal Medicine* has found a clinically significant association between vitamin B12 deficiency and dose and duration of the use of the drug metformin, a drug that improves insulin sensitivity and offers protection against vascular complications from diabetes. Each 1g/day of metformin dose increment resulted in a 188% increase in the risk of developing a vitamin B12 deficiency. The authors call for B12 screening among metformin users and point out that these results underscore the need for monitoring subjects undergoing high-dose or prolonged therapy with this drug. This study reinforces the results of Hermann, Nilsson and Wettre published in 2004, as well as earlier studies.

Ting, R. Z-W. et al. *Risk Factors for Vitamin B12 Deficiency in Patients Receiving Metformin.* **Archives of Internal Medicine**, 2006, Vol. 166, Oct 9, pp. 1975-9.

Hermann, LS et al. *Vitamin B12 Status of Patients Treated with Metformin: a Cross Sectional Cohort*

Study. *British Journal of Diabetes and Vascular Disease*, 2004, Vol 4, No. 6, pp. 401-6

Editor's comment: Individuals on metformin should consider discussing this matter with their physician, some of whom may not be aware of this problem, although it was described in the literature as far back as 1971. Since peripheral neuropathy of diabetes may present with symptoms that are frequently indistinguishable from those caused by B12 deficiency, metformin-induced low serum levels of B12 are of great concern if not recognized and treated. There is some evidence that supplemental calcium can reverse the malabsorption of B12 (*Diabetes Care*. 2000;23:1227-31).

VITAMIN D, BREAST AND OVARIAN CANCER

Exposure to solar ultraviolet B radiation (UVB) has been found to correlate with age-adjusted incidence of ovarian cancer in a study involving 175 countries and based on data from 2002. Not only was an inverse relationship found, but when the correlation with stratospheric ozone, which reduces UVB, was examined, a positive association was found

consistent. These results are consistent with earlier studies that found a north-south gradient for age-adjusted mortality rates for ovarian cancer.

In another recent study, serum levels of the vitamin D metabolite, 25-hydroxyvitamin D, were measured prospectively in 279 Caucasian women with invasive breast cancer, 204 of which had early stage cancer and 75 of which had locally advanced or metastatic disease. Patients with early stage disease had significantly higher circulating levels of 25-hydroxyvitamin D than those with advanced disease. The authors suggest that these results lend weight to the hypothesis that the growth of breast cancer in vivo is inhibited by vitamin D.

Garland, C.F. et al. *Role of Ultraviolet B Irradiance and Vitamin D in Prevention of Ovarian Cancer. American Journal of Preventive Medicine.*, 2006y, Vol 31, No. 6, pp. 512-14.

Palmieri, C. *Serum 25-Hydroxyvitamin D Levels in Early and Advanced Breast Cancer. Journal of Clinical Pathology*, 2006, published on line ahead of print.

THE FRENCH PARADOX—FACT OR FANTASY

The French Paradox is based on the notion that the French eat a diet rich in butter and other fatty sauces, foie gras, fatty cheese, foods high in cholesterol and saturated fat, and have traditionally shunned low-fat products, i.e. theirs is a diet conventional wisdom holds to be bad, and yet the incidence of heart disease is very low compared to many other countries. Another way of describing the paradox is that it describes a lower than expected coronary heart disease (CHD) mortality in a country where the classic CHD risks are no less prevalent than in other industrialized countries and in addition where the diet has been historically high in saturated animal fat [1]. A related issue is illustrated by the title of Mireille Guiliano's amusing and entertaining book, *French Women Don't Get Fat* [2]. The French Paradox was brought to center stage for North Americans in 1991 when the TV program *60 Minutes* examined the evidence for its existence by interviewing doctors, cardiovascular specialists and epidemiologists from both France and the U.S. The conclusion *60 Minutes* put forward was that wine was responsible. The impact this had on the image and sales of wine, and especially red wine, is now part of the lore of the American Wine Industry. It was about a decade earlier that the phrase French Paradox started appearing in the medical literature and what some might consider the landmark paper [3] did not appear until 1992.

In this mini-review we will examine the various issues associated with the French Paradox. In particular, was or is the rate of heart disease really lower among the French, i.e. is there really a paradox? If so, is this due to diet, wine, lifestyle or all of the above? Or is it due to something else? Does the Mediterranean diet have anything to do with the paradox?

The lower coronary heart disease (CHD) mortality seen in France, as compared to other countries is a critical part of the French Paradox. In fact it has been suggested that French physicians underreport CHD mortality. In a just published paper, Jean Ferrières presents data indicating that this is not the case [4]. A comparison of three measures, the official death certificate based CHD mortality rate, a CHD mortality rate that allowed more cases, and the coronary event rate, was carried out for the cities of Glasgow, Scotland and Belfast, Ireland vs. three cities in France. It was revealed that large and significant differences persisted as the criteria were relaxed

to permit the counting of more cases. For example, the death certificate based mortality and the broader CHD mortality figures for men living in Glasgow vs. Toulouse, France were 332 and 365 vs. 53 and 91 per 100,000, respectively. Clower [5] presents data based on World Health Organization numbers showing CHD mortality rates for American vs. French men and women to differ by factors of 2.7 and 3.1, respectively. From other data, a comparison between France and Britain finds mortality ratios of 1 to 4 for men and 1 to 6 for women when the endpoint is coronary heart disease [1]. Thus the first part of the French Paradox stands up to scrutiny. Consistent with the lower CHD mortality rate Balkau *et al* [6] found that the absolute death rates from heart attacks in diabetic men in British and American studies as compared to a French study were higher by factors of about 3 and 2, respectively. Also, there is a lower mortality rate from diabetes in France as compared to the U.S. [5] and a lower prevalence of long-term complications in type 2 diabetes as compared to other countries [7]. Thus the French Paradox would appear to extend to individuals with diabetes.

The other essential aspect of the paradox involves characterizing the French diet as high in fat and cholesterol and in general a bad diet. In a study of European countries, the dietary habits of the French were similar to those who resided in Belfast, Ireland, where CHD mortality is 4-5 times higher [4]. A comparison between France and Finland, Norway, Denmark, Germany and the UK reveals a similar consumption of total meat, beef and butter [1]. In general, the consumption of fruit and fiber by the French is low whereas the intake of saturated fat is very high at 16% of total energy. One survey found the mean fat intake of French adults to be about 39% of total energy intake, mainly because of high consumption of butter [1]. There has also been a “diet quality” study based on conventional ideas about a healthy diet. In a sample from southern France (Languedoc area) only 10 out of 146 subjects had a wholesome diet as judged by these standards. Also, even in the south of France, the dietary habits were not in line with the main characteristics of the traditional Mediterranean diet [1]. In fact, while it is true that among European populations other than the French, only those with a consistent classical Mediterranean-type diet still have a low CHD mortality, the French do not for the most part eat a Mediterranean diet [1]. Thus it does not appear, based on the conventional wisdom, that the French are protected from CHD by the nature of their diet, a diet most North American dietitians would rate as very bad indeed. Thus there is evidence that the dietary aspect of the paradox is true in the sense that the French have a diet that, based on comparison with other countries, would lead to the prediction of much higher rate of CHD mortality than is observed. But this is based on the conventional dietary wisdom (cynics call it dogma) concerning fat and saturated fat. How well this wisdom holds up to critical examination will be discussed at the end of this review.

An important question may not be how much fat the French eat but whether or not their diet in general results in being overweight or obese, conditions which would indirectly impact the risk of heart disease. Thus is the title of the above-mentioned book, *French Women Don't Get Fat*, based on fact or just a cute phrase to sell books? In their discussion of French eating habits, Paul Rozin *et al* provide the following data [8]. The mean body mass index (BMI—weight in kilograms divided by the square of the height in meters) averaged across males and females is 24.4 (not overweight) for French adults and 26.6 (overweight) for American adults. Perhaps what is more important, 22.3 % of Americans are obese (BMI \geq 30) but only 7.4% of French qualify. These were numbers for 2002. Similar comparative figures for obesity of 30% and increasing vs. 8% and holding (!) are quoted in Will Clower's 2003 book *The Fat Fallacy* [5]. Clower is a neurophysiologist at the University of Pittsburgh who spend two years in France as a research fellow at the Institute of Cognitive Sciences in Lyon, which gave him an opportunity to observe the French dietary habits and lifestyle. Clower's book is interesting in that it quotes what might be described as case histories where individuals who have come from North America to live for a few months to a few years in France generally lose weight while having in fact decided to “throw caution to the wind” and eat the typical French diet. Evidently, there was already an impression that the French diet was intrinsically bad. The same theme runs through Mireille Guiliano's book, including her own personal experience upon returning to France from the U.S. as an overweight teenager, and achieving normal weight by adopting the eating habits of France. Thus, in trying to explain the French Paradox, one of the important questions seems to be, why does the French diet not result in the expected frequency of overweight and obese individuals.

An interesting paper by Rozin *et al* [8] addresses this issue. The authors take the position that the reason the French are thinner than the Americans is that they eat less while spending a longer time eating. While this might seem somewhat simplistic, the authors go to some length to justify this view. Compared to the U.S., they document that portion sizes are smaller in French restaurants, the sizes of individual portions of items sold in supermarkets are smaller, the portions specified in French cook books are smaller, and the prevalence of all-

you-can-eat restaurants is much lower in France than in the U.S. Both Clower and Guiliano also characterize the French diet as having smaller portions than those common in America. Also, direct observation in restaurants in the U.S. and France revealed that the French spend significantly longer eating a meal. Rosin *et al* also discuss studies showing that there is a delay before the brain signals that enough has been eaten, and slow eating allows this signal to be sent before overeating has occurred. Thus smaller portions are satisfying. A commonly made observation is that the French put their fork down between each bite, and while this is no doubt to some extent an exaggeration, it is consistent with the premium placed on savoring every bite. Lively conversation around the table and a glass or two of wine would also naturally encourage leisurely eating and more lengthy meals. Probably any North American who has lived in France for any length of time would confirm these observations. Exercise may also help explain the lack of overweight or obese individuals. As Guiliano points out, the French tend to walk more than the Americans as they go about their daily activities, walk to stores and frequently use stairs rather than elevators.

There are also significant differences between the French and the Americans in attitudes regarding food. In a study published in 1999, Rosin *et al* [9] examine this question. The categories compared included (a) Worry—the extent of worry as opposed to savoring food and also worry about weight gain; (b) Diet-Health Link—concern about the impact of food on health; (c) Pleasure and Importance—the pleasure of eating and the importance in life of food; (d) Culinary Associations—culinary as opposed to nutritional association of food; (e) Healthy Eater—Self perception as a healthy eater. Scores were assigned on the basis of a questionnaire. In the Worry and Diet-Health Link categories, the French exhibited much lower scores than the Americans. The reverse was true for Pleasure—Importance and Culinary Associations. Also, the French had a much higher score in the category of self-perception as a healthy eater. Thus as compared to Americans, the French are not as concerned about weight gain or eating what others perceive as unhealthy foods, but for them, eating is associated with great pleasure and this pleasure transcends nutritional considerations. Finally, the French consider themselves healthy eaters to a much greater extent than Americans. Rozin *et al* regard these observations as translating into differences in food-related or meal-time stress, and that this type of stress, which seems quite subtle, could account for part of the French Paradox since stress has negative health connotations, especially in the context of coronary heart disease. In other words, when comparing the French to the Americans, there are profound differences in psychological attitudes toward both food and its consumption that may have a bearing on health. These results probably underestimate the differences in lifestyle between France and North America. Hasty meals have become the norm in North America as individuals rush back to work after lunch or eat dinner almost on the run or at almost random times in order to meet other obligations including those associated with children's activities, which generally require parental taxi service. Couple this with two working parents and you have the ingredients for stress. Changes in the peaceful, leisurely way of life in France where one of the principal pleasures is associated with food may be occurring, but the French Paradox is not a recent phenomenon and CHD takes a while to develop.

Thus possible explanations for the paradox include lifestyle factors based on length of time spent eating, the pure pleasure and fascination associated with food, the disregard for the connection between what is eaten and health, and apparent calorie restriction due to smaller portions. This brings us to the question of alcohol and in particular wine consumed with meals and as well the level of wine and alcohol consumption in France compared to other countries. Let's look at the hypothesis, so dear to the wine industry, that the French Paradox is all about wine.

Two aspects characterize French wine drinking—quantity and regularity. De Lorgeril *et al* describe data from 1989 which found a mean consumption of alcohol of about 30 grams/day for men and only 10 grams/day for women [1]. One glass of wine contains 12-15 grams of alcohol. Another study found roughly the same results expressed as percentage of energy intake from alcohol. For men it was 8% and for women 3.5%. Earlier studies based on grams of wine (not alcohol!) per person per day found France at 195, Italy at 144, Spain at 129, Greece at 84 and the U.K. at 33, obviously huge differences [1]. These are all population-based estimates and thus will encompass wide ranges. As regards drinking patterns, the French tend to drink regularly and with meals rather than concentrate their drinking during weekends or simply binge drink. Drinking patterns appear to be an important issue. In a recent study based in New York, it was found that daily drinkers had a lower risk of heart attack than abstainers, drinking only on weekends increased rather than decreased the risk and those who drank with meals had lower risk than those who drank mainly without food [10]. Similar results were reported recently in the *New England Journal of Medicine* [11] where drinking four or five to seven times a week revealed

greater risk reduction than drinking once a week. Finally there is the observation made several times in the literature that heart attacks are more common early in the week. A study published in the journal *Hypertension* examined blood pressure the fluctuations throughout the week in subjects from France and Northern Ireland [12]. In Northern Ireland, 66% of the total alcohol consumption occurs on Friday and Saturday, whereas in France it is typically spread throughout the week. Blood pressures for the Northern Ireland group peaked on Saturday whereas those of the French showed much less fluctuation with merely a small increase on the weekend. The authors concluded that the fluctuations observed in Northern Ireland could explain the higher incidence of heart attacks on Mondays in countries characterized by high alcohol intake on weekends. An alternative explanation is that many people hate their jobs and thus stress peaks on Monday. Nevertheless, the above results underscore the benefits associated with the French approach to alcohol consumption.

The subject of the association between alcoholic beverages and CHD is too large to examine in this review. However, it is natural to look for a French-based study since a protective effect should be significant if wine is part of the paradox. There appears to be only one prospective (follow-up) study, published in 1999 [13]. For wine as a protective factor in CHD mortality, 22-32 grams of alcohol a day roughly halved the risk and resulted in a 33% reduction of all-cause mortality, but as is frequently found, the benefits disappear with heavier consumption. When these results are compared with a very recent combined analysis of 34 prospective studies [14], it appears that the risk reduction in the French study was larger. While the preponderance of evidence seems to favor the protective hypothesis, critics point to the possibility of confounding. The position of the doubters was strengthened recently with the publication of a study based on telephone interviews with over 250,000 U.S. adults. Data was gathered as to prevalence of cardiovascular (CVD) risks factors among nondrinkers and moderate drinkers. Of the 30 CVD-related risk factors assessed, 90% were significantly more prevalent among nondrinkers. The authors comment that these findings suggest that some or all of the apparent protective effect of moderate drinking may be due to residual or unmeasured confounding [15]. Thus when the studies showing benefit are summarized to indicate that one to three drinks a day are associated with about a 20% reduction of CHD risk [14], this perhaps is an overestimate. It appears that the connection between wine and the French Paradox, while still a hypothesis, is to some extent evidence based. Arguments regarding biological plausibility, while interesting, strengthen but do not prove the point. To settle the alcohol and wine question would require randomized trials which would almost certainly never get past ethics committees. However, if there is a protective effect, then studies are clear on one point, the French are maximizing the benefit by drinking for the most part in adequate but moderate amounts, with meals, and they spread the intake more or less evenly over the week.

Finally, there is the matter of fat. If fats and especially saturated fats are in fact not very dangerous or even neutral in the context of heart disease, then this weakens considerably one of the two pillars on which the French Paradox rests. The French Paradox had its origin at the height of the anti-fat era when many disorders, but especially cancer and heart disease were attributed to fat consumption. Thus it was easy to point a finger at the French diet and pronounce it heart-unfriendly simply because of the high content of fat, and especially saturated fat. In other parts of the world, and especially in North America, low-fat food and low-fat diets became the rage and fat calories were replaced by large amounts of refined carbohydrates. Low-fat diets had a tendency to reduce HDL cholesterol levels and elevate triglycerides levels, two trends not viewed as beneficial to heart health. Also, high intakes of refined carbohydrates increased the risk of developing insulin resistance and eventually type 2 diabetes, neither of which is favorable to heart health. The French did not buy into the low-fat revolution or low-fat foods, but held steady on the traditional course of a high fat diet. Part of the reason may simply be the attitudes about food and health discussed above. Space does not permit examining the heart disease—dietary fat issue in any detail (see the Archives for an extensive discussion of this subject in the research review titled *Dietary Fat and Heart Disease, Is There a Connection?* The review appeared in the November-December 2002 issue of *International Health News* and still seems current today). However, the following brief discussion appears relevant to the French Paradox question.

By the beginning of the new millennium, the view that saturated fat was bad in the context of CHD was firmly established as a dogma and few dared to raise questions that would embarrass the establishment. In 2001 Gary Taubes ruffled some feathers with an article in the journal *Science* titled “The Soft Science of Dietary Fat,” in which he raised serious questions about the evidence for the fat/heart connection and the merits of low-fat diets [16] (available free—Google “Gary Taubes fat”). The establishment’s reply to this “shot over the bow” was in a letter to *Science* [17] which was immediately criticized in the same journal [18]. It was pointed out that the

two reviews cited as refuting Taubes' position either had no references at all or had references that for the most part did not support the defense. While Taubes' *Science* article received considerable media attention, a much more high-profile article was published a year later in the *New York Times Magazine* [19] with the provocative title "What If It's All Been A Big Fat Lie?", which again raised serious question about the low-fat dogma and low-fat diets. This article contained quotes from respected experts (it is also free via the same Google search).

In connection with the French Paradox there are two issues: (a) the CHD danger of high fat diets; and especially (b) the CHD dangers of saturated fat. Already in 1998, Ravnkov published an extensive review of this question in the *Journal of Clinical Epidemiology* [20]. He was not able to find conclusive evidence to justify the claim that saturated fats were bad. About the same time, Hu *et al* from Harvard published a paper on dietary fat intake and the risk of CHD in women which was based on a large prospective study [21]. If one looks at their Table 3 in which results adjusted for confounding are presented, saturated fat intake up to almost 19% (quintile median) of total energy was found to *not* be statistically associated with CHD risk (heart attack or fatal CHD). Nor was a high intake of total fat significant, but a significant inverse association (beneficial) was found for polyunsaturated fat, and enhanced risk was seen for trans fat. No association was found with cholesterol intake up to 275 mg/day (quintile median). Hu *et al* point out that the results of prospective epidemiologic studies of fat and CHD have been inconsistent, with 2 finding a positive association and 6 finding no association. Saturated fat increases LDL levels, but it also increases HDL, the so-called good cholesterol. Obviously there is the potential for these two effects to compensate. Yet the increase in LDL levels caused by saturated fat is at the heart of the establishment case against this particular fat. Saturated fat, incidentally, is a mixture of fats, most of which do not raise LDL [16]. The study by Hu *et al* has recently been updated with a total of 20 years follow-up [22]. The conclusion was the same—"Intakes of total fat, saturated fat and monosaturated fat had no clear relation to CHD regardless of age."

Three recent studies are relevant. A study from Denmark reported in 2004 reached the same conclusion, this time for both men and women. No statistically significant associations were found for either men or women between the intake of saturated or total fat and CHD [23]. This was in spite of not adjusting for confounding to the extent done by the Harvard researchers. The second study is the now famous dietary modification trial which was part of the Women's Health Initiative (WHI). Dietary intervention that reduced total fat intake and increased the intake of vegetables, fruits and grains did not significantly reduce the risk of CHD [24]. Finally, in a multicenter study that included Harvard, it was reported in 2004 that for postmenopausal women with relatively low fat intake, a greater saturated fat intake was associated with *less* progression of coronary atherosclerosis [25]. This result may not be universally applicable since many of the subjects had CHD, were hypertensive or had diabetes, but it is in the wrong direction if one believes the conventional wisdom and the study included women at high risk but free of CHD.

The current recommendation by the National Cholesterol Education Program for men and women at high risk for CHD is that the intake of saturated fat should be reduced to 7% of total energy intake. The American Heart Association (AHA), in its just-published 2007 guidelines for CHD prevention in women, calls for limiting saturated fat intake to 10% and if possible 7% [26]. One might ask, where are the statistically significant data to back up these recommendations? Lots of interested individuals have looked for the data, but don't seem to be able to find it [27]! In the AHA guidelines, they appear to give only one reference directly related to saturated fat and women, a small British study of 2002 [28]. It found no relationship for men, but found risk for women, although the data were not adjusted for confounding to the extent done in the much larger and longer Harvard study mentioned above, which found no connection between CHD risk and fat or saturated fat for women [21,22]. Aside from the WHI study mentioned above, the AHA document does not include in its bibliography any of the negative studies concerning saturated fat and CHD, and in particular the Harvard study, and the guidelines obviously ignore all of these results. Also, this AHA guideline is for women, and yet two of the studies cited concerning diet and CHD risk were done only on men and the British study of both men and women cited found no connection for CHD and saturated fat in men anyway! Thus important studies, including a highly relevant one from the premier center of nutritional epidemiology in the world, are ignored and more or less irrelevant ones cited. The guidelines are titled "evidence based."

Thus the French Paradox appears to be based on an exaggerated and probably even totally wrong view of the importance of dietary fat in general and saturated fat in particular in connection with the risk of CHD. Therefore the paradox may in fact be a fantasy. However, the mystery of the low CHD mortality would remain, and the

possible explanations advanced above would still be relevant since they are not dependent on the fat hypothesis. Some may find the above discussion contains sufficient reasons to imitate selected features of the French lifestyle. For those for whom this notion has appeal, the two books cited above will provide valuable and detailed guidance.

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The Prostate Monitor

Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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1st Year



This issue is devoted entirely to prostate cancer. We start with a discussion of recent results concerning both factors and actions that increase risk and those that decrease it. This is followed by a discussion of several aspects of prostate specific antigen. There has been recent progress in defining age-specific ranges that assist in flagging high-risk cases and perhaps biopsy. Men need to be aware of these results in order to interpret their PSA numbers using the latest research results. Chapter 4 of our book provides the background information. Also, studies have recently helped establish potential cut-offs for APSA velocity that appear useful in making decisions regarding more careful follow-up or biopsy. Three papers that deal with side effects associated with treatment are discussed.

*There has been progress in assessing men with clinical Gleason 8-10 cancer (advanced, 10 is the highest score) in order to judge the merits of surgery or surgery plus hormone therapy. There is also growing interest in what the urologists at Johns Hopkins call expectant management, i.e. postponing definitive treatment in low risk cases until there is evidence that unless treatment is initiated the window of opportunity for a cure will be lost. A recent paper from Johns Hopkins is discussed where the success of the Hopkins criteria for expectant management is up-dated. Expectant management or what some call active surveillance is discussed in our book **The Prostate and Its Problems** and we consider it very important that men be aware of this option and knowledgeable regarding the latest developments. This option can result in avoiding definitive treatment with its side effects for a time period that could be considerable and some men would avoid treatment altogether.*

Wishing you continuing good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at <http://www.yourhealthbase.com/prostate/book.htm>

PROSTATE CANCER

RISKS AND RISK REDUCTION

The relationship between milk and other dairy product consumption and the risk of prostate cancer is unclear with inconsistent results. Studies that attempted to isolate the effect of calcium suggested that at high doses it was a risk factor, especially for advanced or metastatic cancer. In a recent report from Harvard Medical, Giovannucci *et al* [1] update an earlier prospective study (Health Professionals Follow-Up Study) with double the follow-up time (16 years). This study examined the role of both nutritional and supplemental calcium intake on the risk of prostate cancer. Consistent with the earlier study, it was found that calcium intakes exceeding 1,500 mg (1.5 g) of calcium per day carried a significantly enhanced risk. For high-grade cancer (Gleason ≥ 7 , see our book for a discussion of the Gleason score of biopsy samples) the relative risk when high vs. low intake was compared was 89%, whereas no enhanced risk was found for the risk of organ-confined, low-grade prostate cancer. The authors conclude that high levels of calcium may influence the differentiation of cancer cells and increase the formation of poorly differentiated cells associated with advanced cancer. They suggest that middle-aged and older men should consider limiting their total intake of calcium to less than 1,500 mg per day. Men who consume large quantities of over-the-counter antacid tablets may want to check on their intake of calcium. For example, one popular brand contains 750 mg of calcium carbonate per tablet, equivalent to 300 mg of elemental calcium. Another contains 270 mg/tablet of calcium. Intake from these supplements must of course be added to the intake from milk, yogurt, cheese, etc. Calcium ascorbate, a popular source of vitamin C, contains only about 10% elemental calcium.

Two recent studies address the risk of prostate cancer associated with meat consumption. One found no increase risk of early or localized cancer from total, red or white meat. However, more than 10 g/day of very well done meat was associated with a 40-70% increase in risk [2]. In the other study, only high consumption of cooked processed meats (sausages, bacon and hot dogs) was found to contribute to the risk of prostate cancer and this only among black men [3].

Among the various dietary factors thought to be protective in the context of prostate cancer, there is particularly strong support for phytoestrogens (i.e. plant derived estrogens). A recent case control study from Sweden lends support to this view [4]. Phytoestrogen intake was estimated from a food frequency questionnaire which contained 18 phytoestrogen containing foods from which the intake of 14 different phytoestrogens was estimated. High intake of food items rich in phytoestrogens decreased the risk of prostate cancer by about 25%. In this study, flaxseed, rye and wheat bread were important phytoestrogen sources, but in some populations, soy is also significant. An additional recent study from the same group identified the promoter region of an estrogen receptor gene thought to be related to this decreased risk [5].

ISSUES RELATED TO PROSTATE SPECIFIC ANTIGEN (PSA)

Laboratory reports will generally give ≤ 4.0 ng/mL for the normal reference range for this test. However, in recent years, there has been interest in establishing median levels for healthy men stratified by age, since PSA levels tend to increase naturally with age in the absence of prostate cancer. Consequently, frequently quoted figures today give a range of 0.6-0.83 ng/mL for men aged 40-49 years, and 0.7-1.2 for those 50-59. In a recent study reported in the journal *Urology*, Loeb *et al* [6] have examined the risk of developing prostate cancer when values fall above the median value associated with these ranges. This screening study ran from 1991 to 2001 with almost 14,000 men participating. Prostate cancer detection rates, PSA velocity, pathologic features, and treatment outcomes were observed as a function of baseline PSA. For men aged 40-49 years, the median PSA was 0.7 ng/mL whereas for the age group 50-59, the value was 0.9 ng/mL. A baseline PSA level between the median and 2.5 ng/mL was associated with a 14.6-fold and 7.6-fold increase in risk of prostate cancer in men aged 40-49 and 50-59, respectively. A greater baseline value was also associated with more aggressive cancer and a greater death rate due to prostate cancer. There was also a strong relationship between baseline PSA and PSA velocity. The authors comment that clinicians should no longer regard men younger than age 60 with a PSA level of less than 2.5 ng/mL as "normal," but rather encourage individuals with PSA levels greater than the age-specific median to undergo yearly screening to enable the calculation of the PSA velocity and thus estimate the probability of the presence of cancer. But since not all physicians will be aware of these results, it is important that men take them into account when interpreting the results of their PSA test. But this leaves a lot unsaid. PSA screening issues and the interpretation of PSA values are far from simple matters, and yet they are

among the most important aspects of prostate health with which men need to become acquainted. In our book, this subject is discussed at length in a chapter on diagnosis of prostate cancer.

In the paper discussed above, mention was made of using PSA velocity in an attempt to interpret PSA values that were above the age-indicated medians. A study from Johns Hopkins University School of Medicine recently published in the *Journal of the National Cancer Institute* directly addresses this problem [7]. The study examined the ability of PSA velocity measurements carried out over 10-15 years to identify individuals with life-threatening prostate cancer at a time in its evolution where a cure was still possible. These PSA velocity measurements made 10-15 years before diagnosis involved men who for the most part had a baseline PSA below 4.0 ng/mL. It was found that a PSA velocity of 0.35 ng/mL/year was a significant cut off for identifying a high relative risk of serious or life-threatening prostate cancer. The authors comment that determining PSA velocity may provide a reasonable approach to the problem of what absolute PSA cut off to use for triggering a biopsy. Some experts hold that >4.0 ng/mL is satisfactory, others are campaigning for > 2.5 ng/mL. But lowering the cut-off results in an increase in early diagnosis but also the increased detection of biologically irrelevant cancers that otherwise would have gone undetected. Determining PSA velocity may, according to the authors, offer a way to balance this trade-off by initiating screening early in life and performing prostate biopsies on those men who have a PSA velocity suggesting the presence of life-threatening cancer, even if the PSA level is < 4.0 ng/mL, and this would avoid using a single PSA cut-off as an indication for biopsy. The reader is referred to Chapter 4 of *The Prostate and Its Problems* for more information regarding the PSA test and the diagnosis via biopsy. It is anticipated that an ever increasing number of men will be offered this test at about age 40 years, and it can be argued that they need detailed and comprehensive information which will allow them to understand and interpret the lab results presented to them. Some physicians in general practice and some internists as well may not be right up-to-date regarding these more subtle aspects of the use of PSA.

The elderly represent a special case, both with regard to PSA screening and prostate cancer therapy. Most PSA screening guidelines do not recommend testing in elderly men with limited life expectancy because the potential harms outweigh the potential benefits. In particular, the commonly quoted guidelines recommend screening of average risk men aged 50 years and older only if they have more than a 10-year life expectancy, which is usually defined as a 50% probability of 10-year survival. However, life expectancy estimates are more or less just educated guesses and may not be very carefully considered during a 10-minute office visit. In a paper just published in the *Journal of the American Medical Association* [8], the frequency of ordering PSA tests was examined for the year 2003 in a cohort of almost 600,000 veterans without a history of prostate cancer, elevated PSA or prostate cancer symptoms. It was found that 56% of men older than 70 were screened, and for those older than 85, 34% of those in good health and 36% of those in poor health had the PSA test. The authors conclude that these screening rates are too high. In an accompanying editorial [9], Peter Albertsen gives five key questions that should determine whether or not a screening test is performed. (1) Is the disease significant and serious? (2) Is the screening test accurate? (3) Will the test result improve the outcome? (4) Will the test cause harm? (5) Is the test likely to do more harm than good? Using these questions, he comes to the same conclusion, this group was being over-screened. The point is that older men should realize that physicians may order PSA screening when it is inappropriate and they should discuss the issues before agreeing. Some believe that screening tests should never be performed unless there is a clear understanding regarding what actions will be taken if the results are positive or negative and what in fact constitutes a positive or negative result. For example, does it make any sense to screen an eighty-year-old man with heart disease or diabetes but with no indication of prostate cancer? Is it really planned to follow-up on a high PSA result with a 12-14 needle biopsy and possibly surgery or radiation when there is no clinical manifestation of prostate cancer?

TREATMENT OF PROSTATE CANCER

Most men undergoing treatment for prostate cancer are aware that there are side-effects, also termed adverse effects. They may, to the best of their ability, carefully weigh the risk of these side-effects against the anticipated benefits of treatment. This whole exercise is based on probabilities, in some cases with wide ranges or standard deviations. Some men will reject treatment based on risk-reward considerations, but the majority proceeds, in some cases even if the physician involved in the discussion presents a picture where the risks more or less balance or even exceed the benefits. This is discussed in detail in *The Prostate and Its Problems*. It is a problem and a challenge that causes a growing number of men considerable anguish and stress. Three papers will be reviewed that relate to this subject.

The first concerns the risk of a new cancer secondary to the use of radiation therapy confined to the prostate, either as monotherapy or in conjunction with surgery. Since it is well known that radiation has the potential for causing cancer, it is natural to look for excess cancer over and above that which would normal be expected from population statistics in the case of individuals receiving radiation in connection with cancer therapy. In Chapter 10 of a U.S. government publication currently in press [10] (free download available—"Google" NCI Publication # 05-5302, locate the publication and click "available in PDF" link), the results of a huge study covering 1973-2000 is reported. In a 10-year follow-up of patients receiving radiation as part or all of their initial treatment for prostate cancer, the increase in bladder and rectal cancer risk was 53% and 37% respectively, and there was a 31% increase in the risk of myeloid leukemia. These numbers are based on so-called excess malignancies calculated from expected values for non-irradiated individuals. Obviously, the bladder and rectum are in close proximity to the prostate. Modern intensity modulated 3-D conformal radiation techniques may produce lower levels of risk, and the results with high energy protons might be somewhat different. See our book for a detailed discussion of this problem. There are not very many facilities that use high-energy protons for radiation therapy.

The other two papers concern side effects associated with hormone therapy administered either as monotherapy or in conjunction with or after surgery or radiation therapy. One deals with excess incidence of diabetes and cardiovascular disease during hormone therapy (androgen deprivation therapy) for prostate cancer. Over 73,000 men were involved in the follow-up. Men taking so-called GnRH agonists such as leuprolide or goserelin were found to be at enhanced risk of diabetes, coronary heart disease, heart attack and sudden cardiac death. While the increased risks were not great (11% to 44%,) they were statistically significant [11]. In the second study, short-term treatment with GnRH agonists resulted in an increase in fat body mass and a decrease in insulin sensitivity. The authors point out that these changes are associated with increased risk of diabetes and cardiovascular disease in older men. [12]. These two studies taken together add to the risk side of the risk-benefit equation for men debating whether or not to undergo hormone therapy. Obviously much more research is needed given that distinctly different protocols exist for how and when hormone therapy is administered (see our book, Chapter 7, Treatment of Residual, Recurrent and Advanced Prostate Cancer).

Whether to immediately initiate or defer primary hormone therapy (androgen deprivation therapy) is one of the key questions that arises when prostate cancer patients either refuse local definitive treatment (surgery or radiation or both) or are judged not suitable for such therapy either because of life expectancy considerations, advanced tumor stage and/or severe comorbidities. At issue here is the matter of adverse effects which are absent during the deferred period and thus theoretically deferred treatment should result in an a better quality of life, at least until treatment becomes mandatory for palliation. Thus the question: how does deferred hormone therapy impact overall survival, prostate cancer specific mortality and the duration of symptom-free survival? A multi-center, randomized study addressing this question has recently been reported [13]. Patients were either assigned to surgical castration or a GnRH agonist plus an initial antiandrogen (see Chapter 7 of our book for details) or no hormone therapy. Deferred treatment was initiated only when new symptoms of metastases appeared or metastases threatened to produce serious complications such as pathologic fractures or paralysis. Increased pain due to prostate cancer also provided grounds for starting hormone therapy, but the increase had to be significant. Urinary obstruction caused by the primary tumor or a significant decline in prostate cancer related day-to-day performance were also indications for initiation of therapy. The median time to the start of deferred treatment was 7 years. The time from randomization to progression to hormone refractory disease did not differ significantly between the two groups, nor did prostate-cancer specific survival. Overall survival favored the immediate treatment group, but this was due to a slightly larger number of deaths in the deferred treatment group due to non-prostatic cancer causes. However, it was found that the number of patients requiring surgery for bladder outlet obstruction (TURP) was significantly higher in the deferred treatment group. The authors point out that the small increase in overall survival must be weighed on an individual basis against the adverse effects of life-long androgen deprivation, which may be avoided in a substantial number of patients who follow a deferred treatment protocol. Side effects of hormone therapy include loss of libido and erectile function, hot flashes, decreased muscle mass, thinning of bones, increased fracture risk, breast enlargement accompanied by tenderness and pain, anemia, and possibly diminished mental acuity.

One of the ongoing debates in urology concerns the merits of surgical removal of the prostate in cases presenting with evidence of high-grade cancer (Gleason 8-10 on biopsy). A recent paper published in the journal *Urology* attempts to address this question [14]. A group of 168 patients with Gleason scores of 8-10 and a range of pretreatment PSA and percent positive biopsy cores (%PBC) underwent radical prostatectomies at one of two

participating centers (Brigham and Woman's Hospital and the Hospital at the University of Pennsylvania). At each center, only one surgeon was involved for all the operations. The patients were stratified into 6 groups based on PSA and %PBC. There was no significant difference in Gleason score or clinical stage amongst the 6 groups. However, the group with the most favorable PSA (≤ 10 ng/mL) and %PBC ($\leq 50\%$) exhibited a significant difference in biochemical failure-free survival (recurrence as determined by a rising post-surgical PSA). The percent of patients who were disease-free at 5 years in this group was 67% and 23% for all other patients. Thus these two pre-surgical parameters potentially would allow clinicians to identify men with high-grade disease who were most likely to harbor organ confined disease (i.e. tumor that could be completely removed by removing the prostate) and this in turn could influence the decision regarding the merits of surgery and the use of adjuvant hormone therapy. Nevertheless, only 46 of 168 patients fell in this favorable pretreatment category and thus these results also point to the serious nature of disease when men are found to have Gleason 8-10 cancer.

Since 1995 Johns Hopkins University School of Medicine has been sponsoring a program they term *expectant management* but which is also called by some *active surveillance*. This program enrolls men with low-grade low-stage disease who elect to defer treatment until further delay would impact their chances of successful definitive treatment. While there is growing interest in this approach, it still represents a minor post-diagnosis path. A recent paper from Hopkins in the *Journal of the National Cancer Institute* may help increase participation in such programs [15]. At issue is whether or not curability is compromised by expectant management. At Hopkins, eligibility for the program is based on PSA density and the findings of a biopsy (see our book, Chapter 4). Follow-up involves semiannual determinations of free and total PSA, a digital rectal exam and an annual prostate biopsy. In contrast to the protocol at some other institutions, curative surgery is triggered only by the annual surveillance biopsy. Total PSA changes are not considered in triggering surgery, but if a patient wishes to leave the program and undergo a radical prostatectomy, this decision is honored. The question then is whether or not this protocol impacts the success of surgical intervention when triggered, i.e. do those in expectant management who go on to have a prostatectomy have a different rate of what the investigators term non-curable disease than a comparable cohort who received immediate intervention. Non-curable prostate cancer was defined as adverse pathology associated with a less than 75% chance of remaining disease-free for 10 years after surgery. This study found that in fact, delayed prostate surgery for patients with small, low-grade cancer who were involved in the expectant management program did not suffer any compromise of curability. These results should encourage clinicians to apply the Hopkins criteria to patients with small low-grade cancers and if they qualify, inform them that this is an option that may in fact spare them surgery for a number of years without risk of missing the so-called window of opportunity for a cure. At least some men will consider the annual biopsy as it is currently done with minimal risk and discomfort through the use of local anesthetic, pre-op antibiotics and a post-op antiinflammatory to be preferable to major surgery that in fact may not be immediately necessary and perhaps never needed. As studies continue, they will eventually reveal the probability of avoiding treatment over long periods of time in the case of very slowly developing cancers. Newly diagnosed patients need to be aware of these options.

Waiting times for radiation therapy can be quite long in some countries, especially where the major or only health care plan is government operated, chronically short of funds and personnel, and where in some case there is considerable administrative indifference.

A recent paper in the *American Journal of Clinical Oncology* addresses the issue of the impact of waiting on the success of radiation therapy for prostate cancer as measured by the rate of failure, i.e. the rate of so-called biochemical relapse indicated by rising post-treatment PSA levels [16]. This study from McGill University involved 289 patients with a mean follow-up of 6.1 years. Three waiting times were investigated: within 40 days, 41 to 80 days and > than 80 days. The study found that delaying the start of radiotherapy produced little effect on the rate of treatment failure in this group of patients. However, the study showed that after adjusting for known prognostic factors, a delay longer than 80 days after the decision to administer radiotherapy revealed a higher but statistically insignificant risk of biochemical relapse. Thus the question addressed remains an open one for long delays.

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