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William R. Ware, PhD - Editor

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Featured in this issue are two important components of preventive medicine, the long chain omega-3 fatty acids and that constantly recurrent supplement, vitamin D. As readers of this Newsletter know, the evidence for the health benefits of the omega-3 fatty acids found in fish oil are compelling, accrue to all ages from the unborn to the very old, and confer benefits in the prevention of a number of disorders prominent in our society. Acquiring and maintaining a healthy omega-3 status can be accomplished by eating lots of oily fish, taking rather large amounts of cod liver oil, or supplementing inadequate dietary intake with fish oil capsules or capsules containing refined fish oil with enhanced quantities of EPA and DHA, the two critical fatty acids. A recent paper in the "Journal of the American College of Nutrition" reminded me of krill oil, a most interesting source of EPA and DHA. I have reviewed this paper which deals with decreasing inflammation as well as what appear to be the only other randomized trials, one devoted to krill oil and blood lipids, the other dealing with the premenstrual syndrome. The patented brand of oil used in these studies appears to have unique properties as regards bioavailability. All three of these studies were directed entirely, or in part, by university- or hospital-based groups, and thus the extent of support from the patent holder appears minimal. All were randomized studies and two were placebo controlled.

Two papers are reviewed that address the importance of omega-3 supplementation and attention-deficit/hyperactivity disorder. This is an important problem with an amazingly large percentage of young people diagnosed with this disorder. In addition, a study is mentioned that addresses the issue of food additives and hyperactivity in children.

The vitamin D studies reviewed deal with the effect on overall mortality, multiple sclerosis, cardiovascular risk and finally, the safety of mega-doses for therapeutic purposes. If the concern is primary prevention, no one would or probably could take such high doses (over 200,000 IU/day), the absence of adverse effects strongly suggests that the high (2-4000 IU/day) or very high (10,000 IU/day) are apparently very safe. It is unfortunate that some influential groups are still worried about the safety of doses that exceed 400-800 IU/day. Incidentally, I found it interesting in this connection that our local drug store (part of a big national chain) has a large display of vitamin D bottles which contain 1000 IU capsules.

This issue also contains the first of a series of reviews on cholesterol and cardiovascular disease. In part I, the role of cholesterol in atherosclerosis is discussed. Part II will discuss cholesterol and mortality and Part III various aspects of lipid lowering.

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Wishing you continuing good health,

William R. Ware, PhD, Editor

MULTIPLE BENEFITS OF KRILL OIL

Krill is a term used to designate 85 cold deepwater marine species of the plankton family. Krill resemble shrimp and range in length from one to six centimeters. The two major fisheries are the Antarctic Ocean and the North Pacific Ocean along the coasts of Japan and Canada. While about 100,000 tons of krill are harvested annually, this represents only about 0.1% of the estimated existing population. The oil extracted from krill is low in contaminants mostly because the krill are very low in the marine food chain. The health benefits of krill oil have now been examined in three randomized, placebo-controlled trials, the most recent appearing early this year. We will also discuss related earlier papers.

KRILL OIL AND INFLAMMATION

In a paper in 2007 in the *Journal of the American College of Nutrition,* Deutsch *et al* reported on a study of 90 patients with confirmed cardiovascular disease and/or rheumatoid arthritis and/or osteoarthritis. All had C-reactive protein (CRP) levels above 1 mg/dL. They were randomized into two groups, one receiving 300 mg/day of krill oil and the other a placebo. After thirty days of treatment, CRP levels decreased 30.9% in the oil group but increased 25.1% in the placebo group. Standard scoring methods for arthritis severity were employed and revealed significant reduction of arthritic symptoms during the initial 7- and 14-day periods. Parameters included pain, stiffness and functional impairment.

KRILL OIL AND ELEVATED CHOLESTEROL

In 2004 Bunea *et al* reported on a randomized trial of the effect of krill oil on cholesterol and triglyceride levels as compared with a normal fish oil or a placebo when the oil was taken over 90 and 180 days. Doses of krill oil were higher in this study than in the above inflammation study and were either 2-3 g/day on a BMI based dose, or 1-1.5g/day. The fish oil control received 3 g/day of fish oil providing 540 mg/day of eicosapentaenoic acid (EPA) and 360 mg/day of docosahexaenoic acid (DHA). For the krill oil group, 2 or 3 g/day resulted in similar changes in blood lipids (approximate values): total Cholesterol (TC), -18%,; LDL, -38%; HDL, + 57%; triglycerides (TG), -26%. The group on 3 g/d of fish oil had the following changes: TC, -5.96%; LDL, -4.5%, HDL, +4.2% and TG, -3.1% . The placebo group had the following changes: TC, +9.1%, LDL, +13%, HDL +4% and TG, -9.9%. Thus Krill oil had, in comparison with either fish oil or a placebo, a very large impact on serum lipid levels in a direction considered by mainstream medicine to be very favorable. These changes are comparable or better than achieved by the statin cholesterol lowering drugs. The cohort excluded patients with familial hypercholesterolemia, pregnancy, alcohol or drug abuse, or the use of anticoagulant therapy. The authors comment that the bioavailability of polyunsaturated fatty acids such as EPA and DHA depends on factors such as the type of lipids with which they are associated and the physical state such as a lipid solution or a colloidal particle system. The fatty acids in krill oil are already incorporated into phospholipids which is thought to considerably enhance the bioavailability. Krill oil with the brand name NKO from Neptune Bioressources contains 150 mg EPA and 90 mg of DHA per gram of oil. Thus the 2-gram dose of krill oil which was as effective as the 3-gram dose and had lower EPA and DHA levels than the fish oil used in comparison and yet achieved much larger favorable changes in the blood lipid profile.

KRILL OIL FOR MANAGEMENT OF PREMENSTRUAL SYNDROME AND PAINFUL MENSTRUATION

Sampallis *et al* reported in 2003 on a study of efficacy of krill oil in managing the premenstrual syndrome (PMS) and dysmenorrhea (painful and difficult menstruation). In this double blind, randomized trial, patients with diagnosed PMS were treated for three months with either krill oil or ordinary fish oil. Validated questionnaires were used to assess the changes in symptoms. The resultant data showed a significant improvement on interim and final evaluations for the krill oil group as compared to baseline evaluation, and as well as when the krill oil group was compared with the fish oil group. Also, significantly lower amounts of analgesics were consumed by the krill oil group when interim and final evaluations were compared with baseline, and also when krill oil users were compared to those taking fish oil. The authors conclude that krill oil can significantly reduce dysmenorrhea and the emotional symptoms of PMS and was more effective than ordinary fish oil for the management of PMS.

Deutsch, L. Evaluation of the Effect of Neptune Krill Oil on Chronic Inflammation and Arthritic Symptoms. ***Journal of the American College of Nutrition****, 2007, Vol. 26, No. 1, pp. 39-48.*

Bunea, R. et al. Evaluation of the Effects of Neptune Krill Oil on the Clinical Course of Hyperlipidemia. ***Alternative Medicine Review,*** *2004, Vol. 9, No. 4, pp. 420-28.*

Sampalis, F. et al. Evaluation of the Effects of Neptune Krill Oil on the Management of Premenstrual Syndrome and Dysmenorrhea. ***Alternative Medicine Review,*** *2003, Vol. 8, No. 2, pp. 171-9.*

Editor's comments: All of these studies utilized a product trademarked "NKO" and manufactured by Neptune Biotechnologies and Bioressources, Inc. of Laval, Quebec, Canada. This company has a unique patented process of recovering the krill oil which yields phospholipid bound poly unsaturated fatty acids EPA and DHA, making NKO krill oil a unique formulation of these two long-chain polyunsaturated fatty acids. The preparation also contains Vitamins A and E, and a substance called astaxanthin, an antioxidant. The company claims their preparation has 300 times the antioxidant power of vitamins A and E. The research was all done in Quebec or Ontario, Canada. Lead researchers were either from McGill University or the University Health Network Toronto. Only the earliest paper has a coauthor someone who was directly working for Neptune Technologies and Bioressources. Neptune krill oil (NKO brand) is available from health food stores or Internet vendors. It appears to be the only brand used in clinical trials. The company recently entered into a research and development agreement with Nestlé to further investigate the health benefits of krill oil. In addition the company has an agreement with Yoplait to cooperate in the development of dairy products containing krill oil.

In addition to the three papers discussed above, there appear to be only two other studies of this oil in journals covered by the National Library of Medicine (PubMed). Both were rodent studies published in 1994. There is obviously a great opportunity here for more research into this interesting fish oil, and in particular the preparation NKO.

OMEGA-3 FATTY ACIDS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Attention-deficit hyperactivity disorder (ADHD) is a rapidly growing problem in the Western world. It is estimated that 5-10% of school-age children (mostly boys) suffer from the disorder. Major symptoms are difficulty in sustaining attention, hyperactivity, and impulsivity. ADHD is also associated with learning difficulties in reading, spelling, and math and may involve psychiatric problems that follow the child into adulthood. There is considerable evidence that ADHD is linked to a fatty acid deficiency or imbalance. Long-chain fatty acids such as EPA and DHA are essential to proper brain functioning and several studies involving children with ADHD have shown that they are deficient in these essential fatty acids. Two recent studies relate to this topic.

IMPACT OF OMEGA-3 SUPPLEMENTATION ON AN INFLAMMATION MARKER IN ADHD PATIENTS

Germano *et al* recently reported a study that involved testing omega-3 supplementation on both the fatty acid composition of plasma phospholipids and red blood cell phospholipids and as well observing any changes in two measures of the extent of the ADHD. The study, done in Italy, recruited a cohort aged 3.5 to 16 years and included controls and individuals diagnosed with ADHD. The intervention involved approximately 2.5 g/d of fish

oil per 10 kg of body weight which on average gave a dose of about 8.5 g/day of an oil containing 84 % omega-3 fatty acids and a ratio of EPA/DHA of about 2. Attention was focused on the ratio of arachidonic acid (AA) to EPA in the blood samples. This ratio is viewed as a measure of inflammatory status and as well is a related to the dietary omega-6/omega-3 ratio. Before supplementation, the AA/EPA ratio for those with ADHD was about 41 whereas for the controls it was about 28, the difference being significant. Supplementation reduced the ratio to about 4 in the ADHD group and this was accompanied by significant improvement in measures of inattention and hyperactivity. The authors suggest that the results may indicate a connection between ADHD and cell membrane fluidity and architecture, both of which depend on this ratio. They also suggest the ratio be considered as a marker to support ADHD diagnosis even if further research is needed to confirm this assumption.

Germano, M. et al. Plasma, Red Blood Cells Phospholipids and Clinical Evaluation after Long Chain Omega-3 Supplementation in Children with Attention Deficit Hyperactivity Disorder. ***Nutritional Neurosciences,*** *2007, Vol. 10, No. 1-2, pp. 1-9.*

Editor's comments: In a recent review regarding 0mega-3 fatty acids and ADHD (*International Review of Psychiatry*, 2006;18(2):155-72), Richardson lists five randomized, controlled trials of the effect of omega-3 supplementation on ADHD and related developmental disorders in children. Three yielded positive results but the daily amounts of EPA arranged from 80 mg to 558 mg and DHA ranged from 174 mg to 480 mg. Compared to the study of Germano, these are very low doses. By contrast, negative studies involved treatment primarily or exclusively with DHA. The author points out that this is consistent with other studies suggesting that EPA may be more efficient than DHA in treating functional disturbances of attention, cognition or mood. More studies are needed to assess the dose-benefit relationship. However, the impact of very large doses of fish oil on the AA/EPA ratio has been studied by Young *et al* (*Reproductive Nutrition and Development,* 2005;45:549-58). By using 39 g/day of an oil containing 92% EPA and DHA for 12 weeks, the AA/EPA ratio dropped by almost 92%, and the final ratio was 1.4 which is on a par with populations that consume large amounts of fish. Some would have real trouble taking 39 g/day of fish oil!

The observation of Germano that the AA/EPA ratio was significantly elevated in ADHD patients relative to controls is consistent with a study of Antgalis *et al* (*Prostaglandins, Leukotrienes and Essential Fatty Acids*, 2006;75:299-08) where it was found that in ADHD patients, this ratio was 36% higher than in controls. The diagnostic utility of this ratio remains to be studied but these results are suggestive.

The reader is referred to Barry Sears' book *The Anti-inflammation Zone* for a general discussion of the AA/EPA ratio which he calls the "Silent Inflammation Profile." The implications of a high ratio go well beyond ADHD and related disorders, and is important for all age groups. In Canada, at least one nationwide clinical laboratory offers an assay that measures this ratio.

OMEGA-3 SUPPLEMENT BETTER THAN RITALIN

A randomized clinical trial of the effect of omega-3 supplementation on ADHD symptoms has recently reported. It involved 103 Australian children (74% boys) between the ages of 7 and 12 years. The children had all been diagnosed with ADHD and had scores two standard deviations or more above the general population on the Conners abbreviated ADHD Index, a standard ADHD assessment tool. The trial participants were randomized to receive either placebo capsules (palm oil), fatty acid capsules (providing 560 mg/day of EPA, 175 mg/day of DHA, 60 mg/day of gamma-linolenic acid, and 10 mg/day of vitamin E), or fatty acid capsules + a multivitamin tablet containing low (RDA) amounts of vitamin and minerals.

After 15 weeks all children were given fatty acid capsules + daily multivitamin for a further 15 weeks. They were evaluated for ADHD symptoms after 15 and 30 weeks. At 15 weeks their scores on the Conners Parent Rating Scale were significantly reduced in regard to hyperactivity, inattention and impulsivity, and improvement was also noted in the sub-scores for perfectionism and social problems. There was no indication that adding the multivitamin to the fatty acid regimen had any additional benefits. Improvements continued until the end of the trial at week 30 at which time 40-50% of the treated children showed improvements corresponding to at least one standard deviation on the Conners ADHD Index. This improvement is equivalent to, or slightly better than, the improvement observed after 4 weeks of treatment with short-acting methylphenidate (Ritalin).

According to Canadian researchers who performed a meta-analysis of 62 randomized trials of Ritalin, there is no evidence that this drug is effective

beyond 4 weeks and there is considerable evidence of its many adverse effects including decreased appetite, insomnia, headaches, stomach aches, drowsiness, anxiety, irritability, and dizziness.

Sinn, N. and Bryan, J. Effect of Supplementation with Polyunsaturated Fatty Acids and Micronutrients on Learning and Behavior Problems Associated with Child ADHD. Journal of Developmental & Behavioral Pediatrics, *2007,Vol. 28, April, pp. 82-91*

Schachter, HM, et al. How Efficacious and Safe is Short-acting Methylphenidate for the Treatment of Attention-deficit Disorder in Children and Adolescents? Canadian Medical Association Journal, *2001, Vol. 165, November 27, pp. 1475-88.*

MORE POSITIVE RESEARCH RESULTS FOR VITAMIN D

In a milieu that is very strongly against supplements, at least within mainstream medicine, with papers appearing very frequently that report either null results, it is refreshing to observe the rapid progress that vitamin D is making as an established hero in preventive medicine, especially since aside from sun exposure, supplementation is the only practical answer to achieving and maintaining a healthy and desirable vitamin D status. Advice to obtain more vitamin D by sun exposure of course is in direct conflict with the recommendation to severely limit sun exposure and utilize sunscreens to reduce the risk of skin cancer.

VITAMIN D SUPPLEMENTATION AND TOTAL MORTALITY

There are those who believe that total or all-cause mortality is the only really important endpoint for studies of benefit. If an intervention does not cause one to live longer, why bother? However, this is not a universally shared belief and in addition, mortality studies generally must be both large and relatively long-term to yield statistically significant results. This problem can be overcome with a meta-analysis even if all or most of the included studies failed to achieve statistical significance. With the enlarged cohort obtained by combining studies, statistically significant results may be forthcoming. This is the case in the study by Autier and Gandini recently reported in the *Archives of Internal Medicine*. The researchers identified 18 trials for the analysis which included over 57,000 participants and a total of 4777 deaths from any cause. Daily vitamin D supplement doses ranged from 300 to 2000 IU. When the studies were stratified into two groups according to high vs. low statistical power, the nine with high power yielded a significant 8% reduction in mortality associated with vitamin D supplementation. The low power group failed to give statistical significant benefit, and for the nine high-powered studies, individually they all failed to achieve statistically significant evidence of benefit. Nevertheless, it was concluded that ordinary doses of vitamin D appeared to be associated with a decrease in mortality rates.

Only 8 studies reported 25-hydroxyvitamin D levels at baseline and during the study. In the intervention groups, 7 out of 8 studies found mean 25-hydroxyvitamin D levels below 50 nmol/L at baseline, levels that are considered by some to represent a deficiency. Supplementation brought the means up to where most were near or above 50 nmol/L but only 2 out of 8 studies achieved a mean value of over 100 nmol/L. This meta-analysis did not permit examining the question of the impact of dose on mortality. Nor were the results stratified by major causes of death. The authors also remark that the results based on this very large cohort indicate the absence of adverse effects from vitamin D supplementation at the doses involved, most of which were between 400 and 800 IU/day.

In an accompanying editorial, Edward Giovannucci from Harvard comments that the studies in question, which had a range of follow-up from 6 months to 7 years, may have underestimated the potential benefit from vitamin D supplementation since it was not possible to examine the impact of this vitamin on the incidence and development of a variety of diseases. He also points out that questions raised by the meta-analysis include the possibility of even a greater reduction of mortality if higher intakes of vitamin D were employed, if compliance was improved, if higher levels of 25-hydroxyvitamin D were achieved, and if the duration of supplementation were longer.

Autier, P. and Grandini, S. Vitamin D Supplementation and Total Mortality. ***Archives of Internal Medicine****, 2007, Vol. 167, No. 16, pp. 1730-7.*

Giovannucci, E. Can Vitamin D Reduce Mortality? Ibid, pp. 1709-10

ARE HIGH DOSES OF VITAMIN D SAFE?

Kimball *et al* have recently reported on a study done in Toronto, Canada that addresses this question in the context of using very high doses of vitamin D for the treatment of multiple sclerosis (MS). During a 12-week period, 12 patients in an active phase of MS were given 1200 mg/day of calcium and

progressively increasing doses of vitamin D3 which started at 28,000 IU and progressed to 280,000 IU. Mean serum 25-hydroxyvitamin D levels rose from 78 to 386 nmol/L. Adverse effects were sought by monitoring serum calcium levels, the urinary ratio of calcium to creatinine, liver enzymes, serum creatinine, electrolytes, serum protein, and parathyroid hormone. None were found. In particular, these huge doses of vitamin D caused neither elevated serum or urine calcium levels. The authors conclude that the data support the feasibility of pharmacologic doses of vitamin D for clinical research and as well provide objective evidence that vitamin D intake beyond the current upper limit of 2000 IU/day is safe by a large margin. They also point out that there is already evidence that daily doses of 4000 and 10,000 IU/day are safe. This so-called Phase I study concerned with the issue of safety and was not powered to detect changes in clinical outcomes in the patients involved.

Kimball, S.M. et al. Safety of Vitamin D3 in Adults with Multiple Sclerosis. ***American Journal of Clinical Nutrition****, 2007, Vol. 86, pp. 645-51.*

CHILDHOOD SUN EXPOSURE AND MULTIPLE SCLEROSIS: A STUDY OF TWINS

This study from the University of California in Los Angeles examines the influence of childhood sun exposure on the risk of multiple sclerosis (MS) in monozygotic twins, i.e. twins originating from a single egg that have the same gender and identical genetic constitution. By doing this, the investigators eliminated confounding by genetic susceptibility. They recruited a total of 79 twin pairs with MS where there was a quantifiable difference in sun exposure between the pair and where only one twin had MS. A sun exposure index dependent on nine sun exposure related activities was developed to provide a numerical evaluation of sun exposure for each individual. It was found that each of the nine sun exposure related activities during childhood seemed to convey a strong protection against MS in this group of twin pairs, that is, the MS free twin had significantly higher sun exposure index or score than the MS member of the pair. Sun tanning, for example, reduced the risk by 60% for the twin who spent more time at this activity compared to the co-twin. Finally, when the data was stratified by gender, the benefit of sun exposure was restricted to only the female sets of twins. The authors of this beautifully designed and executed study conclude that sun avoidance seems to precede the diagnosis of MS and that this protective effect is independent of genetic susceptibility.

The authors point out that their study is consistent with the strong protective effect of sun exposure during childhood (6-15 years) found in a case-control study conducted in Tasmania. The protective effect (risk reduction) of averaging 2 or more hours per week of sun exposure compared to less than 2 hours was 69%. In addition, they mention a study where indoor and outdoor workers exhibited a dose-dependent protective effect of sun exposure on MS-related mortality. The present study is especially important because it eliminates questions about inheritable factors that might have influence these and other studies.

The mechanism involved in the protective effect is unknown, but MS is an autoimmune disease and exposure to sunlight could, according to the authors, produce protection by several immunosuppressive mechanisms. Or sunlight produced vitamin D could suppress the production of cytokines associated with MS activity. The authors also suggest that the fact that the protective effect was only seen in female twin pairs suggests that there may be a sex-specific vitamin D mediated immunomodulation as has been seen in animal studies.

Islam, T, et al. Childhood Sun Exposure Influences Risk of Multiple Sclerosis in Monozygotic Twins. ***Neurology****,* ***2007****, Vol. 69, pp. 381-88.*

VITAMIN D AND CARDIOVASCULAR RISK

A national survey designed to estimate the prevalence of common chronic conditions and associated risk factors was conducted in the US between 1988 and 1994 (NHANES III). It provided a database which is constantly mined for information about specific questions. A study based on this data was recently published which addresses the question of the association between vitamin D status and the prevalence of risk factors for cardiovascular disease (CVD) using the vitamin D serum marker 25-hydroxyvitamin D. Data for over 15,000 adult participants were available. When individuals with 25-hydroxyvitamin D levels less than 52 nmol/L were compared with those with levels equal to or greater than 92 nmol/L, it was found that those in the low-level group had significantly higher probabilities of have hypertension, abnormal blood glucose, history of diabetes, obesity, and high triglycerides. However, for two prominent risk factors, high total cholesterol or non-HDL cholesterol, no correlations were found. The authors claim that to the best of their knowledge this is the first study to demonstrate significant association between low vitamin D status and CVD risk factors in a nationally representative

sample. In addition, they pointed out that favorable trends for the risk factors for obesity, diabetes and hypertension may well continue to increase at levels greater than 92 nmol/L conferring additional health benefits. In addition, their results were regarded as consistent with the established literature that suggests a role for vitamin D in promoting insulin sensitivity and preventing diabetes. They also present plausible biological mechanisms for some of the observed dependencies on vitamin D.

Martins, D. et al. Prevalence of Cardiovascular Risk Factors and the Serum Levels of 25-Hydrfoxyvitamin D in the United States. ***Archives on Internal Medicine,*** *2007, Vol. 167, June 11, pp. 1159-1165.*

Editor's comments: It is clear that there is a relationship between vitamin D status and a wide variety of disorders. This must be in part due to the role vitamin D plays in a very large number of cellular processes. In addition, as indicated in an article reviewed above, humans tolerate very large doses of vitamin D without any apparent ill effects. Also, a recent paper that presented negative results of an intervention study regarding vitamin D and cardiovascular events (*Circulation*, 2007;115:846-54) will not be reviewed simply because the doses used for vitamin D were so small (400 IU/day) that it is not surprising no effect was seen.

NEWS BRIEFS

FOOD ADDITIVES AND HYPERACTIVE BEHAVIOR IN CHILDREN

A randomized, double-blind, placebo-controlled study has just reported that tested artificial food color and other additives in the context of hyperactivity in 153 3-year olds and 144 8- to 9-year olds. Both parents and teachers were involved in rating the outcomes. Aside from the artificial food-coloring agents, sodium benzoate was the only other additive tested. Significant adverse effects were observed for artificial coloring agents or sodium benzoate preservative or both in that these substances increased hyperactivity in both age groups, a result that the authors suggest extends to the general population of children in these age groups.

McCann, D. et al. Food Additives and Hyperactive Behavior in 3-Year-old and 8/9-year-old Children in the Community. A Randomized, Double-Blinded, placebo-Controlled Trial. ***Lancet****, 2007, published ahead of print (DOI:10.1016/S0140-6736(07)61306-3).*

WAIST-TO-HIP RATIO AND ATHEROSCLEROSIS

Investigators obtained data from the Dallas Heart Study which involved a large, multiethnic urban population of patients on whom electron beam tomography had been done to access coronary plaque and where MRI data was available to determine aortic plaque. It was found that the likelihood of coronary calcification, i.e. coronary atherosclerosis, increased in direct proportion to increases in waist-to-hip ratio (WHR). Individuals in the highest as compared to the lowest quintiles of WHR had greater than a four times increased in risk of prevalent coronary calcification. The result remained after correcting for standard risk factors (twice the relative risk). In addition, for those with MRI data available, the risk of atherosclerotic plaque in the aorta was three times higher in those with the largest WHR compared to the smallest WHR. WHR was also found to be a better predictor of coronary calcification than the body mass index or waist circumference alone. WHR for the lowest and highest quintiles were < 0.906 and > 1.009 for men and < 0.802 and > 0.92 for women.

Abdullah, S.M. et al. The association of Differing Measures of Overweight and Obesity with Prevalent Atherosclerosis. ***Journal of the American College of Cardiology****, 2007, Vol. 50, pp. 752-59.*

MAGNESIUM INTAKE AND THE RISK OF TYPE-2 DIABETES

There have been a number of observational studies of the association of magnesium intake and type-2 diabetes, but the picture that emerged was not totally consistent. In a recent meta-analysis of 7 cohort studies of magnesium from foods or supplements, the combined participant population was 286,669 with 10,912 cases of diabetes. The overall relative risk per 100 mg per day increase in magnesium intake was 0.85 (15% risk reduction) with similar results when the data was stratified for either supplemental or dietary intake. These results from the combined cohort were statistically significant even though 4 of the 7 studies individually failed to achieve statistical significance. The authors point out that one hundred mg of magnesium would be supplied by four slices of whole grain bread, four cups of oatmeal, one cup of beans, 1.4 cup of nuts, 4 tablespoons of peanut butter, ½ cup of cooked spinach or three bananas per day, and would on average yield a 15% reduction of the risk of diabetes.

Larsson, S.C. et al. Magnesium Intake and Risk of Type 2 Diabetes: a Meta-analysis. ***Journal of Internal Medicine****, 2007, Vol. 262, pp. 208-14.*

Editor's comments: One multivitamin pill typically contains 100 to 200 mg of magnesium. Magnesium is readily available as an individual supplement, either alone or combined with calcium. Intakes of considerable more than 100 mg per day are recommended by some experts. The reader is referred to the book by Seelig and Rosanoff, *The Magnesium Factor*, Avery (Penguin, 2003), for an excellent and comprehensive account of the health benefits of adequate magnesium intake.

COENZYME Q-10 AND HIGH BLOOD PRESSURE

Coenzyme Q-10 (CoQ-10) is an integral and essential component of the mitochondrial respiratory chain for energy production and is found in all tissues and organs of the body with the highest concentrations in the heart. Blood levels decrease with aging and cardiovascular disease and are reduced by many statin cholesterol lowering drugs. A CoQ-10 deficiency has been implicated in heart failure and hypertension. A recent analysis of existing trials of CoQ-10 for treating hypertension has just reported. The study examined 12 clinical trials with 362 participants and involved randomized placebo controlled trials, crossover trials and open-label trials. A blood pressure effect was found in all trials. The prospective randomized trials and crossover trials showed similar results with decreases in systolic blood pressure ranging from 11 mm Hg in the crossover to 17 mm Hg in the randomized studies. A decrease in diastolic blood pressure was observed in studies with either of these designs. Open label studies found systolic changes ranging from 10 to 21 mm Hg, and diastolic changes from 7 to 16 mm Hg. Dosages varied from 34 mg/day to 2256 mg/day. In the largest study, it was found that the blood pressure changes came about gradually over several months and required varying doses in different patients (72-360 mg/day) to achieve what was considered a therapeutic dose yielding blood levels of CoQ-10 of > 2.6 µg/ml. The authors comment that patients on statin drugs may require higher doses. Studies reported very few minor side effects, or none at all.

Rosenfeldt, F.L. et al. Coenzyme Q-10 in the Treatment of Hypertension: a Meta-analysis of Clinical Trials. ***Journal of Human Hypertension,*** *2007, Vol. 21, pp. 297.*

Editor's comments: The changes in blood pressure described above are large enough to move one from borderline hypertension to the normal range. Recent attempts to increase the bioavailability of CoQ-10 have resulted in some modern preparations with much higher bioavailability than older preparations such as were used in all of the trials analyzed in the above study. However, care must be taken in purchasing this enzyme to make sure that there is genuine enhanced bioavailability.

VITAMIN B6 AND COLORECTAL CANCER

A recently reported study from Japan found that the intake of vitamin B6 was inversely related to the risk of colorectal cancer. Dietary intake was determined by a questionnaire. Mean intakes were 1.09 mg/day for the lowest quartile and 1.91 mg/day for the highest. When the lowest and highest quartiles were compared, an approximate risk reduction of 69% was found. Men who had an alcohol intake of 150 g/week (about 10 drinks) had more than twice the risk of colorectal cancer than those who drank less if they were in the lowest quartile of intake, but the risk associated with alcohol disappeared for those in the highest quartile. The authors conclude that while higher intake of dietary B6 was associated with reduced risk of colorectal cancer, the effect was primarily seen in men who consumed alcohol. Vitamin B6 was derived from rice, tuna fish, potatoes, beer and sake (Japanese rice wine). All subjects were Japanese.

Ishihara, J. et al. Low Intake of Vitamin B-6 is Associated with Increased Risk of Colorectal cancer in Japanese Men. ***Journal of Nutrition****, 2007, Vol. 137, pp. 1810-14.*

Editor's comments: These results are particularly interesting since the amounts of vitamin B6 are low compared to what is found in typical multivitamin preparations. For example, the Centrum multivitamins contain 3-8 mg, and Life Extension's "Two-per-day" brand contains 75 mg per recommended daily dose.

RESEARCH REPORT

Cholesterol – A Review: Part I

by William R. Ware, PhD

DOES CHOLESTEROL CAUSE ATHEROSCLEROSIS AND CORONARY HEART DISEASE?

"An almost endless number of observations and experiments have effectively falsified the hypothesis that dietary cholesterol and fats, and a high cholesterol level play a role in the causation of atherosclerosis and cardiovascular disease. The hypothesis is maintained because allegedly supportive, but insignificant findings are inflated, and because most contradictory results are misinterpreted, misquoted or ignored." U. Ravnskov, M.D., Ph.D.

INTRODUCTION

Cholesterol causes atherosclerosis and coronary heart disease, or put another but not equivalent way, there is a positive association between cholesterol levels and development and extent of atherosclerosis and thus coronary heart disease. Everyone knows this. This hypothesis has the status of an unquestionable belief, a self-evident truth. It is important, however, to distinguish between atherosclerosis and symptomatic or actual coronary heart disease (CHD). The latter generally includes angina or a history of one or more fatal or non-fatal heart attacks. Thus when CHD is an endpoint in a study, this generally includes clinical manifestations and actual adverse events, whereas if atherosclerosis is the subject of study, merely its presence and extent are at issue. Nevertheless, there is of course a close connection between the two. If an individual has no coronary atherosclerosis at all, the risk of an adverse coronary event is very small, and risk of symptomatic CHD or CHD adverse events increases with the extent of atherosclerosis. Also, the observation of atherosclerotic deposits in the coronary arteries leads to the diagnosis of coronary heart disease which makes itself evident by both symptoms (angina) and events (heart attacks). However, if one restricts their attention to the heart attack event itself, then the situation is somewhat more complex, given what in general is a multi-step process.

One might have thought that the cholesterol hypothesis would have met with resistance. After all, it seems a bit curious that a substance alleged to cause atherosclerosis and thus heart disease in fact comprises 5% of cell membrane lipids and plays a key role in maintaining cell wall structure. It is also the starting point for the synthesis of several groups of very important biochemicals, including male and female sex hormones, vitamin D (via photochemical action in the skin) and bile acids. Cholesterol is also used by the body in natural healing processes and tissue repair. The absorption through the gut of dietary cholesterol is poor, and the body is generally able to compensate for dietary intake by adjusting the endogenous synthesis which occurs mainly in the liver, and thus for most individuals, the serum levels are only very weakly related to dietary intake. Also, cholesterol molecules are never found free in blood since they are insoluble and are transported mainly by so-called lipoproteins of which the high and low density varieties (LDL and HDL) are regarded as bad and good according to the conventional wisdom, in spite of the fact that transport of cholesterol is essential to life. Given the vital functions of this molecule and its lipoprotein transporters, is it not a bit surprising that cholesterol is a cause of atherosclerosis?

Normal progression in science involves falsifying hypotheses rather than proving them. When there are associated with a hypothesis a number of inconsistencies, observations that appear to contradict or falsify the hypothesis, then there should be cause for concern that it is flawed or false and might in fact be leading down a dead-end road. The Bohr atom studied by every high school chemistry student is an example where a beautiful hypothesis (theory) was eventually falsified and replaced by quantum theory. But Einstein spent much time trying to find a so-called thought experiment to demonstrate that one of the essential pillars of the quantum theory was false. Incidentally, he failed but this is how progress is made. But today, anyone who questions the hypothesis that cholesterol in general or LDL cholesterol in particular causes or is a risk factor for atherosclerosis is ignored, branded a nut, or ostracized by professional colleagues, or perhaps told not to worry because it is really oxidized LDL that is important—just wait until this revision becomes a genuine truth that no one can question. Cholesterol is really LDL is really oxidized LDL, no problem. In the literature it is repeatedly stated that the evidence backing the Cholesterol Hypothesis is overwhelming, but when one follows up on references in publications where this statement is made, it turns out to be impossible to find this overwhelming evidence. More about this later. And there indeed are deniers within the medical profession, i.e. those who deny the validity both the causality and association aspects of the Cholesterol Hypothesis, and their voices are occasionally heard, mostly in one of several peer-reviewed British medical journals or in books one can buy at Amazon.com. The quotation given above represents the strong opinion of one high profile denier. This Review will attempt to critically evaluate the merits of the position taken by the deniers, in particular with regard to atherosclerosis.

The cholesterol hypothesis goes back a long way, in fact to the mid-19th century in Berlin where Rudolf Von Virchow found plaques in arteries of cadavers and observed that they contained cholesterol—an amazing observation given the development of medical science at the time. He made no connection with heart disease or heart attacks since these problems did not exist or were not recognized then. In fact the first medical description of a myocardial infarct (heart attack) as a clinical pathologic entity did not appear in the medical literature until 1915. Fifty years after Virchow's observation for some reason or other a Russian named Anitschkov fed rabbits a diet high in cholesterol and observed that their arteries thickened and filled up with cholesterol. But rabbits are not carnivores and cholesterol is totally foreign to their natural diet. Rabbits do not normally eat meat, eggs or milk products. It is doubtful that such studies are at all relevant to humans. After the WWII more cases of heart disease were being identified and there was growing interest as to both the cause and possible therapies. The breakthrough for the Cholesterol Hypothesis came with the study of Ancel Keys from the University of Minnesota, the instigator of the famous "Seven Countries" study of the relationship between heart disease, serum cholesterol levels and fat intake. As was eventually pointed out, Professor Keyes actually selected seven countries from a larger set in order to support his hypothesis. As Dr. Malcolm Kendrick, M.D., in his book *The Great Cholesterol Con* points out, by selecting a different set of seven countries using data available to Keys, one can get exactly the opposite correlation. Also, if one uses all the data the correlation disappears. Keys' work was followed by the famous Framingham Study which provided evidence, albeit rather weak, for a connection between cholesterol and coronary heart disease (CHD), particularly in young men, and by additional studies where rabbits were fed a diet containing cholesterol and fat, and the Hypothesis was well on its way to becoming enshrined. The final pillar was added when it was shown that lowering cholesterol in patients who had suffered a heart attack reduced the risk of a second heart attack (secondary prevention). Add to this the high rate of coronary heart disease among those with a familial predisposition to very high cholesterol levels even at a young age, and the story was complete. Circulating cholesterol caused heart disease and since heart disease involved atherosclerosis, cholesterol must be involved in the development and progression of atherosclerosis as well. Case closed. The evidence was compelling. No reasonable person could conclude otherwise. The end result has been a 55 billion dollar (U.S.) worldwide business in cholesterol lowering drugs, numerous successful careers in academic medicine, and a Nobel Prize for two researchers. Perhaps more importantly, there arose a widespread fear among many individuals of high blood levels of cholesterol as well as dietary cholesterol and fat and the result was psychological stress and in some cases an adherence to diets that may in fact be unhealthy. In addition, a hostile environment now exists for anyone who even suggests that there may be serious problems with what are almost universally viewed as the evidence-based foundations of the Cholesterol Hypothesis.

Today LDL cholesterol or its oxidized form largely replaces total cholesterol (TC) as the agent viewed as responsible for causing coronary heart disease (CHD). But TC and LDL go hand in hand. LDL levels are generally not directly measured but calculated from measurements of triglycerides (TG), HDL and TC. The calculation assumes that the TC can be regarded as the following:

TC = LDL + HDL + 0.2 X TG (values in mg/dL)
TC = LDL + HDL + 0.46 X TG (values in mmol/L)

HDL values are typically 50 ± 10 mg/dL, and if TGs are at 150 mg/dL, they contribute only 30 the total. Increase TG to 200 and this only increases TC by 10. Thus TC reflects mainly LDL, and it can be argued that TC is a fairly good surrogate marker for LDL. The ascension of LDL to the position of villain is probably largely because higher levels of HDL were found to be beneficial and thus higher levels of LDL must be bad, given that TC was bad. But a decrease in the risk of CHD or even CHD mortality due to a drug therapy that reduces TC and LDL does not prove that TC and/or LDL are causative factors. For this to be the creditable, it must at least be demonstrated that the only possible significant action of the drug is the lowering of cholesterol. As will be discussed below, this appears to be far from the truth. To put it another way, if the beneficial effects of cholesterol lowering drugs, which today are mostly statins, is due to actions of the drug that do not involve lowering levels of cholesterol, then the cholesterol lowering itself is irrelevant in this context, even if a dose dependence is observed. That is, the non-lipid lowering mechanism could be dose dependent as well and responsible for all the observed benefits.

In fact the statin cholesterol lowering drugs impact a number of biological processes and this has become a hot research area. Also a number of problems exist which are related in part to inexplicable dose and level dependencies. For example, consider studies that have different initial LDL levels and produce similar percentage LDL lowering. These studies all give similar risk reduction, but the endpoint LDL in one study can be higher than the initial level in another study, and yet the same benefit accrues. There have been a number of such studies and taken together they suggest that the initial and terminal levels of LDL have nothing to do with the risk reduction. A review in 2007 put the matter this way when discussing the use of statin drugs to lower cholesterol: “The relative risk reduction is approximately 20-40% regardless of age, sex, pretreatment level of LDL-C, race or preexisting myocardial infarction” [1]. Such results have caused a number of researchers in this field to look at the possibility that the statin drugs prevent recurrent heart attacks by some other mechanism than cholesterol lowering, and the levels of either TC or LDL are in a large part unrelated to the benefit of the drug treatment. This is now a very active area of research and that alone should suggest just how unacceptable is the argument that the Cholesterol Hypothesis is proven in terms of a causal relationship by the fact that benefits, mostly in secondary CHD outcomes, are produced by cholesterol lowering by drugs. Proposed non-lipid lowering mechanisms include improvement of endothelial dysfunction, reduced inflammatory response, stabilization of atherosclerotic plaques and reduced thrombogenic (clot formation) response [1,2]. It turns out that statins, which block a critical step in the biosynthesis of cholesterol, also eliminate two precursors to a number of biologically important molecules which in turn may be related to the above non-lipid lowering effects of these drugs. Lipid lowering will be the subject of the third review in this series where more documentation will be provided. But the essential point is that there are problems, both logical and factual, with the standard argument that because there is a decrease in risk of CHD when statins are used to lower TC and LDL, that it therefore follows that TC and in particular LDL cause CHD, or atherosclerosis for that matter. It is also of interest that there does not appear to be an explanation for just how LDL is supposed to cause atherosclerosis and coronary heart disease [3]. Rather, it is “work in progress.” In what follows we will look at a number of studies that are either inconsistent with the Cholesterol Hypothesis or appear to actually falsify it.

AUTOPSY STUDIES

If circulating cholesterol causes atherosclerosis and thus coronary heart disease, one might expect to see a correlation between the extent of atherosclerosis and cholesterol levels. The first significant study appears to have been reported back in 1936. Two pathologists from New York University, K. Landé and W. Sperry, studied a large group of individuals who had died from violent incidents [4]. They examined the extent of coronary atherosclerosis observed at autopsy and found no correlation with serum cholesterol levels. Some dismissed these results by claiming that cholesterol values measured after death were not a reliable measure of levels while alive. But other studies enable one to discount this objection. A Canadian study examined a large number of veterans at death [5]. Adequate pre-death cholesterol data were available and levels varied considerably among the individuals but for any given person, they were fairly constant. Autopsy studies on all the veterans who died revealed no connection between the degree of atherosclerosis and blood cholesterol levels. The same results were found in a study from India. Mathur and coworkers [6] studied the changes in cholesterol levels subsequent to death and found them to be stable for at least 16 hours. Thus samples collected shortly after

death, as was done by Sperry and Landé, were representative of pre-death levels. Next, Mathur's group studied 200 individuals who had died in accidents but were free of any preceding disease. No connection was found between cholesterol values and the degree of atherosclerosis. These studies involved what amounted to random selection. In other studies that also were random, similar results were reported [7].

The Framingham investigators also looked at this question. They found a very weak correlation between cholesterol levels and atherosclerosis at autopsy. The correlation coefficient was 0.36. Correlation coefficients of this magnitude generally accompany scatter plots where one can barely detect anything other than a random array of points. In fact, those trained in the physical sciences are generally appalled by the significance attached to small correlation coefficients in other branches of science. Also, in the Framingham cohort at that time, there were 914 deceased individuals, but the Framingham investigators selected only 127 (14%) for the purpose of studying atherosclerosis and cholesterol. Thus apparently this was not a random selection and the report did not describe the selection criteria. Did only 14% of the families involved allow an autopsy? Two studies from Japan claimed a positive correlation, but correlation coefficients were even smaller than found in the Framingham study, and in one study, the correlation appeared only in individuals with low or normal cholesterol levels, and in the other only in the elderly. Also, for those with very high cholesterol, the degree of atherosclerosis was the same whether they were young or old. In a study from Norway, claimed to support the Cholesterol Hypothesis, many people with normal coronary arteries had cholesterol levels as high as those for whom all three coronary vessels were constricted, and those with two constricted vessels had lower levels than those with just one constricted artery [8].

Thus the autopsy studies either do not support at all the connection between circulating cholesterol and the degree of atherosclerosis, or they produce such inconsistent results or very weak correlations as to cast serious doubt on the validity of the hypothesis. And after all, these studies go rather directly to the heart of the matter (no pun intended) by looking at actual atherosclerosis in dissected coronary and other arteries.

CALCIUM SCORES

The use of electron-beam tomography of coronary artery calcium (EBT CAC screening) has become a popular method for determining the extent of plaque formation and thus the degree of coronary atherosclerosis. There is even a popular book for the layman with the catchy title *Track Your Plaque* which has no doubt motivated many people to go out and get a so-called calcium scan. The results of the scan are generally expressed as a calcium score (CAC score), invented by Arthur Agatston M.D., a cardiologist better know to the general public as the author of the best selling book *The South Beach Diet.* As might be expected, there have been studies directly or indirectly addressing the simple question, is there a correlation between the calcium score and cholesterol levels. After all, if high cholesterol levels cause atherosclerosis (and strongly motivate treatment to lower them), then one might expect to see higher calcium scores associated with high levels of circulating cholesterol. The following studies address this issue:

- In a study reported in 2003, 5635 men and women aged 30-76 had CAC score determinations and were followed for an average of 37 months. The positive association between the adverse CHD event frequency and CAC score was not modified by the presence or absence of elevated cholesterol, suggesting no correlation between cholesterol levels and the CAC score and thus the degree of atherosclerosis [9].
- In a study of 6086 men and women of mean age 56-58, for men the CAC score was independent of LDL or TC. For women, only a very minimal CAC score was observed for LDL > 160 mg/dL and TC ≥ 240. For both of these categories, the mean calcium score was 1.0, i.e. negligible [10]. CAC scores in general range from 0 to over 400.
- In the Rotterdam Coronary Calcification Study, which involved 2013 men and women age ≥ 55, after exclusion of subjects on lipid lowering drugs, no association between TC and CAC score was found for men but one was found for women [11]. Nevertheless, women had a mean CAC score that was 1/6 those of men and was quite low.
- A study reported in 2005 compared Japanese and American men, aged 40-49 by determining the CAC score and parameters which included TC and LDL. While TC and LDL were higher in the Japanese cohort, only 13% of the Japanese men but 47% of American men had CAC scores > 0. In addition, when men from the two countries with CAC score > 0 were compared, there were no significant differences in either TC or LDL [12].

- In a study of 546 Brazilian men, when those with CAC score ≥ 75th percentile were compared with those in the < 75th percentile, only slight differences in TC and LDL were found [13].
- The association between racial differences, lipoprotein and lipoprotein particle size, and CAC score was examined as part of the HEART SCORE study. To quote the authors, "we found no significant association between lipoprotein or lipoprotein particle size and the extent of sub-clinical atherosclerosis as measured by CAC, whether in whites or blacks" [14].
- A large study determined CAC scores for over 22,000 men and 8000 women. Hypercholesterolemia was defined as TC > 200 mg/dL or the use of lipid lowering agents. The CAC scores were stratified into the ranges of 0, 1.0-9.9, 10-99.9, 100-399.9, and ≥ 400. For men the percentage with hypercholesterolemia was essentially constant (40-42%) for the three upper CAC ranges and for women the percentages for these three score groups were 49-52%. Thus there was essentially no association between elevated TC and CAC scores over a huge range from 10 to > 400. Unfortunately, these results were not stratified by statin use [15].
- In a study published in 2005, over 4900 asymptomatic persons aged 50-70 were scanned for coronary calcium. It was found that CAC scores predicted CAD events independent of the standard risk factors and in fact more accurately than the standard risk factors or C-reactive protein levels. This study found no correlation between CAC scores and LDL levels. In this cohort, LDL levels were 143 ±33 (standard deviation, not range) and TC was 224 ± 33 mg/dL. Thus the range of levels, which is greater than the standard deviations, were large enough to provide a meaningful test of the association between cholesterol levels and CAC scores [16].
- Hecht *et al* [17] examined the correlation between serum lipids and CAC scores in over 1000 consecutive asymptomatic individuals referred for EBT. They found that TC, LDL, HDL and the TC/HDL ratio did not correlate with either the prematurity or extent of calcified plaque burden.
- In a large multi-ethnic study, Kronmal *et al* [18] found only a very weak to insignificant associations between LDL and HDL and the change in CAC scores over time, i.e. the progression of atherosclerosis.

Thus 10 studies mostly fail to find a significant or clinically meaningful correlation between an established measure of the extent or progression of atherosclerosis and circulating TC or in some cases LDL. In fact, other risk factors such as smoking and hypertension did indeed correlate in many studies, but cholesterol never made the grade. Thus the electron-beam tomography studies are consistent with the autopsy studies, which is gratifying since, if we ignore small differences between visually and EBT identified plaques, both approaches are looking at more or less similar pathology.

CORONARY ANGIOGRAPHY

Coronary angiography involves inserting a catheter into the femoral artery in the groin and pushing it up through the aorta until it reaches the coronary vessels. A contrast medium is then injected to allow imaging of the individual coronary arteries and these images can reveal blockage attributed to atherosclerosis. Thus studies can examine the correlation between serum cholesterol and angiographically identified deposits and narrowing in the coronary arteries. But coronary angiography is not without its morbidity and mortality and is generally performed only on individuals with at very high risk or with severe symptoms of heart disease who are young or middle-aged. Thus these studies are not representative of the asymptomatic public. In addition there will be some patients who have familial hypercholesterolemia. This would introduce a bias since, as will be discussed below, it is not at all clear that the atherosclerosis that accompanies this syndrome can be compared to that found in individuals who do not have the mutation. Any study heavily weighted with individuals having very high cholesterol levels will be confounded by the potential presence of subjects with this syndrome. Also, in many studies, cholesterol lowering drugs were being used, further confusing the question.

Thus if the issue is the Cholesterol Hypothesis, angiographic results do not appear to be a very good way to study its validity. On the other hand, both the autopsy and calcium score approaches allow the examination of asymptomatic individuals which is much more to the point and less subject to confounding and bias. Nevertheless, as Ravnskov [8] discusses at length, angiographic studies that examined the relationship between cholesterol levels, their changes, and the presence and progression of atherosclerosis frequently found inconsistent results where progression occurred in the presence of both increasing and decreasing cholesterol levels. In his words, "to prove that high cholesterol is the villain—not just an innocent bystander—demands that a change in the cholesterol concentration for each individual is followed by a change in the degree of atherosclerosis in the same direction. But in all studies these changes occurred haphazardly." Also, most of the

results are presented as the constants of correlation equations and almost always the degree of correlation is very poor (low correlation coefficient).

HOW ABOUT FAMILIAL HYPERCHOLESTEROLEMIA (FH)?

Individuals with FH have very high TC and LDL due, it is thought, to what is called an LDL-receptor deficiency which results from a mutation. An argument for the Cholesterol Hypothesis involves claiming that members of such families run a great risk of dying form CHD at an early age. Ergo, elevated TC and LDL cause atherosclerosis and CHD. To use individuals with this mutation as "proof" of the Cholesterol Hypothesis requires that the only difference between the FH people and the rest of us is that they produce huge excesses of TC and thus LDL. But it is not that simple. Individuals who inherit from both parents not only have highly abnormal levels of cholesterol in their atherosclerotic deposits, but also in other organs. Cholesterol levels can go to 1000 mg/dL or higher. And lowering their cholesterol levels drastically does not reverse their atherosclerosis. Also, these individuals have blood-clotting abnormalities which may responsible for the elevated rate of heart attacks. It is also argued by some that the nature of the atherosclerosis is different in FH as compared to non-FH individuals [19]. This does not seem to be an ideal group to use in justifying a hypothesis regarding the cause of atherosclerosis or CHD. Nevertheless it is one of the major pillars upon which the hypothesis rests.

An interesting and perhaps unique study from the Netherlands relates to this question. A large pedigree was traced back to a single pair of ancestors in the 19th century and a family tree mortality study conducted which started in the early 1800s. All members had a 50-50 chance of carrying the mutation for familial hypercholesterolemia. Mortality data over the full time span up to modern times was available for this large group as well as for the corresponding general population. Overall mortality was not increased in carriers of the mutation during the 19th and early 20th century. The mortality then rose reaching a maximum between 1935 and 1964. The authors comment that the risk of death varied significantly among patients with FH and that this was, in their opinion an indication of strong interaction with environmental factors. One can of course ask why for over more than a century no excess mortality showed up because of the elevated TC and LDL levels if in fact these lipoproteins cause atherosclerosis and CHD.

Kendrick [3] suggests that perhaps lipoprotein (a) is involved since there seems little doubt that this protein is elevated in those with the FH mutation and that this protein is regarded as a strong independent risk factor for CHD. However, he finds the strongest argument against FH causing CHD is that most people who die with heart disease do not have highly elevated LDL levels and most who have these LDL levels do not die of heart disease, even people with FH.

THE MONICA STUDY

This is an acronym for a huge World Health Organization study of cardiovascular disease. Among other things, the association of CHD deaths and TC was examined for a large number of countries. In one looks at a plot that displays the results from this set of countries, two things jump out at you [8]. First the data, which clusters between TC of about 210 and 250 mg/dL and covers a CHD death rate from some very low number to over 450 events per 100,000, shows that no matter what the cholesterol level is in this range, both very high and very low rates of CHD mortality are found. At a level of about 225 mg/dL the mortality for a number of countries ranges from 70 to 427 deaths per 100,000. Also, when data from several sites within a country are provided, there is a large variation in mortality at a given TC level. Overall, there is no apparent correlation between CHD deaths and TC, contrary to what would be expected on the basis of the Cholesterol Hypothesis. Just two countries are outside the main scatter, China and Japan, and both have both low TC and low rates.

Japan merits a bit of discussion. The Japanese living in Japan in general had both low cholesterol levels and low rates CHD mortality, but immigrants to the U.S. had high cholesterol levels and had CHD mortality comparable to Americans. Convincing proof of the Cholesterol Hypothesis. But let's dig deeper and look at what a British physician found during his Ph.D. research. He looked at the relationship between TC levels and social factors, eating habits and lifestyle among the immigrant Japanese. He found conclusive evidence that it was not the food that raised the cholesterol of the Japanese immigrants, or that elevated cholesterol values increased their risk of CHD death. Rather, he found that those who maintained their cultural traditions were protected against heart attacks, even though their cholesterol increased as much as in the immigrants who adopted the Western lifestyle and diet and who died from CHD at a rate comparable to the Americans. In fact, the Japanese who preferred lean Japanese food but adopted other aspects of the American way of life had CHD

twice as often as those who maintained Japanese traditions but preferred standard American diet [20,21]. These studies, which contradict the Cholesterol Hypothesis, have been largely ignored, in spite of having been published in a high profile peer-reviewed American journal. Thus, if the low rate of CHD among the Japanese has little to do with cholesterol levels and the low mortality is for other reasons, then the MONICA result for Japan are explained. This leaves only one discordant point in an otherwise apparently random scatter of points in the Monica results.

The relationship between cholesterol levels and mortality is actually both complex and fascinating and will the subject of Part II of this review.

FRAMINGHAM RISK SCORES

Framingham is a small town near Boston, MA, and has been the site of a study involving a large number of its inhabitants. The study has been ongoing since 1950 and now even involves the children of the original cohort. Early results from this study had a major impact on the development of the Cholesterol Hypothesis. A commonly used graphical representation of the results regarding cholesterol and the incidence of CHD shows two curves where the percentage of participants with or without CHD is plotted against TC. Both curves rise from around 100-120 mg/dL TC, pass through maxima percentage at around 200-220 mg/dL, and decline to zero at 400 mg/dL except for a small bump at higher TC attributed to those with FH. The CHD patient's (n = 193) curve is slightly displaced to higher TC compared to that of people without CHD (n = 1378). While believers in the Hypothesis point to the added risk associated with elevated TC reflected in the displaced curve, its can also be pointed out that the vast majority of patients with CHD had TC levels similar to participants without CHD, and that the added risk appeared marginal. What this often displayed plot fails to show is that the risk of overall mortality associated with TC disappeared for men above age 48. In addition, in a longer follow-up, for participants whose cholesterol had decreased on its own (i.e. no lipid lowering treatment), for each 1% drop of TC there was an 11% *increase* in coronary and total mortality [22].

The Framingham study also gave rise to the so-called Framingham Risk Score, a risk estimate of having CHD during the next 10 years. This score is widely used in the office setting to assess an individual's risk of CHD. If one looks at the way the score is calculated, as one gets older, age become by far the dominant factor with the importance of cholesterol dropping off dramatically with age until it becomes almost insignificant for men and makes only a slight contribution for women. This is in spite of the arterial exposure to TC and LDL obviously increases with age. This is not a picture of overwhelming support for the Hypothesis.

WHAT ARE THE REAL RISK FACTORS FOR ATHEROSCLEROSIS?

If we use CAC as a surrogate for atherosclerosis, then given that there does not seem to be any connection with serum cholesterol or LDL, are there other traditional or non-traditional risk factors that correlate with plaque burden? Traditional risk factors that consistently turn up as most important in studies of the extent of atherosclerosis are smoking, hypertension, gender and age [13,17,23,24]. However, when the correlation between the Framingham 10-year risk score and the CAC score is examined, generally a very poor correlation is found. In one study, 20% of individuals with very low Framingham risk (≤ 9% 10-year risk) were in fact found to have advanced atherosclerosis as judged by their calcium scores [25]. This study also found that the ability of the CAC score to predict advanced atherosclerosis was improved by adding family history of heart disease, obesity and physical inactivity to the traditional risk factors. But it appears likely that there is still a major factor is being omitted. It is possible that this factor is chronic stress and depression. There is also growing evidence that chronic stress and depression correlate with the extent of coronary calcified plaque [26-28]. Furthermore there is very good evidence that stress in general is a strong predictor of CHD and CHD events [29,30]. In one very large study an attempt was made to identify the major potentially modifiable risk factors for a heart attack. It was found that the major factors were a particular blood lipoprotein (apolipoprotein), smoking, hypertension, diabetes and psychological factors, all of which had approximately equivalent importance [30]. Having psychological factors ranked approximately equal to diabetes, both of which increased the risk of a heart attack by a factor of 2 to 3, suggests that chronic stress and depression may be major factors not seriously considered in routine CHD risk assessment, especially in the office setting. Its omission may account for a part of the failure of sets of risk factors such as the Framingham score to correlate with the extent of atherosclerosis as determined by CAC.

CONCLUSIONS

What we are seeing is that over the years there has been a steady flow of problems and "how come" questions that eat away at the credibility of the cholesterol hypothesis. The resolution of all of these problems is simple—most features of the hypothesis are false. Rephrasing the hypothesis such that it only states that atherosclerosis and CHD are *associated* with cholesterol levels removes what is considered an incorrect attempt to connect observational studies with causality, but the evidence presented above also argues equally well against there being, for the most part, any such association.

In a second Review related to the Cholesterol Hypothesis, we will look in much more detail at the association between TC and LDL levels and overall and CHD mortality. A third Review will deal with cholesterol lowering studies, the current popular notion that the lower the better for LDL, the so-called Polypill proposal, and the question of cholesterol and stroke risk and stroke mortality.

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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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Delaying the development and progression of prostate enlargement should be the goal of every man. In our book "The Prostate and Its Problems" we discuss a number of things one can do to attempt to accomplish this. One is to minimize the so-called modifiable risk factors. In this issue we discuss a recent review that examined what is currently know about these factors and how to minimize their impact. This is followed by a discussion of recent research regarding micronutrients and prostate cancer. Included are the various forms of vitamin E which highlights the importance of the gamma form, and lycopene, which is thought to be the active ingredient of tomatoes, and in particular tomato paste in this context. While there appears to be a shift toward disbelief in the anti-prostate cancer effect of lycopene, the matter is far from simple. A discussion of a commentary by Edward Giovannucci of Harvard hopefully will help clarify the matter.

This issue also includes the results of a meta-analysis (study of studies) that concerns the very important question of early vs. deferred hormonal treatment for locally advanced prostate cancer. This is an important issue for any man with prostate cancer thought to be at this stage since avoiding for as long as possible the adverse effects of the treatment are highly desirable but not advisable if doing this unfavorably impacts the progression of the disease or the mortality.

Wishing you continuing good health,

William R. Ware, PhD, Editor

MODIFIABLE RISK FACTORS FOR BENIGN PROSTATIC HYPERPLASIA

Most men will encounter symptoms of benign prostatic hyperplasia (enlarged prostate) during their lifetime. In the US, recent data indicates that BPH accounts for more than 4.4 million office visits annually and over 100,000 emergency room visits. Its prevalence for men between 60 and 65 is approximately 3 in 4. Obviously, anything that prevents this problem and the associated lower urinary tract symptoms (LUTS) or delays progression is highly desirable. Thus a recent study of modifiable risk factors for this problem is of considerable interest.

Parsons performed a comprehensive review of the literature regarding observational studies done on older men [1]. It was found that obesity and diabetes were modifiable factors consistently and significantly associated with

increased risk of BPH and LUTS whereas increased physical activity and moderate alcohol consumption were beneficial. One can argue that diabetes is not exactly a modifiable factor, but blood glucose control may be an issue here. In two studies that looked at physical activity, walking 2 hours a week or more vs. 0 hours/week yielded a 27% risk reduction. In another study, physical activity greater than 6 times a week resulted in a 51% decrease in risk, whereas when physical activity was quantified in terms of energy used, 862 kcal/day vs. 140 kcal/day gave a 50% reduction in risk. For alcohol consumption, two studies found a 41% decrease in risk, one for 2-3 drinks a day, one for one or more per day. Risk reductions for BPH in a Korean cohort were 74% for those who drank alcohol every day vs. abstainers. The risk reductions in the studies reviewed were with reference to clinical BPH, LUTS and the likelihood of requiring surgical intervention for acute urinary retention and intolerable LUTS. The author points out that it is counterintuitive that alcohol in any amount protects against the development of BPH and LUTS given its potent diuretic effects, but that a potential explanation for the above observations might be by mechanisms similar to those operating to produce the beneficial effects of alcohol on the cardiovascular system. With regard to modifiable factors that increased the risk of BPH and LUTS, diabetes, impaired fasting glucose, hypertension and a large waist circumference (> 109 vs. < 89 cm) produced increases in risk, mainly of LUTS, of approximately a factor of 2 to 3.

MICRONUTRIENTS AND PROSTATE CANCER RISK

Several but not all follow-up studies on the impact of dietary or supplemental vitamin E on the incidence and progression of prostate cancer found a positive benefit, and there is an ongoing clinical trial in this regard involving the combination of vitamin E and selenium (the SELECT phase III trial). A recent study from the National Cancer Institute of the NIH and New York University has contributed to this subject [2]. In this prospective study, Wright *et al* followed a cohort of almost 300,000 who were cancer free at enrollment. Baseline supplemental and dietary intakes of alpha-, beta-, gamma- and delta-tocopherols were obtained from a questionnaire. At the end of 5 years follow-up over 10,000 prostate cancer cases were identified. Supplemental vitamin E (alpha-tocopherol) intake was not found to be associated with prostate cancer risk even at intakes ≥ 800 IU/day. However, dietary gamma-tocopherol was found to be significantly and strongly inversely related to prostate cancer risk, with a 32% risk reduction when the highest vs. the lowest quintiles were compared. The median intake in the highest quintile was 20.8 mg/day with a range of 18.5 to 57.5. Furthermore, this beneficial effect was particularly evident among men with a low selenium intake. Gamma-tocopherol is the most commonly consumed form of vitamin E in the US diet. The authors list as major sources margarine, butter, salad dressings, fried potatoes, oils (mostly corn) cookies and brownies.

The potential anti-cancer properties of gamma-tocopherol appear to be under appreciated, given that most people appear to think of vitamin E only in terms of the common supplement, the alpha form. In a recent review titled *Gamma-Tocopherol--An Underestimated Vitamin?,* Wagner *et al* [3] discuss a number of studies that relate to this question. One found a 5-fold reduction in prostate cancer risk for the highest vs. lowest quintiles of gamma-tocopherol intake. Another serum level study also found the same 5-fold reduction. However, a large trial involving U.S. physicians that also looked at serum levels failed to find a similar association. In addition, Wagner *et al* point out that gamma-tocopherol is more effective than alpha-tocopherol in inhibiting prostate cancer cells, reducing oxidative DNA damage and scavenging certain mutagens. Obviously, more studies are needed, but the evidence of the benefits of gamma-tocopherol in regard to prostate cancer is accumulating. In fact, it may occur to some readers that the SELECT trial may not be using the ideal form of vitamin E and that a negative outcome of this trial when it finally reports might well kill interest in vitamin E in general, including the gamma form.

Gamma-tocopherol is also available in supplements, generally as mixed tocopherols. Careful label reading is required since IU may be quoted (conversion 0.15 IU per mg) but it is common for only a total in IUs or milligrams for the beta, gamma and delta combined to be displayed. Products are available that contain 200 or more mg per capsule of the gamma form. Given that many individuals do not eat foods rich in the gamma form of vitamin E, supplements containing this form appear to be of interest.

A recent study did indeed find a significant risk reduction associated with high serum levels of alpha-tocopherol, but this was in a cohort of smokers [4]. This will not be discussed since it is assumed that the readers of this Newsletter, who presumable are very health conscious, by and large are non-smokers.

Another micronutrient that is frequently associated with prostate cancer is lycopene, the principal source of which is the tomato. Early studies suggested that both tomato products and circulating lycopene were associated with a reduced risk of prostate cancer. Jokes were even made about the merits in this context of eating lots of pizza. Bioavailability issues arose and it was found that products such as tomato paste were preferable to raw tomatoes. Two recent publications relate to this matter, one a report on a follow-up trial, the other a U.S. Food and Drug Administration (FDA) review done because processed food producers wished to make health claims for tomato products.

The follow-up trial was part of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). Participants were selected who underwent annual standardized screening for prostate cancer (PSA at entry and annually for 5 years and a digital rectal exam at entry and annually for 3 years). Thus this was a PSA-era study. No association was found between serum lycopene and total prostate cancer diagnosis risk or aggressive prostate cancer risk. The authors conclude that, consistent with other recent publications, these results suggest that lycopene or tomato-based regimens will not be effective in prostate cancer prevention [5].

The FDA report was based on a review of the literature and found “no credible evidence to support the association between lycopene intake and a reduced risk of prostate…cancer.” However, they mention finding very limited evidence to support the association between tomato consumption and reduced risks of prostate cancer [6].

This latter report prompted Edward Giovannucci, a very well known epidemiologist from Harvard, to write an editorial trying to reconcile the FDA position with earlier studies that did indeed show benefit. His thesis is that the newer studies fail to find benefit from lycopene or tomato products because the studies are all done in the PSA era. Before the widespread use of PSA testing for screening purposes, most cancers that were diagnosed had progressed to a relatively advanced stage. What was being detected were manifestations of advanced disease such as metastasis and tumor growth outside the prostate itself. In the PSA era, most of the cancers detected would never have attracted clinical attenuation and include small, low-grade and indolent tumors. Thus studies of tomatoes and lycopene in the PSA era with the endpoint of cancer diagnosis are looking at the question of benefits during the early stages of disease development, whereas in earlier times, the potential benefit extended over a much longer period in the natural history of the disease. Consistent with this, Giovannucci points out that in the Health Professional’s Follow-Up study (HPFS), the initial analysis of the data for the period 1986 to 1992 found an inverse association between tomato sauce intake and total prostate cancer incidence and the association was stronger for advanced cancer. Later analysis for the period 1992-1998 which was during the PSA era, the association was attenuated and weak but a strong association persisted for metastatic cancer. Combined data for these two periods gave a 66% risk reduction for ≥ 2 servings per week to <1 serving per month. Finally an analysis of the data found no association between tomato sauce and the risk of diagnosis of organ-confined disease. Thus in the PSA era, the benefits of tomato sauce with regard to advanced cancer were swamped by the huge numbers of early non-advanced cases. In the HPFS study, Giovannucci comments that only strict criteria for aggressive behavior such as invasion into the seminal vesicle or metastasis were adequate to detect the association between tomato paste and an increased risk of fatal prostate cancer. He also points out that the FDA review was not designed to take into account these issues and the data needed are sparse.

These same observations apply to the PLCO study which was done in the PSA era. Thus it appears that tomatoes and lycopene provide benefit only in terms influencing advanced cancer or offering benefit that is only significant when the exposure is over the full initiation and progression of the disease, as was the case in the early studies. It would appear that abandoning cooked tomato products like tomato sauce, and as well even supplemental lycopene, on the basis or recent studies is somewhat premature. Furthermore, it may be unrealistic to assume that studies will be carried out that might resolve the issues discussed, given the widespread PSA screening at present is the norm.

Dietary fatty acids have also been the subject of studies in the context of prostate cancer risk. Results have just been reported regarding these nutrients based on data collected in the Physician's Health Study. While this study had as its primary goal the evaluation of aspirin and beta-carotene in the primary prevention of heart disease and cancer, the cohort provided the opportunity for case-control studies of other questions. One such study has just reported [7] which involved almost 15,000 apparently healthy men who provided blood samples in 1982. Blood fatty acid levels were measured for 476 men who developed prostate cancer during the 13-year follow-up and as well as for their matched controls. It was found that higher levels of the long-chain fatty acids mainly found in marine foods, and of linoleic acid, mainly found in non-hydrogenated vegetable oils, were associated with reduced risk of prostate cancer. In both, the relative risk reductions were about 40% when the highest quintile of serum level was compared to the lowest. The authors comment that in addition, their data suggest that the intake of polyunsaturated fatty acids appear unlikely to increase prostate cancer risk and that in addition, the intake of these fatty acids may in addition help prevent other common chronic diseases such as heart disease and diabetes. Thus these substances may have a broad implication in chronic disease prevention.

EARLY VS. DEFERRED HORMONAL TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

Localized prostate cancer generally implies organ-confined disease and the removal of the prostate or its irradiation generally results in a high probability of long-term freedom from recurrence. Locally advanced prostate generally implies that the tumor or tumors extent through the prostatic capsule or have invaded adjacent structures other than the seminal vesicles, and that distant (non-localized) metastasis is absent. Locally advanced disease can be difficult to clinically differentiate from metastatic disease. This is an important question since if the cancer is not localized, local treatment such as surgery or radiation therapy will not deal with the cancer cells or tumors outside the treatment area and while there may still be significant benefits, there is a high risk of recurrence. If it is localized but advanced, then the problem is for the treatment to deal with all locations of the cancer. In order to augment either radiation or surgery, hormone therapy is frequently used. Radiation therapy is the most commonly used treatment in conjunction with hormone therapy employed either before (neoadjuvant), concomitant or after (adjuvant) irradiation. The aim of adding hormone treatment is first to reduce the risk of distant metastases by destroying micro-metastatic deposits at the time of diagnosis. In addition, it reduces the risk of local recurrence, but the detailed mechanism is not clear.

One of nagging questions in this area is when to initiate hormone treatment, i.e. should it be early or deferred until standard care has failed. A recent meta-analysis of randomized clinical trials has addressed this issue [8]. Of 108 trials identified, seven met the inclusion criteria and were of sufficient quality to merit use in the analysis. It was found that early intervention with hormone therapy significantly reduced all-cause mortality, cancer specific mortality, overall progression of the disease and both local and distant progression. Thus it was concluded that for patients with locally advanced prostate cancer, early intervention with hormones offered significant benefits when compared with delayed treatment.

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e-mail: editor@yourhealthbase.com