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The subject of heart disease, diet, atherosclerosis and cholesterol has been an ongoing topic in this Newsletter for sometime. An attempt is made in this issue to bring this discussion to a temporary conclusion with a discussion of an apparent paradox mainstream medicine does not want to consider. The discussion centers around the universal belief that there is a strong and linear relationship between cholesterol and the risk of coronary heart disease and cardiovascular disease acute events, and yet there appears to be no connection whatsoever between the extent of coronary atherosclerosis, a prerequisite precursor of acute coronary events, and cholesterol even though the extent and progression of coronary plaque assessed by the so-called calcium scan is a strong and significant predictor of these events. This apparent paradox is the feature subject of this issue.

The reader will note that in the discussion of this paradox, and as well in the discussions of other studies in this Newsletter, there is considerable emphasis placed on absolute risk reduction vs. relative risk reduction. There is a huge difference between telling a patient that scientific studies prove that taking a certain drug, perhaps for life, will reduce their risk of some disorder by 40%, and telling them that 100 patients need to take this drug for at least 5 years for one patient out of the 100 to experience benefit (based on exactly the same "scientific data"). Yet drug marketing and the setting of guidelines and standards of practice are mainly based on relative risk reduction. The professional term is "spin." It is remarkably common that absolute risk reduction is not explicitly stated in articles and must be calculated by the reader, and the information is almost never available to those who have access only to abstracts. It is also common to find that not enough data is given in articles to permit the calculation. One interpretation of this phenomenon is that some authors have an agenda, a conflict of interest, a bias or the desire or need to be politically correct.

In this issue we also revisit the problem of alcohol consumption and breast cancer and as well examine a recent study concerning how well flu vaccines work. Other topics briefly discussed include blood clots associated with contraceptive drugs and the safety of anti-inflammatory drugs.

This issue also includes a review of the new book "Wheat Belly" by William Davis, MD. Some readers will recognize Dr. Davis as the author of the widely read book "Track Your Plaque".

Wishing you and your family a joyous Holiday Season and good health in the New Year,

William R. Ware, PhD, Editor

Highlights

ANOTHER CHOLESTEROL PARADOX?

In past Newsletters and research reports, the absence of an association between circulating total Cholesterol (TC) and LDL cholesterol and silent atherosclerosis quantified by observation of calcified coronary plaque has been discussed at length.[1] This is a surprising result given that LDL is a high-profile target of mainstream medicine. Yet the evidence seems compelling that there is no correlation between TC or LDL and the prevalence or progression of coronary plaque, which is generally regarded as a prerequisite precursor of acute coronary events. These events form the main endpoints of studies cited as justifying the cholesterol-heart disease hypothesis.

It is widely believed the risk of coronary heart disease (CHD) events is strongly and continuously associated with LDL levels, and thus LDL lowering targets, which can generally only be attained with drugs, form one of the pillars of modern preventive medicine for asymptomatic individuals with and without diabetes. This view is strongly dependent on meta-analyses which involve mostly secondary prevention and may have a strong non-lipid lowering component (pleiotropic effects). A significant fraction of the population in developed countries is taking a statin the hope of benefiting from the 20-30% reduction in relative risk. Probably nobody ever tells them about the dismal reduction in absolute risk of fatal or non-fatal heart attacks (about 1%), the absence of a significant effect at all on overall mortality in the context of primary prevention and the very large number of individuals that must be treated to prevent one event. Thus there is a problem. Cholesterol, we are told, is related in observational studies to the risk of acute CHD which mostly requires the presence of atherosclerosis, and at the same time, the evidence is compelling that neither TC nor LDL is driving atherosclerosis in men or women. There appears to be a paradox.

A way to resolve this paradox is to take the view that the association between TC and LDL and acute coronary events is in fact very weak, and for some segments of the population, nonexistent, a view that goes strongly against the conventional wisdom and guidelines from a number of professional organizations. The literature supporting this contrary view is extensive, spans almost three decades, is in general ignored and has had negligible impact on those who believe in the cholesterol-heart disease hypothesis. A dispassionate examination of this contrarian evidence is thus important.

Put another way, the critical question is simply, does elevated TC and LDL increase the risk of heart disease related acute coronary events? The conventional wisdom is that this question is already answered and that the science is clear with vast and robust evidence, even if the mechanism is far from clear or at least far from proven. If the notion that cholesterol increases the risk of symptomatic heart disease is viewed as a hypothesis, then careful consideration must be given to evidence that falsifies it, since hypotheses are not proven, they survive until falsified (to paraphrase the famous Karl Popper). One is reminded of the black swan example

The latest study. A ten-year follow-up study (HUNT 2) has just reported which examined the association between serum cholesterol (TC) and mortality from cardiovascular disease and ischemic heart disease and all causes.[2] The cohort consisted of Norwegian men and women aged 20—74. The study excluded participants with established CVD at baseline (self-reported heart attack, stroke or angina). The subsequent follow-up and analysis involved 24,253 men and 27,852 women. Four ranges of TC were examined: <193, 193-229, 230-269 and ≥ 270 mg/dL (divide by 38.7 to obtain mmol/L). The level < 193 mg/d l was used as the reference, and hazard ratios obtained which were adjusted for age, smoking and systolic blood pressure. For all ranges of cholesterol above 193 mg/dL and for all three endpoints, the results were insignificant except for all-cause mortality where for men the first two TC ranges were significantly *protective* and for women the per unit increase in cholesterol was also *protective.* There were suggestions of a U or J shaped relationship for ischemic heart disease in women and cardiovascular mortality in men, but these did not achieve statistical significance. Also, for all-cause mortality and CVD mortality, the hazard ratio linearly *decreased* from I.00 between < 193 mg/dL and ≥ 270 mg/dL but each point was not statistically different than the 1.00.

The authors conclude that in the context of the study endpoints, even a limited focus on cholesterol is problematic and suggest as an alternative that total cholesterol could be eliminated from risk estimates. This is an interesting suggestion in view of the recent popularity of the TC/HDL ratio which apparently is mostly taking advantage of the strong protective effect of high HDL. The researchers of course acknowledge that strictly speaking these observations and conclusions apply only to Norwegians. Unfortunately, the results were not stratified by age.

The above study focused on mortality. However, non-fatal CHD events are also important in this context. We will extend this discussion by separately considering women of all ages, the elderly and young men.

Women. A pooled analysis involving 15 observational studies and about 125,000 women examined the association of total cholesterol and total cardiovascular mortality and coronary heart disease mortality.[3] The reference was 160-199 mg/dL. Hazard ratios adjusted for age, diastolic blood pressure, BMI, and alcohol and smoking were calculated. For total cardiovascular mortality, there was no significant association over the full range from < 160 to ≥ 240 mg/dL. For coronary heart disease mortality, the association was weak but significant at levels ≥ 240 mg/dL but this presumably included individuals with familial hypercholesterolemia. This confuses the issue because of the non-lipid related triggers for acute coronary events associated with this disorder.

In 2004, Walsh and Pignone reported on pooled analysis of 6 lipid-lowering trials involving women with endpoints of CHD mortality, total mortality and CHD events.[4] Follow-up was from 3 to 5 years and 5 of the 6 studies used statins. For women without cardiovascular disease, lipid lowering was not associated with total or CHD mortality. For CHD events, the data failed to yield a conclusive result. A more recent meta-analysis found that for women without prior cardiovascular disease, statin therapy did not reduce CHD events nor the risk of total mortality.[5] A similar conclusion was reached in a study motivated by legal aspects of drug company claims of efficacy which found similar results also based on meta-analysis.[6] It is unusual to see a study on this subject in a legal journal, although one of the two authors was a professor of medicine at Harvard.

The famous JUPITER trial was the first to find benefit of lipid-lowering for women. This study enrolled subjects with relatively low LDL (<130 mg/dL, mean 108 mg/dL) with C-reactive protein levels > 2 mg/L.[7] While described as healthy, 42% had the metabolic syndrome and most were overweight and some obese. The study was prematurely terminated at a median follow-up about 2 years with maximum follow-up of 5 years even though the number of events was very small. Using the tabulated events during the study, the absolute risk reduction for any heart attack was 0.41% and for heart attack, stroke or death from cardiovascular causes was 0.83%. Since these span a considerable range of follow-up times, the small magnitudes appear more meaningful than the numbers themselves. Since women and men had similar relative risks, it is probably safe to assume that the absolute risk reductions for women were also very small, although the relative risk reductions were very large. What is generally not recognized about this trial is that Crestor is unique in its very strong influence on vitamin D levels. The increase in vitamin D levels could easily account for the small absolute cardiovascular benefits.[8] Until this potential confounding is taken into account, JUPITER should be viewed with reservations. Serious problems with JUPITER have also been discussed by de Logeril.[9] Put simply, some of the numbers do not make any sense clinically.

These studies involved mostly women over 50. It is of interest to look at the distribution in the general population of women at low, intermediate or high risk based on the Framingham Risk Score which incidentally includes an *inverse* age related total cholesterol factor. Until one reaches the age of 50 all women are in the low risk category.[10]

Thus in view of the above studies it can be reasonably concluded that total cholesterol (which is also a very good surrogate for LDL) is not a significant issue for acute coronary events for women of any age. This of course accounts for the interest from the legal profession.

The Elderly. There have been a number of studies addressing the association between cholesterol and CHD or CVD events and related mortality in the elderly.

- The Framingham studies looked at an elderly subgroup and the data for 60 to 74 years of age assessed statistically and discussed by Larson.[11] For women, the rate ratio for cardiovascular disease showed *enhanced* risk at levels *below* about 200 mg/dL and then no risk until there was a modest increase above 300 mg/dL, a rare level unless one has a genetic predisposition. For men, the curve was U shaped, with small enhanced risk below about 160 mg/dL and a modest increase in risk above 250 mg/L.
- Pekkanen *et al*[12] found no association between cholesterol and CVD or CHD in a group aged 65-75. Systolic blood pressure was the most significant factor, and smoking declined in importance with age.
- Siegel *et al*[13] found for men and women with a mean age of 72 that when the data was adjusted for confounding, cholesterol was not associated with the risk of a first cardiovascular event.
- Krumholz *et al*[14] studied the association between cholesterol and CHD mortality and morbidity in persons older than 70. Their findings did not support the hypothesis that hypercholesterolemia was an important factor for CHD mortality, hospitalization for MI or unstable angina.
- Abbott *et al*[15] found no significant association between the relative risk of CHD and cholesterol at <200 vs. >240 mg/dL in individuals between 65 and 93 years of age.
- Simons *et al*[16] found cholesterol and other lipids predicted CHD in the elderly, but only in those below 70 years of age. However, for the 60-69 age group, a positive hazard ratio was found only for the 5th quintile of TC which for women was 274 and men 294 mg/dL, with no association for lower levels for this age group.
- Petersen *et al*[17] found that that for individuals older than 80 years of age, all cause mortality was highest when TC was lowest and that a review of randomized lipid lowering trials for individuals in that age group found no evidence of an effect on total mortality and there was the possibility that statins may increase all-cause mortality for those in this group without CVD.
- The most frequently cited study in the context of primary prevention with a statin is the PROSPER trial which reported in 2002. This was a combined primary and secondary prevention trial which involved 5800 men and 3000 women aged 70-82. For primary prevention, no statistically significant treatment benefit was observed for CHD death, non-fatal MI or fatal and non-fatal stroke[18]. PROSPER is frequently cited supporting the opposite result, but this is incorrect in the context of primary prevention.

It therefore appears that there is a lack of evidence of a statistically significant association between serum cholesterol levels, and thus also LDL levels, and fatal and non-fatal CHD events in the elderly of either gender, although at very high levels there is merely the suggestion of the appearance of some risk. Nevertheless, lipid-lowering therapy is commonly recommended for the elderly.

Younger men. There seems to be general agreement even among critics of the heart-cholesterol hypothesis that for younger men there is a statistically significant association between the risk of CHD and serum cholesterol or LDL. The reason is unclear but one possibility is that psychological stress, its association with blood pressure and cholesterol, and the cholesterol elevation associated with an exaggerated blood pressure response to stress and aggravation may play a major role. This is the age where men are subjected to high levels of stress associated with academic and career achievement, domestic stress associated with the initial stages of raising children, and finally marriage or relationship break ups. Stress is never considered quantitatively as a confounder, but stress is recognized as a highly significant factor and trigger for acute coronary events.[19-22]

Back to the paradox. The above evidence is rarely discussed and most high-profile journals will not accept discussions, perspectives, letters or analyses that support this viewpoint, although the British Medical Journal is a notable exception. Nevertheless, the simplest resolution of the above described paradox is that the association between serum cholesterol and LDL and the acute coronary events is weak or non-existent. Evidence involving individuals free of CHD/CVD at baseline derived from of lipid lowering studies or observational studies indicates that circulating cholesterol does not present a

clinically significant CHD or CVD risk for women of all ages and the elderly, and cholesterol may only be a marker for stress in younger men where the association may exist. However, younger men have a very low risk of acute CHD events compared to older individuals. For individuals who experienced sudden cardiac death, there is no correlation with cholesterol at all.[23] It is noteworthy that many studies do not stratify endpoint results by both age and gender, historically, women were seriously under-represented in study cohorts of interest in this context. Meta-analyses, which have profound influence on practice and guidelines, are not generally stratified by both age and gender and frequently by neither.

The Framingham Risk Score is widely used to classify individuals for the 10-year risk of acute events. Some algorithms also calculate the absolute 10-year risk of heart disease in general which increases the absolute risk somewhat. If one looks at the Framingham tables used to calculate the risk for fatal and non-fatal heart attacks,[24] some interesting anomalies emerge that relate to the above discussion. The tables calculate points which then allow the estimate of the 10-year risk as an absolute percentage. The points for age increase strongly with age. However, there is an interesting balancing act going on where one has high points for cholesterol at a young age which are neutralized by the low or negative points for age, and low cholesterol points for advanced age balanced by very high points for age. The relationship between points and risk is also much stronger for men than women. To what extent all of this represents playing with the algorithm to achieve the best agreement with actual observations is not clear, but there are some features which are inconsistent with the studies discussed above. For example, the age-weighted points for men and women as regards cholesterol levels are almost identical as are the set of points for age. The well known differences in heart disease risk between men and women is reflected in the much higher number of points required to achieve a given risk level in women as compared to men. From a level of 2% risk upward, the difference in points is almost constant at 8. Thus men need 12 points for a risk of 10%, women need between 19 and 20. If we examine the relatively high TC level of 200-239 mg/dL (for a non-smoker, non-diabetic, not on blood pressure medication with a systolic BP of 120 mm/Hg and an HDL of 50 mg/dL), it is found that as age progresses, a woman's predicted risk goes from 1% to 5% with only 2% for the age range 60-69. For men the risk goes from 1% at a young age to 12% at 70-79 years, crossing the low-intermediate risk threshold (10%) between 50-59 and 60-69years. These trends appear to be at variance with some of the studies discussed above. The Framingham algorithm seems to confirm the statement that for women of any age, high cholesterol is not a significant issue for acute cardiac events, even with the increase in age. For men, the widely held belief that high TC is a risk factor only for men younger than about 50 is inconsistent with the algorithm where even for TC levels of 240-279; the risk does not exceed 6% if there are no other contributors to the score except age.

Thus the Framingham algorithm, with some exceptions, appears to support the notion that TC is at best a weak risk factor. This proposal is strengthen considerably when the larger literature is examined, as seen above.

The presence of age as a major component in the Framingham Risk Score raises interesting questions, the simplest being what is associated with age as an independent factor that has such a powerful influence on risk. One explanation is that coronary plaque increases with age and risk of events increase with the calcium score. This in fact is the origin of the notion of coronary age as a factor that might be calculated and used to modify the Framingham calculation by replacing true age with a modified age factor.[25] Another explanation is that aside from diabetes, no other comorbidities are entered into the Framingham calculation and some are age related to CHD risk. An example is chronic kidney disease.

Another component of the paradox may involve the fact that calcified coronary plaque, while highly significant, does not constitute the totality of coronary plaque. There is also non-calcified plaque and mixed calcified and non-calcified plaque. New contrast enhanced CT methods now allow the examination of all three types. Research that examines the relative importance of each type of plaque as well as the presence of significant coronary stenosis in the context of the above discussed issues

is just picking up steam and may eventually yield a more detailed insight into the paradox being discussed.

Thus for the hypothesis that cholesterol causes heart disease, there appear at present to be quite a few "black swans," and the paradox introduced above may well not exist at all.

ALCOHOL AND RISK OF BREAST CANCER—THE LAST WORD?

The latest in a long series of observational studies regarding the association between alcohol intake and breast cancer has just been published.[26] The data is from the famous Nurses' Health Study which has been ongoing for several decades. The authors indicate that part of the incentive was inconsistent results from earlier studies, which found both positive and null associations, and which suffered from the lack of regular updates regarding drinking habits. In this study which started in 1980, alcohol consumption was updated in 1984 and then every 6 years until 2008. Data was analyzed on the basis of a cumulative average of grams of alcohol consumed per day. A serving of beer (12 oz) was assigned 12.8 g, 11 g per 4 oz of wine, 14 g per standard serving of liquor. The information collected included menopausal status, hormone use, and when a cancer was detected, the ER/PR status was obtained. The relative risk (per 100,000 person years) over about 28 years and corrected for a number of confounding factors was 1.15, 1.22, 1.20, and 1.51 for consumption of 5.9-9.9, 10-19.9, 10-29.9 and ≥ 30 g/day, respectively, when zero consumption was taken as the reference. All were statistically significant. Binge drinking (4 or more drinks at one time) but not frequency of drinking was associated with breast cancer risk after controlling for alcohol intake. Alcohol intake both in the early and late years of adult life carried a similar association with risk. No association was found with the source of the alcohol. There appeared to be a stronger association for post-menopausal women and for ER-positive tumor status. The take-home message appears to be that if a woman consumes at least 30 g of alcohol daily, which is 2 to 3 drinks, the increase in relative risk is about 50% compared to abstainers.

The unadjusted tabular data reported allow the reader to calculate the absolute risk over the period of the study. When zero consumption was compared with ≥ 20 g/d, there was a 2.9% absolute risk increase which is equivalent to about 35 patients consuming ≥ 20 g/d over about 28 years to see one case. The associated unadjusted relative risk increase was about 33%. For the consumption range of 10 to 19.9 g/d, the absolute risk change drops to 1.9%, the relative risk is now 21%, in close agreement with the published adjusted value based on person years as was the figure of 33% given above. Fifty-three women would have to have a cumulative intake in this range in order for one to be diagnosed with breast cancer over 28 years. Heavier drinking which translates into ≥ 30 g/d and this is equivalent to about 3 glasses of wine per day. For this level of consumption, the report gives an adjusted relative risk of 1.51. The authors fail to indicate the size of this cohort but it can be approximated from the relative risk and case numbers given. The absolute risk change increases to 4.5% with the number needed to harm over the course of the study drops to 22 over the 28 year study. However, wines vary from around 11% to >15% alcohol, with full bodied reds generally at the upper end, and many fill glasses to more than 4 oz. The number needed to harm is only approximate because of enrolment over a period of time.

The authors emphasize the importance of considering the totality of a woman's exposure over her lifetime as the best measure, and note that this type of temporal relationship parallels that of hormonal influence on breast cancer risk. In expert commentary published online on *Medpage Today (*November 1, 2001), Dr. David Jernigan from Johns Hopkins School of Public Health pointed out that there is no evidence of a protective effect (cardiovascular) of moderate alcohol use for women below age 40 and that it is this age group that is at highest prevalence of excessive alcohol use. However, another commentator pointed out that heart disease is much more common than breast cancer, but

for women at high risk of breast cancer, the balance shifts. The long time interval of the study seems to make the absolute risks and numbers needed to harm a bit difficult for a person to translate into the context of their own lifestyle, but the general conclusion from a number of studies is that for women, prudent long-term intake should be limited to the equivalent of 1 drink per day. This study adds considerably by finding that how intake is distributed in time, aside from constant binge drinking, does not appear to matter. Presumably, the researchers are saying that bunching up the seven drinks per week into two or three days, e.g. the weekend, is not a mistake, but 7 drinks every Saturday night is not a good idea if done on a regular basis. Furthermore, it appears important to distinguish between wine, beer and hard liquor when judging intake by the drink. Three hard liquor drinks on one night would push one into the binge drinking category.

Alcohol in wine is generally given as a volume percent, the standard bottle contains 750 mL, and beverage alcohol has a density of about 0.8 g/mL. Thus for a half-full glass of the size commonly used by red wind fanciers, the amount of wine is about 200 mL. If the wine is 15% alcohol, this yields 24 g of alcohol per drink. For 12 % which is typical of white wine, it would be 19 g, but this would be for a larger glass than many white wine drinkers seem to prefer. These numbers are considerably larger than those used in the above study to define the relationship between “drink” and alcohol content a glass of wine. Also, the trend among wine makers to produce more full-bodied (knock your socks off) reds has resulted in a higher percentage of reds that are near 15% in alcohol.

Finally, this study, conducted and reported by a group that includes very famous epidemiologists, still does not make it easy to get at absolute risk increases in order to temper the impact of large relative risk increases. They have to be calculated by the reader, and in one case even the subgroup cohort size had to be calculated.

Also, as has been discussed several times in this Newsletter, there is some evidence that folic acid (folate) reduces the association between alcohol and breast cancer. However, the evidence is inconsistent. The most impressive study found a hazard ratio of 2.0 for alcohol consumption of 40 g/d (consistent with the above study) among women who consumed 200 micrograms/day of folate, and an insignificant ratio of 0.77 for the same alcohol consumption accompanied by 400 micrograms of folate per day.[27] Another study found a suggestion of the same effect, but still not statistically significant, and not involving such high consumption levels.[28] A large study is needed where this is the primary endpoint, where folate not folic acid is used, and where there is a realistic range of alcohol consumption. In one of the studies cited above, the upper quintile was only about 7.6 g/d, an intake which is totally unrealistic when considering real-world lifestyles.

NEW ANALYSIS OF FLU VACCINE STUDIES

Seasonal vaccines are formulated before the spectrum of flu viruses that will be encountered is known, and thus the formulation is based on an educated guess. This means that studies of efficacy and effectiveness partly examine the outcome of this gamble. There are two types of seasonal flu vaccines in general use, the trivalent inactivated (TIV) and the live attenuated (LAIV) vaccines. The former is commonly used for those 18 years and older, the latter most frequently for children. Important perspective can be gained by recognizing that there are no randomized controlled trials of TIV in people aged 1-17 or adults 65 years or older. For LAIV, the same situation exists for people 8 to 59 years of age.

The authors of a recent systematic study and meta-analysis generalize the overall picture by pointing out that the evidence from trials and observational studies suggests that presently available formulations can provide moderate overall protection against infection and illness, with LAIV providing a consistently higher lever of protection in children 7 and under.[29] Efficacy is defined in terms of the results of randomized placebo controlled trials,

effectiveness in terms of observational studies. In this study, the meta-analysis included only studies where case identification was based on the reverse transcription polymerase chain reaction method (RT--PCR) or viral culture techniques. The researchers discuss the poor performance of the competitive approach using serological techniques.

For the randomized placebo controlled trials, enough data is presented to allow the calculation of absolute risk reduction. For the pooled results of 8 trials of TIV, the absolute risk reduction was 1.6% (2.73% minus 1.18%) which yields a number needed to treat of 65 to avoid one case during the season. The crude relative risk reduction was 56%, although the authors use a more sophisticated method to obtain around 60%. For LAIV, the absolute risk reduction was 12.3% (15.73% minus 3.39%) with a number needed to treat of 8. The crude relative risk reduction with this vaccine is about 78% with the study author's calculation giving 82%. This illustrates the superior efficacy of the live attenuated virus preparations which are used mostly for children and as well, a rather poor performance for the vaccine mostly used for the age group greater than 18 years of age. It also illustrates the immense promotional value in relative risk reduction vs. absolute risk reduction.

The authors comment on the anomalous situation where it is assumed obvious that all people over 65 should be vaccinated to prevent serious illness and mortality. In fact, an estimated 90%of all seasonal flu related mortality occurs in this group. But this is the age group for which there is the least data supporting either efficacy or effectiveness of flu vaccines to reduce mortality or morbidity. Only LAIV has been found to have significant efficacy in this age group and in only one study. This vaccine is not approved for use in adults older 50 years or older in the US at the time of this writing. Evidence- based medicine?

One alternative to vaccination well known to readers of this Newsletter is vitamin D.[30-32] What is needed is a randomized controlled trial involving a placebo vs. vitamin D at a dose level sufficient to bring up the 25-hydroxyvitamin D levels to values above just sufficient and ideally optimum, i.e. probably 3000--5000 IU/d with a cohort that covers a wide range of age and of course both genders. It only needs to last 6-8 months, but to be definitive must involve at least one blood test which is a serious impediment. While waiting, readers should reflect on the incredible number of benefits that have been reported for having an optimum vitamin D status in the context of numerous health issues, and the apparent total lack of side effects associated with achieving such levels.

NEWS BRIEFS

RISK OF BLOOD CLOTS ASSOCIATED WITH DROSPIRENONE-CONTAINING BIRTH CONTROL PILLS

The FDA has issued a drug safety announcement concerning this issue.[33] In their data summary they list two post marketing industry studies that were negative and 4 non-industry supported studies published between 2009 and 2011 that reported a 1.5- to 3-fold increase in blood clot risk. They also list 9 brands that contain drospirenone at 3 mg as the active ingredient. This hormone is a synthetic progesterone-like molecule. There is also a formulation (Angeliq) containing 0.5 mg which is prescribed to manage menopausal symptoms. Blood clot risk studies, however, appear to focus on the 3 mg doses. Some of the signs of blood clots include persistent leg pain, severe chest pain, or sudden shortness of breath, all of which should be taken very seriously if observed. According to Reuters (October 21, 2009) in 2008, Bayer disclosed that 129 lawsuits had been initiated concerning two drospirenone containing products, Yaz and Yasmin.

FDA ISSUES SAFETY COMMUNICATION ON FENOFIBRATE

The FDA has issued a warning regarding the cholesterol manipulating agent fenofibric acid, stating that the drug may not lower the risk of major cardiovascular events which is the rationale for its use. This was prompted by the ACCORD trial that found no added benefit of the combination of fenofibrate

and simvastatin vs. the simvastatin alone. Furthermore, women receiving the combination may have an increase in risk of a major cardiac event compared to the statin treatment alone. Fenofibrate was approved in 2008 to be used with a statin to reduce triglycerides and increase HDL in diabetics with dyslipidemia and coronary heart disease or at risk of coronary heart disease who were already at their "official" LDL target.

CARDIOVASCULAR SAFETY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS. META-ANALYSIS

A meta-analysis of 31 trials involving about 116,000 patient-years of follow-up examined this question for naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib and placebo.[34] The primary outcome was heart attack. Secondary outcomes included stroke, death from CVD, and death from any cause. It was concluded that "little evidence exists that any of the investigated drugs are safe in cardiovascular terms. Naproxen (Aleve) seemed least harmful." However, the authors comment that this must be weighed against gastrointestinal toxicity and need for concomitant prescription for a proton pump inhibitor in many patients. They do not discuss the long-term problems associated with proton pump inhibitors, a subject visited several time in previous Newsletters.

NEW VIEW OF VITAMIN E TRIAL FAILURES

A recent study by Nadeem *et al*[35] found that in the laboratory, both the natural forms of alpha and gamma tocopherol (vitamin E) became incorporated in LDL, HDL and very low density lipoprotein providing protection from oxidation but there was a surprising pro-oxidant effect on HDL cholesterol. They also carried out a placebo controlled intervention study on 40 healthy subjects with no known history of atherosclerosis and not taking dietary supplements and observed the same results. Its was also found that the gamma form increased the incorporation of the alpha form into lipoproteins which may explain why *in vivo* studies have demonstrated that the gamma forms is more closely association with a beneficial impact on cardiovascular disease. The pro-oxidative effect on HDL is undesirable but the researchers pointed out that simultaneous ingestion of vitamin C has been reported to inhibit this pro-oxidative effect. This is a nice example of a synergistic effect that accompanies obtaining adequate micronutrients from a good diet and supplements.

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BOOK REVIEW

Wheat Belly. Lose the wheat, lose the weight and find your path back to health. William Davis, MD. Rodale, New York, 2011

About 10,000 years ago humans living in the Fertile Crescent started cultivating a wild variety of grain. Over the centuries, this resulted in control over an important source of calories, the raising of animals for food, and the evolution of civilization, cities, countries, societies, agriculture and war. The original grain was a variety of wheat quite different in height and genetic make-up from that grown today. Through extensive hybridization and selection, the most common modern wheat is a short, heavy bearing, high yield variety. One of the issues addressed in this new book by William Davis involves the proteins and other biochemicals in this modern wheat. Most people think of gluten in this context, but hybridization has introduced a number of new forms of this protein. The change in the genetic composition and thus the protein coding has been most rapid in the last half of the 20th century, although evidence of gluten or wheat sensitivity can be found centuries before the present. The impact of these recent changes on humans has never been studied.

Davis is himself wheat-sensitive and carried out an interesting experiment. He obtained wheat that closely resembled the original variety grown by our distant ancestors (einkorn). Bread he made from this variety did not result in his normal and fairly dramatic reaction to wheat, but he was able to reproduce as expected the reaction shortly after trying the “ancient” bread by eating bread he made grinding modern whole grain seed as the source of flour.

In the last half of the 20th century there was another important event. Dietary fat was demonized in response to studies, which while later proven false, had a profound impact on the diet of the developed world. Fat calories were replaced with carbohydrate calories on a grand scale. Low-fat became one of the most successful marketing tools ever dropped in the lap of the food industry. This was followed by the glorification of whole grains, a view that is alive and well today in the guidelines and recommendations of the American Heart Association, the American Diabetes Association, the US Department of Agriculture, the American Dietetic Association, mainstream medicine and virtually all members of the professional nutritional community.

Over the same period when people started buying into and implementing the fat-is-bad notion, obesity, sky-high triglycerides, plummeting HDL cholesterol, heart disease, type 2 diabetes and a vast number of other disorders became remarkably more prevalent. The term “late-onset diabetes” was dropped as diabetes became prevalent in young individuals. High carbohydrate consumption and the accompanying fat production (de novo lipogenesis) increased fat infiltration into the liver with the end result of increased prevalence of non-alcoholic fatty liver disease, a disorder that carries an increased risk of cardiovascular disease. The advice from the establishment was to cut out dietary fat, especially saturated fat, and emphasize whole grains (translate—wheat). But obesity, diabetes and a whole collection of other problems just keep increasing in prevalence, some at an accelerating rate that is frightening both to medical experts and governments paying the health care bills. While the above picture does not prove causation, it is highly suggestive.

We have been told to emphasize complex carbohydrates and focus on whole grains as the path to health and happiness. Follow the official health pyramid with its heavy emphasis on whole grains. Carbohydrates should represent around half of our calories. Diabetics are told to limit saturated fat and to eat carbohydrates to make up the calorie deficit, and control their blood sugar fluctuations with medications and insulin. This is quite different to the advice at the turn of the last century from the famous physician Sir William Osler, MD, who recommended diets with 2% carbohydrates for diabetics, or the observation of Dr. Frederick Banting, the discoverer of insulin, who noted that a hospital diet used to help control urinary glucose in children involved a strict limitation of carbohydrates to 10 grams per day (40 calories!). There was even a popular book published in 1967 (and now in its 13th edition) with the title *Leben ohne Brot verhilft zu besserer Gesundheit* (Life without bread promotes better health).

In *Wheat Belly*, William Davis, MD, a preventive cardiologist, advances a theory that the above history, when examined in much more detail, suggests that the present-day health disaster is due in part not just to the switch to a diet very high in carbohydrate, but also a diet that is high in wheat and thus wheat proteins. These proteins impact the gut, the body acidity, the immune system, the nervous system and the functioning of the brain, just to mention the highlights. He takes the reader on an imaginary tour of his supermarket where it is hard to find an isle or section where wheat containing foods are absent.

Wheat belly is his term for what we all grew up to recognize and call the beer belly and inspired a book about men getting "pregnant." But excessive belly fat collection, which he associates with heavy consumption of both wheat and carbohydrates derived from other sources is just part of a much bigger and far more serious and captivating story. Some, after reading the details, the arguments and the case histories, will view wheat products in a rather different light. But Davis' view is not just theory. Part of the rationale for his position is based on extensive clinical use of wheat elimination in his own practice with significant and in some cases phenomenal success, and in part on a quite considerable body of scientific research which he cites and discusses in this fascinating book.

Wheat Belly is not just another low-carb diet book. Nor is it a book just about gluten sensitivity or Celiac disease, although these topics are central to the pathophysiology associated with certain wheat proteins and are discussed in detail. Avoiding wheat is also not just because of its extraordinarily high glycemic index. Quite the contrary, it is a comprehensive and well documented examination of the most ubiquitous and important carbohydrate source in our diet, and how it has evolved, especially recently, and how it appears associated directly or indirectly with a number of the major afflictions of modern humans. It is interesting that one of its significant dangers is the documented power to cause addiction and, for some, severe withdrawal symptoms. The importance of this book is that it provides significant guidance to those embarking on a low-carb diet or carbohydrate restriction in that it considers in great detail the problem not just of choosing the best carbohydrates but of avoiding those potentially most dangerous. *Wheat Belly* might be regarded as a more modern and scientific examination of the message contained in *Leben ohne Brot.*

Davis devotes a chapter to celiac disease, its dramatic recent increase in prevalence, and the difficulties in diagnosis. He points out that while 50% will experience the classical symptoms, the other half show anemia, migraine headaches, arthritis, neurological symptoms, infertility, depression, chronic fatigue, or a variety of other symptoms that at first glance seem to have nothing to do with celiac disease. Individuals with this disease can also be asymptomatic for years and then exhibit neurological impairment, incontinence, dementia or gastrointestinal cancer. No one knows if new forms of the gluten protein present in the recent hybrids enhance this pathology. It is simply assumed that wheat is wheat, a type of argument also used today instead of the almost impossible testing for adverse effects potentially associated with the new genetically modified foods.

All the above being said, Davis' book should be put in perspective. Not everyone by any means is gluten-sensitive, becomes addicted to wheat products which results in health problems or needs to worry about the wheat vs. non-wheat composition of their diet. A blanket condemnation or advice for everyone to give up wheat products altogether would not reasonable or justified. The challenge is for

individuals to establish if possible the extent to which the message from Davis' book is personally relevant and important. This may not be easy in the absence of experimenting with a totally wheat-free diet for several months. Note the variety of presentations of celiac disease! In addition, food addicts may have great difficulty admitting to themselves that they are driven like a drug addict to overeat or to associate this with wheat, but if this is the case it is obviously a serious situation which gets worse as one progresses from overweight to obese to morbidly obese. Failure to eliminate wheat products would appear to make this situation hopeless.

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