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The theme of this issue is cardiovascular disease and especially stroke. The aftermath of a stroke and a heart attack can be significantly different, with the former frequently resulting in long-term disability, painfully slow rehabilitation and a vastly greater impact on the quality of life than is experienced by many who recover from an acute myocardial infarct. Some profoundly disabled stroke victims may wish their incident had been fatal. Thus stroke prevention should be a big issue. In this issue we briefly examine several recent studies that relate to this.

The risks and apparent benefits of alcohol consumption are also featured. This is a complex issue because the safe window in terms of drinks per day seems both narrow and gender dependent, and because there is the ever-present risk of moderate consumption leading to excessive drinking and addiction. Thus there is understandable reluctance on the part of many health care professionals to even approach this subject with their patients. Nevertheless, the benefits associated with a glass or two of wine with dinner appears to outweigh the risks, and for some of the adverse effects, small amounts of folic acid appear to be protective.

Finally, this issue contains a review of Gary Taubes' recent magnum opus titled "Good Calories, Bad Calories. Challenging the Conventional Wisdom on Diet, Weight Control, and Disease". This is not a diet book, and the title may mislead and in fact cause some to ignore this important work, especially those who are saturated and fed up with the diet book scene. This would be a mistake as it is hoped the review will make clear.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

In the research report included with the February issue there was a brief discussion of cholesterol and stroke. In this issue we will highlight recent research on risk factors for stroke. Stroke and adverse coronary events are frequently considered together under events associated with cardiovascular disease, and the so-called ischemic stroke caused by an occlusion and a hemorrhagic stroke caused by bleeding from a ruptured or leaking blood vessel are also sometimes lumped together for an outcome that is simply described as a stroke. While both stroke and adverse coronary events are major causes of mortality and morbidity, non-fatal stroke seems to be in a special category because of the potential for a very much larger impact on quality of life and a slow recovery from the associated disabilities as compared to residual effects of many non-fatal heart attacks.

NEW STUDIES OF STROKE RISK FACTORS

New data on the risk of stroke derived from the Prospective Cardiovascular Münster study (PROCAM) has just been published. The investigators developed a so-called stroke risk score for ischemic stroke or transient ischemic attack. The results are based on data from about 5900 men and 2200 women followed for at least 10 years. The factors found important were smoking, gender, age, systolic blood pressure and the presence of diabetes. The latter was defined as either a history of diabetes or a fasting blood sugar of at least 120 mg/dL. For example, a 55 year old male who smokes, has a systolic blood pressure between 160 and 164 would have a 5% risk of stroke over then next 10 years. If the individual was diabetic, the risk would jump to 10%. For a woman with the same profile, the corresponding numbers would be 3% and 5%. Serum cholesterol was not a risk factor in this study.[1]

Another study just published looked at the incidence of coronary disease and/or stroke in type 1 diabetic African Americans.[2] The significant risk factors found were age, proteinuria, diastolic blood pressure, depression, body mass index and the severity of retinopathy. Proteinuria is a marker for significant kidney disease and enhances the risk of atherosclerosis. Retinopathy is a degenerate disease of the retina with a number of characteristic features that are evident on ophthalmoscopy with the pupils fully dilated, a procedure included in some physical and eye examinations, although in the former there would be no dilation. In this study serum cholesterol was included in the parameters studied but was not significant in the final analysis.

METABOLIC SYNDROME AND STROKE RISK

The metabolic syndrome involves a cluster of vascular risk factors such as elevated blood pressure, elevated blood glucose, obesity, and an abnormal blood lipid profile. This syndrome is associated with increased risk of cardiovascular mortality and morbidity with risk estimates ranging from 40% to over 300%. However the associated risk of stroke per se is less well established. This issue was addressed as part of the Northern Manhattan Study which followed over 3000 stroke free individuals (mean age 69 years) for a mean of 6.4 years. The metabolic syndrome was defined using the National Cholesterol Education Program guidelines with the following factors: Fasting blood glucose ≥ 100 mg/dL; blood pressure greater than 130/80 mm Hg or a history of hypertension; HDL cholesterol < 40 mg/dL for men and < 50 for women; triglycerides > 150 mg/dL; and a waist circumference of > 40 inches for men and > 35 inches for women. The syndrome is then defined as having any three of these risk factors. In the cohort studied, more than 44% qualified for the diagnosis of metabolic syndrome. Increased risk of stroke was found to be greater for women (100% increase) than for men where the increased risk failed to achieve statistical significance. The authors estimate that elimination of the metabolic syndrome would result in a 19% reduction of overall stroke, 30% reduction in women and 35% reduction in Hispanic individuals.[3]

VITAMIN C AND RISK OF STROKE

In a large European study of over 20,000 participants followed over 10 years, the relationship between the vitamin C status and incidence of stroke (either type) was prospectively examined.[4] Men and women aged 40 to 79 were recruited. Those in the top quartile of plasma vitamin C (≥ 66 µmol/L) had a 42% lower risk of stroke as compared to those in the lowest quartile (< 44 µmol/L). This result was statistically significant and independent of age, sex, smoking, body mass index, systolic blood pressure, cholesterol, physical activity, prevalent diabetes and heart attack, social class, alcohol consumption, and any supplement use. The authors point out that these results are consistent with other smaller and less well powered (statistically) studies. It also agrees with studies that found an inverse relationship between stroke risk and higher fruit and vegetable intake, although in this study the presence or absence of fruit and vegetable intake in the statistical analysis had no effect on the relative risks calculated. Nevertheless, plasma vitamin C was found to be a good biomarker for fruit and vegetable intake in the cohort studied, and since vitamin C supplementation was present in

only a small percentage of the cohort, the vitamin C must have come from food. A 20 µmol /L increase in plasma vitamin C was observed to approximately equal to one serving of fruit and vegetables daily.

The authors comment on the difference between their results and those from intervention trials which found a lack of benefit. They suggest that this may be related to the saturation effect at intakes of > 100 mg/day which could lead to a large fraction of a study population showing little benefit if their intake was already in the range of 100 mg/day. This in fact is one of the strengths of the their study in that the actual circulating concentration of the vitamin was measured rather than estimated from food and supplement intakes, a source of major uncertainties. In an editorial, Padayatty and Levine point out that a 100 mg dose generates a plasma level of about 60 µmol\L for a fasting subject, and 200 mg, which corresponds to an intake of about 5 servings of fruit and vegetables, produces a level of about 70 µmol/L and this does not increase significantly with higher doses.[5]

Finally it was pointed out that about half the risk of stroke is not explained by conventional cardiovascular risk factors and that the predictive value of the traditional risk factors appears to diminish with age. Thus the finding that plasma vitamin C is a risk marker independent of known risk factors for stroke may have value in helping to identify those at risk and help target interventions with established therapies.

ALCOHOL AND STROKE RISK

The most recent study concerning alcohol consumption and the risk of stroke involved a large cohort of Chinese men of age ≥ 40 years who were followed for approximately 10 years. A suggestion of protection was found for 1-6 drinks per week, no effect for 7-20 drinks per week, a significant increase to 22% risk at 21-34 or > 35 drinks per week. Thus in this study there is only a suggestion of a "J" shaped risk vs. dose relationship. These results were adjusted for age, body mass index, physical activity, urban vs. rural, geographic variation, smoking, history of diabetes and education. Comparison was with abstainers. When the results were stratified by stroke type, the results in general failed to achieve statistical significance, but excessive alcohol consumption appeared to be deleterious for hemorrhagic stroke.[6] These results are similar to those reported by Sacco *et al* [7] who found a "J" shaped relationship with maximum protection for ischemic stroke at between 2 and 3 drinks per day with the threshold for enhanced risk at 5 drinks per day and with 7 drinks per day yielding an increased risk of about 200%. This latter study involved approximately 50% women and was multi-ethnic. In an editorial concerning the Chinese study, Sacco points out that the threshold for enhanced risk is still being debated with some arguing that more than 2 drinks/day would possibly increase the stroke risk and five or more definitely would. He cites a meta-analysis that found a 69% increased risk of ischemic stroke risk for 5 or more drinks per day when the comparison was with abstainers and that less than 1 to 2 drinks had a 20-30% protective effect. Sacco also discusses the source of the alcohol and points out that there is some evidence from a meta-analysis that wine is superior to beer for reducing vascular risk. [8]

Concerning the issue of alcohol and cardiovascular health in general, O'Keefe *et al* have recently reviewed the subject. [9] They provide evidence for a "j" shaped relationship for alcohol and all cause mortality (minimum at about 1 drink per day, risk of a heart attack (minimum at 1-2 drinks per day, extent of coronary calcium (minimum at 2 drinks per day), and the risk of diabetes (a broad minimum between 1 and 3 drinks per day). In all of these disorders, the threshold for significantly enhanced risk compared to abstainers was 4 to 5 drinks per day.[9]

ALCOHOL INTAKE AND RISK OF COLORECTAL CANCER

While it is widely recognized that alcoholic drinks and in particular red wine afford some cardio-protection, it would be a mistake to ignore the flip side, the risk of cancer. A recently published multicenter European prospective study (EPIC) addressed this issue in connection with colorectal cancer (CRC). Baseline and lifetime alcohol intake were determined with a questionnaire. There were almost 500,000 study subjects free of cancer at enrolment who were followed for an average of 6.2

years. After adjusting for potential confounding factors, lifetime alcohol intake was significantly and positively associated with CRC risk with an 8% increase per 15g/day (one drink) increase in intake with higher risk (12%) associated for rectal cancer. Similar results were obtained from analysis using baseline intake data. More apparent risk increases were seen for alcohol intakes greater than 30 g/day. An interesting aspect was that folate intake was found to be protective, an observation the authors point out is consistent with other studies of alcohol and this cancer site.[10]

Editor's comments: This study indicates that alcohol provides competing risks and benefits and that as was seen in cardiovascular risks where the threshold at which the association becomes significantly positive is around 2-3 drinks per day, For CRC cancer it may be closer to 2 drinks per day. The effect of folate was also found in studies of alcohol and the risk of breast cancer (see the Research Report on Breast Cancer Prevention available in the Newsletter archives). In the breast cancer studies, the amount of folic acid in one multivitamin pill (400 micrograms) was sufficient to reduce the risk to essentially zero, and while the CRC study did not provide detailed information of folate/folic acid status, food fortification with folic acid is rare in Europe as is supplementation. Thus it is very unlikely that those in the highest tertile of folate, the level where the CRC risk became statistically insignificant, had intakes of more than 400 micrograms/day. On the other hand, there is evidence that high intakes of folic acid (> 600-800 micrograms/day) may increase the risk of CRC, whereas modest amounts such as are found in diets rich in vegetables are protective. This has been briefly discussed in previous newsletters and will be the subject of a forthcoming Research Report.

VITAMIN D AND CARDIOVASCULAR RISK

Recently published research by Wang *et al* addresses this issue in a prospective study of over 1700 men and women with a mean age of 59 years. Vitamin D status was ascertained by the blood levels of the standard marker 25-hydroxyvitamin D (25-OHD). They examined the impact of a deficiency defined either as < 15 ng/mL (38 nmol/L) or < 10 ng/mL (25 nmol/L). For individuals with levels below 15 ng/mL, an increase of about 62% was found for the risk of a first cardiovascular event (stroke or heart attack). When just those with hypertension were examined, the risk more than doubled as compared to those with levels greater than 15 ng/mL. The authors take a conservative view that "experimental studies may be warranted to determine whether correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease." This is consistent with the fact that their study did not examine the risk stratified by 25-OHD levels up to those being widely recommended for cancer protection, i.e. 1000 IU per day, which would put most people in the serum range of over 75 nmol/L.[11]

Editor's comments: The position of the American Heart Association in response to the study by Wang *et al* is interesting (Public release 7 January 2008 quoted on www.eurekalert.org). *"The American Heart Association recommends that healthy people get adequate nutrients by eating a variety of foods in moderation, rather than by taking supplements. Food sources of Vitamin D include milk, salmon, mackerel, sardines, cod liver oil and some fortified cereals. Vitamin or mineral supplements aren't a substitute for a balanced, nutritious diet that limits excess calories, saturated fat, trans fat, sodium and dietary cholesterol."* To obtain about 1000 IU per day from food, the *minimum* amount being recommended, incidentally by organizations representing mainstream medicine, for cancer prevention, avoiding influenza, and for good health in general, would require eating per day approximately 1/2 pound of salmon, 3/4 pound of sardines or mackerel, or 7 packets of instant fortified oatmeal. However, two to three teaspoons of cod liver oil would indeed provide such levels. The AHA position also implies that supplemental vitamin D is different than that found in food, but they then have to explain why supplements raise the level of the same chemical in the blood, 25-OHD, which is the know metabolite of vitamin D from either sun exposure or food.

UNDER ESTIMATION OF CARDIOVASCULAR RISK IN WOMEN

The use of electron bean tomography has revolutionized the detection and measurement of subclinical atherosclerosis. Known as the calcium scan, this non-invasive technique detects calcified plaque in the coronary arteries and generates a so-called coronary artery calcium score (CACS). A report on a large multicenter U.S. study has just appeared which examined the extent of coronary calcium in over 3600 women judged to be at low risk by the Framingham Risk Score which estimates the 10-year risk of coronary heart disease (CHD) based on age, gender, total cholesterol, high density cholesterol (HDL), blood pressure, the use of hypertension medication, and smoking status. In this study of women with a mean age of 60 years, 90% were classified as low risk, i.e. < 10% risk of CHD during the following 10 years. Calcium scans revealed that the prevalence of any coronary calcium was 32%. Compared to women with a zero calcium score, this group had approximately a 6 to 7 fold increase in risk for CHD and a 5-fold increase for cardiovascular disease (CVD). In addition, 4% of the low risk group had a calcium score of over 300 which is generally considered to indicate advanced atherosclerosis. This subgroup had especially high risk of CHD or CVD.

The authors remark that data from the Third National Health and Nutrition Examination Survey (NHANES) found that 95% of U.S. women younger than 70 years are judged low risk according to the traditional Framingham Risk Score and under current guidelines do not qualify for more aggressive management for standard risk. But a majority of women will die from CHD, the largest component of CVD-related mortality, and yet they rarely reach the intermediate- or high-risk status by the Framingham yardstick. But a recent study of lifetime risk found that women with one major CHD risk factor who were judged at low risk had a dramatically shortened life expectancy and thus there should be benefit in aggressively treating even one risk factor under these circumstances.[12]

Editor's comments: This is just the latest in a series of studies that suggest significant underdiagnosis of sub-clinical atherosclerosis. This was discussed in Part I of the Cholesterol Review which appeared in the November 2007 Newsletter. It seems clear that assessment with the traditional risk factors is missing important factors in the development of atherosclerosis and if primary prevention is the goal, this is an important deficiency. Obvious candidates include psychological stress, depression and insulin resistance, all of which drive atherosclerosis through predominantly inflammatory mechanisms.[13] But even the diagnosis of the metabolic syndrome does not provide a reliable diagnosed insulin resistance, and according to Gerald Reaven of Stanford, the diagnosis of the metabolic syndrome has no clinical merit. Instead, he suggests that individual risk factors associated with the syndrome should be treated and that the question of the presence of insulin resistance should be directly addressed.[14,15] Unfortunately, the two-hour glucose tolerance test including several insulin level measurements is not consistent with many primary care models (10 minutes for an office visit, 20 min for a physical exam), no matter how potentially informative the results might be.

POSITIVE STUDY REGARDING SUPPLEMENTS

In a milieu where mainstream medicine is strongly anti-supplementation, it is refreshing to see a peer-reviewed paper presenting positive results. In a cleverly designed study, Block *et al* [16] mined the NHANES III database for data on supplement non-users and single supplement users, and acquired data by questionnaires and physical examination for a group of multiple supplement users. This allowed a comparison between these three groups as regards a variety of measures related to health status including chronic disease-related bio-markers. Supplements consumed on a daily basis by more than 50% of the multiple supplement users included a multivitamin/mineral, B-complex, vitamin C, carotenoids, vitamin E, calcium with vitamin D, omega-3 fatty acids, flavonoids, lecithin, alfalfa, coenzyme Q-10 with resveratrol, glucosamine and a herbal immune supplement. The majority of women also consumed gamma linolenic acid and a probiotic supplement whereas men also consumed garlic, zinc, saw palmetto and a soy protein supplement. After adjustment of the results for age, gender, income, education and body mass index, the multiple supplement users had more favorable concentrations of serum homocysteine, C-reactive protein, HDL cholesterol and triglycerides and lower

risk of prevalent elevated blood pressure and diabetes. For example, as compared to non-users, the multiple supplement users had a 90% risk reduction of having homocysteine > 9 µmol/L, 50% less risk of having low HDL (<40 mg/dL for men, 50 mg/dL for women), a 56% less risk of having triglycerides over 150 mg/dL, and a 39% lower risk of having blood pressure over 120/80. As might be expected, the multiple users were concentrated in the high income (> $70,000/year) and greater education (> high school) categories, but this was taken into account in the adjusted statistical analysis.

ALCOHOL AND TYPE 2 DIABETES

A randomized controlled trial has just been reported that addresses the issue of the influence of alcohol consumption on both fasting and post-meal blood sugar levels.[17] Subjects drank one glass of red or white wine daily during dinner for 3 months in this multicenter trial. Fasting glucose was significantly decreased from a mean of about 140 to 118 mg/dl, but there was no impact on post-meal glucose levels. Patients in the alcohol group with higher HgA1C levels (a measure of long-term average glucose levels) had greater reductions in fasting glucose as compared to patients with low levels of this biomarker. No data was collected regarding insulin levels, degree or changes in insulin resistance or glucose output from the liver. The authors discuss other studies that have demonstrated the benefits of moderate alcohol consumption in this context:

- Alcohol has been associated with a lower risk of developing type 2 diabetes.
- Alcohol consumption is associated with decreasing levels of inflammatory biomarkers and increasing adiponectin, a hormone involved in metabolism.
- Alcohol is linked to lower cardiovascular risk among patients with type 2 diabetes with decreases in risk of 25-66% for total and fatal CHD rate as compared to abstainers.
- Alcohol consumption is associated with a 21-36% lower total mortality rate in type 2 diabetics.
- Red wine taken with meals has been found to significantly reduce oxidative stress and pro-inflammatory cytokines in diabetics who have had a first heart attack.

Editor's comments: The consensus appears to be that moderate is defined as one drink a day for women and two drinks a day for men. Exceeding these limits puts one in the grey zone representing the threshold for increased risk in connection with a number of health issues and that the evidence that heavy alcohol consumption carries significantly elevated health risks is compelling.

NEWS BRIEFS

STATINS AND VITAMIN D

Those who have read the review on cholesterol in the past three issues are aware that there is considerable evidence concerning the non-lipid lowering benefits of the statin class of drug. In a recent issue of the *American Journal of Cardiology*, Aloia *et al* [18] report another benefit. In a randomized study, statin users and non-users were given either 800 IU of vitamin D3 or a placebo. After three years the dose was increased to 2000 IU. The really interesting observation was that at baseline, statin users as compared to non-users had significantly higher 25-hydroxyvitamin D (25-OHD) levels. The effect of supplementation was to raise the 25-OHD levels in both the statin user and non-user groups. The statin users achieved higher levels because the started with higher levels. The authors comment that statin use has been reported to reduce hip fractures and improve hip bone mineral density and they suggest that this may be associated with higher levels of 25-OHD. The mechanism by which statins increase vitamin D levels is not clear.

Editor's comment: As discussed above, vitamin D levels appear to also have cardio protective benefits. Thus there is another non-lipid lowering effect that could be related to the benefits of statins in secondary prevention of CHD. This brings to mind the recent announcement from Merck/Schering-Plough that ezetimibe (Zetia) when added to simvastatin had no added benefit as measured by the progression of carotid atherosclerosis even though the LDL reduction after 2 years was 58% vs. 41% for simvastatin alone.

Zetia is a non-statin drug that lowers cholesterol by interfering with absorption from the gut. Great surprise and disappointment was voiced by the experts, but it may be that the most important message is that Zetia did not provide the non-lipid lowering benefits associated with statins, further reinforcing the notion that lipid lowering is a side effect and that statins are effective mainly because they have other actions which are dose dependent just as is lipid lowering.[19] This vitamin D result seems to further weaken the hypothesis that the causal association between cholesterol and heart disease is proven by the fact that lowering serum levels reduces incidents in individuals at high risk or with preexisting CHD.

PREDICTING HEART DISEASE RISK WITH A TAPE MEASURE

In attempting to relate overweight and obesity to the risk of coronary heart disease (CHD) there has been a progression from weight to body mass index (BMI) to waist circumference and now evidence points to the waist to hip ratio as the best predictor. In a prospective English study reported by Canoy *et* al [20] almost 25,000 men and women between ages 45 and 79 were followed for approximately 10 years. Its was found that the risk of developing CHD increased with higher baseline waist to hip ratios (WHR) even after taking into account body mass index and cardiovascular risk factors. The data also suggested that BMI might not be as sensitive a predictor of disease as the WHR, a result that was consistent with other studies. In the study of Canoy *et al*, it was found that for every increase of roughly 2.5 inches in hip circumference for men and 3.5 inches for women, the risk of developing CHD was reduced by 20%. The WHR used as reference for men was < 0.88 and the highest risk (approximately 50% increase) was associated with a ratio of ≥0.98. For women the corresponding numbers were < 0.74 and ≥ 0.845 which was accompanied by approximate doubling of risk of CHD. The authors suggest the differenced in risk by the anatomic location of fat could reflect differences in metabolic characteristics between abdominal and peripheral body fat, with the increased visceral fat playing a key role in promoting atherosclerosis and adverse coronary events.

DIET AND ALL-CAUSE MORTALITY IN THE U.S.

In the first large prospective study of Mediterranean dietary patterns and overall mortality in the U.S., Mitrou *et al* report on research involving over 200,00 men and women who were followed for approximately 5 years. At issue was the impact of a Mediterranean type diet on all-cause mortality, and as well, cardiovascular disease and cancer mortality. The diet pattern associated with the Mediterranean diet consisted of vegetables (excluding potatoes), fruit and nuts, legumes, grains, fish, and a high monosaturated to saturated dietary fat ratio. It was found that the Mediterranean diet pattern was associated with reduced all-cause and cause specific mortality. Comparisons were made between high and low conformity with the diet pattern. For men the risk reduction was about 20% for all-cause mortality and 17% for cancer mortality, whereas for women it ranged from 20% for all-cause mortality to 12% for cancer mortality. The authors believe that these results provide strong evidence for the benefits of high conformity with this particular diet pattern in the context of cardiovascular disease and cancer.[21]

HEART ATTACKS WITHOUT CHEST PAIN

Patients with heart attacks (acute myocardial infarction or MI) usually present with chest pain. However, atypical presentations are well recognized and are believed to be more common in women. Canto *et al* have recently examined the literature in connection with this matter.[22] Approximately 1/3 of patients in large studies and 1/4 of patients in small studies presented without chest pain or discomfort. This was noted more commonly in women than men, i.e. 37% vs. 27% in large studies and 30% vs. 17% in smaller studies. The authors conclude that these differences are not enough to influence public health messages regarding gender differences of symptoms at presentation. They point to earlier studies that found similar results. Data from Framingham suggest that 25% of acute MIs seen during 30 years of follow-up were only apparent after examination of the ECG and in almost half of these, the MI was truly "silent" and for the remainder, there were only atypical symptoms. They make reference to the American Heart association guidelines available at www.nhlbi.nih.gov/actintime for the current view on warning signs.

Editor's comments: These results should be of interest to men as well as women. Many men may believe that a prerequisite symptom for an acute MI is chest pain, a notion that could significantly delay treatment.

CHILDHOOD WEIGHT AND OBESITY AND CORONARY HEART DISEASE RISK AS ADULTS

A recent Danish study examined over 250,000 school children where height and weight measurements were recorded between 1955 and 1960. A federal vital statistics register was used to examine the risk of CHD in adulthood. The study found that there was an association between higher childhood body mass index and adult CHD with the association stronger in boys than girls. The risk increased across the spectrum of body mass index values. For example, they calculate that in comparison with an average-sized 13-year-old boy, a boy of the same age and height weighing 11.2 kg more (24.6 pounds) had a 33% higher risk of having a CHD event in adulthood; similar results were found for girls. One of the strengths of this study was that it involved personal follow-up rather than computer models of risk and thus produced a potentially more realistic picture, at least in this Danish population.[23]

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BOOK REVIEW

Good Calories, Bad Calories. Challenging the Conventional Wisdom on Diet, Weight Control and Disease

by Gary Taubes
Alfred A. Knopf, New York, 2007

In the past few years several books have been published that present a contrarian's view attacking the conventional wisdom regarding fat, cholesterol and cardiovascular disease. Now a new book by Gary Taubes has just been published. The author's name should already be familiar to readers of this newsletter because his articles in the New York *Times Magazine* have been repeatedly quoted in connection with high vs. low fat diets and the issue of cholesterol and heart disease. He is a highly regarded medical journalist and the only print journalist to have won three Science in Society Journalism awards. In Taubes' latest effort we have a comprehensive treatment of the title subject which includes fascinating early history and a very detailed discussion of the scientific research and clinical and epidemiologic evidence associated with the establishment views of diet, heart disease and diabetes as they have evolved over the last 50 years, views that in some cases have generated dogma now cast in stone, enshrined in medical textbooks and public health policies, and indelibly etched in the minds of both the general public and a substantial fraction of nutritionists and the medical profession. This book critically reviews alternate hypotheses which are contrary to this conventional wisdom and explores in great detail the research that forms their foundations and the culture that is responsible for these hypotheses being ignored and ridiculed. The title of the book is misleading—it is not a diet book in the usual sense, but if one accepts the author's arguments, it could profoundly alter the way the reader looks at the connection between diet and health.

This book represents, according to the author, five years of research which included a comprehensive examination of the published literature and a careful look at the older literature that is so casually dismissed today. Included are interviews with some of the principal players including those now retired, and an examination of the impact, as reflected by the media coverage and official guidelines that periodically appear, on public behaviour, beliefs and public health positions. The author is neither an academic nor an employee of an industry with a vested interest in the status quo, but rather a keen and experienced observer of science and pseudoscience in action, and he brings to this project a fresh viewpoint presumably uncontaminated by the profound influence of dogma and the conventional wisdom, forces that, as this book clearly demonstrates, play a dominant role in undermining science's supposed goal, search for truth. The thrust of the book is best described by quoting his conclusions which most readers will recognize as contradicting the conventional wisdom now firmly enshrined as a set of sacred truths which will probably endure over the professional careers of their influential contemporary proponents. In addition this conventional wisdom will probably continue to influence public health pronouncements and the areas and focus of intense and well supported research. These are consequences which individuals in the developed world may someday come to profoundly regret. Here are his conclusions, which also provide a general outline of the book and its topics.

1. Dietary fat, whether saturated or unsaturated, is not a cause of obesity, heart disease, or any other chronic disease of civilization.
2. The problem is carbohydrates in the diet, their effect on insulin secretion, and thus the hormonal regulation of homeostasis, i.e. the entire harmonic ensemble of the workings of the human body. The more easily digestible and refined the carbohydrates, the greater the adverse effect on our weight, well-being and health.
3. Sugars, and specifically sucrose and high-fructose corn syrup, are particularly harmful, probably because the combination of fructose and glucose simultaneously elevates insulin levels while overloading the liver with carbohydrates.
4. By virtue of their direct impact on insulin and blood sugar, refined carbohydrates, starches and sugars are the dietary cause of coronary heart disease and diabetes. Also, they are the most likely dietary causes of cancer, Alzheimer's disease and other chronic diseases.
5. Obesity is a disorder of excess fat accumulation, not of overeating and or due to a sedentary behaviour.

6. Consuming excess calories does not in general cause humans to become fatter. Expending more energy than we consume does not necessarily lead to long-term loss of weight but it leads to hunger.
7. A disequilibrium in hormonal regulation of adipose tissue and fat metabolism results in fattening and obesity.
8. The primary mediator of fat storage is insulin. When insulin levels are high, either chronically or after eating, we accumulate fat in the fat tissue. When insulin levels fall, there is a release of fat from fat tissue for use as fuel.
9. Carbohydrates make us fat and ultimately cause obesity by stimulating insulin secretion.
10. Carbohydrates also increase hunger and decrease the amount of energy we expend in metabolism and physical activity by driving fat accumulation.

Thus Taubes makes a case for what might be called *The Carbohydrate Hypothesis of Chronic Diseases*, and this book concentrates on the potential impact of this hypothesis on heart disease, vascular disease and diabetes.

In spite of the very high order of scholarship and meticulous research reflected in this work, it is probably not a book that mainstream medicine will welcome, nor is it one that they will recommend to patients, medical students, graduate students, etc. After all, aside from an attack on the conventional wisdom, the message that comes through loud and clear is that we now have a milieu associated with medical and nutritional research where the standards of evidence are considerably more lax than in the hard sciences such as physics, chemistry, molecular biology, etc. and that this has had a strong impact on the time honoured processes associated with getting at the truth concerning questions of great importance.

A lot of what Taubes describes might be called “Official Science,” a term used by Christopher Essex and Ross McKitrick in a book on climate change (*Taken by Storm*, Key Porter Books, 2007, Toronto). Official Science is the end result of the evolution of a hypothesis or mere model to an accepted truth and then to a dogma without any justification for this elevation. The status as Official Science makes it almost impossible to challenge the dogma, publish a contrarian view or results, or even obtain funds to study the matter, and anyone even questioning the dogma runs the risk of becoming a professional outcast. Hypotheses should survive by withstanding attempts at falsification. This is the way science is supposed to work. But this process has been cleverly undermined by using the media, individuals with vested interests and appeals to so-called authority in order to keep alive questionable hypotheses, prevent studies that might invalidate them and allow citation bias, even in refereed journals, to conceal inconvenient truths. Taubes presents case after case to illustrate this deplorable state of affairs in what most people look up to as the sacred and highly esteemed establishment that creates so-called evidence based medicine. Thus this book is in fact an expose of what has fundamentally gone amiss today with science as it is used and manipulated in the fields of health and nutrition.

This book may erode or even destroy the reader’s confidence or belief that medical and nutritional research, as it has been conducted for the past 50 years in fields such as diet, diabetes and heart disease, is capable of providing guidance that is based on sound principles of scientific research and an unemotional, unbiased and open-minded search for the truth. But Taubes’ carefully researched and documented history of the conflict between dogma and authentic science should prove to be of value for anyone trying to sort out the steady stream of conflicting views that have emanated from the recognized experts and their critics, gain a perspective regarding the role of various high profile organizations attempting to influence public health issues and rethink long held beliefs, recognizing that they may only be either hypotheses or in fact merely the result of junk science.

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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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One approach to localized cancer treatment is simply to remove or destroy the tumor and perhaps sufficient surrounding tissue to minimize the risk of recurrence. How well this works is debatable, depends on the tumor site, i.e. brain, colon, kidney, etc., the nature and stage of the cancer and many other factors. Critics point to the failures, proponents to the apparent cures. In the case of prostate cancer, definitive treatment involves the complete removal of the gland or the more or less complete destruction of its tissue. An alternative is discussed in this issue which involves targeting an isolated tumor in the prostate and destroying it along with some surrounding tissue using intense focused heating or cooling or some other localized approach. This is called ***focal prostate cancer therapy*** *and is an emerging therapy of significance. For focal therapy to make sense, it must be possible to find isolated tumors and specify their exact location. Thus closely related to focal therapy is the question of biopsy and imaging techniques that might make this possible. These areas form the main subject of this month's issue.*

Wishing you continuing good health,

William R. Ware, PhD, Editor

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

FOCAL PROSTATE CANCER THERAPY

Focal prostate cancer therapy involves the destruction of a one or more localized tumors with selective ablation while sparing a significant amount of prostate tissue. The debate concerning this new approach is reminiscent of an earlier controversy over the treatment of breast cancer with either radical mastectomy or lumpectomy. Critics raised the obvious concerns about the ramifications of less than complete removal of the all breast tissue, a procedure done with the hope of removing all of the cancer. Nevertheless, today the lumpectomy is an accepted alternative, often with adjuvant therapy. Prostate cancer theoretically presents the same options since some cancers are highly localized and if destroyed, for example by cryoablation, a cure would appear highly likely. Advocates contend that focal therapy for properly selected patients offers recurrence-free and overall survival equivalent to definitive treatments such as the radical prostatectomy or radiation therapy without the adverse effects, but there is no supportive data. Critics take the position that this experimental and unproven therapy, sometimes referred to as the "male lumpectomy," would appear to be inadequate for a cancer known to in general be multifocal and heterogeneous.

The central question of course is simply whether or not localized tumors can be identified, characterized, and their exact location specified such that they can be accurately targeted. Furthermore, for this approach to make sense, there must be a high likelihood that no other significant or threatening tumors are present and that the extent and seriousness of the cancer has not been underestimated. This is of course not a new problem. Quite the contrary, it is similar to the problem of selecting candidates for expectant management. So far, the needle biopsy has been the technique of choice for finding the target tumors, assessing their nature, and obtaining evidence that other tumors had not been missed. To accomplish this requires obtaining a large number of cores, i.e. the use of a large number of needles, and in addition, obtaining accurate information regarding the location of each core relative to the prostate.

The current status of focal therapy has been reviewed by Eggener *et al* representing the International Task Force on Prostate Cancer and the Focal Lesion Paradigm. [1] Their review makes the following important points and observations:

- Both the incidence to mortality ratio and autopsy studies on men dying from non-prostate causes suggest over-detection in the PSA era, i.e. a significant proportion of cancers are being detected that are not destined to metastasize or prove lethal, at least during the natural life span of the individuals in question. This observation applies mostly to the US where screening is very popular, but also to a lesser extent in Europe.

- So-called stage migration has unquestionably occurred in the US. Since the advent of PSA tasting, PSA levels have declined on average from 25 to 8 ng/mL and mean volume of the largest tumor from 5-6 to approximately 2 cc.

- In patients undergoing radical prostatectomy, unifocal tumors have been observed in the removed prostate in 13% to 38% of cases. In patients with multifocal disease, a large percentage of the total tumor volume was attributable to the largest tumor. Secondary tumors are both small and rarely contained higher Gleason scores than the largest tumor and, according to this review, are unlikely to affect overall disease progression.

- Contemporary methods of prostate biopsy and imaging have improved the pretreatment characterization of prostate cancer with regard to extent, size and biological potential. The authors point out that both MRI and a number of other imaging technologies have clinical promise. The more recent biopsy called "Transperineal mapping may also improve the accuracy of biopsy assessment of the location, size and aggressiveness of tumors. In addition, the use of much more extensive sampling in the transrectal ultrasound guided biopsy yields a more accurate picture than the traditional sextant biopsy (6 cores).

- Nevertheless, identifying small volume or unifocal disease, tumor characterization and risk estimation remain imperfect according to the task force assessment. They point out that the consequences of improperly designating a patient for focal therapy may be “profound” and it cannot be assumed that tumors other than the largest will not metastasize.

- The assumption that focal therapy will result in a lower likelihood and severity of treatment related to morbidity needs to be confirmed.

- The authors list the types of therapy adaptable to focal treatment. Included are high intensity focused ultrasound, cryotherapy, intensity modulated radiation therapy, and photodynamic therapy. These procedures, incidentally are described in detail in our book *The Prostate and Its Problems.*

There appear to have been only 4 recent trials of focal cryoablation (also termed cryosurgery). [2-5] In all cases the evidence that the cancer was localized to one region of the prostate was obtained by needle biopsy. However, the reports are very vague on the details and it appears that in these studies, focal means that one lobe was targeted rather than just a specific but smaller volume. That is, the cancer was believed to be unilateral, and the treatment was unilateral and called focal. All of the studies had very good outcomes as measured by the incidence of biochemical failure, cancer detected on biopsy subsequent to treatment, potency for those who were potent prior to treatment, and incontinence. Other side effects were for the most part absent. One of these trials also demonstrated that focal or unilateral cryoablation does not preclude additional treatment if recurrence occurs or if another tumor makes its presence known.

The question of the correlation between biopsy parameters and the pathological outcome (unilateral vs. bilateral disease) is obviously critical to the arguments favoring focal therapy. The typical presentation prior to treatment for a candidate for focal therapy would be low risk and only one or two positive cores on the same side of the prostate in a sextant or greater biopsy. A study recently appeared that addresses this issue. Scales *et al* reporting for the SEARCH Database Study Group examined this question in medical records for 261 men.[6] This was a U.S. multicenter study. They compared the clinical characteristics (prior to surgery) with the results of pathological examination of the specimens after removal. The question concerned the correlation between the clinical prediction of unilateral disease and the actual situation. They found on multivariate analysis that no clinical feature was significantly related to pathologically unilateral or less vs. bilateral or greater disease. In fact, they found that two-thirds of men with unilateral low risk prostate cancer diagnosed at biopsy in fact had bilateral or worse disease following radical prostatectomy. The authors cite other studies which also found similar results. In one, 24% of men with unilateral disease at biopsy had positive surgical margin (cancer has spread outside the prostate) *on the side judged benign*. In another study, 85% or men with a unilaterally positive biopsy in fact had bilateral disease.

Thus in spite of encouraging results from a very limited number of small trials, it appears that the ability of biopsy techniques to identify candidates for focal therapy needs to be further studied in order to establish the most accurate procedures for minimizing the false negatives for bilateral disease that appear to be associated with the protocol used in many institutions. The so-called 3-Dimensional Mapping of the prostate which uses a large number of samples and proceeds via the perineum using a template may offer a solution.[7] One of the studies mentioned above actually used this more advanced biopsy protocol.[4]

The above discussion of focal therapy raises the question of the best biopsy protocol, a question that mainly concerns the number of cores taken and the method of placing the needles. For a general discussion of this topic the reader is referred to our book. Traditionally, 6 cores were taken in what was called the sextant biopsy. Recently, the use of more needles has become common. The needles are placed with the aid of an ultrasound image generated from a probe inserted into the rectum, and this probe is also part of the device for inserting and withdrawing the biopsy needles. Thus the term transrectal ultrasound guided biopsy. A second approach involves approaching the prostate via the perineum, the area between the scrotum and the anus. Two recently reported studies address the issue of the number of cores that are optimal.

One study took another look at the so-called saturation biopsy, an approach that takes a large number of cores, typically between 25 and 40. A large number of cores lead to higher morbidity such as blood in the urine or seminal fluid, acute urinary retention which temporarily requires catheterization plus other less common but

unpleasant side effects. Normally pain is not an issue if local anesthetic is employed and something is given for pain relief during the first 18-24 hours after the procedure. In this study, the transperineal approach was used with 24 to 38 cores. It was found that as a primary biopsy, the saturation biopsy did not improve the detection rate for prostate cancer when compared to an 18-core scheme. However, in the case of a rebiopsy, the saturation approach had a definite edge since it doubled the detection rate as compared to taking 12 or 18 cores.[8]

In another recent study, 10-core were compared to 20-core ultrasound-guided trans rectal biopsies. The 10 and 20 core groups were stratified by PSA level using < 6, 6 to 10 and > 10 ng/mL. It was found that the 20-core biopsy was more efficient than the 10-core protocol, especially in patients with PSA between 3 and 6 ng/mL. However, the authors comment that it is necessary to confirm whether the detected tumors are clinically significant on pathological examination of the radical prostatectomy specimens. They comment that these results support increase in the number of cores taken, especially in patients with low PSA, which is particularly relevant in the screening setting. They call for more studies regarding this issue and the related issue of selecting biopsy sites.[9]

The two subjects raised in this issue of the Prostate Monitor should both be of concern to all men. Sooner or later many readers will be offered a biopsy on the basis of a rising PSA or an abnormal digital rectal examination. Knowledge concerning the types of biopsy and what one should expect with regard to pain control is important. In particular if a 20-needle protocol is offered, it is important to realize that there may be a good reason for selecting this option over the six- or ten-needle protocol. There are other issues men need to address in discussions with their urologist, and these are also discussed in our book. Furthermore, men being offered treatment in centers where cryosurgery is popular may well be offered focal treatment with arguments that are appealing, especially the prospect of a lower incidence and level of side effects. Men need to be aware that this is still an experimental procedure and should explore with their urologist the question of missing bilateral cancer with the biopsy protocol used and, as well, the options if recurrence occurs.

Periodically, one sees TV adds for pharmaceuticals that caution that men should consult with their physician to make sure they do not have prostate cancer prior to taking the advertised medication. In fact, the only way to address this issue with high probability is with a biopsy, and only as the number of cores increases from 6 to many does the probability of missing cancer decline to less than 10%. All a single measurement of PSA tells one is that the higher the value, the higher the probability is of having prostate cancer. Even an age-adjusted PSA results only provides probabilities, not a definitive answer to the question of having the disease. Since presumably no one is going to submit to a 10- to 12-needle biopsy as a prerequisite to starting a new medication, taking medications that potentially can influence the progression of prostate cancer involves simply a calculated risk.

While predicting the future is always chancy, it would not be surprising, given the rate of advancement of imaging techniques, that in a few years a protocol based on some variation of MRI or some other technique will become the gold standard for not only detecting cancer but also defining with high accuracy the exact location and sizes of tumors. This would give a big boost to not only focal therapy but also expectant management, two aspect of prostate cancer that appear to be very important in connection with not overtrading indolent cancers.

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