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This month we feature news on cancer and its prevention by examining research on colorectal and pancreatic cancer and melanoma. Also mentioned is a new prediction regarding the projected rate of cancer during the next 20 years. It is interesting that for the investigators, primary prevention does not appear to be on their radar screen. Perhaps because they are oncologists dedicated to treating cancer rather than preventing it.

Some readers will recall your editor ranting over the proposal of a polypill to prevent coronary heart disease. Well, it took 6 years but now such a pill is being tested in India and there appears to be great enthusiasm in the cardiology community. We seem to be one step closer to having statins and hypertension drugs added to our water supplies. The polypill trial is actually held up as a proof in principle that modern medicine can successfully treat disorders that do not exist, which is in keeping with the philosophy that for cholesterol, the lower the better with virtually no limit. The notion that it is a good idea to treat individuals for hypertension with three drugs even if they do not have hypertension is novel to say the least. What's next is hard to predict, given the mind-boggling philosophy we are now being told is the way of the future.

In this issue there is also a recommendation regarding a book dealing with the fascinating problem of the collapse of bee colonies. It does not appear that politicians have fully comprehended the implications of a world without bees, but Rowan Jacobsen's book "Fruitless Fall" may wake them up. This is an urgent and current problem and Jacobsen's book is highly recommended. It is not only informative, but also highly entertaining.

The question of the risk of living near high-tension power lines is again in the news with a Swiss study showing enhanced risk of Alzheimer's disease and senile dementia. It may be time to get an inexpensive Gauss meter and take a look at the field strengths that exist in our everyday environment. The results may be surprising.

Finally, the April 1 issue of the "Journal of the American Medical Association" contains an article that a few years ago probably would have been rejected. It deals with the huge conflicts of interest between professional medical associations and the drug and device industries. The recommendations, if implemented, would change dramatically how these professional organizations function, and some are saying it would not be for the better, i.e. the conflicts of interest must be tolerated because the financial support is their lifeblood. Interesting dilemma.

This issue also contains a Research Report concerning the alleged risk of eating saturated fat. There appears to be strong evidence that the current guidelines that instruct us to limit, if not reduce, the intake of saturated fat are without any scientific basis whatsoever. Such advice appears to be part of a larger body of mythology that permeates modern medicine and influences practice. This review is intended to be a prelude to a review of carbohydrate restriction, a dietary change that appears to have growing support in the context of diabetes and heart disease.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

HUGE INCREASE IN CANCER PREDICTED

A new study from the M.D. Anderson Cancer Center has just appeared in the *Journal of Clinical Oncology.*[1] It contains the prediction of a 67% increase in the diagnosis of cancer in the age group 65 and older in the next 20 years. In addition, a 99% increase is expected in minorities. What is interesting about this paper is that the major concern discussed is the potential for a crisis in the ability to treat all these patients. The need emphasized is for more facilities and oncologists and new treatments. If one looks for a discussion of prevention, it is to be found buried in a paragraph dealing with the need to train more physicians in oncology-related specialties. The one sentence devoted to prevention mentions vaccination for hepatitis B and human papilloma virus, chemoprevention with tamoxifen and raloxifene, reducing tobacco and alcohol use, and the removal of pre-malignant lesions such as colonic polyps. Evidently the authors and the editor of the journal do not consider as important the recent study by scientists at the American Institute for Cancer research and the World Cancer Research Fund which found that more than 34% of all cancer cases in the U.S. could be prevented simply by eating better, exercising more and maintaining healthier weights. In terms of individual sites, it was found that these changes could prevent as many as 38% of breast cancer cases and 45% of bowel cancers in the U.S. But the practice of oncology is like a repair shop (although with a strikingly lower success rate) where the focus is not on prevention of the problems they make their living attempting to fix. However, this new study should motivate individuals to become more concerned with cancer prevention – otherwise the future is alarming.

TRANS-FATTY ACIDS AND COLORECTAL CANCER

It is widely accepted that colorectal cancers develop from colorectal adenomatous polyps which are viewed as precursor lesions. Thus their prevention is fundamental to preventing colon cancer. The risk presented by polyps is the main justification of the recommendation to undergo a colonoscopy. The consumption of *trans*-fatty acids (TFAs) may lead to an elevated risk of developing colorectal adenomas by altering the concentration of fatty acids or bile acids normally found in the colon, resulting in inflammation and oxidative stress of the colonic mucosa. A study has just reported which examined the association between dietary intake of TFAs and the occurrence of colorectal adenomas among a cohort undergoing a complete colonoscopy.[2] Dietary intake was determined during an interview that employed a food frequency questionnaire. Compared with participants in the lowest quartile (fourth) of TFA consumption, those in the highest quartile had a statistically significant energy adjusted increased risk of 86%. The prevalence odds were independent of the location, size or number of adenoma. Some, but not all other studies have found similar results. The present study had several important strengths. First, a complete colonoscopy was used and all visible adenomas were enumerated, and all slides were examined by a single pathologist experienced in this area. In addition, the collection of dietary data was done with a validated questionnaire. The authors cite two studies which found no increase in the risk of recurrent colorectal adenomas associated with the intake of total or saturated fats. This seems to implicate the specific molecular structure of these unnatural *trans*-fatty acids.

In retrospect, it was clearly a mistake to buy into the philosophy illustrated by the famous phrase “better things for better living through chemistry” in the context of chemical factories producing food for a population that had historically relied on plants and animals instead of factories. We now have three major health concerns regarding TFAs, heart disease, diabetes and colon cancer. Reading ingredient lists of course becomes very important, but it is not hard to imagine that the there are ways to get around declaring the presence of TFAs in processed foods.

UV LIGHT, VITAMIN D AND MALIGNANT MELANOMA

Dermatologists and therefore mainstream medicine have vast numbers of individuals convinced that sunlight numbers among the greatest risks to our health. Given that the focus is on skin cancer, the only type appearing to present a significant risk is melanoma since the other types are for the most part easily cured, frequently during an office visit, and do not have a tendency to metastasize. But a paradox exists. Indoor workers get three to nine times less solar UV exposure (UVB and UVC, i.e. ≤ 320 nm) than outdoor workers, but only indoor workers have an exponentially increasing risk of melanoma which has been going on for about 60 years. Furthermore, it is well known that melanoma frequently appears in body areas not usually exposed to the sun. Since exposure to the sun is the natural and principal way humans evolved to obtain their vitamin D, this raises questions regarding the risk-reward analysis associated with the recommendation to avoid the sun at all costs, use sun screen when it is necessary to venture outdoors, and always wear a hat, long sleeved shirts or tops, and move from shady spot to shady spot.

In a recent issue of *Medical Hypotheses*, Godar *et al*[3] have examined this paradox. They base their resolution on two facts. First, the UV light that passes through windows and is also present is small amounts in fluorescent lights (UVA—321-400 nm) can cause mutations in skin cells that can lead to melanoma and also break down vitamin D formed after outdoor UVB exposure (290-320 nm) which provides protection from the development and progression of melanoma. UVA does not generate the precursor to vitamin D3 in the skin. In the early 20th century there was a movement of workers indoors and there was a trend toward more windows and more daylight indoors. At about this time the incidence of melanoma started to increase and the rate of increase has remained constant (exponential) to this day.

The authors offer the following observations in support of this hypothesis.

- Indoor workers have much lower exposure to UVB than outdoor workers but have a much higher incidence of melanoma.
- Vitamin D blood levels of outdoor workers are much higher than that of indoor workers.
- Pre-diagnostic levels of the vitamin D status marker 25-hydroxyvitamin D are much lower in melanoma patients than in controls.
- The use of UVB-absorbing sunscreens is associated with a significant increased risk of melanoma.
- An all-year tan is protective against melanoma.
- Outdoor activities in childhood (excluding severe sunburns) decrease the incidence of melanoma.
- Melanoma patients who receive regular sun exposures live longer than those who do not.
- UVA promotes skin tumor growth in mice after artificial initiation, and also causes twice as many tumors to form.

This hypothesis covers the following epidemiologic observations related to melanoma: dependence on sun exposure, latitude, prevalence in upper pay scale and white-color occupations, and higher incidence in indoor vs. outdoor workers. While overexposure and sunburns from UVB and UVC (< 290 nm) or exposure to UVA initiate melanoma, UVA exposure and inadequate levels of vitamin D3 in the skin appear to promote it. Decreased skin D3 levels in the winter promote melanoma until by the next spring or summer it becomes large enough to be symptomatic. Unfortunately, it is not clear whether or not oral supplementation with D3 will provide the same level of protection against melanoma that appears to result from UVB exposure. An interesting possibility is that UVB tanning beds, especially in the winter, prevent melanoma. We are of course warned against this as being reckless and foolish.

LIFESTYLE AND RISK OF PANCREATIC CANCER

Pancreatic cancer, while ranking about 10th in incidence in the U.S., ranks 4th in mortality. Thus its prevention is a serious issue. In a similar study to the one described above, almost 500,000 individuals were followed from 1995-6 to 2003 in order to examine the association between lifestyle factors and the incidence of pancreatic cancer.[4] A lifestyle score was developed based on one point

for each of the following factors: nonsmoking, moderate alcohol use, adherence to a Mediterranean diet pattern, body mass index between 18 and 25 (not overweight), and regular physical activity. The highest score of 5 points was associated with a statistically significant 58% reduction in risk of developing pancreatic cancer in all participants. It is important to note that these are all modifiable lifestyle factors.

BRAVE NEW WORLD OF THE POLYPILL

In 2003, Wald and Law[5] proposed that four drugs be combined into a so-called Polypill which they calculated would reduce the incidence of ischemic events (heart attack and stroke) by 80%. The Polypill was to contain a statin, three antihypertensive drugs, 0.8 mg of folic acid, and aspirin. The evidence for the statin component was drawn mainly from studies involving secondary prevention or very high-risk patients. Nevertheless, they proposed the use of the Polypill by everyone in the world 55 and older as well as everyone with existing cardiovascular disease. It is worth noting, as has been pointed out several times in this Newsletter, that the use of statins for primary prevention in women and the elderly is not evidence-based and for everyone else, the absolute benefit is small to negligible. Thus for a significant fraction of those Wald and Law want to take the Polypill, there is risks of serious side effects introduced by the statin which do not appear to be balanced by any benefit. Furthermore, the use of hypertension medicine is generally tailored to the individual, 0.8 mg of folic acid is approaching the range where, when added to other sources, may reach intakes that promote cancer of the breast, colon and prostate, and the risk vs. benefit of aspirin for primary prevention of coronary events is still being debated. Furthermore, the 80% prevention is an 80% *relative risk* reduction which can still represent a small absolute benefit. The promotion of the "one size fits all" philosophy can in fact be viewed as contrary to the prudent practice of medicine. Incidentally, Wald and Law declared in their paper that they had filed a patent application for the combination pill and a trademark application for the name Polypill.

Now the first polypill, called the *Polycap*, has been formulated in India and has been tested in a phase II randomized trial.[6] It contains a statin, three anti-hypertensive drugs, and aspirin. It is noteworthy that participants with only one risk factor were selected to participate in the trial (type 2 diabetes, elevated blood pressure, smoker within the past 5 years, elevated waist to hip ratio, or abnormal cholesterol). Thus the philosophy of this trial is such that a lean, non-diabetic smoker with normal blood pressure and cholesterol still is treated for hypertension, hypercholesteremia and is given daily aspirin. However, the endpoint of the trial was not cardiovascular events but rather whether the combination pill worked as well as the individual components in terms of reducing cholesterol, blood pressure and clotting ability. It does not seem surprising that the trial was a great success with only small differences between the observed and expected declines in blood pressure and LDL. Instead of taking three pills at the same time where the drugs get mixed in the GI tract, mixing them first in a pill works almost as well. To demonstrate this 50 centers and over 2000 participants were involved. In an editorial comment[7] written by a medical scientist with strong ties to the makers of statins, this result was held up as illustrating "the feasibility of the principle that one can treat patients with multiple classes of drugs for cardiovascular risk factors, even if the patients do not have some of these risk factors." This is surely a novel *principle* in preventive medicine which from the point of view of the pharmaceutical industry has great potential. But it must be rare in usual practice for a physician to give someone with normal blood pressure three anti-hypertensive drugs!

The editorialist describes this polypill as a magic bullet for the prevention of heart disease in spite of the fact that the traditional risk factors have been treated together for decades and for many patients with treated hypertension, treating with statins provides only a very small or negligible absolute benefit measured in terms of absolute risk reduction or numbers needed to treat when the goal is primary prevention. In addition, while it is simple just to prescribe one pill that fits all, even the editorialist comments that there is a loss of dose flexibility with the polypill approach, and when side effects arise, the multiple medications complicate assessment and response.[7] Thus while the study cited above is viewed by some as a big step forward, any enthusiasm can also be viewed as evidence of a failure to recognize a fundamental problem and a disturbing trend away from individualized therapy.

LIFESTYLE RISK FACTORS AND TYPE 2 DIABETES IN OLDER ADULTS

As part of the Cardiovascular Health Study, Mozaffarian *et al*[8] have examined the combined impact of lifestyle factors on the incidence of diabetes in later life. Repeated assessments were carried out over a period of 10 years among almost 5000 individuals aged 65 or older at baseline. Low-risk lifestyle groups were defined by physical activity (leisure-time activity and walking pace) above the median, favourable dietary score, never smoked or former smoker more than 20 years ago, light to moderate alcohol use, body mass index < 25, and a waist circumference ≤ 88 cm for women and 92 cm for men. The dietary score ranged from 1 to 5 corresponding to the quintile of intake of higher dietary fiber, lower glycemic index foods, lower trans-fats and higher polyunsaturated fats as compared to saturated fats and these values were summed to compute the total score.

It was found that each of the above lifestyle factors was independently associated with incident diabetes. Overall, the rate of incidence of diabetes was 35% lower for each individual lifestyle risk factor in the low-risk group. For example, individuals whose physical activity, dietary patterns, and smoking and alcohol habits were all in the low-risk group had an 82% lower incidence of diabetes during follow-up compared to all other participants. When the absence of adiposity was added to the other 4 low-risk factors, the risk reduction was 89%. Overall, it was found that 9 out of 10 new cases appeared attributable to these five lifestyle factors. All these results achieved statistical significance.

Given that the development of late-onset (type 2) diabetes indicates serious metabolic dysfunction and that diabetes carries a substantially increased risk of cardiovascular and other vascular diseases these results have much wider implications than simply diabetes. The diet score system used is suggestive of the so-called prudent diet patterns used in studies discussed in Research Reviews in this Newsletter and as well, diets that avoid refined carbohydrates such as sugar and refined flour and emphasize fruits and vegetables and plant and marine sources of polyunsaturated fatty acids.

HEALTH AND THE HONEY BEE

The recommendation to eat lots of fruit and selected nuts has sound scientific backing. It would be surprising if most readers were not consuming fruits and nuts in considerable quantity and looking forward each spring to the appearance of local produce. But most fruits and nuts require the honey bee for pollination. Over a number of years it has become apparent that bees are in trouble. Beekeepers throughout the world have experienced what is called colony collapse disorder, and there is a growing shortfall in the bee population required for pollination. Beekeepers now can make as much or more money renting hives to farmers needing bees for pollination as selling honey. The huge almond industry in California is totally dependent on the honey bee, and thousands of hives are brought from across the country to pollinate the seven hundred thousand acres of almonds trees. No bees, no almonds, and California accounts for 82% of the world's supply. The recent phenomenon of honey bee colonies dying is thus a serious matter if not a crisis. It has just been reported that the honey bee population in Japan has suffered a terrific blow and had been reduced by a factor of 2. Last year about 30% of Europe's 13.6 million hives died and the percentage was as high as 80% in southwest Germany. North America has also been struggling with this problem recent years.

There are a number of theories about what has gone wrong and scientists have been working on the problem, but it does not appear that there is neither a single cause nor a universal solution. Rather than delve into the details of the various theories, your editor suggests the book *Fruitless Fall* by Rowan Jacobsen (Bloomsbury USA, New York, 2008). This is sort of a sequel to *Silent Spring.* Jacobson's book reads like a detective story with a style that is vivid and engaging. Not only does he review the colony collapse disorder in detail as well as the attempts by scientists to figure out why, but he also provides an excellent and fascinating introduction to the life of bees and their role in agriculture. Highly recommended.

POWER LINES AND NEURODEGENERATIVE DISEASE

The connection between exposure to low-frequency (e.g. 50-60 cycle) electromagnetic fields and cancer or neurodegenerative disease has been debated for some time. In 2001 the International Agency for Research on Cancer took the position that exposure to residential electromagnetic fields above 0.4 microtesla (4 milliGauss) was a possible cause of childhood leukemia. Occupational exposure to low-frequency electromagnetic fields has been associated with an increased risk of Alzheimer's disease but data on residential exposure was lacking. A study from Switzerland has now addressed this issue.[9] By using census reports and death certificate records, the researchers were able to establish the incidence of various disorders as a function of how close the subjects lived to high-voltage power lines. They were also able to do a subgroup analysis of individuals who had lived in the same location for 10 or 15 years or more. For mortality associated with Alzheimer's disease, persons living at least 10 years within 50 meters of power lines had an increased risk of 78% and for 15 years or more, the increased risk was 100%. Comparison was with unexposed controls. The pattern was similar for senile dementia mortality, but no significant associations were found for mortality associated with amyotrophic lateral sclerosis, Parkinson's disease or multiple sclerosis. The occupational exposures are typically 0.5 microtesla to 3 microteslas, and studies linking occupational exposure to Alzheimer's disease were around 0.5 microtesla. The researchers comment that the field strength at 50 meters from 275 kilovolt transmission lines is about 0.5 microtesla and at maximum line load can increase to about 1 microtesla. It is interesting that field strengths of this magnitude can also be found in close proximity to some domestic appliances and wiring within buildings. It is possible to purchase inexpensive Gauss meters over the Internet for use in examining this question around the house. Clock radios and electric blankets are the usual suspects but one should also check TVs and computer monitors and in-wall wiring sources in bedrooms or other locations occupied for long periods each day.

Mechanisms that might account for the enhanced risk observed in this study are unknown but there is evidence that low-frequency fields can affect synaptic transmission in neural networks and influence the concentration of free radicals which can damage cellular components and could play a role in the development of Alzheimer's disease.

IMPACT OF VITAMIN D DEFICIENCY ON ADOLESCENT HEALTH

A study reported at the recent American Heart Association Conference on Cardiovascular Disease Epidemiology and Prevention examined the association between the vitamin D status of over 3500 adolescents aged 12 to 19 as measured by a blood marker, and the incidence of a number of disorders. Data were obtained from the National Health and Nutrition Examination Survey. It was found that the group with the lowest levels of vitamin D had 2.36 times the likelihood of having high blood pressure, 2.54 times the likelihood of high blood sugar, and 3.99 times the likelihood of having metabolic syndrome. The presence of the metabolic syndrome increases the risk of future heart disease and type 2 diabetes.

These results are particularly disturbing since a number of studies have found a high prevalence of vitamin D deficiency in adolescents with the situation worsening in the winter. It seems clear that only supplementation will solve this problem which is aggravated by spending a large fraction of each day indoors, infrequently engaging in outdoor sports, using sunscreens, and following the conventional advice to avoid exposure to the sun. Percentages with low vitamin D status were as large as 50%. More evidence is published each month of not only the prevalence of profound deficiency but also its impact on the health of all age groups. It seems time for a general call for universal screening using 25-hydroxyvitamin D as the marker. When a deficiency is identified, the amounts of vitamin D in a multivitamin are inadequate to the point of being insignificant and the same can be said for food, even if fortified. Much higher intake is necessary and the success of the intervention should be measured by additional blood tests. Unfortunately, such an approach does not even appear to be under serious considered for adoption as standard practice.

MODEST WINE CONSUMPTION YIELDS 5-YEAR INCREASE IN LIFE EXPECTANCY

Wine consumption has a long history going back to Neolithic times and its use as medicine is ancient. Many but not all studies have found moderate alcohol or wine consumption to carry health benefits. Moderate alcohol consumption appears to lower the overall risk of coronary heart diseases and ischemic stroke and protects already hypertensive individuals against both CHD and heart failure. It also reduces the risk of type 2 diabetes and favourably impacts glucose and insulin levels and insulin sensitivity. There is also substantial evidence from cohort and case-control studies that moderate and regular consumption of alcohol is associated with a decreased risk of cognitive decline in old age and the dementia of Alzheimer's disease, and possibly its vascular component, and may as well inhibit the progression of mild cognitive impairment to Alzheimer's disease. A recent review in the *International Journal of Wine Research* elaborates on this latter topic and is full-text open-access.[10] Wine consumption during meals is part of the dietary tradition of many cultures including those with abnormally low rates of various diseases.

A recent Dutch study reinforces this view.[11] A cohort of men born between 1900 and 1920 was followed for 40 years with repeated evaluations. The endpoint was cardiovascular mortality and life expectancy. In this cohort, alcohol consumption was rather limited and the investigators stratified it according to 0-20 g/day and > 20 g/d. This cut point is somewhere between one and two drinks per day. It was found that independent of total alcohol intake, long-term wine consumption of, on average, less than half a glass per day was strongly and inversely associated with a 39% decrease in coronary heart disease, a 32 % decrease in cardiovascular disease, and a 27% decrease in all-cause mortality. About 70% of the wine consumed was red. When an alcohol intake of ≤ 20 g/day was compared with no alcohol intake, similar risk reductions were found. These results were statistically significant and could not be explained by socioeconomic status or smoking. An important result was that life expectancy was about 5 years greater for men who consumed wine compared to those who did not use alcoholic beverages.

These apparent benefits of modest alcohol and in particular red wine consumption are unfortunately accompanied by risks of excessive consumption and addiction. The benefits of modest alcohol consumption are frequently described as a J-shaped curve with only a narrow range of beneficial consumption. Furthermore, if someone who has been an abstainer starts drinking, this individual probably has no knowledge of how easy it will be to limit consumption to prudent levels. This is something that everyone contemplating alcohol "self-medication" needs to ponder. For individuals who already are controlled, moderate drinkers, the constant flow of positive studies is simply good news.

The association of alcohol consumption and cancer risk is also an issue. As has been discussed repeatedly in this Newsletter, women should restrict their consumption to ≤ one drink per day due to the apparent enhanced risk of breast cancer. Folic acid in doses found in multivitamins (400 micrograms) appears to offer protection. For cancers of the pharynx, esophagus and larynx, three commonly indicated sites of risk, while the relative risk figures available in the literature are > 1.0, they are not statistically significant for up to 3 drinks per day.[12] No consistent evidence suggests that alcohol intake affects the risk of stomach, pancreatic, lung, endometrial, bladder, or prostate cancer. Heavy alcohol intake however appears associated with liver cancer through the intermediary of cirrhosis of the liver. Results for colorectal cancer are inconsistent suggesting either no risk or a very modest increase, perhaps enhanced by a low folate status.[12]

CONFLICTS OF INTEREST—FINALLY BECOMING A HIGH PROFILE ISSUE

In the April 1 issue of *JAMA* Rothman *et al*[13] present a proposal for controlling conflicts of interest between the pharmaceutical and device industry and the professional medical associations (PMAs) which represent medical specialties such as oncology, cardiology, diabetes, etc. While the problem of conflicts of interest goes well beyond PMAs, they are nevertheless exceptionally relevant because of industry funding of their activities. For example, these industries subsidize annual meetings, and underwrite physician attendance through grants for travel, meals, receptions and

other social activities. They provide honoraria for plenary sessions and lectures, purchase mailing lists and advertising space from PMAs to increase attendance at their satellite symposia which parallel the PMA meetings and are marketing tools. They also fund continuing medical education (CME) offered by PMAs and support the publication of guidelines and information booklets, which in some cases are stamped with industry logos. The opportunities for conflicts of interest are obviously manifold.

Rothman *et al* offer a proposal aimed at limiting financial conflicts of interest related to the sort of industry funding described above. They set as the ultimate goal totally eliminating financial contributions from industry and suggest that a realistic initial goal would be < 25% industry support. As well, PMAs should not collaborate in or profit from industry marketing activities, and the association leaders and executive staff should be free of conflicts of interest as should be the entirety of the board and members of the practice guideline committees. Conflicts of interest within guideline framing committees has been a sore point for some time now and some guidelines are viewed as simply marketing tools of industry rather than sound advice and recommendations where the interests of patient is placed first. This proposal received extensive and unusual discussion on the website www.theheart.org, which deals mainly with the interests of the cardiology community. A number of high profile individuals were quoted who called for a more realistic, slower approach and presented dire warnings if the lifeblood of the PMAs was severely restricted or clamped off completely. The consensus seemed to be that the abuses could be reduced, transparency improved, and public skepticism softened by appropriate action that was less draconian. But physician leaders and governmental officials who are calling for reform on the basis that past practices have undercut scientific integrity and patients' best interests may want more.

Rothman *et al* do not directly address the more general problem of industry support to individual physicians and researchers. However, a bill is before the US congress called the "Physician Payment Sunshine Act" which would require drug and device companies to disclose all payments made to physicians over $100 in any calendar year with the information made public beginning in late 2011. Some prominent universities are already anticipating this by starting conflict of interest websites.

Related to conflicts of inters is an interesting story from Harvard (New York times, March 3, 2009) which started four years ago when a student in a first-year pharmacology class felt belittled when he asked a question about statin side effects. He did some research and found the professor was a paid consultant for five pharmaceutical companies that manufactured statins. The student made somewhat of a "stir" about this which grew into a full-blown movement by 200 Harvard medical students and sympathetic faculty who are intent on exposing and curtailing the industry influences in their classrooms, laboratories and Harvard's 17 affiliated teaching hospitals and institutes. Incidentally, Harvard recently received a grade of F for how well it monitors and controls drug company money on campus, and three of its professors have been subpoenaed in connection with as Congressional investigation into conflicts of interest in medicine. Big changes may be on the horizon.

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Research Report

SATURATED FAT: FRIEND, FOE OR NEUTRAL?

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In so far as a scientific statement speaks about reality, it must be falsifiable; and in so far as it is not falsifiable, it does not speak about reality. Karl Popper.

INTRODUCTION

The centerpiece of modern dietary recommendations concerning specific macronutrients is to decrease saturated fat intake, generally as a percentage of total energy intake. This recommendation appears in the context of both cardiovascular disease and diabetes, and is sometimes qualified by the recommendation that the caloric deficit be made up by unsaturated fats, but substitution with carbohydrates appears common. The central place this piece of advice occupies in mainstream medicine provides motivation for examining the actual evidence that saturated fatty acid intake *per se* presents a health risk, especially since the hypothesis that saturated fat is dangerous has evolved to the status of a widely accepted and unquestioned dogma. Furthermore, saturated fat intake becomes an issue when carbohydrate restriction is being used in connection with diabetes prevention or control, weight loss, atherogenic blood lipid profile modification etc. Carbohydrate restriction, which appears to be undergoing a rebirth, will be discussed in an upcoming Research Report.

Diet is a complex subject to study in humans, either in intervention trials or observational studies. There are only three macronutrients, fat, carbohydrate and protein, but macronutrients are mixtures. Fats can be saturated, monounsaturated, or polyunsaturated, and the latter can be further broken down into subclasses which include the so-called omega-3 and omega-6 types. Fats can also be natural or an industrial product, e.g. *trans*-fats. Carbohydrates vary markedly in their ability to elevate blood sugar and insulin levels and as well contain a wide range of fiber. If intervention studies reduce the amount of one class of macronutrient, the calorie intake will decrease unless the energy intake is topped back up with one or the other of two macronutrients. Thus there is the inherent problem of changing two or more variables at once while trying to study only one. The same problem exists when one type of fat is substituted for another. Also, if energy intake decreases, weight loss may occur which will confuse the issue since there may be a loss of body fat or a change in its distribution which impacts fat and carbohydrate metabolism as well as inflammation. These problems are fundamental to nutritional

studies, but they appear to lead to the attitude that studies must still be done even if the interpretation is almost always going to be debatable. Armies of biostatisticians stand ready to help sort out the confusion. Probabilities are the real end result and in some cases, nonsense.

Observational studies are plagued by problems associated with measuring the intake of macronutrients, breaking down the results by subcategories, and correcting for total energy intake. Dietary habits change after baseline assessment and within the intervals between repeated assessments. Over long periods, the very nature of popular foods changes. Witness the low-fat revolution. Evidence-based medicine is happy only with randomized intervention trials and many of these have the same problems as any observational trial. Randomized trials may also not really recruit a realistic sample of the general population and in fact can involve significant bias. Individuals who participate in trials may be different, and these differences may be hard to account for in statistical adjustment of the data. Furthermore, large randomized intervention trials lasting several years or more suffer from poor compliance, and even the ability of the investigators to detect this problem is limited. Biostatistics play a central role in nutritional studies as they do in most medically related studies, and there is the unending quest for statistical significance no matter how small or possibly clinically insignificant an effect may be. Studies lead to publication which leads to progression up the academic ladder or reprints useful as hand-outs to physicians.

In addition, there is the problem of energy intake. To keep the energy intake from fat constant in studies where, for example, saturated fat is decreased, requires substitution with another fat. But this of necessity means that two fat variables are being changed at once. If benefit is seen it does not prove that the macronutrient increased was beneficial and/or the macronutrient decreased was detrimental. But this is frequently the impression some investigators attempt to establish, partly by demonizing the item decreased even if there is no or only very weak evidence that it is harmful.

To the above can be added the multitude of potential subject characterizes. One can study the overweight, the obese, the lean, hypertensives, premenopausal women, postmenopausal women, individuals with diabetes or prediabetes, patients who have heart disease, individuals with perceived elevated risk of heart disease, men only, women only, children, adolescents, young people, middle-aged people, old people, those who are physically active and those that are not, etc, etc. It is wishful thinking to assume that these characteristics do not really matter and in fact ignoring them is basic to studies that look at various endpoints based on the national consumption of, for example, fat derived from government statistics. Also, studies tend to focus on the impact of diet on one disorder, i.e. heart disease or diabetes, or a surrogate marker such as the blood lipid profile and in particular LDL cholesterol, or insulin resistance or the dyslipidemia associated with the metabolic syndrome. Issues then arise concerning the clinical relevance of small effects which, because they are statistically significant, permit a quantitative measure of risk reduction or elevation. There is also the tendency to accept as important and indicative of meaningful conclusions, numerical correlation coefficients which are so small that the associated scatter plots show no visual correlation at all. In some cases, while there may be a slight suggestion of correlation in a scatter plot, individuals trained in the physical sciences would laugh at any significance being attached to such correlations, given the huge scatter about the line the computer constructed through the points. In older literature, it was common to present such plots with the line, but not give the actual correlation coefficient, presumably because it was so small that any conclusion was wishful thinking. Many of these older studies are today the basis of the evolution of a mere hypothesis to a universal dogma taught to students in nutrition 101, the fat-heart disease connection.

There is also the fundamental problem that people eat meals that are best described in terms of food patterns, not isolated macronutrients and that the characterises of the mix of macronutrient content, e.g. types of fat and carbohydrate, vary from day to day. In addition, there is the matter of how fast the meal is eaten and the social context of the meal (gulp it down and run or spend 1-2 hours in pleasant social interaction with a glass or two of wine). These are issues that are frequently ignored and are in fact hard to measure and quantify. The existence of the so-called French Paradox, discussed in previously in this Newsletter, highlights the importance of aspects of eating that are not generally included in nutritional studies but can be important confounders.

If one wishes to address the question of the merits of carbohydrate restriction in the context of heart disease, diabetes and the metabolic syndrome, then the question of fat intake and the types of fat become a central issue. Papers regarding the debate concerning the merits of carbohydrate restriction are now appearing with

increasing frequency; perhaps because the guidelines that focus on reducing fat in connection with heart disease or diabetes are now starting to be recognized as simply leading to pharmaceutical drug interventions, i.e. they do not work. An added complication in the carbohydrate vs. fat debate is that the terms *low-fat diet* and *low-carbohydrate diet* are poorly defined and in fact there is considerable overlap, misunderstanding and confusion. Carbohydrate restriction is a rather loose term and discussions must clarify exactly the extent of the restriction and the types of carbohydrate being restricted.

With all of this in mind, the evidence regarding the relationship between saturated fat and health will be briefly discussed as a prelude to a forthcoming Research Review on carbohydrate restriction.

SATURATED FAT AND CARDIOVASCULAR DISEASE

Saturated fatty acids have no carbon-carbon double bonds and are thus fully *saturated*. Mono- or polyunsaturated fats have carbon-carbon double bonds. Examples of foods containing a high proportion of saturated fat include cream, cheese, butter, animal fats such as suet, tallow, lard and fatty meat, coconut oil, cottonseed oil, chocolate and some prepared foods. Eggs also contain significant amounts of saturated fat. During the last third of the 20th century, these foods occupied a unique position by being proscribed by governments, nutritionists, and mainstream medicine as being at the root of many of our health problems. Older generations who spread liberal quantities of lard on their bread were regarded as foolish in spite of the fact that coronary heart disease was not common for their generation.

There are a number of saturated fatty acids, the principal ones being lauric, myristic, palmitic and stearic acid, and these have in some cases quite different biological actions which complicates the interpretation of studies that lump all saturated fatty acids together when attempting to study their impact on health. This actually is quite important because there are some curious balancing effects associated with certain endpoints which yield negligible net risk associated with saturated fat intake. But ignoring this is operationally useful—the grease that keeps the nutritional study machine running smoothly.

At issue in this review are the alleged benefits and dangers associated with the dietary intake of saturated fat. In this context, one very important point must be established early on. This involves the correlation between dietary SFA intake and the SFA levels found in the fat carrying blood plasma components. It is quite common to see the comment that dietary intakes are difficult to measure and it is better to use plasma levels when investigating questions such as insulin resistance or the risk of CVD. In a review published in 2008, Volek *et al*[1] point out that for SFAs, the statement that plasma fatty acid content reflects dietary intake is not true. They cite ecologic studies where total fat intake varied from 56.7% to 27.2% with virtually no variation in plasma SFAs. In another type of study, dietary SFA intake was decreased by 50% at constant total fat with no change in the plasma stearic or palmitic acid content. Furthermore, in a widely quoted study which according to the title showed that total fat intake modifies plasma fatty acid composition, the changes in plasma SFAs were insignificant. Similar results were reported by Qi *et al* [2] based on data from the Nurses' Health Study where no significant association was obtained between plasma or erythrocyte (red blood cell) FA content and SFA intake, even stratified by fatty acid type. Thus if one is concerned with the question of the risks or benefits of the dietary intake of saturated fat, studies that use plasma levels are not relevant and in fact relate instead to complex metabolic questions and do not indicate the increase or decrease of saturated fat intake.

In a lengthy and comprehensive review which appeared in 1998 in the *Journal of Clinical Epidemiology*, Ravnskov examined the evidence for and against the hypothesis that saturated fat intake was related to CVD incidence or mortality.[3] A very large number of ecological (population) studies, as well as cross-sectional (snapshot), case-control and cohort follow-up studies were examined. In addition autopsy studies that examined the relationship between saturated fat (animal fat) intake and the extent of atherosclerosis were reviewed. The overall picture that emerged was one of inconsistency with more studies falsifying the hypothesis than supporting it, even when studies of comparable quality were compared in detail. The author concluded that the correlation found by Keys which launched the hypotheses suffered from selection bias (selecting only studies that agreed with the hypothesis from among a much larger number where no correlation existed), a point repeatedly made in the literature, and was not supported by his later Seven Countries study nor by more recent ecological studies. Ravnskov also points out that in fact, there is no real support at all since a hypothesis is unlikely to be correct when a very large number of studies falsify it. Stated simply, according the heart-diet idea, the intake of SFAs promotes CHD and therefore studies that find no difference between the intake of SFAs and

CHD in patients and CHD-free individuals are obviously contradictory. It is important to recognize that hypotheses are made to be falsified, rather than proved. Science progresses by falsifying hypotheses and finding better ones. Scientific progress is hindered, on the other hand, by converting hypotheses into dogma even when they have in fact been falsified. Examples of this go back to ancient times. It is also important to recognize that when a large number of studies directed at a single question give opposing answers, i.e. gross inconsistency, there is a problem with the hypothesis that generated the studies and a high likelihood that bias and confounding are at work to produce the lack of concordance. Ravnskov also does not find convincing evidence up to 1998 that polyunsaturated fatty acids (PUFAs) were beneficial in the context of this review.

In the "Dissent" published in the same issue[4], Golomb actually more or less agreed with Ravnskov. She concluded that the evidence for a beneficial effect of SFA reduction and PUFA augmentation is unconvincing. This was the main conclusion of Ravskov's review.

By 2005, there had been little change in the evidence picture, but the dogma was alive and well. Then during that year, Volek and Forsythe[5] published a paper, the purpose of which was to make the case for not restricting saturated fat in a low-carbohydrate diets. They made 4 points with documentation.

- The proposed atherogenic potential of saturated fats varies greatly depending on the molecular length and whether it is present alone or mixed with foods. Stearic acid, a major saturated fat found in pork, beef and chicken has repeatedly been shown not to raise LDL cholesterol. Palmitic acid, the most abundant saturated fatty acid in the human diet, does not raise LDL in the presence of adequate linoleic acid. If one rejects the hypothesis that LDL drives atherosclerosis, as discussed in a recent Research Review, then the impact of these SFAs on LDL is irrelevant anyway.
- Diets that decrease calorie intake or low total fat diets may show different results than deduced from observational studies. In fact, a recent studied found that for a woman on a relatively low-fat diet, *greater saturated fat was associated with a reduced progression of coronary atherosclerosis.* An editorial termed this "an American Paradox."
- The replacement of carbohydrates with any type of fat results in a decrease in triglycerides and an increase in HDL cholesterol and the effect on HDL is greater for saturated fat compared to unsaturated fat. Reductions in saturated fat compared to unsaturated fat also decrease the anti-atherogenic HDL concentrations, whereas increases in saturated fat increase the anti-atherogenic fraction. Very low-carbohydrate diets rich in saturated fat increase LDL size and enhance the conversion from a high-risk LDL pattern to a lower risk LDL pattern.
- The recommendation to limit saturated fat would be expected to lead to its replacement with carbohydrate which can have undesirable effects on CVD risk factors.

The authors apparently considered that this was clear enough so that no additional comments were necessary. However, in another paper, Volek *et* al[1] present a scatter plot from a frequently quoted paper that is used to demonstrate that saturated fat intake increases cholesterol and therefore represents a CVD risk. If one examines just the part of the plot ranging from 5% to 25% saturated fat intake as a percentage of total energy, a range that encompasses the majority of North Americans who on average consume only 14% of energy as SFA, the correlation is almost impossible to see, and if one looks at the range from 15% to 7%, the change recommended by the current guidelines, the scatter is so great that this decrease in SFA intake appears equally likely to raise as to lower total cholesterol. To quote Volek *et* al, "…the idea that SFA is inherently and unambiguously detrimental becomes fundamentally untenable and dietary recommendations for across-the-board reduction, fundamentally inappropriate." It thus becomes a source of constant amazement to see the exact opposite stated repeatedly in the literature as if it were on a par with the fact that earth goes around the sun.

Gary Taubes in his article on fat and heart disease in the journal *Science*[6] also makes a point of discussing the various SFAs in our diet and concludes that from the CVD risk point of view, eating a nice juicy sirloin steak is a "wash" simply because of minor adverse effects if they exist, from some of the SFAs, are balanced by minor beneficial effects of other SFAs. Again, the issue disappears if one admits that LDL does not drive atherosclerosis.

In 2005 a 20-year update on the famous Nurses' Health Study also looked at the association between dietary fat intake and CHD.[7] The abstract is interesting because it contains no mention of saturated fat, an omission which

might strike the casual reader as odd given the almost universal recommendation by mainstream medicine, the American Heart Association, the National Cholesterol Education Program panel and most of the nutrition community to avoid this dangerous fat. The reason for the omission is evident upon examination of the tabulated results. When corrected for confounding, there was no significant relation between the relative risk of coronary heart disease and saturated fat intake when the lowest vs. the highest quintile were compared. The same in fact applied to total fat intake, but polyunsaturated fat was found to be significantly protective and *trans*-fats significantly harmful. This study involved the analysis of data from a lengthy follow-up study of over 78,000 female nurses.

This subject was again reviewed in 2008 by Accurso *et al*[8] in a paper calling for a critical appraisal of dietary carbohydrate restriction in individuals with type 2 diabetes and/or the metabolic syndrome. In connection with saturated fat intake, they comment on the inconsistent results and cite several critical reviews that have pointed to the general failure to meet the kind of unambiguous outcomes that would justify the blanket condemnation of saturated fat per se. They note that during the current obesity and diabetes epidemic, the proportion of dietary saturated fat decreased and for men the decrease was 14%. They also point to the now famous result of the Woman's Health Initiative study which found no difference in CVD incidence for those who consumed < 10% saturated fat compared or those whose consumption was > 14% of total energy intake. They also comment on the point raised above that increased saturated fat consumption decreases the small, dense LDL, the LDL though to be atherogenic. Finally, they also mention that a greater intake in saturated fat *reduced* the progression of coronary atherosclerosis and greater carbohydrate intake *increased* the rate of progression. For the replacement of fat with carbohydrates, they point out that the result is almost always harmful.

The above discussion is not meant to suggest that this is other than a complex issue. It is true that some saturated fatty acids increase LDL, some decrease it. The same applies to HDL, but HDL is much more strongly related to CHD event risks. But as discussed above, saturated fat intake also dramatically modifies the atherogenic nature of LDL in a favourable direction. In addition, we do not eat individual saturated fatty acids in isolation, we eat mixtures, along with mono- and polyunsaturated fats, protein and carbohydrate and this mixture results in interactions. Finally, if one just focuses on the LDL elevating properties of some saturated fats, then there is still the little problem that LDL levels are totally uncorrelated with the calcified plaque load, the extent of atherosclerosis seen at autopsy or the total plaque load of the coronary arteries as seen by modern contrast enhanced CT scans. This was discussed in last month's Newsletter. And if one believes that atherosclerosis comes before symptomatic heart disease, then this appears to provide a good reason to ignore LDL and look elsewhere for why we get heart disease. This incentive to look elsewhere is reinforced by the recent study showing that over 50% of individuals admitted to hospital for CHD in general and heart attack in particular have low to very low LDL levels.[9]

Thus it seems that when skeptics and simply the curious or cautious students of this subject look for convincing or significant evidence behind the guidelines recommending limiting saturated fat, it is not out there, at least in the context of CVD.

FATTY ACIDS AND INSULIN SENSITIVITY

The reported connection between saturated fat and insulin sensitivity is presumably part of the justification for diabetes guidelines recommending limiting this nutrient. Risérus [10] and Risérus Willett and Hu[11] have reviewed the impact of saturated fat on insulin resistance and also the risk of type 2 diabetes. In six short-term randomized controlled dietary intervention studies reported between 1995 and 2002, the overall results showed no significant association between insulin sensitivity and the intake of saturated fatty acids (SFAs), monounsaturated fatty acids (MUFA) or polyunsaturated fat (PUFA). Four of the studies used mainly healthy subjects whereas in two the participants were type 2 diabetics or individuals with impaired glucose tolerance.

Other randomized intervention trials have been somewhat inconsistent. The largest randomized trial, the so-called KANWU study, examined the effect of elevating SF or MUFA on insulin sensitivity in healthy men and women.[12]. Participants were randomized into two groups. One was given a diet with a high proportion of SF, the other a diet high in MUFA. Each group was also split randomly into two groups, one receiving fish oil containing 3.6 g per day of omega-3 fatty acids (n-3 FA), the other a placebo. There was no difference in insulin sensitivity observed related to n-3 FA intake with either diet. The SF diet reduced insulin sensitivity by about 10% whereas the MUFA diet had no significant effect. When the changes for the two diets were compared, the difference was

only of borderline statistical significance by one measure, and insignificant by another. A second important finding was that subjects with the highest total fat intake with either diet did not show any difference in insulin resistance at all when the two diets were compared. This study is frequently held up as convincing evidence that saturated fat decreases insulin sensitivity and is therefore bad. In fact, the evidence is somewhere between very weak and non-existent.

Finally, these reviews make clear that there seems to be no evidence to suggest that neither increasing n-3 FAs nor decreasing the n-6/n-3 ratio improve insulin sensitivity. There is however some data from a study by Summers *et al* [13] which suggests that substituting SF with n-6 PUFA increases insulin sensitivity. For individuals with diabetes, few data are available on the effects of dietary fat quality and the optimal proportions of SF, MUFA and PUFA are uncertain. Studies that substitute PUFAs for SFs have also been observed to alter the amount of visceral fat and this complicates the interpretation. Whether or not *trans*-fatty acids impair insulin sensitivity remains an open question, although one *trans* form of conjugated linoleic acid was found to impair insulin sensitivity even an intake representing 1% of total energy. Since the evidence for the recommendation to avoid *trans* fats is fairly strong, widely recognized and even the subject of legislation, the danger associated with this type of fat does not seem to any longer be an issue. Its appeal should have always been limited, given that it came out of chemical factories and represented a class of fat almost entirely foreign to human biochemistry.

In spite of what appears to be very weak evidence, both reviews cited above conclude that substituting SFAs and *trans*-fatty acids (TFA) with MUFA or PUFA has a beneficial effect on insulin sensitivity. However, it would seem that if the benefit is real, it is very small since it did not turn up in a number of randomized trials. This conclusion also seems to rely heavily on the KANWU study[12] and the n-6 PUFA study by summers[13] and the adverse effect of on isomer of conjugated linoleic acid. The first two were at best of borderline statistical significance and the relevance of the latter is not obvious. Furthermore, most would agree that substituting *trans*-FAs with unsaturated FAs is a good idea, but why bunch TFAs and SFAs together in a concluding statement?

SATURATED FAT AND DIABETES RISK—EPIDEMIOLOGIC STUDIES

This question was addressed in both the Nurses' Health study[14] and the Health Professionals Follow-up Study[15], the latter restricted to men. Both studies assessed dietary fat intake and in the follow-up, determined the relative risk of diabetes using low intake as a reference. In both studies, when the data was adjusted for potential confounders, there was no significant relationship between dietary saturated fat intake and the risk of type 2 diabetes. Both studies ran for about 12 years prior to the reporting of the above results.

Attempts to establish a connection between saturated fat and diabetes frequently depend on serum markers of intake rather than directly measured intake, and as mentioned at the beginning of this review, for saturated fat this is not a reliable or even meaningful approach. Thus these studies will not be considered even though they appear to influence opinion on the question. Risérus, Willett and Hu[11] reviewed epidemiologic studies that relate to dietary fats, insulin resistance and the risk of type 2 diabetes, but with respect to saturated fats, it seems only studies based on actual intake measurements merit consideration. Aside from the follow-up studies, they discuss cross sectional studies which are not designed to provide a definitive picture, either because of the absence of controls for comparison or because of the absence of any statistical analysis, or because animal fat was measured without regard to its non-saturated fat components. If the data to be considered is restricted as indicated, there is no significant evidence of an association between type 2 diabetes and the intake of saturated fat.

SATURATED FAT AND INFLAMMATION

A search of the literature reveals little by way of definitive studies that address this question. To attempt to look at dietary intake of saturated fat and markers of inflammation carries a high risk of oversimplification of a complex problem. Most of the few studies reported use serum markers for fat intake which presents a serious problem discussed at the beginning of this review, or they study one SFA in isolation where we all eat a mixture of at least 4 or 5 such macronutrients. In addition, inflammation markers are a strong function of the distribution of macronutrients in the diet and the metabolic state of the subjects. Again, many of the problems associated with dietary studies discussed in the introduction arise if one increases or decreases the saturated fat intake because of what else is changed. The question of inflammatory diets or anti-inflammatory diets has been addresses with some success, but to discuss this anticipates the research review on carbohydrate restriction and the association between a variety of dietary patterns and inflammation. To break down the dietary patterns

and point to saturated fat as the agent responsible for increased or decreased inflammatory markers appears to not be justified. There are after all a large and interrelated number of inflammation markers which makes for a much more complex situation, especially with single end point studies using, for example, mortality. Thus the discussion of diet and inflammation will be postponed. However, it is informative in passing to point out that a recent invited commentary in the journal *Current Atherosclerosis Reports*[16] titled *Modulation of Inflammation by Nutritional Interventions* contains no mention at all of saturated fats.

SATURATED FAT, RED MEAT AND CANCER

Associating fat intake with cancer has over the years been part of the "fat is bad" dogma. Only a short summary of the current status of this notion will be given and this by cancer type.

- Prostate cancer. A recent very large prospective study with a follow-up of about 9 years found no association between any dietary fat and prostate cancer.[17] This result was described as consistent with other recent prospective studies.
- Another smaller prospective study with a follow-up of 11 years found no support for the association between total, saturated or monosaturated fat and prostate cancer. The results for the long-chain marine polyunsaturated fatty acids were hard to interpret.[18]
- A recent meta-analysis examined the association between colorectal cancer and fat intake. None was found.[19]
- The question of a relationship between fat intake and breast cancer has been extensively studied over a number of years. Most case-control studies find only weak association with fat intake and usually little or no association has been found in prospective studies.[20] A meta-analysis published in 2005 found only an insignificant association with total fat in either case-controlled or prospective studies, but upon stratification, a weak association was found with saturated fat, but almost all the studies used in this sub-analysis were by them selves non-significant, many with huge 95% confidence limits.[21] Two recent cohort studies claim to have found positive associations, but the examination of the data inspires little confidence. In one, four different methods of adjusting for energy intake were used and extensive statistical manipulation of the intake data was employed. For saturated fat, when the highest vs. the lowest quintile were compared, the hazard ratio (similar to risk ratios) were between 1.13 and 1.06 but the 95% confidence limits suggest the results were not significant since all but one has a lower limit below or at 1.00 and the exception was 1.01. Furthermore, when the cohort was stratified for hormone use, the same comparison yielded entirely insignificant results.[20] This is in contrast to another recent cohort study which found for saturated fat that for menopausal hormone users there was enhanced risk that was greater than that found for non-users but did not vary with saturated fat intake. This study found a positive association with both saturated and total fat intake.[22] It appears that there are inconsistencies in these recent studies.

Thus there appears to be no evidence for prostate or colorectal cancer to suggest that fat is bad, and for breast cancer, the evidence is characterized by inconsistencies which suggest that these studies have simply represented a struggle to deal with confounding and that probably the risk is either small or non-existent.

A recent prospective study examined the impact of meat intake on mortality. While this study will not be discussed in detail, one interesting result was that not only was red meat found to carry a positive risk for all cause mortality, but the greatest risk was seen when deaths not attributed to cancer, cardiovascular disease, or injury or sudden death were examined. That is, removing major causes of mortality increased the residual mortality risk. This would seem to suggest that there may be something wrong with this study since this implies that red meat increases the risk of dying from almost anything. It is hard to imaging a mechanism that makes red meat so universally dangerous.[23] The authors regard saturated fat as one of the culprits and point to what they believe is the connection between saturated fat and cancer. As discussed above, the evidence for this belief appears to be weak or nonexistent.

CONCLUSIONS

The standard guidelines regarding risk and prevention of CVD and diabetes contain the recommendation to decrease fat intake and in particular the intake of saturated fat. Resérus, Willett and Hu[11] conclude that more

controlled long-term studies with sufficient power are needed to identify the optimal dietary fatty acid composition to reduce the risk of type 2 diabetes. But since type 2 diabetes is strongly related to insulin resistance, the small or absent effect of saturated fat on insulin resistance appears to agree with the epidemiologic studies which failed to find an association with diabetes. One can in fact argue without much risk of appearing dull that it might be better to focus on carbohydrates rather than fats. Diets high in refined carbohydrates are disastrous if judged by their effect on HDL and triglycerides, insulin resistance and inflammation.

The recommendation to reduce saturated fat intake in the context of CVD risk or prevention does not appear to be evidence-based at all. Furthermore, the quantitative suggestions for the amount reduction based on % of total energy given in guidelines appear to never have been tested in a convincing manner if at all and by themselves without regard for the patient characteristics and overall diet appear meaningless. If one accepts the proposition that there is no evidence suggesting that saturated fat intake, at least up to the intakes encountered in most North American diets, pose a significant health risk, then how can one come up with a recommended intake as a percentage of total energy that has any basis in reality? A recent paper quoted statistics that the recent daily intake of SFA in the U.S. was 27.7 g/day whereas the recommended intake was 22 g/day.[24] Do the authors really believe that this difference, which is 9.8% vs. 8% of total energy for a 2500-calorie diet, is really clinically significant? Finally, it appears widely recognized that the fat reduction intervention in practice is ineffective as is the attempt to achieve significant weight loss. It in fact appears that dietary recommendations in connection with reducing the risk of either CVD or diabetes frequently fail, and sooner rather than later the patient will be on a pharmaceutical, either a statin or glucose control drug or both.

There seems to be general agreement that eating omega-3 fatty acids is beneficial in the context of CVD. However, now the American Heart Association has come out with recommendations that focus on the importance of omega-6 fatty acids and that it is unwise to severely limit their intake.[25] Thus perhaps the most rational view appears to be that one should be sure the intake of omega-3 fatty acids is adequate if not high, the intake of TFAs nil and then forget about fats except for the fact that they are calorie dense. In other words, they appear neutral.

Dietary advice which focuses on limiting saturated fat or decreasing total fat calories also distracts from other dietary interventions that may well be vastly more beneficial. Carbohydrate restriction is one candidate and will be the subject of an upcoming review. Such diets generally involve increased fat intake. The advent of the “fat is bad” dogma might in fact be described as the beginning of the dark ages in nutritional science from which we are now just beginning to emerge. Critics of the dogma claim that the damage viewed in terms of public health has been phenomenal. Thus if one is restricting carbohydrates or undertaking a low-carbohydrate diet, there is little evidence to suggest a need for concern regarding replacing carbohydrates with saturated fat. However, this in no way diminishes the importance of certain polyunsaturated fats as potential candidates for making up the caloric deficit due to reduced carbohydrates.

The reader is referred to the new book by Gary Taubes titled *Good Calories, Bad Calories* (Alfred A. Knopf, 2007). Part I contains a comprehensive documented discussion of the fat-heart disease--diabetes hypothesis. If one reads Part I, then the justification for Part II, which focuses on carbohydrates, will be very clear—the problem lies with carbohydrates, not dietary fat. In addition his *Science* article cited above is highly relevant to this discussion as is his article in the *New York Times Magazine*, July 7, 2002 titled *What if it’s all Been a Big Fat Lie?* The New York Times article is in the public domain. The article in Science is also on the Internet—just Google the cited article title. The early history of diet and health discussed by Taubes is of particular interest, since it of course predates the fat is bad dogma, randomized trials, the armies of biostatisticians and the politics of nutrition. It simply concentrated on what was generally observed to work in practice. In fact by the early 20th century, the approach to treating obesity and diabetes may well have been more successful than that recommended today, and it bears a striking resemblance to carbohydrate restriction and the recognition that refined carbohydrates such as sugar and refined flour are not healthy.

The bottom line associated with this review and the review on cholesterol and atherosclerosis appears to be that modern medicine has a disturbing component that might be aptly described as mythology.

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