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In 2007 Shannon Brownlee, a well known and respected medical journalist wrote the book "Overtreated: Why Too Much Medicine is Making Us Sicker and Poorer". This book received considerable critical acclaim even from high profile individuals associated with mainstream medicine such as Jerome Groopman from Harvard and Marcia Angell, past editor-in-chief of the New England Journal of Medicine. But this book was intended for the lay audience. Now, the highly respected journal Archives of Internal Medicine has launched a series titled "Less is More" which will address the same subject, but is obviously directed at quite a different audience. We start this issue with a brief review of some of the material in the May 10th issue which inaugurates the series.

This issue of the Newsletter departs from what has been more or less a policy of not promoting prescription drugs and, in fact, concentrating instead on the downside. However, recent results with regard to low-dose naltrexone appear to provide justification for making an exception. We therefore discuss a number of therapeutic applications of low doses of this drug, normally used at much higher doses for the management of alcohol and opiate dependence, for a number of serious and chronic disorders. The most striking success appears to be an integrative approach using both this drug and intravenous alpha lipoic acid for pancreatic cancer deemed incurable.

This Newsletter has kept readers abreast of the implications of the now famous JUPITER trial, and this month we update with critical comments on two papers based on this study that apply to women and the elderly. This is a serious matter since it is anticipated that there will be a huge increase in recommendations to take the statin used in JUPITER by an ever-increasing population of healthy individuals as a life-long therapeutic approach to the primary prevention of cardiovascular disease.

Other topics discussed include new insights into the role of carbohydrates in coronary heart disease, and as well, the specific dangers of high sugar intake. Other brief reports concern the downside of B-vitamin therapy for individuals with diabetic-related kidney disease, and recent results that must have greatly distressed cardiologists, the apparent equivalence of medical vs. invasive intervention for treating angina.

Last, but not least, this issue contains a Research Report concerning the infection hypothesis of atherosclerosis. This seems quite timely since there are a growing number of physicians who are questioning the cholesterol hypothesis.

Wishing you and your family good health and well-being,

William R. Ware, PhD, Editor

Highlights

LESS IS MORE

The May 10th issue of the *Archives of Internal Medicine* tells readers that the journal has initiated an ongoing series of papers that address the issue of excessive health care by publishing articles that provide evidence that performing more of certain health care activities results in less health. The theme is called "*Less is More*." An editorial actually

extends a call for papers, commentary etc.[1] The series is inaugurated in the May 10 issue with five papers on proton pump inhibitors (PPIs), the subject of a Research Review in the April 2010 issue of this Newsletter www.yourhealthbase.com/ihn206.pdf. The five papers document the thesis that PPIs are over-prescribed and prescribed in particular to individuals for whom they are not indicated and as a consequence have been shown to produce more harm than good. Since this subject was just reviewed for Newsletter readers these papers, which include reviews and commentaries, will not be discussed.

An editorial coauthored by the Editor of the journal, Dr. Rita Redberg, provides examples that justify the concern so nicely summarized in *Less is More.*[1]

- Across the U.S., the rate of use of common medical services varies considerably, but measures of health are not better in areas where more services are provided but in fact worse.
- Treating asymptomatic women with postmenopausal hormone therapy, where harms have been shown to exceed benefits.
- Arthroscopic debridement of the knee for treatment of osteoarthritis which randomized trials demonstrated have no benefit but exposed patients to pain and risks associated with surgery.
- Antidepressants have been shown to have little benefit except for individuals with severe depression and the known adverse effects of these drugs thus outweigh the benefits except for carefully selected cases, and yet they are widely used.
- Mammography for younger women, while probably just as effective in reducing the risk of dying of breast cancer as in older women, has an absolute benefit that is lower due to the lower risk in this age group. Thus the false positives, anxiety, overdiagnosis, biopsies and treatment of latent cancers may overwhelm the benefit.
- As discussed in the first *Less is More* series, inappropriate use of PPIs increases the rates of fractures, *Clostridium difficile* infection, the recurrence of diarrhea caused by C. difficile, and previous studies indicate an increased risk of pneumonia. Thus harm will result when these medications are used for conditions where there is no benefit, such as non-ulcer dyspepsia (upset stomach).

It is encouraging that the *Archives of Internal Medicine* has decided to address this significant aspect of health care delivery, a problem which many countries are currently examining. This publication has a high profile and is a major peer reviewed journal with international impact.

LOW-DOSE NALTREXONE. IT'S USE IN CANCER, FIBROMYALGIA AND MULTIPLE SCLEROSIS

The prescription drug naltrexone is used primarily in the management of alcohol and opiate dependence. The typical dose is 50 mg. Low-dose naltrexone implies no more than 4.5 mg/day. There is growing interest in off-label uses of this drug although the clinical evidence is sparse and would certainly not satisfy anyone insisting on evidence-based medicine and randomized controlled trials. However, some of the results seem to be of sufficient interest to deserve mention in the Newsletter. The most significant involves the treatment of pancreatic cancer declared hopeless.

Pancreatic cancer. Dr. Burton Berkson and colleagues at the Integrative Medical Center of New Mexico in Las Cruces, NM (IMCNM) have presented four case studies of the use of oral naltrexone and IV alpha lipoic acid (ALA/N) to treat pancreatic cancer. These studies appeared in several issues of *Integrative Cancer Therapies,* a peer-reviewed journal. While case histories are considered weak evidence, this is frequently where successful treatments are first described and where the incentive arises for clinical trials. Unfortunately, naltrexone is now available as a generic drug and ALA is not patentable and widely taken as an oral supplement. This does not bode well for clinical trials.

- **Case 1**. J.A. (male, age 46) was diagnosed with pancreatic cancer which had metastasized to the liver in October 2002 and after an unsatisfactory experience with chemotherapy in November 2002 he elected alternative treatment with ALA/N. Treatment continued until March 2004 with no progression in his disease status as judged by CT images. From the beginning of the treatment he felt better, and by

2004 felt so well with no symptoms of his disease that he decided to discontinue treatment. Within 4 months a PET/CT scan revealed disease progression confirmed at 9 months. J.A. then elected to resume the ALA/N protocol and as of June 2005 there was no further disease progression.[2] This case study was updated in 2009. Now at 78 months post-diagnosis, JA appears and feels normal and his CT scan now displays attenuation of the pancreatic tumors and liver metastases.[3] To put this in context, individuals with pancreatic cancer have a very poor prognosis, sometimes with anticipated survival times of weeks, but rarely more than a year. The disease is generally diagnosed when advanced and metastasis to other organs is common.

- **Case 2**. GB (female, age 74) was diagnosed with pancreatic cancer and liver abnormalities in February of 2006. She refused conventional therapy on religious grounds and was given 3-6 months to live. At IMCNM she was again offered conventional treatment but declined but consented to the ALA/N protocol. By February 2007 and again in March 2008 she was declared to be in remission by PET scan surveillance. At 39 months after diagnosis, she continues with treatment and has no signs of pancreatic disease.[3]
- **Case 3**. JK (female, age 80) diagnosed in September 2005 with pancreatic cancer with possible metastatic disease of the liver. No treatment was suggested due to the patient's advanced age and she was referred by her family physician to IMCNM. At that time she was barely able to walk, and was jaundiced. A PET scan confirmed the diagnosis. She was offered various conventional treatments but elected to undergo the ALA/N protocol. Over the next few months she put on weight and her blood work improved. Late in June of 2006 a PET scan found no signs of pancreatic cancer. She then stopped the treatment and by August began to feel ill. The return of the cancer was confirmed by CT and she died in November of the same year.[3]
- **Case 4**. RE (male, age 67) diagnosed in May 2006 of inoperable pancreatic cancer. Pervious cancers included prostate cancer treated in 1996 with brachytherapy, and lymphoma diagnosed and treated in 1998. After the 2006 diagnosis, he was provided with a biliary drain which was never fully functional. A second opinion from a large medical center indicated that no treatment was the best choice. In November, 2007 he presented at IMCNM emaciated and apparently in generally poor health. A PET scan confirmed the pancreatic cancer diagnosis with metastasis to the liver. He elected to try the ALA/N protocol. By February 2007 another PET scan showed a resolution of the previously demonstrated pancreatic cancer. RE was feeling so good that he elected to have surgery to improve the function of his biliary drain and he agreed to chemotherapy at the suggestion of his oncologist. His severe abdominal pain returned and he was taken of low-dose naltrexone because of the need for narcotics. He developed septicaemia, became unresponsive and died 12 months after the initial diagnosis. [3]

These cases consist of individuals with dismal prognosis. Diagnosis in each case was presumably certain, and the results of the ALA/N protocol followed by scans with reference baseline scans. These are not like case studies where the patient is reported to have responded well, gone back to work, started playing golf, etc, etc. without any clinical evidence of what really happened to the underlying disease. Thus they appear to be in the class that should be taken seriously. Most physicians can implement this protocol with the help of a compounding pharmacy. The details of the protocol are no doubt available to physicians from Berkson.

B-Cell lymphoma. In a 2006 issue of *Integrative Cancer Therapies*, Berkson and colleagues describe one case history of an individual with this type of lymphoma. A 61-year-old male was diagnosed in June 2004 with B-cell Lymphoma. He rejected the recommendation of chemotherapy and was offered no other options. He remained symptomatic and 15 months after the diagnosis presented at IMCNM. Large cervical nodes were observed, one of which was particularly symptomatic and painful. After a PET scan, the patient was advised to follow conventional treatment but refused and he elected to follow only one aspect of the ALA/N protocol, oral naltrexone (LDN), 3 mg every night. However, he did complete 9 treatments of IV ALA in the first week following his initial appointment. He remained compliant to the LDN oral treatment. Subsequent appointments revealed decreasing node size and by May 2006 his enlarged nodes had almost completely resolved. A second PET scan confirmed significant regression. In a telephone follow-up a year later he reported being symptom free.[4]

Multiple sclerosis. Two so-called pilot trials (small exploratory trials designed to provide insight into the actions, efficacy and safety of a drug or intervention) have been reported for the use of low-dose naltrexone in connection with multiple sclerosis (MS).[5,6] The most recent was an eight–week U.S. based trial using 4.5 mg/day of LDN. The study involved 80 subjects, was of the cross-over design with a placebo control, but had a high drop-out rate. LDN was well tolerated and serious adverse effects were not observed. LDN was associated with significant improvement in quality of life measurements and what were called the Mental Component Summary, the Mental Health Inventory and the Perceived Deficits Questionnaire. It was concluded that LDN significantly improved mental health quality of life issues and the results indicated additional studies were warranted. The authors attempted to estimate the off-label use of LDN in the US where there have been anecdotal reports of improved quality of life form MS patients who have acquired LDN. They estimate that several thousand American MS patients currently use LDN.

The second study was from Italy and involved 40 patients with primary progressive MS. It was found that after six months of LDN therapy there was a significant reduction in spasticity and the data indicated that LDN was safe and well tolerated in patients with this disorder.

***Fibromyalgia*.** While not everyone agrees that this is a real disorder, its symptoms allow the selection of patients for trials. There has been one pilot study involving LDN with a group of 10 women meeting the criteria for fibromyalgia and not taking opioid medication. The study design involved a cross over between the drug and a placebo with each patient on the drug for 8 weeks. The endpoint involved symptom reduction. In the entire cohort, all reported a greater than 30% reduction in symptoms when on the drug vs. the placebo. Laboratory tests of mechanical and heat pain thresholds were also improved and side effects rare. Baseline erythrocyte sedimentation rates, a positive indication of the presence of general inflammatory processes, were also measured. Individuals with higher baseline sedimentation rates had the greatest reduction of symptoms in response to the drug intervention.[7]

***Crohn's disease*.** A study published in 2007 treated 17patients with Crohn's disease with 4.5 mg/day of naltrexone.[8] The Crohn's Disease Activity Index was used to assess the effectiveness of the therapy. This score decreased significantly 4 weeks after completing therapy and remained lower than baseline. Eighty-nine percent of patients exhibited a response and 67% achieved a remission. Surveys of quality of life indicated improvement. The only side effect was sleep disturbances which occurred in 7 patients.

In a review published in 2009, Brown and Pankseep concluded that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Through modulation of the brain biochemistry, the drug may also have a role in promoting stress resilience, exercise, social bonding and emotional well-being, as well as the potential amelioration of psychiatric problems such as autism and depression.[9]

This is obviously an interesting drug, and although some side effects are reported, mostly on the internet, it may have considerable utility for a number of indications. While the philosophy of avoiding prescription drugs whenever possible would appear to have great merit, there are occasions where the benefits appear to significantly outweigh the adverse effects. With the serious disorders discussed above, this may be the case.

CRESTOR FOR THE ELDERLY

Reports continue to appear regularly regarding sub-groups of the cohort of the JUPITER trial which examined the use of the statin Crestor (rosuvastatin) for primary prevention in individuals free of clinical manifestations of heart disease, low or normal LDL and elevated C-reactive protein. The latest concerns adults 70 years and older (median age 74 with 75% younger than 77). This study with primary funding from the maker of Crestor is a so-called secondary analysis of the trial results.[10] An earlier study (PROSPER) found no statistically significant benefit associated with pravastatin for the reduction of vascular events in individuals aged 70-82 when the study group was restricted those without previous vascular disease, i.e. primary prevention.

This just-reported study appears limited by the rather small number of events the biostatisticians had available for analysis. The primary combined endpoint consisted of any of the following: first heart attack, stroke, arterial revascularization, hospitalization for unstable angina or cardiovascular related death. The absolute difference in principal endpoint rate was 0.77 per 100 person-years, and the relative risk reduction was 39%. However, endpoints such as heart attack, cardiovascular death, any death and venous thromboembolism failed to produce statistically significant evidence of benefit. Furthermore, for the primary combined endpoint, there was no statistically significant benefit if one was a non-smoker, of other than the white race, had the metabolic syndrome, hypertension, CRP ≥ 5 mg/L, LDL ≤ 100 mg/dL, a Framingham risk score ≤ 10%, or had triglycerides ≥ 150 mg/dL, all at the start of the study. Furthermore stratification by gender revealed a much weaker effect for men with a risk reduction having an upper confidence limit of near or at 1.0, suggesting a lack of statistical significance. Finally, the lack of specific benefit on mortality bothers some critics of this approach to primary prevention. The abstract paints a considerably more positive picture.

The authors of the accompanying editorial[11] raise the question of defining primary prevention in this age group.[11] They point out that an autopsy study of presumably asymptomatic individuals 70 years or older showed 72% of men and 54% of women had 75% or more blockages of one or more major coronary arteries. Presumably these individuals would be described as having silent CHD. Information regarding the extent of subclinical atherosclerosis in the cohort involved in the above study was not available. They comment that as technology advances in the field of identifying subclinical atherosclerosis, the line between primary and secondary prevention blurs.

When one looks at cumulative incidence plots, the divergence between the placebo and treatment groups aged ≥ 70 starts after only about 3-4 months. The editorial authors commented on this but did not elaborate.[11] When benefits turn up very early, it is commonly assumed that non-lipid lowering effects deserve serious consideration. If it is indeed true that the benefits seen in this trial have nothing to do with lipid-lowering, then finding out what is really going on should have high priority since there may be much more effective interventions which would target the real problem. The increasing popularity of Crestor and the movement to implement its widespread use will only delay real and significant progress in the primary prevention of cardiovascular disease.

As with all the JUPITER trial results, there is no mention of fact that Crestor strongly elevates the circulating vitamin D status marker, 25-hydroxyvitamin D, nor is it discussed in the accompanying editorial.[11] Readers of this Newsletter are no doubt aware that the protective effect of vitamin D is implicated in many of the JUPITER benefits. In addition, it is well known that the age group in this study is generally deficient if not severely deficient in vitamin D. Nevertheless, this study will no doubt have a strong influence on physicians to prescribe life-long Crestor therapy in this age group, and the lack of evidence for individuals 70 or older who are non-smokers, have hypertension, high triglycerides, low LDL, high CRP, the metabolic syndrome, or are non-white will probably be lost in the noise and omitted from drug rep presentations. Yet one or more of these characteristics will no doubt be present in a substantial fraction of those advised to start a life-long statin therapy.

LATEST FROM JUPITER ON PRIMARY CARDIOVASCULAR DISEASE PREVENTION IN WOMEN

When JUPITER initially reported, it appeared to be the first randomized trial that showed benefit of statin therapy for women. In the abstract of this latest report [12] which gives in detail the results for women and compares these with men, the conclusion is stated that JUPITER demonstrated that in primary prevention Crestor reduced CVD events in women with relative risk reductions similar to men. For those who have access to or make the effort to look at the data, a somewhat different picture emerges than the conclusion section of the abstract describes. While it appears true that for the primary endpoint the results for men and women were similar—in fact almost identical, when one looks at the components of this combined endpoint, there was no statistically significant benefit for women for nonfatal heart attack, any heart attack, nonfatal stroke, any stroke, combined heart attack,

confirmed death from CVD causes, venous thromboembolism, death on a known date or any death. All of the above showed statistically significant benefits only for men except for death on a known date or any death. Finally, as with the study on the elderly, there was no benefit regarding mortality.

For women, only arterial revascularization or the combined endpoint of arterial revascularization and hospitalization for unstable angina gave statistically significant benefit, which was also true for men. Revascularisation deserves special comment. The percentage of individuals presenting at the ER door with symptoms suggestive of a heart attack who end up in the so-called cath lab falls in part into the field of medical ethics, and appears strongly dependent on hospital policy, pressure from hospital administrators, and financial considerations on the part of a number of interested parties, interests which some would argue have no place in such decisions. Arterial revascularization is a complex issue since it requires consent from the patient which is strongly dependent on the manner in which the arguments are presented, the state of mind of the patient at the moment, and the pressure from spouses, relatives, nurses, and a variety of residents and attending physicians who may be recruited into influencing the decision making process. Thus revascularization, whether it is angioplasty with or without stents or an express trip to the OR for a coronary artery bypass, is a not the greatest endpoint for judging the merits of a drug intervention. This is not to say that in some cases the indications indeed justify intervention and intervention produces clear benefit.

It must also be kept in mind that large studies have recently reported comparing standard medical treatment with revascularization and angioplasty with or without stents. These studies were able to recruit participants even though they were randomized and, incidentally, they found essentially no difference in outcome (see below for a report on one such study).

Some may argue that the null results for almost all the endpoints for women were due to the low number of events. While this may or may not be true, one can only conclude that the study proved nothing for these endpoints, all of which are obviously of critical importance in seeking guidance on the lifelong use of a drug, and that only a larger study will resolve the issues raised. One can not look at a combined endpoint and then conclude that there is automatically benefit associated with its components even when the results for the individual components say otherwise. What the results for the non-significant endpoints say is that no one knows the answer.

The abstract of this report also states that the results are in agreement with meta-analyses of the use of statins in primary prevention in women. The authors present meta-analysis results, but the biostatisticians include JUPITER in the analysis rather than comparing JUPITER by itself to the pre-existing meta-analyses. It is well known that meta-analyses of this matter that predated JUPITER produced null results. In addition, the meta-analyses presented in this paper found no benefit for total CVD if the group of studies was only predominantly or exclusively rather than exclusively focused on primary prevention. And the meta-analyses where total mortality was the endpoint show no significant benefit even when JUPITER was included. But combining JUPITER with earlier trials does not appear valid since the JUPITER cohort is unique due to the entrance requirement of elevated CRP and the unintentional conversion of many participants from being vitamin D deficient or insufficient to being sufficient or even near optimal. Other statins do not appear to have a significant impact on vitamin D status.

It is interesting that the report and commentary in *Journal Watch* (Stroke section, May 8*),* a high profile mainstream newsletter for physicians, was titled *Women from JUPITER…benefited from rosuvastatin as much as men did.* The statistics clearly presented in the tables of the paper stratified by individual endpoints contradicts this statement but this is not discussed aside from mentioning the major contribution from revascularization, and even the commentary avoids this issue. The commentary calls this a landmark trial, but in fact the female arm of the study probably did not have enough events to provide statistically meaningful results.

CARBOHYDRATES AND CORONARY HEART DISEASE

The conventional wisdom for decades had been that a diet low in fat and high in carbohydrates was the ticket to health. It wasn't so much the high carbohydrate aspect that was being emphasized,

but when fat is drastically decreased it is common to replace the caloric deficit with carbohydrates, an option that was widely embraced without much attention to the type of carbohydrate. When Dr. Robert Atkins told anyone who would listen that they had it backwards and that a diet low in carbohydrates and high in fat and protein was the proper diet, he was ridiculed and even brought before the U.S. congress to determine the truth of the accusation that he was a public enemy. Yet all he had been doing was applying what was in the literature and a bit of endocrinology 101. And for many of his patients it worked! The predictions by the medical and nutrition community that his diet would vastly increase the risk of morbidity and mortality turned out to have no basis in fact, although the low fat hypothesis persists today and is still fundamental to the marketing of many manufactured foods, and "official" guidelines over the past decade have made an indelible imprint in the minds of the general public that fat is bad and clogs up the arteries.

In past Newsletters and Research Reviews the low-fat vs. low-carb debate has been extensively discussed and the literature backing the low-carb diet approach vs. the low fat view has been discussed rather extensively not only in the context of heart disease but also diabetes and prediabetes. Unfortunately, many individuals may have suffered adverse effects from following the low-fat philosophy, partly because those really dedicated to this notion and unfamiliar with merits of the various sources of carbohydrate, managed to lower their HDL cholesterol and raise their triglyceride levels to unfavourable if not actually dangerous levels and in addition, increased their risk of insulin resistance followed by type 2 diabetes.

A paper just published in the *Archives of Internal Medicine* directly relates to this matter.[13] This prospective follow-up study examined the relative risk of coronary heart disease associated with carbohydrate intake as measured by the glycemic load. The large and heterogeneous cohort consisted of almost 50,000 Italian men and women. Glycemic load (the glycemic index times the amount of carbohydrate actually ingested) was determined from dietary questionnaires. CHD events and associated mortality were determined from various public records and confirmed by examination of individual charts and records. During a median of almost 8 years follow-up 463 CHD cases were identified. Women in the highest carbohydrate intake quartile had double the CHD risk as compared to the lowest quartile. Increasing intake of carbohydrate from high-glycemic index foods as distinguished from actual glycemic load was also significantly associated with greater risk of CHD in women (68%). Women in the highest glycemic load from all foods had a statistically significant relative risk of 2.24 (124% increase in risk) when compared to the lowest quartile. In all of these comparisons, there was no significant association in men. These relative risks were corrected for potential confounding.

The authors suggest that one reason for the sharp gender differences seen in this study could be due to adverse changes in HDL cholesterol and triglycerides that could be a stronger risk factor for women than men. They also cite the differences in lipoprotein metabolism which are about twice as fast in women as men due to estrogen and androgen effects. Also, they suggest that hyperglycemia which would result from the high glycemic load diets may be more associated with other CVD risk factors in women than men. Unfortunately, the study did not collect data that might have provided evidence for various hypotheses related to the gender differences. But such differences have, according to the papers cited by the authors, been seen in other studies with CHD as an endpoint.

Insulin resistance, prediabetes and diabetes were not endpoints in this study and therefore men should not view the above results as a reason for adopting a high glycemic load diet. It is also clear that there are many aspects of human nutrition that are not well understood.

NEWS BRIEFS

ADDED SUGAR AND CARDIOVASCULAR RISK MARKERS

A study which got a lot of media attention just appeared in the *JAMA.*[14] At issue was the impact on blood lipids of the consumption of sugar added to foods. The data was derived from the National Health and Nutrition Examination Survey (NHANES) and from data bases containing information on added sugar content of food. Those in the lowest quintile (stratified by percent energy from added sugar) consumed about 10 lbs/year

whereas in the highest it was 155 lbs/year. The latter figure corresponds to 192 g/day or 48 teaspoons full of added sugar. The sugar added at the table apparently was not considered, and thus the total sugar intake was no doubt larger but in the upper quintiles table sugar probably did not significantly add to the total. The results were discussed in terms of the percentage of energy from added sugar but the mean total energy varied only from 2038 to around 2300 cal/day (actually kcal). Table sugar contains about 4 cal per gram.

The largest lipid effect was seen with HDL where for a sugar intake of < 5% of total energy, the mean was about 59 mg/dL and for ≥ 25%, it was about 48 mg/dL. Corresponding values for triglycerides were 105 and 114 mg/dL. There were no gender differences in these two results. For LDL, there was no variation with added sugar intake for men and a small increase for women. These results are not surprising since they describe the type of dyslipidemia repeatedly seen from the consumption of large amounts of refined carbohydrates. The resultant dyslipidemia involves mainly triglycerides and HDL and moves the levels in an adverse direction.

It is interesting to compare this study with the Italian study discussed above which had CHD events as an endpoint and also looked at carbohydrate consumption. Unfortunately the Italian study did not include data on blood lipids, but some would argue that it is better to use event endpoints than surrogate markers such as blood lipids. In the Italian study only women exhibited increased risk with increased dietary glycemic load whereas in the *JAMA* study both men and women experienced the carbohydrate induced type of dyslipidemia. Furthermore, for both men and women in the Italian study, there was no association between sugar intake and the risk of CHD events. For women, the intake ranged from 72 to 152 g/day with similar values for men.

It would seem to follow from these two studies that the basic understanding the relationship of human carbohydrate metabolism and cardiovascular health leaves quite a lot to be desired. Furthermore, given the gender inconsistencies in the two studies, there appear to be problems inferring the increased risk of acute events from changes blood lipids. The science is far from settled, to use the phrase popular with the climate-warming fraternity, and we await definitive studies.

B-VITAMIN THERAPY FOR PATIENTS WITH DIABETIC NEPHROPATHY

Diabetic nephropathy is a significant cause of chronic kidney disease. In addition, high levels of circulating homocysteine have been shown to increase the risk of developing diabetic neuropathy. Therefore, it was logical for the authors of a recent study to advance the hypothesis that B-vitamin therapy known to reduce plasma homocysteine would slow the progression of diabetic nephropathy and prevent vascular events.[15] The trial was a multicenter, randomized placebo controlled study that enrolled type 1 or type 2 diabetics. The primary outcome measure was the progression of nephropathy measured by determining the glomerular filtration rate (GFR). This measure of kidney function decreases with increasing severity of kidney dysfunction. Other outcomes included the need for dialysis, the occurrence of vascular events and all-cause mortality. The intervention involved 2.5 mg/day of folic acid, 25 mg/day of vitamin B6, and 1 mg/day of vitamin B12, or a matching placebo.

Among patients with diabetic nephropathy, this intervention resulted in a decrease in homocysteine over 36 months, but these high doses resulted in a greater decrease in the GFR suggesting increased rather than decreased kidney dysfunction. In addition the treatment resulted in a higher rate of heart attack and stroke and all-cause mortality, with the treatment group showing more than double the risk of the placebo group. Thus what are called pharmacologic doses of the B vitamins, in contrast to physiologic doses encountered in foods, may not be a great idea. It is necessary also to consider that the folic acid used in all these homocysteine lowering studies is a synthetic chemical which at the high doses used is only partially metabolized and results in circulating unmetabolized folic acid which has unknown biochemical actions. This has been discussed several times in this newsletter and is a topic of growing interest as high doses of synthetic folic acid continue to produce adverse effects including increased risk of cancer.

ANGINA—WHICH IS BEST, INVASIVE INTERVENTION OR MEDICATION?

Invasive cardiology, i.e. angioplasty with or without stents and coronary artery bypass surgery, has a significant impact on the financial health of many hospitals and, as well, is an important source of revenue for cardiologists doing invasive interventions. The time from the beginning of a heart attack to the arrival in the so-called cath lab is now a parameter in clinical studies of cardiac mortality and morbidity. Some hospitals have created an express highway. Other hospitals have had to deal with legal challenges regarding excessive intervention or incompetent intervention. Thus a recent study appearing in the *Annals of Internal Medicine* comparing invasive cardiology

with simply giving medications is of great interest.[16] In the study in question, the endpoint was the relief of angina and took the form of a meta-analysis of existing studies. The study was complicated by the change over the years concerning the medication approach and thus only the recent studies really merit consideration. When only recent trials were included in the analysis, the authors described the beneficial edge found in invasive cardiology to be "attenuated." When one looks at the data, attenuated means the differential benefit disappeared into statistical insignificance. The medical therapy used in the non-invasive interventions included aspirin, beta-blockers, Ace inhibitors and statin therapy. The results speak for themselves.

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RESEARCH REPORT

ARE INFECTIONS THE CAUSE OF ATHEROSCLEROSIS?

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INTRODUCTION

This review was inspired by a recent paper in the *Annals of Clinical and Laboratory Science* by Uffe Ravnskov and Kilmer McCully.[1] Ravnskov, a physician and independent researcher, is probably the leading critic worldwide of the cholesterol hypothesis. McCully, a pathologist now associated with the Veterans Affairs Healthcare System in Boston and the Department of Pathology, Harvard Medical School, is famous for proposing the connection between homocysteine and atherosclerosis which is now generally accepted but was rejected when first proposed.

Today it is widely believed that high cholesterol *causes* atherosclerosis and thus cardiovascular disease. The public is reminded of this view frequently through pharmaceutical TV advertising where an actor tells us that now that he has had a heart attack he regrets not paying more attention to his cholesterol and now trusts his heart to a lipid-lowering drug. Few dare challenge this conventional wisdom in spite of the fact that there are serious, even fatal defects in what is really only a hypothesis. Graphic TV advertising also attempts to convince the general public that lipid-lowering drugs halt or reverse atherosclerosis although as regards coronary plaque, the evidence is compelling that this is not the case and that there is no clinically significant evidence to support this assertion.[2] The cholesterol hypothesis of cardiovascular disease (CVD) and in particular coronary heart disease (CHD) has evolved to become dogma. This has seriously impeded scientific research into alternative explanations which might lead to more successful therapy and has led to the tendency to grossly exaggerate the benefits of therapy based on the dogma, principally through the use of relative rather than absolute benefits and the failure to distinguish between true primary prevention and secondary prevention. The peer review process as applied to publications in medical journals and in the research grant approval process provides a high barrier for those critical of conventional wisdom or daring to think outside the box. The engine that drives the current conventional wisdom is in part the huge profits associated with lipid-lowering drugs.

This review will examine what is in fact a very old theory for the explanation of atherosclerosis, namely infections. This was a popular theory a hundred years ago but was supplanted after the Second World War when the cholesterol hypothesis came into vogue. Many consider the failure of trials with antibiotics to have sealed the fate of the infection hypothesis. In what follows, we will first present the Standard Model for the development of atherosclerosis, briefly outline its weaknesses and inconsistencies, and then examine the infection hypothesis as an alternative approach to explaining the relevant biological and clinical characteristics of CVD and CHD.

THE STANDARD MODEL

The first step, according to the Standard Model, a term used in particle physics to designate a prevailing paradigm, is dysfunction or damage to the innermost layer of cells in the artery. This single cell layer is called the endothelium and constitutes the surface over which the circulating blood flows. Damage or dysfunction is viewed as caused by elevated cholesterol, elevated homocysteine, or other toxic factors in the blood. Descriptions of the Standard Model explicitly state that high levels of circulating LDL trigger endothelial cell dysfunction in the artery.[3] The damage is then hypothesized to allow the migration of cholesterol, including LDL, and blood cells (monocytes) into the arterial wall. The next event is the oxidation of the LDL which leads to an immune reaction and this modified LDL is converted by monocyte derived macrophages into lipid-laden foam cells to form the early stage of plaque formation. This is similar to the innate immune system reaction, and is postulated to be triggered by oxidized LDL. This process it viewed as taking place just under the endothelial layer below what is called the basement membrane in what is called the intima.

The final act involves only some of the plaques which are described as vulnerable, which translates into ease or susceptibility of rupture, and the dumping or leaking of the vulnerable plaque contents into the circulation resulting in either a clot-induced reduced blood flow and unstable angina or total blockage and a heart attack.

Many plaques are not vulnerable, in part due to a fibrous cap which protects them for erosion and rupture. The ruptured vulnerable plaques are called “culprit” plaques and can be found and studied in detail at autopsy.

This outline omits many details and variations but represents the essential features of the Standard Model. It is noteworthy that this model involves a process which starts at the inner wall of the artery, the endothelium, and requires a mechanism that involves the penetration of the endothelium by monocytes, the precursors of macrophages which accomplish what is called phagocytosis, part of the end-game in the immune reaction that destroys undesirable and dangerous substances. As well, the penetration of other blood components including cholesterol is postulated. The Standard Model ignores the fact that the artery itself with its smooth muscle core (the media) has an external blood supply called the *vasa vasorum*. The Standard Model seems to view everything that takes place in the artery as using the endothelium as the entrance and exit even though the vascularization of the artery is via the *vasa vasorum* as is the vascularization of arterial plaque. This model also views elevated LDL cholesterol as the driving force behind atherosclerosis and advocates of this hypothesis point to the risk reductions for acute events achieved by cholesterol-lowering drugs in selected individuals, even though the absolute risk reductions are small and the drugs used have many non-lipid lowering actions that may account for the majority of benefits. Furthermore, this view ignores the compelling evidence that there is no correlation between cholesterol or LDL and plaque prevalence or progression. It would appear that various aspects of the pathophysiology are merely selected to fit the prevailing dogma which of necessity must have circulating cholesterol as a major actor since that is what is measured in screening, presents the weak correlations with CVD in selected individuals and is the target for therapy. Historically, there are numerous examples of dogma that turned out to be wrong but had a strong, even official following. Contradictory evidence was ignored since *a priori* it had to be wrong.

A significant portion of the evidence for this hypothesis rests on rodent and rabbit models of atherosclerosis, but we differ from rodents and rabbits in aspects relevant to atherosclerosis. It should be well known that rabbits did not evolve on a diet rich in cholesterol, but are fed diets high in cholesterol for the purposes of studying atherosclerosis. Rabbits presumably never were carnivores or scavenged for eggs and one can question their use in modeling human atherosclerosis. The Standard Model also is partly justified by mechanistic inferences based on what is found in dissected plaques, a practice potentially associated with the risk of being misled.

Ravnskov and McCully[1] summarize and document the major conflicts of the Standard Model with clinical, epidemiological, pathological and experimental observations.

- It is unlikely that elevated LDL causes endothelial dysfunction because there is no association between the blood levels of LDL and the directly measured degree of dysfunction.
- If endothelial damage leads to an influx through the endothelium of LDL, then is difficult to explain why atherosclerotic plaques seen in patients with extremely high cholesterol due to an inborn error in metabolism (familial hypercholesterolemia) do not contain any lipids even though there is pronounced endothelial damage.
- In randomly selected individuals, a number of studies all show that there is no association between cholesterol levels or LDL in the blood and the degree of atherosclerosis seen in the coronary arteries at autopsy.
- In women and the elderly, Framingham studies showed that elevated cholesterol is either a very weak or non-existent risk factor for cardiovascular disease. This must viewed the context that major cardiovascular adverse events occur mainly in those over 65.
- For those with so-called familial hypercholesterolemia (FH), a number of studies find that there is no association between LDL and the prevalence or progress of cardiovascular disease. The higher coronary mortality in young individuals with FH may be due to inherited abnormalities of the coagulation system.
- Evidence exists which indicates that the pathological processes associated with atherosclerosis in rodents differs significantly from that in humans. Artificially elevation of cholesterol in rodents does not by itself in general produce coronary thrombus.
- Fatty arterial streaks are viewed as the precursor lesion, but these streaks are seen in not only newborns and children, they in many cases disappear over the early years of life.

To this list can be added the compelling evidence derived from non-invasive imaging studies that that there is no association between total or LDL cholesterol and the presence or progression of coronary plaque, both calcified and non-calcified, a result consistent with a number of early autopsy studies. Furthermore, lowering LDL with drug therapy has no impact on the progression of coronary atherosclerosis.[2] However, the lipid-lowering trials, mostly involving individuals a high risk of or with established heart disease, have had a huge impact in terms of reinforcing the almost universal belief in the Standard Model even though the absolute benefits were small. Furthermore, although disputed by the experts, lowering event rates by lowering LDL levels does not prove that LDL is a causative factor since the drugs used have a very large number of non-lipid lowering effects, more of which are being discovered every month, and these so-called pleiotropic effects would correlate with lipid lowering since both are, in general, dose dependent.

In addition to these problems with the Standard Model, there is the recent observation from a study that over 50% of a large group of patients hospitalised for a heart attack had normal or low LDL levels (≤ 105 mg/dL), and incidentally low levels were associated with *decreased* 3-year survival.[4] There are many other inconsistencies and contradictions not included in the above list.[5-7] Finally, the small risk of CHD associated with cholesterol levels seen in younger men may have its origin in psychological stress and exaggerated blood pressure response to aggravation with cholesterol acting only as a marker.[8] Obviously, something important is being overlooked.

These problems with the Standard Model have incidentally been described in the medical literature and books and discussed for several decades but ignored by the proponents. Thus the question remains, what is the mechanism where an artery starts out as normal and ends up with vulnerable plaque which rupture and cause cardiovascular morbidity and mortality, while this never happens in veins but may when a vein is transplanted to serve the function of an artery? While mainstream medicine seems comfortable with the Standard Model and it forms the basis of much research and is the foundation upon which officially approved therapy rests, the science seems far from “settled,” to borrow a term from the climate warming debate. Among the alternative hypotheses, the one involving infections as driving atherosclerosis appears to merit serious consideration, and the recent paper cited above should stimulate increased interest. Devout believers in the Standard Model would probably describe this renewed interest as an unjustified exhumation.

THE MICROBIAL HYPOTHESIS

The notion that bacteria and viruses are the main cause of atherosclerosis has a long history going back over a century. Early observations included finding arterial lesions in patients who died from typhoid fever and so-called hardened arteries in many who survived. The duration of an infectious disease and the degree of atherosclerosis found at autopsy appeared correlated, and the famous physician Sir William Osler likened what is now called a vulnerable plaque to a pustule (one common manifestation of acne) which is like a boil. it was generally thought early in the 20th century that arterial plaques were the result of irritation associated with infections or toxins.[1] Studies cited by Ravnskov and McCully[1] as well as a recent review[9] and other studies[10-13] have over the years provided the following circumstantial evidence:

- Heart attacks exhibit a seasonal variation with a maximum in the winter.
- Flu epidemics correlate with an increase in overall CVD deaths.
- Flu vaccinations reduce the incidence of winter heart attacks.
- In the SARS epidemic, 2 out of 5 deaths were due to heart attacks.
- The presence of an acute infection frequently is seen in heart attack patients, and is accompanied by markers of inflammation in the coronary arteries and plaque.
- From a fifth to half of patients experiencing a heart attack or stroke have just had an infectious disease, and this appears independent of the type of infection.
- Autopsy studies suggest that some individuals though to have succumbed to the flu died of a heart attack.
- William Osler pointed out a hundred years ago that atherosclerosis was a common finding among children who had died of infectious diseases.
- There are similarities between arterial plaque and abscesses or boils.
- Bacteremia (bacteria in the blood) is associated with increased risk of cardiovascular disease. It is a severe complication of infections, can cause sepsis and septic shock and can spread infection to distant locations or organs.

- Periodontal infections (e.g. gum disease), as well as urinary tract infections are associated with increased risk of CVD and heart attacks.
- Vaccination against influenza in a group of heart patients reduced the CHD mortality to an extent not achievable by statin treatment.
- C-reactive protein, a marker for infection, is also a significant risk factor for CVD.
- Acute systemic infections are associated with significant increases in inflammatory cells in the atherosclerotic coronary arteries of humans.[10]
- Hepatitis C infection is associated with increased coronary artery atherosclerosis.[11]
- The extent of atherosclerosis appears to be linked to the number of infections an individual has experienced. The risk of advanced atherosclerosis was found to be increased after 3.2 years follow-up by a factor of 2.5 in individuals showing elevated antibodies for 6 to 8 distinct infectious agents as compared with those with 0-3 distinct elevated antibodies. A strong positive association with cardiovascular mortality was also seen after over 3 years follow-up when those positive for antibodies to 6-8 pathogens were compared to those with 0-3.[12]
- Epidemiological studies have revealed that host immune reactions against persistent infectious pathogens such as *Chlamydia pneumoniae, Porphyromonoas gingivalis, cytomegalovirus* (herpes virus) and *Helicobacter pylori* may promote the development of atherosclerosis.[13]

The above provides an indication of the body of evidence which should direct attention to infections as a major actor in both the formation and progression of arthrosclerosis and acute cardiac and other vascular events.

WHAT MIGHT BE THE MECHANISM?

If it is assumed that infectious disease plays a major role in the etiology of atherosclerosis, just how does it do it? The Standard Model focuses on the inner arterial wall and its injury and penetration as events leading to the formation of plaque and acute events. A major point made by Ravnskov and McCully[1] is that this model ignores the *vasa vasorum*, the microcirculation system serving the arteries, which provides another route into the main part of the artery (the media). In addition, they point out that the Standard Model ignores the remarkable role played by LDL particles in the immune system.

Ravnskov and McCully[1] propose the following hypothesis for the sequence of events leading to plaque formation. This hypothesis is based on the aftermath of infection, the primary trigger. They start with the unappreciated role that LDL plays in the immune system. Ravnskov and McCully tabulate 12 studies which demonstrate that LDL binds microbes and microbial products, the most common microbial product being lipopolysaccharide. These LDL complexes stimulate the immune system to attack and destroy them through what is called phagocytosis, a process carried out by macrophages derived from monocytes in the circulation. Furthermore, there is evidence indicating these complexes of LDL and both microbes and their products lead to aggregation of the lipoprotein particles which can result in large particles that have the potential to block the microvasculature. Elevated homocysteine may also increase aggregation of LDL because of complex formation with homocysteine or molecules generated by the reaction of homocysteine with other proteins. In addition, they cite other lipid complexes that infections can promote.

While LDL does not initiate an immune response, its various complexes described above as well as the resultant aggregates do and if this takes place in the arterial wall or in the *vasa vasorum*, multiple end results are possible including the various immune and inflammatory responses that are through to lead eventually to arterial plaque, both fibrous (capped) and vulnerable. Aggregates may block the microvasculature (ischemia) resulting in oxygen deprivation and arterial tissue damage. The stage is set for macrophages generated from monocytes in the circulating blood to mount a campaign which results in the generation of oxidized LDL and a variety of inflammatory products. The nature of the plaque formed will depend on the details of the immune reaction, but the essential point is that this starts from the introduction of immune active molecules and complexes traceable back to infections which enter the artery via the *vasa vasorum* rather than through an injured endothelium as required by the Standard Model. Once a plaque develops the penetration of the endothelium by monocytes adds to the pool of potential macrophage precursors. If the immune system manages the above problems such that there is no permanent change, then no plaque forms, but when the damage is such that the changes are permanent, boil-like plaque can result which can be either innocuous aside from stenosis (partially or even totally

blocking arterial flow) or a vulnerable plaque can rupture resulting in an acute event, the nature of which depends on the extent of blockage caused by the resultant clot.

According to this hypothesis, LDL does not enter the artery through the endothelium but via the capillary system of the *vasa vasorum*. Oxidized LDL is the result of the action of macrophages during the "digestion" of the complexes involving LDL (phagocytosis), not oxidation after the LDL enters trough the endothelium. Oxidized LDL can then further stimulate immune response and creature a vicious circle, but its oxidation is not a primary event. This may be why the use of antioxidants in prevention studies fails to produce significant results. When the aggregates involving LDL complexes obstruct the *vasa vasorum* circulation, local ischemia can occur within the arterial wall along with microbial growth and inflammation. The internal elastic lamina separating the media from the intima is breached as the plaque develops and pushes out the endothelial cell layer.

The authors discuss in some detail the evidence for each aspect of this mechanism and as well, show the mechanism to be consistent with the pathological findings when both stable, fibrous and vulnerable plaque are examined in great detail at autopsy.

THE FAILED ANTIBIOTIC TRIALS

The standard argument against the above infection based hypothesis involves clinical trials using antibiotics. It was in fact these studies that led to the dismissal of the theory a number of years ago. Ravnskov and McCully argue that these unsuccessful trials involved mostly the use of a single antibiotic known to be effective against *Chlamydia pneumoniae*, one of the organisms found in atherosclerotic plaques. However, over 50 different microbial species have been identified in these plaques, but not a single one in normal arterial tissue. Patients typically have on average 12 different microbial species in the plaque. Thus it is highly unlikely that a single antibiotic would be effective. In addition, antibiotics are not effective against viral infections. Also, the trials regarded as falsifying the infection hypothesis were of relatively short duration. There is also the study mentioned above which found a strong association between the number of positive antibody reactions to different pathogens and the degree of atherosclerosis and cardiovascular mortality. This strongly argues against putting much weight on single-antibiotic short-term studies. Thus it would appear that the rejection of the infection hypothesis and its retreat into obscurity were not based on satisfactory evidence but rather on studies that suffered from a flawed design.

IS CHOLESTEROL ACTUALLY PROTECTIVE?

Recognition that LDL cholesterol takes part in the immune process suggests that it has been unjustly demonized. Ravnskov and McCully cite a number of studies providing considerable evidence that cholesterol is protective against infectious diseases. Cholesterol levels have been found to be inversely associated with total mortality in the elderly. In addition there is an inverse association between cholesterol levels and mortality from respiratory and gastrointestinal diseases, most of which have an infectious origin. This inverse association is also found for post-operative mortality from abdominal infections, the risk of being admitted to hospital because of an infectious disease, and the risk of contracting HIV and AIDS. Lipid lowering drugs such as the statins have a large number of non-lipid lowering actions. Some of these may neutralize the risks of infectious disease associated with an artificially induced low a cholesterol level.

It is also noteworthy that high cholesterol predicts longevity rather than increased mortality in older individuals, even those with genetically-related very high cholesterol.[14] Also in many observational studies mortality was found to increase at low serum cholesterol levels. The mortality issue was discussed at length in a three-part Research Review in the November 2007 issue of *International Health News*, which concluded in the February 2008 issue.

THE IRON CONNECTION

Most readers of this Newsletter are aware of the advice to men to avoid multivitamins with iron and that for women the normal reduction of iron stores during menstruation is probably protective in the context of iron-related disorders. The hypothesis that elevated body iron stores were a risk factor for coronary heart disease (CHD) was suggested in 1981 by Jerome Sullivan. It was based in part on the low incidence of CHD in premenopausal women as compared to age-matched men. This was attributed to monthly blood loss and supported by the disappearance of this gender difference in postmenopausal women. Today the iron-heart hypothesis is viewed as valid and testable. One of the most significant obstacles to seriously considering this

theory was that individuals genetically predisposed to iron overload (hemochromatosis) do not experience increased risk of atherosclerosis. In the past few years the recognition of the role of the hormone hepcidin in the regulation of iron balance and recycling has brought the iron-heart hypothesis to a new level of credibility and removed several strong objections. In addition, the iron-heart hypothesis points to the macrophage (the central player in the immune reaction) as an important player and brings us back to the connection with infectious disease where the macrophage releases inflammatory substances during phagocytosis.

If there is anything in cardiology that is beyond question and rests on a rock solid foundation of evidence, it is the fact that there is a very large gender difference in the risk of CVD which decreases in the postmenopausal years. In fact, as Sullivan points out[15] not only are healthy premenopausal women protected from CVD, so are premenopausal women with familial hypercholesterolemia who turn out to have the same rates as women without this genetic disorder. Actually this is another argument against the cholesterol hypothesis. The conventional wisdom views this gender difference as a hormonal phenomenon, but this view is not sustainable in the light of a number of studies and randomized trials involving hormone replacement therapy. Indeed, already in 1963 there was evidence from studies of women who had both ovaries removed and exhibited essentially identical prevalence of atherosclerotic heart disease as controls. That result has never been challenged. Sullivan suggests that these observations point to a uterine rather than ovarian (hormonal) function that is responsible for premenopausal CVD protection.[15] He points out that as part of the Framingham research, natural menopause, premenopausal simple hysterectomy, or premenopausal hysterectomy with ovary removal all were associated with similar increases in heart disease risk. He also cites additional supporting studies. However, the observational Nurses' Health Study provided evidence that contradicts this view in that a simple hysterectomy was not found protective. The reason for this discrepancy is not clear, but the weight of evidence appears to point to a protective function of the intact uterus with its monthly cycle. The iron-heart hypothesis provides a simple explanation. The healthy range of serum ferritin, a measure of iron load, is commonly given as 80-90 mg/L. Menstruating women typically have values below 30 mg/L.[15]

The current understanding of the role of hepcidin in iron metabolism and regulation has had a great impact on the iron-heart hypothesis. This small protein (25 amino acid peptide) appears to have first been isolated and purified in 2000-2001, which in itself is quite remarkable considering the important role it plays in human iron biochemistry. Hepcidin has the following properties:[16]

- Hepcidin binds to the major iron-transport protein and inhibits absorption of iron from the gut and also inhibits the release of iron from macrophages.
- Hepcidin levels are increased (upregulated) by excess iron and by inflammation and decreased (downregulated) by iron deficiency, localized lack of oxygen, and anemia.
- Most forms of the iron-storage disease (known as hemochromatosis) result from a dysregulation of hepcidin and exhibit low levels of this peptide.
- Hepcidin is upregulated by inflammatory cytokines such as IL-1 and IL-6.

These functions and properties make clear the connection between iron status, infection and inflammation. The critical aspect in terms of the infection hypothesis of CVD is hepcidin's role in regulating the release of iron from macrophages and thus its role in the iron content of atherosclerotic plaques which contain both macrophages and the remnants of macrophages which have undergone cell death. As Sullivan discusses in a recent paper,[17] there is growing evidence that iron depletion protects against atherosclerosis and atherosclerotic plaque have been found to have roughly ten times the iron content of the healthy arterial wall. Inflammation may increase levels of hepcidin which in turn promotes iron retention in macrophages within the atherosclerotic plaque and in extreme cases can promote the bursting of the macrophage releasing reactive iron into the interior of the plaque. On the other hand, low levels of hepcidin are associated with hemochromatosis and this would reduce the macrophage iron levels, given that this protein regulates the iron uptake and loss in this immune system cell. This of course would explain the paradox of the lack of association between hemochromatosis and arterial atherosclerosis and remove one of the major obstacles to the iron-heart hypothesis.

HOW IT ALL FITS TOGETHER

According to Ravnskov and McCully, their hypothesis explains a number of clinical and pathological observations. These include why all the classic features of infectious disease are common in a significant number of individuals presenting with a heart attack, and why elevated CRP in individuals with atherosclerosis is

a marker of increased risk of heart attack. Furthermore, fatty streaks, viewed in the Standard Model as plaque precursors, appear in newborns and children and frequently disappear, and this can be viewed as a normal and reversible response to infections.

The hypothesis explains why atherosclerosis is related to elevated blood pressure and the associated hydrodynamic pressure because lipoprotein complexes generated in response to infections are more easily trapped in the arterial *vasa vasorum* due to pressure differentials. Pulmonary hypertension appears to produce the same effect with the development of plaques in pulmonary arteries when conditions arise that lead this type of hypertension.

The current view of the anatomy of the *vasa vasorum* is that these vessels are so-called end-arteries, supplying the smooth muscle core of the artery where blood flow and patency are compressed by the pressure derived from the arterial circulation. When congested with the products of an immune response, end-arteries can burst, depositing elevated concentrations of toxins directly into the arterial tissue, initiating or enhancing the immune response and producing local inflammation.

If irritants directly attacked the endothelium as the Standard Model requires, then atherosclerosis should be just as common in veins, and if elevated LDL were the driving force then atherosclerosis should be a more generalized disease. The hypothesis addresses these issues. Veins function under a different pressure environment, and LDL functions as part of the immune system rather than driving atherosclerosis by invading through the endothelium and then being oxidized to start the process.

There is consistency between the infection hypothesis and other established risk factors. Mental stress increases the risk of infections, partly through its impact on the hormone cortisol. Anger increases homocysteine levels. Smoking predisposes to a number of infectious diseases and also causes an increase in homocysteine levels. Diabetes is a major risk factor for heart disease and diabetics have a higher prevalence of infections than do healthy individuals.

This hypothesis also raises questions regarding the mechanistic role of inflammation since inflammation is a necessary step in the normal healing process but is implicated in the etiology of heart disease. In this context, the connection between inflammation and homocysteine may be part of the answer. Studies suggest that homocysteine in an enhancer of inflammatory activation and as well plays a role in the autoimmune triggering process. Thus its connects inflammatory factors to the acceleration of atherosclerosis.[18] The well known connection between autoimmune diseases such as rheumatoid arthritis and the risk of heart disease is also consistent with the hypothesis since elevated homocysteine is associated with these diseases,[18] and according to the theory of Ravnskov and McCully, complexes of homocysteine with LDL and other proteins are postulated to participate in the immune triggering and *vasa vasorum* blockage that eventually leads to plaque formation.

IMPLICATIONS

Ravnskov and McCully discuss modifiable risk factors associated with this hypothesis. From these one can outline preventive actions.

- Address vitamin B deficiency because of its relationship to elevated homocysteine. However, in North America, B-vitamin deficiency is not common due to widespread fortification. Also, excessive intake of either folic acid or vitamin B6 appears to be unhealthy. Heavy B-vitamin supplementation is controversial since homocysteine-lowering trials have not been successful in reducing CVD events and adverse effects continue to be reported.
- Attempt to deal with mental stress since it increases the susceptibility to infectious diseases. It is incidentally, very strongly associated with the risk of acute CVD events and in fact on a par with diabetes.[19]
- Since many infectious diseases are more prevalent in smokers and diabetics, the actions indicated are clear. In particular, be concerned about prediabetes and attempt to halt its progression and reverse it.
- Bacterial growth is stimulated by iron and atherosclerosis is positively associated with the oxidative stress associated with labile iron. Thus elevated iron levels suggest intervention. For some, frequent blood donation may be the answer. There are also prescription iron chelators used to treat hemochromatosis and the classical EDTA chelation therapy ridiculed by mainstream medicine also removes iron as well as other heavy metals that may be pro-oxidative.[20] This is not just a fantasy. Strongly enhanced heavy metal

excretion is observed in the urine. However this is a complex subject since individuals with hemochromatosis do not have enhanced risk of atherosclerosis. Thus mild to moderate elevation of iron stores may be a problem, but severe elevation due to hepcidin dysregulation may not be, but only in the context of atherosclerosis.

- Periodontal disease is a common chronic infection. This gum problem has in fact been directly associated with the risk of CVD and coronary calcification. Thus dentists can play an important role in atherosclerosis prevention, and oral hygiene is very important, both at home and through periodic visits to the dentist.

Other suggested actions that have appeared in the literature include hand-washing, avoidance of individuals with infectious diseases, vaccinations and diet. It can also be argued that it is a good idea to stay away from hospitals unless absolutely necessary since they offer exposure to antibiotic resistant infections.

The infectious disease hypothesis refocuses attention away from cholesterol to the immune system. Thus a prevention program would also involve maintaining a healthy and effective immune system. The hypothesis also considers a dysfunctional immune system as promoting unstable plaque formation. Naturally, infections can probably never be eliminated and during a lifetime there are bound to be a few serious infections. Perhaps this is why most older individuals have some atherosclerosis. It is noteworthy that optimum vitamin D status appears related to good immune response and a low risk of, for example, of influenza, and the risk of CVD is inversely related to vitamin D status. Furthermore, the gut plays an important role in immunity (see Chapter 3 of *Gut and Psychology Syndrome* by Dr. Natasha Campbell-McBride for a brief introduction), and in the age of excessive antibiotic use and poor dietary patterns, the dysfunctional gut appears to be common and its importance unappreciated.

In his new book *Fat and Cholesterol are Good for You!*, Uffe Ravnskov has a chapter on avoiding heart attacks that follows a chapter describing the hypothesis discussed above and presented in the paper by Ravnskov and McCully. He points out that the really relevant question involves avoiding *premature* death from heart attack or stroke. Once one has reached a ripe old age he points out that it may be better to succumb to a heart attack than die of cancer or problems related to Alzheimer's disease. Aside from actions discussed above, Ravnskov suggests eating a diet low in refined grains and sugars, avoiding ingesting the hundreds of chemicals mixed in with so-called foods and offered at the supermarket, exercising, and paying attention to the huge impact an individual's long-chain omega-3 status (EPA + DHA) has on the risk of sudden death due to "electrical problems." He also recommends that anyone with unstable angina or a victim of a heart attack or stroke should be checked out with a blood culture as soon as possible after admission and any infection targeted immediately. This approach to increasing the chances of avoiding a second acute event may be more effective than the conventional post-heart attack protocol, or may offer considerable benefit when added to the standard protocol.

The preventive strategy outlined above would appear to involve no risks and should provide benefits independent of whether or not the infection hypothesis is correct. It is almost certain that this new view which points to infection as driving atherosclerosis and adverse vascular events will be resisted or ignored by mainstream medicine, but it is hoped that for those who are willing to think outside the box, benefits may derive from a renewed interest in the immune system as potential a major player in CVD.

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