The Failure of Vytorin and Statins to Improve Cardiovascular Health: Bad Cholesterol or Bad Theory?

Brian S. Peskin, B.Sc.
David Sim, M.D.
Marissa J. Carter, Ph.D., M.A.

ABSTRACT

The clinical failure of Vytorin in the ENHANCE trial supports the need to reevaluate the efficacy of widespread use of statin drugs for the treatment and prevention of coronary artery disease (CAD).

Statins were marketed on the precept that lowering so-called "bad" cholesterol while raising "good" cholesterol significantly improves cardiovascular outcomes. The number needed to treat (NNT) is, however, often greater than 100 (99% failure rate) with statin use.

Examination of the biochemical and physiological nature of atherosclerotic plaques suggests a reason for statin failure. Plaques rupture because of oxidized linoleic acid (LA), the parent omega-6 essential fatty acid, and while statins hinder transport of nonfunctional LA (trans and oxidized) entities to the intima, they also lower the bioavailability of fully functional LA. This lower bioavailability promotes platelet adhesion, lowers the anti-inflammatory levels of key prostaglandins, and interferes with cell membrane fluidity and oxygen transmission. Moreover, pharmacologically raising high-density lipoprotein cholesterol (HDL-C)—"good cholesterol"—levels is strongly associated with adverse cardiovascular events.

An alternate treatment paradigm using functional parent omega-6/3, in conjunction with diet and lifestyle measures, is proposed.

The Results of ENHANCE and Other Statin Trials

The clinical failure of the drug Vytorin—the ENHANCE Trial (The Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia)—is prompting a reexamination of the basis for using cholesterol-lowering drugs, the statins.[1]

Statins are sold by several pharmaceutical companies. Merck markets lovastatin (Mevacor) and simvastatin (Zocor); AstraZeneca, rosuvastatin (Crestor); Bristol-Myers Squibb, pravastatin (Pravachol); Novartis, fluvastatin (Lescol); and Pfizer, atorvastatin (Lipitor), the last being the world's best-selling drug. Vytorin is a formulation that combines simvastatin with a non-statin cholesterol absorption blocker, ezetimibe (Zetia), co-marketed by Schering-Plough and Merck.

While there were significant decreases in low-density lipoprotein cholesterol (LDL-C) levels over the two years of the ENHANCE trial, the intima-media thickness (IMT) increased more in the Vytorin group than in the simvastatin group (0.011 mm versus 0.006 mm), though the difference was not statistically significant. Since IMT is considered to be a marker of atherosclerosis,[2] as well as a strong predictor of future myocardial infarction, the change in cholesterol levels did not make a difference in preventing atherosclerosis.

Table 1. Percentages of Linoleic Acid (LA) and Alpha Linolenic Acid (ALA) in Plasma and Classes of Lipids.

Fatty Acid	Plasma Unesterified	Plasma Triglycerides	Plasma Phospholipids	Plasma Cholesterol Esters
LA	17	19.5	23	50
ALA	2	1.1	0.2	0.5
LA:ALA ratio	8.5:1	17.5:1	115:1	100:1

After learning of Vytorin's failure, it took Merck and Schering-Plough an inexplicable 20 months to release the news to the medical community. This communication took the form of a press release[3] rather than a peer-reviewed article in a medical journal. (The trial was eventually published in the *New England Journal of Medicine* in April 2008.[4])

Members of the medical community, including clinical cardiologists, were predictably upset, but the evidence that statins are not effective in reducing adverse cardiovascular events or mortality had already been accumulating. For example, in 2007, as reported in *Lancet*, Abramson and Wright conducted a meta-analysis of eight randomized controlled trials (RCTs) of statins and found a number of disquieting results.[5] First, they determined that total mortality was not reduced. Second, serious adverse events were not reduced either, in the two RCTs that reported such events. Third, the absolute frequency of cardiovascular events was reduced by only 1.5%, which means that the NNT with statins over a 5-year period was at least 67 in order for one patient to benefit. Finally, such benefit was limited to high-risk men aged 30–69 years.

Although there are no universally accepted benchmarks regarding the NNT for an effective treatment, for the sake of comparison antibiotics have an NNT of 1.1, meaning 10 out of 11 patients are cured. Therefore, Bandolier suggests an effective NNT should be no greater than 2–4.[6] Using this criterion, statin treatment is clearly not effective, but rather a dismal failure. A new level of understanding and synthesis of well-understood physiological principles is clearly required.

Actually, the high NNT (low effectiveness) of statins is even worse than reported. In describing statin trials, many publications exaggerate the benefits and omit vital information. They contain misleading mortality statistics, misstated risk factors, and hidden bias, leading to erroneous conclusions.[7,8] For example, the limited statin benefit obtained for high-risk men, as described by Abramson and Wright, is probably no better than could be obtained from a 5-week course of aspirin.[9]

Given clinical failure with statins in the treatment of cardiovascular outcomes, how has application of the cholesterol theory gained such prominence?

The Cholesterol Theory and Its Incorrect Assumptions

By the 1960s, cholesterol had become firmly entrenched in medical discourse as the culprit in the development of atherosclerosis.[10] Total blood cholesterol was the first blood test or marker used as an endpoint, in the initial 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor trials in Japan,[11] but as the biochemistry of cholesterol particles was being elucidated at that time, it was not long before the convenient results of these studies were applied in the development of statins. The theory behind statin development was simple: With no biochemical or physiological basis, it was *assumed* that plaque buildup in atherosclerosis results from the presence of the "wrong" kind of cholesterol ("bad" cholesterol—aka LDL-C). Lowering "bad" cholesterol levels and boosting "good" cholesterol levels (high-density lipoprotein cholesterol [HDL-C]) is then supposed to lower plaque buildup and prevent cardiovascular disease. Although this assumption is categorically false, the pharmaceutical industry convinced physicians and researchers that it was true. Physicians, especially cardiologists, are now in a quandary.

Current recommendations lack a firm biochemical basis. For example, for decades, saturated fat was incorrectly believed to be the cause of arterial plaque. This is clearly not the case, as identified in a landmark article published in 1994.[12] Investigators found that plaque contained more than 10 different compounds, none of which was related to saturated fat. Other independent investigations confirmed this finding.[13,14] Not surprisingly, cholesterol was found in the plaque, but a key study in 1997 demonstrated that cholesterol esterified with nonfunctional linoleic acid (LA), the parent essential unsaturated omega-6 fatty acid (PEFA), was by far the most abundant component in plaque causing arterial stenosis. It was also found that cholesterol esters (chemically attached fatty acid structures) are the predominant lipid fraction in all plaque types, and that both cholesterol and polyunsaturated fatty acids (PUFAs), in particular, abundant parent omega-6, may form oxidized derivatives that are toxic to most types of arterial cells.[15] Most interesting is the conclusion that arterial plaque rupture, which can cause thrombosis and vessel occlusion and increase the potential for myocardial infarction and stroke, was significantly related to oxidation of the LA.

These pathophysiologic findings have been largely ignored because of the misguided popularity of the "bad saturated fat/cholesterol" theory,[16] in which both saturated fat and cholesterol are portrayed as the bad actors. But, by itself, cholesterol is not bad; in fact, it is essential to life and is present in all cells. Consider just a few of its functions: It has a major structural role in the brain, and is required for nerve transmission; it helps maintain the properties of the cell membrane's lipid bilayers and plays a role in glutamate transport and the lipid rafts essential to glutamate receptor function. It protects the skin against absorption of water-soluble toxins and holds moisture to prevent desiccation. It is the precursor to many steroids, such as testosterone, progesterone, and estrogen, and also to bile salts and Vitamin D—and is thus essential for bone strength.

If cholesterol alone were the culprit in atherosclerosis, we should see reductions in IMT in parallel with reductions in cholesterol levels when statins are administered. However, we do not see this result. Moreover, patients with low cholesterol levels ought to have much lower event rates of cardiovascular disease, but they do not. Indeed, Krumholz et al.[17] concluded in 1994 that low cholesterol, by itself, does not significantly prevent heart disease in persons older than 70 years, a population that ought to quickly experience a benefit if lowering cholesterol were beneficial. A British study published in 1993 also determined that blood cholesterol was a poor predictor of coronary heart disease (CAD) and that few people identified on the basis of cholesterol levels would benefit from statins.[18] As early as 1964, the noted heart surgeon Michael DeBakey and his group analyzed the cholesterol levels in 1,700 atherosclerotic surgical patients and found no relationship between the level of cholesterol in the blood and the incidence and extent of atherosclerosis, firmly showing that cholesterol numbers in and of themselves were meaningless.[19] In fact, the patients with the highest LDL-C levels had the least atherosclerosis (an inverse correlation).

Apo-lipoprotein B has now been shown to be both a better predictor of adverse cardiovascular events and a more accurate index of residual CAD risk.[20]

Household cats (true carnivores), eating almost exclusively meat containing lots of cholesterol and saturated fat, do not quickly and routinely die of CAD. We maintain that lipid physiology is not significantly different in carnivores and human omnivores. Furthermore, there is no physiological blood cholesterol sensor, unlike physiological sensors that maintain strict control of glucose, calcium, and sodium levels in the blood. Therefore, the entire LDL/HDL/saturated fact theory is physiologically implausible.

What Is the "Bad Actor"?

If saturated fat and cholesterol are not the real culprits, then what is? Could the cholesterol molecule be attached to the entity that does the damage, thus misleading physicians and researchers? Approximately 70% of the cholesterol in the lipoproteins of the plasma is in the form of cholesterol esters attached to apo-lipoprotein B.[23] Could this path be the key to intervening in the atherosclerotic process?

First, consider cholesterol's connection with parent LA; i.e., esterified cholesterol. Of dietary cholesterol absorbed, 80%–90% is esterified with long-chain fatty acids in the intestinal mucosa,[24] these being the fatty acids in LDL/HDL cholesterol esters. The majority (about 55%) of the cholesteryl ester component is LA.[25]

Second, it is necessary to know the PEFA (parent essential fatty acids) content of plasma lipids (lipoproteins, triglycerides, and esterified cholesterol) to determine the specific bad actor. It is significant to note that the free fatty acids in human plasma ordinarily are composed of about 15% LA and just 1% alpha linolenic acid (ALA), the parent omega-3 fatty acid, with just 2% docosahexaenoic acid (DHA).[26]

The significant fatty acid throughout is LA, with ALA being significantly less, as shown in Table 1. Derivatives such as DHA are even less significant, so they are not listed.

From a detailed analysis of EFA-derivatives, such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and DHA, it is calculated that the plasma LA content in esterified cholesterol is approximately 50%, with ALA comprising a mere 0.5%, and the ratio of esterified LA/ALA is about 100:1 (Table 1). Importantly, DHA is the most abundant ALA-series derivative in the phospholipids, but even in this class of lipids, DHA comprises only 2.2% of the fatty acids, with LA being a factor 10 times greater.[26] In sharp contrast to the high amounts of n-6 series PUFAs, n-3 series PUFA account for only 1.8% of the fatty acids in triglycerides, 3.5% in the phospholipids, and only 1.7% in cholesterol esters. This high

preponderance of LA is pervasive throughout: the LA/ALA ratio in plasma triglycerides is 17.5:1; n-3 PUFA makes up only 1%–2% of fatty acids in plasma.[26] Even in the brain, LA/ALA uptake is 100 times greater.[27] There is not a significant bodily storage mechanism for ALA. Even significantly raising ALA intake does not cause a significant change in adipose tissue LA/ALA storage ratios.[27]

The LA path is highly relevant for understanding why statins have an NNT of 100—a 99% failure rate. What if the cholesterol structure in the arterial intima contained significant amounts of oxidized or nonfunctional parent omega-6 attributable largely to ingestion of foods containing LA oxidized or otherwise damaged in the course of routine food processing, before any in vivo oxidation? We know that the intima consists of a single layer of endothelial cells containing significant LA, but no ALA.[28,29] Consumed, processed LA deposited in arterial intimal cell membranes leads to abnormal oxidation at the vascular injury site, thus causing injurious inflammation. In this case, abnormal oxidation involves formation of a hydroperoxide from LA. What else could cause LA in the endothelial cells to become oxidized? Could significant amounts of LA already defective from routine food processing transported by LDL-C be the real culprit?

Miettinen et al.[37] discovered that LA and most polyunsaturated fatty acids, specifically AA (a derivative of LA) and EPA, a derivative of the parent omega-3 unsaturated fatty acid ALA, were depleted in patients who had experienced heart attacks. Gerhard Spiteller, who has investigated EFAs and their degradation products—specifically, the influence of these substances in mammalian physiology—concluded that consumption of oxidized PUFA-cholesterol esters is responsible for the initial damage to endothelial cells and that cholesterol oxidation products are incorporated into LDL-C in the liver.[38] LDL carries these toxic compounds into the endothelial walls where they cause cell damage, and thus injury is not caused by an increase in free cholesterol but by an increase in oxidized cholesterol esters.[39]

Spiteller clearly connects CAD with cholesterol esters: In atherosclerotic patients LDL-C is altered by oxidation, and this altered LDL is taken up in unlimited amounts by macrophages. Dead macrophages filled with cholesterol esters are finally deposited in arteries.[38] The fact that LDL is rendered toxic by oxidation raises the question: Which constituents of LDL-C are most prone to oxidation? While cholesterol itself can be oxidized, its rate of oxidation is usually less and is dependent on the presence of other PUFAs and the level of antioxidants.[40,41] Therefore, we stress analysis of cholesterol's esterified component instead—in particular LA, focusing on the LA that has already become oxidized prior to ingestion through processing of foods or overheating. Note that peroxidation of PUFA glycerol esters is enhanced by heating in the presence of air.[39] These insights strongly suggest that a new, non-statin-based approach to the prevention of heart disease should be investigated.

Humans obtain AA either from food, such as meat, or from AA that is derived from LA, if it is not processed and is fully intact (biologically functional). Contrary to the belief of many investigators and physicians, AA is not harmful: AA is the precursor to prostacyclin, the most potent anti-aggretory agent and inhibitor of platelet adhesion.[42] Thus, lowering esterified LA through the lowering of LDL-C by statins (or any other mechanism) will automatically decrease the body's natural anti-aggretory AA. Patient platelet adhesion increases while natural antiplatelet activity decreases, increasing the risk of thrombosis.

Furthermore—again contrary to widespread belief—the body's most powerful natural anti-inflammatory agent, prostaglandin PGE_1, is a parent omega-6 derivative, unlike PGE_3 from omega-3, which is much weaker. If functional LA bioavailability is lowered, the potential for inflammation rises, which leads to atherosclerosis. Weiss, for example, has noted that PGE_1 reduces the fibrin deposition associated with the pathogenesis of atherosclerosis.[43]

Since LA is an essential fatty acid, the form in which it is ingested is critical. In the past several decades, processed foods—in particular, frozen foods and restaurant cooking oils—have increasingly incorporated trans fats and other unhealthy fats and oils. Moreover, when heated in air, the LA in these oils changes to hydroperoxides, which are biochemically damaging to the body. This results in less functional LA for incorporation into cell membranes[44,45] and subsequent conversion into important AA. (Omega-3-containing oils, such as flax seed oil and fish oil, are not routinely used by food processors because they are far too unstable.)

If there is a deficiency of fully functional LA in the diet, the body will substitute into cell membranes a nonessential fatty acid, such as oleic acid (omega-9) found in olive oil.[47] This forced substitution results in a marked decrease of cellular oxygen transport with adverse effects on cellular metabolism and function,[47] including possible chronic hypoxia in the heart leading to potential myocardial dysfunction.

LDL-C, the transport vehicle for PEFA delivery into the cell, will transport any kind of LA—defective or not—into cells, including oxidized or trans entities. So, while statins do reduce the amount of LDL-C, thereby automatically reducing the amount of nonfunctional parent omega-6 from processed food that reaches cell membranes, they simultaneously lower the transport of vital oxygenating functional PEFAs into cells.[48] In fact, over a 24-week period in which patients were given 40 mg daily of simvastatin, mean serum *parent* omega-3 levels dropped 34%, and *parent* omega-6 levels dropped 28%; both highly significant amounts.

In addition, statins also significantly lower coenzyme Q10 (CoQ10)[49] (known as ubiquinone), causing endothelial dysfunction, a precursor of atherosclerosis.[50] Therefore, artificially decreasing LDL-C is harmful for a number of reasons.

High-Density Lipoprotein Cholesterol

Another part of the "cholesterol is bad" theory says that while high levels of LDL-C are "bad," high levels of HDL-C are "good." This is incorrect and has no biochemical, physiological, or clinical basis.[51] Attempts to raise HDL levels using the drug torcetrapib with or without the presence of atorvastatin were very successful: 120 mg of torcetrapib daily increased plasma concentrations of HDL-C by 61% and 46% in the atorvastatin and non-atorvastatin cohorts, respectively. Torcetrapib also reduced LDL-C levels by 17% in the atorvastatin cohort.[52] This trial, which began in 2004 and was scheduled to run until 2009 with 15,000 patients, was prematurely terminated since excess mortality started to appear (82 deaths in the torcetrapib group versus 51 deaths in the control group). Patients taking torcetrapib also were more likely to experience heart failure.

The failure of torcetrapib should not have been a surprise. Years before the start of this trial, researchers studied the HDL transport mechanism in mice through gene knockout studies. With no HDL transport, many physicians thought that atherosclerosis would substantially increase, because the concepts current at the time

supported a key role for reverse cholesterol transport (from the periphery to the liver), with defects in the HDL-mediated process contributing to the development of atherosclerotic plaques. This proved to be untrue. Indeed, investigators found that mice lacking HDL did not show impaired hepatobiliary transport, and they concluded that HDL plays little or no role in that process.[53] In commenting upon the work of Haghpassand et al.[54] published in 2001, Tall et al.[55] noted that these findings support the authors' conclusions that HDL plasma levels do not control net cholesterol transport from the periphery, and therefore also call into question the accepted view of reverse cholesterol transport.

Another investigation of the data contained in two previous studies (the IDEAL[56] and EPIC[57] studies) to assess the relationship between HDL-C, HDL particle size, apo-lipoprotein A-1 (ApoA-1, the principal protein in HDL particles), and CAD found that high levels of plasma HDL-C and large HDL particles were associated with an increased risk of CAD when ApoA-1 and ApoB were kept constant in regression analyses[58]—the opposite of what was predicted. In an accompanying editorial, Genest[59] noted that as a therapeutic goal, raising HDL may be fraught with danger, and that no unequivocal data existed showing reduction in cardiovascular risk from pharmacologically increasing HDL-C.

Finally, it is important to understand that the "bad cholesterol" theory and the proliferation of statin use are rarely examined in the context of the vast increase in metabolic diseases we have today. These have been termed "metabolic syndrome," characterized by type 2 diabetes, obesity, and dyslipidemia. In healthy individuals, there is a balance of both pro- and anti-inflammatory cytokines that maintain homeostasis. However, in individuals with such metabolic disorders this balance is upset, resulting in increases in the cyclo-oxygenase (COX) and lipoxygenase (LOX) enzymes, excessive proinflammatory cytokine production, and systemic inflammation leading to CAD and atherosclerosis.[60-63] There is no doubt that Western diets, which feature physiologically improper protein:fat:carbohydrate ratios skewed toward problematic high carbohydrate intake,[22] and supraphysiological omega-6:3 ratios (10:1 to 15:1),[64-67] with significant nonfunctional LA from processed food, are responsible for this pathological situation.

Limited Benefits vs. Substantial Risk

Except for a very small and insignificant minority of patients, simultaneously lowering LDL-C and raising HDL-C does not endow any benefit. Statins do possess some anti-inflammatory activity, which is most likely associated with COX suppression. However, this effect is marginal, given the adverse side effects of statin therapy. This is likely why statin treatment can cause patients to die more often and experience more adverse cardiovascular events.

In addition, serious side effects are seen in 15%–20% of patients. These include peripheral neuropathies, myopathies, and muscle pain. Severe side effects are not new with statin use. In August 2001 Bayer pulled cerivastatin (Baycol) off the market because of fatal rhabdomyolysis (a condition that results in muscle cell breakdown and release of the contents of muscle cells into the blood). All statins carry this risk. Furthermore, a recent study showed a significantly increased risk of cancer with statins.[68] As we have previously discussed,[69] this is likely the result of lower bioavailability of fully functional LA induced by statins. Brain physiology can also be significantly altered because of the alteration of lipid rafts.[70-72]

Finally, studies of lower doses of statins (just 10 mg to 20 mg), have demonstrated that the incidence of peripheral neuropathy can increase by as much as 14-fold compared with non-use.

Practice Guidelines vs. the Evidence

Most caring and conscientious physicians do have a strong desire to practice medicine based on sound scientific evidence. At the present time, the strong economic-driven pressures of the pharmaceutical industry have caused physicians to abandon such true and valid scientific principles and to prescribe statins because of what appears to be expert consensus.

With its 25 member organizations, the current National Heart, Lung, and Blood Institute's (NHLBI) National Cholesterol Education Project (NCEP)[73] Guidelines for Physicians make it difficult for physicians not to use statins because of the NHLBI's mandate that lowering LDL-C is "the primary target of therapy," as well as its recommendations of the ubiquitous so-called heart-healthy diet, focusing on dietary carbohydrates ("50%–60% by calories"). These misguided dietary recommendations actually raise LDL-C.[22] Also, the NCEP states in its program description: "From its inception, the NCEP has based its recommendations and messages firmly on sound scientific evidence." It also states: "A series of recent clinical trials that used cholesterol-lowering drugs called 'statins' has provided conclusive evidence that lowering the level of low-density lipoprotein (LDL) cholesterol, the 'bad' cholesterol, dramatically reduces heart attacks and CHD [coronary heart disease] deaths as well as overall death rates in patients with or without existing CHD."[74]

These statements are not true. The "sound scientific evidence" is far from "conclusive" (as this paper details) and is diametrically opposed to physiologic mechanisms. Lowering LDL-C does not "drastically reduce" heart attacks, CHD deaths, or total death rates. If these incorrect, outdated recommendations are not remedied, modifying wrong surrogates through statins will continue to produce deplorable outcomes, i.e., an NNT of 67—at best—a 98% clinical failure rate. Fortunately, the executive committee gave physicians the last word in patient therapy with the page 1 executive summary statement: "It should be noted that these guidelines are intended to inform, *not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual*" [emphasis added].[73] This allows the physician, at the very least, an alternate, science-based protocol of supplementing statins with a physiological, fully functional LA/ALA supplement.

In light of the current evidence, a physician can now feel well justified and scientifically secure in not prescribing statin treatment for either primary prevention or treatment after a cardiovascular event. It should be recalled that in first approving statin therapy, the FDA intended that the drugs were only to be prescribed when other "lifestyle (diet and exercise) modifications" had failed to demonstrate benefit. Indeed, FDA approval of statin therapy is still predicated on the failure of such nutrition and lifestyle changes, especially the low-fat, high-carbohydrate diets invariably recommended.

We also now know that the term "benefit" must be more strictly and precisely defined. In truth, one must demonstrate a meaningful reduction in cardiovascular events and all-cause mortality rather

than presuming benefit in simply lowering the surrogate "numbers" in an artificially constructed model of the LDL/HDL cholesterol scheme—all of which appears to have very little relevance to the pathophysiology of cardiovascular problems

Conclusions

In summary, while it is important to elucidate the mechanisms involved in atherosclerosis, especially in regard to today's many metabolic diseases, this should not be undertaken with the idea that developing different statins or endless, expensive, and novel inhibitors of key enzymes is the answer. In our opinion, the new path to CAD prevention lies first in solving the defective esterified LA issue by effective supplementation.

Next, changes to diet and nutritional lifestyle must be implemented, to achieve a better balance of protein and natural unprocessed fats, and a much lower intake of carbohydrates.[22] This requires less consumption of processed foods that contain trans fats and oxidized fats.

No longer can physicians conclude that their patients will thrive using statins. The overwhelming evidence demonstrates the best medical advice is to caution patients on the tremendous limitations of statins; specifically, that when 67 patients are treated with a statin protocol over 5 years, 66 patients will experience no benefit—a 98% failure rate. As dismal as this number is, it does not take into account the substantial additional risks associated with prolonged statin usage.

Brian S. Peskin, B.Sc., is chief research scientist at Cambridge International Institute for Medical Science (www.CambridgeMed Science.org). **David Sim, M.D., F.A.C.C.** practices internal medicine and cardiology in Boise, Idaho. **Marissa A. Carter, Ph.D., M.A.,** is president and co-founder of Strategic Solutions, Inc., which is engaged in collaborative medical research, including evidence-based medicine, cost-effectiveness studies, nutrition, and wound care/burns, in Cody, Wyo. Contact: Brian Peskin, P.O. Box 56507, Houston, TX 77256. Tel.: (713) 298-8783. E-mail: prof-nutrition@sbcglobal.net.

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