Exercise and Cardiovascular Disease

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Vytorin Failure Explained – A New View of LDL

by Brian Scott Peskin, BSEE with David Sim, MD

During the last half of the 1990s, almost half of all Americans and Europeans died of heart disease.[1] In 2006, atherosclerotic coronary artery disease (CAD) became the number one killer of Americans, with cancer running a close second. These statistics suggest that by 2010, virtually all American deaths will be either from heart disease or cancer. We will soon discover the common link between both diseases. However, if we go back in time, heart disease and cancer deaths did not always present such a dismal picture. In the nineteenth century, heart disease was much rarer, and even during the period 1910-1920, in the wards of the Massachusetts General Hospital, coronary heart disease was considered rare.[2] As the decades passed, a variety of factors were suggested as the culprits, including the Western diet, and by the late 1970s, cholesterol was considered to be one of the primary bad actors in heart disease. This in turn led to the development of many pharmaceutical interventions and, more recently, the statin family of drugs.

Lowering LDL-Cholesterol (LDL-C) by Statins Called into Question

The clinical failure of the drug Vytorin – the ENHANCE trial – prompted what is being called the "Statin Scandal." Unless you had no access to the broadcast and print media, you have heard about it.[3] Statins are sold by Merck (Mevacor and Zocor), AstraZeneca (Crestor), Bristol-Meyers Squibb (Prevachol), and Pfizer (Lipitor) – the latter being the world's best-selling drug. Vytorin is a formulation that combines the statin Zocor (generic name simvastatin) with another cholesterol-lowering medication called Zetia (a non-statin cholesterol absorption blocker with the generic name ezetimibe), co-marketed by Schering-Plough and Merck. The ENHANCE trial demonstrated that the mean change in the intima-media thickness (IMT) between the effect of Zocor alone and Vytorin (simvastatin and ezetimibe) in their respective groups was 0.006 vs. 0.011 mm. As you might have guessed, there was no statistically significant difference. IMT is a measure of the thickness of artery walls. IMT is considered a descriptive general index of – and a surrogate for – how much plaque has built up, i.e., atherosclerosis, and a *strong predictor of future myocardial infarction*.

Unfortunately, the pace at which *artery-clogging plaques* formed within vessels *almost doubled in patients taking the combination*, compared to those taking Zocor alone. The combination drug's effectiveness was worse, not better than the single drug – a big, unexpected failure. Furthermore, over the two years of the study, even though there was improvement in the LDL cholesterol levels, there was no significant difference in these drugs' ability to slow the growth of plaque in carotid arteries supplying blood to the brain. Now many clinical cardiologists are in a quandary about how to proceed. *Medical News Today* had this to say on January 18, 2008:[4]

- "Patients have begun 'swamping' physician offices to ask whether they should end treatment with the cholesterol medication Vytorin, co-marketed by Merck and Schering-Plough, after a recent study found the treatment *no more effective* than a treatment available in generic form in the prevention of accumulation of plaque on artery walls...
- "... Patients and many physicians are caught in the controversy, uncertain what course to take....
- "[A]lthough the theory that lowering cholesterol is always beneficial has been a core principle of cardiology for decades, now some prominent cardiologists say the results of the study and other research have raised serious questions about the theory."

After learning of Vytorin's failure, it took Merck and Schering-Plough an inexplicable 20 months to release the news to the medical community. The medical community, including clinical cardiologists, was outraged. Allen J. Taylor, head of cardiology at Walter Reed Army Medical Center,[5] stated, "[S]pending so long trying to clean up the data was not appropriate." Harlan Krumholz, a cardiologist at Yale University, said, "By the

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Vytorin Failure

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summer of 2005, Vytorin was already a blockbuster drug. There was only downside [to analyzing the results]."[5] A *Wall Street Journal* article entitled, "Vytorin Makers Try to Explain Timeline,"[6] stated the following:

> But critics said that despite the recounting, they didn't fully understand why the companies spent so long working on the data. **They said the affair shows the problems that can arise when corporate sponsors, rather than independent academic investigators, control how a study is run**. The trial was completed in April 2006, but the companies didn't disclose the disappointing results until Jan. 14 of this year [2008]. **During that time, combined annual sales of Vytorin and a sister drug, Zetia, grew to more than $5 billion** [emphasis added].

Could the pharmaceutical companies have withheld this information showing the drug's failure because they understood the devastating effect this release would have on their corporate profits?

Even politicians are calling for action. In the *Wall Street Journal* article, "Drug Companies Face Political, Scientific Attacks," Michigan Democratic Rep. Bart Stupak stated[7]: "We see puffing, advertising based on untrue facts or facts that can't be substantiated, medically, ethically, or legally."

JAMA Editor-in-Chief Outraged

Catherine DeAngelis, Editor-in-Chief of the *Journal of the American Medical Association* (*JAMA*), has said that she has more articles on the drug industry's role in research coming soon: "I want to show how they *manipulate the data* and why we *have to be so cynical* about them."

Life Systems Engineering Science analysis: When the editor-in-chief of one of America's top medical journals (*JAMA*) goes on the record with "... they manipulate the data..." and "... why we have to be so cynical about them," what are physicians to believe? The answer is: believe the science. Manipulated studies are frequent marketing tools of pharmaceutical companies, predestined to show favorable outcomes. Below, we will show the science that explains precisely why the statins' lack of effectiveness is predictable, along with a simple solution to get both patients' *and* their physicians' cardiovascular systems back in balance.

Physicians may have to re-evaluate the omnipresent statin recommendation. *BusinessWeek's* cover story of January 17, 2008, titled, "LIPITOR: For Many People, Cholesterol Drugs *May Not Do Any Good*,"[3] quotes James M. Wright, MD, university professor and Director of Canada's Therapeutic Initiative, whose purpose is to analyze the data on particular drugs and decide if they really work. Dr. Wright found the following:

> **...No benefit in people over the age of 65, no matter how much their cholesterol declines**, and **no benefit in women of any age**.... He did see a small reduction in the number of heart attacks for middle-aged men taking statins *in clinical trials*. But even for these men, there was **no overall reduction in total deaths or illnesses requiring hospitalization – despite big reductions in "bad" cholesterol**. "**Most people are taking something with no chance of benefit and a risk of harm**," says Wright [emphasis added].

The *BusinessWeek* article continues with how physicians and their patients can be misled: "Data suggest that *for patients without heart disease,* only one in 100 [a *99% failure rate*] is likely to benefit from taking statins *for years*."

Many physicians prescribe statins and cholesterol-lowering drugs prophylactically, hoping to ward off a future heart attack. As the same *BusinessWeek* article makes clear:[3]

> ...**[M]any researchers harbor doubts about the need to drive down cholesterol levels in the first place**. These doubts were strengthened on Jan. 14 [2008] when Merck and Schering-Plough revealed results of a trial with the combination [statin Zocor + non-statin Zetia]. This combination did succeed in driving down patients' cholesterol further than with just the statin alone. **But even with two years of treatment, the *further reductions brought no health benefits*** [emphasis added]**.**

How can so many physicians think statins are required for virtually everyone when the reality is considerably different? The answer lies in the statistics term NNT (number needed to treat). This is an essential number necessary to properly evaluate a drug's effectiveness, and quite often, this is a number that pharmaceutical companies overlook when pitching their "latest and greatest drug" to trusting physicians.

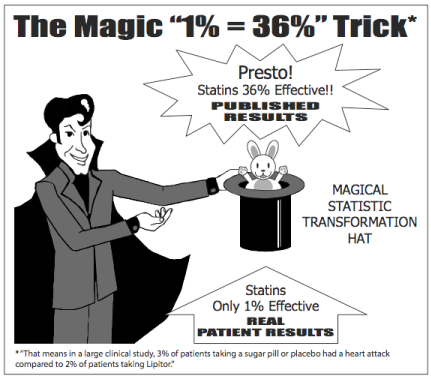
Surprise: *NNT* is What Counts – Not Misleading "Endpoint" Statistics

Many physicians are misled because they have no idea the pharmaceutical companies are allowed to massage statistics. Pharmaceutical companies shockingly, yet legally, get to remove the sample size. When is one patient event *in a million* (drug) *compared to* two patient events *in a million* (placebo) equal to *50% improvement* instead of the statistically correct 1 in 1,000,000 or 0.0001%? Answer: with the fanciful "*pharmaceutical endpoint method*," also termed "relative risk."[8] You will often see the statement, "Lipitor reduces the risk of heart attack by 36% ... in patients with multiple risk factors for heart disease," quoted in drug ads, such as the one on television featuring Dr. Robert Jarvik, inventor of the Jarvik artificial heart. In newspaper ads, the 36% comes with an asterisk (*) saying, "That means in a large clinical study, 3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor."

Life-Systems Engineering Science analysis: The real measure of difference in heart attack risk, the TRUE EFFECTIVENESS, is the difference in events: 3% – 2% = 1% – NOT calculated as (3% – 2%)/3% = 33%, such as the drug companies use and want you to believe. **Shockingly, there is only a miniscule one-percent difference in effectiveness**

between the results with Lipitor and the results with a placebo. This difference is termed *absolute risk* and correctly takes into account sample size like any valid statistic does. This leads to the definition of NNT. In the case of statins, this number is 100 (the reciprocal of the absolute risk). No, this "100" isn't a perfect score; quite the contrary, it is an awful score. It means that to see a positive effect in just one patient, one hundred patients have to be treated. Therefore, *99 out of 100 patients will see no positive effect*. Other medical researchers are convinced that the real NNT in a standard *mixed* population, such as the typical patient a physician treats for CAD, may be closer to 250. Even assuming the lower 100 NNT figure, this is even more problematic for statins' performance because 10% to 15% of statin patients experience negative side effects, including sexual dysfunction, muscle aches – prominently mentioned on Lipitor's label – and significant cognitive problems, including loss of memory.

Pharmaceutical Slight of Hand: "1% = 36%"



Dr. Nortin M. Hadler, Professor of Medicine at the University of North Carolina at Chapel Hill and a long-time drug industry critic, states, "Anything over an NNT of 50 is worse than a lottery ticket; there may be no winners."[3]

To grasp the magnitude of the problem, let's compare NNTs. Antibiotics commonly have an NNT = 1.1. When 11 people are given antibiotics, ten patients are cured of the problem for which the antibiotics were prescribed. Contrast this with statins, where 100 patients are given the drug and one person is helped; NNT = 100.

How to Sell a "Blockbuster" Drug, Regardless of Performance? Lots of Money

Only America and New Zealand allow "direct-to-consumer" pharmaceutical advertising. **One hundred fifty million dollars (US) was the advertising budget to turn Vytorin into a blockbuster.** That's right; an incredible $150,000,000.[9] It's more marketing than science, since in this case the combination drug had no greater effectiveness than the single component drug. By "suggesting" lower and lower LDL blood cholesterol levels, doctors mark the average patient's cholesterol as automatically "too high," and they become "pharmaceutical patients for life." Both Zetia and Vytorin prospered because physicians believe that lowering LDL was all that mattered. Drug companies spent the prior decade convincing everyone that critical LDL cholesterol was "bad." Nothing could be further from the truth as you shall soon discover. But first, we need to explore PEOs – Parent Essential Fatty Acids.

Parent Essential Oils (PEOs): An Essential Difference

The term "essential fatty acids" (EFAs) is so frequently misused that I was compelled to coin a new term, "parent essential oils" (PEOs). There are only two essential fats that the human body demands, both of which occur in nature: parent omega-6 linoleic acid (LA) and parent omega-3 alpha-linolenic acid (ALA). The term parent essential oils (PEOs) refers to the *primary unadulterated forms* of these two essential fats. Adulteration occurs through man-made processes like hydrogenation (where a trans structure is created), interesterification, oxidation by exposure to air, etc.

A Hidden Solution: The PEO Metabolic Pathway

Statins were created to lower cholesterol in the body – specifically, low-density lipoprotein known as LDL-C – and today are credited by the medical establishment with saving lives. What is little known, however, is that statins have anti-inflammatory properties that could be beneficial in treating atherosclerosis unrelated to the lowering of LDL-C. Some of these recognized and potential properties are very similar to the action of essential fatty acids (PEOs), as detailed in a review published in 2001:[10]

> Statins and polyunsaturated fatty acids have similar actions.... In view of the similarity of their actions and that statins influence essential fatty acid metabolism, it is suggested that EFAs [PEOs] and their metabolites may serve as secondary messengers of the action of statins....

We will explore this exciting topic shortly, but first let's continue with the pathophysiology of thrombosis (blood clots forming in arteries) and artery-clogging plaque.

The Unpublicized Role of Adulterated Parent Omega-6 in Plaque and Thrombosis

For decades, saturated fat was believed to be the cause of arterial plaque. Many physicians still think this is true. However, a landmark article published in *The Lancet* over a decade ago, in 1994, challenged this belief.[11] Investigators analyzed plaque and found it contained more than ten different compounds, none of which consisted of saturated fat.[11] This, and other independent analyses by analytical techniques have *confirmed a lack of saturated fat in any arterial plaque*.[12,13] In spite of these published findings over a decade ago by *The Lancet*, the world's most prestigious medical journal, most physicians will still tell you to avoid saturated fat in your diet, and the layman will unquestionably be even less well-informed than the physician.

Cholesterol was found in the plaque, but as we shall soon see, this is likely a normal physiologic

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response to vascular injury or inflammation. Analysis published in a 1997 study showed that cholesterol esterified (combined) with *adulterated* (oxidized) parent omega-6 was by far the most abundant component in the clogged artery (stenosis). Even more important was the conclusion that *rupture of the plaque* – which can lead to clinically devastating results such as thrombosis and vessel occlusion and the potential for myocardial infarction and stroke – was due to *oxidation of the parent omega-6* portion of the esterified cholesterol:[14]

- "**Cholesterol esters are the predominant lipid fraction in all plaque types**...
- "Intimal [innermost arterial lining] macrophages contain *substantial amounts of cholesterol esters*, which are rich in PUFAs.
- "Both [Polyunsaturated Fatty Acids] PUFAs and cholesterol may form *oxidized derivatives that are toxic to most types of arterial cells*.
- "The reduced proportions of omega 6-PUFAs and total PUFAs at the edge of disrupted plaques compared with the center may reflect oxidative damage. **Such damage to PUFAs,** particularly at the edge of disrupted plaques, **where *concentrations of omega 6-PUFAs are greatest***, may promote connective tissue degradation and *influence the prevalence of disruption at this site*. Both PUFAs and cholesterol oxidation products have been detected in the human arterial wall. These are toxic to most arterial cells and to macrophages, in particular, and may provide a milieu for connective tissue degradation" [emphasis added].

How to Keep Plaque From Rupturing

Life Systems Engineering Science analysis: Adulterated parent omega-6 and parent omega-3 EFAs initially were functional PEOs (pure, unadulterated parent omega-6 and omega-3 EFAs), but were altered during commercial food processing. While the food processor was successful in extending the shelf-life of its product, it unknowingly did so by changing the chemical structure of the oils. As we shall see, this alteration of biochemical structure creates a structure that is functionally inadequate in its critical physiologic role of allowing oxygen through the cell wall. Foods containing defective PEOs extensively used by fast-food restaurants are unwittingly consumed by millions of people daily.

Drug/pharmaceutical-financed investigators/researchers with a vested interest in statins likely chose to ignore this information, focusing instead on the simplistic cholesterol hypothesis. Their party-line mantra is, "If cholesterol is present in plaque, then it must be 'bad.'" However, nothing could be further from the truth. Cholesterol by itself is not bad; it is essential for life.

All cells contain cholesterol, and all tissues can manufacture and regulate it. Bones would be hollow without it; cholesterol has a major structural role in the brain and is required in high concentrations; cholesterol enables nerve impulses to transmit; it enhances the permeability barrier properties of the cell's lipid bi-layer; vitamin D manufacture requires cholesterol; bile is manufactured by the liver from cholesterol and is essential for proper fat digestion; and cholesterol protects the skin against absorption of water-soluble toxins and holds moisture in so the organism doesn't dehydrate. In addition to being the precursor for dozens of steroids that the body needs such as testosterone, progesterone, and estrogen,[14] cholesterol also helps preserve the integral structure of cell membranes.

Instead of considering the oxidized, adulterated, omega-6 PEOs attached to the cholesterol as the culprit, most researchers apparently decided that if they could lower the entire LDL cholesterol entity, a.k.a., "bad" cholesterol, then less of the "bad" stuff would end up in arterial plaque, and fewer people would have heart and vascular disease. So with *only partial understanding of the problem*, they promoted statins. **Designating LDL as "bad," because a drug was found that could reduce it, and then calling HDL "good" by default was brilliant *marketing*. Unfortunately, this "good/bad" designation is scientifically absurd. Neither statement is biochemically correct.**

In fact, research published over ten years ago in the *Journal of the American Medical Association* (*JAMA*) concluded that low cholesterol, by itself, did not significantly prevent heart disease in persons older than 70 years, a population that would quickly experience its benefits *if* cholesterol lowering in and of itself was beneficial.[16] A British study published in 1993 had similar conclusions:[17]

- *"Blood cholesterol by itself is a poor predictor* of individual risk of coronary heart disease.
- *"Few people* identified purely on the basis of cholesterol levels *will benefit from treatment* [cholesterol-lowering drugs]..."

These and other poor outcomes prompted several recent published reports in medical journal articles that explore potential misconceptions surrounding LDL cholesterol. For example, the contention that LDL cholesterol is "bad" cholesterol was challenged as being overly simplistic and scientifically untenable, because results from numerous clinical trials, including ENHANCE, failed to demonstrate that merely lowering LDL cholesterol prevented cardiovascular disease or increased longevity.[18] Other studies also showed that the measurement of apolipoprotein B is both a better predictor of adverse cardiovascular events and a more accurate index of residual CAD risk.[19]

Physiologic Importance of Cholesterol

It can't be stressed enough that cholesterol, including LDL cholesterol, is critical in the production of the hormones estrogen, progesterone, and testosterone,[15] in keeping our skin water- and chemical-resistant, in

manufacturing bile salts for digestion of fats, in forming our bones, and in delivering fatty acids containing lots of PEOs to all of our 100 trillion cells.[20] While free cholesterol does exist in the body, 80-90% is esterified, termed cholesteryl, or chemically bound to a fatty acid, with a strong preference given to parent omega-6 linoleic acid, as shown in Figure 1, in which R represents the hydrocarbon portion of the fatty acid.

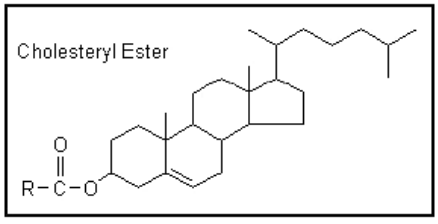

Figure 1: Cholesteryl Ester

There is very little parent omega-3 transported – approximately three percent compared to 80-90% of parent omega-6, because little parent omega-3 is used in tissue (please see Table 2). The cholesterol-PEO connection will be detailed shortly. But first, we must examine cholesterol's structure and discover some little-publicized facts that physicians and researcher investigators need to know.

The *Structure* of Cholesterol Itself *Never* Changes – What Cholesterol *Carries* Does

Cholesterol *structure never changes* whether it be LDL or HDL; only the esterified component, the hydrocarbon portion (R) of the ester group (COOR) varies. Cholesteryl esters are transported throughout the body in lipoprotein particles (Figure 2) that are classified according to the ratio of protein to fat, or more simply, the density of the particle, in the following increasing order: chylomicrons, very low density lipoprotein, intermediate density lipoprotein, low density lipoprotein (LDL), and high density lipoprotein (HDL).[15] *Esterified* cholesterol comprises the majority of LDL, and LDL plays a vital role in the human body. Research studies reported in medical and biochemical journals and textbooks confirm that LDL contains up to 80% lipid, including polyunsaturated fatty acids and cholesterol, predominantly in the form of esters.

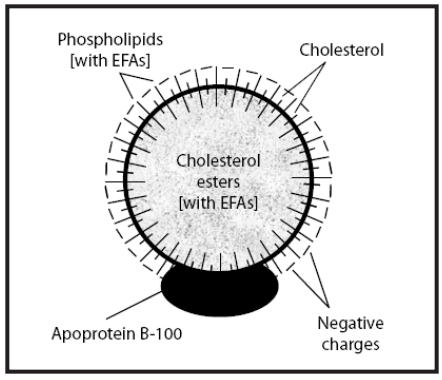

Figure 2: Structure and Composition of a Low-Density Lipoprotein
(*Textbook of Medical Physiology*, p. 874, *Courtesy W.B. Saunders*)

One of the most abundant fatty acids in LDL is linoleic acid, parent omega-6.[21] Removing or considerably lowering the level of LDL cholesterol not only rids the body of valuable PEOs[22] – in particular, parent omega-6 – but also impairs the body's mechanism for removing oxidized fatty acids. These are key points to understand.

Oxidized Cholesterol Insignificant – *Esterified* Parent Omega-6 Is the Problem

As Figure 1 details, the cholesterol structure itself is hard to oxidize. However, Figure 2 shows the substantial amount of *esterified* cholesterol, mainly parent omega-6. Each molecule of cholesterol carries one molecule of parent omega-6, and many of them can be defective. Therefore, this is the significant area of importance.

Vytorin Failure

Critical Information: PEOs and Their Derivatives

Once either PEO, essential LA, or essential ALA is consumed in food, the human body changes only five to ten percent of these parent forms into derivatives as described below.[23-25] From both a scientific as well as a biochemical perspective, referring to these derivatives as "essential fatty acids" or "EFAs" is *incorrect*, because the body has the ability to make them as needed from PEOs. There are a host of products being marketed to physicians and the public as EFAs, which are, in fact, *non-essential* omega-6 and omega-3 derivative-based oils. Among these are eicosopentaenoic acid (EPA), docosahexaenoic acid (DHA) from parent omega-3, and gamma linolenic acid (GLA) from parent omega-6. Fish oils, widely marketed as EFAs, for example, are made up of almost exclusively omega-3 derivatives. Consuming fish oil and other health food store "EFAs" in recommended quantities can also lead to pharmacological overdoses, which can be harmful. (Please see www.CambridgeMedScience.org: "Scientific Calculation of the Optimum PEO Ratio.")

Surprising Tissue Requirements of Parent Omega-6 Versus Parent Omega-3

Many physicians and health care professionals and advisors are unknowingly overdosing their patients on parent omega-3 from flax oil or omega-3 derivatives from fish oil. Tissue analysis clearly shows how much more parent omega-6 the body contains than parent omega-3 (Table 1).[26-28]

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Table 1: Ratio of Tissue Composition

Tissue	Omega 6 PEO	to	Omega 3 PEO
Brain/Nervous System	1	:	1
Skin*	1000	:	1
Organs and Other Tissues	4	:	1
Adipose Tissue (bodyfat)	22	:	1
Muscles	6.5	:	1

*There is virtually NO omega-3 in skin tissue.

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Next, we need to know the percentage of total body weight of each organ/tissue (Table 2). This analysis surprises many physicians.

Table 2: Ratio of Tissue Composition

Tissue	Total Body Weight (%)	Omega-6 PEO	to	Omega-3 PEO
Brain/nervous System	3	1	:	1
Skin	4	1000	:	1
Organs and other tissues	9	4	:	1
Adipose tissue (body fat)	15-35	22	:	1
Muscles	50	6.5	:	1

Most parent omega-6 found on supermarket shelves and in processed foods is highly processed and therefore adulterated or defective. The parent omega-3 available in food isn't usually processed, however, because it can't be used in frying or food processing – it is far too reactive. Most EFA recommendations unknowingly cause overdose of parent omega-3 and its derivatives without addressing the significant amounts of *adulterated* parent omega-6 most people ingest. This excess of omega-3 and its derivatives, as well as of adulterated omega-6, coupled with insufficient omega-6 PEOs (*un*adulterated parent omega-6 EFAs) in diets, needs to be corrected by supplying pure omega-6 to a far greater degree than most physicians realize. (For further details, please see "The Scientific Calculation of the Optimum Omega-6/3 Ratio," available at www.brianpeskin.com/specialmedreports.html.)

Nature's *Natural* Statin: Omega-6 Series Prostacyclin and PGE_1

Humans obtain the omega-6 derivative arachidonic acid (AA) either ready-made in food, such as in meat, or derived in the body from parent omega-6, if it is unadulterated. Contrary to conventional wisdom, AA is not harmful: it is the precursor to prostacyclin – the most potent anti-aggretory agent (natural anti-clotting agent) and inhibitor of platelet adhesion.[29] AA from parent omega-6 (LA) contributes to smooth working of vascular function and increased blood flow. AA provides eicosanoids for response to injury – acting as a healer – helping to heal vascular injury.[13]

Lowering esterified LA through the lowering of LDL cholesterol automatically decreases the body's natural anti-aggretory AA. The body will produce the AA it needs *if* it receives the substrate, parent omega-6 (LA), in sufficient amounts in unadulterated form, although statins adversely impact this biochemical pathway because substrate esterified LA is reduced. Therefore, *through use of statins, patient platelet adhesion increases and natural anti-platelet activity decreases, increasing thrombosis* – horrific outcomes.

Furthermore, **the body's most powerful natural anti-inflammatory, prostaglandin PGE_1, is a parent omega-6 derivative**. If you lower the functional parent omega-6, you increase the potential for inflammation, which leads to atherosclerosis – another horrific outcome.

German physician Claus Weiss, MD, et al. states in *Prostaglandins, Leukotrienes and Essential Fatty Acids* (November 2000; 63 (5): 271-277):

> In summary, infusion *therapy with PGE_1* in patients with peripheral arterial occlusive disease (PAOD) *reduces thrombin formation* and results in a *decrease of fibrin degradation*. PGE_1 may thus *reduce fibrin (thrombosis) deposition involved in the pathogenesis of atherosclerosis*.

Food Processing Adulterates the Majority of Parent Omega-6

Over 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. This has resulted in the availability of much lower amounts of functional parent omega-6 (LA) for incorporation into cell membranes[30,31] and, as we have seen, subsequent conversion into arachidonic acid (which is a source of many crucial prostanoids and leukotrienes used in inflammatory, immune, and signaling functions).

One of the important characteristics of cell membranes is their fluidity, which results from local disordering of the bilayer induced by the *cis* double bonds of unadulterated unsaturated fatty acids (PEOs).[32] Membrane fluidity increases when more PEOs – in particular, functional linoleic acid (LA) – are available to be incorporated into the membrane lipid bi-layer. When natural PEOs are replaced by nonfunctional omega-6-based *trans* fats, the fluidity is reduced, and that can lead to significant reduction in critical cellular oxygen transfer, with potential adverse physiologic effects leading to heart disease.

Even when margarine and other hydrogenated products contain relatively few trans fats – as little as one to two percent – this translates to $1x10^{21}$ (1 billion trillion) molecules of trans fat per tablespoon of oil (please see "The Scientific Calculation of the Optimum Omega-6/3 Ratio," available at www.brianpeskin.com/specialmedreports.html). Therefore, the potential to cause great damage, either integrally in the cellular structure or in biochemical reactions, is highly significant, since many of us consume much more than just a single tablespoon of processed oil each day!

Lack of PEOs = Lethal Substitution with Inferior Oils

If there is a deficiency of unadulterated PEOs in the diet, the body will substitute a non-essential fatty acid, such as oleic acid found in olive oil, in cell membranes, causing physiologic malfunction.[33]

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Unwanted Side-Effect: Statins Lower Essential PEOs Destined for Tissues

Because LDL cholesterol is the transport vehicle for PEO delivery into the cell, LDL cholesterol will transport properly functioning (unadulterated) LA from natural sources, such as walnuts, almonds, Brazil nuts, sunflower seeds, or their unprocessed cooking oils, into the cells *along with adulterated* fatty acids already damaged by food processors. This adulterated parent omega-6 is recognized as playing a prominent role in the pathophysiology of atherosclerotic plaque formation. So, while statins do reduce the amount of LDL cholesterol, thereby automatically reducing the amount of adulterated parent omega-6 from processed food that reaches cell membranes, at the same time, they lower the transport of vital oxygenating unadulterated PEOs into cells.[22]

Statins are known to lower serum levels of PEOs. Over a 24-week timeframe, when patients were given 40 mg daily of simvastatin (generic Zocar), mean serum PEO levels dropped by a staggering 34% (omega-3) and 28% (omega-6).

Life Systems Engineering Science analysis: At baseline, the researchers measured serum LA/ALA ratios to be 54:1, meaning there is 54 times more parent omega-6 than parent omega-3 in serum. If a substantial amount of the parent omega-6 is adulterated, the potential for disaster is obvious.

Another reason for the ineffectiveness of statins to stop atherosclerotic cardiovascular disease is that *statins can't eliminate enough of the defective parent omega-6 EFA that is being transported in LDL esterified cholesterol*.

Failure Again: Another Statin Trial Failure in 2007 (METEOR Trial)

Evidence from the 2007 METEOR trial showed that although Rosuvastatin lowered cholesterol and halted progression of atherosclerosis, patients in the treatment group continued to experience significant cardiovascular events, including heart attack and angina.[34] This finding of the 2007 METEOR trial, coupled with Vytorin's significant increased rate of artery-clogging plaque despite significant cholesterol lowering, confirms the dismal failure of the "cholesterol hypothesis."

Raising HDL – Not the Answer, and Pfizer Knows it

Both Michael P. Cecil, MD, and *Medical News Today* wrote how torcetrapib, Pfizer's "miracle drug," raises HDL. Dr. Cecil stated the following:[35]

> Torcetrapib inhibits cholesterol ester transfer protein (CETP), and it's the first drug of this class studied. An article published in the *New England Journal of Medicine* in April 2004 by Dr. Margaret Brousseau and others described 19 patients with low HDL levels who received torcetrapib. The results were fantastic: treatment with a 120 mg tablet of torcetrapib **raised HDL levels by 46%**, treatment with torcetrapib and Lipitor together **raised HDL levels 61%**, and treatment with torcetrapib 120 mg twice daily **raised HDL levels by a phenomenal 106%!** [Emphasis added].

Then Pfizer abruptly announced they were stopping all trials involving torcetrapib after clinical data showed *more deaths and cardiovascular events occurring among patients who took it*. Pfizer's CEO said that the clinical trial monitoring board's recommendation to stop all studies was "surprising and disappointing." From *Medical News Today*:[36]

> In October, Pfizer said it had found that a combination of torcetrapib and Lipitor significantly increased HDL, or "good," cholesterol and lowered LDL, or "bad," cholesterol compared with patients taking only Lipitor.... Pfizer researcher Steven Ryder, who was overseeing torcetrapib's development, [was informed] that its regular monthly review of the drug found that there were 82 deaths among patients taking torcetrapib in a clinical trial, compared with 51 deaths among trial participants who did not take the treatment. Patients taking torcetrapib also were **more likely to experience heart failure and other problems** than other patients... The trial, which began in 2004 and was scheduled to end in 2009, involved about 15,000 participants who were at high risk for heart attack or stroke. Half of the participants took a combination of torcetrapib and Lipitor, and half took Lipitor alone [emphasis added].

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Raising HDL Known Not to Stop Heart Disease in 2001

Torcetrapib's failure should not have been a surprise. Years ago, researchers removed the HDL transport mechanism in mice. With no HDL transport, many physicians thought death would soon result from atherosclerosis. The researchers were in for a shocking surprise, as they reported in the *Journal of Clinical Investigation*:[37]

- "Current *dogma* supports a key role in reverse cholesterol transport and defects in the HDL-mediated process are thought to contribute to the development of atherosclerotic plaques.
- "Mice lacking HDL *do not* show impaired hepatobiliary [liver] transport, *suggesting that* **HDL plays little or no role in the process**.
- "We conclude that plasma **HDL levels and ABCA1 activity do not control net cholesterol transport from the periphery** via the liver into the bile, indicating **the importance of HDL in reverse cholesterol transport requires re-evaluation**."

Furthermore, the article titled, "Is It Time to Modify the Reverse Cholesterol Transport Model?"[38] makes these amazing statements:

- "...[T]he findings support the author's conclusions that **HDL levels DO NOT control net cholesterol transport from the periphery**...

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- "...**[C]all into question** the accepted **view of reverse cholesterol transport**. Is it time to pull the plug on reverse cholesterol transport?" [Emphasis added].

Because there is no cholesterol sensor in the body, there is no physiological reason to attempt to artificially adjust the cholesterol transport system. When researchers did, tragic results occurred.

Newsflash – 2008: HDL Cholesterol and Large HDL Particles Not Cardioprotective

The online medical newsletter Heartwire relayed the study published in the February 4, 2008 issue of *Journal of the American College of Cardiology*:[39]

- "'Remarkable' new data from two previously published studies suggest that **high levels of plasma HDL cholesterol** and large HDL particles are associated with an **increased risk of coronary artery disease**."
- "...[W]hen apolipoprotein A1 (apoA-1) and a apolipoprotein B (apoB) were kept constant in regression analyses, **increased HDL-cholesterol levels and HDL particle size conferred a risk of major coronary events**...."
- "Dr. Jacques Genest (McGill University) states, 'HDL as a therapeutic goal may be *fraught with dangers*.' So far he notes, there are **no data unequivocally showing that raising HDL cholesterol by pharmacologic means reduces cardiovascular risk** [emphasis added]**.**"

Life Systems Engineering Science analysis: simultaneously lowering LDL-C and raising HDL-C should be utopia for a pharmaceutical company and for anyone still thinking that LDL is "bad" and HDL is "good." However, patients develop increased blood pressure, experience more heart attacks, and die more often with this wrong approach. Pharmaceutical companies have no explanation why this method doesn't work, but we do, as this paper details. Everyone is looking in the wrong place for the answers.

Unwanted Side Effect: Cancer

Just as oxygen deprivation causes heart disease, sustained oxygen deprivation also causes cancer. Over 70 years ago, the Nobel prize-winning physician and master chemist Otto Warburg, MD, PhD, demonstrated that a sustained reduction of 35% in the level of cellular oxygen causes cancer and does so each time oxygen deficiency occurs for an extended period. Oxygen deprivation is cancer's prime cause, and the high ratio of fermentation to respiration is cancer's prime characteristic.[40,41] Lack of oxygen at the cellular level (hypoxia) was shown by American research scientists in the 1950s to cause cancer.[42,43] Please also see the August 2007 *Townsend Letter* at www.brianpeskin.com/townsend.html, for a comprehensive discussion of the relationship between reduced cellular oxygen and ever-increasing cancer rates. For convenience, we present a portion of this information next.

Decreased Parent Omega-6 Transport into Tissue = Decreased Cellular Oxygen

As we have already explained, cholesterol is esterified with large amounts of parent omega-6 before it is combined with lipoprotein as LDL particles for transportation within the body.[44,45] Statins increase tissue uptake of LDL cholesterol from the blood, but decrease overall cellular parent omega-6 available to the cell because absolute levels of cholesterol are decreased.[22] This decrease in parent omega-6 affects oxygen transmission across the cell membrane since the structure of the phospholipids that form a major portion of the cell membrane are a reflection of the composition of unsaturated fatty acids and bioavailability in the blood.[32] This is why statins *indirectly* cause a decrease in tissue and cellular oxygenation, increasing cancer risk, too.[46-48]

Cancer-Causing Problems with Statins Known a Decade Ago

In 1996, physicians Thomas B. Newman and Stephen B. Hulley published a warning against the use of statins.[49] Other similar warnings have since been published, one in *Cancer Research*.[50] A randomized, double-blind trial (meaning that neither the researcher nor the study participant knew whether a participant was getting a drug or a placebo), which lasted an average of five years, linked the use of lipid-altering drugs given to prevent cardiovascular disease events with a demonstrated increase in cancer incidence. This excess of malignancy was statistically significant in elderly subjects and women randomized to the drug groups. Another article published in 2007 in the *Journal of the American College of Cardiology*[51] confirmed the increased incidence of cancer with statins.

Newsflash – 2008: Low Serum Cholesterol Is a Risk Factor for Gastric Cancer

The online medical newsletter Medscape (http://www.medscape.com/viewarticle/570540_print: [2/25/08]) relayed the study published in the February 15, 2008 issue of *International Journal of Cancer* (2008;122:909-914):

- "*Low serum cholesterol* levels are an *independent risk factor* for developing gastric cancer.
- "After adjustment for age and gender, gastric *cancer rates rose significantly with descending quartiles of serum cholesterol* level...
- The *impact of low serum cholesterol* on risk of gastric *cancer remained significant even after adjustment* for *Helicobacter pylori* infection status, smoking habits, and dietary factors, according to the researchers."

Statins are available without prescription in the UK, and the US may soon follow suit. But, as we have seen, statins are far from harmless.

Other Surprising Connections: Intima Contains Parent Omega-6, Not Omega-3

The innermost arterial layer, the *intima*, consists of a single layer of endothelial cells. This endothelial layer is composed of epithelial tissue containing only parent omega-6; there is no omega-3[27,28] (Table 1). Properly functioning intima requires unadulterated parent omega-6. *CAD starts in the intima*. Is it a coincidence that heart disease has become the number 1 killer at the same time adulterated PEOs and omega-3 overdosing have become rampant?

PEOS Are Known to be Depleted in Heart Attack Victims

In 1982, the *British Medical Journal*[52] published a study that showed parent omega-6 and *most* polyunsaturated fatty acids, including AA and EPA, were found depleted in heart attack victims. These researchers concluded that the *fatty acid patterns* of the phospholipids (containing PEOs) constituted an *independent risk factor for heart disease*. While deficiency of PEOs is associated with increased heart attack risk, the solution is not to minimize parent omega-6 (along with parent omega-3), because of oxidation concerns. Most fats and oils are oxidized for energy production, which proceeds in the mitochondria via beta oxidation after activation by acyl-CoA synthesis. However, adulterated parent omega-6 deposits in cell membranes lead to *abnormal* oxidation at the vascular injury site, thus causing injurious inflammation. Abnormal oxidation involves formation of hydroperoxides from the double bonds of the PEOs. This harmful *partial* oxidation is not involved with energy (ATP) production; it causes tissue destruction.

Side-Effect: Statins Lower Important CoQ10 Production

Another negative side effect of statins is significantly lowered coenzyme Q10 (CoQ10),[53] also known as *ubiquinone*, because the substance is used throughout the body by cellular mitochondria. CoQ10 is required for energy production in all cells possessing mitochondria and is an important natural antioxidant for lipids. Therefore, we would expect exhaustion, muscle fatigue, and CAD events with statins, and clinicians often see these problems in their patients. The fact of significant side effects with statin use was published in 2005:[54] "We conclude that *statin-related side effects*, including statin cardiomyopathy, are *far more common than previously published*..."

It gets worse. In 2005, researchers found that endothelial dysfunction, a pre-step of atherosclerosis, occurs with decreased CoQ10, regardless of lipid lowering.[55] Therefore, artificially decreasing LDL-C is harmful for another unforeseen reason. ➤

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Vytorin Failure

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The Solution – The Peskin Protocol

To increase statins' effectiveness and decrease harmful side effects from the widespread use of statins for lowering cholesterol in the treatment of heart disease, attempts should be made to ensure that patients follow *The Peskin Protocol*. This ensures the diet contains generous amounts of unadulterated PEOs (725 mg each/40 lb. of body weight), with a ratio of LA:ALA greater than 1:1 and less than 2.5:1, through the consumption of unadulterated, unprocessed foods. To make this easier to accomplish with non-compliant patients, physicians should consider recommending nutritional supplements.[56] Further, patients should minimize foods containing significant amounts of trans fats, interesterified fats, and other adulterated hypo-oxygenating fats.

For additional information, physicians are encouraged to receive and view this article's accompanying Physician Medical Report titled, "A New Look at Cholesterol, Clogged Arteries, and PEOs," (complimentary download available via www.brianpeskin.com/specialmedreports.html).

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This article is based, in part, on information in *The Hidden Story of Cancer*, written by Brian Peskin with clinical researcher Amid Habib, MD, FAAP, FACE. This book is available from Pinnacle Press, P.O. Box 56507, Houston, Texas 77256, USA, or by phoning +1-713-979-0065 internationally. For more information visit www.BrianPeskin.com and www.CambridgeMedScience.org.

David Sim, MD, is a leading cardiologist practicing in Boise, Idaho, USA.

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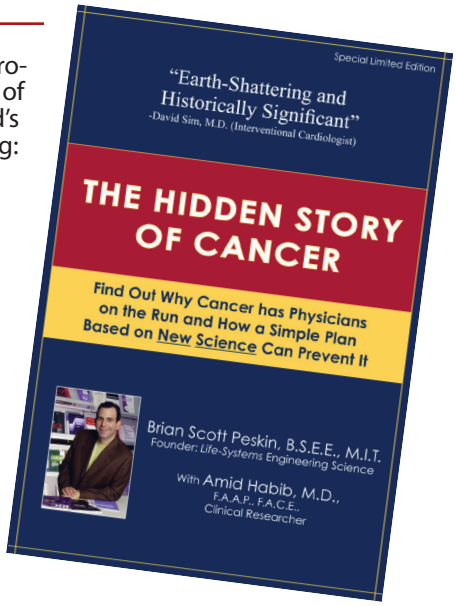

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