Type: Review [7-3-2025 10:00 am]
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Out of the darkness and into the light — Ushering in a new era of anti-inflammatory based medicine by maximizing the D6D metabolic pathway — Essential to reversing CVD & Cancer

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Abstract

This review article examines lipid physiology and its key role in advancing anti-inflammatory medicine; in particular, reversing CVD (the world's #1 killer). Despite recent media claims that omega-6 seed oils are harmful, adequate consumption of these lipids is essential for maximizing systemic anti-inflammation functionality and decreasing CVD; in particular, maximizing production of the body's most powerful anti-inflammatory, PGE_1. The issue lies exclusively in the harmful food / lipids processing.

Omega-6 is an Essential Fatty Acid (EFA). The body can't make it. In fact, both series of EFAs (omega-6 series and omega-3 series) *must* come from food. As the science makes crystal clear, lipids are the "brick and mortar" of our 100 trillion cells. They are required to optimize cellular membrane structure and cellular terrain, increasing cellular oxygenation, and decreasing today's epidemic of chronic inflammation. Parent omega-6 (LA) is the main EFA-based component of our 100 trillion bi-lipid cellular membranes (there is at least 10-fold more Parent omega-6 than Parent omega-3 throughout the tissues and organs). In the body, LA quantities far exceed ALA quantities or long-chain metabolites like EPA / DHA. Of prime importance, Prostaglandin Series 1 (PGE_1) — being the body's most powerful cellular anti-inflammatory — is derived from Parent Omega-6. Nothing in the omega-3 series matches PGE_1's anti-inflammation effectiveness, increased vasodilation, or cellular oxygenating power. Chronic inflammation is now widely recognized as a fundamental element of the leading causes of death, including both cardiovascular disease and cancer. Additionally, chronic epidemics of numerous inflammatory conditions are associated with impairment of the delta-6 desaturase metabolic pathway (D6D). This dysfunctional impairment results in reduced PGE_1 production and chronic (persistent) systemic inflammation. Unless a new era of anti-inflammation-based medicine takes center stage, it is impossible to reverse these epidemics of disease.

Many pivotal lipid physiology research papers remain underpublicized. Without knowledge of and comprehension of these seminal works, it is impossible to fully understand intricate lipids-based connections. This review article provides novel insights into the importance of Parent omega-6 and newly available methods to mitigate D6D pathway impairment and maximize PGE_1 output. Emphasis on anti-inflammatory medicine is vital to reversing the escalating prevalence of both established and newly emerging diseases. Cardiovascular disease — the leading cause of mortality worldwide, and newly created inflammatory-based epidemics, such as type II diabetes and autism, exemplify this need. Notably, type II diabetes was virtually non-existent pre-1940, is now an epidemic, and autism, rare just a

few decades ago, is now also an epidemic affecting over 3% of all children. Both are now known to be inflammatory-based.

Fish/marine oil supplements have become extremely popular. However, when consumed in the quantities often suggested by healthcare professionals and then used by patients, the (supraphysiological) amounts of EPA/DHA consumed directly lead to significant chronic inflammatory issues. Marine oils alter the levels of LA in mitochondria and all other tissues, causing horrific results. By highlighting under-publicized lipids-based research, it is now possible to impartially and objectively scientifically address and reverse the rising prevalence of chronic inflammatory diseases. This article uses cardiovascular disease as the prime clinical example, but the same concepts apply to mitigate the severity of the numerous diseases now known to have a significant, even causal, inflammatory component.

Keywords: essential fatty acids; delta-6 desaturase; eicosanoids; parent essential fatty acids; parent essential oils; PEOs; PUFA; polyunsaturated fatty acids

1. Introduction: Key Biological Lipids General Background — Parent EFAs (PEOs) and Derivatives

Linoleic acid (LA) and alpha-linolenic acid (ALA) are the only true 18-carbon chain essential fatty acids. They cannot be converted into each other nor synthesized by the body and must be obtained from dietary sources. LA is "Parent" omega-6, and ALA is "Parent" omega-3. Metabolites (eicosanoids), derived from LA and ALA, are longer-chain structures produced by the body, as needed, but are not essential because they can be synthesized by the body, and therefore, NOT EFAs. They are properly termed EFA derivatives. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are derivatives. In this review, I refer to LA and ALA as "Parent Essential Oils" (PEOs) or "Parents," while longer-chain metabolites (and eicosanoids) are termed "derivatives." The body produces these derivatives from Parents in small, minuscule amounts, as needed. Literature often confuses these two distinct categories, even inappropriately "lumping together" both Parents and Derivatives.

Cellular membrane lipid physiology

Each of a human's 100 trillion cells consists of a bi-lipid membrane. Importantly, the essential PEOs comprise 25% - 33% of their polyunsaturated membrane lipids.[i] Additionally, every mitochondrion, typically hundreds to thousands per cell, contains PEOs; in particular, Parent omega-6.[ii,iii]. Therefore, PEOs must be considered the "brick and mortar" of every cell, tissue, and organ, including mitochondria. In sharp contrast, aside from the brain, eyes, and nervous system, most tissues and organs contain few derivatives like EPA/DHA in their cellular membranes. By far, the most significant method to physiologically change tissue structure / physiology is through its lipid structure.[i,ii, iii]

2. Organic / Fully Functional / Unprocessed vs Adulterated / Processed EFAs

Not distinguishing an adulterated (processed) nonfunctional EFA-containing lipid versus a fully functional *un*processed fully functional EFA-containing lipid—in particular, omega-6 series LA—is the *prime cause* of confusion leading to both inconsistent clinical trials and poor patient outcomes. The criticality of distinguishing between the effects of adulterated vs unadulterated forms of LA is obvious. Failure to feed rodent chow (and humans) with fully functional LA food has led to the incorrect and misleading conclusion that dietary intake of LA increases disease risk, including CVD risk.[iv] Decades ago, we personally verified this adulteration of mouse chow in a cancer study. We had a sample of mouse chow measured for oxidation. The rancidity level was at least 3Xs greater than the lowest allowable safe rancidity peroxide value (PV) measurement level, i.e., the mouse chow itself was cancer- / heart

disease-causing. The researchers routinely have no idea of this physiologic lipid distortion skewing their trials.

With functional LA deficiency — caused by consuming processed omega-6 cooking oils — there is an enormous increase in permeability of the skin (epithelial tissue) and an increase in capillary fragility, further explaining the pathophysiology of CVD and various skin disorders, along with the path to prevention.[v] Oxidation of LDL-C causes significant depletion of functional cellular LA (Parent omega-6).[vi] This oxidation occurs *ex* vivo from processed oils used in cooking.

By not understanding this lipid physiology, patients are *unknowingly* harming themselves. For example, by ingesting fish oil (EPA/DHA), there is a corresponding decrease in tissue's quantity of LA, causing significant pathophysiologic deficiency of fully functional Parent omega-6 in tissues / organs.[vii]

Of particular note, with ingestion of fish oil (EPA/DHA), there was a corresponding decrease in tissue's LA, adding to pathophysiologic levels of cellular deficiency.[vii]

3. PEO Quantities—Omega-6 Dominates

With the extensive focus on omega-3 series fatty acids today, like EPA / DHA, it is significant to note that the free Parent fatty acids (non-esterified) in human plasma, although minute in quantity, are ordinarily composed of about 15% LA (linoleic acid, Parent omega- 6) and a miniscule 1% of ALA (alpha linolenic acid, Parent omega-3).[viii] Derivatives such as EPA/DHA are naturally significantly less in quantity than LA. In sharp contrast to the high amounts of n-6 series PUFAs, n-3 series PUFAs account for only 1.8% of the fatty acids in triglycerides, 3.5% in the phospholipids, and only 1.7% (ALA is 0.5%) in cholesterol esters. However, the Parent (LA/ALA) ratios in triglycerides are 23:1. N-3 PUFA makes up only 1% - 2% of fatty acids in plasma.[ix] Even in the brain, the LA / ALA uptake (ratio) is an amazingly 100 times greater in favor of LA.[x]

4. Variable Tissue Composition

The significant variable in tissue is its lipid structure. Although the genetics of a particular species precisely specify cellular structure, its lipid composition can vary significantly based on EFA-containing food consumption —in particular, when supra-pharmacologic amounts of long-chain metabolites are consumed — such as the case with fish/marine oil supplements. A pharmacologic overdose can't be oxidized away for energy or otherwise. Consequently, much of this overdose is forced into tissue composition, such as cardiolipin in the mitochondria and the skin, causing an improper tissue composition, often maintaining a linear relationship of the overdose in the plasma, liver, and RBCs.[xi,xii,xiii]. This physiological fact is also underpublicized. Cellular bi-lipid membrane structure and the LDL cholesterol structure warrant intense investigation.

Lipid Physiological Variability in LDL-C

The structure of LDL-C is complex. Its cholesteryl ester is key (**Figure 1**). The structure of cholesterol itself never changes. What changes is exclusively its *esterified* moiety—the acyl side chain. That's a critical difference that many in the medical community may not appreciate. This is a simple condensation reaction, removing the water, catalyzed by the enzyme ACAT (Acyl CoA: Cholesterol Acyl Transferase) between a fatty acid and cholesterol. "R" symbolizes the hydrocarbon portion of the fatty acid. For example, if oleic acid were esterified with cholesterol, then R would be -C7H14CH=CH-C8H17 with the double bond in cis configuration.

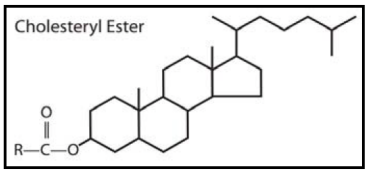

Figure 1. Cholesterol Ester. Lipoproteins transport cholesterol and its esterified PEOs to the tissues via apoprotein B-100 (ApoB100).

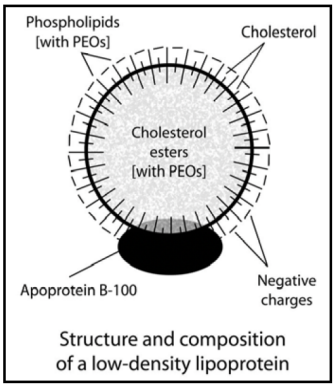

Figure 2. Structure and composition of a low-density lipoprotein showing the significance of its esterified cholesterol structure.

5. LDL-C Is NOT Oxidized in the Body / Bloodstream: It is Oxidized from Food Processing

Cholesterol itself is extremely resistant to oxidation, whereas its main esterified component, Parent omega-6 (LA), is much more easily oxidized, especially *ex* vivo. Dietary LA that has already become oxidized prior to ingestion *ex* vivo is ubiquitous through the processing of foods or overheating, since heating in the presence of air enhances peroxidation of PUFA glycerol esters.[xiv,xv]

It is highly unlikely that LDL can become oxidized in plasma to the extent that it causes foam cell formation and possesses chemotactic and cytotoxic properties. Furthermore, only minimal physical and chemical changes related to oxidation are produced by even a prolonged storage of LDL with oxygen or by incubation with low concentrations of copper ions. Clearly, the quantity of antioxidants is too small for oxidation *in* vivo to be a significant physiologic issue.[vi] Nature doesn't require high quantities of antioxidants in this area because the substances are naturally resistant to oxidation in the body. The PUFA, in particular, LA, is being consumed and entering the body in a dangerous oxidized state.

Confirmation of Exogenous Damage to Parent Omega-6 Prior to Consumption

This lipidology is confirmed by Prof. Gerhard Spiteller, former Chairholder of Biochemistry, Institute of Organic Chemistry at the University of Bayreuth, Germany. He has extensively investigated EFAs and their degradation products, specifically, the influence of these substances on the physiology of mammals. He concluded that consumption of oxidized PUFA-cholesterol esters (from food processing) is responsible for the initial damage to endothelial cells, leading to premature cardiovascular disease. Cholesterol oxidation products are incorporated into LDL cholesterol in the liver.[xvi] Ultimately, tissue Injury is not caused by an increase in free cholesterol but by an increase in the cholesterol esters — the PEOs "magnetized" to the cholesteryl molecule for transportation in the bloodstream.[xvii]

As a clinical example, in atherosclerotic patients, LDL cholesterol is altered /adulterated *ex* vivo by oxidative food-processing, and this altered LDL is taken up in unlimited amounts by macrophages. Dead macrophages filled with cholesterol's previously damaged, functionally impaired esters are then deposited in arteries. LDL-C is effectively transmitting a poison, i.e., nonfunctional and harmful LA. We can now explain the failure of statins to eliminate cardiovascular disease and stop CVD as the world's #1 killer.

By statins lowering of LDL-C, their esterified PEOs are also lowered, both adulterated [good outcome] and fully functional [bad outcome]. This is problematic. By focusing on displacing the *ex* vivo LA that has already become oxidized prior to ingestion through the processing of foods, cooking, or overheating, a solution can be found to mitigate this damage. Consuming organic / unprocessed / fully functional LA overpowers the adulterated LA; the oxidation issue is solved.[xiii]

6. Diseases, Disorders of the Δ-6 Desaturase Pathway Causing Chronic Inflammation

Known inflammatory-based diseases and disorders associated with an impaired Δ-6 desaturase pathway include: Diabetes (both Type 1 & Type II) including associated neuropathy; lipid enveloped viruses (including COVID series); dermatological conditions (Eczema, etc.); cardiovascular disease (including soft plaque, hard, calcified plaque, hypertension, etc.); inflammatory bowel disease; chronic fatigue; fatty liver disease, including NAFLD; Multiple Sclerosis; Dementia /

Alzheimer's; Cancer, and respiratory diseases like COPD.[xviii]

Specific Diseases Newly Re-classified as Inflammatory-Based (a partial selection):

Dementia / Alzheimer's

Although underpublicized, in 2018, Dementia and Alzheimer's have been newly reclassified as directly caused by inflammation, and considered a cardiovascular disease:

- "Inflammation is a MAJOR CAUSE, not just a consequence…. but only now is it identified as THE CAUSE. The new work turns previous thinking around."[xix]

Cardiovascular Disease

Tragically, no field better than cardiology exemplifies *the incredible lack of understanding* of the physiologic effects of lipids. Functional lipids are the key to decreasing cardiovascular disease. The lipid chromatography has been completed and published, if anyone cares to look. We know that LDL-C is the transporter of the esterified lipids. To reverse heart disease, there are two key lipidology-based points that have to be understood:[xx,xxi,xxii]

- There is NO saturated fat in an arterial occlusion (clog).

- As much as 85% of the composition in an arterial occlusion is inflammatory, adulterated / processed Parent omega-6.

Calling omega-6 "inflammatory" is a mistake. This grave mistake came about because one of the components of omega-6 fatty acids, called arachidonic acid, is a (mistakenly termed) "building block" for various inflammation-related molecules. This has led to concern that omega-6 consumption would lead to a greater risk of heart disease. This has been completely disproven, and in 2009 it was stated by no less than the American Heart Association:[xxiii]

- "'***That reflects a rather naive understanding of the biochemistry***,' says William S. Harris, Director of the Metabolism and Nutrition Research Center of the University of South Dakota Sanford School of Medicine and the nutritionist who led the science advisory committee that issued the report in *Circulation*.

- "'*[O]mega-6 PUFAs [Derivatives] also have powerful anti-inflammatory properties* that *counteract any proinflammatory activity*,' say the advisory authors. ***'It's incorrect to view the omega-6 fatty acids as "proinflammatory***.'"

Confirmation was proven by C-Reactive Protein marker (CRP), if anyone would care to look:[xxiv]

- "Conclusions: Serum n-6 PUFAs [AA, etc.] were *not associated* with increased inflammation in men. In contrast, the main n-6 PUFA linoleic acid [Parent omega-6] had a **strong inverse association with the key inflammation marker CRP. "Omega-6 fatty acids do not promote low-grade inflammation.**

- **"The higher the serum linoleic acid [Parent omega-6]** level, the **lower the CRP**. This is an inverse correlation."

How much more incorrect can the medical community be in their current recommendations concerning heart disease? A low-fat diet is still often recommended — a tragedy causing derailment off the path to inflammatory-based medicine.

Prostacyclin (PGI_2) is the body's most powerful natural vascular anticoagulant and is a powerful derivative of arachidonic acid (AA).[xxv] Many, if not most, cardiologists I speak with are unaware of these older, yet undisputable and seminal findings. If these key lipidology facts aren't well-known, understood, and made use of, stopping the epidemic of the world's #1 killer can never occur.

Cancer

Much like the failure of CVD therapies to prevent the ever-increasing levels of heart attacks, the "war on cancer," started in 1971 in the USA, has also been a dismal failure. Again, a woeful understanding of lipidology extends to this area, too. Cancer is not a genetic disease, and the coiner [Weinberg] of the term "oncogene" reversed his theory and now highlights inflammation as cancer's cause back in 2007, if anyone would care to look:[xxvi]

- Cancer researcher Robert Weinberg of MIT states: "The connection between **inflammation and cancer** has **moved to center stage** in the research arena.

- "…[**I]nflammation is the fuel** that feeds it [the malignant cancer].

- "In this **rewriting of the textbook**… This new view implies that rooting out every last cancer cell in the body might not be necessary. **Anti-inflammatory cancer therapy instead** would **prevent pre-malignant cells from turning** fully cancerous or would **impede an existing tumor from spreading** to distant sites in the body. Cancer victims might then be able to survive."

Many oncologists — if not most oncologists, are unaware of this groundbreaking finding. Can this failure of the old guess and new anti-inflammatory-based path to eradicate cancer be any clearer? No. Without state-of-the-art lipidology, we will never "win the war on cancer," regardless of how much money is "thrown" at defeating cancer. Furthermore, **ALL (100%) cancer tumors possess abnormal cardiolipin structure in their mitochondria**. EFA-wise, cardiolipin's EFA structure is supposed to be comprised 100% of Parent omega-6 (LA), but without adequate, fully functional amounts, or excessive EPA / DHA from fish oil, cardiolipin's structure will significantly be impaired.[xxvii]

7. Fish Oil Impedes Cardiac Mitochondrial Functionality by Forcing Out Critically Required LA

Fish oil impairs mitochondrial cardiolipin functionality, as this seminal, yet underpublicized, *Journal of Biological Chemistry* finding makes clear:[xxviii]

- "(18:2) CL_4 [Parent omega-6] rescues [fixes the damage] the major remodeling in the cardiolipin lipidome induced by long-term intake of DHA. [Cardiolipin is in the inner mitochondrial membrane.] Mitochondria are the cellular energy sources. Deficiency also causes chronic exhaustion – the #1 complaint of Americans.]

- …[I]t is not the loss of linoleic acid alone that drives the impairment in enzyme function since the Western diet alone did not impair enzyme activities. Instead, it was the replacement of linoleic acid with DHA that promoted the reduction in activities."

Could it be any clearer? No. Fish oil therapy is a horrific treatment for heart-related disease. Lowering of triglycerides by no means compensates for a heart with insufficient energy, leading to congestive heart failure.

8. Membrane Lipid Structure is Key to Decreased Cellular Inflammation

Another underpublicized yet what should have been an ***"earth-shattering" journal article***, detailed how "[S]ecretary cells [virtually all cells] are ***hypersensitive to their membrane lipids induced by the diet***."[xxix] This gives us the necessary link between *chronic, persistent inflammation* at the cell level and the skyrocketing inflammatory-based epidemics of disease. There is a thermodynamics-based reason that the cells can sense adulterated membrane lipids displacing the fully functional ones.

Today, there is almost an exclusive focus on proteins, with little attention on lipids. This seminal article makes clear that ***lipids control the proteins***. Lipids are the "protein masters." Adulteration /

processing of cooking oil lipids precisely explains this epidemic increase in chronic cellular inflammation.

If there is a deficiency of fully functional LA in the diet, the body will substitute into cell membranes non-functional LA or even a nonessential fatty acid, such as oleic acid (non-essential omega-9), found in olive oil. This *forced* substitution because of inadequate functional LA results in a marked decrease of cellular oxygen transport with adverse effects on cellular metabolism and function.[xxx] Because LDL cholesterol is the transport vehicle for PEO delivery into the cell, LDL cholesterol will transport any kind of LA into cells—defective or not—such as oxidized or *trans* entities (*See* Figure 1).

Adulterated / nonfunctional dietary 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, caused by *ex* vivo adulteration of LA, involves formation of a hydroperoxide from LA by abstraction of a hydrogen atom as a radical from the doubly allylic methylene group between the two double bonds, followed by the addition of oxygen, a diradical, to make a hydroperoxide radical, which can then pick up another reactive hydrogen atom, perhaps from another LA molecule, to form the hydroperoxide. This, in turn, may break the O-O bond to form an alkoxide and a hydroxyl radical, which can continue to make more undesirable oxidized products []^{xxxi}. Therefore, atherosclerosis (the world's #1 killer) can be prevented / arrested if endothelial cells are fully functional by utilizing bioavailable Parent omega-6. [xxxii]

9. Importance of the D6D Anti-Inflammatory Pathway

The delta-6 desaturase metabolic pathway is impaired in the majority, if not all, chronic inflammatory diseases.[xxxiii] Once impaired, this desaturating pathway is not known to be reversible. Fortunately, there is no impairment in the elongase pathway; only in the desaturase pathway (Figure 3). We can help nutritionally compensate for this desaturase impairment by two methods: a) Increase dietary fully functional, Parent Omega-6, and b) Bypass the D6D pathway increase by utilizing naturally occurring GLA-containing seed oils.

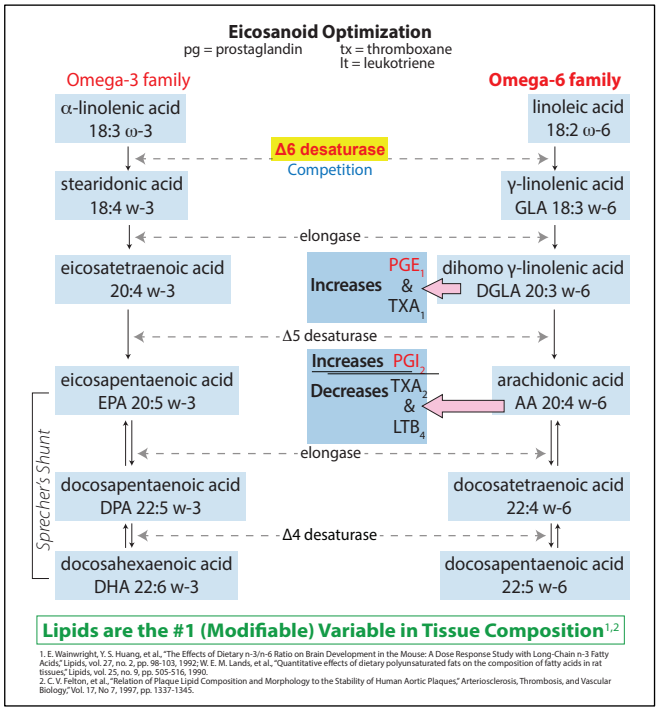

Figure 3. Parent Omega-6 and long chain metabolites (eicosanoids)

The majority of the plasma fatty acids are LA (Parent omega-6). Mitigating the damage caused by *ex* vivo intake of oxidized LA is now possible. Easiest is compensation by ingesting supplemental, fully functional, unadulterated, non-oxidized LA. Importantly, the key metabolites of LA—in particular, **PGE_1** and **PGI_2** (prostacyclin)—are significant vasodilators, increasing critical blood flow along with associated cellular oxygenation and nutrients. PGE_1 is also a potent anti-inflammatory and immune system regulator.[xxxiii] If functional LA bioavailability is lowered, the potential for inflammation significantly rises, leading to atherosclerosis, etc.

Weiss, for example, has noted that PGE_1 (produced from functional Parent omega-6) reduces the fibrin deposition associated with the pathogenesis of atherosclerosis.[xxxiv] Membrane fluidity increases when more functional (undamaged) polyunsaturated fatty acids—in particular, linoleic acid—are available to incorporate into the membrane lipid bilayer,

causing the epidemic of inflammatory-based diseases. Further underpublicized is that lipids are the #1 modifiable in tissue (*See* below).

No Delta-6 / -5 Desaturase Impairment in Healthy Patients Converting Parent Omega-3

Highly accurate, quantitative experiments were performed showing that the average healthy person and animals are both quite capable of metabolizing adequate amounts of DHA from Parent omega-3 (ALA). In a key NIH experiment, rodents naturally produced 50-fold (50Xs) more DHA each day than their brains required.[xxxv] Certainly, Nature would ensure humans the same margin of safety shown to a rodent.

An *American Journal of Clinical Nutrition* article detailed over 60 firefighters and analyzed their conversion of omega-3 long-chain metabolites from Parent omega-3 (ALA), finding conversion adequate with sufficient intake of ALA [Parent omega-3].[xxxvi]

Even vegans consuming no animal food, including fish, a group that absolutely would be expected to manifest gross neurological abnormalities, including both visual impairment and cognitive impairment, do not. There is no clinical evidence of such abnormalities in vegetarians.[xxxvii,xxxviii] Confirmation in 2010 showed that vegetarians with an intake of just 0.3% DHA compared with fish eaters, produced 85% of the EPA levels and 83% of the DHA levels that consumers of fish did. These amounts are well within the "normal" ranges.[xlii] There is no widespread impairment in the typical patient whatsoever; the normal conversion amounts are simply very low, naturally.

10. The Etiology of Cardiovascular Disease: Composition of Arterial Plaque

Current anti-CVD recommendations lack a firm physiologic / biochemical lipids basis. In 1994, using high-resolution chromatography, investigators found that plaque contained more than **10 different compounds, none of which were related to saturated fat**.[xxiv,xxxix,xl] Not surprisingly, cholesterol was found in the plaque. This key finding demonstrated that cholesterol, esterified with nonfunctional linoleic acid (LA)—adulterated Parent omega-6 — was by far the most abundant component in plaques of arterial stenosis. Furthermore, it was also found that cholesterol esters are the predominant lipid fraction in all plaque types, and that oxidized derivatives are toxic to most types of arterial cells.[xlv]

Fish Oil Causes Decreased Prostacyclin Production Leading to Atherosclerosis

Prostaglandins are capable of both limiting thrombosis and reversing thrombosis in atherosclerotic patients.[xli] Prostaglandin PGE_1 is the body's most powerful anti-inflammatory and vasodilator, and prostacyclin (PGI2) is a vasodilator that prevents both platelet adhesion and aggregation. These prostaglandins are both omega-6 metabolites. To the contrary, fish / marine oils increase endothelial platelet aggregation in atherosclerotic patients.[x] In patients with atherosclerosis, prostacyclin (produced in endothelial tissue) biosynthesis fell by a mean of 42% during the fish-oil period, leading to increased adhesion against the arterial walls. [extremely bad outcome]. This finding is underpublicized. Synthesis of the platelet agonist thromboxane A2 (produced in the platelets) declined by 58% [good outcome]. Atherosclerotic patients require increased intimal PGI2 output, not decreased output.[xliii] Furthermore, with marine oil, template bleeding times were significantly prolonged in all patients [bad outcome].

With Dietary Lipid / Eicosanoid Manipulation Lipid Physiology, Atherosclerosis Is Impeded Via Multiple Metabolic Pathways

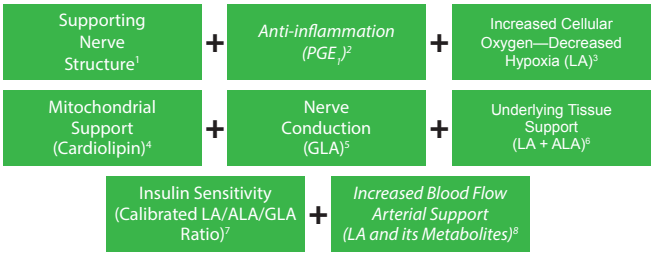

Figure 4. CAC Progression Impeded. Multiple Supporting Metabolic Pathways Optimized. References: [i; xlii; xliii;xliv; xlv; xlvi; xlvii; xlviii]

11. Horrific Pathophysiology of Fish / Marine Oil Consumption in Humans

Fish oil spontaneously oxidizes at room temperature and in *vivo*

Lipid science clearly shows fish / marine oil is expected to contribute to CVD, not prevent it: a) Regardless of the anti-oxidant level added to the fish oil supplement, rancidity / peroxidation upon ingestion is a significant and problematic issue. Because of its high number of bis-allylic bonds — five double bonds in EPA and six double bonds in DHA, these metabolites are highly sensitive to temperature. Spontaneous oxidation of EPA leads to generation of a mixture of aldehydes, peroxides, and other oxidation products. Highly polyunsaturated, long-chained EPA and more so with DHA, due to its additional double-bond, is readily oxidized at room temperature (auto-oxidation) even in the absence of exogenous oxidizing reagents.[xlix] Importantly, *in* vivo, a large increase in tissue and plasma accumulation of fatty acid oxidation products is noted in subjects consuming fish oil, even after the addition of antioxidant supplements to the diet. This deleterious effect led to a 14% decrease in life expectancy in those animals fed fish oil.[l] As shown above, PEOs don't suffer from this problematic *in* vivo oxidation issue. **In fact, DHA is 320Xs more susceptible to attack than** common mono-unsaturated oleic acid (18:1) – like **olive oil** with no bis-allylic hydrogen bonds. Fish / marine oil's EPA / causes excess oxidative stress.[li] DHA Membrane lipid peroxidation should not be perceived solely as a 'damage to membranes' scenario but also as a significant endogenous source of damage to other cellular macromolecules, such as proteins and DNA (including mutations)."[lii]

Another shocking, yet underpublicized, finding was that in primates and humans, such as the monkey, no quantity of *in* vivo antioxidants stops EPA/DHA damage as measured by lipofuscin, the peroxidized "age spots." Lipofuscin was threefold (3Xs) greater in the livers of monkeys fed fish oil. Furthermore, another measure of oxidative damage, the basal thiobarbituric acid reactive substances (TBRS) levels, was four-fold (4Xs) greater than in the monkeys fed (processed) corn oil with no EPA/DHA. The researchers found that even a ten-fold (10Xs) increase in alpha-tocopherol, a potent antioxidant, was not fully able to prevent the peroxidative damage from fish oil.[liii] **It was known in 2000 that fish / marine oil, even in low doses, suppresses the innate immune system**.[liv] Fortunately, not taking years, it takes 18 weeks to fully rid patients of fish oil in the cellular membrane.[lv]

12. Parent Omega-6 to Parent Omega-3 Tissue Composition.

The preponderance of the omega-6 series throughout the body is made clear.[lvi]

Table 1. Preponderance of Parent EFAs LA / ALA Ratios in Tissues & Organs.[lix]

Ratio of LA: ALA Tissue Composition			
Tissue	**% of Total Body Weight**	**Omega 6 PEO**	**Omega 3 PEO**
Brain/Nervous System	3	1	1
Skin	4	1000	1
Organs & Other Tissues	9	4	1
Adipose Tissue (Body Fat)	15-35	22	1
Muscles	50	6.5	1

Parent-to-Derivative Metabolism and Amounts

What percentage of PEOs are converted to long-chain metabolites such as GLA, AA, EPA, DHA, etc.? This most important issue is rarely addressed. The USDA and NIH provide these answers. The conversion amount is much less than the medical field assumes; it is less than 5%—often less than 1%—with at least 95% of PEOs staying in Parent form. They are the "brick and mortar" of our 100 trillion cells. This singular mistake made decades ago in assuming very high conversion amounts, whereas in actuality they are extremely low conversion amounts, led to the irrational fish oil mania and wrong recommendations to limit Parent omega-6 cooking oil consumption; even the essential, fully functional / *un*adulterated.

Contrary to incorrect dogma, the enzymes that produce PEO derivatives (the delta-6 and delta-5 desaturase enzymes) are not significantly impaired in healthy patients.[lvii] ***Conversion of ALA [Parent***

omega-3] to DHA is unlikely to ever normally exceed a mere 1% with less than < 0.1% conversion to DHA.[lviii] Research at the United States Department of Agriculture's USDA food composition laboratory (2001) reported a natural net conversion rate of a mere 0.046% of ALA to DHA & 0.2% to EPA—not the highly misleading often-quoted 15% conversion rate.[lix]

It is important to understand that years ago, NIH researchers determined the amount of DHA utilized in human brain tissue to be **a mere 3.8 mg ± 1.7 mg/day**. Therefore, brain tissue in 95% of all subjects, allowing for variation in brain size, would consume merely 0.4 mg - 7.2 mg of DHA per day.[lvii] New, twenty-first-century quantitative research from both NIH and USDA shows considerably lesser amounts of natural DHA conversion / usage from ALA than the medical community has been led to believe. These conversion amounts are extremely small and naturally limited. ***This dreadful mistake often leads to recommendations that are supra-pharmacologic and can potentially overdose patients by factors of 20-fold to 500-fold***, depending on the specific supplement and amounts consumed. The body cannot simply oxidize these tremendous overdoses of EPA/DHA; they are too great a quantity. Their vast quantity displaces the required LA in tissue, as demonstrated in the congestive heart failure example,[xxx] and the new epidemics of skin disorders like eczema in children in the US.

Amounts of Derivatives EPA / DHA in Fish Oil Supplements

An average 1000 mg health-food-grade fish oil capsule contains approximately 180 mg EPA and 120 mg DHA. Pharmaceutical-grade versions contain higher doses. The American Heart Association states that those with documented CHD are advised to consume about 1 gram of EPA + DHA per day. **Is this advice rational? No**.

Supplemental DHA from fish / marine oil not required

More underpublicized information (to reiterate):

- DHA is made by the body "as needed," from Parent omega-3 (ALA), although in extremely small quantities from Parent omega-3 (ALA). Highly accurate, quantitative experiments were performed showing that the average healthy person and animals are both quite capable of metabolizing adequate amounts of DHA from Parent omega-3 (ALA).
- In a key experiment, rodents naturally produced 50-fold (50Xs) more DHA each day than their brains required.[xxxix] Certainly, nature would ensure humans the same margin of safety shown to a lowly rodent. Importantly.
- It is known that rodents metabolize EFAs the same as humans.[xxxix]

Conclusion: By understanding and fully exploiting solutions to an impaired D6D metabolic pathway, a new era of anti-inflammatory medicine is now available. "Connecting the dots" of several, yet seminal, underpublicized lipid science discoveries gives us the precise answer to combat the current and increasing epidemics of chronic inflammatory-based diseases; in particular, CVD and cancer. This review article provides this underpublicized science.

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