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Why Fish Oil Fails: Two Invited Peer-Review Journal Articles Explaining Why Fish Oil/Marine Oils Are Harmful For The General Population.

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SELECT Trial Results Examined: Why Fish Oil, DHA and "Oily Fish" Are Inflammatory, Leading to Increases in Prostate Cancer, Epithelial Cancers and CVD

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ABSTRACT

In July 2013, using data and plasma collected in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), results were shown consistent with prior results of the controversial 2011 Prostate Cancer Prevention Trial. Both trials exhibited unexpected associations: 1) Fish oil and fish oil's DHA significantly increase prostate cancer in men; in particular, high grade prostate cancer; 2) Harmful trans fats did not exhibit their well-known significant and harmful effects; 3) Omega-6 series fatty acids LA (Parent omega-6) and long-chain metabolite AA were not shown to increase risk of prostate cancer as expected. These unexpected results mystified researchers. However, these clinical results confirm the prevailing medical science; they do not run counter to it. Pre-21st century studies mistook irrelevant associations for cause/effect relationships, disregarding known incontrovertible science. Utilizing established state-of-the-art physiology and biochemistry, these mistakes will be fully explained. When taken prophylactically in the amounts normally recommended, marine (fish) oils will be shown harmful to humans. Marine oil—and, in particular, its component DHA, with its highly reactive 5 *bis-allylic* bonds—will be shown to be highly inflammatory, therefore cancer-causing. These epidemiological studies are complemented by a variety of underpublicized physiological and biochemical findings showing that fish oil heightens premature lipid peroxidation and damages arterial endothelium in a way that increases the risk of all cancers. Most importantly, the cancer-causing effect of fish oil supplements, and all marine oils, will physiologically and biochemically be shown to possibly be significantly more harmful than trans fats.

Keywords: Fish Oil; EFAs; Omega-3 Fatty Acids; ω-3 Fatty Acids; DHA; EPA; Inflammation; Parent Essential Oils; PEOs; PUFA; PGE_1; Epithelial; Cancer; Trans Fats; Prostate Cancer; CVD; IOWA; Select Trial

1. Introduction

The objective of this paper is to provide substantial independent scientific validation to the analysis of the 2013 Select Trialby Brasky *et al*. published in *Journal of the National Cancer Institute* [1].

Validation is given of the statistics of the analysis; type of clinical trial and its use of plasma as a marker of fatty acid intake is given. A review of fatty acid metabolism and functionality is provided. Trans fats' carcinogenic properties are detailed. A small sampling of fish oil's extensive failures in clinical trials is presented. The strong association between increased fish oil consumption and skin cancer is detailed. Evidence is presented that fish oil's supraphysiologic EPA/DHA amounts spontaneously oxidize at room temperature thereby eliciting expected carcinogenic properties, including prostate cancer. Evidence is presented that fish oil causes elevated levels of both harmful Malondialdehyde (MDA) and Thiobarbituric Acid Reactive Substances (TBARS) from extremely harmful oxidative secondary and terminalstage oxidative products. Evidence is presented demonstrating fish oil's significant negative impact on mitochondria functionality. Evidence is presented from the Department of Agriculture (USDA) and National Institutes of Health (NIH) that adequate EPA/DHA, the "active ingredient" of fish oil is naturally derived from dietary alpha-linolenic acid (ALA); there is no epidemic of functionally impacted delta-6/-5 desaturase functionality in the general patient population. Evidence is presented that the country with the highest consumption of fish oil (pre-

dictably) experiences the most prostate cancer. Lastly, a possible explanation is presented why analysis did not show carcinogenic transfats to be causal to prostate cancer.

Prostate cancer is the most diagnosed cancer in men [2]. The 2011 Prostate Cancer Prevention Trial demonstrated that the high concentration of serum phospholipid of long-chain metabolite, ω-3 series fatty acids was associated with a large increase in the risk of high-grade prostate cancer [3].

The 2013 landmark article published in *Journal of the National Cancer Institute* entitled "Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial" [1] confirmed prior post-2007 findings of increased prostate cancer risk among men with high blood concentrations of long-chain metabolites of ω-3 fatty acids from fish oil studies [3,4]. The authors warned, "The consistency of these findings suggests that these fatty acids are involved in prostate tumorigenesis. Recommendations to increase *LC*ω-3*PUFA* [fish oil's EPA/DHA] intake should consider its *potential risks*."

The authors further stated, "It is unclear why high levels of long-chain ω-3 PUFA would increase prostate cancer risk, and further study will be needed to understand the mechanisms underlying the findings reported here." We will fully explain why—based on established physiology and biochemistry—long-chain ω-3 PUFA contained in marine oils/fish oils are expected to increase prostate cancer and all cancers.

The 2013 *JNCI* analysis had multiple strengths: A large number of sites (427) allowing for wide patient diversity, representative of a true broad-based patient population. Almost all prostate cancer cases were reviewed for pathological confirmation. A superior plasma phospholipid analysis was performed (described below), although EPA/DHA in plasma differences are small, which increase is statistically significant and extremely important. Standard deviation from the mean of each particular fatty acid in the statistical analysis was small (0.8% - 6.9%), justifying a very high level of confidence in the analysis. A large number of cancer cases (over 800 confirmed cases) allowed accurate fatty acid assessment, as did the "no cancer" leg (over 1000 patients).

2. Statistical Analysis

2.1. Cox Proportional Hazard Ratio Result and Meaning

The researchers used Cox proportional hazard models. It is important to understand the significance of this fact. This is a "time-to-event" measurement—not merely an occurrence vs. non-occurrence proportion such as the simple relative risk (RR) or odds ratio (OR). The statistic is based on the median (time elapsed until 50% of the cases are "resolved"). Therefore, the clinical question is: If the patient hasn't developed prostate cancer yet, what are the odds patient consuming the most long-chain omega-3 series fatty acids from marine oils, as measured in plasma, will contract prostate cancer first?

The hazard ratio in the Brasky, *et al*., 2013 *JNCI* article was 1.71, with the highest plasma phospholipid amounts of long-chain metabolite, ω-3 series fatty acids—in particular, DHA—found in the high-grade prostate cancer leg. (Significant association was found in low-grade and total prostate cancer, too, and probabilities are calculated in similar fashion as below.) This *does not mean* a 71% greater risk of contracting severe prostate cancer; it is less [5,6]: What are the odds that the patient taking the highest amount of fish oil or consuming oily fish first develops "high-grade" prostate cancer compared to those patients taking the lowest levels of fish oil supplement or consuming "oily" fish? The odds of contracting cancer first is as follows: the probability of contracting cancer first divided by the probability of not contracting cancer first. Therefore, the hazard ratio (time-weighted odds) = $P/(1 - P)$; $P = HR/(1 + HR)$. Therefore with the HR = 1.71:$1.71/(1 + 1.71)$ = a 63% chance in the patient consuming the highest amounts of fish oil developing high-grade prostate cancer first, compared to a patient consuming the lowest amounts of fish oil. Although the increased risk is more accurately 63%, not 71%, the question must be asked: "Why would you expose patients to any increased risk of contracting prostate cancer?"

2.2. Studies & Cause/Effect Relationships Must Be Consistent with Medical Science

Many physicians incorrectly think the determining factor of clinical efficacy is the number of "studies" (often with multiple variables) that "succeed" vs. the number of "studies" that fail—a preponderance of successes thereby proving efficacy. This is categorically wrong.

Many studies are not well done, misleading physicians and researchers with erroneous results. That is why when researchers perform a meta-study analysis many individual studies are disallowed for inclusion.

A study's primary value should be as confirmation for the *established medical sciences of physiology and biochemistry*. Using studies for other purposes is perhaps the single most significant reason that medicine often moves forward at such a slow pace compared to the advances in the other sciences. The established science is the framework, and the study is confirmation of that framework.

For a true cause/effect relationship, an effect must be both *consistent* and *significant* in effectiveness across wide patient populations. *This condition was met in the SELECT Trial*. The mean percentages of total long-chain ω-3 PUFA were statistically significantly higher across

all prostate cancer groups: total number of cancer cases, and both low- and high-grade prostate cancer case subjects compared with the subcohort. Highly accurate lipid analysis is performed by high-resolution chromatography. Elevated DHA was the significant contributor to increased prostate cancer risk, and it is physiologically predictable, given its highly reactive 5 *bis-allylic* bonds, and based on the pathophysiology of cancer (explained below).

2.3. Clinical Trials: Prospective and Retrospective

There are two types of clinical trials, each requiring a specific interpretation of the results. The first type is a case-control/prospective/cohort trial or an experiment, whereby the investigator decides how many subjects with and without the disease will be examined *a priori* (in advance) of the study or experiment in a controlled setting. "Relative risk" is the statistic commonly calculated. The second type, a retrospective/observational study, examines the results after the fact. An "odds ratio" (OR) is calculated as an estimate of the relative risk. A well-conducted observational study can indicate a likely "association," but it can go much further.

2.4. Confounding/Outlying Factors

In SELECT, the researchers did an excellent analysis of possible cofactors/outliers. Conclusions were unchanged. There were additional variable factors not individually subjected to an analysis of variance. Those factors included: aspirin use, Finasteride use, smoking, and alcohol consumption. However, the proportions of each additional factor were approximately the same in each leg (cancer/no cancer), demonstrating no bias. Other possible variables also comprised approximately the same relative percentages in both legs. Therefore a disproportional amount of additional confounding factors were *not* an issue in either group.

Furthermore, since marine oils are purported to have strong anti-cancer effects, those effects would be expected to be strong enough to (at least) compensate against, and override them in spite of (possible) confounding factors like in the IOWA screening experiment [7]. In IOWA, the *plant-based oils* (described in section 4), overpowered all CVD confounding factors.

As shown below, the significant causal variable in SELECT was only the EPA/DHA amounts from fish oil/marine oil as measured in plasma.

2.5. Plasma/Red Blood Cell (RBC) Fatty Acid Measurement

In view of the current emphasis placed on omega-3 series fatty acid metabolites, RBC analysis is now common today. However, *highly accurate* 21*st century quantitative analysis of plasma phospholipid analysis is superior to red blood cell* (*RBC*) *analysis* [8,9]. There are strong but limited correlations in plasma and erythrocyte, e.g., EPA (r = 0.90), DHA (r = 0.76), ALA (r = 0.76), and LA (r = 0.82). However, the amounts and proportions of fatty acid incorporation may be highly misleading based on RBC. For example, experiments show the proportion of LA (Parent omega-6) in plasma can be approximately double of that in erythrocytes. (The term "Parent" will be defined in Section 4.)

Furthermore, as the above experiments showed, the magnitude of the RBC dietary alteration manifests lower than in tissue, and the unsaturated phospholipid fatty acid proportions are different than tissue. For example, inhuman testing, erythrocyte phospholipid ALA (Parent omega-3) levels increased over a 12-month period from 0.1 to 1.6%—a 16-*fold increase*, whereas adipose tissue rose from 0.2 to 17%—an 85-*fold increase*. We see the difference between the RBC measurement and the actual physiologic tissue incorporation here is a 5.3-fold (530%) difference.

Although RBCs survive approximately 90 - 120 days, offering a greater time-based average of dietary lipid consumption, its measurement is not directly representative of actual physiologic tissue incorporation. Therefore, reliance on RBC analysis can be misleading.

Trans fats levels are often 4Xs greater in RBC than plasma (used in SELECT) and are incorporated into tissue as a percentage of dietary consumption [10]. With plasma fatty acid analysis (used in SELECT), it can now be seen and understood the (apparent) demagnification of trans fat amounts compared to an RBC analysis. Clinicians must understand the strengths and limitations of each method in their statistical analyses and conclusions.

Furthermore, *an apparently small increase in a blood marker—such as long chain fatty acids metabolites like EPA/DHA—can be significantly magnified in actual tissue*. These issues cannot be stated strongly enough.

2.6. SELECT Is a Baseline Plasma Measure Only—However, Plasma Lipid Analysis Is an Accurate Time Average

The SELECT plasma lipid measurement was conducted at baseline only. However, this is not problematic because recommendations to consume more fish and more fish oil supplements existed for over a decade prior. The baselines, therefore, on average, are adequately representative (if not a conservative underestimate over the course of the study). In view of these consistent medical and nutritional recommendations to consume more "oily"

fish/fish oil supplements, the measurements would be expected to be lower at baseline compared to the amounts consumed in later years of the study (on average)—not to decrease over time (on average). Statistically, the average of hundreds of patients is valid for this measurement. The sole concern would be whether one leg of the population were increasing or decreasing consumption more than the other leg over time. There is no reason to assume either leg, on average, would differ in this regard.

Though only an initial (single) plasma lipid measurement was performed per patient, it is known that residence times, measured via quantitative *tracer experiments*, show that elevated plasma levels of consumed DHA are maximum at 4 hours after ingestion, returning to baseline at 28 days post consumption. Elevations were increased from baseline for 28 days, providing sufficient averaging of dietary consumption [10,11]. Furthermore, the 2013 *JNCI* article's lead author (Dr. Theodore M. Brasky), in the 2013 analysis of SELECT, used two (2) blood draws in a separate prior trial, showing the same positive correlations between increased marine oil levels and increased prostate cancer cases [3].

Of significant interest and of great importance is that plasma DHA amounts are known to be significantly elevated in the elderly [10] (mean age of 77 years), by at least 40%, and EPA is elevated in the elderly by 50% - 100%. Furthermore, the elderly incurred a 220% elevation in plasma cholesterol esters (CE) after 7 days. That experiment showed approximately a *DHA half-life* (the time for half the substance to dissipate) in *plasma of* 10 *days*—additional confirmation that plasma lipid analysis is valid for a time average of dietary consumption.

From prolonged residence times, there is significant opportunity for EPA's/DHA's peroxidation to occur before tissue incorporation. Seventy percent (70%) of SELECT patients were greater than 60 years of age. Therefore plasma residence times of DHA was increased and their deleterious effects would be magnified.

3. Fish Consumption Is Not Significant to Eskimos

The medical profession has been told the Eskimos obtain significant EPA/DHA primarily from fish. This is false because researchers understood the Eskimo diet wrongly. As a result, generations of physicians, health professionals, and their patients were misled.

Eskimos have less cardiovascular disease (CVD) than many other populations so it was *assumed* that this was from fish consumption. These investigators made a huge mistake—they didn't look at their entire diet.

The high levels of fats in the Eskimo diet come primarily from seal meat (a mammal). Seal does contain EPA and DHA. However, in seal meat, the EPA/DHA is primarily on the first and third positions of the triglyceride chain, whereas in fish oils they are mainly on the second (sn-2) position—*an enormous difference in functionalit*y.

Far from fish being the primary food, Eskimos rely on mammal protein—seal, whale, caribou, bear, muskox—as well as birds and their eggs.

Incredibly, the initial investigation chose to focus merely on the insignificant fish component in the Eskimo diet. This mistake is causing millions of Americans and others around the world to be overdosed with these potentially toxic substances.

3.1. Fish Oil Impairs Normal Cellular Physiology: Pathophysiologic Disorders Are Expected

Fish oil supplements, in their "normal" although supraphysiologic amounts (calculated below), cause changes in membrane properties that impair oxygen transmission into and through the cell. These amounts are often prescribed, and accompanied by the incorporation of adulterated, non-oxygenating, or inappropriate polyunsaturated fatty acids (PUFAs) into the phospholipids of cell and mitochondrial membranes. Trans fats, partially oxidized PUFA entities, and *inappropriate omega-6*/*omega-3 ratios* (*caused by marine oil supplementation*), are all potential sources of unsaturated fatty acids that can disrupt the normal membrane structure, significantly increasing the potential for cancer [12].

All of the supraphysiologic, excess EPA/DHA cannot be beta-oxidized away. Thus, a significant amount of the excess will be physiologically incorporated into all cell membranes, detrimentally.

4. EFAs—Parents (PEOs) and Derivatives (EPA/DHA) and Carcinogenesis

There are only two true 18-chain carbon EFAs: Parent omega-6 and Parent omega-3. Linoleic acid (LA)—Parent omega-6—contains two double bonds, and alpha-linolenic acid (ALA)—Parent omega-3—contains three double bonds. Neither can be manufactured in the body; both must come from food. Longer-chain metabolites are synthesized from LA and ALA. These long-chain metabolites, not essential and incorrectly termed "EFAs," are correctly termed "derivatives."

For example, common derivatives of the omega-3 series are EPA (eicosapentaenoic acid) with five double bonds and DHA (docosahexaenoic acid) with six double bonds.

To clarify the issue in this paper and in general, I term LA and ALA "Parent Essential Oils" (PEOs) or "Parents." I term all long-chain metabolites "derivatives."

The body makes these important *derivatives* from Parents "as needed" in *minute amounts*. The literature often fails to clearly distinguish between these two vastly different substances. The physiology and biochemistry of Parent vs. derivatives are substantial and significant to humans.

A major mistake was made in the 20th century misdirecting researchers. It was *wrongly assumed* the vast majority of "Parents" would be converted into "derivatives." This didn't occur, causing the medical research community to proclaim there were ubiquitous metabolic deficiencies impacting the delta-6 and delta-5 desaturase enzymes. This has been shown to be categorically false by advanced 21st century quantitative methods (described later). Although metabolic disease, such as diabetes, may impact these pathways, the magnitude of the impairment is significantly less than assumed decades ago

In humans, typically no more than one percent (1%) of Parents are *naturally converted* into derivatives. Fish oil mania wrongly (and hazardously) assumes the converse.

4.1. Parent Omega-6 (18:2) Adulteration—The Prime Cause of Carcinogenesis: Decreased Critical Cellular Oxygenation

The 18:1 series are not expected to have the cancer-causing power of the *trans* 18:2 series, because only the unadulterated, fully functional Parent omega-6 series support both anti-cancer membrane functionality and cellular oxygenation, as Nobel Prize-winner Otto Warburg, MD, PhD clearly demonstrated [13-15]. Others have expanded on his seminal discovery [16,17].

4.2. Correlation between Lower Oxygen Tension and Prostate Cancer

Detailed exposition of the oxygen/cancer connection will not be presented here although this inverse relationship applies to any tumor in any organ. However, as an example of specific prostate cancer, it is well supported that hypoxia in the prostate tumor causes greater tumor aggressiveness [18]. Marine/fish oils do nothing to promote cellular oxygenation; that is a key role of Parent omega-6 (LA) [16].

5. Trans Fats

Trans fats are man-made fats chemically created from natural, unsaturated fats with at least one double bond in the *trans* configuration—either mono-unsaturated or poly-unsaturated—in particular, LA (Parent omega-6), formed during (partial) hydrogenation and vegetable oil processing. The sole (insignificant) exception is naturally occurring trans-vaccenic acid from ruminants—found in their milk, meat, cheese, etc. They do not occur naturally in significant amounts.

5.1. Food Processors Require Long Shelf Life

Created by food processors' need for long oil life during frying and baking, trans fats are found in all commercial restaurants, supermarkets' prepared food and frozen food sections, and even in fine dining restaurants' frying oils. The substrate for trans fats is Parent omega-6 (LA).

5.2. Trans Fats' Carcinogenic Properties Were Known in 1939

A study published in 1939 linked processed, hydrogenated cottonseed oil, containing trans fats, to increased risk of skin cancer [19].

Nor is this an isolated case. A 2005 study of 272 cases and 426 controls found a significant correlation between serum phospholipid C18 trans-fatty acids and increased risk of prostate cancer [20].

5.3. Δ9c, 12t 18:2: The Most Significant Trans Fat Found in Humans

The omega-6 series fatty acid isomer of LA—Δ9*c*, 12*t* 18:2—is the most significant trans fat found in humans [21]. If the product contains <0.5 grams per serving of trans fats, the manufacturer is *legally* allowed to claim zero (0) trans fats. This is highly misleading as the analysis below clearly shows.

5.4. Amounts of Trans Fats in Processed Food

A single tablespoon (14 g) of processed cooking oil contains on the order of 100,000 times as many defective LA (Parent omega-6) molecules as there are cells in the body[1]. The food label is legally allowed to state "0 grams," because it is less than 1%. Yet, just 0.5 grams of 1% adulterated oil consumed (a conservative estimate) contains 3600 defective trans fat molecules per cell. It is proven that physiologically, tissue and organs will in-

[1]The molecular weight of a triglyceride (any PEO-containing oil, functional or adulterated) is approximately 1000. A liter (slightly more than a quart) of oil contains approximately 1000 grams (about 2.2 pounds), and a mole (gm molecular weight) of any substance contains about 6×10^{23} molecules. Therefore, there is a mole of triglycerides in a liter of cooking oil. There are 64 tablespoons per liter. Simplifying to 100 gives 6×10^{21} (six thousand million trillion molecules of oil) per tablespoon (10^{23} molecules per 100 tablespoons = 10^{21} molecules). An order of magnitude calculation ignores the 6. A 1% defective amount is therefore (1/100) or 10^{19} molecules. The body contains about 100 trillion (10^{14}) cells. Therefore, the overload potential of trans fats on body cells is $10^{(19-14)}$, or 100,000 *adulterated* trans fats overwhelming each cell. There are actually many more defective molecules than the 100,000-fold factor from a mere 1% adulteration. Cooking oil weighs about 14 grams per tablespoon. Therefore, half a gram is 1/28th of a tablespoon (0.036 tablespoon). Multiply by the 100,000 defective PEOs in a tablespoon to determine the defective overpowering factor transfats have in half a gram of 1% adulterated cooking oil.

corporate both functional LA and defective, adulterated LA (as in trans fats) on a percentage basis of diet; e.g., if 3% trans fats are consumed, tissue and organs will contain approximately 3% harmful trans fat content [22-24].

6. Fish Oil Fails Extensively in Clinical Trials but These Failures Are Often Underpublicized

Since many medical professionals are under the wrong impression that fish oil incontrovertibly works, it is instructive to make clear there are *numerous recent and not so recent fish oil failures occurring across all clinical areas*. There are more (underpublicized) failures than supposed successes.

These failures should cause great pause. For example, in 2013 the *New England Journal of Medicine* announced conclusive failure in a superbly conducted clinical trial of fish oil to prevent CVD [25].

This seminalfailure caused editor-in-chief of *Medscape*, cardiologist Eric Topol, MD, to state, "I have an awful lot of patients that come to me on fish oil, and I implore them to stop taking it [26]."

The article, "Why Fish Oil Fails to Prevent or Improve CVD: A 21st Century Analysis," appearing in this issue, explains precisely why fish oil's failure is predictable and why there was no scientific reason to expect success [7].

Extremely powerful journal articles from other pathologies make clear that fish oil predictably either fails to help, or worse, harms patients. Two more recent journal articles with remarkable findings showed that fish oil did not help in organs with the greatest preponderance of DHA (brain and eyes)—even with low DHA levels (a supposed deficiency).

Alzheimer's victims, even those with low DHA levels, weren't helped [27]. Macular degeneration victims weren't helped by fish oil's significant DHA, either [28]. Once again, researchers were stymied at fish oil's failure to assist in reversing disease states in organs comprised of significant DHA-containing tissue. Logic dictates that if fish oil isn't effective in these organs to solve a DHA deficiency, it certainly can't be expected to be effective in other tissue/organs.

7. Skin Cancer Has Become Epidemic as Fish Oil Supplement Consumption Has Increased and Resulted in a Pathophysiologic Incorporation of DHA into Epithelial Tissue

Fish oil produces a pathophysiology in epithelial tissue, potentially leading to skin cancer. Likewise, adenocarcinoma of the prostate develops from aberrant epithelial cells. We know there are no Parent omega-3 or omega-3 derivatives like EPA/DHA naturally occurring in epithelial tissue [29,30]; therefore, any tissue incorporation is caused by supraphysiologic dietary consumption of marine oil. This consumption leads to a pathophysiologic state of the tissue or organ.

7.1. Increased Carcinoma, Increased Marine Oil Consumption: A Causal Relationship

A very strong melanoma/fish oil consumption association warrants attention. Skin cancer rates and fish oil consumption are both increasing. This is a very troubling (worldwide) association that must be addressed.

It is predictable that the countries consuming the most fish oil supplementation will contract the most skin cancer, and the most prostate cancer—and they do, as will be shown at the end of this section.

There are three quantitative physiologic facts that must be understood in determining the definitive cause-effect relationship with fish oil use and cancer contraction.

Physiologic fact #1: There is no Parent omega-3 [ALA] or omega-3 long-chain metabolites [EPA/DHA] in epithelial tissue [29,30].

Physiologic fact #2: Each of the body's 100 trillion cells, excepting those in epithelial tissue, is comprised of a lipid bi-layer with very little EPA/DHA, but a significant amount (25% - 33%) of LA and ALA [31-34]. The same is true for the mitochondrion, except it contains less ALA. Again, there is a physiologically negligible amount of EPA/DHA [35,36].

Physiologic fact #3: We know excess EPA/DHA displaces the main fatty acid in the membrane, Parent omega-6 (LA) [22].

It must be determined whether the incorporation of a supraphysiologic overdose of the derivatives EPA/DHA into epithelial tissue is the direct cause of the increased skin cancer and therefore all epithelial-related cancers. The logical answer is yes.

Dermatologists are at a loss to explain the increase in skin cancer regardless of recommendations to their patients that they should have less exposure to the sun. The science strongly suggests that fish oil is a significant culprit.

A seminal study in Norway revealed that *fish oil significantly increased the risk of skin cancer.* Highly underpublicized, but reported in *International Journal of Cancer* in 1997, this meticulous study (confirmed by pathology and cancer registry) of over 50,000 Norwegian men and women, showed approximately a 3-fold (3Xs) increase in melanoma in women using cod liver oil (considered a superb fish oil supplement). The study was particularly strong, based on its unbiased approach, high participation and response rate, the fact that dietary data

was collected prior to the onset of cancer, and that each participant had a complete follow-up regarding occurrences of cancer, death and emigration. In fact, all physicians and medical professionals in Norway are required to report malignant diseases to the Cancer Registry, and 98% of these cases are confirmed with microscopic tissue analysis [37].

In Norway, where fishing is a principal industry; they didn't want to see a negative finding and it wasn't publicized. This study shows fish oil causing or associated with an increase in cancer—not prevention of cancer.

7.1.1. Skin Cancer Is Constantly Increasing with No End in Sight

There is a definitive increase in severity of skin cancer every year, as a 2009 *Journal of Investigative Dermatology* article reported. Statistics showed a 3.1% *increase every year* from 1992 (little fish oil use) through 2004 (much more fish oil use), making *malignant melanoma* one of the fastest growing cancers in the world. This has been true both for men and for women. The researchers were careful to observe that this increase was not due to better reporting, but to a true increase in severity [38].

The incidence of cutaneous (skin) *melanoma*, the most lethal of the skin cancers, continues to increase, especially in women. A 2008 study [39] published in the *Journal of Investigative Dermatology* reported that among US Caucasian women there was an increase from 1973 (insignificant fish oil use) to 2004 (much more fish oil use) of from 5.5 *to* 13.9 per 100,000.

Australia and New Zealand are the greatest per capita consumers of fish oil (measured in tons/gross domestic product) [40]. They have the greatest skin cancer rates in the world. Due to Australia's intense sun, causal conclusions cannot be relied on.

However, one can conclusively say that fish oil certainly does not help reduce skin cancer because their rates are not decreasing as would be required *if* fish oil were effective. Therefore, fish oil consumption would not be expected to help any epithelial-based (carcinoma) cancers.

7.1.2. More Fish Oil Consumption to Increased Skin Cancer Risk Correlation

The countries with the greatest fish oil consumption rates, after Australia, are Scandinavia, Canada, and the United States [40]. They each experience extremely high (and increasing) skin cancer rates. Today, marine/fish oil has become America's #1 supplement, and the rest of the world quickly follows America's dietary recommendations. Are these carcinogenic correlations mere coincidence? No. Based on science, they are predictable.

Given that people are in the sun less and use sunscreen more, there are few valid reasons why skin cancer rates should be increasing worldwide. There have been suspicions placed on the ozone layer, and tanning beds for increased skin cancer rates. However, if these were the main causes, the remedies would have worked, and the increase would have reversed. That hasn't happened. Therefore, it is imperative that we examine the elephant in the living room—the consumption, in increasing amounts, of a substance that is scientifically proven to degrade the epithelial tissue. That substance is marine oil/fish oil.

While the above was offered as a compelling example of a strong, explainable *association* of fish oil demonstrating deleterious effects, what follows are true experiments detailing cause/effect pathologic harm by fish oil. The following are experiments with one variable—fish oil, making it a true cause/effect relationship. Results are so conclusive, no rational explanation is sufficient to discount them.

8. Fish Oil Failures Causing Increased Cancer and Metastases

8.1. Animal Experiment

Regarding EFA metabolism, rodents are similar to humans [41]. Fish oil accelerates cancer metastases. Decades ago, we were warned by *Cancer Research* of the damage caused by fish oil use, but few physicians or researchers were made aware of this finding. In 1998 it was demonstrated that rats fed fish oil had an amazing 7-fold (700%) increase in metastases in their liver just one week after colon cancer cells were introduced into their portal vein—increasing to an incredible 10-fold (1000%) in three weeks. This was compared to animals fed a low-fat diet [42]. The researchers stated: "This finding has *serious implications* for the *treatment of cancer patients with fish oil diet* to fight cachexia… [W]ith fish oil administered] over 1000-fold more metastases (size) than were found in the livers of rats on the low-fat diet… [W]e conclude that the enormous effect of Ω-3 PUFA [EPA/DHA] on colon cancer metastasis in the liver is *not mediated via alterations of the immune system*."

The alarming result has nothing to do with the "immune system"; rather, it is simply the supraphysiologic overdose of EPA/DHA. This pro-cancerous result should concern any physician or healthcare professional prescribing fish oil to patients. The researchers also had a subset that were administered (processed) safflower oil instead of fish oil. Using processed oil that is adulterated causes peroxidation problems of its own—*yet the processed oil showed significantly less problems than the fish oil*. All oils were kept at very low temperature and adequate vitamin E was supplied. Yet, *in vivo* fish oil still

caused both increased number—a 10-fold increase—and increased sizes of the metastases—1000-fold larger.

In 2010, *Cancer Research* published a historic article linking fish oil and increased colon cancer risk, as well as increased colitis [43,44]. The researchers had hypothesized that "feeding fish oil enriched with DHA to mice would decrease the cancer risk," but that they found the opposite to be true. Instead, they discovered that the mice *developed deadly*, *late-stage colon cancer* when given high doses of *fish oil.*

They observed *increased inflammation* and that, as a result, it only took four weeks for the tumors to develop. This was true for mice which received the highest doses of DHA as well as those receiving lower doses. The researchers stated, "Our findings support a *growing body of literature implicating harmful effects of high doses of fish oil consumption in relation to certain diseases.*"

The researchers were shocked because they had relied on prior "studies," not medical science, to anticipate the effects of fish oil. Of particular importance was that these researchers even found low doses of fish oil harmful.

In 2009, another significant journal article uncovered pro-metastatic problems with fish oil use, ultimately forcing the researcher to clearly state, "[*H*]*igh pro-metastatic effect of dietary omega* 3 [fish oil] fatty acids (fish oil) *rules out* the generalization that *these* [*fish*] *oils inhibit tumor growth* and progression" [45].

8.2. Human Experiment

Another alarming fish oil failure was reported in 2012 in *JAMA Internal Medicine*, as reported by Reuters. The study's lead author, University of Paris researcher Valentina Andreeva, was expecting to find omega-3 pills to be beneficial regarding cancer risk, but instead found no positive effects on men, and evidence of adverse effects on women [46,47].

The study showed that men on the placebo had the same cancer risk as men taking the omega-3 pills. But the supplements were not harmless for the women in the study, who showed a three-fold (3X) risk of developing cancer, and a five-fold (5X) risk of dying of cancer if they had taken the omega-3 oil. It is proposed that the men may have been less compliant, resulting in the difference between the sexes.

This sample of adverse cancerous effects is more than adequate to cause great concern to the medical community. These deleterious effects are all consistent with the known physiology and biochemistry of EFAs.

9. Tissue Incorporation of Dietary Fats Is Proportional to Consumption

The concentration in adipose tissue triacylglycerols is *roughly proportional* to dietary concentration and is now frequently used as a *measure of relative dietary intakes*, and it has been long known that the fatty acid composition of the diet can influence membrane fatty acid composition [23,24].

10. Inflammation and the Cancer Connection

According to one of the world's most renowned cancer researchers, Robert Weinberg of M.I.T. (originator of the term "oncogene"), "The connection between inflammation and cancer has moved to center stage in the research arena." (*Scientific American*, 2007) He has revised his leading textbook, *The Biology of Cancer* (Garland Science, 2006), to reflect this new understanding.

Fish oil causes inflammation *in vivo* because EPA/DHA spontaneously oxidize at room temperature and much more quickly at body temperature. Their harmful hydroperoxide products become incorporated in esterified cholesterol and it is well known in cardiology that oxidized cholesterol causes the inflammation leading to CVD.

The inflammation/cancer connection is confirmed with the finding that asbestos causes inflammation, reported in 2010 in *Medical News Today*. "For the past 40 years researchers have tried to understand why asbestos causes cancer. This research emphasizes the role of inflammation in causing different types of cancer" [48,49].

Inflammation alone, *regardless of initiating conditions*, *accelerates cancer proliferation*. Since 2007, cancer researchers understand and acknowledge that the fundamental, *prime cause of cancer is inflammation*, *not genetics* [50-52]. A further inflammation/cancer connection was reported in *Cancer Epidemiology*, *Biomarkers & Prevention in* 2005, with the statement that "There is a growing body of evidence supporting the role of chronic inflammation with prostate carcinogenesis and thus the associations of trans-fatty acids with increased inflammatory response may explain their associations with prostate cancer risk" [20].

10.1. Chronic Inflammation from Fish Oil Trumps Trans Fats' Carcinogenic Potential

Carcinogenictrans fats inhibit the delta-6 desaturase enzyme, which would otherwise be free to metabolize LA to PGE_1—the body's most powerful anti-inflammatory [20]. Therefore, a high trans fat level causes those patients to have impaired anti-inflammatory defenses. For EPA/DHA to be so strongly associated with prostate cancer, but not the trans fats with their known carcinogenic capability and their known devastating impact in

reducing the body's most powerful anti-inflammatory, PGE_1, a possible conclusion is that fish oil's inflammatory effect is greater; consequently, fish oil can be more carcinogenic than trans fats.

10.2. Leading Consumer of Fish Oil Also Leads in Prostate Cancer Contraction Rates: Cause-Effect Prediction Comes True

Prostate cancer in Australia/New Zealand—the world's #1 consumer (tons/GDP) of fish oil supplements [40]—also unfortunately leads the world in prostate cancer by nearly 15%. This is a staggering difference compared to the next region on the list, Western Europe, and 25% higher the region on the bottom of the list [53].

As reported by the World Cancer Research Fund (2008 data—"incidence rate"), "Incidence rates for *prostate cancer were highest in Australia/New Zealand*, *Western and Northern Europe and North America* and lowest in Asia. The incidence of prostate cancer is 25 times higher in Australia and New Zealand than in South-Central Asia [*no fish oil supplement consumption*]."

Australia/New Zealand's prostate cancer incidence rate is 104/100,000 population (2008 data—"incidence rate"). The next highest (Western Europe) is 94/100,000 population. *Therefore*, *AU/New Zealand has a* 10.6% *greater prostate incidence contraction rate* than its closest neighbor. This fact is staggering yet predictable.

The *incident rate* and *not the prevalence rate* is the most important measure of disease contraction because incidence is the number of new cases in a given time period in "person-years."

Fatty acid compositional analysis of the human prostate gland has proved difficult to obtain from the literature, but canine analysis is available. The canine prostate is particularly suitable as an experimental model. It is morphologically similar to humans; both human and canines are subject to prostate disease, both benign and malignant [54]. This study, published in *Lipids* in 2003, showed that the n-6/n-3 series content ratio (total lipids) was 11:1 in favor of Parent omega-6 and its derivatives compared to Parent omega-3 and its derivatives.

We see how little Parent omega-3 series fatty acids and its long-chain metabolites comprise prostate tissue. Normal plasma physiologic levels of the omega-3 metabolites EPA and DHA are very low. Once again, a forced supraphysiologic overdose of marine oil's EPA/DHA would alter physiologic tissue amounts of these respective fatty acid series.

11. Physiologic Excess of Omega-3 Series Fatty Acids/Metabolites Are Harmful

It was understood decades ago that consumed physiologic excess of omega-3 series PUFA is detrimental. Burns and Spector showed that the capacity of endothelial cells—relevant to carcinomas—and macrophages to release prostaglandins is reduced when they accumulate n-3 polyunsaturated fatty acids [55]. This is important because prostaglandins produced from PUFAs reduce the adhesion of tumor cells to microvascular endothelium. *Fish oil is known to decrease critical anti-inflammatory PGE_1 output in proportion to the amount of EPA/DHA consumed* [56].

This is another reason why IOWA showed Parent oils to be superior to fish oil regarding CVD; arterial compliance (more flexible arteries) occurred rapidly after fish oil was terminated and Parent Essential Oils (PEOs) initiated [7].

Population samples confirmed *more than* 10 *years improvement in arterial compliance with PEO implementation.* Regarding progression of CVD, fish oil supplements proved to be an *anti* anti-aging substance.

12. Marine Oils Spontaneously Oxidize at Room Temperature and *in Vivo*

This highly underpublicized medical fact goes a long way toward explaining marine oil's tremendous cancer causing potential in humans. Fatty, cold-water fish (the type we are told is best) live in temperatures as low as 32˚F, but warm-water fish may live in 70˚F waters and have 14Xs less EPA/DHA content than their cold-water relatives [57]. *At normal human physiologic temperatures*, *fish oil spontaneously becomes rancid*. This fact alone should cause tremendous concern.

A human placed in ice-cold, frigid waters would suffer hypothermia, freeze, and likely die. Fish don't freeze because they have higher levels of the EFA derivatives EPA and DHA than humans. Our ambient and physiologic conditions are not similar. Fish oil researchers never considered this important fact. EPA/DHA acts as "biological antifreeze" to fish living in frigid waters. Humans don't require such copious amounts because we have an internal temperature of 98.6˚F.

12.1. DHA Spontaneously Oxidizes at Room Temperature and *in Vivo*: Understanding Its Unique Biochemistry

Regardless of the level of anti-oxidants added to the fish oil supplement, rancidity/peroxidation *in vivo* is a very significant and problematic issue. Because of the five double bonds in EPA and six double bonds in DHA, these metabolites are highly sensitive to heat. Oxidation of EPA leads to generation of a mixture of aldehydes, per-oxides, and other harmful products. Even in the absence of exogenous oxidizing reagents, highly polyunsaturated,

long-chained EPA is readily oxidized at room temperature; DHA, with its additional double bond, is more so. 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 additional antioxidant supplementation* to the diet. Again, this effect strongly suggests extensive oxidation of omega-3 fatty acids such as EPA/DHA *in vivo*. This led to a 14% decrease in life expectancy in those animals fed fish oil [58]. These facts should cause great concern to any healthcare practitioner prophylactically recommending fish oil use.

12.2. Primary & Secondary Lipid Oxidation and Hydroperoxides

There is much to know regarding specific lipid oxidation markers. Supplementation with polyunsaturated fatty acids (in particular, EPA/DHA), as opposed to saturated fatty acids, results in a *statistically significant increase in lipid peroxidation in the plasma and liver*. *Oxidative damage to DNA* in bone marrow was recorded in aged, but not observed in young, rats when a polyunsaturated diet was employed [59].

Organ damage occurs from marine oil use, as shown decisively in an important primate (monkey) lipid oxidation experiment where increased *lipofuscin* (a measure of rancidity and cause of "age spots") was formed in the liver. Furthermore, it was demonstrated in humans and primates such as the monkey that no amount of *in vivo* antioxidants stop EPA/DHA damage as measured by lipofuscin. The lipofuscin level was three times (3Xs) greater in the livers of monkeys fed fish oil. Additionally, Thiobarbituric Acid Reactive Substances (TBARS), like malondialdehyde levels, were four times (4Xs) greater than in the monkeys fed corn oil with no EPA/DHA (s*ee* Section 12.4). Most importantly, *these researchers found that even a tenfold increase in alpha-tocopherol*, *a potent antioxidant*, *was not fully able to prevent the peroxidative damage from fish oil* [60].

Lipids—one of the world's top journals in the field—makes clear how fish oil raises levels of extremely harmful malondialdehyde (MDA) [61]… Ingestion of CLO [cod liver oil] was associated with an increase in MDA excretion in all six subjects. The mean increase of 37.5%, from 24.5 ± 3.5 μg to 34.7 ± 2.5 μg MDA (mean + SEM), was [statistically] significant… CLO ingestion again was associated with an increase in MDA excretion in all subjects. The mean increase of 54.3%, from 31.7 μg to 49.1 μg MDA/sample was highly significant."[2]

12.3. Rancidity Determination Requires Multiple Individual Tests

Rancidity is a qualitative term that is not simply quantifiable. Numerous tests are required for a complete analysis of lipid peroxidation and its associated secondary and terminal stage oxidative products. Lipid oxidation involves the continuous formation of hydroperoxides as primary oxidation products that *may* break down to a variety of both volatile and nonvolatile aldehydes. Peroxide value (PV) alone can be meaningless.

As an example, the P-Anisidine test measures the aldehyde content generated during decomposition of hydroperoxides. It correlates well with volatile substances. Volatile aldehydes and other later stage aldehydes leave behind a nonvolatile product that the p-Anisidine test measures well (via correlation).

As an example, "pristine" *fish oil can have an allowable p-Anisidine value of* 19 *showing significant secondary stage oxidation* [62], whereas a plant-based PEO formulation *without fish oil is closer to* 4—confirming fish oil's rancidity *in vivo*.

12.4. Levels of Harmful Thiobarbituric Acid Reactive Substances (TBARS) Increase with Fish Oil/Marine Oil Consumption

A 2000 study reported in *American Journal of Clinical Nutrition* found that plasma TBARS (substances which react to the organic compound thiobarbituric acid, and which are a result of lipid peroxidation) were >21% higher after fish-oil supplementation than after sunflower-oil supplementation, and 23% higher than after safflower-oil supplementation. [Note: this is despite the fact that the usual non-organic sunflower and safflower oils are significantly adulterated.] The article explored the limitations of the various assays available for the measurement of lipid peroxidation *in vivo*, including the F2-isoprostane assay's inability to provide direct information about the peroxidation of 20:5n-3 [EPA] and 22:6n-3 [DHA] [63].

The above article clearly warns that researchers may unknowingly use quantitative tests that are incapable of presenting a full picture of total PUFA oxidation or offer results that are statistically not valid. Researchers must be aware that TBARS measures numerous harmful aldehydes, malondialdehyde being one of them. MDA levels without P-Anisidine and TBARS levels are incomplete and misleading. Higdon *et al*., made clear that significant dietary changes may require a modification of specific

[2]The researchers attempted to show in another group (6 patients), that the oxidation as measured by urinary MDA was minimized. However, on detailed analysis, *that result was NOT statistically significant*—there was more than a 5% error rate, meaning it *should not and cannot be stated as correct—the specific reason the field of statistics was developed*. They put this most important fact in a footnote where few physicians would see it. There is no doubt that MDA increases directly from fish oil consumption.

lipid testing for full utility.

Scientifically, fish oil oxidizes in plasma causing numerous deleterious carcinogenic products. To the contrary, PEOs don't suffer this problematic issue.

12.5. Bis-Allylic Bonds: Fish Oil's Spontaneous Rancidity *in Vivo*

Long-chain fatty acids contain *bis-allylic* hydrogens whereby the -C=C- units are separated by a single-bonded -C- [carbon] atom. The hydrogen atoms attached to each of these intermediate -C- atoms are called *bis-allylic* hydrogens and have the lowest C-H (weakest) bond-energies of the fatty acid chain.

The weak bond makes them *enormously susceptible* to attack by Reactive Oxygen Species (ROS) [64]. DHA with its 6 double bonds contains 5 bis-allylic bonds and is therefore 320 *times more susceptible to oxidative attack*, *i.e.*, becoming rancid, than monounsaturated oleic acid (18:1) which has no bis-allylichydrogens in its chain. A saturated fat membrane containing just 5% DHA (fish oil) is 16 *times more susceptible* to peroxidative damage [65].

Fish oil's DHA is 7 *times more susceptible* to peroxidative damage than LA (Parent omega-6), the most significant fatty acid by both weight and functionality in the cell's bi-lipid membrane. The shifting of the body's antioxidants required to combat this physiologic insult by marine oil supplements causes a shortage elsewhere.

13. Fish Oil Destroys Critical Mitochondrial Physiologic Functionality

13.1. All Tumors Suffer (Often Irreversible) Respiratory Damage

In remarkable research sponsored by the National Cancer Institute and published in 2008 and 2009, researchers found major abnormalities in content or composition of a complex lipid called *cardiolipin* (CL). These abnormalities are "found in all tumors, linking abnormal CL to *irreversible* [as Warburg detailed] *respiratory injury.*" [66]. Cardiolipin is a fat-based complex phospholipid found in all mitochondrial membranes, almost exclusively in the inner membrane, and is intimately involved in maintaining mitochondrial functionality and membrane integrity. It is used for ATP (energy) synthesis, and consists roughly of 20% lipids [67].

With dietary marine/ fish oil supplementation and its EPA/DHA, variation in membrane fatty acid composition, influencing accelerated unnatural lipid peroxidation, significant effects on oxidative damage to many and varied cellular macromolecules occur. For example, peroxidized cardiolipin in the mitochondrial membrane can inactivate cytochrome oxidase by mechanisms similar to hydrogen peroxide as well as mechanisms unique to organic hydroperoxides.

"*Thus lipid peroxidation should not be perceived solely in a* '*damage to lipids*' *scenario*, but should also be considered as a *significant endogenous source of damage* to other cellular macromolecules, such as proteins and DNA (including mutations) [65]."

In another article, Dr. A. J. Hulbert makes clear the importance of mitochondrial functionality with his statement, "The insight that the exceptionally long-living species, Homo sapiens, potentially provides for understanding the mechanisms determining animal longevity, is that the fatty acid *composition of mitochondrial membranes may be much more important than the composition of other cellular membranes*" [64].

Furthermore, the noncharged structure of aldehydes allows their migration with relative ease through hydrophobic membranes and hydrophilic cytosolic media, thereby *extending the migration distance far from the production site*. On the basis of these features alone, *these carbonyl compounds can be more destructive than free radicals and may have far-reaching damaging effects on target sites both within and outside membranes*.

Mitochondrial cardiolipin molecules are targets of oxygen free radical attack, due to their high content of fatty acids—normally containing negligible long-chain omega-3 metabolites like DHA—unless pharmacologically overdosed as with fish oil supplementation. Mitochondrial-mediated ROS generation affects the activity of complex I, as well as complexes III and IV, via peroxidation of cardiolipin following oxyradical attack to its fatty acid constituents [65].

Most importantly, there is naturally *no Parent omega-3 or its metabolites in cardiolipin*. Its main substrate is Parent omega-6 [68].

Alteration of mitochondrial structure by consumption of fish oil was known in 1990, and published at that time in an article in the *Proceedings of the National Academy of Science*, as follows: "Phospholipase A2 activity and *mitochondrial damage are enhanced when mitochondrial membranes* are enriched with *n*-3 *fatty acids* [from fish oil] [69]."

13.2. Mitochondrial Functional Requirement to Defeat Cancer

Oncologists understand that mitochondrial functionality is a prime factor in the prevention of cancer. Fish oil negatively impacts mitochondrial functionality. A seminal experiment appearing in *Cancer Cell* in 2006 is critical to the understanding of how fish oil causes such alarming mitochondrial damage, emphasizing that the connection is between fish oil consumption and cancer

[68].

This test was conducted on live animals, not in a petri dish. Rats were fed fish oil or beef tallow. The scientists then examined the activity of critical mitochondrial enzymes from their kidney cells. The fish-oil-fed animals suffered an incredible 85% enzyme loss, while the beef-tallow-fed animals suffered a 45% enzyme loss. (The *highly processed* beef tallow contained an insignificant amount of critical Parent essential oils—PEOs—less than 4%.)

Fish oil caused a 40% *net additional reduction in critical mitochondrial enzyme production*, *i.e.*, *cellular respiration is highly diminished*.

14. ALA to ω-3 Long-Chain Metabolites EPA/DHA Conversion: Updated 21st Century Analysis

What percentage of PEOs becomes converted (naturally) to long-chain metabolites such as GLA, AA, EPA, DHA, etc.? 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*.

This singular mistake in assuming normal, very high conversion amounts, whereas in actuality they are extremely low natural physiologic conversion amounts, led to the irrational fish oil mania and its inherent harm.

Contrary to dogma, the enzymes that produce PEO derivatives (the delta-6 and delta-5 desaturase enzymes) are not impaired in the vast majority of patients [70]. Conversion of dietary ALA [Parent omega-3] to DHA is unlikely to ever normally exceed 1% in humans [71]. 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* [72]—not the highly misleading 15% conversion rate that is often quoted.

NIH researchers determined the amount of DHA utilized in human brain tissue to be a mere 3.8 mg ± 1.7 mg/day. Therefore statistically, brain tissue in 95% of all subjects, allowing for variation in brain size, would consume or naturally produce a mere 0.4 mg - 7.2 mg of DHA per day [70].

New, twenty-first century quantitative research from both NIH and USDA show considerably lesser amounts of natural DHA conversion/usage from ALA than the medical community and researchers have been led to believe. *These conversion amounts are extremely small and naturally limited*. This mistake often leads to supra-pharmacologic recommendations and can potentially overdose patients by factors of 20-fold to 500-fold, depending on specific supplement and amounts prescribed.

The body simply cannot oxidize these tremendous overdoses of EPA/DHA. Supraphysiologic amounts are forced into tissue, causing gross physiologic imbalance and great potential for harm.

14.1. Rodents Have a 50-Fold Safety Margin: Humans Have a Significant Margin of Safety, Too

More 21st century research from the National Institutes of Health (NIH) confirms extremely low natural conversion rates [73]. Rats fed a DHA-free but α-LNA (n-3 PUFA) [Parent omega-3] adequate diet naturally produced from Parent omega-3 (ALA) fifty times (50Xs) more DHA than required—an enormous "safety factor." We would expect a similar margin of safety in humans.

An experiment measuring plasma fatty acids in 62 firefighters concluded that the consumption of ALA-enriched (Parentomega-3) supplements over a 12-week period elevated long-chain metabolites, EPA and DHA levels. This experiment unequivocally showed the *unimpaired* effectiveness of ALA *conversion* from Parent omega-3. It further stated that the general population could achieve the amounts of ALA required to obtain these effects by modifying their dietensuring adequate ALA (Parent omega-3) [74].

Furthermore, even vegetarians consuming little or no fish (no dietary EPA/DHA) had acceptable EPA/DHA levels [75]. This finding provides incontrovertible evidence that there is no widespread EPA/DHA deficiency requiring marine oil supplementation.

14.2. Amounts of EPA/DHA in Fish Oil—Pharmacological Plasma Overdoses

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. Furthermore, EPA ⇔ DHA. This is not the case with PEOs. Their long-chain metabolites are unidirectional only, increasing in chain length.

As an example, using the USDA food composition research formulas covered earlier, if patients consumed a supplement of 600 mg of Parent ALA, they would naturally convert it to EPA by no more than the (generous) factor of 0.25% = 1.5 mg EPA and 1.5 mg × 0.63 × 0.37 = 0.35 mg to DHA in patient plasma. Therefore, just one capsule provides the amounts shown in the analysis below, and many people are overdosing even more by taking 2 to 4 fish oil capsules each day, likely in part because the cardiology and heart recommendations are often "EPA + DHA ranging from 0.5 to 1.8 grams per day." What overdose does this translate to?

14.3. Potential EPA/DHA Overdoses Are Frequent

Potential Overdose: This equates to the following plasma overdoses: EPA = 180 mg/1.5 mg = 120 times overdose; DHA = 120 mg/0.35 mg = 340 times overdose. These facts should cause great pause and concern. (Technically, more is required for additional metabolic pathways aside from direct tissue incorporation, but it is not a significant amount by weight on a daily basis.) Therefore, physicians and other health professionals may unknowingly be routinely overdosing patients prophylactically with supraphysiologic supplemental amounts of omega-3 derivatives.

15. SELECT: Why Fish/Fish Oil Supplements May Be More Hazardous than Trans Fats

Physiologic/biochemical analysis of the pathophysiologic effects of fish oil's so-called "active components," EPA and DHA, should cause great pause in their prophylactic supplemental recommendations.

Trans fatty acids, like those found in margarine, fried foods and adulterated fats, are a known carcinogenic. But surprisingly in the 2013 SELECT study analysis by Brasky, *et al*., trans fatty acid levels were not shown to be related statistically to prostate cancer risk. There is a plausible explanation for this incredible result: The carcinogenic impact of trans fats is weaker than the carcinogenic impact of fish oil supplements.

As harmful as trans fats are, the marine oils may be *either a faster acting* carcinogen *or a more powerful* carcinogen so that they effectively "masked" the trans fats' carcinogenic effects.

This is analogous to a patient slowly developing a coronary occlusion—that will ultimately result in a heart attack via thrombus—coincidently dying in a car accident prior to arresting. Compared to death from the auto accident, the trans fats' slower acting, yet negative impact on CVD becomes irrelevant to the cause of death.

Marine oil supplements are inflammatory and carcinogenic—in part because of their inherent autoxidation and DNA damaging properties (becoming spontaneously rancid at physiologic temperatures) as the above analysis detailed. *Their damage may occur faster and more powerfully than the carcinogenic damage caused by trans fats*. This (shocking) conjecture from the SELECT Trial analysis cannot be easily dismissed. Additional research is needed to confirm this conjecture.

16. Discussion

Fish oil supplementation and "oily" fish consumption, with their "active ingredients," EPA and DHA, have been recommended as a solution to patient health problems. Such recommendations were based, in part, on specious "associations" of better health with fish consumption in populations such as the Eskimo/Inuit.

In fact, though underpublicized in 2011, the largest and strongest study ever performed—because of its large number of cases—of stroke and cerebral infarction, in an analysis of over 30,000 women, a high consumption of *lean fish* (with *much less oil content*) was *associated with a significantly reduced risk of total stroke*—the opposite of expectations [76]. This finding is consistent with the 2010 IOWA screening experiment finding of decreased vascular compliance ("hardening of the arteries") occurring with fish oil use [7].

Fish oil can't work, based on human physiology and biochemistry. Humans don't live in frigid waters where an "anti-freeze" is required, *i.e*. EPA/DHA. These so-called "active components" spontaneously oxidize at room temperature and are even more problematic at physiologic body temperatures, causing numerous deleterious aldehyde secondary and end products regardless of anti-oxidant levels. Precious anti-oxidants are shuttled away from the areas they normally protect to deal with the unnatural, supplemental dietary overload of EPA/DHA. No amount of anti-oxidant consumption can protect the patient from this supplemental overload [60].

Even a relatively "small" supraphysiologic increase in plasma phospholipid EPA/DHA levels is catastrophic to patient health.

Prostate cancer in Australia/New Zealand—the world's #1 consumer (tons/GDP) of fish oil supplements—also unfortunately *leads the world in prostatecancer by nearly* 15% [53]. Other countries exhibit the same positive correlation with increased fish oil consumption increasing incidence of prostate cancer.

This predicted result based on the deleterious physiology/biochemistry of fish oil supplement's supraphysiologic amounts of EPA/DHA content cannot be dismissed. Dr. Glantz's logic makes clear that the fish oil consumption/prostate cancer *association* coupled with *incontrovertible medical science* makes for a true *cause-effect relationship* [6]. This predictable cause-effect relationship is demonstrated in the highest fish oil consuming population in the world.

It has been clearly shown that the general population does not suffer impairment of delta-6/-5 desaturation enzyme impairments, as previously thought in the 20st century.

The SELECT Trial conclusions are confirmed as prostate and other cancers are predicted to increase in patients consuming supraphysiologic amounts of EPA/DHA (fish oil) on purely theoretical grounds, utilizing known physiology and biochemistry.

17. Conclusion

Fish oil, in the supraphysiologic, prophylactic amounts often consumed, is harmful; possibly even more harmful than trans fats. The medical profession needs to thoroughly review the 21st century physiology and biochemistry and offer the appropriate patient warnings. As Professor of Medicine, Stanton Glantz, makes clear: A statistically analyzed observational study combined with independent evidence (established medical science), allows cause/effect conclusions [6]. The 2013 SELECT analysis and conclusions meet this criterion. It is sincerely hoped that future researchers will approach the fish oil controversy with a more comprehensive grasp of the biochemistry and physiology involved and a healthy skepticism for conclusions based on the simplistic "preponderance of studies (open to misinterpretation)," while disregarding indisputable established medical science.

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Why Fish Oil Fails to Prevent or Improve CVD: A 21st Century Analysis

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ABSTRACT

In May 2013, The Risk and Prevention Study Collaborative Group (Italy) released a conclusive negative finding regarding fish oil for those patients with high risk factors but no previous myocardial infarction. Fish oil failed in all measures of CVD prevention—both primary and secondary. This study was so conclusive that Eric Topol, MD, editor-in-chief of Medscape and Medscape's Heartwire for cardiologists, issued a new directive to patients to stop taking fish oil, *i.e.*, long-chain EFA metabolites of EPA/DHA. Fish oil's failure is shown to be consistent with known physiology and biochemistry: there should never have been any expectation of success. To the contrary, true EFAs, linoleic acid and alpha-linolenic acid, termed Parent Essential Oils (PEOs), fulfill fish oil's failed promise. Fish oil supplements contain supra-physiologic amounts of EPA/DHA. Recommendations are often paramount to pharmacologic overdose. Unlike fish oil, which failed to decrease 19 markers of inflammation, PEOs do decrease inflammation. The first screening experiment comparing fish oil with Parent EFA oils, the seminal IOWA experiment utilizing pulse wave velocity, demonstrated unequivocally that fish oil contributes to hardening of the arteries, aging subjects by nearly 4 years ($P < 0.0001$). To the contrary, PEOs increase arterial compliance, making subjects' arteries "biologically younger" (increased arterial compliance) by more than 11 years compared to subjects taking fish oil fish ($P < 0.001$).

Keywords: Fish Oil; EFAs; Parent Essential Oils; PEOs; LDL-C; PUFA; Arterial Compliance; Cardiovascular Disease; CVD; PGE_1; PGI_2; Prostacyclin; Endothelial; IOWA Experiment; Pulse Wave Velocity (PWV)

1. Introduction

CVD-related pathophysiology, including stroke, is by far the #1 killer in the United States. Fish oil, with its "active ingredients" EPA and DHA, has been recommended as a solution. While pre-2007 cardiovascular studies were associated with an improvement with fish oil, post-2007 studies show significant accumulated failure [1]. Confirmation of fish oil failure was independently summarized in a meta-analysis of 14 studies comprising 20,485 patients and published in 2012 [2].

Of their 1007 articles retrieved, only 14 met the criteria of randomization, double-blindness, and placebo-controlled. Clearly, an enormous number of poorly conducted studies in the journals have conclusions that can't be relied on and are misleading physicians worldwide. The researchers stated, "Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease". The final blow was in May 2013. This clinical trial, one of the most comprehensive and well-conducted trials to date, utilized over 12,000 patients and 860 general practitioners [3]. To understand its full impact, it is important to provide exact quotes of these researchers and reviewers of this landmark study: "In summary, we conducted a randomized trial of n-3 fatty acids [fish oil] in a large population of patients with multiple cardiovascular risk factors but no history of myocardial infarction. The trial incorporated systematic efforts to optimize medical therapies and control cardiovascular risk factors. On the basis of the results, we conclude that there was no significant benefit of n-3 fatty acids [fish oil] in reducing the risk of death from cardiovascular causes or hospital admission for cardiovascular causes."

This monumental failure caused editor-in-chief of Medscape, cardiologist Eric Topol, MD, to state, "I have an awful lot of patients that come to me on fish oil, and I implore them to stop taking it" [4]. The present study,

with its efficacious dose, arms physicians with data to tell patients who have not had an MI and who don't have heart failure that n-3 fatty acid supplementation with fish oil is not effective. He called fish oil a "no-go", noting that if the supplement had no effect in this high-risk patient population, of whom just 40% were taking statins, it's hard to imagine that n-3 fatty acids [fish oil] would provide any benefit in lower-risk subjects. "Fish oil does nothing", continued Topol. "We can't continue to argue that we didn't give the right dose or the right preparation. It is a nada effect."

2. Physiologic Details of LDL and Parent Essential Oils (PEOs) in Arterial Plaque

2.1. Decreased NO by Oxidized LDL

Clearly, fish oil fails, but why? Are researchers looking in the wrong place? As a start, it is well known that nitric oxide (NO) is required for optimal vascular health. Chin and colleagues presented convincing evidence that a lipid component in *oxidized LDL inactivates nitric oxide* [5,6]. The key to improved cardiovascular health is in this lipid component. The answer becomes apparent by focusing on the established physiology and biochemistry of intimal (the matrix of tissue directly lining the artery) plaque. It will be proved how fish oil could never prevent or reverse CVD; there never should have been expectation for success. To the contrary, Parent Essential Oils (PEOs), the only true EFAs, will be shown to both prevent and reverse CVD via multiple metabolic pathways.

2.2. EFAs—Parents (PEOs) and Derivatives

There are only two true 18-chain carbon EFAs: linoleic acid (LA), with two double bonds, and alpha-linolenic acid (ALA) with three double bonds. Neither can be manufactured in the body; both must come from food. LA is termed "Parent" omega-6; ALA is termed "Parent" omega-3. Longer-chain metabolites are synthesized from LA and ALA. These long-chain metabolites, not essential and incorrectly termed "EFAs", are correctly termed "derivatives". For example, common derivatives of the omega-3 series are EPA (eicosapentaenoic acid) with five double bonds and DHA (docosahexaenoic acid) with six double bonds. To clarify the issue in this paper and in general, I term LA and ALA "Parent Essential Oils" (PEOs) or "Parents". I term all long-chain metabolites "derivatives". The body makes these important derivatives from Parents "as needed" in minute amounts. The literature often fails to clearly distinguish these two vastly different substances.

2.3. 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—in particular, when supra-pharmacologic amounts of long-chain metabolites are consumed, such as the case with fish oil supplements. A pharmacologic overdose can't all be oxidized away for energy or otherwise. Consequently, much of "the overdose" is forced into tissue composition, causing an improper structure—often in maintaining a linear relationship as does plasma, liver, and RBCs [7-9]. Cellular bilipid membrane structure and its LDL-C structure warrant intense investigation. Each of a human's 100 trillion cells consists of a bilipid membrane. Importantly, PEOs comprise 25% - 33% of their polyunsaturated lipids [10]. Additionally, every mitochondrion, typically a hundred to thousands per cell contain them too [11,12]. PEOs can be considered the "brick and mortar" of every cell, tissue, and organ, including mitochondria. In contrast, aside from the brain, eyes, and nervous system, most tissue and organs contain few derivatives like EPA/DHA.

2.4. 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, merely its esterified moiety—the acyl side chain. That's a big 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 $-C_7H_{14}CH{=}CH-C_8H_{17}$ with the double bond in cis configuration.

Lipoproteins transport cholesterol and its esterified PEOs to the tissues via apoprotein B-100 ($ApoB_{100}$) (**Figure 2**). Although the molecule itself may become oxidized, that likelihood is extremely low. What is primarily oxidized are the fatty acids esterified to LDL-C (**Figure 1**). Quantities of esterified LA (Parent omega-6) are approximately 85% of its overall 50% fatty acid content [13].

2.5. Failure of LDL-Cholesterol to Prevent CVD

A review of a cholesterol/CVD causal effect categorically failed: Among 12 populations with similar cholesterol levels (clustered around "normal" levels—5.70 to 6.20 mmol per liter (220 to 240 mg per dl), the blood pressure readings and the serum cholesterol levels were not predictive of ischemic heart disease mortality [5]. If it were, a 10% reduction should have had significant positive effects; it didn't. Nothing has changed today regarding LDL-C's dismal success rate in both predicting

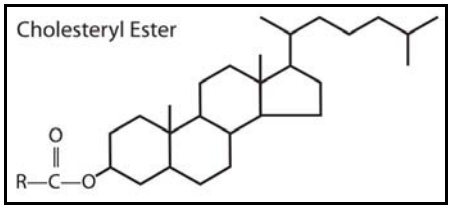

Figure 1. Cholesteryl ester.

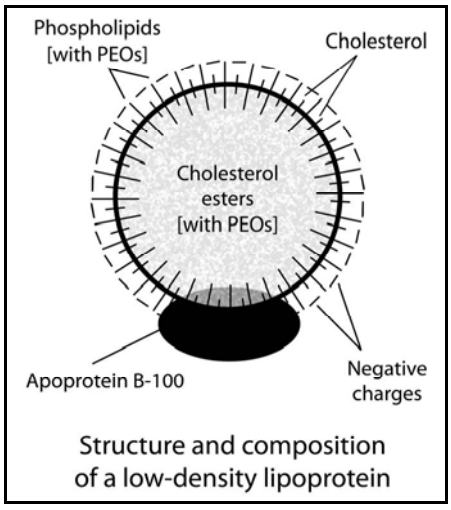

Figure 2. Structure and composition of a low-density lipoprotein showing the significance of its esterified cholesterol structure.

and lowering CVD by its general modification (lowering of LDL-C).

2.6. Esterified Cholesterol Detailed

The cholesterol molecule (better termed cholesteryl) is tied to a structure that *does change*—particularly, its EFA variable "R" component (**Figure 1**). It is well understood that the PEO LA dominates the esterified portion of cholesterol. The majority of the cholesteryl ester component is LA (Parent omega-6) [14]. The cholesterol ester portion is highly significant compared to free cholesterol or phospholipids (**Figure 2**). Approximately 70% of the cholesterol in the lipoproteins of the plasma is in the form of cholesterol esters attached to apolipoprotein B [15]. Of dietary cholesterol absorbed, 80% - 90% is esterified with long-chain fatty acids in the intestinal mucosa [16].

2.7. LDL-C Is NOT Oxidized in the Bloodstream

Cholesterol itself is extremely resistant to oxidization, whereas its main esterified component, Parent omega-6 (LA), is more easily oxidized, especially ex vivo. Dietary LA that has already become oxidized prior to ingestion ex vivo is ubiquitous through processing of foods or overheating, since heating in the presence of air enhances peroxidation of PUFA glycerol esters [17,18]. These insights suggest that looking in a new direction for the prevention of heart disease is warranted.

Strongly supporting this thesis is the fact that normal anti-oxidant levels are lower than would be presumed to be adequate and normal if analysis weren't performed. The sum molar ratio of all antioxidants to PUFA is a mere 1:165 (0.61%), with one antioxidant molecule having to protect the large number of 165 PUFA molecules. The total number of fatty acids bound in the different lipid classes of an LDL particle with a molecular mass of 2.5 million is on average 2700, of which about one-half (1/2) are polyunsaturated fatty acids (PUFAs), mainly linoleic acid (Parent omega-6), with small amounts of arachidonic acid and docosahexaenoic acid (DHA). It is highly unlikely than 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 anti-oxidants is too small for oxidation in vivo to be a significant physiologic issue [5,13]. The sole logical conclusion is that the PUFA, in particular, LA, is being consumed and entering the body in an already oxidized state.

2.8. LDL-C Is Transporting a "Poison"

Prof. Gerhard Spiteller, who is Chairholder of Biochemistry, Institute of Organic Chemistry at the University of Bayreuth, Germany, has investigated EFAs and their degradation products—specifically, the influence of these substances in the physiology of mammals. He 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 cholesterol in the liver [19]. LDL then carries these toxic compounds into the endothelial walls where they cause cell damage. Injury is not caused by an increase in free cholesterol but by an increase in cholesterol esters [20]. In atherosclerotic patients, LDL cholesterol is altered ex vivo by oxidation, and this altered LDL is taken up in unlimited amounts by macrophages. Dead macrophages filled with cholesterol's 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 significant failure of statins. By statin's lowering of LDL-C, its esterified PEOs are also lowered, both adulterated [good outcome] and fully functional [bad outcome]. This is problematic. By focusing on the ex vivo LA that has already become oxidized prior to ingestion through processing of foods, cooking, or overheating, a solution can be found to mitigate this damage.

2.9. Importance of Parent Omega-6 and Metabolites

The majority of the plasma fatty acids are LA (Parent omega-6). Mitigating the damage caused by *ex vivo* intake of already oxidized LA is possible. Compensation by ingesting fully functional, unadulterated, nonoxidized LA is a significant EFA-based anti-CVD solution. Additionally, the metabolites of LA—in particular, PGE_1 and PGI_2 (prostacyclin)—are significant vasodilators. PGE_1 is also a potent anti-inflammatory. If functional LA bioavailability is lowered, the potential for inflammation will rise, leading to atherosclerosis. Weiss, for example, has noted that PGE_1 (produced from functional Parent omega-6) reduces the fibrin deposition associated with the pathogenesis of atherosclerosis [21]. Membrane fluidity increases when more functional (undamaged) polyunsaturated fatty acids—in particular, linoleic acid—are available to incorporate into the membrane lipid bilayer.

If there is a deficiency of fully functional LA in the diet, the body will substitute into cell membranes nonfunctional LA or even a nonessential fatty acid, such as oleic acid (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 [22]. 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.

2.10. Arterial Intima: Endothelial Tissue Comprised of Epithelial Cells

The innermost lining of arterial intima is endothelial tissue, comprised of epithelial cells containing significant LA, but no alpha-linolenic acid (ALA) [23,24].

A significant biologic effect of oxidized LDL is its cytotoxic effect on cultured endothelial cells directly lining the arterial wall [5]. Adulterated 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 [25]. Therefore, atherosclerosis can be prevented/arrested if endothelial cells are fully functional [26].

2.11. Parent Essential Oils—PEO Deficiency: Fully Functional vs. Adulterated

Not distinguishing an adulterated (processed) EFA against a fully functional unprocessed EFA—in particular, LA—is the prime cause of confusion leading to inconsistent clinical trials on cardiovascular health. From the above discussion, the criticality of distinguishing between the effects of adulterated versus unadulterated forms of LA is obvious. Failure to do so has led to the incorrect and misleading conclusion that dietary intake of LA increases CVD risk [27].

With functional LA deficiency 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 how it may be prevented [28]. Oxidation of LDL-C causes significant depletion of LA (Parent omega-6) [5].

With ingestion of fish oil (EPA/DHA) there was a corresponding decrease in tissue's LA, causing pathophysiologic deficiency [29].

2.12. PEOs in Plasma, Lipids, and Esterified Cholesterol

It is necessary to analyze the PEO content of plasma lipids (lipoproteins, triglycerides, and esterified cholesterol) to determine the specific "bad actor" in CVD and confirm LA's prime importance. LDL's esterified linoleic acid is the major source for lipid peroxidation products, yet linoleic acid is highly resistant in LDL against oxidation [30]. This is important to understand.

With all the focus on omega-3 series fatty acids today, both Parent and derivative, 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 just 1% ALA (alpha linolenic acid, Parent omega-3) [30]. Derivatives such as EPA/DHA are naturally much less significant in quantity than LA. 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% (ALA is 0.5%) in cholesterol esters. This high preponderance of LA is pervasive throughout: The LA/ALA ratio in triglycerides is 23:1; n-3 PUFA makes up only 1% - 2% of fatty acids in plasma [31]. Even in the brain, LA/ALA uptake is 100 times greater in favor of LA [31].

2.13. Composition of Arterial Plaque

Current anti-CVD recommendations lack a firm physiologic/biochemical 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 [32,33]. 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 [34].

3. Fish Oil Is Expected to Cause CVD: Pathophysiology of Fish Oil

3.1. Fish Oil Spontaneously Oxidizes at Room Temperature and *in Vivo*

Fish oil is expected to contribute to CVD, not prevent it: a) Regardless of anti-oxidant level added to the fish oil supplement, rancidity/peroxidation upon ingestion is a very significant and problematic issue. Because of the 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 even in the absence of exogenous oxidizing reagents. 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 addition of antioxidant supplements to the diet. Again, this effect strongly suggests extensive oxidation of omega-3 fatty acids such as EPA *in vivo*. This led to a 14% decrease in life expectancy in those animals fed fish oil [35]. As shown above, PEOs don't suffer this problematic issue.

In primates and humans such as the monkey, no quantity of *in vivo* antioxidants will stop EPA/DHA damage as measured by lipofuscin, the peroxidized "age spots." Lipofuscin was three-fold (3Xs) greater in the livers of monkeys fed fish oil. Furthermore, another measure of oxidative damage, the basal thiobarbituric acid reactive substances (TBRS) levels, were four-fold (4Xs) greater than in the monkeys fed 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 [36].

3.2. Fish Oil Causes Decreased Prostacyclin Production

Prostaglandins are capable of both limiting thrombosis and reversing thrombosis in atherosclerotic patients [37]. Prostaglandin PGE_1 is the body's most powerful anti-inflammatory and vasodilator, and prostacyclin (PGI_2) is a vasodilator, and prevents both platelet adhesion and aggregation. These are both omega-6 metabolites. Fish oil increases *endothelial* platelet aggregation in heart patients [38]. In patients with atherosclerosis, prostacyclin (produced in endothelial tissue) biosynthesis fell by a mean of 42% during the fish-oil period [extremely bad outcome]. Synthesis of the platelet agonist thromboxane A_2 (produced in the platelets) declined by 58% [good outcome]. This may first appear a reasonably successful intervention, but that analysis is naïve and very wrong. Atherosclerotic patients require increased intimal PGI_2 output, as vessel wall thrombogenecity and not reduced platelet adhesion, is a much more significant factor for minimizing thrombosis [39]. Template bleeding times were significantly prolonged in all patients [bad outcome].

3.3. Fish Oil Raises Blood Glucose Levels and Decreases the Insulin Response

Elevated resting blood glucose levels are a diabetic's nightmare. Spontaneous auto-oxidation of blood glucose is a significant cause of diabetic patients' elevated increased risk of CVD. Both fish oil supplements and even "oily fish" itself are highly problematic for diabetics. In 2011, researchers looked at the effects on Type II diabetic patients eating more fish. Only from *non-fatty* fish, containing more Parent omega-6 and much less EPA/DHA, did the experiment show significantly decreased blood sugars [good outcome]. Further, those who ate "fatty" fish saw a decreased insulin output of 21% [bad outcome] compared to those not eating "fatty" fish [40]. "Fatty" fish (containing more EPA/DHA), not a supplement, caused the elevated blood glucose. EPA/DHA fish oil supplements cause elevated blood glucose and blunt the insulin response in diabetics. This deleterious finding was known years ago [41,42].

Since "fatty/oily" fish caused the same deleterious effects as the supplement, the only logical conclusion is that fish oil—in any form—is harmful to any diabetic. Diabetes is America's #1 epidemic and both oily fish and fish oil supplements exacerbate the condition.

3.4. Fish Oil Displaces Critical Omega-6 Metabolites Harming Tissue Structure

Importantly, fish oil potentially damages the brains of both infants and adults because critical omega-6 series metabolites are displaced [7]. The medical journal's authors specifically warned against feeding fish oil to human infants. This experiment was performed in rodents but the results are applicable to humans because EFA metabolism is similar and applicable to both mammals and rodents [9]. Systemic rises in fish oil's EPA is largely compensated by decreased Parent omega-6 [29].

3.5. Amounts of 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.

3.6. Parent-to-Derivative Metabolism and Amounts

What percentage of PEOs becomes converted (naturally) to long-chain metabolites such as GLA, AA, EPA, DHA, etc.? 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. This singular mistake in assuming very high conversion amounts, whereas in actuality they are extremely low conversion amounts, led to the irrational fish oil mania.

Contrary to wrong dogma, the enzymes that produce PEO derivatives (the delta-6 and delta-5 desaturase enzymes) are *not impaired* in the vast majority of patients [43]. Conversion of ALA [Parent omega-3] to DHA is unlikely to *ever normally exceed* 1% *in humans* [44]. 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 15% conversion rate that is often-quoted [45].

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 0.4 mg - 7.2 mg of DHA per day [43]. New, twenty-first century quantitative research from both NIH and USDA show 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 mistake often leads to recommendations that are supra-pharmacologic and can potentially overdose patients by factors of 20-fold to 500-fold, depending on specific supplement and amounts consumed. The body cannot simply oxidize these tremendous overdoses of EPA/DHA; they are too great a quantity.

3.7. No Delta-6/-5 Desaturase Impairment in (Average) Patients

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 [46]. Certainly, Nature would insure 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) and found conversion adequate with sufficient intake of ALA [Parent omega-3] [47].

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 [48,49]. Confirmation in 2010 showed vegetarians with an intake of 0.3% DHA compared to fish eaters produced 85% of the EPA levels and 83% of the DHA levels that consumers of fish did. These amounts are within the "normal" ranges [48].

There is no widespread impairment in the typical patient whatsoever; the normal conversion amounts are simply very low.

4. The Most Predictive Physiologic Measurement of Cardiovascular Health

Blood markers have been less than ideal in predicting cardiovascular health. Utilization of LDL-C levels alone has been a dismal failure. The best noninvasive method of evaluating arterial health is pulse wave velocity (PWV). Hardening of the arteries, *i.e.*, arteriosclerosis, is a prime cause of cardiovascular disease and patient death. A stiff artery could result from either or both of the following conditions: 1) physiologic impairment of the arterial tissue, 2) occlusion inside the artery, *i.e.*, atherosclerosis.

Arterial stiffness is an accepted, strong, independent predictor of cardiovascular events and mortality [50]. While direct measurement of PWV is the "gold standard" requiring physician skill and time, a new method based on photoplethysmography is available. Digital pulse analysis (DPA) was the next evolution in photoplethysmography and is based on the measurement of reflected infrared light. Photoplethysmography has been validated for accurately calculating systemic arterial compliance (flexibility) [51]. Subject output is compared to an existing large population database by age. The computer matches the subject to the significant sample database and outputs a "biologic age." Inherent experimental error of the mean is ± 5 years.

Digital Pulse-Wave Analysis (DPA)

The Meridian DPA™ (Meridian Medical Co, Ltd., South

Korea) is an FDA 510(K) cleared device for diagnostic use. A non-invasive screening device, the Digital Pulse Wave Analyzer™, accurately measures arterial stiffness, a composite of both large and small arteries, along with aging based on prior population samples in their database. Because fish oil and plant-based EFA-containing oils are available in unlimited amounts without prescription, and this is also a noninvasive *screening study*, no IRB is required. A non-invasive finger probe (as used with a pulse oximeter) is utilized. The machine self-calibrates and a computer performs the analysis—no interpretation is required. The reading correlates to population biologic age samples—it is impossible to manipulate readings.

The only criteria for subject exclusion of the study was either a reading could not be accurately gained from the subject, e.g., weak pulse or impairment of light through fingernails or for reasons that would invalidate the DPA reading, *i.e*., subject use of beta-blockers, ACE inhibitors, and all medications that artificially lower blood pressure so that the DPA reading would not be valid. Diabetes, high cholesterol, and all high-risk patients, if requested screening, were included. Both accuracy and repeatability of the machine are excellent.

5. Materials and Methods

Subjects were recruited in Iowa. A plant-based EFA supplement high in PEOs, [redacted], was used. Subject consumption amount was 725 mg per each 40 pounds per day of subject bodyweight; the average amount per patient per day being 2,900 mg.

Three (3) groups were screened: Group I—Long-term PEO users (34; 22 females and 12 males, aged 35 - 75 with median age 62; mean usage 90 months, median usage 24 months); Group II—Short-term PEO users (16; 9 females and 7 males, aged 46 - 84 with median age 64; mean usage 3 months, median usage 2.5 months); Group III—Fish oil to PEO usage (15; 8 females and 7 males, aged 46 - 74 with median age 60; mean usage 3.1 months, median usage 4 months).

Various brands of fish oil were used in the "Fish oil to PEO users" (Group III) leg of the screening. Since all oils used are commonly available in any quantity, no Institutional Review Board (IRB) is required. (Peskin is a consultant to Your Essential Supplements, Inc. and other companies.)

Investigating Oils with Respect to Arterial Health: IOWA Screening Experiment

To the author's knowledge, this is the first time PEOs were used to compare their arterial compliance (flexibility) improvements against fish oil. This is a broad-based population screening—the most realistic population to see effectiveness, if any.

6. Results

All statistical analyzes were independently performed by Alexander Kiss, PhD (Biostatistics). Group I (long-term PEOs only) statistics simply looked at the group's average chronologic age vs. their arterial compliance biologic age based on historical populations from the computer's database. For Groups 2 and 3, a "before/after" analysis, the paired t-test, was performed (**Table 1)**. Group I results were an average of 8.8 years decrease in "biological age" compared to their chronological age ($p = 0.001$); NNT = 1.4: 73% of all subjects improved their cardiovascular system. Group II results were an average of 7.2 years decrease in "biological age" ($p = 0.001$); NNT = 2.3: 43% of subjects improved in a very short time frame. Group III results were an average of 11.1 years decrease in "biological age" ($p = 0.0001$); NNT = 1.2: 87% of subjects improved in a very short timeframe; the most significant improvement in any population. Each group's results were highly statistically significant.

Results with Additional Patient Risk Factors

Seven subjects had "high" cholesterol levels while taking fish oil supplements before changing to PEOs. Six of the seven patients decreased their cardiovascular "biological age" by ceasing fish oil and converting to PEOs. NNT = 1.2: an 83% effectiveness rate in this sub-group. One subject with both "high cholesterol" and diabetes improved after replacing fish oil with PEOs. Two subjects taking statins decreased their cardiovascular biological age by 20 years after ceasing fish oil and replacing with PEOs (NNT = 1).

7. Discussion

Arterial compliance is the most accurate physiologic assessment of a subject's cardiovascular health. The highly statistically significant results and excellent NNTs confirm the theoretical predictions of both the failure of fish oil to increase arterial compliance, and the significant success of PEOs to improve arterial compliance across all populations.

Table 1. PEOs increase arterial compliance.

PEO Group	No. Subjects	Median Age	"Biologic Age Compared to Physical Age (yr)"	P-value
Long-term	34	62	−8.8	0.001
Short-term	16	64	−7.2	0.001
Ceasing fish oil/PEOs	15	60	−11.1	0.0001

The most remarkable finding was that subjects taking fish oil prior to PEOs obtained the most improvement. This was anticipated since those subjects started at a greater vascular deficit caused by the fish oil consumption. Ceasing fish oil use allowed the arterial system to revert to "normal". Once the vascular system was back to "normal", the expected improvement from PEOs, as shown by the other groups, was also achieved, resulting in an even greater decrease in biological age. Clearly, fish oil accelerates vascular aging.

It takes 18 weeks to fully rid patients of the negative effects of fish oil [52]. The subjects in the IOWA experiment were measured at an average of 13 weeks after ceasing fish oil usage. If they had been measured at the full 18 weeks, we would expect an even greater decrease in "biological age". Particularly significant is the positive effect of subjects' *additional* 54% *improvement in decreased cardiovascular* "*biological age*" *by merely discontinuing fish oil supplementation*. Furthermore, the greatest effectiveness both on a percentage basis and greatest endpoint effectiveness occurred in the ceasing fish oil/converting to PEO group (NNT = 1.2: an 87% population effectiveness both on a percentage basis and greatest endpoint effectiveness occurred in the ceasing fish oil/converting to PEO group (NNT = 1.2: an 87% population effectiveness), absolutely confirming fish oil's harm to the cardiovascular system when measured by arterial compliance.

Both the success of PEOs as well as the horrific failure and potential harm of fish oil supplements to negatively affect arterial compliance was predicted and consistently demonstrated.

Fish oil use decreased subject's arterial compliance, causing "hardening of the arteries"—a "biologic aging" of the subject group by nearly four years.

Compared to PEOs, fish oil users had an "11-year-older" cardiovascular system as measured by arterial compliance population scans—more than a decade's additional "hardening of the arteries" compared to their physical age.

8. Conclusion

Theoretically, it has been shown why fish oil supplementation with its EPA/DHA active components never had a physiologic or biochemical basis to either prevent or reverse CVD. Worse than doing nothing, fish oil causes harm. It has been explained physiologically what the correct EFA components must be (PEOs) to fulfill fish oil's failed promise and to positively effect cardiovascular health. IOWA is the first clinical screening experiment to measure arterial compliance in subjects using fish oil and PEOs. For the first time, using the most direct and effective physiologic measure, fish oil in the doses suggested, at least in regards to arterial compliance, is unequivocally shown to be an *anti* anti-aging substance.

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