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

- Diabetes (Type 1 & Type 2) including Neuropathy
- Lipid-Enveloped Viruses (including COVID series)
- Alzheimer's
- Dermatological Conditions
- Cardiovascular Disease
- Inflammatory Bowel Disease
- Chronic Fatigue (including post viral syndromes)
- Fatty Liver Disease Including NAFLD
- Multiple Sclerosis (MS)
- Cancer

Respiratory Diseases With Chronic Inflammation

- Mesothelioma
- Idiopathic Pulmonary Fibrosis (IPF)
- Chronic Obstructive Pulmonary Disease (COPD)

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INTRODUCTION:

Most physicians and healthcare professionals have not been exposed to EFA-based science. Although extremely important, the field is mischaracterized by many as simply an exploration of fish oil. It is so much more than that. Because the field of eicosanoid physiology and its strong link to pathophysiology of disease is technically complex, this article is limited to an overview focusing on impaired Δ-6 and a direct consequence of that impairment — decrease in production of PGE_1. Compensating for this impaired pathway has not been fully exploited until now. This article's purpose is to provide introductory insights — with the minimum of complexity — that most physicians have not yet seen.

While treating patients for a particular disease / disorder, physicians may not be aware that the patient may also be suffering from an Essential Fatty Acid (EFA) impairment of the Δ-6 desaturase pathway (D6D). This impairment is increasing rapidly in the general population and in younger select patient populations. The increase in disease can be explained from a biologic, chemical, and pathophysiologic viewpoint. The body's initial modulator of inflammation is PGE_1, which requires ***CIS*-LA** (unadulterated Parent omega-6). This is accomplished via the Δ-6 Desaturase Pathway (*See* illustration - page 18). **PGE_1 is a potent systemic vasodilator, anti-inflammatory, and immune system regulator.**

No modality of patient treatment will be optimized without understanding and optimizing patients' EFA-based metabolic pathways; in particular, the significance of D6D and PGE_1 optimization.

Importantly, PGE_1 can exert both immunosuppressive and immunoenhancing activities in *vivo* — on an "as needed" basis by the body.[1] PGE_1 modulates critical T-cell activation with dysregulated release of interleukin (IL)-6, IL-17, and other cytokines.

Understanding a disease's etiology is crucial. If the Δ-6 desaturase pathway is impaired or inhibited, all subsequent long-chain derivatives (GLA, DGLA, AA, EPA, DHA, etc.) — made via successive desaturate pathways — are also impaired. In addition to exacerbating disease states, this "cascade of impairment" would also be expected to impede wound (e.g., diabetic foot ulcer (DFU), and surgical healing, and it does.

"Auto-immune" diseases / disorders have become epidemic. A physiologic explanation is because an impaired Δ-6 desaturase pathway significantly decreases PGE_1 output. **PGE_1 "throttles down" the inflammation cascade**. [Technically, PGE_1 raises level of cyclic AMP, 15(OH)DGLA – *inhibits conversion of free*

[1] Winkelstein, A and Kelly, VE, "The Pharmacologic Effects of PGE_1 on Murine Lymphocytes," *Blood* (1980) 55 (3): 437-443.

Arachidonic Acid to Leukotrienes & other metabolites of 5- and 12-lipoxygenases, and initiates T Lymphocyte Suppressor cells.]

Important note:
Pharmaceutical "anti-inflammatory" drugs (i.e., steroids / corticosteroids / NASIDs), work by "blocking or impeding" critical pathways (e.g., cyclooxygenase — COX-1 and COX-2, Lipoxygenase, etc.). Long-term, these drugs inhibit the Δ-6 Desaturase enzymatic pathway and decrease critical PGE_1 and PGI_2 signaling molecules — leading to serious side-effects. Short-term, "treat / minimize the symptoms" but inadvertently "feed the cause" — resulting in long-term negative effects.

To the contrary, optimizing PGE_1 output via a properly calibrated EFA formulation, will NOT CAUSE harmful or unintended side-effects (e.g., addiction).*

***** NSAIDs *block* the COX enzymes and reduce production of critically important prostaglandins. Steroids are even more *disruptive* to EFA metabolism, and long-term drug intolerance occurs. TNF inhibitors carry their own black box warnings.

As the following journal article details, there are a multitude of factors causing impairment of the Δ-6 desaturase pathway:[2]

"…Other factors which inhibit D6D activity are diabetes, alcohol and radiation, all of which may be associated with accelerated aging. PGE_1 activates T lymphocytes, inhibits smooth muscle proliferation and thrombosis [blood clotting], is important in gonadal function and raises cyclic AMP levels in many tissues. It is a good candidate for a key factor lost in aging."

An additional and often overlooked significant cause of impairment is because patients consume adulterated cooking oils; often over decades — laying the foundation for this metabolic impairment.[3]

Of course, an impairment in the functioning of one organ / tissue system, can lead to impairment of another organ / tissue system. For example, impairment of diabetic nerve functioning due to hypoxia — inducing reduced blood flow in the vascular system — leads to diabetic retinopathy, nephropathy, and increased cardiovascular distress. Chronic inflammation will start a chain reaction. If anti-inflammatory pathways are not activated, the results can be disastrous (e.g., *See* COVID / SARS below).

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[2] Horrobin, DF, "Loss of Δ-6 desaturase activity as a key factor in aging," *Medical Hypothesis*. (1981) sep;7(9): 1211-20.
[3] Anton SD, et al., "Differential effects of adulterated versus unadulterated forms of linoleic acid on cardiovascular health*," J Integr Med*, 2013; 11(1): 2–10.

I find an illustration may be helpful. Picture a house in Houston, Texas, in late February 2021. The ambient temperature dropped dramatically even though the exterior structure was sound. Many people had to abandon their homes because utilities (electricity, heat, and water) were not properly functioning.

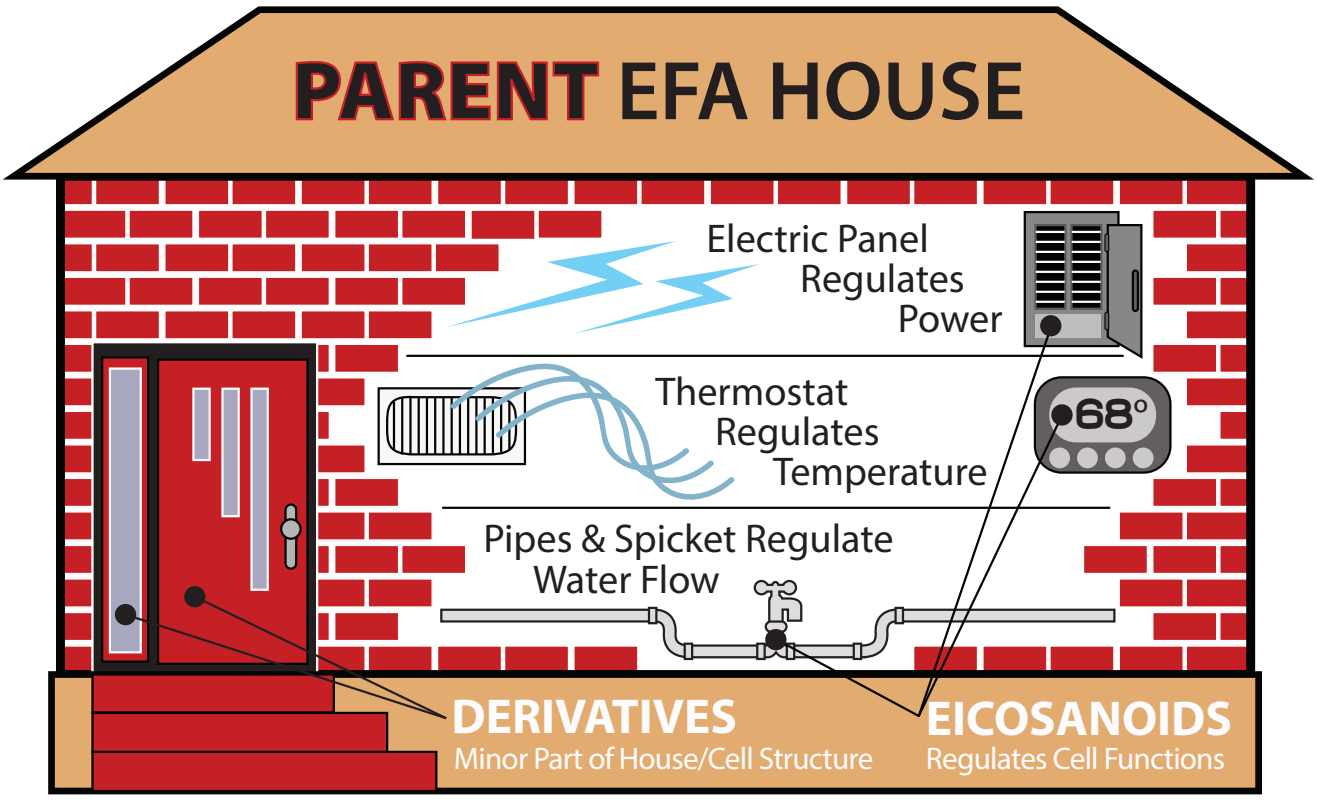
This house / utilities analogy is applicable to what is required from patients' proper EFA metabolism. There are 3 main classes of EFA-related function:

1) **Parents**: The "brick and mortar" of each cell membrane (Parent omega-6 / -3; LA & ALA) — high quantities (25% - 33%) in of each of the body's 100 trillion cell membranes.

2) **Derivatives**: Made from the 2 "Parents" in small quantities (e.g., GLA, DGLA, AA, EPA, DHA, etc.).

3) **Eicosanoids**: The complex signaling molecules. Made from the Derivatives in even smaller quantities. They may not even enter the bloodstream and can be extremely short-acting.

A home with broken / crumbling walls and great heat and water is insufficient for living, just as a home with great structure (lots of Parent EFAs only) and no electricity, heat, or water in winter is insufficient for living.



Note:
Quoted passages are used extensively. I want you seeing the scientist's / researcher's direct statements.

Following is a brief, significantly referenced summary of diseases and disorders caused / associated with Δ-6 desaturase impairment:

Type I and Type II Diabetic Patients Suffer Impaired Δ-6 Desaturase

Diabetic patients often suffer from numerous issues such as retinopathy, neuropathy, nephropathy, and foot ulcers. It is well documented that diabetic patients have impaired Δ-6 desaturase (D6D) metabolic pathways from impaired insulin production.[4,5,6] In particular, this metabolic defect causes a poor anti-inflammatory response in Type I patients. **Even with insulin therapy, the D6D pathway is still deficient** in **Type I patients**:[7]

> "**Diabetes, even when controlled by regular insulin injections, reduces the metabolism of linoleic acid, but the effect [of insulin use] is less than previously published**. The fatty acid compositions of plasma and liver microsomal lipids are not reliable indices of the delta-6 desaturase activity in diabetes."

Type II patients also suffer significant impairment of D6D activity.[8] Compensating for this impaired pathway has not been fully addressed until now.

"Incubation of human erythrocyte membrane with low concentration of prostaglandin E1 [**PGE_1**] or prostacyclin **increased the binding of 125I-labeled insulin** to the membrane…. The effect of prostaglandin E1 on the increased binding of the insulin was found to be **reversible** and depended on the occupancy of the autacoid molecules on the membrane and showed positive cooperativity…. **Binding capacity increased 2-fold**."[9]

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[4] Brenner, RR, "Hormonal modulation of Δ-6 and Δ-5 desaturases: case of diabetes," *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 68 (2003), 151-162.
[5] Das, UN, "Essential fatty acids: biochemistry, physiology and pathology," *Biotechn*., 2006, 1, 420-439.
[6] Mikhailidis, DP, et al., "The effect of dihomogammalinolenic on platelet aggregation and prostaglandin release, erythrocyte membrane fatty acids and serum lipids: evidence for defects in PGE_1 synthesis and Δ^5-desaturase activity in insulin-dependent diabetics," *Diabetes Research* (1986) 3,7-12.
[7] Brown JE, Lindsay RM, Riemersma RA, "Linoleic acid metabolism in the spontaneously diabetic rat: Δ-6 desaturase activity vs. product / precursor ratios," *Lipids*. 2000 Dec;35(12):1319-23.
[8] Huang M, et al., "FADS Gene Polymorphisms, Fatty Acid Desaturase Activities, and HDL-C in Type 2 Diabetes," *Int. J. Environ. Res. Public Health*, 2017, 14, 572.
[9] Ray, TK, et al., "Regulation of insulin receptor activity of human erythrocyte membrane by prostaglandin E1 [PGE_1]," *Biochim Biophys Acta*. 1986 Apr. 25,; 856(3):421-7;

Insulin sensitivity increases with PGE_1 output.[9]
Because of the reversibility of insulin binding, the impaired pathway must be compensated for on a daily basis.

"Levels of PGE_1 in the serum of IDDs [insulin dependent diabetics] were significantly lower than those of the healthy volunteers $p<0.002$ at all sampling times."[10]

"…These results demonstrated that PGE_1 maintained the phenotype of VSMCs [vascular smooth muscle cells] **via the AKT/mTOR-dependent autophagy, which prevented diabetes-induced vascular complications.**[11]

Diabetic patients frequently consume p*rocessed foods containing adulterated oils*.[3] They are at great risk for ***chronic low-grade cellular inflammation — triggering long-term cellular stress.*** The team, led by Professor Ernst, described how the UPR [unfolded protein response] ***senses nonfunctional / adulterated membrane lipids and responds accordingly***, triggering **chronic inflammation**:[12]

"Cells in which the UPR [unfolded protein response] has been activated can produce larger quantities of proteins, but they also become more sensitive [hypersensitive] — a bit like a finely tuned race car. As Robert Ernst explains: 'Whereas a racing car will often fail after completing a hundred super-fast laps because the engine has overheated, a tractor (representing a normal body cell) will continue to drive up and down the field for a lot longer, but also a lot slower.' Why these high-performance cells are so much more sensitive was not known up until now.

"According to this new mechanism, the UPR is activated not only by misfolded proteins, but also by anomalous membrane lipid compositions. Secretory cells [e.g., the pancreas] are particularly sensitive to these changes, because they have already activated their UPR to produce more proteins and therefore at **risk of 'overheating'** [inflamed] — just like the racing car engine described above. The study provides a new perspective on the **active role of *biological membranes*** may be a game changer for the ***understanding of a great variety diseases***.

[10] Mikhailidis, DP, et al., "The effect of dihomogammalinolenic on platelet aggregation and prostaglandin release, erythrocyte membrane fatty acids and serum lipids: evidence for defects in PGE_1 synthesis and Δ^5-desaturase activity in insulin-dependent diabetics," *Diabetes Research* (1986) 3,7-12; Dutta-Roy, A, "Effect of Evening Primrose Oil Feeding on Erythrocyte Membrane Properties in Diabetes Mellitus," *Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine*, Wiley-Liss, NY, 1990, pages 505-511.
[11] An X.-R., et al., "Prostaglandin E1 inhibited diabetes-induced phenotypic switching of vascular smooth muscle cells through activating autophagy," *Cell Physiol Biochem* 2018;50:745–756.
[12] Halbleib, K., et al., "Activation of the Unfolded Protein Response by Lipid Bilayer Stress," *Molecular Cell*, Vol. 67, Issue 4, pp 673-684.e8, August 17, 2017; "Molecular biologists discover an active role of membrane lipids in health and disease," August 4, 2017 in biology / cell & microbiology, phys.org.

"…[D]escribed how the UPR senses membrane lipids and responds accordingly. Working in close collaboration with scientists from Goethe University and the Max Planck Institute of Biophysics, both located in Frankfurt, the research team from the Department of Medical Biochemistry and Molecular Biology at Saarland University has identified a novel mechanism that leads to **UPR activation** and that **can trigger long-term stress in cells** [**chronic inflammation**].

"In 2011, Peter Walter and David Ron, pioneer in the field of human UPR, came to regard the relationship between membrane lipids and the UPR as a central unresolved question in the field.

"Both unfolded proteins and **aberrant membrane lipid compositions**[3] [from consumed processed cooking oils] are sensed by Ire1… the UPR [unfolded protein response] **senses membrane lipids** and responds accordingly. According to this new mechanism, the **UPR is activated** not only by misfolded proteins, but **also by anomalous membrane lipid compositions**. Secretory cells are particularly sensitive to these changes….

> "**We now have the conceptual framework to understand why secretory cells [e.g., the pancreas] are hypersensitive to changes of their membrane lipids induced by the diet**."[12]

Diabetic Neuropathy (*See* separate whitepaper)

Diabetic Wound Healing (also *See* Cancer Section, pg. 15)

See / request the separate whitepaper devoted exclusively to expedited DFU healing. There was a fantastic article in *Developmental Cell* that apparently never made it into the clinical journals, nor did I include it in the DFU paper, so I'll limit this section to its reference.

Fat cells, if fully functional, help to heal a wound; they can be motile and not exclusively stationary:[13]

"Fat body cells in Drosophila [a fly] play a surprising role [in their healing capability] of sealing wounds and preventing infection… The cells, which were previously thought to be immobile, propel themselves forward toward wounds with a wormlike wave motion, rather than adhering to and pushing off of other structures like most motile cells do.

"After arriving at the site of a wound, fat body cells perform several useful functions [including minimizing infections]. "They work a lot harder and are more of a team player than was previously thought.… The fat cells crowd into the wound and waft debris to the edges of it, where the debris can be consumed by the immune cells. The fat cells are large enough that anywhere from one to four cells can plug the wound, playing a role similar to a clot or scab in vertebrates. The cells physically keep bacteria out of the

[13] Franz, A., et al., "Fat Body Cells Are Motile and Actively Migrate to Wounds to Drive Repair and Prevent Infection," *Developmental Cell* 44, 460–470 (2018).

wound while it heals, while helping increase the production of antimicrobial peptides to quell any infections. The fat cells stay at the wound site until it is healed. 'Then they detach and just swim off, as though their job is done,' Martin says."

With processed / adulterated cooking oil consumption, their healing capability is impaired. Does this effect translate to humans? It likely does.

LIPID-ENVELOPED VIRUSES INCLUDING COVID / SARS

If your patient has an impairment in the Δ-6 desaturase pathway and contracts a virus, the effects could be devastating. The majority of viruses are enveloped with lipids. In particular, fatty acids of the omega-6 series are known to inactivate (lipid) enveloped viruses.[14]

"PUFAs have anti-bacterial, anti-viral, anti-fungal, anti-parasitic actions LA, ALA, and AA have bacteriostatic effect on both gram-positive and gram-negative bacteria. Both LA and AA can inactivate animal herpes, influenza, Sendai, and Sind-bis virus within minutes of contact."[15]

"There are millions or billions of these viruses out there. The immune system fights back and attacks the virus; this is what **causes inflammation** and fever. But in extreme cases, the **immune system goes berserk**; particularly in the "Coronavirus" (SARS-CoV-2); [causing a **cytokine explosion**], causing more damage than the actual virus."[16] This harmful effect can be mitigated:

> "**Essential fatty acids** are natural anti-inflammatory agents and therefore **decrease the production of *cytokines and histamine*, which can contribute to neurotransmitter imbalance."**[17]
>
> **PGE_1 activates (Cytotoxic) T Lymphocytes** — the body's powerful "killer cells" of intruders / infections / bacteria / viruses, etc. (British Society for Immunology).

An illustration of viral action will be used with COVID-19 / SARS since this type of virus causes fast-acting tissue / organ distress in patients with an existing Δ-6 desaturase impairment.

[14] Thormar, H., et al., "Inactivation of enveloped viruses and killing of cells by fatty acids and monoglycerides," *Antimicrob Agents Chemother*. 1987 Jan; 31(1): 27–31; Yan, B, et al., "Characterization of the lipidomic profile of human Corona-virus infected cells: implications for lipid metabolism remodeling upon coronavirus replication," *Viruses* 2019 Jan; 11(1): 73.
[15] Das, UN, "Can essential fatty acids reduce the burden of disease(s)," *Lipids In Health And Disease* 2008, 7:9.
[16] Yong, E., "Why the Coronavirus Has Been So Successful" Ed Yong, *The Atlantic*, Science Section (March 20, 2020).
[17] "Essential Fatty Acids" chapter of the book, *Integrative Medicine for Children*, 2009.

Research suggests a direct structural link between LA, COVID-19 pathology, and the virus itself and suggest that both the LA-binding pocket within the S protein and the multi-nodal LA (Parent omega-6) signaling axis, represent excellent therapeutic intervention points against SARS-CoV-2 infections.[18]

Acute respiratory distress syndrome (ARDS) can rapidly occur, causing severe shortness of breath as endothelial cells lining blood vessels and epithelial cells (Parent omega-6) lining airways lose their integrity, and protein rich fluid leaks into adjacent air sacs. For example, COVID-19 can cause insufficient oxygen levels (hypoxia) that has been seen in up to 80% of intensive care unit (ICU) patients exhibiting respiratory distress.[19]

In response to COVID-19 infection, both an immediate systemic innate immune response as well as a delayed adaptive response has been shown to occur. The virus can also cause a dysregulation of the immune response, particularly in the decreased production of T- lymphocytes. Severe cases tend to have lower lymphocyte counts, higher leukocyte counts and neutrophil-lymphocyte ratios, as well as lower percentages of monocytes, eosinophils, and basophils. Severe cases of COVID-19 show the greatest **impairment in T-lymphocytes**.

In the acute phase of COVID-19 infection, blood tests demonstrate elevated erythrocyte sedimentation rate (ESR), C-reactive protein, and other ***elevated inflammatory markers, typical for an innate immune response***.[20] Rapid viral replication can cause death of epithelial and endothelial cells and result in leaky blood vessels and pro-inflammatory cytokine release.

In those with severe disease, an **uncontrolled release of pro-inflammatory cytokines** — *a cytokine storm — can occur*. Cytokine storms originate from an **imbalance in T-cell activation** with dysregulated release of interleukin (IL)-6, IL-17, and other cytokines.

PGE_1 "puts the brake" on "cytokine storm" as detailed in the medical journal articles. Cytokines, proteins, peptides and proteoglycans that modulate the body's immune response, are elevated in patients with mild-to-moderate disease severity.[21]

Massive oxidative damage to the lungs has been observed in areas of consolidation documented on lung radiographs and CT scans in patients with COVID-19. Because disseminated virus can attach itself to cells containing an ACE-2 (angiotensin-converting enzyme 2) receptor, the disease can spread and damage organs and soft tissues throughout the body, including the lungs, heart, intestines, kidneys, blood vessels, fat, testes, and ovaries, etc. The disease can **increase systemic inflammation** and **induce a hypercoagulable state**. Without anticoagulation, intravascular blood clots can be devastating. However:

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[18] Toelzer, C, et al., "Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein," *Science* 10.1126 / science.abd3255 (2020).
[19] Gattinoni, LD, et al., "COVID-19 pneumonia: different respiratory treatments for different phenotypes": *Intensive Care Medicine*, 46 (6): 1099-1102 (2020).
[20] Zhou, FY, et al., "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *The Lancet* 395 (10229):1054-1062.
[21] Upadhyay, JN, et al., "Role of inflammatory markers in corona virus disease (COVID-19) patients: a review," *Experimental Biology and Medicine*, 245 (15): 1368-1375.

PGE_1 increases blood flow (vasodilation) and inhibits platelet aggregation.[22,23]

ALZHEIMER'S

The beta-amyloid hypothesis as the cause of Alzheimer's has failed and pharmaceutical success in the area remains largely ineffective. Alzheimer's is now known as a cardiovascular disease caused by cellular impairment in the (at least 40 million) capillaries in the brain (comprised of exclusively Parent omega-6). The following extraordinary medical journal article published in 1990 "hits the nail on the head":[24]

"**The findings strongly indicate abnormalities in Δ-6 desaturation**. Alteration in PUFA desaturation / elongation processes and resultant membrane abnormalities may play a key role in the pathogenesis of Alzheimer's disease. Membrane phospholipids are not only actual membrane constituents, but also determine membrane function. **…[T]he findings strongly indicate abnormalities of Δ-6 desaturase in Alzheimer's disease**. The decrease in 22:6 (n -3) further supports altered Δ-6 desaturase activities. Abnormalities in the destruction / elongation process [**initiating with Δ-6 desaturase**] of PUFA (polyunsaturated fatty acid) and resultant membrane dysfunction **may play a key role** in the pathogenesis of Alzheimer's disease."

"Evidence is fast accumulating which indicates that **Alzheimer's disease is a vascular disorder with neurodegenerative consequences** rather than a neurodegenerative disorder with vascular consequences."[25]

Furthermore, as the 2011 *Nature Reviews: Neuroscience* article makes clear:[26] "Patients with Alzheimer's disease or other dementia-causing diseases frequently show focal **changes in brain microcirculation**. These changes include the appearance of string vessels (collapsed and acellular membrane tubes), a reduction in capillary density, a rise in **endothelial** pinocytosis, a decrease in mitochondrial content, accumulation of collagen and perlecans in the basement membrane, loss of tight junctions and/or adherens junctions, and

[22] Hissen, W, et al., Effect of prostaglandin E_1 on platelet aggregation *in vitro* and in hemorrhagic shock," *Microvascular Research*," Vol 1, Issue 4, October 1969, pages 374-378.
[23] Weiss, C., et al., "Hemostasis and fibrinolysis in patients with intermittent claudication: effects of prostaglandin E1, *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Nov. 2000; 63(5):271–277.
[24] Nakada, T, et al., "Membrane fatty acid composition shows a Δ-6 desaturase abnormality in Alzheimer's disease, *NeuroReport 1*, 153-155 (1990).
[25] de la Torre, J.C. and Stefano, G.B., "Evidence that Alzheimer's disease is a microvascular disorder: the role of constitutive nitric oxide," *Brain Research Reviews*, Vol. 34, Issue 3, 2000, pages 119-136.
[26] Zlokovic, B., "Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders," *Nature Reviews: Neuroscience*, Vol. 12, December 2011, pages 723-738).

BBB [blood-brain barrier] breakdown with leakage of blood-borne molecules….Increased levels of VEGF [vascular endothelial growth factor], a hypoxia-inducible angiogenic factor, were found in the walls of intraparenchymal vessels, perivascular deposits, astrocytes and intrathecal space of patients with Alzheimer's disease, and were **consistent with the chronic cerebral hypoperfusion and hypoxia that were observed in these individuals**."

> "In a series of ***300 autopsy cases of AD***, Kalaria and Ballard reported 98% CAA [cerebral amyloid angiopathy], ***100% microvascular degeneration***, 31% infarcts of all sizes, and 7% intracerebral hemorrhage, while Olichney, in a cohort of 248 autopsy cases of AD, revealed a total of 48% CVLs [cerebrovascular lesions], with 31% microinfarcts, 12.5% large infarcts, and 13.5% hemorrhages."[27]

"All of these pathologies may **disrupt the integrity of cerebral vessels** and **alter brain perfusion** leading to **neuronal injury and cognitive impairment**. SVD [cerebral small vessel disease] affects small arteries and arterioles and refers to pathological changes similar to atherosclerosis that are termed small vessel arteriosclerosis / atherosclerosis, lipo- or fibrohyalinosis, or hypertensive arteriopathy."[27]

Dermatology: Epithelial / Epidermis Tissue / Atopic Dermatitis

There is an epidemic of dermatologic diseases. An understanding of EFA metabolism is required to combat this rise in cases. "Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by eczematous lesions, skin dryness, and severe itch. AD affects 15–30% of children and 2–10% of adults. Atopic dermatitis (AD) has been related to a deficiency of Δ-6 desaturase…."[28]

The skin (epidermis / epithelial tissue) is comprised essentially of Parent omega-6 (LA) and arachidonic acid (AA) — a long chain omega-6 derivative. It is known that many dermatologic patients suffer from an impairment in the Δ-6 desaturase pathway: "…[S]uggests that the elongation of 18:3n 6 [via Δ-6 desaturase] into 20:3n 6 and its oxygenation to prostaglandins of the E series and lipoxygenase products of the 3-series may play a beneficial role in the management of cutaneous inflammatory hyperproliferative disorders."[29] Furthermore, there is identification of a fatty acid **Δ-6 desaturase deficiency in human skin fibroblasts**:[30] [*Fibroblasts* are in the dermis underneath the outer layer of skin. Fibroblasts also allow skin to generate connective tissue to recover from injury.]

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[27] Attems, Johannes and Jellinger, Kurt A., "The overlap between vascular disease and Alzheimer's disease – lessons from pathology," (Vascular risk factors and Alzheimer's disease), *BMC Medicine*, 2014, 12:206, pages 1-12.
[28] Simon,D, et al., "Gamma-Linolenic Acid Levels Correlate with Clinical Efficacy of Evening Primrose Oil in Patients with Atopic Dermatitis," *Adv Ther* (2014) 31:180–188.
[29] Ziboh, VA and Chapkin, RS, "Metabolism and function of skin lipids," Prog. Lipid Res. Vol. 27, pp. 81-105, 1988.
[30] Willard, DE, et al., "Identification of a fatty acid Δ-6 desaturase deficiency in human skin fibroblasts," *The Journal of Lipid Research*, 42, 2001, pages 501-508.

"In the present study we have investigated PUFA utilization in skin fibroblasts cultured from a female patient with clinical evidence of an inherited abnormality in fatty acid metabolism. The patient had a **history of serious medical problems since shortly after birth**, and GLC analysis of her plasma fatty acid composition indicated a low level of 20:4n-6 and DHA. Polyunsaturated fatty acid (PUFA) utilization was investigated in skin fibroblasts cultured from a female patient with an **inherited abnormality in lipid metabolism**. These deficient human skin fibroblasts (*DF*) **converted 85–95% less** [1-14C] linoleic acid (18:2n-6) to arachidonic acid (20:4n-6) …. **These results suggested that DF are deficient in Δ-6 desaturation**. **This was confirmed**…. A skin biopsy was obtained at the Kennedy Krieger Institute (Johns Hopkins University, Baltimore, MD), and a cultured fibroblast cell line (deficient human skin fibroblasts, DF) was established. Studies with rat liver microsomes indicate that a single Δ-6 desaturase acts on both 18- and 24-carbon PUFA substrates, whereas **similar studies with human malignant cell lines suggest that separate Δ-6 desaturases act on these substrates**. …**These results demonstrate that the DF cells have a major deficiency in Δ6 desaturation**."

Cardiovascular disease

The lining of arteries (intima) and capillaries are comprised entirely of Parent omega-6. If this omega-6 is adulterated / nonfunctional from patients consuming processed foods / cooking oils, then the arteries / capillaries / veins will suffer inflammation, resulting in initiation of plaque, occlusions, and disfunction.[3]

A 1997 study published in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*, reported "Cholesterol esters [cholesteryl esterized with EFAs; in particular, Parent omega-6] are the predominant lipid fraction in all plaque types…" It also stated that "Intimal [innermost arterial lining] macrophages contain substantial amounts of cholesterol esters, which are rich in PUFAs [in particular, Parent omega-6]."[31]

The brilliant pathologist, Vladimir Subbotin, demonstrated to me high resolution images that, the endothelium intima (inner lining of the artery), is actually multi-layer — up to 30 layers in an adult, significantly increasing the potential for CVD.[32]

Intimal hypoxia (lack of oxygen) is also an initiating cause of CVD and fully functional Parent omega-6 significantly improves cellular oxygenation. Dr. Campbell's article, "**Abnormal fatty acid composition and impaired oxygen supply in cystic fibrosis patients**," demonstrates that the Parent omega-6's oxygen in the cell membrane can (reversibly) disassociate (release) oxygen — at physiologic pressure — increasing the tissue cellular oxygenation. **In addition to the bloodstream, oxygen can come from the cell membrane itself**.[33]

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[31] Felton CV, Crook D, et al., "Relation of plaque lipid composition and morphology to the stability of human aortic plaque," *Arteriosclerosis, Thrombosis, and Vascular Biology*, 1997;17:1337–1345.
[32] Subbotin, V., "Excessive intimal hyperplasia in human coronary arteries before intimal lipid depositions in the initiation of coronary atherosclerosis and constitutes a therapeutic target," *Drug Discovery Today*, Vol. 21, No. 10, October 2016.
[33] Campbell, IM, et al., "Abnormal fatty acid composition and impaired oxygen supply in cystic fibrosis patients," *Pediatrics* 1976; 57: 480–486.

Chronic low-grade inflammation plays a role in cardiac hypertrophy and heart failure.[5,34] Both microcirculation and macrocirculation of the heart are improved with **strong anti-platelet aggregation** effect **of PGE_1**.[35] Increased cellular oxygenation / decreased hypoxia also occurs with increased PGE_1.[36] Increased blood flow and cardiovascular support also occur.[37] The **activation** of PPARα (*See* **PPAR and Δ6 desaturation below)** is known to **attenuate or inhibit** the production of mediators of **vascular damage**, lipotoxicity, **inflammation**, reactive oxygen species (ROS), **endothelial dysfunction**, **angiogenesis and thrombosis**…."[38]

A 2000 study reported on the effectiveness of PGE_1. German physician and researcher Clause Weiss, MD, et al., stated, "In summary, infusion therapy with PGE_1 in patients with peripheral arterial occlusive disease (PAOD) reduces thrombin formation. PGE_1 may thus reduce fibrin (thrombosis) deposition involved in the pathogenesis of atherosclerosis."[39]

PGE_1 may help dissolve occlusions / thromboses.

"Microcirculation and macrocirculation of the heart are improved with the strong anti-platelet aggregation **effect of PGE_1**."[40]

PPAR (Peroxisome Proliferator-Activated Receptors) and Δ-6 desaturation

Since the **Δ-6 desaturase gene** is influenced by PPAR, I'll briefly reference it. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. PPARα is mainly expressed in the liver, where it activates fatty acid catabolism. PPARδ is expressed ubiquitously and is implicated in fatty acid oxidation and keratinocyte differentiation. PPARγ2 is expressed exclusively in adipose tissue and plays a pivotal role in adipocyte differentiation. PPARγ

[34] Libby P. "Inflammation in atherosclerosis." *Nature*. 2002 Dec 19–26;420(6917):868–874.
[35] Ren, H-X, et al., "Effect of prostaglandin E1 in patients with advanced lung cancer treated with chemotherapy," *Int J Clin Exp Med* 2018;11(3):2285-2291.
[36] Guo S, DiPietro LA. "Factors affecting wound healing." *J Dent Res.* 2010;89(3):219–229.
[37] Das UN. "A defect in the activity of Δ6 and D5 desaturases may be a factor in the initiation and progression of atherosclerosis." Prostaglandins Leukot Essent Fatty Acids. 2007;76(5):251–268; "[O]mega-6 PUFAs also have powerful anti-inflamatory properties that counteract any proinflammatory activity,' say the advisory authors. 'It's incorrect to view the omega-6 fatty acids as "proinflammatory."' Ref.: Farvid MS et al. "Dietary linoleic acid [LA/ parent omega-6 and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies." *Circulation*. 2014;130:1568–1578; Terano T et al. "Effect of oral administration of highly purified eicosapentaenoic acid on platelet function , blood viscosity and red cell in healthy human subjects." *Atherosclerosis*. 1983;46:321–331.
[38] Savary, S, et al., "Fatty acids — Induced lipotoxicity and inflammation," *Current Drug Metabolism*, 2012, Vol. 13, No. 10, pages 1358-1370.
[39] Weiss, C., et al., "Hemostasis and fibrinolysis in patients with intermittent claudication: effects of prostaglandin E1," *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Nov. 2000; 63(5):271–277; ; Lazaro, I, et al., "Linoleic Acid Status in Cell Membranes Inversely Relates to the Prevalence of Symptomatic Carotid Artery Disease," Stroke. 2021;52:703–706.
[40] Ren, H-X, et al., "Effect of prostaglandin E1 in patients with advanced lung cancer treated with chemotherapy," *Int J Clin Exp Med* 2018;11(3):2285-2291.

is involved in glucose metabolism through the improvement of insulin sensitivity and represents a potential therapeutic target of type 2 diabetes.

> "**The Δ-6 desaturase gene** is known to contain a peroxisome proliferator response element and is **under PPAR transcriptional** control and may be the point of transcriptional control for both receptors within the **essential fatty acid pathways**."[41]

Inflammatory Bowel Diseases

The entire lining of the digestive tract is Parent omega-6. Functional integrity is crucial. "Leaky gut" is caused by defects in the cellular membranes. Furthermore, **PPAR is highly expressed in the colon**, where bacterially induced signals increase its expression via TLR.[5] "The Δ-6 desaturase gene is known to contain a peroxisome proliferator response element and is under PPAR transcriptional control and may be the point of transcriptional control for both receptors within the essential fatty acid pathways."[40]

"Results demonstrated that **pretreatment with PGE_1 decreased the adhesion** between vascular endothelial cells and monocytes**, reduced** the expression of **vascular cell adhesion** molecule-1, intercellular adhesion molecule-1, and E-selectin **in vascular endothelial cells**.

> "In addition, **PGE_1 suppressed TNF-induced** NF-kappaB activation and production of reactive oxygen species. "We concluded that **PGE_1 suppressed the vascular inflammatory process**…."[42]

Chronic Fatigue Including Post Viral Syndromes / Myalgic Encephalomyelitis

Chronic fatigue and exhaustion are widespread. We know that Parent omega-6 (LA) is the prime substrate of *cardiolipin* in the inner layer of the mitochondria — the creators of cellular energy. Additionally, Δ-6 desaturation impairment is a factor of the fatigue / energy impairment:[43]

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[41] Kawashima Y, Musoh K, Kozuka H: "Peroxisome proliferators enhance linoleic acid metabolism in rat liver. Increased biosynthesis of omega 6 polyunsaturated fatty acids." *J Biol Chem*. 1990, 265: 9170-9175; Roberts, L, et al., "The contrasting roles of PPARδ and PPARγ in regulating the metabolic switch between oxidation and storage of fats in white adipose tissue," *Genone Biology* 12, Article number: R75 (2011).

[42] Fang, W, et al., "Effect of prostaglandin E1 [PGE_1] on TNF-induced vascular inflammation in human umbilical vein endothelial cells," *Can J Physiol Pharmacol*. 2010 May;88(5):576-83.

[43] Puri, BK, "Long-chain polyunsaturated fatty acids and the pathophysiology of myalgic encephalomyelitis (chronic fatigue syndrome)," *J Clin Pathol* 2007;60:122–124.

"Evidence is put forward to suggest that myalgic encephalomyelitis, also known as **chronic fatigue** syndrome, may be associated with **persistent viral infection**. In turn, such infections are likely to impair the ability of the body to biosynthesise n-3 and n-6 long-chain polyunsaturated fatty acids by **inhibiting the d-6 desaturation** of the precursor essential fatty acids…

"…**[V]iral infections can prevent the body from biosynthesizing long-chain polyunsaturated fatty acids.** In turn, this ***impairs the biosynthesis of membrane phospholipid molecules in the brain****, as long-chain polyunsaturated fatty acids* are key components at the Sn2 position of these molecules. This leads to a reduced incorporation of the polar head group choline in these molecules (at the Sn3 position). Hence, we should expect to see a raised level of free choline in the brain, which can be assessed using proton neurospectroscopy.

"This is indeed the finding from the first two systematic proton neurospectroscopy studies thus far published on myalgic encephalomyelitis or chronic fatigue syndrome — one by our group. In 1935, Stoesser reported that *acute viral infections were associated with a reduction in the levels of long-chain polyunsaturated fatty acids*.

> **"That the cause of this reduction was the ability of many viral species to inhibit the d-6 desaturation of the precursor essential fatty acids was discovered four decades later by Dunbar and Bayley**.

"As a result of viral or other **inhibition of Δ-6 desaturase**, an inadequate supply of the long-chain polyunsaturated fatty acids is available for incorporation into the membrane phospholipid molecules." **[Note: Most viruses, including Covid / SARS are lipid-enveloped and inactivated by long-chain fatty acids**."[44]]

Fatty Liver Disease Including NAFLD

Fatty liver disease consists of a variety of pathological states ranging from simple buildup of fat in the liver (hepatic steatosis) to nonalcoholic steatohepatitis, cirrhosis, and ultimately liver failure. This disease has reached epidemic proportions with up to 30% of Americans having some level of NAFLD. Reductions in hepatic insulin sensitivity are documented.

"NAFLD is a low-grade systemic inflammatory condition. Increased formation of pro-inflammatory cytokines and eicosanoids and / or reduced formation of anti-inflammatory cytokines and inflammation resolving bioactive lipids may participate in the pathobiology of NAFLD.

[44] Horowitz, B. et al., "Inactivation of lipid-enveloped viruses in labile blood derivatives by unsaturated fatty acids," *Vox Sang*. 1988;54(1):14-20.

"Thus, **release and timely formation of anti-inflammatory bioactive lipids is necessary** to prevent NAFLD and / or resolution of inflammation seen in NAFLD….

"Nonalcoholic fatty liver disease (NAFLD) is associated with **decreased levels** of AA, EPA and DHA and **their anti-inflammatory products PGE_1**, PGD_2, LXs, resolvins and protectins with a concomitant increase in **pro-inflammatory cytokines**, IL-6 and TNF-alpha and bioactive lipids PGE_2, LTs and TXs. The low levels of AA, EPA and DHA can be a result of **decreased activities of Δ^6** and Δ^5 desaturases."[45]

"An important aspect is the pathological process that occurs in **nonalcoholic fatty liver disease (NAFLD),** a condition in which oxidative stress of nutritional origin (fat and carbohydrates overload), in association with obesity, produces a significant and **drastic decrease in the activity** of the Δ-5 and **Δ-6 desaturase enzymes in the liver**."[46]

Multiple Sclerosis (MS)

"Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) of an unknown origin."[47] An impaired D6D metabolic pathway decreases PGE_1. This impairment in the D6D must be compensated for.[47] MS affects approximately 200,000 patients per year. A shortage of EFAs is a risk factor. EFAs are important in the active phase of myelin synthesis. Numerous conditions in addition to impaired myelin synthesis occur, such as: impaired learning, motor, vision, and auditory abnormalities. Both the central and peripheral nervous systems are comprised of significant amounts of Parent EFAs.[48,49] The myelin sheath contains 70-85% lipids.[50]

Cancer & Radiation Therapy

Radiation therapy is widely used for treatment and examination. However, depending on the irradiation dose used, acute injurious effects of radiation on the skin, such as erythema, epilation, desquamation, hyperpigmentation, and erosion — referred to as radiodermatitis — are common side effects. **Chronic radiation-induced skin ulcers are often observed in the region of radiodermatitis**. These are characterized by poor healing and high relapse rate and are generally intractable.

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[45] Das, U, "A defect in the activities of Δ^6 and Δ^5 desaturase and pro-resolution bioactive lipids in the pathobiology of non-alcoholic fatty liver disease," *World Journal of Diabetes*, 2011 November 15:2(11).
[46] Wahli, W. and Michalik, L, "PPARs at the crossroads of lipid signaling and inflammation," *Trends in Endocrinology and Metabolism*, July 2012, Vol. 23, No. 7, 351-363.
[47] Soheila Rezapour-Firouzi, et al, "Erythrocyte membrane fatty acids in multiple sclerosis patients and hot-nature dietary intervention with co-supplemented hemp-seed and evening-primrose oils," *Afr J Tradit Complement Altern Med*. (2013) 10 (6):519-52.
[48] Trapp, B. and Bernsohn, "Essential fatty acid deficiency and CNS myelin: Biochemical and morphological observations," *Journal of Neurological Sciences,* vol. 37, issue 3, July 1978, pages 249-266.
[49] Guest, Jade, et al., "Relationship between central and peripheral fatty acids in humans," *Lipids Health Dis.* 2013 May 28;12:79.
[50] Poitelon, Y, et al., "Myelin fat facts: An overview of lipids and fatty acid metabolism," *Cells* 2020, 9, 812.

"Misoprostol, a [injectable] **prostaglandin (PG) E_1 *analogue***, is *one of the most effective radiation protectors of the PGs investigated to date*:[51]

"Wound healing was significantly delayed because of X-irradiation, but **PGE_1 administration prior to irradiation led to a significantly shorter delay in wound healing** compared with controls."

> "**Decreasing delay in wound healing was correlated with concentration of PGE_1 administrated**…. Thus, **PGE_1-administration may potentially alleviate the radiation-induced skin injury**."[52]

"It has been indicated that experiments in the utilization of EFA in cancer modulation exist regarding intake and effect on cell structure and biochemical interactions within the cell in the **prevention of cancer development."**[53]

> **"A lower level of D6D** was seen in breast tumors compared to normal tissues."[54]

"When cells were exposed to PUFAs **prior to but not during or following gamma-irradiation**, the **radiation treatment was enhanced by GLA** but not EPA or DHA."[30]

"**Chronic inflammation is a major causative factor in human malignances**. Pro-inflammatory cytokines influence tumor microenvironment and promote cell growth and survival and angiogenesis such that tumor cell growth is facilitated."[55]

"EFAs/PUFAs play a significant role in such diverse conditions due to their ability to modulate cell membrane fluidity, possess second messenger action, influence angiotensin converting and HMG-CoA reductase enzymes, **serve as ligands for** nuclear receptors **PPARs** (peroxisome proliferator-activated receptors)…."[56]

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[51] Hanson, WR, et al., "Radiation protection of the murine intestine by misoprostol, a prostaglandin E1 analogue, given alone or with WR-2721, is stereospecific," *Prostaglandins Leukot Essent Fatty Acids*. 1988 Jun;32(3):101-5.
[52] Takikawa, M, et al., "Protective effect of prostaglandin E1 on radiation-induced proliferative inhibition and apoptosis in keratinocytes and healing of radiation-induced skin injury in rats," *J. Radiat. Res*., 53, 385-394 (2012).
[53] Willard, DE, et al., "Identification of a fatty acid Δ-6 desaturase deficiency in human skin fibroblasts," *The Journal of Lipid Research*, 42, 2001, pages 501-508.
[54] Conklin, KA, "Dietary polyunsaturated fatty acids: Impact on cancer chemotherapy and radiation," *Alternative Medicine Review*, Volume 7, No. 1, 2002, pages 4-21.
[55] Das, UN, "Can essential fatty acids reduce the burden of disease(s)," *Lipids In Health And Disease* 2008, 7:9.
[56] Hanson, WR, et al., "Radiation protection of the murine intestine by misoprostol, a prostaglandin E1 analogue, given alone or with WR-2721, is stereospecific," *Prostaglandins Leukot Essent Fatty Acids*. 1988 Jun;32(3):101-5.

"In addition, ***PPARα*** is known to inhibit tumor growth and angiogenesis, which seem to be mediated by direct and indirect antiangiogenic effects and by its anti-inflammatory activity. A possible mechanism for PPARα-mediated tumor growth inhibition may involve suppression of signaling by hypoxia-inducible factor 1α (HIF-1α), as shown in cancer cells."[57]

Effect of prostaglandin E1 in patients with advanced lung cancer treated with chemotherapy:[40]

"Chemotherapy is a common treatment for advanced lung cancer. However, although chemotherapy kills tumor cells, it also causes damage to normal cells.

"**Thrombosis formation is easier in cancer patients than in healthy people** due to their hypercoagulable state and thrombin produced by tumor cell membrane. Patients with advanced lung cancer usually have disorder of coagulation; therefore, they are more likely to develop VTE **[venous thromboembolism**] with chemotherapy treatment. Our study showed that **PGE_1 significantly reduced the incidence of VTE during chemotherapy in patients with advanced lung cancer**.

"**PGE_1** leads to relaxation of smooth muscle and **inhibits** platelet aggregation as well as atherosclerotic lipid plaque formation. ***Chronic hypoxia*** [low cellular oxygen] can also generate secondary polycythemia, increase blood viscosity and hematocrit, increase platelet adhesion effect of microcirculation perfusion, leading to thrombosis in pulmonary circulation and coronary circulation, and potential heart failure. **PGE_1 can dilate bronchial and artery vein blood vessels, and thus increase myocardial contractility**. PGE_1 inhibits the release of TXA2. Therefore, the TXA2 induced strong release and aggregation of platelet was inhibited and vasoconstrictive effect of platelet was reduced. **This could contribute to the prevention of VTE**….

"In addition, **PGE_1 has a direct protective effect on vascular endothelial cells**, which is beneficial to the production of tPA by endothelial cells and the enhancement of local fibrinolytic activity [preventing blood clots]….

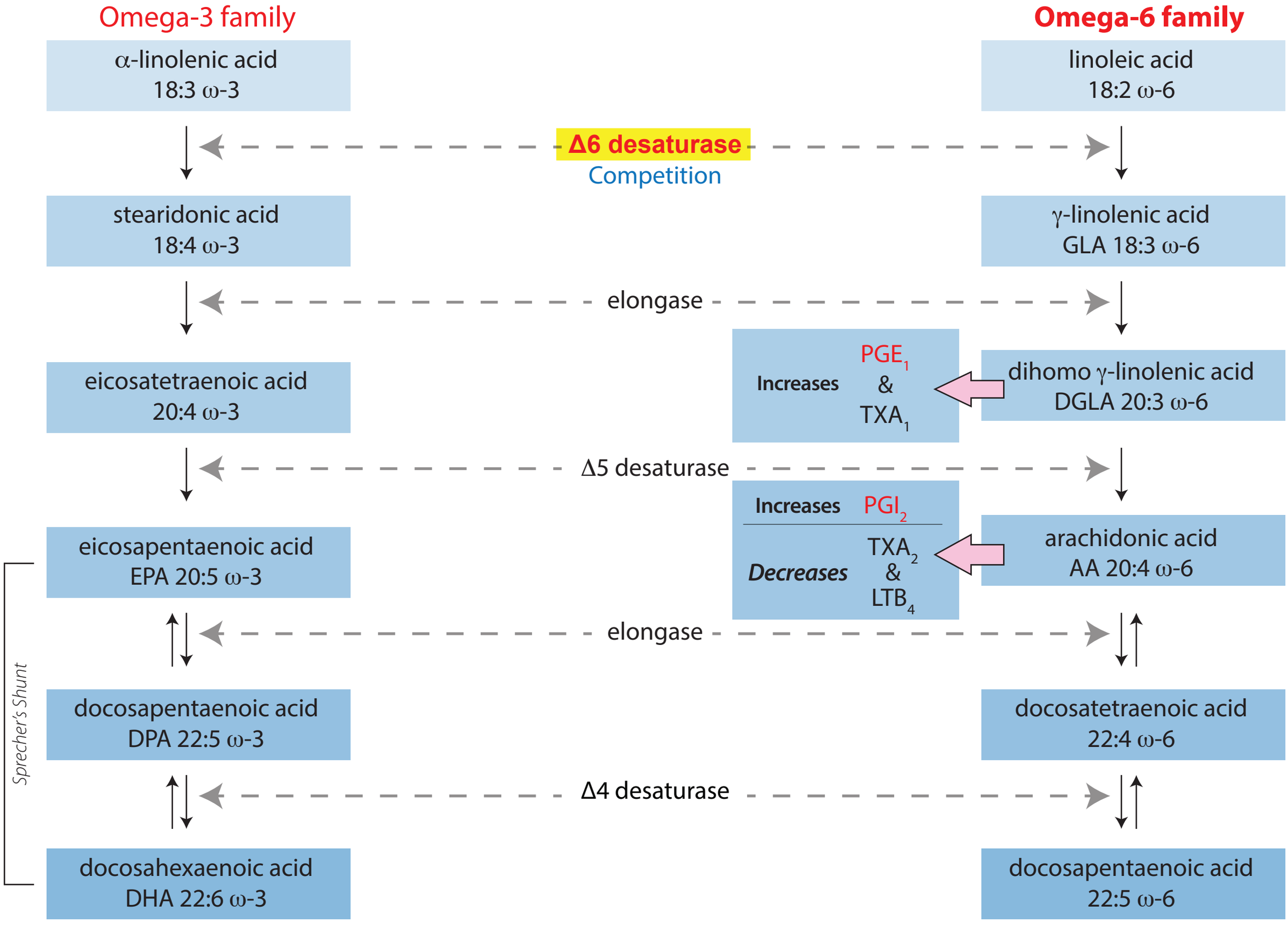
"Furthermore, **chemotherapy will aggravate hyper-coagulable** state and activation of blood coagulation facilitates cancer cells attachment, invasion and transfer which may in turn influence **biology of the tumor, resulting in a poorer out-come of chemotherapy**.

"Patients treated with long-term chemotherapy may experience small pulmonary artery spasms, increase in pulmonary vascular resistance, pulmonary hypertension and increase of right heart load, which may lead to right heart failure or heart failure. Studies show that humoral factors such as prostaglandins [e.g., PGE_1] play an important role in hypoxic pulmonary vasoconstriction."

[57] Echeverria, F, et al., "Long-chain polyunsaturated fatty acids regulation of PPARs, signaling: Relationship to tissue development and aging," *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 114 (2016)28-34.

Eicosanoid Optimization

pg = prostaglandin tx = thromboxane
lt = leukotriene



Lipids are the #1 (Modifiable) Variable in Tissue Composition[1,2]

1. E. Wainwright, Y. S. Huang, et al., "The Effects of Dietary n-3/n-6 Ratio on Brain Development in the Mouse: A Dose Response Study with Long-Chain n-3 Fatty Acids," Lipids, vol. 27, no. 2, pp. 98-103, 1992; W. E. M. Lands, et al., "Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues," Lipids, vol. 25, no. 9, pp. 505-516, 1990.
2. C. V. Felton, et al., "Relation of Plaque Lipid Composition and Morphology to the Stability of Human Aortic Plaques," Arteriosclerosis, Thrombosis, and Vascular Biology," Vol. 17, No 7, 1997, pp. 1337-1345.

Appendix III

A Malignant Flame: The Relationship Between Cancer and Chronic Inflammation

Newsflash 2007: Admitting the "Genetic Basis of Cancer" is WRONG!

Chronic inflamation, which contributes to heart disease, may be a key to unlocking the mysteries of cancer. *Scientific American's* feature article delivered a shocker in the July 2007 issue, pages 60-67.[1] If you read the entire article you will be appalled at the lack of insight into cancer's *prime* cause as proven by Dr. Warburg decades ago. Noticeably lacking was any reference to Warburg or his insight into inflammation as a secondary cause of cancer. The article admits that cancer researchers "have changed focus." Cancer researcher Robert Weinberg of MIT states:

> "The connection between **inflammation and cancer *has moved to center stage*** in the research arena." The article continues…

1 Article references: "Smoldering and Polarized Inflammation in the Initiation and Promotion of Malignant Disease, Balkwill, F., et al., *Cancer Cell*, Vol. 7, No. 3, pages 211-217, March 2005; "Distinct Role of Macrophages in Different Tumor Microenvironments," Lewis, C. and Pollard, J., *Cancer Research*, Vol. 66, No. 2, pages 605-612; January 15,2006; "Paradoxical Roles of the Immune System during Cancer Develpopment," Visser, K., et al., *Nature Reviews Cancer*, Vol. 6, No.1, pages 24-37; January 2006.

"But biologists and immunologists have *begun to realize that progression from diseased tissue to full-blown invasive cancer often requires cells that* ***normally participate in healing cuts and scrapes*** **to be diverted** to the environs of the premalignant tumor….

"…and **inflammation is the fuel** that feeds it [the malignant cancer]

"In this **rewriting of the textbook** …

"**This new view** implies that **rooting out every last cancer cell in the body might not be necessary**. **Anti-inflammatory cancer therapy** instead would prevent premailgnant cells from turning fully cancerous or would **impede an existing tumor from spreading** to distant sites in the body. **Cancer victims might then be able to survive**." (Emphasis added.)

◗ *Life-Systems* Engineering Science Commentary

Although the cancer researchers still won't change their irrational notion that "cancer begins with a series of genetic changes," the author of the "oncogene theory" admits here that there is a new focus, and it *isn't genetic* in basis! The textbook has been rewritten and inflammation has taken center stage. **You have already discovered that parent omega-6 is the biochemical building block for the most powerful anti-inflammatory prostaglandin known, called PGE_1. Parent omega-6 is also the building block of prostacyclin, the most potent anti-aggretory agent (natural blood thinner), and parent omega-6 is the substrate of your body's natural steroids, too.** Some of this information is discussed on pages 298-300 of this book! See the Index for the remaining references. Dr. Warburg already pinned inflammation, not genetics, as a secondary cancer cause, and these scientists should have already been aware of it, if they had cared to look.

The article continues:

Blood Speed and Cancer Metastasis

Blood speed has a connection to the spread of cancer. Here is a surprising, seldom-mentioned fact that was pointed out by world-renowned molecular biologist Robert Weinberg, director of the Oncology Research Laboratory at the Whitehead Institute in Cambridge, Massachusetts:

> "Of those patients who succumb to cancer, fewer than 10% die from tumors that continue to grow at the same site where they originally took root. In the great majority of cases, the killers are the metastases—colonies of cancer cells that have left the site of the original, primary tumor and have settled elsewhere in the body. It is these migrants, or rather the new tumors that they seed, that usually cause death."[15]

How this relates to speed of blood is that **it is frequently a blood clot that causes cancer metastases to "seed" into tissue at a distance from the original tumor**. Without any clots, most cancers are much less harmful, because they can't spread from the original site. In fact, as was reported by Dr. Summer Wood of Boston, Massachusetts in 1958,[16] the number of deaths from cancer is dramatically decreased—**by over 80%**—if blood clots are eliminated. Because higher blood speed goes hand-in-hand with fewer blood clots, making sure blood speed is high dramatically reduces the risk of cancer metastases.

In a 1997 book, *Health and Survival in the 21st Century,* by Ross Horn, the author discussed the results of a study that proved that the absence of blood clots dramatically reduced deaths from cancer:

> "…Dr. L. Michaels of Canada reasoned that if no clots were allowed to form, then metastasis from a primary tumor could not occur, and that people with only primary cancers would in that case be in a much safer situation. This he proved to be

15 *One Renegade Cell: How Cancer Begins,* Robert A. Weinberg, Basic Books, New York, 1998, p. 146.

16 *American Medical Association Archives of Pathology,* Vol. 66, October 1958.

the case. He studied the medical histories of a large number of heart and stroke patients kept on permanent anti-coagulant drug treatment to protect their blood circulation, to ascertain the incidence of cancer deaths among them, and found the incidence to be only **one-eighth** of the expected number. The study covered the equivalent of **1569 patient-years and there was not a single case of death *by cancer metastasis* in the group**."[17] (Emphasis added.)

Insulin and Blood Clotting

Even more support exists that shows that cancer patients should eat low-carbohydrate diets. No less than the *Journal of the American Medical Association* reported in 2000 that **elevated insulin levels cause blood clotting**.[18] We'd be willing to bet, however, that you never heard about this finding.

Insulin levels become elevated as a result of eating lots of carbohydrates. Therefore, this adds another liability to eating excessive carbohydrates, because while doing so already slows blood flow, making the cells more susceptible to cancer (as well as providing "food" for cancer), the elevated insulin levels cause more blood clots, increasing the risk of spread of cancer through metastasis. All these separate facts add up to the same thing: a high carbohydrate diet increases the risk of cancer developing and spreading.

** Newsflash **

With the EFA parent ratios suggested in this book, many people notice their carbohydrate cravings significantly decrease. In light of the above this is a very good thing. What a great and unexpected EFA-related benefit!

17 *Health and Survival in the 21st Century*, Ross Horn, Chapter 13, 1997, HarperCollins Publishers, Pty Ltd., Australia, page 6 of Internet edition at www.soilandhealth.org.

18 *Journal of American Medical Association*; 2000; 283:221-228.

A common element to many life-threatening diseases and disorders is chronic inflammation. Consequently, when chronic inflammation is effectively reduced by addressing and compensating for a deficient D6D pathway, patient outcomes improve.

Mesothelioma

Researchers have been unable to find a cure for Mesothelioma. Thus far, it is known that "***chronic inflammation*** plays a **key role** and is a cardinal feature in the pathogenesis of malignant pleural mesothelioma (MPM) as a result of asbestos exposure."[60] It has also been documented that **elevated patient CRP** strongly supports systemic inflammation in this population, which leads to a poor outcome. The role of inflammation continues to be well-documented and new anti-inflammation therapies are required:[61]

"Thus, there is **compelling evidence that a pronounced *systemic inflammatory* response** is associated with **poorer prognosis**, and that tumour-derived **cytokines** can affect immune reactions peripherally in the **bone marrow as well as locally within the tumour**.

"Despite a modest prolongation of survival by the platinum / pemetrexed combination, the **prognosis of MPM remains poor**.

> "In terms of **potential therapies, 'anti-inflammatory' therapeutics hold great promise**, with the aim of inducing an anti-tumour effect or suppressing angiogenesis, by **dampening the systematic inflammatory response and targeting the local response** within the MPM tumour."

Resistance to therapy is well-known. Furthermore, a cardinal feature in the disease, significantly adding to its destructiveness of tissue and resistance to treatment, is **hypoxia**:[62]

"**Hypoxia is one of the cardinal features** of the mesothelioma metabolome. Hypoxia is capable of profoundly enhancing the growth of mesothelioma cell lines: including clonogenicity, stemness, resistance to chemotherapy, epithelial to mesenchymal transition…

"Malignant pleural mesothelioma (MPM) has **a justified reputation for being resistant to therapy**. …Phase 2 trials of **immunotherapies** have produced **modest** signals **to date**, checkpoint inhibition in real-life clinical settings have reported **limited effects**."

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[60] Pinato, D., et al., "Inflammation-based prognostic indices in malignant pleural mesothelioma," *J Thorac Oncol.* 2012 Mar;7(3):587-94.
[61] Linton, A., et al., "Inflammation in malignant mesothelioma — friend or foe?," *Ann Cardiothorac Surg* 2012;1(4):516-522.
[62] Chu, G, et al., "The immune microenvironment in mesothelioma: Mechanisms of resistance to immunotherapy," *Frontiers In Oncology,* December 2019, Vol. 9, Article 1366.

IPF

IPF is a progressive fibrosing interstitial lung disease in which **innate and adaptive inflammatory processes are activated**. IPF patients suffer excessive inflammatory response. Inflammatory changes seen in IPF occur independently of the primary fibrotic remodeling process. Two initially promising therapeutics for IPF, Nintedanib and Pirfenidone, both approved in 2014, slow the progression of the disease. Unfortunately, they have fallen short of their touted potential. ***What is needed is a new insight into inflammation which will aid those seeking a more effective treatment regimen***.

We already know that, "Idiopathic pulmonary fibrosis (IPF) is a progressive, and **ultimately fatal**, chronic interstitial lung disease characterized by enhanced extracellular matrix deposition. Repetitive alveolar **epithelial injury** triggers the early development of fibrosis. These injuries, in combination with **dysregulated wound repair** and fibroblast dysfunction, lead to ongoing tissue remodeling and fibrosis seen in end-stage pulmonary fibrosis.":[63]

"Over the past three decades several therapeutic prospective, double-blind, randomized clinical trials have been executed to find clinical benefit in IPF. Several of these landmark trials used anti-inflammatory drugs (anti-TNF-α, prednisone) or immunomodulatory agents (IFNγ, simtuzumab) **and all these trials failed to meet their primary endpoints** (change in FVC, time to disease progression or survival) or even had detrimental effects."

COPD

There has been extensive interest over many years in agents that could be used to **reduce inflammation in COPD**. The reduction of inflammation in COPD may reduce the increased risk of CVD and lung cancer that occurs in this context, although the clinical trials that have addressed this issue are very limited:[64]

> "**[Current] pharmaceutical therapy for the treatment of inflammatory process in COPD is relatively ineffective**. **Corticosteroids** remain the cornerstone of asthma treatment but are generally relatively **ineffective** in **COPD**.

"Chronic obstructive pulmonary disease (COPD) is characterized by lung **inflammation** that persists after smoking cessation. **This inflammation is heterogeneous** but the key inflammatory cell types involved are macrophages, neutro-phils and T cells. Other lung cells may also produce inflammatory mediators, particularly the **epithelial cells**. The main inflammatory mediators include tumor necrosis factor alpha, interleukin-1, interleukin-6, reactive oxygen species and proteases.[60]

[63] Moor, C, et al., "Inflammation and immunity in IPF pathogenesis and treatment," *Respiratory Medicine*, Volume. 147, P79-91, February 1, 2019.
[64] King, "Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer," *Clin Trans Med* (2015) 4:26.

"COPD is also associated with **systemic inflammation** (presence of inflammatory / immune response mediators that are **present in the peripheral blood with levels that are elevated** in COPD when compared to smoking controls (without COPD)), and there is a **markedly increased risk of cardiovascular disease** (particularly coronary artery disease) and **lung cancer** in patients with COPD. **There is strong associative evidence that the inflammatory cells / mediators in COPD are also relevant to the development of cardiovascular disease and lung cancer."**:[60]

"**Systemic inflammation** has been defined as the Systemic inflammation as measured by the biomarkers; **C-reactive protein** (CRP), leukocytes and fibrinogen is **associated with a <u>two to four-fold increased risk</u> of comorbidities including cardiovascular disease and lung cancer**."

"Chronic obstructive pulmonary disease (COPD) is **characterized by chronic lung inflammation that results in progressive and <u>irreversible</u> airflow obstruction with periodic acute episodes of worsening, exacerbations**.

"Neutrophils are generally more inflammatory than macrophages and are most prominent in acute exacerbations in the lung airways. Other inflammatory cell types involved in COPD include eosinophils, dendritic cells, and mast cells.

"**The epithelial cells** also have an important role in **mediating inflammation** in COPD."

Researching a new approach is warranted. The traditional treatment protocols use drugs that block and impede metabolic pathways. A more novel approach that should be studied entails working cooperatively with the body by finding pathways to enhance and maximize: naturally impeding inflammatory pathways, and supporting epithelial and other tissues. Chronic systemic inflammation is present in many disorders and diseases, therefore focus on the impaired D6D is both rational and required.