Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression

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Abstract: Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most concise, detailed, up-to-date, and clinically relevant description of fatty acid metabolism that has ever been published in a single article.

INTRODUCTION

Chiropractic and naturopathic physicians are the only doctorate-level healthcare providers with graduate-level training in therapeutic nutrition and are emerging as the leaders in the treatment and prevention of long-term health disorders, including nearly all of the chronic diseases seen in clinical practice such as obesity, hypertension, adult-onset diabetes, hypercholesterolemia, allergies, asthma, arthritis, depression and a long list of other musculoskeletal and non-musculoskeletal conditions.[1,2] With the increasing substantiation of the effectiveness and cost-effectiveness of the nutritional management of these problems, and the documentation of the excessive cost and adverse effects generally associated with pharmaceutical medications, we are approaching a paradigm shift in healthcare which will eventually (re)position the practitioners of holistic natural healthcare in their proper place—at the forefront of patient management.

Healthcare providers of all disciplines are obligated to act responsibly to protect the health of the public. Current research published in peer-reviewed medical journals suggests that over-utilization of allopathic medical care endangers patients' health by exposing patients to prescribing errors[3], hospital injuries, and what is described as "substandard care."[4] A recent article in the *New England Journal of Medicine*[5] concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians[6] stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than $136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children[7] and adults[8,9,] and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.[10] Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.[11, 12] Many anti-inflammatory drugs for the treatment of joint pain actually promote joint destruction[13, 14, 15] and the newer selective cyclooxygenase inhibitors carry an unjustifiable cost[16, 17] and fail to deliver improved efficacy[18] despite significantly increasing the risk for kidney damage, hypertension, myocardial infarction, stroke, and sudden death.[19, 20, 21] On the other hand, natural treatments such as dietary improvements and fatty acid supplementation have been shown to safely reduce the need for medical treatments, to improve health, to alleviate many common diseases, and to prolong life at lower cost, negligible risk, and with improved overall outcomes.[22, 23] **In order to reduce costs, promote health, and reduce iatrogenic disease, our healthcare paradigm must change from "disease treatment with drugs and surgery" to "health promotion with therapeutic nutrition and lifestyle improvements."** It is safe and reasonable to predict that in the near future, customized dietary improvement, therapeutic nutrition, lifestyle modification, and fatty acid supplementation will be viewed as integral components of patient care for all patients with all diseases. Doctors must therefore be informed of new research on how to use these interventions skillfully.

The combination of dietary improvement and skillful nutritional intervention as reviewed by the current author in the first article in this series[24] and in greater detail elsewhere[25] is the single most powerful approach for the effective treatment of a wide range of conditions. Following closely behind general dietary modification, fatty acid supplementation offers clinicians the opportunity to improve the health of their patients in ways that no other single treatment can.

FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

An accurate and detailed understanding of fatty acid metabolism is important for the complete and effective management of many clinical conditions including mental depression, coronary artery disease, hypertension, diabetes, other inflammatory/autoimmune disorders, and many of the musculoskeletal conditions encountered in clinical practice. The practical application of this information is

relatively straightforward, and with a detailed understanding of precursors and modulators of fatty acid, prostaglandin, and leukotriene metabolism, clinicians can facilitate or restrict the production of bioactive chemicals to promote the desired clinical result. The basics of fatty acid metabolism were reviewed previously; here we focus on clinical applications. We will focus on the fatty acids with the greatest promise for clinical benefit: alpha-linolenic acid, gamma-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and oleic acid. Biochemical pathways and clinical implications of fatty acid metabolism are detailed in Figures 1 and 2.

Figure 1. Metabolism of omega-3 fatty acids and related eicosanoids

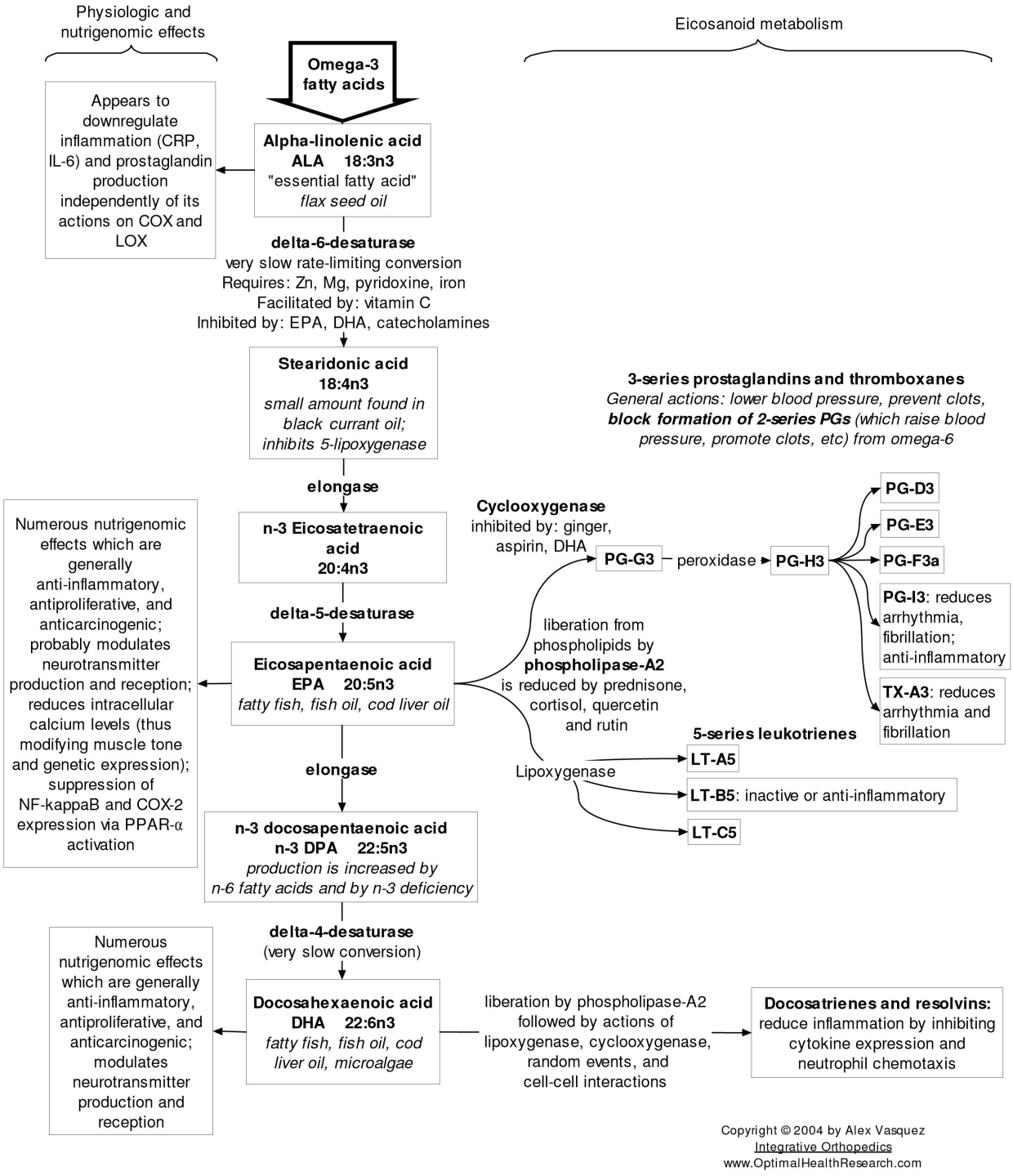

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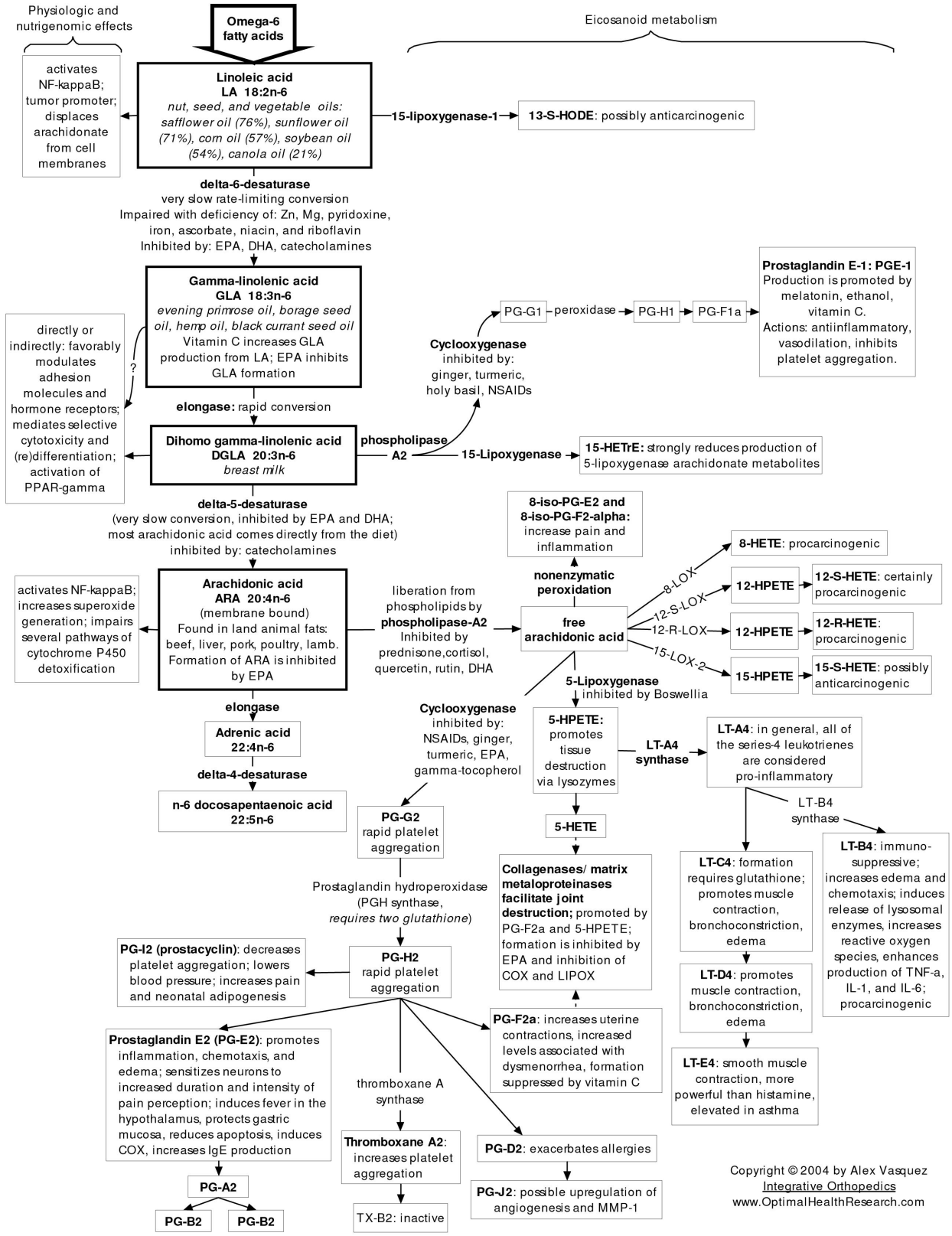
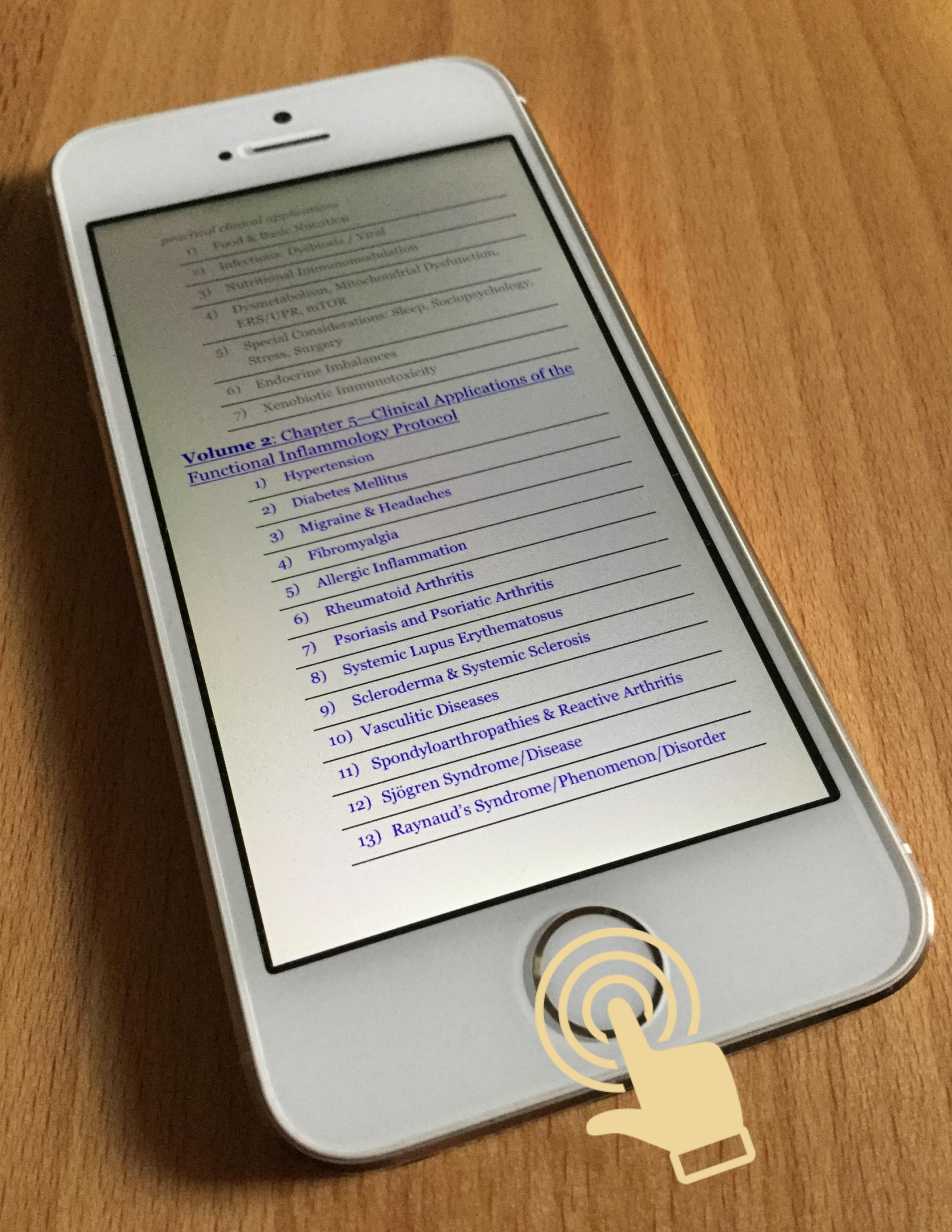
Figure 2. Metabolism of omega-6 fatty acids and related eicosanoids



THE HEALTH-PROMOTING FATTY ACIDS: ALA, EPA, DHA, GLA, AND OLEIC ACID

- ***Alpha-linolenic acid: ALA, α-LNA, ALNA, 18:3n3:*** ALA is an essential fatty acid as it is the "first in line" in the family of omega-3 polyunsaturated fatty acids (PUFA). Sources include flax seed oil (57% ALA), canola oil (9% ALA), soy oil, breast milk, English/black walnuts, soybeans, pine nuts, green vegetables, and beans. Conversion of ALA to the more biologically active EPA and DHA does not reliably or efficiently occur in humans.[26] No increase in DHA has been consistently observed in humans after supplementation of ALA[27]; in fact, supplementation with flax seed oil has actually been shown to reduce DHA levels in humans.[28] Although ALA can reduce blood pressure and cardiovascular mortality[26], it does not reduce serum lipids as do EPA and DHA. In a study of men with metabolic syndrome, ALA was shown to have anti-inflammatory benefits independent of its conversion to EPA or DHA.[29] The mechanism of action appears to be downregulation of NF-KappaB (the main "amplifier" for the expression of proinflammatory gene products[30]) rather than the direct modulation of eicosanoid biosynthesis. One study using flax oil as a source of ALA to treat rheumatoid arthritis found no clinical or biochemical benefit (i.e., no change in Hgb, CRP, ESR)[31]; however, the poor results of this study may have been due to the inferior quality of the flax oil product that was used which only supplied 32% ALA compared with the much higher concentration of 57% found in most products. Moderate intakes of ALA from flax oil profoundly reduce production of proinflammatory prostaglandins (e.g., PG-E2, measured by urinary excretion) by 52% to 85% in humans[32] which is superior to the 42% reduction induced by rofecoxib (the drug "Vioxx").[33] In summary, increased intake of ALA appears to provide cardioprotective[34] and anti-inflammatory benefits[29,32], and ALA can help reduce the frequency and severity of migraine headaches when used as part of a comprehensive natural treatment plan that includes diet change and nutritional supplementation.[35]
- ***Eicosapentaenoic acid: EPA, 20:5n3:*** EPA is essentially absent in vegan diets since the major dietary source is fish oil. Dietary EPA is incorporated into cell membranes where it modulates neurotransmitter and hormone receptor function and where it is stored before liberation by phospholipase for eicosanoid production. EPA-derived eicosanoids have anti-inflammatory properties, including a reduction in the production of proinflammatory eicosanoids such as LT-B4, PAFs, and cytokines such as TNF-alpha and IL-1, and a large reduction in PG-E2 and TX-B2.[36] Unfortunately, EPA can decrease production of DGLA, the metabolite of GLA that has health-promoting properties.[37] EPA doses of at least 4 grams per day are needed to increase bleeding time.[38] EPA supplementation reduces urinary excretion of calcium in patients with hypercalciuria and may therefore help prevent the development of calcium urolithiasis.[39] Due to its anti-inflammatory, membrane-enhancing, and other nutrigenomic benefits, EPA supplementation has proven beneficial for patients with lupus,[40] cancer[41], borderline personality disorder[42], mental depression[43, 44, 45], schizophrenia[46], and osteoporosis (when used with GLA).[47]
- ***Docosahexaenoic acid: DHA, 20:6n-3:*** DHA is found only in plants of the sea, phytoplankton/microalgae, and consumers of microalgae (such as fish). Like EPA, DHA is an important component of cell membranes and generally appears to improve cell membrane function via improving receptor function and signal transduction. In late 2003, bioactive metabolites of DHA—the docosatrienes and resolvins—were discovered to mediate potent anti-inflammatory benefits.[48] Animal studies have shown that induction of DHA deficiency causes memory deficits and a reduction in hippocampal cell size[49], and DHA deficiency in humans is consistently associated with mental depression, learning disorders (e.g., ADD/ADHD), and other neuropsychiatric disorders such as schizophrenia. DHA levels are reduced by ethanol consumption.[50] DHA appears essential for optimal cognitive function in infants and adults, and DHA also provides protection against thrombosis, arrhythmia, cardiovascular death, Alzheimer's disease[51], otitis media (when used with nutritional supplementation[52]), and coronary restenosis following angioplasty.[53] Supplementation with DHA (often in the form of fish oil, which includes EPA) has been shown to benefit patients with bipolar disorder[54], Crohn's disease[55], rheumatoid arthritis[56, 57, 58], lupus[59], cardiovascular disease[60], psoriasis[61], and cancer.[62] DHA appears to have an "anti-stress" benefit manifested by 30% reductions in norepinephrine and improved resilience to psychoemotional stress.[63, 64] Supplementation with EPA+DHA is extremely safe and reduces all-cause mortality.[60]
- ***Gamma (γ)-linolenic acid: GLA, 18:3n6:*** The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most powerful health-promoting n-6 fatty acid, GLA is found in varying concentrations in evening primrose oil, borage seed oil, hemp seed oil, and black currant seed oil. Most if not all of the actions of GLA are mediated following its elongation to the biologically active DGLA, from which eicosanoids that have cardioprotective and anti-inflammatory benefits are derived. Low levels of DGLA are associated with increased risk for stroke and myocardial infarction.[37] DGLA metabolites reduce the formation of the arachidonate-derived 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor.[65] GLA supplementation results in the formation of two biologically active metabolites from DGLA formed by cyclooxygenase and lipoxygenase. Prostaglandin E-1 (PG-E1) is the main metabolite formed from DGLA by cyclooxygenase and its production is increased by vitamin C.[66] PG-E1 decreases platelet aggregation[37], inhibits vascular smooth muscle cell proliferation *in vitro*[67], causes vasodilation[36], and thus helps lower blood pressure.[37] PG-E1 has anti-inflammatory benefits and is probably the most potent prostaglandin with respect to bronchodilation.[66] Additionally, PG-E1 may have a mood elevating effect insofar as levels are elevated in patients with mania, reduced in patients with depression, and are elevated by ethanol intake.[68] Production of PG-E1 is increased by n-3 fatty acids.[69] 15-HETrE is the second main metabolite from GLA/DGLA and is formed from DGLA via 15-lipoxygenase. 15-HETrE has potent anti-inflammatory action by inhibiting the conversion of arachidonic acid to leukotrienes via inhibition of 5-lipoxygenase and 12-lipoxygenase.[37, 70] Clinically, this is very important because several common and serious health problems including allergy, asthma, cardiovascular disease, and cancer are at least partially dependent upon the function of lipoxygenase for the production of leukotrienes. Notably, prostate cancer cells can be rapidly killed *in vitro* by lipoxygenase inhibition.[71] Clinical benefit associated with GLA supplementation is seen in patients with, eczema[72], breast cancer (when used with tamoxifen[73]), premenstrual syndrome[74], rheumatoid arthritis[75, 76], diabetic neuropathy[77], migraine headaches (when used with ALA[35]), and respiratory distress syndrome (when used with EPA).[78]

- ***Oleic acid:*** N-9 oleic acid appears to have health-promoting benefits, namely cardioprotection and anti-inflammation which are both partially mediated via suppression of NF-kappaB.[79] Most studies that have used oleic acid have used olive oil, which is a complex mixture of oleic acid, squalene, and phenolic antioxidants/anti-inflammatories; therefore, determination of the benefits of oleic acid alone (i.e., without squalene and phenolics) is difficult. Other sources of oleic acid include flax seed oil and borage oil. Olive oil should be consumed in the diet to attain sufficient quantity of oleic acid along with the health-promoting, anti-inflammatory, anti-cancer, and cardioprotective squalene and phenolic antioxidants. Dietary consumption of olive oil is consistently associated with reductions in cancer and cardiovascular disease, particularly when used as a component of a health-promoting diet.[80, 81]

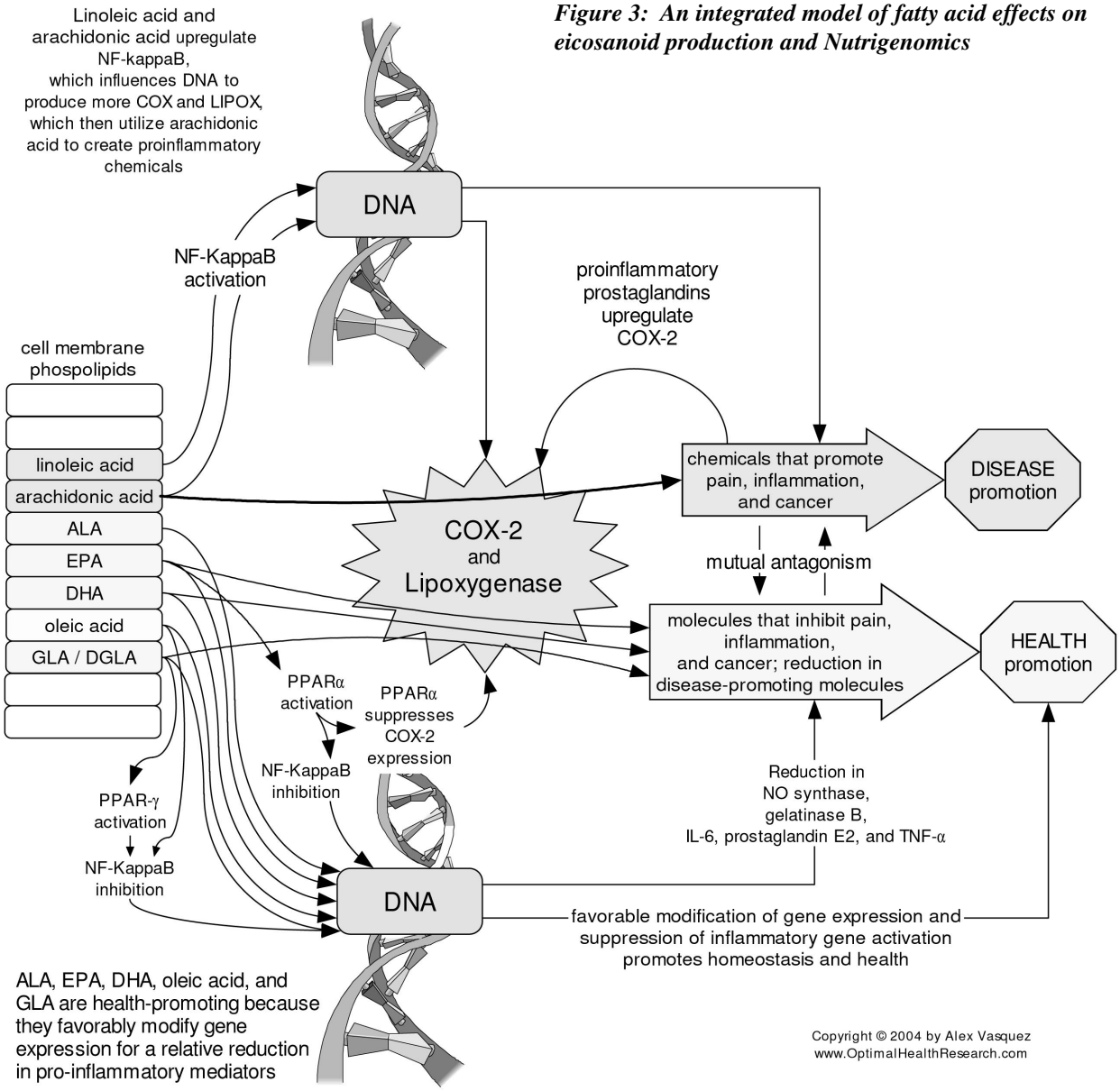
NUTRIGENOMICS: MODULATION OF GENETIC EXPRESSION VIA INTERVENTIONAL NUTRITION

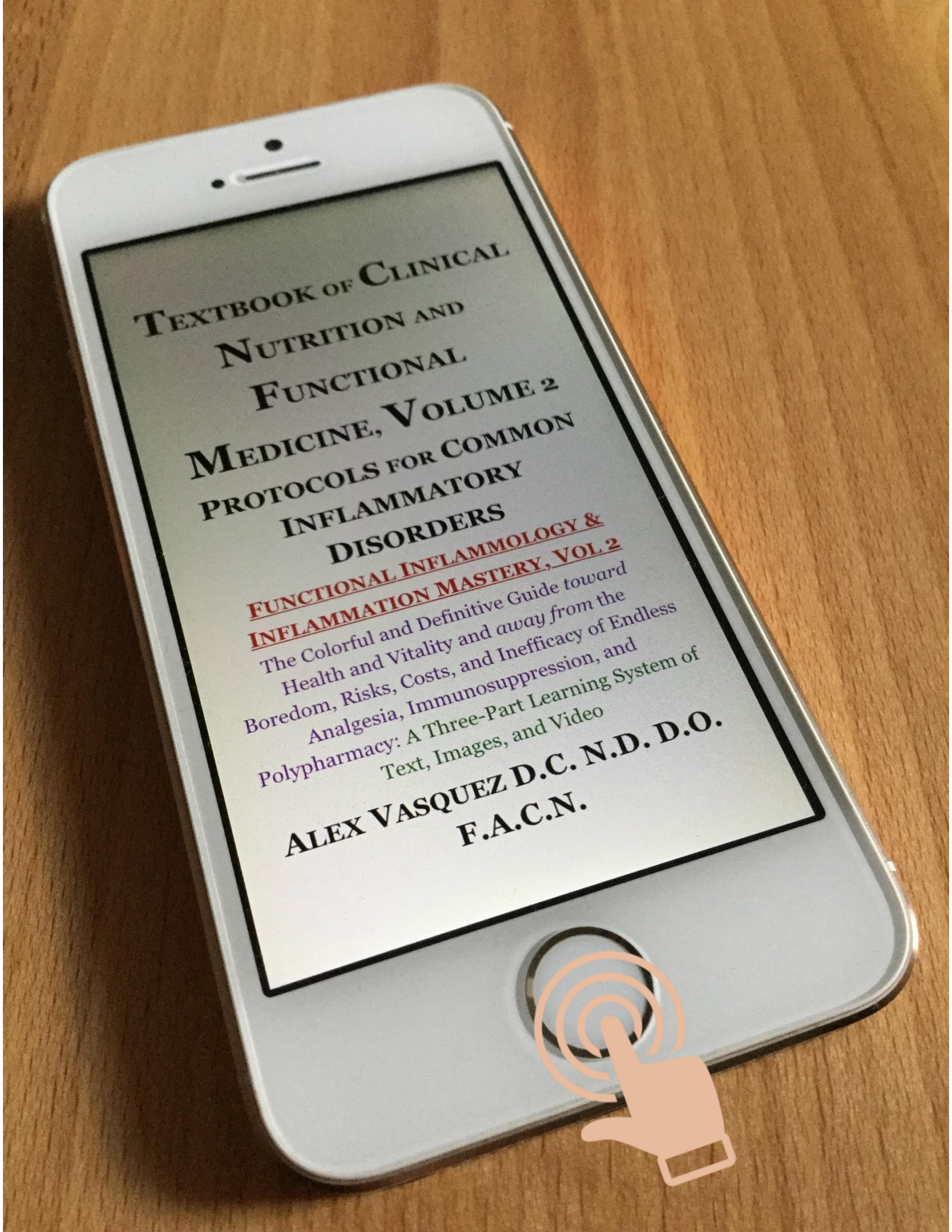
The study of how dietary components and nutritional supplements influence genetic expression is referred to as "nutrigenomics" or "nutritional genomics" and has been described as "the next frontier in the postgenomic era."[82] Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as proinflammatory NF-kappaB. Indeed, the previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional level. Whereas pharmaceutical modulation of genetic expression will require billions of dollars and decades of research before clinical implementation, the power of health-promoting nutritional interventions is available to us immediately at comparatively negligible cost.

Fatty acids and their end-products modulate genetic expression in several ways, as these examples will illustrate. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease. Corn oil, probably as a result of its high n-6 LA (linoleic acid) content, rapidly activates NF-kappaB and thus promotes tumor development, atherosclerosis, and elaboration of pro-inflammatory mediators such as TNFa.[83, 84, 85] Similarly n-6 arachidonic acid increased production of the free radical superoxide approximately 4-fold when added to isolated Kupffer cells *in vitro*. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases

genetic expression of cyclooxygenase and IL-6; thus, inflammation manifested by an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein.[86] The unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, inhibition of NF-kappaB, and impairment of estrogen receptor function.[87, 88] Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans[32], and this effect is probably mediated by down-regulation of proinflammatory transcription, as evidenced by reductions in CRP, IL-6, and SAA.[29] EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation via activation of PPAR-alpha[89] and thus reducing elaboration of proinflammatory mediators.[90] EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels and thus activating protein kinase R which impairs eukaryotic initiation factor-2alpha and inhibits protein synthesis at the level of translation initiation, thereby mediating an anti-cancer benefit.[91] DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for proinflammatory IL-1, inhibit TNFa, and reduce neutrophil entry to sites of inflammation.[48] Therefore, we see that fatty acids directly affect gene expression by complex and multiple mechanisms. These effects are summarized in Figure 3.

Figure 3: An integrated model of fatty acid effects on eicosanoid production and Nutrigenomics

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BIOCHEMICAL AND CLINICAL SUPERIORITY OF USING FATTY ACIDS IN BALANCED COMBINATION

For the majority of clinical situations, the use of fatty acids in isolation is inferior to using fatty acids in balanced combination for several reasons. First, fatty acid defects/deficiencies generally occur *in combination* rather than in isolation, and therefore more than one fatty acid is generally needed when fatty acid supplementation is required. Second, since fatty acids compete for space in cell membranes, supplementation with a single fatty acid can exacerbate depletion of other fatty acids. Supplementation with EPA and DHA (ie, fish oil) leads to a reduction in DGLA and deprives patients of the benefits of PG-E1 and 15-HETrE[92]; therefore GLA should be supplemented when EPA and DHA are used. ALA supplementation[32] and fish oil supplementation[93] both reduce tissue levels of oleic acid and this is believed to have negative effects; therefore ALA and fish oil supplementation should include additional oleic acid. GLA supplementation causes a harmful reduction in EPA and a harmful increase in arachidonic acid unless EPA and DHA are supplemented along with the GLA.[94] Because of these adverse effects noted with the use of single sources of fatty acids, **the current trend in the research literature and in clinical practice is to use fatty acids *in combination*.** In other words, clinical benefits are generally improved significantly when doctors and patients use a fatty acid supplement that contains the health-promoting omega-3, -6, and -9 fatty acids *in combination* and *in their proper ratios*.

Clinical studies using mixed fatty acid preparations have shown clinically powerful benefits. The combination of ALA and GLA was shown to dramatically reduce the severity, frequency, and duration of migraine headaches when used with vitamin supplementation and a reduction in dietary arachidonate.[35] Combination therapy with EPA, DHA, GLA, and arachidonate was found beneficial for children with symptoms of ADD/ADHD.[95] Combination therapy with EPA and GLA improved biochemical and clinical indexes in adult patients with acute respiratory distress syndrome.[78] Supplementation with GLA, EPA, and calcium is superior to calcium alone in the treatment and prevention of osteoporosis.[47] In a recent placebo-controlled trial with pregnant women, the combination of EPA, DHA, and GLA appeared to protect women from eclampsia and edema.[96] Similarly, in patients with asthma, the combination of EPA and GLA was well tolerated and reduced leukotriene-B4 production.[97] Recently, the combination of EPA+DHA in a 2:1 ratio with GLA was estimated to reduce the risk for myocardial infarction in women by 43%.[98] Thus, using combinations of health-promoting fatty acids from the n-3 family (i.e., ALA, EPA, DHA) and n-6 family (i.e., GLA) along with n-9 oleic acid to prevent the decrease in oleic acid that occurs with ALA, EPA, and DHA supplementation will most certainly prove clinically beneficial for the treatment and prevention of an impressively wide range of health disorders; the research is already showing a clear trend in this direction.

CONCLUSIONS AND CLINICAL IMPLEMENTATION

Fatty acid imbalances and deficiencies are common in industrialized societies such as America that consume nutritionally deficient diets with a lack of vitamins, minerals, and n-3 fatty acids and a superabundance of artificial foods and over-reliance upon grains.[99, 100] The consistent theme in the research is that supplementation with ALA, EPA, DHA, GLA, and oleic acid provides clinically significant health-promoting benefits in a wide range of patient groups with various health disorders. In the treatment of inflammatory, cardiovascular, and malignant diseases, concomitant reduction in dietary arachidonic acid accentuates the benefits of ALA, EPA, DHA, and GLA supplementation.[101] Paradoxically, preservation of or an increase in tissue levels of arachidonic acid can be uniquely beneficial in patients with neuropsychiatric illness such as depression, attention deficit / hyperactivity disorder, and schizophrenia when treated with fatty acid supplementation.[95, 102, 103]

The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids. The low frequency of drug interactions and adverse effects is to be expected from these fatty acids which are synthesized within the body and/or available from common foods, though in insufficient amounts to be clinically therapeutic. Very high doses of n-3 fatty acids may have a clinically significant anticoagulant effect and should be used cautiously in patients with bleeding tendencies and those taking anticoagulant medications such as coumadin/warfarin, aspirin, or plavix/clopidogrel.

Supplementation with ***all*** of the health-promoting fatty acids—ALA, EPA, DHA, GLA, and oleic acid—is expected to provide doctors and patients with benefits superior to those attained with the use of single fatty acids in isolation. Doses are tailored to patient size/weight and health status and are kept within the safe boundaries established in published research. Oleic acid is safe at high doses as its is consumed *ad libitum* in Mediterranean diets. The highest daily dose of ALA reported in the literatures is 10,700 mg used in a 4-week study of lactating women.[27] Two studies have used 13,000 mg EPA+DHA per day without adverse effects in hypertensive patients[104] and cancer patients.[105] Four grams per day of GLA has been safely

used in adults, and proof of safety was established in a study of infants with eczema given doses of 3 grams per day.[72] Clinical effectiveness of fatty acid supplementation for most conditions (e.g., cancer and all inflammatory/ autoimmune diseases) will be increased by implementing a diet low in linoleic and arachidonic acids, which is achieved via avoidance of vegetable oils, nut oils, milk/dairy, and most grain-fed beef, liver, pork, lamb, and, to a lesser extent, turkey and chicken. Food allergens are avoided and the underlying immune dysfunction is addressed with orthomolecular immunomodulation.[25] Balanced, complete fatty acid supplementation along with a health-promoting diet[24,25], multivitamin supplementation[106], and assurance of optimal vitamin D status[25,107] forms the foundational treatment plan for nearly all patients with all diseases. For many patients, regardless of their official "diagnosis", this simple, safe, cost-effective approach of overall health improvement is all the treatment they require. Doctors who use this approach will have achieved a significant clinical advantage in the treatment of patients with premenstrual syndrome, diabetic neuropathy, respiratory distress syndrome, Crohn's disease, lupus, rheumatoid arthritis, cardiovascular disease, hypertension, psoriasis, eczema, migraine headaches[108], bipolar disorder[109], borderline personality disorder, mental depression[110] schizophrenia, osteoporosis[111], polycystic ovary syndrome[112], multiple sclerosis[113], and musculoskeletal pain.[25,114,115] Patients with highly complex illnesses and multiple health disorders may require additional treatment, as will be described in future articles in this journal following a comprehensive synthesis of current research for chiropractic and naturopathic physicians.[25]

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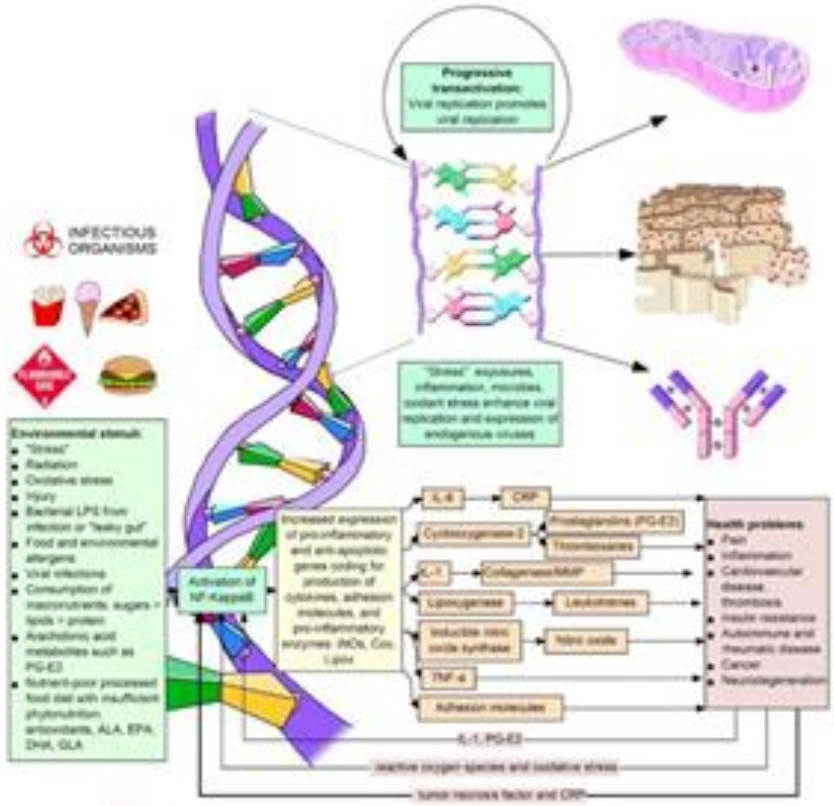

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Additional articles and book excerpts have been amended to the previous publication in order to provide context and orientation to the author's main works.

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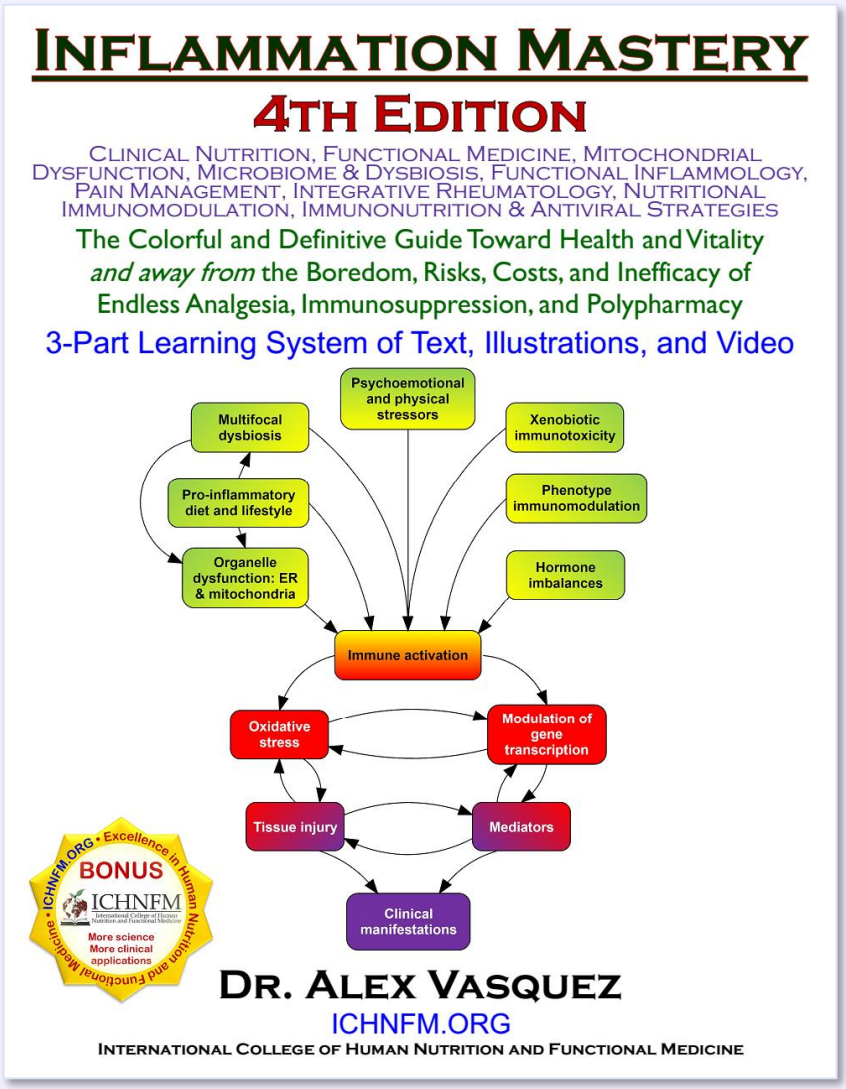
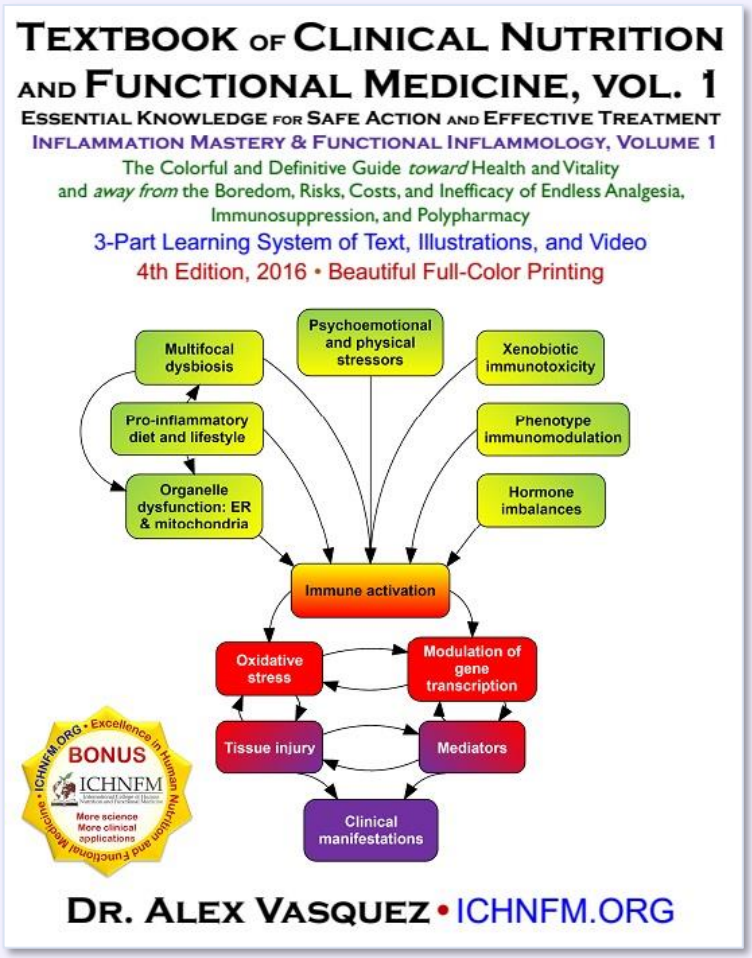
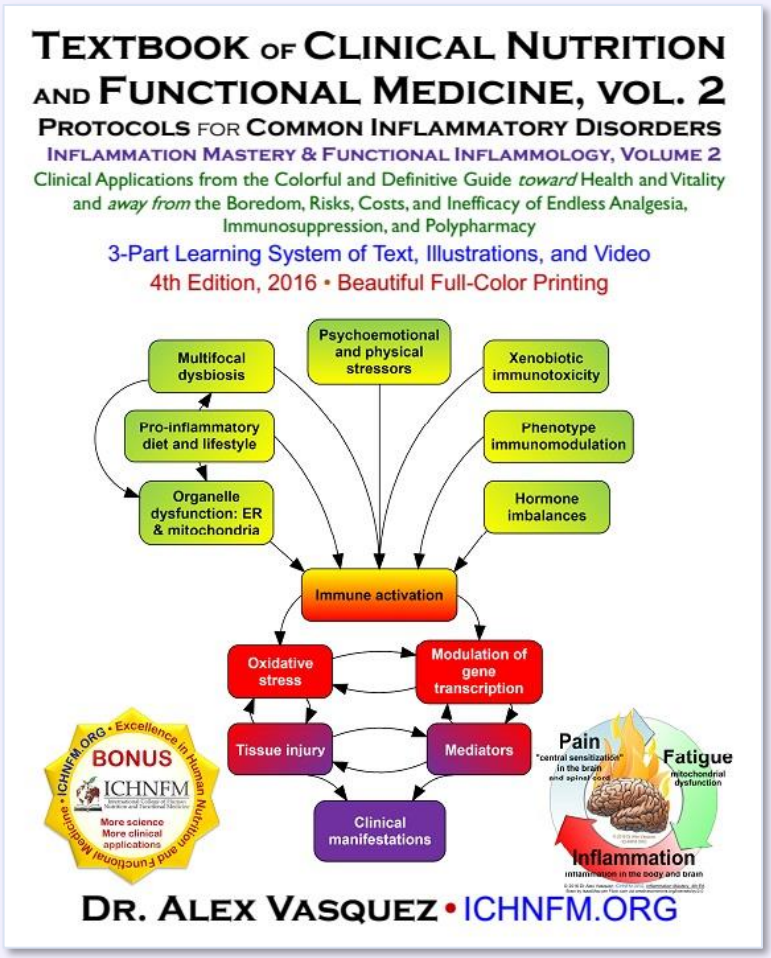






Inflammation Mastery

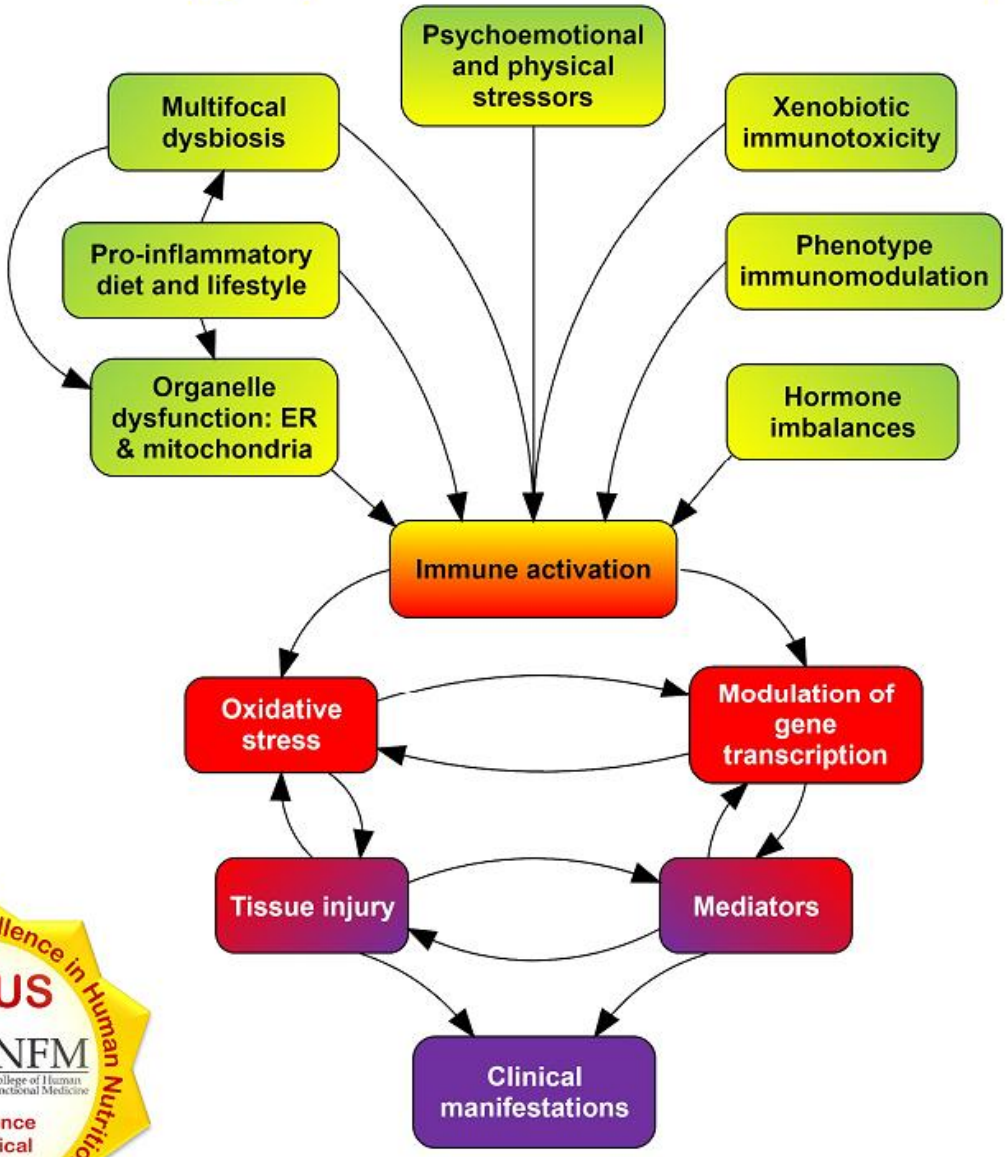
4th Edition

Clinical Nutrition, Functional Medicine, Mitochondrial Dysfunction, Microbiome & Dysbiosis, Functional Inflammology, Pain Management, Integrative Rheumatology, Nutritional Immunomodulation, Immunonutrition & Antiviral Strategies

The Colorful and Definitive Guide Toward Health and Vitality

and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy

3-Part Learning System of Text, Illustrations, and Video



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Inflammation Mastery

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A Three-Part Learning System of Text, Images, and Video

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Affirmation and consistency of common themes in an interconnected reality; the importance of transitioning from reception to comprehension to conception to behavior

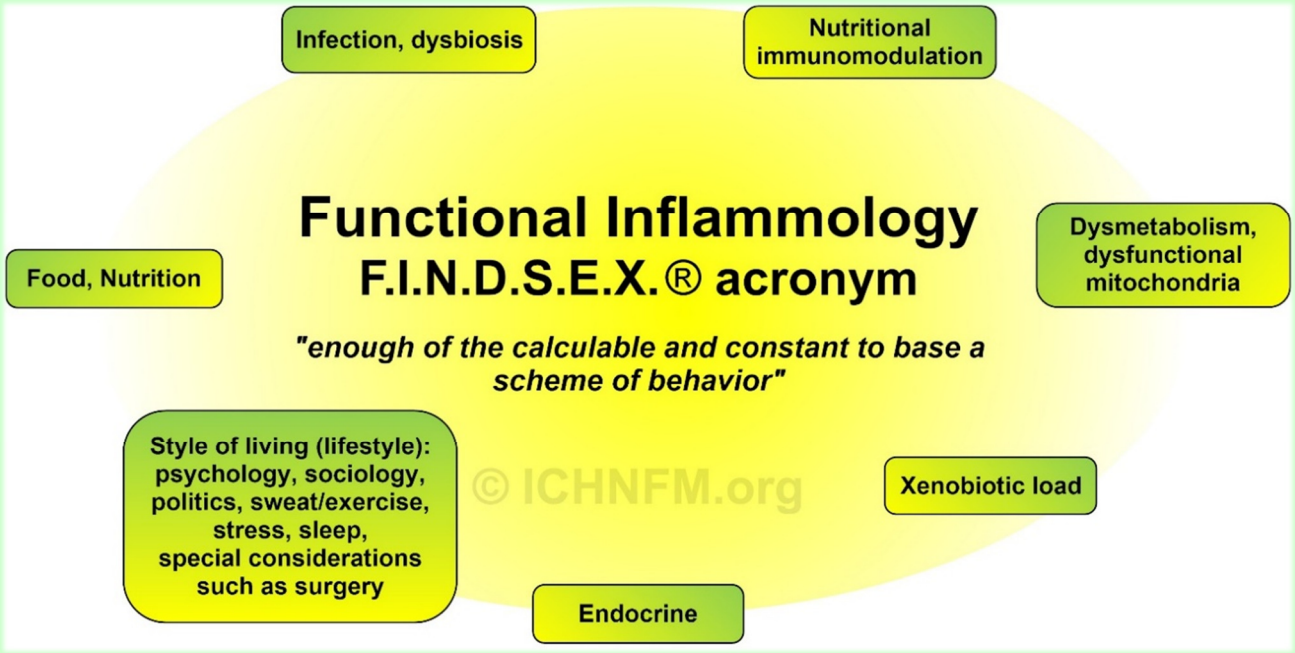
"The fact that today I still stand by these ideas, **that in the intervening time they themselves have constantly become more strongly associated with one another, even to the point of growing into each other, intertwining, and becoming *one***, that has reinforced in me the joyful confidence that they may not have originally developed in me as single, random, or sporadic ideas, but up out of common roots, from some fundamental *will for knowledge* ruling from deep within, always speaking with greater clarity, always demanding greater clarity.

In fact, this is the only thing appropriate and proper for a philosopher. **We have no right to be isolated in any way: we are not permitted to make isolated mistakes or to run into isolated truths**. Our ideas, our values, our affirmations and denials, our *if*s and *but*s—these rather grow out of us from the same necessity which makes a tree bear its fruit—totally related and interlinked amongst each other: witnesses of one will, one health, one soil, one sun."

Nietzsche FW. *On the Genealogy of Morals*, 1887, Preface essay #2

"In order for a particular species to maintain itself and increase its power, **its conception of reality must comprehend enough of the calculable and constant** for it to **base a scheme of behavior on it**."

Nietzsche FW. *Will to Power*,1901, #480



"If this book is incomprehensible to anyone and jars on his ears, the fault, it seems to me, is not necessarily mine. It is clear enough, assuming, as I do assume, that one has first read my earlier writings and has not spared some trouble in doing so: for they are, indeed, not easy to penetrate. Regarding my *Zarathustra*, for example, I do not allow that anyone knows the book who has not at some time been profoundly wounded and at some time profoundly delighted by every word in it; for only then may he enjoy the privilege of reverentially sharing in the halcyon element out of which that book was born and in its sunlight clarity, remoteness, breadth, and certainty. In other cases, people find difficulty with the aphoristic form: this arises from the fact that today this form is not taken seriously enough. An aphorism, properly stamped and molded, has not been "deciphered" when it has simply been read; rather, one has then to begin its exegesis—its explanation, its extraction, for which is required an art of searching, deciphering. To be sure, one thing is necessary above all if one is to practice reading as an art in this way, something that has been unlearned most thoroughly nowadays—something for which one has almost to be a cow and in any case not a "modern man": *rumination*—taking time to pause, to reflect, to consider...

Friedrich Nietzsche, *On the Genealogy of Morals*, Preface, Section #8
Sils-Maria, Upper Engadine, July 1887

❶ Food: Diet and Basic Nutritional Supplementation

Major Concepts in this Section

"Food" is the first part of the protocol and the foundation of the overall plan, not simply for improving nutritional status, but for setting the biochemical stage for more profound improvements in immune balance, mitochondrial function, et al. Patients can and should appreciate that they have near complete control over what they consume; unfortunately and conversely, however, in countries such as the United States where much of the food supply is contaminated with pesticide residues and genetically manipulated food-type (GMO) products, consuming a health-promoting diet can present unique challenges.

Contents of this section:

Introduction to Nutrigenomics: Pro-Inflammatory and Anti-Inflammatory Effects of Foods and Nutrients

We must look beyond the nutritional properties of foods to appreciate that dietary patterns and the consumption of specific foods can influence genetic expression and either promote or retard the development of inflammation and related clinical disorders. The purpose of this section is to help clinicians attain a more profound understanding of the value of nutrition and its critical role as a foundational component in the treatment plan of patients with inflammatory disorders. The "correct" diet for the vast majority of patients with inflammatory disorders is the "supplemented Paleo-Mediterranean diet" which I have described in several other publications. The diet is modified for the specific exclusion of allergenic foods; it is implemented on a rotation basis, and it allows for periodic fasting and vegetarianism/veganism. The implementation of health-promoting dietary modifications is an *absolutely mandatory* component of the treatment plan, upon which other treatments depend for their success. The study of how dietary components and nutritional supplements influence genetic expression is referred to as *nutrigenomics* or *nutritional genomics* and has been described as "the next frontier in the postgenomic era."[7] Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as pro-inflammatory NFkB (NFkB) and the anti-inflammatory peroxisome-proliferator activated receptors (PPARs).[8,9,10,11] **The previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional**

[7] Kaput J, Rodriguez RL. Nutritional genomics: the next frontier in the postgenomic era. *Physiol Genomics*. 2004 Jan 15;16(2):166-77. Very important article.
[8] Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. *Lancet*. 1999;354:141-8
[9] Ehrmann et al. Peroxisome proliferator-activated receptors (PPARs) in health and disease. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2002 Dec;146(2):11-4
[10] Kliewer SA, Xu HE, Lambert MH, Willson TM. Peroxisome proliferator-activated receptors: from genes to physiology. *Recent Prog Horm Res*. 2001;56:239-63
[11] Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. *J Endocrinol*. 2001;169(3):453-9

Important Enzymes in Fatty Acid Metabolism

Fatty acids are converted to other fatty acids in the same family by the desaturase and elongase enzymes. The major "direction" of these reactions is depicted in the diagrams; however these reactions, like nearly all enzymatic reactions, are reversible to a limited extent. Fatty acids are converted to biologically active end-products by enzymes such as the cyclooxygenases, lipoxygenases, cytochrome P-450 enzymes and by nonenzymatic conversion. Four important concepts need to be understood in relation to the enzymes that interconvert fatty acids:

1) **These enzymes do not work with equal efficiency**, and thus their end-products may not be produced in sufficient amounts to be biologically or clinically significant. Therefore, *on paper*, the cascade of fatty acid metabolism appears to flow easily from one fatty acid to its downstream progeny; in reality however, this process is often slow and therefore not immediately reliable when one is looking for rapid and reliable clinical results. The desaturase enzymes are slow and rate limiting, whereas the elongase enzymes function efficiently and rapidly. For example, Horrobin noted, "Because the 6-desaturation step is so rate-limiting, it is impossible to produce any significant elevation of DGLA levels in humans by increasing linoleic acid intake."[411]
2) **These enzymes are subject to significant interpatient variability** due to inherited and acquired factors that can reduce enzyme activity. For example, many patients (especially those with eczema and diabetes) have extreme reductions in the activity of delta-6-desaturase, the rate-limiting enzyme in the fatty acid cascades from ALA and LA. When delta-6-desaturase is slow to perform its conversions, synthesis of all downstream fatty acids is greatly reduced.
3) **All enzymes require coenzymes (organic [carbon-containing] molecules, such as vitamins) and/or cofactors (inorganic molcules, such as minerals).** If the patient is deficient in cofactors/coenzymes, the efficiency of enzymatic conversions is greatly impaired. Since micronutrient deficiencies are common even in developed countries, and since people can have clinically significant micronutrient deficiencies (i.e., "marginal malnutrition"[412]) yet still be "apparently healthy", a wise clinical strategy is to ensure that the patient's micronutrient status is adequate by encouraging the patient to consume a nutritious organic[413] whole-foods diet along with a high-potency broad-spectrum multivitamin and multimineral supplement. Patients with magnesium deficiency show impaired fatty acid metabolism because desaturase enzymes are unable to function properly without sufficient magnesium.[414] Animal studies suggest that vitamin B-6 deficiency can reduce the function of delta-6-desaturase by 64% and lead to reductions in EPA and DHA.[415]
4) **Substrates compete for enzymatic conversion.** In several instances, the same enzyme must act upon two different fatty acids in two different omega families. For example, delta-6-desaturase converts the omega-3 linolenic acid to stearidonic acid, yet this same enzyme also converts the omega-6 linoleic acid to gamma-linolenic acid. If the diet contains an absolute or relative excess of linoleic acid, then on a molecular and functional level, this excess linoleic acid will disproportionately utilize delta-6-desaturase and conversion of available linoleic acid to gamma-linolenic acid will be reduced. As reviewed by Dupont[416], "A competitive interaction between fatty acids exists so that those of the [alpha-linolenic acid, omega-3] family suppress the metabolism of those of the [linoleic acid, omega-6] family, and the [linoleic acid, omega-6] family suppress metabolism of the [linolenic acid, omega-3] family although less strongly. Both the [linoleic acid, omega-6] and [alpha-linolenic acid, omega-3] fatty acids suppress metabolism of the [oleic acid, omega-9] fatty acids." Stated more plainly by Pizzorno[417], "…a relative excess of one fatty acid will tend to hog an enzyme system, resulting in decreased conversion of the other fatty acids." In reviewing clinical evidence that EPA supplementation leads to significant reductions (50%) in DGLA levels, Horrobin[418] noted, "However, the n-3 EFAs are much more effective in inhibiting n-6 EFA metabolism than vice versa." A practical example: in a patient who is deficient in both omega-3 and omega-6 fatty acids, supplementation exclusively with flax oil will exacerbate the deficiency of gamma-linolenic acid.

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[411] Horrobin DF. Interactions between n-3 and n-6 essential fatty acids (EFAs) in the regulation of cardiovascular disorders and inflammation. *Prostaglandins Leukot Essent Fatty Acids*. 1991 Oct;44(2):127-31
[412] Allen LH. The nutrition CRSP: what is marginal malnutrition, and does it affect human function? *Nutr Rev*. 1993 Sep;51(9):255-67
[413] Bob Smith. *Journal of Applied Nutrition* 1993; 45: 35-39
[414] Galland L. Impaired essential fatty acid metabolism in latent tetany. *Magnesium*. 1985;4(5-6):333-8
[415] Tsuge H, Hotta N, Hayakawa T. Effects of vitamin B-6 on (n-3) polyunsaturated fatty acid metabolism. *J Nutr*. 2000 Feb;130(2S Suppl):333S-334S
[416] Dupont J. Lipids. In: Brown ML (ed). *Present Knowledge in Nutrition. Sixth Edition*. Washington DC: International Life Sciences Institute;1990 page 62
[417] Pizzorno JE. *Total Wellness*. Rocklin: Prima; 1996 page 170
[418] Horrobin DF. Interactions between n-3 and n-6 essential fatty acids (EFAs) in the regulation of cardiovascular disorders and inflammation. *Prostaglandins Leukot Essent Fatty Acids*. 1991 Oct;44(2):127-31

- **Delta-6-desaturase (D6D):**
  - In omega-3 fatty acid metabolism, D6D converts linolenic acid to stearidonic acid. In omega-6 fatty acid metabolism, D6D converts linoleic acid to gamma-linolenic acid. D6D is the rate-limiting enzyme in fatty acid metabolism, meaning that it is the slowest functioning enzyme in the cascade of fatty acid conversions. Recall that in biochemistry the first enzyme in a series of biochemical reactions tends to be the rate-limiting enzyme for the sake of avoiding unnecessary downstream conversions. D6D is inhibited by trans fatty acids.[419] Action of this enzyme is increased during essential fatty acid deficiency.[420] Patients with eczema and diabetes have been noted to have defects in the function of D6D.[421]
  - Efficient function of D6D requires iron, magnesium, zinc, pyridoxine, niacin, and riboflavin. Administration of supraphysiologic doses of enzyme cofactors can improve function of defective or mutated enzymes.[422]
  - The catecholamines epinephrine and norepinephrine inhibit D5D and D6D.[423]
- **Delta-5-desaturase (D5D):**
  - In omega-6 fatty acid metabolism, D5D converts DGLA to arachidonic acid. However, this enzyme is slow, so that virtually all arachidonic acid found in body tissues originated from the consumption of land animal fats/meats[424] such as beef, liver, pork, lamb, and poultry. Additionally, some people (such as those with X-linked retinitis pigmentosa[425]) have reduced action of D5D and therefore have low levels of DHA. D5D is inhibited by EPA.[426] Released in increased amounts during stress and anxiety, the catecholamines epinephrine and norepinephrine inhibit D5D and D6D.[427]
- **Delta-4-desaturase**
  - Action of this enzyme is increased during essential fatty acid deficiency.[428]
- **Elongase**: These enzymes efficiently add carbon groups to the fatty acid chain.
- **Prostaglandin synthase complex (PGS)**: This is the major enzyme system that is responsible for prostaglandin biosynthesis. PGS includes phospholipase A2 and cyclooxygenase.[429]
- **Phospholipase-A2**
  - Crucial to the arachidonic acid cascade since cyclooxygenase can act only on free arachidonate (i.e., after arachidonate has been liberated from membrane phospholipids); this is the rate-limiting step in the formation of arachidonate-derived prostaglandins.[430]
  - Contact of IgE with mast cells stimulates the release of arachidonate, which must occur via phospholipase A2[431]
  - Inhibited by adrenal steroids (cortisol) and prednisone
- **Cyclooxygenase (COX) (also called "prostaglandin synthase" or "PGS" or "prostaglandin endoperoxide synthase")**
  - COX-1 is "constitutive" and is found in all cells, while COX-2 is inducible by stimulation from monocytes/macrophages following stimulation by PAF, IL-1, or bacterial lipopolysaccharide; its induction is inhibited by glucocorticoids.[432]

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[425] Hoffman DR, et al. Impaired synthesis of DHA in patients with X-linked retinitis pigmentosa. *J Lipid Res* 2001 Sep;42(9):1395-401
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[428] "The delta 4 desaturase activity is increased in essential fatty acid deficiency similar to delta 6 desaturase." Christophersen BO, et al. Eicosapentaenoic- and arachidonic acid metabolism in isolated liver cells. *Scand J Clin Lab Invest Suppl*. 1986;184:55-60
[429] Delvin TM. *Textbook of Biochemistry with Clinical Correlations*. New York: Wiley-Liss, 1997. Pages 431-441
[430] Delvin TM. *Textbook of Biochemistry with Clinical Correlations*. New York: Wiley-Liss, 1997. Pages 431-441
[431] McGlivery RW. *Biochemistry: A Functional Approach. Third Edition*. Philadelphia: WB Saunders, 1983. Pages 747-750
[432] Delvin TM. *Textbook of Biochemistry with Clinical Correlations*. New York: Wiley-Liss, 1997. Pages 431-441

- COX is irreversibly inhibited following acetylation by aspirin.
- The expression of COX is inhibited by glucocorticoids,[433] which also inhibit phospholipase A2.
- **COX forms TXs and PGs, while LIPOX form LTs.**
- The COX metabolite PG-F2alpha is necessary for the formation of matrix metalloproteinase-2 and other collagenases which are utilized for the destruction of connective tissue[434]
- **COX is apparently activated by either n-6 fatty acids or the oxidized metabolites of n-6 fatty acids.[435] Therefore, consumption of n-6 fatty acids alone—*without trauma or inflammatory stimuli*—is sufficient for the increased production of the harmful arachidonate-derived prostaglandins and leukotrienes**. Thus, by definition, a diet high in n-6 fatty acids may subtly yet significantly promote pain, inflammation, joint destruction, and cancer.
- A well-established consequence of inhibiting COX is that of increasing LIPOX metabolites. Inhibiting COX will decrease COX metabolites, yet will cause an increase in LIPOX metabolites because of increased substrate levels; i.e., the liberated arachidonate that is not metabolized by COX is now available to be metabolized by LIPOX. Thus, inhibiting COX produces a "metabolic shunt" effect that increases production of inflammatory mediators such as HETE and the leukotrienes. Additionally, inhibition of COX inhibits formation of the beneficial anti-inflammatory DGLA metabolites.
- Arachidonate metabolites from COX function for the most part to increase inflammation and pain.[436]
- Increased expression of COX-2 increases production of PG-E2 and has been associated with increased production of anti-apoptotic proteins and a reduction in pro-apoptotic proteins in cultured rat intestinal cells.[437]
- The activity of lipoxygenase and cyclooxygenase produces reactive oxygen species (ROS) intermediates.
- The paradox of how a single enzyme such as cyclooxygenase can produce such a wide array of metabolites from a single substrate such as arachidonic acid is solved by recognizing that arachidonate is three-dimensionally rearranged once within the cyclooxygenase enzyme and that these random arrangements favor the production of different metabolites by the preferential molecular modification of the original arachidonate.[438] Additionally, cyclooxygenase may become slightly rearranged as well, thus further promoting the heterogeneity of progeny.

- **Lipoxygenases**: a family of enzymes that form leukotrienes
  - Corneal lipoxygenase is inhibited by vitamin C[439]
  - The activity of lipoxygenase and cyclooxygenase produce ROS intermediates
  - **5-lipoxygenase, 5-LOX**
    - This is a pro-inflammatory enzyme that has different basal levels of activity in different people and in different disease conditions. Proinflammatory variances of this enzyme are seen in Africans (24%), Asians and Pacific Islanders (19.4%), other racial/ethnic groups (18.2%), Hispanics (3.6%) and whites (3.1%) and are associated with accelerated atherosclerosis and elevations in CRP especially when the diet is high in arachidonic acid and low in EPA[440]

[433] Tapiero H, et al. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. *Biomed Pharmacother*. 2002;56(5):215-22
[434] "Specific metabolites of each pathway, i.e. PGF2 alpha and 5-HPETE, are able to transcend the block and restore collagenase production, invasiveness in vitro and metastatic activity in vivo." Reich R, Martin GR. Identification of arachidonic acid pathways required for the invasive and metastatic activity of malignant tumor cells. *Prostaglandins* 1996 Jan;51(1):1-17
[435] " …due to activation of cyclooxygenase either by oxygenated metabolites of n-6 fatty acids or by the n-6 fatty acids themselves." Rubin D, Laposata M. Cellular interactions between n-6 and n-3 fatty acids: a mass analysis of fatty acid elongation/desaturation, distribution among complex lipids, and conversion to eicosanoids. *J Lipid Res*. 1992 Oct;33(10):1431-40
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- 5-LOX has been described as "procarcinogenic" due to its role in producing LT-B4 which has mitogenic and anti-apoptotic actions[441]
- The 5-LOX metabolite 5-HPETE is necessary for the formation of matrix metalloproteinase-2 and other collagenases which are utilized for the destruction of connective tissue[442]

- **8-lipoxygenase, 8-LOX**
  - 8-LOX is upregulated in animal models of cancer and has been described as "procarcinogenic" due to its role in producing 8-HETE, which has genotoxic effects and which is found in humans[443]
- **12-R-lipoxygenase, 12-R-LOX**
  - 12-R-LOX has been described as "procarcinogenic" due to its role in producing 12-R-HETE[444]
- **12-S-lipoxygenase, 12-S-LOX**
  - 12-S-LOX has been described as "procarcinogenic" due to its role in producing 12-S-HETE[445]
  - Expression of 12-S-LOX is directly correlated with aggressiveness, stage, and grade in human prostate cancer[446]
- **15-lipoxygenase-1, 15-LOX-1**
  - 15-LOX-1 metabolizes n-6 linoleic acid into 13-S-HODE, which appears to have *anti*cancer actions[447]
- **15-lipoxygenase-2, 15-LOX-2**
  - 15-LOX-2 metabolizes n-6 arachidonic acid into 15-S-HETE, which appears to have *anti*cancer actions[448]
- **12/15-lipoxygenase, 12/15-LOX**
  - Earlier works cited previously described 12 LOX and 15 LOX separately; more recent reviews have described "12/15-LOX" as a single enzyme; in this moment, whether this term is being used to describe the 12 and 15 forms *separately yet in conjunction* or as a different enzyme from the other 12 and 15 forms is not clear, and the differentiation may not be of practical clinical importance at this time. However, what is relevant is the connection between Western high-fat diets, LOX activity, and mitochondrial dysfunction as contributors to insulin resistance; an impressive review article published in 2013 by Mabalirajan and Ghosh[449] noted that high-fat Western diets (in animal models) lead to activation of 12/15-LOX and resulted in oxidative modification of fatty acids and sequential mitochondrial impairment, ER stress, UPR, and insulin resistance. Beyond the intellectual gratification of enhanced understanding, this data suggests that LOX inhibition—such as for example via ginger or bioavailable curcumin—might be an additional therapeutic strategy against organelle (e.g., mito and ER) dysfunction and subsequent pathoclinical complications.

[441] "These targets include procarcinogenic lipoxygenases (LOXs), including 5-, 8-, and 12-LOX, and anticarcinogenic LOXs, including 15-LOX-1 and possibly 15-LOX-2." Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. *Cancer Res*. 2001 Sep 1;61(17):6307-12
[442] "Specific metabolites of each pathway, i.e. PGF2 alpha and 5-HPETE, are able to transcend the block and restore collagenase production, invasiveness in vitro and metastatic activity in vivo." Reich R, Martin GR. Identification of arachidonic acid pathways required for the invasive and metastatic activity of malignant tumor cells. *Prostaglandins* 1996 Jan;51(1):1-17
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[444] Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. *Cancer Res*. 2001 Sep 1;61(17):6307-12
[445] Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. *Cancer Res*. 2001 Sep 1;61(17):6307-12
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[447] Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. *Cancer Res*. 2001 Sep 1;61(17):6307-12
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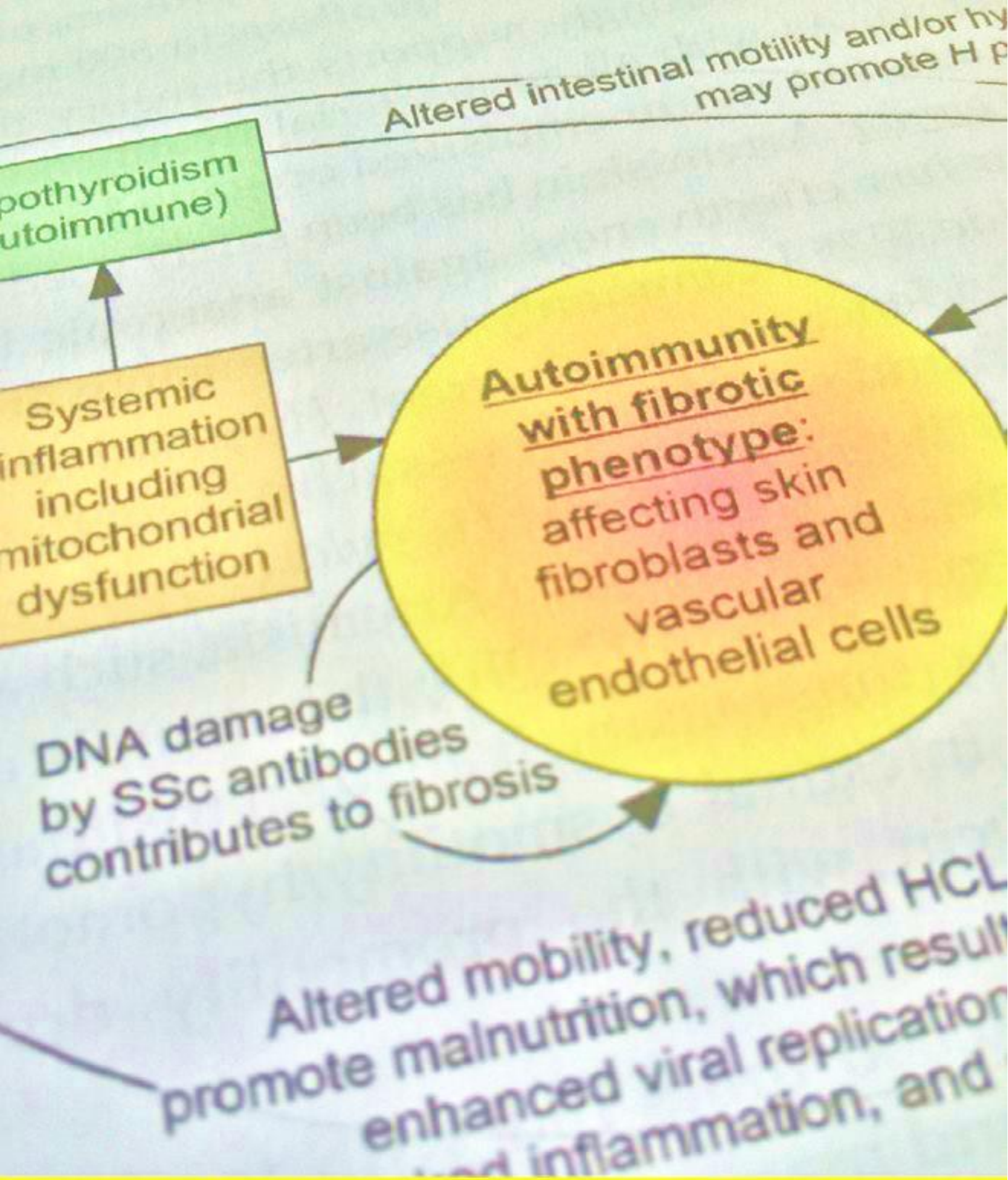
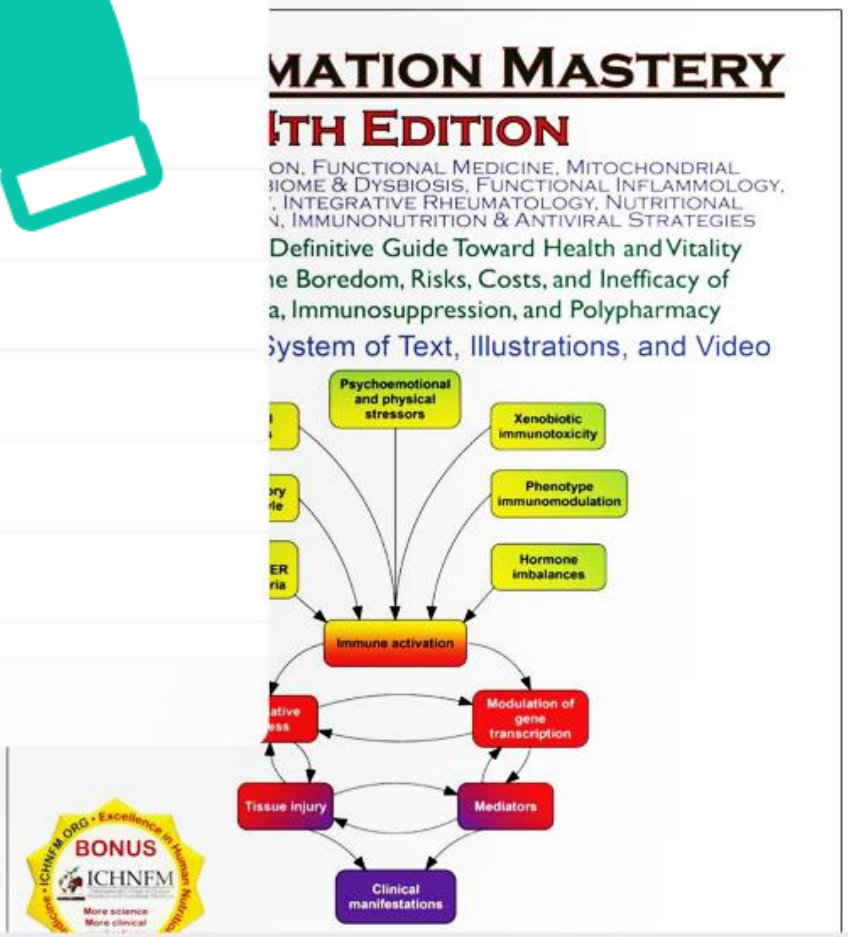
Real natural food is a human right: Corporate profiteers state that food and water are not human rights, but—in contrast to historical precident and social interests—corporate property. In this manner, private corporations become stronger than governments, when they control access to food, water, and thus very foundation of daily life and and thus national stability. When multinational corporations control the grain and water supply, then they also control the supply of poultry, cattle/livestock, and—increasingly—farm-raised fish.Corporations that control a society's food/water supply have control over that society, and they have the wealth to buy politicians, laws, and selective enforcement.





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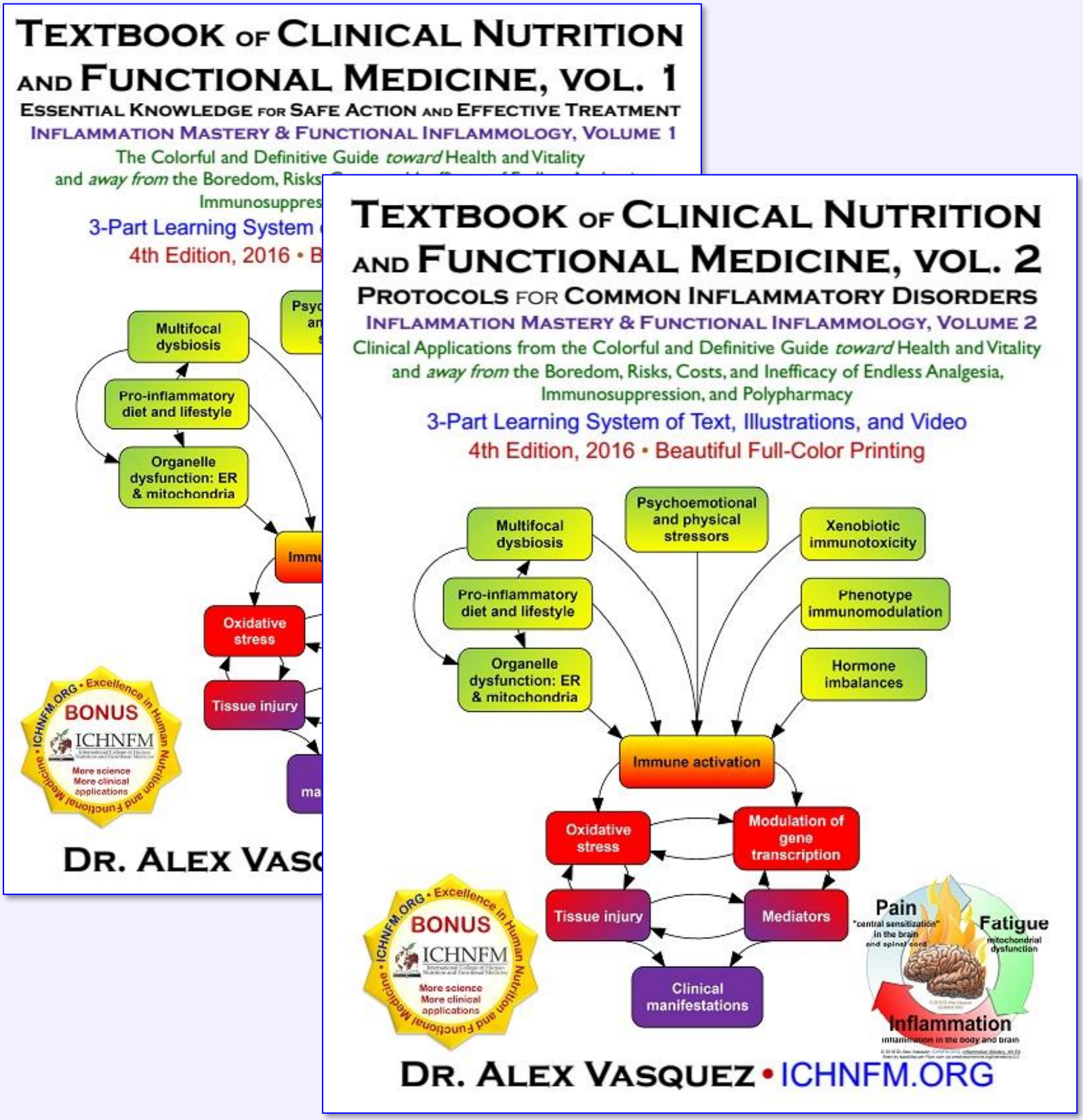

associated with complications such as pancytopenia, organ failure, and death[408], it is not a treatment to be taken lightly nor should inexperienced physicians administer it. Colchicine can be administered orally, but its low therapeutic efficacy in relation to its moderate gastrointestinal toxicity limits its applicability. In a poorly designed study by Schnebel and Simmons[409], orally administered colchicine was no better yet was more toxic than placebo; this study appears to have been designed specifically to show inefficacy and toxicity of colchicine since the patients were either given *no treatment* alternating with a *gastroirritative toxic dose* of colchicine.

Statue of Silvius Brabo, a mythical Roman soldier who is said to have killed a giant and thrown his hand into the river, hence the name of the city Antwerp, which translates to "hand throwing." Photo at Antwerp City Hall, Belgium 2012 by DrV.

[408] "Bone marrow depression has been reported, primarily in cases of acute colchicine intoxication, and intravenous administration of the drug has been associated with severe pancytopenia and death." Levy M, Spino M, Read SE. Colchicine: a state-of-the-art review. *Pharmacotherapy*. 1991;11(3):196-211

[409] Schnebel BE, Simmons JW. The use of oral colchicine for low back pain. A double-blind study. *Spine*. 1988 Mar;13(3):354-7 Use of colchicine in this study varied from abstinence for 3 days followed by a toxic dose on day 4; therefore patients in the treatment group were subjected to no treatment for 75% of the time, followed by a dose that caused gastrointestinal toxicity—vomiting and diarrhea—the other 25% of the time. At neither phase of the study were patients exposed to a treatment that had any possibility of being effective in relation to the potential toxicity. This study was so poorly designed that its publication brings into question the editorial quality of *Spine* during this era.

nutritional supplement and whole foods industries have failed to provide adequate support for the naturopathic profession in proportion to the increase in nutrition supplement sales and the public's increasing appreciation for *and purchase of* whole and organic foods, both of which have been supported by the naturopathic profession. Naturopathic schools are not without some occasional administrative incompetence and political pettiness; notable events during 2013 within two schools caused the unnecessary loss of intellectual power and internationally-respected irreplaceable academic/clinical/intellectual leadership from the profession in ways that clearly violate the profession's social, humanitarian, and intellectual values, despite administrative declarations to the opposite. Overall, the naturopathic profession continues to make positive albeit slow progress. Because the naturopathic profession's philosophy of healthcare stems from and extends back to life itself, naturopathic medicine is, at present and without any legitimate question, the only philosophy and model of primary healthcare (contrasted to allopathic and osteopathic) capable of salvaging, reforming, and optimizing healthcare outcomes in particular and human life in general.

Barefoot physician (Wahkeena Falls, Oregon): "Let us spend one day as deliberately as Nature, and not be thrown off the track by every nutshell and mosquito's wing that falls on the rails [train tracks]. Let us rise early and fast, or let us break the fast gently and without perturbation; let company come and let company go, let the bells ring and the children cry—determined to make a day of it. Why should we knock under and go with the stream? ... Let us settle ourselves, and work and wedge our feet downward through the mud and slush of opinion, and prejudice, and tradition, and delusion, and appearance, that alluvion which covers the globe, through Paris and London, through New York and Boston and Concord, through Church and State, through poetry and philosophy and religion, until we come to a hard bottom and rocks in place, which we can call *reality*." Thoreau HD. *Walden*. 1854

The End

- "It was during the years of my lowest vitality that I ceased to be a pessimist. The instinct of self restoration forbade me a philosophy of poverty and discouragement. As it were, that is how those years appear to me now. I soon discovered life anew…including myself. I turned my will to health, to life, into a philosophy….into the will to power."
- "The time is now past when accidents could befall me; and what ***could*** now fall to my lot which has not already be my own!? It returns only, it comes home to me at last—mine own Self. And such of it as has been long abroad, and scattered among things and accidents. And one thing more do I know: I stand now before my last summit, and before that which has been longest reserved for me."
- "You have within you the power to merge everything you have lived through – attempts, false starts, errors, delusions, passions, your loves and your hopes – into your highest goal, with nothing left over."
- "At every step one has to wrestle for truth; one has to surrender for it almost everything to which the heart, to which our love, our trust in life, cling otherwise. That requires greatness of soul: the service of truth is the hardest service…"
- "With your love go into your isolation and with your creativity, my brother; and only later will justice limp after you.
- "What makes a person heroic?" Answer: "To simultaneously face one's greatest fear and one's highest hope."
- "My principle article of faith is that one can only flourish among people who share the identical ideas and the identical will."
- "Not around the inventors of new noise but around the inventors of new values does the world revolve."

Friedrich Nietzsche (German classical Scholar, Philosopher and Critic of culture, 1844-1900)

Ceiling of Café de La Pedrera in Barcelona: 2014 photo by DrV

Index:

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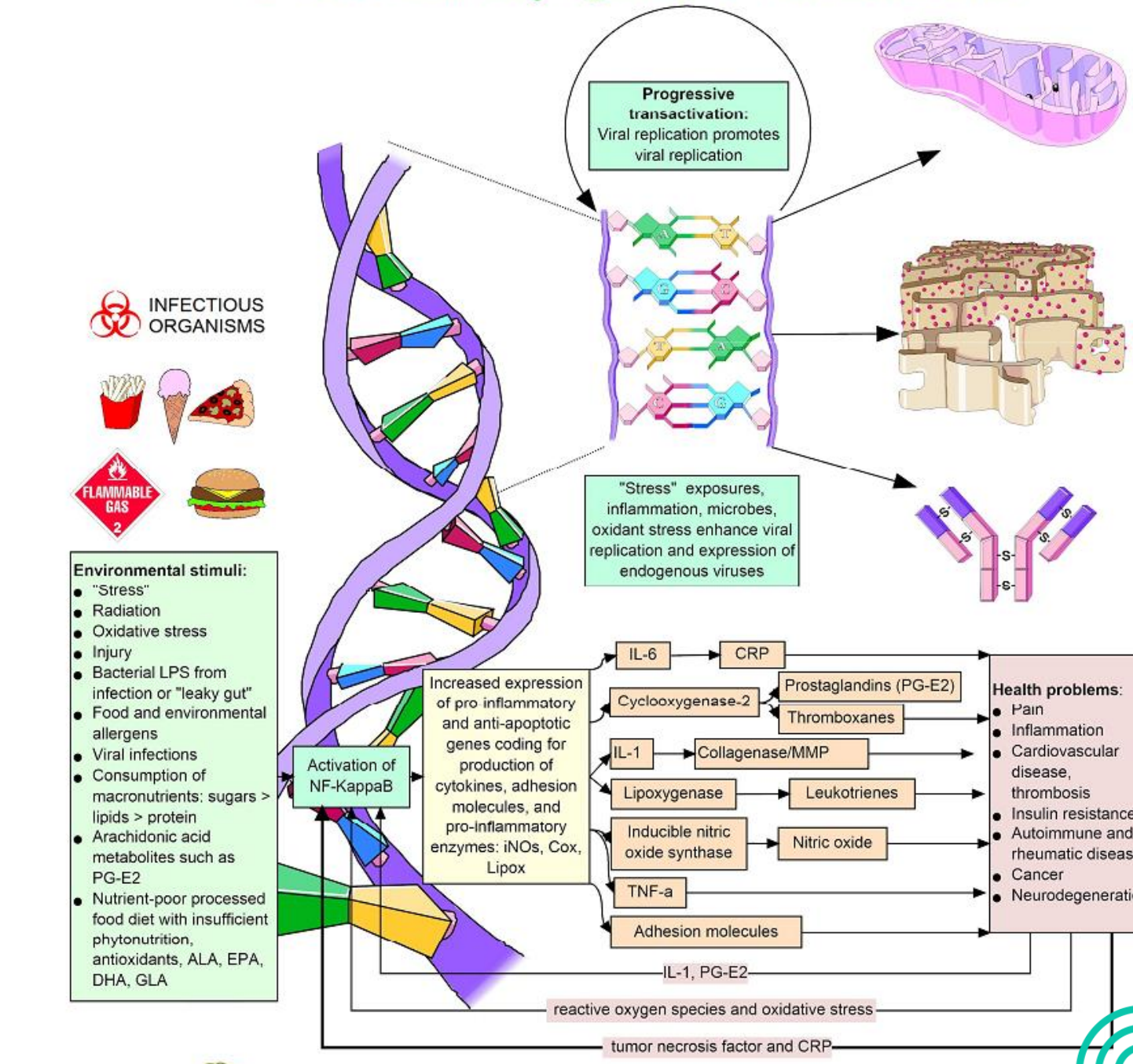

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THE PATH AHEAD

Concerns About The Integrity of The Scientific Research Process—Focus On Recent Negative Publications Regarding Nutrition, Multivitamins, Fish Oil And Cardiovascular Disease

Alex Vasquez, DC, ND, DO; Joseph Pizzorno, ND, Editor in Chief

Abstract

The next step in reestablishing credibility seems to us honesty and recognizing we all share a common goal of the health and wellness of the human community and the planet. Everyone agrees that the current healthcare system, despite its many incredible successes, is also showing its limitations and is no longer sustainable. We believe the solution starts with us the researchers and editors. A good first step might be formally recognizing the errors and showing how we can and *intend* to get better.

Evidence-based medicine—by definition—requires objective, reliable and accurate research and reviews from which to make the best decisions in patient care and public policy. The causes of inaccurate information, ranging from presumably innocent mistakes all the way to apparently intentional fraud, affect all scientific and biomedical disciplines.[1] While these accidental and intentional errors can derail our understanding of diseases and impact tens of thousands of affected patients, such inaccuracies in the field of nutrition c… worldwide.[2] While… a specific disease… human populatio… nutrition researcl… particularly conte… nutrition researcl… healthcare profess… nutrition. Clinical… vast majority of … medical training p… are obviously i… gastroenterology[7]… training in clini… proclaims itself a… including the entire territory of clinical nutrition.[10] A major and serious problem arises when unskilled and invalid research is published by authors (including nonphysician journalists[11]) in major journals which mischaracterizes the validity of nutrition interventions (e.g., essentially always concluding that nutritional interventions are inefficacious or potentially hazardous) and then such research is used politically and in the media to disparage, restrict and regulate practitoners and nutrition supplement industry[12] to the detriment of human health.

Several factors disrupting the integrity of nutrition research are commonly found in studies published by "elite" universities in "top-tier" journals, which are then republished and distributed as "headlining news" in newspapers, magazines, and television via which they …ent policy and …ons of people. … examples of …lications, lists …sed solutions. …pendent upon …stigative and …s of clinical …rovements are … ignorance in …

…tion

…eview recent examples of questionable or inaccurate publications related to nutrition. Perceived shortcomings are documented with both citations here and links to more detailed and authoritative reviews and video presentations. In some instances, speculations regarding the cause and consequences of identified errors are provided.

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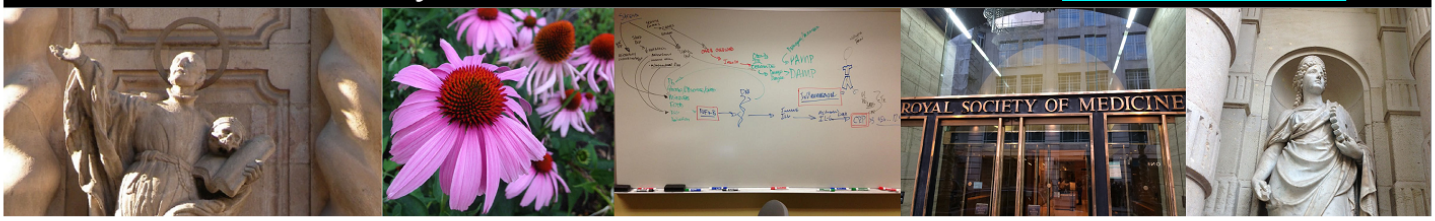

Perspective, Opinion, Editorial • Education • Academia • Wage Theft • Corruption

Ending the Exploitation of Experts Begins with Educating Them about Employment, Curbing Enthusiasm to Preserve Enthusiasm

Alex Vasquez DC ND DO FACN

My own paths toward and perspectives on Education

My passion for teaching and education began "formally" when I was about 9 years of age, sitting on the floor of Ms Hall's 4th grade classroom; from that vantage as I sat somewhat near my best friend Robert, I saw the destructive power of bad teaching and discrimination, and from that day I started analyzing teachers, teaching methods, educational and social structures, and ways to convey knowledge and inspire students. Additionally inspired by my teacher of English and Literature in my final years at Riverside Military Academy, I began college with the plan of eventually teaching "something—most likely English and Literature" because I appreciated and valued teaching, proper grammatical structure, and nuanced use of language; I later developed and interconnected my interests in teaching, writing, language, physiology, medicine, and nutrition to complete three doctorate degrees in the health sciences and publish more than 120 articles, letters, rebuttals, monographs, and books on a wide range of topics, with those publications ranging from dense 1-page Letters and Responses to published research up to single-author textbooks of more than 1,180 pages. I have taught at various colleges and universities at the undergraduate, graduate/Masters, and Doctorate levels and have lectured internationally for post-graduate medical education. I see teaching not simply as effective transferal of information, but also as a means to interconnect and inspire generations of people, notably in a reciprocal manner. At its best, teaching and learning are activities that reflect and support love for life itself.

Oh, the stories I could tell you about the innards of Academia, "nonprofits", and "accredited" schools

I would be happiest to tell you that Academics and Administrators are vanguards
support for fellow Professors, and
commitment is to truth and realit
setting ablaze the passions of the
they teach, lead, and supervise; I'
in flower fields like a professoria
singing a rhythmical rendition of "*The Hills are Alive…with the…Passions of Education and Intellectual Integrity*." But a pollyannic representation of my observations would be a misrepresentation of the realities I have seen and experienced. I have seen university presidents lie to their students, expel experts for the sake of maintaining their own petty powers and preferences, and I have seen entire academic administrations lie (misrepresent) in unison to their boards of trustees and their accreditation commissions. I have seen stand-alone academic programs make millions of dollars in profit, while its administrators refuse to pay a living wage to doctorate-level infrastructure and while allowing themselves 6-week European vacations during major institutional initiatives. I have seen administrators lie to accreditors and allow students to cheat their way through graduate programs (by bypassing faulty examination software in online programs), and I have seen accreditors turn a blind eye to obvious university corruption, made worse when the accreditation commission is infiltrated by university administrators—thus did "accreditation" come to lose its value. I have seen "nonprofit educational institutions" underpay their faculty, plagiarize from their faculty, resell the work of other professionals without notice or compensation, and then pay their upper administrators in excess of US$160,000 for less than part-time work—thus did "nonprofit organization" come to lose its value. I have seen schools blackmail excellent professors and leaders in education with gag orders, legal threats, and financial bribery (range US$25,000 up to $250,000) to buy their silence about institutional corruption. I have corresponded with employment attorneys, State Attorneys General, and US Department of Education, most of whom shrugged their shoulders and said, "That's the way it is in academia." Sorry

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Tutorial & Editorial • Scientific Writing • Journal Editing • Professional Experience • Video

How to Improve Scientific Writing and Journal Editing: A Short Narrative-Video Guide, Part I

Alex Vasquez DO ND DC FACN

Introduction

"Hello everyone, Dr. Alex Vasquez here, and today I'm going to start a different series of videos, and this time the conversation is going to focus around journal editing and writing. I'm calling this "*Editing and Writing Tips #1*", and I'm going to start with a few of my own perspectives and experiences, then I'll talk about a few basics, and a few influential ideas. In later videos, I will talk about some more specific examples, and then perhaps at some point we will have a review and conclusion.

Early Experiences and Influences

Very briefly I'll talk about some of my own experiences, and the reason for my doing this is to share with you and segue into some examples that I think are very important. Basic though they might be, a lot of our success in various fields of life actually comes from respecting and appreciating and utilizing those basic concepts.

Let us start here with some of my initial experiences. I started becoming aware of language and the fact that I had some facility for it, first, when I was about 12 years old. I remember writing a poem in class, and again this is somewhat peripheral to the main topic of today, but I do remember that e
kind of my entryway, I think, i
that our assignment was to wr
remember writing this poem in cl
on and on, and—compared with s
I just realized that writing for me

Then again, when I wa
military school, I remember in ou

being asked questions, and I remember just how the answers to understanding grammar and language just came very easy to me, and I do remember feeling like I had some facility for the structure of language.

Another influential experience I had when I was about 11 years old, totally unrelated to language, is that we took, in the late 1970s or early '80s, a Computer Science class in our elementary school, and I remember that class also specifically having some influence on me, in terms of structuring logic. We basically had to write our own computer programs and this was back when computers were very new. Obviously today everybody has computers; back in the late '70s, computers were a novelty. I consider myself lucky to have taken this Computer Science class; it was obviously extremely basic, but we did have to write some code and what I remember from that is just the sequential manner in which communication has to take place in order to be successful. In this case, we were writing programs for computers and doing basic

> "Writing comes from the entirety of one's experience."
> Dr Alex Vasquez

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JOURNAL OF ORTHOMOLECULAR MEDICINE

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PUBLISHED: MARCH 2019

Editorial

Misrepresentations of Clinical Nutrition in Mainstream Medical Media: Growing Importance of Legitimate Expertise in Independent Peer-Reviewed Publications - Part 1

2018 As a Milestone in the Post-Truth Era

Among the various topics that have either interested or fascinated me throughout my youth and well into my adult years, Nutrition has certainly reigned supreme. My personal routine has been to read as much as reasonably and practically possible on the topic, while not doing so to the exclusion of other topics in biomedicine, psychosociology and philosophy. Thus, with roughly 30 years of experience in reading books and primary research in the field of Nutrition, I could not help but notice the radical departures that occurred in 2018 from the previous norms to which I had grown accustomed.

Of course, 2018 was not the first year during which "bad research" was published in mainstream medical journals and then replicated throughout the echo chamber of mass media; one could observe this periodically occurring throughout the past 50 years, starting not at least with the demonization of dietary cholesterol and the glorification of processed foods, especially refined grains and so-called vegetable oils. But in 2018 what many of us observed was not simply poorly performed research but, in s
es, radical departures from any attempt to pre
descriptions that could be considered "reason
previous standard.[1] Especially related to the
trition, mainstream medical journals and the
which parrots their conclusions have begun
overt misrepresentations of Nutrition with re
gard for science, logic, biomedical history and

One has to be aware of a few key ironies
terize mainstream medical discussions of nutri
that 1) medical physicians receive essentially
in clinical nutrition in their graduate school e
in their post-graduate residency training[2], 2)
sicians and organizations publish "research"
commentaries (both of which commonly conc
tritional interventions are inefficacious or unsafe), despite their lack of formal education on the topic, and then 3) mainstream medical voices consistently call for "regulating the nutrition supplement industry" despite their lack of training on the topic and because of negative conclusions based on their own poorly conducted research and self-serving conclusions. As such, not only are the map-makers blind, but they mislead their blind followers, and then both groups promote themselves as expert cartographers and guides when advising the public on an area that none of them have studied or understood. We should have no surprise whatsoever when the "medical community" publishes poorly conducted and self-serving "research" on the topic of nutrition, to reach their desired conclusion that nutrition is unsafe and inefficacious, and that the profitable market needs to be managed of course by the selfsame "medical community" that is never received a decent 15 minutes on the topic of therapeutic nutrition. Pervasive and persistent ignorance on the topic of nutrition among medical physicians must be understood as intentional and strategic, because otherwise this problem would have been solved 30 years ago when it was first discussed during what was called at the time the "golden age of nutrition."[3] The easiest way to manipulate people and to keep them in a perpetual state of confusion, ineffectiveness, and dependency is to

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when pondering the probable future of intellectual integrity and the products of education.

 ISSN 0317-0209

Mitochondrial Medicine Arrives to Prime Time in Clinical Care: Nutritional Biochemistry and Mitochondrial Hyperpermeability ("Leaky Mitochondria") Meet Disease Pathogenesis and Clinical Interventions

Alex Vasquez, DC, ND, DO, FACN

Alex Vasquez, DC, ND, DO, FACN, is director of programs at the International College of Human Nutrition and Functional Medicine in Barcelona, Spain and online at ICHNFM.org. (*Altern Ther Health Med.* 2014;20(suppl 1):26-30.)

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E-mail address: avasquez@ichnfm.org

MITOCHONDRIAL MEDICINE ARRIVES TO GENERAL PRACTICE AND ROUTINE PATIENT CARE

Mitochondrial disorders were once relegated to "orphan" status as topics for small paragraphs in pathology textbooks and the hospital-based practices of subspecialists. With the increasing appreciation of the high frequency and ease of treatment of mitochondrial dysfunction, this common cause and consequence of many conditions seen in both primary and specialty care deserves the attention of all practicing clinicians.

We all know that mitochondria are the intracellular organelles responsible for the production of the currency of cellular energy in the form of the molecule adenosine triphosphate (ATP); by this time, contemporary clinicians should be developing an awareness of the other roles that mitochondria play in (patho)physiology and clinical practice. Beyond being simple organelles that make ATP, mitochondria play clini… ce—contains inflammati… kinase and disease such… omparatively disorders su… n) and—like stated durin… h active and Nutrition a… that need to September … to appreciate mitochond… the highest mitochondrial dysfunction to clinical diseases must be considered on a routine basis in clinical practice. *Mitochondrial medicine* is no longer an orphan topic, nor is it a superfluous consideration relegated to boutique practices. Mitochondrial medicine is ready for prime time—now—both in the general practice of primary care as well as in specialty and subspecialty medicine. What I describe here as the "new" mitochondrial medicine is the application of assessments and treatments to routine clinical practice primarily for the treatment of secondary/acquired forms of mitochondrial impairment that contribute to common conditions such as fatigue, depression, fibromyalgia, diabetes mellitus, hypertension, neuropsychiatric and neurodegenerative conditions, and other inflammatory and dysmetabolic conditions such as allergy and autoimmunity.

BEYOND BIOCHEMISTRY

Structure and function are of course intimately related and must be appreciated before clinical implications can be understood and interventions thereafter applied with practical precision. The 4 main structures and spaces of the mitochondria are (1) intramitochondrial matrix—the innermost/interior aspect of the mitochondria containing various proteins, enzymes of the Krebs cycle, and mitochondrial DNA; (2) inner membrane—the largely impermeable lipid-rich convoluted/invaginated membrane that envelopes and defines the matrix and which is the structural home of many enzymes, transport systems, and important structures such as cardiolipin and the electron

importance; just as we have come to appreciate the

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Editorial

Orthomolecular Medicine, Catalytic Creativity, and the Psychosocial Ecosystem

Transitioning From One Year to the Next

Various cultures since time immemorial have marked and celebrated the winter solstice with celebrations, meals with friends and family, and time away from work; transitioning from one calendar year to the next has given people pause and a moment to reflect on the events that happened in the past year and what might be anticipated in the next. Reflection with anticipation along with the realization that the future is somewhat malleable inclines people to imagine how the future might be shaped by the exertion of some modicum of creativity and effort. Any realistic conception of how we might improve the near future must segue from our recent past; we must have an awareness of what is going on around us as we look toward the future to visualize ourselves living within it and also acting upon it. What is going on in the world and how might I act upon that trend and flow in order to improve both its transition and its destination? What should each of us do on a personal level to (in the words of Mahatma Gandhi) be, embody, and materialize the change(s) that we want to see in the world?

Salutation and Introduction From the Journal's New Editor

Over the past few years I have reflected on several occasions how much I enjoy editing, and so I was correspondingly surprised and pleased when I was offered the opportunity to be the next Editor for the *Journal of Orthomolecular Medicine.* I began studying nutrition and orthomolecular concepts in my teen years and more diligently as I entered graduate school in the early 199 trition" book that I reac *Your Nerves* (1975) by this was followed imm tures of Jonathan V Wr of whom would later b University. By the mid- Jeffrey Bland PhD had tional medicine, which and personal[3] reasons. By this time my own personal library contained several hundred books, mostly dedicated to nutrition and health with another large section on philosophy and psychology. In 1994, I joined the Review Staff of the *Journal of Naturopathic Medicine,* and I started publishing nutrition articles, perhaps most of which might be seen as practice in preparation of an important letter published in 1996 by the American College of Rheumatology in their journal *Arthritis and Rheumatism.* Since those early years and during the course of three doctorate degrees and teaching thousands of students/attendees internationally, I have reviewed for[4] and published in[5] a wide range of refereed journals in addition to publishing commissioned books, chapters, and independent publications and videos. Being an author and reviewer for many different publications—along with my experiences teaching internationally, treating patients in various settings, designing and directing academic programs, and producing educational videos—has given me a wide range of experiences and insights that I hope to bring to the benefit of the *Journal of Orthomolecular Medicine.*

We Must Work Together if We Are Going to Succeed

I have to start this conversation with a few hopes, assumptions, and beliefs, namely that you (the reader) and I (the author and new Editor) have a few things in common. On a professional level, by virtue of the fact that you are reading this essay, I will assume that you are interested or actively engaged in healthcare, medicine, nutrition, research and/or public health. I might also imagine that some smaller percentage of our new and established readers are perhaps less inclined toward the mechanisms and more drawn to the *Journal of Orthomolecular Medicine* for its potential humanistic insights and social contributions; we can reasonably competent healthcare ate nutrition) are basic mit a counterargument of my assertions, they more to the point, my rdless of personal po- share some common the following:

- We each want to receive and deliver the best healthcare possible: If we have a problem, then we each want the best possible solution. Efficiency of time or money is not the top priority when we are seeking solutions

CME
CONTINUING MEDICAL EDUCATION

THE CLINICAL IMPORTANCE OF VITAMIN D (CHOLECALCIFEROL): A PARADIGM SHIFT WITH IMPLICATIONS FOR ALL HEALTHCARE PROVIDERS

Alex Vasquez, DC, ND, Gilbert Manso, MD, John Cannell, MD

Alex Vasquez, DC, ND is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractic doctor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. He is a former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University. **Gilbert Manso, MD**, is a medical doctor practicing integrative medicine in Houston, Texas. In practice for more than 35 years, he is Board Certified in Family Practice and is Associate Professor of Family Medicine at University of Texas Medical School in Houston. **John Cannell, MD**, is a medical physician practicing in Atascadero, California, and is president of the Vitamin D Council (Cholecalciferol-Council.com), a non-profit, tax-exempt organization working to promote awareness of the manifold adverse effects of vitamin D deficiency.

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Appreciate and identify the manifold clinical presentations and consequences of vitamin D deficiency
2. Identify patient groups that are predisposed to vitamin D hypersensitivity
3. Know how to imple
proper doses and wi

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While we are all familiar with the important role of vitamin D in calcium absorption and bone metabolism, many doctors and patients are not aware of the recent research on vitamin D and the widening range of therapeutic applications available for cholecalciferol, which can be classified as both a vitamin and a pro-hormone. Additionally, we also now realize that the Food and Nutrition Board's previously defined Upper Limit (UL) for safe intake at 2,000 IU/day was set far too low and that the physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.[1,2] With the discovery of vitamin D receptors in tissues other than the gut and bone—especially the brain, breast, prostate, and lymphocytes—and the recent research suggesting

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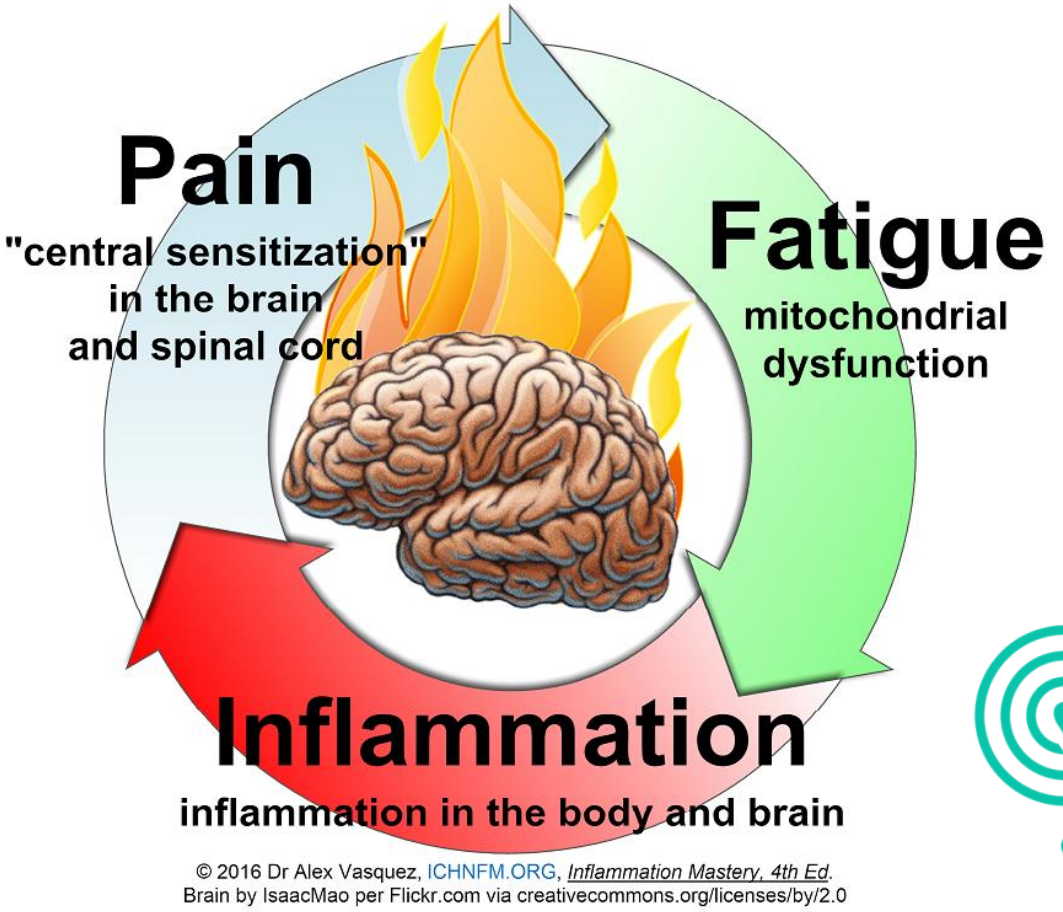

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Reducing Pain and Inflammation Naturally Part I: New Insights into Fatty Acid Biochemistry and the Influence of Diet

Alex Vasquez, DC, ND

PAIN AND INFLAMMATION ARE NEUROCHEMICAL MANIFESTATIONS of physiologic imbalances which originate biochemically, structurally, and/or neurologically. Beyond the obvious relevance to the treatment of conditions associated with pain and inflammation, the implications of the data presented will provide therapeutic insight for doctors treating a wide range of complex chronic illnesses. Given the strength and momentum of this research, combined with the public's increasing interest in alternatives to dangerous, expensive, and often ineffective pharmaceutical treatments, the time has come for the chiropractic profession to assume a more empowered leadership position in the provision of healthcare and the prevention and treatment of most chronic health problems.

INTRODUCTION:

Since its inception, the chiropractic profession has recognized and affirmed the importance and benefits of whole-patient healthcare.[1,2] In contrast to the medical model of disease, which generally seeks to use synthetic drugs to target isolated biochemical pathways, the holistic model of health and disease appreciates that a multifaceted approach including physical (structural, biomechanical, anatomical), biochemical (nutritional, hormonal, neurochemical), and psychoemotional assessments and interventions is commonly safer, more effective, and less expensive in the long-term for the restoration and preservation of optimal health.[3] Extensive documentation in support of these concepts and their clinical applications has recently been compiled by the current author in a 486-page manuscript.[4]

While the benefits, safety, and cost-effectiveness of physical medicine and spinal manipulation have been well established in journal articles and commissioned reports,[5,6] it is only within the past few years that we have seen a literal explosion of high-quality research supporting the concept that skillful phytonutritional interventions can have a powerful and beneficial influence on patient outcomes for a wide range of health concerns. Thus, as the only nationally-licensed healthcare providers with training in nutrition, chiropractic physicians should claim their proper position of leadership in the management of chronic health disorders.

The research increasingly points to inflammation as a common determinant of many diseases, including cancer, cardiovascular disease, neurologic conditions, diabetes, arthritis, and the so-called autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis. Additionally, new research is also documenting the powerful influence of nutrition on optimal cell membrane dynamics, neurotransmitter/hormone receptor function, and modification of gene expression. The most powerful, cost-effective, and fundamental means for effectively addressing all of these processes—1) inflammation, 2) cell membrane dynamics, 3) neurotransmitter/hormone receptor function, and 4) gene expression—is with skillful nutritional intervention: dietary improvement and phytonutritional supplementation. In particular, modulation of fatty acid metabolism by supplementation with nutritional oils is the most efficient means to achieve all four of the above-mentioned goals.

FOOD AND INFLAMMATION:

The adage "One man's food is another man's poison" finds particular relevance when we are dealing with patients experiencing pain and inflammation. Although dietary recommendations must always be customized for each individual patient, we can confidently make certain general recommendations to help these patients overcome their health problems and to feel and function better. Conceptually, we can organize our ideas about foods into the following categories: 1) foods to avoid, 2) foods to consume, 3) customized recommendations with regard to allergies, sensitivities, and intolerances.

Foods to Avoid: Many doctors and patients are unaware of the pro-inflammatory nature of many commonly eaten foods.[7] As long as patients continue to consume pro-inflammatory chemicals in their foods on a daily basis, then they will continue to fight an uphill battle against pain and inflammation. Generally speaking, eating is itself a pro-inflammatory event, with sugars and fats inducing more inflammation than protein-containing foods.[8] Therefore, simple sugars and high-fat foods should be avoided. Two fatty acids in particular, linoleic acid (LA) and arachidonic acid (ARA) from the n-6 family should be reduced or eliminated from the diet to the extent possible. LA increases inflammation by several mechanisms, one of which is activation of NF-kappaB.[9] (Phytonutritional modulation of NF-kappaB[10] will be reviewed in upcoming articles in this series.) Therefore, rich sources of LA should be avoided as much as possible. LA is abundant in most nut, seed, and

vegetable oils such as canola oil (21%), safflower oil (76%), sunflower oil (71%), corn oil (57%), soybean oil (54%), and cottonseed oil (54%). Similarly, ARA is the direct precursor to the isoprostanes—chemicals that are formed from the non-enzymatic oxidation of ARA and which exacerbate pain and inflammation. ARA is the precursor for and increases the production of inflammatory and noxious chemicals, particularly the prostaglandins and leukotrienes. Additionally, laboratory research has found that ARA also promotes activation of NF-kappaB and can cause a 400% increase in superoxide production in Kupffer cells.[9] The most obvious method for *reducing production of chemicals derived from ARA* is to *reduce dietary intake of ARA;* this means avoiding the richest sources of ARA such as whole milk, beef, liver, pork, lamb, and to a lesser extent turkey and chicken. Additionally, many of these problematic foods, especially beef, liver, pork, and lamb, are also major sources of dietary iron, which promotes joint inflammation independently from its contribution to iron overload and hemochromatoic arthropathy. Indeed, as I have discussed in this journal[11] and elsewhere[12], all patients with polyarthropathy should be tested for iron overload. In summary, patients with inflammatory conditions should avoid foods that are high in fat, simple carbohydrates, linoleic acid, arachidonic acid, and iron. Artificial and processed foods should also be avoided since they are commonly rich in *trans*-fatty acids and are depleted of antioxidants.

Foods to Consume: Fruits and vegetables are rich sources of health-promoting nutrients such as vitamins, minerals, fiber, fatty acids such as squalene, and—perhaps most important—a wide range of phytochemicals including limonoids, carotenoids, terpinoids, isothiocyanates, flavonoids, proanthocyanidins and other polyphenols. Dietary antioxidants have important anti-inflammatory benefits that extend beyond their abilities to quench free radicals. Additionally, components of whole foods, such as the sterols and sterolins found in vegetables, have significant immune-modulating effects and have shown benefit in alleviating the inflammation of rheumatoid arthritis. Fruits and vegetables contain over 5,000 different phytochemicals that act additively and synergistically to maximize antioxidant protection and to protect health.[13] Vegetarian, vegan, and plant-based whole-foods diets are naturally low in fat, linoleic acid, arachidonic acid, iron, and trans-fatty acids. Extra virgin olive oil contains oleic acid, squalene, and phenolic compounds which work synergistically to reduce inflammation, pain, and cardiovascular disease. Whey, soy, and cold-water fatty fish provide health benefits in addition to the provision of high-quality protein. Green tea shows anti-inflammatory, antioxidant, and anti-cancer actions. Diets with a strong foundation of whole fruits and vegetables help patients increase their intake of antioxidant and anti-inflammatory vitamins, minerals, fiber, and phytonutrients while helping to reduce intake of pro-inflammatory iron and fatty acids. Lastly, a significant portion of the health benefits and anti-inflammatory effects of increased consumption of fruits and vegetables is due to favorable alterations in gastrointestinal microflora[14] rather than the direct nutritive values of foods.

Customized Recommendations and Food Allergies: We are all aware that, in certain patients, specific foods and combinations of foods may exacerbate joint pain and inflammation.[15,16] Therefore the diet must be customized for each patient with regard to food allergies, food sensitivities, and food intolerances. Not only must problematic foods be avoided, but patients' gastrointestinal and immune status must be evaluated and improved.[4] Although many doctors are aware of the elimination-and-challenge technique, most doctors do not direct sufficient attention to improving gastrointestinal status and immune function so that the immune system is no longer hyper-responsive to benign food constituents.[4]

AN INTRODUCTION TO FATTY ACID METABOLISM

We can think of the major biologically active fatty acids as originating from three major categories or "families" based on their molecular configuration and thus their physiologic properties. We can then ascribe general properties to these families and the individual members within each group. The most clinically important fatty acids are "unsaturated", meaning they have one or more carbon-to-carbon double bonds rather than carbon-to-carbon single bonds, the latter being "saturated" with the full number of hydrogen molecules. Double bonds strongly influence the biochemical and clinical effects of fatty acids, making these fatty acids more reactive and biologically active than their saturated counterparts, as well as more prone to oxidation, rancidification, and hydrogenation.

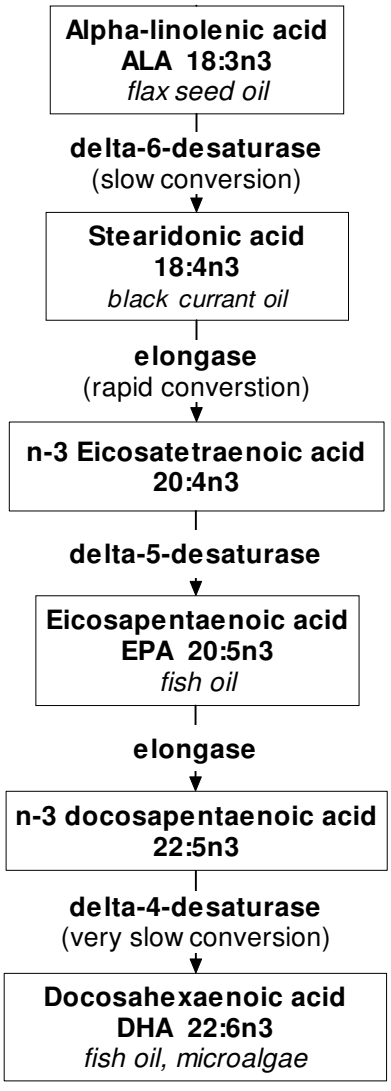
Within each family, fatty acids progress from predecessors to progeny by a series of enzymatic steps catalyzed by desaturase and elongase enzymes. The desaturase enzymes are very slow in their conversions compared to the elongase enzymes, and the clinical relevance of this difference will become apparent as this article and series of articles progresses. We also note that fatty acids never change from one family to another: e.g., an omega-3 fatty acid will always remain in the omega-3 family and will never become a member of the omega-6 or omega-9 family. This is because the defining characteristic on a molecular level is never altered: omega-3 fatty acids have their first carbon-to-carbon double bond starting at the third carbon from the methyl group; omega-6 fatty acids have their first carbon-to-carbon double bond starting at the sixth carbon from the

methyl group; omega-9 fatty acids have their first carbon-to-carbon double bond starting at the ninth carbon from the methyl group. For the sake of efficiency and accordance with nomenclature conventions, we will hereafter abbreviate "omega" as "n" for the n-3, n-6, and n-9 fatty acids, respectively.

N-3 fatty acids: The n-3 family of fatty acids begins with alpha-linolenic acid, commonly referred to as one of the two "essential fatty acids" because it cannot be produced within the human body and must therefore be provided by the diet. Manifestations of n-3 fatty acid deficiencies are generally subtle when contrasted to those of the n-6 family and include behavioral and visual impairment, endocrinologic alterations, and a tendency toward the development and progression of several chronic degenerative diseases.[17]

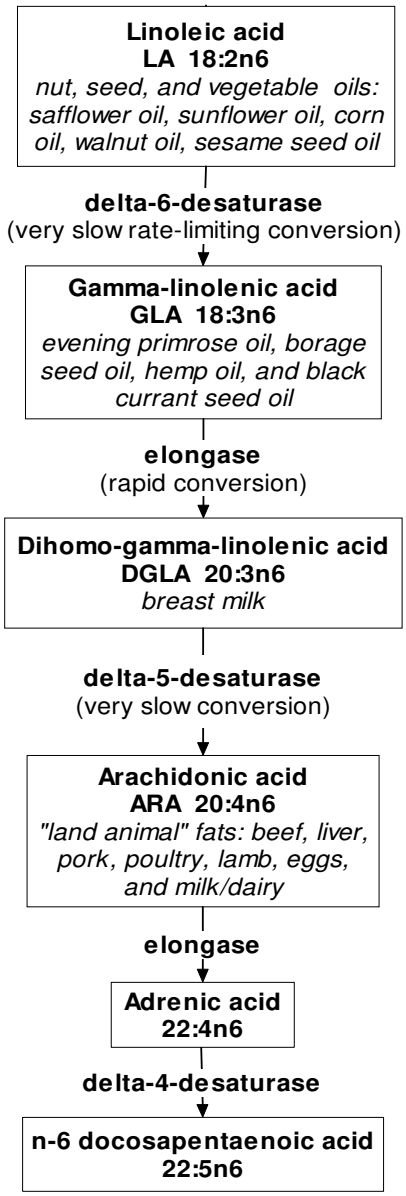
Abundant in flax oil (~57%), alpha-linolenic acid (ALA) is converted to stearidonic acid by delta-6-desaturase. Stearidonic acid (SDA) is elongated to n-3 eicosatetraenoic acid, which is then converted to eicosapentaenoic acid (EPA) by delta-5-desaturase. EPA is elongated to n-3 docosapentaenoic acid (n-3 DPA), which is then converted to docosahexaenoic acid (DHA) by delta-4-desaturase. These substrates and conversions are illustrated in Figure 1 (modified with permission from Integrative Orthopedics[4]).

Figure 1. Metabolism of n-3 fatty acids



N-6 fatty acids: The n-6 family of fatty acids begins with linoleic acid (LA), also referred to as an "essential fatty acid" because it cannot be synthesized *de novo* within the human body. LA is abundant in most nut, seed, and vegetable oils such as canola oil (21%), safflower oil (76%), sunflower oil (71%), corn oil (57%), soybean oil (54%), and cottonseed oil (54%).[18] LA is converted by delta-6-desaturase to gamma-linolenic acid (GLA), which is quickly elongated to dihomo-gamma-linolenic acid (DGLA). DGLA is slowly converted by delta-5-desaturase to arachidonic acid (ARA), which is elongated to adrenic acid, which is finally converted to n-6 docosapentaenoic acid by delta-4-desaturase. These substrates and conversions are illustrated in Figure 2 (modified with permission

Figure 2. Metabolism of n-6 fatty acids



from Integrative Orthopedics[4]).

Note that the term "eicosatetraenoic acid" can apply to both 20:4n6 (arachidonic acid) of the omega-6 fatty acid family[19] and to 20:4n3 of the omega-3 fatty acid family.[20] Therefore, to avoid the confusion that would result from the use of the term "eicosatetraenoic acid" by itself, "n-6 eicosatetraenoic acid" should be used when referring to 20:4n6 (arachidonic acid) and "n-3 eicosatetraenoic acid" should be used when referring to 20:4n3. Similarly, 22:5n3 of the omega-3 fatty acid family[21,22] and 22:5n6 of the omega-6 fatty acid family[23,24,25] are both referred to as "docosapentaenoic acid." Therefore using the term "docosapentaenoic acid" will be ambiguous unless the appropriate n-3 or n-6 designation is stated. "N-3 docosapentaenoic acid" should be used to refer to 22:5n3 and "n-6 docosapentaenoic acid" should be used for 22:5n6.

N-9 fatty acids: The primary n-9 fatty acid in the human diet is oleic acid, the predominant monounsaturated fatty acid in olive oil. While oleic acid is certainly biologically active and therefore clinically important, due to the complexity of olive oil as the primary source of oleic acid, we are not yet able to clearly determine from epidemiological studies how much of the benefit of olive oil consumption is due to the oleic acid compared to the benefits derived from the powerful antioxidant and anti-inflammatory actions of the phenolics, the relatively high content of squalene, or other confounding variables in diet and lifestyle.[26,27]

ENZYMATIC CONVERSION: CHEMICAL FLOWCHARTS VERSUS THE REALITY OF CLINICAL EFFECTIVENESS

If conversion of one fatty acid to the next proceeded as efficiently as depicted in biochemical flow charts, then n-3 ALA and n-6 LA could be supplemented to provide all of the downstream fatty acids and their metabolites, presumably in the proper ratios. However, clearly this is not the case due to intrinsic as well as genotypic (inherited) and phenotypic (manifested) defects in enzyme effectiveness. Clinicians need to understand the individual characteristics of these enzymes in order to successfully employ therapies which modulate fatty acid metabolism. Since the conversions catalyzed by elongase are quite efficient and are almost never discussed as cause for concern in the medical and nutritional literature, we will focus on the desaturase enzymes, which are noted to have significant variances in phenotypic expression and which can be adversely affected by common vitamin and mineral deficiencies.

Delta-6-desaturase: The first step in the n-3 and n-6 pathways is the action of delta-6-desaturase (D6D) in converting ALA to SDA and LA to GLA, respectively. Enzymatic conversions by D6D are rate-limiting due to 1) its strong need for several vitamin and mineral co-factors, 2) its genotypic impairment, such as in patients with eczema,[28] 3) its phenotypic impairment in patients with diabetes,[29] and its impairment by trans-fatty acids,[30] stress neurotransmitters,[31] and other environmental and nutritional influences.[4] The slow conversions by D6D explain why, as Horrobin noted, "…it is impossible to produce any significant elevation of DGLA levels in humans by increasing linoleic acid intake."[32] Similarly, conversion of ALA to the downstream and clinically desirable fatty acids EPA and DHA is unreliable, with most studies showing only a modest increase in EPA and no increase in DHA following supplementation with ALA. Cofactors required for efficient action of D6D include iron, zinc, magnesium, pyridoxine, riboflavin, and niacin; when these vitamins and minerals are deficient, D6D function will be impaired and defects in fatty acid metabolism will result.[33]

Delta-5-desaturase: Delta-5-desaturase (D5D) slowly converts n-3 eicosatetraenoic acid to EPA, and in the n-6 pathway, DGLA to ARA. Supplementation with GLA has been shown to result in a slight to modest increase in ARA that may or may not be clinically significant. Impairment of D5D is seen in patients with the blinding eye disease retinitis pigmentosa, resulting in marked reduction in retinal DHA levels.[34]

Delta-4-desaturase: Delta-4-desaturase (D4D), like the other desaturase enzymes, is also very slow-acting. While impaired conversion of adrenic acid to n-6 docosapentaenoic acid appears to be of little or no consequence, reduced bioavailability of DHA due to its slow conversion from n-3 docosapentaenoic acid has tremendous implications in the etiology of schizophrenia, a disease associated with impaired D4D activity.[35]

By understanding the biochemical efficiency of these enzymes, doctors are better able to understand how to implement clinical strategies for modulating fatty acid balance in their patients. In the n-3 family, supplementation with ALA increases (in order of decreasing efficiency) ALA, SDA, and EPA but does not consistently elevate DHA. Therefore, although consumption of flax oil has many important benefits and may be used to modestly increase EPA levels, it cannot be relied upon to increase DHA levels.[36] Supplementation with SDA increases EPA levels, but DHA is not significantly increased due to the slow conversion by D4D.[37] Supplementation with EPA proportionately increases EPA but does not consistently increase DHA.[38] DHA supplementation is the most effective and reliable means for increasing DHA levels.[39]

In the n-6 family, supplementation with LA does not lead to clinically significant increases in GLA or DGLA.[32] Supplementation with GLA greatly increases DGLA and

leads to a modest increase in ARA.[40] Diets high in ARA lead to increased tissue levels of ARA. Consumption of EPA lowers levels of GLA/DGLA[29] and oleic acid[41]; likewise, consumption of GLA lowers levels of EPA.[40] **Overall, the implications are that when a particular fatty acid is desired for its physiologic effect and clinical benefits, it should be supplied directly from the diet or supplements.**

CONCLUSION:

In this brief article, we have introduced and reviewed the foundational terminology and concepts which will facilitate the introduction of more advanced concepts as presented in the upcoming articles in this series. Dietary improvement and custom-tailored prescription of individual fatty acids is consistently providing patients and doctors with greater health and superior clinical results. Alleviation, prevention, and effective treatment of many diseases previously considered to be "untreatable" is now possible with fatty acid supplementation, diet modification, and the use of other vitamins, minerals, and botanical medicines. The skillful use of these interventions by the chiropractic profession, whether as adjunctive treatment to spinal manipulation or as primary therapy, is in accord with our holistic philosophy and promises to advance the prominence of our profession in the healthcare arena. Since the pharmaceutical-surgical paradigm delivers many unnecessary risks and unsatisfactory outcomes in the management of chronic disease[42-49], now is the time for chiropractic physicians to step forward and deliver the safest, most effective and cost-effective therapies ever before seen in American healthcare for the management of chronic health problems.

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Mini-Review • Continuing Education • Microbiome • Dysbiosis • Infectious Disease

Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts

Alex Vasquez DC ND DO FACN

Experience and Perspectives

Many years ago when I published my first books[1,2] and articles[3] detailing "dysbiosis", the word could hardly be found in the Medline index, the topic was controversial at best and ethereal at worst, the term "microbiome" (first published in French in 1949 and in English in 1988) was virtually unknown, and I spent most of the time and space in my lectures and articles substantiating and defending the condition's existence. These days, everyone is talking about microbiome, dysbiosis, "leaky gut" (thanks largely to Leo Galland MD), and my 1996 article on "Silent Infections and Gastrointestinal Dysbiosis" has been downloaded at least 4,000 times and is one of the top 1% most popular articles on Academia.edu.[4] In the preparation of my dysbiosis lecture at a major functional medicine conference in 2010, I found that only 180 Medline articles indexed the term "dysbiosis", and now—slightly less than five years later—more than 1,200 articles index that term. Obviously, the dysbiosis concept has

"Dysbiosis" is an important concept, but doctors cannot treat concepts.

We have to define, describe, and deconstruct the microbes, molecules, and mechanisms into their components, then rebuild a conceptual scaffold and intellectual structure that becomes a useful tool that, with study and experience, can be used in a clinical setting to effective benefit.

practical application is a bit indelicate and cumbersome beyond the most commonly repeated advice of advocating probiotics, avoiding antibiotics, perhaps delving into using botanical antimicrobials and laboratory testing. Breath testing (an insensitive test for only one subtype of gastrointestinal dysbiosis) and microbiologic testing have become popular to the point of overuse as doctors grapple for clinical clues. (Noteworthy in the conversation on functional laboratory testing is that one functional medicine laboratory in particular used inaccurate proprietary microbe-identification methods to extract

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PDF articles: Full-text archives of the author's articles are available:

- https://ichnfm.academia.edu/AlexVasquez
- https://www.inflammationmastery.com/reprints
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COMMENTARY

Biological plausibility of the gut–brain axis in autism

Alex Vasquez

**Organic abnormalities with neuroinfl
purine metabolism, neurotransmitte
noted in autism, and many of these ab
metabolites, and heightened serum le**

Keywords: gut–brain axis; autism; m

In their recent review, Sherwin
among many other issues, the re
gut microbiome–brain axis with
section subtitled "Microbiota-bas
the treatment of autism: hype or
et al.[1] largely discuss preclinical
the 2017 open-label study by K
used a sequence of oral vancomy
polyethylene glycol laxative, a
human fecal microbiota transpl
clinical benefit in subjects with au

Readers will likely benefit from
tional relevant clinical studies, in
lication by Sandler *et al.*[3] showin
of autistic manifestations followin
oral vancomycin, as well as cas
ing positive impact of various an
apies (metronidazole, ketoconaz
cillin) in patients with autism.[4,5]
have been shown to have gut dys
as well as *Clostridia* species,[6] th
group of bacteria noted for their pr
rotoxic substances. International
consistently demonstrated that
have heighted production of 3-(3-
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trointestinal tract.[7,8] HPHPA rep
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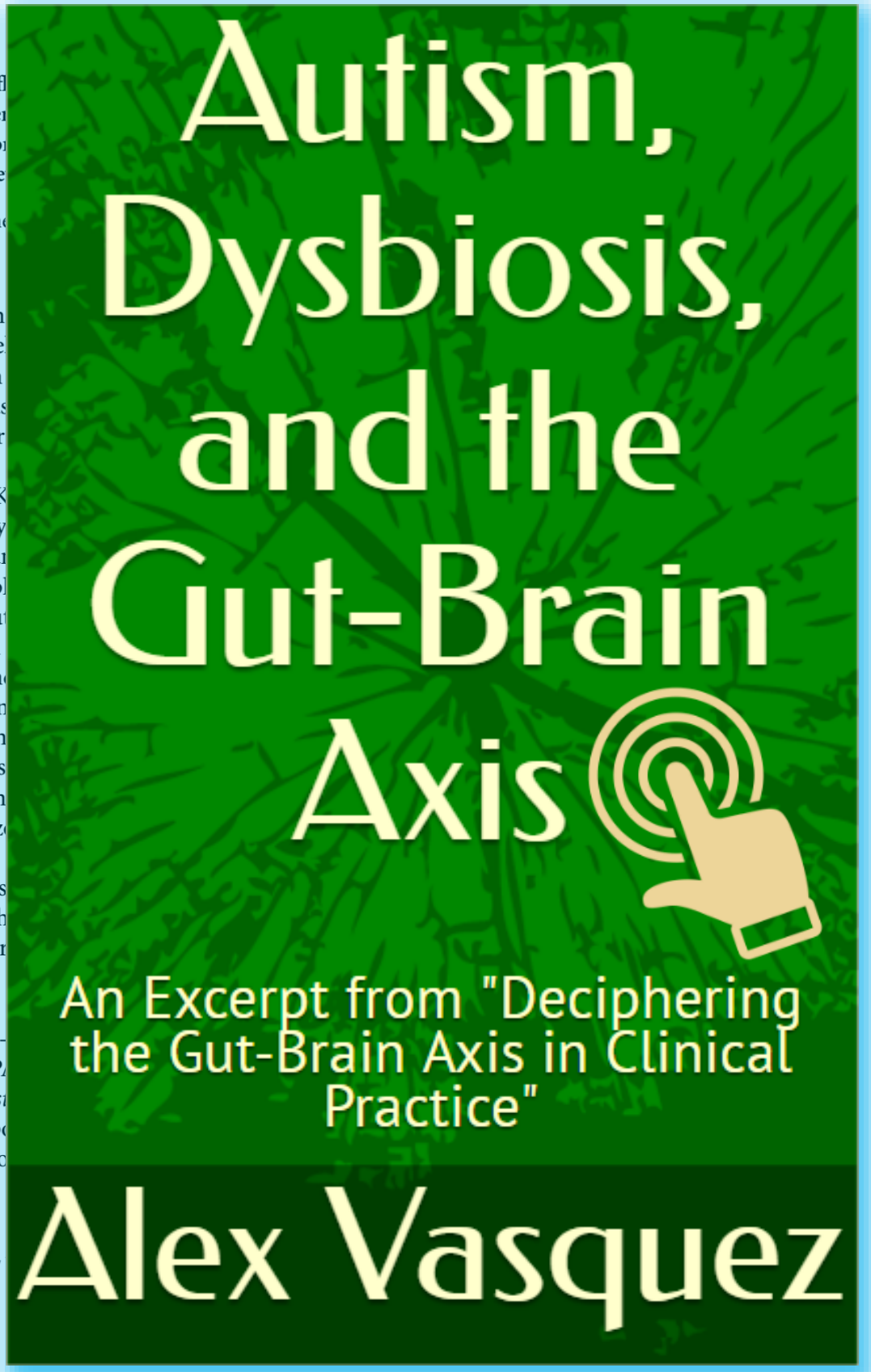

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