

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 errors³, 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 Physicians⁶ 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 children⁷ 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 efficacy¹⁸ 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 series²⁴ and in greater detail elsewhere²⁵ 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.

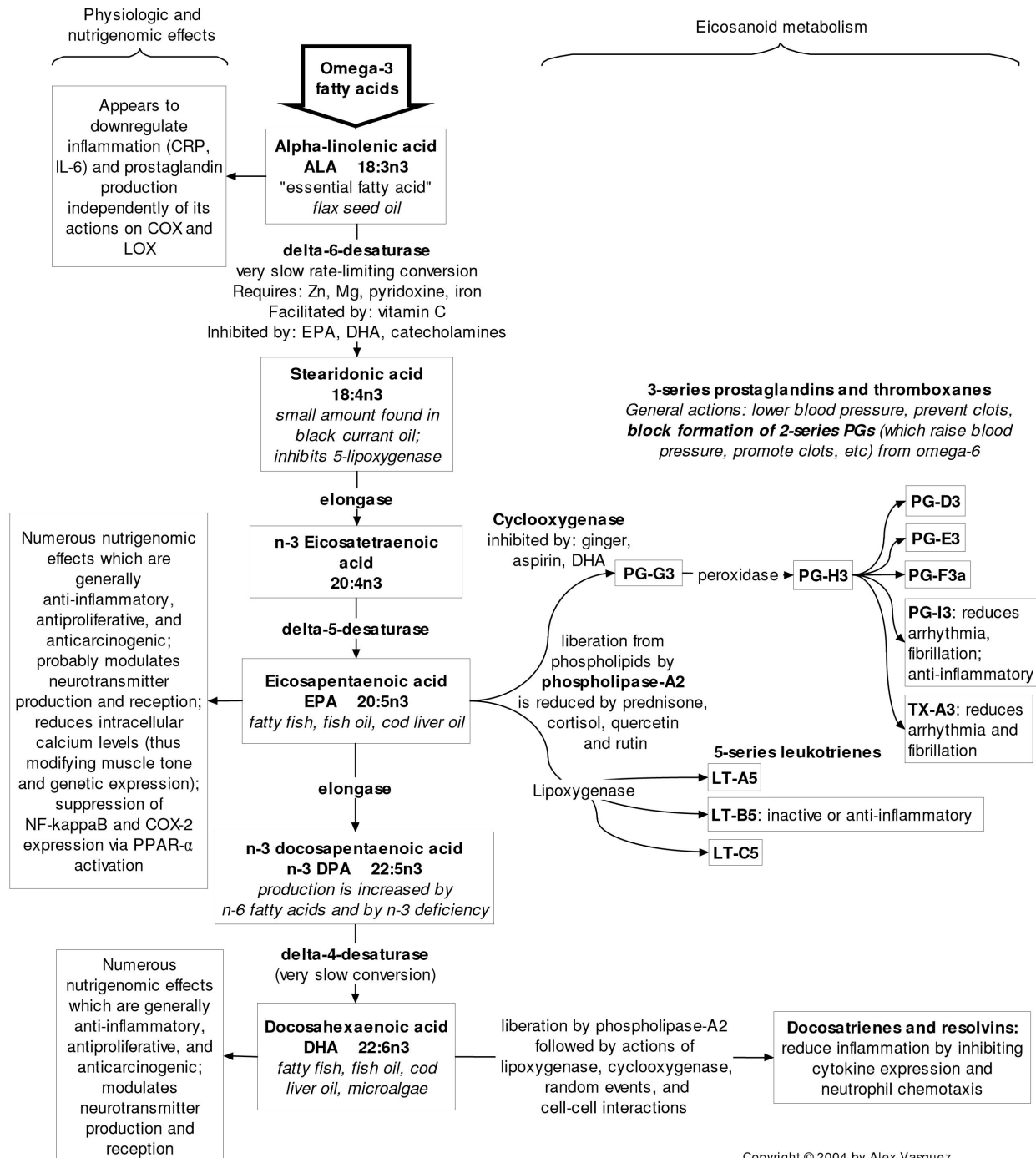
FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

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

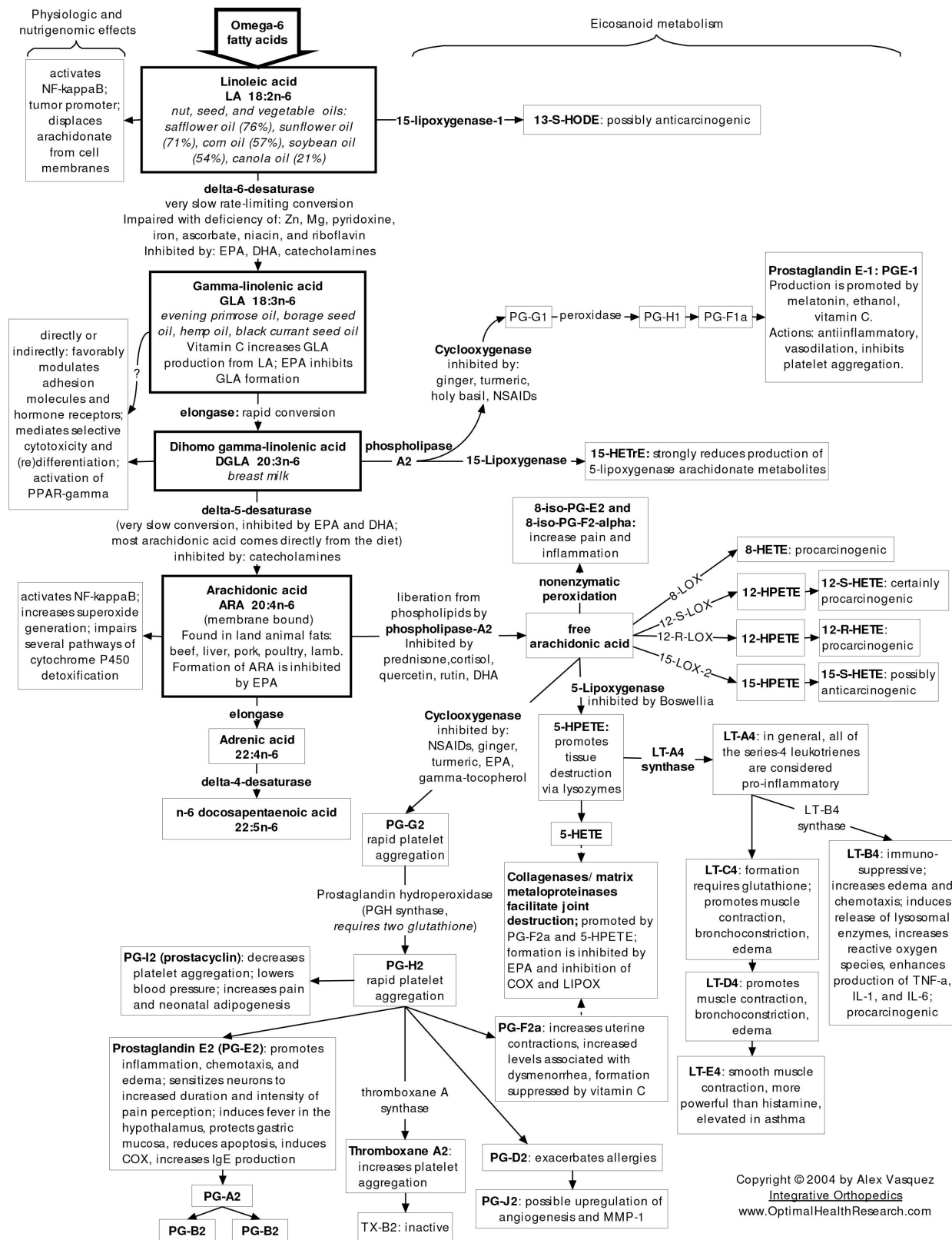
clinical applications. We will focus on the fatty acids with the greatest promise for clinical benefit: alpha-linolenic acid, gamma-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and oleic acid. Biochemical pathways and clinical implications of fatty acid metabolism are detailed in Figures 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



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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 ALA²⁷; 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 mortality²⁶, 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 products³⁰) 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 humans³² which is superior to the 42% reduction induced by rofecoxib (the drug “Vioxx”).³³ In summary, increased intake of ALA appears to provide cardioprotective³⁴ 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 pro-inflammatory 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 cancer⁴¹, borderline personality disorder⁴², mental depression^{43, 44, 45}, schizophrenia⁴⁶, 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 size⁴⁹, 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 disease⁵¹, otitis media (when used with nutritional supplementation⁵²), 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 disorder⁵⁴, Crohn’s disease⁵⁵, rheumatoid arthritis^{56, 57, 58}, lupus⁵⁹, cardiovascular disease⁶⁰, psoriasis⁶¹, 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

As of 2019 and for the foreseeable future, the most current versions of all major patient management and clinical treatment protocols are published in *Inflammation Mastery, 4th Edition* as a single volume of 1,182 pages available in full-color print at discounted pricing directly from ICHNFM from <https://www.ichnfm.org/im4>, while the digital formats are available via several different platforms, including Amazon's Kindle (free) software, Barnes and Noble's Nook, Apple iBook, etc as hyperlinked below. Per popular request by students who were studying (as a required textbook) only one section at a time, "IM4" was also published in two easier-to-carry separate volumes under the name *Textbook of Clinical Nutrition and Functional Medicine*, which contain chapters 1-4 (pages 1-712+index) and 5 (713-1154+index), respectively. Video access is included with IM4 and TCNFM,1+2.

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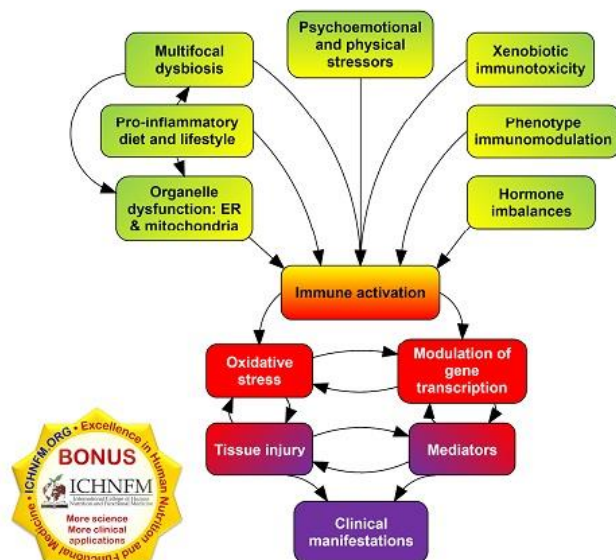
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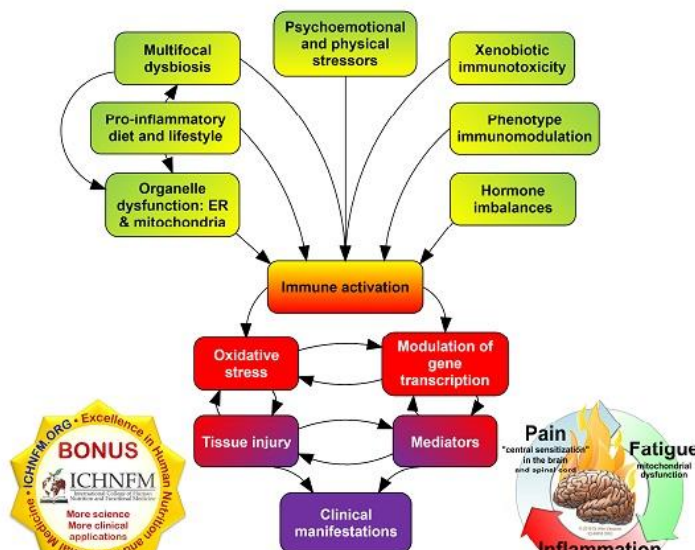
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most powerful health-promoting n-6 fatty acid, GLA is found in varying concentrations in evening primrose oil, borage seed oil, hemp seed oil, and black currant seed oil. Most if not all of the actions of GLA are mediated following its elongation to 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 aggregation³⁷, inhibits vascular smooth muscle cell proliferation *in vitro*⁶⁷, causes vasodilation³⁶, 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, eczema⁷², breast cancer (when used with tamoxifen⁷³), premenstrual syndrome⁷⁴, rheumatoid arthritis^{75, 76}, diabetic neuropathy⁷⁷, migraine headaches (when used with ALA³⁵), 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}

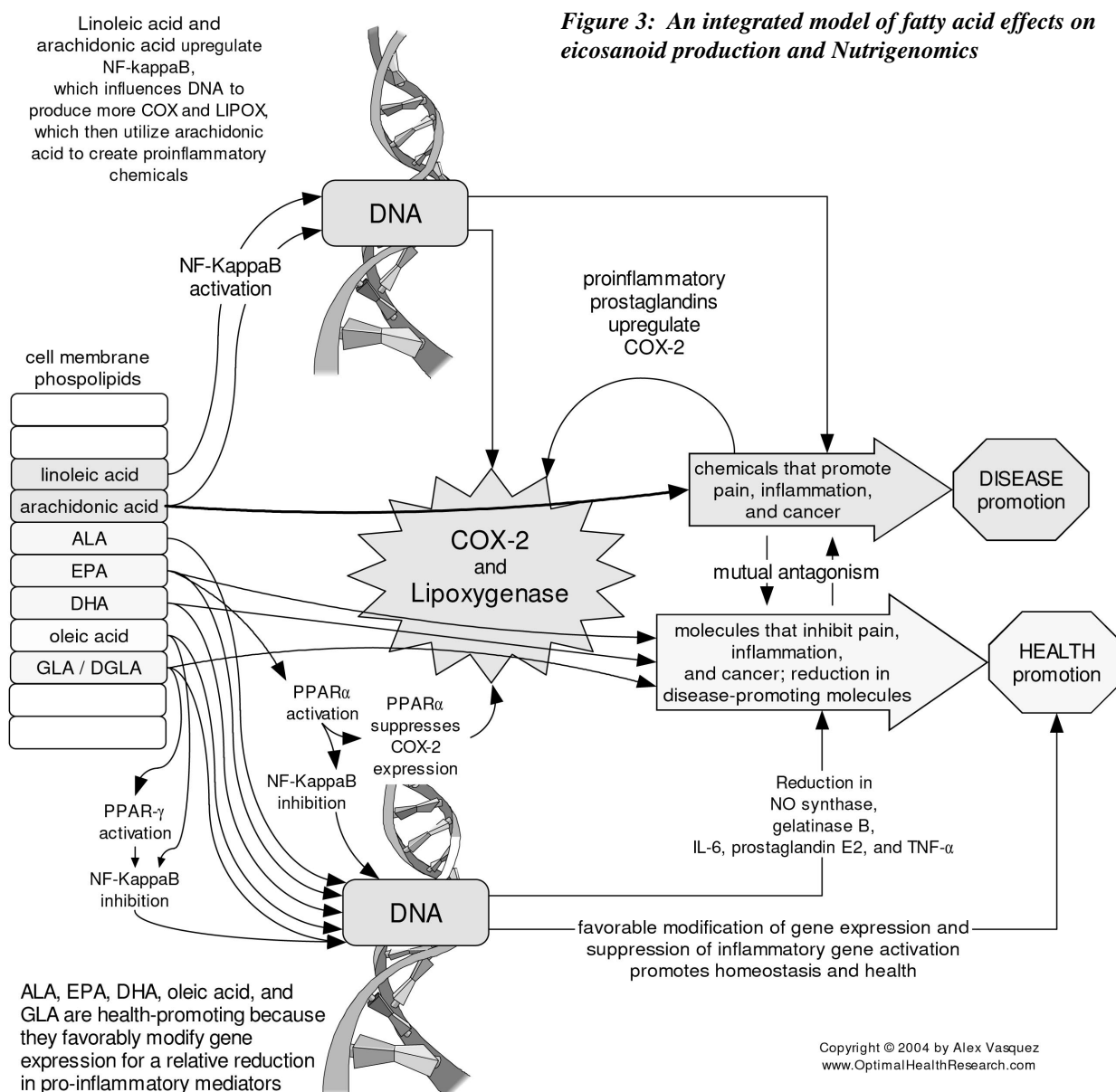
NUTRIGENOMICS: MODULATION OF GENETIC EXPRESSION VIA INTERVENTIONAL NUTRITION

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 humans³², 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-alpha⁸⁹ 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.



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-HETrE⁹²; therefore GLA should be supplemented when EPA and DHA are used. ALA supplementation³² and fish oil supplementation⁹³ 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 it 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 patients¹⁰⁴ 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 supplementation¹⁰⁶, 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 headaches¹⁰⁸, bipolar disorder¹⁰⁹, borderline personality disorder, mental depression¹¹⁰ schizophrenia, osteoporosis¹¹¹, polycystic ovary syndrome¹¹², multiple sclerosis¹¹³, 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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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.

BOOK EXCERPTS, CHAPTERS:

- <https://www.amazon.com/Dr-Alex-Vasquez/e/B00AT5764Y>
- <https://www.ichnfm.org/im4>
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- Main: <https://www.ichnfm.org/> This is actually a very rich website with many blogs and videos
 - <https://www.ichnfm.org/antiviral2019> and the long series starting with <https://www.ichnfm.org/antiviral>, <https://www.ichnfm.org/antiviral2>, <https://www.ichnfm.org/antiviral3>, <https://www.ichnfm.org/antiviral4>, and continuing...
 - <https://www.ichnfm.org/braininflammation>

SOCIAL MEDIA UPDATES: Note that updates are made on a regular basis to the following social media pages, with some overlap but also some topic-specific specialization, which is self-explanatory by the titles of these pages:

- Dr Alex Vasquez 's Inflammation Mastery <https://www.facebook.com/InflammationMastery>
- Migraine Headaches, Hypothyroidism, and Fibromyalgia <https://www.facebook.com/MigraineHypothyroidismFibromyalgia>
- International Journal of Human Nutrition and Functional Medicine <https://www.facebook.com/IJHNFMM>
- International College of Human Nutrition and Functional Medicine (higher quality and academic news) <https://www.facebook.com/IntCollHumNutrFunctMed>
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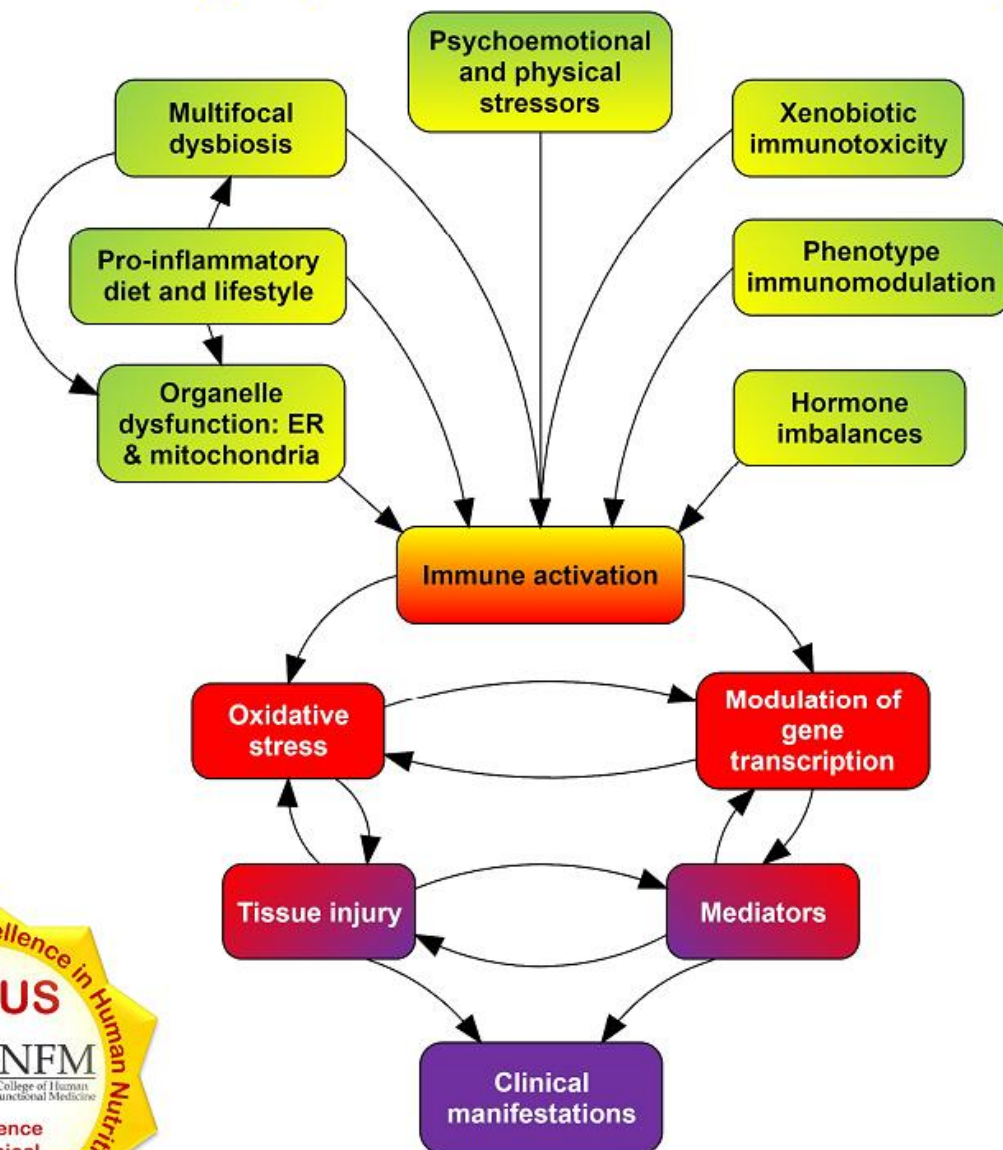
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i

1.	Patient Assessments, Laboratory Interpretation, Clinical Concepts, Patient Management, Practice Management and Risk Reduction: <i>This chapter introduces/reviews/updates patient assessments, laboratory interpretation, musculoskeletal emergencies, healthcare paradigms; the common and important conditions hemochromatosis and hypothyroidism are also included in this chapter since these need to be considered on a frequent basis in clinical practice</i>	1
2.	Wellness Promotion & Re-Establishing the Foundation for Health: <i>Reviewed here are diet, lifestyle, psychosocial health, and—given the pervasiveness of persistent organic pollutants and their increasingly recognized clinical importance—an introduction to environmental medicine</i>	187
3.	Basic Concepts and Therapeutics in (Nondrug) Musculoskeletal Care and Integrative Pain Management: <i>Nonpharmacologic management of musculoskeletal problems is preferred over pharmacologic (e.g., NSAID, Coxib, steroid, opioid) management because of the collateral benefits, safety, and cost-effectiveness associated with manual, dietary, botanical, and nutritional treatments. A brief discussion of the current crisis in musculoskeletal medicine is provided for contextualization and emphasis of the importance of expanding clinicians' knowledge of effective nondrug treatments</i>	243
4.	The Major Modifiable Factors in Sustained Inflammation: <i>Major components of the “Functional Inflammology Protocol” are reviewed here, from concepts and molecular biology to an emphasis on practical clinical applications</i>	303
	1) Food & Basic Nutrition	307
	2) Infections: Dysbiosis* / Viral** <i>*This section specific to bacterial dysbiosis was also published separately as a clinical monograph titled Human Microbiome and Dysbiosis in Clinical Disease (Discounted Black and White Printing, https://www.amazon.com/dp/1512360295) and in full-color printing https://www.amazon.com/Human-Microbiome-Dysbiosis-Clinical-Disease/dp/0990620417 ** This section specific to viral infections is also published separately in full-color paper printing as Antiviral Strategies and Immune Nutrition: Against Colds, Flu, Herpes, AIDS, Hepatitis, Ebola, and Autoimmunity https://www.amazon.com/dp/1502894890 and as a digital ebook Antiviral Nutrition https://www.amazon.com/dp/B00OPDQG4W</i>	396 / 540
	3) Nutritional Immunomodulation	609
	4) Dysmetabolism, Mitochondrial Dysfunction, ERS/UPR, mTOR	622
	5) Special Considerations: Sleep, Sociopsychology, Stress, Surgery	674
	6) Endocrine Imbalances	688
	7) Xenobiotic Immunotoxicity	699
5.	Clinical Applications	713
	1) Hypertension	727
	2) Diabetes Mellitus	819
	3) Migraine & Headaches*	863
	4) Fibromyalgia* <i>*These two sections specific to migraine and fibromyalgia were also published separately as Pain Revolution (full-color printing; https://www.amazon.com/dp/B01AR3NX0S) and Brain Inflammation in Chronic Pain, Migraine and Fibromyalgia: The Paradigm-Shifting Guide for Doctors and Patients Dealing with Chronic Pain (black-and-white printing; https://www.amazon.com/dp/B01EQ9KMH6/); both versions are also available in digital ebook formats for reading on phone, computer, iPad via the free Kindle software</i>	901
	5) Allergic Inflammation	984
	6) Rheumatoid Arthritis	1019
	7) Psoriasis and Psoriatic Arthritis	1038
	8) Systemic Lupus Erythematosus	1053
	9) Scleroderma & Systemic Sclerosis	1074
	10) Vasculitic Diseases	1094
	11) Spondyloarthropathies & Reactive Arthritis	1108
	12) Sjögren Syndrome/Disease	1119
	13) Raynaud's Syndrome/Phenomenon/Disorder	1127
	14) Clinical Notes on Additional Conditions: Behçet's Disease, Sarcoidosis, Dermatomyositis and Polymyositis	1131

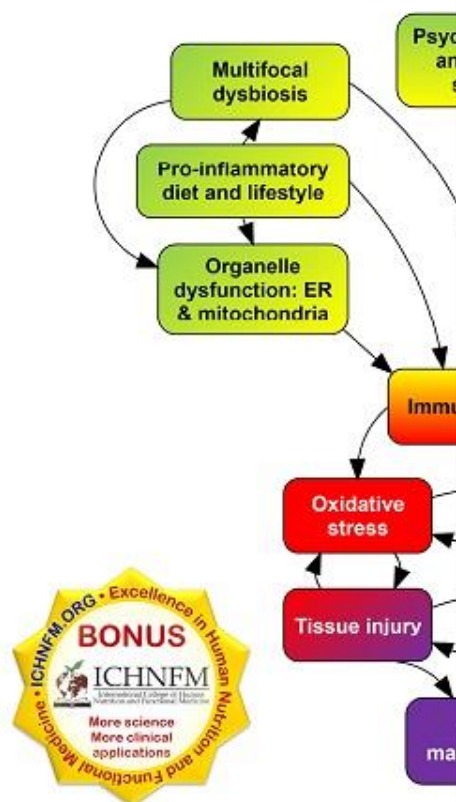
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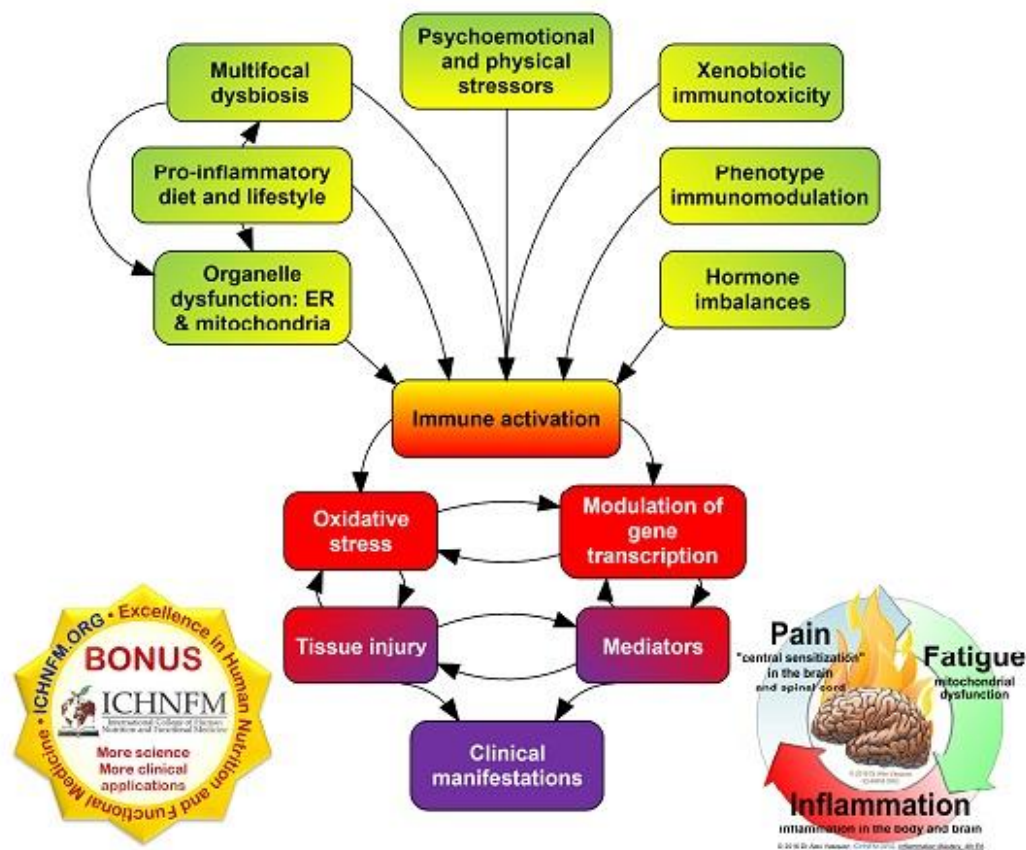
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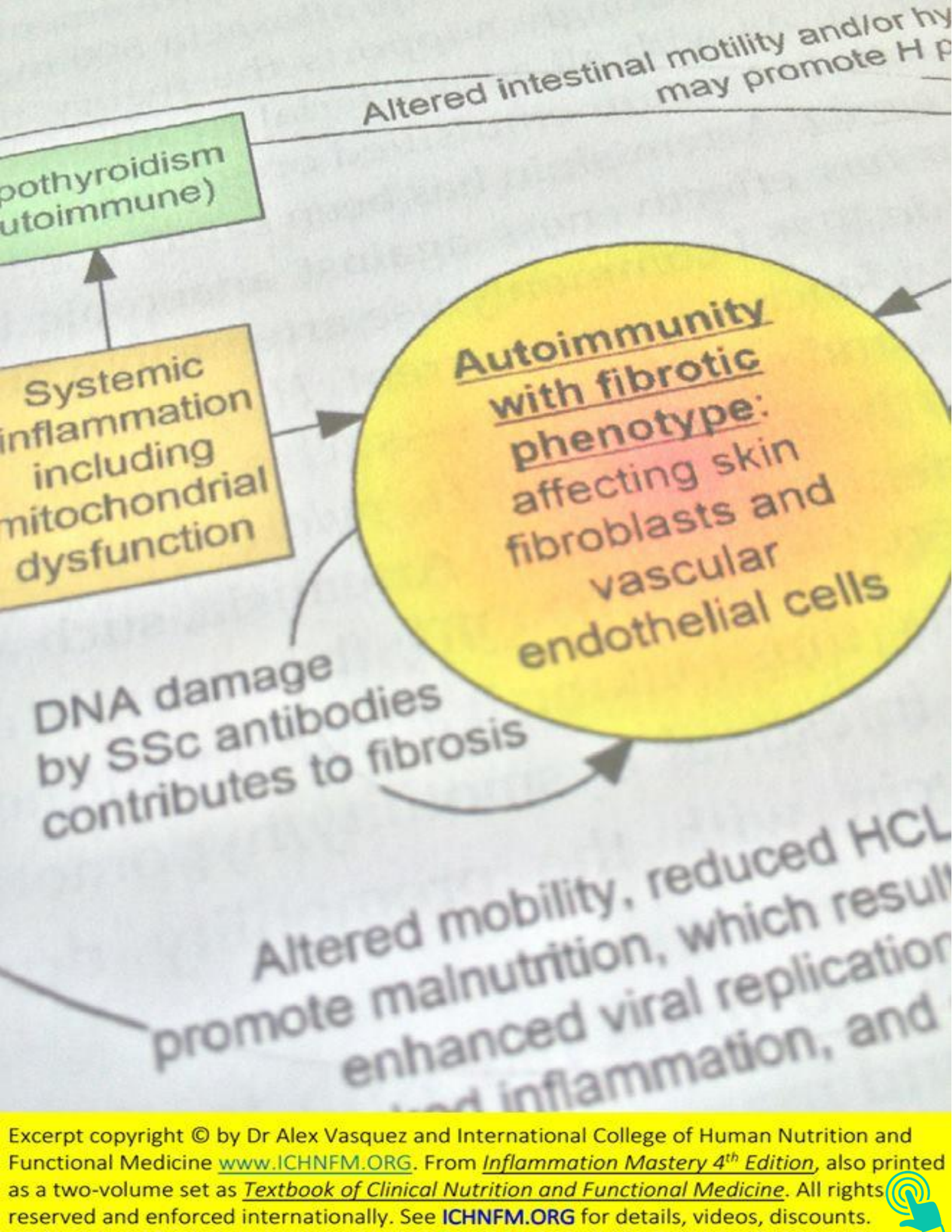
ALEX VASQUEZ D.C. N.D. D.O. F.A.C.N.

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 - Former Faculty (2004-2005, 2010-2013) and Forum Consultant (2003-2007), The Institute for Functional Medicine
 - Former Adjunct Professor (2011-2013) of Pharmacology, Evidence-Based Nutrition, Immune and Inflammatory Imbalances, Principles of Functional Medicine, Psychology of Wellness
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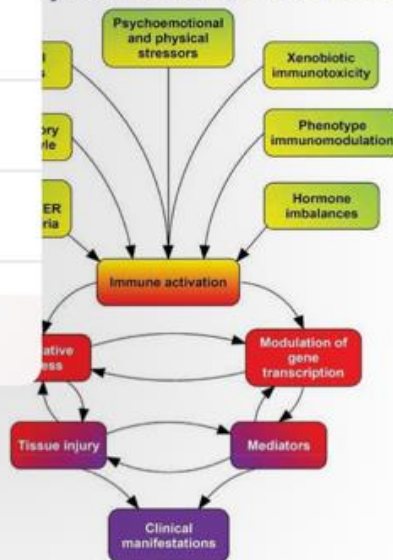


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Chapter and Introduction

Preamble

Volume 1

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Volume 2: Chapter 5—Clinical Applications of the Functional Inflammation Protocol

1) Hypertension

2) Diabetes Mellitus

3) Migraine & Headaches

4) Fibromyalgia

5) Allergic Inflammation

6) Rheumatoid Arthritis

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8) Systemic Lupus Erythematosus

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Index & Appendix



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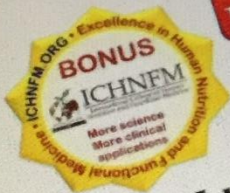
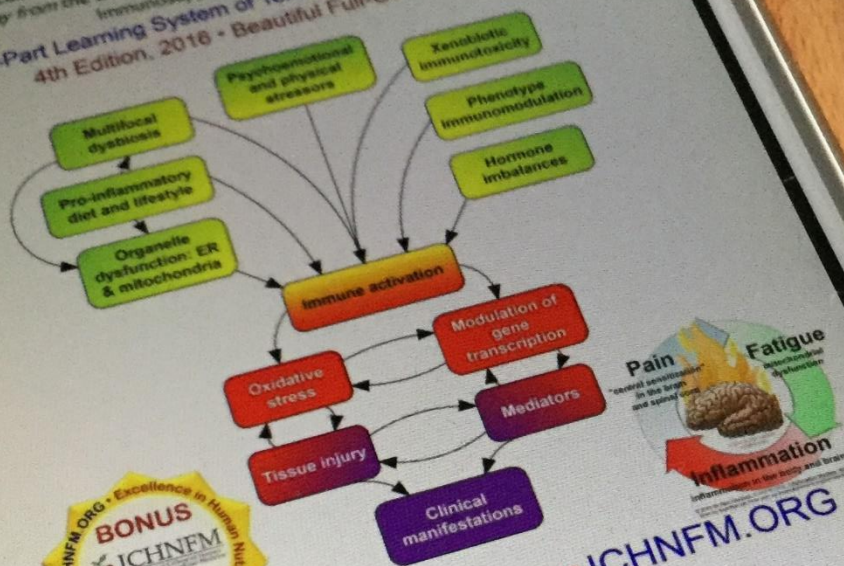
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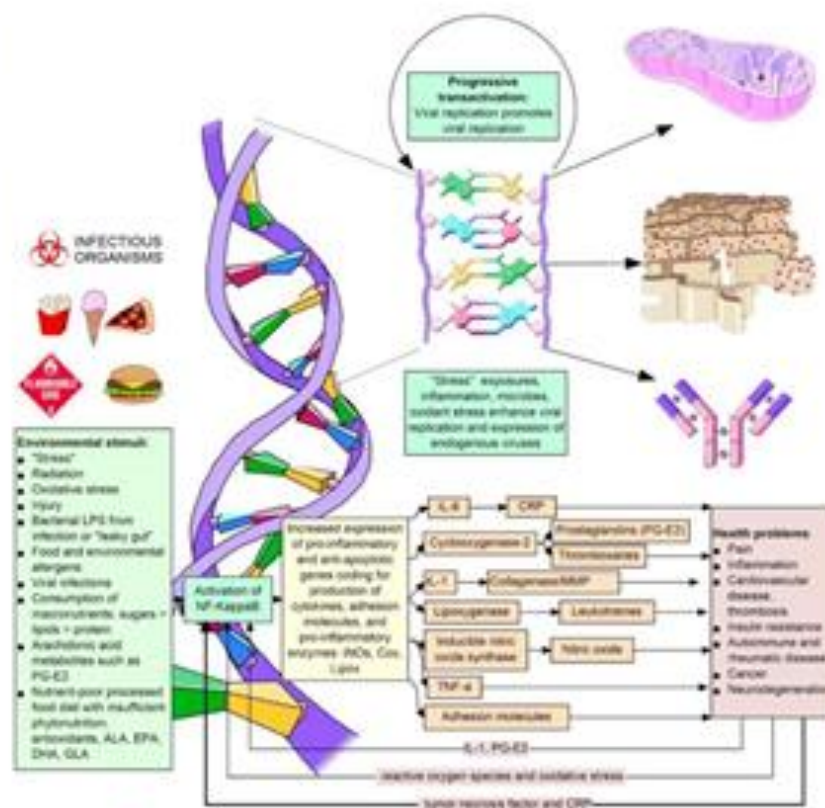
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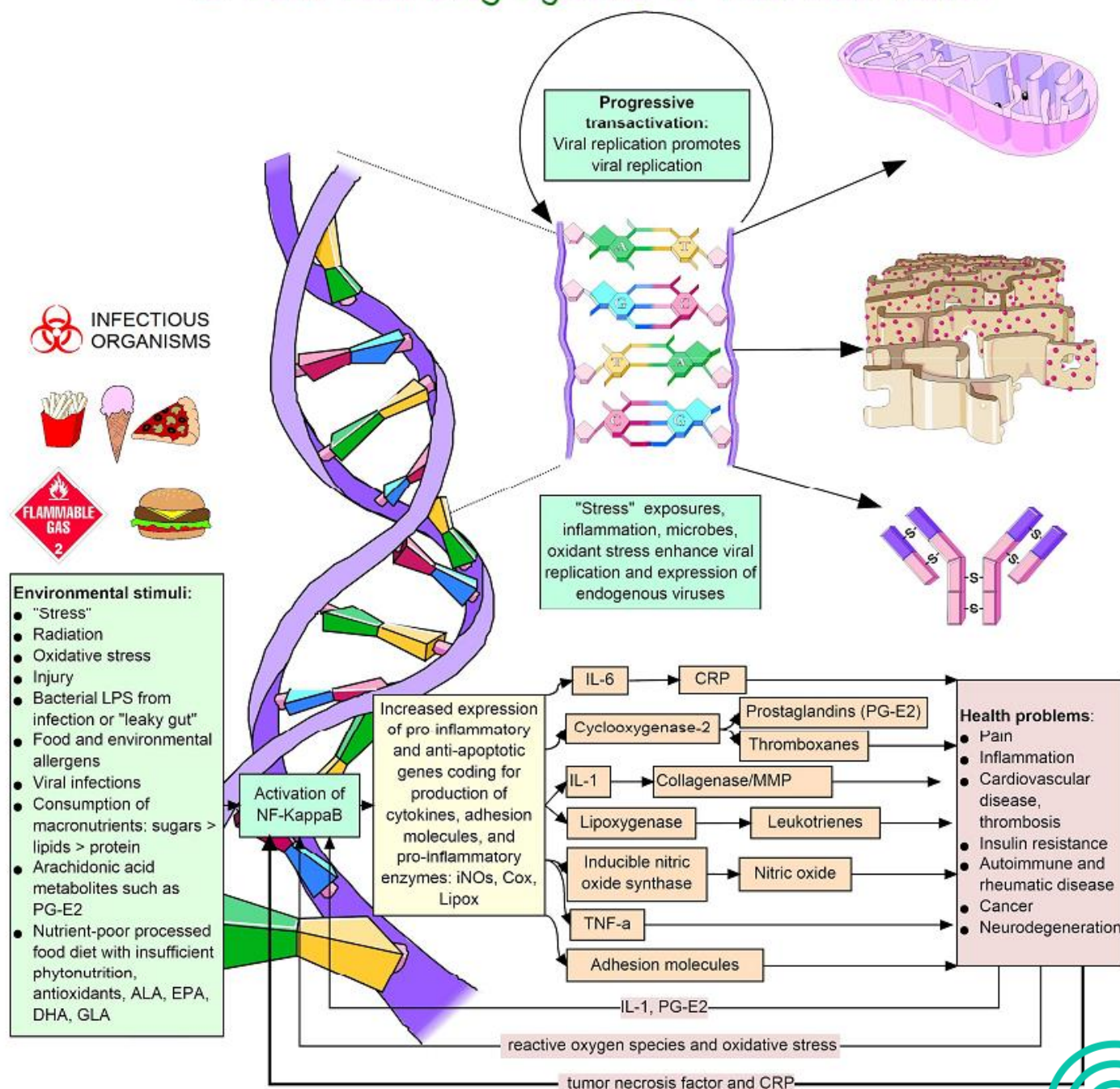


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THE PATH AHEAD

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 is worldwide.² While a specific disease human population nutrition research particularly concerning nutrition research healthcare professions nutrition. Clinical vast majority of medical training programs are obviously in gastroenterology⁷ training in clinical proclaims itself as including the entire and serious problem arises when unskilled and invalid research is published by authors (including nonphysician journalists¹¹) 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 practitioners and nutrition supplement industry¹² 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 ulations, lists sed solutions. pendent upon stigative and ts of clinical rovements are ignorance in

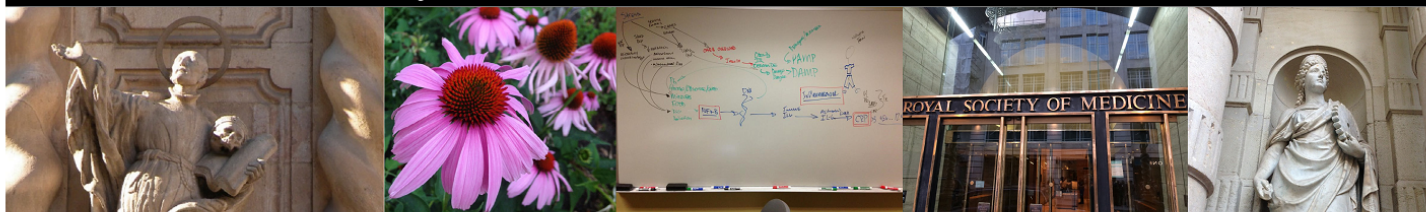
tion

review recent 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.

PDF articles: Full-text archives of the author’s articles are available per the following:

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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 transfer 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 Academia, "nonprofits", and "Education"

I would be happiest to tell you about the support for fellow Professors, and commitment to truth and reality setting ablaze the passions of those they teach, lead, and supervise in flower fields like a professor.

singing a rhythmical rendition of *"The Hills are Alive...with the...Passions of Education and Intellectual Integrity."* But a Pollyannaic 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

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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 early on, in that kind of my entryway, I think, in that our assignment was to write a poem, and I remember writing this poem in class, on and on, and—compared with some of the other students—I just realized that writing for me was not a struggle.

Then again, when I was in a military school, I remember in our

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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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 some instances, radical departures from any attempt to provide descriptions that could be considered “reasonable” by previous standard.¹ Especially related to the topic of nutrition, mainstream medical journals and the media, which parrots their conclusions have begun to make overt misrepresentations of Nutrition with regard for science, logic, biomedical history and

One has to be aware of a few key ironies that characterize mainstream medical discussions of nutrition: that 1) medical physicians receive essentially no training in clinical nutrition in their graduate school education and in their post-graduate residency training², 2) medical physicians and organizations publish “research” and commentaries (both of which commonly conclude that nutritional interventions are inefficacious or unsafe) despite their lack of formal education on the topic, and

stream 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 keep them ignorant on important topics; our educational sys-

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- **VIDEO:** Bad Science in Medical Nutrition: Politics of Fish Oil <https://vimeo.com/314997927>

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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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). In this time, contemporary clinicians 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 compartmentalized membrane that separates the matrix from the intermembrane space; (3) intermembrane space—the space between the inner and outer membranes; and (4) outer membrane—the outermost layer of the mitochondria, which is relatively smooth and contains various proteins and enzymes. The inner membrane is very lipid-rich and with active and passive transport systems for select molecules that need to enter and exit the mitochondria. Clinicians need to appreciate that mitochondrial membrane integrity is of the highest importance; just as we have come to appreciate the

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stated during the recent International Conference on Human Nutrition and Functional Medicine¹ in Portland, Oregon, in September 2013, we have collectively arrived at a time when mitochondrial therapeutics and the contribution of mitochondrial dysfunction to clinical diseases must be

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 moved to a health school in the early 1990s. My "nutrition" book that I read as a teenager was *Your Nerves* (1975) by me. This was followed immediately by the lectures of Jonathan V Wright, MD, of whom would later be my mentor at the University. By the mid-1990s, I had read the book by Jeffrey Bland PhD had introduced me to integrative medicine, which I studied for personal and professional reasons. By the late 1990s, I had contained several hundred articles on 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 for⁴ and published in⁵ 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 applications; we can reasonably assume that (and competent healthcare providers (adequate nutrition) are basic to submit a counterargument for all of my assertions, they are and more to the point, my assertions are regardless of personal position—we share some common ground including the following:

and deliver the best health solution. Efficiency of time or money is not the top priority when we are seeking solutions

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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 articles³ 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 dysbiosis. In 2010, I found "dysbiosis" more than 1,200 times. The concept has become popular, but to do with it in *International Journal of Human Nutrition and Functional Medicine*, the complete microbiota project, the number of scientific papers linking the microbes that live in our gut to diseases ranging from diabetes and colitis to anxiety and depression has grown exponentially. Yet, these tantalizing connections have yielded few benefits from a therapeutics standpoint.⁴ To the extent that this information is being integrated into clinical practice at all, the current level of


"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 culture of gastrointestinal popular to the clinical clues. Laboratory testing particular used methods to extract they only to suffering and


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International College of Human Nutrition and Functional Medicine

ICHNFM has many videos on the topics of dysbiosis, persistent infections, and dysbiotic clinical conditions such as fibromyalgia at www.Vimeo.com/ICHNFM



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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

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tice 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 at risk for vitamin D deficiency and hypersensitivity.
3. Know how to implement proper doses and with appropriate monitoring.

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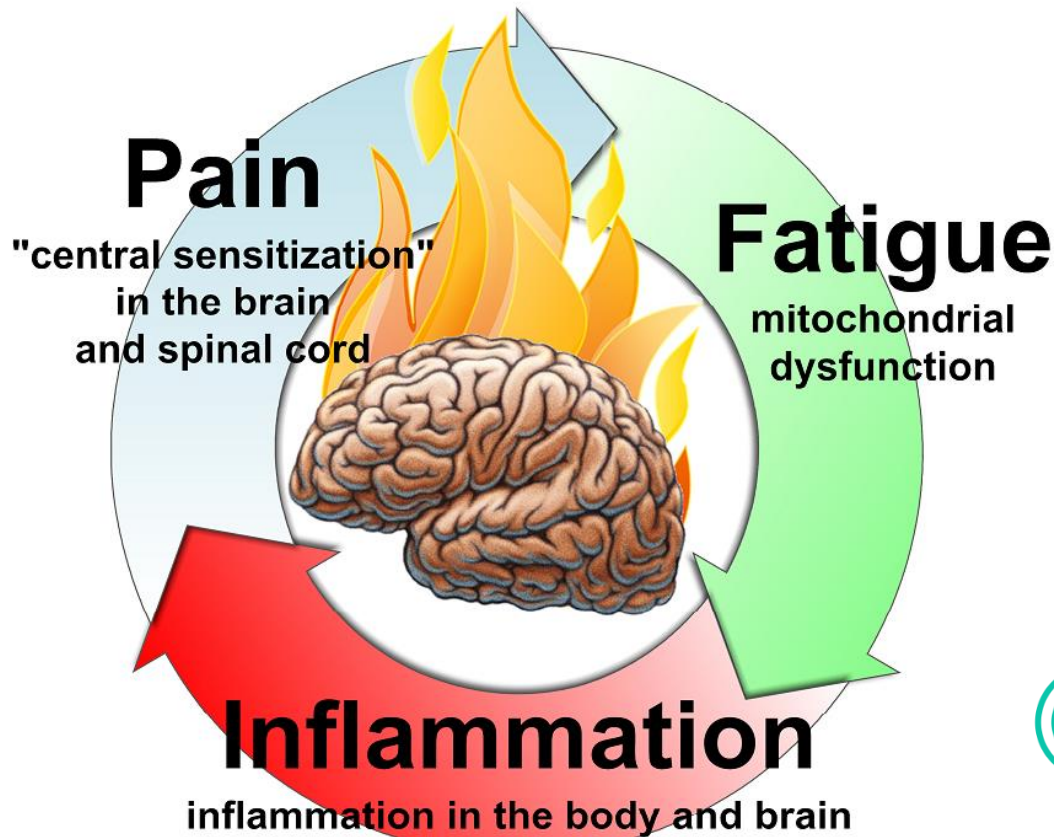
While we are all familiar with the important role of vitamin D in calcium absorption and bone metabolism, many doctors and patients are not aware of the recent research on vitamin D and the widening range of therapeutic applications available for cholecalciferol, which can be classified as both a vitamin 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 tis-

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BRAIN INFLAMMATION IN CHRONIC PAIN, MIGRAINE AND FIBROMYALGIA

THE PARADIGM-SHIFTING GUIDE FOR DOCTORS AND
PATIENTS DEALING WITH CHRONIC PAIN



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Biological plausibility of the gut–brain axis in autism

Alex Vasquez 

Organic abnormalities with neuroinflammation, purine metabolism, neurotransmitter metabolism, and many of these abnormalities are noted in autism, and many of these abnormalities are metabolites, and heightened serum levels of these metabolites.

Keywords: gut–brain axis; autism; metabolism

In their recent review, Sherwin² and colleagues, among many other issues, the relationship between the gut microbiome–brain axis with autism. In this section subtitled “Microbiota-based approaches to the treatment of autism: hype or reality?”¹ *et al.*¹ largely discuss preclinical studies and the 2017 open-label study by Karpman³ who used a sequence of oral vancomycin, followed by polyethylene glycol laxative, and then human fecal microbiota transplantation. The study showed clinical benefit in subjects with autism.

Readers will likely benefit from additional relevant clinical studies, including the indication by Sandler *et al.*³ showing the resolution of autistic manifestations following oral vancomycin, as well as case reports showing positive impact of various antibiotics (metronidazole, ketoconazole, ampicillin) in patients with autism.^{4,5} These studies have been shown to have gut dysregulation as well as *Clostridia* species,⁶ the group of bacteria noted for their production of neurotoxic substances. International studies have consistently demonstrated that subjects with autism have heightened production of 3-(3-hydroxypropionic acid (HPHPA), a phenylalanine metabolite of *Clostridia* in the gastrointestinal tract.^{7,8} HPHPA reported to be associated with the conversion of dopamine to

Autism, Dysbiosis, and the Gut–Brain Axis



An Excerpt from "Deciphering
the Gut-Brain Axis in Clinical
Practice"

Alex Vasquez

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