Reducing Pain and Inflammation Naturally – Part 3: Improving Overall Health While Safely and Effectively Treating Musculoskeletal Pain

Alex Vasquez, D.C., N.D.

Abstract: Following the optimization of diet and fatty acid balance, the next therapeutic steps in the treatment of pain and inflammation can include the use of vitamin D, chondroitin sulfate, niacinamide, and botanical medicines such as Boswellia. In direct contrast to so-called "anti-inflammatory drugs" which always have significant toxicity, each of these natural treatments has been proven in controlled clinical trials to significantly reduce pain and inflammation without major adverse effects. Chondroitin sulfate has actually been shown to reduce cardiovascular mortality in humans while it safely and effectively ameliorates the pain and inflammation of osteoarthritis. Similarly, vitamin D supplementation has been proven effective in the treatment of hypertension, depression, migraine headaches, polycystic ovary syndrome and in the prevention of type-1 diabetes. By failing to fully cover chiropractic and naturopathic healthcare services, insurance companies which comprise and contribute to the American healthcare system are losing profitability and forcing patients to use drug and surgical treatments that are commonly less effective, more dangerous, and more expensive than the natural treatments described in this paper. Services provided by chiropractic and naturopathic physicians are supported by peer-reviewed research and deserve equitable coverage and status in America's healthcare system.

INTRODUCTION

As primary care providers with specialized training in musculoskeletal medicine, chiropractic physicians typically play a dual role in clinical practice on a daily basis, generally striving to simultaneously accomplish two related goals in each patient: 1) promoting overall wellness and professionally-supervised patient-implemented preventive healthcare, and 2) alleviating acute and chronic musculoskeletal pain. Both of these goals are important given the tremendous financial and social impact of musculoskeletal pain and the progressive deterioration of Americans' health. At any given time, nearly thirty percent of the American population suffers from musculoskeletal pain, joint swelling, or limitation of movement, and approximately 1 of every 7 (14% of total) visits to a primary healthcare provider is for the treatment of musculoskeletal pain or dysfunction. Resulting in more than $100 billion in US healthcare costs each year, back pain is the most prevalent medical problem in the US, is the leading cause of long-term disability, and is the second leading cause of restricted activity and the use of prescription and non-prescription drugs.[1] The preventive healthcare and wellness promotion advocated and implemented by chiropractic and naturopathic physicians is now more important than ever since the health of the American population is consistently and progressively declining: obesity and diabetes are "ever-growing" epidemics among children and adults,[2] infant mortality has recently increased for the first time in 40 years,[3] and self-reported health status and health-related quality of life among adults are declining.[4] In the 25 years between 1975 and 2000, the incidence of cancer increased significantly, and the number of people diagnosed with cancer is expected to double in the next several decades.[5] Despite these negative health trends, America spends more on healthcare than does any other nation—an unprecedented $1.55 trillion, which is roughly 15% of the US gross domestic product.[6] From the perspective of cost-effectiveness, the medically-dominated American healthcare system delivers a very poor return on investment, and it appears that assertive wellness promotion and increased utilization of chiropractic and naturopathic healthcare may provide improved outcomes and decreased overall healthcare costs.[7,8]

Numerous adverse effects are produced as a direct result of medical/pharmaceutical management of benign musculoskeletal pain. According to a 1998 review by Singh,[9] "Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures for all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated." More recently following the withdrawal of the arthritis drug rofecoxib (Vioxx) in late September 2004, Topol[10] extrapolated that as many as 160,000 adverse cardiovascular events (including stroke, myocardial infarction, and death) may have resulted from the collusion of Merck's intentional failure to withdraw what was known for years to be a dangerous drug, the FDA's failure to enforce regulatory standards to protect the public, and the overutilization of Vioxx by the medical profession, which was well informed of the lethality of Vioxx for several years[11] before Merck's confessionary and belated withdrawal of the drug. Soon thereafter, several other so-called "anti-inflammatory drugs" such as valdecoxib (Bextra),[12] celecoxib (Celebrex),[13] and naproxen (Aleve)[14] were likewise associated with excess cardiovascular injury and death. Although the advertising-induced feeding frenzy on Celebrex made it the most successful drug launch in US history with more than 7.4 million prescriptions written within its first 6 months,[15]

within 2 years of its release, evidence linking the drug to increased cardiovascular events (including death) was accumulating,[11] and the drug has since been linked to a wide range of adverse effects such as membranous glomerulopathy and acute interstitial nephritis,[16] acute cholestatic hepatitis,[17] and toxic epidermal necrolysis.[18] When compared with placebo in cardiac surgery patients, Bextra/valdecoxib is associated with a 3-fold to 4-fold increased risk of heart attack, stroke, and death,[19] and currently 7 million arthritis patients, many of whom are already at high risk for cardiovascular disease, are being treated with this drug.[12]

Increasingly aware of the negative effects of pharmaceutical management of musculoskeletal pain, patients and healthcare providers alike are looking to natural treatments and chiropractic healthcare[20,21] with the hopes of avoiding the risks of iatrogenic disease, such as drug-induced renal failure,[22] hepatotoxicity,[23] gastrointestinal ulceration and hemorrhage,[24] osteonecrosis,[25,26] joint degeneration,[27,28] hypertension,[28] myocardial infarction,[11] and premature death[11,12] that are associated with the non-steroidal anti-inflammatory drugs ("NSAIDs"), non-NSAID analgesics such as acetaminophen, and the relatively new selective cyclooxygenase-2 inhibitors (cox-2 inhibitors, or "coxibs"). It is tragically paradoxical that many of the pharmaceutical drugs used for the suppression of arthritis symptoms and advertised as "arthritis relief" actually exacerbate joint destruction and chronic inflammation by interfering with the biosynthesis of the glycosaminoglycans that are essential components of joint cartilage while also promoting destruction of subchondral bone.[25,26,27,28] This places chiropractic physicians in an ethical dilemma when helping patients who have been prescribed potentially dangerous medications by their medical doctors. On the one hand, chiropractic physicians are aware of the research showing that, for example, coxibs provide little clinical benefit while promoting increased cardiovascular mortality and other potentially lethal adverse effects. On the other hand, if a chiropractic physician advises discontinuation of the medication, he or she may be reprimanded for "practicing medicine." It appears that chiropractic physicians will need to obtain limited prescription rights for the sake of helping protect their patients from iatrogenic and drug-induced disease. Given that chiropractic physicians are already duly trained in basic and clinical sciences sufficient for primary care, post-graduate certification courses in pharmacology would be sufficient if additional training is deemed necessary to obtain these prescription rights.

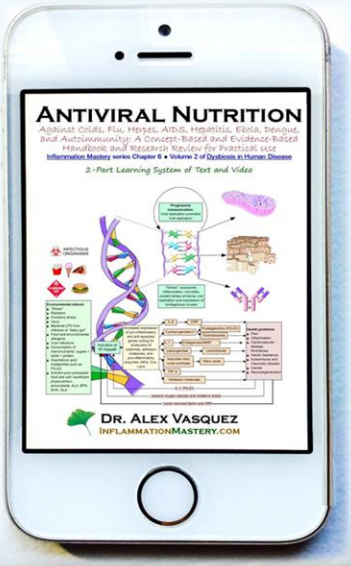
The first two articles in this series reviewed the importance of diet and fatty acids in the alleviation of pain and inflammation. This article reviews the most commonly used and well-researched nutritional and botanical interventions for the treatment of pain and inflammation, namely vitamin D, glucosamine and chondroitin sulfate, niacinamide, vitamin D, proteolytic enzymes, Devil's Claw *(Harpagophytum procumbens)*, Willow bark (*Salix* spp), and Boswellia *(Boswellia serrata)*. This review will provide chiropractic and naturopathic physicians with clinically useful information to help their patients attain improved health and well-being. Osteoarthritis and chronic low-back pain, the two most prevalent musculoskeletal afflictions, will serve as prototypes for this discussion.

SELECTED NUTRITIONAL AND BOTANICAL THERAPEUTICS FOR THE ALLEVIATION OF JOINT PAIN AND INFLAMMATION

Subsequent to the overall health improvement and anti-inflammatory benefits provided by the supplemented Paleo-Mediterranean diet described previously, many patients who require additional anti-inflammatory interventions can be safely and effectively treated with the following phytonutraceuticals, each of which is supported by experimental and clinical data in humans. Mechanism(s) of action, indications, contraindications, dosage, and common drug interactions (if any) are listed for each.

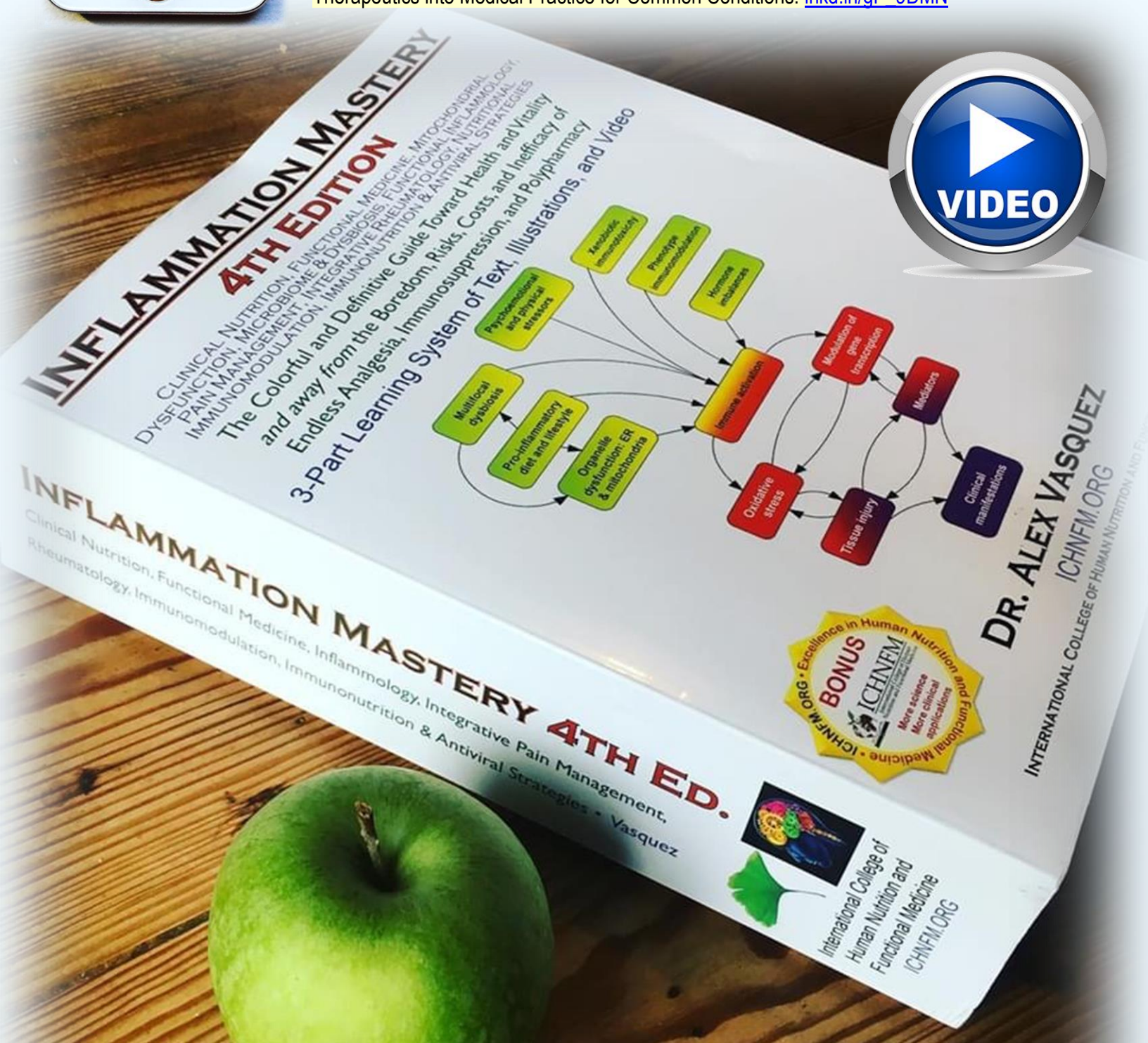
Glucosamine and chondroitin sulfate: Glucosamine and chondroitin are the "building blocks" from which cartilage is built and oral supplementation is intended to enhance cartilage anabolism and to thus counteract the enhanced cartilage catabolism seen in destructive arthritic processes. Clinical trials with glucosamine and chondroitin sulfates have shown consistently positive results in clinical trials involving patients with osteoarthritis of the hands, hips, knees, temporomandibular joint, and low-back.[29,30,31,32,33,34] For example, glucosamine sulfate was superior to placebo for pain reduction and preservation of joint space in a 3-year clinical trial in patients with knee osteoarthritis.[36] Arguments against the use of glucosamine due to inflated concern about inefficacy or exacerbation of diabetes[37] are without scientific merit[38,39] as evidenced by a 90-day trial[40] of diabetic patients consuming 1500 mg of glucosamine hydrochloride with 1200 mg of chondroitin sulfate which showed no significant alterations in serum glucose or hemoglobin A1c and by the previously cited 3-year study which found significant clinical benefit and no adverse effects on glucose homeostasis. The adult dose of glucosamine sulfate is generally 1500-2000 mg per day in divided doses, and the dose of chondroitin sulfate is approximately 1000 mg daily. Both treatments are safe for multiyear use, and rare adverse effects include allergy and nonpathologic gastrointestinal upset. Clinical benefit is generally significant following 4-6 weeks of treatment and is maintained for the duration of treatment. In contrast to coxib and other mislabeled "anti-inflammatory " drugs that consistently elevate the incidence of cardiovascular disease,

Download your personal copies from inflammationmastery-com-ichnfm-org.dpdcart.com



1. **VIDEO**: Integrating Functional and Naturopathic Medicine Concepts and Therapeutics into Medical Practice for Primary Care and Specialty Conditions
    - View for free https://www.InflammationMastery.com/medical
2. **PDF eBOOK**: **Antiviral Nutrition** 2014-2020
3. **VIDEO**: Re-Introduction to DrV's Antiviral Strategies and Immune Nutrition (1hour)
4. **VIDEO**: Antiviral Use of the Amino Acid NAC, N-acetyl-L-cysteine (1hour42minutes)
5. **VIDEO**: Antiviral Nutrition against C-V-1-9 (1hour)
6. **VIDEO**: Antiviral Nutrition 2020 Risk Management, Laboratory Assessment of Common Interventions

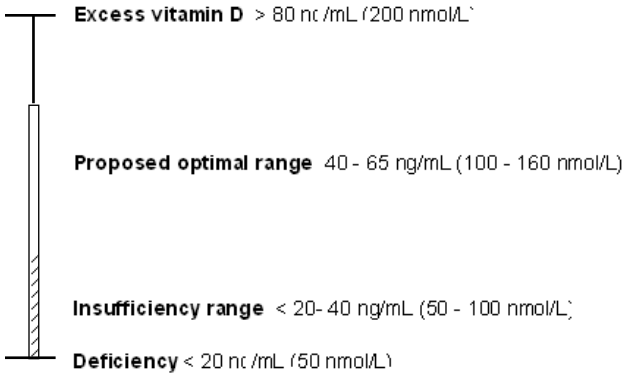
FREE PDF eBOOK: Integrating Functional and Naturopathic Medicine Concepts and Therapeutics into Medical Practice for Common Conditions: lnkd.in/gP_9DMN



death, and other adverse effects, supplementation with chondroitin sulfate appears to safely reduce the pain and disability associated with osteoarthritis while simultaneously reducing incidence of cardiovascular morbidity and mortality.[41,42] In a study with animals that spontaneously develop atherosclerosis,[43] administration of chondroitin sulfate appears to have induced regression of existing atherosclerosis. In a six-year study with 120 patients with established cardiovascular disease, 60 chondroitin-treated patients suffered 6 coronary events and 4 deaths compared to 42 events and 14 deaths in a comparable group of 60 patients receiving "conventional" therapy; chondroitin-treated patients reported enhancement of well-being while no adverse clinical or laboratory effects were noted during the 6 years of treatment.[44]

Vitamin D (cholecalciferol): Vitamin D insufficiency is epidemic in the United States and is extremely prevalent (>90%) among patients with chronic musculoskeletal pain[45] limb pain,[46] and low-back pain.[47] The mechanism by which this pain is produced has been clearly elucidated: 1) vitamin D deficiency causes a reduction in calcium absorption, 2) production of parathyroid hormone (PTH) is increased to maintain blood calcium levels, 3) PTH results in increased urinary excretion of phosphorus, which leads to hypophosphatemia, 4) insufficient calcium phosphate results in deposition of unmineralized collagen matrix on the endosteal (inside) and periosteal (outside) of bones, 5) when the collagen matrix hydrates and swells, it causes pressure on the sensory-innervated periosteum resulting in pain.[48] In patients with vitamin D deficiency, oral supplementation with vitamin D clearly produces anti-inflammatory benefits,[49,50] and treatment with vitamin D can safely lead to dramatic reductions in musculoskeletal pain in a large percentage of patients.[46,47] Routine annual measurement of vitamin D status should be the standard of care[51] since failure to diagnose vitamin D deficiency and to provide adequate replacement doses are both ethically questionable and scientifically unjustifiable in light of the low cost, manifold benefits, rare adverse effects, and high prevalence of vitamin D deficiency.[52,53] Physiologic requirements are approximately 4,000 IU per day in men[54] and can only be achieved with high-dose oral supplementation or full-body sun exposure on a frequent or preferably daily basis. As reviewed in the recent monograph by Vasquez et al,[55] relative contraindications include the use of thiazide diuretics or presence of a vitamin D hypersensitivity syndrome such as primary hyperparathyroidism, adrenal insufficiency, hyperthyroidism, hypothyroidism, or granulomatous disease such as sarcoidosis, Crohn's disease, or tuberculosis). Serum calcium is periodically monitored in patients receiving moderate doses of vitamin D (adult range 4,000 – 10,000 IU per day), since hypercalcemia is the best laboratory indicator of vitamin D excess. High doses of vitamin D (up to 100,000 IU per day) have been safely used during pregnancy[56,57] periodic testing of serum calcium is required to monitor and for hypercalcemia. Vitamin D supplementation has been proven effective in the treatment of hypertension, depression, migraine headaches, polycystic ovary syndrome and in the prevention of cancer and type-1 diabetes. [55]

Figure 2. Normal and optimal ranges for serum 25(OH) vitamin D levels based on current research.
Used with permission from Vasquez A. Integrative Orthopedics. (OptimalHealthResearch.com): 2004



Proteolytic enzymes: Oral administration of proteolytic enzymes (such as pancreatin, bromelain, papain, trypsin and alpha-chymotrypsin) for therapeutic purposes is well established on physiologic, biochemical, and clinical grounds, and a brief review of their historical use is warranted. One of the first experimental studies was published by Beard in 1906 in the *British Medical Journal* wherein he showed that proteolytic enzymes significantly inhibited tumor growth in mice with implanted tumors,[58] and a year later in that same journal, Cutfield[59] reported tumor regression and other objective improvements in a patient treated with proteolytic enzymes. In the American research literature, anti-cancer effects of proteolytic enzymes were reported during this same time in the *Journal of the American Medical Association* in anecdotal case reports of patients with fibrosarcoma,[60] breast cancer,[61] and head and neck malignancy[62]—all of whom responded positively to the administration of proteolytic enzymes; no adverse effects were seen. Although nearly a century would pass before Beard's study and results were replicated with modern techniques,[63,64] by now it is well established that orally administered proteolytic enzymes are well absorbed from the gastrointestinal tract into the systemic circulation[65,66] and that the anti-tumor, anti-metastatic, anti-infectious, anti-inflammatory , analgesic, and anti-edematous actions result from synergism between a variety of mechanisms of action, including the dose-dependent stimulation of reactive oxygen species production and anti-cancer cytotoxicity in human neutrophils,[67] a pro-differentiative effect,[68]

reduction in PG-E2 production,[69] reduction in substance P production,[70] modulation of adhesion molecules and cytokine levels,[71] fibrinolytic effects and a anti-thrombotic effect mediated at least in part by a reduction in 2-series thromboxanes.[72] Unfortunately, enthusiasm for the enzyme treatment of cancer waned prematurely when trypsin was judged to not be a "miracle cure", when the mechanism of action could not be determined, and as enthusiasm surrounding drug and radiation treatments grabbed the attention of allopaths.[73] However, modern controlled clinical trials in cancer patients have established the value of enzyme therapy, which produces important clinical benefit (e.g., symptom reduction and prolonged survival) for little cost and with negligible adverse effects.[74,75,76] Research in other clinical applications for proteolytic enzymes has consistently shown benefit when properly formulated and manufactured preparations are administered appropriately in the treatment of cellulitis, diabetic ulcers, sinusitis, and bronchitis.[77] For example, in a double-blind placebo-controlled trial with 59 patients, Taub[78] documented that oral administration of bromelain significantly promoted the resolution of congestion, inflammation, and edema in patients with acute and chronic refractory sinusitis; no adverse effects were seen in any patient.

When not treating patients with cancer or infectious disease, chiropractic and naturopathic physicians today use these enzymes mostly for the treatment of inflammatory and injury-related disorders. Reporting from the Tulane University Health Service Center, Trickett[79] reported that a papain-containing preparation benefited 40 patients with various injuries (e.g., contusions, sprains, lacerations, strains, fracture, surgical repair, and muscle tears); no adverse effects were seen. In a recent open trial of patients with knee pain, Walker et al[80] found a dose-dependent reduction in pain and disability as well as a significant improvement in psychological well-being in patients consuming bromelain orally. Most of the studies reviewed by Brien et al[69] were suggestive of a positive benefit in patients with knee osteoarthritis, but inadequate dosing clearly prohibited the attainment of optimal results. Bromelain also attenuates experimental contraction-induced skeletal muscle injury,[81] reduces production of hyperalgesic PG-E2 and substance P, is generally effective in the amelioration of trauma-induced injury, edema, and inflammation, and is practically non-toxic.[70] Although bromelain may be used in isolation, enzyme therapy is generally delivered in the form of polyenzyme preparations containing pancreatin, bromelain, papain, trypsin and alpha-chymotrypsin.

Niacinamide: Niacinamide is a form of vitamin B3 that was first shown to be highly effective in the treatment of osteoarthritis by Kaufman more than 50 years ago.[82] Furthermore, Kaufman's documentation of an "anti-aging" effect of vitamin supplementation in general and niacinamide therapy in particular[83] is consistent with recent experimental data demonstrating rapid reversion of aging phenotypes by niacinamide through possible modulation of histone acetylation.[84] A recent double-blind placebo-controlled repeat study found that niacinamide therapy improved joint mobility, reduced objective inflammation as assessed by ESR, reduced the impact of the arthritis on the activities of daily living, and allowed a reduction in medication use.[85] While the mechanism of action is probably multifaceted, inhibition of joint-destroying nitric oxide appears to be an important benefit.[86] The standard dose of 500 mg given orally 6 times per day is more effective than 1,000 mg 3 times per day. Hepatic dysfunction is rare when daily doses are kept below 3,000 mg per day, yet Gaby[87] suggests measurement of liver enzymes after 3 months of treatment and yearly thereafter. Antirheumatic benefit is generally significant following 2-6 weeks of treatment, and patients may also notice an anxiolytic benefit, which is probably due to the binding of niacinamide to GABA/benzodiazepine receptors.[88]

Boswellia (Boswellia serrata): *Boswellia* shows anti-inflammatory action via inhibition of 5-lipoxygenase with no apparent effect on cyclooxygenase. A recent clinical study showed that *Boswellia* was able to reduce pain and swelling while increasing joint flexion and walking distance in patients with osteoarthritis of the knee.[89] While reports from clinical trials published in English are relatively rare, a recent abstract from the German medical research[90] stated, "In clinical trials promising results were observed in patients with rheumatoid arthritis, chronic colitis, ulcerative colitis, Crohn's disease, bronchial asthma and peritumoral brains edemas." Additional recent studies have confirmed the effectiveness of Boswellia in the treatment of asthma[91] and ulcerative colitis.[92] Minor gastrointestinal upset has been reported. Products are generally standardized to contain 37.5–65% boswellic acids, which are currently considered the active constituents with clinical benefit. The target dose is approximately 150 mg of boswellic acids thrice daily; dose and number of capsules/tablets will vary depending upon the concentration found in differing products. Lower doses are effective when used as a part of a comprehensive, multicomponent treatment plan.

Devil's Claw (Harpagophytum procumbens): *Harpagophytum* has a long history of use in the treatment of musculoskeletal complaints, and recent clinical trials have substantiated its role as a moderately effective analgesic suitable for clinical utilization. At least 12 clinical trials have been published on the use of *Harpagophytum* in

International Journal of Human Nutrition and Functional Medicine (ISSN 2378-4881) ICHNFM.ORG/journal

Paradigm Shift • **Clinical Nutrition** • Primary Care • Prevention • Medicine • Metabolism • Politics

Vitamin D Bolus Reconsidered: Physiologic Dosing *versus* Pandemic Consequences of Codified Confusion

Alex Vasquez DO DC ND (USA) FACN

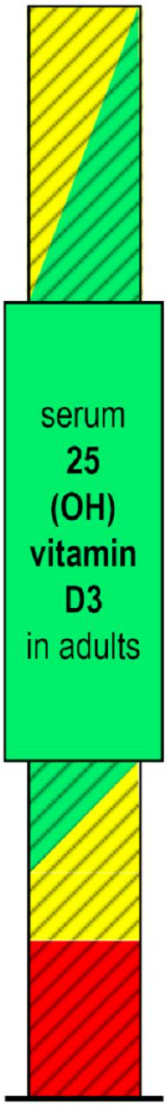
Vitamin D: Metabolism Dogma

The "vitamin D metabolism dogma"—as discussed here and familiar to many adults—is that vitamin D is produced in the skin following the exposure of intradermal (7-

the dogma of "vitamin D toxicity from physiologic dosages." Any one of these five citations was more than sufficient scientifically to shift the paradigm of perception and patient care, but intellectual inertia and drug-centered dogma have

statistically attributed to vitamin D insufficiency and could potentially be avoided by eliminating vitamin D insufficiency. ... Given the dynamics of the COVID-19 pandemic and the proven safety of vitamin D supplementation, it therefore appears highly debatable and potentially even unethical to await results of such trials before public health action is taken." Governmental/medical failure to implement population-wide physiologic dosing of vitamin D3 or 25(OH)D (both of which are found in foods and can thus be categorized as nutritional supplements) is medically unethical and socially irresponsible and will continue to result in unnecessary deaths, infections, falls, fractures, chronic pain, drug dependence, inflammatory diseases, diabetes, neuropsychiatric complications and mental depression—all of which could have been avoided with simple, affordable, and available vitamin D supplementation. Forcing populations to live quarantined in "lockdown" conditions deprives them of sunshine-dependent vitamin D production, and we can expect catastrophic consequences to manifest, the most obvious and immediate of which will be mental depression and vulnerability to infectious diseases.

Oh, the misanthropic irony, disguised as public health! **With quarantines/lockdowns and canceled summer vacations, millions of people have been forced into worsened vitamin D deficiency under the pretense of "protecting them" from a viral infection that thrives among and preferentially kills people who are vitamin D deficient.**



Pharmacologic dosing (eg, cancer, multiple sclerosis): 200–300 ng/mL (500–750 nmol/L)
Requires professional supervision, diet modification, laboratory surveillance per Charoenngam and Holick, *Nutrients* 2020 Jul

Potentially toxic if accompanied by clinical hypercalcemia: > 150 ng/mL (325 nmol/L)
per Grant and Holick, *Altern Med Rev* 2005 Jun

Supraphysiologic: > 100 ng/mL (250 nmol/L)
Higher levels of 25-hydroxy-cholecalciferol are clinically problematic if accompanied by hypercalcemia, calcinosis or urolithogenic hypercalciuria (especially with alkaline urine). Levels above 90-100 ng/mL (225-250 nmol/L) are generally supraphysiologic, but not inherently problematic.

Optimal physiologic range: 50-90 ng/mL (125-225 nmol/L)
Clinical example: prevention/treatment of SAS-2 coronavirus per "Participants were randomised to receive daily 60 000 IU of [Vit D3]... cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml..." per Rastogi et al. *Postgrad Med J* 2020 Nov
Populations in sunny climates (Grant and Holick, *Altern Med Rev* 2005 Jun): pregnant rural Africans 58 ng/mL (147 nmol/L) per Luxwolda, *Eur J Nutr* 2013 Apr; USA or Israel lifeguards 59-65 ng/mL (148-163 nmol/L), farmers in Puerto Rico 90 ng/mL (225 nmol/L) per Vieth, *Am J Clin Nutr* 1999 May
Review: Clinical importance of vitamin D: paradigm shift with implications for all healthcare providers. *Altern Therap Health Med* 2004 Sep
Context: Supplemented Paleo-Mediterranean Diet. *Nutritional Perspectives* 2011 Jan academia.edu/39751813

Sufficiency (more health, less depression): 40-50 ng/mL (100-125 nmol/L)
Clinical example: enhanced well-being at 40g/ml, reduced use of antidepressant drugs per Bergman et al, *BMC Res Notes* 2015 Sep
Populations: nonpregnant rural Africans 46 ng/mL (115 nmol/L) per Luxwolda et al, *Eur J Nutr* 2013 Apr

Marginal sufficiency, increased mortality: < 30-40 ng/mL (75-100 nmol/L)
Garland et al, *Am J Public Health* 2014 Aug

Insufficiency (increased PTH, respiratory infections, ARDS): < 32 ng/mL (80 nmol/L)
Requires 114 mcg/d (4600 IU/d), per Heaney et al, *Am J Clin Nutr* 2003 Jan

Depletion (osteomalacia, chronic pain, weakness, infections): < 20 ng/mL (50 nmol/L)
Persistent, nonspecific musculoskeletal pain per Plotnikoff and Quigley, *Mayo Clin Proc* 2003 Dec

the treatment of musculoskeletal pain, and all trials have found the botanical to be clinically valuable and with adverse effects comparable to placebo.[93] *Harpagophytum's* clinical benefit appears to derive chiefly from its analgesic effect, since administration of the herb does not alter eicosanoid production in humans. In patients with osteoarthritis of the hip and knee, *Harpagophytum* is just as effective yet safer and better tolerated than the drug diacerhein.[94,95] In a study involving 183 patients with low-back pain, *Harpagophytum* was found to be safe and moderately effective in patients with "severe and unbearable pain" and radiating pain with neurologic deficit.[96] Most recently, *Harpagophytum* was studied in a head-to-head clinical trial with the formerly popular but dangerous selective cox-2 inhibitor Vioxx (rofecoxib); the data indicate that *Harpagophytum* was safer and at least as effective.[97] About 8% of patients may experience diarrhea or other mild gastrointestinal effects, and fewer patients may experience dizziness; *Harpagophytum* may potentiate anticoagulants. Treatment should be continued for at least 4 weeks, and many patients will continue to improve after 8 weeks from the initiation of treatment.[98] Products are generally standardized for the content of harpagosides, with a target dose of at least 30 and up to 60 mg harpagoside per day. However, the whole plant is considered to contain effective constituents, not only the iridoid glycosides. Chrubasik[99] noted that while *Harpagophytum* appears to be safe and moderately effective for the treatment musculoskeletal pain, different proprietary products show significant variances in potency and clinical effectiveness. Data suggest that *Harpagophytum* is better than placebo and at least as good as commonly used NSAIDs, suggesting that Harpagophytum should be clinically preferred over NSAIDs due to the lower cost and what appears to be greater safety.

Willow bark (Salix spp): In a double-blind placebo-controlled clinical trial in 210 patients with moderate/severe low-back pain (20% of patients had positive straight-leg raising test), extract of willow bark showed a dose-dependent analgesic effect with benefits beginning in the first week of treatment.[100] In a head-to-head study of 228 patients comparing willow bark (standardized for 240 mg salicin) with Vioxx (rofecoxib), treatments were equally effective yet willow bark was safer and 40% less expensive.[101] Actions of willow bark are manifold including anti-oxidative, anti-cytokine, along with cyclooxygenase- and lipoxygenase-inhibiting effects. A non-purified extract of the phytomedicinal is required for full clinical benefit. The daily dose should not exceed 240 mg of salicin, and products should include other components of the whole plant. Except for rare allergy, no adverse effects are known, yet use during pregnancy and with anti-coagulant medication is discouraged.

SPINAL MANIPULATION: MECHANISMS OF ACTION AND SYNERGISM WITH NUTRITIONAL/BOTANICAL INTERVENTIONS

Select nutritional interventions as surveyed in this paper may have enhanced effects and benefits when combined with spinal manipulative therapy. For example, enhanced respiratory burst clearly carries both antitumor and antimicrobial benefits, and this physiologic effect can be induced by oral consumption of proteolytic enzymes as well as by chiropractic spinal manipulative therapy.[102] Likewise, we would expect synergism between spinal manipulative therapy[103] and nutritional[104] and botanical (e.g., Boswellia) interventions in the treatment of asthma, particularly since these treatments are mediated primarily via different mechanisms—namely the neurophysiologic inhibition of neurogenic inflammation and the biochemical reduction in pro-inflammatory mediators such as leukotrienes, respectively. As a final example, synergism would be expected in the treatment of low-back pain when spinal manipulation, therapeutic exercise, proprioceptive retraining, oral vitamin D supplementation, and botanical medicines such as *Harpagophytum* and Willow Bark are used together in holistic, integrative, multicomponent treatment plans.[105] Taken together, these data form an integrative model that incorporates and mechanistically validates the chiropractic "triad of health" which appreciates the interconnectedness of physical, biochemical, and neurologic aspects of human physiology.[105]

CONCLUSIONS

The chiropractic profession continues to develop and mature over time and with advances in research that further our understanding of health and disease and the value of diet, nutrition, exercise, spinal manipulation and other natural therapeutics. In contrast to our allopathic counterparts, chiropractic and naturopathic physicians are the only healthcare providers trained to consider each patient as an integrated being and to give specific attention to the physiological and biochemical aspects of health and disease, including structural, spinal, musculoskeletal, neurological, vascular, nutritional, emotional and environmental relationships.[106] The anti-inflammatory and analgesic nutritional and botanical medicines described in this review are generally appropriate for the treatment of inflammatory and degenerative musculoskeletal conditions, and they comprise an attractive alternative to the too-often lethal effects of pharmacologic anti-inflammatory and anti-rheumatic drugs.

If we consider that medical/surgical interventions result in an excess of 110,000 – 225,000 iatrogenic American deaths each year,[107,108] we could reasonably conclude that

undue restriction of chiropractic and naturopathic physicians to practice preventive healthcare and the discriminatory legal and financial barriers that inhibit patients from accessing alternatives to drugs and surgery ultimately deny patients' access to safe, effective, cost-effective, empowering, affordable healthcare by simultaneously restricting them to interventions that carry greater risk for harm and greater financial expense. With ever-increasing costs and ever-worsening health outcomes, the American healthcare system is destined for collapse unless we change the model upon which our healthcare system is founded—namely the belief that surgery and chemical drugs are the solutions to chronic diseases induced by nutritional deficiencies, oxidative stress, impaired detoxification, defects in fatty acid metabolism, altered gastrointestinal function, and neuromusculoskeletal dysfunction. We have reached an irrevocable impasse in which our current healthcare system dominated by drugs and surgery is no longer consistent with the balance of scientific research.[109] The time has come for patients and practitioners of natural healthcare to demand change and equitable access within the healthcare arena.

ABOUT THE AUTHOR:

Dr. Alex Vasquez is a licensed naturopathic physician in Washington and Oregon, and licensed chiropractor in Texas, where he maintains a private practice and is a member of the Research Team at Biotics Research Corporation. As former Adjunct Professor of Orthopedics and Rheumatology for the Naturopathic Medicine Program at Bastyr University, he is the author of more than 20 published articles and a recently published 486-page textbook for the chiropractic and naturopathic professions, "Integrative Orthopedics: The Art of Creating Wellness While Managing Acute and Chronic Musculoskeletal Disorders" available from OptimalHealthResearch.com.

ACKNOWLEDGEMENTS:

Pepper Grimm BA of Biotics Research Corporation reviewed the draft of this manuscript before submission.

REFERENCES:

1. Legorreta AP, Metz RD, Nelson CF, Ray S, Chernicoff HO, Dinubile NA. Comparative analysis of individuals with and without chiropractic coverage: patient characteristics, utilization, and costs. Arch Intern Med. 2004;164:1985-92
2. Bloomgarden ZT. Type 2 diabetes in the young: the evolving epidemic. Diabetes Care. 2004;27:998-1010
3. Nelson R. US infant mortality shows first rise in 40 years. Lancet. 2004;363(9409):626
4. Zack MM, Moriarty DG, Stroup DF, Ford ES, Mokdad AH. Worsening trends in adult health-related quality of life and self-rated health-United States, 1993-2001. Public Health Rep. 2004;119:493-505
5. Weir HK, Thun MJ, Hankey BF, Ries LA, Howe HL, Wingo PA, Jemal A, Ward E, Anderson RN, Edwards BK. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst. 2003;95(17):1276-99
6. US health care: a state lottery? Lancet. 2004 Nov 20;364(9448):1829-30
7. Legorreta AP, Metz RD, Nelson CF, Ray S, Chernicoff HO, Dinubile NA. Comparative analysis of individuals with and without chiropractic coverage: patient characteristics, utilization, and costs. Arch Intern Med. 2004;164:1985-92
8. Orme-Johnson DW, Herron RE. An innovative approach to reducing medical care utilization and expenditures. Am J Manag Care. 1997 Jan;3(1):135-44
9. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med. 1998;105(1B):31S-38S
10. Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. N Engl J Med. 2004 Oct 21;351(17):1707-9
11. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286(8):954-9
12. Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. N Engl J Med. 2004;351(26):2767
13. "Patients in the clinical trial taking 400 mg. of Celebrex twice daily had a 3.4 times greater risk of CV events compared to placebo. For patients in the trial taking 200 mg. of Celebrex twice daily, the risk was 2.5 times greater. The average duration of treatment in the trial was 33 months." FDA Statement on the Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex.http://www.fda.gov/bbs/topics /news/2004/NEW01144.html Available on January 4, 2005
14. "Preliminary information from the study showed some evidence of increased risk of cardiovascular events, when compared to placebo, to patients taking naproxen." FDA Statement on Naproxen. http://www.fda.gov/bbs/topics/news/2004/NEW01148.html Available on January 4, 2005
15. Monsanto, Pfizer celebrate Celebrex. St. Louis Business Journal. July 20, 1999
16. Markowitz GS, Falkowitz DC, Isom R, Zaki M, Imaizumi S, Appel GB, D'Agati VD. Membranous glomerulopathy and acute interstitial nephritis following treatment with celecoxib. Clin Nephrol. 2003;59(2):137-42
17. Grieco A, Miele L, Giorgi A, Civello IM, Gasbarrini G. Acute cholestatic hepatitis associated with celecoxib. Ann Pharmacother. 2002;36(12):1887-9
18. Berger P, Dwyer D, Corallo CE. Toxic epidermal necrolysis after celecoxib therapy. Pharmacotherapy. 2002 Sep;22(9): 1193-5

19. Lenzer J. Pfizer criticised over delay in admitting drug's problems. BMJ. 2004;329(7472):935
20. The Growth of Chiropractic and CAM: More Bad News for Medicine. Dynamic Chiropractic October 8, 2001, Volume 19, Issue 21 http://www.chiroweb.com/archives/19/21 /03.html accessed November 11, 2004
21. Kessler RC, Davis RB, Foster DF, Van Rompay MI, Walters EE, Wilkey SA, Kaptchuk TJ, Eisenberg DM. Long-term trends in the use of complementary and alternative medical therapies in the United States. Ann Intern Med. 2001 Aug 21;135(4):262-8
22. Segasothy M, Chin GL, Sia KK, Zulfiqar A, Samad SA. Chronic nephrotoxicity of anti-inflammatory drugs used in the treatment of arthritis. Br J Rheumatol. 1995 Feb; 34(2): 162-5
23. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM. 2003 Nov;96(11): 787-91
24. Blower AL. Considerations for nonsteroidal anti-inflammatory drug therapy: safety. Scand J Rheumatol Suppl. 1996;105:13-24
25. Prathapkumar KR, Smith I, Attara GA. Indomethacin induced avascular necrosis of head of femur. Postgrad Med J. 2000 Sep; 76(899): 574-5
26. Newman NM, Ling RS. Acetabular bone destruction related to non-steroidal anti-inflammatory drugs. Lancet. 1985 Jul 6; 2(8445): 11-4
27. Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. Am J Med. 1987; 83(5A): 29-34
28. "Systolic blood pressure increased significantly in 17% of rofecoxib- compared with 11% of celecoxib-treated patients (P = 0.032) at any study time point." Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM; SUCCESS VI Study Group.Cyclooxygenase-2—specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther 2001 Mar-Apr;8(2):85-95
29. Thie NM, Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: a randomized double blind controlled 3 month clinical trial. J Rheumatol. 2001;28(6):1347-55
30. Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. Br J Sports Med. 2003;37(1):45-9
31. Matheson AJ, Perry CM. Glucosamine: a review of its use in the management of osteoarthritis. Drugs Aging. 2003; 20(14): 1041-60
32. Uebelhart D, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage. 2004;12:269-76
33. van Blitterswijk WJ, van de Nes JC, Wuisman PI. Glucosamine and chondroitin sulfate supplementation to treat symptomatic disc degeneration: biochemical rationale and case report. BMC Complement Altern Med. 2003;3(1):2
34. Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol. 1996;23(8):1385-91
35. Mazieres B, Combe B, Phan Van A, Tondut J, Grynfeltt M. Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study. J Rheumatol. 2001;28(1):173-81
36. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001;357(9252):251-6
37. Adams ME. Hype about glucosamine. Lancet. 1999;354(9176):353-4
38. Cumming A. Glucosamine in osteoarthritis. Lancet. 1999;354(9190):1640-1
39. Rovati LC, Annefeld M, Giacovelli G, Schmid K, Setnikar I. Glucosamine in osteoarthritis. Lancet. 1999;354(9190):1640
40. Scroggie DA, Albright A, Harris MD. The effect of glucosamine-chondroitin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. Arch Intern Med. 2003;163(13):1587-9
41. Morrison LM. Treatment of coronary arteriosclerotic heart disease with chondroitin sulfate-A: preliminary report. J Am Geriatr Soc. 1968;16(7):779-85
42. Morrison LM, Branwood AW, Ershoff BH, Murata K, Quilligan JJ Jr, Schjeide OA, Patek P, Bernick S, Freeman L, Dunn OJ, Rucker P. The prevention of coronary arteriosclerotic heart disease with chondroitin sulfate A: preliminary report. Exp Med Surg. 1969;27(3):278-89
43. Morrison LM, Bajwa GS. Absence of naturally occurring coronary atherosclerosis in squirrel monkeys (Saimiri sciurea) treated with chondroitin sulfate A. Experientia. 1972 Dec 15;28(12):1410-1
44. Morrison LM, Enrick N. Coronary heart disease: reduction of death rate by chondroitin sulfate A. Angiology. 1973 May;24(5):269-87
45. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc. 2003;78(12):1463-70
46. Masood H, Narang AP, Bhat IA, Shah GN. Persistent limb pain and raised serum alkaline phosphatase the earliest markers of subclinical hypovitaminosis D in Kashmir. Indian J Physiol Pharmacol. 1989;33:259-61
47. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low-back pain in Saudi Arabia. Spine. 2003;28:177-9
48. Holick MF. Vitamin D deficiency: what a pain it is. Mayo Clin Proc. 2003 Dec;78(12):1457-9
49. Timms PM, Mannan et al.. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic

disorders? QJM. 2002;95:787-96
50. Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab. 2003;88(10):4623-32
51. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004;79(3):362-71
52. Heaney RP. Vitamin D, nutritional deficiency, and the medical paradigm. J Clin Endocrinol Metab. 2003;88(11):5107-8
53. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr. 2004;79(5):717-26
54. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77(1):204-10
55. Vasquez A, Manso G, Cannell J. The Clinical Importance of Vitamin D (Cholecalciferol): A Paradigm Shift with Implications for All Healthcare Providers. Alternative Therapies in Health and Medicine 2004; 10: 28-37
56. O'Leary JA, Klainer LM, Neuwirth RS. The management of hypoparathyroidism in pregnancy. Am J Obstet Gynecol. 1966;94(8):1103-7
57. Goodenday LS, Gordon GS. No risk from vitamin D in pregnancy. Ann Intern Med. 1971;75(5):807-8
58. Beard J. The action of trypsin upon the living cells of Jensen's mouse-tumour. Br Med J 1906; 4 (Jan 20): 140-1
59. Cutfield A. Trypsin Treatment in Malignant Disease. Br Med J. 1907; 5: 525
60. Wiggin FH. Case of Multiple Fibrosarcoma of the Tongue, With Remarks on the Use of Trypsin and Amylopsin in the Treatment of Malignant Disease." Journal of the American Medical Association 1906; 47: 2003-8
61. Goeth RA. Pancreatic treatment of cancer, with report of a cure. Journal of the American Medical Association 1907; (March 23) 48: 1030
62. Campbell JT. Trypsin Treatment of a Case of Malignant Disease. Journal of the American Medical Association 1907; 48: 225-226
63. Saruc M, Standop S, Standop J, Nozawa F, Itami A, Pandey KK, Batra SK, Gonzalez NJ, Guesry P, Pour PM. Pancreatic enzyme extract improves survival in murine pancreatic cancer. Pancreas. 2004;28(4):401-12
64. Batkin S, Taussig SJ, Szekerezes J. Antimetastatic effect of bromelain with or without its proteolytic and anticoagulant activity. J Cancer Res Clin Oncol. 1988;114(5):507-8
65. Gotze H, Rothman SS. Enteropancreatic circulation of digestive enzymes as a conservative mechanism. Nature 1975; 257(5527): 607-609
66. Liebow C, Rothman SS. Enteropancreatic Circulation of Digestive Enzymes. Science 1975; 189(4201): 472-474
67. Zavadova E, Desser L, Mohr T. Stimulation of reactive oxygen species production and cytotoxicity in human neutrophils in vitro and after oral administration of a polyenzyme preparation. Cancer Biother. 1995;10(2):147-52
68. Maurer HR, Hozumi M, Honma Y, Okabe-Kado J. Bromelain induces the differentiation of leukemic cells in vitro: an explanation for its cytostatic effects? Planta Med. 1988 Oct;54(5):377-81
69. Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies. Evidence-based Complementary and Alternative Medicine. 2004;1(3)251–257
70. Gaspani L, Limiroli E, Ferrario P, Bianchi M. In vivo and in vitro effects of bromelain on PGE(2) and SP concentrations in the inflammatory exudate in rats. Pharmacology. 2002;65(2):83-6
71. Leipner J, Saller R. Systemic enzyme therapy in oncology: effect and mode of action. Drugs. 2000 Apr;59(4):769-80
72. Vellini M, Desideri D, Milanese A, Omini C, Daffonchio L, Hernandez A, Brunelli G. Possible involvement of eicosanoids in the pharmacological action of bromelain. Arzneimittelforschung. 1986;36(1):110-2
73. The trypsin treatment of cancer. British Medical Journal 1907; March 2: 519-20
74. Gonzalez NJ, Isaacs LL. Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. Nutr Cancer. 1999;33(2):117-24
75. Sakalova A, Bock PR, Dedik L, Hanisch J, Schiess W, Gazova S, Chabronova I, Holomanova D, Mistrik M, Hrubisko M. Retrolective cohort study of an additive therapy with an oral enzyme preparation in patients with multiple myeloma. Cancer Chemother Pharmacol. 2001 Jul;47 Suppl:S38-44
76. Popiela T, Kulig J, Hanisch J, Bock PR. Influence of a complementary treatment with oral enzymes on patients with colorectal cancers—an epidemiological retrolective cohort study. Cancer Chemother Pharmacol. 2001;47 Suppl:S55-63
77. Taussig SJ, Yokoyama MM, Chinen A, Onari K, Yamakido M. Bromelain: a proteolytic enzyme and its clinical application. A review. Hiroshima J Med Sci. 1975;24(2-3):185-93
78. Taub SJ. The use of bromelains in sinusitis: a double-blind clinical evaluation. Eye Ear Nose Throat Mon. 1967 Mar;46(3):361-5
79. Trickett P. Proteolytic enzymes in treatment of athletic injuries. Appl Ther. 1964;30:647-52
80. Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults.Phytomedicine.2002;9:681-6
81. Walker JA, Cerny FJ, Cotter JR, Burton HW. Attenuation of contraction-induced skeletal muscle injury by bromelain. Med Sci Sports Exerc. 1992 Jan;24(1):20-5
82. Kaufman W. Niacinamide therapy for joint mobility. Therapeutic reversal of a common clinical manifestation of the "normal" aging process. Conn State Med J 1953;17:584-591
83. Kaufman W. The use of vitamin therapy to reverse cer-

tain concomitants of aging. J Am Geriatr Soc 1955;3:927-936
84. Matuoka K, Chen KY, Takenawa T. Rapid reversion of aging phenotypes by nicotinamide through possible modulation of histone acetylation. Cell Mol Life Sci. 2001;58(14):2108-16
85. Jonas WB, Rapoza CP, Blair WF. The effect of niacinamide on osteoarthritis: a pilot study. Inflamm Res 1996 Jul;45(7):330-4
86. McCarty MF, Russell AL. Niacinamide therapy for osteoarthritis—does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? Med Hypotheses. 1999;53(4):350-60
87. Gaby AR. Literature review and commentary: Niacinamide for osteoarthritis. Townsend Letter for Doctors and Patients. 2002: May; 32
88. Mohler H, Polc P, Cumin R, Pieri L, Kettler R. Nicotinamide is a brain constituent with benzodiazepine-like actions. Nature. 1979; 278(5704): 563-5
89. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. Phytomedicine. 2003 Jan;10(1):3-7
90. Ammon HP. [Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases] [Article in German] Wien Med Wochenschr. 2002;152(15-16):373-8
91. Gupta I, Gupta V, Parihar A, Gupta S, Ludtke R, Safayhi H, Ammon HP. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res. 1998 Nov 17;3(11):511-4
92. Gupta I, Parihar A, Malhotra P, Singh GB, Ludtke R, Safayhi H, Ammon HP. Effects of Boswellia serrata gum resin in patients with ulcerative colitis. Eur J Med Res. 1997 Jan;2(1):37-43
93. Gagnier JJ, Chrubasik S, Manheimer E. Harpgophytum procumbens for osteoarthritis and low-back pain: a systematic review. BMC Complement Altern Med. 2004 Sep 15;4(1):13
94. Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine 2000;7(3):177-83
95. Leblan D, Chantre P, Fournie B. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. Joint Bone Spine 2000;67(5):462-7
96. Chrubasik S, Junck H, Breitschwerdt H, Conradt C, Zappe H. Effectiveness of Harpagophytum extract WS 1531 in the treatment of exacerbation of low-back pain: a randomized, placebo-controlled, double-blind study. Eur J Anaesthesiol 1999 Feb;16(2):118-29
97. Chrubasik S, Model A, Black A, Pollak S. A randomized double-blind pilot study comparing Doloteffin and Vioxx in the treatment of low-back pain. Rheumatology (Oxford). 2003 Jan;42(1):141-8 See www.WellBody-Book.com/articles.htm for the full-text of this article.
98. Chrubasik S, Thanner J, Kunzel O, Conradt C, Black A, Pollak S. Comparison of outcome measures during treatment with the proprietary Harpagophytum extract doloteffin in patients with pain in the lower back, knee or hip. Phytomedicine 2002 Apr;9(3):181-94
99. Chrubasik S, Conradt C, Roufogalis BD. Effectiveness of Harpagophytum extracts and clinical efficacy. Phytother Res. 2004 Feb;18(2):187-9
100. Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. Treatment of low-back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med. 2000;109:9-14
101. Chrubasik S, Kunzel O, Model A, Conradt C, Black A. Treatment of low-back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low-back pain. Rheumatology (Oxford). 2001;40:1388-93
102. Brennan PC, Triano JJ, McGregor M, Kokjohn K, Hondras MA, Brennan DC. Enhanced neutrophil respiratory burst as a biological marker for manipulation forces: duration of the effect and association with substance P and tumor necrosis factor. J Manipulative Physiol Ther. 1992 Feb;15(2):83-9
103. Balon J, Aker PD, Crowther ER, Danielson C, Cox PG, O'Shaughnessy D, Walker C, Goldsmith CH, Duku E, Sears MR. A comparison of active and simulated chiropractic manipulation as adjunctive treatment for childhood asthma. N Engl J Med. 1998 Oct 8;339(15):1013-20
104. Vasquez A. Reducing Pain and Inflammation Naturally. Part 2: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression. Nutr Perspect 2005; January: 5-16
105. Vasquez A. Integrative Orthopedics: The Art of Creating Wellness While Managing Acute and Chronic Musculoskeletal Disorders. Houston; Natural Health Consulting Corporation. (OptimalHealthResearch.com): 2004
106. American Chiropractic Association. What is Chiropractic? http://amerchiro.org/media/whatis/ Accessed January 9, 2005
107. Starfield B. Is US health really the best in the world? JAMA. 2000 Jul 26;284(4):483-5
108. Holland EG, Degruy FV. Drug-induced disorders. Am Fam Physician. 1997 Nov 1;56(7):1781-8, 1791-2
109. Hyman M. Paradigm shift: the end of "normal science" in medicine understanding function in nutrition, health, and disease. Altern Ther Health Med. 2004;10(5):10-5, 90-4

Inflammation Mastery

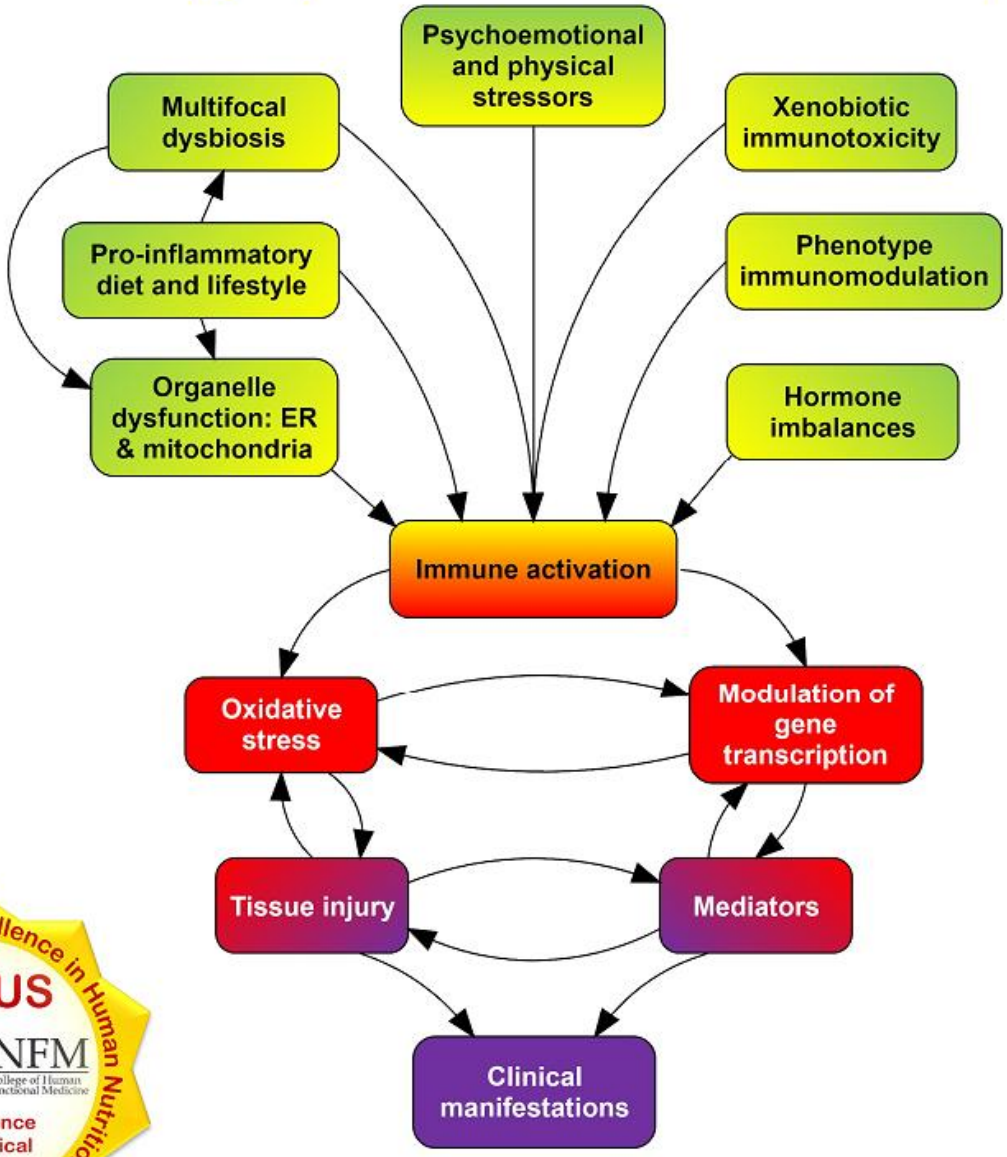
4th Edition

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

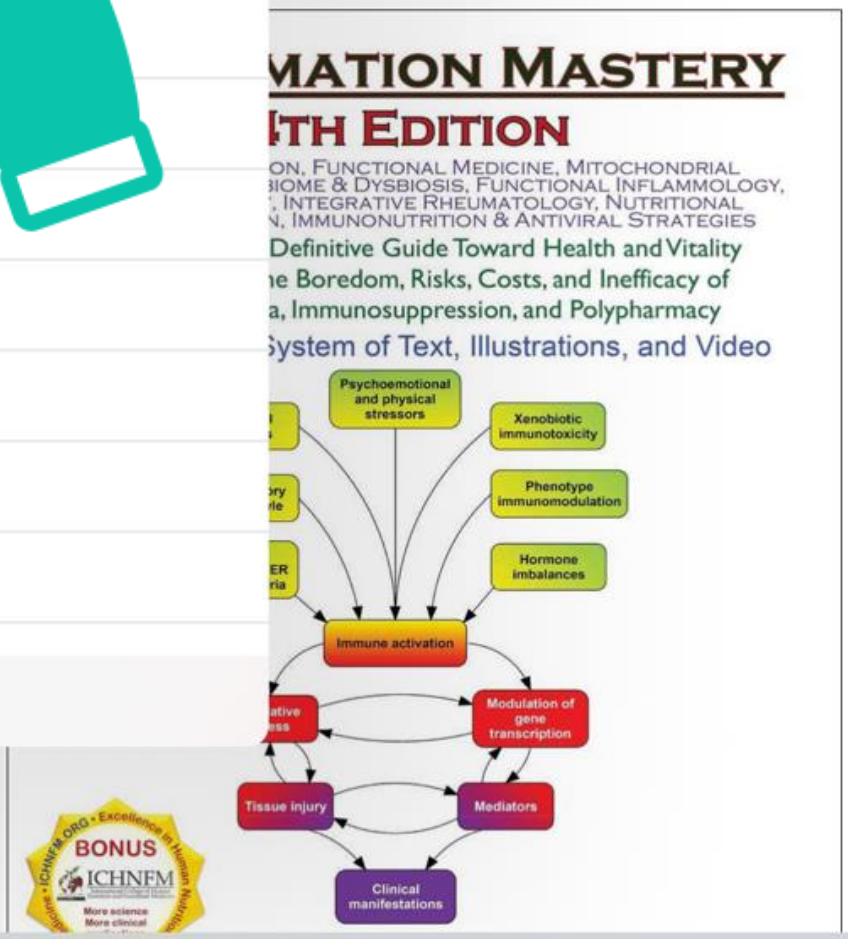
3-Part Learning System of Text, Illustrations, and Video



Dr. Alex Vasquez

ICHNFM.ORG

International College of Human Nutrition and Functional Medicine



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.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 2 hours.

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 implement vitamin D supplementation in proper doses and with appropriate laboratory monitoring

Reprint requests: InnoVision Communications, 169 Saxony Rd, Suite 103, Encinitas, CA 92024; phone, (760) 633-3910 or (866) 828-2962; fax, (760) 633-3918; e-mail, alternative.therapies@innerdoorway.com. Or visit our online CME Web site by going to http://www.alternative-therapies.com and selecting the Continuing Education option.

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 that higher vitamin D levels provide protection from diabetes mellitus, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, several autoimmune diseases, and cancers of the breast, prostate, and colon, we can now utilize vitamin D for a wider range of preventive and therapeutic applications to maintain and improve our patients' health.[3] Based on the research reviewed in this article, the current authors believe that assessment of vitamin D status and treatment of vita-

min D deficiency with oral vitamin D supplements should become a routine component of clinical practice and preventive medicine. Vitamin D supplementation with doses of 4,000 IU/day for adults is clinically safe and physiologically reasonable since such doses are consistent with physiologic requirements.[2] Higher doses up to 10,000 IU/day appear safe and produce blood levels of vitamin D that are common in sun-exposed equatorial populations.[1,2] Periodic assessment of serum 25-OH-vitamin D [25(OH)D] and serum calcium will help to ensure that vitamin D levels are sufficient and safe for health maintenance and disease prevention. Clinical research supporting the use of vitamin D in the management of type 2 diabetes, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, multiple sclerosis, polycystic ovary syndrome, musculoskeletal pain, depression, epilepsy, and the prevention of cancer and type 1 diabetes is presented along with our proposals for the interpretation of serum 25(OH)D laboratory values, for the design of future research studies, and for supplementation in infants, children, adults, and during pregnancy and lactation.

BASIC PHYSIOLOGY OF VITAMIN D

Vitamin D is obtained naturally from two sources: sunlight and dietary consumption. Vitamin D3 (cholecalciferol) is the form of vitamin D produced in the skin and consumed in the diet. Vitamin D2 (ergocalciferol), which is produced by irradiating fungi, is much less efficient as a precursor to the biologically active 1,25-dihydroxyvitamin D (calcitriol). Additionally, since ergocalciferol shows altered pharmacokinetics compared with D3 and may become contaminated during its microbial production, it is potentially less effective and more toxic than cholecalciferol.[4] Although ergocalciferol is occasionally used clinically and in research studies, cholecalciferol is the preferred form of supplementation and will be implied in this article when supplementation is discussed.

Vitamin D can be described as having two pathways for metabolism: one being "endocrine" and the other "autocrine" (within the cell) and perhaps "paracrine" (around the cell). This elucidation, recently reviewed by Heany,[5] is vitally important in expanding our previously limited conception of vitamin D from only a "bone nutrient with importance only for the prevention of rickets and osteomalacia" to an extraordinary molecule with far-reaching effects in a variety of cells and tissues. Furthermore, Heany's distinction of "short-latency deficiency diseases" such as rickets from "long-latency deficiency diseases" such as cancer provides a conceptual handle that helps us grasp an understanding of the differences between the acute manifestations of severe nutritional deficiencies and the delayed manifestations of chronic subclinical nutritional deficiencies.[5]

In its endocrine metabolism, vitamin D (cholecalciferol) is formed in the skin following exposure to sunlight and then travels in the blood to the liver where it is converted to 25-hydroxyvitamin D (calcidiol, 25(OH)D) by the enzyme vitamin D-25-hydroxylase. 25(OH)D then circulates to the kidney for its final transformation to 1,25-dihydroxyvitamin D (calcitriol) by 25-hydroxyvitamin D3-1alpha-hydroxylase (1-OHase).[6] Calcitriol is the most biologically active form of vitamin D and increases calcium and phosphorus absorption in the intestine, induces osteoclast maturation for bone remodeling, and promotes calcium deposition in bone and a reduction in parathyroid hormone (PTH). While increased calcium absorption is obviously important for nutritional reasons, suppression of PTH by vitamin D is also clinically important since relatively lower levels of PTH appear to promote and protect health, and higher levels of PTH correlate with increased risk for myocardial infarction, stroke, and hypertension.[7,8] Relatedly, Fujita[9] proposed the "calcium paradox" wherein vitamin D or calcium deficiency leads to elevations of PTH which increases intracellular calcium and may thereby promote a cascade of cellular dysfunction that can contribute to the development of diabetes mellitus, neurologic diseases, malignancy, and degenerative joint disease.

In its autocrine metabolism, circulating 25(OH)D is taken up by a wide variety of cells that contain both 1-OHase as well as nuclear vitamin D receptors (VDR). Therefore, these cells are able to make their own calcitriol rather than necessarily relying upon hematogenous supply. Cells and tissues that are known to contain 1-OHase, and which therefore make their own calcitriol, include the breast, prostate, lung, skin, lymph nodes, colon, pancreas, adrenal medulla, and brain (cerebellum and cerebral cortex).[3,10] Cells and tissues with nuclear, cytosolic, or membrane-bound VDR include islet cells of the pancreas, monocytes, transformed B-cells, activated T-cells, neurons, prostate cells, ovarian cells, pituitary cells, and aortic endothelial cells.[11] Indeed, given the wide range of cells and tissues that metabolize vitamin D in an autocrine manner, we see that there is biological potential for vitamin D to influence function and pathophysiology in a wide range of metabolic processes and disease states.

Since many cells and tissues of the body have the ability to metabolize vitamin D, we should not be surprised that vitamin D plays a role in the function of these cells. Calcitriol is known to modulate transcription of several genes, notably those affecting differentiation and proliferation such as c-myc, c-fos, and c-sis,[6] and this may partially explain the inverse relationship between sun exposure (eg, vitamin D) and cancer mortality.[12,13] Vitamin D appears to modulate neurotransmitter/neurologic function as shown by its antidepressant[14] and anticonvulsant[15] benefits. Vitamin D is obviously immunoregulatory as manifested by its ability to reduce inflammation,[16,17] suppress and/or prevent certain autoimmune diseases,[18-20] reduce the risk for cancer,[12] and possibly reduce the severity and frequency of infectious diseases, such as acute pneumonia in children.[21]

CLINICAL APPLICATIONS AND THERAPEUTIC BENEFITS OF VITAMIN D

Support for a broad range of clinical applications for vitamin D supplementation comes from laboratory experiments, clinical trials, and epidemiologic surveys. Despite the imperfections of current data, we can still see significant benefits from vitamin D supplementation in a variety of human diseases, as briefly reviewed below.

Cardiovascular Disease

Deaths from cardiovascular disease are more common in the winter, more common at higher latitudes and more common at lower altitudes, observations that are consistent with vitamin D insufficiency.[22] The risk of heart attack is twice as high for those with 25(OH)D levels less than 34 ng/ml (85 nmol/L) than for those with vitamin D status above this level.[23] Patients with congestive heart failure were recently found to have markedly lower levels of vitamin D than controls,[24] and vitamin D deficiency as a cause of heart failure has been documented in numerous case reports.[25-29]

Hypertension

It has long been known that blood pressure is higher in the winter than the summer, increases at greater distances from the equator and is affected by skin pigmentation—all observations consistent with a role for vitamin D in regulating blood pressure.[30] When patients with hypertension were treated with ultraviolet light three times a week for six weeks their vitamin D levels increased by 162%, and their blood pressure fell significantly.[31] Even small amounts of oral cholecalciferol (800 IU) for eight weeks lowered both blood pressure and heart rate.[32]

Type 2 Diabetes

Hypovitaminosis D is associated with insulin resistance and beta-cell dysfunction in diabetics and young adults who are apparently healthy. Healthy adults with higher serum 25(OH)D levels had significantly lower 60 min, 90 min and 129 min postprandial glucose levels and significantly better insulin sensitivity than those who were vitamin D deficient.[33] The authors noted that, compared with metformin, which improves insulin sensitivity by 13%, higher vitamin D status correlated with a 60% improvement in insulin sensitivity. In a recent clinical trial using 1,332 IU/day for only 30 days in 10 women with type 2 diabetes, vitamin D supplementation was shown to improve insulin sensitivity by 21%.[34]

Osteoarthritis

Many practitioners know that vitamin D helps prevent and treat osteoporosis, but few know that the progression of osteoarthritis, the most common arthritis, is lessened by adequate blood levels of vitamin D. Framingham data showed osteoarthritis of the knee progressed more rapidly in those with 25(OH)D levels lower than 36 ng/ml (90 nmol/L).[35] Another study found that osteoarthritis of the hip progressed more rapidly in those with 25(OH)D levels lower than 30 ng/ml (75 nmol/L).[36]

Multiple Sclerosis

The autoimmune/inflammatory disease multiple sclerosis (MS) is notably rare in sunny equatorial regions and becomes increasingly prevalent among people who live farther from the equator and/or who lack adequate sun exposure. In a clinical trial with 10 MS patients, Goldberg, Fleming, and Picard[19] prescribed daily supplementation with approximately 1,000 mg calcium, 600 mg magnesium, and 5,000 IU vitamin D (from 20 g cod liver oil) for up to two years and found a reduction in the number of exacerbations and an absence of adverse effects. This is one of very few studies in humans that employed sufficient daily doses of vitamin D (5,000 IU) and had sufficient duration (2 years). More recently, Mahon et al[37] gave 800 mg calcium and 1,000 IU vitamin D per day for six months to 39 patients with MS and noted a modest anti-inflammatory effect.

Prevention of Type 1 Diabetes

Type 1 diabetes is generally caused by autoimmune/inflammatory destruction of the pancreatic beta-cells. Vitamin D supplementation shows significant preventive and ameliorative benefits in animal models of type 1 diabetes. In a study with more than 10,000 participants, Hypponen et al[18] showed that supplementation in infants (less than one year of age) and children with 2,000 IU of vitamin D per day reduced the incidence of type 1 diabetes by approximately 80%. Relatedly, several studies using cod liver oil as a rich source of vitamin D have also documented significant reductions in the incidence of type 1 diabetes.

Depression

Seasonal affective disorder (SAD) is a particular subtype of depression characterized by the onset or exacerbation of melancholia during winter months when bright light, sun exposure, and serum 25(OH)D levels are reduced. Recently, a dose of 100,000 IU of vitamin D was found superior to light therapy in the treatment of SAD after one month.[38] Similarly, in a study involving 44 subjects, supplementation with 400 or 800 IU per day was found to significantly improve mood within five days of supplementation.[14]

Epilepsy

Seizures can be the presenting manifestation of vitamin D deficiency.[39] Hypovitaminosis D decreases the threshold for and increases the incidence of seizures, and several "anticonvulsant" drugs interfere with the formation of calcitriol in the kidney and further reduce calcitriol levels via induction of hepatic clearance. Therefore, antiepileptic drugs may lead to iatrogenic seizures by causing iatrogenic hypovitaminosis D.[40] Conversely, supplementation with 4,000–16,000 IU per day of vitamin D2 was shown to significantly reduce seizure frequency in a placebo controlled pilot study by Christiansen et al.[15]

Migraine Headaches

Calcium clearly plays a role in the maintenance of vascular tone and coagulation, both of which are altered in patients with migraine. Thys-Jacobs[41] reported two cases showing a reduction in frequency, duration, and severity of menstrual migraine attacks following daily supplementation with 1,200 mg of calcium and 1,200–1,600 IU of vitamin D in women with vitamin D deficiency.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a disease seen only in humans and is classically characterized by polycystic ovaries, amenorrhea, hirsuitism, insulin resistance, and obesity. Animal studies have shown that calcium is essential for oocyte activation and maturation. Vitamin D deficiency was highly prevalent among 13 women with PCOS, and supplementation with 1,500 mg of calcium per day and 50,000 IU of vitamin D2 on a weekly basis normalized menstruation and/or fertility in nine of nine women with PCOS-related menstrual irregularities within three months of treatment.[42]

Musculoskeletal Pain

Patients with non-traumatic, persistent musculoskeletal pain show an impressively high prevalence of overt vitamin D deficiency. Plotnikoff and Quigley[43] recently showed that 93% of their 150 patients with persistent, nonspecific musculoskeletal pain were overtly deficient in vitamin D. Masood et al[44] found a high prevalence of vitamin D deficiency in children with limb pain, and vitamin D supplementation ameliorated pain within three months. Al Faraj and Al Mutairi[45] found vitamin D deficiency in 83% of their 299 patients with low-back pain, and supplementation with 5,000–10,000 IU of vitamin D per day lead to pain reduction in nearly 100% of patients after three months.

Critical Illness and Autoimmune/Inflammatory Conditions

Deficiency of vitamin D is common among patients with inflammatory and autoimmune disorders and those with prolonged critical illness. In addition to the previously mentioned epidemic of vitamin D insufficiency in patients with MS, we also see evidence of vitamin D insufficiency in a large percentage of patients with Grave's disease,[46] ankylosing spondylitis,[47] systemic lupus erythematosus,[48] and rheumatoid arthritis.[20] Clinical trials with proper dosing and duration need to be performed in these patient groups. C-reactive protein was reduced by 23% and matrix metalloproteinase-9 was reduced by 68% in healthy adults following bolus injections of vitamin D that resulted in an average dose of 547 IU per day for 2.5 years.[17] A recent trial of vitamin D supplementation in patients with prolonged critical illness showed a significant and dose-dependent "anti-inflammatory effect" evidenced by reductions in IL-6 and CRP.[16] However, the insufficient dose of only 400 IU per day (administered intravenously) for only ten days precluded more meaningful and beneficial results, and we present guidelines for future studies later in this paper.

Cancer Prevention and Treatment

The inverse relationship between sunlight exposure and cancer mortality was documented by Apperly in 1941.[13] Vitamin D has anti-cancer effects mediated by anti-proliferative and proapoptotic mechanisms[3] which are augmented by modulation of nuclear receptor function and enzyme action,[49] and limited research shows that synthetic vitamin D analogs may have a role in the treatment of human cancers.[50] Grant[12] has shown that inadequate exposure to sunlight, and hence hypovitaminosis D, is associated with an increased risk of cancer mortality for several malignancies, namely those of the breast, colon, ovary, prostate, bladder, esophagus, kidney, lung, pancreas, rectum, stomach, uterus, and non-Hodgkin lymphoma. He proposes that adequate exposure to ultraviolet light and/or supplementation with vitamin D could save more than 23,000 American lives per year from a reduction in cancer mortality alone.

The aforementioned clinical trials using vitamin D in a wide range of health conditions have helped to expand our concept of vitamin D and to appreciate its manifold benefits. However, in light of new research showing that the physiologic requirement is 3,000–5,000 IU/day for adults and that serum levels plateau only after 3-4 months of daily supplementation,[2] we must conclude that studies using lower doses and/or shorter durations have underestimated the clinical efficacy of vitamin D. Guidelines for the critique and design of clinical trials are proposed later in this article to aid clinicians and researchers in evaluating and designing clinical studies for the determination of the therapeutic efficacy of vitamin D.

ASSESSMENT OF VITAMIN D STATUS WITH MEASUREMENT OF SERUM 25-OH-VITAMIN D

Current laboratory reference ranges for 25(OH)D were erroneously based on average serum levels for the "apparently healthy" nonrachitic, nonosteomalacic American population, a large proportion of which is vitamin D deficient. Currently, laboratories do not report optimal levels so they will mislead the practitioner unless he or she is aware of current research. For the majority of labs, the bottom of the reference range is set too low due to the previous underappreciation of the clinical benefits of and physiologic requirement for higher vitamin D levels, and the top of the range is too low due to previous misinterpretations of the research resulting in an overestimation of vitamin D toxicity.[1,2,51,52] Therefore, new reference ranges need to be determined based on the current research, and we present our proposals in Figure 1 and in the following outline:

- **Vitamin D Deficiency: less than 20 ng/mL (50 nmol/L).**

Serum 25(OH)D levels below 20 ng/mL (50 nmol/L) are clearly indicative of vitamin D deficiency. However, several authorities note that this level appears to be too low; Heaney[5] and Holick[51] both state that 25(OH)D levels should always be greater than 30 ng/mL (75 nmol/L).

- **Vitamin D Insufficiency: less than 40 ng/mL (100 nmol/L).**

According to Zittermann,[11] hypovitaminosis D, wherein tissue levels are depleted and PTH is slightly elevated, correlates with serum levels of 30–40 ng/mL (75–100 nmol/L). Independently, Dawson-Hughes et al[53] showed that serum levels of PTH begin to elevate when 25(OH)D levels fall below 45 ng/mL (110 nmol/L) in elderly men and women, and these findings were supported by Kinyamu et al[54] who found that optimal PTH status deteriorates when 25(OH)D levels fall below 49

ng/mL (122 nmol/L) in elderly women. Therefore, in order to maintain physiologic suppression of PTH, serum levels of 25(OH)D need to be greater than 40 ng/mL (100 nmol/L).

• Optimal Vitamin D Status: 40–65 ng/mL (100–160 nmol/L)

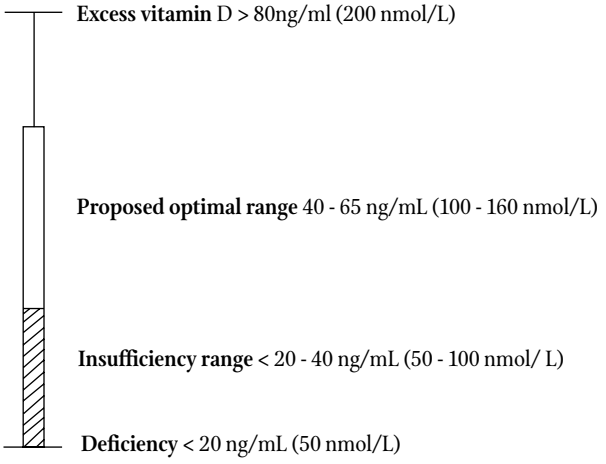
Based on our review of the literature, we propose that the optimal—"sufficient and safe"—range for 25(OH)D correlates with serum levels of 40–65 ng/mL (100–160 nmol/L).[55] This proposed optimal range is compatible with other published recommendations: Zittermann[11] states that serum levels of 40–80 ng/mL (100–200 nmol/L) are "adequate," and Mahon et al[37] recently advocated an optimal range of 40–100 ng/mL (100–250 nmol/L) for patients with multiple sclerosis. The lower end of our proposed range is consistent with suggestions by Mercola[56,57] who advocates an optimal range of 45–50 ng/mL (115–128 nmol/L) and by Holick[51] who states that levels should be 30–50 ng/mL (75–125 nmol/L). The upper end of our proposed optimal range is modified from the previously mentioned ranges offered by Zittermann[11] (up to 80 ng/mL [200 nmol/L]) and Mahon et al[37] (up to 100 ng/mL [250 nmol/L]). According to the authoritative monograph by Vieth,[1] there is no consistent, credible evidence of vitamin D toxicity associated with levels below 80–88 ng/mL (200 –220 nmol/L). Vieth[1] states, "Although not strictly within the 'normal' range for a clothed, sun-avoiding population, serum 25(OH)D concentrations of 220 nmol/L (88 ng/mL) are consistent with certain environments, are not unusual in the absence of vitamin D supplements, and should be regarded as being within the physiologic range for humans." Similarly, in his very thorough review of the literature, Zittermann[11] concludes that serum 25(OH)D concentrations up to 100 ng/mL (250 nmol/L) are subtoxic. Additional support for the safety of this upper limit comes from documentation that sun exposure alone can raise levels of 25(OH)D to more than 80 ng/mL (200 nmol/L)1 and that oral supplementation with 10,000 IU/day (mimicking endogenous production from sun exposure) in healthy men resulted in serum levels greater than 80 ng/mL (200 nmol/L) with no evidence of toxicity.[2] Until more data becomes available, we have chosen 65 ng/mL (160 nmol/L) rather than 80 ng/mL (200 nmol/L) as the upper end of the optimal range to provide a safety zone between the optimal level and the level which may possibly be associated with toxicity, and to allow for other factors which may promote hypercalcemia, as discussed below. Long-term prospective interventional studies with large groups and clinical trials involving patients with vitamin D-associated illnesses (listed above) will be needed in order to accurately define the optimal range—the serum level of vitamin D that affords protection from illness but which does not cause iatrogenic complications. In reviewing much of the current literature, we found no evidence of adverse effects associated with a 25(OH)D level of 65 ng/mL (160 nmol/L), and we found that this level is considered normal by some medical laboratories[6] and that it can be approximated and safely exceeded with frequent full-body exposure to ultraviolet light[1] or oral administration of physiologic doses of 5,000–10,000 IU cholecalciferol per day for 20 weeks.[2] Prospective studies and interventional clinical trials comparing different serum levels of 25(OH)D with clinical outcomes are necessary to elucidate the exact optimal range in various clinical conditions. While no acute or subacute risks are associated with the 25(OH)D levels suggested here, research shows clear evidence of long-term danger associated with vitamin D levels that are insufficient.

• Vitamin D Excess: Serum Levels Greater than 80 ng/mL (200 nmol/L) with Accompanying Hypercalcemia

Serum levels of 25(OH)D can exceed 80 ng/mL (200 nmol/L) with ultraviolet light exposure in the absence of oral vitamin D supplementation[1,6] and with oral supplementation with 10,000 IU per day as previously mentioned[2]—in neither scenario is toxicity observed. 25(OH)D greater than 80 ng/mL (200 nmol/L) are not indicative of toxicity unless accompanied by clinical manifestations and hypercalcemia. Vieth[1] notes that hypercalcemia due to hypervitaminosis D is always associated with serum 25(OH)D concentrations greater than 88 ng/mL (220 nmol/L), and Holick[6] previously stated, "Vitamin D intoxication does not occur until the circulating levels of 25(OH)D are over 125 ng/mL [312 nmol/L]." Assessment for hypervitaminosis D is performed by measurement of serum 25(OH)D and serum calcium.

MONITORING FOR VITAMIN D TOXICITY WITH 25(OH)D AND SERUM CALCIUM

Hypercalcemia can occur with vitamin D supplementation by either directly causing direct toxicity (rare) or by being associated with a vitamin D hypersensitivity syndrome (more common). If serum calcium becomes abnormally high, then vitamin D supplementation must be discontinued until the cause of the hypercalcemia is identified; however, direct vitamin D toxicity will rarely be the sole cause of the hypercalcemia.



***** Modified from: Vasquez A. *Integrative Orthopedics: Concepts, Algorithms, and Therapeutics.* Houston; Natural Health Consulting Corporation. 2004: 417-419 with permission.

FIGURE 1. Proposed normal and optimal ranges for serum 25(OH)D levels based on current research*****

The most important indicator of direct vitamin D toxicity is elevated serum calcium associated with a 25(OH)D level greater than 90 ng/ml (225 nmol/L). Elevated 1,25(OH)D levels are commonly—though not always—seen with vitamin D toxicity. Severe vitamin D intoxication is rare and usually seen only with industrial accidents, such as overdosing the fortification of milk, or with long-term administration of more than 40,000 IU of vitamin D per day. Severe hypercalcemia may require urinary acidification and corticosteroids to expedite the reduction in serum calcium.[58]

Induction of vitamin D toxicity generally requires 1–4 months of 40,000 IU per day in infants.[58] In adults, toxicity generally requires several months of supplementation of at least 100,000 IU per day. Hypercalcemia appears to be the mechanism of vitamin D toxicity (rather than a direct toxic effect of the vitamin), and 25-OH-vitamin D levels may be normal in patients who are vitamin D toxic and hypercalcemic, particularly with vitamin D hypersensitivity syndrome. It has therefore been suggested that serum calcium be measured on a weekly and then monthly basis in patients receiving high-dose vitamin D. Manifestations attributable to hypervitaminosis D and hypercalcemia include anorexia, nausea, and vomiting followed by weakness, nervousness, pruritus, polyuria, polydipsia, renal impairment, and soft-tissue calcifications.

As a cause of hypercalcemia, vitamin D hypersensitivity syndromes are more common than vitamin D toxicity, and they generally arise when aberrant tissue uncontrollably produces the most active form of the vitamin—calcitriol. Primary hyperparathyroidism, granulomatous disease (such as sarcoidosis, Crohn's disease, and tuberculosis) and various forms of cancer may cause the syndrome. 25(OH)D levels are normal or even low in vitamin D hypersensitivity while serum calcium and 1,25(OH)D levels are elevated. Additional causes include adrenal insufficiency, hyperthyroidism, hypothyroidism, and adverse drug effects, particularly with thiazide diuretics. Whatever the cause, patients with persistent hypercalcemia should discontinue vitamin D supplementation and receive a thorough diagnostic evaluation to determine the cause of the problem.

Interventional Strategies to Treat Vitamin D Deficiency by Increasing Serum Vitamin D Levels

Human physiology adapted to and was shaped by a natural environment with ample exposure to sunlight.[5, 61] Full-body exposure to ultraviolet light on clear days in equatorial latitudes can easily provide the equivalent of 4,000–20,000 IU of vitamin D.[1,61] Slightly longer durations of full-body sun exposure of approximately 30 minutes (3x the minimal erythemal dose) will produce 50,000 IU of vitamin D in lightly pigmented persons, while 5x longer durations are required for more darkly pigmented people to attain the same vitamin D production.[61] The oral dose of vitamin D required to obtain adequate blood levels depends on latitude, sun exposure, body weight, skin pigmentation, dietary sources, efficiency of absorption, presence of intestinal disease (eg, intestinal resection or malabsorption), and medication use, for example with the vitamin D-depleting actions of common anticonvulsant drugs.[40]

Past and Future Vitamin D Studies: Critique and Design

Nearly all published clinical trials have suffered from flawed design, including inadequate dosing, inadequate duration, wrong type of vitamin D (ie, ergocalciferol, D2), failure to test serum vitamin D levels, and/or failure to ensure that serum vitamin D levels entered into the optimal range. The following guidelines are provided for clinicians and researchers using vitamin D in clinical practice and research to improve the quality of research and patient care.

1. Dosages of vitamin D must reflect physiologic requirements and natural endogenous production and should therefore be in the range of 3,000–10,000 IU per day

The physiologic requirement for vitamin D appears to be 3,000–5,000 IU per day in adult males.[2] Full-body exposure to ultraviolet light (eg, sunshine) can produce the equivalent of 10,000–25,000 IU of vitamin D3 per day.[1] Therefore, intervention trials with supplemental vitamin D should use between 4,000 IU/day, which is presumably sufficient to meet physiologic demands, and 10,000 IU/day, which is the physiologic dose attained naturally via full-body sun exposure. Based on these physiologic criteria, we see that the majority of intervention studies in adults have used inadequate, subphysiologic doses of vitamin D. Therefore, studies that failed to identify therapeutic benefits from vitamin D supplementation were flawed due to insufficient therapeutic intervention—the dose of vitamin D was too low.

2. Vitamin D supplementation must be continued for at least 5-9 months for maximum benefit

Since serum 25(OH)D levels do not plateau until after 3-4 months of supplementation,[2] and we would expect clinical and biochemical changes to become optimally apparent some time after the attainment of peak serum levels, any intervention study of less than 5-9 months is of insufficient duration to determine either maximum benefit or that vitamin D supplementation is ineffective for the condition being investigated. Conversely, since vitamin D supplementation can alter intracellular metabolism within minutes of administration,[11] benefits seen in short-term studies should not be inaccurately attributed to statistical error or placebo effect.

3. Supplementation should be performed with D3 rather than D2

Although cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are both used as sources of vitamin D, D3 is the human nutrient and is much more efficient in raising and sustaining serum 25[OH]D levels. Vitamin D2 is a fungal metabolite and has been associated with adverse effects due to contamination and altered pharmacokinetics.[4] The type of vitamin D must always be clearly stated in published research reports.

4. Supplements should be tested for potency

Some products do not contain their claimed amount. This problem was illustrated in the study by Heaney et al[2] who found that the vitamin D supplement they used in their study, although produced by a well-known company, contained only 83% of its stated value. To ensure accuracy and consistency of clinical trials, actual dosages must be known.

5. Effectiveness of supplementation must include evaluation of serum vitamin D levels

Supplementation does not maximize therapeutic efficacy unless it raises serum 25(OH)D levels into the optimal range. To assess absorption, compliance, and safety, serum 25(OH)D levels must be monitored in clinical trials involving vitamin D supplementation. Assessment of serum levels is important also to determine the relative dose-effectiveness of different preparations of vitamin D, as some evidence suggests that micro-emulsification facilitates absorption of fat-soluble nutrients.[56,59,60] Measurement of 1,25-dihydroxyvitamin (calcitriol) is potentially misleading and is not recommended for the evaluation of vitamin D status.

6. Serum vitamin D levels must enter the optimal range

The majority of clinical intervention studies using vitamin D have failed to use supplementation of sufficient dosage and duration to attain optimal serum levels of vitamin D. Our proposed optimal range for 25(OH)D is 40–65 ng/mL (100–160 nmol/L) and is presented in Figure 1.

The above-mentioned criteria will aid future researchers in designing interventional studies that can accurately evaluate the relationship between vitamin D status and human illness. Clinicians, who are not conducting research but rather are interested in attaining clinical improvement in their patients, should follow these guidelines as well when using vitamin D supplementation in patients, while remembering to monitor for toxicity with the triad of clinical assessments, serum 25(OH)D, and serum calcium. Clinicians and researchers need to remember, however, that optimal clinical effectiveness often depends on synergism of diet, lifestyle, exercise, emotional health, and other factors. Single intervention studies are a reasonable research tool only for evaluating cause-and-effect relationships based on the presumption of a simplistic, linear model that is generally inconsistent with the complexity and multiplicity of synergistic and interconnected factors that determine health and disease. Thus, single intervention studies with vitamin D supplementation will be useful from an intellectual standpoint insofar as they will help us to further define the role of vitamin D in human physiology and pathophysiology. However, optimal clinical results with individual patients are more easily attained with the use of multicomponent treatment plans that address many facets of the patient's health.[55]

Vitamin D Supplementation in Adults

When 28 men and women were administered 4,000 IU per day for up to five months, in the absence of UVB from the sun, serum 25(OH)D levels reached approximately 40 ng/mL (100 nmol/L), and no toxicity was observed.[4] When 67 men were administered 5,000 and 10,000 IU of cholecalciferol per day for twenty weeks, again in the absence of UVB from the sun, serum levels of 25(OH)D increased to approximately 60 ng/mL (150 nmol/L) and 90 ng/mL (225 nmol/L), respectively, and no toxicity was observed.[2] Therefore, given that endogenous vitamin D production following full-body sun exposure at lower latitudes can produce >10,000 IU[1] and that 4,000 IU per day is a safe level of supplementation[4] that meets physiologic needs in adults,[2] we recommend at least 4,000 IU per day for adults, with efficacy and safety ensured by periodic measurement of 25(OH)D and serum calcium.

Vitamin D Supplementation in Pregnant Women

In 1966, two case reports and a brief review of the literature showed no adverse effects of 100,000 IU per day of vitamin D in hypoparathyroid pregnant women.[62] In 1971, a study of 15 hypoparathyroid pregnant women was reported wherein the women received more than 100,000 IU per day of vitamin D with no adverse effects to the mother or child, leading the authors to conclude that there was "no risk from vitamin D in pregnancy."[63] Doses of vitamin D for pregnant women were extensively reviewed by Hollis and Wagner[61] immediately prior to the completion of this article, and the authors concluded that doses of 100,000 IU per day were safe for pregnant women. The authors write, "Thus, there is no evidence in humans that even a 100,000 IU/day dose of vitamin D for extended periods during pregnancy results in any harmful effects." Data from several placebo-controlled clinical trials with pregnant women show that vitamin D supplementation results in superior health status for the mother and infant. The current daily reference intake (DRI) for vitamin D of 200–400 IU per day is therefore "grossly inadequate," and administration of less than 1,000 IU vitamin D per day to pregnant women is scientifically unjustifiable and ethically questionable. Hollis and Wagner[61] conclude that up to 4,000 IU per day is necessary for pregnant women, and this conclusion is consistent with previously cited research on physiologic requirements[2] and endogenous vitamin D production.[1] In order to ensure safety and efficacy in individual patients, we encourage periodic measurement of serum calcium and 25(OH)D levels.

Vitamin D Supplementation in Infants and Children

In Finland from the mid-1950s until 1964, the recommended daily intake of vitamin D for infants was 4,000–5,000 IU, a dose that was proven safe and was associated with significant protection from type 1 diabetes.[61] More recently, in a study involving more than 10,000 infants and children, daily administration of 2,000 IU per day was safe and effective for reducing the incidence of type 1 diabetes by 80%.[18] Thus, for infants and children, doses of 1,000 IU per day are certainly safe, and higher doses should be monitored by serum calcium and 25(OH)D levels.

Options for Raising Vitamin D Blood Levels

We have two practical options for increasing vitamin D levels in the body: oral supplementation and/or exposure to ultraviolet radiation. Sunlight is commonly unavailable on rainy or cloudy days, during the winter months, and in particular geographic locations. Topical sunscreens block vitamin D production by 97%-100%. Furthermore, since many people work indoors where sunshine is inaccessible, or they are partially or fully clothed when outside, reliance on sunshine to provide optimal levels of vitamin D is generally destined to provide unsatisfactory and inconsistent biochemical and clinical results. The use of UVB tanning beds can increase vitamin D levels; but this option is more expensive and time-consuming than oral supplementation, and excess ultraviolet radiation exposure expedites skin aging and encourages the development of skin cancer. Given the impracticalities and disadvantages associated with relying on sun exposure to provide optimal levels of vitamin D year-round, for the majority of patients, oral vitamin D supplementation is the better option for ensuring that biochemical needs are consistently met.

Vitamin D is either absent or present in non-therapeutic amounts in dietary sources. One of the only major dietary sources of vitamin D is cod-liver oil, but the amount required to obtain a target dose of 4,000 IU per day would require patients to consume at least three tablespoons of cod-liver oil, or the amount contained in >18 capsules of most commercial preparations.[55] Clearly this would be unpalatable and prohibitively expensive for most patients, and it would result in very low compliance. Additionally, such a high dose of cod-liver oil may produce adverse effects with long-term use, particularly with regard to excess vitamin A, and perhaps an increased tendency for bleeding and reduced biological activity of gamma-linolenic acid due to the high content of eicosapentaenoic acid.[55,64] Oral supplementation with "pure" vitamin D supplements allows the dose to be tailored to the individual needs of the patient.

DISCUSSION AND CONCLUSIONS

Vitamin D is not a drug, nor should it be restricted to prescription availability. Vitamin D is not a new or unproven "treatment." Vitamin D is an endogenous, naturally occurring, photochemically-produced steroidal molecule with essential functions in systemic homeostasis and physiology, including modulation of calcium metabolism, cell proliferation, cardiovascular dynamics, immune/inflammatory balance, neurologic function, and genetic expression. Insufficient endogenous production due to lack of sufficient sun exposure necessitates oral supplementation to meet physiologic needs. Failure to meet physiologic needs creates insufficiency/deficiency and results in subtle yet widespread disturbances in cellular function which appear to promote the manifestation of subacute long-latency deficiency diseases such as osteoporosis, cardiovascular disease, hypertension, cancer, depression, epilepsy, type 1 diabetes, insulin resistance, autoimmune disease, migraine, polycystic ovary syndrome, and musculoskeletal pain. In case reports, clinical trials, animal studies, and/or epidemiologic surveys, the provision of vitamin D via sunlight or supplementation has been shown to safely help prevent or alleviate all of the aforementioned conditions.

Vitamin D deficiency/insufficiency is an epidemic in the developed world that has heretofore received insufficient attention from clinicians despite documentation of its prevalence, consequences, and the imperative for daily supplementation at levels above the current inadequate recommendations of 200–600 IU.[65] For example, at least 57% of 290 medical inpatients in Massachusetts, USA were found to be vitamin D deficient,[66] and overt vitamin D deficiency was recently found in 93% of 150 patients with chronic musculoskeletal pain in Minnesota, USA.[43] Other studies in Americans have shown vitamin D deficiency in 48% of patients with multiple sclerosis,[37] 50% of patients with fibromyalgia and systemic lupus erythematosus,[48] 42% of healthy adolescents[67] and African American women,[68] and at least 62% of the morbidly obese.[69] International studies are consistent with the worldwide prevalence of vitamin D deficiency in various patient groups, showing vitamin D deficiency in 83% of 360 patients with chronic low-back pain in Saudi Arabia,[45] 73% of Austrian patients with ankylosing spondylitis,[47] up to 58% of Japanese women with Grave's disease,[46] more than 40% of Chinese adolescent girls,[70] and 40%-70% of Finnish medical patients.[71] As a medically valid diagnosis (ICD-9 code: 268.9 Unspecified vitamin D deficiency) with a high prevalence and clinically significant morbidity, vitamin D deficiency deserves equal attention and status with other diagnoses encountered in clinical practice. Given the depth and breadth of the peer-reviewed research documenting the frequency and consequences of hypovitaminosis D, failure to diagnose and treat this disorder is ethically questionable (particularly in pregnant women[61]) and is inconsistent with the delivery of quality, science-based healthcare. Failure to act prudently based on the research now available in favor of vitamin D supplementation appears likely to invite repetition analogous to the previous failure to act on the research supporting the use of folic acid to prevent cardiovascular disease and neural tube defects—a blunder that appears to have resulted in hundreds of thousands of unnecessary cardiovascular deaths[72] and which has contributed to incalculable human suffering related to otherwise unnecessary neural tube defects, cervical dysplasia, cancer, osteoporosis, and mental depression. Currently, Grant[12] estimates that at least 23,000 and perhaps as many as 47,000 cancer deaths[73] might be prevented each year in America if we employed simple interventions (ie, sunshine or supplementation) to raise vitamin D levels. Of course, additional lives may be saved and suffering reduced by alleviating the morbidity and mortality associated with hypertension, autoimmune disease, depression, epilepsy, migraine, diabetes, polycystic ovary syndrome, musculoskeletal pain, osteoporosis, and cardiovascular disease. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases. Safety and effectiveness of supplementation are assured by periodic monitoring of serum 25(OH)D and serum calcium.

References

1. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999;69(5):842-56.
2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr.* 2003;77(1):204-10.
3. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79(3):362-71.
4. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr.* 2001;73(2):288-94.
5. Heaney RP. Long-latency deficiency disease: insights from calcium and vitamin D. *Am J Clin Nutr.* 2003;78(5):912-9.
6. Holick MF. Calcium and Vitamin D. Diagnostics and Therapeutics. *Clin Lab Med*. 2000;20(3):569-90.
7. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone levels predict coronary heart disease: the Tromso Study. *Eur J Cardiovasc Prev Rehabil*. 2004;11(1):69-74.
8. Sato Y, Kaji M, Metoki N, Satoh K, Iwamoto J. Does compensatory hyperparathyroidism predispose to ischemic stroke? *Neurology.* 2003;60(4):626-9.
9. Fujita T. Calcium paradox: consequences of calcium deficiency manifested by a wide variety of diseases. *J Bone Miner Metab.* 2000;18(4):234-6.
10. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab*. 2001;86(2):888-94.
11. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr.* 2003;89(5):552-72.
12. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer.* 2002;94(6):1867-75.
13. Apperly FL. The relation of solar radiation to cancer mortality in North America. *Cancer Res.* 1941;1:191-5.
14. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology* (Berl). 1998;135(4):319-23.
15. Christiansen C, Rodbro P, Sjo O. "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. *Br Med J.* 1974;2(913):258-9.
16. Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. *J Clin Endocrinol Metab.* 2003;88(10):4623-32.
17. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM*. 2002;95:787-96.
18. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet.* 2001;358(9292):1500-3.
19. Goldberg P, Fleming MC, Picard EH. Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. *Med Hypotheses.* 1986 Oct;21(2):193-200.
20. Cantorna MT. Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? *Proc Soc Exp Biol Med*. 2000;223(3):230-3
21. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. *Eur J Clin Nutr.* 2004;58(4):563-7.
22. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. *Int J Epidemiol.* 1981;10(4):337-41
23. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol.* 1990;19(3):559-63.
24. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol.* 2003;41:105-12.
25. Gulati S, Bajpai A, Juneja R, Kabra M, Bagga A, Kalra V. Hypocalcemic heart failure masquerading as dilated cardiomyopathy. *Indian J Pediatr.* 2001;68(3):287-90.
26. Brunvand L, Haga P, Tangsrud SE, Haug E. Congestive heart failure caused by vitamin D deficiency? *Acta Paediatr.* 1995;84(1):106-8.
27. Kini SM, Pednekar SJ, Nabar ST, Varthakavi P. A reversible form of cardiomyopathy. *J Postgrad Med.* 2003;49(1):85-7.
28. Olgun H, Ceviz N, Ozkan B. A case of dilated cardiomyopathy due to nutritional vitamin D deficiency rickets. *Turk J Pediatr.* 2003;45(2):152-4.
29. Price DI, Stanford LC Jr, Braden DS, Ebeid MR, Smith JC. Hypocalcemic rickets: an unusual cause of dilated cardiomyopathy. *Pediatr Cardiol.* 2003;24(5):510-2.
30. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension.* 1997;30(2 Pt 1):150-6.
31. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet.* 1998;352(9129):709-10.
32. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab.* 2001;86(4):1633-7.
33. Chiu KC, Chu A, Vay LWG, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr.* 2004; 79:820-5.
34. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract.* 2003;57(4):258-61.
35. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, Rush D, Wilson PW, Jacques P. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med.* 1996;125(5):353-9.
36. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, Nevitt MC. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum.* 1999;42(5):854-60.
37. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J Neuroimmunol.* 2003;134(1-2):128-32.
38. Gloth FM 3rd, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging.* 1999;3(1):5-7
39. Johnson GH, Willis F. Seizures as the presenting feature of rickets in an infant. *Med J Aust.* 2003;178(9):467; discussion 467-8.
40. Ali FE, Al-Bustan MA, Al-Busairi WA, Al-Mulla FA. Loss of seizure control due to anticonvulsant-induced hypocalcemia. *Ann Pharmacother.* 2004;38(6):1002-5
41. Thys-Jacobs S. Vitamin D and calcium in menstrual migraine. *Headache*. 1994 Oct;34(9):544-6.
42. Thys-Jacobs S, Donovan D, Papadopoulos A, Sarrel P, Bilezikian JP. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. *Steroids*. 1999;64(6):430-5.
43. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc.* 2003;78(12):1463-70
44. Masood H, Narang AP, Bhat IA, Shah GN. Persistent limb pain and raised serum alkaline phosphatase the earliest markers of subclinical hypovitaminosis D in Kashmir. *Indian J Physiol Pharmacol.* 1989;33(4):259-61.
45. Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine.* 2003;28(2):177-9.
46. Yamashita H, Noguchi S, Takatsu K, Koike E, Murakami T, Watanabe S, Uchino S, Yamashita H, Kawamoto H. High prevalence of vitamin D deficiency in Japanese female patients with Graves' disease. *Endocr J.* 2001;48(1):63-9.
47. Falkenbach A, Tripathi R, Sedlmeyer A, Staudinger M, Herold M. Serum 25-hydroxyvitamin D and parathyroid hormone in patients with ankylosing spondylitis before and after a three-week rehabilitation treatment at high altitude during winter and spring. *Wien Klin Wochenschr.* 2001;113(9):328-32.
48. Huisman AM, White KP, Algra A, Harth M, Vieth R, Jacobs JW, Bijlsma JW, Bell DA. Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. *J Rheumatol.* 2001;28(11):2535-9.
49. Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs--a brief overview. *Mol Cell Biochem.* 2003;253(1-2):247-54.
50. Trouillas P, Honnorat J, Bret P, Jouvet A, Gerard JP. Redifferentiation therapy in brain tumors: long-lasting complete regression of glioblastomas and an anaplastic astrocytoma under long term 1-alpha-hydroxycholecalciferol. *J Neurooncol.* 2001;51(1):57-66
51. Holick MF. Vitamin D deficiency: what a pain it is. *Mayo Clin Proc*. 2003;78(12):1457-9
52. Wright JV. Vitamin D: Its Role in Autoimmune Disease and Hypertension. *Townsend Letter for Doctors and Patients*. 2004; May #250: 75-78.
53. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. *Am J Clin Nutr.* 1997;65(1):67-71.
54. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr*. 1998;67(2):342-8.
55. Vasquez A. *Integrative Orthopedics: Concepts, Algorithms, and Therapeutics.* Houston; Natural Health Consulting Corporation (www.OptimalHealthResearch.com): 2004. Pages 417-419 and website updates.
56. Mercola J. Available at: http://www.mercola.com/forms/vitamind.htm. Accessed July 23, 2004.
57. Mercola J. Test Values and Treatment for Vitamin D Deficiency. Available at: http://www.mercola.com/2002/feb/23/vitamin_d_deficiency.htm. Accessed July 23, 2004.
58. Berkow R, Fletcher AJ. *The Merck Manual of Diagnosis and Therapy.* Fifteenth Edition. Rathway; Merck Sharp and Dohme Research Laboratories. 1987: 928, 974-5.
59. Bucci LR, Pillors M, Medlin R, Henderson R, Stiles JC, Robol HJ, Sparks WS. Enhanced uptake in humans of coenzyme Q10 from an emulsified form. Third International Congress of Biomedical Gerontology; Acapulco, Mexico: June 1989.
60. Bucci LR, Pillors M, Medlin R, Klenda B, Robol H, Stiles JC, Sparks WS. *Enhanced blood levels of coenzyme Q-10 from an emulsified oral form.* In Faruqui SR and Ansari MS (editors). Second Symposium on Nutrition and Chiropractic Proceedings. April 15-16, 1989 in Davenport, Iowa
61. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 2004;79(5):717-26.
62. O'Leary JA, Klainer LM, Neuwirth RS. The management of hypoparathyroidism in pregnancy. *Am J Obstet Gynecol.* 1966;94(8):1103-7.
63. Goodenday LS, Gordon GS. No risk from vitamin D in pregnancy. *Ann Intern Med*. 1971;75(5):807-8.
64 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;44(2):127-31.
65. Utiger RD. The need for more vitamin D. *N Engl J Med*. 1998;338:828-9
66. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338(12):777-83.
67. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med.* 2004;158(6):531-7.
68. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* 2002;76:187-92.
69. Buffington C, Walker B, Cowan GS Jr, Scruggs D. Vitamin D Deficiency in the Morbidly Obese. *Obes Surg.* 1993;3:421-424.
70. Fraser DR. Vitamin D-deficiency in Asia. *J Steroid Biochem Mol Biol.* 2004;89-90:491-5
71. Kauppinen-Makelin R, Tahtela R, Loyttyniemi E, Karkkainen J, Valimaki MJ. A high prevalence of hypovitaminosis D in Finnish medical in- and outpatients. *J Intern Med*. 2001;249(6):559-63.
72. Ellis A. Inertia on folic acid has caused thousands of unnecessary deaths. *BMJ*. 2003;326(7398):1054.
73. Grant WB. Personal communication by email, "My current estimate is 47,000 premature cancer deaths/year." June 3, 2004.

CME

CONTINUING MEDICAL EDUCATION

CME TEST INSTRUCTIONS

To receive 2.0 hours of CME credit for this article, visit www.cecmeonline.com, log in, purchase the CME course for $10 and take the online test. This test is valid for 1 year from the date of publication. Within 3 to 4 weeks of InnoVision Communications receiving your completed online test, you will receive a CME certificate.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. InnoVision Communications designates these educational activities on an hour-for-hour basis toward category 1 credit of the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

CME TEST QUESTIONS*

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

In the following questions, only one answer is correct.

1. In clinical trials, augmentation of vitamin D levels with ultraviolet light exposure or oral supplementation has been shown to benefit which of the following conditions:
   A. Osteoporosis; Hypertension
   B. Depression; Multiple sclerosis
   C. Back pain; Insulin resistance
   D. All of the above

2. In the absence of vitamin D supplementation, ultraviolet light exposure (ie, sunshine) can produce 25(OH)D levels that exceed current laboratory reference ranges:
   A. True
   B. False

3. Which of the following can cause hypercalcemia?
   A. Sarcoidosis and Crohn's disease
   B. Adrenal insufficiency and hypothyroidism
   C. Coadministration of vitamin D and thiazide diuretics
   D. All of the above

4. According to the current research literature reviewed in this article, which of the following may be considered long-latency deficiency diseases associated with insufficiency of vitamin D?
   A. Metabolic syndrome
   B. Autoimmune disease such as multiple sclerosis and type 1 diabetes
   C. Depression and cancer
   D. All of the above

5. If a patient has hypovitaminosis D and a vitamin D-responsive condition such as depression, hypertension, insulin resistance, or multiple sclerosis, which of the following is appropriate first-line treatment?
   A. Drugs only
   B. Vitamin D only
   C. Correction of the vitamin D deficiency, and co-administration of medications if necessary
   D. Use of synthetic vitamin D analogs

6. Since vitamin D is highly effective for the prevention and alleviation of several health problems, and because it has a wide range of safety, physiologic doses should be regulated as a prescription drug and prohibited from public access:
   A. True
   B. False

7. Given the prevalence and consequences of vitamin D deficiency, failure to test for and treat vitamin D insufficiency is ethical:
   A. True
   B. False

8. Since vitamin D has a wide margin of safety, patients should be administered vitamin D routinely and receive which of the following types of monitoring:
   A. Periodic measurement of serum 1,25-dihydroxyvitamin D (calcitriol) and urinary creatinine
   B. Periodic measurement of serum 25-hydroxyvitamin D (calcidiol) and serum calcium
   C. Clinical assessments only
   D. Liver function tests and electrocardiography

See page 94 for Self-Assessment answers

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.

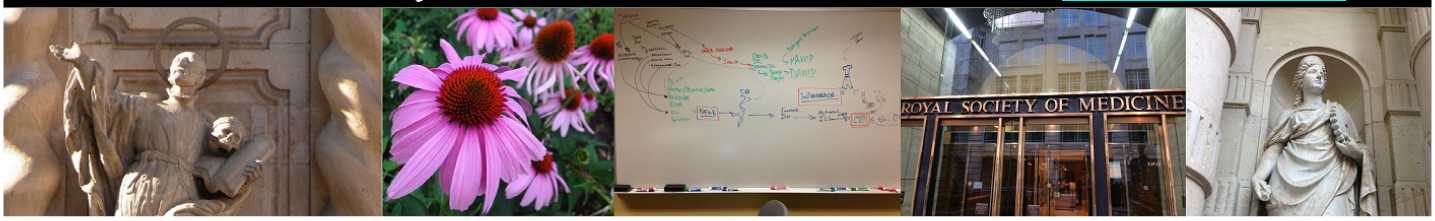
Evidence-based medicine—by definition—requires objective, reliable and accurate research and reviews from which to make the best decisions in patient care and public policy. The causes of inaccurate information, ranging from presumably innocent mistakes all the way to apparently intentional fraud, affect 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 ent policy and worldwide.[2] While ons of people. a specific disease examples of human populatio lications, lists nutrition researcl sed solutions. particularly conte pendent upon nutrition researcl stigative and healthcare profess s of clinical nutrition. Clinical rovements are vast majority of ignorance in medical training p are obviously i gastroenterology[7] tion training in clini proclaims itself a eview recent including the enti publications 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 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:

- https://ichnfm.academia.edu/AlexVasquez (main archive/repository)
- https://www.ichnfm.org/public
- **VIDEO**: BRIEF Critique of "Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" https://vimeo.com/287650812
- **VIDEO:** Bad Science in Medical Nutrition: Politics of Fish Oil https://vimeo.com/314997927

International Journal of Human Nutrition and Functional Medicine www.ICHNFM.ORG



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 Academia, "nonprofits", and "

I would be happiest to tel
Administrators are vanguard
support for fellow Professors, a
commitment is to truth and rea
setting ablaze the passions of t
they teach, lead, and supervise
in flower fields like a professo

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

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

- https://ichnfm.academia.edu/AlexVasquez (main archive/repository)
- https://www.inflammationmastery.com/reprints (cloud-based PDF folder)
- https://www.ichnfm.org/public

Updates: The most complete version
Functional Medicine ® ISSN 2378-48

Citation: Vasquez A. Ending the Exploitation of Experts Begins with Educating Them about Employment, Curbing Enthusiasm to Preserve Enthusiasm. *Int J Hum Nutr Funct Med* 2016; epub in press

International Journal of Human Nutrition and Functional Medicine (ISSN 2378-4881) ICHNFM.ORG/journal

Barceloneta sunset © 2019 by Dr Vasquez

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

How to Improve Scientific Writing and Journal Editing: A Short Narrative-Video Guide, Part 1

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

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

- https://ichnfm.academia.edu/AlexVasquez (main archive/repository)
- https://www.inflammationmastery.com/reprints (cloud-based PDF folder)
- https://www.ichnfm.org/public
- **See original video here: https://vimeo.com/318326979**

Source: *International Journal of Human*
International College of Human Nutritio
Citation: Vasquez A. How to Improve S
Med 2019;7:1 https://www.ichnfm.org/jo Externally archived at https://www.academia.edu/38426978

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
- https://www.ichnfm.org/volume-1-essential-knowledge
- https://www.ichnfm.org/volume-2-inflammatory-disorders

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

- **https://ichnfm.academia.edu/AlexVasquez (main archive/repository)**
- https://www.**researchgate**.net/profile/Alex_Vasquez2 (archive/repository)
- https://www.inflammationmastery.com/**reprints** (cloud-based PDF folder)
- https://www.ichnfm.org/public

VIDEOS: Access to public videos is available per the following:

- **Main archive: https://vimeo.com/drvasquez**
- See also: https://www.ichnfm.org/public
- And to a lesser extent: https://www.**youtube**.com/channel/UCPR2pgwFw9L2GUnBgupQ5Aw

WEBSITES:

- **Main: https://www.inflammationmastery.com/**
  - Antiviral: https://www.inflammationmastery.com/**antiviral**
  - Fibromyalgia: https://www.inflammationmastery.com/**fibromyalgia**
  - Migraine: https://www.inflammationmastery.com/**migraine**
  - Complete protocol: https://www.inflammationmastery.com/**book-nutrition-functional-medicine**
- **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**

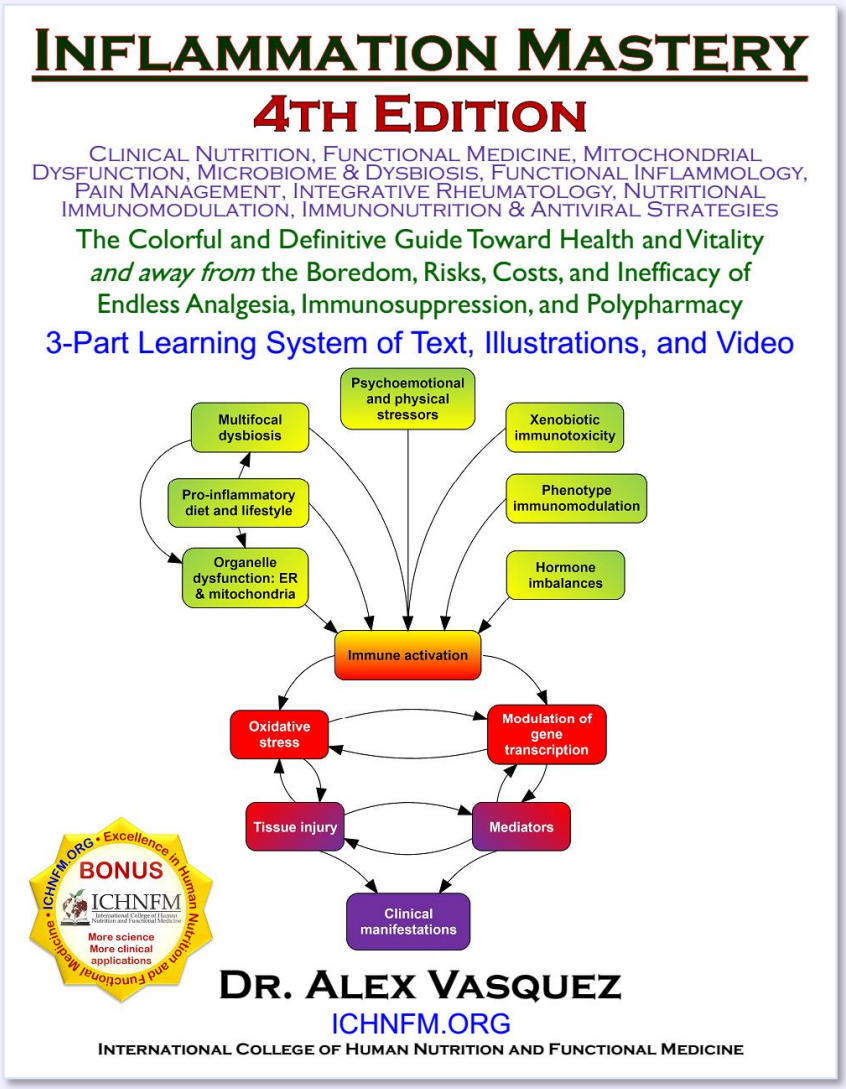
SOCIAL MEDIA UPDATES: Note that updates are made on a regular basis to the following social medial pages, with some overlap but also some topic-specific specialization, which is self-explanatory by the titles of these pages:

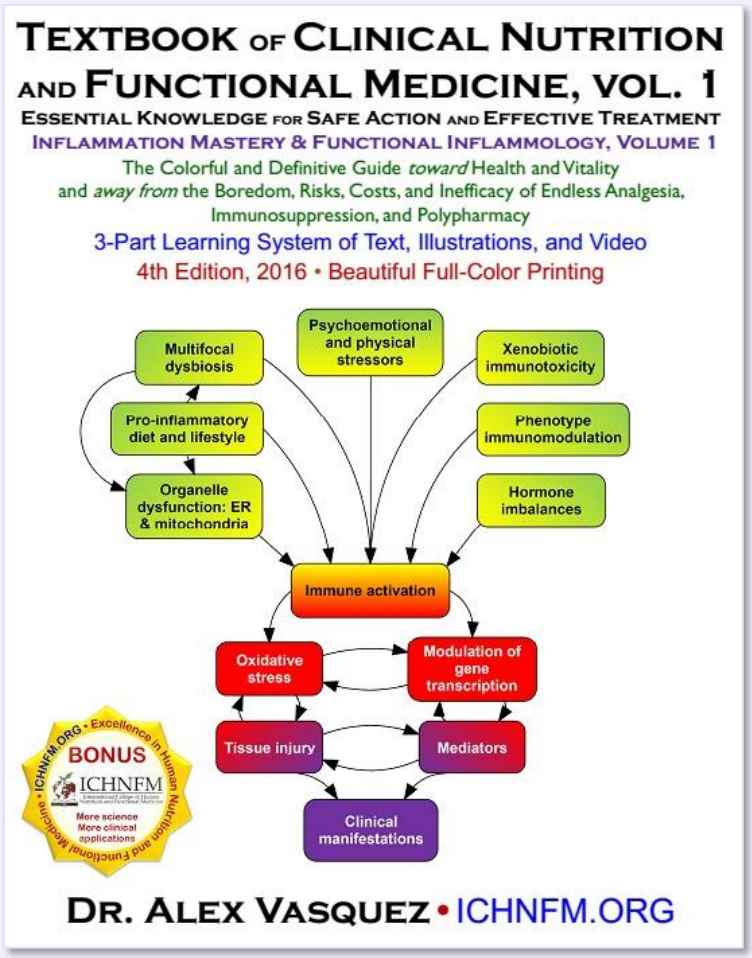
- **Dr Alex Vasquez 's Inflammation Mastery https://www.facebook.com/InflammationMastery**
- Migraine Headaches, Hypothyroidism, and Fibromyalgia https://www.facebook.com/MigraineHypothyroidismFibromyalgia
- International Journal of Human Nutrition and Functional Medicine https://www.facebook.com/IJHNFM
- International College of Human Nutrition and Functional Medicine (higher quality and academic news) https://www.facebook.com/IntCollHumNutrFunctMed
- Revista Latinoamericana de Nutrición Humana y Medicina Funcional https://www.facebook.com/RevLatinoNutrHumMedFunc
- Antiviral Nutrition https://www.facebook.com/AntiviralNutrition
- NaturopathicRheumatology https://www.facebook.com/NaturopathicRheumatology

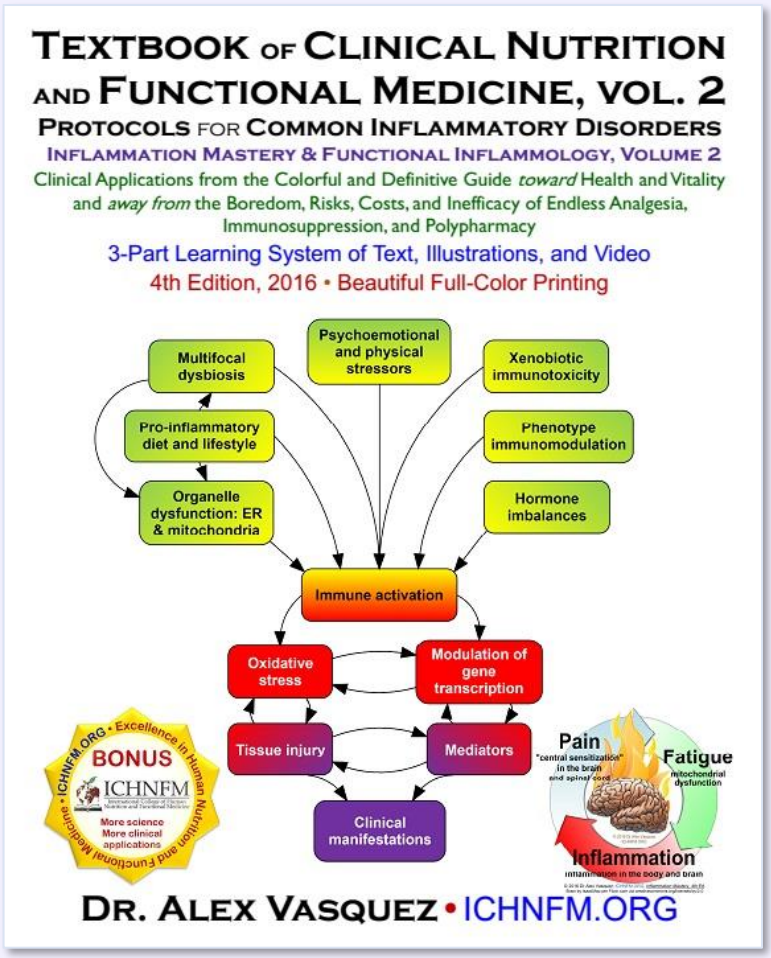
As of 2019 and for the foreseeable future, the most current versions of all major patient management and clinical treatment protocols are published in ***Inflammation Mastery, 4th Edition*** as a single volume of 1,182 pages available in full-color print at discounted pricing directly from ICHNFM from 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***.

Availability in print and digital formats (examples):

- https://www.**ichnfm**.org/im4
- https://www.**amazon**.com/Inflammation-Mastery-4th-Immunosuppression-Polypharmacy-ebook/dp/B01KMZZLAQ
- https://books.**apple**.com/us/author/alex-vasquez/id1139497284
- https://www.**barnesandnoble**.com/w/inflammation-mastery-4th-edition-alex-vasquez/1123259586?ean=9780990620464







Inflammation Mastery

4th Edition: The Colorful and Definitive Guide toward Health and Vitality and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy

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

Alex Vasquez D.C. N.D. D.O. F.A.C.N.

- Doctor of Osteopathic Medicine, graduate of University of North Texas Health Science Center, Texas College of Osteopathic Medicine (2010)
- Doctor of Naturopathic Medicine, graduate of Bastyr University (1999)
- Doctor of Chiropractic, graduate of University of Western States (1996)
- Fellow of the American College of Nutrition (2013-present)
- Former Overseas Fellow of the Royal Society of Medicine
- Editor, *International Journal of Human Nutrition and Functional Medicine* IntJHumNutrFunctMed.org. Former Editor, *Naturopathy Digest*; Former/Recent Reviewer for *Journal of Naturopathic Medicine*, *Alternative Therapies in Health and Medicine*, *Autoimmune Diseases*, *International Journal of Clinical Medicine*, and *PLOS One*
- Private practice of integrative and functional medicine in Seattle, Washington (2000-2001), Houston, Texas (2001-2006), Portland, Oregon (2011-2013), consulting practice (present)
- Consultant Researcher and Lecturer (2004-present), Biotics Research Corporation
- Teaching and Academics:
    - Director of Programs, International College/Conference on Human Nutrition and Functional Medicine ICHNFM.org
    - Founder and Former Program Director of the world's first accredited university-affiliated graduate-level program in Functional Medicine
    - Adjunct Professor, Integrative and Functional Nutrition in Immune Health, Doctor of Clinical Nutrition program at Maryland University of Integrative Health
    - Former Adjunct Professor (2009-2013) of Laboratory Medicine, Master of Science in Advanced Clinical Practice
    - 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
    - Former Adjunct Professor of Orthopedics (2000), Radiographic Interpretation (2000), and Rheumatology (2001), Naturopathic Medicine Program, Bastyr University
- Author of more than 100 articles and letters published in *JAMA—Journal of the American Medical Association*, *BMJ—British Medical Journal*, *TheLancet.com*, *JAOA—Journal of the American Osteopathic Association*, *Annals of Pharmacotherapy*, *Journal of Clinical Endocrinology and Metabolism*, *Alternative Therapies in Health and Medicine*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics*, *Integrative Medicine*, *Current Allergy and Asthma Reports*, *Nutritional Wellness*, *Evidence-based Complementary and Alternative Medicine*, and *Arthritis & Rheumatism*: Official Journal of the American College of Rheumatology

International College of Human Nutrition & Functional Medicine

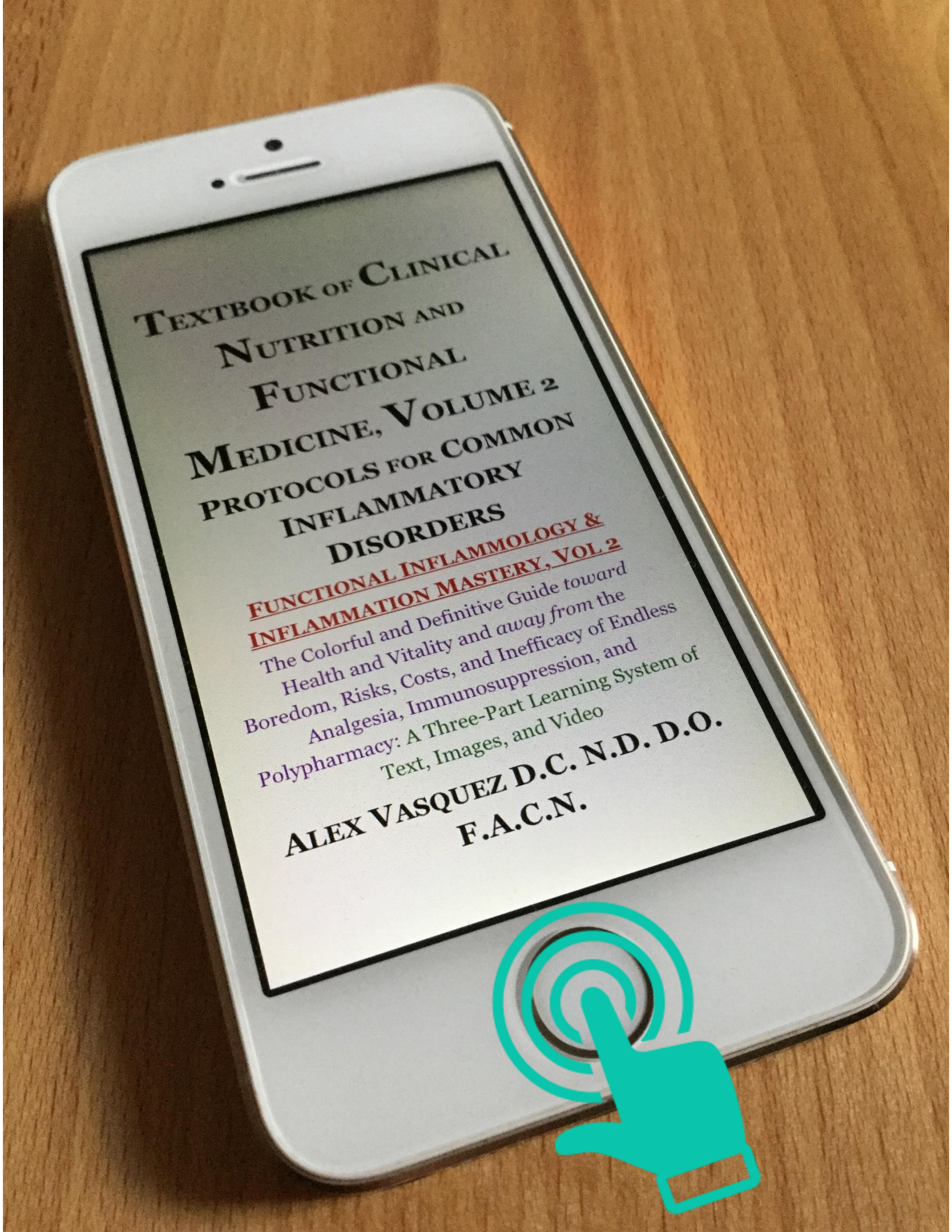
ICHNFM.ORG

practical clinical applications

1) Food & Basic Nutrition
2) Infections: Dysbiosis / Viral
3) Nutritional Immunomodulation
4) Dysmetabolism, Mitochondrial Dysfunction, ERS/UPR, mTOR
5) Special Considerations: Sleep, Sociopsychology, Stress, Surgery
6) Endocrine Imbalances
7) Xenobiotic Immunotoxicity

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

1) Hypertension
2) Diabetes Mellitus
3) Migraine & Headaches
4) Fibromyalgia
5) Allergic Inflammation
6) Rheumatoid Arthritis
7) Psoriasis and Psoriatic Arthritis
8) Systemic Lupus Erythematosus
9) Scleroderma & Systemic Sclerosis
10) Vasculitic Diseases
11) Spondyloarthropathies & Reactive Arthritis
12) Sjögren Syndrome/Disease
13) Raynaud's Syndrome/Phenomenon/Disorder

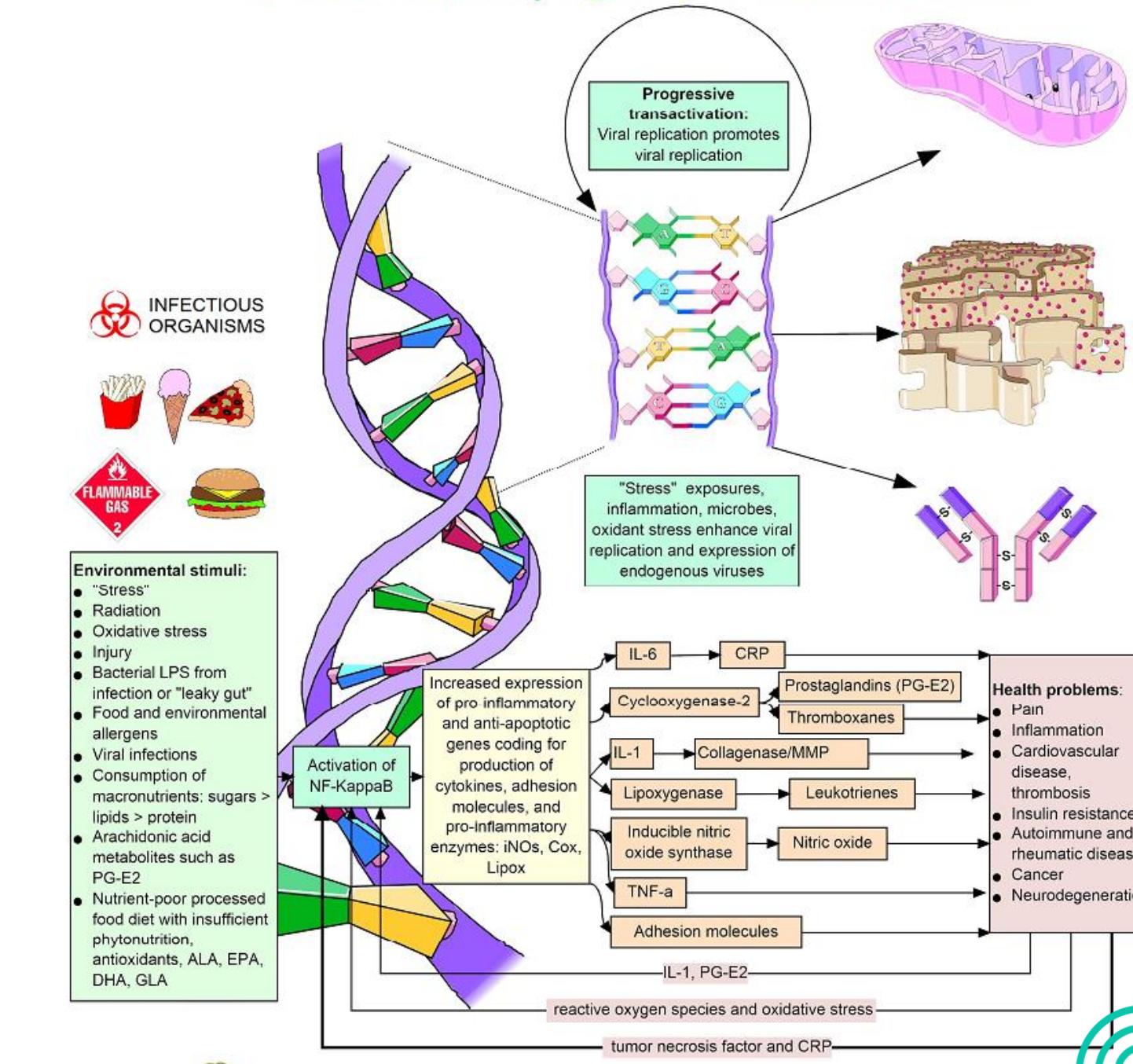

Textbook of Clinical Nutrition and Functional Medicine, Volume 2
Protocols for Common Inflammatory Disorders
Functional Inflammology & Inflammation Mastery, Vol 2
The Colorful and Definitive Guide toward Health and Vitality and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia, Immunosuppression, and Polypharmacy: A Three-Part Learning System of Text, Images, and Video
Alex Vasquez D.C. N.D. D.O. F.A.C.N.

Antiviral Strategies and Immune Nutrition

Against Colds, Flu, Herpes, AIDS, Hepatitis, Ebola, Dengue, and Autoimmunity: A Concept-Based and Evidence-Based Handbook and Research Review for Practical Use

Inflammation Mastery series Chapter 6 ♦ Volume 2 of Dysbiosis in Human Disease

2-Part Learning System of Text and Video



Dr. Alex Vasquez

InflammationMastery.com

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 34, NUMBER 1
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 some instances, 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 uns 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-

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

- https://ichnfm.academia.edu/AlexVasquez (main archive/repository)
- https://www.ichnfm.org/public
- **VIDEO**: BRIEF Critique of "Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" https://vimeo.com/287650812
- **VIDEO:** Bad Science in Medical Nutrition: Politics of Fish Oil https://vimeo.com/314997927

 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.)

Corresponding author: Alex Vasquez, DC, ND, DO, FACN
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

Nutrition and Functional Medicine[1] 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 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

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

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 33, NUMBER 6
PUBLISHED: DECEMBER 2018

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 mo school in the early 1990s. trition" book that I read as *Your Nerves* (1975) by me this was followed immedi tures of Jonathan V Wrigh of whom would later be m University. By the mid-199 Jeffrey Bland PhD had int tional medicine, which I and personal[3] reasons. By contained several hundred tion 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 human- utions; we can reasonably and competent healthcare dequate nutrition) are basic submit a counterargument r all of my assertions, they and more to the point, my regardless of personal po- —we share some common uding the following:

nd deliver the best health- roblem, then we each want the best possible solution. Efficiency of time or money is not the top priority when we are seeking solutions

International Journal of Human Nutrition and Functional Medicine www.ICHNFM.org

Photos © by Dr Vasquez, 2013-2015

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 art… dysbiosis le… 2010, I fou… "dysbiosis" … than 1,200 … concept has … popular, bu… to do with it … *Medicine* … microbiota … *the comple… 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*."[5] To the extent that this information is being integrated into clinical practice at all, the current level of 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 …opular to the …nical clues. …ratory testing …rticular used …ods to extract …ney only to …uffering and

"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.

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

- https://ichnfm.academia.edu/AlexVasquez (main archive)
- https://www.inflammationmastery.com/reprints (PDF folder)
- https://www.ichnfm.org/public
- **See various videos and course excerpts here: https://www.ichnfm.org/image-gallery-dysbiosis-course**

…M
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

Citation: Vasquez A. Translating Microbiome (Microbiota) and Dysbiosis Research into Clinical Practice: The 20-Year Development of a Structured Approach that Gives Actionable Form to Intellectual Concepts. *Int J Hum Nutr Funct Med* 2015;v3(q2):p1

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.

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The learner should study the article and its figures or tables, if any, then complete the self-evaluation at the end of the activity. The activity and self-evaluation are expected to take a maximum of 2 hours.

OBJECTIVES

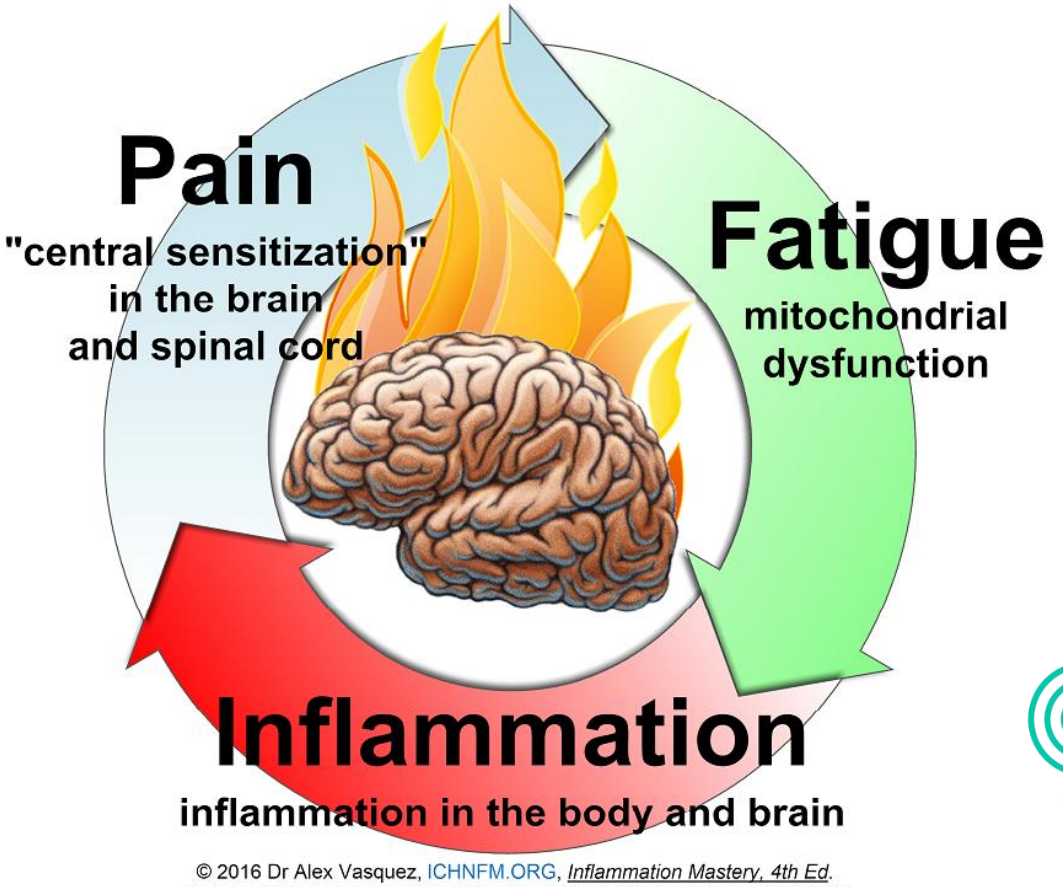
Upon completion of this article, participants should be able to do the following:

1. Appreciate and identify the manifold clinical presentations and consequen
2. Identify patient grou
hypersensitivity
3. Know how to imple
proper doses and wi

Reprint requests: InnoVision Communic
phone, (760) 633-3910 or (866) 828-29
innerdoorway.com. Or visit our online C
-therapies.com and selecting the Continu

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-

Brain Inflammation
in Chronic Pain, Migraine and Fibromyalgia
The Paradigm-Shifting Guide for Doctors and Patients Dealing with Chronic Pain



Alex Vasquez, D.C., N.D., D.O., F.A.C.N.
ICHNFM.ORG • InflammationMastery.com/pain

DOWNLOAD FREE SAMPLE: https://www.amazon.com/Dr-Alex-Vasquez/e/B00AT5764Y

- **VARIOUS VIDEOS AND BLOGS**: https://www.ichnfm.org/braininflammation
- **INFO**: https://www.inflammationmastery.com/fibromyalgia
- **INFO**: https://www.inflammationmastery.com/migraine
- From ***Inflammation Mastery, chapter 5***, the 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 format for phone, computer, iPad via the free Kindle software

The New York Academy of Sciences 200 Years

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Annals *Reports*
COMMENTARY

Biological plausibility of the gut–brain axis in autism

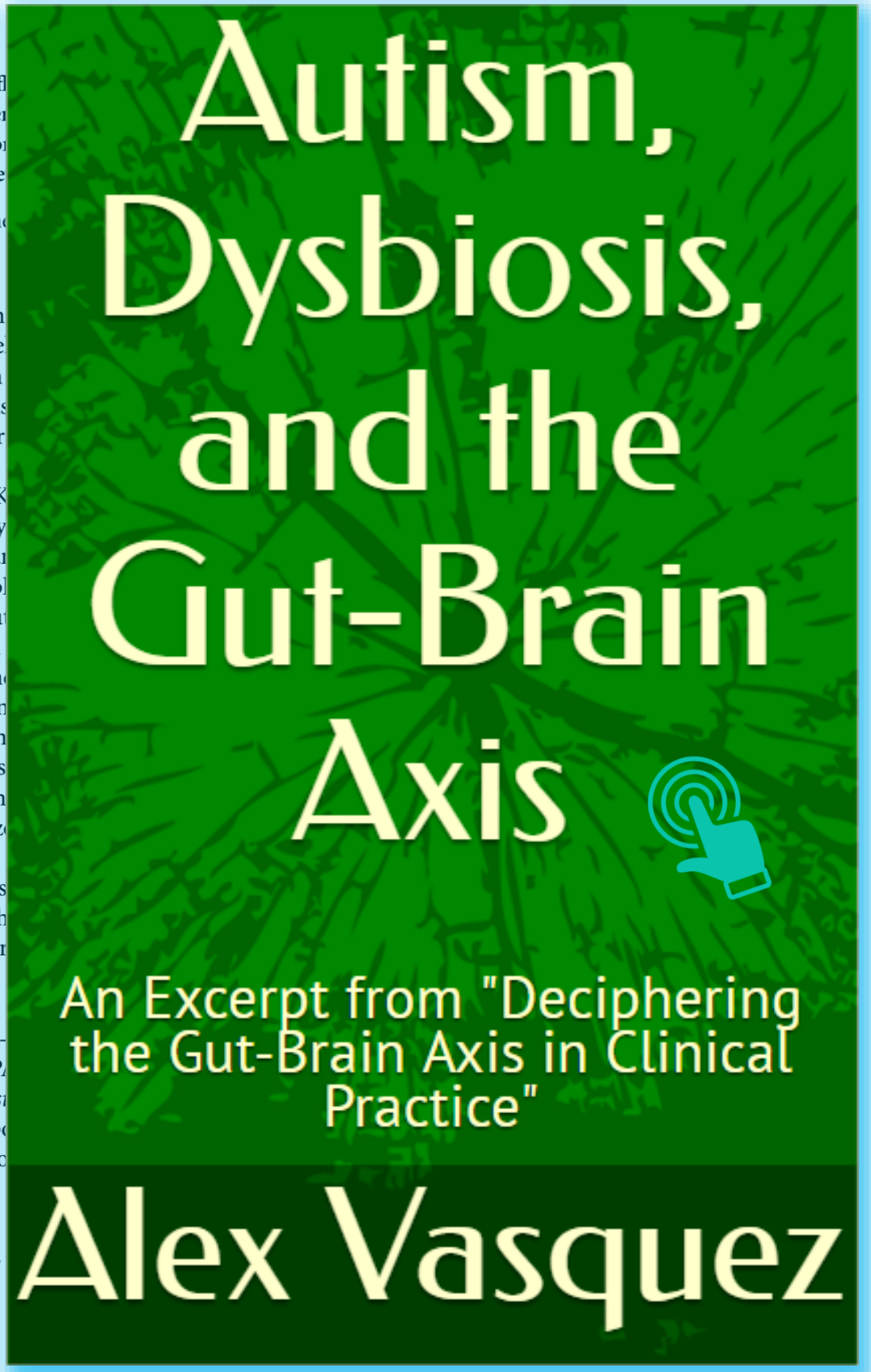
Alex Vasquez

**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-
3-hydroxypropionic acid (HPHP
phenylalanine metabolite of *Clos*
trointestinal tract.[7,8] HPHPA rep
with the conversion of dopamine to



doi: 10.1111/nyas.13516
Ann. N.Y. Acad. Sci. 0 (2017) 1–2

Textbook of Clinical Nutrition and Functional Medicine, Vol. 2

Protocols for Common Inflammatory Disorders

Inflammation Mastery & Functional Inflammology, Volume II

Clinical Applications from 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

4th Edition, 2016 • Beautiful Full-Color Printing

BONUS

ICHNFM

More science
More clinical
applications

ICHNFM.ORG • Excellence in Human Nutrition and Functional Medicine

Dr. Alex Vasquez • ICHNFM.ORG

Intended for healthcare professionals

Research

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study

BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l1161 (Published 03 April 2019)
Cite this as: BMJ 2019;365:l1161

Linked editorial

The remarkable impact of bivalent HPV vaccine in Scotland

Linked opinion

Bivalent HPV vaccine in Scotland is having a considerable and sustained effect

- Article
- Related content
- Article metrics
- Rapid responses
- Response

Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination

(Word count without footnotes and citations: 934)

In April 2019, Palmer et al [1] published a retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland, and the authors attributed a reduction in HPV prevalence among unvaccinated women with “herd protection.” However the authors did not mention Scotland’s population-wide public health campaigns to address endemic