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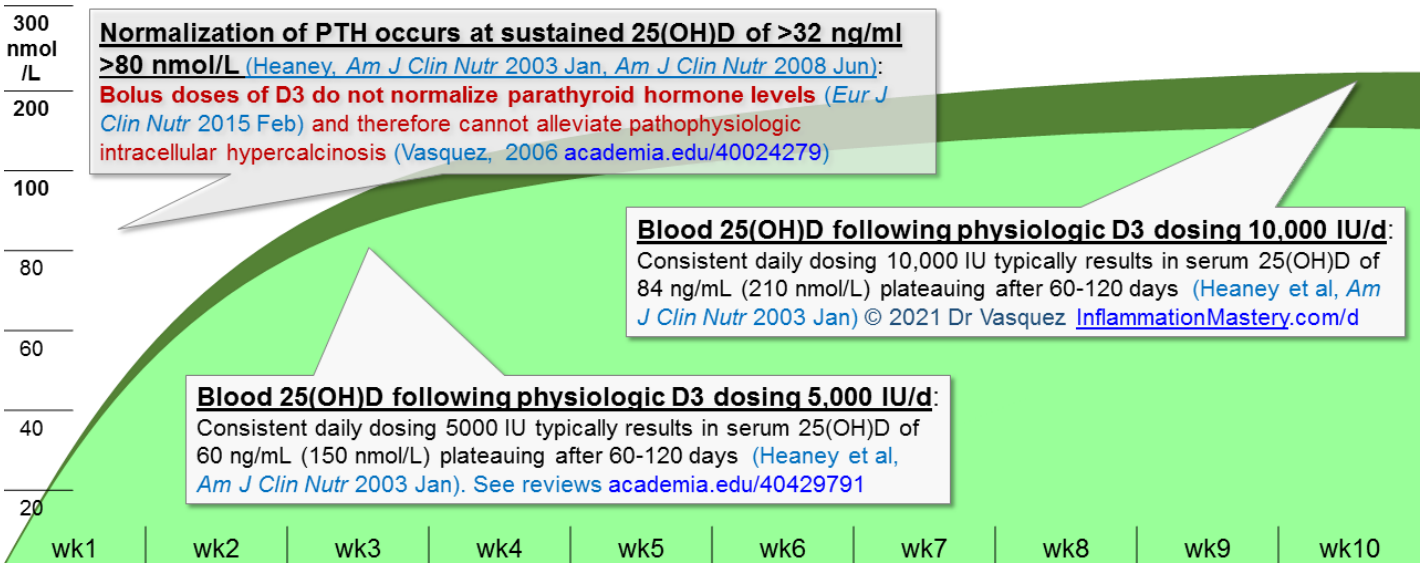
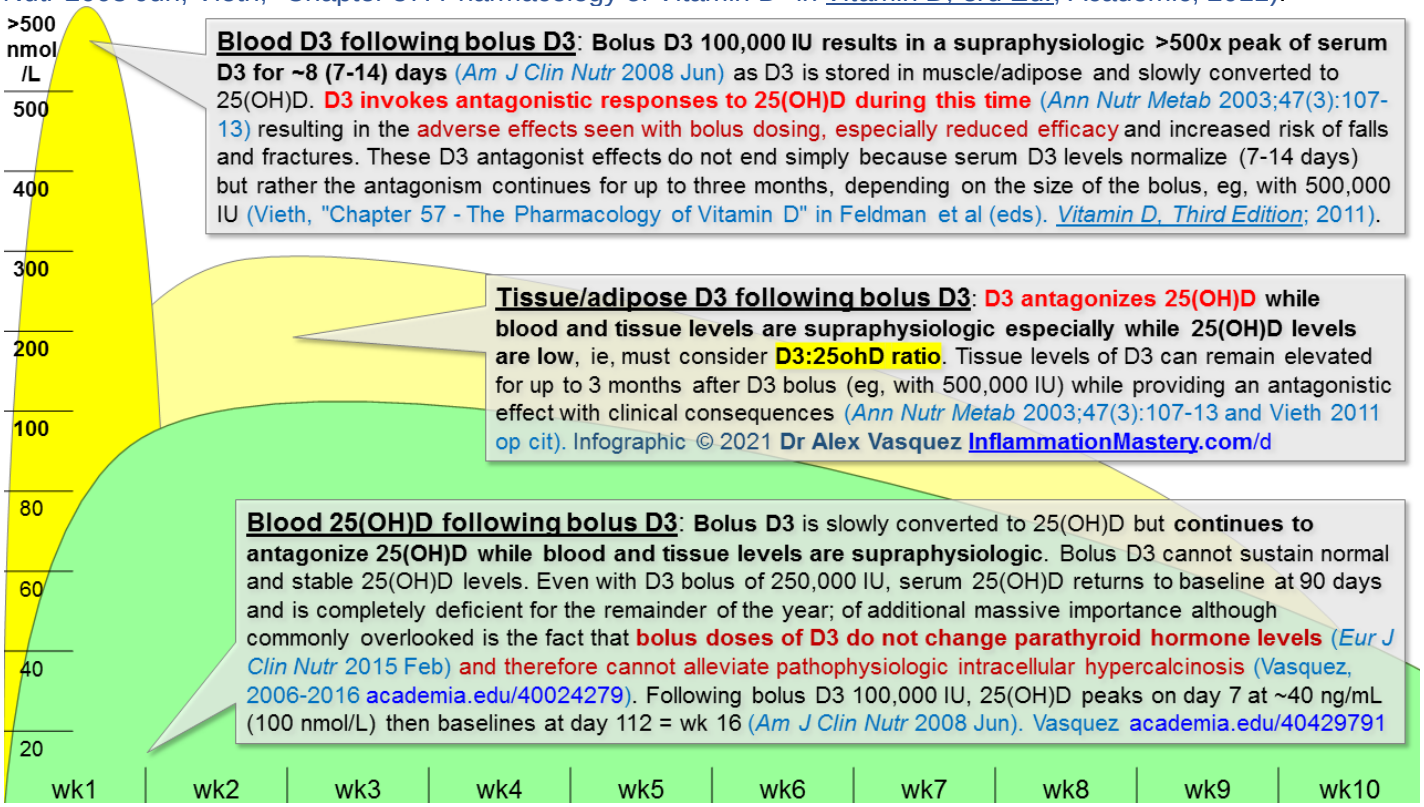
Vitamin D3 Pharmacology Infographic: Physiologic Dosing *versus* Bolus Roulette

Alex Vasquez D.O., D.C., N.D. (USA), F.A.C.N.



Infographics: D3 dose size determines clinical effect: Modest physiologic doses (demonstrated above) follow first-order pharmacokinetics characterized by a dose-response relationship that is predictable and also which does not result in significant accumulation of D3 relative to 25(OH)D; in contrast, unnatural bolus dosing of D3 follows unpredictable zero-order kinetics resulting in >500x non-physiologic elevations of D3 relative to deficient 25(OH)D with antagonistic biochemical/physiological effects leading to negative clinical consequences (Heaney *Am J Clin Nutr* 2008 Jun; Vieth, "Chapter 57: Pharmacology of Vitamin D" in *Vitamin D, 3rd Ed.*, Academic, 2011).



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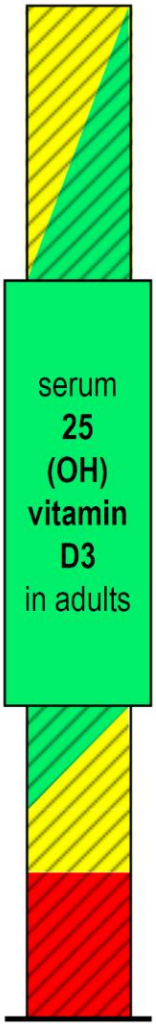

Pharmacologic dosing (eg, cancer, multiple sclerosis): 200–300 ng/mL (500–750 nmol/L)
Requires professional supervision, diet modification, laboratory surveillance per Charoenngam and Holick, *Nutrients* 2020 Jul

Potentially toxic if accompanied by clinical hypercalcemia: > 150 ng/mL (325 nmol/L)
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Supraphysiologic: > 100 ng/mL (250 nmol/L)
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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
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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

Infographic: Interpretation of serum 25-hydroxy-cholecalciferol levels in adults: Interpretation of any laboratory variable requires clinical contextualization; assessing renal function and measuring 1,25-dihydroxy-cholecalciferol prior to the initiation of vitamin D3 supplementation is reasonable, especially in patients with higher probability of renal insufficiency or granulomatous/malignant disease, respectively. Coadministration of calcium-sparing drugs (e.g., thiazides) warrants caution; periodic measurement of serum calcium is advised, especially during the first year of higher-dose vitamin D supplementation. Supplementation with cholecalciferol should generally be accompanied by adequate magnesium intake and/or supplementation with magnesium 600 mg/d for adults; vitamins K1 and K2 should also be utilized to optimize calcium metabolism. Dietary optimization, moderation of sodium intake, broad-spectrum nutritional supplementation, and avoidance of diet-induced metabolic acidosis are likewise important; see citations listed below for proper implementation. Treatment should be supervised by a nutrition-knowledgeable clinician.

Infographic citations included in images; see also:

1. Vasquez et al. Clinical importance of vitamin D: a paradigm shift for all healthcare providers. *Altern Thera Health Med* 2004 Sep
2. Vasquez A. *Textbook of Clinical Nutrition and Functional Medicine*. ICHNFM.ORG, 2016
3. Vasquez A. How to Plan Studies Using Vitamin D. *Int J Hum Nutr Funct Med* 2017 academia.edu/31412957
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6. Heaney et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003 Jan;77(1):204-10. doi: 10.1093/ajcn/77.1.204
7. Heaney et al. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. *Am J Clin Nutr*. 2008 Jun;87(6):1738-42. doi: 10.1093/ajcn/87.6.1738

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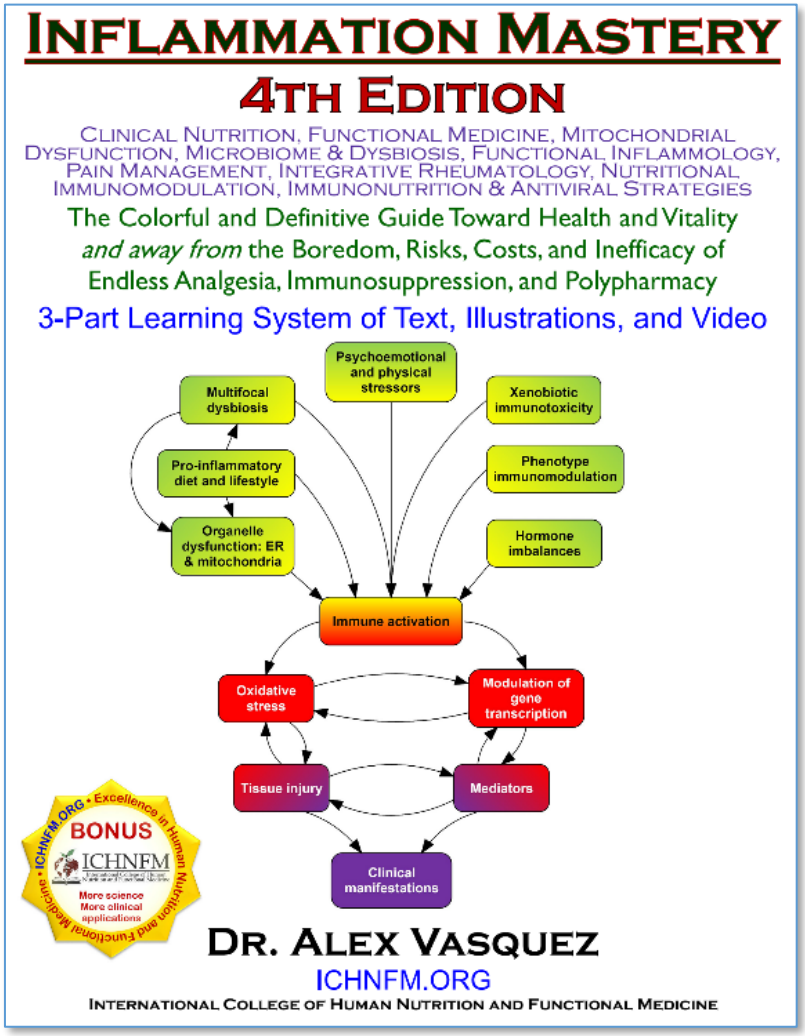
About the author and presenter: Alex Kennerly Vasquez DO ND DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding Program Director of the world's first fully-accredited university-based graduate program in Human Nutrition and Functional Medicine, Dr Alex Vasquez is recognized internationally for his high intellectual and academic standards and for his expertise spanning and interconnecting many topics in medicine and nutrition. Dr Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic Medicine (Doctor of Osteopathic Medicine, 2010). Dr Vasquez has completed hundreds of hours of post-graduate and continuing education in subjects including Obstetrics, Pediatrics, Basic and Advanced Disaster Life Support, Nutrition and Functional Medicine; while in the final year of medical school, Dr Vasquez completed a Pre-Doctoral Research Fellowship in Complementary and Alternative Medicine Research hosted by the US National Institutes of Health (NIH). Dr Vasquez is the author of many textbooks, including Integrative Orthopedics (2004, 2007 2012), Functional Medicine Rheumatology (Third Edition, 2014), Musculoskeletal Pain: Expanded Clinical Strategies (commissioned and published by Institute for Functional Medicine, 2008), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Brain Inflammation in Migraine and Fibromyalgia (2016), Mitochondrial Nutrition and Endoplasmic Reticulum Stress in Primary Care, 2nd Edition (2014), Antiviral Strategies and Immune Nutrition (2014), Mastering mTOR (2015), Autism, Dysbiosis, and the Gut-Brain Axis (2017) and **the 1200-page Inflammation Mastery 4th Edition (2016) also published as the two-volume set Textbook of Clinical Nutrition and Functional Medicine**. "DrV" has also written approximately 100 letters and articles for professional magazines and medical journals such as *TheLancet.com*, *British Medical Journal* (BMJ), *Annals of Pharmacotherapy*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics* (JMPT), *Journal of the American Medical Association* (JAMA), *Original Internist*, *Integrative Medicine*, *Holistic Primary Care*, *Alternative Therapies in Health and Medicine*, *Journal of the American Osteopathic Association* (JAOA), *Dynamic Chiropractic*, *Journal of Clinical Endocrinology and Metabolism*, *Current Asthma and Allergy Reports*, *Complementary Therapies in Clinical Practice*, *Nature Reviews Rheumatology, Annals of the New York Academy of Sciences,* and *Arthritis & Rheumatism*, the Official Journal of the American College of Rheumatology. Dr Vasquez lectures internationally to healthcare professionals and has a consulting practice and service for doctors and patients. DrV has served as a consultant, product designer, writer and lecturer for Biotics Research Corporation since 2004. Having served on the Review Boards for *Journal of Pain Research, Autoimmune Diseases, PLOS One, Alternative Therapies in Health and Medicine, Neuropeptides*, *International Journal of Clinical Medicine, Journal of Inflammation Research, BMC Complementary and Alternative Medicine* (all PubMed/Medline indexed), and *Journal of Naturopathic Medicine* and as the founding Editor of *Naturopathy Digest*, Dr Vasquez is currently the Editor (2013-) of *International Journal of Human Nutrition and Functional Medicine* and Former Editor (2018-2019) of *Journal of Orthomolecular Medicine*, published for more than 50 consecutive years by the International Society for Orthomolecular Medicine.



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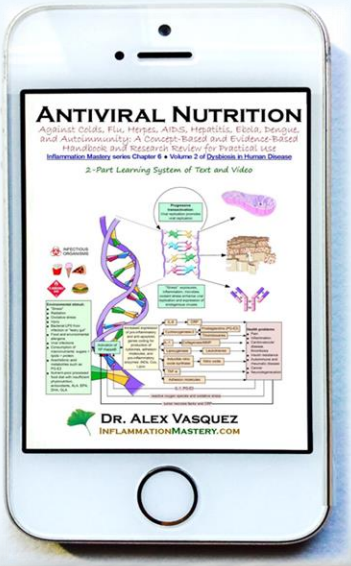

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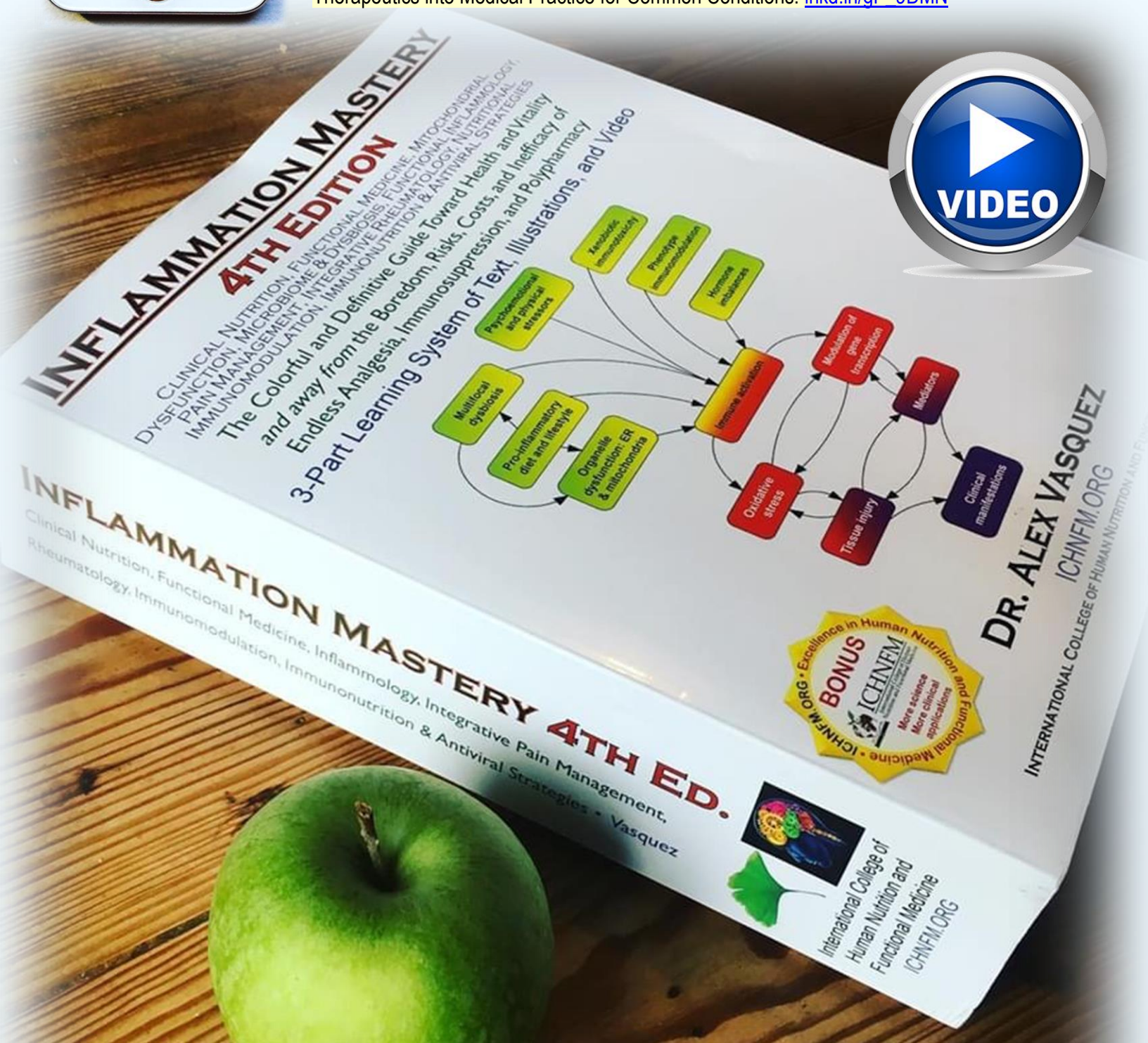

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Paradigm Shift • **Clinical Nutrition** • Primary Care • Prevention • Medicine • Metabolism • Politics

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

Alex Vasquez DO DC ND (USA) FACN

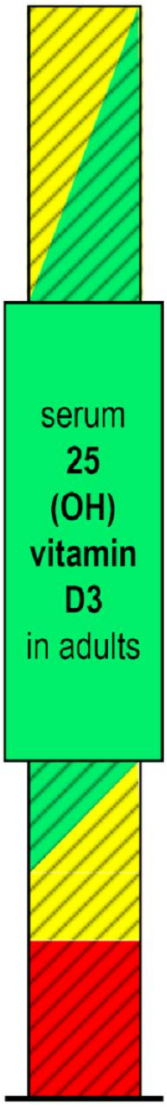
Vitamin D: Metabolism Dogma

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.**



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bmj.com

Calcium and vitamin D in preventing fractures

Data are not sufficient to show inefficacy

EDITOR—The study by Porthouse et al had two major design flaws.[1] Firstly, the dose of vitamin D (800 IU per day) is subphysiological and therefore subtherapeutic. Secondly, their use of "self report" as a measure of compliance is unreliable.

The dose of vitamin D at 800 IU daily was not determined scientifically but determined arbitrarily before sufficient scientific methodology was available.[2-4] Heaney et al determined the physiological requirement of vitamin D by showing that healthy men use 4000 IU cholecalciferol daily,[2] an amount that is safely attainable with supplementation[3] and often exceeded with exposure of the total body to equatorial sun.[4]

We provided six guidelines for interventional studies with vitamin D.[5] Dosages of vitamin D must reflect physiological requirements and natural endogenous production and should therefore be in the range of 3000-10 000 IU daily. Vitamin D supplementation must be continued for at least five to nine months. The form of vitamin D should be D_3 rather than D_2. Supplements should be assayed for potency. Effectiveness of supplementation must include measurement of serum 25-hydroxyvitamin D. Serum 25(OH)D concentrations must enter the optimal range, which is 40-65 ng/ml (100-160 nmol/l).

Since the study by Porthouse et al met only the second and third of these six criteria, their data cannot be viewed as reliable for documenting the inefficacy of vitamin D supplementation.

Alex Vasquez, *researcher*

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John Cannell, *president*

Vitamin D Council, 9100 San Gregorio Road, Atascadero, CA 93422, USA

Competing interests: AV is a researcher at Biotics Research Corporation, a drug manufacturing facility in the United States that has approval from the Food and Drug Administration.

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1. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ* 2005;330: 1003. (30 April.)[Abstract/Free Full Text]
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Related Article

Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care
Jill Porthouse, Sarah Cockayne, Christine King, Lucy Saxon, Elizabeth Steele, Terry Aspray, Mike Baverstock, Yvonne Birks, Jo Dumville, Roger Francis, Cynthia Iglesias, Suezann Puffer, Anne Sutcliffe, Ian Watt, and David J Torgerson
BMJ 2005 330: 1003. [Abstract] [Full Text]

CME
CONTINUING MEDICAL EDUCATION

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

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

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

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OBJECTIVES

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

1. Appreciate and identify the manifold clinical presentations and consequences of vitamin D deficiency
2. Identify patient groups that are predisposed to vitamin D hypersensitivity
3. Know how to implement vitamin D supplementation in proper doses and with appropriate laboratory monitoring

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

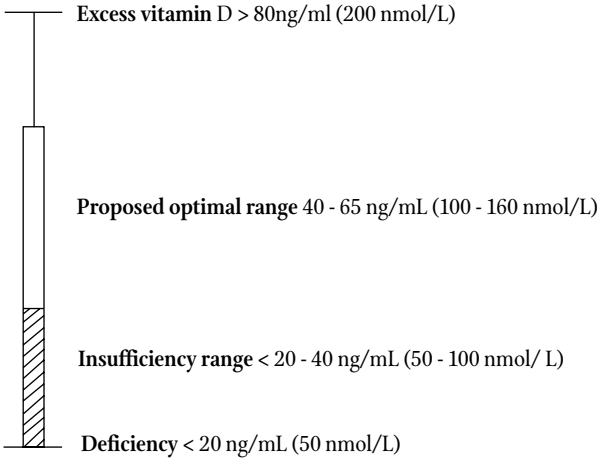

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FIGURE 1. Proposed normal and optimal ranges for serum 25(OH)D levels based on current research*****

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.

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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

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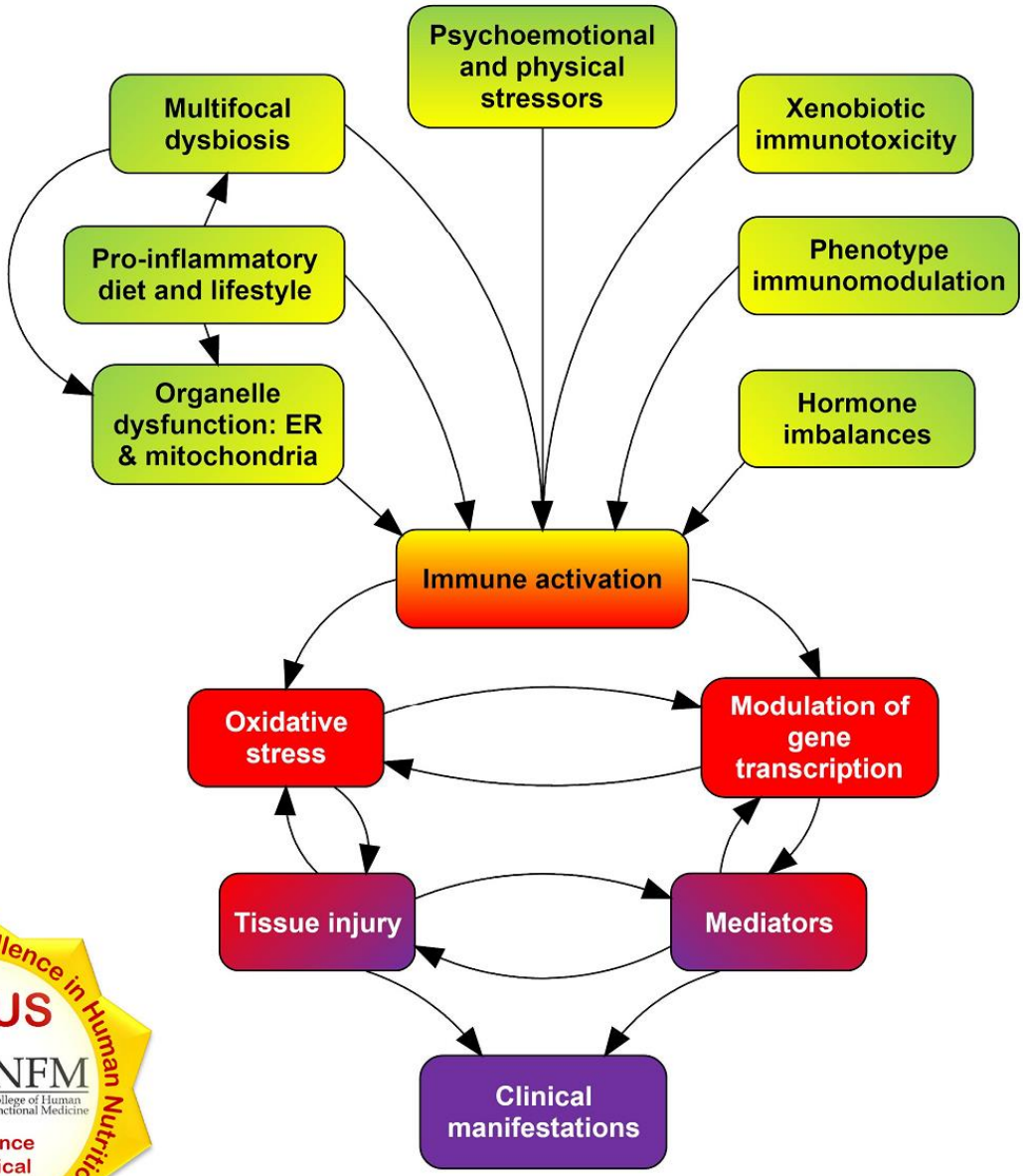

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Chapter 4:
Introduction to DrV's Functional Inflammology Protocol: The Seven Major Modifiable Factors in Systemic Inflammation, Allergy, and Autoimmunity

Major Modifiable Influences on Immune and Inflammatory Balance

This section reviews clinically-relevant information related to the pathogenesis and etiology of inflammatory/allergic/autoimmune conditions. Following extensive reviews of the research literature in conjunction with the author's impressively successful clinical experience with patients with "idiopathic" and inflammatory/autoimmune disorders, the original version of this information was published in the first edition of *Integrative Rheumatology* (2006). This section is a distillation of thousands of research articles, abstracts, seminar notes, conversations with colleagues, one-on-one patient encounters and the author's own considerations and reflections.

Following my review and perusal of thousands of research articles in addition to the attentive application of my interest in these conditions throughout three doctoral programs, I have come to appreciate seven major modifiable factors that are chiefly relevant for the initial and long-term management of patients with inflammatory conditions and rheumatic diseases. These 7 factors are:

1. Food intake and nutritional status: The pro/anti-inflammatory effects of diet, including food allergies and intolerances, nutrient deficiencies and dependencies,
2. Infections and dysbiosis: Chronic exposure to microbial effectors/effects,
3. Nutritional modulation of the immune system: Nutrigenomic modification of immunocyte phenotype,
4. Dysmetabolism and Dysfunctional organelles, most notably mitochondria: Especially the pro-inflammatory, pro-oxidant, and anti-apoptotic consequences of dysfunctional mitochondria (DysMito or MitoDys); more recently the conversation has extended beyond mitochondrial dysfunction to include endoplasmic reticulum stress/dysfunction (ERS) and resultant unfolded protein response (UPR),
5. Stress, sleep deprivation vs sleep sufficiency, spinal health, social and psychological considerations: Included in this section is a collection of important considerations which—in the first draft of this acronym—started with stress management, sleep hygiene, and pSychological and social factors. Later versions have included spinal health (chiropractic model), somatic dysfunction (osteopathic model), surgery, specialized supplementation, and "stamp your passport"—sometimes we all just need to vacate for a while and implement some *geographic cure* for the sake of inspiration, life enhancement, exposure to new ideas and lifestyles, and the breaking of (dysfunctional) thought patterns and routines,
6. Endocrine imbalances: Hormones can promote or retard the genesis and perpetuation of inflammation/allergy/autoimmunity; therapeutic correction with prescription or nonprescription interventions can have a profound anti-inflammatory benefit.
7. Xenobiotic immunotoxicity: Exposure to and accumulation of toxic chemicals and/or toxic metals can alter immune responses toward allergy and autoimmunity and away from immunosurveillance against infections and cancer.

Common diseases such as psoriasis and rheumatoid arthritis are greater public health concerns and are more commonly encountered in clinical practice than are the more rare conditions; proportionate mention is made in the following section. Importantly, readers should appreciate that the information in various sections likely applies either conceptually or specifically to conditions described in other sections and that therefore the best way to understand inflammatory/allergic/autoimmune disorders in their totality is to appreciate the nuances of each and the common themes among all.

I am quite pleased to see that the original five variables that I defined in the first two editions of *Integrative Rheumatology* (2006, 2007) have stood the tests of time, science, and clinical practice: in fact, all have been strengthened in the intervening years.

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

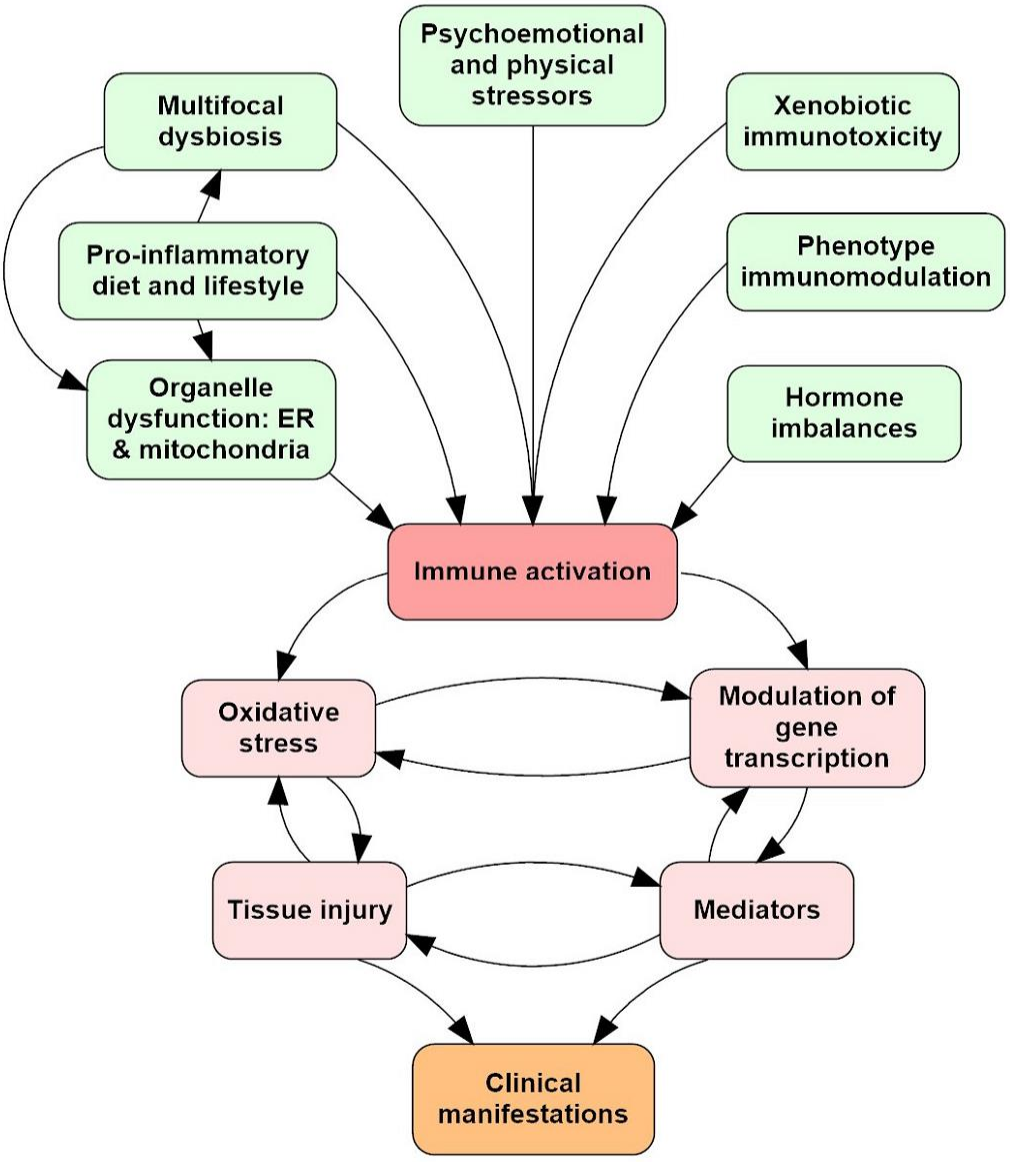
"The fact that today I still stand by these ideas, **that in the intervening time they themselves have constantly become more strongly associated with one another, even to the point of growing into each other, intertwining, and becoming *one***, that has reinforced in me the joyful confidence that they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

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

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

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

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



Inflammation in a simple cause-and-effect diagram: The major causative factors amenable to clinical implementation are represented, along with the pathophysiologic consequences and clinical effects. Molecular details, clinical assessments, and therapeutic interventions are introduced/reviewed in this chapter; in later volumes of this work, clinical protocols detail the drugs and doses, etc.

❶ Food: Diet and Basic Nutritional Supplementation

Major Concepts in this Section

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

Contents of this section:

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

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

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level. Fatty acids and their *eicosanoid*, *leukotriene*, and *isoprostane* intermediates and end-products modulate genetic expression in several ways. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease. Corn oil, probably as a result of its high n-6 LA (linoleic acid) content, rapidly activates NFkB and thus promotes tumor development, atherosclerosis, and elaboration of proinflammatory mediators such as TNFa.[12,13,14] Similarly n-6 arachidonic acid increases production of the free radical *superoxide* approximately 4-fold when added to isolated Kupffer cells *in vitro*. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases genetic expression of cyclooxygenase and IL-6; thus, an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein.[15] Some of the unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, resultant inhibition of NFkB, and impairment of estrogen receptor function.[16,17] Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans[18], and this effect is probably mediated by downregulation of proinflammatory gene transcription, as evidenced by reductions in CRP, IL-6, and serum amyloid A.[19] EPA appears to exert much of its anti-inflammatory benefit by suppressing NFkB activation and thus reducing elaboration of proinflammatory mediators.[20,21] EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels and thus activating protein kinase R which impairs eukaryotic initiation factor-2alpha and inhibits protein synthesis at the level of translation initiation, thereby mediating an anti-cancer benefit.[22] DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for IL-1, inhibit TNFa, and reduce neutrophil entry to sites of inflammation.[23] Oxidized EPA activates PPAR-alpha and thereby suppresses NFkB.[24,25] Other nutrients that inhibit the activation of NFkB include vitamin D[26,27], lipoic acid[28], green tea[29], rosemary[30], grape seed extract[31], resveratrol[32,33], caffeic acid phenethyl ester (CAPE) from bee propolis[34], indole-3-carbinol[35], N-acetyl-L-cysteine[36], selenium[37], and zinc.[38] Therefore, we see that fatty acids and nutrients

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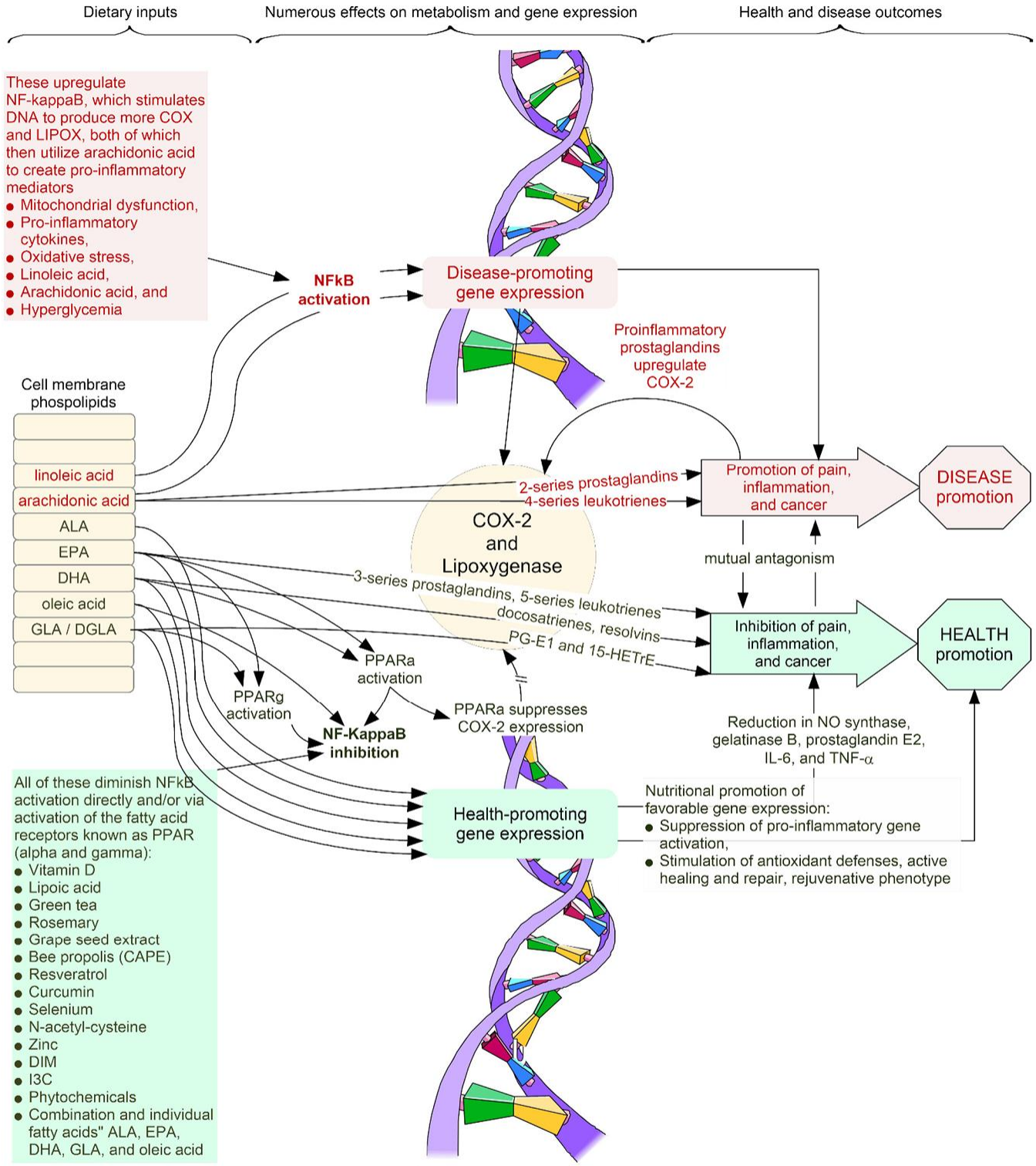
directly affect gene expression by complex and multiple mechanisms, as graphically illustrated in the accompanying diagram, and the synergism and potency of these anti-inflammatory nutraceuticals supports the rationale for the use of nutrition and select botanicals for the safe and effective treatment of inflammatory disorders.



Schematic Representation of Simultaneous Nutrigenomic and Metabolic Effects of Nutrients: Although conceptually accurate, this diagram is highly simplified and not all-inclusive; rather, this diagram focuses exclusively on nutrients that affect the NFkB pathway. Updated from Vasquez 2005.[39]

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A Five-Part Nutritional Wellness Protocol That Produces Consistently Positive Results: Brief Review of Scientific Rationale

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nutritionalwellness.com/archives/2005/sep/09_vasquez.php

Introduction: When I am lecturing here in the U.S., as well as in Europe, doctors often ask if I will share the details of my protocols with them. Thus, in 2004, I published a 486-page textbook for doctors that includes several protocols and important concepts for the promotion of wellness and treatment of musculoskeletal disorders.[40] In this article, I will share with you what I consider a basic protocol for wellness promotion. I've implemented this protocol as part of the treatment plan for a wide range of clinical problems. In my next column, I will provide several case reports of patients from my office to exemplify the effectiveness of this program and show how it can be the foundation upon which additional treatments can be added as necessary.

Nutrients are required in the proper amounts, forms, and approximate ratios for essential physiologic function; if nutrients are lacking, the body cannot function normally, let alone optimally. Impaired function results in subjective and objective manifestations of what is commonly labeled as "disease." Thus, a powerful and effective alternative to treating diseases with drugs is to re-establish normal/optimal physiologic function by replenishing the body with essential nutrients.

Of course, many diseases are multifactorial and therefore require multicomponent treatment plans, and some diseases actually require the use of drugs. However, while only a relatively small portion of patients actually need drugs for their problems, I am sure we all agree that everyone needs a foundational nutrition plan, as outlined and substantiated below.

1. Health-promoting diet: Following an extensive review of the research literature, I developed what I call the "supplemented Paleo-Mediterranean diet," which I have described in greater detail elsewhere.[41] In essence, this diet plan combines the best of the Mediterranean diet with the best of the Paleolithic diet, the latter of which has been detailed and popularized by Dr. Loren Cordain in his book, *The Paleo Diet*, and his numerous scientific articles.[42] This diet places emphasis on fruits, vegetables, nuts, seeds, and berries that meet the body's needs for fiber, carbohydrates, and most importantly, the 8,000+ phytonutrients that have additive and synergistic health benefits.[43] Preferred protein sources are lean meats such as fish and poultry. In contrast to Cordain's Paleo diet, I also advocate soy and whey for their high-quality protein and anticancer, cardioprotective, and mood-enhancing benefits. Rice and potatoes are discouraged due to their relatively high glycemic indexes and high glycemic loads, and their lack of fiber and phytonutrients (compared to other fruits and vegetables). Generally speaking, grains such as barley, rye, and wheat (e.g., the "toxic triad" of inflammatory gluten) are discouraged due to the high glycemic loads/indexes of most breads and pastries, as well as the allergenicity/immunogenicity of gluten, a protein that appears to help trigger disorders such as migraine, celiac disease, psoriasis, epilepsy, and autoimmunity. Sources of simple sugars such as high-fructose corn syrup (e.g., cola, soda) and processed foods (e.g., "TV dinners" and other manufactured snacks and convenience foods) are strictly forbidden. Chemical preservatives, colorants, sweeteners and carrageenan are likewise prohibited. In summary, this diet plan provides plenty of variety, as most dishes comprised of poultry, fish, soy, fruits, vegetables, nuts, berries, and seeds are allowed. The diet also provides plenty of fiber, phytonutrients, carbohydrates, potassium, and protein, while simultaneously being low in fat, sodium, arachidonic acid, and "simple sugars." The diet must be customized with regard to total protein and calorie intake, as determined by the size, status, and activity level of the patient, and individual food allergens should be avoided. Regular consumption of this diet has shown the ability to reduce hypertension, alleviate diabetes, ameliorate migraine headaches, and result in improvement of overall health and a lessening of the severity of many common "diseases." This diet is supplemented with vitamins, minerals, and fatty acids as described below.
2. Multivitamin and multimineral supplementation: Vitamin and mineral supplementation finally received endorsement from "mainstream" medicine when researchers from Harvard Medical School published a review

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article in *Journal of the American Medical Association* that concluded, "Most people do not consume an optimal amount of all vitamins by diet alone. ...It appears prudent for all adults to take vitamin supplements."[44] Long-term nutritional insufficiencies experienced by the majority of the population promote the development of "long-latency deficiency diseases" such as cancer, neuroemotional deterioration, and cardiovascular disease.[45] Impressively, the benefits of multivitamin/multimineral supplementation have been demonstrated in numerous clinical trials. Multivitamin/multimineral supplementation has been shown to improve nutritional status and reduce the risk for chronic diseases[46], improve mood[47], potentiate antidepressant drug treatment[48], alleviate migraine headaches (when used with diet improvement and fatty acids[49]), improve immune function and infectious disease outcomes in the elderly[50] (especially diabetics[51]), reduce morbidity and mortality in patients with HIV infection[52,53] alleviate premenstrual syndrome[54,55] and bipolar disorder[56], reduce violence and antisocial behavior in children[57] and incarcerated young adults (when used with essential fatty acids[58]), and improve scores of intelligence in children.[59] Vitamin supplementation has anti-inflammatory benefits, as evidenced by significant reduction in C-reactive protein, (CRP) in a double-blind, placebo-controlled trial.[60] The ability to safely and affordably deliver these benefits makes multimineral-multivitamin supplementation and essential component of any and all health-promoting and disease-prevention strategies. Vitamin A can result in liver damage with chronic consumption of 25,000 IU or more, and intake should generally not exceed 10,000 IU per day in women of childbearing age. Iron should not be supplemented except in patients diagnosed with iron deficiency by the blood test ferritin. Additional vitamin D should be used, as described in the next section.

3. Physiologic doses of vitamin D3: The prevalence of vitamin D deficiency varies from 40 percent (general population) to almost 100 percent (patients with musculoskeletal pain) in the American population. I described the many benefits of vitamin D3 supplementation in the previous issue of *Nutritional Wellness* and in the major monograph published in 2004.[61] In summary, vitamin D deficiency causes or contributes to depression, hypertension, seizures, migraine, polycystic ovary syndrome, inflammation, autoimmunity, and musculoskeletal pain such as low-back pain. Clinical trials using vitamin D supplementation have proven the cause-and-effect relationship between vitamin D deficiency and these conditions by showing that each of these could be cured or alleviated with vitamin D supplementation. In our review of the literature, we concluded that daily vitamin D doses should be 1,000 IU for infants, 2,000 IU for children, and 4,000 IU for adults. Cautions and contraindications include the use of thiazide diuretics (e.g., hydrochlorothiazide) or any other medications that can promote hypercalcemia, as well as granulomatous diseases such as sarcoidosis, tuberculosis, and certain types of cancer, especially lymphoma. Effectiveness is monitored by measuring serum 25-OH-vitamin D, and safety is monitored by measuring serum calcium.
4. Balanced and complete fatty acid supplementation: A detailed survey of the literature reveals five major health-promoting anti-inflammatory fatty acids found in the human diet.[62] These are alpha-linolenic acid (ALA; omega-3, from flaxseed oil), eicosapentaenoic acid (EPA; omega-3, from fish oil), docosahexaenoic acid (DHA; omega-3, from fish oil and algae), gamma-linolenic acid (GLA; omega-6, most concentrated in borage oil), and oleic acid (omega-9, mainly from olive oil, also found in flaxseed and borage oils). Each of these fatty acids has health benefits that cannot be fully attained from supplementing a different fatty acid. The benefits of GLA

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(borage oil) are not attained by consumption of EPA and DHA (fish oil); in fact, consumption of fish oil can actually promote a deficiency of GLA.[63] Likewise, consumption of GLA alone can reduce EPA levels while increasing levels of proinflammatory arachidonic acid; both of these problems are avoided with co-administration of fish oil any time borage oil is used. Using ALA (flaxseed oil) alone only slightly increases EPA but generally leads to no improvement in DHA status and can lead to a reduction of oleic acid; thus, fish oil, olive oil (and borage oil) should be supplemented when flaxseed oil is used.[64] Obviously, the goal here is a balanced intake of all of the health-promoting fatty acids; using only one or two sources of fatty acids is not balanced and results in suboptimal improvement, at best. In clinical practice, I routinely use combination fatty acid therapy comprised of ALA, EPA, DHA, and GLA for essentially all patients. The product also contains a modest amount of oleic acid, and I encourage use of olive oil for salads and cooking. This approach results in complete and balanced fatty acid intake, and the clinical benefits are impressive.

5. Probiotics /gut flora modification: Proper levels of good bacteria promote intestinal health, proper immune function, and support overall health. Excess bacteria or yeast, or the presence of harmful bacteria, yeast, or "parasites" such as amoebas and protozoans, can cause "leaky gut," systemic inflammation, and a wide range of clinical problems. Intestinal flora can become imbalanced by poor diets, excess stress, immunosuppressive drugs, antibiotics, or exposure to contaminated food or water, all of which are common among American patients. Thus, as a rule, I reinstate the good bacteria by the use of probiotics (good bacteria and yeast), prebiotics (fiber, arabinogalactan, and inulin), and the use of fermented foods such as kefir (in patients not allergic to milk). Harmful yeast, bacteria, and other "parasites" can be eradicated with the combination of dietary change, drugs, and/or herbal extracts. For example, oregano oil in an emulsified, time-released form has proven safe and effective for the elimination of various parasites encountered in clinical practice.[65] Likewise, the herb *Artemisia annua* (sweet wormwood) commonly is used to eradicate specific bacteria and has been used for thousands of years in Asia for the treatment and prevention of infectious diseases, including malaria.[66]

Conclusion: In this brief review, I have outlined and scientifically substantiated a fundamental protocol that can serve as effective therapy for patients with a wide range of "diseases." Customizing the Paleo-Mediterranean diet to avoid food allergens, using vitamin-mineral supplements along with physiologic doses of vitamin D and broad-spectrum balanced fatty acid supplementation, and ensuring gastrointestinal health with the skillful use of probiotics, prebiotics, and antimicrobial treatments provides an excellent health-promoting and disease-eliminating foundation and lifestyle for many patients. Often, this simple protocol is all that is needed for the effective treatment of a wide range of clinical problems. For other patients with more complex illnesses, of course, additional interventions and laboratory assessments can be used to customize the treatment plan. However, we must always remember that the attainment and preservation of health requires that we meet the body's basic nutritional needs. This five-step protocol begins the process of meeting those needs. In my next article, I'll give you some examples from my clinical practice and additional references to show this protocol's safety and effectiveness.

Ayurvedic proverb

"When the diet is wrong,
medicine is of no use.
When the diet is correct,
medicine is of no need."

Implementing the Five-Part Nutritional Wellness Protocol for the Treatment of Various Health Problems

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Introduction: In my last article in *Nutritional Wellness* I described a 5-part nutritional protocol that can be used in the vast majority of patients without adverse effects and with major benefits. For many patients, the basic protocol consisting of 1) the Paleo-Mediterranean diet, 2) multivitamin/multimineral supplementation, 3) additional vitamin D3, 4) combination fatty acid therapy with an optimal balance of ALA, GLA, EPA, DHA, and oleic acid, and 5) probiotics (including the identification and eradication of harmful yeast, bacteria, and other "parasites") is all the

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treatment that they need. For patients who need additional treatment, this foundational plan still serves as the core of the biochemical aspect of their intervention. Of course, in some cases, we have to use other lifestyle modifications (such as exercise), additional supplements (such as policosanol or antimicrobial herbs), manual treatments (including spinal manipulation) and occasionally select medications (such has hormone modulators) to obtain our goal of maximum improvement.

The following examples show how the 5-part protocol serves to benefit patients with a wide range of conditions. For the sake of saving space, I will use only highly specific citations to the research literature, since I have provided the other references in the previous issue of *Nutritional Wellness* and elsewhere.[67]

- A Man with High Cholesterol: This patient is a 41-year-old slightly overweight man with very high cholesterol. His total cholesterol was 290 (normal < 200), LDL cholesterol was 212 (normal <130), and his triglycerides were 148 (optimal <100). I am quite certain that nearly every medical doctor would have put this man on cholesterol-lowering statin drugs for life. ***Treatment***: In contrast, I advised a low-carb Paleo-Mediterranean diet because such diets have been shown to reduce cardiovascular mortality more powerfully that "statin" cholesterol-lowing drugs in older patients.[68] Likewise, fatty acid supplementation is more effective than statin drugs for reducing cardiac and all-cause mortality.[69] We added probiotics, because supplementation with *Lactobacillus* and *Bifidobacterium* has been shown to lower cholesterol levels in humans with high cholesterol.[70] Finally, I also prescribed 20 mg of policosanol for its well-known ability to favorably modify cholesterol levels.[71] ***Results***: Within ***one month*** the patient had lost weight, felt better, and his total cholesterol had dropped to normal at 196 (from 290!), LDL was reduced to 141, and triglycerides were reduced to 80. Basically, this treatment plan was "the protocol + policosanol." Drug treatment of this patient would have been more expensive, more risky, and would not have resulted in global health improvements.
- A Child with Intractable Seizures: This is a 4-year-old nonverbal boy with 3-5 seizures per day despite being on two anti-seizure medications and having previously had several other "last resort" medical and surgical procedures. He also had a history of food allergies. ***Treatment***: Obviously, there was no room for error in this case. We implemented a moderately low-carb hypoallergenic diet since both carbohydrate restriction[72] and allergy avoidance[73] can reduce the frequency and severity of seizures. Since many "anti-seizure" medications actually cause seizures by causing vitamin D deficiency[74], I added 800 IU per day of emulsified vitamin D3 for its antiseizure benefit.[75] We used 1 tsp per day of a combination fatty acid supplement that provides balanced amounts of ALA, GLA, EPA, and DHA, since fatty acids appear to have potential antiseizure benefits.[76] Vitamin B-6 (250 mg of P5P) and magnesium (bowel tolerance) were also added to reduce brain hyperexcitability.[77] Stool testing showed an absence of *Bifidobacteria* and *Lactobacillus*; probiotics were added for their anti-allergy benefits.[78] ***Results***: Within about 2 months seizure frequency reduced from 3-5 per day to one seizure every other day: ***an 87% reduction in seizure frequency***. Patient was able to discontinue one of the anti-seizure medications. His parents also noted several global improvements: the boy started making eye contact with people, he was learning again, and intellectually he was "making gains every day." His parents considered this an "amazing difference." Going from 30 seizures per week to 4 seizures per week while reducing medication use by 50% is a major achievement. Notice that we simply used the basic wellness protocol with some additional B6 and magnesium. It is highly unlikely that B6 and magnesium alone would have produced such a favorable response.
- A Young Woman with Full-Body Psoriasis Unresponsive to Drug Treatment: This is a 17-year-old woman with head-to-toe psoriasis since childhood. She wears long pants and long-sleeved shirts year-round, and the

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psoriasis is a major interference to her social life. Medications have ceased to help. ***Treatment***: The Paleo-Mediterranean diet was implemented with an emphasis on food allergy identification.[1] We used a multivitamin-mineral supplement with 200 mcg selenium to compensate for the nutritional insufficiencies and selenium deficiency that are common in patients with psoriasis; likewise 10 mg of folic acid was added to address the relative vitamin deficiencies and elevated homocysteine that are common in these patients.[79] Combination fatty acid therapy with EPA and DHA from fish oil and GLA from borage oil was used for the anti-inflammatory and skin-healing benefits.[80] Vitamin E (1200 IU of mixed tocopherols) and lipoic acid (1,000 mg per day) were added for their anti-inflammatory benefits and to combat the oxidative stress that is characteristic of psoriasis.[81] Of course, probiotics were used to modify gut flora, which is commonly deranged in patients with psoriasis.[82] ***Results***: Within a few weeks, this patient's "lifelong psoriasis" was essentially gone. Food allergy identification and avoidance played a major role in the success of this case. When I saw the patient again 9 months later for her second visit, she had no visible evidence of psoriasis. Her "medically untreatable" condition was essentially cured by the use of my basic protocol, with the addition of a few extra nutrients.

- A Man with Fatigue and Recurrent Numbness in Hands and Feet. This 40-year-old man had seen numerous neurologists and had spent tens of thousands of dollars on MRIs, CT scans, lumbar punctures, and other diagnostic procedures. No diagnosis had been found, and no effective treatment had been rendered by medical specialists. ***Assessments***: We performed a modest battery of lab tests which revealed elevations of fibrinogen and C-reactive protein (CRP), two markers of acute inflammation. Assessment of intestinal permeability with the lactulose-mannitol assay showed major intestinal damage ("leaky gut"). Follow-up parasite testing on different occasions showed dysbiosis caused by *Proteus*, *Enterobacter*, *Klebsiella*, *Citrobacter*, and *Pseudomonas aeruginosa*—of course, these are gram-negative bacteria that can induce immune dysfunction and autoimmunity, as described elsewhere.[1] Specifically, *Pseudomonas aeruginosa* has been linked to the development of nervous system autoimmunity, such as multiple sclerosis.[83] ***Treatment***: We implemented a plan of diet modification, vitamins, minerals, fatty acids, and probiotics. The dysbiosis was further addressed with specific antimicrobial herbs (including caprylic acid and emulsified oregano oil[84]) and drugs (such as tetracycline, Bactrim, and Augmentin). The antibiotic drugs proved to be ineffective based on repeat stool testing. ***Results***: Within one month we witnessed impressive improvements, both subjectively and objectively. Subjectively, the patient reported that the numbness and tingling almost completely resolved. Fatigue was reduced, and energy was improved. Objectively, the patient's elevated CRP plummeted from abnormally high at 11 down to completely normal at 1. Eighteen months later, the patient's CRP had dropped to less than 1 and fatigue and numbness were no longer problematic. Notice that this treatment plan was basically "the protocol" with additional attention to eradicating the dysbiosis we found with specialized stool testing.
- A 50-year-old Man with Rheumatoid Arthritis. This patient presented with a 3-year history of rheumatoid arthritis that had been treated unsuccessfully with drugs (methotrexate and intravenous Remicade). The first time I tested his hsCRP level, it was astronomically high at 124 mg/L (normal is <3). Because of the severe inflammation and other risk factors for sudden cardiac death, I referred this patient to an osteopathic internist for immune-suppressing drugs; the patient refused, stating that he was no longer willing to rely on immune-suppressing chemical medications. His treatment was entirely up to me. ***Assessments and Treatments***: We implemented the Paleo-Mediterranean diet and a program of vitamins, minerals, optimal combination fatty acid therapy (providing ALA, GLA, EPA, DHA, and oleic acid), and 4000 IU of vitamin D in emulsified form to overcome defects in absorption that are seen in older patients and those with gastrointestinal problems.[85] Hormone testing showed abnormally low DHEA, low testosterone, and slightly elevated estrogen; these problems were corrected with DHEA supplementation and the use of a hormone-modulating drug (Arimidex) that lowers estrogen and raises testosterone. Specialized stool testing showed absence of *Lactobacillus* and *Bifidobacteria* and intestinal overgrowth of *Citrobacter* and *Enterobacter* which was corrected with probiotics and antimicrobial treatments including undecylenic acid and emulsified oregano oil. Importantly, I also decided to

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[85] Vasquez A. Subphysiologic Doses of Vitamin D are Subtherapeutic: Comment on the Study by The Record Trial Group. *TheLancet.com* Accessed June 16, 2005

inhibit NFkB (the primary transcription factor that upregulates the pro-inflammatory response[86]) by using a combination botanical formula that contains curcumin, piperine, lipoic acid, green tea extract, propolis, rosemary, resveratrol, ginger, and Phytolens™ (an antioxidant extract from lentils that may inhibit autoimmunity[87])—all of these herbs and nutrients have been shown to inhibit NFkB and to thus downregulate inflammatory responses.[88] ***Results***: Within 6 weeks, this patient had happily lost 10 lbs of excess weight and was able to work without pain for the first time in years. **Follow-up testing showed that his hsCRP had dropped from 124 to 7 mg/L—a drop of 114 points—95%!—in less than one month: better than had ever been achieved even with the use of intravenous immune-suppressing drugs!** This patient continues to make significant progress. Obviously this case was complex, and we needed to do more than the basic protocol. Nonetheless, the basic protocol still served as the foundation for the treatment plan. Note that vitamin D has significant anti-inflammatory benefits and can cause major reductions in inflammation measured by CRP.[89] The correction of the hormonal abnormalities and the dysbiosis, and downregulating NFkB with several botanical extracts were also critical components of this successful treatment plan.

Summary and Conclusions: These examples show how the nutritional wellness protocol that I described in the September issue of *Nutritional Wellness* can be used as the foundational treatment for a wide range of health problems. In many cases, implementation of the basic protocol is all that is needed. In more complex situations, we use the basic protocol and then add more specific treatments to address dysbiosis and hormonal problems, and we can add additional nutrients as needed. However, nothing will ever replace a healthy diet, sufficiencies of vitamin D and all five of the health-promoting fatty acids (i.e., ALA, GLA, EPA, DHA, and oleic acid), and normalization of gastrointestinal flora. Without these basics, survival and the appearance of health are possible, but true health and recovery from "untreatable" illnesses is not possible. In order to attain optimal health, we have to create the conditions that allow for health to be attained, and we start this process by supplying the body with the nutrients that it needs to function optimally. In the words of naturopathic physician Jared Zeff from the *Journal of Naturopathic Medicine*, "The work of the naturopathic physician is to elicit healing by helping patients to create or recreate the conditions for health to exist within them. Health will occur where the conditions for health exist. Disease is the product of the conditions which allow for it."[90]

Common Oversights and Shortcomings in the Study and Implementation of Nutritional Supplementation

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Introduction: An impressive discrepancy often exists between the low efficacy of nutritional interventions reported in the research literature and the higher efficacy achieved in the clinical practices of clinicians trained in the use of interventional nutrition (i.e., naturopathic physicians). This discrepancy is dangerous for at least two reasons. First, it results in an undervaluation of the efficacy of nutritional supplementation, which ultimately leaves otherwise treatable patients untreated. Second, such untreated and undertreated patients are often then forced to use dangerous and expensive pharmaceutical drugs and surgical interventions to treat conditions that could have otherwise been easily and safely treated with nutritional supplementation and diet modification. Consequently, the burden of suffering, disease, and healthcare expense in the US is higher than it would be if nutritionally-trained clinicians were more fully integrated into the healthcare system.

Obstacles to Efficacy in the Use of Nutritional Supplementation: Below are listed some of the most common causes for the underachievement of nutritional supplementation in practice and in published research. While this list is not all-inclusive, it will serve as a review for clinicians and an introduction for chiropractic/naturopathic

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students. In both practice and research, the problems listed below often overlap and function synergistically to reduce the efficacy of nutritional supplementation.

1. Inadequate dosing (quantity): Many clinical trials published in major journals and many doctors in clinical practice have used inadequate doses of vitamins (and other natural therapeutics) and have thus failed to achieve the results that would have easily been obtained had they implemented their protocol with the proper physiologic or supraphysiologic dose of intervention. The best example in my experience centers on vitamin D, where so many of the studies are performed with doses of 400-800 IU per day only to conclude that vitamin supplementation is ineffective for the condition being treated. The problem here is that the researchers failed to appreciate that the physiologic requirement for vitamin D3 in adults is approximately 3,000-5,000 IU per day[91] and that therefore their supplemental dose of 400-800 IU is only 10-20% of what is required. Subphysiologic doses are generally subtherapeutic. In this regard, I have had to correct journals such as *The Lancet*[92], *JAMA*[93], and *British Medical Journal*[94] from misleading their readers (many of whom are major policymakers) from concluding that nutritional supplementation is impotent; rather, their researchers and editors were not sufficiently educated in the design and review of studies using nutritional interventions. These journals should hire chiropractic and naturopathic physicians so that they have staff trained in natural treatments and who can thus provide an educated review of studies on these topics.[95]
2. Inadequate dosing (duration): Often the effects of long-term nutritional deficiency are not fully reversible and/or may require a treatment period of months or years to achieve maximal clinical response. For example, full replacement of fatty acids in human brain phospholipids is an ongoing process that occurs over a period of several years; thus studies using fatty acid supplements for a period of weeks or 2-3 months generally underestimate the enhanced effectiveness that can be obtained with administration over many months or several years of treatment. Relatedly, recovery from vitamin D deficiency takes several weeks of high-dose supplementation in order to achieve tissue saturation and subsequent cellular replenishment; studies of short duration are destined to underestimate the results that could have been achieved with supplementation carried out over several months.[96]
3. Failure to use proper forms of nutrients (quality): Nutrients are often available in different forms, not the least of which are "active" versus "inactive" and "natural" versus "unnatural." Most vitamin supplements, particularly high-potency B vitamins, are manufactured synthetically and are not from "natural sources" despite the marketing hype promulgated by companies that, for example, mix their synthetic vitamins with a vegetable powder and then call their vitamin supplements "natural." The simple fact is that production of high-potency supplements from purely natural sources would be prohibitively wasteful, inefficient, and expensive. Thus, while it is not necessary for vitamins to be "natural" in order to be useful, it is necessary that the vitamins are useable and preferably not "unnatural." The best example of the use of unnatural supplements is the use of synthetic DL-tocopherol in the so-called "vitamin E" studies; DL-tocopherol is 50% comprised of the L-isomer of tocopherol which is not only unusable by the human body but is actually harmful in that it interferes with normal metabolism and can exacerbate hypertension and cause symptomatic complications (e.g., headaches). Further, tocopherols exist within the body in relationship with the individual forms of the vitamin, such that supplementation with one form (e.g., alpha-tocopherol) can result in a relative deficiency of another form (e.g., gamma-tocopherol). One final example of the failure to use proper forms of nutrients is in the use of pyridoxine HCl as a form of vitamin B6; while this practice itself is not harmful, clinicians need to remember that pyridoxine HCl is ineffective until converted to the more active forms of the vitamin including pyridoxal-5-phosphate. Since this conversion requires co-nutrients such as magnesium and zinc, we can easily see that the reputed failure of B6 supplementation when administered in the form of pyridoxine HCl might actually be due to untreated insufficiencies of required co-nutrients, as discussed in the following section.
4. Failure to ensure adequacy of co-nutrients: Vitamins, minerals, amino acids, and fatty acids work together in an intricately choreographed and delicately orchestrated dance that culminates in the successful completion of

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[95] Vasquez A. Allopathic Usurpation of Natural Medicine. *Naturopathy Digest* 2006 Feb naturopathydigest.com/archives/2006/feb/vasquez.php
[96] Vasquez A, Manso G, Cannell J. The clinical importance of vitamin D (cholecalciferol): a paradigm shift. *Altern Ther Health Med*. 2004 Sep-Oct;10(5):28-36

interconnected physiologic functions. If any of the performers in this event are missing (i.e., nutritional deficiency) or if successive interconversions are impaired due to lack of enzyme function, then the show cannot go on, or—if it does go on—impaired metabolism and defective function will result. So, if we take a patient with "vitamin B6 deficiency" and give him vitamin B6 in the absence of other co-nutrients needed for the proper activation and metabolic utilization of vitamin B6, we cannot honestly expect the "nutritional supplementation" to work in this case; rather, we might see a marginal benefit or perhaps even a negative outcome as an imbalanced system is pushed into a different state of imbalance despite supplementation with the "correct" vitamin. In the case of vitamin B6, necessary co-nutrients include zinc, magnesium, and riboflavin; deficiency of any of these will result in a relative "failure" of B6 supplementation even if a patient has a B6-responsive condition. Notably, overt magnesium deficiency is alarmingly common among patients and citizens in industrialized nations[97,98,99], and this epidemic of magnesium deficiency is due not only to insufficient intake but also to excessive excretion caused by consumption of high-glycemic foods, caffeine, and a diet that promotes chronic metabolic acidosis with resultant urinary acidification.

5. Failure to achieve urinary alkalinization: Western/American-style diets typified by overconsumption of grains, dairy, sugar, and salt result in a state of subclinical chronic metabolic acidosis which results in urinary acidification, relative hypercortisolemia, and consequent hyperexcretion of minerals such as calcium and magnesium.[100] [101] Thus, the common conundrum of magnesium replenishment requires not only magnesium supplementation but also dietary interventions to change the internal climate to one that is conducive to bodily retention and cellular uptake of magnesium.[102]
6. Use of mislabeled supplements: Even in the professional arena of nutritional supplement manufacturers, some companies habitually underdose their products either in an attempt to spend less in the manufacture of their products or as a consequence of poor quality control. If a product is labeled to contain 1,000 IU of vitamin D but only contains 836 IU of the nutrient, then obviously full clinical efficacy will not be achieved; this was a problem in a recent clinical trial involving vitamin D.[103] The problem for clinicians is in trusting the companies that supply nutritional supplements; some companies do "in house" testing which lacks independent review, while other companies use questionable "independent testing" which is not infrequently performed by a laboratory that is a wholly owned subsidiary of the parent nutritional company. Manufacturing regulations that are sweeping through the industry will cleanse the nutritional supplement world of poorly made products, and these same regulations will sweep some unprepared companies right out the door when they are unable to meet the regulatory requirements.
7. Failure to ensure/assess bioavailability and optimal serum/cellular levels: Clinical trials with nutritional therapies need to monitor serum or cellular levels to ensure absorption, product bioavailability, and the attainment of optimal serum levels. This is particularly relevant in the treatment of chronic disorders such as the autoimmune diseases, wherein so many of these patients have gastrointestinal dysbiosis and often have concomitant nutrient malabsorption.[104] Simply dosing these patients with supplements is not always efficacious; often the gut must be cleared of dysbiosis so that the mucosal lining can be repaired and optimal nutrient absorption can be reestablished.
8. Coadministration of food with nutritional supplements (sometimes right, sometimes wrong): Food can help or hinder the absorption of nutritional supplements. Phytate and tannins in grains and teas, respectively, are notorious for inhibiting mineral absorption. Some supplements, like coenzyme Q10, should be administered with fatty food to enhance absorption. Other supplements, like amino acids, should be administered away from

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[99] "Suboptimal levels were detected in 33.7 per cent of the population under study. These data clearly demonstrate that the Mg supply of the German population needs increased attention." Schimatschek et al. Prevalence of hypomagnesemia in an unselected German population of 16,000 individuals. *Magnes Res*. 2001 Dec;14(4):283-90
[100] Cordain L, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005 Feb;81(2):341-54
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[103] Heaney RP, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003 Jan;77(1):204-10
[104] Vasquez A. Nutritional and Botanical Treatments Against "Silent Infections" and Gastrointestinal Dysbiosis. *Nutritional Perspectives* 2006; January

protein-rich foods and are often better administered with simple carbohydrate to enhance cellular uptake; this is especially true with tryptophan.

9. Correction of gross dietary imbalances enhances supplement effectiveness: If the diet is grossly imbalanced, then nutritional supplementation is less likely to be effective. The best example of this is in the use of fatty acid supplements, particularly in the treatment of inflammatory disorders. If the diet is laden with dairy, beef, and other sources of arachidonate, then fatty acid supplementation with EPA, DHA, and GLA is much less likely to be effective, or much higher doses of the supplements will need to be used in order to help restore fatty acid balance. Generally speaking, the diet needs to be optimized to enhance the efficacy of nutritional supplementation.

Conclusion: In this brief review, I have listed and discussed some of the most common impediments to the success of nutritional supplementation. I hope that naturopathic students, clinicians, and researchers will find these points helpful in their design of clinical treatment protocols.

Revisiting the Five-Part Nutritional Wellness Protocol: Supplemented Paleo-Mediterranean Diet

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Abstract: This article reviews the five-part nutritional protocol that incorporates a health-promoting nutrient-dense diet and essential supplementation with vitamins/minerals, specific fatty acids, probiotics, and physiologic doses of vitamin D3. This foundational nutritional protocol has proven benefits for disease treatment, disease prevention, and health maintenance and restoration. Additional treatments such as botanical medicines, additional nutritional supplements, and pharmaceutical drugs can be used atop this foundational protocol to further optimize clinical effectiveness. The rationale for this five-part protocol is presented, and consideration is given to adding iodine-iodide as the sixth component of the protocol.

Introduction: In 2004 and 2005 I first published a "five-part nutrition protocol"[105,106] that provides the foundational treatment plan for a wide range of health disorders. This protocol served and continues to serve as the foundation upon which other treatments are commonly added, and without which those other treatments are likely to fail, or attain suboptimal results at best.[107] Now as then, I will share with you what I consider a basic foundational protocol for wellness promotion and disease treatment. I have used this protocol in my own self-care for many years and have used it in the treatment of a wide range of health-disease conditions in clinical practice.

This nutritional protocol is validated by biochemistry, physiology, experimental research, peer-reviewed human trials, and the clinical application of common sense. It is the most nutrient-dense diet available, satisfying nutritional needs and thereby optimizing metabolic processes while promoting satiety and weight loss/optimization. Nutrients are required in the proper amounts, forms, and approximate ratios for critical and innumerable physiologic functions; if nutrients are lacking, the body cannot function *normally*, let alone *optimally*. Impaired function results in subjective and objective manifestations of what is eventually labeled as "disease." Thus, a powerful and effective alternative to treating diseases with drugs is to re-establish normal/optimal physiologic function by replenishing the body with essential nutrients, reestablishing hormonal balance ("orthoendocrinology"), promoting detoxification of environmental toxins, and by reestablishing the optimal microbial milieu, especially the eradication of (multifocal) dysbiosis; this multifaceted approach can be applied to several diseases, especially those of the inflammatory and autoimmune varieties.[108]

Of course, most diseases are multifactorial and therefore require multicomponent treatment plans, and some diseases actually require the use of drugs in conjunction with assertive interventional nutrition. However, while only a smaller portion of patients actually need drugs for the long-term management their problems, all clinicians should agree that everyone needs a foundational nutrition plan because nutrients—not drugs—are universally required for life and health. This five-part nutrition protocol is briefly outlined below; a much more detailed substantiation of the underlying science and clinical application of this protocol was recently published in a review of more than 650 pages and approximately 3,500 citations.[109]

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[106] Vasquez A.Five-Part Nutritional Protocol that Produces Consistently Positive Results.*NutrWellness*2005Sep nutritionalwellness.com/archives/2005/sep/09_vasquez.php
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1. Health-promoting Paleo-Mediterranean diet: Following an extensive review of the research literature, I developed what I call the "supplemented Paleo-Mediterranean diet." In essence, this diet plan combines the best of the Mediterranean diet with the best of the Paleolithic diet, the latter of which has been best distilled by Dr. Loren Cordain in his book "The Paleo Diet"[110] and his numerous scientific articles.[111,112,113] The Paleolithic diet is superior to the Mediterranean diet in nutrient density for promoting satiety, weight loss, and improvements/normalization in overall metabolic function.[114,115] This diet places emphasis on fruits, vegetables, nuts, seeds, and berries that meet the body's needs for fiber, carbohydrates, and most importantly, the 8,000+ phytonutrients that have additive and synergistic health effects[116]—including immunomodulating, antioxidant, anti-inflammatory, and anti-cancer benefits. High-quality protein sources such as fish, poultry, eggs, and grass-fed meats are emphasized. Slightly modifying Cordain's Paleo diet, I also advocate soy and whey protein isolates for their high-quality protein and their anticancer, cardioprotective, and mood-enhancing (due to the high tryptophan content) benefits. Potatoes and other starchy vegetables, wheat and other grains including rice are discouraged due to their high glycemic indexes and high glycemic loads, and their relative insufficiency of fiber and phytonutrients compared to fruits and vegetables. Grains such as wheat, barley, and rye are discouraged due to the high glycemic loads/indexes of most breads, pastries, and other grain-derived products, as well as due to the immunogenicity of constituents such as gluten, a protein composite (consisting of a prolamin and a glutelin) that can contribute to disorders such as migraine, epilepsy, eczema, arthritis, celiac disease, psoriasis and other types of autoimmunity. Sources of simple sugars and foreign chemicals such as colas/sodas (which contain artificial colors, flavors, and high-fructose corn syrup, which contains mercury[117] and which can cause the hypertensive-diabetic metabolic syndrome[118]) and processed foods (e.g., "TV dinners" and other manufactured snacks and convenience foods) are strictly forbidden. Chemical preservatives, colorants, sweeteners, flavor-enhancers such as monosodium glutamate and carrageenan are likewise avoided. In summary, this diet plan provides plenty of variety, as most dishes comprised of poultry, fish, lean meats, soy, eggs, fruits, vegetables, nuts, berries, and seeds are allowed. The diet provides an abundance of fiber, phytonutrients, carbohydrates, potassium, and protein, while simultaneously being low in fat, sodium, arachidonic acid, and "simple sugars." The diet must be customized with regard to total protein and calorie intake, as determined by the size, status, and activity level of the patient; individual per-patient food allergens should be avoided. Regular consumption of this diet has shown the ability to reduce hypertension, alleviate diabetes, ameliorate migraine headaches, and result in improvement of overall health and a lessening of the severity of many common "diseases", particularly those with an autoimmune or inflammatory component. This Paleo-Mediterranean diet is supplemented with vitamins, minerals, fatty acids, and probiotics—making it the "supplemented Paleo-Mediterranean diet" as described below. The main considerations/contraindications to recommending increased intake of fruits and vegetables are 1) increased intake of vitamin K in the few patients taking warfarin for anticoagulation, and 2) increased intake of potassium in patients with pre-existing renal insufficiency as discussed in this video tutorial: vimeo.com/152296851 also at vimeo.com/152293616.
2. Multivitamin and multimineral supplementation: Vitamin and mineral supplementation has been advocated for decades by the chiropractic/naturopathic professions while being scorned by so-called "mainstream

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[113] Cordain L, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005 Feb;81(2):341-54
[114] "A high micronutrient density diet mitigates the unpleasant aspects of the experience of hunger even though it is lower in calories. Hunger is one of the major impediments to successful weight loss. Our findings suggest that it is not simply the caloric content, but more importantly, the micronutrient density of a diet that influences the experience of hunger. It appears that a high nutrient density diet, after an initial phase of adjustment during which a person experiences "toxic hunger" due to withdrawal from pro-inflammatory foods, can result in a sustainable eating pattern that leads to weight loss and improved health." Fuhrman J, Sarter B, Glaser D, Acocella S. Changing perceptions of hunger on a high nutrient density diet. *Nutr J*. 2010 Nov 7;9:51 nutritionj.com/content/9/1/51
[115] "The Paleolithic group were as satiated as the Mediterranean group but consumed less energy per day (5.8 MJ/day vs. 7.6 MJ/day, Paleolithic vs. Mediterranean, p=0.04). Consequently, the quotients of mean change in satiety during meal and mean consumed energy from food and drink were higher in the Paleolithic group (p=0.03). Also, there was a strong trend for greater Satiety Quotient for energy in the Paleolithic group (p=0.057). Leptin decreased by 31% in the Paleolithic group and by 18% in the Mediterranean group with a trend for greater relative decrease of leptin in the Paleolithic group." Jonsson T, Granfeldt Y, Erlanson-Albertsson C, Ahren B, Lindeberg S. A Paleolithic diet is more satiating per calorie than a Mediterranean-like diet in individuals with ischemic heart disease. *Nutr Metab* (Lond). 2010 Nov 30;7(1):85.
[116] Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am J Clin Nutr* 2003;78(3 Suppl):517S-520S
[117] "With daily per capita consumption of HFCS in the US averaging about 50 grams and daily mercury intakes from HFCS ranging up to 28 µg, this potential source of mercury may exceed other major sources of mercury especially in high-end consumers of beverages sweetened with HFCS." Dufault R, et al. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health*. 2009 Jan 26;8:2 ehjournal.net/content/8/1/2
[118] Vasquez A. *Integrative Medicine and Functional Medicine for Chronic Hypertension: An Evidence-based Patient-Centered Monograph for Advanced Clinicians*. IBMRC; 2011. See also: Reungjui S, et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. *J Am Soc Nephrol*. 2007 Oct;18(10):2724-31

medicine." Vitamin and mineral supplementation finally received bipartisan endorsement when researchers from Harvard Medical School published a review article in *Journal of the American Medical Association* that concluded, "Most people do not consume an optimal amount of all vitamins by diet alone. ...it appears prudent for all adults to take vitamin supplements."[119] Long-term nutritional insufficiencies experienced by "most people" promote the development of "long-latency deficiency diseases"[120] such as cancer, neuroemotional deterioration, and cardiovascular disease. Impressively, the benefits of multivitamin/multimineral supplementation have been demonstrated in numerous clinical trials. Multivitamin/multimineral supplementation has been shown to improve nutritional status and reduce the risk for chronic diseases[121], improve mood[122], potentiate antidepressant drug treatment[123], alleviate migraine headaches (when used with diet improvement and fatty acids[124]), improve immune function and infectious disease outcomes in the elderly[125] (especially diabetics[126]), reduce morbidity and mortality in patients with HIV infection[127,128], alleviate premenstrual syndrome[129,130] and bipolar disorder[131], reduce violence and antisocial behavior in children[132] and incarcerated young adults (when used with essential fatty acids[133]), and improve scores of intelligence in children.[134] Multivitamin and multimineral supplementation provides anti-inflammatory benefits, as evidenced by significant reduction in C-reactive protein (CRP) in a double-blind, placebo-controlled trial.[135] The ability to safely and affordably deliver these benefits makes multimineral-multivitamin supplementation an essential component of any and all health-promoting and disease-prevention strategies. A few cautions need to be observed; for example, vitamin A can (rarely) result in liver damage with chronic consumption of 25,000 IU or more, and intake should generally not exceed 10,000 IU per day in women of childbearing age. Also, iron should not be supplemented except in patients diagnosed with iron deficiency by a blood test (serum ferritin).

3. Physiologic doses of vitamin D3: The prevalence of vitamin D deficiency varies from 40-80 percent (general population) to almost 100 percent (patients with musculoskeletal pain) among Americans and Europeans. Vasquez, Manso, and Cannell described the many benefits of vitamin D3 supplementation in a "paradigm-shifting" review published in 2004.[136]

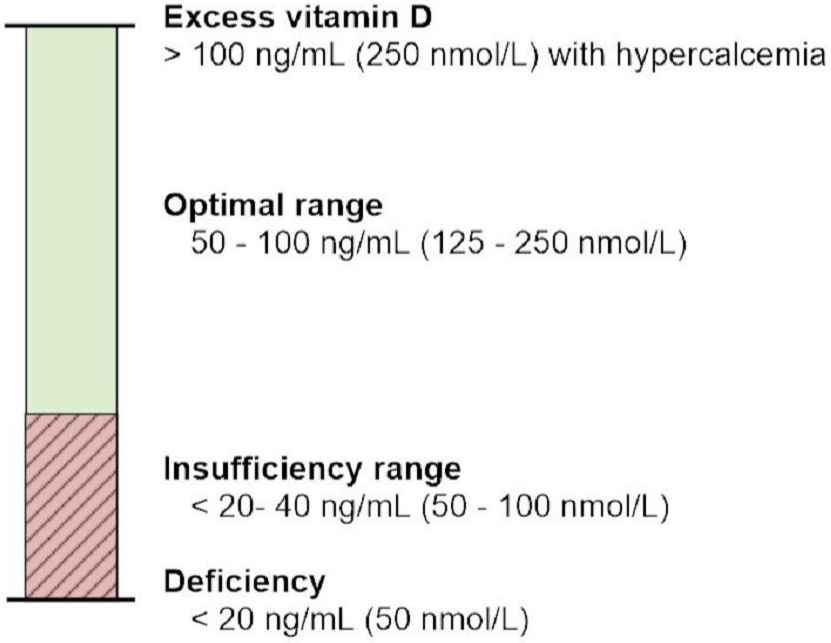

Image right: Interpretation of serum 25(OH) vitamin D levels: Updated from Vasquez et al, *Alternative Therapies in Health and Medicine* 2004 Sep

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Our review showed that vitamin D deficiency causes or contributes to depression, hypertension, seizures, migraine, polycystic ovary syndrome, inflammation, autoimmunity, and musculoskeletal pain, particularly low-back pain. Clinical trials using vitamin D supplementation have proven the cause-and-effect relationship between vitamin D deficiency and most of these conditions by showing that each could be cured or alleviated with vitamin D supplementation. Per our review, daily vitamin D doses should be 1,000 IU for infants, 2,000 IU for children, and 4,000 IU for adults, although some adults respond better to higher doses of 10,000 IU per day. Cautions/contraindications include the use of thiazide diuretics (e.g., hydrochlorothiazide) or any other medications that promote hypercalcemia, as well as granulomatous diseases such as sarcoidosis, tuberculosis, and certain types of cancer, especially lymphoma. Effectiveness is monitored by measuring serum 25-OH-vitamin D, and safety is monitored by measuring serum calcium. Dosing should be tailored for the attainment of optimal serum levels of 25-hydroxy-vitamin D3, generally 50-100 ng/ml (125-250 nmol/l) as illustrated.

4. Balanced and complete fatty acid supplementation: A detailed survey of the literature shows that five fatty acids have major health-promoting disease-preventing benefits and should therefore be incorporated into the daily diet and/or regularly consumed as dietary supplements.[137] These are alpha-linolenic acid (ALA; omega-3, from flaxseed oil), eicosapentaenoic acid (EPA; omega-3, from fish oil), docosahexaenoic acid (DHA; omega-3, from fish oil and algae), gamma-linolenic acid (GLA; omega-6, most concentrated in borage oil but also present in evening primrose oil, hemp seed oil, black currant seed oil), and oleic acid (omega-9, most concentrated in olive oil, which contains in addition to oleic acid many anti-inflammatory, antioxidant, and anticancer phytonutrients). Supplementing with one fatty acid can exacerbate an insufficiency of other fatty acids; hence the importance of balanced combination supplementation. Each of these fatty acids has health benefits that cannot be fully attained from supplementing a different fatty acid; hence, again, the importance of balanced combination supplementation. The benefits of GLA are not attained by consumption of EPA and DHA; in fact, consumption of fish oil can actually promote a deficiency of GLA.[138] Likewise, consumption of GLA alone can reduce EPA levels while increasing levels of proinflammatory arachidonic acid; both of these problems are avoided with co-administration of EPA any time GLA is used because EPA inhibits delta-5-desaturase, which converts dihomo-GLA into arachidonic acid. Using ALA alone only slightly increases EPA but generally leads to no improvement in DHA status and can lead to a reduction of oleic acid; thus, DHA and oleic acid should be supplemented when flaxseed oil is used.[139] Obviously, the goal here is physiologically-optimal (i.e., "balanced") intake of all of the health-promoting fatty acids; using only one or two sources of fatty acids is not balanced and results in suboptimal improvement. In clinical practice, I routinely use combination fatty acid therapy comprised of ALA, EPA, DHA, and GLA for essentially all patients; when one appreciates that the average daily Paleolithic intake of n-3 fatty acids was 7 grams per day contrasted to the average daily American intake of 1 gram per day, we can see that—by using combination fatty acid therapy emphasizing n-3 fatty acids—we are simply meeting physiologic expectations via supplementation, rather than performing an act of recklessness or heroism. The product I use also contains a modest amount of oleic acid that occurs naturally in flax and borage seed oils, and I encourage use of olive oil for salads and cooking. This approach results in complete and balanced fatty acid intake, and the clinical benefits are impressive. Benefits are to be expected in the treatment of premenstrual syndrome, diabetic neuropathy, respiratory distress syndrome, Crohn's disease, lupus, rheumatoid arthritis, cardiovascular disease, hypertension, psoriasis, eczema, migraine headaches, bipolar disorder, borderline personality disorder, mental depression, schizophrenia, osteoporosis, polycystic ovary syndrome, multiple sclerosis, and musculoskeletal pain. The discovery in September 2010 that the G protein-coupled receptor 120 (GPR120) functions as an n-3 fatty acid receptor that, when stimulated with EPA or DHA, exerts broad anti-inflammatory effects (in cell experiments) and enhances systemic insulin sensitivity (in animal study) confirms a new mechanism of action of fatty acid supplementation and shows that we as clinician-researchers are still learning the details of the beneficial effects of commonly used treatments.[140]

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5. Probiotics /gut flora modification: Proper levels of good bacteria promote intestinal health, support proper immune function, and encourage overall health. Excess bacteria or yeast, or the presence of harmful bacteria, yeast, or "parasites" such as amoebas and protozoans, can cause "leaky gut," systemic inflammation, and a wide range of clinical problems, especially autoimmunity. Intestinal flora can become imbalanced by poor diets, excess stress, immunosuppressive drugs, and antibiotics, and all of these factors are common among American patients. Thus, as a rule, I reinstate the good bacteria by the use of probiotics (good bacteria and yeast), prebiotics (fiber, arabinogalactan, and inulin), and the use of fermented foods such as kefir and yogurt for patients not allergic to milk. Harmful yeast, bacteria, and other "parasites" can be eradicated with the combination of dietary change, antimicrobial drugs, and/or herbal extracts. For example, oregano oil in an emulsified, time-released form has proven safe and effective for the elimination of various parasites encountered in clinical practice.[141] Likewise, the herb *Artemisia annua* (sweet wormwood) commonly is used to eradicate specific bacteria and has been used for thousands of years in Asia for the treatment and prevention of infectious diseases, including drug-resistant malaria.[142] Restoring microbial balance by providing probiotics, restoring immune function (immunorestoration) and eliminating sources of dysbiosis, especially in the gastrointestinal tract, genitourinary tract, and oropharynx, is a very important component in the treatment plan of autoimmunity and systemic inflammation.[143]

Should combinations of iodine and iodide be the sixth component of the Protocol?*: Both iodine and iodide have biological activity in humans. An increasing number of clinicians are using combination iodine-iodide products to provide approximately 3-6 mg/d [changed/corrected*]. Collectively, iodine and iodide provide antioxidant, antimicrobial, mucolytic, immunosupportive, antiestrogen, and anticancer benefits that extend far beyond the mere incorporation of iodine into thyroid hormones.[5] Benefits of iodine/iodide in the treatment of asthma[144,145] and systemic fungal infections[146,147] have been documented, and many clinicians use combination iodine/iodide supplementation for the treatment of estrogen-driven conditions such as fibrocystic breast disease.[148] While additional research is needed and already underway to further establish the role of iodine-iodide as a routine component of clinical care, clinicians can reasonably begin incorporating this nutrient into their protocols based on the above-mentioned physiologic roles and clinical benefits. *See update/addendum following this reprint.*

Summary and Conclusions: In this brief review, I have described and substantiated a fundamental protocol that can serve as effective therapy for patients with a wide range of diseases and health disorders. Customizing the Paleo-Mediterranean diet to avoid patient-specific food allergens, using vitamin-mineral supplements along with physiologic doses of vitamin D and broad-spectrum balanced fatty acid supplementation, and ensuring "immunomicrobial" health with the skillful use of probiotics, prebiotics, immunorestoration, and antimicrobial treatments provides an excellent health-promoting and disease-eliminating foundation and lifestyle for many patients. Often, this simple protocol is all that is needed for the effective treatment of a wide range of clinical problems, even those that have been "medical failures" for many years. For other patients with more complex illnesses, of course, additional interventions and laboratory assessments can be used to optimize and further customize the treatment plan. Clinicians should avoid seeking "silver bullet" treatments that ignore overall metabolism, immune function, and inflammatory balance, and we must always remember that the attainment and preservation of health requires that we first meet the body's basic nutritional and physiologic needs. This five-step protocol begins the process of meeting those needs. With it, health can be restored and the need for disease-specific treatment is obviated or reduced; without it, fundamental physiologic needs are not met, and health cannot be obtained and maintained. Addressing core physiologic needs empowers doctors to deliver the most effective healthcare possible, and it allows patients to benefit from such treatment.

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***Update and addendum to information on iodine and iodide**:

- Authoritative enthusiasm for high-dose iodine-iodide: Several authoritative articles/authors stated that an advisable level of intake for iodine-iodide for the prevention and treatment of various conditions is approximately 12 mg/d. Because of these well-referenced and apparently authoritative publications, many clinicians and nutrition professionals began using higher doses iodine-iodide with patients and clients, quite often with benefit and nearly always with the absence of serious adverse effects. Several popular nutritional supplements used by clinicians and nutritionists contain both iodi*n*e (the *n*atural, diatomic form) and iodi*d*e (the *d*ivided/ionic form most commonly consumed in *d*ietary supplements, such as potassium iodi*d*e); both forms of this volatile metal have biologic properties in humans. Benefits of iodine-iodide supplementation focus mostly on the mucolytic, antimicrobial, and anti-estrogen effects.
    - Dr Jonathan V Wright (*Nutrition and Healing* 2002 Nov and 2005 May): In *Nutrition and Healing* (2002 Nov), well-respected nutrition expert, pioneer, and clinician Jonathan V. Wright MD advocated high-dose iodine-iodide for a wide range of conditions, particularly those related to inflammation, excess estrogen, and microbial infections. In another issue of *Nutrition and Healing* (2005 May) Dr Wright wrote "12.5 milligrams (that's 12,500 micrograms) is the optimal daily amount of iodine, not only for your thyroid but for the rest of your body, too." In that same article, Dr Wright stated, "The Japanese have traditionally consumed more iodine, mostly from seaweed, than any other population. The average daily intake of iodine in Japan [is] 13.8 milligrams…", and throughout the article Dr Wright advocates that 12.5 mg/d is "the optimal daily dose" of combined iodine-iodine.
    - Extrathyroidal benefits of iodine (*Journal of American Physicians and Surgeons* 2006 Winter): Independently and in a peer-reviewed publication, Donald Miller MD (Professor of Surgery, Division of Cardiothoracic Surgery, University of Washington School of Medicine) supported the daily intake of 12.5 mg/d in *Journal of American Physicians and Surgeons* and even supported higher doses with the statement "More than 4,000 patients in this project [Iodine Project] take iodine in daily doses ranging from 12.5 to 50 mg, and those with diabetes can take up to 100 mg /day." Miller also noted that dermatologists "treat inflammatory dermatoses, like nodular vasculitis and pyoderma gangrenosum, with SSKI (supersaturated potassium iodide), beginning with an iodine dose of 900 mg/day, followed by weekly increases of up to 6 g/day as tolerated. Fungal eruptions, like sporotrichosis, are treated initially in gram amounts with great effect."
    - Iodine deficiency and therapeutic considerations (*Alternative Medicine Review* 2008 Jun): In 2008, Patrick wrote "Estimates of the average daily Japanese iodine consumption vary from 5,280 mcg to 13,800 mcg…" and this again supported and reinforced enthusiasm for doses of approximately 12 mg/d of iodine-iodine. However, in this article, Patrick did not advocate any specific daily dosage, citing 3-6 mg/d as beneficial and without adverse effect.
- Review, reanalysis, and caution: Soon after these enthusiastic publications, Alan Gaby MD published in several magazines, presented in post-graduate educational events, and discussed in his book *Nutritional Medicine* a review and reanalysis of the original data and concluded that the estimated average daily intake of iodine-iodine in Japan had been *overestimated* by a mathematical error (mistakenly interchanging wet and dry weights of seaweed and thus overestimating the daily Japanese intake of iodine-iodine). Per Gaby (*Nutritional Medicine*, page 175), the true intake of iodine-iodide in Japan averages 330-500 mcg/d, which is 25-fold lower than the estimate of 13.8 mg/d, upon which rested much of the rationale for implementing high-dose iodine-iodide supplementation empirically and routinely.
- Benefits, perspectives, and additional research: Many clinicians including the current author have used high-dose iodine-iodide ranging from approximately 12-48 mg/d for variable periods of time without personally experiencing or clinically observing apparent adverse effects; that statement does not imply endorsement of routine universal high-dose iodine-iodide supplementation. Some degree of caution is advised in consideration of the risks of inducing thyroid dysfunction (hyperthyroidism, hypothyroidism), intestinal hemorrhage[149], and

[149] Kinoshita et al. Severe duodenal hemorrhage induced by Lugol's solution administered for thyroid crisis treatment. *Intern Med.* 2010;49(8):759-61

anaphylaxis-like reactions.[150] Topical and systemic antimicrobial benefits of iodine-iodide are well known and well documented; oral high-dose iodine-iodide has been used to treat drug-resistant fungal infections (cited below). When applied for sufficient concentrations and durations, both diatomic iodine and ionic iodide possess potent broad-spectrum antimicrobial properties; essentially no "drug resistance" against iodine-iodide exists for bacteria, fungi, viruses, and protozoans. Iodine also has documented molecular and clinical anti-estrogen effects, thus providing scientific explanation for its ability to treat and prevent estrogen-related disorders ranging from fibrocystic breast disease to cancer. Indeed, iodine treatment of breast cancer cells has been shown to increase the mRNA levels of several genes involved in estrogen metabolism and "detoxification" such as cytochrome p450-1A1 while also decreasing the levels of estrogen responsive genes such as TFF1 and WISP2; also noted following iodine treatment is upregulation of gene expression for the enzyme glutathione peroxidase, an important selenium-dependent component of antioxidant defense mechanisms.[151]

- Ultra-high dose iodide for sporotrichosis in childhood (*Pediatric Dermatology* 2007 Jul-Aug): Nineteen pediatric patients with proven sporotrichosis were successfully treated with potassium iodide per the following quoted protocol: "All patients were initially treated with potassium iodide (KI), and only those who were unresponsive or who developed side effects were given itraconazole. The dose of KI used was 1–3 g/day, starting at 1 g/day and increasing until the dose of 3 g/day was reached. … Treatments were sustained until remission was reached, which ranged from 3 to 6 months."[152] Per the review by Miller[153] cited previously, KI 1g (1,000 mg) contains 770 mg of iodide. Thus, the pediatric patients in this case series were treated with 770-2,310 mg/d of iodide for successful antimycotic treatment. Two patients from the original group of 23 patients experienced nausea and vomiting from the KI and were switched to itraconazole; two other patients were lost to follow-up. The authors note that, "Side effects occur in 5% to 10% of patients, mainly presenting as gastrointestinal symptoms as well as headache and rhinorrhea to a lesser extent."
- Ultra-high dose iodide for rhinofacial zygomycosis—case report (*Journal of European Academy of Dermatology and Venereology* 2007 Jan): A 19-year-old male "was put on oral SSKI at an initial dose of 0.5 mL three times daily. This was gradually increased by 0.1 mL/dose/day until a dose of 5 mL three times daily was reached."[154] Generic formulation of "saturated solution of potassium iodide" (SSKI) contains 1000 mg of KI per mL of solution, which provides roughly 750 mg iodide; thus, SSKI dosed at 5 mL thrice daily = 15 mL/d = 11,250 mg/d (slightly more than 11 grams per day) of iodide for this adult patient with rhinofacial zygomycosis. Treatment was continued for at least 12 months without report of adverse effect.
- Modest dose iodine replacement in fibrocystic disease of the breast (*Canadian Journal of Surgery* 1993 Oct): Ghent and colleagues[155] sought to determine the response of patients with fibrocystic breast disease to "iodine replacement therapy" and reviewed three clinical studies of different design containing 233, 145 (later up to 1365), and 23 subjects; overall, subjective alleviation of pain and objective alleviation of breast fibrosis was seen in approximately 70% of patients. Consistent with other reports and impressions, the authors noted that, "Molecular iodine is nonthyrotropic and was the most beneficial." The dose of molecular iodine averaged 0.08 mg/kg body weight, which for an average 140-lb (63-kg) patient equates to approximately 5 mg/d.
- Modest dose iodine in patients with cyclic mastalgia (*Breast Journal* 2004 Jul-Aug): Kessler[156] reports a randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted with 111 otherwise healthy euthyroid women with a history of breast pain and fibrosis; subjects received molecular iodine for 6 months. Physicians assessed breast pain, tenderness, and nodularity each cycle; patients assessed breast pain and tenderness with the Lewin breast pain scale at 3-month intervals and with a VAS at each cycle. All iodine-treated subjects improved compared to no improvement seen in

[150] Indraccolo et al. Anaphylactic-like reaction to Lugol solution during colposcopy. *South Med J* 2009 Jan;102(1):96-7
[151] "Quantitative RT-PCR confirmed the array data demonstrating that iodine/iodide treatment increased the mRNA levels of several genes involved in estrogen metabolism (CYP1A1, CYP1B1, and AKR1C1) while decreasing the levels of the estrogen responsive genes TFF1 and WISP2." Stoddard FR 2nd, et al. Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. *Int J Med Sci*. 2008 Jul 8;5(4):189-96
[152] Bonifaz A, et al. Sporotrichosis in childhood: clinical and therapeutic experience in 25 patients. *Pediatr Dermatol*. 2007 Jul-Aug;24(4):369-72
[153] Said of KI, "The standard dose was 1g, which contains 770 mg of iodine." Miller DW. Extrathyroidal benefits of iodine. *J Am Physicians Surgeons* 2006;Winter,106-10
[154] Tripathy et al. Rhinofacial zygomycosis successfully treated with oral saturated solution of potassium iodide. *J Eur Acad Dermatol Venereol*. 2007;21:117-9
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[156] Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J*. 2004 Jul-Aug;10(4):328-36

the placebo group. "Reductions in all three physician assessments were observed in patients after 5 months of therapy in the 3.0 mg/day (7/28; 25%) and 6.0 mg/day (15/27; 18.5%) treatment groups, but not the 1.5 mg/day or placebo group. Patients recorded statistically significant decreases in pain by month 3 in the 3.0 and 6.0 mg/day treatment groups, but not the 1.5 mg/day or placebo group; more than 50% of the 6.0 mg/day treatment group recorded a clinically significant reduction in overall pain. All doses were associated with an acceptable safety profile. No dose-related increase in any adverse event was observed." Notably, the failure of the 1.5 mg/day dose implies that this dose is inadequate and thereby justifies higher routine dosing.

- Clinical implementation and the author's perspective: Iodide has a stronger effect on thyroid function and provides tissue-penetrating antimicrobial benefits from oral administration. Molecular iodine has anti-estrogen effects that correlate with the clinical alleviation of cyclic breast pain and fibrocystic breast disease; other anti-estrogen benefits such as an anti-cancer benefit are reasonably anticipated from supplemental iodine. Products with combined iodine and iodide are available and reasonable for clinical use, and a daily dose range of 3-6 mg does not appear unreasonable and has been shown to be beneficial in human studies. Iodine and iodide are impressively well tolerated. Nicely summarized in a personal email from Michael Gonzalez DSc PhD in November 2012, an overview of iodine-iodine's clinical applications may be stated as follows:

  "Different tissues of the body respond to different forms of iodine. The Iodide form is believed to be particularly useful for the thyroid. But the supplement of choice for the breast is "iodine" not "iodide." Lugol's formula is Iodine 5% + Potassium iodide (KI) 10% in distilled water. Because different tissues concentrate different forms of iodine, using a supplement that contains both iodine and iodide is preferable to using a supplement that contains only one form. With different tissues responding to different forms of iodine, it would make common sense that a greater therapeutic benefit from iodine will be achieved by using a combination of iodide and iodine. … The most frequent adverse reactions to potassium iodide are stomach upset, diarrhea, nausea, vomiting, stomach pain, salivary gland swelling/tenderness, acne and skin rash."

  Antioxidant support in general and supplementation with selenium in particular are recommended always, and particularly when iodine-iodide doses greater than 1-3 mg/d are used. Selenium 200 mcg/d has been shown in several studies to have an ameliorating effect on thyroid autoimmunity and a supportive effect on peripheral thyroid hormone metabolism. Although iodine is generally considered nonthyrotropic, periodic assessment of thyroid function and for thyroid autoimmunity is reasonable for patients taking long-term high-dose treatment. Clinicians should take advantage of iodine-iodide's safe and effective mucolytic, antimicrobial, and anti-estrogen benefits.

Distinguishing iodiNe from iodiDe

iodiNe

- **Natural** elemental form—diatomic.
- **Nonthyrotropic**—no immediate adverse effects on thyroid function.
- **Nuclear**—affects gene expression, for example by promoting estrogen detoxification and reducing estrogen responsiveness.
- **Nixes microbes**, antimicrobial—very broad spectrum; povidone iodine is one of the most widely used topical antimicrobials in the history of microbiology and medicine.

iodiDe

- **Divided**—ionic, nondiatomic.
- **Dietary** form, such as in iodized salt which typically contains potassium iodate, potassium iodide, sodium iodate, or sodium iodide.
- **Dissolves mucus**—mucolytic benefits advantageous in the treatment of asthma, bronchitis and respiratory tract infections. Potassium iodide is thought to act as an expectorant by increasing respiratory tract secretions and thereby decreasing the viscosity of mucus; iodide levels increase in respiratory secretions within approximately 15 minutes after oral administration.
- **Directly thyrotropic**—necessary for thyroid hormone production; high doses can cause thyroid dysfunction, which may be problematic (exacerbation of thyroid autoimmunity, hypothyroidism, or hyperthyroidism) or therapeutic (inhibition of thyroid hormone production during hyperthyroidism).
- **Deals death to microbes**, antimicrobial—very broad spectrum, used in the form of potassium iodide (KI, SSKI) for the treatment of microbial infections such as zygomycosis and sporotrichosis.

Purple coneflower (*Echinacea purpurea*) with honey bee (*Apis* genus): Portland Oregon 2011, photo by DrV

Progressive awakening

"**Only that day dawns to which we are awake.**"

Henry David Thoreau, *Walden*[412]

"In virtually all of the great spiritual and philosophical traditions of the world there appears some form of the idea that most human beings are sleepwalking through their own existence. **Enlightenment is identified with waking up.** Evolution and progress are identified with an expansion of consciousness."

Nathaniel Branden, *Six Pillars of Self-Esteem*[413]

"**And once you are awake, then shall you ever remain awake.**"

Friedrich Nietzsche, *Thus Spoke Zarathustra*[414]

[412] Thoreau HD. (Owen Thomas, Ed). *Walden and Civil Disobedience*. New York; WW Norton and Company: 1966, page 221
[413] Nathaniel Branden *The Six Pillars of Self-Esteem*, p. 67
[414] Nietzsche FW. *Thus Spoke Zarathustra*.

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AUTOIMMUNITY (TK TARRANT, SECTION EDITOR)

Reply to "Role of Western Diet in Inflammatory Autoimmune Diseases" by Manzel et al. in *Current Allergy and Asthma Reports* (Volume 14, Issue 1, January 2014)

Alex Vasquez

Published online: 20 June 2014

To the Editor,

Regarding the recent review "Role of Western Diet in Inflammatory Autoimmune Diseases" [1], while I appreciate the importance of this topic and the authors' review, I noted several shortcomings in this review and have questions about the omission of certain information. The authors failed to include relevant and important human data while instead relying on animal studies (their Table 1). The authors also include erroneous information, without appropriate citation.

The authors state that "a high-fat diet is a prominent factor in promoting obesity" but failed to provide citation for this. Importantly, other researchers have shown that high-fat ketogenic diets promote weight loss rather than obesity.

I found the reliance on animal data (especially their Table 1) and the exclusion of human data inappropriate for a review article of this nature and at this time in biomedical history. Several clinical trials have already documented the effectiveness of dietary intervention in human autoimmune diseases. For example, diets which emphasize increased consumption of plant foods (excluding gluten-containing grains) and dietary alteration of gastrointestinal flora have already shown clinical benefits [2]. Exclusion of gluten is of critical importance for some patients, and well established is gluten's role in inflammation, alteration of gastrointestinal flora, increasing intestinal permeability, and direct stimulation of inflammatory pathways. The authors mentioned hypertension four times in their review but failed to mention the remarkable efficacy of therapeutic fasting for this condition [3]. Clinical trials showing the safety and efficacy of dietary fatty acid supplementation were also excluded from the review, despite showing remarkable clinical safety and antirheumatic efficacy [4]. Antiinflammatory mechanisms of dietary intervention not mentioned in their review include alleviation of oxidative stress, alleviation of dysbiosis, reduced reactivity to dietary antigens, normalization of intestinal hyperpermeability, and alleviation of proinflammatory mitochondrial dysfunction [5].

This article is part of the Topical Collection on *Autoimmunity*

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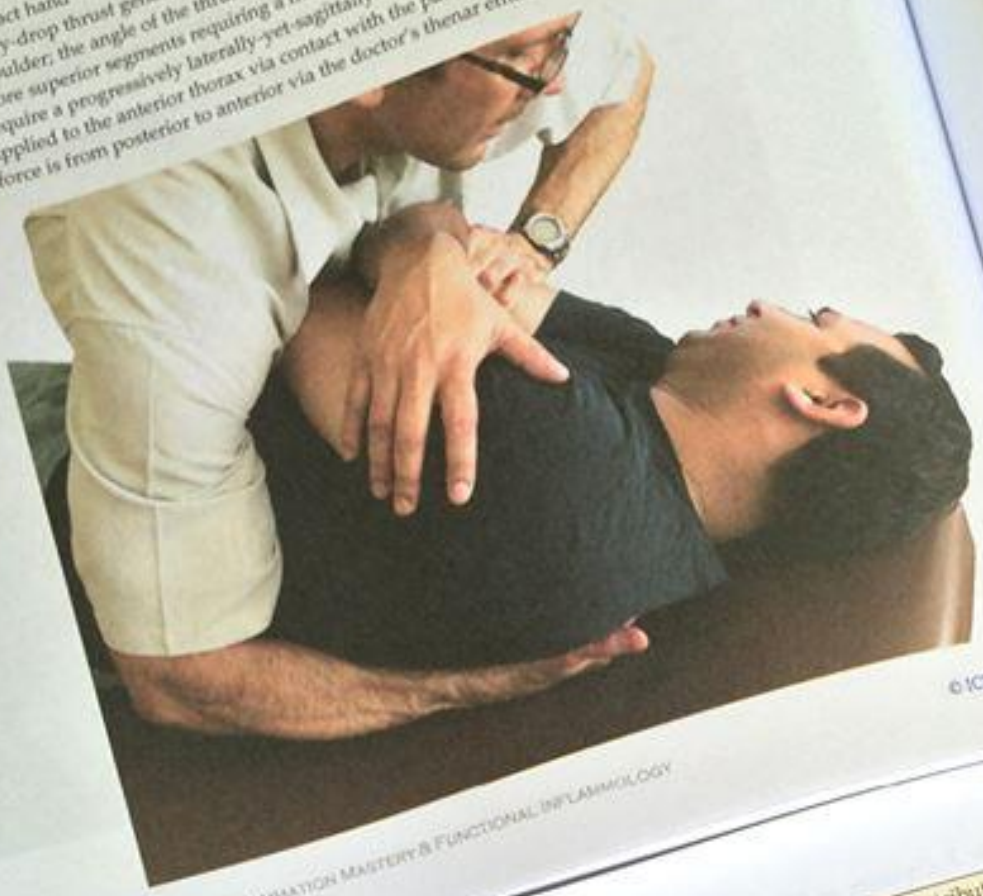
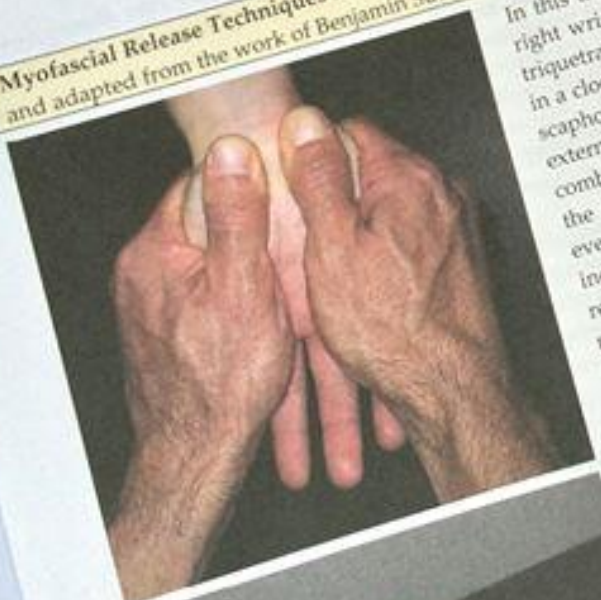
- manipulative th
- Patient is supine; after p
upper arm, then pulls downward
not muscular force) while raising the
contact hand
- Body-drop thrust generally superiorly and laterally
shoulder; the angle of the thrust changes depending on the
more superior segments requiring a more superiorly directed thrust,
require a progressively laterally-yet-sagittally directed thrust. Notably, the manipulative
applied to the anterior thorax via contact with the patient's upper arm, yet the true manipulative
force is from posterior to anterior via the doctor's thenar eminence positioned posteriorly.



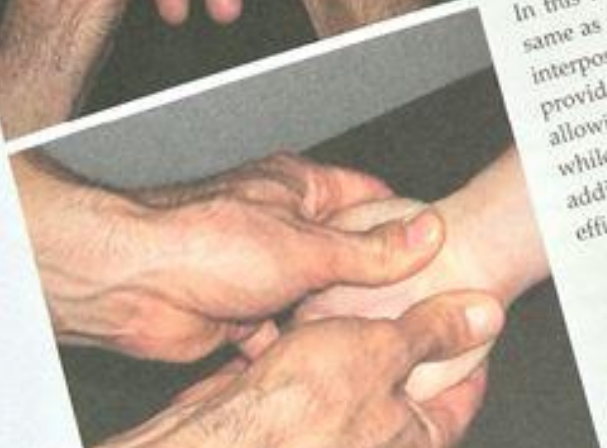
Proprioceptive Rehabilita

The central nervous system pla
the prevention of joint injuri
essential for proper musculo
either by injury or more co
chronic pain. **Muscle spasm**
a context that appreciate
painful musculoskeletal

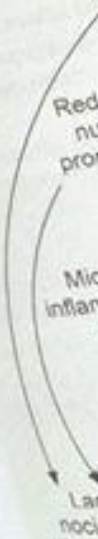
Myofascial Release Techniques for the Treatment of Carpal Tunnel Syndrome: Respectfully attributed to and adapted from the work of Benjamin Sucher, D.O.[368,369,370]



In this demonstration, the doctor is working on the patient's right wrist. In the doctor's right hand, the patient's triquetral, and hamate bones are grasped and rolled externally, in a clockwise direction. In the doctor's left hand, the patient's scaphoid and trapezium bones are grasped and rolled externally from midline, in a counterclockwise direction. The combination of these two motions generates strong tension in the transverse carpal ligament (flexor retinaculum) that eventually leads to relaxation of the ligament and allows for increased cross-sectional area within the carpal tunnel, thus relieving pressure on its contents, particularly the median nerve. This maneuver is generally referred to as the *opponens roll*, and the following techniques are variations of same.



In this maneuver, the doctor's contacts and motions are the same as above, except that in this case the doctor's fingers are interposed between those of the patient. This positioning provides for greater control of the patient's distal palm, allowing the doctor to force the patient's wrist into extension while applying tension to the transverse carpal ligament. The addition of wrist extension appears to increase the clinical efficacy of the maneuver.



ions are the same as above, *but the*
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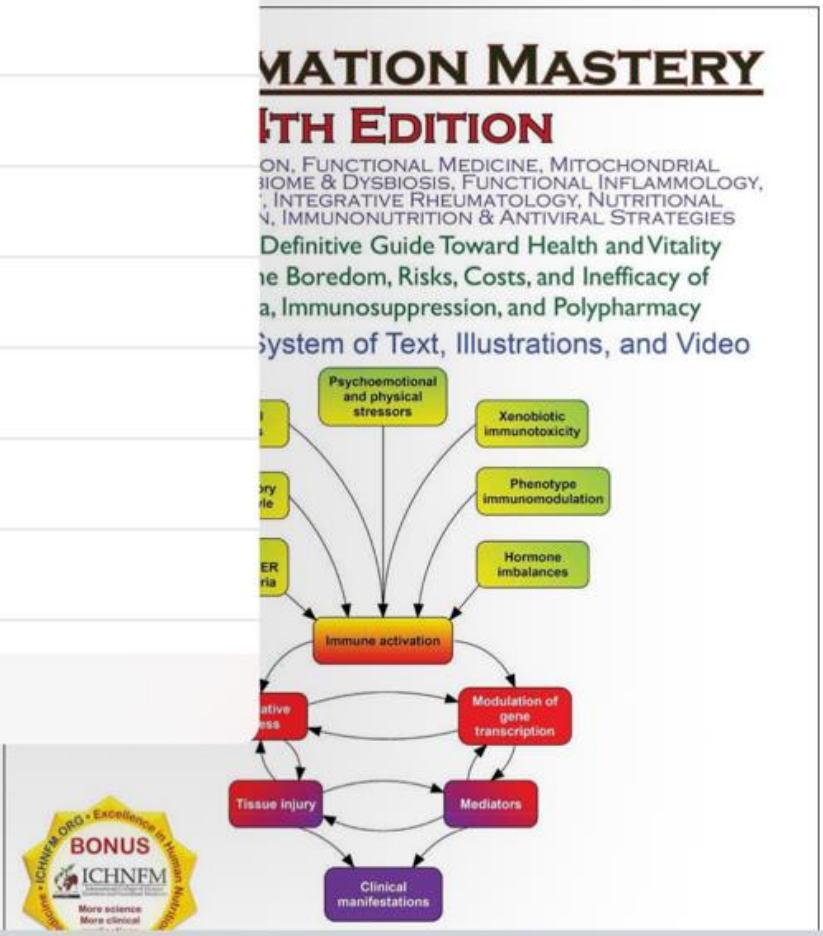

potassium:chloride ratio (chloride reduces effectiveness and retention of potassium), and the overall pH/acid-base balance of the human host (i.e., metabolic acidosis reduces effectiveness and retention of potassium, while an alkaline state improves retention and effectiveness of potassium). Importantly, magnesium status is an important positive-direct determinant of potassium status, particularly in patients with recalcitrant hypokalemia and/or hyperaldosteronism.[122] Respective amounts of potassium per serving of food or juice (1 cup = 8 fluid ounces =240 milliliters) are provided in the table below; renal insufficiency and potassium-sparing drugs/diuretics promote hyperkalemia, generally contraindicate high intake of potassium, and mandate periodic assessment of serum potassium.

Potassium content of common foods

Food serving	Potassium in mg (Na as available)
One papaya	780
One cup of mixed vegetable juice	740 (35-630 mg Na)
One cup of prune juice	700
One cup of carrot juice	520 (160 mg Na)
One cup plain low-fat yogurt	510 (150 mg Na)
One cup of cantaloupe	490
One cup of orange juice	470
One small banana	465
One cup of honeydew melon	460
One-third cup of raisins	365
One cup of carrot-orange juice	360 (35 mg Na)
One medium mango	320
One medium kiwi	250
One small orange	240
One medium pear	210

The importance of potassium

"**Adults should consume at least 4.7 grams of potassium per day to lower blood pressure**, blunt the effects of salt, and reduce the risk of kidney stones and bone loss. However, most American women 31 to 50 years old consume no more than half of the recommended amount of potassium, and men's intake is only moderately higher."

Food and Nutrition Board of the Institute of Medicine of the National Academies. "Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate." Released: February 11, 2004 iom.edu/Reports/2004/Dietary-Reference-Intakes-Water-Potassium-Sodium-Chloride-and-Sulfate.aspx

Antihypertensive mechanisms of potassium include vasodilator activity, diuretic and naturietic effects, and suppression of renin, angiotensin, and adrenergic tone.[123] In February 2004, the Institute of Medicine (IOM) set the Adequate Intake of potassium for adults at 4.7 grams a day—more than double previous recommendations; more than 90% of American adults do not meet these recommendations. If 90% of the population is not meeting recommended intakes of potassium, and these recommendations from the IOM come after an extensive review of the scientific literature, then potassium assessment and supplementation should be routine components of patient care; furthermore, this shows to the inadequacy of current laboratory assessments for evaluating potassium status and potassium balance.

- Randomized trial with 1-year follow-up and a title that says it all: Increasing the dietary potassium intake reduces the need for antihypertensive medication (*Annals of Internal Med* 1991 Nov): Forty-seven patients with medication-controlled hypertension completed one year of dietary treatment (or control nonintervention); dietary intervention focused on potassium-rich foods, with compliance monitored by 3-day food records and 24-hour urinary potassium excretion. Results showed: "After 1 year, the average drug consumption (number of pills per day) relative to that at baseline was 24% in group 1 (potassium-rich diet) and 60% in group 2 (control diet). By the end of the study, blood pressure could be controlled using less than 50% of the initial [drug] therapy in 81% of the patients in group 1 compared with 29% of the patients in group 2. … CONCLUSION: Increasing the dietary potassium intake from natural foods is a feasible and effective measure to reduce antihypertensive drug treatment."

[122] "Magnesium deficiency is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia and renders it refractory to treatment by potassium. Herein is reviewed literature suggesting that magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion. A decrease in intracellular magnesium, caused by magnesium deficiency, releases the magnesium-mediated inhibition of ROMK channels and increases potassium secretion. Magnesium deficiency alone, however, does not necessarily cause hypokalemia. An increase in distal sodium delivery or elevated aldosterone levels may be required for exacerbating potassium wasting in magnesium deficiency." Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol*. 2007 Oct;18(10):2649-52

[123] Patki et al. Efficacy of potassium and magnesium in essential hypertension: a double-blind, placebo controlled, crossover study. *BMJ*. 1990 Sep 15;301(6751):521-3

Practical overview of common abnormalities on the chemistry/metabolic panel—*continued*

Low values—considerations	Analyte	High values—considerations
Hypokalemia can cause fatal cardiac arrhythmias and needs to be taken seriously. Replacement is generally via oral administration of potassium-rich foods, juices, or supplements such as potassium citrate (best option) or potassium chloride (KCl, inexpensive and therefore commonly used in medical settings even though KCl is clearly not optimal therapy due to the acidifying effect of the chloride anion). Recalcitrant hypokalemia is often a sign of magnesium depletion.[95] Causes of hypokalemia include diarrhea, vomiting, diuretics, Cushing disease/syndrome, dietary insufficiency, overhydration with mineral-free fluids, hyperaldosteronism and renal artery stenosis. Acute metabolic acidosis should cause relative or absolute elevations in serum K; the finding of normal or low serum K in a patient with acidosis (e.g., diabetic ketoacidosis) indicates (severe) potassium depletion.	**Potassium**: 3.6 - 5.2 mEq/L (mmol/L)	**Hyperkalemia is defined as a potassium level greater than 5.5 mmol/L. Severe hyperkalemia (>7 mmol/L) can be fatal and needs to be taken seriously.** In severe hyperkalemia, treatment and emergency management should be implemented before a complete evaluation and differential diagnosis are performed.[96] ❶ Ensure that blood sample was not hemolyzed. Repeat test if patient is stable and time allows. ❷ If hyperkalemia is severe or patient is symptomatic or has electrocardiographic changes, treat hyperkalemia with intravenous calcium, beta-adrenergic agonists (e.g., albuterol), bicarbonate, insulin and glucose; magnesium sulfate may also help alleviate arrhythmias; oral sodium polystyrene sulfonate (SPS, also known as Kayexalate) is a frequently used potassium-binding agent. ❸ DDX includes adrenal insufficiency, potassium-sparing diuretics, ACE-inhibitors and ARBs, NSAIDs, rhabdomyolysis, renal failure, and massive cell necrosis such as with tumor lysis syndrome.
Evaluate hypocalcemia clinically with Chvostek's sign (~30% sensitive) and Trousseau sign (~90% sensitive) which may also be present in hypomagnesemia; evaluate clinically for arrhythmia, muscle spasm/hypertonicity, and hyperreflexia. Measure serum albumin and perform equation for "corrected calcium" if albumin is low. DDX includes renal failure, hypoparathyroidism, malabsorption, and drug effect (e.g., rarely a loop diuretic such as furosemide). Chronic mild hypocalcemia is treated with oral vitamin D and calcium supplementation; subacute symptomatic hypocalcemia can be treated with intravenous calcium gluconate especially if cardiac arrhythmias are present.	**Calcium**: 8.6 - 10.2 mg/dL	Outpatient hypercalcemia is potentially serious and needs to be evaluated in a stepwise manner: ❶ repeat the test to rule out lab error unless you are confident in the performance of the laboratory and stability of the submitted sample,❷ review drug list for adverse effect, such as from hydrochlorothiazide (HCTZ) or rarely from excess cholecalciferol intake, ❸ test intact parathyroid hormone (iPTH) to evaluate for hyperparathyroidism, ❹ evaluate for possible granulomatous disease such as sarcoidosis, tuberculosis, Crohn's disease, and possible leukemia or lymphoma, ❺ consider metabolic bone disease such as Paget disease of bone or metastatic bone disease, ❻ evaluate for cancer, ❼ test urine calcium for familial hypocalciuric hypercalcemia, ❽ refer to specialist such as internist or endocrinologist if hypercalcemia persists and answer is not forthcoming.

Corrected calcium (cCa) equations: Used when both serum calcium and albumin are low
American units: cCa (mg/dL) = serum Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL])
International units: cCa (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L])

[95] "Herein is reviewed literature suggesting that magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion." Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol*. 2007;18:2649-52 jasn.asnjournals.org/content/18/10/2649

[96] "If the hyperkalemia is severe (potassium >7.0 mEq/L) or if the patient is symptomatic, begin treatment before diagnostic investigation of the underlying cause." Garth D. Hyperkalemia in emergency medicine treatment and management. *Medscape Reference* emedicine.medscape.com/article/766479-treatment#a1126 Accessed June 2011

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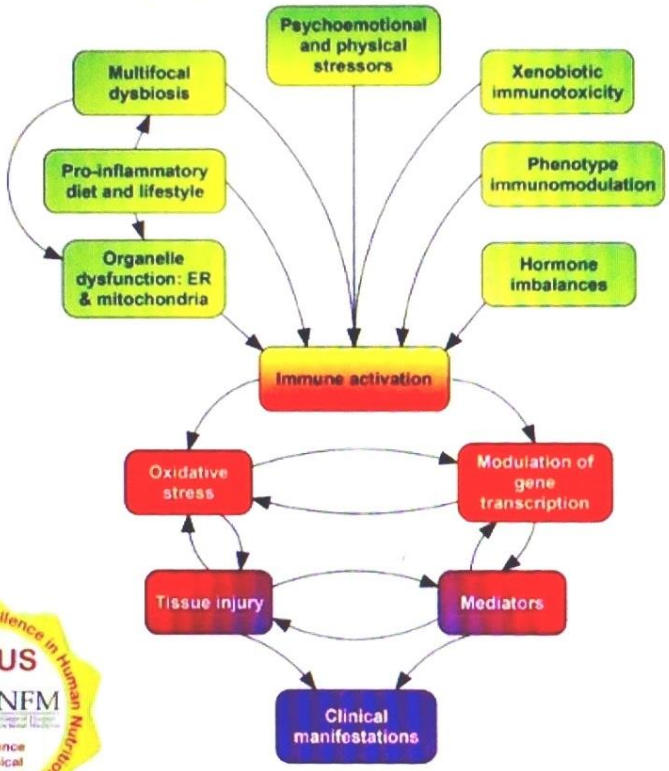

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Notices: The intended audiences for this book are health science students and doctorate-level licensed medical clinicians. This book has been written with every intention to make it as accurate as possible, and each section has undergone peer-review by an interdisciplinary group of clinicians. In view of the possibility of human error and as well as ongoing discoveries in the biomedical sciences, neither the author nor any party associated in any way with this text warrants that this text is perfect, accurate, or complete in every way, and all disclaim responsibility for harm or loss associated with the application of the material herein. Information and treatments applicable to a specific *condition* may not be appropriate for or applicable to a specific patient; this is especially true for patients with multiple comorbidities and those taking pharmaceutical medications, which are generally associated with multiple adverse effects and drug/nutrient/herb interactions. Given that this book is available on an open market, lay persons who read this material should discuss the information with a licensed medical provider before implementing any treatments and interventions described herein.

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

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

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

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

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