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

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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)

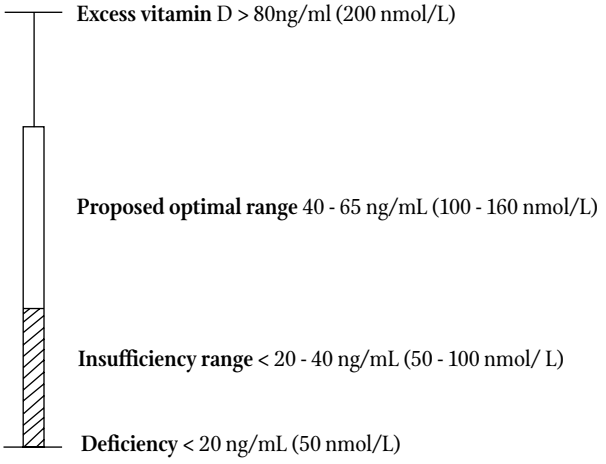
Based on our review of the literature, we propose that the optimal—"sufficient and safe"—range for 25(OH)D correlates with serum levels of 40–65 ng/mL (100–160 nmol/L).[55] This proposed optimal range is compatible with other published recommendations: Zittermann[11] states that serum levels of 40–80 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.



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

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

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

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

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

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

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

Past and Future Vitamin D Studies: Critique and Design

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

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

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

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

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

3. Supplementation should be performed with D3 rather than D2

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

4. Supplements should be tested for potency

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

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

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

6. Serum vitamin D levels must enter the optimal range

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

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

Vitamin D Supplementation in Adults

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

Vitamin D Supplementation in Pregnant Women

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

Vitamin D Supplementation in Infants and Children

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

Options for Raising Vitamin D Blood Levels

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

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

DISCUSSION AND CONCLUSIONS

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

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

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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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Photo of town center and Roman aqueduct in Segovia Spain © 2016 by Dr Vasquez

Expert Perspectives • Clinical Nutrition • Research Methodology • Publication Analysis

How to Understand, Refute, and Plan Studies Using Vitamin D

Alex Vasquez DO ND DC FACN

Defining the problems

1. The (primary) problem: Most doctors and researchers have zero expert-level training in Nutrition (let alone Clinical Nutrition, Therapeutic/Interventional Nutrition, Functional Nutrition) and therefore the studies they design using vitamin D are methodologically flawed, as described below.
2. The (secondary) problem: Too many studies using vitamin D (cholecalciferol) have used vitamin D in 1) doses that are inadequate, 2) for durations that are inadequate, and thus these studies are therapeutically underpowered, tending to lead to lackluster or negative (inefficacious) results, thereby leading to the false conclusion that vitamin D is ineffective when in fact it either *is* or *might be* effective.
3. The (tertiary) problem: As a result of therapeutically underpowered studies, too many research articles paint a false picture of inefficacy when in fact vitamin D is or may be highly efficacious; as a result, patients are denied a safe and effective therapeutic route that offers low-cost efficacy, high safety, and numerous collateral benefits.
4. The (quaternary) problem: Another major problem is that too many doctors and researchers are unaware of the major paradigm-shifting studies that should have resulted in major acceptance of vitamin D utilization in preventive public health and clinical medicine; as a result of this ignorance, too many research projects are essentially starting from zero or a very shallow foundation rather than progressively building on a foundation of good science and appropriate pattern recognition. Researchers who have not studied the history of nutrition and the decades of literature are essentially ignorant of the history and direction of the field into which they enter; one can be amused by the prospect of a researcher placed in a position of authority to shape and define the direction of a field which he/she has never studied, ie, many researchers quite obviously wear no clothes.

Guidelines for vitamin D clinical trials were broadly published in 2004 and 2005

In 2004 and 2005, I was the principal author on several publications published in peer-reviewed journals, and in each of these I listed criteria for the design and therefore evaluation of studies using vitamin D; I will list these publications here with hyperlinks to their full text and then describe these criteria with any updates.

1. Vasquez, Manso, Cannell. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med* 2004 Sep[1]: PDF, PMID 15478784
2. Vasquez, Cannell. Calcium and vitamin D in preventing fractures: data are not sufficient to show inefficacy. *British Medical Journal* 2005 Jul[2]: PDF, PMID 16002891
3. Vasquez. Subphysiologic doses of vitamin D are subtherapeutic: comment on the study by the Record Trial Group. *TheLancet.com* 2005 May PDF

According to the pioneering clinical trial by Heaney et al (*Am J Clin Nutr* 2003 Jan[3]), "Healthy men seem to use 3000–5000 IU cholecalciferol/d"; a daily dose of 3,000–5,000 IU cholecalciferol/d corresponds to a serum 25-OH-vitamin D of 60 ng/ml (150 nmol/L). However, according to this study, serum 25-OH-vitamin D should be equal to or greater than 80 ng/ml (200 nmol/L) in order to alleviate secondary relative hyperparathyroidism; the daily dose of vitamin D3 required to lower/normalize

serum parathyroid hormone (PTH) is 10,000 IU (250 mcg) per day. Therefore, we can roughly conclude that a reasonable daily dose of vitamin D ranges from 4,000–10,000 IU per day, and that the lowest acceptable serum 25-OH-vitamin D levels corresponding with adequate supplementation is 60 ng/ml (150 nmol/L) whereas a level of 80 ng/ml (200 nmol/L) is required to alleviate secondary (relative) hyperparathyroidism. Several of my publications (listed as #4 and #5 below) have also included a description of the minimal values and optimal therapeutic ranges for serum 25-OH-vitamin D; the perhaps obvious importance of these ranges is to define effective treatment (ie, sufficient vitamin D supplementation/nutriture) and to therefore differentiate adequate from inadequate supplementation dosages.

4. Vasquez. Musculoskeletal Pain: Expanded Clinical Strategies, continuing medical education (CME) monograph commissioned and published by the Institute for Functional Medicine 2008 PDF*
5. Vasquez. Revisiting the five-part nutritional wellness protocol: the supplemented Paleo Mediterranean diet. *Nutritional Perspectives* 2011 Jan PDF* This article from 2011 is excerpted from my 2016 textbook *Inflammation Mastery, 4th Edition* to provide necessary updates; this article also describes the clinical use of vitamin D within the context of a foundational clinical nutrition protocol.

"This insight also illuminates a double-standard in research: whereas no legitimate drug study would use a subtherapeutic dose of a pharmaceutical agent and then (falsely) assert inefficacy, poorly designed and therapeutically underpowered (eg, using 10% of the known effective dose) nutrition studies are published and make headlines and shape policy (mostly by maintaining the status quo of nutritional inaction and ignorance) on weekly basis. For example, a study using an antibiotic or antiseizure drug that failed to administer a therapeutic dosage or achieve a therapeutic serum level would never be accepted for publication in a headlining medical journal; yet, underdosed nutrition studies are commonly published in headlining journals and then reported to mainstream media as proof of the inefficacy of nutritional intervention."
Dr Alex Vasquez

Past and Future Vitamin D Studies: Critique and Design

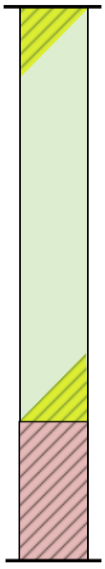
A large percentage of published clinical trials have suffered from flawed design, including inadequate dosing, inadequate duration, wrong type of vitamin D (ie, ergocalciferol, D2), failure to test serum vitamin D levels, and/or failure to ensure that serum vitamin D levels entered into the optimal range. The following guidelines have been 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 is 3,000–5,000 IU per day in adult males. Full-body exposure to ultraviolet light (eg, sunshine) can produce the equivalent of 10,000–25,000 IU of vitamin D3 per day. 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 within a short period of time outdoors. Also, the higher dose of 10,000 IU/day is necessary in some patients who have absorption defects and therefore need a higher oral dose to "force absorption" and/or who are obese and therefore need a higher dose to achieve tissue saturation for a larger body mass. Based on these physiologic criteria, we see that the majority of intervention studies in adults have used inadequate, subphysiologic doses of vitamin D. Therefore, many 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. This insight also illuminates a double-standard in research: whereas no legitimate drug study would use a subtherapeutic dose of a pharmaceutical agent and then (falsely) assert inefficacy, poorly designed and therapeutically underpowered (eg, using 10% of the known effective dose) nutrition studies are published and make headlines and shape policy (mostly by maintaining the status quo of nutritional inaction and ignorance) on weekly basis. For example, a study using an antibiotic or antiseizure drug that failed to administer a therapeutic dosage or achieve a therapeutic serum level would never be accepted for publication in a headlining medical journal; yet, underdosed nutrition studies are commonly published in headlining journals and then reported to mainstream media as proof of the inefficacy of nutritional intervention.
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 120 days or 4 months of supplementation, 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 6-9 months is of insufficient duration to determine either maximum benefit or inefficacy of vitamin D supplementation. Conversely, since vitamin D supplementation can alter intracellular metabolism within minutes of administration, benefits seen in short-term studies should not be inaccurately

attributed to statistical error or placebo effect. The vitamin D trial does not begin with the initiation of supplementation but rather the study *begins* after the achievement of vitamin D sufficiency (defined below).

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. 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[3] 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 emulsification facilitates absorption of fat-soluble nutrients. Measurement of 1,25-dihydroxyvitamin (calcitriol) is potentially misleading and is not recommended for the evaluation of vitamin D status; however, measurement of calcitriol levels is increasingly used clinically to evaluate for the severity or presence of inflammatory and malignant diseases, as discussed in *Inflammation Mastery* (2016).
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 50-100 ng/mL (see updated figure and PDF excerpt).
7. Patients must be taken from a state of absolute or relative deficiency to absolute sufficiency: If patients are deficient at the start and the end of the study, then no adequate treatment has taken place. If patients were not deficient at the start of the study, then little improvement would be expected in moving them from "vitamin D adequate" to "vitamin D supra-adequate" in most cases.

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. Furthermore and by extension, these criteria help us form a checklist with which to evaluate planned and published research.



Excess vitamin D: >100 ng/mL (250 nmol/L)
Higher levels of 25hydroxycholecalciferol are clinically problematic if accompanied by hypercalcemia or urolithogenic hypercalciuria

Optimal-high vitamin D: 90-100 ng/mL (225-250 nmol/L)
These levels can be physiologic, but may be higher than necessary for some patients, excepting severe illness with vitamin D-responsive conditions.

Optimal range: 50-90 ng/mL (125-225 nmol/L)

Sufficiency range: 40-50 ng/mL (100-125 nmol/L)

Insufficiency range: 20-40 ng/mL (50-100 nmol/L)

Deficiency: < 20 ng/mL (50 nmol/L)

Interpretation of serum 25-hydroxy-cholecalciferol levels: 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/inflammatory disease, respectively.

Vitamin D-responsive conditions*

- Depression
- Autism
- Seizures/epilepsy
- Musculoskeletal pain, especially low-back pain and "fibromyalgia"
- Opioid dependence for pain
- Hypertension
- Autoimmunity such as systemic lupus erythematosus and multiple sclerosis
- Migraine
- Diabetes and insulin resistance
- Polycystic ovarian syndrome
- Cancer, especially prostate cancer
- Infectious diseases, especially including viral and bacterial infections

*following correction of deficiency

How to Critique Vitamin D Studies—A Checklist

1. Did the study subjects receive at least 4,000-10,000 IU per day? If not, then the study likely used inadequate dosage to produce optimal physiologic effects.
2. Is the duration of the study at least 6-9 months? If not, then body stores of vitamin D were likely not replaced in time for clinical effect to occur. Daily supplementation with vitamin D requires 120 days (4 months) to reach plateau of serum 25-OH-vitamin D levels; therefore, the replenishment or "induction" phase of any clinical trial must have a duration of at least 4 months or—alternatively—use supranormal doses of vitamin D3 in order to more rapidly achieve optimal serum levels and tissue saturation.
3. Did the study use vitamin D3 (cholecalciferol) rather than fungally-derived erogcalciferol? Ergocalciferol is not a human nutrient, and it is more toxic and less effective than is cholecalciferol.
4. Was the product validated for potency? If not, then the intervention may have failed due to an erroneously produced or falsely labeled product.
5. Were serum 25-OH-vitamin D levels measured? If not, the product potency and nutrient absorption were not ensured.
6. Did serum 25-OH-vitamin D levels enter the optimal range at least 2-6 months before the end of the study? If not, then the patients may have been vitamin D deficient for the entire duration of the study.
7. Were the patients deficient at the start of the study and then robustly replaced with vitamin D? If not, then "deficiency→deficiency" is not a competent study design and intervention, nor is "replete→replete." The appropriate intervention is to change deficiency to repletion.
8. Vitamin D supplementation should be stopped for roughly 20-30 days before serum testing because 25-hydroxyvitamin D3 (calcidiol) has a half-life of 15 days.[4] The goal with serum testing of 25-OH-vitamin D levels is to assess tissue saturation, not acute absorption. Testing vitamin D serum levels within a few days of vitamin D supplementation is more likely to reflect absorption and hepatic conversion rather than providing the more important and more accurate assessment of vitamin D tissue stores.

Obviously, clinical trials need to control for factors that increase vitamin D status (eg, sun exposure, fish oil especially cod liver oil) and those which promote vitamin D deficiency, especially antiseizure drugs, cholestyramine. Research and editorial integrity cannot be assumed in mainstream headlining journals.[5]

> "The vitamin D trial does not begin with the initiation of supplementation but rather the study begins after the achievement of minimal vitamin D sufficiency, as documented by a serum 25-OH-vitamin D level of at least 50 ng/ml or 125 nmol/L."
> Dr Alex Vasquez

Clinical take-home

Clinicians, who are not conducting research but rather are interested in attaining clinical improvement in their patients, should follow the above guidelines 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.

A reasonable goal with vitamin D supplementation is the downward normalization of parathyroid hormone (PTH) levels; relative elevations of PTH (excluding pathologic and primary elevations of PTH) signify compensation for insufficient intake and/or absorption of calcium. According to the clinical trial by Heaney et al[3], the dose required to achieve this is 10,000 IU (250 mcg) per day corresponding to serum 25-OH-vitamin D of 80 ng/ml (200 nmol/L). Therefore, and also given that such levels are physiologically attained with sun exposure, a target of 80 ng/ml (200 nmol/L) is quite reasonable.

2017 vitamin D supplementation guidelines

In early 2017, "vitamin D supplementation guidelines" were published[6] endorsing the following supplementation regimens:

- Neonates (i.e. younger than one month): 1,000 IU/day (25 mcg/day),
- Infants older than 1 month and toddlers: 2000-3000 IU/day (50-75 mcg/day),
- Children and adolescents aged 1 to 18 years: 3000-5000 IU/day (75–125 mcg/day),
- Adults and the elderly: 7000–10,000 IU/day (175–250 mcg/day) or 50,000 IU/week (1250 mcg/week).

The authors also note that obese patients need up to 300% more vitamin D than do persons of normal weight, and that—as noted previously and consistently throughout the literature—"the dose of 10,000 IU/d was also found as the no-observed-adverse-effect level (NOAEL)." Consistent

with the clinical guidelines that I have published since 2008, these 2017 guidelines state "It is generally accepted that a serum 25(OH)D concentration of up to 100 ng/mL (250 nmol/L) is safe for children and adults, with the exception of those who have a hypersensitivity to vitamin D." They further note that "The Endocrine Society guidelines concluded that vitamin D toxicity is not only extremely rare, but 25(OH)D concentration of at least 150 ng/mL (375 nmol/L) is required before there would be evidence of vitamin D toxicity."

Vitamin D's safety and efficacy have already been established, justifying routine use; to continue inertia and inaction is actually dangerous and unethical

We established the safety, efficacy, and clinical imperative of vitamin D supplementation in our landmark review in 2004 by Vasquez, Manso, and Cannell, *Altern Ther Health Med* 2004 Sep[1]:

> "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) 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 and which has contributed to incalculable human suffering related to otherwise unnecessary neural tube defects, cervical dysplasia, cancer, osteoporosis, and mental depression. ... 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."

Given cholecalciferol's low cost, high safety, and numerous direct and collateral benefits, no legitimate reason exists for routinely denying vitamin D3 supplementation to patients; vitamin D supplementation (and/or sun exposure) should be recommended and supported routinely in virtually all patients

> "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."[1]

According to the 2011 clinical trial by Hollis et al[7], "Vitamin D supplementation of 4,000 IU/day for pregnant women was safe and most effective in achieving sufficiency in all women and their neonates regardless of race." A 2016 review supported the same dose of 4,000 IU/d for pregnant women.[8]

For active hyperlinks, associated PDF articles and videos, and any updates, please see: http://www.ichnfm.org/d

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Main citations:

1. Vasquez A, Manso G, Cannell J. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med*. 2004 Sep-Oct;10(5):28-36
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Additional articles and book excerpts have been amended to the previous publication in order to provide context and orientation to the author's main works.

BOOK EXCERPTS, CHAPTERS:

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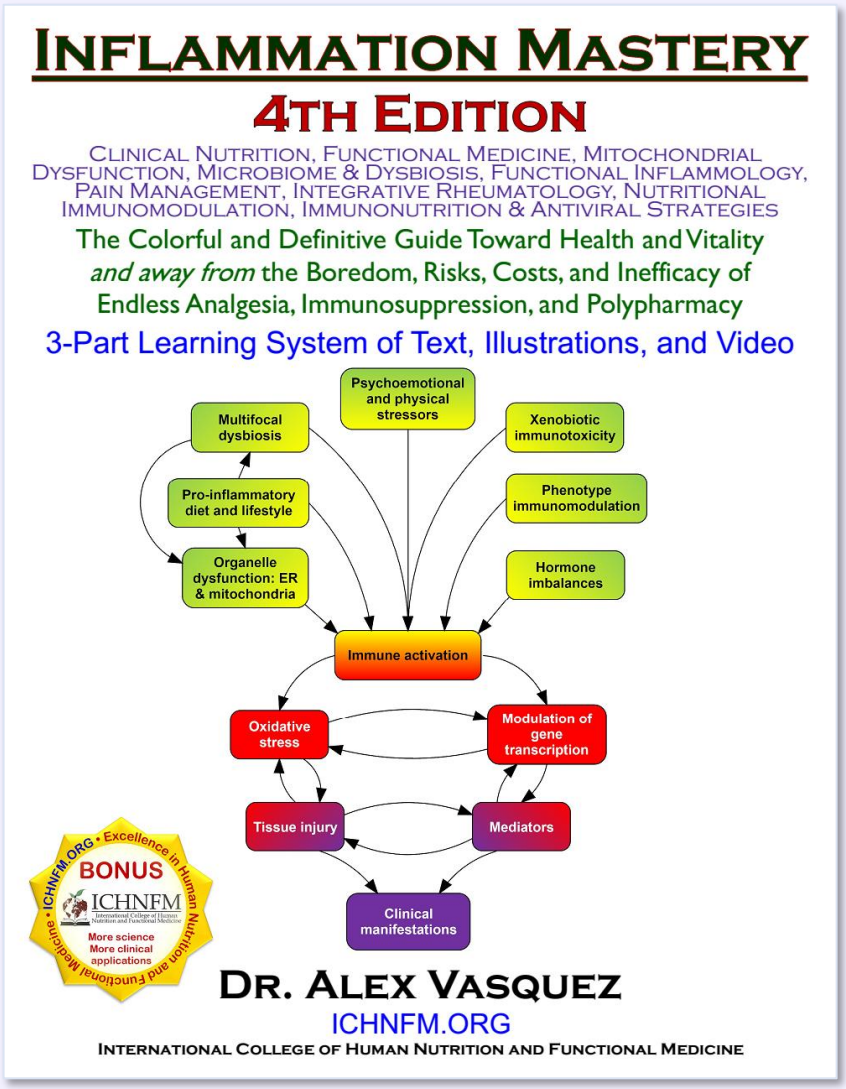

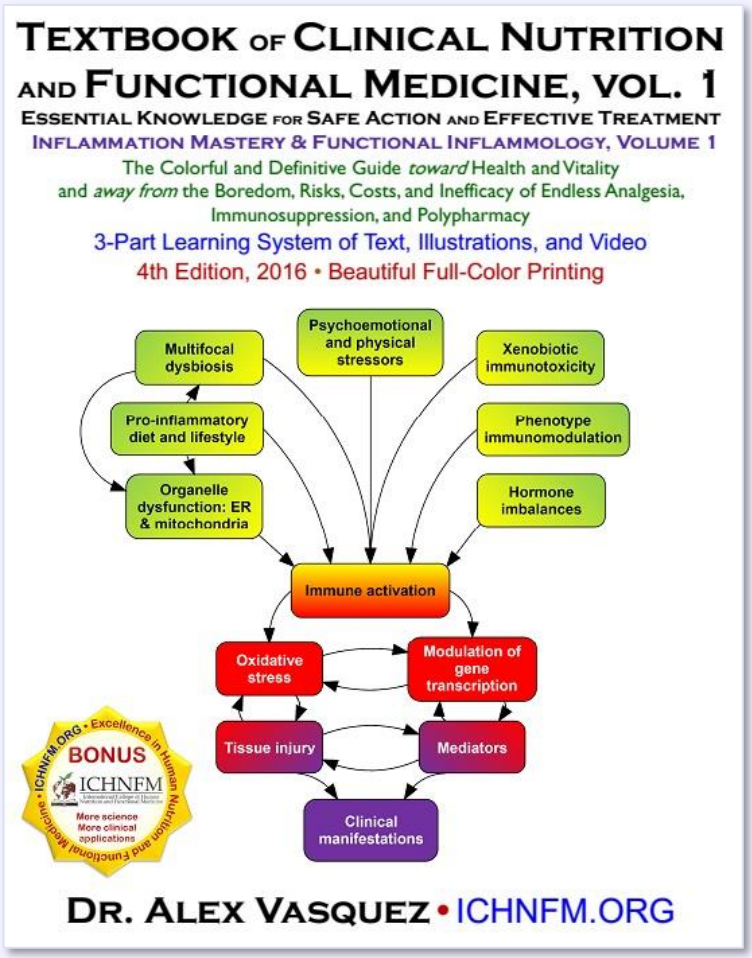

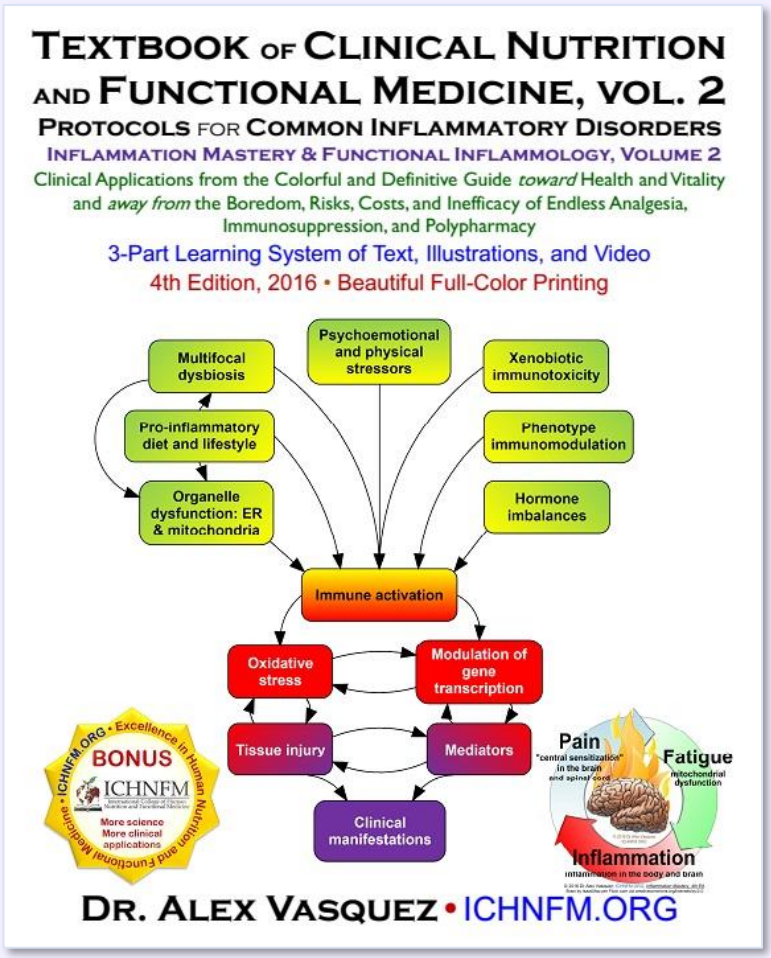

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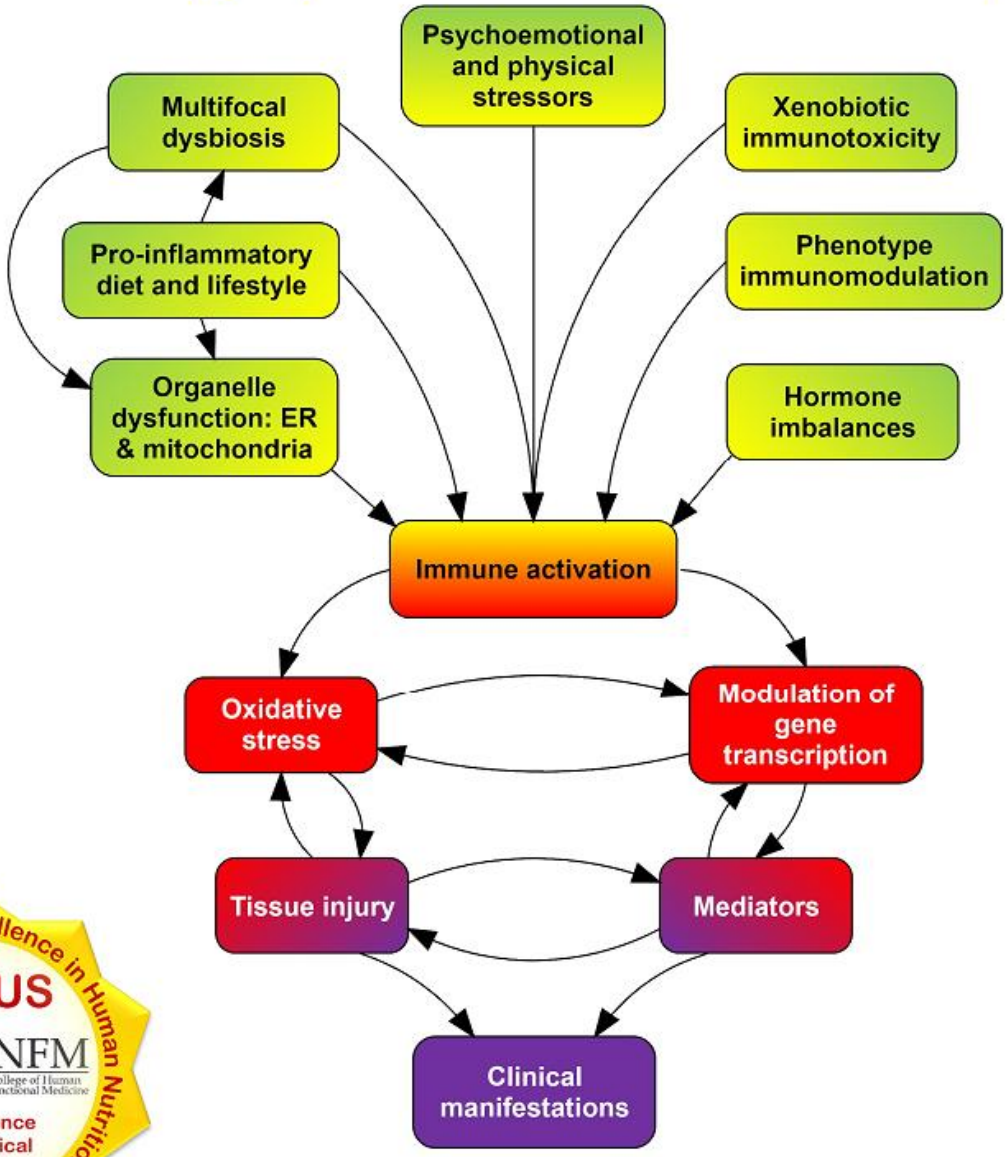

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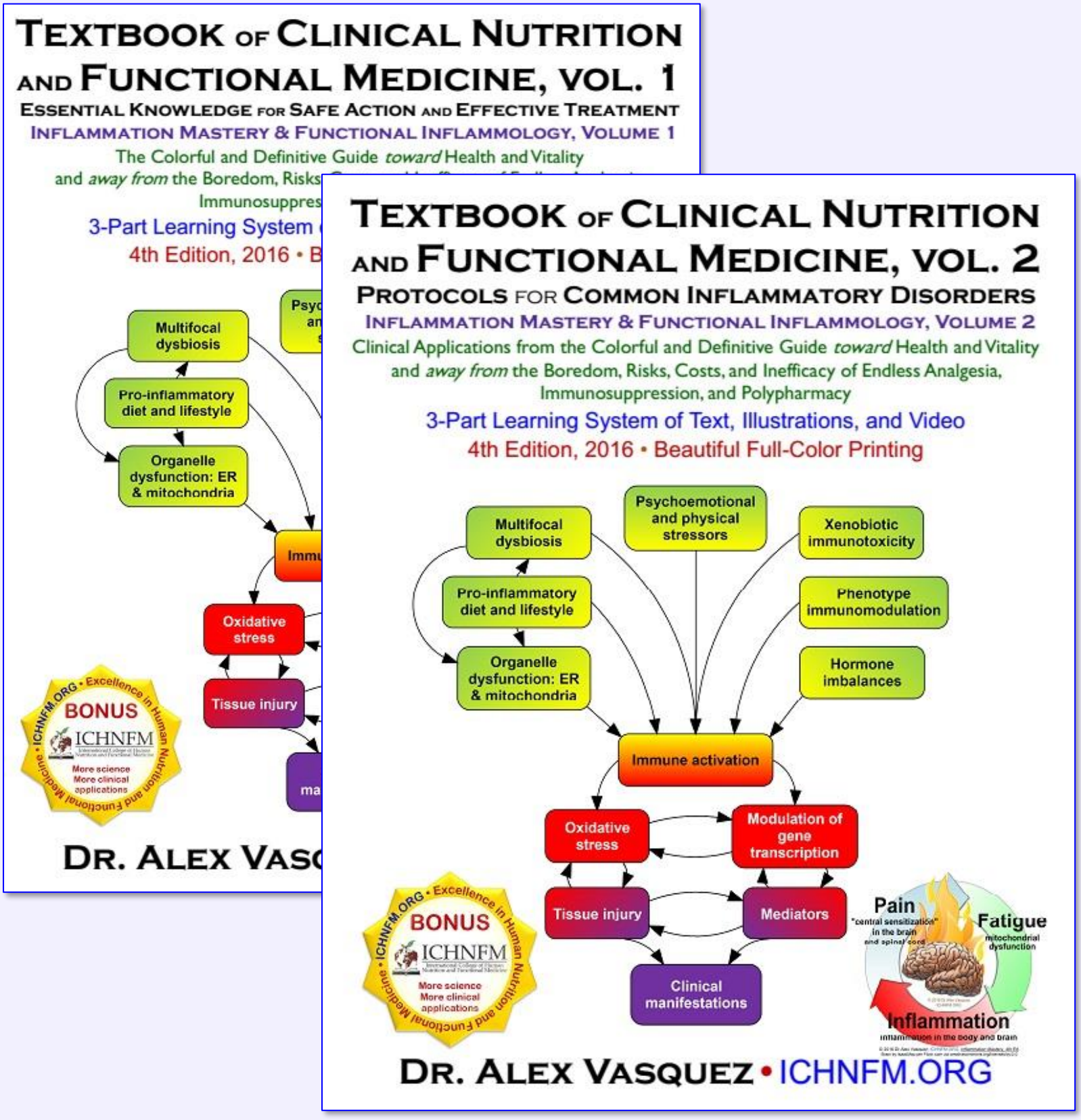

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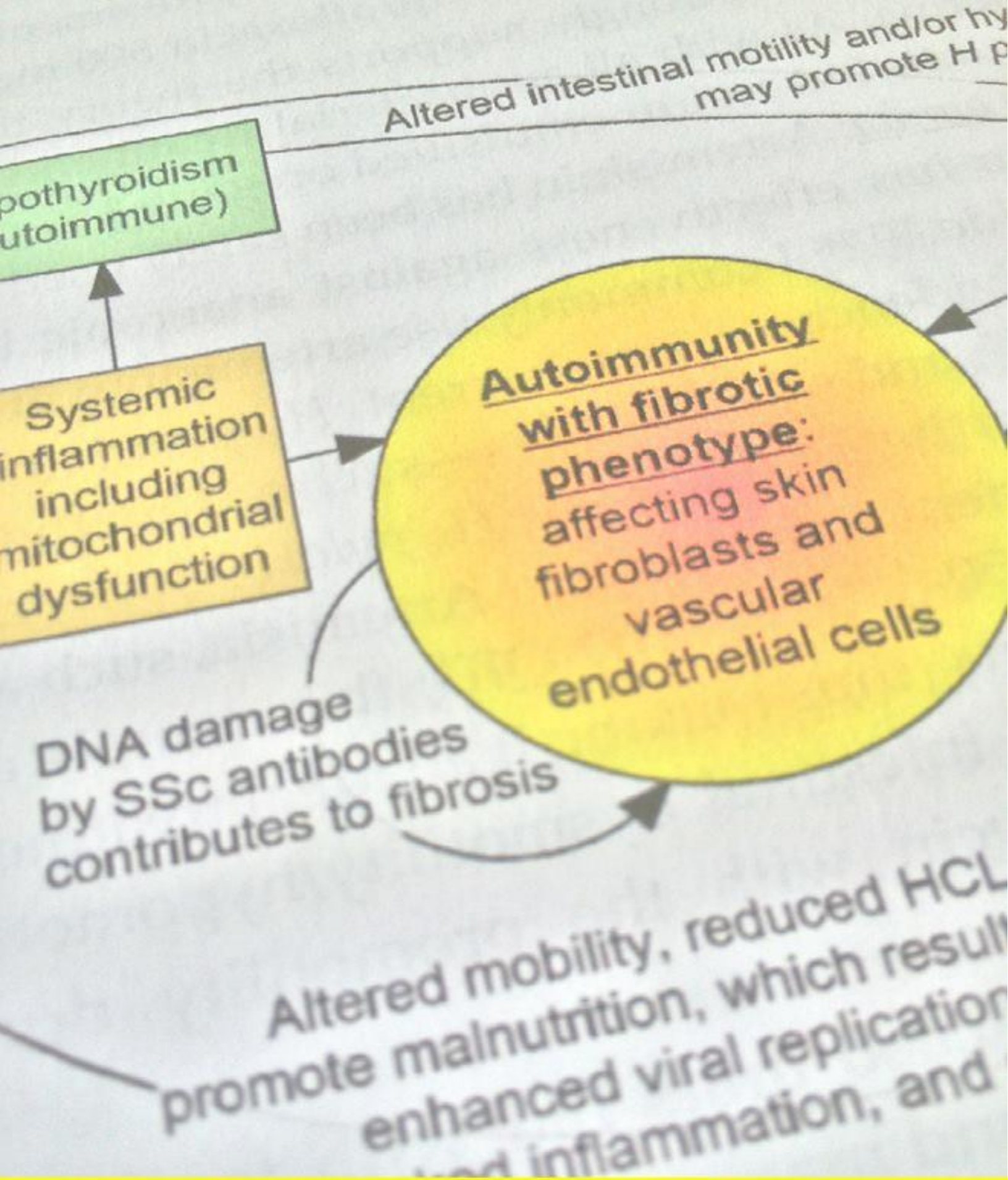

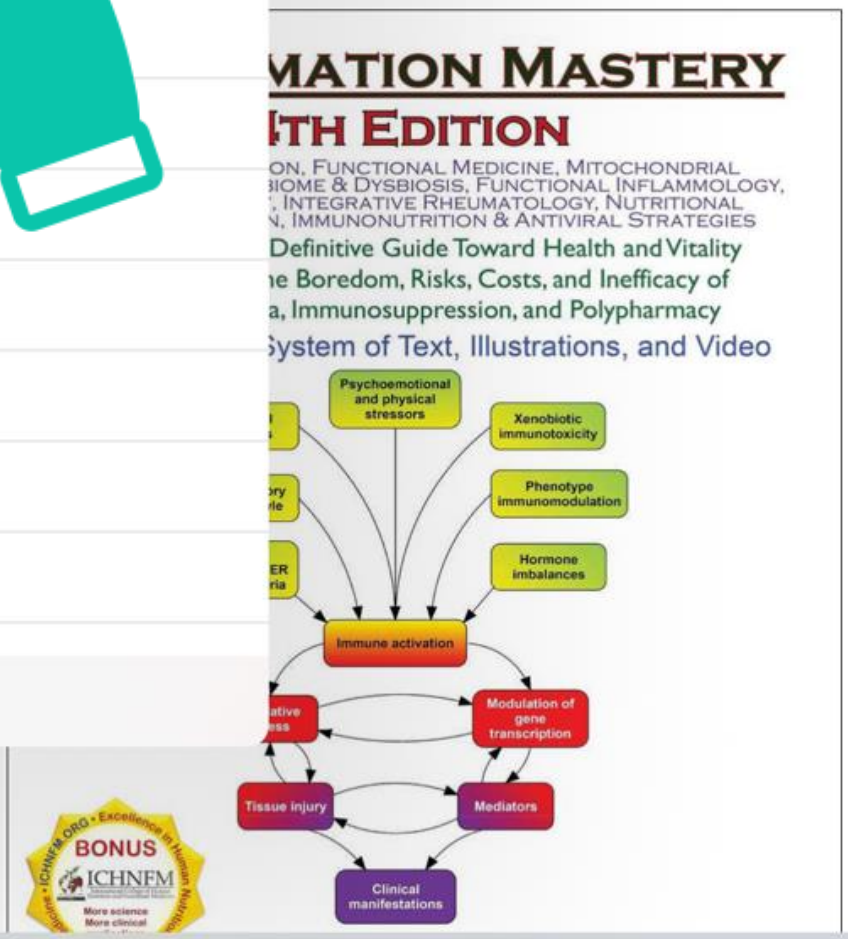

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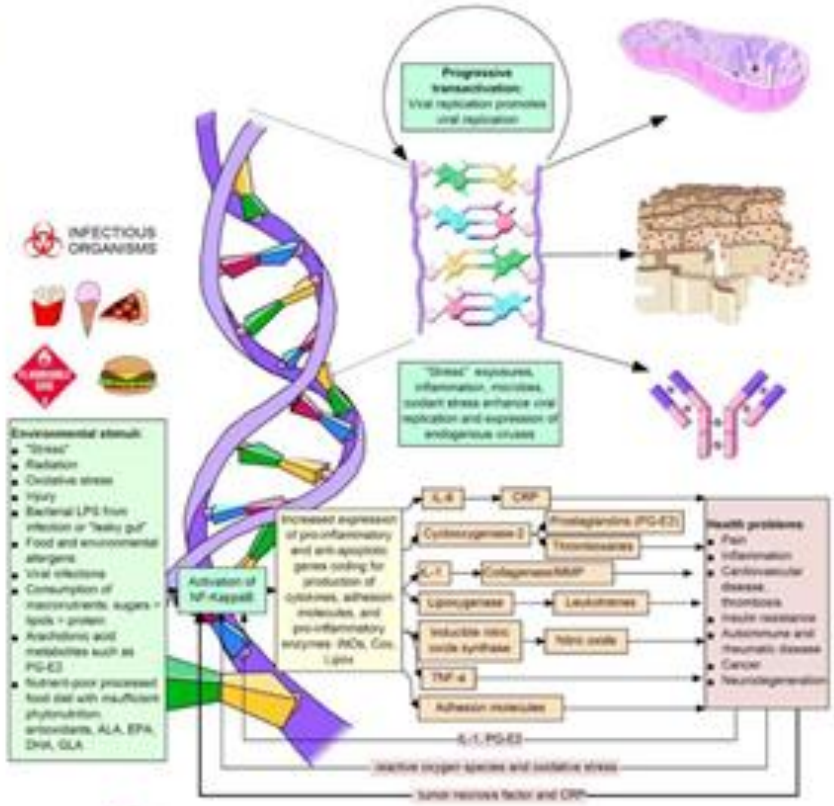

DR. ALEX VASQUEZ

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Antiviral Strategies and Immune Nutrition

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

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

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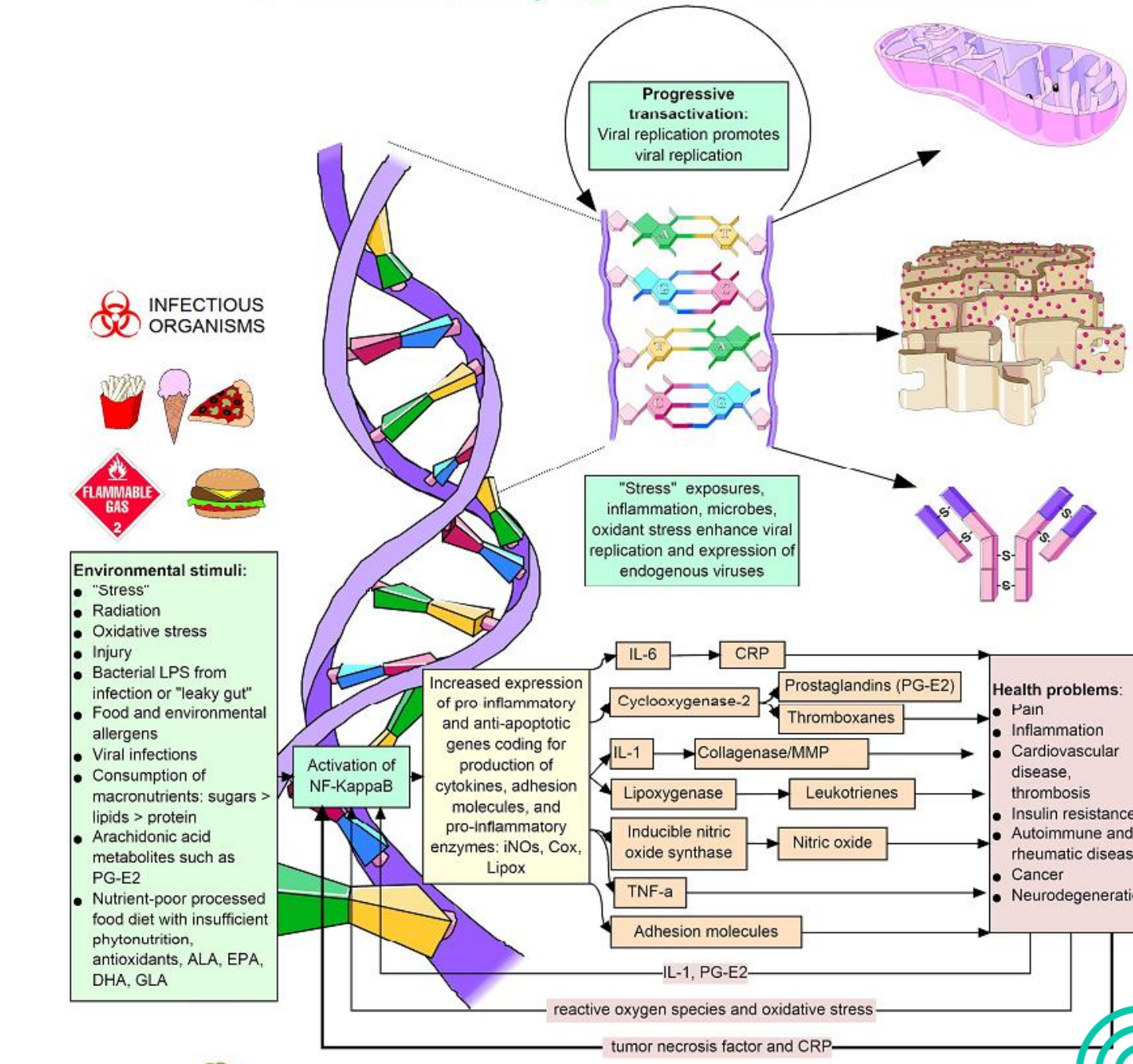

Dr. Alex Vasquez

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

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

Abstract

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

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

Several factors disrupting the integrity of nutrition research are commonly found in studies published by "elite" universities in "top-tier" journals, which are then republished and distributed as "headlining news" in newspapers, magazines, and television via which they related to nutrition. Perceived shortcomings are documented with both citations here and links to more detailed and authoritative reviews and video presentations. In some instances, speculations regarding the cause and consequences of identified errors are provided.

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

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- **VIDEO**: BRIEF Critique of "Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" https://vimeo.com/287650812
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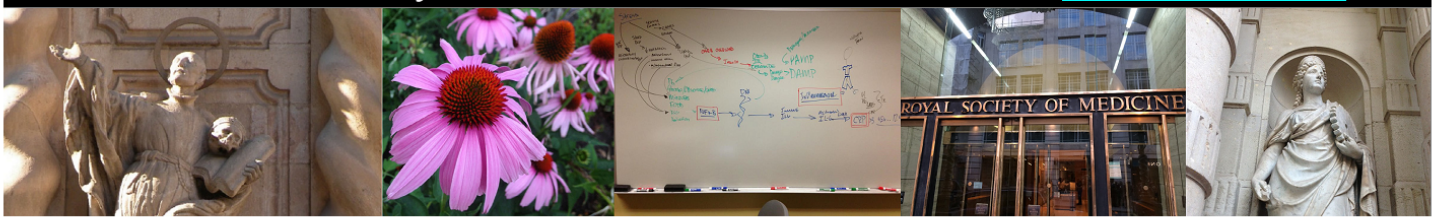

Perspective, Opinion, Editorial • Education • Academia • Wage Theft • Corruption

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

Alex Vasquez DC ND DO FACN

My own paths toward and perspectives on Education

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

Oh, the stories I could tell you Academia, "nonprofits", and "

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

singing a rhythmical rendition of "*The Hills are Alive…with the…Passions of Education and Intellectual Integrity*." But a pollyannic representation of my observations would be a misrepresentation of the realities I have seen and experienced. I have seen university presidents lie to their students, expel experts for the sake of maintaining their own petty powers and preferences, and I have seen entire academic administrations lie (misrepresent) in unison to their boards of trustees and their accreditation commissions. I have seen stand-alone academic programs make millions of dollars in profit, while its administrators refuse to pay a living wage to doctorate-level infrastructure and while allowing themselves 6-week European vacations during major institutional initiatives. I have seen administrators lie to accreditors and allow students to cheat their way through graduate programs (by bypassing faulty examination software in online programs), and I have seen accreditors turn a blind eye to obvious university corruption, made worse when the accreditation commission is infiltrated by university administrators—thus did "accreditation" come to lose its value. I have seen "nonprofit educational institutions" underpay their faculty, plagiarize from their faculty, resell the work of other professionals without notice or compensation, and then pay their upper administrators in excess of US$160,000 for less than part-time work—thus did "nonprofit organization" come to lose its value. I have seen schools blackmail excellent professors and leaders in education with gag orders, legal threats, and financial bribery (range US$25,000 up to $250,000) to buy their silence about institutional corruption. I have corresponded

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

Barceloneta sunset © 2019 by Dr Vasquez

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

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

Alex Vasquez DO ND DC FACN

Introduction

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

Early Experiences and Influences

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

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

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

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

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

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

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- https://www.ichnfm.org/public
- **See original video here: https://vimeo.com/318326979**

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

JOURNAL OF ORTHOMOLECULAR MEDICINE

OPEN ACCESS
VOLUME 34, NUMBER 1
PUBLISHED: MARCH 2019

Editorial

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

2018 As a Milestone in the Post-Truth Era

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

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

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

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 ISSN 0317-0209

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

Alex Vasquez, DC, ND, DO, FACN

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

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E-mail address: avasquez@ichnfm.org

MITOCHONDRIAL MEDICINE ARRIVES TO GENERAL PRACTICE AND ROUTINE PATIENT CARE

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

We all know that mitochondria are the intracellular organelles responsible for the production of the currency of cellular energy in the form of the molecule adenosine

Nutrition and Functional Medicine[1] in Portland, Oregon, in September 2013, we have collectively arrived at a time when mitochondrial therapeutics and the contribution of mitochondrial dysfunction to clinical diseases must be considered on a routine basis in clinical practice. *Mitochondrial medicine* is no longer an orphan topic, nor is it a superfluous consideration relegated to boutique practices. Mitochondrial medicine is ready for prime time—now—both in the general practice of primary care as well as in specialty and subspecialty medicine. What I describe here as the "new" mitochondrial medicine is the application of assessments and treatments to routine clinical practice primarily for the treatment of secondary/acquired forms of mitochondrial impairment that contribute to common conditions such as fatigue, depression, fibromyalgia, diabetes mellitus, hypertension, neuropsychiatric and neurodegenerative conditions, and other inflammatory and dysmetabolic conditions such as allergy and autoimmunity.

BEYOND BIOCHEMISTRY

Structure and function are of course intimately related and must be appreciated before clinical implications can be understood and interventions thereafter applied with practical precision. The 4 main structures and spaces of the mitochondria are (1) intramitochondrial matrix—the innermost/interior aspect of the mitochondria containing various proteins, enzymes of the Krebs cycle, and mitochondrial DNA; (2) inner membrane—the largely

passive transport systems for select molecules that need to enter and exit the mitochondria. Clinicians need to appreciate that mitochondrial membrane integrity is of the highest importance; just as we have come to appreciate the

JOURNAL OF ORTHOMOLECULAR MEDICINE

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Editorial

Orthomolecular Medicine, Catalytic Creativity, and the Psychosocial Ecosystem

Transitioning From One Year to the Next

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

Salutation and Introduction From the Journal's New Editor

Over the past few years I have reflected on several occasions how much I enjoy editing, and so I was correspondingly surprised and pleased when I was offered the opportunity to be the next Editor for the *Journal of Orthomolecular Medicine.* I began studying nutrition and orthomolecular concepts in my teen years and mo school in the early 1990s. trition" book that I read as *Your Nerves* (1975) by me this was followed immedi tures of Jonathan V Wrigh of whom would later be m University. By the mid-199 Jeffrey Bland PhD had int tional medicine, which I and personal[3] reasons. By contained several hundred tion and health with another large section on philosophy and psychology. In 1994, I joined the Review Staff of the *Journal of Naturopathic Medicine,* and I started publishing nutrition articles, perhaps most of which might be seen as practice in preparation of an important letter published in 1996 by the American College of Rheumatology in their journal *Arthritis and Rheumatism.* Since those early years and during the course of three doctorate degrees and teaching thousands of students/attendees internationally, I have reviewed for[4] and published in[5] a wide range of refereed journals in addition to publishing commissioned books, chapters, and independent publications and videos. Being an author and reviewer for many different publications—along with my experiences teaching internationally, treating patients in various settings, designing and directing academic programs, and producing educational videos—has given me a wide range of experiences and insights that I hope to bring to the benefit of the *Journal of Orthomolecular Medicine.*

We Must Work Together if We Are Going to Succeed

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

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

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

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

Alex Vasquez DC ND DO FACN

Experience and Perspectives

Many years ago when I published my first books[1,2] and articles[3] detailing "dysbiosis", the word could hardly be found in the Medline index, the topic was controversial at best and ethereal at worst, the term "microbiome" (first published in French in 1949 and in English in 1988) was virtually unknown, and I spent most of the time and space in my lectures and articles substantiating and defending the condition's existence. These days, everyone is talking about microbiome, dysbiosis, "leaky gut" (thanks largely to Leo Galland MD), and my 1996 article on "Silent Infections and Gastrointestinal Dysbiosis" has been downloaded at least 4,000 times and is one of the top 1% most popular art… dysbiosis le… 2010, I fou… "dysbiosis" … than 1,200 … concept has … popular, bu… to do with it … *Medicine* … microbiota … *the comple… Project, the number of scientific papers linking the microbes that live in our gut to diseases ranging from diabetes and colitis to anxiety and depression has grown exponentially. Yet, these tantalizing connections have yielded few benefits from a therapeutics standpoint*."[5] To the extent that this information is being integrated into clinical practice at all, the current level of practical application is a bit indelicate and cumbersome beyond the most commonly repeated advice of advocating probiotics, avoiding antibiotics, perhaps delving into using botanical antimicrobials and laboratory testing. Breath testing (an insensitive test for only one subtype of gastrointestinal …opular to the …nical clues. …ratory testing …rticular used …ods to extract …ney only to …uffering and

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

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

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- **See various videos and course excerpts here: https://www.ichnfm.org/image-gallery-dysbiosis-course**

…M
International College of Human Nutrition and Functional Medicine

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

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

CME
CONTINUING MEDICAL EDUCATION

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

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

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

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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 consequen
2. Identify patient grou
hypersensitivity
3. Know how to imple
proper doses and wi

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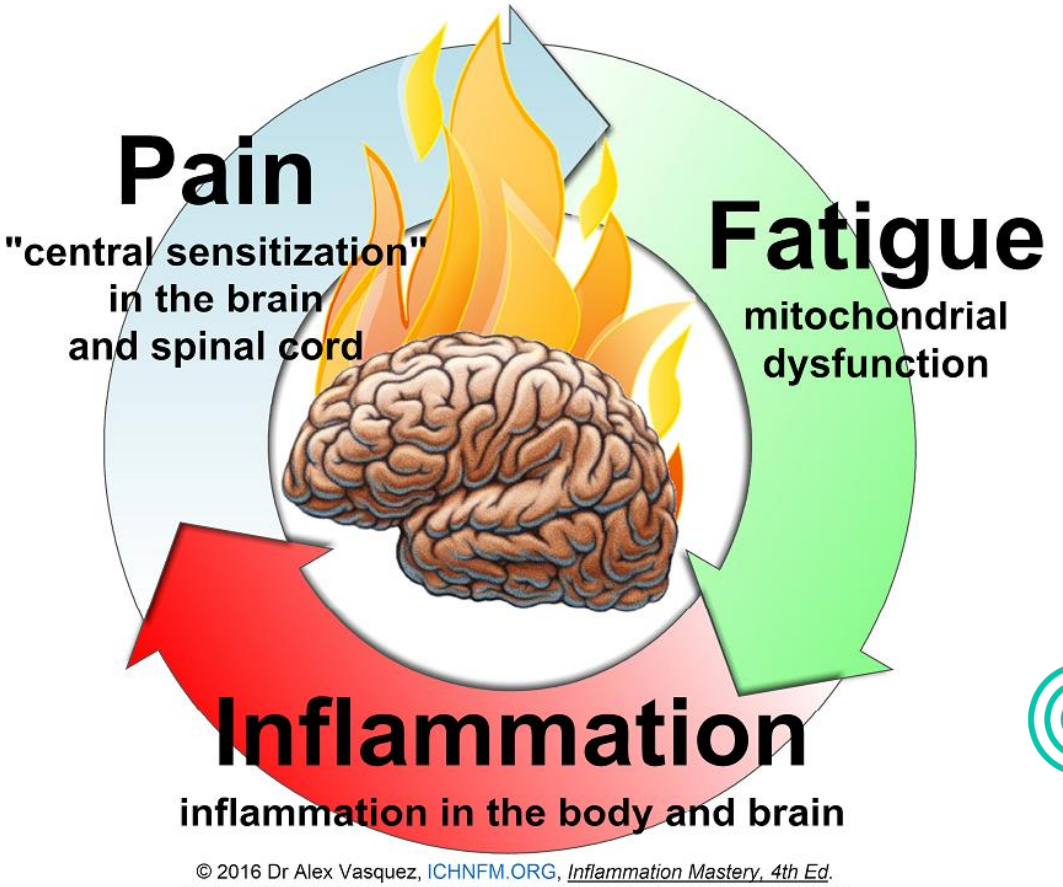
-therapies.com and selecting the Continu

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

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



Alex Vasquez, D.C., N.D., D.O., F.A.C.N.
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- **INFO**: https://www.inflammationmastery.com/migraine
- From ***Inflammation Mastery, chapter 5***, the two sections specific to migraine and fibromyalgia were also published separately as ***Pain Revolution*** (full-color printing; https://www.amazon.com/dp/B01AR3NX0S) and ***Brain Inflammation in Chronic Pain, Migraine and Fibromyalgia: The Paradigm-Shifting Guide for Doctors and Patients Dealing with Chronic Pain*** (black-and-white printing; https://www.amazon.com/dp/B01EQ9KMH6/); both versions are also available in digital ebook format for phone, computer, iPad via the free Kindle software

The New York Academy of Sciences 200 Years

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

Biological plausibility of the gut–brain axis in autism

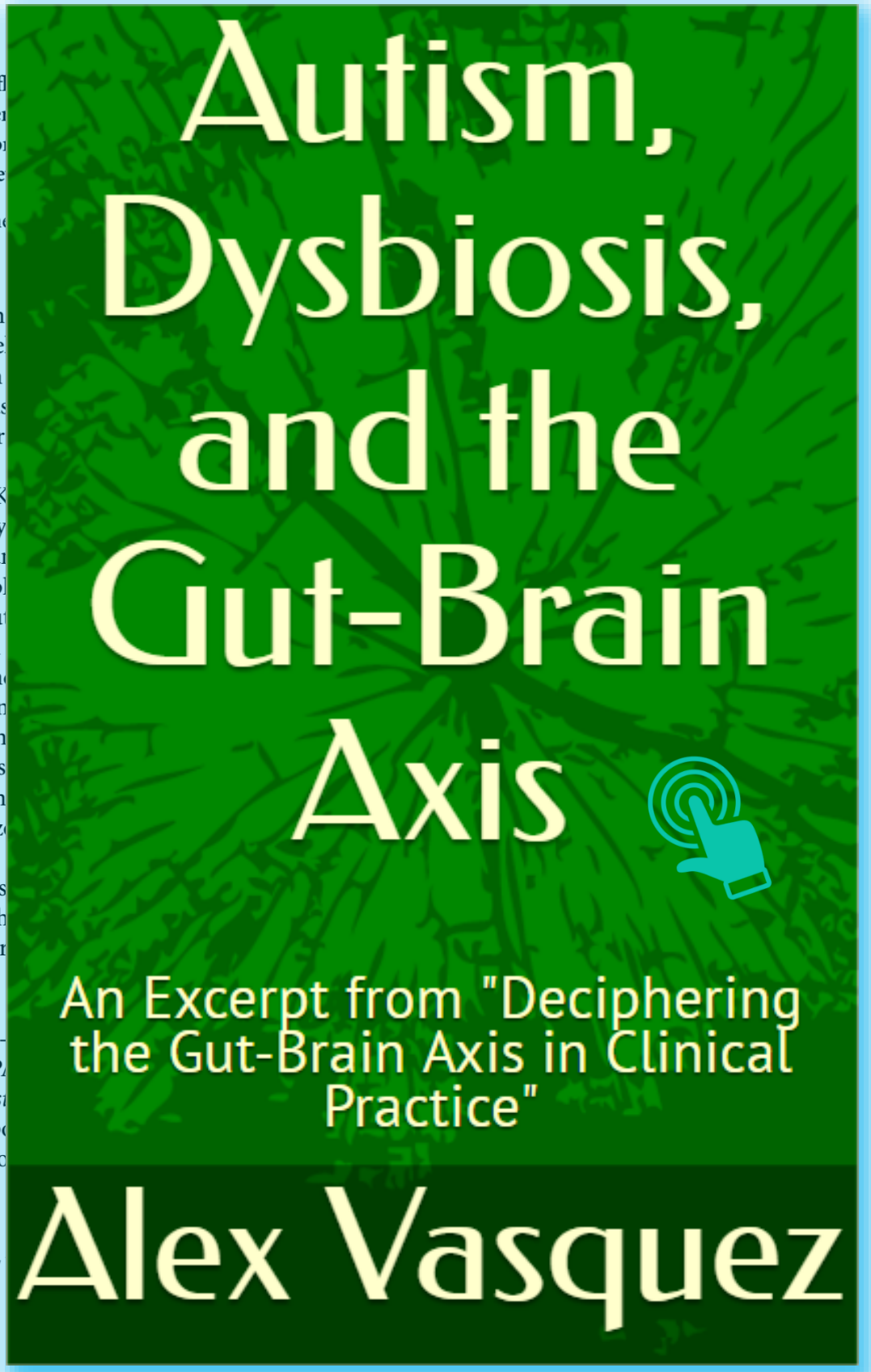
Alex Vasquez

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

Keywords: gut–brain axis; autism; m

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

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



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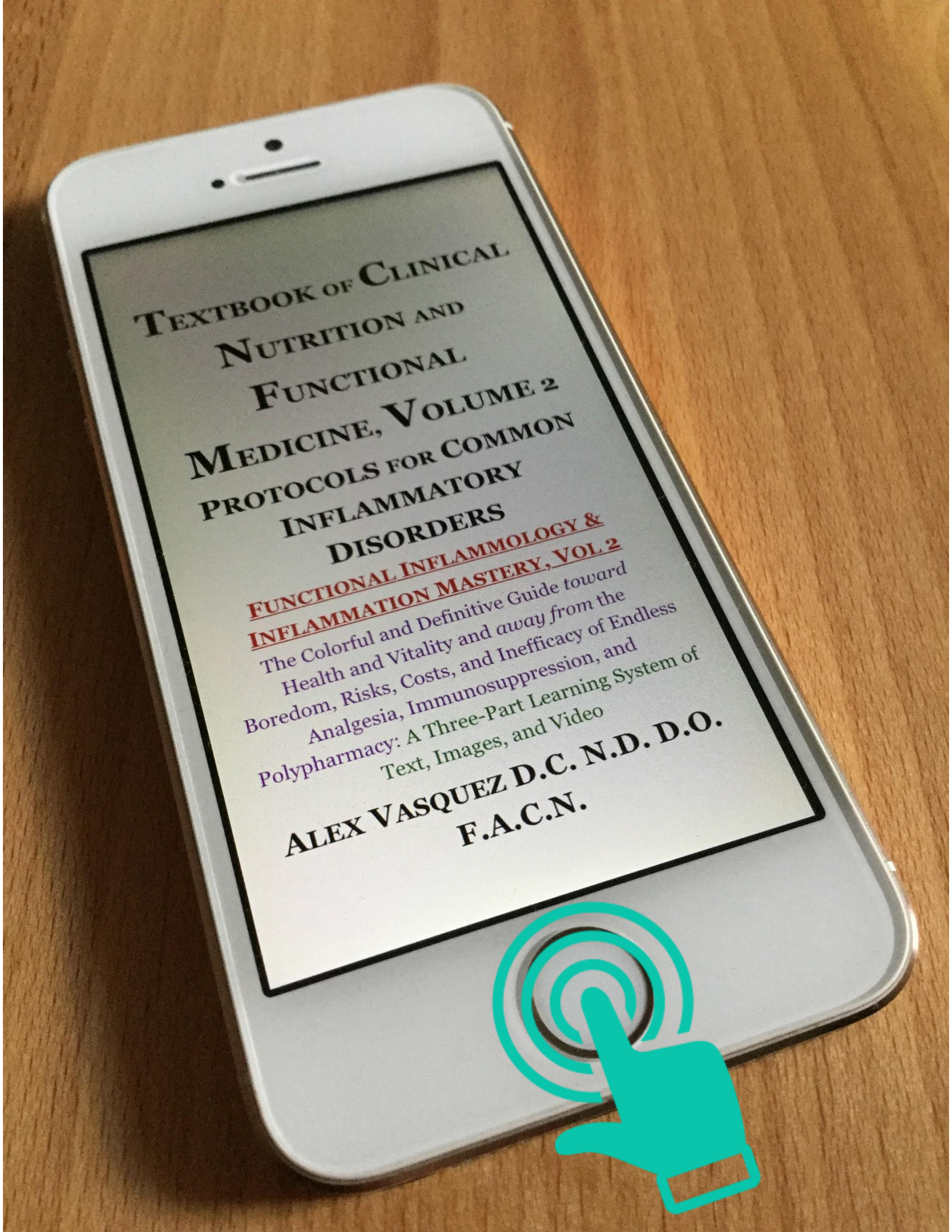
Textbook of Clinical Nutrition and Functional Medicine, Volume 2
Protocols for Common Inflammatory Disorders
Functional Inflammology & Inflammation Mastery, Vol 2
The Colorful and Definitive Guide toward Health and Vitality and away from the Boredom, Risks, Costs, and Inefficacy of Endless Analgesia,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