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

Alex Vasquez DO DC ND (USA) FACN

Vitamin D: Metabolism Dogma

The "vitamin D metabolism dogma"—as summarized here and familiar to many adults—is that vitamin D is produced in the skin following the exposure of intradermal (7-dehydro)cholesterol to ultraviolet B radiation, resulting in the nonenzymatic temperature-dependent production of vitamin D3. Alternatively, vitamin D3 is obtained from some food sources but in generally insufficient amounts with the exception of concentrated foodstuffs such as cod liver oil. If dermal production and dietary procurement are both insufficient, then a person (or population) must rely on supplementation of this substance in the form of liquid, pills, or injection. Whether sourced from photosynthesis or foraging, now-endogenous vitamin D3 is converted in the liver to 25-hydroxy-vitamin D3 which is commonly considered the storage form of the vitamin and which is also the form of the vitamin measured to assess clinical deficiency or sufficiency (see accompanying infographic: "Interpretation of serum 25-hydroxy-cholecalciferol levels in adults"). As needed, 25-hydroxy-vitamin D3 is converted to the so-called "active form" 1-25-dihydroxy-vitamin D3 within the kidney; hopefully by now most people know that this final activation reaction occurs in essentially all tissues and cell types.

This vitamin D metabolism dogma is sufficient knowledge for most patients, students, and clinical practitioners, except those who want expert insight and those who want to avoid being manipulated by policies founded upon erroneous and outdated dogma. I think that from this time forward (actually earlier, e.g., Vasquez et al 2004 per Ovesen, Brot, Jakobsen 2003), this level of understanding is insufficient for physicians and clinicians; accurate though it is, is incomplete and thus leaves us vulnerable to manipulation.

Vitamin D: Toxicity Dogma

Folklore and medical miseducation dogma hold that vitamin D toxicity is a common event, especially among "health food faddists", those who consume nutritional supplements for psychological reasons, and people with "expensive urine."

This folklore and miseducation were completely overthrown by Vieth in 1999, mocked by Vasquez et al in 2004, and further trampled by numerous primary investigators, especially Heaney et al in 2003 and 2008. Amazingly, Hyppönen et al, 2001 had started the overthrow as early as 1966 and collected data for more than 31 years, with each passing day among their 10,000 subjects further dismantling the dogma of "vitamin D toxicity from physiologic dosages." Any one of these five citations was more than sufficient scientifically to shift the paradigm of perception and patient care, but intellectual inertia and drug-centered dogma have largely continued to subvert progress, perpetuating more expensive and inefficient patient care, millions of premature deaths, and various forms of human suffering that cannot be quantitatively measured.

Vitamin D: The Bolus/Depot Dosing Fallacy

If vitamin D3 is biologically inert, and 25-hydroxy-vitamin D is the storage form awaiting its metered conversion to the active form of 1,25-dihydroxy-vitamin D, then administering large doses of virgin D3 might seem reasonable for patients whose sun exposure and oral intakes are insufficient to prevent deficiency. A massive oral dose or injection of 100,000-600,000 international units (IU) could be administered once or twice per year at the convenience of the doctor and patient. No need to think about complexity or modify anything on a regular basis when one can simply step in and out of nutritional consciousness on an annual or biannual basis.

But this facile façade has always shown its cracks. Such bolus or depot dosing has never worked as well as frequent, especially daily, dosing. Why not? Antinutrition propogandists—unhindered by their ignorance—tell the masses that "Vitamins and Supplements Are a Waste of Money" (Wilson 2019). Somehow, the pathways that depend on these substances are themselves wrong and the fact that we have a nuclear transcription factor that binds to vitamin D must simply been an artifact, and one that we never studied in medical school anyway. So, it must not be important.

Vitamin D administration to older patients prevents **falls and fractures**, *but not when delivered in bolus/depot doses* (Gallagher 2016). Vitamin D administration prevents **upper respiratory tract infections**, *but not when delivered in bolus/depot doses* (Martineau 2017). Studies in the year 2020 showed that vitamin D could effectively treat clinical **coronavirus infections** (Castillo, Rastogi), *but not when delivered in bolus/depot doses* (Murai).

Maybe instead of trying to resolve the superficial inconsistency, we should give up on Nutrition and try to find something easier. We could focus all our efforts and resources on injectable and liability-free drug products based on a theory born of medieval assumptions before we even knew things about transverse myelitis, acute disseminated

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encephalomyelitis, autoimmune disease induction by adjuvants, negative efficacy, and linked-epitope suppression. Besides, we never learned about Nutrition in medical school anyway. This must be the reason. Or maybe we were wrong. Or maybe we're just stupider than we should be. Or maybe we just never learned the appropriate fundamental facts. If we are unguided or misguided from our point of departure (e.g., medical school) then the entire voyage will be lost, or—at best—delayed, more expensive, and circuitous. The cool thing about medical education and about being a medical doctor is that the entire field of Nutritional Sciences can be ignored and one can still maintain the illusion and façade of professionalism and competence, because one's peers are identically ignorant. It's "mind over matter", when what is not in the mind does not matter, especially within a social-professional bubble of mirrored ignorance, impenetrable vanity, incentivized pharmacocentric monotheism and revivalist vaccine evangelism.

The vitamin D bolus fallacy is the erroneous belief that periodic megadoses of vitamin D3 function anywhere near an equivalent manner to frequent/daily dosing with physiologic amounts. The practice of administering vitamin D in bolus quantities should be considered mostly fraudulent (especially if vitamin D2 is used instead of vitamin D3), frequently maleficent, albeit arguably better than complete malnutrition or negligence. Not too many people think about the fact that bolus D3 dosing floods the system with a weak agonist which thereby functions as a relative antagonist, but that's what I will explore in the following sections.

Mechanistic Explanation for the Failure of the Bolus

Vitamin D3 is either produced in the skin following exposure to ultraviolet B radiation, consumed in various foods, and/or taken as a dietary nutritional supplement; as reviewed previously, D3 is converted in the liver to 25(OH)D and in the kidney to 1,25(diOH)D. Unknown to most people are the facts that D3 has biological activity, as does 25(OH)D, with the latter also found in various foodstuffs, especially meats, offal, and egg yolks. Once we appreciate that D3 and 25(OH)D have biological activity, then we must take these aspects of vitamin D pharmacology seriously, not simply conveniently, nor conveniently simplistically. Serum D3 levels are normally near 0 (zero) but can spike to more than 520 nmol/L following bolus dosing (with 100,000 IU), resulting in altered pharmacokinetics and the storage of the supraphysiologic D3 in biologically active tissues such as adipose where D3 is expected to have activity *while being unmeasurable in the blood*. If we accept the common estimate that D3 has five-fold (range 2-6x) less biological activity than does 25(OH)D — alternatively stated that 25(OH)D has five-fold the biological activity of D3— then we have to comprehend that D3 administration to a patient who is deficient in 25(OH)D could lead to a functional imbalance as the weak agonist behaves as a partial antagonist, especially when administered in supraphysiologic bolus/depot doses to patients who are deficient in 25(OH)D and other nutrients (especially magnesium, deficiency of which is very common, affecting 30-60% of most populations and which impairs vitamin D metabolism, thereby delaying the necessary enzymatic conversions). The biological activity of 25(OH)D is estimated to be 400-fold less than that of 1,25(diOH)D; however, the physiologic concentration of 25(OH)D is 500-fold greater up to 1000-fold greater (Chun, Shieh, Gottlieb, et al, 2019) than that of 1,25(diOH)D so that the resulting physiologic effect-per-serum-level gives 80% of the activity to 25(OH)D (Ovesen op cit, 2003). Relatively modest doses of vitamin D3 administered on a regular/daily/weekly basis follow first-order kinetics with rapid conversion of D3 to 25(OH)D, thereby avoiding the problem of D3 acting as a partial antagonist. Conversely and consequently, supraphysiologic bolus/depot doses of D3 follow zero-order kinetics (Heaney et al, 2008) wherein the serum spike of D3 is followed by tissue deposition of D3 which is slowly metabolized to the more active 25(OH)D; while awaiting this enzymatic conversion, the patient is vulnerable to any inhibitory/dysmetabolic effects of D3. This proposal explains that bolus D3 dosing floods the system with a weak agonist which apparently functions as a relative antagonist when at supraphysiologic serum/tissue levels, paradoxically impairing D metabolism while eventually raising serum 25(OH)D levels.

Although human physiology is not restricted to mathematical outcomes, we must respect the influence of these biochemical and pharmacologic properties in the study of nutrition just as we do when studying drug pharmacology. If we take 1,25(diOH)D as the standard and assign it an arbitrary unit of 1 for its referent activity, then 25(OH)D would be represented by 1/400 and D3 relative to 25(OH)D would be 1/5 thus making it 1/2000 relative to 1,25(diOH)D. 25(OH)D activity is 1/400 but its concentration is 500x to 1,000x thereby giving it more biological activity than the referent (r) 1,25(diOH)D in some biological activities. At least in some circumstances D3 activity is 20% (0.2) that of 25(OH)D but acute bolus dosing (e.g., 100,000 IU) increases serum levels at least 100-fold (e.g., from 5 to 515 nmol/L per Heaney et al, 2008) thereby making it competitive (0.2 r potency x 100 concentration = 20 r effect) with 25(OH)D. Higher concentration of a weaker metabolite that competes for the same functions would be expected to result in pharmacodynamic antagonism, thereby possibly explaining the negative results seen with bolus dosing, which may or may not be limited to the time duration of the measurable (i.e., serum) imbalance. Following supraphysiologic bolus dosing, serum D3 levels peak on day 1 and normalize back to baseline of approximately zero on day 14; however, levels of D3 remain elevated in tissues (e.g., adipose but also in other cells of medical consequence) for several months (Heaney et al, 2008). Further adding to the inhibitory effect of bolus doses of vitamin D3 is the megadose-induced expression of enzymes that convert 25(OH)D and 1,25(diOH)D to their inactive/excretable 24-hydroxylated metabolites. Thus, in summary: bolus dosing is neither qualitatively nor quantitatively similar to physiologic dosing (Vasquez 2004), and it has practically zero clinical value; annual bolus dosing of D3 does not work; even at a D3 dosage of 250,000 units, serum levels return to baseline at 90 days and are completely deficient for the remainder of the year (Kearns 2015).

Selective and Self-Serving Nutritional Ignorance

The medical-research machinery is impressively retarded in the study of Nutrition when it selectively ignores

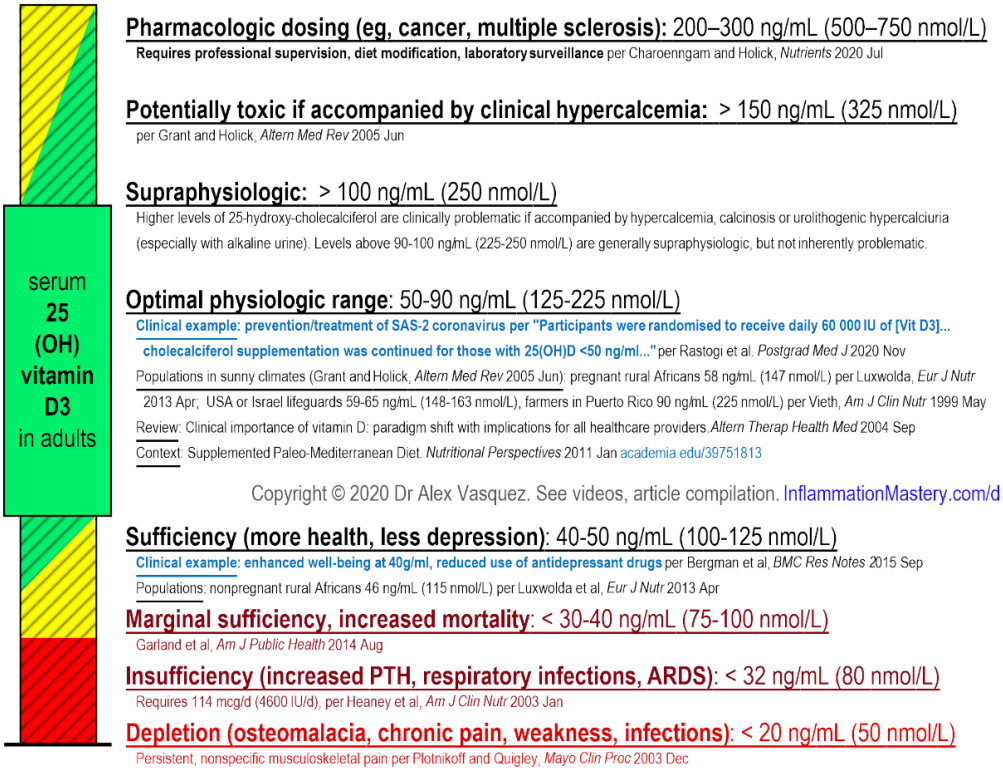
pharmacologic principles in the study of nutritional therapy, thereby perpetuating for its own benefit the "mystery" and "unreliability" of Nutrition, which would be its biggest therapeutic competitor. Principles of Biochemistry and Physiology and Mathematics are commonly applied to drug dosing such that exacting measurements of peaks and troughs can be calculated with precision down to the minute; but these same physicians and researchers feign to look upon calculators with dead batteries when they are studying Nutrition. Suddenly millennia of study in Mathematics evaporates, the slide rule disassembles, and the abacus beads fall to the floor and are swept under the rug. Nutrients can have thousands of years of clinical use, hundreds of supported modern citations in peer-reviewed journals and can be completely ignored as "needing more research" while a new never-before drug technology can pop onto the market and be accepted, endorsed, purchased, and distributed within a few months, demonstrating the ***power of paradigm,*** unquestioning ***pharmacotheism***, the self-reinforcing **pharma echo chamber** and power vortex (Vasquez 2019). To maintain financial, political and social dominance, the medical profession must ignore its faults and aggrandize its self-proclaimed superiority while ensuring that any competition is neutralized legally, strategically, and conceptually (Getzendanner *JAMA* 1988); for this, the medical and pharmaceutical institutions must produce a constant stream of confusion and misinformation with regard to any nondrug alternatives (Vasquez and Pizzorno 2019), even employing the highest (or lowest) levels of sabotage and absurdity. Only in a completely dumbed-down population could a "medical school professor" completely slaughter the ironic (not iconic) significance of Pascal's gamble and then misapply it to clinical therapeutics solely for the purpose of trying to make nutritional therapy appear decerebrate; only in a system designed to perpetuate ignorance and confusion could such an author gain paid syndication and exposure to millions in a platform specifically designed for the infotainment of medical physicians (Wilson 2020). Only in a completely dumbed-down population could a "leading medical journal" published by no less than the venerated American Medical Association codify and distribute complete nonsense such as "Changes in dietary composition within prevailing norms can affect physiological adaptations that defend body weight" (Pereira 2004) instead of simply and directly advising people to consume a reasonable low-carbohydrate diet to reduce systemic inflammation by 50% and reduce the risk of cardiovascular disease and diabetes. Medical obscuritanism is the nation's leading killer, but cancer, cardiovascular disease, diabetes, depression, and infectious diseases get the blame.

The Costs of our Confusion

Human adult physiology requires 3000 to 5000 international units (IU, units) of vitamin D3 per day to maintain baseline metabolic and steady-state dynamics (Heaney et al in 2003). The medical fallacy is to assume that this physiologic need can be met with periodic and extreme bolus dosing, such that 4000 international units per day can be conveniently achieved with an annual dose of 100,000 to 300,000 units, a clinical practice which fails grade school mathematics. I trust that any neurocompetent child over the age of 10 could multiply 4k times 365 to arrive at 1,460,000. This makes the bolus model look even more ridiculous when it lacks even superficial internal consistency. If we calculate that people need 1.5 million units and we give them 100,000 units or 300,000 units then we are not behaving in a neurocompetent, nor ethical manner let alone a scientific or medical or professional manner at any adult level.

Given that adult humans need D3 ~4000 IU/d then giving them a bolus dose of 100,000 units has no natural or physiologic basis. If we agree that adult humans need to drink 2-3 liters of water per day, but instead of giving people what they need on a daily basis we force them to be completely dehydrated for the entire month and then at the end of the month we force them to drink their quota of 60-90 liters of water within one hour or one day, then we would expect the production of mass casualties under the guise of "giving people what they need." Likewise, if we were to say that people need one hour of exertional physical activity per day, but we then crammed all of that metabolic demand into a one-hour period one day per month, we would likewise expect to exceed physiologic capacity and result in deaths, not physical fitness, even though the daily average per month is accurate. Likewise, because bolus dosing is dangerously unphysiologic, we must declare that **bolus dosing of vitamin D is dead**: it was based on erroneous thinking and ignorance of Nutritional Pharmacology, leveraged to the convenience of the physician and not to the benefit of the patient. Moving forward, it has little or no place in the practice of medicine, preventive healthcare, research, or clinical practice of nutrition. It embarrasses science and the profession of medicine by its fallacious lack of internal consistency. It creates confusion in the research literature and prevents the advancement of science. As such, it fuels and sustains ignorance, confusion, inaction, and political dependence on topics related to healthcare, specifically chronic pain, depression, inflammatory diseases and the treatment of infectious disease and viral pandemics (Vasquez 2004, 2017, 2020; 2014). In November 2020, the United Kingdom government decided to declare itself generous in giving "for free" a small fraction (2.7M of 54M = 5%) of its population 400 IU to compensate for winter and a year of forced quarantine that essentially put the entire populace on house arrest. Again, this is mathematically incompetent and medically ridiculous. No scientific or medical body in the entire world would think that 400 IU is sufficient for adults—in fact it's only 10% of what has been clinically and scientifically proven to be necessary; furthermore, how could they possibly justify helping only 5% of their population when the entire population is at risk for vitamin D deficiency. The most we can say is "at least they did something" whereas other countries have completely ignored the topic. Of course, one could argue whether ignoring the topic is better or worse than addressing the topic in a completely incompetent manner that is designed to fail. Intentional confusion and the resulting inaction have cost millions of lives, incalculable human suffering and —now in 2020— contributes to the enslavement of the global population by hindering effective prevention and treatment of a viral pandemic, just as predicted (Vasquez et al 2004): "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. ... 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 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... 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." In a research letter titled "Vitamin D Insufficiency May Account for Almost Nine of Ten COVID-19 Deaths: Time to Act", Brenner and Schottke (2020) wrote, "… these results imply that 87% of COVID-19 deaths may be statistically attributed to vitamin D insufficiency and could potentially be avoided by eliminating vitamin D insufficiency. ... Given the dynamics of the COVID-19 pandemic and the proven safety of vitamin D supplementation, it therefore appears highly debatable and potentially even unethical to await results of such trials before public health action is taken." Governmental/medical failure to implement population-wide physiologic dosing of vitamin D3 or 25(OH)D (both of which are found in foods and can thus be categorized as nutritional supplements) is medically unethical and socially irresponsible and will continue to result in unnecessary deaths, infections, falls, fractures, chronic pain, drug dependence, inflammatory diseases, diabetes, neuropsychiatric complications and mental depression—all of which could have been avoided with simple, affordable, and available vitamin D supplementation. Forcing populations to live quarantined in "lockdown" conditions deprives them of sunshine-dependent vitamin D production, and we can expect catastrophic consequences to manifest, the most obvious and immediate of which will be mental depression (and suicide), weight gain/obesity, and vulnerability to infectious diseases, as these are the most common manifestations of marginal vitamin D deficiency. *Oh, the misanthropic irony, disguised as public health!* With quarantines/lockdowns and canceled summer vacations, millions of people have been forced into worsened vitamin D deficiency under the pretense of "protecting them" from a viral infection that thrives among and preferentially kills people who are vitamin D deficient. Vitamin D deficiency in COVID infection quadruples death rate (McCall 2020).



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

Infographic citations included in image; see also:
1. Vasquez et al. Clinical importance of vitamin D: a paradigm shift for all healthcare providers. *Altern Thera Health Med* 2004 Sep
2. Vasquez A. *Textbook of Clinical Nutrition and Functional Medicine*. ICHNFM.ORG, 2016
3. Vasquez A. How to Plan Studies Using Vitamin D. *Int J Hum Nutr Funct Med* 2017 academia.edu/31412957
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5. Videos/excerpts 2020, articles and correspondence compilation 2004-2019. InflammationMastery.com/d

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