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Editor's note: Given the international viral crises occurring in late 2014, publication and distribution of this article is a priority; the fact that these viral-infection health crises exist is prima facie evidence of the failure of current systems and the need—not for new treatments within the same model—for a new model better suited for international distribution, disease prevention, and broad-spectrum effectiveness.

Unified Antiviral Strategy published by ICHNFM

Alex Vasquez DC ND DO FACN in Bogota, Colombia

History and Perspectives

What we as doctors learn in medical school about viral infections is summarized within the following course titles: Microbiology, Pathology, and Pharmacology. Following this instruction, the treatments that we use are sanitation, vaccination, and antiviral drugs, respectively. Based on training and my experience with other doctors, I suggest here that most medically-trained doctors are—at least per their formal training—unable to see beyond these blinders and limited options. My intention in writing this article is to broaden those conceptual and therapeutic horizons via the outlining of a structured antiviral strategy that includes the previously mentioned sanitation, vaccination and antiviral drugs but extends well beyond those limited options. Additional citations, support, and clinical details (e.g., dosing and contraindications) for this strategy are available in a digital format constantly updated[1]; the purpose of this article is to structure the strategy, to shift the paradigm.

The fact that most doctors learn nothing about the science of Nutrition in medical school is well known publicly and within medical school academics.[2] Typically, most medical students read one chapter about pathologies caused by extreme nutritional deficiencies, but they learn essentially nothing about therapeutic nutrition and how it can be applied in the prevention and treatment of disease. Does ignoring Nutrition force doctors *by default* to over-rely on drugs and surgery? Would not public health be better served if information were distributed on the nutritional prevention of viral infections, so that patients and doctors alike would have more options?

What I have noticed through the various doctorate programs I have attended is that clinical training in the management of viral infections remains mostly phenomenalistic and enigmatic, rather than deciphered and structured. As an educator, and researcher and writer, I have learned through experience to structure information in such a way that the accessibility and retention of the information is enhanced by students/readers (e.g. the DDIRRT for risk management [e.g., defensive mindset, duration of treatment, interactions, referral, return visit, treatment plan], MYBESTPLAIDFIG for nutritional

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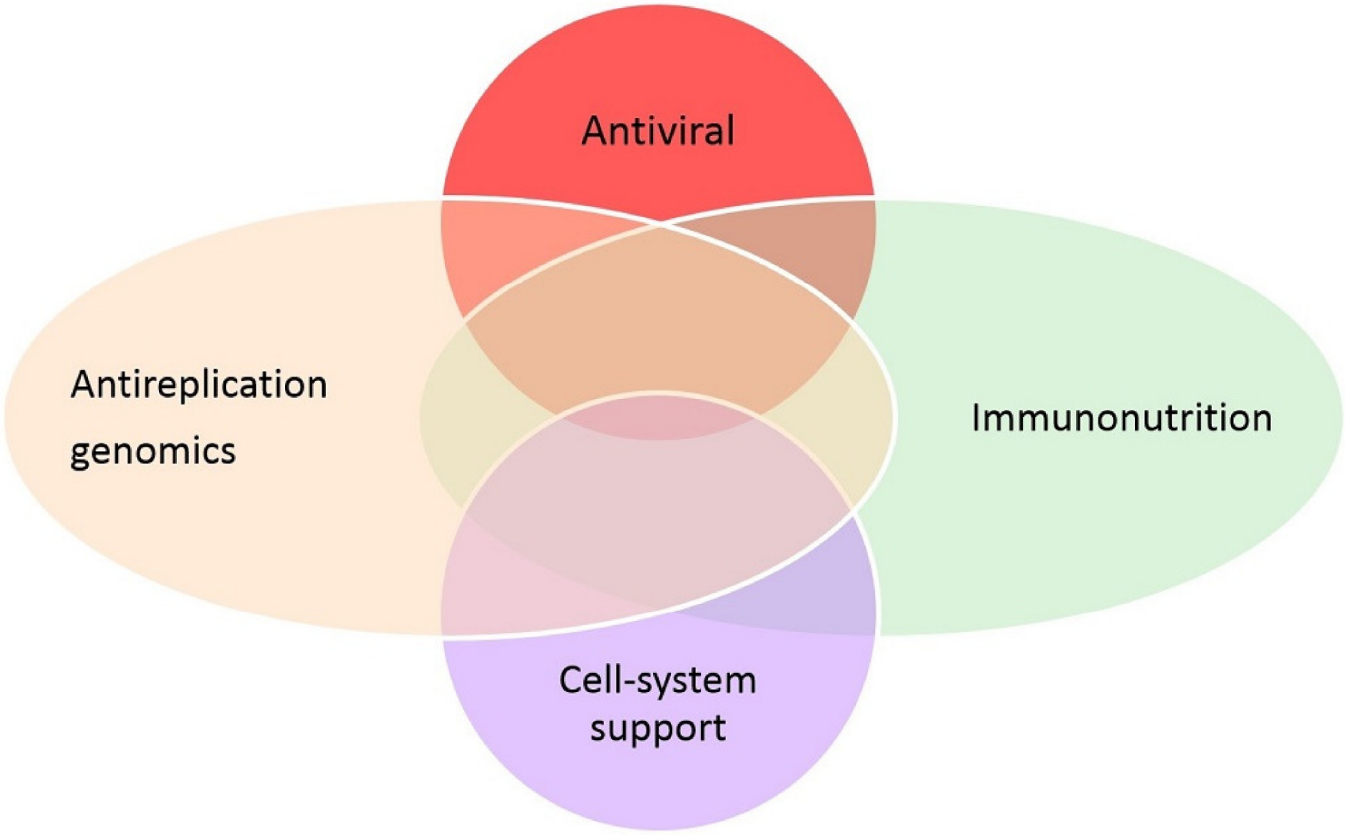
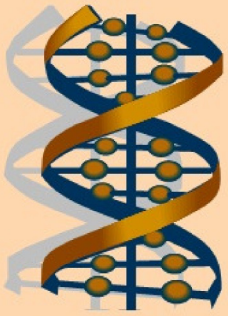
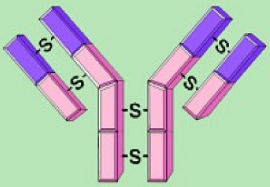
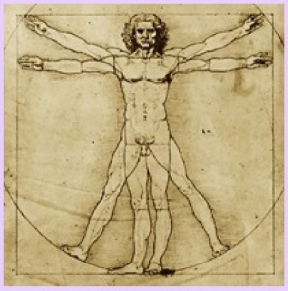
immunomodulation[3], and FINDSEX® acronyms[4]). My main purpose in writing this essay is to demonstrate a unique and structured antiviral strategy and to provide representative examples of its practical application.

Rather than viewing viral infections in a manner that is phenomenalistic and enigmatic, and therefore unwieldy, leading to clumsy prevention and treatment strategies, we should deconstruct the complexity of the infectious process. Doing so – at least in the manner that I have described – gives us four areas upon which we can focus our efforts: 1) targeting the virus directly, 2) blocking viral replication, 3) supporting immune function, and 4) supporting cellular and whole-body health. These are illustrated in the accompanying diagram and briefly described and exemplified in the four respective paragraphs that follow.



Antiviral	Antireplication	Immunonutrition	Cell-system support
			
Direct action against the virus itself, using nutrients and botanicals and drugs, targeting the machinery and blocking viral mutations	Inhibition of viral use of human DNA and replicative machinery; viruses can only replicate by "hijacking" human genetic process	Support and occasional stimulation of humoral (antibody, immunoglobulin) cell-mediated, and cytokine-mediated immunity	Supporting the intracellular systems (mitochondria and endoplasmic reticulum) and whole-body health to optimize immune response, limit damage, promote recovery, prevent recurrence

Multicomponent Antiviral Strategy

1. **Targeting the virus directly**: Targeting the virus directly has been the focus of medical practice and public health efforts through sanitation, vaccination, and –more recently– the use of disease-specific antiviral drugs. Several nutrients and botanicals are also very effective for directly targeting viral infections, and I will provide two examples here. The mineral selenium has a wide margin of safety and provides antiviral benefits through several mechanisms, two of which are blocking viral mutation and also blocking viral replication; anti-infectious clinical benefits are proven in humans with HIV/AIDS.[5] The botanical medicine and common herbal tea licorice (*Glycyrrhiza glabra*) has demonstrated antiviral effectiveness in experimental studies and human clinical trials against several different pathogenic viruses, including hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV), influenza A virus, human immunodeficiency virus (HIV-1), severe acute respiratory syndrome (SARS)-related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus, and vesicular stomatitis virus[6]; this botanical has a an excellent history of safety spanning several thousand years, with adverse/beneficial effects including a pseudoaldosterone effect (sodium retention and potassium depletion) and a testosterone-lowering effect, and mechanism of action including via direct virus binding, inhibition of viral replication, enhancement of immunity, inhibition of inflammation, and blocking the activity of specific enzymes. Antiviral nutrients and botanicals can be used alone, in combination, and alongside medications for additive and synergistic benefits.
2. **Blocking viral replication**: Inhibition of viral replication is the therapeutic goal of many antiviral drugs, while several nutrients can also provide a similar effect. Because viruses are unable to self-replicate and must therefore rely on host/human genetic and synthetic machinery for their replication, nutrients that modulate genetic expression can have therapeutic value here, namely via DNA methylation and blockade of the transcription factor NFkB. The few nutrients which promote DNA methylation and which also have proven clinical effectiveness against viral infections include folic acid[7] (now used clinically in the forms of folinic acid and methyl-folate), vitamin D3[8], betaine and S-adenosyl-methionine.[9] Inhibition of the NFkB pathway for antiviral effectiveness is well-documented, with two examples being with NAC against influenza[10] and lipoic acid against viral hepatitis and HIV.[11]
3. **Supporting immune function**: The performance and regulation of the immune system is heavily dependent on optimal nutritional status, and without proper nutrition, the immune system is slanted simultaneously toward underactivity (deficiency-induced immunosuppression) and hyperactivity manifesting as inflammation and autoimmunity.[12] Nutritional deficiencies are very common in the general population and thereby contribute to epidemics of infectious and inflammatory diseases. Human clinical trials using nutrients alone or in combination to support immune function in general have shown outstanding safety and efficacy against infectious diseases, especially use of glutamine, whey protein isolate, vitamin A, vitamin D, fish oil, and zinc.[13] Nutritional supplementation has been shown in several instances to improve immunological response to vaccinations; for example, cystine and theanine were noted to increase seroconversion of influenza vaccination in elderly persons.[14]
4. **Supporting cellular and whole-body health**: Viral infections have numerous adverse effects on cellular and whole-body health. Intracellular consequences of viral infections include mitochondrial dysfunction[15] and endoplasmic reticulum stress[16], manifesting clinically as prolonged inflammation, fatigue and – likely – in the case of herpes simplex infections, Alzheimer's disease.[17] Among the more than 30 interventions to improve mitochondrial function and alleviate endoplasmic reticulum stress, we see that exercise, low-carbohydrate diets, coenzyme Q-10, lipoic acid, and acetyl-L-carnitine are preeminent in their safety, effectiveness, and collateral benefits.[18] Osteopathic manipulative medicine, perhaps via promotion of improved respiration and lymphatic flow and distribution of chemokines, has also shown benefit in the nonpharmacologic amelioration of infectious disease.[19]

In summary, via the use of a structured antiviral strategy, pharmacologic and nonpharmacologic interventions can be applied with greater clinical and public health effectiveness, thereby alleviating the clinical, social, financial, and political burdens of these infectious diseases.

Conclusion and Application

The recent international outbreaks of viral infections have made one thing very clear: we need a new antiviral strategy in modern times to combat ongoing scourges of viral infections; pandemic spread of these infections in late 2014 is proof that the usual medical and public health measures of sanitation, vaccination, and medication are insufficient. The ideal antiviral strategy would be both generally and specifically effective, widely available, low-cost, with few or negligible adverse effects and drug/disease interactions. For most of medical and public health history, the tools used against viral infections have been sanitation and vaccination, with the more recent addition of molecularly-targeted antiviral drugs specific for each virus. My purpose in writing this essay is not to discuss or debate sanitation nor vaccination nor medication, but rather to point out several other intervention strategies that can be used additionally and to great patient and public health benefit. These evidence-based interventions have proven safety, effectiveness, and cost-effectiveness with wide and immediate international availability and generally negligible adverse effects and drug/disease interactions.

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Estrategia antiviral unificada para médicos y el público

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Historia y perspectivas

Como médicos lo que aprendemos en la escuela de medicina acerca de las infecciones virales se resume en los siguientes títulos de cursos: 1) Microbiología, 2) Patología, y 3) Farmacología. Siguiendo estas instrucciones, los tratamientos que usamos son 1) saneamiento, 2) vacunas y 3) medicamentos antivirales, respectivamente. Basado en la formación médica y mi experiencia con otros médicos, les sugiero aquí que más la mayoría de los médicos capacitados son — al menos por su entrenamiento formal — incapaces de ver más allá de las opciones limitadas a las que fueron expuestos. Lo que me gustaría hacer en el presente artículo es ampliar los horizontes conceptuales y terapéuticos mediante una estrategia estructurada antiviral que incluye el saneamiento, vacunación y medicamentos antivirales previamente mencionados, pero que se extiende más allá de estas opciones limitadas. Los datos clínicos (por ejemplo, dosificación y contraindicaciones) de esta estrategia, apoyo y referencias adicionales están disponibles en formato digital constantemente actualizado [1]; el propósito de este artículo es proveer una estrategia para cambiar el paradigma actual de la estructura.

El hecho de que la mayoría de médicos no se les enseña acerca de la ciencia de la nutrición en la Facultad de medicina es conocido públicamente.[2] Por lo general, la mayoría de los estudiantes de medicina leen solamente un capítulo sobre patologías causadas por deficiencias nutricionales extremas, pero aprenden esencialmente nada acerca de nutrición terapéutica y cómo puede ser aplicada en la prevención y tratamiento de la enfermedad. ¿Ignorando nutrición obliga a médicos por desconocimiento a confiar demasiado en medicamentos y cirugía? ¿Sería la salud pública mejor servida si se distribuye información sobre la prevención de infecciones virales y beneficios nutricionales para que los pacientes y médicos por igual tengan más opciones

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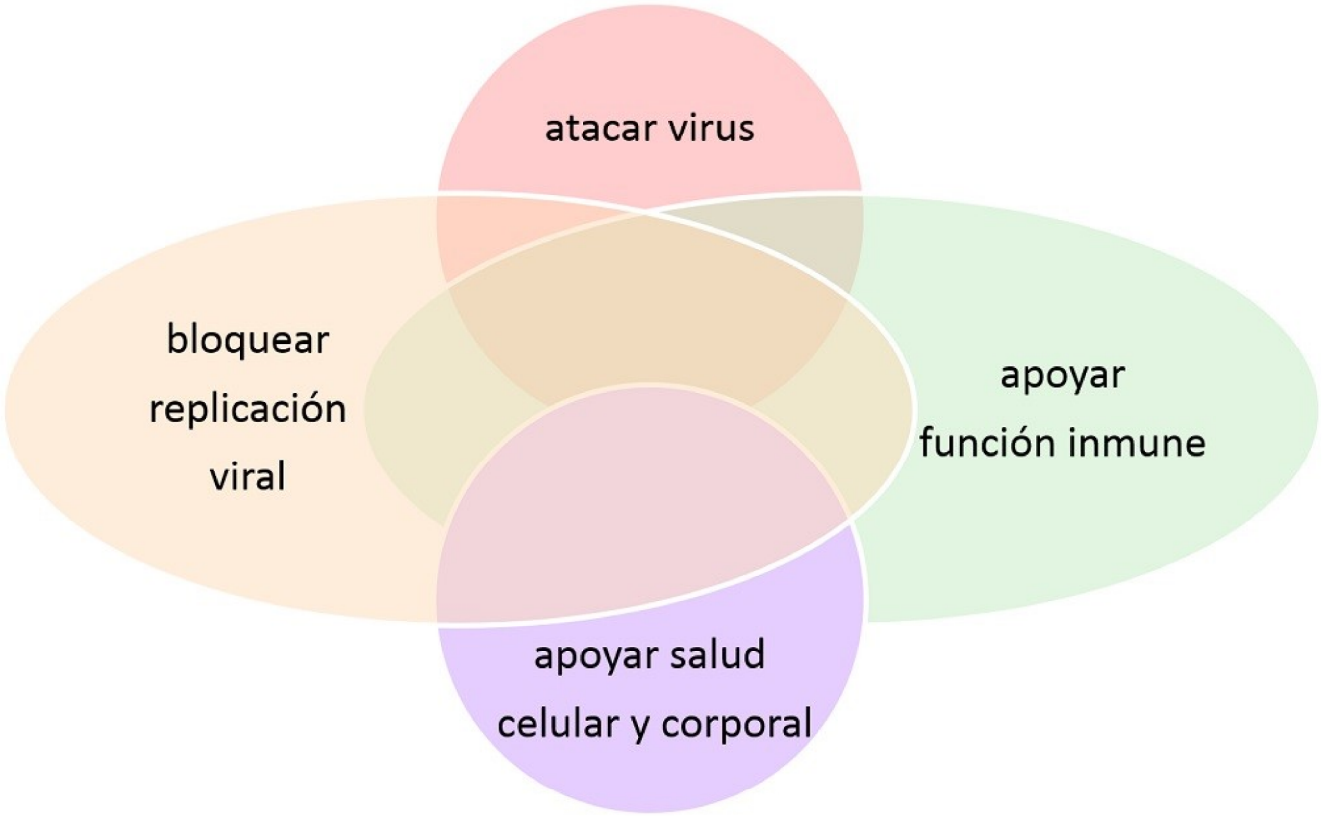
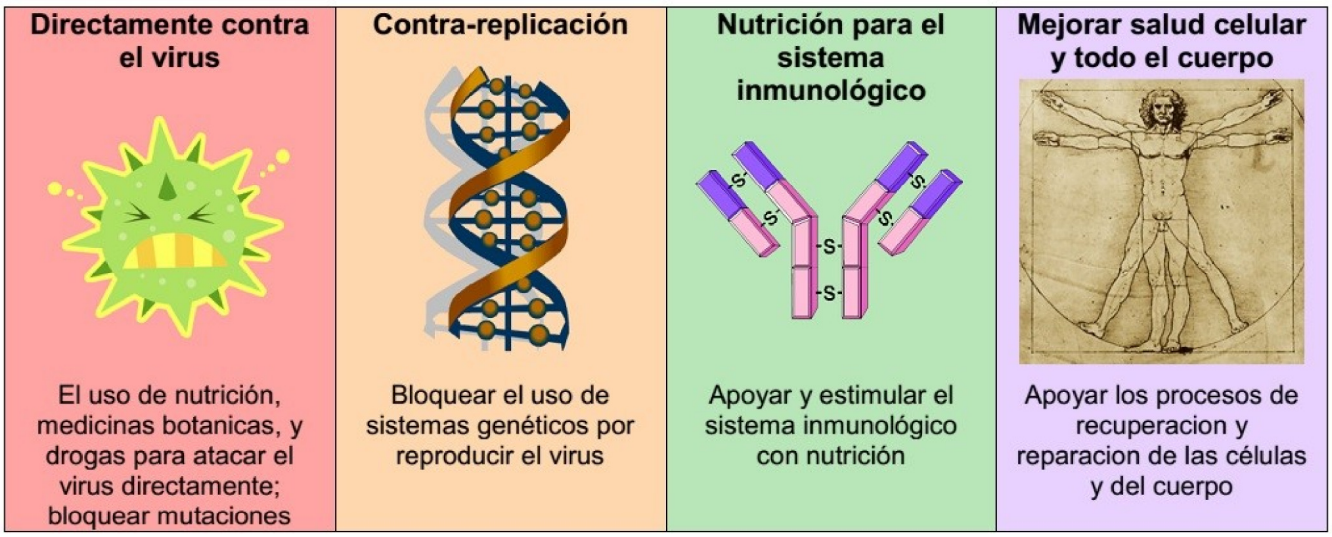
terapéuticas? ¿Estamos tratando insuficiencias nutricionales con medicamentos?

Lo que me he dado cuenta a través de los diversos programas de doctorado que he asistido es que la capacitación clínica en el tratamiento de infecciones virales sigue siendo en su mayoría fenomenalista y enigmática, en lugar de descifrada y estructurada. Como educador, investigador y escritor, he aprendido a través de la experiencia que para estructurar efectivamente la información de tal manera que la accesibilidad y la retención de la información se ve reforzada por los estudiantes/lectores (por ejemplo el acrónimo MYBESTPLAIDFIG para la inmunomodulación nutricional [3] y FINDSEX ® por tratamientos integrativos contra inflamación [4]). Mi propósito principal al escribir este ensayo es demostrar una estrategia única y estructurada antiviral y proporcionar ejemplos representativos de su aplicación práctica.

En lugar de ver las infecciones virales de una manera que es fenomenalista y enigmática y por lo tanto, difícil de manejar, llevando a estrategias de prevención y tratamiento inefectivos, nosotros debemos disminuir la complejidad del proceso infeccioso. Hacerlo – al menos en la forma que he descrito – en la cual nos da cuatro áreas en las cuales podemos enfocar nuestros esfuerzos: 1) contra el virus directamente, 2) bloqueando la replicación viral, 3) apoyando la función inmune y 4) apoyando la salud celular y de todo el cuerpo. Estos son ilustrados en el diagrama adjunto y brevemente descritos y ejemplificados en los cuatro apartados respectivos que siguen.





Estrategia antiviral multicomponente

1. **Ataque directo al virus**: Atacar directamente el virus ha sido el foco de los esfuerzos de salud pública y la práctica médica a través de saneamiento, vacunación y – más recientemente – el uso de medicamentos antivirales específicos. Varios nutrientes y productos botánicos también son muy efectivos para atacar directamente las infecciones virales, y daré dos ejemplos aquí. El mineral selenio tiene un amplio margen de seguridad y proporciona beneficios antivirales a través de varios mecanismos, dos de los cuales bloquean la replicación viral y también bloquean la mutación viral; beneficios antiinfecciosos clínicos son probados en seres humanos con VIH/SIDA.[5] La medicina botánica y té de hierbas Glycyrrhiza glabra ha demostrado eficacia antiviral en estudios experimentales y ensayos clínicos en humanos contra varios patógenos virales diferentes, incluyendo el virus de la hepatitis B (VHB), virus de la hepatitis C (VHC), virus del herpes simple (VHS), un virus de influenza, virus de inmunodeficiencia humana (VIH-1), el síndrome respiratorio agudo severo (SARS)-relacionados con el coronavirus, virus respiratorio sincitial, arbovirus, virus de la vaccinia y virus de la estomatitis vesicular [6]; este botánico tiene una excelente historia de seguridad que abarca varios miles de años, con pocos efectos adversos incluyendo un efecto de pseudoaldosterona (agotamiento de potasio y retención de sodio) y un descenso de testosterona, efecto y mecanismo de acción incluyendo vía la unión del virus, inhibición de la replicación viral, mejora de la inmunidad, la inhibición de la inflamación y el bloqueo de actividad de enzimas específicas. Botánicos y nutrientes antivirales pueden utilizarse solos, en combinación y junto con medicamentos para beneficios aditivos y sinérgicos.
2. **Bloqueo de la replicación viral**: Inhibición de la replicación viral es el objetivo terapéutico de muchos fármacos antivirales, mientras varios nutrientes también pueden proporcionar un efecto similar. Debido a que los virus son incapaces de replicar por si solos y por lo tanto deben contar con una maquinaria genética y de síntesis de su anfitrión humano para su replicación, nutrientes que modulan la expresión genética pueden tener valor terapéutico, es decir mediante la metilación del ADN y bloqueo del factor de transcripción NFkB. Los pocos nutrientes que promueven la metilación del ADN y que también han demostrado eficacia clínica contra las infecciones virales incluyen el ácido fólico [7] (ahora utilizado clínicamente en las formas de ácido folínico y metilo y 5 metil folato), vitamina D3 [8], betaína y S-adenosil-metionina.[9] inhibición del NFkB como mecanismo efectivo antiviral ha sido probada, con dos ejemplos: NAC (acetil-l-cisteina) contra gripe [10] y el ácido lipoico contra hepatitis viral y el VIH.[11]
3. **Apoyo a la función inmune**: El funcionamiento y regulación del sistema inmune es fuertemente dependiente del estado nutricional óptimo y sin una nutrición adecuada, el sistema inmunitario está inclinado simultáneamente hacia hipoactividad (inmunodepresión inducida por deficiencia o insuficiencia) y la hiperactividad que se manifiesta con inflamación y autoinmunidad.[12] Las carencias son muy comunes en la población general y contribuyen a epidemias de enfermedades infecciosas e inflamatorias. Ensayos clínicos en humanos usando nutrientes solos o en combinación para apoyar la función inmune en general han demostrado eficacia contra las enfermedades infecciosas y con una seguridad excepcional, especialmente el uso de glutamina, proteína, vitamina A, vitamina D, zinc y aceite de pescado.[13] Ha sido demostrado en varios casos que los suplementos nutricionales mejoran la respuesta inmunológica a las vacunas; por ejemplo, fue observado que cistina y teanina aumentan la seroconversión de vacunación contra la influenza en las personas mayores. [14]
4. **Apoyo a la salud celular y corporal**: Las infecciones virales tienen numerosos efectos adversos sobre la salud celular y todo el cuerpo. Consecuencias intracelulares de infecciones virales incluyen la disfunción mitocondrial [15] y estrés del retículo endoplasmático [16], que se manifiesta clínicamente como inflamación prolongada, la fatiga y – probablemente – en el caso de infecciones por herpes simple, la enfermedad de Alzheimer.[17] Entre las más de 30 intervenciones para mejorar la función mitocondrial y aliviar el estrés del retículo endoplasmático, vemos que el ejercicio, las dietas bajas en carbohidratos, ácido lipoico, coenzima Q-10 y acetil-l-carnitina son preeminentes por su seguridad, eficacia y beneficios colaterales.[18] La manipulación osteopatíca, quizás mediante la promoción del mejoramiento de la respiración y el flujo linfático y la distribución de las quimiocinas, también ha demostrado beneficio en el mejoramiento no farmacológico de las enfermedades infecciosas.[19]

En resumen, mediante el uso de una estrategia estructurada antiviral, las intervenciones farmacológicas y no farmacológicas pueden aplicarse con mayor eficacia clínica y de salud pública, aliviando las cargas de estas enfermedades infecciosas clínicas, sociales, financieras y políticas.

Conclusión y aplicación

Los brotes recientes internacionales de infecciones virales han hecho una cosa muy clara: necesitamos una nueva estrategia antiviral en los tiempos modernos para combatir estos nuevos flagelos virales en curso; la pandemia de propagación de estas infecciones en 2014 es prueba de que las medidas médicas habituales y las de salud pública de saneamiento, la vacunación y medicación son insuficientes. Para la mayoría de médicos y funcionarios de salud pública, éstas han sido las herramientas utilizadas contra las infecciones virales con la más reciente adición de fármacos antivirales molecularmente orientados específicamente para cada virus. Bajo esta premisa la estrategia antiviral ideal sería tanto en general y específicamente eficaz, ampliamente disponible, de bajo costo y con pocos o insignificantes efectos adversos e interacciones. Mi propósito de escribir este ensayo no es discutir, ni debatir el saneamiento ni vacunas, ni medicamentos, sino señalar otras estrategias de intervención que pueden beneficiar el paciente además de la salud pública. Estas intervenciones basadas en evidencia han demostrado seguridad, eficacia y rentabilidad con amplia e inmediata disponibilidad internacional y generalmente insignificantes efectos adversos y no interacciones con medicamentos y enfermedades.

Publication history, author disclosures, citation format: The primary goal of this article is to outline a more complete strategy to counter the personal and population-wide impacts of viral infections; representative citations supporting these concepts are provided. This article underwent legitimate peer-review by an international interdisciplinary team of professionals; *IJHNFM* Editorial Board is listed online ichnfm.org/publications). Dr Vasquez has authored several of the books and articles cited in this article. Dr Vasquez has served as a Lecturer and Researcher for Biotics Research Corporation. Because this is a conceptual essay, citations to literature have been compiled together for efficiency.

Citations/reference

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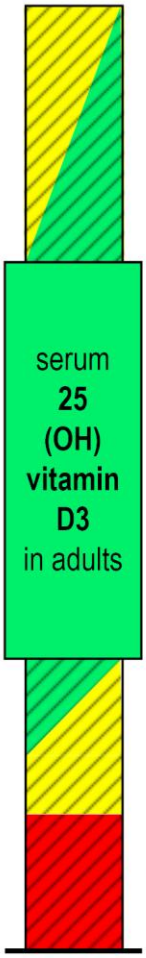
Quick Clinical Guide Infographic • **Patient Education** • Primary Care • Prevention • Medicine

Optimal serum 25-hydroxy-vitamin D

Alex Vasquez DO DC ND (USA) FACN



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

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

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

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

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

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

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

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

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/inflammatory 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 knowledgeable clinician.

Citations included in image; see also:

1. Vasquez et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Alternative Therapies in Health and Medicine* 2004 Sep academia.edu/40429791/
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
4. Vasquez A. Revisiting the Supplemented Paleo-Mediterranean Diet. *Nutritional Perspectives* 2011 Jan academia.edu/39751813
5. Videos/excerpts 2020, articles and correspondence compilation 2004-2019. InflammationMastery.com/d

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Editorial

Vitamins Against Viruses: Implausible Pro-Vaccine Publications Contrasted Against Ignored Public Health Campaigns and Double-Blind Placebo-Controlled Clinical Trials

Introduction

As an author, presenter, editor, and careful reader of research and public policy, I have been concerned for several years about potentially false attribution of efficacy to vaccines during public health campaigns and major infrastructure investments that concurrently provided access to education, improved sanitation, improved diet (alongside immune-enhancing nutritional supplementation, most commonly with vitamins A and D, zinc, and iron), relocations of millions of people along with changes in their living and working circumstances (which would be expected to change infectious disease patterns, e.g., relocating people away from farms obviously reduces their exposure to *Clostridium tetani* [the anaerobic bacillus of tetanus] which is found primarily in soil contaminated by fecal material from [especially ruminant] animals such as cattle, sheep, and goats). With the April 2019 publication of several very unusual articles stemming from the *British Medical Journal (*BMJ*)*, the time arrived to explore some of these concerns in a structured and public format. A legitimate concern is that science and public opinion are being inappropriately manipulated to favor a pharmaceutical/vaccination paradigm while lower cost, more widely available, safer and more efficacious nutritional interventions are being sidelined or intentionally ignored. In the current instance, overzealous endorsement and praise was given to a pharmaceutical intervention while a nationwide nutritional supplementation program supported by double-blind placebo-controlled trials was completely—and perhaps intentionally and strategically—ignored, then blocked by the journal from further discussion.

Pro-pharma echo chamber resounds: I first became aware of the two new (April 2019) BMJ publications (article by Palmer et al[1] and editorial by Brotherton[2]) via the derived "news" article published on 4 April in *The Guardian* titled "HPV rates tumble after routine vaccination" by Sarah Boseley, the publication's "Health Editor." With review of their website I found that The Guardian has published an impressive number of pro-vaccine articles devoid of critical thought or balanced analysis, including "Cervical cancer could be eliminated in most countries by 2100 – Millions of cases could be prevented with high HPV vaccine and screening coverage" (20 Feb 2019), "Teenage boys to be vaccinated against cancer-causing HPV: Inoculation program will be expanded to cover 12- and 13-year-old boys in England" (24 Jul 2018), "Boys should get HPV jab to protect against cancer, health advisers say: Ministers urged to take swift action to extend immunization under a gender-neutral program" (18 Jul 2018), "Cervical cancer deaths in over-50s predicted to rise sharply in England – Rates of diagnoses and death set to rise in women not vaccinated against HPV, but likely to be almost eradicated in younger women" (19 Dec 2017), and "HPV vaccination should be extended to gay men" (12 Jun 2012). One could hardly envision a more pro-drug publication, regularly producing "news articles" that function as infomercials, glorifying any real or imagined benefits of drugs while making zero or minimal mention of any adverse effects, or refuting adverse effects, but without sufficient substantiation, as in "Cervical cancer vaccination 'most unlikely' to have caused girl's death" (29 Sep 2009). Likewise, the BMJ article was re-reported and exalted throughout print and video media in the United States by outlets such as Fox News' "UK's HPV vaccination program 'dramatically' reduces risk of cervical cancer"[3] and the physician-oriented Medscape.[4] Such articles obviously serve to direct public and political opinion in favor of medicalization to the delight of the pharmaceutical and mainstream medical industries; the combined reach of the original articles and their echo-chamber derivatives is certainly in the tens of millions if not hundreds of millions of people. With regard to the recent article, the imbalanced praise and absence of rational concerns published in favor of the vaccine appeared quite biased; I soon accessed the original research, as discussed below.

BMJ's landmark publications in erroneous conclusions: Anyone who has studied research design is aware of different types of clinical investigations and the limitations inherent in each. The "gold standard" of clinical research has been the randomized double-blind placebo-controlled clinical trial, preferably with a large population-representative cohort, preferably with a cross-over design if practical depending

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on the logistics of the intervention. In any placebo-controlled trial, the placebo needs to be an inert substance, not—as is common with pharmaceutical and especially vaccine studies—a mislabeled "placebo" capable of causing harm and therefore reducing and obfuscating the relative risk (RR) compared to the active/test agent. Science is corrupted when unscrupulous researchers use active agents misbranded as "placebos" in order to make a given intervention look comparatively safe and effective (when compared against a harmful placebo, such as the recent studies using high-cost high-dose prescription fish oil against a false placebo of petroleum mineral oil)[5] or comparatively dangerous or ineffective (when compared against a safe and therapeutically active placebo, such as the recent reviews comparing low-dose fish oil against low-dose olive oil, both of which are antiinflammatory and cardioprotective).[6] Thus, the strategic use of inappropriate placebos and/or the intentional ignoring of confounding variables (such as population-wide health campaigns) serves to glorify the preselected pharmaceutical victor while providing the necessary "evidence of effectiveness" and justification for widespread implementation and multimillion $/£/ € purchase. To the extent that such publications obfuscate the data and minimize appreciation of effective nutritional interventions, doctors and patients are inappropriately corralled into drug dependency while nutritional interventions with lower cost, wider availability, greater safety and efficacy—along with the numerous collateral benefits typically seen with nutritional supplementation—are withheld from general consideration. As detailed below, BMJ published a retrospective population-wide study that impossibly ascribed efficacy (by design, such studies cannot determine efficacy) to the HPV vaccine while ignoring the time-synchronized national public health campaign to improve vitamin D nutriture, whereas the latter has numerous lines of evidence supporting its clinically important efficacy against various types of HPV infection.

Dr Vasquez replies with two "rapid responses" posted on BMJ.com: To its credit, BMJ has a "rapid response" system that allows readers to publicly respond to articles and occasionally receive replies from the original authors; from the rapid responses posted, the journal's Editors supposedly choose from among the responses those few deemed worthy of publication in the print and indexed version of the journal, as they did with my 2005 reply to an article that misused vitamin D in a clinical trial and then erroneously reported that vitamin D was inefficacious.[7] For the April 2019 BMJ publications, my first rapid response received no reply; the following two rewritten responses, both of which were posted on BMJ.com in response to the editorial and the original research, are contextualized and provided below. The complete texts of these replies are included here both for the convenience of readers and to also document these posted responses in the event that—as is common these days—the editors delete any legitimate questioning of the high-profit vaccine paradigm. At the time of this writing, my replies are posted online at "Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends" (https://www.bmj.com/content/365/bmj.l1375/rr-4 and externally archived at https://www.academia.edu/39207517) and "Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination" (13 April 2019, https://www.bmj.com/content/365/bmj.l1161/rr-8, externally archived at https://www.academia.edu/39201317).

The editorial posted by the BMJ to accompany and contextualize the original research was unusual in several aspects. First, the editorial is described as "commissioned" which implies that the journal paid the author to write the piece, presumably—as noted by former BMJ Editor Richard Smith[8] –to sell reprints to the pharmaceutical industry and/or governmental and other pro-vaccine groups as "proof" in order to convince people to accept this intervention as valid and thereby promote sales and the resulting profit and political power; as such, their editorial functions as an infomercial and advertisement for vaccine sales. Second, and consistent with the view that the editorial is simply a publicity piece, the journal specifically notes that the editorial was "not peer-reviewed" which is remarkable considering that most people think that all articles in the so-called "top tier" and "big five" medical journals are legitimately processed and refereed prior to publication and indexing in Medline's Pubmed (ncbi.nlm.nih.gov/pubmed/30944088). Third, I noticed that the disclosure as posted "The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: JMLB's employer has received partial, unrestricted support (in the form of equipment) to conduct a randomised trial of primary HPV screening from Roche Molecular Systems" makes zero mention of the author's research supported by Merck, makers of the HPV vaccination being discussed, revealed elsewhere as "JMLB has been an investigator on HPV epidemiology studies that received partial, unrestricted funding from Seqirus/Merck for laboratory components" (Int J Gynecol Obstet 2017; 138 (Suppl. 1): 7–14 DOI: 10.1002/ijgo.12186) and "JMLB has been an investigator in HPV epidemiological studies that have received partial unrestricted grants to support HPV typing components (cervical cancer typing study from Seqirus Australia, recurrent respiratory papillomatosis study from Merck Sharp and Dohme) and is an investigator on the Compass trial, which has received equipment and funding from Roche Molecular Systems and Roche Tissue Diagnostics, but JMLB reports no personal financial benefits" (*The Lancet*, 2019 February thelancet.com/public-health Vol 4;e87). Fourth, Brotherton's editorial is scientifically untenable, giving outlandish praise and stretching the boundaries of biological plausibility in support of the HPV vaccination advocated by the pro-vaccination group for which she works (Victorian Cytology Service [VCS] Foundation);[9]

she states that the results "unequivocally show high vaccine effectiveness" despite the fact that they completely ignored Scotland's concurrent nationwide programs to improve vitamin D status, including giving free vitamin D supplements and advocating sunbathing. Fifth, everyone associated with this publication appears to have ignored the fact that retrospective population-wide studies cannot establish causality as can double-blind placebo-controlled trials but at best can establish temporal relationships, but only if all impactful factors are considered, which was obviously not done with this primary publication nor its glorifying editorial. Sixth, consistent with my model of the pharmaceutical echo chamber and the financial matrimony binding media with drug companies , international newspapers and other media trumpeted to the world the glory of this vaccine, failing to mention any risks, qualifications, other scientific interpretations and therapeutic possibilities. Seventh, the scientifically responsible action that the BMJ could have taken is to issue a public statement clarifying the appropriate interpretation of its published research and reigning in this unscientific hysteria; but the BMJ has failed to do so. The text of my rapid response to the Editorial posted on BMJ.com is as follows:

Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century, with key publications starting in 1999 [3-6]. We now have increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements (and sun exposure) to combat the high prevalence of vitamin D deficiency in Scotland [11-23].

Vitamin D supplementation has been the subject of several placebo-controlled trials documenting anti-inflammatory, antiviral, and anticancer effects. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" in which they summarized, "In conclusion, vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism, plasma NO, TAC, GSH and MDA levels." In 2018, Vahedpoor and colleagues [39] published "Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3" in which they noted, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

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In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity; use of nutritional supplements that contain or potentiate vitamin D had started to increase in the population by 2003. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially misleading, especially when these authors make no account whatsoever of the national program for vitamin D supplementation which started in the same time-frame. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

Following the posting of my rapid response critiquing the editorial (11 Apr 2019), BMJ posted my resubmitted response rebutting the original research two days later (13 Apr 2019). Some but not all of the problems with the editorial are also noted in and originate from the primary research and therefore my critiques are similar, but not identical, with the second response a bit more refined and also with changes in a few citations. The major errors in the primary article are as follows: First, the study design of "retrospective population study" is incapable of determining causal relationships; at best such a study design can only determine temporal relationships, i.e., two events occurring together within the same time-period or one event following the other. As such, their reporting of any causal relationship is erroneous because this type of study cannot establish causality. Subsequently, the editorial and mass media derivatives are likewise erroneous. Second, attribution of effectiveness to the vaccine while ignoring any and all education surrounding the vaccine conflates inoculation with behavior-modifying education. Telling a young girl in essence that "the vaccination is directed toward a sexually transmitted infection in the form of a virus that could infect her vagina and cervix if she has unprotected sex with a boy" is a behavior-changing conversation likely to reduce sexual intercourse, with boys, especially without barrier protection; this primary study by Palmer and colleagues completely failed to account for any effect of education, instead giving all credit—indeed premature and inappropriate credit—to the vaccine. The age correlation that they reported—less HPV with earlier vaccination—could easily be explained or confounded with earlier education that changes sexual behavior. The authors failed to consider anything other than vaccination, so of course they found a correlation between vaccination and reduced HPV-related disorders. Third, the authors ascribe "herd immunity" to the observation that unvaccinated girls also showed a reduction in HPV-related disorders; but this could have easily and perhaps more convincingly been attributed to the nationwide vitamin D supplementation programs, which were completely ignored and never mentioned despite the fact that vitamin D has been proven effective against HPV infections via a variety of levels of evidence. Their concluding statement "The bivalent vaccine is confirmed as being highly effective vaccine and should greatly reduce the incidence of cervical cancer" is overzealous and is an epidemiologic error when they failed to consider any other interpretive options. Indeed, such considerations—controlling for other possible factors—is the defining characteristic of competent epidemiology. The authors followed their egregious overstatement (quoted previously) with a confirmatory understatement: "It is possible therefore that vaccine effectiveness was over-estimated." Neither the accompanying editorial nor the publications for the mass media mention of the probable overestimation of vaccine effectiveness. My rapid response to the original article is as follows:

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

In April 2019, Palmer et al [1] published a retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland, and the authors attributed a reduction in HPV prevalence among unvaccinated women with "herd protection." However, the authors did not mention Scotland's population-wide public health campaigns to address endemic vitamin D deficiency. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. Vitamin D deficiency results in impaired mucosal and immune defenses and correlates in a dose-dependent manner with increased cervicovaginal HPV infection [2]. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century with landmark publications such as Vieth's authoritative documentation of safety in 1999 [3], Zittermann's "Vitamin D in preventive medicine" in British Journal of Nutrition in 2003 [4], and Vasquez's "Clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers" in 2004 [5] followed by an important partial summary of vitamin D usage guidelines in British Medical Journal in 2005 [6]. These and similarly themed articles have contributed to increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral

infections and various types of cancer. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements to combat the high prevalence of vitamin D deficiency in Scotland [11].

Widespread vitamin D deficiency in Scotland was followed by widespread recommendations for vitamin D supplementation starting in 2006 and 2009. In 2006, Burleigh and Potter published in Scottish Medical Journal [12] stating that, "The prevalence of vitamin D deficiency is high in older outpatients in this geographical area." In 2007, Hyppönen and Power [13] showed that among British adults "Prevalence of hypovitaminosis D in the general population was alarmingly high during the winter and spring, which warrants action at a population level rather than at a risk group level." In 2008, Rhein [14] further specified that "Vitamin D deficiency is widespread in Scotland." In 2009, the Scottish Government acknowledged the need to educate its population about the importance of vitamin D3 supplementation [15]. From that time until the present, the Scottish Government, United Kingdom National Health Services, and various advocacy groups and programs (e.g., ScotsNeedVitaminD.com[16], Healthy Start, which provides vitamin D supplements to all children and pregnant women in Scotland [17]) continue assertive public health campaigns recommending vitamin D supplementation and increased vitamin D production via sun exposure via the "Shine on Scotland" program initiated in 2009 [18] for all of its citizens [19-23].

Vitamin D supplementation has been the subject of many clinical trials documenting anti-inflammatory, antiviral, and anticancer benefits. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (cervical intraepithelial neoplasia [CIN] 1-2): vaginal vitamin D treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they found that vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism and antioxidant status. In 2018, Vahedpoor and colleagues [39] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they observed, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially invalid and misleading, especially when the authors make no account whatsoever of the national program for vitamin D supplementation which started in the same timeframe. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

My reply makes quite obvious the shortcomings of their biased research publication. One should reasonably wonder why the BMJ would publish such a flawed report, and then pay for a "commissioned" "editorial" which was "not peer-reviewed." Then, the editors collectively stifled any further conversation regarding the antiviral action of vitamin D delivered to the same population in the same time-frame, despite its proof of clinical effectiveness. Such a compilation of errors could hardly seem accidental, although they would synergize fantastically for promoting sales and government mandates of the HPV vaccine.

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And now for the silent treatment from BMJ editors: Reasonably anticipating that the BMJ would share my well-cited concerns with their readership via publication in a Letter to the Editor or Reply, I waited to hear from the Editors. When no response arrived by several weeks later, I emailed the Letters Editor and the Editor in Chief along with two other associate editors. The probability of none of them receiving my email nor noting my two posted rapid replies is essentially zero, and they have offered no response nor explanation for why their publications omitted this key data.

From: Dr Alex Vasquez
Date: Thu, May 9, 2019 at 4:34 PM
Subject: Re: Letters timeframe
To: Davies
Cc: Doshi, Godlee, Ludwig

Thank you for your earlier replies. I am following-up with interest in publishing the concerns raised in my rapid responses, because the original research appears to have looked at a chronological correlation without looking at the national health campaigns that started in the same time-frame. In particular, the public health campaign that I detailed has double-blind placebo-controlled evidence of clinical effectiveness, so it is worthy of consideration.

Of the two rapid responses posted (thank you), the second is a bit more refined and has (a few) better citations (I think I changed 2 of them).

1. Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends *https://www.bmj.com/content/365/bmj.l1375/rr-4*

2. Scotland's public health campaigns to improve vitamin D nutriture occurred within the same timeframe as HPV vaccination *https://www.bmj.com/content/365/bmj.l1161/rr-8*

As noted in my responses, vitamin D demonstrates antiinflammatory, microbiome-modifying, immune-supporting (eg, antimicrobial peptides, sIgA) and it specifically demonstrates effectiveness against HPV. I trust that we share the same goal of helping patients avoid HPV-related disorders, and cholecalciferol clearly shows benefit, safety, wide availability, and low cost.

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Thank you,
Dr Alex Vasquez

Again expecting the journal's editors might value research accuracy, journalistic integrity, and the importance of ethical standards in clinical care and research, I was a bit surprised that these five BMJ Editors would collectively fail to reply to cited concerns about the quality of their publication. BMJ claims on its website that it hosts and/or represents an "international community of readers, authors, and editors" but apparently this sense of "community" does not apply to the questioning of publications that show obvious bias by ignoring other influences and funneling the results toward vaccine endorsement.

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Basic components of research integrity: Tutorial articles published in journals as well as textbooks such as *The Lancet Handbook of Essential Concepts in Clinical Research*[11] can inform the implementation and evaluation of research. Ideally (but largely theoretically), research is performed honestly and competently, critically reviewed postproduction and prepublication by independent scientists/scholars, and then refereed by at least one expert-level Editor prior to publication and dissemination; the fourth component of research integrity is post-publication critique by readers and correspondence between such readers and the original authors. A fifth component of research integrity is the publication of article-specific editorials/commentaries that provide context and perspective for the new information presented; as with the original research, such Editorials should be independently peer-reviewed in a blinded manner by internal or external reviewers prior to publication.

Authorial and editorial bypassing of research integrity: A notorious pitfall in the publication of descriptive and retrospective studies such as the one by Palmer et al being discussed here is that of false attribution; that is, the erroneous assumption that because an intervention was followed by an observation that the former caused the latter. This error is intellectually grave as it can lead to erroneous conclusions about cause-and-effect relationships, thereby misleading government policy and clinical care. This error is also described as overstepping the data, erroneous inference, and—in Latin—post hoc ergo propter hoc which translates to "after this, therefore because of this", also known as the post hoc fallacy. In truth, causal relationships can only be established in appropriately conducted clinical trials; non-interventional retrospective population studies such as this one lead by Palmer can add only accessory information but are incapable of establishing or refuting causality, especially when the study itself fails to control for other variables and considerations.

"Errors" in study design may be accidental or intentional. In addition to the failure to consider other causes for an observed outcome, investigators can also accidentally or intentionally "stack the deck" in order to make a certain conclusion more or less likely. Strategically or innocently, researchers can select patients that may have covariables that are of major importance to the outcome being studied. Indeed, the authors noted that "partial immunization was associated with increased deprivation, having left school, and increasing age" but they failed to follow-up on these considerations and their HPV-relevant implications. Co-variables that correlate with more vaccination are better financial status, better healthcare insurance coverage, better nutrition, less sexual promiscuity and less social inequality/defeat stress. Improved nutrition obviously provides an anti-viral effect by reducing inflammation-promoted viral replication and also by enhancing immune defenses; wealthier and better educated persons are known to consume more nutritional supplements. A reduced number of sexual exposures would obviously affect the prevalence of a sexually transmitted diseases (STD). Less socioeconomic stress would lead to a relative improvement in immune function compared to a group with stress-induced immunodysfunction and immunosuppression. Obviously—and completely ignored by all of the authors and editors of this BMJ publication—is the fact that the act of vaccination itself with its attendant information (ie, behavior-changing education) regarding the risks of sexual behavior (ie, promiscuity verses abstinence) and the value of STD-blocking barrier methods (e.g., condoms) would be clearly expected to reduce HPV-related disease. As noted in *The Lancet Handbook of Essential Concepts in Clinical Research* (page 35), "When selection bias or information bias exists in a study, irreparable damage results. Internal validity is doomed." Also (page 46), "Although assessment of many outcomes is often cited as a positive attribute of cohort studies, this feature can be abused. For example, testing the associations between exposure and many outcomes, but only reporting the significant ones, represents misleading science."

In this case, the authors quite obviously failed to consider anything other than their chosen vaccine program, and then they assumed that the vaccine program was responsible for the observation that cervical disease was decreased in the vaccinated group. How these researchers were able to remain ignorant of a well-publicized government-endorsed nationwide public health campaign emphasizing improved nutrition and vitamin D supplementation[12] (which is proven with a variety of clinical research to reduce the burden of HPV infections, to improve general immunity, and to reduce inflammation) is unclear; one can only reasonably speculate why the journal's editors would fail to publish commentary and consideration in this regard.

Bizarrely, BMJ allowed the study's lead author to post additional commentary on his own research, as if the publication needed any additional biased aggrandizement. Not surprisingly, Palmer[13] agreed with his own perspective and endorsed the greatness of his research, stating that his research revealed "a veritable triumph for medicine" and that the intervention he endorses is "the only feasible solution" to preventing HPV-related cervical cancer. As would be expected in one of the "mainstream medical journals", zero mention was made of nutritional immunorestoration, microbiome modification, nor antiviral nutrition strategies—all of which have a clear role in the prevention of HPV-related cervical disease. Clearly, if the only intervention considered is vaccination, and all other social and biological interventions are ignored, then the only possible solution will appear to be vaccination, regardless of the lack of merit of this conclusion. Whether or not one "believes in" the common oversimplified model of HPV-induced cervical disease and/or the promul-

gated "value" of vaccination, we should all want the research to be accurate and for all variables and treatment options to be considered for this condition, especially when the promoted vaccine appears responsible for a large number of injuries and deaths.[14] As noted recently (2018) by former BMJ Editor Richard Smith, the BMJ and its publishing group sells millions of dollars/pounds/euros worth of "product advertising" (e.g., £2.7m) and article reprints (£1.98m or $2,497,770 United States dollars); most of these advertisements and article preprints are purchased by the medical device and drug (including vaccine) industry to promote sales of their products.[15]

The case for postpublication retraction: According to the Committee on Publication Ethics,[16] journal editors should strongly consider retracting a publication if any of the following occur: 1) evidence that the findings are unreliable, either as a result of misconduct [e.g. data fabrication] or honest error [e.g. miscalculation or experimental error], 2) redundant publication, 3) plagiarism, 4) unethical research. In my opinion, any legitimate critical reading of this article would have easily led to its pre-publication rejection or its post-publication retraction, but because the article has financial value by promoting a multibillion dollar vaccine paradigm and up to thousands/millions of dollars in article reprints and pharmaceutical advertising, it was published, editorially praised, and then publicly glorified without (to my knowledge) any scientific criticism. In the irony of ironies, lead author Palmer was quoted by Medscape (op cit) as stating: "One of the things this study really does hammer home is that the anti-vaccine lobby are actually peddling falsehoods."

The importance of nutritional expertise and independent publications in the post-truth and pro-pharmaceutical era: The international community has been living in the post-truth era—defined as being dominated by utter disregard for truth in the service of financial and political power—now for many years.[17] Given that nutritional education is generally excluded from medical education and post-graduate training, the only way for clinicians to learn about the clinical use of vitamins and minerals to prevent and treat a wide range of diseases—including but not limited to HPV-related diseases—is to access independent publications such as *Journal of Orthomolecular Medicine*,[18] expert-level textbooks,[19] nutrition-inclusive conferences and online courses. A clinician will likely never learn that HPV diseases can be prevented and treated by nutritional interventions by reading and following the mainstream medical journals and mass media. But from the orthomolecular perspective, the rationale supporting such interventions is quite obvious and strongly grounded in legitimate science, biological plausibility, and clinical trials (e.g., antiviral nutrition strategies).[20]

Author information: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, human microbiome and immunonutrition. Dr Vasquez has served as a consultant to Biotics Research Corporation. Dr Vasquez has archived the PDF versions of the herein-discussed rapid replies in free-access depositories, specifically https://ichnfm.academia.edu/AlexVasquez and https://www.researchgate.net/profile/Alex_Vasquez2.

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Calcium and vitamin D in preventing fractures

Data are not sufficient to show inefficacy

Alex Vasquez, researcher, Biotics Research Corporation, 6801 Biotics Research Drive, Rosenberg, TX, USA

John Cannell, president, Vitamin D Council, 9100 San Gregorio Road, Atascadero, CA, USA

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

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

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

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

Notes

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

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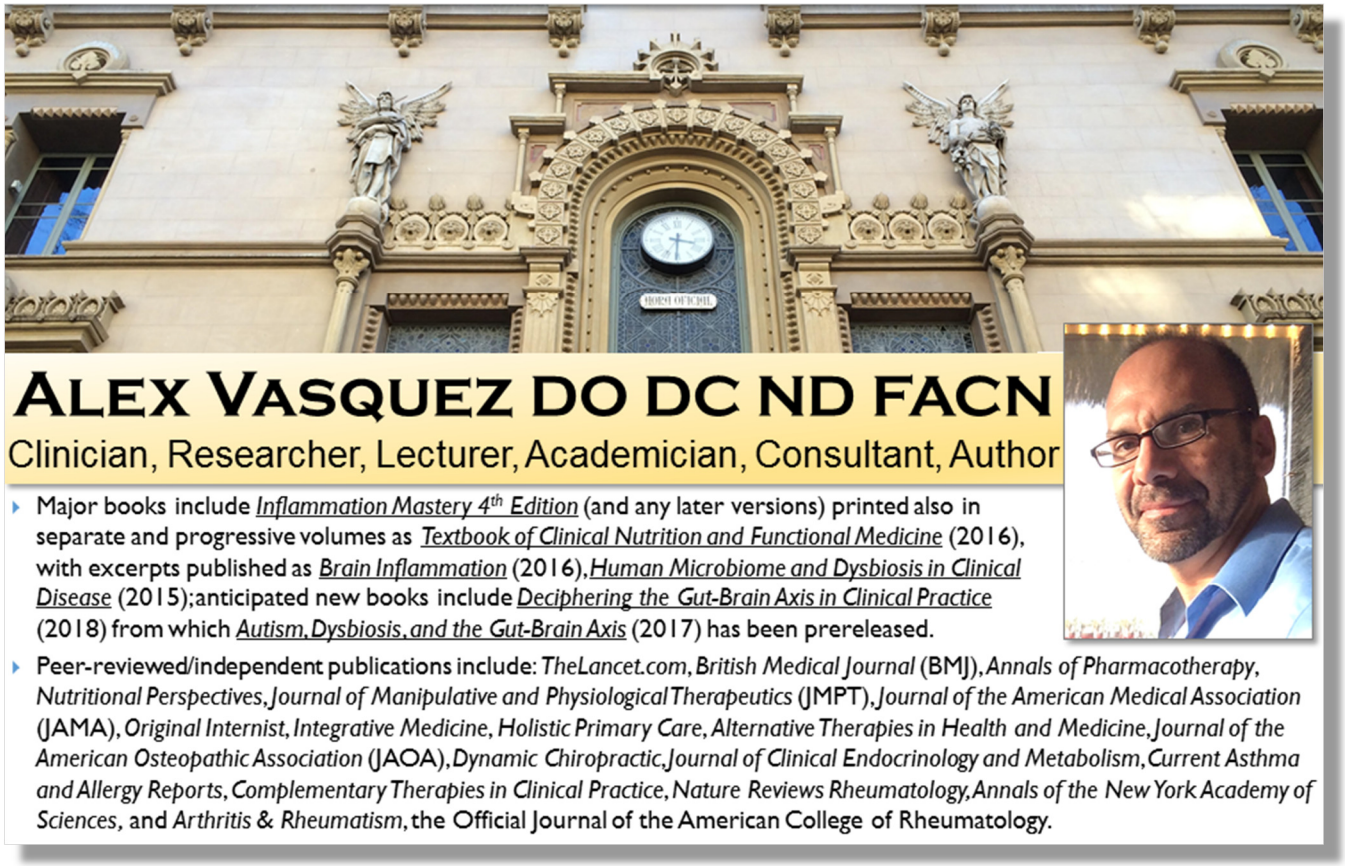
Antiviral Nutrition Update #1 for 2018:
Clinical Trial of Vitamin D3 against HPV/CIN1



The video of this presentation is archived at ichnfm.org/hpv1, and the transcript in PDF format—which is considered the final and citable version—is archived at academia.edu/35808436; any corrections or updates will be made to the PDF file. Observe that this video presentation is truly an *update* subsequent to previous publications and that therefore not all sources are cited; for citations, see the video, and for complete citations regarding the protocol in its entirety, see the book *Antiviral Strategies and Immune Nutrition* or the ebook version titled *Antiviral Nutrition*.

"Hello everyone, Dr Alex Vasquez here with our next video which is going to discuss antiviral nutrition. This will be the first update for 2018.

If I'm providing an update, then obviously that information will be founded upon and predicated upon some previous information. So let's take a look at those sources right now. This series of updates builds upon previously published books, articles, videos and blogs. In 2014, I published a small book called ***Antiviral Strategies and Immune Nutrition***; it's also available as an ebook through the Amazon Kindle platform, that was published under the name of ***Antiviral Nutrition***. I also published kind of an editorial journal article called "Unified Antiviral Strategy" in 2014, you can get that online for free. And I also did a presentation in 2016 at the International Congress on Naturopathic Medicine in Barcelona, you can see that on the internet for free as well and I've provided you the website address. Also in 2014, I published a series of videos which you can find online for free if you're interested in looking at those.

1. **Book**: Antiviral Strategies and Immune Nutrition (2014) https://www.amazon.com/dp/1502894890/
2. **eBook**: Antiviral Nutrition (Kindle ebook, 2014) https://www.amazon.com/dp/B00OPDQG4W
3. **Journal**: Unified Antiviral Strategy published by ICHNFM. *International Journal of Human Nutrition and Functional Medicine* 2014:v2(q4);p1 ichnfm.org/antiviral5

4. **Conference**: Vaccines—The Truth: International Congress on Naturopathic Medicine in Barcelona 2016 ichnfm.org/antiviral4
5. **Tutorials**: AntiViral Strategies and Immune Nutrition: Antiviral Nutrition (video, 2014) https://vimeo.com/109318556

If you want an independent view of some of these topics, the best article that I could recommend for you would be this one from *British Journal of Nutrition* 2007, "Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses." So if you want kind of an independent view of some of the things we're going to talk about today, then you might look at that article, *British Journal of Nutrition*, 2007 October.

So when we talk about viral infections which is mostly what we're talking about, we're going to talk about viral infections—a particular viral infection called HPV: human papilloma virus—and its relationship to vitamin D status and response to vitamin D supplementation.

So again, kind of laying the foundation and putting all of this in a reasonable context, when we talk about the treatment of viral infections, we have to have a comprehensive way of looking at that, not just talking about virus *here* and virus *there*. As you can imagine, with the book, I've developed not simply an antiviral strategy but also a more cohesive and comprehensive way of looking at viral infections and their clinical complications.

So as I said, in 2014, I'll state it again here, ***if you don't have a structured understanding of a good, comprehensive antiviral strategy, then you really don't have either an understanding or a strategy***. And I can say that, after having gone through three different doctoral programs: we never learned an antiviral strategy, we never learned how to understand viral infections in a comprehensive way that would really leverage the clinical tools that we have for optimal effectiveness. And when you look at my strategy, you get to see some ways that you can intervene and understand how these viral infections progress and how the body responds and that provides you some insight into ways that you could treat these virus-infection-related diseases, whether those are acute infections or persistent infections that go on to have other complications. So at the very least, let's touch upon these major four categories.

1. **Antiviral**: Starting with antiviral interventions, we can target the virus itself.
2. **Antireplication**: We can use antireplication intervention, so that is targeting the machinery of viral replication, we can attack that process as well.
3. **Immunonutrition**: We can use immunomodulation and immunonutrition because obviously, the immune system does usually a very competent job, protecting us from these viral infections. So let's optimize immune function and that usually means nutritional supplementation.
4. **Cell and systemic support**: We can also use cell and systemic support to mitigate some of the consequences of viral infections and of course, I'm talking about inflammation, oxidative stress and of course, mitochondrial dysfunction which accompanies many viral infections.

So when we start to ***deconstruct this phenomenon*** of viral infections and we look at each of these components, we can intervene at each of these levels/layers and provide better treatment, whether we're treating ourselves or whether we're treating our clients. So today, we're going to talk about vitamin D in the treatment of a very common type of viral infection and most of that work is going to put us here in this third category of immunonutrition, but also, you'll see some implications for this antireplication category as well. (See book and video for explanatory diagrams: http://www.ichnfm.org/hpv1)

So let us go ahead and start taking a look at this article that we're going to focus on today which is "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status…" associated with cervical intraepithelial neoplasia. This article comes from *Hormones and Cancer*, February of 2017. You've got the digital object identifier here as well. This is a randomized double-blind placebo-controlled trial with 58 women with cervical intraepithelial neoplasia grade one (CIN1). The intervention was 50,000 international units (IU) of vitamin D3 each two weeks, so that averages out to a bit over 3,500 IU per day for six months. And overall, I consider that intervention to be reasonable; the dose is reasonable but certainly not heroic, nor assertive.[1]

[1] Vasquez A. How to Understand, Refute, and Plan Studies Using Vitamin D. *International Journal of Human Nutrition and Functional Medicine* 2017 http://www.ichnfm.org/d

Vitamin D3 dosed at 4,000 IU per day is considered to be the minimum for replacing vitamin D in patients who are deficient. We might use higher doses closer to 10,000 IU; I think that would have been a bit more robust and not necessarily heroic; six months of duration is certainly the minimum. We wouldn't want to see a study for example for two months or three months or four months but six months is acceptable, and the dose is acceptable. So we can evaluate this study, thinking that this might actually be a reasonable representation of competent clinical practice.

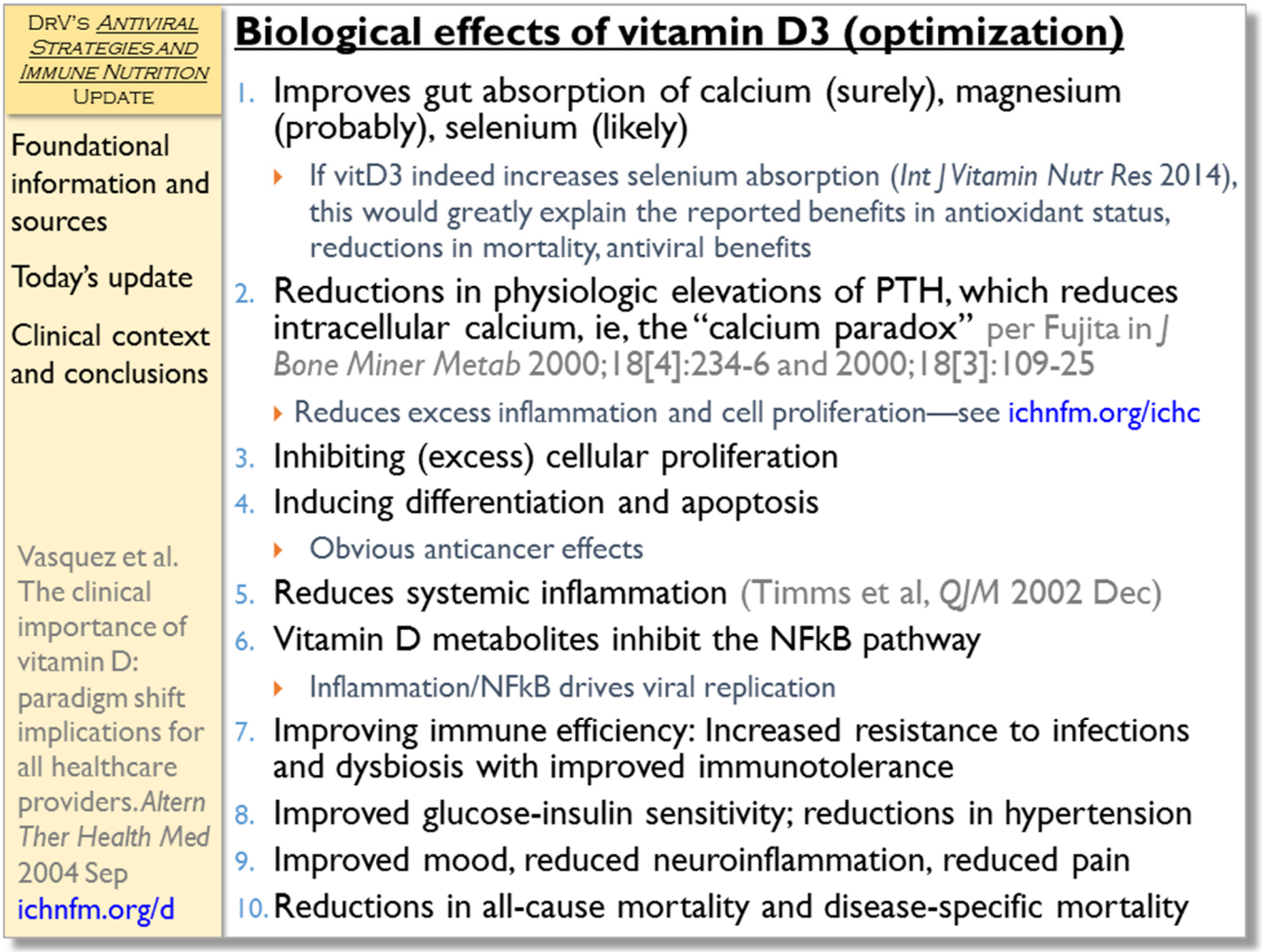
And that's an important place for us to start because a lot of these studies using vitamin D have used **inadequate dosing** and **inadequate duration** and they reached the false conclusion that vitamin D is inefficacious for whatever it is that they're investigating. And really, vitamin D is not at fault. The fault lies with the researchers for poorly designing their studies. I have published guidelines on the use of vitamin D in clinical practice as well as guidelines for designing clinical trials in *Alternative Therapies in Health and Medicine*[2], *British Medical Journal*,[3] and *International Journal of Human Nutrition and Functional Medicine.* You can download those articles from the internet for free at http://www.ichnfm.org/d. Results of the study show the following:

1. After six months of vitamin D administration, a greater percentage of women in the vitamin D group had regressed their cervical intraepithelial neoplasia grade one, 84% success versus 33% in the placebo group.
2. They had improved vitamin D status, that's another thing that we always want to look for in studies; they always need to actually measure vitamin D levels, not simply give people vitamin D and assume it was a properly manufactured supplement with good absorption, et cetera. We actually have to measure vitamin D response by looking at 25 hydroxyvitamin D in the serum.
3. These patients also benefited from showing reduced serum insulin levels and improved insulin sensitivity.
4. They had improved antioxidant defenses, they had elevated glutathione levels, relative to the placebo group and they had reduced oxidative stress as well.
5. Excellent safety.
6. The authors barely mentioned modulation of the vaginal microbiome, and I think that this beneficial microbiome-specific effect is likely of major importance. This is probably where a lot of the power of this intervention is coming from against HPV/CIN1. Not necessarily the systemic administration of vitamin D but the effect that that vitamin D has on systemic inflammation but also immune function and the modification of the vaginal microbiome via improved immune function, via vitamin D supplementation. I think that's probably where the action is here in terms of mechanisms of effect of this intervention.

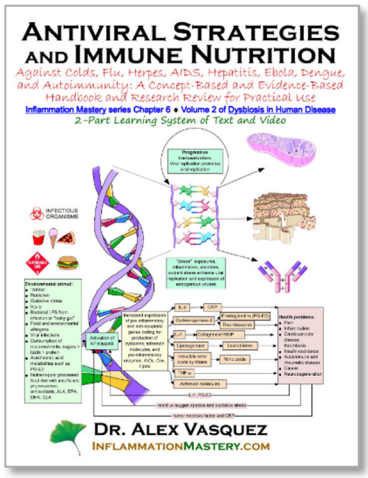
Let's look at some more details and how we might understand this study a bit more; here I will review several of the **Biological effects of vitamin D3**: When we're talking about optimizing serum levels and therefore body reserves. Vitamin D improves gut absorption of **calcium**—we are quite sure about that, **magnesium** probably and also we see some new data showing that vitamin D might also improve **selenium** absorption. If vitamin D3 indeed increases selenium absorption, this would greatly explain the reported benefits in antioxidant status, reductions in mortality and the antiviral benefits that are apparently being reported here. So selenium has antiviral effects, number one, by blocking viral replication and number two, by blocking viral mutagenesis; those are very important when the body is trying to combat these persisting viral infections. Reductions in physiologic elevations of parathyroid hormone which reduces intracellular calcium—this is referred to as the "calcium paradox." I've also published an article detailing "intracellular hypercalcinosis"[4] (reprinted online http://www.ichnfm.org/ichc), and it's also republished in my book *Inflammation Mastery, 4th Edition* as well as in *Textbook of Clinical Nutrition and Functional Medicine, Volume 1*. This reduction of parathyroid hormone reduces intracellular calcium which promotes a reduction in excess inflammation and cell proliferation. Inhibiting excess cellular proliferation is one of the physiologic and clinical benefits of vitamin D. Also, inducing differentiation and apoptosis—obviously effects have anticancer benefits. Vitamin D also reduces systemic inflammation, this has been very well documented. One very nice study back in December of 2002 published in the *Quarterly Journal of Medicine* showed this very conclusively. Vitamin D metabolites inhibit the NFkB pathway. This is very important because **the NFkB pathway drives viral replication. So anything that's going to block that NFkB pathway, whether it's vitamin D, selenium, zinc, et**

[2] Vasquez et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med.* 2004
[3] Vasquez et al. Calcium and vitamin D in preventing fractures: Data are not sufficient to show inefficacy. *BMJ: British Medical Journal* 2005
[4] Vasquez A. Intracellular Hypercalcinosis. *Naturopathy Digest* 2006 September. See reprint online: http://www.ichnfm.org/ichc

cetera, is going to probably provide some antiviral benefit by reducing viral replication. Vitamin D also improves immune efficiency, increased resistance to infections and dysbiosis with improved immunotolerance. People commonly have a simplistic "bipolar" view of the immune system, whether it's "overactive"—resulting in allergies and autoimmunity, or "underactive"—resulting in an increased susceptibility to infections. But what we see with vitamin D is ***actually improved resistance against infections and dysbiosis*** and also ***improved tolerance*** at the same time. The expected result would be a reduction in allergy and autoimmunity; certainly a reduction in autoimmunity has been documented and also some increased resistance to infections. Now in this context, when we're talking about cervical intraepithelial neoplasia (CIN), we have to talk about not simply the HPV virus, the human papillomavirus but also the bacterial microbiome within the vagina which obviously affects the cervix. **So what I suspect is happening in this study is that the administration of vitamin D is improving immune function, modulating the bacterial microbiome within the vagina—obviously that's directly adjacent to the cervix. When the immune system of the vaginal mucosa is improved, that favorably modulates the bacterial microbiome within the vagina to reduce inflammation and the reduced inflammation leads to a reduction in viral mutagenesis and viral replication. I suspect that this is the mechanism of action here.** As I mentioned before, these patients also showed improved glucose insulin sensitivity; that same result has been shown in several other studies, so I think we can believe quite strongly in that. Several studies have shown reductions in elevated blood pressure as well. We consistently see with vitamin D supplementation improved mood, reduced neuroinflammation and reduced pain and—well documented by William Grant's work—reductions in all-cause mortality and disease-specific mortality.

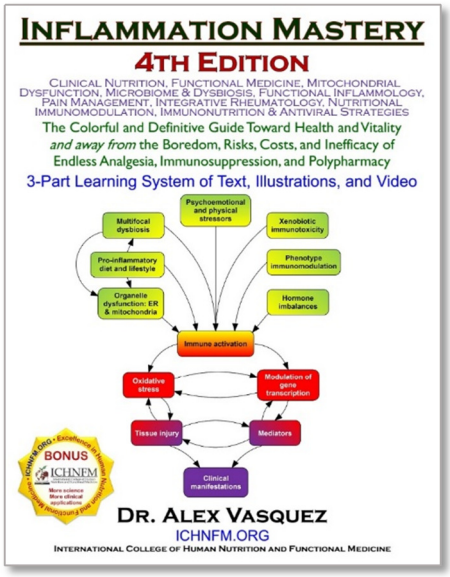


I will conclude with a brief summary and clinical contextualization. This study—"Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" published in February of 2017 in the journal *Hormones and Cancer*—is a small trial but it is placebo-controlled and does provide encouraging data consistent with known benefits of vitamin D supplementation, whether that's provided systemically (for an endocrine effect) or directly vaginally (for endocrine [systemic absorption], and local paracrine and autocrine effects)—specifically the effects that that vitamin D has on the vaginal microbiome via its antiinflammatory and eubiosis-promoting effects.



Enhancement of self-resolution I think is one of the major keys here. Given the well-established fact that most people clear various human papillomavirus infections without consequence, research (such as this) should be emphasizing those natural and endogenous factors that promote viral clearance.

Medical interventions related to HPV disease include PAP smears and these should be continued every one to three years. The controversial anti-HPV vaccination is expensive and has produced many biologically-proven adverse effects, including autoimmunity (e.g., acute disseminated encephalomyelitis[5]), neuroinflammation[6], infertility[7], and death[8]. And of course, that vaccine provides zero collateral benefits.



In contrast, nutritional interventions such as vitamin D and methylfolate or calcium folinate safely provide numerous disease specific and general collateral benefits. What we need in the future are well-performed clinical trials using a complete antiviral nutrition protocol such as the one that I published back in 2014.

So thank you for your attention during this short video. What we're going to talk about in one of the upcoming videos is again, the role of vitamin D in modulating the vaginal microbiome, reducing inflammation and reducing the clinical consequences of various diseases.

Citation: Vasquez A. Antiviral Nutrition Update # 1 for 2018. Video presentation (ichnfm.org/hpv1) and official transcript (academia.edu/35808436) 2018 January

Primary reference—same information in different formats and contexts:

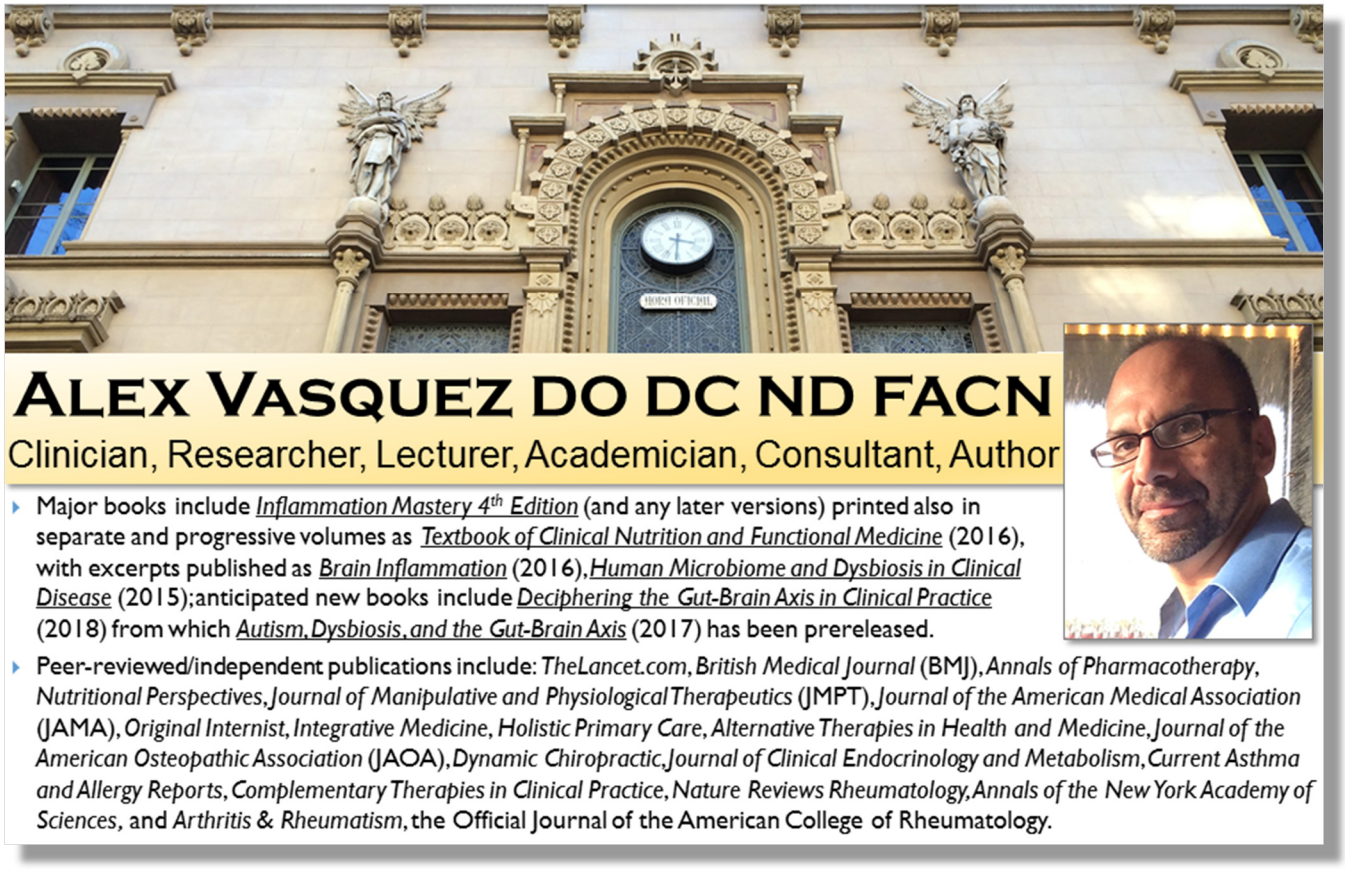
- *Antiviral Strategies and Immune Nutrition* https://www.amazon.com/dp/1502894890/
- also published in digital ebook format as *Antiviral Nutrition* (Kindle ebook) https://www.amazon.com/dp/B00OPDQG4W.
- Also published in *Inflammation Mastery, 4th Edition* https://www.amazon.com/dp/B01KMZZLAQ/ and
- *Textbook of Clinical Nutrition and Functional Medicine, vol. 1: Essential Knowledge for Safe Action and Effective Treatment* https://www.amazon.com/dp/B01JDIOHR6/

Introductory videos:

- Video introduction to books: http://www.ichnfm.org/im4
- Conference presentation—introducing the clinical protocol: http://www.ichnfm.org/video-funct-inflam-1

[5] Sekiguchi et al. Two Cases of Acute Disseminated Encephalomyelitis Following Vaccination against Human Papilloma Virus. *Intern Med*. 2016;55(21):3181-3184
[6] Takahashi et al. Immunological studies of cerebrospinal fluid from patients with CNS symptoms after human papillomavirus vaccination. *J Neuroimmunol.* 2016 Sep 15;71-8
[7] Martínez-Lavín M, Amezcua-Guerra L. Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series. *Clin Rheumatol*. 2017 Oct;36(10):2169-2178
[8] "The adverse reaction reports detail 26 new deaths reported between September 1, 2010 and September 15, 2011 as well as incidents of seizures, paralysis, blindness, pancreatitis, speech problems, short term memory loss and Guillain-Barré Syndrome. The documents come from the FDA's Vaccine Adverse Event Reporting System (VAERS) which is used by the FDA to monitor the safety of vaccines." Lind P. U.S. court pays $6 million to Gardasil victims. *The Washington Times* December 31, 2014 https://www.washingtontimes.com/news/2014/dec/31/us-court-pays-6-million-gardasil-victims/

Antiviral Nutrition Update #2 for 2018
Clinical Trial of Selenium against HPV/CIN1



The video of this presentation is archived at ichnfm.org/hpv2, and the transcript in PDF format—which is considered the final and citable version—is archived at academia.edu/35798286; any corrections or updates will be made to the PDF file. Observe that this video presentation is truly an *update* subsequent to previous publications and that therefore not all sources are cited; for citations, see the video, and for complete citations regarding the protocol in its entirety, see the book *Antiviral Strategies and Immune Nutrition* or the ebook version titled *Antiviral Nutrition*.

"Hello, everybody. Dr. Alex Vasquez here with ***Antiviral Nutrition*** **Update #2 for 2018**.

Again, these updates are based upon the foundational information and sources that I discussed previously. Namely, the books, articles, videos/presentations, and blogs. You have those listed for you again here.

1. Book: Antiviral Strategies and Immune Nutrition (2014) https://www.amazon.com/dp/1502894890/
2. eBook: Antiviral Nutrition (Kindle ebook, 2014) https://www.amazon.com/dp/B00OPDQG4W
3. Journal: Unified Antiviral Strategy published by ICHNFM. *International Journal of Human Nutrition and Functional Medicine* 2014:v2(q4);p1 ichnfm.org/antiviral5
4. Conference: Vaccines—The Truth: International Congress on Naturopathic Medicine in Barcelona 2016 ichnfm.org/antiviral4
5. Tutorials: AntiViral Strategies and Immune Nutrition: Antiviral Nutrition (video, 2014) https://vimeo.com/109318556

Again, the book *Antiviral Strategies and Immune Nutrition* was published as an ebook under the title of *Antiviral Nutrition*. I also have two journal articles here, also a conference presentation, and a series of video tutorials that help to support this information.

As I mentioned before, one of our goals is to have a structured understanding of viral infections, and from that structured understanding to arrive at a comprehensive antiviral strategy. In other words, if you can't deconstruct the pathophysiologic event—in this case we're talking about viral infections—then you're pretty much *trapped in the phenomena* of viral infections. Achievement of goals is effected via strategies, and each strategy is effected by its tactics. What that looks like visually is we have ***goals***—in this case the prevention and treatment of viral infections. Supporting that ***goal*** is the ***strategy*** of addressing each one of the major components of a viral infection. So, we want to deconstruct and address each major aspect of what we call viral infections generally, and to support that ***strategy***, we're going to use a specific ***tactic***, and that is the use of these clinical protocols for each component of the above-mentioned strategy.

Graphically, that's represented by these two images from my book. Again, *Antiviral Strategies and Immune Nutrition*, published as an Amazon Kindle ebook as *Antiviral Nutrition* (the Kindle software is free from Amazon and allows reading on any smartphone, iPad/tablet or computer). We want to address 1) the viral component, we want to address 2) the replication of that virus, we want to address 3) immunonutrition, and we want to 4) support cellular and systemic health, as well.

In ***Antiviral Nutrition*** **Update #1 for 2018** (archived at ichnfm.org/hpv1), we looked at this article "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia." You've got all of the information summarized for you here, so I won't go through it in its entirety, but you're certainly welcome to pause the video and read the screen if you want to get the information from our previous conversation. Likewise, I also reviewed the biological effects of vitamin D3 supplementation/optimization mostly specific to the treatment of viral infections. Then, I provided some clinical context and conclusions. Again, you're welcome to pause the video and review that previous information. My previous publications on vitamin D from *Alternative Therapies in Health and Medicine*[1], *British Medical Journal*[2], *JAMA—Journal of the American Medical Association*[3], and *Journal of Clinical Endocrinology and Metabolism*[4] are available as a PDF download archived at ichnfm.org/d.

One of the preventative measures for HPV viral infection related illness is the antiHPV vaccination. I consider that vaccination to be expensive and the data has shown quite conclusively that this vaccination can produce many biologically proven adverse effects including autoimmunity (e.g., acute disseminated encephalomyelitis[5]), neuroinflammation[6], infertility[7], and death[8], and it really doesn't provide any collateral benefits. As published in *The Washington Times* (December 31, 2014):

> "Judicial Watch announced it has received documents from the Department of Health and Human Services (HHS) revealing that its National Vaccine Injury Compensation Program (VICP) has awarded $5,877,710 dollars to 49 victims in claims made against the highly controversial HPV (human papillomavirus) vaccines. … The adverse reaction reports detail 26 new deaths reported between September 1, 2010 and September 15, 2011 as well as incidents of seizures, paralysis, blindness, pancreatitis, speech problems, short-term memory loss and Guillain-Barré Syndrome. The documents come from the FDA's Vaccine Adverse Event Reporting System (VAERS) which is used by the FDA to monitor the safety of vaccines. … **That's 26 reported deaths of young, previously healthy, girls after Gardasil vaccination in just one year**."

So, when we actually look at the data, we do see some concerns about the human papillomavirus vaccine. You can see that this was published by the American College of Pediatricians in January of 2016, citing some concern about premature ovarian failure, premature menopause.[9] These are legitimate concerns related to the aluminum

[1] Vasquez et al. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med*. 2004
[2] Vasquez et al. Calcium and vitamin D in preventing fractures: Data are not sufficient to show inefficacy. *BMJ: British Medical Journal* 2005
[3] Muanza, Vasquez et al. Isoflavones and postmenopausal women [letter]. *JAMA: Journal of the American Medical Association* 2004
[4] Gordon et al. Treatment of Hypovitaminosis D in Infants and Toddlers. *Journal Clinical Endocrinology Metabolism* 2008
[5] Sekiguchi et al. Two Cases of Acute Disseminated Encephalomyelitis Following Vaccination against Human Papilloma Virus. *Intern Med*. 2016;55(21):3181-3184
[6] Takahashi et al. Immunological studies of cerebrospinal fluid from patients with CNS symptoms after human papillomavirus vaccination. *J Neuroimmunol.* 2016 Sep 15;71-8
[7] Martínez-Lavín M, Amezcua-Guerra L. Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series. *Clin Rheumatol*. 2017 Oct;36(10):2169-2178
[8] "The adverse reaction reports detail 26 new deaths reported between September 1, 2010 and September 15, 2011 as well as incidents of seizures, paralysis, blindness, pancreatitis, speech problems, short term memory loss and Guillain-Barré Syndrome. The documents come from the FDA's Vaccine Adverse Event Reporting System (VAERS) which is used by the FDA to monitor the safety of vaccines." Lind P. U.S. court pays $6 million to Gardasil victims. *The Washington Times* December 31, 2014 https://www.washingtontimes.com/news/2014/dec/31/us-court-pays-6-million-gardasil-victims/
[9] American College of Pediatricians, primary author Scott S. Field, MD. New Concerns about the Human Papillomavirus Vaccine. January 2016. acpeds.org/the-college-speaks/position-statements/health-issues/new-concerns-about-the-human-papillomavirus-vaccine. Citation of this publication does not imply endorsement of the organization.

adjuvant[10], especially when combined with another vaccine component, polysorbate 80 (a patented form of which is sold under the name "Tween 80"[11]), which has been shown to cause reproductive abnormalities in animal studies.[12] Importantly noted is the clinical investigation published in *Annals of Allergy, Asthma & Immunology*—the scholarly medical journal published by the American College of Allergy, Asthma and Immunology—which stated, "Polysorbate 80 was identified as the causative agent for the anaphylactoid reaction of nonimmunologic origin in the patient. Polysorbate specific IgE antibodies were not identified in enzyme-linked immunosorbent assay and immunoblot examinations, confirming the nonimmunologic nature of the anaphylactoid reaction. CONCLUSIONS: Polysorbate 80 is a ubiquitously used solubilizing agent that can cause severe nonimmunologic anaphylactoid reactions."[13]

In the human clinical literature, we see documentation of series adverse events after HPV vaccination. This was a critical review of randomized trials and post-marketing case series. From *Immunology Research* 2017, "Severe Somatoform and Dysautonomic Syndromes after HPV vaccination" was a case series and review of the literature. Here also, we see immunological studies showing abnormalities in cerebral spinal fluid from patients with CNS symptoms after HPV vaccination.

In our last conversation, we talked about vitamin D. We looked at some of the information showing that it can actually promote regression of cervical intraepithelial neoplasia grade one (CIN1), and that's been shown in an oral study using approximately 3500 international units (IU) per day of vitamin D3. This was also shown in a topical study using vaginally applied vitamin D and you can see that described here in a publication from *DermatoEndocrinology* in 2014.

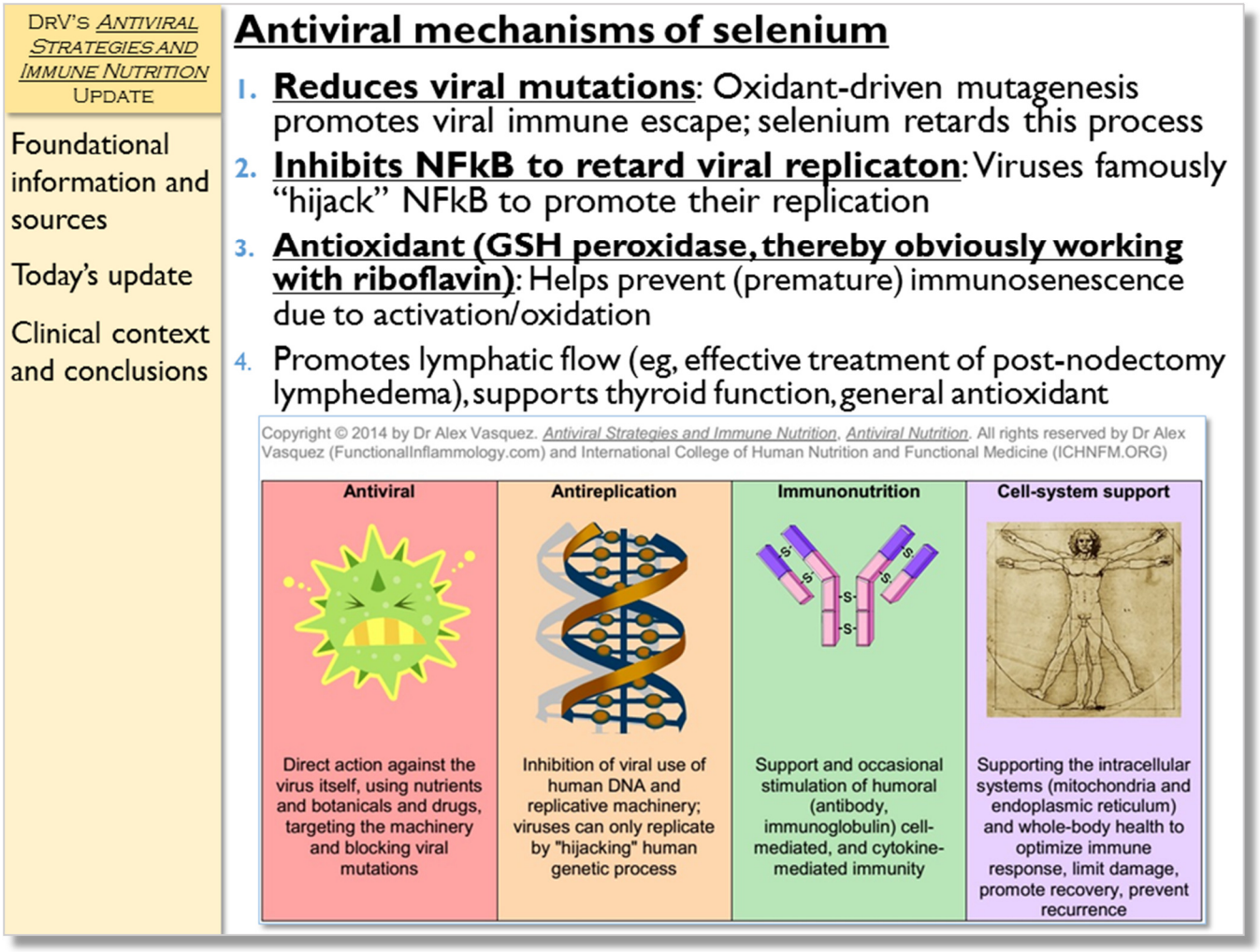
We're going to maintain this theme talking about nutrition against HPV infection and its consequences today. For ***Antiviral Nutrition*** **Update #2 for 2018**, we're going to look at this article from the *British Journal of Nutrition* 2015, "The Favorable Effects of Long-term Selenium Supplementation on Regression of Cervical Tissues and Metabolic Profiles of Patients with Cervical Intraepithelial Neoplasia." This, like the other one, is a randomized, double-blind, placebo-controlled trial. You've got the citation and you also have the digital object identifier (DOI) in the upper right hand corner. You can pause the video if you want to read the abstract. Otherwise, I'll provide you my summary here.

Again, the title of this article: "The Favorable Effects of Long-term Selenium Supplementation on Regression of Cervical Tissues and Metabolic Profiles of Patients with Cervical Intraepithelial Neoplasia" [caused by HPV viral infection], *British Journal of Nutrition*, December of 2015. This is a randomized, double-blind, placebo controlled trial, with approximately 50 women with cervical intraepithelial neoplasia grade one. The intervention here was 200 mcg of selenium for six months. The results showed that after six months of taking selenium supplements, a greater percentage of women in the selenium group had regressed their CIN1 that was 88% versus 56% in the placebo group. They also noted significant decreases in fasting plasma glucose levels, reduced insulin levels, improved insulin sensitivity, reduced triglycerides, and elevated HDL. That suggests greatly improved metabolic efficiency in terms of using glucose and insulin sensitivity, versus insulin resistance. They showed improved antioxidant defenses with elevated glutathione and a reduction in oxidative stress markers, and as we would expect, they showed excellent safety from 200 mcg of selenium for six months.

Let's look at some of the antiviral mechanism of selenium. Number one, selenium reduces viral mutations. So, when we look at the antiviral strategy that I've outlined, we see that selenium has antiviral effects by blocking viral mutations. Oxidant driven mutagenesis promotes viral immune escape and selenium clearly retards this process. So, that might be one of the mechanisms of benefit here from selenium supplementation in the treatment of HPV related disease. Number two, we also know that selenium inhibits the NFkB pathway to retard viral replication. Viruses famously hijack this NFkB pathway to promote their own replication. So, again, selenium helps

[10] Gherardi et al. Biopersistence and brain translocation of aluminum adjuvants of vaccines. *Front Neurol*. 2015 Feb 5;6:4 https://doi.org/10.3389/fneur.2015.00004
[11] U.S. National Library of Medicine National Center for Biotechnology Information. pubchem.ncbi.nlm.nih.gov/compound/443315. Polysorbate 80 is a nonionic surfactant, emulsifier, and excipient that is used to stabilize aqueous formulations of medications including vaccinations for parenteral administration. Tween 80—Tween is a registered trademark of Croda Americas, Inc.
[12] "Neonatal female rats were injected ip (0.1 ml/rat) with Tween 80 in 1, 5 or 10% aqueous solution on days 4-7 after birth. Treatment with Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus. The relative weight of the uterus and ovaries was decreased relative to the untreated controls. Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation. Ovaries were without corpora lutea, and had degenerative follicles." Gajdová et al. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. *Food Chem Toxicol*. 1993 Mar;31(3):183-90
[13] Coors et al. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Ann Allergy Asthma Immunol.* 2005 Dec;95(6):593-9

with a direct antiviral effect and it also blocks viral replication. Number three, selenium provides some antioxidant benefits via glutathione peroxidase specifically. Thereby, obviously working in tandem with riboflavin, which is the co-factor for glutathione reductase. Selenium helps to prevent premature immunosenesence due to immunoactivation and oxidation. Number four, selenium promotes lymphatic flow. This has been demonstrated in studies showing that selenium is effective in the treatment of post-nodectomy lymphedema. Selenium also supports thyroid function and—again—it is a general antioxidant. So, I think we could reasonably say that selenium provides cellular and systemic support in addition to its other benefits in combating viral infections and supporting immune health.



Now, let's contextualize this within the overall strategy, the *Antiviral Nutrition* strategy. Our **goal** with this strategy is the safe and effective prevention and treatment of viral infections and diseases that are secondary to those viral infections. Our ***aspirational goal*** beyond that rather narrow primary goal is the ideal, which is our treatments should be safe, they should have no side effects, they should be effective, they should be widely available and affordable. They should have minimal or no drug interactions and we'd love some collateral benefits. Furthermore, we also want to respect patient autonomy and human rights. This was previously known as "medical ethics" before the era of mandatory medicalization.

Our strategy to support those **goals** is to deconstruct the phenomena of what we think of when we talk about viral infections into its main components, and our **tactic** is to effectively address each component with an effective, and safe clinical protocol. Thus far, in this conversation for 2018, we've discussed vitamin D3 and here, I've discussed selenium.

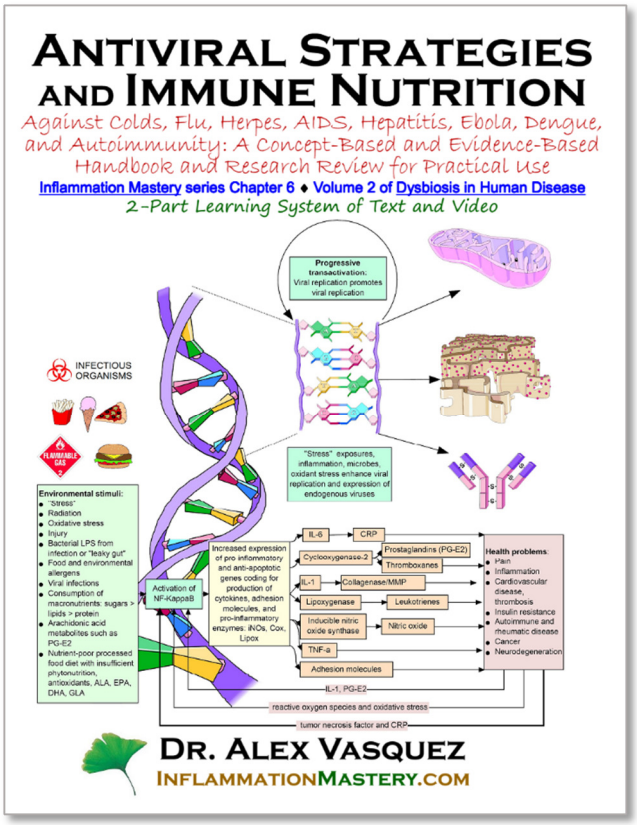
Thank you very much for attending this very brief video update and I will provide some more information as this series progresses. Again, here, you've got the previously mentioned foundational information upon which we're providing these updates. Specifically, antiviral strategies and also antiviral nutrition. That was also published in my 2016 book ***Inflammation Mastery*** and also in a smaller volume, the two-volume set published under the title ***Textbook of Clinical Nutrition and Functional Medicine***. In this case, it was in chapter 4; so, that's Volume One.

Thank you again for your attention during this very brief and efficient video update and I look forward to sharing more information with you soon.

Citation: Vasquez A. Antiviral Nutrition Update #2 for 2018. Video presentation (ichnfm.org/hpv2) and official transcript (academia.edu/35798286) 2018 January

Primary reference—same information in different formats and contexts:

- *Antiviral Strategies and Immune Nutrition* https://www.amazon.com/dp/1502894890/
- also published in digital ebook format as *Antiviral Nutrition* (Kindle ebook) https://www.amazon.com/dp/B00OPDQG4W.
- Also published in *Inflammation Mastery, 4th Edition* https://www.amazon.com/dp/B01KMZZLAQ/ and
- *Textbook of Clinical Nutrition and Functional Medicine, vol. 1: Essential Knowledge for Safe Action and Effective Treatment* https://www.amazon.com/dp/B01JDIOHR6/



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Pharma Echo Chamber, Sociopolitical Matrix, and Power Vortex: A Diagram-Centric Conceptualization

Alex Vasquez DO ND DC FACN

Current Status of Vortex Diagram and Descriptions

Due to escalating political misbehavior in March 2019, the main diagram has been updated and is now being further developed and more widely distributed. This version was updated on March 3, 2019, and updated versions will be periodically uploaded to the archival website: https://www.academia.edu/38476348

Previous versions

1. This diagram originated spontaneously during the production of a review—titled "Introduction to #Cardionutrition: Kidney Stones and the Ketogenic Diet"—published in video and text format in 2018.
2. The diagram was again published with additional explanation in a peer-reviewed editorial published in 2019: Vasquez A, Pizzorno J. Concerns About The Integrity of The Scientific Research Process—Focus On Recent Negative Publications Regarding Nutrition, Multivitamins, Fish Oil And Cardiovascular Disease. *Integrative Medicine* 2019 Feb; 8-15

Commentary

The recent censorship of information that has occurred—originating from the United States but also influencing access to information worldwide—requires commentary, context and concrete documentation of its existence. **Perhaps the most important contribution of this article is the demonstration of the interconnectedness of the systems that originate and sustain thought-control and intellectual censorship in what otherwise might appear to be democratic societies.** This article contends that information requires context and that while isolated facts may be very important by themselves they cannot be more important or influential than their overall context and the resulting synergistic-exponential influence they produce; furthermore, the appreciation of these components that occur over time establishes that these events are systematic and coordinated rather than incidental and isolated.

Data and Citations

1. **Medical journals are inherently biased toward publishing drug-praising articles that can also serve as advertisements and infomercials for the pharmaceutical industry, which commonly pays millions of dollars for journal reprints**: Medical journals/organizations publish pro-drug research which becomes paid advertising when the drug companies buy reprints or direct advertising for millions of dollars (Smith, *PLOS Medicine* 2005).
2. **Headline-making newspapers, magazines, and television programs re-publish pro-drug information to the delight of their drug advertisers**: Positive news about drugs and vaccines is headlined and featured, while actionable information about nutrition is unavailable or tainted with controversy. Medicine-positive television features "medical heroes" reinforcing medical authority, medical dependency, and the drugs-as-salvation paradigms. News stories highlighting fear of infectious diseases serve to maintain constant fear, medical dependency, and xenophobia (e.g., "Africanized" bees, Zika, El Niño, Asian flu, Xenophobia: Ebola Stigma, Discrimination for Africans. *Time Magazine* 2014). Many of these stories are revealed as lies after they have served their political purposes; PolitiFact named the panicked US response to Ebola as the 2014 "Lie of the Year", *Time Magazine* 2014.
3. **Science and popular media become an echo chamber of biased pro-drug propaganda**; drug companies pay US politicians to promote pro-drug laws (e.g., mandatory vaccinations), protect drug companies from liability (e.g., National Childhood Vaccine Injury Act of 1986), and promote international expansion of US drug sales. US politicians gag and censure free speech on topics related to medical dangers by pressuring bookstores and social media to burn books and ban documentary films. Documentary and case report films of vaccine-induced injury and death are labeled "anti-vaccine movies" and are disappeared from bookstores and

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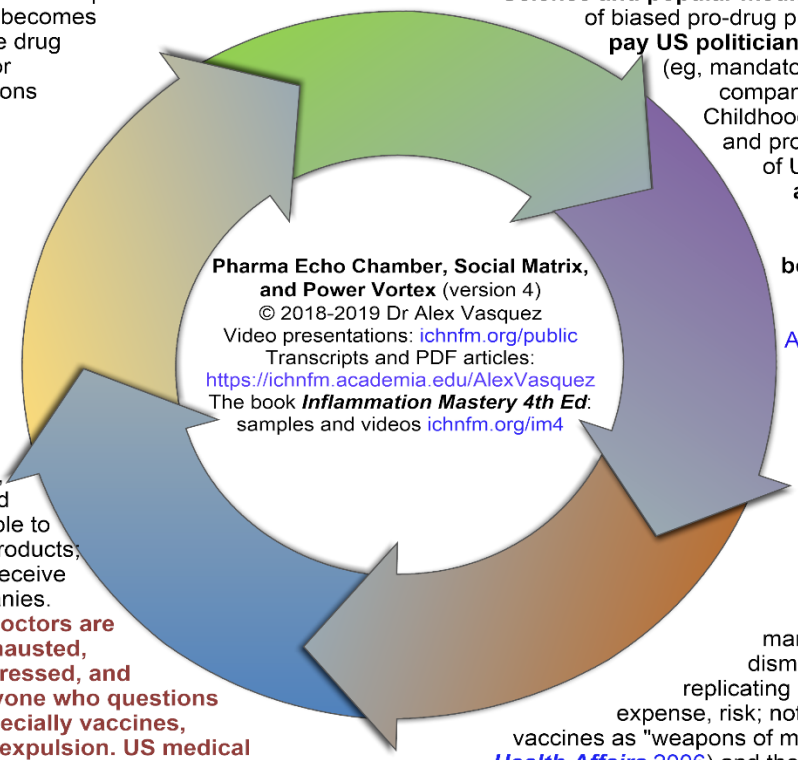
Headline-making newspapers, magazines, and television programs re-publish pro-drug information to the delight of their drug advertisers. Positive news about drugs and vaccines is headlined and featured, while actionable information about nutrition is unavailable or tainted with controversy. **Medicine-positive television features "medical heroes" reinforcing medical authority, medical dependency, and the drugs-as-salvation paradigms. News stories highlighting fear of infectious diseases serve to maintain constant fear, medical dependency, and xenophobia** (eg, "Africanized" bees, Zika, El Niño, Asian flu, Xenophobia: Ebola Stigma, Discrimination for Africans Associated with Disease. ***Time Magazine*** October 29, 2014). **Many of these stories are revealed as lies after they have served their political purposes**; ***PolitiFact*** named the panicked US response to Ebola as the 2014 "Lie of the Year", ***Time Magazine*** Dec 15, 2014

Medical journals/organizations publish pro-drug research which becomes paid advertising when the drug companies buy reprints or direct advertising for millions of dollars (Smith, ***PLOS Medicine*** 2005)

Science and popular media become an echo chamber of biased pro-drug propaganda; **drug companies pay US politicians to promote pro-drug laws** (eg, mandatory vaccinations), protect drug companies from liability (eg, National Childhood Vaccine Injury Act of 1986), and promote international expansion of US drugs. **US politicians gag and censure free speech on topics related to medical dangers by pressuring bookstores and social media to burn books and ban documentary films.** Anti-vaccine movies disappear from Amazon after CNN Business report. ***CNN Business***, March 1, 2019



Drug companies infiltrate media, television shows, education, and public policy. Defunding public science forces schools and journals to rely on pharma funding. Drug companies pay "researchers",professors, and editors to publish and teach information favorable to the drug paradigm and products; medical schools love to receive funding from drug companies. **Medical students and doctors are kept insanely busy, exhausted, suicidally depressed/stressed, and fearfully compliant; anyone who questions the drug paradigm, especially vaccines, is a target for censure, expulsion. US medical physicians have the highest rates of suicide.** Physicians Experience Highest Suicide Rate of Any Profession. ***Medscape*** May 07, 2018

Drug companies become more profitable and therefore more powerful than governments. Drug companies utilize US political and military power by influencing international trade agreements, eg, enforcing mandatory drug/vaccine policies, dismantling consumer protections, replicating US's healthcare bureaucracy, expense, risk; note the Orwellian description of vaccines as "weapons of mass protection" (Milstien et al, ***Health Affairs*** 2006) and the deployment of military forces under the banner of humanitarian health aid (National armies for global health? ***Lancet*** 2014 Oct 25)*

*Notice the language of such **"free trade" agreements, "seek the elimination of government measures such as price controls and reference pricing** which deny full market access for United States products in overseas markets... **legalizing direct to consumer advertising (DTCA) via the internet**: Each Party shall permit a pharmaceutical manufacturer to disseminate… information regarding its pharmaceuticals that are approved for sale in the Party's territory…" Lopert R, Gleeson D. The High Price of "Free" Trade: U.S. Trade Agreements and Access to Medicines. ***Journal of Law, Medicine & Ethics*** 2013 Apr, 199-223. "The United State seeks to redesign national health care systems in its own image... By concluding bilateral and regional agreements, the **United States is gaining greater influence over the domestic health care and drug coverage programs of its trading partners**... The U.S. (and Australian) pharmaceutical industry perceived a free trade agreement to present an opportunity to **undermine the evidence-based, strict and effective procedures** underpinning Australia's Pharmaceutical Benefits Scheme (PBS)... After the treaty's conclusion, however, drug manufacturers expressed delight with the implications for prices, profits and investment... Free trade agreements reflect the U.S.' enduring adherence to market-based solutions, coupled with a conviction that government intervention is unnecessary and unhelpful. Thus the U.S. Trade Representative is mandated to pursue "the elimination of government measures such as price controls and reference pricing which deny full market access for United States products" in overseas markets. This is **despite the U.S. health care system itself exhibiting the characteristics of market failure**... enabling triple damages for patent violations... The United States deploys an aggressive trade agenda to expand markets for U.S. goods and services " Tully SR. Free Trade Agreements With The United States: 8 Lessons For Prospective Parties From Australia's Experience. ***British Journal of American Legal Studies*** **2016** Dec, 395-418. "There is growing international concern about the risks posed by direct-to-consumer advertising (DTCA) of prescription pharmaceuticals, including via the internet. Recent trade agreements negotiated by the United States, however, incorporate provisions that may constrain national regulation of DTCA. Some provisions explicitly mention DTCA; others enable foreign investors to seek compensation if new regulations are seen to harm their investments." Gleeson D, Menkes DB. Trade Agreements and Direct-to-Consumer Advertising of Pharmaceuticals. ***International Journal of Health Policy and Management*** **2013** Feb, 98-100. "Opposition to Breast-Feeding Resolution by U.S. Stuns World Health Officials. When that failed, they turned to threats, according to diplomats and government officials who took part in the discussions. Ecuador, which had planned to introduce the measure, was the first to find itself in the cross hairs. The Americans were blunt: If Ecuador refused to drop the resolution, Washington would unleash punishing trade measures and withdraw crucial military aid. The Ecuadorean government quickly acquiesced." ***New York Times*** July 8, 2018 "Trump Stance on Breast-Feeding and Formula Criticized by Medical Experts: Global health experts say breast milk is especially important for babies in poor countries, where unsafe water supplies can make powdered infant formula dangerous.The Trump administration's aggressive attempts to water down an international resolution supporting breast-feeding go against decades of advice by most medical organizations and public health experts." ***New York Times*** July 9, 2018

media outlets. (*CNN Business* 2019). This government-representative-directed action must be noted as a violation of the First Amendment of the United States Constitution that explicitly protects "free speech" among American citizens; in the 2019 situation, the books and documentary films were effectively banned from public access when a US politician sent a "warning letter" to various social media platforms and media retailers, thereby using government influence to restrict privately-distributed access to information. U.S. Constitution, First Amendment: "Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or **abridging the freedom of speech**, **or of the press**; or the right of the people peaceably to assemble, and to petition the government for a redress of grievances."

4. **Drug companies become more profitable and therefore more powerful than governments**. Drug companies utilize US political and military power by influencing international trade agreements, eg, enforcing mandatory drug/vaccine policies, dismantling consumer protections, replicating US's healthcare bureaucracy, expense, risk; note the Orwellian description of vaccines as "weapons of mass protection" (Milstien et al, *Health Affairs* 2006) and the deployment of military forces under the banner of humanitarian health aid (National armies for global health? *Lancet* 2014)
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6. **International political agreements are written to the favor of drug companies rather than to the citizens of those countries**: Notice the language of such "free trade" agreements, "seek the elimination of government measures such as price controls and reference pricing which deny full market access for United States products in overseas markets... legalizing direct to consumer advertising (DTCA) via the internet: Each Party shall permit a pharmaceutical manufacturer to disseminate… information regarding its pharmaceuticals that are approved for sale in the Party's territory…" Lopert R, Gleeson D. The High Price of "Free" Trade: U.S. Trade Agreements and Access to Medicines. *Journal of Law, Medicine & Ethics* 2013. "The United State seeks to redesign national health care systems in its own image... By concluding bilateral and regional agreements, the United States is gaining greater influence over the domestic health care and drug coverage programs of its trading partners... The U.S. (and Australian) pharmaceutical industry perceived a free trade agreement to present an opportunity to undermine the evidence-based, strict and effective procedures underpinning Australia's Pharmaceutical Benefits Scheme (PBS)... After the treaty's conclusion, however, drug manufacturers expressed delight with the implications for prices, profits and investment... Free trade agreements reflect the U.S.' enduring adherence to market-based solutions, coupled with a conviction that government intervention is unnecessary and unhelpful. Thus the U.S. Trade Representative is mandated to pursue "the elimination of government measures such as price controls and reference pricing which deny full market access for United States products" in overseas markets. This is despite the U.S. health care system itself exhibiting the characteristics of market failure... enabling triple damages for patent violations... The United States deploys an aggressive trade agenda to expand markets for U.S. goods and services " Tully SR. Free Trade Agreements with The United States: 8 Lessons For Prospective Parties From Australia's Experience. *British Journal of American Legal Studies* 2016. "There is growing international concern about the risks posed by direct-to-consumer advertising (DTCA) of prescription pharmaceuticals, including via the internet. Recent trade agreements negotiated by the United States, however, incorporate provisions that may constrain national regulation of DTCA. Some provisions explicitly mention DTCA; others enable foreign investors to seek compensation if new regulations are seen to harm their investments." Gleeson D, Menkes DB. Trade Agreements and Direct-to-Consumer Advertising of Pharmaceuticals. *International Journal of Health Policy and Management* 2013. "Opposition to Breast-Feeding Resolution by U.S. Stuns World Health Officials. … When that failed, they turned to threats, according to diplomats and government officials who took part in the discussions. Ecuador, which had planned to introduce the measure, was the first to find itself in the cross hairs. The Americans were blunt: If Ecuador refused to drop the resolution, Washington would unleash punishing trade measures and withdraw crucial military aid. The Ecuadorean government quickly acquiesced." Opposition to Breast-Feeding Resolution by U.S. Stuns World Health Officials. *New York Times* 2018 "Global health experts say breast

milk is especially important for babies in poor countries, where unsafe water supplies can make powdered infant formula dangerous. The Trump administration's aggressive attempts to water down an international resolution supporting breast-feeding go against decades of advice by most medical organizations and public health experts." Trump Stance on Breast-Feeding and Formula Criticized by Medical Experts. *New York Times* July 9, 2018

Current status of Vortex Diagram

This article is currently being updated, cited and substantiated. This version was updated on March 3, 2019, and upcoming versions will be uploaded to the archival website: https://www.academia.edu/38476348

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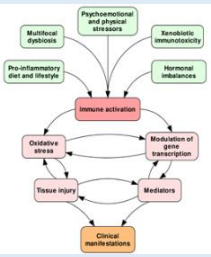
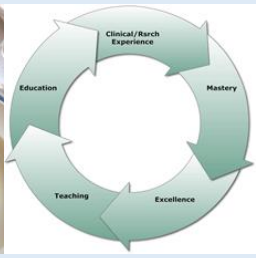
About the author and presenter: Alex Kennerly Vasquez DO ND DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding Program Director of the world's first fully-accredited university-based graduate 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 a two-volume set titled 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), *Integrated Blood Pressure Control, Journal of Biological Physics and Chemistry*, 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 Editor (2018-present) of *Journal of Orthomolecular Medicine*, published for more than 50 consecutive years by the International Society for Orthomolecular Medicine.

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Notable publications in 2014—❶ Lab Fraud in Functional Medicine, ❷ ISIFMC Position on HPS2-THRIVE; ❸ Unified Antiviral Strategy, ❹ Metabolic Correction: www.ichnfm.org/journal

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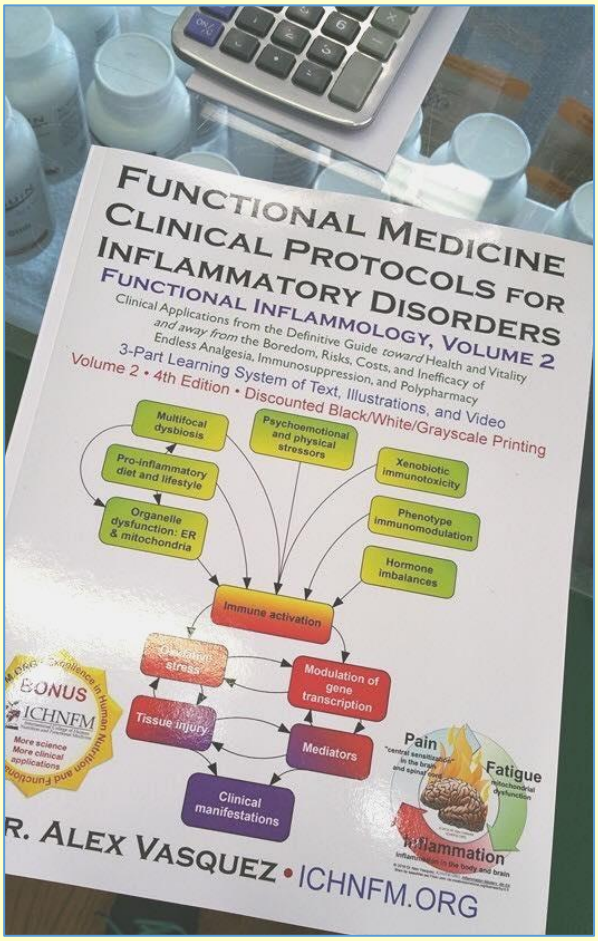

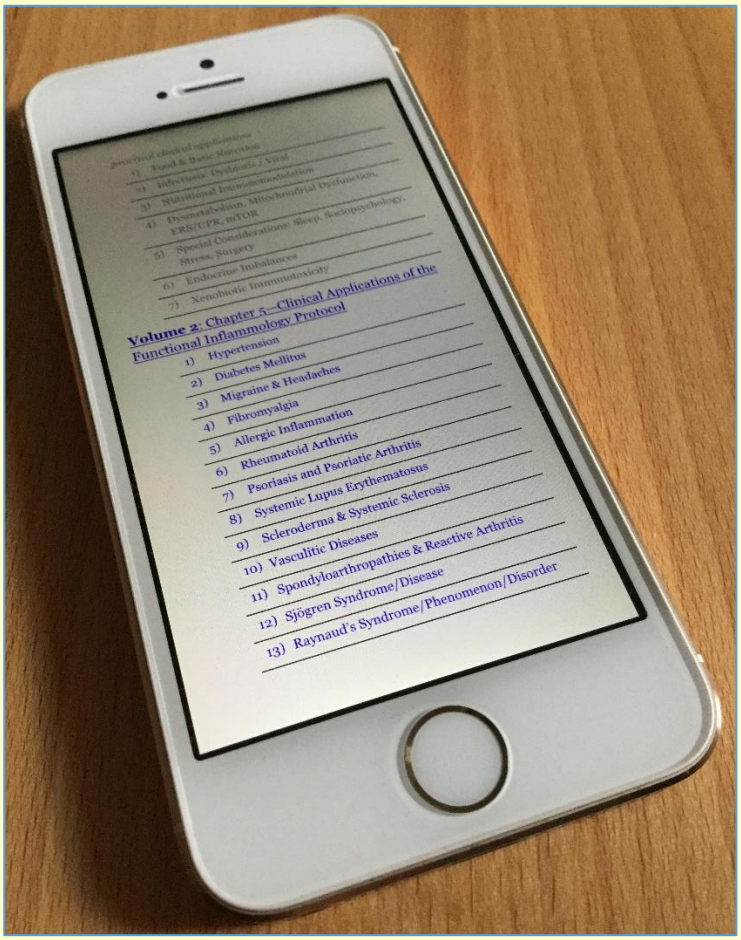

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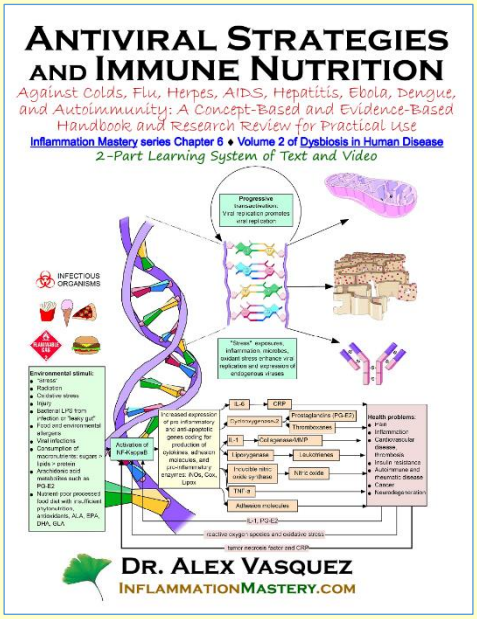

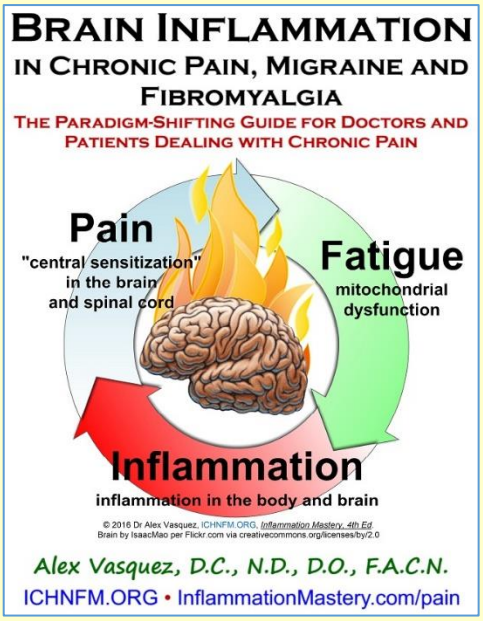

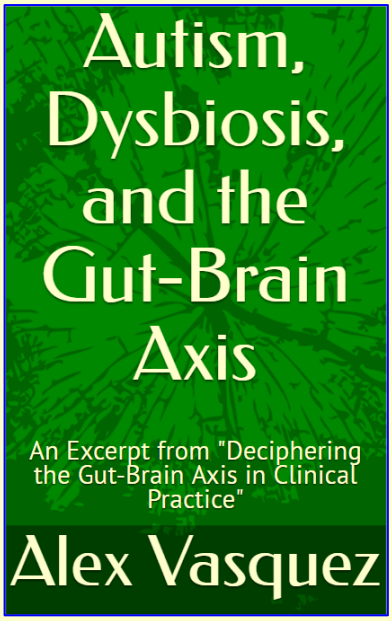

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"The purpose of life is to live it, to taste experience to the utmost, to reach out eagerly and without fear for newer and richer experience."
Eleanor Roosevelt (1884 - 1962)
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Concerns About The Integrity 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 can impact hundreds of millions of people worldwide.[2] While fractions of the population succumb to a specific disease that may need drug therapy, the entire human population eats food and is directly affected by nutrition research. Further, the science of nutrition is particularly contentious and territorial. A great irony of nutrition research is that most of it is conducted by healthcare professionals with little to no formal training in nutrition. Clinical therapeutic nutrition is not taught in the vast majority of medical schools[3-5] nor in post-graduate medical training programs[6], including those specialties that are obviously impacted by dietary intake such as gastroenterology[7] and cardiology.[8,9] Despite this absence of training in clinical nutrition, the medical profession proclaims itself authoritative on all health-related topics, including the entire territory of clinical nutrition.[10] A major 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 ultimately influence patient care, government policy and health outcomes for tens/hundreds of millions of people. This editorial provides several recent examples of questionable nutrition research and publications, lists possible causes and suggests some proposed solutions. Given that all aspects of healthcare are dependent upon the integrity of the educational, investigative and publication processes, the advancements of clinical medicine and population-wide health improvements are hindered by accidental and intentional ignorance in nutrition education and research.

Recent examples of questionable nutrition publications from major journals

In the following subsection, we review recent examples of questionable or inaccurate publications related to nutrition. Perceived shortcomings are documented with both citations here and links to more detailed and authoritative reviews and video presentations. In some instances, speculations regarding the cause and consequences of identified errors are provided.

Vitamin and Mineral Supplements: What Clinicians Need to Know (*JAMA—Journal of the American Medical Association* 2018 Mar). In this recent publication, authors Manson and Bassuk[10] attempt to review "what clinicians need to know" about "vitamin and mineral supplements" within a span of two pages. Such a publication apparently attempts to simplify the entire field of clinical nutrition to a ridiculous diminution and by such brevity must contain oversimplifications that are ultimately misleading. Oddly and clearly discordant with most reviews on pharmacotherapeutics, such nutrition reviews in medical journals commonly start with overtures reviewing the popularity of nutritional supplements ("52% of US adults reported use of at least one supplement product"), the financial size of the market ("$30 billion industry in the United States"), sweeping generalizations that claim inefficacy of the entire genre ("most randomized clinical trials of vitamin and mineral supplements have not demonstrated clear benefits"), and allusions to "harmful effects" and the need to "curb inappropriate use of such supplements except that "clinicians may wish to favor prescription products."Revealingly, the authors make several mentions of "folic acid" but without any mention of the other and clinically preferred forms of the nutrient as folinic acid and methylfolate; likewise, "vitamin B_{12}" is discussed without differentiation of its various forms: cyanocobalamin, hydroxocobalamin, adenosylcobalamin and methylcobalamin. "Vitamin D" is referenced without distinction of ergocalciferol from cholecalciferol as if these are equipotent when in fact the latter is generally considered more potent and has some important physiological differences.[13-15] Further, inaccurate dosage recommendations are made despite overwhelming evidence that the cited doses are inadequate by an order of magnitude.[16-20] This is further aggravated by the foundational misperception that a nutrient can be studied as an isolated molecule like a drug, but in reality nutrients always function within biochemical networks of interaction and inderdependency that require multiple nutrients and affect multiple pathways and physiologic systems. Studying supplemental vitamin D without paying attention to the status of magnesium, vitamins A and K_2 is an effective way to ensure negative results and adverse reactions. Citing clinical trials that failed to assess baseline nutrient intake is akin to a drug trial that failed to inquire about and document baseline pharmacotherapy and polypharmacy. "Vitamin K" is mentioned without distinction of important dosing and effect differences among K_1 (phylloquinone), K_2 (menaquinone-4), K_3 (menadione), and K_7 (menaquinone-7).[21] As a final example, the authors state that "calcium supplements may increase the risk for kidney stones" but make no mention whatsoever of mitigating this risk with diet modification, magnesium, citrate or urinary alkalinization.[22] In short, their review is impressively lacking in important details that clinicians legitimately need to know regarding vitamin and mineral supplements; as such we consider it a misleading representation of the field, especially given that the publication is directed to an audience of medical physicians with no formal training and thus no background information nor evaluative perspective on the topic.

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals (*JAMA Cardiology 2018 Mar).* Conclusions from this meta-analysis[23] were echoed (See illustration 1: The pharmaceutical-journal-news echo chamber.) in newspapers, magazines, and throughout the internet, thereby ultimately influencing hundreds of millions of healthcare recipients.[24] Per video critique by Vasquez[25], important shortcomings of this review include (1) unjustified selective exclusion of data, (2) non-therapeutic dosing, (3) use of unnatural/semisynthetic form of fish oil, (4) conclusions at odds with data, (5) pro-pharma conflicts of interest among authors, publication, and supporting organizations, and—related to critique #2 aforementioned—(6) no mention anywhere in the article of the importance of the omega-3 index, the concept and use of which is highly important as documented more than 20 years previously[26] and repeatedly validated and widely published in leading scientific[27] and cardiology specialty journals.[28]

Supplemental Vitamins and Minerals for CVD Prevention and Treatment (*Journal of the American College of Cardiology* 2018 Jun). Problems with this publication[29] include (1) paid conflicts of interest among the journal's editorial/review staff[30], (2) conflicts of interest with the drug and processed food industries, (3) unscientific exclusion of data, (4) removal of data that countered the overall narrative of the article, eg, "Studies containing selenium were removed from the analysis of antioxidants due to the high percentage of these studies of the left side of the unity line versus the right side of the unity line in the antioxidant forest plot. This is compared to other components of antioxidant mixtures. Removal of the selenium studies resulted in a significant increase in all-cause mortality", (5) failure to maintain basic clinical and pharmacologic standards, and (6) confusion and equivocation with regard to details of nutritional interventions.[31]

Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus (*New England Journal of Medicine* 2018 Aug/Oct). Known as the ASCEND study[32], this large long-term clinical trial compared effects of low-dose fish oil against low-dose olive oil, looking for a difference in effect on cardiovascular outcomes. Per critiques by Vasquez[33], major shortcomings of this trial include (1) erroneous description and use of olive oil as "placebo", and (2) conflicts of interest with the pharmaceutical industry, including supervision of key meetings by drug

industry sponsors. In one of the most bizarre statements we have ever read in our 60+ years of reviewing medical literature, this article notes, "Mylan, Solvay and Abbott had nonvoting representation at meetings of the steering committee of the study and provided comments regarding the trial design and draft manuscript…" Olive oil cannot be considered a placebo given the well-established facts that it is one of the most potent anti-inflammatory and cardioprotective foods ever discovered; in fact, a short review published 15 years ago in the self-same *New England Journal of Medicine* noted that olive oil consumption in the Mediterranean diet provides such consumers with "very low rates of coronary heart disease and certain types of cancer and [had] a long life expectancy."[34] Cardioprotective, anti-inflammatory and antioxidant components of olive oil include squalene, oleic acid, and the numerous and abundant phytochemicals. The metabolic and cardioprotective benefits of olive oil are realized with consumption of low doses.[35] In fact, the antiinflammatory benefits of olive oil are so potent that a clinical trial[36] published in 1991 stated, "Olive oil can no longer confidently be used as a placebo control." Further, 10% of ASCEND subjects were already taking fish oil (n3) supplementation at baseline, with corresponding omega-3 indexes of 6.6% and 7.1%, remarkably higher than the average 4% typical of Western societies.[37] Consistent with the post-publication peer-review process, Vasquez[38] punctually submitted a guideline-conforming critique of this research; but the critique was rejected by the *New England Journal of Medicine with the excuse that the journal did not have sufficient print space for a critique of less than 175 words despite the original article length of roughly 7,000 words.*

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (*New England Journal of Medicine* 2019 Jan) and Prescription-strength omega-3 fatty acids to prevent heart disease?"A drug made from a highly purified fat from fish reduced cardiovascular events in people with heart disease or diabetes" (*Harvard Heart Letter* 2019 Feb): The original article[39] and related publication by Harvard Medical School/Harvard Heart Letter[40] both report a trial sponsored by the prescription drug manufacturer wherein 4 grams per day of "prescription-strength omega-3 fatty acids" from fish oil were compared against "a placebo that contains mineral oil." As noted by Vasquez[41], 4 grams per day of concentrated fish oil would be expected to produce more robust benefits than did the previously mentioned articles that used only 25% of this dose; as one would expect from the study of pharmacology, fish oil is similar to any other therapeutic in that its distribution and effects demonstrate a dose-response relationship Furthermore, the mineral oil purportedly used as a "placebo" is very clearly not an inert substance, as has been well known and documented, for example in the *Journal of the American Medical Association, for more than 70 years.*[42-45] Mineral oil is known to block absorption of fat-soluble antiinflammatory, anti-oxidant, and cardioprotective nutrients, specifically but not exclusively vitamin A, vitamin D, and beta-carotene. Mineral oil may also reduce absorption of cardioprotective drugs, as noted in the original study by Bhatt et al, who questioned the possibility "if mineral oil in the placebo affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups"; the authors made no attempt to assess for this possibility nor for iatrogenic malabsorption of nutrients. Not surprisingly, and perhaps also due to pro-inflammatory stimulation of the immune system, administration of mineral oil causes significant and measurable adverse effects on markers of cardiovascular disease risk, as noted in a remarkably insightful article by Herper[46] published in *Forbes. Mineral oil is absorbed from the intestines and is deposited in skin, subcutaneous tissues, intestinal wall, regional lymph nodes, liver, spleen, lungs, and bone marrow.*[47-49] The paradoxical use of a high-dose fish oil product against metabolically adverse/deleterious mineral oil would be expected to greatly favor the fish oil product, as noted by Herper.

Why Is So Much Of The Nutritional Medicine Research So Flawed?

Trying to think through why these obviously erroneous studies where published, we see basically only two options: ignorance or medical/financial priorities.

Ignorance

We are willing to consider that the following are due to lack of adequate education in nutrition.

Olive Oil Is Not Inert. Comparing two compounds that are both effective is obviously not going to show much difference in outcomes. Some of the studies critiqued above used fish oil VS olive oil. The authors and editors should have been aware that olive oil is cardioprotective and antiinflammatory since the data has been consistently published for almost 60 years, including in the *NEJM*.

Mineral Oil Is Not Inert. On the other hand, plenty of research shows multiple adverse physiological effects of mineral oil, making it a profoundly inappropriate placebo. Relative to long-term administration of mineral oil, almost anything "not too toxic" will look good by comparison. Examples of the ill effects of mineral oil are noted above.

Ignorance of Previous Standards For Assessing Omega-3 Status. The omega-3 index was validated some 20 years ago. Why wasn't it used to assess both initial status and impact of intervention? How can a major review of fish oil trials—especially in a cardiology specialty journal—fail to make any mention whatsoever about appropriate dosing, adjustments for body size (especially given that many subjects were overweight or obese), and the objectively measurable (for compliance and treatment effect) and consistently validated omega-3 index?

Figure 1. The pharmaceutical-journal-news echo chamber: Medical journals have inherent biases to publish pro-drug and anti-nutrition articles, both to please their pharmaceutical sponsors and to maintain their pharmacocentric paradigms. Newspapers and television repeat the conclusions from medical journals, thereby dispersing the information to hundreds of millions of persons. Television shows also glorify medicine and drugs in programs featuring "medical heroes" ranging from Doogie Howser MD to MASH to House MD. As the drug paradigm is strengthened financially and socially, drug companies have more money to buy more political influence (ie, transitioning from "echo chamber" to "power vortex"), including directly paying politicians to pass drug-friendly protective laws and mandatory drug requirements. Influence from the pharmaceutical and processed food industries is noted in international policies determining use of (for example) vaccines, genetically modified foods, and breast feeding. Meanwhile, medical professionals are kept overly busy, burnt-out, and untrained in nutrition, thereby leaving them vulnerable to misinformation, especially in nutrition. Drug companies pay for and "supervise" research via universities, while also paying textbook authors, journal editors, and medical societies that publish treatment guidelines.

Medical/Financial Political

Obviously, research integrity is jeopardized when it becomes dependent or overly close with funding sources or political organizations. "Research for profit" is often hidden or obfuscated.

Pay-To-Play Research. The Oxford study ASCEND claimed that all authors were "independent scientists" but the online documents showed that the majority of authors were rewarded by drug companies; and the article itself stated that the drug company supervised key meetings where their paid consultants were working; several drug companies "had nonvoting representation at meetings of the steering committee of the study and provided comments regarding the trial design and draft manuscript…" Could the financial conflicts of interest or potential for industry influence be more obvious? Why

weren't the conflicts of interest printed within the same publication wherein the authors called themselves "independent investigators." Why were university and nonprofit affiliations listed so clearly whereas drug industry connections were omitted from the printed article and available only in separate documents online?

Hidden Data. The 2018 NEJM "fish oil vs mineral oil" study obscured the identity of the placebo and also hid the adverse effects in the online materials *separate from the main publication*. This means very few researchers or busy doctors saw the adverse effects by reading the published study. Separating key data from the main publication by the inconvenient or unsuspected use of cumbersome online "supplemental materials" surely prevents many if not most readers from seeing important information and making appropriate and contextualized interpretations of the data. Why was important information separated from the primary publication? When physicians are given a reprint of the study, most of them will not have immediate access to the accessory online documents that contain important information.

Common Problem of Inaccuracy In Published Abstracts. The reading of any study begins with the reading of the title and abstract of the article. Many and perhaps most busy healthcare professionals, among those who are even willing to independently keep up with the research, read only the abstracts, not the full study. "Abstract-only" reading is usually due to time limitations, but many major journals require a fee to access the full study, while the abstract is available for free either at the publisher's website or within a cataloged database. Unless they are part of an academic health center or a clinical organization that is large enough to afford the huge subscription fees, most clinicians never see the actual research. Many studies of clinical trial abstract quality have been published, consistently showing multiple types of problems. A review study published a full 20 years ago found that 18%-68% of the abstracts in 5 major medical journals (*Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet*, and *New England Journal of Medicine*) contain multiple factual inaccuracies.[50] Another example study looked at major journals like *NEGM*, *JAMA*, *BMJ* and *Lancet* and found less than 10% clearly defined blinding, less than 15% reported numbers lost to follow up and only half reported ADRs.[51] In our extensive reading of medical research, we have found multiple examples of abstracts that report the exact opposite of the actual data in the study (See IMCJ editorial 14.4 for an example). We are admonished to practice evidence-based medicine. But what happens when the "evidence" presented in the published abstract is exactly wrong?

Now, with the growing and strategic popularity of separating key findings and authors' financial ties in online "supplementary materials", has medical publishing yet further and paradoxically obscured and encumbered the proper evaluation of scientific publications?

Problem Of Drug Advertising Distorting Publication Of Stuides On Dietary Supplements. Readers of research articles assume, appropriately but not accurately, total separation of a journal's editorial and marketing divisions. Unfortunately, such separation of scientific content from industry payments (and thus influence) does not appear to be the norm in many major journals. One study looked at the correlation between the number of pharmaceutical advertisements in 11 major medical journals and their publication of articles on dietary supplements. They found that journals with the most pharmaceutical ads published: (1) fewer major articles about dietary supplements, (2) when such articles were published they were far more likely to conclude that dietary supplements were unsafe, and (3) were 50% more likely to publish studies showing dietary supplements were clinically ineffective. All these findings of bias were statistically significant.[52]

Pay-To-Publish. The authors are not the only ones with conflicts of interests. With the huge surge in "open-access journals", authors commonly pay journals (and thus editors) for publication. The potential for conflict of interest is obvious and substantial: editors of such journals have a financial incentive to accept articles, likely including those that they might have otherwise rejected. Several studies have documented predatory behaviors by editors to recruit fees, high susceptibility to falsified credentials in editorial board members, and little to no rigor in their review processes.[53] We are not saying that all open-access journals are problematic, but rather that the potential for conflict of interest, ie, "incentivized acceptance", is especially high.

Thoughts on How to Improve Nutrition Research

The flaws we documented and exemplified above are clearly preventable by researchers making better study design decisions. Equally clear is that editors should not accept papers until such obvious problems are resolved. We propose the following for consideration by both authors and editors.

Micromanagement. We can develop formal rules and governing bodies to certify and monitor editors. In turn, the editors in a very formalized and rigorous manner micromanage authors to prevent problems such as: systematic bias, nutrients being studied at inappropriate dosages, in ineffective forms, or with no attention to the full matrix in which they function, etc. We are not advocating for this authoritarian solution, but must admit it is a pathway.

Improve the Quality of Abstracts. The CONSORT reporting guidelines for the abstracts of randomized clinical trials is a good starting point. It provides clear guidelines and a checklist. Unfortunately, virtually no journals are following these guidelines. One study evaluated the abstracts of 395 randomized clinical trials published in anesthesia journals in 2010 and in 2016 to

determine adherence to CONSORT and trend using a 16 point scale. The good news is that there was a statistically significant improvement. The bad news is that the average rating increased from only 4 to only 6 points out of a total of 16 possible quality points. Not a single abstract scored 16 and 75% met fewer than ½ the guidelines.[54]

Competence in Nutrition. We can teach editors, researchers and doctors to be nutritionally competent (which they should have learned in medical school) so that when they evaluate or use nutrition research, they hold it to a higher level of intellectual and scientific competence so that junk research is not published in the first place nor thereafter accepted by medical professionals.

Reestablish Integrity. We need to think more broadly about how we teach ethics. Medical students commonly receive training in "medical ethics", but most of the exercises are specific to clinical situations appropriate for inexperienced and naïve medical students. We as educators need to teach broader conceptualizations of ethics that serve to create and maintain a healthy and empowered healthcare community making clinical decisions based on the best real research. In addition, journals themselves need to be more accepting and responsive to post-publication critiques. They must be willing to retract, or at least bring substantial attention, to previously published articles that are shown to be problematic.

Update Education of Current Practitioners and Reform Licensing Bodies. Clinicians who want to independently stay up with the research need to be better taught to recognize and combat unreliable research. However, in this authoritarian age we also need to curtail overzealous licensing boards from restricting a practitioner from exercising his or her best clinical judgment.

Summary

The next step in reestablishing credibility seams 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.

Full disclosure. JP: As fully detailed in Editorial 8.6, JP is a scientific consultant to Bioclinic Naturals, a bioceuticals company. No studies using any of their proprietary products have been published in *IMCJ*.
AV: In addition to having authored approximately 100 articles and letters in a wide range of disciplines and peer-reviewed journals, AV is the author of the 1200-page *Inflammation Mastery, 4th Edition (2016),* also published in two volumes as *Textbook of Clinical Nutrition and Functional Medicine* with sections excerpted as *Human Microbiome and Dysbiosis in Clinical Disease, Antiviral Nutrition, and Brain Inflammation in Chronic Pain, Migraine, and Fibromyalgia.* Dr Vasquez has served as a consultant to Biotics Research Corporation.

In This Issue

We start this issue with appreciation for Associate Editor David Riley, MD who set up and lead the excellent Case Report series for *IMCJ*. With great sadness we announce that David is retiring from his editorial position. Thank you David for your excellent work demonstrating that carefully and rigorously designed patient reports are a credible way of providing scientific documentation of efficacy of the personalized medicine we advocate.

As usual, Associate Editor Jeffrey Bland, PhD kicks off this issue. His very interesting Commentary dives deeply into the fasting and para-fasting research. Having myself supervised hundreds of 4- to 30-day water-only fasts, I've substantial experience in this area. This is a good example of how using PubMed-indexed research totally misses the hundreds of years of successful clinical fasting expertise that is found in natural medicine books and clinicians. A good example to the non-MD community of the importance of documenting our work. Those interested in learning more about this very useful therapeutic modality will find the fasting chapter (first published in 1985) in my *Textbook of Natural Medicine* very helpful, as well as the patient handouts in the Appendix.

George W. Cody, JD, MA, continues his series on the origins of integrative medicine. In this article he covers some of the key contributions from the chiropractic profession.

Regular contributor John Weeks discusses the huge challenge facing doctors of integrative medicine who use compounding pharmacists to personalize drug prescriptions for their patients. This problem is fully addressed by attorney Alan Dumoff, JD, MSW who has lead the fight to protect this important resource for our patients. The article he wrote for IMCJ can be found in issue 17.3. As usual, he has many other interesting briefs about the politics and business of this medicine. The results of the poll assessing the percent of cancer patients who believe alternative medicine has a cure are quite surprising.

Tom Blue has written two interesting articles on public interest in this medicine and the many challenges facing clinicians trying to make this work financially. His several suggestions are worth serious consideration. His considerable experience with concierge medicine provides useful insights.

One of the most fun and gratifying responsibilities as editor is being able to interview the special people who have created and practice this medicine. Managing Editor Craig Gustafson interviewed expert functional medicine neurologist and my friend David Haase, MD. His insightful ideas on stress, pain, and addiction are very helpful, especially in this era of prescription pain medication abuse.

Original research by David S. Riley, MD; Viktor G. Lizogub, PhD; Marianne Heger, MD; Petra Funk, PhD;Heiko Mueller, Walter Lehmacher evaluates the efficacy of *Pelargonium sidoides* root in the treatment of the common cold. This multi-center, randomized, double-blind phase III clinical trial with 105 adults showed clear efficacy. Having personally used Umcka for over 10 years, I can attest that these results are consistent with my experience.

Self-insured corporations have, in my experience, been the most receptive to health promotion. Corporate wellness programs are a great way to demonstrate the efficacy of the concepts of our medicine. Managing editor Craig Gustafson interviewed Richard E. Johnson, JD, a health strategy expert. Those interested in working in this area will find a lot of value here.

Remarkable serendipity that Associate Editor Bill Benda, MD finishes the issue with the same concerns with which we started: Time to get back to the Truth. Journals of science are published as part of our community efforts to objectively understand the world. The truth decay in research which Alex and I addressed seems a sad symptom apparently escalating throughout our society.

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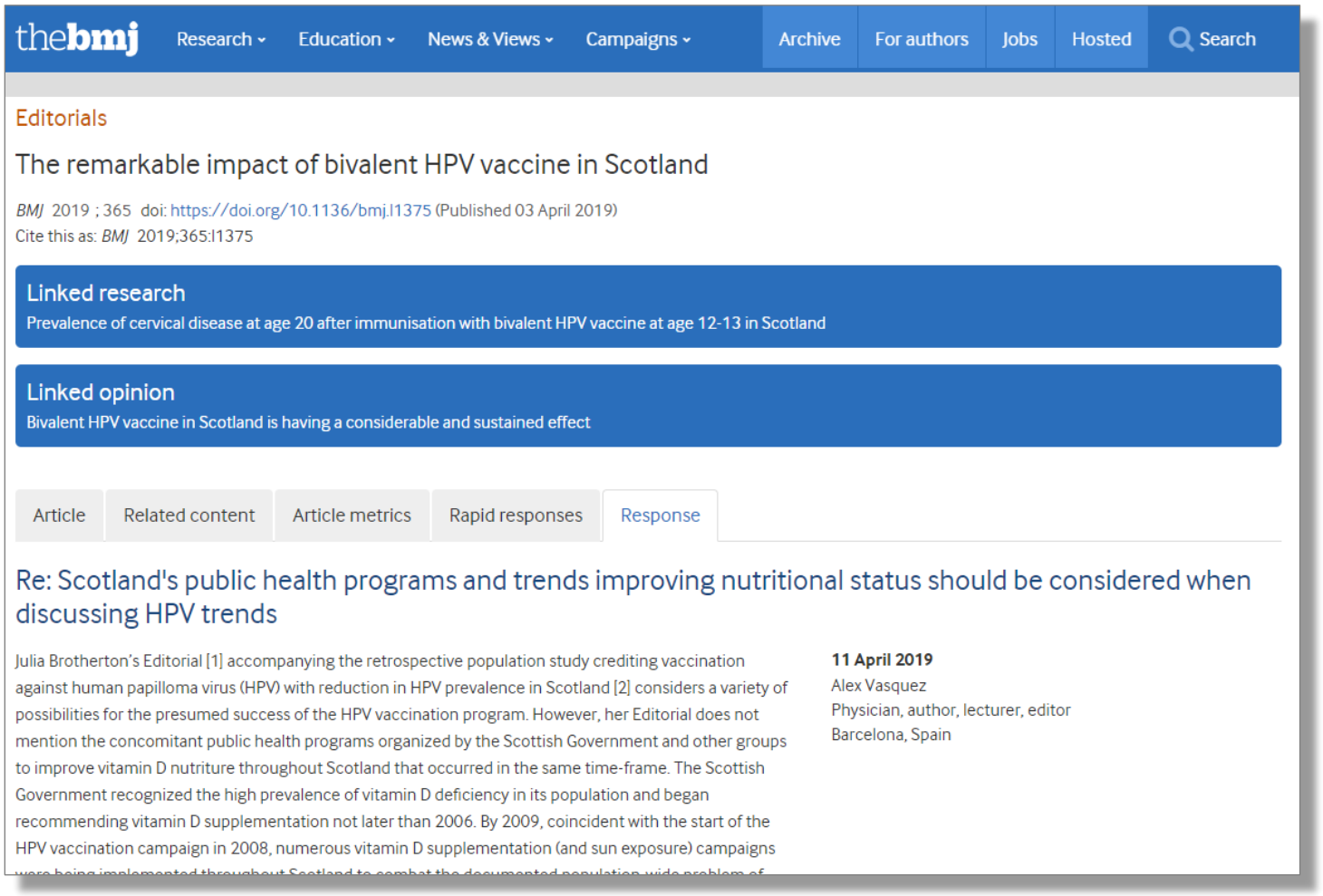

Re: Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends

Julia Brotherton's Editorial [1] accompanying the retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland [2] considers a variety of possibilities for the presumed success of the HPV vaccination program. However, her Editorial does not mention the concomitant public health programs organized by the Scottish Government and other groups to improve vitamin D nutriture throughout Scotland that occurred in the same time-frame. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century, with key publications starting in 1999 [3-6]. We now have increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary

supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements (and sun exposure) to combat the high prevalence of vitamin D deficiency in Scotland [11-23].

Vitamin D supplementation has been the subject of several placebo-controlled trials documenting anti-inflammatory, antiviral, and anticancer effects. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (CIN I, CIN II): vaginal vitamin D (high dose) treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published "Effects of Long-Term Vitamin D Supplementation on Regression and Metabolic Status of Cervical Intraepithelial Neoplasia" in which they summarized, "In conclusion, vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism, plasma NO, TAC, GSH and MDA levels." In 2018, Vahedpoor and colleagues [39] published "Long-Term Vitamin D Supplementation and the Effects on Recurrence and Metabolic Status of Cervical Intraepithelial Neoplasia Grade 2 or 3" in which they noted, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity; use of nutritional supplements that contain or potentiate vitamin D had started to increase in the population by 2003. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially misleading, especially when these authors make no account whatsoever of the national program for vitamin D supplementation which started in the same time-frame. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

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Competing interests: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, and the human microbiome. Dr Vasquez has served as a consultant to Biotics Research Corporation.

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

In April 2019, Palmer et al [1] published a retrospective population study crediting vaccination against human papilloma virus (HPV) with reduction in HPV prevalence in Scotland, and the authors attributed a reduction in HPV prevalence among unvaccinated women with "herd protection." However the authors did not mention Scotland's population-wide public health campaigns to address endemic vitamin D deficiency. The Scottish Government recognized the high prevalence of vitamin D deficiency in its population and began recommending vitamin D supplementation not later than 2006. Vitamin D deficiency results in impaired mucosal and immune defenses and correlates in a dose-dependent manner with increased cervicovaginal HPV infection [2]. By 2009, coincident with the start of the HPV vaccination campaign in 2008, numerous vitamin D supplementation (and sun exposure) campaigns were being implemented throughout Scotland to combat the documented population-wide problem of vitamin D deficiency.

Our views of vitamin D experienced a paradigm shift in the early part of this century with landmark publications such as Vieth's authoritative documentation of safety in 1999 [3], Zittermann's "Vitamin D in

preventive medicine" in British Journal of Nutrition in 2003 [4], and Vasquez's "Clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers" in 2004 [5] followed by an important partial summary of vitamin D usage guidelines in British Medical Journal in 2005 [6]. These and similarly themed articles have contributed to increased awareness of vitamin D's safety and roles in preventive medicine and public health, including reducing the burden of infectious diseases such as viral infections and various types of cancer. Consistent with this evidence of safety and benefit, along with evidence that the human daily requirement is an order of magnitude greater than previously believed [7], use of vitamin D supplementation began to increase slowly and then exponentially in the United States [8] and other countries, especially English-speaking societies, most notably the United Kingdom. Indeed, according to the Scottish Health Survey 2003 [9], use of dietary supplements such as vitamins (including vitamin D), fish oils (a source of vitamin D) and minerals (magnesium supplementation improves vitamin D status and is necessary for vitamin D activation, binding, transport, metabolism, and gene expression [10]) had already begun to increase between 1998 and 2003. Certainly not later than 2006, the Scottish Government was already recommending widespread use of vitamin D supplements to combat the high prevalence of vitamin D deficiency in Scotland [11].

Widespread vitamin D deficiency in Scotland was followed by widespread recommendations for vitamin D supplementation starting in 2006 and 2009. In 2006, Burleigh and Potter published in Scottish Medical Journal [12] stating that, "The prevalence of vitamin D deficiency is high in older outpatients in this geographical area." In 2007, Hyppönen and Power [13] showed that among British adults "Prevalence of hypovitaminosis D in the general population was alarmingly high during the winter and spring, which warrants action at a population level rather than at a risk group level." In 2008, Rhein [14] further specified that "Vitamin D deficiency is widespread in Scotland." In 2009, the Scottish Government acknowledged the need to educate its population about the importance of vitamin D3 supplementation [15]. From that time until the present, the Scottish Government, United Kingdom National Health Services, and various advocacy groups and programs (e.g., ScotsNeedVitaminD.com[16], Healthy Start, which provides vitamin D supplements to all children and pregnant women in Scotland [17]) continue assertive public health campaigns recommending vitamin D supplementation and increased vitamin D production via sun exposure via the "Shine on Scotland" program initiated in 2009 [18] for all of its citizens [19-23].

Vitamin D supplementation has been the subject of many clinical trials documenting anti-inflammatory, antiviral, and anticancer benefits. Correction of vitamin D deficiency has significant anti-inflammatory [24] and immunomodulatory [25] benefits. Vitamin D and its direct metabolites promote production of antimicrobial peptides which have antibacterial and antiviral properties, while also reducing viral replication by inhibiting the NF-kappaB pathway. Consistent with these immunomodulatory and antiviral mechanisms, data from several placebo-controlled trials shows that vitamin D provides benefit in a variety of infectious conditions including human immunodeficiency virus (HIV) [26], hepatitis C virus [27-29] and upper respiratory infections [30-31]. Vitamin D administration displays impressive clinical effectiveness against dermal HPV as shown in case reports, clinical series, and placebo-controlled trials, with remarkable safety, high efficacy, and a consistent trend toward complete resolution of lesions [32-36]. In 2014, Schulte-Uebbing et al [37] published "Chronical cervical infections and dysplasia (cervical intraepithelial neoplasia [CIN] 1-2): vaginal vitamin D treatment" showing that among 200 women with cervical dysplasia, vitamin D vaginal suppositories (12,500 IU, 3 nights per week, for 6 weeks) provided "very good anti-inflammatory effects" and "good antidysplastic effects" in women with CIN 1. In 2017, Vahedpoor and colleagues [38] published a double-blind placebo-controlled trial of vitamin D in women with HPV, in which they found that vitamin D3 administration for 6 months among women with CIN1 resulted in its regression and had beneficial effects on markers of insulin metabolism and antioxidant status. In 2018, Vahedpoor and colleagues [39] published a

double-blind placebo-controlled trial of vitamin D in women with HPV, in which they observed, "The recurrence rate of CIN1/2/3 was 18.5 and 48.1% in the vitamin D and placebo groups respectively", thereby clearly favoring treatment with vitamin D over placebo.

In Scotland, programs advocating HPV vaccination (started in 2008) and vitamin D supplementation (started not later than 2006 and again in 2009) occurred in close chronologic proximity. Crediting the reduction in HPV-related disease solely to vaccination via retrospective population study is potentially invalid and misleading, especially when the authors make no account whatsoever of the national program for vitamin D supplementation which started in the same timeframe. Numerous studies have shown that vitamin D provides immunomodulatory, anti-inflammatory, microbiome-modifying, antiviral and anti-HPV benefits with high safety, good efficacy, low cost, wide availability, and clinically important collateral benefits.

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13 April 2019

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Competing interests: Dr Alex Vasquez is a lecturer and author of numerous articles, letters, and books related to topics of nutrition, clinical medicine, neuroinflammation, and the human microbiome. Dr Vasquez has served as a consultant to Biotics Research Corporation.

A Reprint From the *Textbook of Functional Medicine*

WEB-LIKE INTERCONNECTIONS OF PHYSIOLOGICAL FACTORS

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Introduction

Understanding the scientific basis and clinical applications of functional medicine and a "whole patient" approach to health care requires that clinicians fully appreciate the interconnectedness of organ system function with biochemical and physiological processes. Simplistic models of health and disease developed decades ago may no longer be accurate or clinically useful insofar as they fail to reflect the more recently discovered complex and multifaceted interrelationships. (Figure 10.2 uses the functional medicine matrix to depict some of this complexity.) Numerous mechanisms mediate these interrelationships, including, but not limited to, those that can be described as biochemical, hormonal, neurological, immunological, piezoelectric, and physical or mechanical. Ultimately, we are forced to dissolve the artificial intellectual boundaries we have created between organ systems and expand our appreciation of individual molecules, cellular messengers, and the physiologic mechanisms that mediate intercellular communication and coordinate interorgan function.

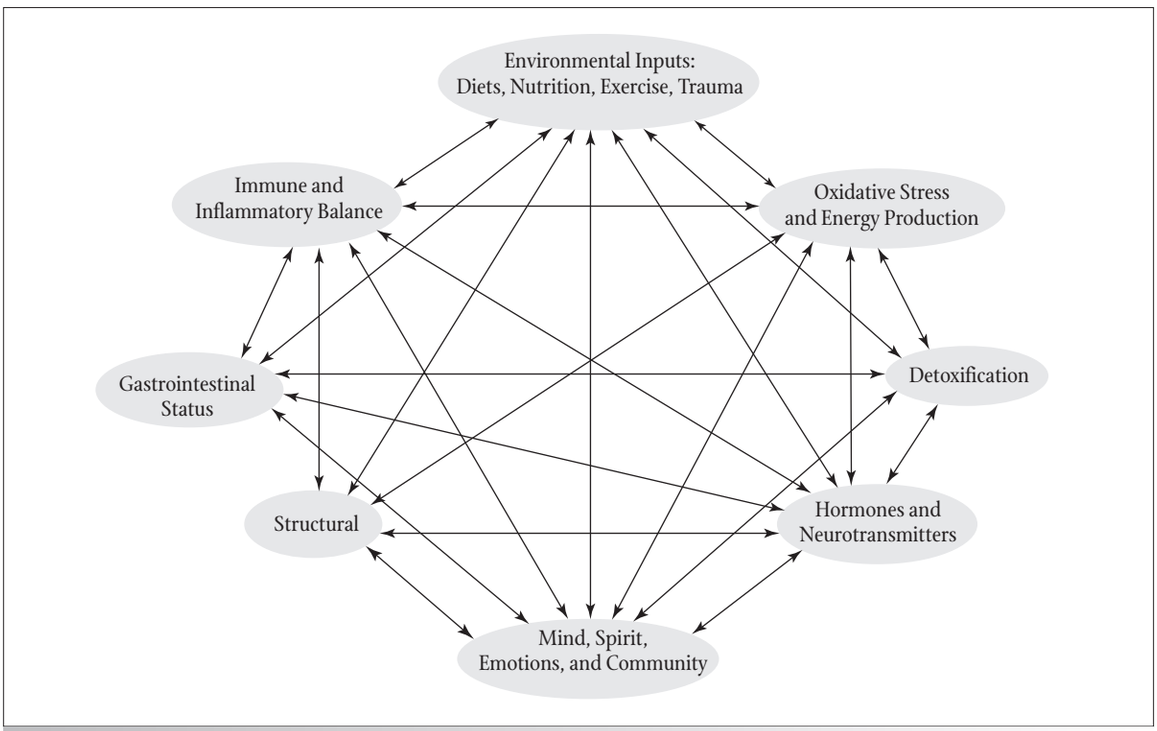

FIGURE 10.2
FUNCTIONAL MEDICINE MATRIX

Web-like Interconnections of the Functional Medicine Matrix

The following discussion provides some specific examples of this profound interconnectedness that is a foundational principle of functional medicine. We will survey current research literature documenting the interconnected nature of some key organ systems and disease processes. With these examples, clinicians will better appreciate how the gastrointestinal, immune, cardiac, neurologic, and other systems interact with and depend upon each other for optimal physiologic function. Likewise, clinicians will understand more completely how essentially any dysfunction or lesion in the body can have clinically significant implications and distant adverse effects. From this perspective, individualized clinical interventions can be designed and employed to deliver better health outcomes.

Gastrointestinal Tract and Liver

While the liver and the gastrointestinal tract share an obvious anatomic connection via the portal circulation, the functional clinical implications of this connection are often not fully appreciated. Not only is the gastrointestinal tract the recipient of massive amounts of "external information" in the form of nutrients, toxicants, and allergens that weigh in at more than 1,538 pounds (700 kilograms) per year, but the gastrointestinal tract is also a reservoir for the several hundred species and subspecies of yeast, bacteria, and other microbes with the potential to modify hepatic function (e.g., detoxification) and overall health (e.g., immune response) by numerous mechanisms and with positive effects or negative consequences.

The various organs and tissues of the gastrointestinal tract perform the complex functions of digestion, absorption, exclusion, excretion, immunologic defense, antigen sampling, and temporary storage of food residues and other substances that have been ingested. The mucosa is selectively permeable and allows the absorption of nutrients and other molecules via transcellular and paracellular routes. Compromise of mucosal integrity due to injury from antigens, infection, systemic inflammation, or toxicants such as ethanol or nonsteroidal anti-inflammatory drugs, increases absorption of potentially harmful substances that are normally excluded when mucosal integrity has not been breached. Materials that are harmless when rejected by the selectivity of the intestinal mucosa can, when inappropriately absorbed, serve as a source of inflammatory and immunogenic stimuli for the embedded macrophages in the liver (Kupffer cells) and also for the systemic immune system and the brain's embedded astrocytes and microglia. This phenomenon is clearly demonstrated by the neurological complications and focal white-matter lesions seen in the brains of patients sensitized to the dietary antigen gluten; in this scenario, it appears that dietary antigens cross a damaged mucosal lining and escape filtration by the liver to produce a systemic inflammatory response that manifests clinically as neurologic disease.[23,24] It seems likely that other antigens are also capable of inducing a systemic inflammatory response in susceptible individuals.

The two most voluminous substances in the gastrointestinal tract are food antigens and microbial metabolites and debris, notably lipopolysaccharides (LPS, endotoxin) from gram-negative bacteria. These foreign substances normally excluded by an intact mucosa can serve as mediators of physiologic disruption (hence the importance of their exclusion), and indeed this is what has been observed in experimental and clinical data. For example, in patients with autism, increases in inflammatory mediator production are seen following exposure of monocytes to dietary allergens and LPS.[25] We also note that LPS is a potent inhibitor of numerous cytochrome P450 biotransformation pathways, thus leading to impaired drug metabolism as demonstrated in recent clinical trials.[26,27] The implications of these data are profound and correlate closely with phenomena observed in clinical practice, namely that patients with irritable bowel syndrome—a condition causatively associated with both food intolerance and bacterial overgrowth of the small bowel—commonly report environmental sensitivity and medication intolerance. One plausible answer to the conundrum of the chronically unwell patient—typified by the patient with chronic fatigue or environmental illness—now becomes clear: overgrowth of the small bowel with LPS-producing bacteria leads directly to the gastrointestinal symptoms of gas and bloating, with immune system activation,[28] and also reduces hepatic clearance of metabolites, toxicants, and xenobiotics to which the patient eventually becomes sensitized (immunologically and/or non-immunologically). This explains, at least in part, the rationale for and impressive clinical efficacy associated with the implementation of clinical therapeutics that simultaneously improve intestinal microecology, improve mucosal integrity, and provide biochemical/nutritional support for the processes of detoxification.[29,30]

Gastrointestinal Tract and Immune System

Any discussion of the role of the gastrointestinal tract in relation to the immune system must include a view of the gut that is inclusive of its contents of food antigens, intraluminal microbes, and their debris and metabolic products. When the gut is simply pictured as a passive semi-sterile tube with food entering one end and feces exiting the other, then it would appear an unlikely locus of immunogenic stimulation and neurogenic inflammation that can have systemic health consequences.[30-35] Conversely, appreciation of the manifold quantitative and qualitative variables that can exist hidden from both the clinician's external view and the endoscopist's internal

camera enables practitioners to have a more realistic perspective on the influence that gastrointestinal function, dietary antigens, and microflora can have on extra-gastrointestinal processes and overall health.[36,37]

The combination of a hypersensitive/dysregulated immune system and exposure to dietary antigens sets the stage for the clinical phenomenon commonly described as "food allergy." Diverse in frequency, duration, severity, and quality, these immune-mediated adverse reactions to foods can precipitate or exacerbate a wide range of clinical manifestations including rhinoconjunctivitis, chronic sinusitis, dermatitis, epilepsy, migraine, hypertension, joint inflammation, and mental depression.[38,39] The immunopathogenesis generally includes multiple mechanisms and is not limited to mediation via IgE antibodies and histamine. Indeed, the pathophysiology of "food allergy" is commonly seen with numerous (not singular) aberrations in physiologic function, including responses mediated by or resultant from antibodies (including IgE, IgG, and/or possibly IgA classes of antibodies), cytokine-mediated responses (e.g., TNF-α), increased intestinal permeability, occult gastrointestinal inflammation, and alterations in gastrointestinal microflora.[40] To be more complete, our conceptualization of "food allergy" must also include awareness of enterometabolic disorders (i.e., the inter-connections between food, intestinal flora, and systemic health[41]) as well as contributions from neurogenic inflammation (i.e., the translation of immunogenic inflammation to a neurologic signal with systemic proinflammatory effects[42]).

Aberrations in gastrointestinal microflora can provoke a cascade of physiologic responses that may lead to widespread physiologic imbalances and result in a variety of clinical manifestations that may or may not conform to a recognized pattern or named disease even though the patient is highly symptomatic.[43] Furthermore, we can conclude from recent literature that the concept of molecular mimicry is now well established and that it provides us a model with which to apprehend the induction of immune dysfunction (especially autoimmunity) by microorganisms with immunogenic epitopes that are structurally similar to those in human tissues.[44] Thus, the link between "dysbiotic" gastrointestinal flora such as *Klebsiella pneumoniae* and systemic immune-mediated inflammatory disorders such as ankylosing spondylitis and chronic uveitis has a biological and scientific basis. Individualized assessment and treatment of such dysbiotic loci, whether in the gut, genitourinary tract, or nasopharynx, are likewise supported by current research and offer the hope of cure rather than an endless and additive cycle of anti-inflammatory and anti-rheumatic drugs. For example, evidence now shows that the systemic autoimmune disease Wegener's granulomatosis may be triggered and perpetuated by molecular mimicry with occult respiratory infections caused by *Staphylococcus aureus*, and that eradication of the infection can result in clinical improvement and reduced need for ongoing anti-rheumatic medication.[45-47] In addition to molecular mimicry, microbes (i.e., occult infections and environmental exposures) can also alter immune regulation by serving as a source of superantigens, which cause widespread and multifaceted immune dysfunction with resultant proinflammatory effects contributing to the exacerbation of allergy and autoimmune disease.[48]

Immune System and Cardiovascular System

The role of subclinical inflammation in the etiopathogenesis of atherosclerosis is no longer an issue of conjecture, as it has become a well-established aspect of the disease process. Even slight elevations in high-sensitivity C-reactive protein are associated with a significantly increased risk for cardiovascular morbidity and mortality in otherwise "apparently healthy" individuals.[49] With the increasing irrefutability of these data, pharmaceutical companies have scrambled to develop and sell drugs that can reduce this low-level inflammation, while physicians with a broader perspective have directed their energies toward intensifying their patient-centered search for the source(s) of inflammation in each individual patient. For example, subclinical inflammation can result from dietary indiscretion,[50] disturbed sleep,[51] and vitamin D deficiency;[52] in any of these situations, addressing the underlying causes of the inflammation with multicomponent nutritional/lifestyle interventions may deliver more effective health improvement than can the long-term use of inflammation-suppressing medications.[53-55]

Gastrointestinal Tract, Liver, and Neurologic Systems

The last several years have witnessed an increased appreciation for the influence that the gut and liver have on the brain, and advancements in functional assessments are now documenting analytically what was at one point known only clinically—that the status of the gut and liver have profound effects on the functioning of the brain. Evidence supporting the existence of a clinically important gut-brain interconnection has been published consistently over many decades and in major journals. Today, among the most poignant examples are Parkinson's disease and the autistic spectrum disorders. Indeed, the strength of evidence supporting the hepatogastrointestinal link with these "neurologic" conditions is so strong that it could be logically argued that any treatment of these conditions that does not address the hepatic and enteric aspects of these diseases is therapeutically incomplete.

Although Parkinson's disease was once considered idiopathic, we now recognize it as being a multifaceted

disorder associated with defective mitochondrial function, impaired xenobiotic detoxification, and occupational and/or recreational exposure to toxicants, particularly pesticides. These associations align to create a new model for the illness based on exposure to neuro-toxicants such as pesticides,[56] which are ineffectively detoxified[57] and then accumulate in the brain,[58] inducing mitochondrial dysfunction[59] and oxidative stress,[60] and leading to the death of dopaminergic neurons. Therefore, from the perspective of both prevention and treatment, the clinical approach to Parkinson's disease must include pesticide avoidance and optimization of detoxification to prevent the neuronal accumulation of neurotoxic mitochondrial poisons. The plan must also include optimization of nutritional status, antioxidant capacity, and mitochondrial function.[61]

The view that autism is a behavioral problem unfortunately continues to permeate present-day medical treatment of this condition, and many pediatricians and psychiatrists still advise only behavioral therapy and medicalization with psychoactive pharmaceuticals, particularly selective serotonin reuptake inhibitors (SSRIs).[62,63] While these interventions produce modest improvements over those seen in control groups, neither intervention remotely addresses the complex underlying physiology nor offers the possibility of cure, and SSRI use in children is highly controversial due to the association with increased incidence of suicide.[64] We now know that autism is a multifaceted disorder associated with gastrointestinal inflammation, nutritional deficiencies,[65] multiple food allergies and intolerances,[66] impairments in liver detoxification and resultant accumulation of xenobiotics, the majority of which have neurotoxic and/or immunotoxic effects.[67] Thus, autism is not a behavioral disorder *per se*; rather, it is a gastrointestinal-allergic-immunological-toxicant-nutritional-environmental disorder, and the behavioral/cognitive abnormalities are symptoms of the underlying complex and interconnected pathophysiology.

Musculoskeletal System, Neurologic System, Immune System

The adverse effects of a dysregulated immune system upon the musculoskeletal system are well known for their contributions to autoimmune diseases such as rheumatoid arthritis. In this classic scenario, the immune system is the effector, and periarticular structures, synovium, and joint surfaces are the targets of inflammatory and destructive processes that result in joint destruction and pain that affect the musculoskeletal and neurologic systems, respectively. This model holds that the direction of events flows from the immune system (autoimmunity) to the musculoskeletal system (target site) to the nervous system (perception of pain). This popular model must be updated in light of current research.

The phenomena of neurogenic inflammation and neuronal plasticity demonstrate the active, effector functions of the sensory nervous system and exemplify the extent to which the Cartesian model of the sensory nervous system (i.e., as exclusively afferent and passively receptive) is no longer valid.[68,69] Much of the musculoskeletal inflammation seen in clinical practice appears due, in large part, to inflammation that originates from and is mediated by the sensory nervous system through the release of proinflammatory mediators from sensory nerves in periarticular tissues.[70,71] Furthermore, evidence is accumulating that neurogenic inflammation can result from a heterogenous group of diverse stimuli, including allergens, environmental chemicals, and pain distant from the site of arthritis.[72,73] Likewise, evidence that intentional relaxation[74] as well as acupuncture[75] can modulate inflammatory pathophysiology indicates that psychoemotional variables and nonbiochemical therapeutics are important clinical considerations for patients with inflammatory diseases.

Evidence also suggests that musculoskeletal therapeutics such as spinal manipulation may influence immune responsiveness. Brennan et al.[76,77] showed that chiropractic spinal manipulation resulted in an acute increase in phagocytic capacity of polymorphonuclear neutrophils, and that this result was seen only following authentic (versus sham) manipulation, and that the effect was proportional to the increase in serum levels of substance P, a multifunctional molecule that acts as a neurotransmitter as well as a proinflammatory messenger. While the clinical implications of these data are yet to be clarified, they clearly demonstrate that the immune system is sensitive to mechanical stimuli.

Beyond Biochemistry and Neurophysiology: Piezoelectricity as a Mechanism for Intersystem Connectedness

Piezoelectricity, the continuum between mechanical stress and bioelectric conduction, is a well-established aspect of organic matter, affecting all vertebrates and, therefore, humans. Notably, the nervous system in general and the spinal cord in particular demonstrate an intrinsic dipole moment that is demonstrable across species of vertebrates.[78,79] In 1977, Lipiski from Tufts University School of Medicine[80] summarized the current research of the day and speculated on the effects of spinal manipulation, yoga, and acupuncture as mediated via the body's inherent pyroelectric and piezoelectric properties. Lipinski's literature review (particularly including the work of Bassett[81]) suggests that "piezo-electricity present in many biological systems may theoretically control cell nutrition, local pH, enzyme activation and inhibition, orientation of intra- and extra-cellular macromolecules, migratory and proliferative activity of cells, contractility of permeability of cell mem-

branes, and energy transfer." With these concepts and possibilities considered, we can construct a conceptual bridge linking mechanical stimuli such as massage, manipulation, exercise, and yoga, and (neuro)electrical stimuli such as acupuncture, meditation, prayer and intentionality, to plausible biochemical/physiological effects that translate into observed clinical benefits. This integrated model helps to explain the effects of "energetic" therapeutics such as moxibustion, acupuncture, and yoga that may be mediated by nonbiochemical physiologic mechanisms. Furthermore, this model also helps us to understand hitherto unexplainable phenomena such as the well-reported sensitivity that some people display to changes in the weather and the positioning of their bodies in relation to electromagnetic fields of the planet, electrical equipment, and power lines. Piezoelectricity may also be the physiologic conduit that transmits the effects of "distance healing," prayer, and intentionality.[82-84]

Summary

Human physiology is complex and treatment plans must be multifaceted to reflect this complexity. Cells, tissues, and organ systems work in concert—not in isolation—and therefore effective intervention generally requires improvement in numerous organ systems. As the artificial boundaries between organ systems dissolve, a unifying theme emerges, namely that the attainment, preservation, and re-establishment of health must be all-encompassing. Programs and paradigms related to the treatment of disease and the attainment of optimal health must reflect appreciation of environmental, physical, mental/emotional, nutritional, biochemical, hormonal, immunologic, neurologic, and gastrointestinal components of our existence that coalesce without boundaries to make the human body and our experience of life itself. Thus, new frontiers in health care will be reached not solely when new discoveries occur, but also when the integration of these discoveries into a cohesive, multifaceted, unified healthcare model prepares the way for more accurate understanding and more effective interventions. Healthcare providers of diverse backgrounds (e.g., ND, DC, MD, DO, RD, RN, LAc, and others) can and must work together to offer scientifically-based, multifactorial interventions that are adapted to the specific needs of individual patients.

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Correction • Post-Publication Review • Editing • Public Health • Media • Medical Misinformation

Correcting the Misinforming of Millions in *New York Times*' "Supplements for Coronavirus Probably Won't Help, and May Harm" published March 23, 2020

critique by Dr Alex Vasquez

Introduction

The scaffolding of our institutionalized ignorance (discussed later) requires structural support from publications and organizations that pretend to inform and empower us while simply leaving us dumber and weaker than before. On March 23 of 2020, *New York Times* (NYT) published the article "Supplements for Coronavirus Probably Won't Help, and May Harm: Worried Americans are scrambling to buy wellness products they think will protect against coronavirus. Some may do harm."[1] This critique will sequentially outline the structure and errors of the above-mentioned publication.

Critique en breve

1. Start with zero, and do not advance: The article opens with meaningless trivia and anecdotes. If this article had been intended to actually and legitimately inform its paying readers, then the author would have begun the article with an engaging description of science. Written as it is, the article is neither informative nor engaging; it simply fills space and time, replacing legitimate writing and informing. Not only is the author ignorant of the topic, but the persons cited in the article as interviewees are likewise ignorant; thus, the resulting pseudojournalism is a mixed salad of inconsequential commentary and reflexive opinions.

> "A **red herring** is something that **misleads** or **distracts** from a relevant or important question. It may be either a **logical fallacy** or a **literary device that leads readers or audiences toward a false conclusion**." *Wikipedia*

2. Innuendos rather than science: The statement "Dietary supplement sales have surged nationwide as panicked consumers stock up on vitamins, herbs, extracts, and cold and flu remedies. None of these products have been shown to lower the likelihood of

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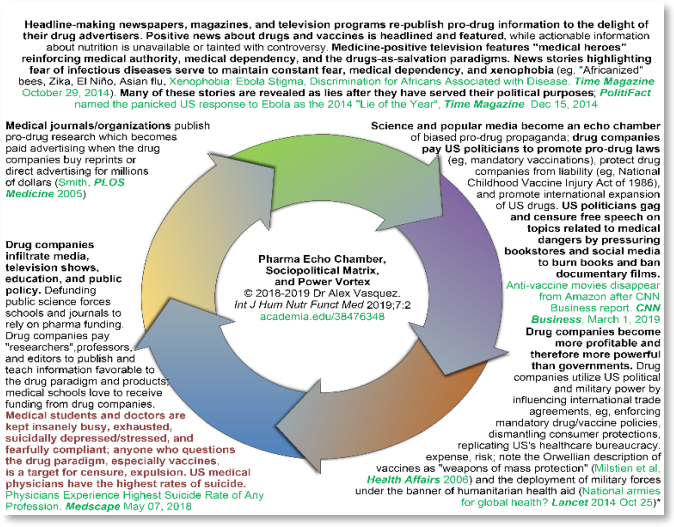
contracting the coronavirus or shortening its course, and taking large doses of them can potentially do harm" is the typical sleight of hand and pulling of the rug. The truth of the matter is that nutritional supplements have a long history of use against infectious diseases, and several have shown promise against various infections caused by coronaviruses, as I have recently (March 4, 2020) reviewed in an online video presentation[2] (Antiviral Strategies for Coronavirus) and previously in my 2014 ebook, *Antiviral Nutrition*.[3]

3. By starting the article with innuendo and suspicion, everything that follows is tainted: The statement "sales of zinc, a popular remedy for colds and respiratory illness, shot up 255 percent" could have been—but was not—contextualized by the fact that 30% of the world population is zinc deficient and—given that zinc sufficiency is necessary for proper immune function and zinc deficiency causes impaired defenses against a wide range of infectious diseases—**zinc deficiency contributes to more than 1 MILLION deaths every year**. While Americans commonly think of nutritional deficiencies as affecting only persons in other countries, the fact is that nutritional deficiencies run rampant (albeit mostly invisibly) throughout the American population; one recent study showed that 30% of American adults were at risk for adverse inflammatory and infectious events due to zinc deficiency. Relatedly, deficiency of the mineral selenium affects 15% of the world population, and deficiency of selenium increases risk for viral infections and mutation of those viruses into more aggressive infections (as documented in Vasquez, Coronavirus video, 2020 and *Antiviral Nutrition*).
4. Insignificant filler chit-chat about vitamin D (and melatonin) leaves readers nonadvanced: Instead, the author could have cited the 2017 meta-analysis and review published in the *British Medical Journal* showing that vitamin D supplementation reduces the risk of respiratory infections. Given that up to 30% of upper respiratory infections in adults are due to coronaviruses, the data showing vitamin D's general effectiveness against respiratory infections *implies* that vitamin D helps against coronaviruses.
5. Misunderstanding melatonin: The NYT chose the low-hanging fruit of "the growth in melatonin [sales] was probably related to an increase in stress-related sleep disruptions" instead of crediting buyers with their knowledge that melatonin is—in addition to a natural agent that promotes relaxation and sleep—antiinflammatory, antiviral, and anti-infectious. Their noninforming conversation about melatonin could have been substituted by data showing that melatonin has been used safely and effectively in a wide range of clinical studies, and that melatonin has been proven to save lives against infectious diseases such as sepsis in newborns.[3]
6. Positive comments about nutrition are buried in a bog of ambiguity: Positive comments attributed to clinical trials supporting the use of zinc, vitamin D, and elderberry are made impotent within the context of meandering babble written with the intention to dissuade.
7. More misinformation among the seemingly positive statements. The statement "Whole foods like fruits, vegetables, fish, poultry, nuts, legumes and milk contain a wide range of vitamins, minerals and phytochemicals — including zinc and vitamin D — that work in synergy to protect your health" appears reasonable and informative until one realizes that food sources (with the exception of cod liver oil) are insignificant sources of vitamin D, the daily requirement for which is approximately 4,000 IU (100 micrograms) per day, or—for larger and obese persons—more than double that amount. The legitimate nutritional need for vitamin D on a daily basis cannot be met by a "healthy diet" but can be met only with regular vitamin D supplementation and/or sun exposure. Again, optimization of vitamin D status for the prevention of infectious disease cannot be attained by diet alone without either supplementation or full-body sun exposure to maintain optimal levels.[4]
8. Fearmongering, both unjustified and undefined: The comment "overload their systems with large doses of supplements" is simply fear fodder. This article could have given useful information but instead provides grammatical mush with neither information nor utility. As such, this NYT article services the need of the medical-pharmaceutical echo chamber by 1) wasting time and opportunity that could have been used for reader-productive conversation and 2) directly discounting the importance of nutrition, thereby promoting drug-dependency by default.



Vicious cycle image: from *IJHNFM* 2019 academia.edu/38476348 See also citations[5,6]

Contextualization and Conclusion

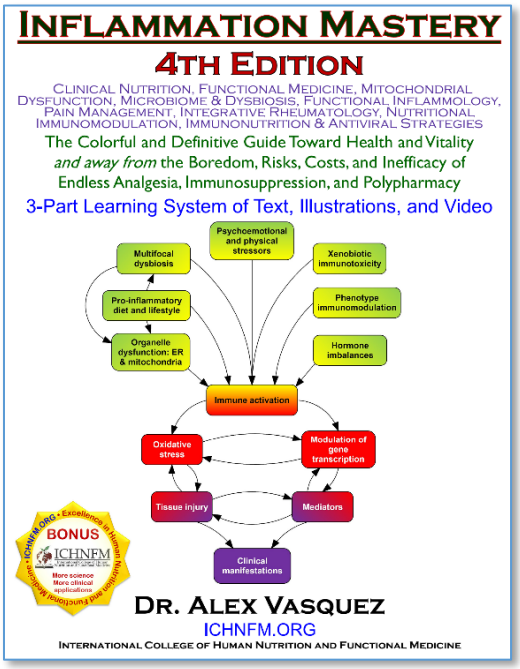
For propaganda and misinformation to function, they must have 1) a driving force behind them, 2) a receptive audience, 3) positive feedback, rewards for both parties. The driving forces behind medical misinformation and nutritional nihilism are a) the drug industry that wants patients and doctors to exclusively rely on drugs and injections, b) the medical profession that wants patients and doctors to exclusively rely on drugs, injections, and surgery, c) media outlets such as newspapers, magazines, journals, and television that receive hundreds of millions of dollars from drug companies in advertising revenue and—in the case of medical journals—article reprints that then function as advertisements in the hands of drug company representatives visiting doctors in their offices[7], d) hack writers and editors—generally without any training in the topics on which they write and approve, respectively—who are mostly trying to keep their jobs and increase profitability of their employing publication. Creating and maintaining a receptive audience for misinformation is numerically more grand but easier in design: 1) start by filling peoples' minds at a young age with illogical stories and impossible false realities to which the child must conform for the sake of approval, love, food and survival so that from childhood forward the now-adult has learned to turn-off critical thinking for the sake of superficial social acceptance, 2) make the process of education both *nearly worthless* and *completely exhausting* so that the noun *education* and the verb *study* will forever be repugnant and thus critical thought itself will be reflexively shunned, and 3) ensure that the tsunami of misinformation is so permeating and constant that people will either resign to be swept away with the current of simple-minded conformity or will abandon the conversation altogether and withdraw from any meaningful engagement. With either option, the dominating power structure maintains control of the disseminated narrative and the structure-serving thought and action that result. Different scripts and entirely different blueprints for practically-achievable positive potentialities are readily available, but people have to disengage from the mainstream zombie trough and seek real and guiding intellectual sustenance elsewhere. In our current situation with the 2020 pandemic, these are issues of justice, law, order, life and death; the alternate narrative to doom, gloom and helplessness is readily available to everyone. I have already reviewed these in ❶ *Antiviral Nutrition* (2014, republished in 2020), ❷ the re-introduction to my antiviral nutrition protocol in 2019 (3 hours of video at InflammationMastery.com/antiviral [free access]), and ❸ my more recent Antiviral Strategies for Coronavirus video (produced in March 2020).

Postscript regarding our institutionalized ignorance

I think the acknowledgement of our "systematized stupidity" is important if we are to deal with and overcome the same; however, I realize that some readers may bristle at the thought of it so I will provide some citations, experiences, and justification here, concluding with an optimistic solution.

1. First, from reflecting on my own educational experiences from ranging from having attended schools that are at least representative of commonplace education all the way to my completion of three doctorate degrees within fully accredited universities in the United States (also including a Pre-Doctoral Research Fellowship funded by the US National Institutes of Health), I can see that none of these educational programs taught anything related to critical analysis or the "higher order thinking" that they braggingly praised in their sales catalogs. All of these programs aimed to produce minimal competence and barely succeeded at that if they did at all. *Nutrition is untaught in medical education*.
2. Second, anyone can read the popular and well-respected *Dumbing Us Down* by John Taylor Gatto to gain legitimate insight into the role played by educational systems in keeping students and citizens imprisoned in ignorance and ineffectiveness.
3. Third, the influential scholar and educator Noam Chomsky has discussed this situation in some of his works and essays (e.g., How the Young Are Indoctrinated to Obey[8]) and most clearly in a lecture available in various locations online (e.g., youtube.com/watch?v=JVqMAlgAnlo) wherein he discusses his perspective that "Education Is a System of Indoctrination of the Young."
4. Fourth, a great example of structured ignorance is the multidecade observation that medical physicians receive zero training in Nutrition[9] despite the fact that many of the conditions they will treat for the rest of their professional lives are malnutrition-induced and/or modifiable or curable with the skilled use of clinical/therapeutic/functional nutrition. I have discussed these concepts in the more than 100 professional articles (free archive) that I have published in a wide range of journals, several hundred free videos (available at vimeo.com/drvasquez) as well as in my larger textbooks such as the 1200-page *Inflammation Mastery: Textbook of Clinical Nutrition and Functional Medicine*.[10]

The more independent study that one pursues, the more one reads legitimate works of culture and art such as Rand's *Fountainhead*, Nietzsche's *Zarathustra*, and even Orwell's *Nineteen-eighty-four*, then the more obvious becomes the systematic nature of our having been "dumbed down" and the more enthusiastically one can pursue its remediation. We are all undereducated, undertrained, and ignorant in areas where we would benefit from being knowledgeable, and we—individually and collectively—are the only ones who can improve our situation. The solution requires daily action.



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 a two-volume set titled 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 Editor (2018-2019) of *Journal of Orthomolecular Medicine*, published for more than 50 consecutive years by the International Society for Orthomolecular Medicine.

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CME
CONTINUING MEDICAL EDUCATION

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

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

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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.

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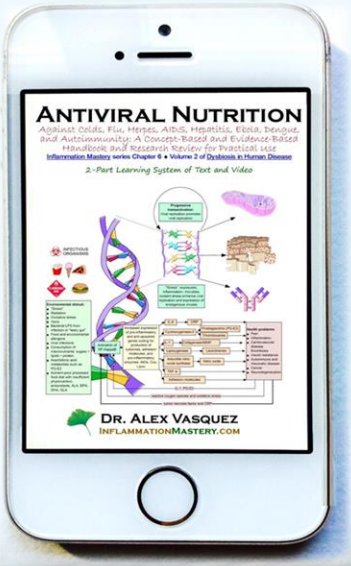

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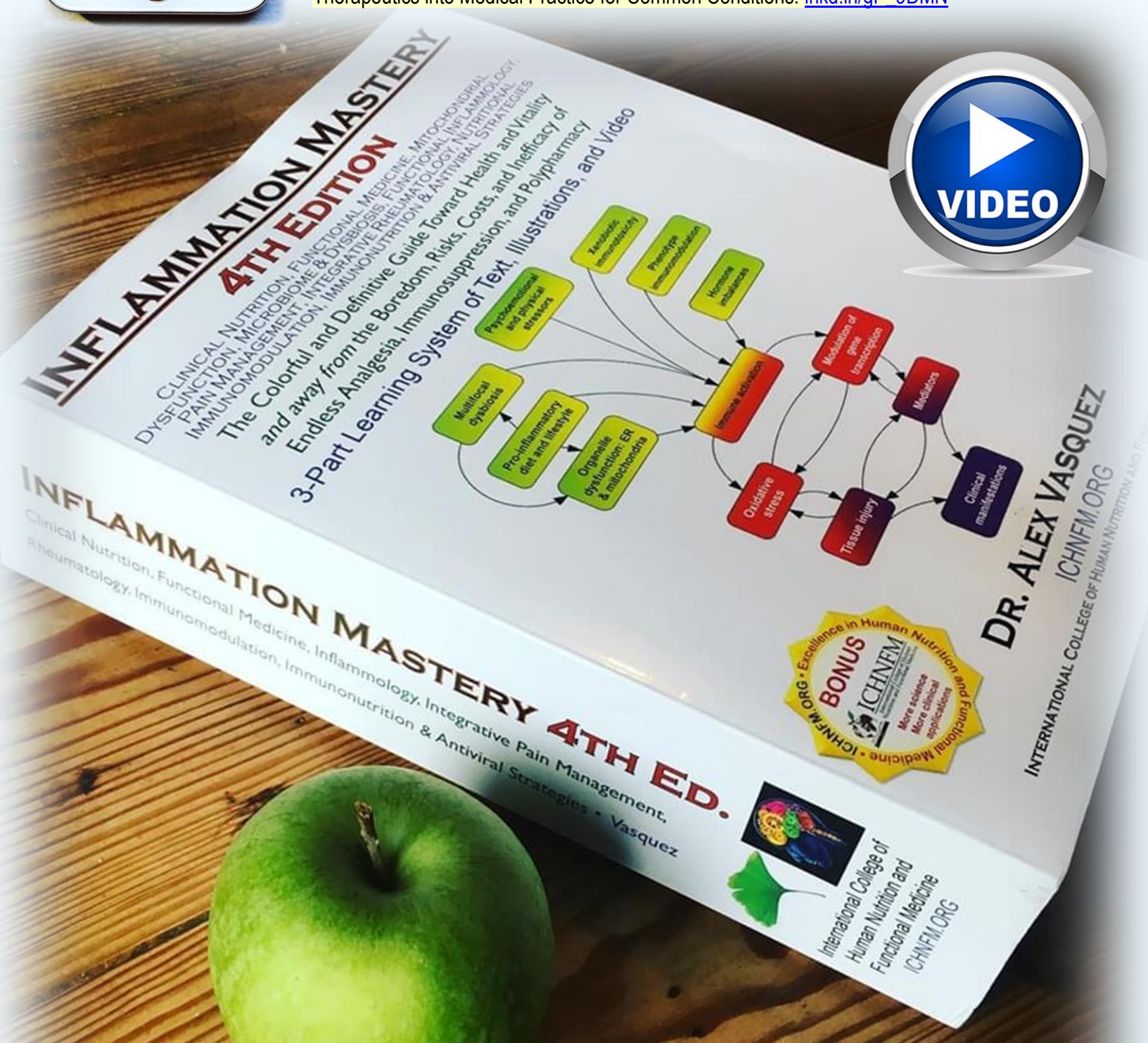


Polycystic Ovary Syndrome

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)

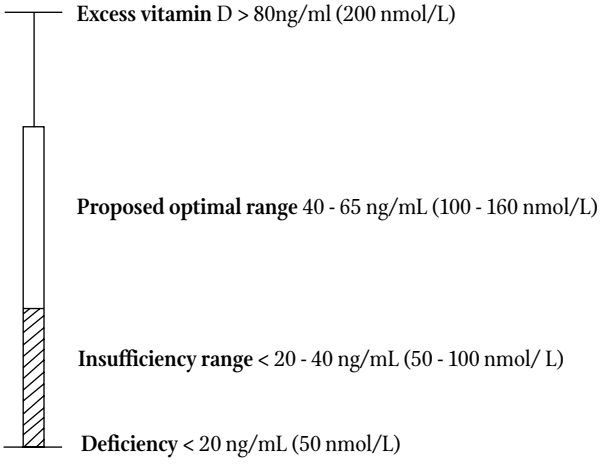
Based on our review of the literature, we propose that the optimal—"sufficient and safe"—range for 25(OH)D correlates with serum levels of 40–65 ng/mL (100–160 nmol/L).[55] This proposed optimal range is compatible with other published recommendations: Zittermann[11] states that serum levels of 40–80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

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

Alex Vasquez DO DC ND (USA) FACN

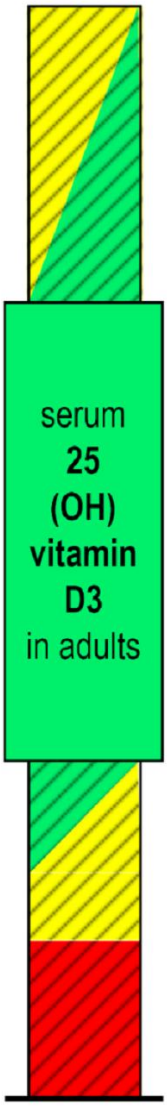
Vitamin D: Metabolism Dogma

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

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

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

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



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

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

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

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

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

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

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

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

4. Supplements should be tested for potency

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

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

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

6. Serum vitamin D levels must enter the optimal range

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

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

Vitamin D Supplementation in Adults

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

Vitamin D Supplementation in Pregnant Women

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

Vitamin D Supplementation in Infants and Children

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

Options for Raising Vitamin D Blood Levels

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

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

DISCUSSION AND CONCLUSIONS

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

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

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CME TEST QUESTIONS*

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

In the following questions, only one answer is correct.

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

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

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

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

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

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

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

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

See page 94 for Self-Assessment answers

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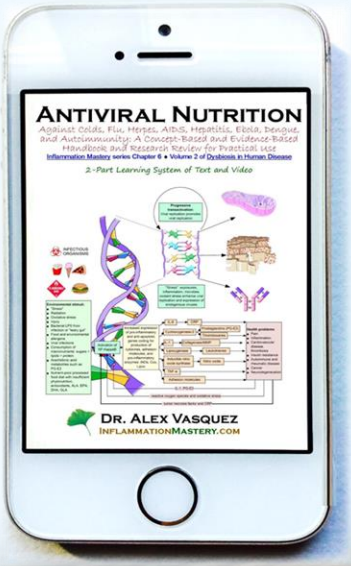

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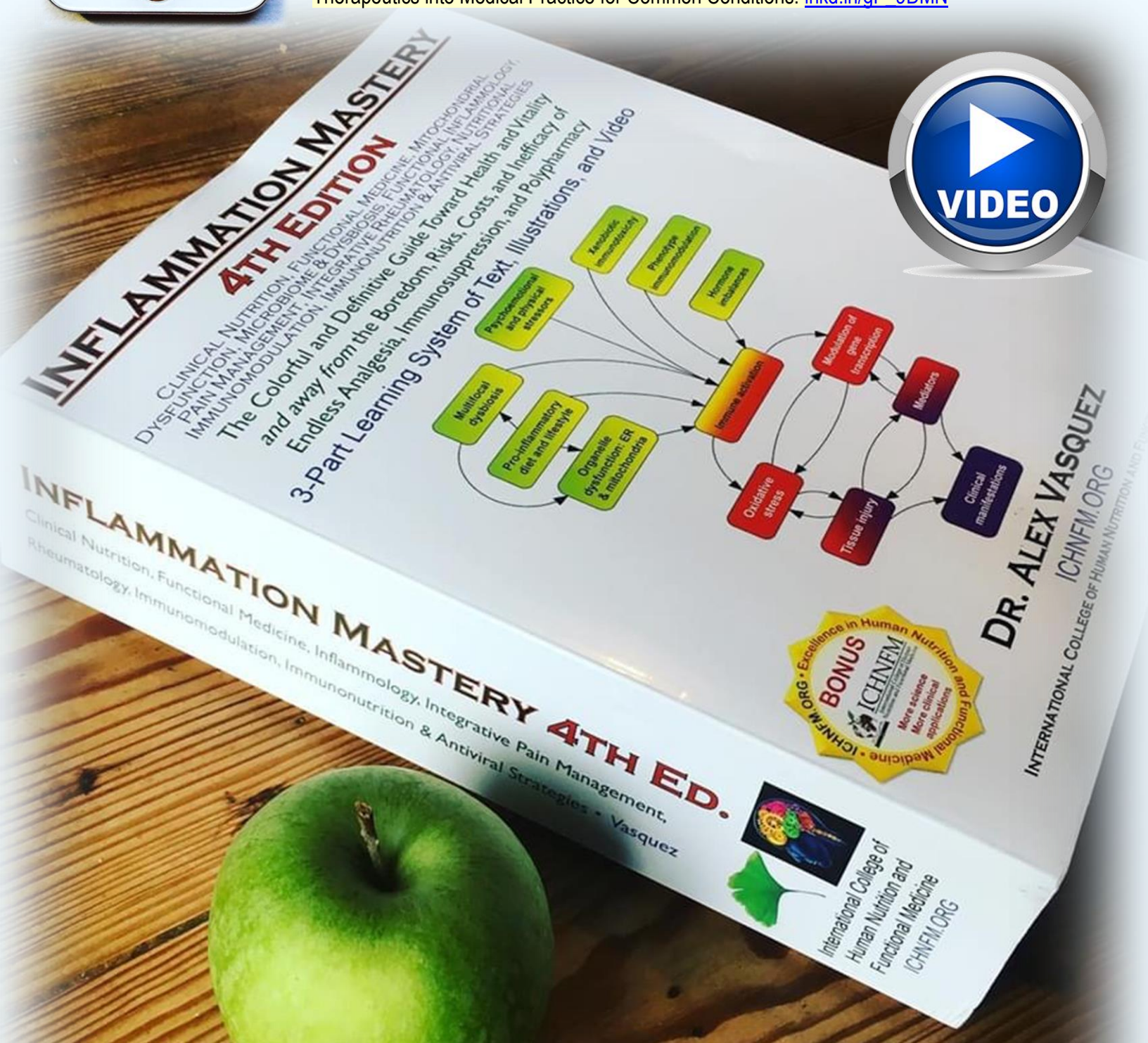


Call for Retraction (preprint): Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19 *JAMA* 2021

Alex Vasquez DO DC ND (USA)

Citation, summary, and implications

- **Citation**: Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: Randomized Clinical Trial. *JAMA—Journal of the American Medical Association* February 17, 2021
- **Authors**: Igor H Murai PhD, Alan L Fernandes PhD, Lucas P Sales MSc, Ana J Pinto BSc, Karla F Goessler PhD, Camila S C Duran MD, Carla B R Silva MD, André S Franco MD, Marina B Macedo MD MSc, Henrique H H Dalmolin MD, Janaina Baggio MD, Guilherme G M Balbi MD, Bruna Z Reis PhD, Leila Antonangelo MD PhD, Valeria F Caparbo PhD, Bruno Gualano PhD, Rosa M R Pereira MD PhD
- **doi**: 10.1001/jama.2020.26848
- **Purported conclusions**: Via their inappropriate (bolus) and unprofessional (failure of competent literature review) use of the intervention and more than 11 days of delay between the onset of symptoms and the implementation of treatment, the authors inappropriately conclude that vitamin D is ineffective in the management of COVID-19 infections.
- **Implications**: Their publication misrepresents appropriate clinical management of this condition and directly leads to confusion among medical physicians, the general public and political policymakers. This unreliable research will adversely affect medical treatment and international healthcare policy for hundreds of millions of patients.
- **Reviewer's expert summary**: For the reasons outlined in the following sections, this unprofessional and unethical research should have never been published and should now be withdrawn immediately.
- **Preprint (20 Feb 2021)**: academia.edu/45159442 *Note that this manuscript will be continuously updated until accepted for peer-reviewed publication; refresh/review the hyperlink provided above for the most recent version/updates*
- **Original spontaneous video review (18 Feb 2021)**:
  ❶ rumble.com/vdze3h-jama-2021-effect-of-single-high-dose-vitamin-d3-on-hospital-length-stay-in-.html
  ❷ youtube.com/watch?v=_sfGV_xz0_Q
  ❸ brighteon.com/11397575-a1bf-4afc-86df-26f6c6efa299

Criteria for withdrawal of biomedical publications— widely accepted professional standards

Editors of biomedical journals are expected to perform within certain parameters of professionalism and competence. Documents accepted for publication should reflect current science and clinical practice rather than recycling/republishing outdated/refuted ideas and practices that are inconsistent with quality healthcare and expectations in the practice of medicine. Guidelines for the retraction/withdrawal of published research have been published by Committee on Publication Ethics (COPE)[1] and include the following:

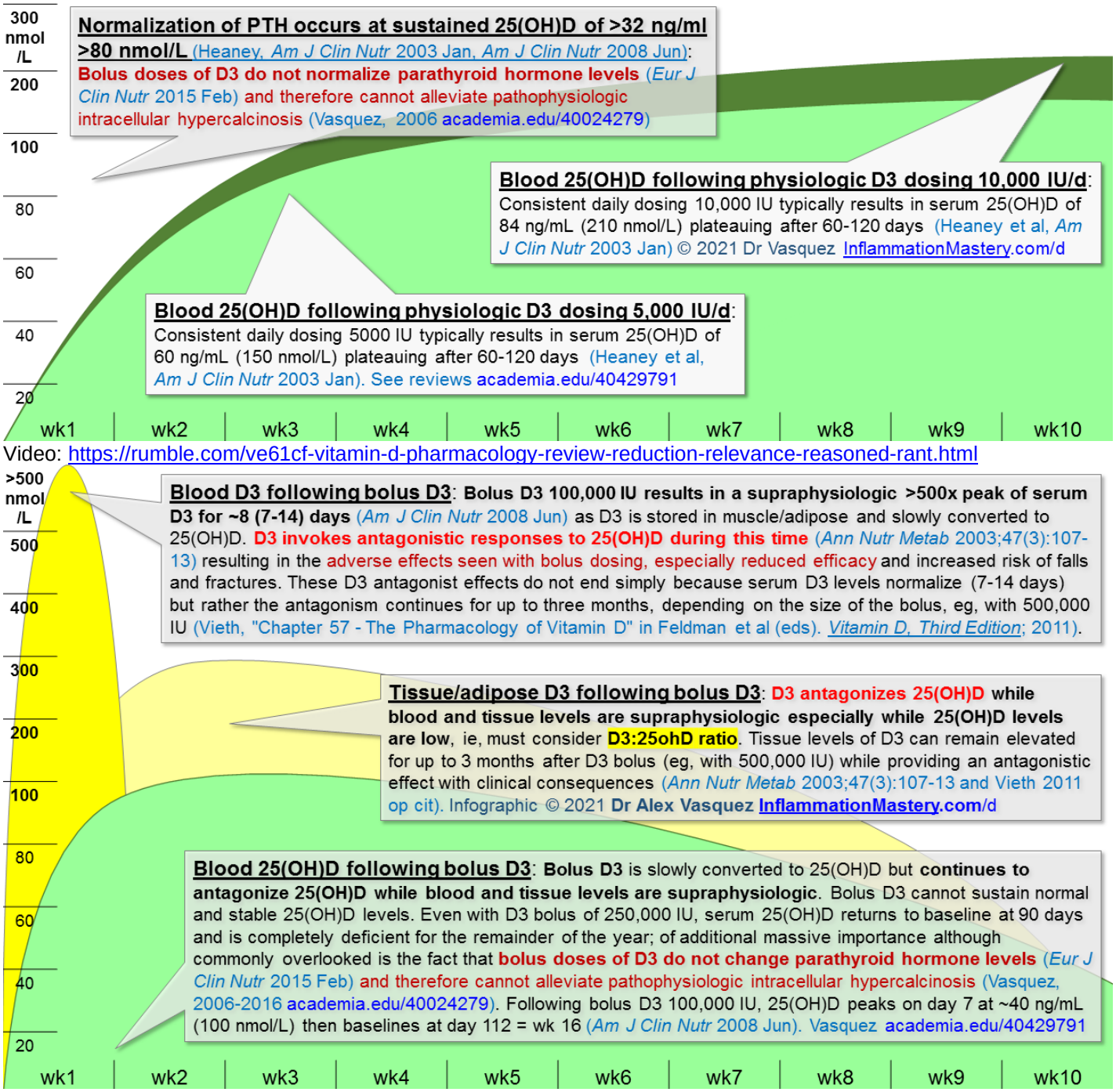
1. **Findings are unreliable as a result of major error, fabrication or falsification**
2. Plagiarism
3. Redundant/duplicated publication
4. Unauthorized use of private data
5. Copyright infringement, libel, privacy violation
6. **Unethically conducted research**
7. Compromised or manipulated peer review process
8. "The author(s) failed to disclose a major competing interest (a.k.a. conflict of interest) that, in the view of the editor, would have unduly affected interpretations of the work or recommendations by editors and peer reviewers."

On the basis of these independent and broadly accepted criteria, the article in question should be withdrawn because the findings are unreliable as a result of major error and because the research was not conducted ethically—the investigators knowingly **1) delayed treatment** in a manner that had consequences for the patients/subjects involved in the study and which negatively affected the conclusions in a way that is misleading to the readers— physicians, doctors, researchers, patients, politicians, policymakers, and the investigators **2) inappropriately administered the treatment in the form of bolus doses** by failing to administer smaller doses over the course of treatment, and the investigators knowingly **3) performed laboratory testing at the end of hospital discharge rather than at the beginning of treatment**, thereby creating a false picture that their treatment was efficacious (e.g., that appropriate serum levels were met early in the course of the illness and its treatment) when it could not have possibly been efficacious based on the known/published pharmacology of the intervention; furthermore, the authors acknowledge that **4) their treatment completely failed to reach therapeutic serum levels in more than 13% of patients**.

Inventory of errors and problems in this publication

Problems in study design, performance, randomization, review/acceptance of this article include but are not limited to the following:

1. **Unethical treatment, inappropriate delivery of treatment**: Bolus dosing (the unphysiologic administration of large doses on a single occasion rather than smaller doses on a daily/weekly basis) of vitamin D3 was already proven to be less effective or ineffective against respiratory infections in a major meta-analysis published in the *British Medical Journal* in 2017 ("**Treatment with large boluses of vitamin D has been associated with reduced efficacy** for non-classic effects, and in some cases an **increased risk of adverse outcomes**.")[2]; thus, this current study was designed to fail before it was even started. The authors were obviously aware of the aforementioned publication (their citation number 9) and the evidence that their intervention would be less efficacious when administered as a bolus dose than if it had been administered in small physiologic doses. **The administration of any treatment in an ineffective manner is unethical, and on this basis alone the article should be withdrawn.** To make this point more clear: such a research study would never be accepted in the treatment of serious disease with pharmaceutical drugs; for example the inappropriate administration of an antibiotic in patients suffering from any acute infection would never be accepted as reasonable or ethical treatment. This hypocrisy of allowing unethical research to be published misrepresents the appropriate use of therapeutics in general and nutrition in particular.



Video: https://rumble.com/ve61cf-vitamin-d-pharmacology-review-reduction-relevance-reasoned-rant.html

Infographics: D3 dose size determines clinical effect: Modest physiologic doses (top image) follow first-order pharmacokinetics characterized by a dose-response relationship that is predictable and also which does not result in significant accumulation of D3 relative to 25(OH)D; in contrast, unnatural bolus dosing of D3 follows unpredictable zero-order kinetics resulting in >500x non-physiologic elevations of D3 relative to deficient 25(OH)D with antagonistic

biochemical/physiological effects leading to negative clinical consequences (Heaney *Am J Clin Nutr* 2008 Jun; Vieth, "Chapter 57: Pharmacology of Vitamin D" in *Vitamin D, 3rd Ed.*, Academic Press, 2011).

2. **Inexcusable and unprecedented delay in treatment**: Treatment/intervention with vitamin D was delayed for more than 10 days from the onset of symptoms and this delay is medically and ethically inappropriate. Such practice does not reflect legitimate clinical nutrition practice which would have implemented treatment immediately, nor does it reflect "unprofessional" personal self-care because most laypeople in the general public would not delay a potentially effective treatment by 10 days (if they were properly informed about such treatment). The authors of this original publication completely fail to acknowledge this **structural lag time** in the title of the article as well as the abstract of the article which are the only parts of the article that are read by the majority of physicians and journalists. "**The mean (SD) time from the onset of symptoms to randomization was 10.3 (4.3) days and from hospitalization to randomization was 1.4 (0.9) days" thus a total of 11.7 days passed from the onset of symptoms to the initiation of vitamin D supplementation, with a range of variance as long as 14.6 days and 2.3 days, respectively, for a total of 16.9 days from the onset of symptoms to the initiation of treatment**. **This is medically and ethically inappropriate, both in clinical care and the publication of research.** Any properly educated medical student or pharmacology student would know that treatments have an expected "window of opportunity" in which to function and delaying treatment for 2-2½ weeks for an acute infection is clearly beyond the window of opportunity for the majority of interventions. As I have said before in previous research reviews, the unprofessional behavior that is tolerated in nutrition research when performed by the medical world would never be tolerated by that same community if it were the study of drugs and infectious disease, for example. No legitimate excuses provided for this treatment delay, and at least the article should be retitled to reflect the fact that intervention was delayed in a manner that is clearly out of any standard of care—the authors and journal editors should have used a more accurate title for this publication: **Two-week delayed administration of inactive vitamin D3 in a single ineffective bolus dose to obese comorbid polypharmacy patients does not alleviate COVID-19**. Furthermore, certain antiviral drugs (eg, oseltamivir/Tamiflu) are known to require administration within a very defined and limited timeframe following the onset of symptoms (within 48 hours of symptoms) so the **hypocrisy and failure to follow a reasonable standard of care** in the publication of this article appears to be quite political. This research was not ethically conducted. This research inappropriately models unethical behavior for clinicians. Because research serves as an example of what is acceptable and within standards of care, this article misleads healthcare providers into thinking that such delays in treatment are somehow justified. **Any clinician who knowingly delays effective antimicrobial treatment for two weeks after the onset of acute infectious disease would probably be liable for malpractice for any resulting complications, injuries or deaths—so how could these authors and editors have possibly modeled such behavior in this publication?**
3. **Failure of adequate literature review and appropriate planning**: The authors knew that bolus dosing was ineffective (or at least less effective than smaller frequent dosing), and they also ignored the pharmacokinetics of vitamin D3. **Following administration of supraphysiologic bolus dosing of vitamin D3, serum levels peak and remain elevated far into the supraphysiologic range for up to 14 days** ("In the acute study, subjects receiving a single 100000-IU dose of vitamin D3 had a rise in serum cholecalciferol to a mean of 521 nmol/L at 1 d and then a fall to near-baseline values by 7–14 d.").[3] During this time, vitamin D3 has antagonistic effects which have been described in previous literature, and the authors should have been well aware of these facts before using this treatment especially in the setting of acute infectious disease. **Conversion of vitamin D3 to the active form 25 hydroxy vitamin D3 requires approximately two weeks** which these acutely sick patients could ill afford; adding this two-week physiologic lag time atop the **structural lag time in the implementation of treatment which was reported by the authors to be at least 11 days** makes the **total lag time 25 days from the onset of symptoms to the receipt of active unantagonized vitamin D therapy**. The pharmacology of vitamin D has been well described and is accessible to all researchers; in fact, one could simply access the article by Vieth titled "the pharmacology of vitamin D"[4] to learn about the pharmacology of vitamin D as the authors of the study question should have performed. If they had read this expertly written article titled *the pharmacology of vitamin D* then they would have learned how and why bolus dosing is inappropriate, less efficacious, and occasionally harmful for up to three months following administration.
4. **Intentional or accidental failure of randomization**: The experimental (vitamin D) group was significantly sicker than the placebo group. Table 1 provides evidence that the vitamin D group was significantly more sick than the placebo group with more or more severe obesity, cough, fever, sore throat, joint pain, hypertension, diabetes, rheumatic disease, chronic obstructive pulmonary disease, chronic kidney disease, anticoagulant drug use, corticosteroid drug use, antihypertensive drug use.
5. **Clear underperformance of authors and journal editors**: The authors and reviewers and editors involved with this article clearly underperformed for their level of responsibility and education/training. The authors claim graduate/doctorate-level credentials with 19 diplomas at the graduate degree level or higher, and yet not a single one of them appears to have adequately reviewed the literature nor even studied the pharmacology of the intervention being used. For any high-profile medical journal, we could reasonably expect at least 2 to 3 reviewers at the doctorate level plus the review from an associate editor and the chief editor for an additional four-five graduate/doctorate level diplomas in charge of the review and acceptance of this manuscript for publication. Thus, for approximately 25 graduate/doctorate level diplomas, not a single one of them functioned to produce a competent document.
6. **Insufficient treatment dose**: Administration of vitamin D3 as 200,000 international units (IU) over the course of 10 days is only 20,000 units per day which is equal to less than half an hour of midday equatorial/tropical sunbathing and certainly not any heroic or skillful intervention by any standard whatsoever, especially for patients who are acutely ill, obese, polymedicated, and sick with other diseases. Importantly, the authors claim that they justify this dose based on what is within the range of appropriate dosing for healthy people but apparently they selectively overlook the fact that their patient population was obese, acutely ill with

an infectious disease, and sick with various comorbidities and affected by polypharmacy. Corticosteroid drugs are known to result in the destruction of vitamin D—this has been known since at least 2009 via publication by the American Academy of Family Physicians in their journal *American Family Physician* ("A common cause of [vitamin D] deficiency is medication use, such as anticonvulsants or glucocorticoids, which can increase catabolism and actively destroy vitamin D.").[5] So what appears to be justification is actually completely stupid in the real world. Furthermore, the authors could have easily provided the same 200,000 units *bolus* as 20,000 units *daily* over the course of 10 days and this would have been much more physiologic and would have been more likely to result in clinical benefit.

7. **Inappropriate dose selection for ill, comorbid, and obese patients**: The authors state that they chose their interventional dose based on what was appropriate for healthy persons but the subjects/patients in the study were clearly not healthy and were noted to have several comorbidities; all the subjects were obese in addition to having an acute infection. Therefore and obviously, utilizing a dose that is deemed appropriate for lean/normal-weight healthy unmedicated people is completely inappropriate for an 1) obese 2) acutely infected 3) comorbid 4) polymedicated group. Furthermore these authors repeatedly ignore the physiologic time lag in the conversion of vitamin D3 to the active form 25-hydroxy-vitamin D; this physiologic lag time is characterized by a **supraphysiologic spike of inactive or antagonistic vitamin D3 which requires 7 to 14 days to normalize** while 25-hydroxy-vitamin-D levels increase over the course of approximately 10 days but obviously do not reach full physiologic benefit for several weeks or months. Numerous studies have shown that tissue saturation requires 20-60 days following administration of vitamin D supplementation.[6]
8. **Inappropriate form of treatment for an acute illness**: The form of vitamin D used in this study is inappropriate for any type of rapid response for acute illness, and this data is well known on pharmacologic basis as well as previous clinical studies. Bolus doses of vitamin D3 require approximately 7-14 days to normalize after administration, and during those first 7-14 days vitamin D3 is unquestionably functioning in an antagonistic role against normal vitamin D metabolism. Furthermore and as previously documented, the authors note that treatment was delayed until at least 11 days following the onset of symptoms.
9. **The entire patient/subject population was obese with an average BMI of ~31.5**: The patient population was obviously obese, and serves as a reasonable surrogate marker for other nutritional deficiencies, gastrointestinal dysbiosis, and consumption of a pro-inflammatory diet pattern characterized by ultra-processed foods (UPF), which represent approximately 60% of Western diets.
10. **Documented failure of treatment to achieve therapeutic serum levels**: 14% of patients in the vitamin D group did not respond to supplementation and were still deficient throughout the study. The hypocrisy of the publication of this study is astounding because in an analogous study of antibiotic therapy for infectious disease or antiseizure therapy in the treatment of epilepsy, no competent journal would publish a study in which such a large percentage of patients did not achieve therapeutic serum levels of the antibiotic or antiseizure medication, respectively.
11. **Serum levels of 25-hydroxyvitamin D were unknown during the treatment period and only normalized at the end of treatment**: Measuring serum levels of 25-hydroxyvitamin D at the end of the study was completely inaccurate and inappropriate because the researchers should have sought to normalize these levels at the start of therapy not at the end of hospital discharge. Patients/subjects in the study were almost certainly deficient in vitamin D for the majority of time they were under the care of these clinicians/investigators—this does not represent competent research or clinical care but clearly the opposite.
12. **Inaccurate and unphysiologic definition of vitamin D sufficiency**: The authors defined vitamin D sufficiency as 30 ng/mL and this is not physiologically ideal and is less than the minimum of 32 ng/mL at which parathyroid hormone levels begin to normalize.
13. **Inappropriate and delayed administration did not provide time for expected physiologic effects and benefits**: The authors appear to have zero awareness that vitamin D is necessary for the transcription of 3000 different gene/DNA docking sites as well as regulation of the gut microbiota. All of these can have an impact on outcomes and under no circumstances whatsoever could all of these be expected to normalize with a vitamin D level that was minimally normalized on the last possible day of hospitalization, but only in approximately 85% of subjects
14. **Impressively high exclusion rate; questionable representativeness of real-world sample**: 1240 patients were assessed for eligibility and 1000 of these were excluded (including two that died); thus, more than 80% of potential patients were excluded from the study. Roughly 10% of the initial group received placebo and the other 10% received vitamin D, albeit in ineffective bolus dosing and more than a week-and-a-half after the onset of symptoms. Although we appreciate the importance of gaining "clean" investigative data, we also need data that reflects the real-world experience of clinicians and patients. Avoiding a physiologic intervention when we know that the global population shows 60-90% deficiency of vitamin D is illogical.

Conclusions

This document is still in process, but the conclusions are included in the points above. This document is not to be considered in its final form until it is presented in its final edited peer-reviewed form as stated within the PDF document itself .

About the author and presenter: Alex Kennerly Vasquez DO ND DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding Program Director of the world's first fully-accredited university-based graduate program in Human Nutrition and Functional Medicine, Dr Alex Vasquez is recognized internationally for his high intellectual and academic standards and for his expertise spanning and interconnecting many topics in medicine and nutrition. Dr Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic

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

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[1] Committee on Publication Ethics. https://publicationethics.org/retraction-guidelines

[2] Adrian R Martineau, David A Jolliffe, Richard L Hooper, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583 PMID: 28202713 PMCID: PMC5310969 DOI: 10.1136/bmj.i6583

[3] Robert P Heaney, Laura A G Armas, Judith R Shary, Norman H Bell, Neil Binkley, Bruce W Hollis. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr. 2008 Jun;87(6):1738-42. doi: 10.1093/ajcn/87.6.1738

[4] Reinhold Vieth, "Chapter 57 - The Pharmacology of Vitamin D" in Editor(s): David Feldman, J. Wesley Pike, John S. Adams. *Vitamin D, Third Edition* (ISBN 9780123819789), Academic Press, 2011;1041-1066

[5] Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. Am Fam Physician. 2009 Oct 15;80(8):841-6.

[6] Robert P Heaney, K Michael Davies, Tai C Chen, Michael F Holick, M Janet Barger-Lux. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003 Jan;77(1):204-10. doi: 10.1093/ajcn/77.1.204.

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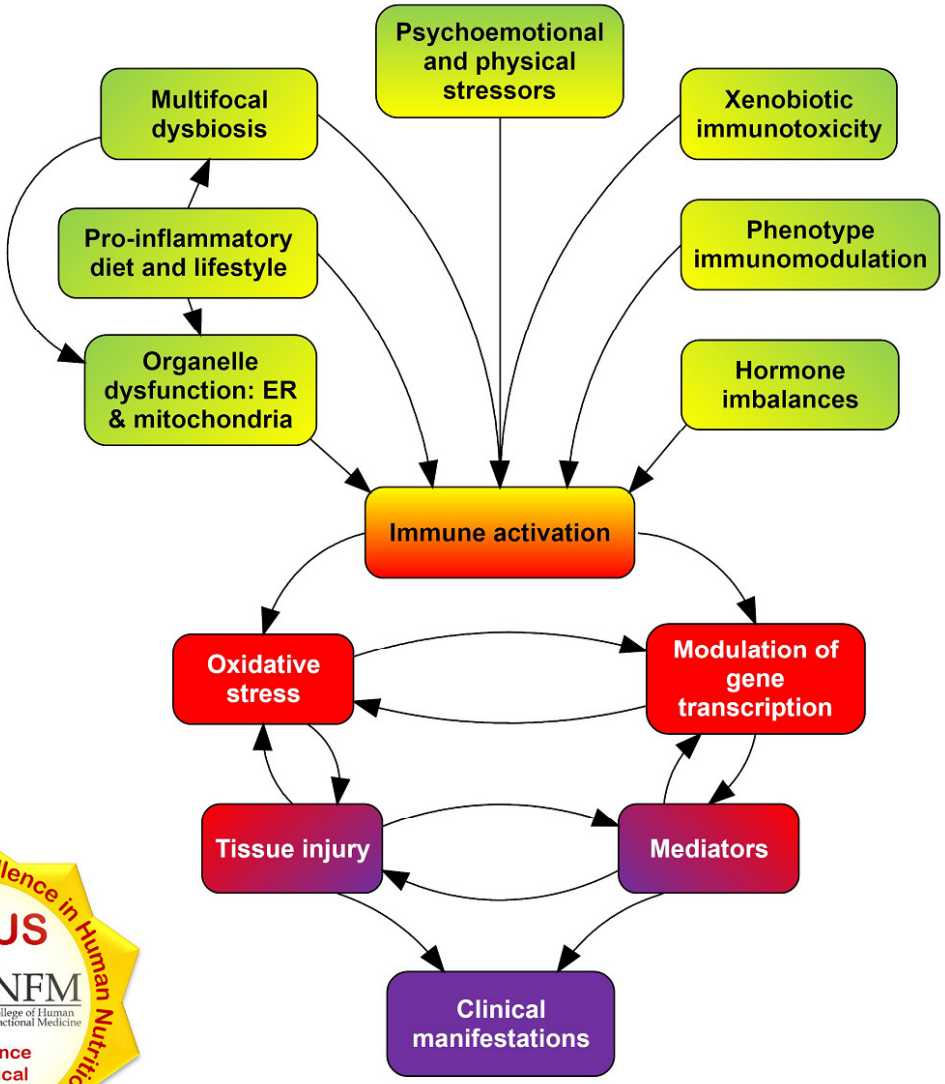

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Revisiting the Five-Part Nutritional Wellness Protocol: The Supplemented Paleo-Mediterranean Diet

Alex Vasquez, DC, ND, DO

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

INTRODUCTION:

In 2004 and 2005 I first published a "five-part nutrition protocol"[1, 2] that provides the foundational treatment plan for a wide range of health disorders. This protocol served and continues to serve as the foundation upon which other treatments are commonly added, and without which those other treatments are likely to fail, or attain suboptimal results at best.[3] Now as then, I will share with you what I consider a basic foundational protocol for wellness promotion and disease treatment. I have used this protocol in my own self-care for many years and have used it in the treatment of a wide range of health-disease conditions in clinical practice.

REVIEW:

This nutritional protocol is validated by biochemistry, physiology, experimental research, peer-reviewed human trials, and the clinical application of common sense. It is the most nutrient-dense diet available, satisfying nutritional needs and thereby optimizing metabolic processes while promoting satiety and weight loss/optimization. Nutrients are required in the proper amounts, forms, and approximate ratios for critical and innumerable physiologic functions; if nutrients are lacking, the body cannot function *normally,* let alone *optimally.* Impaired function results in subjective and objective manifestations of what is eventually labeled as "disease." Thus, a powerful and effective alternative to treating diseases with drugs is to re-establish normal/optimal physiologic function by replenishing the body with essential nutrients, reestablishing hormonal balance ("orthoendocrinology"), promoting detoxification of environmental toxins, and by reestablishing the optimal microbial milieu, especially the eradication of (multifocal) dysbiosis; this multifaceted approach can be applied to several diseases, especially those of the inflammatory and autoimmune varieties.[4]

Of course, most diseases are multifactorial and therefore require multicomponent treatment plans, and some diseases actually require the use of drugs in conjunction with assertive interventional nutrition. However, while only a smaller portion of patients actually need drugs for the long-term management their problems, all clinicians should agree that everyone needs a foundational nutrition plan because nutrients—not drugs—are universally required for life and health. This five-part nutrition protocol is briefly outlined below; a much more detailed substantiation of the underlying science and clinical application of this protocol was recently published in a review of more than 650 pages and approximately 3,500 citations.[5]

1. Health-promoting Paleo-Mediterranean diet: Following an extensive review of the research literature, I developed what I call the "supplemented Paleo-Mediterranean diet." In essence, this diet plan combines the best of the Mediterranean diet with the best of the Paleolithic diet, the latter of which has been best distilled by Dr. Loren Cordain in his book "The Paleo Diet"[6] and his numerous scientific articles.[7, 8, 9] The Paleolithic diet is superior to the Mediterranean diet in nutrient density for promoting satiety, weight loss, and improvements/normalization in overall metabolic function.[10, 11] This diet places emphasis on fruits, vegetables, nuts, seeds, and berries that meet the body's needs for fiber, carbohydrates, and most importantly, the 8,000+ phytonutrients that have additive and synergistic health effects[12]—including immunomodulating, antioxidant, anti-inflammatory, and anti-cancer benefits. High-quality protein sources such as fish, poultry, eggs, and grass-fed meats are emphasized. Slightly modifying Cordain's paleo diet, I also advocate soy and whey protein isolates for their high-quality protein and their anticancer, cardioprotective, and mood-enhancing (due to the high tryptophan content) benefits. Potatoes and other starchy vegetables, wheat and other grains including rice are discouraged due to their high glycemic indexes and high glycemic loads, and their relative insufficiency of fiber and phytonutrients compared to fruits and vegetables. Grains such as wheat, barley, and rye are discouraged due to the high glycemic loads/indexes of most breads, pastries, and other grain-derived products, as well as due to the

notorious for inhibiting mineral absorption. Some supplements, like coenzyme Q10, should be administered with fatty food to enhance absorption. Other supplements, like amino acids, should be administered away from protein-rich foods and are often better administered with simple carbohydrate to enhance cellular uptake; this is especially true with tryptophan.

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

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

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

This article was originally published in the January 2011 issue of *Nutritional Perspectives*

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

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

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

Of course, most diseases are multifactorial and therefore require multicomponent treatment plans, and some diseases actually require the use of drugs in conjunction with assertive interventional nutrition. However, while only a smaller portion of patients actually need drugs for the long-term management their problems, all clinicians should agree that everyone needs a foundational nutrition plan because nutrients—not drugs—are universally required for life and health. This five-part nutrition protocol is briefly outlined below; a much more

[105] Vasquez A. *Integrative Orthopedics: The Art of Creating Wellness While Managing Acute and Chronic Musculoskeletal Disorders*. 2004, 2007, 2012
[106] Vasquez A.Five-Part Nutritional Protocol that Produces Consistently Positive Results.*NutrWellness*2005Sep nutritionalwellness.com/archives/2005/sep/09_vasquez.php
[107] Vasquez A. Common Oversights and Shortcomings in the Study and Implementation of Nutritional Supplementation. *Naturopathy Digest* 2007 June.
[108] Vasquez A. Integrative Rheumatology. IBMRC: 2006, 2009.

detailed substantiation of the underlying science and clinical application of this protocol was recently published in a review of more than 650 pages and approximately 3,500 citations.[109]

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

[109] Vasquez A. *Chiropractic and Naturopathic Mastery of Common Clinical Disorders*. IBMRC: 2009
[110] Cordain L. *The Paleo Diet*. John Wiley and Sons, 2002
[111] O'Keefe JH Jr, Cordain L. Cardiovascular disease resulting from a diet and lifestyle at odds with our Paleolithic genome. *Mayo Clin Proc*. 2004 Jan;79(1):101-8
[112] Cordain L. Cereal grains: humanity's double edged sword. *World Rev Nutr Diet* 1999;84:19-73
[113] Cordain L, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005 Feb;81(2):341-54
[114] "A high micronutrient density diet mitigates the unpleasant aspects of the experience of hunger even though it is lower in calories. Hunger is one of the major impediments to successful weight loss. Our findings suggest that it is not simply the caloric content, but more importantly, the micronutrient density of a diet that influences the experience of hunger. It appears that a high nutrient density diet, after an initial phase of adjustment during which a person experiences "toxic hunger" due to withdrawal from pro-inflammatory foods, can result in a sustainable eating pattern that leads to weight loss and improved health." Fuhrman J, Sarter B, Glaser D, Acocella S. Changing perceptions of hunger on a high nutrient density diet. *Nutr J*. 2010 Nov 7;9:51 nutritionj.com/content/9/1/51
[115] "The Paleolithic group were as satiated as the Mediterranean group but consumed less energy per day (5.8 MJ/day vs. 7.6 MJ/day, Paleolithic vs. Mediterranean, p=0.04). Consequently, the quotients of mean change in satiety during meal and mean consumed energy from food and drink were higher in the Paleolithic group (p=0.03). Also, there was a strong trend for greater Satiety Quotient for energy in the Paleolithic group (p=0.057). Leptin decreased by 31% in the Paleolithic group and by 18% in the Mediterranean group with a trend for greater relative decrease of leptin in the Paleolithic group." Jonsson T, Granfeldt Y, Erlanson-Albertsson C, Ahren B, Lindeberg S. A Paleolithic diet is more satiating per calorie than a Mediterranean-like diet in individuals with ischemic heart disease. *Nutr Metab* (Lond). 2010 Nov 30;7(1):85.
[116] Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am J Clin Nutr* 2003;78(3 Suppl):517S-520S
[117] "With daily per capita consumption of HFCS in the US averaging about 50 grams and daily mercury intakes from HFCS ranging up to 28 μg, this potential source of mercury may exceed other major sources of mercury especially in high-end consumers of beverages sweetened with HFCS." Dufault R, et al. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health*. 2009 Jan 26;8:2 ehjournal.net/content/8/1/2
[118] Vasquez A. *Integrative Medicine and Functional Medicine for Chronic Hypertension: An Evidence-based Patient-Centered Monograph for Advanced Clinicians*. IBMRC; 2011. See also: Reungjui S, et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. *J Am Soc Nephrol*. 2007 Oct;18(10):2724-31

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

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

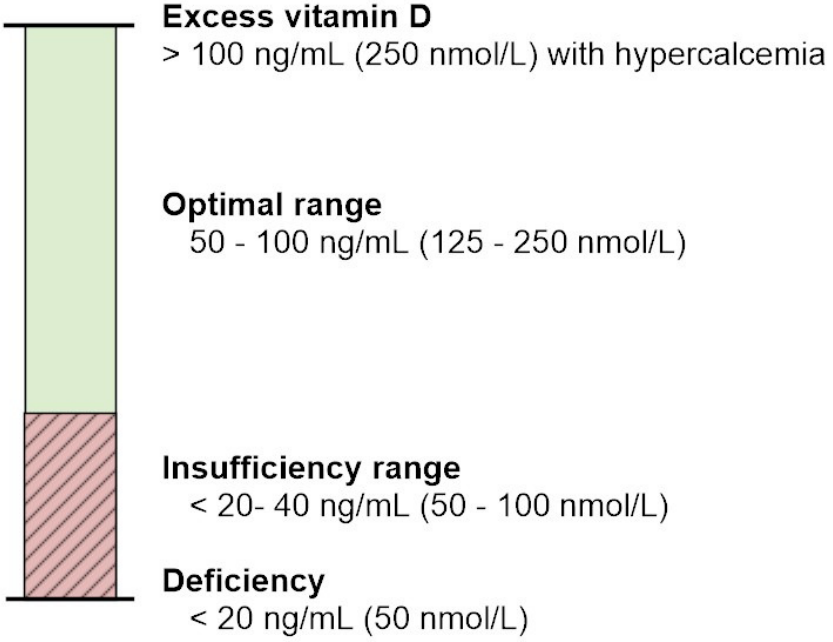

Image right: Interpretation of serum 25(OH) vitamin D levels: Updated from Vasquez et al, *Alternative Therapies in Health and Medicine* 2004 Sep

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[134] Benton D. Micro-nutrient supplementation and the intelligence of children. *Neurosci Biobehav Rev* 2001;25:297-309
[135] Church TS, Earnest CP, Wood KA, Kampert JB. Reduction of C-reactive protein levels through use of a multivitamin. *Am J Med* 2003;115:702-7
[136] Vasquez A, Manso G, Cannell J. The clinical importance of vitamin D (cholecalciferol). *Alternative Therapies in Health and Medicine* 2004;10:28-37

Proof of the cause-and-effect relationship between vitamin D deficiency and chronic musculoskeletal pain comes from clinical trials among deficient patients showing that vitamin D monotherapy alleviates pain. The exemplary study by Al Faraj and Al Mutairi[35] showed that among patients with "idiopathic chronic low back pain," 83% (n = 299) were vitamin D deficient, and supplementation with 5000 to 10 000 IU/d of cholecalciferol for 3 months alleviated or cured the low back pain in more than 95% of patients. The authors concluded that, in the evaluation of chronic musculoskeletal pain among populations with a sufficiently high prevalence of vitamin D deficiency, "Screening for vitamin D deficiency and treatment with supplements should be mandatory in this setting."

Vitamin D has a wide range of safety according to an extensive review of the literature performed by Vieth.[228] Doses of 2000 IU/d of vitamin D3 have been given to children starting at 1 year of age and were not associated with toxicity but led to a reduction in the incidence of type 1 diabetes by 80%, consistent with the vitamin's anti-infective and immunomodulatory roles.[229] A 2004 review[36] on the clinical importance of vitamin D proposed that optimal vitamin D status is defined as 40 ng/mL to 65 ng/mL (100–160 nmol/L) and that "until proven otherwise, the balance of the research indicates that oral supplementation in the range of 1000 IU per day for infants, 2000 IU per day for children and 4000 IU per day for adults is safe and reasonable to meet physiological 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." Current data and laboratory reference ranges support a higher top limit for serum 25(OH)D of approximately 100 ng/mL (250 nmol/L). Vitamin D hypersensitivity is seen with primary hyperparathyroidism, granulomatous diseases (such as sarcoidosis, Crohn's disease, and tuberculosis), adrenal insufficiency, hyperthyroidism, hypothyroidism, and various forms of cancer, as well as adverse drug effects, particularly with thiazide diuretics. Thiazide diuretics are known to potentiate hypercalcemia.

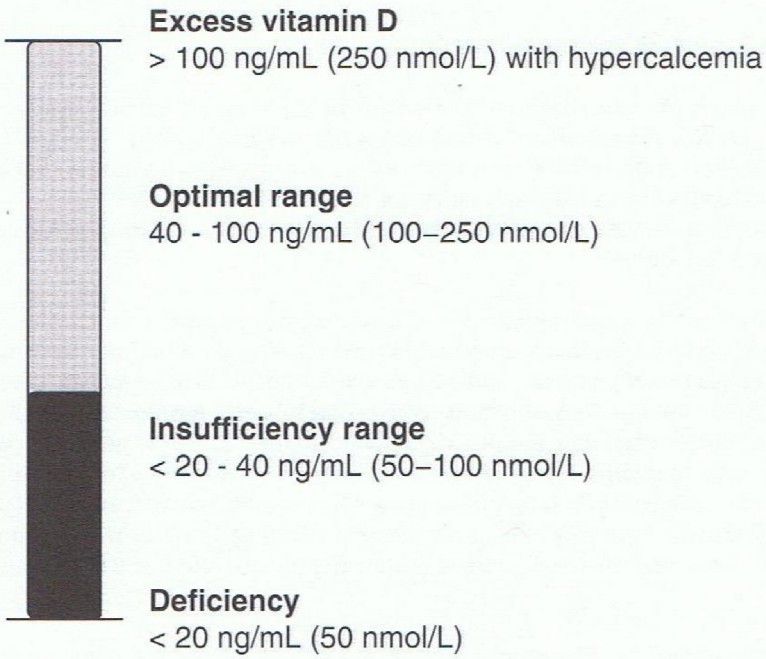

Figure 2.1—Interpretation of Serum 25(OH)D Levels

Adapted from Vasquez A, Manso G, Cannell J. *Altern Ther Health Med.* 2004;10:28-37.36

Vasquez A. *Musculoskeletal Pain: Expanded Clinical Strategies.* Institute for Functional Medicine, 2008: This peer-reviewed monograph on common pain syndromes was approved for continuing medical education (CME).

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

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

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

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

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

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

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

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

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

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

[150] Indraccolo et al. Anaphylactic-like reaction to Lugol solution during colposcopy. *South Med J* 2009 Jan;102(1):96-7
[151] "Quantitative RT-PCR confirmed the array data demonstrating that iodine/iodide treatment increased the mRNA levels of several genes involved in estrogen metabolism (CYP1A1, CYP1B1, and AKR1C1) while decreasing the levels of the estrogen responsive genes TFF1 and WISP2." Stoddard FR 2nd, et al. Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. *Int J Med Sci*. 2008 Jul 8;5(4):189-96
[152] Bonifaz A, et al. Sporotrichosis in childhood: clinical and therapeutic experience in 25 patients. *Pediatr Dermatol*. 2007 Jul-Aug;24(4):369-72
[153] Said of KI, "The standard dose was 1g, which contains 770 mg of iodine." Miller DW. Extrathyroidal benefits of iodine. *J Am Physicians Surgeons* 2006;Winter,106-10
[154] Tripathy et al. Rhinofacial zygomycosis successfully treated with oral saturated solution of potassium iodide. *J Eur Acad Dermatol Venereol*. 2007;21:117-9
[155] Ghent et al. Iodine replacement in fibrocystic disease of the breast. *Can J Surg*. 1993 Oct;36(5):453-60
[156] Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J*. 2004 Jul-Aug;10(4):328-36

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

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

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

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

Distinguishing iodiNe from iodiDe

IodiNe

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

IodiDe

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

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

should appreciate that, especially regarding "~~chronic~~" (i.e., sustained) health problems, any treatment plan that allows the patient to resume his/her previous lifestyle is by definition doomed to fail because a return to the patient's previous lifestyle and activities that allowed the onset of the disease/disorder in the first place will most certainly result in the perpetuation and recurrence of the illness or disorder. **Stated more directly: for *healing* to truly be effective, the comprehensive treatment plan must generally result in a permanent and profound change in the patient's lifestyle and emotional climate, which are the primary modifiable determinants of either health or disease.**

Barcelona's tradition of honoring intellectuals—Plaça de George Orwell: George Orwell is best known for his brilliant books *1984* and *Animal Farm* which creatively tell complex tales of herd mentality, politics, and various forms of social control and the manufacture of public consent and conformity. Less well-known is his *Homage to Catalonia*, in which he describes his experience as a volunteer in the Spanish Civil War (during which he was shot in the neck by a sniper) against the fascist regime of Francisco Franco, then supported by Hitler's Nazi Germany and Mussolini's Fascist Italy. His required-reading book *1984* has recently been summarized in a brilliant audio version[66] (and a short free video[67]) to increase its accessibility. In 2014, people protesting government surveillance and unjust imprisonments in Thailand were arrested for reading *1984*.[68]

[66] Moustaki N (Author), Podehl N (Narrator). *1984: CliffsNotes*. Audible. cliffsnotes.com/literature/n/1984/book-summary and amazon.com/1984-CliffsNotes/dp/B004S8NFZ2/

[67] Video SparkNotes: Orwell's 1984 Summary. https://youtube.com/watch?v=pTqIVvUPAjw

[68] Associated Press. 23 June, 2014. Protesting Thai reader of Orwell's *1984* dragged off by police in Bangkok. "Police in Thailand yesterday arrested eight people for demonstrating against the nation's increasingly repressive military junta, including a man dragged away by undercover officers for reading a copy of George Orwell's *Nineteen Eighty-Four*. The arrest was the first known case of anyone being detained for reading as a form of protest since the military seized power last month. ... A Thai reporter who witnessed the lone man reading Orwell's classic said he was taken away by half a dozen plainclothes police. The reporter said the man held the book up as officers approached. ... Another of the arrests was of a woman wearing a T-shirt with the words "Respect My Vote" on it." *South China Morning Post* scmp.com/news/asia/article/1538616/protesting-thai-reader-orwells-1984-dragged-police-bangkok. See also Campbell C. A Yellow Shirt Leader Says the Thai Coup Was Planned in 2010. *Time* 2014 Jun 23. time.com/2910484/thai-coup-planned-2010-suthep-thaugsuban/. "My friends told me when they read 1984 for the first time they could never imagine there would be a country like that, but it's happening now in Thailand," says Pimsiri. "People are really watching you, your computers are being monitored… and many people have been detained in undisclosed locations." *Christian Science Monitor* csmonitor.com/World/Asia-Pacific/2014/0530/Orwell-s-1984-suddenly-fashionable-on-Bangkok-streets

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

Progressive awakening

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

Henry David Thoreau, *Walden*[411]

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

Nathaniel Branden, *Six Pillars of Self-Esteem*[412]

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

Friedrich Nietzsche, *Thus Spoke Zarathustra*[413]

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

associated with complications such as pancytopenia, organ failure, and death[407], it is not a treatment to be taken lightly nor should inexperienced physicians administer it. Colchicine can be administered orally, but its low therapeutic efficacy in relation to its moderate gastrointestinal toxicity limits its applicability. In a poorly designed study by Schnebel and Simmons[408], orally administered colchicine was no better yet was more toxic than placebo; this study appears to have been designed specifically to show inefficacy and toxicity of colchicine since the patients were either given *no treatment* alternating with a *gastroirritative toxic dose* of colchicine.

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

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

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

Living color, more vitality: The "colorization" process for the interior of this book began in April 2014 in Bogota (above) and Cartagena Colombia (below).

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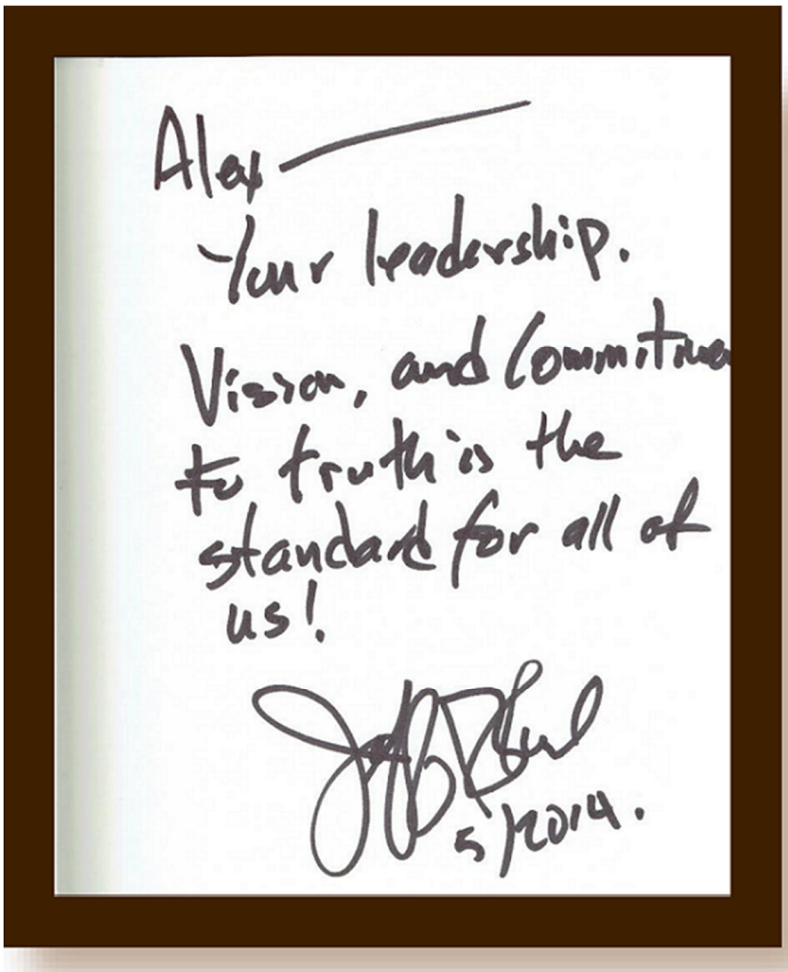
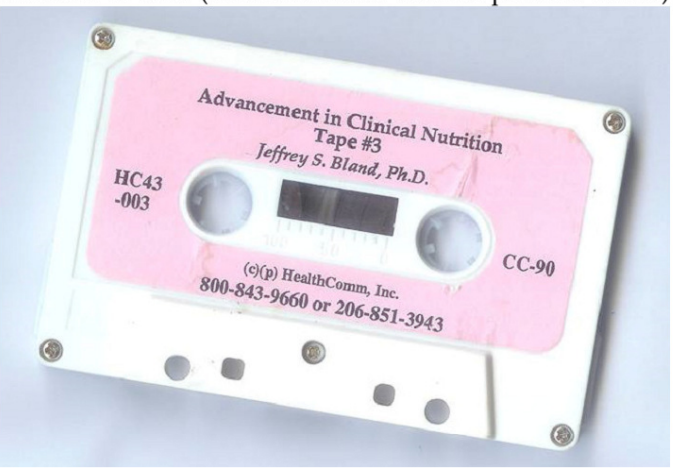


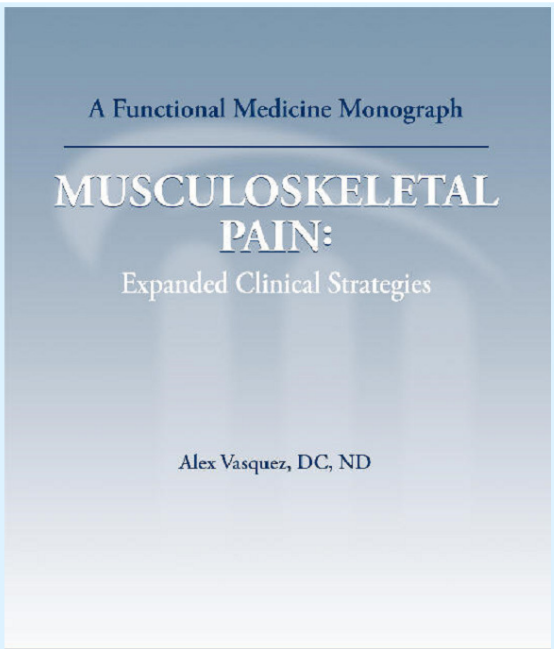
Pictured above—Personal inscription from Dr. Jeffrey Bland at a book signing event for his book *Disease Delusion*: My inclusion of Dr Bland's personal note above is not meant to imply that he is endorsing this book; he might very well reject any or all of it. Further, this inclusion does not imply that he carries those same sentiments beyond the day that he wrote them to me in May of 2014. Rather, my inclusion signifies our mutual respect as colleagues, and my personal respect for his thought and demeanor, and his influence on my life and work. I have respectfully honored him in this book as the founder of what most clinicians in America know as Functional Medicine, and I have developed and extended my own version of his concept—that disease states are *malleable* rather than *destined*—to the clinical management of inflammatory disorders under the name of Functional Inflammology. Importantly and personally—but not paradoxically if one understands the true goals of mentorship, affiliation, and friendship—due to the support of friends and colleagues, this book also represents a departure from concern that I had for endorsement from or agreement with other people, professions, universities, or organizations. In this book, I have presented the truth as I see it—without apology—and without any filtering other than as the limitations imposed by time, space, my own abilities, and limitations imposed by human physiology. This work—now published as *Inflammation Mastery, 4th Edition* —has been "in progress" since its origin as course notes for Orthopedics and Rheumatology which I taught at Bastyr University in Seattle in 2000-2001 and through its previous publications in many books starting with *Integrative Orthopedics* (2004) and *Integrative Rheumatology* (2006) and peer-reviewed publications in journals such as *Annals of Pharmacotherapy* (2005), *Alternative Therapies in Health and Medicine* (2004, 2014), *British Medical Journal* (2005), and *Nature Reviews Rheumatology* (2016). In addition to spanning more than 16 years, this work has also spanned various countries and cultures—including Houston, Fort Worth, Austin (Texas), Seattle (Washington), Portland (Oregon) in the United States, then to Bogota Colombia and Barcelona Spain. I consider this volume to be my highest presentation of truth, accuracy, clinical application and—most importantly for me: contextualization—that I could humanly muster while maintaining my own health, relationship, and other obligations. I will remain open to the correction and the updating of this work as the weight of evidence indicates. The goals of healthcare should be the optimization of physical health and psychosocial-intellectual freedom.

Functional Medicine

Introduction and personal experiences/perspectives: "Functional Medicine" as most of us know and appreciate it was developed from initial concepts that spawned from the genius of Dr Jeffrey Bland, a PhD biochemist drawn into the world of nutrition by a project of one of his graduate students, and who later made many paradigm-shifting contributions to the fields of clinical biochemistry and clinical practice of physicians world-wide. I (DrV) consider myself to have been a student and apprentice of Dr Bland starting in 1994, when I started attending his *Nutritional Biochemistry* presentations (vicariously, via audio cassettes) and every post-graduate conference and symposium I could attend, which was a considerable number (more than 300 hours of post-graduate training by the time I was 25yo), since I had by then relocated to the Pacific Northwest region of the United States, a few hours from where Dr Bland had HealthComm, the Functional Medicine Research Center, and later the Institute for Functional Medicine. Dr Bland's work quite obviously influenced me greatly, along with the work of Jonathan Wright MD (also in the Pacific Northwest), Leo Galland MD, and especially Alan Gaby MD; under their "nutritional influences", I basically "grew up" in an intellectual house of clinical nutrition and functional medicine. I would basically listen to audios of their lectures constantly, until the tapes wore out. Dr Bland's presentation *Advancement in Clinical Nutrition* in 1994 (cherished audio cassette pictured below)



struck me with particular profundity; I listened to it so often that I had parts of it memorized because of the combination of verbal eloquence for which Dr Bland is famous and for the intellectual independence and lucidity with which Dr Bland articulated a new vision for medicine: that of moving beyond the *static* pathology-based models of disease toward appreciating illnesses as disorders of impaired *function*. Most people familiar with my work know that nutritional biochemistry and functional medicine are best described as my second interests following psychology and philosophy; indeed, I spent most of any "free time" during my 20s while completing two consecutive doctorates engaged with athletics, philosophy/psychology, and functional nutrition/medicine. The combination(s) of studying Gaby, Wright, Bland, Galland simultaneously with Rollins, Nietzsche, Bradshaw, Bly, Hillman, Lee, Meade, Kipnis, Moore, Miller, Deida, Branden, professionals and various personal groups gave me a unique view of health(care) and human potential; what appeared clear and obvious from these eclectic viewpoints was unknown or unspeakable among the majority of professors and students in the classes and clinics where I studied and learned.



Dr Vasquez was selected by the Institute for Functional Medicine to write its peer-reviewed CME monograph on disorders of pain and inflammation: *Musculoskeletal Pain: Expanded Clinical Strategies*, published by the Institute for Functional Medicine in 2008. Parts of this section were originally derived from the pre-edited draft of the introduction to that book, and any variations are used here with permission. Modifications were made to this section during revisions in 2011 and again in 2014. *Musculoskeletal Pain* contained an introduction to functional medicine and a review of assessments and therapeutics, followed by the clinical topics: migraine headaches, fibromyalgia, back pain, and rheumatoid arthritis. As would be expected, all of these topics have been discussed to a higher level of detail in more recent editions of *Integrative Orthopedics* (3rd Edition and later), *Integrative Rheumatology* (3rd Edition and later), *Fibromyalgia in a Nutshell* (2012), and the *Inflammation Mastery* series starting in 2014.

Reviews of previous and recent works:

- "Alex is the master of painful conditions and metabolic treatments." *Public comment by an award-winning neurosurgeon and functional medicine practitioner, 2016*
- "I love this course and your approach to the material. I am learning so much. Each article you assigned was strategically chosen and offered support and insight. I was pleasantly surprised by the exam and thought it was very fair. … Thank you for sharing your knowledge and experience with us!" *Doctorate Student under Dr Vasquez, 2016*
- "I appreciate the lecture yesterday and I am truly fascinated by your topic and your vast knowledge. ... I for one feel having people like you on our faculty can only strengthen the credibility of our school. ... I appreciate your education, knowledge and clearly you are the authority in your field. I have listened to all your lectures on YouTube - fantastic!" *University Faculty and Doctorate Student under Dr Vasquez, 2016*
- "Thank you most kindly for your incredible dedication and kindness in sharing your knowledge with us. I am due to start med school next semester and thanks to you and all those who have taught you, I'll be way ahead of the curve." *Premedical/Medical student 2015*
- "Dr Vasquez, I have followed your work extensively and admire your intellect and passion. Thank you for your passion for teaching with integrity!" *Chiropractic doctor 2015*
- "I just wanted to tell you how much I appreciate the information I have received from you. I am still digesting most of it. I feel I have learned quite a bit already yet also feel I have barely scratched the surface." *Doctor and Graduate student under Dr Vasquez, 2013*
- "Dr. Vasquez, Thank you for all you do. **Your conference was simply amazing**. No one wanted to leave the room. I met medical professionals and very interesting lay people who were stimulated and invigorated to change their lives and the lives of others. **I am in awe at your intellectual integrity and veracity.** Best of luck to you in all of your future endeavors." *Medical physician and ICHNFM 2013 Conference Attendee*
- **2014 review of Functional Inflammology, Volume 1: "A truly comprehensive text on the vast subject of inflammation. I consider this book to be an essential addition to any health care practitioner who wishes to operate within the realm of Function Medicine. Please be aware that this book is dense in its content, and its 700 plus pages are full of deeply insightful information. I think Dr. Vasquez is one of the most prolific functional medicine contributors and books such as this should cement his reputation as such."**
- "I attended the last ICHNFM conference in Portland (and am still basking in the amazing information received)." *Email from Clinical Oncology Dietitian, in late February 2014*
- "Thanks for a fantastic conference!" *ICHNFM 2013 Conference Attendee*
- "Your discourse today reflected not only your passion and commitment to the wellness of our planet but most importantly the clarity and sincerity of your spirit/ heart/ mind. Always good to be with you and look forward to seeing you soon. Hope we can spend more time then." *Medical physician attendee 2014*
- "I was so refreshed by the 'unfiltered excellence.' What humanness. Breaths of fresh air." *ICHNFM 2013 Attendee*
- "Keep in mind Alex, that humanity is a better place because of you. I know you can't undo it all, but think about how many people would be worse off if it wasn't for your wonderful knowledge being shared with all us docs. Things that I have learned from you have changed peoples' lives for the better." *Naturopathic physician, 2014*
- "Just got back to Guam. Great experience at the International Conference on Human Nutrition and Functional Medicine. Exciting concepts on functional medicine. Thanks Dr Alex Vasquez and team!" *ICHNFM 2013 Conference Attendee*
- "Already waiting in line to buy next year's ticket! **Dr. Vasquez you crushed it!** The future is looking fun already ☺" *ICHNFM 2013 Conference Attendee*
- "Had an incredible time at the 2013 International Conference on Human Nutrition and Functional Medicine. Got to meet some amazing people and hear from some of the top researchers/health professionals about human nutrition and functional medicine approaches. It was definitely worth every penny and can't wait to go back next year!" *ICHNFM 2013 Conference Attendee*
- "I miss you! Your confidence in a program you believed in. I miss your live classes where we would get off topic on a clinical pearl. I miss your way of teaching in a laid back atmosphere that made me feel comfortable, not intimidated. I just needed to let you know, this program is not the same, I am almost done, otherwise, I would have bailed out! I am grateful for the last 18 months I did have with you at the helm. ... You ignited in me my passion for learning again. You sparked the minds of all of us with your enthusiasm. Don't ever let anyone take that away. It has given birth to your new endeavor, and we will follow where you lead. Enjoy your new surroundings and celebrate your new beginnings. I know I look forward to what is ahead." *Doctor and Graduate student under Dr Vasquez, 2013*
- "Wonderful conference! Thanks so much." *ICHNFM 2013 Conference Attendee*
- "Really wonderful conference! Lots of material ready to implement Monday morning! **Congrats to Alex Vasquez on a herculean job very well done**!" *ICHNFM 2013 Conference Attendee*
- "Thanks for a great conference. I really enjoyed all of the speakers, but your lectures were by far the most useful for implementing ideas into my clinical practice. And the most entertaining." *ICHNFM 2013 Conference Attendee*

Columbia River Gorge: Wahkeena Falls, Oregon *above*, Dog Mountain, Washington *below.*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Appendix—2015 media and excipients for common vaccines from the US Centers for Disease Control (CDC): Observance is made here—with selected highlights of common allergens and immunogens—of potential allergens to which patients may respond; by use of this information, clinicians can make better choices regarding the selection or avoidance of particular vaccines in patients with known allergies or possible hypersensitivity reactions. For example, according to the recent study by Zug et al[1], among 883 North American children approximately 60% have positive (ie, allergic) responses to substances via patch testing, and neomycin sulfate (a component of come vaccines) sensitivity is one of the more common allergies/hypersensitivities. Thus this list helps clinicians identify potential hypersensitivity reactions that might be triggered by vaccine ingredients. This document is available as of early 2016 via the CDC website at this location: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf

Vaccine Excipient & Media Summary

Excipients Included in U.S. Vaccines, by Vaccine

This table includes not only vaccine ingredients (e.g., adjuvants and preservatives), but also substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities. In addition to the substances listed, most vaccines contain Sodium Chloride (table salt).

Last Updated February 2015

All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here. If in doubt, check the manufacturer's package insert.

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Adenovirus	sucrose, D-mannose, D-fructose, dextrose, potassium phosphate, plasdone C, anhydrous lactose, micro crystalline cellulose, polacrilin potassium, magnesium stearate, cellulose acetate phthalate, alcohol, acetone, castor oil, FD&C Yellow #6 aluminum lake dye, human serum albumin, fetal bovine serum, sodium bicarbonate, human-diploid fibroblast cell cultures (WI-38), Dulbecco's Modified Eagle's Medium, monosodium glutamate	March 2011
Anthrax (Biothrax)	aluminum hydroxide, benzethonium chloride, formaldehyde, amino acids, vitamins, inorganic salts and sugars	May 2012
BCG (Tice)	glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, Iron ammonium citrate, lactose	February 2009
DT (Sanofi)	aluminum potassium sulfate, peptone, bovine extract, formaldehyde, thimerosal (trace), modified Mueller and Miller medium, ammonium sulfate	December 2005
DTaP (Daptacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-Phenoxyethanol, Stainer-Scholte medium, modified Mueller's growth medium, modified Mueller-Miller casamino acid medium (without beef heart infusion), dimethyl 1-beta-cyclodextrin, ammonium sulfate	October 2013
DTaP (Infanrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium	November 2013
DTaP-IPV (Kinrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, Vero (monkey kidney) cells, calf serum, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium	November 2013
DTaP-HepB-IPV (Pediarix)	formaldehyde, gluteraldehyde, aluminum hydroxide, aluminum phosphate, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, yeast protein, calf serum, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium, Vero (monkey kidney) cells	November 2013
DTaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, formaldehyde, sucrose, gutaraldehyde, bovine serum albumin, 2-phenoxethanol, neomycin, polymyxin B sulfate, Mueller's Growth Medium, Mueller-Miller casamino acid medium (without beef heart infusion), Stainer-Scholte medium (modified by the addition of casamino acids and dimethyl-beta-cyclodextrin), MRC-5 (human diploid) cells, CMRL 1969 medium (supplemented with calf serum), ammonium sulfate, and medium 199	October 2013
Hib (ActHIB)	ammonium sulfate, formalin, sucrose, Modified Mueller and Miller medium	January 2014
Hib (Hiberix)	formaldehyde, lactose, semi-synthetic medium	March 2012
Hib (PedvaxHIB)	aluminum hydroxphosphate sulfate, ethanol, enzymes, phenol, detergent, complex fermentation medium	December 2010

[1] Zug et al. Patch testing in children from 2005 to 2012: results from the North American contact dermatitis group. *Dermatitis*. 2014 Nov-Dec;25(6):345-55

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Hib/Hep B (Comvax)	yeast (vaccine contains no detectable yeast DNA), nicotinamide adenine dinucleotide, hemin chloride, soy peptone, dextrose, mineral salts, amino acids, formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, sodium borate, phenol, ethanol, enzymes, detergent	December 2010
Hib/Mening. CY (MenHibrix)	tris (trometamol)-HCl, sucrose, formaldehyde, synthetic medium, semi-synthetic medium	2012
Hep A (Havrix)	aluminum hydroxide, amino acid supplement, polysorbate 20, formalin, neomycin sulfate, MRC-5 cellular proteins	December 2013
Hep A (Vaqta)	amorphous aluminum hydroxyphosphate sulfate, bovine albumin, formaldehyde, neomycin, sodium borate, MRC-5 (human diploid) cells	February 2014
Hep B (Engerix-B)	aluminum hydroxide, yeast protein, phosphate buffers, sodium dihydrogen phosphate dihydrate	December 2013
Hep B (Recombivax)	yeast protein, soy peptone, dextrose, amino acids, mineral salts, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, formaldehyde, phosphate buffer	May 2014
Hep A/Hep B (Twinrix)	formalin, yeast protein, aluminum phosphate, aluminum hydroxide, amino acids, phosphate buffer, polysorbate 20, neomycin sulfate, MRC-5 human diploid cells	August 2012
Human Papillomavirus (HPV) (Cerverix)	vitamins, amino acids, lipids, mineral salts, aluminum hydroxide, sodium dihydrogen phosphate dehydrate, 3-O-desacyl-4' Monophosphoryl lipid A, insect cell, bacterial, and viral protein	November 2013
Human Papillomavirus (HPV) (Gardasil)	yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate	June 2014
Human Papillomavirus (HPV) (Gardasil 9)	yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate	December 2014
Influenza (Afluria)	beta-propiolactone, thimerosol (multi-dose vials only), monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, neomycin sulfate, polymyxin B, egg protein, sucrose	December 2013
Influenza (Agriflu)	egg proteins, formaldehyde, polysorbate 80, cetyltrimethylammonium bromide, neomycin sulfate, kanamycin, barium	2013
Influenza (Fluarix) Trivalent and Quadrivalent	octoxynol-10 (Triton X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, sodium deoxycholate, sucrose, phosphate buffer	June 2014
Influenza (Flublok)	monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20, baculovirus and host cell proteins, baculovirus and cellular DNA, Triton X-100, lipids, vitamins, amino acids, mineral salts	March 2014
Influenza (Flucelvax)	Madin Darby Canine Kidney (MDCK) cell protein, MDCK cell DNA, polysorbate 80, cetyltrimethlyammonium bromide, β-propiolactone, phosphate buffer	March 2014
Influenza (Fluvirin)	nonylphenol ethoxylate, thimerosal (multidose vial–trace only in prefilled syringe), polymyxin, neomycin, beta-propiolactone, egg proteins, phosphate buffer	February 2014
Influenza (Flulaval) Trivalent and Quadrivalent	thimerosal, formaldehyde, sodium deoxycholate, egg proteins, phosphate buffer	February 2013
Influenza (Fluzone: Standard (Trivalent and Quadrivalent), High-Dose, & Intradermal)	formaldehyde, octylphenol ethoxylate (Triton X-100), gelatin (standard trivalent formulation only), thimerosal (multi-dose vial only) , egg protein, phosphate buffers, sucrose	2014

Centers for Disease Control and Prevention
Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition April, 2015

From: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf on 2016 January

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Influenza (FluMist) Quadrivalent	ethylene diamine tetraacetic acid (EDTA), monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gentamicin sulfate, egg protein	July 2013
Japanese Encephalitis (Ixiaro)	aluminum hydroxide, Vero cells, protamine sulfate, formaldehyde, bovine serum albumin, sodium metabisulphite, sucrose	May 2013
Meningococcal (MCV4-Menactra)	formaldehyde, phosphate buffers, Mueller Hinton agar, Watson Scherp media, Modified Mueller and Miller medium, detergent, alcohol, ammonium sulfate	April 2013
Meningococcal (MCV4-Menveo)	formaldehyde, amino acids, yeast extract, Franz complete medium, CY medium	August 2013
Meningococcal (MPSV4-Menomune)	thimerosal (multi-dose vial only), lactose, Mueller Hinton casein agar, Watson Scherp media, detergent, alcohol	April 2013
Meningococcal (MenB – Bexsero)	aluminum hydroxide, *E. coli*, histidine, sucrose, deoxycholate, kanomycin	2015
Meningococcal (MenB – Trumenba)	polysorbate 80, histodine, *E. coli*, fermentation growth media	October 2015
MMR (MMR-II)	Medium 199 (vitamins, amino acids, fetal bovine serum, sucrose, glutamate) , Minimum Essential Medium, phosphate, recombinant human albumin, neomycin, sorbitol, hydrolyzed gelatin, chick embryo cell culture, WI-38 human diploid lung fibroblasts	June 2014
MMRV (ProQuad)	sucrose, hydrolyzed gelatin, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium phosphate dibasic, neomycin, bovine calf serum, chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells	March 2014
Pneumococcal (PCV13 – Prevnar 13)	casamino acids, yeast, ammonium sulfate, Polysorbate 80, succinate buffer, aluminum phosphate, soy peptone broth	January 2014
Pneumococcal (PPSV-23 – Pneumovax)	phenol	May 2014
Polio (IPV – Ipol)	2-phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B, monkey kidney cells, Eagle MEM modified medium, calf serum protein, Medium 199	May 2013
Rabies (Imovax)	Human albumin, neomycin sulfate, phenol red indicator, MRC-5 human diploid cells, beta-propriolactone	April 2013
Rabies (RabAvert)	β-propiolactone, potassium glutamate, chicken protein, egg protein, neomycin, chlortetracycline, amphotericin B, human serum albumin, polygeline (processed bovine gelatin), sodium EDTA, bovine serum	March 2012
Rotavirus (RotaTeq)	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum, vero cells *[DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.]*	June 2013
Rotavirus (Rotarix)	amino acids, dextran, sorbitol, sucrose, calcium carbonate, xanthan, Dulbecco's Modified Eagle Medium (potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red) *[Porcine circovirus type 1 (PCV-1) is present in Rotarix. PCV-1 is not known to cause disease in humans.]*	May 2014
Smallpox (Vaccinia – ACAM2000)	human serum albumin, mannitol, neomycin, glycerin, polymyxin B, phenol, Vero cells, HEPES	September 2009

Centers for Disease Control and Prevention
Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition

April, 2015

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Td (Decavac)	aluminum potassium sulfate, peptone, formaldehyde, thimerosal, bovine muscle tissue (US sourced), Mueller and Miller medium, ammonium sulfate	March 2011
Td (Tenivac)	aluminum phosphate, formaldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate	April 2013
Td (Mass Biologics)	aluminum phosphate, formaldehyde, thimerosal (trace), ammonium phosphate, modified Mueller's media (containing bovine extracts)	February 2011
Tdap (Adacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, ammonium sulfate, Stainer-Scholte medium, dimethyl-beta-cyclodextrin, modified Mueller's growth medium, Mueller-Miller casamino acid medium (without beef heart infusion)	March 2014
Tdap (Boostrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80 (Tween 80), Latham medium derived from bovine casein, Fenton medium containing a bovine extract, Stainer-Scholte liquid medium	February 2013
Typhoid (inactivated – Typhim Vi)	hexadecyltrimethylammonium bromide, formaldehyde, phenol, polydimethylsiloxane, disodium phosphate, monosodium phosphate, semi-synthetic medium	March 2014
Typhoid (oral – Ty21a)	yeast extract, casein, dextrose, galactose, sucrose, ascorbic acid, amino acids, lactose, magnesium stearate. gelatin	September 2013
Varicella (Varivax)	sucrose, phosphate, glutamate, gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, sodium phosphate monobasic, potassium chloride, EDTA, residual components of MRC-5 cells including DNA and protein, neomycin, fetal bovine serum, human diploid cell cultures (WI-38), embryonic guinea pig cell cultures, human embryonic lung cultures	March 2014
Yellow Fever (YF-Vax)	sorbitol, gelatin, egg protein	May 2013
Zoster (Shingles – Zostavax)	sucrose, hydrolyzed porcine gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, neomycin, potassium chloride, residual components of MRC-5 cells including DNA and protein, bovine calf serum	February 2014

A table listing vaccine excipients and media *by excipient* can be found in:

Grabenstein JD. *ImmunoFacts: Vaccines and Immunologic Drugs* – 2013 (38th revision). St Louis, MO: Wolters Kluwer Health, 2012.

From: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf on 2016 January

Functional Inflammology (.com): Definition and Scope: An evidence-based clinical approach to the prevention, management, comanagement, and cure of the majority of so-called "chronic diseases" that are increasingly in epidemic proportions worldwide; examples include diabetes, hypertension, obesity, migraine, neurodegeneration, fibromyalgia, and disorders of allergic and autoimmune inflammation. Safety, Efficacy, Ethics: Remarkable safety and efficacy; allows clinicians to meet all criteria of medical ethics: ❶ beneficence, ❷ non-malfeasance, ❸ autonomy, ❹ informed consent, ❺ distributive justice. Refutations/Affirmations: The "chronic disease model" is refuted and replaced by the view that **most so-called "chronic inflammatory diseases"** are simply **"sustained inflammatory responses"** to factors which can be clinically corrected; these seven primary factors are effectively addressed by the Functional Inflammology Clinical Protocol.

Inflammation Mastery 4th Edition combines the recently updated Functional Inflammology and Dr Vasquez's previous Integrative Rheumatology into a new colorized updated textbook of almost 1,200 pages. This work is the culmination of several thousand research publications combined with Dr Vasquez's many years of clinical experience and teaching graduate-level students and doctorate-level clinicians worldwide. With radiographs, photos, acronyms, illustrations, flowcharts, and detailed-yet-simplifying explanations, Dr Vasquez makes it easier than ever for clinicians to grasp important concepts in integrative care and functional medicine and then to translate the basic science research and molecular biology into treatment plans that can be explained and used in "the real world" of clinical practice with patients. The associated video tutorials and recorded live conference presentations further help students and clinicians "get it" via Dr Vasquez's effective teaching style which embraces complexity while always emphasizing clinical applicability and psychosocial context. The **Inflammation Mastery & Functional Inflammology series of books and videos** translates important concepts and nutritional/biomedical science into easy and practical clinical applications for the prevention and treatment of disorders of sustained inflammation, which Dr Vasquez describes as "patterns of metabolic disturbance and inflammatory dysfunction" existing in three sequential and overlapping categories: 1) metabolic inflammation, 2) allergic inflammation, 3) autoimmune inflammation. This book includes access to video presentations which introduce the origin and components of the Functional Inflammology Protocol and FINDSEX® acronym. Post-publication updates to this information and important social and clinical contextualization are made available in videos and online repositories (access provided in the book), and the e-newsletter available from InflammationMastery and FunctionalInflammology.com. This textbook also provides access, via reprints or hyperlinks, to Dr Vasquez's published articles—an example of which is his recent paradigm-shifting editorial published in the journal *Alternative Therapies in Health and Medicine* (2014 January). The updated section on pain management allows students and clinicians to understand and apply manual, pharmacologic, nutritional and botanical medicine treatments for musculoskeletal pain, thereby providing better relief for patients and avoiding the hazards of NSAIDs, coxibs, steroids, opioids, immunosuppressants and biologics.

About the author—Dr Alex Vasquez: Dr Alex 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 is the author of many textbooks, including Integrative Orthopedics (2004/2012), Integrative Rheumatology (2006/2014), Musculoskeletal Pain: Expanded Clinical Strategies (published by the Institute for Functional Medicine, 2008), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Fibromyalgia in a Nutshell (2012), Migraine Headaches, Hypothyroidism, and Fibromyalgia (2012), Mitochondrial Nutrition and Mitochondrial Medicine for Primary Care Conditions (2014), and Dysbiosis in Human Disease (2014), which is also an excerpt from Functional Inflammology: Volume 1. "DrV" has also written more than 110 letters and articles for professional magazines and medical journals such as *British Medical Journal* (BMJ), *TheLancet.com*, *Annals of Pharmacotherapy*, *Journal of Clinical Endocrinology and Metabolism*, *Journal of the American Medical Association* (JAMA), *Alternative Therapies in Health and Medicine*, *Journal of the American Osteopathic Association* (JAOA), *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics* (JMPT), *Current Allergy and Asthma Reports*, *Integrative Medicine*, and *Arthritis & Rheumatism*, the Official Journal of the American College of Rheumatology. Dr Vasquez has lectured worldwide to healthcare professionals and provides expert consultations to physicians and patients internationally. All of DrV's books are available on Amazon.com with videos at Vimeo.com/DrVasquez and audio recordings of lectures at iTunes.

About the International College of Human Nutrition and Functional Medicine (ICHNFM): International College of Human Nutrition and Functional Medicine was founded by a group of internationally-located world-class experts to provide higher-level training in nutrition and functional medicine to students and clinicians worldwide in Spanish, English, Portuguese, Catalan, and other languages. Originally founded in North America (Portland Oregon USA) and launched with the tremendously successful 2013 International Conference on Human Nutrition and Functional Medicine (described at ICHNFM.ORG with select videos available at Vimeo.com/ICHNFM), the organization is also now established in Europe (Spain) with several important publications also generated from in South America (Colombia). Dr Vasquez and his colleagues at ICHNFM provide educational courses, videos, written materials, and mentoring for students and clinicians to promote the expert-level application of clinical nutrition and functional medicine. Via forums and live interactive online classes, professors and students are able to interact, network, and share important insights, clinical experiences and case reports, effective doses of nutrients and prescription medicines, additional citations to research, important clinical pearls, and expanded discussions on various topics as the research and clinical practice of human nutrition and functional medicine continuously advance. International College of Human Nutrition and Functional Medicine ®, *International Journal of Human Nutrition and Functional Medicine* ® (IntJHumNutrFunctMed.ORG), and International Conference on Human Nutrition and Functional Medicine ® are all registered trademarks™ legally held and internationally protected by the International College of Human Nutrition and Functional Medicine.

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Functional Medicine
Integrative Medicine
Internal Medicine
Pain Management
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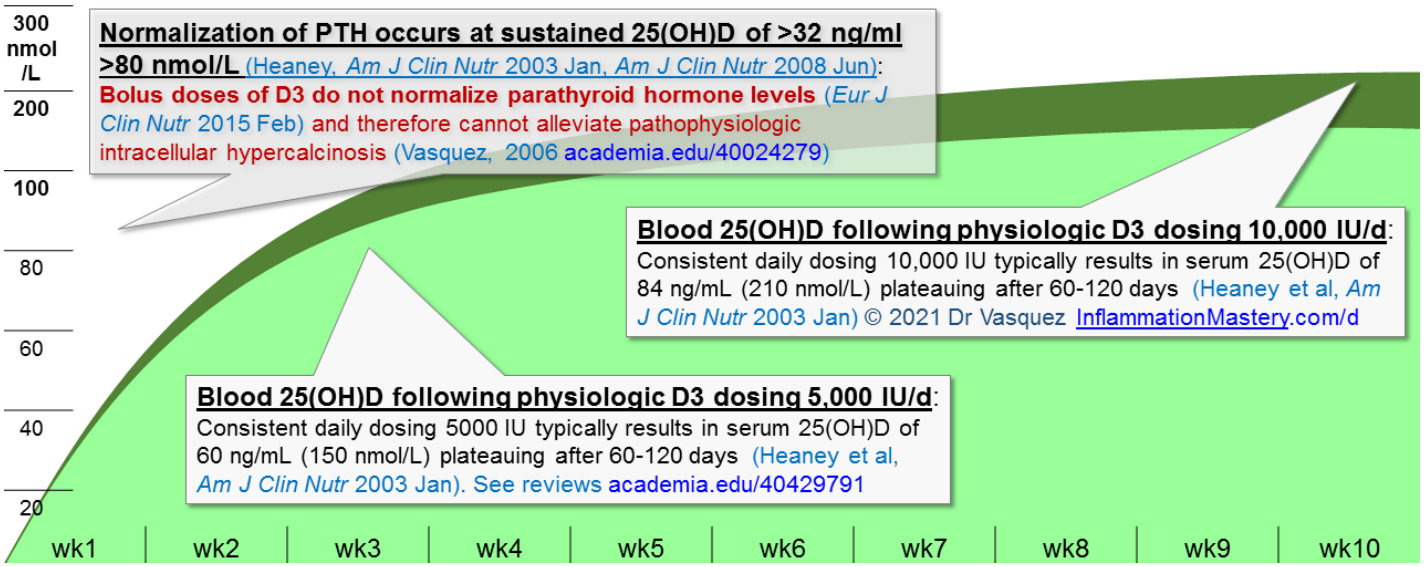
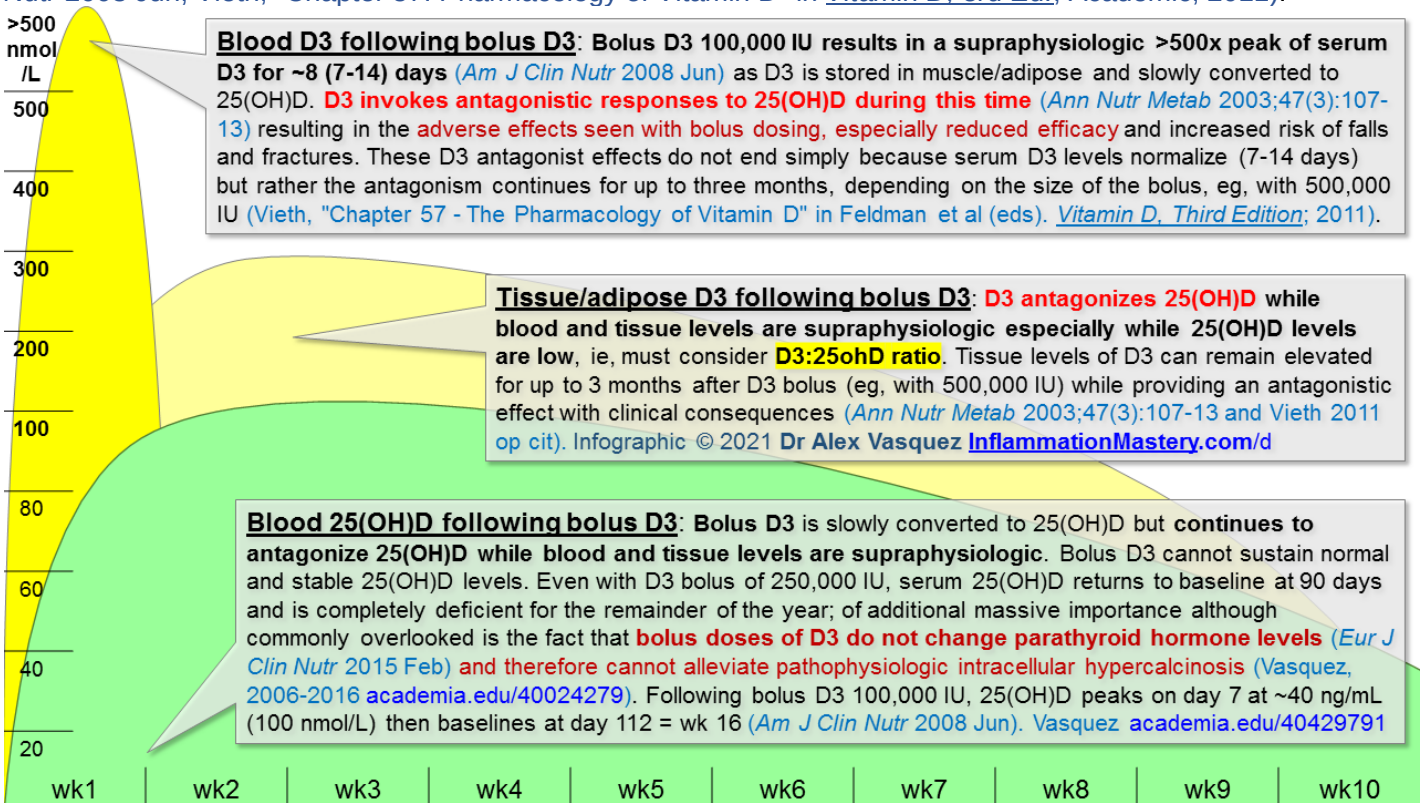
Vitamin D3 Pharmacology Infographic: Physiologic Dosing *versus* Bolus Roulette

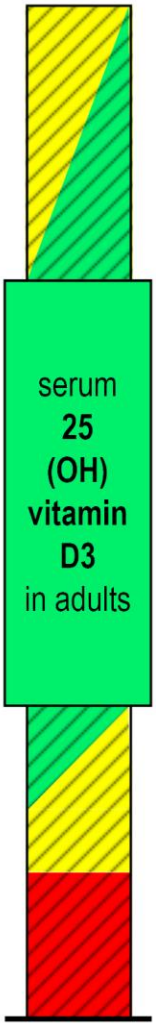
Alex Vasquez D.O., D.C., N.D. (USA), F.A.C.N.



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



Citation: © Vasquez A. Vitamin D3 Pharmacology Infographic: Physiologic Dosing versus Bolus Roulette. *Int J Hum Nutr Funct Med* ® 2021 Feb;9:3 ichnfm.org/journal. Externally archived at ichnfm.academia.edu/AlexVasquez and InflammationMastery.com/d; article updated 24-Feb-21



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

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

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

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

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

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

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

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

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

Infographic citations included in images; see also:

1. Vasquez et al. Clinical importance of vitamin D: a paradigm shift for all healthcare providers. *Altern Thera Health Med* 2004 Sep
2. Vasquez A. *Textbook of Clinical Nutrition and Functional Medicine*. ICHNFM.ORG, 2016
3. Vasquez A. How to Plan Studies Using Vitamin D. *Int J Hum Nutr Funct Med* 2017 academia.edu/31412957
4. Vasquez A. Revisiting the Supplemented Paleo-Mediterranean Diet. *Nutr Perspect* 2011 Jan academia.edu/39751813
5. Videos/excerpts 2020, articles and correspondence compilation 2004-2019. InflammationMastery.com/d
6. Heaney et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003 Jan;77(1):204-10. doi: 10.1093/ajcn/77.1.204
7. Heaney et al. 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. *Am J Clin Nutr*. 2008 Jun;87(6):1738-42. doi: 10.1093/ajcn/87.6.1738

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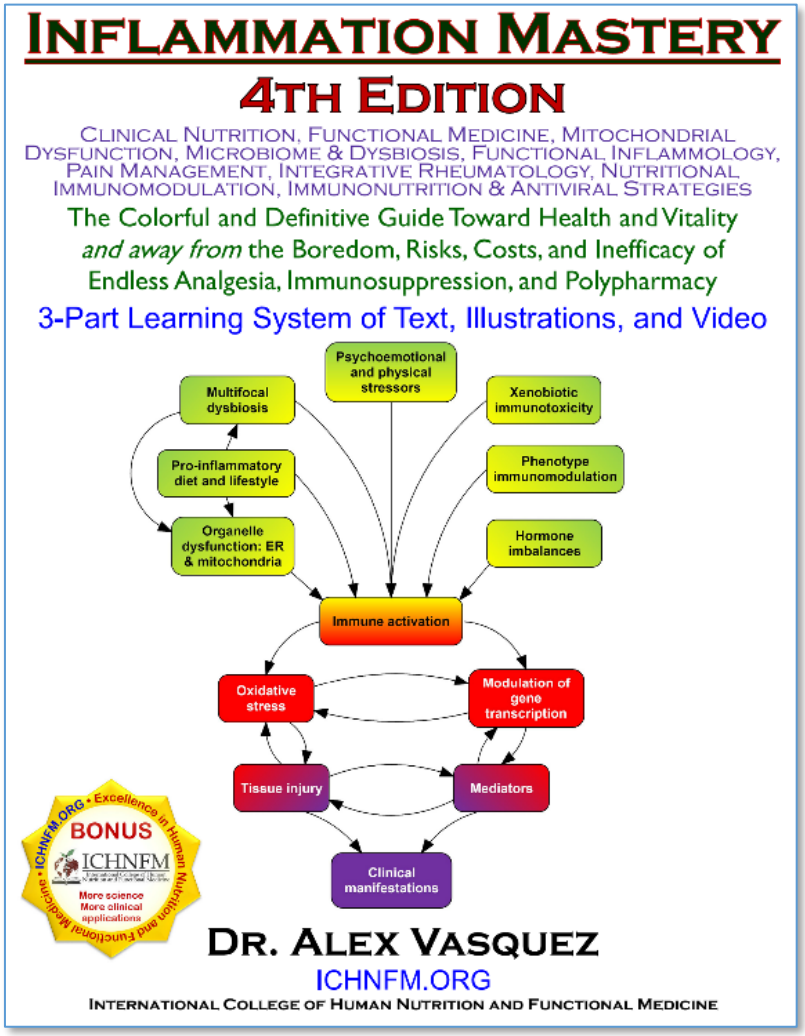
About the author and presenter: Alex Kennerly Vasquez DO ND DC (USA), Fellow of the American College of Nutrition (FACN), Overseas Fellow of the Royal Society of Medicine: An award-winning clinician-scholar and founding Program Director of the world's first fully-accredited university-based graduate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



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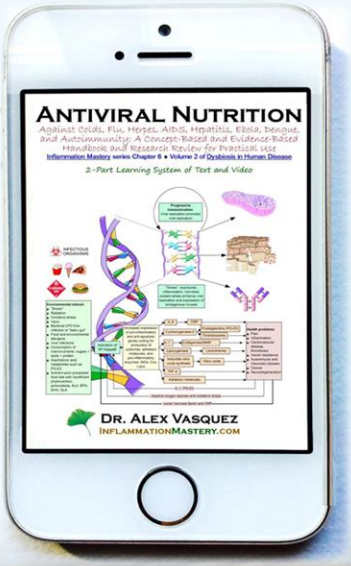

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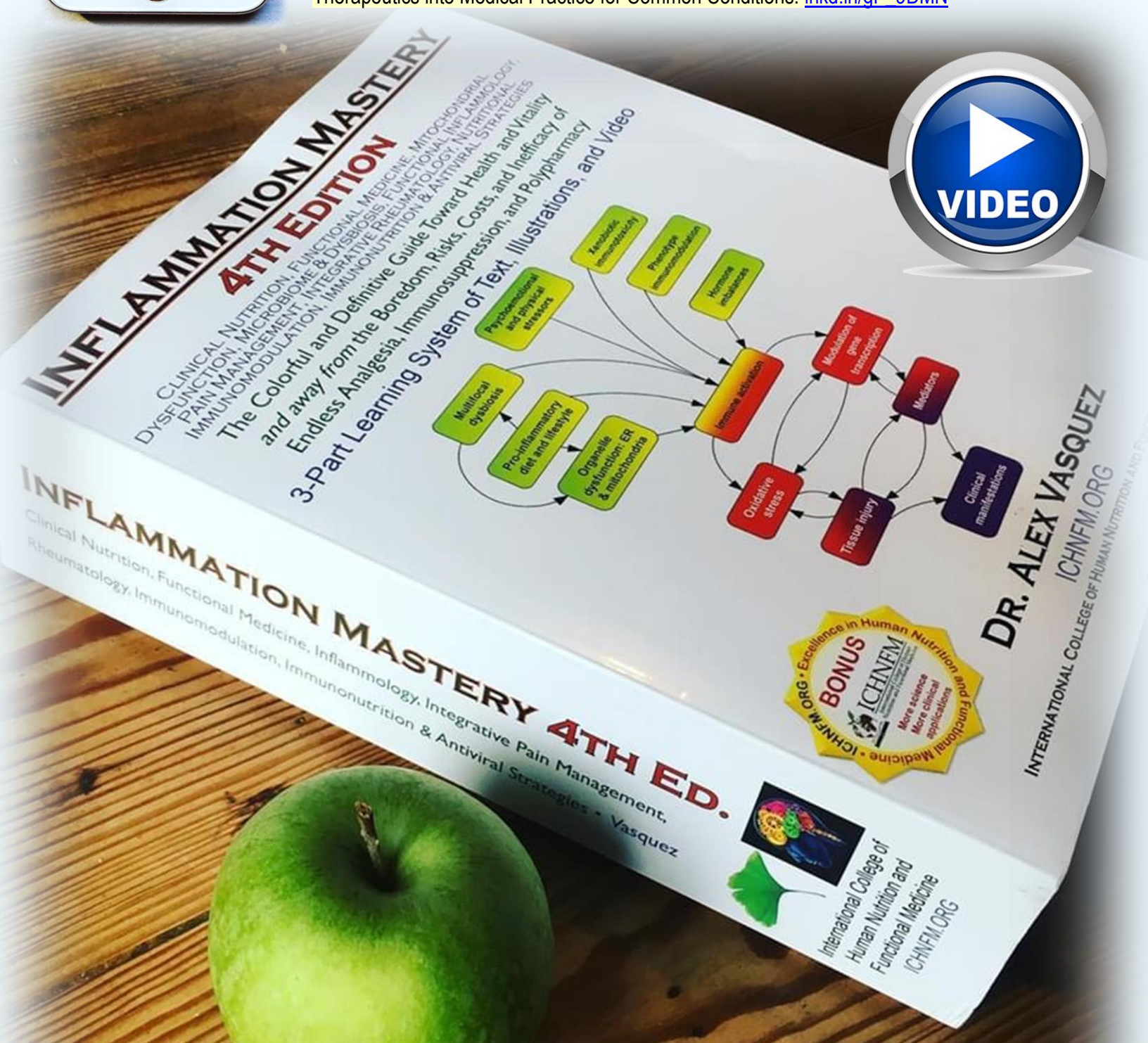

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Paradigm Shift • **Clinical Nutrition** • Primary Care • Prevention • Medicine • Metabolism • Politics

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

Alex Vasquez DO DC ND (USA) FACN

Vitamin D: Metabolism Dogma

The "vitamin D metabolism dogma"—as 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

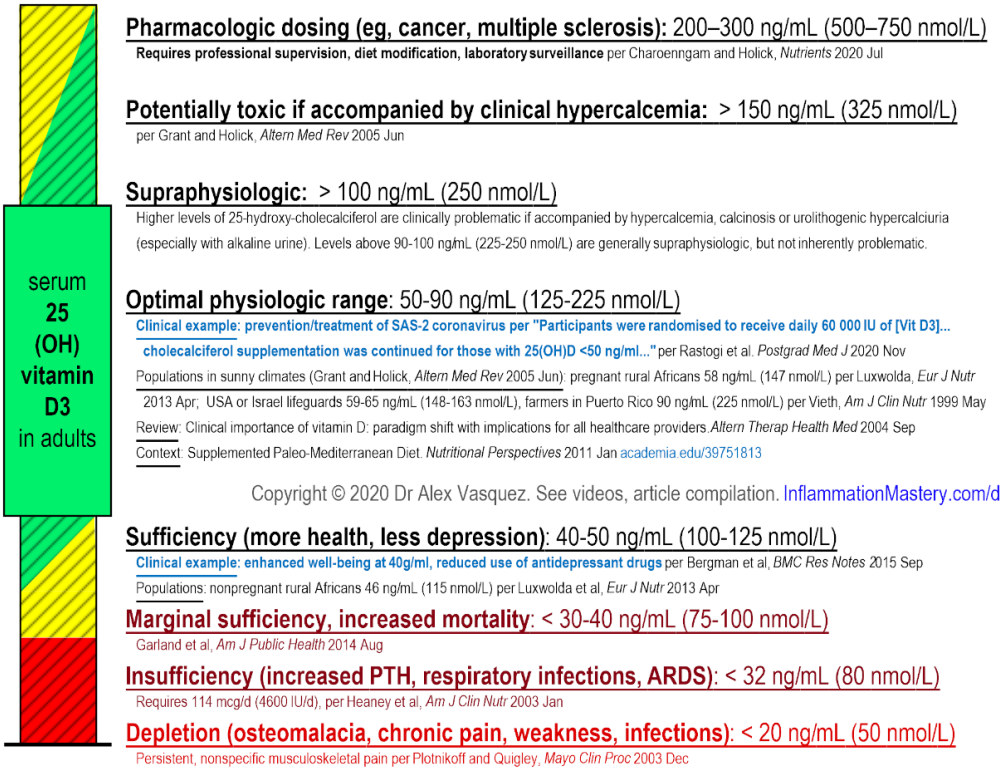
pharmacologic principles in the study of nutritional therapy, thereby perpetuating for its own benefit the "mystery" and "unreliability" of Nutrition, which would be its biggest therapeutic competitor. Principles of Biochemistry and Physiology and Mathematics are commonly applied to drug dosing such 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
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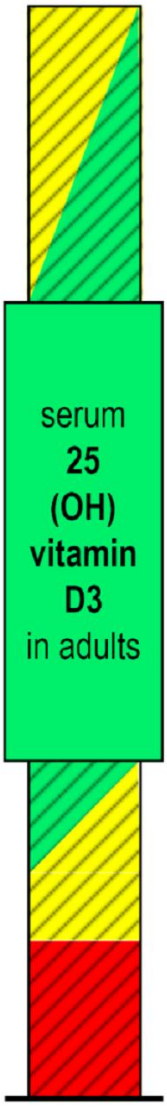
The "vitamin D metabolism dogma"—as discussed here and familiar to many adults—is that vitamin D is produced in the skin following the exposure of intradermal (7-

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

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

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



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

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

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

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

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

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

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

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

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Pharma Echo Chamber, Sociopolitical Matrix, Power Vortex: A Diagram-Centric Conceptualization. *IJHNFM* 2019

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  - 2019 reply Scotland's public health programs and trends improving nutritional status should be considered when discussing HPV trends bmj.com/content/365/bmj.l1375/rr-4
- 2017 blog: ichnfm.org/d3
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- 2020 pharmacology of the D3 bolus, explanation for confusing clinical results: academia.edu/44701698

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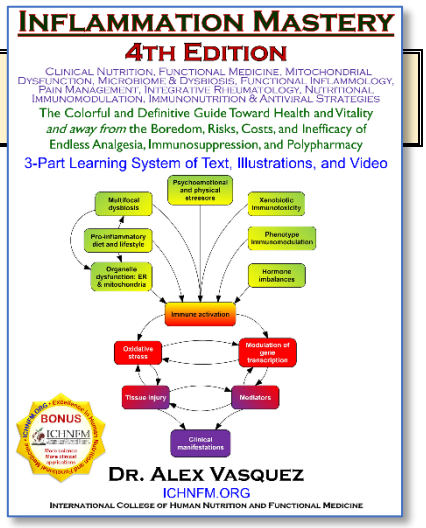

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2019 BMJ.com Response to Article "Prevalence of cervical disease at age 20 after _____ with bivalent HPV _____ at age 12-13 in Scotland": public health campaigns to improve vitamin D nutriture occurred within same timeframe as HPV _____ [rapid response].

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