Alex Vasquez, DC, ND, DO, FACN: Mitochondrial Dysfunction and the Emerging "Mitochondrial Medicine"

Interview by Craig Gustafson

Alex Vasquez, DC, ND, DO, FACN, *will present at the 2013 International Conference on Human Nutrition and Functional Medicine in Portland, Oregon, September 25-29, 2013. He is a clinician, lecturer, and author in the field of functional medicine. Dr Vasquez currently serves as program director for the International College/Conference of Human and Functional Medicine and editor of International Journal of Human Nutrition and Functional Medicine, all of which are described at ICHNFM.ORG. As an award-winning educator and leader, "DrV" lectures doctors and health care professionals inter-nationally and has also taught courses in pharmacology, nutrition, orthopedics, and rheumatology at Bastyr University and for post-graduate audiences internationally. Dr Vasquez is author of more than 100 articles and 10 books, with publications appearing in several peer-reviewed medical journals including The Lancet, JAMA, British Medical Journal, Journal of the American Osteopathic Association, and Alternative Therapies in Health and Medicine.*

***Integrative Medicine: A Clinician's Journal* (*IMCJ*):** Would you briefly explain the role of mitochondria in the cell?

Dr Vasquez: The traditional biological view that we all learned in medical school and in our basic science courses has held that the exclusive role of the mitochondria is to produce cellular energy in the form of ATP. Most basic science students are also taught that the primary fuel source for ATP production is carbohydrate, and therefore, in sum: Mitochondria function to produce cellular energy in the form of ATP via biochemical reactions largely dependent on carbohydrate as the primary fuel source.

We now appreciate that while this information may be somewhat accurate, it is very clearly incomplete. Clinicians and researchers in these modern times must appreciate that the mitochondria do more than simply produce ATP and that in many cases carbohydrate (especially fructose) consumption *impairs* rather than promotes the production of cellular energy. Furthermore, and very importantly, mitochondria play critically important roles in cancer pathophysiology, insulin resistance and type 2 diabetes, the detection of infectious microorganisms, and—in the case of mitochondrial dysfunction—the promotion of sustained inflammation and increased production of free radicals and reactive oxygen species. In sum, we have completely changed our view of mitochondria from that of its being an organelle that receives carbohydrate and produces ATP to a more mature understanding of the mitochondria as a key player in systemic health and the inhibition or progression of various disease states, including Parkinson's disease, Alzheimer's disease, autoimmunity, allergic inflammation, diabetes mellitus, hypertension, fibromyalgia, migraine headaches, and chronic fatigue syndrome.

***IMCJ*:** You seem to be suggesting that we should be shifting our nutritional habits away from carbohydrates. How should we recompose our diets for optimum mitochondrial function and, thus, energy production?

Dr Vasquez: That is exactly what I'm saying: For numerous health benefits *in addition to and beyond the optimization of mitochondrial function*, most of us need to reduce our intake of carbohydrates. Mitochondria function best on minimal carbohydrate intake. Now, of course what I'm talking about here is framed within the context of discussing regular daily activities and disease prevention; some situations obviously benefit from increased consumption of carbohydrates, namely postexercise recovery and muscle glycogen supercompensation. Additionally, carbohydrate/insulin-mediated alterations in plasma amino acid levels can facilitate tryptophan entry into the brain to help alleviate feelings of anxiety and depression. However, as a general rule, we should—according to current literature as well as innumerable past studies—strongly lean toward a low-carbohydrate diet. Low-carbohydrate diets have proven effective for a wide range of conditions including autoimmune diseases, type 2 diabetes, hypertension, and seizure disorders. The research literature and successful clinical experience showing the efficacy of low-carbohydrate diets for these conditions is irrefutable. Relatedly, our rapidly developing understanding of the relationship between glucose, mitochondria, insulin, and cancer is also strongly suggesting a place for low-carbohydrate diets in the prevention—and, in selected cases, treatment—of cancer.

***IMCJ*:** What are some of the things that can negatively influence the "health" and efficiency of mitochondria?

Dr Vasquez: Many things can negatively influence mitochondrial function, and once initiated, mitochondrial dysfunction becomes a self-perpetuating and progressive

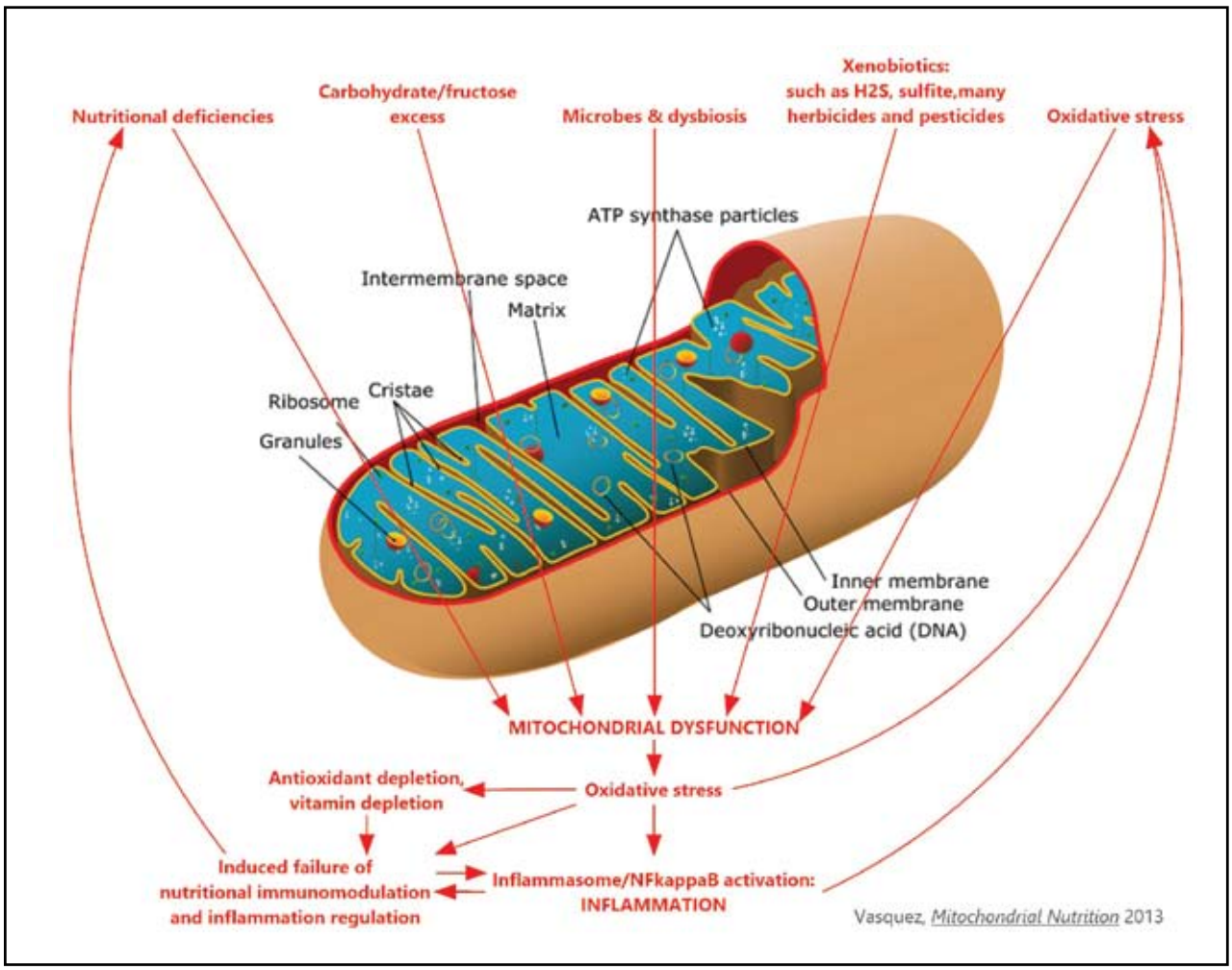

Figure 1. Mitochondrial Dysfunction

vicious cycle. Vitamin and mineral deficiencies clearly and commonly cause mitochondrial dysfunction. Many pharmaceutical drugs and toxic environmental chemicals like herbicides and pesticides are also mitochondrial poisons. Metabolic toxins produced by endogenous bacteria within the gastrointestinal tract also cause mitochondria dysfunction; some of these toxins include D-lactic acid, hydrogen sulfide, and bacterial lipopolysaccharide. Other dietary and environmental toxins such as sulfites found in red wine and cyanide found in tobacco smoke are also mitochondrial poisons.

***IMCJ*:** Leaving inflammation aside for the moment, what are some of the other outcomes that mitochondrial dysfunction causes?

Dr Vasquez: I'll frame my answer within a discussion of common conditions rather than orphan diseases and very clear examples of mitochondriopathy, such as Leigh syndrome and Leber's hereditary optic neuropathy. The first example is diabetes: Given that the pancreatic secretion of insulin and the peripheral reception of insulin both require proper mitochondrial function, diabetes mellitus type 2 (and insulin resistance/hyperinsulinemia) is an obvious outcome of mitochondrial dysfunction. Relatedly. therefore, so-called primary or essential hypertension often carries a component of mitochondrial dysfunction as well. Primary headache syndromes such as migraine show a "dose-dependent" relationship between headache severity and frequency with the severity of the underlying mitochondrial dysfunction. The best evidence on chronic fatigue syndrome and fibromyalgia shows that these are noninflammatory diseases caused largely or exclusively by microbial infections/colonizations that directly or indirectly impair mitochondrial function. Pathophysiologic processes of complex illnesses rarely occur in isolation, and, of these—once initiated—mitochondrial dysfunction tends to be self-perpetuating and progressive. (See Figure 1.)

***IMCJ*:** In one of your seminars, you will explain how to prevent and treat three categories of inflammatory disease. What are these categories and how are they linked to mitochondrial dysfunction?

Dr Vasquez: Per my description of various inflammatory diseases in my "functional inflammology protocol," I distinguish the three major categories of sustained/chronic inflammation as (1) metabolic, (2) allergic, and (3) autoimmune. In truth, the delineation of these categories is perceptual and conceptual rather than actual, given that significant overlap exists between states of metabolic, allergic, and autoimmune inflammation. Mitochondrial dysfunction plays a role within each of these subcategories of clinical disease. Some of the simplest truths we can articulate to describe this landscape are (1) mitochondrial dysfunction causes inflammation, and inflammation causes mitochondrial dysfunction; (2) mitochondrial dysfunction increases free radical generation, and increased free radical generation promotes mitochondrial dysfunction via several mechanisms; and also that (3) nutrient deficiencies promote mitochondrial dysfunction, and the reverse is also true. Lastly in introducing the connection between inflammation and mitochondrial dysfunction, we can note that some of the so-called anti-inflammatory drugs—including the prototype prednisone—actually cause/exacerbate mitochondrial dysfunction. Thus in this situation we note the following paradox: A drug used in the treatment of inflammatory/allergic/autoimmune diseases could actually promote the same diseases via pharmaceutical-iatrogenic induction of mitochondrial dysfunction.

***IMCJ*:** In a general way, how are these categories useful for examining and treating chronic inflammation?

Dr Vasquez: Long-term management of inflammatory/allergic/autoimmune disorders that relies primarily or exclusively on inflammation-suppressing drugs reveals either the error of circular logic (ie, "Inflammatory diseases cause themselves and therefore inflammation must be treated with anti-inflammation drugs") or the failure to appreciate that the body does not sustain so-called chronic inflammation without cause. We are all taught in medical school and in the medical textbooks that these are conditions of "chronic inflammation"; I refute this promulgation by declaring that for the vast majority of long-term inflammatory diseases, so-called chronic inflammation does not exist. These are not conditions of "chronic" inflammation; they are conditions of "sustained" inflammation. The clinicians' task is therefore to determine the cause(s) that are sustaining the inflammatory response, and then to intervene with therapeutic precision, efficacy, and safety.

Doctors need to treat inflammatory disorders as manifestations of immune dysfunction and inflammation dysregulation by working to restore and recalibrate homeodynamic systems and by removing the causative triggers that sustain the inflammatory response. I have been detailing this for many years in my books and seminars, and I first learned the concept from my teacher Dr Jeffrey Bland back in the late 1990s. By this time in 2013, per the accumulation (quantity, quality, diversity) and appreciation of patterns within the biomedical research literature over the past many years, we are rapidly approaching a time—and perhaps we have already arrived at that time—when treating inflammation, allergy, and autoimmune diseases primarily or exclusively with manifestation-suppressing drugs is going to appear overly simplistic and inefficient if not inappropriate and unethical. Of course, all of us appreciate the need for acute anti-inflammatory interventions in cases of acute inflammatory exacerbations, most prototypically exemplified by giant cell arteritis, status asthmaticus, neuropsychiatric lupus, transverse myelitis, and occlusive vasculitis. But everyone familiar with the research literature is in agreement that the popular current model of drug management for so-called chronic inflammatory disorders is highly inefficacious, expensive, inefficient, wrought with adverse effects, and it promotes dependence on the part of doctors and patients to rely almost exclusively on the pharmaceutical industry, as if—somehow—disease treatment and health promotion necessitated mandatory drug dependence. By appreciating the continuum of inflammatory disease categorization and by recognizing the primary contributory etiologies of chronic/sustained inflammatory states, researchers and clinicians are better able to manage these diseases by treating the causes of the problem.

***IMCJ*:** Can you perhaps provide a brief example of how mitochondrial intervention was used within your "functional inflammology protocol" to help one of your patients?

Dr Vasquez: Of course. I have a great case of a patient with rheumatoid arthritis who was the first person I treated with the updated protocol. I've been developing this protocol since I first taught rheumatology for the Naturopathic Medicine Program at Bastyr University in 2001; the first five parts of the protocol were published in my textbook *Integrative Rheumatology* in 2006. Although I have continued to update and refine the protocol on a monthly basis, the protocol experienced a quantum leap in March 2012, when I integrated new research and two new components just before leaving for some presentations in Europe. I used the complete new protocol to help a woman with "severe aggressive rheumatoid arthritis" who had been treated with all of the usual DMARDs and biologic drugs to no avail; her rheumatologist was suggesting that the patient take new experimental drugs, since the standard drug protocol failed to provide benefit. She had also been treated at our local naturopathic clinic, and she had undertaken a 26-day water-only fast; neither of these steps provided sustainable benefits. In March 2012, we started her on the updated protocol. At the first visit, her CCP antibody was >250; CCP is the best blood test for rheumatoid arthritis, and the elevation of the CCP level corre-

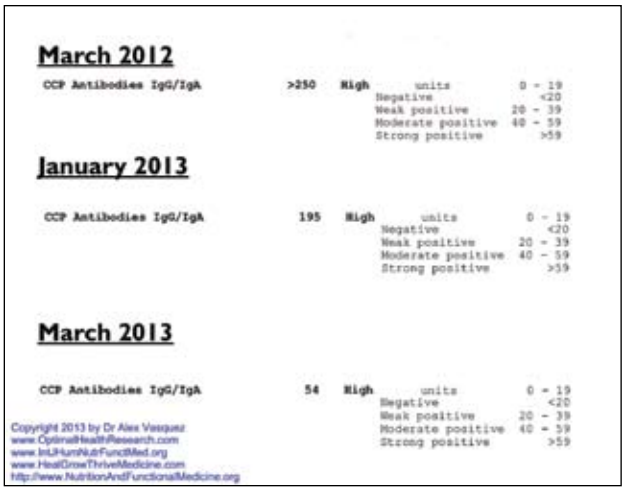

Figure 2. Lab Results

sponds directly with the severity and recalcitrance of the disease. With time and refinement of her treatment plan, her CCP reduced to 195 in January 2013, coinciding with alleviation of many of her symptoms. With additional time and further customization of her plan, when we retested her CCP antibodies in March of this year, her CCP levels had dropped to 54, coinciding with nearly complete alleviation of her symptoms despite not using any anti-inflammatory drugs. She reports feeling great, losing about 40 pounds of weight, and regularly performing manual labor on her farm. When I saw her at her third visit, I hardly recognized her; she looked completely transformed. Her lab results are presented in Figure 2.

***IMCJ*:** Once one has adopted this paradigm, what is the next step in addressing chronic inflammation through mitochondrial optimization?

Dr Vasquez: The treatment plan of course always has to be tailored to the individual patient, but some of the general categories of considerations for mitochondrial optimization include: diet and nutrition, lifestyle/exercise, detoxification, and therapeutic/interventional disinhibition. The latter—which some readers will appreciate is an extension of the naturopathic philosophy of "removing obstacles to cure"—addresses treatable impairments to mitochondrial function such as chronic bacterial and viral infections/dysbiosis; this is an important consideration because the sophomoric approach of course is always to push the mitochondria with various metabolic stimulants whereas a more effective approach emphasizes the removal of factors which actually block mitochondrial function. For example, microbe-induced mitochondrial dysfunction can be caused by bacterial toxins such as lipopolysaccharide, D-lactic acid, and hydrogen sulfide in addition to direct intracellular bacterial and viral infections which directly impair, deplete, or destroy mitochondria.

***IMCJ*:** What are a few of the ways in which nutrition can support mitochondrial function?

Dr Vasquez: Many ways, and my initial list of mitochondrial enhancement and mitochondrial disinhibition includes at least 26 different therapeutic interventions, most of which are natural and nutritional and a few of which are pharmacologic. On that last note, I readily acknowledge and appreciate the appropriate use of pharmaceutical drugs in the treatment of chronic inflammatory states; however, among the pharmaceutical interventions that I use for the treatment of inflammation, virtually none of these drugs are "anti-inflammatory" drugs. The use of anti-inflammatory drugs for the treatment of "inflammatory diseases" is circular logic—if it can be called logic—which appears to be based on the presumption that inflammatory diseases cause themselves; such a presumption has minimal scientific substantiation and is therefore readily discarded by those of us who believe in a rational universe characterized by cause-and-effect relationships rather than pseudoscientific shibboleths such as spontaneous generation and magical thinking.

The most basic nutritional approach for the optimization of mitochondrial function is that which emphasizes nutritional density—specifically increased intake of vitamins and minerals at the expense of carbohydrate intake; this strategy serves to provide micronutrients and sufficient substrate while also promoting endogenous production of β-hydroxybutyrate to stimulate the electron transport chain for greater efficiency of ATP production. An example of interventional disinhibition would be that of using vitamin B_{12} in the form of hydroxocobalamin to chelate specific mitochondrial toxins such as sulfite and cyanide.

***IMCJ*:** Would you discuss a couple of other examples that you find particularly useful?

Dr Vasquez: We always have to begin with an in-depth study of and appreciation of the complexity of mitochondrial function in particular and physiologic and systems-based interconnections in general. For the latter, various versions of the functional medicine approach are very useful here. For the former, we have to not only appreciate the biochemical reactions and nutritional needs for ATP production, but we also have to appreciate the inner-mitochondrial and extra-mitochondrial processes involved and which regulate mitochondrial function and populations. If we simply think of mitochondrial biochemistry, the Krebs cycle, and the electron transport chain, then of course we use nutritional supplementation to support mitochondrial function. However, if we extend our view beyond the mitochondria, then we can appreciate—for example—the benefits of therapeutic induction of mitochondrial destruction (ie, mitochondrial purging, mitophagy), achieved, for example, with exercise and carbohydrate restriction. We

can't simply think of mitochondria as if they are a homogenous population; we have to appreciate the mitochondrial population includes Olympians as well as misfits. Therefore, when viewed clinically, "Olympian" mitochondria perform better with nutritional supplementation, while dysfunctional "misfit" mitochondria can either be rehabilitated or—if not—then selectively deleted. By culling the mitochondrial herd through the use of therapeutic exercise and diet, and supporting this approach with appropriate nutritional supplementation, we ultimately end up with a higher functioning population of mitochondria. That is the ultimate goal. But of course, this is looking at only one aspect of sustained inflammatory processes, their generation and treatment.

***IMCJ*:** How does optimizing mitochondrial function impact the brain and neurological function?

Dr Vasquez: The brain is very ATP-dependent and has a very high density of mitochondria. Therefore, as we would logically anticipate, proper mitochondrial function is essential for proper neurologic function. Here again, we have to expand our vision from the common perception of neurologic function and this organ that we generally refer to as "the brain." Sure, mitochondrial optimization is a requirement and prerequisite for neurologic and intellectual optimization; more accurately: It is necessary but not sufficient, given that true intellectual optimization requires more than biochemistry and physiology and necessitates proper psycho-epistemology and social constructs as well. That should be self-evident at this time. As clinicians, researchers, and thinkers, we have to extend our vision of the brain beyond that of being "an organized and orchestrated collection of neurons"; we need to integrate new data on the role of astrocytes and microglia and the influence that these have on neurophysiology, which ultimately manifests as influences on intellectual and emotional performance.

***IMCJ*:** Your seminar on Thursday, September 26, will discuss peer-reviewed research that demonstrates specific approaches toward improving nutrition and outcomes for patients with organic brain diseases and mood disorders. How much research is available on these topics, and is it conclusive? How so?

Dr Vasquez: Those are excellent questions, answers to which can be supported or refuted based on perspective. Therefore, the approach we will use will be to combine a thorough survey of the research literature along with our practical and clinical experiences. The actual truth always exists somewhere between the polarities of scientific positivism and therapeutic nihilism. We will present the data and our case reports in an organized manner so that individual clinicians and researchers attending our conference will have the intellectual freedom to make their own evaluations. From intellectual and scientific perspectives, this is exactly what we should do. Dr David Haase has pioneered some excellent clinical interventions and has substantiated their efficacy with neurophysiologic testing; I am very excited to see his new presentation.

***IMCJ*:** What general consensus does this research reveal?

Dr Vasquez: Regardless of the diagnostic label being applied, whether it is neuropsychiatric or neuropathologic or infectious or traumatic, all patients with all neurologic conditions deserve nutritional interventions.

***IMCJ*:** What more will attendees learn about treating mitochondrial dysfunction and inflammation at the 2013 International Conference of Human Nutrition and Functional Medicine?

Dr Vasquez: We have a very powerful day on Friday—our "Mitochondria in Medicine" day—with presentations by Dr Michael Gonzales, Dr Matthew Hershey, Dr Garth Nicolson, and myself; each of us have published numerous articles/books/presentations on the role of mitochondrial function and dysfunction in health and disease. Among the four of us, we have approximately 1000 scientific publications, spanning molecular and basic science research to clinical applications and outcomes with patients. I will introduce the day and briefly conclude the day with a summary of major concepts and clinical "take–home" applications for clinical use and lifestyle integration. Very importantly, conference attendees will see how the themes presented and summarized on Friday also segue perfectly with the "brain nutrition" presentations on Thursday by Drs Deanna Minich, Tom O'Bryan, and David Haase and the diet and exercise and lifestyle information presented on Saturday and Sunday by Drs Loren Cordain, James O'Keefe, Lynda Frassetto, and Professors Pedro Bastos and Maelán Fontes. Of additional note, Jeffrey Smith's presentation on genetically modified foods during the lunch hour on Friday will further clarify the role of modern diets in health and disease.