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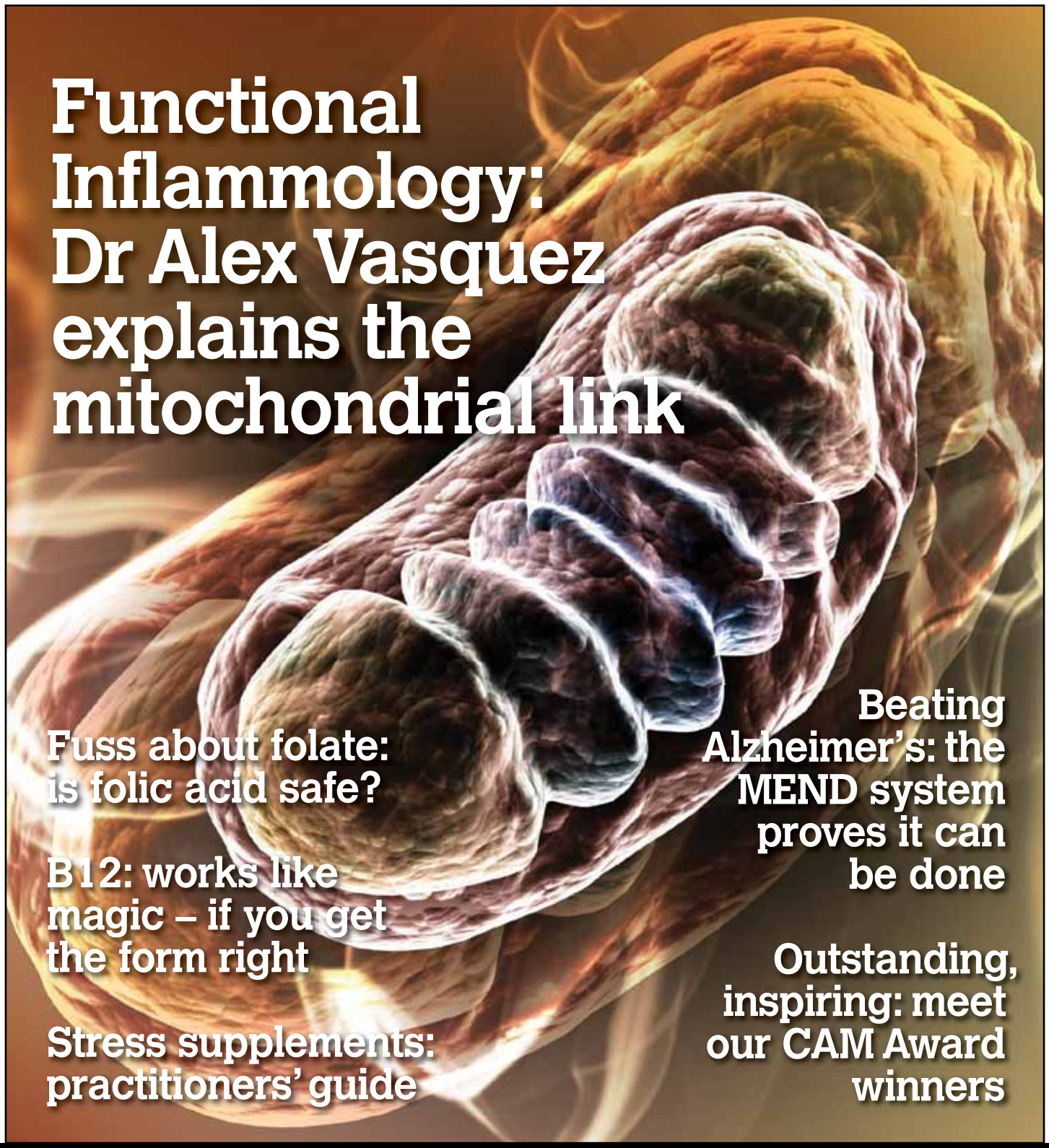
The magazine for complementary and alternative medicine professionals

DECEMBER 2014 £6



Functional Inflammology: Dr Alex Vasquez explains the mitochondrial link

Fuss about folate: is folic acid safe?

B12: works like magic – if you get the form right

Stress supplements: practitioners' guide

Beating Alzheimer's: the MEND system proves it can be done

Outstanding, inspiring: meet our CAM Award winners

PLUS How to steer the brain/gut conversation ■ In Practice ■ Women's fertility needs selenium ■ PCOS linked to leaky gut ■ When oats are toxic ■ Latest news and research

Functional Inflammology: the mitochondrial link

In his "functional inflammology" protocol, **Dr Alex Vasquez**, BSc, DC, ND, DO, FACN, director of programmes for the International College of Human Nutrition and Functional Medicine, (based in the US and Spain), and author of the 702-page textbook on the functional medicine approach to inflammation, distinguishes between three major categories of sustained/chronic inflammation. He explains how mitochondrial dysfunction plays a role within each of them. Dr Vasquez will be speaking at one of our 2015 *CAM* conferences.

***CAM:* What's wrong with the traditional view of mitochondria?**

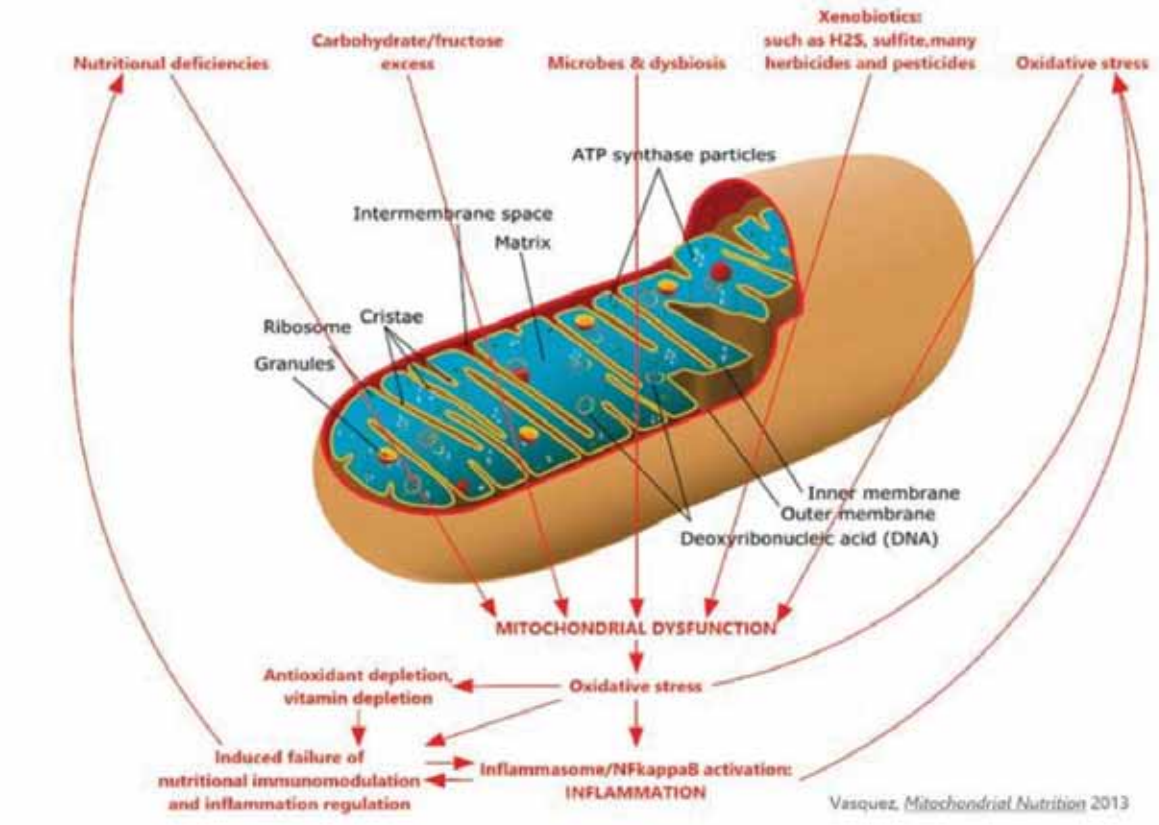
Dr Alex Vasquez: The traditional biological view that we all learnt in medical school and in our basic science courses has held that the exclusive role of the mitochondria is to produce cellular energy in the form of ATP. Most basic science students are also taught that the primary fuel source for ATP 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.

We have completely changed our view of a mitochondrion from that of its being an organelle that receives carbohydrate and produces ATP, to a more mature understanding of mitochondria as key players in systemic health and the inhibition or progression of various disease states, including Parkinson's, Alzheimer's, auto-immunity, allergic inflammation, diabetes mellitus, hypertension, fibromyalgia, migraine headaches and chronic fatigue syndrome.

***CAM:* So we should shift our nutritional habits away from carbohydrates. What's the best diet for optimum mitochondrial function and energy production?**

AV: For numerous health benefits in addition to



Schematic overview of mitochondrial dysfunction's major causes and consequences: notice the presence of vicious cycles, whereby cause becomes consequence, and then consequence becomes cause. Several dietary, nutritional, botanical, pharmaceutical/microbiologic, and sociopolitical interventions are obvious from the diagram. (Graphic from Vasquez, A 2014: *Mitochondrial Nutrition for Optimal Health and Performance: The Streamlined Digital Companion* excerpted from Dr Vasquez's textbooks. International College of Human Nutrition and Functional Medicine. Kindle Edition.)

and beyond the optimisation of mitochondrial function, most of us need to reduce our intake of carbohydrates. Mitochondria function best on minimal carbohydrate intake. Now this is framed within the context of discussing regular daily activities and disease prevention; some situations obviously benefit from increased consumption of carbohydrates, namely post-exercise recovery and muscle glycogen super-compensation. 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.

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

AV: 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. Many things can negatively influence mitochondrial function, and once initiated, mitochondrial dysfunction becomes a self-perpetuating and progressive vicious cycle.

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

AV: 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/hyperinsulinaemia) is an obvious outcome of mitochondrial dysfunction. 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 non-inflammatory diseases caused largely or exclusively by microbial infections/colonisations 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.)

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

AV: 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.
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.

***CAM:* How are these categories useful for examining and treating chronic inflammation?**

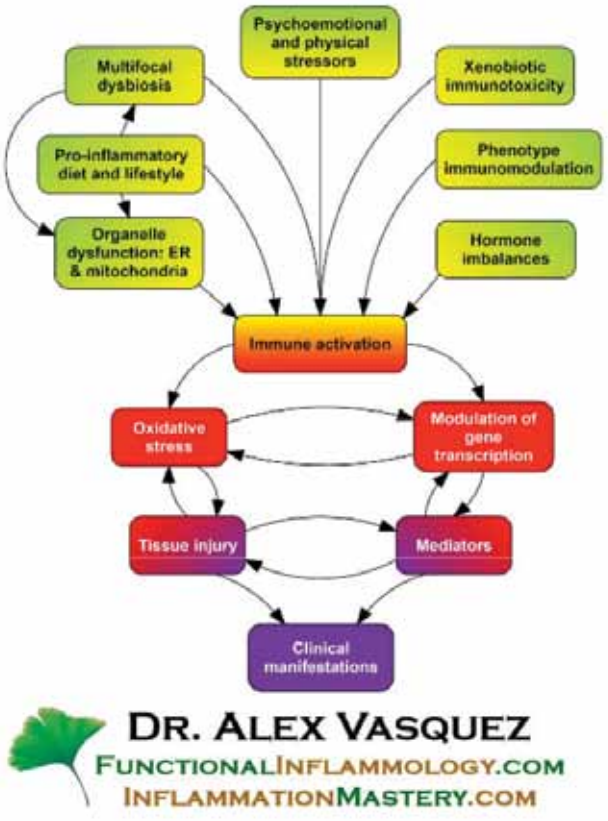
AV: Long-term management of inflammatory/allergic/autoimmune disorders that relies primarily or exclusively on inflammation-suppressing drugs reveals either the error of circular logic (ie, "Inflammatory diseases cause themselves and therefore inflammation must be treated with anti-inflammation drugs"), 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 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 learnt the concept from my teacher, Dr Jeffrey Bland, back in the 1990s.

By now, through 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 – 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 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 categorisation, and by recognising the primary contributory aetiologies of chronic/sustained inflammatory states, researchers and clinicians are better able to manage these diseases by treating the causes of the problem.



***CAM:* Can you give an example of how you used your "functional inflammology protocol" to help one of your patients?**

AV: 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 programme at Bastyr University in 2001; the first five parts of the protocol were published in my textbook *Integrative Rheumatology* in 2006 (now updated to a new textbook published in 2014, entitled *Functional medicine rheumatology v3.5*). 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 (cyclic citrullinated peptide) is the best blood test for rheumatoid arthritis, and the elevation of the CCP level corresponds 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 customisation of her plan, when we retested her CCP antibodies in March 2013, 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 labour on her farm. When I saw her at her third visit, I hardly recognised her; she looked completely transformed.

***CAM:* What is the treatment plan?**

AV: It of course always has to be tailored to the individual patient, but some of the general categories of considerations for mitochondrial optimisation 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 is always to push the mitochondria with various metabolic stimulants, whereas a more effective approach emphasises the removal of factors which actually block mitochondrial function.

For example, microbe-induced mitochondrial dysfunction can be caused by bacterial toxins →

→ such as lipopolysaccharide (LPS), d-lactic acid, and hydrogen sulfide, in addition to direct intracellular bacterial and viral infections which directly impair, deplete, or destroy mitochondria.

***CAM:* How do you use nutrition to support mitochondria?**

AV: 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". The most basic nutritional approach for the optimisation of mitochondrial function is to emphasise 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 beta-hydroxybutyrate [BHB, a ketone] to stimulate the electron transport chain for greater efficiency of ATP production. An example of interventional disinhibition would be that of using vitamin B12 in the form of hydroxocobalamin to chelate specific mitochondrial toxins such as sulfite and cyanide.

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

AV: 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. 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.

"…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, almost exclusively on the pharmaceutical industry, as if – somehow – disease treatment and health promotion necessitated mandatory drug dependence."

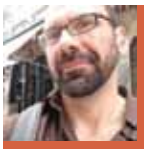
We can't simply think of mitochondria as if they are a homogenous population; we have to appreciate the mitochondrial population includes Olympians as well as misfits. Therefore, when viewed clinically, "Olympian" mitochondria perform better with nutritional supplementation, while dysfunctional "misfit" 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.

***CAM:* How does optimising mitochondrial function impact the brain and neurological function?**

AV: The brain is very ATP-dependent and has a very high density of mitochondria. Therefore, 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 optimisation is a requirement and prerequisite for neurologic and intellectual optimisation; more accurately, it is necessary, but not sufficient, given that true intellectual optimisation requires more than biochemistry and physiology and necessitates proper psycho-epistemology and social constructs as well. That should be self-evident by now. As clinicians, researchers and thinkers, we have to extend our vision of the brain beyond that of being "an organised 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. cam

* Adapted from an interview by Craig Gustafson originally published in *Integrative Medicine*, August 2013.

*** Resources:** recommended by editor Simon Martin as a "relatively" easy introduction to Alex's truly massive body of work – that he adds to on a weekly basis – is the recently-published *Mitochondrial Nutrition for Optimal Health and Performance: The Streamlined Digital Companion*, which is excerpted from Dr Vasquez's textbooks. This is a mere 161 pages – short by his standards – and in the Kindle edition links "live" to hordes of videos and papers. It is a steal at $9.99/£6.40. Easy to read but not easy to grasp: Alex makes few concessions, but if you put the time in, you will reap the rewards!



About the author

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). He is the author of many textbooks, including *Integrative Orthopedics* (2012), *Integrative Rheumatology* (2014), *Musculoskeletal Pain: Expanded Clinical Strategies* (published by the Institute for Functional Medicine, 2008), and *Mitochondrial Nutrition and Mitochondrial Medicine for Primary Care Conditions* (2014). "DrV" has also written more than 100 letters and articles for professional magazines and medical journals such as the *British Medical Journal (BMJ)*, The Lancet.com, *Journal of the American Medical Association (JAMA)* and the like. Dr Vasquez lectures worldwide to healthcare professionals and provides expert consultations to physicians and patients internationally. Dr Vasquez is the chief editor of the *International Journal of Human Nutrition and Functional Medicine*, and he helps moderate the "nutrition and functional medicine forum" at NutritionAndFunctionalMedicine.org/edu. A description of Dr Vasquez's other projects, books, audios, and videos is updated at his website; InflammationMastery.com. All of DrV's books are available on Amazon.com, with videos at Vimeo.com/DrVasquez and audio recordings of lectures at iTunes. Interested readers should be aware that all of Dr Vasquez's books are currently being reformatted and updated for full-colour printing with presentation slides and accompanying videos, starting with Functional Inflammology Volume 1: see FunctionalInflammology.com.

* Websites: www. InflammationMastery.com, www.ICHNFM.ORG and www.NutritionAndFunctionalMedicine.ORG.

* Videos: http://vimeo.com/ichnfm.