

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

Alex Vasquez, DC, ND, DO, FACN

Alex Vasquez, DC, ND, DO, FACN, is director of programs at the International College of Human Nutrition and Functional Medicine in Barcelona, Spain, and online at ICHNFM.org.

Corresponding author: Alex Vasquez, DC, ND, DO, FACN
E-mail address: ichnfm@gmail.com

Mitochondrial Medicine Arrives to General Practice and Routine Patient Care

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

We all know that mitochondria are the intracellular organelles responsible for the production of the currency of cellular energy in the form of the molecule adenosine triphosphate (ATP); by this time, contemporary clinicians should be developing an awareness of the other roles that mitochondria play in (patho)physiology and clinical practice. Beyond being simple organelles that make ATP, mitochondria play clinically significant roles in autoimmunity, inflammation, cancer, insulin resistance, cardiometabolic disease such as hypertension and heart failure, and neurologic disorders such as Alzheimer’s and Parkinson’s diseases. As I stated during the recent International Conference on Human Nutrition and Functional Medicine¹ in Portland, Oregon, in September 2013, we have collectively arrived at a time when mitochondrial therapeutics and the contribution of mitochondrial dysfunction to clinical diseases must be considered on a routine basis in clinical practice. *Mitochondrial medicine* is no longer an orphan topic, nor is it a superfluous consideration relegated to boutique

practices. Mitochondrial medicine is ready for prime time—now—both in the general practice of primary care as well as in specialty and subspecialty medicine. What I describe here as the “new” mitochondrial medicine is the application of assessments and treatments to routine clinical practice primarily for the treatment of secondary/acquired forms of mitochondrial impairment that contribute to common conditions such as fatigue, depression, fibromyalgia, diabetes mellitus, hypertension, neuropsychiatric and neurodegenerative conditions, and other inflammatory and dysmetabolic conditions such as allergy and autoimmunity.

Beyond Biochemistry

Structure and function are of course intimately related and must be appreciated before clinical implications can be understood and interventions thereafter applied with practical precision. The 4 main structures and spaces of the mitochondria are (1) intramitochondrial matrix—the innermost/interior aspect of the mitochondria containing various proteins, enzymes of the Krebs cycle, and mitochondrial DNA; (2) inner membrane—the largely impermeable lipid-rich convoluted/invaginated membrane that envelopes and defines the matrix and which is the structural home of many enzymes, transport systems, and important structures such as cardiolipin and the electron transport chain (ETC); (3) intermembrane space—contains noteworthy molecules: creatine-phosphokinase and cytochrome c; and (4) outer membrane—comparatively more permeable (to molecules <10 000 Dalton) and—like the inner membrane—very lipid-rich and with active and passive transport systems for select molecules that need to enter and exit the mitochondria. Clinicians need to appreciate that mitochondrial membrane integrity is of the highest importance; just as we have come to appreciate the importance of mucosal integrity of the gastrointestinal tract and the pathophysiologic complications of barrier defects (eg, “leaky gut”), so must we also now appreciate the clinical importance of defects in mitochondrial membranes (eg, “leaky mitochondria”). Hyperpermeability of the mitochondrial inner membrane (MIM) compromises ATP

production and promotes loss of function and cell death; consider the implications for mitochondrial dysfunction in the brain (eg, dementia, Parkinsonism), muscle (eg, fibromyalgia), and pancreas and peripheral tissues (eg, diabetes, insulin resistance). Hyperpermeability of the outer membrane releases cytochrome c into the cytosol, likewise triggering cell death by apoptosis. Thus, the clinical implications of leaky mitochondrial membranes are immediately apparent. Leaky mitochondrial membranes cause mitochondrial impairment promoting progressive functional loss resulting in clinical disease. The pattern of clinical expression and thus the accompanying diagnosis are dependent on many variables, including the location of the most affected tissues, severity of impairment, resilience and adaptation, and other concomitant influences such as age, nutritional status, microbial colonizations, hormonal balance, and xenobiotic accumulation.² Note that each of these latter-mentioned variables also contains virtually innumerable subvariables, hence the multitude of disparate-yet-related entities that are encountered clinically, depending on the host's unique combination of dysfunctions.

Clinicians must appreciate that mitochondrial disorders are varied and heterogenous, ranging from simple (1 focal defect) to complex (several simultaneous defects), including primary (genotropic), secondary (acquired), and mixed (gene defect along with acquired mitochondrial impairment) etiologies. Severe genotropic mitochondrialopathies are rare in outpatient clinical practice; much more common are the milder mitochondrialopathies of secondary or mixed origin. Mitochondrial performance can be casually described along a continuum starting with optimal (think *Olympian*: healthy and with abundant physiologic reserve) with a conceptual midpoint of average (think of your average person who can give a full day's work but who gets winded and has to rest when climbing stairs [eg, low physiologic reserve, fails when stressed]) to a terminal endpoint of a very frail and fragile mitochondrion, whose performance barely sustains life and whose performance becomes subvital when stressed for example by the addition of some physiologic insult such as toxin exposure, infection, or nutrient deficiency. In order to obtain and maintain optimal health, we as clinicians need to promote optimal mitochondrial function, moving the frail and failing mitochondria toward average, and the average (suitable for low performance but intolerant of stressors and incompatible with optimal longevity and health) toward optimal, Olympian status, at least ideally.

Memorization of part or all of the ATP production pathway is a common requirement for biochemistry courses in medical schools; yet, ironically, few medical graduates go on to apply this information clinically. Familiarity with the main components of the ATP production pathway allows us to visualize locations of defects and anticipate the pathophysiologic sequelae. In my visualization of this pathway, I consider the 5 main

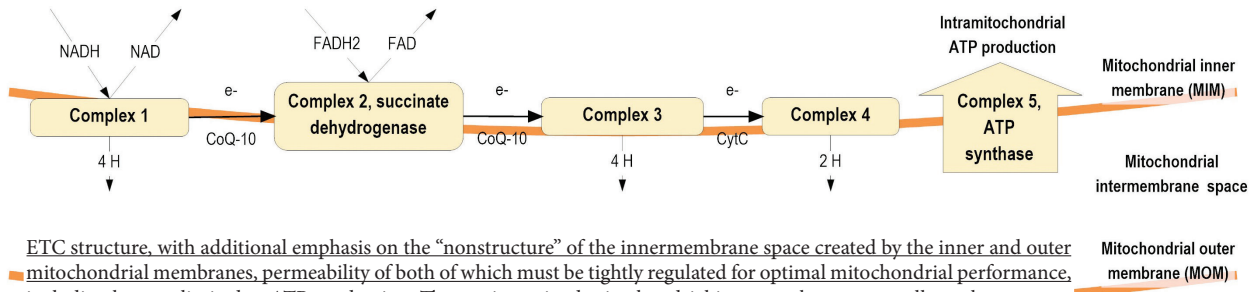
components to be (1) glycolysis—the cytoplasmic enzymatic conversion of sugars into pyruvate/lactate; (2) pyruvate dehydrogenase complex—enzymatic and nutrient-dependent conversion of pyruvate to acetyl-CoA; (3) Krebs/citric acid cycle—intramitochondrial enzymatic degradation of acetyl-CoA into its constituent carbon and hydrogen atoms to fuel ATP production; leading finally to (4) the ETC complexes 1 to 5, the last also called ATP synthase. A fifth component—(5) accessory fuel sources—feeds other sugars such as fructose into the glycolysis pathway and feeds nonsugar fuels such as alcohol, amino acids, and fatty acids into the Krebs cycle as acetyl-CoA. Genotropic defects can occur at any of the enzymatic and transport steps along this pathway; likewise, certain microbial and xenobiotic toxins impair specific points along the ATP production pathway. For example, the food preservative sulfite ($-\text{SO}_3^{2-}$) impairs the conversion of glutamate by glutamate dehydrogenase into α -ketoglutarate, an important fuel source for the Krebs cycle; by this mechanism, sulfite can cause a 50% reduction in ATP production in various human/animal cell types, with human brain neurons suspected to be the most vulnerable³ whereas clinically sulfite is known to exacerbate migraine headaches.⁴ The microbial toxin hydrogen sulfide (H_2S) poisons the ETC, with potency greater than that of cyanide.⁵

Speaking as a former medical student who memorized and could graphically recite every step of the 5 components of the ATP production pathway (see diagram online⁵), I see now an important shortcoming to this academic and biochemistry-centric approach. Such an approach focused almost exclusively on substrates and enzymatic conversions but without consideration of the anatomy and physiology of the surrounding subcellular milieu; furthermore, our memorization of biochemical pathways was—except for the inclusion of various fuel sources—essentially devoid of the real-world implications of diet and the effects of particular foods on mitochondrial function. Isolated biochemical pathways only exist as a simplification of reality for the sake of our comprehension, so that we can grasp one particular facet of a phenomenon; in reality, pathways do not exist outside of the networks in which they are contained, interconnected, and influenced.⁶ This “clinical contextualization” is what makes all the difference when translating our basic science education and research into real-life clinical effectiveness. Let us look at 4 examples in the following paragraph by contextualizing mitochondrial function with respect to (1) fructose as a fuel source, (2) ROS-induced damage to the MIM, (3) exposure to microbes, and (4) exposure to xenobiotics (persistent organic pollutants, or POPs).

If we simply draw all glycolytic and ATP-producing pathways on paper, the flow of fructose into the glycolytic pathway gives the appearance that fructose is a benign fuel

⁵Complete diagram of the ATP production pathway is available at <http://www.ichnfm.org/pdf/>.

Figure. The Clinical Significance of the Mitochondrial Intermembrane Space



ETC structure, with additional emphasis on the “nonstructure” of the innermembrane space created by the inner and outer mitochondrial membranes, permeability of both of which must be tightly regulated for optimal mitochondrial performance, including but not limited to ATP production: The semicontained mitochondrial intermembrane space allows the accumulation of protons from the ETC to concentrate into a “pressurized” electromechanical gradient that powers ETC complex No. 5, also called ATP synthase. ATP synthase is powered via the transmittal of protons from their high concentration gradient in the intermembrane space through the structure of the ATP synthase enzyme, which acts as a “pore” or “pressure valve” allowing protons to move to an area of lesser concentration inside the mitochondria. If the ATP synthase enzyme is bypassed because of a defective or “leaky” inner membrane that allows protons to leak back into the mitochondria, then the production of cellular energy will be reduced, leading to metabolic impairments such as increased free radical production (as the ETC works harder to compensate for reduced efficiency) and clinical manifestations such as fatigue, dyscognition, and muscle (eg, heart) impairment including body aches and pains consistent with clinical presentations of fibromyalgia and chronic fatigue syndrome. Transmembrane potential of the MIM is essential for the electromechanical gradient that drives ATP synthase; compromise of this membrane caused by dietary faults (eg, fatty acid deficiency, antioxidant deficiency) or biochemical faults (eg, overproduction of free radicals, which damage the MIM) will lead to hyperpermeability of the MIM (“leaky mitochondria”) and reduced ATP synthesis.

suitable for human (over)consumption; in reality, fructose’s conversion to fructose-1-phosphate drains ATP from the cell, promotes a dramatic inflammatory response, and leads to clinical features of insulin resistance, hypertension, and metabolic syndrome via several mechanisms, one of which is increased production of uric acid.⁷ Clearly, therefore, not all carbohydrate substrates are equivalent; carbohydrate type and dietary context affect mitochondrial function independently of calorie quantification. The clinical importance of the integrity of the MIM has been demonstrated by the research of Nicolson reviewed in an accompanying article in this issue⁸ and is discussed below. Briefly, Nicolson’s clinical trials have shown significant reductions in subjective and objective measures of fatigue (the most common clinical syndrome associated with mitochondrial dysfunction) with the use of orally administered phospholipids targeted to rebuild/restore the mitochondrial inner membrane; reduction of MIM permeability restores the potency of the trans-MIM electromechanical gradient necessary for optimal and efficient protonic propulsion of ETC complex 5 (ATP synthase) for its energy-dependent phosphorylation of adenosine diphosphate (ADP) into ATP. Microorganisms such as viruses and Gram-negative bacteria greatly affect mitochondrial function and can promote the clinical phenotype of mitochondrial disease (ie, microbial mitochondriopathy). Herpes simplex virus destroys mitochondrial DNA⁹ and likely contributes to Alzheimer’s disease,¹⁰ a condition that is well known to have a significant mitochondriopathic component.¹¹ Endotoxin (lipopolysaccharide, or LPS) from Gram-negative bacteria impairs cellular bioenergetics, as evidenced by postexposure increased lactic acid production,¹² which probably originates from immunocytes.¹³ LPS activates of the mammalian/mechanistic target of rapamycin

(mTOR)¹⁴ and induces mitochondrial polarization, which increases inflammatory mediator production and skews the clinical phenotype toward one consistent with autoimmunity, as seen for example in patients with systemic lupus erythematosus (SLE, lupus).^{15,16} Finally, environmental toxins such as POPs are bioaccumulative, and the body burden of POPs in humans correlates with induction of human disease such as diabetes mellitus¹⁷ and Parkinson’s disease¹⁸ via mitochondrial impairment, what I refer to as *xenobiotic mitochondriopathy*. Thus, per these simple examples, we can appreciate at least 4 types of acquired mitochondrial disorders—dietary, oxidative, microbial, and xenobiotic; readers can ponder the overlapping effects of these mitochondriopathic influences when combined together as they always are in the real world. Picture the prototypic pristine mitochondria performing prodigiously, and now contextualize that otherwise-perfect mitochondria within a patient who overconsumes high-fructose corn syrup, has multiple antioxidant deficiencies caused by poor diet choices and lack of nutritional supplementation, harbors small intestinal bacterial overgrowth with Gram-negative bacteria, and has accumulation of POPs; now you should see how mitochondrial function is critically affected by lifestyle choices, occult infections/dysbiosis, and environmental exposure to corporate pollution. You now see the development of a sufficient recipe, augmented by adding an inactive lifestyle and perhaps (optionally) genetic predispositions, for pandemics of obesity, allergic and autoimmune disorders, neurodegenerative diseases, diabetes, and dysinsulinemic and inflammation-driven cardiovascular diseases.

Reasons for the emergence of routine mitochondrial medicine include (1) progress in basic sciences—increased awareness of the full spectrum of roles played by

mitochondria in health and disease; (2) changes in clinical landscape—increased prevalence of mitochondriopathy-related disorders ranging from diabetes to neurodegeneration; (3) increased awareness of the adverse effect that certain foods can have on mitochondrial function—consumption of mitochondria-impairing foods such as high-fructose corn syrup can promote hypertension and insulin resistance; and (4) awareness that many common pollutants impair mitochondrial function—we are all exposed to pollutants, particularly herbicides and pesticides, and many of us also to mitochondria-poisoning medications.¹⁹ Science in “mitochondriology” has advanced at the same time as the prevalence of diseases associated with mitochondrial dysfunction, thus culminating in a perfect storm for the condensation of a “new” clinical science and therapeutic opportunity: mitochondrial medicine.

In this issue of *Integrative Medicine: A Clinician's Journal*, Professor Nicolson reviews the literature and his primary research experience regarding the importance of and means for enhancing mitochondrial function in clinical practice. Two aspects of his work and perspective that I like most are as follows: (1) the approach he advocates is safe, effective, and logical, and I am a fan of each of these; and (2) Dr Nicolson's approach focusing on MIM restoration is unique in its respect for the importance of restoring subcellular structure as a means by which to improve physiologic function and thereby positively influence the patient's clinical presentation. Thus, the effectiveness of his approach provides proof of principle, validating and underscoring the importance of mitochondrial membrane integrity for the alleviation of human diseases related to mitochondrial dysfunction. Proton leak across the MIM, which occurs in several types including basal (transmembrane), augmented (via uncoupling proteins), and xenobiotic/pharmacologic (eg, salicylic acid and 2,4-dinitrophenol) forms, is biologically expensive, commonly accounting for 20%-35% of biological energy expenditure in different cell types from various species. The work of Dr Nicolson and his colleagues emphasizes the use of oral supplementation with phospholipids unique to the MIM to restore its structure and function by replacing damaged MIM phospholipids and thereby reducing MIM hyperpermeability to protons; again, MIM hyperpermeability reduces ATP production via oxidative phosphorylation by reducing the electromechanical gradient necessary to physically drive ATP synthase's rotary catalysis. Stated simply, if the MIM is leaky because of oxidative damage, then the “ATP-producing pump” (ETC complex No. 5, the ATP synthase enzyme) cannot function at optimal efficiency because the protons will leak across the hyperpermeable MIM in a random manner rather than being funneled through the channel of ATP synthase.

Clinical Applications

Genotropic mitochondrial disorders generally manifest in infancy and childhood; however, some genotropic mitochondrial disorders have a surprising presentation later in adulthood following an apparently normal childhood and adolescence. Secondary or acquired mitochondrial disorders can present at any age but are more common in adults, for example following acquisition of persistent microbial colonizations or accumulation of organic pollutants. Clinicians have to base their evaluation and treatment on the perceived genesis and severity of the patient's presentation.

On one end of the spectrum might be an infant with failure to thrive, seizures, and neurodevelopmental delay suggesting the possibility of a rare, specific, severe “primary” genotropic mitochondrial disorder; such cases necessitate full evaluation (likely including genetic testing, neuroimaging, and cell/tissue analysis) and are best managed by a subspecialist. More commonly, clinicians in outpatient practice will encounter either “secondary” or “mixed” mitochondrial disorders, which are of mild-moderate severity and which do not necessarily require extensive or specialized laboratory assessments.

The clinical approach to assessing and treating mitochondrial disorders can be simple or complex; the clinician's experience and the patient's presentation are important determinants of the need (if any) and extent and expense of the evaluation. Some clinicians like to profit from the use of numerous “justifiable” laboratory tests, whereas others of us focus on patient-centered clinical efficacy (see Author Disclosure Statement). Assessment of mitochondrial disorders may need to take very different routes depending on the age of the patient, nature of the disorder, speed of onset, severity of manifestations, and overall clinical picture and the presence/absence of multisystem disease. In general outpatient practice, the assessment and treatment of most mitochondrial disorders is best performed empirically, based on the clinician's ability to pattern recognize, correlating the patient's complaint(s) with known data from published research; response to mitochondria-enhancing treatment supports the assessment (ie, success of prospective treatment supports/confirms the diagnosis).

The full spectrum of assessments for mitochondrial disorders can range from relatively simple laboratory tests (eg, serum lactate, serum coenzyme Q₁₀, blood/urine organic acid analysis), to analysis of cells and tissues (eg, measurements of mitochondrial function in skin cells, peripheral blood monocytes, muscle biopsy), to genetic analysis and neurodiagnostic tests; most of these tests are best reserved for the evaluation of more severe cases of suspected mitochondrial disease, because their routine use in the evaluation of the more commonplace mild forms of mitochondrial impairment emphasized in this article is clinically unnecessary while adding unnecessary financial burden to patients and the health care system.

The authentic “objective” need for laboratory and invasive assessments is determined by clinical severity of the presentation; perceived “subjective” needs for such tests include patient reassurance and the desire of some clinicians to financially profit from expensive tests. More commonly than not, clinicians can implement mitochondria-enhancing interventions without the use of specialty testing. Furthermore and very important, when treating secondary/acquired mitochondrial disorders, we obviously have to “think outside of the mitochondria” to address the cause(s) of the mitochondrial impairment, most commonly arising from various combinations of nutrient deficiencies, carbohydrate excess, toxin exposures, and microbial colonizations. My approach to treating mitochondrial dysfunction includes 3 main categories of interventions: (1) promotion of mitophagy, (2) mitochondrial support and stimulation, and (3) therapeutic disinhibition.¹

Conclusions

Whether they appreciate mitochondrial disorders or not, practicing clinicians see patients with mitochondrial impairment virtually every day in their clinical practices. As noted in the popular article by Pieczenik and Neustadt,²⁰ clinical disorders associated with mitochondrial dysfunction include schizophrenia, bipolar disease, dementia, Alzheimer’s disease, epilepsy, migraine headaches, stroke, neuropathic pain, Parkinson’s disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes mellitus, hepatitis C, and primary biliary cirrhosis; to that list I will add/specify hypertension,²¹ allergy, autoimmunity, and many acute care disorders such as those treated in intensive care units, including sepsis and trauma.²² Many clinical conditions involve vicious cycles of oxidative stress, mitochondrial impairment, tissue damage, and inflammatory/immune responses; the cycle can and must be addressed from as many facets as possible.² Given the wealth of information implicating mitochondrial dysfunction in the common health disorders that are encountered in routine clinical care, one finds a very curious underreporting of this association in the standard clinical medicine literature. This information-practice discordance could be attributed to the typical bench-to bedside translational time lag, but it is probably strongly promoted by the fact that the main interventions for restoring and optimizing mitochondrial function are not drugs but are nutrients: vitamins, minerals, fatty acids, phospholipids, and phytonutrients—therapeutics not generally taught in standard medical schools.^{23,24} If clinical practice is to be science-based, and if we as clinicians are to deliver the best possible care to our patients, then mitochondrial interventions need to be implemented on a routine basis to many of the conditions that we commonly see in clinical practice. The data are already published, the

model is sufficiently substantiated, and the therapeutics are safe and effective. Similar to the paradigm shift by Vasquez, Manso, and Cannel²⁵ that this journal published 10 years ago on the clinical importance of vitamin D, we are ready for another paradigm shift and change in clinical practice: this time, for mitochondrial interventions. Indeed, the time for action is now.

Author Disclosure Statements

Clinical preference for intervention rather than extensive/superfluous laboratory testing: Regarding the management of many nonurgent clinical problems, I acknowledge my personal bias in favor of empiric treatment, because effective treatment and not extensive testing is what helps patients and provides the ultimate proof of the diagnosis and clinician’s skill; I have reasonable concern that too many clinicians charge exorbitant fees and profiteer by running unnecessary laboratory tests in their “functional medicine boutiques” wherein superfluous testing is a major profit center of the business at significant and sometimes debilitating cost in time and money to the unsuspecting patient. A recent patient of mine was charged more than \$15 000 for an initial visit with a prominent functional medicine expert largely for the sake of receiving a detailed genetic and biochemical analysis, for which the clinician lacked the skill to translate into an effective therapy. Financial disclosure: Dr Vasquez has served as a researcher and lecturer for Biotics Research Corporation. Dr Vasquez is the author of many books and is the Director of Programs for the International College of Human Nutrition and Functional Medicine.

References

1. Vasquez A. ICHNFM 2013: conference presentation slides from Dr Alex Vasquez, with accompanying videos available online. Presented at: International Conference/College of Human Nutrition and Functional Medicine; September 25–29, 2013; Portland, Oregon. VIMEO.com/ICHNFM. Accessed December 10, 2013.
2. Vasquez A. *Integrative Rheumatology and Inflammation Mastery*. 3rd ed. Seattle, WA: CreateSpace, 2014. In press.
3. Zhang X, Vincent AS, Halliwell B, Wong KP. A mechanism of sulfite neurotoxicity: direct inhibition of glutamate dehydrogenase. *J Biol Chem*. 2004;279(41):43035–43045.
4. Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. *Pediatr Neurol*. 2003;28(1):9–15.
5. Fujita Y, Fujino Y, Onodera M, et al. A fatal case of acute hydrogen sulfide poisoning caused by hydrogen sulfide. *J Anal Toxicol*. 2011;35(2):119–123.
6. Bland JS. Role of the microbiome. Presented at: American College of Nutrition Conference 2013: Controversies in Nutrition; November 13–16, 2013; San Diego, CA.
7. Perez-Pozo SE, Schold J, Nakagawa T, Sánchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)*. 2010;34(3):454–461. doi: 10.1038/ijo.2009.259.
8. Nicolson GL. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. *Altern Ther Health Med*. 2013;20(1):18–25.
9. Saffran HA, Pare JM, Corcoran JA, Weller SK, Smiley JR. Herpes simplex virus eliminates host mitochondrial DNA. *EMBO Rep*. 2007;8(2):188–193.
10. Ball MJ, Lukiw WJ, Kammerman EM, Hill JM. Intracerebral propagation of Alzheimer’s disease: strengthening evidence of a herpes simplex virus etiology. *Alzheimers Dement*. 2013;9(2):169–175.
11. Yan MH, Wang X, Zhu X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med*. 2013;62:90–101.
12. Bundgaard H, Kjeldsen K, Suarez Krabbe K, et al. Endotoxemia stimulates skeletal muscle Na⁺-K⁺-ATPase and raises blood lactate under aerobic conditions in humans. *Am J Physiol Heart Circ Physiol*. 2003;284(3):H1028–H1034.
13. Michaeli B, Martinez A, Revelly JP, et al. Effects of endotoxin on lactate metabolism in humans. *Crit Care*. 2012;16(4):R139.
14. Scirocco A, Matarrese P, Petitta C, et al. Exposure of Toll-like receptors 4 to bacterial lipopolysaccharide (LPS) impairs human colonic smooth muscle cell function. *J Cell Physiol*. 2010;223(2):442–450.
15. Fernandez D, Perl A. Metabolic control of T cell activation and death in SLE. *Autoimmun Rev*. 2009;8(3):184–189.
16. Gergely P Jr, Grossman C, Niland B, et al. Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2002;46(1):175–190.
17. Lee HK. Mitochondrial dysfunction and insulin resistance: the contribution of dioxin-like substances. *Diabetes Metab J*. 2011;35(3):207–215.
18. Kanthasamy AG, Kitazawa M, Yang Y, Anantharam V, Kanthasamy A. Environmental neurotoxin dieldrin induces apoptosis via caspase-3-dependent proteolytic activation of protein kinase C delta (PKCdelta): implications

- for neurodegeneration in Parkinson's disease. *Mol Brain*. 2008 Oct 22;1:12. doi: 10.1186/1756-6606-1-12.
19. Neustadt J, Pieczenik SR. Medication-induced mitochondrial damage and disease. *Mol Nutr Food Res*. 2008;52(7):780-788.
 20. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol*. 2007;83(1):84-92
 21. Puddu P, Puddu GM, Cravero E, De Pascalis S, Muscari A. The putative role of mitochondrial dysfunction in hypertension. *Clin Exp Hypertens*. 2007;29(7):427-434.
 22. Kozlov AV, Bahrami S, Calzia E, et al. Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? *Ann Intensive Care*. 2011;1(1):41.
 23. Adams KM, Kohlmeier M, Zeisel SH. Nutrition education in U.S. medical schools: latest update of a national survey. *Acad Med*. 2010;85(9):1537-1542.
 24. Vetter ML, Herring SJ, Sood M, Shah NR, Kalet AL. What do resident physicians know about nutrition? An evaluation of attitudes, self-perceived proficiency and knowledge. *J Am Coll Nutr*. 2008;27(2):287-298.
 25. Vasquez A, Manso G, Cannell J. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers. *Altern Ther Health Med*. 2004;10(5):28-36.