Mitochondria
Crucial Roles Beyond Cellular Energy

Mitochondrial Medicine:
Diving Deep into the Secrets of Cellular Health
As basic science and clinical research cross paths, a new understanding of the importance of mitochondria in health and disease has emerged

On March 20, 2014, FOCUS moderated an international Skype conversation between Michael Ash, BSc, DO, ND, F.DipION, and Alex Vasquez, BS, DC, ND, DO, FACN on the new epoch of mitochondrial medicine. Michael Ash is co-founder of Nutri-Link Ltd, a subsidiary of Allergy Research Group, LLC. Endnotes that reference relevant studies and sources have been added for readers and physicians.

Focus: Mitochondria are the many "power plants" inside our cells that produce the energy that fuels metabolic processes and reactions. Why all the excitement and furor about mitochondria these days? Are we really seeing a new era in integrative and functional medicine?

AV: Several important events have occurred recently which have catalyzed our new appreciation of mitochondria and the clinical application of "mitochondrial medicine." First of all, the basic sciences have advanced. From a classic biology standpoint people were focused primarily on ATP production for decades, without awareness of intracellular and mitochondrial signaling consequences.[1] A typical example is the 2012 publication by Springer of a new 450 page textbook with twenty chapters, entitled, Advances in Mitochondrial Medicine.[2] The editors point out that mitochondria are far more than the "powerhouse" of the cell as they have classically been described. A growing number of studies also assign a significant pathogenic role to damaged mitochondria. Damaged mitochondria release various molecules that are known as damage associated molecular patterns (DAMPS).[3]

Focus: DAMPS sound very interesting. Can you explain them a little bit more?

MA: I'll jump in here with an insight. It seems that injured mitochondria trigger an immune response that is similar in outcome to one triggered by infection. DAMPS actually affect the body like pathogen-associated molecular patterns (PAMPs), through a small group of specialized receptors. Similar to microbially induced inflammation, this sterile inflammation is marked by the recruitment of neutrophils and macrophages and the production of pro-inflammatory cytokines and chemokines, notably tumor necrosis factor (TNF) and interleukin 1β (IL-1β) and interlukin 18 (IL-18). The leading origin theory is that mitochondria were once bacteria that long ago in the evolution of life, invaded eukaryotic cells, and eventually became the mitochondria of modern day cells, which form plants and animals. But they still retain their ancient innate signaling patterns and their own DNA wrapped in their membranes. Our immune system does not only respond to pathogens, but it also responds to endogenous intracellular alarms released during cell and mitochondrial damage. Under conditions of cellular stress or injury, these molecules are released into the extracellular environment by dying cells and mitochondria and trigger inflammation under sterile conditions. This is why the immune response to infection and to trauma can look similar. And this is why, in a hospital setting, severe trauma can lead to systemic inflammatory response syndrome (SIRS) and severe infection to sepsis, and they look much the same.

Focus: So what disease states are influenced by mitochondrial injury

and DAMPS?

MA: You see it in different diseases: ischemia/reperfusion injury, neurodegenerative diseases, cancer with its dramatic sequelae (i.e., metastasis), metabolic syndrome, and diabetes II hyperlipidemias, just to mention a few of the most important pathologies.[4] These DAMPS leak out of the mitochondria and cell and include molecules crucial to energy production, such as ATP and ADP, and Krebs cycle molecules. They also include oxygen, reactive oxygen species (ROS), actual mitochondrial DNA, potassium and urate (a form of uric acid). All these bind to specialized receptors and are often referred to as alarmins.[5] The 'sterile inflammation' that ensues either resolves the initial insult, at which point homeostasis is restored, or if chronic, it leads to disease.[6]

AV: As practitioners we are starting to see a powerful correlation with clinical disease, in particular increased autoimmune illness and states of chronic inflammation that define most clinicians' patient concerns.[7] We are probably also witnessing an actual increase in mitochondrial-related illnesses, if for no other reason than environmental toxicity, which is evolving as an expanded area of investigation.[8] While many medicines, including antibiotics, are understood to be toxic to mitochondria, it has been harder to link exogenous environmental toxins to mitochondrial damage. Valproic acid, carbon monoxide, cyanide, glyphosate and aminoglycoside antibiotics, along with smoking and alcohol, are all known to be mitochondrial toxins, mediated by genetic susceptibility and level of exposure.[9] Research findings now indicate that well-defined medical conditions appear to be influenced by mitochondria.[10]

We appreciate an increasingly wide scope of chronic illnesses for which mitochondrial dysfunction are at least partially causative and therefore treatable via improving mitochondrial function. I have personally seen strong correlations with neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, many cancers, metabolic syndrome, diabetes, cardiovascular disease, and others which are conditions described as being attributable to sterile inflammation which is partly but powerfully driven by altered mitochondrial membrane permeability and leakage of mitochondrial contents.[11,12,13]

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An important driving force behind the recent popularity of what I call "the new mitochondrial medicine"[14] is the fact that we have so many clinical interventions already available to us, so that clinicians can actually engage this new treatment model with clinical effectiveness and improved outcomes. Mitochondrial function powerfully influences immune balance in ways we didn't appreciate before. And so, for instance, looking at improving mitochondrial function when we are treating autoimmune disease or inflammation is really helpful.

MA: I was medically educated during the 1980's, in an era when chronic illness was just starting to be linked to the oxidative stress model. Free radicals were the *de rigueur* explanation for a wide range of diseases and dysfunctions. Oxidative stress remains as a credible explanation, but now we are also looking downstream and recognizing the interplay of immune effects, and beginning to understand how profound mitochondrial integrity and membrane quality are in health and longevity. In mitochondria, reactive oxygen species are also capable of causing oxidation of cardiolipin (CL). Cardiolipin is the most prevalent fatty acid in the mitochondrial membrane, and absolutely critical to its function as it contributes to the function of many proteins in the inner mitochondrial membrane, where it is actively involved in the integrity and flux of the electron transport chain. Cardiolipin remodeling, where the fatty acid composition is adversely altered, has been implicated in mitochondrial dysfunction and is associated with a host of pathophysiological conditions.[15] Cardiolipin is essential for mitochondrial inner membrane (MIM) structure and function as well as maintaining MIM transmembrane potential.[16]

Viewing medicine through the functionality of the mitochondria is very elegant, because the related explanations cross over very neatly with that of oxidative stress and free radicals. The oxidative stress theory was modified by defining mitochondrial respiration as the major cellular source of reactive oxygen species - estimated at 95% of all reactive oxygen species. More recently the existence of a "vicious cycle" was proposed, in which the reactive oxygen species directly impair the mitochondrial DNA and its functions. Then, in turn, the formation of reactive oxygen species is elevated due to mitochondrial dysfunction. Mitochondrial DNA mu-

tations can also be accelerated by this "vicious cycle," which can lead to accelerated inflammation via immune triggers such as the inflammasome. Inflammasomes are intracellular complexes composed of proteins. They detect environmental toxins, pathogenic microbial molecules (PAMPS) and sterile stressors (DAMPS) and respond by producing the pro-inflammatory cytokines IL-1β and IL-18. These cytokines cause a wide variety of biological effects associated with infection, inflammation and autoimmune processes. I've been talking more and more about the role of the inflammasome, as it is a unique sensor capable of responding to external environmental, internal endogenous and pathogenic triggers. That's profound, because if unbalanced and excessive, it can lead to a vicious cycle of inflammation. The exact composition of the inflammasome varies as there are a number of these complexes, but it is best understood as being responsible for the activation of vital innate inflammatory processes.

Each cell is a collection of living organelles that interact and guide cell metabolism. We can actually measure their capabilities through the presence of key cytokines which allow us to infer problems such as those with the mitochondria. In particular, an enzyme called caspase correlates with mitochondrial function. Caspases are activated by the mitochondria when their membranes become permeable. Permeable mitochondrial membranes can be created by a variety of situations, including infection and metabolic dysregulation. That permeability disrupts the electron transport chain that creates energy and allows the cell to function. Then ATP levels in the cell decline due to membrane permeability and electron leakage. That is really important, because electron transfer across the mitochondrial membrane is how cellular energy is generated. When electrons and DAMPS spill into the intracellular environment they function both as free radicals and triggers of inflammation. The inflammation and oxidation that occurs almost instantaneously creates a bright 'chemical flare' warning other cells of danger. At that moment, mitochondria are like the well-known canaries in the coal mine. They are letting the cell itself know there is trouble.

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Here's the key takeaway: immune imbalance induces mitochondrial dysfunction, and mitochondrial dysfunction induces immune imbalance. That cycle, that cross-talk, between these precious organelles and the immune system, is a key element of many chronic illnesses, including unhealthy aging.[17,18]

Cardiovascular disease, cancer, oxidative stress, metabolic syndrome—all can be due in part to changes in the mitochondria. However, even now, the information available on mitochondria, membrane morphology and biogenesis and repair work is so complex and sophisticated it's hard for practicing doctors to translate it into functional medicine and apply it to real life clinical practice. I think both Alex and I, on our different continents, are trying to make that happen more easily.

Focus: How do you translate mitochondrial medicine for physicians?

AV: That's a relevant question, since I recently completed a post-graduate presentation and new book focusing on the clinical applications of mitochondrial nutrition and mitochondrial medicine.[19]

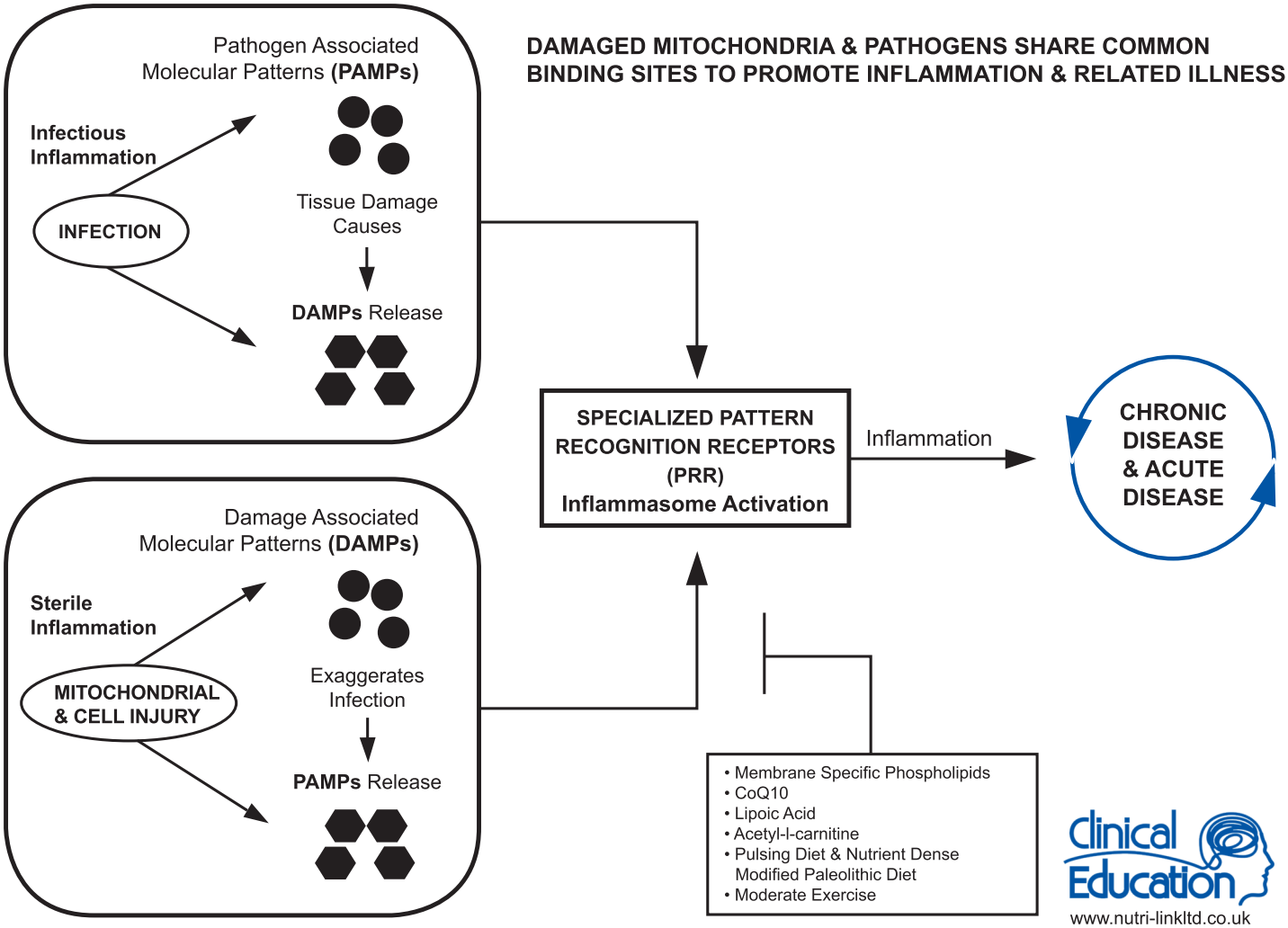
Let me rewind a bit. One of the ways I introduce this protocol is to present recent work on mitochondria, as I mentioned above. I particularly like the work of immunologist Douglas Green, who holds an endowed Chair of Immunology at St Jude Children's Research Hospital in Nashville. He's been working on mitochondria for decades, and one of his most recent reports, in 2012, co-authored with the world expert on mitochondria and cell death, Guido Kroemer, looks at how alterations of mitochondrial functions are linked to multiple degenerative or acute diseases.

Another way of introducing mitochondrial medicine is to show that we've actually been doing it for years without knowing exactly that we were treating mitochondrial dysfunction. It's almost embarrassing that for years we treated people with hypertension and heart disease with CoEnzyme Q10 and yet we didn't really understand why or how it was working. I wrote a book on hypertension in 2010 and I remember commu-

nicating with Peter Langsjoen, MD, who for many years has been one of the world's most foremost experts on the use of CoQ10 to treat cardiac disease. At that time, he thought that CoQ10 was improving systolic and diastolic function of the heart. And it was, but with all due respect, years ago none of us were thinking specifically about the mitochondria in relationship to CoQ10. Of all the cells in your body, your heart muscle cells have the most mitochondria. There are about 5,000 per cell, as opposed to 200 per muscle cell in other parts of the body. The ceaselessly beating heart has an extra-special demand for ATP to keep it pumping over an entire lifetime. And now it's widely known that CoQ10 is a key component in mitochondrial bioenergy transfer. Even a small increase in the coenzyme Q10 concentration of mitochondrial membranes can lead to an increase in mitochondrial respiration.

I have personally seen strong correlations between mitochondrial dysfunction and neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, many cancers, metabolic syndrome, autoimmune disease, diabetes, and cardiovascular disease.

MA: I totally agree. We now know that mitochondria, these organelles, are quite plastic. They respond to both internal and external triggers. They communicate intracellularly. They manipulate our immune system and our biochemical systems and in turn are manipulated by these systems. Now we can look back at three or four decades of molecular biochemistry and immunology as being reflective of mitochondrial function and see it all through a different mindset, and with our greater understanding of the use of natural agents and lifestyle changes to improve mitochondrial



function, provides us with a modified route to recovering health.[20] It's terrifically exciting.

Focus: So what is your essential protocol for healthy mitochondria?

AV: As I mentioned before, the great thing is, we can actually do something about improving mitochondrial function these days. Doctors don't really care about a problem if they can't actually fix it, but in this case, we have plenty to offer. I've identified at least 30 interventions for improving mitochondrial function, and I have five key strategies I typically recommend right out of the gate. Number one: a simple, low carbohydrate, moderate-high protein, plant-based, nutrient-dense diet, rich in vitamins, minerals and fatty acids. Part of the reason for these choices is their effect on gut dysbiosis/eubiosis and the microbiome. Generally pathogenic bacteria feed on carbs. But in addition, a nutrient-dense, low carb diet helps the mitochondria repair mechanisms to function better.

MA: Let me add my perspective here about a low carb, high protein diet. First, gut bacteria are highly responsive to your food choices, so choosing foods high in polysaccharides from vegetables will actually facilitate the growth of preferential bacteria and increase the production of mucins. Mucins are the glycosolated proteins that form into mucus to coat the epithelial cells of all our mucosal tissues. The mucins are composed of two major families: secreted mucins and membrane-associated mucins. Mucins can reduce the overall inflammatory response. For someone with autoimmune or chronic disease that's well-defined, this is a very good diet and should include onions, garlic, leeks, yams, chicory root, dandelion greens, artichoke root, agave, jicama, and bananas, among other foods.

Add modest exercise, which favors healthy mitochondria and also stimulates their biogenesis. Let there be days of more modest caloric intake, rest periods if you will, in which the mitochondria can repair themselves, and tidy up the cell by actually cleaning up those mitochondria that are damaged beyond repair and morphing those that are marginally damaged into new more viable units and in doing so reduce mitochondrial-induced DAMPs.

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With this simple, powerful approach people will see increased energy and function, decreased body mass, resolution of longstanding ailments, control of inflammation and they will feel really good about that. But even so, as clinicians we need to ease them into this lifestyle pattern, and not demand a daily diet that is very restrictive, such as the proverbial Atkins diet. Higher protein foods are more difficult to gorge on than carbohydrates. Vegetables and fruits clearly contain many nutrients essential to mitochondrial function. Food choices can include meats, fish, eggs, plants and fruits, but should avoid simple refined foods and sugars.

AV: Great points. You mentioned exercise. My number two intervention is mild to moderate exercise. Not too strenuous. My third intervention is ubiquinone. I just recommend regular CoEnzyme Q10, not ubiquinol, unless the individual is suffering congestive heart failure, for which ubiquinol has been definitively demonstrated to be more effective. Regular CoQ10 works well, and is much less expensive, for most people. A typical dose ranges from 50 mg - 300 mg. My fourth and fifth interventions are lipoic acid, 200-400 mg three times a day, and acetyl-carnitine, 1-2 grams twice a day. The latter two are mostly based on the work of Bruce Ames, PhD, who showed in animal studies that the two work really well together. They have been compared to a potential fountain of youth. [21]

MA: I agree with that protocol, except that I add in membrane specific phosopholipids, an oral preparation of phospholipids and co-factor nutrients, shown in human and animal trials to increase the quality of mitochondrial function and increase inner membrane levels of cardiolipin. Cardiolipin is the lipid most prevalent in the mitochondrial membrane and essential for its inner membrane integrity and mitochondrial bioenergetics.[16] I take it myself every day. It's on my counter, I've taken it now for two years, and if I stop for a few days I slowly get less functional. Once I start taking it again I feel a distinct sense of improvement and capability and I sleep well and wake up feeling good. Considering my extensive work loads and travel, Lipid Replacement Therapy has helped me in a meaningful way.

AV: Actually, Lipid Replacement Therapy is now becoming part of my strategy, too, especially after I listened to Dr. Garth Nicolson at the International Conference on Human Nutrition and Functional Medicine in Portland, Oregon last September.[22]

MA: I'll pitch in a nice simple patient story here. I have a 72-year-old patient who came to me two years ago. He had always been fit, and a golfer, but after he went through a period of stress and his wife went through an illness, he found himself unable to play his 18 holes. Even worse, he said, was the fact he could no longer complete his daily numbers game, called SUDOKU, a well known mathematical challenge game, in fifteen minutes. We changed his diet to a low-carbohydrate, nutrient-dense diet, and added just a few supplements, including CoEnzyme Q10 and lipid replacement powder. It was astonishing, but in just a matter of weeks he was feeling better. He just emailed me last week and boasted that he is now able to play 36 holes of golf in a day, his handicap has been cut to 3 again, and he can finish his numbers game in ten minutes. He added that he refuses to tell any of his friends what his supplement regimen is, because he wants to keep his advantage on the course!

AV: I have a great patient story, too, though it may not be quite as colorful as yours. I also started working with a patient two years ago, a woman with extensive rheumatoid arthritis. Within one year of my protocol, her arthritis had completely reversed. The most important antibody marker, CCP, was down from 250 to 54. Anti-CCP antibodies are extremely important surrogate markers for rheumatoid arthritis, and can aid in early detection. That kind of drop is simply unheard of when drug-based protocols are used in rheumatology. Addressing her mitochondrial function was a very important component.

MA: Alex, it looks like we've been working our way through this complex but unifying concept independently of each other on separate continents.[23] I think it is fair to say that the greatest excitement in our professional lives is seeing and hearing how simple, well-structured and mostly very safe interventions can unwind people from often miserable health states into functioning happy and healthy individuals.

Note to the reader: Alex Vasquez and Michael Ash are presenting their latest insights and protocols on metabolic and mitochondrial medicine in a series of lectures across the United States in August of 2014 and subsequently in Europe in the spring 2015.

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