Mark Pettus MD: Welcome to the Health Edge, translating the science of self-care. Giving you news to use. Scouring the unbelievable and rapidly evolving research that has so much implication for how we manage health in our lives. I'm Mark Pettus, joined by my great friend and colleague John Bagnulo. John, how are you doing?

John Bagnulo PhD: Doing well, Mark, it's great to be with you. How are you?

Mark Pettus MD: Doing Great. We're in the deep freeze here, in the Berkshires. The polar vortex has set in. We've had a pretty milder than average winter so far, but man, it has been cold and windy. Really blustery.

John Bagnulo PhD: Here, as well. You get spoiled with the fifty-degree weather in December.

Mark Pettus MD: Definitely. We've got a really interesting topic, John, this morning that follows up on this concept of the metabolic tune-up that you and I briefly alluded to in our last podcast, as we were talking about magnesium and the growing prevalence of micronutrient deficiencies that we know impact metabolism on many levels. Many of which can easily be addressed with more thoughtful nutrition and on occasion supplements. This notion of a metabolic tune-up, John, also brings us into the category of mitochondria and how mitochondria function. Again, something that we touch on periodically, in various topics that we've done over the last several months.

There's a lot of relevance, here, in terms of day-to-day application, and I think it's a construct that is very cool and very important, and maybe a little bit of fun to dive into it.

John Bagnulo PhD: Absolutely, Mark. What we started talking about last week, with the differences between overt deficiencies which produce symptoms like scurvy, and beriberi and pellagra, and how rare those are today, in the modern world; however, those are pretty extreme health consequences, or outcomes. They don't really reflect the true picture of sub-optimal intake or suboptimal levels of these micronutrients. Something that Bruce Ames, who you and I are both big fans of for a lot of reasons, really spearheaded or pioneered this work back in the mid-nineties. I remember I was in grad school and he was doing his work on mutagenic deficiencies, showing that if you've got a folate deficiency or you have suboptimal levels of vitamin C, thinks that govern methylation, for instance, that it's every bit as damaging to the DNA as being exposed to high levels of radiation or particular mutagens.

This field has been growing over the last couple decades and it's really eye opening. We have a tale of two cities, really. We have people that basically eat whatever they want in this country, and they go to convenience stores and diners and they just order off the menu with very little regard for what might be healthy, or better choices. Then you've got a large number of people, Mark, as you know, who are trying to do their best and they're eating let's say a plant-base diet and it's mostly fruits and vegetables, not really paying attention to some important micronutrients.

It would be hard to say with respect to a lot of different conditions who's at greater risk, because it's really clear to me after years of being in this field that being a vegetarian, let's say, and being extremely health-conscious, and trying to eat low-fat, low-cholesterol, low-sodium, it's got its own set of inherent risks that a lot of people don't truly appreciate. Part of that reason again goes back to, well how was it we assess suboptimal intake of these nutrients. Are we working of the RDAs that are, again, have been developed to protect against some of these conditions that are with extreme deficiency. When you start to look at Bruce Ames's work, and others, McCann, who works closely with Dr. Ames on this, you see that a large number of Americans have levels of nutrient intakes that may not put them at risk for some of those extreme outcomes, but certainly leave as you just mentioned, their mitochondria at greater risk for pathology, or leave their DNA at greater risk for not being able to repair and maintain those gene sequences as necessary.

It's easy to look at nutrition as a "Well everything's in excess." Right? Too much sugar, too many calories, but its not that simple. We've got a lot of people who certainly fall into that category, and in addition to being in an excess state calorically, they've got a lot of micronutrient deficiencies that really compound the problems.

Mark Pettus MD: That's a great context to open this up with, John. You can touch a little bit, John, down the road here, on what certain critical micronutrient deficiencies might be, and people who are vegetarian or vegan ... Something jumps out at me when I look at this topic, John, and go back to Bruce Ames sentinel work that you refer to, in the nineties, is that consensus around aging and accelerated aging, and the routes of chronic complex disease have a lot to do with the burden of oxidative stress that we accumulate in our lives. You and I have touched on this repeatedly. The burden of oxidative stress being very tightly connected to lifestyle.

We know that unhealthy foods and processed foods and sleep deprivation, and overwhelming stress and difficulty managing environmental toxins, chronic infections, whether it by Lyme Disease or an EBV type situation, we know that all of those situations do tend to enhance inflammation, increase oxidative stress, and the demand that we have in modern life for nutrient-dense foods that can in some way neutralize the effects of that ongoing oxidation becomes even more critical. Mitochondria stand out in some respects in that A, they've got their own DNA, and even though the proteins that allow mitochondria to function are also encoded in the DNA that's in the nuclei of all of ourselves, mitochondrial DNA doesn't have the same repair capacity.

As you point out, John, the DNA of our mitochondria that comes from our mothers is particularly vulnerable. There's susceptibility there to oxidative stress and excess burden of reactive oxygen species, and free radicals, that it will not be able to adapt appropriately. Over time you're going to get damage to DNA, and you're going to get alteration of oxidative metabolism. We're seeing more and more evidence, John, that in some respects, mitochondrial dysfunction is central to most chronic, complex diseases. It goes hand-in-hand with inflammation and insulin resistance. In the brain that might be experienced as depression, or cognitive impairment, or Parkinson's Disease. In the heart, it might be manifested as congestive heart failure, or cardiomyopathy. In the liver it might manifest as fatty liver. On and on that list goes.

What I loved about Ames's early conceptualization of this is that the genetic studies now tell us, and you and I talk a lot about epigenetics and these SNPs, these single nucleotide polymorphisms, typos in our book of life that we come into the world with. Some of which are probably meaningless and trivial from a clinical perspective, but some of which are essential in coding for the enzymes that run our machinery. We know that many people probably have these patterns, these snip patterns, where enzymes that, just to give our listeners an example, make neuro-transmitters, or help make ATP, the energy that drives our metabolism, or things that drive our immune balance.

The presence of these certain patterns of snips affect the efficiency of these enzymatic pathways, and as a result, require much higher concentrations of micronutrients for those pathways to regain their efficiency. This individuality that we often talk about on a genetic basis that may put certain people at risk for how they detox, or make neurotransmitters or whatever the case might be, places a very different context and the notion again of a deficiency state, above which you're fine, below which you're in trouble.

Alternatively, this large gray zone where an individual may need much higher concentrations of certain micronutrients based on their unique genetic fingerprint. We know from the RDS studies that have been done that if you take deficiencies based on traditional thinking of our standards, and then you apply the standard of genetic predisposition, requiring even higher amounts, you begin to appreciate just how often individuals find themselves, perhaps with a "normal" level of magnesium or B12, yet insufficient amounts of magnesium or B12 based on their genetic fingerprint, to maintain optimal physiology and function. That's what was so revolutionary about Ames's way of thinking about this, John.

John Bagnulo PhD: Yeah, Mark. That's a great description of the issue that we're trying to illustrate here this morning. The thing that we could add to that is, the body is incredible at substituting in one micronutrient that is available for the one that's optimal. That allows us to continue to function and to survive. It's a survival mechanism that obviously over the course of human evolution, there were food shortages, there were limitations of certain nutrients, whether it was seasonal or due to other factors. The fact that the body can use this triage theory, again this is something that Bruce Ames gains most of the credit for, is just incredible. We don't get those red flags. We don't have something really grab our attention physically when we have these suboptimal intakes, because the body can substitute something in there that'll kind of be a patchwork type of solution for a while. Because of that, things continue to appear normal, maybe on the surface, but when you dig deeper you see that those enzymes aren't running quite as effectively as they would be otherwise.

It's a double-edged sword. It's great we have this survival mechanism that's allowed us to survive food shortages and micronutrient deficiencies over the course of human history, but the downside is that it can be insidious, right? We can get in tow hundred and twenty-five milligrams of magnesium or thirty milligrams of vitamin C, you can do that for a long time, and you don't necessarily develop bleeding gums or high blood pressure, but over the course of time, everything starts to run a little less effectively in the body.

Mark Pettus MD: It also makes me think, John, of this concept we've been discussing really a lot about in recent podcasts, of a physiologic sweet spot; so we know that in nature, and this concept of hormesis, small amounts often exerting very diverse and significant metabolic and biologic effects in human physiology. There's another concept, John, and I have a paper that I'll upload on our website. This notion of mitohormesis, where we know that low levels of stress, low levels of producing reactive oxygen species, whether it's through exercise or through, say, intermittent fasting, has a significant beneficial effect. You're revving up, to some extent, in exposure to those short, intermittent physiological stress states. You are ramping up your defense systems. In the example of mitochondria, low levels of this reactive oxygen and oxidative stress is very important in actually up regulating, or driving our defense systems. The key is maintaining a certain window within which we're not overdoing it.

As we think about metabolic tune-ups, I think it's fair to say there's a lot of uncertainty still as to the notion of a lot more being a lot better. We know that more is probably better for a lot of people who just aren't getting enough critical or conditional essential nutrients. At the same time, there is probably a point beyond which you can over-replace, and begin to alter how sensitive these systems are to hormetic stress, John. That's another concept here that I think is really important. It's a little bit maybe geeky, but again, there's a sweet spot in terms of what we're talking about here, and having enough for optimal function, which is probably higher than an RDA target for many people, but we're not talking about mega dose vitamins, minerals, and things. It may have some value, perhaps, but I think have not been well studied. Based on what we know of nature's tendency to evolve around that sweet spot, one I think just needs to be thoughtful in how they think about this.

John Bagnulo PhD: Absolutely, Mark, that's a good point. The other point that's critical to discuss is that notion that we can get everything through our diet. Which, I would be a big fan of, if I thought it were always possible. I think it may be possible for some individuals, depending upon the time and resources that they have available to commit to their diet. An example of that would be if an individual can eat liver once or twice a week, and eat eggs every morning, and have oily fish a few times a week, and have brassicas, and bright berries, and garlic, and let's say you're folate-rich greens. There is, I feel, the capacity for us to do that; I think it's a full-time job. I think people have to understand that. I don't know how many people are able to do that, to commit to that type of menu. I think it's possible, but I think it's, for a lot of people, it's a major challenge.

That's the one thing I always here is, people say to me and at one time I felt this way as well, Mark, was that I just want my food to provide me with everything that my body needs. There are days where I don't think that's possible. There may be weeks or months for some people where that are not possible, either due to travel or limitations, resources that they have. That's an important discussion is, what is it that we can more easily get from food? In the case of something like magnesium, which we discussed last time, that's a reasonable goal for people to get that from their diet, let's say. When it comes to things like, we can get into these in a while, when it comes to things like, let's say, creatine, which I'm a big fan of in terms of offering people a lot metabolically, I don't know if people are willing to eat the red meat or the organ meats that would be required for them to get three to five grams of creatine a day.

You can maybe pick your micronutrients, maybe people after listening to this will identify a few that they say wow, I think I might be a little under-protected in that area. There are others that I think are other ... Like vitamin C, if someone eats berries and broccoli and lemons and limes, things like that, you can easily get a couple hundred milligrams of vitamin C per day from it. Most people are more; it's easier for people to identify vitamin C-rich foods than it would be, let's say, selenium, or sulfur. It's a fascinating discussion and a lot comes into it, but I wanted to put that out there. I'm sure you hear that as well, people say "Why can't I just get everything from my diet?"

Mark Pettus MD: The other point that you raised, John, which is such a good one, is that the environment that we live in, the conditions of modern life, place metabolic demands on us as modern humans that can make it very hard to sustain and maintain the micronutrient levels necessary to optimize human health. There is this ongoing vigilance, even beyond whole diets that for some can raise potential benefits with additional supplementation.

Maybe this would be a good place, John, to go through a checklist of what, and you've already opened this discussion, what would constitute a good strategy for metabolic tuning, both in terms of food and in terms of supplement, and in terms of lifestyle, recognizing that so much of what we talk about, from sleep to the gut, all impact our metabolic efficiency. The nutrients are important, and it's a great place to start, but as we often remind folks, if there are other central aspects of one's life or quality of life that aren't in balance, you may not see the effect that you would otherwise see if those things were.

Ames's original work, and a lot of it was based on the published literature measuring micronutrients, those that jumped out, John, when I went back to review his work, were the fat-soluble vitamins: vitamin A, vitamin D, E, K. The B vitamins, this family of B vitamins central to so many aspects of human physiology, are frequently insufficient. I almost hate to use the word deficient, again, you may have a low normal B12 level, but if you have a snip, if you have one of these genetic alterations, your ability to methylate may not be a hundred percent. We talk about the tetrahydrafolate reductase, the MTHFR snip, which as many as perhaps ten percent of Americans have, might in those individuals, require a different strategy with respect to B vitamins, folate, things that we know can be altered by that pathway.

Ames identified a lot of those central vitamin issues, and then there were the mineral issues, some of which you've touched on, John. The magnesium, the selenium, the zinc, the omega-3s, choline. Those are maybe, as I look at it, John, those are nutrients that are conditional, in that often we need much more than we're getting. Part of that may reflect what's happening in our lives at a particular time, but in general if there is vulnerability, it tends to be in those micronutrients. A lot of Ames's work I know focused on that.

John Bagnulo PhD: Those are a lot of great examples of micronutrients that if you can really look across various demographics, in our country you're going to find significant populations with suboptimal intakes, or they're just not getting let's say the ideal version of a molecule. Vitamin A really stands out, Mark. People could make an argument in this country, anyway, that people get plenty of vitamin A, because if they eat just a couple servings of fruits or vegetables, even something like ketchup, which you and I wouldn't really categorize as a fruit or vegetable in the form that it ends up on the plate.

People make the argument that these carotenoid-rich fruits and vegetables give us all the vitamin A we need. You can't really put vitamin A in its natural retinoic acid, retinal form; you can't put that in the same equivalent as, say, carotenoids. They play different roles. Even though the body can convert carotenoids to vitamin A, it's really clear that getting vitamin A in a fully physiologically-available form from something like liver or egg yolks is going to have benefits, as opposed from getting your vitamin A from sweet potatoes and carrots.

Not to say that, and I know that you agree with this, not to say that we would in any way devalue those foods, because they're also very rich in other micronutrients and phytonutrients, which offer us a lot of protection and have major benefits,

Mark Pettus MD: When we look at what we know are common deficiencies, like the fat-soluble vitamins, like some of the minerals, zinc, and magnesium. How, in terms of diet ... You've touched on a lot of this, but a vegetarian or vegan, for example, may not be getting sufficient amounts of certain B vitamins, things that are found pretty much in animal sources. Elaborate a little bit on that, and then we'll look at some metabolic tune-up supplements that people can think about and bring it home from there.

John Bagnulo PhD: That's a great thing to dive into, Mark. Again, so many people look at vegetarianism or veganism as being a very high level of let's say nutritional evolution, like if you've gotten there, wow. You're on a whole food, plant-based diet. You must be getting everything that you need from all these nutrient-dense fruits and vegetables. I certainly wish that were the case. It would maybe make things much simpler for people, but there are certain micronutrients that you're just going to have a very, very difficult time getting from a vegetarian or entirely plant-based diet.

Most of those, Mark, are going to be your minerals and trace minerals, which in plants tend to be bound. They're chelated, so they're held onto very tightly in plan sources. Zinc is a prime example of that. Zinc that is found in navy beans is not going to be bio-available. The zinc found in wheat germ is going to be really latched onto by these phytates within those plant matrices. I look at zinc as being a real important micronutrient to consider supplementing with. It's really clear that we need fifteen to twenty milligrams of zinc. That might not be enough for a lot of us, depending upon those snips that govern particular enzyme roles. Zinc is really important for protecting us against oxidative stress. There are several enzymes that are found throughout the body that have pivotal roles in anti-cancer, anti-oxidation roles. I look at zinc as something that should be very high on the list of nutrients to consider supplementing with, if someone is a vegetarian or has had a long history of being a vegetarian.

I also look at sulfur, even though it's one that tends to fly under the radar in comparison to let's say vitamin D or vitamin K2, which have become very common for people to look at now in their diet. Sulfur really still isn't. If you don't eat eggs or meat, it's going to be hard to get the amount of sulfur that you need for sulfation, which we've talked about briefly in the past. That might mean that someone uses a supplement like MSM, which is found in powder form, capsule form, however people want to use it. Sulfur and zinc and choline, choline is an important methylation or methylating-driving molecule. It's a lot like a B vitamin. It's also found in egg yolks in very high quantities, as well as being found in fish and shellfish. I would look at zinc, sulfur, and choline.

I mentioned creatine, which is a real simple array of amino acids, just a couple amino acids in it's complexity, but very, very difficult for the body to produce all that is necessary for optimal health if we're not getting any augmented creatine from our diet. Those would be a few that would really stand out.

Mark Pettus MD: That's great, John. Looking at certain supplementation and recognizing that the research is very much evolving here, but some of Ames's earlier work in animals ... If you assess an animal's cognitive function by how quickly it runs through the maze to get the cheese, or how resilient it is when confronting stress, how it is metabolically, activity-wise, even social. A lot of these determinants in Ames's work and others show certain nutrients that are known to assist mitochondrial function and to render the mitochondria a bit more resistant around those oxidative stress states.

He looked at supplements like a CoQ10, what we offer refer to ubiquinol, as the reduced form, the more bio-available form. A lot of that research looked at two hundred milligrams twice a day of ubiquinol. Acetyl-L-carnitine, carnitine very important in shuttling nutrients in and out of the mitochondria, for oxidative metabolism. Upwards five hundred to a thousand milligrams twice a day. Alpha-lipoic acid, these are the big three in Ames's work. CoQ10, Acetyl-L-carnitine, and Alpha-lipoic acid. Also an antioxidant that is fat-soluble, two hundred milligrams twice a day of Alpha-lipoic acid.

You mentioned, John, the creatine, and I know some providers and some of the research looks at alkalinized, this creatine cre-alkalyne, the alkalinized form being perhaps a bit more physiologic. That can be encapsulated, taken in powder form as well. The other biggie in some of the research ... Again, a lot of this animal work, but I'm seeing a growing number of published articles, John, looking at these mitochondrial cocktails, as they're often referred to, in people with MS or Parkinson's or ALS or anything degenerative, neurologic, or systemic. Fibromyalgia, chronic fatigue, where the mitochondria appear to be playing a more central role. That supplement is N-acetyl cysteine, what we often refer to as NAC. Cysteine being a great source of sulfur, John, that you just allude to, and sulfur so much a part of our detoxification processes, and mitochondrial function. That N-acetyl cysteine in what has been published is in doses of six hundred milligrams twice daily.

So CoQ1-, Acetyl-L-carnitine, Alpha-lipoic acid, Creatine, the crealkalynized form of creatine, N-acetyl cysteine, are all interesting molecules, John. When I look at this, it's hard to know how much, how long, what does one measure or monitor, but I do think that for some, these are probably safe and worth considering, particularly if they're struggling with a neurologic issue that's progressing, or a chronic fatigue, or fibromyalgia chronic pain type issue. Even depression. Often what I will do is recommend a mitochondrial cocktail, in addition to a very balanced nutritional program, of course, and to guide someone's symptoms. See how they do. People often will notice their pain improves, their mood improves, and their energy improves. You might see things in the blood work like improved insulin sensitivity, or lower levels of abnormal liver function from fatty liver, things like that.

For the person trying this and for the caregiver partnering with that individual, you are on a bit of uncharted waters here, but these are targeted nutrients, which is what I like about the work that's been done, and how one can think about using these. They're targeted molecules that seem to confer particular effects on mitochondrial function. That whole cocktail concept, John, is a really interesting one and one that I continue to explore with a lot of patients. I have to say that more times than not, they work, and they work pretty well.

I don't know what your experience has been there, John, but those are the other cocktail mitochondrial, metabolic tuning interventions that I would often think about.

John Bagnulo PhD: Those are great, Mark. I take most of those on a regular basis. Selenium is the one that I would add to that. I take two hundred micrograms of that, and I also take taurine, which is also an amino acid-based supplement, a lot like creatine in many ways. I couldn't agree more. I think that many individuals have had a history of either infection or some source of inflammation, and in addition to that, Mark, they've built their cellular physiology around particular substrates or versions of macro nutrients that are really not conducive for protecting the mitochondria.

A prime example of that would be if I were to meet with someone who has snacked on walnuts and sunflower seeds and has cooked with canola oil or sunflower oil, and has had a very high degree of polyunsaturated fat within their diet, it's axiomatic to understand that those polyunsaturated fats have been incorporated into their mitochondrial membrane. If you couple that with a diet high in fructose, a large amount of stress because of various factors of their life, you've really had a table that's been set for inflammation. In a case like that, those individuals, there's very little downside to taking the Acetyl-L-carnitine like you mentioned, the Alpha-lipoic acid, maybe the R-lipoic acid, which is really beneficial for some slightly different reasons.

I couldn't agree more, Mark. A lot of people have an opportunity to make significant health gains with some of these supplements that you mentioned being used in moderate doses. Again, we're not talking about mega-dosing here with three thousands micrograms of selenium or something, that's shown to be toxic. We're talking about a couple hundred micrograms here, maybe five hundred milligrams of Acetyl-L-carnitine, real moderate doses by physiological standards. If you take a look at the research, it's really clear. There can be some major upsides for people, especially those people you mentioned who already have some level of pathology, either neurologically or cardiovascular, and other area.

Mark Pettus MD: I look at this risk-benefit proposition, John, from the perspective of limited downside, uncertain though potentially significant upside, as you refer to. When people are struggling with systemic health issues and are otherwise against, just hitting the wall, this becomes a very hopeful and for many a novel way to be thinking about altering their biology and consequentially, improving their symptoms and quality of life.

As we bring this home, John, as I think about metabolic tuning, mitochondrial tuning, we come back to this consistent script of recommending lifestyle interventions that, in addition to being aligned with that which our primal ancestors evolved to be aligned with, that they become very important, again as part of any health-promoting program, John. I reflect on other things that we always talk about. Elimination of grains and dairy elimination trial.

Anything one can do to reduce inflammation will lighten the burden of mitochondrial oxidative stress. We're always talking about functional movement and full-spectrum light exposure, and loving, nurturing relationships, and sleep hygiene. All these factors we know in synergy can create tremendous metabolic shift that for many, whether it be pain or whether it be fatigue, or whether it be cognition and mood, can begin to significantly begin to turn around. That's always the point of emphasis in what we discuss.

John Bagnulo PhD: Absolutely. That's the foundation. These things can be significant difference makers, but we wouldn't want anyone to think they could take a long list of supplements and then not address the real core components of a healthy lifestyle. It's certainly a very important thing to emphasize.

Mark Pettus MD: We will upload some of those reference articles, John, some of Bruce Ames's work. People hopefully will gain some benefit from that as they think about this. I've also been preparing, John, a presentation that I'm doing in a few other settings, venues, for medical education, on metabolic tuning. I will upload that PowerPoint. It's pretty up-to-date. A lot of good references. People can look through that. This is a very hard topic to blow through in forty-five minutes or so. I do think it will give people some affirmation of a lot of the principles that we've talked about here this morning.

John Bagnulo PhD: Definitely.

Mark Pettus MD: We thank our listeners for tuning in. Again, feel free to check out our website, which is thehealthedgepodcast.com. We're working on some videotaping, John, so hopefully very soon we can start getting some video out of these podcasts as well, with links both on our website and soon we'll have a YouTube channel out there, so people can see as well as listen. That ought to be a lot of fun.

John Bagnulo PhD: Yeah, that'll be great.

Mark Pettus MD: John, as always, it's been great being with you. Look forward to connecting again real soon.

John Bagnulo PhD: Likewise, Mark. Take care.