Mitochondrial Mastery with Dr. Mark Tarnopolsky

Speakers: Host (Interviewer), Mark (Guest)
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[00:00]
Host: Well, we have Dr. Mark Tarnopolsky with us, who is a world expert in mitochondria and lots of other interesting things. Thank you so much for your time.

Mark: Thanks for having me.

[00:20]
Host: To start and probably frame the conversation, I'd love to just get everyone on the same page so we know what we're talking about. Can you explain why mitochondria are central to health and longevity?

Mark: Sure, so mitochondria have existed with us for probably close to two billion years. It was thought that the mitochondria was a bacteria that early in evolution formed a symbiotic relationship with what was called a proto-eukaryotic cell to make the current cells that we're all built of; all mammals are, and many other critters, and that is the eukaryotic cell. Essentially, what people believe is that we took on the mitochondria to allow us to extract more energy from our food but also to detoxify oxygen because at the time during evolution, the world's oxygen concentration was going up. Throughout evolution, the mitochondria have lost most of the DNA that's used to make them to what's called the nucleus, so the nucleus is where the DNA from our mom and dad, which comes together containing 22,000 genes, exist, and about 1,200 of those are used to make these beautiful little engines inside every one of our cells. But the mitochondria have this little circular piece of DNA called the mitochondrial DNA, which is inherited from our moms, and it sort of forms the backbone of this energy extraction system. Traditionally, the mitochondria are used to make energy; they're very efficient at doing so, and without them, our cell relies on what's called anaerobic metabolism, which is very inefficient. To a first approximation, if your mitochondria don't work well, you don't have enough energy for important things like protein synthesis, making new enzymes, etc., and as a consequence, if you think about a simplistic thing like protein synthesis, if we don't make muscle, for example, as we get older, when our mitochondria don't work, our muscles will get smaller, and there's a reasonable relationship between mitochondrial dysfunction and thin muscles, and that's probably the easiest way to think about mitochondria not working and a consequence which affects all of us as we get older, called sarcopenia, which is the loss of muscle.

[02:27]
Host: What do you think of the current state of people's mitochondrial health across the board and what impact the modern-day lifestyle has on that?

Mark: It's very clear that mitochondria respond to stimuli, and the main stimulus for increasing mitochondrial mass is exercise. We're all born with different mitochondria; we have different mitochondrial DNA from our mom, and then from both of our parents, the rest of it is built, so our mitochondria inherently are slightly different in their efficiency just from natural genetics, but we can change that through exercise. For example, in skeletal muscle, if we're sedentary, about 2% of the total mass of our muscle are mitochondria, and we've done studies that after three months of training, we can bring that up to 4%. It's different in different tissues; for example, in heart, almost 20% of the mass is mitochondria; other tissues like skin, it's very low, but they are important in every tissue, and when they don't work well, we can see the manifestations from heart not working well to skeletal muscles getting thin, graying of hair, cataracts, cognitive decline are all to a large extent, or at least definitely some extent, related to mitochondrial dysfunction.

[03:46]
Host: My understanding is you originally got into this by studying people who are born with genetic defects in mitochondria. What have you learned about people who have been dealt that hand, and what lessons can we infer for people who don't have those diseases, and what it tells us about normal mitochondrial function?

Mark: What we find is patients who have genetic mitochondrial disease have severe impairments in some cases. For example, I'm sometimes called to the neonatal intensive care unit for a child who's floppy; their lactic acid, which is a reflection of the mitochondria not working, is very high, and these children can have seizures, there can be enlargement of the heart, and it can be so devastating that children can die within the first few days of life with mitochondria that are not working properly. To the other end of the spectrum, we have milder mitochondrial impairment, which really leads to premature aging, the most common of which is something called chronic progressive external ophthalmoplegia, and with chronic progressive external ophthalmoplegia, these individuals get cataracts, they have droopy eyelids, they get premature hearing loss and some muscle weakness, which, as you think about it, really, that's just accelerated aging, and that's why there's this inherent relationship between mitochondrial dysfunction and aging, but really, we're seeing this premature aging in the milder genetic mitochondrial diseases, but very accelerated aging and severe tissue dysfunction in the more severe forms.

[05:20]
Host: Okay, so when we're thinking about our mitochondria, if someone who doesn't have a genetic disease or a bad genetic hand with regards to the mitochondria, what signs of poor mitochondrial function would people have before we get into sort of how to optimize and how to get them healthy?

Mark: I think probably the easiest way of thinking about it is what happens to us when we age. I used to be an athlete; I raced nationally and internationally. My VO2 max, which we can talk

about, is a reflection of your total mitochondrial abundance and how they're working at their maximum capacity; that clearly goes down. I go with my buddy; we were very competitive trail runners, and we're clipping along, feeling we're going as fast as we can; we look at our watch, and oh my goodness, we're 30% or 40% slower now that we're in our 60s versus when we were in our 30s. Right there, that's probably the most dramatic thing that most people can relate to, that increase in fatigability, the decrease in your capacity to exercise as we get older is very strongly related to that decline in VO2 max that happens as we age, and to a large extent, it's due to dysfunctional mitochondria because they're the ultimate oxygen acceptor, taking the food we eat, the oxygen we breathe to make energy, and if they're not working properly, you're not as efficient in that process. Other things like cataracts, for example, oxidative stress and mitochondrial dysfunction, almost everyone on this podcast, when you get to your 75th birthday, you're going to have some degree of cataracts. Absolutely everyone on this podcast, even if you're in your 50s, you're already losing your high-frequency hearing, and as a consequence, my daughter had this little app where they would press a button, and there was this high-pitch sound, which is high frequency, and I was going up to a ski race, and all the 16, 17-year-olds were freaking out because they could hear this; my wife and I were blissfully in the front, completely not hearing this high-pitch sound, and they even have apps now on your computer where you can listen to a sound, and the frequency will gradually increase, and where you can no longer hear it is plus or minus about three years of your chronological age, so that's just another function of mitochondrial dysfunction.

[07:46]
Host: They have these things outside houses in London to ward off unwanted youths, and they're silent to most people, but if you're of a certain age, you can hear it; it's quite piercing. Okay, so a lot of problems if mitochondria health is declining at a premature rate. You mentioned exercise is one of the best tools we have against mitochondrial decline and, I guess, for lack of a better word, optimization. What kind of exercise, what kind of exercises really move the needle? Is it high intensity, is it weights, or is it a blend?

Mark: The very traditional answer to that is endurance exercise is the main stimulus to increase mitochondria, and there's no question that that's been so well documented by innumerable individuals for the last 40, 50 years, and that is absolutely true. Whether it's cycling, running, rowing, whatever it might be, that's going to cause a stimulus in the muscles that are working to increase your mitochondria, and as I mentioned before, in several of our studies, it's very well documented we can double mitochondrial mass in about three months of endurance exercise training. However, Marty Gibala, friend and colleague of mine, has done quite a bit of work with higher intensity activity, so instead of going for what we call moderate intensity continuous activity, you're doing very high intensity bouts for 30 seconds, a minute, taking a bit of a break and going again, and that's a very time-efficient way of exercising, but it can result in similar mitochondrial biogenesis, we call it, over the short period in research studies. I think practically, for some people, that might be great from a time perspective, but as we get older, sometimes it's a little harder to enjoy or want to do those high-intensity types of activities, and there's a slightly greater risk of musculoskeletal injury as we get older doing that, but again, some people do

enjoy it. I was never a big fan of high intensity, but whatever works, and if you really like that, you're still going to get some benefit. Now with weights, traditionally in younger individuals, what the weight training, resistance training, your three sets of 12 to 15 repetitions, for example, with a fairly heavy weight, leads to muscle hypertrophy, but not a hypertrophy of the mitochondrial reticulum, and so generally, the mitochondria will get larger, but the muscle mass gets bigger, so proportionately, we're really not increasing the mitochondria. Now, we published some papers a few years ago showing that it's a little bit different when you get older, so in older individuals, and that's those over the age of 65 in our studies, when we did weight training, we actually saw an improvement in mitochondrial function, and it's a slightly different mechanism. So what we feel is going on, and there's now a lot of studies coming together to show this, and that is that when you're under the stress of weight training, for example, we put the mitochondria under a bit of stress, and those that, throughout decades, let's say, of dysfunction, little fractions of the mitochondria that aren't working as well as they should will be identified and removed through a process called mitophagy, which essentially is self-eating of the mitochondria. I think of that process; most of us would understand pruning a tree; if you prune your tree in the spring, it grows much better, and it's the same thing that if we have areas of our mitochondria, which they're not little sort of balls that are floating around, they're really a reticulum within the cell, so if an area becomes dysfunctional, and that's identified and targeted and cleaved off through mitophagy, you get more pure, more clean, better mitochondria, and that we found with work with my grad student Johnny Parise; we do see improvements in the older adults with exercise training. I think of it as going through a physiologic stress, a filter of exercise, and coming out the other side after you recover with better quality mitochondria, which is much more apparent as we get older and accumulate these dysfunctional mitochondria.

[11:60]
Host: Okay, so as we get older, there's more dysfunctional mitochondria, so the need for mitophagy, which is the sort of self-renewal process that you described, pruning a tree, is more needed, and you can get that through all types of exercise, including lifting weights, right?

Mark: Yeah, so the weights, we were quite surprised that we saw quite an increase in mitochondrial mass, which was not observed in the young people, and what we saw was the deletions of the mitochondrial DNA that are occurring; those are actually lower after we trained, so that's reflective of this pruning of the tree.

[12:35]
Host: Okay, so a takeaway for someone listening who's might be on sort of older end of the spectrum here would be if they are out and about and enjoy the endurance sports, wonderful, but maybe take up a weight or two here and now again.

Mark: I think the main value of weights is not so much that it's going to improve your mitochondrial function, which it will, is more so that as we get older, even at top sport endurance athletes, we really start to lose strength and functional capacity, and I always tell folks, people like me who've been endurance athletes, you got to start adding in some weight training and

resistance training as you get older. There were studies even by the late great Bengt Saltin, who was one of the top physiologists in the world, where they were looking at the leg strength of marathoners in their 70s, and it really was not different from the sedentary population, so I think multiple studies have shown the benefits of weight training, more so from a functional capacity, getting out of a chair, going upstairs, picking up your grandchildren, going shopping, etc., and endurance training, well, great for your VO2, doesn't give you the same benefits with respect to balance and with respect to strength and functional capacity that things like resistance, especially more dynamic type of activity resistance training, really confers. So I think the optimal for health span is a mixture of endurance and resistance exercise; however, for top sport performance, when you're young, you really got to be very sport-specific, and although weights are advantageous to some types of activity, they have to be very sport-specific to optimize your performance.

[13:53]
Host: Okay, that's super clear. So when it comes to mitochondrial biogenesis, which is the creation of new mitochondria, how much of mitochondrial health, the optimization, is seeking things to create new mitochondria, and how much is just general optimization of mitochondria, giving it the fuel it needs?

Mark: Essentially, with exercise, which is why it's such a beautiful evolutionarily conserved way that we can improve our health, is there's so many things that occur, and that's why no supplement or anything's going to replace exercise. So one of the things that happens is that we increase something called VEGF, which is the vascular endothelial growth factor, and so we get more capillaries, so we are delivering more oxygen to each muscle fiber, and Johnny Parise and others have shown that with the endurance exercise, there's more capillaries per fiber, so you can deliver more oxygen because your VO2, or your ability to consume oxygen, is a function of your DO2, or delivery of oxygen to muscle, and the extraction, which is a function of your mitochondrial capacity. So one of the benefits of exercise is increased DO2, or delivery of oxygen, with the capillaries, and then at the mitochondrial level itself, that reticulum is just much larger, so there's more contact sites, there's more area for the mitochondria to actually function and extract and mix the oxygen and what's called complex 4 with the food that's coming in at complex one and two of the mitochondria, and that whole process becomes more efficient when there's more mitochondrial mass, which is biogenesis, is bigger mass. Now, throughout evolution, unless you have mitochondrial disease, the function per mitochondria really doesn't change that much, so when we exercise train, the mass goes up, but per unit mitochondria, their efficiency is really not that much better, and that makes sense because if we've evolved for two billion years, Darwinian selection would predict that we would have selected for pretty much the optimal function of an individual mitochondrial unit, so nature now responds to physiologic stress like exercise to not increase the efficiency, which you really can't; what you do is you increase the total mass. Now, I should caveat that the only known supplement in strategy to increase the efficiency, it'll go up a little tiny bit in some studies, but not all, with exercise, but beetroot extract, which has nitrates, a study in Cell Metabolism a few years ago showed that that actually can slightly increase the efficiency of each mitochondrial unit, so that's how the

beetroot extract works, is not really to cause more mitochondria but to increase their functional efficiency.

[17:09]
Host: Okay, so if I've heard you right, so the actual increasing the functional efficiency of mitochondria is sort of, you're majoring in a minor, if that makes sense; there's only so much you can actually increase the efficiency, when actually, if you just increase the load of total mitochondria, that's where you're going to get the most back.

Mark: Yep, and that's what Mother Nature has done. I mean, doubling mitochondrial mass is crazy when you think about it; three months, you double the amount of mitochondrial mass in skeletal muscle, and in the leg muscles of both men and women when we do training, whereas the efficiency per mitochondria is minimal; in some cases, it's not measurable, it's probably a little bit better, but minimal by comparison to that increase in this engine that we have.

[17:51]
Host: Wonderful, so two follow questions from that is, in that study, what was the baseline of people going into that three months of exercise, and then how do you measure mitochondrial capacity?

Mark: We've done innumerable different studies, from very overweight and obese and sedentary individuals to top sport athletes, but in those studies, we generally take kinesiology students who are not doing more than three times per week exercise, so playing a little bit of recreational football or whatever, not varsity team level folks, and so those are sort of have some experience with activity, but not habitually very, and then we put them into generally about a 5-day-a-week exercise program at about 65 to 70% of VO2 max, and we can double the mitochondrial mass in those individuals. The other question was how do you measure that. The VO2 max is a rough measure of your total mitochondrial capacity, but to actually look at the number of mitochondria, we do a muscle biopsy. I've done over 18,000, more than anyone in the world by far, from newborn babies for diagnosis, and we've done innumerable studies with the kinesiology department and our studies over the decades, and we take the muscle biopsy, and we can do it many, many different ways; we can measure the enzyme activity of the mitochondria, we can measure the protein content, which are usually, at least in physiology, pretty well correlated, which kind of goes to my last point, that is, the more you have, the higher the enzyme activity per unit muscle. We can also look under the microscope, so what we do is we can look under the electron microscope, and we can look at different areas, so there's what's called the subsarcolemmal, which are just under kind of the skin of the muscle, called the sarcolemma, and then we can look at the ones that are there present between the contraction component of muscle, called the intermyofibrillar mitochondria, so with electron microscope, we can measure the area of those mitochondria and how they relate to those two main regions of the muscle cell, and both of those do expand; both the intermyofibrillar and the subsarcolemmal mitochondria do go up with exercise training.

[20:03]
Host: Okay, so a muscle biopsy is probably inaccessible, and most people probably won't want to do it because apparently it's quite painful, but is it safe to say that if your VO2 max is increasing, your mitochondrial capacity is also increasing?

Mark: To a first approximation, those are going to be tightly correlated, and certainly, on average, that's really what the average person can use as their metric that the mitochondria is going up, and there are some apps now on some of these wearable devices that will give you a rough estimate, but the real way to measure VO2 max is to actually go on a treadmill or a bike, and what they do is you measure the oxygen concentration in air, which is 20.93%, to their maximal; what you can do is measure the total amount of air going in and out, and you can look at the difference in oxygen from the room, which is 20.93%, to 16%; you look at the difference in that, multiply it by the total volume, and that's how you get your VO2, usually expressed per kilogram of body mass is what's best correlated with good health outcomes over people's lifespan.

[21:14]
Host: Those tests are absolutely horrible, but very interesting to get done at least once or twice, right?

Mark: Yeah, you got to really go for it.

[21:23]
Host: Okay, so exercise seems to be the sort of the bulk of it, right, the main way to boost mitochondrial capacity. What other methods are interesting to you at the moment?

Mark: There's really not much that's going to increase mitochondria. There's all sorts of discussion about different supplements which will increase mitochondria, but there's a lot of hype, and you can certainly see in animals and cell culture, there's many things that will be shown, and that's a real problem because we've done many studies in cell culture, and you can add things that are antioxidants, things that are not antioxidants, and you can put them in different concentrations for different periods of time; you can stress the cell, which is, every cell will respond to stress; if you overstress it, it'll die, but if you stress a cell, it'll generally respond to protect itself against that stress, so the stress is less; that's physiologic adaptation, which has been known for many, many decades, and so pretty much anything you can use, light, you can use oxygen deprivation, you can use different chemicals, some of which are supposedly good; even vitamin E, vitamin C, you give too much to a cell, and you can kill it, but you give it a little bit, and you'll get mitochondrial biogenesis, so a lot of supplements or claims are based on what people have observed in a Petri dish, but I can pretty much take 90% of the chemicals in my lab, figure out the concentration to cause mitochondrial biogenesis, which really is just stressing the cell, and the cell is going to respond. Next is animals, and the same thing holds true that there's a number of different strategies that will induce mitochondrial biogenesis, but what's interesting is some of the things that you would think, like an antioxidant, may not even be

beneficial, so what I mean by that is if we cause oxidative stress, which is essentially release of these free radicals, which can be formed in the mitochondria, they actually can stimulate mitochondrial biogenesis, so by definition, and there have been some studies that have shown this, that if you take certain antioxidants and you exercise train, you can actually blunt the benefits, which almost seems paradoxical, and there was a study in, I think it was 2017, by a fellow Ristow, and they used vitamin E and vitamin C and trained fairly sedentary individuals and showed essentially none of the benefits when they exercise trained with vitamin E and vitamin C, and yet many people think, oh, these are great, they're antioxidants, they're going to be good for me, and as I get older, I have more oxidative stress in my muscle, which you do, and therefore taking antioxidants is good, but not necessarily. Now, there have been a whole, probably the two biggest supplements that people think help their mitochondria is the NAD precursors; there's a variety of them, the most common of which is nicotinamide adenosine riboside as a precursor for NAD, and the theory there is, ultimately, in the mitochondria, NAD comes into complex one and provides energy, so the theory there is that by providing these NAD precursors, you can give more fuel to the mitochondria, but quantitatively, it's a tiny, tiny amount. I mean, we're getting hundreds of grams of carbohydrate and fat, protein precursors coming in to the cell to make NAD, and to take an extra gram or two of NAD outside of that just seems like a tiny amount, and again, some really nice stuff in animals, but I've got four papers up here showing that in humans, it's really doing essentially nothing. One really nice study out of Denmark, because they were claiming that it helped with your ability to utilize glucose, no benefit, when we look at body composition, which many people are exercising, taking supplements for, there is a slight increase actually in body fat and no increase in lean body mass, so the sort of luster on that supplement is kind of faded, which again, I think most supplements, especially single ingredients, will come and go, and you had, prior to us talking, mentioned this one called urolithin A, great marketing, some people with clearly plastic surgery on their face I've seen marketing this, I'm sure they have great scientific credibility, but lots of plastic surgery going on, great marketing, beautiful name, Mitopure, purify the mitochondria, which is really what they're claiming, and that is that, take this urolithin A, and what it's going to do is it's going to activate mitophagy, it's going to clean up your mitochondria, and again, can show almost anything in a Petri dish, that's great, but when you actually look at one of the seminal studies, which was done in middle-aged men and women, 30 people in three groups, on a placebo, low dose, and higher dose urolithin A, but if you take a very, very close look at the paper, in their figure five, they've got mitochondria markers, two of them, and then they've got a marker of mitophagy, and where the mitophagy marker was going up, there was no increase in mitochondria; when the mitochondrial markers were going up, there was no increase in mitophagy, so right there, that link really wasn't tight, so it's tough mechanistically, you say that's how it's working, but you don't show a relationship, that's one thing; the other thing with that study, which has never been explained to me, is there were 30 people per group, but then, if you actually look very carefully at the numbers, there's a dot for each individual; there were six to seven people in each group; what happened to the 23, 24 people; were they cherry-picked, what happened to those, and look carefully at figure two in that paper, panel A and panel B are absolutely identical, supposedly for different metrics, so again, great fanfare, published in a good journal, but 99% of people, even my colleagues, when I showed them this, oh, I didn't

notice that, I thought this was great, it's really turning on your mitochondria, so I mean, it may do something, but sadly, I've seen, now that I'm an old guy, I've seen so many things come and go over the years.

[27:56]
Mark: Now, again, we've had a concept that part of the reason why many of these supplements fail is that you're only targeting one pathway, and so what we proposed, or I proposed with Clint Beall, back in 2001, is that to target aging, muscular dystrophy, neurologic disease, where all of the final common pathways of oxidative stress, inflammation, mitochondrial dysfunction are converging, we need to have multi-ingredient approaches, and we first tested that in 2007 in genetic mitochondrial patients, where we used alpha-lipoic acid, which is an antioxidant in the mitochondria, coenzyme Q10, which is one of the carriers of electrons in the mitochondria, vitamin E, which is a membrane antioxidant, and creatine monohydrate, which many of you might be familiar with, which is essentially a buffer of energy in the cytosol of the cell outside of mitochondria, so we gave that to patients with genetic mitochondrial disease, and we showed two markers of oxidative stress were lower, and lactate was lower, and the lactate really, when it's high, it's a function of your mitochondrial dysfunction, especially in your mitochondrial patients, so showing a lowering of lactate implies an improvement in mitochondrial function in those patients. Now, we were criticized because, for 50 years, everyone's drank the Kool-Aid from Big Pharma, and that is one target, one small molecule that you can patent, engage the target at the PK, do an animal study, do a phase one, two, and three clinical trial, and Big Pharma wants to destroy, and this is my personal feeling, they want to pooh-pooh exercise, they want to pooh-pooh proper nutrition, because it takes away from market share; if you're selling insulin or any diabetic medication or obesity medication, you don't want people to exercise, you don't want people to have good nutrition, because every person who benefits from a good exercise or nutrition program is going to take away from market share, and so we were sadly criticized with that paper, saying, oh my goodness, four ingredients, we don't know which one's doing what, and my point was, well, you didn't read our paper in 2001, it was designed as such because we feel that's the only way you're going to target these complex biochemical processes. So then, with, again, with my own personal money, fortunately, I was a physician, had a little bit of extra cash at the end of the year that I could get back to the university or used for research, anyhow, we did a study with very high dose coenzyme Q10, 600 milligrams twice a day, in 30 patients with genetic mitochondrial disease, and did we find a change in oxidative stress or mitochondria, absolutely not, no reduction in lactate, no reduction in oxidative stress, so again, not surprising that things like just creatine with ALS, vitamin E with Parkinson's disease, Q10 with Parkinson's disease, pretty much any single antioxidant supplement, and even look at vitamin E for cardiovascular disease, it actually increased risk of some cardiovascular events; any single agent, I don't think is going to be the ultimate solution.

[31:14]
Host: I think it's a hangover from the sort of old school medicine, though, you know, that there's something, there's a problem from external, and it's come internal, it must be one thing to try and target, i.e., bacterial infection or whatever it is, and you can, I feel like urolithin A is the

pharma playbook equivalent on a nutraceutical, and you can see it a mile off, and you know the connotations of, I don't want to get myself into trouble here, but the connotations and the branding and the funding are all of that world, but if you think about medicine, for example, medicine is siloed into, you're a gastroenterologist, you look at the gut, you're a neurologist, which I am, you look at the brain and the muscle, once, early my career, I got into mitochondrial medicine, I realized that I have to be a jack of all trades and master of none, because the mitochondria are in every cell in our body except for our red blood cells, and so when you have somebody where they have problems that cross different organ systems, you know, they've got cardiomyopathy, they've got pancreatic dysfunction, and they've got strokes and seizures, they'll come to see me, but when they've got all these other systems, boom, think mitochondria, because they are ubiquitous, so we have to think across disciplines, but by the same token, it's almost an analogous issue, and that is that when a mitochondria doesn't work, it isn't just that you're not getting energy, you also have an increase in oxidative stress, you activate inflammation, there's a thing called the inflammasome that gets activated, you activate something called apoptosis, so again, there's multiple effects from mitochondrial dysfunction, and so by targeting the mitochondria and dealing with all of these sort of spin-off deleterious effects, I think is the only way, and you know, conflict of interest, yes, we've created a company based on this concept of multi-ingredient supplements for treatment of obesity by targeting the mitochondria, and lo and behold, it actually worked well.

[32:56]
Host: And is that, are those supplements the things you mentioned, ALA, CoQ10, vitamin E, creatine?

Mark: What happened is we used the concept coming from our trial in mitochondrial patients that alpha-lipoic acid, coenzyme Q10, vitamin E, and creatine would be beneficial, but what we did is we also added in beetroot extract because after that, our 2007 paper came out, the beetroot stuff had come out, so we put those five together, we called it a mitochondrial enhancer, then what we did is we went to the literature and we said, well, what are the top supplements for weight loss, conjugated linoleic acid, green tea extract, black tea extract, green coffee bean extract, and something called forskolin, which is a mint extract, so we reviewed the literature, said, this probably best evidence for all of these, so we took a pre-clinical mouse model of obesity, and we looked at the mitochondrial five, we looked at the weight loss five, we looked at all of them together, and what we found was that the mitochondrial enhancers on their own really was, they did something, but it wasn't very powerful, the weight loss stuff, as everyone can imagine, there's multiple evidence that that would work, and it did, but when we put them all together, it was like the mitochondrial enhancer synergized those weight loss components, but then, what we found is, unlike Ozempic and all of these other drugs, which blunt your ability to want to eat, and then you lose weight, in all of those cases, you lose a substantial amount of muscle, so what we found was that we could preserve muscle, so these animals were losing fat but holding on to muscle, and we reasoned that it was probably the creatine doing that, but to our surprise, we pulled creatine out, and then other people were saying, oh, I'm sure it's just the conjugated linoleic acid that's causing the body fat, we pulled

that out, and we also pulled out black tea extract, and we had seven ingredients left, and they were actually as good, if not slightly better; in fact, paradoxically and almost unexpectedly, it led to an increase in a protein called UCP1, which is really the main sort of jewel in the crown from an obesity perspective, because that leads to something called futile cycling, and we kind of just burn energy as heat through these uncoupling proteins in your white adipose tissue, and so, again, sometimes you never know, you have these hypotheses, but unless you experimentally test them, which again is a real problem, I think, for probably 95% of every supplement on the market, is people throw things together and say, I've put vitamin E, vitamin C, selenium, blah, blah, blah, this is an antioxidant, but we've had many experiments where we gave this to humans or animals or cell culture, and what appeared to be an antioxidant became a pro-oxidant, so once you go through the biology of a human, you really have to measure in that person, is your combination functioning as you think it is, and sometimes you're surprised.

[36:14]
Host: It's such an interesting point. I mean, you can never merely do one thing in the body, right? I mean, vitamin C, taken at a high dose, just taken orally, is an antioxidant, but intravenously at a super high dose, it's a pro-oxidant, so it's complicated, and it seems to be, doing this podcast and speaking to really people yourself, is the biggest things that move the needle with health don't merely do one thing, right? Exercise is brilliant, but there's thousands of things downstream of exercise that we don't even know about yet, but we know it's great, right? Another thing in that realm is the ketogenic diet, and you could do all sorts of wonderful things with the ketogenic diet; do you feel it has a place on the sort of the Mount Rushmore of mitochondrial health?

Mark: It's a tough one. I think there's a few things; number one, practically, I think it's difficult for most people to stay on a ketogenic diet for a long period of time. We use it in some of our children with intractable epilepsy, and kids tell it like it is, I don't like this, it's horrible; many kids, at most, we can keep them on it for three or four years. Now, there's the bodybuilder types say, this is amazing, but some of these people have incredibly restrictive diets and are incredibly regimented, and for them, it's probably not a big deal. I think for the average person, I think it would be very hard to stay on a ketogenic diet. I think the challenge with a ketogenic diet also from a socioeconomic perspective, going out and focusing on special keto products is going to be very expensive, so that's just sort of an overall caveat, I think, to these. Now, there's clearly some definite benefits that have been shown, and there's different types of ketogenic diets; some are high in protein plus the high fat to get the ketogenesis, others are very high in fat, like the traditional one for epilepsy is very, very high in fat, but I think probably the more prudent thing and the easier thing for people would be to have a fairly high protein intake, which, Stu Phillips and many others, and our work, has also shown that as we get older, we need a higher protein intake, again, balanced protein, making sure that you have complementary amino acids and getting all of the essential amino acids, so that would make sense, good quality fats that also contain other vitamins and minerals do make some sense, and I think the key point really, at the end of the day, is to avoid highly processed foods, simple carbohydrates, and cut back on alcohol a bit; just those things alone, I think, for most people, you can have an enjoyable

repertoire of foods, an enjoyable life, but also a very healthy life by keeping protein intake high, and I really don't think, at the end of the day, that the high fat diet's going to play a practical role, even though there is some evidence that you can sort of activate mitophagy and UCP1, but we've certainly found, in some of our animal studies with a high-fat diet, you can actually end up with a fatty liver, depending on how that's done, and especially, practically, for humans, if you're on a ketogenic diet, but you're not compliant, and you're getting simple sugars coming in every once in a while, well, on a high fat diet, that can increase your risk for fatty liver disease, so it's never been something that I thought was particularly practical for the broad population.

[39:39]
Host: I'm inclined to agree, and if there's a study that shows some efficacy, well, compared to what, you know, the exercise is way more robustly researched from a mitochondrial point of view, and it moves the needle a lot more. I appreciate we're coming up to time, so maybe just one more to finish. I know you got to go. When it comes to, you know, you're in the field, you're testing all these things, you're researching it, when it comes to actually what you do on a daily basis, what does your protocol, your regimen, your supplementation, diet look like?

Mark: I've been exercising; I used to race internationally. I still, winning some masters races, my wife and I, a small little woman, we broke her hip, we kept going, and we ended up with a broken pelvis, and we still ended up winning a masters adventure race last year. So, my VO2's dropped; at one point, it was 88.6, and it's definitely down into the high 60s now, but I'm still doing pretty much the same thing, so I train seven days a week. I've definitely increased resistance activity; I do 360 crunches, 240 push-ups, some dumbbells, some arm flies, I do those every single day of my life. I do a ski ergometer two or three times a week, and five to six times a week, I will run and bike and cross-country ski, generally an hour to an hour and a half every day; I'm doing a mixture of both the endurance and resistance, mostly endurance, and on the weekends, usually two hours of running, 3 hours of cycling, or three hours of skiing every weekend, each day, and I know I shouldn't, but I go seven days a week; Monday is my rest day, but I still get over 10,000 steps, run 3K, do my sit-ups, push-ups, crunches, and all that stuff. And so, what do I eat? So, I have started, even though my first paper in 1988 was the top sport endurance athletes needed more protein, and now, with the work from Stu and others, showing that as we age, we need more protein, I bumped up my protein intake, so we've published studies, and Stu Phillips published one with a multi-ingredient supplement with creatine and high-quality protein, was milk-based; I'm lactose intolerant, but the milk isolate does not have lactose, so I take 40 grams of the product, why, because it has the whey and casein plus the creatine, plus calcium, plus vitamin D, so I take that every day with breakfast. I have cereal, multigrain toast, at least a cup of milk, usually half a cup of blueberries or strawberries, and then I also take 2,000 units of vitamin D every day, I take two teaspoons of omega-3 fish oil, I take a multivitamin, and then I take half of our mitochondrial enhancer, what we call TRIM7, which is the alpha-lipoic acid, CoQ10, vitamin E, beetroot extract, green coffee bean extract, green tea extract, and the forskolin, so, as you can probably see, I'm not overweight or obese, but that's more from a mitochondrial support perspective, and then, for, I usually fast generally during the day, I try to take either a gram or two of creatine or a bit more protein, and then for dinner, I

always have a massive salad with lots of nuts and stuff and cheese on top of it, tomatoes, and carrots, and always a large piece of some form of meat, be it chicken breast or meat, and then usually a carbohydrate, rice, or some sort of bread, and that's pretty much it every day.

[43:46]
Host: Love, you practice what you preach, I mean, I love that you eat your own cooking, Mark, which is wonderful. I'm going to up my hours of cardio, because I like to think I do a lot, but yeah, you're an animal; that's a load of cardio. VO2 max above 80 was, that's astounding, and it's still in the 60s, right, you said?

Mark: Yeah, so when I was younger, I mean, we used to compete doing VO2 max tests; we were racing internationally at the time; I was representing Canada in ski orienteering and racing all over Ontario and cross-country skiing, and Mike Waddington, who was the North American orienteering champion, we were always within about one ml per kilogram, and there's people say, oh, well, the machine must be broken, but we have at least 10 measurements over 80, and it was a certified lab, so I was able to find my highest that I had the official documentation, and I think that was 87, and so, in VO2max.com, at one point, I think I was 12th in the world for the highest VO2, but that doesn't necessarily translate to performance, because there's many other components, but naturally, I think, I chose my parents well, trained, and ate well, but that has come down, as expected, as we get older, the VO2, no matter what you do, because I'm still training exactly the same, slower, but still same volume, and my VO2 is, I think I cracked 68, 67 last time I was checked a couple of years ago.

[45:18]
Host: I mean, I don't know how old you are, but that's still outstandingly high. Just because I can't help myself, would you say the key to building a massive VO2 max is volume of training or intensity of training?

Mark: It's choosing your parents correctly, because there's no question, we're born into a window. I mean, clearly, you are more of a hypertrophic individual, so you could train for the rest of your life, and you're not going to get a VO2 over 80; I could train right from the time I was young, and I would never be close to being able to bench press or lift what you can lift, so, and we see this, naturally, some of us tend, like my wife, she looks at a weight, and she gets hypertrophic; for me, I trained my face off as a teenager, and I barely put on any muscle mass; my coach kept saying, Mark, go endurance, go endurance, so all joking aside, you are, to some extent, born with your VO2 and your mitochondrial capacity; you can train it, you can bump it up 20, 25, 30%, but if, naturally, your VO2 was 35, you're never going to get up to, much less over 50, and definitely not in the 60s, 70s, or 80s, so definitely, you're born with a window, you can work within that window, and the way to work within that is clearly proper training, proper nutrition, and proper rest, which becomes more and more important as we get older. Recently, there's some data showing that very good quality sleep speaks to our mitochondria through clock genes, so our circadian rhythms also interact with our mitochondria, so that's, to some

extent, why you feel so crappy if you've had a bad sleep; you're just not rejuvenating your mitochondria through this circadian rhythm clock gene-mediated process.

[46:60]
Host: There's some interesting things about near-infrared light and different spectrums of light and effects on mitochondria, but maybe for another time, because I appreciate you've got better things to do than talk to me all day, but Dr. Mark Tarnopolsky, thank you so much, that was a real privilege to sit down with you. Where can we keep up with your work and follow what you're doing?

Mark: Probably the best way to look at research on any individual, and also, if someone makes a claim for a supplement, I would encourage people to go to what's called PubMed; it's freely available to anyone; most articles, you can download and see if there's actually evidence, because there's certain individuals who have lots of claims, and they say lots of stuff, but if you PubMed them, for lack of a better term, you'll see that they've actually never even published, and if you haven't been in the trenches doing the actual research, it's, I think, it's dangerous to be making claims about different supplements or coming up with different combinations, and so, if someone's making a claim, and you think that, let's see the evidence for it, go into PubMed, and again, even that urolithin A paper that I was mentioning, top colleagues of mine that are in the obesity and exercise physiology world didn't notice those small things, but then people read the introduction, they read the conclusions, and then they spew that out and say that's the truth, and unfortunately, now, with certain changes that are happening in the United States, with X now, with Facebook, people can say pretty much anything they want, and unfortunately, that's difficult, but question things if they sound too good to be true, and go to the original sources would be my closing statement, I think, to everybody.

[48:41]
Host: Wonderful, wonderful, and do as much cardio as Mark does, that would be another one to move the needle. Well, look, thank you so much for coming on; that was a real privilege, and yeah, thanks, thanks so much, have a good day.