A Deep Dive Into Eccentric vs. Concentric Exercise
A Special Interview With Georgi Dinkov and Tyler LeBaron
By Dr. Joseph Mercola

Dr. Joseph Mercola:

So, we've got two amazing guests, Georgi Dinkov, who is the pro-metabolic expert with respect to integrating and recommending Ray Peat's work and doing a lot of independent work from himself of course. And then Tyler LeBaron, who has been on this podcast previously before. Tyler is a – I think you're a professor? Is exercise physiology one of the courses you teach?

Tyler LeBaron:

Yeah. It's chemistry, exercise physiology and then master's class of exercise, nutrition and sports bioenergetics. So, I'm an adjunct instructor or adjunct professor, depending on how you define that area. But yeah, those are the classes I teach.

Dr. Joseph Mercola:

Okay. He is really smart, he's got a great brain and understands biology and chemistry pretty well. And I was with Tyler at the Biohacking event in Orlando just recently. And I was excited to share with him because Tyler's also an elite athlete. I mean, he's definitely elite, almost world-class and probably in his specific niche. But, definitely, in the independent events that he competes in – distance running, resistance training, world-class arm wrestler. In fact, I'm going to show this video how I was able to actually beat someone half my age and [with] significantly more muscular mass than I had with the skills that he taught me.

But anyway, his passion is exercise. I love exercise, but I'm not as deep into the science. And I shared with Tyler the recommendation from the pro-metabolic community that the eccentric exercise is actually not that good compared to the concentric. So, from here – that's my simple summary. I went into a little more detail that Tyler has some concerns on, so I just wanted to have a pro and con dialogue here. So Georgi, why don't you state your position, because you know it really well, of the reasons why concentric exercise would be far preferable to improving your mitochondrial biogenesis as opposed to eccentric [exercise], which would actually impair mitochondrial reproduction.

Georgi Dinkov:

So, really, two main claims here: One is that, at least in the studies that I've seen, concentric exercise increases the mitochondrial biogenesis, the density and the size of the mitochondria, a lot more than eccentric does. Second thing is that concentric exercise has been shown to improve glucose uptake into the cell and reduce the synthesis of lactic acid. Third is that the concentric exercise, but not so much eccentric. In fact, almost no effect of the eccentric – depending on the cell, concentric exercise allows the muscle cells to synthesize a lot of these protective steroids that we've discussed on the podcast. In males, specifically testosterone. And in females, surprisingly, things like dehydroepiandrosterone (DHEA), which is supposed to be predominantly of adrenal origin. Turns out that it's not and muscles can produce it as well.

While eccentric seems to be mostly good for hypertrophy and maybe in corroboration to that, during eccentric exercise only it's been shown that the muscles produce predominantly estrogen, which, as we've discussed several times, is more involved in cellular proliferation. So, you can get bulkier on eccentric exercise but probably not stronger and not as metabolically healthy if you assume that a good oxidation of glucose and production of these anticatabolic hormones, such as pregnenolone, progesterone, DHEA, testosterone for males and mostly DHEA for women, is what we're after. That's really the nutshell.

Dr. Joseph Mercola:

Okay, thanks. Perfect. So Tyler?

Tyler LeBaron:

Yeah. Well Georgi, thanks for explaining that. You probably know more about this specific area than I do just because I haven't looked at these specific things. But I do teach exercise physiology, so I'll just give some of my thoughts on this. I think it's important you did clarify one point that Dr. Mercola didn't say before regarding the concentric versus eccentric in terms of the mitochondrial biogenesis. That, yes, I would agree with. There's a lot of data that would show that eccentric exercise, such as eccentric running, eccentric cycling, a lot of these simply don't have as much oxygen consumption. The O2 cost is a lot lower. And also, during that eccentric exercise you're damaging the contractile proteins, you're breaking down the architecture of the sarcomeres. So yes, in those regards, it doesn't seem that there would be any stimulus. At least not near as much compared to concentric exercise for mitochondrial biogenesis, and for oxygen uptake and the ATP (adenosine triphosphate) demands and everything. Eccentric exercise just doesn't require that.

And then I also would agree with your statement regarding the hypertrophy aspect. That's exactly what I was telling Dr. Mercola. That eccentric exercise is really key for the hypertrophy and for the strength. Then what are the superiorities, in my opinion, of eccentric exercise? Well, a lot of studies, including meta-analysis and systematic reviews, have shown that in terms of strength, performance and hypertrophy, depending on how you're going to measure it, eccentric exercise ends up winning. Now, there's a couple caveats to this, but let me just explain what, in general, I would say that the research [is] suggesting.

First off, as we said before, is the eccentric exercise that's damaging the muscular architecture – that damage to the muscle cells is one of the potent stimuli for anabolism, for muscle protein synthesis. It's not the only one, of course, metabolic waste and many other stimuli are also important, but eccentric exercise damaging the actual muscle fibers is a potent stimulus. So, some of these studies, for example, when they did just a concentric exercise without the eccentric portion, there was hardly any benefit in terms of increased strength and or increased hypertrophy versus a group that did only eccentric and not the concentric portion. So, essentially, they're doing half the amount of reps because they're doing the concentric portion, that's halfway. And then the other group's only doing only the lowering phase, right? So, essentially, doing half the

amount they were able to improve just as much, if not often more in different parameters, in terms of strength and hypertrophy.

And the other part that was interesting is, doing that eccentric portion of the exercise seems to increase the muscle hypertrophy longitudinally. Basically, you're putting sarcomere, the functional unit of the muscle, in series and that could have some benefits. You have maybe more muscle growth at the distal lens of the muscle. And that could explain even some differences between why, say, powerlifters who are lifting extremely heavy weight often do eccentric loading, their muscles and the way they look is different than a bodybuilder where they're trying to train their muscles to look a certain way versus for absolute strength. So, going back to what we agree with, yeah, mitochondrial biogenesis, all the oxygen utilization, that makes much more sense for a concentric exercise. But I would still say, in terms of muscle strength and hypertrophy, the eccentric exercise is very important.

But one other interesting caveat that Dr. Mercola, you'll appreciate, there was a study – and I don't know if there's more on this, but I thought it was very interesting. With blood flow restriction (BFR) training, it appeared that in that case concentric exercise was probably more important and more effective. Which sort of makes sense because when you do eccentric exercise with blood flow restriction, you're not lifting very much weight. So, you're not going to be able to break down the architecture of the muscles very much. So, the primary stimulus in that case is the metabolic waste. And so, the blood flow restriction, you're going to get a lot more of that when you're forcing the mitochondria, the creatine phosphate system, the glycolysis. All of these producing all the metabolic waste is going to primarily come from concentric exercise because [with] the eccentric exercise, like Georgi said earlier, you're not creating as much metabolic energy because it's not as metabolically demanding as the concentric portion. So, with BFR, concentric is probably more important than the eccentric phase, but not with standard resistance training.

Georgi Dinkov:

So, I guess if I'm hearing correctly, we can say that eccentric exercise is like a hormetic response because you are damaging the muscle periodically and then you have an overresponse by the growth, while the concentric exercise is mostly stimulating oxygen consumption and oxidation of glucose. I have a counter example, because you said that powerlifters do a lot of eccentric. I'm originally from Bulgaria and one of the few sports that we used to be known for but not anymore was Olympic powerlifting.

Tyler LeBaron:

Yes.

Georgi Dinkov:

Actually weightlifting, not powerlifting because it's different.

Tyler LeBaron:

It is different.

Georgi Dinkov:

So, they never do eccentric exercises. They're doing snatches. They're doing like push and then drop. They never ever do, in the actual training portion, eccentric exercise. They don't run either. They basically lift the weight once and they drop it. And studies on that, several have shown that they have probably the highest muscle contraction force per square inch that has been measured so far. How do you explain that?

Tyler LeBaron:

Well-

Georgi Dinkov:

Or would you agree that concentric is better for strength while eccentric is for hypertrophy?

Tyler LeBaron:

Okay, this is amazing. This is great. So first I would say that they're both true, but it's not totally a paradox. It's because now we're talking about elite levels. And this goes into terms of specificity. In general, all in all, eccentric exercise is going to make you stronger and it's going to grow your muscles more. But when you start getting to that elite level, now you start talking about sports specificity. And if you're going to do really, really good at eccentric exercise, you're going to get really, really good at eccentric exercise. Not necessarily maximal concentric, voluntary concentric action.

And so, when you take elite level athletes or people who are extremely well resistance-trained, and you have one group do 100% concentric, partial repetitions and these different things and isometric static holds, and another group that does just the eccentric portion, well then at the end of whatever the study, eight weeks or whatever you decide to do, and then you measure the parameters, you're going to find that the group that did the isometric is going to perform the best in isometric and not as well in the eccentric or concentric. And the group that does the concentric performs the best in concentric, but not as well in isometric or eccentric. And the group that does eccentric is going to perform the best in eccentric, but not as well in the other two groups. And they're both going to see these improvements and some might even see a little bit decrease.

I would still say that the eccentric group will probably see the least decrease in the other two, but still not as good as just the concentric. But again, this is the elite level. And so of course, I don't want to say that I'm elite. I know Dr. Mercola, you're always like, "Oh." But I'm just saying as an experience for me, I like to do one arm pull-ups for arm wrestling training. And so, I will often take another dumbbell with my other hand, 25 to even 35 pounds, as high as a 45-pound dumbbell, do a pull-up, hold with this arm, and I'll just hold and slowly go down like this. And that's an eccentric portion.

Georgi Dinkov:

Yeah.

Tyler LeBaron:

And I was really working on that and I was getting pretty good at doing a number of slow petitions with 45 extra pounds. And then I was excited to see just how easy it would be to do my normal one arm pull. Maybe I could hit five or six or seven repetitions. I go and do it, and it's harder than it's ever been before. What that tells me is, I certainly got better at the eccentric portion doing eccentric exercises, but that didn't fully translate to my concentric action. But that's largely because I'm at this level where I have been training for so many years at this high level that it doesn't give me that same advantage that it might give somebody else. The No.1 recommendation that we give people who can't do a pull-up is to just hold yourself over the bar and lower yourself down slowly.

And [if] you have one group [that] does that, and the other group that just tries to pull as hard as they can or do jumping pull-ups, the group that does the as eccentric, they'll be able to do a pull-up much faster than the other group. That works for the less trained individuals. And it makes sense because [in] the eccentric exercise, that reduces neural inhibition of – because you have the Golgi tendon organs, for example, you have different things. So, it's going to reduce that area. It's also going to increase the muscle activation of the agonist muscles to help you activate those muscle fibers more. So, it's going to increase that neural drive, as well as it decreases the coactivation of the antagonistic muscles. Because often as you're lifting, like trying to do a bicep curl, your triceps are also contracting a little bit, and you want to be able to decrease that activation.

Eccentric exercise helps to do that. And then you also are facilitating more equipment of Type 2 muscle fibers and even making the transition from more of the Type 1 to Type 2 muscle fibers. Your Type 2X muscle fibers become more Type 2-like. So in general, I would say those benefits are [what] you're going to see the most when you're talking about an untrained and relatively trained population. But it starts to be diminished at the high-elite level because of sport specificity.

Georgi Dinkov:

I really like what you just said. Basically the eccentric will favor the increase of the Type 2 muscle fibers, which favor fatty acid oxidation. They're not really glycolytic. So maybe, in summary, we can say that eccentric exercise will allow you to apply for longer lower amount of force, which will still be much higher than baseline, while concentric will create [the] ability to apply much higher peak force at peak, but for much shorter times. Does that sound reasonable?

Tyler LeBaron:

Yes. And because we are talking about the Type 2 muscle fibers – just for clarification, our Type 2 muscle fibers, those are our fast twitch muscle fibers.

Georgi Dinkov:

Yeah.

Tyler LeBaron:

So they're using more of glycolysis-

Georgi Dinkov:

Glycolytic, yeah.

Tyler LeBaron:

And so yeah, in that case – And I also wanted to point out another thing that would be good to talk about is the force velocity relationship with our muscle fibers. So, if we can draw a little graph and we have on – on our Y-axis, we're going to say that's going to be the strength of contraction, and then on our X-axis would be the velocity. What we know is when we lift something, the faster we're able to lift something, it means the less amount of weight we're able to lift. Like, [if] we're doing a maximal lift with a bench press or something, we're not going super fast. We're barely being able to move it, right? And so, that's a curved, linear inverse relationship that the heavier the weight, the slower the velocity. And that's true for concentric exercise. And for strength training, it's often good to work along this entire curve. So, sometimes you're lifting at a lower weight but you're keeping that velocity along that curve so you can continue feeding your Type 2 muscle fibers and getting the recruitment of all fiber type distributions.

But that relationship is actually different for the eccentric exercise. With the eccentric exercise, as the speed of contraction increases, the amount of weight that can be maneuvered also increases. And so, you're able to lift an enormous amount of weight eccentrically at a faster velocity. And so, going to what you were saying before, that right there is also really going to help to activate your Type 2 muscle fibers in that recruitment even more so.

Georgi Dinkov:

What about, let's say, for NFL (National Football League), the football players, it's my understanding based on some people that have emailed me, they claim to be either working with NFL players or the retired ones, that for strength, they're doing most of the concentric things such as flipping this massive tire or pushing this sled, while for muscle mass and actually, really, for bulk, they're doing their regular weightlifting, which is I guess half concentric, half eccentric. At least that's what they're being told by the coaches. How do you respond to that?

Tyler LeBaron:

Well, that was a little bit difficult because you have to do what works. And because you're talking about elite level and NFL football players, that might be going back into the realm of sports specificity. Your football players are super strong, but no NFL football player is setting world records in the bench press or the squats or the deadlifts, right? And so, it's about accumulating mass and strength, and having the specificity toward football as opposed to specifically just the weight training and setting a PR (personal record) or something. So, I think that probably goes hand in hand, but maybe the coaches are wrong. Maybe they would find that there'd be actually better benefits if they would adjust their training protocol a little bit more to

focus more on certain areas of the eccentric portion because you do want to get that – that muscle breakdown, that's terrible.

You get the DOMS, the delayed onset muscle soreness, and if you're able to do eccentric enough, then you'll prevent DOMS from happening. In fact, you get what's called the repeated bout effect, where doing a heavy day of eccentric exercise and then the very next day doing another set, it doesn't really break down the muscular architecture even more. There's a protective effect and your body can adapt quite quickly to doing this. And there could be some benefits to that so that when you're actually in the game, you're pushing yourself so hard and there's a lot of acceleration and de-acceleration at very high speeds, this could potentially help prevent injuries [and] increase your tendon strength, your muscle motor neuron connection, your muscle fibers. There could be benefits there that I could hypothesize. So maybe it would be good if they changed a little bit of their training to focus on those things some more.

Georgi Dinkov:

Okay.

Dr. Joseph Mercola:

Georgi, I'll bet dimes of dollars that you've got some pro-metabolic interventions to address DOMS. I could think of a few.

Georgi Dinkov:

To address what?

Dr. Joseph Mercola:

The DOMS, the delayed onset muscle soreness.

Georgi Dinkov:

Oh, yeah. I mean, the methylene blue, the thiamine, the niacinamide-

Dr. Joseph Mercola:

Yeah, why don't you just review them like we haven't discussed them before? Because Tyler wasn't here when we discussed that. That's a really good point. And I know it's not specifically about the concentric versus eccentric, I think it's an important tangent though. Because if you're participating in exercise resistance training, seriously, you're going to encounter DOMS and it's-

Georgi Dinkov:

However-

Dr. Joseph Mercola:

Something you want to avoid.

Georgi Dinkov:

Some scientists actually like the buildup of lactic acid and they're saying it's one of the primary growth factors for hypertrophy, so they're going for it. Now if you don't want that, if you don't want the lactic acid to build up, some of the most extensive evidence is for taking vitamin B1, maybe about an hour before exercise, and that will stimulate-

Dr. Joseph Mercola:

How much is the dose?

Georgi Dinkov:

Depends on the type. So the studies that I've seen are with regular thiamine hydrochloride, 300 to 500 milligrams, some use much higher. And then [for] the lipophilic analogs, the studies are mostly done in Korea and Japan because that's where those were synthesized, and [they] were taking a 100 to 150 milligrams single dose before the exercise. And that about half the rising lactate is a result of the extensive effects. I think the Korean study was with elite Taekwondo players, and the Japanese I think did it with baseball players, runners and I think sumo players as well.

The Japanese were using allithiamine and the Koreans were using fursultiamine, I think, which is another lipophilic analog. And that lowered the lactic acid rise by about 50%. Whether you like that or not, it's a separate story. I know several coaches are specifically saying, "Don't fear the muscle burn, you need it for muscle growth." And I think there's some truth to that because the reductants are acting as pseudo-hypoxants and are stimulating the muscle cell proliferation. But I have a question about eccentric and concentric in regards to a protein known as myostatin, which you're probably familiar with. Multiple studies demonstrate that when you're doing eccentric exercise, initially the amount of myostatin in the muscles decreases. However, depending on how long you do that, eventually it goes back to baseline and even increases, which is what one study uses as an explanation why, let's say, long distance runners are never hypertrophic.

I mean, there may be another reason, but they adapt. They cannot carry this tremendous muscle mass for all these, what, 26 miles? But you see that effect even in shorter durations such as competitive rowing, which I used to do in college. Even the heavyweights of this sport, in the first and second year, they look like bodybuilders, but after that, I guess towards the senior year, when they adapt, basically, they started to look lean. And one of the studies said that this is basically a result of the adaptive increase in myostatin, if you do chronic eccentric exercise predominantly.

Tyler LeBaron:

Yeah, that's interesting. Okay, so a couple things that I find interesting – number one, yeah, the thiamine. I haven't heard that before. It would be interesting. I'll have to look at that. But I'm just assuming that perhaps that mechanism is because thiamine is a cofactor for the PDH, the pyruvate dehydrogenase complex, to help shuttle pyruvate into the mitochondria. And if you're low on that for whatever reason, especially if you drink alcohol, that could be problematic. So

that's interesting. But then the other thing, you're going to love this, lactic acid – I have a personal problem with that term because as you probably know-

Dr. Joseph Mercola:

Oh yes, yes.

Georgi Dinkov:

Lactate, yeah.

Tyler LeBaron:

Yeah, lactate. And it's hard to say lactate because everyone thinks about, "Are you lactating?" or lactation or something, right? But I have to talk about this because it's one of my favorite topics, but it's important that we recognize that lactic acid is never actually formed in the body. And almost all textbooks even get that wrong. In fact, I have this textbook, one of my exercise physics textbooks here that mentions lactic acid. And generally, what they do is they say that the lactic acid molecule is produced and then as soon as it's shuttled out of the cell, it converts to lactate and the hydrogen ion.

Georgi Dinkov:

Yeah.

Tyler LeBaron:

But that's actually not even true itself. That lactic acid is never formed, only lactate. That pyruvate, as the end part of glycolysis, you take pyruvate and you add onto that two hydrogens and two electrons. And so, the formation of lactate actually increases the pH of the body. So, Georgi, what you were saying earlier about the benefits of lactate, well that's a big one right there. So, I just want to talk a little bit about the benefits of lactate as I'm explaining how lactic acid itself doesn't exist in the body. First off, if you were to take pyruvate and lactate dehydrogenase, and put it in water to pH of 7 and make the reaction go forward, you'd actually see the pH rise of the water because again, you are requiring a hydrogen ion from the solution, so the pH actually rises. And that's critical because it is the production of lactate that retards acidosis.

And two reasons: One, because it's [an] increase in intracellular pH from the formation of lactate from pyruvate. And then two, when it does go into the cell, it goes through the cell into the blood, it has to go through a transporter, which is this model carboxylate transporter, which requires an either cation or a hydrogen ion in order to transport out. So basically, for every lactate molecule that gets excreted into the blood, you are losing two hydrogen ions. And so the pH of the cells is able to maintain that higher pH a lot more effectively. And of course, the blood is full of bicarbonates and hemoglobin, and then many buffering molecules in protein. So, it can easily handle that for the most part.

But the other big thing is that production of lactate causes, and you guys probably talked about this a lot, but causes that regeneration of NAD+ (nicotinamide adenine dinucleotide) so that the

glycolysis can continue. That's the No. 1 reason why we start producing lactate in the first place. Like when you start sprinting, there's actually plenty of oxygen available, there's enough oxygen available to maintain a maximal sprint and to make the ATP, it's just you can't do it because of the enzyme kinetics in order to make ATP fast enough.

Dr. Joseph Mercola:

That's the Warburg Effect?

Tyler LeBaron:

Yes-

Georgi Dinkov:

Anaerobic glycolysis, basically. You have a buildup of NADH (reduced nicotinamide adenine dinucleotide). And since they cannot oxidize quickly enough to the Krebs [cycle] and the electron transport chain, glycolysis works much easier by using pyruvate as the oxidant.

Tyler LeBaron:

Exactly, yeah. So you're always able to regenerate that NAD+. So that's key. And then what you were saying earlier, Georgi, I think it's very important that – I agree that lactate is a neuromodulatory hormone that has so many benefits. It increases benefits to stimulating muscle protein synthesis, for example. It correlates with acid production and metabolic waste like inorganic phosphate, calcium, all these metabolic waste, which we know has the stimuli for protein synthesis. And then lactate is actually a preferred energy source of the brain as well, interestingly enough. It has very therapeutic effects in the brain. Maybe it has the relevance to increasing BDNF, brain derived neurotrophic factor. So I love lactate. I think it's great. And the mitochondria can also uptake lactate. There's a transporter, mitochondrial lactate transporter, that can actually uptake and oxidize lactate as well. So anyway, I just wanted to go off that topic a little bit.

And then going to the interesting point about the endurance runners, right? They're doing a lot of eccentric running, basically. They're hitting the ground, it's a lot of muscle damage to their legs, yet they're not huge. Their muscles are very, very small, like mine. I run so much that it's a benefit to having a certain size and diameter of your legs, so you can have very good running efficiency. And I agree with you that I think that with the myostatin, that is certainly what is happening initially. Of course, myostatin levels decrease and then it goes back to baseline and increases even further, which makes sense because the eccentric exercise is a potent stimulator of hypertrophy. And so, the higher the hypertrophy myostatin levels are going to be.

You already said that's just one of the reasons. But some of those other reasons, of course, is you're still not doing your typical Type 2 muscle fiber recruitment. A 30-second type of exercise. You're running for hours at a time even, and that's not going to be the same stimulus. And in fact, you're activating AMPK (AMP-activated protein kinase) and PGC-1alpha (proliferator-activated receptor-gamma coactivator-1alpha) and the peroxisome proliferator-activated receptors, your PPAR gamma areas. And that is-

Georgi Dinkov:

You're emulating fasting basically.

Tyler LeBaron:

Yeah, exactly. So all the oxidative phosphorylation (OXPHOS) pathways, mitochondria, that's certainly not going to increase your muscle hypertrophy, your muscle fiber size and things.

Dr. Joseph Mercola:

Terrific. Interestingly, we were talking previously about KAATSU or about blood flow restriction training, and I neglected to mention to Georgi that one of the known mechanisms is myostatin inhibition. It has a direct impact on that. So, it's one of the ways that seems to work. But getting back to DOMS prevention, one of the other ways that I found, personally, as useful is red light therapy, done as soon as possible after the precipitating event, ideally almost immediately after, but up to a half hour. Near infrared would work too, or both. Red and near infrared both seem to work in the mitochondria. I'm not sure of the mechanism, but it seems to be helpful for that.

Tyler LeBaron:

In my- [crosstalk 00:29:57]

Georgi Dinkov:

I can suggest something-

Tyler LeBaron:

I was just saying, it seems like it could probably be helpful just because in order to fix the DOMS, it requires quite a bit of ATP synthesis and you've got to clear out all the metabolic waste, the tissues. You've got to do a lot of degradation of damaged muscle fibers and then rebuilding all of those. And so, you want to have some sort of active blood flow, just things going on in the cells. And the red light therapy, I could envision this accelerating that process because of its effect on mitochondrial ATP synthesis and some of the other things going on. But I guess-

Dr. Joseph Mercola:

So, you're saying that nitric oxide from complex 4?

Tyler LeBaron:

Yeah, exactly.

Georgi Dinkov:

There are two other mechanisms. Specifically, red light, and not infrared light, increases the actual amount of pyruvate dehydrogenase that is in the cell. So it somehow stimulates its synthesis-

Dr. Joseph Mercola:

Oh, I didn't know it that.

Georgi Dinkov:

Another thing it does is-

Dr. Joseph Mercola:

How does it do that?

Georgi Dinkov:

Russians have a lot of study on it with LLLT, low-level laser therapy.

Dr. Joseph Mercola:

Yeah. Yeah.

Georgi Dinkov:

And specifically, just with a very minor amount, [a] very focused dot of red laser, they've been doing things like trying to treat several muscular dystrophic diseases such as Huntington and even ALS (amyotrophic lateral sclerosis). So they noticed the PDH increase, [but] they don't know the mechanism yet. Another thing that red light does is if complex 4 is somehow blocked, usually by nitric oxide or, god forbid, carbon monoxide, red light can break that bond. So, you freeze your complex 4, which is usually the rate limiting step, assuming your Krebs cycle is working. So-

Dr. Joseph Mercola:

It liberates carbon monoxide, too. I did not realize that.

Georgi Dinkov:

Yeah, it's a very strong bond, I think it's covalent, but red light can break it. Methylene blue is another thing that can break the bond.

Dr. Joseph Mercola:

Yeah. Yeah. Wow. I think the indications for methylene blue in the emergency room is carbon monoxide poisoning along with cyanide.

Georgi Dinkov:

That's what it shows, but you got to do it quickly before the hypoxia [crosstalk 00:31:55]-

Dr. Joseph Mercola:

In my view, [that's] really the only legitimate indication for intravenous methylene blue. Otherwise, oral is fine. But when seconds count you need it.

Tyler LeBaron:

I was thinking about the methylene blue, and I'll have to look – I mean, haven't tried it. We actually use it to measure hydrogen gas concentration and water. You can use methylene blue.

Dr. Joseph Mercola:

Oh, is that what it is?

Tyler LeBaron:

Yeah, it's methylene blue.

Dr. Joseph Mercola:

I didn't know it was methylene blue, but it makes sense. I never knew it was methylene blue.

Tyler LeBaron:

Yeah, methylene blue. Of course, you have to have a platinum catalyst in it. So, there's platinum nanoparticles inside, and then that activates the hydrogen gas to electrons and protons, and then that way it has a reaction. And when we study hydrogenase enzymes, for example, methylene blue is a very common thing to use because the methylene blue simply acts as the final electron acceptor and that way you can basically monitor the electron transport chain of the hydrogenase enzymes.

But it's interesting, though, because thinking about the mechanism just of how methylene blue might be acting in the mitochondria and in the cells, it's possible that it might actually be easier for the methylene blue to regenerate the NAD+ and go through this pathway. And then oxygen that's around is going to oxidize the leucomethylene blue back to the methylene blue, as opposed to the methylene blue interacting directly with the complex 4. I'm just thinking about, in the inner membrane – because the inner mitochondrial membrane, it's very difficult for biomolecules to penetrate that membrane. The outer membrane is easy, of course a lot of things can, but the inner mitochondrial membrane-

Dr. Joseph Mercola:

Well, hydrogen goes through that in a heartbeat.

Tyler LeBaron:

What's that?

Dr. Joseph Mercola:

Molecular hydrogen goes through that-

Tyler LeBaron:

Yeah. That's one of the benefits about hydrogen gas, it's one of the few things that can easily penetrate that inner mitochondrial membrane. So, anyway, it's just kind of interesting-

Dr. Joseph Mercola:

Georgi, I neglected to mention one of the other characteristics for Tyler. He's the founder of the Molecular Hydrogen Institute and pretty much-

Georgi Dinkov:

Well, nice.

Dr. Joseph Mercola:

-responsible for introducing molecular hydrogen as a therapeutic [crosstalk 00:34:17]-

Georgi Dinkov:

I think it's great. I fully agree with all the benefits that are being claimed about molecular hydrogen. Couple things on methylene blue. It's also clinically used for cancer diagnosis because cancer cells are in such a high reductive state. Over production of lactate, to be specific. When they do some kind of scoping thing, such as an endoscopy or colonoscopy, if they see a suspicious region, which they don't think warrants biopsy, they inject methylene blue and then they measure how quickly the color disappears. There are apparently these tables, which tell you basically whether the tissue is cancerous. If it gets fully reduced, in other words colorless, within let's say blankly 10 seconds, then that tissue is cancerous and needs to be biopsied. So, another thing it does, just like you said, it definitely does re-oxidize directly NADH back to NAD+. That has already been proven in solution. It does not need any enzymatic help.

I don't know that the mechanism [if] is well understood. How exactly it breaks the bond between nitric oxide and complex 4. But it's been proven, and I think that's one of the reasons why it's also been used for carbon monoxide poisoning because it does that too. I don't think the mechanism has been fully elucidated. I've looked into that, and all it says is that methylene blue has been known for a hundred years to be able to treat early stages of carbon monoxide poisoning, but I haven't seen an explanation how it actually breaks that bond.

Tyler LeBaron:

Fascinating. Yeah, that's interesting. Because I know they also do [a] similar type of injections with cancer, like with radio-labeled glucose molecules to see how quickly it gets oxidized. So that makes sense with doing that with the methylene blue.

Dr. Joseph Mercola:

And you can also use it as a marker for spoiled milk. Right, Georgi?

Georgi Dinkov:

Yes, how quickly it will get decolorized. You can also use it to test for the presence of vitamin C. Actually, there's a cancer drug on the market, which is vitamin C with a quinone, but it's vitamin K3 in this case because just like methylene blue, it accepts I think two electrons from vitamin C. It becomes dehydroascorbic acid, which is picked up by the cancer cells by the exact same transport as glucose. But the oxidized version of vitamin C, dehydroascorbic acid, lowers the pH of the cancer cell, and that results in immediate apoptosis. The drug is called Apatone, A-P-A-T-

O-N-E. I think [it's] already approved for prostate cancer, but now they're finding this exact same mechanism works for many other cancers. In other words, lowering the pH of the cancer cell by giving it a molecule that is very greedy for, in this case, the oxidized vitamin C.

Tyler LeBaron:

That's fascinating. And I think you said something that I want to elaborate on a little bit more. About how lowering the pH of the cancer cell can induce apoptosis. So many people that have this idea that cancer cells are acidic and they can't survive in an alkaline environment-

Georgi Dinkov:

We just discussed this with Dr. – Yeah, yeah.

Tyler LeBaron:

Oh, yeah. I hear this, and it goes back to this fault attribution to Dr. Otto Warburg, and they say that he said-

Georgi Dinkov:

He never said that.

Tyler LeBaron:

-he was the one to apprise that cancer can't survive in an oxygen-rich or alkaline environment. And of course, he didn't say that. And in fact, his research shows the very opposite of that. And I think it's very important we understand that. And I think cancer – you're right, the acidic pH will kill the cancer and it's going through glycolysis so much that the pH will get really low and it'll kill itself. And so, it develops these transporters to excrete the proton, really effectively.

Georgi Dinkov:

Yep.

Tyler LeBaron:

And so, out in the blood, those areas, the interstitial space and the [inaudible 00:38:12] fluids, it's possible that those areas can have a slight lower pH because the cancer cells are screening all of this acid. But the cancer cell itself is becoming more and more alkaline. It's the alkalization that can induce metastasis and the cancer progression and everything. And so, I think it's a very good point. I guess you guys have talked about it, but I want to talk about it again because it's such a big misunderstanding.

Dr. Joseph Mercola:

Yeah, it's fascinating. It's the core – really, [with] pro-metabolic therapy with respect to cancer, the thesis is that the mitochondria is dysfunctional, largely through its focus on fatty acid oxidation instead of glucose. And it has to do with the Randle Cycle too, because if you have too much fat, speculate about 30% or so, then you're unable to preferentially oxidize glucose in the mitochondria, so it shifts to glycolysis. And if you do this systemically in large amounts, it's this shift in the percentage of the cells that are involved in glycolysis that sets up potentially the

Warburg effect that contributes to the development of the cancer and the eventual spread of metastasis.

Georgi Dinkov:

Two things I would like to add. There is a drug called acetazolamide. It's a carbonic anhydrase inhibitor, so it raises mitochondrial levels – basically, it prevents the breakdown of carbon dioxide. Every single cancer tried in vitro or in vivo with acetazolamide, basically the drug induces almost immediate apoptosis. So now they're trying it for humans. In other words, acidifying the cancer cell, because carbon dioxide is the Lewis acid, may be a cure for many types of cancer. Already in human trials. If you just type acetazolamide cancer, at least a thousand studies will come up on PubMed.

Dr. Joseph Mercola:

And we talked about it even simpler. A non-drug therapy, which is simple bicarb, a teaspoon [of] bicarb a few times a day.

Georgi Dinkov:

Yep.

Tyler LeBaron:

Well, that is the opposite though, right? I mean, I think we need to talk about that because bicarbonate increases the pH and we're talking about lowering the pH. And so, there's a paradox that I think we should reconcile.

Dr. Joseph Mercola:

Well, but I think it increases it intracellular because of lactic acid or lactate.

Tyler LeBaron:

Well, yeah. So, what we can do is we have the cancer cell itself that we want to lower its pH, we want to lower the pH of the cancer cell, and now it's going to induce apoptosis.

Dr. Joseph Mercola:

Right.

Tyler LeBaron:

But the cancer cell is putting out a lot of acid into the blood and extracellular – well, first interstitial, but really quickly, extracellular space. And so, by taking bicarbonate, then your body can regulate and buffer that extra acid load a lot more effectively.

Dr. Joseph Mercola:

Yeah. So, the internal cell is not required to excrete it. It retains it, and thus lowers the pH.

Tyler LeBaron:

Yeah, it's going to lower the pH because it's going to have a – well, actually, we can talk about concentration gradients, right?

Dr. Joseph Mercola:

Yeah.

Tyler LeBaron:

As long as the concentration gradient is high enough to allow the proton to be excreted very easily, then it's going to make a very favorable transaction, so to speak. And so, that's probably why there are some indications where bicarbonate could be helpful. But there are some studies where bicarbonate actually has the opposite effect because maybe you're inducing alkalosis. And when you have a situation of alkalosis, now it's making that gradient not as favorable because the pH of the cancer cell is already really high, and then the pH of the blood is high. And so, it's going to be contraindicated. I'm just saying, if somebody has cancer, it's not the best idea for every situation and every case to go get some extra bicarbonate. That may not be what you want to do.

Georgi Dinkov:

If there's elevated lactate in the blood, wouldn't that indicate that bicarbonate would be warranted? Because mostly these people, if you test their bicarbonate levels, [they] are extremely low.

Tyler LeBaron:

Yes, I would test the bicarbonate levels to see what that is. And you can test the pH, you can test the PCO2 (partial pressure of carbon dioxide), you can test the – I'm not a medical doctor, so I don't want to start going too far off, but I think there are probably ways you could measure those areas, and then that'll give you an indication of whether it makes sense for you or not to take bicarbonate.

Dr. Joseph Mercola:

More than likely would benefit, but ideally you would want to do those measurements first clinically, so you're not giving the therapy incorrectly.

Tyler LeBaron:

Yeah. Yeah.

Georgi Dinkov:

Couple of cancer cells with bicarbonate demonstrated disappearance of already existing metastasis and prevention of the formation of new ones, both in vitro and I think two rat studies and whatnot. But again, with human tumors, there were xenograft models.

Dr. Joseph Mercola:

These are your studies, Georgi?

Georgi Dinkov:

Not mine. I think one is from Harvard and the other one is from Stanford, I believe. But I have it on my blog, I can send them over.

Tyler LeBaron:

Yeah, I've seen similar ones. Well not those specifically, but I've seen ones, and that's why I'm saying I think that there are benefits there, but maybe it's not for everybody, right?

Georgi Dinkov:

Okay.

Tyler LeBaron:

And there are some other studies where alkalinization of the tumor cell, for example, it promotes this metastasis and further progression. And so, we have to be careful with that. And the other thing I wanted to say, just going back to cancer and the mitochondria, it is interesting because as cancer gets – I don't know, dependent on the cancer cell and how much ATP it's getting from mitochondrial versus the glycolysis. But the mitochondrial ATP production is still pretty high in cancer cells. It's still going up quite high. But some cancer cells, they try to shut off the mitochondria because the mitochondria is really smart and it'll recognize something's not quite right, and so it'll send out a signal. They'll release a cytochrome C, for example, which will induce apoptosis-

Georgi Dinkov:

Apoptosis, yeah.

Tyler LeBaron:

So yeah, there's another drug, you probably know the name of it, but basically, it's to inhibit glycolysis to promote all the ATP production from just the mitochondria. And then as soon as it does that, it really wakes the mitochondria up and then the mitochondria sends out cytochrome C-

Dr. Joseph Mercola:

Aspirin will do that.

Tyler LeBaron:

What's that?

Dr. Joseph Mercola:

Aspirin will do that.

Georgi Dinkov:

Aspirin will do that. And another thing is, another factor controlling both glycolysis and PDH is the ratio of ATP to ADP (adenosine diphosphate).

Tyler LeBaron:

Yes.

Georgi Dinkov:

So, cancer cells are producing a lot of ATP through any means, basically. This means that glycolysis may be high, but PDH will be low. So, one way is to lower ATP. And I think also lowering glycolysis – if [a] cancer cell is producing its ATP predominantly via glycolysis, that ratio will drop and it will probably allow the pyruvate to go further.

Tyler LeBaron:

Yeah. And acidifying the cancer cell itself is going to actually help to lower glycolysis because, that's of course with exercise, one of the reasons for fatigue among the many is the lowering of the muscular pH, 6.8 or so. That's going to shut off your phosphofructokinase enzyme, for example, which is [the] rate limiting step of glycolysis. So, if you can do that with a cancer cell also, well then you shut it off from being able to do glycolysis and you also increase the phosphorylation of the PDH kinase (PDK), which is going to inhibit that. And then all the hypoxia, that's also going to decrease the activation of the mitochondria. And so pretty much, like you said, you decrease the amount of ATP in the cancer cell. Unless you do those things, the cancer cell already has more ATP than it needs.

Georgi Dinkov:

Yeah, it’s true.

Tyler LeBaron:

It’s not doing all the metabolism to get energy. It's doing all the metabolism maybe to get carbon substrates for anabolism and to grow and spread and so forth. So, it's probably a pretty good target to try to shut down how much of the ATP. Because soon as you do that, it’s not just about stopping this energy supply, but stopping the reactions from occurring because those carbon molecules are what's needed for the cancer to grow. And you're basically stopping that process to continue going.

Georgi Dinkov:

And the latest offshoot of that approach is basically they're saying, “Let's not worry about the absolute levels of ATP, let's look at how the ATP is produced.” And if you look at the cancer cells, every single type of tumor seen so far produces most of its ATP as a result of beta-oxidation. And that's why it's wasting the glucose into lactate. Because when you oxidize predominantly fat, that lowers the NAD to the NADH ratio, which puts the cell in a more reductive state. And also, NAD to the NADH ratio is one of the controlling levers on pyruvate dehydrogenase.

So some studies lately, over the last maybe not two or three years, one of them used meldonium, which is a drug that inhibits the transport and of course the oxidation of the longer chain fatty acids. A Russian drug invented back in the 70s. It's also a doping drug because it increases endurance. So, they demonstrated complete removal of human neuro glioblastoma in a mouse

model by doing nothing else but lowering basically the excessive oxidation of fats, which allows more glucose to be oxidized, and it shifts the cancer cell. First, it doesn't change the ATP production, it remains the same. But mitochondrial NAD to the NADH ratio rises and the cell acidifies, which basically allows it to either return to normal metabolic state or commit apoptosis if it's too damaged to continue.

Tyler LeBaron:

Okay. So let me see if I understand this. This is interesting because we talked about in one example where you're trying to inhibit glycolysis, force the cancer to use the mitochondria, and then that causes cytochrome C release and induce apoptosis. And now-

Georgi Dinkov:

But if you're inhibiting glycolysis in the context of high fatty acid oxidation, you're not going to be doing anything about that. So, the glycolysis you inhibited – but until the break on PDH is released, which appears to be, aside from deficiencies in the cofactors, appears to be predominantly the mitochondrial NAD to the NADH ratio, which beta-oxidation potently lowers-

Tyler LeBaron:

Yes.

Georgi Dinkov:

Inhibiting glycolysis will not have the – you may have somewhat of a therapeutic effect, but not to the point where you're restoring glucose oxidation.

Tyler LeBaron:

Okay, yeah. So, I get that on our initial part, but this other [one], where you're essentially inhibiting beta-oxidation, so you don't have that harmful ratio, that higher NADH and FADH2 (flavin adenine dinucleotide) levels.

Georgi Dinkov:

Exactly.

Tyler LeBaron:

So yeah, I can see in cancer cells that's going to be problematic. And I actually would say that even people who try to do a high-fat diet for prolonged periods of time, chronic high-fat diets, probably are going to have similar issues.

Georgi Dinkov:

We just discussed it with Dr. Mercola.

Tyler LeBaron:

Yeah, okay. Yeah. Because you are creating a reductive stress-

Georgi Dinkov:

Yeah.

Tyler LeBaron:

You are increasing NADH levels. You are going to potentially cause reverse electron transport.

Georgi Dinkov:

Yep.

Tyler LeBaron:

And a lot more free radicals.

Georgi Dinkov:

Not potentially. A study [that] just came out said all that is required for the reverse electron transport to occur is a sufficient drop in any of the oxidized versus reductive ratios. Ubiquinone to ubiquinol was a specific study we looked at. NAD to the NADH, pyruvate to lactate, oxidized glutathione to reduced glutathione, acetoacetate versus beta hydroxy – any of these are an indication of the redox status. Any of these mitochondrial ratios dropping is going to put the cell into reductive stress, buildup of pyruvate and, of course, buildup of lactate reactively.

Tyler LeBaron:

Right, right. Yeah, I can see it. That would make sense. Now, just maybe a pushback, because you do create some extra free radicals with a reverse electron transport chain. So, I would say, similar to exercise, we all know that exercise is great for you when you only do it periodically. I mean, every day for an hour or whatever, as opposed to 24/7.

Dr. Joseph Mercola:

With some rest days.

Georgi Dinkov:

Yeah.

Dr. Joseph Mercola:

Right.

Tyler LeBaron:

Or rest hours, for me. But as opposed to doing it for 24/7. And so, I would say that doing it maybe even [on] a periodization type approach where – maybe doing fasting or a high fat-diet. For a small amount of time where you actually are increasing free radical production through the reverse electron transport, that's hormetic. And there's a number of studies showing a hormetic effect and beneficial effect of raw signaling. But by definition of hormesis, it's only hormesis until it becomes toxic.

Georgi Dinkov:

Exactly.

Tyler LeBaron:

So, you can't take something that's hormetic and just keep on doing it because now it's poison. It's toxic, right?

Dr. Joseph Mercola:

Which is the vast majority of people with the reductive stress. They're in it 24/7 continuously. They don't take a break from it.

Tyler LeBaron:

Yeah. They're doing it 24/7, like a ketogenic diet or something like that, then it's terrible. But I would say, we can't say, "Well, everybody is stressed, so therefore nobody should do this type of cycling."

Dr. Joseph Mercola:

No, no. Right. It's right. It has to be periodic. It can't be continual.

Tyler LeBaron:

Exactly. So, if somebody is already super stressed, then that doesn't mean that they should never do any other stressful exercises, stressful hormetic approaches. If you're super stressed, then that means that you probably aren't going to be able to handle going out and running 20 kilometers, 30 kilometers just out of the blue. You want to take it easy, but do want to do something. So, do a little bit of exercise, [like] cycling, running. Maybe change your diet a little bit. Doing something for a small period of time to get that hormetic stressor, but just be really careful you're not doing it too much that you're causing the very damage and problems you're trying to reduce.

Georgi Dinkov:

Another thing that I wanted to mention, which I'm sure you know, but most experts and most books kind of completely miss, is that the reactive oxygen species - everybody's afraid of them, we talked about [that] they may have a hormetic effect. However, apparently, more than 97% of the reactive oxygen species are produced through reverse electron transport. Only 1% to 3% are produced through forward. Now, if excessive fatty acid oxidation – excessive, of course we have to define it. It's not-

Dr. Joseph Mercola:

I thought it was 0.5%?

Georgi Dinkov:

Oh, 0.5%. Yes, I'm sorry. Thank you, Dr. Mercola.

Dr. Joseph Mercola:

It was 99.9%.

Tyler LeBaron:

It's like 0.1% to 0.3%, 0.5% is what is my most recent [inaudible 00:53:14] when you are functioning normally.

Georgi Dinkov:

Exactly, but that's only through forward.

Tyler LeBaron:

Exactly.

Georgi Dinkov:

Apparently, as soon as you start doing [the] reverse, you're generating massive amounts of ROS (reactive oxygen species), way beyond the chromatic response. And fatty acid oxidation is the best at inducing that response.

Tyler LeBaron:

Yeah. I would fully agree. And that's why I would say that I've never been a proponent for high fat diets especially – First off, there's two things. One, the benefits and problems of the high-fat diet. And just briefly, the benefit of course is you are going to create some more free radicals, you do get a hormetic response, you can potentially activate mitochondrial biogenesis. You can have all these things if you do it for the right amount of time and not chronically. And of course, the downside of that is it's not too difficult to do it for too long of [a] time and have a lot of damage, and you're not ready to do it because your body has to adjust. It takes time just to do that, right?

And then number two, kind of [a] different tangent, but just the benefits of carbohydrates, I think people haven't really realized. I mean, carbohydrates have a lot of benefits for [the] immune system, for the brain function, for a lot of things that maybe we can go into a little bit later. But focusing on this area, the hormetic effect of fatty acid oxidation, I completely agree with what you said. That a reverse electron transport chain can be very damaging if it's excessive.

But then to your point, we have to define what does that mean? And for somebody who is maybe a super trained endurance athlete and is healthy and everything, they can probably go obviously longer and they can make more of those true radicals and get more of a hormetic response before they start having problems. And our body, our mitochondria, are really amazing. And so, it's not like we accidentally, unfortunately, are making free radicals. We have specific enzymes in places to make these free radicals for a very specific reason. And so, we'll make superoxide, for example. Superoxide will be produced and then, in a very specific location, it does a very specific signaling, and then it's converted to say, hydroperoxide. And then there's even aquaporin right next where hydroperoxide is produced. A little channel where hydroperoxide can go

through and do a little bit more signaling, and then it's converted by say, catalase, to water and oxygen.

And so, everything is very tightly regulated. We absolutely want to have free radicals, but normally we get enough free radicals just by living, breathing, doing mild exercise and so on. And we can get some hormetic responses by having fluctuations in our diet, where we have an overnight fast, we have a higher fat meal and higher protein than normal. And this is a variation that we have evolved to do as opposed to six months or several years on just a high-fat diet. That's not something that we have been adapted to.

Dr. Joseph Mercola:

Well, even with forward electron flow, you're going to get 0.5% reactive oxygen species. So, you need them. The issue is, what's the level? Is it excessive?

Georgi Dinkov:

The only physiological state where you want more and they're usually produced through the forward electron transportation [is] if you have an infection. That's probably the only time that I can think of superoxide or the hydroxyl radical being needed in higher than normal amounts, higher than 0.3% to 0.5%, but it's very tightly controlled.

Tyler LeBaron:

It is, but that's talking about the mitochondria. Because typically during an infection, we're talking about [an] increase in superoxide with the NOX enzymes, NADPH oxidase, which are specifically designed to combat the infection. I'm not so sure that superoxide from the mitochondria should make it all the way to – it can't even go through the cell membrane. It has to be proteinated, maybe it can go. But its half-life is so short. So, it's not even the mitochondria versus the electron transport chain. It's these other enzymes that are our body – We've developed specific enzymes for when the infection does come. We can produce levels of hypochlorite and nitric oxide and superoxide and everything else to attack that infection.

Dr. Joseph Mercola:

And peroxynitrite.

Georgi Dinkov:

Do you know of a study that has looked strictly at the mitochondrial production of the ROS or any of them in the context of long-term production and disease? The ones that I've seen invariably say that's a bad thing. They can damage DNA, right? Actually, the most recent study that I sent Dr. Mercola said that just a simple drop in the redox indicator, in this case ubiquinone to ubiquinol, causes the cell to physically destroy complex 1. I don't know why. Maybe it's just a signal that the cell doesn't need it. It's energetically expensive to maintain. But that's enough to cause structural damage, which for a long time medicine said, "Now, functional and structural are different –" Structural can cause functional [damage]. But functional, unless you're getting some kind of a mutagen, we don't really think [it] can cause damage to the DNA and the structural machinery. It turns out that a very simple drop in shift towards reduction is capable,

and complex 2, too. And conversely, shifting back into the oxidized state allowed the cell to regenerate both complexes.

Tyler LeBaron:

Yeah. It is interesting how fast the cells will work. So, during [a] period of hypoxia, you'll quickly activate the hypoxia-inducible factor, and this transcription factor will then increase enzymes that will phosphorylate PDH, for example, to slow down the entire complex. It would be a decrease in the Krebs cycle. As well as changing out complex 4 that can handle the low oxygen levels better, because otherwise, in hypoxic conditions you get a great mismatch between oxygen availability and the electron flow. And so, you get a lot more oxidative damage. And so, it's very quick the response of the cells to degrade the current complex and manufacture, synthesize other complexes so they can handle these different oxygen tensions. Like you said earlier, everything is so tightly controlled and regulated, and this is a good example of just how tightly it is and how quick it can happen.

And just because I do research on hydrogen gas, I think I wanted to mention why, again, hydrogen gas is so interesting in these areas, specifically in the realm of ischemia and reperfusion. So ischemia, for the audience, is where you don't have the oxygen present, so you have a hypoxic environment. And that's going to cause some free radical damage because, like I said, you get a mismatch between oxygen availability and the electron flow when you're trying to get ATP and everything-

Dr. Joseph Mercola:

And clinically-

Tyler LeBaron:

And then you get – Go ahead.

Dr. Joseph Mercola:

Clinically, that would be a stroke-

Georgi Dinkov:

Heart attack. Ischemic-

Dr. Joseph Mercola:

Heart attack, same thing. That's where you're going to see it.

Tyler LeBaron:

Exactly. Anytime there's a stop in blood flow, right?

Dr. Joseph Mercola:

Yeah.

Tyler LeBaron:

But most of the damage comes from the reperfusion side, where now you've got the heart to start beating again. And you clear the blockage, so the oxygen-rich blood is able to travel through those tissues. Well, now you're waking up the mitochondria, and now it's trying to get active again and you end up producing a lot of free radicals and oxidative damage.

And hydrogen gas, the first study that really showed its therapeutic effect was in Nature Medicine published in 2007, and they administered simply 2% hydrogen gas. It was a stroke model, and they found 2% hydrogen gas completely prevented the brain damage. I mean, you can look at the images of the brain and it's completely different, where the one without hydrogen gas [shows] all the white area, the dead part of the brain, versus the other group, the 2% hydrogen gas really prevented that. And hydrogen gas does a couple things, but it kind of is a pre-treatment to improve the oxygen handling capacity of the mitochondria. And in fact, I was talking with Dr. Mercola at the comps a little bit, but some data indicate that molecular hydrogen somehow acts as an electron transport chain, a rectifier. So, in some-

Dr. Joseph Mercola:

Yeah, we never finished that conversation actually. [Crosstalk 01:01:39], we never finished it.

Tyler LeBaron:

Okay. Yeah, we started a little bit with it. But this is extremely fascinating because we talk about how the electron transport chain is so important that we want forward electron transport chain, so we can get ATP production and we can get a little bit of free radicals that we can handle. Sometimes we can get a little bit of reverse electron transport chain, a little bit more free radical just for some hormetic effects. We don't want to go too far out of that homeostatic range. And hydrogen gas is able to really modulate this entire process as a rectifier. And it does so because in some cases, it’s going to help act as an electron sync and sometimes an electron donor to get things to go where it needs to be. And-

Dr. Joseph Mercola:

This is in the mitochondria?

Tyler LeBaron:

Yeah, this is the mitochondria, the electron transport chain.

Dr. Joseph Mercola:

Okay.

Tyler LeBaron:

And actually, if you look at the redox potential of the different complexes - complex 1, 2, 3 and 4 - and then you look at the redox potential of hydrogen gas at physiological pH, it's right in line with where you would want it to be so that it can participate as being a rectifier of the electron transport chain. Now, the actual primary targets and mechanisms are not fully elucidated. We're getting closer. There was a paper published from some of my colleagues in China, where one of

the targets is the iron porphyrin, which is rich in red blood cells, hemoglobin and the mitochondria. And this is a biosensor redox catalyst of the molecular hydrogen. And this might be why it can help participate in this redox homeostasis.

As well as, this is another interesting area, but we talked about carbon monoxide poisoning and carbon monoxide having lots of negative effects, but we didn't say that carbon monoxide also has a lot of therapeutic effects when, again, it is produced at very low concentrations, at the right space, at the right time and in the right levels. There's thousands of studies about carbon monoxide as a very important gasotransmitter. And hydrogen gas, it has this ability, by acting through this iron porphyrin catalyst, to convert some of this CO2 to carbon monoxide, and then carbon monoxide can do some of this therapeutic signaling. It's a small amount and more research needs to be done on this in vivo. But this has been demonstrated at least in vitro, and it could explain some of the pleiotropic effects and benefits of molecular hydrogen. And that could explain why, in some cases, we see that with administration of hydrogen, we see increases in electron transport chain activity, increases in ATP production in all of these areas, but in other cases we can see the opposite. We'll see actually a suppression of free radicals.

So one example, we often will see a decrease in free radical production through hydrogen gas, especially like NADPH oxidase systems or anytime things are too active, we will see a decrease in the production of free radicals. And that's one reason it can have antioxidant effects. But we also see – we have shown this in several of our studies, both clinical studies and in vitro studies, we can show that hydrogen gas can actually act as a hormetic agent to mildly increase free radicals. So, like a small amount [of] extra superoxide production, for example. And it's only a brief period of time. It depends on the timetable, the time scale, when you're measuring it, because if you measure it in an early stage, you might see a small amount and then later on it's going to be a decreased amount followed by an induction of the NRF2-KEAP1 pathway.

And so again, hydrogen is able to – another reason why it can act as an antioxidant is because it’s able to activate the NRF2-KEAP1 pathway and it modulates this. So, it doesn't just activate it like sulforaphane or other compounds that's just always going to activate it. It's a regulator of this pathway to maintain redox homeostasis and it also acts as this mitochondrial electron transport chain rectifier.

Dr. Joseph Mercola:

Nice. Thanks for the explanation. So, we've got to probably get going in a bit because we've been out for a while. But I have one final question for you and Georgi, and that would be – mostly you though, since you're the expert in molecular hydrogen. It seems to me like it would be a really powerful synergy with methylene blue.

Tyler LeBaron:

That would be very interesting. I want to run a research [a] little bit more about the methylene blue area of that. It's possible, and I actually have some ideas that make me excited about why it could be as synergistic. There are some ideas about why it could be synergistic with red light therapy and other oxidative-type therapies. Especially now that we know more of the mechanism

with this iron porphyrin biocatalyst. But, scientifically, we don't just look for reasons why it should work, we try to look for reasons why it probably doesn't work.

Dr. Joseph Mercola:

Right. Yeah, the negative. Right.

Tyler LeBaron:

Yeah. So, before I get too excited about saying, "Yes, that's a really good idea." I'm trying to go through maybe why it's not going to be as good as we would like it to be. Of course, I don't know of any clinical studies that have looked into this.

Dr. Joseph Mercola:

Of course not, no.

Tyler LeBaron:

But maybe that's something that we should look into. That would be interesting.

Dr. Joseph Mercola:

For sure. Any comments, Georgi?

Georgi Dinkov:

First, I wanted to go back a little bit to hydrogen. Are you familiar with a product called carbogen? So, it's 5% carbon dioxide, 95% oxygen. Multiple studies on it demonstrating the exact same protective effect, especially during the reperfusion stage in ischemic events, both cardiovascular-

Dr. Joseph Mercola:

Interesting.

Georgi Dinkov:

Yeah. And basically, carbon dioxide, just as you mentioned, hydrogen can work both ways, kind of shuttles electrons when needed. Even though carbon dioxide does not directly do that, it's actually a Lewis acid, so it helps shuttle them along the pathway. So, it can modulate, it can restructure a dysfunctional mitochondria. [It] also drops the pH of the cell, which is one reason why some people have proposed that raising carbon dioxide in the cell is good for cancer, which is what the drug acetazolamide does. But as far as methylene blue, there are actually studies with it for several diseases, not metabolic or at least they're not-

Tyler LeBaron:

I mean, I did the gas and methylene blue [crosstalk 01:08:14]-

Georgi Dinkov:

Oh, both combined?

Dr. Joseph Mercola:

Yeah, it's combined, the synergy of the two. I think there's a high likelihood there-

Tyler LeBaron:

I know there are clinical studies with methylene blue individually, but it would be interesting to look at.

Georgi Dinkov:

Yeah, I don't know of any combination, but I think the hydrogen will be very good at neutralizing the already existing reactive oxygen species, preventing them as well. And methylene blue definitely preventing, by preventing this buildup of electrons that happens at any step along the chain. A lot of people are referencing methylene blue as an electron transport chain specific molecule. But I think there is example also in helping the Krebs cycle. If you have a buildup of citric acid or succinic acid that cannot go to fumaric acid, the methylene blue-

Tyler LeBaron:

In the dehydrogenase areas, yeah. NADH is, in just my ignorant opinion, probably doing more there than in the other NAD+ and NADH areas, directly acting with them [rather] than in the electron transport chain itself. Because the electron transport chain itself is extremely tightly regulated and perfect for oxygen to be used right there. So, it probably has its other areas.

Georgi Dinkov:

[Inaudible 01:09:24] I think there's studies showing-

Tyler LeBaron:

Yeah, that's a succinate dehydrogenase.

Georgi Dinkov:

Yeah.

Tyler LeBaron:

In the Krebs cycle. The FADH2 is the exact same enzyme that is in the Krebs cycle, it's just membrane-bound.

Georgi Dinkov:

Yeah. So, succinate dehydrogenase is also complex 2, right?

Tyler LeBaron:

Yes, it is the same. Yeah, exactly.

Dr. Joseph Mercola:

So, I have never heard anyone speculate the mechanism of methylene blue was also in the Krebs cycle. This is a first. I think you may have come up with it, Tyler. But it makes sense. Makes sense. It's really good. Novel thinking.

Tyler LeBaron:

That was fun. Georgi, it's a pleasure to meet you and talk with you. So, Dr. Mercola, thanks for setting this up.

Dr. Joseph Mercola:

Well, thank you for participating.

Georgi Dinkov:

Thank you.

Dr. Joseph Mercola:

It was a pleasure to be part of this. So, thanks again and we'll get together soon sometime.

Tyler LeBaron:

All right, sounds good.

Georgi Dinkov:

Looking forward to it.

Dr. Joseph Mercola:

All right. Thanks guys. All right.

Tyler LeBaron:

Yep.

Georgi Dinkov:

Thank you.