Paleo Solution - 282

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Hi folks. Robb Wolf here. Another edition of the PaleoSolution podcast. Very excited for today's guest. Dr. Ronda Patrick has been one of the hottest, brightest entities in this whole ancestral health, biomedical research scene. She has performed primary research in areas ranging from cancer to vitamin D metabolism. She is currently working with one of the demi gods of research, Dr. Bruce Ames who if I had a list of hero posters on my wall, Bruce Ames would probably one of those folks on there. Dr. Patrick, how are you doing?

Dr. Patrick: I'm doing well. Yes, I agree with you on Bruce Ames. He is amazing and awesome and I feel super fortunate to be able to talk science with him every day, so.

Robb Wolf: I'm not like outright jealous of that many people. Like I enjoy my life pretty thoroughly but when I heard that you were essentially one of his

post docs, I was like oh man, that's something that's yeah not very many people get to have that claim to fame. That is awesome.

Dr. Patrick: Yeah, well thanks for having me on the podcast. I'm excited to have a conversation with you.

Robb Wolf: Huge honor to have you on the show. So tell folks a little bit more thorough treatment of your background. You just have an amazing background and it would be great to get folks more familiar with you. I'm sure that everybody is listening to your wildly popular Found My Fitness podcast and YouTube channel. But if they had not dug that up yet, tell folks a little bit more about yourself.

Dr. Patrick: Great. Yeah no problem. So I am a scientist. I started out as a chemist at UCSD. I studied organic chemistry and biochemistry and I did research at Illumina which is now one of the huge giants in making these microchip arrays. But back when I was working there when I was in college, I was you know, doing all these chemistry and basically synthesizing peptides and doing all this stuff that became not so fun, after a while I kind of got bored. So I decided I was going to go try biology out.

So before I went to graduate school, I went to work at the Salt Institute for Biological Sciences in Quay California. I joined a lab that as an aging lab. So they – this lab used C. elegans which are a little nematode worm that have a very short lifespan about 15 days or so and they've got a lot of the same genes that are conserved with humans and you can – they have like around a thousand cells or so in their body and you can follow every cell and see every cell they have. So they're a great research model for aging research.

So I worked there for a couple of years and I had the privilege of working with the post doc that was doing a really hot project at the time that happened to be related to Alzheimer's disease. So I was able to hop on that project and learn quite a bit and subsequently was able to have a – you know, be a co-author on a science paper which was pretty exciting for me since had never been published before and certainly this is my first introduction to real biology. I had spent so much time doing chemistry I fell in love with biology and decided when I go to graduate school.

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Somehow I got on to the cancer train where I was very interested in cancer and specifically in pediatric cancer. So I wanted to go to St. Jude Children's Research Hospital which was the – it's one of the leading

research institutes in pediatric cancer. So I packed up from San Diego and moved to the south which was quite a culture shock for me.

Robb Wolf: [Laughs]

Dr. Patrick: And you know, blues and barbeque for the first couple of years and I got tired of that.

Robb Wolf: Right.

Dr. Patrick: But at St. Jude, I did research on mitochondrial metabolism. I started out with cancer and looking at how cancer cells you know, evade cell death. How to figure out how to not die when they're supposed to. And then my project just led me into this mitochondrial metabolism and I became a complete mitochondriac for like five years. It was all mitochondria. I spent hours and hours looking at mitochondria under the electron microscope, light microscopy doing all sorts of biochemical sub fractionating mitochondria from their outer membrane, inner membrane space, inner –you know, it's just complete crazy mitochondriac and I learned quite a bit about mitochondrial metabolism.

And then from there because I was getting into this mitochondrial metabolism, you know, sort of hand in hand with that is health and because metabolism, mitochondrial metabolism is fundamental core of pretty much all of the health of most of our cells. So I got into this micronutrient sort of saying where I became interested in how micronutrients are important for mitochondrial metabolism, how they're cofactor for all these metabolic pathways in our cells and how we get them from our diet and how we're not getting enough of them.

And so that led me to Bruce Ames who's really one of the leaders in the micronutrient field and also he's done quite a bit of work on mitochondrial metabolism in his day. So I decided to go work with him. He's a professor emeritus at UC Berkeley but he has moved his lab from UC Berkeley to Children's Hospital Open Research Institute where he has set up an entire nutrition and metabolism center there.

So I have been working with him for the past three years and I've got about five projects that I'm working on. I also decided that I wanted to take all of this hardcore biochemistry and cell biology that I had learned from graduate school and bring it to the clinical arena. So you know, I've now been doing assays and pioneering different assays on using people's peripheral blood as my research model so to speak.

So I'm getting blood from people, all sorts of people, different ages, different health backgrounds, people that are insulin resistant, people that are not. You know, on and on and I'm looking at a variety of different things. I'm looking at damage accumulated. I'm looking at mitochondrial function and I'm looking at you know, just a lot of different biomarkers for health.

Also I'm doing a lot of research on vitamin D and vitamin D's role in the brain and also omega-3s and omega-3s role in the brain. So I've got you know, a variety of different projects going on there. So that's kind of where I'm at and in addition to that, I like to communicate science to people and I like to –you know, I basically developed this sort of like this platform called Found My Fitness where I talk about things that I think are important for health. You talk about my own research and other people's research that some of the most important things that I think are important for living a healthy life and for you know, extending the healthy part of your lifespan you know, into old age. So those are some of my goals right now.

Robb Wolf: So I have like 600 questions to ask you. I'm green with envy but one of my first questions, do you get all this stuff done with caffeine, Provigil or cocaine or a combination of all those?

Dr. Patrick: [Laughs] So I tend to generate more work for myself and I figured it out because I'm sort of a hypochondriac and I've looked at all of my gene polymorphisms. I've got this gene polymorphism that allows me to deal with stress better. I think because I can do that, I take on more stress. [Laughs] But actually I drink a lot of green tea.

Robb Wolf: Okay.

Dr. Patrick: So that's my drug of choice.

Robb Wolf: Unfortunately I detest green tea. I'm more of an espresso guy but I get nowhere near as much done as you do so I'm just completely envious there. So I meant to send you some papers on some of this stuff and folks don't know this but I tried to get Dr. Patrick on the recording yesterday and I had a complete disaster for my new office and so we're going today.

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But one of my favorite papers is a – I forget the authors but It's Secrets Of A Lack Operon and these folks talk a lot about mitochondrial biogenesis, also mitochondrial senescence and they make a point that for healthy cells, healthy aging in general, we need some metabolic flexibility.

One of the things that occurs is that both in cancer and in just general cell senescence is that we tend to see a shifting in metabolism towards glycolysis and lactate production. But it's really interesting. You just had George Brooks on your podcast recently and he was talking about the powerful benefits of lactate as a fuel substrate for like traumatic brain injury and also for as a cell signaling molecule. I usually ascribed ketone bodies in those types of roles. But what are your thoughts on that interplay of the loss of normal respiratory function, normal mitochondrial function? You know, what's going on there?

I've definitely been biased towards more of a ketogenic type of intervention for preventing cell senescence but George Brooks really makes a strong argument for maintaining that lactate pathway and the aerobic pathway. What's going on in all that story?

Dr. Patrick: Yes. So well they're actually not mutually exclusive because so lactate, the production of lactate like you mentioned is occurs in cells that are not using their mitochondria to make energy. It's you know, they're using something called glycolysis and glycolysis does not make a lot of energy in the form of ATP but it does do it quicker.

So some of our cells are red blood cells which don't have mitochondria, re glycolytic, are immune cells, are mature immune cells or T cells are glycolytic. Our muscle cells when we exercise you know, become glycolytic because the energy demand is so high they need to make more energy and we can't breathe in enough oxygen quick enough to get it to our mitochondria to be able to do mitochondrial metabolism. So we also when we're exercising our muscle cells also become glycolytic and our astrocytes in our brain are glycolytic which is very interesting.

Robb Wolf: Uh-hum.

Dr. Patrick: Because astrocytes actually outnumber the amount of neurons in our brain and they are –they basically are supporting cells for our brain. They provide a variety of different nutrients. You know, they make lactate for one and a certain type of astrocytes called oligodendrocytes make myelin for our neuron. So that the really interesting thing about lactate is I also thought about it in a negative way for a very long time and for my cancer biology background, I always thought of lactate as bad because cancer cells also become glycolytic as you mentioned.

Robb Wolf: Yeah. Yeah.

Dr. Patrick: There's this metabolic change that occurs after our cells acquired so much damage, damage in their mitochondria, damage to their genome, just tons of damage and we don't really know why they shift to become glycolytic. I mean for a hundred years later after Otto Warburg first observed this, we still don't know the actual real mechanism why cancer cells become glycolytic. There are a lot of hypothesis and a lot of people putting theories and there's some data to put forth ideas but it's really I haven't seen any real solid data to go okay this is why and we can prove this by making you know, if you take it like for example our immune cells our glycolytic. Well they're not cancer cells. So it's not like just the act of becoming glycolytic causes a cell to be cancer right?

It's a little more complicated than that because then or immune cells would all be cancer.

Robb Wolf: Right.

Dr. Patrick: But they're not. I'm mentally kind of going down this bunny trail here but I do want to say something that I've thought about in terms of cancer and why they become glycolytic . I think also a major reason they shift obviously they've got a lot of damage to their mitochondria. Their mitochondria is still working and I wanted nothing more than to believe mitochondria weren't working when I was doing all these cancer biology because that would have made my publication come out a lot quicker.

Robb Wolf: [Laughs]

Dr. Patrick: But I couldn't. I was so upset because that was just I really, really wanted to believe that mitochondria don't work. They do work and they can work. They are dysfunctional in many cases and less efficient and they're pouring out more you know, byproducts called reactive oxygen species. I think that's probably one of the major reasons why cancer cells shift to glycolytic metabolism is because a cancer cell is primed to die. We have a lot of biological mechanisms that are protecting us from getting cancer and there's like these prodeath signals that get turned on and say okay it's time to die.

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But cancer cells find a way to overcome that by saying no, I'm going to turn on all these anti-death signals so it's like a balance between these prodeath and antideath. All it takes is a little bit of more prodeath to kill it and that's a lot of the, that's a major mechanism by which chemotherapy drugs work. They're pushing it over the – they're both pushing it into the death arena.

Well mitochondria make reactive oxygen species like no matter what. We're making them right now I'm making them as I talk, as I breathe in oxygen, as I make energy. That's just normal metabolism. When metabolism is dysfunctional, you make more of those products but those products actually kill cells and I think cancer cells don't want mitochondria to work and I think that's one of the reasons why activating mitochondria with certain chemicals, DCA for one can kill cells because then your mitochondria become metabolically active and they generate reactive oxygen species which kill a cancer cell.

Anyways, just a thought I had and I totally went off topic but -

Robb Wolf: There is no topic here. I don't know if you've ever listened to the show but it's about as freeform as it gets so.

Dr. Patrick: Did you follow what I was saying?

Robb Wolf: Absolutely, yeah, yeah.

Dr. Patrick: Okay, cool. Yeah so sorry --

Robb Wolf: No, no go for it. Go for it.

Dr. Patrick: all right so back to the lactate because it's –you know, it is very interesting. Lactate is so you can convert glucose into pyruvate and pyruvate then they're sort of like this fork. You can convert it into lactate or you can import it into the mitochondria and then it can undergo you know, this TCA cycle oxidative phosphorylation where you couple it then to oxidant to produce a lot more energy like 32 molecules of ATP I think or something like that.

Robb Wolf: Right.

Dr. Patrick: And if you don't do that, making lactate, you don't make a lot of energy. I mean what is it like four or something? Something very or eight. Something like just very small. You don't make a lot of energy but you don't have to go through all of these processes as well so it's quicker.

But making the lactate is very interesting because once you have lactate, lactate actually there are transporters and this is where George Brooks who is a professor at University of Berkeley, California Berkeley he found or he discovered these transporters that are called monocarboxylate transporters. I also often refer to them as lactate transporter. They're on the cells, they're on cell surface, cell surfaces, and they're also on

mitochondria. So these lactate transporters transport lactate into the cell. They transport lactate into the mitochondria and lactate can then be converted back into pyruvate. That does not require energy to do that.

So it's energetic, it's thermodynamically favorable to have a lactate you know, molecule come into the mitochondria and then shunt in to that TCA cycle. So now it can be you know, used to basically generate the same energy that glucose would have been used to do through the whole getting converted into pyruvate and going to the TCA cycle.

Ketone bodies, you mentioned ketone. You often think of ketone bodies as an alternative source of energy. Well they actually do this, they get transported in through the same transport mechanism. The monocaboxyte transporter. And to convert a ketone body for example, beta-hydroxybutyrate. I think most people are familiar with that one, into acetyl CoA that also is epigenetically favorable That does not require energy to do. Whereas it requires energy to convert you know, the glucose into pyruvate and then to transport the pyruvate into the mitochondria all that requires energy.

So it is thermodynamically bearable to use lactate as a source of energy or to use ketone bodies as a source of energy. I kind of think of the two as similarly being used as these energy sources. Lactate and ketone bodies. Lactate you know is being generated all the time by your red blood cells, by your immune cells and then when you exercise you actually make a lot more of it and it's been shown that when you exercise for example the lactate in your circulation gets preferentially taken up into the brain. So it crosses over the blood brain barrier. There's MCT transporters across the blood brain barrier. It gets taken up and it's used as a source of energy and that's been shown.

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It's been shown in people when they radio labeled glucose and then lactate and administered lactate they show that during exercise that the lactate gets preferentially taken up to brain. It's also been shown that when you disrupt the astrocyte's ability to produce lactate that it disrupts our long term memory. This also to problems because neurons, neurons want to use lactate as opposed to glucose and you can think of you know they want to use ketone bodies as opposed to glucose.

The reason for that is because the one I just mentioned if a neuron has to use glucose to convert them into pyruvate it has to use up energy to do that. But if it just takes the lactate that the astrocytes are making that doesn't require you know, getting energy and then it just uses the

lactate to convert it into you know, pyruvate and then goes to the TCA cycle.

So you know, that's energetically favorable and the same goes with ketone bodies, which go can get transported in through these transporters the monocarboxyl transporter and could be converted into acetyl CoA and goes through the TCA cycle. So that's neurons prefer that and this allows for glucose to then be what's called spared. Glucose can then be shunted into another biochemical pathway called the pentos phosphate pathway to generate something called NABPH which is required to basically make and use glutathione which is the primary antioxidant in the brain.

So you can imagine under times of stress, traumatic brain injury things like that you're going to want to use that glucose not for energy. You're going to want to use it to make and be able to utilize glutathione in the brain because there's a lot of damage that occurs. So using, being able to use lactate as an alternative source of energy is very powerful. So --

Robb Wolf: And for the brain let's say like in a traumatic brain injury scenario, I don't understand the mechanism of why the brain becomes insulin resistant but with a traumatic brain injury events the brain does become very insulin resistant so we don't get glucose into the brain. We are then not able to take advantage of that lactate kind of bioenergetic advantage and that's where if we do have some ketone bodies they can play an alternate fuel substrate and maybe be beneficial for the brain under those circumstances. But if we're lacking let's say we're very insulin resistant systemically and have the traumatic brain injury then we're not really producing ketone bodies well and we're skinny on glucose and lactate as a substrate and then we end up with cell death. Is that a pretty good--

Dr. Patrick: Right.

Robb Wolf: --characterization?

Dr. Patrick: Right, yeah. I mean I don't understand either why first of all I don't understand why astrocytes stop using glucose under traumatic brain injury. I don't understand why you know, insulin resistance occurs. I think people are trying to figure that out but you're absolutely right. In that situation, you know, ketone bodies can come to the rescue in that they can then be used as a source of energy. Lactate if it's coming from the circulation can cross over the blood brain barrier and that's been shown in people that have had traumatic brain injury that hasn't been so severe that the blood brain barrier is very disruptive meaning that the oxygen,

you know, they're still getting oxygen in their brain so they're not ischemic.

If you administer lactate in and I'm sure ketone bodies would do a similar thing in the circulation it gets, crosses over to the blood brain barrier and it showed like it dramatically improved various different markers of you know, brain function and things like that. So yeah I think that it's very interesting how these ketone bodies and lactate you know, are thermodynamically favorable in the sense that they're a source of energy that is just there and available and you don't have to make use energy to use them like you would for glucose. And then on top of that, it allows glucose to then use to make these you know, reducing this type of reducing equivalent that's important to make glutathione and to use glutathione.

So that's all very interesting and the other thing also that I find interesting is that you know, when you're exercising and you do make more lactate, it's been shown that Parkinson's people with Parkinson's disease which I always think of traumatic brain injury as like brain aging in real time. So I think of you know, one of the projects I'm working on with Bruce is involves APOE4 and its role in Alzheimer's disease. So I have this paper I'm writing up and trying to understand all the mechanisms.

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But what I've been doing to understand Alzheimer's disease and to understand APOE4 biology in general is I've been researching traumatic brain injury. Because traumatic brain injury is like I mean it really is like Alzheimer's disease in like real time. Like it's accelerated brain injury.

Robb Wolf: Right.

Dr. Patrick: And people with APOE4 also have a much, much worse outcome with traumatic brain injury and they're also you know, much more likely to get Alzheimer's disease. So I'm trying to understand you know, the interplay between metabolism and what this you know, gene is doing and what it's not doing if you have a certain isoform of it. So but anyways back to the Parkinson's disease, what's really interesting is that very vigorous exercise has been shown to alleviate some of the symptoms of Parkinson's. So people with Parkinson's if they're forced to exercise really hard which of course I'm like okay well they're producing more lactate because when you're exercising more hard like if that's one of the things that happens, their symptoms, their tremors improve and their gait improves things like that.

And it's been recently shown in drosophila a fly model for Parkinson's disease that administering them L lactate helps with the mitochondrial dysfunction and helps improve, protecting and cell death and things like that. So I was wondering possibly if part of the mechanism of this exercise helping the Parkinson's patients has to do with the fact that lactate because they're dopaminergic neurons in their substantia nigra so part of problem with Parkinson's there's lots of things going on is that their dopaminergic neurons are dying.

One of the reasons they're doing is because their mitochondria are so dysfunctional they're not making energy and so they can't – you have to be able to use lactate, to be able to use ketone bodies, you have to have mitochondria that are functional otherwise you can't use those substrates as energy right?

Robb Wolf: Right, right.

Dr. Patrick: But what was really interesting is that they were able to at least in the fly model the lactate was able to help you know, help with that mitochondrial function and I'm not exactly sure how that was. You know, maybe it's easier to not have to make energy to use the lactate instead of using glucose. But anyways, regardless, I think that the lactate as a source or alternative source of energy for the brain is very interesting and people like George Brooks are now doing research to look at various different mechanisms for how that can occur. Like mentioned a signaling molecule is able to increase BDNF in the brain.

Robb Wolf: Right.

Dr. Patrick: And that's very interesting. I didn't even know that.

Robb Wolf: Yes. So get that synergistic effect, you get an alternate fuel substrate and you're getting some biogenesis in the brain so you know, lots of good stuff happening.

Dr. Patrick: Yeah. Yeah, exactly and it has been shown when you disrupt the astrocyte's ability to produce lactate that learning and memory and all those things are disrupted probably also through not making enough BDNF.

The other question is is you know, when you exercise, you make more BDNF in the brain and it's part of that because lactate is getting across, because you'll generate more lactate in the circulation which is getting into the brain and doing that. That's possible. I mean there's lots of things

that this lactate can be doing. It's also been shown to get into – it gets into your muscle mitochondria and helps your muscle mitochondria. It gets into other tissues, your heart, your liver, you know. So exercise is just one more reason why exercise is pretty awesome and it really has – George has really changed my view on lactate in general.

The other thing that's really interesting is that this all applies to the gut as well.

Robb Wolf: Uh-hum.

Dr. Patrick: So you know, the gut is –your gut epithelial cells, they need energy to goblet cells. I guess I should be more precise. Your goblet cells in your gut are the cells that are producing what's called mucin which Is what makes up the gut barrier. In order to produce mucin, that requires energy. You need energy to make that mucin and if your gut goblet cells are dysfunctioning and they're not getting enough energy you're not going to make mucin and so the mucin is going to break down and you're going to have breakdown of the gut barrier or as most people on the internet like to call it leaky gut. That's one possible cause. There's lots of things that can lead to breakdown of the gut barrier but I always like to think of it from an epigenetic standpoint from you know, we know that all these cells have mitochondria and their mitochondria is making – is you know, required to make energy to do their function.

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But what do goblet cells do? They make mucin so they need energy to make mucin. But lactate which is found in for example probiotics, different probiotics make lactate. Lots of the lactobacillus type of bacteria in our gut make lactate. One of the reasons they make lactate is because it makes a more acidic environment and that does not allow for some of the more pathogenic type of bacteria to grow because they can't grow in a more sick environment.

But the other reason I think is because it's literally feeding. It's feeding other commensal bacteria which eat lactate, but it's also feeding our gut cells.

Robb Wolf: Uh-hum.

Dr. Patrick: And I think that it's feeding them you know, without the gut cells needing glucose they get this lactate and it's like boom right into the mitochondria. It's a quick source of energy that's used so that's also another possible benefit of the lactate and you know, that's found in yogurt and probiotics and…

Robb Wolf: And this is one of the confounders for me when you start looking at folks that let's say they're showing some neurological symptoms of early Alzheimer's or early onset dementia. You could maybe make an argument on the brain level for a ketogenic diet to provide an alternative fuel substrate. But ketogenic diets tend to be very, very low in fermentable carbohydrate and then we're possibly damaging the gut and that whole process which then you know, feed forward into enhanced you know,--

Dr. Patrick: Yes.

Robb Wolf: --immune response and potentially increased levels of intestinal permeability ironically even though there may be some other dietary or lifestyle factors that fed into some initial intestinal permeability then that ketogenic diet may end up feeding forward on that. So there's maybe some arguments now for making sure that you get plenty of fermentable carbohydrate and then maybe supplementing with MCTs and coconut oil as a way of providing dietary substrate for those ketone bodies without starving the gut lining.

Dr. Patrick: That's interesting. I've been thinking a lot about this recently and I have been doing a lot of self-experimentation with my own diet and looking at the changes in my gut, you know, bacteria species that are in my gut to look at the microbiome I guess people call it. I have been wondering and I haven't really seen any literature but I've been wondering exactly what a ketogenic diet like a strict real ketogenic diet does to the composition of the gut microbiome how it changes it.

Now I know there are certain bacteria that hydrolyze fatty acids more I'm sure that you shift more to that but in terms of like the commensal bacteria and commensal bacteria making short chain fatty acids. They're making lactate, they're making butyrate, they're making acetate, they're making propionic acid all these things that not only feed other commensal bacteria but they feed our gut cells, yeah exactly. So it's interesting because I've been thinking of the same thing in terms of like what a ketogenic diet or ketogenic diet would do to the commensal bacteria.

Robb Wolf: Right.

Dr. Patrick: I'm really not sure. I'm not sure like you know, on the one hand, it's I think you really do need these fermentable types of fiber, you know to get to feed those good bacteria, the commensal bacteria. But on the

other hand you do see there are a lot of therapeutic benefits from a ketogenic diet. The question is like are those benefits like is it a short term sort of thing where if you were to stay in a ketogenic diet for five years then will you start to have problems with your gut? I don't know.

I think some gut problems happen pretty quickly.

Robb Wolf: Right, right.

Dr. Patrick: So you would imagine that would start to happen pretty quickly. And

Robb Wolf: Okay. I tracked down, I was doing some research on shift work and we can find elevated so you can become insulin resistant literally with like one night of poor missed sleep.

Dr. Patrick: Right.

Robb Wolf: And I started digging around on glycoproteins and also intestinal permeability and one of the first things that go south are lipoproteins like LDL particle count and then also intestinal permeability are immediately affected with one night of poor sleep.,

Dr. Patrick: Uh-hum.

Robb Wolf: So you know, and that's just a completely lifestyle factor. It's not even taking in food as a consideration and you immediately get alterations in the gut microbiome and also the intestinal integrity. So yeah it seems like that stuff is very dynamic in how it responds to dietary and lifestyle factors.

Dr. Patrick: Yeah. You know, you mentioned the shift work. Well you know, every cell on our body is on a certain clock right, a circadian rhythm where we at certain times of the day, we express certain genes that are – you know, where our metabolism is increased where repairs and DNA repairs are increased things like that. And then at certain times of the day it's decreased and other things are increased and this is like the circadian rhythm.

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Well the bacteria in our gut are also and a circadian rhythm. So when you lose a night of sleep or you know, obviously with shift work it's much, much worse, the bacteria, the commensal bacteria produce short chain fatty acids and they are on a circadian rhythm. So if they don't – if that circadian rhythm is disrupted in the gut as well, then they're not going to be able to produce those short chain fatty acids and then I can see what

would happen next is then your gut cells aren't getting the energy they need and so you know, it's like this cycle.

But what's also really interesting and actually I just read this paper like three days ago. It was a nature paper published actually I think it was last June so it was pretty recent. I didn't know about this but insulin resistance can occur in the gut.

Robb Wolf: Hmm.

Dr. Patrick: Right? We always think about it in the liver, muscle, like we don't really think about it in the gut and I found it so interesting because I have been trying to figure out the mechanism. What is it about eating refined carbohydrates, about eating you know, these high sugar diets that causes breakdown of the gut barrier? You know there's a lot of possibilities but I don't think we really know the real mechanism yet. So when I read this paper, I was like oh wow, this maybe one way we break down the gut barrier because if you think about it, so our intestinal cells this paper was actually it was even in the upper intestine which is even more surprising because I usually think about the lower intestine where all the immune cells are and lots more bacteria are. But what they showed was that you know, chronic sugar feeding causes the epithelial cells to become insulin resistant and they therefore can't take up sugar.

So while the bacterial cells are still getting all the sugar they want and they're thriving, the gut cells aren't taking it up. And guess what happens? What I just mentioned, your goblet cells don't get food then they can't make energy and they can't make energy the gut barrier breaks down.

This is how I think fermentable fibers and you know taking ketone body or like administering beta hydrobutyrate or lactate will obviously help because then you're getting that you know, substrate.

Robb Wolf: Sidestepping that.

Dr. Patrick: Right, right.

Robb Wolf: Yeah.

Dr. Patrick: So anyways I thought that was really interesting that that can actually occur in the gut and because we never really think about that and you know, the gut really is a very, very – it's a nexus for health because if you think about it, it's the largest concentration. If you ask anyone I think you

know, where is the largest concentration of immune cells, I think people would say oh the spleen or circulation no it's actually the gut.

The gut has the largest concentration of immune cells and there's a reason for that. I mean because the gut is exposed to the external environment right? Food.

Robb Wolf: Right.

Dr. Patrick: So it needs to have those immune cells. We need to be able to fight off things that are pathogenic. The gut also is the organ that has you know, the highest concentration of bacterial cells.

Robb Wolf: Right.

Dr. Patrick: So you know, what do you know immune cells plus bacteria is a bad thing especially when they're you know, in contact. And the barrier is what separates those two things. Right? It's important to have that barrier because as soon as it starts to break down your immune cells which are you know in the epithelial part of the apex I guess get in contact with those immune cell. I mean the bacteria cells and then it's kind of fire away. They start just firing off all these proinflammatory cytokines and then the bacteria start releasing endotoxin and that's really that --

Robb Wolf: Right, yes, yeah, yeah. So I'm bleeding from my ears trying to keep up with all these but I have a thought I'll throw out to you, so one of the theories of kind of insulin resistance then also I think mitochondrial dysfunction is just basically overloading these systems with energy. So even though they need energy if you're putting too much throughput in these systems then you can get damage. So one of the I guess adaptations to overfeeding is insulin resistance and a tendency to store nutrients in the form of fat because it's less biologically reactive.

So that's a piece and then another piece there was a paper looking at dense carbohydrates basically refined carbohydrates versus cellular carbohydrates and these cellular carbohydrates potatoes and minimally processed grains and stuff like that tend not to be metabolized in the upper portions of the small intestine, tend to provide more fermentable substrate.

[0:40:16]

If we're eating this refined carbohydrate, could we induce and overfeeding scenario in those early parts of the intestinal lining which induces insulin resistance, breakdown in the intestinal lining, LPS,

lipopolysaccharide makes its way into the system . It's interesting, sepsis which is caused by an LPS is almost indistinguishable from really poorly controlled type 2 diabetes.

Dr. Patrick: Uh-hum.

Robb Wolf: You know, when you look at the two of them, it's virtually impossible to tell the difference on the two of them. Could that maybe be some of the mechanism that's going on there that we get insulin resistance at a local tissue level in that early part of the digestive tract and then because of the systemic inflammatory features that occur from that then we end up pushing insulin resistance out to the rest of the body?

Dr. Patrick: I think that's absolutely possible and that's a very interesting way of looking at it that I hadn't thought about --

Robb Wolf: Almost fractal in a way.

Dr. Patrick: Yeah well what's also really interesting is that this inflammation that's induced both locally and then systemically inflammation causes the insulin receptor to become dysfunctional by inhibiting all these kinases and things that are important to activate it and that's also a part of how the insulin resistance occurs. So then it becomes this huge like vicious cycle because now you've got the inflammation. You know endotoxin, releasing endotoxin into the circulation is so incredibly bad for many reasons.

I don't know if I want to go into this, cholesterol thing, Should I go there?

Robb Wolf: Yeah, please, do, yeah, yeah.

Dr. Patrick: Okay.

Robb Wolf: Because I mean this is one of the things when I do some talks with hospital systems just we're not looking at the gut as a driver of elevated lipoproteins and I think that this is --

Dr. Patrick: It is. Okay, I'm going to go there.

Robb Wolf: We're just missing the heck out of us, yeah, yeah.

Dr. Patrick: Okay, here we go. So inflammation when I say inflammation you know, it's really just meaning your immune system that's getting activated and it's producing all sorts of chemicals that are damaging. These are often

called proinflammatory cytokines. They also produce reactive oxygen species and they basically the other thing about inflammation is because when it's happening in the gut, the bacteria in your gut have a cell wall and that's composed of lipopolysaccharide also called endotoxin gets released when the bacteria are dying. And that gets released into the circulation.

Well the reason inflammation it increases LDL particles synthesis well it increased BLDL and then LDL eventually but the reason for that is because LDL particles actually bind endotoxin. They bind it up. They soak it up like a sponge. So when you're – that's why it's always important to get your cholesterol measured more than once because let's say you are inflamed, you're stressed, some catastrophic event happened in your life and then the next day you went and got your cholesterol, your lipid particle measured and it's really high

Well that really is not indicative of your health because inflammation increases the production of these cholesterol particles, of LDL specifically. And so when I say endotoxin binds to it, there's – so you need LDL cholesterol. LDL cholesterol, I say LDL cholesterol it's not actually cholesterol. It's transporting cholesterol, transporting triglycerides and other lipids but I think it's easier for simplistic terms to just call it LDL cholesterol because that's how most people think about it.

You know, LDL is bringing cholesterol to your cells, all your cells and it's giving them cholesterol that they need to repair any damage they have. So every cell membrane, every cell in your body is a cell membrane which is made of cholesterol . It's also made of other fatty acids but this cholesterol plays a very important role in the structure of the cell which then in turn plays a role in the function of the cell. So you need LDL cholesterol. Any time you have damage to your cell, LDL is there giving a little piece of this cholesterol and to the cell and then the LDL goes back to the liver and it gets recycled.

Well the problem is that endotoxin when it's released from your gut binds to LDL cholesterol and it binds to what's called the LDL receptor which are these docking sites on the LDL cholesterol that allow it to get taken up by the liver and also by cells. But to get taken up back into the liver to be recycled to that LDL isn't staying around in your circulation for very long.

[0:45:12]

The problem is that when endotoxin binds those LDL receptors, it occupies this site that allows to then get recycled into the liver. And then it can't get recycled into the liver and so it's sticks around in the

circulation. So I think a lot of people that are more informed you know, while it's not the health isn't really about your LDL cholesterol. It's about the particle size and you know, these small dense LDL particles have been associated with heart disease, with atherosclerosis, with mitochondrial function, on and on.

Robb Wolf: But those small dense fractions are the ones that bind preferentially to the LPS.

Dr. Patrick: Exactly.

Robb Wolf: Yeah.

Dr. Patrick: So what happens you get a small one because after the LDL particle donates some cholesterol to the cell it's smaller. It gets cleaved off by lipoprotein lipases and you know, because that's how it donates what it means to give to the cell and now it's smaller. Well these smaller ones bind to the endotoxin and now what you have is a smaller LDL particle with a bacterial signal floating around and your immune cells go oh my god, endotoxin is here. So then macrophages come and they try to kill this bacteria but it's not bacteria. It's LDL with endotoxin bound to it.

So now you end up getting you know, the start of a foam cell and it's just like a whole cascade of inflammation because then these immune cells start secreting all these other signals which recruit more immune cells and it's just awful and it's stuck there because the LDL particle cannot be recycled back into the liver.

So I think really the problem with the cholesterol is not the actual cholesterol. It's not eating dietary cholesterol. It's things that are going to cause inflammation. It's eating refined carbohydrates. It's eating refined sugars. It's things that are going to cause your gut barrier to break down and for your immune cells to then start killing bacteria in your gut and releasing endotoxin into your circulation. That is what is I think is the major, major problem with heart health, major problem with cholesterol.

You know, 20 years ago we thought it was cholesterol and it's like well all we know is that cholesterol is associated with heart disease and it's bad and what can we do. Well let's not eat cholesterol. Let's just go with that, which caused all sorts of problems because then people started to eat more refined sugars, more carbohydrates.

They start to get more inflammation and you know, that's the real culprit. In addition to that, all the trans fats came out which have all sorts of

problems because they – it's like trans fats basically cause your cell membrane to become stiffer which is what happens with age. So it's like aging in real time and it just screws up everything. So anyways that's a whole other story. You know, that's a whole all sorts of problems.

Robb Wolf: Right. And you know it's really lent itself to this macronutriennt war, is it high carb, is it low carb and we really forgot the characteristics of the carbohydrate. Again these cellular bound carbohydrate sources fruit, potato, sweet potatoes, minimally processed grains, they tend to digest in a very different way than they digest once they have been milled and processed. So it's not just a carbohydrate content but it's the qualitative nature of the carbohydrate.

Dr. Patrick: Exactly and I completely agree. I've stayed out of those words but yeah it's just because people haven't understood the mechanism and they know that something is not right. Like they know it's not just about you know, the cholesterol. They know it's just not about the fact but they don't know exactly what's going and so they sort of like get pushed into this battle where they're like you know, they're fighting for something that they know makes sense but they don't quite know how.

So because biology is often more complicated, it's just not black and white. It's not like this or that. You know, it's not like you know, all sugar. Well yeah like you said fruits, fruit have fermentable fibers. They also have organic acids that can feed gut cells and things like that. So you know, it's not just about avoiding sugar, all sugar. Although you know, you don't want to have like you don't want to become insulin resistant.

But again I think the insulin resistance also comes down to the inflammation.

Robb Wolf: Right.

Dr. Patrick: And the gut health is really key. It really is. So I've been really just like diving into this gut health because I really want to understand it and I want to help people that I care about that are unhealthy. [Laughs]

Robb Wolf: Well you know, I've still been trying to unravel all this stuff for myself and really looking at early life circumstance like were you – like for me I 'm pretty sure my mother had gestational diabetes while I was in utero. Both parents died from type 2 diabetes complications. Both parents had autoimmune disease.

[0:50:17]

I had a vaginal birth. No breastfeeding. I was on tetracycline from the age of 14 to about 24 for acne. So I've got a bunch of kind of early life things that you know like I don't tolerate carbs that well. Like I tend to do a little bit better on the lower carb side of things and I've really been getting in and looking at eubiome and some other things trying to ferret out what I've got going on on that gut level. I've seen my LDL particle count range from as high as 2800 to as low as 800 when I've been able to keep all the lifestyle and sleep and everything else really dialed versus if I'm out on the road doing a book tour or something like that then everything starts going totally sideways.

Dr. Patrick: Yes.

Robb Wolf: It is bedeviling. Like ten years ago I thought I had this stuff figured out, alpha, omega done and every day I feel like I get dumber and dumber about this stuff. But if there's any kind of like you know, safe spot that I go back to, it seems like gut health seems to be a pretty argument for like well let's at least start here. Wherever ignorance is, let's at least start with gut health and start working our way out from there.

Dr. Patrick: Yeah. No I didn't know that inflammation caused your you know, the increased production of the LDL and now I know why. But you know, that's just so many physicians will get you know, order a lipid panel test for a patient to look at it once and they'll get them on statins. And it's you know, it's just awful. It's awful because for many reasons. You know, but the fact that they're on the end of one, I mean physicians should know. They should know that inflammation increases the production of these lipoproteins.

So that's just it's one real – if you ever go out and you're getting your blood lipid panel make sure you get more than one to really know what's going on.

Robb Wolf: Yeah and I would definitely recommend getting a particle count on --

Dr. Patrick: Oh yeah absolutely.

Robb Wolf: Yeah.

Dr. Patrick: Well it's really like I said, I think it's about the inflammation so particle count, you know, other markers of inflammation are also really important.

Robb Wolf: Uh-hum. What are your maybe three to five favorite inflammatory markers? I mean like C reactive protein is kind of a give me but do you have any others that you really are looking at?

Dr. Patrick: We're actually trying in our lab. I have some colleagues that are trying to identify ones that are more sensitive than C reactive protein. You know, the problem with some of the cytokines is they're so --

Robb Wolf: Localized and transient.

Dr. Patrick: Yeah, exactly and I was having a conversation yesterday with a friend and I was like why can't we measure endotox. Like I want people to be able to go and measure endotoxin in their circulation. Because it's so indicative of overall health. Like if you could –you know, endotoxin is higher in obese, it's higher in type 2 diabetics. It's higher in people that are insulin resistant but not type 2 diabetic. You know it's higher in people that are metabolically like insulin resistant but not obese. So but it's really, really a hard assay to do because endotoxin is everywhere. It's in the air. You know, bacteria are releasing. I mean it's part of the bacterial cell wall so it's you have to be really fastidious in the way you're measuring it and you have to be multiple replicates because you can get a lot of artifact.

Robb Wolf: Uh-hum.

Dr. Patrick: But you know, so in terms of like the inflammation, it's I don't have a lot of good markers for it that I think are really accurate. You know, C-reactive proteins obviously probably the one that's the – it's not as sensitive as I would like to see it. You know? So like my C-reactive protein often it's like zero to 0.02 and I'm like well it's really, is it really zero? Like I don't know.

Robb Wolf: Right.

Dr. Patrick: But so I'm not sure that that's really the best marker for inflammation and I have some colleagues that are trying to find different –they're doing metabolomics types of studies and they're trying to find different possible amino acids even that can maybe be be a biomarker for inflammation.

Robb Wolf: Interesting.

Dr. Patrick: But that's to come in the future.

Robb Wolf: Right.

Dr. Patrick: You know?

Robb Wolf: You're probably familiar with this but it was a huge eye opener for me when I started looking into pharmacology of metformin which is a commonly prescribed insulin resistance diabetes drug. It improves insulin sensitivity but it has two other really interesting features. It improves intestinal permeability and it also mitigates the liver toxicity associated with LPS.

[0:55:13]

Dr. Patrick: I didn't know that.

Robb Wolf: It is . There's another fun rabbit hole to go down.

Dr. Patrick: Yeah.

Robb Wolf: Like I would --

Dr. Patrick: I know those --

Robb Wolf: -- I was on the metformin terror for about six months and a lot of these docs they're like yeah, metformin, who cares? But I'm like and it's really interesting when you start putting together what metformin does and then overlay that against this idea of maybe endotoxemia as a driver for a ton of inflammatory processes. Like it's a really interesting kind of drug model that mitigates the effects that we're suspecting or going on there.

Dr. Patrick: Yeah. I know that you know, I'm always weary of any sort of pharmacological drug just because of the feedback loops when they're doing this and that to receptors. You know, other things get down regulated. But metformin is an interesting one because there's just so many positive benefits to it. I haven't dove into the literature but I do plan on it at some point.

Robb Wolf: Right. I have a very big file I'll ship it to you and I'll save a little bit of PubMed poking around. I have a couple other questions and I want to be very respectful of your time but you talk a lot about increasing life span. I really like how you draw a distinction between the biological tradeoffs between growth versus longevity and that's something that struck me a long time ago. I kind of take an economics evolutionary biology kind of look at all this stuff and there's always tradeoffs with any decision, any type of process. You know there's pluses and minuses depending on how you want to drive the boat with that.

I also read a series papers from Michael Rose a number of years ago where he made the argument that a lot of these extended life spans that we see from caloric restriction in various types of animals would probably not apply to humans because of the genetic reaction norms of humans. The genetic reaction norms involve the relative energetic inputs for offspring. Even though I feel like having two daughters the energetic inputs are massive apparently for humans. It's a lot less than like fruit flies or mice or something like that.

But he basically made an argument that the most austere, severely caloric restricted program that you could put together would at best improve average human life span about like five to seven years. And I'm curious what your thoughts are on that? I know you talk a lot about saunas and in different ways of optimizing telomere you know maintenance and whatnot. But have you looked into the genetic reaction norms or any thoughts on you know, how you could get – you know, what are some tweaks and fiddles for getting the best out of some performance, health, longevity you know, considerations?

Dr. Patrick: So I haven't looked. I don't know what exactly genetic reaction norms means. Can you explain?

Robb Wolf: It's basically kind of an economic look at how much energy does an organism put into offspring production.

Dr. Patrick: Okay, so yeah.

Robb Wolf: If you add something like fruit flies apparently and I don't fully understand this stuff either. I'm not a geneticist by any stretch. But theoretically if you have an organism that has a very high genetic input or energetic input for their offspring, caloric restriction will tend to impart at a very pronounced longevity factor because what it's trying to do is get those organisms to a point down the road where the nutrients are more available and then they can have more offspring. Whereas organisms that don't have a big energetic input calorie restriction really isn't that big of a consideration for longevity.

Dr. Patrick: Yeah. So I mean those – that theory that comes down to this reproductive like fitness and being able to allocate the resources you know, the energetic resources towards having offspring, that's just kind of one component of it. I do think that they have – studies have shown that if you calorically restrict earlier, then you have you know, the

maximal benefits of life span extension versus if you just do it after you've already reproduced. And then you start caloric restriction.

You're not going to have as robust of a lifespan extension at least if you're a worm or a fly.

Robb Wolf: Right.

Dr. Patrick: But in terms of humans, I tend to agree. I don't think you're going to extend your lifespan beyond five to seven years. Generally speaking if you practice caloric restriction even in the strictest sense, you know, the things –there's a lot of things going on with caloric restriction.

[1:00:06]

You know, one thing is that it's a activating a lot of these genes that are involved with longevity. So it's activating FOXO3 which is a transcription factor that activates a whole host of genes that are involved in increasing autophagy. So you're basically going to – autophagy is when cells eat themselves and this is very important because cells that are senescent are sitting around. When a cell becomes senescent, either because it's acquired so much damage through the years or if you're accelerating the damage by doing things like smoking or other bad lifestyle habits, your cell will become senescent as a protective mechanism as to not get cancer.

So it's still there but it's not really doing much . It's metabolically active but actually it's just it's not able to do a function. It's not able to reproduce and make more cells. All it does is sit there and secrete bad stuff. It secretes inflammatory cytokines which damage other nearby cells. It secretes other damaging products like reactive oxygen species.

So autophagy allows for those cells to get out of your system. So you want to be able to increase autophagy and so FOXO3 does that and caloric restriction activates FOXO3. The sauna, heat, stress, exercise, also activates it. Anything that's stressful activates this gene because it's a gene, a transcription factor that is involved with dealing with stress.

So I think that you know, it also activates genes that repair damage, repair damage to proteins, they repair damage to DNA, repair damage to cell membranes. It activates proteins that are involved in degrading bad stuff. So getting rid of, clearing out all the bad gunk that's accumulated in your cells. You know, so that's very important to do.

Caloric restriction in addition to that, it activates other genes sirtuins and other genes that are involved that control different epigenetic

mechanisms that regulate aging you. So as we age, our gene expression changes and we make less of good things. So a lot of the genes that are you know, doing good things like making neurotropic factors that cause brain cells to grow you know, these genes that I mentioned that are repairing damage, we make less and less as we age. What that means is that not only do we accumulate more damage because that's part of life. I mean we can't escape it breathing in oxygen. You have to breathe and that's like one of the fundamental ways you make damage through mitochondrial metabolism.

Well you know, not only is it accumulating more of the damage but you can't repair it as well. So it's like usually when you're younger, you have these systems in play that can repair damage and we're pretty equipped well to do that. But as we age, we aren't able to go as well in part because you know, our gene expression changes and this happens at the epigenetic level . Its' been shown several different studies now have shown that people if you look at you know, a variety of different age groups of people ranging from age you know, four to a hundred, they have epigenetic signatures. Meaning so epigenetic are these things like methyl groups, the seal groups that will sit on top of your DNA. They'll sit on top of histones which are DNA protein complexes and they turn genes on and turn genes off and I'm totally over simplifying this for people.

But those things there's patterns of them and as we age the patterns change. And it's so there's such a tight pattern that researchers are able to identify people's age plus or minus three years. Like and it's like 96% accuracy. So they can take your blood cell or they can take a muscle biopsy or they can take you know a prostate biopsy, they've done it from multiple different organs, multiple different tissuues and they can say you're 40 years old and you maybe 37 or you maybe 43 but regardless, that's pretty damn cool that they can guess your age by looking just at epigenetic signatures, you know, on your DNA. In addition to that, you know cancer cells have epigenetic signatures that look much, much older than the person's chronological age.

So I think you know, exercise, caloric restriction, you know, heat, stress, these things that are stressful in the body they're inducing positive changes by increasing the expression of genes that can deal with the stress.

That's going to help. That's going to help you throughout your life span if you continually do that. It's you know, part of the reason why exercise is so good and you know some these genes like FOXO3 for example people have polymorphisms in that gene.

[1:05:01]

So polymorphism is essentially like a mutation where the sequence of the DNA is mutated but it occurs in like a percentage of the population that's greater than 1%. So it's considered not a mutation which is often random. It's considered to have been selected for us so there's probably a reason why it occurs even if there's a bad function associated with it. You may often find a good function associated if you look hard enough.

Robb Wolf: Like sickle cell anemia for example.

Dr. Patrick: Right. Exactly. So that's a great example but the point I was getting at is that people that have polymorphisms in FOXO3 that make it more active all the time which is what exercise does. It makes it active, It's what heat, stress does, which is what caloric restriction and amino fasting done. They are more likely to live to be a centenarian. In fact they're like three times more likely. So they'll live to be a hundred which is pretty good.

Robb Wolf: Uh-hum.

Dr. Patrick: Pretty good and so I do think that an then in addition to that, there's the whole IgF1 right? You know, IgF1 is a growth factor that is very good for a lot of reasons. It you know, it's involved in growing muscle, repairing muscle damage. It's important in the brain for growing new neurons. I mean you know as you're growing it's important to grow. Right? So there's a lot of good things about IgF1 but if you have a lot of damage in your cells so if you're older and you have a lot of damaged cells that accumulate or you have a poor lifestyle, like we were discussing earlier where you're eating these types of refined carbohydrates and refined sugars that are basically poking holes in your gut to put it in simplified terms, and causing inflammation. Inflammation is damaging your cells, IgF1 in that case is not so good because it's a grow signal and it doesn't differentiate between a cell that's damaged and a cell that's not damaged.

A cell that's damaged also wants to keep living even though it's damaged. We have protective mechanism that say no if you're damaged die, we don't want you to potentially get to dysfunction that you become cancer cell that growth factors can allow them to overcome that. IgF1 is one that can do that.

So I think you know, caloric restriction also decreases IgF1 but it really depends on what you eat.

Robb Wolf: Right.

Dr. Patrick: So yeah studies have shown in like if you do it in monkey their IgF1 goes down. You get a mouse, your IgF1 goes down. People now this has been a topic that I've been interested in and did a lot of reading there's two things that regulate IgF1 in people. Energy for one but protein also.

Robb Wolf: Uh-hum.

Dr. Patrick: Protein is the major regulator and that makes sense because IgF1 activates MTor which is a signaling pathway involved to you know for amino acid synthesis when you're – when you eat protein is you want to be able to use that protein that you're eating. So it makes sense that protein would activate that. It doesn't mean that you know eating – I think there's a study from Valter Longo's lab at UCLA that came out not too long ago that kind of had people on a tizzy because it's basically first of all it totally over simplified things like the way it came out in media but it said let's see, eating a high protein diet is like as bad as smoking or something like that.

Robb Wolf: Right, right.

Dr. Patrick: And it was like what, it doesn't make any sense. And so I started digging into that and I'm sure you're probably really interested in this topic Robb. And I came to the conclusion that one, yes protein does activate IgF1 and so like I said that could be a good or bad thing depending on the context, depending on what else is going on. You know, so if you're someone who doesn't eat refined carbohydrates. If you're someone that's eating you know, whole foods, eating the fermentable type of carbohydrates, the more you know the healthier type of carbohydrates vegetables and you know, some of these whole grains like you mentioned also can be okay I think if you're not eating a bunch of other crap.

Robb Wolf: Right.

Dr. Patrick: And you're eating protein, fish, chicken, meat, red meat, you exercise then that IgF1 that you're going to be making when you're eating this protein is going to be taken up into your muscle cells and it's going to be repairing muscle damage and growing muscle and it's going to be taken up into your brain and it's going to be used to make new brain cells. What it's not going to be doing is allowing all these damaged cells to grow and become cancer because guess what you don't have a lot of damaged cells. You don't have a lot of inflammation going on. So you know I think really you know, with Valter Longo's study, it was interesting because you showed mechanistically that yes protein does increase IgF1 and when

you know they did this epistudy which of course is confounded by all sorts of things. In general I think most of the people that probably were eating meat were also eating a bunch of other crap because that's usually what people do.

[1:10:03]

And then in the mouse studies what he did was he and this is key because if you put a mouse on a high protein diet, it's not going to get cancer. Like well eventually as you get older mice get cancer but it's not going to cause the mouse to get cancer. If you inject IgF1 into the mouse and it's just eating a normal diet, it's not going to cause it to get cancer. If you inject tumor cells into a mouse, those are damaged cells. Those are cells that have already been damaged and then you put it in a high protein diet and allow it to make a lot of IgF1 then the IgF1 is going to allow the tumor cells that are already there to grow.

You know, so I think that's an important thing to realize is that you know, eating a high protein diet is not going to give you cancer. Eating a high protein diet and eating a bunch of refined carbohydrates and things that are going to cause inflammation that are going to damage your cells that's a bad combo.

Robb Wolf: Right.

Dr. Patrick: And that's pretty much a take-home but back to the caloric restriction, and I'm talking so much I'm sorry, the thing that was so interesting is I started reading studies and it was like oh caloric restriction doesn't decrease IgF1 in humans. I was like oh my god. You think that would be so well concerned but it makes no sense. So then I started reading, I looked to the studies more carefully and more studies came out later showing well people tend when they're doing a caloric restricted type of diet they tend to eat a high protein diet.

Robb Wolf: Uh-hum. Uh-hum.

Dr. Patrick: And that and so that was why your IgF1 wasn't going down. So then when people are doing, put on a caloric restriction diet, where their protein is restricted to 10% which is typical of like what you're doing like a ketogenetic diet so actually other caloric restricted diet became a ketogenetic diet.

Robb Wolf: Funny.

Dr. Patrick: And then their IgF went down. So that was very interesting and I mentioned energy also regulates that there's the proteins that bind igF1

but IgF1 binding proteins those are regulated by sugar. You know, so there's a lot of complications and we tend to just simplify it down to one thing but I think the take-home is that you know, if you are eating protein, a high protein diet, then you know you better not eat a bunch of other refined crap with it and you should exercise. Like that's --

Robb Wolf: Right.

Dr. Patrick: And I think most people that are following a paleo type of lifestyle do that right?

Robb Wolf: This is one of those confounders that one of the key correlates with effective aging is maintaining a decent level of muscle mass you know, so it's yeah, yeah. Yeah. Yeah.

Dr. Patrick: Yeah when you get older, if you make it past –you know, if you make it to 80, you're likely not going to get cancer. But what you are going to probably what's going to take you out is breaking your hip. You know?

Robb Wolf: Uh-hum.

Dr. Patrick: So people with low muscle mass are very prone to just bone fractures and it's – and that will take out an old person. You know, not being able to --

Robb Wolf: Bounce back from that.

Dr. Patrick: Bounce back from that. Yeah exactly. So muscle mass yeah, increased higher in that – and there's been studies showing that right where it's been people with a higher density of muscle mass have a longer life span.

Robb Wolf: Right, right, oh that's awesome. Doc, we're an hour and 10 minutes in. Do you have time for one more question on supplements?

Dr. Patrick: Absolutely, I'm having fun. It's all good.

Robb Wolf: Okay, great. Awesome. I could spend six hours talking with you about this stuff. So we'll probably have like a 30% suicide rate from people just overwhelmed with this but that's just fine. It's almost like apoptosis or some sort of cellular selection on the listener level so it's totally fine.

Dr. Patrick: Yeah. I'm not sure I actually answered your question but I did sort of like --

Robb Wolf: You totally did.

Dr. Patrick: Give some thoughts.

Robb Wolf: You absolutely did. So supplements. On the one hand it appears that a lot of people are quite nutrient deficient, micronutrient deficient, vitamins, minerals, antioxidants, polyphenolics. On the other side of the story though there appears to be some cryptic you know, implications from supplementation. Some increased cancer rates, you know, supplementing whey protein with folate and stuff like that. Again I think that you probably addressed this you know, with your previous answer talking about if you're going to provide an organism with a lot of really good nutritional foundations you should probably be steering the boat in a direction that's healthy overall versus something that's unhealthy because if we select for an unhealthy environment, then we're selecting for inflammation and cancer and all that type of stuff.

But you know, what's the deal with supplementation? Like who needs it, who doesn't need it, what are we usually deficient in and what are some of the confounders with these supplement studies that seem to implicate you know some supplements as being deleterious to health?

Dr. Patrick: Yeah. So I'll try to keep this as short and clear as possible.

[1:15:05]

Robb Wolf: You just go wild, whatever you want to do.

Dr. Patrick: I could go on.

Robb Wolf: You go wild.

Dr. Patrick: You know, so you started out by talking about micronutrient deficiencies and that's absolutely true. You know we know from a variety of different national health surveys that people are not getting enough micronutrients which are very important because your micronutrients are about 30 to 40 or so essential vitamins, minerals, amino acids and essential fatty acids. So vitamin D is one where people about 70% of the US population doesn't have what's considered to be adequate levels of vitamin D which are blood levels that are around 30 nanograms per milliliter. Vitamin D gets converted into a steroid hormone and it does a lot of things in the body. You know, 60% of the population does not get enough vitamin E. 45% of the population doesn't get enough magnesium. You know, magnesium is required for cofactors that repair damage to DNA. It's required to make energy. 38% of people don't get enough

calcium. Obviously you need calcium for – calcium is required as a cofactor for many different enzymatic reactions in the body and also for bones. About 35% or so don't get enough vitamin K which is very important for both coagulation and for also making sure calcium gets out of your blood vessels and goes to where it needs to be like the bone.

Vitamin C, 25% of people don't get enough vitamin C or vitamin A. You know, 34% of the people don't get enough vitamin A. So you know, there are definitely micronutrient deficiencies and these micronutrients while you may not see an acute effect. For example, you're not getting enough vitamin C, well you're not going to like wake up every morning and see your gums falling off. But there's other consequences that may happen like not getting enough magnesium. Well you may not be able to repairing your DNA damage as well and so you're not going to know that but eventually you will when you end up with cancer earlier in life because you're just damaging your DNA over and over again.

So you know, these micronutrients are very important and anyone that's heard me talk can go back and listen. I talked endlessly about and so I'll kind of cut that part short. I think that the best way to get these micronutrients is to eat a balanced diet. Really relying heavily on eating a lot of really good plants. You know getting your broad spectrum vegetables, getting your dark green, you know, your dark greens which are high in vitamin K they have magnesium, they have folate. They have calcium, they happen in the right rations. You know getting, they also have vitamin C. Getting your tomatoes and your carrots, your onions these things have precursors that can make vitamin A or they have other good things like luteins, xanthem, you know, other things that are also very important for a variety of things.

But eating whole foods is probably the best way to get, is the best way to get these micronutrients and I really, really recommend people doing it. I like to make a smoothie every morning that I have a recipe on my website for my smoothie and all the micronutrient breakdown of it. But I like to get a broad spectrum every day. In addition to that, getting your omega-3 fatty acids by eating fish, I like to eat a lot of salmon and cod wild authentic salmon and cod and making sure you're getting your protein especially for those of you that are working out a lot. You know eating your chicken or your grass-fed beef or whatever.

So that's really the main way to get these micronutrients. Now the thing is that people it's really hard to do. It's really hard to do for me and I take time to do it, you know, every day and it's still really hard. The people

that need it most are the people that are poor, the people that are not as educated. They're not people that are into the paleo community. They aren't people that are thinking about you know, how our ancestors ate and figuring out you know, these are people that are working, you know, they're working hard, they're working crappy jobs and they don't have a lot of time or money to prepare food and you know, those are probably the people that are the most, you know, insulin resistant, the most obese. They are the ones that are getting cancer at a higher rate and they're the ones that need these micronutrients because they're starving more than you and I are, more of us people are more educated. So --

Robb Wolf: That's something that Bruce Ames put together the Chori Bar?

Dr. Patrick: Yes.

Robb Wolf: Is that how you pronounce it Chori?

Dr. Patrick: Yes, yes, that's correct, exactly. So vitamin supplementation there has been a lot of controversy in the literature on vitamin supplements, are they good, are they bad. I think that it really depends on the context. It depends on the type of vitamin and it depends on the health of the person.

[1:20:05]

So you had mentioned cancer for example well all the studies that have been done with cancer have been with folic acid, which is the oxidized form of folate that's more stable. That people that were given folic acid, they already had cancer. So these aren't people that didn't have cancer that people that already had polyps for example and their colon. They were given folic acid to see what the effects are.

Well folic acid folate is used for a couple of important things in the body. It's used to make new DNA so it's required for a precursor to make thiamine which is a DNA nucleotide. It's also used for epigenetics like the solar pathway. So you can imagine someone that has cancer, well cancer cells want to make more DNA because they want to reproduce to make more cancer cells. They're rapidly dividing cells. So giving cancer cells folic acid is not a good thing because it's like fuel to grow more. It absolutely will cause a cancer cell to grow more rapidly. But the alternative to that is not getting enough folate so about 10% of the population do not meet requirements for folate. And that's not most people because folic acid is fortified in a bunch of food. Now folic acid is I think that I prefer you know, I prefer taking folate or getting folate.

Folic acid although it can help with these people that are poor and not going to eat their greens as long as they don't take it in a high enough dose, because then once you get to a certain dose, they can start to basically interfere with other pathways in the folic acid metabolism.

So it's just, it's kind of a tricky thing but again 10% of the population doesn't get enough folate and 50% of those people are the poor. That's a huge percentage. So we're talking I mean when I say I'm just dividing that tenth of the population saying most of those people of the 10% of the population are the poor.

So and not getting enough folate actually causes double stranded breaks in your DNA and Bruce Ames have shown this, other people have shown this. In fact they've shown it that having a level of what 10% of the poor have in the blood causes strand breaks in their DNA which actually can lead to cancer. So that's not good. You know, so I don't think that you really have to be careful when studies come out and they say you know, vitamins cause cancer. Well you have to read the study, you have to look at the context. You have to understand the mechanism.

You have to know what folate is doing in the body and folic acid what it can do in the body and what that means for someone who has cancer and someone who doesn't have cancer. Now if you give a folic acid supplement 400 mcg folic acid you know, supplement to a poor person that you know, does not have enough folate, that's probably going to do them more good than harm. To give it to someone that has a polyp in their colon, that's probably going to do more harm than good. So that's – you know, there's other examples of this.

So I think that generally speaking, it's good to supplement with a few things. Vitamin D I think is goo to supplement with because you know, it's so important for so many processes and most of us are not getting enough vitamin D. You know, it depends on so many different factors regulate it right? I mean I'm sure many people have come on your podcast talking about it so you guys you know the importance of vitamin D. Omega-3 fatty acids are also very important. I think those are important to supplement with.

And you know, eating fish is also, is paramount but there have been randomized control trials that have shown that supplementing with one two to grams of fish oil reduces all cost mortality by 29% over the course of two years, the supplementing of the core six years. It also reduces mortality from heart attacks which is the number one killer in the United States by 30%.

So not only are there you know, the short term benefits that it's so important for so many things. I mean I could just go on and on about omega-3 fatty acids but you know the long term effects all cost mortality reduction I think is pretty --

Robb Wolf: Pretty compelling yeah.

Dr. Patrick: Pretty compelling yeah. And then the other thing was you mentioned you know, what – that antioxidants, I think that's one that I'm a little more hesitant on because while people are not getting enough vitamin C and vitamin E, taking supplemental antioxidants I'm not a big fan of. I used to supplement with two grams of vitamin C a day and that was based off of some studies that I have read where it had lower you know, C-reactive protein, it was lower –you know, there was benefits to it. But I do get a lot of my vitamin C from vegetables. I eat a lot of vegetables everyday so I'm pretty sure that I'm okay with my vitamin C levels.

[1:25:04]

Now the reason I don't supplement with vitamin C is because other studies have shown that some of the benefits of exercise or intermittent fasting or any of these things that cause a little bit of stress on the body, the mechanism by which you know, the stress activates all the good genes that are involved in stress response has to do with the burst of reactive oxygen species that are generated. So when you're exercising, you create a lot more reactive oxygen species. When you're intermittent fasting, you also do and this does a couple of things. One it activates these genes that are involved in dealing with stress like FOXO3. Two it also increases the production of more mitochondria called mitochondrial biogenesis.

So and if you take supplemental antioxidants like vitamin C or vitamin E they can sequester those reactive oxygen species and prevent that positive effect.

Robb Wolf: Uh-hum.

Dr. Patrick: So I think that they're a little more hesitant on taking supplemental antioxidants. Not to mention there's a whole other complication with vitamin E. There's lots of different types of vitamin E and if you most – the major supplemental form is alpha tocopherol. Alpha-tocopherol is also the most potent at sequestering these reactive oxygen species. Well it just so happens that when you take high doses of it, above what the RDA is which is like around 22.4IUs, you end up depleting another form of vitamin E called gama tocopherol in your cells. Gama tocopherol does a

completely separate function of than alpha-tocopherol does. It's involved in negating inflammatory reactive nitrogen species which are generated from inflammatory molecules and signaling.

So when you deplete your gama tocopherol, you're doing yourself harm so foods like avocado, foods that are hot and that's foods that have high vitamin E have all the tocopherols and tocotrienols. So it's good to get vitamin E from a food source in my opinion.

Robb Wolf: Loren Cordain never ended up publishing this paper but he – I think he went through the USDA database and pulled out you know kind of representative whole foods and did kind of a 3D mapping of the amounts and ratios of the nutrients in various foods. It was a really interesting kind of histogram. And then he started overlaying that versus most supplements. What you found was that you – the supplements never looked like the profiles that you found in foods and had massive super physiological doses.

Dr. Patrick: Yeah.

Robb Wolf: So that was kind of his thing was that if we were to do some sort of a supplement, we would really try to want to emulate the amounts and ratios that we would find in foods.

Dr. Patrick: Exactly.

Robb Wolf: Yeah.

Dr. Patrick: It's very important. I mean some people when they find out something is a good thing they want just as much of it as they can. And that's not necessarily a good thing. And the ratios are also very important. You know calcium and magnesium the calcium, magnesium ratio is important. You have – you want a two to one calcium to magnesium ratio because you know there's enzymes in your body that require calcium to work and there's enzymes in your body that require magnesium to work. But there's twice as many of the ones that require calcium and magnesium.

The problem is that calcium and magnesium structurally look like each other. You know, minerals are very small and calcium and magnesium are next to each other on the periodic table of elements. So if you're flooding your system with magnesium and you're not getting enough calcium, then the calcium depend on enzymes take the magnesium thinking it's calcium and it causes dysfunction.

Robb Wolf: Uh-hum.

Dr. Patrick: You know, so it is – that's one thing that with supplementation that you know people tend to go overboard and just take more of it and they don't realize that the ratio is important. The amounts are important and you know, with that said, I do think that supplementing can help people and I take supplements myself. I take fish oil. I take vitamin D. I take vitamin K2 to make sure that my calcium's is not staying around in my blood vessels. I take a B complex and the reason I take a B complex is because well for multiple reasons. I looked at my genes and found that you know, I have certain gene polymorphisms that make me have lower levels of certain B vitamins. I also have a partial NTFHR polymorphism. So my enzyme that allows folate to be used to make all these epigenetic stuff that that I've talked about doesn't work as well.

So I take methyl folate with – it's part of my B complex. I take a multivitamin that has it's called – it's from Pure Encapsulations.

Robb Wolf: Uh-hum. Uh-hum.

Dr. Patrick: It's called one and I really it's probably like one of my favorite ones because it doesn't have high doses of all this stuff and it really just has – it has 2000 units of vitamin D and it has you know, trace elements in some of the like selenium and iodine and things that I want to get. And it doesn't have like you know, just overbearing amounts of stuff. So I take that as well.

[1:30:17]

Robb Wolf: Fantastic.

Dr. Patrick: So the Chori Bar, I just want to briefly mention – you mentioned that.

Robb Wolf: Yeah, please do.

Dr. Patrick: Because it is, it was developed by Bruce Ames and my colleagues in my lab. And the bar basically has a variety of vitamins and minerals and it has DHA. It has a polyphenolic rich matrix of fruits, walnuts and other dark chocolate, the polyphenols in dark chocolate. It has a lot of fiber, different types of fiber in it. It was designed to get it into the poor to basically get –you know, basically it's like a – I want to say like a candy bar but it's not a candy bar. It's like a just a bar that has all these vitamins and minerals and fiber and polyphenols and good things to try to help bring them up to an adequate status for a lot of these vitamin D minerals and things that they're not going to eat.

And so there's been like 14 or 15 clinical trials that have been going on in the Ames laboratory that I work in and I have not been involved in most of them. I just recently started doing some work with the Chori Bar trials. But you know, there's two publications that have come out from that lab and from the Chori Bar. One have shown that when it's given to people that are lean and they're metabolically lean as well and they eat it twice a day for two weeks, they raise their HDL like significantly. Like by 30% and they raise their glutathione levels or C-reactive protein goes down. So that's pretty, pretty cool that even people that you already think are healthy, people that are already you know, they're probably like they think that they're at their optimal health status. Well they ate these Chori bar twice a day and their HDL went up by quite a bit.

Robb Wolf: Right.

Dr. Patrick: But the cool thing was is the second publication that was just published a couple of months ago was done in people that are overweight and obese. The --

Robb Wolf: And they didn't modify their diet other than --

Dr. Patrick: No.

Robb Wolf: -just putting the Chori bar in.

Dr. Patrick: Exactly.

Robb Wolf: Yeah that's what was really interesting, yeah.

Dr. Patrick: it's really interesting that they were told not –you know, not to –you know you don't have to modify your diet in any way and just eat this twice a day and what was – there's a couple of interesting things. That's the first that we're able to see positive things without them changing. And these people are eating a terrible diet. I mean they're eating a lot of fast food not exercising at all.

So the interesting thing was is that we had to separate people into inflamed versus not inflamed. Because the people that were inflamed so there was like a C-reactive protein cutoff level to the define who was inflamed and who wasn't inflamed. But the people that were inflamed we didn't see any changes you know, after two weeks, after four weeks so it took like really eight weeks before HDL started to go up in these people that were inflamed.

And we think that's because they had to deal with the inflammation first.

Robb Wolf: Uh-hum. Uh-hum.

Dr. Patrick: And that had to be resolved before anything else could happen. Whereas the people that were overweight, obese, but didn't have high C-reactive protein the bar was able to raise their HDL in four weeks or something like that. I think. So anyways it's very interesting that giving people these vitamins and mineral fiber was very important. You know, the fiber and DHA so there's lots of things in this bar and there's lots of – there are mechanistic studies now trying to figure out what exactly in the bar is doing it and you know, can we take out, can we just give them one component or is it the whole thing. And you know, we talked about vitamins and supplements and ratios and the difference between whole foods and vitamin supplements.

The bar was designed to kind of mimic a Mediterranean like diet in a way where it's like they wanted to make sure the vitamins and minerals had this you know, matrix fiber. There were polyphenols and other things that are present in whole foods there. So it is a little different than just giving people a bunch of supplements I think.

Robb Wolf: And it was interesting to me and that it would theoretically address nutrient deficiencies, polyphenolics that would feed gut bacteria and provide some more naturally occurring levels of antioxidant status. And then also it was providing fermentable fiber for the gut.

Dr. Patrick: Exactly. Yeah.

Robb Wolf: So yeah it was really kind of a one-stop shop. So I know science being science they're like well what's the one thing in here that's doing it? It's like well the one thing is the shit inside the wrapper it's a bar so.

Dr. Patrick: Right, right. I have a feeling that's probably what the conclusion is going to be.

[1:35:04]

Robb Wolf: Right, right. That's hilarious. Well Dr. Patrick, it's such a huge honor to finally have you on the show. I've been trying to put this together since I've met you at Paleo FX two years ago. So really a huge honor. Where can folks track you down on the inner webs? You have an amazing website and just an outstanding podcast and video series.

Dr. Patrick: Well first of all, thank you Robb. It's been my pleasure and I really, really enjoy speaking with you. You're very intelligent and we should totally talk on a more regular basis.

Robb Wolf: Yay, I'm in.

Dr. Patrick: [Laughs] With that said, so I have also got a podcast on iTunes and if you just search Found My Fitness or Ronda Patrick it will come up. I have been really excited about the podcast lately. I've been doing more of them. I just recently filmed one with Tim Ferris and it's a really interesting one to talk all about the ketogenic diet and things like that. So you can find them on iTunes and also in addition to that, I write articles for a lot of videos that I put out on YouTube and for a lot of the things that I talk about and I have them on my newsletter. So you can sign up for my newsletter or you can download a free report on my micronutrient smoothie that I talked about for example and it talks all about what's in a smoothie. You know, it talks about anti nutrients and all this stuff that people are worried about and all that good stuff. So if you want to sign up for my newsletter, that's another way that you can get all the articles that I write and in addition to that, you can find them on YouTube and also I have a website called FoundMyFitness.com where you can find all of those things. I'm also on Facebook and Twitter. On Facebook I have a fan page called Found My Fitness. I interact with people quite a bit on Facebook and answer questions and talk to people a lot so it's kind of fun me and for the people to ask me things.

I think that's about it.

Robb Wolf: Awesome.

Dr. Patrick: That's where to find me.

Robb Wolf: Well I'm so grateful for the work you're doing. Really excited that you are – amidst your already insanely busy schedule that you're putting so much effort into being accessible and getting this information out to folks. It's you know, like I said earlier like I feel dumber now than I did ten years ago because there's just so much information to stay on top of and folks like you are really just so critical for taking the research that's occurring day to day and getting it out into a medium that's accessible to people and really gives them some you know, cost benefit tradeoffs as well as some really easily actionable ways to put this information that we have and into effect in their daily lives. So I'm very grateful for the work you're doing.

Dr. Patrick: Thank you so much Robb. I really appreciate you having me on the podcast. It's been a lot of fun talking with you.

Robb Wolf: Well huge honor and maybe six months or so down the road we can do a Q&A. We can open up to folks and get some questions from listeners and we'll get you back on.

Dr. Patrick: Yeah sure. It sounds fun.

Robb Wolf: Awesome Doc. So take care and I'll talk to you soon.

Dr. Patrick: Take care.

Robb Wolf: Okay. Bye-bye.

[1:38:10] **End of Audio**