Paleo Solution - 342

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Robb: Hey, folks, Robb Wolf here, another edition of the Paleo Solution Podcast. Today's guest is Dr. Bryan Walsh. Dr. Walsh is an expert in human physiology and metabolism and we're going to be talking about the incredibly controversial topic of adrenal fatigue, what it is, what it's not, and what none of us apparently know about it. Dr. Walsh, huge honor to have you on the show. Thanks for taking the time to do this.

Bryan: It's an honor to be here. Thanks so much.

Robb: Doc, I gave you a very paltry introduction there. Can you flesh out more of your background for folks so that they know a bit more about who you are and what kind of orients your thinking on all of these topics?

Bryan: Yeah. Actually, I have to say, I really like your intro. I think shorter and sweeter is far better. I don't like the long ones. I guess, I can say I'm a naturopathic physician. I've been practicing for probably about ten years. I've always been interested in health. I know a lot of people out there like yourself can relate to this to some degree. Reading about nutrition in junior high school, just fascinated with it, and fascinated how the human body worked and exercise.

And where I am today in terms of being a naturopath is I believe that conventional medicine has a lot of really great things to it but they also fail in some places. They offer us a lot of information about some of the mechanisms, physiologically and biochemically. And we owe a great deal to them for the science and the reductionism that they've given us. A place that alternative medicine, which has so many names now, functional medicine, integrative medicine, complementary and alternative medicine, that space is great and does a lot of things really well but it also fails.

And we owe a great deal to that space for a lot of things. And where I exist is I honestly try to be a bridge between the two areas. For example, we have adrenal fatigue in our industry. Conventional medicine says that it doesn't exist. Is there some kind of in between -- and that's hopefully what we'll talk about today. Is there something in between that we and the integrative space can say maybe it's not adrenal fatigue but, "Here's biochemically and physiologically what's actually going on."

In conventional medicine, can they say, "All right, low cortisol is real. It does cause people problems. It does cause people symptoms. It doesn't have to be

Addison's disease. And so we'll listen to what you'll have to say." So, I really try to be that bridge where I appreciate and love the science but I also love the tradition and some of the things that go on in our space admitting that both conventional and alternative medicine succeed at some things but fail at others.

Robb: Doc, I mean, I had a pretty sneaky suspicion that something -- we'll call it adrenal fatigue -- but something was going on with folks. Like we've seen this in police, military and fire where we see really consistent patterns of disordered sleep and kind of hypogonadic effects and we'll see like a flipped circadian rhythm both in the way that the person is active or not active but also in their cortisol response. I had both kind of an empirical and also kind of a biochemical sense that something is going on there.

But like you said, a lot of folks in the more allopathic medical scene just dismiss this notion out of hand. And we often seem to circle this thing of, well, how much cortisol is being released in total and if that follows within some normal bounds then we're good to go. Why has this thing maybe existed right under all of our noses and only certain people have been able to see it or to contemplate it and for other people it just really doesn't exist?

Bryan: Yeah. I think that that's -- In conventional medicine -- That's a really good question. I will just kind of take a stab at it. I genuinely think that if they don't understand something or have an explanation for it then it just doesn't exist and that it's not important to even consider. As you said, low cortisol, no matter how you test it, you can test it in serum, you can test it in urine, you can test it in saliva, and there are people out there that have low cortisol. And it's not Addison's.

And what comes with that, of course, is a host of different symptoms from the neurological symptoms and depression and mood and then there's fatigue, a higher, or I should say, lower tolerance to pain. They experience more pain. Of course, there's sleep dysregulation and a number of other things. And I think what happens is that the conventional medical industry sees low cortisol, looks at these symptoms and just doesn't have an explanation. Like I don't know why your cortisol is lower than it should be.

They can look at the lab and say, "Yes, I agree. It's lower than it should be." But they don't have any explanation for it. And so, I think, that that's probably the main reason why it gets dismissed. Then in the alternative industry or the nutritional industry, they for a long time, and maybe we'll cover this, they are still holding on to the original work of Hans Selye who showed that there was an alarm stage and a resistance stage and then an exhaustion stage.

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It turns out, and there's even some papers that explicitly state this, that that is wrong. It's actually profoundly wrong information. Basically, thank you, Hans Selye for doing such an amazing job and really bringing glucocorticoids to our attention but the theories of physiology that you espoused are not just kind of wrong. They're really wrong.

Robb: Well, Doc, could you do a compare and contrast of what the classic model of adaptation is within that Selye model and then kind of where we are today understanding it, looking back at it with much more depth?

Bryan: Yeah. So, I often call this adrenal physiology then, and that's sort of what we've been taught. This is what we're currently taught. And because dogma takes a long time to kind of unwind itself, it's still being taught. And then I call it adrenal physiology now. This is based on scientific studies and literature that really hasn't made its way into education or in the textbooks. And I say education of, honestly, naturopaths or medical doctors, et cetera.

So, Hans Selye, his model in brief is that when an organism is stressed and he used mice and physical stress -- Now, this could apply theoretically to humans with mental, emotional or perceived stress. But basically, that there's an alarm stage. And it's the first phases of stress. It turns out that he didn't use these in his experiments. But researchers today, to stress out a mouse, there's a variety of ways of doing this, but you can simply restrain their hind legs and they have a stress response. They have a cortisol response.

And so what happens in this alarm phase is, basically, it's an acute stress response and cortisol, which is the primary hormone that we'll talk about today, goes up considerably. If the stress continues, what he suggested is that cortisol starts to go down and in what's called the resistance phase, that the body is kind of adapting to the stress, cortisol isn't as high because it wasn't acute stress. It's still under a stressful situation but cortisol starts to drop.

And then eventually, if the stress continues, the cortisol will actually go below the original basal levels prior to the stress and then that's what he dubbed the exhaustion phase. Now, what that's done for our industry, the integrative medicine industry, is that that's where this, I think, this idea of adrenal fatigue came from, is that why is cortisol so low. Well, surely, as the name would suggest, exhaustion, that the adrenal glands just weren't able to produce cortisol anymore. They don't have the capacity to produce it. They're not producing it. It's because they're tired, they're worn out, and they're exhausted.

And that perspective remains today. In fact, I will admit, that's how I was taught. And you better bet that my first patients when I first started practicing, I'd run

cortisol test on them and if it was low, guess what I told them? I told them what I just said. "Your adrenal glands are wiped out. You've obviously been stressed for a very long time and you have this thing called adrenal fatigue." Unfortunately, how we start out is just doing what we were taught.

But then I was starting to have some questions about this. As you know, Robb, in physiology and biochemistry, the more you know the more you're really able to question some of these concepts that are dogma and that we've been taught. And so, basically, what I've spent the past few years doing is going into the literature to say what's updated about adrenal physiology, what are we not being taught about as practitioners and are still pushing forward to our patients, and is there an explanation for low cortisol biochemically and physiologically that would, number one, better inform how we treat these patients?

And also, speak to, if we can, conventional medicine and say this is real. People are suffering with this. And it doesn't have to be Addison's disease. So, I don't know if you want me to go into some of the -- Actually, I don't know if it's better to quickly go through what sort of old adrenal physiology dogma is, the HPA axis. And then we can sort of pick that apart.

Robb: I think that would be fantastic, yeah.

Bryan: Cool. And this is, obviously, just in the interest of time, a real broad overview. But if there is some kind of stress, whether it's physical stress, it could be temperature, it could be some kind of injury or what I'd like to call perceived stress, which is more of a mental-emotional stress, that can be a stress of some event that's not actually happening. So, for example, you can be mentally-emotionally stressed because you're in the middle of a difficult relationship. Or maybe your finances are low and you're in debt.

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That's a real mental-emotional stress. You can have a mental-emotional stress if all of a sudden somebody asks you to get up and speak in front of a thousand people just impromptu and you have nothing to say. That would probably elicit a stress response. We can be stressed about what's going to happen in a week and it hasn't even happened yet. So, it doesn't really seem to matter but if the brain perceives a stress -- And again, just be real simple with all of this -- a couple of things happen.

One is there's a very quick 200-mile an hour response from your brain down your spinal cord out the sympathetic nerves to all the organs that help us basically get out of a bad situation. The pupils dilate, the heart rate goes up, the heart contractility and heart volume or the cardiac volume goes up, respiratory rate

will increase, blood gets shunted to the muscles away from the gastrointestinal tract. Most people have probably heard of those things.

The second and slower response then is -- And again, I should say with that same response. The adrenal medulla, the inner part of the adrenal gland, receives that lightning fast neuron message and releases epinephrine or some people know it as adrenaline. Now, the second slower response is that same perceived stress, there's a part of the brain called the hypothalamus and the hypothalamus is kind of -- some people call it the master gland. It knows a lot. It knows what's going on inside your body. It knows what's going on outside your body.

And the hypothalamus releases a hormone, a peptide called corticotrophin releasing hormone. I'll just abbreviate it CRH. Now, right below the hypothalamus in the brain is this little dangly thing called the pituitary. And the hypothalamus and the pituitary are connected. There's a little hose between the two of them. So, the hypothalamus, when the brain perceives stress of some kind, whether real or perceived, releases CRH, drips it down this little hose into the pituitary, the CRH. The pituitary receives this hormone and says, "Okay, we need a stress response."

And it releases a hormone called adrenocorticotropic hormone or ACTH, which goes in the bloodstream. And this is why it's a slower response. It takes a little while longer for ACTH to eventually circulate its way around to the adrenal glands who then receives that ACTH signal and as a consequence releases a couple of hormones, the primary one we'll talk about today is cortisol. And that can stay, it depends on the acute stress, which we can talk about timing. But it probably increases and peak around 15 to 30 minutes.

And if there's no other stress other than that, just one stress that you had, will probably drop down to basal levels in around 60 to 90 minutes or so. And that's considered to be the HPA axis, hypothalamic-pituitary-adrenal axis, and is what we've been taught as dogma and this is the classic stress response. If you like me to continue--

Robb: Keep going. You're on fire, yes, please.

Bryan: So, that's cool and that's what I've have learned and that's probably what you learned. And at some point, I started questioning this. I said, well, there's got to be more to this. And I was seeing patients that weren't responding to certain things that we were doing, the typical adaptogens. If somebody has low cortisol, you give them adaptogens, you give them licorice root. If you're feeling brave, you can give pregnenolone and DHEA. But it wasn't working. Things weren't working with certain patients and I thought there's something else going on. I've

always loved looking at physiology and biochemistry so I started going to literature a little bit.

Just to give you an example of how little I will say that we know about physiology, and when I lecture I often bring this fact up. You've probably seen this. But in the past couple of years, Italian researchers identified a new ligament in the knee, for example. And more recently, the fifth quadriceps muscle, to make it -- Not a quadricep.

Robb: A quintucep.

Bryan: Yeah, right. And my whole argument is if we're still finding parts that have likely been there the whole time and we've been dissecting and doing surgery on people for a really long time, how well do you think we really have a handle on physiology and biochemistry? If we're still identifying pieces that have been there the whole time. I still believe we know far less than we think we do in terms of the physiology and biochemistry, which this podcast will probably be obsolete in, I don't know, another five years or so.

But some of the things physiologically that I found, and these things are just awesome and they don't even make sense -- I mean, if you want to do a little quiz, I can quiz you although I'm sure you probably know these things. So, if one were to sever the infundibulum, the little hose between the hypothalamus and the pituitary, physiologically, one would expect that ACTH would go down because, remember, the hypothalamus is dripping the CRH towards the pituitary who receives this and then produces the ACTH as a response.

So, if you were to cut that contact, that communication between the hypothalamus and the pituitary, you'd expect, well, the pituitary doesn't receive CRH anymore so it's going to stop producing ACTH. And it turns out the total opposite is true. ACTH, it gets jacked up.

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So, right there, things like that just totally fall in the face of what we think we know. Another really great one -- you might appreciate this. So, there's this study that looked at what was CRH knockout mice. So, these are mice, totally healthy, otherwise, they had -- They didn't make CRH. The hypothalamus did not make CRH. So, as you can expect, physiologically, no CRH means no ACTH means no cortisol. And, in fact, there's no rhythm to the cortisol. They're just flat line cortisol.

And what researchers did was they gave them a constant infusion of CRH. Now, physiologically, which is always what we go back to, physiologically, if you have a

constant infusion of CRH then you'd expect a constant increase in ACTH and a constant increase throughout the entire day, no rhythm, of cortisol. But what they found was in these CRH knockout mice, they didn't make CRH, a constant CRH infusion didn't produce chronically alleviated cortisol. It restored the circadian rhythm.

So, they had normal cortisol in the morning, low cortisol at night but yet they were getting a constant infusion of CRH. So, when you hear things like that, or at least when I hear things like that, I'm like, man, we really don't know what we're talking about.

Robb: It's not nearly as straightforward mechanism as what we would have liked to think it is.

Bryan: It's counterintuitive to what physiology, our understanding of physiology would suggest that if CRH, if it's truly the HPA axis, if CRH was continually high then cortisol should be continually high. And that's not how it works. Also, we realize that cortisol is produced in the brain and in the intestines and in the thymus and in the skin. ACTH is actually produced by lymphocytes. Now, is it enough to stimulate -- I guess, the point, is it enough to influence serum cortisol levels, which is what we're measuring? And quite honestly, probably not.

But our understanding is that this HPA axis is far too myopic, that there's so many other influences and even more potent ones which we'll talk about in just a second especially from the immune system. But it's not just the HPA axis. In fact, there's so much more to this. I guess, we'll jump to that. So, it turns out that the adrenal glands themselves make a number, produce a number of their own, well, I should say, immune molecules. So, cytokines. Like interleukins, for example.

The adrenal gland has been found to have receptors for almost all the interleukins, or I should say some of them. Interleukin one, two, six, for example, tumor necrosis factor alpha, interferon gamma. They have receptors. They have receptors for these things in the first place. It also, the cortex, makes tumor necrosis factor alpha and some of the resident macrophages of course will make these as well. But tumor necrosis factor alpha, interleukin-6, interferon gamma, and in a paracrine fashion where the tissue releases something and it acts on that tissue, it has potent, potent influences on cortisol synthesis, steroidogenesis or cortisol synthesis as well as cortisol release.

And this, when I started researching this, I was finding these things, these little factoids that I told you about that the lymphocytes make ACTH, that cortisol has produced in a number of different tissues not just the adrenal glands, that some of these things that we think would make sense in terms of severing the

infundibulum and what would happen to ACTH or these CRH knockout mice that had constant infusion of CRH, this really started -- when I found those, that started to kind of mess up my mind and I thought there's something to this. I'm really going to dive into this a little bit more.

And if we're talking about adrenal fatigue, it turns out that this goes far beyond the HPA axis. That, for example, tumor necrosis factor alpha, which is considered to be a pro-inflammatory immune marker or cytokine, causes inhibition of the adrenal glands to both make and release cortisol, specifically, and this is what's interesting -- So, you can imagine this physiologically. You have a patient that comes in or a patient that has low serum cortisol, low salivary, low urinary cortisol and has elevated ACTH.

Now, what that suggests is that the body, the brain is trying to get the adrenal glands to make more cortisol via that high ACTH. The pituitary is coaxing the adrenal glands like saying, "Come on, man, give me a little cortisol."

Robb: Something. Right.

Bryan: ACTH is high but the adrenal glands aren't responding. It turns out that tumor necrosis factor alpha is a very potent inhibitor of cortisol release even in the presence of elevated ACTH. So, what researchers say is it inhibits ACTH induced cortisol release. Meaning, ACTH is there. It's trying to get the adrenal glands to make and release cortisol. But in the presence of tumor necrosis factor alpha, the adrenal glands don't respond to ACTH. And what makes it even more interesting is that tumor necrosis factor alpha is inhibitory and it seems, according to the studies that I found, is especially under lower concentrations.

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So then it begs the question to make it more clinical is how many people out there today have some kind of sub clinical, let's just say, smoldering fire of inflammation of some kind, doesn't even have to be something like full blown rheumatoid arthritis, but has higher than normal sort of sub clinical levels of tumor necrosis factor alpha that's causing this "adrenal fatigue."

Now, getting back to the adrenal fatigue, what practitioners will say is, what I used to say, unfortunately, is your adrenal glands are wiped out, they're shriveled up, they're tired, they can't make cortisol anymore, you've obviously been stressed for a really long time, and to boot, it takes a couple of years to rebuild the adrenal glands with supplements. And on the other hand, if it's tumor necrosis factor alpha and it's causing inhibition of the adrenal glands, all one has to do is lower tumor necrosis factor alpha and cortisol should come up.

And I found this really great study that did look at rheumatoid arthritis patients and researchers gave them an anti tumor necrosis factor alpha drug lowering tumor necrosis factor alpha. Not only did their symptoms improve but their cortisol levels went up just as a consequence. And low cortisol is really common in a lot of autoimmune conditions but in rheumatoid arthritis especially. And all they did was just block the amount of tumor necrosis factor alpha that was available in the body and their cortisol came up, which is again, I'm not saying proving. It's hard to prove a lot of things in science. But suggesting that in all these people running around there today with low cortisol and "adrenal fatigue" that has nothing to do with fatigue or wiped out adrenal glands that can't make cortisol anymore. But it's rather inhibition. I'll pause for a second, let you ask some questions.

Basically, instead of fatigue, what I want to suggest is it's either adrenal inhibition or what I'll call functional adrenal insufficiency. And I can cover a few of those things. But it's either the adrenal glands can't make it for a biochemical reason, nutrient deficiencies or mitochondrial dysfunction, or endoplasmic reticulum stress, something is wrong with the adrenal glands. If you fix it, they'll be able to make cortisol again. It's not fatigue though. Or it's an inhibition or suppression intelligently by the body because the body wants no cortisol or low cortisol right then.

Robb: In an autoimmune scenario, it's interesting because cortisol helps modulate the immune response kind of mitigating it to some degree. So, is this a scenario we're really wired up for acute inflammatory events and infections and we're really not wired up so well for dealing with, say, like intestinal permeability and chronic inflammation and so it's just kind of a mismatch between acute phase adaptation versus that longer phase but clearly quite a bit different than the Hans Selye model?

Bryan: Yeah, no, really I love the question. I have two responses to that. I'll take the second part of it first. You're right, it does seem that we're set up for acute stress and not chronic. I'll give you a couple of reasons why. And this is ultimately getting to -- I don't believe it's adrenal fatigue. I think there's something else involved. So, interleukin-1 interestingly causes an acute cortisol release as do -- and I'll get to this in a second -- lipopolysaccharides. So, if you or I were to get an injection of interleukin-6 or lipopolysaccharides and we were healthy, very likely our cortisol levels would go up pretty quickly.

But it turns out that interleukin-6 chronically causes a blunted cortisol response. And as far as I could tell, and I've looked into, researches aren't entirely clear but what it seems to be is that chronic interleukin-6 may cause apoptosis or cell death of a number of cells including adrenal cells and they're no longer producing cortisol as well. Now, the lipopolysaccharides, and I love that question

that you just asked, the lipopolysaccharide story is very interesting. And this is why when people are researching adrenal physiology, they have to be really careful as to whether it was acute or chronic.

Acutely, if you and I were to get an injection of lipopolysaccharides we'd have a stress response. We'd have inflammation and our cortisol would jump up. But there's been some really awesome studies. And one of the ones that they did was they take a couple groups of mice and each group, one group they gave saline injections and the other group they gave lipopolysaccharide injections continuously. So, one group never had any exposure to lipopolysaccharides, the other group had a continuous exposure to lipopolysaccharides.

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Then what they really wanted to do is they gave each group of mice an injection of lipopolysaccharides. The group that was getting the saline injections had an acute cortisol response. The group that had been receiving lipopolysaccharide the whole time had an extremely blunted cortisol response. And they called it endotoxin tolerance. And this is the interesting thing. Who of us out there is getting a spike of lipopolysaccharides? That's like you said. If somebody has dysbiosis and intestinal permeability, it's going to be a chronic exposure.

That chronic exposure of lipopolysaccharides, according to studies, is highly suggestive of causing a blunted cortisol response. So, again, I say, is low cortisol adrenal fatigue or is it dysbiosis intestinal permeability chronic exposure to lipopolysaccharide and what they're calling endotoxin tolerance? The way I look at it is like habituation with the nervous system. That when you first put on cologne, if somebody wears cologne, that you smell it but then half hour later you don't smell it anymore and you don't even think you're wearing cologne because you've habituated to that stimulus.

So, it would appear that it's the same thing in the body in that we have exposure to certain things like lipopolysaccharides that we become almost tolerant to that as the new norm and, therefore, the body doesn't see it, like you said, as an acute stress but actually as this chronic stress and, therefore, we don't really respond to it as much anymore. Regarding the autoimmune comment that you talked about, you're right. Here's what I think. Cortisol is so much involved with the immune system.

One of the problems that I have is -- we learned this in school. They'll say that the cortisol suppresses the immune system. That's not entirely true. Cortisol, and I don't really love the whole TH1 TH2 conversation that people are having. I think it's been grossly oversimplified although there's some real clinical utility to it for

sure. But cortisol suppresses the TH1 arm of the immune system. It actually enhances the TH2 arm of the immune system.

The TH1 side of the immune system is involved when something is -- the way that I put it is if it's a small invader versus a big invader, that if you imagine like natural killer cells or cytotoxic T cells or neutrophils or macrophages, that these by and large are the same size as our own cells. And so if our cells get infected by a virus, if our cells become cancerous, then these immune cells that are the same size -- Basically, the way I look at it is two dogs attacking each other. If they're the same size and they can attack and they can have a good fight. If one is too big than the other one we need to call in something else.

So, the TH1 side of things is, the TH1 part of our immune system gets involved with it's viral, when it's cancer, or when it's a small bacteria. Again, it's kind of an oversimplification. Cortisol suppresses the TH1 side of things. On the other hand, the TH2 side of the immune system goes after larger things, larger bacteria, parasites, and instead of attacking these things head on because their cells are too small, it launches grenades or mortars at these things in the form of antibodies.

So, cortisol suppresses the TH1 system. So now think about this. This is still speaking to the autoimmune conversation or question that you had. So, if we have a virus, and this is -- I asked people to think about this and say if you are the designer of the body and all of a sudden you got invaded with the virus, and you know that you want this TH1 immune response to go crazy, you want as many natural killer cells, cytotoxic T cells, neutrophils, macrophages, to go after these things as much as possible.

And then you learn that cortisol suppresses the TH1 side of things. Then what's the next best thing that you would do to maximize TH1 would be to suppress cortisol. So, I'll say that again. If cortisol suppresses TH1 and you want TH1, by extension you'd say, "Well, the less cortisol we have the more TH1 activity we have." And so in many autoimmune cases you very often will see -- Actually, I'll say this. In cancer patients, in somebody that has an active viral infection and in many autoimmune cases, you'll see low cortisol and it would appear as though the body is desiring low cortisol, that's saying, "Adrenal glands, do not release cortisol right now so that we can maximize this immune response to attack the virus or to attack the cancer cells or, in the case of autoimmune conditions, to accidentally attack our self tissue," if that makes sense.

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So, to your question about autoimmunity, cortisol does regulate the immune system. I think that the body in its innate wisdom, which is far smarter than all of

us combined, wants low cortisol in certain situations which is why I think adrenal fatigue is more aptly named cortisol suppression or cortisol inhibition.

Robb: Oh, man, it's fascinating. Doc, my understanding of this is nowhere near your level but I've been looking at some things like DUTCH testing where they're looking at a variety of hormones. I've been noodling on this a little bit related to not just the supply side story but in stage metabolism. That's made some sense to me with if cortisol is low, is it low simply because there's not enough being produced or is it actually getting metabolized and we find it some downstream in products? What are your thought around that? How does that integrate into fleshing all this out?

Bryan: Yeah, that's a fantastic question. So, if a hormone -- we'll talk about if -- we're talking mostly about if cortisol is low. But just to make it easier, if a hormone is elevated it's because -- and you just said it actually. If a hormone is elevated, it's because you're either making too much or you're not clearing it out fast enough. If a hormone is low -- and that's really the only reason. If a hormone is low, you're either not making enough or you're metabolizing it, like you said, and clearing it out too fast. I think those are totally valid.

Now, I will and I realize that this is blasphemy right now in the blog-o-sphere. I'm not sold on the DUTCH test yet. I feel stones being thrown at me when I say that. I will just say I'm a very late adopter when it comes to testing. I've been in the game not as long as some but long enough to see certain tests come out, it's the next best latest greatest gold test out there and then it's not scientifically validated or some studies come out showing that it's not reliable or specific or sensitive for what it's testing for.

I've also seen certain tests drop off for the same reason. They used to offer these tests like the lactulose mannitol, which some people still offer, but it's really been disproven. The food sensitivity, the IGG food sensitivity test has really been disproven. So, I'm a late adopter, I will admit, when it comes to testing. I've seen a lot of DUTCH tests with patients. I get asked about it frequently. I'm familiar with the methodology of it and I like what I see. I haven't done a lot with it.

When talking about adrenal fatigue, I mean, really what you're looking at is low cortisol. So, could the clearance be a part of it? Could excess metabolism, which is essentially what you're asking, be a part of it? Absolutely. A question that I have is the frequency of that. And I would generally say -- this is purely based on my experience -- is if anything, I see individuals that have hormone levels or, I should say, that have the inability to metabolize and clear out hormones in an optimal level. The sex hormones.

So, does cortisol fit into that? It's tough to say. But realistically, these sex hormones, steroid hormones, I should say more accurately, are metabolizing clearly pretty much in the same way. And so what I have personally seen in my practice is more people that have a slow clearance, if you will, of the steroid hormones and incidentally I have some of it with testing of my own patients. When people have perhaps low clearance, if we give nutritional supplements to support biotansformation pathways namely of the liver, namely phase two of the liver, that can help some of these pathways that I will see in a matter of six weeks hormone levels drop considerably and the only change that was done was giving them some supplemental phase two biotransformation support.

So, it's possible. But in terms of probably or how frequently something like that happens, I will admit it's really hard for me to say. We will get into this too but salivary testing, for example, tests the free fraction. If somebody has a lot of the binding protein that transports cortisol around the body they'll have low free fraction and that person will get diagnosed with adrenal fatigue when, in fact, if you run their blood, they may actually have elevated cortisol. And so the testing is still nuanced and it's not performance. Blood, urine and saliva all test different things. Whoever you ask usually will have a strong opinion saying that one is better than the other. I will tell you that they test different things. And so they're really good at testing for what they're testing but they do miss other pieces of the puzzle.

Robb: Shocker. That's pretty shocking that we would need some nuance to get a more clear picture on that whole story.

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Bryan: Yeah. Well, that's the nature of our industry. We don't have as much science, scientific validity behind these things to really back them up. What would be interesting and granted some people would argue against this but to do blood, urine and saliva all the same time. And if there are some discrepancies, to try to biochemically and physiologically figure out why that might be because it may be that every single one of the tests are valid but they're testing different things and, therefore, require different interpretation.

Robb: Interesting. What do you feel like is the main or maybe the main three, main five things that are bringing people to this "adrenal fatigue" state? I mean, we talked a bit about endotoxemia. It seems like -- This is so fascinating to me too. So many of these things become -- it's unclear if it's push or pull on this. So, alterations and cortisol function can alter circadian rhythm and sleep but sleep disturbances particularly in say like shift workers or people traveling internationally, that can cause these adrenal alterations.

This is something that, to me, is kind of maddening as to what the chicken and egg is there. But we have like traumatic brain injury. We have endotoxemia. We have altered circadian rhythm. What are the things that are getting people into this situation?

Bryan: Yeah. It's a great question. I think, a couple of comments on that. One is I really think you have to define the demographic first. Because I will tell you that in my practice, I don't see shift workers. I don't see people that have had traumatic brain injuries. And I would suggest that while, yes -- Or PTSD. That while, yes, that there are many causes for low cortisol and some of which I'll even try to touch upon.

I personally have experienced with a certain segment of the population and, therefore, when I say what I think is causing this the most, it's mostly just based on my own perspective and experience. What I can tell you is that it's probably not. And this is kind of a way of telling you all the different ways that can cause low cortisol technically. And that's in the literature to some degree, or at least suggestive. This is really important to know.

Cortisol, all steroid hormones actually, I should say, are synthesized in a very similar way. It all starts out with cholesterol. Cholesterol can either come into the cell that makes the hormone or these cells happen to be really, really good at making cholesterol themselves. Cholesterol, the first step, cholesterol is brought into the mitochondria and the first and what's called the rate limiting step is when cholesterol is turned into pregnenolone. And this is true for making testosterone or estrogen or progesterone or DHEA or cortisol.

Then in the case of most of these but cortisol leaves the mitochondria as pregnenolone, goes into an organelle called endoplasmic reticulum, the smooth endoplasmic reticulum, goes through a number of enzymatic steps there. And in the case of cortisol, comes back into the mitochondria one more time to go through its final conversion to cortisol. Excuse me. Now, you're very familiar with the phrase mitochondria dysfunction.

Mitochondrial dysfunction is recognized thankfully by conventional medicine. It's a real thing. There's another one called endoplasmic reticulum stress. This is a very real thing that's going on today in people. And just by describing how cortisol was made you must have proper mitochondrial function, proper endoplasmic reticulum function to even have a chance of making cortisol in the first place.

So, one of the questions that I have is of the people, to answer your question, of the people that are walking around today who have low serum cortisol or salivary or urinary, what degree of mitochondrial dysfunction is going on with

these individuals? And it's real. There's studies suggesting -- well, not suggesting -- saying that, yes, mitochondrial function is absolutely critical for proper steroidogenesis or steroid hormone synthesis or, in this case, cortisol synthesis. So then you have to look at all the different things that could potentially cause mitochondrial dysfunction.

Of course, excess oxidative stress can do this. Now, what you might find really interesting is the synthesis of cortisol actually generates, excuse me, quite a bit of oxidative stress, reactive oxygen species. And in essence, so let's say, if we wanted to say that Selye was right, could it be that in the acute phase where somebody has an acute stress response, they're making a lot more cortisol than normal, that they're generating a lot of reactive oxygen species at the same time which is causing, if they don't have the antioxidant buffers, is causing mitochondrial dysfunction or cellular dysfunction at this point in the cortex.

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And that you see a steady decline in the amount of cortisol that they can make and what would be, therefore, exhaustion or adrenal fatigue. But I would argue again that it's not exhausted adrenal gland. It's adrenal gland that may have had too many reactive oxygen species, poor mitochondrial function or endoplasmic reticulum stress, for example. And that if you were to support the mitochondria -- there's quite a bit of antioxidant found in the adrenal glands incidentally.

Support antioxidants, support mitochondrial function, support cellular function that would cortisol come back up. So, your question was: What do you think of the most common causes? What I'm going to say is here's some reasons but I don't think these are the most common. I'll end with what I think is the most common if that's right. Another real one but I have no idea how much this translates from science to people is chemical and toxin exposure.

No, one thing I don't like about the alternative industry is how much they talk about toxins and detoxified and died and we're all toxic and we need to detoxify. Especially you see these programs at the beginning of the year. There's no proof to these things actually, detoxifying chemical toxins out of our body. But what is really well-established is -- and I've seen some great tables on this -- is they will take, researchers will take every single enzymatic step from cholesterol transport to cortisol, all the steps in between, mitochondria, endoplasmic reticulum, and they will pair up each of those enzymes with every single chemical that's been found to inhibit that enzyme.

So, dioxins and phthalates and insecticides and pesticides. There's a lot of drugs, especially antifungals, for example. And when you look at this long list of things that is known to inhibit these enzymes then that's a real possibility that if we

have chemical or toxic exposure could that theoretically inhibit some of these enzymes that are making cortisol? To make it clinical, however, if cortisol was the only low hormone in somebody and a guy, let's say normal testosterone but low cortisol, then those chemicals are probably not doing it because they would likely inhibit that enzyme for any of the hormones that were made.

But here's one that's interesting. You're familiar with Roundup from Monsanto. I found this great but horrible study showing that Roundup, which is considered an endocrine disruptor. Now, most of the time, when we say endocrine disruptor to somebody, they think estrogen, testosterone, or sex hormones. Well, it turns out that at least in these mice, that Roundup at levels far below what the EPA considers to be a no-observable adverse effect level per day far less cause cortisol suppression.

It was in the neighborhood of, if I remember correctly, it's like ten milligrams per kilogram body weight per day, I think, in these mice cause cortisol suppression. And the EPA says it's 500 milligrams per day per, milligrams per kilogram bodyweight per day or something like that. I may be wrong in the numbers but it was pretty intense. So, yeah. Could it be toxic exposure? Could it be roundup exposure causing all these adrenal fatigue? Who knows?

So, those are possibilities. There's toxins and nutrient deficiency, which I won't get into, oxidative stress, some of those things. So, to answer, finally, your question, as to what I think is most common is I think it has to do -- and this is in the general population. This is not somebody with a traumatic brain injury, somebody that's experienced significant stress and, therefore, PTSD. Although it may be working for them in some degree.

But I think it has to do with immune suppression of the adrenal gland's ability to make and release cortisol. And that could be, and because of the immune system, some kind of underlying infection whether it's viral -- and I have a really fascinating hypothesis paper on that, which I'll mention in a second. Viral, whether it's autoimmune, whether it's lipopolysaccharides, like I talked about, or some really interesting studies, a couple of them, on sepsis.

And these, when I read these studies, this, to me, was kind of the nail in the coffin for adrenal fatigue. Now, what researchers did was you don't know who's going to get sepsis, systemic bacterial infection. You don't know who's going to get sepsis beforehand so you can't, so the controls happened after somebody had this systemic bacterial infection and ended up in the hospital. And what researchers have done in a couple of studies was they, in the hospital with these patients, they took their serum, basal cortisol levels, and gave them the ACTH stimulation test.

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And I'm so glad that they have this idea and I did this. So, the ACTH stimulation test, and someone like you and I who are supposedly healthy, if you inject us with ACTH then cortisol should just get jacked up, should go really high. If cortisol doesn't respond or the adrenal glands don't respond by releasing more cortisol, if you get an injection of ACTH then that is how doctors diagnose adrenal insufficiency, which makes sense.

The body is pumping out ACTH where you get an injection of it, the adrenal glands don't make cortisol. So, that's what they did to these septic patients. They're in the hospital, they have sepsis, they're being treated for it, they measure their basal cortisol levels and gave them an ACTH stimulation test. Patients in the hospital with sepsis had low basal cortisol levels and had adrenal insufficiency. Meaning, they have the injection of ACTH and their adrenal glands didn't respond with cortisol.

Now, in the alternative world, they would say, "Well, they had adrenal fatigue." But the problem is, researchers, thankfully, two weeks after the people that survived, left the hospital and there's no more sepsis, they redid the same test two weeks later out of the hospital. Their basal cortisol levels were normal and they had a normal ACTH stimulation test. So, to put that really simply, they had adrenal fatigue in the hospital and then were cured of it two weeks after they got out of the hospital.

Robb: And with no licorice root or DHEA.

Bryan: And it didn't take two years to "rebuild" the adrenals, exactly. And so because of studies like that, because of the effects of chronic LPS or lipopolysaccharide exposure, because of the effects of chronic cytokines, tumor necrosis factor alpha interleukin-6 and because, the last little bit I want to say is there's one -- It's the only fantastic paper. I obviously get really excited about kind of silly things but, man. So, this is the medical -- It was in the Medical Hypothesis Journal. And what they did was they sequenced the amino acid sequence of certain viruses like SARS and a couple of influenza viruses.

And it turns out that they looked at the amino acid sequence -- this is brilliant, man -- the amino acids sequence of these viruses and found that the amino acid sequence of these viruses were almost identical to many mammalian ACTH hormone. So what happens then is when we get these viruses, and Mother Nature, man.

Robb: Oh, they're suppressing our immune system so they can hang out.

Bryan: Well, they do but listen. So, your immune system sees the virus that has a certain amino acid sequence, it's going to go after that, and usually goes after something that has similar -- It's called molecular mimicry. And so it turns out that we make antibodies against ACTH when we're infected with some of these viruses. But if you're killing, if you're shooting, like at a shooting range, when they say pull and a little disc goes out, that's ACTH and you're blasting every ACTH out of the sky before it gets to your adrenal glands, you don't have any ACTH to even make cortisol.

And to make matters worse, these antibodies bind onto the ACTH receptors. So, during a viral infection -- and this was great because this explained to me why so often you see somebody with a viral infection has low cortisol, that perhaps we want low cortisol to maximize TH1 in a viral infection, which makes sense. Perhaps it's a virus that has a similar amino acid sequence as ACTH and so we make antibodies against ACTH to affect the cortisol and how it's affecting the immune system so the virus can survive longer.

At any rate, again, in a very long winded way answer your question, I personally think, in the larger demographic, which is men and women living their life fairly normally, exercising, supplementing, eating a good diet, you know the type, the type that listens to your podcast, that it's some kind of small ring fire, underlying chronic viral infection, some kind of dysbiosis in the gastrointestinal tract, intestinal permeability increasing the lipopolysaccharide, for example, or some kind of low level chronic inflammation that's relieving low amounts of tumor necrosis factor alpha, just as an example.

Because all these things have been shown to inhibit cortisol production. One other one I forgot to add. There's a compound called defensins. It's also known as corticostatin. These are molecules made by the immune system only during infection. And as the name corticostatin would suggest or defensin, that this also suppresses cortisol production and release.

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So, the point being is this is why I said earlier there is functional adrenal insufficiency. That's mitochondrial dysfunction. That's nutrient deficiency. That's excess reactive oxygen. It's something that's making the adrenal glands not able to produce cortisol but it's not adrenal fatigue. It's give the nutrients, cut out the reactive oxygen species, fix the mitochondria, reduce the toxins.

On the other hand, what I think is more common is adrenal suppression. The body wants lower cortisol levels likely for some immunological reason whether it's a viral infection, cancer would be horrible, or some kind of bacterial infection in the gastrointestinal tract, lipopolysaccharides, those studies on sepsis. So, I

suspect that today we have -- There's a lot of people that have some chronic infections going on. H. pylori, there's so many different infections that people could have today.

At any rate, I think that that's what's going on. And, therefore, we don't need to be getting adaptogens per se though they're great. I love them as a class of botanicals. But rather perhaps we should be supporting the body's ability to get rid of these infections to support the TH1 system using certain botanicals and thereby allowing the body to increase cortisol because it feels, I guess in the funny way of saying, it feels safe to do so, if that makes sense.

Robb: Absolutely. Doc, are you using anything like ketogenic or fasting, mimicking diets to try to get some mitochondrial biogenesis and reset that side of the story? I know oftentimes low carb or ketogenic diets or fasting can be contraindicated in the classic adrenal fatigued individual. But if so much of this is hovering mitochondrial dysfunction that seems like a really slick way to reset that system.

Bryan: Yeah, good question. I don't use that therapeutically for that reason, for mitochondrial biogenesis. Again, it depends on the demographic. If someone is not exercising -- Listen, exercise is a great way to stimulate mitochondrial biogenesis. I seriously question mitochondrial function and do we need more mitochondria or do we need the ones that we have to actually work better?

I'm not opposed to ketogenic diets short term for therapeutic purposes. But I would -- I quite like them. I mean, myself, I tend to do well on it. But I would tend to want to give things support glutathione synthesis or give glutathione directly for mitochondrial function, things like carnitine, alpha-lipoic acid, n-acetylcysteine for reasons of glutathione. And some of these nutrients that have been really well established to support mitochondrial function.

I don't think you have to go ketogeic. I think that a lower carb sort of Paleo Mediterranean, whatever new diet is out there. But relatively lower carbohydrate, refined carbohydrate, that I think is already been shown to help enhance the function of complex three, for example, in the electron transport chain. So, I don't know if someone needs to go to those extremes. I would have to see some pretty compelling evidence on it in order to do that. So, no, I don't do it therapeutically for that particular reason because I feel like the people that are coming to me could use some other support first, although I'm not opposed to that.

Robb: Right. Fascinating. Holy smokes. Well, I could keep asking you questions for hours. This is totally fascinating and you're about 30 levels above my pay grade on your understanding of this material. Would you be game for coming back on the show maybe in about three months and we could do some questions out to

the listeners and then we can actually get some interaction with folks? Because I know they're going to have a ton of questions.

Bryan: Sure. Absolutely. Yeah, I'd be happy to.

Robb: That would be awesome. Doc, let folks know where they can track you down on the interwebs?

Bryan: Yeah. I don't have a sexy website. I'll be honest with you, I'm too busy researching.

Robb: I like the fact that you and your kids are out there in the garden there. That's actually awesome to me.

Bryan: You saw that? Yeah, we just had baby number five two weeks ago.

Robb: Congrats.

Bryan: So, we're up to five under the age of eight. That's why I don't have a great website is because I'm so busy.

Robb: You're tougher than I am. We stopped at two. That was my breaking point.

Bryan: Yeah. It's so great though, man. It's so great. Yeah, drwalsh.com would be the easiest one. Just drwalsh.com. I keep meaning to get back to that site and do some stuff with it and write some blog posts or do some things but that's a way of getting hold of me. I think a couple of the courses that I offer that have actually been fairly popular with even the lay public can be accessed from there as well.

Robb: Fantastic. Well, Doc, thank you so much for coming on today. What an incredible education on this topic. I felt like I was reasonably well informed on this and I was not. So, thanks for raising the standards on that.

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Bryan: I want to turn around and thank you because, quite honestly, my motivation is to get the best information out there that I possibly can to try to help the most people quite honestly. There's a lot of people that are suffering. There's a lot of people that are looking for answers. And I can only see a finite number of patients as anybody knows.

But you, with the platform that you've built and you've spent so many years and worked so hard to build an audience that you reach, I have to thank you

because, quite honestly, I love researching this stuff. My motivation is truly to help people and if it weren't for people like you that gives someone like me, in this case, a voice to be able to try to help other people out there, so I want to turn that around and say thanks to you as well for all your years of hard work and dedication to build yourself to be what you are so that this information can actually reach a fair number of people.

Robb: Thank you. A long time ago, I had this sneaky suspicion that if I could help a ton of folks I would probably figure out a way to make a decent living facilitating that process and it's worked out reasonably well, yeah. So, thank you. Well, Doc, I will circle back around off line to figure out a date maybe three, four months down the road. We'll collect some emails and I'm really looking forward to having you back on the show.

Bryan: Perfect, man. It's a lot of fun.

Robb: Okay. Well, take care and congrats on the new addition to your family.

Bryan: Yeah. Thanks, Robb.

Robb: Okay, Doc. Take care.

Bryan: Bye.

Robb: Bye.

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