



THE

FATIGUE

SUPER

CONFERENCE

**Why mitochondria, not adrenals,
are at the heart of fatigue**

Guest: Ari Whitten

Alex: Welcome to The Fatigue Super Conference and I'm super excited for this interview. I'm talking with Ari Whitten and I'm interested in this from a couple of points of view partly because Ari and I have a few mutual friends in common. Particularly Niki Gratrix, who's played a key role in helping bring together this conference, and has been saying to me for a number of years there's this awesome guy Ari, you guys would get on great, you guys need to connect. It's never really happened, but it's finally happening now, so I'm excited to connect with Ari from that point of view, but also, I think he and I have quite a lot in common in terms of the people that we are talking to and working with. We're perhaps at slightly different ways of coming that. Ari's work, particularly his focus towards energy enhancement, but inevitably that of course includes many people that are suffering from fatigue as well.

Just to give Ari's more formal introduction before I welcome him. Ari Whitten is a best-selling author and creator of the Energy Blueprint System. He's an energy and fatigue specialist who focuses on taking an evidence-based approach to energy enhancement. He's also the host of the extremely popular Energy Blueprint podcast, which brings together leading experts on the subject of fatigue and energy enhancement to talk about their approach to health optimization. For the last five years he's been working with the world top fatigue researchers to develop the most comprehensive program in the world on the science of overcoming fatigue and increase the energy the energy blueprints. Ari great have you. Thanks so much for making the time.

Ari: Yeah, my pleasure. Thank you for having me. I'm honoured.

Alex: So I think let's just jump straight into it. You shared with me some talking points beforehand, all of which sound pretty meaty, and I'm keen to pick your brain on some of this. So let's start off with adrenal fatigue. Adrenal fatigue is something that there's been a lot of noise about for getting on for I guess probably 30 years in the functional medicine world. And I know you've been deep into some of the science and some of the research on this and I'm

curious as to, you put some debunking adrenal fatigue as a talking point. I have a sense of where you're going to go with this. But yeah, let's just jump in from there.

Ari: Well, let me let me start by saying that my perspective on this is not any sort of perspective that you probably would hear from anyone else. And the reason why is that I've actually myself have done the most extensive review of the scientific literature on this topic that's been done of the link between fatigue syndromes of various kinds, and we can talk about what I mean by that, and cortisol and adrenal function in HPA axis function. And I've actually published it all publicly, it's freely available on my site for anyone to review including literally, this includes every single study that has been done on the relationship between fatigue and cortisol and adrenal function and HPA axis function, that's the hypothalamic-pituitary-adrenal axis, that's literally in existence from 1995 to 2019. And I've published the whole list in chronological order including the actual screen shots of the findings from the research. So like the graphs of cortisol.

Typically the studies compare normal healthy people measure their cortisol compared to people with fatigue syndromes of various kinds and they, you know, map out what the cortisol levels are. So I published that all on my site. So there's one article called 'Is Adrenal Fatigue Real' where there's 79 studies published, it's a long chart. It's basically a short book so it's about 40 pages long. A very extensive literature review and then I just recently also published a broader examination of the whole theory of adrenal fatigue that also looks at the relationship of chronic stress and any link between that and cortisol levels and chronic disease and cortisol levels. So there's these sort of three layers that we can examine to assess the validity of the adrenal fatigue theory.

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And let me back up for just a moment in case somebody's not totally familiar. I'm assuming people are familiar with what adrenal fatigue is, but the basic idea to give the very short explanation is chronic stress, whether psychological stress or depending on who you talk to they may also look at it more broadly as chronic stressors of all types. Whether it's toxin exposures or infections or any sort of total body stress loader, allostatic load, creates a demand on our stress response system, which is often conceptualised as the adrenals or the HPA axis. And this stress load demand on this stress response system over time if the stress load is too high, it sort of wears out the system and eventually the adrenals fatigue or get exhausted or get burned out and as a result can't produce enough cortisol and then you get symptoms. The symptoms that are claimed for adrenal fatigue are obviously fatigue low energy levels, but then a variety of other things like insomnia sugar and salt cravings.

So fatigue, sleep issues these cravings and anxiety and depression and a few others.

So that's the gist of adrenal fatigue, as I said, I've done basically the most extensive review of the literature that you can do on this that has ever been done on this subject. And there's sort of three layers that we could examine to assess the validity of this theory. One is we can look at the relationship of chronic stress of various kinds and see if that actually results in low cortisol levels or any sort of detectable, any sign of adrenal fatigue or low adrenal function.

Another one would be we can look at overt chronic diseases, which are obviously a very, that's a good measure of total body stress load. For example, if somebody has diabetes and heart disease we can obviously imagine that they have a very high chronic total body allostatic load. And so we can assess is there any sort of clear reliable link between chronic diseases and adrenal fatigue or low cortisol levels. And then the other layer, perhaps most important is, we can look directly at the fatigue syndromes. So chronic fatigue syndrome and then there's also several other recognised fatigue syndromes. And slight digression here but adrenal fatigue is not a recognised medical condition. Many people listening to that may not know this but conventional medicine does not recognise adrenal fatigue as a legitimate condition. It's totally not accepted as a legitimate thing. And also there's virtually no research in existence on adrenal fatigue. So if somebody wants to go to Google Scholar right now and type in adrenal fatigue in quotes you'll see that there's literally almost nothing on that subject. So despite this idea of being around for decades, there's almost zero formal research and no research to speak of that has actually validated the theory and shown that adrenal fatigue is a real thing. That's why endocrinologists, MD's who specialise in hormones, do not accept it as a legitimate thing.

So anyway, the third layer is we can look at the evidence around the fatigue syndromes. So the recognised fatigue syndromes are things like chronic fatigue syndrome and then there's a few different names that this goes by depending on the specific researchers and part of the world. But you see things like stress-related exhaustion disorder, burnout syndrome or clinical burnout. And even things like vital exhaustion and maybe a couple different names here and there but the basic idea of those conditions is essentially synonymous with the basic idea of adrenal fatigue, which is that chronic stress taxes the system and over time leads to fatigue and exhaustion. That part is well established. The part of adrenal fatigue. The difference with adrenal fatigue is adrenal fatigue is specifically positing a specific physiological mechanism. They're saying the reason these symptoms emerge is because of what they're doing to the adrenals and cortisol levels, so that's the

difference between adrenal fatigue versus stress-related exhaustion disorder clinical burnout and so on.

So all of this evidence is compiled on my site in a very systematic way, but here's the gist of it to summarise what was literally years of my life to put all this together. So first layer is chronic stress. We can look at lots and lots of different kinds of chronic stressors, so we can look at psychological stress, we can look at 10 different types of psychological stress, from work overload and being in a job that is stressful and is way too demanding. We can look at chronic stress from unemployment, the opposite sort of end of the spectrum. We can look at it from financial stress, relationship stress. Lots of different things. We can look at chronic metabolic stress from cigarette smoking and we can look at the cortisol levels in heavy smokers versus people who don't smoke or light smokers. We can look at it in heavy drinkers versus moderate drinkers versus non drinkers, another kind of metabolic stressor. We can look at it in terms of chronic pain, which is another really good one to assess. We can look at it in terms of over training, too much physical exercise. So we can assess every type of chronic stressor imaginable and these studies exist examining the relationship of these chronic stressors with cortisol.

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Almost invariably, like 99.8 percent of the time, these studies show no link whatsoever with any type of chronic stress in any severity for any duration of time and low cortisol levels. There is no reliable link at all between chronic stressors of any kind and low cortisol levels or anything that remotely resembles any kind of deficit in cortisol production or adrenal dysfunction. And that's across the board. Same thing if we look at chronic disease. Almost every type of chronic disease imaginable, whether we're talking about diabetes or obesity or heart disease or even psychological or psychiatric conditions, various kinds of cancers. I mean almost any conceivable thing that you could think up, even something like autoimmune hypothyroidism, which is often claimed in many health circles to be associated with low adrenal levels or adrenal fatigue. The only research in existence on that subject links it with elevated cortisol levels. And almost across the board with every type of chronic stress that we could look at, every type of chronic disease that we could look at, what we see is either relatively normal cortisol levels or slightly elevated cortisol levels chronically. There is never a point at which never a point at which anything resembling this idea that cortisol goes up initially and then it goes down. There's no research to support this idea of the phase 3 of adrenal fatigue where the adrenals can't produce enough cortisol. Absolutely just flat-out does not exist, absolutely not supported by the scientific literature.

So basically there's a gap here between sort of common understandings of this idea of adrenal fatigue and what is a popular idea in theory and many

especially functional medicine holistic health circles, versus what the actual scientific evidence says. And to be quite honest from what I can tell nobody has actually really gone and reviewed the evidence in that in depth of a way because the evidence is very clear that it does not support this idea of adrenal fatigue. And yet you still have tens of thousands of practitioners claiming to diagnose people with adrenal fatigue.

So the last layer to the story is the fatigue syndromes and there's lots and lots of studies again about 79 studies going back to 1995 through to now looking at these different fatigue syndromes. So some with chronic fatigue syndrome. This idea that chronic fatigue syndrome or fatigue is caused by adrenal fatigue or low cortisol levels is actually been around for decades. So it's been thoroughly tested by researchers all over the world for a long time now. And that research exists, chronic fatigue syndrome, also fibromyalgia also clinical burnout syndrome and stress-related exhaustion disorder and so on and to summarise the whole body of literature here. Basically, here's how the results play out in terms of the numbers. So about 20 of those 79 studies are systematic literature reviews. So there are other scientists who are reviewing the existing research and then there's 59 individual studies. So these are 59 studies where the typical thing is, as I said before, basically get a group of people with let's say burnout syndrome and a group of normal healthy people that are age matched and have similar habits and so on and compare their cortisol levels. And again, there are screenshots of the actual comparison of the cortisol levels between these two groups here's what they find out of these 59 studies, 15 of them showed slightly lower morning cortisol levels. Still total like almost always they still showed normal total 24-hour output. Okay, but specifically as far as the morning increase in cortisol there's, a we got a burst in the morning of cortisol and then declines throughout the rest of the day. In terms of that morning burst about fifteen to 59 studies have evidence for slightly lowered morning cortisol in the fatigued group versus the non-fatigue group. 11 of the 59 studies showed the opposite finding. So they showed slightly elevated levels of morning cortisol and 33 of the 59 studies showed no detectable difference whatsoever between people with fatigue, often times overt, you know, full-blown chronic fatigue syndrome and normal healthy people.

So what this clearly tells you, you know for anybody who's doing a sort of intellectually honest review of this literature, you know, if this was any other case like let's say somebody had a theory that type 2 diabetes was caused by some, herpes simplex virus six or whatever and then they did 25 years of testing researchers all over the world did dozens of tests to see if this virus was present in people with type 2 diabetes and there was some sort of clear link there. And 80% of the studies found that people with type 2 diabetes did not have this virus. What would immediately happen is that the theory would

be discarded that we would all recognise that it's obvious that this virus cannot be causing these symptoms and this is exactly what's gone on with adrenal fatigue in this whole idea that adrenal dysfunction or deficiency and cortisol is causing these symptoms. The evidence is very clear that that's not what's causing these fatigue syndromes and yet we still have, unfortunately tens of thousands of practitioners that are absolutely still convinced that it's cortisol and adrenal function. And honestly, I think that people are just chasing after ghosts here and they haven't actually looked at the literature because we're chasing after this thing that quite clearly is not the cause of these conditions.

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Alex: It's fascinating and there's also an interesting clinical picture that seems to be the case that there are certain patient populations that even if there isn't the deficiencies we're talking about still seem to respond to adrenal support protocols. So I'm kind of wondering how that fits into and how you see the mechanisms of what's happening here. Where be that glandulars, be that bioidentical hormones, be that looking at some of the precursor ingredients there. But yes, it's curious as to how you see that and explaining that kind of vibe literature.

Ari: So there's a lot of nuances here, but let's just say well, I'm trying to figure out where to start here. So, let's say that I have a wacky theory where I say your fatigue is caused by herpes simplex 6 or it's caused by mold spores in your environment or it's caused by, you know, just whatever so some inflammatory cytokine that's gone wacky or whatever and so I say, let's address this issue. By, you know actually let me give you one more example. Let's say it's caused by some gene variant some SNIP of the MTHFR gene and you have poor methylation status. And so I come up with this very elaborate explanation for what's causing your symptoms. And then I say to you here's what I want you to do. I want you to start meditating and I want you to sleep more and I want you to eat more broccoli. Okay, so I come up with specific interventions and strategies to improve your health, which are presented to you as being to fix this particular problem of this virus or the cytokine or this gene variant. Okay, but the reality is that broccoli doesn't just affect methylation. Sulforaphane affects lots and lots of different processes in the body and has anti-inflammatory effects. It affects things going on in the brain it affects hormones, it affects mitochondrial function. Sleep doesn't just affect adrenal function. Okay, sleep affects many, many dozens of different neurotransmitters and hormone systems in the body and mitochondria. Just to give you one example melatonin directly is one of the most powerful mitochondrial protective compounds in the world. Melatonin actually penetrates inside of the mitochondria, protects mitochondria from damage

and boosts internal production of glutathione, catalase, superoxide dismutase. It also affects the neurotransmitters in the brain and as far as sleep and circadian rhythm habits. So what's going on here is a lot of people are saying hey you have adrenal fatigue, sleep more and then if sleep helps them they say see it's because it's fixing your adrenals. The reality is you can tell somebody with poor sleep who has perfectly normal cortisol levels in adrenal function to sleep more and they'll get lots of benefits through lots of physiological mechanisms that have nothing to do with adrenal function.

Now, let's test it more directly. What would happen if you directly modulate, in control for all these confounding variables that I just mentioned, you directly modulate just cortisol levels. Well there there are studies where they've given key people with chronic fatigue syndrome Hydrocortisone and the best controlled studies show that it's no better than a placebo. And the reason the last studies were done on this, back and around 2001 or 2003 and it hasn't even been studied in over 15 years, is because the studies were so unimpressive that researchers stop studying. And that's why it's not common practice. It's not because it's so cutting edge and novel that no one's ever thought of it's because it was around literally 40 years ago and has been tested extensively and found not to work and not only found not to work but comes with a potential host of side effects. Now importantly, when I say not to work better than placebo that doesn't mean that there's some portion of people who won't report benefits because the truth is that in both the placebo group and the cortisone group there was some portion of let's say 20 or 30% of people that claim to have a big improvement in their symptoms and claim to get better. But the important distinction is it was no more than the people who were given a sham treatment and a placebo.

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So, you know, and then we could look at adrenal glandulars. Is there any support for that? No, there's no research basically in existence for it. We could also look at adaptogenic herbs, which are often claimed to support, you know, the adrenal function. The research is very, very unimpressive that these adaptogens have the ability to raise cortisol levels. In fact, you'd be hard-pressed to find anything other than liquorice that has any sort of reliable cortisol boosting effect and liquorice is not an adaptogen. But most of the cases and also this is the same thing as sleep. So I'm not saying adaptogenic herbs are bad. In fact, they have a lot of proven benefits, but they act on many, many different systems of the body different neurotransmitter systems. They act at the mitochondrial level and they certainly do not just act at the adrenal level and there's almost no research in existence to suggest that they're boosting cortisol levels. So you know sort of every layer that you could

look to assess the validity of this adrenal fatigue theory just either the research isn't there at all or it overtly contradicts it.

Alex: What it makes me think of is I remember in the early 2000s that was myself and a couple of other key people here in the UK that were doing a lot of work, working with psychology and what we would call a maladaptive stress response in the chronic fatigue, fibromyalgia and ME population and we notice that by doing certain things to calm down the nervous system and support being in a deeper state of parasympathetic healing that after a while that would have sometimes quite dramatically and sometimes more slowly but have a significant impact in terms of supporting recovery.

Then what started to happen is that it was almost like we started to try to reverse-engineer to try to explain what is the mechanism that's doing this. And this guy called Ashop Gupta he was saying it's the amygdala. So the whole thing kind of came about this amygdala retraining program. And then there was a guy called Phil Parker who it was all adrenal over stimulation. There was some reverse therapy guys, and they were saying it was the hypothalamus so it was almost like people could see there was something going on and when you did it there was an effect and then it was almost like well, we need to find a way to explain that effect that's happening. And it's certainly true in the fatigue population that there are experiences of, we'll come on mitochondria in a moment, but traditional energy production runs out and then they go on to what one might call their reserve tank where they feel tired but wired, over stimulated or indeed for people that are crash the energy comes back and it goes to the nervous system and you see this kind of kind of over stimulatedness which is actually tired but there's a frantic energy that's there.

Adrenal fatigue has been a useful way to explain that because it was a neat almost reverse engineering well that explains this effect that we're seeing. It sounds like, what I'm hearing you saying, for what I kind of started to discover going deeper into some of the stuff partly through learning from you and also from a few others commented in different ways is we might have been a little bit lazy and a little bit quick in terms of trying to explain physiologically something that we know is a true effect in terms of what's happening. Which makes me wonder, I'd be curious as to what language you would use to then explain these effects given that it's not just one hormone or not one part of the brain that that's going on.

Ari: I love what you said right at the end there. I think humans have a weird psychological kink in our armour in the sense that we all have this tendency to want to find the one thing. You know, we want to it's got to be this one thing. No, it's got to be that one thing. You know, we have you know, as you

mentioned Ashop Gupta who's very focused on the amygdala and the limbic system. We have other people who are specifically focused on the adrenals and the HPA axis and other people who are focused on infections and other people who are focused on you know, you have Raymond Parn who's very focused on the lymph system and toxin clearance. And his method for curing fatigue is sort of this lymph drainage therapy and, you have lots of different variations on that. Some people say it's the gut you know on and on and on or it's the autonomic nervous system etc. I think Robert Naviaux work is really interesting because he's done some seminal work with the cell danger response and the metabolic features of chronic fatigue syndrome. And what they did was a meta metabolomic study where they mapped over 600 different biochemical markers and metabolites in the blood in people with chronic fatigue syndrome and they found abnormalities in something like eighty percent of the overall 600 different biochemicals.

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Now what that should tell anybody paying attention is that it's very clearly not just one thing. It's everything. And there may be some key needle movers within that but there's widespread dysfunction. We have to understand that everything in the body, all the major systems in the body are very deeply intertwined. So there's research, for example, now coming out just in the last year or two about how the brain in the mitochondria are intertwined. About how the gut and the mitochondria are intertwined. About the gut brain axis, about the autonomic nervous system, how that impacts neurotransmitters and in the polyvagal theory and how that's modulating. Whether we're in more of a stress state or we're in a safety state which also impacts other things like the gut and inflammation levels and mitochondrial function and hormonal levels and so on. You look at something like circadian rhythm and sleep, circadian rhythms can sleep have widespread hormonal and neurotransmitter effects and mitochondrial effects. So if people can picture what I'm just talking about what you really have is you have these nodes of let's say the brain and the mitochondria and the gut the autonomic nervous system and the liver and the neurotransmitters and hormones and all these different nodes of this network. There's a web connecting all of these different nodes. So it's basically a big spider web of inter related and interconnected factors and it is almost always the case that when one of those key nodes of the system starts to dysfunction, you get dysfunction in the other notes as well. So I like more holistic systems thinking than trying to reduce everything down to its this one thing, let's focus on this one thing.

Now having said that, if you just focus on one thing there is some portion of people for whom doing that will be enough to get significant results. So for example, there's research showing that just working on your gut can

completely cure sometimes people with chronic fatigue syndrome. There's some portion of people who do the Lightning Process or do Ashop Gupta's program who are completely cured by it just by addressing the psychological and neurological sort of aspect of the condition. There's some people who just work on their diet and get amazing results from that. There's some people who just do mitochondrial therapies and get amazing results from that. There's some people, I'm really big into circadian rhythm and sleep, that's the sort of step one of where I start people and just by doing that you modulate neurotransmitters and hormones and mitochondrial function. I've see people very frequently double their energy levels in two weeks by doing that. So you can do just one thing and just work on one node of the network and get amazing results of it. But if you understand that all of these nodes are into interconnected, why wouldn't you want to also create positive inputs into the other nodes of the network.

(35:11)

Alex: And I think often that's the challenge for people when they're on it on a healing path and indeed it's the challenge of practitioners, which if you're going to focus on a few things to start with because sometimes it could be too overloaded to say too many things and other times it can just be confusing of actually, what's happening, what effect is where do you where do you start in that process? And I'd like to come back a bit to what you said about sleep and circadian rhythms. But before we come there may be such a bit more in terms of mitochondria in the brain and how they impact upon energy levels because I think they'll be people that have been listening to as might be thinking but **Ari** you have just torn apart my whole world view. I was told I had adrenal fatigue and I signed up for the fatigue super conference because it said it was good to talk about adrenal fatigue. So if that's not it, what do you see as being the key regulators in terms of people's energy?

Ari: Well, I want to say one thing just to make sure that those people are not really terribly angry with me. I want to be clear about that. Some people don't get this when I debunk adrenal fatigue, they think I'm de-legitimising their symptoms or saying their symptoms aren't real. Your symptoms are absolutely real. I'm just saying the evidence absolutely does not support the idea that it's adrenal fatigue that are causing those symptoms. So we can talk about what is causing those symptoms. Well, there's known research linking many different kinds of dysfunctions as I was just getting at. So there's research showing, for example, in people with chronic fatigue syndrome specific brain abnormalities and activation in certain brain areas that are abnormal or blood flow to certain brain areas that are abnormal. There's been numerous studies that have shown mitochondrial problems. There's numerous studies that have shown that leaky gut and high levels of LPS or endotoxin leaking into the

bloodstream can be a factor for many people and dysbiosis in the gut can be a factor for many people. So yeah, I think basically neurotransmitter abnormalities, hormonal abnormalities, mitochondrial abnormalities, brain abnormalities and those correlate to different lifestyle habits, but there are many, many different layers of those biochemical abnormalities that contribute to these symptoms and are easy to explain all of the symptoms, anxiety, depression sleep issues and fatigue through mechanisms that have nothing to do with cortisol levels or adrenal function.

Alex: It's a failed diagnosis not that the symptoms don't exist. I appreciate you clarifying that point because I realise you're right the certain people are like, what are you saying it's not real but actually it's simply that people have been mis-categorised in terms of what's happening.

(39.11)

Ari: So, I think the brain is a really interesting thing. I think there are a lot of nuances to the brain. I think Ashop Gupta's work is correct in a number of fronts and I think that he's definitely identified a key piece of the puzzle. I think that is also very much interconnected with Steven Porges work around the autonomic nervous system and the polyvagal theory and vagal activation and basically this aspect of our autonomic nervous system deciding whether we are in danger or we're safe and then influencing a number of other, influencing gut function in neurotransmitters and hormones and mitochondrial function in a way that shifts the system either more towards a stress fatigue state or a highly energetic sort of peacetime metabolism state. I also think as I mentioned before, Dr Robert Naviaux's work around the cell danger response is really, really critical in terms of understanding mitochondria as not just these mindless cellular energy generators, but as exquisitely sensitive environmental sensors, and basically, detecting the presence of things like are their toxins present. Is there inflammation present. Is there other pathogens present. Is their psychological stress present and there's even some recent research from researcher from Canada called Martine Picard where they've looked at psychological stress and how that directly impacts mitochondrial function. And also Douglas Wallace. Douglas Wallace, a very famous mitochondria researcher, was part of that research and he said something to the effect of not going to get this quite right but that something like mitochondrial DNA is literally the most sensitive thing in your body.

Now I actually had a little bit of back and forth with Ashop Gupta when I had him on my podcast where he's very convinced the brain is the top of, is the most upstream thing, and I think as Douglas Wallace just said that mitochondria are actually the most upstream thing. And they showed like within a matter of minutes that psychological stress leads to mitochondrial

DNA leakage into our bloodstream and then that leakage of mitochondrial DNA acts as basically a danger signal for the rest of the body to shift more into a defensive state. Now what Dr. Robert Naviaux's work on the cell danger response showed is that basically when mitochondria detect that there is a stressed, there's a danger state whether it's inflammation or toxins or any of these other things, they shift out of energy production towards defense mode and they coordinate a whole cascade of events that shifts the cells out of energy production towards defending against threats. And this is a this is not a mistake. This is not by accident and it's not a pathology. It's the body's intelligent adaptation to these kinds of stressors. And that's important to understand is you know fatigue is not just a pathology, fatigue is a smart adaptation by your body that helps it survive. So when it's under threat from in a microbe, for example, a pathogen, shifting into a fatigue state is part of your body's recovery mechanism. So as you know, making this very practical think of the last time you got a cold or a flu. What was one of the symptoms it was of course fatigue, you know, and that's by design. That's how your body is designed it's when those mitochondria pick up on the danger signals, they shut down energy production and direct resources towards recovery and fending off the threat. The problem is that it's possible to get sort of locked into a chronic fatigue, chronic defense mode state and/or chronic cell danger response state and then have difficulty sort of finding your way back into like retraining your body and your cells and your mitochondria to understand that they're not in danger anymore and it's okay to go back into peacetime metabolism and energy mode.

Alex: What you're say is fascinating it and it brings up a question and I'm mindful of you and I could like a probably disappear down a rabbit hole here of exploration. But what are your thoughts then, given what you've been saying around adrenal fatigue, what are your thoughts, because I think mitochondrial function is something that as you mentioned is increasingly well supported in terms of the literature around fatigue. Would you say that mitochondrial dysfunction, how much of that do you think is kind of like one would look at adrenal fatigue a fatiguing of production of energy or how much of that is a sympathetic nervous system response and therefore producing what you've just described as what I would call a maladaptive stress response and that then being an impact on the mitochondria. Like I guess really the question is what would you say are the primary causes of mitochondrial dysfunction in fatigue?

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Ari: I don't conceptualise it as a sort of wearing down or an exhaustion of the mitochondria. It's a switching off of the mitochondria as a result of danger signals. And that it's a little tricky because there's some nuances here because

damage to the mitochondria and dysfunction of the mitochondria also coincide with this. So factors that damage the mitochondria also shut them down. So there's sort of these multiple layers to it that mitochondria are being shut down, but they're also becoming more damaged and dysfunctional at the same time. And that is also coinciding, I don't think it's necessarily a linear chain of causation, but that's coinciding with some of these other pathologies like different blood flow to certain brain areas and higher activation of the limbic system and shifting more out of ventral vagal dominance in the autonomic nervous system to more of a sympathetic or dorsal vagal dominance that more of a stress state. And many other neurotransmitter abnormalities and other hormonal abnormalities that go along with it. And then also at the same time the more your body shifts into that state you also get effects directly on the gut, so you get gut permeability. And then what does that do now you have toxins leaking in your blood causing chronic inflammation and immune dysregulation and immune over activity that are further draining your energy levels through different mechanisms.

So I think once you get the dysfunction occurring to a significant degree, once it sort of exceeds a certain threshold, then it creates vicious cycles where there's lots and lots of other layers of dysfunction. And even you know, just to name some more, at the cellular level you also can measure things like increased oxidative stress and there's a variety of studies showing for example higher levels of reactive oxygen species and reactive nitrosative of damage, nitrosative stress as well. And you can measure peroxy nitrite and there's sort of infinite opportunities to go down a myopic reductionistic pathway and say it's this one thing, it's that one thing. I mean, there's a hundred different biochemicals that you could identify as abnormal and say this is the one thing that's causing the problem. From my perspective there's a vicious cycle of systems wide dysfunction and the more you can correct as many of those systems of the body through positive inputs and reverse downward spirals of dysfunction and vicious cycles and more and more symptoms and cellular dysfunction and mitochondrial shut down. The more you can reverse that into positive upward spirals of improved cellular function in mitochondrial function and less and less symptoms more and more energy, the more you can break that cycle the vicious cycles.

Alex: Yes, and you mentioned a little bit earlier about the role of sleep and circadian rhythms, maybe touch on that a bit more in terms of what you're really at. What I'm really hearing you say is that it's stress on multiple levels. It's not just psycho emotional stress or physical stress. It's also potentially toxic stress. It's all kinds of different pieces that have the most effect which makes sense. So what are some of the key things like you mentioned sleep and circadian rhythms? What are some of the ways that people can start to reverse these the cycles?

Ari: So circadian rhythm is a big one in my opinion for people who are unfamiliar with it let me give a very brief overview of what it entails. Basically we have a circadian clock in our brain that regulates our 24 sleep and wake cycles and it's pretty much a 24-hour clock. And in response to certain inputs from the environment, in particular light being the main one, this circadian clock then regulates the expression of many different neurotransmitters, many different hormones, many different biochemical processes that directly impact on our energy levels and our sleep.

So just to name a few of the mechanisms here and I have an article where I go through nine different mechanisms by which circadian rhythm can lead to fatigue, but just to name a few, circadian rhythm directly impacts on the neurotransmitters dopamine, serotonin, Gaba and orexin. So dopamine and serotonin are involved in mood and happiness and motivation and energy levels to some degree. Orexin is a key neurotransmitter that not a lot of people have heard of that's actually our primary energy and wakefulness neurotransmitter directly impacted by light exposure and circadian rhythm. And Gaba is a calming, relaxing neurotransmitter that helps us transition out of stress mode and out of activity mode into rest rejuvenation and sleep mode, especially in evenings at night. It's very important.

So what happens, just as one example of this, what happens when you have a deficit in orexin? Well, you have lower energy levels. What happens if you have a deficiency in Gaba? Well, you're going to have racing thoughts at night, higher tendency towards anxiety, harder time sleeping and so on. What happens if you have a harder time sleeping now as a result of that? Well now you start to create vicious cycles where now that impaired sleep leads to other mechanisms which lead to lower energy levels and so on. One other layer that we could talk about is melatonin itself. As I mentioned before, is one of the most important antioxidants and protectors of our mitochondria, our cellular energy generators. It's one of the very few things that penetrates into our mitochondria and there's research actually directly comparing, really cool research, directly comparing the protective effects of melatonin versus some of these synthetic, you know, very expensive mitochondrial antioxidants like Mydo E and Mydo Q the synthetic version of CoQ10 penetrates in the mitochondria. Melatonin is more powerful in protecting our mitochondria. And it stabilises the mitochondrial membrane and, as I mentioned before, it also very importantly boosts internal production of very powerful antioxidant and detoxification compounds like glutathione, catalase, superoxide dismutase, that then sort of create other secondary effects as far as how they protect the cell against a broad range of stressors including toxins and so on.

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So you get these very powerful effects. Now what happens, just as an example, if you live in them in the modern world where you have lots of artificial light exposure at night that is suppressing your melatonin levels and light into the eyes at night, especially blue and green wavelengths of light directly suppresses melatonin production by your pineal gland in your brain. Most people think melatonin is just a hormone that's involved in helping us sleep but as I just explained it's also directly involved in energy production at the cellular level and protecting your mitochondria from damage. So what happens if that hormone that's so critical for protecting your cellular energy generators, is only produced at 50% of the amount that it should be produced every night? For week after week, month after month, decade after decade. Well, what happens over time is now your mitochondria are not being protected and stabilised and the cells are not producing enough glutathione and superoxide dismutase and all these important compounds to be able to protect themselves from damage. So over time you're weakening yourselves, weakening your mitochondria and making them highly susceptible to being damaged and dysfunctional and to lowering what I call your resilience threshold. Which is your cellular capacity to handle the stressors of life, whether psychological stress or toxins or anything. You're lowering that resilience threshold and making it so the mitochondria are much more easily overwhelmed by those stressors and are much more likely to be shut down and go into cell danger response mode where they turn off energy mode and shift into defence mode.

So, that's just to name a couple of the key mechanisms of how circadian rhythm works. One other one that I want to mention it's a nice point for maybe some of your listeners familiar with Raymond Parn's work is circadian rhythm optimisation and optimising your light exposure habits also impacts the depth in the quality of your sleep. So just as it impacts melatonin, just as it impacts these neurotransmitters, it also helps you sleep a lot deeper. Well one of the things we now know, just in the last couple years is this glymphatic system of the brain, which has been shown to basically clear out toxins and damaged and dysfunctional cellular waste products, our cell parts and waste products of the neurons in the brain. That happens when we sleep at night. Now circadian rhythm directly impacts the depth and the quality of your sleep. So it impacts on the ability of your brain to drain itself of the accumulated toxins and waste products and damaged cell parts each night. So it directly links up with Raymond Parn's ideas as well. So if you have disturbed sleep and circadian rhythm, you're also much more likely to have those talks and drainage problems. And one more point I'll mention here is autophagy which is cellular repair and regeneration, cleaning up these damaged cell parts and mytophagy, cleaning up the damaged mitochondria and rebuilding new healthy ones. That also occurs during sleep. So if you have poor circadian rhythm habits, you have poor quality sleep you have less

efficient autophagy and mytophagy, which means over time you're running basically today on yesterday's cell parts and mitochondrial parts, instead of rebuilding and recycling them as you should be doing. So that's just to name, I think what was that four of the nine mechanisms of how rhythm impact energy levels.

Alex: It's fascinating and I just want to touch on something that people that are thinking oh great melatonin for example is really important. I'm just going to go and supplement melatonin. Maybe just say a bit about how effective some of these things can be in shifting that versus just trying to take a very crude intervention with a bio identical hormone for example.

Ari: In general I think there's a place for melatonin but I think it's more as a short-term intervention to help re-regulate a really dysfunctional sleep and circadian rhythm pattern. But there seems to be some negative aspects of melatonin supplementation. It's an interesting thing because I see that there's kind of a discrepancy between the anecdotes I see versus the research. And there's really a lot of very positive research on melatonin use but then, sort of on a more anecdotal level we see lots of people who get dependent on it who seem to be unable to sleep without it and so in other words, it's sort of interfering most likely with your body's own natural production of melatonin. So I think there's some problems with it. It's always best to optimise your body's own production of hormones rather than relying on external hormones. And that's what's melatonin is, even though it's sold as a nutritional supplement. It's important to understand this is a hormone that's produced by your body, produced by your brain. In accordance with the signals that it's getting from the environment so you don't want to just say I'm going to fix it by popping a pill. What you really want to do is correct the underlying causes for why you might have a deficiency of that in the first place.

(56.37)

Alex: Absolutely and I'm mindful of time but just before we come to how people can find out more about you and your work maybe just any other kind of key points, almost like a whistle stop tour of things to check out in terms of you've talked about circadian rhythms about importance of getting quality sleep. What are some of the other pointers are the bits that you would recommend people make sure that they're touching them?

Ari: Well, I'll just give a quick overview of my system so people can get an idea of the factors I think are really important. Module 1 is circadian rhythm and sleep. Module 2 is brain and nervous system inputs and Niki Gratrix is actually a big part of that module of the program talking about her work with regards to how the brain functions and how to use strategies to reprogram

your brain and your autonomic nervous system. Module 3 is nutrition for energy enhancement. So how to use nutrition to optimise hormones and neurotransmitters mitochondrial function. Module 4 is healing the gut so fixing gut permeability and gut dysbiosis. Module 5 is detoxification. So specific protocols to help get rid of accumulated pollutants and heavy metals and BPA and phthalates and other chemicals that bio accumulate. Module 6 is hormesis, which is actually my favourite topic and we didn't really get into here but is basically the concept of transient metabolic stressors and how those create beneficial adaptations in our body. In particular how they can build up the mitochondria to be bigger and stronger and become capable of producing more energy. And one other thing that's a big part of my work is light as well. So light is an extremely important part of optimising our health that not a lot of people are aware of but there's five different types of bioactive light, UV light, far infra red, near-infrared, red light and blue light and they all have various layers of important physiological facts. I consider them light nutrients, in much the same way we conceptualise nutrients from food. We need adequate amounts of these nutrients from different wavelengths of light to optimise our cellular and hormonal and mitochondrial function as well. So that's sort of a brief overview of the general factors that I think are really important

Alex: Fascinating. I wish we had more time but in the interest of time for people that want to find out more about you and your work, what's the best way to do that?

Ari: They can go to my site theenergyblueprint.com I have lots of articles and podcasts available for people, lots and lots of free content. I'll also have a free eBook on a guide to supplement science-based guide to supplements for energy enhancement overcoming fatigue. So, that's the theenergyblueprint.com

Alex: Awesome. Ari thank you so much. I really enjoyed this conversation. Thank you.

Ari: Yeah me to. Thank you so much for having me.