KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

ADAPT Bonus Interview with Thomas Guilliams, PhD

Chris Kresser: I'm really excited to be talking with Dr. Thomas Guilliams today about the myth of adrenal fatigue.

Thomas Guilliams earned his doctorate from the Medical College of Wisconsin in Milwaukee, where he studied molecular immunology in the Microbiology Department. Since 1996, he has spent his time studying the mechanisms and actions of natural-based therapies and is an expert in the therapeutic uses of nutritional supplements. As the Vice President of Science and Regulatory Affairs for Ortho Molecular Products, he has developed a wide array of products and programs which allow clinicians to use nutritional supplements and lifestyle interventions as safe, evidence-based, and effective tools for a variety of patients. Tom teaches at the University of Wisconsin School of Pharmacy, where he holds an appointment as a clinical instructor, and at the University of Minnesota School of Pharmacy and is a faculty member of the Fellowship in Anti-Aging, Regenerative, and Functional Medicine, A4M. He lives outside of Stevens Point, Wisconsin, with his wife and children.

The Point Institute was founded by Dr. Guilliams as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals—dietary supplements, herbs, vitamins, minerals, etc.—as therapeutic and preventative agents in clinical practice.

As you know, we're using Dr. Guilliams' excellent book, The Role of Stress and the HPA Axis in Chronic Disease Management, as the textbook for the HPA axis dysfunction unit in the ADAPT Level One Functional Medicine Training Program. I came across this book some time ago, and I had, for many years, been skeptical of the so-called adrenal fatigue hypothesis because I was never able to find any research to support it in the peer-reviewed literature. It just didn't really match with my understanding of the HPA axis and the sympathoadrenal medullary system and the role that they play in regulating stress tolerance and how stress affects the body in health and disease. I had done a lot of my own research, but I had never come across a resource that summarized all of the problems with the adrenal fatigue hypothesis and then replaced it with a more cogent explanation of what's going on that is in much closer alignment with the current scientific evidence base, and that is definitely Dr. Guilliams' book, so I'm really excited to be speaking with him in this bonus interview for the ADAPT Program, and I hope you enjoy it.

Dr. Guilliams, thank you so much for talking with me. I've been really looking forward to it.

Thomas Guilliams, PhD: I've been looking forward to this, as well.

Chris Kresser: Maybe before we jump into the meat and potatoes, you could just tell us a little bit about your background and how you got interested in the adrenal fatigue hypothesis and when you started to question that.

Thomas Guilliams, PhD: OK, well, my background is a PhD in molecular biology, which I finished in the molecular immunology area back in the mid '90s. I made it sort of not intentionally into sort of a functional medicine, integrative medicine community, being put in charge of the science and regulatory affairs of a company and was working with healthcare professionals in the dietary supplement world. That's where I started two decades ago, and maybe unbeknownst to me at the time, if you remember the mid '90s, DHEA was going to be the supplement that was going to be the anti-aging—

Chris Kresser: Cure everything. Yeah.

Thomas Guilliams, PhD: Yeah, cure everything. So at that time, there were a few labs, and a number of labs were breaking off from some of the early labs that had done some of the initial salivary testing, salivary cortisol, and DHEA and some other things. I knew one of the smaller labs at the time, BioHealth Diagnostics, and the person that was running it, Bill Timmins, and so I initially got sort of integrated into that in talking with him years ago. Of course, at that time, the language, as you mentioned, the adrenal fatigue language and a lot of the phenomena that I've since sort of come to question or at least maybe needs to be tweaked a little bit. At that time, nobody was really looking into it in detail, and I had written about stress and adrenal issues back in the late '90s on that, and it was only probably in the last 10 years that a number of different people, myself included … I think maybe you know Lena Edwards and Andy Haman and some of those people. There were a lot of discussions about the fact that the literature wasn't really confirming these things, but as far as I could see at the time, nobody was really truly fully investigating it. Two years ago, I was renewing one of the projects I was working on and doing this series of roadmaps, and I decided to plunge neck deep into this and to really figure it out, or at least try to get farther in figuring it out than currently was out there. The book that came out last year was sort of the culmination of what I would say is phase one of that investigation. What I learned wasn't overly surprising, but what I learned is that the functional medicine community was pretty advanced in looking at certain things that other parts of the medical community wasn't looking at, and that is the role of stress in chronic disease, but they had sort of really not fully investigated where the science was moving in the clinical research community, and so that's one of the things that obviously I tried to accomplish in this project.

Chris Kresser: Right, which is a fantastic book, by the way. We're using it as a kind of textbook in the HPA axis section of my training program, so everyone listening to it should probably be familiar with the basic concepts, and we can just kind of dive right into it today as we talk, with that assumption in mind.

From your perspective, what are the biggest problems with the adrenal fatigue model? If I could just summarize it briefly, the typical adrenal fatigue hypothesis is based on Hans Selye's general adaptation syndrome. The idea is that you'll see a progression of cortisol and DHEA levels over the course of time that goes from high cortisol in stage one, and DHEA and pregnenolone start to drop. Stage two, cortisol starts to fall and DHEA and pregnenolone continue to drop, and then stage three, they're all three continuing to drop until they reach failure or exhaustion. I think everyone who is listening to this show is familiar with that model and has been exposed to it to some degree, so what's the problem with that?

Thomas Guilliams, PhD: Well, there are a couple of different issues with that as a model, and we can maybe talk about Hans Selye. Whether he was really at fault for causing us to go down this road or not, I'm not sure, but there are a couple of different issues. One is just because we're measuring adrenal hormone output does not necessarily mean we're measuring adrenal function, meaning that in many cases, as we'll talk about, that the changes, either high or low, of adrenal hormone, especially cortisol output, are being driven almost exclusively by the brain. So modulations or changes, especially those that decrease cortisol output, are mostly an adaptation to something, usually stress or some other phenomenon going on, a chronic disease phenomenon, that is occurring in the brain, and it doesn't necessarily—in fact, in almost no cases is it related to fundamental inability for the adrenal gland to produce more cortisol.

Unfortunately, the adrenal glands obviously are involved—it's the HPA axis, after all—and oftentimes fatigue may be part of the phenomenon. So unfortunately, over time, it became sort of easy to view adrenal downregulation or low levels of cortisol as being equivalent to atrophy of a gland or time or something like that. Or maybe even beta cell function with the pancreas. And so this phenomenon just started gaining its own momentum. Unfortunately, and maybe we don't have time to get into this, but adrenal insufficiency, once you get into secondary and tertiary adrenal insufficiency, even that language should be really changed because most of that also is in the brain. Other than primary adrenal insufficiency, most secondary and tertiary adrenal insufficiency also from a traditional nomenclature, should really be HPA axis downregulation, as well. So the problem is not just with the functional medicine community. It's really with our whole understanding of these phenomena.

Chris Kresser: Right, and what's interesting to me about that is I have a friend and colleague who has studied the neurobiology of weight loss, and he has argued—as well as many people in the field argue—that it's a similar situation with insulin and leptin regulation, primarily is the hypothalamus in the brain, and the mechanisms that govern the homeostatic and hedonic regulation of weight exist primarily in the brain, and the downstream effects of those mechanisms show up in fat cells and muscle cells, but the regulation is really happening in the brain. It sounds like you're saying something with the adrenals, where the adrenals are the kind of final result of where they produce cortisol or don't produce it, but all of that signalling is coming from further upstream.

Thomas Guilliams, PhD: Right. Obviously there are some subtle things. Obviously the adrenal glands are involved in the process and there are some subtleties, but I think it's helpful and maybe

more correct to think of it as an adaptation going on in the brain because most of the controlling factors are occurring in the hypothalamus and maybe even in the higher orders of the brain and then the feedback processes that allow cortisol as a signal in the brain to be interpreted by those tissues. So the adrenal glands are not completely out of the loop, but for the most part, the corrective that we need to do is stop talking about adrenals and really start thinking about the stress response and the HPA axis, and then, I think, when we get back into the nuances, there are some things that we can talk about that the adrenal glands may be part of, but I think we've certainly overemphasized that to the degree that it's not helpful.

Chris Kresser: Right, and I think you raised a great point about how it's compelling, in a way, and that probably explains why it has become so entrenched to the extent that it might be difficult to reverse.

Thomas Guilliams, PhD: Right.

Chris Kresser: Someone who is really tired can kind of simply relate to the idea that their adrenals might be tired, too, and unable to produce cortisol. It's just a kind of easy way of explaining it to patients. Patients can kind of get that, and it fits with their subjective experience of what's going on, but I think having a more accurate framework is really important because you talk about, in your book, the four primary drivers of HPA axis dysregulation being perceived stress, which is, of course, what most people think of when they think of stress, but then circadian disruption and inflammation and glycemic dysregulation as stressors. I think what's important to me as a clinician and even what should be important for patients or consumers who are hearing about this stuff is when you move away from the idea that it's just tired adrenals and that it's dysregulation of this complex system called the HPA axis, you start to understand that these other factors like inflammation and circadian disruption and glycemic dysregulation are just as important as perceived stress in terms of affecting this axis, and it's not all about the adrenals.

Thomas Guilliams, PhD: Right. I think one of the aspects of getting away from the oversimplification is that now we can realize that the leveraging points that we have are also outside of the adrenal glands. For instance, when we think of, well, my adrenals are tired, so I need to give them some help, there are very limited things that we can do that really, truly support the ability for the adrenal gland to take ACTH as a signal and upregulate or change its cortisol output, but there's lots we can do to affect the HPA axis, the incoming signals like we just mentioned. What is causing the brain to believe that it needs to create a signal or change the adaptation to the stress response? And second of all, there's lots that we can do on the other side that is at the tissue level, managing the cortisol sensitivity and the cortisol response at the tissue level, outside of the adrenal glands, as well. When we start thinking big picture, then we realize that there actually is a lot more we can do to help a patient with HPA axis dysfunction.

Chris Kresser: OK, so we know that when cortisol is low, and we could talk more about whether cortisol is actually low in a lot of patients that have so-called adrenal fatigue, but let's assume that it is low in some of these patients, and let's assume that they don't have Addison's disease or they haven't been on long-term glucocorticoid therapy, which are two of the main reasons that you

might actually see low cortisol that's caused by poor adrenal output or adrenal insufficiency. What are some of the mechanisms? We don't have to go into a lot of detail because I cover them in the course, but what are some of the mechanisms that have nothing or little to do with the adrenals themselves that could lead to hypocortisolism?

Thomas Guilliams, PhD: Well, probably one of the most classic examples would be PTSD, where you have a traumatic downregulation of the HPA axis, and what we typically think of when we think of PTSD, maybe it seems obvious that the body is trying to protect itself from excess production of cortisol, which is a catabolic hormone, and so at very high levels. So if you look at other compensatory changes in, especially, adults with PTSD, you'll see low cortisol output, but you'll also see elevated levels of cortisol-binding globulin, which is another way to protect the body from free cortisol, and you'll see, in many cases, high levels of DHEA, which is also another way to protect. In that case, it's more of an acute downregulation.

Let's take seasonal affective disorder. Here's a situation where, especially in the winter, you'll see people with a lower cortisol output, especially in the morning, whereas in the summer it will be close to normal. Here you have probably a circadian or a light-induced suppression of the HPA axis, so you might see that downregulation in some patients with depression, and we're learning perhaps now that really the brain itself is seeing the information. The feedback inhibition for cortisol in the brain is hypersensitive, and it's reducing the levels of the need for cortisol output.

These are a number of different situations, and what we see in the literature, in true burnout where we have a stressful scenario that has gone on long enough, you will see what used to be considered sort of stage three, where we actually see a hypercortisol-induced hypocortisolism. All of these would be sort of seen as a downregulation of the HPA axis. Ironically, interestingly, when you go to some native cultures, like the Tsimane tribes in South America, when they looked at their salivary cortisol levels, they found them to be very low, and there are sort of two interpretations for that. One was, well, they have low amounts of stress, but when they started looking at the other things, they realized that they did have some stressors in their life, but low cortisol levels can also be a compensatory effect for a need for a high immune function because cortisol is an immune suppressor. There are a number of different things that are out there. I think the ones that you're going to run into the most are the ones I just mentioned.

Chris Kresser: Right, and this gets even more complex when you start talking about the potential discrepancies between cortisol that can be measured in the saliva and serum and hair and urine and the tissue-specific bioavailability of cortisol. I know I've seen some studies—and you were just alluding to this, I think, with the Tsimane—on infection, both acute and chronic, where you see impaired cortisol signalling at the tissue level and cortisol receptance, downregulation of the receptor sensitivity or even just downregulation of receptor expression, and the challenge, it seems, is that's not going to show up on a lab test, at least none of the ones that are available to us as clinicians right now, where you could actually see high levels of cortisol, but physiologically the patient is suffering from hypocortisolism.

Thomas Guilliams, PhD: Right. I think one of the things that was eye-opening to me in this process, which I should have expected because working with clinicians for the last decade or so and talking to them about various tests, mostly salivary hormone testing, and the complications and the number of patients that didn't seem to fit the profile or fit into what they were analyzing from other stress-induced issues, tells us that, yeah, there's a lot more going on, and the generic serum levels that may be coming out in saliva—or in urine, even—are modulated at the tissue level with either glucocorticoid receptor sensitivity and changes that are posttranslational changes because there's really only one gene for that, or changes in cortisol-binding globulin. We thought the liver was the producer of cortisol-binding globulin just like naively that's been taught in medical school, that the liver produces whatever hormone or enzyme or protein that we talk about. Then we learn all of a sudden there's cortisol-binding globulin produced in the brain and in other tissues, and we realize now every tissue is sort of modulating its own cortisol response in a very unique way, so that obviously alters our understanding of what's happening in the patient.

Chris Kresser: Right, and we now know that even corticotropin-releasing hormone is expressed in the skin locally and in the gut, and I've read that some consider that there's a mini-HPA axis in the skin. It's really so much more complex than the adrenal fatigue idea originally let on.

Thomas Guilliams, PhD: Exactly. The whole CRH story is very interesting. Not only are there CRH receptors in many, many tissues—and actually there are two different types of receptors, CRH1 and CRH2—but then we have the production of CRH from other tissues, especially immune cells in the gut, that we know about, but like you mentioned, the whole idea of the skin. We're learning about almost a whole separate signalling cascade that occurs in the skin. But I guess, in some ways, you could have predicted that or maybe should have predicted that something would be going on because the skin and the GI tracts are surveillance systems, just like the brain, and so coordinating these in a tight fashion, allowing them to protect themselves in a stress response manner, might be what we would expect.

Chris Kresser: And even just observationally, Stokes and Pillsbury back in the '20s and '30s were talking about the gut-brain-skin axis and this triad of symptoms, and anyone who has been in clinical practice for a while will know that it's very common to see symptoms along that triad in patients. So even without knowing the science, it seems like there's some connection there.

Thomas Guilliams, PhD: Right.

Chris Kresser: Let's talk a little bit more about the three-stage model, and, yeah, feel free to talk a little bit about the history with Hans Selye. What is right about that model and what is wrong about that model when we use it to talk about the progression of this syndrome?

Thomas Guilliams, PhD: If you go back to Hans Selye, he put animals in stressful situations, and he was able to sort of follow them along, and his interpretation or his definition of stress was sort of very pathophysiological changes and erosions in the gastrointestinal tract, hypertrophy of the adrenal glands, and shrinking of certain lymphatic tissues. He was looking at sort of really gross

changes, which he was causing to have happen in animals in ways that you can't really stress animals anymore legally, and most of these animals were unable to compensate for those stressors because they were direct. Either they were tying animals down or doing other things to them that they couldn't escape. Obviously, in some ways, that is somewhat of an artificial way of stressing humans, although we do see people that have gone through traumatic experiences like that have dramatic HPA axis responses.

So in one respect, he saw these three stages. There is this immediate change in pathophysiology, which he called the alarm stage. Eventually they seemed to adapt to that, or at least the physiological changes were no longer as obvious in those animals, but then eventually they would have what he called the exhaustion stage, the inability to adapt any longer to that stressor and it eventually could kill the animal. Those gross, big changes were thought to be occurring in all stages over time. He didn't measure corticosteroid levels in the classic way that we do now, so he didn't really measure hypercortisolism and then a normal cortisol level and then a depletion. That is something that we layered on afterwards, but it is true that there seems to be, in some individuals, especially when there's been a chronic stressor, and probably the majority of studies that this has been done in are, I hate to say it, but government employees that have been working a long time, or teachers oftentimes are studied with this classic long-term burnout and these kinds of things, and I think you do see a trend where people go through a hypercortisol level, and this hasn't been done well in the literature over time, but I think we see it especially in the morning. So if you take somebody who has a stressful job, for instance, and you look at their morning cortisol levels, they're typically higher than somebody who has a less stressful job. Then eventually, and usually this takes decades, but eventually you will see people who are determined to have what is clinically referred to as burnout, to have low levels of cortisol.

Ironically, when you look at the studies, and there was actually a study that looked at this, and they had some anomalies when they started looking at the salivary cortisol levels versus the serum cortisol levels, and this is the problem with averaging. What they did is they averaged people without burnout with people with burnout, and they found out the people that had burnout had higher levels of serum cortisol, but they saw two groups of individuals, and some of them had low salivary cortisol levels. Well, they went back into that group, and they realized they didn't have one group of burnout people, they had two groups. One was truly in burnout, and they defined them as people who were producing low ACTH, low serum and low salivary cortisol, but they found another group of individuals who had elevated ACTH, elevated serum cortisol, but they still had low levels of free cortisol, and they found out that the first adaptation, or what they presumed the first adaptation was, they were upregulating their cortisol-binding globulin to protect themselves from that. So it does seem like there are phases by which an elevation of the stress response, elevation of ACTH, eventually turns into an adaptation of what we might determine as hypocortisol. I think it's probably gradual, and there are probably not stages. Those are very convenient for some individuals who are experiencing certain aspects. I think it's probably true that if you have someone with a gradual, chronic stressful situation that's been going on for a long period of time, that you might see these sort of stages or progression; however, there are many other things going

on that would be sudden, that would be much quicker, and we wouldn't see these sort of discrete little phase one, phase two, and phase three.

Chris Kresser: Right. It's not mechanical like that, and it seems to happen differently in different people, and there are exceptions to the rule, where if someone could maybe go straight to phase three or someone could stay at phase one—so-called—for an indefinite period of time.

Thomas Guilliams, PhD: Right, and that's why I'm trying to get the language away from even the idea of stages or phases. I think it's just better for us to describe what it is—hypocortisol, hypercortisol—and we can talk a little bit later about pregnenolone, but the chart that most people see—in fact, one that I've used in the past and I show in the book as a way of explaining it—where pregnenolone is seen sort of as the hormone that can go one way or the other, is very misleading, but it gives the idea that the adrenal glands have the angel on one side and the devil on the other. Which do I need to make? Do I need to make DHEA, or do I need to make cortisol? And eventually it goes one way and not the other. That's a very misleading understanding of how the adrenal glands function.

Chris Kresser: Mm-hmm. You mentioned pregnenolone, the pregnenolone steal. Let's talk about that since that's another kind of key pillar of the adrenal fatigue model, this idea that there's a pool of pregnenolone available for production of hormones, and when a patient is under stress, they divert more of that pregnenolone into cortisol production, and then less is left over for anabolic hormone production, like DHEA and then estrogen and testosterone. What's wrong with that picture?

Thomas Guilliams, PhD: Well, it's interesting because this has been taught by lots of people for many years and seems very logical because most clinicians, most people, learn steroidogenesis from these large charts that show all the different hormones available from cholesterol all the way down to androgens, the estrogens, and of course, cortisol and the other hormones. While it's very convenient to learn steroidogenesis that way, what is often not understood, or not remembered, is that all of those pathways are not available to every steroidogenic cell. This is sort of just a biochemical way of explaining how, if those enzymes were available, you would convert these. As it turns out, the adrenal cortex is three different steroidogenic cells. What makes a steroidogenic cell steroidogenic is the ability to convert cholesterol to pregnenolone. All three of the zona reticularis, fasciculata, and... my brain is blanking on the third, but all three are able to convert cholesterol into pregnenolone—and that, of course, occurs in the mitochondria, by the way—there's no way that we know of to take that pregnenolone and shift it from the zona fasciculata, for instance, that produces cortisol, to the reticularis, or vice versa. That initially is sort of a problem.

Number two, the regulation or the ability for those tissues to determine what they're going to do is regulated by many, many different factors, so the idea that there is cholesterol being produced, made into pregnenolone, and there's sort of a central pool for all these tissues, all these different cells, to come in and say, "I'm going to take the pregnenolone out and use it for cortisol so there's not enough available to make DHEA," is just not biochemistry. It's not part of it. But probably more convincing than anything else, is the fact that, unfortunately, when we look at salivary levels,

salivary cortisol and salivary DHEA levels, they all are fairly close. They all are very similar in concentration. However, what most people don't realize is that the daily production of DHEA—sulfate primarily, because most of it is sulfated—the daily production of DHEA sulfate is orders of magnitude higher than cortisol, maybe up to a thousand times more, maybe even more if you take the whole day's amount into play. So the idea that cortisol, which if you needed, let's say, the precursor of pregnenolone to make cortisol, it's about 0.2 to 0.5 percent of the available pregnenolone needed to make DHEA, so even if you doubled or tripled or quadrupled the need for cortisol, you're not taking away enough pregnenolone—if there were a pool—to change the DHEA sulfate production. So biochemically and just mathematically and all these kinds of things, this idea is just not at all a feasible explanation. However, it's one that some of the labs have promoted as a way of explaining why, under stressful situations, DHEA levels decrease. It guess it's a convenient way, and there have been online videos and all kinds of things explaining this, but from my discussion with a number of adrenal steroidogenic people and, of course, just the math itself, I think it's completely a debunked idea.

That's not to say, again, that there's not some regulation, probably ACTH-driven and inflammatory-driven processes, which can cause a lowering of DHEA in stressful situations. That's clearly true. I don't want to make it sound like stress doesn't perhaps accelerate the ability for the zona reticularis to reduce its ability to produce DHEA, DHEA sulfate.

One of the other things that was probably eye-opening for me in this process was the lack of understanding that we have in exactly how the zona reticularis functions, and it has a lot to do with the fact that animals that we study, mostly laboratory animals, don't produce DHEA from their adrenal glands. They produce it in their gonads. So we would have to study primates to really understand how the zona reticularis, which isn't even really formed when we're born, how that develops over time, peaks in its production around 25 to 30 years of age, and then slowly begins to atrophy. We know virtually nothing about that process. It is very likely that stress and the HPA axis, stress does perhaps accelerate zona reticularis atrophy or dysfunction, and so that's something we need to learn more and more about.

Chris Kresser: Right, but it's not via the mechanism of pregnenolone steal.

Thomas Guilliams, PhD: Exactly. Right.

Chris Kresser: Yeah. Let's move on to talking a little bit about saliva cortisol testing. This is the form of testing of all of the different ways of testing cortisol that has been favored in the functional and integrative medicine community, and there's a lot of evidence that supports saliva cortisol measurement, so it's not necessarily a problem with saliva cortisol testing inherently. It's maybe more of a problem of how it's being deployed and interpreted that we're facing in terms of this adrenal fatigue hypothesis. So let's talk a little bit about some of the problems with the currently available commercial assays for the adrenal stress index and the instructions that are provided with those labs.

Thomas Guilliams, PhD: This is an area I spent quite a bit of time on because initially I got involved in this with the idea of trying to understand the testing side of things over a decade ago. One of the things that I spent quite a bit of time on is this particular area, and thankfully, I've been able to take this information and the book that I have written and many things, and we were able to invite, I think, seven of the labs that are probably the most common labs that provide salivary cortisol and DHEA testing to the functional medicine community and present this information, and I can just tell you that they received it well. They, I think, collectively understood that they had maybe neglected to stay up to speed on many of these things, and many of the things that I critique in the book are starting to change. Several of the labs are offering things they didn't offer before. If we go back and we say most clinicians will realize that, I think, the majority of the labs still offer what I consider the standard four-point cortisol test, and this is usually spinning in a tube or a salivette that you can put in your mouth, and typically the labs will collect a morning cortisol, a mid-morning, a mid-afternoon, and then before bed. We actually went through, I think, 10 different labs that offer this, and we couldn't find two that actually described the timing the same, which was pretty shocking actually. Some of them were very close to what we would recommend. That would be first morning cortisol at 30 minutes after awakening. Probably 30 to 45 minutes is probably acceptable, as long as the lab is collecting those.

Something I didn't mention and I've just recently seen in the literature is that women seem to have a salivary cortisol peak that's closer to 45 minutes, men, closer to 30 minutes. That may account for the 30 to 45 minutes that you see when you're using both men and women, but interestingly, the women seem to be slightly delayed from men. I'm not even sure why or if that's been discovered why.

But what we learned was there were several labs that would say things like take the first salivary cortisol test within an hour of awakening. Others would say to do it between 6 and 8 a.m., not specifying how that related to awakening. Other labs did specify something like 30 or 45 minutes after awakening, but maybe didn't emphasize how important that was. So unfortunately, when you collect between 6 and 8 a.m. and you happen to wake up at 5:30 in the morning, obviously 7:45 is not really going to be very helpful if it's two hours after awakening. What we learned from that is that the cortisol awakening response, which is a very specific HPA axis response to awakening, occurs in saliva 30 to 45 minutes, and if you miss that window, you will often maybe unfortunately diagnose somebody with hypocortisol levels because the total amount you're going to measure in the saliva is going to be greatly impacted by that first collection.

Chris Kresser: That first cortisol awakening response represents 50 percent or more of the total cortisol produced in a day.

Thomas Guilliams, PhD: Right.

Chris Kresser: So if you miss that 45 minutes or an hour, you're way low.

Thomas Guilliams, PhD: Right, and so I think what has happened oftentimes is clinicians have overdiagnosed low cortisol levels because they've missed that, or it has confused the process quite a bit because they've missed that. And maybe even when they retest, if they didn't do it right the first time and they changed it the second time, following a very poorly described way of doing it, a clinician may try to interpret that as being a change when really it was sampling error or sampling difference, not a physiological difference.

Chris Kresser: Right. That's one problem here. Another problem... or maybe not a problem, but something that would be nice to have access to as clinicians is, as you point out in your book, there's so much literature on the CAR, cortisol awakening response, and its relationship to various diseases and disease outcomes, and yet we don't really have commercial tests for CAR available to us. I mean, we can kind of hack it by just getting the four tubes and doing it and measuring the percentages, but it's not going to look nice in a report, and the patient is going to be confused. Did you have any discussions with any of the providers at that meeting about offering CAR? Have you heard any progress on that?

Thomas Guilliams, PhD: Obviously if your listeners have read the book they know the details of what we're talking about, about the CAR itself, but there are two things that I had advocated. One is to actually offer within the test menus a true CAR, which means time zero, 15, 30, 45, and 60, or something like that, where you're sure to span the peak and understand the dynamic between the time they awaken and about an hour later and you can capture that whole dynamic peak. That's one thing that I believe that labs should offer as a separate test, with the instructions there, because probably that's the most used salivary cortisol analysis for stress research, so if a clinician wants to compare a patient with something they've read in the literature or whole groups of pieces of information that are in the literature, they can do that.

The other trend that is, I think, probably more acceptable or more broadly used is a trend that's used in the literature where we incorporate a diurnal cortisol, which is what most people are sort of familiar with, but also including a time zero. You start with the first salivary sample at time zero. Typically the second one is going to be 30 minutes afterwards, and then follow that up with two or three more, so probably five would probably be a good number to have, and that way you can see what's happening throughout the day. You can see that sharp drop between the cortisol awakening response and, let's say, noon, which should be sharper than the flattened between, let's say, noon and before bed. But you can also maybe capture things like a hypoglycemic event, or you might be able to capture exercise that you wouldn't necessarily be able to capture in that first hour only.

I'm an advocate for both, and I know several labs are now telling clinicians that they offer, like, six tubes and they can do different things. I don't know specifically that any have created either a true CAR or they actually show exactly with new instructions on how to do that. I know several of them are working on that. One of the issues that they run into is they have to create new reference ranges and these kinds of things for these tests, so it's not something that they can come up with immediately, but I'm going to continue to push them, and hopefully soon they'll be offering that.

Chris Kresser: Yeah, and it requires a whole reeducation process for clinicians and patients taking the test.

Thomas Guilliams, PhD: Exactly.

Chris Kresser: Yeah, that's interesting. It's like a hybrid of the CAR plus the diurnal rhythm, and there is quite a bit of research on nighttime cortisol levels in various disease states, so I think it is helpful to have that as a value.

Thomas Guilliams, PhD: Right. Exactly.

Chris Kresser: Well, tell us about phase two. You mentioned that this book that you wrote was phase one, and I'm curious to know what you're investigating now, where your research has taken you in terms of phase two for the HPA axis.

Thomas Guilliams, PhD: Well, obviously I hinted in the book on several occasions that I had to leave certain areas off the table to make sure I could get the book done, but I think there are a couple of different areas. One would be the whole aspect of the thyroid and the interaction between the HPA axis and thyroid function and how they interact with one another. I think that's a big area that I want to make sure I cover in this next one. And probably the other area that I think is important to understand is the broad research now that we understand on the HPA axis and stress on brain function and memory and the functions of not just, obviously, the hypothalamus, but the hippocampus and the amygdala. I think we're learning more about the effects of stress on the brain, on neurons, neuroregeneration or the lack thereof, in some cases, atrophy of certain tissues in the brain, and the ability to protect brain function by perhaps some of the stress response that we're seeing. I think one of the things is maybe getting deeper into some of the things that I talked about here, being able to flesh that out a little more. Hopefully within a couple of years we'll see even more research in some of these areas where we can flesh some of that out and give clinicians a better idea of ways of treating patients or modulating the stress response that we didn't know yet. This area is surprisingly fertile in areas of research. There are some areas that are obviously more abundant than others, as far as the amount of research being done, but those are probably the two big areas that we're going to explore in the second edition of the book.

Then probably we're going to expand the whole clinical aspects. Maybe now that I have several labs sort of helping me in some discovery of some things, hopefully we'll be able to actually get some of the lab data because actually the labs have collected lots and lots of data but they don't really dig into that data as much, and so I've been talking to several of the laboratory directors on access to their data, and maybe we'll be able to correlate other pieces of information, for instance, cortisol-to-DHEA ratio first time in the morning with age. They have all that data. All we'd have to do is sift through it and look at that and maybe create what I would consider sort of a cortisol-to-DHEA aging and correlate that with a biological age and then other chronic diseases and maybe create sort of a gauge for clinicians to have. That kind of information is out there. There are

thousands of data points that just haven't been collected, so those are the kinds of things that I'd like to explore for this second phase.

Chris Kresser: Right. Yeah, that would be fascinating to see kind of like a catabolic disease index.

Thomas Guilliams, PhD: Right.

Chris Kresser: And it seems really important now, particularly the relationship between the SAS and HPA axis in the brain, given the pretty dramatic and alarming rise in neurodegenerative disease that we're facing today with Alzheimer's and dementia and Parkinson's. It just seems like it's really an epidemic. You mentioned it's a fertile area of research. I've certainly seen a lot of research in that area now, and I know that there's a lot more that can be done. As the population continues to age, it seems more and more important to get some insight into that.

Thomas Guilliams, PhD: Yeah, I'm convinced that the HPA axis is a lot more involved globally with chronic disease because really it's managing sort of the metabolic burden of the body. Of course, cortisol is a very potent glucocorticoid, so it's managing metabolism. It's a potent antiinflammatory, it's immune modulating, it's GI modulating, so it really has a very potent effect, but it's a very blunt tool, meaning that any stress sort of creates the same response. So it's very important that we manage the buffering capacity of the HPA axis if we're going to manage chronic disease. That's why I think it's such a critical aspect to look at.

Chris Kresser: Yeah, I agree and I like the discussion in your book about depletion of resilience and metabolic reserve. I think that's a key concept for clinicians to understand. It really relates to what you were just talking about, and certainly you would expect that as we age and the stresses of life accumulate and have a cumulative effect, they deplete our metabolic reserve. That's where you start to see all of these systems failing and chronic disease arising, and I don't think it really gets enough attention. There's a lot of discussion—and rightfully so—on nutrition, diet, and physical activity, but I've found, at least personally as a clinician, that this is often the elephant in the room in the interaction with a patient, and it's frankly unfortunately much more difficult to get patients to focus in this area—and even to get clinicians to focus in this area—because the changes that are often required are behavioral and lifestyle changes, not just taking a pill, although pills can be helpful. That's asking a lot of people, and it's not quite as simple, but I think it's every bit as important.

Thomas Guilliams, PhD: Yeah, I think you're right on. It's just like anything. Maintaining something that's healthy is a lot easier than trying to rebuild the health when it's gone because the capacity of the cell to maintain itself is there. One of the analogies that I use in the book is it's like paddling a canoe. When the river is wide and you don't have a lot of current against you, you can do whatever you want. You can go here, you can go there. But once you're farther downstream in the river and you have a lot of current, now it's a little harder to paddle, and if you let up for a little bit, you're going to go a lot further and you can't get back. So maintaining and helping the cells keep

their resilience and what I call metabolic reserve at all these levels is where we want to begin, and that's, of course, fundamentally what preventative medicine should be.

Chris Kresser: Absolutely. I was going to say that's another big plug for preventative medicine, and explaining this stuff to patients. Everyone who's listening, it's that concept we've talked about before from engineering of tolerance. As Tom said, it's a lot easier to maintain a system in its range of operating function than it is to get it back there once it's gone off the rails, so to speak.

Thomas Guilliams, PhD: Right.

Chris Kresser: Tom, thanks so much for spending the time with us. I know all of the ADAPT participants are really going to get a lot out of this. And thanks so much for your fantastic book. It was a real revelation for me. I've been thinking about this stuff for a long time, and I've read a lot of the studies that you talked about in your book, but I had never seen it all put together in one place in such a cogent and accessible way, so thank you so much for that.

Thomas Guilliams, PhD: Well, thank you. It's nice to have the right audience be appreciative of that kind of labor that went into that, so I appreciate it, and hopefully it helps them with their patients, which really is the goal for this in the first place.

Chris Kresser: Absolutely. OK, thanks again, Tom. Have a great evening.

Thomas Guilliams, PhD: OK. I wish you well.