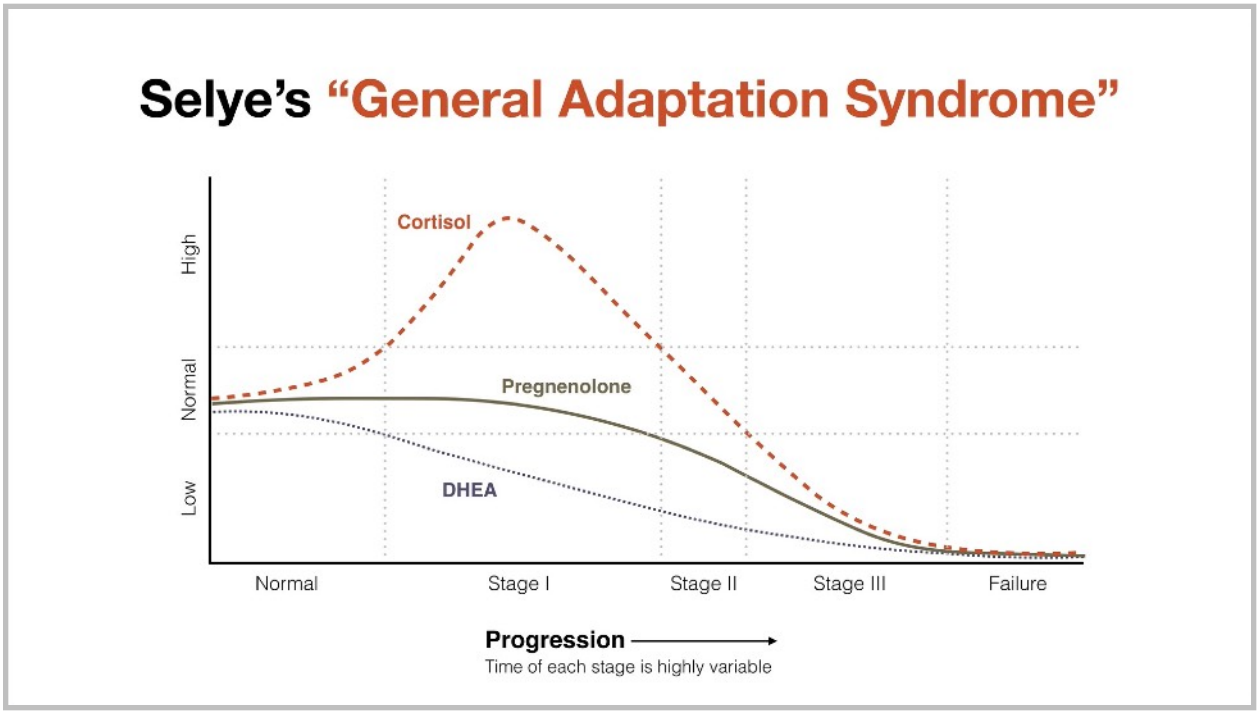
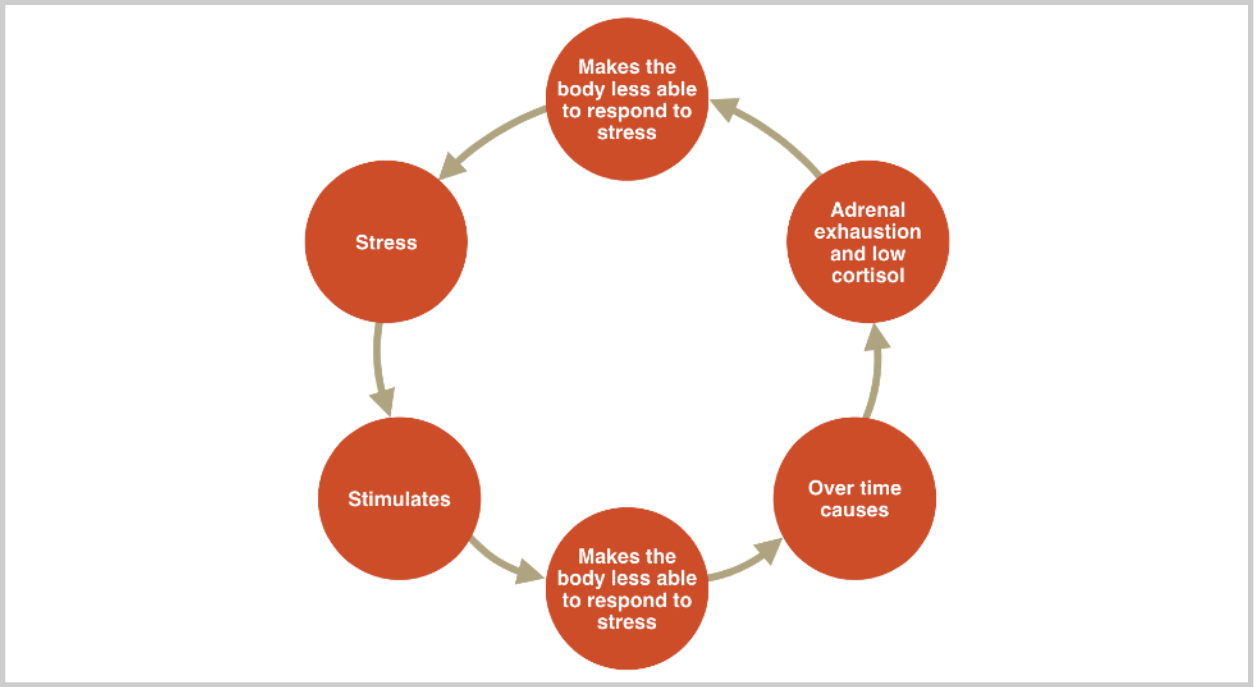
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

HPA-D or Adrenal Fatigue? Part 1

Hey, everybody, in this presentation I'm going to argue that the concept of adrenal fatigue is not supported by the current scientific evidence. It should be replaced by more specific terms that are in line with decades of research on how stress impacts physiology.



Hans Selye proposed the general adaptation syndrome. This suggests that acute or chronic stressors eventually cause the HPA axis to move from being hyper-responsive in the early stages to hypo-responsive in later stages, and it predicts levels of cortisol, DHEA and pregnenolone that are shown in the figure on this slide. So in stage one, you'd see an increase in cortisol and a decline in pregnenolone and DHEA, and this stage could last many months or even years. Eventually, an adaptation occurs that results in reduced cortisol production, as seen is stage two. And in this stage, cortisol may actually even be in the normal range, as it falls toward low output, but what distinguishes stage two from normal HPA axis function would be the lower levels of DHEA and pregnenolone. And then in stage three, all three hormones continue to fall until they reach, ultimately, failure or exhaustion.



Now this led to a three-stage model of understanding so-called adrenal fatigue in functional and alternative medicine. Now, Hans Selye actually didn't measure cortisol or DHEA or glucocorticoids; that part of the figure on the last slide was overlaid by integrative or alternative medicine practitioners later on. Selye just did a lot of testing with animals and observed their response to stress and noticed that they moved from a hyper-response to a hypo-response over time. He didn't talk anything about cortisol and DHEA; that was a later addition. So this three-stage model in the functional and integrative medicine world culminates in the final stage of so-called adrenal fatigue or adrenal exhaustion, where the adrenals are no longer able to respond to the stimulating actions of ACTH and produce adequate amounts of cortisol, and a corollary of this model is the idea that ACTH will drive cortisol up in stage one and deplete DHEA production via something called the pregnenolone steal. However, there is some really big problems with this three-stage model, as well as the notions of the pregnenolone steal and adrenal fatigue in general.

Free cortisol is
NOT the best marker for
overall cortisol production.

Let's start with the adrenal fatigue concept. In many if not the majority of cases where people are diagnosed or self-diagnosed with adrenal fatigue, they don't actually have low cortisol. In the integrative or functional medicine world, most clinicians use salivary cortisol testing, particularly the adrenal stress index, in order to identify adrenal fatigue. The cortisol measured in saliva is free-fraction, or unbound to protein carriers, and this is the most potent form because only free cortisol has cell signaling effects and is available to activate the cellular transcription response. But free cortisol is only about 3 to 5 percent of the total cortisol in the body at any given time. The rest of the cortisol in the body is cleared by several metabolic pathways before it's conjugated and excreted into the urine. In the serum, cortisol is bound to cortisol-binding globulin, and cortisol-binding globulin varies a lot, even among healthy individuals, and is affected by many disease states and drugs. So therefore, free cortisol, while it is the most potent form, is not the best marker for overall cortisol production, and in fact, measuring the metabolites of cortisol, since most cortisol is excreted in the urine, measuring urine metabolites of cortisol is the best way of estimating overall production.

Is cortisol *really* low in "adrenal fatigue"?

For those with "low" UFF, but not <10 (suppressed), % of patients with TCM in different groups are as follows:

Low	285	15%
Low Normal	450	23%
High Normal	639	33%
High	548	29%
	1922	

For those with "suppressed" UFF (<10) % of patients with TCM in different groups are as follows:

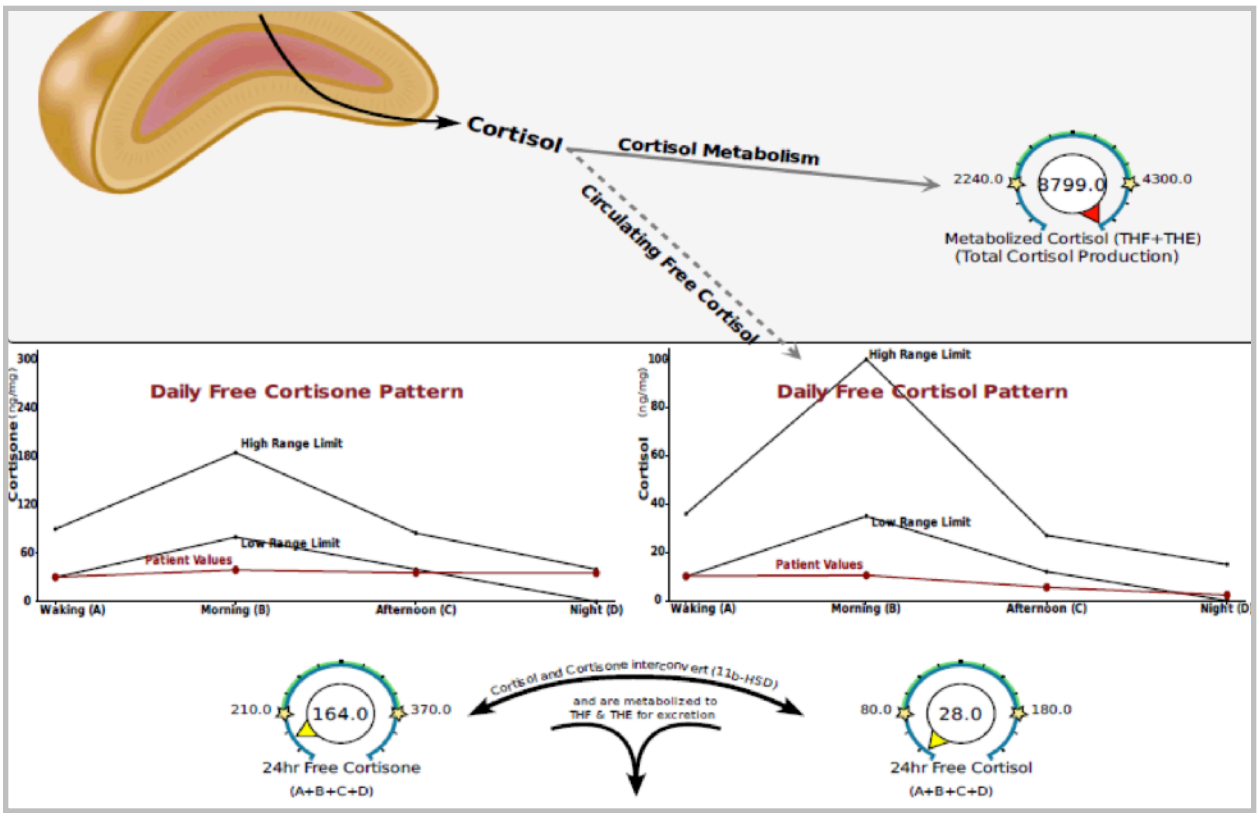
Low	32	64%
Low Normal	8	16%
High Normal	6	12%
High	4	8%
	50	

Using a cutoff of 5.0 for "Suppressed" 100% of patients show TCM not just "low" but all below our "Addison's Cutoff" of 1000 for TCM.

n=1,922 test subjects from **Precision Analytical Laboratory**

A key point to understand is that it's possible to have a low free cortisol, as measured on a saliva or urine test, but normal or even high metabolized or total cortisol. And in fact, that's quite common. Here on the slide is data from Precision Analytical, who offers the DUTCH urine test that I'll be teaching later on in this unit, and this is data from 2,000 test subjects. It shows that among those who had low free cortisol in the urine, only 15 percent also had low total cortisol. The other 85 percent had either high, high-normal or low-normal total cortisol. So put a different way, people with low free cortisol are more likely to have normal or high total cortisol than they are to have low total cortisol. Studies have found that this pattern, where people have low free

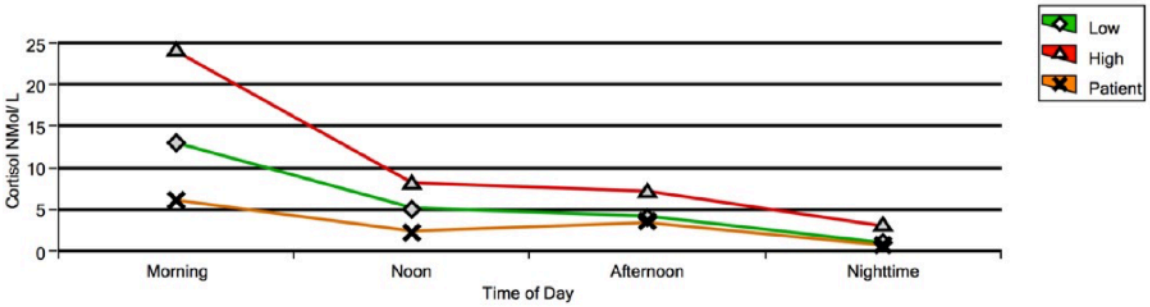
cortisol and high total cortisol, is observed in subjects that have insulin or leptin resistance and are overweight, which of course accounts for about two-thirds of the US population right now, and it can also be caused by things like chronic stress, glucocorticoid use, including steroid inhalers for things like asthma, hyperthyroidism, and chronic fatigue syndrome.



Here's an individual lab example of this. If you only tested free cortisol in this person with a saliva test, it would show that they have low cortisol, and as you can see at the bottom of the slide, they do have low free cortisol and low free cortisone. They also have a flattened diurnal cortisol rhythm, so if you just looked at the free cortisol aspect of this, it would look like so-called adrenal fatigue. However, when you look at the metabolized cortisol level on the upper right, you can see that it's nearly 9,000, which is two times the upper end of the lab range, and this person does not have low cortisol, in fact they have very high total cortisol production. This lab is from a patient that is obese, 420 pounds, with significant insulin and leptin resistance. She did not have adrenal fatigue, she had significant metabolic dysfunction. So if we give this patient licorice and other things to increase cortisol, we could very well make them worse.

Functional Adrenal Stress Profile - 201

Parameter	Result	Reference Range	Units
Cortisol - Morning (6 - 8 AM)	**6.1***	13.0 - 24.0	nM/L
Cortisol - Noon (12 - 1 PM)	**2.2***	5.0 - 8.0	nM/L
Cortisol - Afternoon (4 - 5 PM)	**3.6***	4.0 - 7.0	nM/L
Cortisol - Nighttime (10 PM - 12 AM)	**0.7***	1.0 - 3.0	nM/L
Cortisol Sum	**12.6***	23.0 - 42.0	nM/L
DHEA-S Average	4.41	2.0 - 10.0	ng/mL
Cortisol/DHEA-S Ratio	**2.86***	5.0 - 6.0	Ratio



Another factor that contributes to the adrenal fatigue concept is different ranges used by labs that do saliva testing. So here is a result on this slide from BioHealth, a popular saliva testing lab, and it's suggestive of so-called adrenal fatigue. You see low cortisol in the morning and at all four time points, and a low estimated sum cortisol.

Tests Ordered

Salivary Cortisol X4, Timed

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Salivary Cortisol X4, Timed					
#1 Salivary Cortisol	0.020		ug/dL		01
Draw date/time: 11/09/15 - 00:01					
Reference Range:					
Children and Adults:					
8:00a.m.:	0.025 - 0.600				
Noon:	<0.010 - 0.330				
4:00p.m.:	0.010 - 0.200				
Midnight:	<0.010 - 0.090				
#2 Salivary Cortisol	0.141		ug/dL		01
Draw date/time: 11/09/15 - 08:00					
#3 Salivary Cortisol	0.058		ug/dL		01
Draw date/time: 11/09/15 - 12:00					
#4 Salivary Cortisol	0.123		ug/dL		01
Draw date/time: 11/09/15 - 16:00					

But here's another lab result from the same exact patient, drawn on the same day at the same time. So we intentionally did this as a split test to compare actual values as well as ranges, and this result is from LabCorp. But unlike the result on the last slide, you can see that all of the four values for this particular patient are within the laboratory reference range.

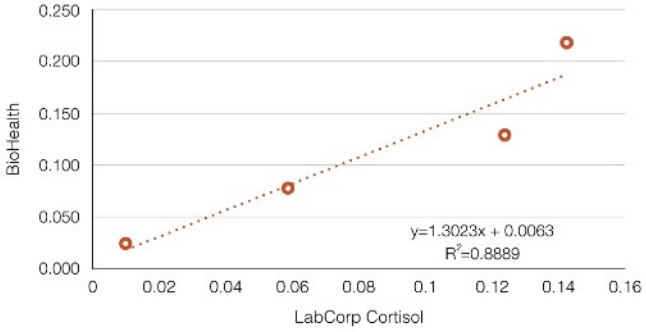
Saliva Comparison

BioHealth

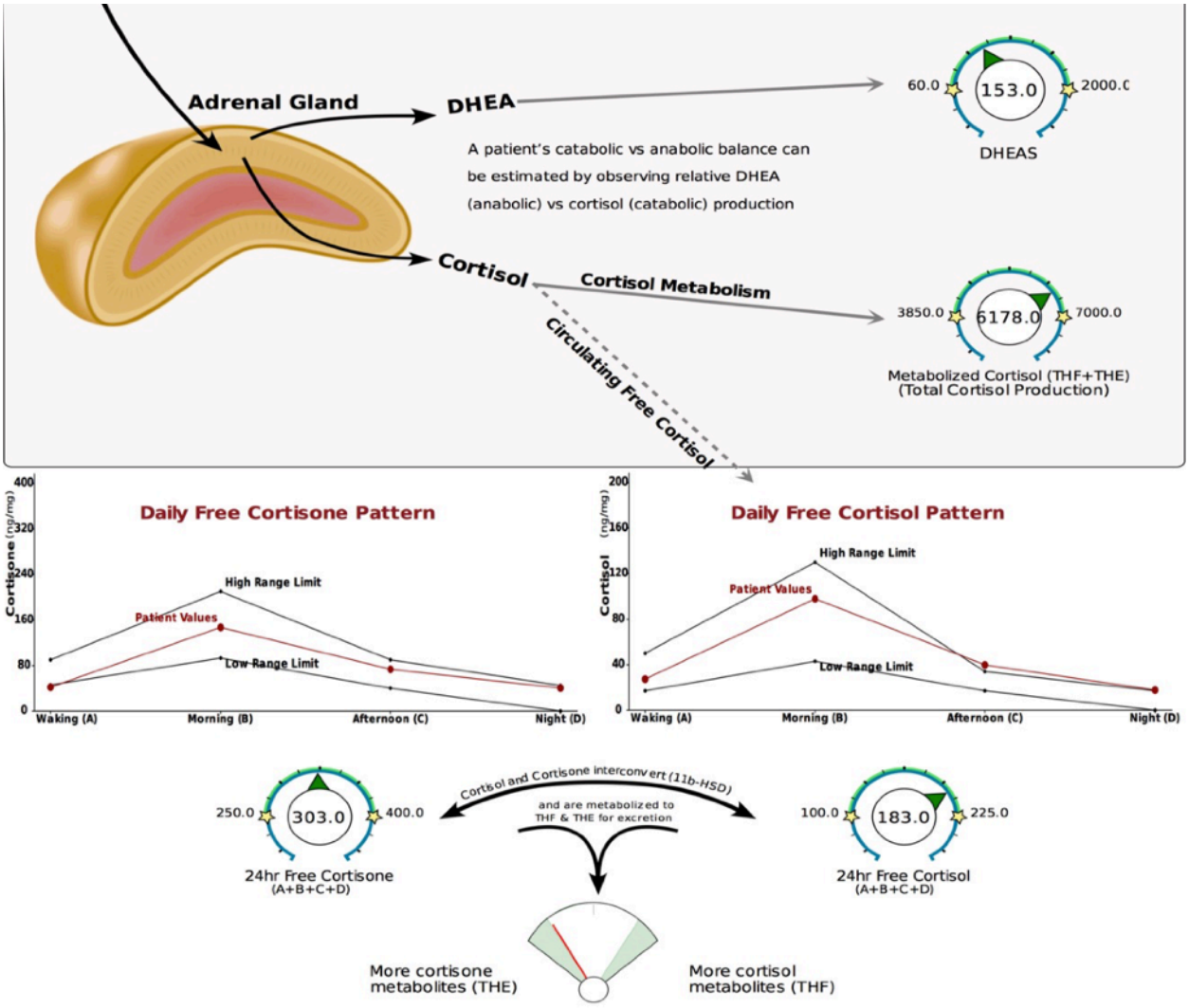
	Low	High	Sample value
8am	0.472	0.871	0.221
Noon	0.182	0.290	0.080
4pm	0.145	0.254	0.131
Bed	0.036	0.109	0.025

LabCorp

	Low	High	Sample value
8am	0.025	0.6	0.141
Noon	0.01	0.33	0.058
4pm	0.01	0.2	0.123
Bed	0.01	0.09	0.01



It's very difficult to compare results from saliva labs, because different labs use different measurement units. However, I converted the results from the previous two labs, the LabCorp and BioHealth result, into the same units, and I put them in two tables here on the slide, and then I plotted the results on a graph. As you can see, the 8AM and the noon samples are extremely close. The afternoon and evening samples are not quite as concordant, they're not quite as close, but they're still pretty close. The biggest difference that we see here are not the values that are measured, but the ranges that the labs use, particularly the lower end of the range in the morning and at noon. The low end of the range is .025 for LabCorp, but it's .472 for BioHealth. That's almost twenty times higher lower end of the range, and the same thing is true for the lower end of the lab range at noon. Now of course, it's possible that BioHealth's ranges are correct and Lab Corp's are not. Conventional ranges are often inaccurate, as I've already argued and will continue to argue throughout the course, but the difference between the functional and the lab range is rarely if ever twenty-fold as it is here. I'm not sure how BioHealth determine their ranges, but it's possible that the ranges have been influenced by the adrenal fatigue concept and the idea that low cortisol is a common pathology, and it's plausible that they adjusted these ranges upward to catch more so-called adrenal fatigue patients.



As another point of comparison, here is the same patient's results on the same day from the DUTCH test. So we actually did a three-split sample here. I'm going to be talking more about the DUTCH test in the diagnosis section. It's a dried urine test, and samples are collected four times a day. It has some of the advantages of both saliva and urine hormone testing. As you can see here, cortisol is definitely not low in this case. Look at the metabolized cortisol levels, they're at the upper end of the range. Then when you look at free cortisol, the 24-hour free cortisol is at the upper end of the range and is actually elevated in the afternoon, and 24-hour free cortisone matches quite nicely with the free cortisol. Now if you compare this to LabCorp, they use a more classic reference range of plus or minus two standard deviations, and if you take LabCorp's morning ranges as an example, the high end of the range is 25 times higher than the low end, so it's a very broad reference range. With the DUTCH hormone test, the difference between the low end and the high end of the lab range is three to four times, so it's a tighter range. DUTCH is looking at the 20th to the 80th percentile as normal, whereas LabCorp looks at the fifth to 95th percentile as normal. So as is often the case, functional lab ranges are

a little bit tighter because we're looking for optimal function rather than just frank disease. Even within the context of this range in the 20th to 80th percentile, this patient does not exhibit signs of low cortisol. His total cortisol is normal, and even his free cortisol is falling within the normal range and if anything is high-normal.