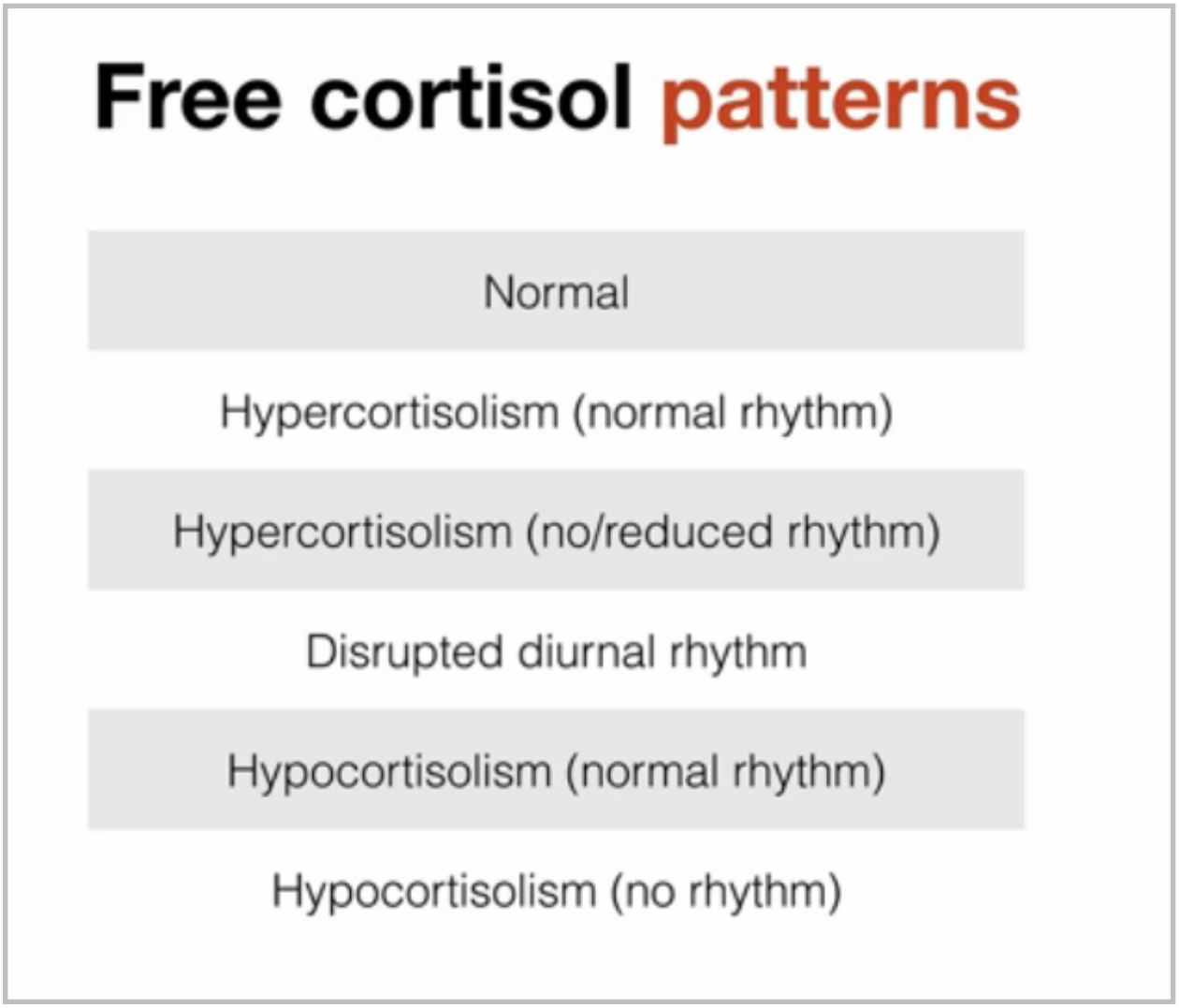
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

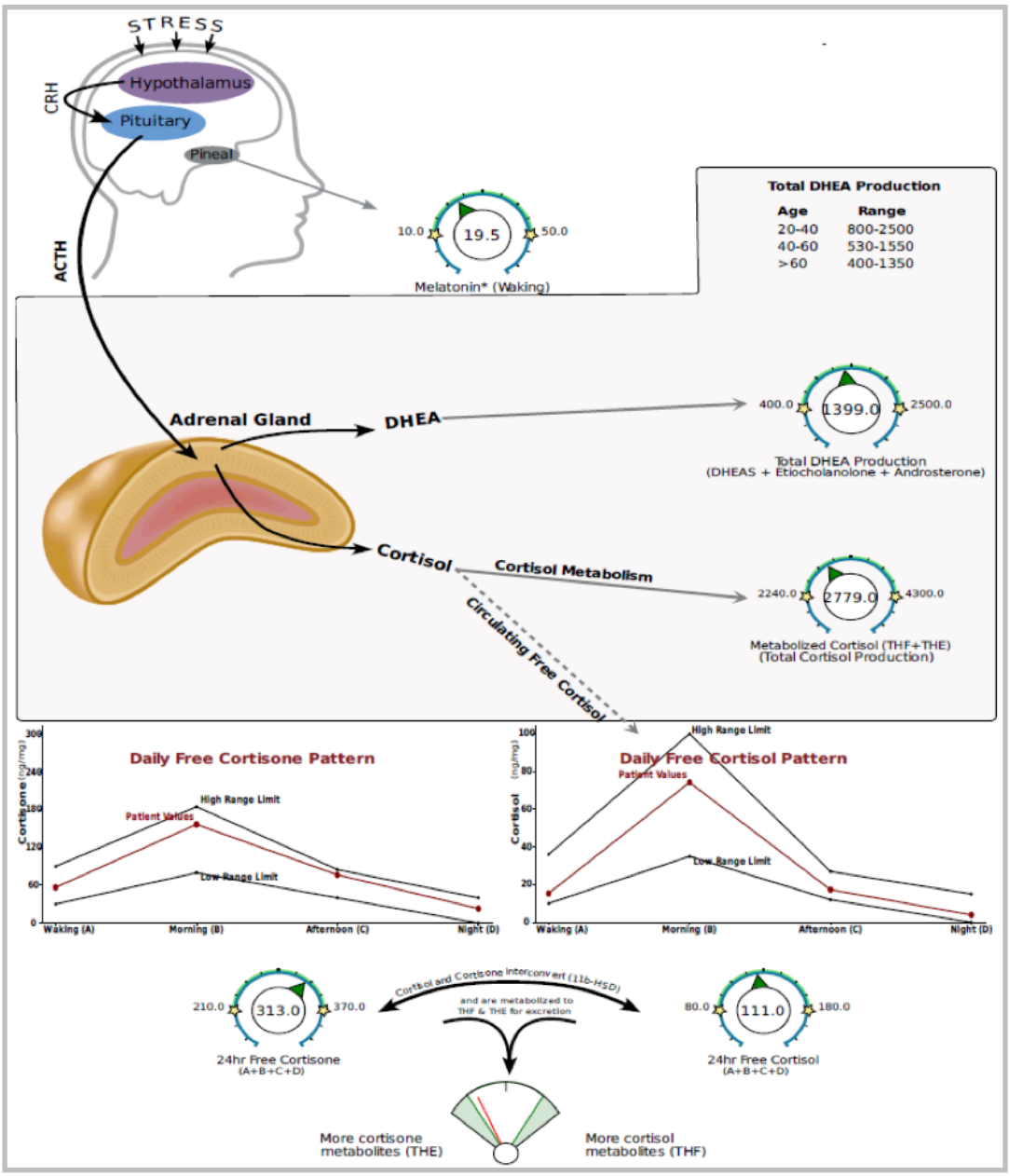
HPA-D: DUTCH Test I - Part 2

All right. Now, let's dive into some patterns and test results. I'm going to show you example test results and the indications for each. So, we're going to start with free cortisol patterns, and I've listed them on the slide here.



We're going to show you some examples and go into a little more detail, but we have just a normal presentation. We have hypercortisolism with a normal rhythm. We have hypercortisolism with no rhythm or a reduced rhythm. We have disrupted diurnal production of free cortisol. Then we have hypocortisolism with a normal rhythm and hypocortisolism with a blunted or flattened curve.

So here's what a completely normal test result looks like:

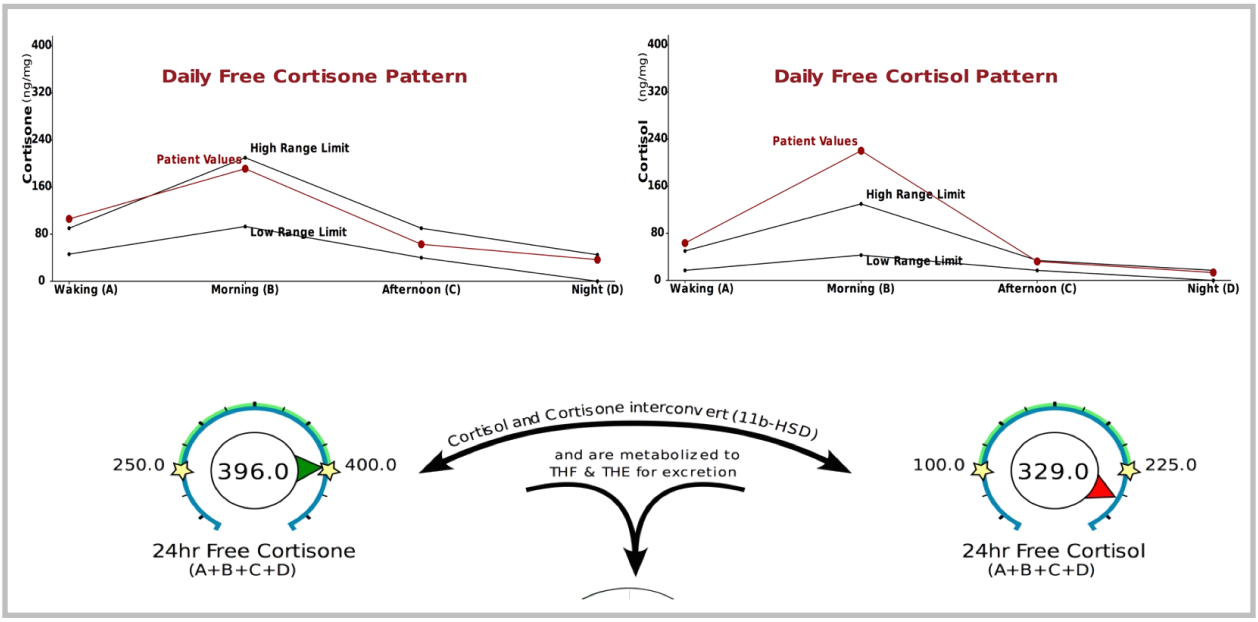


When you look at the DUTCH test, we're looking at several different markers here. We're looking at 24-hour free cortisol, and here we see down in the lower right that that is normal. A 24-hour free cortisone, we see on the lower left that that is normal as well. We're looking at the daily free cortisol pattern, so is cortisol produced in the proper diurnal fashion, and we see that

that is normal. The red line is the patient's results, and the two black lines are the reference range. If the red line is in between those two black lines, that indicates that it is a normal result.

We're looking at the daily free cortisone pattern, and that's normal here as well. Then we're looking at the balance between cortisol and cortisone, which is a measure of the biological activity of those metabolites. That's at the very bottom. It looks kind of like a fuel gauge, and that is normal. It's at the bottom of the range there. This patient is swinging more towards cortisone metabolites than cortisol, but it is normal.

Then we're looking at metabolized cortisol, which is a combination of tetrahydrocortisol and tetrahydrocortisone, and this is the best indicator of total or overall cortisol production. Then we're looking at total DHEA production, which is DHEA sulfate plus etiocholanolone plus androsterone, and that's normal. That's in the middle of the page toward the right. Then we're looking way at the top in the middle, and that's melatonin, and that is normal. So, a completely normal test result here.

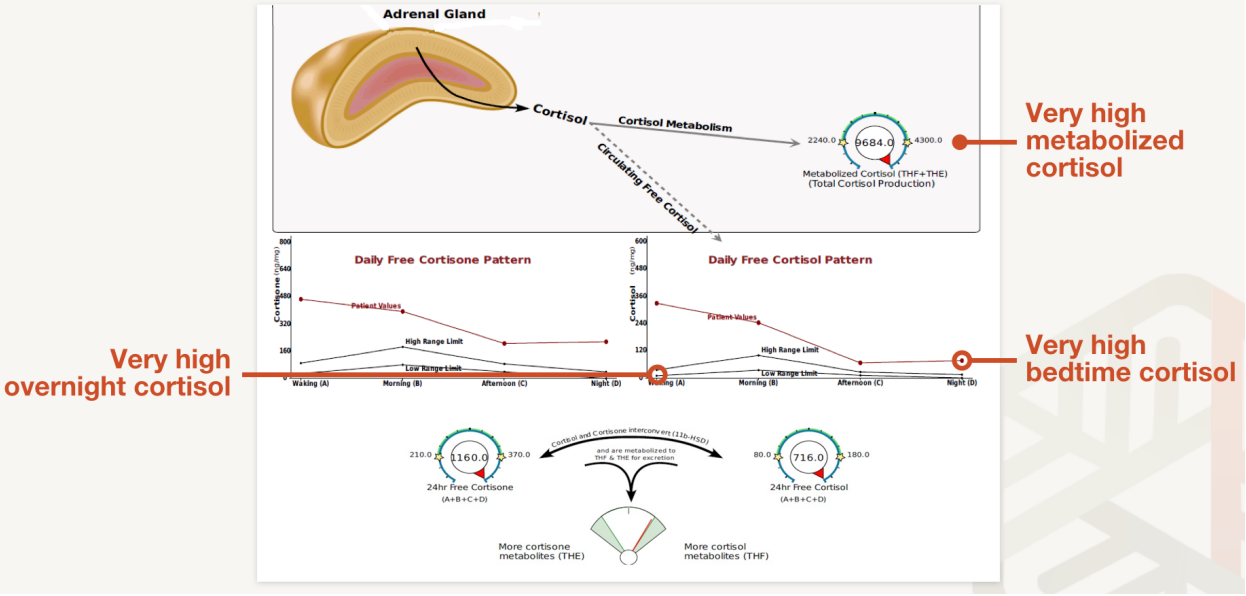


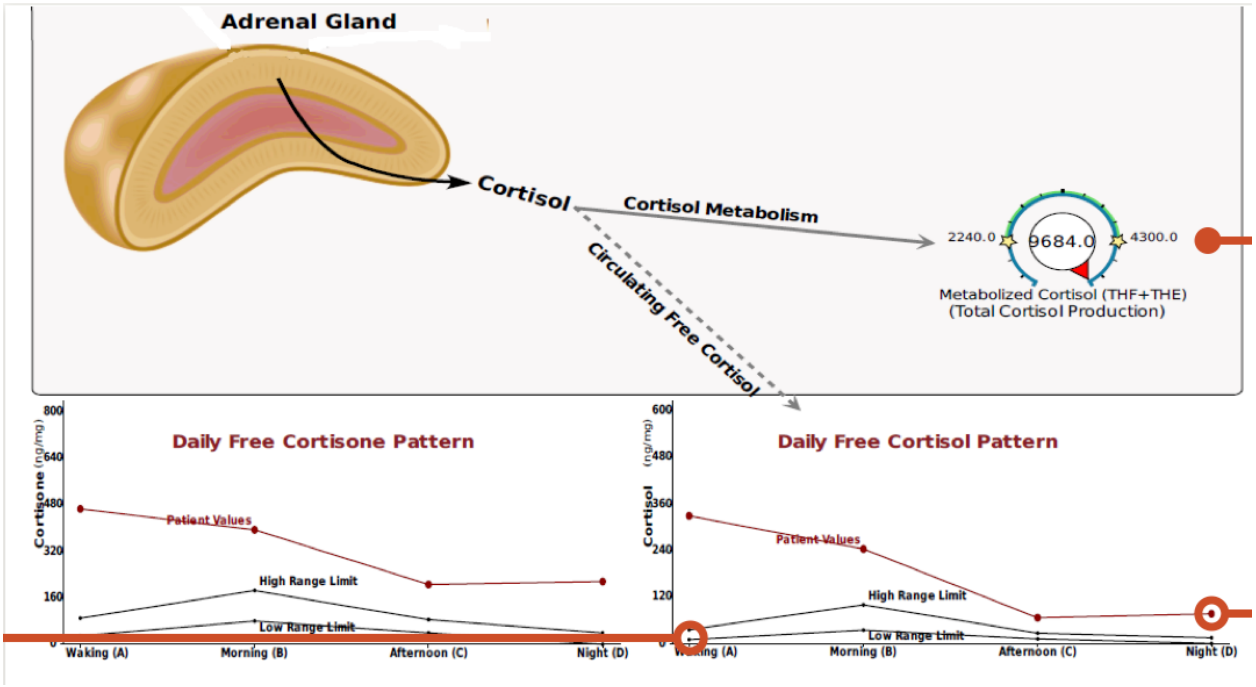
Here is an example of hypercortisolism, high cortisol with a normal rhythm. This patient has high free cortisol at every time point except for the nighttime reading, which is high-normal on both cortisone and cortisol, so even though cortisol is high, it is still kind of mimicking the expected shape of the curve in terms of cortisol production. His total free cortisol is elevated. It's 329 in a range that goes up to 225. Total free cortisone is not out of the reference range, which goes up to 400, but it's right at the top at 396. The free cortisone rhythm is also high or high-normal at most time points.

This patient, which you can't see here on this screenshot, was favoring active cortisol over cortisone, and one of the major causes of this is inflammation, and he certainly had a lot of it. This test result is from a 37-year-old male who had just been hospitalized for a severe ulcerative colitis flare. He is an air traffic controller, which is a tremendously stressful job, and he also worked an alternating night shift, so he had severe circadian disruption. So this is a good example of inflammation that is driving high free cortisol.

High free cortisol is associated with numerous pathological conditions in the scientific literature. Active stress response is the most obvious. This is seen in trauma, Alzheimer's caregivers, parents of autistic kids, and other conditions characterized by high perceived stress. High free cortisol and disrupted cortisol rhythm have been observed in major depressive disorder, also in dementia and cognitive disorders. In general, when you see high free cortisol, you should be thinking about perceived stress, inflammation, circadian disruption, and also Cushing's disease if it's extremely high.

Cushing's Disease/Pseudo-Cushing's Syndrome?





Here is an example of hypercortisolism that still exhibits some diurnal rhythm, but it's quite reduced. As you can see here, metabolized cortisol is extremely high, more than two times the upper end of the reference range. Free cortisol is also very high, four times the upper end of the reference range, and it's significantly above the cutoff at every time point. In Cushing's disease patients, there is virtually no diurnal drop in cortisol, which means the midnight reading will be

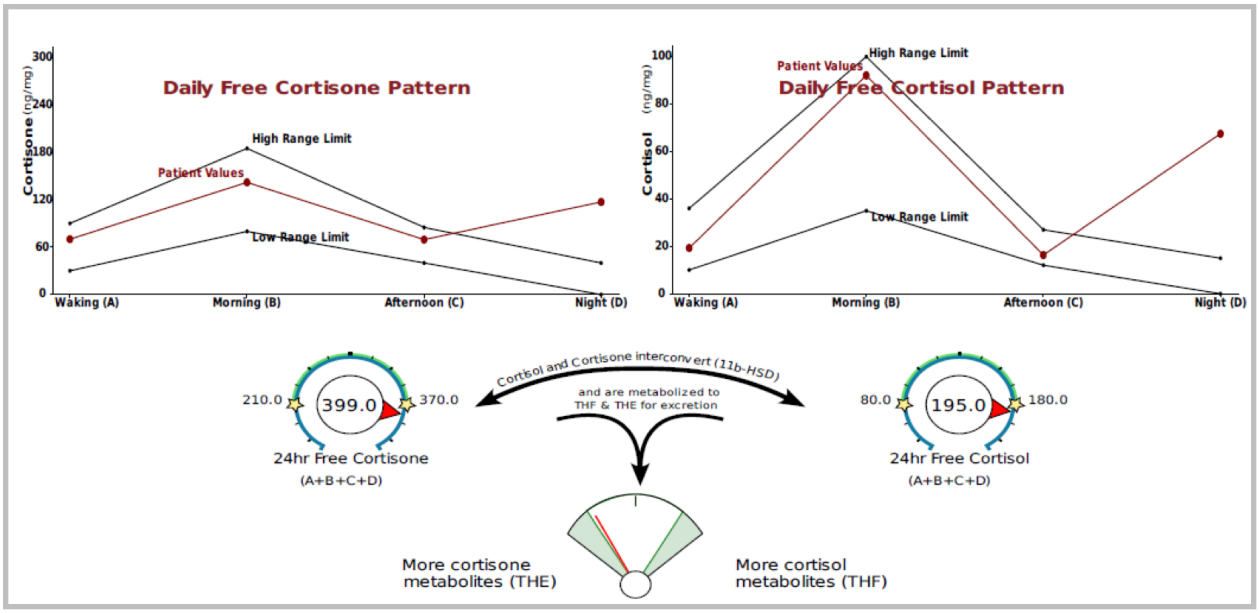
almost the same as the waking reading. In pseudo-Cushing's syndrome patients, they still have circadian rhythm, but the late morning, afternoon, evening, and midnight readings are higher. In the research literature, they are now using midnight cortisol saliva readings as a way of differentiating between Cushing's disease and pseudo-Cushing's syndrome.

So, what to look for, for these conditions, would be a nighttime value that is three to four times above the lab range, and then you would look for high cortisol metabolites. The literature says it should be four times above the range, but two to three times above the range would not rule it out. Then you're looking for high total free cortisol at about three to four times the lab range. Given what we're seeing on this slide, this could be a pseudo-Cushing syndrome patient, and if you see this kind of presentation, I would definitely refer out to an endocrinologist.

High evening/nighttime cortisol

Depression
Sleep deprivation
PTSD
Cognitive impairment
Low bone density
Circadian disruption
PCOS
Type 2 diabetes
Cushing's syndrome/disease

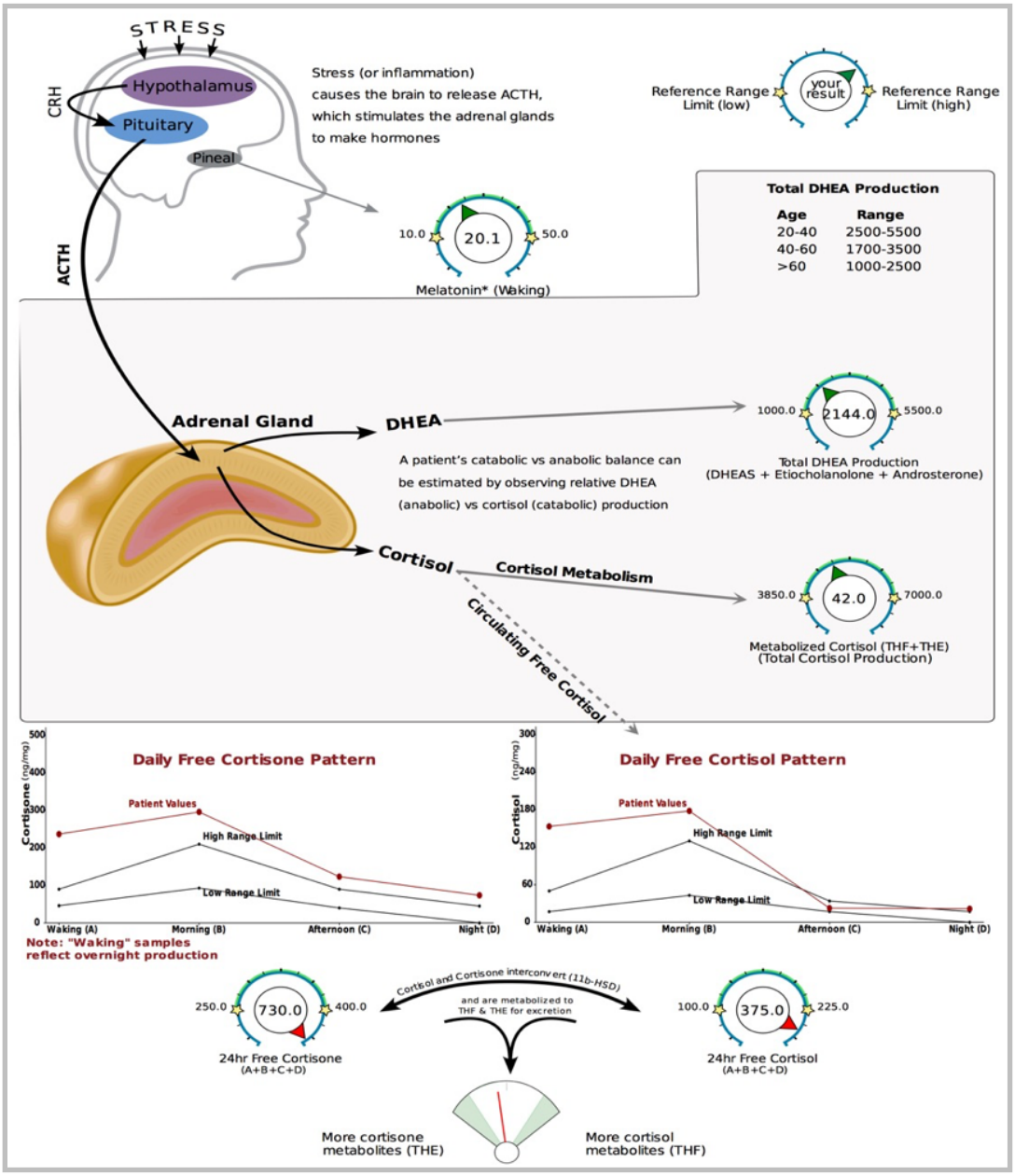
The next pattern is high nighttime/evening cortisol, and this has been observed in several conditions, including depression; sleep deprivation; post-traumatic stress disorder; cognitive impairment; memory deficit; low bone density, particularly in the elderly; circadian disruption; PCOS; and Cushing's. High evening cortisol has also been shown to be an independent predictor of mortality and systolic heart failure, and it's also been shown to predict type 2 diabetes risk progression.



Here is a patient with high nighttime free cortisol. Her total free cortisol is also high, as is her total free cortisone. You can be almost certain this patient won't be sleeping well because cortisol opposes melatonin, and melatonin is the hormone that helps us to fall asleep and to stay asleep. So this is a patient who will typically identify as a night owl or the patient who gets a second wind late at night. They are tired maybe in the morning or later in the day, but then they get a burst of energy late at night and stay up working or watching TV or whatever it is.

It is important to point out that recent research has identified that different people have different chronotypes, so some people have a natural tendency to stay up later and wake up later the next morning, whereas others have a tendency to go to bed earlier and wake up earlier the next day. The difference here is that we see really high cortisol production at night, and with someone who has just a shifted chronotype where they go to bed late, you're not typically going to see really high cortisol levels at night, so this is indicative of a pathology, whereas a natural chronotype is not.

The patient whose results these are is a 45-year-old mom who was in the habit of using the computer or her tablet after she put her kids to bed and would often stay up quite late browsing the web or on Facebook. She was suffering from a lot of stress, and her main complaint was depression and anxiety, so there is a little bit of a chicken and egg here. I think the stress and anxiety were in part contributing to her use of these devices late into the night, but her use of them was also suppressing melatonin production and possibly causing cortisol release. This is part of why it is so important to have these discussions about behavior and lifestyle with your patients.



The next patient here is a 45-year-old male with low energy, brain fog especially late in the day as his main complaints. He didn't sleep well. He falls asleep fine but is restless throughout the night and wakes up feeling unrefreshed. If you look at his nighttime free cortisol and free cortisone, you see that they are both high, but his waking cortisol and cortisone are both really high. Remember, urine is a reflection of the previous 90 minutes of cortisol production, so the waking sample, the one that they take 10 minutes after they wake up, is actually more reflective of cortisol production in the very early morning hours and through the night. This is especially

true if the patient collects a third nighttime sample because that is averaged into the overnight calculation.

So very high waking cortisol often indicates overproduction of cortisol through the night, and that explains this patient's symptoms very well. It explains why he was waking up throughout the night because cortisol is high. It is probably having a suppressive effect on melatonin, although his melatonin levels are in the normal range. They are toward the lower end, as you can see. Then his morning cortisol is still elevated outside the lab range, but then it really dips in the afternoon, the free cortisol. The free cortisone stays high, but his free cortisol dips in the afternoon, and that could explain his energy dips late in the day. Note that in this patient his metabolized cortisol is actually normal. There is a typo on the lab results here. It's not 42, but where the arrow is pointing is the proper level.