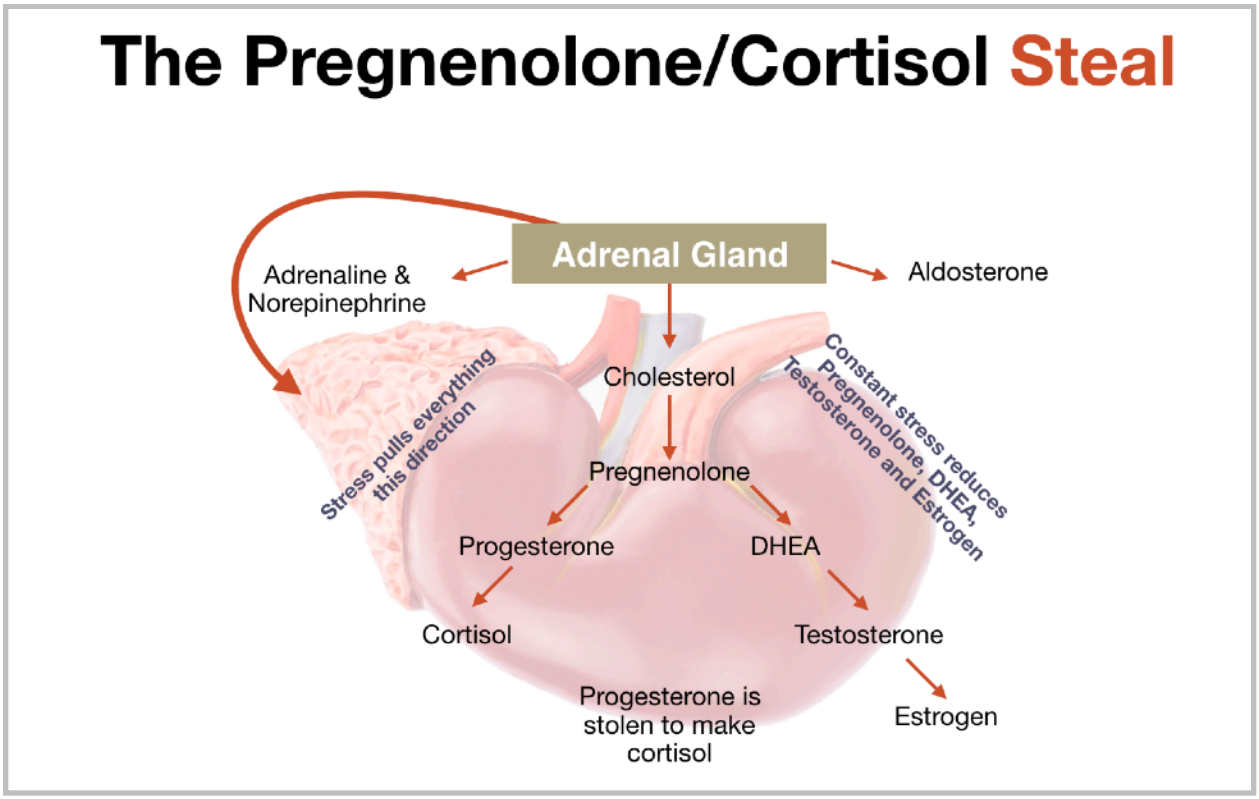
HPA-D or Adrenal Fatigue? Part 3

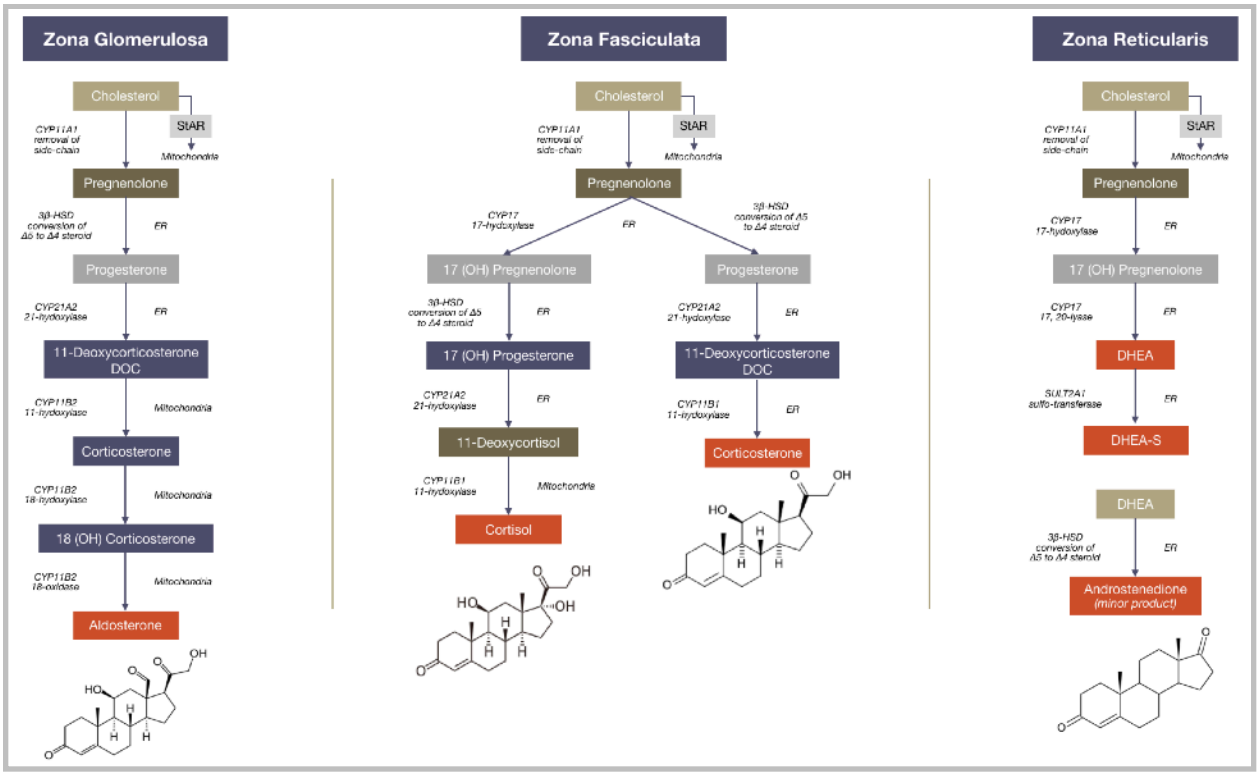
Another possible mechanism that could lead to low cortisol is increased sensitivity to negative feedback on the HPA axis. Studies have shown that patients with rheumatoid arthritis that are given steroid drugs that suppress cortisol like dexamethasone and prednisolone experience greater suppression of cortisol production when compared to controls. It's not clear whether the enhanced sensitivity to negative feedback that's seen in these patients is a cause or an effect of the condition, but it's at least plausible that it's a cause. A number of other conditions that may be stress-related, such as PTSD, sexual abuse, burnout syndrome, and chronic pelvic pain, are associated with increased sensitivity to negative feedback in the HPA axis as well, and that suggests that stress may be a common mechanism in all of these conditions.

None of these mechanisms leading to low cortisol has anything to do with the adrenals being fatigued or unable to produce it. This explains why you don't find the term "adrenal fatigue" in the scientific literature. That said, there is some evidence that low cortisol may occasionally be caused by a reduced ability of the adrenal glands to produce it. The few studies I've seen that suggest low cortisol being caused by adrenal insufficiency are in chronic fatigue syndrome. One study showed that chronic fatigue syndrome patients have reduced volume of the adrenal cortex compared to controls; another study found decreased basal cortisol levels and blunted cortisol in response to ACTH stimulation. This data is extremely limited though, compared to the data on mechanisms I mentioned on the previous slides.

It's far more likely if we see low cortisol that it's caused by brain, central nervous system, or tissue-specific mechanisms. And it's worth pointing out that even in the cases I've mentioned on this slide where free cortisol was low in chronic fatigue patients, it may have only been free cortisol that was low, because those studies often didn't measure total cortisol, and as we found on the previous slide in this presentation, that Jerjes et al. study where they measured both free cortisol and metabolized cortisol in chronic fatigue patients, there was no difference in metabolized cortisol levels between chronic fatigue patients and controls, so it may just be that in these studies they're not measuring total cortisol, so it only appears that cortisol is low.



Another popular concept within the adrenal fatigue model that needs to be revisited is the pregnenolone steal. So I put a visual example of this theory on the slide here; the idea is pregnenolone is the precursor of all steroid hormones, which is true, and in times of stress, pregnenolone is diverted into the production of cortisol at the expense of DHEA, testosterone and estrogen. This is a very popular concept; I accepted this explanation myself until I took the time to look more deeply into the topic and learned that there's really no support for it in the scientific literature.

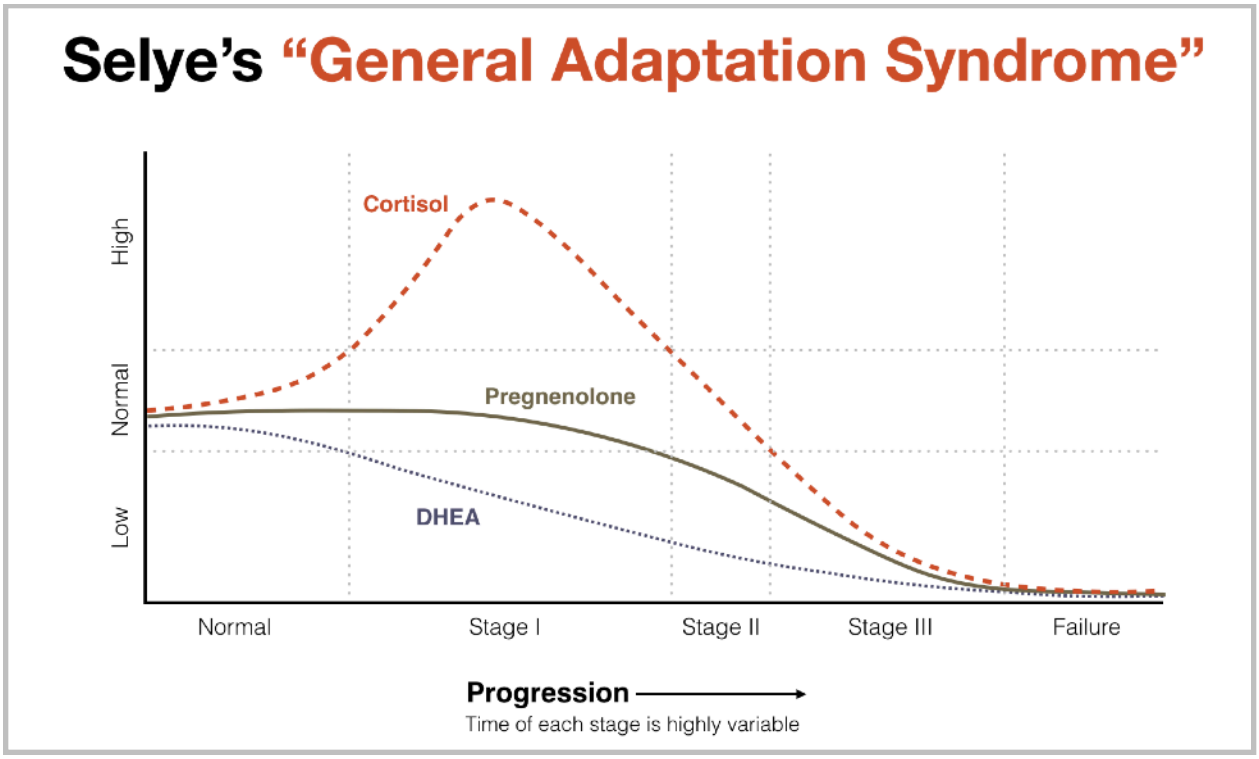


It is true that chronic stress can lead to a drop in DHEA, but this effect is not caused by a reduced availability of pregnenolone because it's being "stolen" for cortisol production. That theory assumes that there's a single pool of pregnenolone in the adrenal glands from which both DHEA and cortisol are produced. However, DHEA and cortisol are produced in the mitochondria of individual cells, not from a central pool of pregnenolone. What's more, they're produced in completely different parts of the adrenal cortex. DHEA is produced in the zona reticularis, and cortisol is produced in the zona fasciculata. There is no known mechanism by which pregnenolone can be stolen from inside of the mitochondria of cells in the zona reticularis, which are producing DHEA, and be transferred to the mitochondria of cells in the zona fasciculata, to produce cortisol. Now if you suggest this to a scientist who studies steroid hormones, prepare to be laughed at.

Cortisol production primarily **regulated outside adrenals.**	Cortisol production **dwarfs DHEA production.**	**No evidence** that oral pregnenolone increases DHEA.

Second, as I've mentioned, cortisol production is regulated primarily by cell-specific enzyme concentration and signaling coming from outside of the adrenal glands themselves. Third, the amount of cortisol produced dwarfs the amount of DHEA produced. So if there were an adrenal pregnenolone pool that had enough pregnenolone to handle the higher levels of cortisol we produce in the morning or during stress, then that pool would also be available for the orders of magnitude smaller amount of DHEA we need when cortisol synthesis drops even a little, either after the cortisol awakening response or after the stress has passed. Finally, there's no convincing research suggesting that oral pregnenolone supplements increase DHEA levels.

So what does lower DHEA when cortisol is high? This is governed by regulatory processes like negative feedback inhibition, receptor signaling, genomic regulation of enzymes, etc. For example, studies of diabetics with high cortisol and low DHEA showed that the enzyme necessary for DHEA formation in the zona reticularis, which is 1720-lyase, was limiting the production of DHEA.



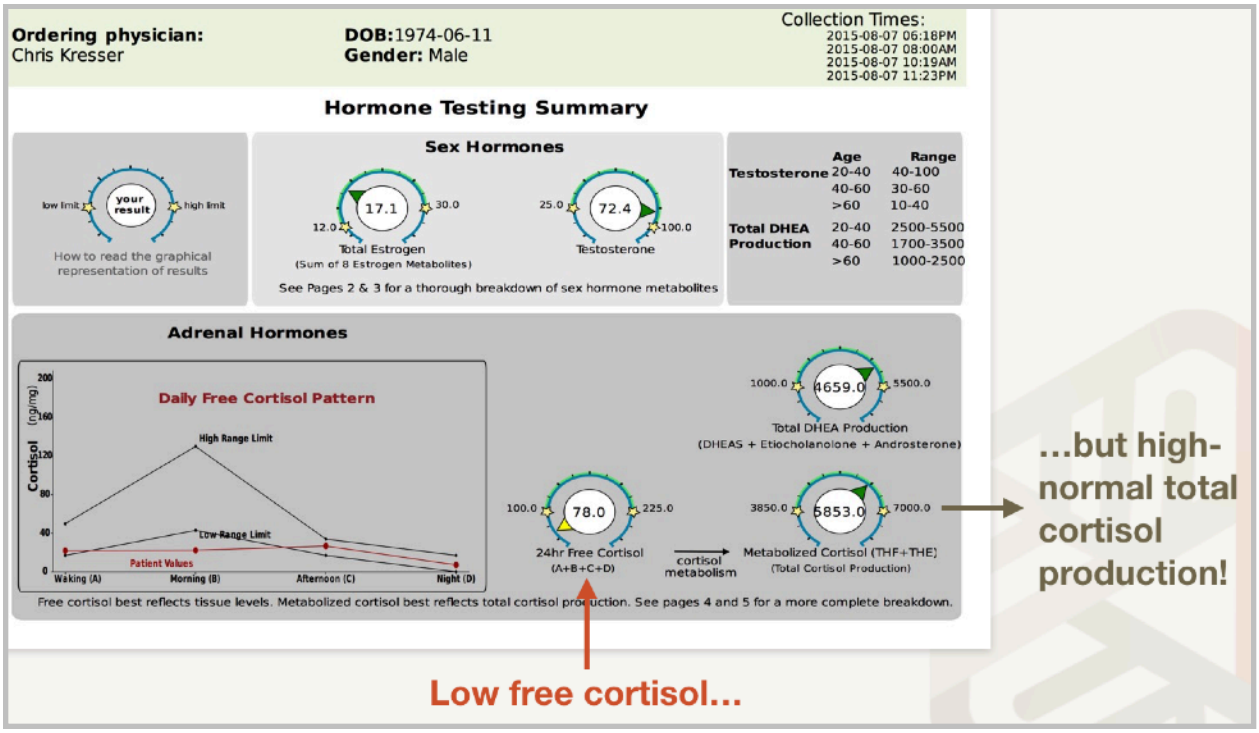
The last aspect of the adrenal fatigue concept that needs a closer look is the three-stage model. We talked about this earlier. It's the idea that our response to stress progresses through three clear stages, stage one, two, and three, and then into exhaustion or failure. As Tom Guilliams says in his book, however, models may explain but they do not diagnose. The three-stage model is based on a number of unproven assumptions from animal studies, particularly on Hans Selye's early work with the general adaptation syndrome. Now there is some evidence to

support the idea, or Selye's observations that we progress from an initial response of hypercortisolism to an eventual response of hypocortisolism.

So for example, in PTSD patients who experienced a traumatic event, you see a very dramatic increase in cortisol, and then you see a couple of things happen: typically the first thing that happens is an increase in cortisol-binding globulin, and this is effectively to reduce the amount of free cortisol that's available, insulate the body from the effects of this high cortisol state; and the second thing that happens is the entire HPA axis is downregulated, so you don't just see a decrease in cortisol, you see a decrease in ACTH. So this implies that these are brain central nervous system mechanisms that are reducing cortisol, not low cortisol due to the adrenals being unable to produce it. However, not everyone proceeds through these stages in a clear and defined manner, and in some cases, someone, for example, could go very quickly to stage three with low cortisol output.

We talked earlier about how early life events can reprogram the HPA axis permanently, so that person could experience a stressful event early in life and have low cortisol for the rest of their life, unfortunately. In some cases, people will stay at high cortisol levels for virtually forever, they never drop, their cortisol levels stay high for years and years, so they would effectively be stuck at stage one, except maybe their DHEA levels are also high, and you can see this in obese patients. So it's not as neat and tidy as in this three-stage model, not everybody progresses through it in this order, and even when people do progress from a hypercortisol state to a hypocortisol state, they may do that at very different rates.

So why does this matter? I think there are several reasons. First, having a more clear understanding of what's actually happening leads to more appropriate and better treatment outcomes. So, for example, if a patient has low free cortisol but high metabolized cortisol, and then they're misdiagnosed with adrenal fatigue and given supplements or even medications like hydrocortisone to increase cortisol, that's not going to help in most cases, and it may even cause harm. In addition, it may even distract us from the true cause of the problem. So when free cortisol is high, we might assume that the patient is producing way too much cortisol and give them things to lower their cortisol, but what if their metabolized cortisol is low? In that case, it can indicate a thyroid issue or a problem with liver function, and the solution might be to address those things rather than to focus exclusively on the HPA axis.



And then in a common example, let's look at the slide here. The patient on this slide has very low free cortisol and a flattened cortisol rhythm, but their metabolized cortisol was high-normal, as was their DHEA. So this is not "adrenal fatigue"; in this case it turned out to be early insulin and leptin resistance, and this patient wasn't significantly overweight, they were kind of skinny-fat, but they had high fasting blood sugar, they had high hemoglobin A1c. I did a more advanced metabolic panel and some of their other markers were indicating a progression towards diabetes. Looking at these test results led me to do that further testing even though the patient didn't look like someone that was on the way to diabetes, and we discovered these issues and were able to treat them. But if you only do the saliva test and you saw the low free cortisol, you wouldn't get any of that information, and you might just give the patient things to increase cortisol, which in this case could actually make them worse, so it's very important in terms of how we approach patients clinically.

The second reason it's important is that if we want to maintain credibility among patients and other medical providers and continue to advance functional medicine, we need to align our diagnostic and therapeutic methods as much as possible with research related to the HPA axis. So if you diagnose your patients with adrenal fatigue and they go online, which most patients will do, and they look it up, they might find this fact sheet on the Endocrine Society website that says, "Adrenal fatigue is not a real medical condition. There are no scientific facts to support the theory that long-term mental, emotional or physical stress drains the adrenal glands and causes many common symptoms." Now, I don't think they mean to say that there are no scientific facts proving stress causes many common symptoms because that would just be absurd. There are thousands and thousands of studies showing that. What I think they mean to say here is that

there are no facts to support the idea that those symptoms are caused by drained adrenal glands, and that is definitely consistent with what the research says.