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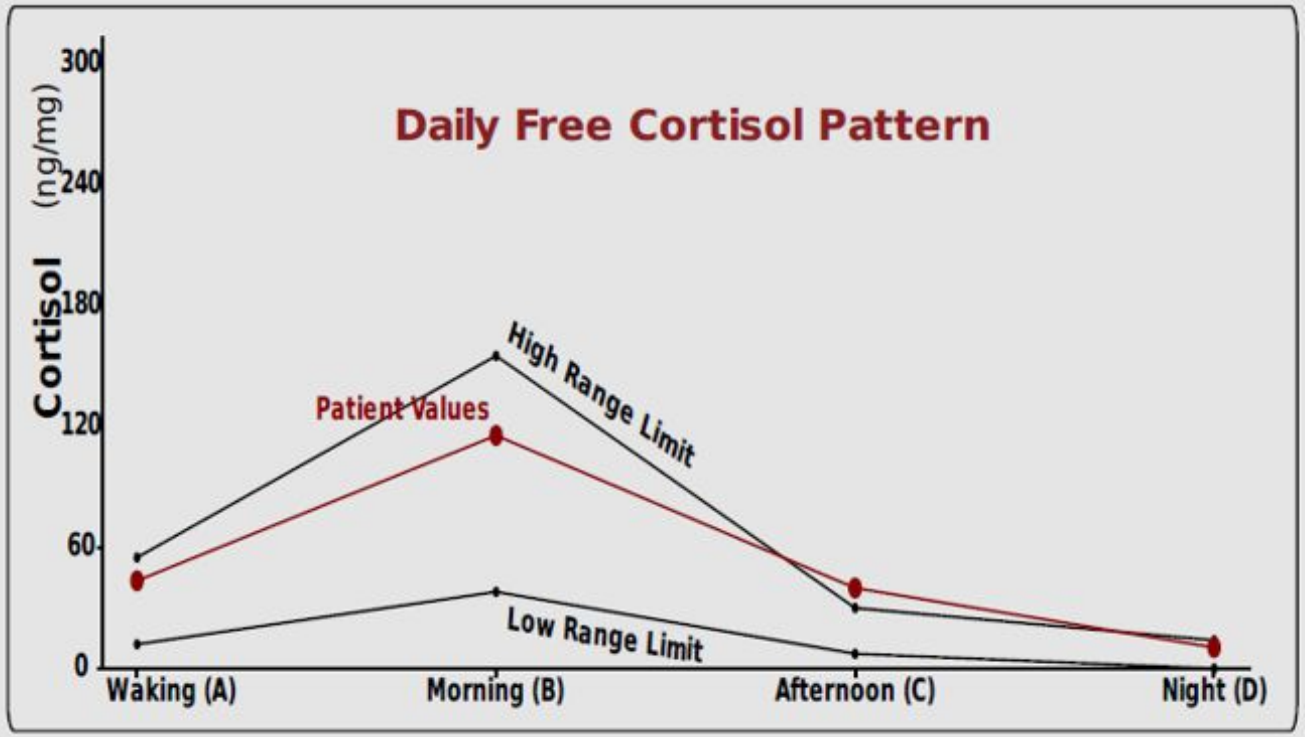
Clinical Insights into HPA Axis Dysfunction and the Common Cortisol Patterns: How to recognize them and what to do.

Carrie Jones

ND, MPH, RPh, CCN, MT

A Naturopathic Physician and FABNE board certified, Jones has a Master's degree in Public Health and 15+ years of experience in the field of functional and integrative medicine.



24hr Free Cortisol
(A+B+C+D)

cortisol
metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Clinical Insights into HPA Axis Dysfunction and the Common Cortisol Patterns:

How to recognize them and what to do.

Carrie Jones, ND, FABNE, MPH

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Disclosures:

Dr. Carrie Jones is the Medical Director for Precision Analytical Inc and the Clinical Expert for the Stress Recovery Program (SOS) for the Lifestyle Matrix Resource Center

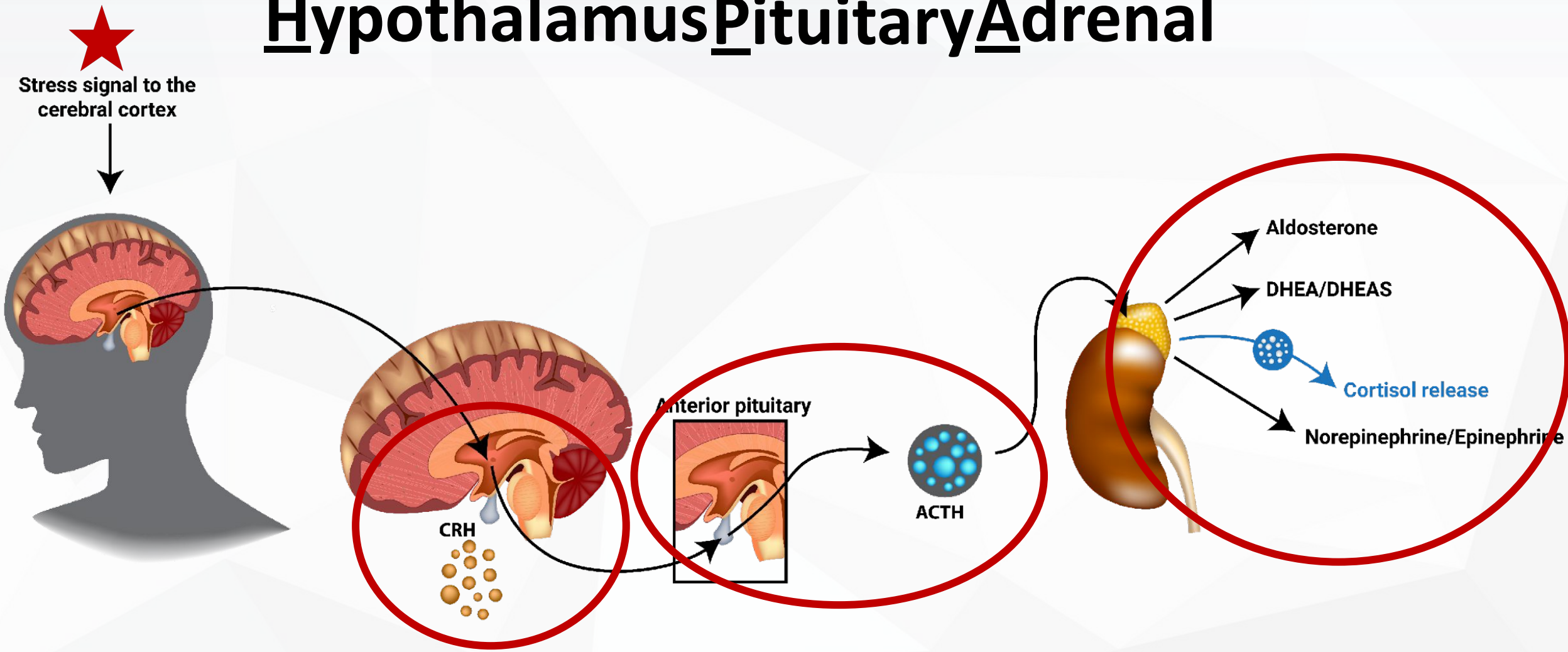
First, so we are all on the same page…

- We are discussing **cortisol**
- Known as a **"steroid hormone"**
- It is derived from **cholesterol**
- It is **lipophilic** (fat-loving)
- It easily diffuses across cell membranes

Next, what is the HPA axis?

What is the HPA Axis?

HypothalamusPituitaryAdrenal



Key Disease States: Addison's or Cushing's

- **Addison's disease** = autoimmune disease of the adrenal glands resulting in too little production of cortisol and aldosterone

- **Cushing's Syndrome** = excessive amounts of cortisol in the body regardless of the cause
  - Commonly due to steroid use

- **Cushing's Disease** = excessive cortisol due to a tumor

Functional Endocrinology

Traditional Endocrinology Disease Model

Functional Endocrinology

Traditional Endocrinology Disease Model

Functional Endocrinology Model

Functional Endocrinology

We must properly identify the extreme disease states when we see it (Cushing's/Addison's)

But "generalized HPA dysfunction" is what more commonly occurs in this system ***and must be addressed***

What about “Adrenal Fatigue?”

- Unless it’s Addison’s disease, the adrenals do not “fatigue” and give out themselves and stop producing cortisol
- They do not go through menopause, like the ovaries.
- While the symptoms are very real…
- The description of “My adrenals have fatigued out” is misleading.
- Look at the broader HPA axis from the brain to the mitochondria

How do you test
"HPA Axis Dysfunction"
And what are you looking for?

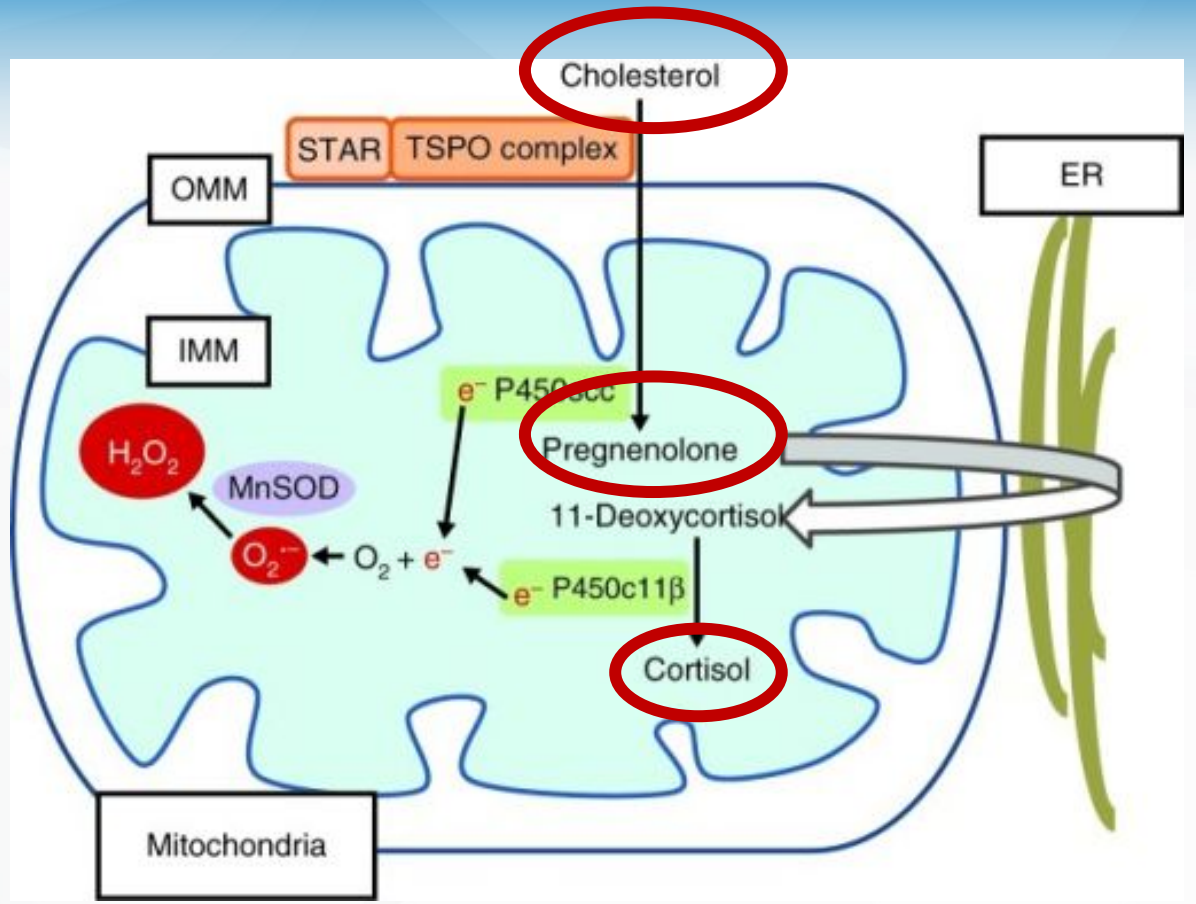
Some hormones are made from circulating precursors, but **cortisol production is not made this way**

It's **not** made from circulating pregnenolone or progesterone

Guilliams T. (2015). The Role of Stress and the HPA Axis in Chronic Disease and Management. Point Institute. Stevens Point, WI

Cortisol production starts in the brain

1. **CRH (CRF)** tells the pituitary to make **ACTH**
2. **ACTH** binds to the zona fasciculata of the adrenal glands
3. This signals the **mitochondria** to pull cholesterol in and produce **cortisol**



"Your cortisol production starts and ends in the mitochondria!"

~Dr. Carrie Jones

Pic:https://openi.nlm.nih.gov/detailedresult?img=PMC4045218_JOE130346f02&req=4

Let's talk about cortisol

- Cortisol is not stored for immediate release
- Normal ½ life with a healthy liver is 1-2 hours (depending on research)
- Bound by cortisol binding globulin/transcortin (mostly) and albumin in circulation
- **Free cortisol is <5%** circulating **but is the active form**
- **Gets metabolized in the liver to cortisol metabolites then is urinated out**
- Cortisone is the inactive form – it can't activate Glucocorticoid receptors

Fink G (Eds). (2010). Stress Science Neuroendocrinology. San Diego, CA. Elselvier.

Why is it helpful to know the metabolized cortisol?

Metabolized cortisol represents 80% of total cortisol production

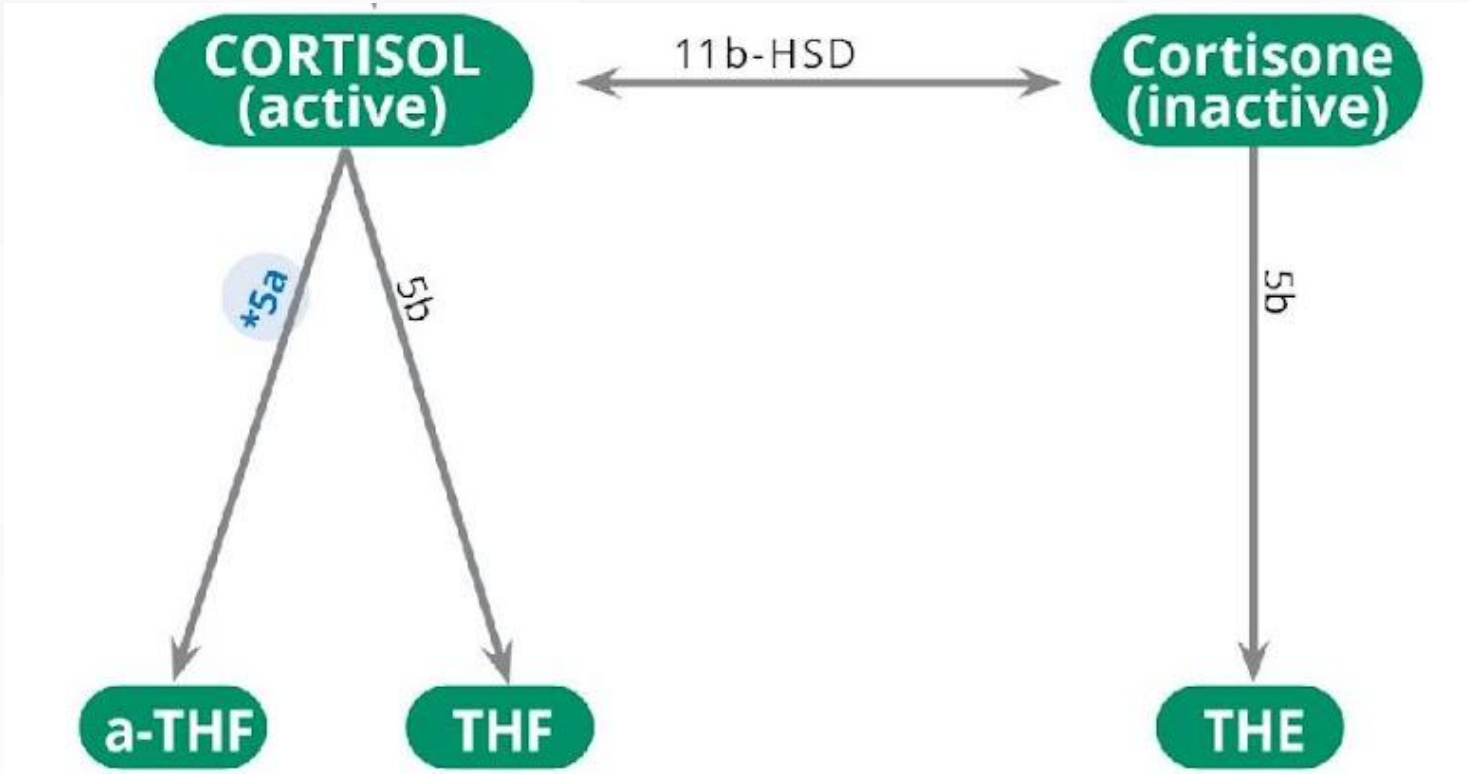
Free cortisol = 1% (ish)

(Stewart and Krozowski, 1999)

Metabolized Cortisol

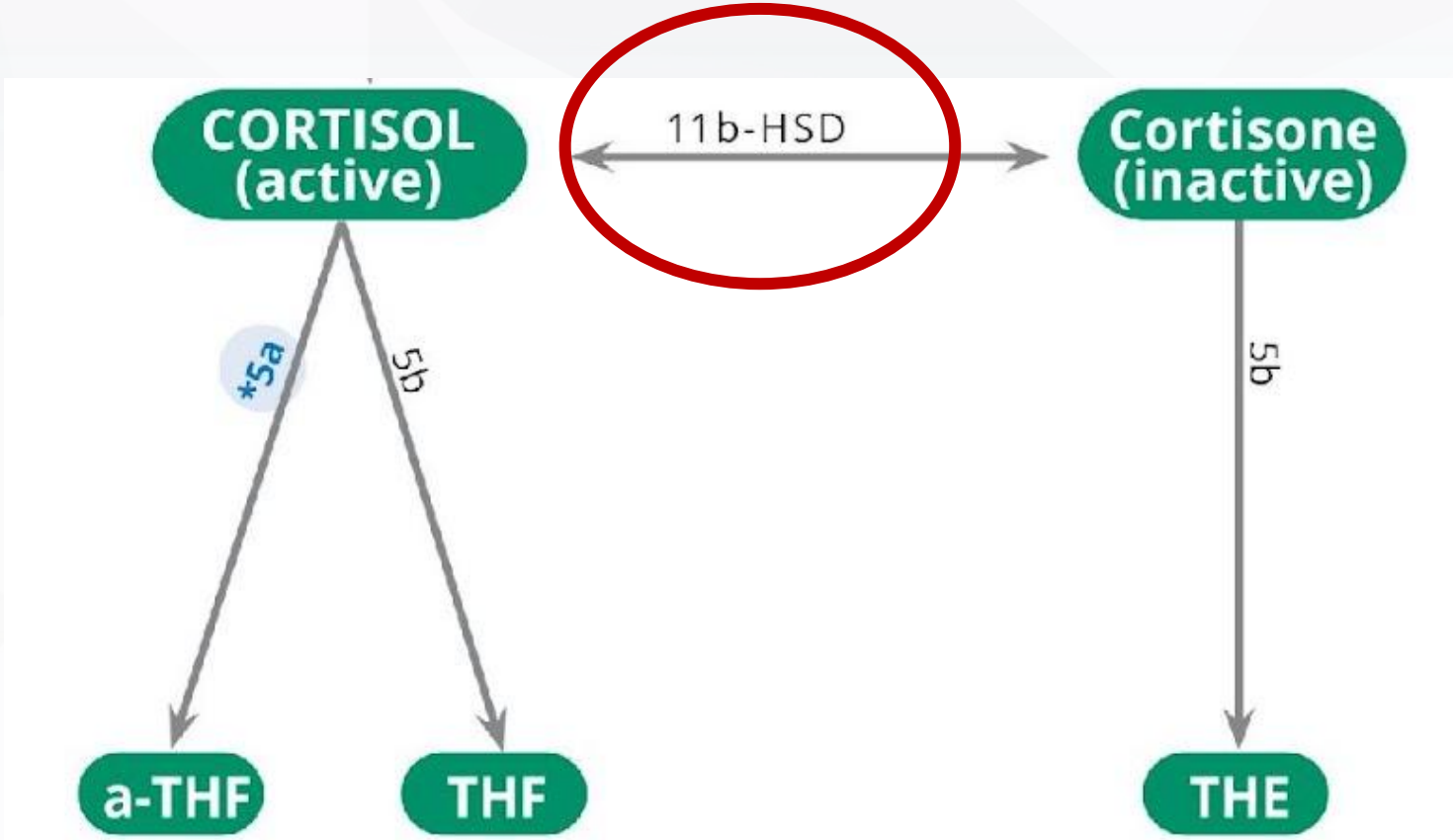
- Gives us a rough idea of how much cortisol is being made and metabolized in the day **IN TOTAL.**
  - **"In total, can you make cortisol?"**
- Then use the **free cortisol** to assess:
  - **How much is available/active?**
  - **Is the circadian rhythm normal (or not)?**

How is cortisol metabolized?



Tetrahydrocortisol (THF) **Tetrahydrocortisone (THE)**

How is cortisol metabolized?



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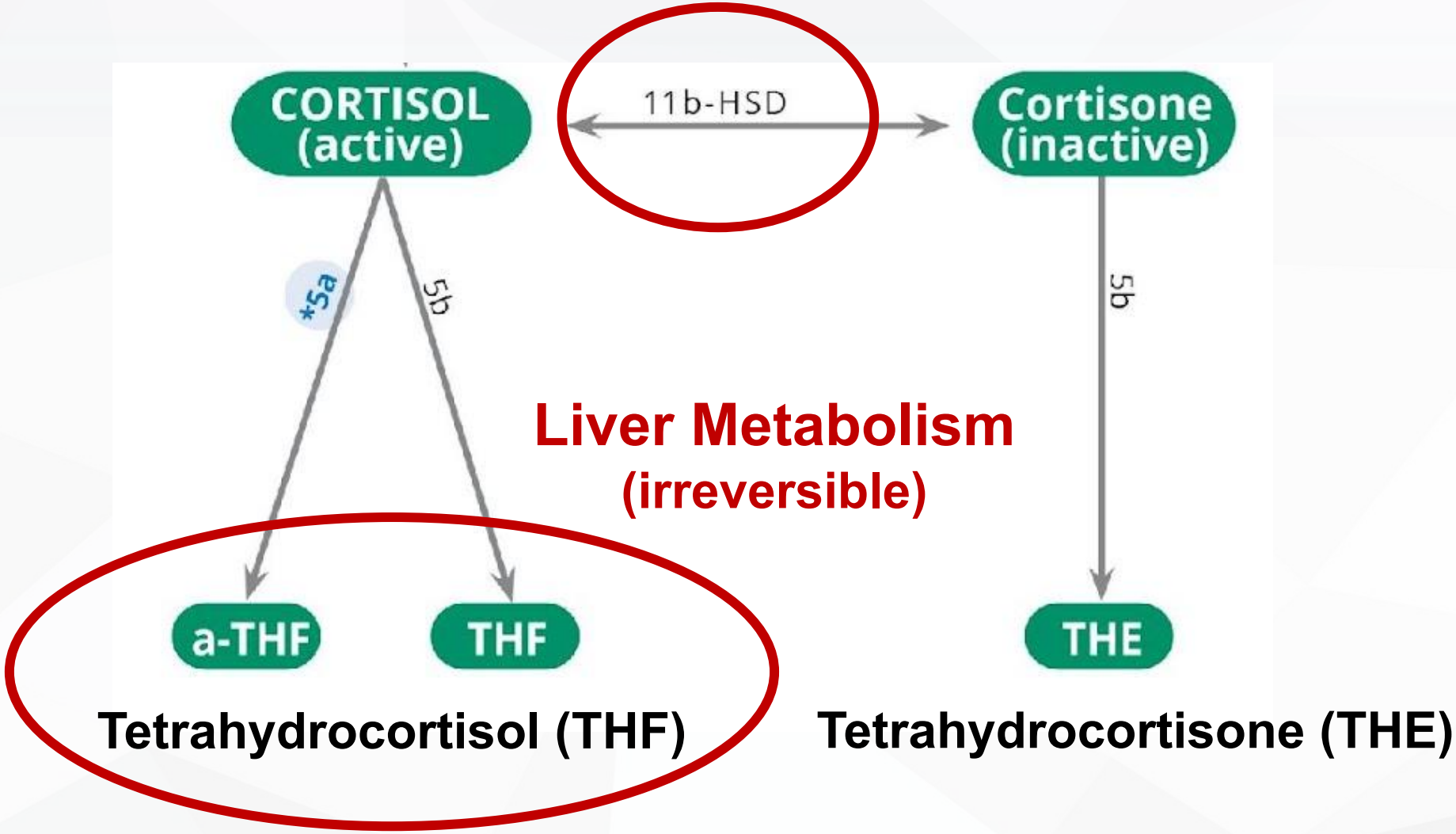

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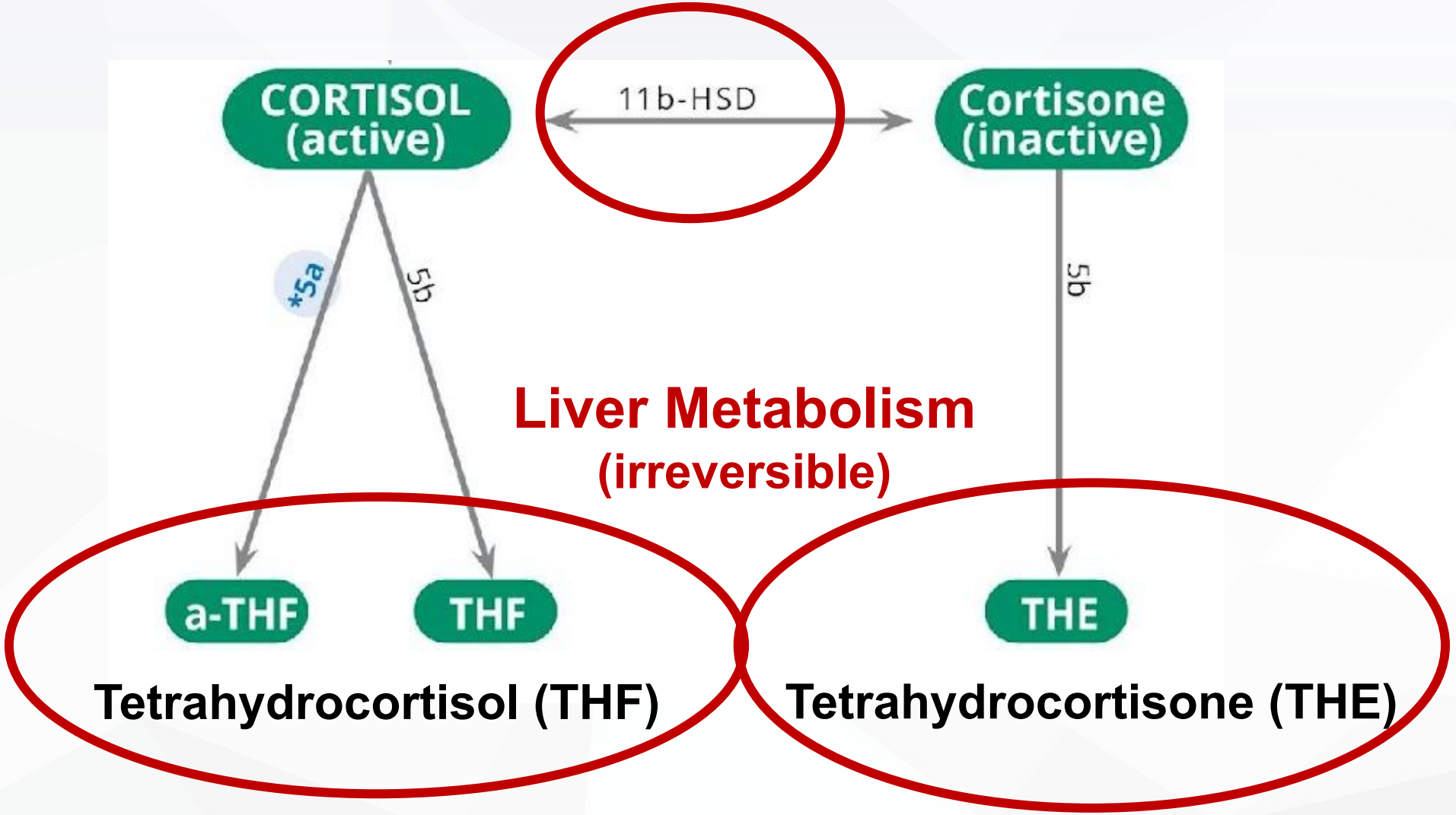
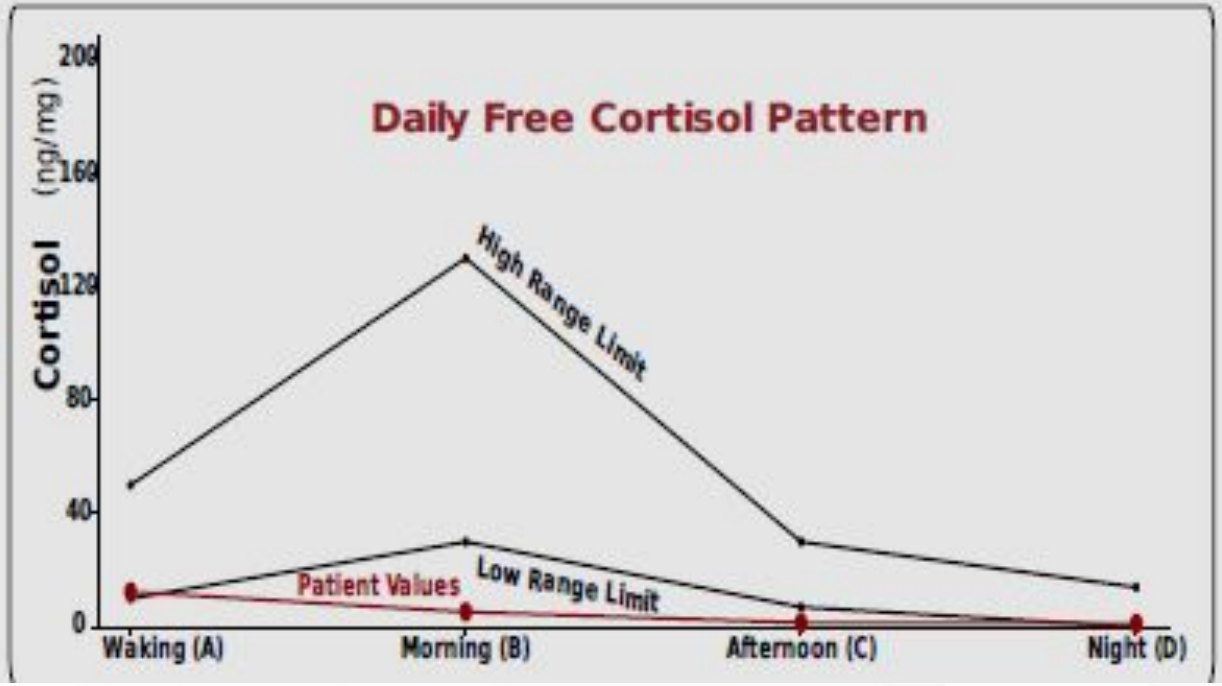


What if you only ran a free cortisol?



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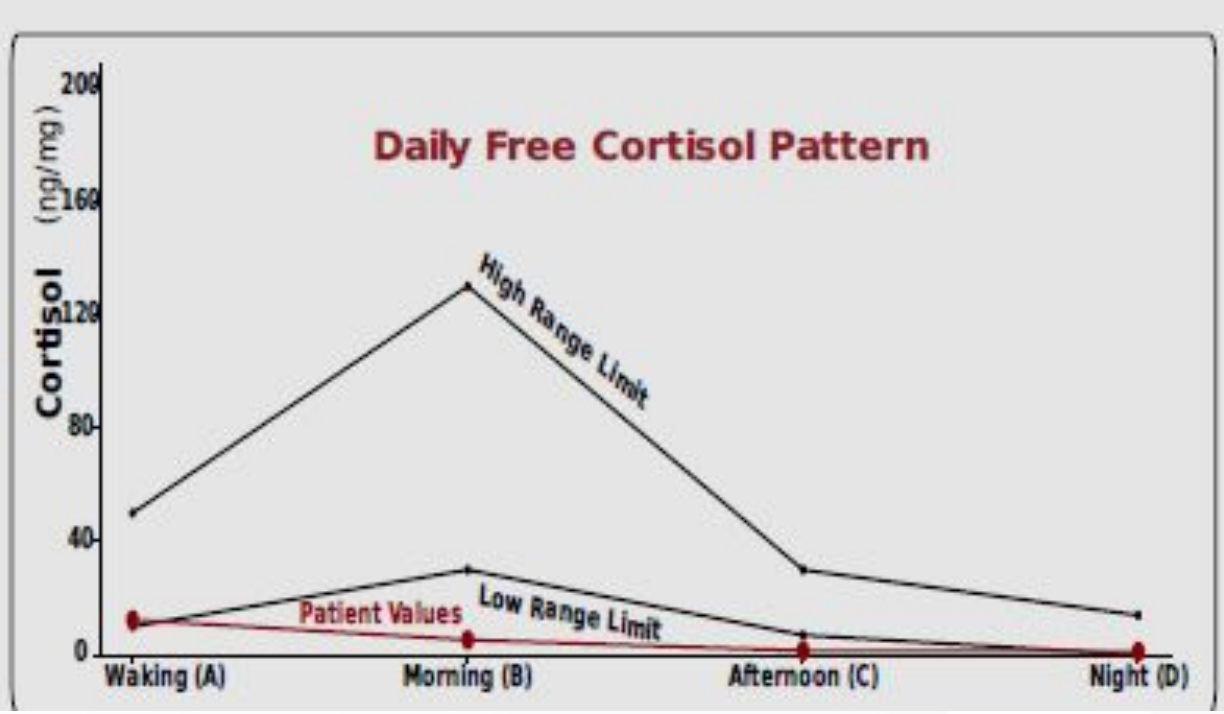
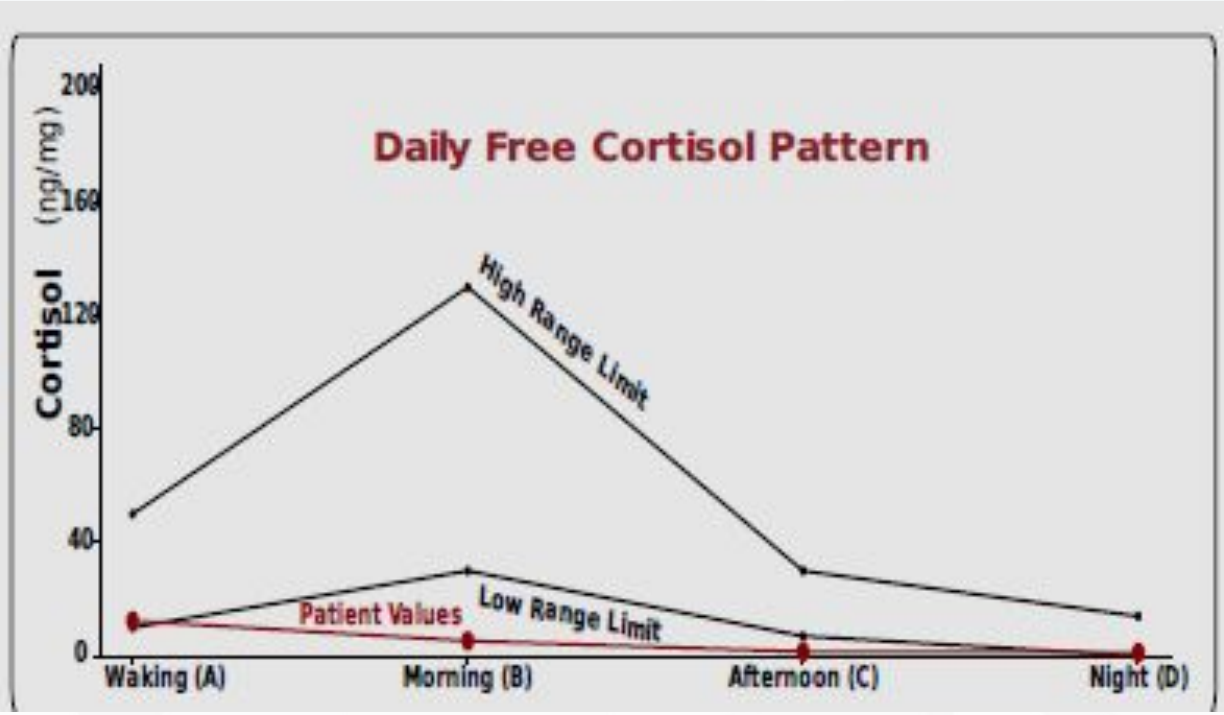
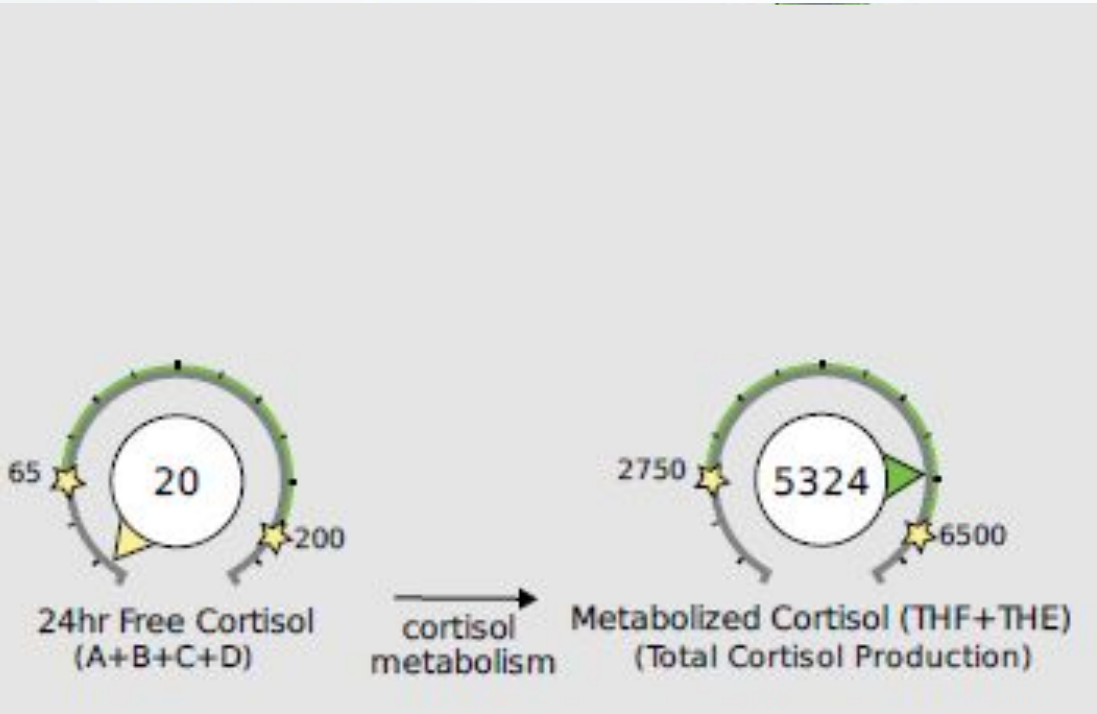


Free cortisol is low = 20
The circadian rhythm is low all day

Would you give them heavy HPA axis support to try to raise their cortisol?

Adding in the metabolized cortisol





Their metabolized cortisol is on the upper end of the range
This means they make it and metabolize it out quickly.
Cortisol production is likely not their problem.

Summary, when testing cortisol…

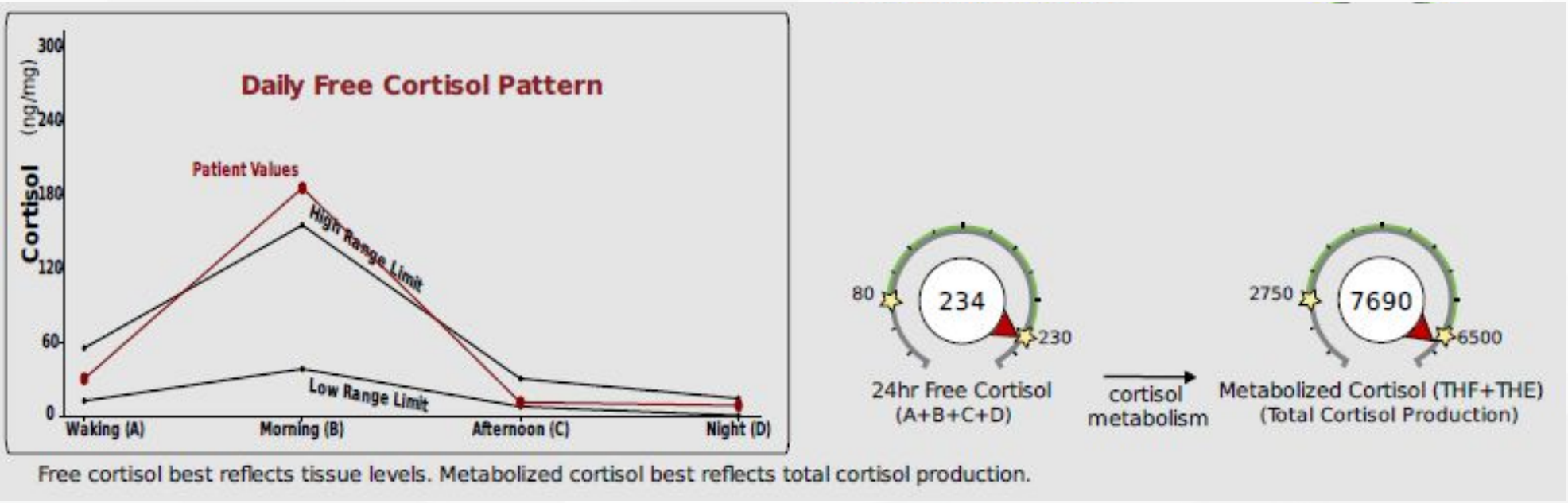
You want to know:

1. How much is free and available?
2. What is their circadian rhythm?
3. Are they deactivating to cortisone?
4. What is their metabolized cortisol?

Looking at the common Free Cortisol and Metabolized Cortisol Patterns

Pattern 1: High Free and High Metabolized

- Because free cortisol levels are high, the higher levels of metabolites simply confirm the ***high output of cortisol***.
- Treatment? Address the cause and calm the HPA axis as needed

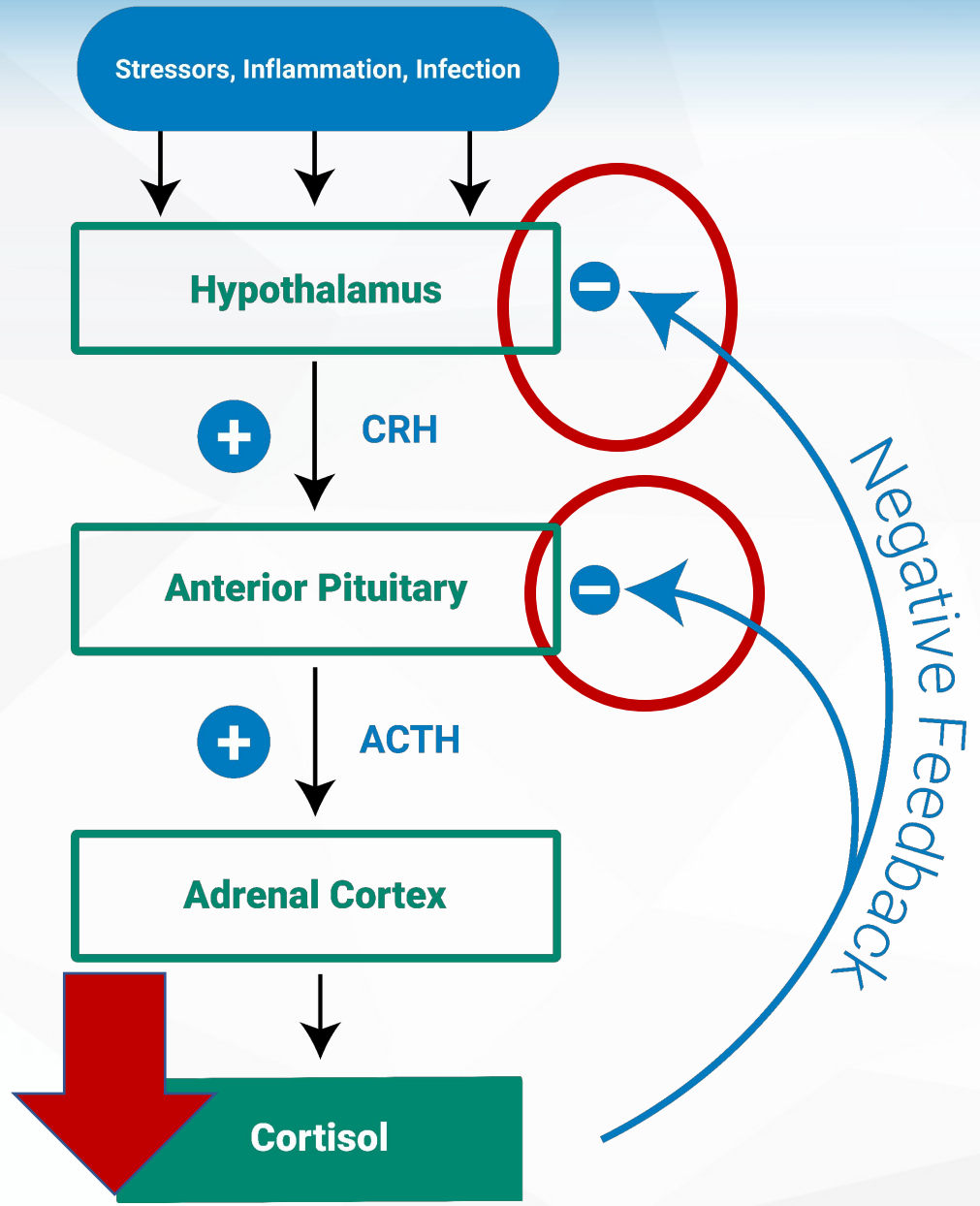


Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

Over Time, High Cortisol Can Result in Low Cortisol

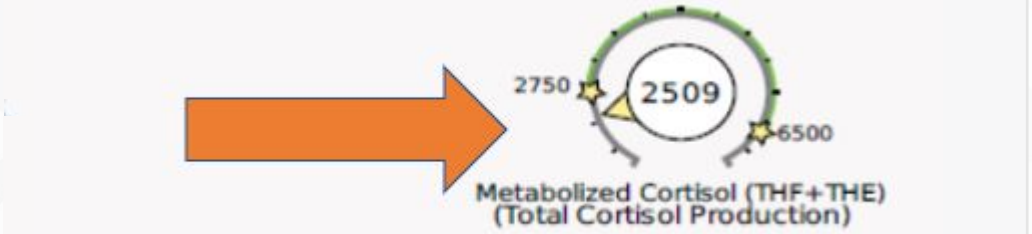
Always keep the feedback loop in mind with chronic conditions

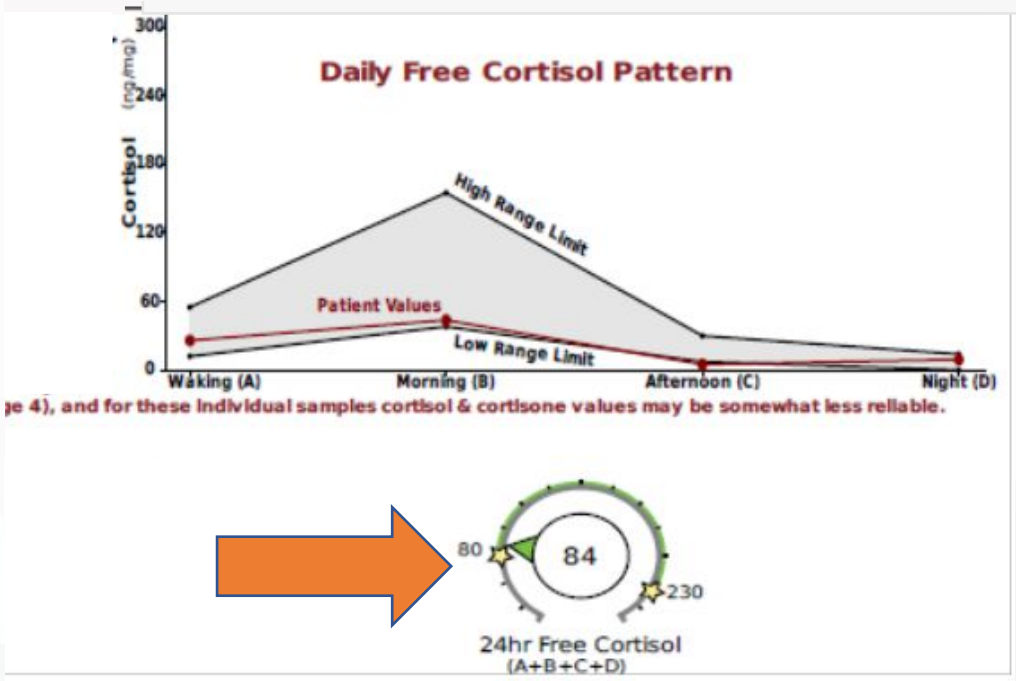
Remember the cortisol feedback loop



Pattern 2: Low Free and Low Metabolized

- Because free cortisol levels are low, the lower levels of metabolites simply confirm ***the low output of cortisol***.
- Treatment? Address the cause and support the entire HPA axis





Pattern 2: Ask them about medications

- Medications that are known to suppress the HPA axis
  - **Corticosteroids**
    - Injections, pills, inhalers, nasal sprays, topical
  - **Opioid pain medications**
    - Will also suppress the HPO and HPG axis

Patterns 3 & 4:

Metabolized and Free Cortisol Don’t Match

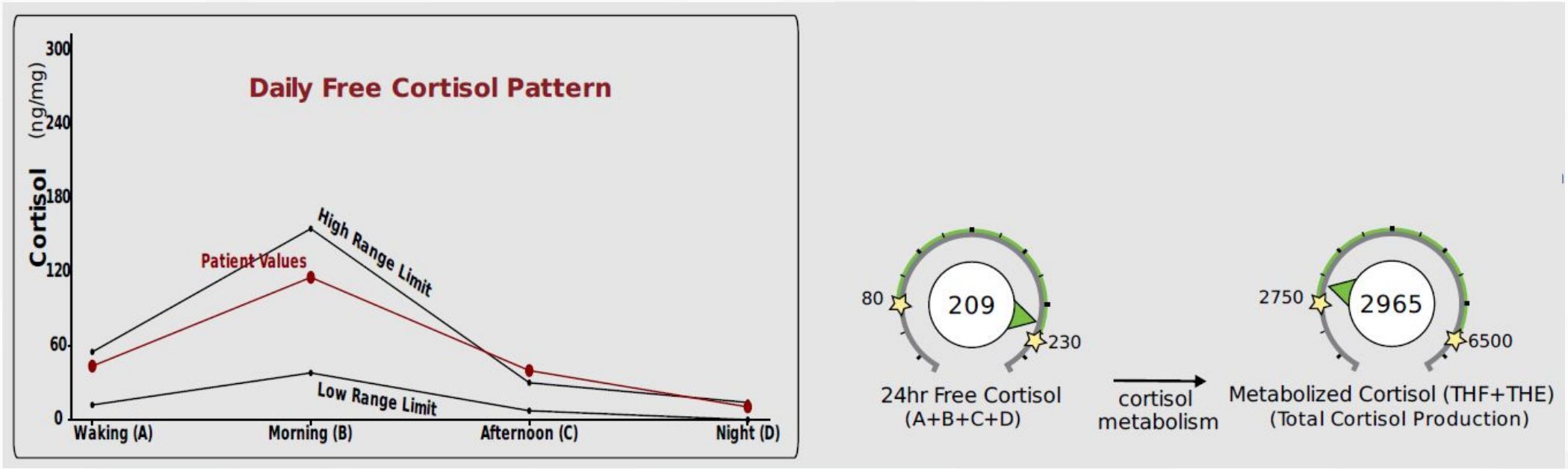
When free and metabolized cortisol is decidedly different

(one is much lower or higher than the other)

abnormal cortisol clearance is implied.

Pattern 3: High Free and Low Metabolized

- If metabolite levels are generally lower than free cortisol, the patient may have ***sluggish cortisol clearance***



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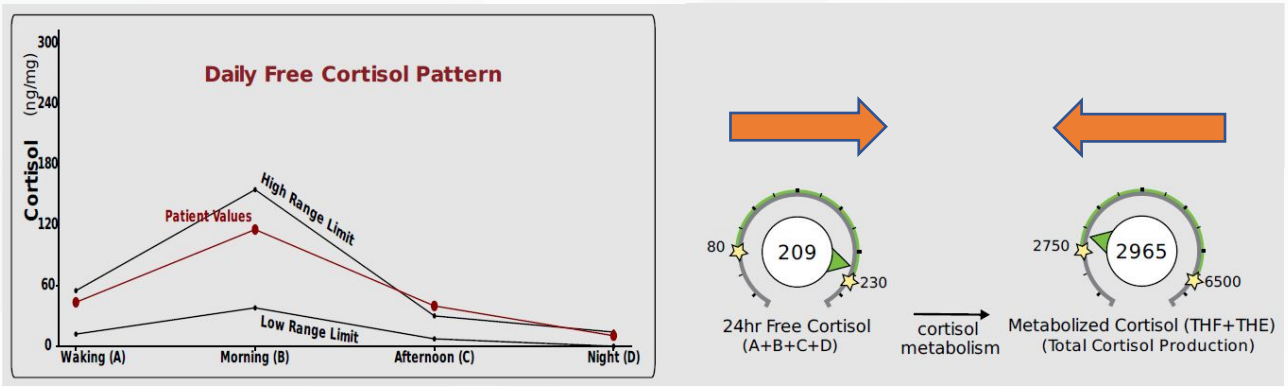
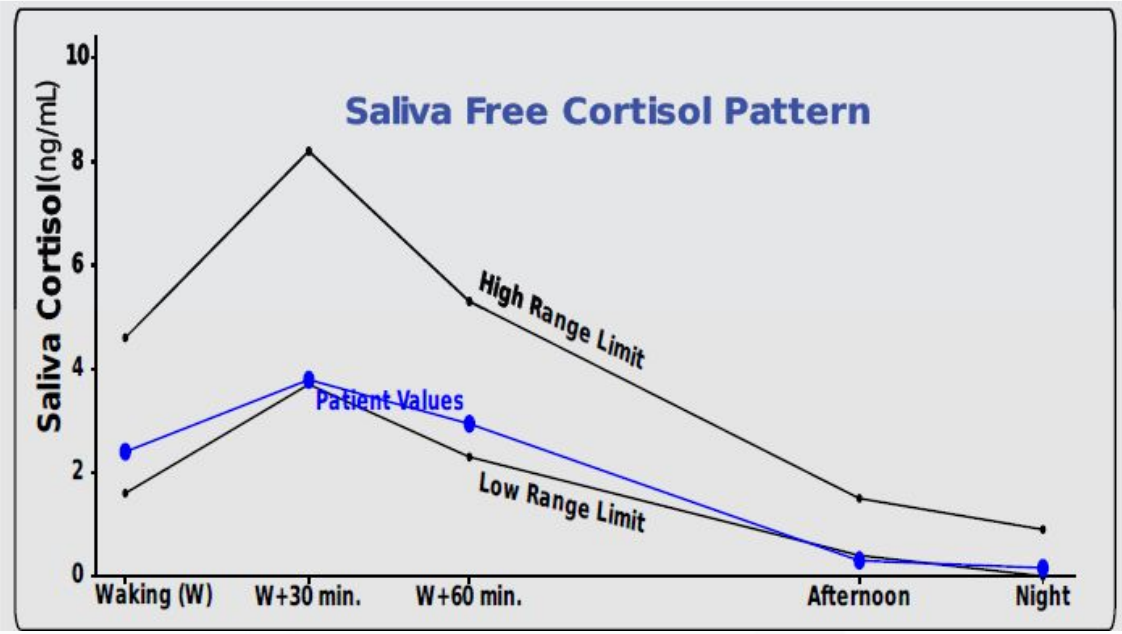
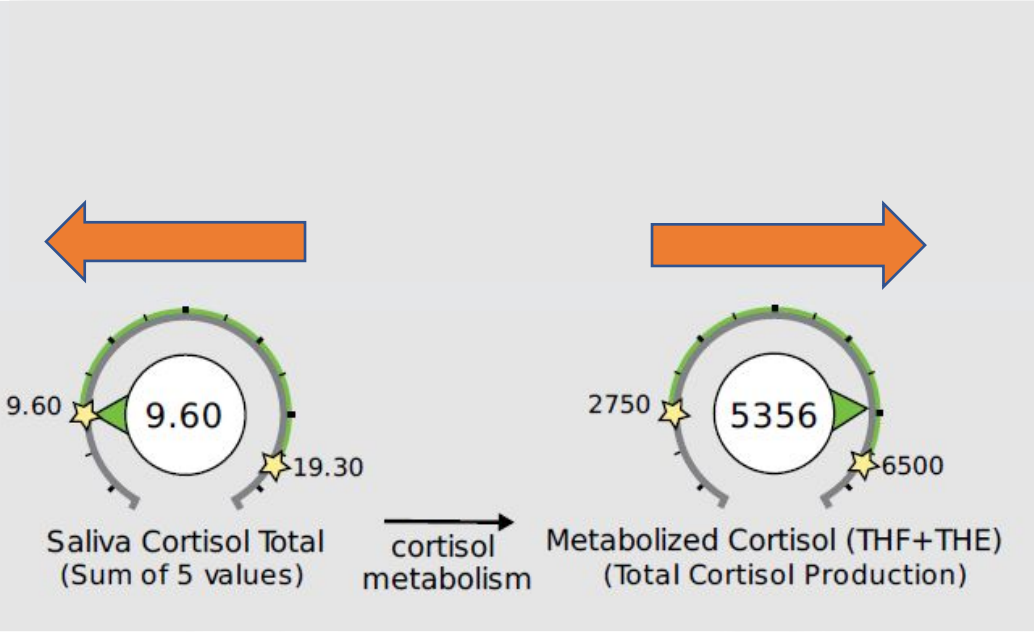


- This pattern is common in patients with ***hypothyroidism***
- Also observed with ***poor liver function, anorexia and serious illness.***

Pattern 4: Low Free and Higher Metabolized

- If metabolite levels are generally higher than free cortisol, the patient may have ***rapid cortisol clearance***





Pattern 4: Low Free and Higher Metabolized

- Even though free cortisol is low, cortisol production is higher.
- This pattern of ***rapid cortisol clearance/metabolism*** is seen in:
  - Obesity
  - Hyperthyroidism patients
  - Possibly with long-term stress
  - Possibly with chronic fatigue (research is mixed)
- Treatment? Address the cause and support the HPA axis without stimulating more cortisol production

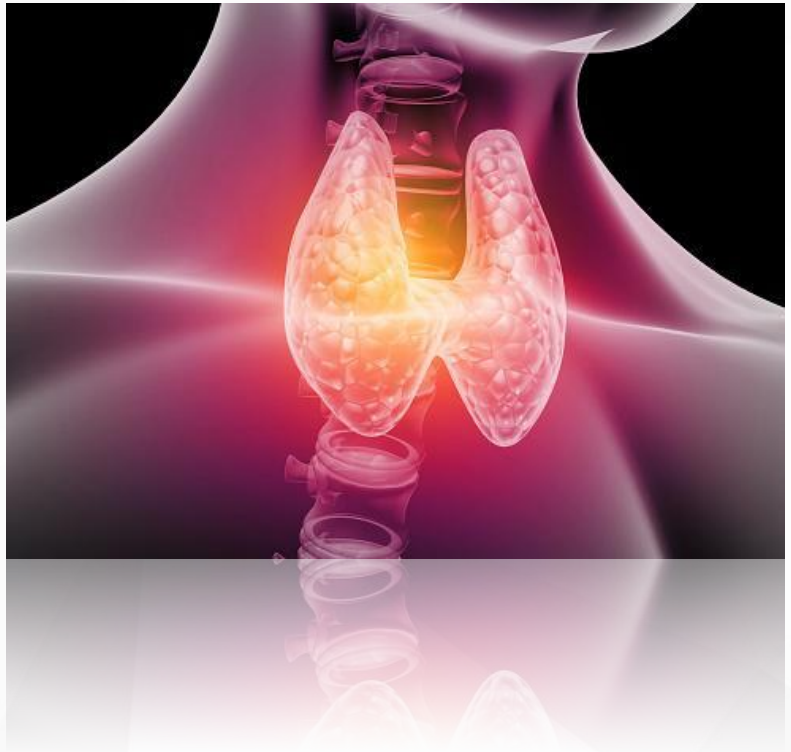
1. Cleare A. The neuroendocrinology of chronic fatigue. Endocrine Reviews. 2003;24(2):236-252.
2. Jerjes WK, Taylor NF, Peters TJ, et al. Urinary cortisol and cortisol metabolite excretion in chronic fatigue syndrome. Psychosom Med. 2006;68(4):578-582.

Adipose acts a little differently

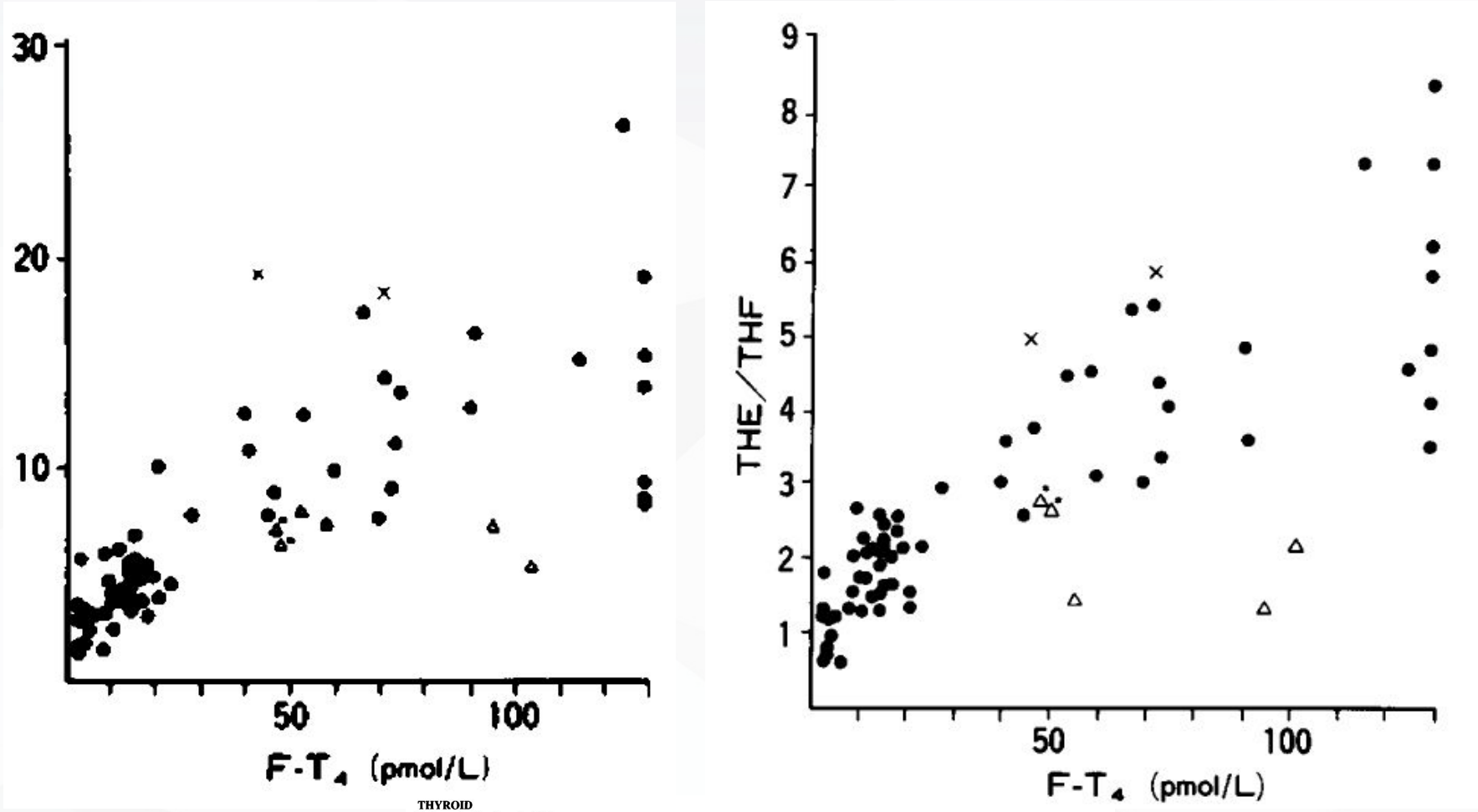
- The enzyme that activates cortisone into **cortisol is 11bHSD1**
- Adipose tissue (especially visceral fat) **has higher levels of 11bHSD1 = more cortisol**
- Visceral fat drains directly into the **portal vein**
- Excess visceral fat creating excess cortisol goes to the liver and is metabolized = **higher metabolized cortisol**

- Andrews RC, Herlihy O, Livingstone DEW, Andrew R, Walker BR. Abnormal Cortisol Metabolism and Tissue Sensitivity to Cortisol in Patients with Glucose Intolerance The Journal of Clinical Endocrinology & Metabolism. 2002; 87(12):5587-5593.
- Mauvais-Jarvis F, Clegg DJ, Hevener AL. The Role of Estrogens in Control of Energy Balance and Glucose Homeostasis . 2013; 34(3):309-338.

How does the thyroid affect cortisol results



Thyroid Directly Impacts Cortisol Clearance

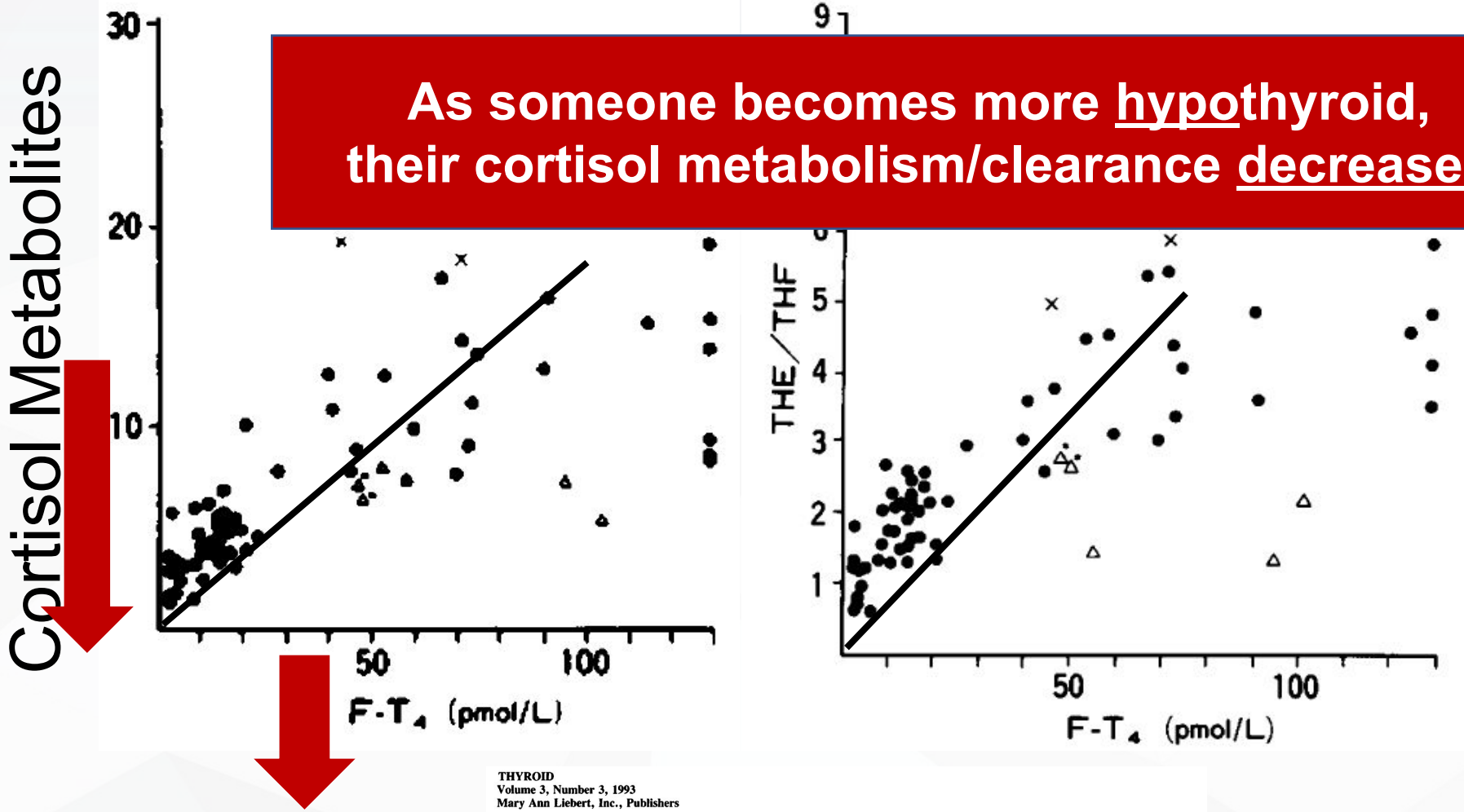


THYROID
Volume 3, Number 3, 1993
Mary Ann Liebert, Inc., Publishers

Urinary Cortisol Metabolites in the Assessment of Peripheral Thyroid Hormone Action: Application for Diagnosis of Resistance to Thyroid Hormone

Thyroid Directly Impacts Cortisol Clearance

As someone becomes more <u>hypo</u>thyroid, their cortisol metabolism/clearance <u>decreases</u>



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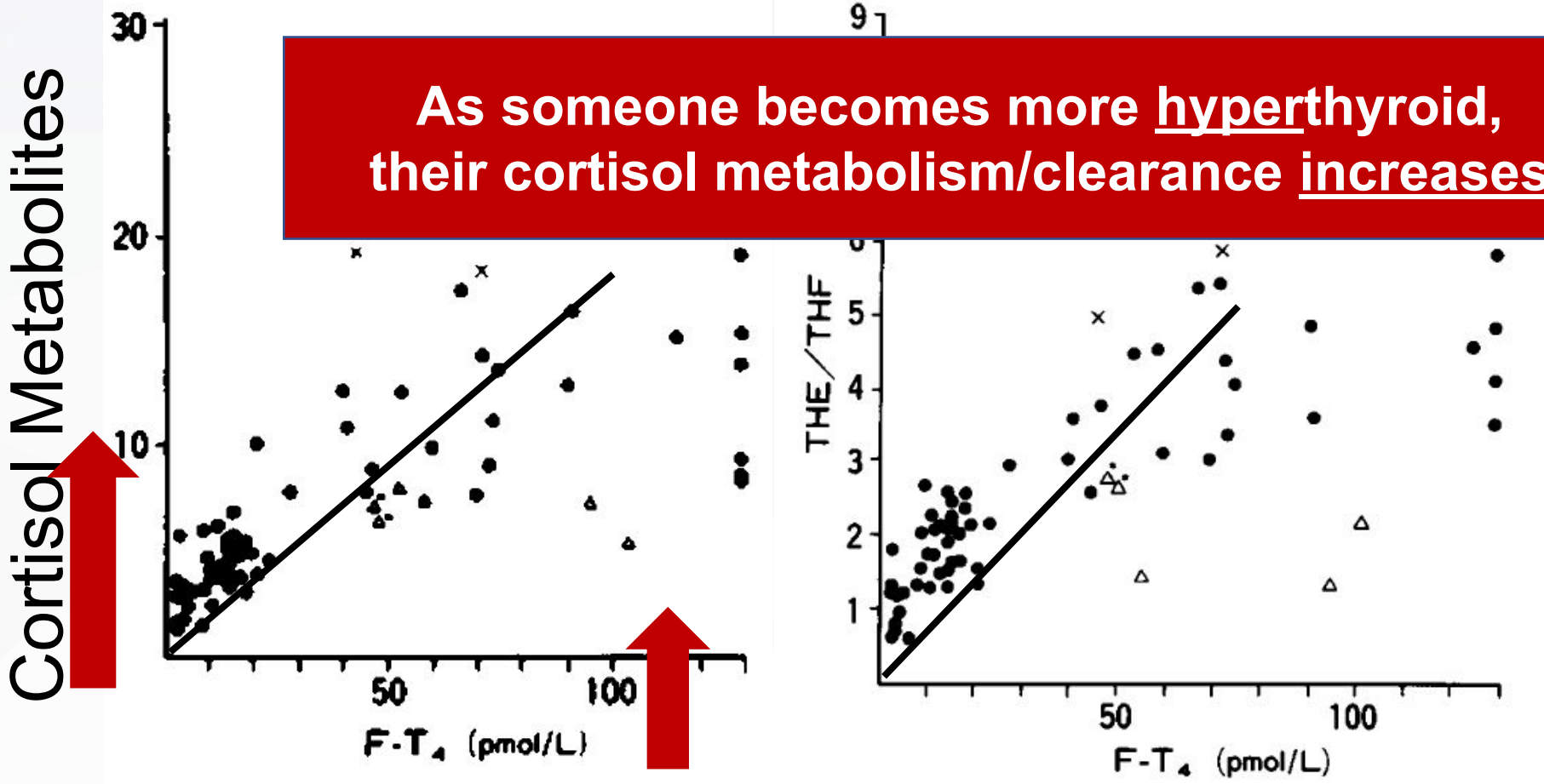

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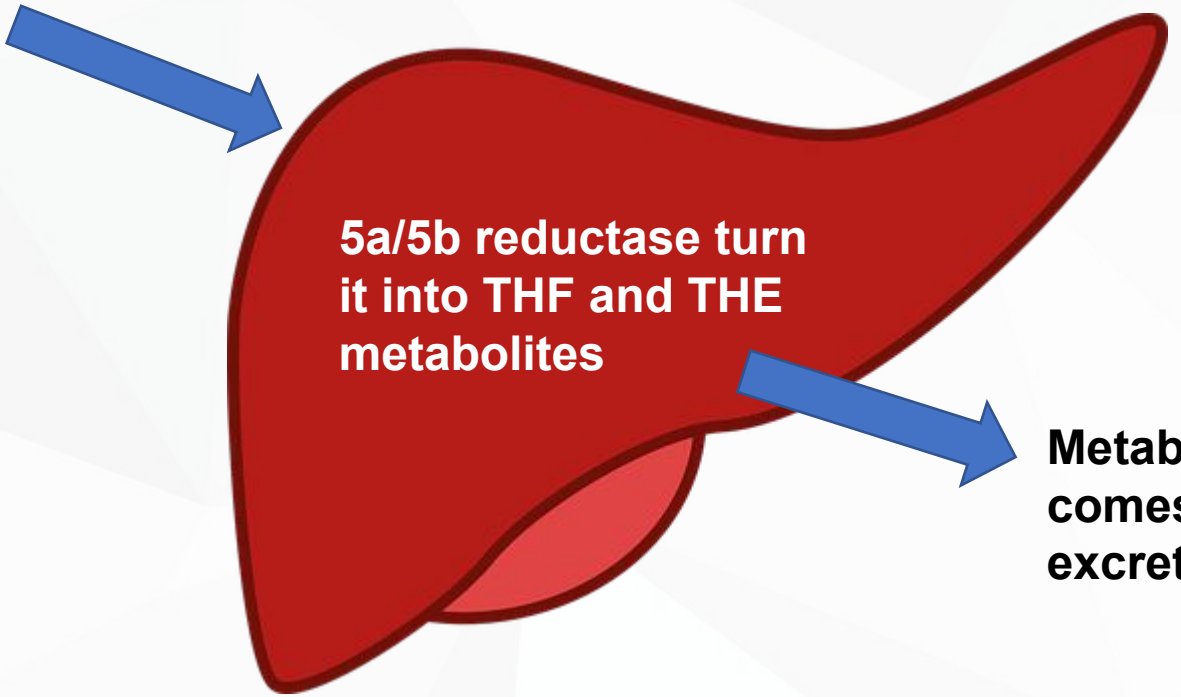
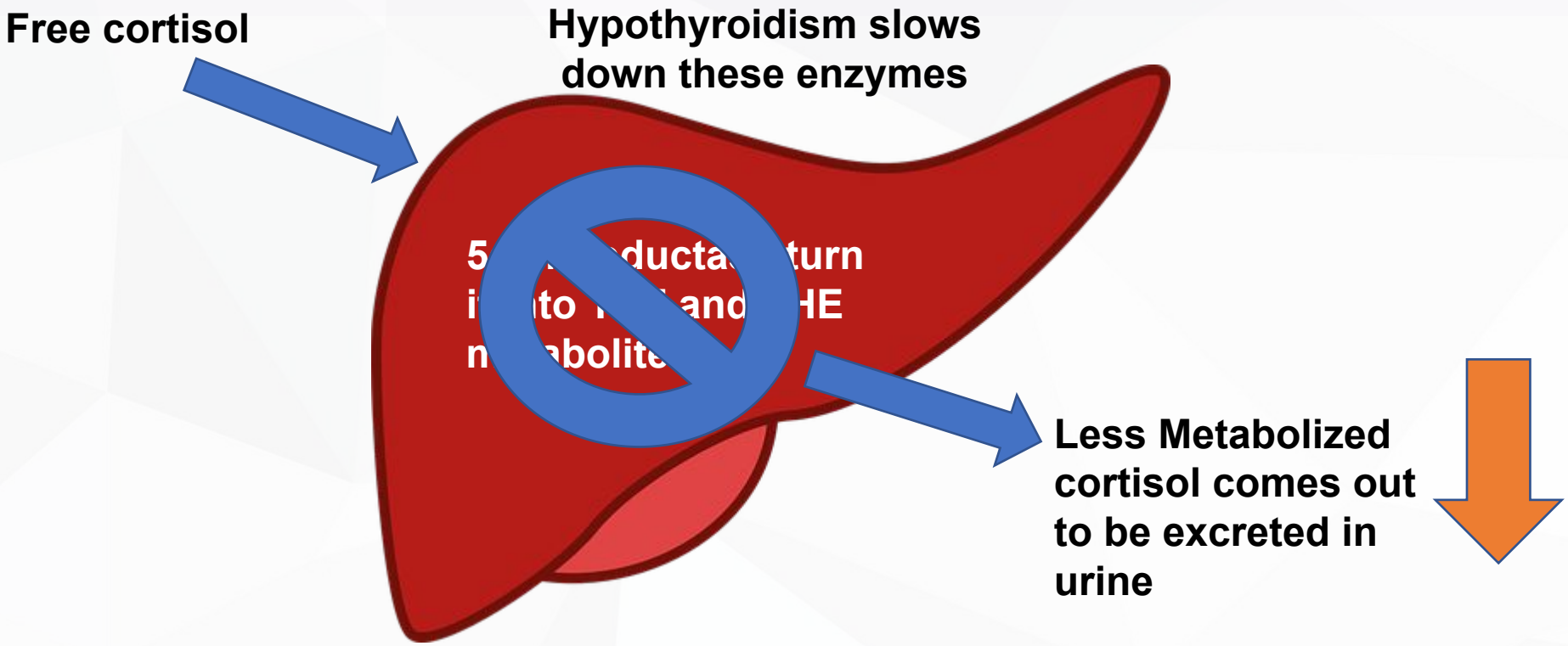
The 5a/b reductase in the liver

Most but not all free cortisol comes in



Metabolized cortisol comes out and is excreted in urine

The 5a/b reductase slow down in the liver



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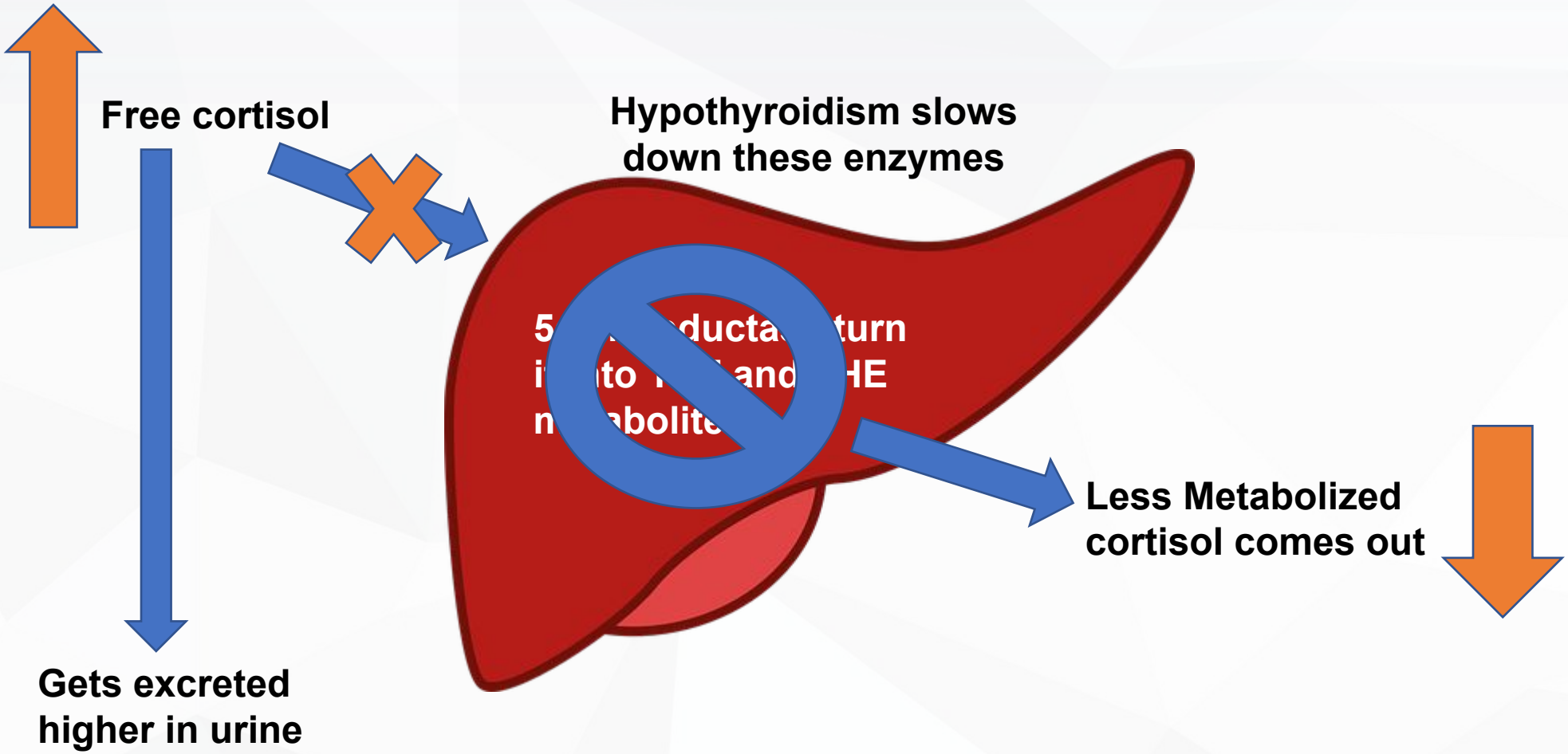

Thyroid Can Directly Impact Cortisol Metabolism

In these 2 patterns, you might want to consider **treating the thyroid first when there is an abnormal thyroid serum (specifically Free T3)**
(but okay to support the HPA at the same time)

Citations

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- Chrousos GP. Hypothalamic –pituitary-adrenal axis and immune mediated inflammation. *N Engl J Med*. 1995; 332(20): 1351-1362
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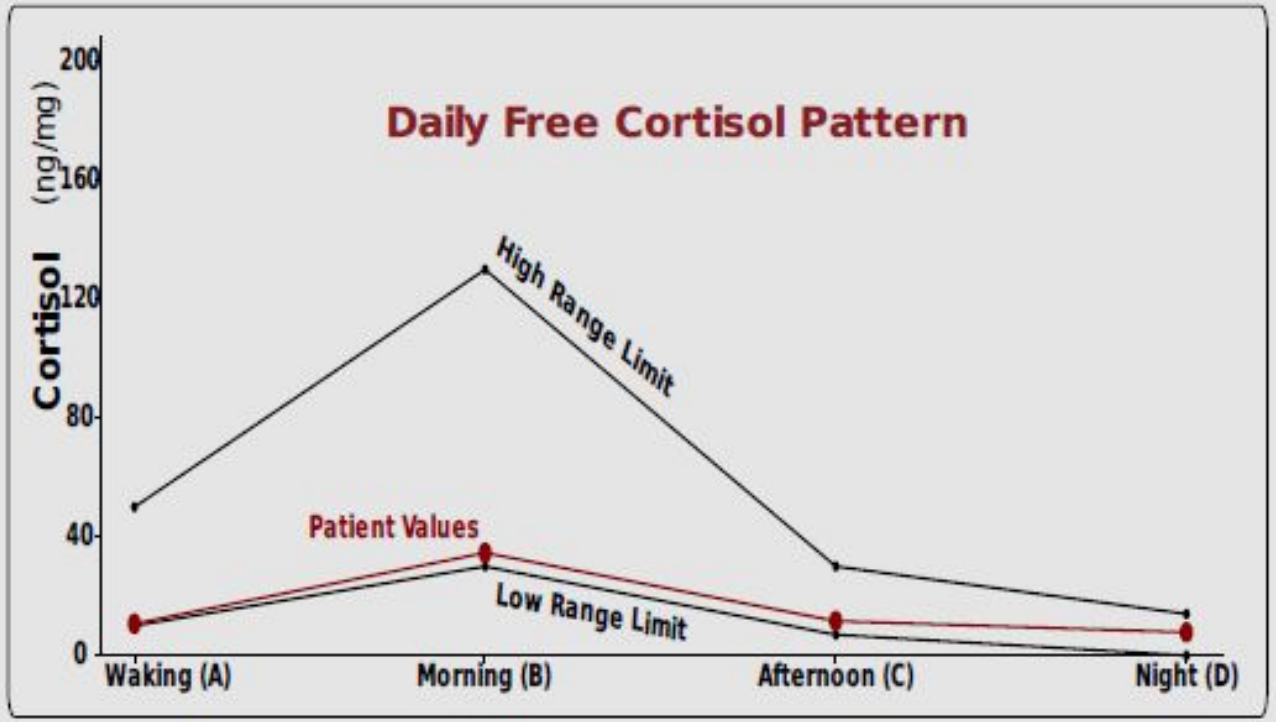
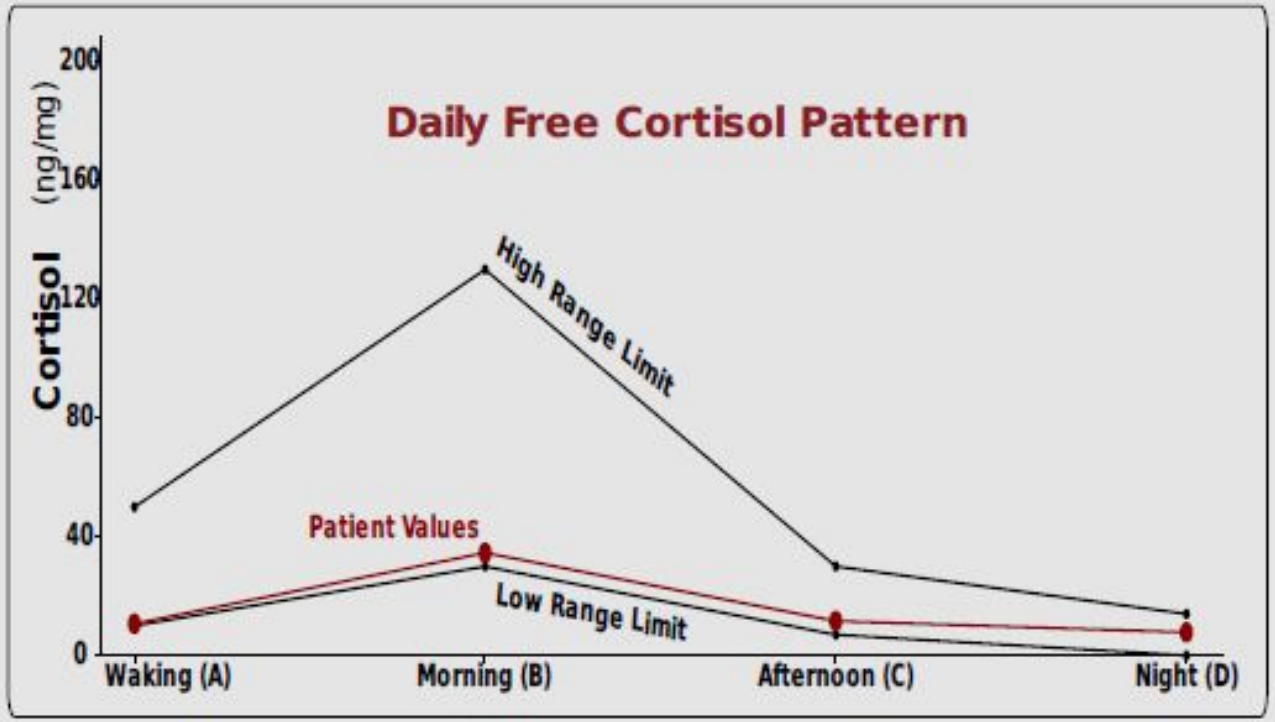
- Holtorf K. Peripheral thyroid hormone conversion and its impact on TSH and metabolic activity. J Restorative Medicine. 2014;3:30-52. DOI:10.14200/jrm.2014.3.0103

Pattern 4.5: Normal Metabolized, Low Free?

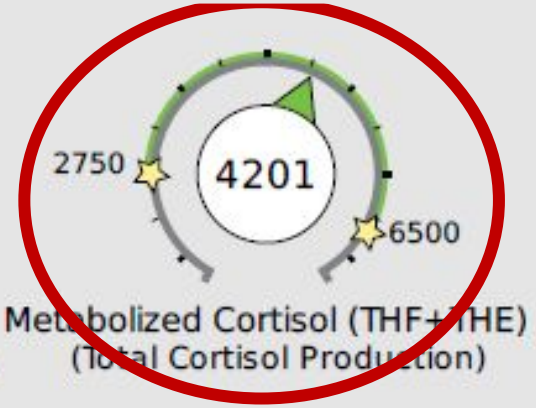


cortisol metabolism

Pattern 4.5: Normal Metabolized, Low Free?



cortisol metabolism



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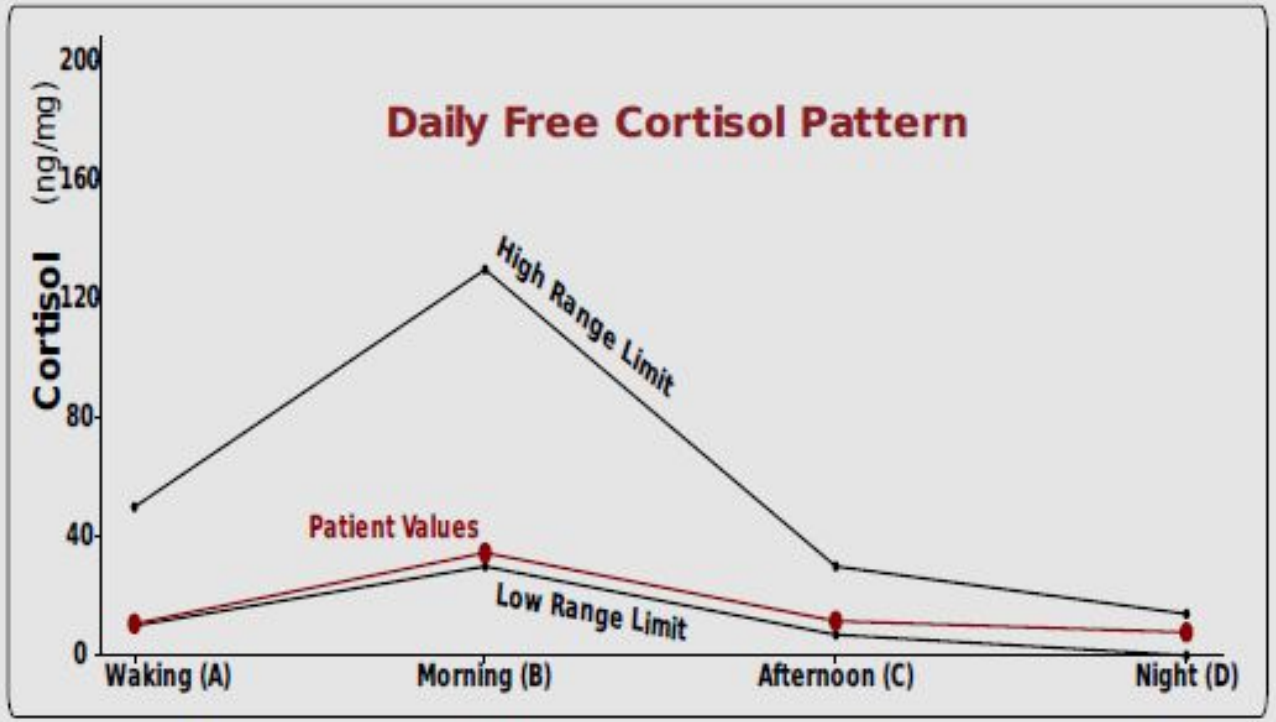
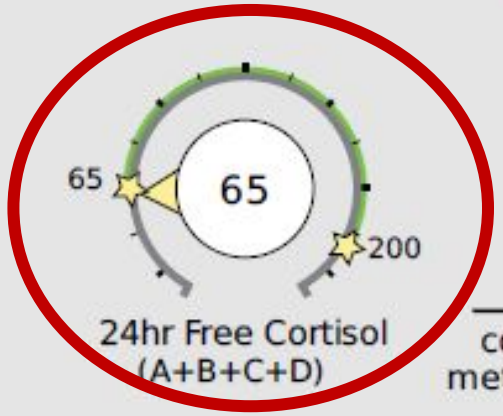
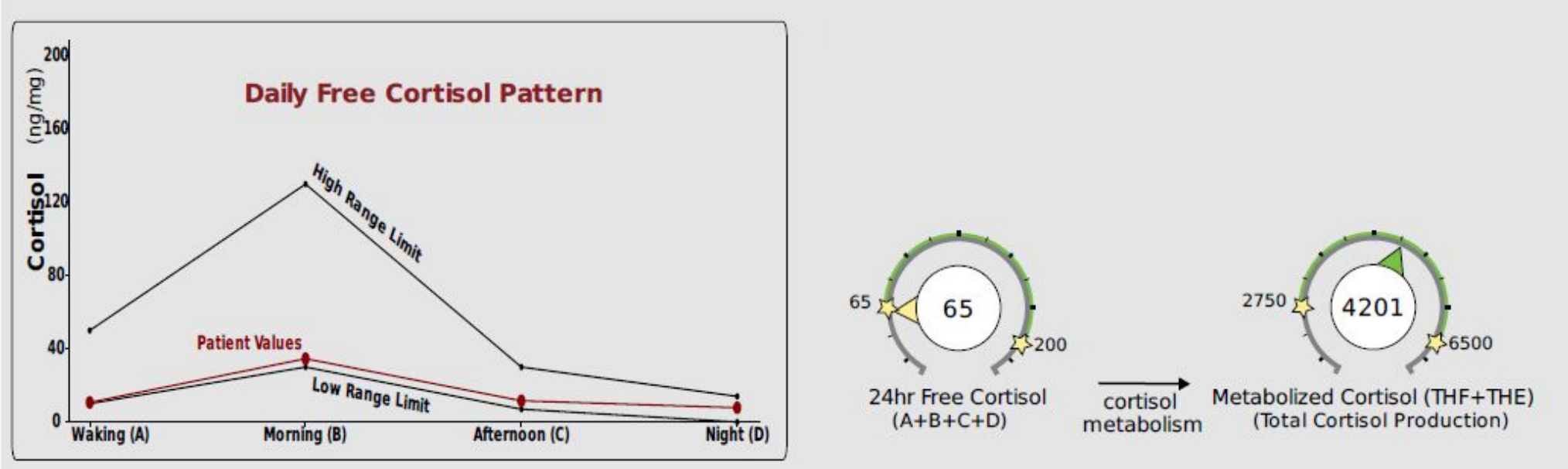




cortisol metabolism

Normal Metabolized, Low Free?

- Do they deactivate/favor 11bHSD2 = more cortisone?
- Do they have elevated cortisol binding globulin(CBG)/Transcortin?



Summary:

1. Cortisol signaling starts in the brain…
2. …and ends in the mitochondria.
3. HPA axis dysfunction is very real beyond Addison's or Cushing's.
4. The thyroid has a huge impact on the HPA axis output.
5. Proper cortisol testing gives you broader, more comprehensive answers.

…and that concludes our talk

Thank you for listening.

Lecture questions?
info@dutchtest.com

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