Cortisol: A Key Biomarker

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Disclaimer

This lecture and the cited scientific literature, when referring to women/females or men/males, are referring to individuals born biological females or males.

Objectives

- Quick review from past 2 webinars: Just the facts
- Debunking the myth: there is no pregnenolone steal
- Cortisol and the stress response
- DHEA and the stress response
- Why measure cortisol, cortisol metabolites, and the cortisol awakening response
- Assessing HPA axis function and dysfunction

Review

Females: What Tests Do We Do?

- Serum laboratory testing
  - CBC, CMP, SHBG
    - 1st year: baseline, 3, 6, 12 months
    - Ongoing: 2-3x year
  - E2, TT, FT (LC-MS/MS)
    - 1st year: baseline, 3, 6, 12 months
    - Ongoing: 2-3x a year
  - FSH, LH, prolactin
    - Prolactin: baseline
    - FSH, LH: baseline
  - Other
    - TFT's, vitamin D, etc.
    - Glycemic parameters

- GYN exam, mammography, BMD
  - GYN, mammography
    - 1st year: baseline, per guidelines on MHT
  - BMD
    - Baseline, per guidelines
      - Osteopenia/osteoporosis Q2 years
- DUTCH testing
  - 1st year: baseline, 6, 12 months, 2-3x year
  - HPA axis: saliva or urine
  - Hormones
    - To evaluate hormone metabolism
    - Evaluate total androgen production and activity
    - To optimize detoxification pathways

Females and E2

- Determine reproductive stage using the modified straw criteria
- Peri and postmenopausal females < 6 years from menopause probably do best with trough serum LC-MS/MS levels ~ 45pg/mL, range 40 to ≤ 60pg/mL, or DUTCH levels 1.8 to 2.0ng/mg
- Postmenopausal females > 6 years, but < 10 years from menopause probably do best with trough serum LC-MS/MS levels ~ 30-40pg/mL, range > 20 to < 40pg/mL, or DUTCH levels > 0.7-1.8ng/mg
- Postmenopausal females > 10 years from menopause or > 60 years old do best with trough serum LC-MS/MS levels ~ 30pg/mL, range 20 to < 40pg/mL, or DUTCH levels 0.7 to ~ 1.3-1.5ng/mg

Female Starting E2, E3, and Pg Doses

- Compounded E2 and E3 creams or gels
  - DS does not recommend vaginal E2 for hormone replacement therapy
  - Peri and PMP females < 6 and up to 10 years from menopause start with
    - A 50/50 mix: 0.5mg E2/E3
      - Biest (50/50) 2mg/mL using a topiclick (0.25mL/click), apply 2 clicks daily
  - Peri and PMP females > 10 years from menopause start with
    - A 50/50 mix: 0.25mg E2/ 0.25 E3
      - Biest (50/50) 2mg/mL using a topiclick (0.25mL/click), apply 1 clicks daily
    - An 80/20 mix: 0.80 E3 /.20 E2
      - Biest (80/20) 2mg/mL using a topiclick (0.25mL/click), apply 2 clicks daily
- Patch E2 therapy
  - Start with a TD E2 0.025mg/d patch

Female Starting E2, E3, and Pg Doses

- Pellet E2 therapy
  - In females with a uterus, never
  - In females without a uterus, start with creams/gels/patches and transition to pellets once understand how they metabolize hormones and have pellet experience
  - Pellet dose in females without a uterus typically 6mg
- Vaginal E3
  - Typical dose: 0.5mg at HS x 2 weeks, 2x a week x 2 weeks, then prn
- Progesterone
  - Oral micronized progesterone: 200mg at HS
  - Vaginal micronized progesterone: 100mg at HS
  - Don’t use transdermal topical progesterone to protect the endometrium

Females and T: What Do We Know?

- TD/vaginal/pellet T therapies improve symptoms AND clinical outcomes at serum levels ≥ upper limit of the reference range
- Females synthesize ~ 0.2-0.25mg/d with mid-luteal levels ranging from 15-228ng/dL with a mean ~ 58ng/dL (LC-MS/MS)
- Dosing should be 1/10th to 1/15th a male dose: Typical male starting T gel dose = 50mg/d: 3.5-5.0mg/d to maintain physiologic levels
- Most T studies document that serum total T, FT, bioavailable T levels at the high end of the RR are important for improved clinical success
  - T patch: 0.3mg/d; T gel: up to 10mg/d or 50mg/week; T cream: up to 10mg/d; T pellets: 1.0-1.5mg/kg every 3-4 months or ~ 75mg/Q3-4 months

Davis SR, et al. J Clin Endocrinol Metab. 2019; 104(10): 4660–4666.
Parish SJ, et al. J Sex Med. 2021; 18(5): 849-867.

Female Testosterone Starting Doses

- Compounded creams and gels
  - Typical starting dose for topical application is 1.0mg/d
  - Typical starting dose for vaginal application is 0.5mg/d
- Injections
  - Typical starting dose is 5mg/week
- Pellets
  - Pharmacokinetics: pellets last ~ 100-120 days
  - In general, for every 75ng/dL want to increase TT, give 75mg
  - Factors to consider include weight, activity, HPA axis, gut
    - Site reactions are often related to HPA axis dysfunction

Testosterone Female Pellet Dosing

- Pellet dosing
  - Wide dosing range in the literature
  - Dosing is weight based, but consider activity level, typical starting doses (1.0-1.5mg/kg)
    - < 100 pounds: 50-75mg pellet
    - 100-120 pounds: 75-100mg pellet
    - 120-145 pounds: 100-112.5mg pellet, consider another delivery system until lose weight
    - 145-165 pounds: 112.5mg pellet, consider another delivery system until lose weight
    - > 165 pounds: choose another delivery
- TTh monitoring
  - If trough TT levels are > 60ng/dL or < 35ng/dL, consider adjusting dose or frequency
    - Pellets, creams, gels, or patches: after 3 months
    - Injections: after 1-2 months

Males: What Tests Do We Do?

- Serum laboratory testing
  - CBC, CMP, SHBG
    - 1st year: baseline, 1, 3, 6, 12 months
    - Ongoing: 2-3x year
  - Total testosterone (TT), free T (FT), E2 (LC-MS/MS)
    - 1st year: baseline, 1, 3, 6, 12 months
    - Ongoing: 2-3x a year
  - FSH, LH, prolactin
    - Prolactin: baseline
    - FSH, LH: baseline, ± 1, 3 months
      - Gonadorelin, clomid, TTh
  - Other
    - TFT's, vitamin D, etc.
    - Glycemic parameters

- PSA, DRE, testicular exam
  - PSA and DRE
    - 1st year: baseline, 3, ± 6, 12 months
  - Testicular exam
    - Baseline
    - Ultrasound: if diagnosis is unsure
- DUTCH testing
  - 1st year: baseline, 6, 12 months, 2-3x year
  - HPA axis: saliva or urine
  - Hormones
    - To evaluate hormone metabolism
    - Evaluate total androgen production and activity
    - To optimize detoxification pathways

Raising TT Levels in Males

- Regardless of delivery, a serum trough TT level > 500ng/dL improves sexual function, body composition, BMD, and CV outcomes
- Serum total LC-MS/MS E2 levels should be maintained between 20-40pg/mL, goal 30-35pg/mL for optimum benefit
- Young males on clomid, gonadorelin, kisspeptin
  - Clomid: 25mg QOD to QD depending on baseline TT, E2, FSH, LH
    - Anastrozole need dependent on baseline and treatment E2 levels (LC-MS/MS)
  - Kisspeptin: 100-200mcg 1-2x per week
  - Gonadorelin: 100mcg 1-2x per week
- Young males with pretreatment high-end LH (1.5-9.3mIU/mL), may need TTh + gonadorelin

Formulation	Typical Starting Dose	Advantages	Disadvantages
Patch	• Available in 2.5 and 5mg • Typical starting dose is 5mg • Apply to clean dry area • Rotate areas	• Re-creates circadian rhythm	• Skin irritation, contact dermatitis
Gel or cream	• Available as FDA-approved or compounded products • **Initial T gel dose: 50mg/d** • Consider adding Chrysin 2.5-4% to start (an aromatase inhibitor)	• Dosing flexibility • Application is easy • Well tolerated • Erythrocytosis < than with injections and pellets	• Potential transference • Creams – decreased absorption with common versa base • Increase absorption using an atrevis base
Intranasal gel (Natesto)	• **11mg total** (2 pumps, one in each nostril [5.5mg each]) **3 times a day** (6-8 hours apart)	• **Daily dose is 33mg/d** • Minimal transfer risk	• 3 times a day application inconvenient • Nasal issues limit its use
Oral capsule (Jatenzo)	• Available as FDA-approved • Initial dose: **237mg BID with food** • Dose range: 158-396mg BID	• Lipophilic and absorbed through the lymphatics • Bypasses first-pass metabolism	• May increase BP and possibly CV events • Would avoid in older men
Oral capsule (TLANDO)	• Available as FDA-approved • Initial dose: **225mg BID with food**	• Available as FDA-approved	• May increase BP and possibly CV events • Would avoid in older men

Injections: SQ* or IM
*SQ delivery require a lower dose than IM
	• Cypionate or enanthate: ½ life ~ 12 days
	  ○ 50-100mg weekly
	  ○ **25-50mg 2x week**
	• Propionate: ~ 4.5 days
	  ○ 10-25mg 3x week
		• Inexpensive
		• Bi or Triweekly injections avoids the highs and lows
		• Use enanthate in older males to avoid water retention commonly seen with cypionate
			• Invasive, painful, injection site reactions
			• Highest incidence of erythrocytosis

Pellets	• **Average starting dose is 600-750mg** • Note: for every 75ng/dL increase in TT, insert a 75mg pellet • Baseline TT = 300ng/dL, goal is 900ng/dL, dose 600mg	• Infrequent administration – leave it and forget it for ~ 100-120 days	• Requires understanding of hormone metabolism and detoxification • Requires surgical incision • Pellets may extrude • Rarely: local hematoma, infection

Males and Prostate

- Testosterone, TTh, DHT do not cause prostate cancer
- DHT may increase prostate size and BPH symptoms
- Urology consult if:
  - The PSA increases > 1.4ng/mL in any 12-month period, a PSA > 4.0ng/mL at any time (some experts suggest a PSA > 3.0ng/mL at anytime)
  - The PSA velocity is ≥ 0.25ng/mL/year using the PSA level after TTh for 6 months when the PSA is ≤ 2.5ng/mL
  - The PSA velocity is ≥ 0.75ng/mL/year using the PSA level after TTh for 6 months when the PSA is 4-10ng/mL

Cortisol Physiology

Debunking the pregnenolone steal myth

psychologicalscience.org

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How Is Cortisol Made?

Some hormones are made from circulating precursors; however, CORTISOL is not one of those hormones

Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

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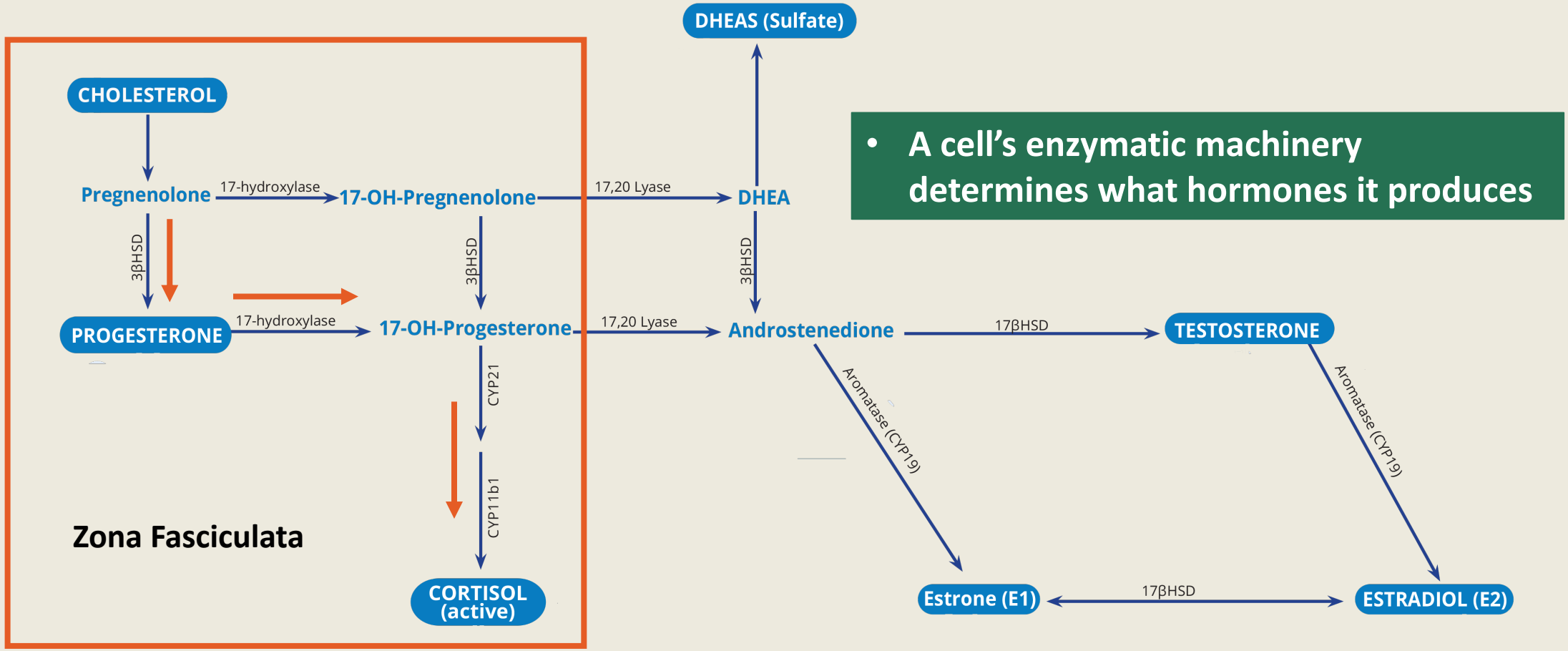
There is NO "Pregnenolone Steal"



- **A cell's enzymatic machinery determines what hormones it produces**

Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

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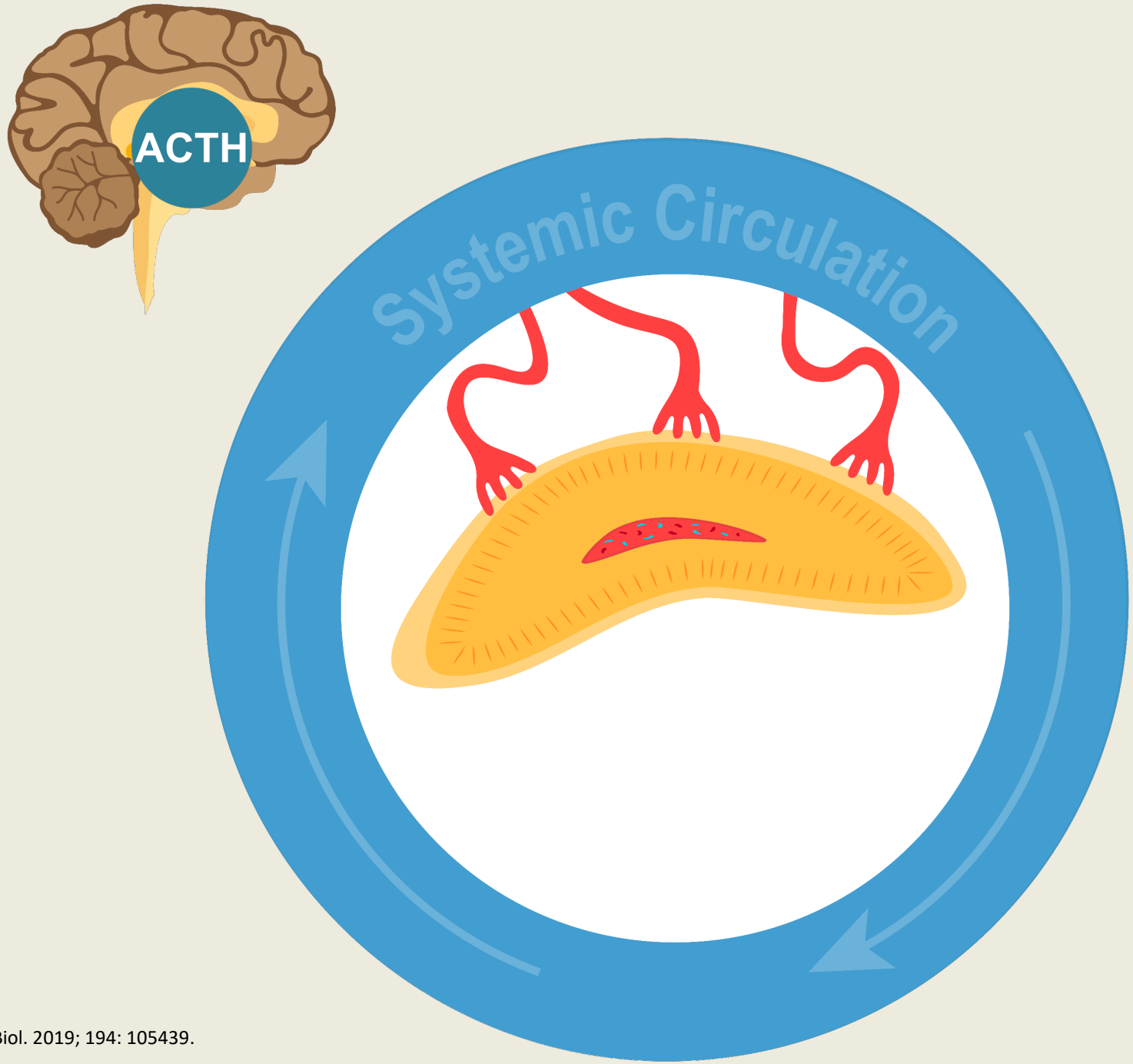
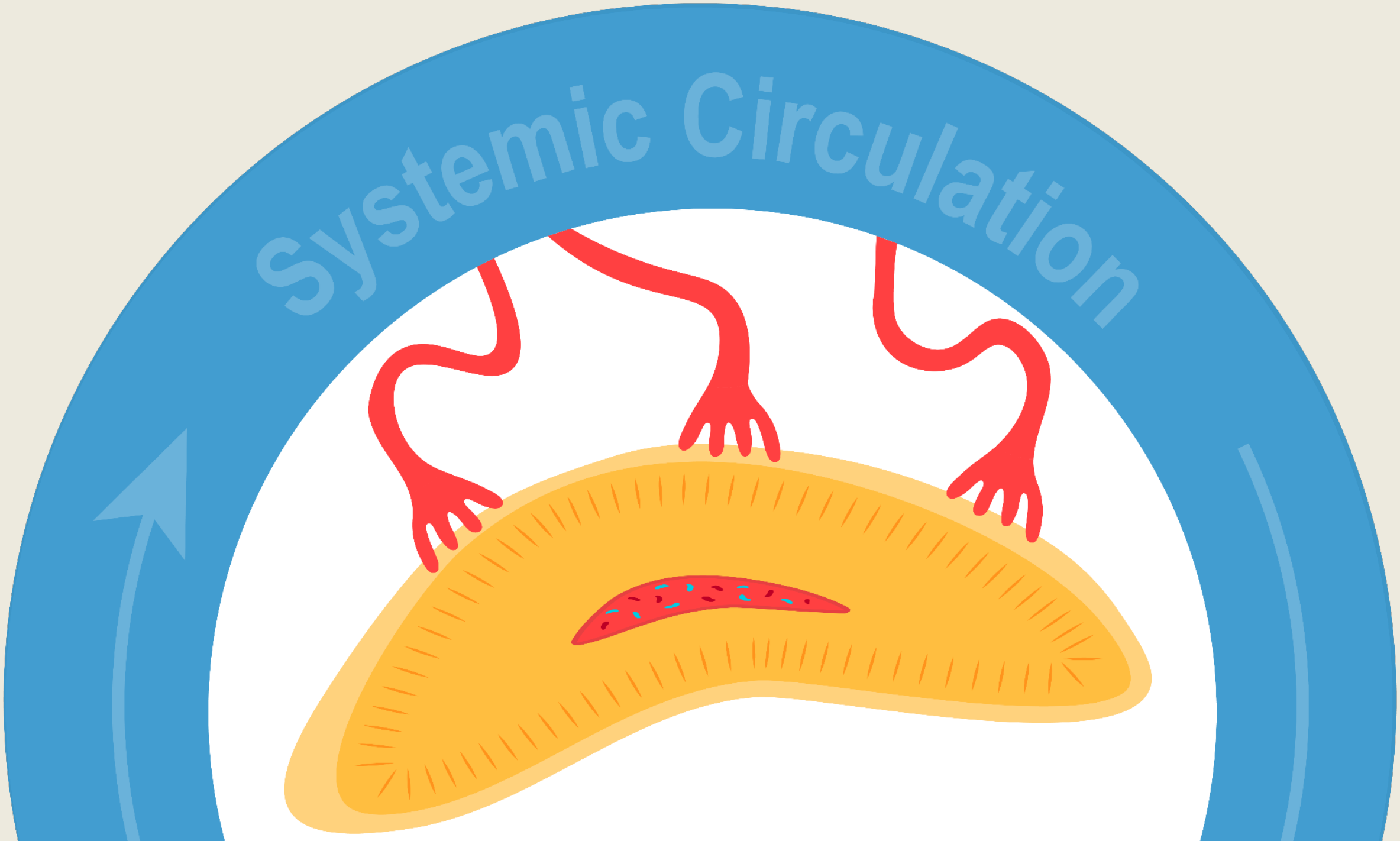
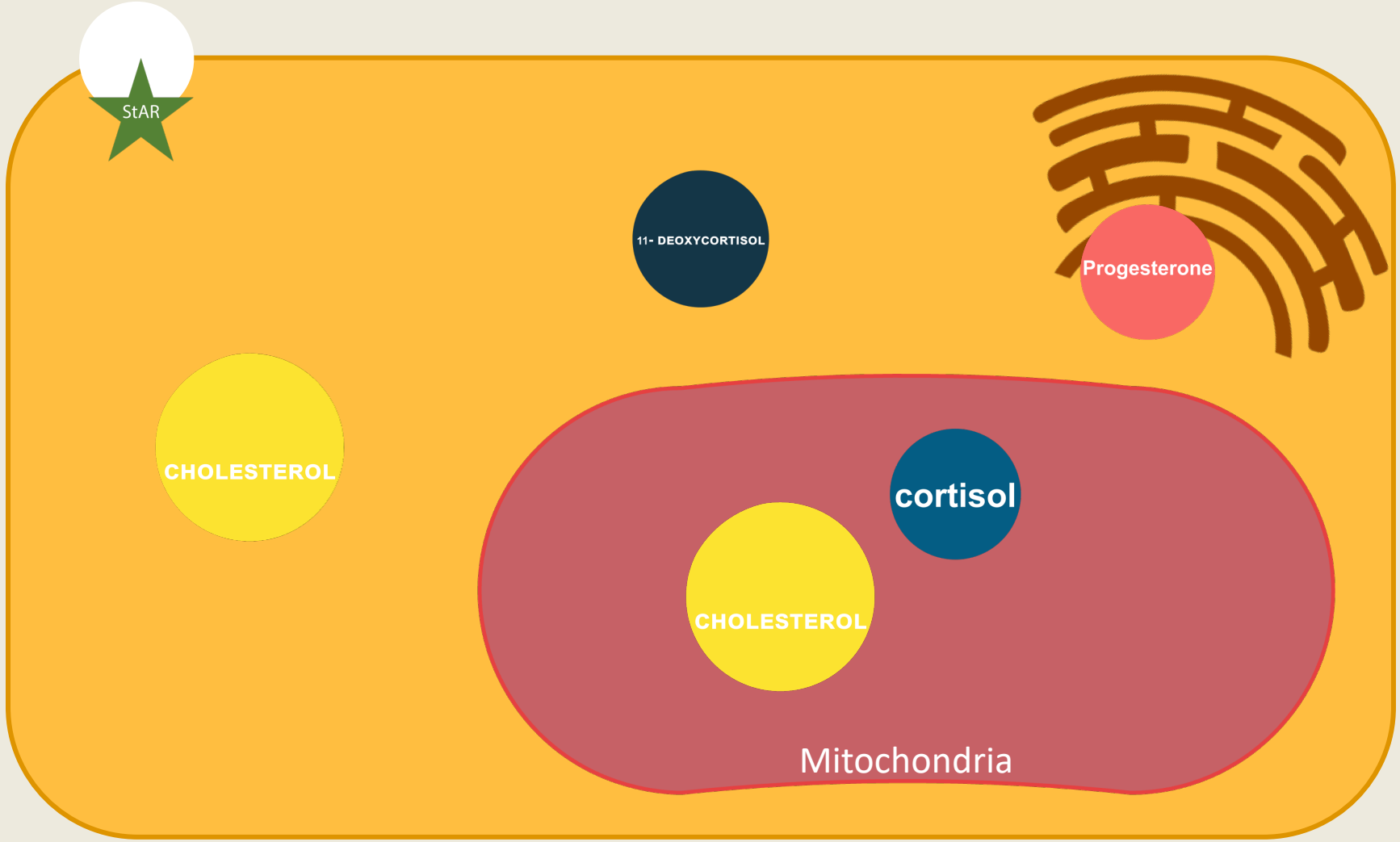
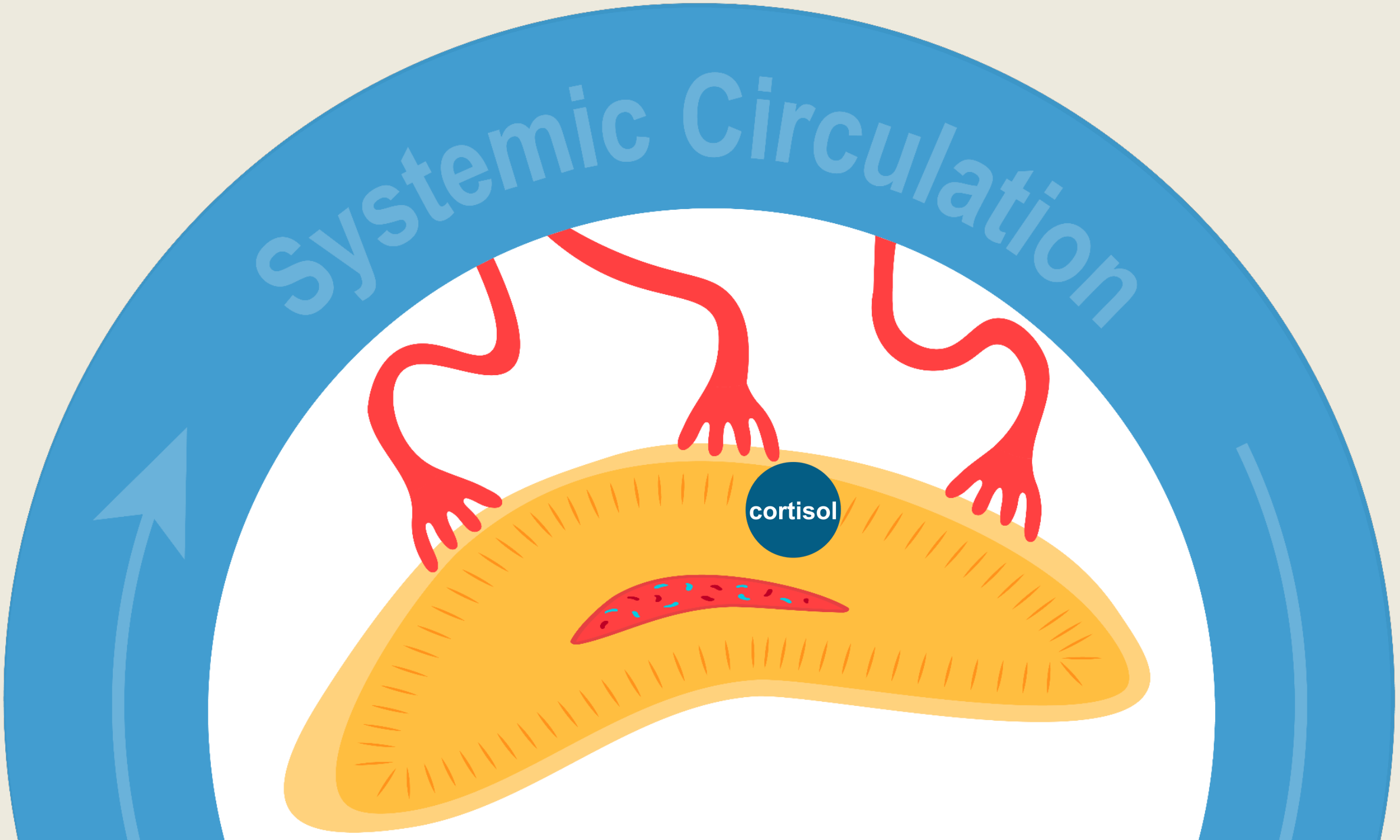


Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

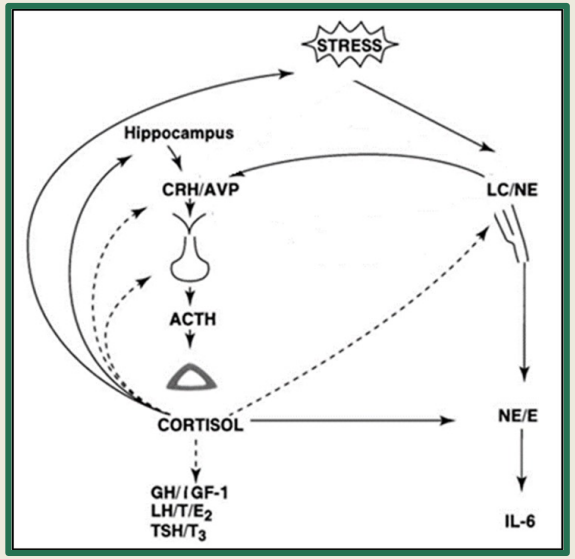

Systemic Circulation

Adrenal Cortex Cell




Systemic Circulation
cortisol

Cortisol and the Stress Response



Tsigos C, Chrousos GP . J Psychosom Res. 2002; 53(4): 865-871.

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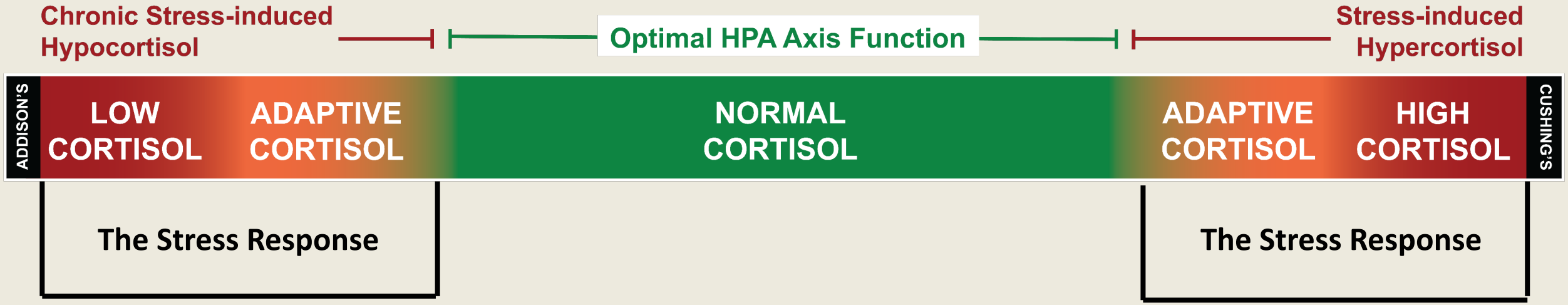
Cortisol and the Functional Endocrinology Model

Traditional Endocrinology Disease Model

Functional Endocrinology Model



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Allostatic Load, Allostatic Overload, Resiliency, and Toxic Stress

- Allostasis is the ability to adapt to a changing environment
  - Through allostasis the HPA axis, ANS, cardiometabolic, and immune systems protect the body by responding to internal/external stressors
- Allostatic load is the accumulated wear and tear resulting from daily life, which may lead to disease over time
  - Long-term effects of stress over time
  - Results from too much stress or from inefficient stress management

McEwen BS. N Engl J Med. 1998; 338(3): 171-179.
Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.
Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101

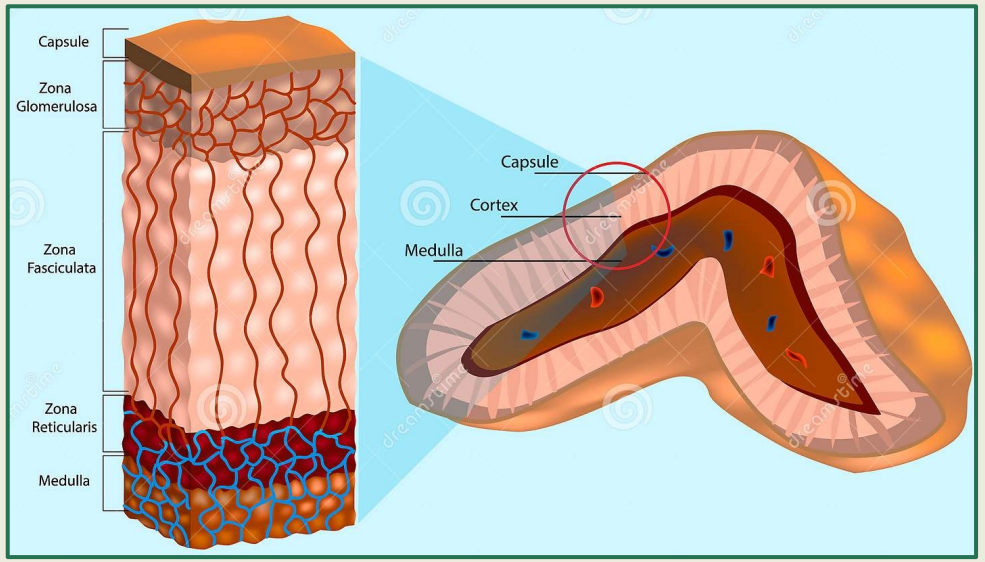
Allostatic Load, Allostatic Overload, Resiliency, and Toxic Stress

- Resiliency is the ability to quickly bounce back from stressful situations; coping ability
  - Dependent upon how one perceives stressor
  - One's physical health and reserve (genetics, lifestyle)
  - Necessitates positive experiences with rewards and a sense of meaning and purpose
- Allostatic overload occurs when demands exceed coping resources
  - Demands > supply
- Toxic stress occurs when there is strong, frequent, and/or prolonged activation of the stress response without adequate reserve
  - Demands >>> supply

McEwen BS. N Engl J Med. 1998; 338(3): 171-179.
Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.
Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101

Stress Response Hormones

- Adrenal gland hormone production
  - Adrenal cortex has 3 zones for hormone production
    - Zona fasciculata: cortisol
    - Zona reticularis: DHEA/DHEA-S
    - Zona glomerulosa: aldosterone
  - Adrenal medulla produces catecholamines
    - Epinephrine and norepinephrine



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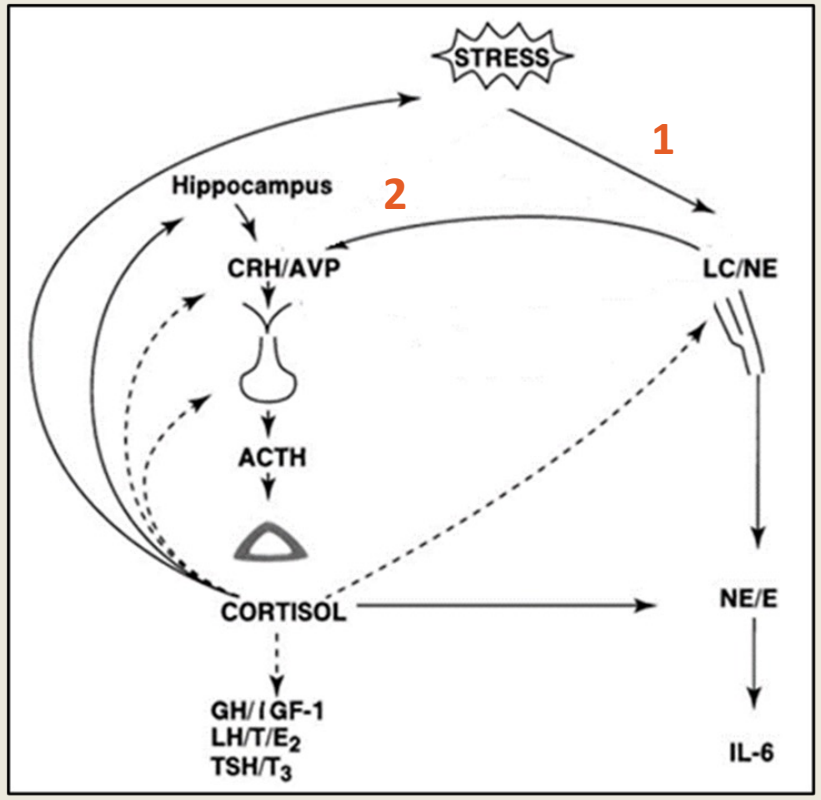
The Stress Response: Cortisol vs Catecholamines

- Catecholamines (adrenal medulla): FAST
  - Immediate release of stored epinephrine and norepinephrine
  - The body makes then stores to be ready for a threat
  - Signaling from both the locus coeruleus (brainstem) and the spinal cord
- Cortisol (adrenal cortex): SLOW
  - The body makes cortisol as needed when signaled, it is not made then stored
  - Lag time is usually about 10 minutes after epinephrine/NE have been released



Tsigos C, Chrousos GP . J Psychosom Res. 2002; 53(4): 865-871.

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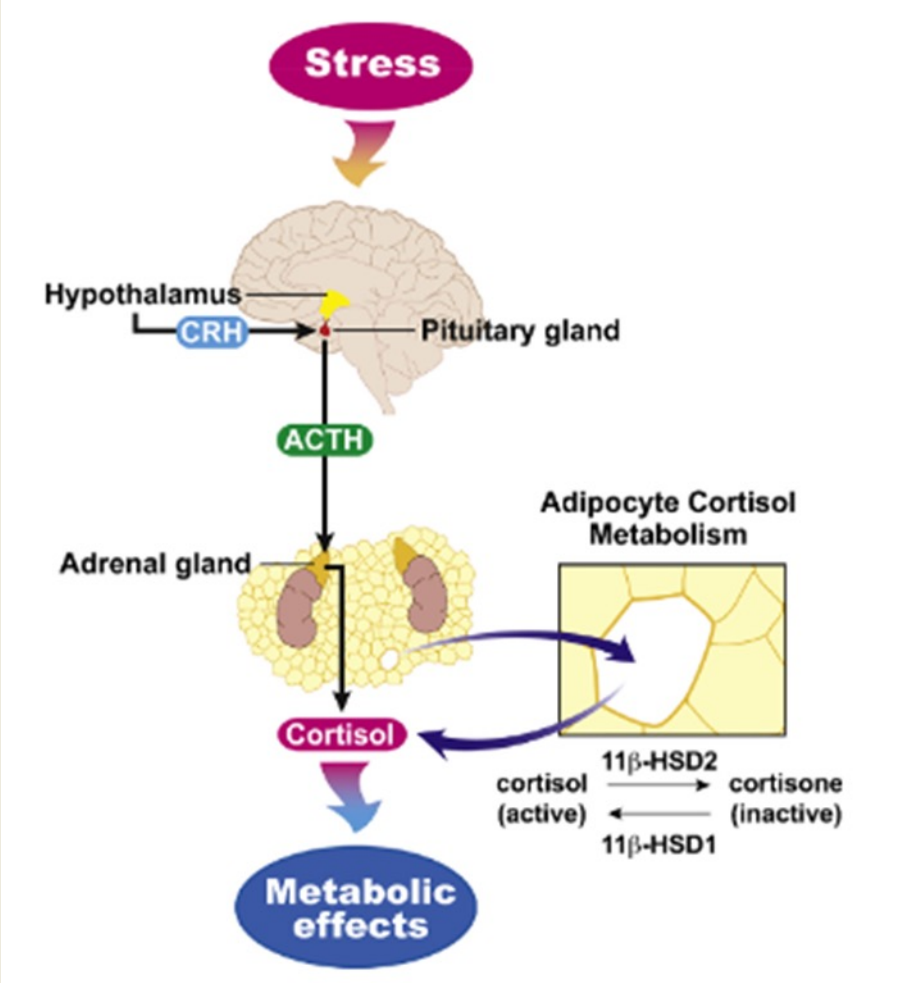
The Stress Response

- Hypothalamic-pituitary-adrenal axis (HPA axis)
  - Hypothalamus releases CRH (In the PVN)
  - CRH binds to anterior pituitary gland receptors
  - Anterior pituitary then releases ACTH
  - ACTH binds to adrenal cortex zona fasciculata receptors
  - Adrenal cortex releases cortisol



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Acute vs Chronic Cortisol Effects

- Acute cortisol effects: Fight or Flight
  - Maintains glucose levels for energy
    - Gluconeogenesis: mobilizes glucose from fat and liver cells
    - Blocks insulin to maintain blood sugar for energy
  - Increased focus: mental and physical
  - Increased HR, blood pressure (vasoconstriction), muscle blood flow
  - Decreased digestive effort
  - Decreased sex hormone response
  - Decreased immune response

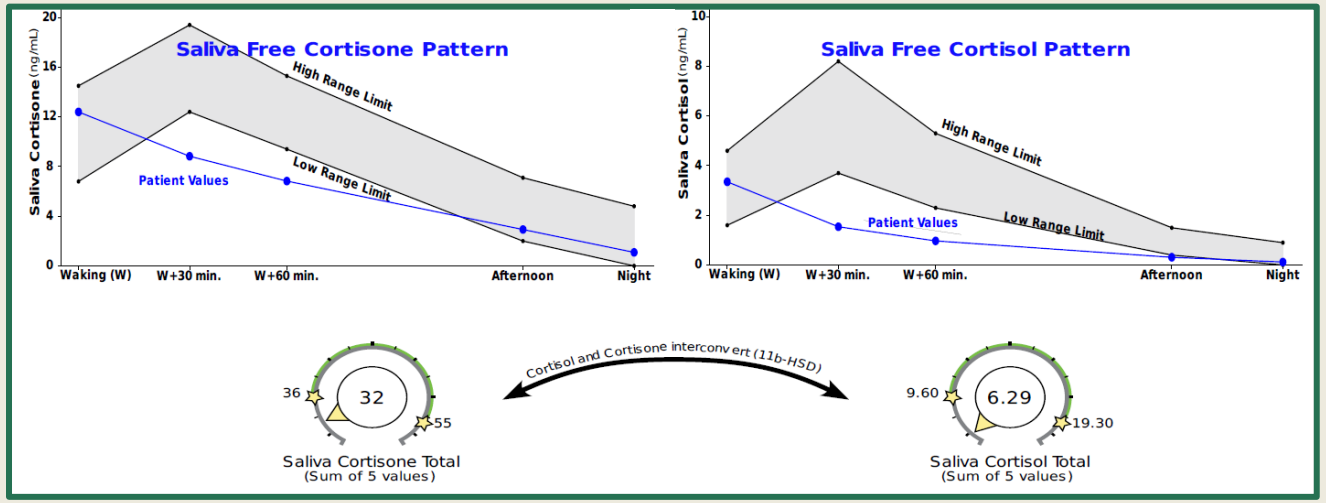
Acute vs Chronic Cortisol Effects

- Chronic cortisol effects
  - Insulin dysregulation, dysglycemia, IR/diabetes
  - Central adiposity
  - Immune dysregulation, immune suppression, and inflammation
  - Chronic fatigue
  - Gastrointestinal effects: parasympathetic nervous system suppression
  - Cardiovascular effects: HTN, hyperlipidemia, endothelial dysfunction
  - Sex hormone imbalance
    - Females: infertility, irregular periods, heavy periods, decreased libido
    - Males: infertility, low testosterone, decreased libido, erectile dysfunction

Stress vs Disease

- Cushing's disease
  - Cushing's disease is secondary to a pituitary tumor → high cortisol levels
  - Tumor encourages improper and constant signaling to release cortisol
- Addison's disease
  - Addison's disease is an autoimmune disease resulting in low cortisol or aldosterone
  - Without treatment this can be life-threatening

Free Cortisol and Free Cortisone



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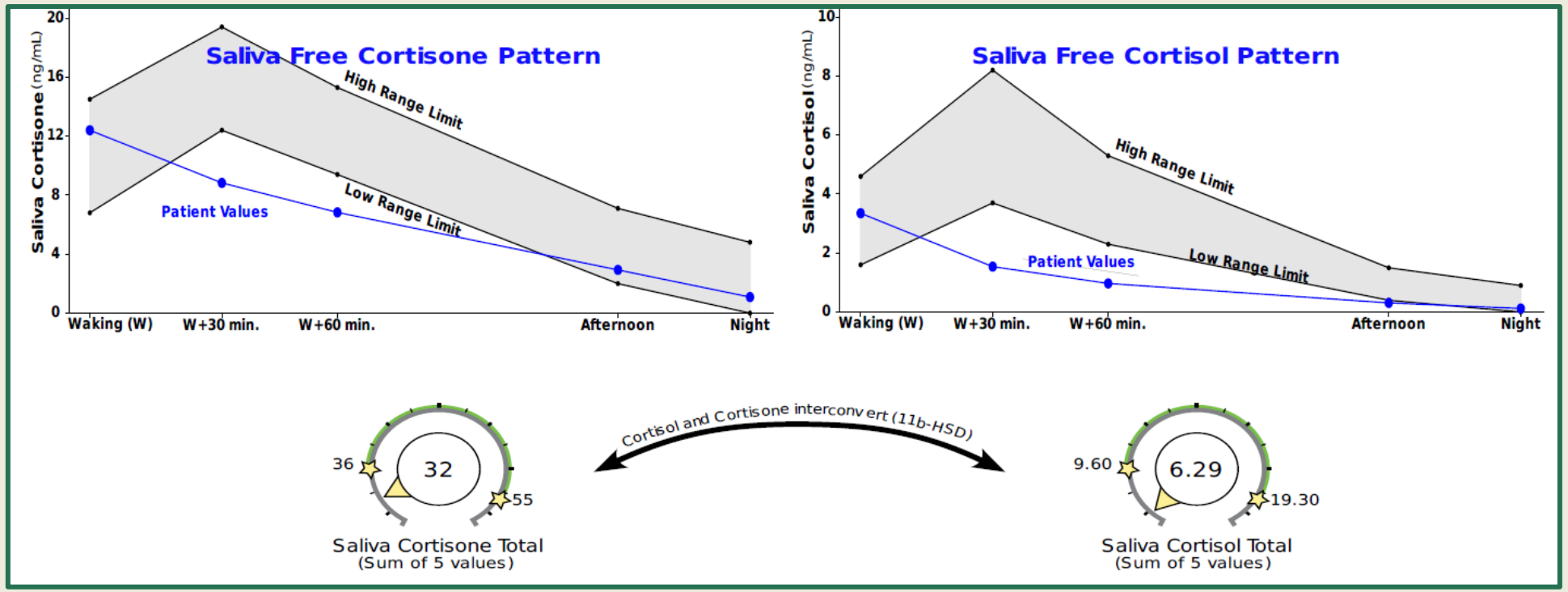
Free Cortisol and Free Cortisone

- Free cortisone **IS** free cortisol
  - These two hormones are ever-interchanging when in circulation
- Cortisol is primarily bound to corticosteroid-binding globulin (CBG)
  - 80-90% bound to CBG, 5-10% bound to albumin, and up to 10% is free
- Free cortisol and free cortisone follow a diurnal pattern, meaning that as the sun comes up, cortisol rises, as the sun sets, cortisol decreases
- Most of free cortisol's release should occur in the morning
- Spikes at other times during the day indicate an abnormal stress response

Free Cortisol and Free Cortisone



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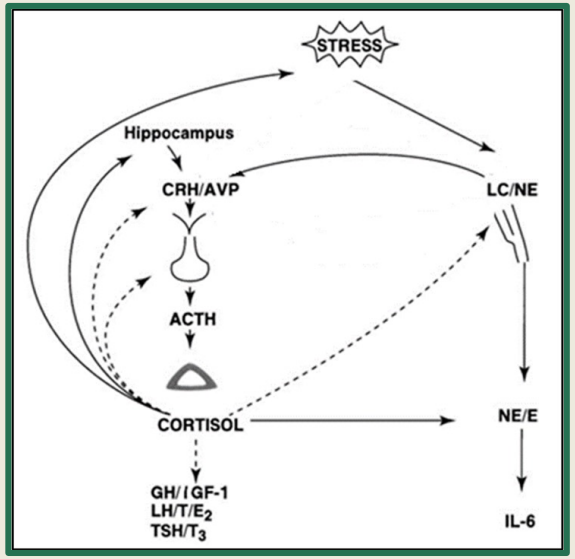
DHEA and the Stress Response



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DHEA and the Stress Response

- DHEA synthesis
  - Occurs in the adrenal cortex (zona reticularis), gonads, and brain
- DHEA is a parent hormone
  - A precursor to most other steroid hormones
  - All estrogens are synthesized from androgens
- DHEA is involved in the stress response
  - An immune modulator and anti-inflammatory hormone
  - Acute stress biomarker (increases within 1 hour)

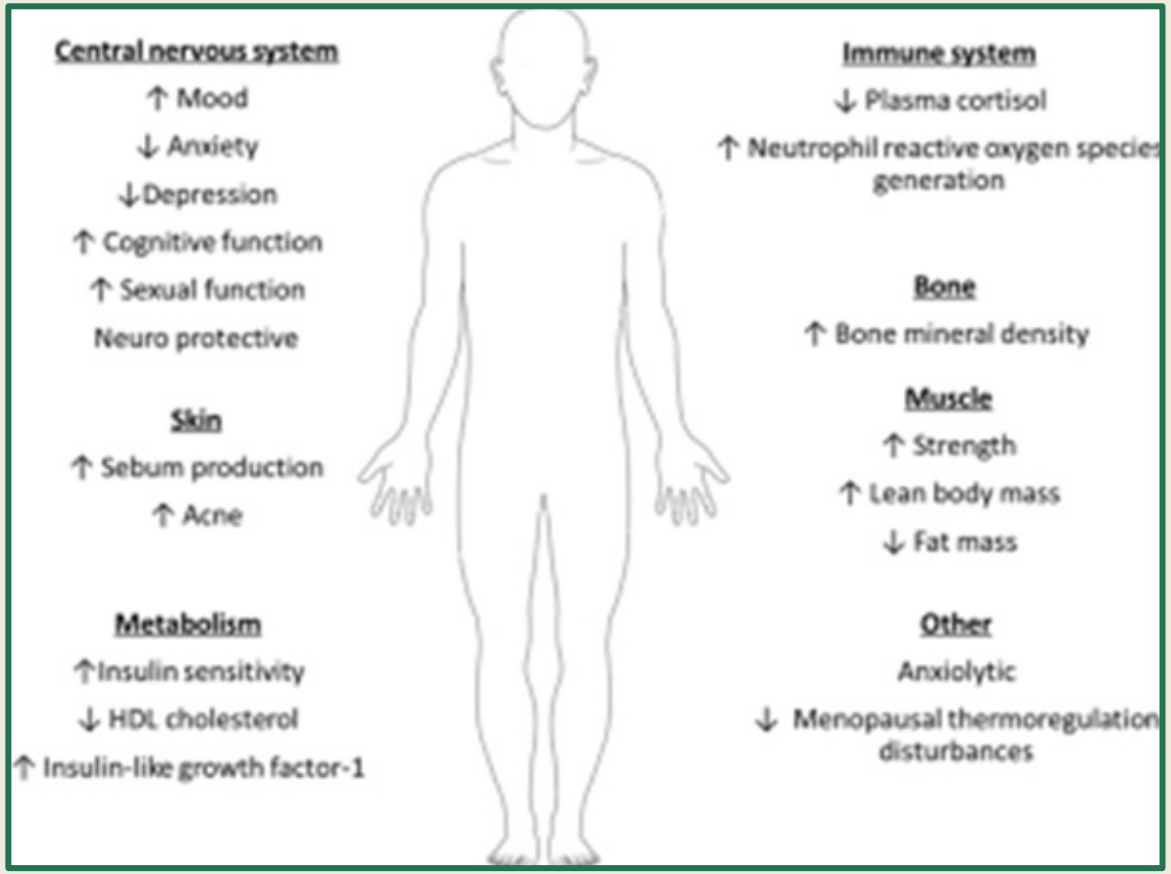
Dutheil F, et al. Front Psychiatry. 2021; 12: 688367.

DHEA and the Stress Response

- DHEA-S
  - DHEA-S does not cross the BBB
  - Sulfur group stabilizes DHEA in blood so that can reach target tissues
  - DHEA-S does not follow a diurnal pattern, it is constant
  - DHEA-S is probably a better measure of adrenal reserve
- DHEA Replacement: start low and go slow
  - Females: 2.5-25mg BID
  - Males: 10-50mg BID
  - Too much DHEA
    - Females: acne, facial hair, weight gain
    - Males: increased aggression, hostility, irritability

Morales AJ, et al. J Clin Endocrinol Metab. 1994; 78(6): 1360-1367.

DHEA Systemic Effects



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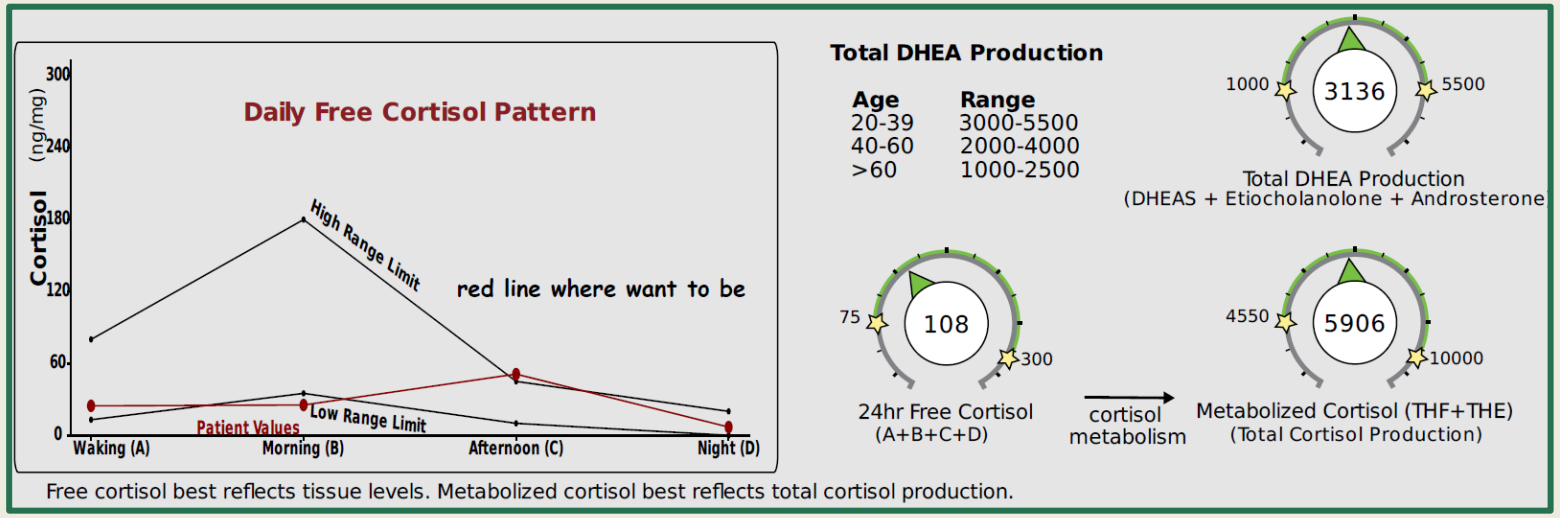
Key Points

- Cortisol is the universal stress marker
- There is no pregnenolone steal
- Cortisol is synthesized from de-novo LDL cholesterol
- Acute cortisol effects are different than chronic cortisol effects
- DHEA has numerous systemic effects
- DHEA is released in response to acute stress
- DHEA-S does not have a diurnal pattern and is a better marker of adrenal reserve

Why Test Cortisol?



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

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Why Test Cortisol?

Cortisol drives inflammation, inflammation is the root cause of most, if not all, inflammatory diseases

Why Test Cortisol?

What does the evidence tell us about saliva and urine testing and clinical outcomes?

- Are there studies linking free cortisol and cortisol patterns to clinical endpoints?

Cortisol and CVD

- INTERHEART Study (2004)
- CARDIA Study (2006)
- WHITEHALL II Study (2011)
- InCHIANTI Study (2010)

INTERHEART STUDY: [1] Yusuf S, et al. Lancet. 2004; 364(9438): 937-952. [2] Fioranelli M, et al. Front Immunol. 2018; 9:2031.
CARDIA STUDY: Mathews K, et al. Psychosom Med. 2006; 68(5): 657-661.
WHITEHALL II STUDY: Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485
URINE CORTISOL AND CVD MORTALITY: Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964.

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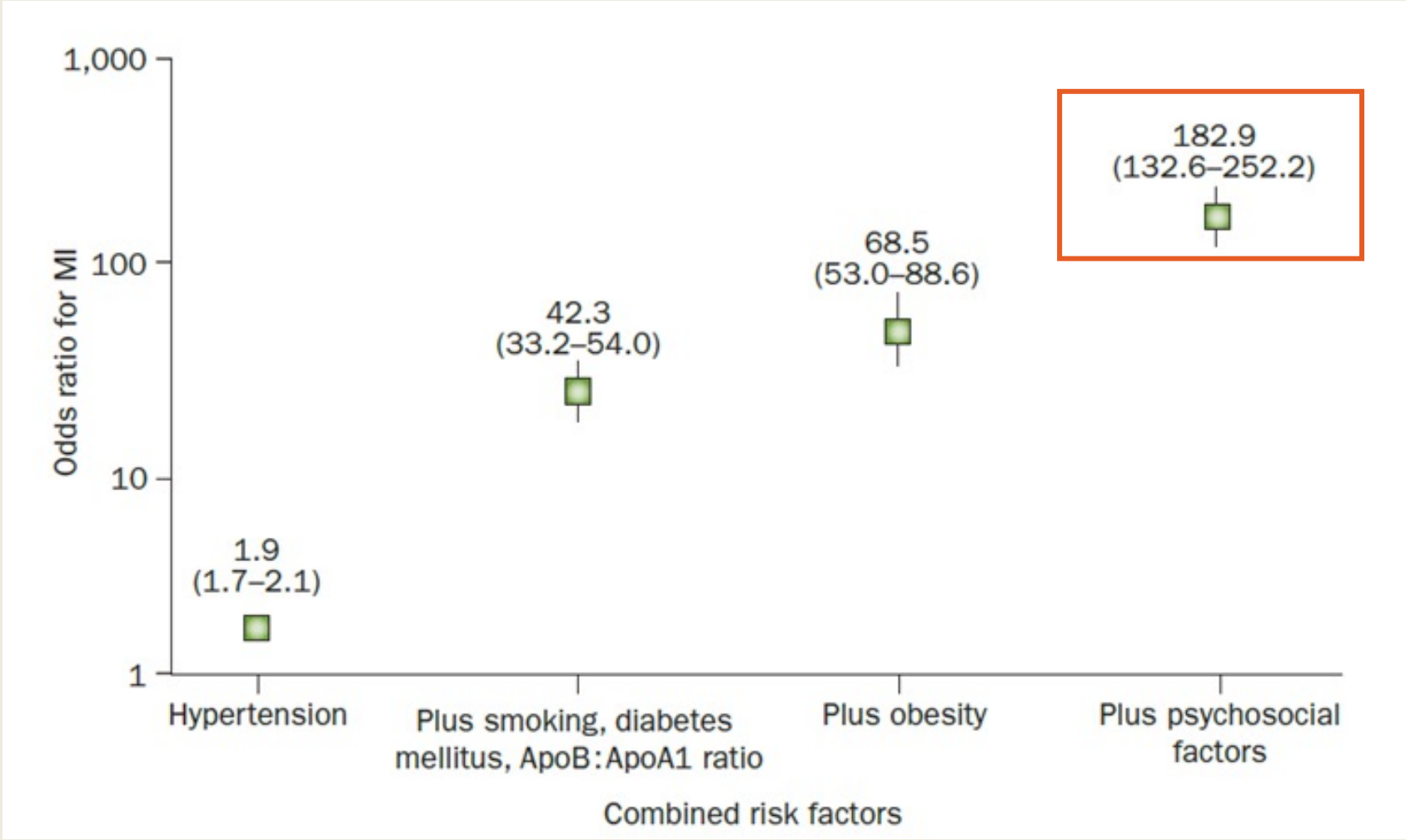
Cortisol and T3

- INTERHEART case-controlled study (2004)
  - Largest study to assess long-term stress and CAD; 4-year study
  - Study: 15,152 MI patients, 14,820 controls from 52 countries world-wide between 1999-2003; stress documented by questionnaire
  - Objective: determine the strength of the association between RF and AMI
  - Results:
    - The odds ratio of an MI was more than doubled in individuals with chronic stress in addition to conventional risk factors when compared to stress-free individual
    - A similar pattern of associations was found in men and women, old and young, across all continents
- **Concluded that psychosocial stressors are significantly related to AMI risk in all populations**

Yusuf S, et al. Lancet. 2004; 364(9438): 937-952.
Fioranelli M, et al. Front Immunol. 2018; 9:2031.

Cortisol and T3



Steptoe A, Kivimaki M. Nat Rev Cardiol. 2012; 9(6): 360-370.

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Salivary Cortisol and CaC: Cardia Epidemiologic Study 2006

Diurnal Cortisol Decline is Related to Coronary Calcification: CARDIA Study

KAREN MATTHEWS, PHD, JOSEPH SCHWARTZ, PHD, SHELDON COHEN, PHD, AND TERESA SEEMAN, PHD

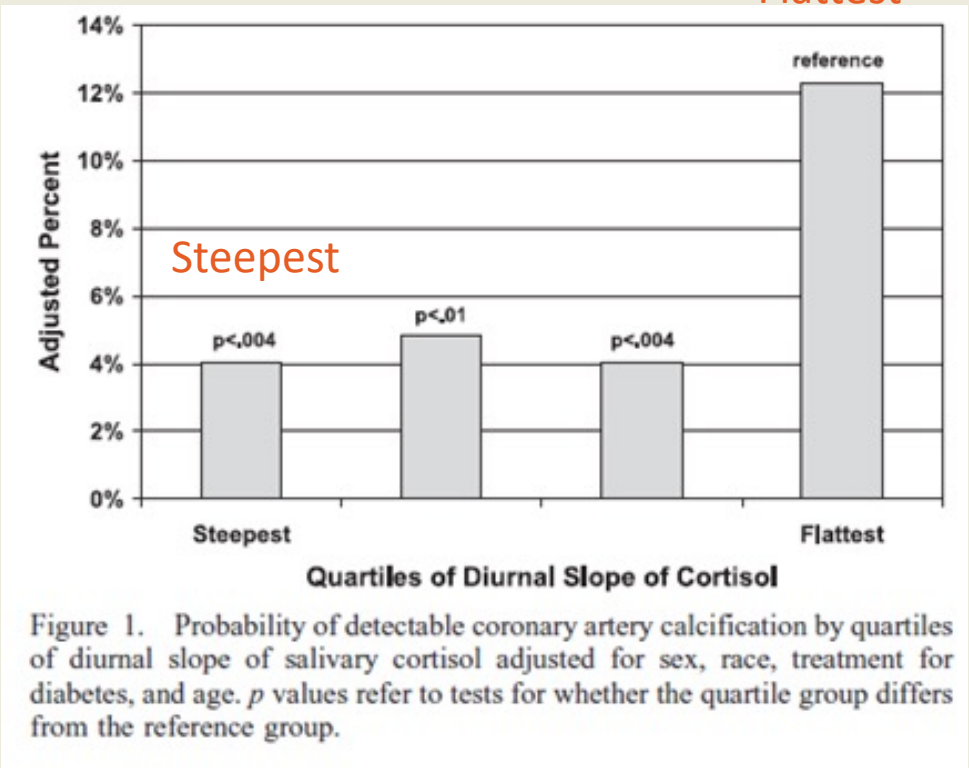

Figure 1. Probability of detectable coronary artery calcification by quartiles of diurnal slope of salivary cortisol adjusted for sex, race, treatment for diabetes, and age. *p* values refer to tests for whether the quartile group differs from the reference group.

- First study linking cortisol patterns to CAD; used saliva testing
- Study: 718 young participants (average age 40); 15-year follow-up
- Objective: to determine if CaC was associated with average daily cortisol levels and the diurnal slope

Mathews K, et al. Psychosom Med. 2006; 68(5): 657-661.

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Salivary Cortisol and CaC: CARDIA Epidemiologic Study 2006

Diurnal Cortisol Decline is Related to Coronary Calcification: CARDIA Study

KAREN MATTHEWS, PHD, JOSEPH SCHWARTZ, PHD, SHELDON COHEN, PHD, AND TERESA SEEMAN, PHD

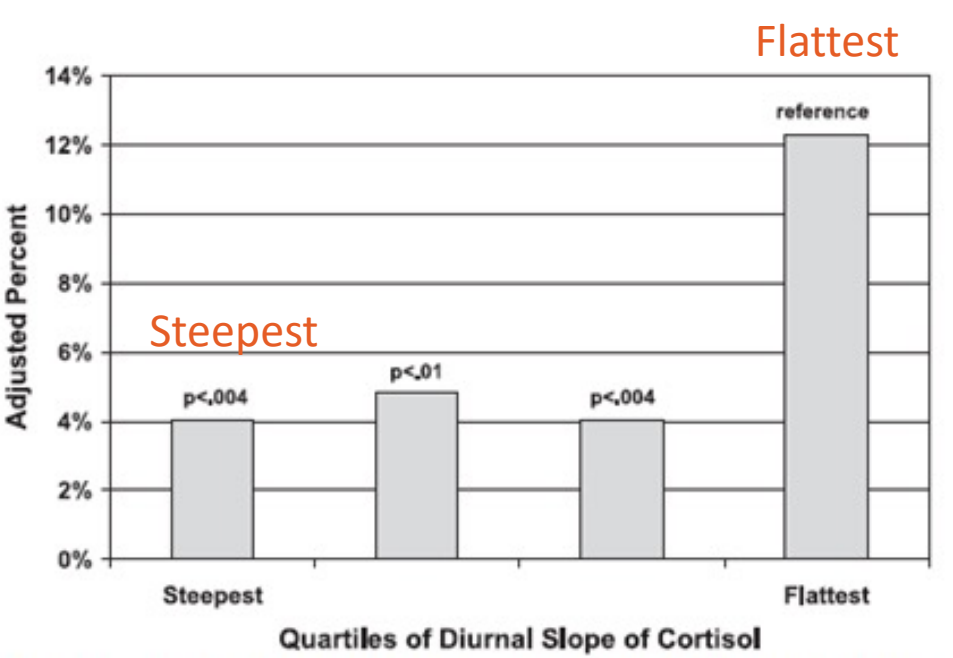

Figure 1. Probability of detectable coronary artery calcification by quartiles of diurnal slope of salivary cortisol adjusted for sex, race, treatment for diabetes, and age. *p* values refer to tests for whether the quartile group differs from the reference group.

Mathews K, et al. Psychosom Med. 2006; 68(5): 657-661.

- Results: A flat diurnal cortisol curve associated with CaC
  - The flattest cortisol slopes was SS associated with CaC
  - When compared to the group with the steepest slope, the group with the flattest slope were 3 ⅓ more likely to have CaC

- **Conclusion: HPA axis dysfunction may affect CAD risk**

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Salivary Cortisol and CVD Mortality: Whitehall II Prospective Cohort Study (2011)

Association of Diurnal Patterns in Salivary Cortisol with All-Cause and Cardiovascular Mortality: Findings from the Whitehall II Study

Meena Kumari, Martin Shipley, Mai Stafford, and Mika Kivimaki

Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom

TABLE 3. HR of all-cause, cardiovascular, and noncardiovascular mortality among 4047 participants of the Whitehall II study from phase 7 (2002–2004) through to January 2010 by z-scores of measures of cortisol

	All-cause mortality	Noncardiovascular deaths	Cardiovascular deaths
Waking cortisol	0.94 (0.80–1.12)	0.93 (0.77–1.13)	0.95 (0.67–1.36)
CAR	0.94 (0.80–1.12)	0.90 (0.74–1.10)	1.12 (0.79–1.57)
Slope across the day	1.30 (1.09–1.55)	1.17 (0.96–1.43)	1.87 (1.32–2.64)
Bedtime cortisol	1.33 (1.11–1.59)	1.17 (0.96–1.44)	1.98 (1.39–2.81)

Slope across the day and CV deaths: Z-score: 1.87 ~ p = 0.03 (P < 0.05)
Bedtime cortisol and CV deaths: Z-score: 1.98 ~ p = 0.02 (P < 0.05)

- First study to document that daily salivary diurnal cortisol patterns are predictive of subsequent CV mortality in men and women
- Study: 4047 men and women, average age 61, mean FU 6.1 years
- Objective: to examine the association between cortisol patterns, CV and non-CV mortality

Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485.

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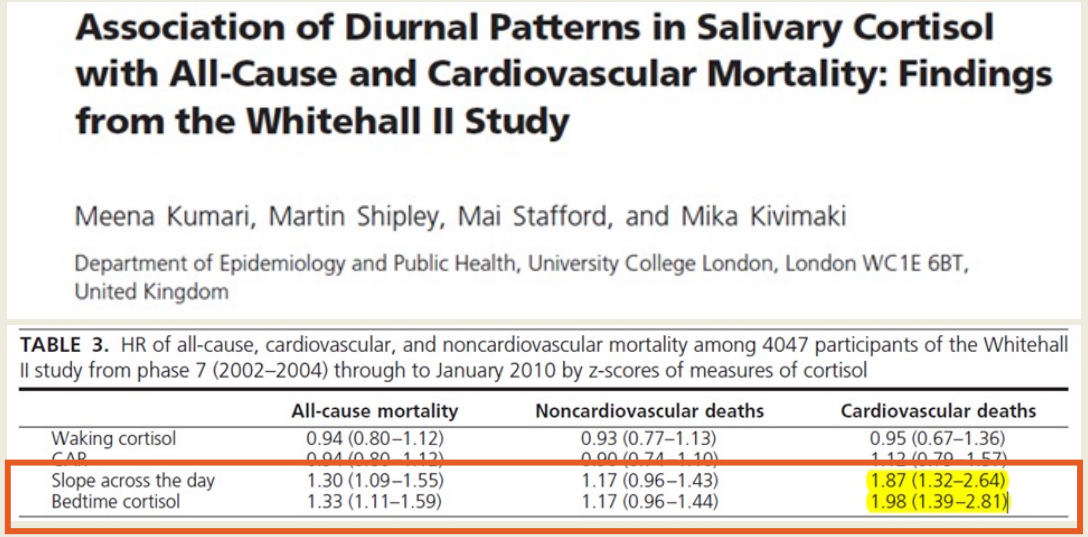
Salivary Cortisol and CVD Mortality: Whitehall II Prospective Cohort Study (2011)



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- Slope across the day and CV deaths: Z-score: 1.87, p = 0.03 (P < 0.05)
- Bedtime cortisol and CV deaths: Z-score: 1.98, p = 0.02 (P < 0.05)

- Results: A flattened cortisol curve was SS associated with increased CV mortality; elevated PM cortisol was an independent predictor of subsequent CV mortality
  - No association between waking cortisol, CAR, and mortality

- **Conclusion: A flattened cortisol curve and elevated PM cortisol levels are robust CV mortality predictors in middle-aged adults**

Kumari M, et al. J Clin Endocrinol Metab. 2011; 96(5): 1478-1485.

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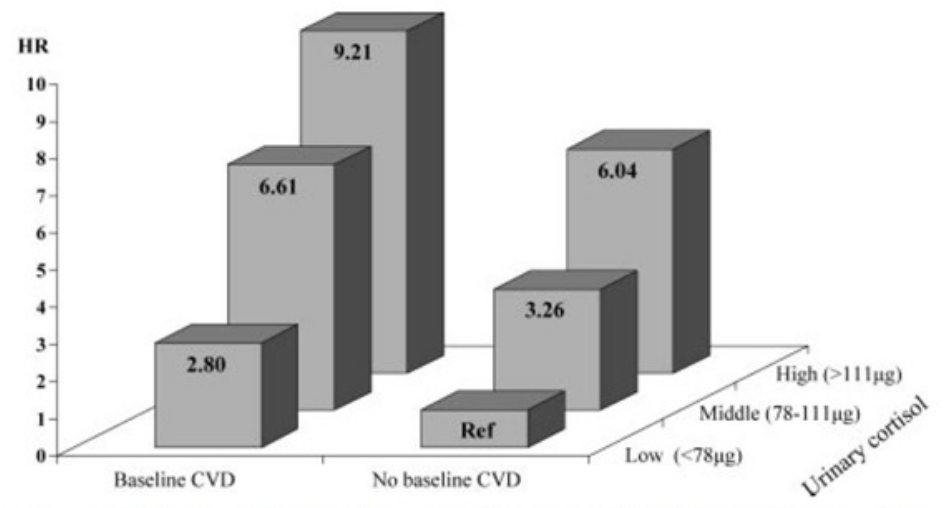
Urinary Cortisol and CVD Mortality: InCHIANTI, a Prospective Cohort Study (2010)

Urinary Cortisol and Six-Year Risk of All-Cause and Cardiovascular Mortality

Nicole Vogelzangs, Aartjan T. F. Beekman, Yuri Milaneschi, Stefania Bandinelli, Luigi Ferrucci, and Brenda W. J. H. Penninx



- First urine study to document that 24-hour urinary free cortisol (UFC) levels predict CV mortality
- Study: 862 older individuals, mean age 74, 55% women; 6-year study; samples at baseline
  - UFC divided into 3 terciles: low < 78µg; moderate: 78-111µg; high: > 111µg
- Objective: To determine whether 24-hour UFC levels predict all-cause and CV mortality

Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964.

Urinary Cortisol and CVD Mortality: InCHIANTI, a Prospective Cohort Study (2010)

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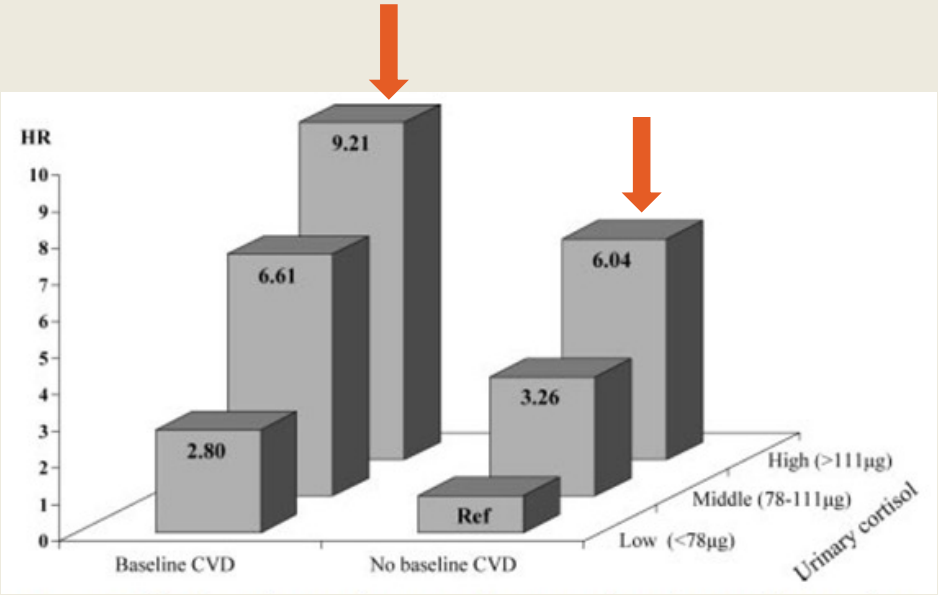

- Results: UFC strongly predicts CV mortality, not non-CV mortality in persons with and without baseline CVD
  - Risk increased with increasing UFC levels
  - Those in the highest tercile had a 5x increased CVD mortality risk over 6 years
    - No baseline CVD: 6x increased risk of dying from CVD
    - Baseline CVD: 9.2x increased risk of dying from CVD

- **Conclusion: UFC is a strong CVD mortality predictor in persons with and without baseline CVD**

Vogelzangs N, et al. J Clin Endocrinol Metab. 2010; 95(11): 4959-4964.

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How Do We Translate This Into Clinical Practice?

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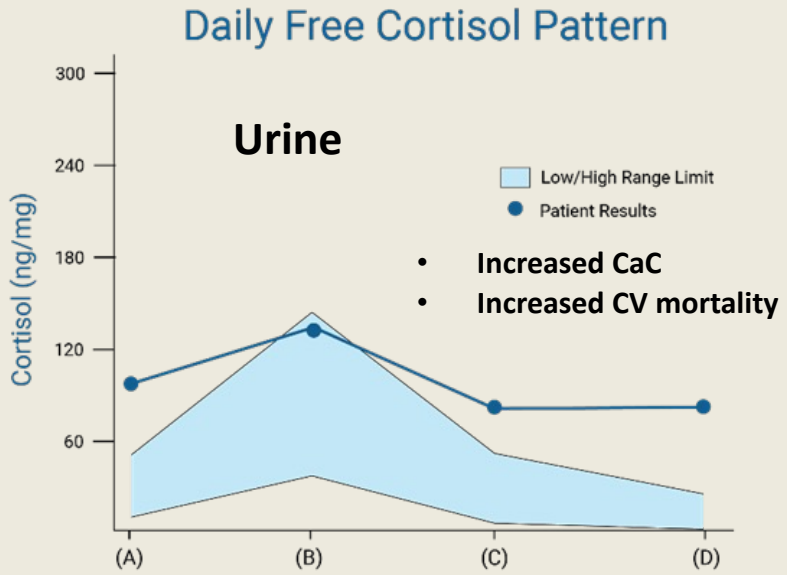
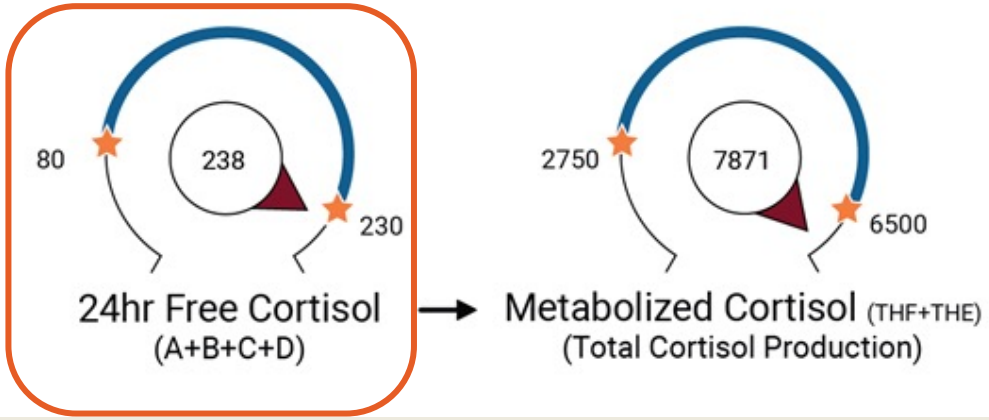
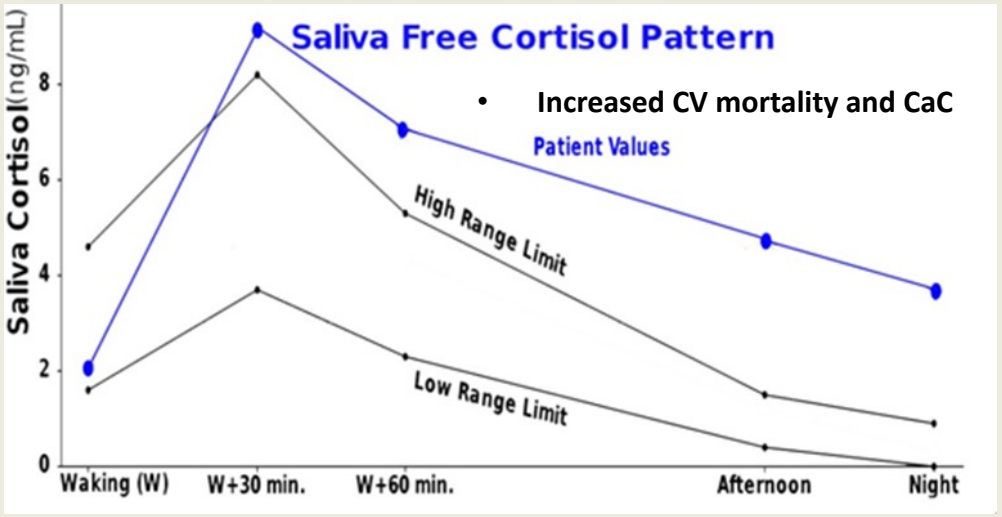


- Increased CaC
- Increased CV mortality

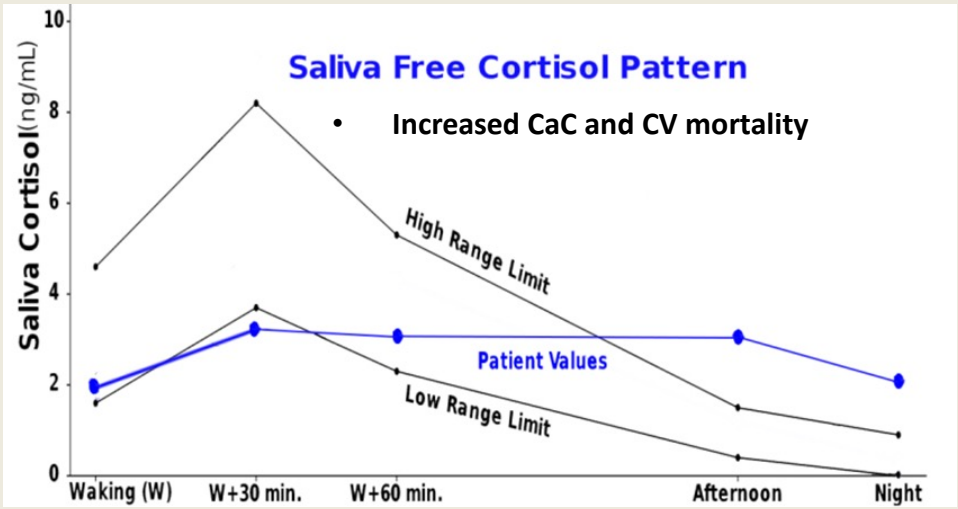
Urine

- Increased CV Mortality





- Increased CV mortality and CaC



- Increased CaC and CV mortality

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Key Points

- Cortisol “drives” inflammation
- Chronic stress is significantly associated with MI risk
- Cortisol is a strong predictor of CVD risk, events, and mortality
  - Salivary flattened diurnal cortisol pattern with high PM cortisol
  - Urinary Cortisol: elevated 24-hour UFC strong predictor of CVD mortality in persons with and without preexisting CVD
- How do we measure this risk?
  - Saliva and cortisol awakening response (CAR)
  - Urine and metabolites

DUTCH Saliva vs DUTCH Urine

The test you choose depends on the question you are asking

DUTCH saliva

- Diurnal cortisol curve
- Cortisol awakening response (CAR)
  - HPA axis resiliency

DUTCH urine

- Diurnal cortisol curve
- Cortisol metabolites
  - Best marker for total cortisol production and use
- Metabolic preference cortisol vs cortisone
  - 11β-HSD1 vs 11β-HSD2

Wang Y, et al. Bioanalysis. 2018; 10(24): 2015-2026.

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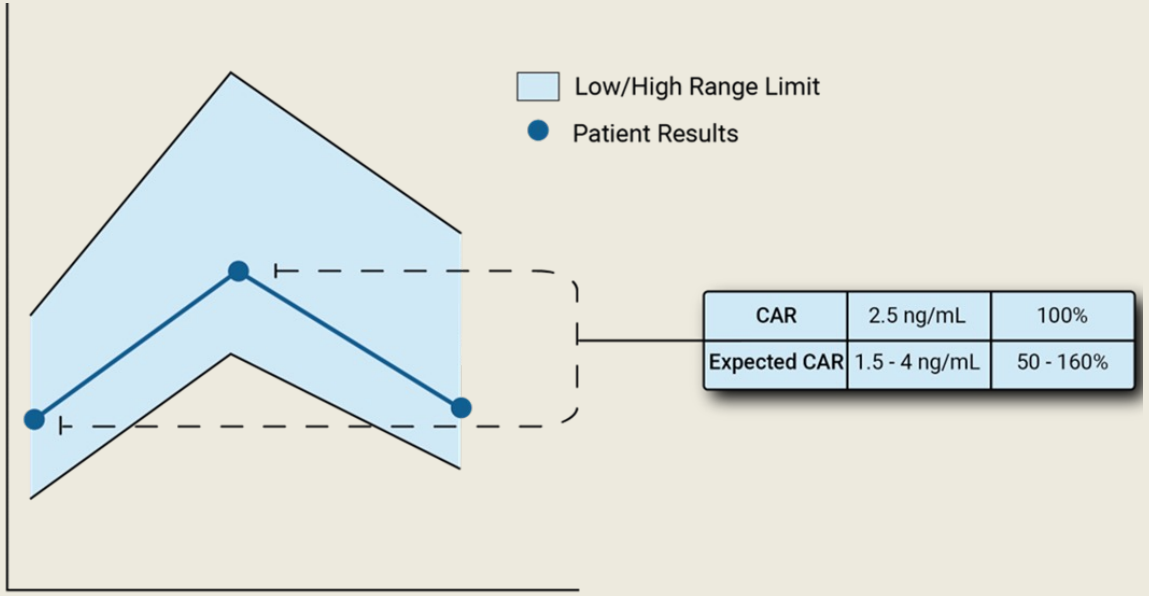
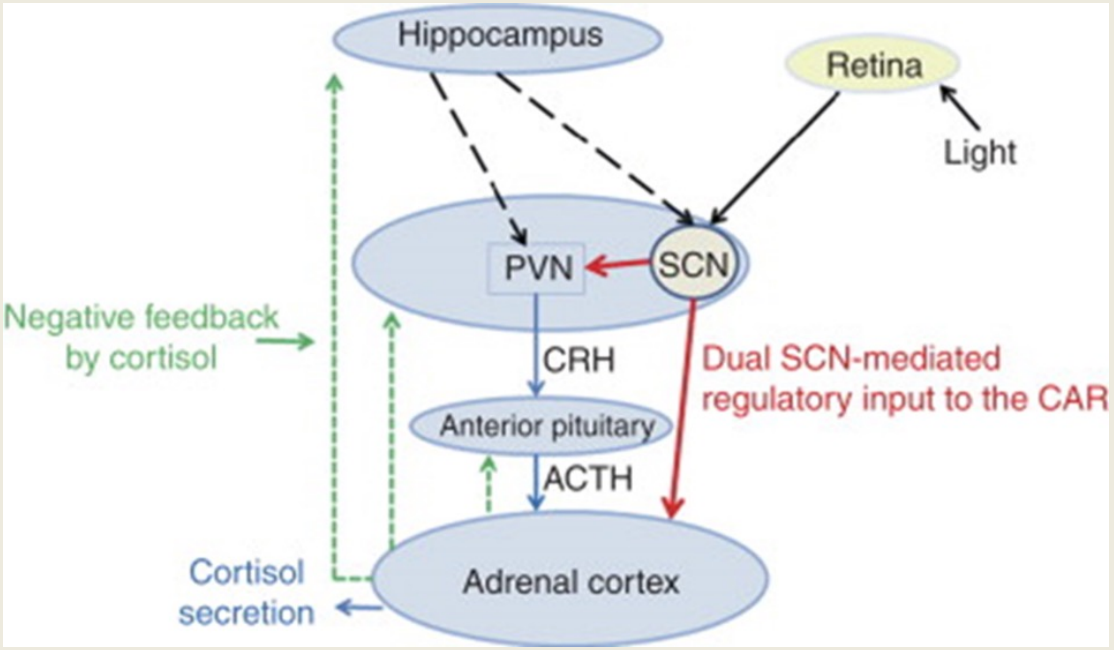
Cortisol Awakening Response (CAR)

- Mini-Stress Test
- HPA axis resiliency marker
- Abnormal response signals neuroendocrine maladaptation



- Eyes open, light hits back of the retina
- Stimulates hypothalamic SCN, which signals both the hypothalamic PVN and the adrenal cortex directly
- Resulting in sharp cortisol spike as go from conscious to alert



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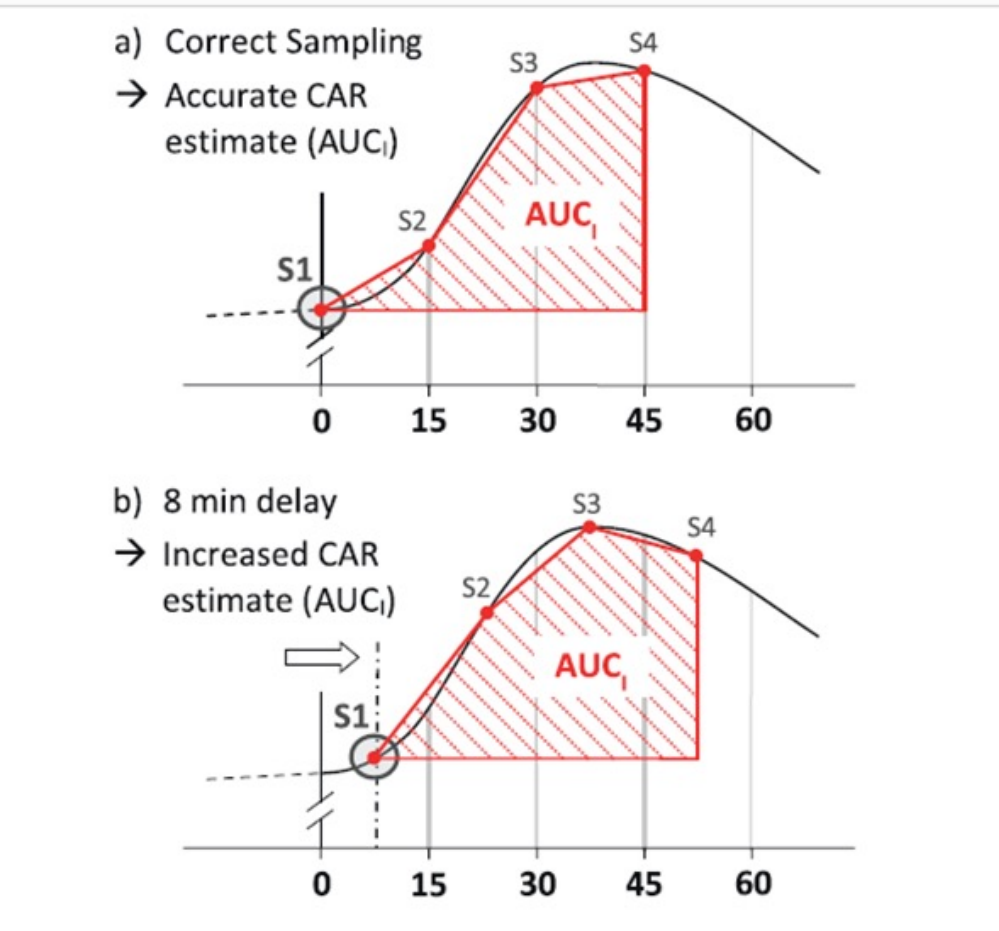
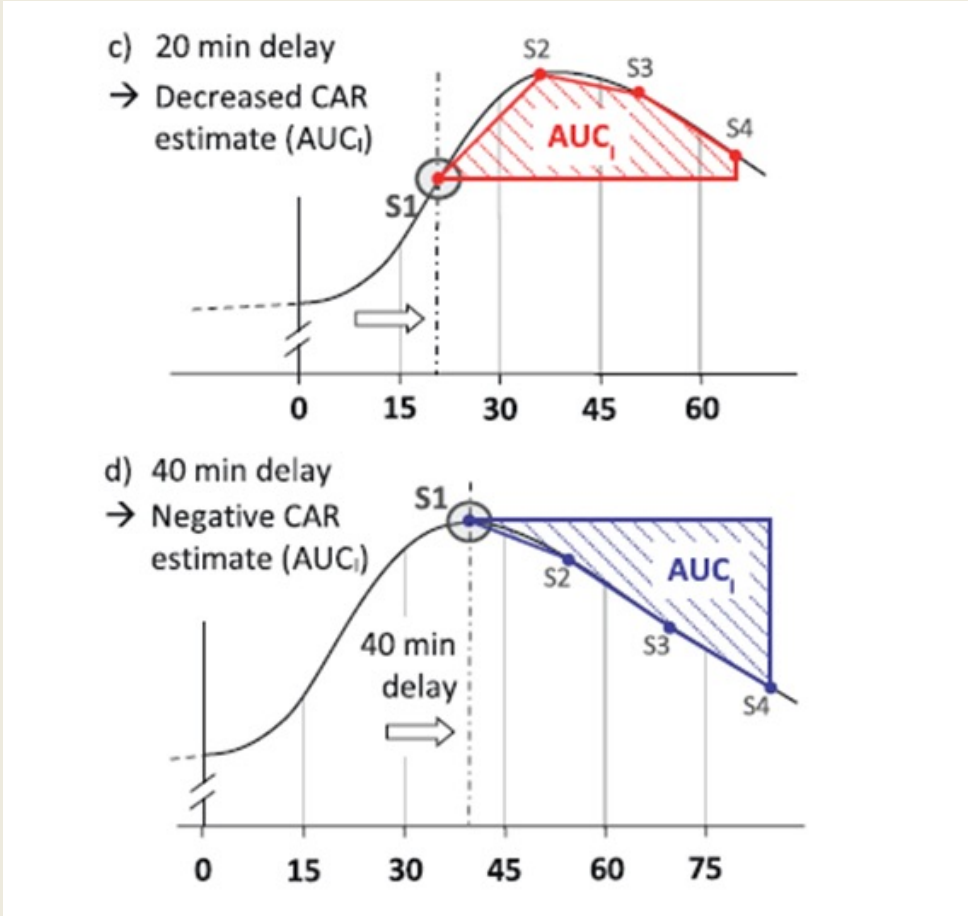
CAR Timing





Stalder T, et al. Psychoneuroendocrinology. 2016; 63: 414-432.

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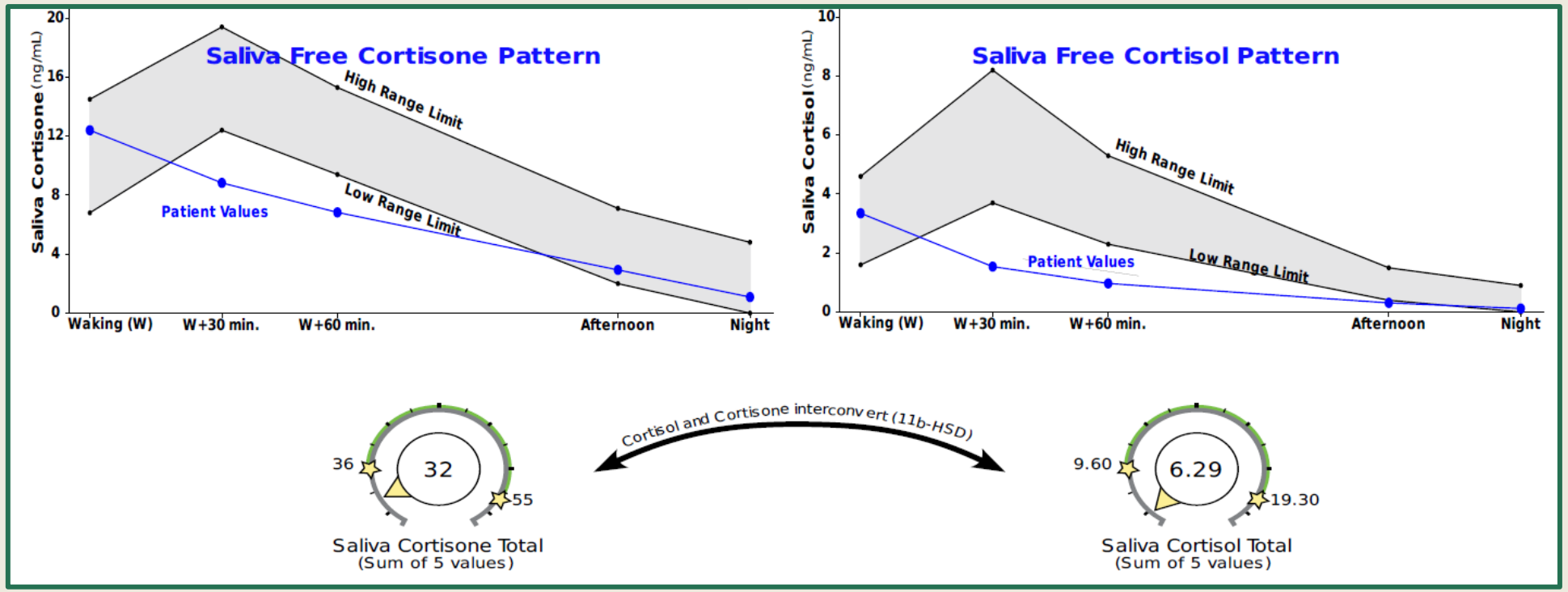
Free Cortisol and Free Cortisone



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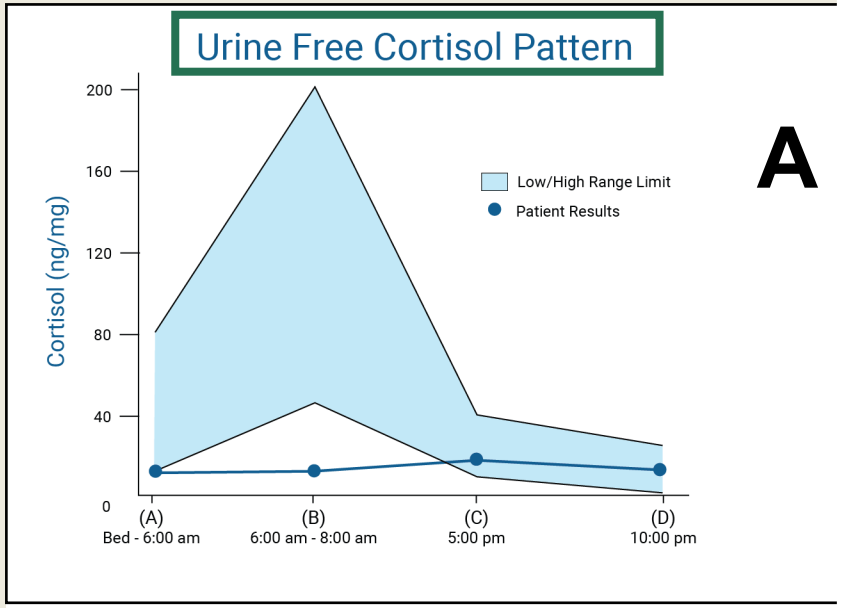
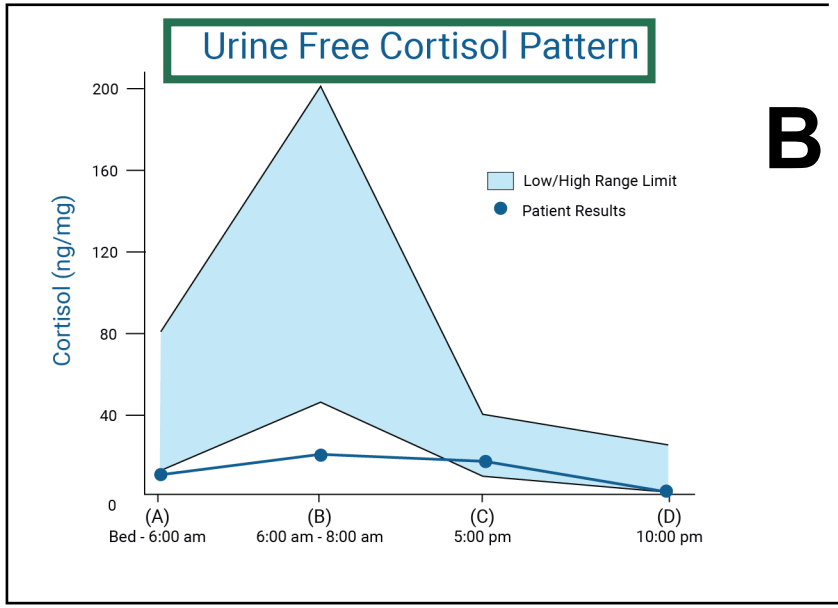


A



B

CAR

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Cortisol Metabolites

Why measure cortisol metabolites?

- Free cortisol is the best way to assess the HPA axis
- Cortisol metabolites are the best way to assess utilization and production

Cortisol Metabolites

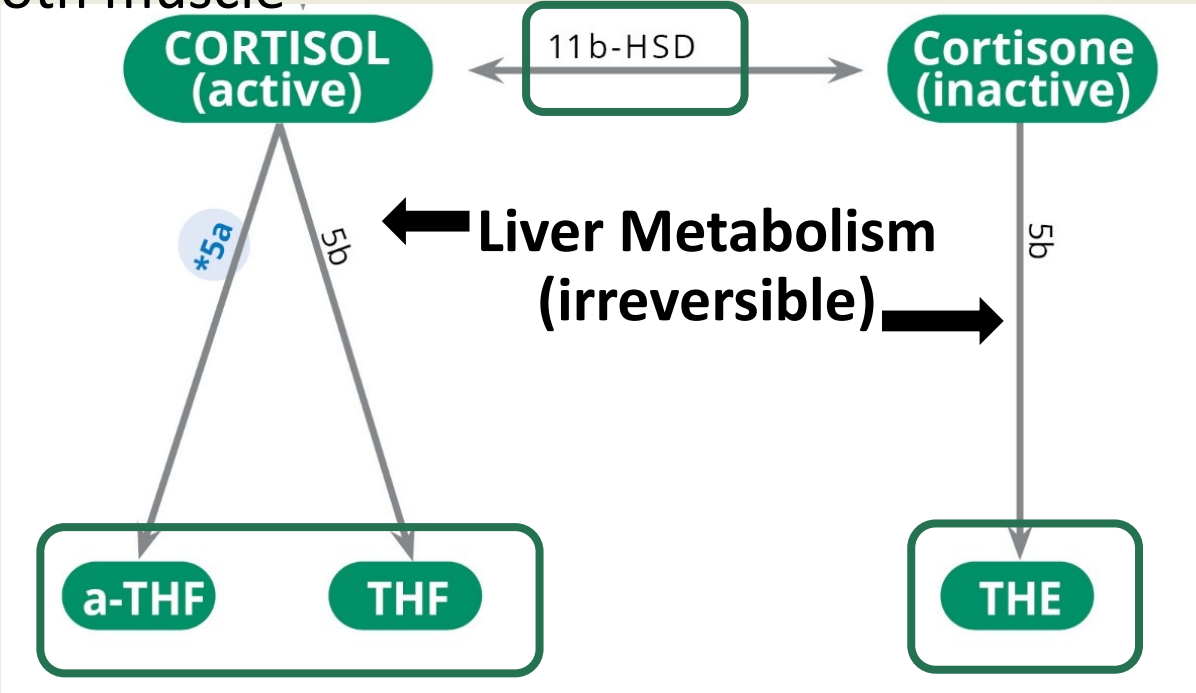
Activation to Cortisol

- **Liver**
- **Adipose**
- Gonads
- Brain
- Vascular smooth muscle

11b-HSD1 ⟵
⟶ 11b-HSD2

Deactivation to Cortisone

- **Kidneys**
- Colon
- Salivary gland



- **5α metabolism informs about global metabolism**

- **5β metabolism informs about liver metabolism**

Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

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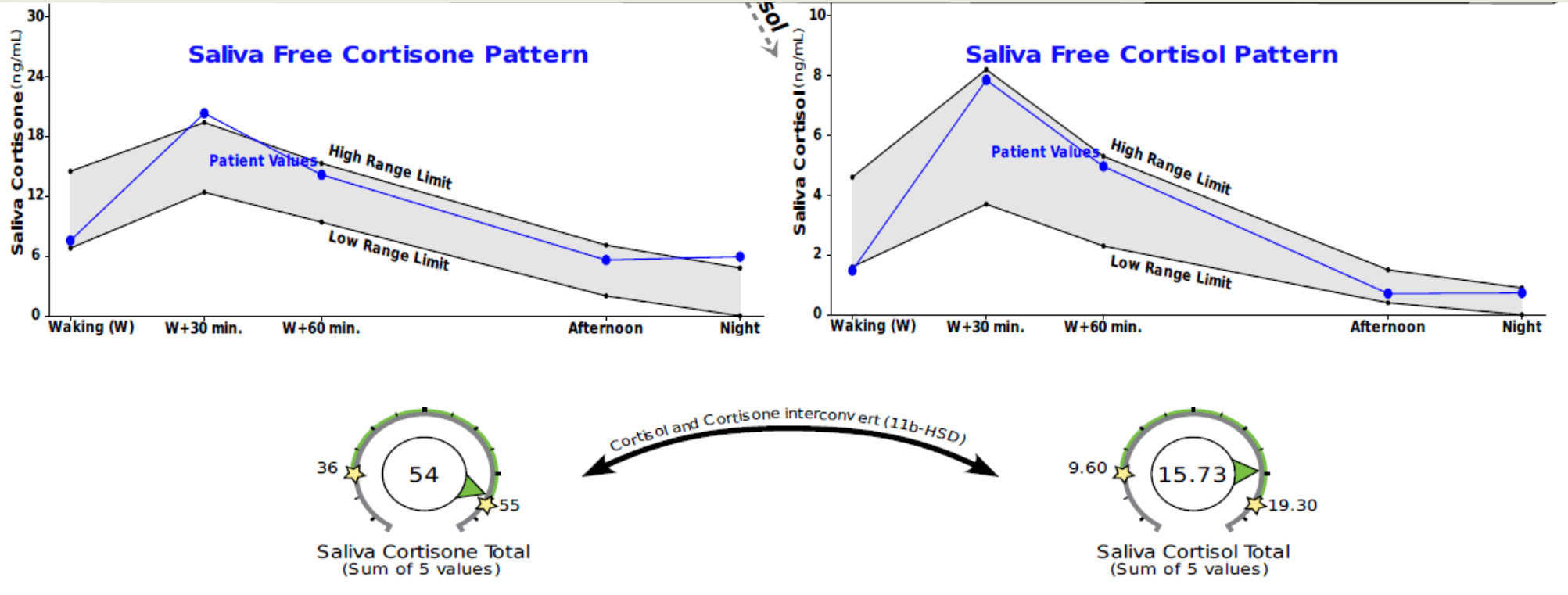
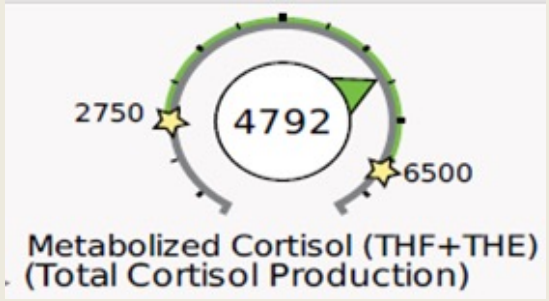
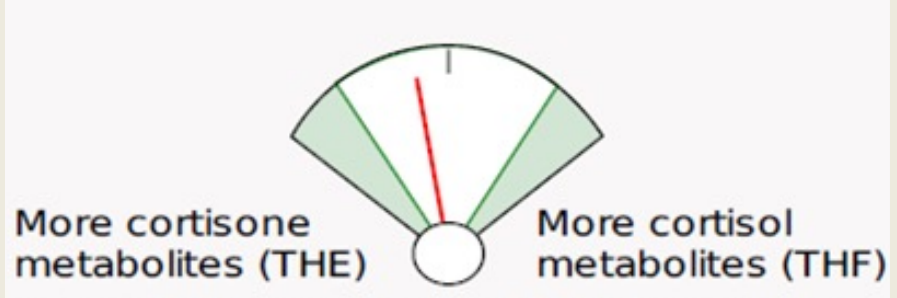
Metabolized Cortisol

- DUTCH's metabolized cortisol dial represents the total free cortisol and free cortisone processed by the liver on the day of testing
  - The liver is the primary sites of cortisol metabolism
- More THF (cortisol) suggests that the body had a high need for active cortisol, and circulating free cortisol was predominant
  - This is seen in high stress states, inflammation, or with habitual licorice use
    - Licorice inhibits 11β-HSD2 preventing cortisol inactivation to cortisone
- More THE (cortisone) suggests that the free cortisol was circulating mainly as inactive hormone, not being readily used by the tissues before finally processed through the liver for clearance
  - This primarily seen with chronic stress, no inflammation

Metabolized Cortisol







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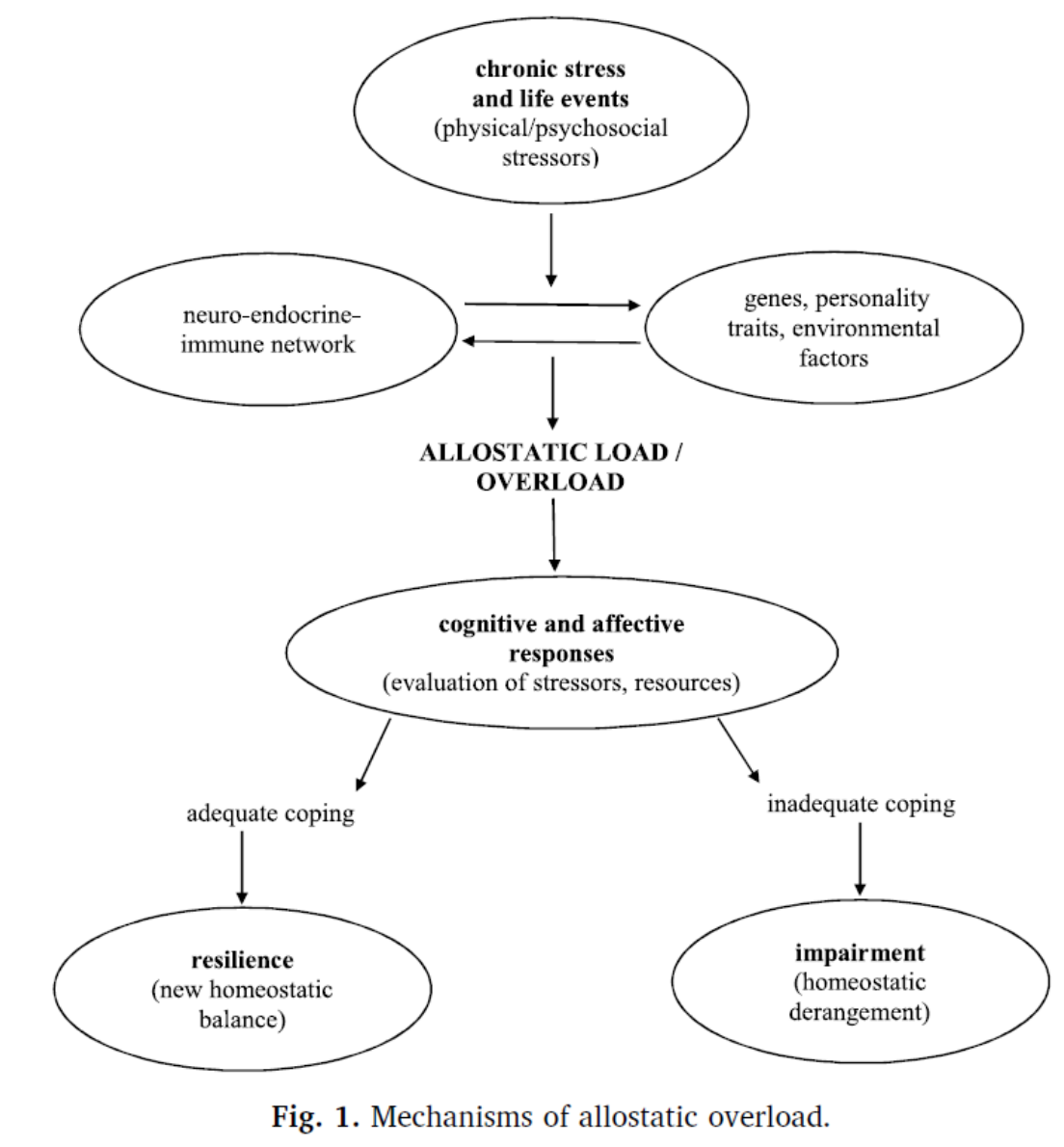

Fig. 1. Mechanisms of allostatic overload.

Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101.

How do we determine where someone is along the HPA axis continuum?

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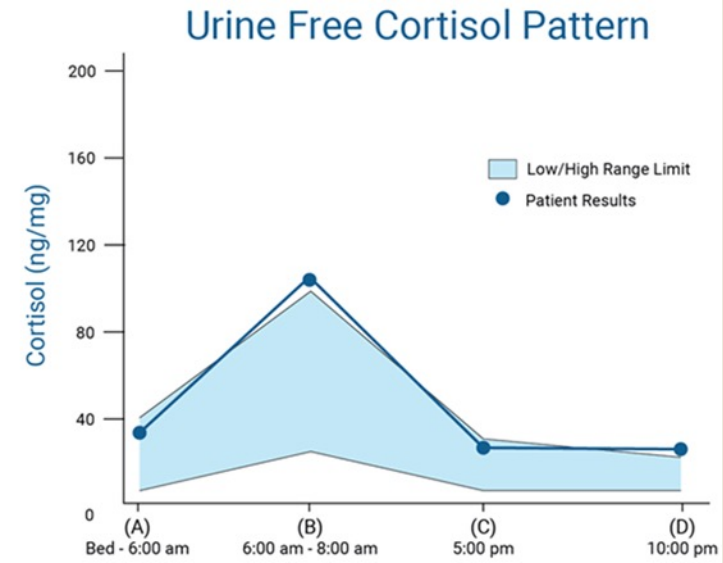
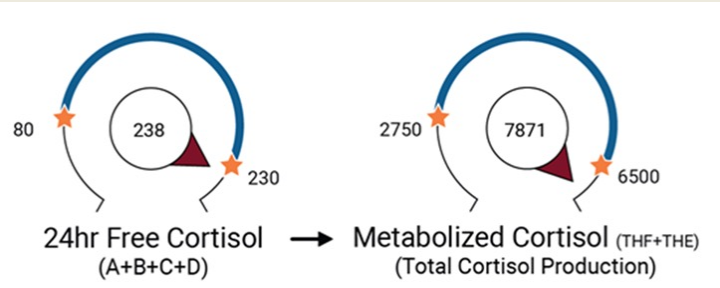
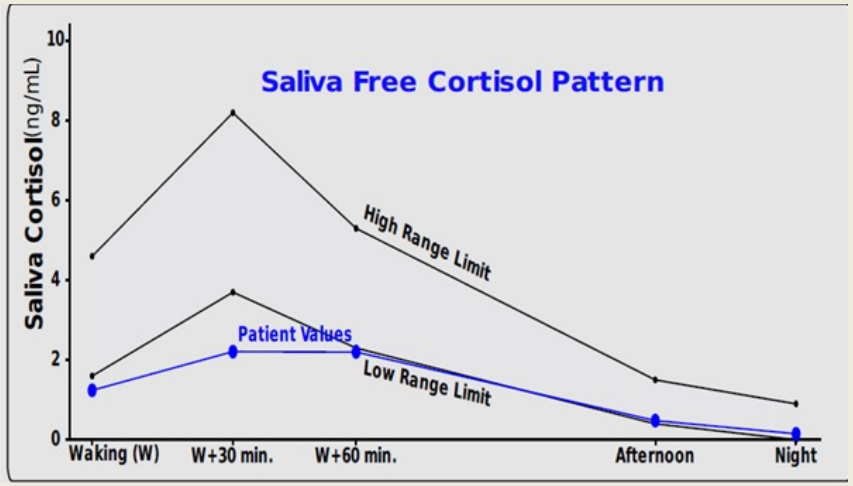
The HPA Axis Continuum

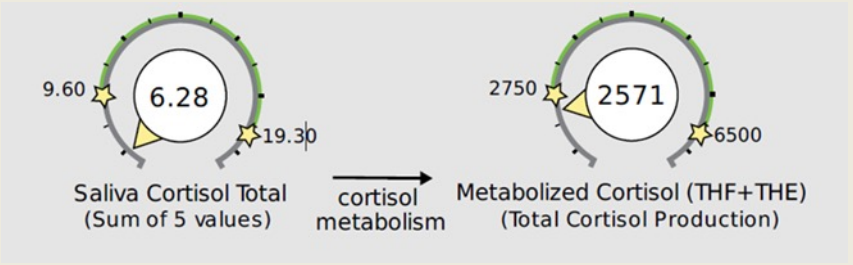
Fight-or-flight response





Exhaustion or burnout





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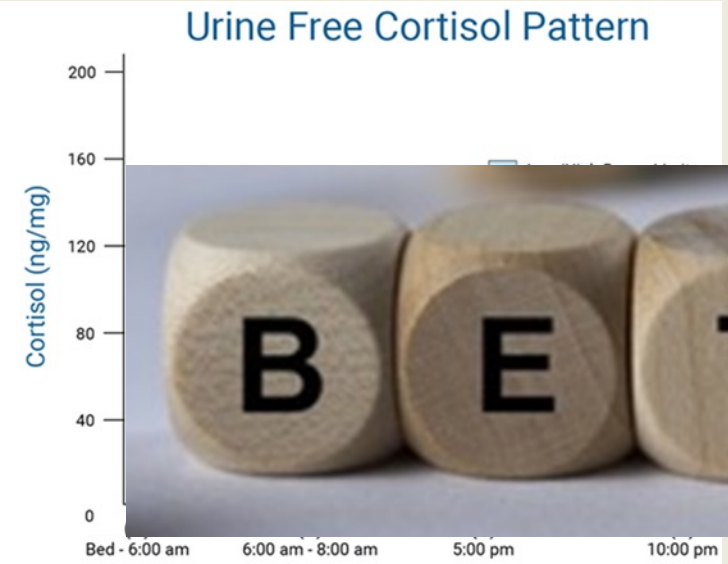
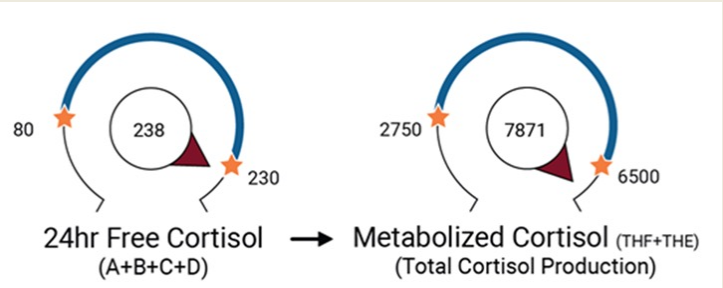
The HPA Axis Continuum

Fight-or-flight response





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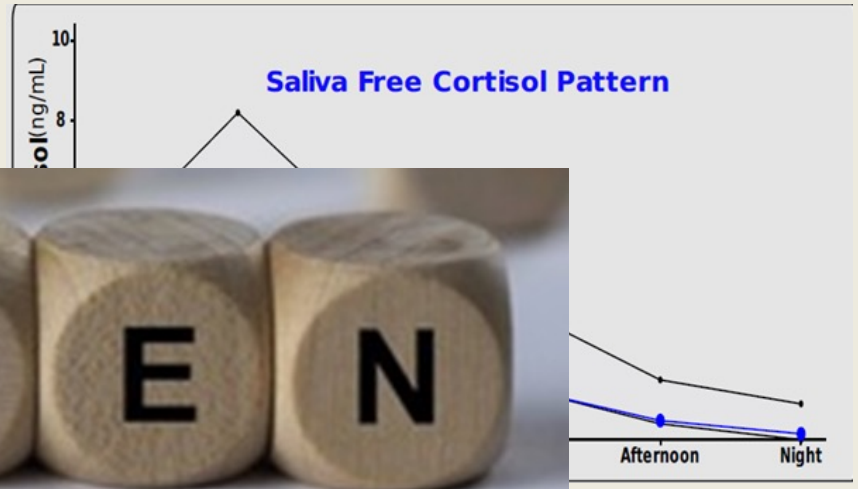

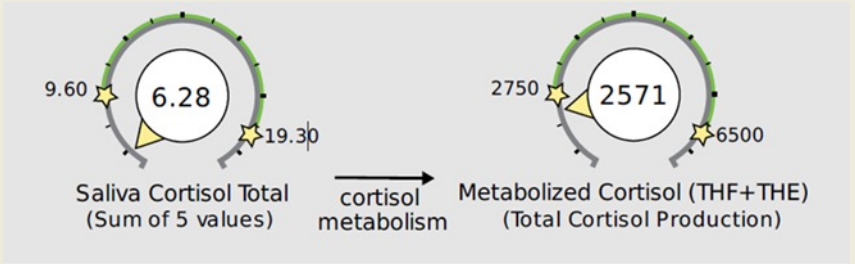

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Allostatic Overload: Clinical Criteria

Table 1
Clinical criteria for allostatic overload (A through B are required).

Criterion A	The presence of a current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated
Criterion B	The stressor is associated with one or more of the following features, which have occurred within 6 months after the onset of the stressor: 1. at least two of the following symptoms: difficulty falling asleep, restless sleep, early morning awakening, lack of energy, dizziness, generalized anxiety, irritability, sadness, demoralization 2. significant impairment in social or occupational functioning 3. significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)

Criteria A: type of stressor
Criteria B: clinical manifestations associated with the stressor

Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101.

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Allostatic Overload Questionnaire

ALLOSTATIC OVERLOAD			
Criteria		**Answer**	
Criterion A: The presence of at least one current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated	**A1.** In the last 12 months, ☐ Did a family member or a close friend die? ☐ Did you separate or divorce from your partner? ☐ Did you change job? ☐ Did you move? ☐ Did you have severe economic difficulties? ☐ Did you have legal problems? ☐ Did you start a new relationship? ☐ Did you feel under pressure at work? ☐ Did you have problems with co-workers? ☐ Have you been a victim of bullying, stalking or severe interpersonal pressure? ☐ Did you have problems with your spouse / partner or other family members? ☐ Did you feel tension at home? ☐ Has at least one family member been seriously ill? ☐ OTHER _____ _____ _____	YES	NO
	A2. Have you had the feeling that life is asking you too much?	YES	NO

Criterion B: The stressor is associated with one or more of the following features, which have occurred within 6 months after the onset of the stressor: (1) At least two of the following symptoms: difficulty falling asleep, restless sleep, early morning awakening, lack of energy, dizziness, generalized anxiety, irritability, sadness, demoralization	**B1.** Within 6 months after the onset of (NAME OF THE STRESSOR), ☐ Did it happen to take a long time to fall asleep? ☐ Did you wake up many times during the night? ☐ Did you wake up too early and could not get back to sleep? ☐ Did you feel tired, without energy? ☐ Did you feel a sense of instability, dizziness? ☐ Did you feel nervous or anxious? ☐ Did you feel irritable? ☐ Did you feel sad or depressed? ☐ Did you feel demoralized?	YES	NO
(2) Significant impairment in social or occupational functioning	**B2.** Did you have problems or difficulties at work, at home or in relationships with other people?	YES	NO
(3) Significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)	**B3.** Did you feel overwhelmed by the demands of everyday life?	YES	NO

- **Is the patient clinically stressed?**
  - Any A1 = Yes, + A2 = Yes
    +
  - B1 and/or B2 and/or B3 (any 2 B's) = Yes

Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101.

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Signs/Symptoms and Stress-Induced HPA Axis Dysfunction

High Cortisol

- Irritability/anxiety/depression
- Wired and tired
- Sleep disturbances
- Nigh sweats/ hot flashes
- Carbohydrate/sugar cravings
- Elevated BP
- Memory issues/brain fog
- Increased susceptibility to infections and cancer (decreased TH-1 helper cells)

Low Cortisol

- Irritable/atypical depression
- Tired and exhausted
- Sleep disturbances
- Chronic pain syndromes
- Irritable bowel
- Autoimmune diseases (favors TH-1 immunity)
- Chronic disease syndromes

Stress-Induced HPA Axis Syndromes and Disease States

High Cortisol

- Obsessive compulsive disorder
- Panic disorders
- Anorexia
- Melancholic depression
- Diabetes
- Central obesity
- Malnutrition
- Hyperthyroidism
- Pregnancy
- Chronic diseases – early on

Low Cortisol

- Chronic fatigue syndrome
- Fibromyalgia
- PTSD
- Hypothyroidism
- Post partum
- Chronic diseases – later stage

Key Points

- DUTCH urine is a reasonable alternative to DUTCH saliva testing
- The question being asked will determine the cortisol test
  - Saliva: CAR
  - Urine: metabolites
  - Both: DUTCH Plus
- History and validated questionnaires will help assess where along the HPA axis continuum a patient is

Thyroid and the Stress Response

coem.com

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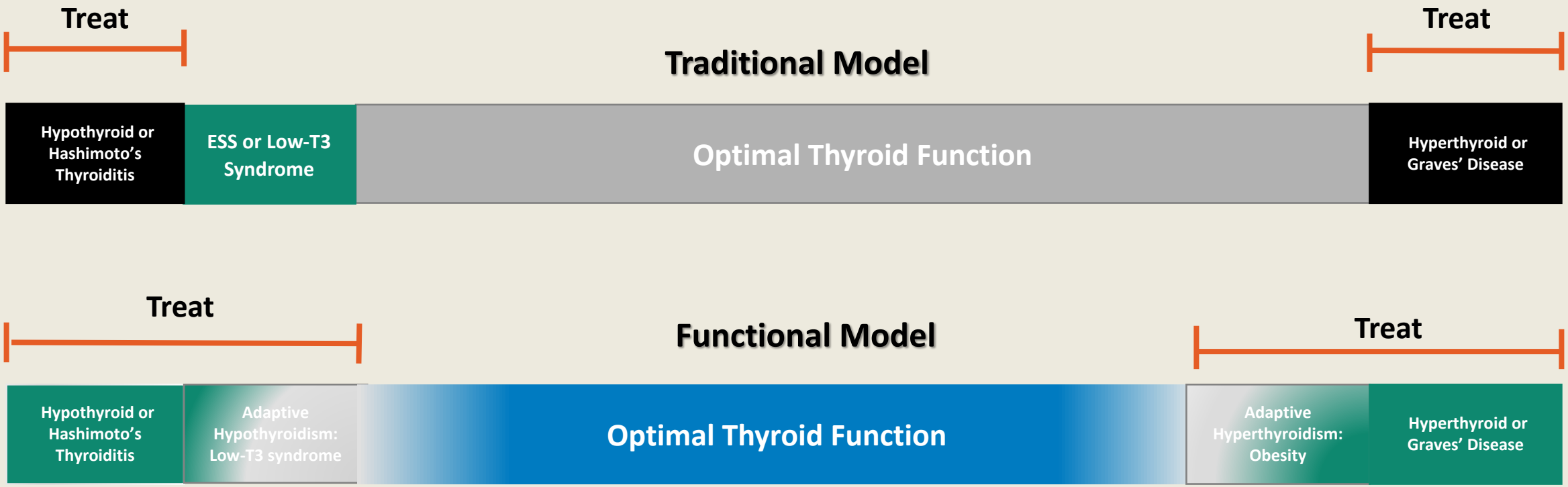
Thyroid and the Functional Medicine Model



Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.

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Allostatic Load, Allostatic Overload, Resiliency, and Toxic Stress

- Allostasis is the ability to achieve stability through change
  - Ability to adapt to a changing environment
  - Through allostasis the HPA axis, ANS, cardiometabolic, and immune systems protect the body by responding to internal/external stressors
- Allostatic load is the accumulated wear and tear resulting from daily life, which may lead to disease over time
  - Long-term effects of stress over time
  - Results from too much stress or from inefficient stress management

McEwen BS. N Engl J Med. 1998; 338(3): 171-179.
Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.
Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101

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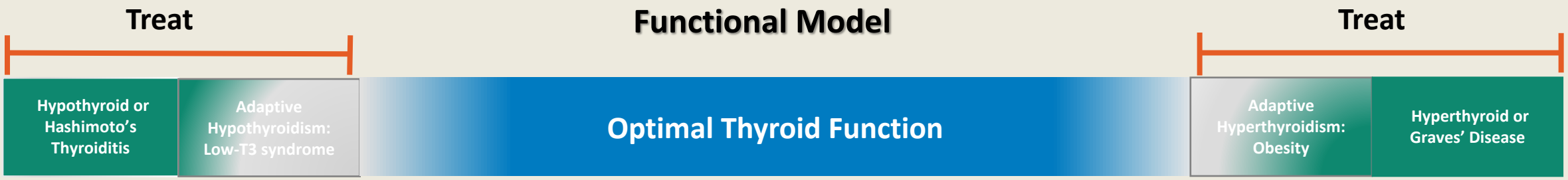
Allostatic Load, Allostatic Overload, Resiliency, and Toxic Stress

- Resiliency is the ability to quickly bounce back from stressful situations; coping ability
  - Dependent upon how one perceives stressor
  - One's physical health and reserve (genetics, lifestyle)
  - Necessitates positive experiences with rewards and a sense of meaning and purpose
- Allostatic overload occurs when demands exceed coping resources
  - Demands > supply
- Toxic stress occurs when there is strong, frequent, and/or prolonged activation of the stress response without adequate reserve
  - Demands >>> supply

McEwen BS. N Engl J Med. 1998; 338(3): 171-179.
Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.
Fava GA, et al. Psychoneuroendocrinology. 2019; 108: 94-101

The Thyroid Adapts to the Allostatic Load



- During restful times, thyroid under tight control
- With chronic stress, inflammation, inflammatory syndromes, and disease states, the thyroid adapts to the allostatic load
- **Referred to as thyroid adaptation to type 1 and 2 allostasis**

Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.

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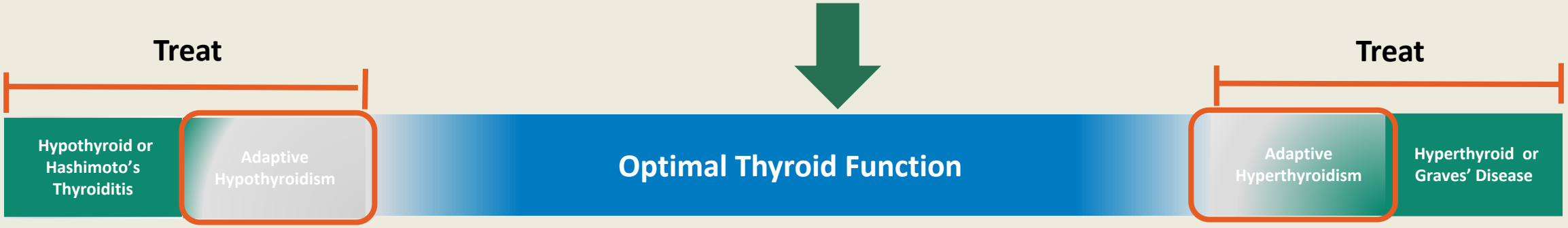
The Thyroid Adapts to the Allostatic Load



- **The thyroid is an energy-consuming organ**
- **Thyroid activation is associated with glutathione, ATP, and oxygen consumption**

Type 1 allostatic load

- **Energy demands exceeds the energy supply (sum of energy intake and energy reserve)**
- Without adequate glutathione, ATP, etc., thyroid hormone is down-regulated
- Examples: chronic illness, chronic stress, exhaustion
- **Labs: low TSH, low T3, low T4, increased RT3**

Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.

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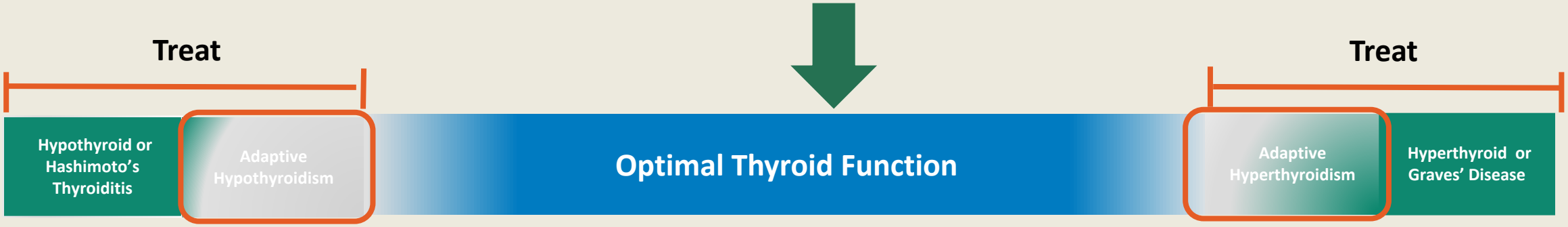
The Thyroid Adapts to the Allostatic Load



- **The thyroid is an energy-consuming organ**
- **Thyroid activation is associated with glutathione, ATP, and oxygen consumption**

Type 1 allostatic load

- **Energy demands exceed sum of energy intake and energy reserve**
- Without adequate glutathione, ATP, etc., thyroid hormone is down-regulated
- Examples: chronic: stress, inflammation, illness, exhaustion
- **Labs: low TSH, low T3, low T4, increased RT3**

Type 2 allostatic load

- **Expected increase in energy demands with adequate reserve**
- With adequate stores, thyroid hormone is upregulated to meet demands, i.e., increased T3
- Examples: obesity, endurance activity, pregnancy
- **Labs: normal/increased TSH, normal/increased T4, increased T3, decreased RT3**

Chatzitomaris A, et al. Front Endocrinol (Lausanne). 2017; 8:163.

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Key Points

- The thyroid is an energy consuming organ and adapts to the HPA axis
- Thyroid adaptation to the HPA axis is important as not to overtreat the thyroid
- Treating the thyroid will not improve thyroid function without treating the HPA axis

Treatments

news.mit.edu

Lifestyle

- Lifestyle: 45-60 days to make a change
- Diet: small frequent meals (4-6x days, stabilizes blood sugar); whole fresh foods, high fiber, nuts and seeds, complex carbohydrates; gluten/dairy free
- Sleep: 8-hours of restful sleep practicing good sleep hygiene
- Mindfulness: HRV, meditation, yoga, prayer, increase (+) attitude
- Social support: avoid isolation, increase pleasurable activities

Basic Supplements

- Multivitamin: make sure good quality, ensure includes or may need to add:
  - B complex: Cofactors in hormone production: B5 (1000-1500mg/d, B6 (P5P, 50-100mg/d), Biotin (1000mcg/d), methyl folate (400-800/d)
- Nutrients: **vitamin C:** 1 - 2 grams, anti-oxidant blend; **magnesium:** 400-800mg/d, preferably not oxide; **O3 fish oil:** 1-4 grams/d; **zinc:** 25-50mg/d; caution with doses > 50mg/d, can alter copper and iron metabolism/function and immune function
- Vitamin D: test don't guess; levels > 40; **goal 50-80ng/mL**

Adaptogens

High Cortisol

- Ashwagandha
- L-theanine (mind racing)
- Relora (food cravings)
- Rhodiola (anxiety, performance, decreases CAR)
- Holy Basil (immune modulator, supports BS)
- Phosphatidyl Serine (PS)
- RG3 (CNS immune modulator)
- Melatonin

Mixed Cortisol

- Ashwagandha
- Rhodiola
- Cordyceps: decreases oxidative stress
- PS: decreases cortisol
- RG3 (CNS immune modulator)
- Melatonin

Low Cortisol

- Licorice: inhibits 11β-HSD2 activity (cortisol to cortisone)
- Glandulars: support

Start low and go slow!

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Final Thoughts

- We live in a stressful world
- Most, if not all, patients have some degree of HPA axis dysfunction
- HPA axis dysfunction impacts all systems, including sex hormones
- Cortisol is the universal stress marker, drives inflammation, and all inflammatory diseases/syndromes
- Lifestyle interventions are the most effective, but hardest treatments to comply with
- Without lifestyle changes, other treatments will probably not be successful

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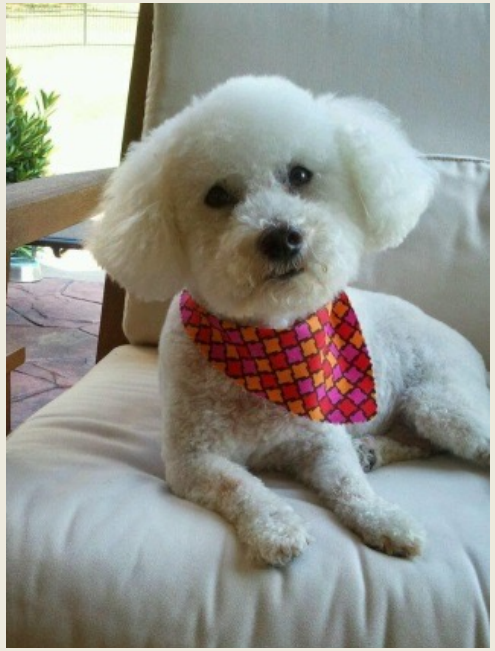

i'm not telling you it is going to be easy, i'm telling you it's going to be worth it.

Questions?

guides.library.uq.edu.au

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Thank You!

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