Demystifying Medicine: Addison's Disease Meets Chromatin Biology

4/25/2017

Lynnette K. Nieman
DEOB, NIDDK

Daniel R. Larson
LRBGE, NCI

Disclosure

- Adrenal Section editor and author, UpToDate

Cortisol is a bi-modal hormone

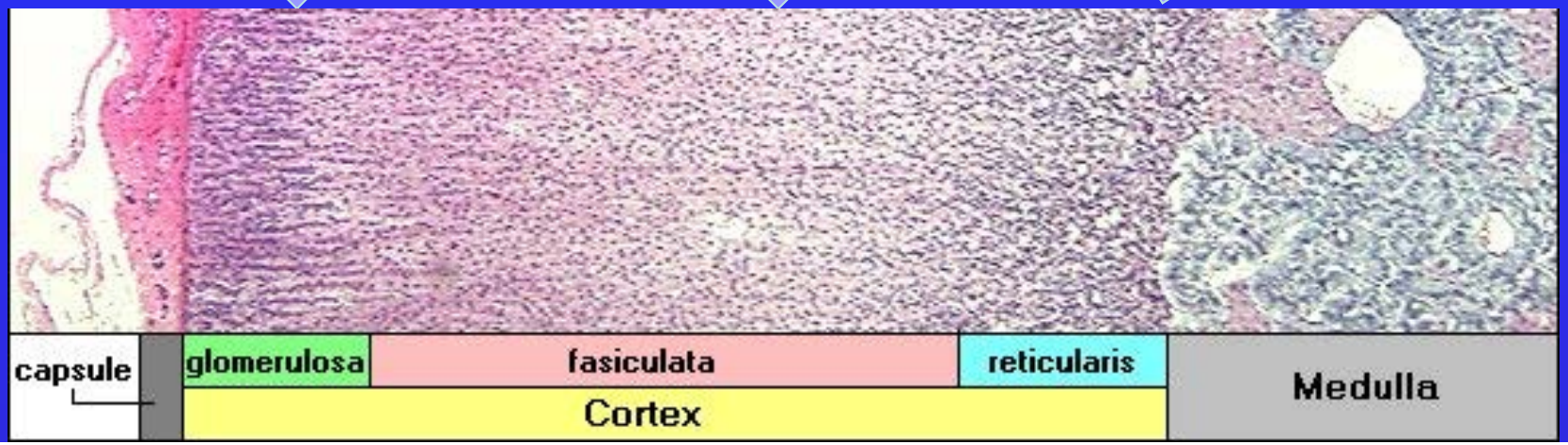
- Made by the adrenal gland cortex (outer layer)
- Baseline/day-to-day control of metabolism (fuel)
- Stress → increased amounts immunosuppressant and anti-inflammatory

Adrenal Gland Hormones

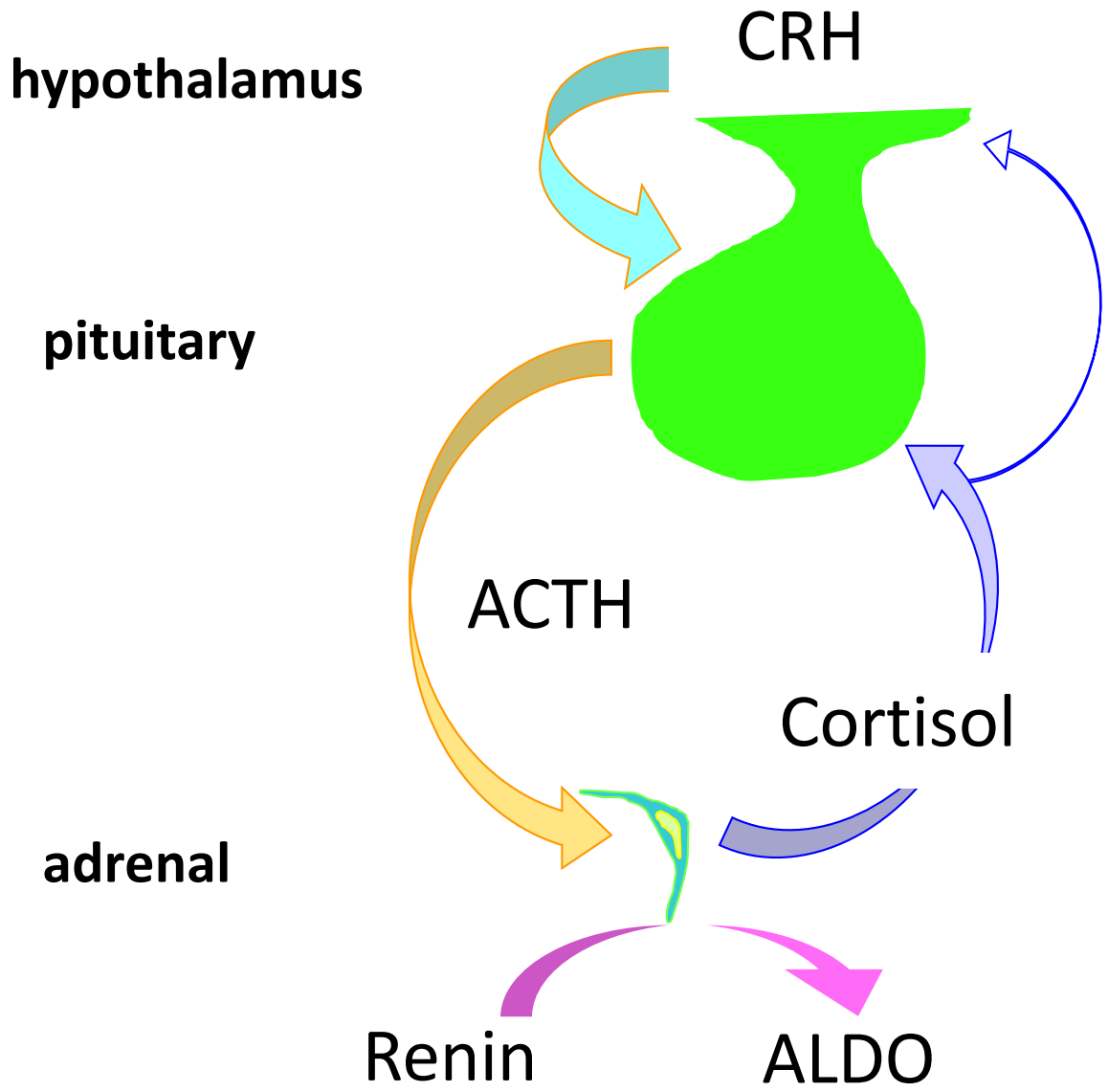
Cortisol (glucocorticoids)

Aldosterone (mineralocorticoids)

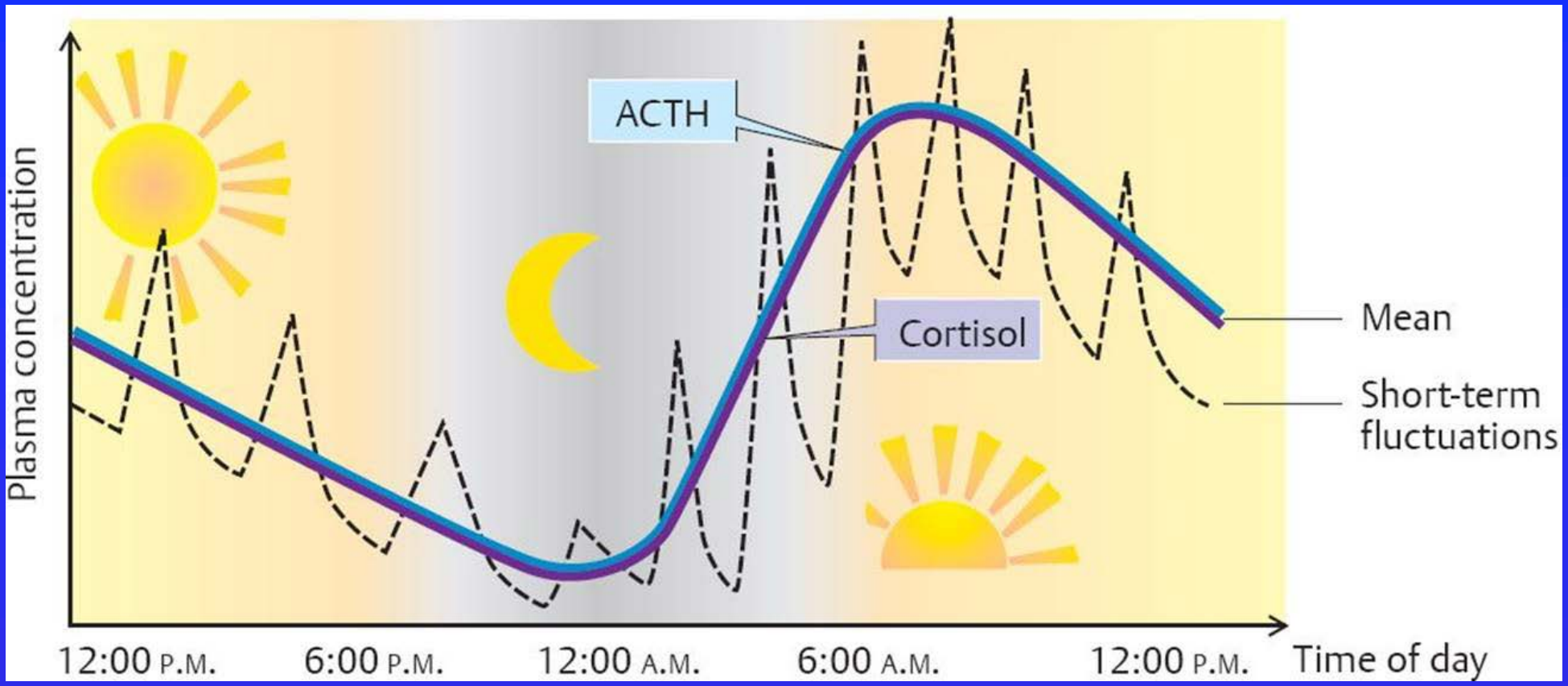
DHEA (androgens)



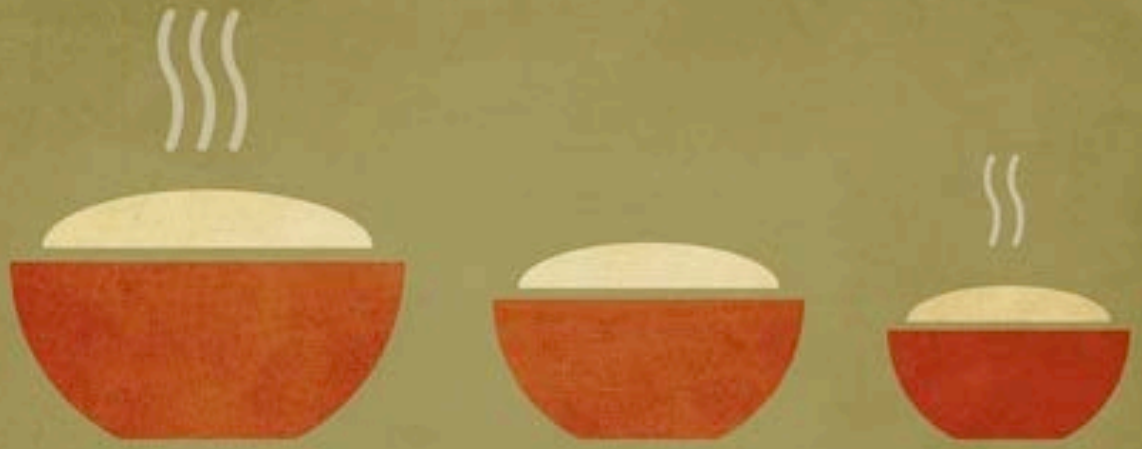
Hypothalamic-Pituitary-Adrenal Axis



Cortisol daily rhythm



The right amout of cortisol is critical



Too much **Just right!** **Too little**

Cushing's Syndrome

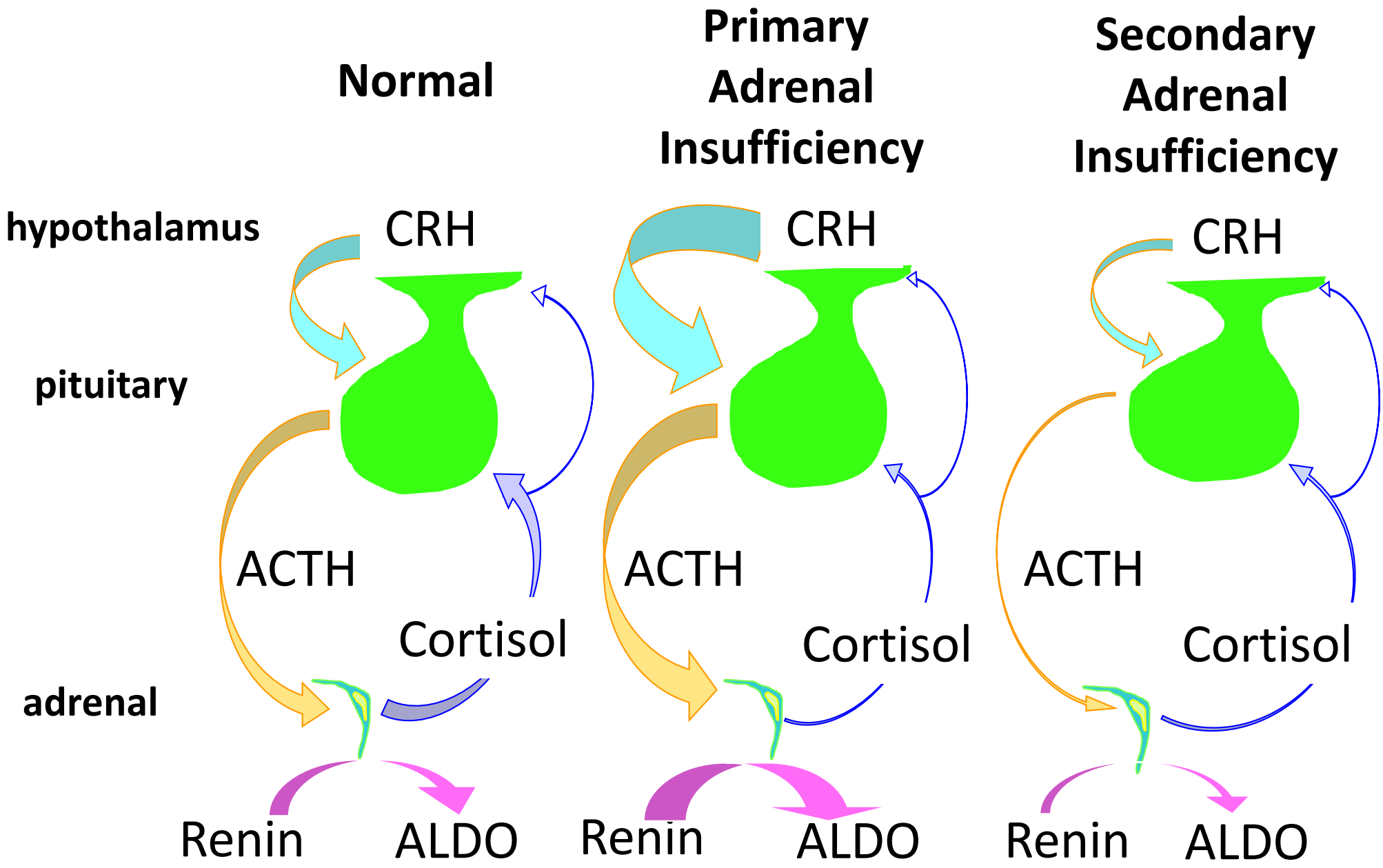
Adrenal Insufficiency

Untreated, complete adrenal insufficiency leads to circulatory collapse and death.

FAQs about Adrenal Insufficiency

- Causes
- Diagnosis
  - Clinical Features
- Adrenal fatigue
- Steroid Replacement

The HPA Axis in Adrenal Insufficiency



Primary Adrenal Insufficiency: Causes

Causes	Suggestive features
Primary AI	Pigmentation, hypotension
Idiopathic Autoimmune	Most common
Infections: TB, fungal, AIDS-associated (CMV)	15% of patients in US series
Space occupying mass	Metastases (lung, breast, kidney, gut, lymphoma), blood, heparin Rx
Bilat Adx or Rx	Ketoconazole, mitotane, aminoglutethimide, metyrapone, etomidate
Polyglandular Failure 1	Hypopara, candidiasis, vitiligo; < 20y
Polyglandular Failure 2	IDDM, hypothyroid, alopecia areata, hypogonadal; >40 yo
Adrenoleukodystrophy	X-linked; cognitive, gait, paraparesis

Secondary Adrenal Insufficiency: Causes

Causes	Suggestive Clinical Features
Suppression of the HPA axis by endogenous/exogenous GCs	Rx history; Cushing's history
Traumatic brain injury	Usually ICU admission; also sports-related
Structural lesions of the hypothalamus or pituitary: tumors, destruction by infiltrating disorders, x-ray, lymphocytic hypophysitis.	Other pituitary deficiencies
Isolated ACTH deficiency	

FAQs about Adrenal Insufficiency

- Causes
- Diagnosis
  - Clinical Features – recognition
- Adrenal fatigue
- Steroid Replacement

Adrenal insufficiency is suggested by clinical features and confirmed by biochemical testing.

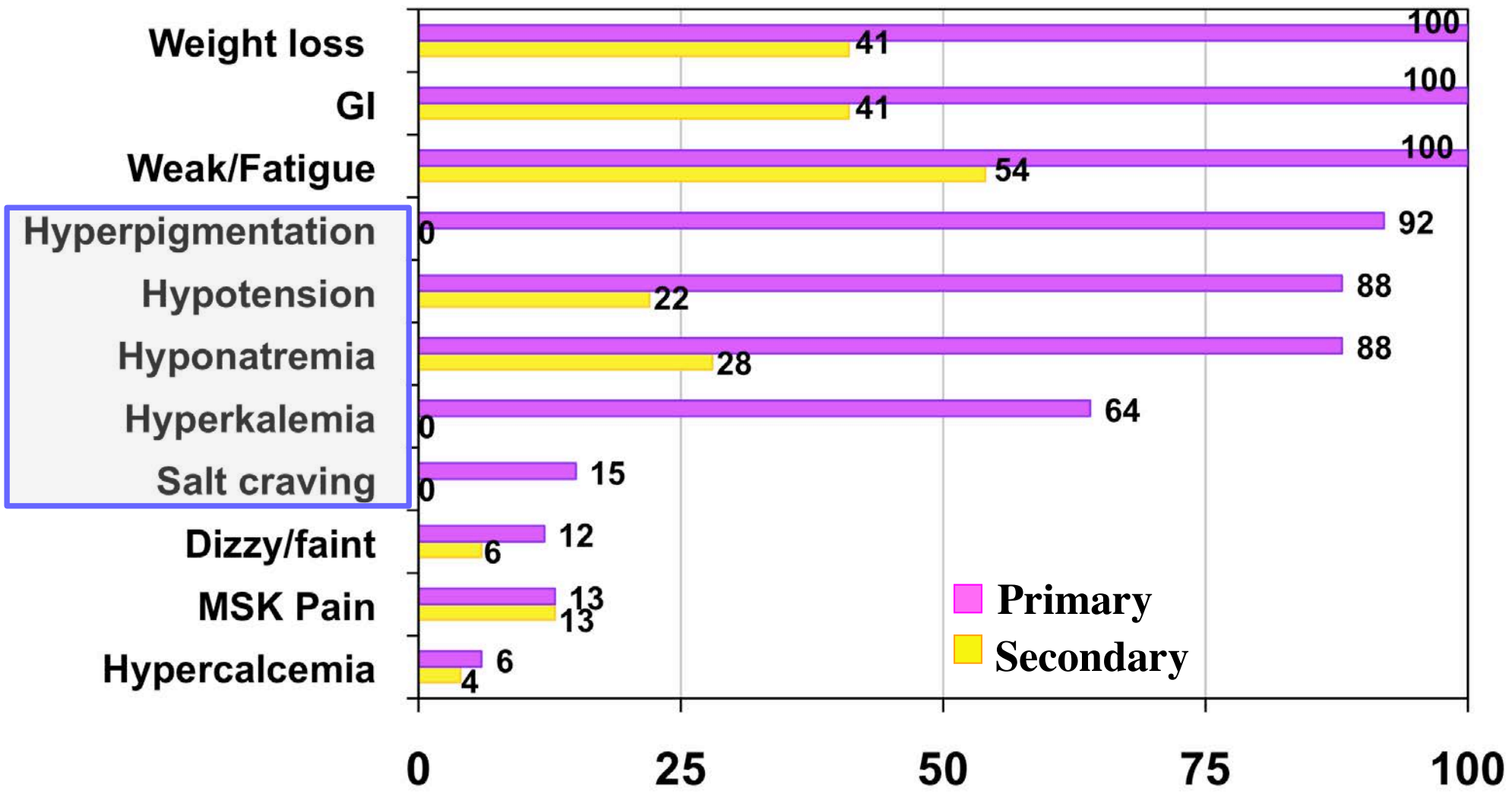
Clinical Acumen in Adrenal Insufficiency: Classic presentation

- Classic symptoms: fatigue, malaise, anorexia, weight loss, abdominal pain, vomiting
- Hyponatremia +/- hyperkalemia
- Presentation related to rate of onset and severity of deficiency
- Primary adrenal failure – both glucocorticoid and mineralocorticoid deficiency
- Secondary adrenal failure – may have manifestation of other hormone deficiencies

Primary Adrenal Insufficiency

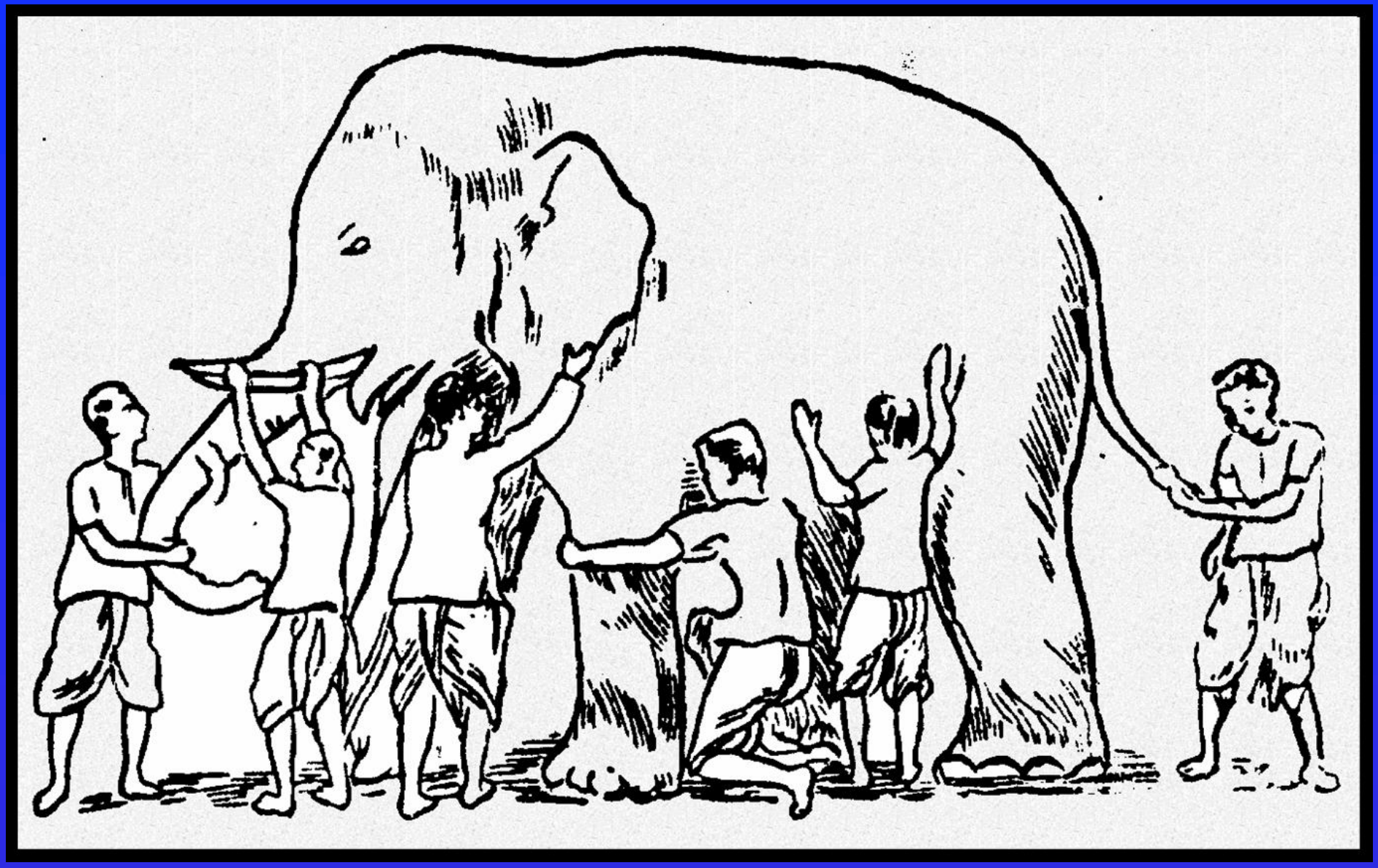
- **Acute:** orthostatic hypotension, circulatory collapse, fever, and hypoglycemia
- **Chronic:** fatigue, anorexia, weight loss, joint and back pain, and darkening of the skin
- Since all layers of the adrenal cortex are involved, both mineralocorticoid and glucocorticoid secretion is impaired. Thus, laboratory findings include hyponatremia and hyperkalemia.

Frequency of signs/symptoms (%)



Carroll PB et al. N Y State J Med 1990

Recognition (pre-test probability) depends on perspective



The Rheumatologist's perspective

- Knee pain
- Knee flexion
- Failure of knee extension
- Back pain
- Migratory arthalgias
- Myalgias

Sathi, et al. Clin Rheumatol 28:631, 2009
Shapiro et al. Postgraduate Med J 64:222, 1988

The psychiatrist's perspective

- Psychosis
- Anxiety, depression
- Lethargy, weariness "too tired to vomit"
- "Most of our [untreated] patients are hypoglycaemic in the early morning, being difficult to rouse from sleep, and their attitude towards those who make the attempt being surly and resentful.
- I do not suggest, of course, that such behaviour is confined to Addisonian patients."

Dunlop K. Eighty-six cases of Addison's disease. BMJ 5362:887, 1963

The Dermatologist's perspective: Primary AI

- Increased pigmentation of mucosa, creases, scars, nipple
- Generalized hyperpigmentation
- Vitiligo
- Nail bed lines

Skin features of primary adrenal insufficiency: Bronzing

Photos courtesy of DL Loriaux

Hyperpigmentation

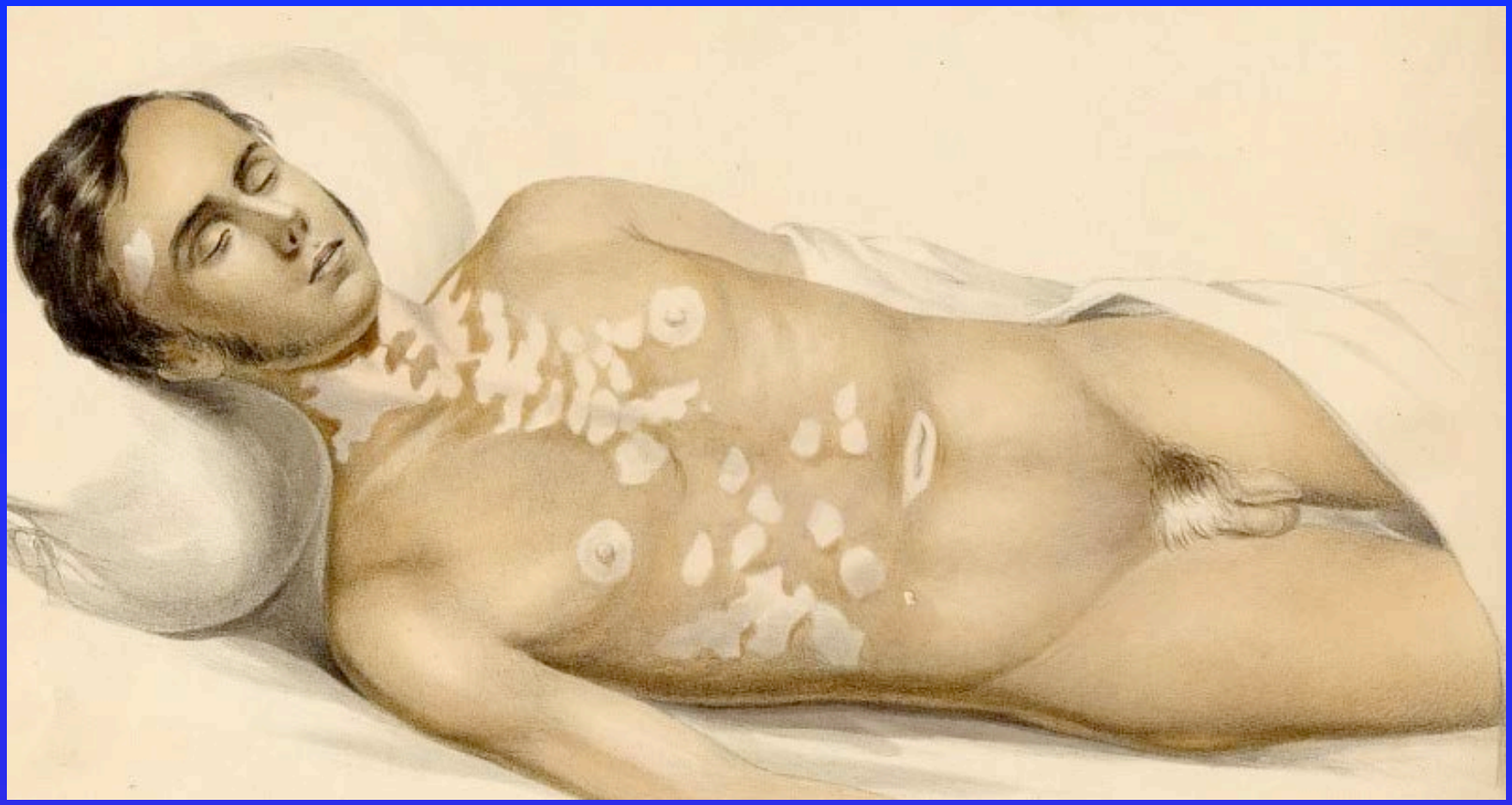
Skin features of primary adrenal insufficiency: Hyperpigmentation

Skin features of primary adrenal insufficiency: Hyperpigmentation

Hyperpigmentation?

Skin features of primary autoimmune adrenal insufficiency: Bronzing & vitiligo

Addison's diagram of vitiligo and hyperpigmentation



Thomas Addison, *On the constitutional and local effects of disease of the supra-renal capsules*.

Refresher course for general practitioners (1950): Addison's Disease

- "Hiccup, yawning, conjunctivitis, grimaces, involluntary cries, negativism, contrariness and apathy.
- Sensitivity to cold, with curling up under the bedclothes, and subnormal temperature.
- A man age 36 was operated on for a perforated duodenal ulcer…" Nothing was found. At necropsy, TB of adrenals
- Normal pregnancy, vomiting, malaise, in a dark skinned woman

Simpson SL. BMJ 4689: 1164, 1950

Neurology and Psychiatry

- Collapse and syncope "sinking spells"
- Hiccough
- Pain (back, abdomen, chest, thighs, epigastrium, head, knees, plantar feet)
- Pseudoperitonitis (7%)
- Irritability, insomnia, restlessness, poor concentration
- Suspiciousness, agitation, delusions, hallucinations, bizarre posturing, confusion

Drake F. Neuropsychiatric-like symptomatology of Addison's disease. Am J Med Sci 234:106, 1957

Confusing clinical presentations

- Pregnancy: Early symptoms easily confused with hyperemesis gravidarum
- HIV/CMV: Fatigue mis-interpreted
- ICU: Etomidate effects overlooked
- Drugs (injection, skin whitening): Cushing's syndrome may be suspected
- Celiac disease: GI symptoms overlap

FAQs about Adrenal Insufficiency

- Causes
- Diagnosis
  - Clinical Features
- **Adrenal fatigue**
- Steroid Replacement

Adrenal Fatigue

Adrenal fatigue

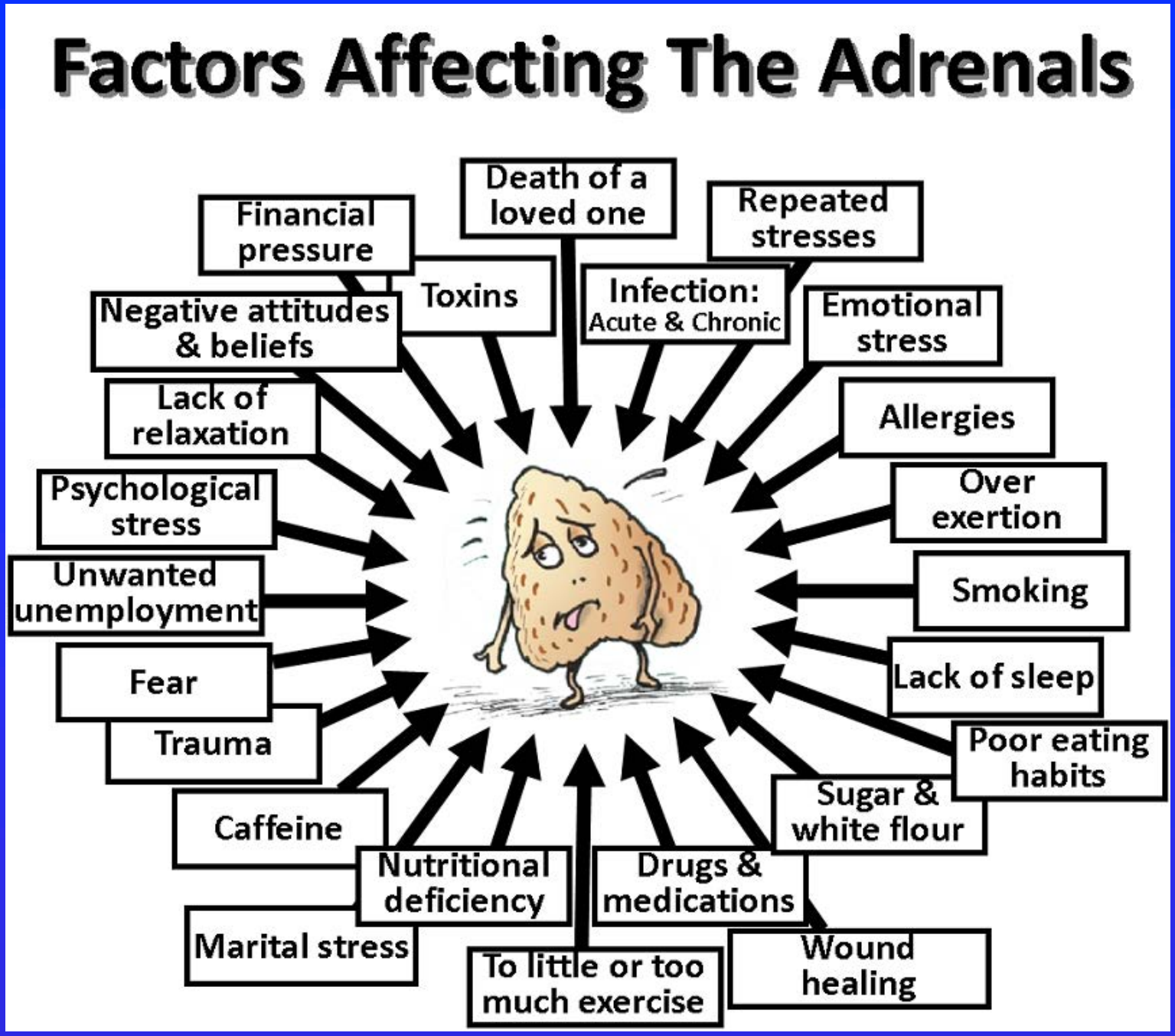
- A collection of nonspecific symptoms, such as body aches, fatigue, nervousness, sleep disturbances and digestive problems.
- A mild form of adrenal insufficiency caused by chronic stress so that the adrenal glands are unable to keep pace with the demands of perpetual fight-or-flight arousal.
- Usually “diagnosed” via questionnaire or salivary cortisol samples
- Conventional tests for adrenal insufficiency not done

Questions to diagnose adrenal fatigue

- You may be experiencing adrenal fatigue if you regularly notice one or more of the following:*
- You feel tired for no reason.
- You have trouble getting up in the morning, even when you go to bed at a reasonable hour.
- You are feeling rundown or overwhelmed.
- You have difficulty bouncing back from stress or illness.
- You crave salty and sweet snacks.
- You feel more awake, alert and energetic after 6PM than you do all day.

http://www.adrenalfatigue.org

Causes of adrenal fatigue



Treatment of adrenal fatigue

- Supplements for “adrenal gland support” + 2-5 g Vit C; Ca, Mg, licorice root extract; Vit E
- Diet (regular meals; chew well; slow carb; no junk food; 5-6 veggies/d; sea salt; Vit E with mixed tocopherols; B-complex
- Lying down during work breaks (preferably at 10 a.m. and again anytime 3 - 5 p.m.)
- Sleeping until 9 a.m. often
- Laughing; do something fun each day
- Exercising
- Minimizing stress
- Taking negative people out of your life

Endocrine society/ the Hormone Health Network ‘fact sheet”

http://www.hormone.org

FAQs about Adrenal Insufficiency

- Causes
- Diagnosis
  - Clinical Features
- Adrenal fatigue
- **Steroid Replacement**

Treatment of adrenal insufficiency

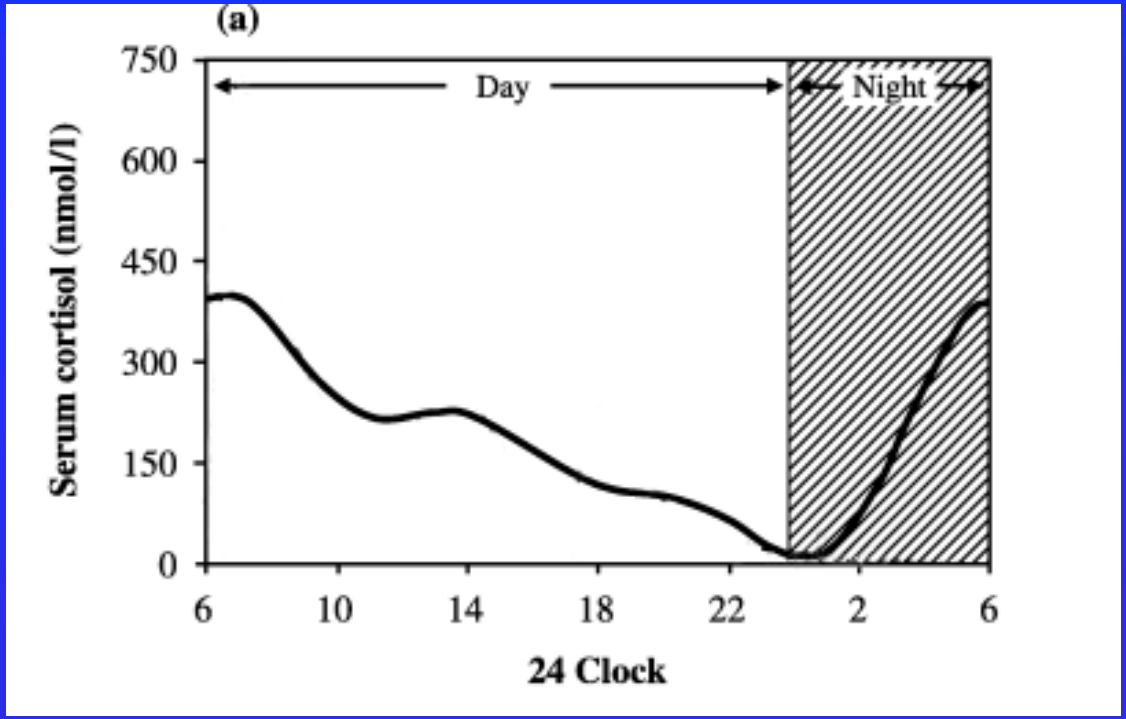
- Acute: Saline, hydrocortisone (dexamethasone)
- Chronic:
  - Glucocorticoid: Hydrocortisone (10 - 12 mg/M2) OR prednisone (4 - 7.5 mg) OR dexamethasone (250 - 500 ug)
  - Mineralocorticoid: Florinef (50 - 400 mg)/ liberal salt
  - Consider dose adjustment and metabolism issues
  - Androgen: DHEA not proven except for puberty

What is the goal of glucocorticoid replacement?

Mimic normal physiology

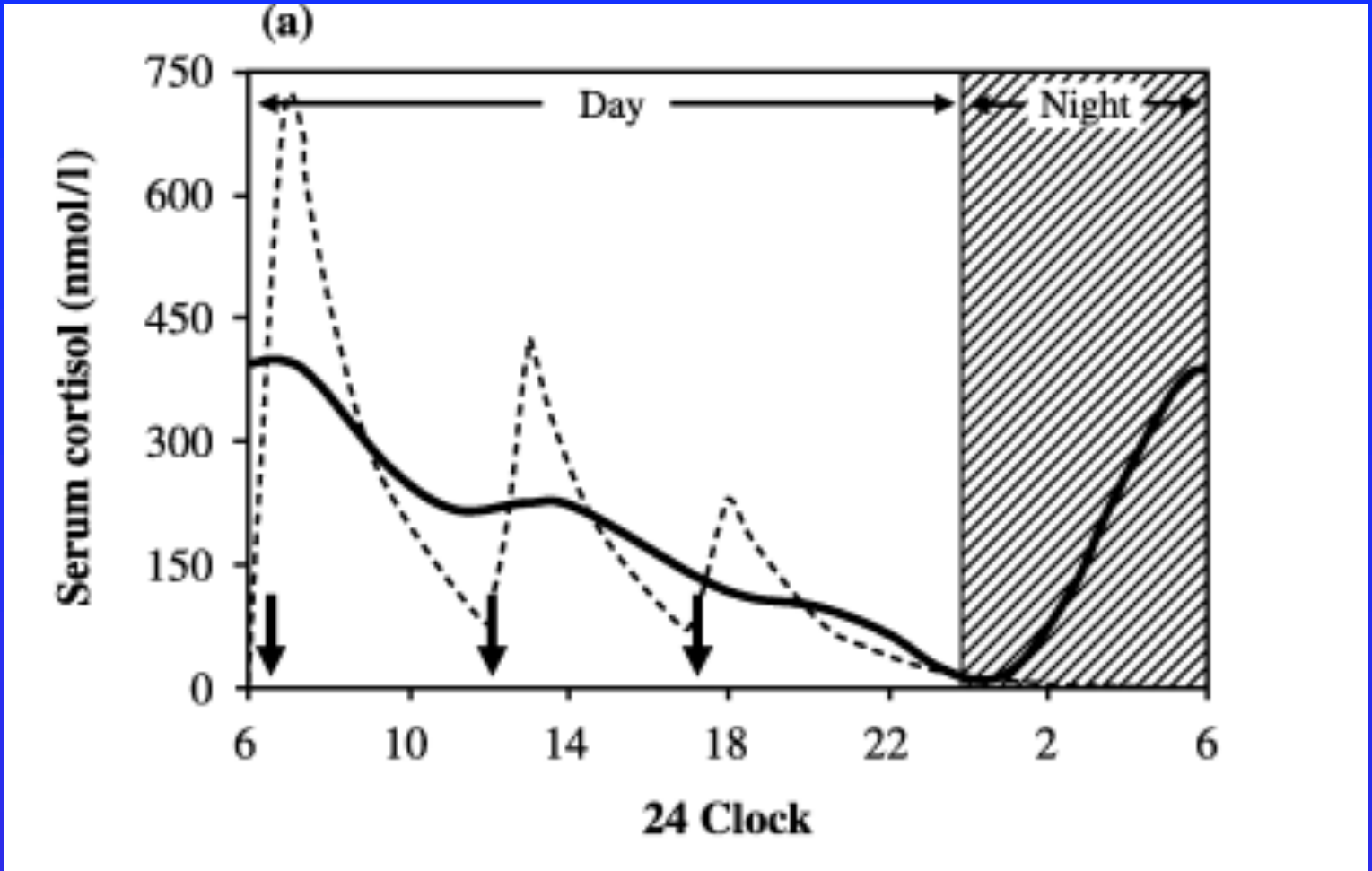
amount of cortisol production

pattern of production



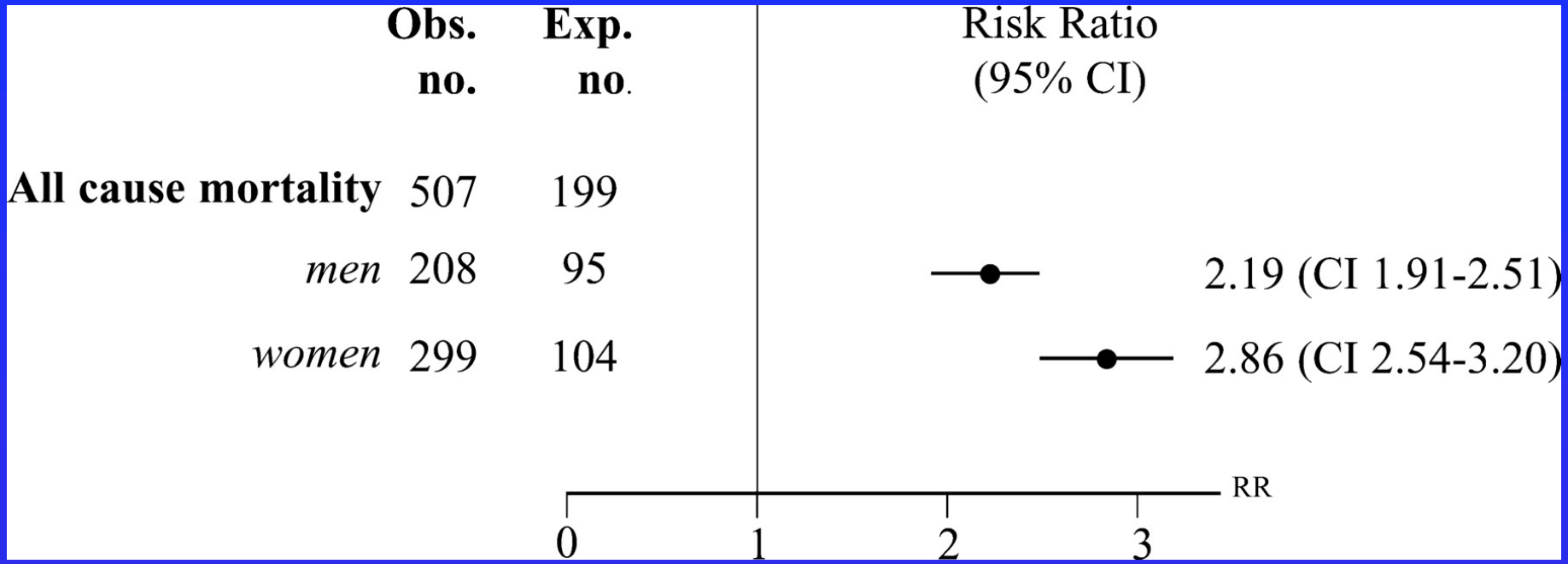
Mah et al. Clin Endo 2004

What's Best?
Once, twice, or thrice?



Actually, it is not well studied. Patients differ in their preference.

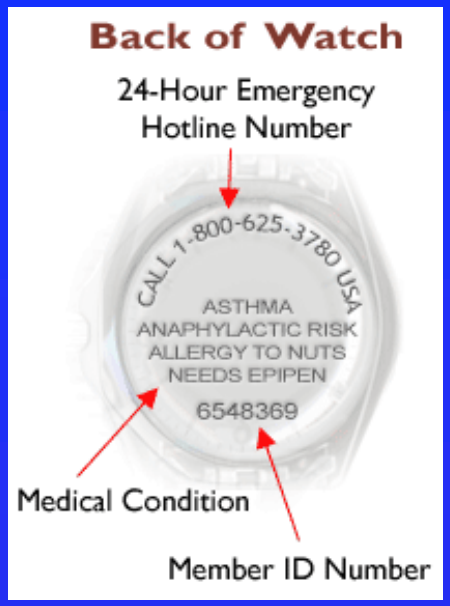
The RR and 95% CI for all-cause mortality in patients with Addison's disease in Sweden from 1987-2001



Bergthorsdottir, R. et al. J Clin Endocrinol Metab 2006;91:4849-4853

Other "treatment"

- MedicAlert or similar jewelry



- Injection and stress doses teaching
- Education

Thank you!

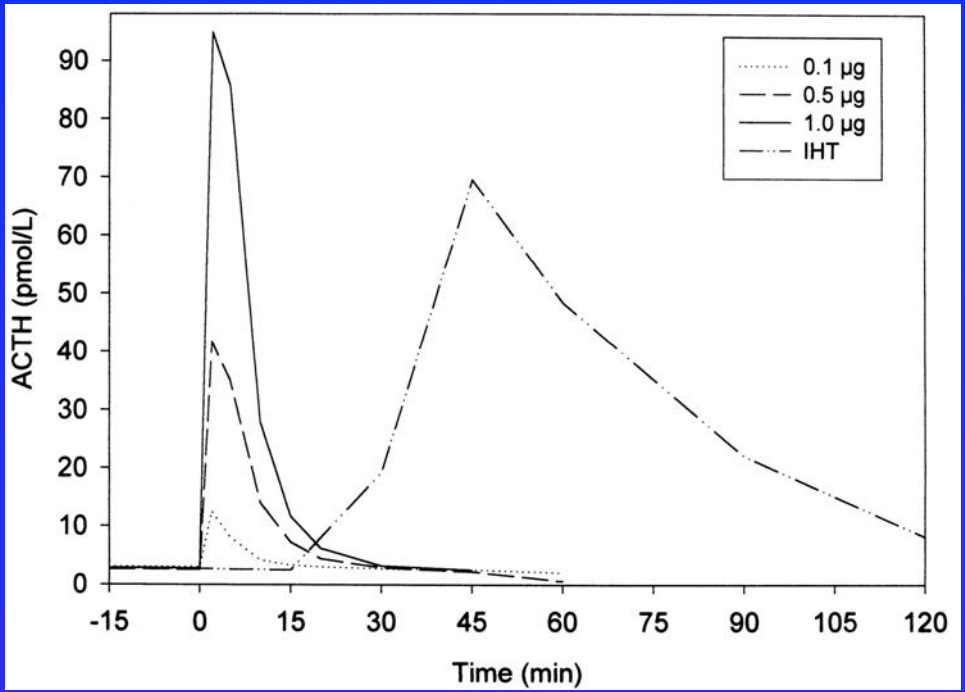
Hydrocortisone

- Split dose for most people (2 – 3 x daily)
- Take first dose on wakening, or earlier with alarm
- Take second dose in afternoon– patient can determine time
- For severe evening tiredness, a small dose
- Maintain total daily dose within the split
- New formulations are coming

Medication adjustments

- Clinical signs of excess (Cushingoid, osteoporosis)/deficiency (salt craving, fainting, fatigue, weight loss)
- Primary
  - Renin levels, potassium
  - Adjust mineralocorticoid first
  - ACTH levels remain elevated
- Measure bone mineral density
- Quality of life measurements?
- Sick day rules

Plasma ACTH levels after ACTH-(1–24) and insulin

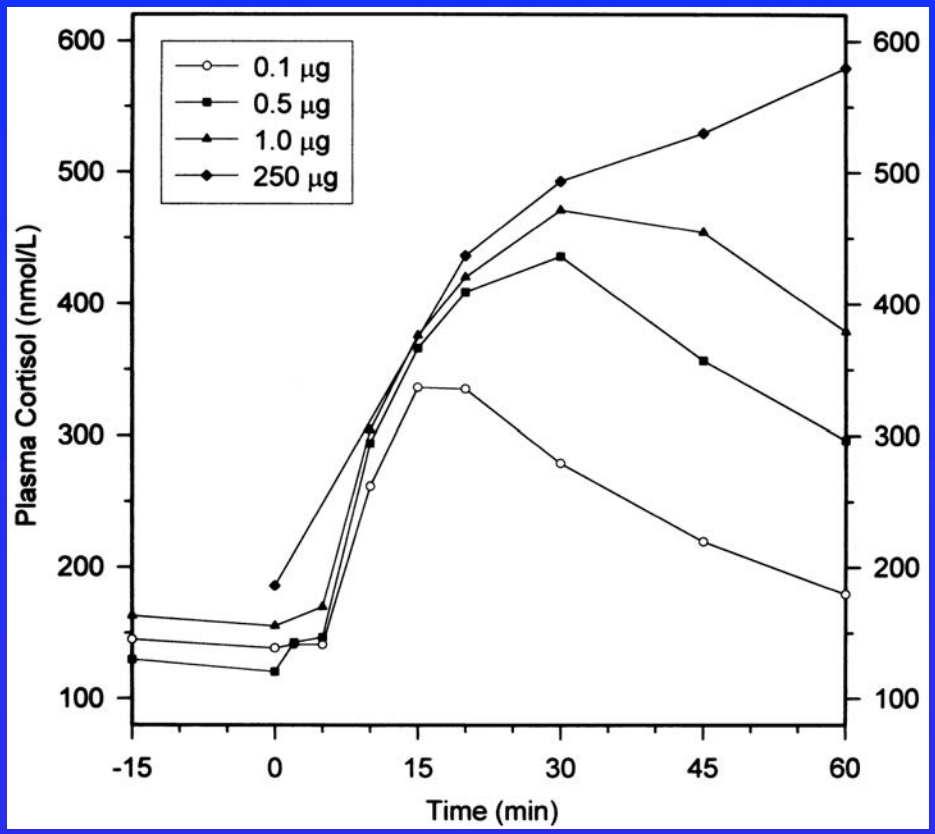


- Mean peak ACTH after insulin: 69.6 ± 9.3 pmol/L (range, 33.6–126.0 pmol/L).
- This level was lower than after 1.0-µg ACTH: 120.2 ± 15.5 pmol/L.
- The duration of the increase in plasma ACTH during the insulin hypoglycemia test was about 7-fold greater than after 1.0-µg ACTH

Nye EJ et al. J Clin Endocrinol Metab 84:3648, 1999

Adrenal Support

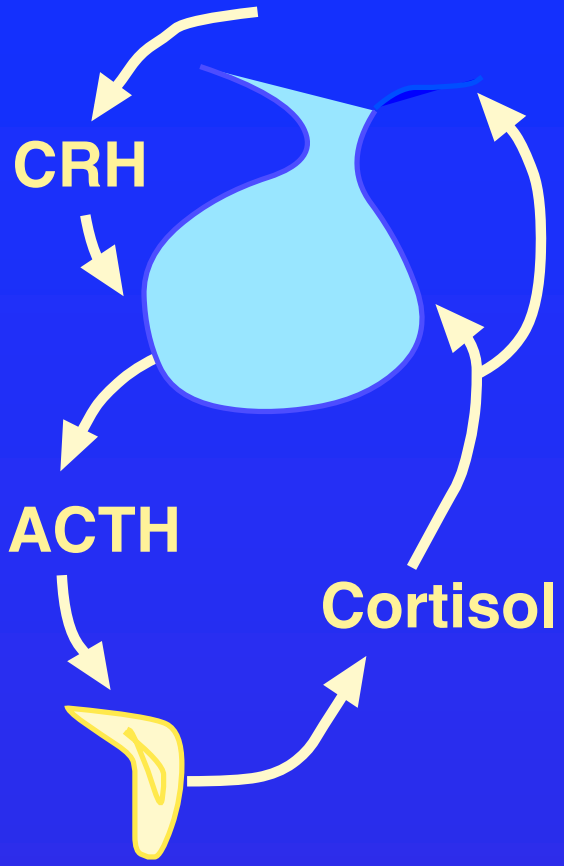
Dose-dependent effects of ACTH



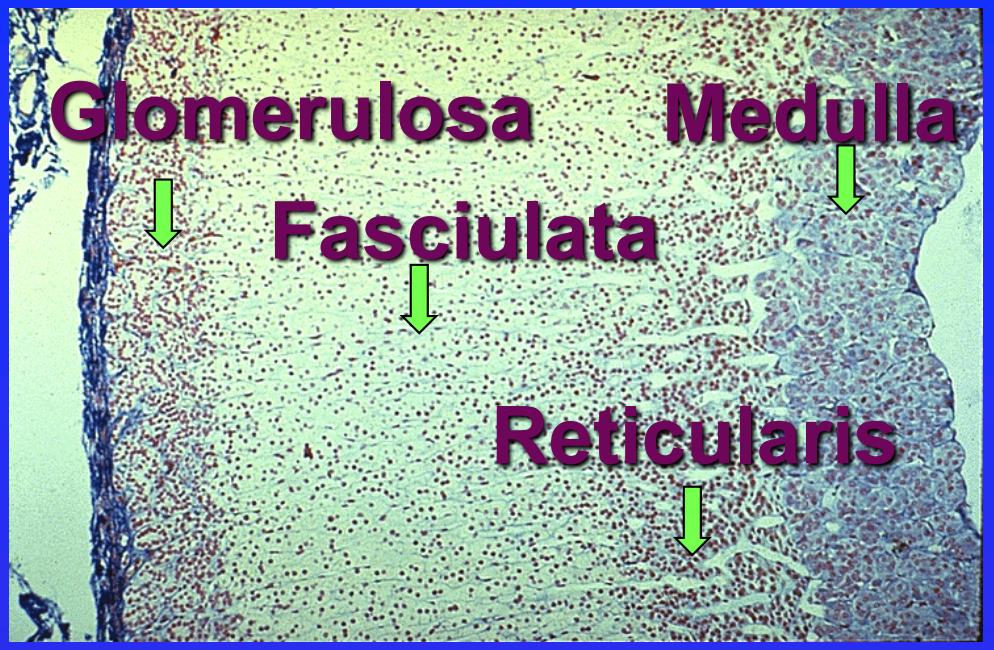
Nye EJ et al. J Clin Endocrinol Metab 84:3648, 1999

- Compared to the HDT the cortisol responses in the LDTs were shorter , with all levels declining at 60 min.
- Peak cortisol levels in all LDTs were significantly lower than those in the HDT.
- The cortisol level and range at 30 min were similar in the 1.0-µg LDT and the HDT).

The Adrenal Axis

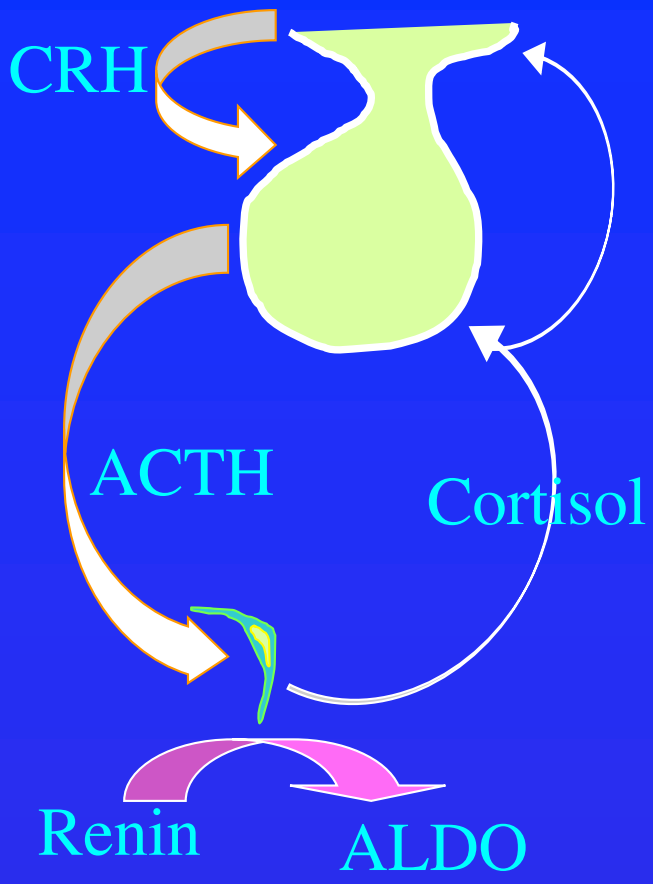


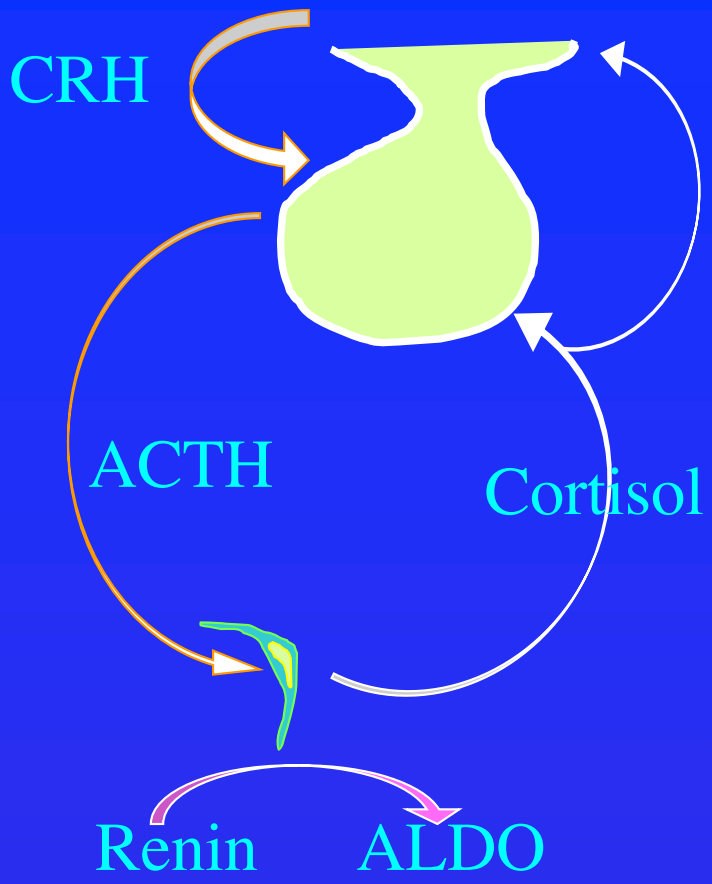
Normal

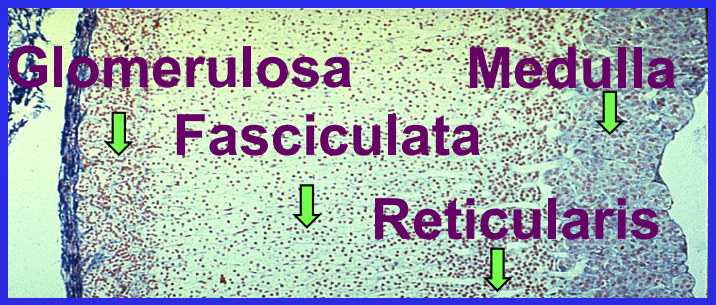


http://www.udel.edu

Adrenal Insufficiency Physiology

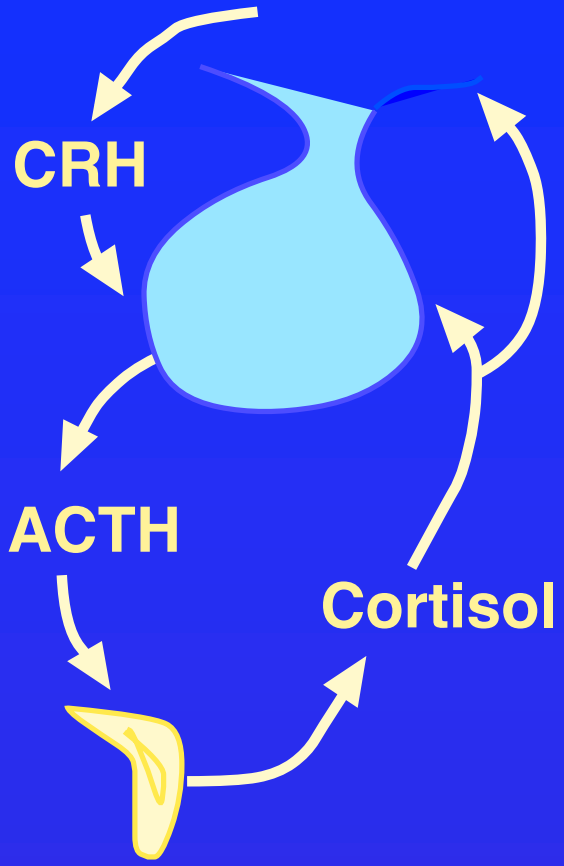




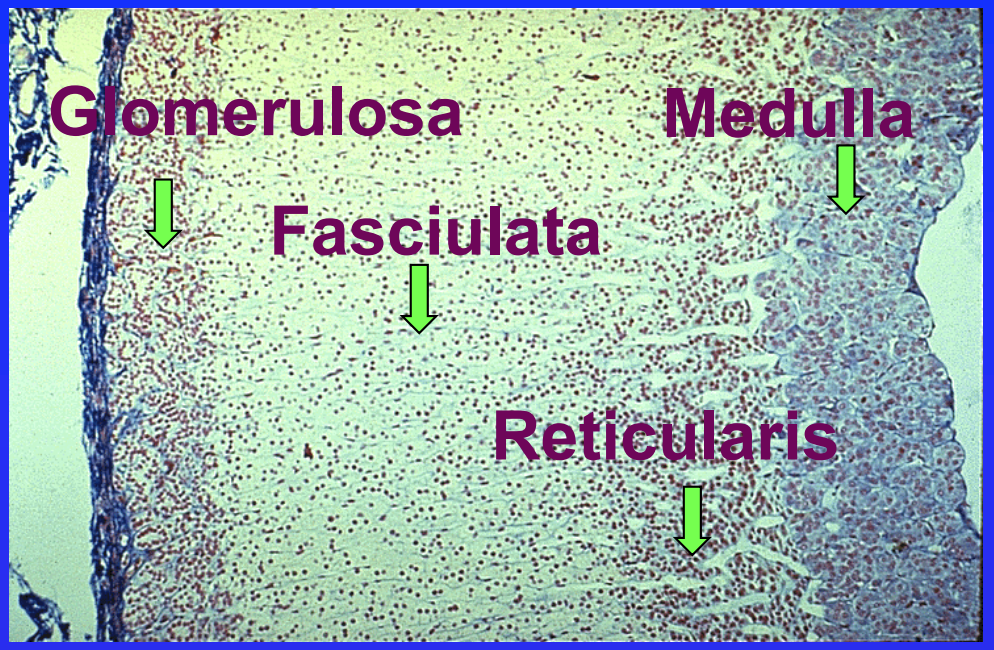


http://www.udel.edu

The Adrenal Axis



Normal



http://www.udel.edu

For more information

- Consult Dr. Wilson's book, ***Adrenal Fatigue: The 21st Century Stress Syndrome***. It contains a wealth of insights and a series of tests you can do at home, as well as lab tests like the saliva test for adrenal hormones to help you determine if you are experiencing adrenal fatigue.* Also see Could I be experiencing adrenal fatigue?

- http://www.adrenalfatigue.org