“Adrenal fatigue” and New therapies in Adrenal Dysfunction

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SPED Semiannual Convention

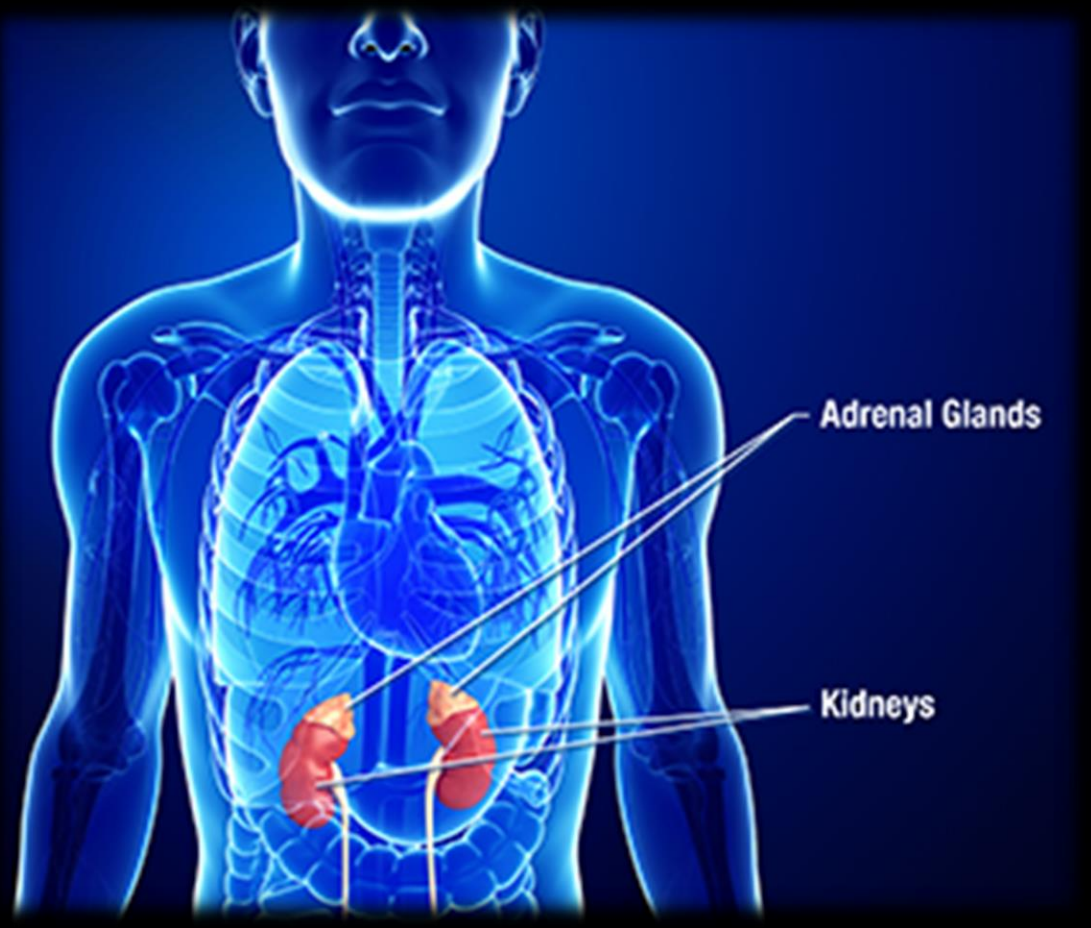
December 2020

Disclosures

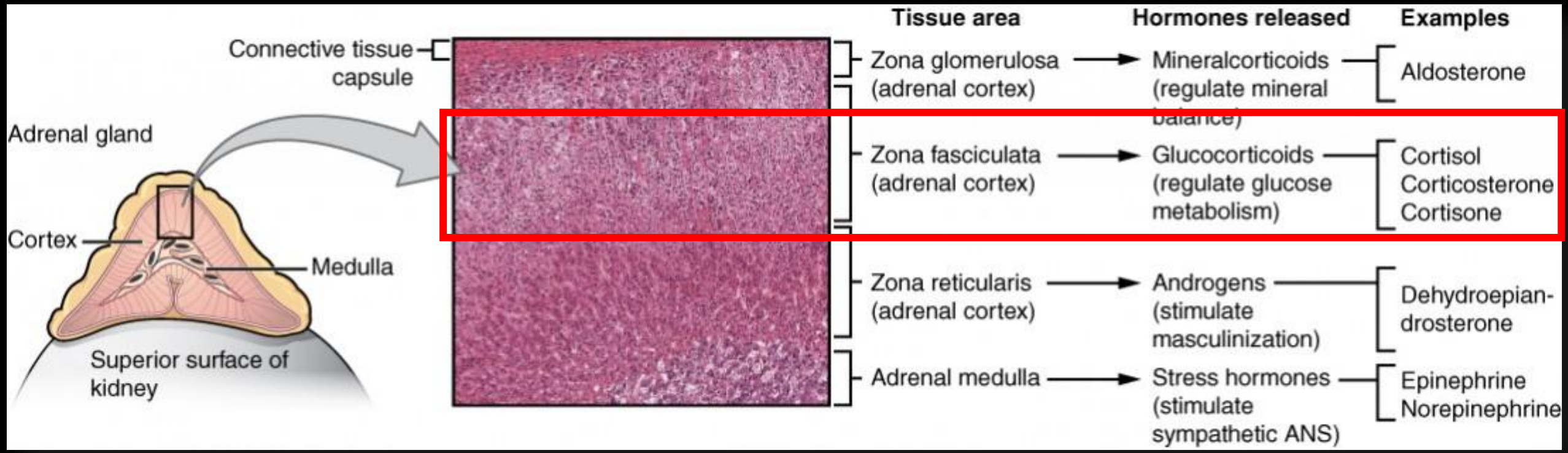
- No conflict of interest to disclose.

Objectives

- Define Adrenal Insufficiency and the concept of “Adrenal Fatigue”
- Review corticosteroid replacement in patients with adrenal insufficiency
- Discuss new therapies for patients with adrenal insufficiency



Adrenal steroids



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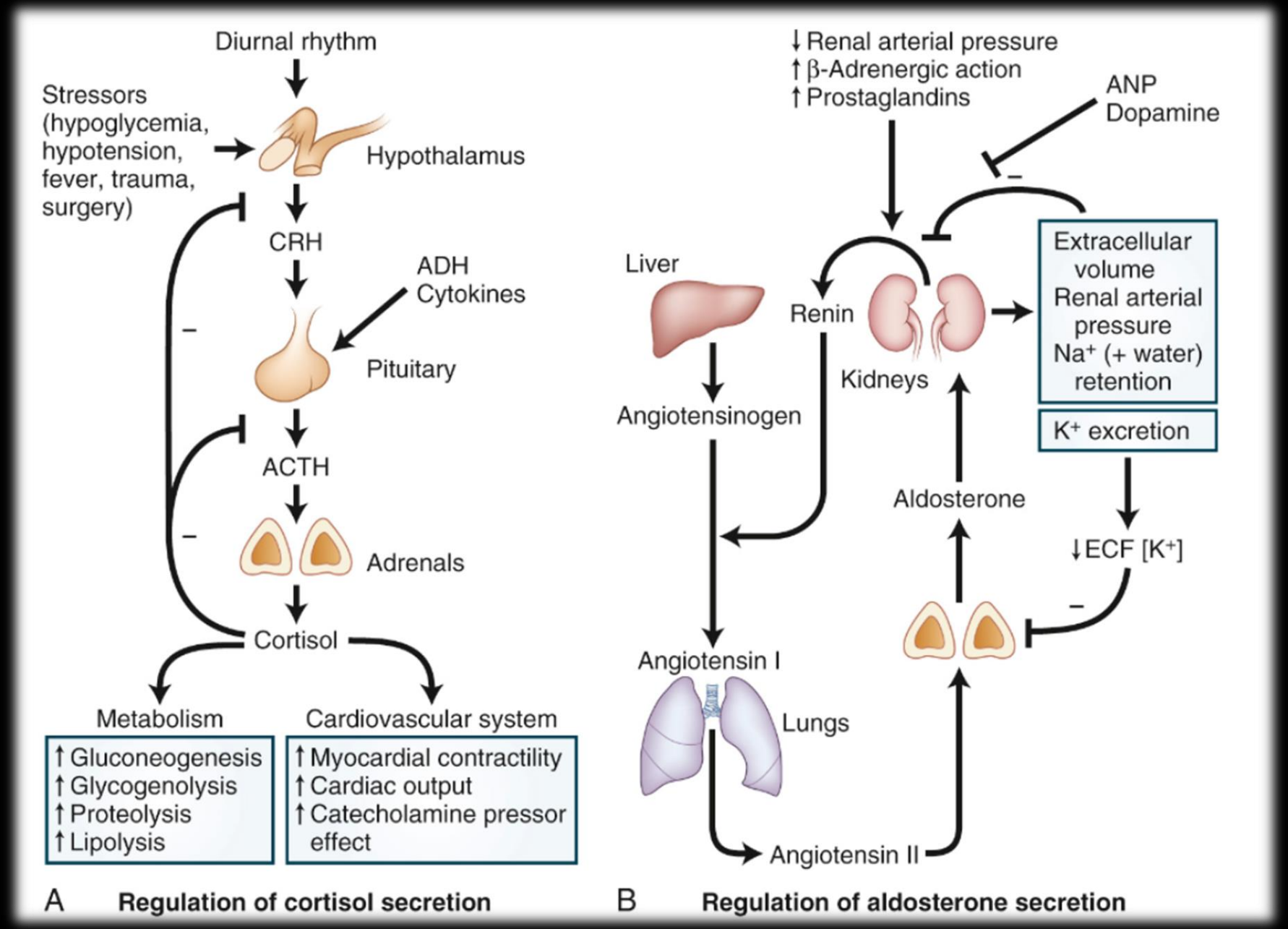
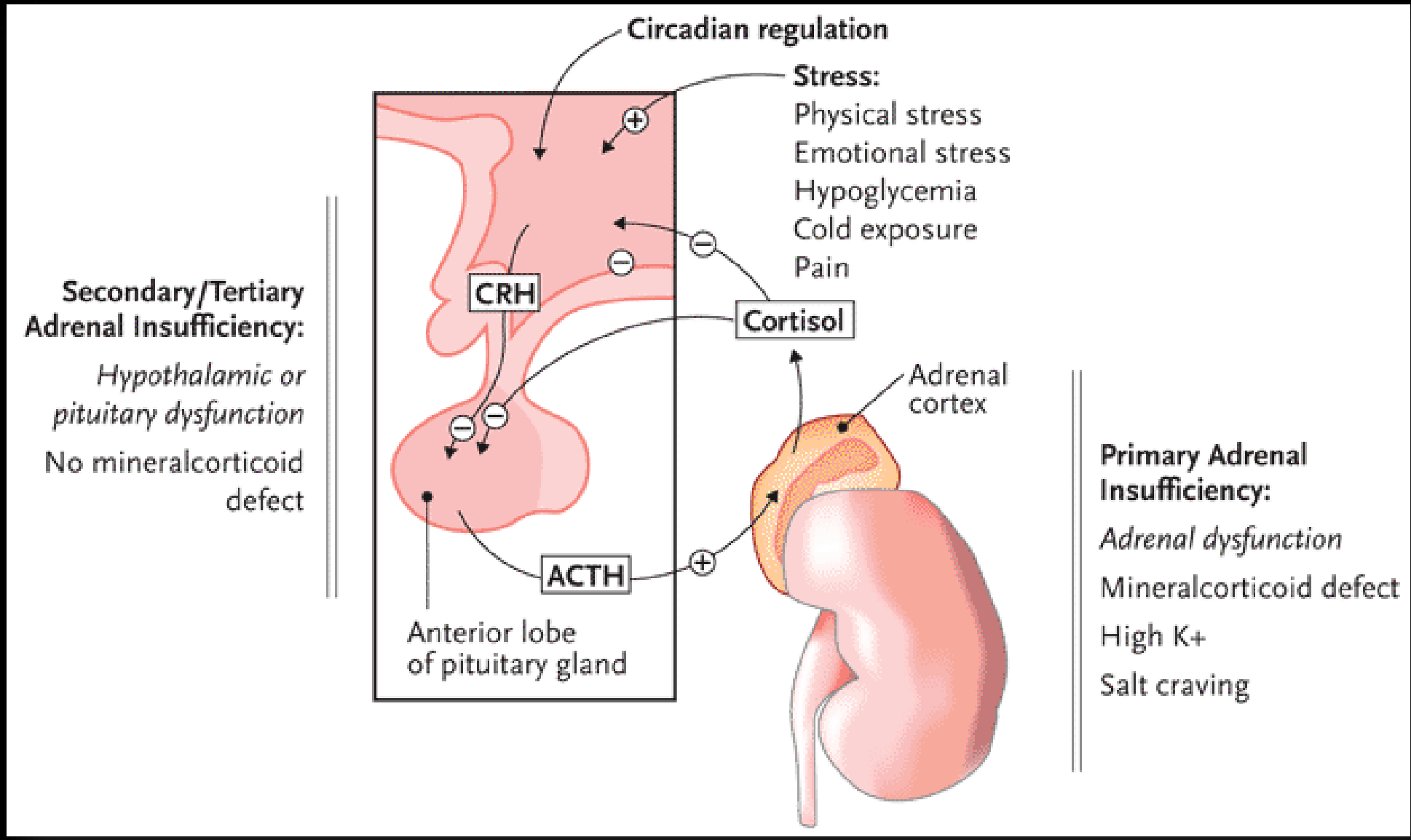
Regulation of Cortisol Secretion



In: Williams Textbook of endocrinology (2016) 13th edition.

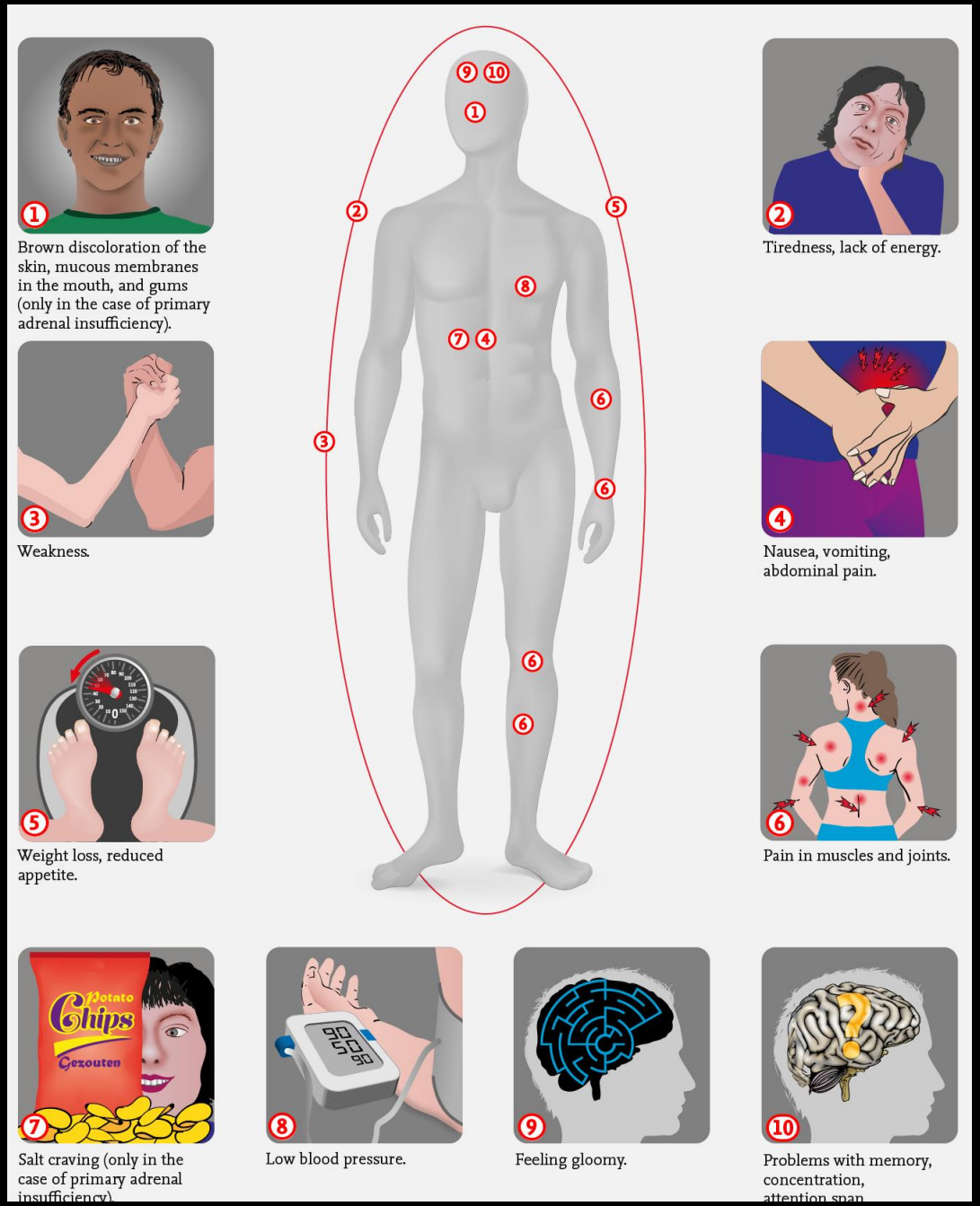
Adrenal Insufficiency



http://healthfoxx.com/wp-content/uploads/2012/02/primary-secondary-adrenal-insufficiency.jpg

Adrenal Insufficiency

- Symptoms and signs depend upon:
  - Rate and extent of loss of adrenal function
  - Whether mineralocorticoid production is preserved
  - Degree of stress
- Onset – often very gradual
  - May go undetected until an illness or other stress precipitates adrenal crisis



https://adrenals.eu/wp-content/uploads/2016/03/Adreneal-inssinss-160208V2Engels-2.png

Clinical and laboratory findings suggesting Adrenal Insufficiency/Adrenal crisis

Dehydration, hypotension, or shock out of proportion to severity of current illness

Unexplained hypoglycemia

Unexplained fever

Nausea and vomiting with a history of weight loss and anorexia

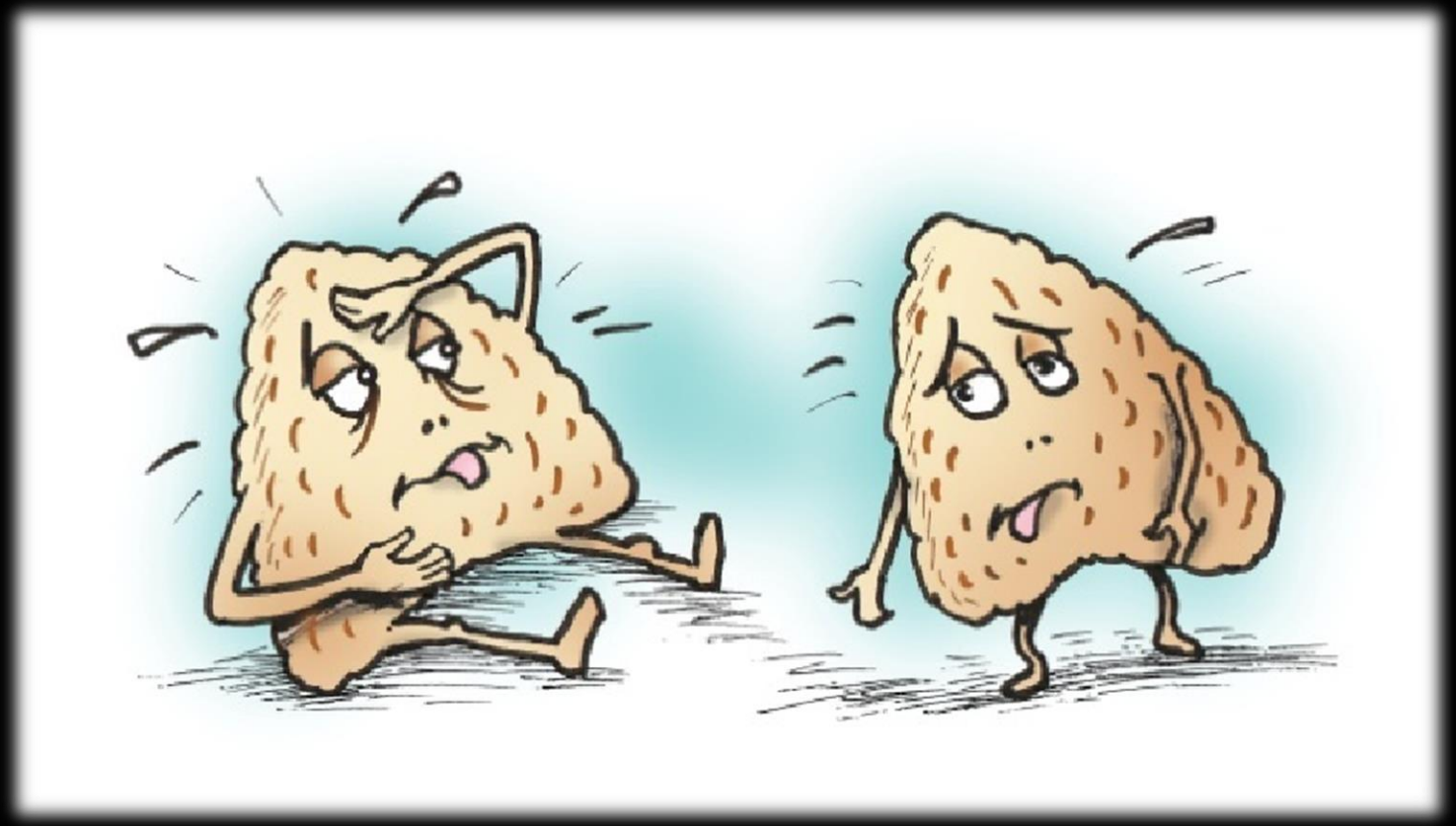
Hyponatremia, hyperkalemia, hypercalcemia

Abdominal pain “acute abdomen”

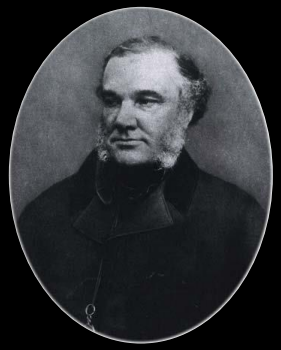
Hyperpigmentation or vitiligo

Other autoimmune endocrine deficiencies

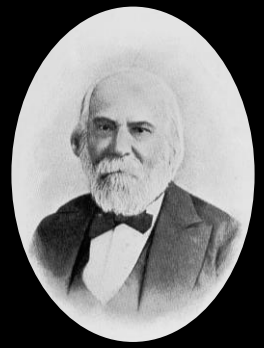
“Adrenal Fatigue”



History of adrenal glands and the concept of "Adrenal Fatigue"



1855
Thomas Addison



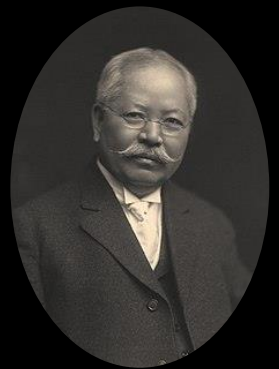
1856
Charles-Eduoard Brown-Séquard

1858
George Harley

1895
George Oliver

1895
Edward Schäfer

1899
John Jacob Abel



1901
Jokichi Takamine

1901
Thomas Aldrich

1909
William Osler

1911
Charles Eucharist de Medici Sajous

Tattersall RB. Med Hist. 1999 Oct;43(4):450-67.

Charles Eucharist de Medici Sajous

Proposed three clinical forms of hypoadrenia:

- Functional hypoadrenia, a form in which the adrenals, though not the seat of organic lesions, are functionally deficient because of tardy development, debilitating influences such as fatigue, starvation, etc. and old age
  - In adults it developed when "as a result of the vicissitudes of our existence" the adrenals were exhausted by the strain of exercise or labour.
- Progressive hypoadrenia or Addison 's disease, a form in which the functions of the adrenals or their secretory nerves are progressively impaired by organic lesions, tuberculosis, cancer, fibrosis etc.
- Terminal hypoadrenia, a late complication of infectious diseases and toxaemias, owing to exhaustion of the secretory activity of the adrenals during the earlier and febrile stage of the causative disease.

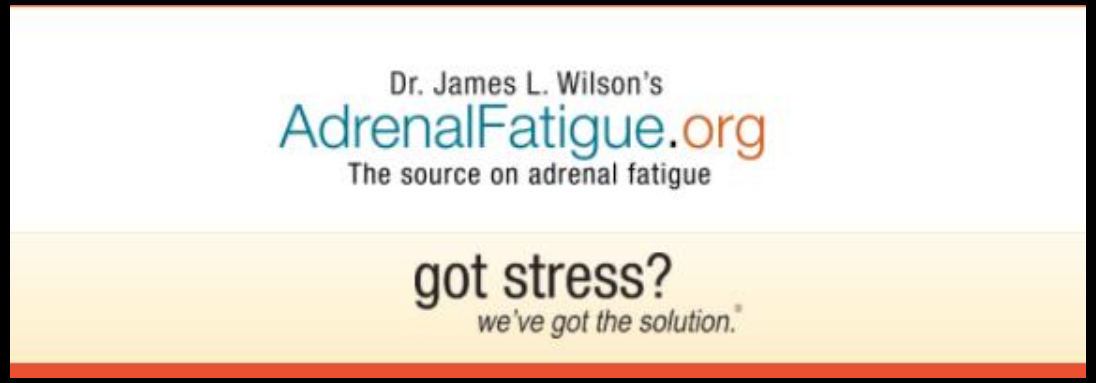
Tattersall RB. Med Hist. 1999 Oct;43(4):450-67.

the ADRENAL FATIGUE solution

During the 1920s, 1930s and 1940s thousands of patients were diagnosed and treated for hypoadrenia. However this diagnosis of hypoadrenia gradually became less frequent. There was no test accurate enough to diagnose the milder form of adrenal dysfunction, and hypoadrenia did not get the recognition given to full Addison's. Endocrinologists focused on conditions and diseases that were more readily diagnosed and treated. After that point, awareness fell until the late 1990s, when the work of Dr. Wilson, combined with more accurate saliva cortisol testing, once more enabled healthcare professionals to make a reliable diagnosis of Adrenal Fatigue.

Fortunately, the tide seems to have turned. As functional medicine and naturopathy become more and more accepted (Canadian naturopaths can now give prescriptions, just like MDs), so Adrenal Fatigue is beginning to enter mainstream medical thought. This will take some time, but it now seems inevitable. In the meantime, your functional doctor or naturopath is perfectly equipped to give you a correct diagnosis of Adrenal Fatigue.

https://adrenalfatiguesolution.com/history-of-adrenal-fatigue/



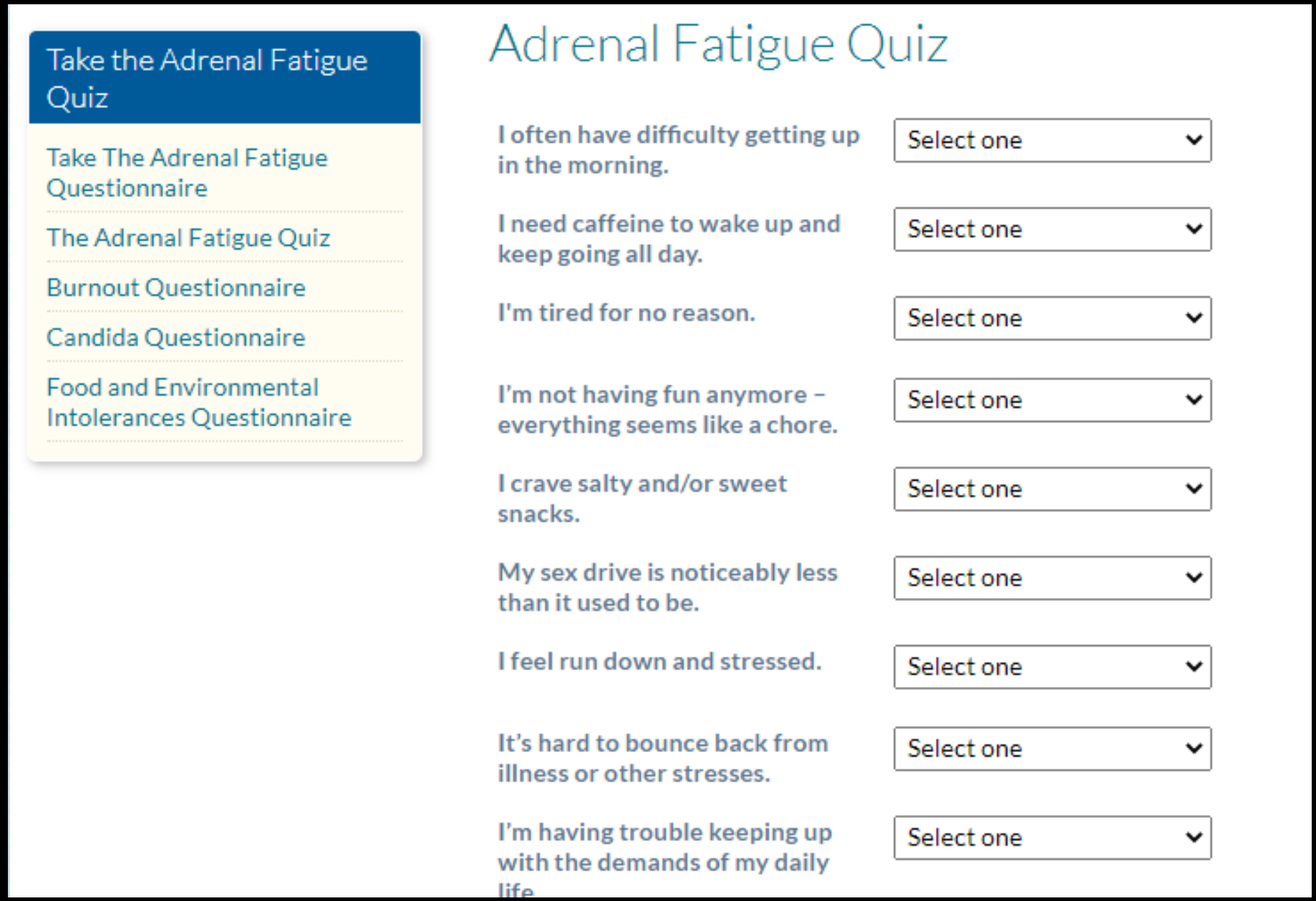
Has stress and pervasive tiredness hijacked your life? Is caffeine your best friend? Is sugar, fat and salt your primary food group?

Do you find it all just too much effort (even sex!)? Have you tried different fixes and maybe even different doctors to no avail? Do you even remember fun!?

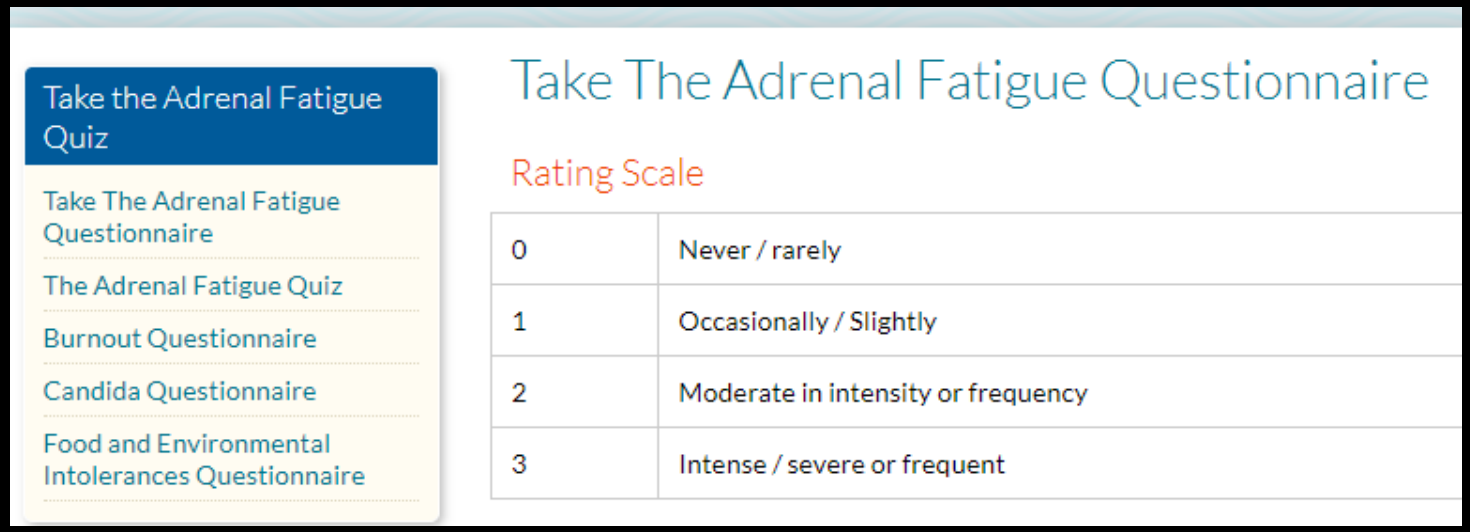
If so you're not alone and, most importantly, you've come to the right place.

Dr. Wilson created adrenalfatigue.org specifically to help you and the many others experiencing this very common problem caused by too much stress. Take the Adrenal Fatigue Questionnaire to see if low adrenal function may be your problem. Learn more about adrenal fatigue and how stress and adrenal function can affect your health and other related health conditions. Follow the guidelines for adrenal recovery Dr. Wilson developed over decades of clinical practice and research. Find a health professional familiar with adrenal fatigue to help you. Best of all, discover that you can reclaim your vitality and thrive in a stressful world!

https://adrenalfatigue.org/



https://adrenalfatigue.org/



- Predisposing factors
- Key signs and symptoms
- Energy Patterns
- Frequently Observed Events
- Food Patterns
- Aggravating Patterns
- Relieving Factors

The total points are used to determine the degree of severity of your adrenal fatigue. If you ranked every question 3 (the worst) your total points would be 279. If you scored under 40, you either have only slight adrenal fatigue or none at all. If you scored between 49-92, then overall you may have a mild degree of adrenal fatigue. This does not mean that some individual symptoms are not severe, but overall your symptom picture reflects mildly fatigued adrenals. If you scored between 93-136, you may have a moderate degree of adrenal fatigue. If you scored above 136, you may be suffering from severe adrenal fatigue.

This is the sum of the answers to the questions marked by an asterisk (*) for the "Now" column. If this total is more than 6, we strongly recommend that you consult a physician who is familiar with stress and adrenal function.

https://adrenalfatigue.org/

What is Adrenal Fatigue?

Adrenal fatigue is a collection of signs and symptoms, known as a syndrome, that results when the adrenal glands function below the necessary level. Most commonly associated with intense or prolonged stress, it can also arise during or after acute or chronic infections, especially respiratory infections such as influenza, bronchitis or pneumonia. As the name suggests, its paramount symptom is fatigue that is not relieved by sleep but it is not a readily identifiable entity like measles or a growth on the end of your finger.

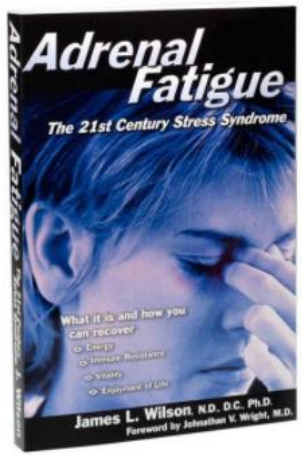
You may look and act relatively normal with adrenal fatigue and may not have any obvious signs of physical illness, yet you live with a general sense of unwellness, tiredness or "gray" feelings. People experiencing adrenal fatigue often have to use coffee, colas and other stimulants to get going in the morning and to prop themselves up during the day.

This syndrome has been known by many other names throughout the past century, such as non-Addison's hypoadrenia, sub-clinical hypoadrenia, neurasthenia, adrenal neurasthenia, adrenal apathy and adrenal fatigue. Although it affects millions of people in the U.S. and around the world, conventional medicine does not yet recognize it as a distinct syndrome.

Adrenal fatigue can wreak havoc with your life. In the more serious cases, the activity of the adrenal glands is so diminished that you may have difficulty getting out of bed for more than a few hours per day. With each increment of reduction in adrenal function, every organ and system in your body is more profoundly affected.

https://adrenalfatigue.org/

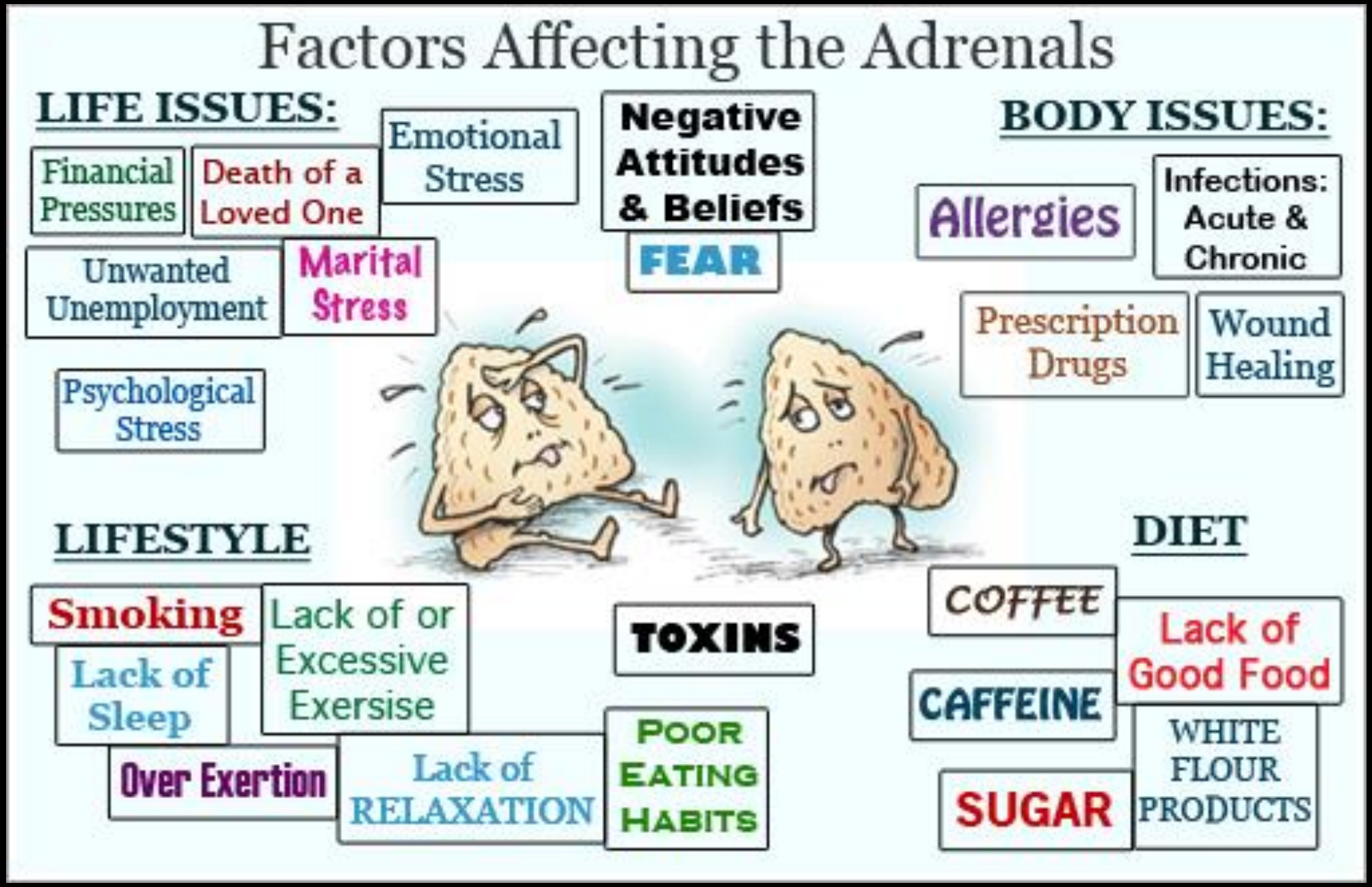
Most medical doctors are not aware of adrenal fatigue. They only recognize Addison's disease, which is the most extreme end of low adrenal function. Astute doctors who are familiar with the varying degrees of decreased adrenal function usually test the adrenal hormone levels in the saliva. This is a simple and relatively inexpensive test that has recently become available from a few labs and is an accurate and useful indicator of adrenal fatigue. A kit can be obtained from the lab and the test completed at home by simply spitting into the test tubes four times throughout a 24-hour day. The samples are mailed in and the results are sent back to either the patient or the attending physician. There are some other lab tests but they need special interpretation by physicians trained to recognize and treat adrenal fatigue. There are other common lab tests that can be used more indirectly to detect adrenal fatigue, but the majority of medical doctors do not know how to interpret these tests for indications of adrenal fatigue. The adrenal fatigue questionnaire on page 61 of *Adrenal Fatigue: The 21st Century Stress Syndrome* is one of the most widely used tools for assessing adrenal fatigue.



Adrenal Fatigue: The 21st Century Stress Syndrome™ by Dr. James L. Wilson

https://adrenalfatigue.org/faq-on-adrenal-fatique/

Factors Affecting the Adrenals



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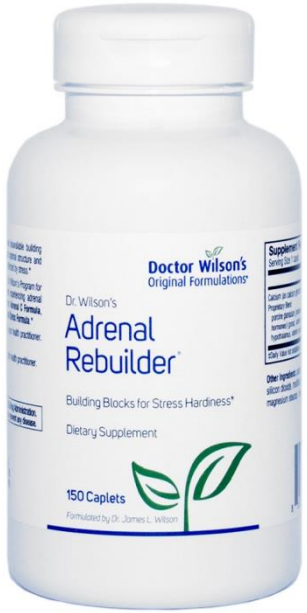
What can you do?

Basic Supplement Support Protocol

People experiencing mild adrenal fatigue have found the Basic Protocol most beneficial.*

Time	Adrenal Rebuilder®	Adrenal C Formula®	Super Adrenal Stress Formula®	Herbal Adrenal Support Formula®
On rising	1 caplet	1 caplet	1 caplet	20 drops in water or non-citrus juice
Noon meal	1 caplet	1 caplet	1 caplet	20 drops in water or non-citrus juice if there is a mid-afternoon low
2:30 PM				
Bedtime	1 caplet	1 caplet	1 caplet	20 drops in water or non-citrus juice

Many people with adrenal fatigue find that they feel better when they drink salted water (⅛ – ¼ teaspoon salt in an 8 oz. glass of water) on rising and again in the afternoon. We suggest you try it to find what works best for you. Supplements may be taken with plain or salted water, non-citrus juice or milk.



Supplement Facts

Serving Size 1 caplet — Servings Per Container 150

	Amount Per Serving	% Daily Value
Calcium (as calcium glycerophosphate)	15 mg	1%
Proprietary Blend	830 mg	‡
porcine glandulars (*processed to remove hormones*) (gonad, adrenal cortex, hypothalamus, anterior pituitary), inositol		

‡Daily Value not established

Other Ingredients: food glaze, cellulose, silicon dioxide, modified cellulose gum, stearic acid, magnesium stearate, micro wax

Supplement Facts

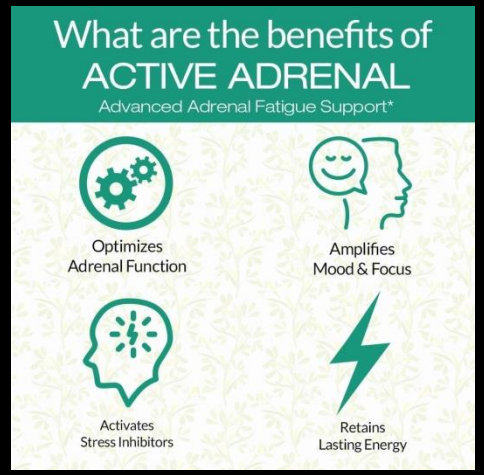
Serving Size: 1 scoop (15 gm) — Servings Per Container: 30

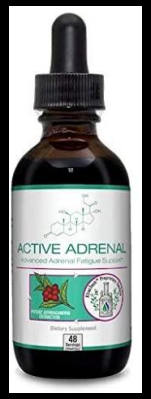
	Amount Per Serving	% Daily Value
Vitamin A (as palmitate)	1,375 mcg	153%
Vitamin C (as ascorbic acid, magnesium, sodium & zinc ascorbates)	180 mg	200%
Vitamin D3 (as cholecalciferol)	5 mcg	25%
Vitamin E (as mixed tocopherols)	20 mg	133%
Thiamine (as hydrochloride)	12.5 mg	1,042%
Riboflavin (as riboflavin-5-phosphate)	12.5 mg	962%
Niacin (as inositol hexaniacinate)	13 mg	81%
Vitamin B6 (as pyridoxine HCl & P-5-P)	50 mg	2,94%
Folic Acid	300 mcg	7%
Biotin	250 mg	83%
Pantothenic Acid (as calcium pantothenate)	400 mg	8,000%
Calcium glycerophosphate	80 mg	6%
Calcium	51 mg	4%
Magnesium (as citrate, glycinate & ascorbates)	260 mg**	62%
Zinc (as ascorbate)	8 mg**	73%
Selenium (as selenomethionine)	25 mcg**	45%
Copper (as gluconate)	0.5 mg**	56%
Manganese (as citrate)	5 mg**	217%

‡Daily Value not established
**quantity given for all minerals is for its elemental content in one serving

	Amount Per Serving	% Daily Value
Chromium (as picolinate)	100 mcg**	286%
Sodium (as ascorbate/chloride)	10 mg**	0.4%
Potassium (as chloride)	2 mg**	.04%
Choline Bitartrate	25 mg	5%
Proprietary Blend of Powdered:	3,980 mg	‡
L-glycine, porcine glandulars (pituitary, adrenal, gonad, hypothalamus), oat [bran], ashwagandha [root], L-serine, maca [root], L-threonine, licorice [root], pantethine, EDTA (calcium), eleuthero [root], kelp, L-tyrosine, ginger [root], ginkgo [leaf], citrus bioflavonoids (citrus fruit peels, including grapefruit peel)		

https://adrenalfatigue.org/product-category/all-supplements/

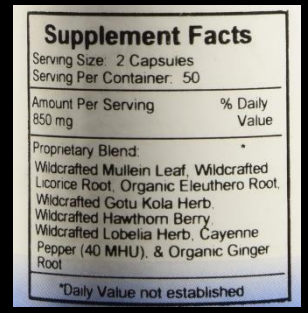

What are the benefits of
ACTIVE ADRENAL
Advanced Adrenal Fatigue Support*
Optimizes Adrenal Function
Amplifies Mood & Focus
Activates Stress Inhibitors
Retains Lasting Energy


ACTIVE ADRENAL
Advanced Adrenal Fatigue Support


DrJockers.com
DrJockers.com
DrJockers.com
DrJockers.com
ADAPT-STRONG
BRAIN CALM MAGNESIUM


NATURE'S SUPPLEMENTS
ADRENAL SUPPORT
Adrenal Support Formula 1300mg
With Ashwagandha, Licorice Root, Rhodiola Rosea & Other Herbs
Stress Support Formula
DIETARY SUPPLEMENT
120 CAPSULES

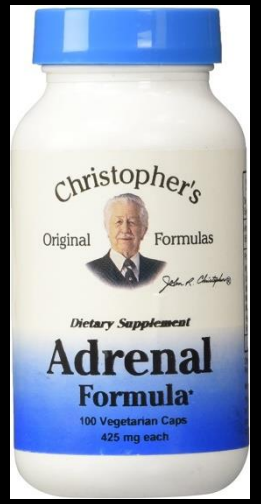

BioMatrix
SUPPORT ADRENALS
A Dietary Supplement

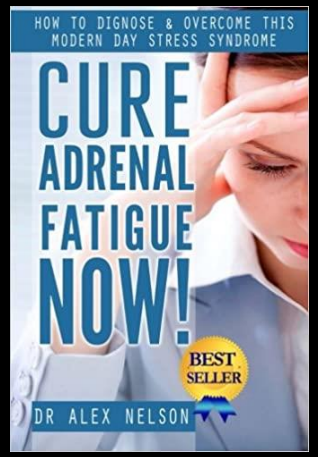

Supplement Facts
Serving Size: 2 Capsules
Serving Per Container: 50
Amount Per Serving
850 mg
% Daily Value
Proprietary Blend:
Wildcrafted Mullein Leaf, Wildcrafted Licorice Root, Organic Eleuthero Root, Wildcrafted Gotu Kola Herb, Wildcrafted Hawthorn Berry, Wildcrafted Lobelia Herb, Cayenne Pepper (40 MHU), & Organic Ginger Root
*Daily Value not established


ADRENAL
FATIGUE
TIREDNESS
NEEDING
SALT
MORNING
INDUSTRY
FALLING
UNABLE
EXHAUSTED
SUPPLEMENTS
ASLEEP
ADRENAL
STIMULANTS
FATIGUE
DAY
SALIVARY
FORMS
LARGELY
CONDITION
PRIMARILY
HORMONES
CRAVING
ADRENAL
TREAT
PRACTITIONERS
SUPPORTING
RISE
MARKETED
CASES
ADEQUATE
SYMPTOMS
CAFFEINE
COMMUNITY
MEDICINE
EVIDENCE
COLLECTION
APPLIED
INEFFECTIVE
DIAGNOSIS
TESTING
TESTS
CONCEPT
LACK
ACTUAL
CONFUSED
UNREGULATED
GLANDS
BASIS
DIETARY
DIAGNOSE
WAKING
TROUBLE
PRODUCE
ALTERNATIVE
OFFERED
MEDICAL
DANGEROUS
INSUFFICIENCY
QUANTITIES
CORTISOL
NONSPECIFIC
GLUCOCORTICOID
DESCRIBE
BELIEF
DYSFUNCTION
RECOGNIZED
SUGAR


Top 5
Essential Oils
For Adrenal Support
TRADITIONAL Cooking School


SUPPLEMENT FACTS


Christopher's
Original Formulas
Dietary Supplement
Adrenal
Formula
100 Vegetarian Caps
425 mg each


HOW TO DIGNOSE & OVERCOME THIS MODERN DAY STRESS SYNDROME
CURE ADRENAL FATIGUE NOW!
BEST SELLER
DR ALEX NELSON


High absorption
Stress & Adrenal Support


Herbs and Supplements to Improve
ADRENAL FATIGUE
B5
C
Mg


Nutraliant
ADRENAL 911
Advanced Complex
60 CAPSULES DIETARY SUPPLEMENT


HEALTHS HARMONY
ADRENAL HEALTH
POWERFUL CORTISOL SUPPORT†
Helps Support:
• Adrenal Health†
• Adrenal Gland†
• Energy†
NON GMO
60 CAPSULES | DIETARY SUPPLEMENT


Gold Nature's Harmony
ADVANCED
ADRENAL
HEALTH SUPPORT
SUPERIOR STRESS SUPPORT
60

Over-the-Counter "Adrenal Support" Supplements Contain Thyroid and Steroid-Based Adrenal Hormones.

TABLE 3. Total Types of Thyroid and Adrenal Hormones in Over-the-Counter Adrenal Supplements

Sample ID no.	Total types of thyroid hormones	Total types of steroid hormones
1	1	1
2	1	2
3	1	1
4	1	3
5	1	1
6	1	1
7	1	—
8	1	4
9	1	—
10	1	—
11	1	—
12	1	—

ID = identification.

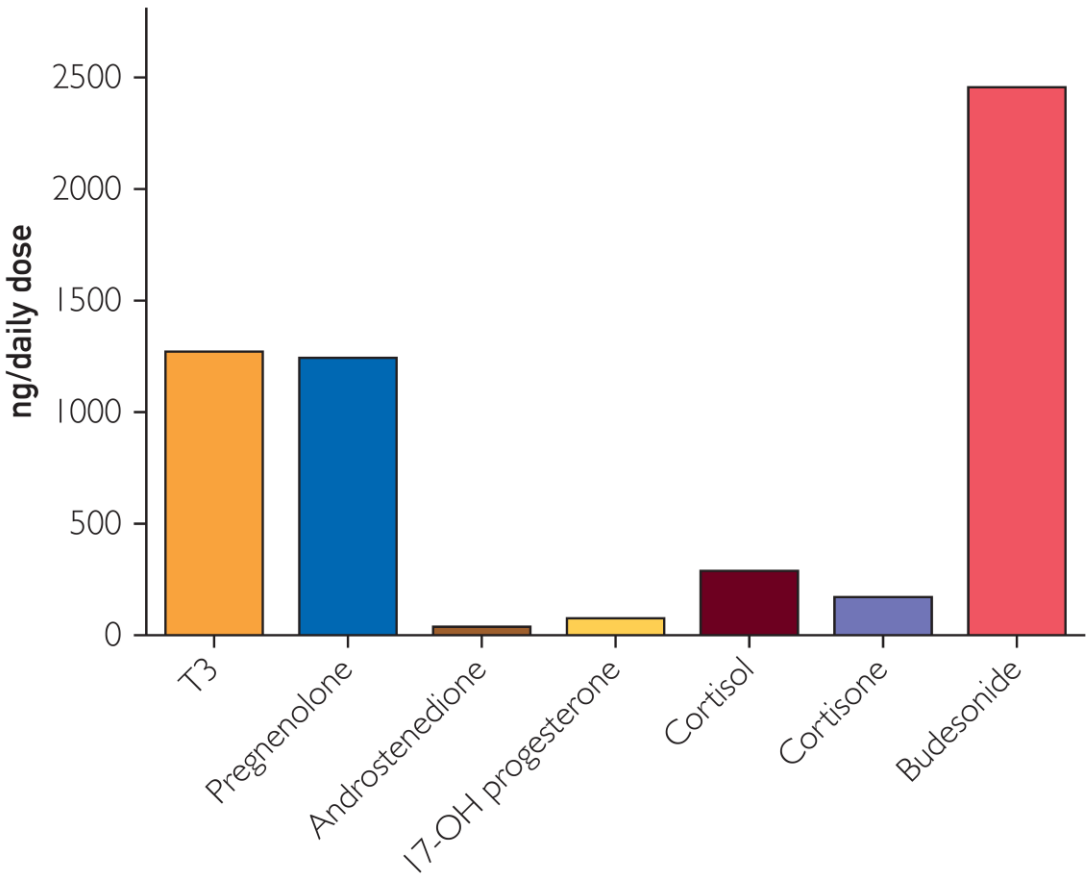


FIGURE. Comparison of maximum daily exposure of hormones.

Akturk HK et al. Mayo Clin Proc. 2018 Mar;93(3):284-290.

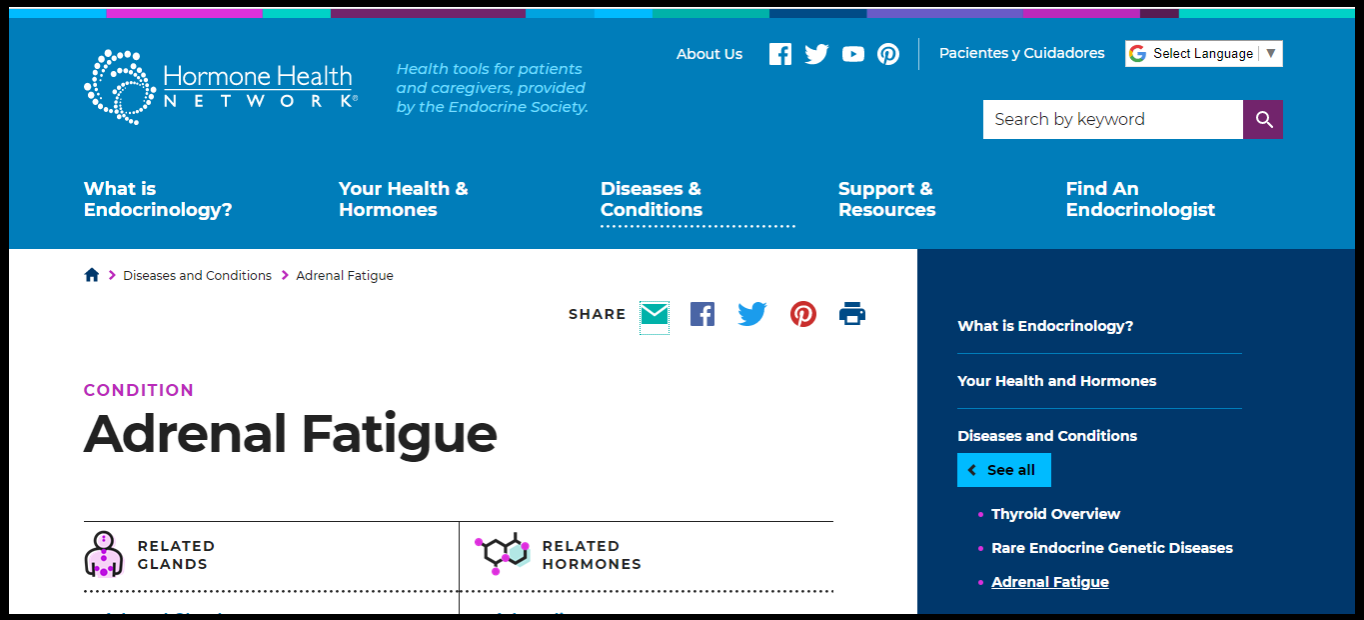
STATEMENT

We are tired of 'adrenal fatigue'

I L Ross,[1] MB ChB, FCP (SA), FRCP (London), Cert Endocrinology and Metabolism (SA), PhD (Medicine); **J Jones**,[2] BPharm; **M Blockman**,[2] BPharm, MB ChB, PG Dip Int Res Ethics, MMed

[1] *Division of Endocrinology and Diabetic Medicine, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *Division of Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*

Ross IL et al. S Afr Med J. 2018 Aug 28;108(9):724-725.



Hormone Health Network."Adrenal Fatigue | Hormone Health Network." Hormone.org, Endocrine Society, 9 December 2020, https://www.hormone.org/diseases-and-conditions/adrenal-fatigue

Etiology of symptoms

- Anemia
- Arthritis
- Diabetes
- Heart Failure
- Obstructive Sleep Apnea
- Fibromyalgia
- Autoimmune disease
- Depression
- Anxiety disorder
- Poor diet
- Tobacco/alcohol
- Stress at work or home
- Deconditioning
- Lack of exercise

Adrenal Insufficiency

	Primary adrenal insufficiency	Secondary adrenal insufficiency
Autoimmune	Can occur in isolation or as part of autoimmune polyglandular syndromes Isolated Addison's disease (30–40% of patients with autoimmune adrenalitis) Autoimmune polyglandular syndromes type 1 (5–10%; also termed autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy): caused by *AIRE* mutations; adrenal insufficiency in combination with other endocrine disorders (hypoparathyroidism [76–93% of patients], premature ovarian failure [17–50%], type 1 diabetes mellitus [2–12%]), non-endocrine autoimmune disease (mucocutaneous candidiasis [73–100%], alopecia [29–37%], vitiligo [8–15%], coeliac disease [15–22%], pernicious anaemia [13–15%], autoimmune hepatitis [12–20%], Sjögren's syndrome [12%]), and ectodermal dystrophy (dental enamel hypoplasia [77–82%]) Autoimmune polyglandular syndromes type 2 (60%): adrenal insufficiency in combination with other endocrine autoimmune disease (hypothyroidism or hyperthyroidism [60%], premature ovarian failure [7–21%], type 1 diabetes mellitus [1–15%], pernicious anaemia [5–12%], vitiligo [6–14%], coeliac disease [1–4%], and alopecia [2–6%])	Lymphocytic hypophysitis: rare, might occur in relation to pregnancy; can present as pan-hypopituitarism or isolated adrenocorticotropic hormone deficiency, sometimes in combination with primary autoimmune-mediated hypothyroidism
Compression or replacement of normal tissue	Bilateral adrenal metastasis (mostly originating from solid-organ tumours such as lung, breast, and colon cancers)	Pituitary macroadenomas (pituitary carcinoma is very rare), craniopharyngioma, meningioma, ependymoma, intrasellar and suprasellar metastases (mostly lung, breast, colon cancers)
Infection	Tuberculosis, HIV, cytomegalovirus, fungal infections	Tuberculosis, histoplasmosis, actinomycosis
Haemorrhage or necrosis or thrombosis	Thrombocytopenia, Waterhouse-Friderichsen syndrome, trauma, lupus erythematosus, antiphospholipid syndrome, panarteritis nodosa, treatment with anticoagulants, treatment with tyrosine-kinase inhibitors	Pituitary apoplexy (mostly in the setting of a pituitary macroadenoma), Sheehan's syndrome due to transient hypocirculation and subsequent necrosis of the pituitary (eg, due to large blood loss)
Infiltration	Sarcoidosis, amyloidosis, haemochromatosis, histiocytosis, lymphoma	Wegener's granulomatosis, sarcoidosis, amyloidosis, haemochromatosis, lymphoma
Surgery or trauma	Bilateral adrenalectomy	Treatment of hypothalamic-pituitary tumours with surgery or radiation; traumatic brain injury
Monogenic causes of adrenal insufficiency	Congenital adrenal hyperplasia variants: 21-hydroxylase deficiency (>95% of congenital adrenal hyperplasia cases); 11β-hydroxylase deficiency; P450 oxidoreductase deficiency; 3β-hydroxysteroid dehydrogenase type 2 deficiency; 17α-hydroxylase deficiency; X-linked adrenoleukodystrophy or adrenomyeloneuropathy; autoimmune polyglandular syndromes type 1	Combined pituitary hormone deficiency (CPHD) variants: CPHD2, CPHD3, CPHD4, CPHD5, and CPHD6; isolated adrenocorticotropic hormone deficiency due to mutations in *TBX19*

The most frequent causes of primary adrenal insufficiency are autoimmune adrenalitis and congenital adrenal hyperplasia. Secondary adrenal insufficiency is most frequently caused by hypothalamic-pituitary tumours and their treatment. For additional details and for rarer causes see appendix. For drug-associated causes see panel 1.

***Table*: Causes of adrenal insufficiency according to underlying pathogenesis**

Bancos I et al. Lancet Diabetes Endocrinol. 2015 Mar;3(3):216-26.

Panel 1: Drugs that interfere with adrenal function

Increased metabolism of glucocorticoids

Concomitant use reduces corticosteroid concentrations

- Inducers of CYP3A4 (resulting in increased inactivation of cortisol by 6β-hydroxylation)—mitotane, phenytoin, rifampicin, troglitazone, phenobarbital

Impaired glucocorticoid action

Peripheral glucocorticoid insensitivity

- Glucocorticoid receptor antagonist—mifepristone
- Suppression of glucocorticoid-induced gene transcription—chlorpromazine, imipramine

Suppression of hypothalamic-pituitary-adrenal axis

- Downregulation of endogenous adrenocorticotropic hormone release—chronic exogenous glucocorticoid administration (including topical, inhaled, oral, intra-articular, or parenteral administration), megestrol acetate, medroxyprogesterone acetate, cyproterone acetate, opiates

Inhibition of steroidogenic enzymes involved in cortisol production

- Inhibition of mitochondrial (type 1) cytochrome P450 enzymes (CYP11A1, CYP11B1, CYP11B12)—ketoconazole, fluconazole, itraconazole, etomidate, metyrapone, aminoglutethimide
- Inhibition of 3β-HSD2—trilostane

Adrenal haemorrhage

- Anticoagulants—heparin, warfarin

Autoimmune hypophysitis

- Anti-CTLA4 antibody—ipilimumab

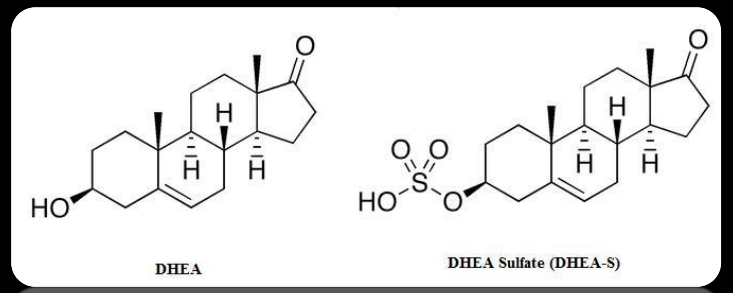
For additional details and for rarer causes see appendix.

Bancos I et al. Lancet Diabetes Endocrinol. 2015 Mar;3(3):216-26.

Diagnosis of Adrenal Insufficiency

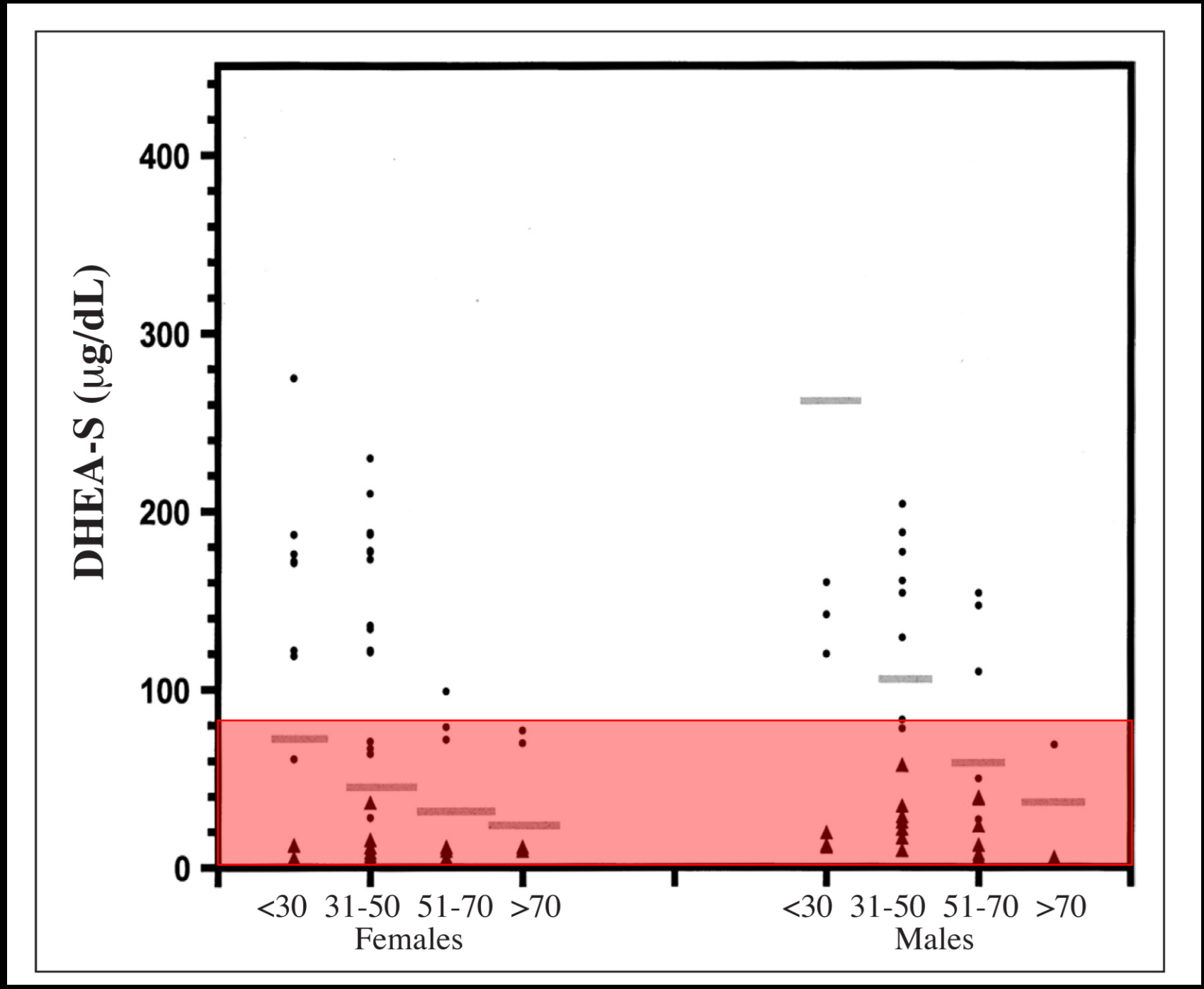
- Basal Cortisol
  - < 5 µg/dL (< 3 µg/dL)
  - > 15µg/dL – normal
- ACTH concentration elevated more than 2-fold above the upper limit (PAI)
  - ACTH > 66 pmo/L- maximum stimulus for cortisol secretion
- DHEAS
  - If > 80 µg/dL – AI unlikely
- Plasma renin and aldosterone – PAI to r/o mineralocorticoid deficiency
- Dynamic testing
  - Corticotropin stimulation - gold standard for primary adrenal insufficiency
  - Insulin Tolerance Test – gold standard for secondary adrenal insufficiency
  - Metyrapone
  - CRH stimulation

Bornstein SR et al. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89.



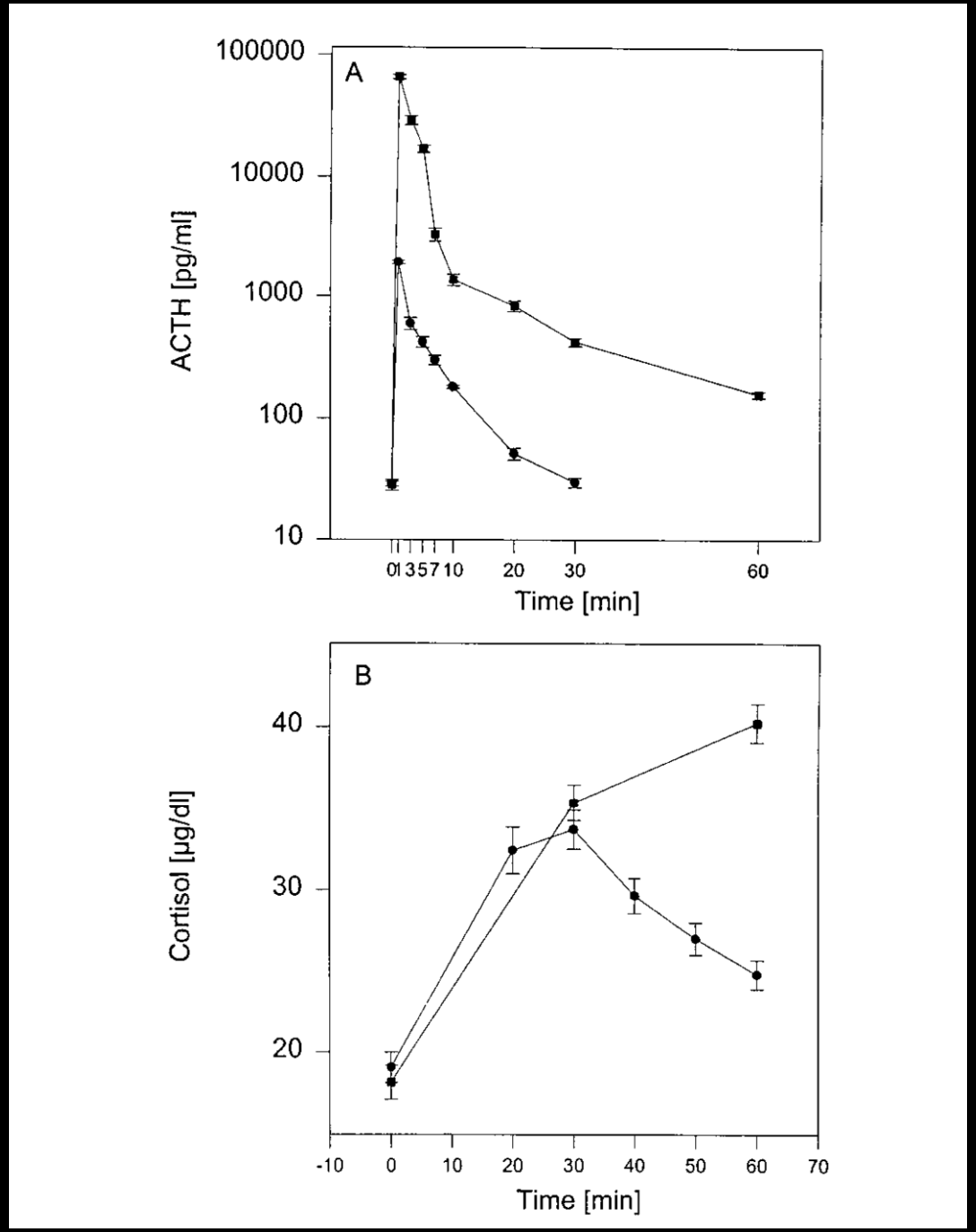
Biochemical diagnosis of adrenal insufficiency: the added value of DHEAS measurements

Al-Aridi R et al. Endocr Pract. 2011 Mar-Apr;17(2):261-70.



Dynamic testing

- Corticotropin Stimulation tests
  - 250 mcg corticotropin IV
- Peak cortisol levels < 18 µg/dL (assay dependent) at 30 or 60 minutes
  - 30 mins – 15.2 – 20.8 µg/dL
- Consider factors that can affect the interpretation of results
  - Factors that alter protein binding of cortisol to CBG and albumin
    - Critical illness
    - Nephrotic syndrome
    - Liver disease
    - OCP use or pregnancy
  - Assay



Mayenknecht J et al. J Clin Endocrinol Metab. 1998 May;83(5):1558-62.

Assay-specific estimated lower reference limits

Table 4. Assay-specific estimated lower reference limits for post-adrenocorticotrophin cortisol according to gender and oral contraceptive pill (OCP)-status

Assay	Males		Non-OCP females		Combined male and Non-OCP female subjects*		OCP females	
		µg/dL		µg/dL		µg/dL		µg/dL
GC-MS	418	15.15	421	15.26	420	15.22	643	23.31
Centaur	448	16.24	446	16.17	446	16.17	619	22.44
Architect	430	15.59	416	15.08	NA		577	20.91
E170	574	20.80	524	19.00	NA		791	28.67
Immulite (2000)	469	17.00	478	17.33	474	17.18	688	24.94
Access	459	16.64	455	16.49	NA		604	21.90

El-Farhan N et al. Clin Endocrinol (Oxf). 2013 May;78(5):673-80.

Biotin interference

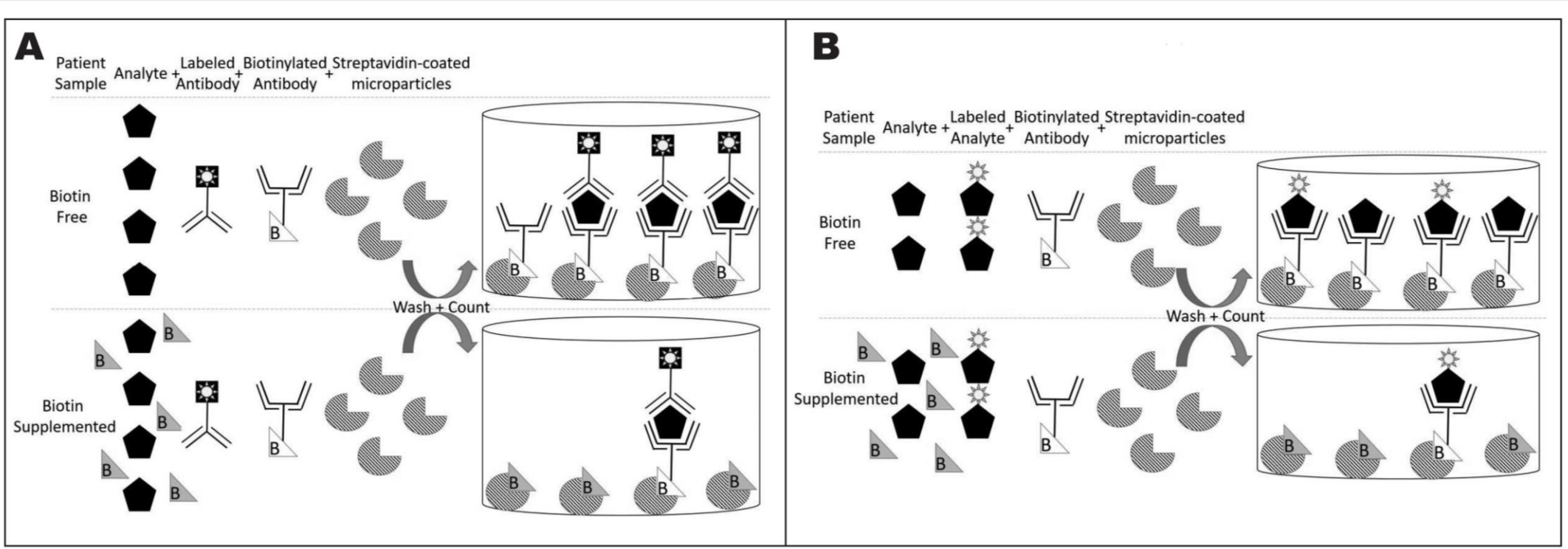


Fig. 1. Mechanisms of biotin assay interference. *A*, Sandwich immunoassay. In these formats, 2 antibodies (1 labeled, and 1 biotinylated) bind to different epitopes on the analyte, and the sandwich is bound to a streptavidin-coated solid phase. The signal intensity of the washed solid phase is proportional to the analyte concentration. Supplemental biotin interferes with the binding of the sandwich to the solid phase, decreases the signal intensity, and causes a falsely low result. *B*, Competitive immunoassay. In these formats, the analyte in the sample competes with a labeled analyte reagent for binding to a biotinylated antibody. The biotinylated antigen/antibody complex binds to a streptavidin-coated solid phase. The signal intensity of the washed solid phase is inversely proportional to the analyte concentration. Supplemental biotin interferes with the binding of antigen/antibody complexes to the solid phase, decreases the signal intensity, and causes a falsely elevated result.

Samarasinghe S et al. Endocr Pract. 2017 Aug;23(8):989-998.

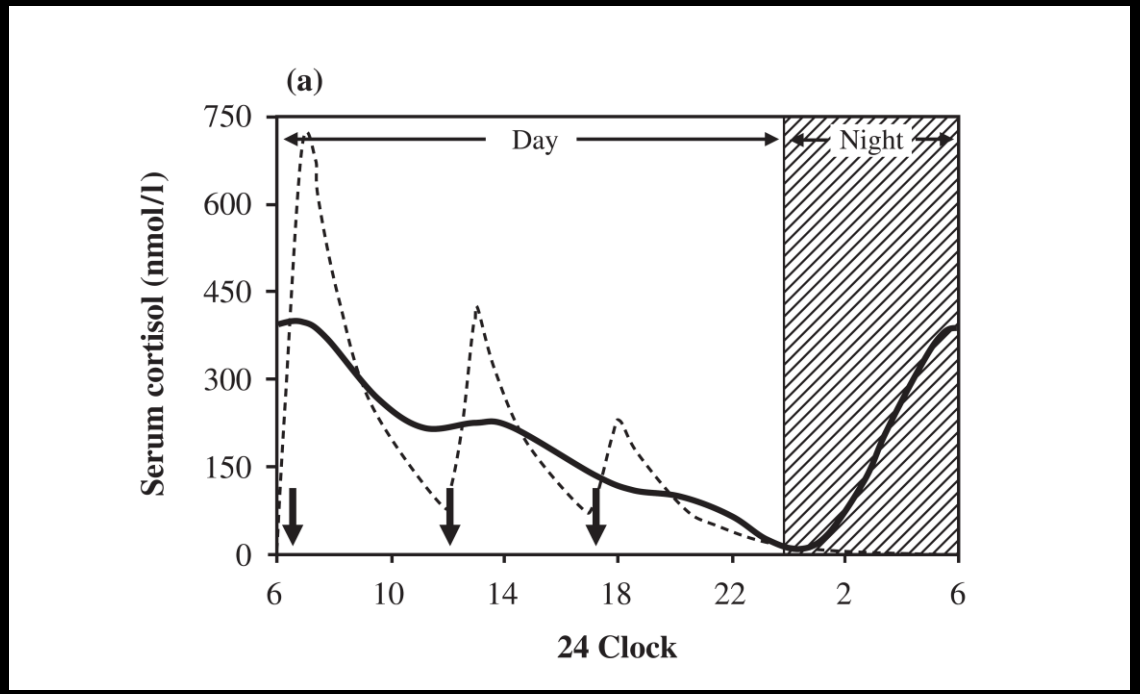
Glucocorticoid Replacement Therapy

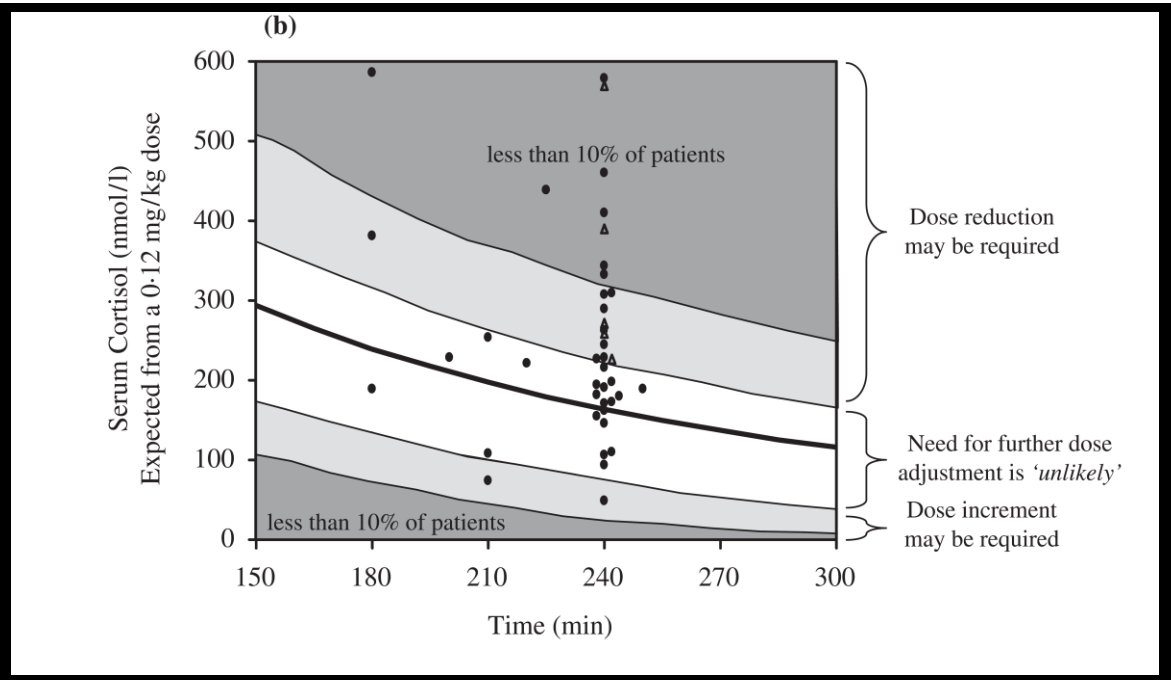
- Endocrine Society Clinical Practice Guideline (2016)
  - Recommend glucocorticoid therapy in all patients with confirmed PAI
  - Hydrocortisone 15-25 mg or cortisone acetate 20-35mg in 2-3 divided doses per day
  - Prednisolone 3-5 mg/d once or twice daily
  - Do not use dexamethasone
  - Monitor using clinical assessment: body weight, postural blood pressure, energy levels, signs of glucocorticoid excess
  - No hormonal monitoring

Bornstein SR et al. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89.

Table 3 Suggested hydrocortisone dosing regime using 10 mg HC (Hydrocortone, Merck Sharp & Dohme) and dividing tablets into 2·5 mg quanta using a tablet cutter

Patient weight (kg)	Total dose per day (mg)	First morning dose (mg)	Second midday dose (mg)	Third evening dose (mg)
50–54	10·0	5·0	2·5	2·5
55–74	15·0	7·5	5·0	2·5
75–84	17·5	10·0	5·0	2·5
85–94	20·0	10·0	7·5	2·5
95–114	22·5	12·5	7·5	2·5
115–120	25·0	15·0	7·5	2·5

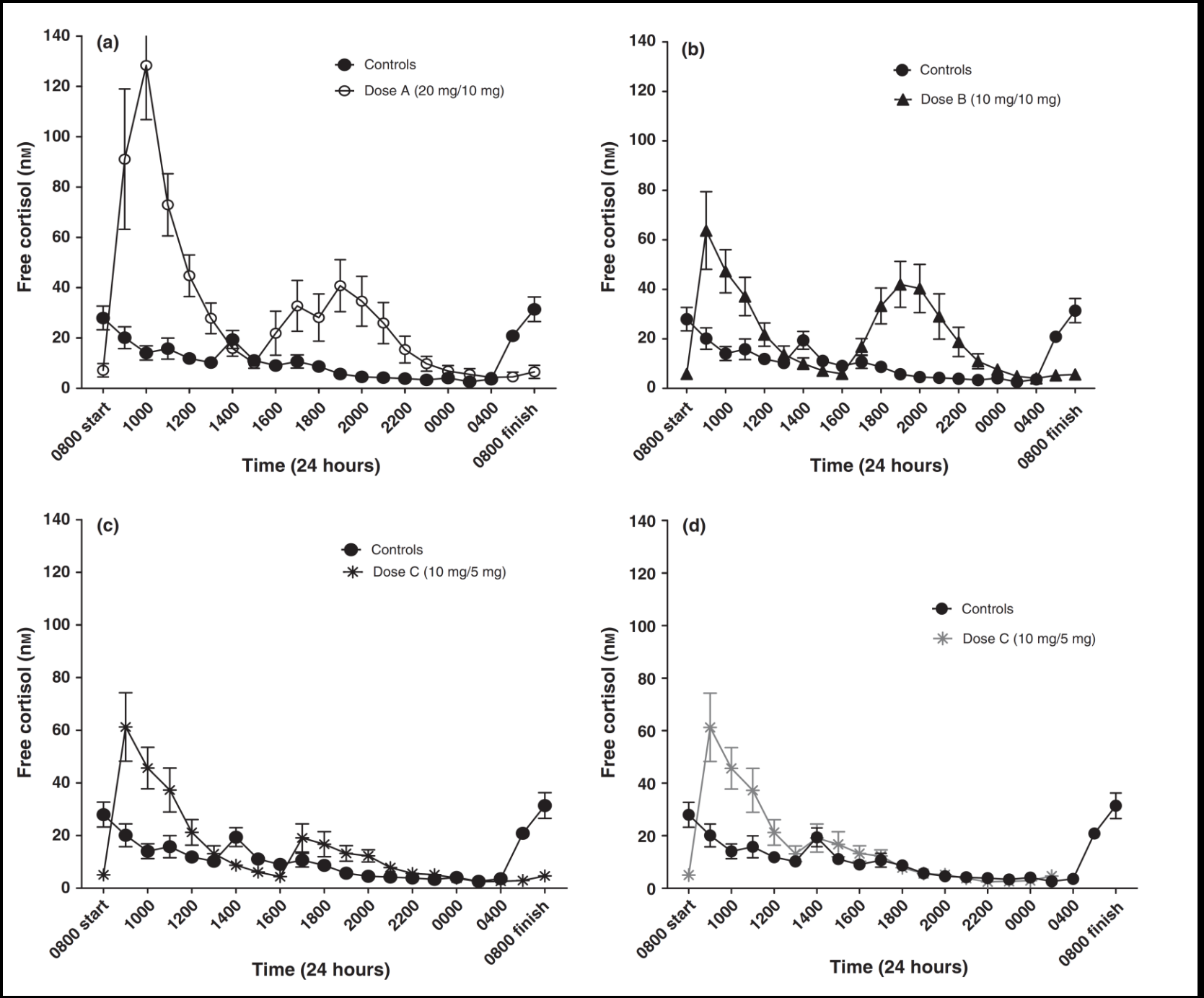




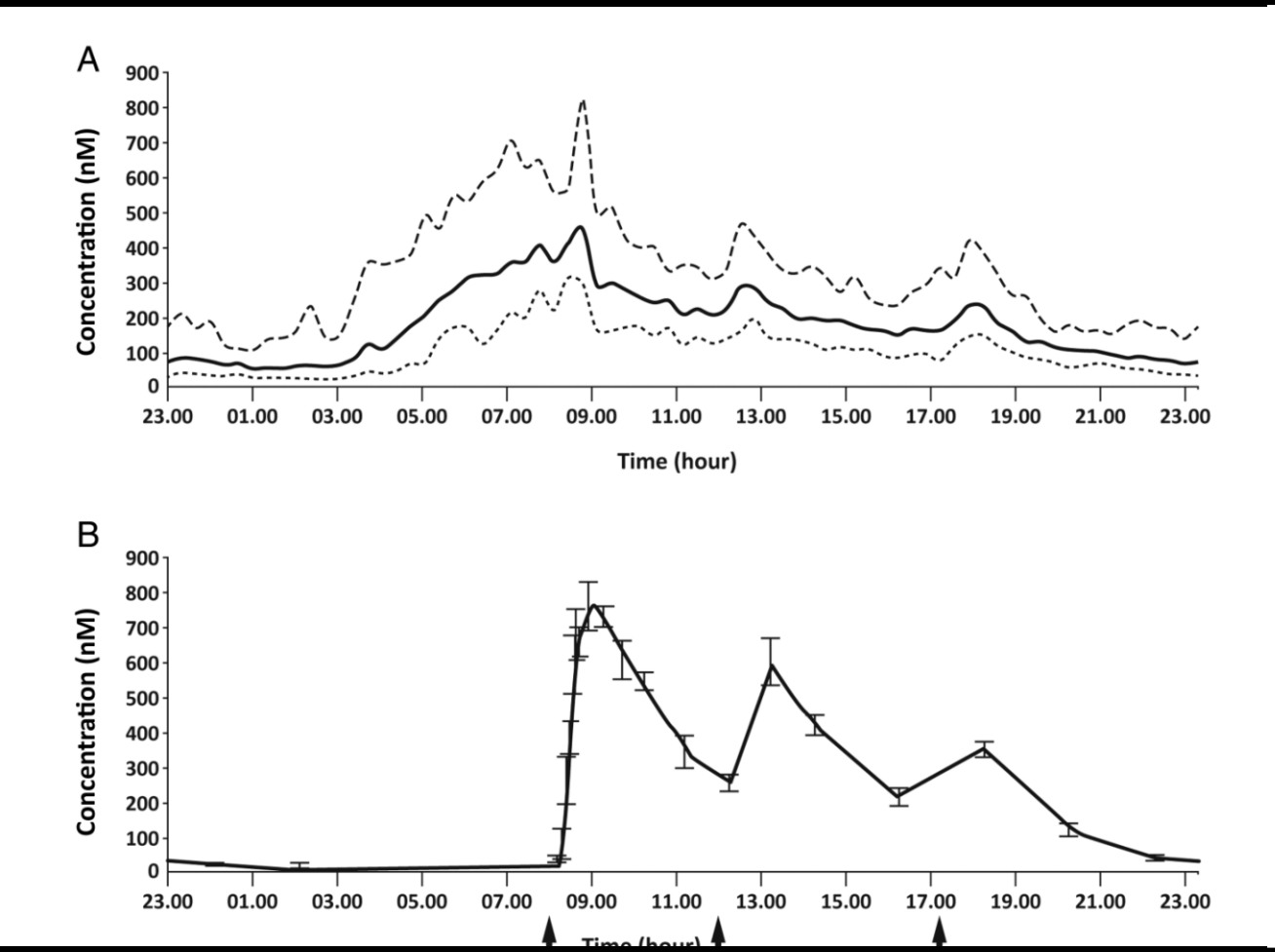
Mah PM et al. Clin Endocrinol (Oxf). 2004 Sep;61(3):367-75.

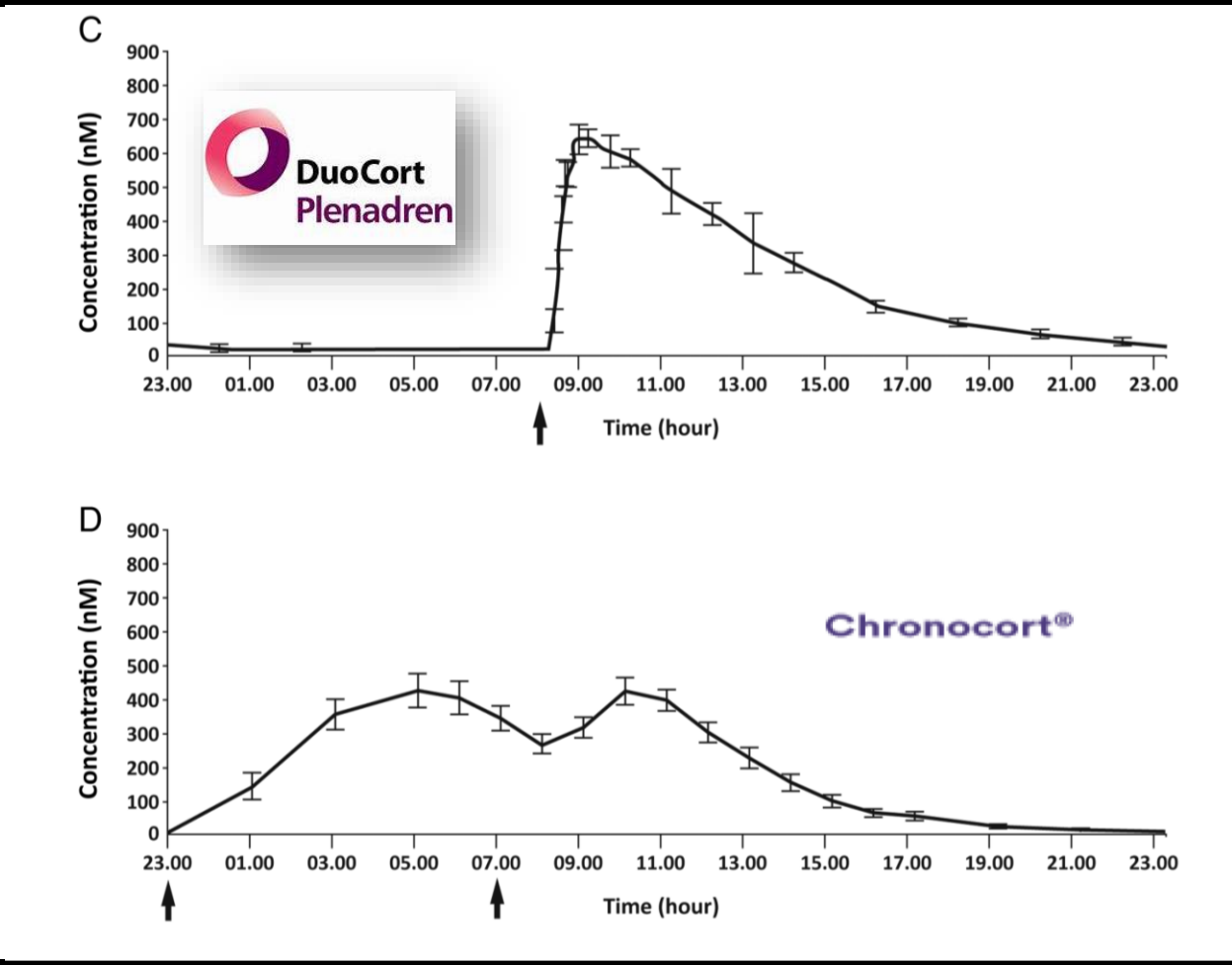
Optimizing glucocorticoid replacement therapy in severely adrenocorticotropin-deficient hypopituitary male patients

Behan LA et al. Clin Endocrinol (Oxf). 2011 Oct;75(4):505-13.



Modified-Release Hydrocortisone





Porter J et al. Arch Dis Child. 2017 Feb;102(2):199-205.

Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial

Andrea M Isidori, Mary Anna Venneri*, Chiara Graziadio, Chiara Simeoli, Daniela Fiore, Valeria Hasenmajer, Emilia Sbardella, Daniele Gianfrilli, Carlotta Pozza, Patrizio Pasqualetti, Stefania Morrone, Angela Santoni, Fabio Naro, Annamaria Colao, Rosario Pivonello, Andrea Lenzi*

Restoration of a more physiological circadian glucocorticoid rhythm by switching to a once-daily, modified-release regimen reduces bodyweight, normalises the immune cell profile, reduces recurrent infections, and improves the quality of life of patients with adrenal insufficiency.

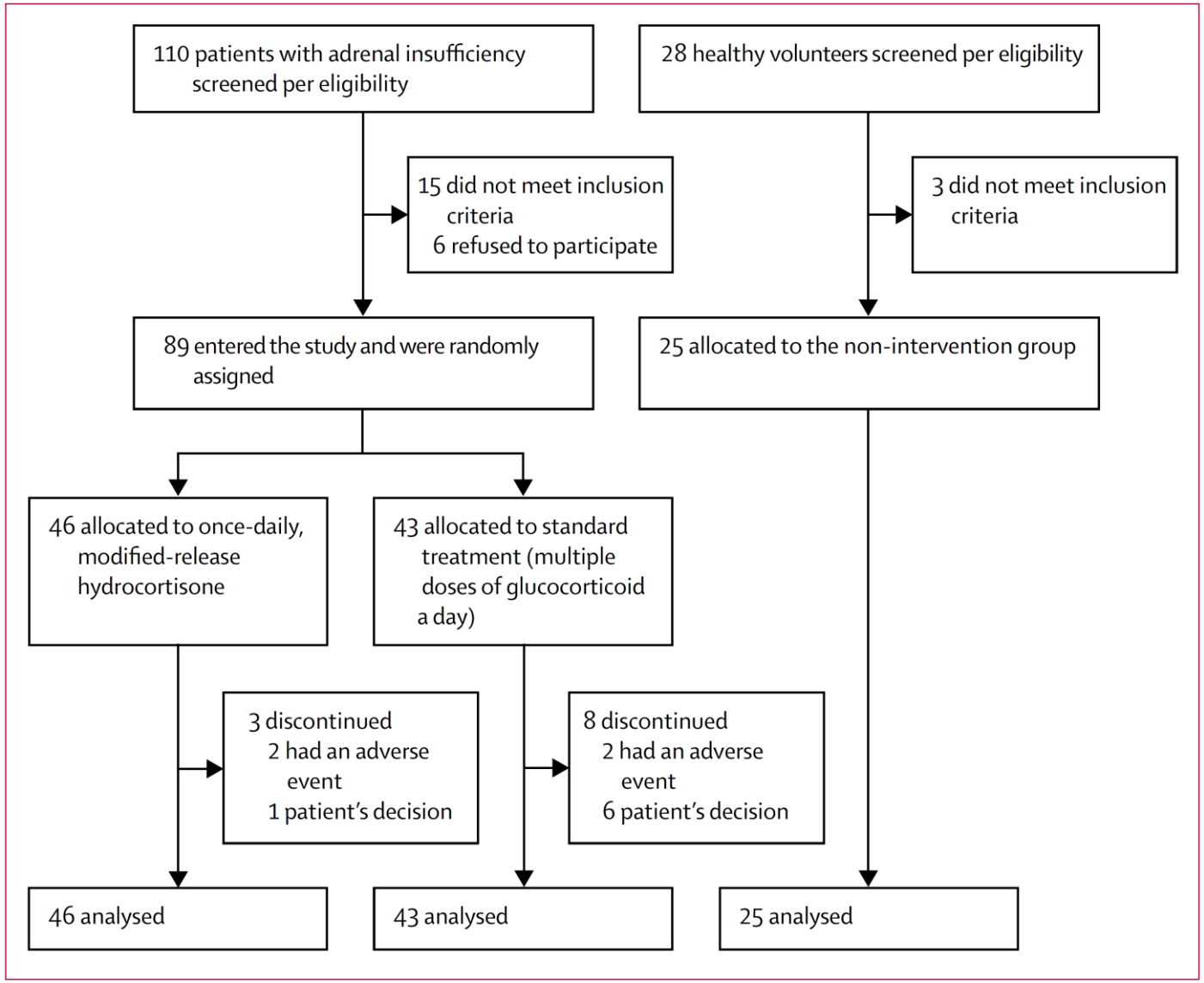
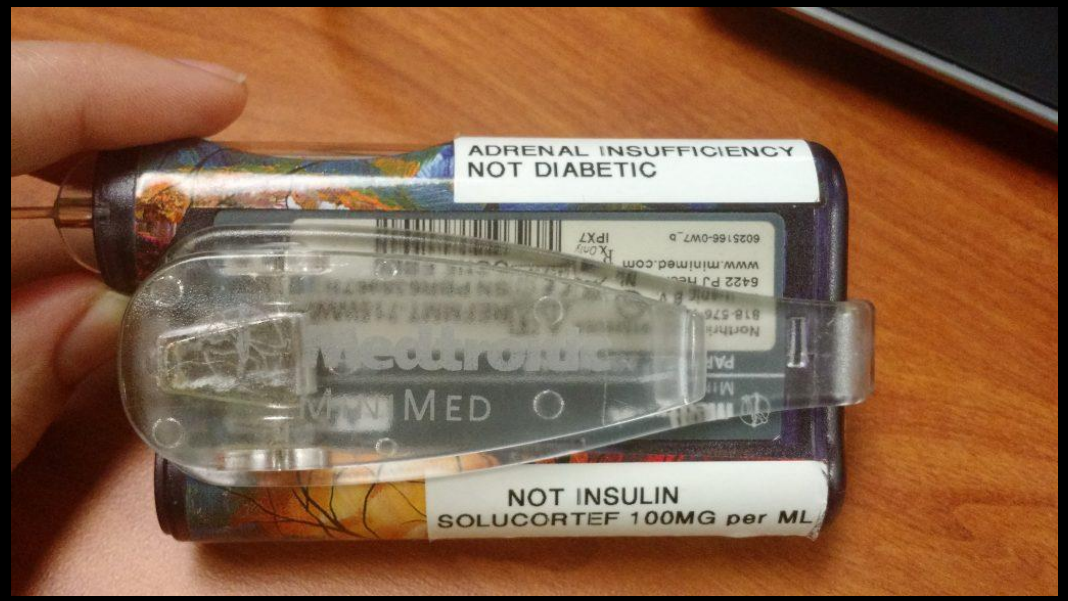


Figure 1: **Trial profile**

Isidori AM et al. Lancet Diabetes Endocrinol. 2018 Mar;6(3):173-185.

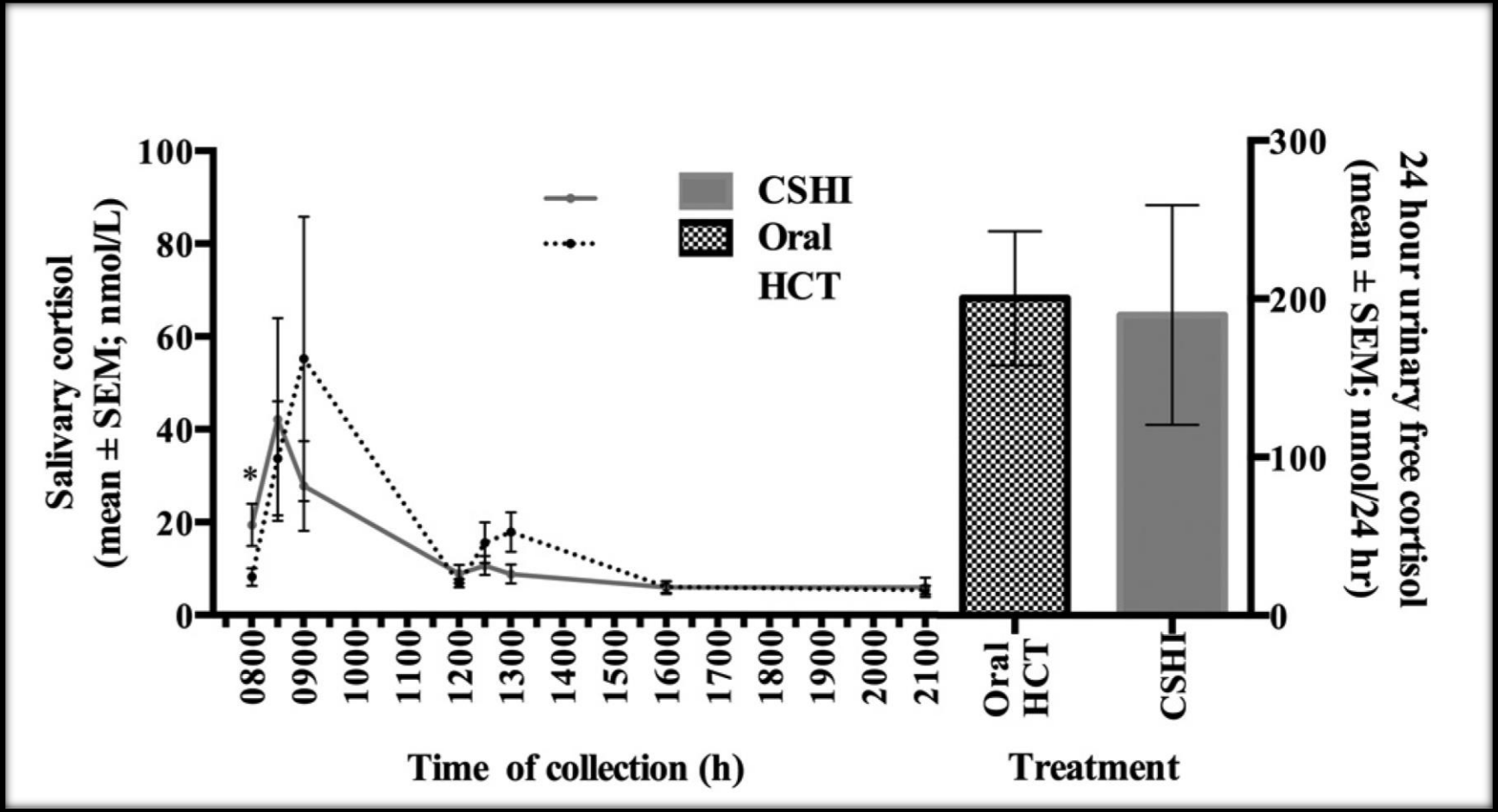
Continuous subcutaneous glucocorticoids (Hydrocortisone pumps)



https://clearlyaliveart.com/wp-content/uploads/2015/05/cortisol-pump-back-1024x576.jpg?189db0&189db0

http://media.endocrinologyadvisor.com/images/2016/10/25/insulinpumpset1016_1079868.jpg?format=jpg&zoom=1&quality=70&anchor=middlecenter&width=320&mode=pad

Continuous Subcutaneous Hydrocortisone Infusion Therapy in Addison's Disease: A Randomized, Placebo-Controlled Clinical Trial

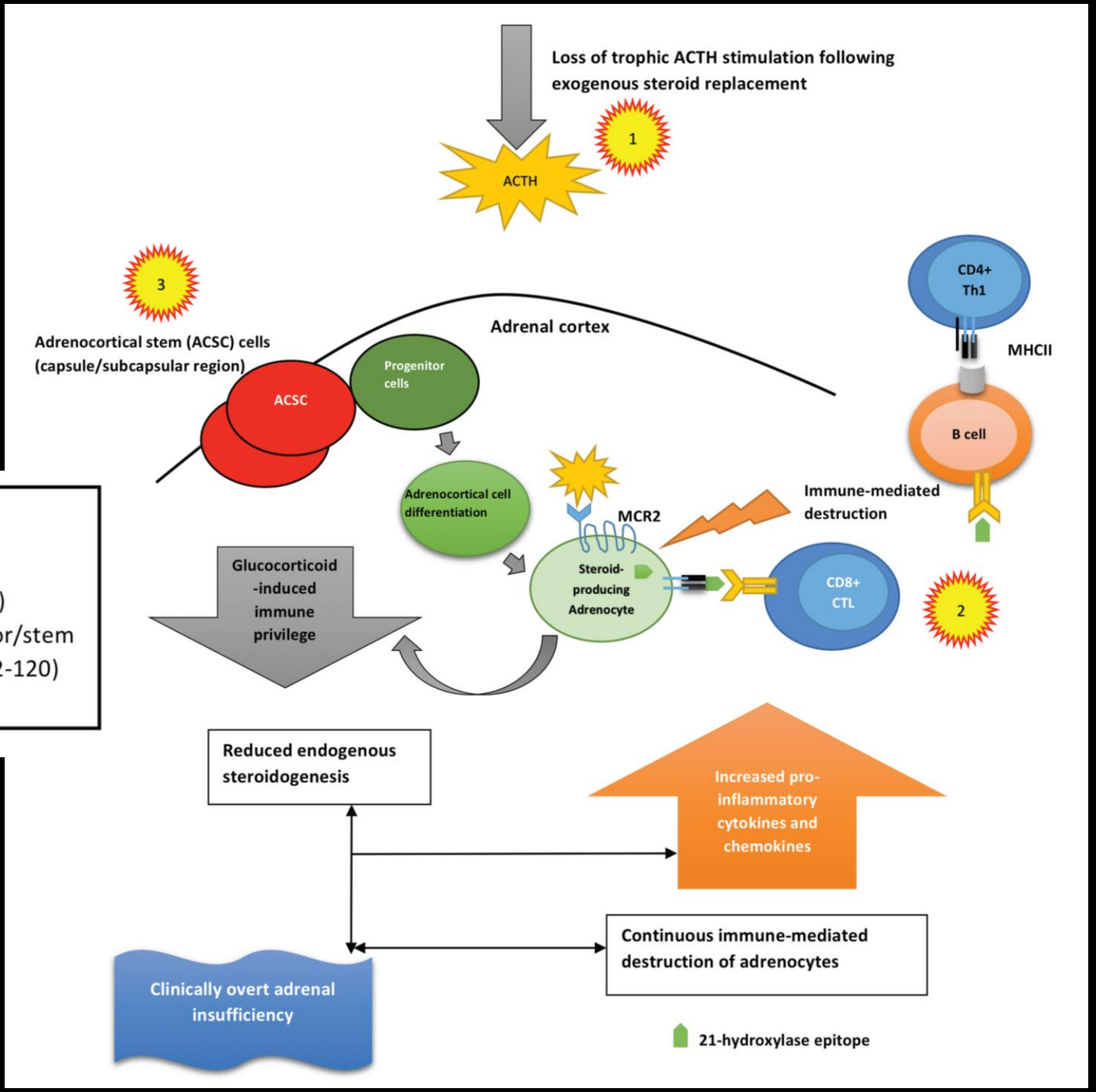


Gagliardi L et al. J Clin Endocrinol Metab. 2014 Nov;99(11):4149-57.

Immunomodulatory and Regenerative therapies

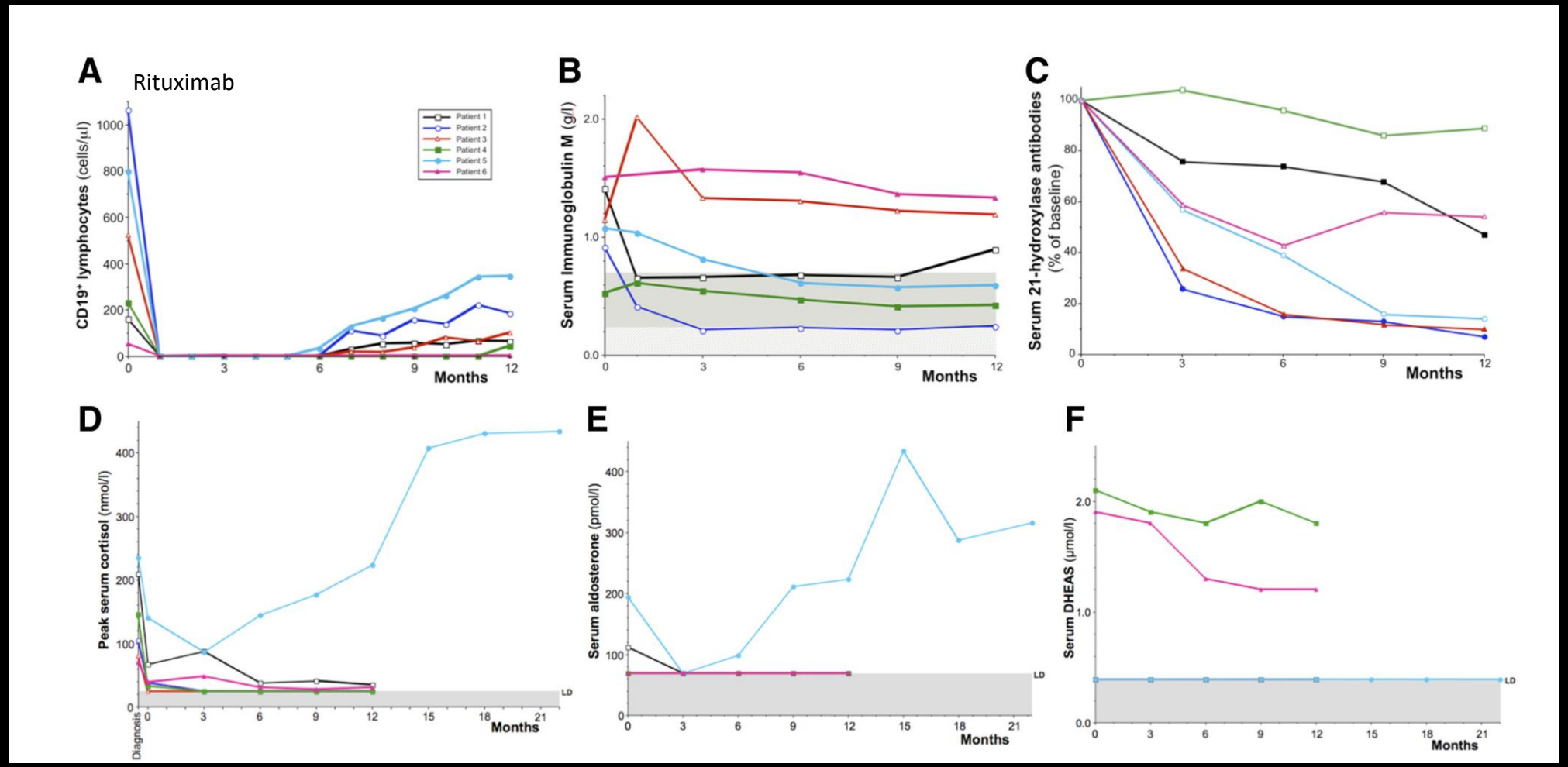
Potential novel therapeutic approaches in AAD

1. High-dose $ACTH_{1-24}$ therapy in AAD (108)
2. Immunomodulatory therapy- B-cell depletion therapy in AAD (104)
3. Cellular reprogramming/ manipulation of adrenocortical progenitor/stem cells – cell line/ animal studies only; no clinical study available (112-120)



Gan EH, Pearce SH. Eur J Endocrinol. 2017 Mar;176(3):R123-R135

Restoration of Residual Adrenal Function



Pearce SH et al. J Clin Endocrinol Metab. 2012 Oct;97(10):E1927-32.

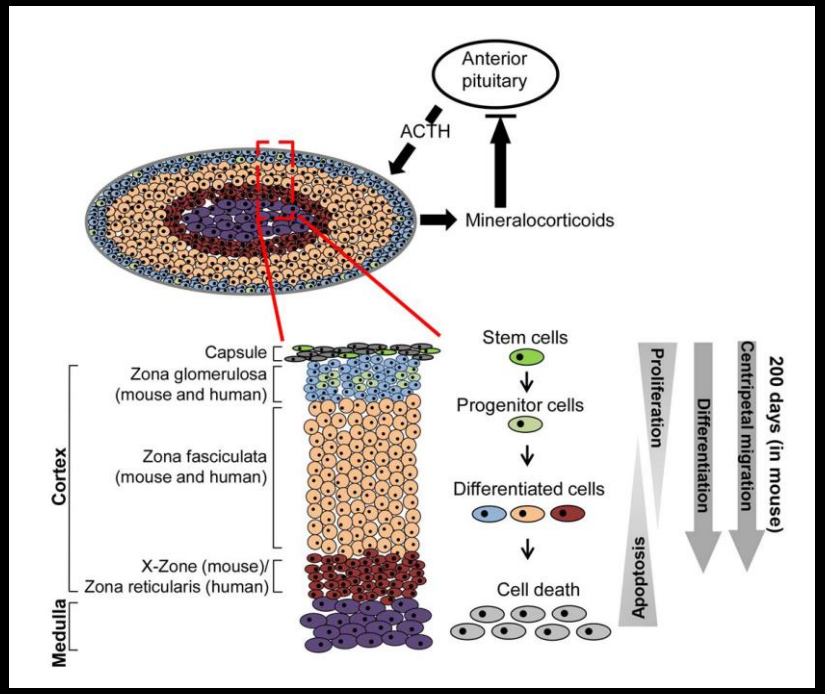
Residual Adrenal Function in Autoimmune Addison's Disease—Effect of Dual Therapy With Rituximab and Depot Tetracosactide

Intervention: All participants received dual therapy with B-lymphocyte–depleting immunotherapy (rituximab 1 g given twice) and repeated depot tetracosactide (1 mg on alternate days for 12 weeks).

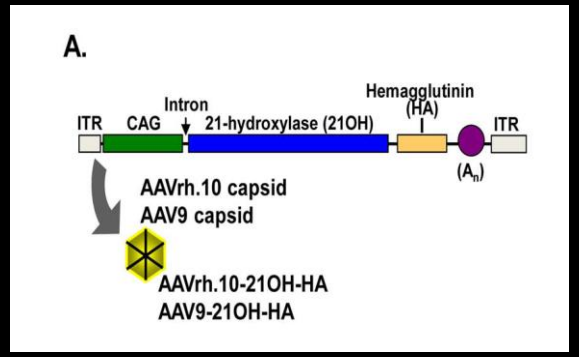
Conclusion: Combined treatment with rituximab and depot tetracosactide did not restore normal adrenal function. Nevertheless, adrenocortical plasticity is demonstrated in some patients, and this has the potential to be exploited to improve adrenal function. **(*J Clin Endocrinol Metab* 105: e1250–e1259, 2020)**

Napier C et al. J Clin Endocrinol Metab. 2020 Apr 1;105(4):e1250–9.

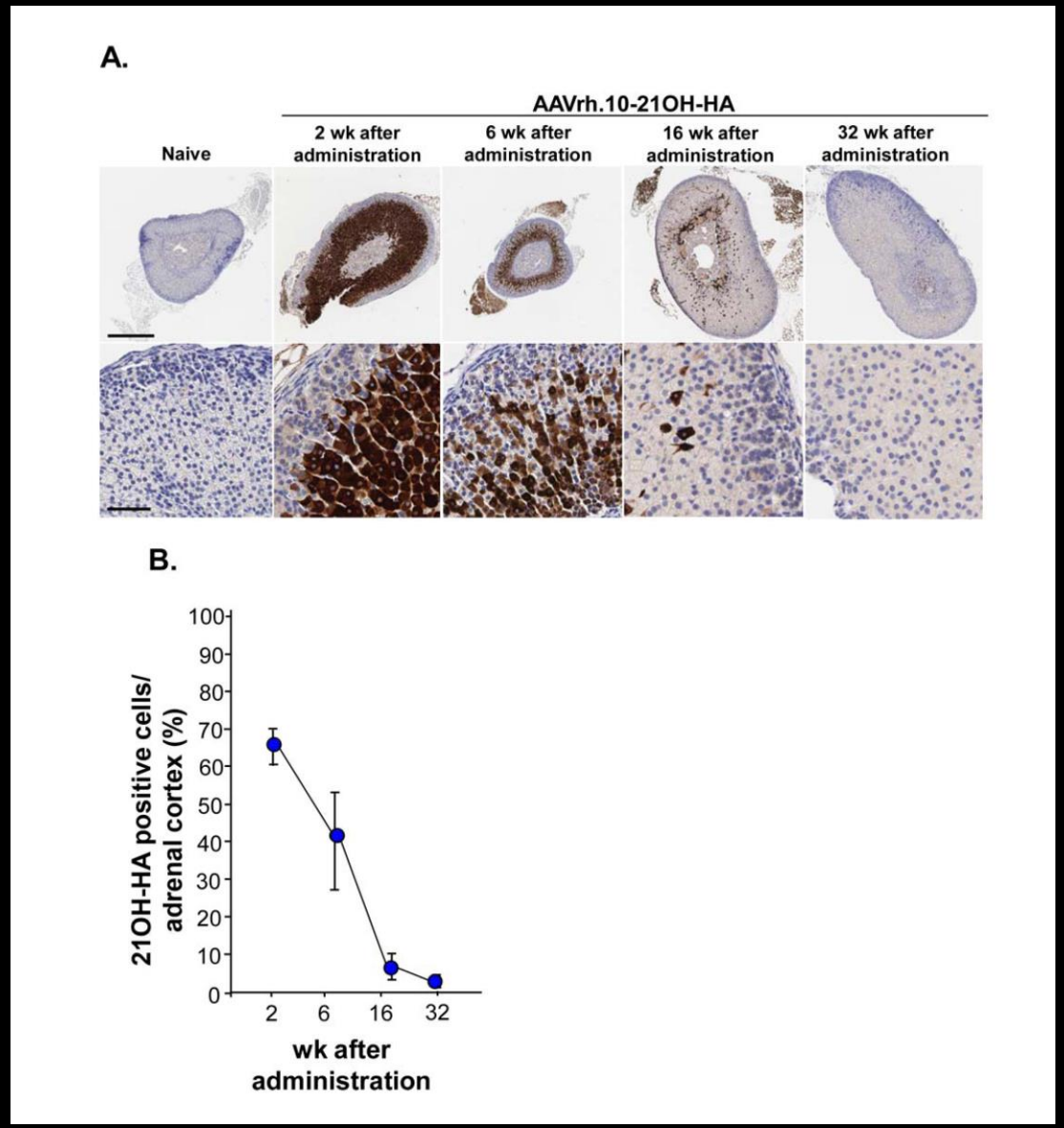
Gene Therapy



Adrenal zonation and cell renewal



Design of the vectors

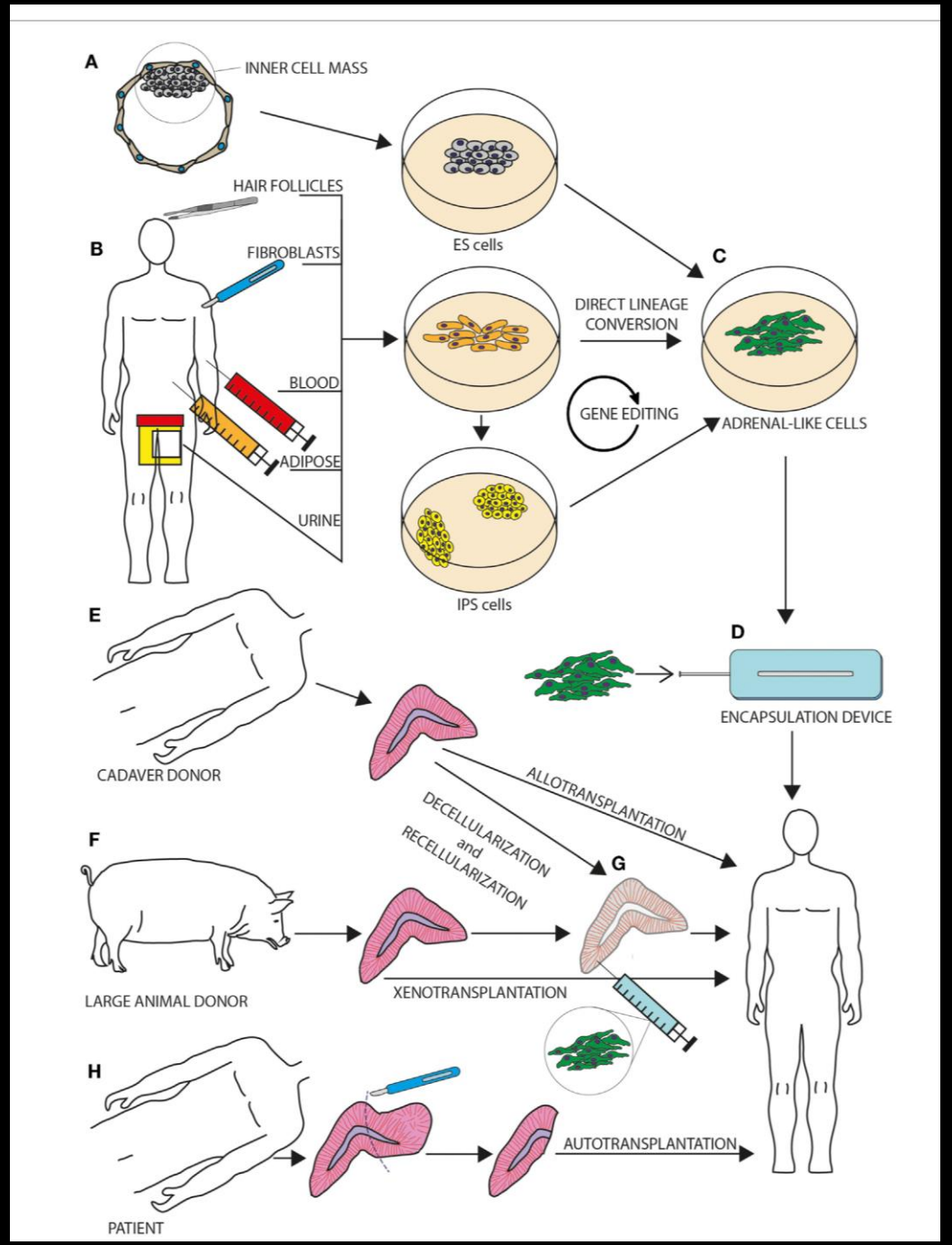


Markmann S et al. Hum Gene Ther. 2018 Apr;29(4):403-412.

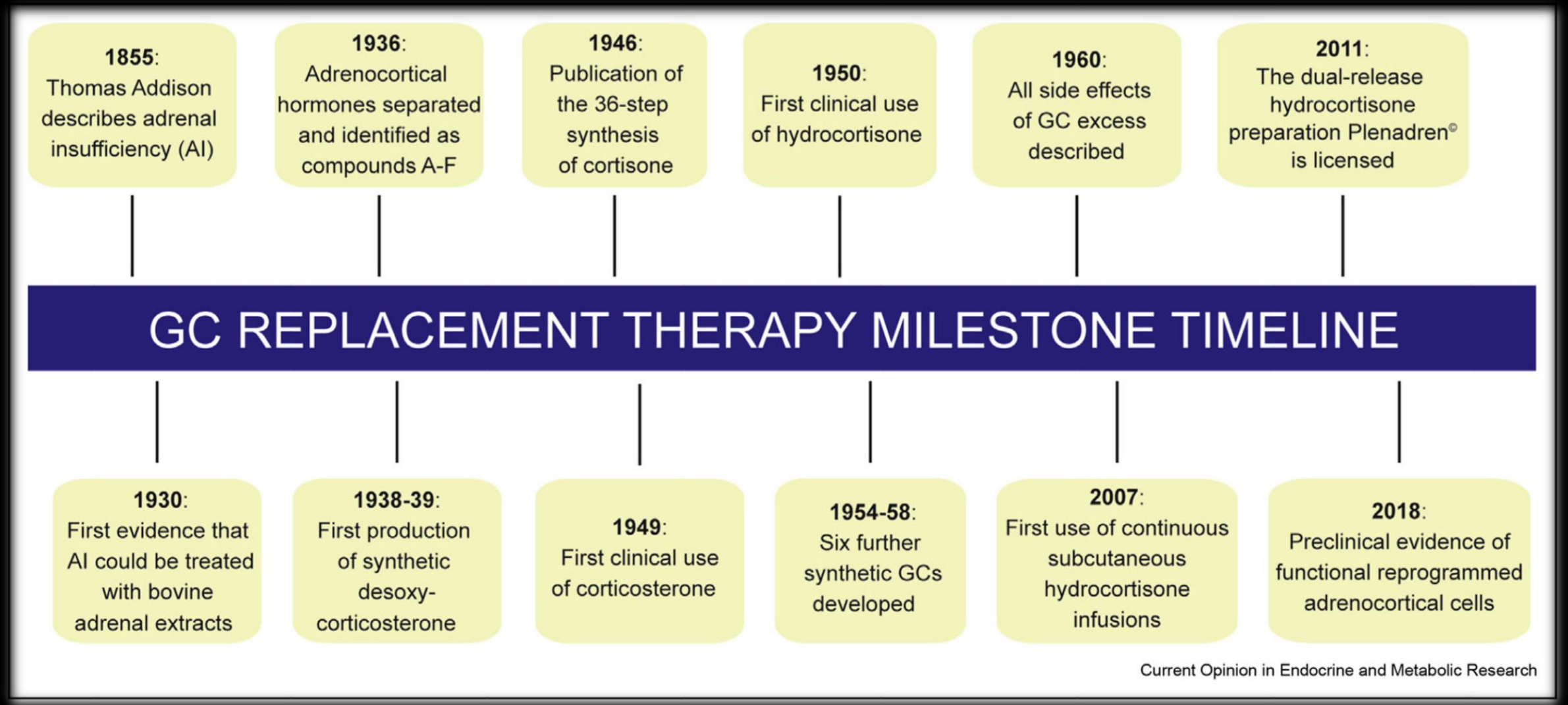
Novel and tested strategies for the treatment of adrenal insufficiency: Cell Transplantation

TABLE 1 | Details of published studies on adrenocortical or adrenogonwadal reprograming.

PMID	Article	Cells	Origin	Methodology
9199334	Crawford PA, et al. *Mol Cell Biol* (1997)	Embryonic stem cells (ESC)	Mouse (RW4 129/SvJ)	Stable transfection of SF1
15569155	Gondo S, et al. *Genes Cells* (2004)	Bone marrow stem cells (BMCs)	Mouse [C57BL/6Tg14 (act-EGFP)osbY01]	Adenovirus SF1
16728492	Yazawa T, et al. *Endocrinology* (2006)	Bone marrow stem cells (BMCs)	Human (hMSChTERT-E6/E7)	Stable transfection of SF1
17975261	Tanaka T, et al. *J Mol Endocrinol* (2007)	Bone marrow stem cells (BMCs)	Human (commercial cell line)	Adenovirus SF1
18566117	Gondo S, et al. *Endocrinology* (2008)	Adipose mesenchymal cells (AMCs)	Mouse (C57BL/6J) (B6)	Adenovirus SF1
19359379	Yazawa T, et al. *Endocrinology* (2009)	Bone marrow stem cells (BMCs)	Human (hMSChTERT-E6/E7)	Retrovirus SF1/LRH-1
20133449	Yazawa T, et al. *Mol Endocrinol* (2010)	Umbilical cord blood (UCB-MSCs)	Human (umbilical cord blood)	Retrovirus SF1
21129436	Yazawa T, et al. *Mol Cell Endocrinol* (2011)	Embryonic stem cells (ESC)	Mouse (EBRTcH3)	Retrovirus (inducible SF1)
21610156	Jadhav U, et al. *Endocrinology* (2011)	Embryonic stem cells (ESC)	Mouse (R1 ES cell line)	Stable transfection of SF1
21764617	Mazilu JK, et al. *Mol Genet Metab* (2011)	Mesoderm-derived cells	Human	Adenoviral SF1/Dax1/Cited2/ Pbx1/WT1
22324479	Wei X, et al. *Cell Prolif* (2012)	Umbilical cord mesenchymal stem cells (UC-MSCs)	Human (umbilical cord)	Adenovirus SF1
22778223	Sonoyama T, et al. *Endocrinology* (2012)	Embryonic Stem cell (ESC) iPS (from fibroblasts)	Human (H9 and KhES1) human (201B7)	Mesoderm diff. and nucleofection SF1

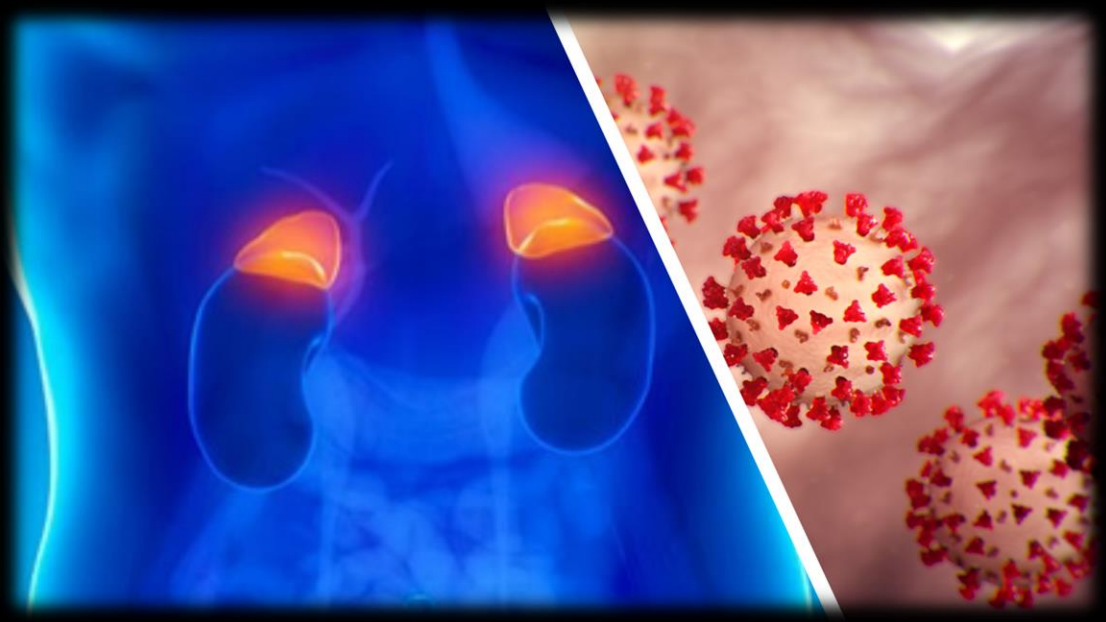


Ruiz-Babot G et al. Front Endocrinol (Lausanne). 2015 May 6;6:70.



Liew SY et al. Curr Opin Endocr Metab Res. 2019 Oct;8:152-159.

Adrenal Insufficiency and COVID-19



- Patients with adrenal insufficiency have an increased risk of infection due to their depleted innate immunity, characterised by increased monocytes and decreased cytotoxic natural killer cells, which could facilitate the worsening of a SARS-CoV-2 infection into severe acute respiratory distress syndrome.

Isidori AM at al. Lancet Diabetes Endocrinol. 2020 Jun;8(6):472-473.

Adrenal Insufficiency and Glucocorticoid Use During the COVID-19 Pandemic

Table 1 - Recommendation of GC therapy for adrenal insufficiency (AI) patients with suspected or confirmed COVID-19 diagnosis.

COVID-19 symptoms	Glucocorticoid (GC) dose
Mild symptoms: Fever, tiredness, dry cough, aches and pains, nasal congestion, runny nose, sore throat, diarrhea.	Double GC dose as soon as symptoms start: - 40 mg hydrocortisone early morning and 20 mg hydrocortisone at 2-3 pm. Consider an additional dose of 20 mg at night if severely fatigued. or - 10 mg prednisone early morning. Consider an additional dose of 2.5-5 mg at night if severely fatigued. - For patients with primary AI: maintain the usual dose of fludrocortisone (0.05-0.1 mg/day on average).
Warning symptoms: Trouble breathing, persistent pain or pressure in the chest, confusion, or cyanosis.	- Hydrocortisone (100 mg) by intravenous injection in bolus, followed by - Hydrocortisone (50 mg) intravenously every 6h or 200 mg/day by continuous intravenous infusion.

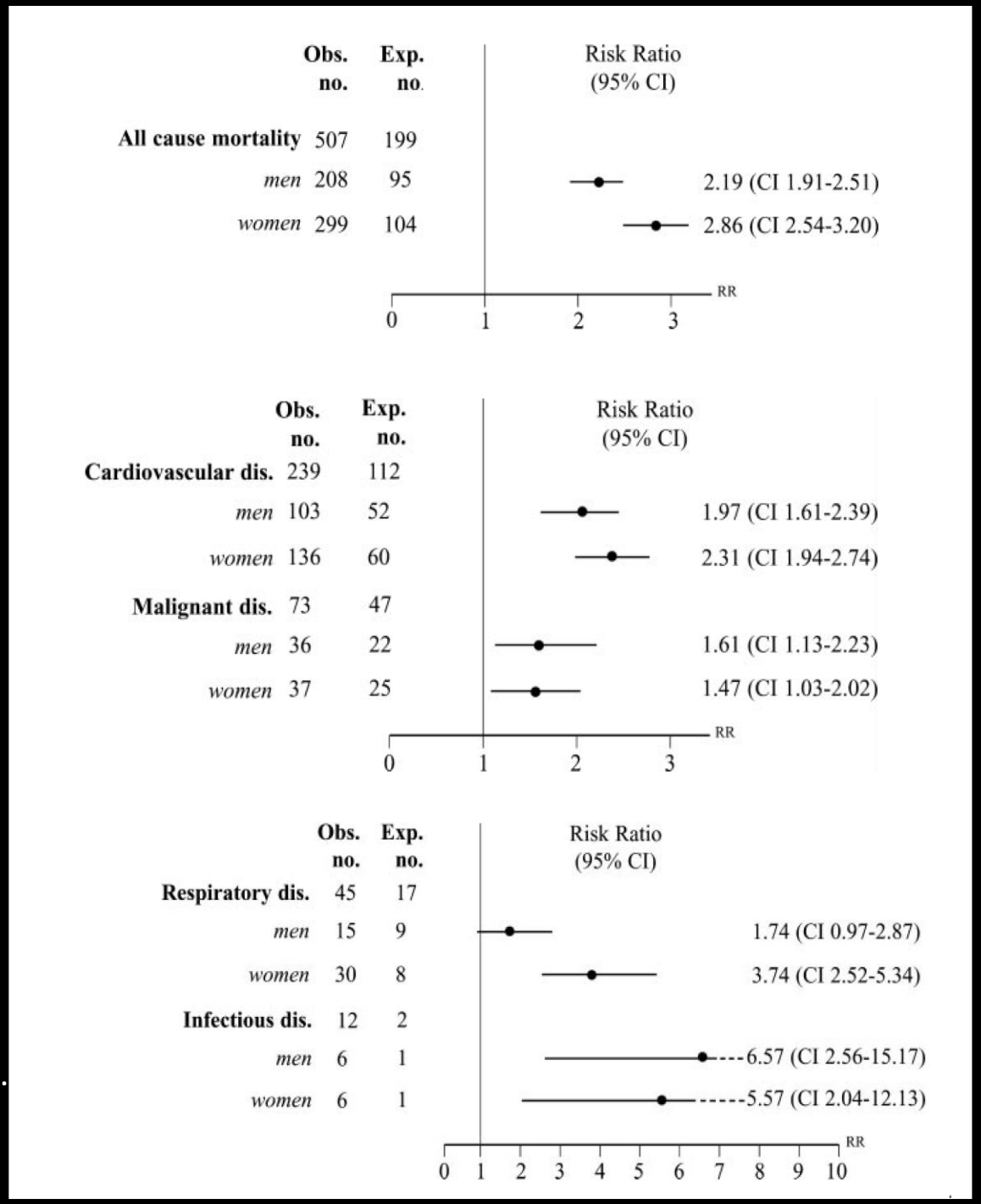
Almeida MQ, Mendonca BB. Clinics (Sao Paulo). 2020 Jun 12;75:e2022.

- In cases of persistent fever or progression of respiratory damage to severe pneumonia, an initial bolus of 50–100 mg of hydrocortisone followed by continuous intravenous infusion of 200 mg of hydrocortisone would be the most appropriate replacement for patients with adrenal insufficiency.

Isidori AM at al. Lancet Diabetes Endocrinol. 2020 Jun;8(6):472-473.

Mortality in patients with adrenal insufficiency[1]

- Infectious diseases
- Cardiovascular disease
- Malignancy
- Adrenal crisis
  - 15% of patients[2]



1 Bergthorsdottir R et al. J Clin Endocrinol Metab. 2006 Dec;91(12):4849-53.
2 Erichsen MM et al. Eur J Endocrinol. 2009 Feb;160(2):233-7.

Precipitating factors of Adrenal Crisis

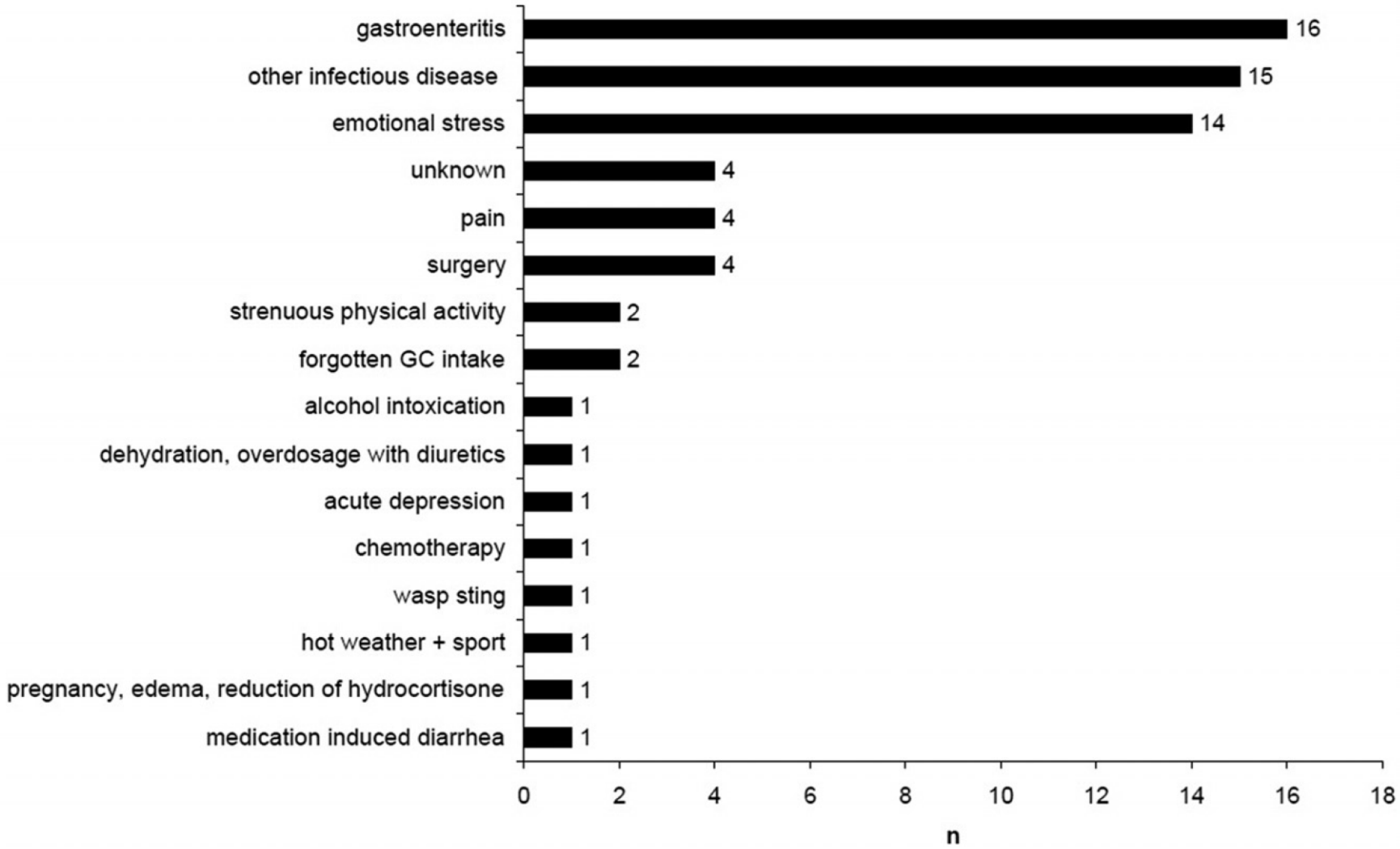
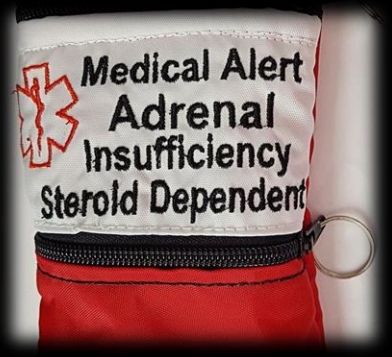


Figure 1. Precipitating factors of adrenal crisis in 46 patients during a prospective follow-up analysis. Multiple answers were possible.

Hahner S et al. J Clin Endocrinol Metab. 2015 Feb;100(2):407-16.

Patient Education



Patient education

- General information on adrenal physiology, adrenal insufficiency, hormone replacement therapy and adrenal crisis
- Sick day rules:
  - oral dose adaptation under conditions of mild and moderate stress (e.g. at least doubling of GC dose in case of feverish infection)
  - Necessitiy of parenteral GC administration in case of gastroenteritis or other severe health deterioration
- General actions needed to be taken in case of emergency

Patient Equipment

- Emergency Card in combination with medical records documenting the diagnosis of AI
- Emergency Set containing additional GC tablets, 100 mg hydrocortisone vials, syringes, needles and written information on emergency management

Practical Training

- Practical training in hydrocortisone self-injection (patients and relatives)

Fig. 1. Recommended measures for prevention of AC.

Hahner S. Ann Endocrinol (Paris). 2018 Jun;79(3):164-166.

ADDISON'S DISEASE?

It is when the adrenal glands stop to produce cortisol och aldosteron. Nobody can live without cortisol. A normal dayly amount is approximately 20 mg of hydrokortison and must be taken every day for the rest of life.

WHAT IS AN ADDISON CRISIS?

It is when the body needs more than the normal daily dose of cortisone. What happens is that the the blood pressure becomes dramatically low and can cause a chock with a heart failure.

An Addison crisis can develop rapidly and is a very serious condition.
Untreated, an Addison crisis can lead to death.

Symtoms in an Addison crises is:
vomiting, headache, stomachache, low blood pressure and confusion.

HOW TO STOP AN ADDISON CRISIS!

A Person having an Addison crises must promtly get to the nearest hospital's emergency care to rapidly get intravenous 100mg hydrocortison and fluids with i.v. saline solution.

IMPORTANT!
Do not wait for examination or lab test results!

If it's far to the hospital one can give an injection with 100mg hydrocortisone deep into the thigh muscle. If the person is unconscious it is critically important to give an injection of hydrocortisone immediately.

WHAT CAN CAUSE AN ADDISON CRISIS?

Vomiting, infection, flu, diarrhea, burn, trauma, etc can cause an Addison crisis.

IMPORTANT!
A person with Addison's disease must have instant medical care in these cases. If the person is unconscious or in a crises it is very important to give hydrocortisone and fluids first, then treat possible injury or disease immediately after.

HOW TO INJECT SOLU CORTEF

Wash your hands if possible.

MIX THE CONTENTS.

Mix the contents by pushing down the yellow top of the bottle and shake until the liquid is clear. Attach the thickest needle on to the syringe. Never touch the needle. Remove the yellow top from the bottle and push the needle through the rubber top of the bottle.

TURN THE BOTTLE UPSIDE DOWN.

Turn the bottle upside down and suck all the liquid into the syringe. If you have got the time change to a thinner needle. Hold up the syringe and squeeze out the air at the top.

PUSH THE NEEDLE DEEP DOWN.

If possible, change needle. Then push the needle deep down into the thigh muscle and inject all the liquid.
Don't hesitate, it can be a matter of life and death.

Call an ambulance!

QUESTIONS?