Adrenal Glands: the source of the stress system

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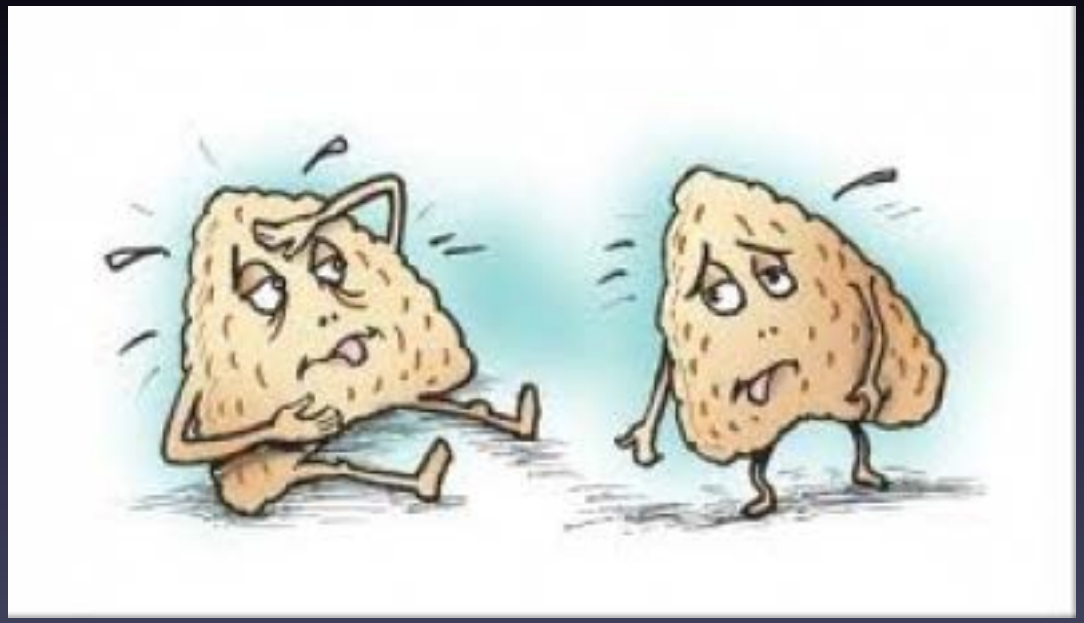
FOREWORD BY ABRAHAM VERGHESE

WHEN BREATH BECOMES

air

PAUL KALANITHI

Adrenal Insufficiency



Adrenal insufficiency

- 90% of cases are autoimmune
- Co-syntropin stimulation test
- Urgent hormone replacement is more important than waiting for test results
- Etiology: infections, cancer metastasizing the adrenal gland, hemorrhage, medications

Adrenal insufficiency

Metabolic effects of adrenal disorders		
	Cushing syndrome (hypercortisolism)	Addison disease (hypoadrenalism)
Potassium	Low	High
Blood pressure	High	Low
Glucose	High	Low
Leukocytosis	Neutrophilia	Eosinophilia
Imbalance	Metabolic alkalosis	Metabolic acidosis

First Clue: Clinical Manifestation

Symptoms:

Fatigue, lassitude, malaise, weakness, anorexia

Postural dizziness, syncope

Gastrointestinal Symptoms
- *Nausea*
- *Vomiting*
- *Abdominal Pain*
- *Diarrhea*
- *Constipation*

Myalgias, arthralgias, rarely flexion contractures

Decreased libido, amenorrhea

Signs:

Weight loss

Hyperpigmentation

Hypotension

Thinning of axillary and pubic hair

Vitiligo

Second Clue: Routine Laboratory Abnormalities

- Hyponatremia: common in primary & secondary AI
  - Why? GC exert negative feedback on vasopressin secretion and deficiency of cortisol may result in nonosmotic stimulation of vasopressin
- Hyperkalemia: due to deficiency of mineralocorticoids but not seen in all primary AI
- Hypercalcemia
- Hypoglycemia – rare more in secondary
- Metabolic Acidosis
- Lymphocytosis, eosinophilia

Imaging abnormalities

- Primary: bilateral adrenal enlargement or masses particular when enlargement is with the normal contour of the adrenal glands
- Atrophic adrenals
  - Secondary: pituitary or sellar mass
- Calcifications – tuberculosis
- Bleeding- hx of anticoagulation use, malignancy, coagulation disorders
- Tumors
- Most times images **cannot rule in or out** the diagnosis and cannot tell if primary or secondary AI.

Causes of Cortisol Deficiency

Most common is iatrogenic

- All exogenously administered glucocorticoids regardless of dose or route of administration may suppress the HPA axis
- Endogenous cortisol will suppress in 50% of patients who receive intra-articular or oral GC and 5-10% of patient who received inhaled or topical GC

Causes of AI

- Pituitary or Sellar tumors
- Granulomatous diseases of pituitary or bilateral adrenals
- Autoimmune destruction of Adrenals
- Hypophysitis of Pituitary
- External Bean Radiation to Sella/Pituitary
- Hemorrhage: Bilateral Adrenals, Pituitary Apoplexy, Sheehan's
- Adrenal Infiltration due to Lymphoma
- Infectious Adrenalitis (TB, Fungal, HIV, Syphilis)
- Metastasis: Pituitary or Bilateral Adrenals
- Surgical Resection: Hypophysectomy or bilateral adrenalectomy

Medications

- **Who is at risk? Anyone but particularly in individuals with limited pituitary and/or adrenal reserve**
- Mechanism: Inhibit cortisol biosynthesis- aminoglutethimide (antiepileptic), etomidate (anesthetic-sedative) , ketoconazole (antimycotic) and metyrapone
- Mechanism: Adrenolytic – Mitotane (DDT derivative)
- Mechanism: Drugs that accelerate the metabolism of cortisol and most synthetic glucocorticoids by inducing hepatic CYP3A4 enzyme
  - Phenytoin, barbiturates, and rifampin

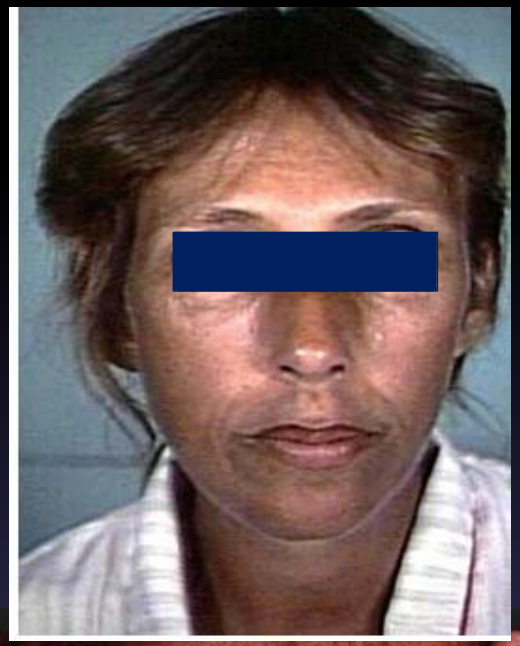
Medications

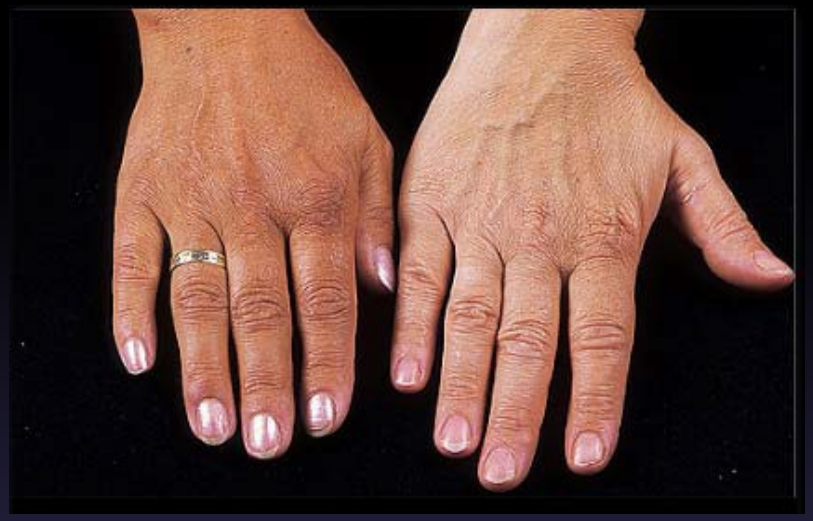
- Opioids- secondary/tertiary ; modify ACTH release
- Psychotropic medication – secondary
- Benzodiazepines (alprazolam), atypical antipsychotics (olanzapine, quetiapine) - secondary
- CTLA-4 monoclonal antibody induced hypophysitis (eg ipilimumab) -secondary
- GR antagonist (mifepristone) - primary

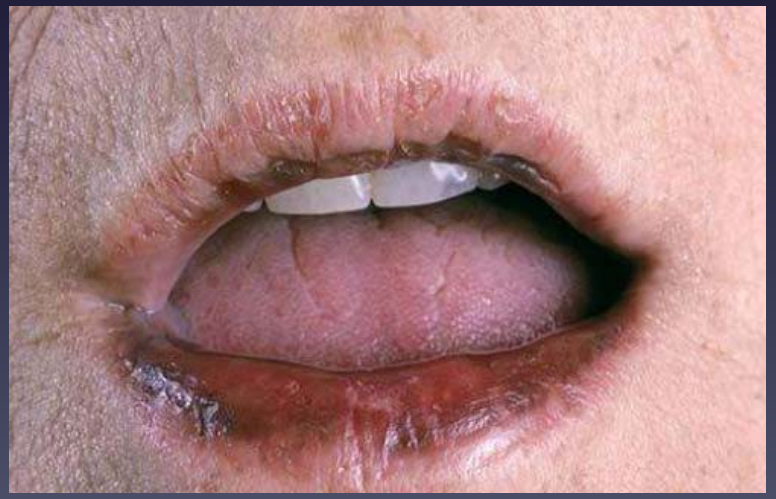
Genetic disorders

- Congenital adrenal hyperplasia
- X-linked Adrenoleukodystrophy Autoimmune polyglandular syndromes
- ACTH insensitivity (familial glucocorticoid deficiency)
- Adrenal hypoplasia congenita
  Transcription factor defects

Addison's Disease- Primary AI







Finding the Etiology AI is important!

- Primary AI is rare! So etiology should be pursued due to additional consequences of the diagnosis
  - Children look for genetic causes
  - 21- hydroxylase Ab
  - Young men Adrenal X- linked leukodystrophy

21 Hydroxylase Antibody

- Cause of autoimmune Addison's disease
- Should be checked in all cases of primary AI
- Sensitivity 90% Sensitivity 100% but immunofluorescence technique is less sensitive
- Young male with primary AI and antibody negative check very long chain fatty acids for Adrenal X- linked leukodystrophy

Polyglandular Autoimmune Syndromes

- Type 1
  - "APECED"
    - Autoimmune PolyEndocrinopathy
    - Chronic Mucocutaneous Candidiasis
    - Ectodermal Dysplasia (dental enamel hypoplasia, pitted nails, alopecia)
  - Autosomal recessive disorder due to mutation in autoimmune regulator (AIRE) gene
  - Onset in infancy
  - Equal gender incidence
  - Classic triad of mucocutaneous candidiasis, AI hypoparathyroidism and Addison's disease
  - Other manifestations: gonadal failure, hypoplasia of dental enamel, alopecia, vitiligo, intestinal malabsorption, type 1 diabetes, pernicious anemia, hypothyroidism

Polyglandular autoimmune syndrome type 1

Component Disease	Frequency at Age 40 Yr (%)	Recommended Evaluation
Autoimmune Polyendocrine Syndrome Type I		
Addison's disease	79	Sodium, potassium, ACTH, cortisol, plasma renin activity, 21-hydroxylase autoantibodies
Diarrhea	18	History
Ectodermal dysplasia	50-75	Physical examination
Hypoparathyroidism	86	Serum calcium, phosphate, PTH
Hepatitis	17	Liver function test
Hypothyroidism	18	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies
Male hypogonadism	26	FSH/LH
Mucocutaneous candidiasis	100	Physical examination
Obstipation	21	History
Ovarian failure	72	FSH/LH
Pernicious anemia	31	CBC, vitamin B_{12} levels
Splenic atrophy	15	Blood smear for Howell-Jolly bodies; platelet count; ultrasound if positive
Type 1 diabetes	23	Glucose, hemoglobin A_{1c}, diabetes-associated autoantibodies (insulin, GAD65, IA-2)

Polyglandular autoimmune syndromes

- Type 2
  - HLA-related
  - Multiple types of inheritance described (AD, AR, polygenic)
  - Onset in adulthood
  - Female predominance
  - Autoimmune diseases occurring in multiple endocrine systems
  - Two or more of the following:
    - Primary adrenal insufficiency
    - Graves' disease
    - AI thyroiditis
    - Type 1 diabetes
    - Primary hypogonadism
    - Myasthenia gravis
    - Celiac disease

Polyglandular autoimmune syndrome type 2

Component Disease	Frequency at Age 40 Yr (%) with type 1 diabetes.	Recommended Evaluation
Addison's disease	0.5	21-Hydroxylase autoantibodies
		ACTH stimulation testing if positive
Alopecia		Physical examination
Autoimmune hypothyroidism	15-30	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies
Celiac disease	5-10	Transglutaminase autoantibodies; small-intestine biopsy if positive
Cerebellar ataxia	Rare [†]	Dictated by signs and symptoms of disease
Chronic inflammatory demyelinating polyneuropathy	Rare [†]	Dictated by signs and symptoms of disease
Hypophysitis	Rare [†]	Dictated by signs and symptoms of disease
Idiopathic heart block	Rare [†]	Dictated by signs and symptoms of disease
IgA deficiency	0.5	IgA level
Myasthenia gravis	Rare [†]	Dictated by signs and symptoms of disease
Myocarditis	Rare [†]	Dictated by signs and symptoms of disease
Pernicious anemia	0.5-5	Anti–parietal cell autoantibodies
		CBC, vitamin B_{12} levels if positive
Serositis	Rare [†]	Dictated by signs and symptoms of disease
Stiff-man syndrome	Rare [†]	Dictated by signs and symptoms of disease
Vitiligo	1-9	Physical examination

Infections of the adrenal gland

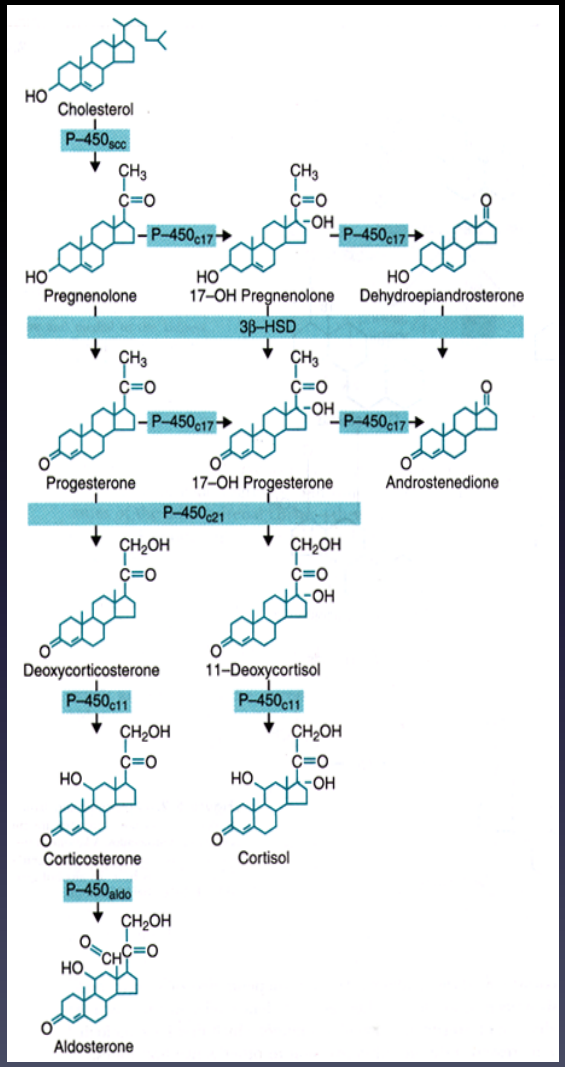
- Tuberculosis
  - Major worldwide cause of AI
  - From hematogenous spread
- Fungal (histoplasmosis, cryptococcus)
- CMV
- HIV

Adrenal hemorrhage

- Adrenal gland is prone to hemorrhage, especially in patients with sepsis, coagulopathy or trauma
- Clues:
  - Hypotension or shock
  - Abdominal or flank pain
  - Fever
  - Drop in hemoglobin
- Waterhouse-Friederichson syndrome
  - Adrenal hemorrhage occurring in patients with sepsis (classically meningococcal sepsis)

Congenital Adrenal Hyperplasia

- Family of autosomal recessive disorders resulting in impaired production of cortisol
- Presentation varies depending on the particular mutation and the particular enzyme involved



Adrenoleukodystrophy

- X-linked recessive disorder
- Mutations in ABCD1 gene
- Defect in oxidation of fatty acids within peroxisomes

  →Elevated serum levels of very-long-chain fatty acids

  →Accumulation in cell membranes

  →Demyelination within the nervous system
- Progressive neurologic dysfunction and adrenal insufficiency

Adrenal hypoplasia congenita

- X-linked
- Mutation in DAX-1 gene
  - Nuclear receptor of unknown function
  - Expressed in adrenal cortex, gonads, and hypothalamus
- Present with congenital adrenal insufficiency and hypogonadotrophic hypogonadism

Metastases to the adrenal gland

- 40-60% of patients with disseminated breast or lung cancer have adrenal metastases at autopsy
- Frank AI is uncommon

Causes of 2˚ Adrenal Insufficiency

1. Exogenous glucocorticoids
2. Exogenous glucocorticoids
3. Exogenous glucocorticoids
4. Hypothalamic/pituitary disease

H-P disease resulting in 2° adrenal insufficiency

- Tumors
- Hemorrhage
- Infarction
- Infiltrative disorders
- Traumatic brain injury

Tumors resulting in 2˚ adrenal insufficiency

- Space-occupying lesions cause hypopituitarism by destroying the pituitary gland or by disrupting the hypothalamic-hypophyseal portal venous system

  - Pituitary adenomas

  - Other CNS tumors (meningioma, epidermoid tumors)

  - Metastases (breast cancer)

Pituitary hemorrhage resulting in 2˚ adrenal insufficiency

- Often due to bleeding into a previously undiagnosed pituitary adenoma
- Severe headache and visual changes may be prominent
- Often called “Pituitary apoplexy”

Pituitary infarction resulting in 2˚ adrenal insufficiency

- Most commonly occurring peripartum ("Sheehan's syndrome")
- Hypotension along with vasospasm of the hypophyseal arteries compromise arterial perfusion of the anterior pituitary

Infiltrative disease resulting in 2° adrenal insufficiency

- Langerhan's histiocytosis
  - Infiltration of multiple organs by well-differentiated histiocytes
  - Diabetes insipidus, anterior pituitary hormone deficiency
- Sarcoidosis
  - Multisystem granulomatous disorder characterized by the presence of noncaseating granulomas in involved organs
  - Diabetes insipidus, anterior pituitary hormone deficiency

Infiltrative disease resulting in 2˚ adrenal insufficiency

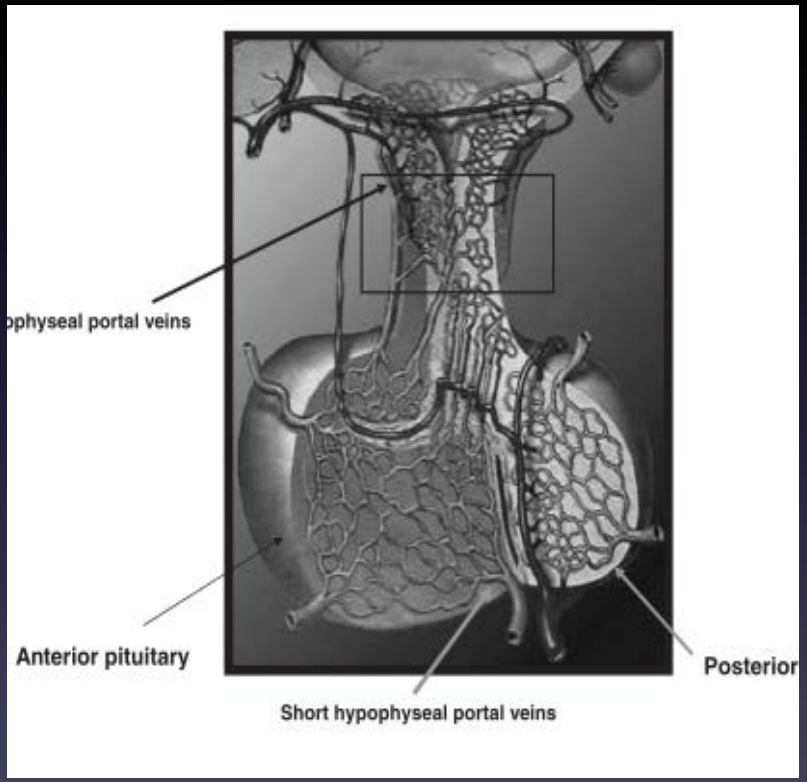
- Hemochromatosis
  - Excessive iron deposition in the tissues
  - Hypogonadotropic hypogonadism
  - Deficiency of TSH, GH and ACTH later in the course of disease

Traumatic brain injury

- Prevalence of hypopituitarism - up to 68.5%
- Mechanisms

  - compression of the pituitary gland and/or hypothalamic nuclei due to edema

  - direct mechanical injury to the hypothalamus, pituitary stalk (hypophysial vessels, portal capillaries) or the gland
- Growth hormone deficiency – most common pituitary deficit



Diagnostic Testing- Basal Serum Cortisol

- Can be used alone to **exclude** all forms of AI in MOST patients
- Cortisol has strong diurnal rhythm
- AM cortisol before 9:00 am is diagnostically useful
- Basal cortisol values < 3 ug/dl highly suggestive but not always diagnostic (clinical correlation needed)
- BUT if cortisol drawn at any time of day is > 11 ug/dl is 99% specific for predicting a cortisol increase greater than 18 ug/dl during an ITT
- Basal cortisol values 3-11 ug/dl are inconclusive and require additional testing

Diagnostic Testing-ACTH

- AM ACTH value itself not used to excluded adequate cortisol production
- If cortisol is low < 5ug/dl the ACTH is useful to distinguish etiology of AI
  - Primary AI: ACTH > 100 pg/ml
  - Secondary AI: ACTH < 5 pg/ml (or inappropriately low)

Serum Aldosterone & Plasma Renin Activity

- Not deficient in secondary AI
- Only deficient in primary AI (but not always)
- Aldosterone will be low or undetectable in primary AI but only interpretable with an appropriately elevated renin (>2 ng.ml/h)

250 ug Cosyntropin Stimulation Test

- Indication: Definitively exclude primary adrenal insufficiency or *longstanding* secondary adrenal insufficiency (>2 weeks)
- Protocol: IV or IM bolus with sampling baseline, 30 min and 60 min
- Can be done ANYTIME OF DAY
- NORMAL: A peak cortisol at 30-60min of greater than 18 ug/dl
- Basal cortisol values vary by time of day and clinical status and should never be used as a diagnostic criterion
- Aldosterone normally doubles in response to cosyntropin which can be helpful

Other dynamic testing- recommend endocrine involvement

- Insulin Tolerance Test
  - GOLD STANDARD TEST for all forms of AI
  - Tests the entire HPA axis
  - Measures the counter regulatory hormone response to hypoglycemia
  - Useful in equivocal cases of other dynamic testing & secondary AI
  - Contraindications to test: seizure disorders, significant cardiovascular disease, inability to verbalize symptoms of hypoglycemia

Other diagnosis

- Adrenal Fatigue: Doesn't exist
- Relative Adrenal Insufficiency: according to endocrinologist doesn't exist, possibly exists in critical care literature
  - Circulating cortisol is about 10% free hormone and 90% bound
  - The affinity of cortisol for the GC receptor is about .362 ug/dl
  - So a total serum cortisol of 7 ug/dl is about .7 ug/dl free cortisol which is nearly enough to saturate the GC receptor.
  - So during stress even "low" amounts is often enough

Acute Ill Management withAI

- Aggressive volume replacement with normal saline
- Use of vasocontraction medications
- If not response
  - Hydrocortisone (solu-cortef) as IV bolus or infusion, IM ok as well if no IV access
- Exact dose not critical just get some in ASAP
- 20mg HC will sufficiently raise serum cortisol concentrations

Acute Management ofAI

- Presumed maximal output of hydrocortisone during severe stress is 200-300mg/day
- Doses of 50mg q6 will raise serum cortisol to 40-120mg/dl
- 50 mg IV bolus then 25 q6… if shock 50 q6..stay away from 100 q8
- MOST IMPORTANT is to continue the dosing until patient is well then can take oral regimen

Acute Management ofAI

- Doses of hydrocortisone greater than 40mg/dl per day also have a mineralocorticoid effect so do not need fludrocortisone replacement
- If use solumedrol or dexamethasone, need to give florinef
- Pts promptly respond to the first dose of hydrocortisone

ACTH Stimulation Test in AI During Critical Illness

- Often does not provide any additional meaningful information when accounting for possible delay in care

Chronic GC replacement

- 10-12mg/ m2 (BSA)
- Usually 15-20mg divided into 2 or 3 doses
- Dose to match the normal diurnal rhythm
- Two peaks of cortisol 8am and 4pm
  - BID regimen with hydrocortisone
  - 1st dose upon awakening or 30 min prior to arising
  - Next dose 8hrs later and before 6pm
  - Less preferred is prednisone and dexamethasone since they are long acting and need to be metabolized in the liver to the active hormone

Maintenance therapy

- Mineralocorticoid replacement
  - Fludrocortisone 0.05 to 0.2 mg daily
  - Adjust based on serum potassium
  - Not needed in 2˚ adrenal insufficiency
- Liberal salt intake

Treatment

- Treatment of adrenal insufficiency should be initiated as soon as the diagnosis is confirmed, or even sooner if the patient presents in adrenal crisis.
- Patients with primary adrenal insufficiency require life-long glucocorticoid and mineralocorticoid replacement therapy

  - **All patients should wear Medic-alert bracelet!!**

Case 1

- Asked to see pt regarding diagnosis of adrenal fatigue in 19 y/o man complaining of panic attacks accompanied by palpitations and weakness.
- Diagnosis of adrenal fatigue made by a salivary cortisol profile.
- Pt's mother at the visit

PE

- Healthy male
- Normal skin pigmentation
- 124/74 HR 60
- BMI 21
- PE=normal
- Early morning cortisol 1.2 ug/dl

Which of the following tests would you obtain next?

- A. Plasma ACTH
- B. 250 ug ACTH stimulation test
- C. Pituitary MRI
- D. DHEA-S

Results

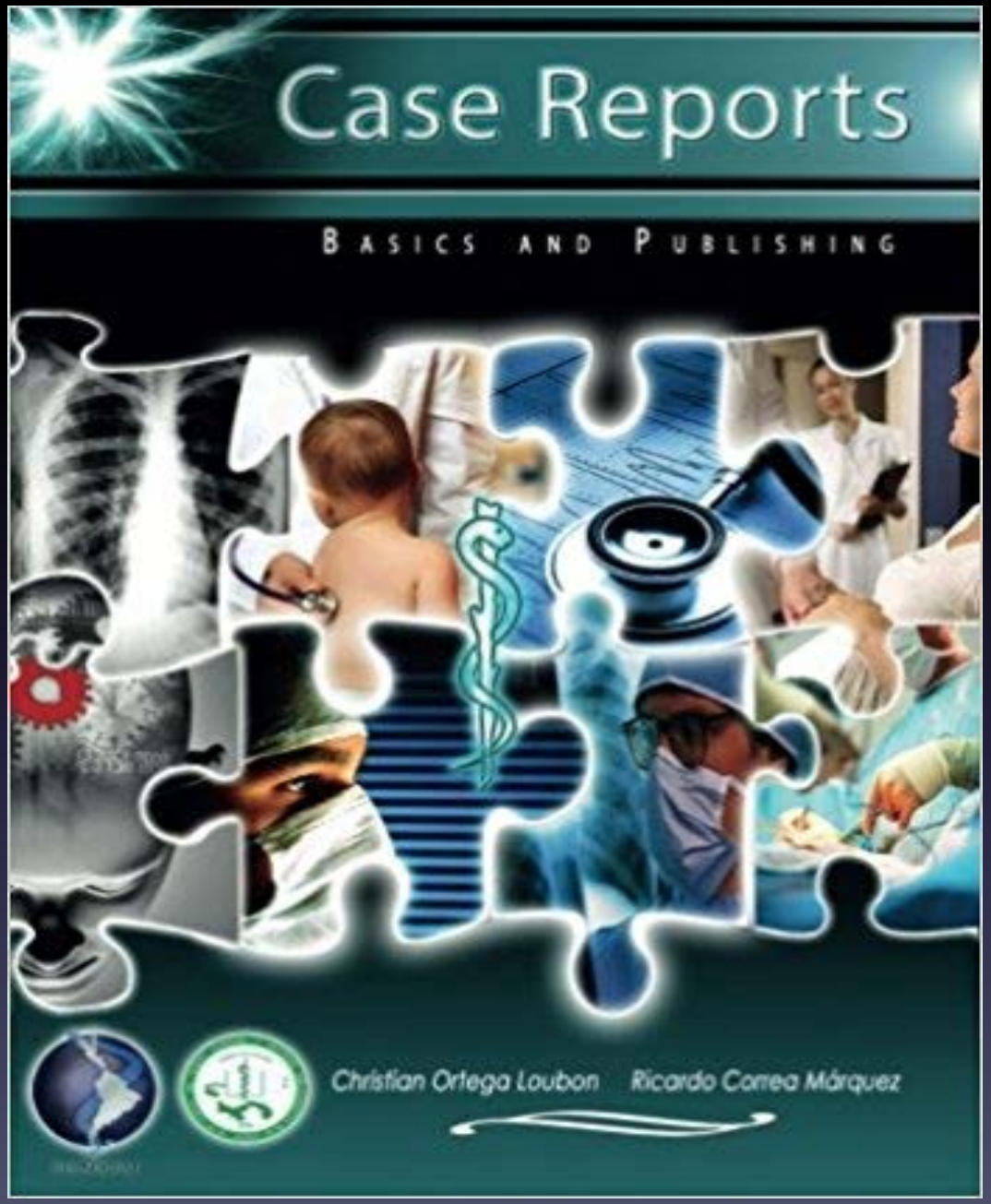
- 250 ug Stim test was done and peak cortisol was 11.6 ug/dl
- Basal ACTH < 5
- Total T, Free T4, IGF-1 wnl
- Which of the following studies would you get next?
- A. Pituitary MRI
- B. ITT
- C. 1 ug cosyntropin stimulation test
- D. Renin level

- Pituitary MRI is normal
- Which of the following studies would you get next?
- A. Measurement of long chain fatty acids
- B. 21 Hydroxylase antibodies
- C. Synthetic glucocorticoid screen
- D. 17 Hydroxyprogestone (Congenital Adrenal hyperplasia)

- Synthetic GC screen negative
- Two weeks later the initial visit, the patient's mother calls you and finds what in his drawer?
  - Opoid

    ??? Does he really have adrenal insufficiency

    ??? Should you treat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