Adrenal Disorders: Adrenal Insufficiency, Cushing's Syndrome and Hyperaldosteronism

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Disclosure

- Disclosures: I have no conflicts of interest to report.

FOREWORD BY ABRAHAM VERGHESE

WHEN BREATH BECOMES

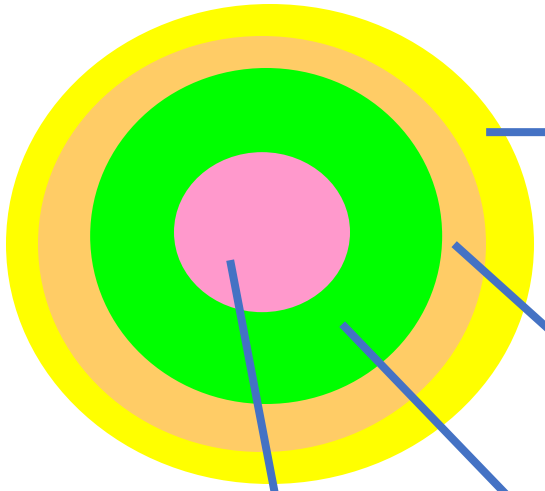
air

PAUL KALANITHI

Learning Objectives

- Review the clinical features and investigations of cortisol excess (Cushing's) and cortisol deficiency (Addison's disease)
- Review mineralocorticoid excess/deficiency
- Review principles of replacement therapy

Adrenals



Cortex

Zona Glomerulosa

Mineralocorticoids (Aldosterone)

Na+, K+ and water homeostasis

Zona Fasciculata

Glucocorticoids (Cortisol)

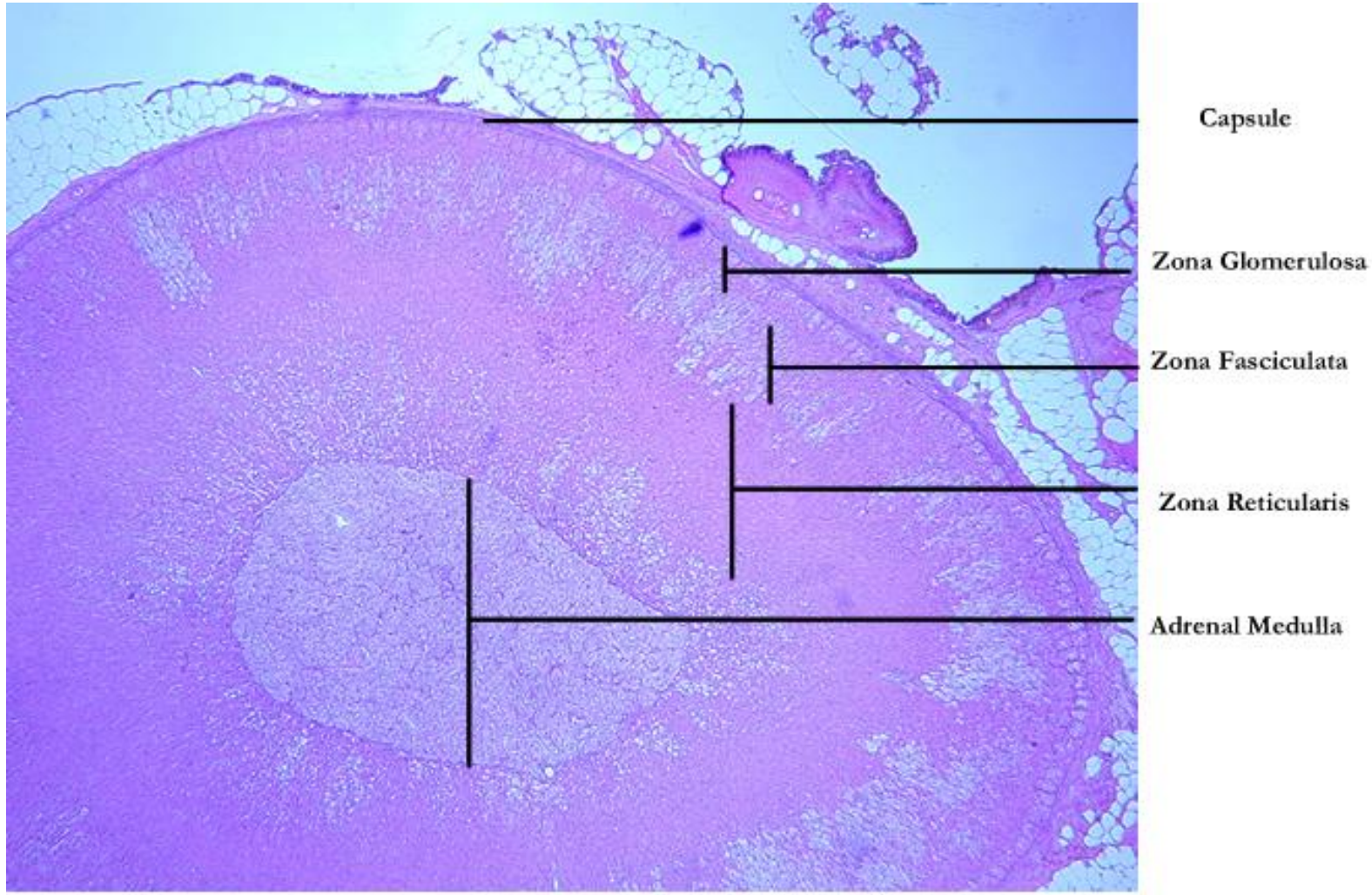
Glucose homeostasis and many others

Zona Reticularis

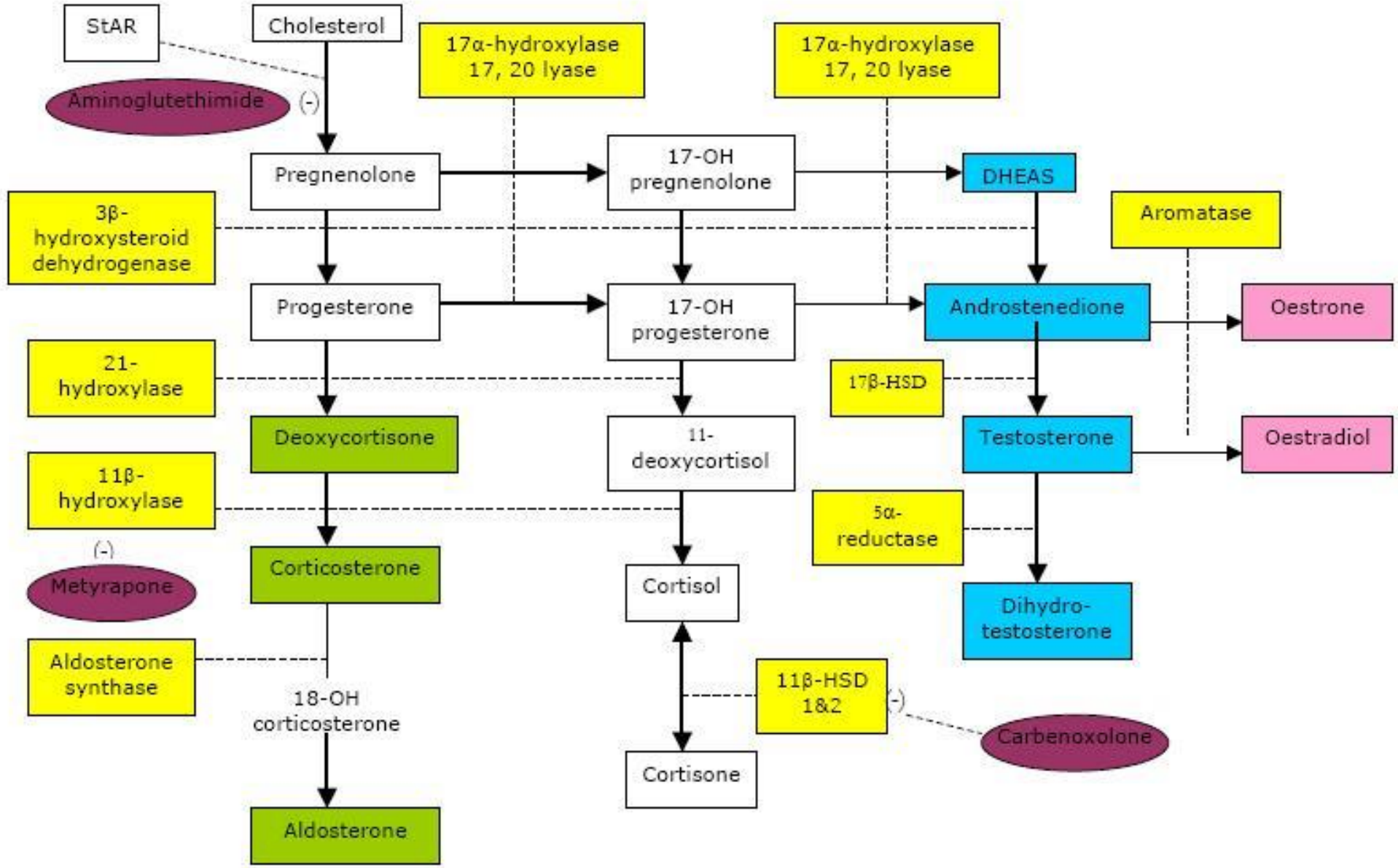
Sex steroids (androgens)

Medulla: "Catecholamines"

Epinephrine, Norepinephrine, dopamine



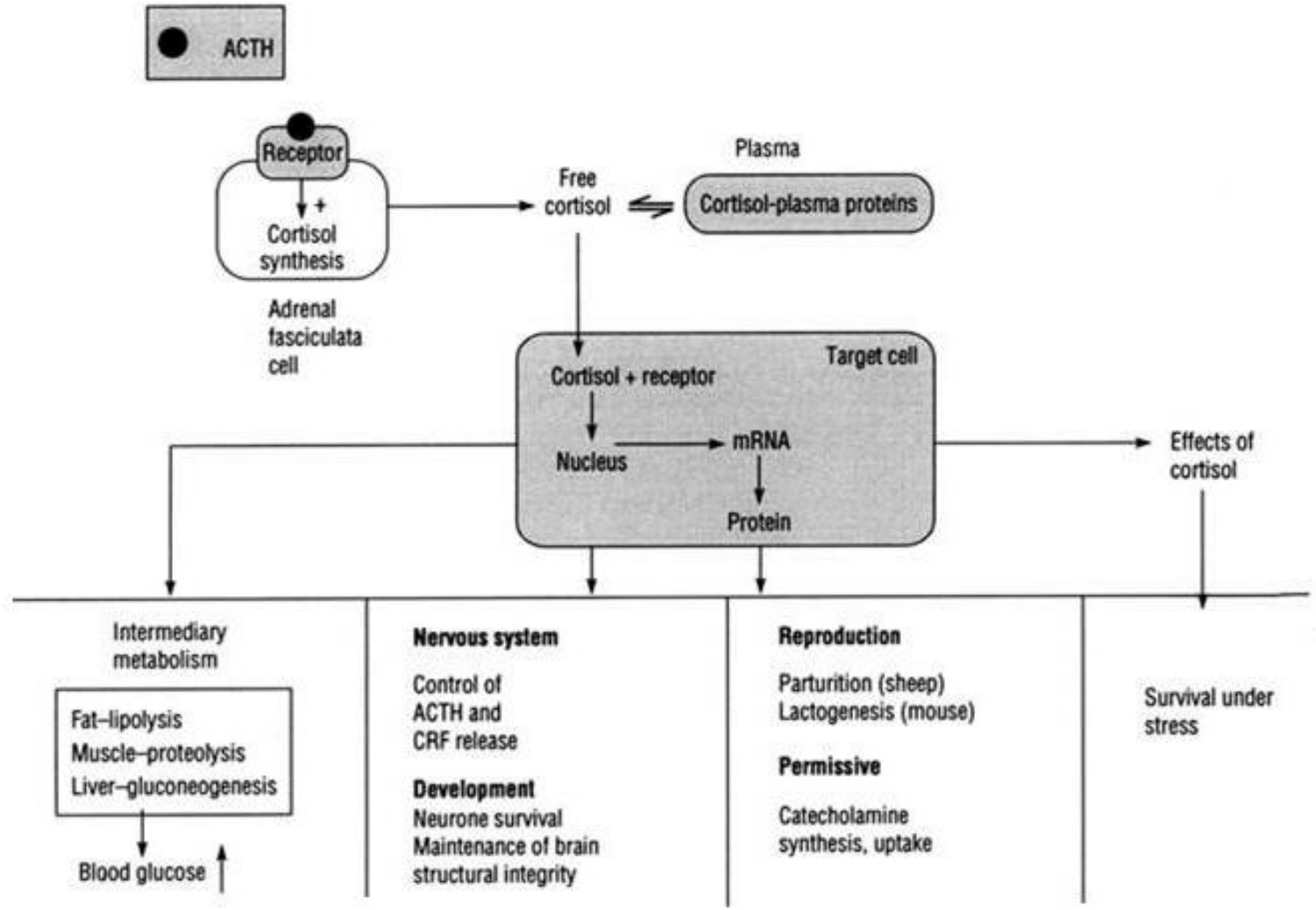
Adrenal Gland (40x)


StAR
Cholesterol
17α-hydroxylase 17, 20 lyase
17α-hydroxylase 17, 20 lyase
Aminoglutethimide
(-)
Pregnenolone
17-OH pregnenolone
DHEAS
3β-hydroxysteroid dehydrogenase
Aromatase
Progesterone
17-OH progesterone
Androstenedione
Oestrone
21-hydroxylase
17β-HSD
Deoxycortisone
11-deoxycortisol
Testosterone
Oestradiol
11β-hydroxylase
5α-reductase
(-)
Metyrapone
Corticosterone
Cortisol
Dihydro-testosterone
Aldosterone synthase
11β-HSD 1&2
(-)
18-OH corticosterone
Carbenoxolone
Cortisone
Aldosterone

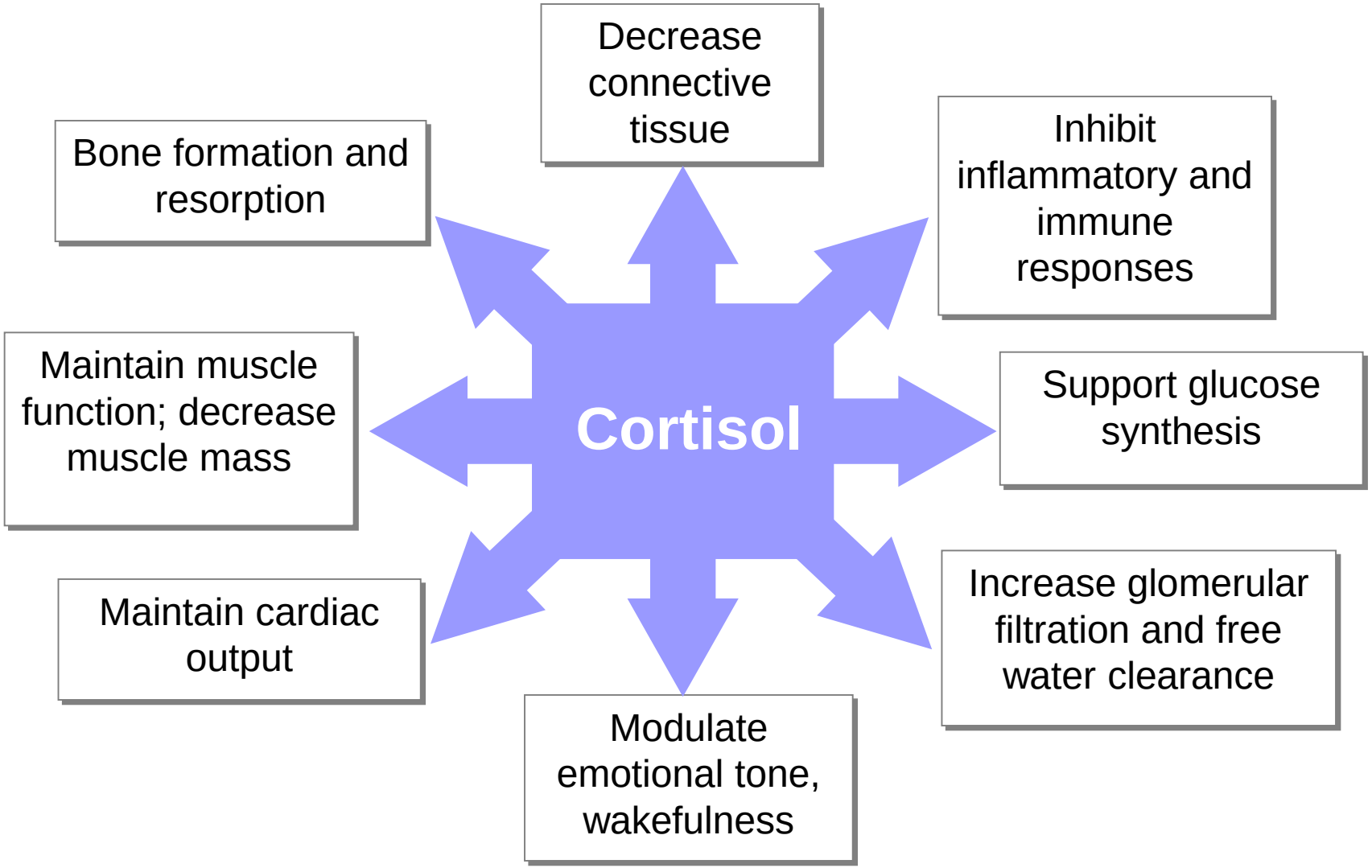
Adrenal cortex diseases

Glucocorticoids	Mineralocorticoids	Androgens
<u>Cushing Syndrome:</u> **- primary:** autonomous adrenal cortisol production - **central:** increased stimulation of adrenal cortisol production (ACTH)	<u>Primary hyperaldosteronism:</u> autonomous adrenal aldosterone production	<u>Hyperandrogenism</u>: In females only: signs of male hormone excess
<u>Adrenal insufficiency:</u> **- primary:** destruction of zona fasciculata or steroidogenesis enzymatic defect - **central:** inadequate stimulation of adrenal cortisol production (ACTH)	<u>Mineralocorticoid deficiency</u> destruction of zona glomerulosa or steroidogenesis enzymatic defect	<u>Androgen deficiency</u> - inadequate stimulation of adrenal cortisol production (ACTH) - destruction of zona reticularis - steroidogenesis enzymatic defect

Glucocorticoids: Cortisol



Cortisol is not just a stress hormone...



What does cortisol do?

Effect on:	How?	Effect of too much cortisol
Blood pressure	• Up-regulates of alpha 1 receptors on arterioles (→ sensitivity to catecholamines) • Binds to aldosterone receptor	Hypertension
Glucose, lipid and protein metabolism	• Increases insulin resistance (→more sugar) • Increases glucose production (→more sugar) • Increases fat and protein catabolism (→decreased lean mass and more sugar)	Diabetes mellitus
Fibroblasts	• Decreases fibroblast activity • Decrease fibril and collagen production	Striae
Bones	• Decreases osteoblast activity → decreases bone formation • Increases bone resorption	Osteoporosis, fractures
Inflammatory and immune responses	• Decreases eosinophils, production of IL-2, leukotrienes, prostaglandines and histamine release • Increases neutrophils	Infection, decreased allergic response
Appetite, sleep	• Modulates sleep, increases appetite	Weight gain

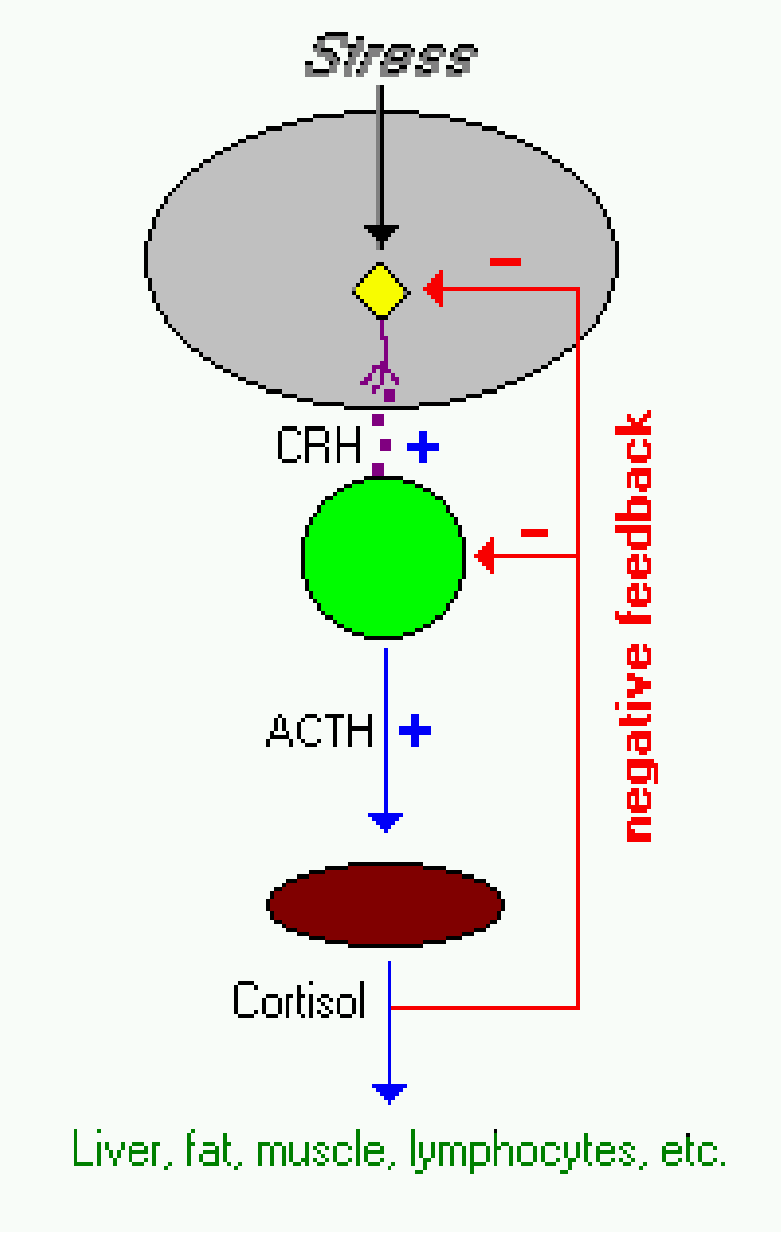
Stress

Adrenal glands are the stress glands of the body.

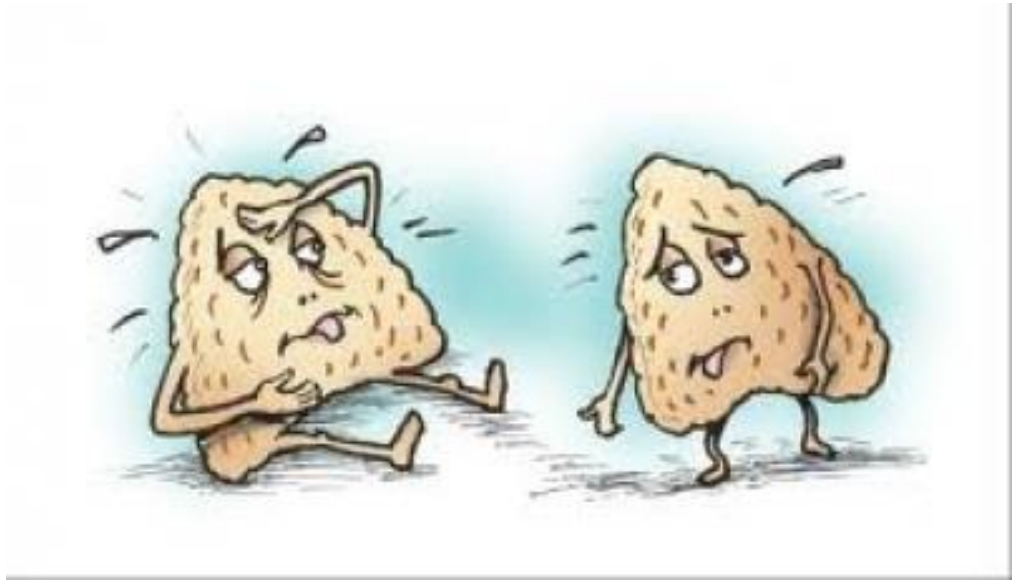
There are four major categories of stress:

1. **Physical stress:** such as overwork, lack of sleep, athletic overtraining.
2. **Chemical stress:** environmental pollutants, allergies to foods, diets high in refined carbohydrates, endocrine gland imbalances.
3. **Thermal stress**: over-heating or over-chilling of the body
4. **Emotional and mental stress**

- During stress cortisol must simultaneously provide more blood glucose, mobilize fats and proteins for a back-up supply of glucose, modify immune reactions, heartbeat, blood pressure, brain alertness and nervous system responsiveness.
- If cortisol level cannot rise in response to these needs, maintaining your body under stress is nearly impossible.



Adrenal Insufficiency



Adrenal insufficiency

- Primary adrenal insufficiency (adrenal gland)
  - autoimmune disease, infiltrative disease, malignancy, medications, hemorrhage,
- Secondary adrenal insufficiency – (pituitary gland or HT)
  - tumor or hypophysitis
  - exogenous steroids

Adrenal insufficiency

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

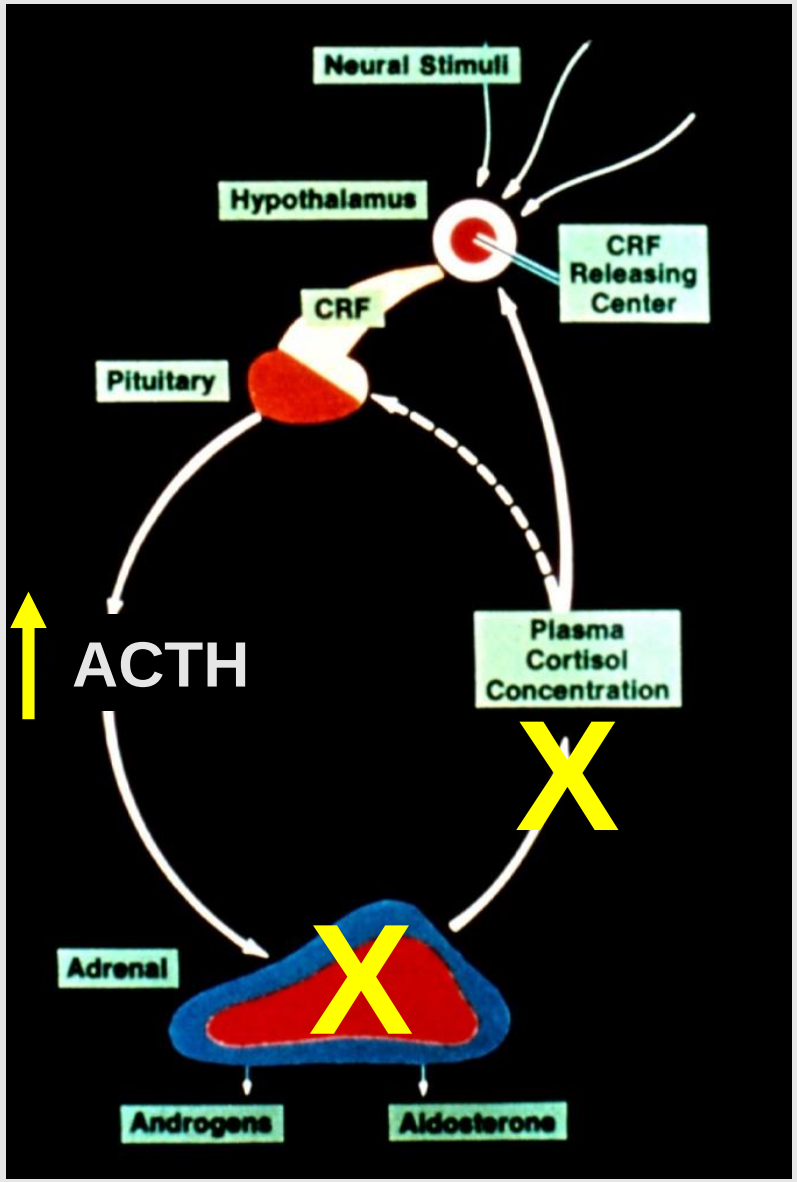
Adrenal insufficiency

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

Causes of primary adrenal insufficiency

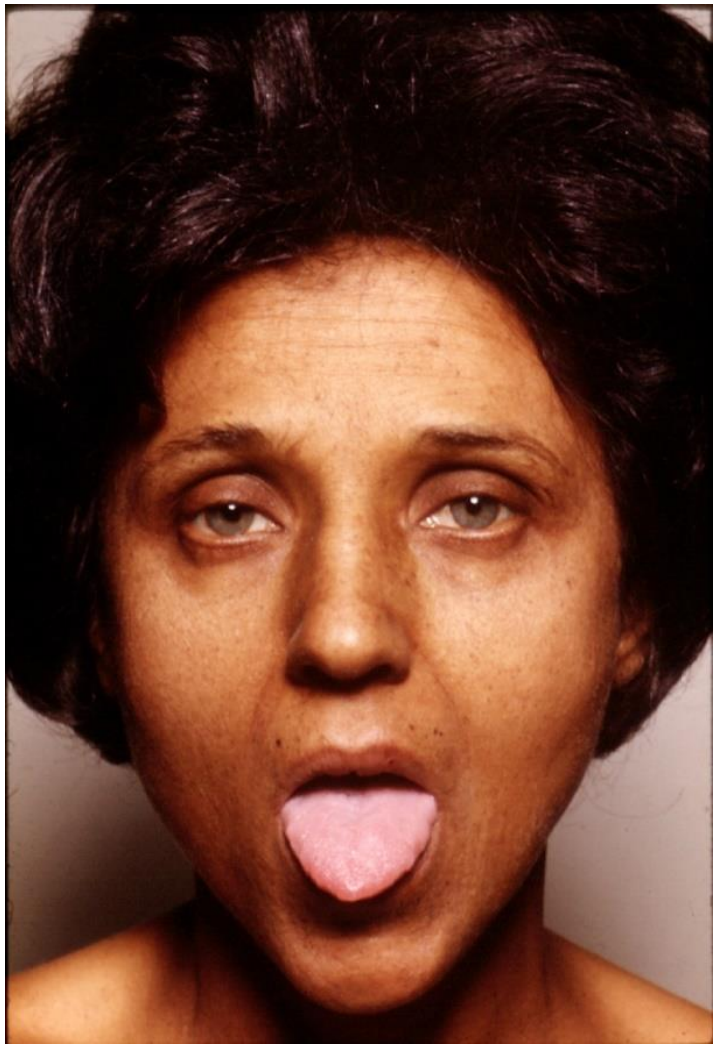
- Autoimmune disease (Addison's disease)
  - 50% of patients have another autoimmune disorder (thyroid disease, vitiligo, type 1 diabetes mellitus, pernicious anemia)
- Infections - HIV, TB, fungal
  - Paracoccidioidomycosis
  - Adrenal glands often calcified
- Infiltrative disease (metastases, lymphoma – bilateral)
- Bilateral hemorrhage
- Bilateral adrenalectomy
- Medications - ketoconazole

Primary adrenal insufficiency
Addison's disease



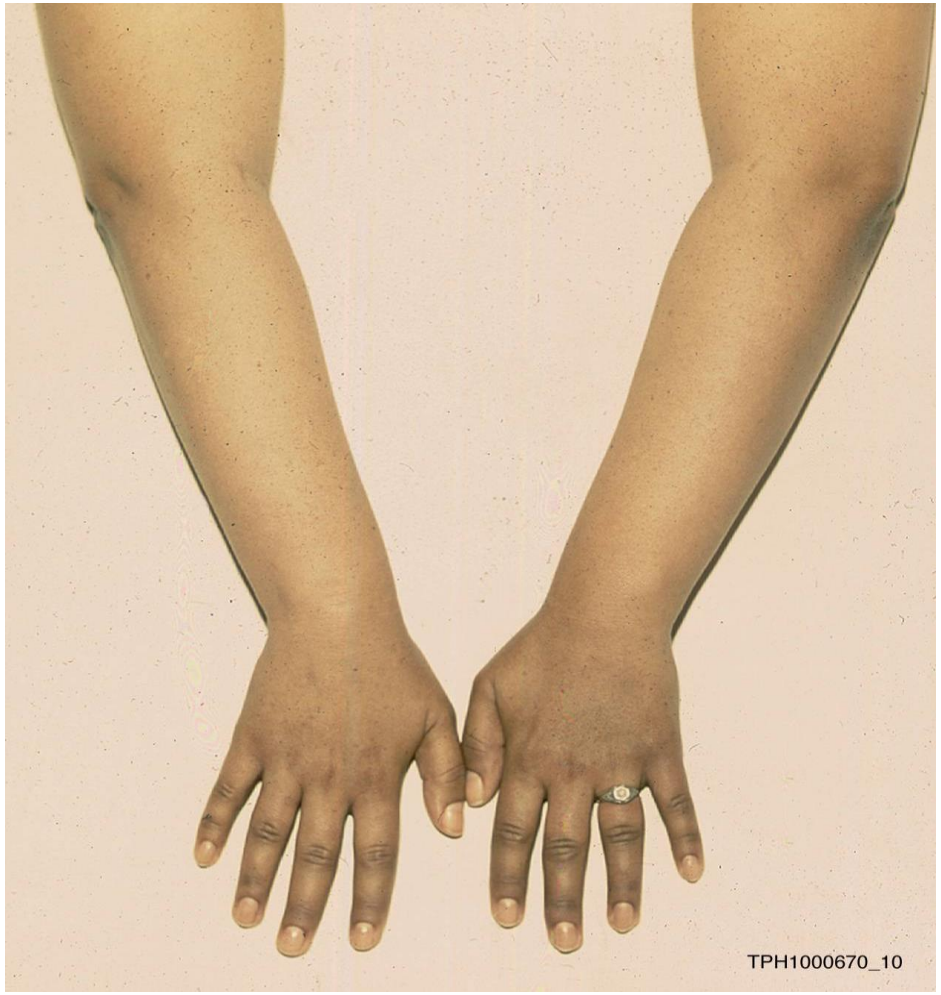
Note: the autoimmune process destroy all layers Of the adrenal cortex

Primary adrenal insufficiency – Too little cortisol

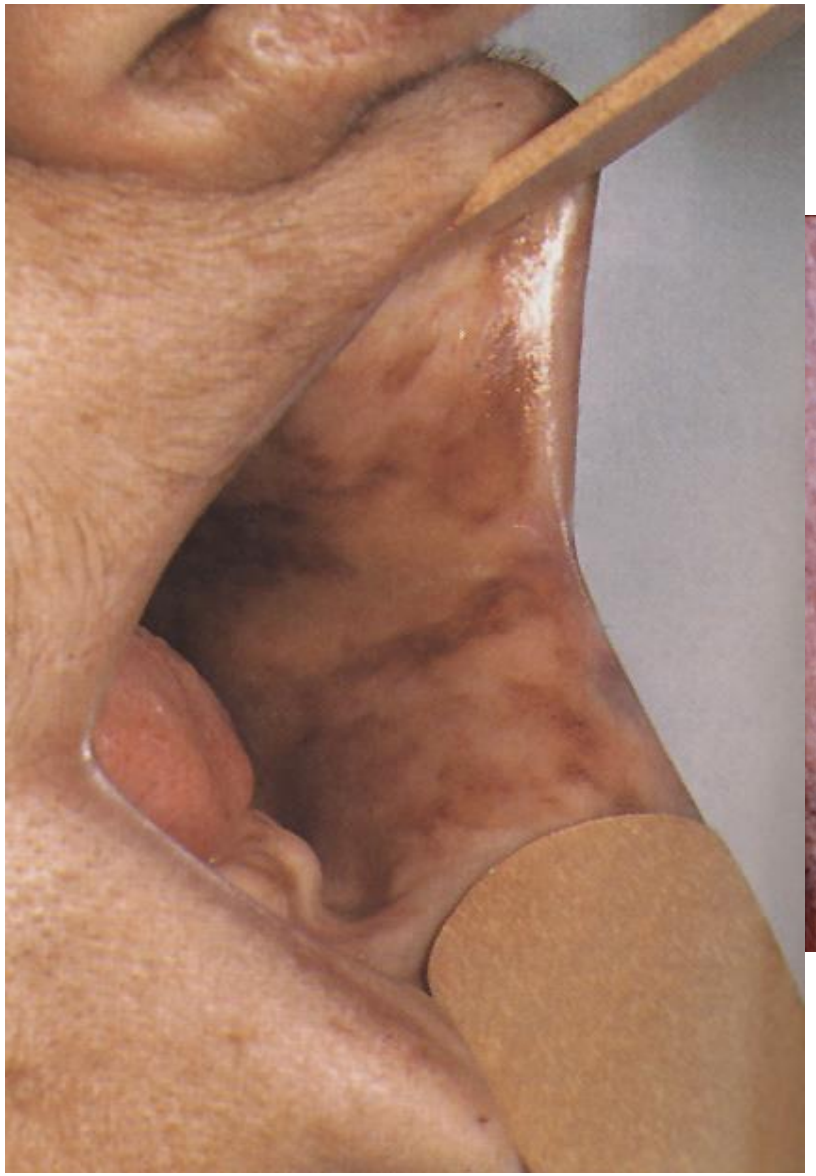


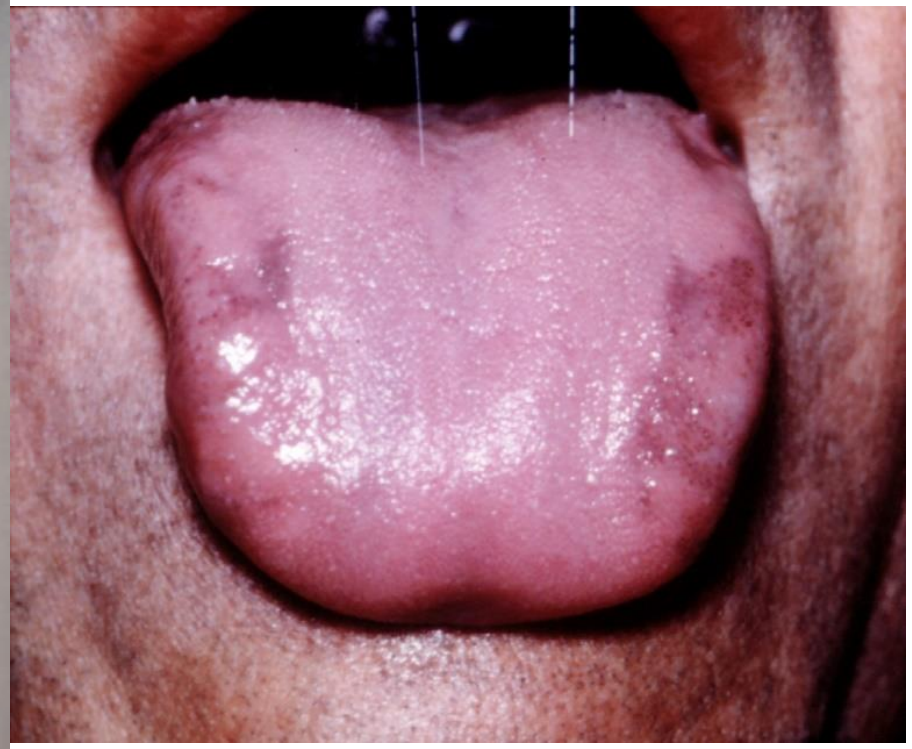
- Fatigue
- Skin darker (stimulation of ACTH production)
- Decreased appetite and nausea
- Dizzy
- Felt like she had the flu

Pigmentation at trauma sites (knuckles, elbows, knees and new scars)



Buccal pigmentation





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

Clinical presentation

Chronic

- Fatigue, muscle aches, arthralgia
- Loss of appetite, nausea, vomiting, weight loss, diarrhea, grumbling abdominal pain
- Postural dizziness
- Na and K
- Eosinophilia
- Hyperchloremic acidosis
- Hyperpigmentation – skin and mucous membranes

Acute

- Usually with unrecognized adrenal insufficiency and intercurrent illness

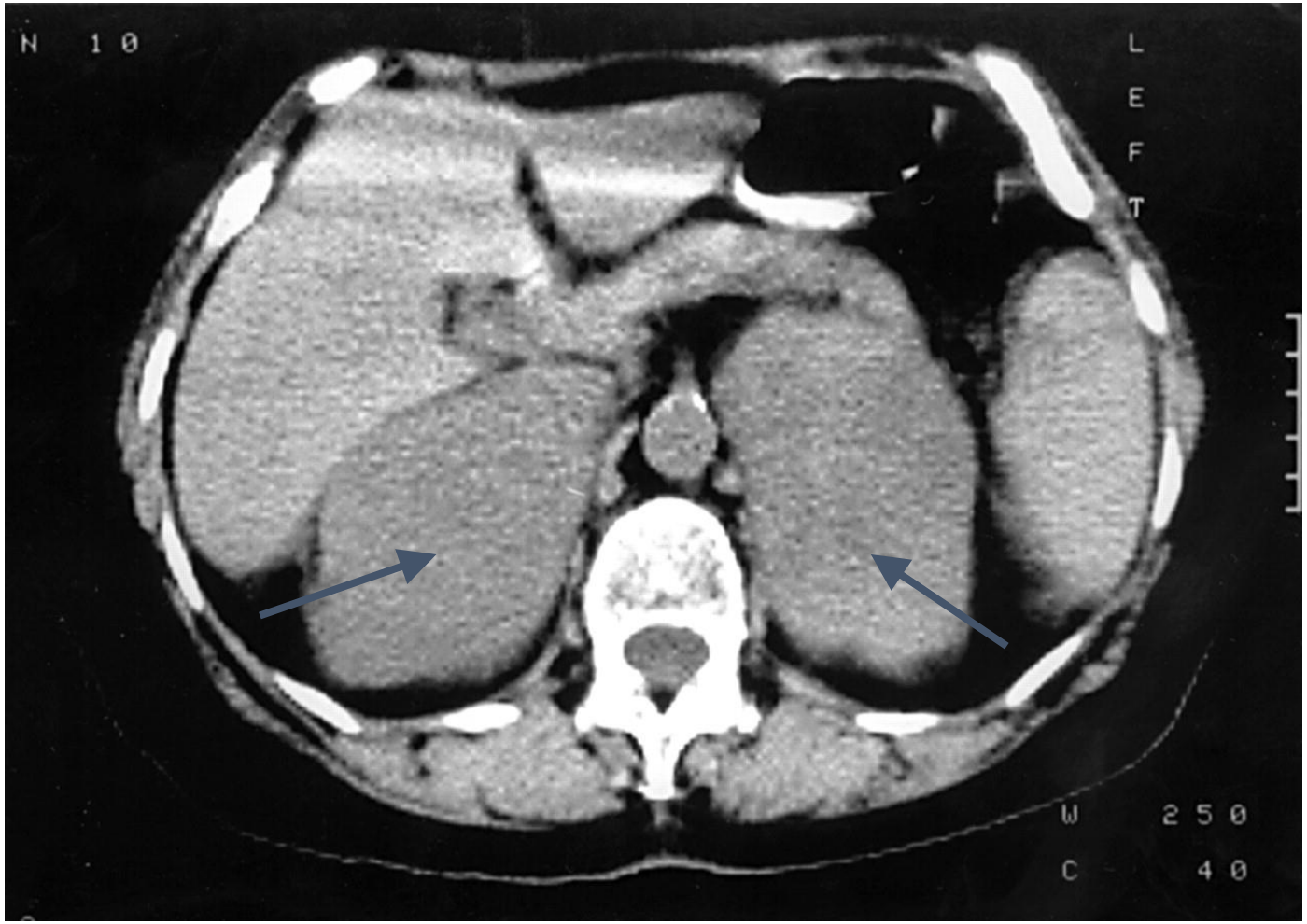
Present with:

- Dehydration and hypotension
- Abdominal pain, nausea and vomiting (acute abdomen)
- Unexplained fever
- Hyponatremia, hyperkalemia
- Eosinophilia

Imaging abnormalities

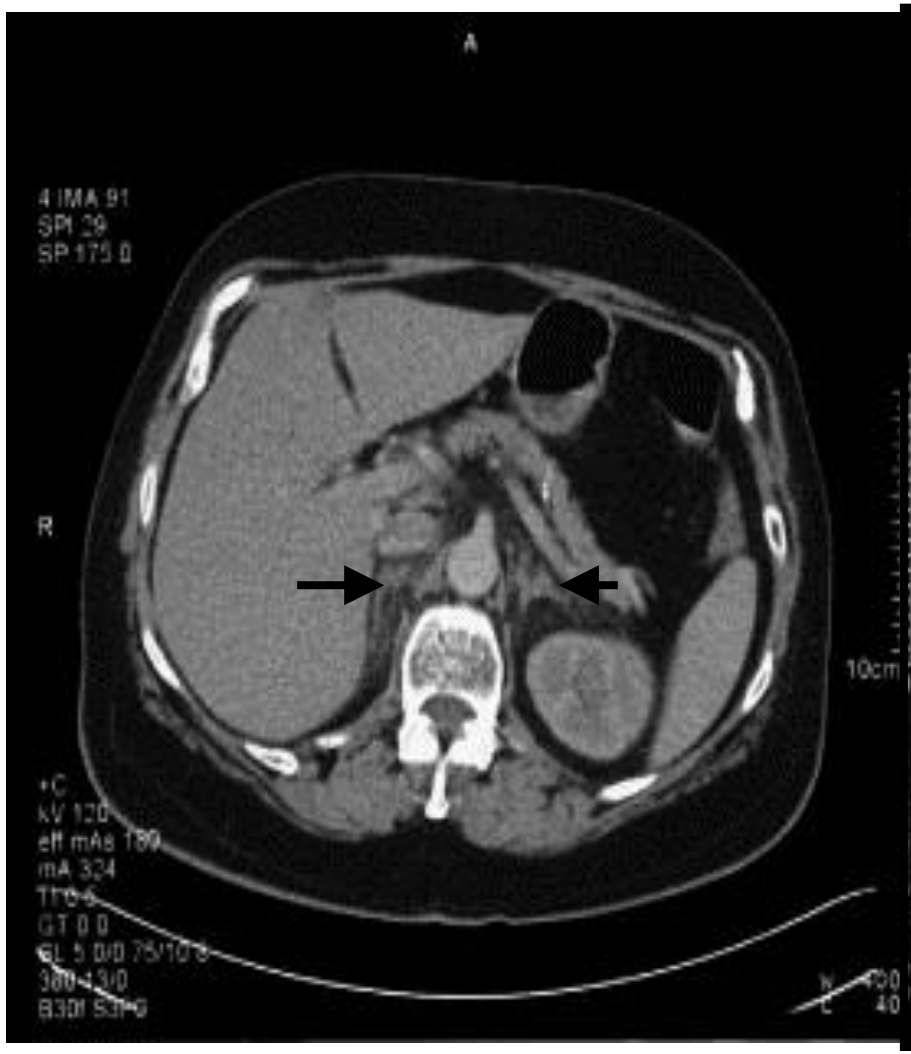
- Primary: bilateral adrenal enlargement or masses particular when enlargement is with the normal contour of the adrenal glands
- Atrophic adrenals
  - Secondary: pituitary or sellar mass
- Calcifications – tuberculosis
- Bleeding- hx of anticoagulation use, malignancy, coagulation disorders
- Tumors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

Adrenal insufficiency due and non-Hodgkin's lymphoma

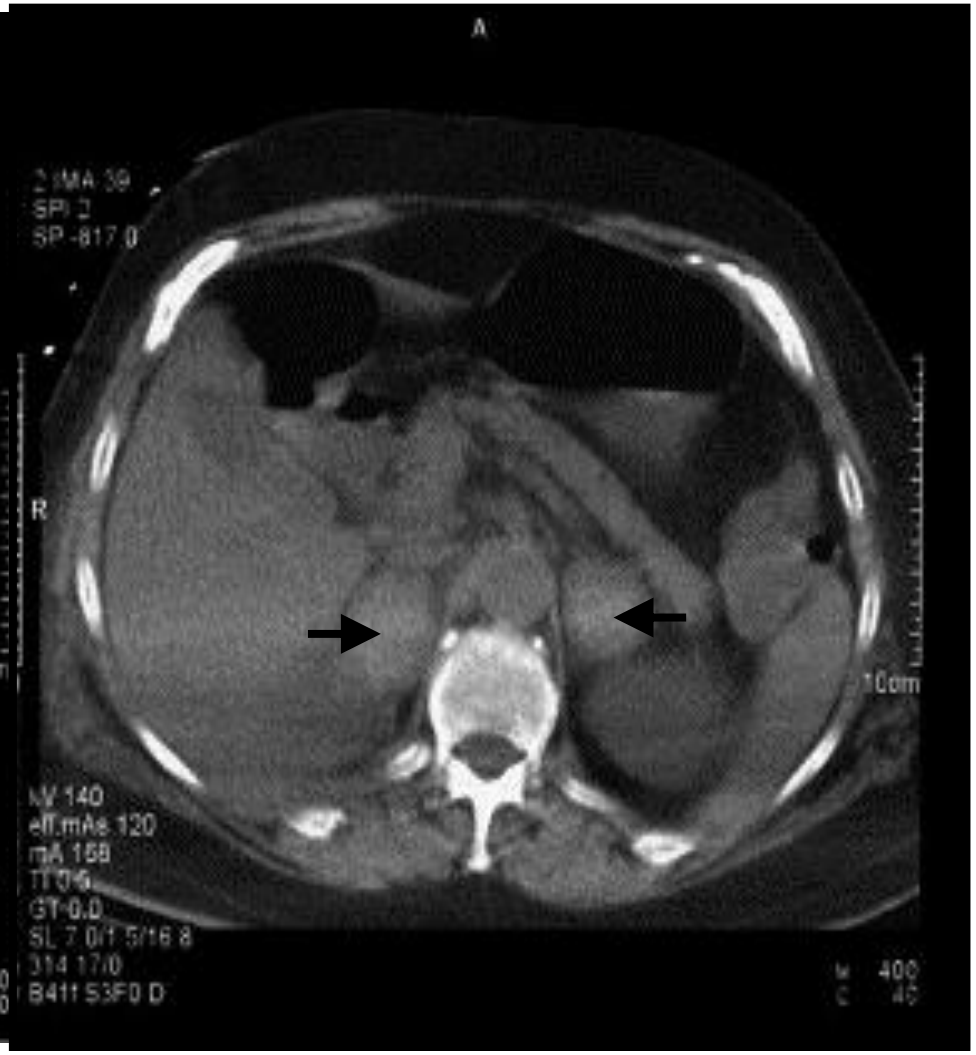


Acute adrenal insufficiency

Normal adrenal glands



Bilateral adrenal hemorrhage following anticoagulation



Causes of Cortisol Deficiency

Most common is iatrogenic (secondary AI)

- 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 Secondary 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
- Metastasis: Pituitary 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

Evaluation for possible adrenal insufficiency

- Morning serum cortisol level is not a good screening test
  - Pulsatility, milder forms of adrenal insufficiency may present with cortisol in lower end normal range
- Cortrosyn stimulation test (synthetic ACTH) used to confirm diagnosis in most cases – maximum cortisol stimulation to ≥ 18 µg/dL is a normal result
- Low serum cortisol in combination with elevated ACTH is diagnostic of primary adrenal insufficiency

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

Treatment of chronic adrenal insufficiency

- Glucocorticoids
- 10-12mg/ m2 (BSA)
- Usually 15-20mg divided into 2 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

Treatment of chronic adrenal insufficiency

- Mineralocorticoid replacement (primary AI only): Fludrocortisone
  - 0.05-0.1 mg daily
  - normal electrolytes
  - absence of edema
  - absence of postural hypotension

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!!**

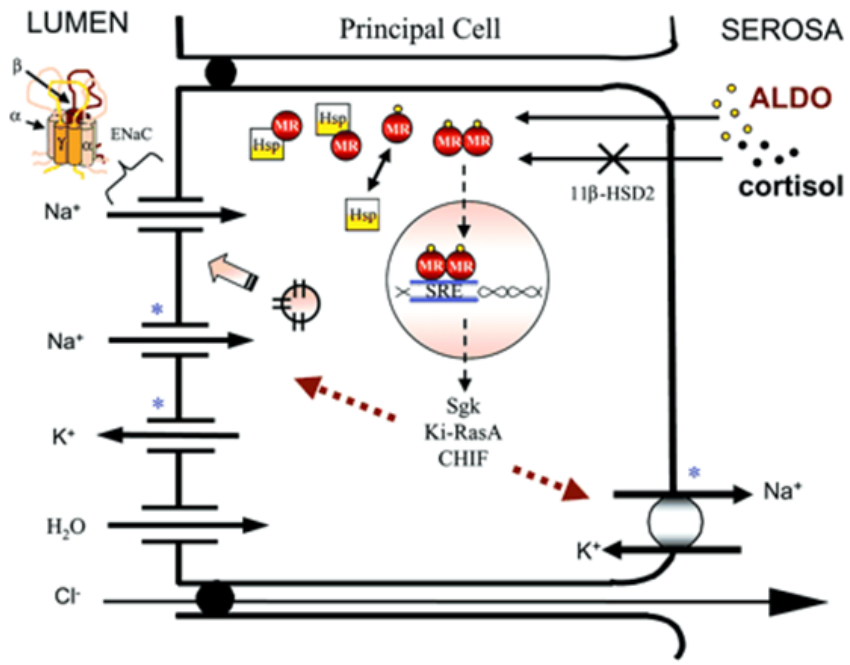
Fludrocortisone (Flurinef)

Mechanism

- Aldosterone analog
- Increase renal tubular reabsorption of sodium and renal tubular excretion of potassium

Clinical use

- Primary adrenal insufficiency



Booth R E et al. Advan in Physiol Edu 2002;26:8-20

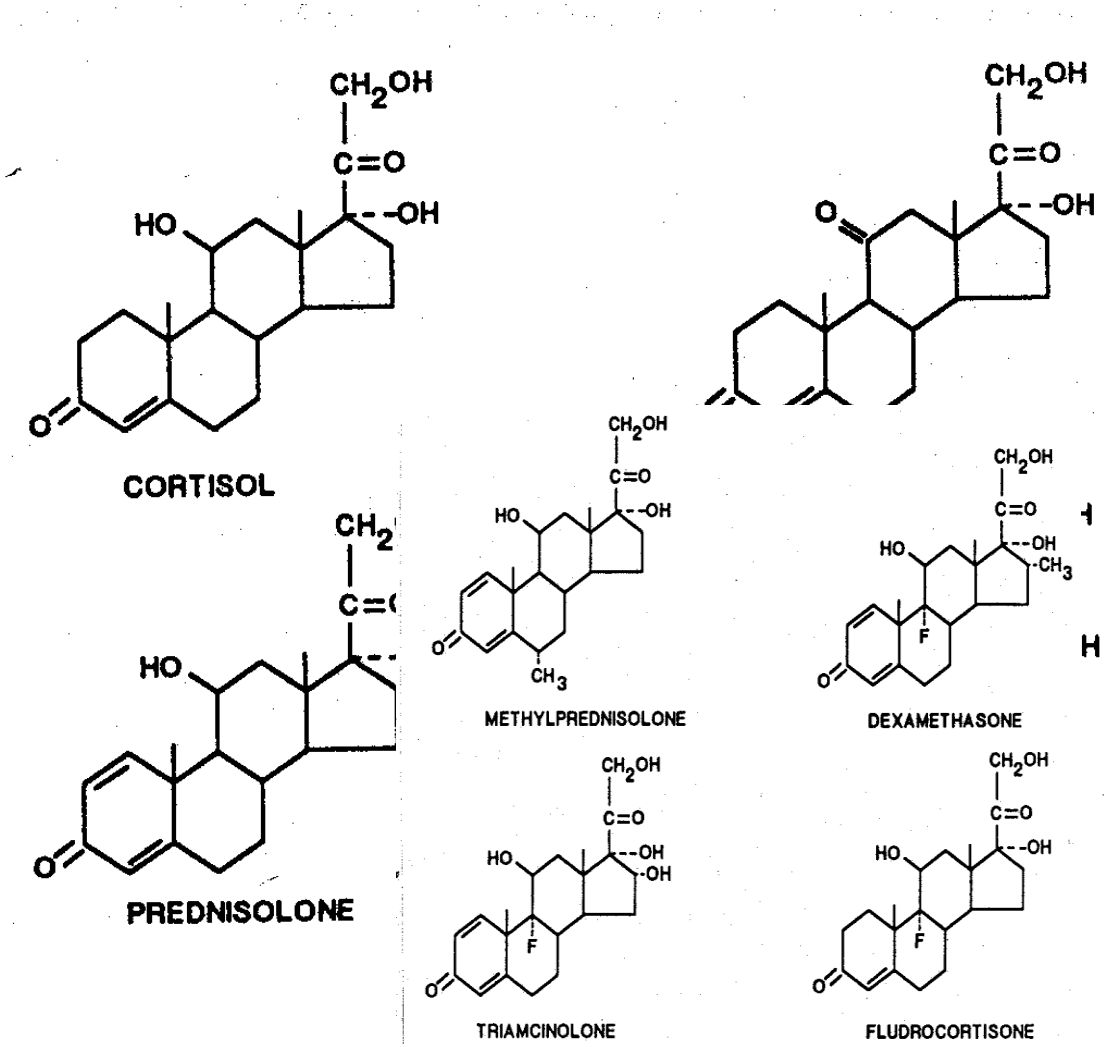
Side effects/contraindications

- Hypokalemia
- Edema
- Hypertension

Other

- none

Synthetic Steroids



- Actions are identical to endogenous steroids
- Different t1/2 may be clinically useful
- Different solubilities
- Varying degrees of mineralocorticoid vs. glucocorticoid vs. androgenic action

Synthetic Steroid Potencies

	Anti-inflam	Glucocort	Mineralo
• Hydrocortisone	1	1	1
• Prednisone	3	4	0.75
• Methylprednisone	6	4	0.5
• Fludrocortisone	0	0	125
• Triamcinolone	5	4	0
• Dexamethasone	26	17→?	0

Note: hydrocortisone (cortisol) has been arbitrarily assigned a potency level of 1 in each of the 3 categories above. For e.g. – prednisone has 4 times glucocorticoid properties compared to cortisol, and 0.75 mineralocorticoid properties compared to cortisol, and 3 times the anti-inflammatory properties of cortisol.

Impact of steroid excess

- Exogenous steroid effects - same as endogenous Cushing's.
- Weight gain
- Acne
- Hypertension
- Diabetes
- Osteoporosis
- Proximal myopathy
- Thin skin / bruising
- Infections
- Depression / Psychosis
- Side effects peculiar to exogenous steroids
- Avascular necrosis of the hips, knees, shoulders
- Cataracts

Case

- 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)

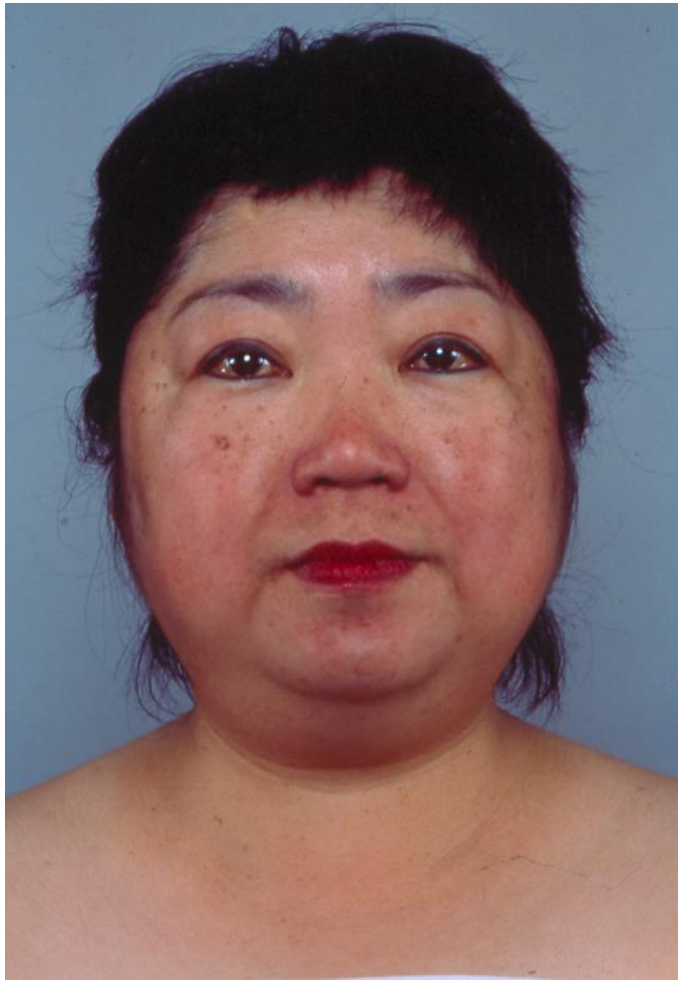
- Synthetic GC screen negative

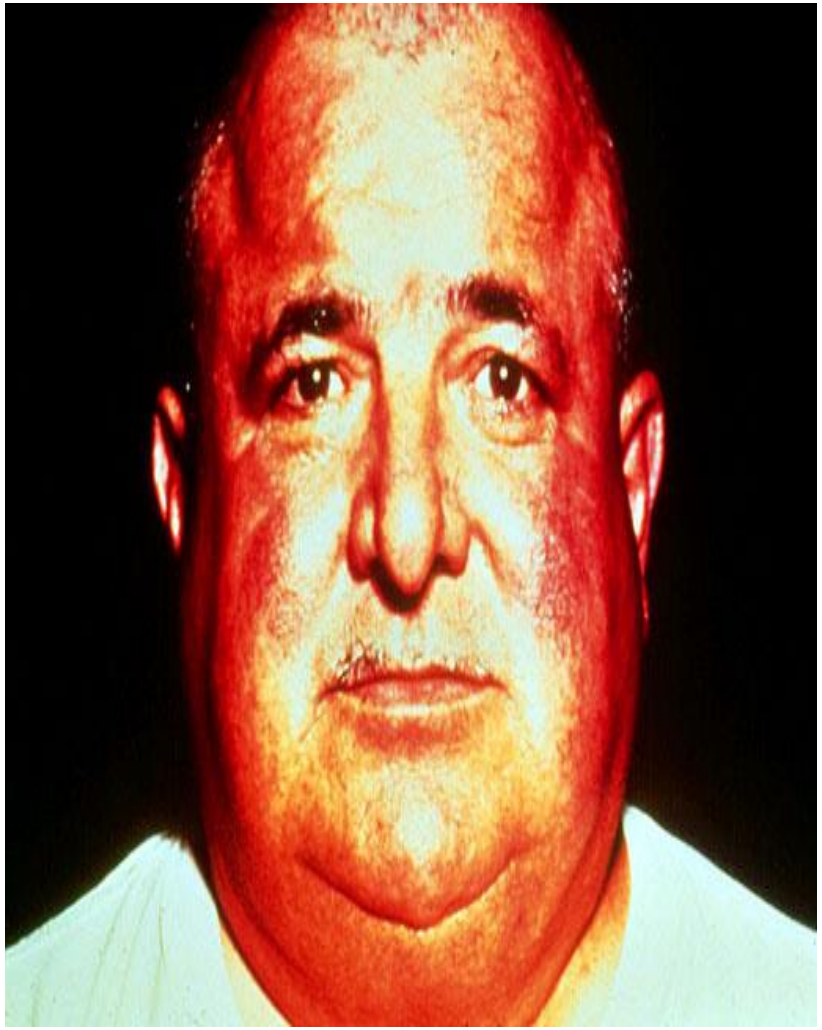
  - Two weeks later the initial visit, the patient's mother calls you and finds what in his drawer?
    - Opioid

      ??? Does he really have adrenal insufficiency

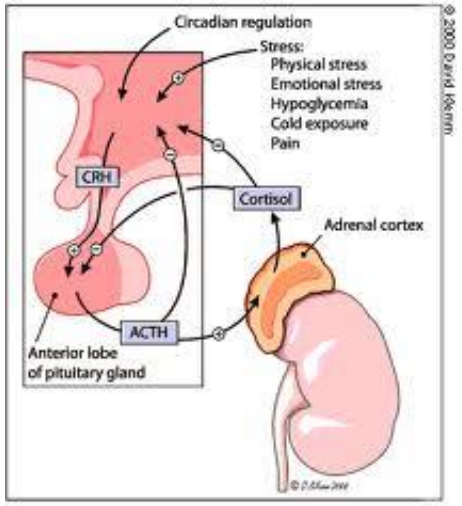
      ??? Should you treat

Cushing's Syndrome – too much cortisol





Hypercortisolism

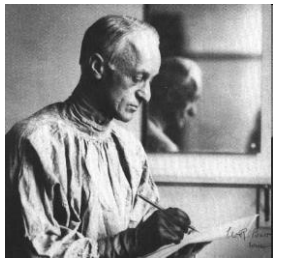


Causes of Hypercortisolism	
Etiology	Frequency
Pituitary adenoma	65%-70%
Ectopic ACTH	10%-15%
Adrenal adenoma	10%
Adrenal cancer	5%-10%

Hypercortisolism

- ACTH dependent Cushing's syndrome:
  - Pituitary adenoma
  - Ectopic ACTH production (often in the lung)
- ACTH independent Cushing's syndrome:
  - Adrenal adenoma
  - Adrenal cancer
  - Adrenal hyperplasia
- Other causes of hypercortisolism:
  - Depression
  - Alcoholism
  - Obesity, and stressful situation

Cushing's Syndrome – too much cortisol



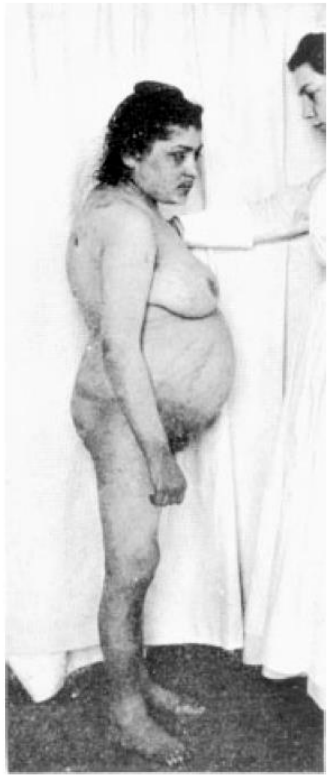
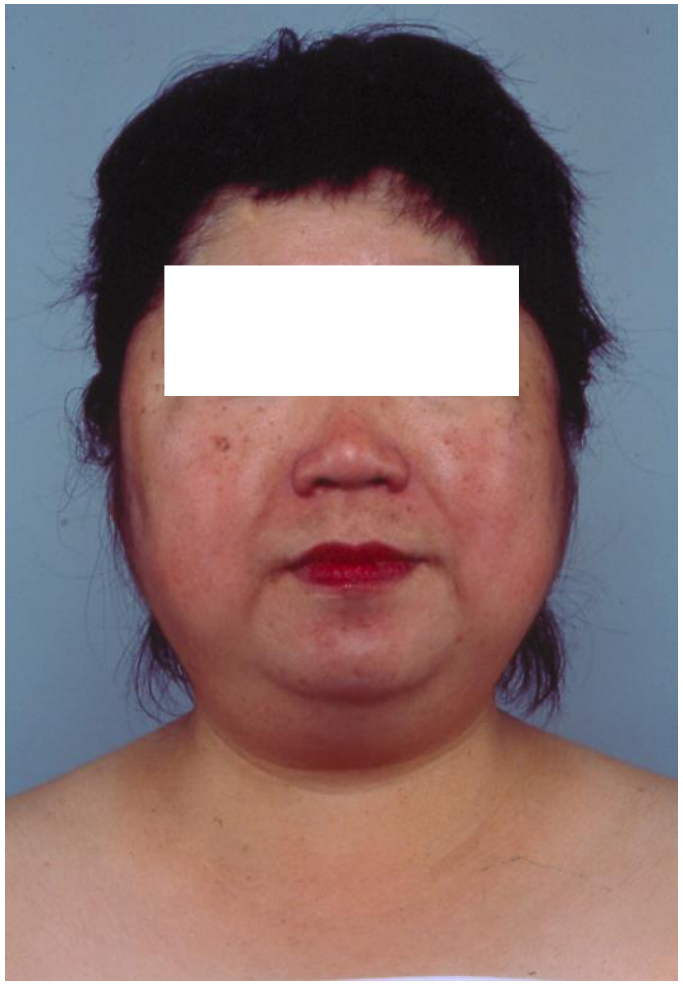


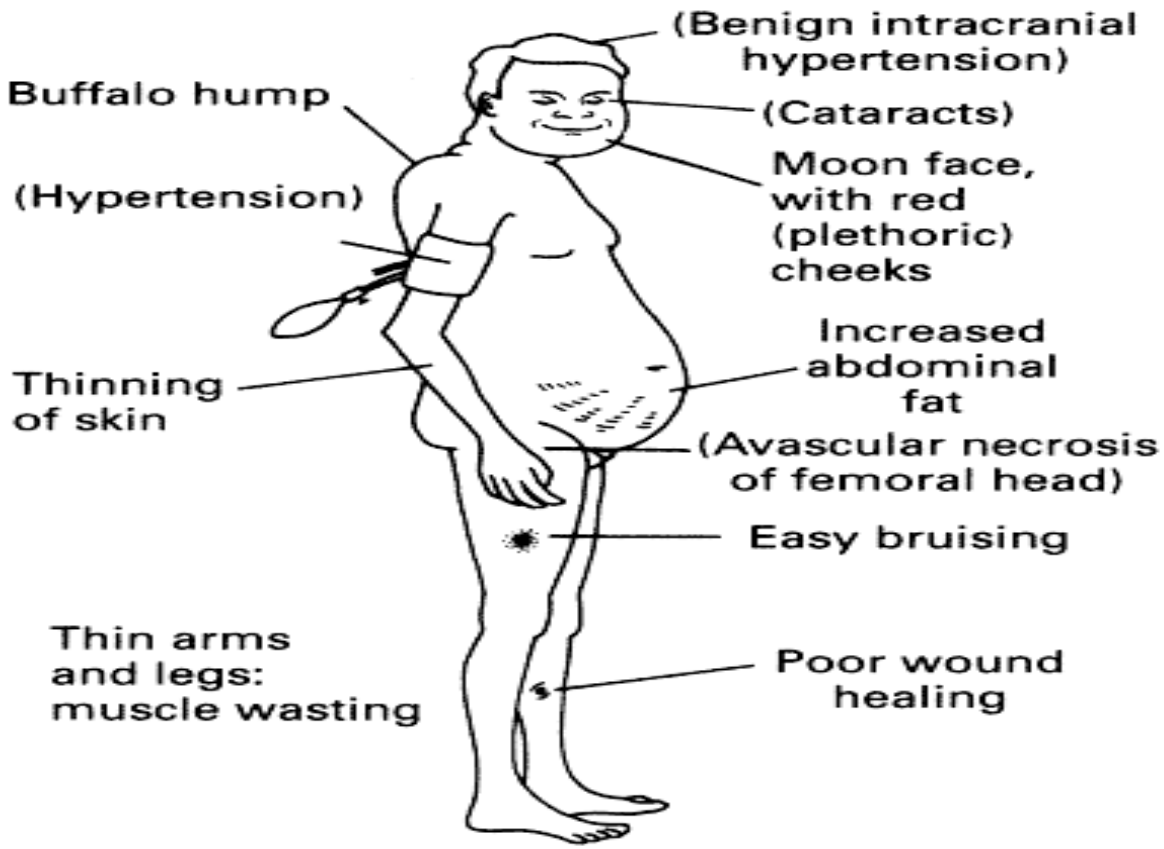
Fig. 3. Minnie G. Harvey Cushing's patient. Reported in The Pituitary Body and its Disorders, 1912.



- Harvey Cushing first described a patient with hypercortisolemia in 1932

- Observed signs/symptoms:
  - Weight gain
  - Muscle weakness
  - Irregular menstrual cycles
  - Headache and vision changes
  - Large round face
  - Striae
  - Insomnia
  - Inability to concentrate
  - Fits of irritability alternating with periods of depression

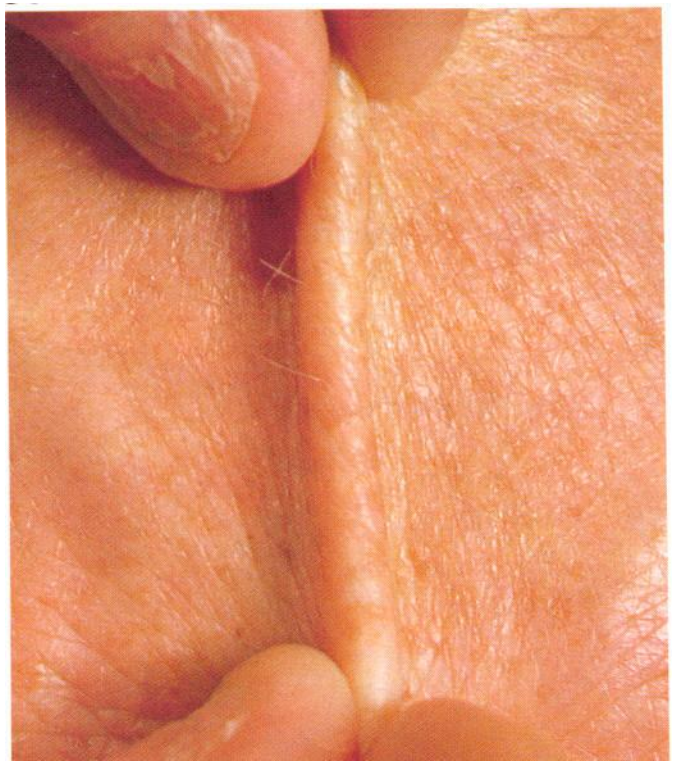
Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)



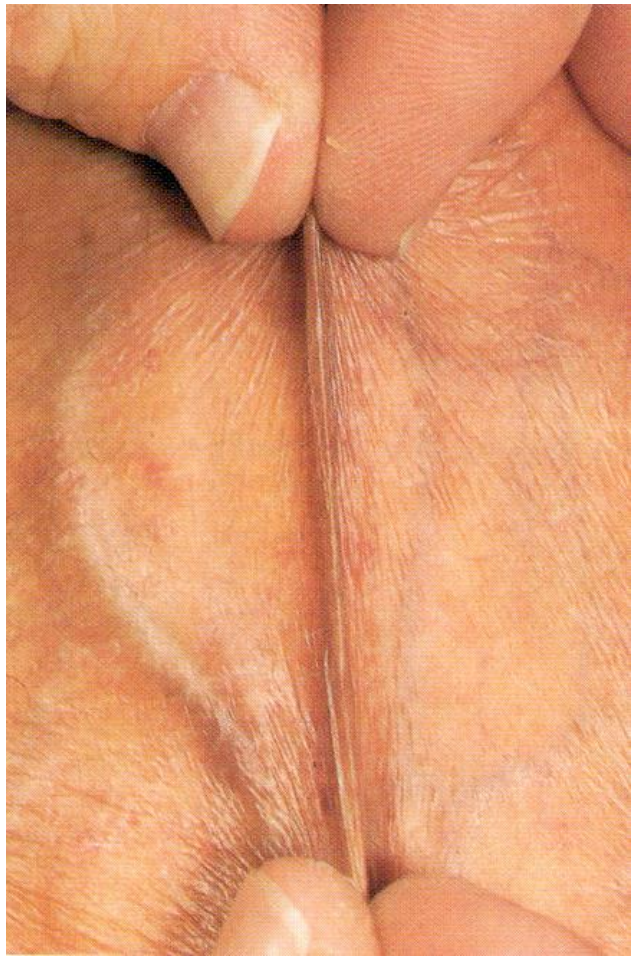
Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

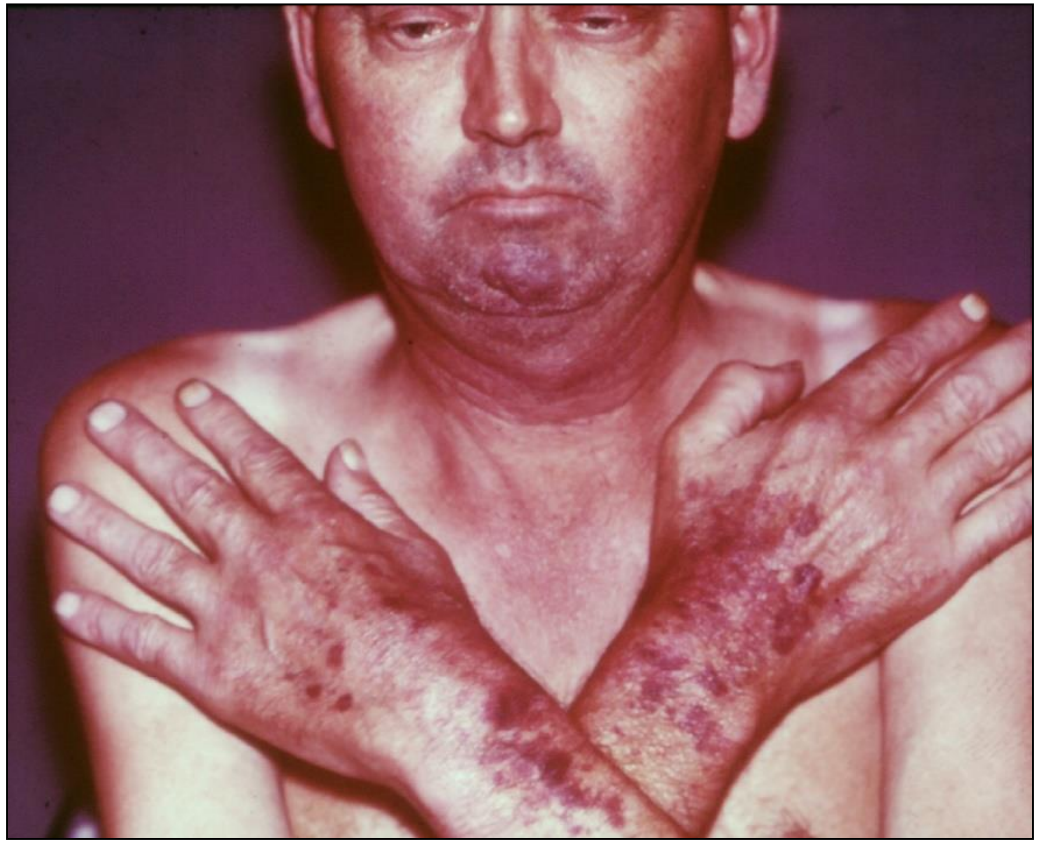
Cushing's Syndrome – thin skin



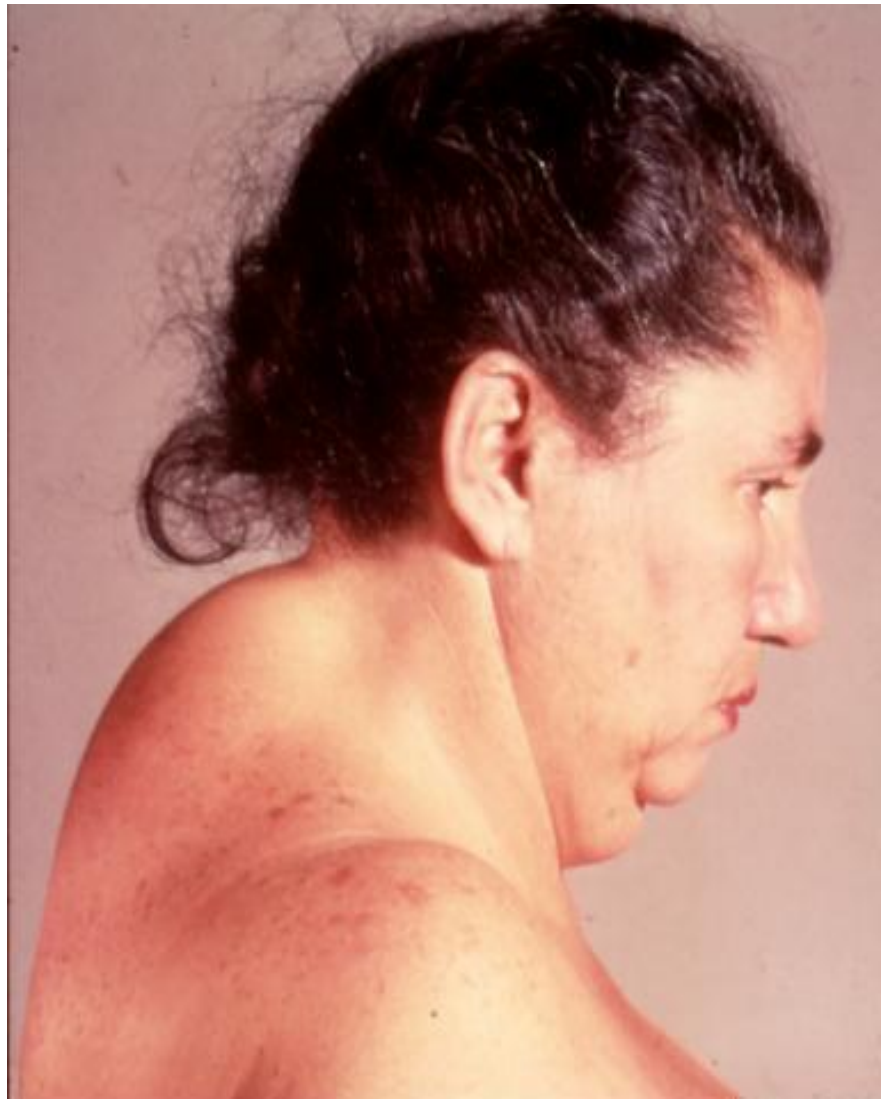
No Cushing's



Cushing's

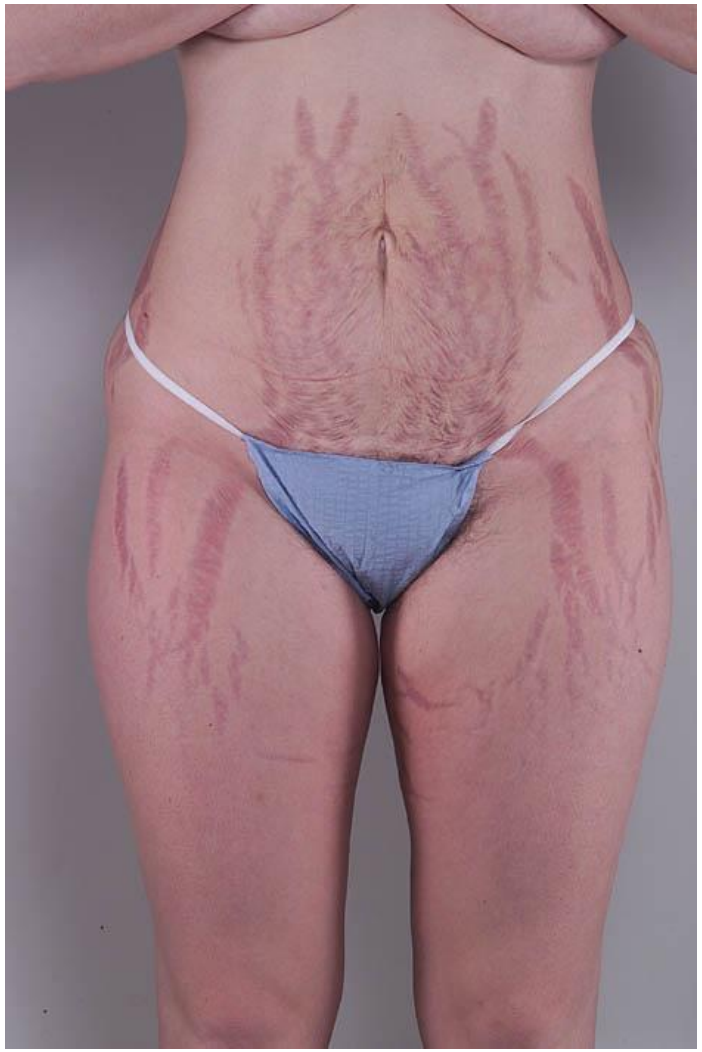


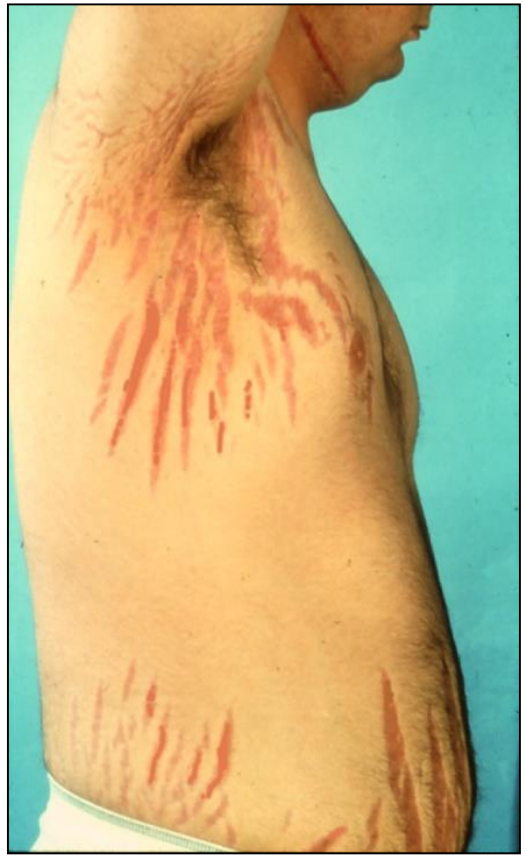
Bruising



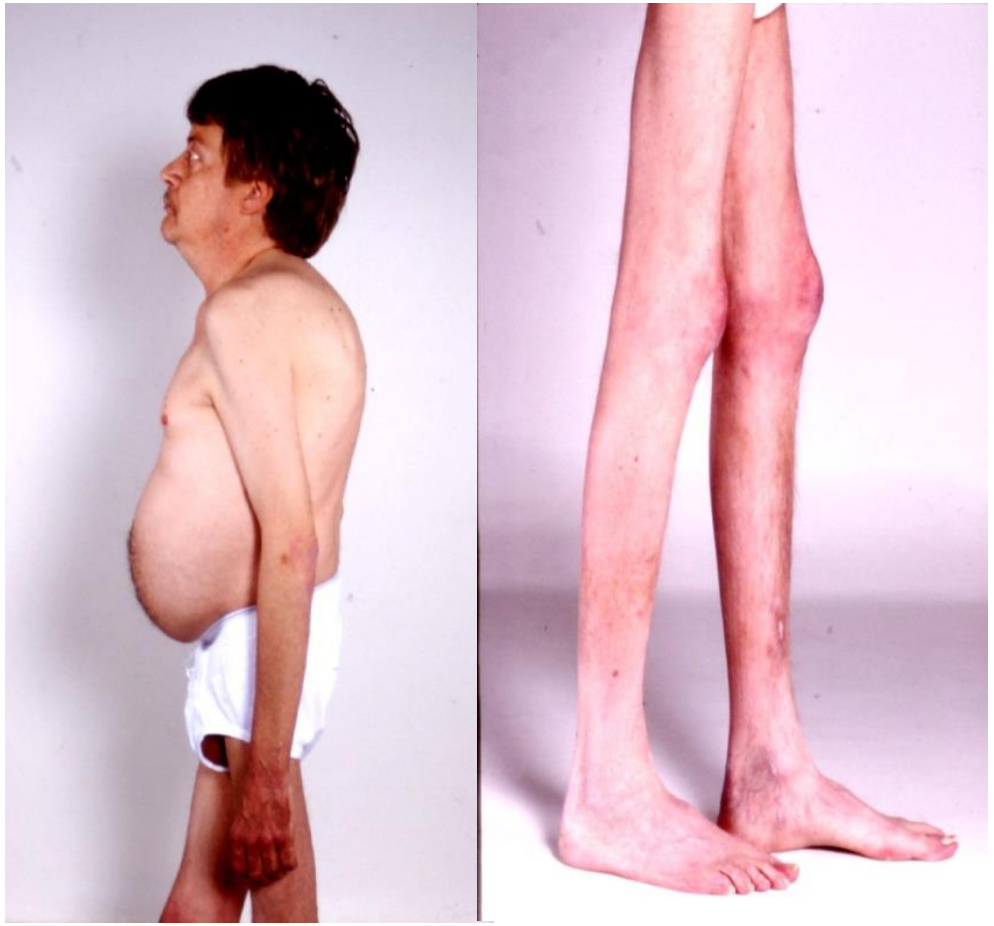
Dorsocervical fat pad

Striae

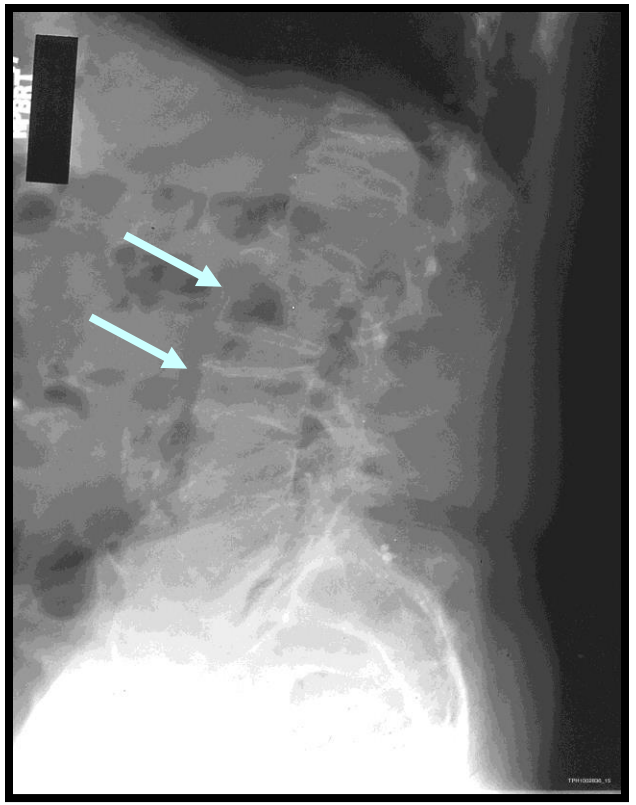




Cushing's syndrome



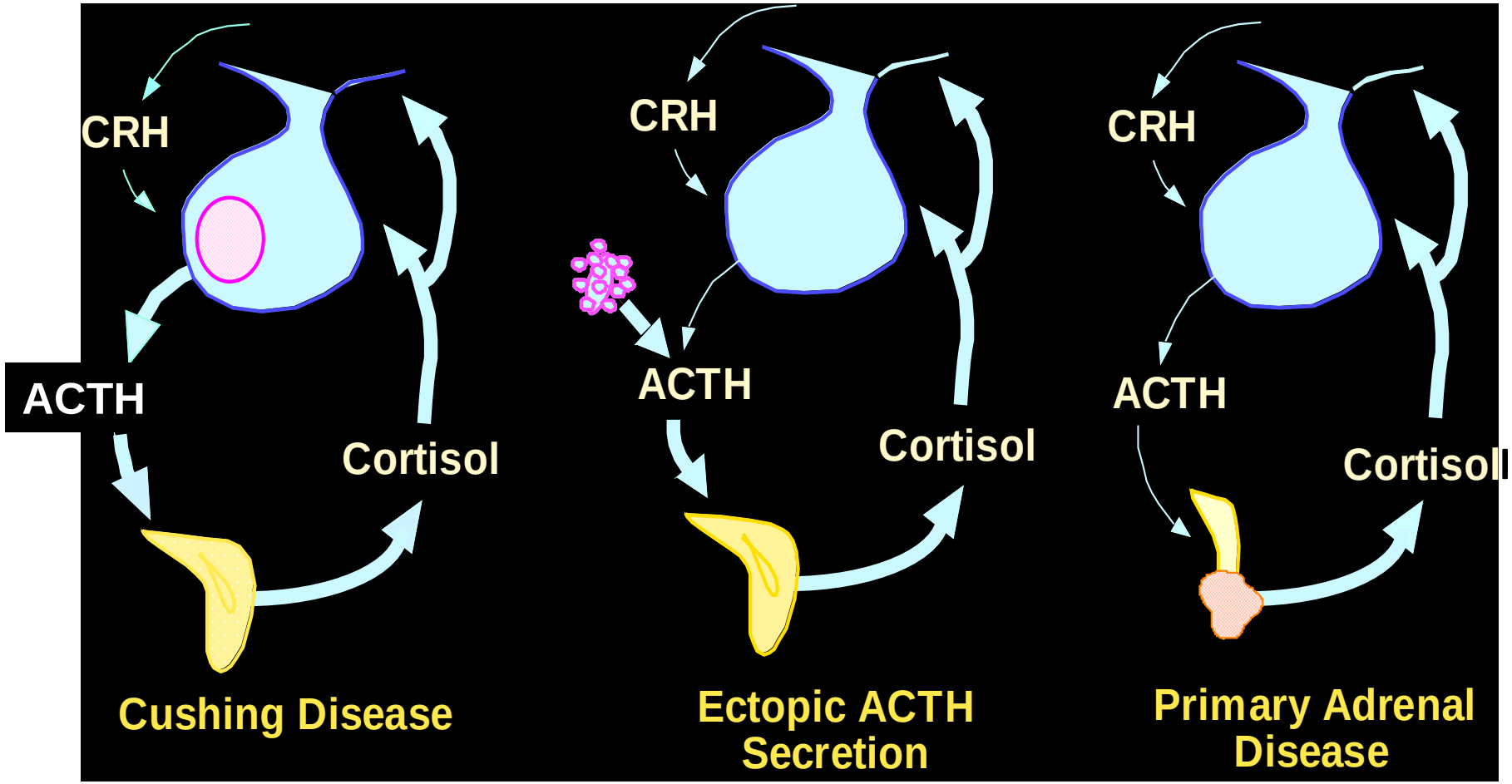
- Central obesity
- Peripheral muscle wasting (proximal myopathy)
- Thoracic compression fractures



Cushing's Syndrome

- Results from excessive glucocorticoid secretion
- Associated with a distinct clinical phenotype
- 2-3 cases per million per year
- Female : male ratio
  - Cushing's disease 3.5 : 1
  - Ectopic Cushing's 1 : 1

Differential Diagnosis of Cushing's Syndrome



Diagnostic stepwise approach

- Screening and confirmation - Does the patient have Cushing's syndrome? (clinical suspicion plays a big role in interpretation of the result)
- Subtype evaluation – is the Cushing's syndrome ACTH-dependent (pituitary or ectopic source) or ACTH-independent (adrenal adenoma)?
- Localization – where is the source of ACTH secretion in ACTH-dependent disease (pituitary or ectopic)?

Who should be screened?

- Unusual features for age (osteoporosis, HTN)
- Multiple and progressive features (review of old photographs)
- Children with decreasing height percentile and increasing weight
- Adrenal incidentaloma compatible with an adenoma
- Sudden worsening of DM and HTN control
- Recommend against widespread testing in other patient groups

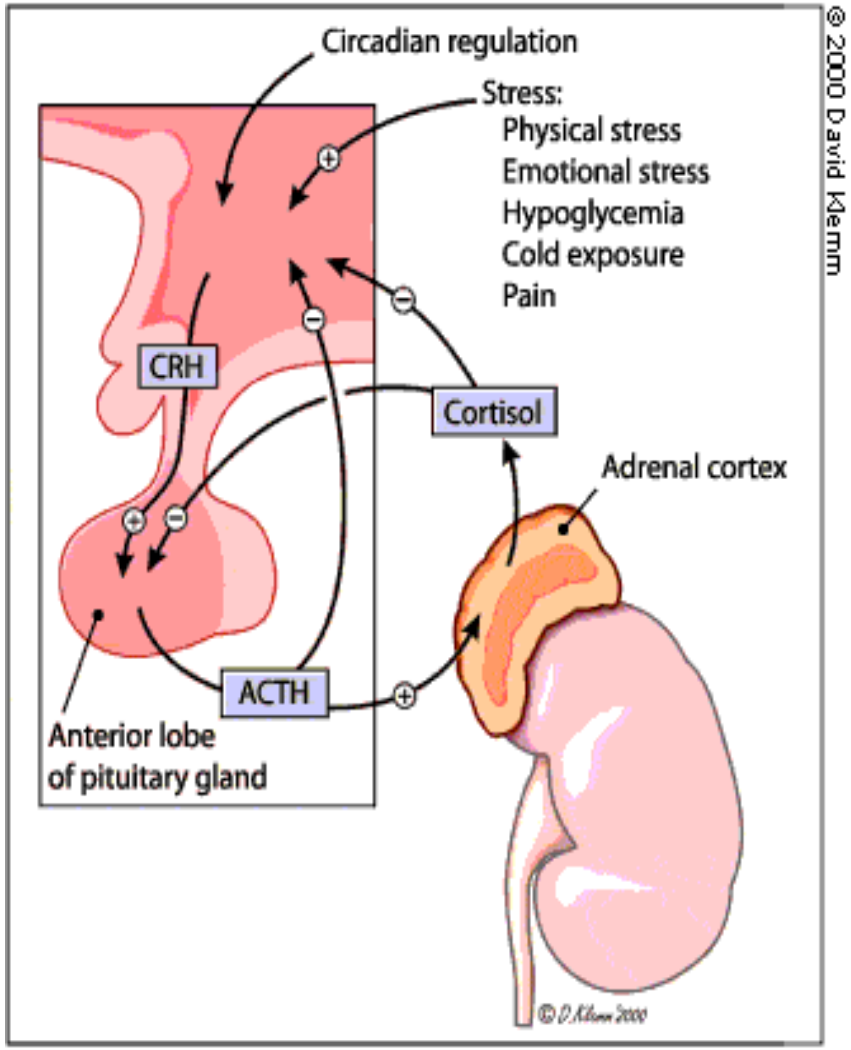
Screening for Cushings

- Random plasma cortisol level not helpful:
- May be elevated in normal patients
  - pulsatility
  - cortisol-binding globulin (estrogen replacement, oral contraceptives)
  - pseudoCushing's
- May be intermittently normal in patients with Cushing's
  - periodic hormonogenesis

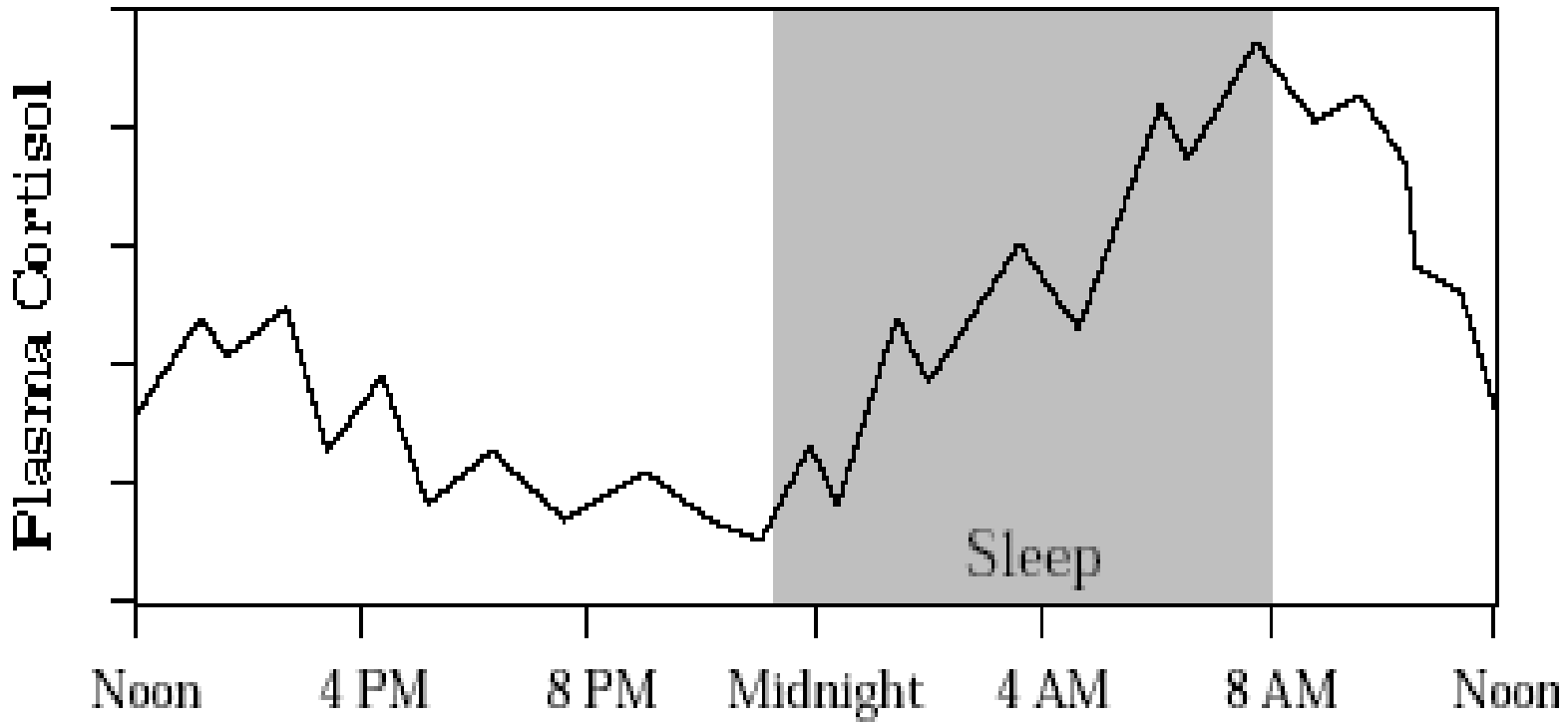
Pseudo Cushing's – activation of CRH

Causes

- Major depression or psychotic disorders
- Stress
  - surgical
  - medical
- Chronic alcoholism

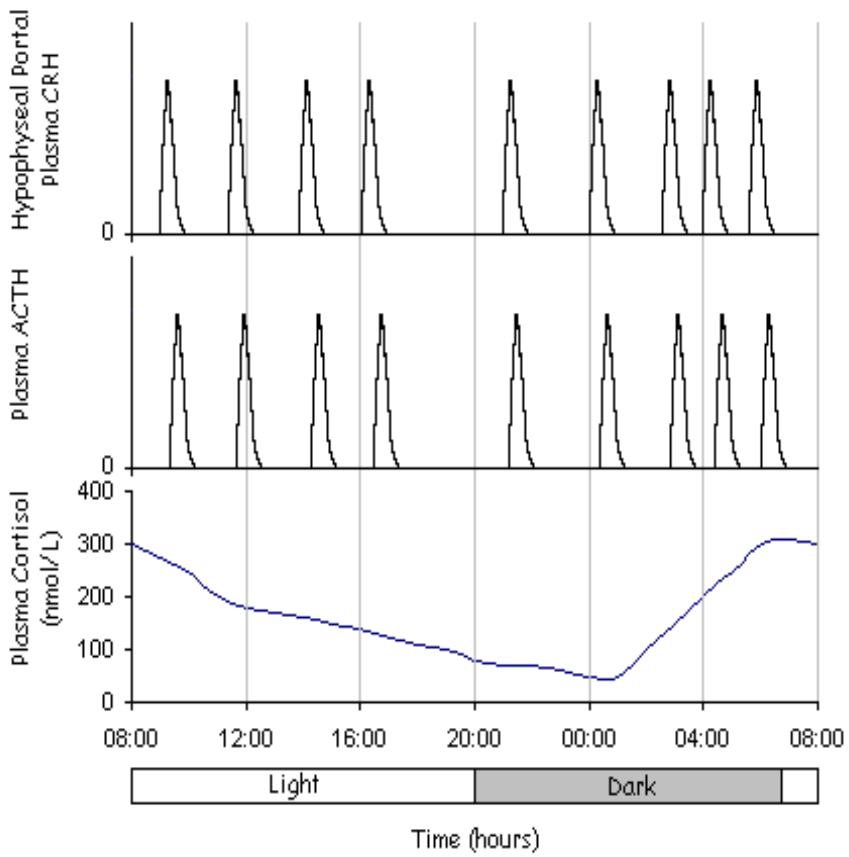


Diurnal Rhythm



Diurnal cortisol levels

- What does diurnal cortisol measure?
- Adjust for time difference
- Indwelling line
- Patient resting in bed
- Cutoff values: midnight cortisol levels above 7.5 µg/dl → Cushing's syndrome

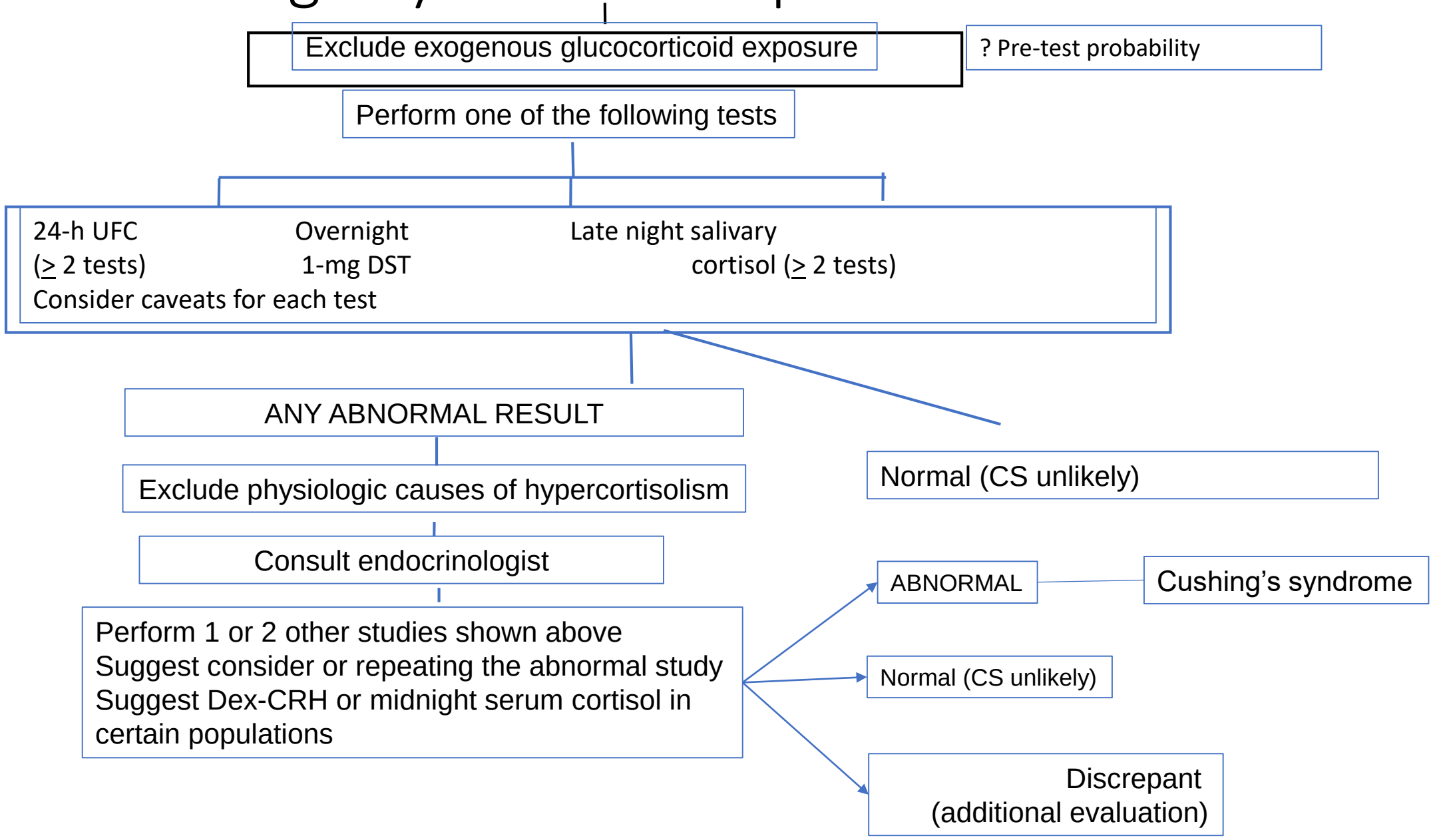


Screening for Cushing's

- Options:
- 24 hour urine free cortisol
- Midnight salivary cortisol test
- Dexamethasone suppression tests

- All of these tests must be interpreted in clinical context – clinical features of Cushing's must be present to make a diagnosis

Cushing's syndrome suspected



Determining the cause of hypercortisolism

- Measurement of Plasma ACTH
  - < 5 pg/mL
    - ACTH-independent
  - > 20 pg/mL
    - ACTH-dependent
    - Higher in Ectopic Cushing's
  - 5 - 20 pg/mL
    - Indeterminate
  - Collect blood into prechilled EDTA tube, place on ice bath. Plasma should be separated rapidly and stored at -40^0 C to avoid degradation & false-negative results

Treatment of Cushing's Syndrome

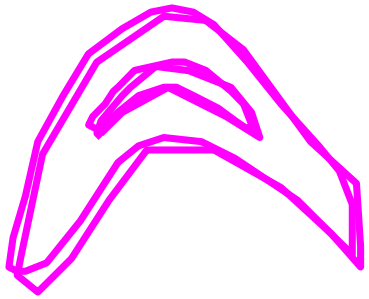
- Cushing's Disease
- Trans-sphenoidal surgery
- Bilateral adrenalectomy
- Medical therapy to block cortisol synthesis or action

- Cushing's Syndrome
- Remove adrenal mass
- Treat source of ectopic ACTH
- Medical therapy to block cortisol synthesis or action

Medical treatment

- Control of hypercortisolemia
  - Before surgery - minimize surgical complications
  - Awaiting results of radiation treatment
  - Surgery unsuccessful or contraindicated
- Control of hypertension and hyperglycemia
- Prophylaxis for opportunistic infection
- Prophylaxis for venous thrombosis

Steroidogenesis Inhibitors



Cortisol

Ketoconazole/etomidate

Metyrapone

Aminoglutethimide

Mitotane

Trilostane

Drugs that decrease ACTH secretion:

Octreotide, Paseriotide, Cabergoline, Bromocriptine

Glucocorticoid antagonist: Mifepristone

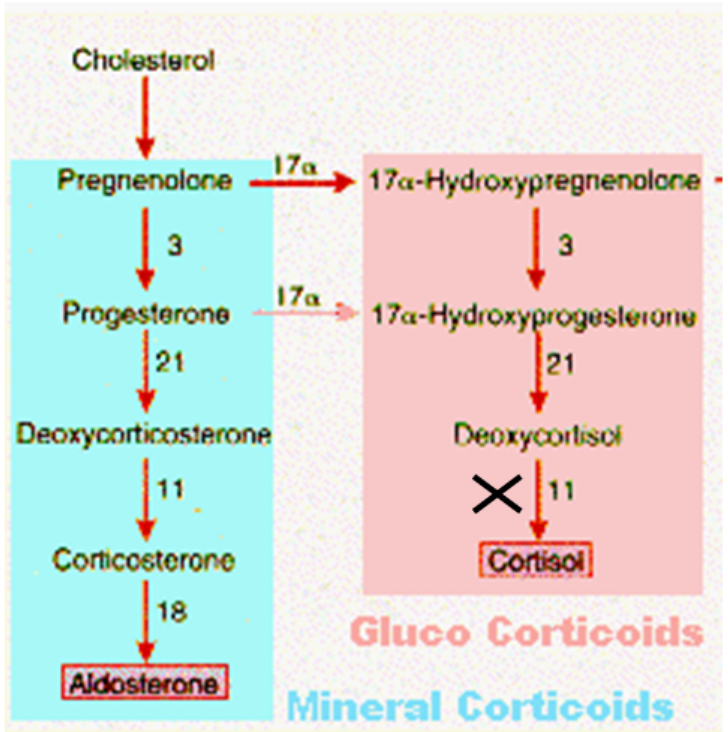
Ketoconazole

Mechanism

- Blocks 11 beta hydroxylase (and other steps in the steroid pathway)

Clinical use

- Medical treatment of Cushing's



Side effects/contraindications

- Symptoms of adrenal insufficiency
- Severe or life threatening/fatal liver disease

Other

- FDA warning issued regarding its use

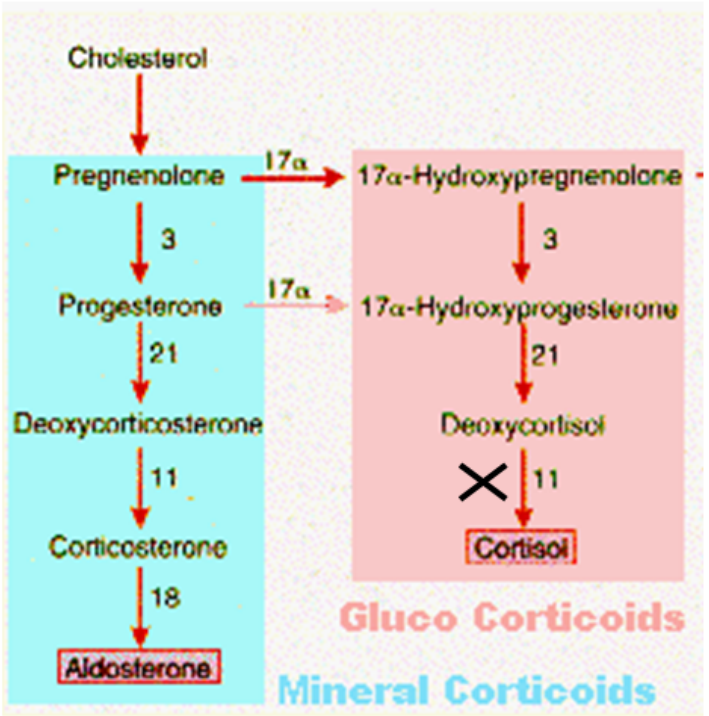
Metyrapone

Mechanism

- Blocks 11 beta hydroxylase

Clinical use

- Medical treatment of Cushings



Side effects/contraindications

- Symptoms of adrenal insufficiency

Other

- Not widely available

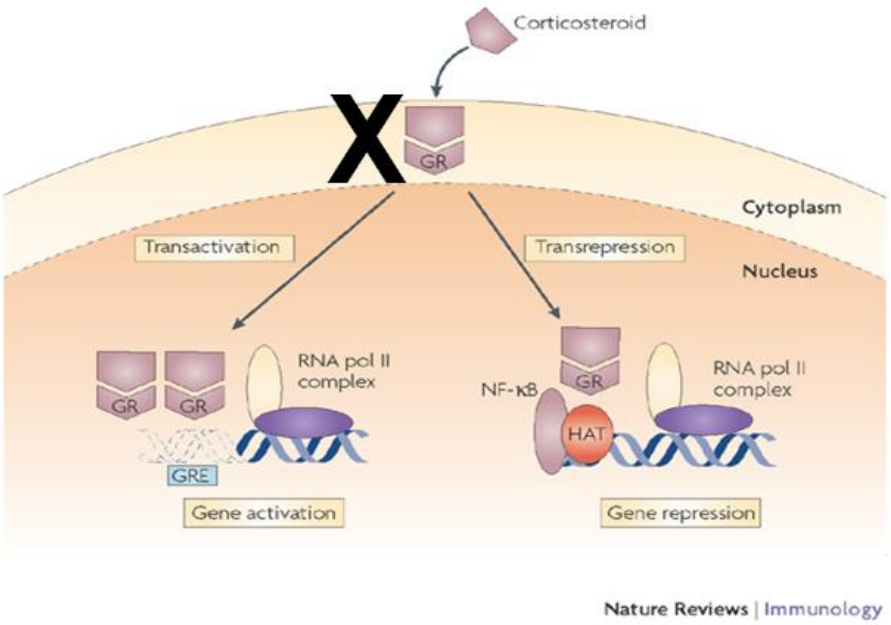
Mifepristone (Korlym)

Mechanism

- Glucocorticoid receptor antagonist

Clinical use

- Medical treatment of Cushing's



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Side effects/contraindications

- Hypokalemia
- GI upset – pain, nausea, vomiting
- Adrenal insufficiency

Other

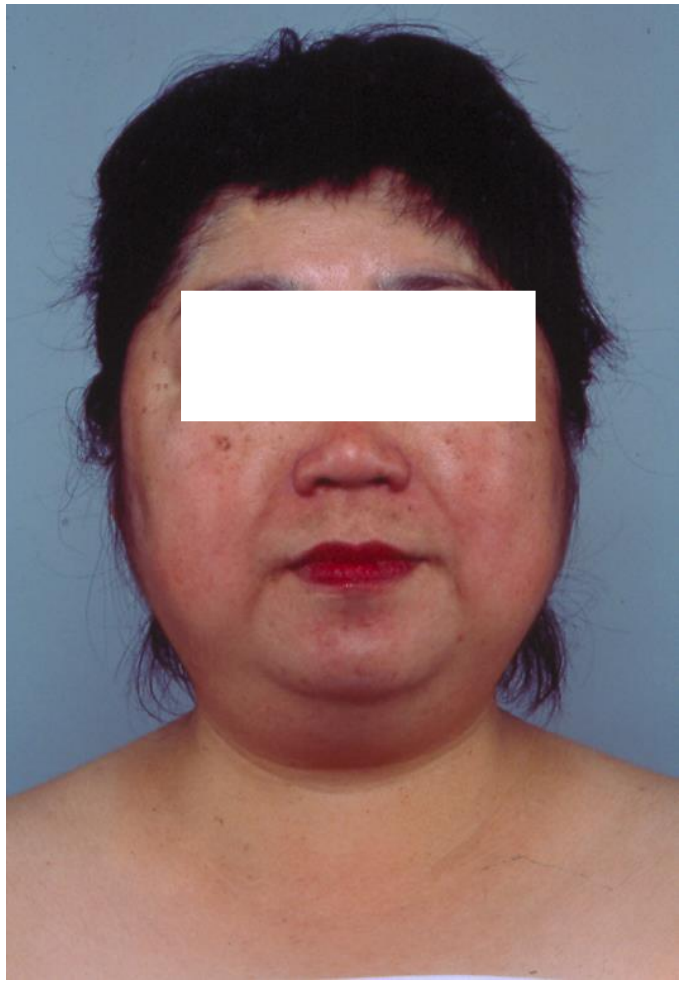
- Also has anti-progesterone activity
- Results in increased cortisol levels

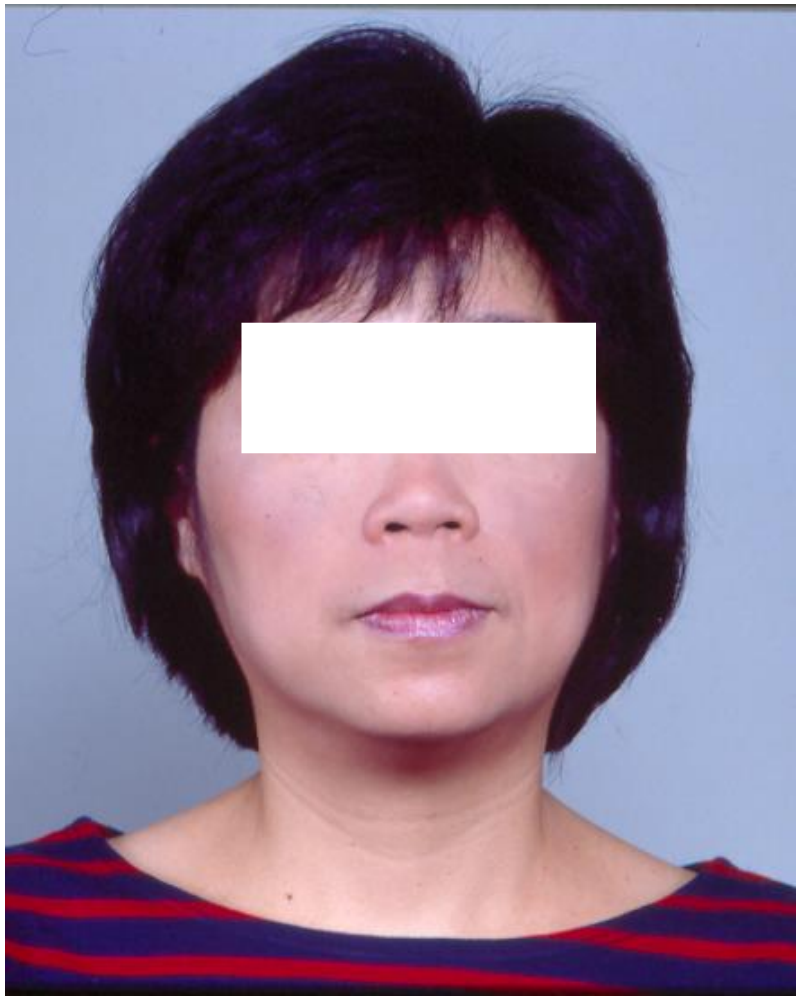
Which drug?

Drug	Pros	Cons
Ketoconazole	Quick action	SE: GI, LFTs (death) Needs stomach acid Drug interactions (CYP3A4 substrate)
Metyrapone	Quick action	SE: GI, hirsutism, acne, HTN, rarely neutropenia, Hard to obtain
Mitotane	Effective	Long wait to efficacy Cannot follow serum cortisol levels SE: GI, neurologic, ↓WBC, teratogenic
Etomidate	Quick action, IV → pts unable to take oral	Needs to be initiated in the ICU Temporary measure
Paseriotide	Effective	Injectible, can worsen/cause diabetes
Mifepristone	FDA approved	Cannot follow serum cortisol levels Anti-progestin (abortifacient, vaginal bleeding), hypokalemia

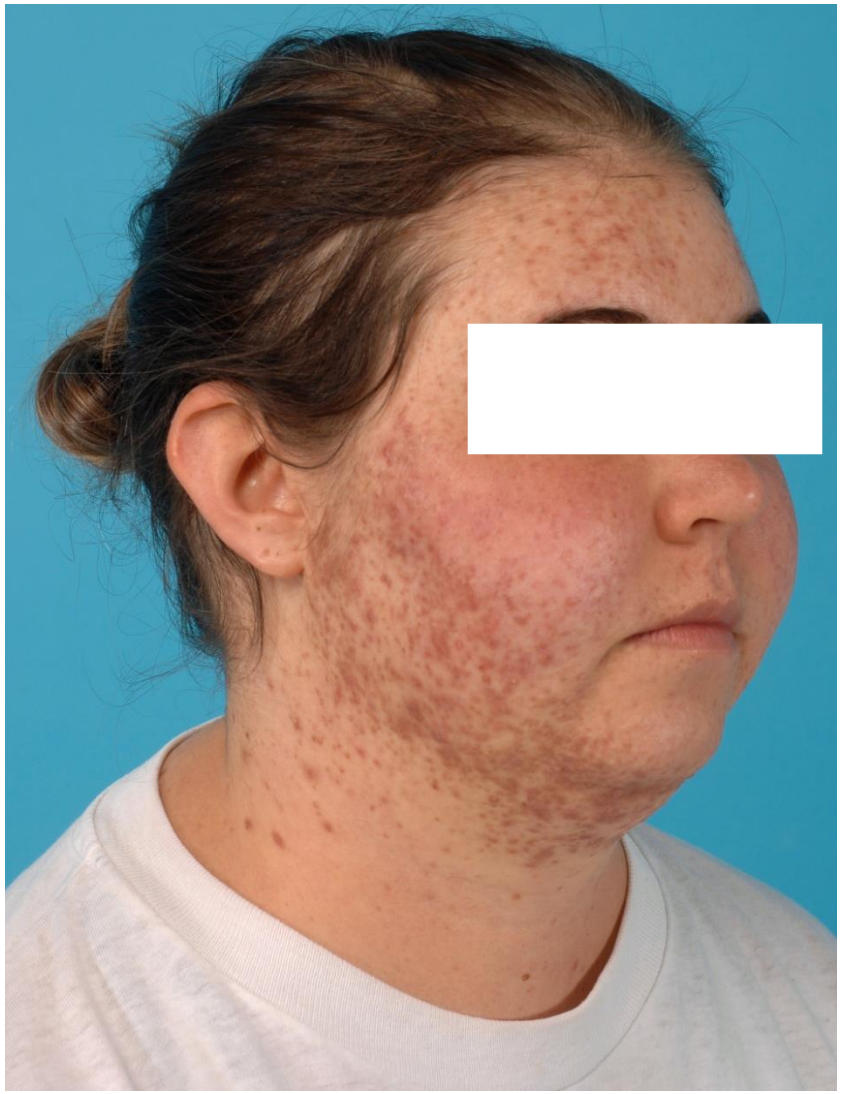
Goal of treatment: UFC in the normal range
Serum cortisol 6-12 mcg/dl (before AM meds)

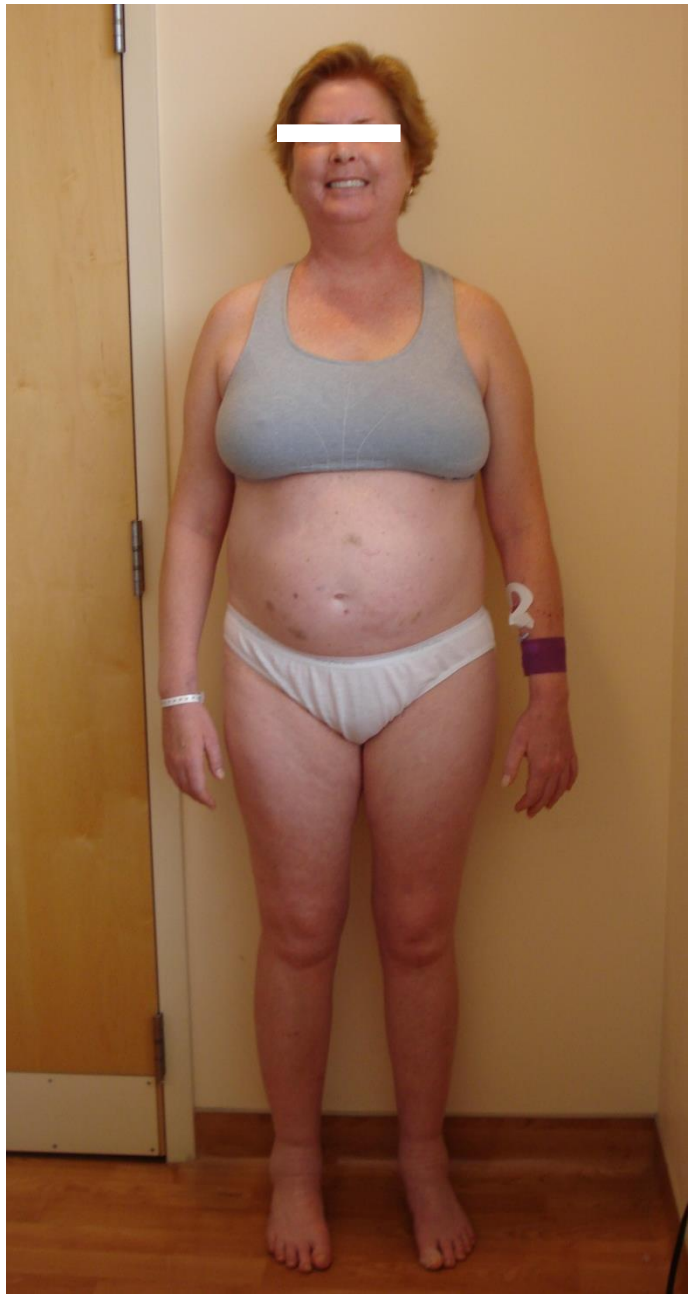
Cushing's syndrome

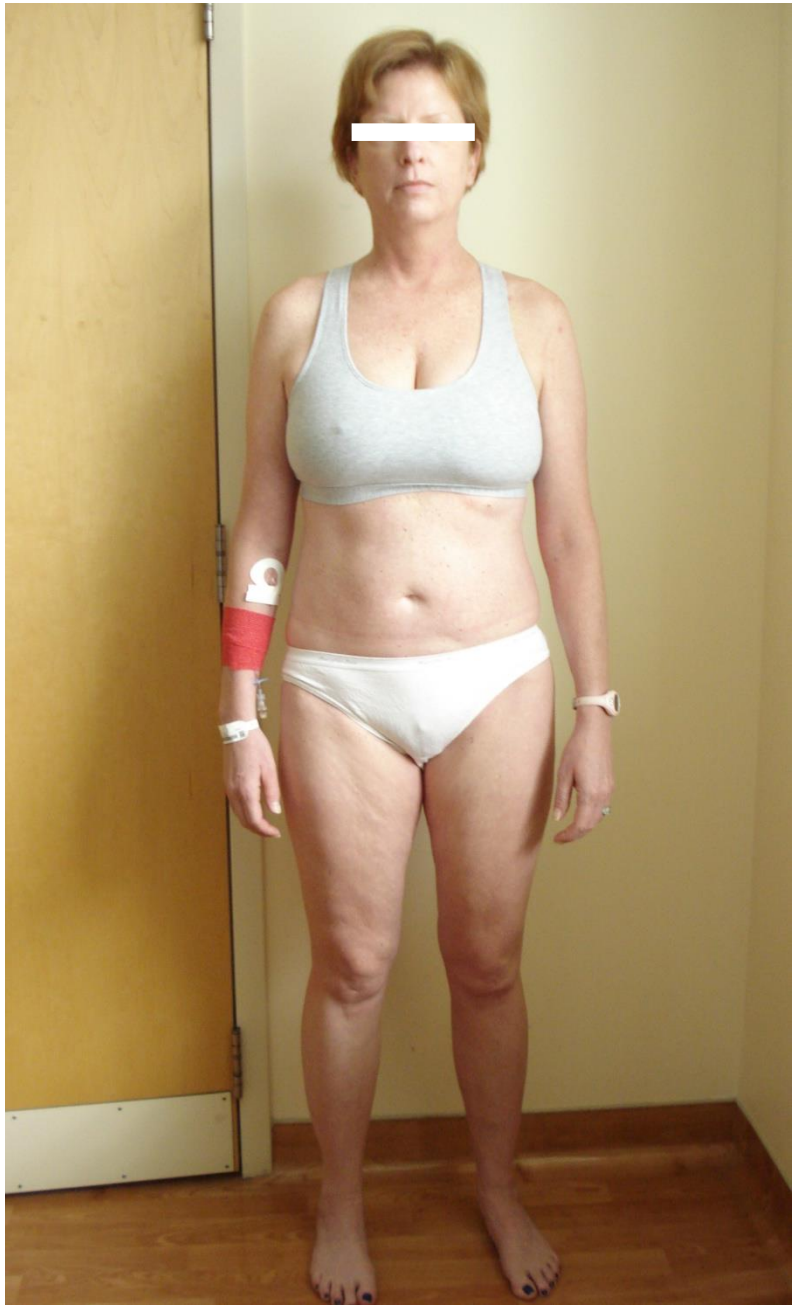




12 months after cure







Hypercortisolism

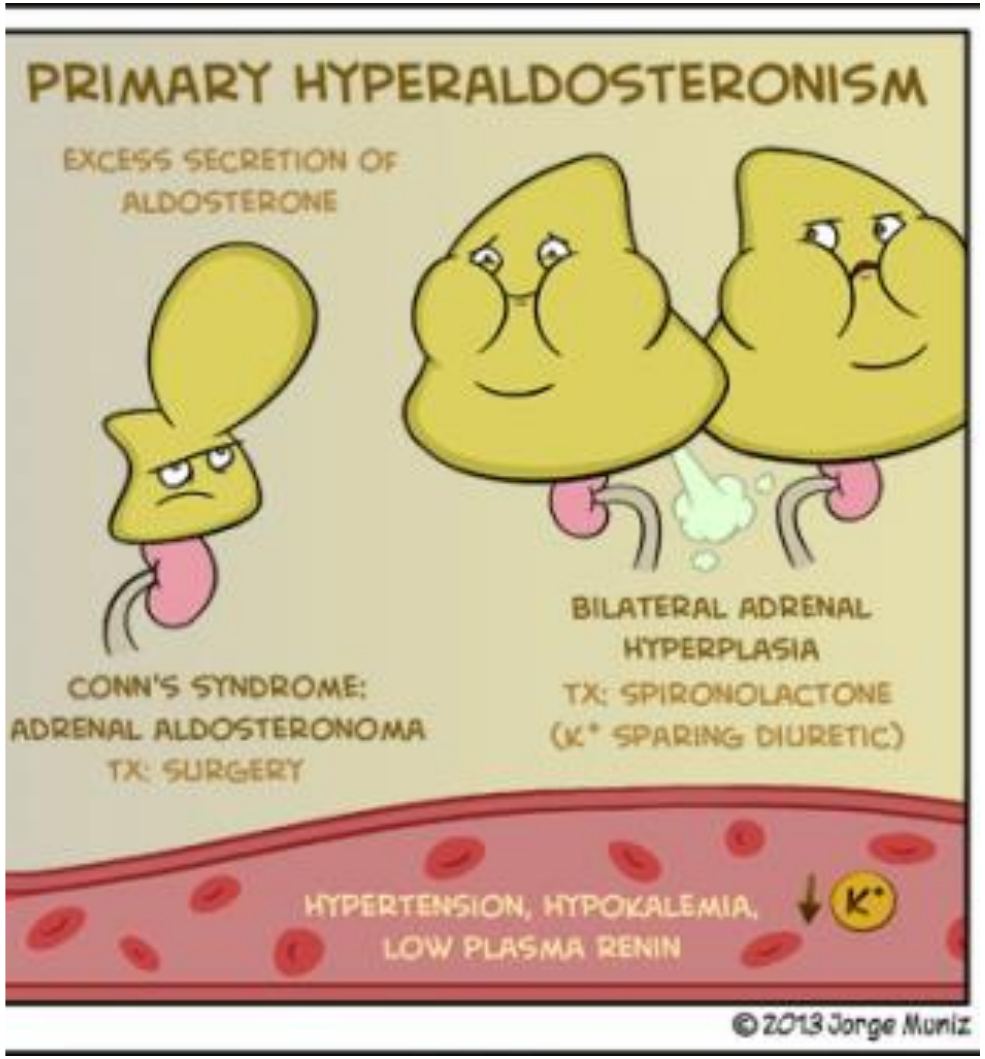
- Which of the following would you do first to confirm the etiology of hypercortisolism in a person with a decreased ACTH level?

a. Inferior petrosal sinus sampling
b. MRI of the pituitary
c. CT of the adrenals
d. High dose dexamethasone suppression test
e. Corticotropin-releasing hormone stimulation and petrosal sinus sampling

Hypercortisolism

- Overproduction or exogenous administration
- Which of the following is the most common cause of hypercortisolism?

a. Pituitary (Cushing's disease)
b. Adrenal (Cushing's syndrome)
c. Ectopic ACTH production
d. Prednisone use
e. Ectopic corticotropin releasing hormone (CRH)


PRIMARY HYPERALDOSTERONISM
EXCESS SECRETION OF ALDOSTERONE
CONN'S SYNDROME: ADRENAL ALDOSTERONOMA
TX: SURGERY
BILATERAL ADRENAL HYPERPLASIA
TX: SPIRONOLACTONE (K+ SPARING DIURETIC)
HYPERTENSION, HYPOKALEMIA, LOW PLASMA RENIN
K+
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Primary hyperaldosteronism

- Common: autonomous production of aldosterone from one or both adrenal glands (a small benign adrenal tumor, bilateral nodules / hyperplasia)
  - TREATMENT: Adrenalectomy (if unilateral process) or mineralocorticoid receptor antagonists (Spironolactone / Eplerenone)
- Very rare: Glucocorticoid remediable hyperaldosteronism
  - TREATMENT: steroids +/- mineralocorticoid receptor antagonists
- Clinical symptoms:
  - Hypertension
  - Water and salt retention → edema
  - Sometimes hypokalemia

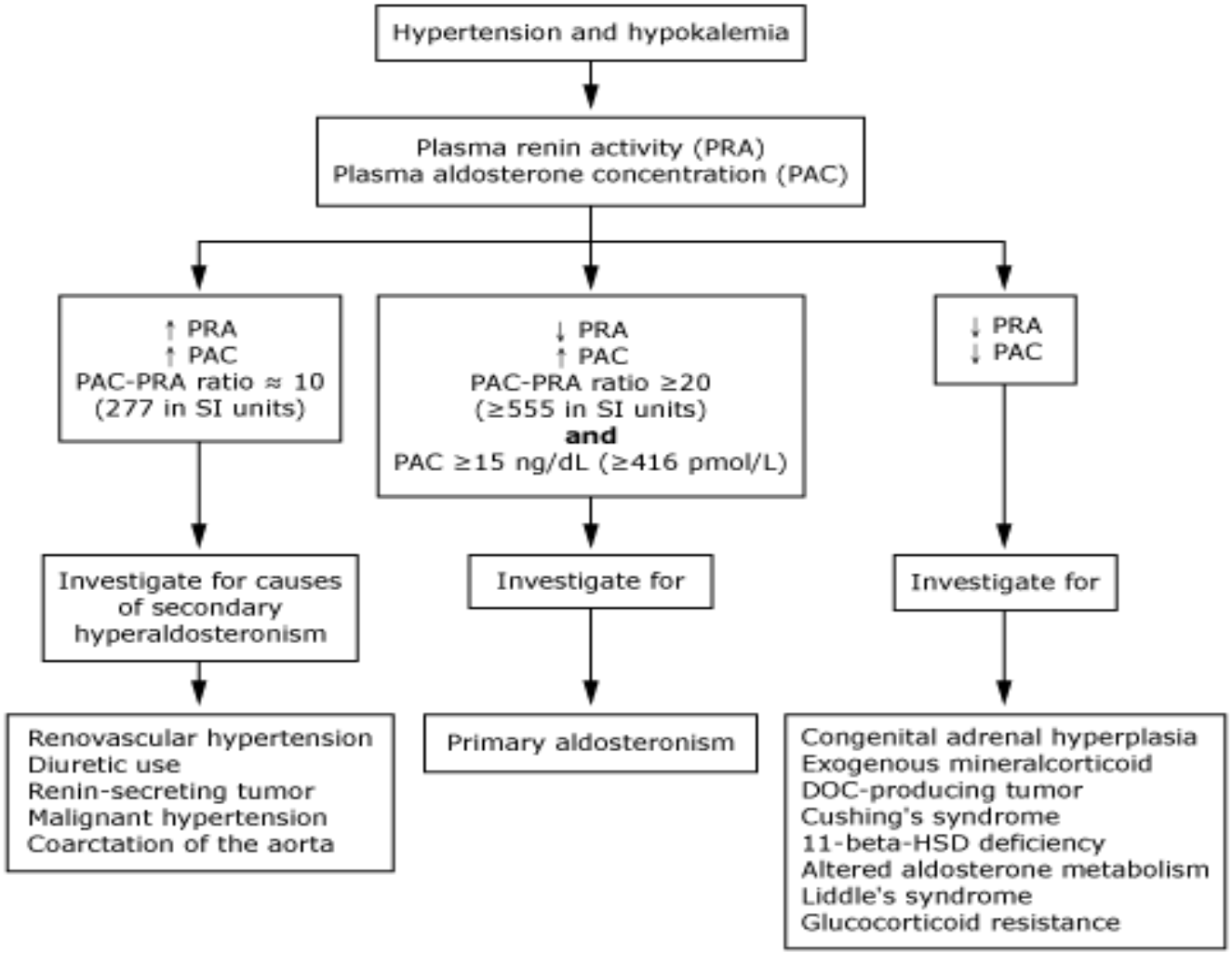
Etiology of Primary Aldosteronism

- **Unilateral Disease**
  - Adenoma (APA) 85% vs. Hyperplasia (IHA) 14% vs Cancer 1%
- **Bilateral Disease**
  - Adenoma (rare) vs. Hyperplasia (IHA)
- **Aldosterone-Producing Adrenocortical Carcinoma**
- **Genetic Diseases**
  - Familial Hyperaldosteronism type I (Glucocorticoid Remediable Aldosteronism)
  - Familial Hyperaldosteronism type II

Prevalence of Primary Aldosteronism

- Used to be LOW: < 1%
- Use of aldosterone to renin ratio (ARR) has allowed detection of many more cases
- Currently, prevalence is at > 10% in both general and specialty settings

Primary hyperaldosteronism



Clinical Features

- Hypertension
  - Hypervolemia due to sodium and water retention→ increased systemic vascular resistance
  - Suppression of plasma renin
- Hypokalemia
  - Metabolic alkalosis
  - Muscle cramps
  - Fatigue

Who should be screened for PA?

Patient Groups	Prevalence of PA
Moderate/severe hypertension JNC 7 Staging: Stage 2 >160/100 **OR** Stage 3 >180/110	Overall: 6.1% Stage 1 (mild): 2% Stage 2 (moderate): 8% Stage 3 (severe): 13%
Resistant/Drug-resistant Hypertension (defined as BP of < 140/90 despite treatment with 3 anti-hypertensive meds	17-23%
Hypertensive patients with spontaneous or diuretic induced hypokalemia	NA
Hypertension with adrenal incidentaloma	Median 2% (range, 1.1%-10%)
Hypertension AND a family history of early onset hypertension or stroke at a young age (<40 yrs)	NA

Screening

- Measurement of morning, ambulatory labs:
  - Aldosterone (>15 ng/ml)
  - Plasma renin activity (PRA) (<0.6 ng/ml/hr)
- Ratio of aldosterone/PRA
  - should be >20
- Interfering Medication*
  - Verapamil, hydralazine, prazosin, terazosin, doxazosin do not interfere with aldo or PRA levels

Screening

- Aldosterone/PRA ratio:
  - Nishizaka, 2005:
    - Sensitivity 78%, Specificity 83%
    - PPV 56%, NPV 93%
- Role of hypokalemia in screening?
  - Only 9-37% PA pts had K<3.5 (Mulatero 2004)
  - 50% of APA, 17% IHA pts with K<3.5 (Rossi 2006)

Screening Conditions

- ARR interference
  - Testing conditions
    - Position
    - Sample collection
    - Time of day
  - Medications
  - Hypokalemia

Medication effects

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
Beta-adrenergic blockers	↓	↓ ↓	↑ (FP)
Central alpha-2 agonists (e.g., clonidine, alpha-methyldopa	↓	↓ ↓	↑ (FP)
NSAIDs	↓	↓ ↓	↑ (FP)
K+-wasting diuretics	→ ↑	↑ ↑	↓ (FN)
K+-sparing diuretics	↑	↑ ↑	↓ (FN)
ACE inhibitors	↓	↑ ↑	↓ (FN)
ARBs	↓	↑ ↑	↓ (FN)
Ca2+ blockers (DHPs)	→ ↓	↑	↓ (FN)
Renin inhibitors	↓	↓ ↑*	↑ (FP)*
			↓ (FN)*

Testing Conditions

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Potassium status			
Hypokalemia	↓	→ ↑	↓ (FN)
Potassium loading	↑	→ ↓	↑ (FP)
Dietary sodium			
Sodium restricted	↑	↑ ↑	↓ (FN)
Sodium loaded	↓	↓ ↓	↑ (FP)
Advancing age	↓	↓ ↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑ ↑	↓ (FN)
Renovascular HT	↑	↑ ↑	↓ (FN)
Malignant HT	↑	↑ ↑	↓ (FN)

Medications that do not interfere with ARR

Medication	Dose
Verapamil	120-240 mg BID
Hydralazine	25-75 mg TID
Terazosin	1-10 mg QHS
Prazosin	1-15 mg BID/TID
Doxazosin	1-16 mg QD

Differential Diagnosis of Hypertension and Hypokalemia

Suspicion of 2° HTN due to RAAS		
↑Aldo ↑Renin	↑Aldo ↓Renin	↓Aldo ↓Renin
-Renovascular -Hypovolemia -Vascular (other) -LVF	-Adenoma -Hyperplasia -Familial (GRA) -Carcinoma	-Licorice -11-beta HSD mutations -DOC tumor -Cushing Syndrome
-Renin-secreting tumor	-Ectopic Aldosterone secretion	-Liddle's Syndrome -CAH: 11 and 17 hydroxylase -Glucocorticoid resistance

Confirmatory Testing

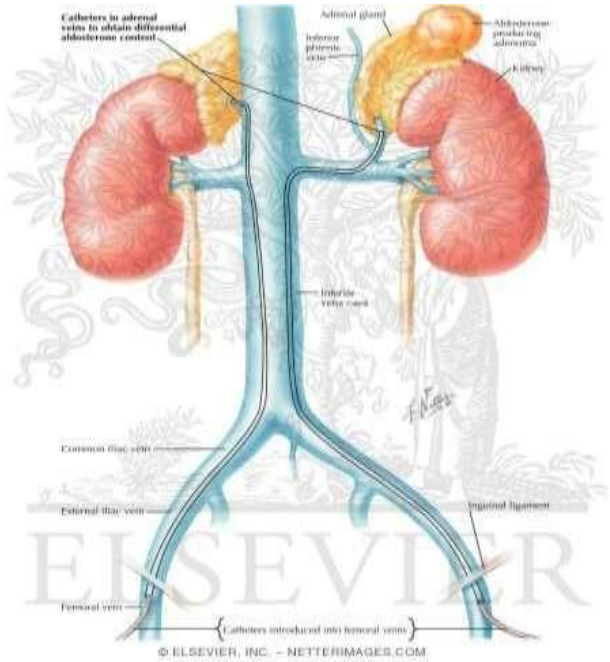
- Oral salt loading
- Saline suppression test
- Fludrocortisone suppression test
- Captopril Challenge

Unilateral vs. Bilateral

- **AVS**
- Other tests:
  - CT scan
  - ACTH stimulation testing
  - 18-Hydroxycorticosterone levels
  - Posture testing
  - Iodocholesterol scintigraphy

Adrenal Venous Sampling

- Cosyntropin stimulated
  - Minimized stress-induced fluctuations
  - Maximize gradient of cortisol from adrenal vein to IVC
  - Maximize secretion of aldosterone
- Cortisol-corrected aldosterone ratios
  - Proper cannulization (10:1)
  - Lateralization (4:1)
- Downsides:
  - Complications
  - Skilled IR
  - Contrast



Treatment

- Unilateral Adrenalectomy
- Medical Treatment
  - Mineralocorticoid Receptor Antagonists
    - Spironolactone
    - Eplerenone
  - Sodium Channel Antagonists
    - Triamterene
    - Amiloride

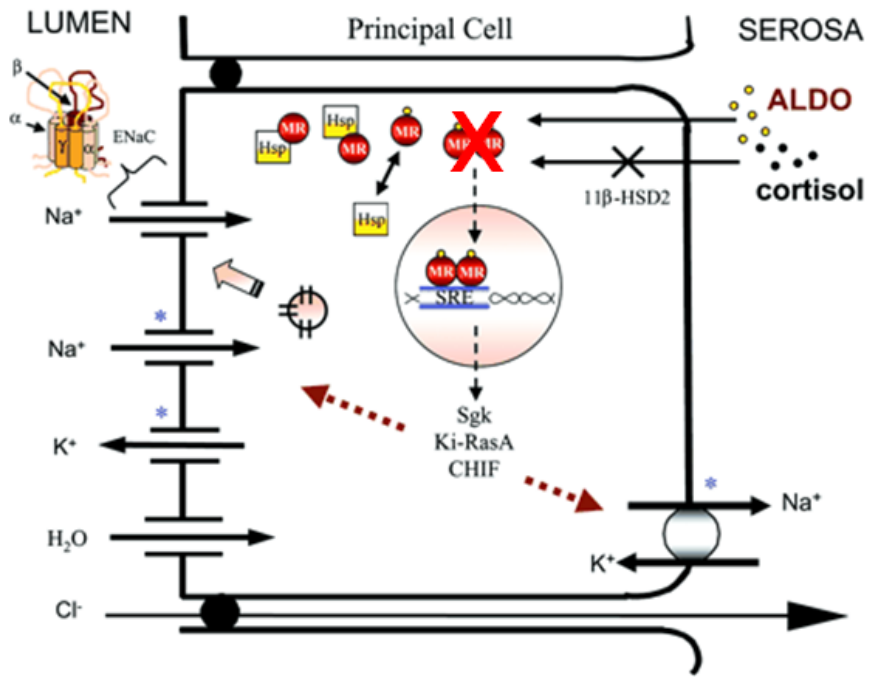
Surgical Cure of Hypertension

- Rule of “Thirds”
  - ~33% cured
  - ~33% reduced BP medications
  - ~33% no change in BP medications
- Who will Benefit?
  - Lack of family hx of HTN
  - Shorter duration of HTN (<6 yrs) +1
  - Female sex +1
  - Two or fewer BP meds +2
  - BMI<25 +1

Spironolactone (Aldactone)

Mechanism

- Aldosterone receptor antagonist
- Inhibits actions of aldosterone



Booth R E et al. Advan in Physiol Edu 2002;26:8-20

Clinical use

- Primary aldosteronism
- Secondary aldosteronism
  - CHF
  - cirrhosis

Side effects/contraindications

- Hyperkalemia
- Gynecomastia
- GI upset

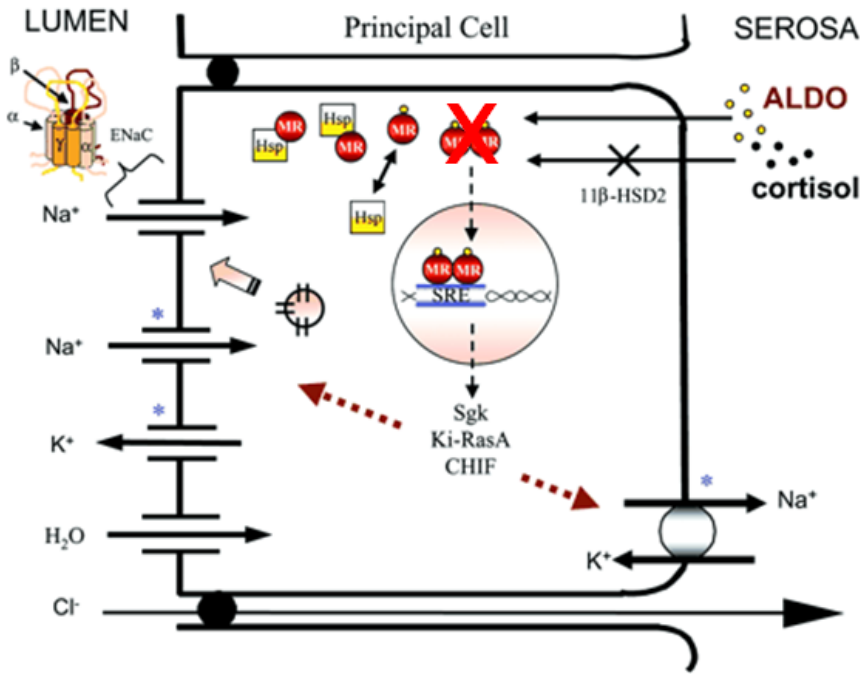
Other

- Blocks action of testosterone at its receptor
- Increases serum estrogen levels

Eplerenone (Inspra)

Mechanism

- Aldosterone receptor antagonist
- Inhibits actions of aldosterone



Booth R E et al. Advan in Physiol Edu 2002;26:8-20

Clinical use

- Primary aldosteronism
- Secondary aldosteronism
  - CHF
  - cirrhosis

Side effects/contraindications

- Hyperkalemia
- GI upset

Other

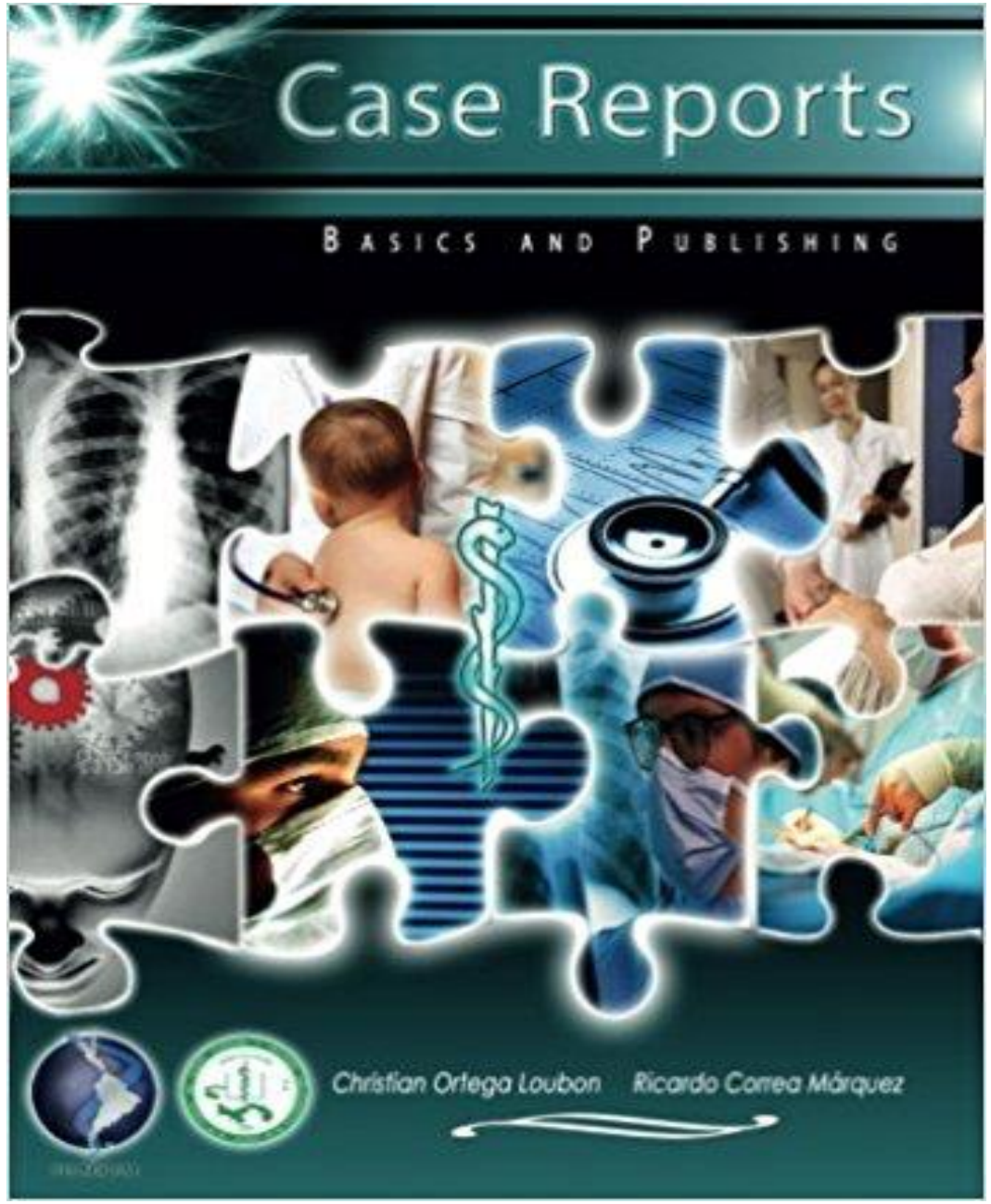
- Does not have significant testosterone receptor blockade effect

Surgical Cure of Hypertension

- Rule of “Thirds”
  - ~33% cured
  - ~33% reduced BP medications
  - ~33% no change in BP medications
- Who will Benefit?
  - Lack of family hx of HTN
  - Shorter duration of HTN (<6 yrs) +1
  - Female sex +1
  - Two or fewer BP meds +2
  - BMI<25 +1

Summary

- Cushing Syndrome (cortisol excess)
- Adrenal insufficiency (cortisol deficiency)
- Mineralocorticoid excess/deficiency
- Congenital adrenal hyperplasia
- Therapy for various types of Cushing syndrome/ mineralocorticoid excess
- Principles of adrenal replacement therapy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