Adrenal Disorders

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Objectives

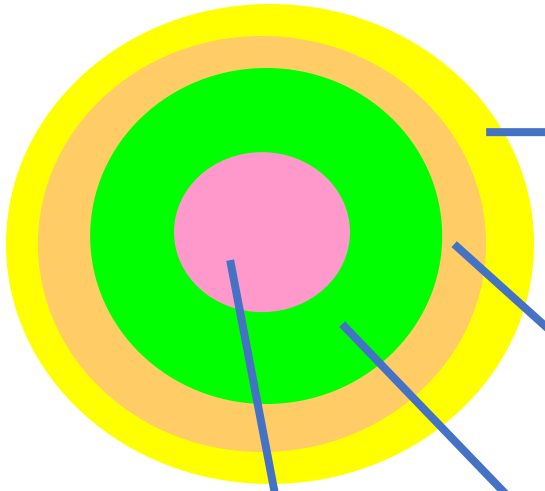
- Review pathogenesis and clinical presentation
  - Adrenal incidentaloma
  - Cortisol excess (Cushing's)
  - Mineralocorticoid excess
- Review principles of diagnosis and therapy for each conditions

A 62-year-old lady comes to see you because she has gained weight and feels depressed. She generally feels weak particularly if she climbs stairs. Her past medical history is also significant for borderline diabetes mellitus. She has been under a lot of stress recently because of the death of her mother and her daughter is undergoing a divorce. On examination: her face is a bit puffy and she has bruises over her arms. There are no abdominal striae. She has a fungal infection in her mouth. 24-hour urine free cortisol is 190 ug/24 hours (normal range 5-55 ug/24hrs).

Which part of the adrenal is most likely affected

a. Zona glomerulosa of the adrenal cortex
b. Zona fasciculata of the adrenal cortex
c. Zona reticularis of the adrenal cortex
d. Adrenal Medulla

Adrenals



Cortex

Zona Glomerulosa

Mineralocorticoids (Aldosterone)

Na+, K+ and water homeostasis

Zona Fasciculata

Glucocorticoids (Cortisol)

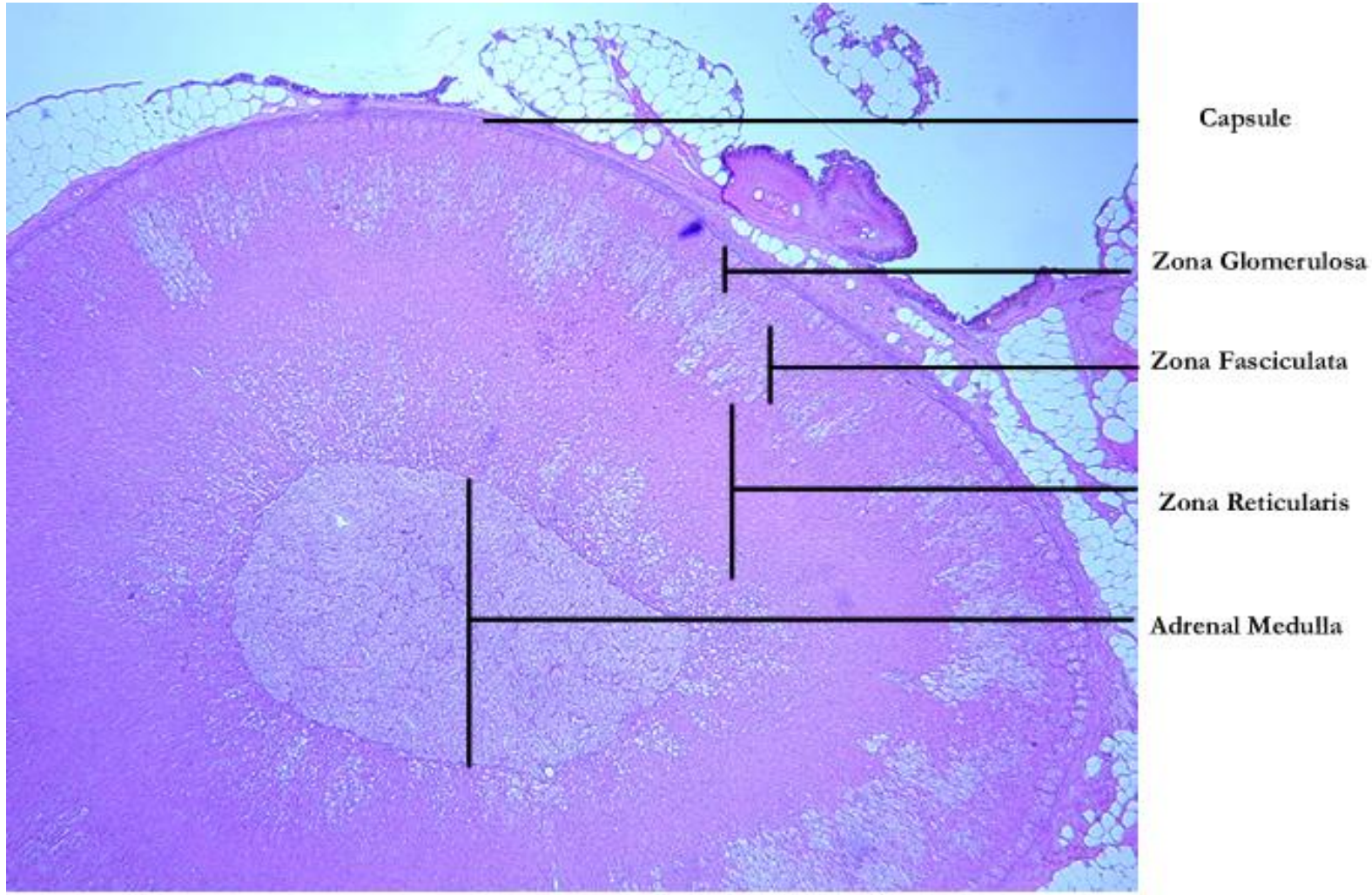
Glucose homeostasis and many others

Zona Reticularis

Sex steroids (androgens)

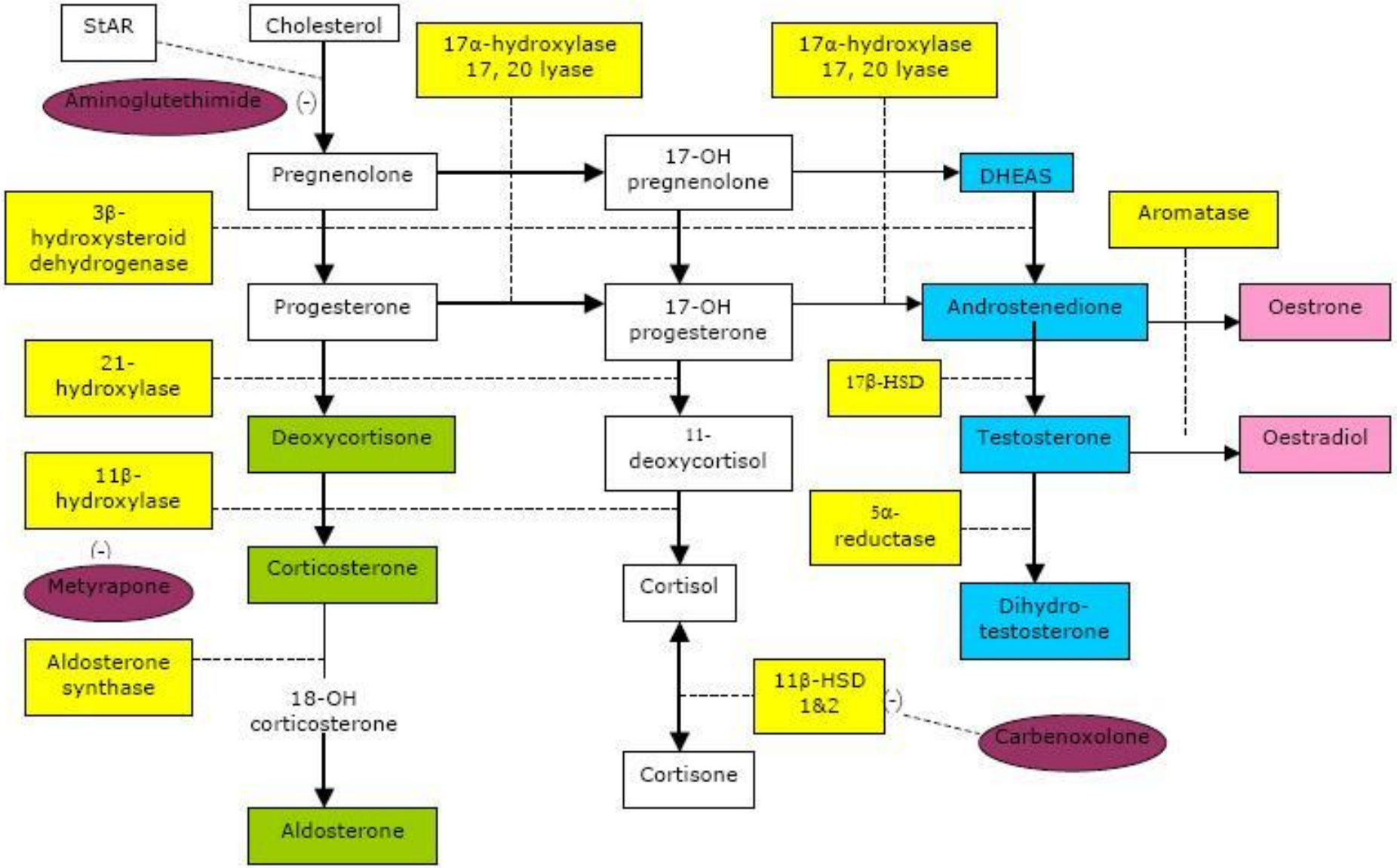
Medulla: "Catecholamines"

Epinephrine, Norepinephrine, dopamine

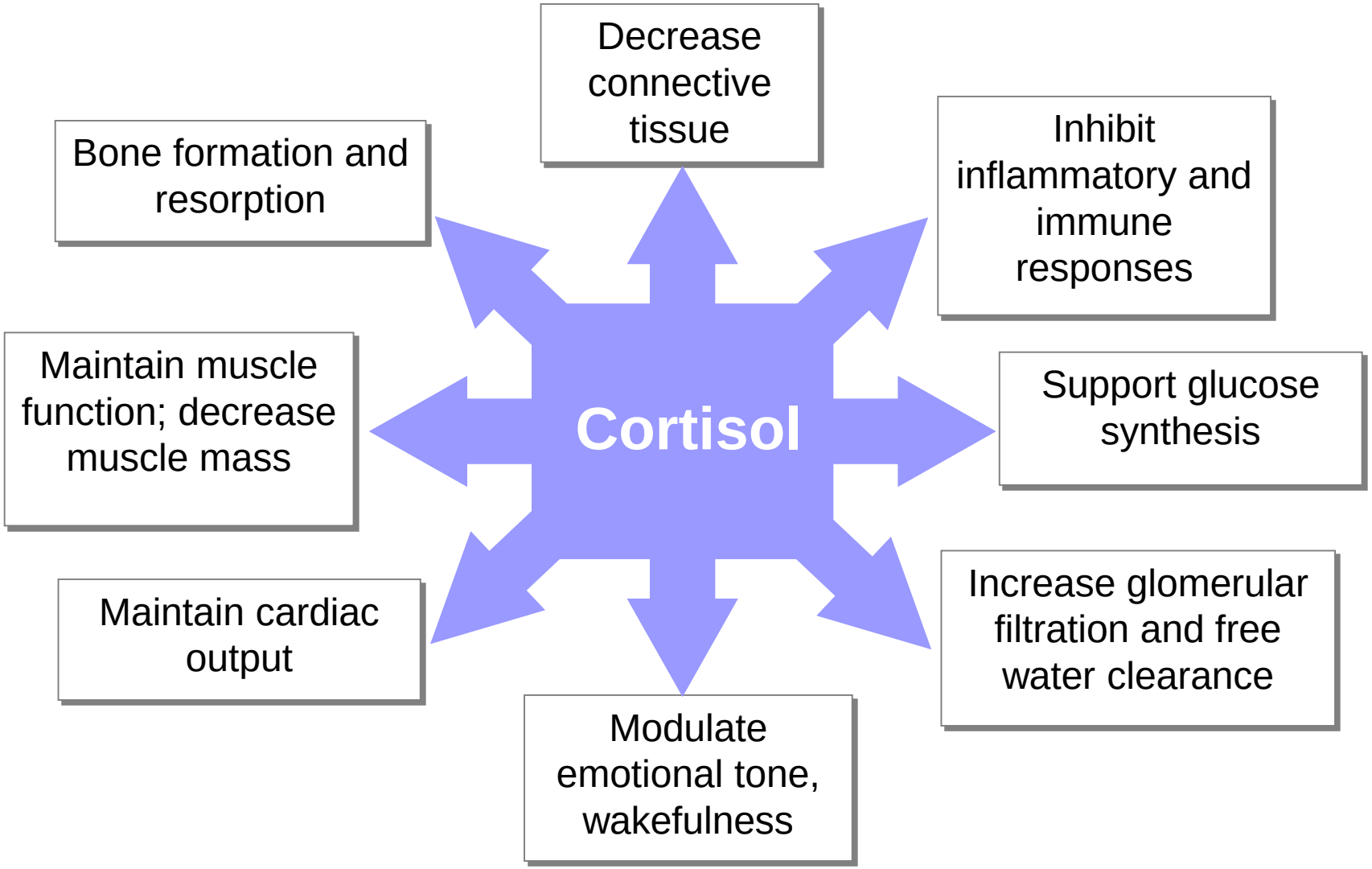


Adrenal Gland (40x)

Biosynthesis steroid Hormones



Cortisol is not just a stress hormone...



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

A 33-year-old man has been referred to you for evaluation of Cushing syndrome. He has had a 20-lb (9.1-kg) weight gain in the past 9 months accompanied by the onset of hypertension and edema. He has noted marked weakness, especially when climbing stairs. His family history is negative for any endocrine disorders. He takes no medications.

On physical examination, he has facial rounding and supraclavicular and dorsocervical fat accumulation. His blood pressure is 168/110 mm Hg, and pulse rate is 94 beats/min. His height is 75 in (190.5 cm), and weight is 220 lb (100 kg) (BMI = 27.5 kg/m2). He has wide, violaceous striae on his abdomen; proximal muscle weakness; and 2+ pretibial edema.

Laboratory test results:

- Sodium = 142 mEq/L (136-142 mEq/L) (SI: 142 mmol/L [136-142 mmol/L])
- Potassium = 3.0 mEq/L (3.5-5.0 mEq/L) (SI: 3.0 mmol/L [3.5-5.0 mmol/L])
- Creatinine = 1.1 mg/dL (0.7-1.3 mg/dL) (SI: 97.2 µmol/L [61.9-114.9 µmol/L])
- Urinary free cortisol = 632 µg/24 h (4-50 µg/24 h) (SI: 1744 nmol/d [11-138 nmol/d])
- Late-night salivary cortisol = 2.1 µg/dL (<0.13 µg/dL) (SI: 58 nmol/L [<3.6 nmol/L])
- DHEA-S = 678 µg/dL (65-334 µg/dL) (SI: 18.4 µmol/L [1.76-9.05 µmol/L])
- Basal plasma ACTH = <5 pg/mL (10-60 pg/mL) (SI: <1.1 pmol/L [2.2-13.2 pmol/L])

Which of the following imaging studies descriptions are most likely in this man?

A. 4 cm adrenal nodule with Hounsfield units = -2

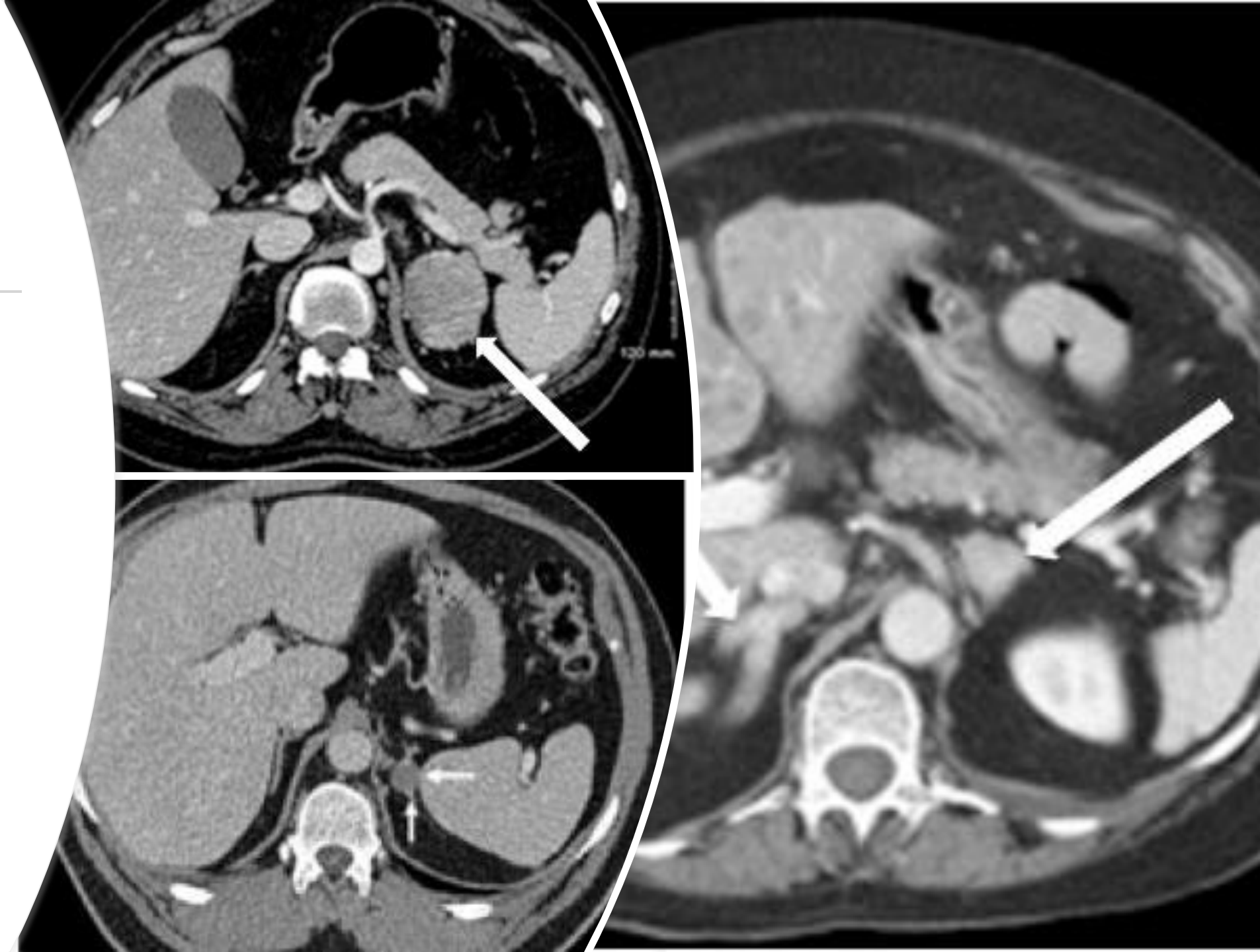
B. 3 cm adrenal nodule with Hounsfield units = 20 with washout of 58%

C. 7 cm adrenal nodule with Hounsfield units = 78 with washout of 12%

D. 3 cm adrenal nodule with Hounsfield unit = 10

Adrenal incidentaloma

- Detection of an unsuspected adrenal mass on radiologic imaging.
- Patients have no symptoms or clinical evidence of adrenal disease
- Excludes patients undergoing imaging procedures as part of staging and work-up for cancer



Adrenal incidentaloma

- 80% nonfunctioning adenoma
- 5% subclinical Cushing syndrome
- 3% pheochromocytoma
- 1% primary hyperaldosteronism
- <5% adrenocortical carcinoma
- 2.5% metastatic lesion

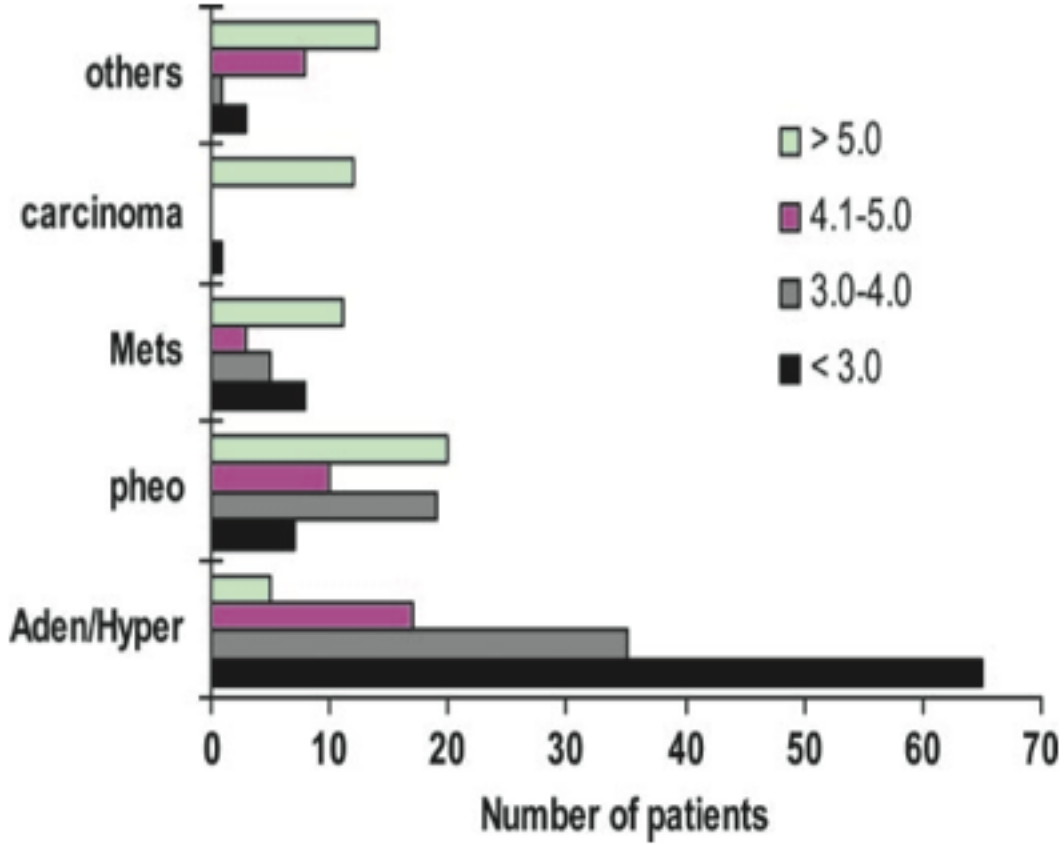
Evaluation

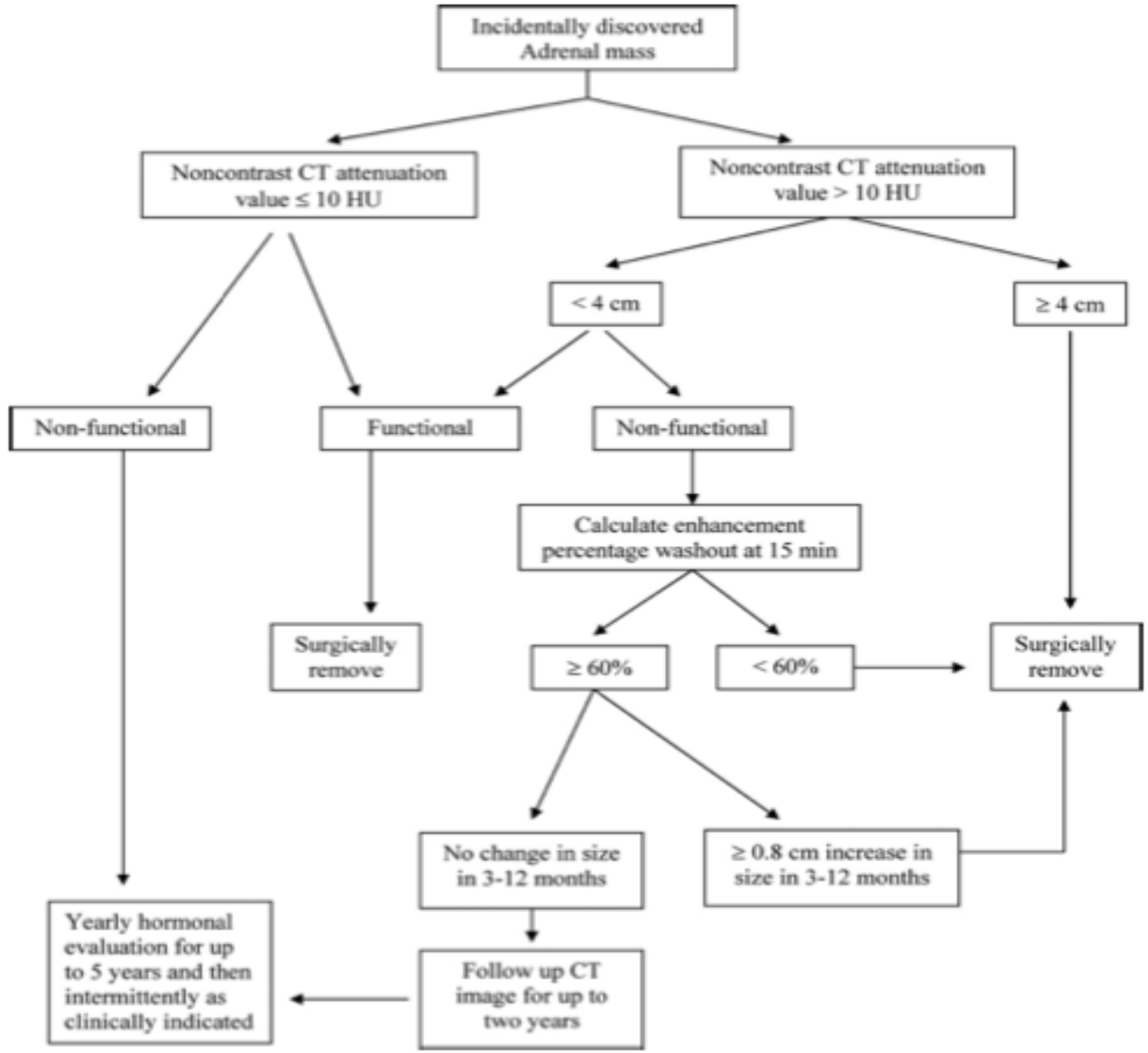
- Is it malignant?
    - features on imaging studies
    - tumor size

Imaging features

- The intracellular lipid content is used to distinguish adenomas from non adenomas
- Adenomas often contain abundant intracytoplasmatic fat and thus have low attenuation **(<10 HU)** on nonenhanced CT scan
- CT scan with enhancement washout is valuable in differentiating lipid poor (noncontrast HU >10) adenomas from non-adenomas
- An absolute enhancement washout percentage of **less than 50%** at 15 minutes after giving contrast strongly suggests a non-adenoma

Tumor size


others
carcinoma
Mets
pheo
Aden/Hyper
> 5.0
4.1-5.0
3.0-4.0
< 3.0
0
10
20
30
40
50
60
70
Number of patients


Incidentally discovered Adrenal mass
Noncontrast CT attenuation value ≤ 10 HU
Noncontrast CT attenuation value > 10 HU
< 4 cm
≥ 4 cm
Non-functional
Functional
Non-functional
Calculate enhancement percentage washout at 15 min
Surgically remove
≥ 60%
< 60%
Surgically remove
No change in size in 3-12 months
≥ 0.8 cm increase in size in 3-12 months
Yearly hormonal evaluation for up to 5 years and then intermittently as clinically indicated
Follow up CT image for up to two years

Evaluation

- Is it functional?
  - 6-20% of patients with adrenal incidentalomas have hormonal abnormalities

- Subclinical Cushing's syndrome (SCS)

-Cushing's syndrome

- Pheochromocytoma

- Primary hyperaldosteronism

A 48-year-old woman has sustained 2 left metatarsal fractures in the past 18 months and is found to have low bone density (mean total hip T score of –2.4). She has a history of poorly controlled hypertension, and her cardiologist performs a chest CT to exclude coarctation of the aorta (negative), but a 1.4-cm left adrenal nodule (2 Hounsfield units) is discovered. Her medications are lisinopril, amlodipine, and metoprolol.

On physical examination, her blood pressure is 152/96 mm Hg and pulse rate is 64 beats/min. Her height is 64 in (162.6 cm), and weight is 136 lb (61.8 kg) (BMI = 23.3 kg/m2). Examination findings are normal.

Which of the following would be the most sensitive test for the diagnosis of autonomous cortisol secretion from this nodule?

A.Early-morning serum cortisol measurement

B.24-hour urinary free cortisol measurement

C.Late-night salivary cortisol measurement

D.MRI of adrenal glands

E.Overnight 1-mg dexamethasone suppression test

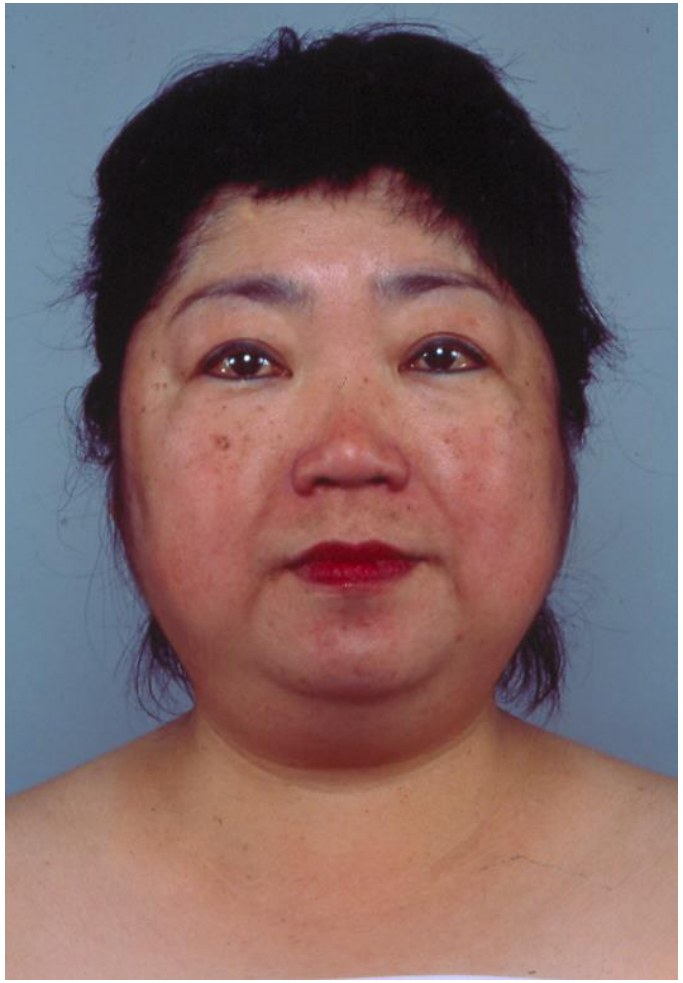
Mild Hypercortisolism

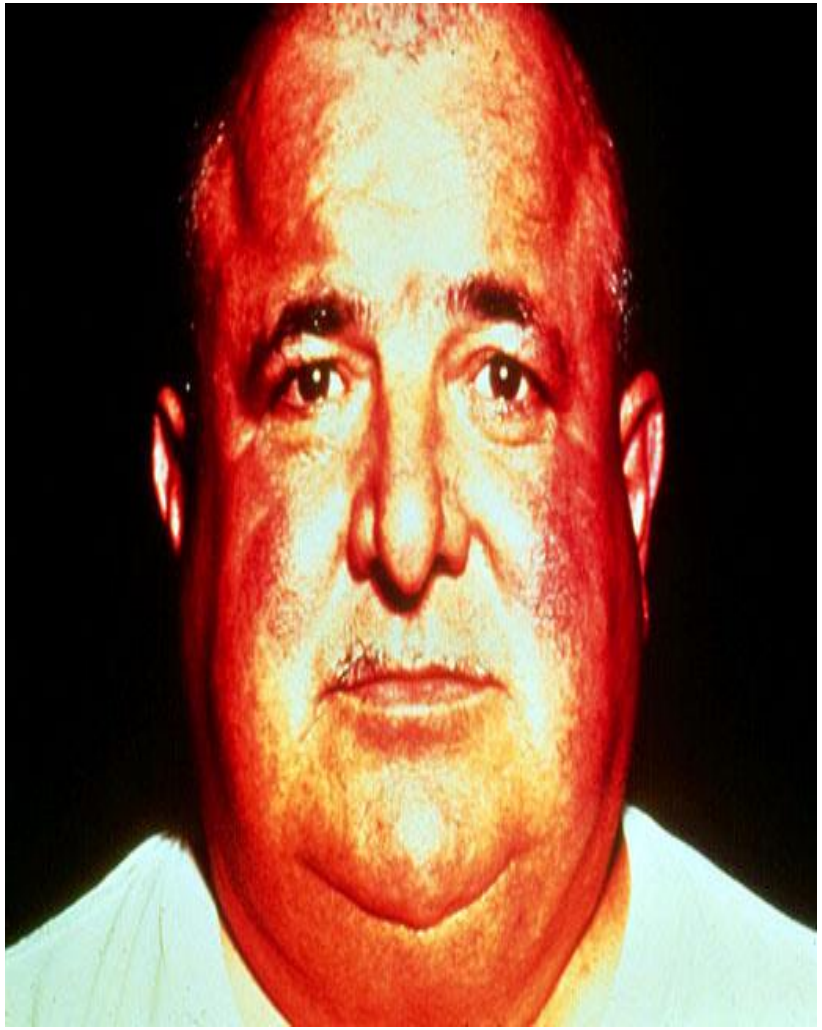
- Prevalence of about 5%
- Past known as Subclinical Cushing's syndrome
- Mild autonomous cortisol secretion
- Increased frequency of hypertension, glucose intolerance, diabetes and possibly osteopenia compared with the general population
- 1 mg dexamethasone suppression test
  - cortisol level of 1.8-5
    - > 5 ug/dL is considered to be clinically significant (specificity is 91%)

Management:
Surgical vs Conservative

- Retrospective study of 41 patients with adrenal incidentaloma and SCS followed for 18-48 months
- Significant improvement in blood pressure and fasting blood glucose who underwent surgery
- Significant worsening of blood pressure and fasting glucose in those who were managed conservatively
- Depends on the age and comorbidities
  - A reasonable strategy is to operate on younger patients (<40 years old) with a recent onset or worsening of diabetes, hypertension or osteoporosis

Cushing's Syndrome – too much cortisol

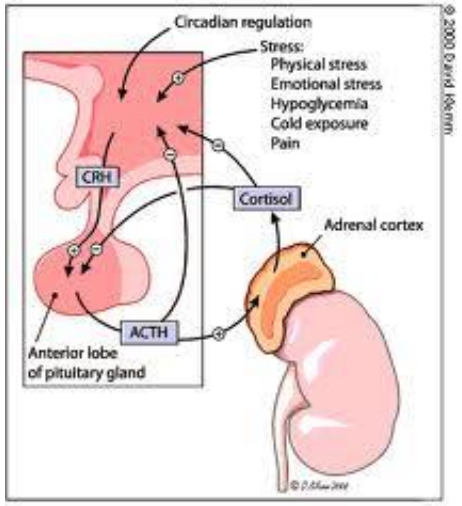




- Which of the following is the most common cause of hypercortisolism?

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

Hypercortisolism

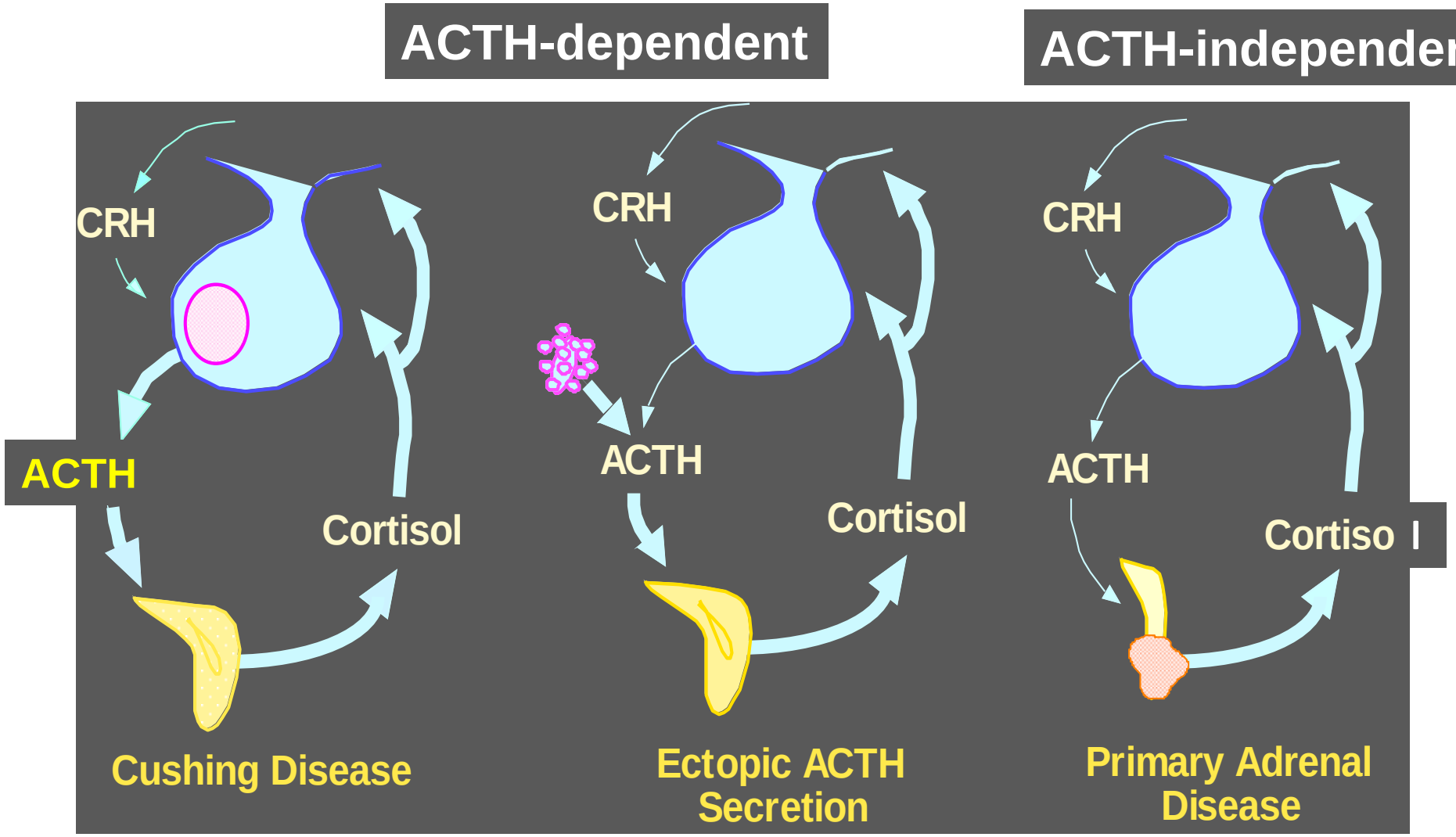


Causes of Hypercortisolism	
Etiology	Frequency
Pituitary adenoma	65%-70%
Ectopic ACTH	10%-15%
Adrenal adenoma	10%
Adrenal cancer	5%-10%

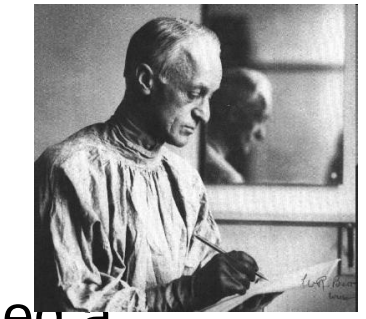
Cushing's Syndrome

- 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



Cushing's Syndrome – too much cortisol



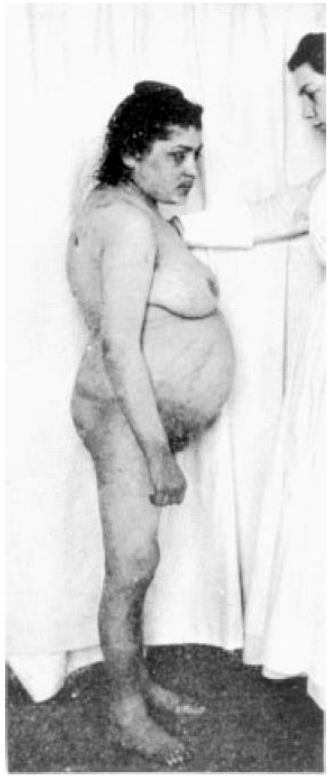
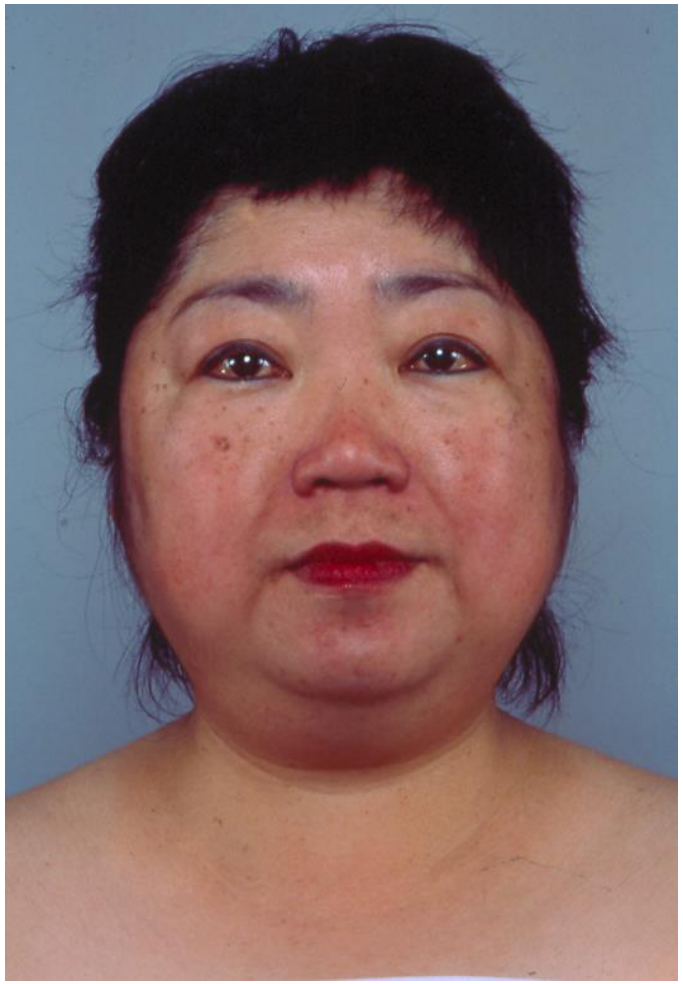


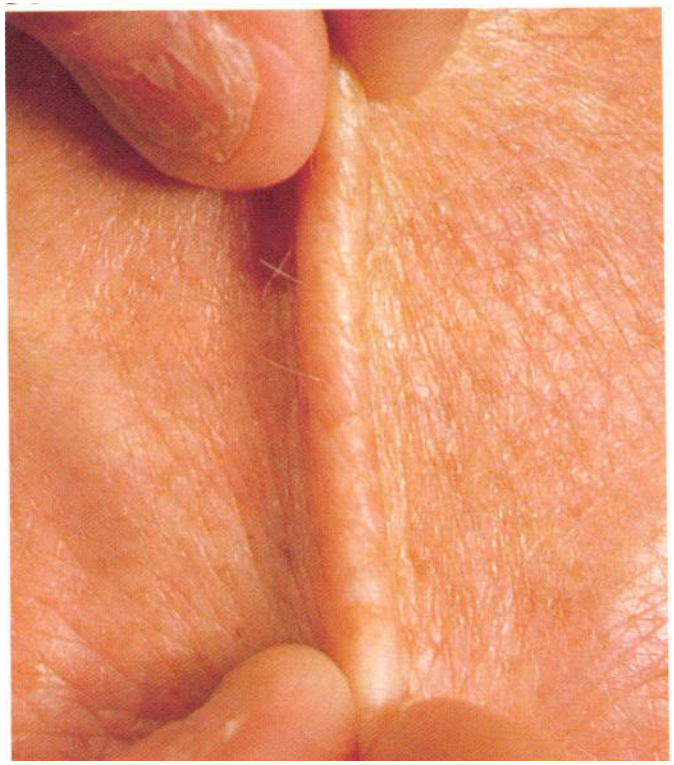
Fig. 3. Minnie G. Harvey Cushing's patient. Reported in The Pituitary Body and its Disorders, 1912.



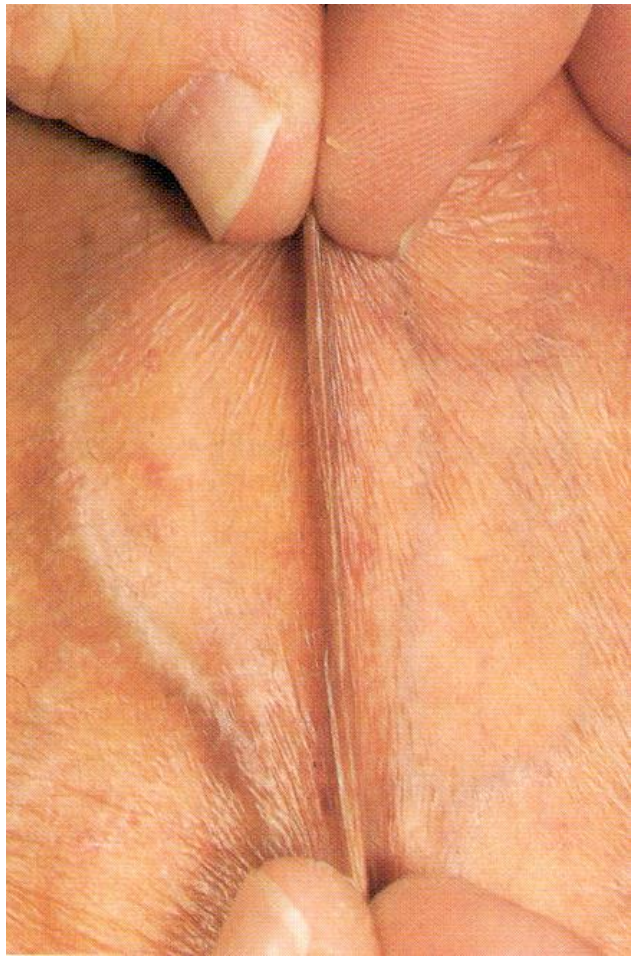
- Harvey Cushing first described a patient with hypercortisolemia in 1932

- 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

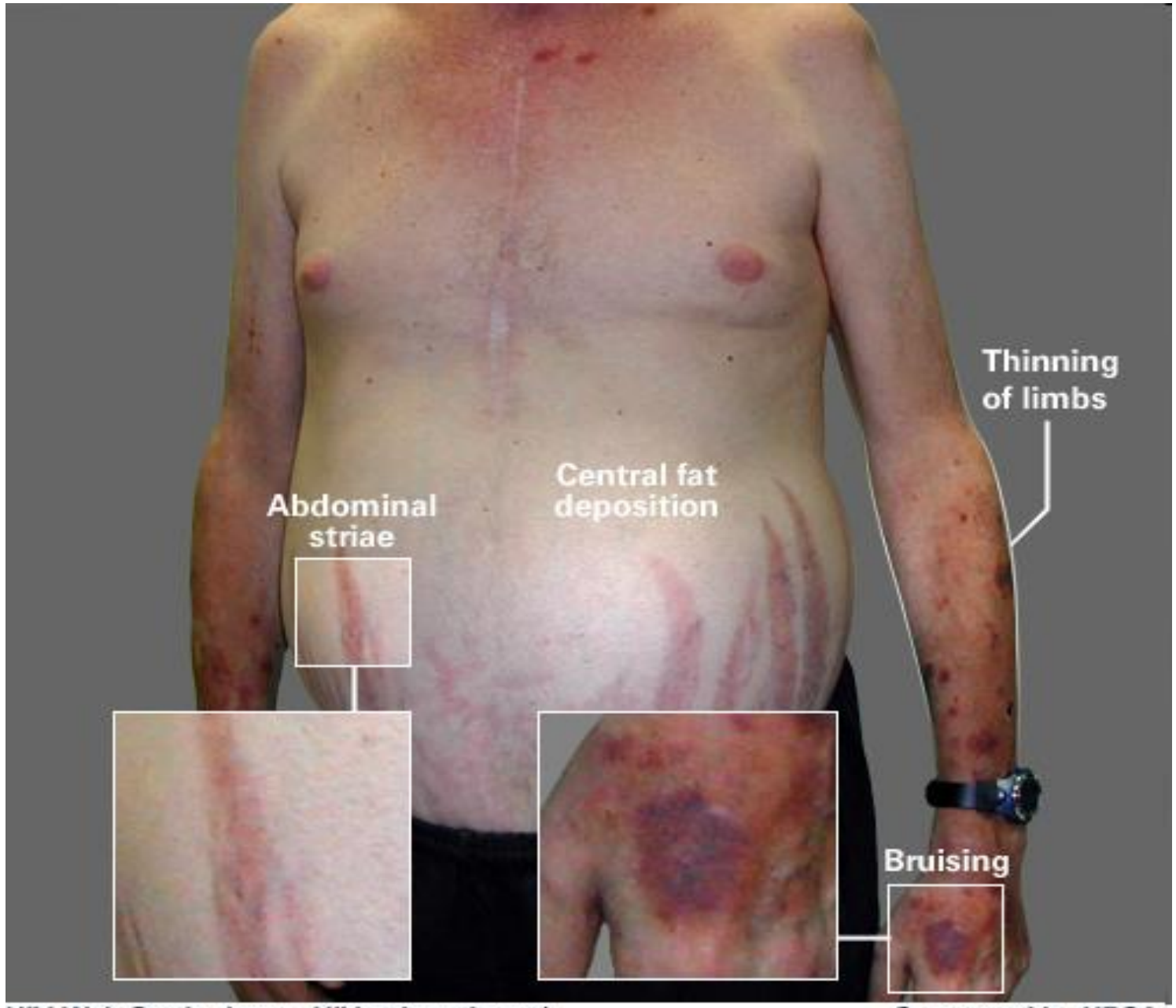
Cushing's Syndrome – thin skin

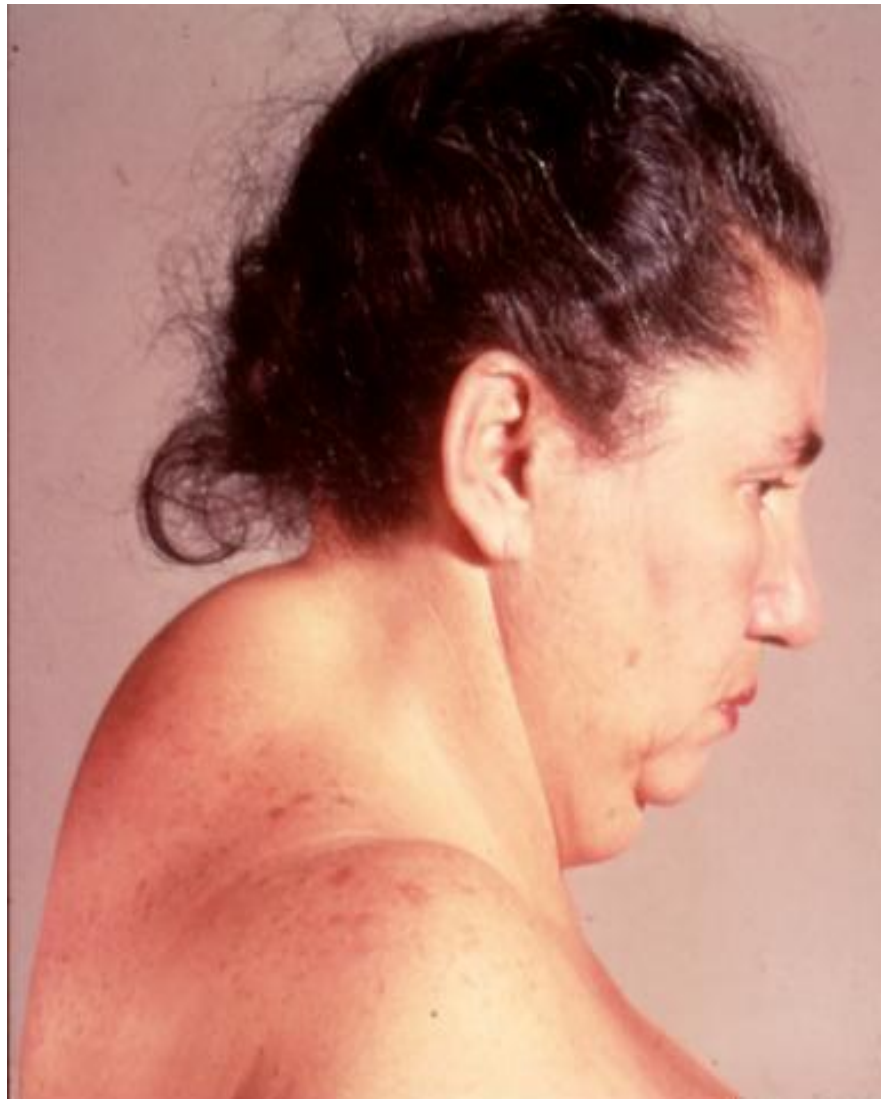


No Cushing's



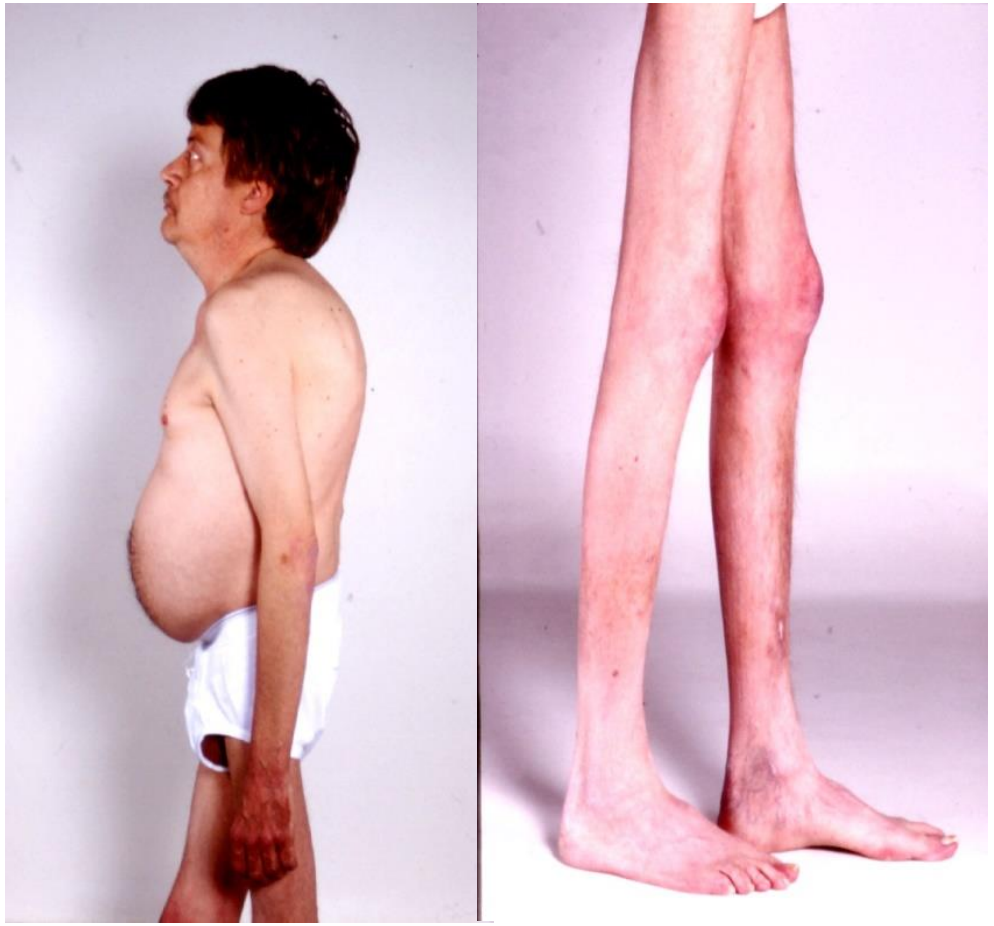
Cushing's


Thinning of limbs
Central fat deposition
Abdominal striae
Bruising
HIV Web Study (www.HIVwebstudy.org)
Supported by HRSA

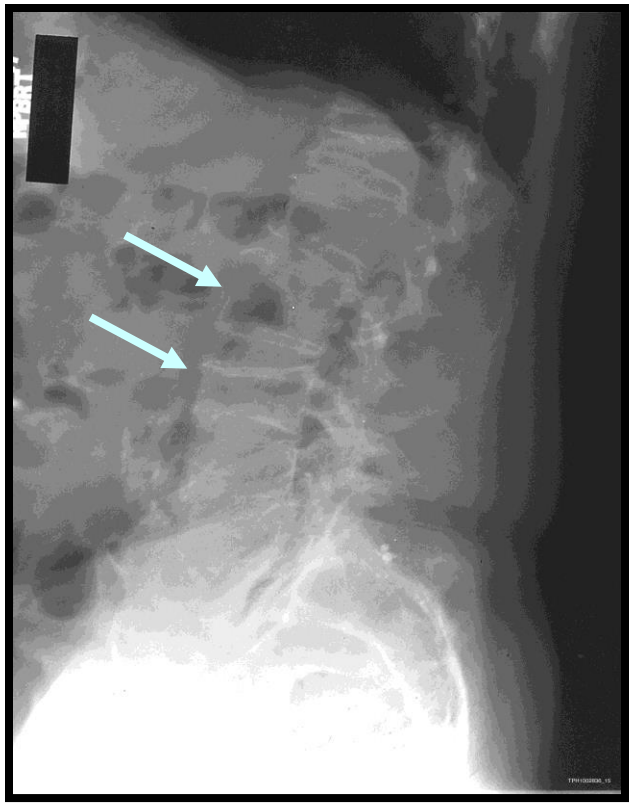


Dorsocervical fat pad

Cushing's syndrome



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



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

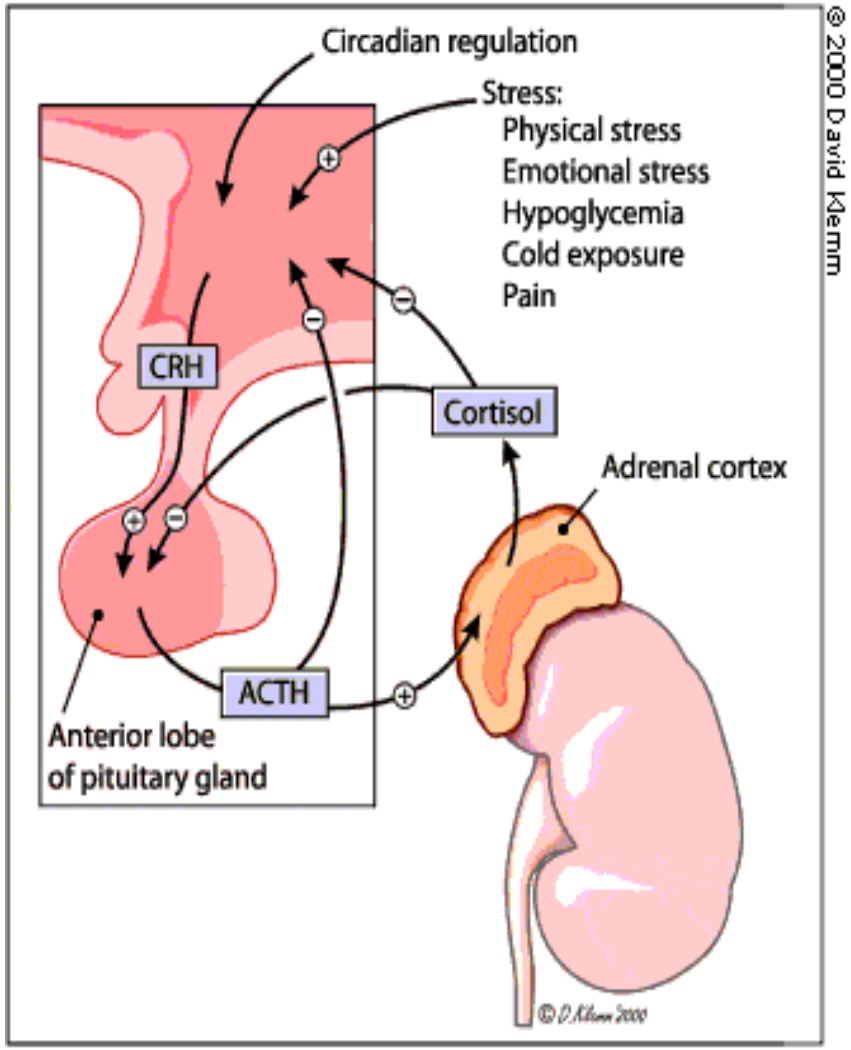
Screening for Cushing's

- 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

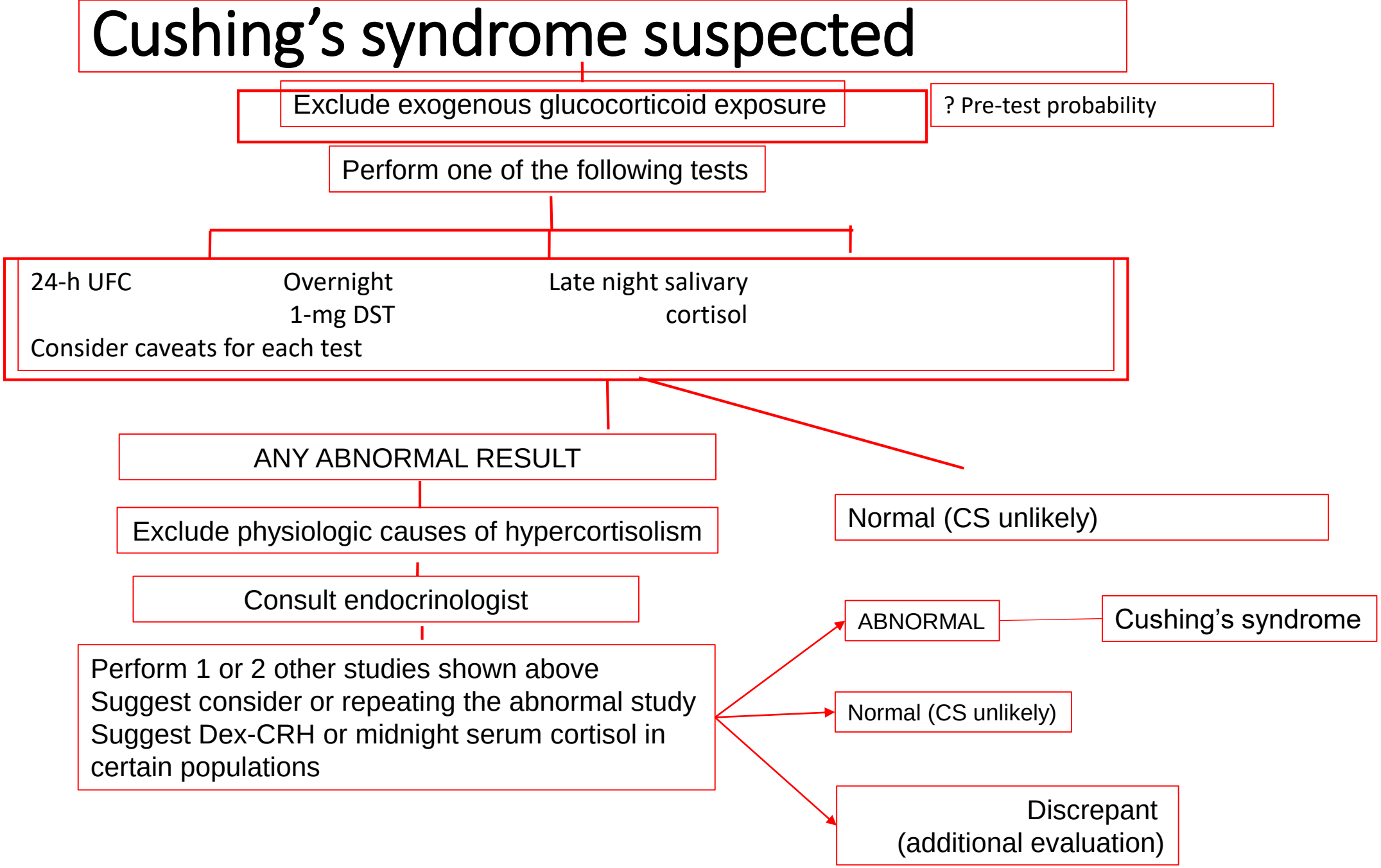
- Major depression or psychotic disorders
- Stress
  - surgical
  - medical
- Chronic alcoholism



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
Exclude exogenous glucocorticoid exposure
? Pre-test probability
Perform one of the following tests
24-h UFC
Overnight 1-mg DST
Late night salivary cortisol
Consider caveats for each test
ANY ABNORMAL RESULT
Exclude physiologic causes of hypercortisolism
Consult endocrinologist
Perform 1 or 2 other studies shown above
Suggest consider or repeating the abnormal study
Suggest Dex-CRH or midnight serum cortisol in certain populations
Normal (CS unlikely)
ABNORMAL
Cushing's syndrome
Normal (CS unlikely)
Discrepant (additional evaluation)

- 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

Determining the cause of hypercortisolism

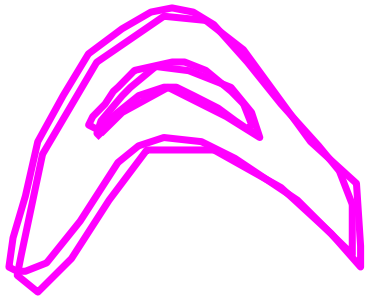
- Measurement of Plasma ACTH
  - < 5 pg/mL
    - ACTH-independent
  - > 20 pg/mL
    - ACTH-dependent
    - Higher in Ectopic Cushing's
  - 5 - 20 pg/mL
    - Indeterminate
  - Collect blood into prechilled EDTA tube, place on ice bath. Plasma should be separated rapidly and stored at -40^0 C to avoid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

Steroidogenesis Inhibitors



Cortisol

Ketoconazole/etomidate

Metyrapone

Aminoglutethimide

Mitotane

Trilostane

Drugs that decrease ACTH secretion:

Octreotide, Paseriotide, Cabergoline, Bromocriptine

Glucocorticoid antagonist: Mifepristone

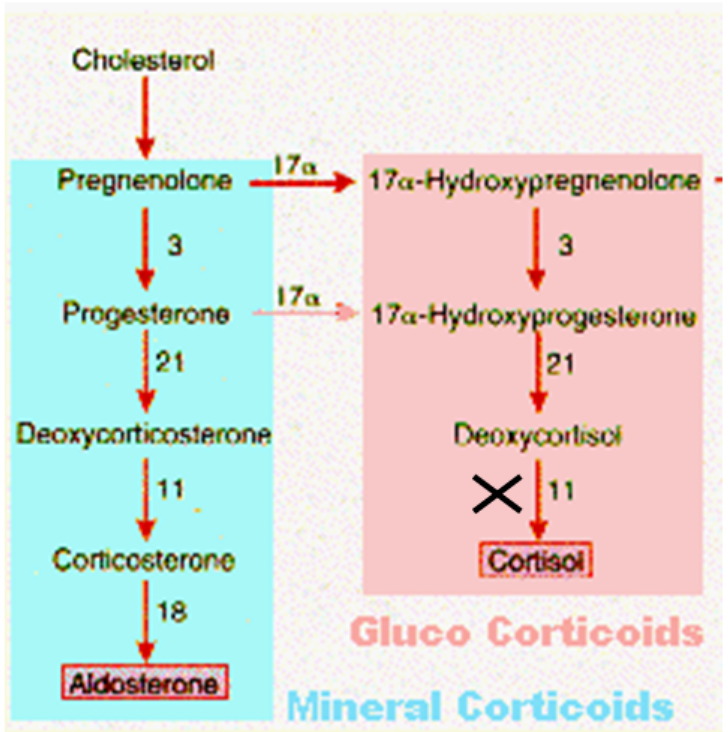
Ketoconazole

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

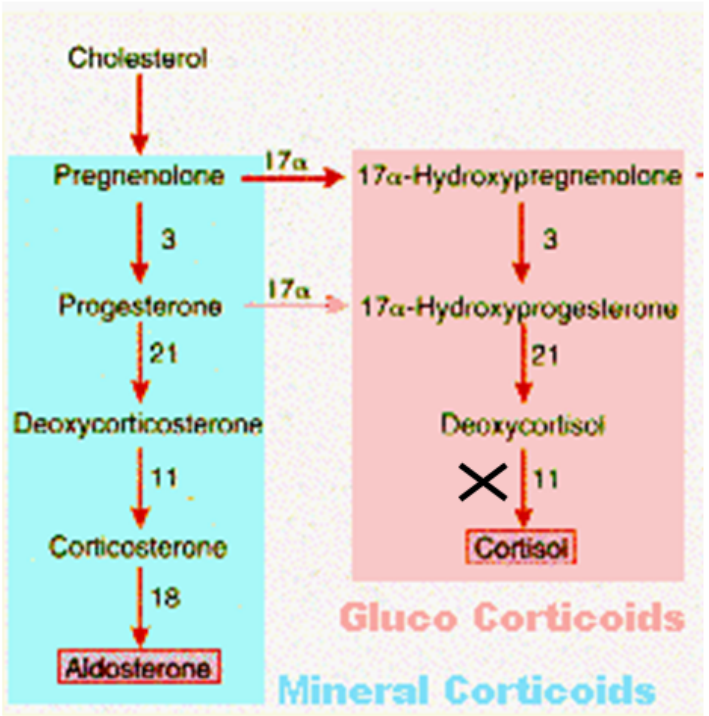
Metyrapone

Mechanism

- Blocks 11 beta hydroxylase

Clinical use

- Medical treatment of Cushings



Side effects/contraindications

- Symptoms of adrenal insufficiency

Other

- Not widely available

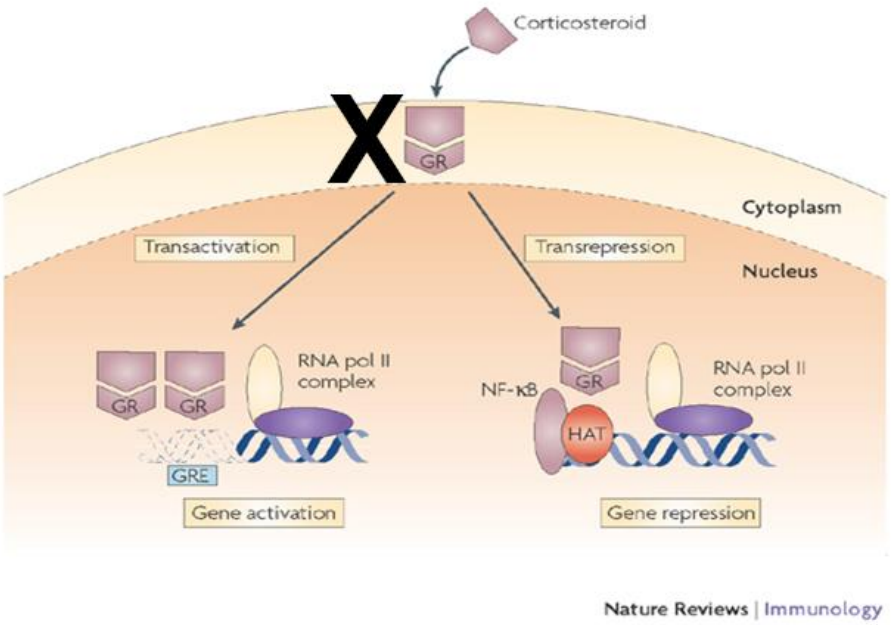
Mifepristone (Korlym)

Mechanism

- Glucocorticoid receptor antagonist

Clinical use

- Medical treatment of Cushing's



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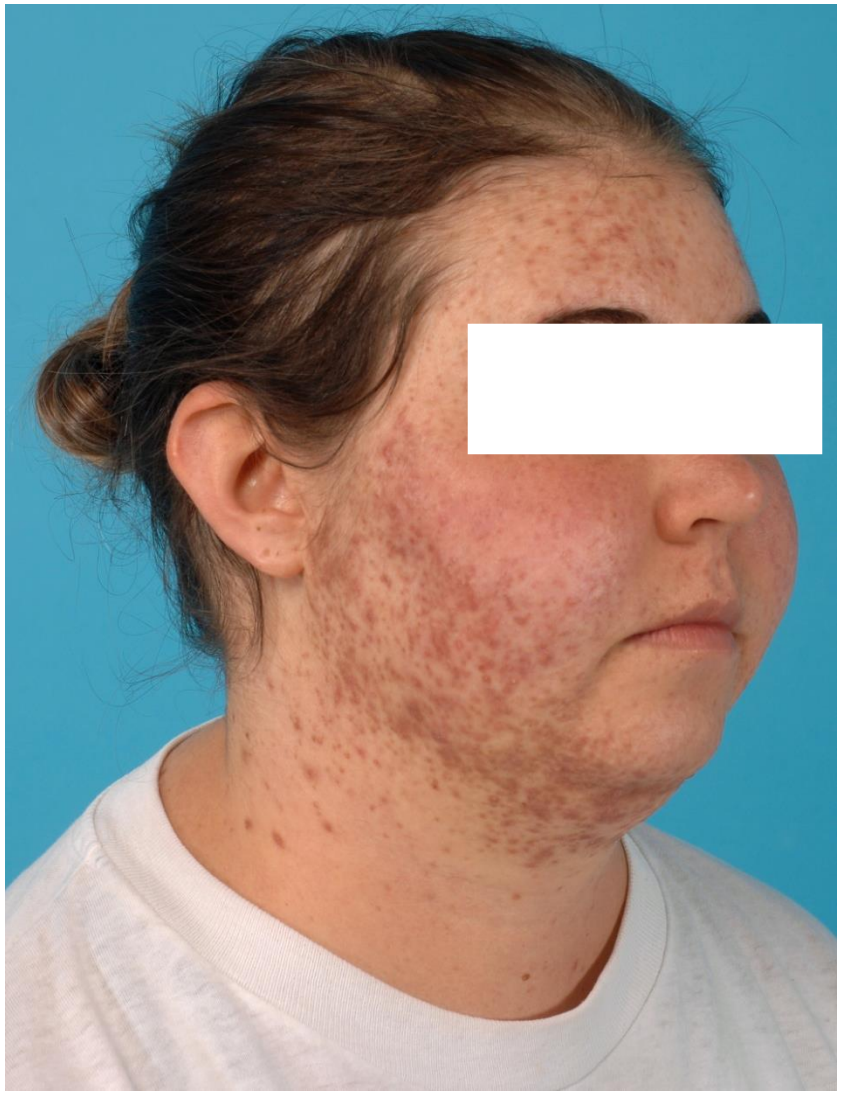
Side effects/contraindications

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

Other

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



A 33-year-old man has been referred to you for evaluation of Cushing syndrome. He has an 11-year history of HIV infection. He is taking antiretroviral therapy, including didanosine, tenofovir, and ritonavir. His viral load is zero and his CD4 cell count is normal. He has developed asthma in the past 6 months and has been taking fluticasone/salmeterol twice daily and an albuterol metered-dose inhaler as needed. He has gained 30 lb (13.6 kg) in the past 3 months. Hypertension and fasting hyperglycemia have developed.

On physical examination, he has a very cushingoid appearance, with wide, violaceous abdominal striae and proximal muscle weakness.

Which of the following laboratory profiles is most likely to be found in this man?

Answer	Plasma ACTH	DHEA-S	Cortisol
A.	Normal	Normal	Normal
B.	⇑	⇑	⇑
C.	⇓	⇓	⇑
D.	⇓	⇓	⇓
E.	⇑	⇓	⇓

A 33-year-old woman returns to your clinic for continued management of her hypertension. She reports compliance with lifestyle modifications and prescribed anti-hypertensive medications including lisinopril, metoprolol, and losartan. She reports feeling fatigued and has noted slight abdominal distention. Her blood pressure at this visit is 155/92 mmHg. Serum laboratory tests show potassium 3.1 mEq/L and sodium 144 mEq/L.

What is the next step?

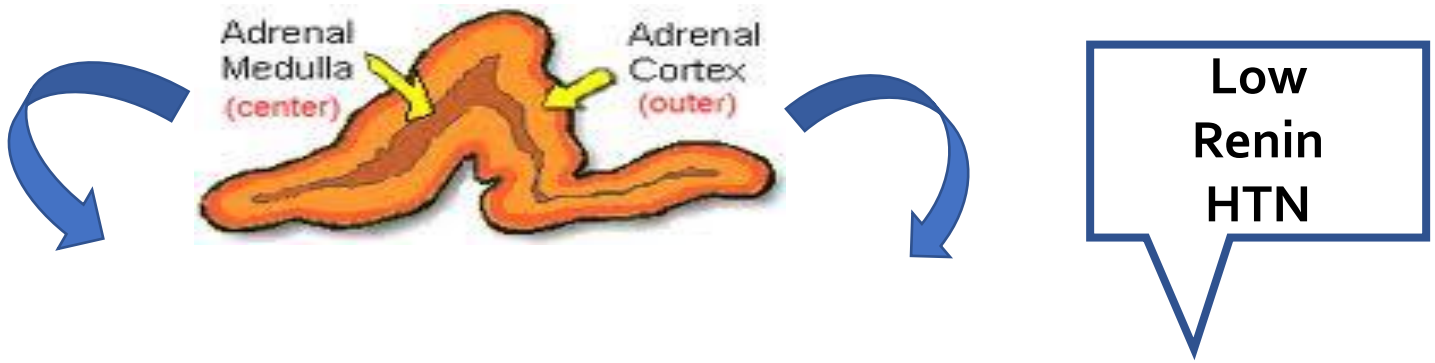
A. Measure plasma renin and aldo

B. CT abdomen

C. Saline suppression test

D. Start spironolactone

Adrenal Hypertension



Adrenal Medulla

- Pheochromocytoma

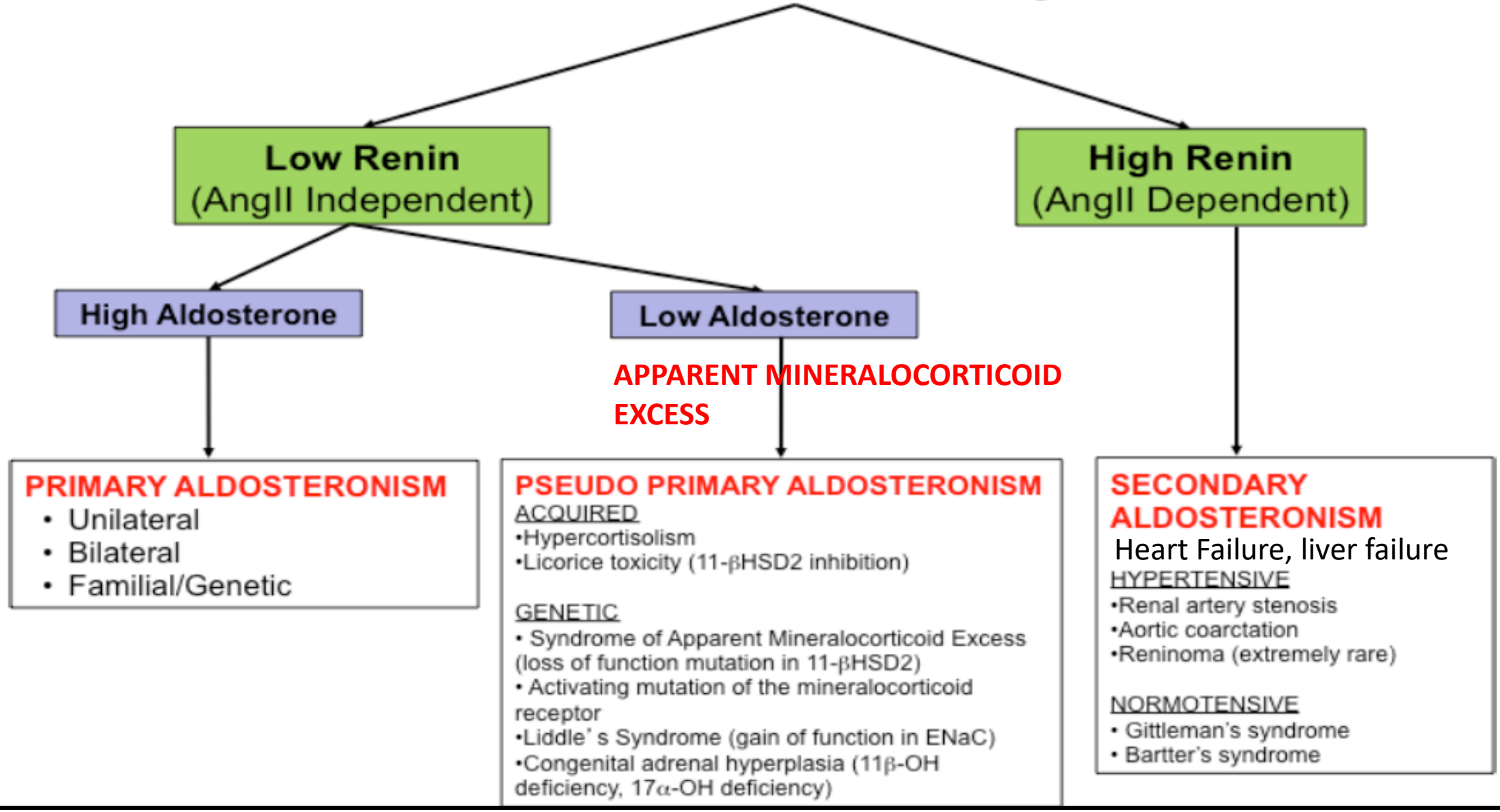
Adrenal Cortex

- Cushing's Syndrome
- **Primary Aldosteronism (PA)**
- Congenital Adrenal Hyperplasia (11β or 17α deficiency)
- Familial Glucocorticoid Resistance
- Apparent Mineralocorticoid Excess

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 use to be low <1 % now is more >15%

Mineralocorticoid Excess Syndrome



Clinical Presentation

- Hypertension is common ranging form mild and intermittent to persistent and severe.

- Hypokalemia
  - frequent cramps, fatigue, muscle weakness, nocturia and polyuria.
  - Metabolic alkalosis may be also present.
  - Renal Cysts

- Adrenal incidentaloma

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 (>12 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

Caveats to testing with ARR

FALSE POSITIVE ARR

- Beta-Blockers
- Alpha-agonists (clonidine , methyldopa)
- NSAIDs
- Sodium loading
- Old age
- Premenopausal women
- Renal Failure

LOOK AT ALDOSTERONE LEVELS IN THESE CASES

FALSE NEGATIVE ARR

- Hypokalemia
- Sodium restriction
- ACE inhibitor, ARBS
- Diuretics
- K+ sparing diuretics
- Malignant Hypertension

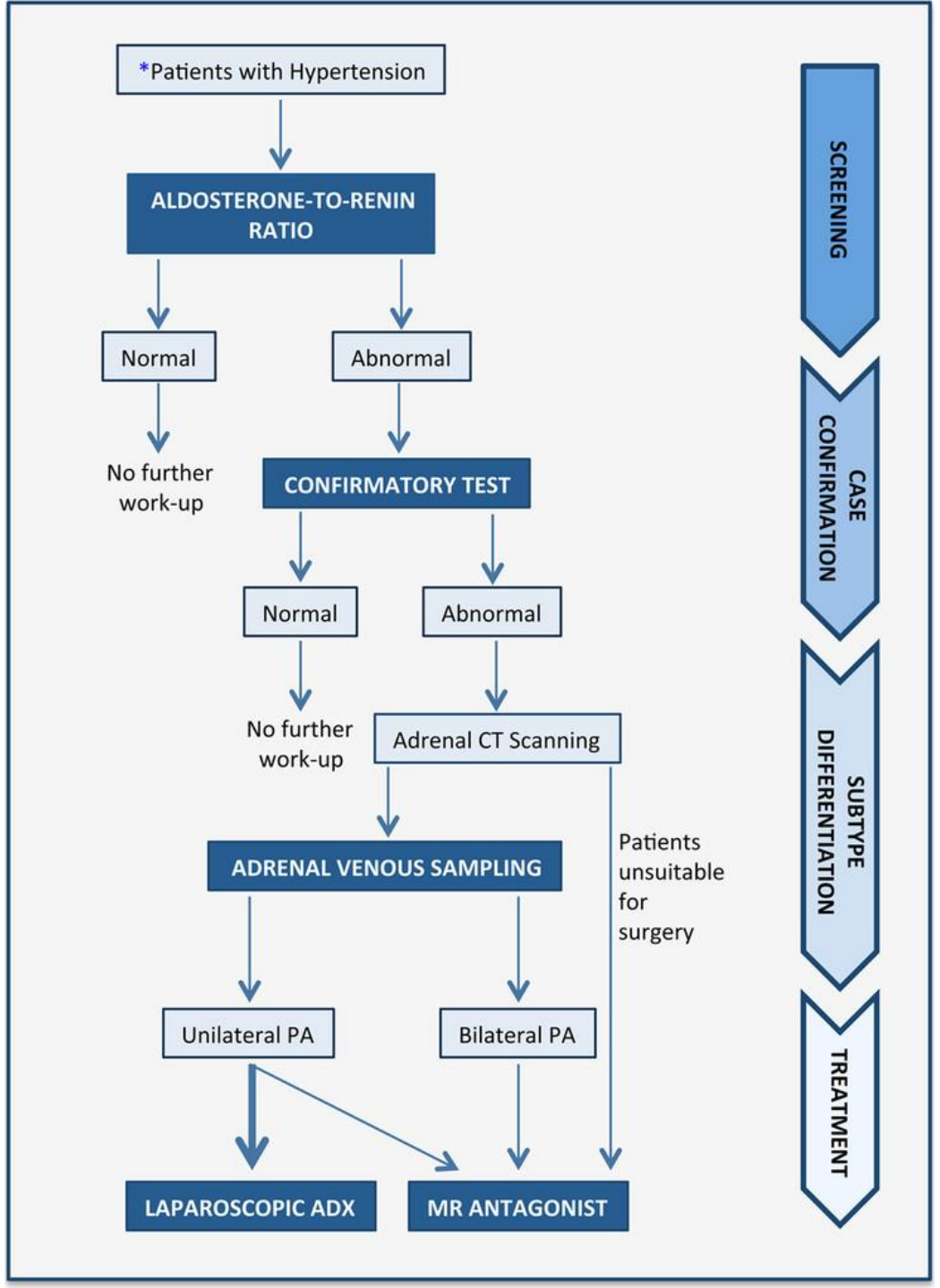
IF ARR IS HIGH IN PATIENTS ON THESE DRUGS, YOU HAVE A POSITIVE SCREENING TEST

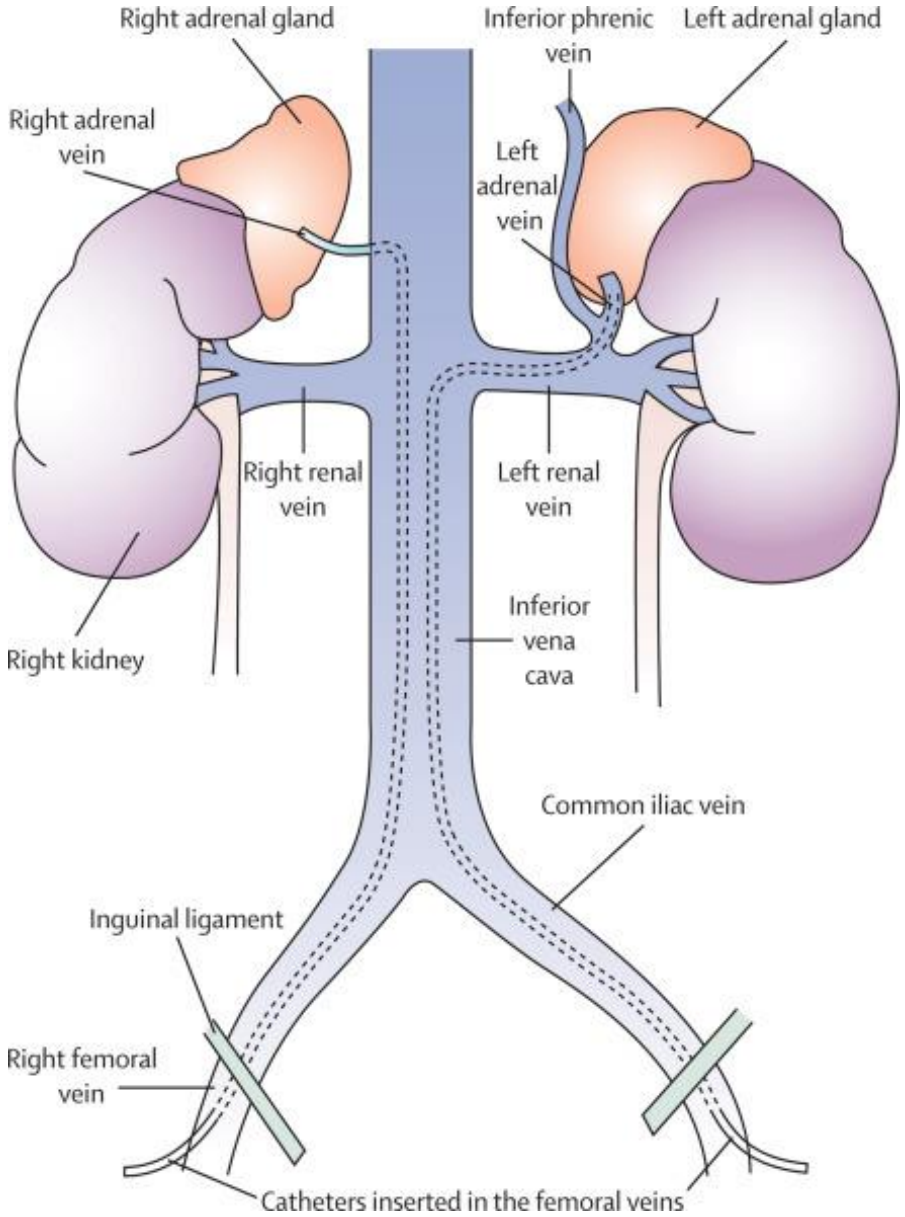
Confirmatory testing: Primary Hyperaldosteronism

TEST	METHOD	CUT-OFFS	PRECAUTIONS
ORAL SALT LOADING	Salt load 6g/day for 3 days with adequate K+	Day 4, 24 hr urine aldosterone > 12 mcg, urine Na >200 mmol	Avoid in renal failure, CHF, uncontrolled HTN
SALINE SUPPRESSION TEST	2L normal saline infused over 4 hours (seated/recumbent)	Post-saline Aldosterone >10ng/dl	Avoid in renal failure, CHF, uncontrolled HTN
FLUDROCORTISONE SUPPRESSION TEST	Fludrocortisone 0.1 mg every 6 hrs, K+ tabs every 6 hrs, Na 30 mmol tid qac for 4 days	Day 4 , 10 am aldosterone >6 ng/dl	Cumbersome, not much experience
CAPTOPRIL CHALLENGE TEST	Captopril 25-50 mg once	Aldosterone at 0,1 or 2h Suppression of aldosterone <30%	Substantial False negatives

– CT scan

– **AVS**


*Patients with Hypertension
ALDOSTERONE-TO-RENIN RATIO
Normal
Abnormal
No further work-up
CONFIRMATORY TEST
Normal
Abnormal
No further work-up
Adrenal CT Scanning
ADRENAL VENOUS SAMPLING
Patients unsuitable for surgery
Unilateral PA
Bilateral PA
LAPAROSCOPIC ADX
MR ANTAGONIST
SCREENING
CASE CONFIRMATION
SUBTYPE DIFFERENTIATION
TREATMENT



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 (ALDOSTERONAMA)
- Medical Treatment (BILATERAL HYPERPLASIA)
  - Mineralocorticoid Receptor Antagonists
    - Spironolactone
    - Eplerenone
  - Sodium Channel Antagonists
    - Triamterene
    - Amiloride

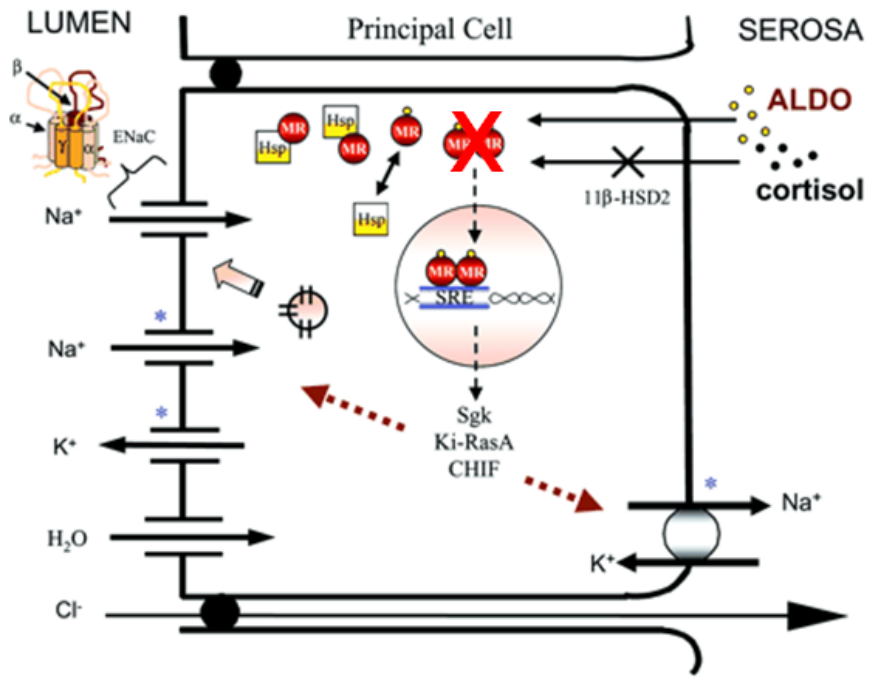
Surgical Cure of Hypertension

- 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

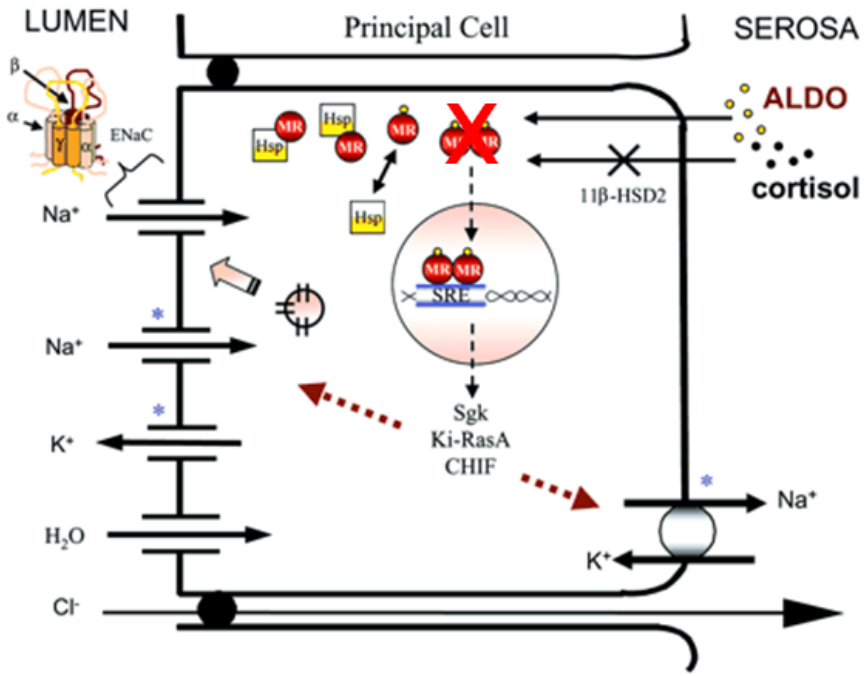
Other

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

Eplerenone (Inspra)

Mechanism

- Aldosterone receptor antagonist
- Inhibits actions of aldosterone



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Clinical use

- Primary aldosteronism
- Secondary aldosteronism
  - CHF
  - cirrhosis

Side effects/contraindications

- Hyperkalemia
- GI upset

Other

- Does not have significant testosterone receptor blockade effect

A 60-year-old male has uncontrolled hypertension resistant to multiple antihypertensives. Abdominal CT shows the presence of bilateral adrenal hyperplasia. Which one of the following is consistent with a diagnosis of primary hyperaldosteronism?

A. Decrease ACTH level
B. Increase renin level
C. ARR increase >30
D. Hypokalemic acidosis

Thanks

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