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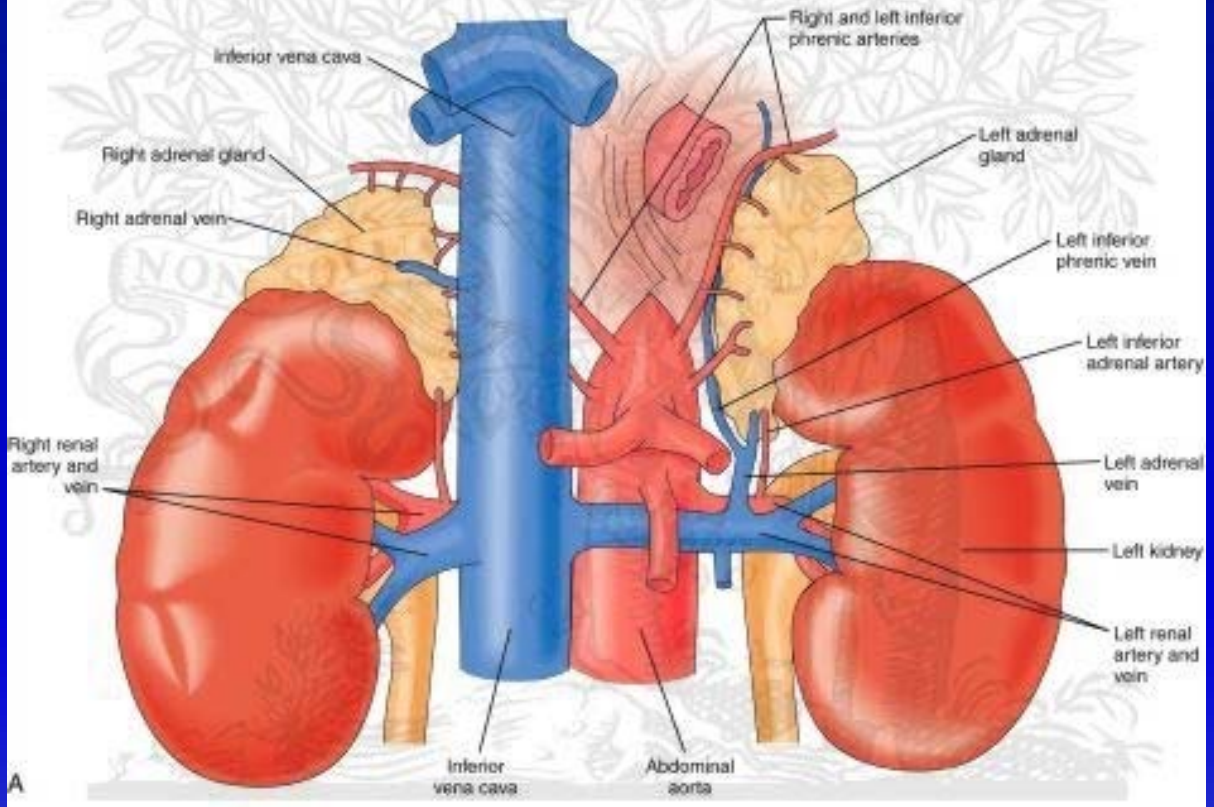
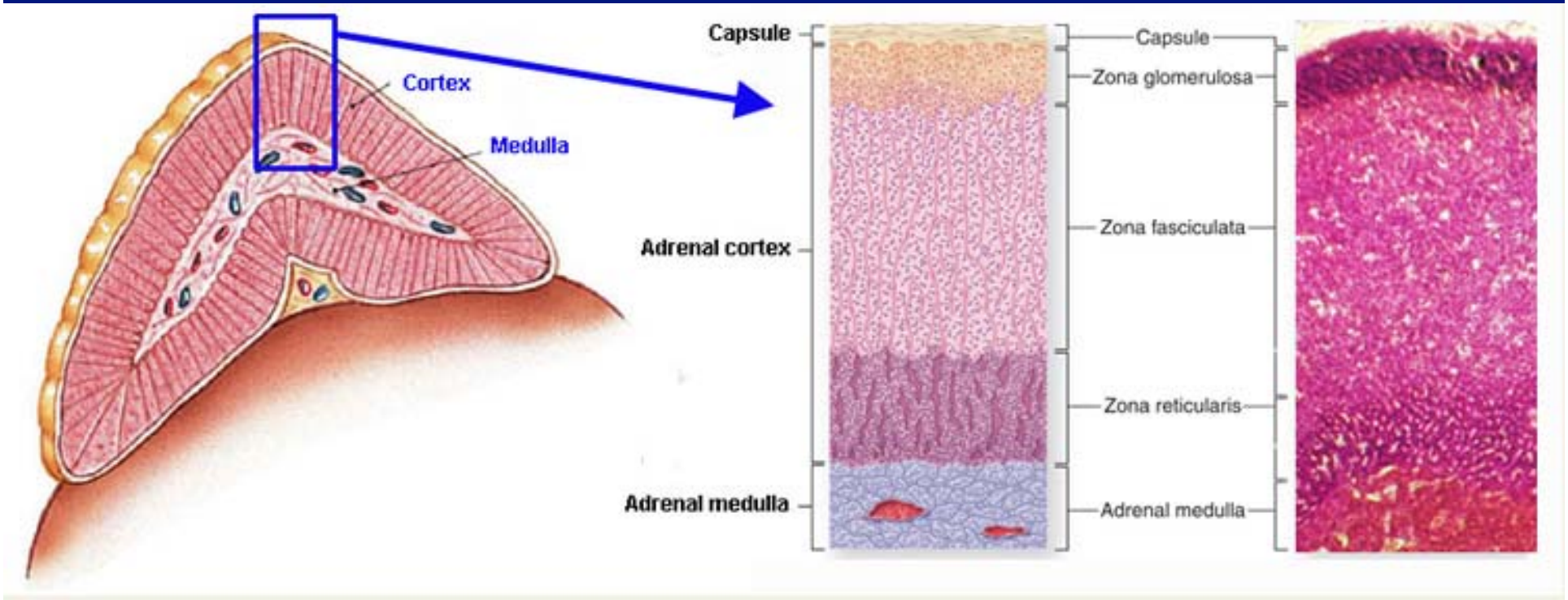
ADRENAL INSUFFICIENCY

Learning Objectives

- Distinguish the clinical and laboratory findings of primary and secondary adrenal insufficiency
- Appropriately use and interpret the results of basal and dynamic tests of adrenal function
- Basic understanding of the controversy in diagnosis and management of adrenal insufficiency of critical illness
- List the drugs that interfere with the hypothalamic-pituitary adrenal axis and cortisol metabolism

Adrenal Anatomy





Cortex consists of 3 different zones

- Zona Glomerulosa- mineralocortidoids
- Zona Fasciculata- cortisol
- Zona Reticularis- sex hormones

Medulla

- Chromaffin cells- metanephrines and catecholamines

Adrenal Insufficiency

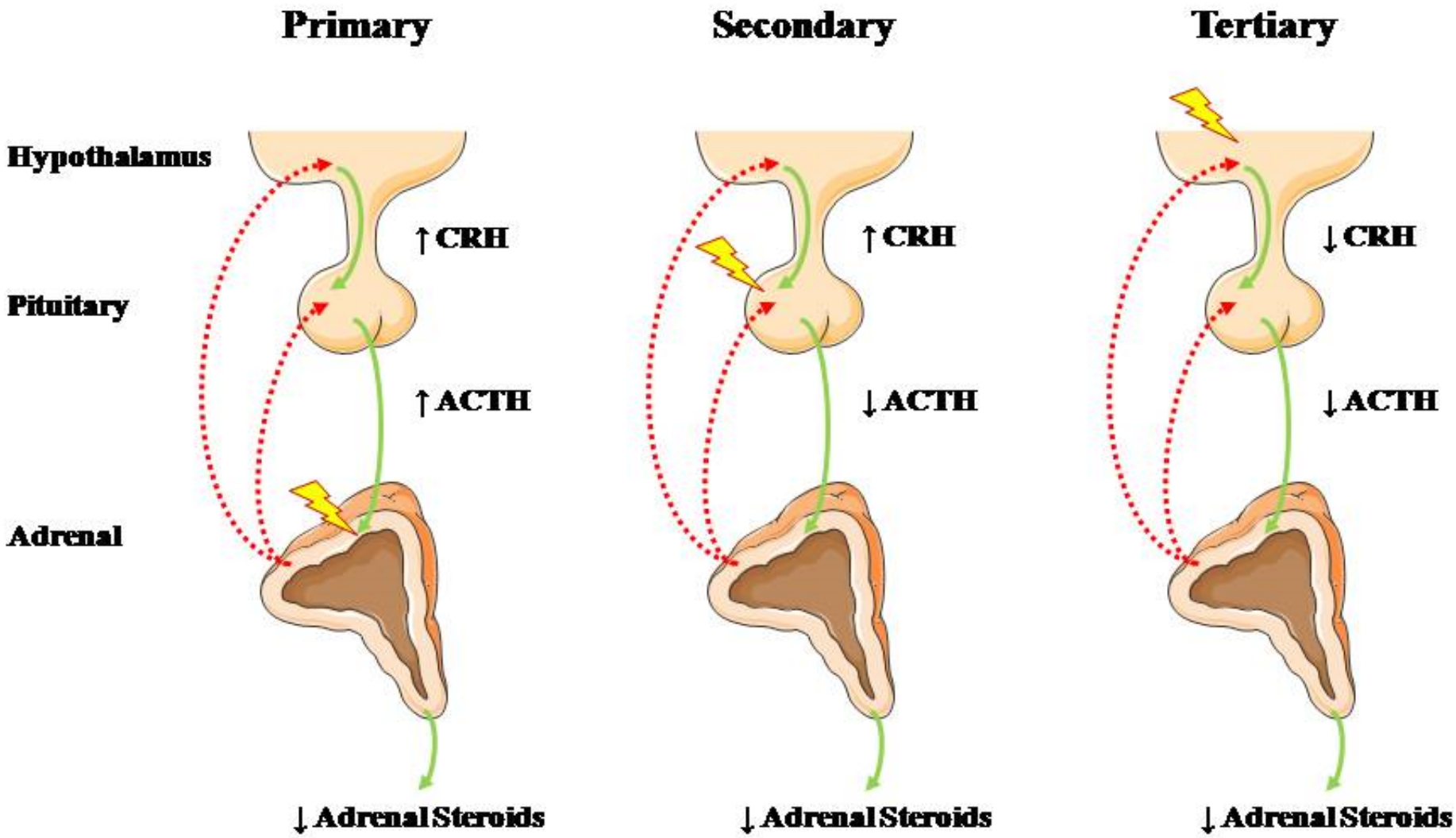
Life threatening disorder, arising from disruption of the normal hypothalamic-pituitary-adrenal (HPA) axis regulation of steroidogenesis. Deficient production or action of glucocorticoids and/or mineralocorticoids and occasionally adrenal androgens.

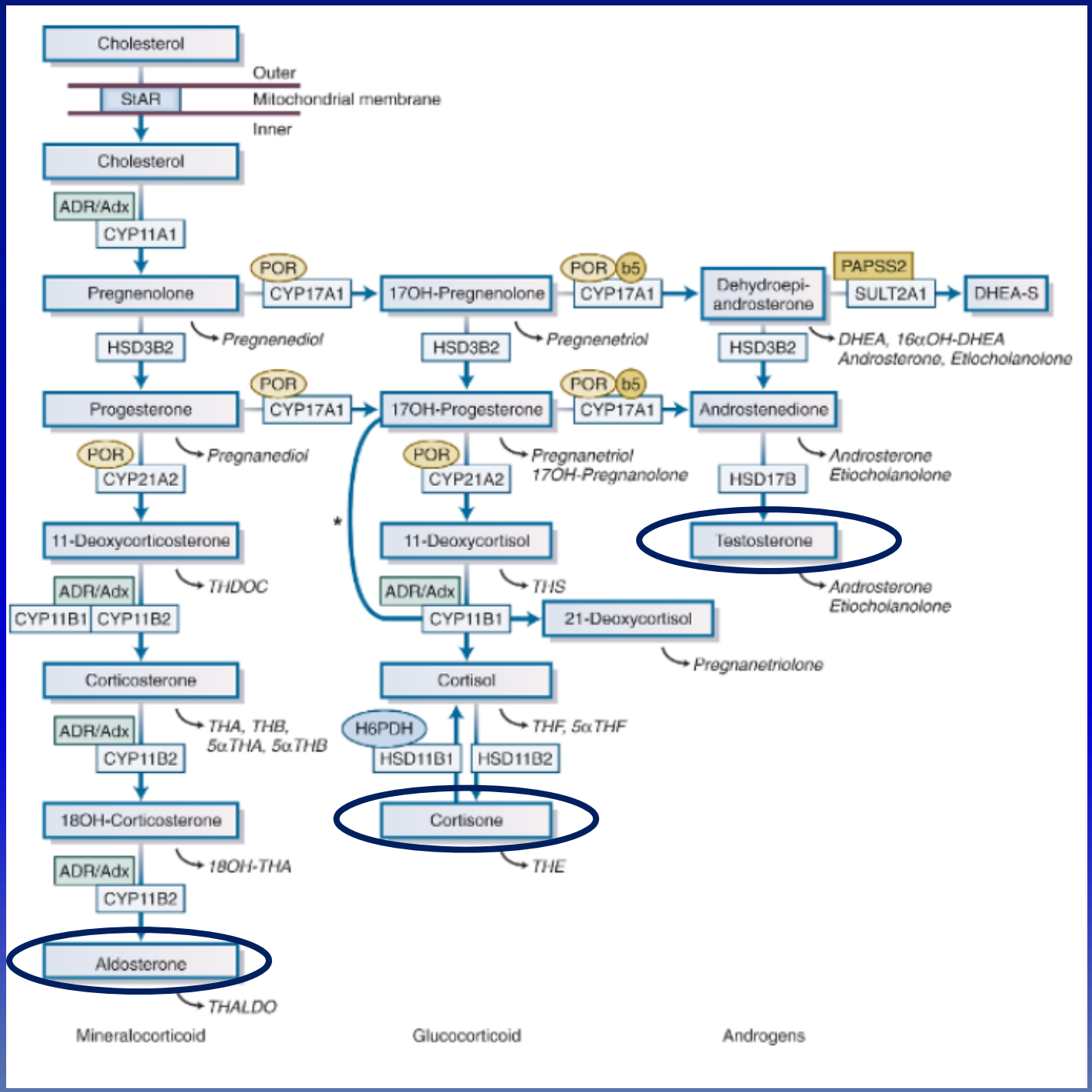
Central/Secondary

Tertiary Adrenal Insufficiency (Hypothalamic)

Secondary Adrenal Insufficiency (Anterior Pituitary)

Primary Adrenal Insufficiency (Adrenal)


Primary
Secondary
Tertiary
Hypothalamus
Pituitary
Adrenal
↑CRH
↑ACTH
↓Adrenal Steroids
↑CRH
↓ACTH
↓Adrenal Steroids
↓CRH
↓ACTH
↓Adrenal Steroids


Cholesterol
Outer
StAR
Mitochondrial membrane
Inner
Cholesterol
ADR/Adx
CYP11A1
Pregnenolone
POR
CYP17A1
17OH-Pregnenolone
POR b5
CYP17A1
Dehydroepi-androsterone
PAPSS2
SULT2A1
DHEA-S
HSD3B2
Pregnenediol
HSD3B2
Pregnenetriol
HSD3B2
DHEA, 16αOH-DHEA
Androsterone, Etiocholanolone
Progesterone
POR
CYP17A1
17OH-Progesterone
POR b5
CYP17A1
Androstenedione
POR
CYP21A2
Pregnanediol
POR
CYP21A2
Pregnanetriol
17OH-Pregnanolone
HSD17B
Androsterone
Etiocholanolone
11-Deoxycorticosterone
11-Deoxycortisol
Testosterone
THDOC
THS
Androsterone
Etiocholanolone
ADR/Adx
CYP11B1 CYP11B2
ADR/Adx
CYP11B1
21-Deoxycortisol
Pregnanetriolone
Corticosterone
Cortisol
ADR/Adx
CYP11B2
THA, THB,
5αTHA, 5αTHB
H6PDH
HSD11B1
HSD11B2
THF, 5αTHF
18OH-Corticosterone
Cortisone
ADR/Adx
CYP11B2
18OH-THA
THE
Aldosterone
THALDO
Mineralocorticoid
Glucocorticoid
Androgens

First Clue: Clinical Manifestations

- Fatigue
- Weakness
- Anorexia
- Unexplained Weight loss
- Nausea
- Vomiting
- Abdominal Pain
- Diarrhea (can alternate with constipation)
- Hyperpigmentation (Primary Only)
- Dizziness
- Shock
- None provide very good sensitivity or specificity

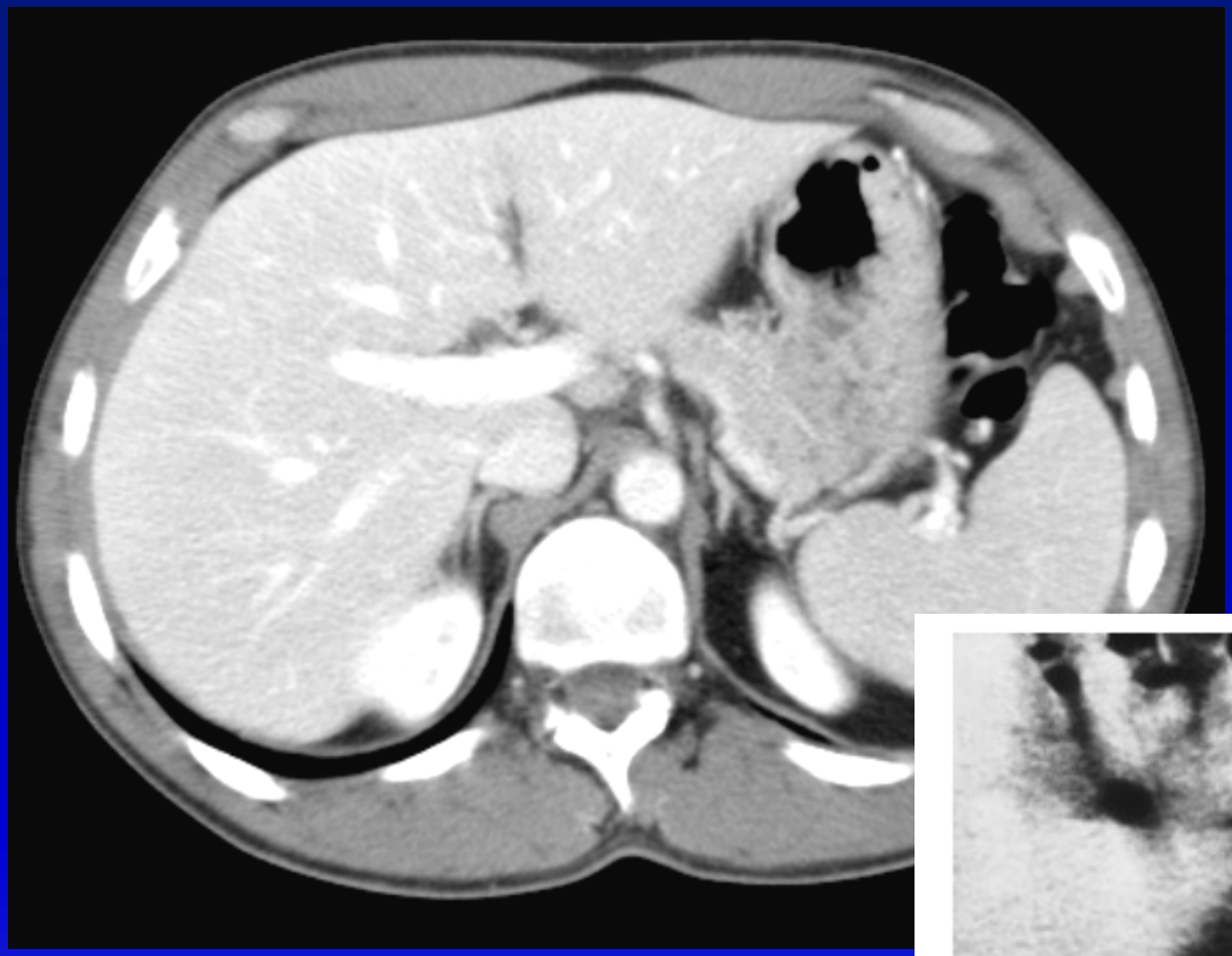
Very Rarely are AI patients gaining weight unless have other organ failure disease

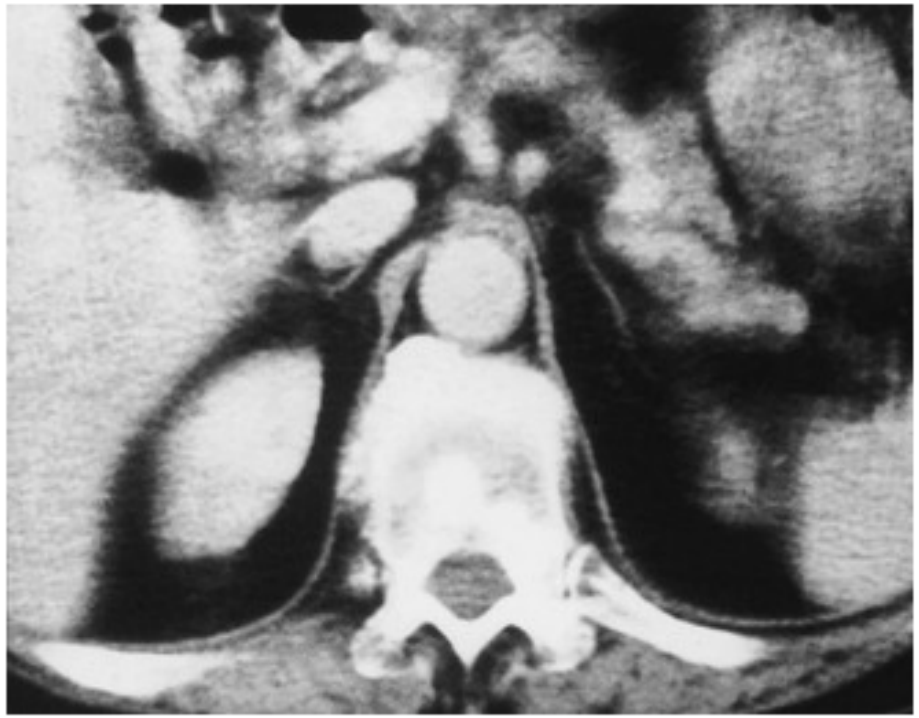
Second Clue: Routine Laboratory Abnormalities

- Hyponatremia: most common in primary & secondary AI
  - Why? GC exert negative feedback on vasopressin secretion and deficiency of cortisol may result in nonosmotic stimulation of vasopressin
- **unexplained hyponatremia
- 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

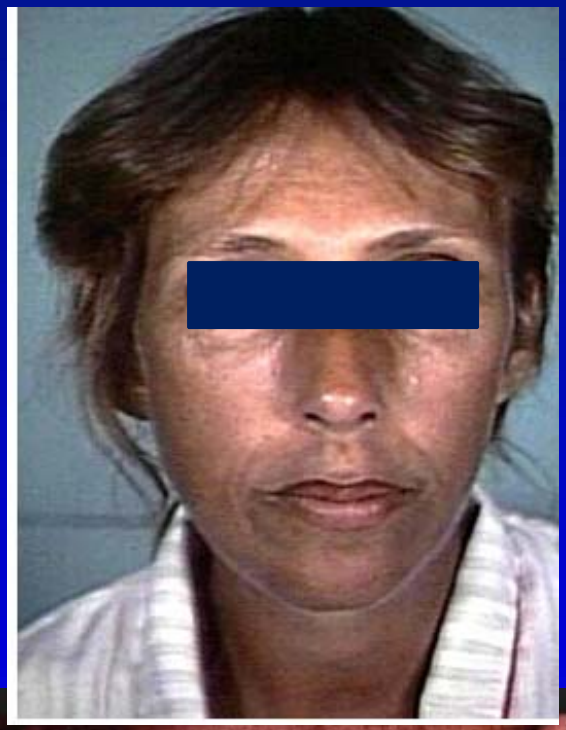
Medications

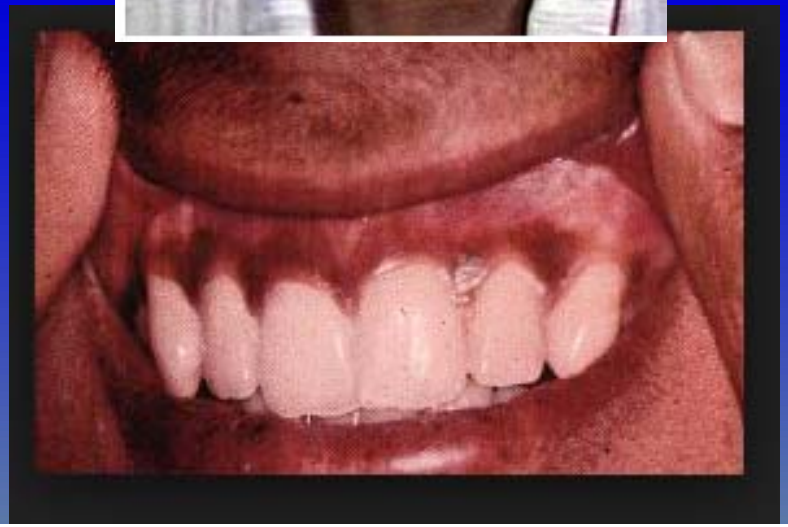
- Opioids- secondary/tertiary ; modify ACTH release
- Psychotropic medication – secondary
- Benzodiazepines (alprazolam), atypical antipsychotics (olanzapine, quetiapine) - secondary
- CTLA-4 monoclonal antibody induced hypophysitis (eg ipilimumab) -secondary
- GR antagonist (mifepristone) - primary

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





Outside of iatrogenic causes **AI is rare**

- Probability of AI is extremely low in absence of specific clinical features:
  - hyperpigmentation
  - hypotension
  - hypoglycemia
  - vitiligo
  - known pituitary disease
  - weight loss
  - anorexia

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 < 3-5 ug/dl highly suggestive but not always diagnostic (clinical correlation needed)
- BUT if cortisol drawn at any time of day is > 14 ug/dl is 99% specific for predicting a cortisol increase greater than 18 ug/dl during an ITT
- Basal cortisol values 5-14 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 < 15-20 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**
- **Protocol: IV 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**
- **Delta of 9 ug/dl not required if peak is >18 ug/dl**

Other dynamic testing- recommend endocrine involvement

- 1 ug cosyntropin stimulation test
  - Controversial use
  - Used in diagnosis of secondary AI
- 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

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
- Less commonly positive in children or adults > 60 yr. old
- 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

Special Conditions

- Cortisol Binding Deficiency
  - Very rare
  - Low serum cortisol 0.5-2 ug/dl
  - Lack features of AI
  - Can be with severe protein def/losing states

Plasma Free Cortisol During CST

- Useful for patients with hypoproteinemia (critical illness, anasarca)
- Pts on oral contraceptives which cause high CBG
- Free cortisol can be measured in saliva or plasma

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 with AI

- #1 Aggressive volume replacement with normal saline
- #2 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 of AI

- 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 of AI

- 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

Adrenal Insufficiency in the ICU patient with no known previous diagnosis

- Many studies have serious limitations and conflicting results
- NO definitive cut off values, must have clinical correlation
- Most studies did not account for hypoproteinemia which reduces plasma cortisol binding thus higher serum free cortisol to total cortisol concentration

Normal HPA Axis in Critical Illness

- Persistent Hypercortisolemia often 7-10 fold increase in serum free cortisol levels
- Due to the decrease in clearance from the inhibition of 11BHSD2 in the kidney that converts active cortisol to inactive cortisone.
- Neutrophil elastase cleaves liganded CBG releasing cortisol to sites of inflammation

Case findings for partial AI

Look at clinical setting and prior history for risk factors

- Prior history of GC or drugs that have GC affect

  -Megace

  -Etomidate (decrease secretion by inhibiting 11 B hydroxylase enzyme, effect can last up to 24hrs)

  -personal or family hx of autoimmune illness

  -known hypothalamic/pituitary illness

  -hx brain irradiation

Diagnostic Testing

- If patient has near normal serum binding proteins (albumin >2.5 g/dl) then total cortisol in critical illness is reliable
- Albumin > 2.5 g/dl, Total cortisol ≥ 14-15 ug/dl are expected in critical illness
- If patient has low serum binding proteins (albumin < 2.5 g/dl) then total cortisol in critical illness is not reliable
- If albumin <2.5 ug/dl, Total cortisol ≥ 7-11 ug/dl are expected in critical illness

ACTH Stimulation Test in AI During Critical Illness

- Often does not provide any additional meaningful information when accounting for possible delay in care
- If test is preformed, must interpret in context!
  - The total cortisol as it corresponds to the protein level
  - The stimulated cortisol will be exaggerated as compared to the ambulatory patient
  - The delta of 7-9 should not be a criterion for defining normal or abnormal adrenal function but can correlated to potential response to HC
  - Normal is peak cortisol at 30-60 min >18 ug/dl
  - Test may be “normal” if AI is secondary and of recent onset which does not allow enough time for adrenal atrophy

- ACTH, Aldosterone, Renin not diagnostically helpful in critical illness
  - Disconnect between acth and cortisol due to impaired cortisol clearance
  - Changes in sensitivity of ACTH to its receptor
  - Changes post translation processing of ACTH
  - Aldo and renin levels can decrease in prolonged serious illness reason unknown
- Consider DHEA-s measurement (which would be low) in AI… if < 65 y/o…takes time to come back
- Random serum free cortisol expected to be > 1.8 ug/dl in most critically ill patients
  - Very reliable
  - Not routinely commercially available
  - Can take 1 week to come back

Partial Adrenal Insufficiency

- Diagnosis in the outpatient setting is difficult which makes the diagnosis in critical illness even more challenging
- Usually presumption is that patient has enough cortisol reserve for normal daily life but may not have enough reserve at times of severe physiologic stress
- Not necessarily picked up by acth stim test

- The routine us of GC during critical illness is not justified expect when AI is properly diagnosed or in others who are hypotensive, septic and unresponsive to standard therapy.
- Give HYDROCORTISONE at the LOWEST DOSE for the SHORTEST period of time
- Hydrocortisone should be tapered and discontinued as clinically indicated in those who receive the drug without definitive diagnosis to avoid iatrogenic HPA suppression
- Presume you are treating the underlying illness and not AI

Chronic GC replacement

- 10mg/ m2 (BSA)
- Usually 15-20mg divided into 2 or 3 doses
- Dose to match the normal diurnal rhythm
- Two peaks of cortisol 7am and 8pm

  BID regimen with hydrocortisone
  - 1st dose upon awakening or 30 min prior to arising
  - Next dose 8hrs later and before 6pm
  - TID regimen as well
  - Less preferred is prednisone and dexamethasone since they are long acting and need to be metabolized in the liver to the active hormone
  - Florinef- ONLY In primary AI usually 0.05-0.2mg/day suffices
    - Watch K and BP

SICK DAY rules

- High fever, diarrhea, vomiting== double or rarely triple dose until completely well for 1 day then resume normal dose
- If cannot take meds orally, given IM hydrocortisone shot (should always have) and got to ER
- Planned surgeries , 50 mg IV x once prior to induction of anesthesia for surgeries < 4hrs
- Routine outpatient procedures: double the dose morning of procedure

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

Corticosteroid Comparison Chart

	Equivalent Glucocorticoid Dose (mg)	Potency relative to Hydrocortisone: Anti-Inflammatory	Potency relative to Hydrocortisone: Mineral-Corticoid	Half-Life: Plasma (minutes)	Half-Life: Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	- -

Reference: Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Commonly Prescribed Replacement Steroid Equivalents

Prednisone		Cortisone		Dexamethasone		Hydrocortisone (Cortef)
5 mg	=	25 mg	=	0.75 mg	=	20 mg

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 ager 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

Case 2

- 73 y/o man with T2DM was admitted with lobar pneumonia diagnosed 6 days prior. During the last 36 hrs he developed fever, hypotension, and decreased urine output and transferred to the ICU requiring intubation, mechanical ventilation and sedation.
- He receive aggressive isotonic fluid resuscitation, BS antibiotics and IV insulin.
- Na, K wnl Glucose controlled
- Calcium 7.9 mg/dl
- Albumin 1.9 mg/dl

- Intensivist performed assessment of adrenal function
- Basal serum cortisol was 11ug/dl
- 250 mcg acth stim test peak cortisol 17.5 ug/dl, increment of 6.5 ug/dl
- Serum aldosterone 3.5 ug/dl
- Plasma renin activity 12 ng/mg/h
- Basal Plasma ACTH 17 pg/ml

Does he have adrenal insufficiency based on laboratory evaluation?

- Partial Adrenal Insufficiency
- AI of critical illness
- Relative Adrenal Insufficiency
- Primary AI
- Secondary AI

Which of the following tests would you do next?

A. Administer hydrocortisone with fludrocortisone

B. Initiate high dose dexamethasone

C. Measure plasma free cortisol and/or salivary cortisol

D. Obtain pituitary MRI