

# RUTGERS

THE STATE UNIVERSITY  
OF NEW JERSEY



Annual Internal Medicine Review

# ENDOCRINOLOGY

## PART 1

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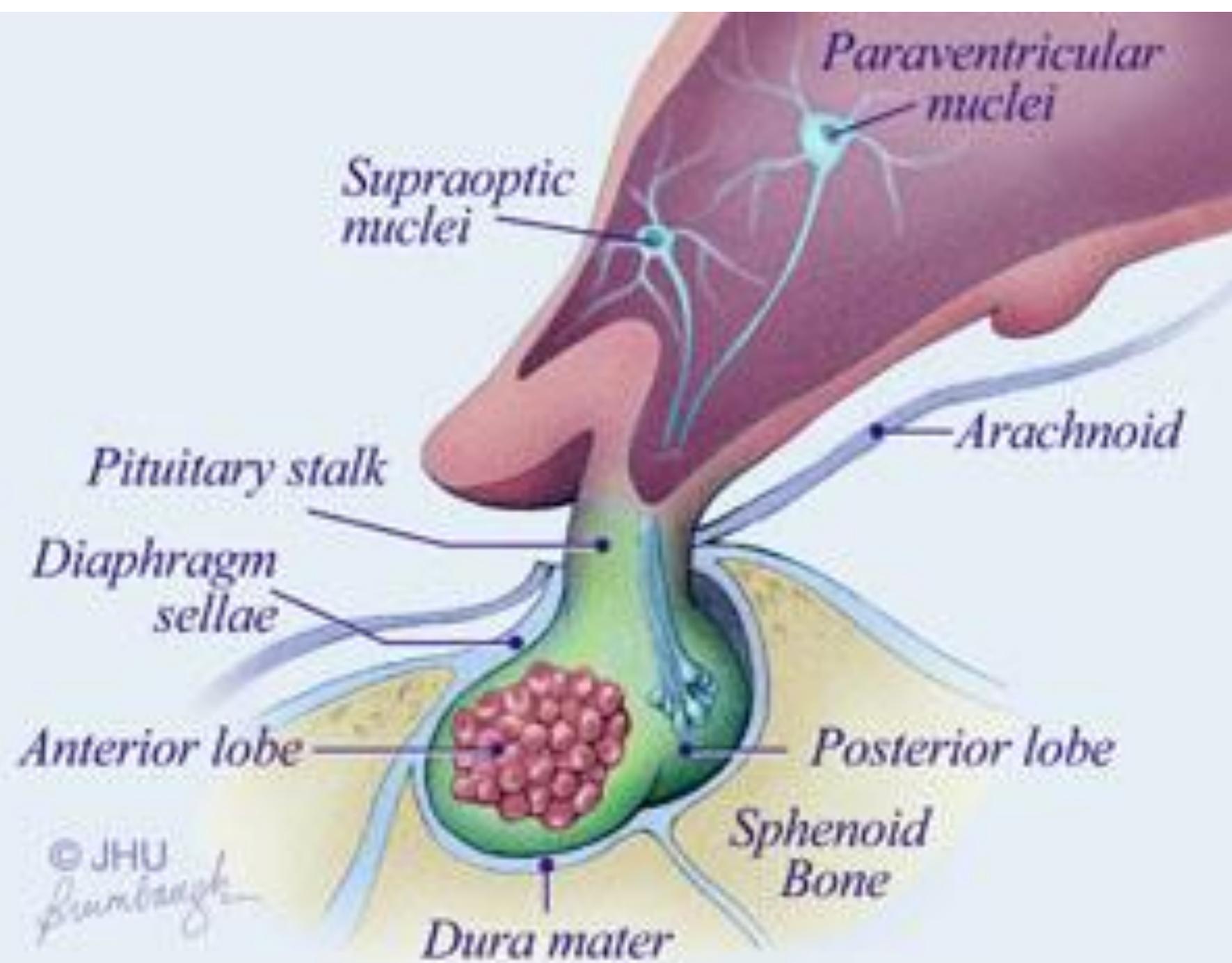
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## Question 1

- A 27-year-old female gives birth to a 8 lb, 8 oz boy but upon delivering the placenta starts to bleed heavily. The obstetrician estimates the blood loss at 2000 ml (normal <500 ml). She recovers well after IV saline infusion and 2 units of packed red blood cells.
- After one week, she notices that her milk never "let down" and she is unable to breast feed her child.
- One year later, she has still not had a menses, and she complains of fatigue, cold intolerance, weight gain despite dieting, and hair loss.

## Question 1

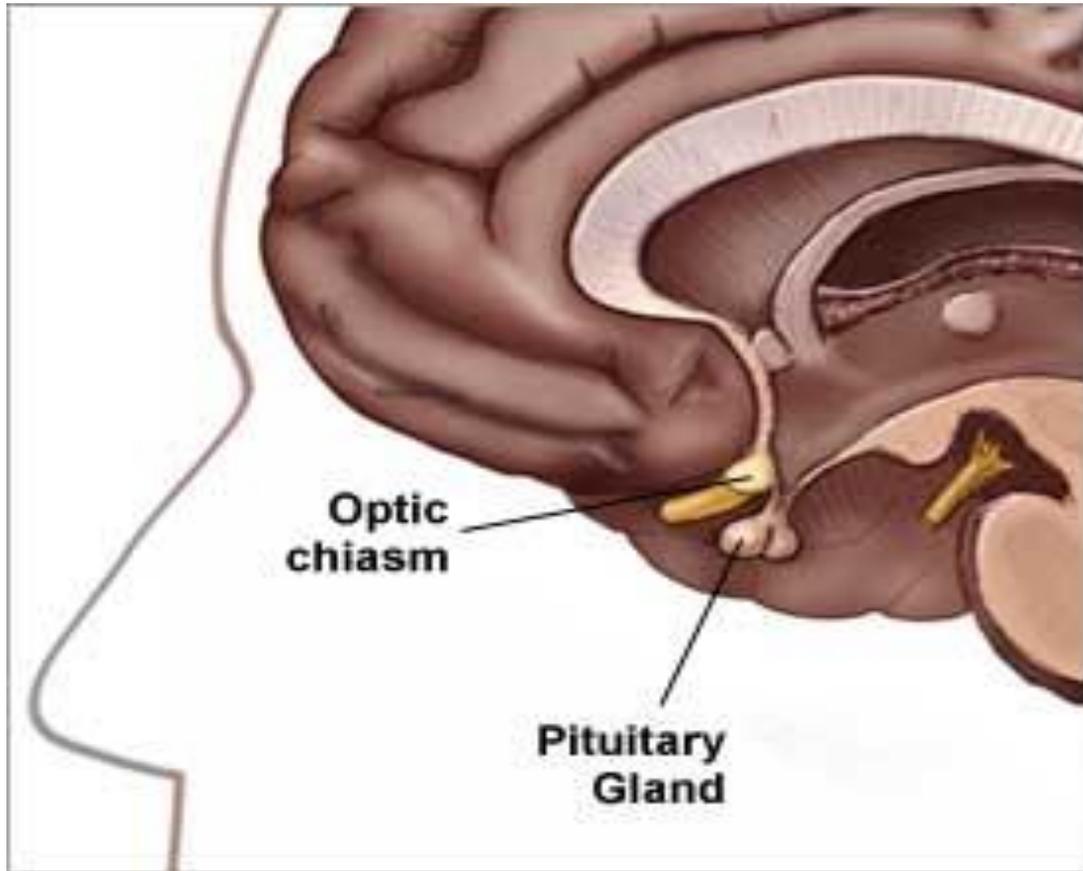
What is the most likely cause of her symptoms?

- A. Addison's disease
- B. Sheehan's syndrome
- C. Hashimoto's thyroiditis
- D. Cushing's syndrome
- E. Empty Sella Syndrome

# Pituitary Disorders

- Pituitary Hypersecretory Syndromes
  - PRL > GH > ACTH > TSH
- Anterior Pituitary Dysfunction
  - ACTH < TSH < LH/FSH < GH
- Posterior Pituitary Dysfunction
  - SIADH
  - DI
- Mass effect
  - Headaches
  - CN II, III, IV, V<sub>1</sub>, V<sub>2</sub>, VI
- Apoplexy

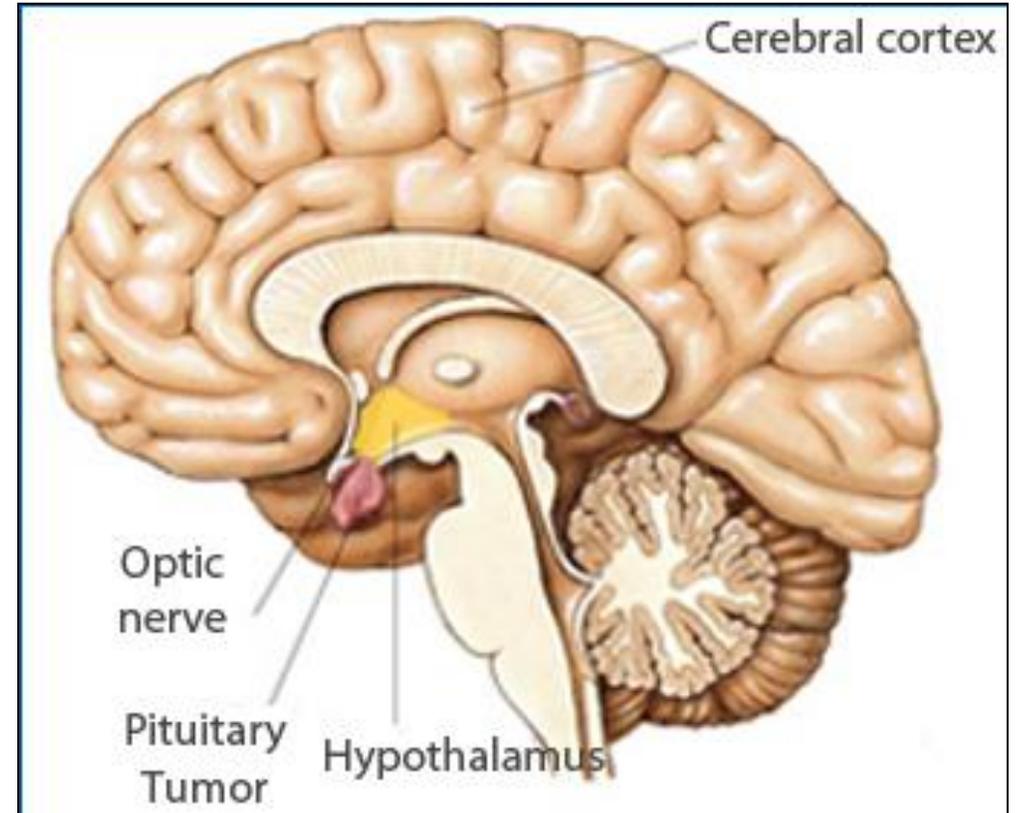
# Mass Lesions of the Pituitary Gland



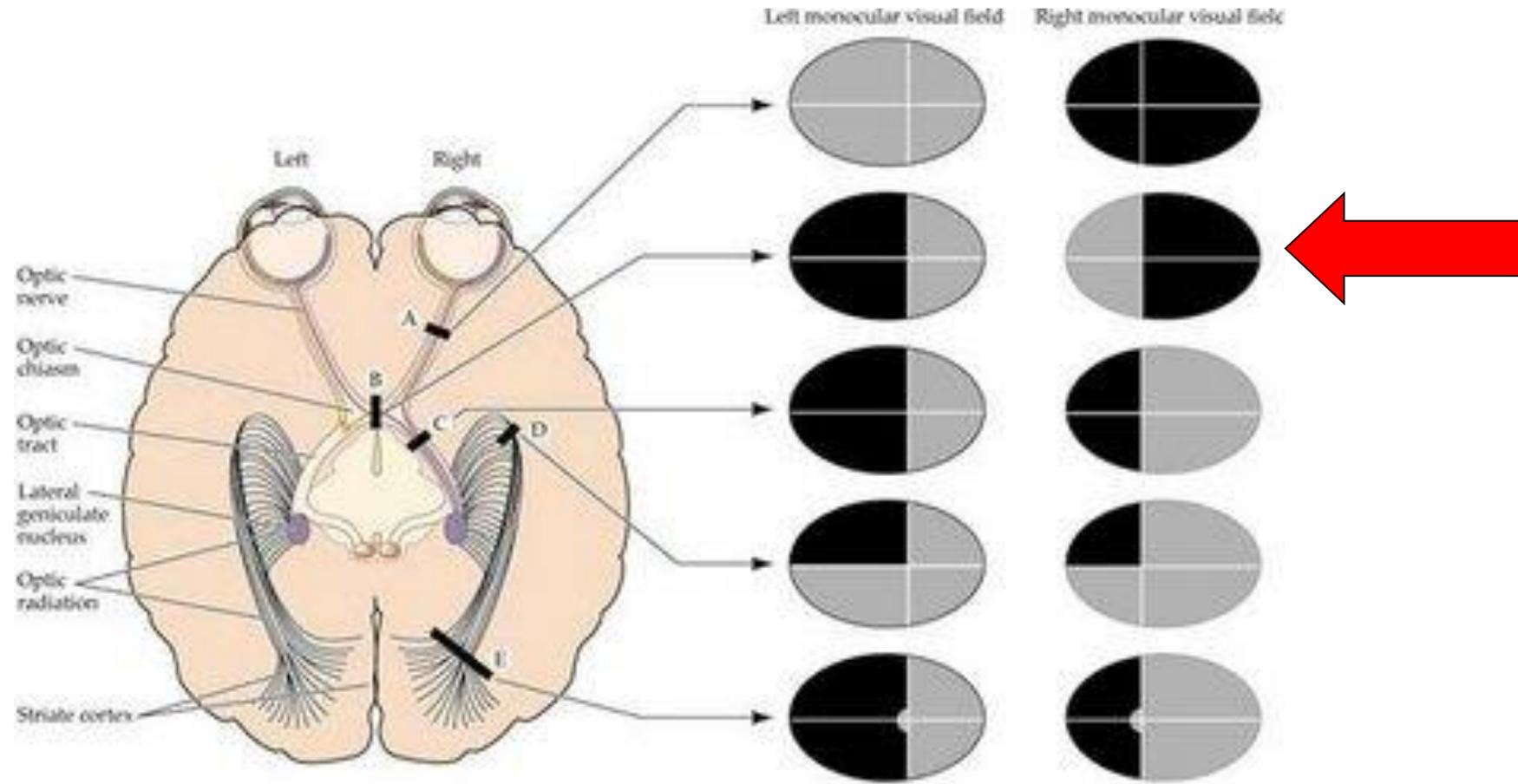
- Usually Benign
- Size
  - $<1\text{cm}$  = microadenoma
  - $>1\text{cm}$  = macroadenoma
- Functional or Non-functional (null cell)

# Mass Lesions of the Pituitary Gland

- Compressive Symptoms
  - Headaches
  - Visual Field Defects
- Hormone Symptoms
  - Under or Overproduction of each hormone leads to a unique syndrome



# Mass Lesions of the Pituitary Gland



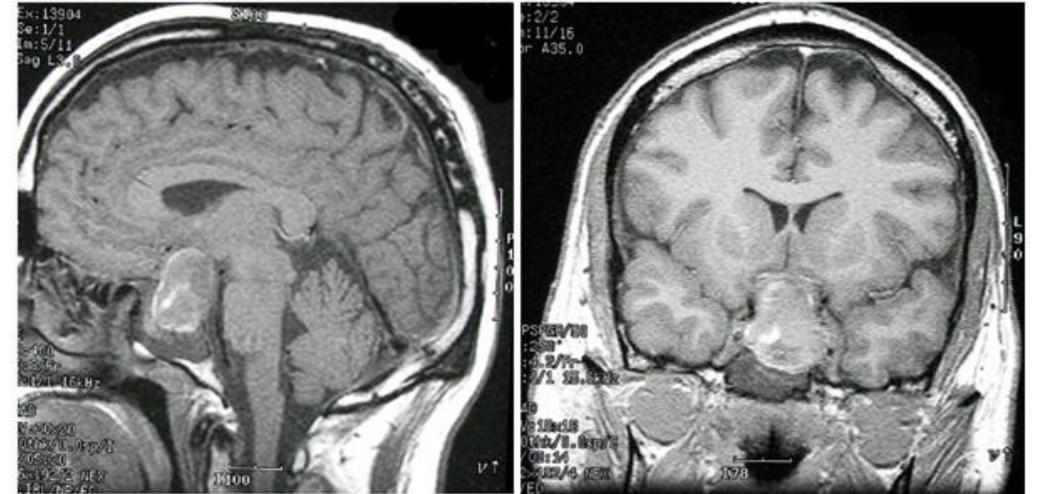
**BITEMPORAL HEMIANOPSIA**

# Hypopituitarism

- Causes:
  - Mass lesions – pituitary tumors, cysts
  - Pituitary surgery, pituitary radiation
  - Infiltrative lesions – Hemochromatosis, Sarcoidosis, metastatic disease
  - Infarction – Sheehan Syndrome
  - Apoplexy
  - Empty Sella Syndrome
  - Lymphocytic Hypophysitis
  - Ipilimumab (Anti-CTLA4 Antibody)

# Pituitary Apoplexy

- Definition: Pituitary Infarction-Bleeding into the pituitary gland
- Causes
  - Expansion of tumor
  - Blood Clot
- Symptoms
  - Severe Headache
  - Double Vision/Blurry Vision (ophthalmoplegia)
  - Nausea
  - Confusion
  - Low Blood Pressure
- Treatment
  - Emergency surgery for decompression
  - Hormone Replacement



# Sheehan's Syndrome

- Definition: Hypopituitarism following life-threatening blood loss while giving birth
- Cause: Hypertrophy of Lactotrophs during pregnancy causing increase in size of the pituitary without increase in blood supply
- If blood is not flowing to the pituitary it infarcts (Pituitary Stroke)
- Leads to loss of one or all pituitary hormones

## Question 2

A 43 year-old male presented to the ER after slipping on ice while shoveling the driveway

He had a laceration across his scalp and an obvious deformity of his right forearm. As part of the work-up he was sent for a head CT that described “fullness of the pituitary gland”

He was scheduled for orthopedic surgery and told to follow-up with his primary care doctor regarding the abnormality seen on the CT

On follow-up with his PMD the CT report was reviewed and as per the radiologist recommendations the patient was sent for a pituitary dedicated MRI study “to better visualize the pituitary gland”

## Question 2

Past medical history is significant for hypertension well controlled on HCTZ 25mg daily

On review of systems he has no complaints except for pain/weakness of his right forearm since the injury. He denies headaches, vision changes, decreased libido, or weight changes.

On exam there are no stigmata of Cushing's or Acromegaly. He has normal muscle mass and tone and a full beard. Neurologic exam including visual fields are grossly intact

## Question 2

What is the next step in the patient's management?

- A. Refer to a neurosurgeon for resection
- B. Send the patient for visual field testing
- C. Order a follow-up MRI in 3 months
- D. No further follow-up required
- E. Check prolactin level

# Pituitary Incidentalomas

- All patients with or without symptoms should be screened for hypersecretion
- All patients with or without symptoms should be screened for hypopituitarism
- All patients should have an MRI scan to evaluate the pituitary incidentaloma (if it was initially only diagnosed by CT) to better delineate the nature and extent of the incidentaloma
- All patients presenting with a pituitary incidentaloma abutting the optic nerves or chiasm on MRI should undergo a formal visual field examination

# Pituitary Incidentalomas

- Indications for surgical therapy:
    - Visual field deficit or other visual abnormalities due to the lesion
    - Lesion abutting or compressing the optic nerves or chiasm on MRI
    - Hypersecreting tumors other than prolactinomas
  - Nonsurgical follow-up for patients who do not meet criteria for surgery
    - Follow-up MRI scans
      - 6 months for a MACROincidentaloma
      - 1 year for a MICROincidentaloma
    - If no change in first follow-up scan
      - Every 1 year for MACROincidentaloma
      - Every 1-2 years for MICROincidentaloma
- for the following 3 years and gradually less frequently

# Pituitary Function Concepts

1. NEGATIVE FEEDBACK

2. SCREENING  CONFIRMATION  LOCALIZATION

3. TO TEST FOR *OVERPRODUCTION*

MEASURE HORMONE AT *NADIR* TIME 

TRY TO *SUPPRESS* THE GLAND

TO TEST FOR *UNDERPRODUCTION* 

MEASURE HORMONE AT *PEAK* TIME

TRY TO *STIMULATE* THE GLAND

## Question 3

A 60-yo man with a history of a surgically resected non-functioning adenoma 3 years ago is evaluated for persistent fatigue, malaise, and inability to lose weight. He does not have dizziness, orthostasis, nausea, vomiting, or constipation.

Medications include levothyroxine 125mcg daily, testosterone 5g/day. He is adherent with therapy. On physical examination, he is in no acute distress; the blood pressure is 130/80 mm Hg, and the pulse rate is 78/min. He has central adiposity and BMI 29.

Laboratory testing: normal electrolytes, LFTs, and CBC. TSH is 0.5  $\mu$ U/mL (nl 0.4-4.5), free T4 1.7 ng/mL (nl 0.9-1.8), and testosterone 450 ng/dL (nl 220-880). Cosyntropin (ACTH) stimulation test is normal

### Question 3

Which of the following medication changes should you consider?

- A. Increase thyroid hormone dose
- B. Increase testosterone dose
- C. Start hydrocortisone replacement
- D. Start DDAVP replacement
- E. Start growth hormone replacement

# Regulation of Growth Hormone Secretion

- GH secretion controlled primarily by hypothalamic GHRH stimulation and somatostatin inhibition
- Highest levels while sleeping
- GH works directly on the bones and has metabolic effects
- GH acts on the liver to synthesize IGF-1

# Actions of Growth Hormone

- Linear growth in children by acting directly and indirectly on the epiphyseal plates of long bones
- Increased lipolysis and lipid oxidation, which leads to mobilization of stored triglyceride
- Stimulation of protein synthesis
- Antagonism of insulin action
- Phosphate, water, and sodium retention

# Growth Hormone Deficiency

- Random serum samples of GH not useful due to pulsatile pattern of release
- Screening Test: IGF-1 (somatomedin C)
- Confirmatory Tests
  - GH measurement after insulin-induced hypoglycemia
  - GH measurement after stimulation with GHRH-arginine or ghrelin agonist
- No need to do confirmatory tests if IGF-1 is low and the patient has deficiencies in 3 or more pituitary axes

# Acromegaly - History and Physical Examination

- Macrogynathia – enlarged jaw
- Frontal bossing
- Widened spaces between teeth
- Enlarged tongue and lips
- Deepening of the voice
- Enlargement of hands and feet



# Acromegaly - History and Physical Examination

- Enlargement of the soft tissues of the pharynx – can lead to obstructive sleep apnea >50% of patients
- Thickening of skin, skin tags, increased sweating
- Paresthesias in the hands – *Carpal Tunnel Syndrome* in 20% of patients
- Increase in visceral organs - thyroid, heart, liver, kidneys, and prostate
- Hypertension, left ventricular hypertrophy, and cardiomyopathy

# Acromegaly - History and Physical Examination

- Fatigue, weakness
- Joint pain due to Synovial tissue and cartilage enlargement -hypertrophic arthropathy of the knees, ankles, hips, spine and other joints
- Hyperglycemia, glucose intolerance
- Hyperprolactinemia in approx. 30% of patients

# Acromegaly - Diagnosis

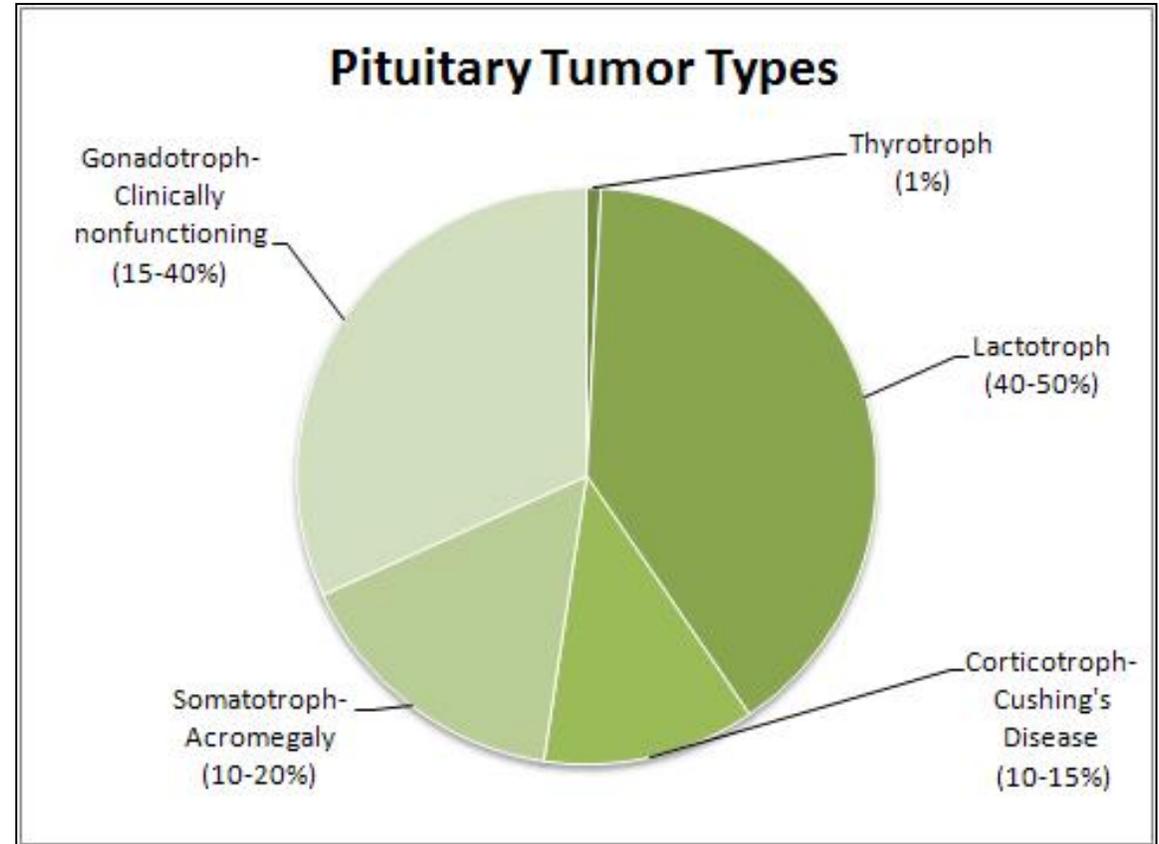
- The best SCREENING test for the diagnosis of acromegaly is measurement of serum **IGF-I**
  - Must be interpreted according to patient's age
  - Does not vary over the course of the day or in response to sleep, food, exercise like GH does
- Most specific dynamic test for establishing the diagnosis of acromegaly is an **oral glucose tolerance test**
  - 75 g oral glucose load is given and GH and glucose levels are checked at time 0, 1 hr and 2 hrs.
  - In normal subjects, the GH levels fall below 1 ng/mL within two hours of the glucose load

# Acromegaly - Treatment

- GH-secreting adenoma: Trans-sphenoidal surgery
- If surgery is not curative:
  - Medical therapy with Somatostatin Analogs
  - Medical therapy with GH receptor antagonist
    - Ex. Pegvisomant
  - Medical Therapy with Dopamine Agonists
  - Radiation Therapy

# Thyrotroph Adenoma

- TSH producing adenomas of the pituitary are very rare
- Treated with surgery
- Second line therapy: somatostatin analog



## Question 4

- 32-year-old man with a history of a surgically resected craniopharyngioma is evaluated for fatigue. Since his surgery 5 years ago he has had panhypopituitarism. For hypothyroidism he takes levothyroxine 125mcg daily. For hypogonadism he takes depot testosterone 200mg IM every 2 weeks. For adrenal insufficiency he takes Hydrocortisone 20mg in the morning and 10mg in the afternoon. For growth hormone deficiency he takes recombinant somatropin 0.4mg SQ QD.
- He reports shaving his facial hair every other day and good libido. He denies polyuria or polydipsia.
- On physical examination, he is in no acute distress; the blood pressure is 128/80 mm Hg, and the pulse rate is 78/min, he is not orthostatic. He has good strength and muscle mass.

## Question 4

- Laboratory testing:
  - normal electrolytes
  - normal hepatic panel
  - normal CBC
  - TSH 0.04  $\mu\text{U}/\text{mL}$  (normal 0.4-4.5)
  - Total Testosterone 650  $\text{ng}/\text{dL}$  (normal 220-880)
  - IGF-1 191  $\text{ng}/\text{mL}$  (normal 114-323)

## Question 4

What is the best next step in the evaluation and treatment of this patient?

- A. Decrease dose of levothyroxine
- B. Increase testosterone frequency to once weekly
- C. Check free T4 level
- D. Check growth hormone level
- E. Increase dose of hydrocortisone

# Central Hypothyroidism

- TSH Deficiency/Central or Secondary Hypothyroidism
  - Clinically similar to primary hypothyroidism in terms of history and exam
  - Diagnosis: T4 and T3 levels
  - Serum TSH alone should not be used as a screening test for hypothyroidism in patients who have pituitary or hypothalamic disease

## Question 5

A 28 yo woman is evaluated for fatigue, weight gain, irregular menstrual cycles, and milky discharge from both breasts for 6 months. She has had no change in vision and is not taking any medications.

Physical examination reveals a small goiter, dry skin, bilateral expressible galactorrhea, and normal visual fields. Laboratory results include a negative pregnancy test and a serum prolactin level of 55 ng/mL (nl 4.8-23.3 ng/mL)

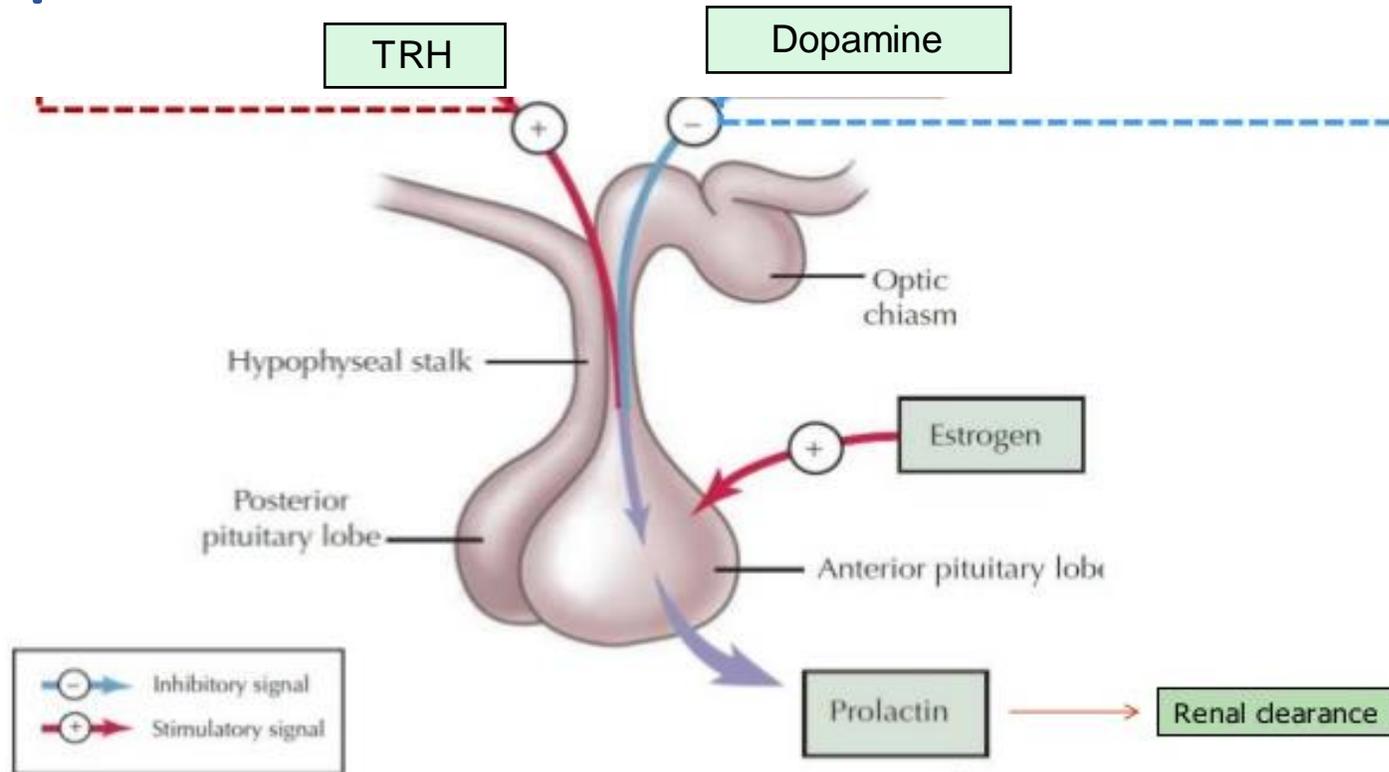
MRI of the head shows an enlarged pituitary gland that extends to within 1 mm of the optic chiasm.

## Question 5

Which of the following is the most appropriate next step in the management of this patient?

- A. Re-measure serum prolactin
- B. Start estrogen/progestin cyclic therapy
- C. Start dopamine agonist therapy
- D. Measure thyroid stimulating hormone
- E. Refer to neurosurgeon for pituitary surgery

# Hyperprolactinemia



- Prolactin is tonically inhibited by dopamine
- Hyperprolactinemia results from conditions that cause hypersecretion of prolactin from pituitary cells or decreased renal clearance

# Causes of Hyperprolactinemia

- Physiologic causes:
  - Pregnancy - (10-fold increase)
  - Nipple stimulation: suckling, exercise, breast exam, chest wall injury or lesions (ex. burns or herpes zoster)
  - Stress
- Medications - usually medication-induced hyperprolactinemia is associated with an elevation of prolactin in the range of 25-100 ng/mL

# Causes of Hyperprolactinemia

- Psychiatric Medications:
  - Risperidone, olanzapine, phenothiazines, haloperidol, butyrophenones, bupropion
  - MAO-Inhibitors, tri-cyclic anti-depressants
  - SSRIs (mild elevation)
- GI medications
  - Metoclopramide, cimetidine
  - prochlorperazine
- Anti-hypertensives
  - Verapamil, methyldopa
- Estrogens
- Opiates

# Causes of Hyperprolactinemia

- End-stage Renal Failure (usually  $< 100$  ng/ml)
- Cirrhosis
- Primary Hypothyroidism
- Ectopic production from ovarian tumors
- Idiopathic

# Causes of Hyperprolactinemia

- Hypothalamic Abnormalities
  - Sarcoid, craniopharyngioma, granuloma, dysgerminoma
- Pituitary Tumors
  - Prolactinomas
  - Non-secreting or other secreting tumors which cause stalk compression

# Hyperprolactinemia - Diagnosis

- Laboratory Evaluation
  - bHCG to exclude pregnancy in female patients
  - TSH to exclude hypothyroidism
  - Prolactin
- Single basal serum prolactin measurement is sufficient to determine excess
  - If only slightly elevated can be repeated fasting
  - PRL deficiency not a usual clinical concern

# Hyperprolactinemia - Diagnosis

- If other causes are ruled out OR you are unable to stop the possible offending medication, MRI imaging should be done to detect a pituitary adenoma or lesion affecting the pituitary stalk
- Prolactin levels  $>250$  are almost always due to a pituitary tumor

# Hyperprolactinemia - Treatment

- If NOT caused by a prolactinoma – treat the underlying cause (hypothyroidism, chest wall lesion or stimulation, discontinue offending medications)
- For prolactin-secreting tumors –
  - Dopamine agonists – bromocriptine, cabergoline
  - Observation- in female patients with microadenoma, regular menses and not desiring fertility
  - Surgery is the last option for prolactinomas

# GNRH and Gonadotrophs

- Gonadotrophs: Cells in anterior pituitary that produce LH and FSH
- Synthesis and secretion stimulated by Gonadotropin Releasing Hormone
- Pulsatile secretion of GnRH and inhibin cause distinct patterns of LH and FSH secretion
- Required for estrogen/progesterone production and ovulation in women
- Required for testosterone and sperm production in men

# Regulation of LH / FSH

- Overproduction of prolactin can cause hypogonadism – shuts off GnRH pulsatility
- Stress, Illness, Anorexia, and Opioids can lead to hypothalamic dysfunction

## Question 6

A 20-year-old man comes to you for evaluation. He started a vigorous running regimen about 4 months ago. Despite this, he continues to feel that his libido is poor and he lacks energy. You observe that he is very tall and has an unusually long arm span. Laboratory work from his prior physician included a low level of testosterone and a low LH and FSH.

## Question 6

Which of the following is most likely?

- A. His body habitus suggests his deficiency occurred prior to his recent lifestyle change
- B. He is likely to have an extra X chromosome on karyotyping
- C. He has a history of mumps orchitis
- D. He will have normal testicular size and consistency on exam
- E. His testosterone is low due to increased aromatization of testosterone to estrogen

# Hypogonadotropic Hypogonadism

- Symptoms:
  - In Men – decreased libido, erectile dysfunction, fatigue, decreased strength, osteoporosis
  - In Women – oligo/amenorrhea, infertility, hot flashes, vaginal dryness, osteoporosis
- Differential Diagnosis:
  - Kallmann's syndrome
  - Prader Willi Syndrome
  - Pituitary Dysfunction
  - Hyperprolactinemia

## Question 7

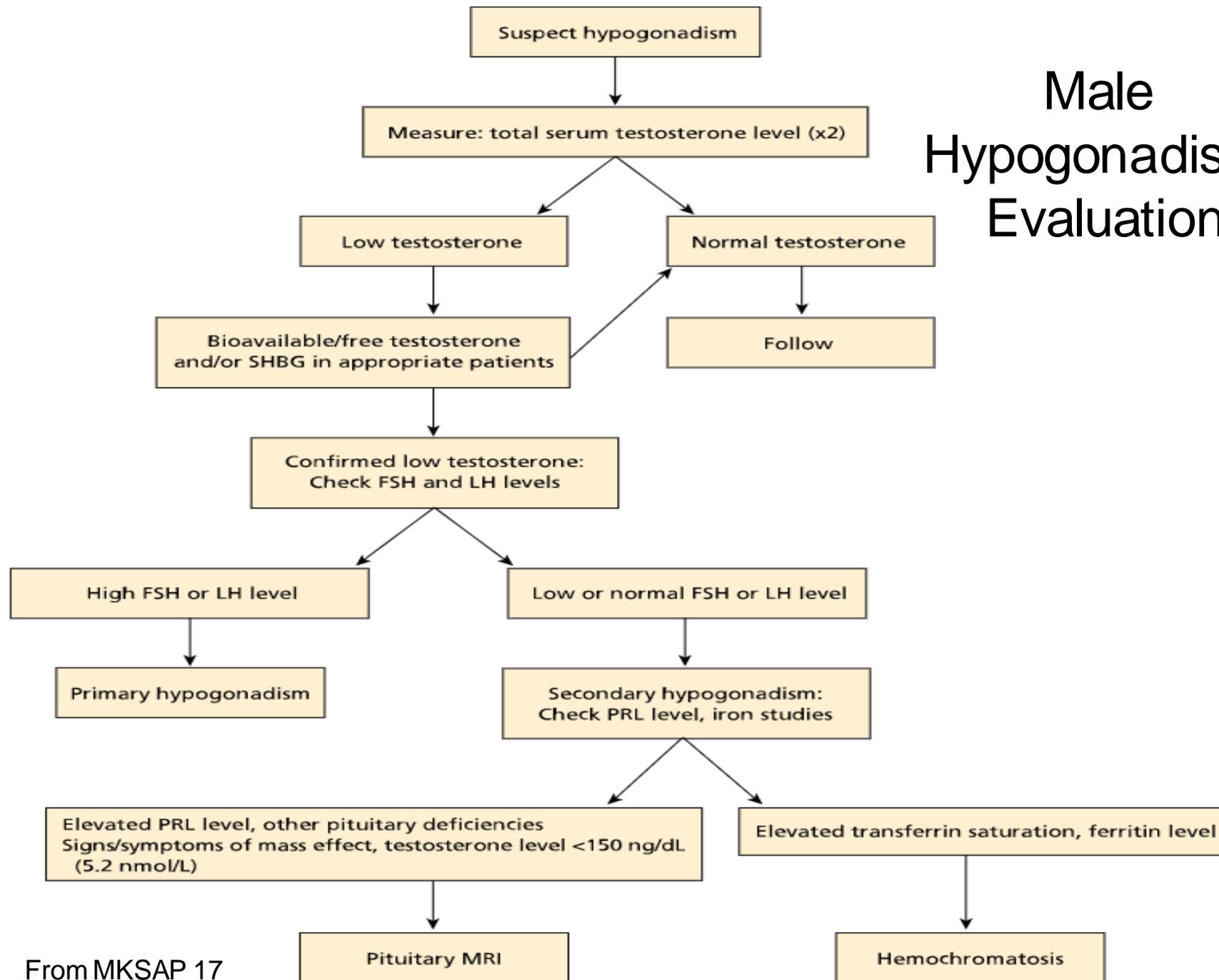
- A 35 yo man is evaluated for a 2-month history of low libido. The patient had normal puberty. Family history is unremarkable. He drinks two beers/week and takes no medications.
- On examination vital signs are normal; BMI 23. Visual field examination and testicular size is normal. There is no gynecomastia.
- Lab Studies: FSH 6mU/mL(nl 1.6-8), LH 5mU/mL (nl 1.5-9.3), TSH 2.5 U/mL (nl 0.5-4.5) Total Testosterone at 4pm 200 ng/dL (nl 270-1070 )

## Question 7

Which of the following is the most appropriate next diagnostic test?

- A. Measurement of serum ferritin and iron saturation
- B. Random serum free testosterone level
- C. Morning fasting serum total testosterone level
- D. MRI pituitary gland
- E. Testicular ultrasound

# Male Hypogonadism Evaluation

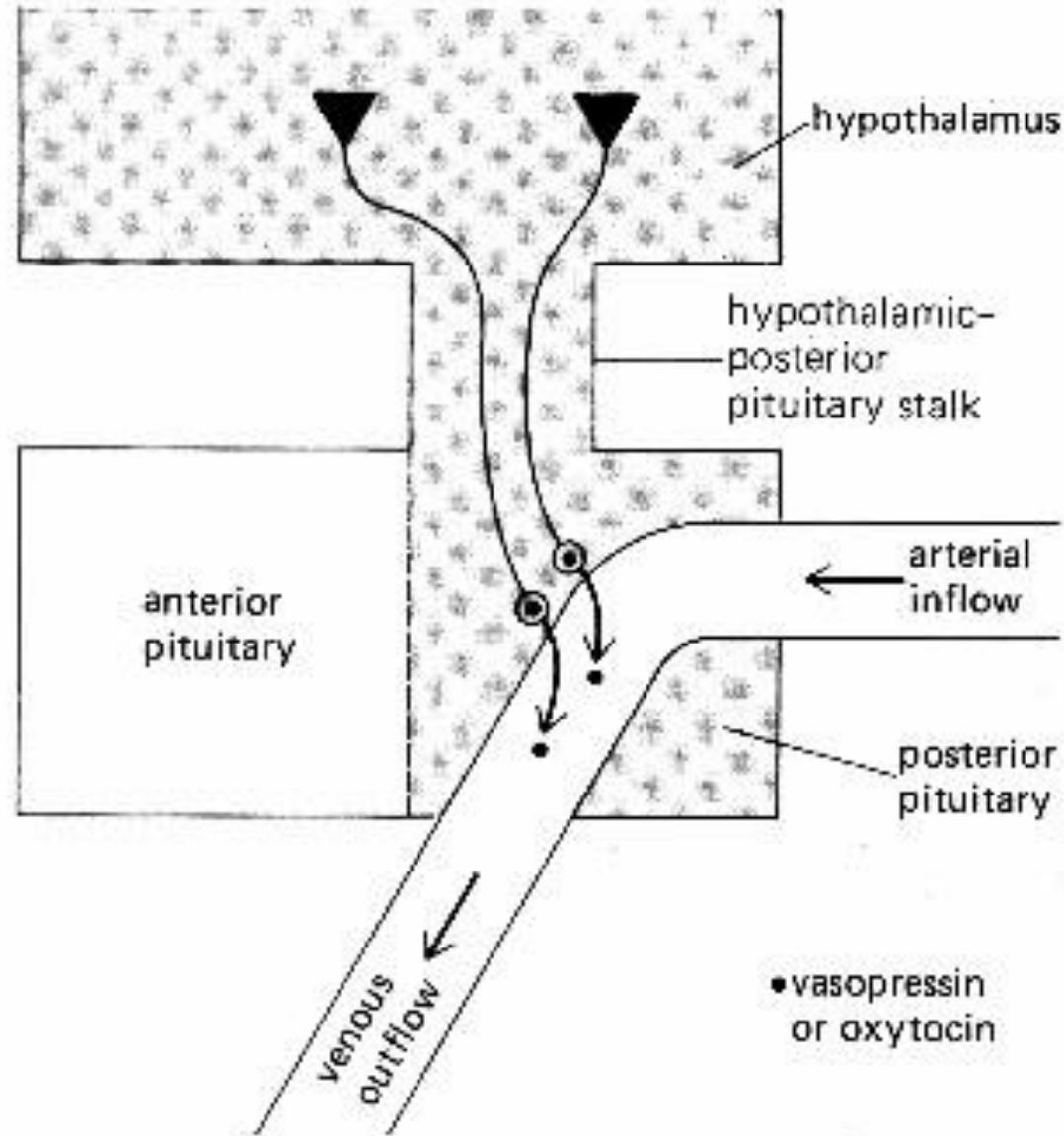


From MKSAP 17

# Risks of Testosterone Replacement Therapy

- Dyslipidemia
  - High Triglycerides
  - Low HDL
- Hypertension
- Polycythemia (monitor hematocrit)
- Prostatic growth (monitor PSA)
- Worsening of sleep apnea
- ? Cardiac risk

# Hypothalamus and the Posterior Pituitary



## Question 8

- A 34-year-old woman is evaluated for polyuria and polydipsia. She takes no medications. She reports craving ice-water.
- Fasting plasma glucose is 80 mg/dL. Urinalysis is negative for glucose and specific gravity is <1.005 (normal 1.005-1.028). Measured 24-hour urine output is 7.6 L. Serum sodium is 145 meq/L (normal 135-145). Electrolytes are otherwise normal.
- A water deprivation test is performed. During the test the serum sodium rises to 149 meq/L, and the urine osmolality remains <300 mosm/kg H<sub>2</sub>O and the plasma osmolality increases to 299 mosm/kg H<sub>2</sub>O (normal 289-308). Despite no oral intake during the test, her urine output remains on average 275 mL/hour. At this time, blood is collected for measurement of antidiuretic hormone, and 1 µg of vasopressin is administered subcutaneously. One hour later, the urine osmolality increases to 600 mosm/kg H<sub>2</sub>O, and the urine output decreases to less than 100 mL/hour. The blood antidiuretic hormone level is still pending.

## Question 8

Which of the following is the most likely diagnosis?

- A. Psychogenic polydipsia
- B. Nephrogenic diabetes insipidus
- C. SIADH
- D. Central diabetes insipidus
- E. Diuretic abuse

# Disorders of the Posterior Pituitary Hormones

- Excess
  - Syndrome of Inappropriate ADH (SIADH)
  - Ectopic ADH production
- Deficiency/Insufficiency
  - Diabetes Insipidus
    - Central
    - Nephrogenic

# Antidiuretic Hormone (ADH)

- AKA: Vasopressin, Arginine Vasopressin
- Released when the body is dehydrated or nauseous and causes:
  - Kidneys to conserve water
  - Concentrating the urine
  - Reducing urine volume
- Achieves this by insertion of additional water channels (*Aquaporins*) into the apical membranes of the tubules/collecting duct epithelial cells
- At very high doses causes vasoconstriction

# Diabetes Insipidus

## Central

- Idiopathic
  - autoimmune
- Neurosurgery, head trauma
- Cerebral hypoperfusion
- Tumor
  - Craniopharyngioma, pituitary adenoma, suprasellar meningioma, pineal gland, metastasis
- Infiltration
  - Hemachromatosis, Sarcoid, Histiocytosis X

## Nephrogenic

- X-linked recessive
- Renal disease: after ATN, postobstructive uropathy, RAS, renal transplant, amyloid, Sickle cell anemia
- Hypokalemia or Hypercalcemia
- Sjogren's
- Drugs:
  - **Lithium**, 20% of chronic users
  - Demeclocycline, amphotericin, colchicine

# Diabetes Insipidus Diagnosis

- History: polyuria, urine output exceeding 3 L/day in adults; polydipsia
- Labs: Mild Hyponatremia – Na usually greater than 140 mg/dl, increased plasma osmolality, decrease in urine osmolality

# Polydipsia with a Dilute Urine

- Diabetes Insipidus
  - Hi-normal serum sodium (142-145 mEq/L)
  - Polydipsia (crave cold fluids)
  - Polyuria, Nocturia → sleep disturbance
- 1° Psychogenic Polydipsia
  - Low-normal serum sodium (135-137 mEq/L)
  - Psychiatric illness
  - Drugs that cause dry mouth
  - Polyuria, Nocturia → sleep disturbance

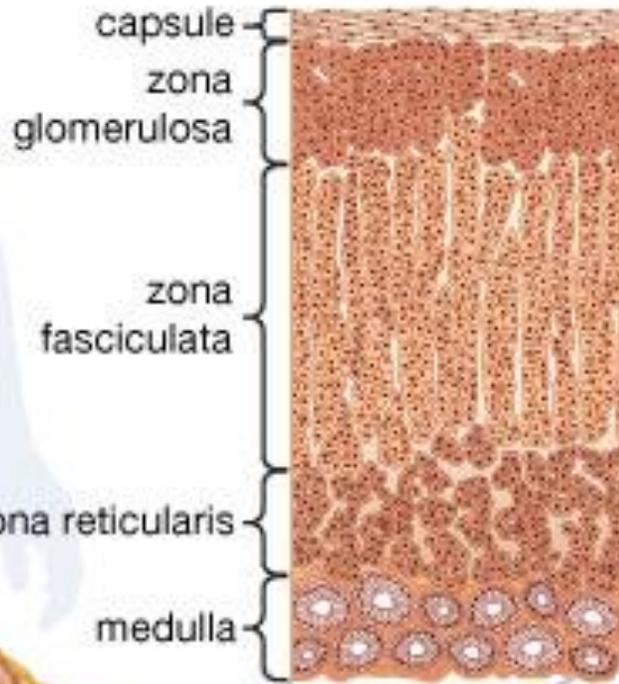
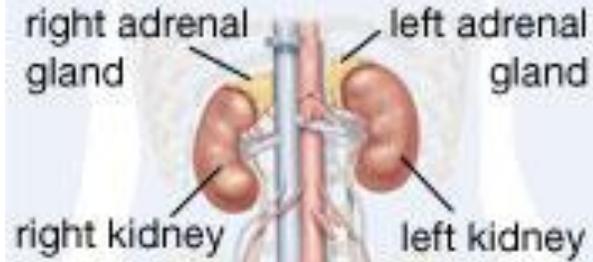
# Diabetes Insipidus Diagnosis

- Water Restriction Test
  - Normal response is the ability to concentrate urine - urine osmolality reaches a clearly normal value (above 600 mOsmol/kg, indicating that both ADH release and effect are intact)
  - Patients with DI will not be able to concentrate their urine
  - Then a dose of Desmopressin (synthetic vasopressin) is given to distinguish central from nephrogenic DI
    - If the patient is able to concentrate the urine in response to desmopressin the diagnosis is CENTRAL DI

# Treatment of ID

- Hydration
  - NS initially if ECFv contraction
  - Then IV D5W or enteral free water to lower serum [Na]
    - 1-2 mEq/h if Na > 160, symptomatic or acute
    - Otherwise 0.5-1.0 mEq/h
- Desmopressin
  - Reduces urine output and therefore simplifies fluid therapy
  - Long t<sub>1/2</sub>: duration 8-12h, up to 24h
- AVP, Aqueous vasopressin
  - Only parenteral form, 5-10 U SC q2-4h
  - Lasts 2-6h
  - Can cause HTN, coronary vasospasm

# Adrenal gland

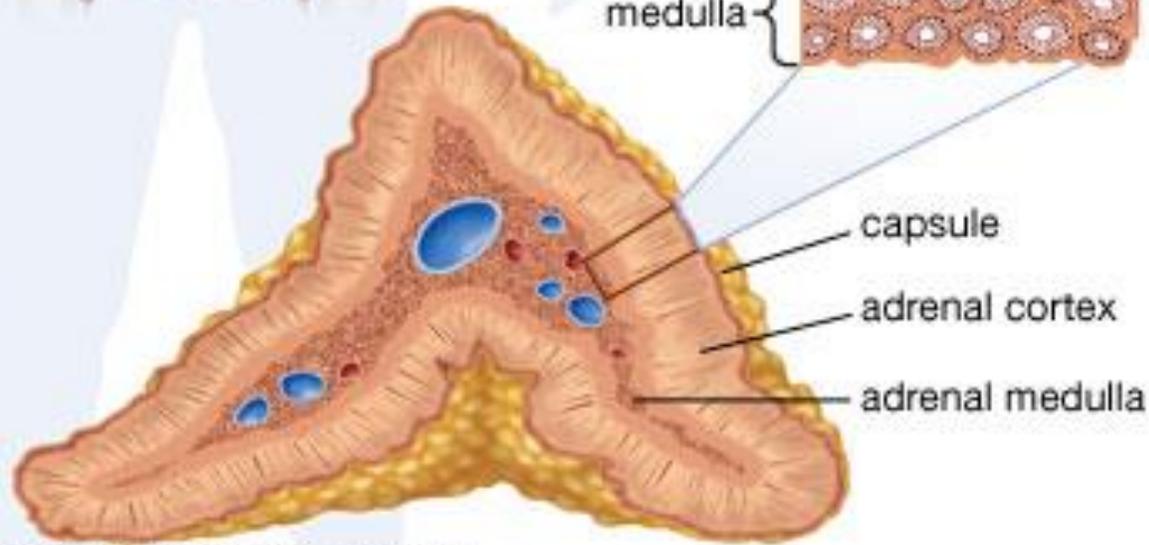


**Mineralocorticoids**

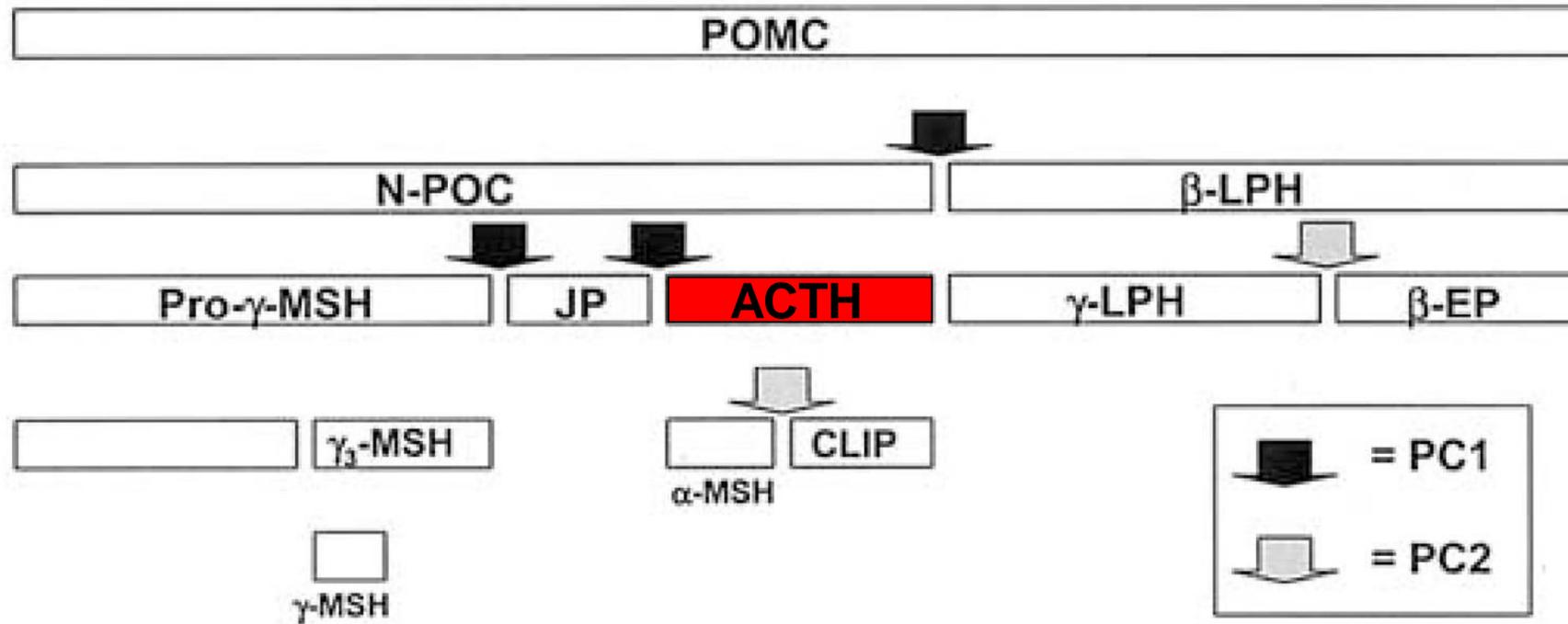
**Glucocorticoids**

**Androgens**

**Catecholamines**



# ACTH synthesis



Processing and cleavage of pro-opiomelanocortin (POMC)

# ACTH (Adrenocorticotrophic Hormone)

- ACTH regulates adrenal cortex and synthesis of corticosteroids
  - Made up of 39 amino acids
    - a-MSH resides in first 13 AA of pro-hormone
    - a-MSH stimulates melanocytes and can darken skin
  - Overproduction of ACTH may accompany increased pigmentation due to a-MSH
    - Seen in primary adrenal insufficiency and ectopic ACTH production

# ACTH /Cortisol Regulation

- Circadian pattern of release
  - Highest levels of cortisol are in early AM following ACTH release
  - Depends on sleep-wake cycle
- Increased cortisol production seen in physiologic and pathologic states
  - Physiologic States: Stress, Illness, Strenuous exercise, Anorexia, Pregnancy
  - Pathologic States
    - Pseudo-Cushing's
    - ACTH-dependent Cushing's
    - ACTH-independent Cushing's
    - Exogenous Sources – Iatrogenic Cushing's

# Adrenal Insufficiency - Symptoms & Signs

- Cortisol Deficiency:
  - Weight Loss, Fatigue, Weakness
  - Anorexia, Nausea, Vomiting, Abdominal Pain
  - Fasting Hypoglycemia
  - Inability to Excrete Free Water (hyponatremia)
  - Decreased Responsiveness to Catecholamines
- Mineralocorticoid Deficiency *only in Primary Adrenal Insufficiency*:
  - Inability to Conserve Na or Excrete K → Hyponatremia, Hyperkalemia, Dehydration, Hypotension, Azotemia, Decreased Cardiac Output

# Diagnosis of Adrenal Insufficiency

## **SCREENING: 8 am Cortisol**

- < 3 mcg/dl – strong evidence of cortisol deficiency
- 3 – 18 mcg/dl – requires further evaluation
- > 18 mcg/dl – indicates ACTH secretion is sufficient

## **CONFIRMATION: Cosyntropin (ACTH) Stimulation Test**

- 0.25 mg of Cosyntropin – measure baseline, 30 min and 1 hr cortisol – rise above 18 mcg/dl is considered a normal response

# Addison's Disease - Primary Adrenal Insufficiency

- Disease in which patients lack cortisol from zona fasciculata, and thus lack negative feedback that suppresses ACTH production
- Result: overproduction of ACTH
- Skin color will darken
- Labs may show hypoglycemia, hypercalcemia and eosinophilia



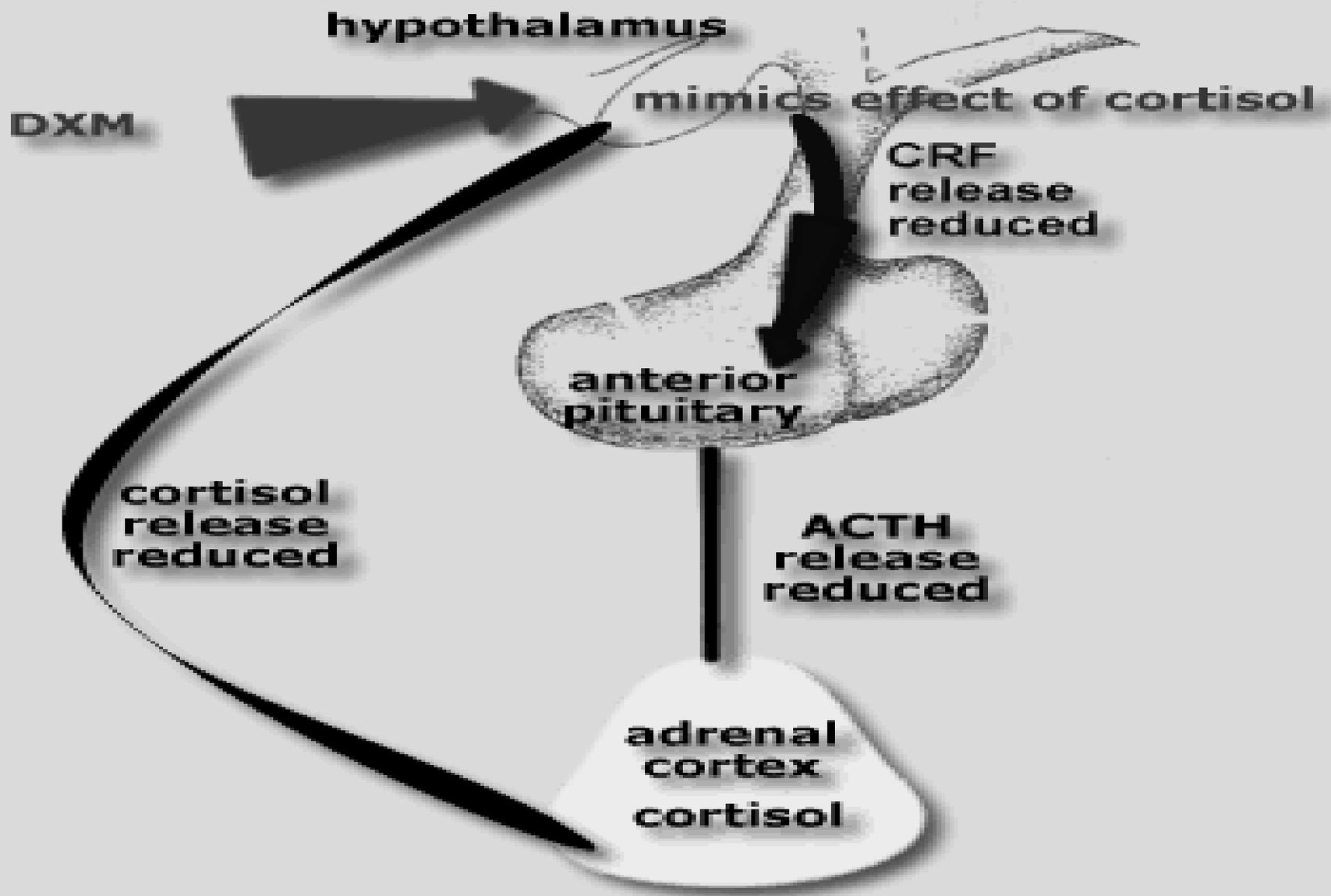
# Etiology of Primary Adrenal Insufficiency

- Autoimmune (MOST COMMON CAUSE IN THE US)
- Infectious - TB, MAI, AIDS, CMV, toxoplasmosis, KS
- Hemorrhage
  - Waterhouse-Friderichsen, lupus anticoagulant, antiphospholipid Ab, ITP, heparin
- Metastatic disease
- Drugs
  - Decreased synthesis (ketoconazole, metyrapone, aminoglutethamide, mitotane, etomidate)
  - Increased catabolism (rifampin, phenytoin, phenobarbital)
- Familial - Familial glucocorticoid deficiency, adrenoleukodystrophy, adrenomyeloneuropathy

# Etiology of Secondary Adrenal Insufficiency

- Exogenous steroid administration
- Pituitary/hypothalamic disease
  - Infiltrative tumor, granuloma,
  - hemorrhage, autoimmune, etc.
- Surgery
- Congenital

# Dexamethasone suppression of ACTH release



# Adrenal Crisis: Endocrine Emergency

- Patients present in Shock
- Symptoms/Signs
  - Fever
  - Hypotension
  - Vomiting
  - Severe abdominal pain
  - Anemia
  - Renal Failure
  - Hypoglycemia
  - Mental Status Changes, Coma
  - Death

# Adrenal Insufficiency Treatment

- Adrenal Crisis: Treat with IV glucocorticoids and IV fluids
- Long term management:
  - Glucocorticoids
    - Hydrocortisone, dexamethasone, prednisone
  - Mineralocorticoids (for primary insufficiency)
    - Fludrocortisone
- Treatment of minor illness or stress:
  - Increase glucocorticoid dose 2-3 fold
- Treatment of major illness, stress, or pre-operatively
  - Use stress dose steroids with quick taper back to maintenance

A Sickly Looking John F. Kennedy  
Five Months After the Onset of Addison's Disease  
February 10, 1948



# President Kennedy with Treatment for Addison's disease



## Question 9

- You are evaluating a patient who was recently diagnosed with Cushing's syndrome.
- Hormonal assessment shows the following results: Moderately elevated ACTH levels, no suppression of ACTH or cortisol levels with low dose dexamethasone test and suppression of ACTH and cortisol levels > 50% of baseline values with high dose dexamethasone test.

## Question 9

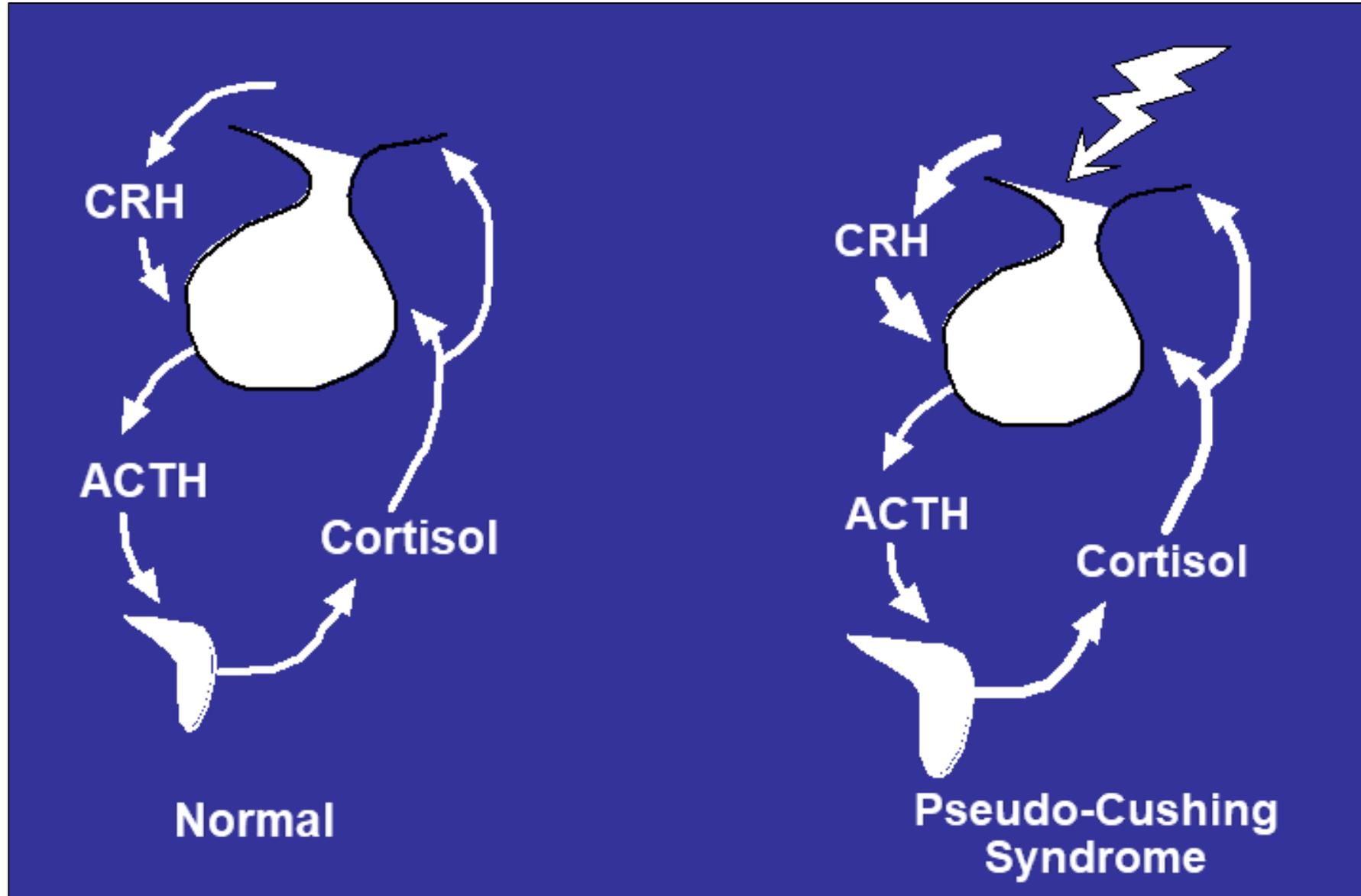
What is the most likely etiology of this patient's Cushing syndrome?

- A. Small cell carcinoma of the lung
- B. Ovarian ACTH secretion
- C. Pituitary tumor
- D. Adrenal adenoma

# Signs/Symptoms of Cortisol Excess: Cushing's Syndrome

- Diabetes Mellitus
- Hypertension
- Central obesity
- Skin abnormalities
  - Violaceous striae, easy bruisability, acne, hirsutism
- Psychiatric abnormalities
- Menstrual irregularities, decreased libido
- Myopathy
- Osteoporosis
- Infections

# Pseudo-Cushing Syndrome



# Pseudo-Cushing States with High Cortisol

- Exercise
- Pregnancy
- Uncontrolled diabetes
- Sleep apnea
- Pain
- Alcoholism
- Psychiatric disorders
- Stress
- Extreme obesity

# Etiologies of Cushing Syndrome

- Pituitary: Cushing's Disease
  - High ACTH
  - High Cortisol
- Adrenal Gland
  - High Cortisol
  - Low ACTH
- Ectopic Production (Lung Cancer)
  - High ACTH
  - High Cortisol
- Exogenous : Prescribed Glucocorticoids
  - Low ACTH
  - Low Measured Cortisol

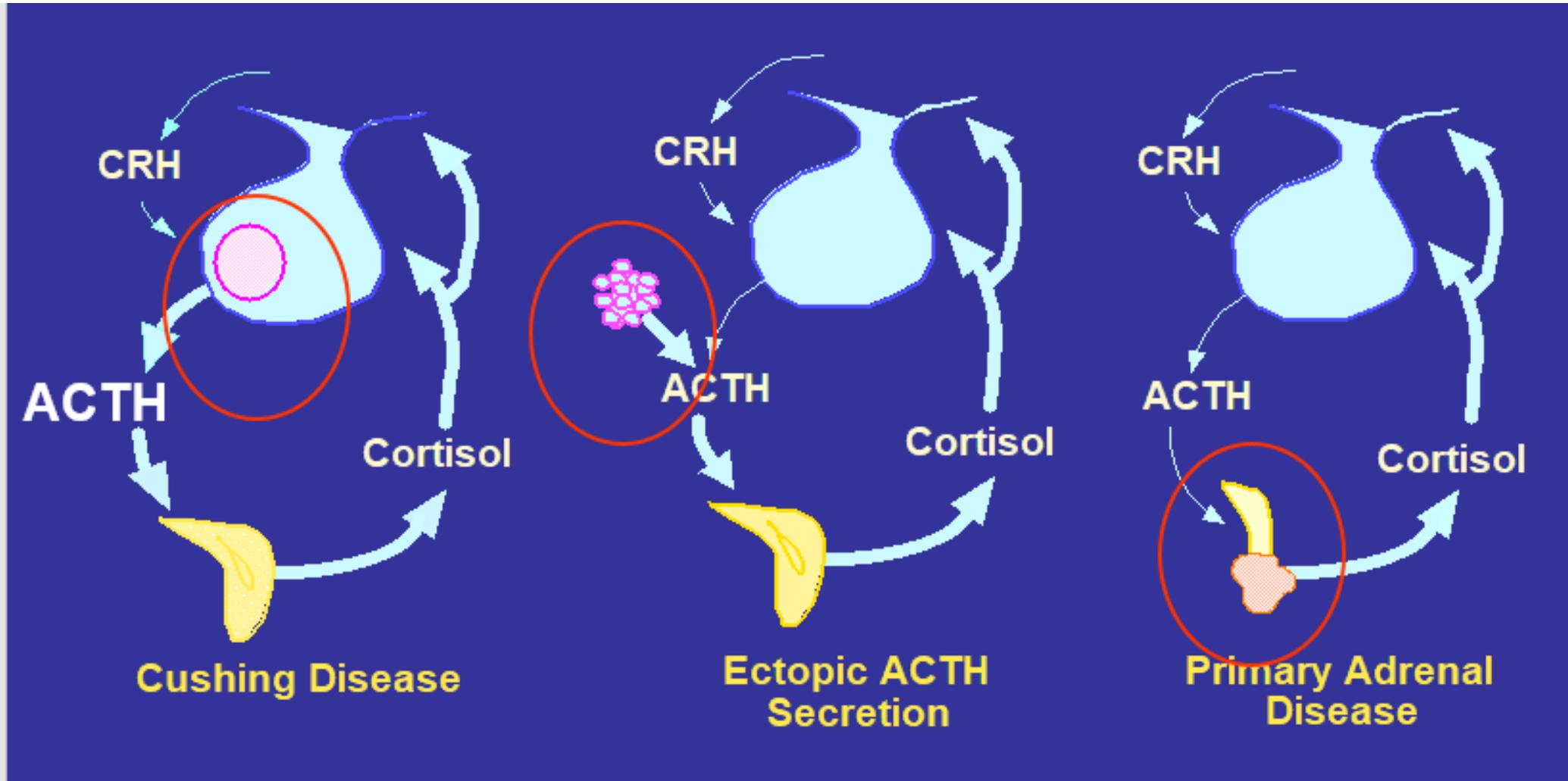
# Cushing Syndrome

- The evaluation for Cushing's Syndrome includes a careful history to exclude exogenous glucocorticoid intake
- Most commonly due to oral prescribed glucocorticoids such as prednisone, but Cushing's syndrome also can be caused by other oral, injected, topical, and inhaled glucocorticoids

# Cushing Syndrome Diagnosis

- 24 hr Urine Free Cortisol
  - 1 mg Overnight Dexamethasone Suppression Test
  - Midnight Salivary Cortisol
  - Midnight Serum Cortisol
- 
- If one test is slightly abnormal, do another test!
  - Pseudo-Cushing's may cause mild elevations in urine cortisol or dex suppression test

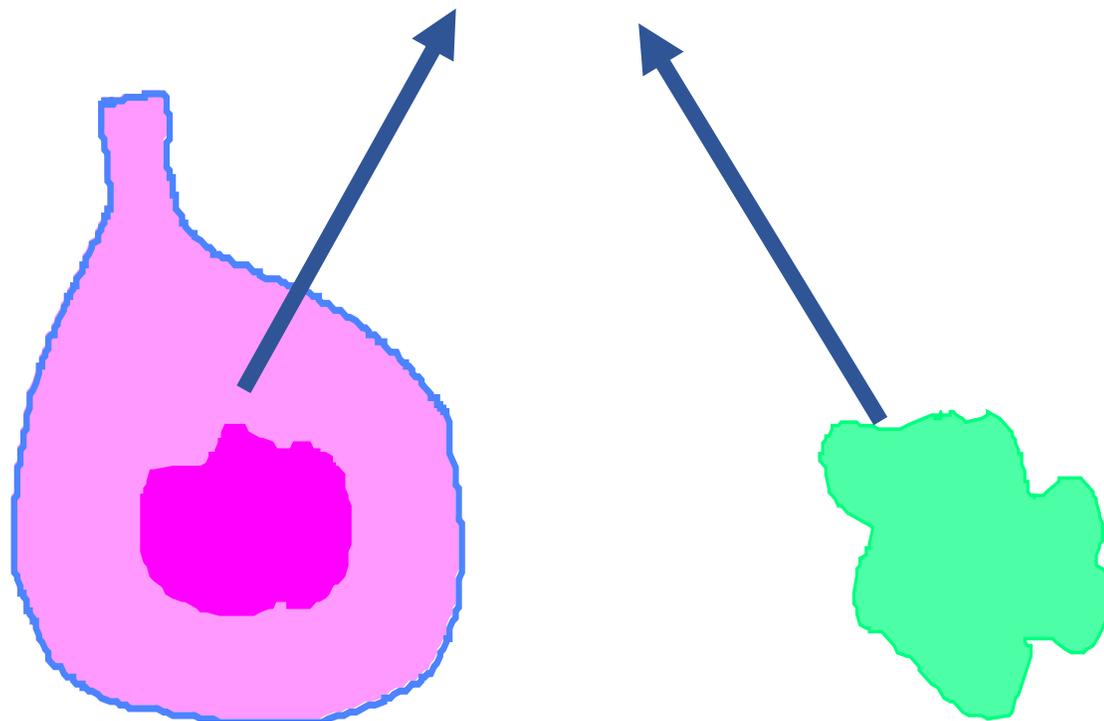
# Cushing Syndrome Localization



# Cushing Syndrome Localization: ACTH Dependent or Independent

- Determine whether the hypercortisolism is **ACTH-dependent** (ie, due to a pituitary or nonpituitary ACTH-secreting tumor), or **ACTH-independent** (ie, due to an adrenal source) by *measuring plasma ACTH*
- A low plasma ACTH concentration (<5 pg/mL) in a patient with a high serum cortisol concentration (>15 µg/dL) is evidence of ACTH-independent disease= adrenal source of cortisol

**High Level of ACTH:**



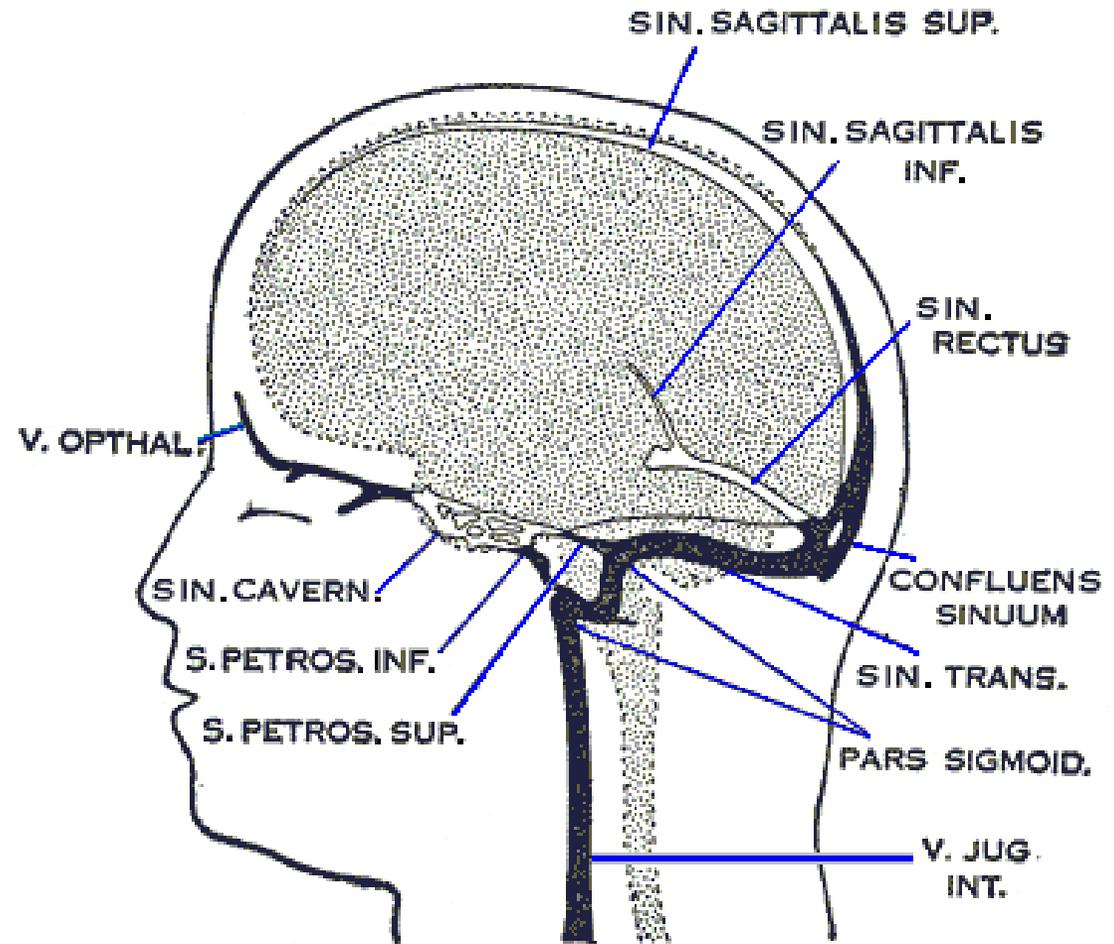
**Pituitary**

**OR**

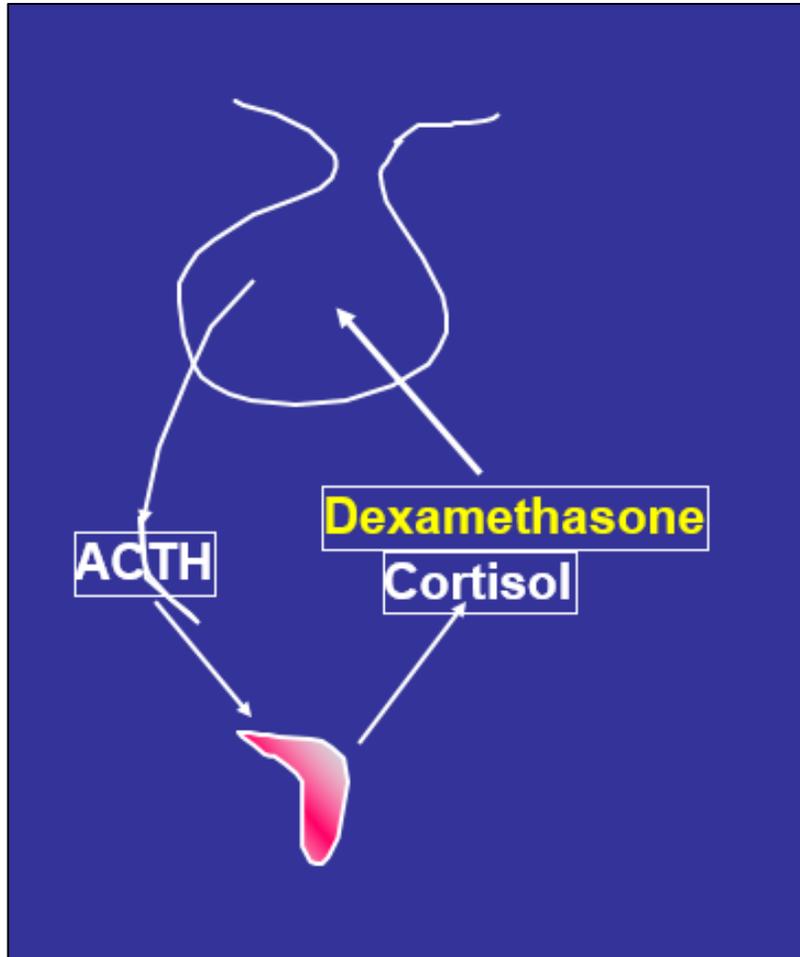
**Ectopic?**

# Pituitary or Ectopic ACTH Overproduction

- CRH stimulation test
- High dose dexamethasone suppression test
- Bilateral inferior petrosal sinus sampling



# Dexamethasone Suppression Test



**Low Dose:** 1mg dexamethasone given at 11pm and check plasma cortisol the next morning. If patient with Cushing's syndrome (any cause) AM cortisol will not be suppressed

**High Dose:** 8mg dexamethasone given at 11pm and check plasma cortisol the next morning. If patient with Cushing's Disease (pituitary cause) AM cortisol will suppress to 50% of baseline. Ectopic production will NOT suppress cortisol

# Tumors Most Frequently Causing the Ectopic ACTH Syndrome

1. Small cell carcinoma of the lung
2. Thymoma
3. Pancreatic islet cell carcinoma
4. Carcinoid tumors
5. Thyroid Medullary Carcinoma

# Cushing Syndrome Treatment

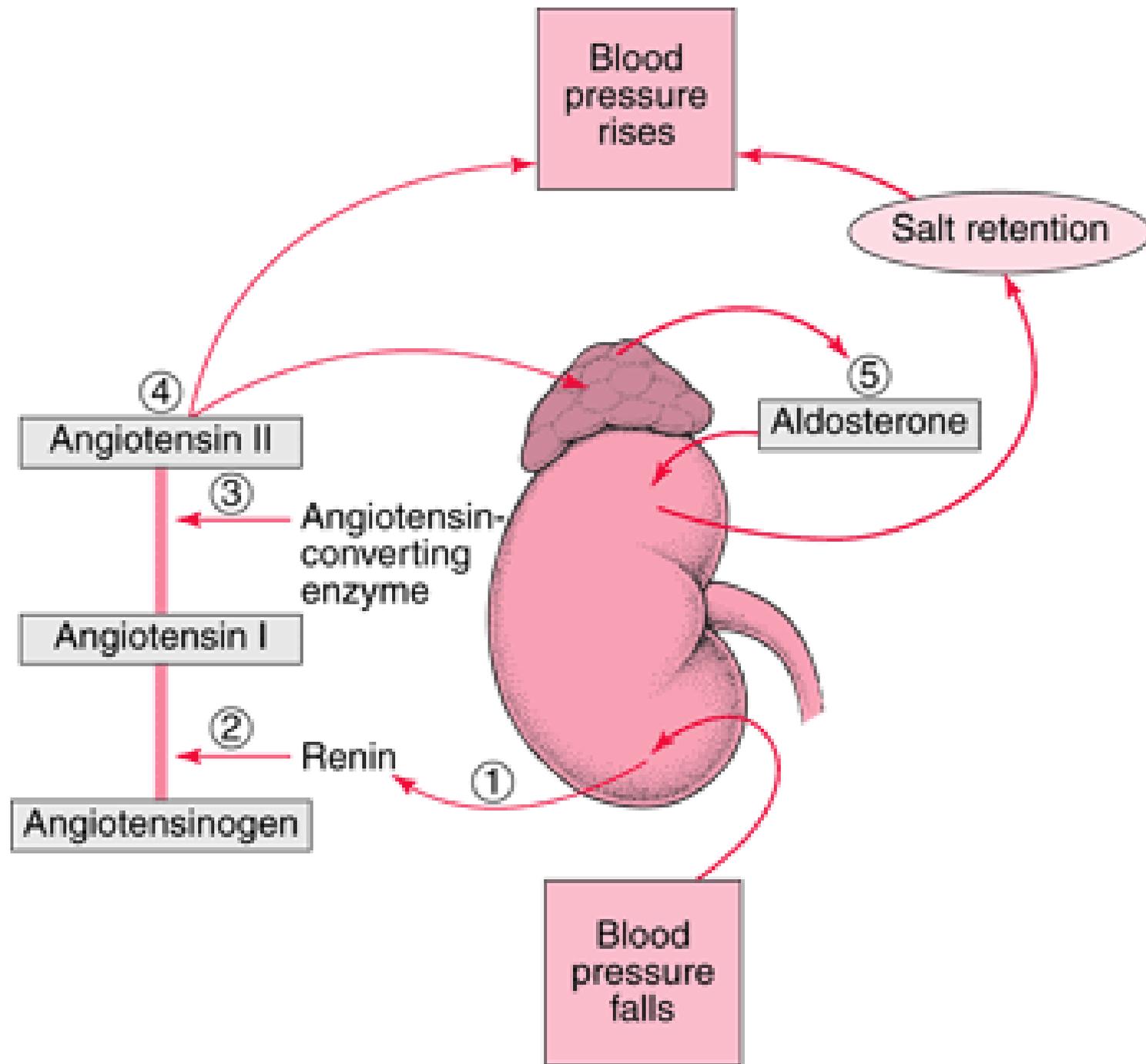
- Pituitary Cause: Neurosurgery to remove the tumor
- Ectopic Cause: Surgery to remove the tumor (usually lung cancer)
- Adrenal Cause: Adrenal Surgery

## Medical Therapy:

- Inhibits Production of Cortisol
  - Metyrapone, Ketoconazole, Etomidate
- Inhibits Production of ACTH
  - Pasireotide (somatostatin analog)
- Cortisol Receptor Blocker
  - Mifepristone

# Primary Mineralocorticoid Excess: Conn's Syndrome

- Etiology:
  - Aldosterone producing adrenal adenoma
  - Bilateral Adrenal Hyperplasia (most common)
  - Adrenal Carcinoma (1%)
- Clinical Presentation:
  - Hypertension
  - Hypokalemia
  - Metabolic Alkalosis



# Diagnosis of Primary Hyperaldosteronism

- Screening: morning ambulatory serum aldosterone and plasma renin activity
  - Elevated aldosterone ( $>15$ ) and elevated aldosterone to plasma renin activity ratio ( $>20$ ) suggestive of diagnosis
- Confirmation: \*
  - Oral or IV salt loading to try to suppress aldosterone
- Localization:
  - CT scan of adrenal glands
  - Adrenal vein sampling

# Treatment of Primary Hyperaldosteronism

- Unilateral Adenoma: Surgical Resection
- Bilateral Hyperplasia: Medical therapy
- Not a surgical candidate: Medical therapy
  
- Medical Therapy = Spironolactone
  - Aldosterone antagonist
  - Anti-androgen (side effect: gynecomastia in men)
  - Potassium sparing diuretic

# Adrenal Medullary Disorder: Pheochromocytoma

- The P's:
  - Pressure (HTN)
  - Pain (Headache)
  - Perspiration
  - Palpitations
  - Pallor
  - Paroxysms
- The Classical Triad:  
Pain (Headache), Perspiration, Palpitations

# Pheo: Paroxysms, 'Spells'

- Typical 15-20 min duration
- Frequency: daily to monthly
- Spontaneous
- Precipitated by:
  - Diagnostic procedures, I.A. Contrast (I.V. is OK)
  - Drugs (opioids, unopposed  $\beta$ -blockade, anesthesia induction, histamine, ACTH, glucagon, metoclopramide)
  - Strenuous exercise, movement that increases intra-abdominal pressure (lifting, straining)
  - Micturition (bladder paraganglioma)

# Diagnosis of Pheochromocytoma

- Confirmation:
  - Urine Fractionated Metanephrines and Catecholamines
  - Serum Metanephrines
- Localization:
  - CT or MRI of adrenal glands
  - Iodine 131-metaiodobenzylguanidine (MIBG) scan

# Treatment of Pheochromocytoma

- Once pheochromocytoma is diagnosed ALL patients should be treated with surgery
- Prior to 1951, reported mortality for excision of pheochromocytoma 24 - 50 %
  - HTN crisis, arrhythmia, MI, stroke
  - Hypotensive shock
- Currently, mortality: 0 - 2.7 %
  - Improvement due to pre-operative preparation, anesthesia monitoring techniques

# Diagnosis of Pheochromocytoma

- Preparation for surgery:
  - FIRST: Alpha blockade (1-2 weeks)
    - Traditionally using phenoxybenzamine selective alpha-1-adrenergic blocking agents are utilized in many centers
  - THEN: Beta blockade (at least 3 days)
  - Aggressive IV Hydration
  - If unable to use beta-blocker can use calcium channel blocker

# Familial Pheochromocytoma

- MEN 2a (AD inheritance RET)
  - 50% Pheo, MTC, HPT
- MEN 2b (AD inheritance RET)
  - 50% Pheo, MTC, mucosal neuroma, marfanoid habitus
- Von Hippel-Landau (AD inheritance VHL)
  - 50% Pheo, retinoblastoma, cerebellar hemangioma, RCC, renal/pancreas cysts
- NF1 (Von Recklinghausen's AD inheritance)
  - 2% Pheo (50% if NF-1 and HTN)
  - Café-au-lait spots, neurofibroma, optic glioma
- Familial paraganglioma syndromes
- Familial pheochromocytoma & islet cell tumor
- Other: Tuberous sclerosis, Sturge-Weber, ataxia-telangiectasia, Carney's Triad (Pheochromocytoma, Gastric Stromal Tumor, Pulmonary Chondroma)

# Multiple Endocrine Neoplasia Syndromes

- MEN1
  - Pituitary Tumor
  - Hyperparathyroidism
  - Pancreas Tumor
    - Insulinoma
    - Gastrinoma (ZES)
    - Glucagonoma
    - VIP-oma
- MEN2a
  - Medullary Thyroid
  - Pheochromocytoma
  - Hyperparathyroidism
- MEN2b
  - Medullary Thyroid
  - Pheochromocytoma
  - Ganglioneuroma

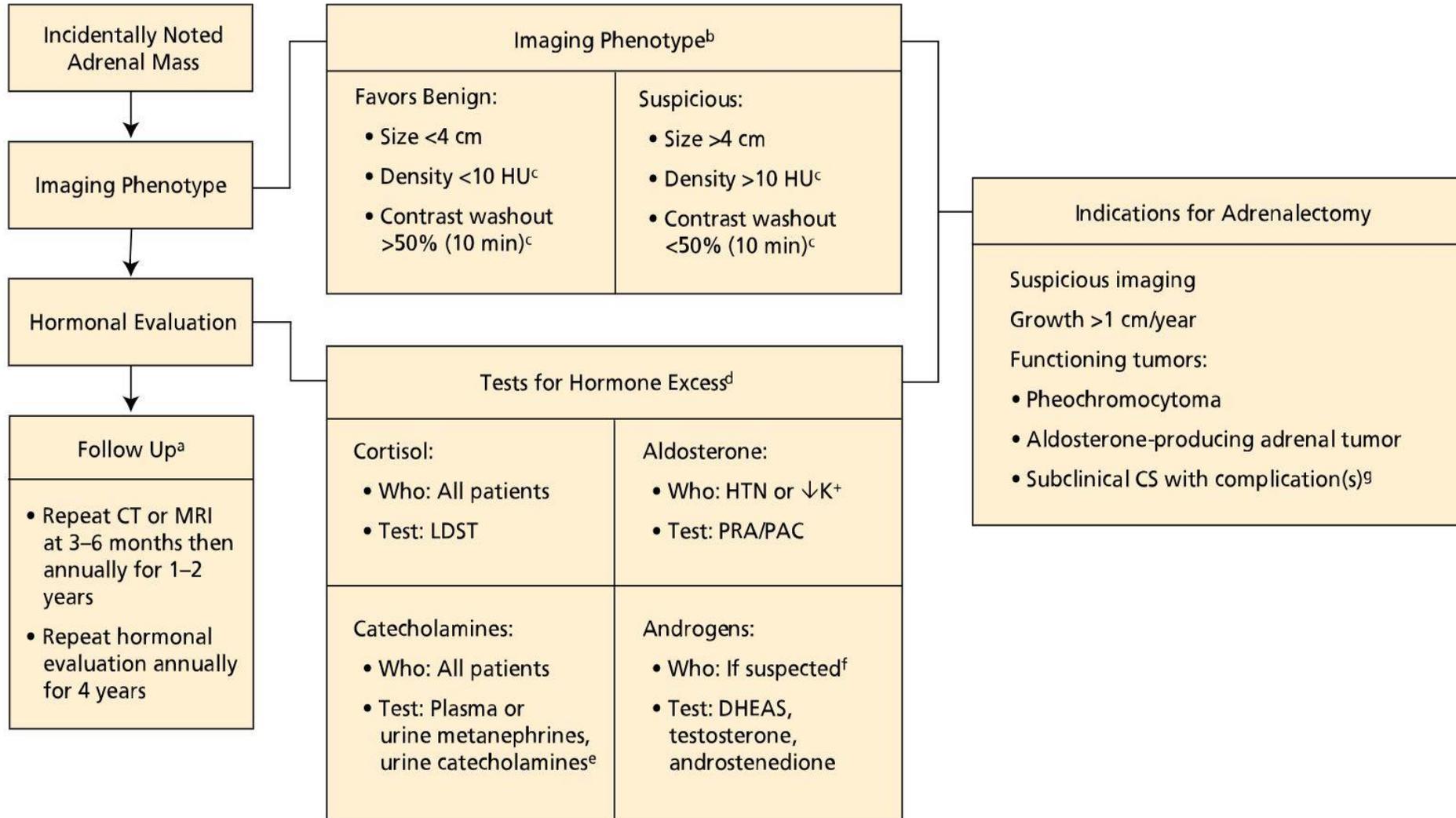
# MEN2b with Ganglioneuromas of Tongue



# Adrenal Masses

- Usually incidentally discovered during imaging
  - Unexpected adrenal masses found in 4.4% of abdominal CT scans
- May be functioning (25%) with subclinical symptoms
- Differential Diagnosis:
  - Benign cortical adenoma
  - Cortisol secreting benign adrenocortical adenoma
  - Aldosterone secreting benign adrenocortical adenoma
  - Pheochromocytoma
  - Adrenocortical carcinoma (0-5%)
  - Metastatic cancer

# Evaluation of Adrenal Incidentaloma



# Adrenocortical Carcinoma

- Diagnosis
  - CT guided biopsy
  - Surgery if mass is > 4cm
  - Hormone Testing for Hypersecretion
    - **DHEAS (DHEA) may be elevated in adrenocortical carcinoma NOT usually in benign adenomas**
- Treatment:
  - Surgery
  - Mitotane and other chemotherapies
- Prognosis:
  - Often metastasized at the time of diagnosis
  - 5 year survival 20-35%

## Question 10

- A 22-year-old woman is evaluated for bothersome facial and chest hair. She has 2-4 menses per year since menarche at age 14. She is not sexually active and does not want to become pregnant. She has had no changes in her voice or muscle mass, does not bruise easily, and has gained about 3.6 kg per year for the past 4 years.
- Physical examination shows that she has terminal hair stubble on her chin, upper lip, and sides of her face that appears recently shaven. There is no clitoral enlargement or pustular acne, no striae or bruises, and no galactorrhea or acanthosis nigricans.

## Question 10

- On lab testing:
  - Total Testosterone is 80 ng/dL (nl 5-60)
  - DHEAS 200  $\mu$ g/dL (nl 45-270)
  - 17-hydroxyprogesterone 40 ng/dL (nl 15-120)
  - Prolactin 20 ng/mL (nl 2-29)
  - After taking 1mg of dexamethasone at 12am serum cortisol at 8am is 0.7  $\mu$ g/dL (nl <1.8)

## Question 10

What is the most appropriate next step in this patient's management?

- A. CT scan of the adrenal glands
- B. Offer therapy with spironolactone or an oral contraceptive pill
- C. CT scan of the ovaries
- D. Offer therapy with dexamethasone, 0.25 mg at bedtime
- E. Pituitary MRI

# Androgen Excess in Women

- **Clinical Features:**

- Hirsutism
- Oily facial skin, acne on face neck and shoulders
- Menstrual irregularities
- Male pattern hair loss
- Virilization – deepening of voice, clitoromegaly, male escutcheon

- **Differential Diagnosis:**

- Familial Hirsutism
- Cushing's Syndrome
- Congenital Adrenal Hyperplasia
- Polycystic Ovarian Syndrome
- Ovarian or Adrenal Tumor

Rapid onset virilization  
or a Testosterone >200  
or a DHEAS >800 is a  
tumor until proven  
otherwise

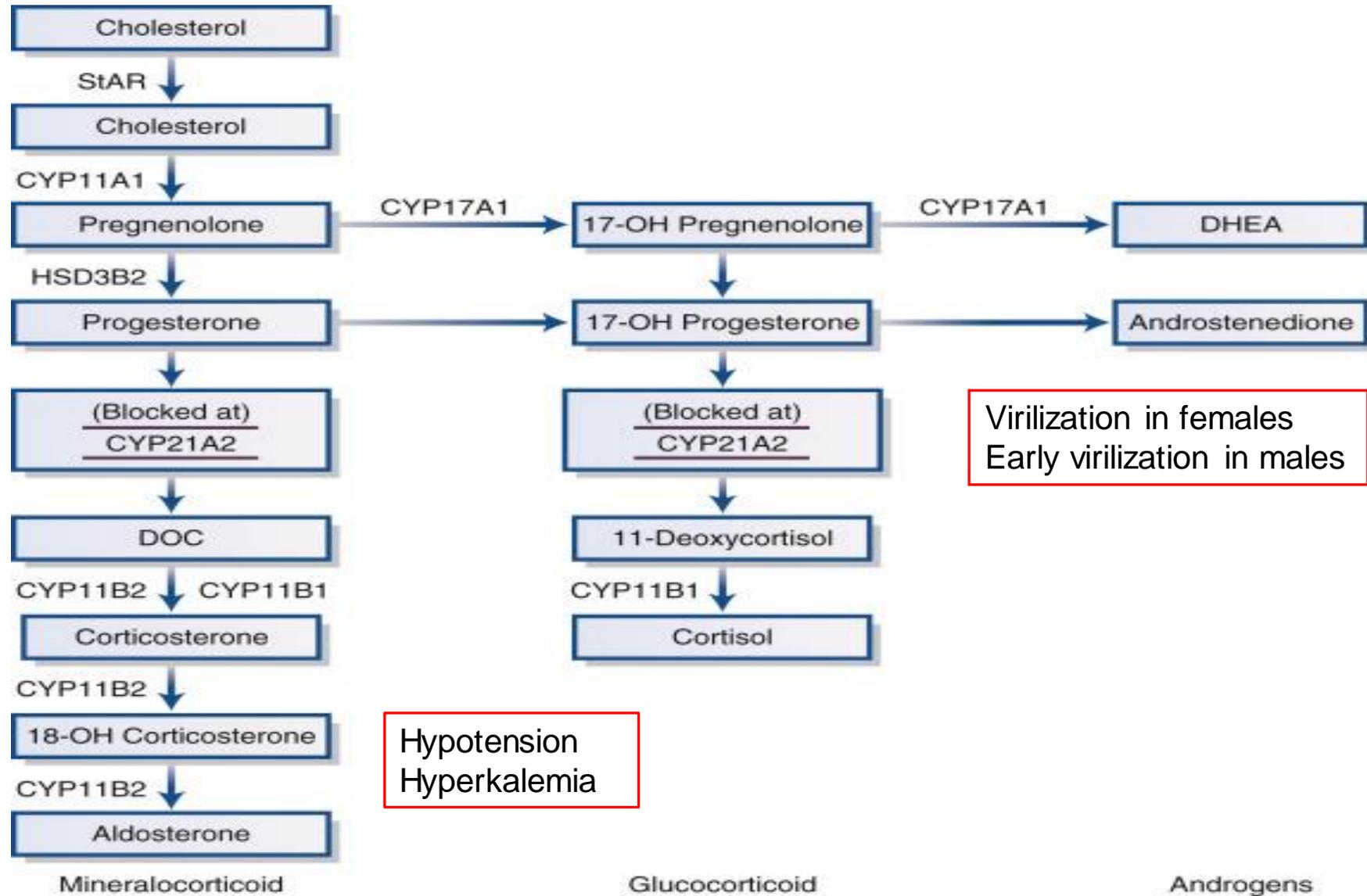
# Congenital Adrenal Hyperplasia

- Disorders of adrenal steroid biosynthesis that result in glucocorticoid and mineralocorticoid deficiencies
- Because of deficient cortisol synthesis, ACTH levels are increased which leads to adrenal hyperplasia and overproduction of steroids that precede the blockage
- All syndromes transmitted in autosomal recessive pattern
- “Classic” syndrome occurs at birth
- “Non-classic” is diagnosed later in life

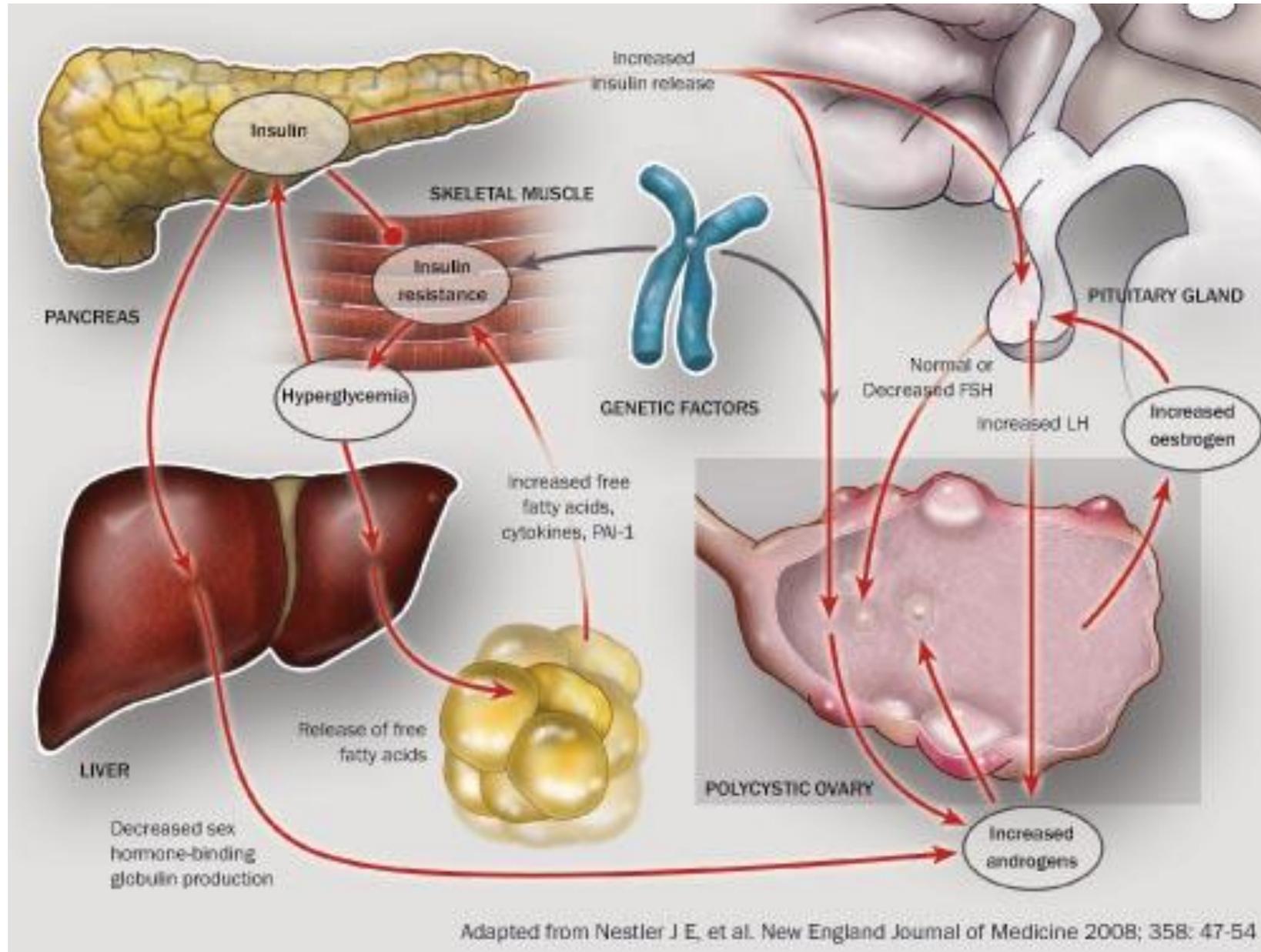
# 21-Hydroxylase Deficiency

- Classic Form:
  - Salt wasting (present in shock 1-2<sup>nd</sup> week of life)
  - Ambiguous genitalia in female infants
- Non-classic form:
  - Mild enzyme defect, no salt wasting
  - 7% Ashkenazi Jewish heterozygous
  - Common cause of hirsutism and oligomenorrhea and infertility
- Diagnosis: **Elevated 17-hydroxyprogesterone**
- Treatment:
  - Replace glucocorticoids +/- mineralocorticoids
  - Anti-androgens

# 21-Hydroxylase Deficiency



# Polycystic Ovarian Syndrome



# Polycystic Ovarian Syndrome

- Diagnosis of Exclusion, then 2 of the 3
  - Oligomenorrhea
  - Excess Androgens
  - Polycystic Ovaries
- Complications
  - Type 2 DM – 4.5 fold increased risk
  - Metabolic Syndrome
  - Infertility
  - Endometrial Cancer

# PCOS Treatment

- Weight loss
  - Diet/Medications/Surgery
- Medications to enhance insulin sensitivity:
  - Metformin
- Medications for fertility
  - Clomiphene
  - Metformin
  - Letrozole
- Medications to change estrogen/androgen balance
  - Estrogen/Progestin combination pills (OCPs)
  - Anti-androgens (Spironolactone)

# Thank You

Next in the Series

April 21, 2021

April 28, 2021