

Case Studies in Endocrinology

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Topics Covered Elsewhere

- Thyroid
- Diabetes
- Lipids
- Female Reproduction
- Osteoporosis

4 Cases

- Hyperparathyroidism
- Incidental Adrenal Nodule
- Hyperprolactinemia
- Male Hypogonadism

Case #1

67 yo woman with a history of HTN and hypothyroidism found to have a calcium of 11.1 mg/dl (nl < 10.5) on routine labs prior to a screening colonoscopy

Approach to hypercalcemia in the office setting

Calcium Regulation

- Parathyroids regulate PTH secretion based on iCa

- PTH increases serum Ca

Bone

- ↑ mobilization of Ca

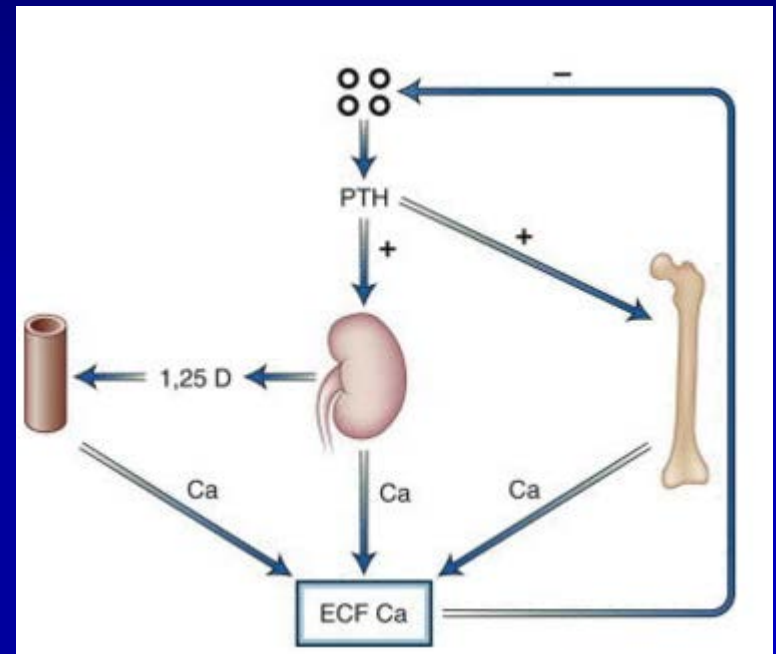
Kidney

- ↑ calcium reabsorption
- ↑ 1 alpha hydroxylase

GI

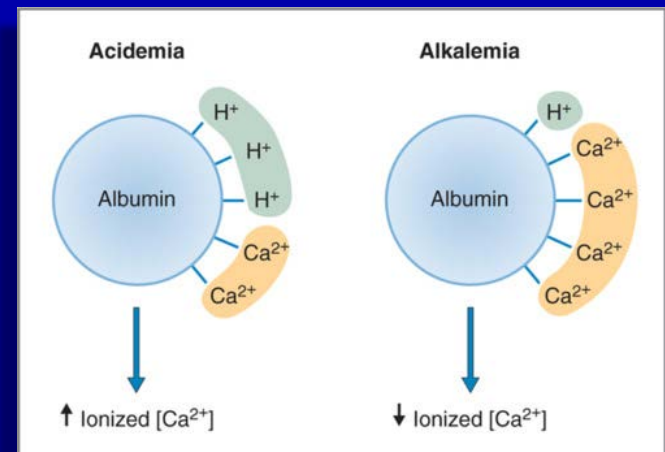
- ↑ dietary Ca absorption

- PTH decreases serum phos



Circulating Calcium Concentration

- Only ~50% of circulating calcium is ionized
 - 10% bound to inorganic anions (phos, etc.)
 - 40% bound to Albumin
- Percentage bound is determined by pH
 - Acidosis- ↓ bound , ↑ free
 - Alkalosis- ↑ bound, ↓ free



Causes of Hypercalcemia

- #1= PTH-dependent
- #2= Malignancy
- Others
 - Milk-Alkali
 - Sarcoid, granulomatous disorders
 - Excess intake
 - Vitamin D excess
 - Sarcoid, granulomatous disorders
 - Excess intake
 - Increased bone turnover
 - Hyperthyroidism, Pagets, immobilization, vitamin A

PTH - INDEPENDENT

PTH – Dependent Hypercalcemia

- Adenoma (85%)
- Hyperplasia (15%)
 - Spontaneous
 - MEN I & IIA, Jaw Tumors Syndrome
 - Tertiary hyperparathyroidism
- Rare
 - Carcinoma
 - Ectopic PTH
 - Lung, Ovarian, Thymus CA, PNET, Islets Tumor
 - FHH/NSHP/AHH
 - Abnormal Ca-sensing receptor
 - Meds- Lithium

Normocalcemic Primary Hyperparathyroidism

Initial Evaluation

- Calcium, albumin (+/- ionized Ca)
- Phosphate
- PTH

If PTH suppressed:

- 25-OH vit D; 1,25 (OH)₂ vit D; PTHrP; TSH; ACE; Alk phos +/- bone scan
- Imaging studies-CA, granulomatous dz

Case #1 Labs

- Repeat calcium 10.9 mg/dl (*nl* <10.5)
- Albumin 3.6 g/dl
- Phosphate 2.2 mg/dl (*nl* >2.5)
- PTH 105 pg/ml (*nl* <60)

Diagnosis = 1° Hyperparathyroidism

Additional work-up?

Hyperparathyroidism: Epidemiology

- Common since the introduction of multi-channel autoanalyzers
 - 100,000 new cases/yr
 - ~30 cases/100,000
- Prevalence increases with age
- More common in women (3:1)
 - ~2-3% of postmenopausal women
- Most cases sporadic w/o clear risk factors

Hyperparathyroidism: Symptoms (Then & Now)

- Bones
 - Osteitis fibrosa cystica, pseudogout → osteopenia/osteoporosis
- Stones
 - Staghorn kidney, stones, DI → stones
- Groans
 - Pancreatitis, PUD → constipation, Abd pain
- Psychiatric Overtones
 - Stupor, delirium → fatigue, depressed mood

Asymptomatic incidental finding

Additional Work-Up

- 25-OH vitamin D
- Assessment of renal function
 - BUN/Creatinine
- *24h urine calcium and creatinine**
 - r/in hypercalciuria & r/o hypocalciuria
 - *Stone risk profile**
- *Abdominal imaging (U/S, X-ray, CT)**
- *Bone density & asses vertebral spine**
 - DXA (lumbar spine, hip, & *distal 1/3 radius*)
 - *DXA-VFA or X-ray*

Indications for Surgery

- Serum Ca > 1.0 mg/dl above ULN
- BMD w T scores < -2.5 at any site
 - *or vertebral fracture on imaging**
- Age < 50 yo
- Crt clearance < 60 ml/min ? ‡
- Presence *or* ↑ *risk of kidney stones**
 - *24h UCa > 400 mg or stones on imaging*
- Relative indications:
 - Symptoms
 - Vitamin D deficiency
 - Patient preference, poor follow-up

Parathyroidectomy

- Localization
 - U/S
 - Sestamibi Scan
 - CT
 - Good Surgeon !!!!
- Surgical techniques
 - Neck exploration
 - Minimally invasive
- Complications
 - Hypocalcemia
 - Hungry bone

Case #1 Work-Up

- 67 yo, no h/o fractures or kidney stones
- Labs:
 - Calcium 10.9 mg/dl, (PTH 105 pg/mL)
 - 25-OH vitD – 38 ng/mL (nl>32)
 - (Creatinine clearance > 60 ml/min)
- DEXA
 - T:- 2.0 spine, -2.4 fem neck, **-2.7 in hip**, **-2.8 wrist**
 - VFA: no vertebral frx
- 24h Urine calcium – 220 mg Ca
- Abd U/S- no kidney stones

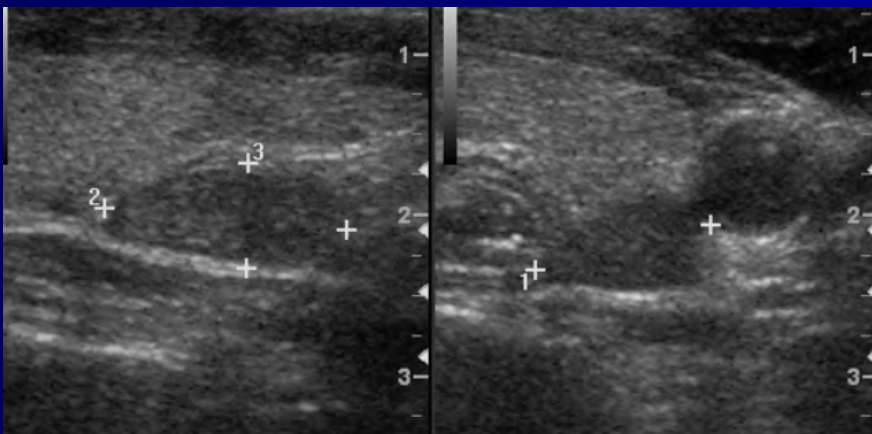
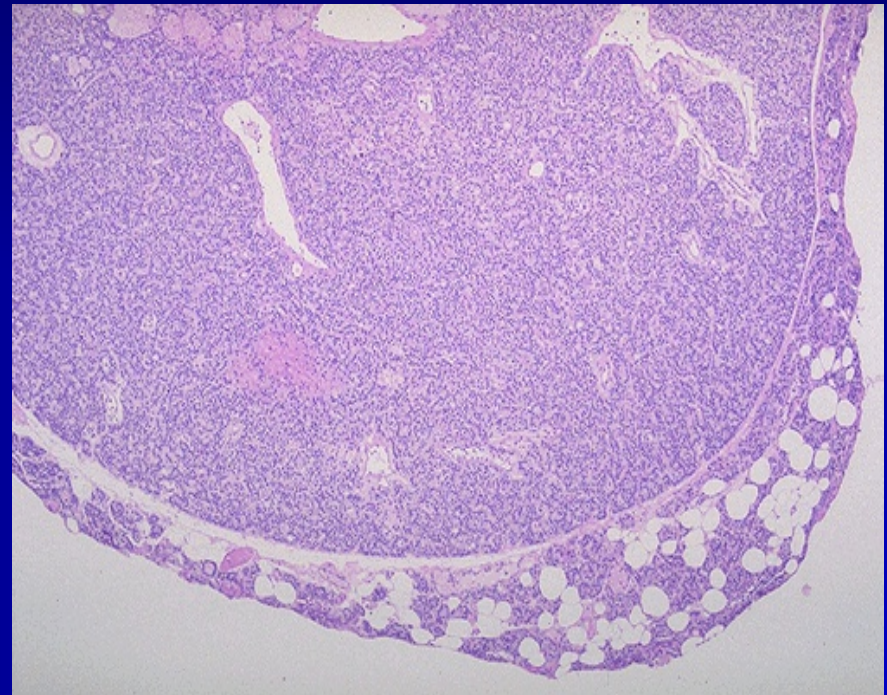
Osteoporosis as indication for surgery

Case #1

Parathyroidectomy

- Tech-99 Sestamibi SPECT suspicious for a R lower parathyroid adenoma
- Neck ultrasound confirmed
- Resection of enlarged gland
 - intraop PTH 112 → 45 pg/ml
- Path- 900 mg gland w little stromal fat c/w adenoma

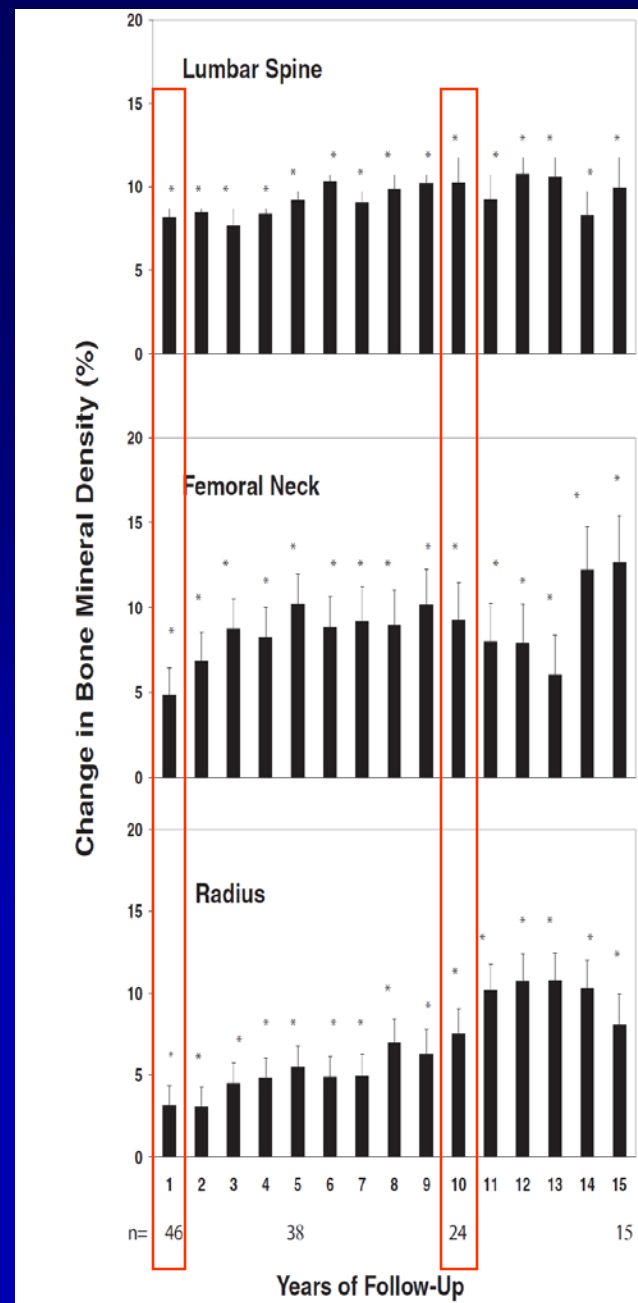
Parathyroidectomy



Improvement in BMD

Post-surgical improvement

- Spine
 - 9% after 1 yr
 - 12% after 10 yr
- Femoral Neck
 - 5% after 1 yr
 - 10% after 10 yr
- Radius
 - 3% after 1 yr
 - 7% after 10 yr



What If...

...BMD had been normal

- If no indications for surgery, monitor:
 - Serum calcium annually
 - Serum creatinine annually
 - BMD every 1-2 yrs*
 - *Vertebral fracture assessment* *if clinical signs**
 - *Renal stone assessment* *if clinical signs**

- Biochemical levels did not change significantly in > 10 yr of f/u

- However, accelerated bone loss may occur

What If...

...Patient refused surgery

- Available medical therapy include:
 - Bisphosphonates
 - Calcimemetic Agents

Case #2

65 yo man with a history of HTN , DM, dyslipidemia, and gout found to have a 2 cm right adrenal mass on a CT done to evaluate RLQ abdominal pain which has since resolved.

He is currently on lisinopril, HCTZ, and metoprolol for his HTN which is marginally controlled.

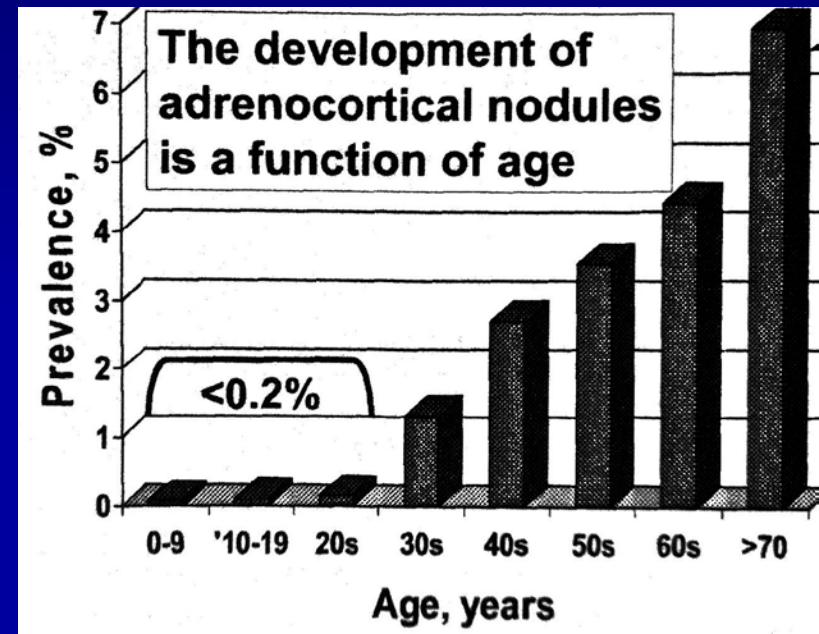
Approach to the adrenal incidentaloma

Adrenal "Incidentaloma"

- Adrenal mass >1 cm
- Incidentally discovered during radiographic evaluation
- Increasing in incidence because of widespread use of abdominal imaging

Prevalence of Adrenal Nodules

- Autopsy ~ 6%
 - » Young. 2000
- Abdominal CT ~ 4%
 - » Bovio.2006
- Prevalence increases with age
 - 20-30 yo ~ 0.2%
 - 40-50 yo ~ 3%
 - >70 yo ~ 7%
 - » Kloos.1995



EVALUATION

- IS IT FUNCTIONAL?
- IS IT MALIGNANT?

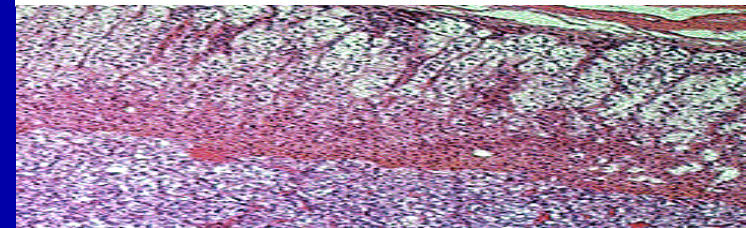
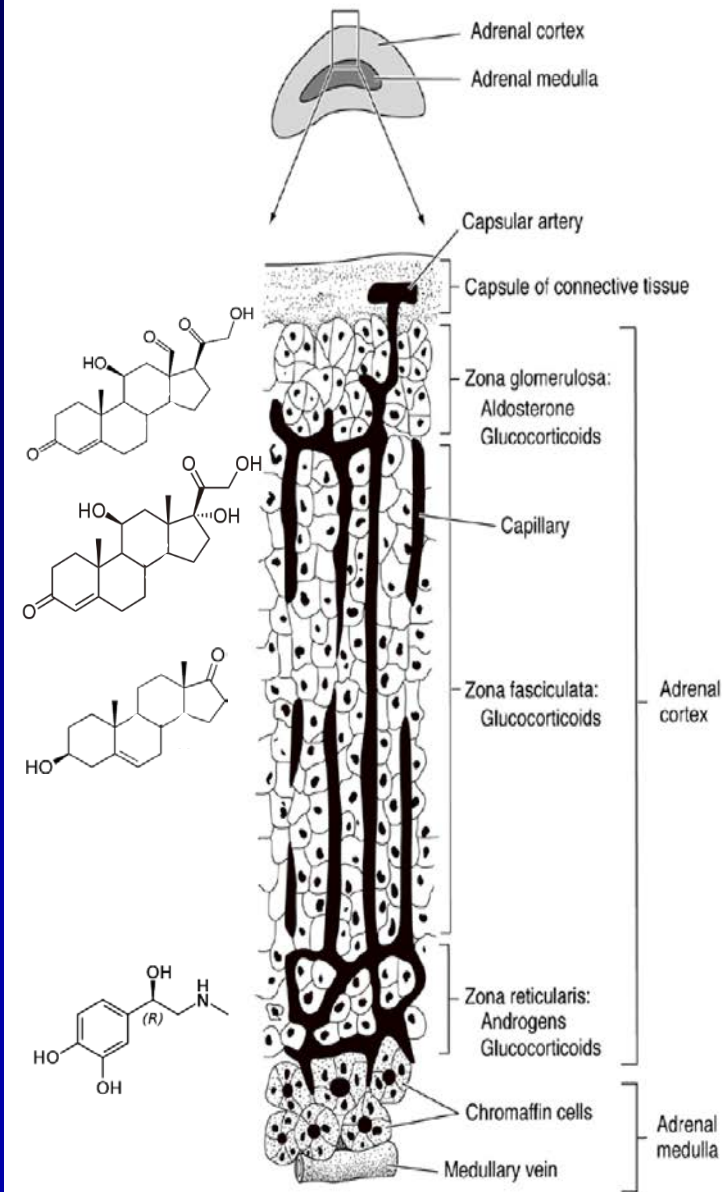
Adrenal Physiology

- CORTEX

- Glomerulosa – Aldosterone
- Fasciculata – Cortisol
- Reticularis – DHEA

- MEDULLA

- Chromaffin- Epinephrine



Functional Adrenal Incidentalomas

- Cortisol secreting adenomas
 - ~5% of incidentalomas
 - May have subclinical Cushing's w/o typical findings of hypercortisolemia
- Pheochromocytomas
 - ~ 3% of adrenal incidentalomas
 - 60% of pheochromocytomas discovered incidentally as adrenal masses
 - Only ~50% of incidentally discovered pheos had HTN
- Aldosterone secreting adenomas
 - ~1% of incidentalomas
 - Most with HTN

Initial Evaluation

- History and physical
- Hormonal testing
- Radiographic phenotype

Cushing's (+/-Subclinical)

History and Physical

- Moon facies, plethora
- Central obesity, subclavicular, dorsocervical fat pads
- Depression, emotional lability
- HTN
- Fungal infections
- ***Easy bruising**
- ***Violaceous, wide striae**
- ***Proximal muscle weakness**

Laboratory Findings

- ***Hypokalemia**
- Hyperglycemia/DM
- Leukocytosis with relative lymphopenia
- Osteopenia/osteoporosis

Pheochromocytoma

History and Physical

- Pounding headaches
- Palpitations
- Pressure abnormalities
 - HTN / Orthostasis
- Perspiration
- Pallor
- Paroxysmal or persistent spells
- “Phever”
- Plugging= constipation
- Anorexia
- Anxiety, tremor
- Lid lag

Laboratory Findings

- Hemoconcentration w elevated Hct
- Hypercalcemia
- Hyperglycemia

Hyperaldosteronism

History and Physical

- HTN
- +/- symptoms of hypokalemia
 - Muscle weakness / cramping
 - Parasthesias
 - Palpitations
 - Polyuria / polydipsia

Laboratory Findings

- ***Hypokalemia (<70%)**
 - May result in insulinopenia → hyperglycemia
- Metabolic alkalosis

Hormone Evaluation

- **1 mg Dexamethasone Suppression**
 - Preferred as subclinical Cushing's may have nl 24h UFC
 - Abnormal if post suppression cortisol > 5 ug/dl (? 1.8 ug/dl)
- **Plasma Fractionated Metanephrines**
 - Plasma metanephrines
 - Sensitivity >96%, specificity 75-89%
 - 24 h urine metanephrines & catecholamines
 - Sensitivity 91%, specificity 98%
- **If HTN, Plasma Aldosterone Concentration / Plasma Renin Activity (PAC / PRA)**
 - Abnormal if PAC/PRA ratio > 20 AND PAC > 15 ng/dl
 - Can be done on any BP meds EXCEPT spironolactone, eplerenone, and amiloride

Confirmatory Testing

If initial hormone testing is abnormal, need confirmatory testing [REFER]

- **Cushing's Syndrome**

- 24h Urine Free Cortisol, midnight salivary cortisol, ACTH

- **Pheochromocytoma**

- 24h Urine metanephrine, I¹²³MIBG

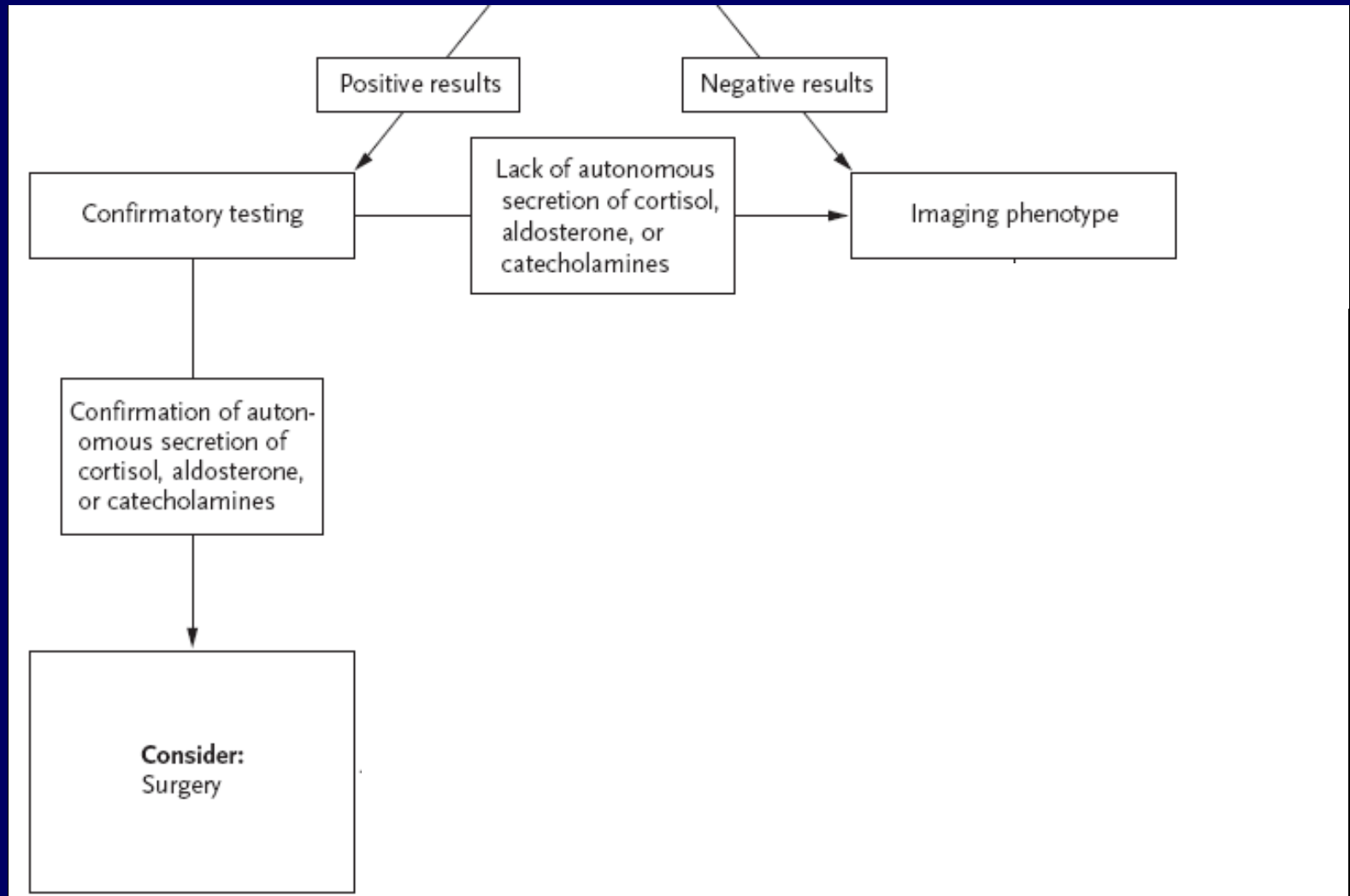
- **Hyperaldosteronism**

- Aldosterone suppression test
 - NS IV or 3 day salt load
- +/- Adrenal vein sampling

**If adrenal nodule confirmed to be hyperfunctional
→ SURGERY**

Evaluation Algorithm

Hormonal Testing (DST, metanephrines, PAC/PRA)



Radiographic Phenotype

- **High fat content = Adenoma**

- **CT**

- low attenuation (<10 HU)
- Rapid washout of contrast (>50% washout in 10', >60% in 15'')

- **MRI**

- signal loss on out-of-phase images in chemical shift MRI (lipid sensitive mode)

- **Low fat content**

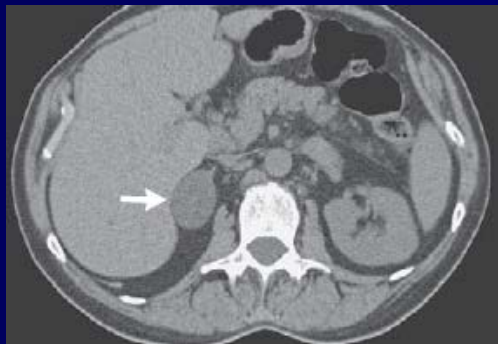
- **CT**

- Increased attenuation (prominent vascularity)
- Delayed washout of contrast

- **MRI**

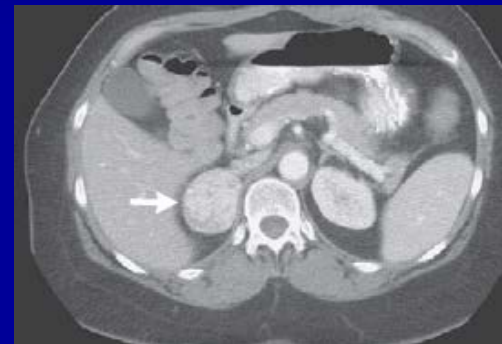
- high signal intensity in T2 imaging

Pheochromocytoma



Adenoma

3.6cm
-18 HU
>60% washout



4.5 cm
40 HU
<50% washout

Malignancy



7.5 cm
30 HU
<50% washout

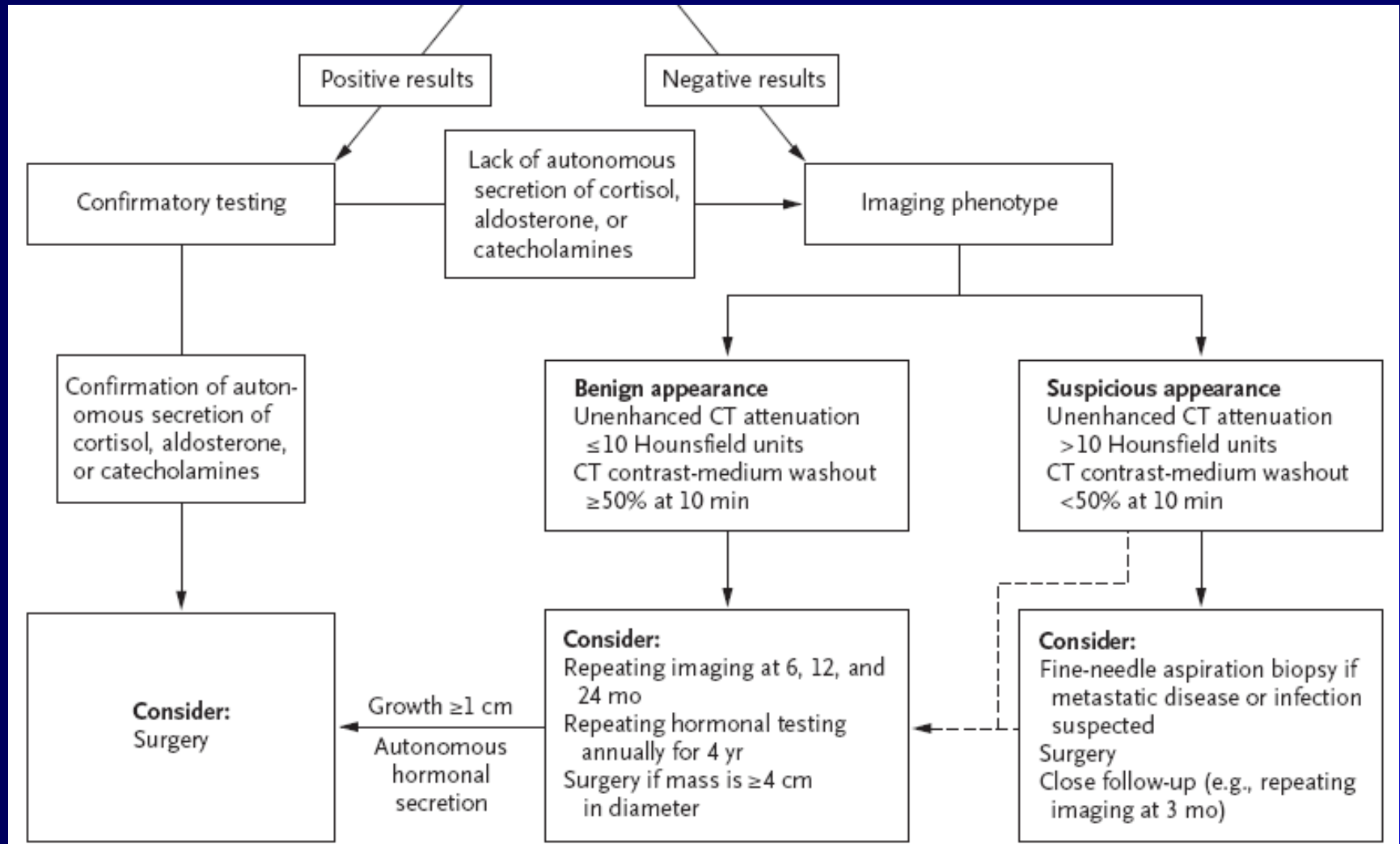
Predictors of Malignancy

- Cancer history
 - History of cancer (esp. lung, breast, kidney, GI)
 - 20-50% of adrenal masses are mets (often bilaterally)
 - No known cancers
 - >85% represent benign tumors
- Size of Mass (if no h/o CA)
 - <4 cm- ~ 2% malignant (adrenal cortical CA)
 - >6 cm- ~ 25% malignant (adrenal cortical CA)
- Radiographic Phenotype

<u>Good</u>	<u>Bad</u>
smooth	irregular
homogenous	heterogeneous
<10HU, ↑washout	> 30 HU, ↓washout
Slow growth (<1cm/yr)	rapid growth (>1cm/yr)

Evaluation Algorithm

Hormonal Testing (DST, metanephrines, PAC/PRA)



Case # 2

- Obese, HTN, DM but no other suggestive clinical findings (nl K+, etc)
- Hormonal Testing
 - DST, metanephrines, Aldo/Renin all WNL
- Adrenal Protocol CT
 - 2 cm, homogenous, smooth borders
 - -5 HU, > 60% washout at 15 minutes

DX= Benign Adrenal Adenoma

- Follow-up
 - Yearly hormonal tests x 4 yrs
 - F/U imaging to confirm lack of growth

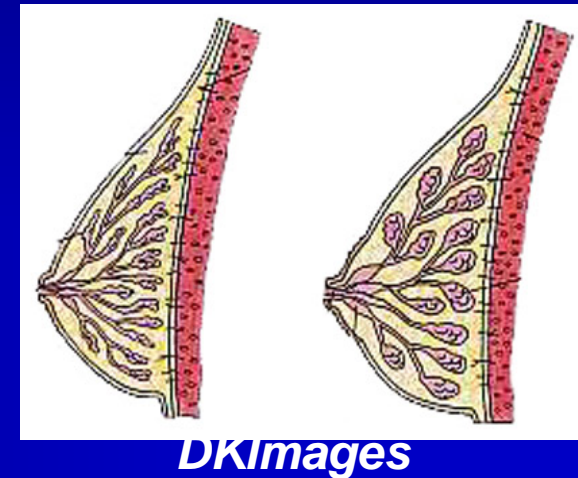
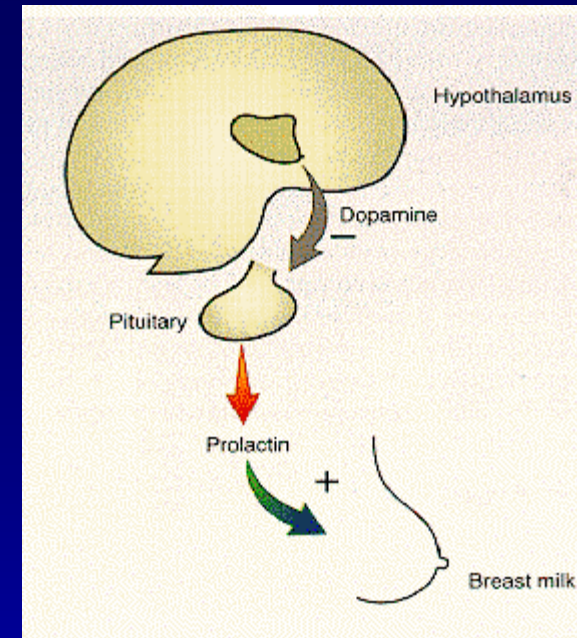
Case #3

32yo G2P2 woman with history of anxiety found to have a prolactin level of 56 ng/ml (nl <20) during evaluation of persistent amenorrhea 6 months after she stopped nursing her youngest child.

Approach to the patient with
hyperprolactinemia

Prolactin Physiology

- Prolactin secretion from pituitary lactotrophs under tonic **inhibitory** hypothalamic control
- INHIBITORY SIGNALS
 - **Dopamine**
- STIMULATORY SIGNALS
 - TRH**
 - Serotonin
 - Histamine
 - Estrogen**
 - Breast/chest wall stimulation** (spinal afferent)
 - Stress**, food-insulin, exercise, intercourse, **sleep**
- Prolactin is released in a pulsatile fashion 4-9 pulses/day w levels rising during late sleep
 - Levels < 25 ng/ml in women (<20 ng/ml in men)
- Primary function is the regulation of lactation
 - Prolactin increases in pregnancy (200's ng/ml)
 - Lactation when estrogen levels fall
 - PRL inhibits LH, FSH secretion



DDX of Hyperprolactinemia

- Pregnancy
- Hypothyroidism

- Drug-Induced
- CNS abnormalities
- Prolactinoma

- Other
 - Breast stimulation, chest wall lesions (zoster, etc), seizure
 - Renal failure, liver dz

Drug-Induced

TABLE 1. Medications That May Cause Hyperprolactinemia

Antipsychotics (neuroleptics)
Phenothiazines
Thioxanthenes
Butyrophenones
Atypical antipsychotics
Antidepressants
Tricyclic and tetracyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Other
Opiates and cocaine
Antihypertensive medications
Verapamil
Methyldopa
Reserpine
Gastrointestinal medications
Metoclopramide
Domperidone
Histamine ₂ receptor blockers?
Protease inhibitors?
Estrogens

TABLE 2. Effects of Psychotropic Medications on Prolactin Levels*

	Increase in prolactin†
Antipsychotics	
Typical	
Phenothiazines	+++
Butyrophenones	+++
Thioxanthenes	+++
Atypical	
Risperidone	+++
Molindone	++
Clozapine	0
Quetiapine	+
Ziprasidone	0
Aripiprazole	0
Olanzapine	+
Antidepressants	
Tricyclics	
Amitriptyline	+
Desipramine	+
Clomipramine	+++
Nortriptyline	-
Imipramine	CR
Maprotiline	CR
Amoxapine	CR
Monoamine oxidase inhibitors	
Pargyline	+++
Clorgyline	+++
Tranylcypromine	±
Selective serotonin reuptake inhibitors	
Fluoxetine	CR
Paroxetine	±
Citalopram	±
Fluvoxamine	±
Other	
Nefazodone	0
Bupropion	0
Venlafaxine	0
Trazodone	0

*CR = isolated case reports of hyperprolactinemia but generally no increase in prolactin levels.

†0 = no effect; ± = minimal increase but not to abnormal levels; + = increase to abnormal levels in small percentage of patients; ++ = increase to abnormal levels in 25% to 50% of patients; +++ = increase to abnormal levels in more than 50% of patients.

CNS Disorders

Hypothalamic Disorders

- Tumors
 - Craniopharyngiomas
 - Meningiomas
 - Dysgerminomas
 - Gliomas
 - Lymphoma
 - Metastatic disease
- Infiltrative dz/ infection
 - Sarcoid
 - Tuberculosis
 - Eosinophilic Granuloma
- Other
 - Irradiation, trauma

Pituitary Disorders

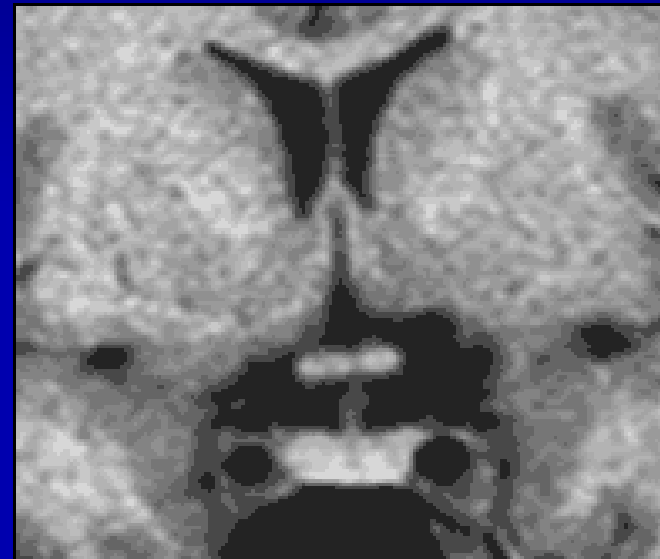
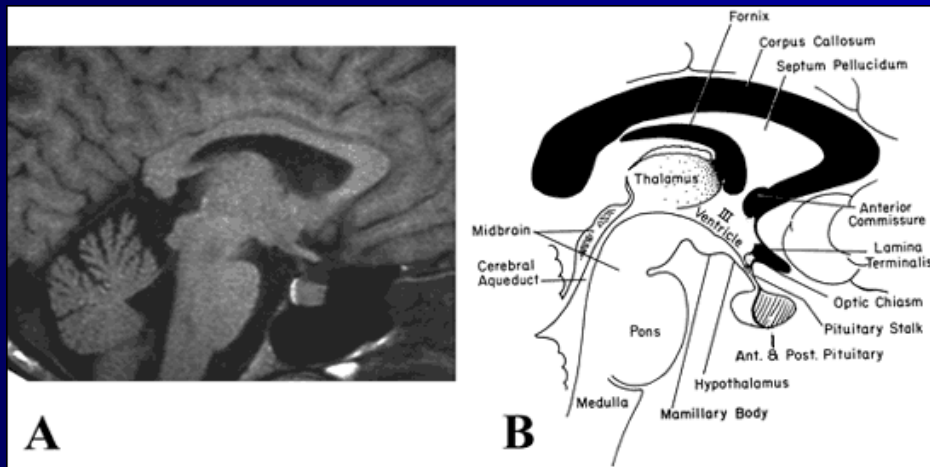
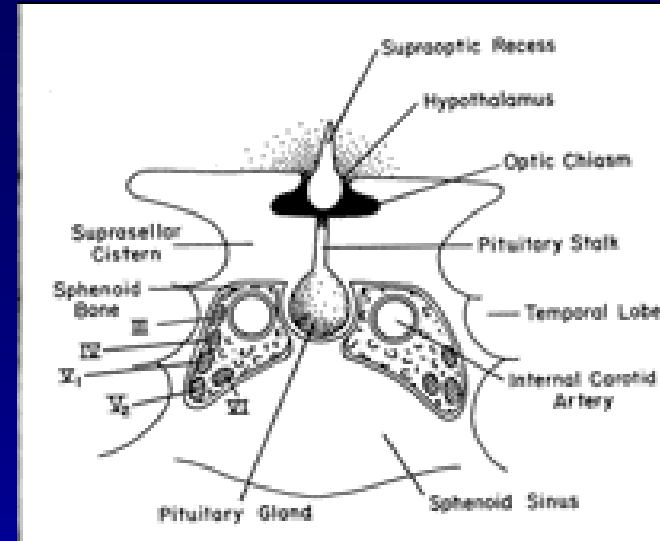
- Stalk disorders
 - Trauma
 - Tumors
 - Infiltration
 - Arterial aneurysm
- Pituitary Macroadenomas
 - Stalk compression

Prolactinoma

- Benign pituitary adenomas
- Most common hormone secreting pituitary tumor
 - Account for ~40 % of pituitary tumors
- > 90% are small and slow growing
- Tumor size is correlated to prolactin levels
 - Macroadenoma (>1 cm) → PRL usually >200 ng/ml
 - If prolactin < 100-150 ng/ml
 - Non-prolactin tumor w stalk compression
 - Hook effect- assay artifact at very high PRL concentration
 - Idiopathic hyperprolactenemia (<2-3mm)

Pituitary Anatomy

- Anterior pituitary
 - Lactotrophs- laterally
- Cranial Nerves
- Chiasm
- Vessels
- Sphenoid sinus



Clinical Presentation

Women

- Amenorrhea/oligomenorrhea
- Infertility
- Galactorrhea
 - Up to 80%, not all symptomatic
- Tumor effects
 - Rare in women as most tumors are small
- Osteopenia

Men

- Tumor effects
 - HA
 - CN palsy
 - Visual field defects
 - Hypopituitarism
- Hypogonadism
 - Decreased libido
 - Erectile dysfunction
 - Infertility
- Osteopenia
- NOT galactorrhea
 - Exceedingly rare

Initial Evaluation

- History and physical
 - Meds
 - Evidence of secondary causes
 - Mass effect
- Labs
 - Repeat prolactin (+/- serial dilutions)
 - hCG, TFTs, BUN/Crt, LFTs
 - +/- other pituitary function tests
 - IGF-1, LH, FSH, gonadal steroids, cortisol
- Imaging studies
 - MRI with gadolinium better than I+ CT
 - If macroadenoma → formal visual field testing

Case # 3

- No physiologic or known secondary causes, no other symptoms besides amenorrhea
- Exam unremarkable except for expressive galactorrhea
- Laboratory Tests
 - Repeat PRL 70 ng/ml
 - hCG negative
 - BUN/Crt, LFT's, TSH, FT4, IGF-1 all WNL
 - LH, FSH, and estrogen suppressed
- MRI showed a 5 mm pituitary adenoma not impinging on chiasm
- Not interested in further fertility

Indications for Treatment

- Macroadenoma or tumor growth
- Hypogonadism
- Infertility
- Symptoms
 - Galactorrhea
 - Hirsutism

Conservative monitoring is an option for pts not interested in fertility & no other indication

Treatment Options

- Dopamine agonists
 - Bromocriptine
 - Cabergoline
- OCP
 - If small microadenoma in pt not desiring further fertility and whose only indication for trx is amenorrhea
- Surgery
 - Unable to tolerate medical tx, unresponsive to tx (persistent chiasmal compression, ↑ tumor size), apoplexy
 - High recurrence rate
- XRT
 - More definitive but higher risk of panhypopituitarism

Bromocriptine vs Cabergoline

- Cabergoline is easier to administer
 - Cabergoline has a longer half life (can be dosed weekly)
 - Bromocriptine has more side effects
 - Nausea, vomiting (50%)
 - HA (20%)
 - Orthostasis (20%)
- Cabergoline more effective
 - PRL normalization (80% vs 60%)
 - Pts achieving >50% tumor shrinkage (96% vs 64%)
 - Persistently normal PRL after trx d/c'ed (60% vs 33%)
 - Cabergoline effective for tx of bromocriptine resistant tumors
- Bromocriptine preferred when fertility is an issue
 - More experience w bromocriptine in pregnancy

Nasal Congestion
Constipation
Fatigue, anxiety

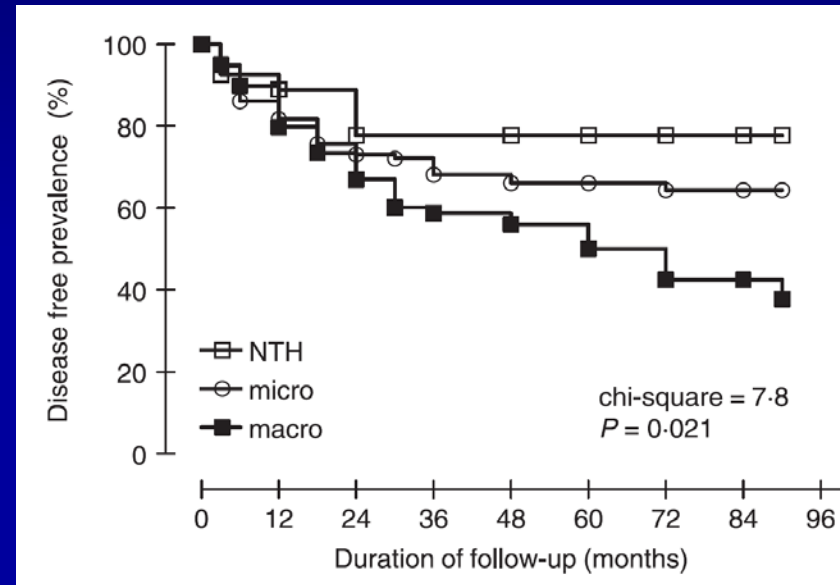
Case # 3

- Treatment
 - Dopamine agonist [or OCP]
- Follow-up
 - Prolactin- yearly
 - MRI
 - If clinical evidence of tumor expansion
 - If considering trial off dopamine agonists
 - After > 2yrs of uninterrupted treatment
 - Persistently normal prolactin measures

Cabergoline Withdrawal

If initial adenoma < 2cm AND PRL has normalized, tumor shrank by >50%, & no evidence of cavernous sinus invasion, can attempt to d/c cabergoline after 2 yrs of trx

- Long-term remission possible based on tumor size
 - Before TX:
 - Non-tumoral ~ 75%
 - Microprolactinoma ~ 66%
 - Macroprolactinoma ~ 50%
 - After TX:
 - No remnant tumor ~80%
 - Remnant tumor ~50%
- Renewed tumor growth was not seen 5 yrs after cabergoline w/d



Additional Consideration

NEJM - January 4, 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D., Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D., Ph.D.

- Long-term use of cabergoline for \uparrow prolactin a/w TR but of unclear clinical significance
 - Mod TR in cabergoline vs controls: 54% vs 18%
- Use lowest dose of cabergoline to normalize prolactin & consider withdrawal trial depending on response

Colao.JCEM.2008; Kars.JCEM.2008; Melmed.JCEM.2011.

Case #4

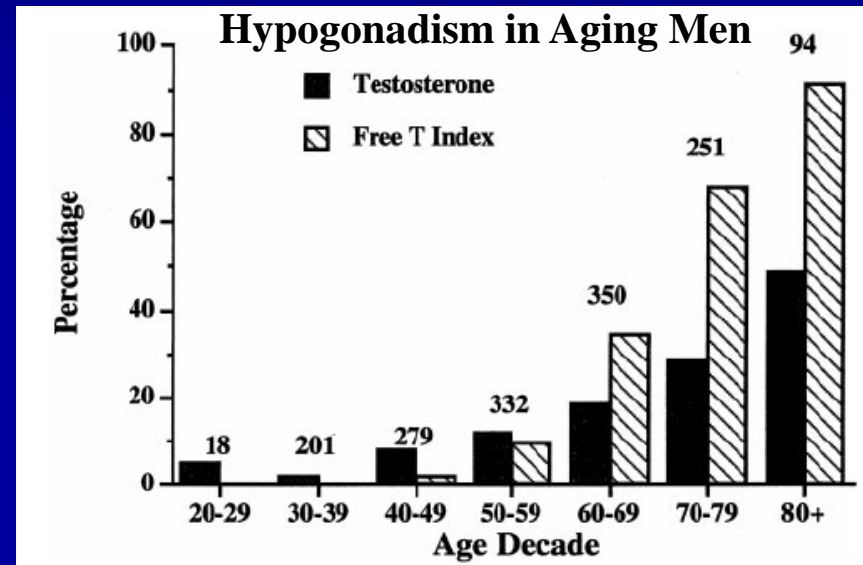
58 yo man with a history of DM, HTN, and dyslipidemia was found to have an afternoon testosterone level of 185 ng/dl (nl >270) after complaining of erectile dysfunction, diminished libido, and decreased energy.

Approach to the patient with androgen deficiency

"Andropause"

Several cross-sectional and longitudinal studies have demonstrated a decline in serum testosterone with age

- Testosterone levels ↓ at a fairly constant rate
 - average ↓ 3.2 ng/dl / year
Baltimore Longitudinal Study of Aging
- Increased frequency of testosterone values in the hypogonadal range with aging



Harman. 2001

Who Has Androgen Deficiency?

Endocrine Society Clinical Practice Guideline

“We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels”

Challenges

“We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels”

- Signs and symptoms are non-specific
 - Common with age
 - Often seen in patients with normal testosterone levels
- Many barriers in determining what constitutes “unequivocally low” testosterone levels

Androgen Deficiency

Clinical findings depend on age of onset

- Fetal- hypospadias, microphallus, cryptorchidism
- Prepubertal-incomplete sexual maturation
- Adulthood- regression of sexual function, infertility, hot flashes

Most signs and symptoms are non-specific

More reliable features

- Abnormal sexual development
 - Prepubertal testes
 - High pitched voice
 - Eunuchoid proportions
- ↓ virilization
- Azoospermia
- New gynecomastia
- Hot flashes
- Fragility fracture
- Impaired sexual function*, ↓ libido*, ↓ spontaneous erections*

Less reliable features

- Mild anemia
- Decreased energy
- Decreased aggressiveness
- Depressed mood
- Decreased muscle/strength
- Impaired memory
- Increased adiposity

Signs and Symptoms of Sexual Dysfunction are Common

- High prevalence of sexual problems even in young men(<60 yo)
 - By age 40, 40% of men reported some level of impaired sexual function

Wu. NEJM.2010; Laumann. JAMA.1999

- There is a waning in sexual function and libido with each decade

Massachusetts Male Aging Study (Feldman.1994, Araujo.2004)

- Decline in sexual function is associated with co-morbid conditions

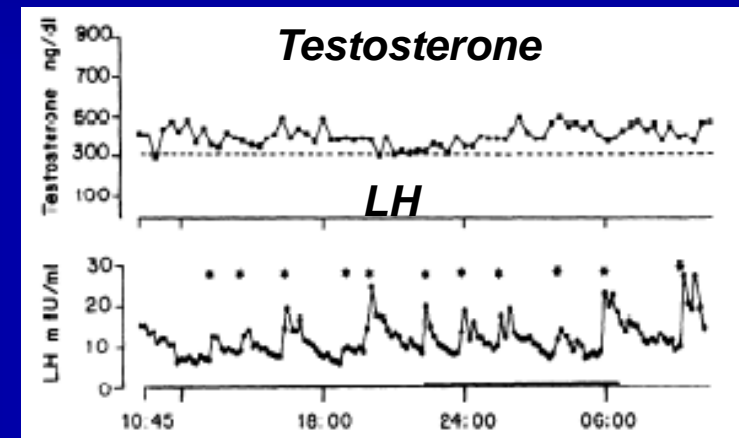
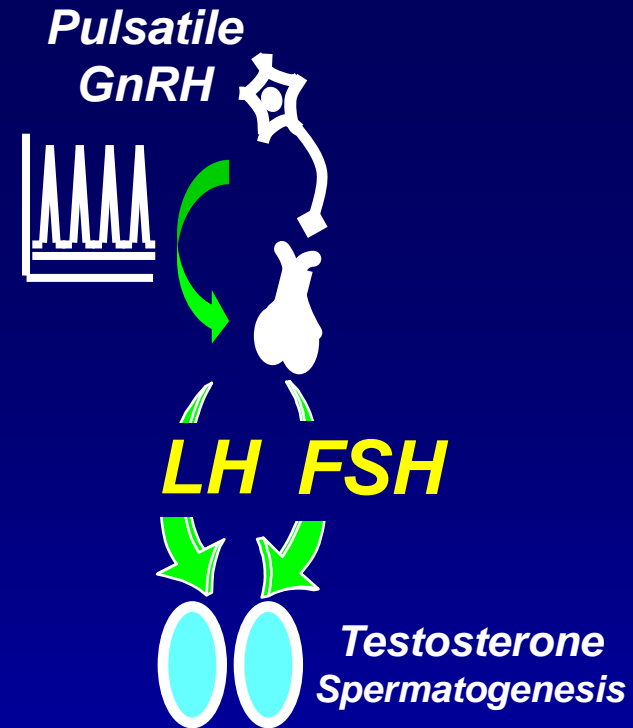
Health Professional Follow-up Study (Bacon.2003)

Challenges in Testosterone Measurements

- Physiologic variations
 - Pulsatile secretion
 - Circadian variation
 - Protein binding
- Technical challenges
 - Tissue conversion and intracellular receptors
- No established physiologic testosterone threshold to guide therapy or confirm the diagnosis of androgen deficiency
 - Only population norms
- Effect of medicines and co-morbid conditions

Normal Physiology

- Hypothalamic-Pituitary-Gonadal (HPG) Axis
 - GnRH
 - LH, FSH
 - Testosterone, gametogenesis
- Pulsatile gonadotropin secretion
 - ~10-12 pulses/d
 - Significant fluctuations in testosterone levels (can be >50%)
- Circadian variation
 - Morning > evening
 - ~20% of normal subjects with testosterone levels occasionally dipping into the “hypogonadal” range in a 24h period



Circulating Testosterone

- Protein binding
 - “Bioavailable” testosterone is non-SHBG bound fraction
 - ~55% tightly bound to SHBG
 - ~45% weakly bound to Albumin
 - ~1-3% free
- Several factors alter SHBG levels

Conditions that ↑ SHBG

Aging

Hepatitis

Hyperthyroidism

HIV

Estrogen

Anticonvulsants

GH deficiency

Conditions that ↓ SHBG

Obesity

Nephrotic syndrome

Hypothyroidism

Acromegaly

Androgens

Insulin

Glucocorticoids

Progestins

Familial

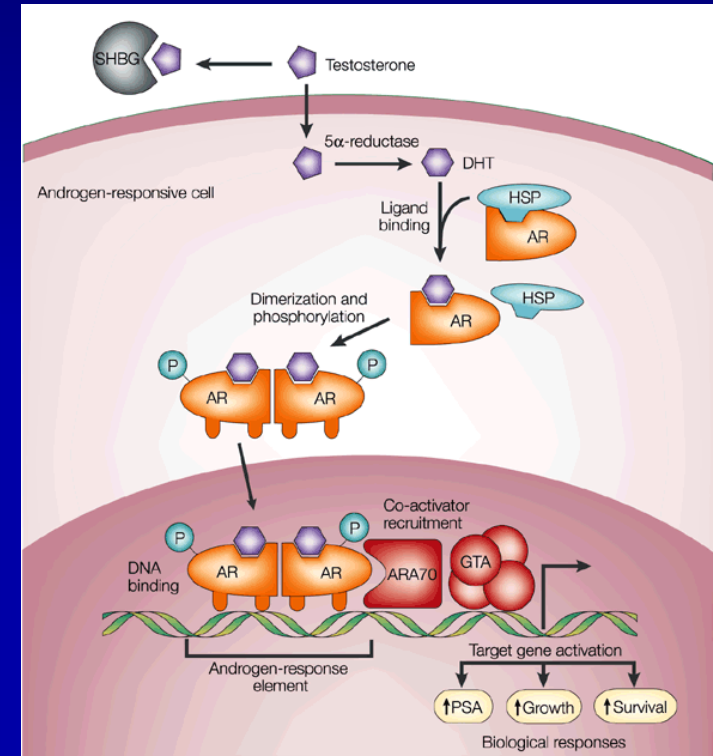
Testosterone Measurements

- Reliable assays for free or bioavailable testosterone are not widely available
 - Commonly available free testosterone measurements are not very reliable
 - Can estimate bioavailable androgens from total testosterone and SHBG concentration
- Normative ranges in healthy young men vary among laboratories & assays
 - Use lower limits of nl for reference lab

30% of pts in the mildly hypogonadal range have normal levels on repeat measurement

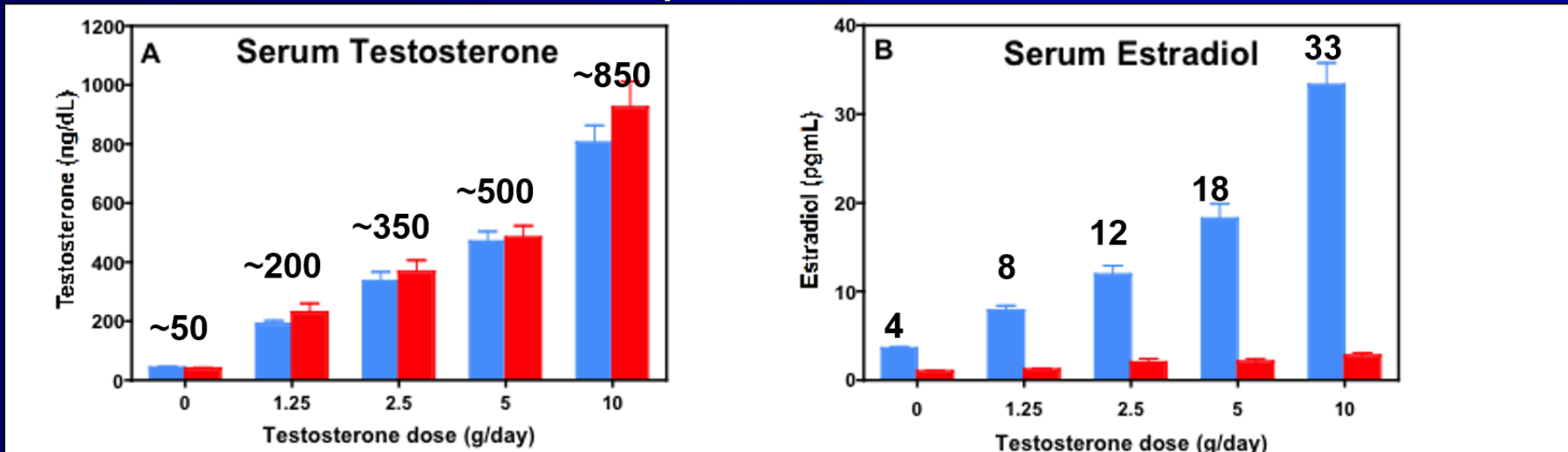
Additional Limitations

- Testosterone is a pro-hormone
 - Enzymatic conversion in tissue
 - Dihydrotestosterone (*5 α Reductase*)
 - Estrogen (*Aromatase*)
 - Inactivated (*3 α Reductase*)
- Affect is mediated through intracellular receptor
- No clear physiologic threshold for hypogonadism has been established



Hypogonadism in Men (HIM), Hypogonadism with Estrogen Removal (HER)

- Chemical castration with different doses of testosterone add-back (HIM)
 - 0, 1.25, 2.5, 5, or 10 g of testosterone gel
- + Aromatase inhibitor (HER)
 - Evaluate dose-response of various outcomes



Finkelstein, Lee, Burnett-Bowie, Pallais, et al NEJM.2013.

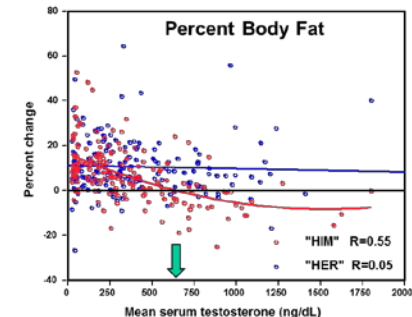
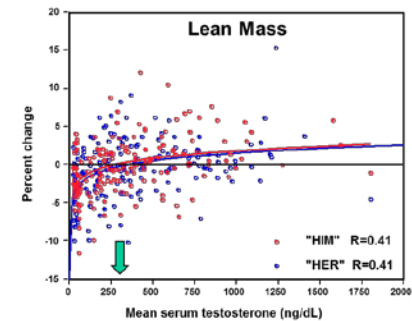
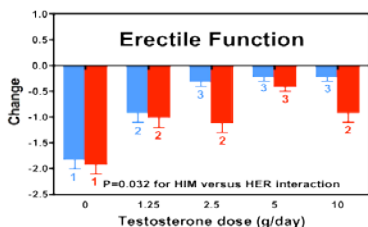
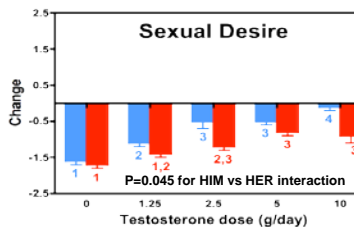
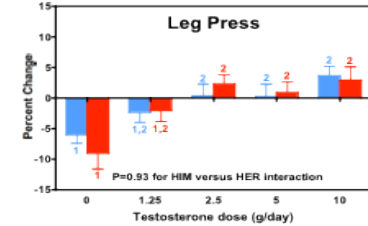
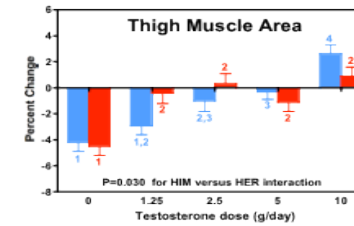
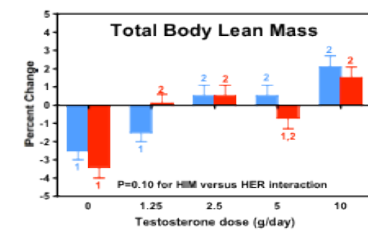
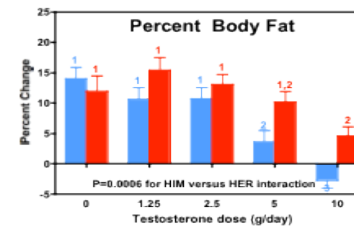
Physiologic Outcomes

Testosterone's effects on many physiologic outcomes were dependent on estradiol levels

- Pure androgenic effects
 - PSA, Hct, lean mass, strength
- Strong estrogen effect
 - ↑ sexual fnx
 - ↓ **body fat**
 - ↓ **bone turnover**

Different outcomes had different testosterone “thresholds”

Finkelstein, Pallais, et al. NEJM.2013 & unpublished data



Diagnostic Gray Zones

- Symptoms
- Testosterone
 - Measurements
 - Levels (\pm Estrogen)
- Cause and effect vs reverse causation
 - $\downarrow T \rightarrow$ disorder, or
 - disorder $\rightarrow \downarrow T$
 - RCT are rare



Photo by Marco Belluci

Evaluation

- Morning testosterone & SHBG measurement
 - Confirm by repeating on more than one occasion
- LH & FSH to differentiate between primary and secondary causes
 - Primary- high LH & FSH
 - Secondary- inappropriately low LH & FSH (may be within the “normal” range)

Primary Hypogonadism

- Testicular defect
- High LH, FSH, low testosterone
- Causes
 - Viral orchitis
 - Toxins
 - Radiation, chemotherapy
 - Drugs
 - Alcohol, ketoconazole, spironolactone, metronidazole, etomidate
 - Trauma
 - Systemic diseases
 - Cirrhosis, renal failure, granulomatous dz, HIV
 - Klinefelter Syndrome (47, XXY)



Secondary Hypogonadism (Hypogonadotropic Hypogonadism)

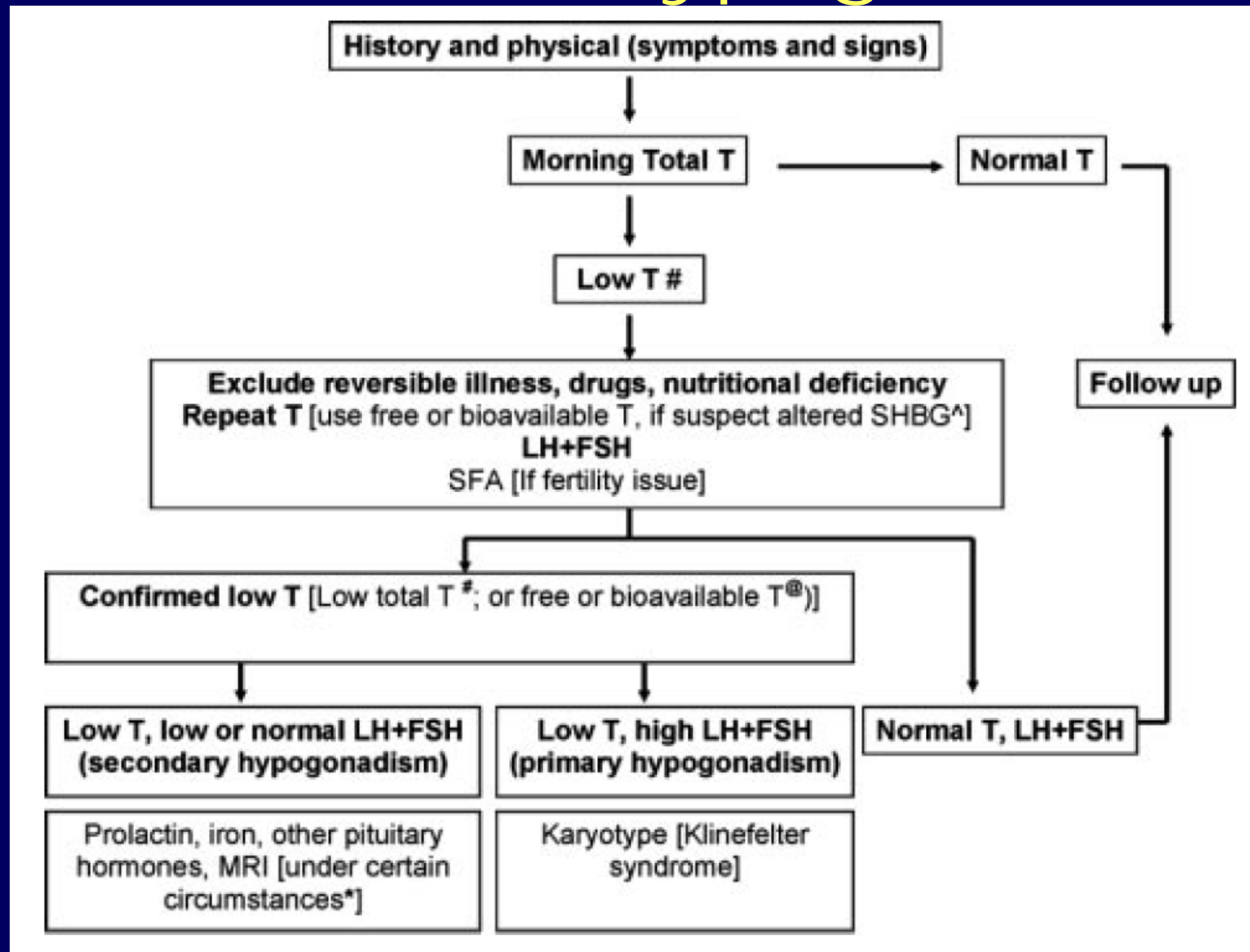
- Central defect
- Inappropriately low LH, FSH, low testosterone
- Causes
 - Hypothalamic or pituitary disorders
 - Tumors, infiltrative diseases, head trauma
 - Hyperprolactinemia
 - Hemochromatosis
 - Functional
 - Acute illness, eating disorders, depression, excessive exercise, AIDS
 - Drugs
 - Glucocorticoids, opiates, MJ, digitalis, exogenous estrogens
 - Idiopathic
 - Anosmic vs normosmic



Primary vs Secondary

- Further evaluation
 - Primary
 - **Karyotype**- including test for mosaic 46,XY/47,XXY
 - Secondary
 - **MRI**
 - **Prolactin**
 - **Pituitary function testing**
 - **Iron studies**
 - **ACE-levels**
 - **Genetic testing / counseling for IHH**
 - Consider BMD for any cause of hypogonadism
- Implications for fertility
 - Better success achieving fertility in secondary hypogonadism

Evaluation of Hypogonadism



Who to treat?

Endocrine Society Clinical Practice Guideline

“We recommend testosterone therapy for symptomatic men with the classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density.”

Treatment

- Contraindications
 - Prostate cancer
 - Breast cancer
- Relative contraindications
 - Prostate nodule or induration
 - Unexplained PSA elevation
 - Severe BPH
 - Erythrocytosis (Hct > 50%)
 - Untreated obstructive sleep apnea
 - Unstable CHF

Treatment

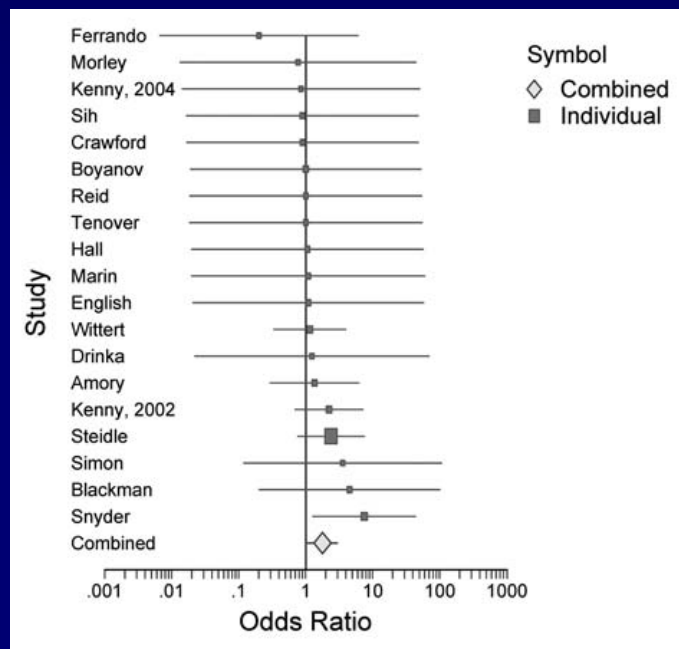
- Benefits
 - Improved sexual function
 - Improved bone density (*no fracture data*)
 - Improved body composition
 - Improved anemia
- Side effects
 - Adverse prostate effects
 - Worsening BPH and prostate cancer
 - Cardiovascular events?*
 - Reduced sperm production and fertility
 - Induction or worsening of obstructive sleep apnea
 - Erythrocytosis
 - Gynecomastia
 - Acne and oily skin
 - Male pattern balding

Effects on the Prostate

- Moderate increase in prostate volume
- Increase in PSA within the normal range (0.2-0.5 ng/ml)
- Reviews of variable quality trials (3mo - 3yr) have shown conflicting results in the rate of all combined prostate events in testosterone treated group c/t placebo
 - prostate CA, biopsy, PSA>4 ng/ml, ↑IPSS>4
- Insufficient years of follow-up to determine clear effect on prostate cancer

Effects on the Prostate

Composite prostate outcomes higher in T group vs controls
OR 1.8 (p<0.05)



Calof. J Gerontology.2005

RR (CI) T tx Controls

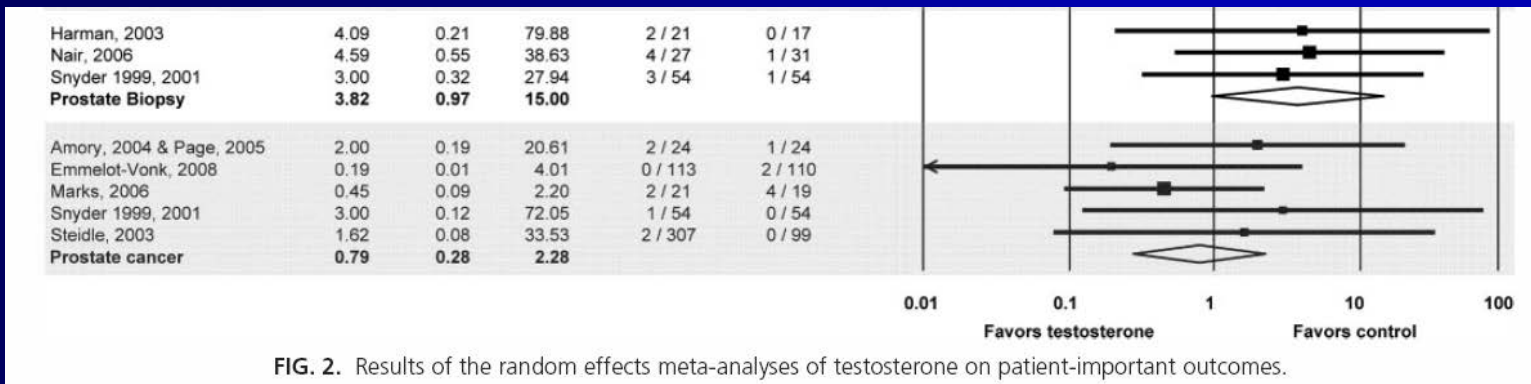
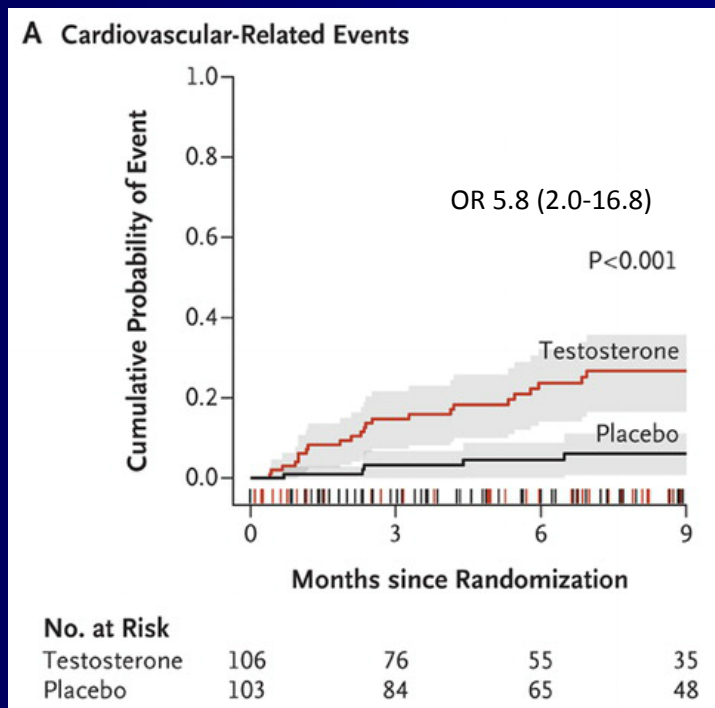


FIG. 2. Results of the random effects meta-analyses of testosterone on patient-important outcomes.

Cardiovascular Effects

- Testosterone treatment increased the rate of CV events in men with multiple risk factors

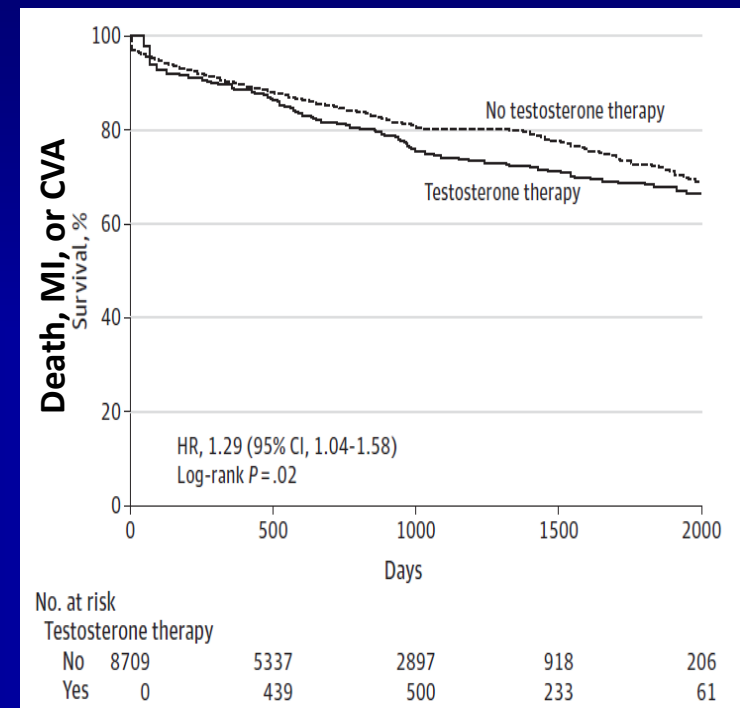
RCT in frail men (avg age 74 yo)



OR 5.8 (p<0.001)

***Basaria.NEJM.2010**

Observational study s/p cardiac cath



HR 1.29 (p=0.02)

***Vigen.JAMA.2013**



- **Drug Safety Communication about possible CV risks (1/2014)**
 - *“(FDA) is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.”*
- **Label Warning about potential venous blood clots (6/2014)**
 - *“(FDA) is requiring manufacturers to include a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins.”*
- **Advisory panel recommends label change limiting the use of testosterone to treat lifestyle issues (9/2014)**

The Business of "Low T"

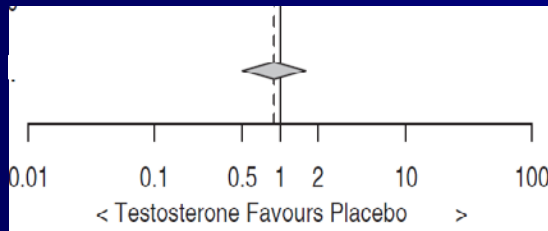
Confessions of a "Low T" ghost-writer

Braun.JAMA IM. 2013

- Accurate but unbalanced data presentation
 - Emphasizing benefits & understating risks
- Controversial guideline omissions
 - Caution about long-term risks given low quality of available data
 - Analogous to HRT prior to WHI
 - Transient state of symptomatic hypogonadism
 - Analogous to functional hypothalamic amenorrhea

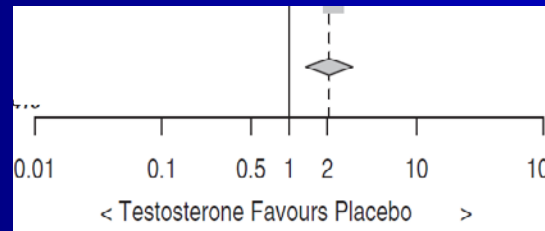
CV events in RCT of testosterone Rx varied by source of funding

Pharma Funded



OR 0.89 [0.5 - 1.6]

NOT Pharma Funded



OR 2.06 [1.34 - 3.17]

Xu. BMC Medicine. 2013

Treatment

- The risk/benefit ratio for testosterone replacement in older men is more difficult to determine than in younger men
- No mortality data available for the long term use of testosterone replacement

Testosterone Formulations

- Intramuscular
 - Testosterone enanthate/cypionate- 100 mg/wk or 200 mg /2 wks
 - Supraphysiologic peak and hypogonadal trough levels
 - Testosterone undecanoate- 750 mg q 10 wks
 - Concern for pulmonary oil microembolism and anaphylaxis
- Transdermal
 - Patch (5 mg)- 1 or 2 patches/night
 - Skin irritation
 - 1% /1.62%/2% Gel – ~30-100 mg/d to extremities/trunk/axilla
 - Potential transfer to female partner or child by direct contact
 - Moderately high DHT levels (lowers T:DHT ratio)
- Buccal bioadhesive tablets / Nasal Spray
 - 30 mg bioadhesive tablets bid / 5.5 mg – 2 pumps tid
 - Mucosal irritation, altered taste
- Testosterone pellets
 - 75 mg pellets- 2-6 pellets implanted sc q 3-6 months
 - Surgical insertion, may extrude spontaneously

Goals and Follow-Up

- Evaluate for response & side effects at 3-6 months and then annually
- Measure testosterone levels 3-6 months after starting therapy & then yearly
 - Aim for testosterone levels in the mid-nl range
- Check Hct at baseline, 3-6 months, & then yearly
 - Stop tx if Hct>54% until it drops to safe level & evaluate pt for hypoxia and sleep apnea
- If >40-50 yo, digital rectal exam & PSA at baseline, 3-6 months, and then in accordance to guidelines
 - Refer if: 1) abnl exam, 2) \uparrow PSA > 1.4 ng/ml within a yr, 3) PSA velocity >0.4 ng/ml-yr for periods >2 yrs

Case # 4

- History & Physical
 - Pt recently started on **narcotics** for back injury
 - Reported increased **stressors** at work & home
 - **ED was long-standing**
 - Had h/o peripheral vascular disease
 - On multiple antihypertensive agents
 - Fatigue temporally correlated to his injury
 - Father and uncle with prostate cancer
 - Obese with BMI 34, no other signs of hypogonadism
- **Lab tests normalized after narcotics d/c'ed**
 - Repeat morning testosterone measurements
 - T 300-400 ng/dl range with low SHBG levels
 - LH, FSH, & prolactin WNL

Case # 4

- Pt initially disappointed to have “low” T levels
- Discussed
 - Problems related to testosterone measurements (physiologic variations, not a measure of physiologic activity, unclear what constitutes “normal” values)
 - How testosterone levels tend to be lower in obesity (bec of ↓SHBG)
 - Effects of drugs & stress on the HPG axis
 - Likely multi-factorial cause of his ED
 - Potential risk factors with testosterone therapy
- Testosterone replacement not initiated and pt had a good response to tadalafil

Thank You!

