Pituitary for the Internist

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Objectives

- Recognize potential causes of pituitary insufficiency
- Describe appropriate hormone workup for pituitary insufficiency/hormone excess
- Know how to treat endocrinopathies related to pituitary dysfunction

Why is this important?

- Very few hospitals have inpatient endocrinology coverage!
- Neurosurgeons are not endocrinologists
- YOU will be the one consulted for endocrine issues (including pituitary)
- The cases presented here are from my own experience as a hospitalist

Gonad GH Prolactin

Thyroid

Adrenal

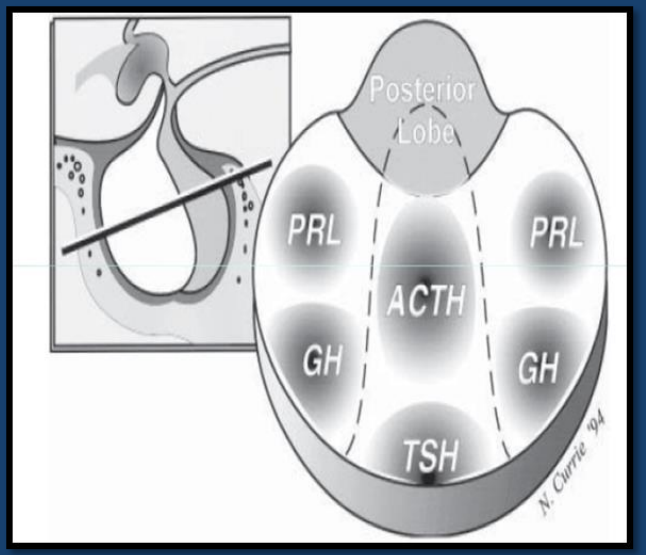
+ ADH

(posterior pituitary)

Pituitary pathology – keep it simple!

- Mass effect (ie threat to vision/apoplexy)?
- Hormone excess ?
- Hormone deficiency ?

Anterior pituitary axes



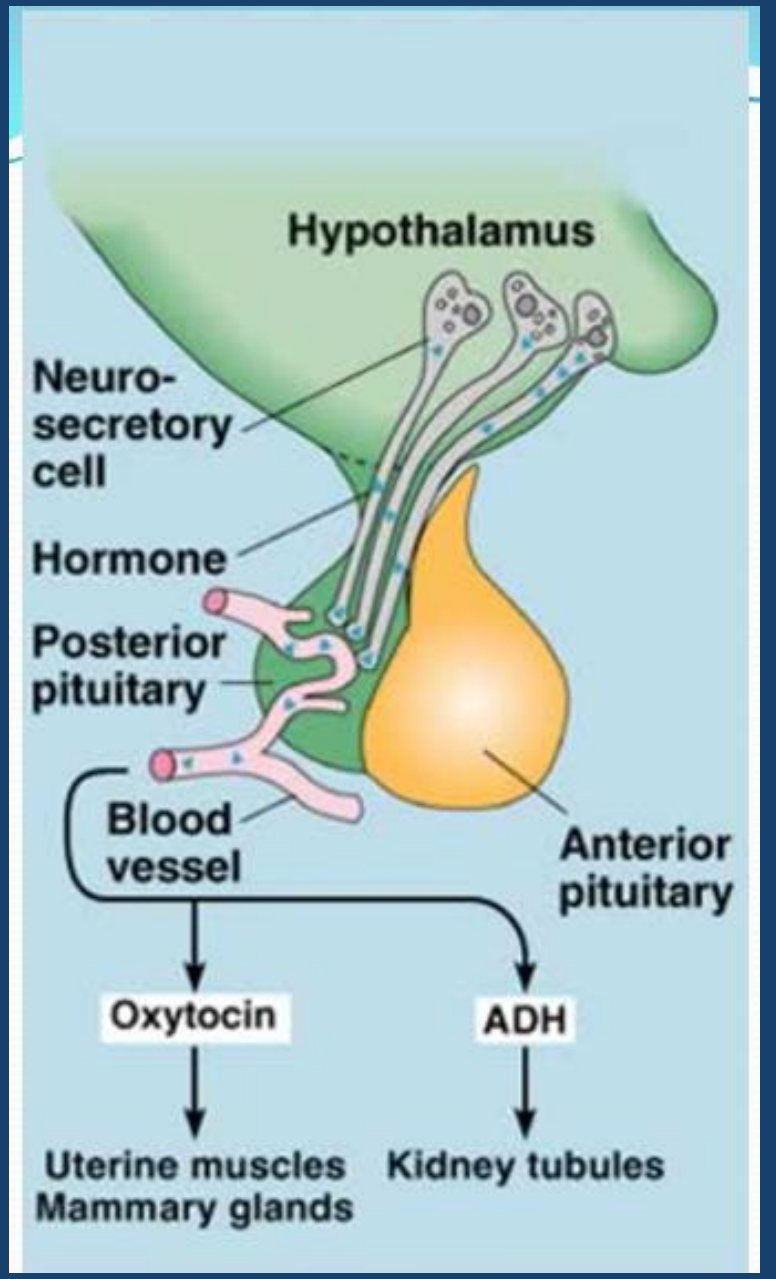
- Adrenal (HPA): CRH → ACTH → cortisol
- Thyroid (HPT): TRH → TSH → T4
- Gonadal (HPG): GnRH → FSH/LH → testosterone, estradiol
- Growth hormone (GH): GHRH → GH → IGF-1 (liver)
- Prolactin: regulated by negative feedback from dopamine

- Clinical signs/symptoms can suggest pituitary dysfunction, but definitive diagnosis requires biochemical confirmation

- Labs to order: ACTH/cortisol, TSH, free t4, FSH/LH, testosterone/estradiol, IGF-1, prolactin

Posterior pituitary

- Anti-diuretic hormone (ADH), (ie vasopressin, arginine vasopressin AVP)
- Responsible for maintaining serum osmolality and blood pressure
- ADH → stimulates aquaporin channel upregulation in the collecting tubule
- Too much ADH → hyponatremia
- Too little ADH → hypernatremia



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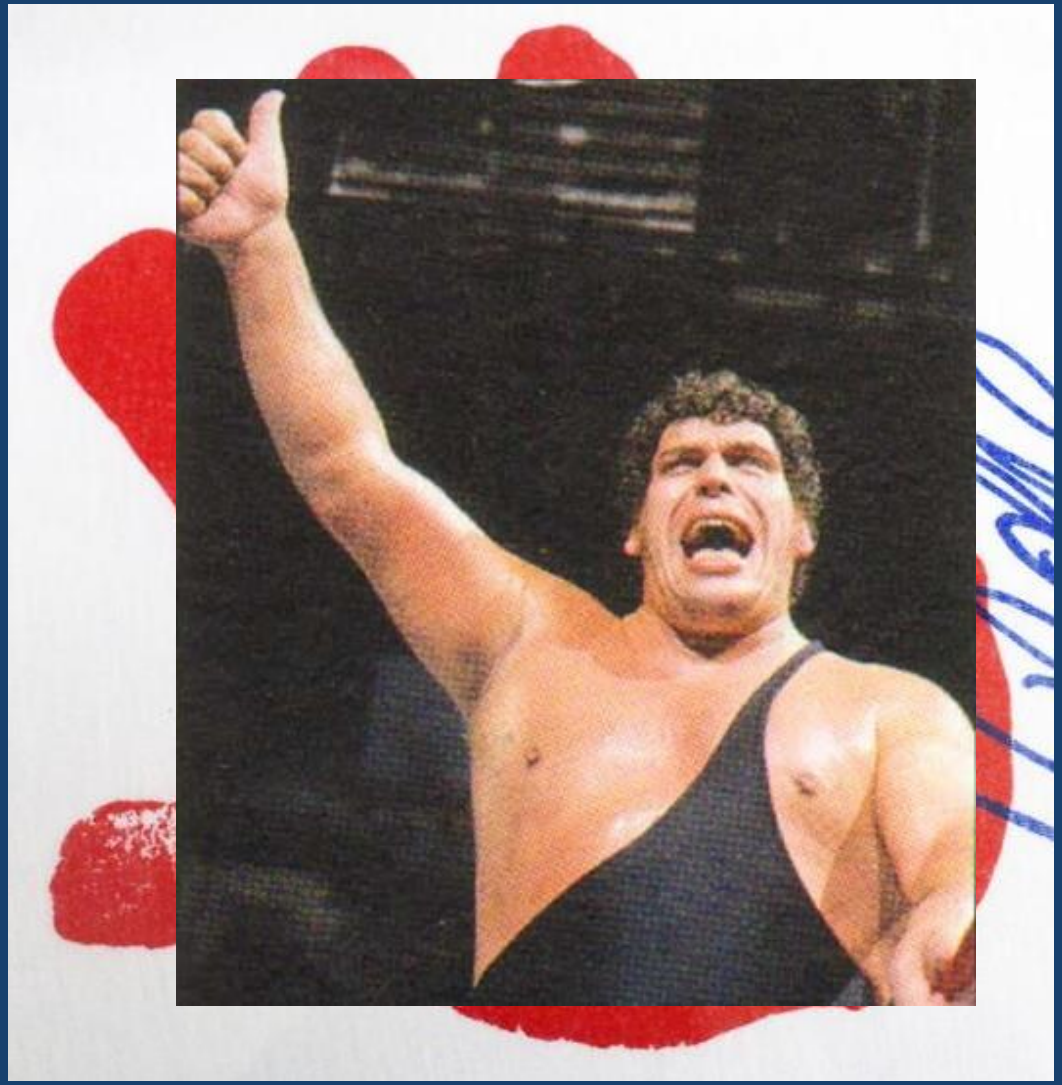

Adrenal

+ ADH

(posterior pituitary)

Case 1 – “I have an easy admit for you.”

- 76 yo M is being admitted for hip fracture after a ground level fall with a head strike. CT scan of the head done in the ER incidentally reveals a 2 cm pituitary mass with no compression of the optic chiasm. He is scheduled to go to the OR soon for operative repair of hip fracture. You are asked to “clear” the patient for surgery. The patient complains of recurrent lightheadedness on standing, fatigue, and constipation. BP 110/60 with positive orthostatics. TSH normal at 1.6.

- What is the next best step in management?
  - A) proceed with surgery and do pituitary workup as an outpatient
  - B) postpone surgery pending pituitary hormone testing
  - C) STAT MRI with neurosurgical consult
  - D) start empirically on IV hydrocortisone

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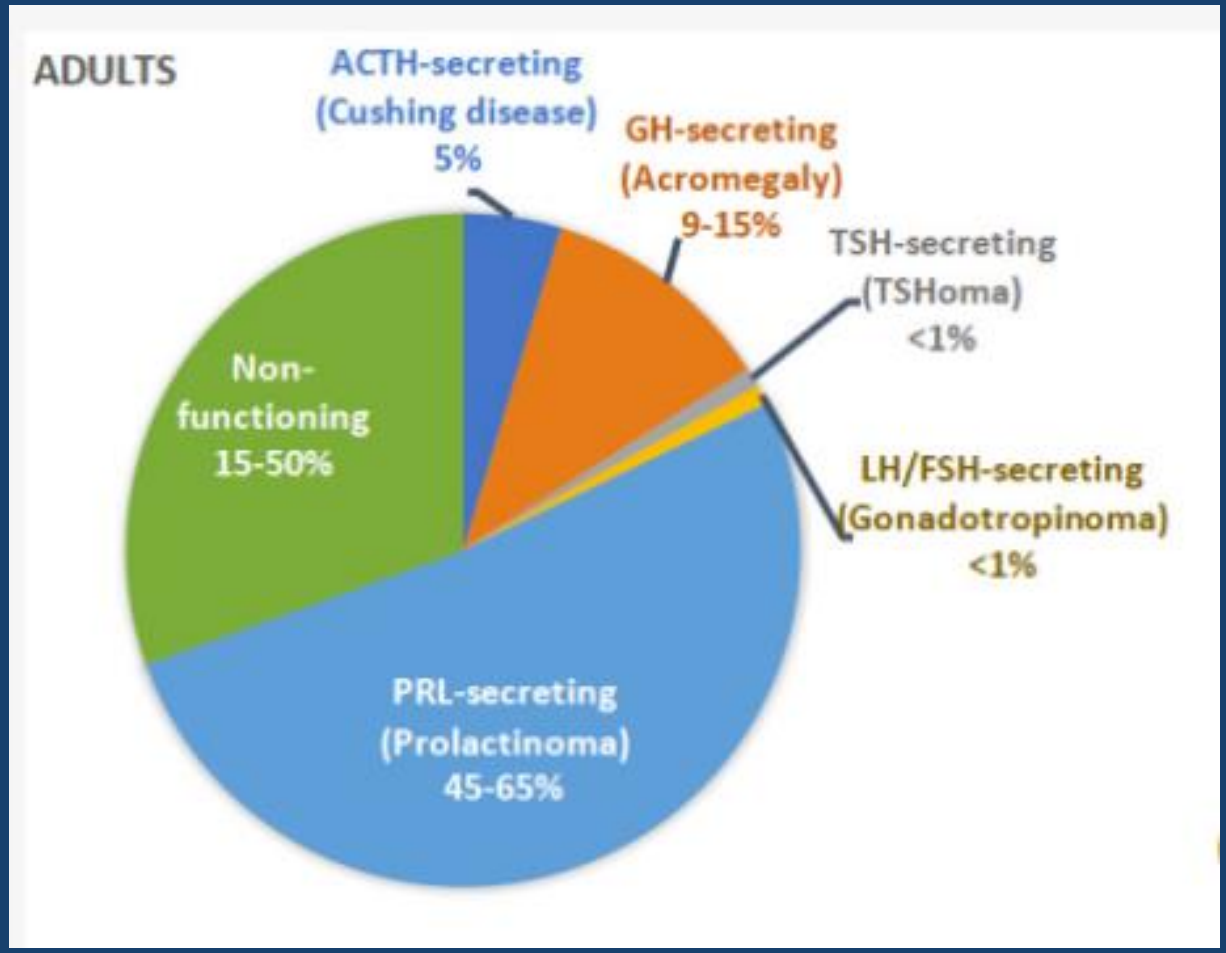
Pituitary macroadenoma

- Macroadenoma > 1cm
- Microadenoma < 1cm

1) Mass effect on chiasm?

2) Hormone excess?

3) Hormone deficiency from “squished” pituitary?



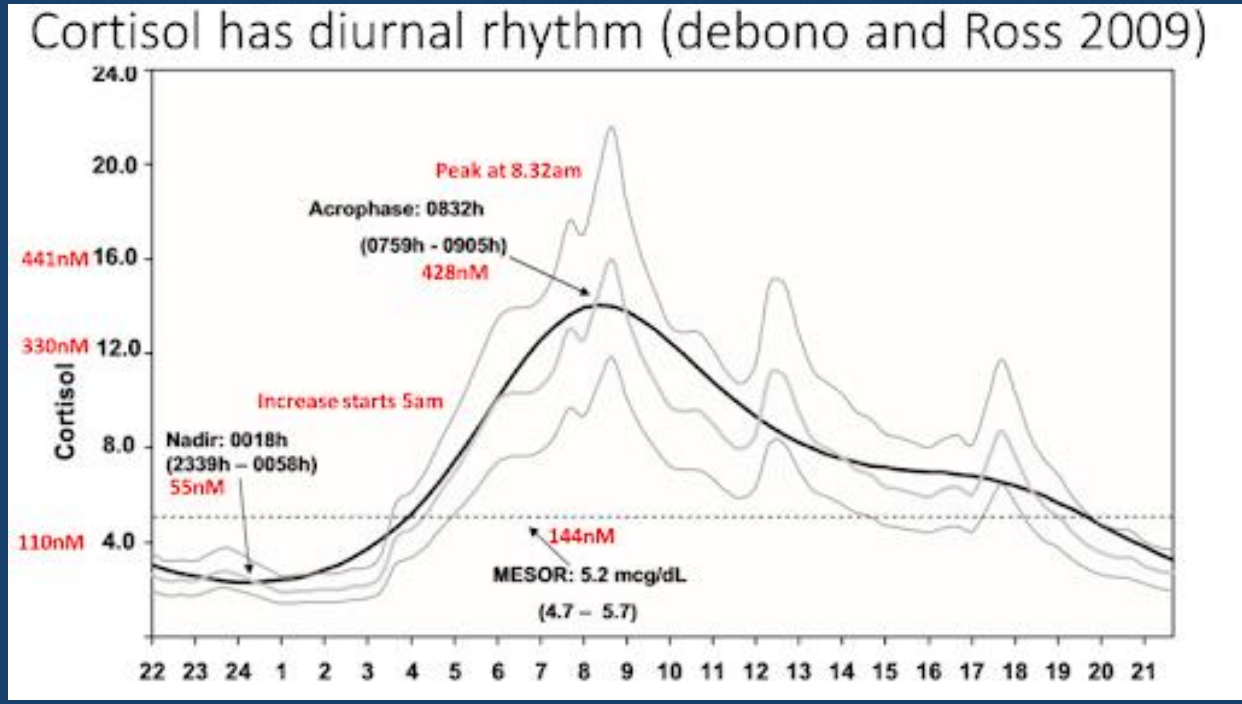
Pituitary hormone evaluation

1) Adrenal axis:

- ACTH producing tumor (ie Cushing's disease)
  - 1mg dexamethasone suppression test
  - Late night salivary cortisol
  - urine free cortisol

- Adrenal insufficiency from tumor compression → AM cortisol or ACTH stim test
  - AM cortisol < 3, AI is likely
  - AM cortisol 3-15, equivocal
  - AM cortisol > 15, AI is unlikely

(J Clin Endocrinol Metab, November 2016, 101(11):3888-3921)



Pituitary hormone evaluation

2) Thyroid axis:

- TSH producing adenoma (TSHoma) → elevated TSH and free T4
- Central hypothyroidism → decreased OR NORMAL TSH and low free T4

- **Cannot rely on TSH alone in pituitary disease – must use free T4**

3) Gonadal axis:

- Excess: FSH/LH producing tumor: RARE; most gonadotroph tumors are nonfunctional
- Deficiency: central hypogonadism → decreased or "inappropriately normal" FSH, LH, and low testosterone/estradiol

- What time of day should testosterone always be checked?
- Estradiol can be checked at any time

Pituitary hormone evaluation

- 4) GH axis – IGF-1
  - Screening test
  - Abnormal results will be followed by definitive testing
- 5) Prolactin
  - Prolactin elevation in prolactinomas is proportional to the size of the adenoma
  - Many causes of elevated prolactin levels!

Etiology	N (%)	Mean PRL (range) (ng/mL)
Macroprolactinomas	250 (20.2)	1422.9 ± 3134.7 (108-21,200)
Microprolactinomas	444 (36)	165.6 ± 255.1 (32-525)
Idiopathic	45 (3.6)	163.9 ± 81.8 (46-328)
Macroprolactinemia	115 (9.3)	119.5 ± 112.9 (32.5-404)
Drug-induced	180 (14.6)	105.1 ± 73.2 (28-380)
Acromegaly	40 (3.2)	99.3 ± 57.4 (28-275)
NFPA	82 (6.6)	80.9 ± 54.5 (28-490)
Primary hypothyroidism	78 (6.3)	74.6 ± 42.4 (30-253)

NFPA: Non-functioning pituitary adenomas. Adapted from Ref. 34.

Case 2 – “I’m going out of town.”

- 65 yo F underwent transsphenoidal resection of a nonfunctional pituitary macroadenoma. She was admitted to the ICU postoperatively and is being managed by the neurosurgical team. You are called to evaluate the patient 3 days post-op for asymptomatic hyponatremia. BP 120/85, p 70, Na 126 (preop 137), K 4.0, Cr 0.95. Exam is unremarkable. Preoperative pituitary function is normal.

- Which of the following are possible causes of this patient’s hyponatremia?
  - A) central adrenal insufficiency
  - B) central hypothyroidism
  - C) central hypogonadism
  - D) GH deficiency
  - E) SIADH
  - F) cerebral salt wasting

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Post-pituitary surgery hyponatremia

- Differential diagnosis
  - SIADH (most common)
  - Central adrenal insufficiency
  - Central hypothyroidism
  - Cerebral salt wasting (RARE)

- Workup:
  - SIADH - Serum osm, urine osm, urine sodium
  - AM cortisol (ACTH stim test not accurate in acute pituitary dysfunction!
  - Free T4

Bonus points – how to differentiate between SIADH and CSW?

VOLUME STATUS

Case 3 – “Sepsis admit”

- 55 yo F is brought to the ED with AMS, and fever, and hypotension requiring vasopressors. CT scan of the head reveals 3 cm pituitary mass with hemorrhage and optic nerve compression.

- What is the next best step in management?
  - A) Neurosurgical consult
  - B) Hydrocortisone 100mg IV q8h
  - C) Levothyroxine 100mcg IV
  - D) test pituitary hormone function prior to initiation of therapy

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Pituitary apoplexy

- Sudden hemorrhage into the pituitary gland (pituitary adenoma)
- Headache, visual impairment, neurologic
- Dx with CT/MRI
- Can cause:
  - Mass effect on optic chiasm with acute visual loss → surgical emergency
  - Pituitary hormone deficiency (any)
  - Central adrenal insufficiency can be life-threatening (50-80%)
- Treatment:
  - Empiric corticosteroid replacement
  - Surgical decompression (some patients can be managed conservatively in absence of visual loss)

Adrenal crisis in apoplexy

- Hypotension, altered mental status, fever, hyponatremia is concerning for adrenal crisis
- Hyperkalemia may not be present in secondary AI; RAAS system is intact and thus adrenal gland can still produce mineralocorticoid (aldosterone)
- Start empiric steroids before testing has resulted (but draw cortisol level prior if possible)!
- ACTH stim test will NOT be accurate in the setting of acute pituitary dysfunction!
- Hydrocortisone 100 mg IV q8h

Case 4 – “Consult for medical management”

- You are asked to admit 70 yo M who is admitted to undergo resection of a 2.5 cm pituitary adenoma in the afternoon. You are consulted for “medical management”. You note the following preoperative pituitary labs:
  - ACTH 30, AM cortisol 15 (normal)
  - 1mg dexamethasone suppression test < 1 (normal)
  - TSH 3.0, free T4 1.3 (normal)
  - FSH/LH normal, testosterone 190 (300-1000)
  - IGF-1 130 (normal)
  - Prolactin – specimen hemolyzed, no result

  - What is the next best step in management?
  - A) proceed to surgery
  - B) check prolactin level prior to proceeding to surgery
  - C) start on testosterone replacement
  - D) transfer to a medical center with inpatient endocrinology services

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Prolactinoma

- Prolactin secreting tumor of the anterior pituitary gland
- They can be large and press on optic chiasm
- Treatment is primarily medical therapy; they typically respond very well to dopamine agonist therapy (bromocriptine/cabergoline)
- Prolactin production is proportional to size
- Beware of the assay "hook effect" – very high levels of prolactin will interfere with the capture antibody and produce a falsely LOW number.
- Can check diluted prolactin level

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Case 5 – “I have a hyponatremia admit for you.”

- 68 yo F with hx of metastatic NSCLC comes to the ED complaining of profound fatigue, lightheadedness, headache, and nausea. She mentions that she is on “chemo”. Review of the oncology note shows that she is on immune checkpoint inhibitor therapy (ipilimumab+nivolumab). BP 100/60, p 80, Na 124, glucose 101, Cr 0.80, TSH 1.5. CT scan of the head shows an enlarged pituitary gland and no optic nerve compression.

- What is the next best step in management?
  - A) oral hydration, increase salt intake
  - B) fluid restriction
  - C) check pituitary hormones
  - D) start empiric hydrocortisone and levothyroxine

Case 5

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Immune checkpoint inhibitors and hypophysitis

- Class of immune therapy used increasingly more for treatment of several types of cancer (lung, melanoma, urothelial, etc etc)
- Endocrine and non-endocrine side effects
- Hypophysitis, thyroiditis, autoimmune DMt1, adrenalitis
- In hypophysitis, can affect any pituitary axis:
    - Central AI
    - Central hypothyroidism
    - Central hypogonadism
    - Central GH deficiency
    - Diabetes insipidus (rare)

- Treatment: hormone replacement of affected axis, consider high dose steroids
- Find an endocrinologist

Labs

- ACTH <5
- AM cortisol 1.1
- TSH 1.5
- Free T4 0.3
- FSH 3
- LH 2
- Estradiol 5
- IGF1 133
- Prolactin 12

- Panhypopituitarism = 3 or more pituitary hormone deficiencies

- What order would you replace hormones, and why?

*REPLACING THYROID HORMONE PRIOR TO REPLACING GLUCOCORTICOIDS CAN PRECIPITATE ADRENAL CRISIS

Case 6 – “Can I run a case by you?”

- 19 yo M with hx of craniopharyngioma s/p resection and XRT is admitted from a long-term care facility with polydipsia and polyuria. He is drinking constantly and urinating throughout the day and night. They are concerned he may have diabetes. Meds: hydrocortisone 10mg BID, levothyroxine 150mcg daily. Labs: Na 145, K 4.0, glucose 96, UA spec grav <1.005, urine sodium 35, urine osm 120, serum osm 301.

- What is the most likely diagnosis?
  - A) euglycemic DKA
  - B) diabetes insipidus
  - C) primary polydipsia
  - D) cerebral salt wasting

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Central Diabetes Insipidus

- Lack of ADH = hypotonic polydipsia
- Associated with pituitary surgery/XRT, pituitary mets, autoimmune hypophysitis, granulomatous disease (sarcoid), idiopathic, very rarely adenomas
- Ddx of polyuria:
  - Osmotic diuresis
  - Polydipsia/IVF
  - Central DI (complete or partial)
  - Nephrogenic DI
- When to suspect DI:
  - LOTS of dilute urine, day and night (polyuria is defined as > 3L of UOP/day)
  - Sodium > 140
  - > 300cc UOP for 3 consecutive hours
  - Urine osm < 200
  - Urine spec grav 1.005
  - Absence of hyperglycemia or other cause of osmotic diuresis

Central diabetes insipidus

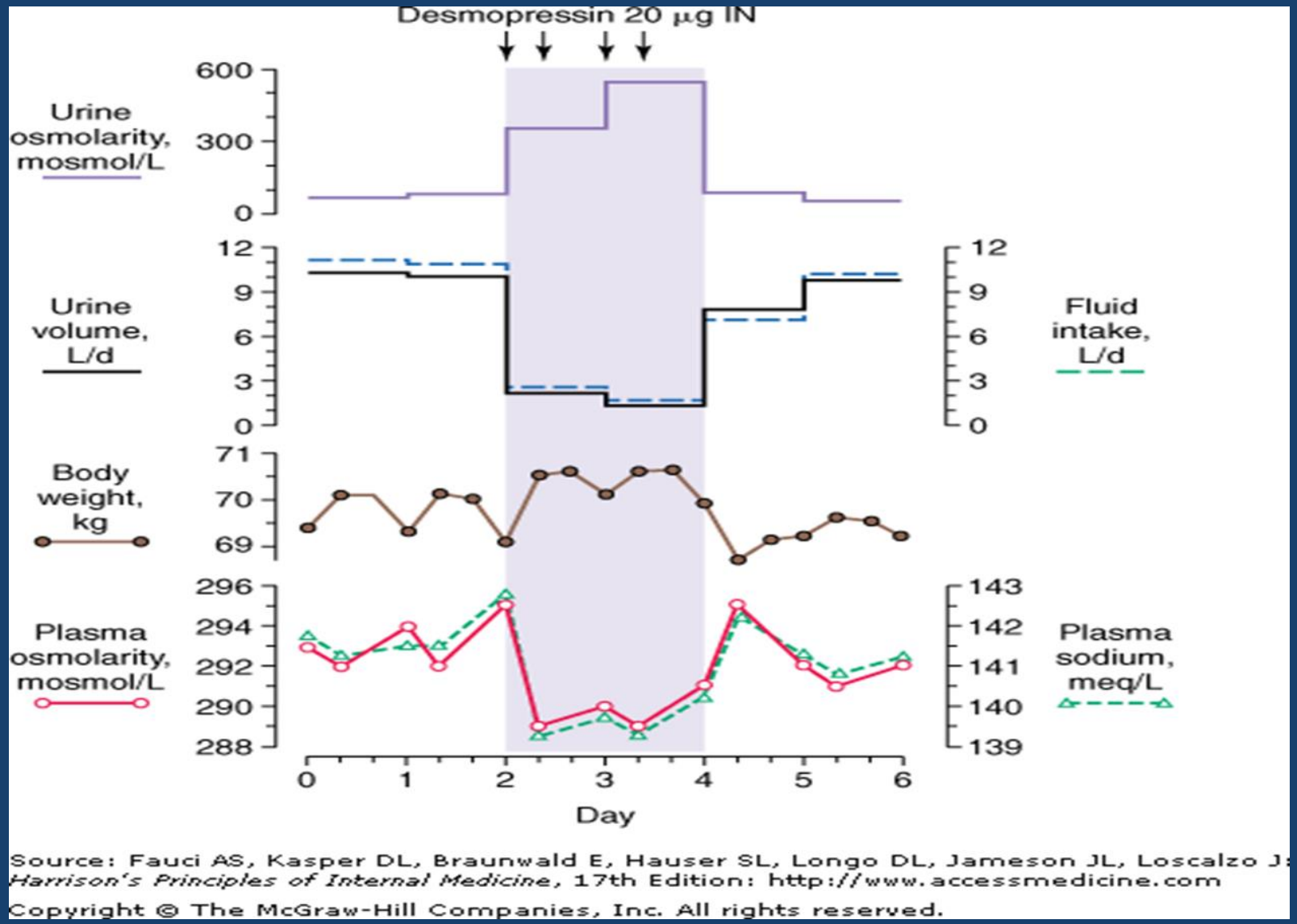
- Diagnosis: water deprivation test

Table 4-1. Interpretation of the Water Deprivation Test*

	Increase in Urine Osmolality above 280 mOsm/kg with Dehydration	Further Response to ADH
Normal subjects	Yes	No
Diabetes insipidus	No	Yes
Partial diabetes insipidus	Yes	Yes
Nephrogenic diabetes insipidus	No	No

- Treatment: replacement ADH (desmopressin) IV/IM, nasal, oral
- If thirst mechanism is intact, let them drink to thirst (and discuss with RN!)
- find an endocrinologist

Central diabetes insipidus



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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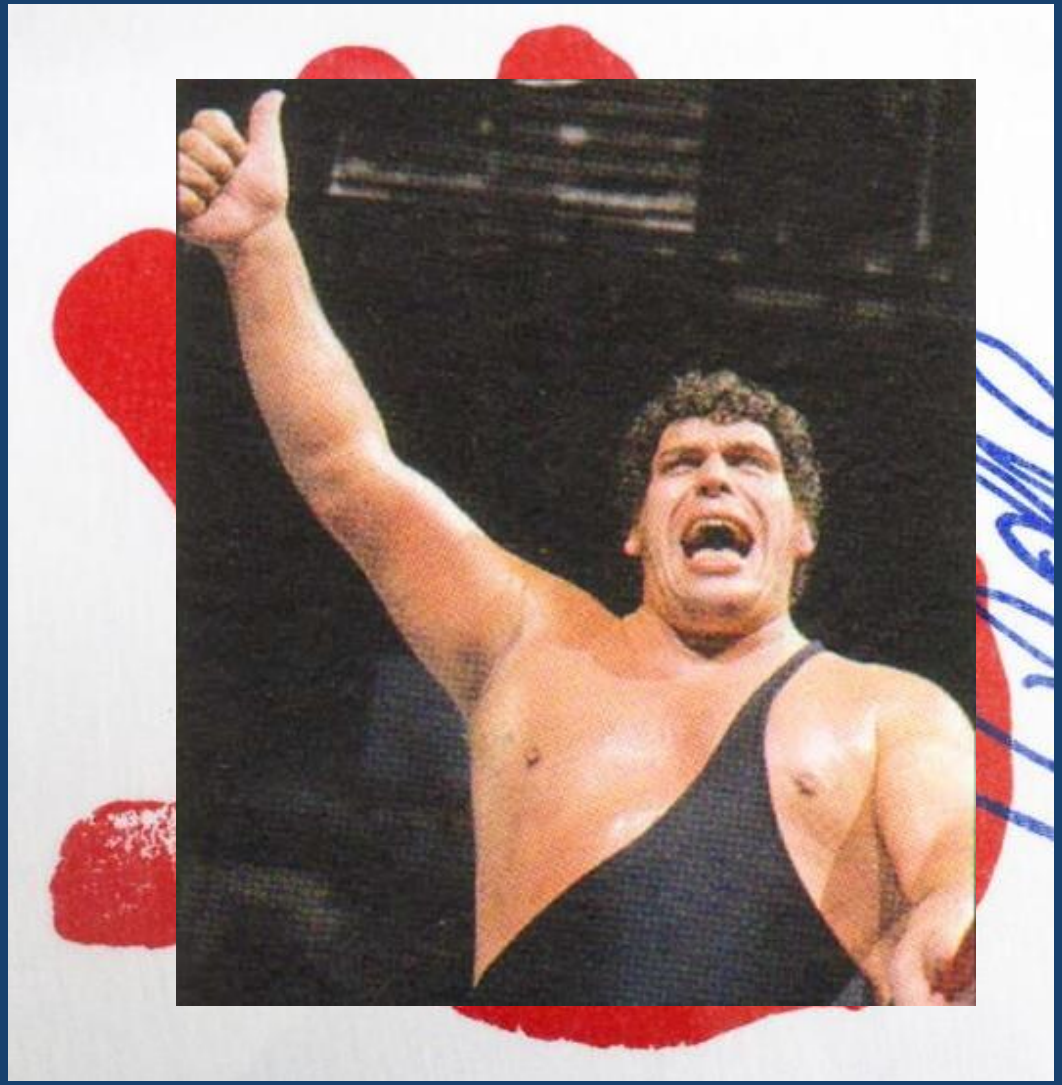

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End

- Questions?