

# Morning Report

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  - Clinical focus: Primary Care & Endocrinology
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- I have no disclosures to report.

# Objectives

- Use case vignettes to highlight challenges in:
  - Management of diabetes
  - Evaluation of:
    - Fever of unknown origin
    - Hypogonadism

# Image of the Day

- 25 year old gentleman comes to see you for better control of his diabetes.
- His past medical history is notable for type 2 diabetes first diagnosed 6 years ago and hypertension diagnosed 3 years ago.
- Initially, he was placed on metformin but due to gradually poorer control of his diabetes, he was started on insulin.

# Image of the Day

- Current regimen:
  - Metformin 1000 mg bid
  - Insulin glargine 20 U qhs
- Very motivated, carefully follows an ADA diet and exercises on a regular basis.
- Frustrated that his lifestyle changes are not making a difference in his diabetes control. His blood sugars are in the 200s again.

What would you do next?







# Signs and Symptoms of Acromegaly

- Enlarged jaw
- Enlarged, swollen hands and feet
- Coarse facial features
- Nose enlargement
- Spreading of teeth
- Joint pains
- Skin tags
- Macroglossia
- Voice deepening
- Diabetes
- Hypertension
- LVH
- Organomegaly
- Colonic polyps and colon cancer
- Sleep apnea

# Diagnosis of Acromegaly

- Insulin growth factor -1 (IGF-1)
- If IGF-1 elevated
  - OGTT with growth hormone levels
  - Suppression of GH to  $< 1\text{ng/mL}$  in normals

# Patient Course

- IGF-1 and Growth Hormone levels were elevated
- Imaging confirmed a pituitary tumor
- Transphenoidal surgery with cure

# Secondary Causes of Hyperglycemia

- Acromegaly
- Cushing's Syndrome
- Pheochromocytoma
- Adrenal Insufficiency
- Hyperthyroidism
- Glucagonoma
- Somatostatin-secreting tumors
- Pancreatic disease
- Medications (i.e. glucocorticoids, atypical antipsychotics, HIV protease inhibitors)

# Case

59 year old man with an extensive cardiac history including CAD and VT, who presented with epistaxis.

He had been quite ill over the last 4 weeks.

## 4 weeks previously

- The patient was hospitalized for AICD interrogation due to multiple discharges.
- During his 10-day hospital stay both a fractured lead and malfunctioning epicardial patch were replaced via thoracotomy.

## 4 weeks previously

- Post-operative fevers were treated with 5 days of vancomycin, cefazolin and levofloxacin. All cultures were negative, and antibiotics were discontinued.
- The patient was still having low grade temperatures when he was discharged.



# Presentation

- In the post-discharge period, the patient experienced malaise, fatigue, anorexia with an 8 lb weight loss, and diarrhea.
- He reported no tactile fevers.
- One day prior to admission, he developed a right-sided headache, without visual changes, nuchal rigidity, altered speech or local weakness.

# Day of admission

- On the day of admission, the patient developed new epistaxis that did not resolve with local compression. He also noticed blood in the sclera of his right eye.
- On route to the ED, family members noted left leg and right arm shaking associated with mild confusion but no loss of consciousness.

# Additional ROS

- No bladder or bowel incontinence.
- No chest pain, orthopnea or palpitations.
- No head trauma.

# Past Medical History

- DM2
- CAD (s/p MI and CABG in 1996)
- ICM (EF=40%)
- VT (s/p AICD placement in 1999, revised 4 weeks previously)
- Diverticulitis
- CVA in 1997
- Hypertension
- Hypercholesterolemia
- Obesity

# Medications

- Lisinopril 40 mg po qd
- Atenolol 50 mg po qd
- Amiodarone 200 mg po qd
- Warfarin 5mg po qd
- Aspirin 325 po qd
- Ranitidine 150 mg po bid

**Allergies:** NKDA

**Soc Hx:** Lived in the North End with a male partner. No known TB risk factors. No tobacco, intravenous drugs, or significant alcohol use.

**Fam Hx:** Father- lung cancer, Mother - stroke

# Physical Exam

T-101.4°F    P-80    BP-146/60    RR-20

O<sub>2</sub> sats - 96% on 2L oxygen by NC

**General:** Awake, diaphoretic, soaked through his clothes, confused but followed simple commands.

**Skin:** Multiple ecchymoses. Mild incisional erythema, but no evidence of external chest wound breakdown or drainage. Poor skin turgor.

# Physical Exam (cont'd)

- **HEENT**: Right conjunctival hemorrhage. EOMI.
- **Neck**: supple. JVP flat.
- **Lungs**: Bibasilar crackles.
- **CV**: RRR. 2/6 SEM. No peripheral edema.
- **Neuro**: Tremulous. Reflexes 3-4+.



# Labs

9.5 10.5 243  
31.2

139	107	55	132
4.4	27	1.1	

MCV- 87

PTT- 55.6

INR – 12.7

Ca-9.5

Mg-1.6

PO<sub>4</sub>-4.4

TP-5.9

Alb-4.7

CKMB (-)

# Studies

**CXR** - Cardiomegaly, no infiltrates, AICD in place

**ECG** - Old anterior-septal MI. No change from previous study

**Head CT** - Subdural hematomas affecting bilateral frontal areas; right internal capsule CVA (likely old)

# Hospital Course

- FFP and vitamin K therapy were initiated.
- Persistent fevers developed with Temps 101-102°F. Blood, sputum and stool samples were obtained for microbiologic study. Pan CT scans showed no source of infection.
- ID and Neurology consultations were obtained.
- Phenytoin was initiated for question of seizure-like activity.

# Hospital Course (cont'd)

- The patient remained febrile.
- Blood cultures, lumbar puncture, echocardiography and serologies for HIV and syphilis failed to explain the fevers.
- By hospital day 5, severe hyponatremia developed (Na 123) with worsening mental status.
- Temp was 104.5. RR 40

What would you do next?

**TABLE 1**  
**Classification of Fever of Unknown Origin (FUO)**

<i>Category of FUO</i>	<i>Definition</i>	<i>Common etiologies</i>
Classic	Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital	Infection, malignancy, collagen vascular disease
Nosocomial	Temperature >38.3°C Patient hospitalized ≥24 hours but no fever or incubating on admission Evaluation of at least 3 days	<i>Clostridium difficile</i> enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
Immune deficient (neutropenic)	Temperature >38.3°C Neutrophil count ≤500 per mm <sup>3</sup> Evaluation of at least 3 days	Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus
HIV-associated	Temperature >38.3°C Duration of >4 weeks for outpatients, >3 days for inpatients HIV infection confirmed	Cytomegalovirus, <i>Mycobacterium avium-intracellulare</i> complex, <i>Pneumocystis carinii</i> pneumonia, drug-induced, Kaposi's sarcoma, lymphoma

*HIV = human immunodeficiency virus.*

*Adapted with permission from Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. Curr Clin Top Infect Dis 1991;11:37.*

TABLE 2

**Common Etiologies of Fever of Unknown Origin****Infections**

Tuberculosis (especially  
extrapulmonary)

Abdominal abscesses

Pelvic abscesses

Dental abscesses

Endocarditis

Osteomyelitis

Sinusitis

Cytomegalovirus

Epstein-Barr virus

Human immunodeficiency virus

Lyme disease

Prostatitis

Sinusitis

**Malignancies**

Chronic leukemia

Lymphoma

Metastatic cancers

Renal cell carcinoma

Colon carcinoma

Hepatoma

Myelodysplastic syndromes

Pancreatic carcinoma

Sarcomas

**Autoimmune conditions**

Adult Still's disease

Polymyalgia rheumatica

Temporal arteritis

Rheumatoid arthritis

Rheumatoid fever

Inflammatory bowel disease

Reiter's syndrome

Systemic lupus erythematosus

Vasculitides

**Miscellaneous**

Drug-induced fever

Complications from cirrhosis

Factitious fever

Hepatitis (alcoholic,  
granulomatous, or lupoid)

Deep venous thrombosis

Sarcoidosis

# Rare Miscellaneous Causes

- Atrial myxoma
- Familial Mediterranean Fever
- Histiocytosis
- Pheochromocytoma
- Whipple's disease
- Thyroiditis and Thyrotoxicosis



# Hospital Course

- TFTs ordered:
  - TSH <0.01 (0.5 -5 uU/mL)
  - T4 18.5 (4.5-10.9 ug/dL)
  - THBI 2.51 (0.77-1.23)
  - FT4I 46.4 (4.5-10.9)
  - T3 343 (60-181 ng/dL)
- Concern was for amiodarone induced hyperthyroidism

# Treatment

- Methimazole 30 mg per rectum q6 hrs was initiated, but later changed to propylthiouracil (PTU) 400 mg pngt q 6 hrs.
- Methylprednisolone 60 mg iv q12 hrs
- Iopanoic acid 1 gm qd

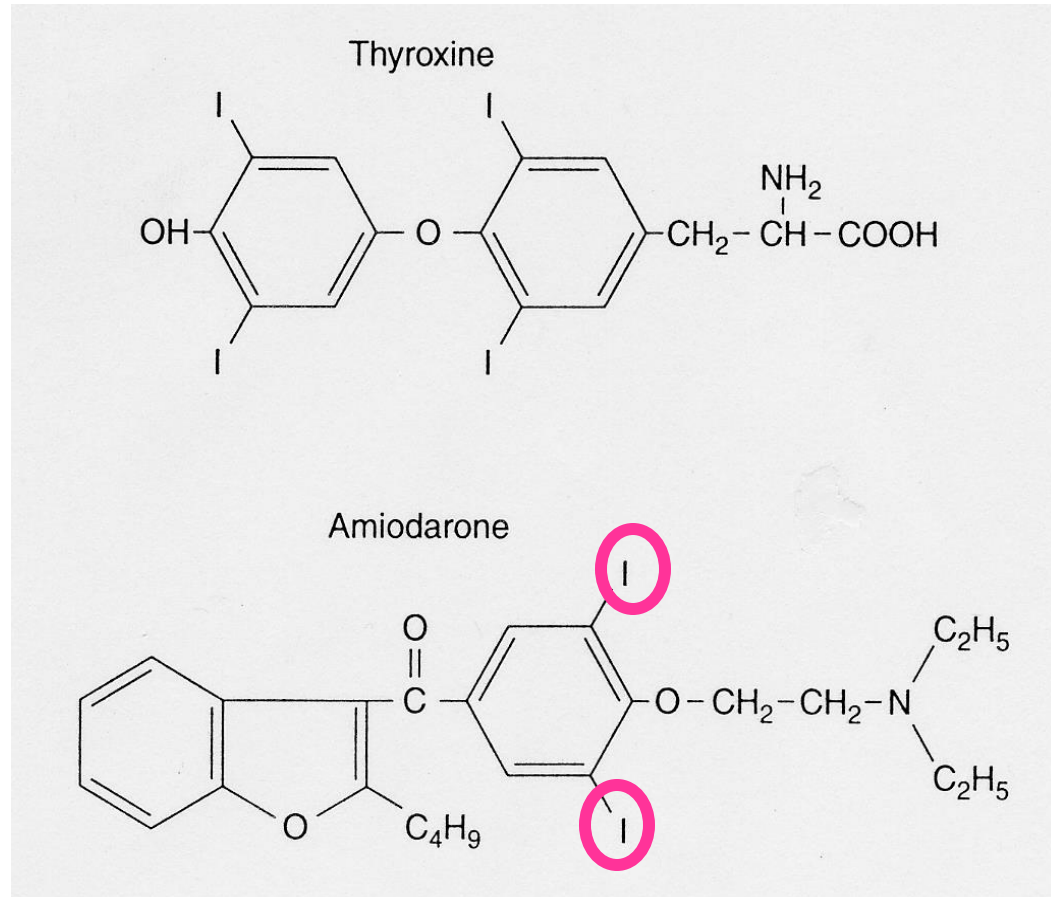
# Treatment

- Pulmonary aspiration was felt to have occurred in the setting of delirium and agitation.
- Despite anti-thyroid therapy, the patient developed hyperpyrexia ( $T=107^{\circ}\text{F}$ ) and increased clonus.
- A diagnosis of Thyroid Storm was made, and the patient underwent thyroidectomy.

# Follow-up

- The patient's temp dropped quickly after the thyroidectomy.
- The patient was discharged after a 3 week hospital course.
- At follow-up, he had returned to his previous level of function.

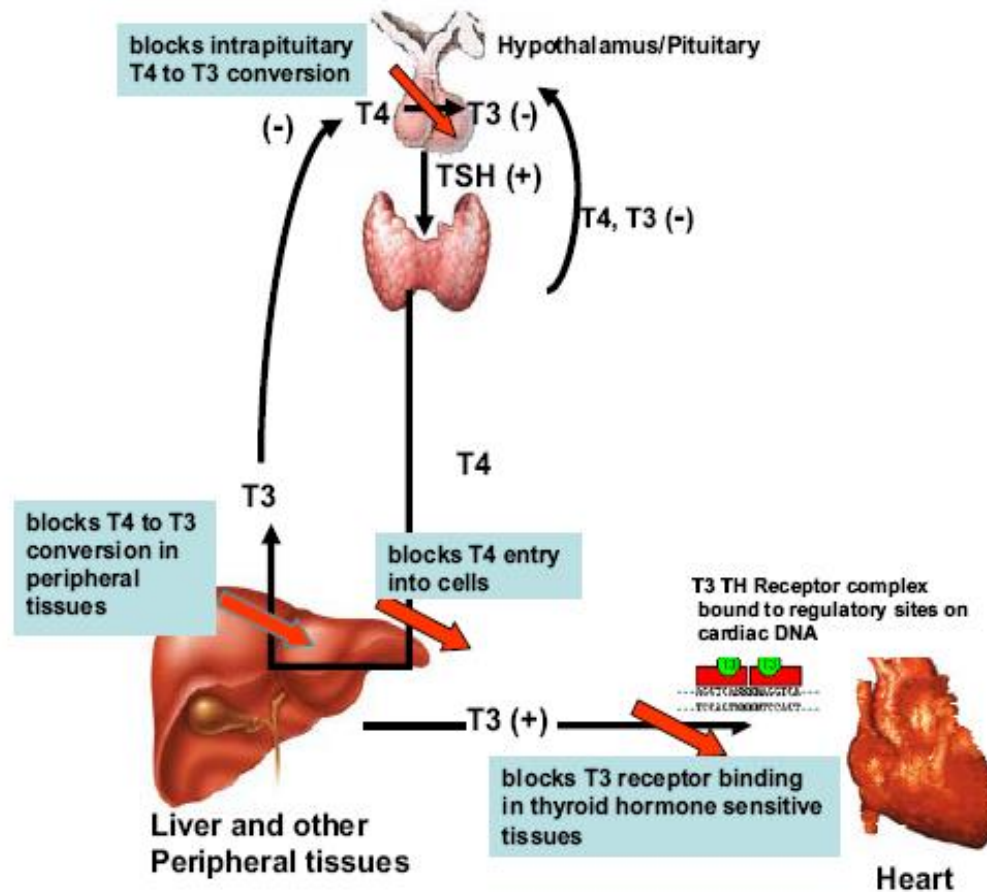
# Thyroxine and Amiodarone



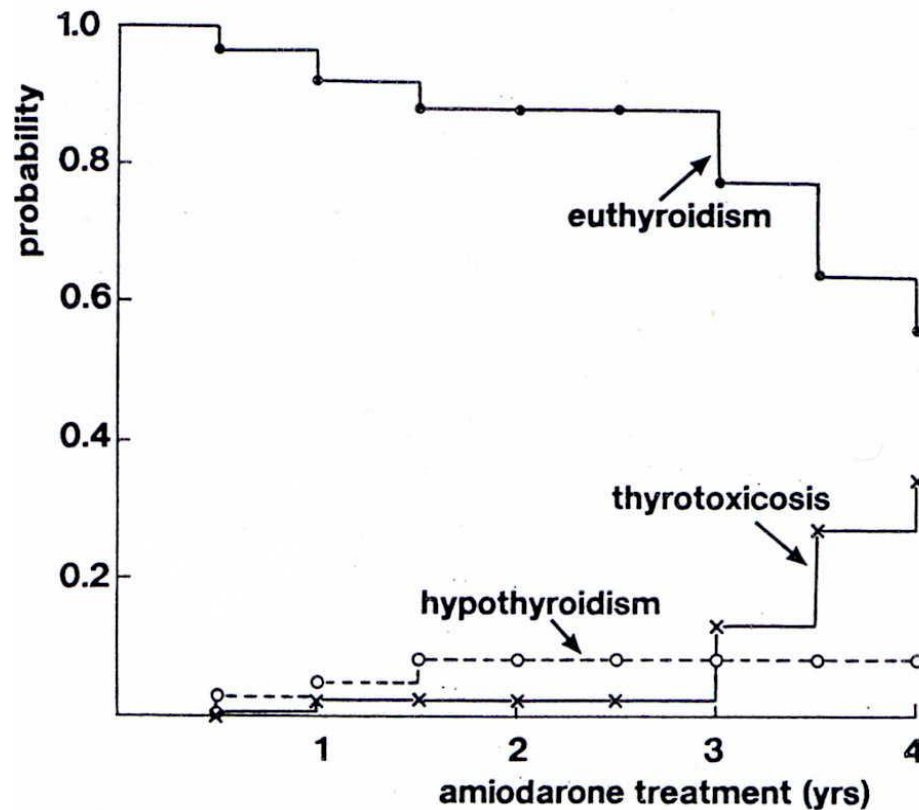
# Amiodarone

- 75 mg of iodine per 200 mg tablet
- 10% of iodine released as free iodide daily
- Average daily iodine intake in US is 0.15-0.30 mg.
- $\frac{1}{2}$  life is 100 days

# Amiodarone and Thyroid Function



# Probability of Thyroid Disease with Amiodarone Treatment





# Amiodarone and Hyperthyroidism

	Type I AIT		Type II AIT Destructive thyroiditis
	Toxic nodular goiter	Graves' disease	
Baseline thyroid condition	Nodular thyroid	"Latent" Graves'	Normal thyroid
Thyroid exam	Nodular thyroid	Normal size or diffuse goiter. Bruit may be present.	Normal size or diffuse goiter
Ultrasound	One or more nodules	Diffuse goiter	Heterogeneous pattern
CFDS	Normal or increased flow	Normal or increased flow	Decreased flow
Thyroid autoantibodies	Absent	Present	Generally absent
IL-6	Normal or high	Normal or high	Very high
24-h radioiodine uptake	Low, normal, or high <sup>a</sup>	Low, normal, or high <sup>a</sup>	Very low
Therapy	Methimazole or Propylthiouracil	Methimazole or Propylthiouracil	Prednisone
	Perchlorate may be necessary	Perchlorate may be necessary	Rarely surgery
	? <sup>131</sup> I	? <sup>131</sup> I	
	Surgery	Surgery	

<sup>a</sup> Based on European experience (see text).

# Severe Hyperthyroidism - Treatment

- **Thyroid gland**
  - Inhibit synthesis – PTU, Methimazole
  - Inhibit TH release – Iodine, Lithium
  - Surgery
- **Peripheral Effects of TH**
  - Inhibit T4 to T3 conversion – PTU, steroids, iopanoic acid, propranolol
  - Removal of excess thyroid hormone – plasmapheresis
- **Systemic Decompensation**
  - Treat hyperthermia – Tylenol, cooling
  - Correct dehydration and nutritional deficits – fluids, electrolytes
  - Supportive therapy – pressors, treat CHF, steroids

# Anticoagulation and Hyperthyroidism

- Hyperthyroidism increases metabolism of vitamin K-dependent clotting factors
- Altered protein binding of warfarin
- Enhanced affinity of warfarin for its receptors

# Lab of the Day

- 36 year old woman with diabetes, liver disease, and HIV comes to see you in follow-up.
- She says that her blood glucose has been very elevated – consistently in the 250s.
- She believes this is due to poor diet.
- You counsel her regarding diet and exercise, refer her to a nutritionist, and order a hemoglobin A1c.

# Lab of the Day (cont'd)

- Her HgB A1c returns at 6.8%.
- You are surprised at this hemoglobin A1c. What value did you expect?

<b>Hemoglobin A1c (%)</b>	<b>Average blood glucose (mg/dL)</b>
6	135
7	170
8	205
9	240
10	275

**(Hemoglobin A1c x 33) - 60**

# Lab of the Day (cont'd)

- Why is there a discrepancy?
  - Glucometer
  - Timing of testing
  - Assay
  - Treatment of iron, folate, or vitamin B12 deficiency
  - Hemolysis

# Hemoglobin A1c

- Red blood cells are freely permeable to glucose
- Glucose irreversibly attaches to the hemoglobin
- The hemoglobin A1c represents 3 months of blood sugar readings because of the lifespan of red blood cells
- Increases in red blood cell turnover → falsely low hemoglobin A1c



# Our patient

- Hct 36%
- Iron studies, folate, and B12 all normal and not on recent treatment for deficiencies
- LDH 285 (107-235 U/L)
- Haptoglobin <8 (30-200 mg/dL)
- She has hemolysis – probably from her liver disease.
- How could you check her blood sugar control?

# Fructosamine

- Measure of glycosolated end products
- Her level was 538 (0-285  $\mu\text{mol/L}$ ).

# Case

44 year old private investor presented to his PCP with low libido of one year's duration.

He has been married for seven years. Had his first child one year ago.

The decline in his libido was gradual.

He is healthy and active, loves outdoor activities and building ships.

Increasing fatigue over the past year has limited his time outdoors.

Does not feel depressed. Has no other signs or symptoms of a systemic illness including no fevers, chills, headaches, weight changes, changes in his hair or skin texture, bowel movements.

His only medical problem is mild hand arthritis.

What more would you want to know?

# Low libido

- Psychiatric: *depression, anxiety disorder*
- Medications: *SSRIs, anticonvulsants, antihypertensive medications*
- Systemic illness
- Recreational drugs
- Androgen deficiency
- Thyroid disease
- Hyperprolactinemia
- Erectile dysfunction

Normal pubertal development.

In addition to the low libido, he has noticed decreased morning erections and decreased ejaculatory volume.

No change in frequency of shaving, no breast enlargement, or change in testicular size.

No headaches, vision changes.

No medications.

No tobacco, rare ETOH, no illicit drug use.

Family history unremarkable for thyroid disease, delayed puberty, infertility.



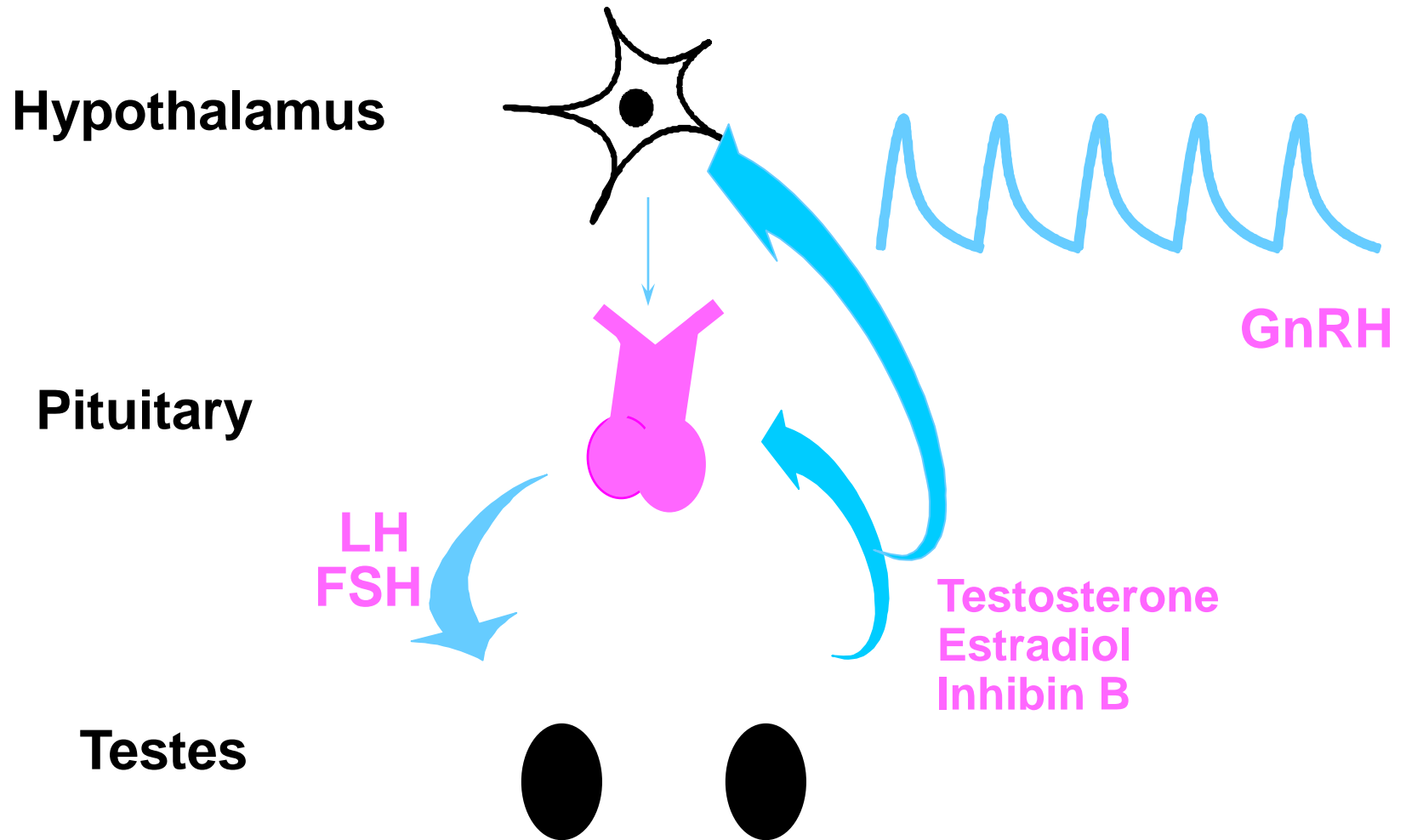
- Ht 6'4", Wt 162 lb, BP 128/82, P 84, RR 10
- Gen: non-eunuchoidal
- HEENT: PERRL, EOMI, Visual fields full
- Thyroid: normal in size and without nodules.
- No gynecomastia
- Lung, cardiovascular, and abdominal exams normal.
- GU: testes 10 cc bilaterally, nl phallus
- Hair: No change in male distribution of body hair
- Neuro: normal muscle bulk and strength.

# Labs

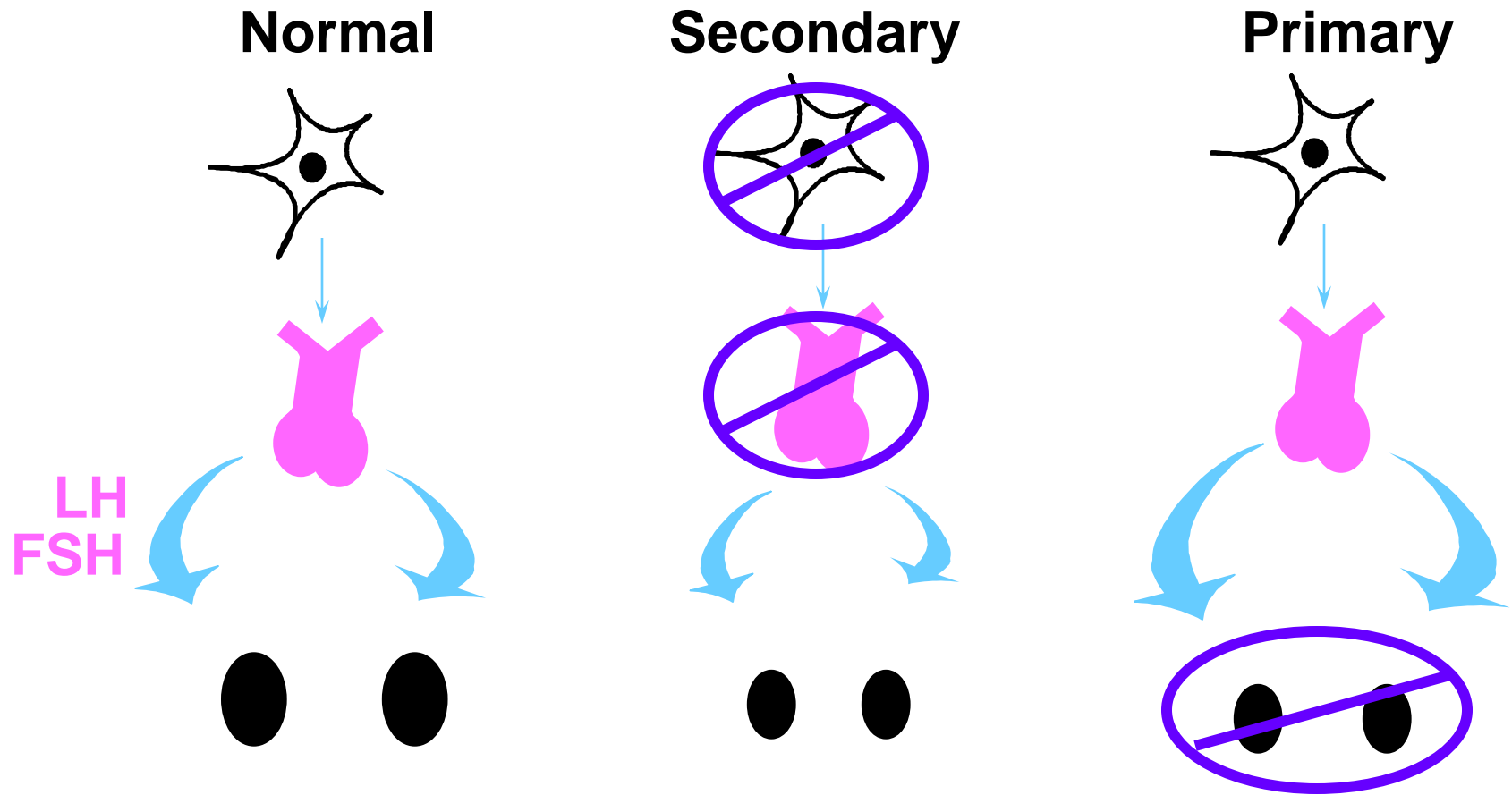
- Testosterone 36 ng/dL (270-1190)
- TSH and prolactin normal

What would you do next?

# Male Hypothalamic-Pituitary-Gonadal Axis



# Male Hypothalamic-Pituitary-Gonadal Axis



# Labs

- Testosterone 40 ng/dL
- LH 1.5 U/L (2.4-5.9)
- FSH 1.3 (0.9-15.0)

What would you do next?

# Further Evaluation

- MRI of the pituitary gland revealed no masses.
- Bone density scan: spine T score -2.5
- Semen analysis – azoospermia
- CBC Hct 36.1%

# Secondary Hypogonadism: Acquired

- Benign tumors & cysts
- Malignant tumors
- Infiltrative diseases
- Infections
- Pituitary apoplexy
- Trauma
- Radiation
- Hyperprolactinemia
- Critical Illness
- Chronic systemic illness
- Glucocorticoids
- Chronic opiate use
- Adult-onset Hypogonadotropic Hypogonadism
- Steroid withdrawal

# Infiltrative Diseases

- ***Hemochromatosis***
- Sarcoidosis
- Eosinophilic granulomatosis
  
- Fe = 219 ug/dL (40-159 ug/dL)
- TIBC = 257 ug/dL (250-450 ug/dL)
- Transferrin saturation =  $\text{Fe/TIBC} = 85.2\%$
- Ferritin = 2435 ug/L (20-400 ug/L)
  
- HFE testing: C282Y homozygote



# Hemochromatosis and hypogonadism

- Secondary
  - Deposition in the pituitary gland
- Primary – much less common
  - Deposition in the testes

# Hemochromatosis and recovery of function

- Little, if any, data
- Most say that if >40 years old, gonadal function does not recover

(Cundy et al., Clin Endo, 1993)

# Summary

- Secondary causes of diabetes
- Acromegaly
- Fever of unknown origin
- Amiodarone and the thyroid
- Extreme hyperthyroidism/thyroid storm
- Potential inaccuracies in hemoglobin A1c
- Hypogonadism
- Hemochromatosis

# References

- Bhasin S et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018; 103: 1715.
- Daniels GH. Amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 2001; 86: 3.
- Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Med Clin North Am 2012; 96: 385.

- I have no disclosures to report.