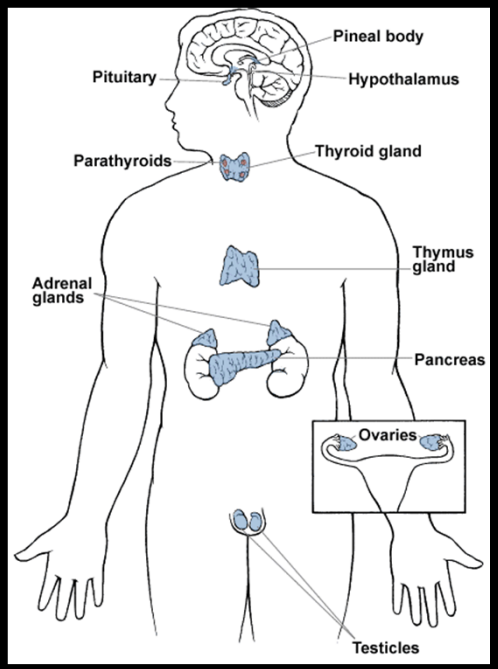
Pathology of the Endocrine System II:

Case Studies to Illustrate Principles of Endocrine Pathology and the Role of the Clinical Laboratory in the Delivery of Care



APPROVED

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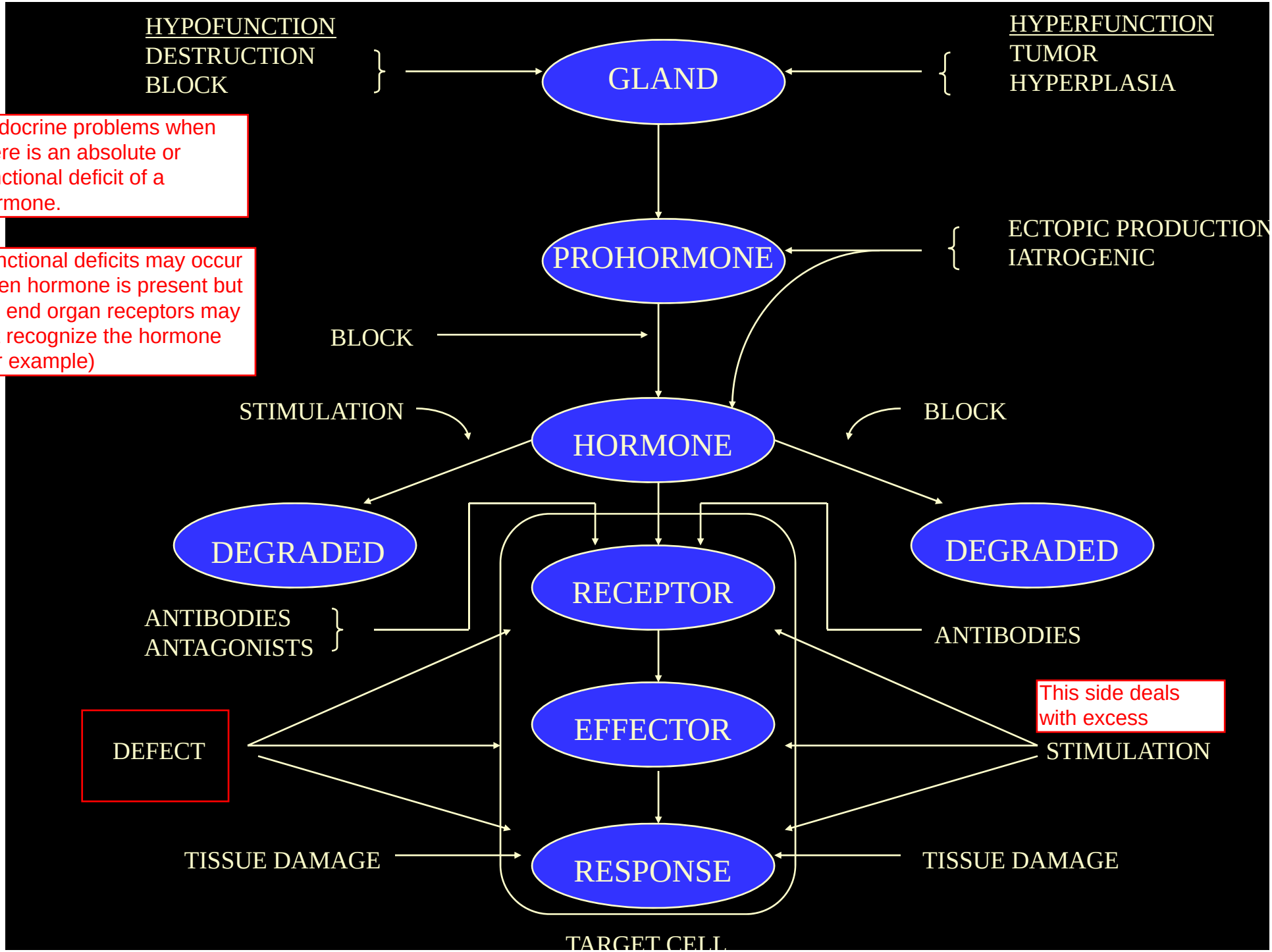
Learning Objectives

- By the conclusion of this session/lecture students will be able to:
  - broadly characterize endocrinopathies as disorders of hypo- or hyperfunction and for each type list several general abnormalities that can contribute to the pathogenesis of endocrine disease;
  - realize how clinical test “numbers” must be interpreted in their proper physiological/clinical context to provide meaningful information to the caregiver; and
  - appreciate the importance of the clinical laboratory in the routine differential diagnosis of endocrine disorders.


HYPOFUNCTION
DESTRUCTION
BLOCK
HYPERFUNCTION
TUMOR
HYPERPLASIA
GLAND
Endocrine problems when there is an absolute or functional deficit of a hormone.
PROHORMONE
ECTOPIC PRODUCTION
IATROGENIC
Functional deficits may occur when hormone is present but the end organ receptors may not recognize the hormone (for example)
BLOCK
STIMULATION
HORMONE
BLOCK
DEGRADED
DEGRADED
RECEPTOR
ANTIBODIES
ANTAGONISTS
ANTIBODIES
This side deals with excess
EFFECTOR
DEFECT
STIMULATION
TISSUE DAMAGE
RESPONSE
TISSUE DAMAGE
TARGET CELL

Case Studies to Illustrate Principles of Endocrine Pathology and Use of the Endocrine Laboratory

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

- Patient's visit to the local ER was prompted by a nasty coffee burn. He was driving his delivery van through a complicated intersection, shifting gears and balancing a cup of very hot coffee, when the spill occurred, The burn extended over his anterior thighs and upper abdomen and quickly blistered.
- The ER physician was more impressed by patient's appearance than by the burns. At age 39 patient's past medical history was largely unremarkable, but he had noticed some changes over the past several years. His weight had increased about 30 pounds, most of it distributed in his trunk and face. He also noted some purple stretch marks on his abdomen, mild but persistent facial acne, and a slightly scaly patchy discoloration of his chest and back. He always looked red-faced, as if he had been out in the sun or wind. His muscle strength had decreased. Loading and unloading his van was more difficult and he even had difficulty getting out of his easy chair, needing to use his hands to pick himself up.

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

- **Physical Examination**

- **Vital Signs:** **Blood Pressure 160/80; pulse 98**
- **Skin:** **Tinea versicolor of the upper chest and second degree burns of the upper abdomen and mid-thighs bilaterally**
  Violaceous pigmented striae of the abdomen
- **HEENT:** **Normal**
- **Chest:** **Normal**
- **Abdomen:** **Protuberant without palpable organomegaly**
- **Extremities:** **Thin compared to body size, no edema**

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Laboratory Studies (Initial)

Test	Patient	Normal
ABC	Normal	Normal
Serum Sodium	140 mEq/L	135-145
Serum Potassium	3.1 mEq/L	3.5-5.0
Glucose (random)	162 mg/dL	70-99 mg/dL, fasting
Creatinine	0.9 mg/dL	0.3-1.5 mg/dL
BUN	10 mg/dL	8-22 mg/dL

No hematological abnormalities

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

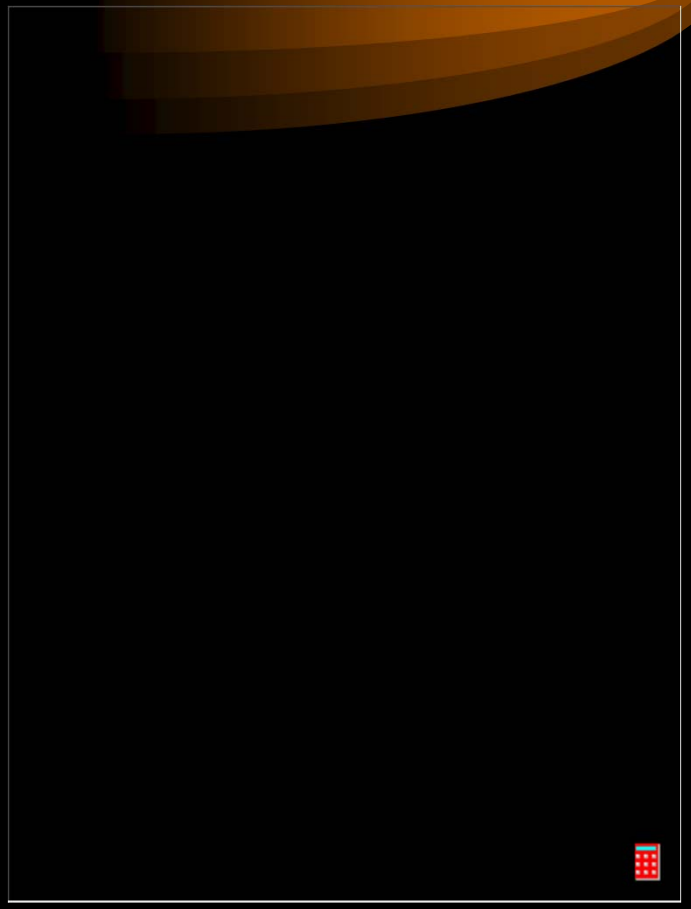
Laboratory Studies (Initial)

Test	Patient	Normal
Glucose (random)	162 mg/dL	70-99 mg/dL, fasting 70-140 mg/dL, non-fasting

162 is elevated even in the non-fasting reference range. (It should be noted that the blood glucose in the ER is NOT a fasting glucose since the patient came in unexpectedly and did not fast)

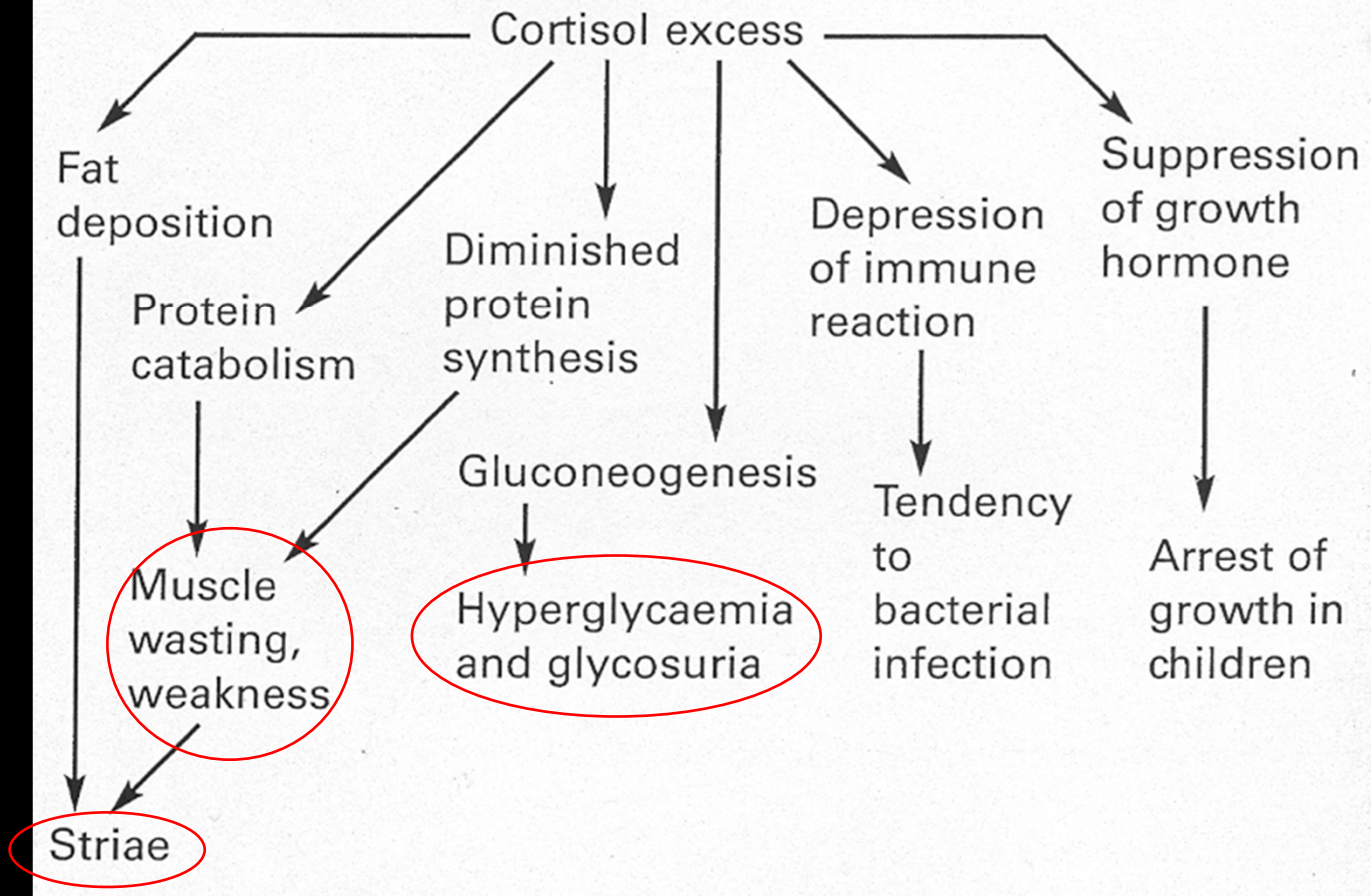
Which of the following hormones can exert well- documented effects on blood pressure, serum potassium concentration, and carbohydrate, fat and protein metabolism?

A. Cortisol
B. Prolactin
C. Parathyroid Hormone
D. Secretin



Symptoms in this case are marked

Clinical effects



In addition:
1. Osteoporosis → kyphosis
2. Hypertension
3. Degree of virilism common in women.

Clinical Features of Cushing's Syndrome

The red highlighted symptoms of Cushing's are the ones that were present in the case on previous slides

- Centripetal obesity
- Hypertension
- Facial fullness
- Hirsuitism
- Menstrual disorders
- Muscle weakness
- Back pain
- Striae
- Acne
- Emotional lability
- Bruising
- Edema
- Diabetes mellitus
- Hypercalciuria
- Hypokalemia

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Follow-up studies for previous case

Laboratory Studies (Follow-up)

Test	Patient	Normal
Glucose (fasting)	143 mg/dL	70-100 mg/dL, fasting
Cortisol (10 a.m.)	29 μg/dL	8 a.m.: 5-25 μg/dL 4 p.m.: 3-12 μg/Dl

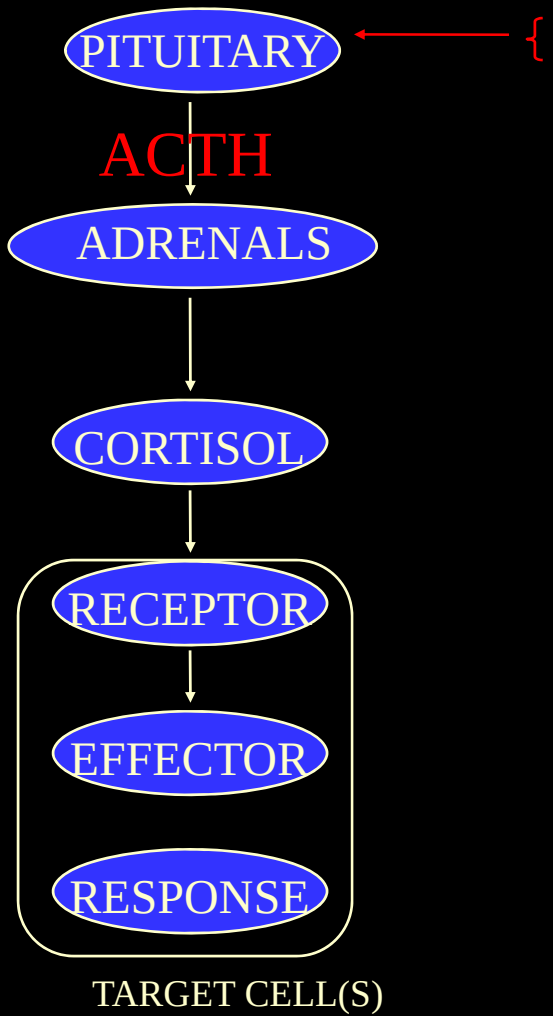
Why would we have two times listed for Cortisol?

Answer: Cortisol secretion is based on a circadian rhythm. In the morning, cortisol secretion is at its peak.

Cushing's disease vs Cushing's syndrome - same presentation but different pathology - more to come.

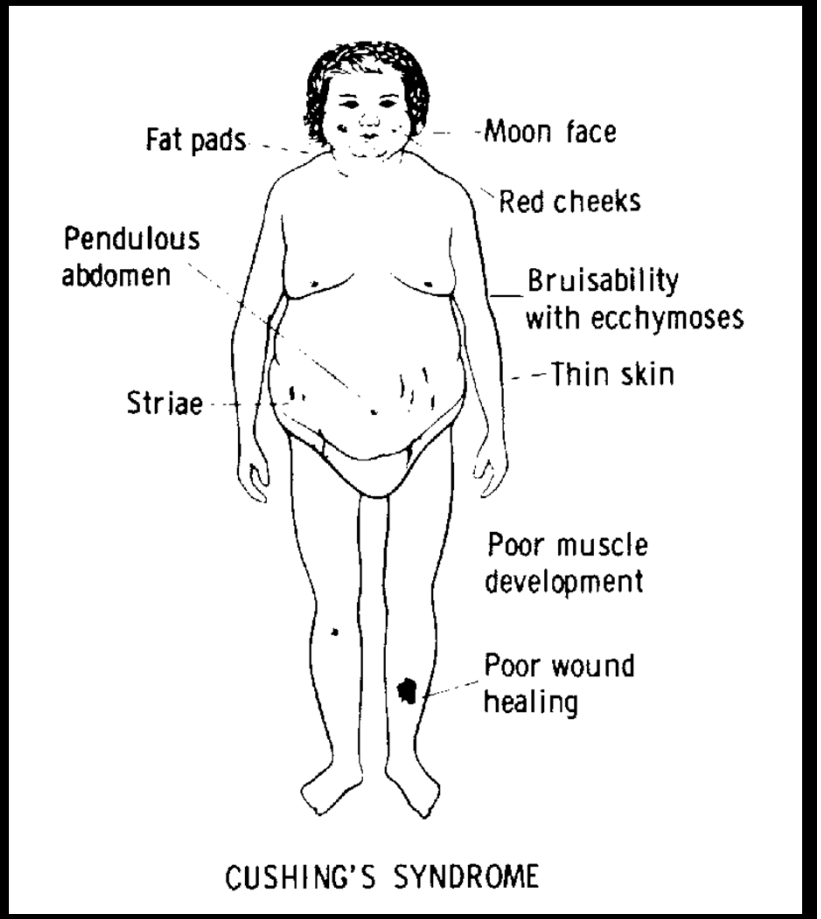
Pathogenetic Mechanism of Cushing's Disease

Pituitary abnormality



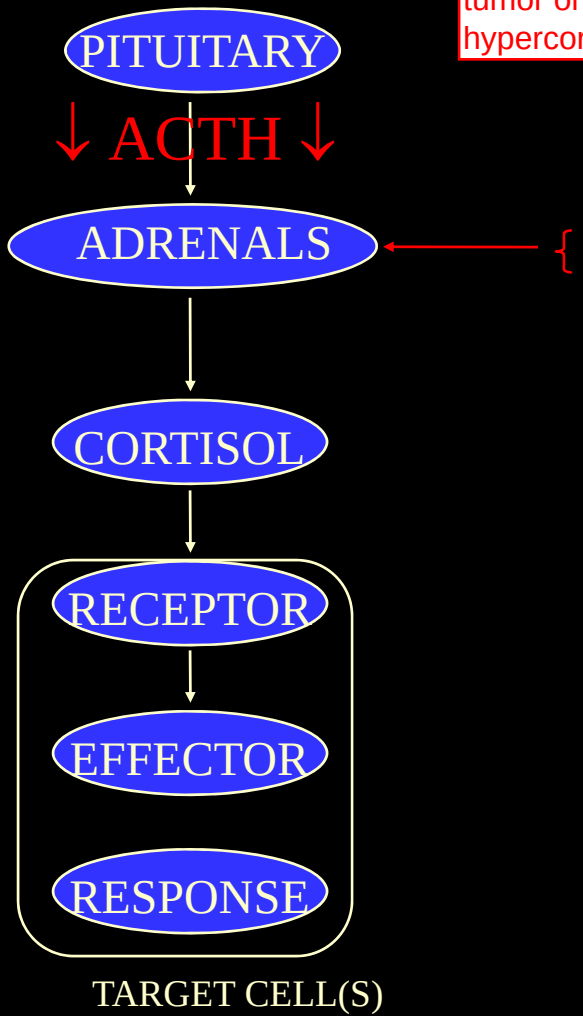
HYPERFUNCTION TUMOR

also due to hypertrophy of pituitary

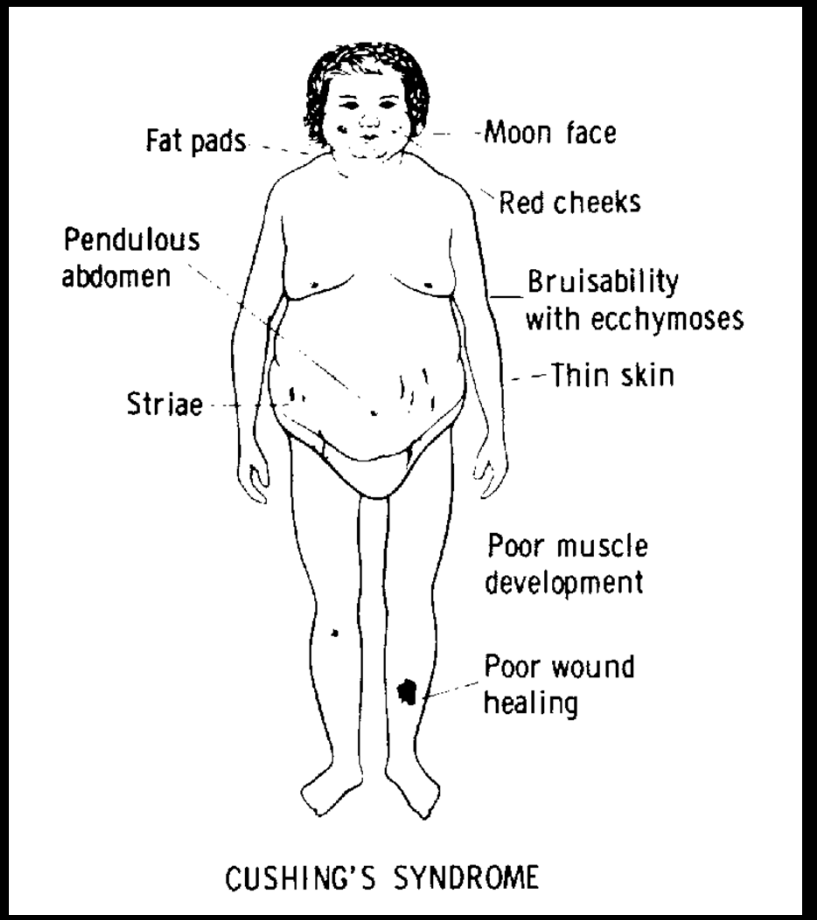


Pathogenetic Mechanism #1 of Cushing's Syndrome

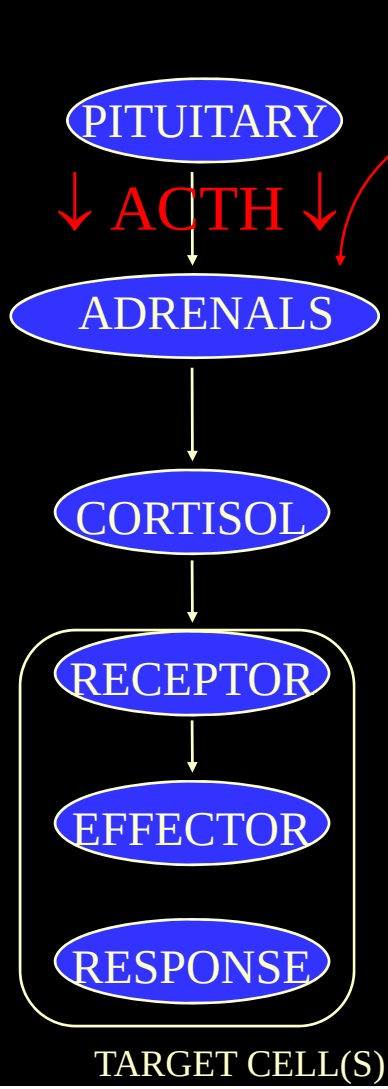
Mechanism #1 - With a normal pituitary - abnormal adrenal tumor or hypertrophy can cause hypercortisolism



HYPERFUNCTION TUMOR



Pathogenetic Mechanism #2 of Cushing's Syndrome



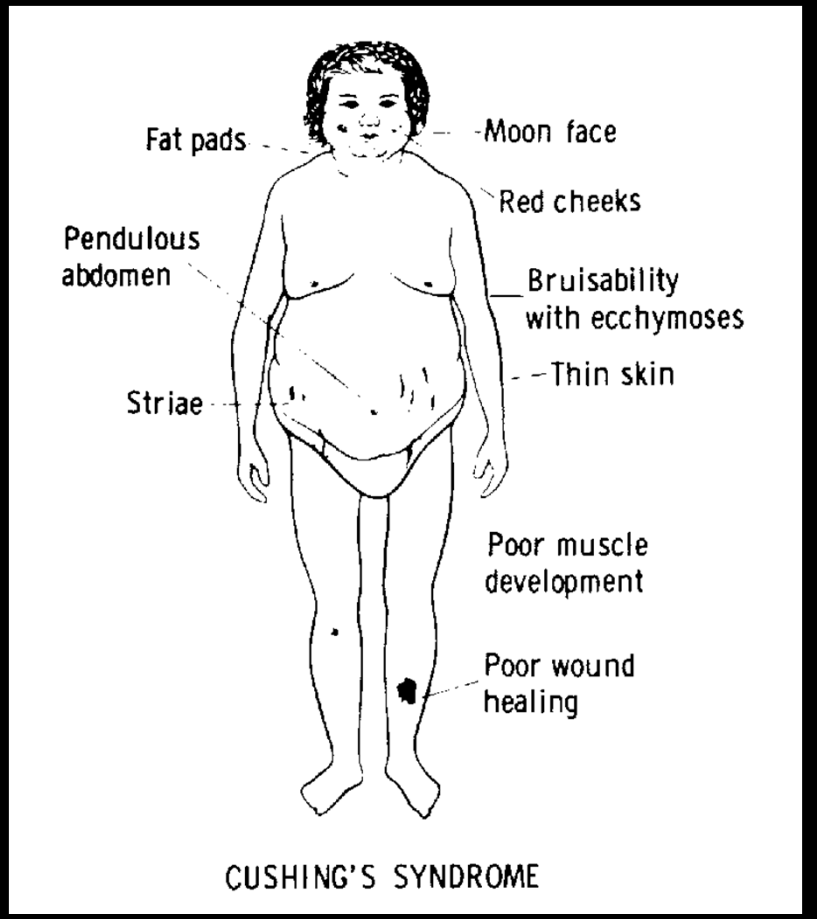
{ HYPERFUNCTION
ECTOPIC PRODUCTION

ACTH

Mechanism #2 - ectopic production of ACTH contribute to ACTH from pituitary causing hypercortisolism

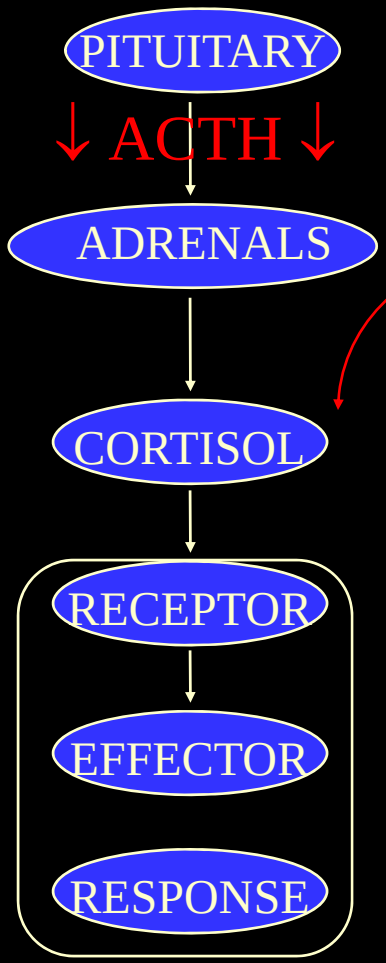
Lung tumors are one such tumor that commonly secretes ACTH as a paraneoplastic process.

While endogenous ACTH may decrease by negative feedback, ACTH from tumor is unregulated and ACTH levels will be above normal.



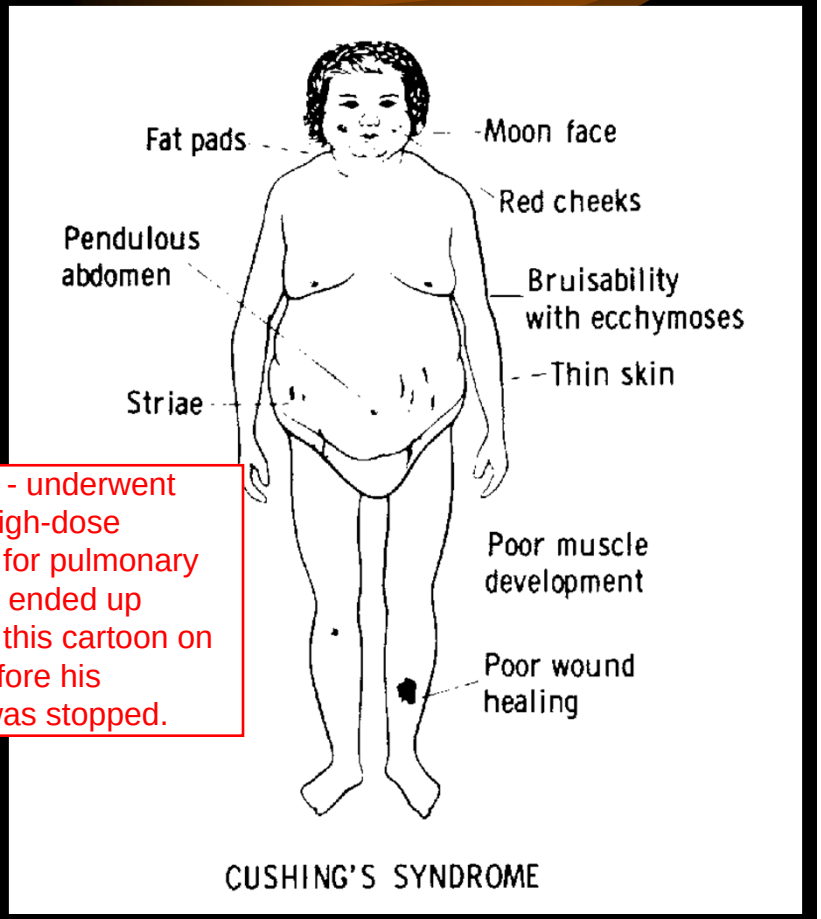
Pathogenetic Mechanism #3 of Cushing's Syndrome

Mechanism #3 - Cortisol or cortisol mimics (steroids) are taken either illicitly or by prescription - causes same syndrome. We would expect decreased ACTH levels from the pituitary.



HYPERFUNCTION
IATROGENIC

Jerry Lewis - underwent long-term high-dose prednisone for pulmonary fibrosis and ended up looking like this cartoon on the right before his treatment was stopped.



Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Laboratory Studies (Follow-up)

Test	Patient	Normal
Cortisol (8 a.m.)	39 μg/dL	8 a.m.: 5-25 μg/dL 4 p.m.: 3-12 μg/dL
ACTH (8 a.m.)	62 pg/mL	8 a.m.: <80 pg/mL
Cortisol, timed urine	425 μg/d	20-70 μg/d

High side of normal

Why are we interested in urine cortisol vs. serum?

Timed urine cortisol allows 24-period surveillance and avoids seeing anomalies in instantaneous cortisol levels due to pulsatile secretion.

Though this normal level may not immediately indicate Cushing's disease vs. Cushing's syndrome - cannot rule out this possibility - there is no black & white in laboratory science

Which of the following is always true about a diagnostic test's reference range?

A. Distinguishes between apparently healthy and diseased individuals

B. Follows a normal (bell-shaped) distribution

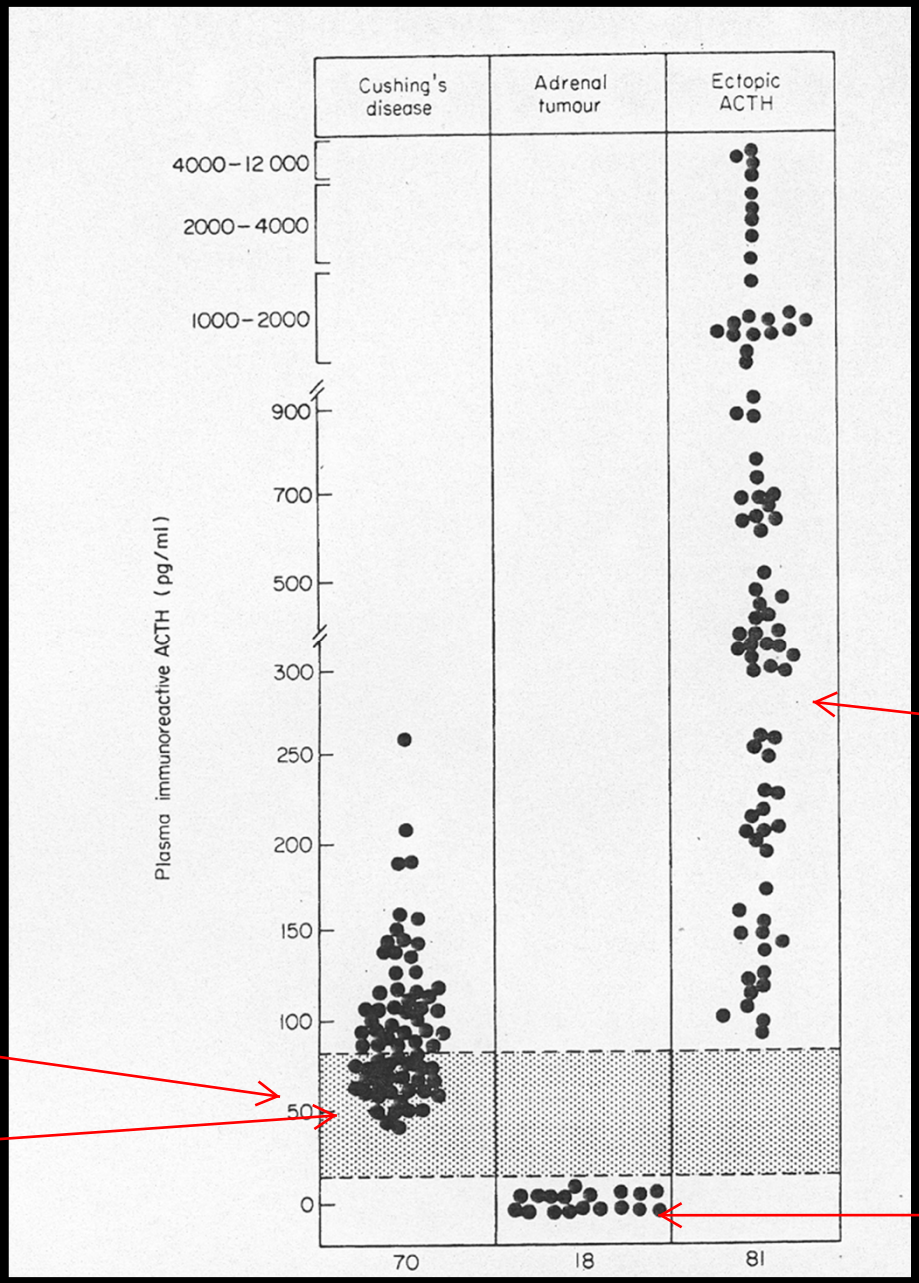
C. May vary according to the time of sample collection, sex and age of patient and analytical method

D. All of the above

Don't always have an absolute differentation of diagnostic test as was mentioned about the ACTH panel on the previous slide.

Question about bimodal distribution based on sex - some hormones follow gender differences - some don't
PTH, for example, is similar across the sexes
Testosterone on the other hand will have very different ranges in males vs. females.

While many tests follow a normal distribution - some do not.



Reference range for ACTH

Notice many Cushing's disease patients fall within normal range

More absolute separation in ectopic ACTH production

Adrenal tumor causes hyposecretion of ACTH as expected

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

Study to differentiate Cushing's disease/syndrome pathologies

24h Urinary Free Cortisol
Low-dose dexamethasone suppression

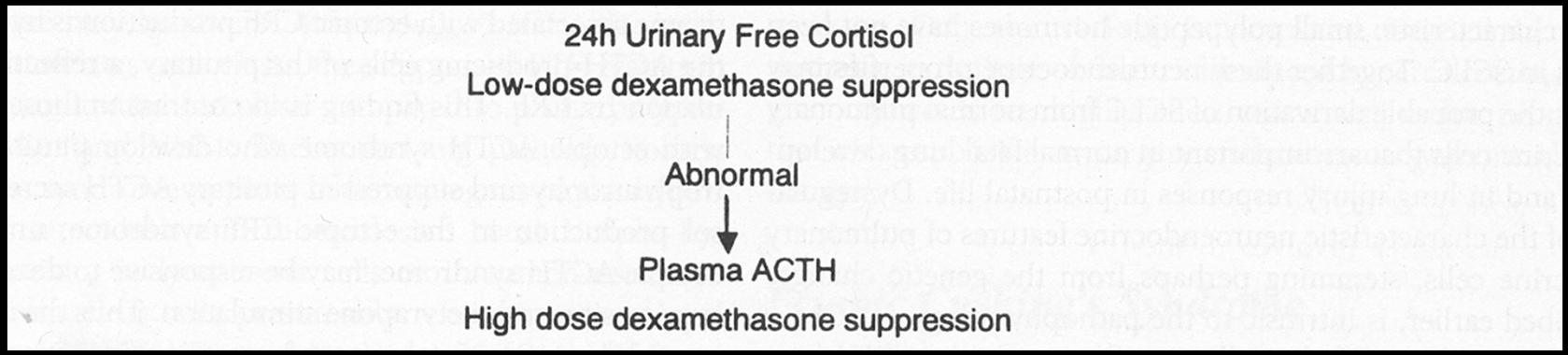
Laboratory Studies (Follow-up)

Day	Condition	Cortisol 8 a.m.	Cortisol Timed Urine
	Normal	5-25 µg/dL	20-70 µg/d
1	Baseline	39	425
2	Baseline	42	389
3	Low-dose dex	38	392
4	Low-dose dex	39	402

Use steroids to see if cortisol production responds - can indicate which type of cortisol pathology is present

After low-dose dexamethasone treatment, cortisol levels show very little effect if any

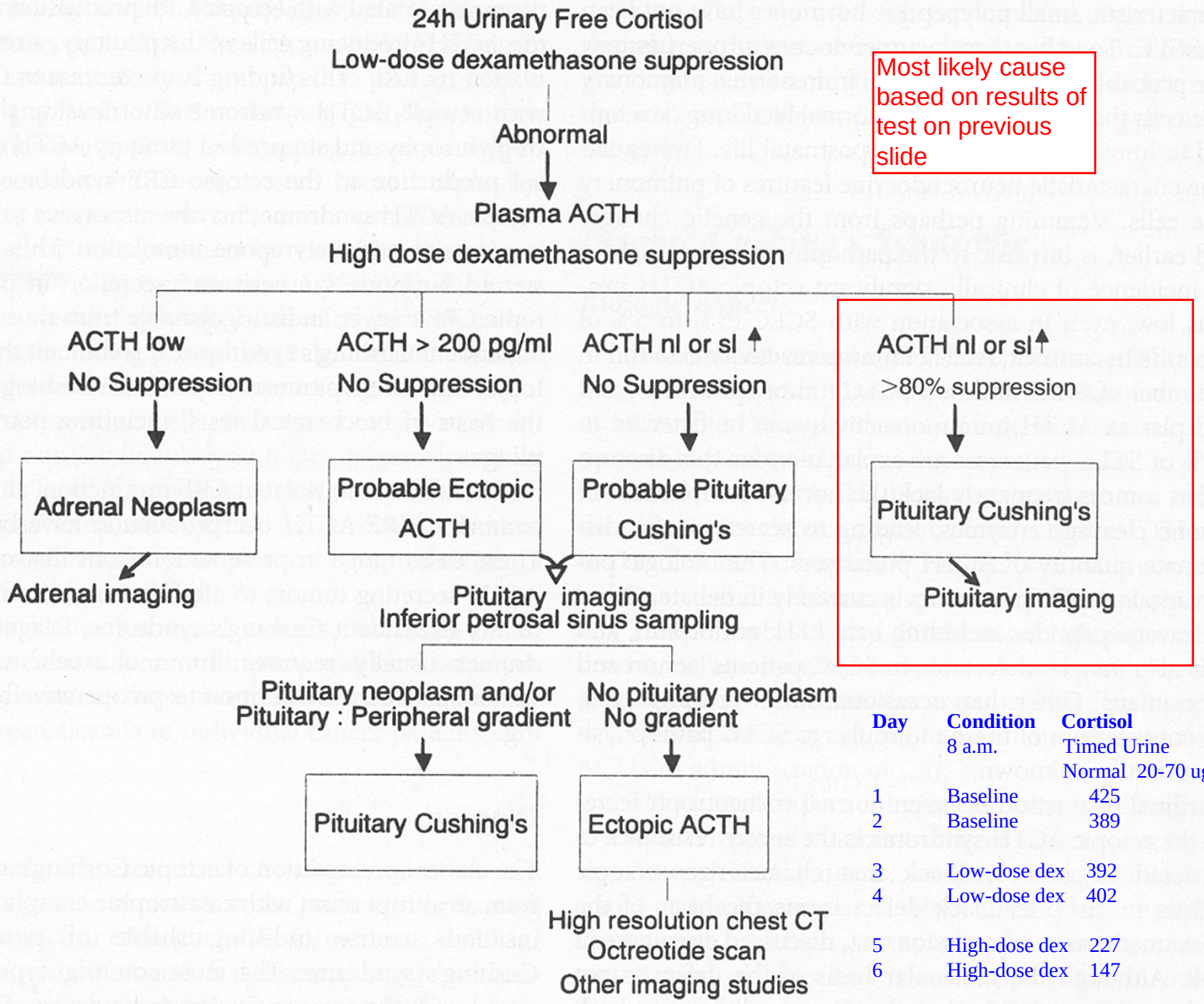
Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man



Laboratory Studies (Follow-up)

Day	Condition	Cortisol 8 a.m.	Cortisol Timed Urine
	Normal	5-25 μg/dL	20-70 μg/d
5	High-dose dex	19	227
6	High-dose dex	9	147

High dose dexamethasone caused reductions in both serum and urine cortisol levels

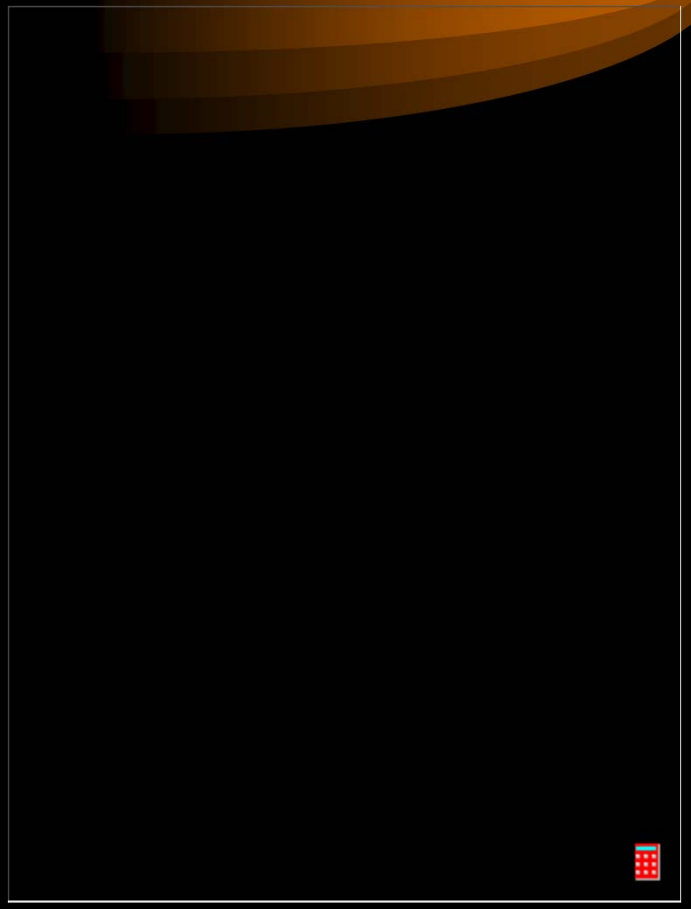


Most likely cause based on results of test on previous slide

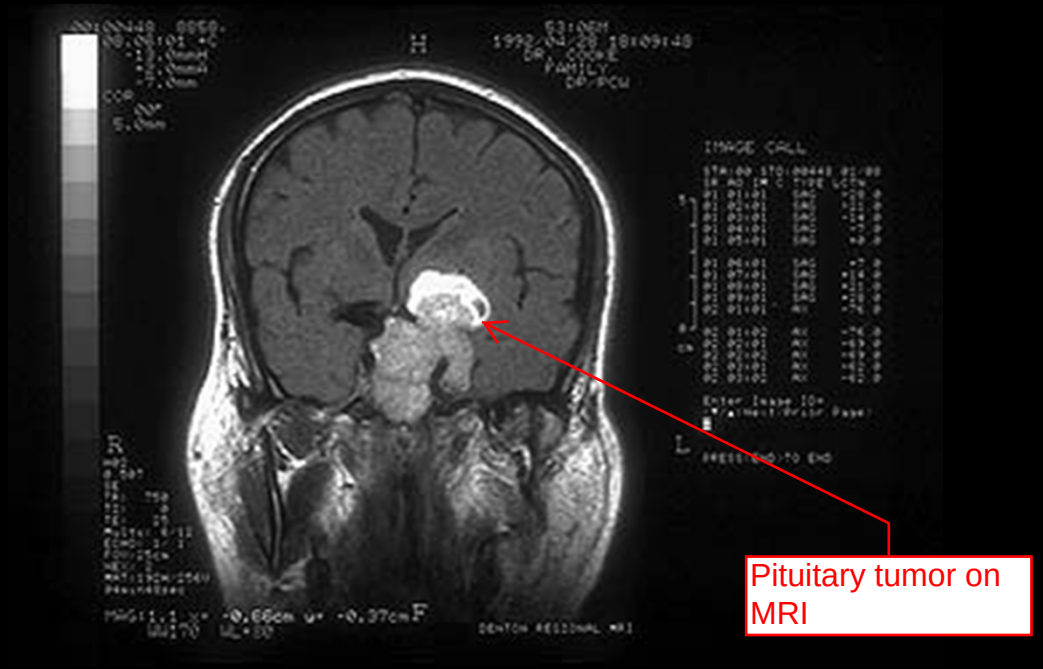
Day	Condition	Cortisol
	8 a.m.	Timed Urine
		Normal 20-70 ug/d
1	Baseline	425
2	Baseline	389
3	Low-dose dex	392
4	Low-dose dex	402
5	High-dose dex	227
6	High-dose dex	147

The patient's 6-day dexamethasone suppression results are most consistent with which of the following diagnoses:

A. Normal health
B. Cushing's Disease (Pituitary)
C. Cushing's Syndrome (Adrenal)
D. Cushing's Syndrome (Ectopic)
E. Cushing's Syndrome (Iatrogenic)



Magnetic Resonance Imaging (MRI) of Pituitary



Therapeutic Options for Cushing's Disease

- Surgery with removal of the pituitary adenoma
- Radiation therapy
- Bilateral adrenalectomy

After completing the tests, the patient underwent successful transphenoidal hypophysectomy with removal of the adenoma seen on MRI. Pathology studies revealed a benign tumor with histologic and staining characteristics consistent with an ACTH-secreting adenoma.

Case A: Truncal obesity, striae, hypertension and glucose intolerance in a 39-year old man

- Perioperatively the patient was “covered” with “stress steroids” and postoperatively his dose was tapered down to a physiologic dose. After a few weeks of physiologic replacement, he was tapered gradually to no exogenous cortisol. Over the next several months his body weight decreased by about 20 pounds, his facial redness decreased, his blood pressure improved, and glucose intolerance was no longer present. The stretch marks are still there, but they are less colorful and, in general, the patient feels better. His muscle strength has improved significantly. By 6 months postoperatively his morning cortisol level was normal, at 23 μg/dL.
- At some point it would be useful to test the patient’s hypothalamic-pituitary-adrenal axis for stress responsiveness, to be sure that full, stress-responsive function of the system has returned.

Case B: Coma and hypercalcemia in an older man

- Although he usually loved to walk on the beach in the sun, this summer the patient found himself with less and less energy. On a hot August afternoon he was found by his grandson in a comatose state in his urine-soaked bed.
- In the ER, he was barely responsive and clearly volume depleted. Physical examination revealed a supine blood pressure of 110/70 that fell to 90/60 when he was propped up. His pulse went from 90 to 120 with that maneuver. His mucous membranes were dry. His general physical exam was otherwise unremarkable, except for the neurologic exam, which revealed an obtunded man who could barely respond to simple questions. He was able to move all extremities on command.

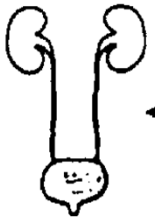
Case B: Coma and hypercalcemia in an older man

Laboratory Studies (Initial)

Test	Patient	Normal
Glucose (random)	88 mg/dL	70-110 mg/dL, fasting
Toxic screen	Negative	Negative
Calcium	13.6 mg/dL	8.5-10.5 mg/dL
Phosphate	5.9 mg/dL	3.0-4.5 mg/dL
Albumin	5.0 g/dL	3.5-5.5 g/dL
BUN	55 mg/dL	8-22 mg/dL
Creatinine	2.0 mg/dL	0.3-1.5 mg/dL
Alkaline Phosphatase	65 U/L	30-120 U/L

Apparently there was some concern about an overdose because a toxic screen was ordered in addition to normal blood chemistry

Blood Ca and P Homeostasis



Output

175 mg

Excretion

PTH

(-) Calcium

(+) Phosphate

900 mg

Blood

[Calcium]

[Phosphate]

Normal adult consumption

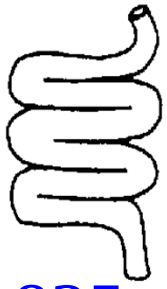
Input

1000 mg

300 mg

Absorption

1,25 D (+)



125 mg

825 mg

300 in, 125 back into intestine - net is about 175 mg

500 mg

Resorption

PTH (+)

1,25 D (+)

500 mg

Accretion

PTH (+)

1,25 D (+)

Calcium is stored long term in skeleton

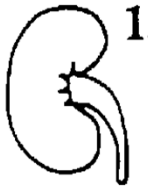
Exchange

Modulators

PTH

Calcium (-)

1,25 D (+)?



1,25 D

PTH (+)

Calcium (-)

Phosphate (-)

Hormonal form of vitamin D formed in kidney

Case B: Coma and hypercalcemia in an older man

ER physician found the Ca and Phosphate abnormalities to be of the most concern and ordered the following studies

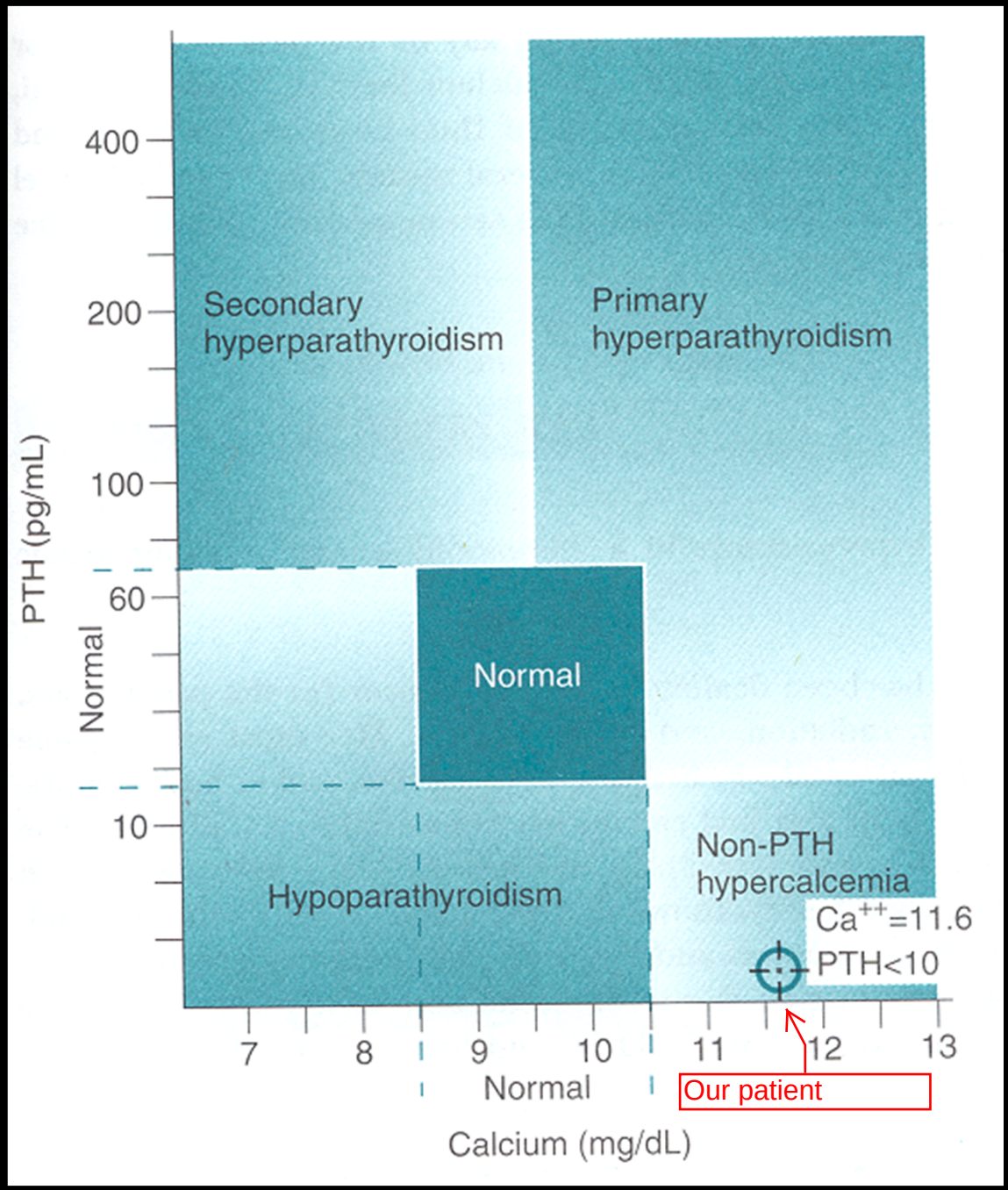
Laboratory Studies (Follow-up)

Test	Patient	Normal
Calcium	11.6 mg/dL	8.5-10.5 mg/dL
Phosphate	5.2 mg/dL	3.0-4.5 mg/dL
BUN	21 mg/dL	8-22 mg/dL
Creatinine	1.7 mg/dL	0.3-1.5 mg/dL
PTH, Intact	<10 pg/mL	10-65 pg/mL
25-OH-Vitamin D_3	352 ng/mL	30-100 ng/mL

remained elevated even after hydrating patient to bring down Calcium

These are the most important diagnostically

Despite elevated calcium, PTH is coming up subnormal, while 25-D is abnormally high


400
200
100
60
10
PTH (pg/mL)
Normal
Secondary hyperparathyroidism
Primary hyperparathyroidism
Normal
Hypoparathyroidism
Non-PTH hypercalcemia
Ca++=11.6
PTH<10
7
8
9
10
11
12
13
Normal
Calcium (mg/dL)
Our patient

Causes of Hypercalcemia

Common

Malignancy

Usually hypercalcemia isn't the first sign that alerts patient to malignancy

Hyperparathyroidism

Uncommon

Vitamin D Poisoning

Thyrotoxicosis

XS thyroid hormone over a long time period

Rare

Sarcoidosis

Tuberculosis

Thalizide Diuretics

Pheochromocytoma

Immobilization

Milk-Alkali Syndrome

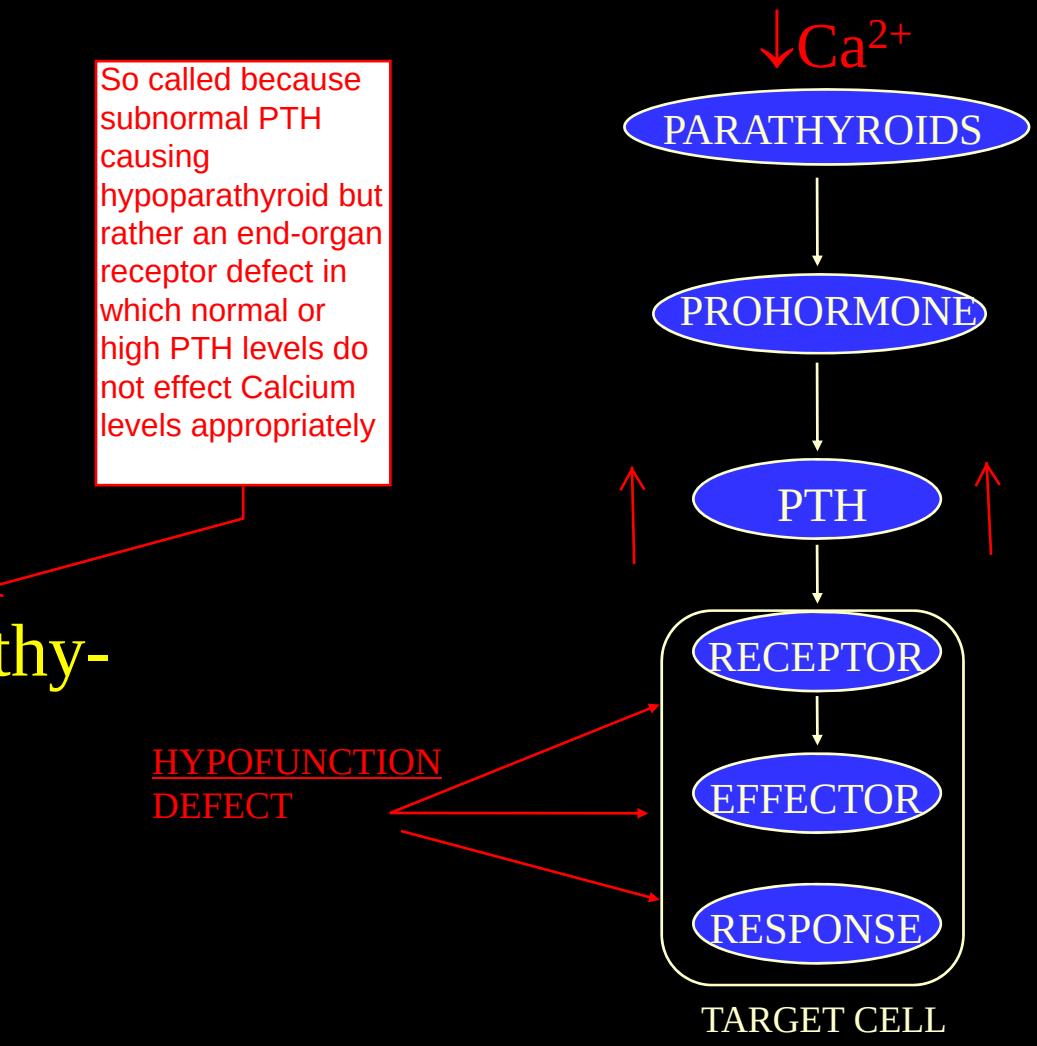
Familial Hypocalciuric Hypercalcemia

Recovery Phase of Acute Renal Failure

Hypercalcemia in the presence of subnormal PTH would NOT be anticipated in which disorder:

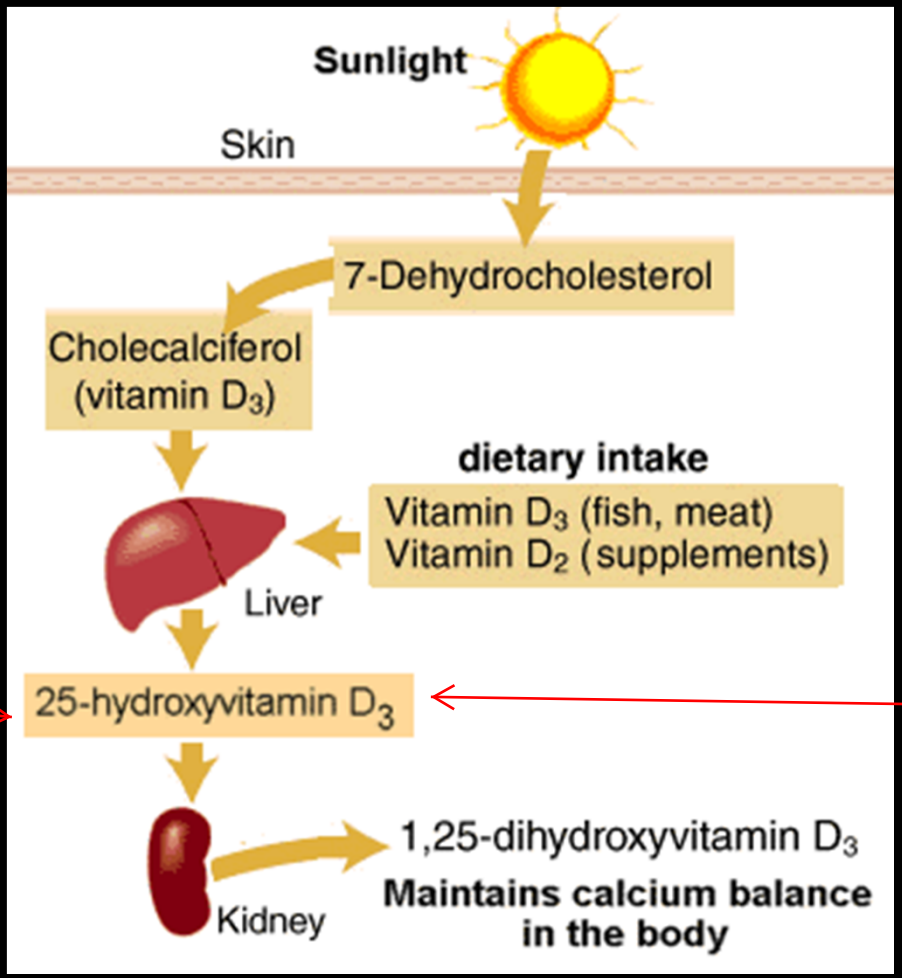
A. Malignancy-associated hypercalcemia
B. Vitamin D intoxication
C. Pseudohypoparathy-roidism
D. Thyrotoxicosis

So called because subnormal PTH causing hypoparathyroid but rather an end-organ receptor defect in which normal or high PTH levels do not effect Calcium levels appropriately



Case B: Coma and hypercalcemia in an older man

- After 6 hours and 3.5 L of i.v. saline, the patient's blood pressure and mental status dramatically improved. He was able to relate his past medical history, which was remarkable for significant osteoarthritis,principally involving his knees. The patient was somewhat vague about what medications, if any, he was taking.
- Later in the day his grandson came to visit and brought with him a bag full of medications that he found in his grandfather's bathroom. In addition to aspirin, acetaminophen and ibuprofen, a number of vitamin supplements were found. When the contents of the bag were reviewed with the patient, he admitted, rather sheepishly, that he had , in fact, been taking a large number of items in the bag. The salesman at the health food store had been quite convincing that BONEALL contained everything needed to strengthen bones and might help with the osteoarthritis that had plagued him for years. Although the directions clearly stated that only one should be taken daily, the patient did as he often did with medications—he took them when and as often as he wanted to. He felt that BONEALL was really helping and ended up taking 16 to 20 of the large tablets each day. Both BONEALL and several of the other vitamin preparations contained vitamin D.



We measure this, not 1,25 D which actually maintains calcium - This is because 1,25 production is a matter of substrate (25 D) not hormonally production in the kidney and 25 D levels are representative

Vitamin D supplement caused increase in vitamin D levels which increases Calcium absorption in the gut which caused the hypercalcemia in this case

Case B: Coma and hypercalcemia in an older man

- The patient is no longer taking any of the pills in the bag or anything from the health food store. His calcium level is slightly elevated but controlled by the three or four quarts of fluid he drinks each day and the extra salt he adds to his food. After several months the vitamin D level is still elevated, but closer to normal, and his serum calcium usually is at the upper end of the normal range.

Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

- A 67-year old white female in apparent good health scheduled a routine physical with a new physician following a recent out-of-state move.
- Her only medication is levothyroxine 0.2 mg daily for presumed hypothyroidism (after presenting with symptoms of fatigue quarter century earlier).
- The new physician ordered a thyroid panel (i.e. free thyroxine [FT4] and thyroid stimulating hormone [TSH] to assess the patient's current thyroid function.
- Physical examination demonstrates a normal-appearing woman. Height 65 in, weight 140 lbs, blood pressure 122/80, pulse 70. The exam is entirely normal and the patient denies any tachycardia, nervousness, heat intolerance, palpitations or diarrhea.

Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

Laboratory Studies (Initial)

Test	Patient	Normal
FT4	1.05 ng/dL	0.52-1.21 ng/dL
TSH	0.03 mIU/mL	0.34-5.66 mIU/mL

This normal level is due, in large part, to this patient's thyroid supplement that she is receiving.

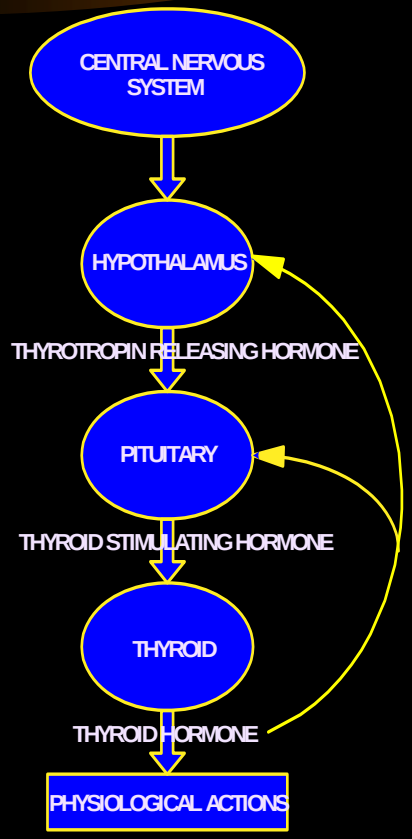
Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

- The suppressed TSH with “normal” FT4 and an absence of clinical symptoms is consistent with subclinical hyperthyroidism. Like subclinical hypothyroidism the disorder is manifested only as an abnormal TSH result. The most common cause is overadministration of thyroid hormone supplement.
- The physician attempts to decrease the dosage of levothyroxine but is met with resistance from the woman who claims the thyroid medicine “makes me feel good.” Nevertheless, on the next prescription the doctor reduces the dosage to 0.1 mg daily.
- After several weeks the patient reports feeling weak and tired and asks to go back to the higher dosage but agrees to continue the lower level a while longer. After 2 months the TSH remains suppressed at 0.03 mIU/mL.

Still some controversy about this definition - XS thyroid hormone relative to body's physiologic need

Why use a pituitary hormone (TSH) to evaluate thyroid function?

- TSH is the trophic hormone which stimulates release of thyroid hormone



Why use a pituitary hormone (TSH) to evaluate thyroid function?

- The best immunoassay methods for TSH are simpler in design, more precise, less sensitive to interference, and more easily automated than the best assays for Free Thyroxine (FT_4).

There is log-linear relationship and since TSH tests are easier and more precise - they are generally used more often.

Case C: 67-year old woman in apparent good health given thyroid supplementation for 25 years presenting for a routine physical

- The dosage is further reduced to 0.05 mg daily, but the patient continues to feel weak and requests referral to an endocrinologist. After 2 months on the 0.05 mg/day supplement TSH is remeasured at 0.21 mIU/mL (Reference Range 0.34-5.66 mIU/mL).
- Despite strenuous objections the woman's thyroid hormone supplementation was eventually discontinued altogether and TSH concentrations returned to normal. Over time the patient's symptoms of fatigue subsided and she is doing well off all medication.
- There are thousands of individuals on thyroid hormone supplementation who presented to their physicians as tired and/or overweight with a low basal metabolic rate. Many of these were diagnosed in the 1950's or 1960's when accurate thyroid function tests were not available and physicians had little data by which to guide therapy. Most probably never had hypothyroidism.

A similar phenomenon is currently happening with overprescription of allergy medication without diagnosed allergy leading to dependence which results in withdrawal upon removal of medication

There was a question about atrophy of the thyroid in a case like the last one presented

Answer: While noticeable atrophy doesn't usually occur, functional depletion of thyroid production will occur as was seen in this case.