

Cushing's Disease and Addison's: What Laboratorians Need to Know

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Objectives

- Overview of major adrenal disorders
- Describe the normal and abnormal laboratory findings associated with the adrenal cortex.
- Distinguish the characteristics, pathology, and findings associated with Cushing's diseases and Addison's disease, including genetic markers
- Given laboratory data pertaining to adrenal disease, be able to determine probable disease state and confirmatory testing needed.

Adrenal Gland

- Adrenal cortex
- Layers
 - Glomerulosa
 - Fasciculata
 - reticularis
- Hormones produced
 - Aldosterone
 - cortisol
- Negative Feedback
 - ACTH, CRH

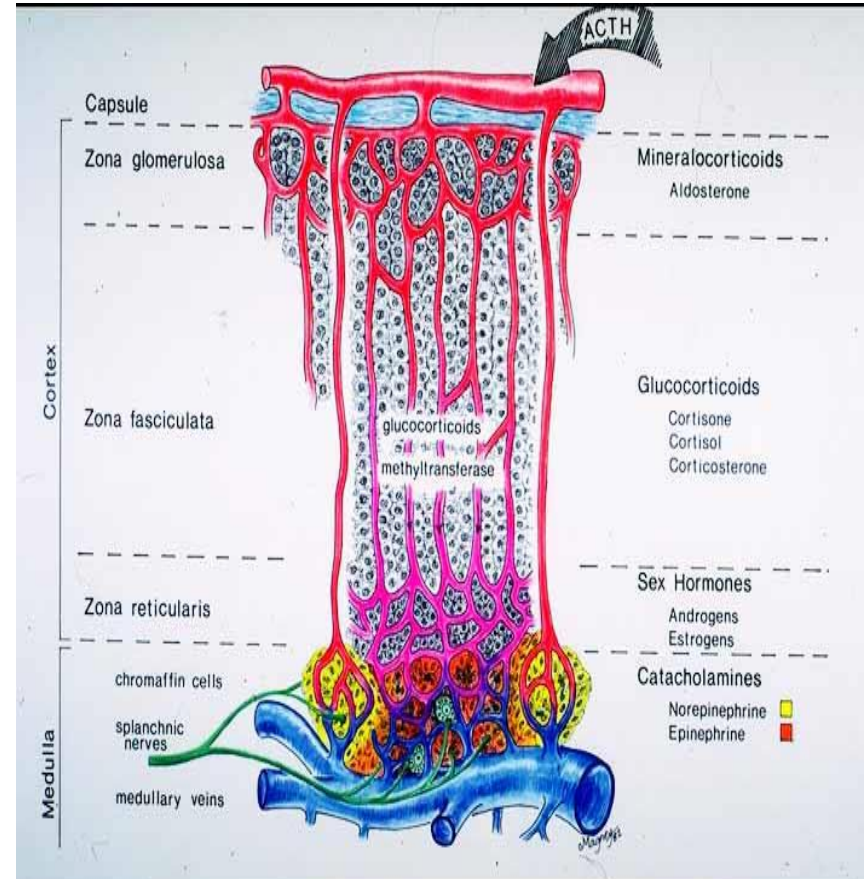
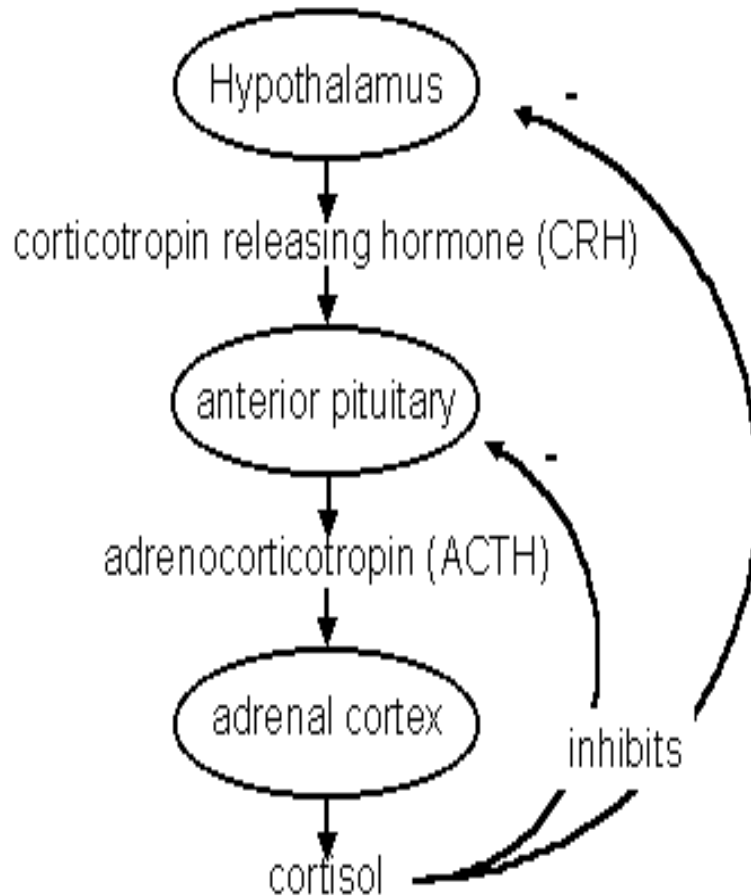


Figure 21. Schematic showing the cellular zonation of the adrenal cortex and blood flow through the cortex to the collecting veins in the medulla.

Cortisol functions

- Hormone affects all of body
- Functions include:
 - Blood pressure and cardiovascular function
 - Slows inflammatory response by inhibiting Antibody formation
 - Helps balance insulin effect on blood glucose by increasing blood glucose levels
 - Helps regulate protein, carbohydrate, and fat metabolism.

Negative Feedback system

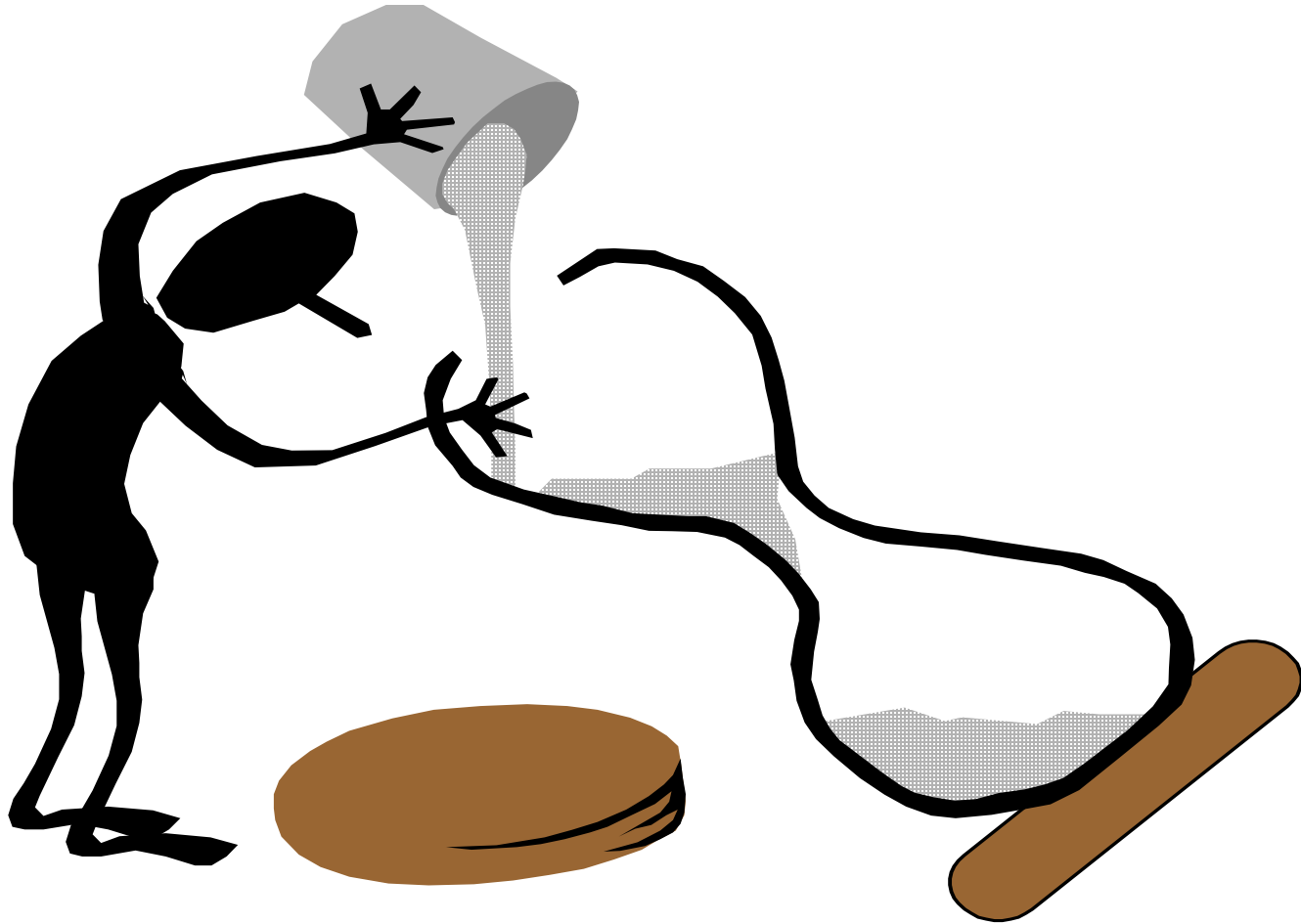


- Pituitary secretes ACTH
- Hypothalamus secretes CRH
- ACTH stimulates the adrenal cortex to release cortisol
- Negative feedback to Hypothalamus, Pituitary

Case #1

- Female patient complains of muscle weakness, loss of appetite, but craves salt, low blood pressure, some diarrhea, and a dark pigmentation of her elbows and knees.
- Lab testing shows:
 - glucose = 68 mg/dL (Range: 80-100mg/dL)
 - potassium = 5.9 mmol/L (Range: 3.5-5.2 mmol/L)
 - ACTH = 8.4 umol/L (Range: 2-5 umol/L)

Ideas????



Addison's Disease

- Primary adrenal insufficiency
 - Affects 1 in 100,000 people
 - Gradual destruction of adrenal gland
 - 90% loss of adrenal cortex before see insufficiency
- Secondary adrenal insufficiency
 - Most common form of disease
 - Lack of ACTH

Addison's disease

- Primary adrenal insufficiency
 - Lack of cortisol and aldosterone seen
 - Only adrenal gland affected is called “idiopathic insufficiency”
 - When other glands affected besides adrenal is called “poly-endocrine deficiency syndrome”
 - Type I usually affects children
 - Type II affects young adults
 - Both may be inherited

Causes for Addison's disease

- Autoimmune disorders = 70% of cases
- Tuberculosis, 20%
 - In 1849, Dr. Addison found 70-90% of disease due to TB
 - Treatment has reduced this to 20%
- Chronic infections, usually fungal
- Amyloidosis
- Surgical removal of adrenal glands

Laboratory

- Biochemical testing leads to diagnosis of Addison's disease
- Testing cortisol, glucose, potassium, ACTH
- In Addison's disease, we see:
 - low glucose
 - elevated K⁺
 - decreased cortisol (blood and urine)
 - elevated ACTH
- In secondary Addison's, we see decreased ACTH

ACTH stimulation tests for Addison's diagnosis

- Use synthetic ACTH, inject into patient
- Measure blood and urine cortisol levels before injection
- Wait 30 to 60 minutes, draw blood and urine cortisols again
- Normal patient response is to see cortisol rise after ACTH
- Adrenal insufficiency response is no rise in cortisol

Addison's Crisis

- Approximately 25% of Addison's disease cases are not detected until a stressful event occurs
- When stressed these patients can go into Acute Adrenal Insufficiency
- Untreated these cases can become fatalities

Addison's Crisis

- Symptoms include:
 - Penetrating pain to lower back, abdomen, or legs
 - Severe vomiting and diarrhea
 - Dehydration follows
 - Low blood pressure with $\uparrow K^+$, \downarrow glucose
 - Loss of consciousness
 - Untreated = fatality

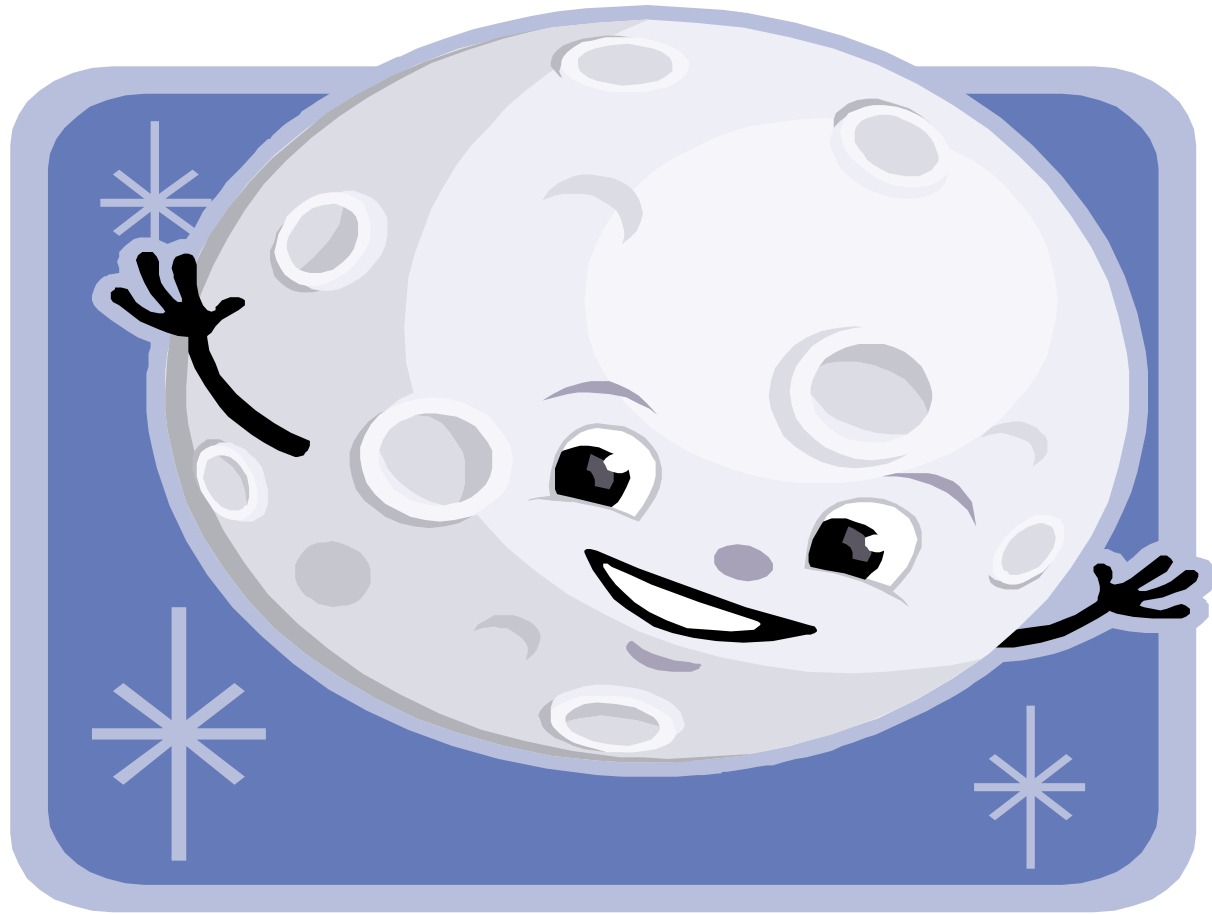
Case #2

- 45 year old female with hypertension, easy bruising, hypertension, upper body obesity, and abnormal bone density scan seeks answers from her physician for her condition.
- Lab tests are ordered for cortisol, ACTH, glucose, potassium, renal function, thyroid testing and CT scan.

Case #2

- Our patient has a blood cortisol of 28 ug/dL with a range of 8-23 ug/dL
- Glucose was 134 mg/dL (RR= 80-100 mg/dL)
- BUN and creatinine were within reference range values
- Potassium 3.0 mmol/L (RR= 3.5-5.2 mmol/L)
- ACTH was lower than the reference range
- TSH was high and T4 was low

Probable Diagnosis??

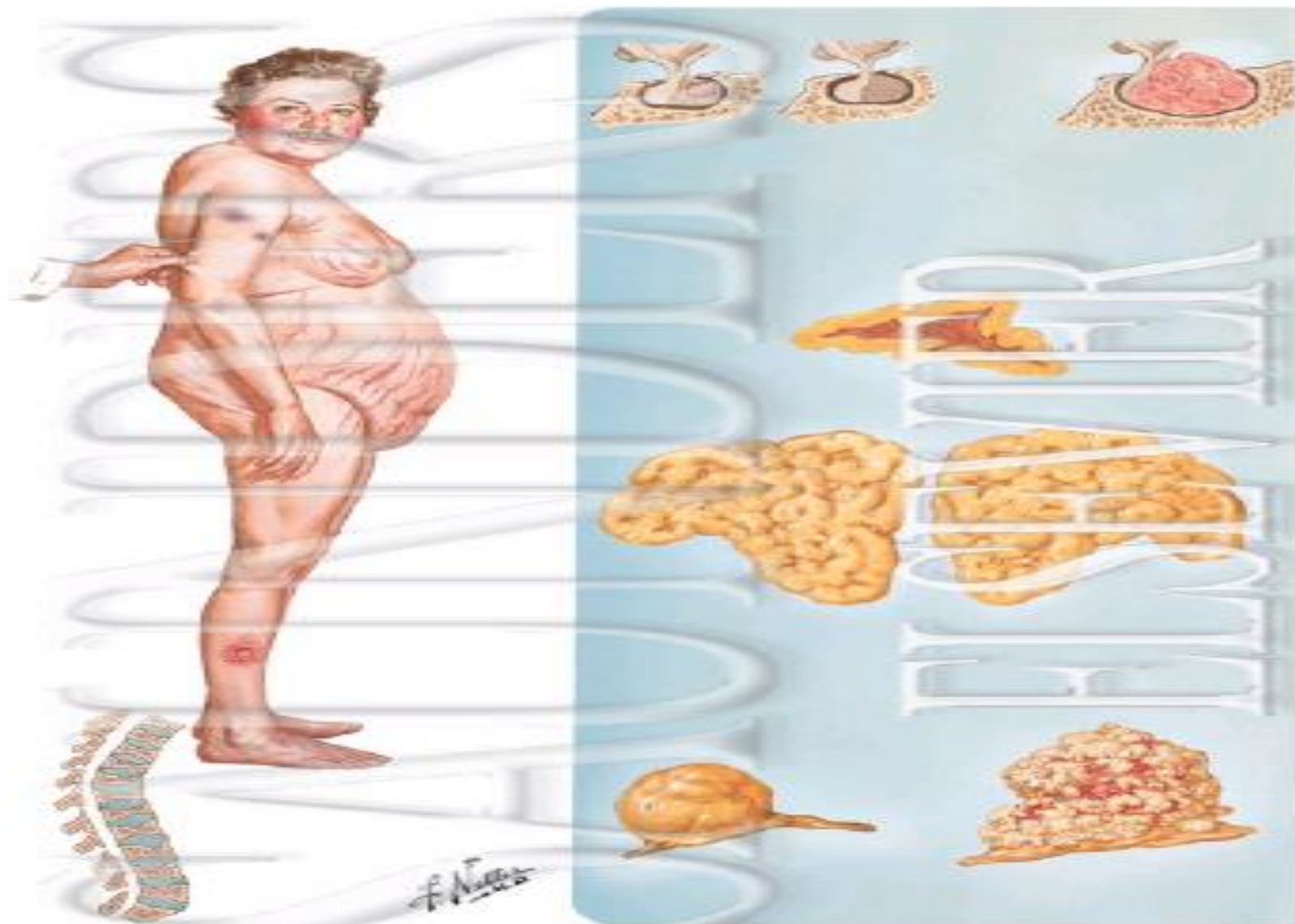


Cushing's Syndrome

- Affects 10-15 million people per year
- Age range for first symptoms = 20-50 years old
- Condition can lead to prolonged exposure to high levels of cortisol
- Cortisol excess leads to glucose problems, suppression of immune system, and depression

Cushing's Syndrome Symptoms

- Upper body obesity
 - Round face, increased fat about neck
 - Thinning arms and legs
- Fragile skin
 - Easy bruising, purple stretch marks on abdomen, thighs, arms, buttocks, breasts
- Hypertension and diabetes
- Excess hair growth, fertility issues



Causes of Cushing's Syndrome

- Environmental
 - Taking prednisone, anti-inflammatory agent
- Cortisol overproduction
 - Pituitary adenomas
 - Ectopic adenomas
 - Adrenal tumor
- Familial Cushing's Syndrome
 - Primary Pigmented Micronodular Adrenal Disease
 - Multiple Endocrine Neoplasia Type I (MEN I)

Not Cushing's

- Polycystic Ovarian Syndrome
 - Obesity, excess hair growth, sometimes insulin action impaired leading to diabetes
 - DO NOT have elevated cortisol levels
- Metabolic Syndrome X
 - Elevated blood pressure
 - Increased cholesterol and triglycerides
 - Insulin resistance
 - Normal Cortisol levels

Cortisol Overproduction

- Most common cause of excess cortisol
- Called “Cushing’s disease” to separate it from adrenal gland Cushing’s syndrome
- Pituitary Adenomas = excess ACTH leading to excess cortisol
- Frequency is 5 to 1 women to men with this form of the disease

Cortisol Overproduction

- Ectopic tumors
 - Lung tumors cause 50% of these cases
 - Oat cell or small cell lung Cancer leading to ACTH producing tumor most often; also thymomas, pancreatic islet cell tumor, or medullary carcinoma of thyroid can lead to ACTH-producing tumor
 - Frequency is 3 to 1 men to women

Over production

- Adrenal tumors leading to Cushing's syndrome
- Adrenal adenoma not cancerous
 - Excess cortisol
- Adrenocortical carcinomas– very rare
 - Excess cortisol, androgens, other cortical hormones

Diagnosis of Cushing's

- Testing for 24-hour urinary free cortisol
 - Values > 50-100 ug/day suggest Cushing's
- Dexamethasone Suppression test
 - Use synthetic glucocorticoid
- CRH stimulation test
 - Inject CRH, look for pituitary rise in ACTH, then cortisol
- Radiologic visualization= CT, MRI

Dexamethasone Suppression Test

- Dexamethasone is synthetic glucocorticoid so it acts like cortisol to inhibit ACTH
- In test, give dexameth every 6 hours for 4 days. First 2 days low dose drug, last 2 days high dose drug.
- Collect 24 hour urine before drug, every day after drug
 - Normal response is to lower ACTH, decrease blood and urine cortisol
 - If ectopic tumor, ACTH and Cortisol levels stay high

Dexamethasone test

- False-positive results with this test can occur
- Depression, Alcohol abuse, elevated Estrogens, acute illness, and stress can do this
- Drugs that like phenytoin and phenobarb can cause False-Negative results

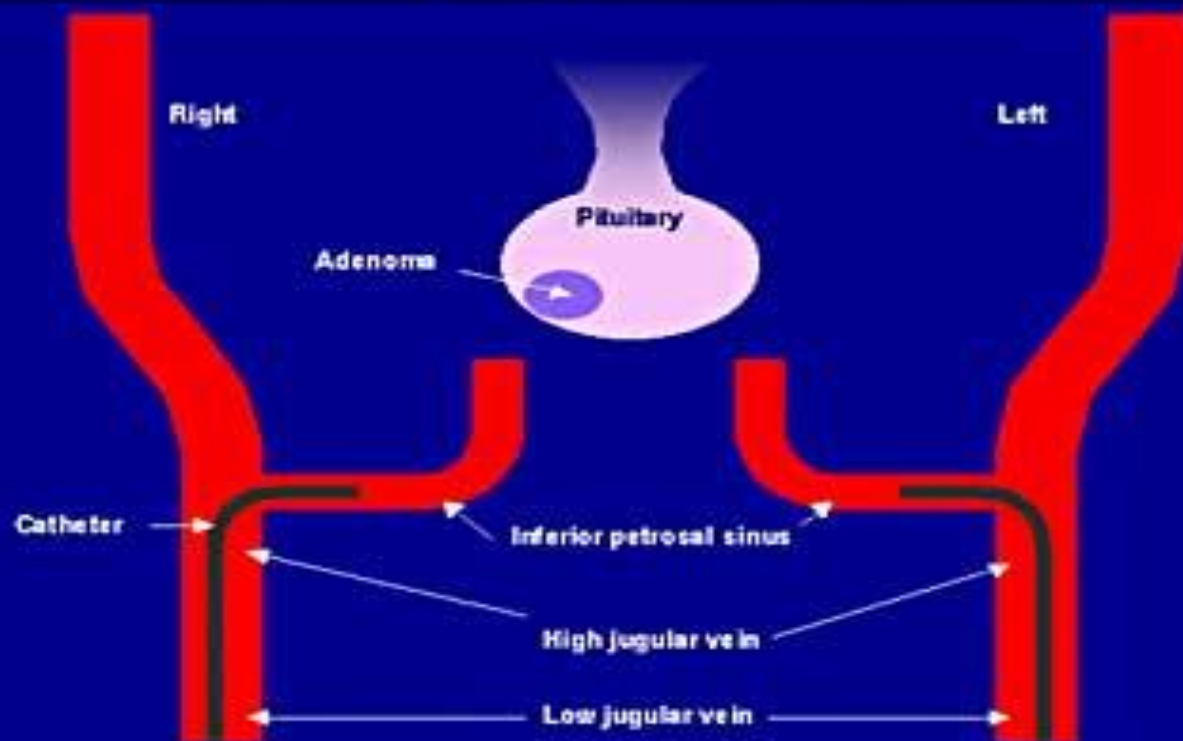
CRH Stimulation test

- Inject CRH
- Should stimulate the Pituitary and lead to increased ACTH and cortisol levels, IF the cause is a pituitary tumor
- Ectopic ACTH tumors will not respond, so ACTH and cortisol levels should remain where they originated.

Petrosal Sinus Sampling

- Elevated cortisol values with inconclusive stimulation tests can lead to the need for Petrosal Sinus Sampling
- This test used to separate Ectopic ACTH tumors from Pituitary tumors
- Petrosal sinuses are veins that drain the pituitary. Catheters are threaded from groin or thigh up into the petrosal sinuses.
- CRH stimulation thru these leads to pituitary release of ACTH
- Measure from arm and from petrosal sinus
- Pituitary adenoma shows higher ACTH in petrosal sinus

Simultaneous bilateral inferior petrosal sinus sampling for ACTH



	Plasma ACTH (ng/l) after hCRH 100ug I.V.		
	0 min	5 min	10 min
Left inferior petrosal sinus	18	30	34
Right inferior petrosal sinus	19	490	300
Simultaneous peripheral vein	16	17	30

Pseudo-Cushing's Syndrome

- Originally seen in depression and patients with alcohol abuse.
- See elevated cortisol levels without Cushing's symptoms
- Does not have the same long term effects on patient as Cushing's syndrome
- Does not require treatment directed at adrenal gland

Pseudo-Cushing's

- A Dexametasone-CRH stimulation test is done to distinguish this disorder from Cushing's syndrome
- Patients with Cushing's will be detected, especially if ectopic ACTH is the cause for the elevated cortisol value. Patients with Pseudo-Cushing's will have a normal patient response
- Testing thus helps identify patient's with Cushing's versus Pseudo-Cushing's

Treatment for Cushing's

- Pituitary adenomas
 - Surgery= transsphenoidal adenomectomy
 - Specialized surgery, 80% cure rate
 - ACTH drops abruptly afterward, need supplements of hydrocortisone and prednisone
 - Radiation
 - Adults 40-50% improve, children 80%
 - Radiation plus mitotane (Lysodren®)
 - Other drugs include aminoglutethimide, metyrapone, trilostane, ketoconazole

Treatment of Cushing's

- Ectopic ACTH tumor- remove cancerous tissue by:
 - Surgery
 - Radiation
 - Chemotherapy
 - Immunotherapy or combination

Genetic Connections

- Pituitary adenomas
 - Amplification of H-ras and c-myc
 - Inactivation of p53, nm23, Rb
- Microarray analysis
 - C-mer proto-oncogene tyrosine kinase gene is overexpressed
 - Ornithine decarboxylase gene is under-expressed

Genetic Markers

- Cushing's syndrome
 - No known inheritance patterns have been found to date
- Addison's disease
 - HLA-DQA1, HLA-DQB1, and HLA-DRB1
 - CIITA, CTLA4, CYP27B1
 - MICA, NLRP1, PTPN22

Case #3

- 35-year old female complains of menstrual irregularities, hyperglycemia, hypertension, and hirsutism (hair growth).
- Her physician receives the following abnormal blood results:
 - Cortisol = 57 ug/dL (Range: 8-23 ug/dL)
 - ACTH = 1.2 umol/L (Range: 2-5 umol/L)
 - Glucose = 167 mg/dL (Range: 80-100)

What appears to be the disorder here?

Case #4

- A 25-year old female went to her dentist complaining about bleeding gums and bad breath. Her dentist noticed oral discolorations in her mouth and a lack of papilla on her tongue. He referred her to her family physician for a full workup.
- The patient told her physician she was not sleeping well and was often fatigued.
- Her laboratory findings included:
 - HgB = 7.9 g/dL
 - Glucose= 70 mg/dL (Range: 80-100 mg/dL)
 - Cortisol = 2.4 ug/dL (Range: 8-23 ug/dL)

Summary

- References from National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, National Cancer Institute, as well as articles from American Family Physician
- Thank you for kind attention
- Any questions?