The Endocrine System Blueprint

Brunilda Cordero, MD FAAP

Board Certified Pediatric Endocrinologist

Disclosure

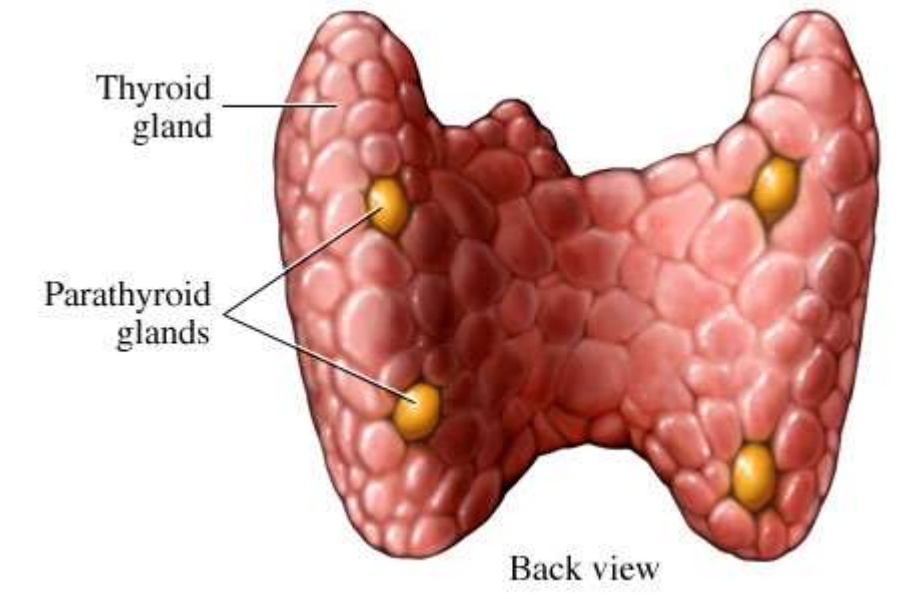
- I have no relationships with commercial interests to disclose.

- This lecture has received no commercial support

OBJECTIVES

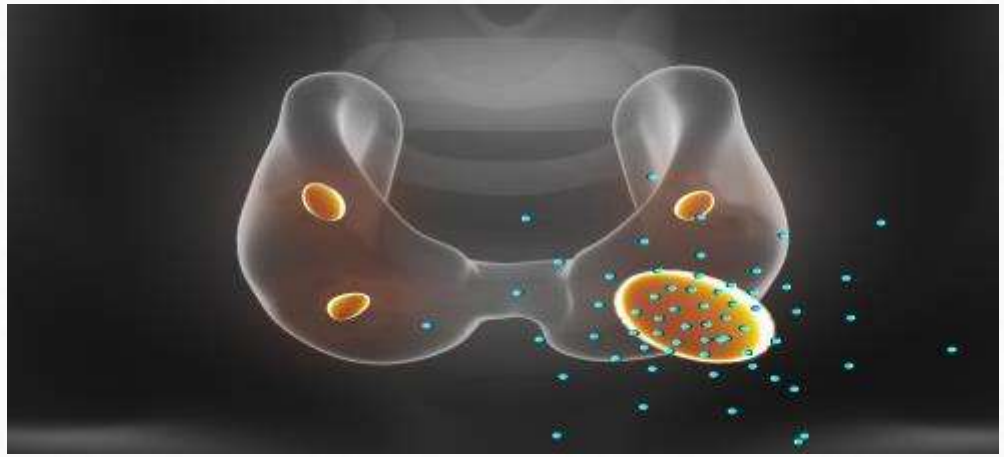
- Review functions of endocrine organs, metabolism of their hormones and their effects on the body
- Review and understand the pathogenesis and pathophysiology of diseases of pituitary, thyroid, parathyroid, adrenal, pancreas, testes and ovaries.
- Review most current diagnostic testing and pharmacotherapy for endocrine related disorders

Disorders of the Parathyroid and Thyroid Glands



Primary Hyperparathyroidism

- Excess PTH secretion from one or more of the parathyroid glands leading to hypercalcemia (calcium >11 mg/dL)
- A single benign parathyroid adenoma is found in 80-90% of cases.
- Parathyroid carcinoma is extremely rare



Clinical Presentation

- 80% of cases of hyperparathyroidism are asymptomatic.
- Fatigue
- Nocturia and polyuria: hypercalcemia inhibits ADH secretion
- Constipation
- Neuromuscular dysfunction: muscle weakness
- Neuropsychiatric disturbance: depression, personality disorders

- Mnemonic:
  - Bones
  - Stones
  - Abdominal moans
  - Psychic groans
  - hyper tones

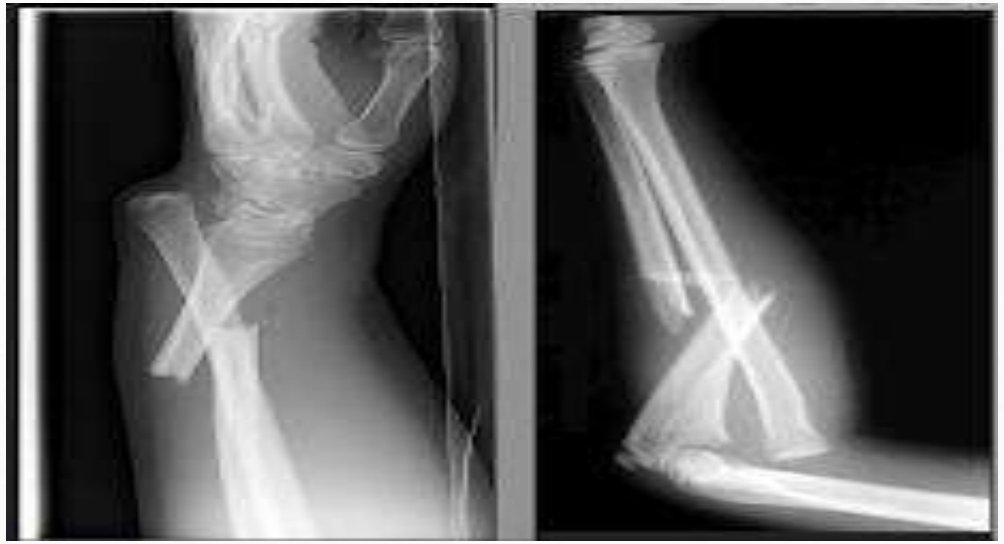
Skeletal Complications

Severe bone pain

Fractures of the bones

Osteoporosis

Kidney stones



Diagnostic Testing

Laboratory Findings

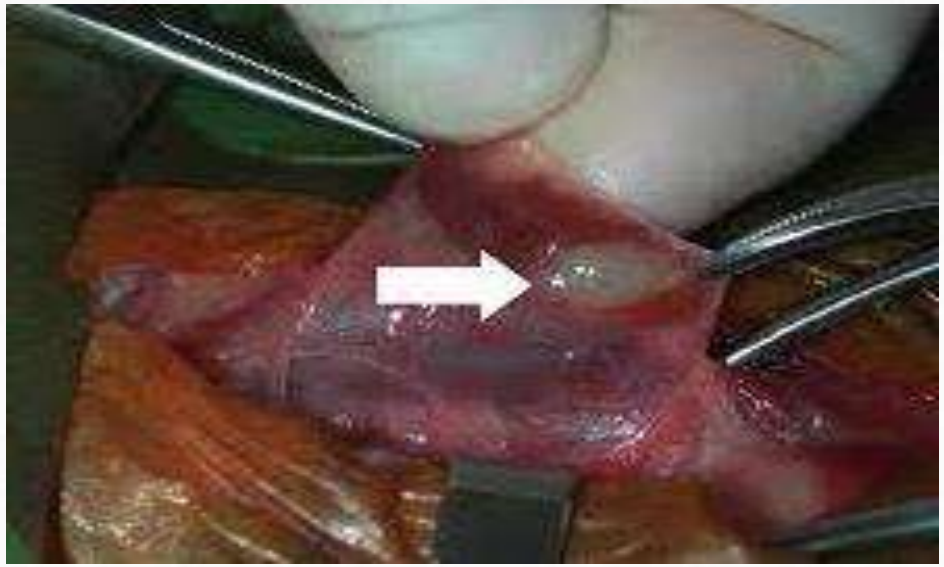
- Elevated PTH >60 pg/mL
- Elevated serum calcium level >10.5 mg/dL
- Serum phosphorus is low (<2.5 mg/dL)
- Elevated 24 hour urine calcium creatinine ratio >300 mg/day

Imaging

- TC-99m Sestamibi scan
  - Gold standard
  - Sensitivity and Specificity is >95%

Treatment

- Parathyroidectomy
  - Is the definitive treatment for primary hyperparathyroidism
  - Complications:
    - Damage to the recurrent laryngeal nerve



Hypoparathyroidism

- Inappropriately low secretion of PTH
  - Hallmark:
    - Low PTH
    - Low calcium level (hypocalcemia)
    - **Elevated phosphorus (hyperphosphatemia)**
    - Low 24 hour urinary calcium excretion
    - Low 1,25(OH)D3

Clinical Presentation

- Paresthesia
  - Numbness and tingling of the extremities
  - Carpopedal spasms
- Life threatening laryngeal stridor due to laryngeal spasm
- CNS manifestations
  - Seizures
  - Confusion
  - Irritability
  - Worsening dementia in adults

Surgical Hypoparathyroidism

- The most common cause of hypoparathyroidism is due to removal or destruction of the PTH glands.
- Patient's with Grave's disease undergoing thyroidectomy are most likely to experience hypocalcemia
- Tetany ensues 1-2 days postoperatively

Diagnostic Testing

- Low serum calcium or iCa
- Low PTH level
- **High phosphorus level**

- Electrocardiography
  - Prolongation of the QTc interval and shortening of the RR interval

Treatment of hypocalcemia

- IV calcium
  - Calcium gluconate
- Oral calcium
  - Calcium carbonate 1-3 grams/day
- Vitamin D supplementation
  - Vitamin D2 (ergocalciferol)
  - Vitamin D3 (cholecalciferol)
  - Calcitriol (1,25 (OH)2D)

The Thyroid Gland

- Hormones secreted by the thyroid gland:
  - Thyroxine (T4)
  - Triiodothyronine (T3)
  - Thyroid-binding globulin (TBG)
  - Plasma calcitonin [tumor maker for medullary carcinoma of the thyroid (MTC)]

Antibodies to the Thyroid Gland

Thyroid peroxidase antibody (TPO)

Is a marker for autoimmune hypothyroidism (Hashimoto's Thyroiditis)

Thyroglobulin antibody (ATA)

Is a marker for autoimmune hypothyroidism

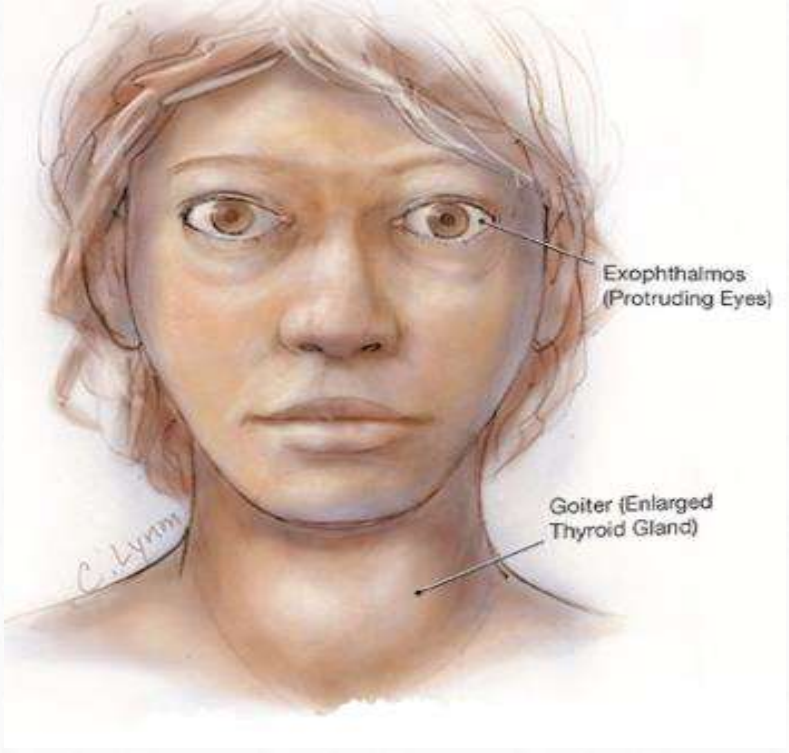
TSH receptor antibody

Thyroid stimulating immunoglobulin (TSI)

- Always positive in Grave's disease
- Best markers for diagnosis of autoimmune hyperthyroidism (Grave's)

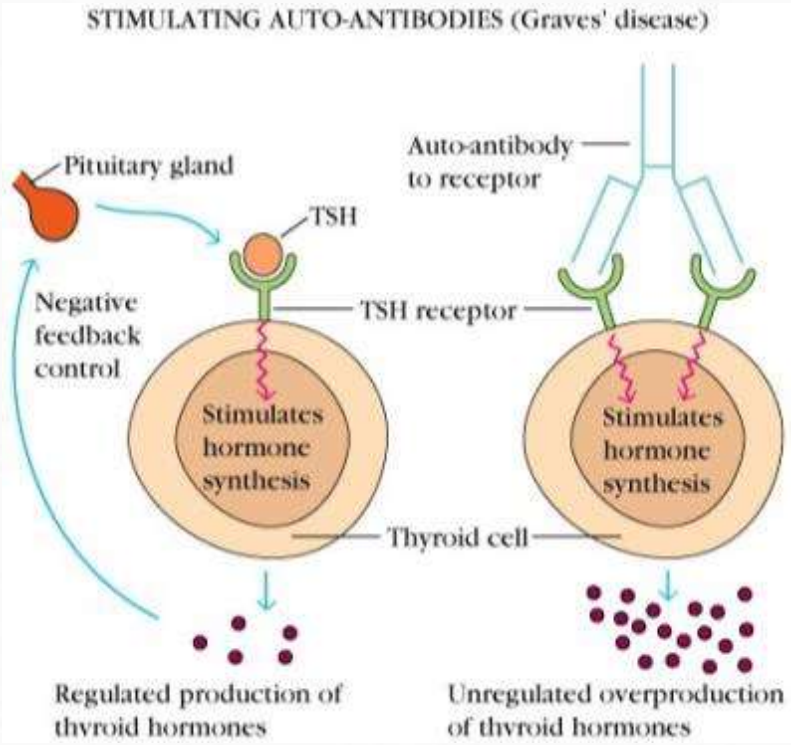
Grave's Disease

- Is the most common form of hyperthyroidism
- Females are affected about 5 times more than males
- Peak incidence is 20-40 years
  - Consists of the following features
    1. Thyrotoxicosis
    2. Goiter
    3. Ophthalmopathy (exophthalmos)
    4. Dermopathy (pretibial myxedema)



Pathogenesis of Grave's Disease

- Autoimmune disorder
  - Thyroid stimulating Immunoglobulin (TSI) also known as thyroid-stimulating antibody (TSAb):
    - binds to the TSH receptor and mimics the effects of TSH



Symptoms of Hyperthyroidism

- Heat intolerance with increased sweating
- Weight loss with increased appetite
- Anxiety, irritability
- Chest palpitations
- Oligomenorrhea
- Fatigue and weakness
- Brisk reflexes
- Tremors of the hands
- Lid lag, stare
- Atrial fibrillation
- Sinus tachycardia
- Hair loss
- Muscle weakness and wasting

Diagnostic Testing

- Plasma TSH: suppressed or low
- Free T4, T4 and T3: elevated
- Thyroglobulin: elevated
- Thyroid receptor Ab or TSI: always positive
- Thyroid peroxidase Ab: positive or negative

Treatment

- Radioactive Iodine therapy (I131)
  - Is the preferred treatment of choice for almost all patients with Grave's disease
  - Cannot be used during pregnancy or during lactation
  - It has proven to be safe and does not cause fertility problems or cancer.
  - Complications: Hypothyroidism

Oral Medication

Propylthiouracil (PTU)

- It blocks peripheral conversion of T4 into T3
- 250 - 400 mg every 6 hours
- Is the preferred treatment during pregnancy in the first trimester

Methimazole (Tapazole)

- Inhibits thyroid hormones synthesis
- 10-20 mg daily
- Should be used after the first trimester to prevent aplasia cutis (congenital absence of the skin)
- Agranulocytosis
- Rash

Thyroid Surgery

- Is preferred if the patient has failed thyroid radioactive iodine treatment in two different occasions.
- Complications:
  - Hypoparathyroidism
  - Injury to recurrent laryngeal nerve causing permanent vocal cord paralysis

Thyroid Storm

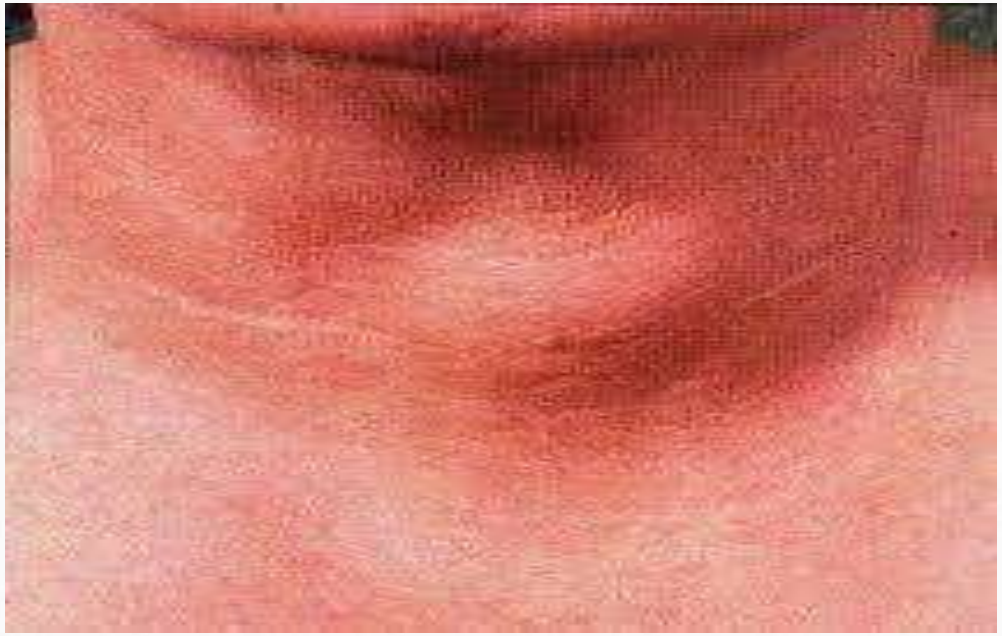
- Acute exacerbation of thyrotoxicosis
- Is a life threatening condition
    - Malignant fever associated with flushing and sweating
    - Marked tachycardia with atrial fibrillation
    - Elevated blood pressure
    - Heart failure
    - Delirium and coma

Management of thyroid storm

- Admission to ICU
- Propranolol 1 to 2 mg IV every 5-10 minutes
- PTU or Methimazole rectal suppository if person cannot swallow
- Potassium Iodine solution: 10 drops twice daily
- Hydrocortisone 50 mg IV
- Cooling blankets
- Acetaminophen
- IV fluids
- Oxygen, diuretics and digoxin for heart failure
- Plasmapherisis or peritoneal dialysis to remove high levels of circulating thyroid hormones

Other forms of Hyperthyroidism

- Toxic Adenoma
  - Hyper secretes T3 and T4
  - Start our as small nodule and slowly increases in size
  - Benign in nature
  - Ophthalmopathy is never present



Hashimoto's Thyroiditis

- Is the most common cause of acquired hypothyroidism in the USA
- The thyroid gland is damaged by cell-mediated immunity: TPO and ATA
- More common in women
- Increases in prevalence with age
- Diffuse goiter without tenderness

Hypothyroidism

Children and Adolescents

- Signs and Symptoms
  - Retarded growth and short stature
  - Decreased school performance due to lack of concentration.
  - Tiredness and fatigue
  - Excessive sleep time
  - Irregular menstrual cycles

Adults

- Signs and Symptoms
  - Easy fatigability
  - Cold sensitivity
  - Weight gain
  - Constipation
  - Menorrhagia
  - Muscle cramp

Diagnostic Testing

- Elevated TSH
- Low free T4
- Thyroid peroxidase antibody (TPO) always positive in autoimmune thyroiditis
- Thyroglobulin antibody (ATA) may be positive or normal in autoimmune thyroiditis

Treatment

- Synthroid or Levothyroxine

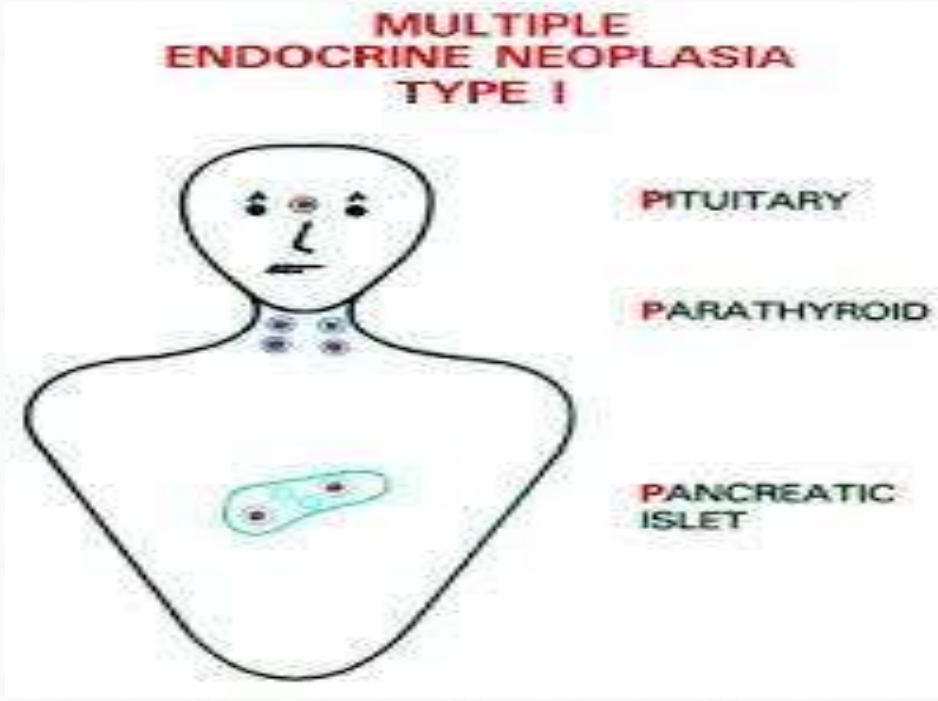
Age	Dose (mcg/kg/day)
0-3 months	10-15
4-6 months	8-10
7-12 months	6-8
1-5 years	5-6
6-12 years	4-5
> 12 years/puberty incomplete	2-3
> 12 years/puberty complete	1.7

Subacute Thyroiditis

- Also known as de Quervain's or granulomatous thyroiditis:
  - Painful and tender goiter
  - Transient hyperthyroidism followed by transient hypothyroidism
  - It usually occurs after an upper respiratory tract infection infection
- Treatment:
  - Beta blocker if hyperthyroid symptoms are moderate
  - NSAIDS for the thyroid pain
  - Corticosteroids may be used in severe cases
  - Transient hypothyroidism can be treated with Synthroid

Neoplastic Disease of the Parathyroid Glands

- Multiple Endocrine Neoplasia 1 (MEN1)
- Defect in the gene encoding tumor suppressor menin
    - Parathyroid adenoma
    - Pancreatic tumors
    - Pituitary adenomas
- Autosomal dominant
- Hypercalcemia is found in 95% of cases and is the most predominant symptom.



MEN2A and MEN2B

- MEN2A
  - Parathyroid Adenoma
  - Medullary thyroid cancer
  - Pheochromocytoma

  - Autosomal dominant
  - Defects in the RET proto-oncogene

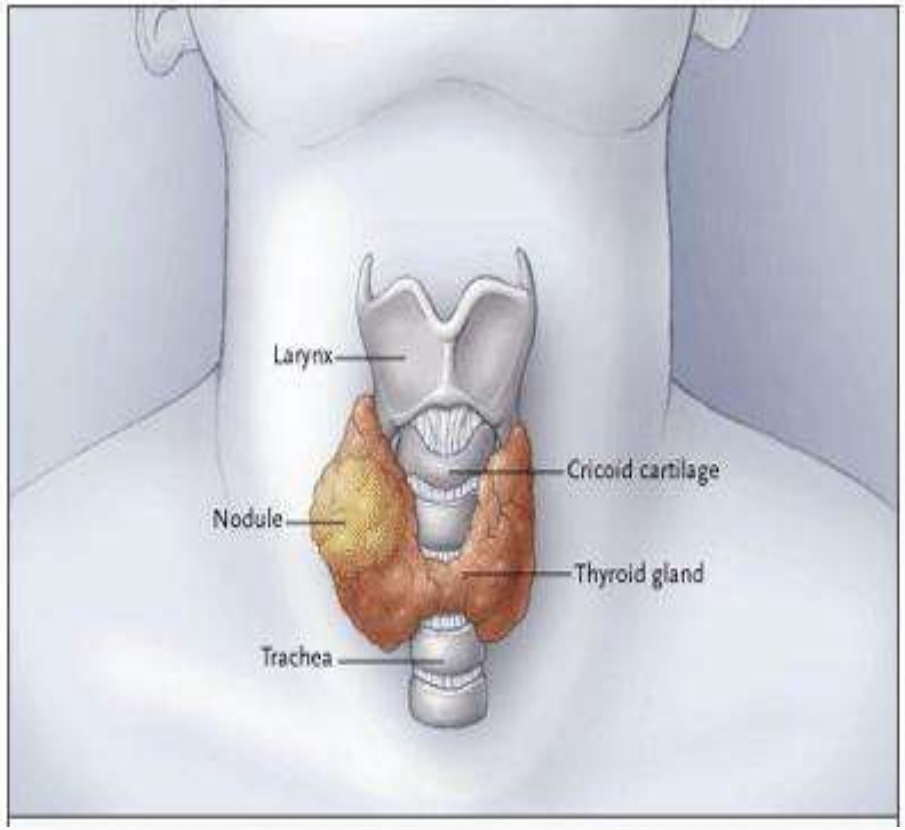
MEN2B

- Medullary thyroid carcinoma
- Pheochromocytomas
- Mucosal Neuromas

- Marfanoid body habitus

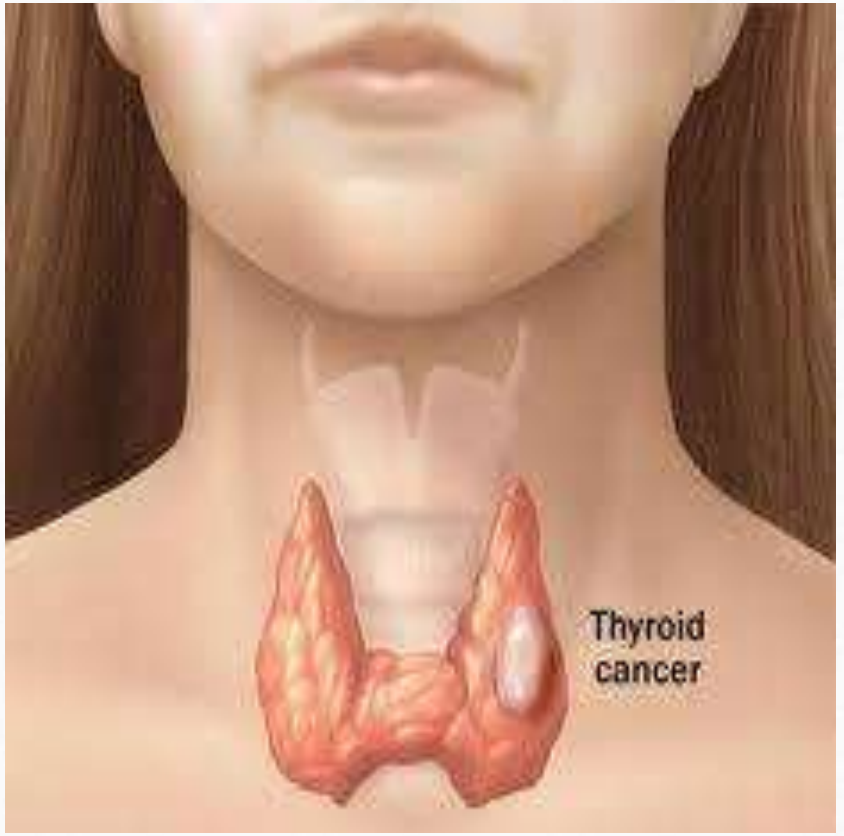
Thyroid Nodules

- --Thyroid nodules are common and the incidence increases with age
- --Most nodules are benign in nature
- --Painless lump in the neck discovered by the physician
- --Nodules <1 cm only require closed follow up.
- --Nodules >1 cm require fine needle aspiration (FNA)
- --Nodules >2 cm should be remove as they can become hyperplastic.



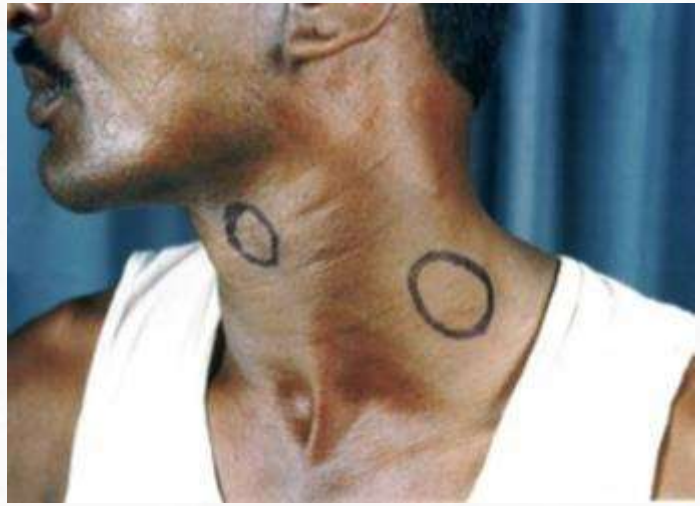
Thyroid Carcinoma

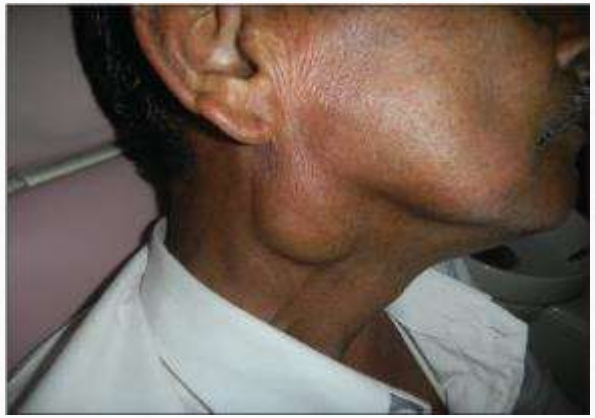
- Risk for carcinomas:
  - <20 years of age with cervical lymphadenopathy
  - History of head or neck radiation
  - Family history of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) Type 2A or 2B
  - Hard fixed fast growing nodule
  - Hoarseness due to invasion of recurrent laryngeal nerve
  - Most people have no symptoms



Papillary Carcinoma

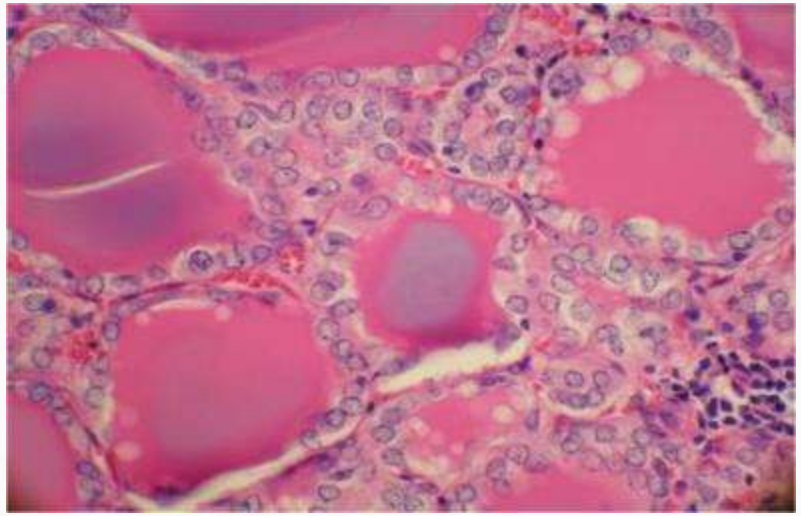
- The most common type of thyroid cancer (80%)
- Slow growing tumor that remains localized for many years.
- Metastasizes first to cervical lymph nodes

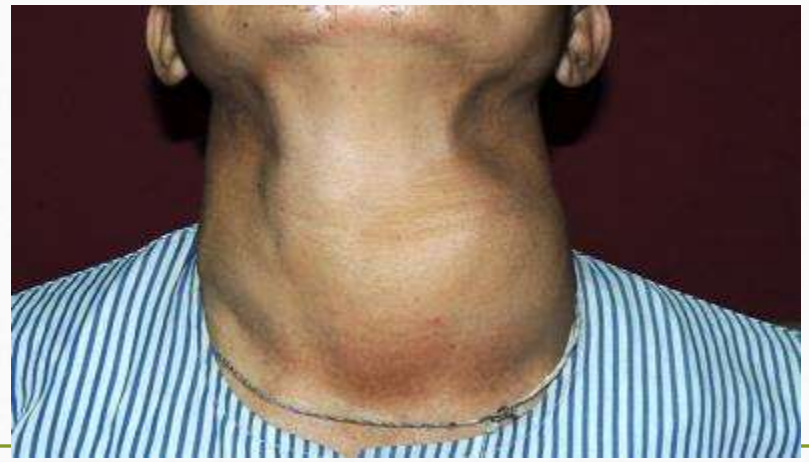




Follicular Carcinoma

- Follicular Carcinoma
  - Accounts for 15% of thyroid tumors
  - Is more aggressive than papillary carcinoma
  - Metastasize early to lungs and bones
- Anaplastic Carcinoma
  - Rare
  - Rapidly progressive thyroid cancer
  - Poor prognosis



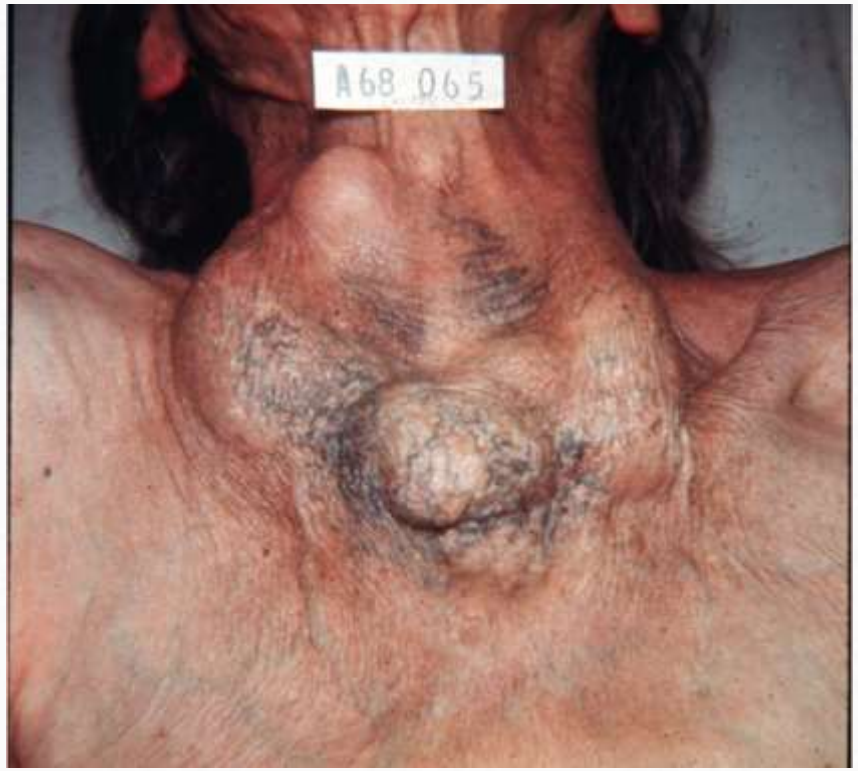


Anaplastic thyroid carcinoma

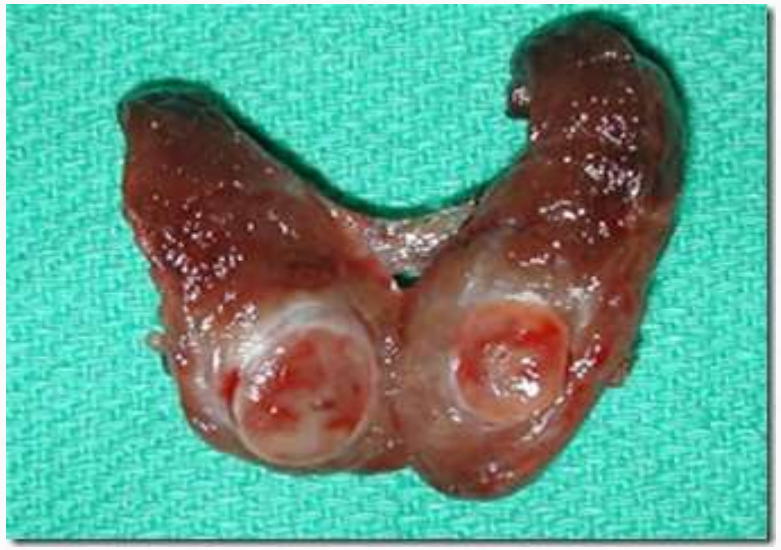
--Rare

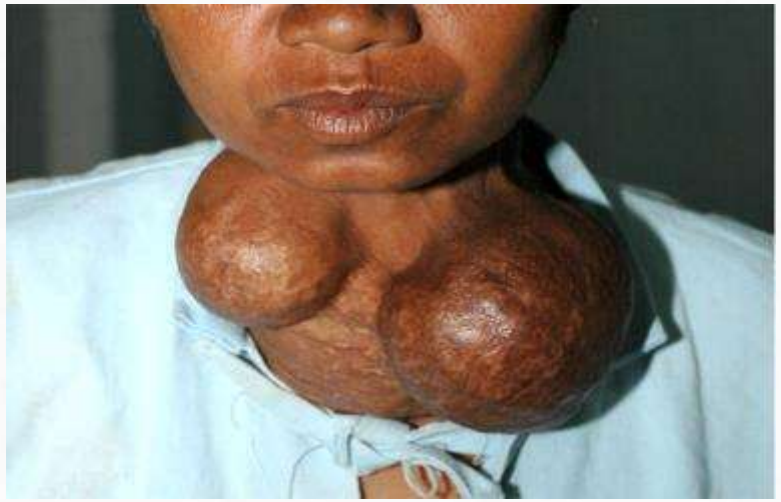
--Rapidly progressive thyroid cancer

--Poor prognosis



- Medullary thyroid carcinoma (MCT)
  - Arises from C cells (parafollicular cells)
  - Secretes plasma calcitonin that is always elevated and is useful for diagnosis
  - MCT is a component of the MEN 2A and 2B





Diagnosis of thyroid carcinoma

- **Most patients are asymptomatic**
- TSH, free T4, T4, T3 = are always normal
- The best diagnostic procedure of choice: Fine needle aspiration (FNA)

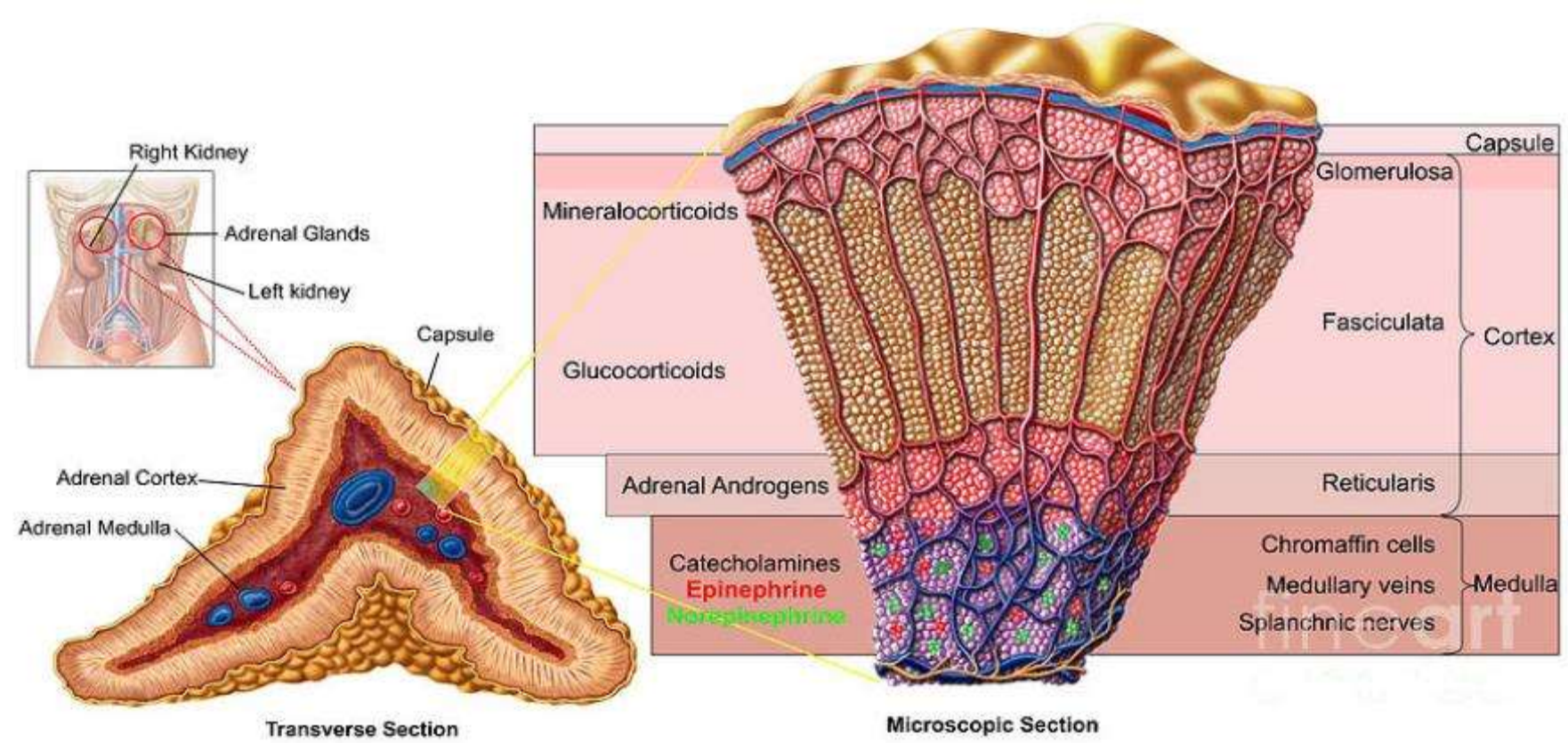
Treatment

- Total Thyroidectomy: initial treatment
- Radioactive Iodine Ablation (1odine 131)
  - Due to high re-occurrence of thyroid cancer, thyroid ablation is performed
- Synthroid or Levothyroxine to treat the hypothyroidism

Life long-monitoring

- Whole body scan are performed yearly until 2 scans are negative.
- Plasma thyroglobulin: a rising thyroglobulin indicates tumor recurrence
- Calcitonin: Rising calcitonin level indicates recurrence of MTC

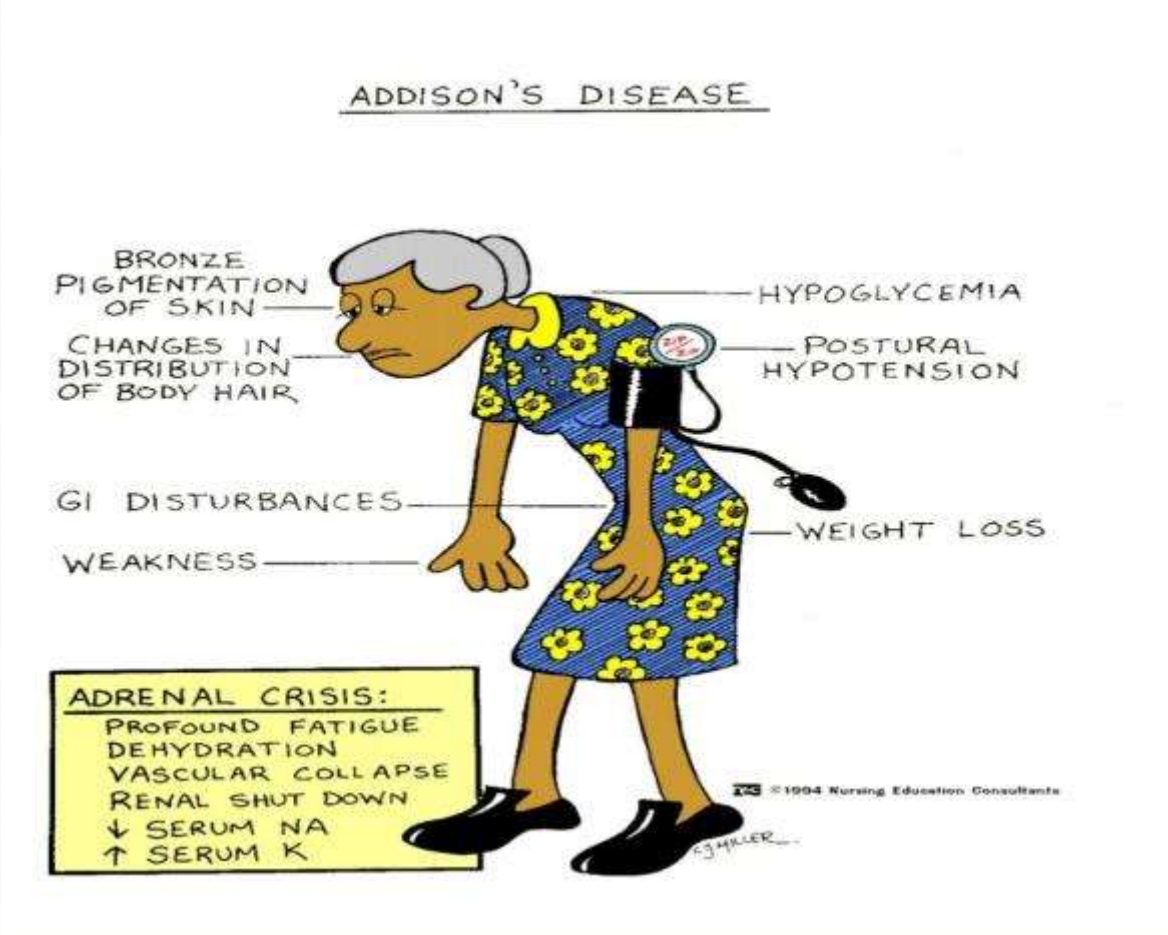
The Adrenal Gland



Addison's Disease

- Rare disorder
- Female to male ratio 2:1
- Diagnosis is difficult as patients can have the disease for a prolong time until a stressor precipitates an adrenal crisis.

Adrenal Crisis



- Electrolytes Abnormalities
  - ↓ sodium
  - ↑ potassium
  - ↓ chloride
  - ↓ glucose
  - ↓ bicarbonate

Diagnostic Testing

- Basal cortisol Measurements:
  - Must be drawn before 9 AM (never in the afternoon)
    - Cortisol >19 mcg/dL rules out adrenal insufficiency (5-23 mcg/dL)
    - Cortisol <3 mcg/dL suspicious for adrenal insufficiency

Adrenal antibodies are detected in 90% of patients with autoimmune adrenal insufficiency:

A) Adrenal Cortex Antibody (ACA)

B) 21-Hydroxylase Antibody (CYP21A2)

The presence of both antibodies make the diagnosis likely up to 99% in most cases.

Corticotropin Stimulation Test (Synthetic ACTH)

- Gold standard to establish diagnosis of adrenal primary adrenal insufficiency:
  - Draw plasma ACTH and cortisol levels
  - Give corticotropin (synthetic ACTH)
    - 250 mcg IV push (adult)
    - 1 mcg IV push (children)
  - Draw plasma cortisol at 30 and 60 minutes post corticotropin push:
    - Cortisol >18 mcg/dL = NO ADRENAL INSUFFICIENCY

Maintenance Therapy

Children

- Hydrocortisone (10-20 mg/m2/day) divided in 2-3 equal doses per day
  - Double the dosage during illness
- Fludrocortisone 0.05 - 0.2 mg once or twice daily. It is titrated base on renin levels and electrolytes

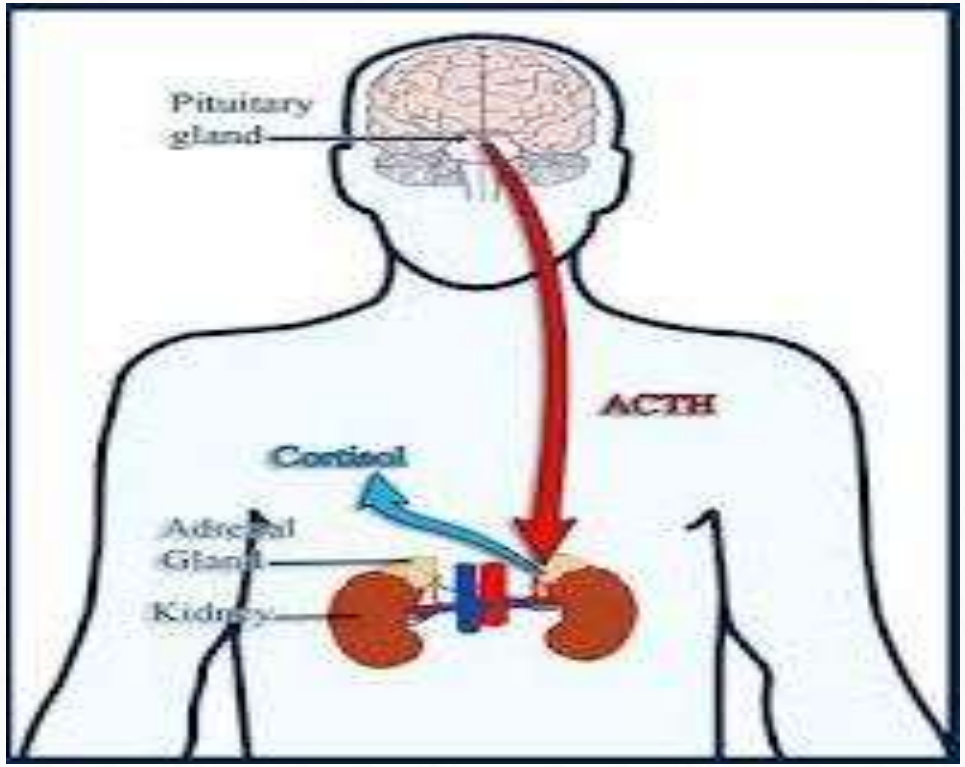
Adults

- Prednisone 4 - 7.5 mg/day
  - Double the dosage during illness
- Fludrocortisone 0.5 - 2 mg once or twice daily.

Cushing Disease

- Excessive ACTH secretion from pituitary tumor resulting in increase cortisol and androgen levels
- Accounts for 80% of cases

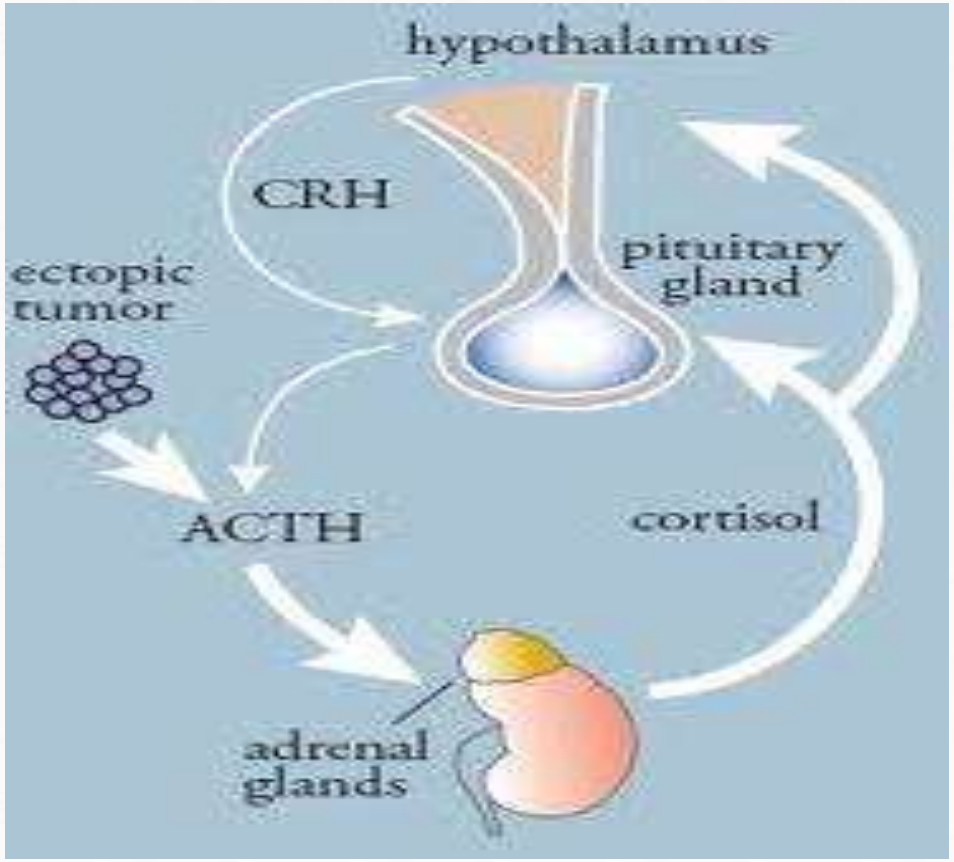
- Elevated ACTH and cortisol
  - **can be suppressed with Dexamethasone**



Ectopic ACTH Hypersecretion

- ACTH secretion from non-pituitary tumor:
  - Bronchial carcinoid
  - Small cell carcinoma
  - Prognosis is poor
- Accounts for 10% of cases

- Elevated ACTH and cortisol
  - **Cannot be suppressed with Dexamethasone**



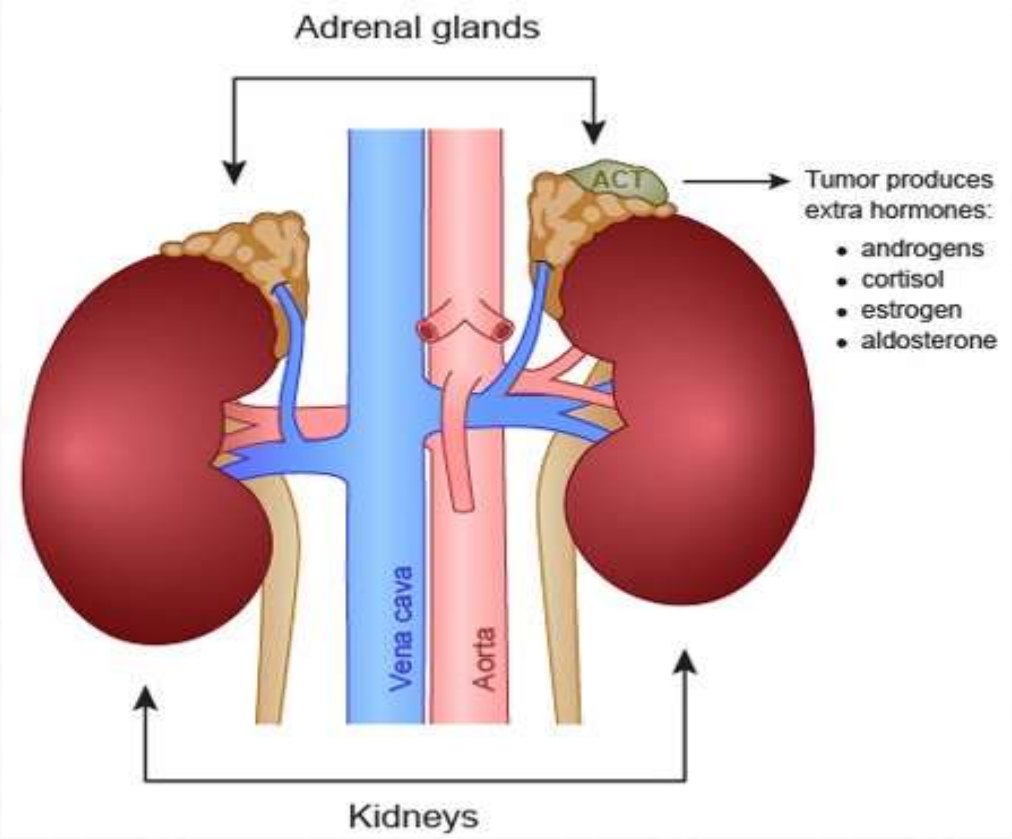
Primary Adrenal Gland Tumors

Adrenal tumors:

- Adenomas: 10% of cases
- Carcinomas: rare

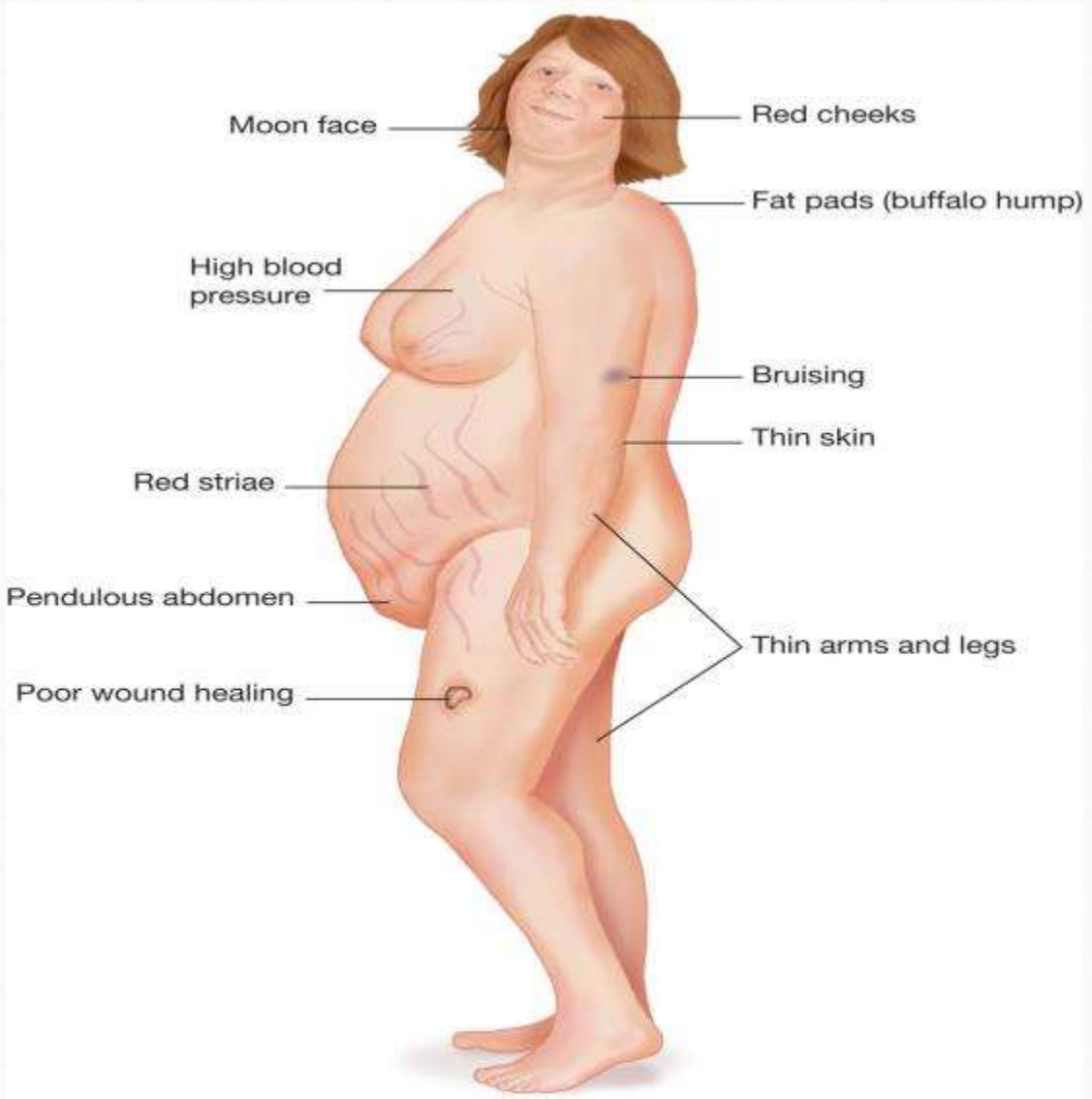
Elevated Cortisol level

Suppressed ACTH level

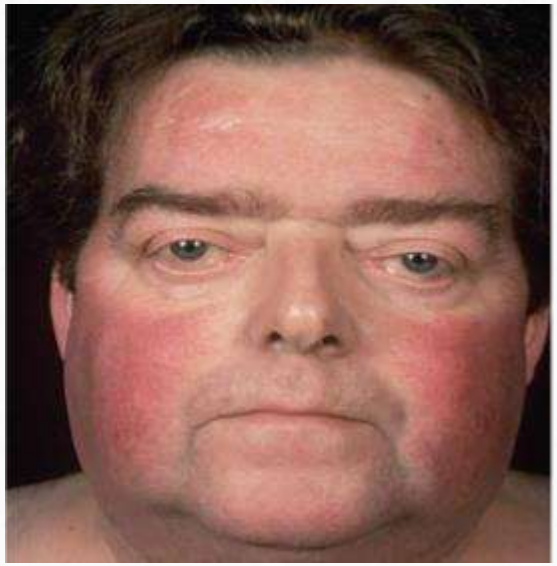


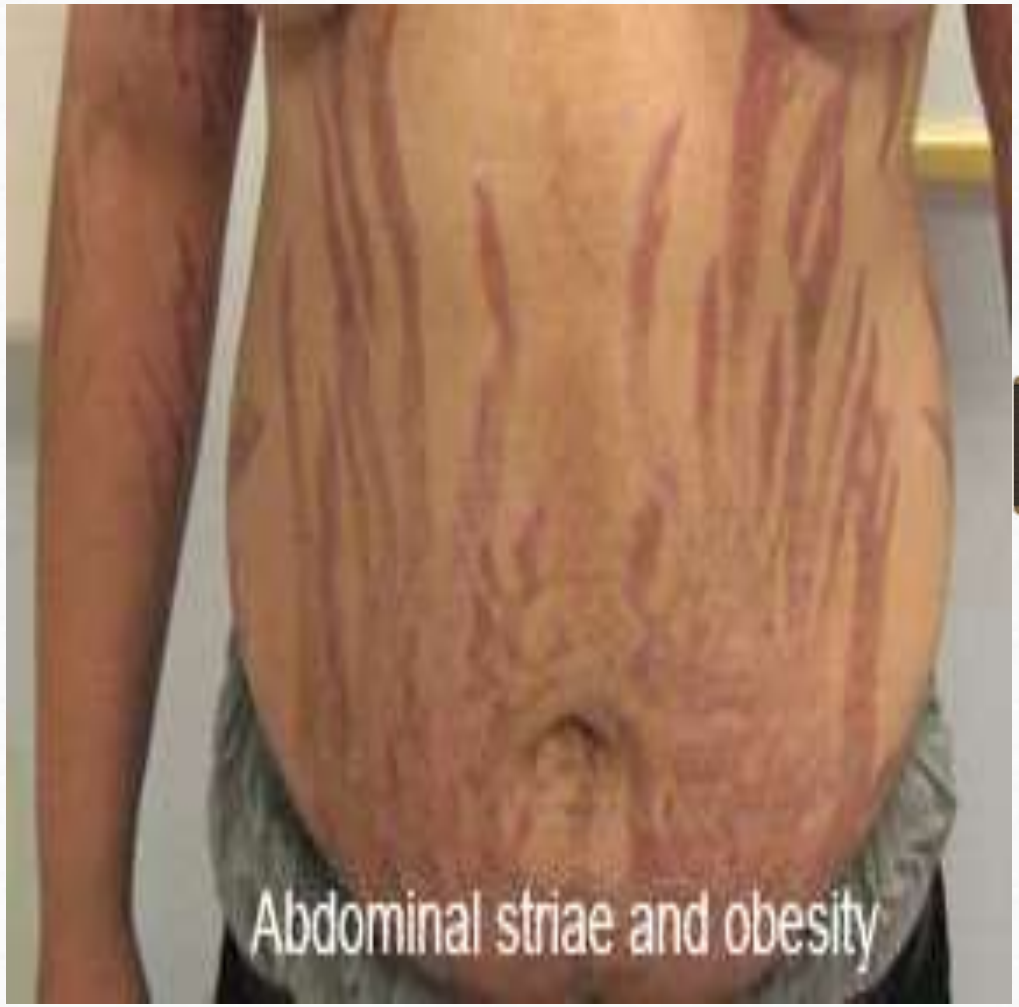
Symptoms and Signs of Cushing's

- Obesity
  - Most common manifestation
  - Central obesity:
    - Neck = posterior fat pad
    - Trunk
    - Abdomen
    - Moon face



- Skin Changes in Cushing's
  - Atrophy of the epidermis
  - Thinning of the skin
  - Facial plethora
  - Red to purple striae
  - Pustular acne





Diagnostic Testing

1)Dexamethasone Suppression Test

- Dexamethasone 1 mg is given at 11 PM
- Cortisol levels are drawn by 8 AM the next day
  - If <1.8 mcg/dL then is normal. NO Cushing!

2) 24 hour urine free Cortisol (≥2 tests)

- >50 ug/24 hours (must be 3-4 times of the normal range

3) Late night salivary test

11 pm salivary radioimmunoassay if greater than 0.15 ug/dL then suspicious for Cushing's

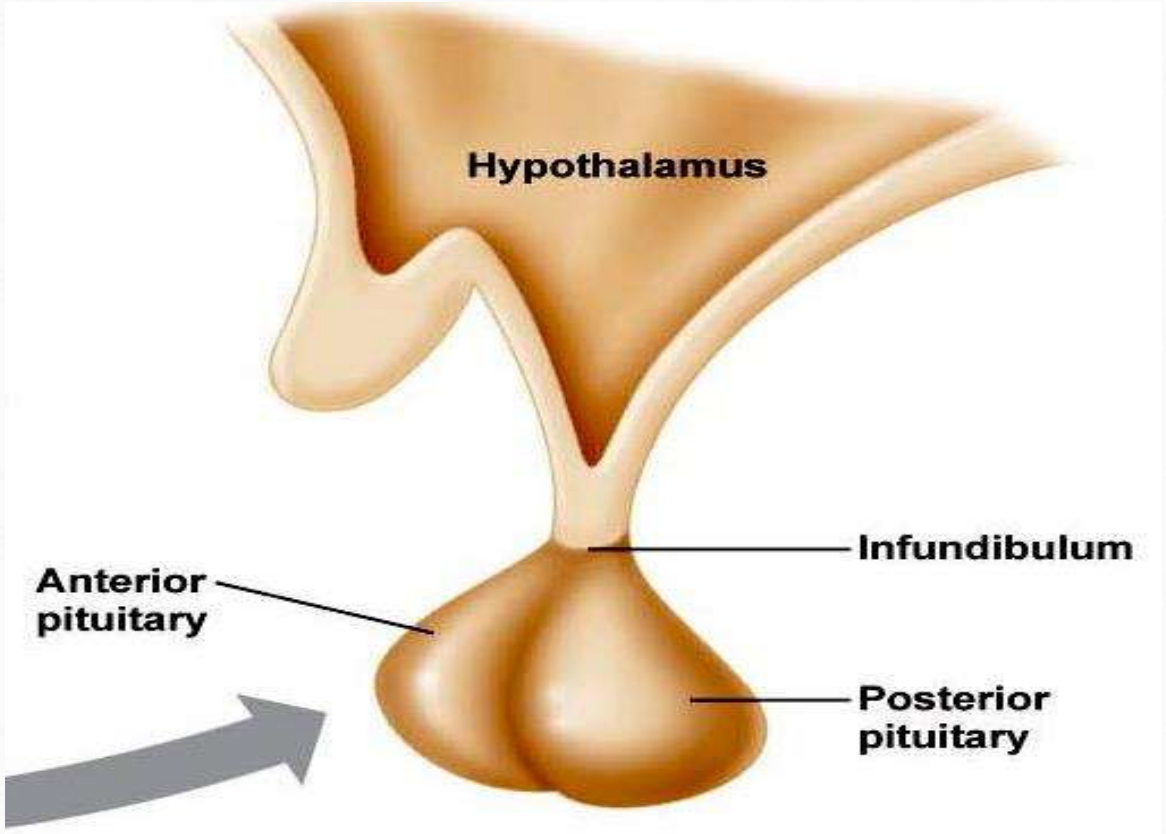
Imaging

- MRI of the Brain to locate pituitary tumor
- MRI or CT scan of adrenal glands to locate tumor
- MRI or CT scan of the chest for ectopic ACTH producing tumor

Treatment

- Pituitary adenoma: Trans sphenoidal surgery
- Adrenal Adenoma: unilateral adrenalectomy
- Adrenal Carcinoma: unilateral adrenalectomy and mitotane therapy.
- Ectopic ACTH producing tumor: Surgery

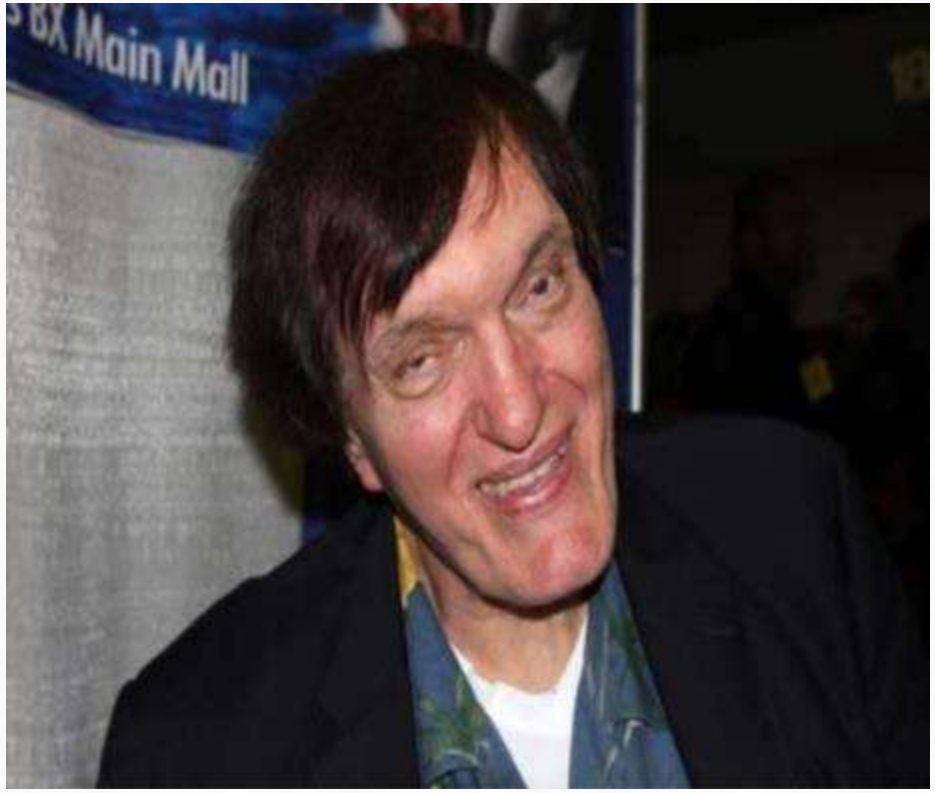
Disorders of the Pituitary Gland



Acromegaly

- Pituitary Adenoma with excess growth hormone production:
    - Post-pubertal phase: Acromegaly
    - Pre-pubertal phase: Gigantism
- Rare disorder: 3 cases per 1 million
- Insidious resulting in a lag time between onset and diagnosis

Acromegaly: Post-pubertal phase



Gigantism: Pre-pubertal phase

Signs and Symptoms

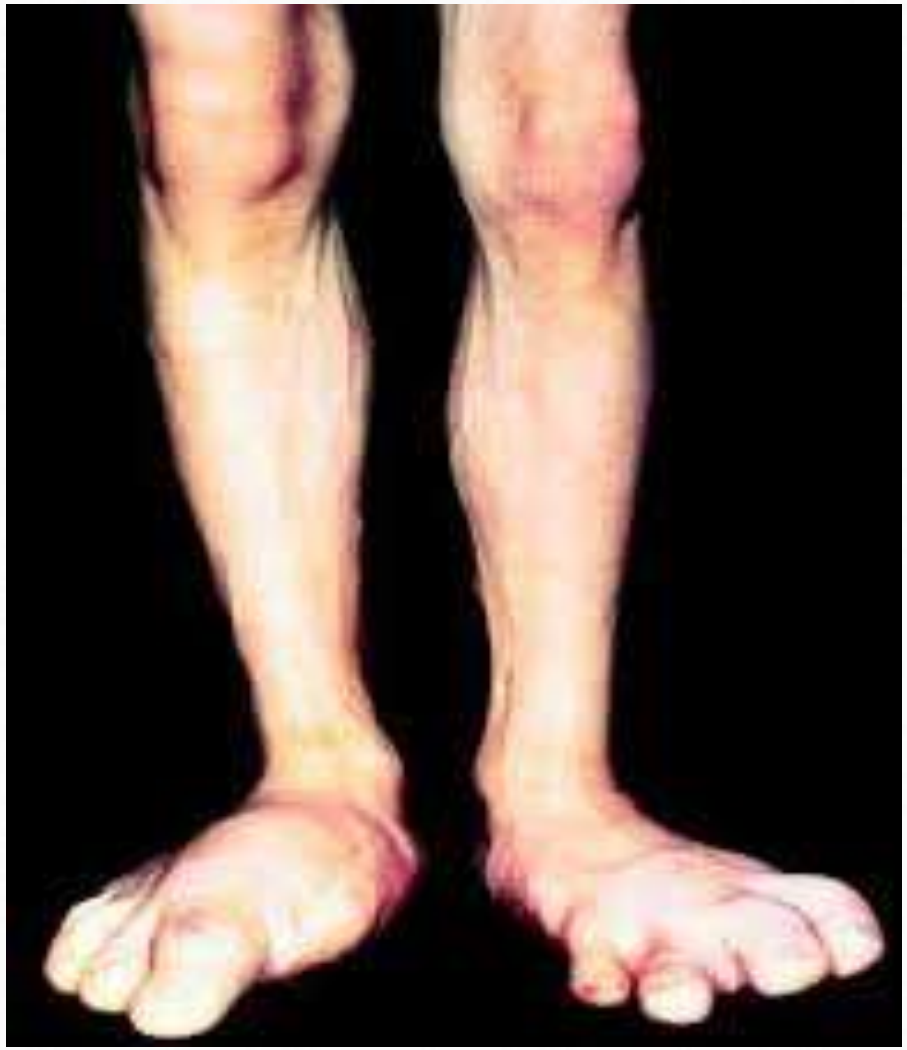
- Increase in hat, ring or shoe size
- Headache is the second most common symptom
- Coarsen facial features:
  - Mandible more prominent: pragmatism and malocclusion
  - Macroglossia
  - Deep coarse voice due to hypertrophy of laryngeal muscles

Signs and Symptoms

Arthralgia and myalgia will be present in 30-70% of patients due to bone overgrowth

Paresthesia related to carpal tunnel syndrome

Visual disturbances



Diagnostic Testing

- IGF-1 and GH (growth hormone) levels
- Oral glucose tolerance test (OGTT)(gold standard)

--Draw glucose and growth hormone level at base line

--Give 75 grams of oral glucose

--Measure glucose and growth hormone every 30 minutes for 2 hours:

If GH level falls to <0.3 mcg/L = no acromegaly

- MRI with and without contrast
- Radiograph of the skull may show enlarged sella and thickened skull
- Echocardiography will show interventricular septum and left ventricular hypertrophy

Medications

- Somatostatin Analogs:
  - Octreotide (Sandostatin) 10 mg SC monthly
  - Lanreotide (Somaline) 60 mg SC monthly
  - Pegvisomant (Somavert) 10 mg SC daily
- Dopamine Agonists:
  - Carbegoline 0.25 - 1.0 mg twice weekly

Surgical Management

- Surgical Management is considered if pharmacological treatment fails.
  - Trans sphenoidal surgery
  - Conventional Radiation Therapy (not preferred)
  - Stereotactic radio-surgery: gamma knife
- Chemotherapy

Dwarfism

- Growth hormone deficiency
  - Most cases are idiopathic
  - Small percentage of the cases are secondary to pituitary neoplasm
    - Craniopharyngioma most common pituitary tumor associated with growth hormone deficiency