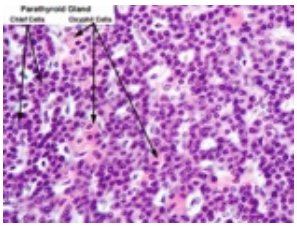
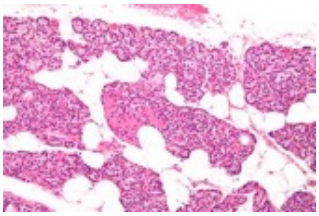
PARATHYROID GLANDS

- Majority of people have 4 parathyroid glands, but ~10% have fewer
- Superior glands arise from 4th pharyngeal pouch, while the inferior glands arise from 3rd pharyngeal pouch



CHIEF CELLS produce parathyroid hormone (PTH); basophilic

OXYPHIL CELLS have eosinophilic cytoplasm that contains numberous mitochondria; function is unknown

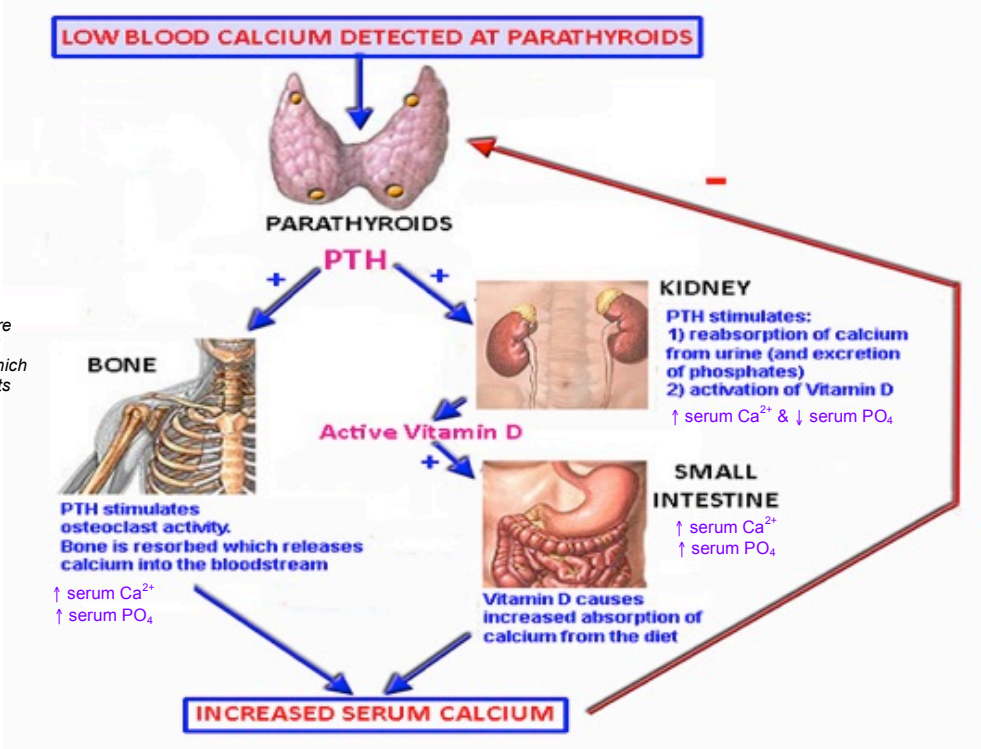


In childhood, there is no or little adipose tissue. Adipose tissue within the gland increases w/ age reaching a plateau of 30% around 30y

PARATHYROID GLANDS: Function

- FUNCTION OF **PTH**: Control Calcium Homeostasis
- Secretion of PTH is regulated by the level of free (ionized) Ca^{2+} in the bloodstream
- ↓ Free Ca^{2+} stimulates secretion of PTH
- PTH acts on surface receptors of target tissues, activating a G protein & ↑ cAMP
- ↑ Free Ca^{2+} inhibits PTH secretion

Note: *PTH receptors are on osteoblasts, so PTH activate osteoblasts, which then activate osteoclasts for bone resorption.*



PARAYTHYROID GLANDS: Pathology

- **Hyperparathyroidism**: ↑ function (↑PTH production) → Hypercalcemia
- **Hypoparathyroidism**: ↓ function (↓PTH production) → Hypocalcemia
- *Parathyroid neoplasms manifest w/ hyperparathyroidism, not mass effect as some thyroid neoplasms*

HYPERCALCEMIA	
HIGH PTH	**LOW PTH**
Hyperparathyroidism (Primary, Secondary, Tertiary) Familial Hypocalciuric Hypercalcemia	Hypercalcemia of *malignancy* Vitamin D Toxicity, Immobilization, Thiazide diuretics, Sarcoidosis

HYPERPARATHYROIDISM: ↑PTH

Primary, Secondary, Tertiary-compensatory hyperplasia, but parathyroid hyperactivity persists after removal of initiating cause

PRIMARY HYPERPARATHYROIDISM: Overproduction PTH By Parathyroid (↑Ca^{2+}, ↓PO_4)

- **Primary Hyperparathyroidism** is the Most Common cause of **ASYMPTOMATIC Hypercalcemia**
- More come in **FEMALES** (4:1); usually **50+ years old**
- **CLINICAL PRESENTATION:** "Painful bones, Renal stones, Abdominal Groans, & Psychic moans"
- **Parathyroid Adenoma is the Most Common cause of Primary Hyperparathyroidism** (85-90%)
  - Other Causes: Sporadic Parathyroid Hyperplasia (9%) & Parathyroid Carcinoma (1%)
- **PATHOGENESIS**
  - Overexpression of **CYCLIN D1** (key regulator of cell cycle) caused by inversions in the Cyclin D1 gene
  - Mutations in **MEN1** gene, a TSG found in 30% of sporadic adenomas
    - *Parathyroid adenomas & hyperplasia are components of MEN Type 1*
- **DIAGNOSIS**: Incidental discovery of Hypercalcemia in 80% of causes

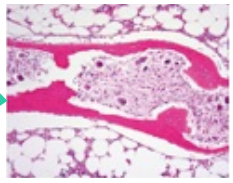
PRIMARY HYPERTHYROIDISM: Symptomatic Vs. Asymptomatic

- Routine assessment of serum Ca^{2+} has made Asymptomatic Hyperparathyroidism much more frequent than Symptomatic Hyperparathyroidism
- **PRIMARY HYPERPARATHYROIDISM** is the Most Common cause of **ASYMPTOMATIC Hypercalcemia**
- **HYPERCALCEMIA OF MALIGNANCY** is the Most Common cause of **SYMPTOMATIC Hypercalcemia**

PRIMARY HYPERPARATHYROIDISM: Clinical Manifestations

BUT Renal Function is Normal!

- BONE LESIONS: *Osteoporosis, Brown Tumors, Osteitis Fibrosa Cystica*
- KIDNEYS: Nephrolithiasis (obstructive uropathy), Nephrocalcinosis (renal parenchymal calcification)
- STOMACH, LUNGS, HEART, BLOOD VESSELS: *Metastatic calcification*
- GI TRACT: *Constipation, Acute pancreatitis*, Gallstones, Peptic ulcers
- CNS: ***Depression, Lethargy, Seizures***
- NEUROMUSCLAR: Weakness & fatigue

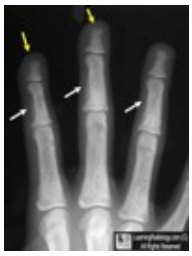


PRIMARY HYPERPARATHYROIDISM – OSTEOPOROSIS

- **Phalanges, Vertebrae, & Proximal Femur** are most affected
- Bone resorption affects cortical bone (subperiosteal & endosteal)
- Medullary bone affected in characteristic fashion known as **Dissecting Osteitis**: *Osteoclasts penetrate into the trabeculae producing a "railroad track" appearance*

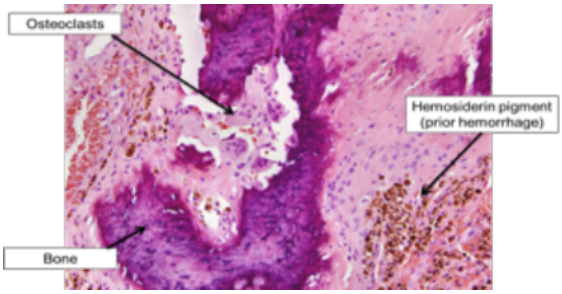
Salt & Pepper Skull

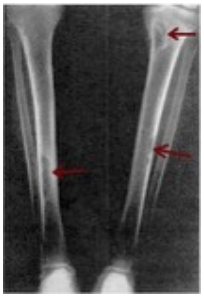
Subperiosteal resorption in phalanges due to ↑ parathyroid activity



PRIMARY HYPERPARATHYROIDISM – BROWN TUMORS

- Bone resorption leads to Recurring Microfractures & Hemorrhages
- Reparative tissue rich in **hemosiderin-laden macrophages**





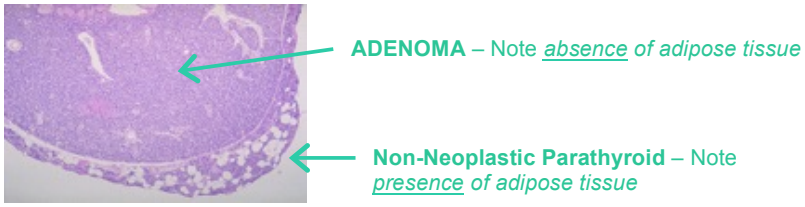
PRIMARY HYPERPARATHYROIDISM – OSTEITIS FIBROSA CYSTICA (von Recklinghausen Disease of Bone)

- The most advanced stage of SEVERE Primary Hyperparathyroidism

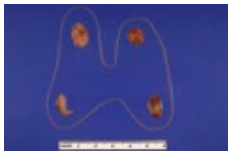
- *One of the causes of bone pain*

1. PARATHYROID ADENOMA: Primary Hyperparathyroidism

- Most common cause of Primary Hyperparathyroidism
- **GROSS:** Well-circumscribed nodule surrounded by compressed normal parenchyma
- **HISTOLOGICAL:** Pattern-less sheets of **chief cells** w/ occasional oxyphil cells

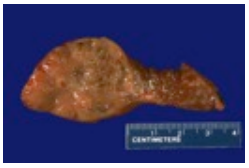


2. PARATHYROID HYPERPLASIA: Primary Hyperparathyroidism



- Involvement of glands may be asymmetrical
- Adipose tissue is markedly reduced
- Hyperplasia is often associated w/ monoclonality, suggesting that hyperplasia & adenoma may be a continuum

3. PARATHYROID CARCINOMA: Primary Hyperparathyroidism



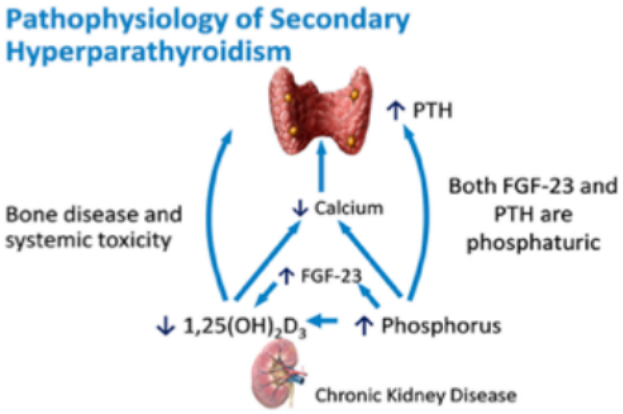
- RARE cause of Primary Hyperparathyroidism (1%)
- May attain large size
- **Invades surrounding neck structures**
- 1/3 recur locally & 1/3 have distant metastases
- 50% 5 year survival

HYPERCALCEMIA OF MALIGNANCY: Symptomatic Primary Hyperparathyroidism

- **Most Common Causes:** Tumors of BREAST, LUNG, head/neck, KIDNEYS, & hematologic malignancies (Multiple Myeloma)
- **TWO MECHANISMS:**
  - Most causes (80%) are due to production of **Calcemic Humoral Substances** by the tumor itself. Most frequent is PTH-related peptide (PTHrP).
    - **PTHrP is the Most Common PARANEOPLASTIC SYNDROME**
  - 20% of cases due to Bone Metastases w/ destruction of bone – *Not a paraneoplastic syndrome*
- **DIAGNOSIS: LOW PTH & HIGH PTHrP**, measured in the blood by radioassay

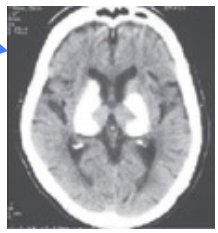
SECONDARY HYPERPARATHYROIDISM: Compensatory Hyperplasia w/ ↓Ca^{2+} + ↑PTH

- Calcium decrease causing an increase in PTH → COMPENSATORY HYPERPLASIA
- Normal levels of serum Ca^{2+} are restored, *at the expense of bone*
- **Most Common Cause of SECONDARY HYPERPARATHYROIDISM: CHRONIC RENAL FAILURE**
  - In renal failure: ↓PO_4 excretion → ↑ serum PO_4 binds free Ca^{2+} → ↓ free Ca^{2+} → ↑PTH secretion
- Other Causes: Steatorrhea, insufficient Ca^{2+} intake, Vitamin D deficiency

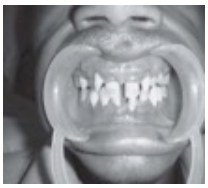


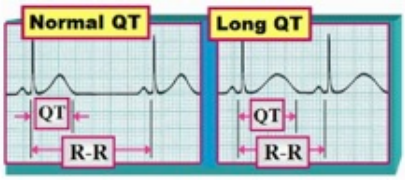
HYPOPARATHYROIDISM: ↓TSH → ↓Ca^{2+}, ↑PO_4

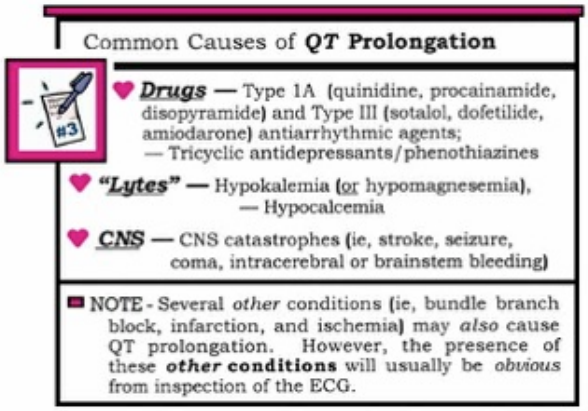
- Uncommon endocrine deficiency characterized by inappropriately low levels of PTH in circulation w/ resultant low serum Ca^{2+} & elevated serum PO_4^{+} levels
- **Most Common Cause of HYPOPARATHYROIDISM: Surgical Removal of Parathyroids**
  - Unintentional removal of all 4 parathyroid glands during thyroidectomy
  - Excision of parathyroids mistaken for lymph nodes during radical neck dissection for malignancy
  - Removal of too much parathyroid tissue when treating Primary Hyperparathyroidism
- **Rare Causes:** Autoimmune, Inherited, Congenital Absence
  - **Autoimmune Polyendocrine Syndrome (APS1)**: Caused by mutations of autoimmune regulator (AIRE) gene; characterized by *chronic candidiasis, hypoparathyroidism, & adrenal insufficiency*
  - **Autosomal Dominant Hypoparathyroidism**: Caused by GOF mutations of the Calcium-sensing receptor (CASR) gene, which leads to ↑sensitivity to serum Ca^{2+} levels
  - **Familial Isolated Hypoparathyroidism**: Caused by AD or AR mutations leading to impaired PTH synthesis or parathyroid development
  - **Congenital Absence** – **DiGeorge Syndrome** *(Chromosome 22 – Loss of 3rd & 4th pharyngeal pouches)*
- **CLINICAL MANIFESTATIONS: Due to HYPOCALCEMIA**
  - **TETANY** due to neuromuscular irritability
    - Perioral numbness
    - Carpopedal spasm
    - Laryngospasm causing hoarseness
    - Generalized seizures
  - **CHVOSTEK SIGN & TROUSSEAU SIGN**
    - **Chvostek Sign –** Tapping on facial nerve causes contraction of muscles of eye, mouth, nose
      - *Ask the patient to relax his facial nerves. Next, stand directly in front of him & tap the facial nerve either just anterior to the earlobe or below the zygomatic arch & the corner of the mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of the hypocalcemia.*
    - **Trousseau Sign** – Occluding circulation to forearm causes carpal spasm that reverses after circulation is restored **(BP CUFF)**
  - Mental Status Changes **–** *Anxiety, emotional instability, depression, hallucinations, psychosis*
  - CALCIFICATIONS of Basal Ganglia + ↑ Intracranial pressure



  - Cataracts
  - Prolongation of QT on ECG
  - Dental abnormalities *when it occurs in children*







- **TREATMENT** w/ Calcium & Vitamin D; *Hormone Replacement Therapy for those who don't respond adequately*

PSEUDOHYPOPARATHYROIDISM

- Hypoparathyroidism due to resistance of target organs to PTH effect: ***End-Organ Resistance***
- Associated w/ *hypocalcemia, hyperphosphatemia, ↑PTH*
- Hereditary cause of end-organ resistance to PTH is often caused by mutations in **GNAS, which encodes the α subunit of the G_s protein**