Parathyroid Glands
- The size of the gland ranges from 2-7 mm (thickness)

- Kidney shaped, soft and brown-rust colored

- Composed of chief cells, oxyphil cells, fibrous stroma and variable amounts of fat
Embryology

- Endoderm of pharyngeal pouches III and IV
- Inferior parathyroid glands arise from pouch III
  - Migrate down with the thymus
  - Usually located at inferior pole of the thyroid
  - Associated with most variability in location
- Superior parathyroid glands arise from pouch IV
  - Located just above the intersection of recurrent laryngeal nerve and the inferior thyroid artery
- Usually 4 glands, supernumerary glands in 15%
Embryology

- Longer migration path → may be localized along the entire line of migration from the angle of the jaw to the pericardium:
  - < glands are often embedded within the thymus or somewhere in the mediastinum
  - DiGeorge syndrome may have no parathyroids
- pair travel a shorter distance → more constant location
Anatomy

The superior parathyroid glands are most commonly found about the middle third of the thyroid lobe, at the level of the cricothyroid junction, and near the point where the recurrent laryngeal nerve passes beneath the inferior pharyngeal constrictor to enter the larynx.
Anatomy

The inferior glands are usually found near the lower pole of the thyroid lobe or below the lobe in the thyro-thymic ligament. They commonly lie below the inferior thyroid artery and anterior to the recurrent laryngeal nerve.
**Ectopic Locations**

**Superior parathyroid**
- Can be located inferior to inferior glands
- Between aortopulmonary window and base of skull

**Inferior parathyroid**
- As low as the aortic notch
- 2X likely to have an adenoma than superior
- Common ectopic site is thymus
• **Arterial supply:**
  inferior thyroid artery (superior thyroid, throidea ima)

• **Venous drainage:**
  inferior, middle, superior thyroid veins

• **Adult parathyroid gland**
  50% parenchyma 50% fat

• **Cell types:**
  chief cells (water clear cells), oxyphil cells
Histology

- 50/50 parenchymal cells, stromal fat
- Chief cells – secrete PTH
- Waterclear cells
- Oxyphil cells
Microscopy (1)

- **Chief** cells and **oxyphil** cells:
  - Chief cells secrete PTH (secretory granules)
  - Clear cells are chief cells rich in glycogen
  - Oxyphil cells (appear after puberty) show abundant pink cytoplasm (mitochondria)

- Fibrovascular stroma and fat lobules

- Fat content varies depending on age (sparse in infant and children) and on functional state of the glands

- Mass of functioning chief cells remains relatively constant once growth stops
Microscopy (2)

- Polyhedral cells

- Pale eosinophilic to amphophilic cytoplasm:
  - Membrane bound secretory granules (PTH)
  - Glycogen granules
  - Fat droplets
Parathyroid hormone (PTH) secretion

- PTH gene is located in chromosome 11
- PTH is synthesized as a 110 amino acid polypeptide called pre-pro-PTH
- It is cleaved to pro-PTH (90 amino acids) and then PTH (84 amino acids)
- PTH is the major storage, secreted and biologically active form of the hormone. Ca regulates synthesis, release and degradation of PTH
PHYSIOLOGY

• Parathyroid Hormone (PTH)
  – Secreted by the Chief cells
  – Levels are inversely controlled by $[\text{Ca}^{2+}]$

• Effects:
  – Tubular reabsorption of $\text{Ca}^{2+}$
  – Osteoclastic resorption of bone
  – Intestinal absorption of $\text{Ca}^{2+}$
  – Synthesis of 1-25DHCC (active Vit. D)
  – Excretion of phosphate
Parathyroid Hormone

- secreted by chief cells
- Release of PTH
  
  Increased by: low serum calcium
  
  Decreased by: high serum calcium, low magnesium, 1,25 dihydroxy vitamin D

vitamin D3 $\rightarrow$ 25-OH vitamin D $\rightarrow$ 1,25 OH$_2$ vitamin D

skin $\rightarrow$ liver $\rightarrow$ kidney
Figure 1. The Parathyroid Axis.
The synthesis of parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHRP) is shown on the left, and their target sites of action are shown on the right. Both act by means of the same receptor (also termed the type 1 PTH receptor). Negative feedback of 1,25-dihydroxyvitamin D is not shown. See the text for further descriptions. An excess or deficiency of parathyroid hormone may be treated either at the level of parathyroid hormone release (and the parathyroid hormone receptors) or at selected sites distal to the parathyroid hormone receptors. Blue arrows indicate extracellular calcium flow.
Parathyroid Hormone

- Type I PTH receptors present in bone, kidney and intestine

**Bone**
- + osteoclasts - osteoblasts
- increased bone resorption
- calcium and phosphorus release

**Kidney**
- increased calcium resorption
- increased phosphorus excretion
- increased conversion of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D

**Intestines** (indirect effect through vitamin D)
- increased calcium absorption
Once secreted, PTH is rapidly taken up by the liver and kidney (PTH cleaved into amino and carboxyl fragment) and cleared by the kidney.

Half life of PTH is 2-4 minutes.

The biologic activity of PTH resides in its amino terminus.

The effects of PTH are initiated by binding of PTH to PTH receptors in the target tissues (type 1).

Type 2 receptors have been found in brain and intestines (function unknown).
Calcium-PTH interactions

The PTH response to hypocalcemia

- Seconds to minutes- exocytosis of PTH
- Minutes to 1 hour- reduction in intracellular PTH degraded
- Hours to days- increase in PTH gene expression
- Days to weeks- proliferation of parathyroid cells
Important that serum ionized calcium concentration be maintained within a very narrow range

**PTH and calcitriol** are the major hormones modulating calcium and phosphate homeostasis

**Increase in serum ionized calcium** leads to calcium receptor complex acting via one or more guanine nucleotide binding protein and second messengers leading to inhibition of PTH

**Decreased serum ionized calcium** leads to deactivation of receptors, which leads to stimulation of PTH
Biological effects of PTH

1. Skeletal actions of PTH

- PTH acts on bone to mobilize Calcium from readily available skeletal stores (immediate effect)
- Later it stimulates Calcium and phosphate release by bone resorption
2. Renal actions of PTH

- PTH acts on distal tubules to stimulate calcium absorption
- It inhibits proximal resorption of phosphorus
3. Synthesis of calcitriol (1,25 dihydroxyvitamin D)

- Stimulates the synthesis of 1-alpha hydroxylase in proximal tubules leading to conversion of calcidiol to calcitriol

4. Intestines

- Indirect effect of PTH
- Produces calcitriol which leads to ↑ intestinal absorption of calcium and phosphorus
Calcium Regulation

- 99% of body calcium in skeleton
- 40% bound to protein, 13% complexed with anions, 47% free ionized
- PTH: Increased Ca, Decreased PO4, Increased Vitamin D
- Vitamin D: Increased Ca, Increased PO4, Decreased PTH (slow)
- Kidney, Bones, GI Tract
HORMONAL REGULATION OF CALCIUM AND PHOSPHATE HOMEOSTASIS

- PTH
- Vitamin D
- Calcitonin
TARGET ORGANS FOR PTH

• Bone
• Kidney
ACTIONS OF PTH ON BONE

• Rapid Phase (1-3hrs.) - osteocystic osteolysis
• Slow Phase (12-24hrs.) – osteoclastic osteolysis
Normal Bone Metabolic Unit
**PTH STIMULATED OSTEOCYTIC OSTEOLYSIS**

- Transfer of calcium from canalicular fluid into osteocytes
- Transfer of calcium via osteocyte syncytial processes to extracellular fluid
- Replenishment of canalicular fluid calcium from partially mineralized bone
- Phosphate is not mobilized
- Bone mass does not change
PTH STIMULATED OSTEOCLASTIC OSTEOLYSIS

- Increased osteoclastic size and number

- Increased osteoclastic collagenase and lysosomal enzyme activity

- Increased osteoclastic acid phosphatase, carbonic anhydrase, lactic acid and citric acid concentrations

- Increased bone resorption

- Mobilization of calcium, magnesium and inorganic phosphate
PTH ACTION ON BONE FORMATION

- Increased osteoblastic number
- Increased collagen synthesis
- Increased alkaline phosphatase activity
- Increased local growth factors: IGF and transforming factors
PTH ACTIONS ON KIDNEY

- Increased calcium and magnesium reabsorption from ascending loop and distal tubule
- Increased chloride reabsorption from proximal tubule
- Decreased phosphate, sodium and bicarbonate reabsorption from the proximal tubule
- Increased proximal tubule 1-alpha-hydroxalase activity
↓ Plasma [Ca\(^{2+}\)]

↑ PTH secretion

**BONE**
- ↑ Bone resorption

**KIDNEY**
- ↓ Phosphate reabsorption (phosphaturia)
- ↑ Ca\(^{2+}\) reabsorption
- ↑ Urinary cAMP

**INTESTINE**
- ↑ Ca\(^{2+}\) absorption (indirect via 1,25-dihydroxycholecalciferol)

↑ Plasma [Ca\(^{2+}\)] toward normal
ACTIONS OF VITAMIN D ON THE SMALL INTESTINE

- **Rapid phase (1-6hrs)** - increased calcium absorption via increased Na/Ca exchange activity
- **Slow phase (48-96hrs)** - increased calcium absorption via increased synthesis of calcium binding proteins (calbindins)
ACTIONS OF VITAMIN D ON BONE RESORPTION

- Increased osteocytic osteolysis
- Increased osteoclastic number and activity
ACTIONS OF VITAMIN D ON BONE FORMATION

- Increased osteoblastic activity via increased fibronectin and osteocalcin production
- Increased alkaline phosphatase activity
CALCITONIN

- Polypeptide hormone
- Synthesized and secreted by the parafollicular C-cells of the thyroid gland
ACTIONS OF CALCITONIN ON BONE

- Decreased osteoclastic number
- Decreased osteoclastic activity
- Actions are proportional to baseline rate of bone turnover
Pathology

- Anatomical (morphological) changes

- Functional changes:
  - Hyperparathyroidism
  - Hypoparathyroidism
Anatomical Changes

- Hereditary and developmental disorders
- Parathyroid hyperplasia
- Parathyroid adenoma
- Parathyroid carcinoma
Hereditary and Developmental Disorders

- Developmental disorders of the third and fourth branchial pouches, often the results of genetic anomalies
- Cysts and hamartomas
- Some forms of immune disorders:
  - DiGeorge’s syndrome
  - Autoimmune polyglandular syndrome
- Unresponsiveness to PTH (pseudohypoparathyroidism)
- Associated with hypoparathyroidism
Hypoparathyroidism

- Primary (congenital)
- Secondary (acquired)
Primary Hypoparathyroidism

- DiGeorge’s syndrome and velocardiofacial syndrome – agenesis
- Pseudohypoparathyroidism – peripheral resistance to PTH
Pseudohypoparathyroidism

- Hereditary conditions with hypocalcemia due to insensitivity to PTH:
  - Mutation in 20q → decreased activity of $G_s$ → abnormal c-AMP in hormone receptor interaction
  - Some patients have a normal $G_s$ activity

- Characteristic phenotype of Albright hereditary osteodystrophy:
  - short stature, obesity
  - mental retardation
  - subcutaneous calcification
Secondary Hypoparathyroidism

- Usually iatrogenic from inadvertent removal of glands or disruption of blood supply during thyroid, parathyroid, or carotid surgery
- Idiopathic
  - Usually associated with other autoimmune disorders (primary adrenal insufficiency, Hashimoto’s, pernicious anemia)
Secondary Hypoparathyroidism

- Metastatic carcinoma
- Infiltrative disorders (sarcoidosis, Wilson’s, hemochromatosis)
- Hypo/hypermagnesemia
- Drugs: chemotherapy, cimetidine
- Sepsis, pancreatitis, burns
Clinical Features

- PTH deficiency leads to hypocalcemia
- Effects depend on severity and rate of drop
- Neuromuscular features:
  - Paresthesias (perioral, fingertips)
  - Muscle weakness and cramps, fasciculations
  - Tetany (Chvostek’s and Trousseau’s signs)
Chvostek’s sign

- Elicited by tapping over facial nerve causing twitching of ipsilateral facial muscles
Trousseau’s sign

- Carpal spasm in response to inflation of BP cuff to 20 mm Hg above SBP for 3 min
Figure 17–16. Position of fingers in carpal spasm due to hypocalcemic tetany. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 16th ed. Appleton & Lange, 1993.)
Clinical Features

- CNS manifestations
  - Depression
  - Irritability
  - Confusion
  - Focal or generalized seizures
- CVS
  - Decreased myocardial contractility
Clinical Features

- Bradycardia
- Hypotension
- CHF
- CVS features seen particularly in patients with underlying cardiac disease, or those on digoxin or diuretics
- ECG: prolonged QT
- Laryngeal or bronchospasm (rare)
Differential for Hypocalcemia

- **Vitamin D Deficiency**
  - Congenital rickets
  - Malnutrition
  - Malabsorption
  - Liver disease
  - Renal disease
    - Acute on chronic RF
    - Nephrotic syndrome
  - Hypomagnesemia
  - Sepsis
  - Anticonvulsants (phenytoin, primidone)

- **Pseudohypoparathyroidism**
  - PTH resistance

- **Ca Chelation**
  - Hyperphosphatemia
  - Citrate
  - Free fatty acids
  - Alkalosis
  - Fluoride Poisoning
<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Confusion, Weakness, Mental retardation, Behavioral changes</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Paresthesias, Psychosis, Seizures, Carpopedal spasms, Chvostek’s and Trousseau’s signs, Depression, Muscle cramping, Parkinsonism, Irritability, Basal ganglia calcifications</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Prolonged Q–T interval, T wave changes, Congestive heart failure</td>
</tr>
<tr>
<td>Ocular</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Dental</td>
<td>Enamel hypoplasia of teeth, Defective root formation, Failure of adult teeth to erupt</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Laryngospasm, Bronchospasm, Stridor</td>
</tr>
</tbody>
</table>
Investigation

- PTH
- Phosphorus
- Total serum Ca
- Ionized Ca is physiologically active
  - 0.1 increase in pH increases iCa by 3-8%
  - 10 g/L decrease in albumin increases iCa by 0.2
Differential diagnosis of laboratory evaluation of hypocalcemia

<table>
<thead>
<tr>
<th></th>
<th>Ca</th>
<th>PO₄</th>
<th>PTH</th>
<th>25-Vit D</th>
<th>Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoparathyroidism</strong></td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Pseudohypoparathyroidism</strong></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↓ N</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td>↓</td>
<td></td>
<td>↑</td>
<td>↓</td>
<td>↓ N</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↓ N</td>
</tr>
</tbody>
</table>
Treatment

- Symptomatic:
  - Parenteral Ca
    - 10% CaCl2: 10 cc ampule contains 360 mg of elemental Ca
    - 10% Ca gluconate: 10 cc ampule contains 93 mg of elemental Ca
  - Recommended dose: 100-300 mg of elemental Ca over 10-20 min followed by an infusion of 0.5-2 mg/kg/h
Treatment

- Side effects:
  - Nausea
  - Vomiting
  - Flushing
  - Hypertension
  - Bradycardia, heart block (patients should be monitored)
Treatment

- Asymptomatic
  - Oral Ca supplementation
    - 1-4 g/day in divided doses
  - If patient has concurrent hypomagnesemia, Ca replacement alone will not correct hypocalcemia unless Mg is also replaced (2-4 g IV for symptomatic patients)
Hypoparathyroidism: Treatment

- Parathyroid hormones
- Parathyroid Auto graft
- Calcitrol (One alpha)
Hypercalcemia

I. Parathyroid-related
   - Primary hyperparathyroidism
   - Lithium therapy
   - Familial hypocalciuric hypercalcemia

II. Malignancy-related
   - Solid tumor with metastases (breast)
   - Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
   - Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

III. Vitamin D-related
   - Vitamin D intoxication
   - $\uparrow 1,25(\text{OH})_2\text{D}$; sarcoidosis and other granulomatous diseases
   - Idiopathic hypercalcemia of infancy

IV. Associated with high bone turnover
   - Hyperthyroidism
   - Immobilization
   - Thiazides
   - Vitamin A intoxication

V. Associated with renal failure
   - Severe secondary hyperparathyroidism
   - Aluminum intoxication
   - Milk-alkali syndrome

**Primary hyperparathyroidism and cancer account for 90% of cases of hypercalcemia**
Primary/Secondary/Tertiary Hyperparathyroidism

- **Primary**
  - **Adenoma** 90%
  - Hyperplasia 10%
  - Carcinoma < 0.1%

- **Secondary**
  - PTH appropriate to low Ca 2+
  - Chronic Renal Failure
  - Vitamin D Deficiency
  - Pseudohypoparathyroidism

- **Tertiary**
  - Continued excess PTH secretion following prolonged secondary hyperparathyroidism.
    (MC)
Hereditary Factors

- **MEN1** - Multiple endocrine neoplasia type 1 (previously Wermer syndrome); tumors of parathyroid, pituitary, and pancreas
- **MEN2A** - Multiple endocrine neoplasia type 2A (previously Sipple syndrome); medullary carcinoma of the thyroid, adrenal pheochromocytoma, and parathyroid tumors
- **HPT-JT** - Hyperparathyroidism, jaw tumor syndrome
- **FIHPT** - Familial isolated hyperparathyroidism
- **ADMH** - Autosomal dominant mild hyperparathyroidism or familial hypercalcemia with hypercalcuria
- **FHH** - Familial hypocalciuric hypercalcemia
- **NSHPT** - Neonatal severe hyperparathyroidism
Hyperparathyroidism

- **Primary Hyperparathyroidism**
  - Normal feedback of Ca disturbed, causing increased production of PTH

- **Secondary Hyperparathyroidism**
  - Defect in mineral homeostasis leading to a compensatory increase in parathyroid gland function

- **Tertiary Hyperparathyroidism**
  - After prolonged compensatory stimulation, hyperplastic gland develops autonomous function
Parathyroid Hyperplasia (PH)

- Commonly *chief cells* are hyperplastic.
- Primary *clear cell* hyperplasia, very rare.
- By definition all four glands are involved (as opposed to adenoma which usually involves one gland).
- Always associated with *hyperparathyroidism* (↑ serum levels of PTH).
- Can be primary or secondary.
Primary and Secondary PH

- **Stimulus for cellular proliferation in primary PH** still is not well characterized:
  - most cases are sporadic and monoclonal
  - 1/3 of cases are seen in patients with **MEN syndromes**
    - types I (germ-line mutation in MEN-1 gene)
    - type IIa (germ line mutation in RET protooncogene)

- **Most common cause of secondary PH** is **chronic renal failure**:
  - ↓ phosphate excretion ⇒ hyperphosphatemia ⇒ ↓ serum calcium (parathyroid stimulation)
  - loss of renal substance ⇒ ↓ α-1-hydroxylase (necessary for active vitamin-D synthesis) ⇒ ↓ intestinal absorption of Ca^{++} (parathyroid stimulation)
Parathyroid Adenoma

- Accounts for 80% of all cases of primary hyperparathyroidism
- Can be:
  - sporadic (rearrangement and over-expression of \textit{cyclin D1}, a proto-oncogen identified on chromosome 11), or
  - associated with MEN-1 (mutation in the \textit{MEN-1} gene, located also on chromosome 11)
- 75% are seen in the lower glands
- With a functioning tumor, the other three glands tend to be atrophic
Gross Features of PA

- Well circumscribed, encapsulated
- 1-3cm
- Reddish-brown
- Hemorrhage and cystic changes are occasionally noted
Parathyroid Adenoma: inferior rim of normal parathyroid tissue admixed with adipose tissue cells
Microscopy (PA)

- Sheets and trabeculae of neoplastic chief cells:
  - Occasionally clear and oxyphil cells may be seen
  - Bizarre, multinucleated cells and other atypical nuclear and cytoplasmic features also may be present
- Richly vascular stroma
- No fat
A rim of normal parathyroid tissue is usually evident outside the capsule (help to distinguish an adenoma from hyperplasia):
On occasion, the neoplastic cells are arranged in *pseudorosette* around blood vessels or as follicles containing an eosinophilic, colloid-like material resembling thyroid tissue. Might need some type of IHC staining (PTH)
Parathyroid Carcinoma (PC)

- < than 5% of all cases of primary hyperparathyroidism
- As opposed to other endocrine carcinomas, PC is usually a functioning tumor
- Like adenomas, some PC also show over expression of *cyclin D1*
- PC are usually larger than adenomas
Pathology

- **Grossly:**
  - lobulated, firm, tan
  - unencapsulated mass that is often adherent to surrounding structures

- **Microscopy:**
  - trabecular pattern
  - mitotic activity
  - Cellular atypia less conspicuous than seen in adenomas (Dx depend on invasion or metastasis)

- Recurrence is common

- Cause of death is most often hyper-parathyroidism rather than carcinomatosis
Primary Hyperparathyroidism

- One of the most common endocrine disorders
- An important cause of hypercalcemia (over production of PTH)

- Most affected persons are asymptomatic (detected on routine laboratory testing)
- When symptomatic: skeletal system, kidneys, nervous system, GI tract are affected
Primary Hyperparathyroidism

Epidemiology

- 25/100,000
- 50,000 new cases yearly
- F > M
- Incidence increases w/ age
- Most in > 50 years old
Etiology

- Unknown cause
- Single gland adenomatous disease
- Multiglandular disease – exogenous stimulus
- Overexpression of PRAD1 oncogene – controls cell cycle
- Ionizing radiation exposure
Hypercalcemia - DDx

- Hyperparathyroidism (most common)
- Malignancy (most common in hospitalized)
  - Lytic metastases to bone
  - PTHrP producer
- Sarcoidosis / granulomatous disease
- Vit D intoxication
- Thiazides
- Hyperthyroidism
- Familial hypocalciuric hypercalcemia
Signs / Symptoms

- Asymptomatic (mild, < 2.99)
- “Bones, stones, abdominal groans, psychic moans”

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bones</td>
<td>Bone pain, #’s, arthralgia</td>
</tr>
<tr>
<td>Renal</td>
<td>Stones, polyuria</td>
</tr>
<tr>
<td>G.I.</td>
<td>Pain, duodenal ulcer, pancreatitis</td>
</tr>
<tr>
<td>Neuro.</td>
<td>Depression, apathy</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Hypertension, heart block</td>
</tr>
</tbody>
</table>
Renal Complications

- Generally the most severe clinical manifestations
- Many have frequency, polyuria, polydipsia
- Usually present w/ nephrolithiasis (20-30%)
- Calcium phosphate or Calcium oxalate
- Nephrocalcinosis (in 5-10%) – calcification w/in parenchyma of kidneys
  - Severe renal damage
- Hypertension secondary to renal impairment
Bone Disease

- Osteitis fibrosa cystica
- In early descripts of disease, many had severe bone disease (50-90%), but now 5-15%
- Subperiosteal resorption – pathognomonic of hyperparathyroidism
Osteitis Fibrosa Cystica

R femur with long-standing severe osteopenia and bony cystic formation secondary to primary Hyperparathyroidism.

R. Cotran, Robbins Pathologic Basis of Disease, 4th ed. 1989
Articular and Soft Tissue

- Chondrocalcinosis and Pseudogout 3-7%
- Deposits of Calcium pyrophosphate in articular cartilages and menisci
- Vascular and Cardiac calcifications
- Calciphylaxis
Calciphylaxis
Gastrointestinal Manifestations

- Peptic Ulcer disease
- Pancreatitis
- Cholelithiasis – 25-35%
Emotional Disturbances

- Hypercalcemia of any cause – assoc w/ neurologic or psychiatric disturbances
  - Depression, anxiety, psychosis, coma
- Severe disturbances not usually correctable by parathyroidectomy
Neuromuscular complications

- Muscular weakness, fatigue
- More commonly in proximal muscles
- Sensory abnormalities also possible
Hyperparathyroid crisis

- Most pts w/ hyperparathyroidism chronically ill w/ renal and skeletal abnormalities
- Rarely can become acutely ill
- Rapidly developing weakness, N/V, weight loss, fatigue, drowsiness, confusion, Azotemia
- Uncontrolled PTH production, hyperCa, polyuria, dehydration, reduced renal function, worsening hyperCa
Hyperparathyroid Crisis

- Definitive therapy - resection

- Must reverse hyperCa first
  - Diuresis - Saline hydration then Lasix to excrete Ca
  - Calcitonin - rapid affect, inhibits bone resorption
  - Steroids - take up to a week
  - Mithramycin - rapidly inhibiting bone resorption
Laboratory Diagnosis

- Elevated Serum Ca and PTH
  - Must measure Ionized Ca (subtle cases of hyperPTH will have normal Serum Ca)
- 50% will have hypophosphatemia
- Elevated Alkaline Phosphatase in 10-40%
- Hyperchloremic metabolic acidosis
- Low Mg in 5-10%
- High Urinary Ca in almost all cases
Work-Up

- Wrist, spine and hip DEXA

- Consider KUB, IVP or CT to evaluate for kidney stones
Primary HPT: Clinical Features
Preoperative Evaluation

- No consensus on whether preoperative localization is necessary.
- Preoperative localization can allow for unilateral focused parathyroidectomy.
- The combination often used is:
  - Sestamibi for localization.
  - Ultrasound for information on size and relationship of the abnormal glands to surrounding tissue.
- Sestamibi scanning is limited in identifying multiple adenomas and 4 gland hyperplasia.
- Preoperative localization is essential in reoperation cases.
Preoperative Evaluation

- neck ultrasound
- MRI
- thallium-technetium dual isotope scintigrapy
- technetium-99m sestamibi scan
- SPECT sestamibi scan: allows for 3-D localization but is expensive
Neck Ultrasound showing
Left Lower Parathyroid Adenoma
Sestamibi Tc-99 (Cardiolite)

- Introduced in 1984 for cardiac stress tests
  "99Tcm Sestamibi--A New Agent for Parathyroid Imaging."
- Radionucleotide concentrated in areas of increased metabolism
  - Molecule passes cells membranes passively; the driving force is the negative membrane potential
  - Once intracellular it further accumulates in the mitochondria where the membrane potential is even lower
- Tissues rich in mitochondria
  - Heart
  - Salivary glands
  - Thyroid
  - Parathyroids
Sestamibi Tc-99
Planar scan

- Injected IV
- Time lapse
- XR
- Metabolized by liver
Sestamibi Scan

**Advantages**
- Fast
- Safe
- Reliable
  - ID’s 90% solitary adenomas (sensitivity)
  - 98% of these are the offending gland (specificity)
- Reveals eptopic glands

**Disadvantages**
- Misses some 2° adenomas (17%)
- Misses hyperplastic glands
  - Provides little value in cases of 4 gland hyperplasia
Localization

- Location of Ectopic glands:
  - Paraesophageal (28%)
  - Mediastinum (26%)
  - Intrathymic (24%)
  - Intrathyroidal (11%)
  - Carotid sheath (9%)
  - High cervical (2%)
Technetium-99m Sestamibi Scan

- technetium 99m taken up by the thyroid
- sestamibi taken up by both the parathyroid and thyroid tissue
- sestamibi washes out of the thyroid faster
Localization: Sestamibi
Technetium-99m Sestamibi Scan

20 Min

2 Hrs
Scintigraphy Images

Traditional Sestamibi

Sestamibi-SPECT
SPECT Scan

- Single photon emissions CT
- Fusion of Sestamibi + CT scan
- 2D/3D imaging
- Highly valuable in locating ectopic parathyroids
- Cost effectiveness vs. BNE+US is questionable
Localization

• Angiography w/ or w/o selective venous sampling (Angioablation)
Medical Management

- Asymptomatic patients may elect to be closely followed and managed medically
  - A recent study of pts with asymptomatic primary HPT showed that the majority of pts followed for ten years did not demonstrate an increase in serum calcium or PTH levels—25% of patients had progressive disease including worsening hypercalcemia, hypercalciuria and reduction in bone mass—younger patients more likely to have progression of disease

- Patients opting not to have surgery should have a serum calcium level drawn every 6 months and should have annual bone densiometry at all three sites
Medical Management Primary HPT

- **Estrogen**
  - Dose required is high

- **SERMs**
  - Reduction in serum calcium and markers of bone turnover after 4 weeks

- **Bisphosphonates**
  - Studies have shown increase in lumbar spine and femoral neck mineral density

- **Calcium/Vitamin D**

- **Calcimimetic agents (Cinacalcet)**
  - Under investigation for primary HPT
Medical Management

• Severe Hypercalcemia:
  – Saline-furosemide diuresis
  – Bisphosphonates (onset of action 24-48h)
  – Calcitonin (immediate onset)
  – Hemodialysis
Who should have surgery?

- NIH Consensus statement 1991
- All symptomatic
- If asymptomatic
  - Markedly elevated serum Ca
  - H/o episode life-threatening hypercalcemia
  - Reduce renal function
  - Kidney stone on Radiograph
  - Markedly elevated urinary Ca excretion
  - Substantially reduce bone mass
Surgical Intervention in Primary Hyperparathyroidism

Any of the following:

- serum calcium > 1mg/dL above normal
- history of life threatening hypercalcemia
- abnormal serum Cr
- elevated urine calcium, > 400mg/day
- kidney stones
- < 50 years old
- bone density less than two standard deviations below the norm
- neuromuscular symptoms
Surgical Management

• Adenoma
  – Unilateral vs. Bilateral Exploration
  – rPTH vs. Frozen Section
• Hyperplasia/Multiple adenomata
  – Subtotal – less hypocalcemia
  – Subtotal w/ autotransplantation – MEN, Renal Failure
  – Total w/ Cryopreservation – up to 1 year
Autotransplantation

- Iced saline bath
- 20-30 mg; 10-20 1-2 mm slices
- SCM vs. Brachioradialis
- Pockets marked with clips
- Up to 50% failure rate
Options:

- bilateral neck exploration
- unilateral focused parathyroidectomy
- endoscopic parathyroidectomy
- video assisted parathyroidectomy
Surgical Management

• New Tools of the Trade: Minimally Invasive Surgery
  – Pre-operative Sestamibi
  – Intraoperative ultrasound
  – Intraoperative rapid PTH (50%, 80%)
  – Hand-held gamma probe
Intra-operative Gamma probe work.
**PTH Assay**

- collection from a peripheral venous sample, IJ sampling may be inaccurate
- baseline measures are pre-incision and post-manipulation
- propofol will interfere with the assay
- samples sent at fixed time intervals after resection
- Different standards for what constitutes a successful resection
  - Drop of at least 50% from highest baseline value
  - Return of PTH level to normal (used at DHMC)
Intraoperative parathormone assay.

- allows confirmation of removal of an adenoma
- decreases operating time
- decreases complications
- is superior to preoperative localization with sestamibii scan
- is inferior to gamma probe localization
Operative Requirements

1. **Equipment**
   1. **Surgical Instrument (preference lists)**
   2. **Accessory equipment**

2. **Procedure Overview**
   1. **Objectives**
      1. **Excisional**
   2. **Procedure**
      1. **Opening**
         1. **Landmarks**
         2. **Risky aspects**
      2. **Localisation, Identification, Excision, ID2X**
      3. **Wound Closure**
         1. **Deep**
         2. **Superficial**
         3. **Drainage**
         4. **Dressing**
What Things Look Like

- Joll Thyroid Retractor
- Rutherford Morrison Forceps
- Metzenbaum Dissecting Scissors
- Curved Mayo Scissors
- Plain Dressing Forceps
- Babcock Metzenbaum Dissecting Scissors
- Rampley’s Sponge Holding Forceps
- Langenbeck Retractor
- Skin Hook Retractor
- Fine Non-Toothed Dissecting Forceps
- Mixture Right Angle Forceps
- Rake Retractor
- Debakey Atraumatic Forceps
- Lahey Angle/Spencer Wells Forceps
Patient Positioning
Parathyroidectomy

- Must find all four glands
- Intraoperative frozen section, PTH measurement useful
- If single gland enlarged, removal usually curative
- If multiple glands enlarged, removed. Normal just biopsied
- If all 4 enlarged (generalized parathyroid hyperplasia) - subtotal (3 1/2 removed)
  - Can reimplant into forearm muscle
Opening
Opening
1. The thyroid lobe
   1. Elevated-off the common carotid artery
   2. Retracted-medially.

2. The inferior thyroid artery
   1. Identified-blunt and sharp dissection of the areolar tissue anteriorly and medially to the common carotid artery and posteromedially to the thyroid lobe

3. The recurrent laryngeal nerve

4. The intersection of the inferior thyroid artery and the recurrent laryngeal nerve is an important landmark

5. The superior parathyroid glands
   1. Located
      1. Dorsal to the upper 2/3 of the thyroid lobe
      2. Posterior to the recurrent laryngeal nerve.

6. The inferior glands-Less consistent in location
   1. Located
      1. Inferior to the inferior thyroid artery
      2. Ventral to the recurrent laryngeal nerve.
      3. Usually within 1 cm of the inferior lobe of the thyroid gland.
Localisation

Recurrent laryngeal nerve

Parathyroid adenoma
Identification-Part 1-Vis/RadioGuided
Excision
Closure

• **Deep**
  - Vicryl 2-0

• **Superficial**
  - Dexon 4-0
  - Steri-Strips
  - Large plaster

• **Both**

• **Absorbable**

• **Synthetic**

• **Multi-filament**
Post-Operative Requirements

1. Discussion with Family Members
   1. Operation
   2. Prognosis
2. Documentation
   1. Dictation to Primary care physician
   2. Chart documentatation
3. Wound Management
   1. Inspect for infection
   2. Change Dressing
   3. Stitches removed by GP
4. Rx
   1. Pain-Paracetemol
   2. Abx-Nil
5. Symptoms
6. Nutrition
7. Discharge
   1. Per patient
   2. Rx-Vita D, Calcium

• Follow up
  • 6/52
    • Symptoms, Scar, PTH, Ca
Specific Risks Associated with Parathyroid Surgery

1. Post-Op Bleed
   1. Pre-tracheal hematoma - airway obstruction
   2. Sub-platysmal hematoma - aspiration

2. Hoarseness of the Voice
   1. Permanent in up to 1-2% of cases
      • Recurrent laryngeal damage
      • Superior laryngeal damage (voice weakness)

3. Post-Op Hypocalcemia - (6-12/12)
   1. Hungry Bone syndrome - aches/pain, seizure, arrhythmia, prolonged Q-T, numbness, tetany, paraesthesias, Chvostek’s sign, Trousseau’s sign
      • Pre-op: Vita D
      • Post-op: Vita D, Oral Calcium
Specific Risks Associated with Parathyroid Surgery

4. **Scarring**
   - Keloid formation - *Silicone gel tapes, steroids*

5. **Persistent hyperparathyroidism**
   - 5% of parathyroid tumors cannot be found at operation and the blood calcium will remain elevated

6. **Recurrent hyperparathyroidism**
   - Remaining glands overreact causing hypocalcemia
Success of Surgery

- 95% of cases cured at initial neck exploration
- If failed initial procedure, can try to localize with Radionuclide, detect with gamma probe
  - Sestamibi concentrates in parathyroid tissue
  - Increasingly used in initial operation
  - Limits dissection
  - Limits operative time
- May need mediastinoscopy
Persistent Hyperparathyroidism

- 5-10% of patients have persistent disease

- Location of the abnormal glands at second operation
  - neck: 30-54%
  - mediastinum: 16-34%
  - retroesophageal: 14-39%
  - upper cervical area: 8%
  - aortic arch area: 5%
Persistent Hyperparathyroidism

- Localization studies necessary prior to reoperation
- Sestamibi, MRI and ultrasound together identify abnormal glands in 87% of patients
- Invasive studies used if non-invasive methods cannot localize the abnormal gland
  - Selective arteriography
  - Selective venous sampling
  - FNA and PTH assay
- Complication rate at reoperation for recurrent laryngeal nerve injury or hypoparathyroidism 1-2%
Hyperparathyroidism: Miscellany

- Parathyroid carcinoma
  - Hi PTH, palpable neck mass, Hi Ca post-op
  - Regional/distant mets in 25-30%, Local recurrence 30%
  - Surgery: Ipsilateral thyroid lobe, skeletonization of RLN, paratracheal nodes

- Hyperparathyroidism-Jaw Tumor Syndrome
  - Severe hypercalcemia in teenager
  - Multiple parathyroid adenomas; 10% parathyroid carcinoma
Brown Tumor of Hyperparathyroidism
Parathyroid Carcinoma

- Occurs in ~1% of patients with hyperparathyroidism

- Associated with genes: cyclin D1, MEN1, HRPT2

- Risk Factors
  - neck irradiation
  - ESRD
  - familial hyperparathyroidism (not MEN syndromes)
  - hyperparathyroidism- jaw tumor syndrome
Parathyroid Carcinoma

- more severe hypercalcemia 3-4 mg/dl above normal
- nephrolithiasis 56%
- renal insufficiency 84%
- pathologic fractures or radiographic evidence of bone disease 40%
- palpable neck mass 50%
- hypercalcemic crisis 10%
Parathyroid Carcinoma

Appearance

» Adenoma: round, soft and reddish-brown

» Parathyroid carcinoma: lobulated firm and adherent to surrounding tissue

» Carcinoma often localized to inferior parathyroid glands

» difficult to distinguish benign and malignant tumors histologically
Parathyroid Carcinoma

Management

» en bloc resection: ipsilateral thyroid lobe, overlying strap muscles and involved soft tissue
» examination of all four parathyroid glands
» modified radical neck dissection if lymph nodes involved (5% of the time)
» intraoperative PTH monitoring
» 90% long term survival
» if microscopic features of parathyroid carcinoma show up in post-op path reoperation is not indicated
Parathyroid Carcinoma

Postoperatively

» hungry bone syndrome: symptomatic hypocalcemia from calcium and phosphorus deposition into the bones
» if hypocalcemia severe it’s treated with iv calcium and vitamin D
» metastatic disease: cervical nodes, lung > liver > bone
» metastatic disease should be resected → decreased tumor burden
» no role for chemotherapy or XRT as primary therapy
» XRT may be useful in the postoperative setting
Parathyroid Carcinoma

Hypercalcemia

» biggest problem in disseminated parathyroid carcinoma

» acute management of hypercalcemia consists of:
  - normal saline
  - diuretic
  - osteoclast inhibitor (calcitonin, bisphosphonates)
  - calcimimetic agent (cinacalcet)
Familial Syndromes

- MEN I
- MEN IIA
- Familial Hypocalciuric Hypercalcemia
- Hyperparathyroidism-jaw tumor syndrome
  - Fibro-osseous jaw tumors
  - Renal cysts
  - Solid renal tumors
- Familial isolated hyperparathyroidism
- Neonatal Severe Hyperparathyroidism
Multiple Endocrine Neoplasia

- **MEN I**
  - Moderate-severe hyperPTH in 85%
  - Zollinger-Ellison, prolactinomas
  - Auto Dominant, MEN1(tumor suppressor), Chromosome 11

- **MEN IIa**
  - Mild hyperPTH in 70%
  - Medullary Carcinoma 100%
  - Pheochromocytoma
  - Auto Dominant, RET proto-oncogene
MEN I

- **MEN I**
  - 1 in 30,000 persons
  - **Features:**
    - Hyperparathyroidism (95%)
      - Most common and earliest endocrine manifestation
    - Gastrinoma (45%)
    - Pituitary tumor (25%)
    - Facial angiofibroma (85%)
    - Collagenoma (70%)

- **HPT in MEN I**
  - Early onset
  - Multiple glands affected
  - Post-op hypoparathyroidism more common (more extensive surgery)
  - Successful subtotal parathyroidectomy followed by recurrent HPT in 10 years in 50% of cases
STIGMATA OF MEN I

- Lipomas
- Collagenomas
- Angiofibromas
MEN IIA (Sipple’s Syndrome)

- **Features:**
  - MTC (95%)
  - Pheochromocytoma (50%)
  - HPT (20%)

- RET mutation (98%)

- 1 in 30,000-50,000 people

- Usually single adenoma but may have multi-gland hyperplasia
Familial Hypocalciuric Hypercalcemia

This benign condition can be easily mistaken for mild hyperparathyroidism. It is an autosomal dominant inherited disorder characterized by hypocalciuria (usually < 50 mg/24 h), variable hypermagnesemia, and normal or minimally elevated levels of PTH. These patients do not normalize their hypercalcemia after subtotal parathyroid removal and should not be subjected to surgery. The condition has an excellent prognosis and is easily diagnosed with family history and urinary calcium clearance determination.
Secondary Hyperparathyroidism (1)

- Seen mostly in patients with chronic renal failure:
  - renal retention of phosphate $\rightarrow$ chronic hypocalcemia
  - inadequate production of active vitamin D, $1,25(OH)_2D$ by the diseased kidneys
  - some degree of skeletal resistance to PTH

- Identical microscopic appearance of primary and secondary parathyroid hyperplasia
Secondary Hyperparathyroidism (2)

- PTH levels tend to be much higher than in primary hyperparathyroidism (compensatory mechanisms above)

- Surgical removal of hyperplastic glands may be necessary to control bone disease (renal osteodystrophy)

- May become autonomous and create what is known as tertiary hyperparathyroidism:
  - Hyperplasia may not regress after renal transplant, necessitating surgical removal of hyperplastic glands
  - Monoclonality of hyperplasia seen with most patients
Clinical presentation
  - Usually asymptomatic

Diagnosis
  - Elevated PTH in the setting of low or normal serum calcium is diagnostic
  - If phosphorous is elevated, cause is renal
  - If phosphorous is low, other causes of vit D deficiency should be sought
- Prevention
  - Vit D replacement
  - Phosphorus binders [Sevelamer]

- Treatment
  - Medical
    » Calcimimetic agents
  - Surgical
    » Considered in cases of refractory severe hypercalcemia, severe bone disease, severe pruritis, calciphylaxis, severe myopathy
      » subtotal parathyroidectomy
      » total parathroidectomy with autotransplantation
Secondary Hyperparathyroidism

Bone Disease

Calcification

CVD / PVD

Nervous system

Immunologic

Cutaneous

Renal Failure

PTH

↓ Ca^{++}

Vit D

PO_{4}

↓

↑

Systemic Toxicity

- Calcification
- CVD / PVD
- Nervous system
- Immunologic
- Cutaneous
Osteitis fibrosa cystica (OFC)

- **Cause:** secondary hyperparathyroidism (SHPT)
- Increased bone resorption, extensive osteoclastic activity and endosteal fibrosis
- **Biochemical profile:** high Phos, low active vitamin D, relative low Ca, high PTH, elevated AP and osteocalcin (secreted by osteoblasts, marker of bone turnover)
Normal Bone

- Mineralized bone
- Osteoid
- Bone marrow cells
- Fat cell
Normal Bone Metabolic Unit
Osteitis Fibrosis Cystica
Dissecting Osteitis
Other Causes of Secondary Hyperparathyroidism

- Dietary deficiency of vitamin D or of calcium
- Tissue resistance to vitamin D
- Severe hypomagnesemia
- Pseudohypoparathyroidism
# Clinical Features of Primary vs. Secondary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Serum Ca++</em></td>
<td>↑ (11-12 mg/dl)</td>
<td>Low Nl. to ↓</td>
</tr>
<tr>
<td><em>PTH level</em></td>
<td>Slight ↑ (1-3x Nl.)</td>
<td>Mod. to Mrk. ↑ (5-30x Nl.)</td>
</tr>
<tr>
<td><em>Parathyroid Morphology</em></td>
<td>Adenoma (80-90%)</td>
<td>Hyperplasia (100%)</td>
</tr>
<tr>
<td><em>Bone Diseases</em></td>
<td>Mod. to Severe</td>
<td>Often severe</td>
</tr>
<tr>
<td></td>
<td>(Now rare: early Dx &amp;Rx)</td>
<td></td>
</tr>
<tr>
<td><em>Treatment</em></td>
<td>Surgery or observation</td>
<td>Treat underlying disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery, only if severe bone disease</td>
</tr>
</tbody>
</table>
Tertiary Hyperparathyroidism

- after renal transplant or as a progression of secondary hyperparathyroidism
- hyperparathyroidism and hypercalcemia
- 1/3 of transplant patients
- hypercalcemia can threaten the graft
- usually subsides within months to years
- 1-3% of patients require parathyroidectomy
  » subtotal parathyroidectomy
  » total parathyroidectomy with autotransplantation
Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism develops in patients with long-standing secondary hyperparathyroidism, which stimulates the growth of an autonomous adenoma. A clue to the diagnosis of tertiary hyperparathyroidism is intractable hypercalcemia and/or an inability to control osteomalacia despite vitamin D therapy.

Surgical Referral
- calcium-phosphate product > 70
- severe bone disease and pain
- intractable pruritus
- extensive soft tissue calcification with tumoral calcinosis
- calciphylaxis
Lab Abnormalities

- **Primary HPT**
  - Increased serum calcium
  - Phosphorus in low normal range
  - Urinary calcium elevated

- **Secondary HPT (renal etiology)**
  - Low or normal serum calcium
  - High phosphorus

- **Tertiary HPT (renal etiology)**
  - High calcium and phosphorus