Parathyroid Diseases

Dr. Osama H. Alsallaq
MD. General and Oncology Surgeon MD, MRCS
European Board of Surgical Oncology
Department of Surgery
King Hussein Cancer Center
Mu'tah University

Embryology and Surgical Anatomy

- Four parathyroid glands develop from the 3rd and 4th pharyngeal pouches between the 5th and 12 weeks of gestation
- Superior → 4th , inferior → 3rd
- Yellow brown in color
- Wt. 60-80 gm
- 5% supernumerary (>4) glands

- The blood supply of both the superior and inferior parathyroid glands arises from the **inferior thyroid artery**

Related

- The inferior parathyroid gland and the thymus arise from the third pharyngeal pouch: More variable location and more likely to be ectopic

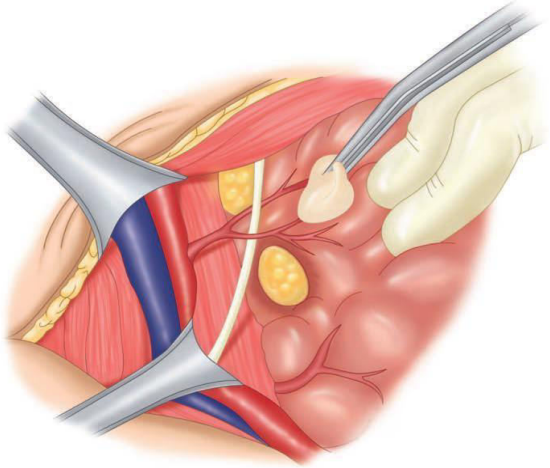
Superior are usually fixed / inferior ectopic anywhere: Thymus, carotid, esophagus

- The superior parathyroid glands arise from the dorsal portion of the fourth pharyngeal pouch.

Relation to RLN

- Superior parathyroids : Found lateral to recurrent laryngeal nerves (RLNs), posterior surface of superior portion of gland, above inferior thyroid artery (1 cm around the junction of the inferior thyroid artery and the recurrent laryngeal nerve)

- Inferior parathyroids : Found medial to RLNs, below inferior thyroid artery



recurrent laryngeal is positioned obliquely, thus explains the relation

Physiology :

- **PTH** – (5–40 pg/mL)
- increases serum Ca
- ↑ kidney Ca++ reabsorption in the distal convoluted tubule, ↓ kidney PO4- absorption
- ↑ osteoclasts in bone to release Ca (and PO4 –)
- ↑ vitamin D production in kidney (↑ 1-OH hydroxylation) → ↑ Ca-binding protein in intestine → ↑ intestinal Ca reabsorption

Active kidney co-transporter stimulates PO4 excretion

Net result ↑Ca ↓PO4

- **Vitamin D** – ↑ intestinal Ca++ and PO4- absorption by increasing calcium-binding protein

osteoblast activation

- **Calcitonin** – decreases serum Ca
- ↓ bone Ca resorption (osteoclast inhibition)
- ↑ urinary Ca and PO4 excretion

Hypercalcemia

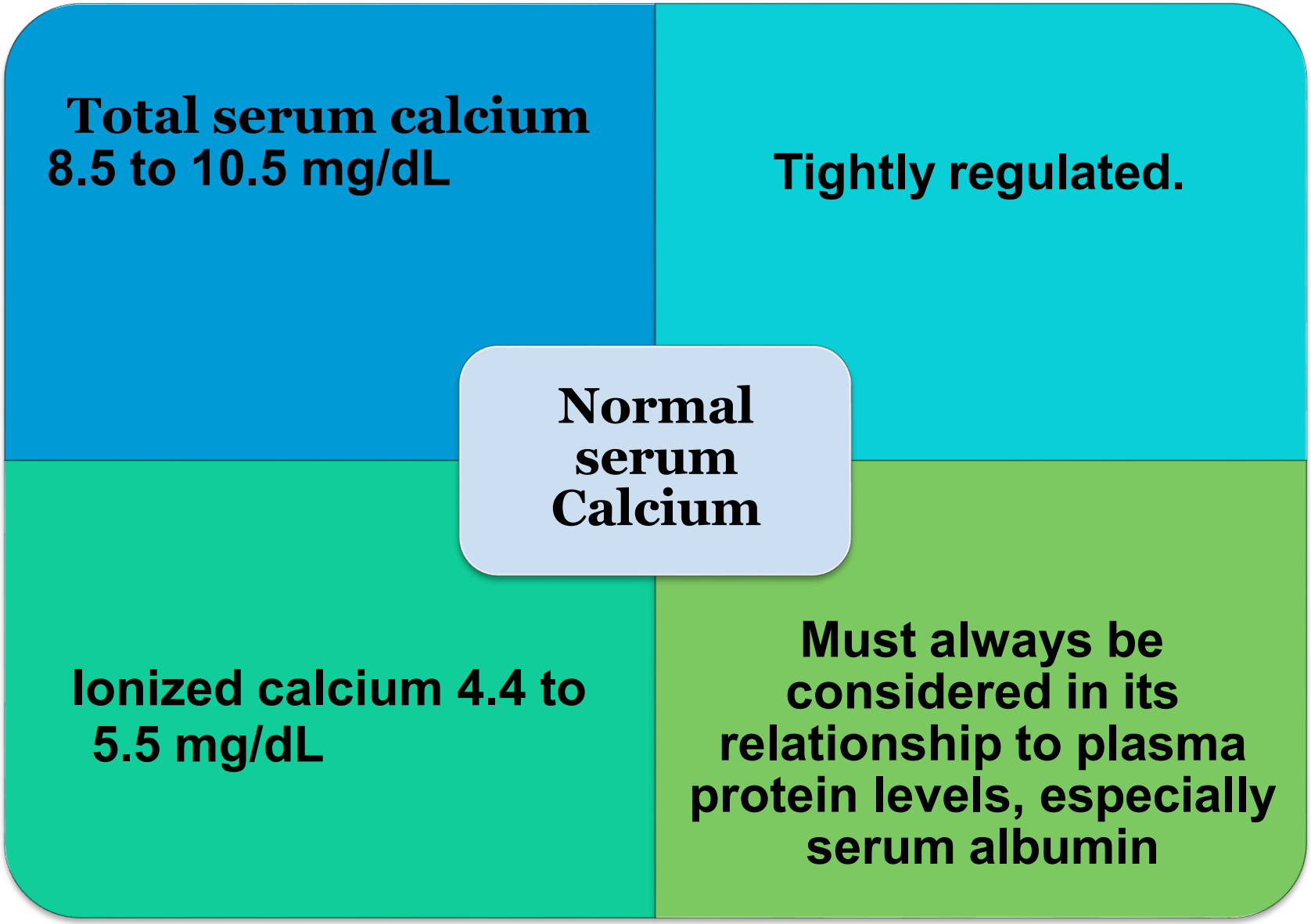
CALCIUM IS THE MOST ABUNDANTCATIONINHUMAN BEINGS

We measure total calcium, though one can manifest with Hypocalcemia symptoms despite having normal tital levels, due to having low ionized calcium levels

factors affecting ionized calcium binding to albumin :

1- Acidosis

2- Alkalosis


Total serum calcium
8.5 to 10.5 mg/dL
Tightly regulated.
Normal serum Calcium
Ionized calcium 4.4 to 5.5 mg/dL
Must always be considered in its relationship to plasma protein levels, especially serum albumin

Malignancy is the most common in hospitalized patients

D.Dx of Hypercalcemia

- Primary hyperparathyroidism (Most common in out-patients)
- Tertiary hyperparathyroidism
- Familial hypercalcemic hypocalciuria
- Lithium therapy
- Paraneoplastic syndrome (humoral hypercalcemia of malignancy)
- Osteolytic metastases
- Multiple myeloma
- Drug-induced hypercalcemia
- Granulomatous disease
- Hypervitaminosis D
- Milk-alkali syndrome
- Nonparathyroid endocrine disease
- Immobilization
- Idiopathic

Primary Hyperparathyroidism (PHPT)

- **Occurs in 0.1% to 0.3% of the general population**
- **More common in women (1:500) than in men (1:2000).**

Disease Mechanisms

Increased PTH production → Hypercalcemia via:

- **Increased GI absorption of calcium**
- **Increased production of vitamin D3**
- **Reduced renal calcium clearance**
- **• ↑ osteoclasts in bone to release Ca (and PO4 –)**

Primary Hyperparathyroidism

- **PTH is elevated relative to the serum calcium level.**

Causes

Single

- **Parathyroid adenoma (80%)**
- **Multiple adenomas (<4%)**
- **Parathyroid hyperplasia (15%)**
- **Parathyroid carcinoma (<1%).**

Clinical Picture

Most patients have no symptoms – ↑ Ca found on routine lab

Classical mnemonic :"stones, bones, groans, moans, and psych overtones,"	
Stones	**Urolithiasis**
bones	**Bone diseases including bone resorption with cyst (osteitis fibrosa cystica) and brown tumor formation, fractures**
groans	**Abdominal pain from peptic ulcers or pancreatitis, renal stones, constipation**
moans	**Diffuse joint and muscle pains, fatigue and lethargy**
psych overtones	**Neuropsychiatric abnormalities including depression or worsening psychosis**

++ Hypertension and renal impairment

Currently most patients are found incidentally from investigating hypercalcemia

In outpatients

- The most common cause of hypercalcemia is primary hyperparathyroidism

In hospitalized pts

- The most common cause is malignancy, either via paraneoplastic syndrome or bony metastases (e.g. breast cancer, MM)

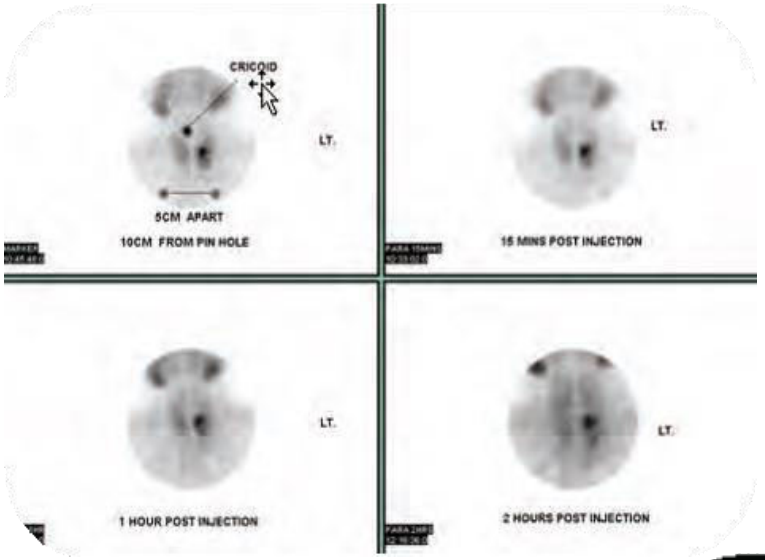
Diagnosis :

- **Serum phosphate is often low**
- **Renal function is normal** PTH ↑
- **↑ Ca, ↓ PO_4 – ; Cl – to PO_4 – ratio > 33; ↑ renal cAMP; HCO_3 – secreted in urine**
- **hyperchloremic metabolic acidosis**
- **KFT**
- **IMAGING :**

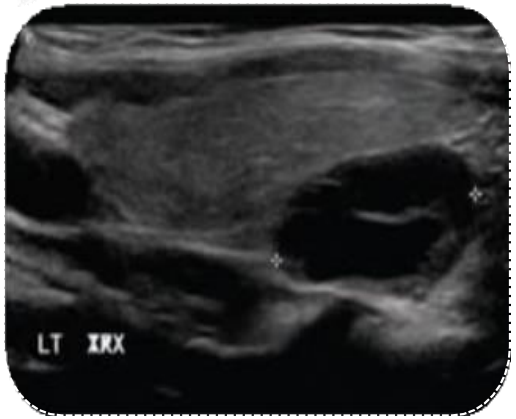
-NECK U/S, MRI, CT

- SESTAMIBI scan (most sensitive)

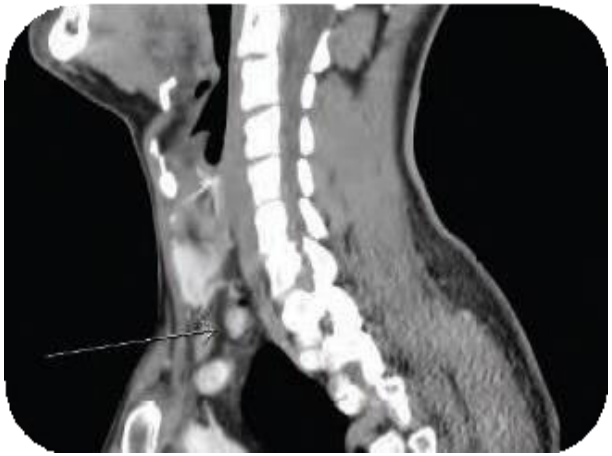
gold standard, Nuclear med



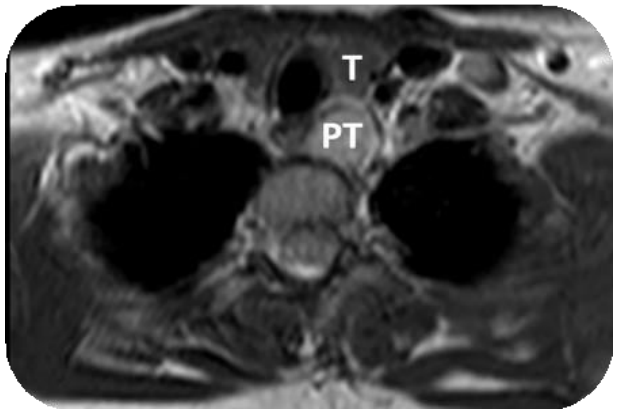
Nuclear medicine-based studies (sestamibi scanning)



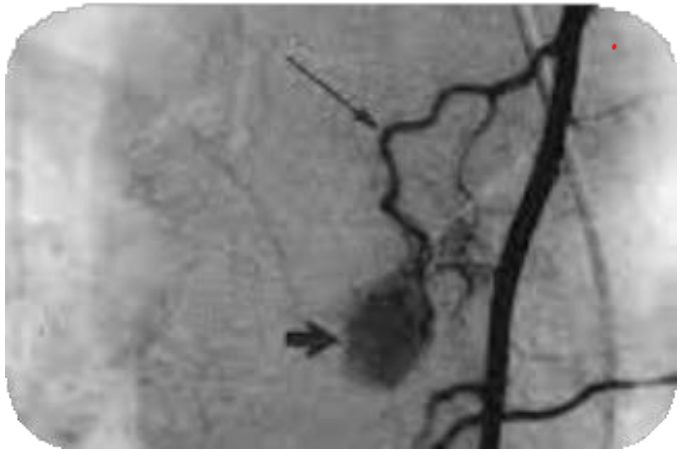
Ultrasonography



4D-CT



MRI



Parathyroid angiography and venous sampling for PTH

Treatment

Medical :

- Severe hypercalcemic crisis:
- large-volume saline infusion (300ml/hr)
- Lasix, bisphosphonate, dialysis
- There is no definitive medical treatment for primary or tertiary hyperparathyroidism

Surgical:

- Patient selection criteria for parathyroidectomy

Treatment is mainly surgery

symptomatric patients are indicated For surgery

NIH Criteria for Parathyroidectomy

+ Asymptomatic renal Stones

Age < 50 (even if asymptomatic): Long life expectancy, cuz disease will worsen
Nephrolithiasis
Osteitis fibrosa cystica Brown tumour, due to osteoblasts over activation
Serum calcium >1.0 mg/dL above reference range (typically >11.5)
Hypercalciuria (>400 mg/day)
Bone mineral density T score reduced by >2.5 SD measured at one or more sites
Creatinine clearance reduced by 30% compared to age-matched normal range
History of an episode of life-threatening hypercalcemia
Neuromuscular symptoms: documented proximal weakness, atrophy, hyperreflexia, and gait disturbance

Symptomatic disease always need parathyroidectomy

Treatment

• **Adenoma** – resection; inspect other glands to rule out hyperplasia or multiple adenomas

• **Parathyroid hyperplasia**

- resect 3½ glands or total parathyroidectomy and autoimplantation in arm or sternomastoid

• **Parathyroid CA** → need radical parathyroidectomy (need to take ipsilateral thyroid lobe) +/- neck dissection

Parathyroid must be tested after 10 mins of removal intra-operatively, to make sure it's not ectopic secretion

Intraop PTH levels → can help determine if the causative gland is removed (PTH should go to < ½ of the preop value in 10 minutes)

Missing gland: check ectopic sites (MC in thymus)

Still cannot find gland – close and follow PTH; if PTH still ↑, get sestamibi scan to localize

- **Post-op Hypocalcemia** – from bone hunger syndrome or failure of parathyroid remnant/graft
- Bone hunger – normal PTH, decreased HCO_3 –
- Aparathyroidism – decreased PTH, normal HCO_3 –

- **Persistent hyperparathyroidism (1%)** – most commonly due to missed adenoma remaining in the neck

- **Recurrent hyperparathyroidism** – occurs after a period of normocalcemia

- Can be due to **new adenoma** formation
- Can be due to **tumor implants** at the original operation that have now grown
- **recurrent parathyroid CA**

Observation Vs. Operation

Observation rather than operation is not safe for noncompliant patients.

Observation requires active surveillance :

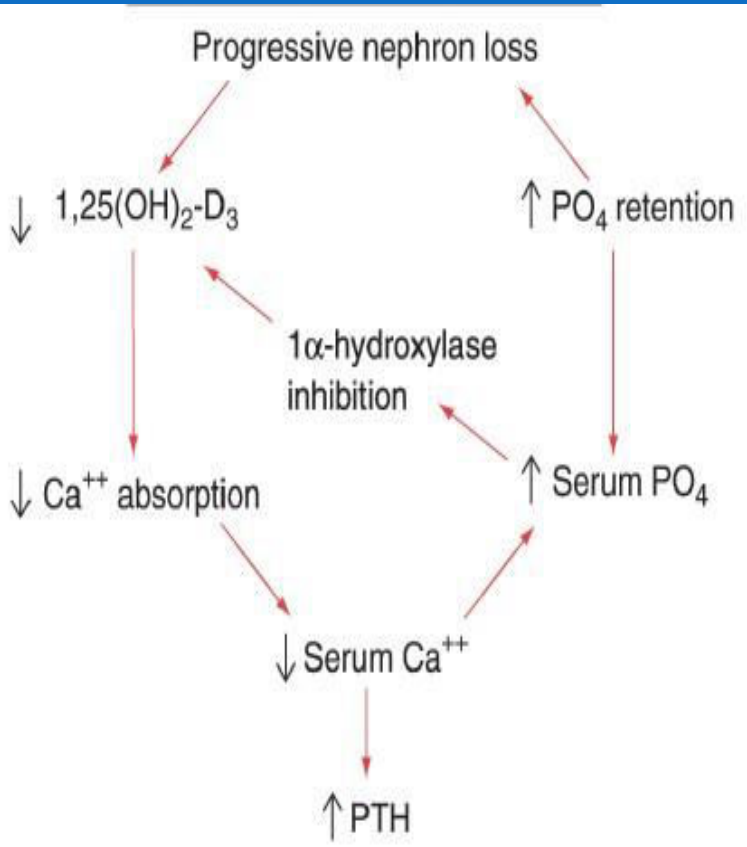
- **biannual serum calcium levels**
- **annual serum creatinine measurement**
- **annual bone mineral density determination**

Secondary Hyperparathyroidism

Causes

- **Chronic renal failure**
- **Inadequate calcium intake**
- **Decreased vitamin D**
- **Malabsorption**

Pathophysiology



Secondary Hyperparathyroidism

- **↑ PTH in response to low Ca**
- **Most do not need surgery (95%)**

Clinical picture:

- **Bone pain,**
- **Ectopic Soft tissue calcifications (calcinosis), osteoporosis**
- **Pruritus**
- **Calciphylaxis (calcific uremic arteriopathy)**

Labs:

- **Increased PTH**
- **Normal/low calcium**
- **high phosphate**

Mainly medical : treat cause

Treatment

Medical

- **For end-stage renal disease**
  - Dialysis
  - Calcium and Vitamin D supplements
  - Oral phosphate binders
  - cinacalcet

Surgical

- For end-stage renal disease: transplantation
- Parathyroidectomy for
  - bone pain (most common indication), fractures, or pruritus (80% get relief)
  - Ongoing bone loss
  - Soft tissue calcifications
  - calciphylaxis

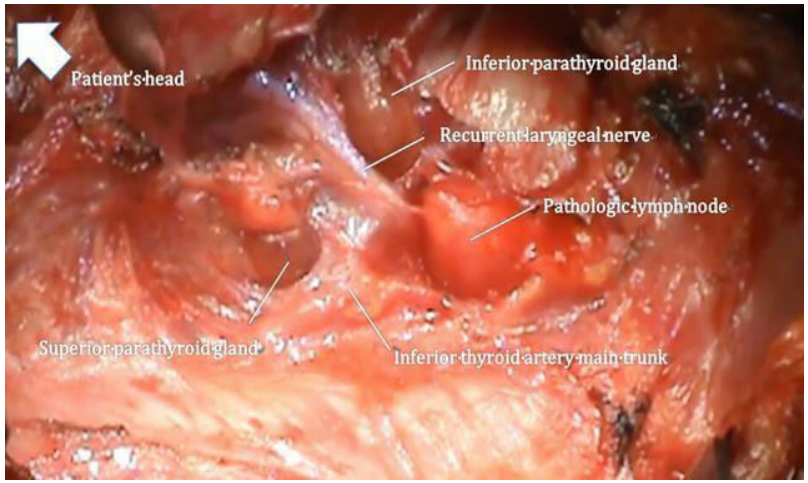
Persistant

Calcium deposition in arterioles → Skin necrosis

Usually bad sign of the disease

- **Since secondary hyperparathyroidism is always multiglandular, Surgery involves total parathyroidectomy with autotransplantation (in forearm) or subtotal parathyroidectomy (three and one-half glands)**

for ease of removal if symptoms persist or in recurrence



Tertiary Hyperparathyroidism

- **Definition**

secondary with renal transplant, but glands are autonomous. Persistant elevated PTH

- **Renal disease now corrected with transplant**
- **One or more of the hyperplastic glands of becomes an autonomous producer of PTH**
- **similar lab values as primary hyperparathyroidism (hyperplasia)**

- **Patients who remain on dialysis and spontaneously progress from secondary to tertiary hyperparathyroidism marked by the onset of hypercalcemia.**

Surgery for Tertiary Hyperparathyroidism

- Guided by the intraoperative findings, most often multiglandular disease.

- Total parathyroidectomy with forearm autotransplant or subtotal 3.5 parathyroidectomy

FAMILIAL HYPERCALCEMIC HYPOCALCIURIA (FHH)

- Patients have **↑ serum Ca and ↓ urine Ca** (should be ↑ if hyperparathyroidism)
- Caused by **defect in PTH receptor** in distal convoluted tubule

  Receptors are More sensitive
- ↑ resorption of Ca
- Dx: Ca 9–11, have normal PTH (30–60), ↓ urine Ca
- Tx: nothing (Ca generally not that high in these patients); **no parathyroidectomy**

  usually asymptomatic

PARATHYROID CANCER

- Rare cause of hypercalcemia
- ↑ Ca, PTH, and alkaline phosphatase (can have extremely high Ca levels)>15mg/dl
- Lung most common location for metastases
- Tx: wide en-bloc excision (parathyroidectomy and ipsilateral thyroidectomy) +/- LN dissection
- 50% 5-year survival rate
- Mortality is due to hypercalcemic crisis
- Recurrence in 50%

Elevated/normal PTH plus Hypercalcemia

Primary and tertiary hyperparathyroidism	**Familial hypercalcemic hypocalciuria (FHH, also called familial benign hypercalcemia),**	**Vitamin D deficiency**	**Lithium induced hypercalcemia**

substances similar to PTH secreted by the cancer cells, causing hyperparathyroidism

Hypercalcemia of malignancy

Serum parathyroid hormone–related peptide (PTHrP) level might be useful when occult malignancy is a concern:

-Bronchial squamous cell carcinoma is the commonest. – Other sources: breast, renal, and ovarian	Bone destruction by primary cancers (e.g., multiple myeloma) or lytic bony metastases causes hypercalcemia without PTHrP elevation	Vitamin D analogues are secreted by some tumors (e.g., lymphoma) and can produce hypercalcemia without PTH or PTHrP elevations

cancers causing osteoblastis bone destruction, like multiple myeloma as well

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

- Familial endocrine tumor syndromes
- Inherited as autosomal dominant
- Divided into three types

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN-1) (3P's)

Glands and Sites Involved	Type of Disease
Parathyroid (100%)	**Hyperplasia (first presentation)**
Pancreas (70%)	**Islet cell tumors (MC gastrinoma)** **MCC of mortality**
Pituitary (70%)	**Adenoma (prolactinoma)**
Mutation in MEN-1 Gene	
Always need to Correct hyperparathyroidism first	

Screening:

genetic testing first in all pts with family history

Should begin during the 2nd or 3rd decade

Screening tests include	**Calcium, prolactin, fasting glucose and insulin, gastrin**

Calcium and PTH levels should be measured in all patients

The absence of hyperparathyroidism virtually excludes MEN-1

Gastrinoma is the most common cause of death, 50% multiple/ 50% malignant

Parathyroid Disease in MEN-1

Primary hyperparathyroidism is the most common endocrine disorder in MEN-1

- **In over 90% of cases**
- **Only3% of all cases of primary hyperparathyroidism.**

Mean age of onset is 25 years

- **Much younger than for sporadic primary hyperparathyroidism**
- **Affects all parathyroid glands**

Patients with hypercalcemia and hypergastrinemia should undergo parathyroidectomy first for optimal control of gastrin secretion

- **total (four gland) parathyroidectomy with forearm autotransplant**
- **The cervical thymus should always be removed because supernumerary glands can occur and are usually within the thymus**

Treatment

Therapeutic goals :controlling symptoms of hormonal excess and malignancy excision

Gastrinomas are usually multiple, malignant and resection requires pancreaticoduodenectomy	**Surgery is appropriate for all insulinomas**	**Parathyroidectomy should be first**

Multiple Endocrine Neoplasia Type 2A, Type 2B, And Familial Medullary Thyroid Carcinoma

- **RET-proto-oncogene mutation**
- **Medullary thyroid cancer (MTC) is the hallmark of the disease.**

Medullary thyroid cancer Most common cause of death **MEN-2A** **2P's, 1 M**	No Parathyroid **MEN-2B** **1P, +2M's**	**Familial Medullary Thyroid Carcinoma (FMTC)**
• **MTC (100%)** → First Manifestation **-FIRST to present (diarrhea)** **-MCC of death** • **Adrenal pheochromocytoma** • **Primary hyperparathyroidism**	• **MTC (100%)** **-FIRST to present (diarrhea)** **-MCC of death** • **Adrenal pheochromocytoma** • **Mucosal neuromas** • **Marfanoid habitus** • **Megacolon**	**MTC**

- always Need to correct pheochromocytoma first

Screening

- **Genetic screening(RET DNA analysis)**
- **calcitonin screening is not useful as it indicates that MTC already occured**

Medulla scan

Performed soon after birth and is performed once in a lifetime.	**Patients at risk but with negative RET testing do not require further screening.**	+ prophylactic lymph node dissection **Positive RET results lead to prophylactic thyroidectomy at age of 2 (in MEN-IIB) or 6 (MEN-IIA) and further evaluation**

THANK YOU