FORWARD TOGETHER
AAO-HNSF 2022
ANNUAL MEETING & OTO EXPERIENCE
SEPTEMBER 10-14 PHILADELPHIA, PA

Parathyroid Surgery (in 25 min!)

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Sidney Kimmel Cancer Center at Jefferson
NCI – designated
Until every cancer is cured

Thomas Jefferson University

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- **Elizabeth Cottrill, MD,** faculty for this accredited education activity has no relevant financial relationships with ineligible companies to disclose.

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Principles of Parathyroid Surgery

1. Confirm the diagnosis
2. Review the indications for surgery
3. Plan the approach
    1. Knowledge of Anatomy
    2. Pre-operative Imaging
    3. Adjunct tools
        1. Intraoperative PTH
        2. Radio-guidance
        3. Autofluorescence
4. Pearls for successful surgery

Confirm the Diagnosis

Hyperparathyroidism: 1, 2, 3!

Primary:
- hypercalcemia due to **inappropriate secretion of PTH from one or more parathyroid glands** in the absence of a known stimulus to parathyroid enlargement.

Secondary:
- typically associated with low or normal concentrations of serum calcium, and increased PTH secretion **represents an adaptive respon**se, most commonly in patients with hypocalcemia or hyperphosphatemia associated with **renal failure**.

Tertiary:
- refers to **autonomous parathyroid hyperfunction** in patients who have a history of prior secondary hyperparathyroidism.

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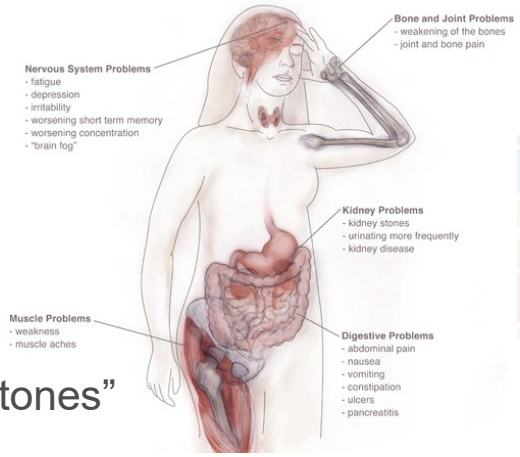
Hypercalcemia: Presentation of Disease

1. Symptomatic
2. Asymptomatic

"Bones,
Stones,
Groans,
Moans,
Psychiatric overtones"



American College of Endocrine Surgeons

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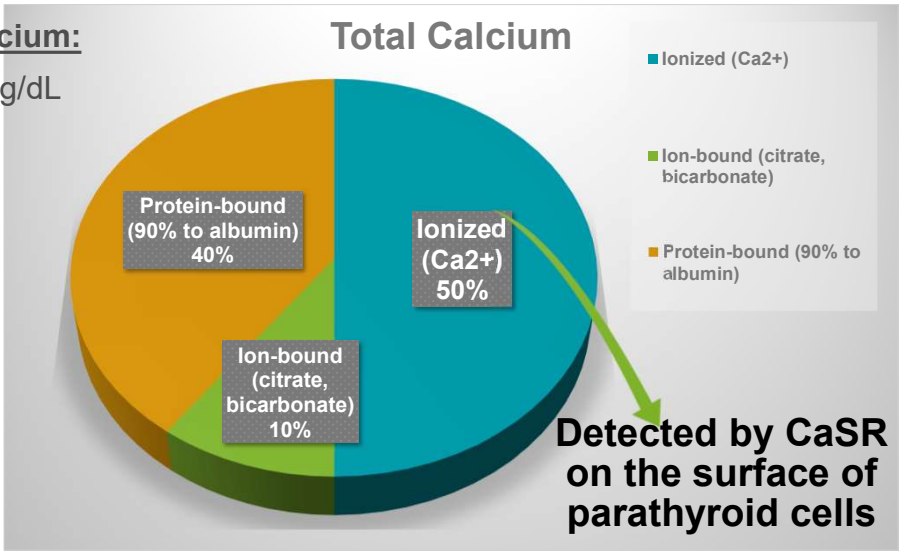
Hypercalcemia: How do we define it?

- **Serum Calcium:**
- 8.5- 10.2 mg/dL



Corrected calcium (mg/dL) = (0.8 [4.0 –albumin (g/dL)]) + total calcium (mg/dL)

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Regulation of PTH synthesis and secretion

Stimulate	Inhibit
low Ca	high Ca
high PO_4	low PO_4
low vitamin D	high vitamin D

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DDx for Hypercalcemia:

1. PHPT
   - Sporadic
   - Inherited (MEN-1, others)
   - Parathyroid carcinoma (<1%)
2. Malignancy
   - Tumor secretion of PTHrP (~75%)
   - PTHrP: Most common: Squamous Cell Carcinomas (lung>vulva, esophagus, H&N), Clear Cell (renal, ovarian)
   - Osteolytic bone lesions (~25%)
     - Multiple Myeloma
     - Prostate mets
     - Breast mets

PTHrP→ high Ca, low PO4, low PTH

Bone lysis→ high Ca, high PO4, low PTH

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DDX HYPERCALCEMIA
+ Hyperparathormonemia

- PHPT
- Malignancy
  - Osteolytic bone mets
  - Tumor secretion of PTHrP
  - Multiple Myeloma
  - Parathyroid carcinoma (<1%)
- prolonged tourniquet time during blood draws
- Paget's Disease
- Prolonged immobilization
- Sarcoidosis (1-25-dihydroxyvitamin D production)
- Milk Alkali Syndrome (excess calcium ingestion)
- Hyper-vitaminosis D and A
- Drugs
  - Thiazide Diuretics
  - Lithium
  - Antacids
- FHH
- Renal impairment
- Addisonian Crisis
- Cushing's
- Hyperthyroidism

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PHPT Risk Factors→ Lithium

- Shortly after initiation of lithium, an elevation in serum calcium is often noted, related to **an increase in parathyroid cell calcium set-point with a reduction in urinary calcium excretion**.
- Short-term use: hypercalcemia resolves with its discontinuation.
- **Long-term use**: parathyroid gland hyperplasia or adenomas with persistence of hypercalcemia after its discontinuation in 10–15%.
- **More common in younger females** (mean age 41 years) than patients with classical PHPT.

Familial **HYPO**calciuric **HYPER**calcemia

- Autosomal dominant disease caused by mutations in the renal calcium sensing receptor. FHH is a benign condition of lifelong hypercalcemia and hypocalciuria that rarely requires treatment.
- Unrecognized FHH can be a cause of unnecessary parathyroid surgery.
- The AAES and AACE recommend obtaining a 24-hour urinary calcium level in all patients suspected to have PHPT.
- **24-hr Urine-Ca:**
  - **>400 mg/dL consider PHPT and evaluate for stone risk**
  - **<100 mg/24hr should be considered for FHH**
- FHH can be differentiated from PHPT by calculation of the calcium/creatinine clearance ratio (CCCR):

$$\mathbf{CCCR = (24\text{-}hr\ Ca_{urine} / Ca_{serum}) / (24\text{-}hr\ Cr_{urine} / Cr_{Serum})}$$

- <0.01 = FHH
- >0.02 = PHPT

- Discontinue confounding medications if possible (HCTZ, Lithium, etc) then re-check labs in 1-3 months
- Normalize Vitamin D (>20r s (25-OH VitD)
- Check the Kidneys: Create Stage 3 CKD has been associated with increased PTH and wi
- Rule out Familial Hypocalc
  - 24 hour Urine Ca and Cr
  - Ca/Cr clearance ratio < 0.01
- Consider Serum Phosphate and Alk Phos especially if concerned for increased bone turnover

IMAGING is NOT a part of the diagnosis of hyperparathyroidism

Primary Hyperparathyroidism

- Inappropriately high PTH levels in the setting of a normal or high calcium
- Incidence of 50-100 per 100,000 in the US
- 50,000 new cases each year
- Male to Female ratio 1:3
- Increases after menopause (~2 per 1000 in women over 60)

Primary hyperparathyroidism

- Sporadic
  - 85% solitary Adenoma
  - 15% MGH
- Menin gene on Chr 11q13
  - MEN-1
  - 10-20% sporadic adenoma
- RET protooncogene on Chr 10
  - MEN-2A:
- Hyperparathyroidism-Jaw Tumor Syndrome: locus on Chr 1q24 (HRPT-2; CDC73)
- Parathyroid carcinoma (~0.5%)

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Indications for Parathyroidectomy

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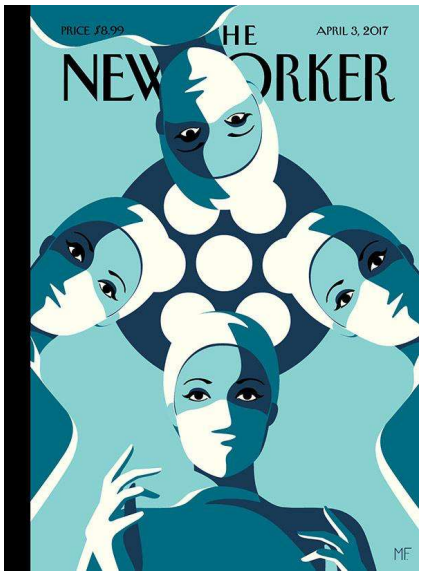

"Although many pharmacologic agents have been used in an attempt to reduce the serum calcium level or stabilize BMD, none have improved both. In formal cost effectiveness analyses, pharmacologic treatment is not optimal at any life expectancy."

JAMA Surg. 2016;151(10):959-968.
doi:10.1001/jamasurg.2016.2310

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Why do we treat hyperparathyroidism?

To remediate or prevent:

- Bone disease
- Renal dysfunction (including stone disease)
- PUD
- Pancreatitis
- HTN, cardiac conduction disorders
- Neuropsychiatric symptoms

NEJM 1999;341(17):1249-1255

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When to operate?

- **Symptomatic** pHPT
- Serum calcium level is greater than 1mg/dL above normal, regardless of symptoms **(>11.2)**
- Patients with **objective evidence of renal involvement**, including:
  - silent nephrolithiasis on renal imaging
  - nephrocalcinosis,
  - hypercalciuria (24-hoururine calcium level >400mg/dL) w/ stone risk
  - impaired renal function (glomerular filtration rate <60 mL/min)
- Patients with **osteoporosis**, fragility fracture, or evidence of vertebral compression fracture on spine imaging
- When PHPT in a patient **<50 years old** regardless of symptoms.
  - Patients 50 years or younger at diagnosis require prolonged monitoring and compared with older patients have a higher incidence of progression

JAMA Surg. 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

Who should operate?

- The success rate for surgeons who perform fewer than 10 parathyroidectomies per year is lower than for experienced surgeons
- **Volume of operations inversely correlates with complications, cost, and length of stay.**
- Parathyroidectomy should be conducted by surgeons with adequate training and experience in PHPT management.

JAMA Surg. 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

Pre-operative Planning

1. Knowledge of Anatomy
2. Pre-operative Imaging—does it localize
3. Type of Procedure planned
4. Adjunct tools

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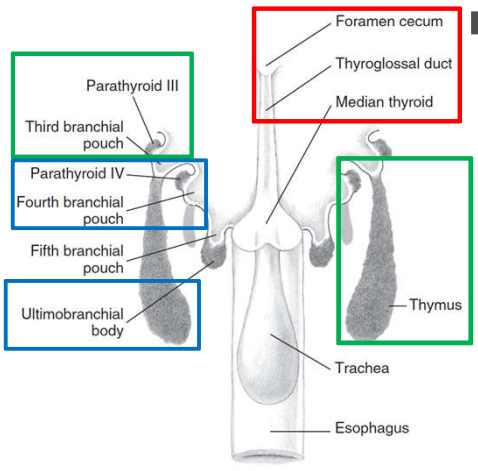
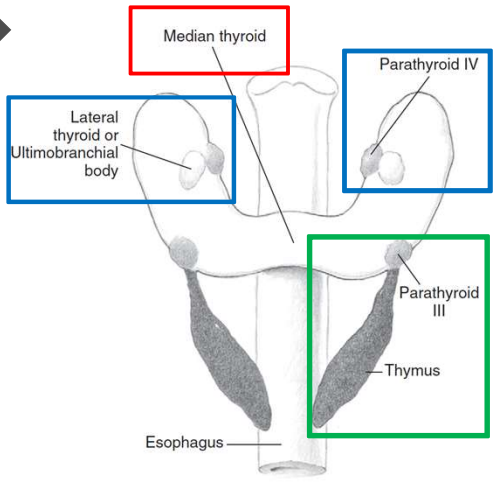
Embryology: Parathyroid and Thyroid



3rd BP:
- Inferior parathyroids
- Thymus

4th BP:
- Superior parathyroids
- Ultimobranchial Body→Parafollicular C-cells (neural crest origin) Lateral thyroid

Tuburculum Impar
- Thyroglossal Duct
- Median thyroid



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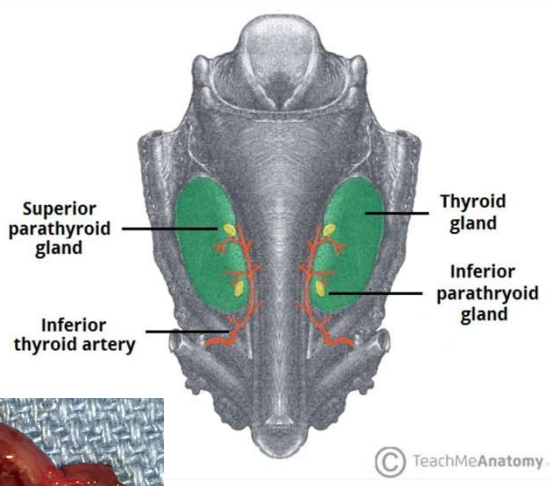
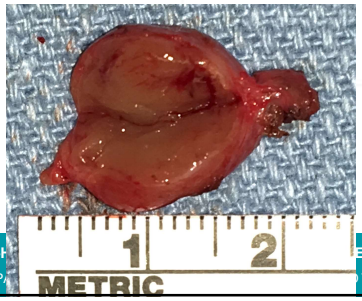
Anatomy

- >80% have 4 parathyroid glands
  - Autopsy studies: 3 glands (~1-7% of cases) and 5 glands (3-6%)
- Supplied by the **inferior thyroid artery**
- Variable size: ~30-40mg, ~6x3x2mm
- "Ocre" color (light yellow/brown)
- Polar vessel, fat cap





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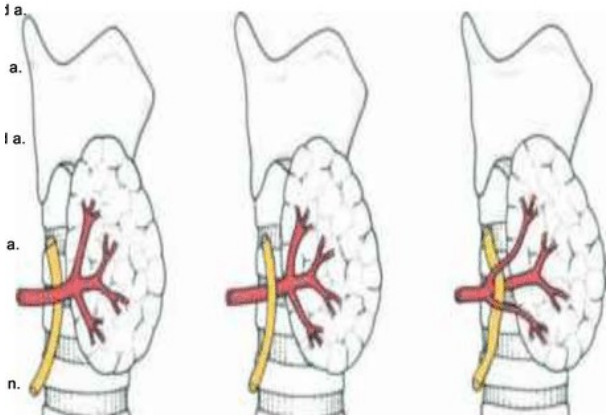
RLN & inferior thyroid aa.



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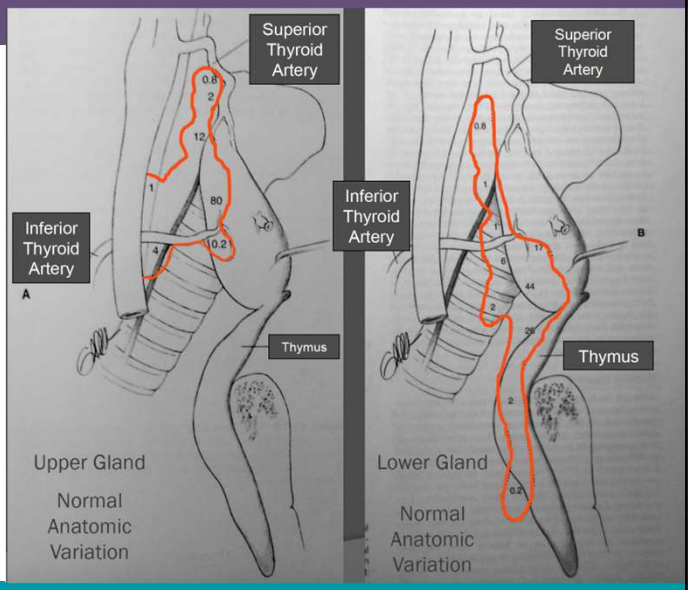
Intraoperative localization

- **Superior**: more reliable
  - (80%): near the junction of the RLN + Inf. Thyroid artery, deep to RLN
- **Inferior**: less reliable: superficial to RLN
  - 42% inf pole,
  - 39% thyrothymic ligament,
  - 15% lateral to thyroid,
  - 2% mediastinal

Aberrant Locations

Inferior: para-tracheal, Thymus, Intra-thyroidal

Superior: posterior neck, retropharyngeal–esophageal space, carotid sheath, and posterior mediastinum.



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Localizing Studies

- **Ultrasound**
  - Radiologist performed
  - Surgeon performed
  - Endocrinologist performed
- **Tc-99m Sestamibi**

Overall success rate >85% for single adenoma

Always opt for the *combination of an anatomic scan and an uptake scan*

Evaluate for concomitant THYROID PATHOLOGY

- **CT** (including SPECT-CT/4-D CT)
- MRI
- FNA with PTH washout level *
- Selective Venous Sampling *

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Pre-operative Imaging

HEAD & NECK
JOURNAL OF THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK

CLINICAL REVIEW

American Head and Neck Society Endocrine Surgery Section update on parathyroid imaging for surgical candidates with primary hyperparathyroidism

Mark Zafereo MD, Justin Yu BS, Peter Angelos MD, PhD, Kevin Brumund MD, Hubert H. Chuang MD, PhD, David Goldenberg MD, Miriam Lango MD, Nancy Perrier MD, Gregory Randolph MD, Maisie L. Shindo MD, Michael Singer MD, Russell Smith MD, Brendan C. Stack Jr MD, David Steward MD, David J. Terris MD, Thinh Vu MD, Mike Yao MD, Ralph P. Tufano MD, MBA ... See fewer authors

First published: 19 April 2019 | https://doi.org/10.1002/hed.25781 | Citations: 31

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High-resolution cervical ultrasonography

- 7-12 MHz transducer
- Scan from angle of jaw to clavicle, and from SCM to SCM
- Perpendicular views
- Adenoma: ovoid, hypoechoic, with clear separation from thyroid

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Ultrasound

Zafereo, M, Yu, J, Angelos, P, et al. American Head and Neck Society Endocrine Surgery Section update on parathyroid imaging for surgical candidates with primary hyperparathyroidism. *Head & Neck*. 2019; 41: 2398– 2409. https://doi.org/10.1002/hed.25781

- **90% sensitivity**
- **Safe (no radiation)**
- **Quick**
- **Well-tolerated (non-invasive, less claustrophobia)**
- **Less expensive**

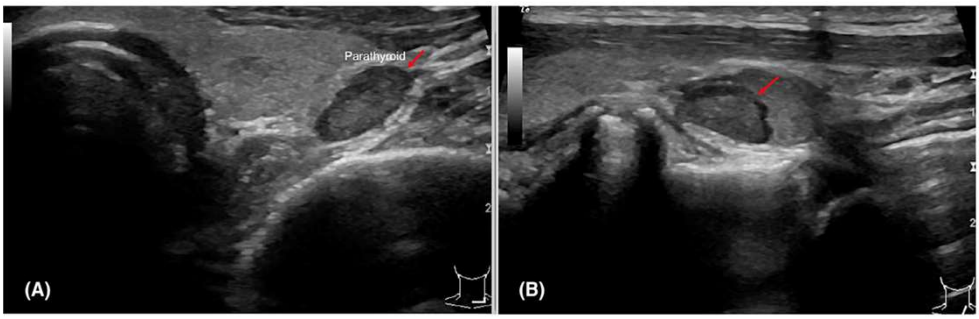

FIGURE 1 High-frequency grayscale neck ultrasound axial (A) and longitudinal (B) views shows a hypoechoic oval extrathyroidal parathyroid adenoma (arrow) abutting the posterior lateral margin of the thyroid [Color figure can be viewed at wileyonlinelibrary.com]

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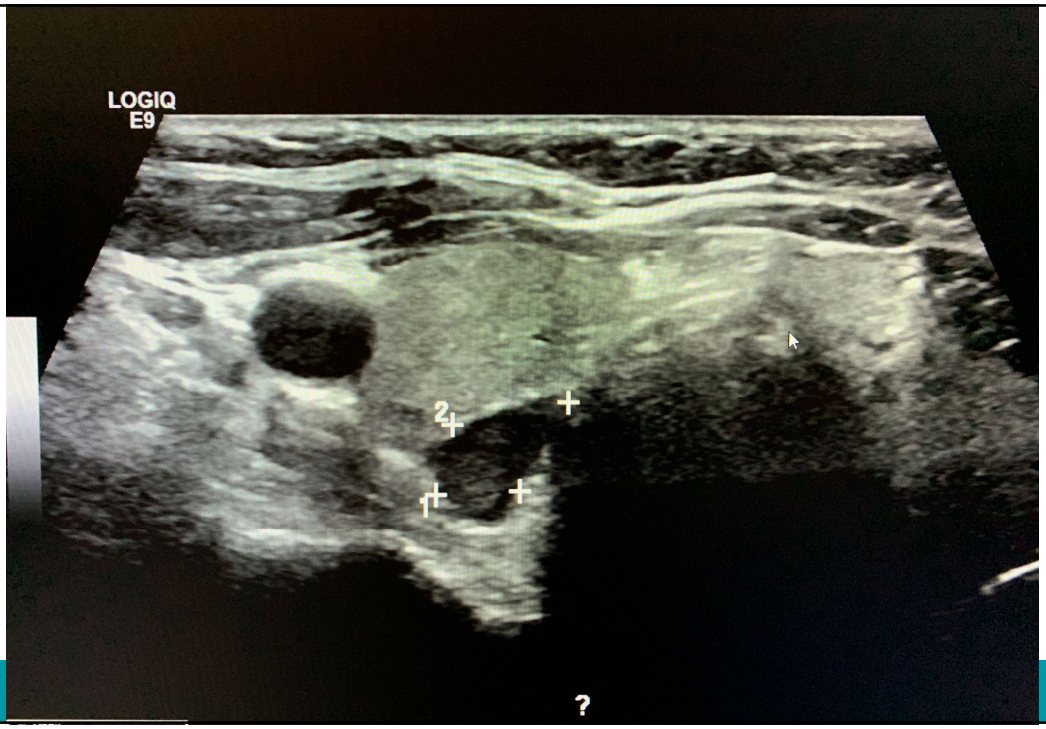

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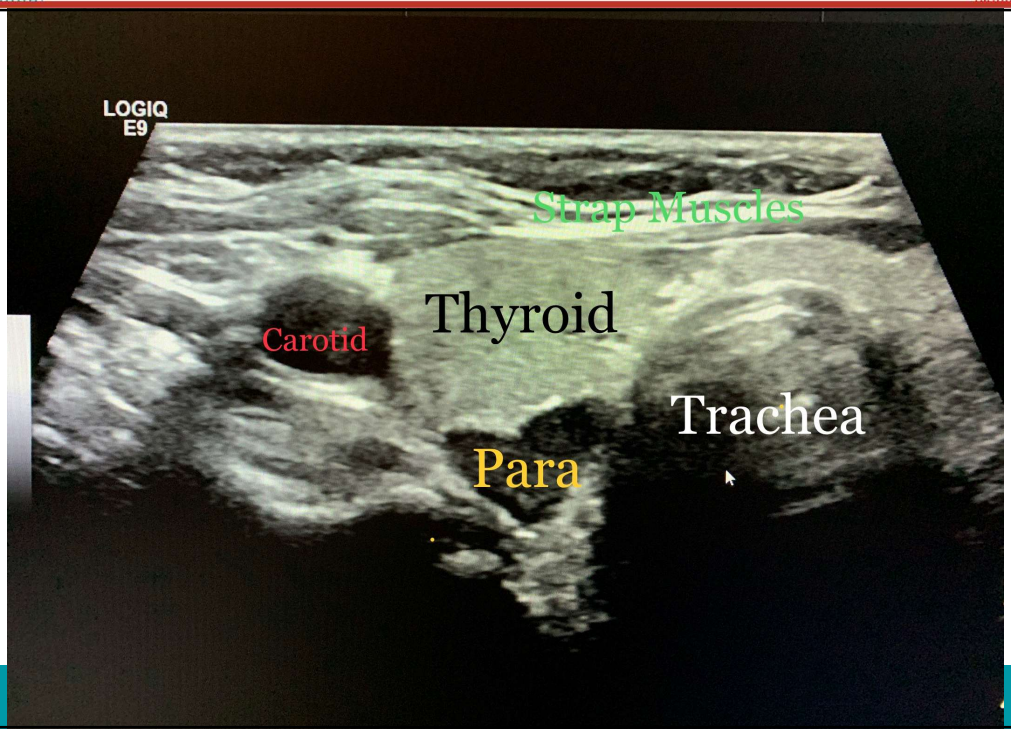

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Tc-99m sestamibi

- parathyroid scan
- adult dose: 20 mCi IV
- Tc99m-taken up by cells with a high concentration of mitochondria
- When the radiopharmaceutical is used for parathyroid imaging, immediate and delayed imaging of the neck and mediastinum is performed - parathyroid adenomas are best demonstrated on delayed imaging (1-2 hours).

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SPECT/CT

- Combines single photon emission commuted tomography with traditional CT scan
  - Functional Information
  - Anatomic Information

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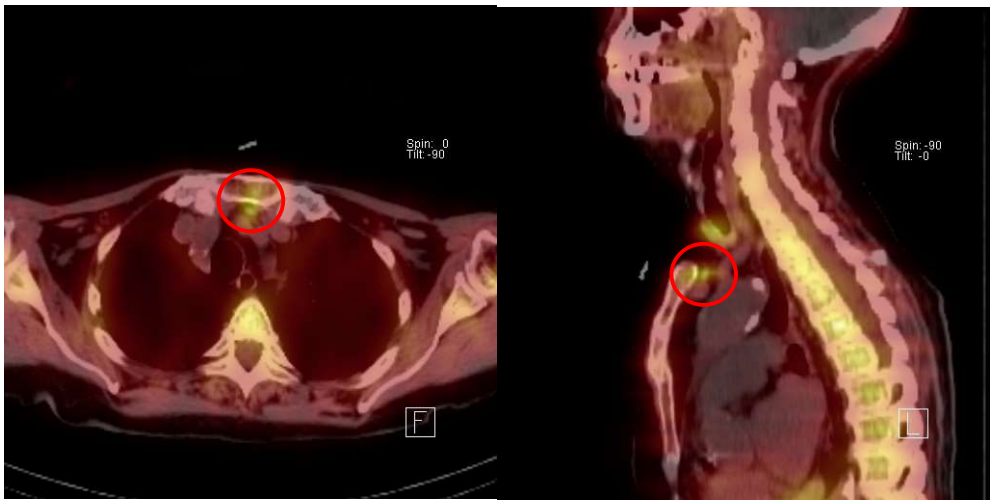

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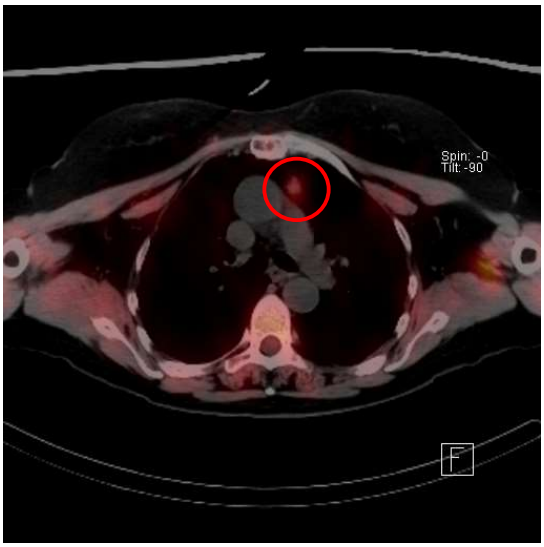

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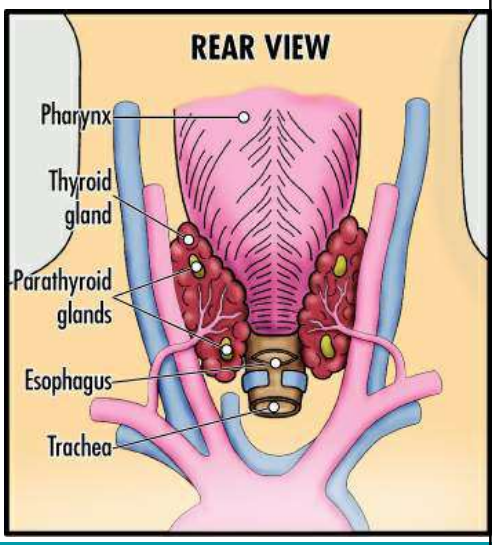
Conventional 4-Gland Exploration Parathyroidectomy

- Non-localizing imaging:
  - *Suspected MGH, double adenoma, small single adenoma, other reason for non-localizing imaging.*
- 4 gland identification is planned
- *Pre-op and intraop PTH levels used to ensure biochemical cure*
- *Can use adjuncts:*
  - *Gamma Probe*
  - *Selective venous sampling*
  - *NIRAF*
- 1-2% complication rate for high volume surgeons



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My Back Table:

4-Gland or Non-loc

LU

RU

Size:

Gamma:

Size:

Gamma:

LL

RL

Time	PTH

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Minimally Invasive Parathyroidectomy

- One or more pre-operative imaging studies localize a likely single adenoma
- limit dissection, hasten recovery, reduce postoperative discomfort, and reduce incision length.
- MIP can achieve cure in 97% to 99% of selected patients when adjunctive intra-op PTH is used to confirm biochemical cure
- *NOT for patients with known or suspected MGD or non-localizing scans*
- *Failure to achieve biochemical cure should prompt conversion to bilateral exploration*

JAMA Surg. 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

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"Minimally Invasive Parathyroidectomy"

- **MIP:** unilateral, focused exploration "Directed Parathyroidectomy"
- **MIRP:** use of intraoperative gamma probe
- **MIVAP:** use of video scope through incision or trocar

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2016.2310

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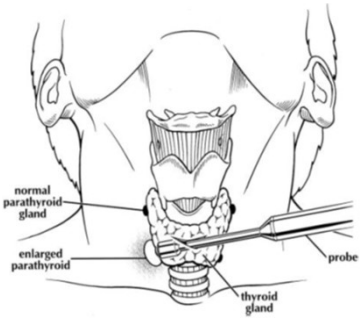
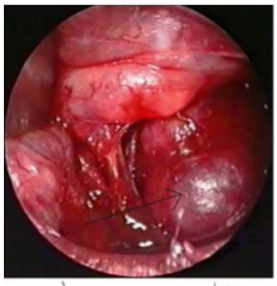
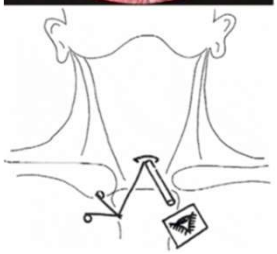
MIRP



MIVAP





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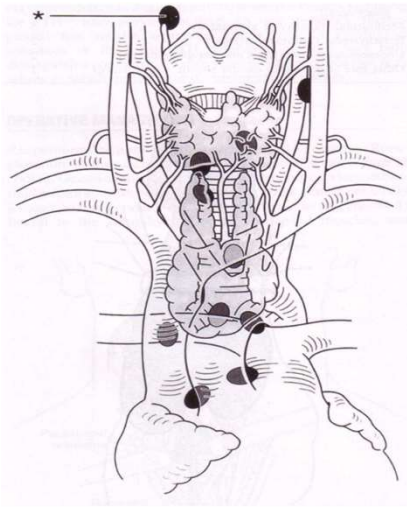
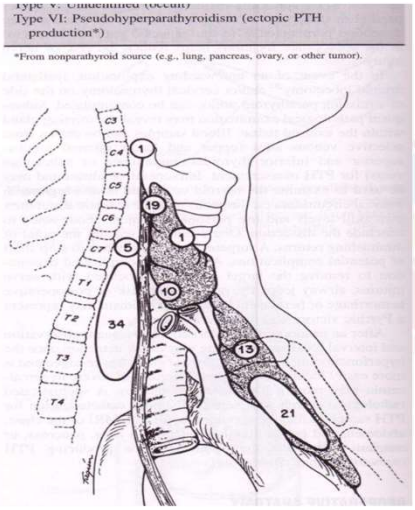
Radio-guidance: Usefulness

- **Ectopic glands**
  - 6-16% of glands are ectopic
  - Common reason for parathyroidectomy failure
- **Supernumerary glands** (breadcrumbs)
  - ~20% of pts
  - Thymus or retroesophageal
- **Small adenomas**





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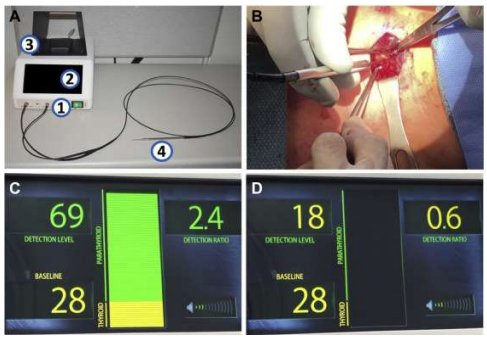
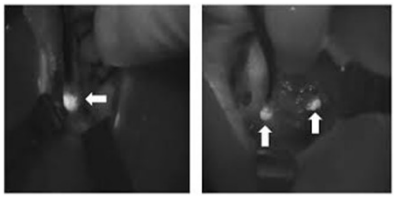
Near-infrared Autofluorescence

- **PTeye™ :** intra operative probe-based technology that aids surgeons in confirming suspected parathyroid tissue during thyroid and parathyroid surgery.
- label-free (no injection)
- Accuracy of 96% in confirming parathyroid tissue
- Adjunctive tool intended to aid in the identification of parathyroid tissue by confirming parathyroid tissue already visually located by the surgeon.



- Others: FluoBeam (Uses a camera and screen)

NIRAF does NOT confirm vascular supply or viable tissue



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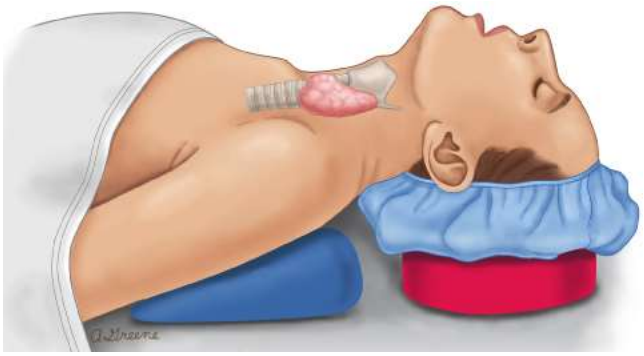
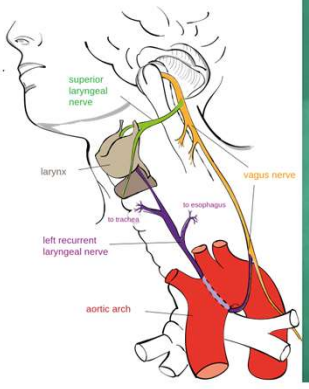
Intra-op Planning: Position and Incision

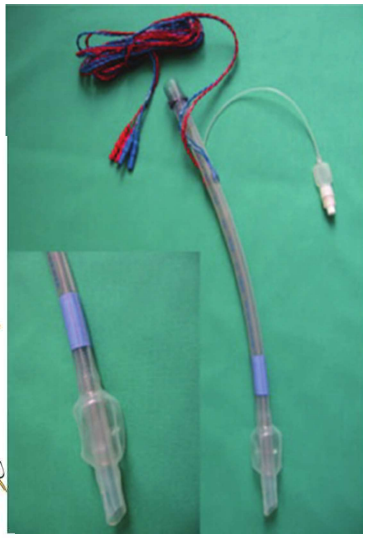
- Review imaging
- Confirm tools and adjuncts
  - Pre-op nuc med injection/gamma probe
  - Video-scopes/tower, endoscopic tray
  - PtEye/FLuoBeam
- Baseline PTH before induction of anesthesia
- Neck in slight extension
  - Be aware of patients with cervical spine issues!
- Protect the eyes
- **Esophageal Temp probe
- POCUS if available
- Plan the incision
  - Palpate landmarks
  - Find natural skin creases



Nerve Integrity Monitoring

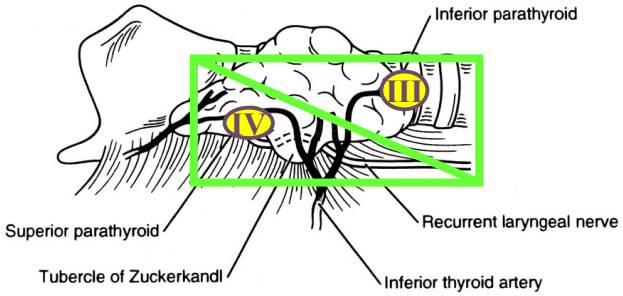
- Useful in non-localizing cases or any time you know there will be 4 gland exploration
- General Anesthesia
- *Useful when teaching residents…*
- *Useful in the setting of "professional voice users"…*
- *Useful in the setting of legal cases…*

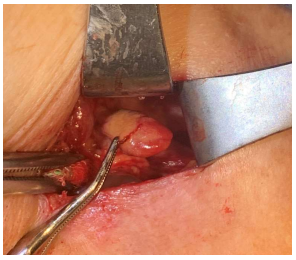




Intra-op: Parathyroids

- **Superior**: more reliable
  - (80%): near the junction of the RLN + Inf. Thyroid artery, deep to RLN
- **Inferior**: less reliable: superficial to RLN
  - 42% inf pole,
  - 39% thyrothymic ligament,
  - 15% lateral to thyroid,
  - 2% mediastinal





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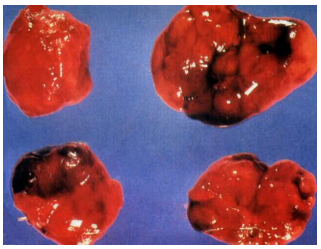
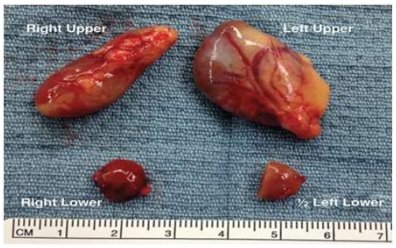
- Single adenoma* 85%
- Double adenoma* 2%
- Multiglandular hyperplasia 12%
- Carcinoma <1%



Hyperplasia



Adenomas

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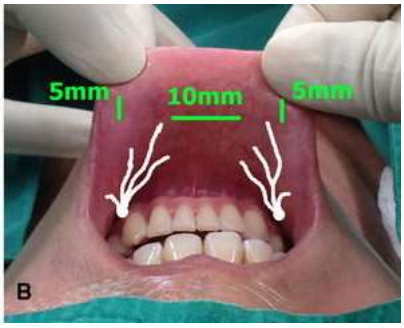
Intrathyroidal Parathyroid

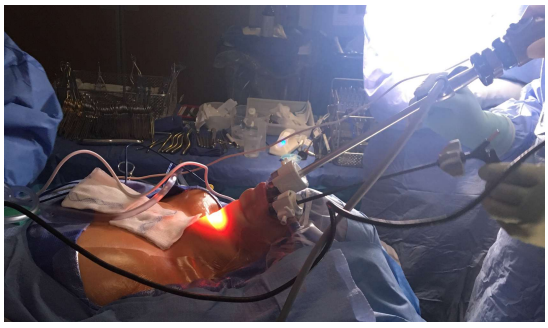
- Should be differentiated from subcapsular parathyroid glands
- **Incidence 0.5 - 4%,** and their frequency seems to be higher in case of hyperfunctioning glands.
  - **prevalence on the right side and the inferior 1/3 of the thyroid lobe.**
- Can be either PIII or PIV and even supernumerary glands.
- The possibility of an intrathyroid parathyroid adenoma *justifies careful palpation of the thyroid parenchyma during an operation for hyperparathyroidism when a gland, both inferior and superior, is missing*. Intraoperative PTH measurement after careful thyroid lobe palpation may reveal a rise in PTH levels and thus indicate a pathologic intrathyroidal gland.
- *Preoperative or even intraoperative ultrasonography* may be helpful in intrathyroidal gland identification when it is pathologic.
- True intrathyroidal hyperfunctioning parathyroid glands require thyroidotomy. A plane of cleavage always exists between the thyroid and the parathyroid, so it is usually possible to enucleate the gland.

Transoral thyroidectomy and parathyroidectomy – A North American series of robotic and endoscopic transoral approaches to the central neck

Jonathon O. Russell [a,*], James Clark [a], Salem I. Noureldine [a], Angkoon Anuwong [b], Mai G. Al Khadem [a], Hoon Yub Kim [c], Vaninder K. Dhillon [a], Gianlorenzo Dionigi [d], Ralph P. Tufano [a], Jeremy D. Richmon [a]



Surgical Endoscopy January 2018, Volume 32, Issue 1, pp 456–465



Oral Oncology 71 (2017) 75–80

Definitions

- **Persistent hyperparathyroidism** – biochemical evidence of HPT within 6 months after operation.
  - Failure to find the causative adenoma or second adenoma; or failure to recognize hyperplasia
- **Recurrent hyperparathyroidism** – disease occurring 6 months after exploration
  - Growth of hyperplastic tissue left behind, or metachronous second adenoma

Re-operative parathyroid surgery: 10 Questions

1. Is it a true diagnosis?
2. Is the patient symptomatic?
3. Who did the first operation? (high volume vs casual endocrine surgeon)
4. What are the details of the prior op-report?
5. What are the details of the pathology report? (How many/which glands were removed? Were they hypercellular/normocellular?)
6. Was there RLN injury? (Confirm this with NPL prior to surgery)
7. Is the culprit gland(s) localized?
8. Any discrete/suspicious lesions of the thyroid gland?
9. Any role for PTH washout? Selective Venous Sampling?
10. What are we willing to dissect or resect for non-localizing disease? Retropharyngeal space? Carotid sheath? Thyroid? Thymus?

Dr. Ehmad Kandil, Tulane

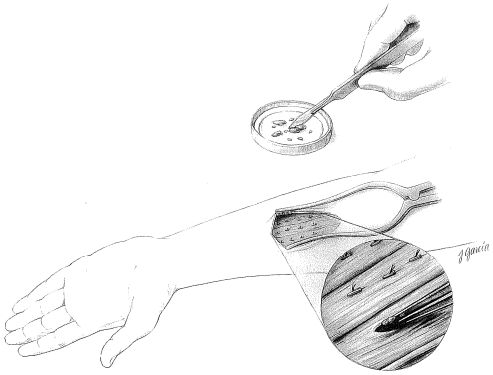
Complications of parathyroid surgery - 1

- Inability to find hyperactive gland(s)
- Compressive cervical hematoma (1%)
- Recurrent laryngeal nerve injury (0.5 – 3.0%)
  - Unilateral – hoarseness
  - Bilateral – vocal cords are in paramedian position→ tracheotomy
- Superior laryngeal nerve (external branch) *likely underreported for central neck surgery*
  - Weak voice
  - Voice fatigue
  - Singers cannot sustain high notes

Complications of parathyroid surgery - 2

- Hypoparathyroidism
  - Temporary (2 – 15%)
  - Permanent (0.5 – 3.0%)
- Hungry bone syndrome

Chvostek's and Trousseau's sign



Primarily autotransplanted tissue functions adequately in 90-95% of patients.
Secondarily transplanted cryopreserved tissue functions in 60-65% of patients.

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Parathyroid Surgery Pearls

1. Always review imaging with a critical eye
2. Pre-op PTH prior to induction of anesthesia
3. Anticipate anatomy and possibility of >1 adenoma even with localizing scans
4. Don't devascularize thyroid (or parathyroid) unnecessarily
5. For MGH, be prepared for re-implantation and/or cryopreservation
6. Volume=experience=good outcomes=happy patients/surgeon

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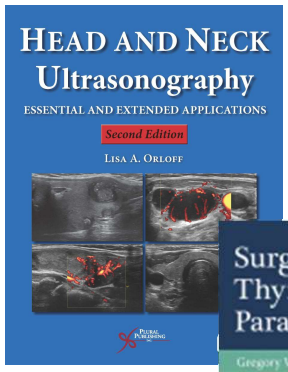
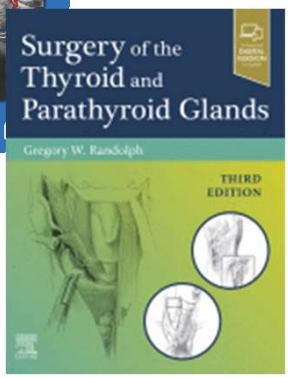
Resources





AHNS Website/Publications

AAES Website/Publications

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THANK YOU!

"Investment in knowledge pays the best interest."
Benjamin Franklin

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Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

John P. Bilezikian, Maria Luisa Brandi, Richard Eastell, Shonni J. Silverberg, Robert Udelsman, Claudio Marcocci, and John T. Potts Jr

Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones[a]

	1990	2002	2008	2013
Measurement[b]				
Serum calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: Z-score <−2.0 (site unspecified)	BMD by DXA: T-score <−2.5 at any site[b]	BMD by DXA: T-score <−2.5 at any site[b] Previous fragility fracture[c]	A. BMD by DXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius[b] B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR reduced by >30% from expected B. 24-h urine for calcium >400 mg/d (>10 mmol/d)	A. eGFR < 60 cc/min B. 24-h urine for calcium not recommended	A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis[d] C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age, y	<50	<50	<50	<50

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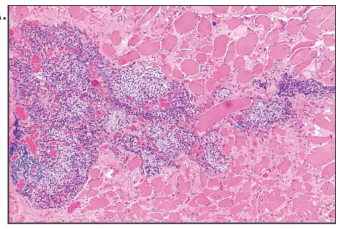
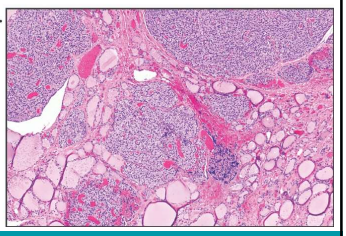
Parathyroid carcinoma

- Rare malignancy; 0.5% of patients with HPT
- Profound hypercalcemia (>14) and hyperparathormonemia (>1,000)
- Cancer is palpable in 50% of patients
- Suspected at operation if parathyroid is hard, white, has an irregular capsule, or is invasive; rarely diagnosed preoperatively
- Surgery: en bloc resection of ipsilateral thyroid lobe and central compartment lymph nodes; resection of local recurrent or metastatic disease if possible
- Indolent malignancy: local or distant metastases occur over many years
- 5 year survival is 40-69%
- Palliative bisphosphonates can help maintain eucalcemia with metastatic disease

A.



B.



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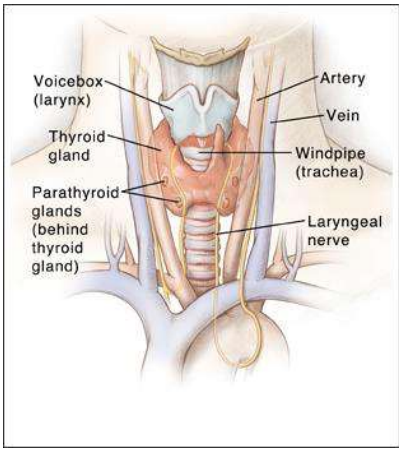
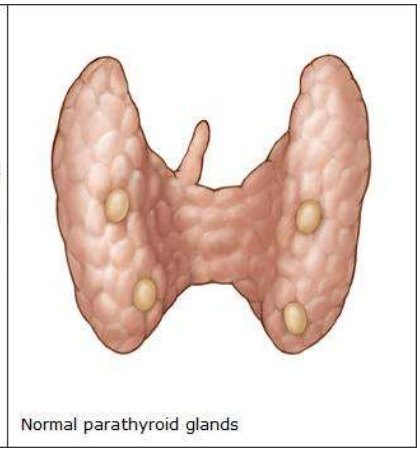
ANATOMY QUICK REVIEW: Parathyroid Glands




Normal parathyroid glands

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Parathyroid Cyst

- **RARE!**
- Usually involve the lower parathyroid glands
- Usually **LARGE (1-6cm)**
- Sometimes referred to as **third pharyngeal pouch cysts**
- Unilocular, smooth walled, and contain **watery clear fluid**, which is **high in PTH content.**
- Immunostaining of the cyst for PTH will demonstrate strong reactivity in the lining cells
- Can be difficult to distinguish from a cystic thyroid nodule. The aspiration sample almost always consists of watery clear fluid, which can be assayed for PTH to confirm

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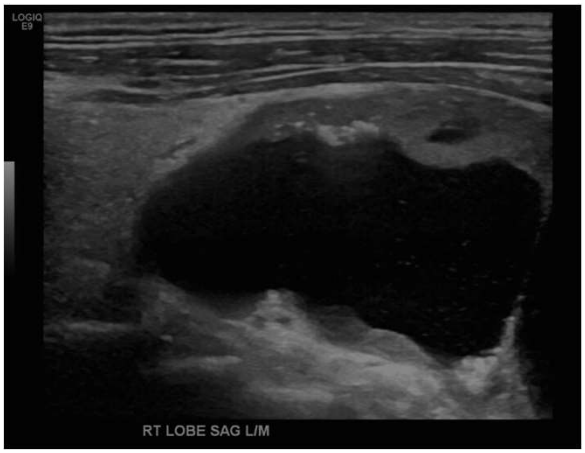
- 58yoM presents to the ED with acute abdominal pain and nausea/vomiting as well as "not himself" "talking nonsense" per his family members→ diagnosed with acute pancreatitis and admitted. During his workup, Ca was found to be 16.8. On exam he was found to have a palpable mass just to the right of the trachea above the right clavicle.
- Imaging: U/S of the neck-->
- PTH: 1120



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- **Mild** – may be treated as outpatient with hydration and reduced oral calcium intake
- **Marked** (**hypercalcemic crisis**) – dehydration, excessive thirst, loss of appetite, lethargy, confusion, nausea and vomiting, constipation, muscle and joint pains
  - Often requires admission, with monitoring
  - EKG changes such as shortened QT interval and broad QRS complex and/or T-waves
  - Tx:
    - **Aggressive hydration** with normal saline 200-300ml/hr
    - **Calcitonin** + **IV bisphosphonate** (zolendronic acid or pamidronate)
    - Corticosteroids
    - Loop diuretic once hydrated—only if heart or renal failure
    - Oral phosphate
    - Plicamycin (mithramycin)
    - Dialysis
    - Parathyroidectomy

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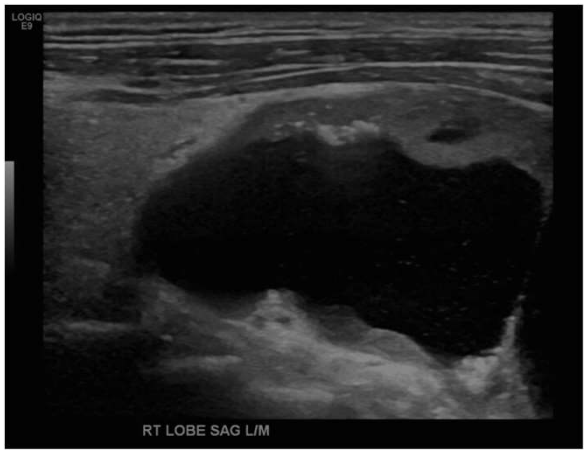
- Parathyroid Ca
- Other malignancy
  - Especially in the setting of very high PTHrP
- Parathyroid Cyst
- PHPT
- Granulomatous disease



63

Parathyroid carcinoma

- Rare malignancy; 0.5% of patients with HPT
- Profound hypercalcemia (>14) and hyperparathormonemia (>1,000)
- Cancer is palpable in 50% of patients
- Suspected at operation if parathyroid is hard, white, has an irregular capsule, or is invasive; rarely diagnosed preoperatively
- Surgery: en bloc resection of ipsilateral thyroid lobe and central compartment lymph nodes; resection of local recurrent or metastatic disease if possible

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Parathyroid carcinoma - 2

- Indolent malignancy: local or distant metastases occur over many years
- 5 year survival is 40-69%
- Palliative bisphosphonates can help maintain eucalcemia with metastatic disease
- Pearl: *a palpable neck mass in a patient with hypercalcemia is usually a thyroid nodule, but can be parathyroid cancer*

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Rare Diseases: Parathyroid Cyst

- **RARE!**
- Usually involve the lower parathyroid glands
- Usually **LARGE (1-6cm)**
- Sometimes referred to as **third pharyngeal pouch cysts**
- Unilocular, smooth walled, and contain **watery clear fluid**, which is **high in PTH content.**
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- Can be difficult to distinguish from a cystic thyroid nodule. The aspiration sample almost always consists of watery clear fluid, which can be assayed for PTH to confirm

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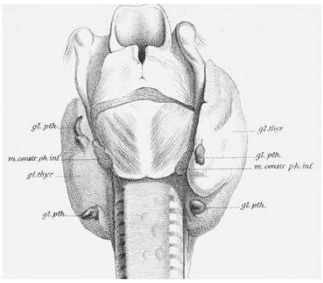
History

1850: English anatomist Richard Owen dissecting an Indian rhinoceros who died in the London zoo. Published in 1852.

1852 — **1880**

Credit for the discovery of the parathyroid glands is often given to the Swedish anatomist and histologist Ivar Sandström who published the first systematic review of the glands in 1880.



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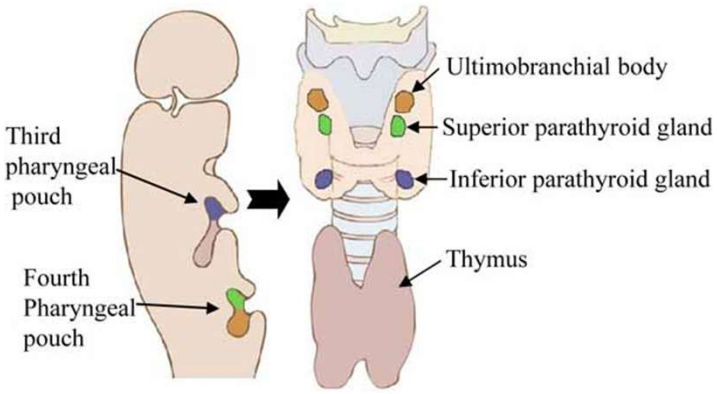
- Endodermal
- Derived from third (Inferior) and fourth (Superior) branchial pouches.
- Superiors (IV): located near the posterior and middle aspects of the thyroid laterally.
- Inferiors (III): found at the inferior poles of thyroid or in the thyro-thymic ligament.



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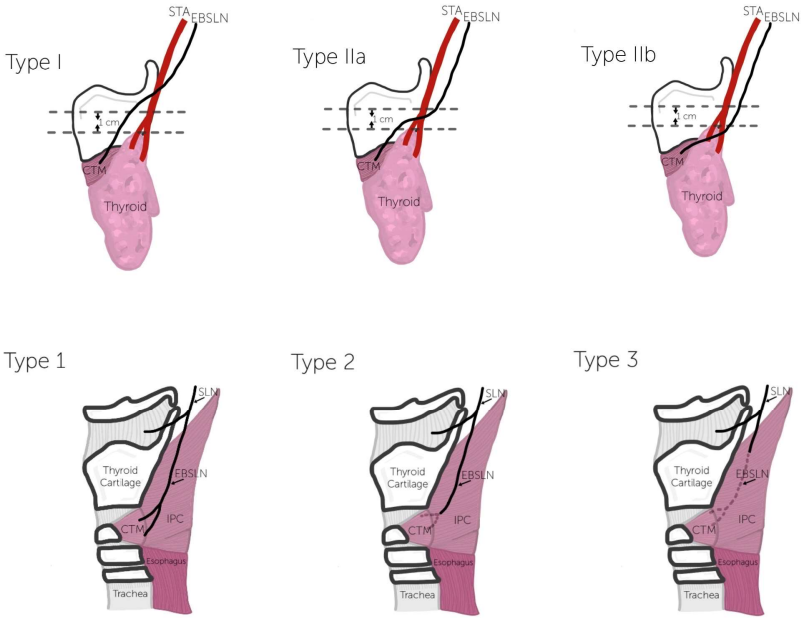
Surgical Anatomy:

External Branch of Superior Laryngeal Nerve



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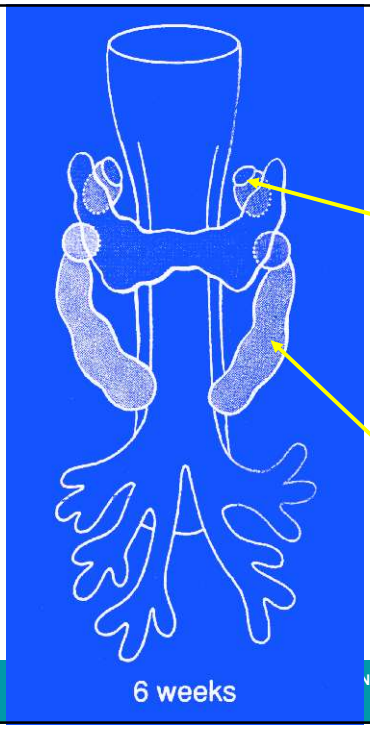
Parathyroid Embryology



Superior Parathyroid (Branchial Pouch IV)

Median Thyroid Component

Inferior Parathyroid (Branchial Pouch III)

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Hypercalcemia – Symptoms/Signs

	Basis	Rapid onset	Mild and gradual	
Bone	PTH induced osteoclastic activity	Bone pain	Bone pain, fractures	Bones
			Osteitis fibrosa cystica	
Neuro/ Muscular	Suppression of synaptic transmission, excitation/contractio	Impaired intellect	Altered mental status	Moans
		Weakness	Malaise, fatigue	
			Constipation	
Kidneys	Hypercalciuria	Nephrogenic DI (polyuria/thirst)	Nephrogenic DI (polyuria/thirst)	
			Urolithiasis (Ca Phosphate	Stones
			Renal insufficiency	
GI		Anorexia, nausea	Anorexia, nausea	
	Gastrin production		**Peptic ulcer disease**	Groans
	Hypercalcemia		Pancreatitis	
Other			Extra-osseous calcification: valvular and arterial	
			Hypertension	

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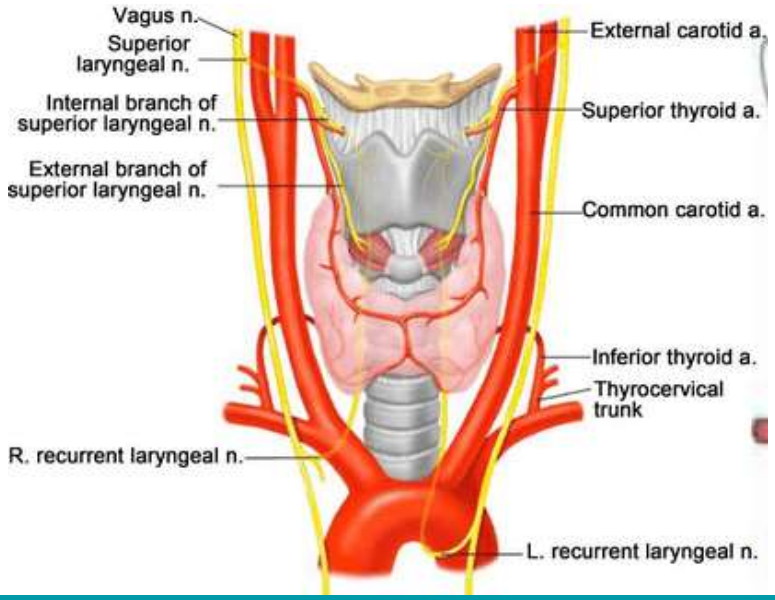

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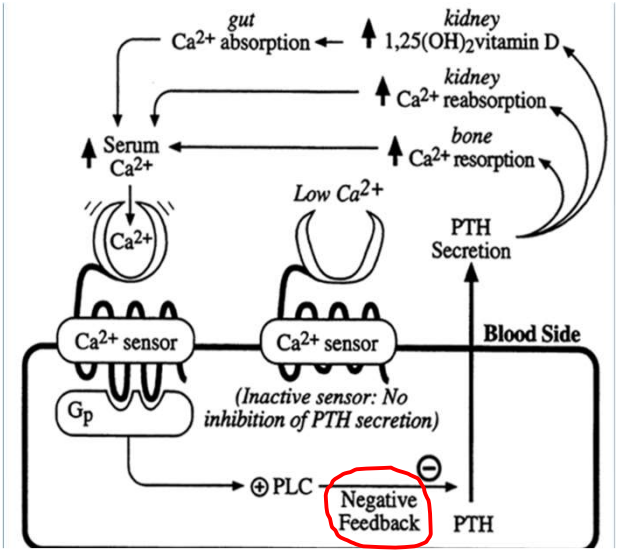
- Vital for muscle and nerve function, hormone synthesis and release, cell signaling, coagulation, etc.
- Maintained by the parathyroid glands by release of PTH
  - CaSR
  - Negative feedback loop



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Case #3, operation and findings

- Reoperation done under general anesthesia, though only left side explored.
- 600mg left upper parathyroid located in normal anatomic position.
- IOPTH: 204 → 28
- Path: Hypercellular parathyroid
- Post-op Ca = 9.6
- Lessons learned

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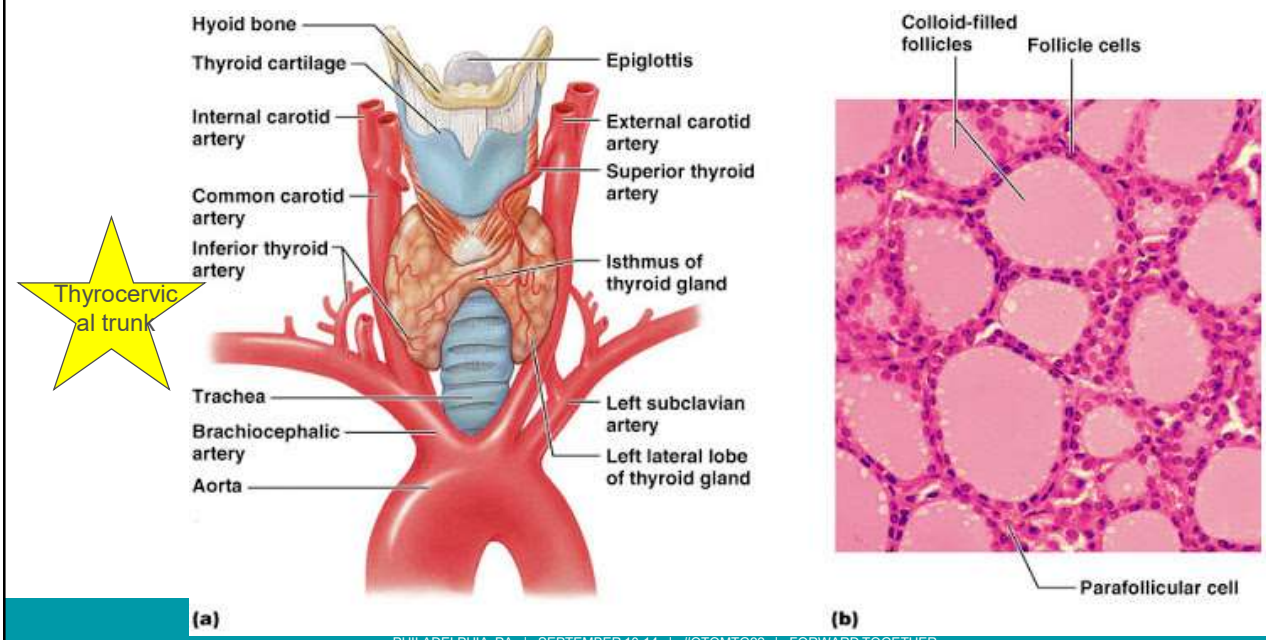
ANATOMY QUICK REVIEW: Thyroid Gland



75

- Oral calcium supplementation
  - Start with 500mg PO TID; max is about 4500mg daily
- Parenteral calcium
  - One ampule (1gm) calcium gluconate as needed
  - Calcium gtt (6 amps of calcium in 500cc D5W, run as 1ml/kg/hr)
    - Requires cardiac monitoring
- Vitamin D repletion (25-OH and 1,25-$(OH)_2$)

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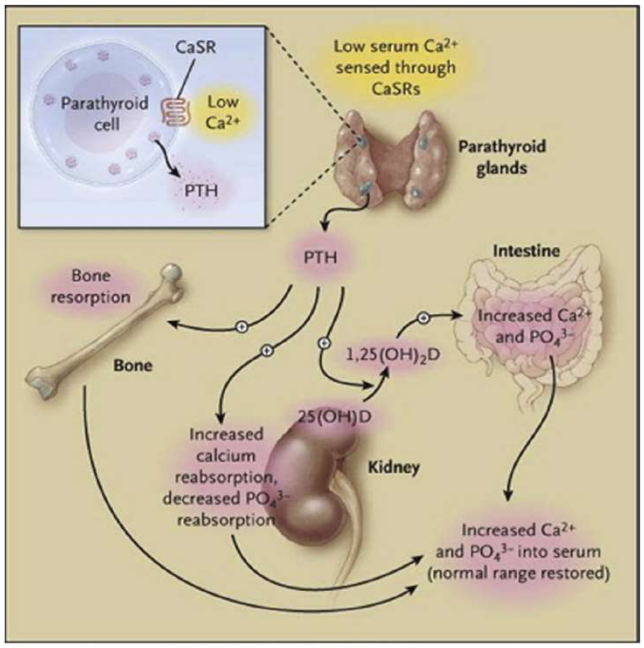

Calcium Homeostasis and Parathyroid Hormone

Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med 2008;359:391–403.

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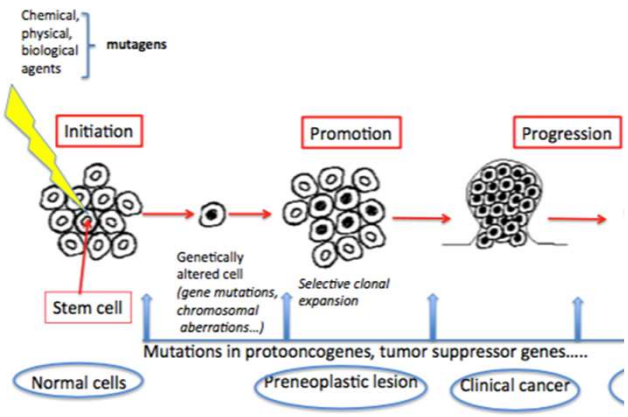
Parathyroid Adenoma: what causes it?

- Current paradigm for neoplasia: a single cell has acquired **a competitive growth advantage** as the result of a **heritable change in gene function**, and gives rise to a *clone of cells* that at first are genetically and phenotypically identical.
  - **somatic** mutation
  - **epigenetic** change in gene expression
- **Mono-phenotypic,** probably as a result of growth from a single genetically dysfunctional cell.
- If the dysfunction is due to a mutation,
  - **hereditary** genetic abnormality
  - **exposure** to external mutagens(irradiation)
  - **unknown**



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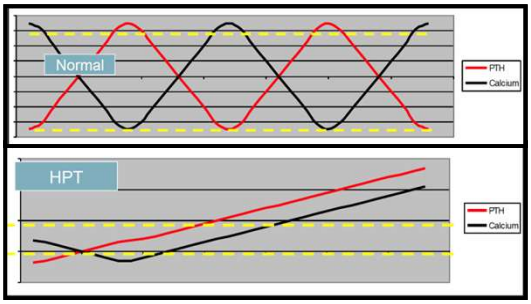
PTH: Osteocatabolic or anabolic?

- 1990s: Rat studies by Dobnig et al. showed that PTH could serve primarily a catabolic or anabolic role depending upon the way in which the hormone was administered.
- While continuous 24-hour exposure to PTH in rats resulted in the expected catabolic effects, in animals treated with low doses of PTH once daily (i.e., intermittently), marked anabolic effects on the skeleton were observed. This finding was confirmed in human subjects.
- At the cellular level, gene expression profiling of continuous versus intermittent PTH administration in vivo and in vitro suggests that the two modes of administration of PTH can regulate different sets of genes, the first favoring bone resorption and the second favoring bone formation.



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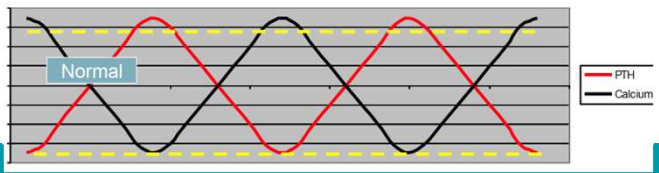
PTH effect on the kidney

- Primary action: **phosphate and calcium transport** (spatially separated along the nephron)
- **Regulation of acid– base balance** (far less prominent)
- Affects **renal metabolism**—may become important under pathological settings or stress, where renal gluconeogenesis can contribute significantly to support glucose homeostasis.
- Specific mechanisms in the kidney selectively **remove PTH from circulation**, thereby contributing to the rapid decline in circulating PTH levels and the important intermittent pulsatile pattern of PTH that is critical for bone anabolism and skeletal repair and turnover.



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PHPT: Genetics

- **Cyclin D1 (PRAD1 or CCND1**) and **MEN1** , are the most solidly established molecular drivers of sporadic (non-familial) parathyroid adenomas, the most common form of primary parathyroid neoplasia.
- Other possiblities:
  - CDKN1B and other CDKI genes
  - EZH2 ,
  - POT1
  - CTNNB1
  - CDKI
  - CASR
  - AIP

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PHPT Risk Factors→ Radiation

- **Ionizing radiation** is a recognized risk factor for the development of sporadic PHPT due to parathyroid adenomas.
- Use of therapeutic head/neck radiation in the 1930s and 1940s in the United States for benign conditions such as acne has been associated with surgery for parathyroid adenomas three decades thereafter.

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What are the indications for surgical intervention in an asymptomatic patient with PHPT?

Box 2. Guidelines for Surgery in Asymptomatic pHPT as Outlined in the 2014 Consensus Conference[a]

Serum Calcium (>upper limit of normal): 1.0 mg/dL (for millimoles per liter, multiply by 0.25)

Skeletal
- BMD by DXA: T score of less than −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius
- Vertebral fracture by radiography, CT, MRI, or VFA

Renal
- Creatinine clearance of less than 60 mL/min
- 24-hour urine sample results for calcium more than 400 mg/dL (>10 µmol/d) (for millimoles per liter, multiply by .25) and increased stone risk by biochemical stone risk analysis
- Presence of nephrolithiasis or nephrocalcinosis by radiography, ultrasound, or CT

Age Younger Than 50 y

Abbreviations: BMD, bone mineral density; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; pHPT, primary hyperparathyroidism; VFA, vertebral fracture assessment.

[a] Adapted with permission.[1]

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- Magnesium oxide (400mg 1-2x per day)
- Hydrochlorothiazide
- Forteo

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