

PRESENTATION 1

HYPERCALCEMIA, OSTEOPOROSIS AND HYPERPARATHYROIDISM



ALBANY MEDICAL CENTER

KNOWN FOR OUR EXPERTISE. CHOSEN FOR OUR CARE.

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Impact of Hypercalcemia

1. Calcium >2.6 mmol/L

Stones (kidney or biliary)

Bones (bone pain)

Groans (abdominal pain, nausea and vomiting)

Thrones (polyuria)-nephrocalcinosis

Psychiatric overtones (30% depression, anxiety, coma)

2. Negative bathmotropic effect

calcium blocks sodium channels, ↓ excitability

inhibits depolarization of nerve and muscle

↓ reflexia, tonicity of smooth and skeletal muscle

3. EKG changes

Short QT intervals

Hypercalcemia

Differential Diagnosis

90% { Hyperparathyroidism (out patient)
Malignancy (hospital)

- ▣ Endocrine diseases - hyperthyroidism
addisonian crisis
- ▣ Sarcoidosis and other granulomatous disease
- ▣ Milk - alkali syndrome
- ▣ Drugs - Thiazide diuretics
Lithium
Vitamin A & D intoxication

- ▣ Familial hypocalciuric hypercalcemia
- ▣ Paget's disease
- ▣ Immobilization

Treatment of Hypercalcemia

1. Hydration

2. ↑ salt intake ↑ body fluid volume
 ↑ urine sodium excretion
 ↑ urine potassium excretion

3. Loop diuretic (e.g. furosemide)

minimize overload

depress calcium resorption by kidney

4. Bisphosphates (pyrophosphate analogues)

high affinity for osteoclasts

inhibit bone resorption

etidronate, alendronate, zoledronate

5. Calcitonin

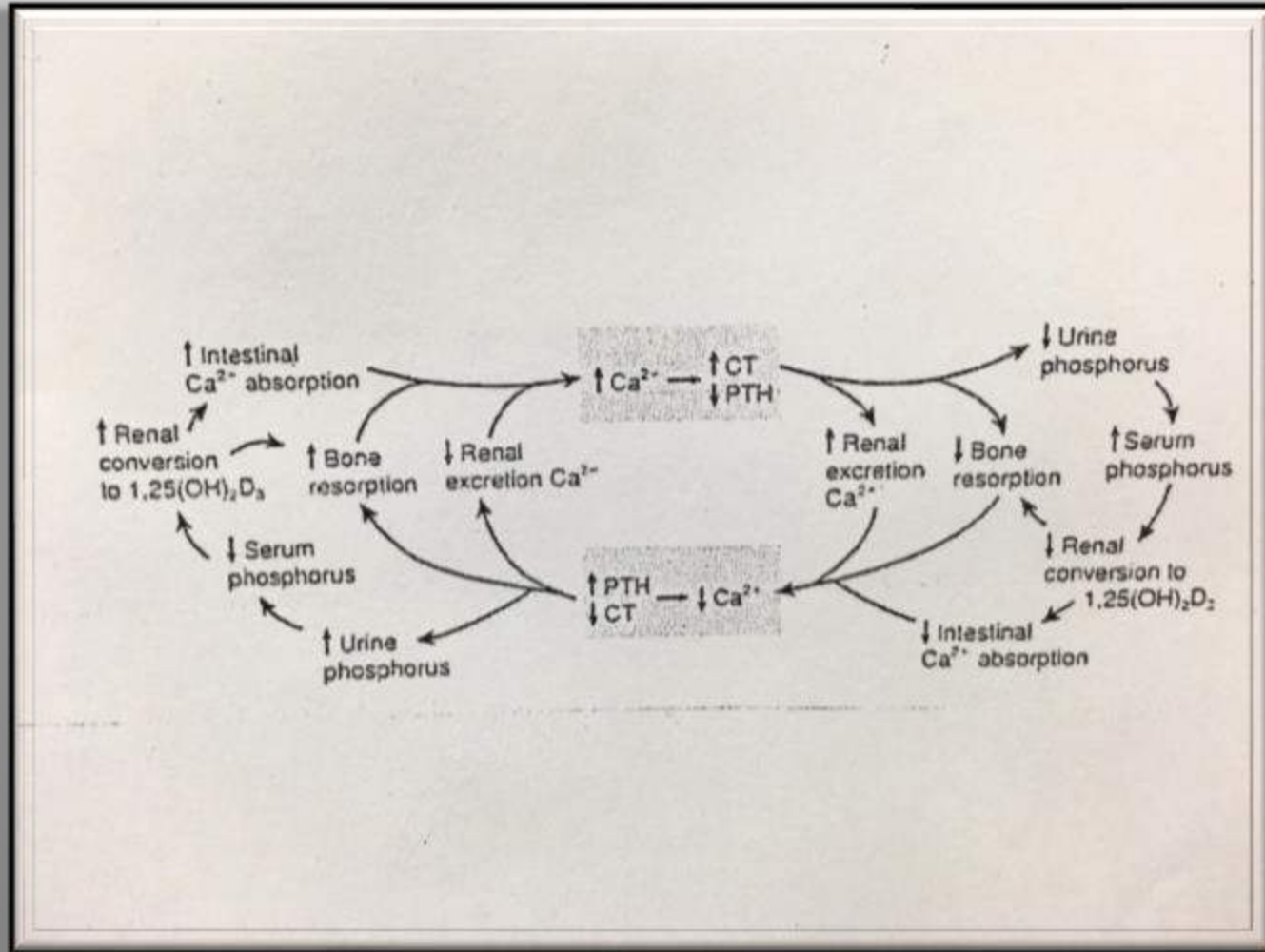
blocks bone resorption

inhibits calcium resorption by kidney

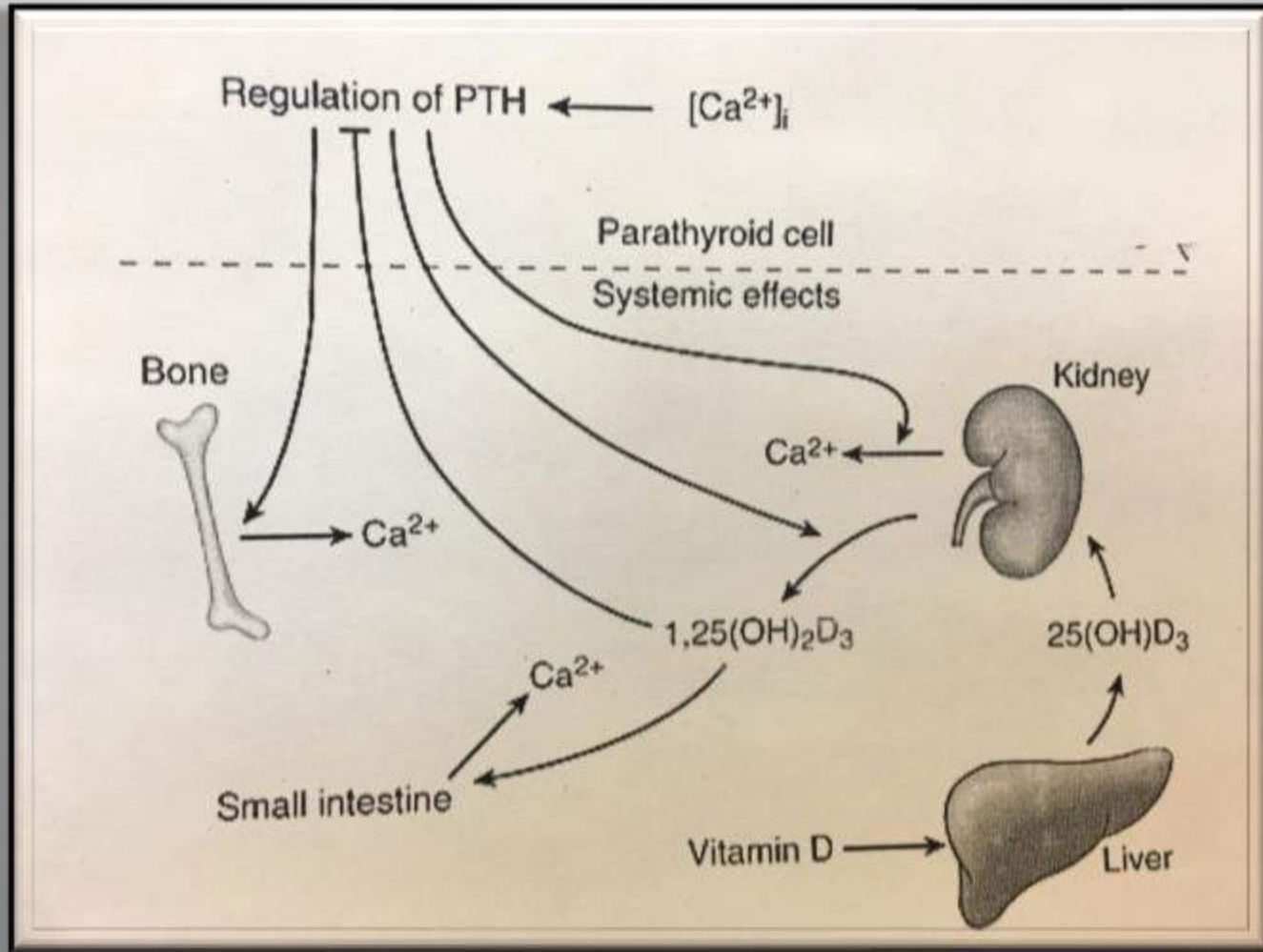
Hypercalcemic Crisis

1. > 3.5 mmol/L (> 14 mg/dL)
2. Oliguria, somnolence, coma
3. Check for hyperparathyroidism
4. Extensive hydration
5. Calcitonin
6. Bisphosphonates
7. Surgery for neck exploration
if 1° hyperparathyroidism

Calcium Physiology



Calcium Physiology



Osteoporosis

- ▣ Most prevalent disease of the skeleton
- ▣ More than 200 million people in the world suffer from osteoporosis
- ▣ Low bone mass, progressive deterioration leading to susceptibility to fracture
- ▣ Definition ≥ 2.5 SD below young healthy female T score on bone densitometry

Osteoporosis

- ▣ > 33% of women age 60-70 have osteoporosis
- ▣ > 66% of women > 80 years old have osteoporosis
- ▣ 20% minimum have an osteoporotic fracture in their lifetime
- ▣ fragility fracture- fall from a standing height
- ▣ silent disease, seen only in low bone density until fracture occurs

Osteoporosis

- ▣ Primary Osteoporosis
 - Explained by changes of aging
 - Explained by hormonal changes of menopause and a decrease in estrogen
- ▣ Secondary Osteoporosis
 - Inflammatory (RA, SLE, Crohn's, UC)
 - Hypogonadism (premature menopause – auto immune, surgical, drugs)
 - Endocrinopathies
 - ▣ Hypopituitary
 - ▣ Hypercortisolemia (Cushing's syndrome)
 - ▣ Hyperthyroidism
 - ▣ Hyperparathyroidism
 - ▣ Hyperprolactinemia

Mechanism for Osteoporosis

- ▣ Estrogen decrease -> increase in cytokines

- ▣ IL-1, IL-6, TNF- α
 - stimulatory to osteoporosis
 - Inhibitory to osteoblasts

Selected Regulators of Bone Remodeling

	Osteoblasts	Osteoclasts
Stimulatory	BMPs	IL-1
	FGFs	IL-6
	Insulin	IL-17
	PTH	M-CSF
	TGF-β	RANKL
	Wnt	TNF-α
Inhibitory	DKK1	IFN-γ
	IL-1	IL-3
	IL-6	IL-4
	SOST	IL-10
	TNF-α	IL-12
		OIP-1
	OPG	

Estrogen Effects in Bone Physiology

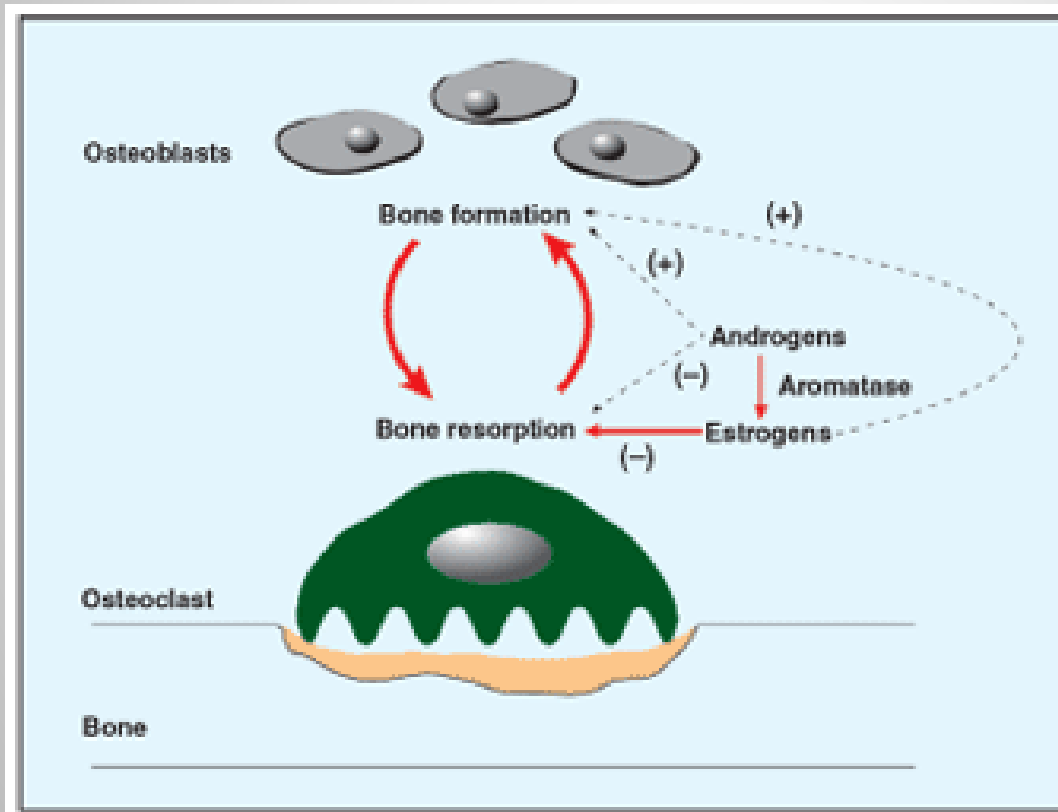


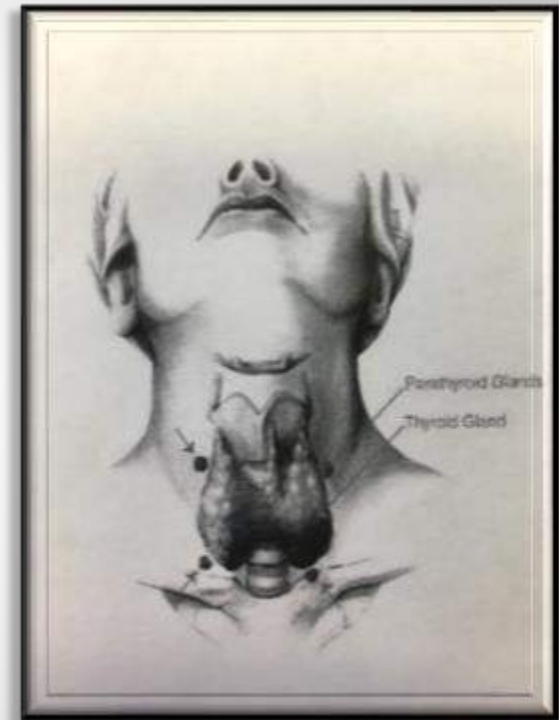
Figure 1: Mechanism of Action— Estrogen regulates physiologic bone remodeling by suppressing osteoclast-mediated bone resorption. During aromatase inhibitor-associated or postmenopausal estrogen deficiency, bone resorption and osteoblast-mediated bone formation are imbalanced, leading to net bone loss.

Secondary Osteoporosis

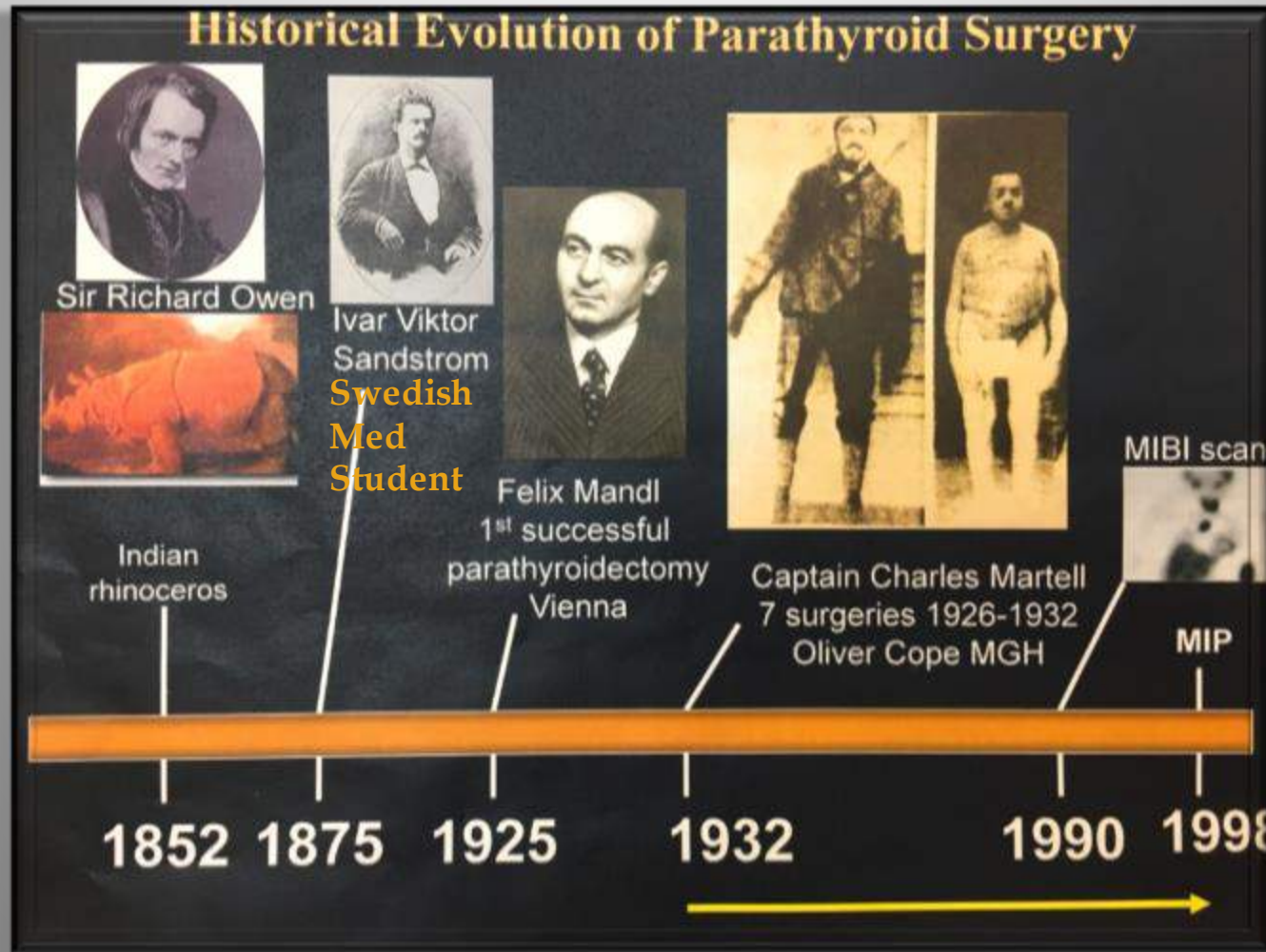
- ▣ Hyperparathyroidism
- ▣ Surgical treatment can result in reversal (cure) of osteoporosis

PRIMARY HYPERPARATHYROIDISM

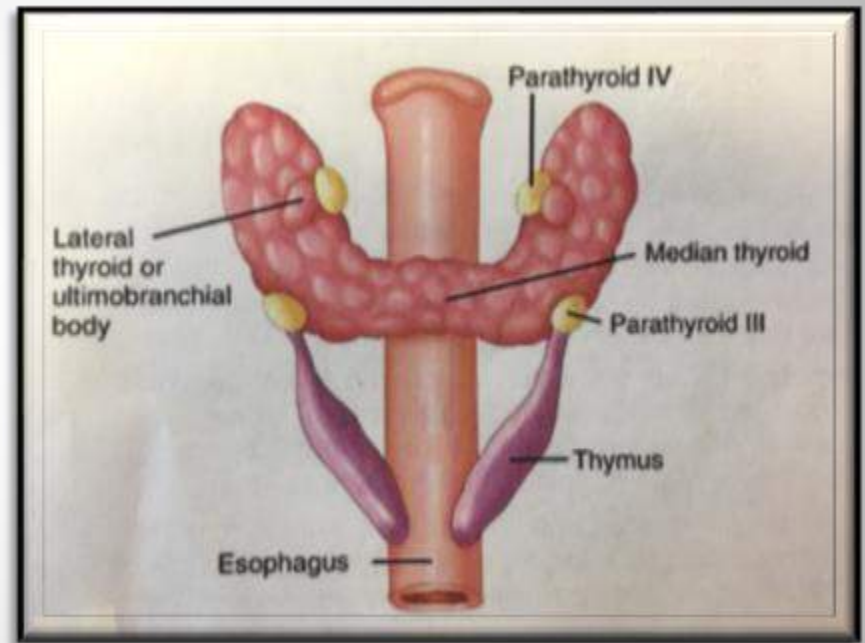
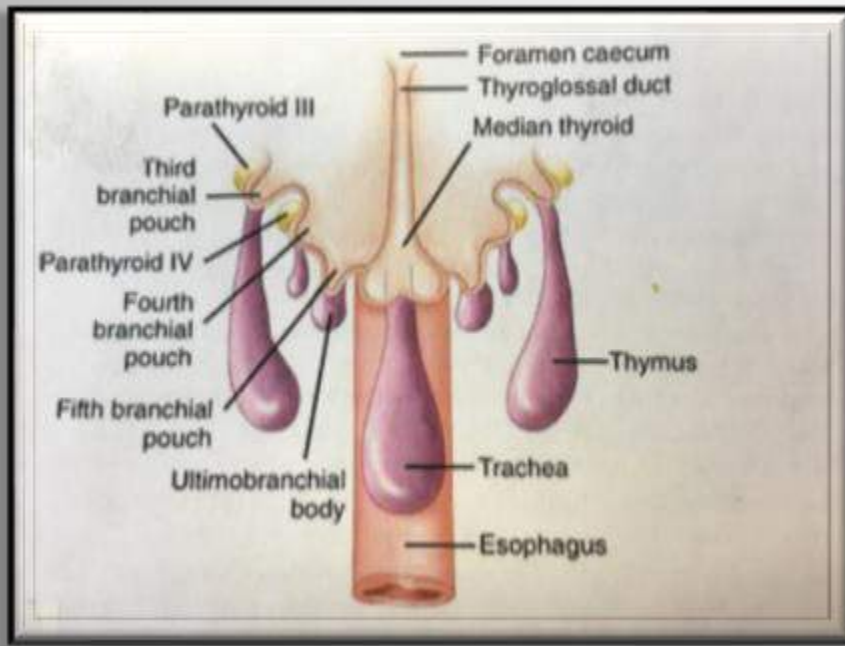
- 100,000 new cases/year in US
- 0.1 to 0.3 % of general population
- More common in women
- 1:500 women
- 1:2000 men
- ↑ PTH production → hypercalcemia
 - ↑ GI calcium absorption
 - ↑ Vitamin D3
 - ↓ renal calcium clearance
- ↑ PTH independent of calcium level



History of Parathyroid in Humans



Embryology of Parathyroids



Henry, J in Randolph, G, ed. Surg of Thyroid & Parathyroid Glands. 2003.

PRIMARY HYPERPARATHYROIDISM

Clinical Presentation

“Bones, stones, abdominal groans, and psychic moans”

Renal

- Nephrocalcinosis
- nephrolithiasis
- calciuria
- polyuria
- overflow incontinence

Bone

- Osteitis fibrosa cystica
- osteopenia/osteoporosis
- bone pain
- pathological fractures

Gastrointestinal

- Nausea/vomiting
- Anorexia
- Constipation
- abdominal pain
- Pancreatitis
- Reflux
- peptic ulcers

Cardiovascular

- Hypertension

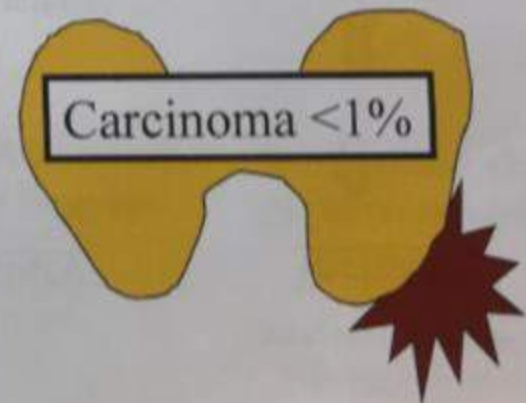
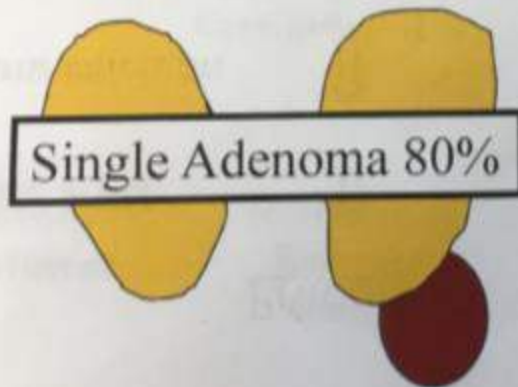
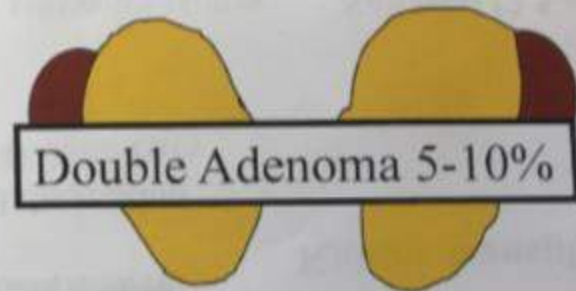
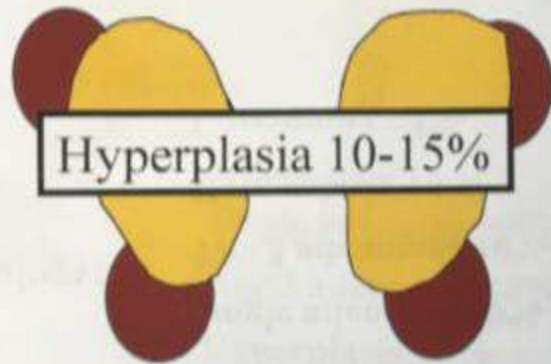
Neuropsychiatric

- Depression
- Anxiety
- psychosis
- memory loss
- concentration problems

Neuromuscular

- Fatigue
- Myalgias
- muscle weakness

Etiology- 1°HPTH



Primary

Secondary

Tertiary

Serum PTH:



Serum calcium:



Etiology: Single adenoma 80%
2 or 3 adenomas 10%
Hyperplasia 10%
Carcinoma $\leq 1\%$

Renal failure

Malabsorption

Vit D deficiency

Kidney transplant

Surgical Treatment: Resection
of Enlarged
glands

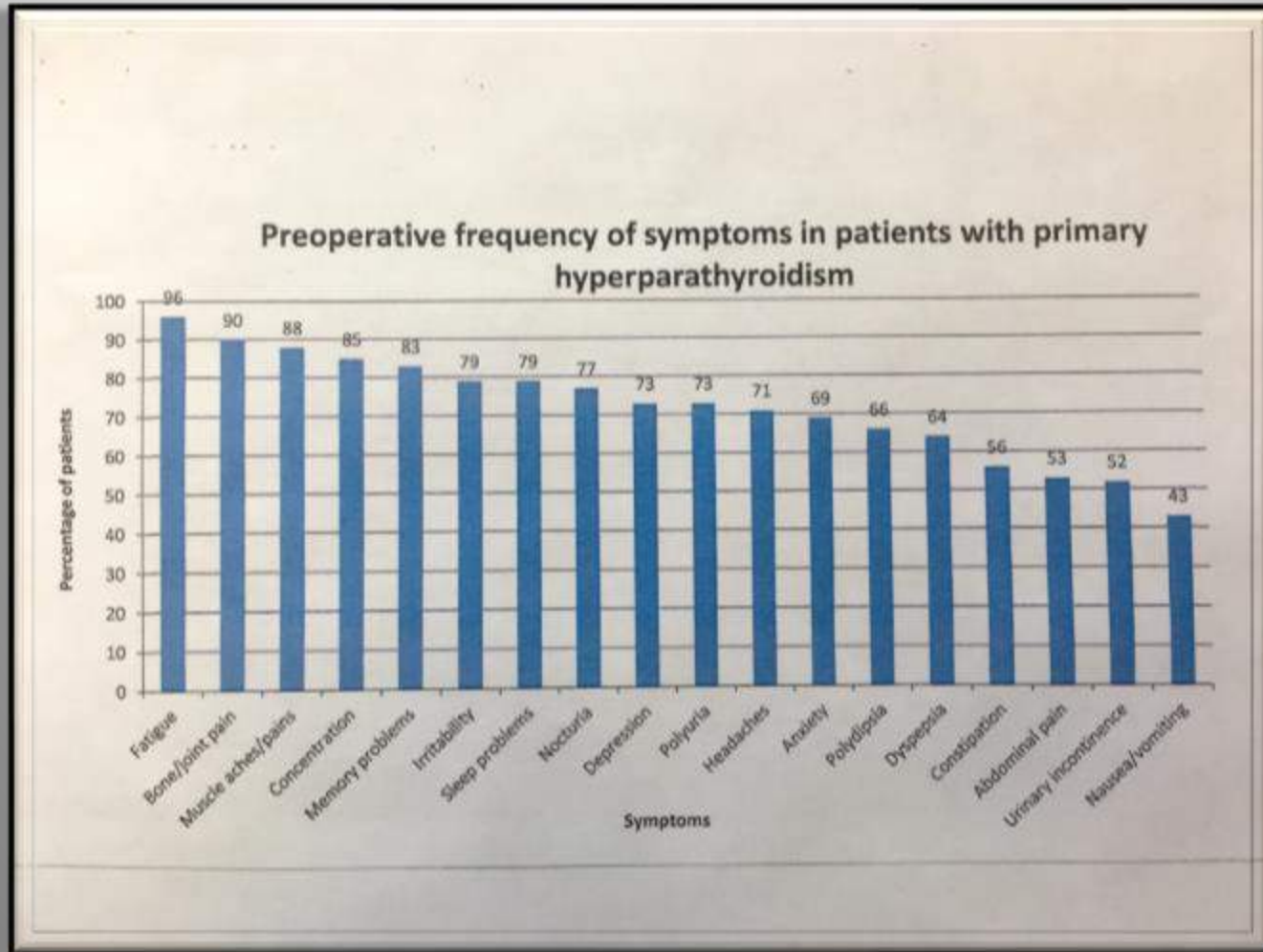
Total para-
thyroidectomy
with implant

Subtotal (3.5 gland)
parathyroidectomy

Subtotal (3.5 gland)
parathyroidectomy

Total para-
thyroidectomy with
implant

Debate over “Asymptomatic Hyperparathyroidism”



AAES Guidelines 2016

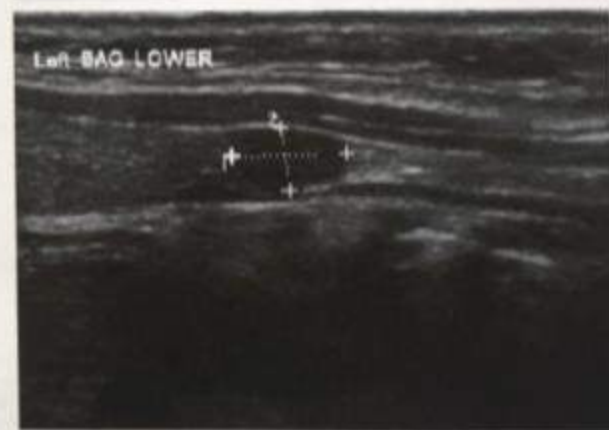
1. Parathyroidectomy recommended for all symptomatic patients; consider for most asymptomatic patients
2. Parathyroidectomy is more cost effective than observation or pharmacologic therapy
3. Pre-op cervical ultrasound is recommended
4. Avoid pre- op parathyroid biopsy
5. Minimally invasive parathyroidectomy (MIP)- recommend intra op PTH monitor
6. Assess thyroid disease pre-op and manage post-op

Pre-operative Localization

Ultrasound



- **Non-invasive**
- **No radioactivity**
- **Very operator dependent**



Surgeon-Performed Ultrasonography: as good as (or better than) the radiologist

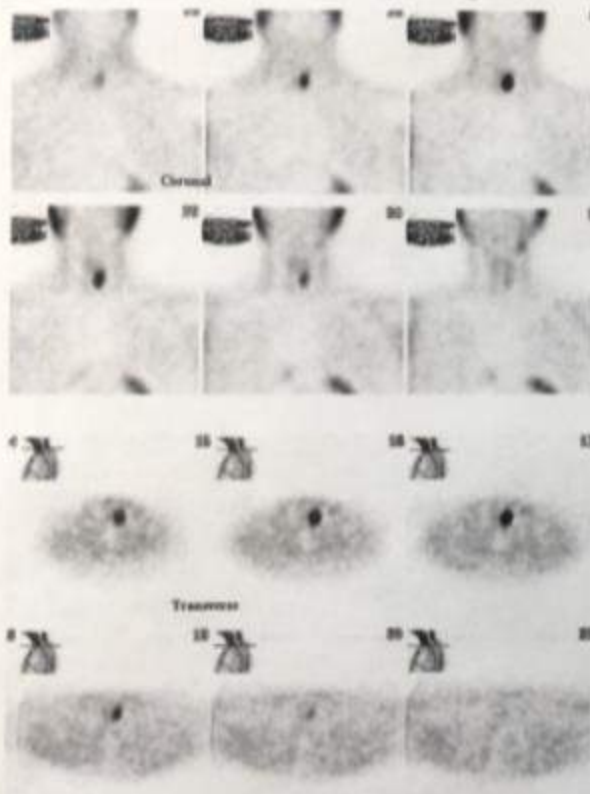
Table 5 Test characteristics of SUS and RUS in single gland disease

	Sensitivity	Specificity	Positive predictive value	Likelihood ratio of positive test result
SUS	89.9%	87.5%	98.6%	7.2
RUS	89.3%	76.5%	96.7%	3.8

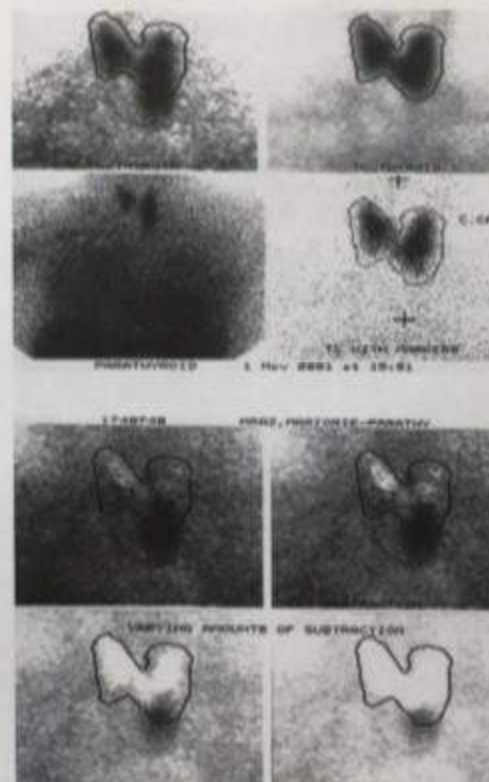
Soon P, et al: World J Surg 32:766-771, 2008

Pre-operative Localization

Nuclear Imaging



Tc-99m Sestamibi- SPECT



Thallium Tc-99m Subtraction

Primary Hyperparathyroidism

▣ Goals at surgery

- Distinguish between unilateral (adenoma) vs. multi-gland disease

- Adenoma(s)
- Hyperplasia

- 3.5 gland (subtotal) vs. 4 gland (total)
parathyroidectomy plus implant

Options for Parathyroidectomy

- ▣ Traditional 4-gland exploration
- ▣ Sestamibi-guided unilateral exploration
- ▣ Scan-guided surgery with 'quick' PTH
- ▣ Outpatient parathyroidectomy
- ▣ Parathyroidectomy under local anesthesia
- ▣ Scan directed parathyroidectomy with intraoperative gamma probe (physiologic approach)
- ▣ Endoscopic parathyroidectomy
 - Cervical
 - Mediastinal
 - Thoracic
 - Transaxillary
 - Video-assisted parathyroidectomy

MINIMALLY INVASIVE PARATHROIDECTOMY

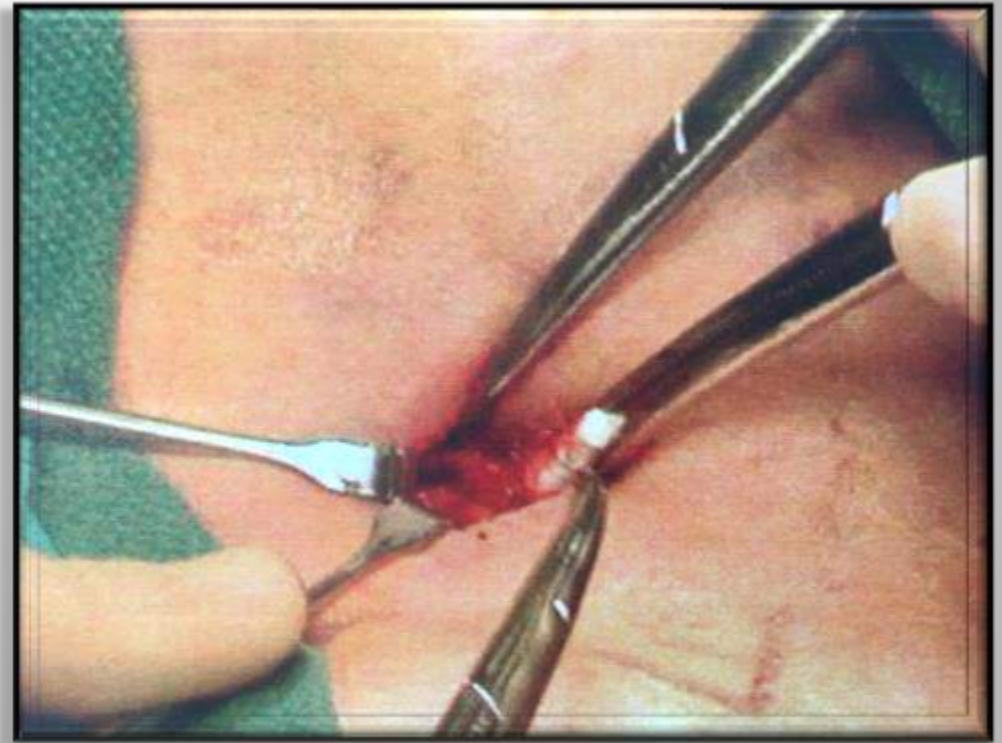
INTRA-OPERATIVE PTH MONITORING

- ▣ PTH has a half-life of only 2-3 minutes
- ▣ Within 2-3 half-lives the blood level should fall by $\geq 50\%$
- ▣ 95% accurate at predicting cure
- ▣ Very accurate in patients with single gland disease

MINIMALLY INVASIVE PARATHYROIDECTOMY

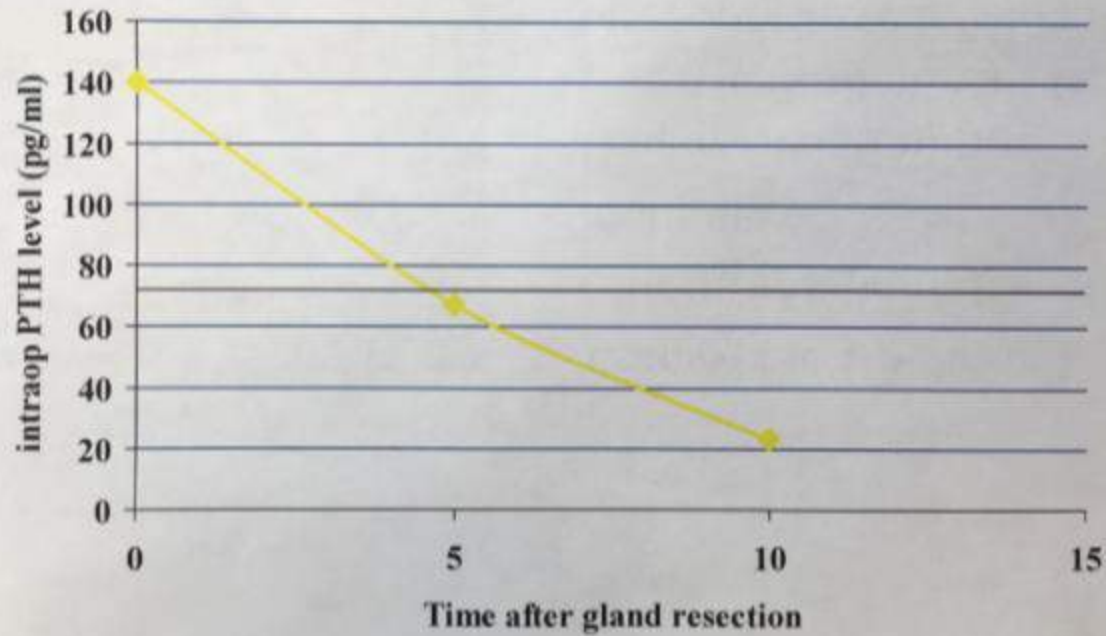
SURGICAL TECHNIQUE

- Transverse 1-3 cm in length
- Can target gland based on imaging
- If operative findings consistent, then wait for intraoperative PTH results
- If operative findings inconsistent, then 4 gland exploration



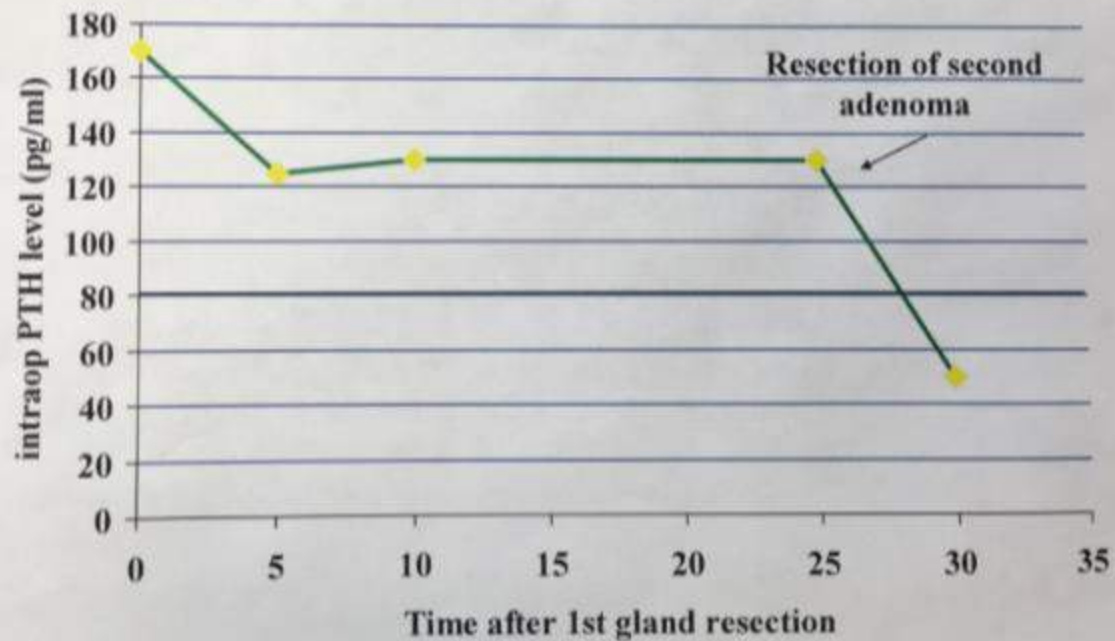
PTH Monitoring For:

Single adenoma



PTH Monitoring For:

Double adenoma



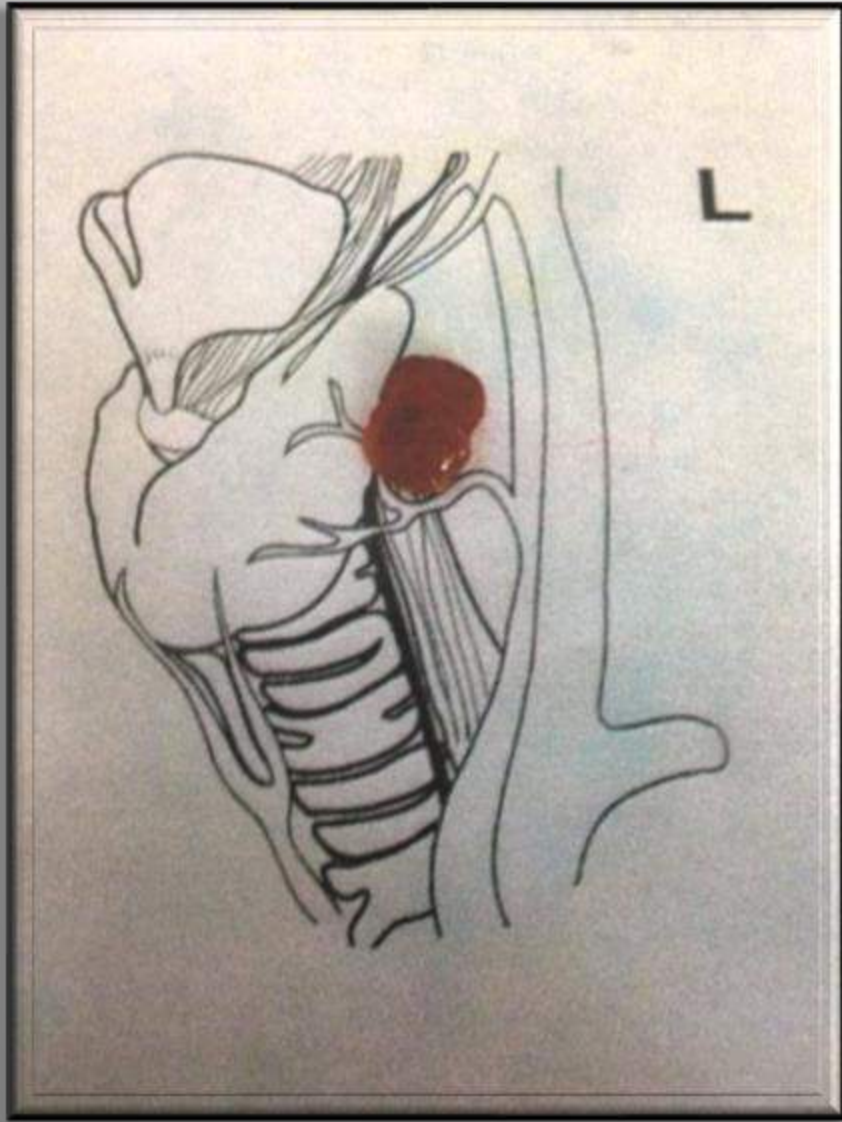
Recurrent Laryngeal Nerve Monitoring

- ▣ 1970 Flisberg & Lindhorn
 - Electrical stim of RLN during thyroid surgery
- ▣ Observe EMG activity to minimize trauma to nerve
- ▣ Verify integrity of nerve prior to closure
- ▣ Evidence - based studies

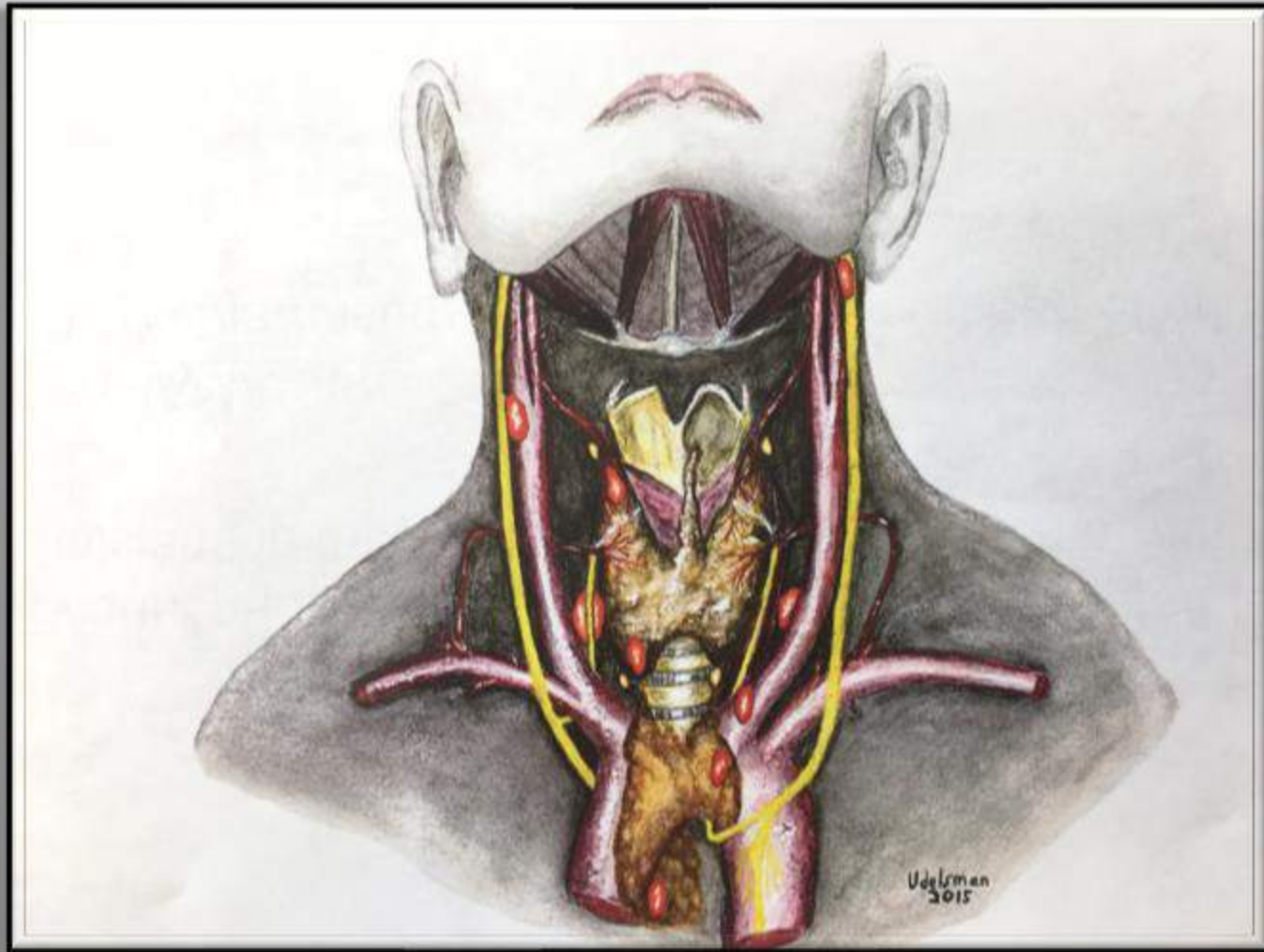
Parathyroid Surgery Outcomes

- ▣ Cure = normocalcemia at 6 months
- ▣ 95%
- ▣ Complications
 - Recurrent laryngeal nerve injury 0.5-1%
 - Superior laryngeal nerve
 - Hypocalcemia
 - Hematoma

Parathyroid Images



Anatomical Relationships of Eutopic & Ectopic Parathyroid Glands



Inherited Parathyroid Disease

▣ MEN 1

- Primary hyperparathyroidism 90%
- Pancreas
- Pituitary

- 4 gland hyperplasia
- 20% supernumerary glands
- Asymmetric gland enlargement

- Mutation MEN 1 gene
- Subtotal parathyroidectomy or total & implant

▣ MEN 2A

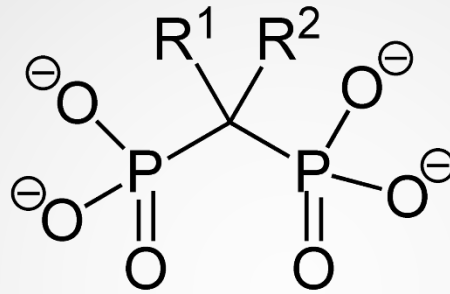
- Medullary thyroid cancer
- Pheochromocytoma
- Primary hyperparathyroidism 20-30%
- Mutation RET gene
- Usually single enlarged PT

Parathyroid Carcinoma

- ▣ $\leq 1\%$
- ▣ Serum calcium ≥ 14 mg/dl (≥ 3.5 mmol / L)
- ▣ Difficult to distinguish on path evaluation
- ▣ Aggressive surgery

Medical Therapy for Osteoporosis

1. Bisphosphonates



2. Two phosphate groups
similar structure to pyrophosphate
3. Bisphosphates adhere to binding site on bone
osteoclasts take up this attached drug
inhibit osteoclast activity.
4. Adverse effects
 - GI
 - osteonecrosis of jaw

Indications for Bisphosphonates

- ▣ Osteoporosis
- ▣ Chronic steroid therapy
- ▣ Paget's disease of the bone
- ▣ Cancer metastasis to the bone
- ▣ Multiple myeloma
- ▣ Hypercalcemia in cancer patients

Types of Bisphosphonate Drugs

- ▣ Nitrogenous forms
 - Zometa/Reclast (Zolendronate) IV
 - Aredia (pamidronate) IV
 - Fosamax (alendronate) PO
 - Boniva (ibandronate) PO
 - Actonel (risendronate) PO
 - Skelid (tiludronate) PO
- ▣ Non-Nitrogenous forms
 - Didronel (etidronate) IV/PO
 - Bonefos, Loron, Ostac (Clodronate) IV/PO

Rankl Inhibitor

- ▣ Rankl receptor activator of *NFKAPPA B*
 - TNF Superfamily
 - Osteoclast Differentiation Activation

Rankl inhibitor

Prolia

Xgeve

Denosumab

60mg q 6 month

120mg q month

Associated with osteonecrosis jaw

No Osteonecrosis Jaw Risk

- ▣ Evista(Raloxifene)

SERM – selective estrogen receptor modulator

- ▣ Forteo (Teriparatide)

PTH fragment

Short Burst

Activate osteoblasts \geq

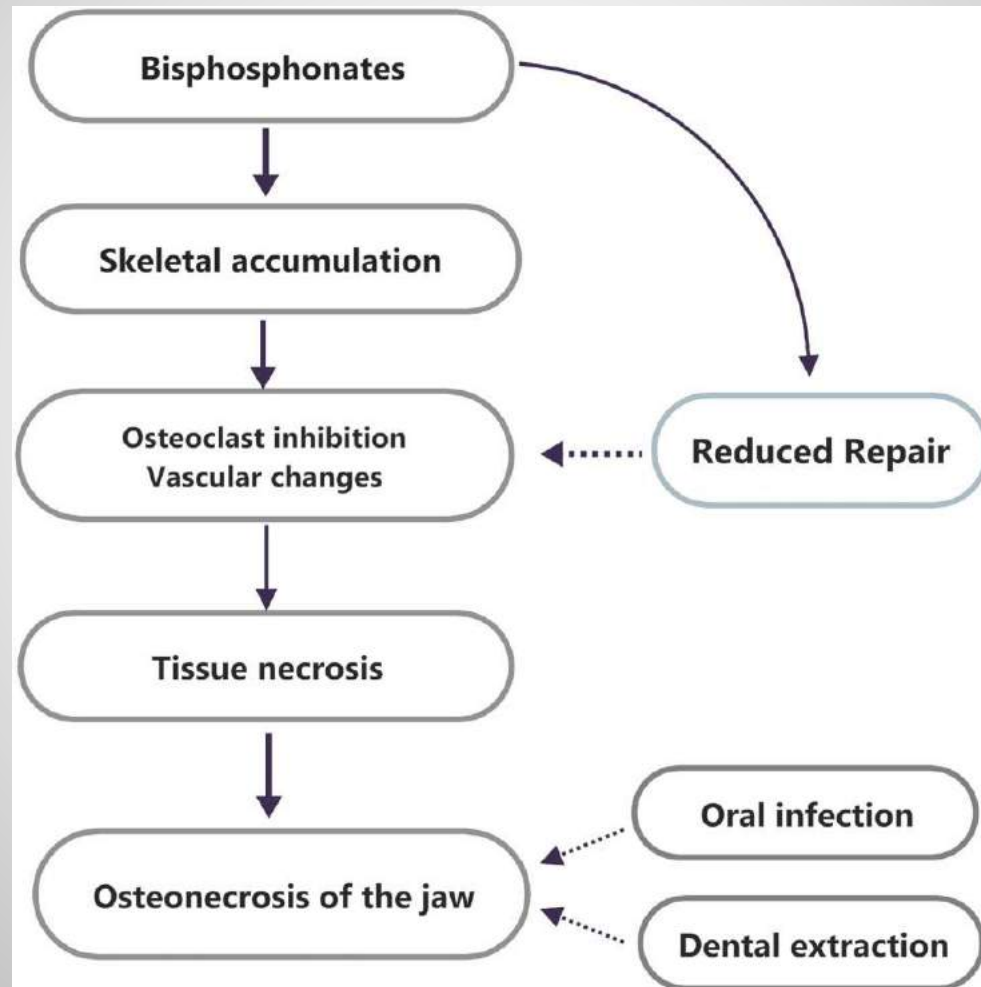
osteoclasts

Avoid if risk osteosarcoma

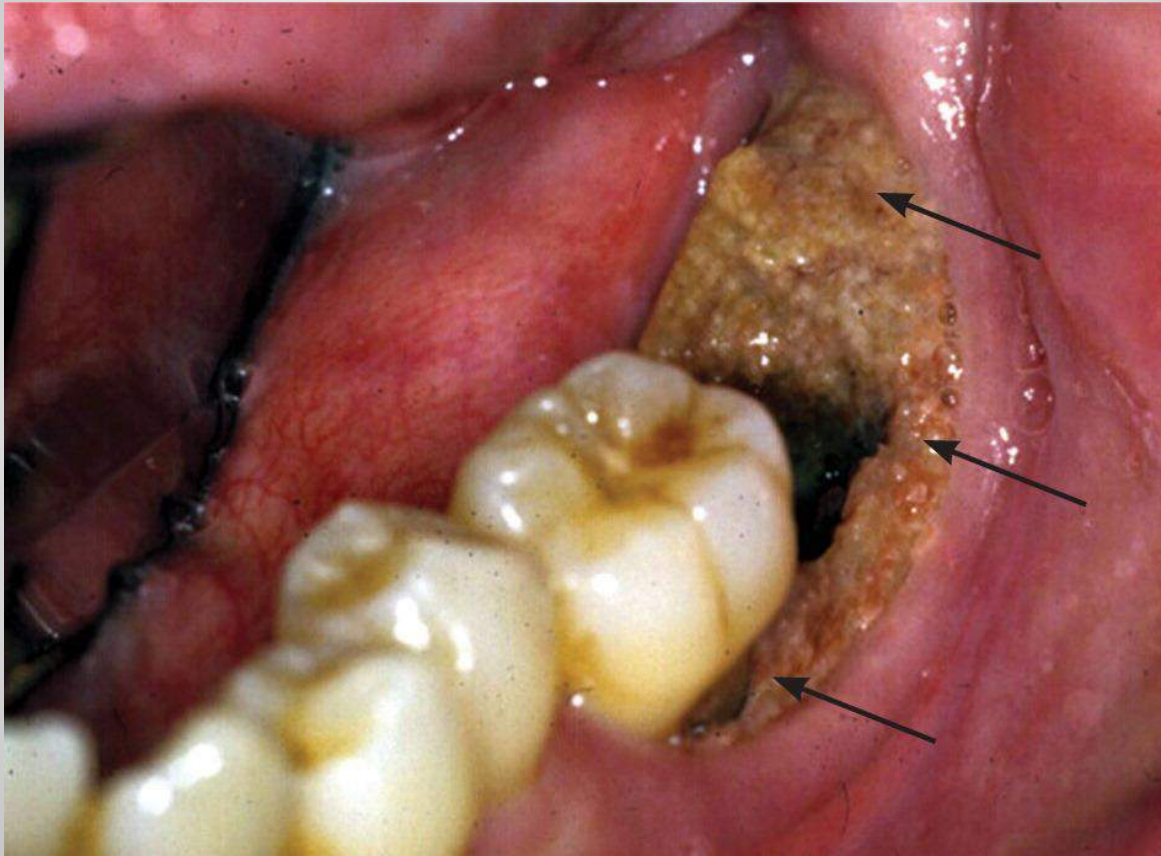
Bisphosphonate Related Osteoporosis of the Jaw

- ▣ Exposed necrotic bone in maxillofacial region, present at least 8 weeks
- ▣ Pathogenesis – localized vascular insufficiency
- ▣ BP cause antiangiogenesis
- ▣ Rare with oral admin (0.10%) more common with high intravenous doses for cancer metastases
- ▣ Diagnosed often after dental procedure

Mechanism of BP-osteonecrosis



Clinical Picture of Osteonecrosis



Conclusions 1

- ▣ Osteoporosis is the most prevalent disease of the skeleton
- ▣ Progressive deterioration of bone mass which can lead to fracture
- ▣ Consider hyperparathyroidism and other secondary causes which can cure the disease (increased calcium, elevated PTH)

Conclusions 2

1. Hyperparathyroidism- no debate on surgical indications for
osteoporosis, fragility fracture, associated kidney stones, age ≤ 50
2. “Asymptomatic” hyperparathyroidism
 - Long term studies needed
 - Refer to surgeon for discussion
3. Medical management
 - a. Bisphosphonates
 - b. Estrogen receptor modulator risk
 - c. Calcimimetics & Cinacalcet (Sensipar)
ESRD on dialysis, unresectable cancer

Summary

- ▣ Adequate vitamin D supplements in recent studies
- ▣ Calcium intake in the diet (? pills)
- ▣ Exercise (weight-bearing and muscle strengthening)
- ▣ Quit smoking
- ▣ Decrease caffeine and alcohol consumption
- ▣ Fall prevention

NIH osteoporosis and related bone diseases

National Resource Center