CALCIUM DISORDERS

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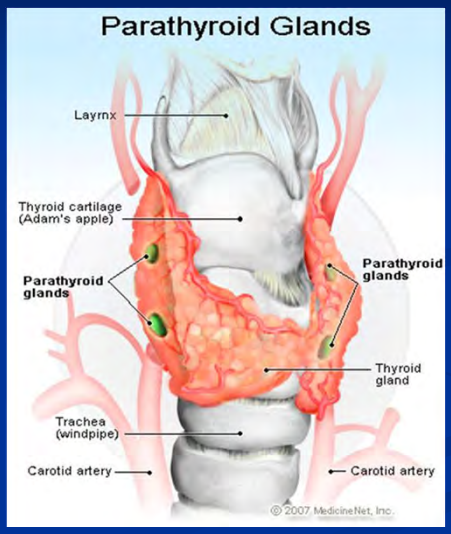
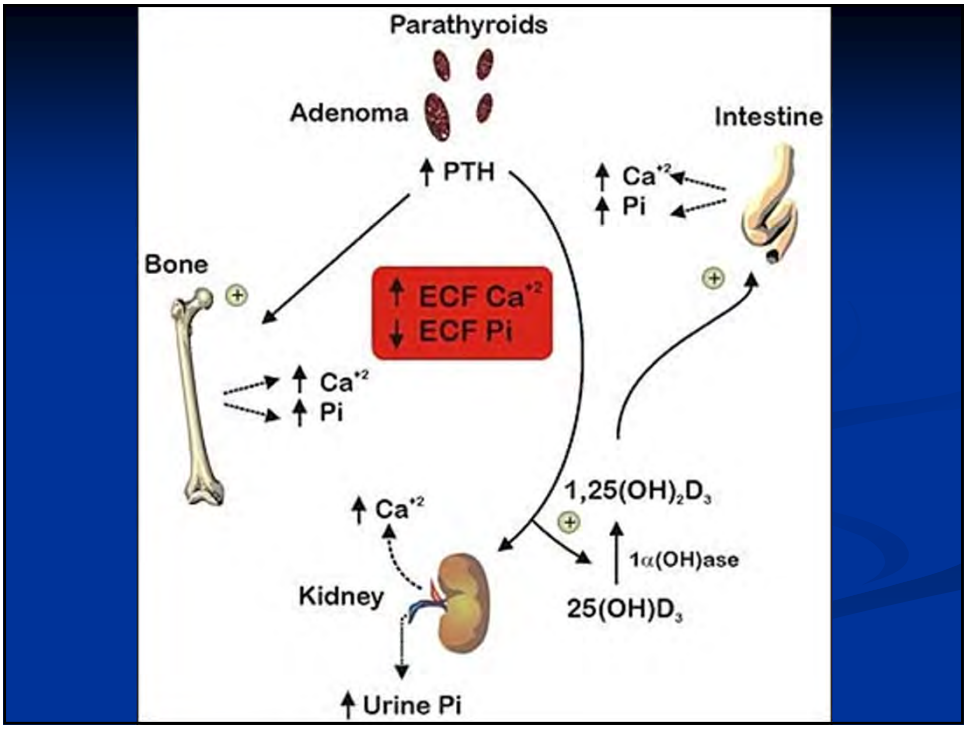
PARATHYROID DISORDERS



Regulators of calcium balance

NB!

- PTH
- Vitamin D
- NOT CALCITONIN



The most important questions with calcium abnormalities

For hyper- and hypocalcaemia:

- What is the PTH?
- What is the phosphate?

For hypocalcaemia:

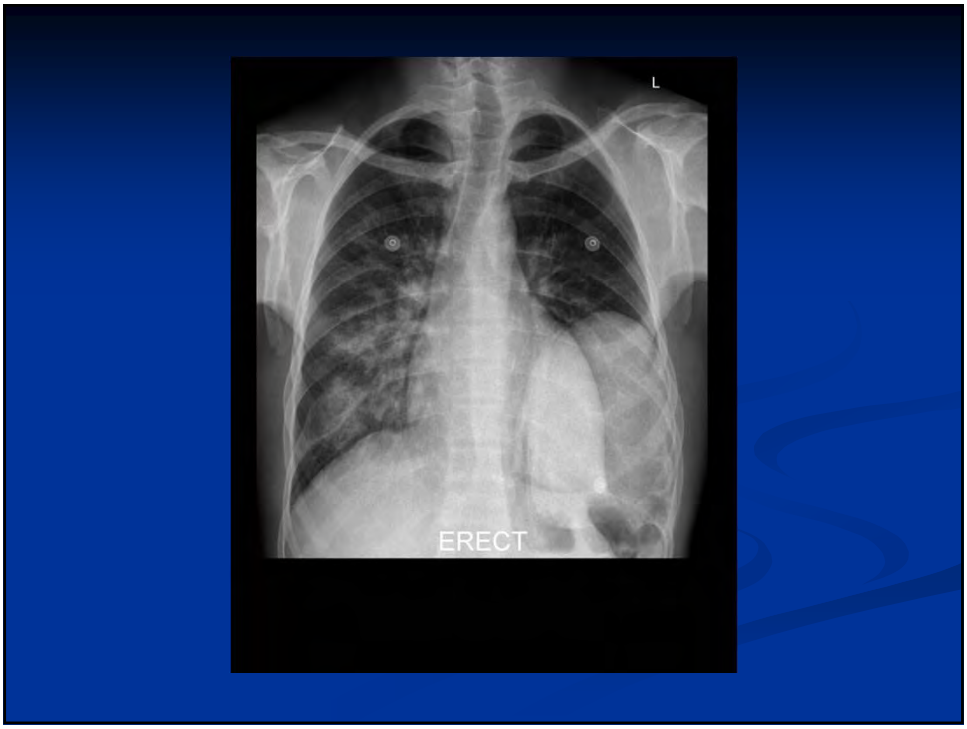
- What is the Vitamin D (25 OH- and 1,25 OH-vit D level)?
- What is the magnesium?

HYPERCALCAEMIA

Case presentation

- Mr GF, 24 year old man
- Single, two children
- Never smoked, alcohol only socially
- Unemployed
- Never worked in mines; grew up in the Western Cape

- Presented with:
  - Weight loss of >10kg over 8 months
  - Chest pains (especially left posterior)
  - Coughing
  - Weakness, tiredness, depression
- 3 x sputums negative for TB at clinic
- CXR: large mass in his left lung
- Referral to the hospital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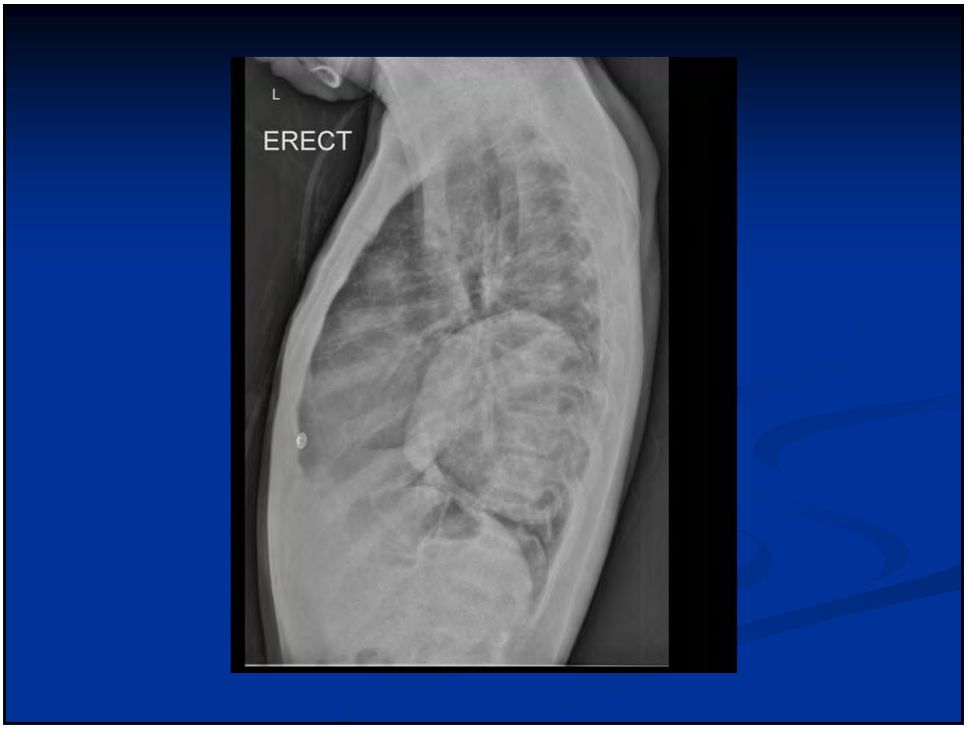
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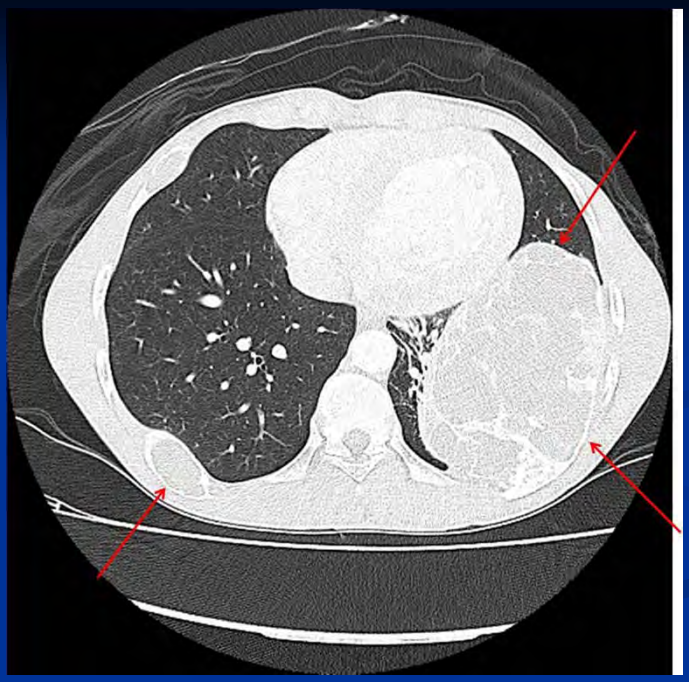
On examination:

- Hypertensive (BP 170/100)
- Emaciated
- No significant lymphadenopathy
- Local bony tenderness over left lung posterior
- Areas of tenderness also over right ribs lateral
- Decreased air entry left lower lobe, with basal crepitations
- Clear left ventricular hypertrophy, with 1+ protein in the urine, and gr 2 hypertensive changes of the fundi

Blood results:

Date:	5/6/09	21/6/9	26/6/9	4/7/09	Range:
Na	143	139	141	139	135-147
K	3.7	5.0	4.2	4.2	3.3-5.3
Cl	108		106	107	99-113
Urea	6.4	6.5	7.6	7.7	2.6-7.0
Creat	132	140	158	141	60-120

- Normal FBC
- Normal TFT
- HIV negative
- Glucose: 4.8



Date:	5/6/09	21/6/09	26/6/09	Range:
Ca	2.87	2.90	3.00	2.05-2.56
Alb	37	39	44	35-52
Corr Ca	2.93	2.92	2.92	2.05-2.56
Mg	0.67	0.63	0.71	0.65-1.10
Phosph		0.68	0.73	0.80-1.40

HYPERCALCAEMIA

- Hyperparathyroidism is the most common cause in adults (outpatients)
- Second most common cause is malignancy (especially if Ca > 3.25mmol/L) (inpatient: commonest cause)
- Hyperparathyroidism and cancer account for 90% of cases
- First confirm hypercalcaemia before workup
- Hypercalcaemia in an asymptomatic adult is usually due to hyperparathyroidism

NB!

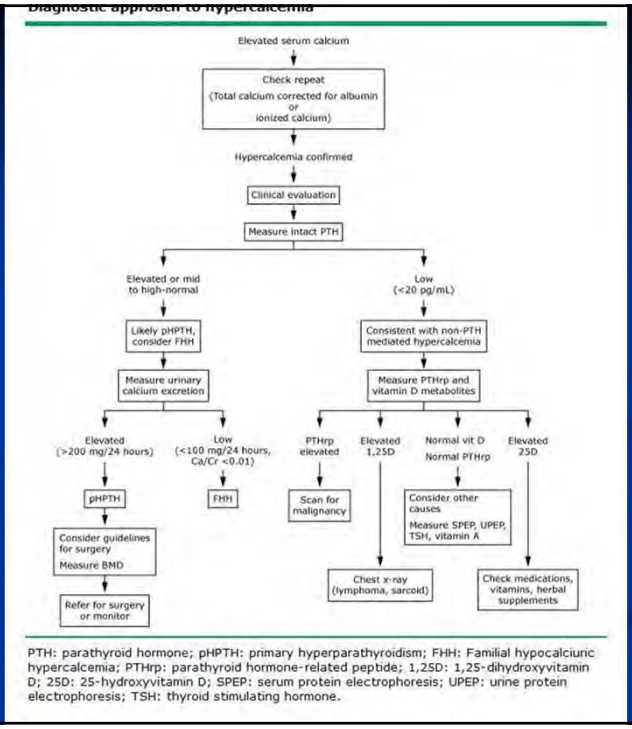
- After confirming hypercalcaemia:

- Is PTH high or low?

CAUSES OF HYPERCALCAEMIA

- **PTH-mediated (PTH high or inappropriately N):**
  - Primary hyperparathyroidism
    - solitary adenomas
    - hyperplasia
  - Familial
    - Familial hypocalciuric hypercalcaemia
    - Multiple endocrine neoplasia (MEN-I, IIA)
  - Tertiary hyperparathyroidism

- **PTH-independent (PTH low):**
  - Hypercalcaemia of malignancy
  - Vitamin D intoxication
  - Chronic granulomatous diseases
  - Medications (eg thiazide diuretics, lithium)
  - Endocrine conditions: - hyperthyroidism
    - phaeochromocytoma
    - acromegaly
    - adrenal insufficiency
  - Other: milk alkali syndrome, immobilization, parenteral nutrition



PTH: parathyroid hormone; pHPTH: primary hyperparathyroidism; FHH: Familial hypocalciuric hypercalcemia; PTHrp: parathyroid hormone-related peptide; 1,25D: 1,25-dihydroxyvitamin D; 25D: 25-hydroxyvitamin D; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; TSH: thyroid stimulating hormone.

Possibilities in our patient

We thought he had most likely:

- Hypercalcaemia of malignancy
  = Secondary to lung tumour (? sarcoma)

HYPERCALCAEMIA OF MALIGNANCY

- Relatively common in malignancy (10-20% of cases)
- NB: usual scenario: **low PTH**

Mechanisms of hypercalcaemia in malignancy

- **Most important 3 mechanisms:**

(1) Osteolytic metastases

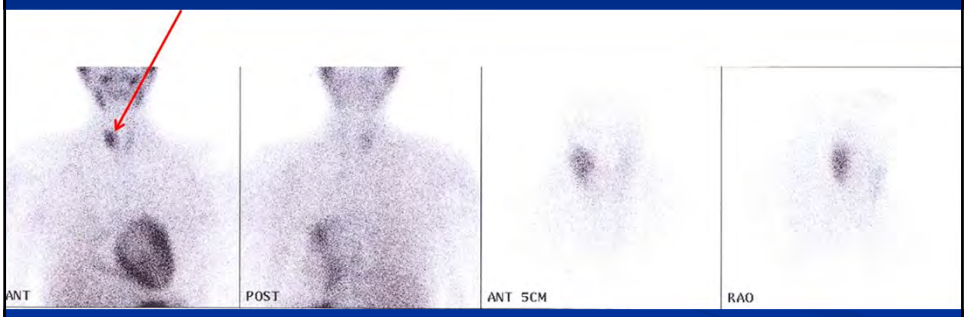
(2) Parathyroid hormone-related protein (PTHrP)

(3) Tumour production of calcitriol (active vitamin D)

For completeness sake…

Date:	23/6/08	4/7/08	11/7/08	Range:
PTH	70.9	149.8		1.2 - 8.5 pmol/l
Creat clear		61.2	56.6	85-125

Parathyroid scan



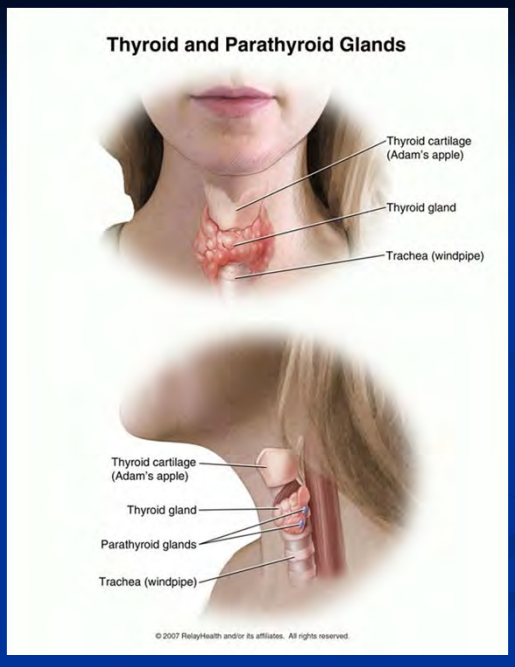
Working diagnosis

Hypercalcaemia due to a combination of:

- Local infiltration by a lung tumour (?sarcoma) with osteolytic bone metastases
- Coexisting primary hyperparathyroidism due to a parathyroid adenoma

HYPERPARATHYROIDISM

- PTH increases the serum calcium (and decreases serum phosphate) through different mechanisms
- Primary hyperparathyroidism: ↑ PTH, leads to ↑ calcium, ↓ phosphate
- Usually caused by an adenoma, or diffuse hyperplasia of the parathyroids



PRIMARY HYPERPARATHYROIDISM

- Generalized disorder of calcium, phosphate, and bone metabolism due to ↑ PTH
- Symptoms vary greatly, from:
  - asymptomatic hyperparathyroidism; to:
  - hypercalcaemic parathyroid crisis
- Often coincidental finding
- Annual incidence = 0.2% in patients > 60; estimated prevalence = ≥ 1%

Symptoms and signs

- Patients can have symptoms of hypercalcaemia
- Ca < 2.9: often asymptomatic
- > 2.9-3: symptoms more common
- > 3.2: calcification in kidneys, skin, vessels, lungs, heart, stomach; renal insufficiency
- > 3.7-4.5: = medical emergency; coma, cardiac arrest

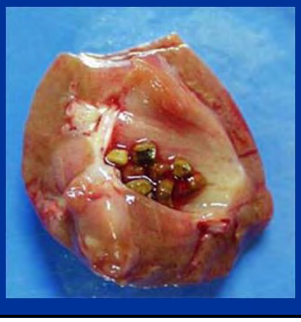
Symptoms and signs (cont)

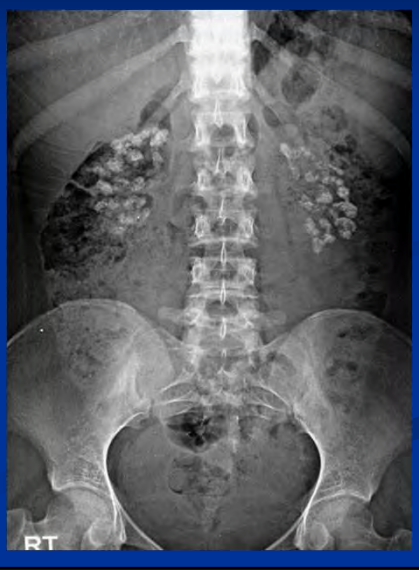
- "Stones"
- "Bones"
- "Psychic moans"
- "Abdominal groans"

Symptoms and signs (cont)

- "Stones":

- renal stones
- nephrocalcinosis
- polyuria
- polydipsia
- uraemia

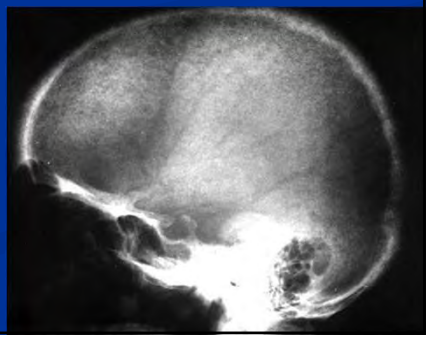


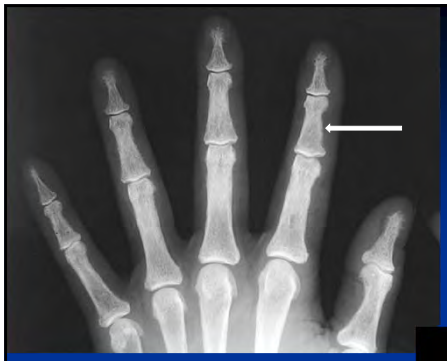


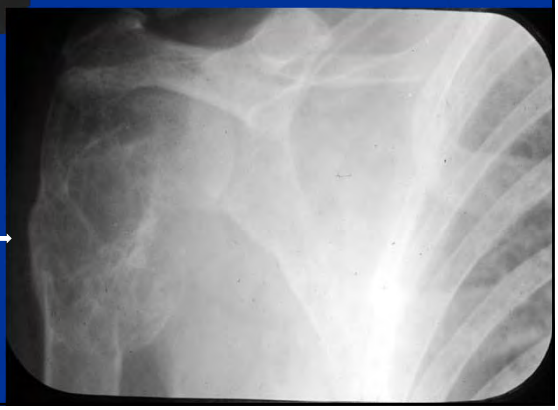
Symptoms and signs (cont)

- "Bones":

- radiologic osteoporosis
- osteomalacia or ricketts
- arthritis
- osteitis fibrosa cystica with:
  - subperiostal resorption
  - osteoclastomas
  - bone cysts
  - "salt and pepper" skull





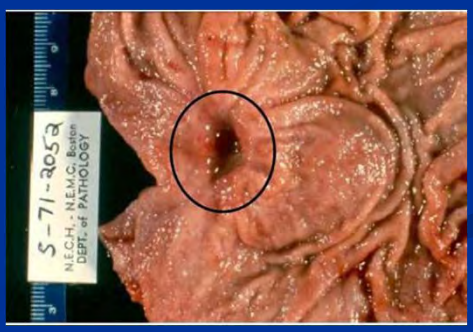


- "Psychic moans":

- lethargy, fatigue
- depression
- memory loss
- psychoses / paranoia
- personality change, neurosis
- confusion, stupor, coma

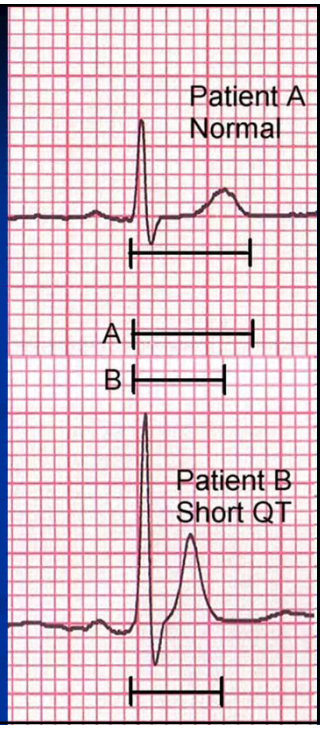
- "Abdominal groans":

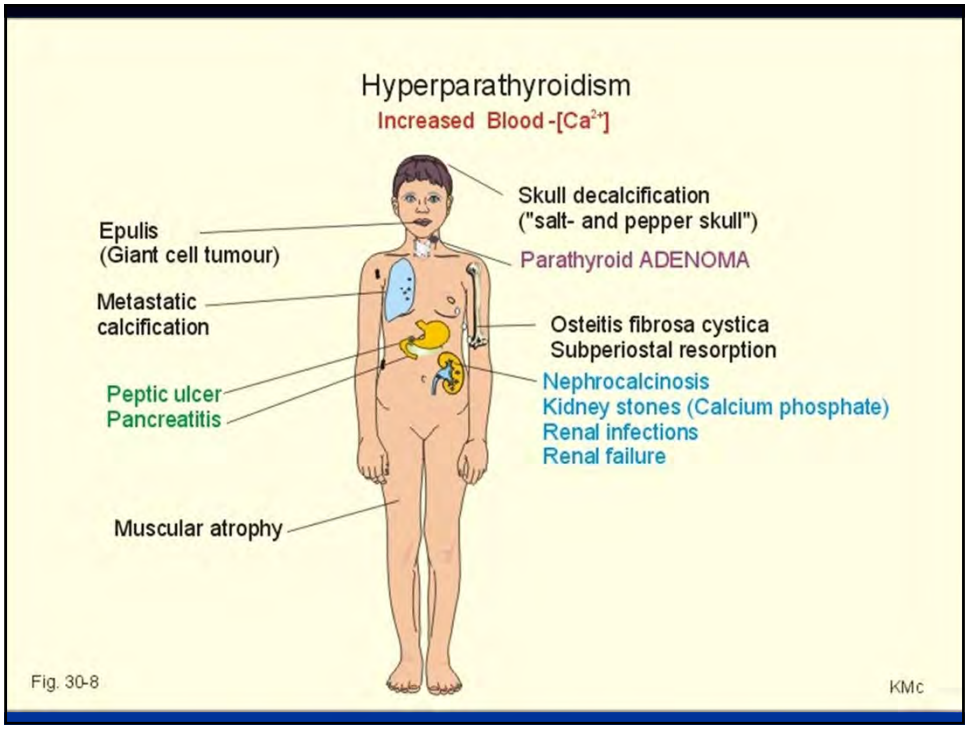
- indigestion, nausea, vomiting
- constipation
- peptic ulcer
- pancreatitis



- Other:

- proximal muscle weakness
- keratitis, conjunctivitis
- hypertension
- itching
- short QT interval, dysrhythmias



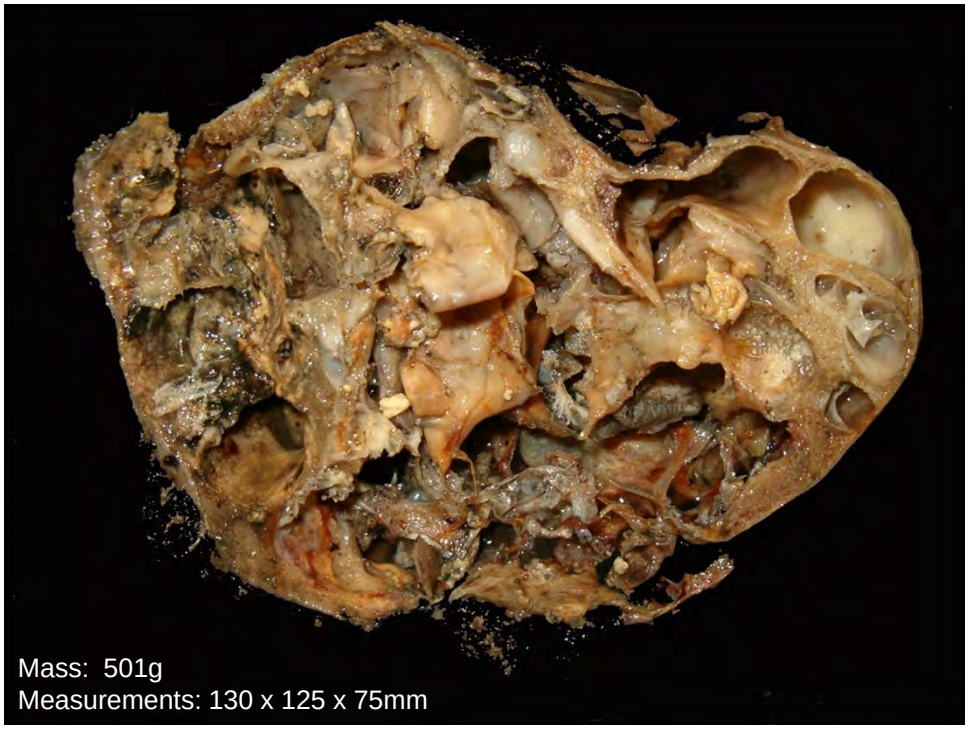


Causes of primary hyperparathyroidism

- Solitary adenoma: 80% of cases of hyperparathyroidism
  - seldom: multiple adenomas
- Hyperplasia: 12-15% of cases
  - usually as part of MEN syndromes
- Carcinoma: 1-2% of cases

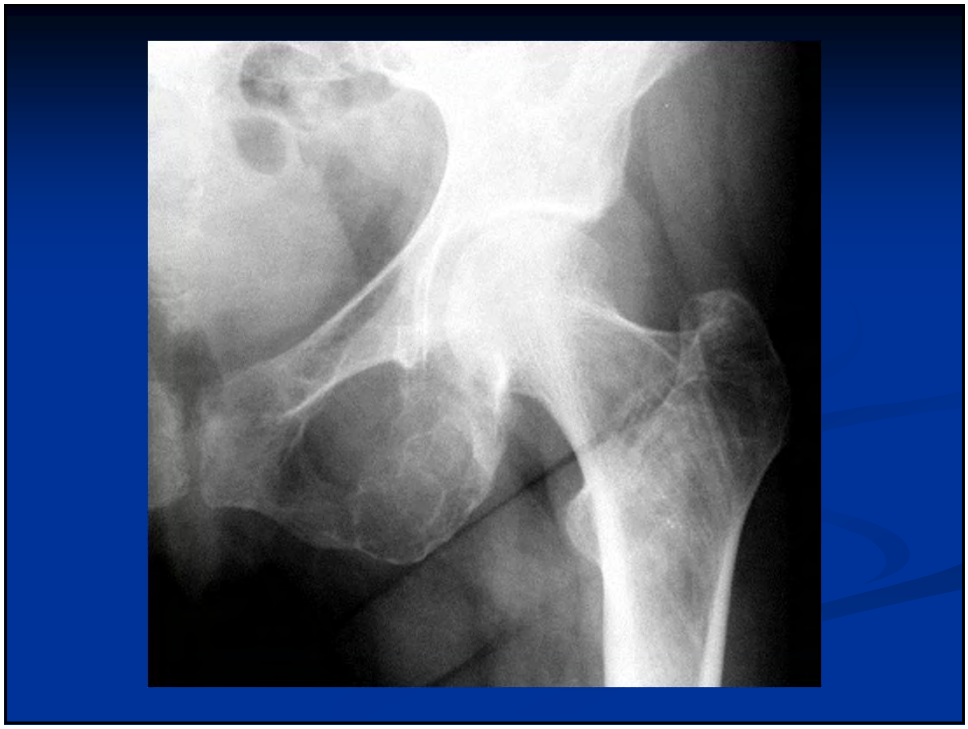
Our patient (continue)

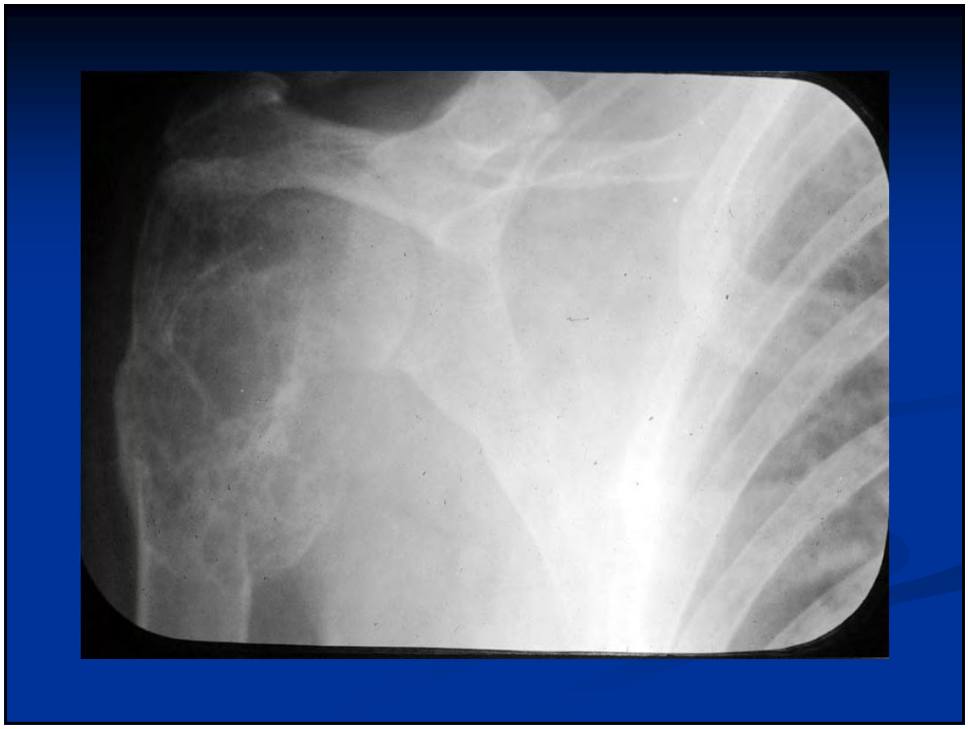
- Thoracotomy performed
- Large tumour removed, weight = 501g

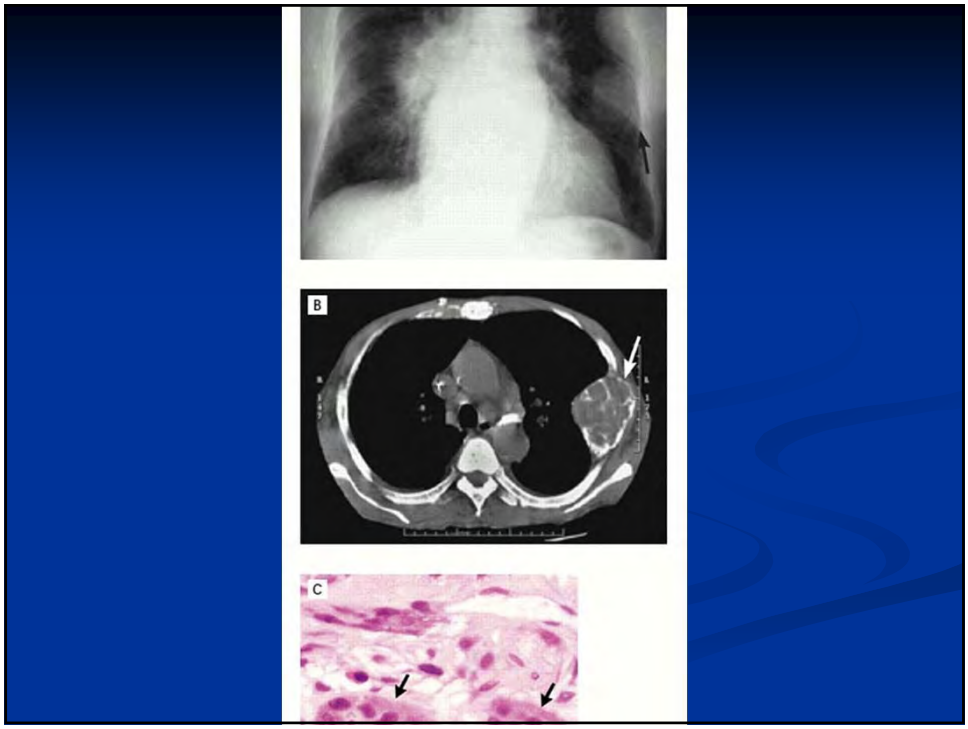


Histology in keeping with:

- Brown tumour of hyperparathyroidism (osteitis fibrosa cystica)







Treatment of 1º hyperparathyroidism

- Severe hyperparathyroidism (Ca>3.7-4.5): surgery is mandatory as soon as diagnosis is confirmed
- Asymptomatic hyperparathyroidism: can probably manage it medically if patient age > 50 and no indications for surgery

Medical therapy

- Careful follow-up:
  - at time of initial evaluation: creatinine clearance, 24h u-Ca, abd X-r +- U/S
  - Ca 2x/year
  - serum creatinine annually
  - bone density annually (lumbar spine, hip, forearm)
- Bisphosphonates eg alendronate
- Raloxifene (SERMS)
- Calcimimetics (still experimental)

Surgery indicated in primary hyperparathyroidism if:

- Serum Ca >0.25mmol/L above upper limits of normal
- Previous episode of life-threatening hyperCa
- Creatinine clearance < 60ml/min
- Kidney stone(s)
- BMD: T-score < -2.5 any site and / or past fragility fracture
- Patient < 50 years
- Long-term medical surveillance not desired / possible

Surgery

- Adenoma: usually already localized preop by parathyroid scan (99mTc sestamibi scan)
- Examine all 4 parathyroids intraoperatively; remove diseased one
- Minimally invasive approach
- If hyperplasia: remove 3 ½ glands, can implant ½ on forearm
- If malignant: be careful to remove with capsule intact

Treatment of severe hypercalcaemia

Most useful therapies:

- Hydration with saline
- Forced diuresis: saline + loop diuretic
- Bisphosphonates (IV)
- Calcitonin

Special use therapies:

- Glucocorticoids
- Dialysis

SECONDARY HYPERPARATHYROIDISM

Occurs in:

- End-stage renal failure (most often)
- Vitamin D deficiency
- Idiopathic hypercalciuria
- Long-term lithium therapy

→ Hypocalcaemia = common denominator in initiating 2° hyperparathyroidism

TERTIARY HYPERPARATHYROIDISM

- Occurs in chronic renal failure
- Long-standing hypoCa leads to hyperplasia of the parathyroids = 2° hyperparathyroidism
  (↑ PTH, ↓ Ca, ↑ phosphate)
- One or more previously hyperplastic parathyroid gland develops autonomous function (overactivity)
- Now: ↑ PTH, ↑ Ca, ↓/N phosphate
- Requires surgery

MEN

- Rare autosomal dominant condition
- Hyperplasia / adenomas / malignancies in multiple endocrine glands
- MEN 1 (3 P's)
  - Primary hyperparathyroidism
  - Pituitary tumours
  - Endocrine pancreas tumours
- MEN 2A
  - Primary hyperparathyroidism
  - Medullary thyroid Ca
  - Phaeochromocytoma

HYPOCALCAEMIA

Case presentation

- 16 year old patient from Mamelodi
- Admitted to SBAH ICU with:
  - status epilepticus
  - aspiration pneumonia
- Already intubated
- Only history available: known epileptic x 1 year (on Epanutin)

Blood tests:

- Ca = 0.96 mmol/L (2.15-2.45)
- Ca(corr) = 1.18 mmol/L (2.15-2.45)
- Ionized Ca = 0.87 mmol/L (1.20-1.38)
- Phosphate = 2.09 mmol/L (0.80-1.40)

CAUSES OF HYPOCALCAEMIA

- **PTH absent:**

- hereditary hypoparathyroidism
- acquired hypoparathyroidism
- hypomagnesaemia

- **PTH ineffective:**

- chronic renal failure
- active vitamin D lacking
  - ↓ dietary intake or sunlight
- active vitamin D ineffective
  - malabsorption
- pseudohypoparathyroidism

- **PTH overwhelmed:**

- severe, acute hyperphosphataemia
  - acute renal failure
  - rhabdomyolysis
- after parathyroidectomy in a patient with osteitis fibrosa

Signs and symptoms

- **Cardiac:**
  - prolonged QT interval
  - refractory congestive cardiac failure

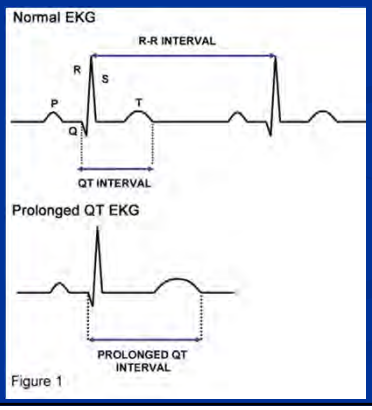
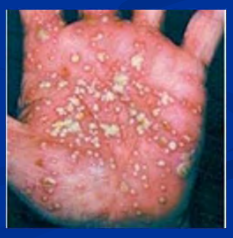


Figure 1

Signs and symptoms (cont)

- **Opthalmologic:**
  - subcapsular cataract

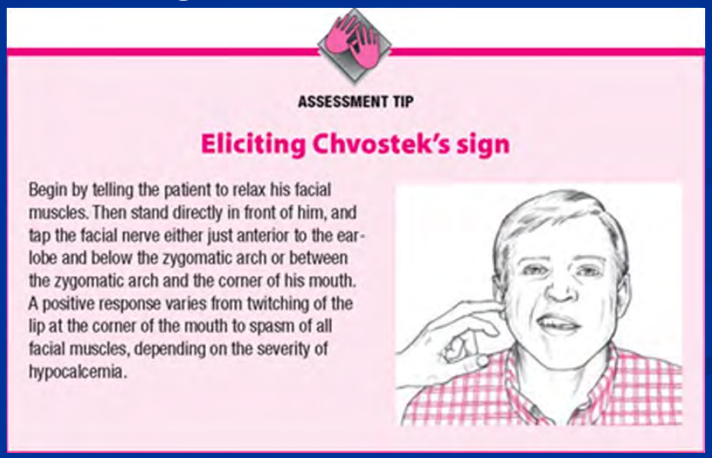
- **Dermatologic:**
  - skin dry, flaky; nails brittle
  - impetigo herpetiformis
  - pustular psoriasis



Signs and symptoms (cont)

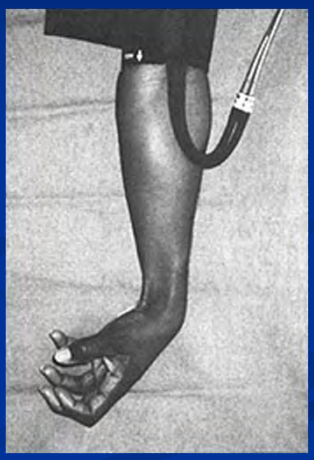
- **Neuromuscular:**

- Chvostek's sign



Signs and symptoms (cont)

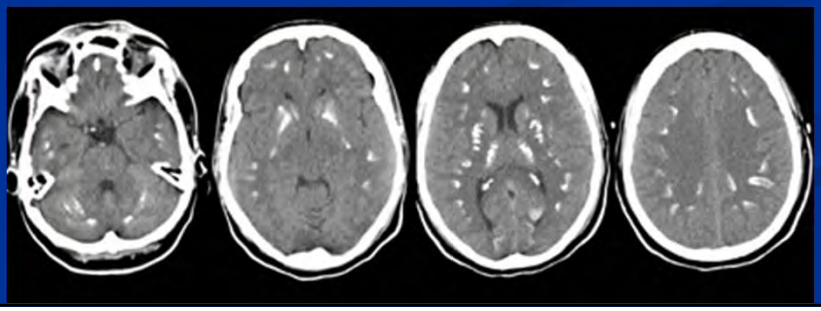
- **Neuromuscular:**
  - tetany, carpopedal spasm
  - Trousseau's sign



Signs and symptoms (cont)

- **Neuromuscular:**

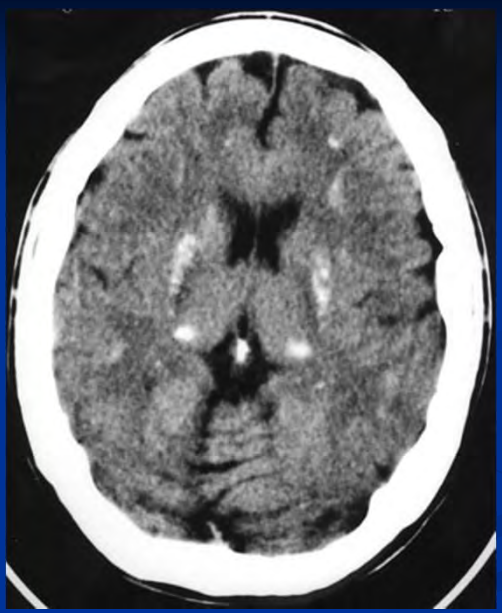
- mental retardation in children
- other: pseudotumour cerebri, papilloedema, confusion, lassitude, laringo/brochospasm
- basal ganglia calcifications



Our patient's results

- Mg = 0.51 mmol/L (0.65-1.10)
- 25-OH-Vitamin D = 51 nmol/L (49.92-174.72)
- PTH = <1.0 ng/L (12 – 88)

- NB: Correct magnesium deficiency first!
- PTH remained low
- Epileptiforme changes on EEG
- Brain calcifications



Final diagnosis

- = Primary hypoparathyroidism

HYPOPARATHYROIDISM

- **Acquired:**

  - Surgery
  - Infiltration
  - Radiation-induced
  - Infection
  - Transient hypoparathyroidism post surgery for hyperparathyroidism

- **Hereditary:**
  - idiopathic/hereditary hypoparathyroidism
  - polyglandular autoimmune type 1 deficiency

Autoimmune Poly-endocrine syndromes

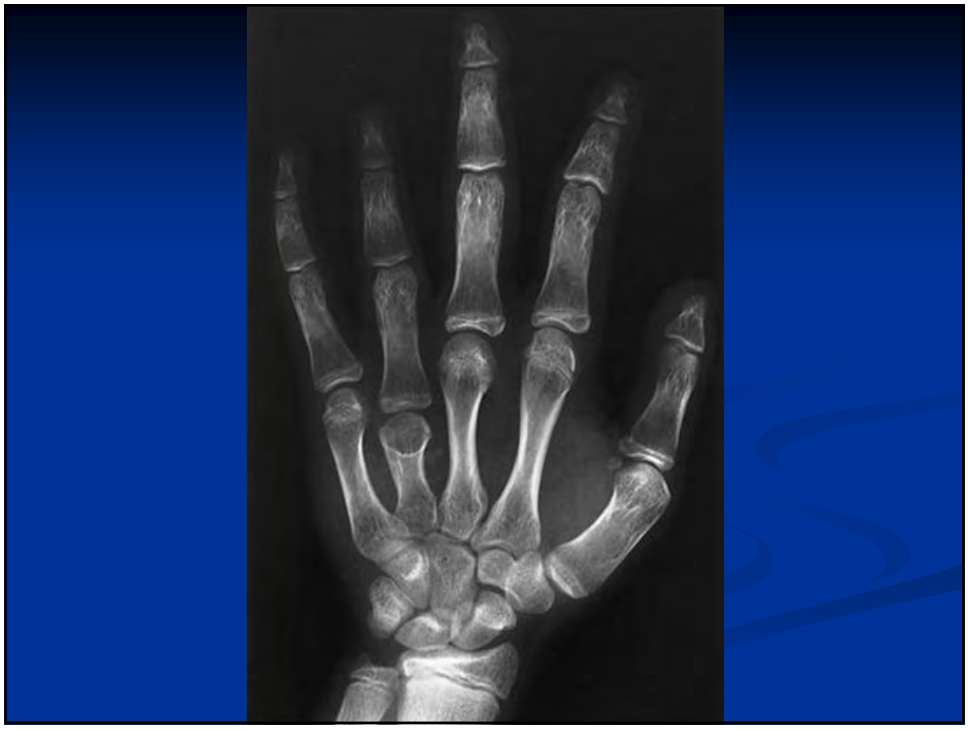
- **Type 1**
  - Addisons (60%)
  - Hypoparathyroidism (89%)
  - T1DM (4%)
  - Primary hypothyroidism (12%)
  - Gonadal failure (45%)
  - Mucocutaneous candidiasis (75%)
  - Manifest early in life, usually before 15 yr
- **Type 2**
  - Addisons (100%)
  - Autoimmune thyroid disease (70%)
  - T1DM (50%)
  - Gonadal failure (5 – 50%)
  - Vitiligo
  - Pernicious anaemia
  - Manifest between 20 and 30 yr

PSEUDOHYPOPARATHY-ROIDISM (PHP)

- Hereditary disorder, characterized by symptoms and signs of hypoparathyroidism, typically in association with distinctive skeletal and developmental defects
- Deficient end-organ response to PTH (resistance)
- ↓ Ca, ↑ phosphate, ↑ PTH

- Type Ia (Albright's hereditary osteodystrophy = AHO)
  - short stature
  - round face
  - skeletal anomalies (brachydactyly; short 4^{th}, 5^{th} metacarpals, metatarsals)
  - heterotopic calcifications (also basal ganglia)

  + other endocrinopathies esp hypothyroidism



PSEUDOPSEUDOHYPO-PARATHYROIDISM (PPHP)

- Normal Ca, phosphate, PTH
- But: clinically Albright's hereditary osteodystrophy
- Occurs sometimes in families with PHP (somatic phenotype, without Ca disturbances)
- No treatment necessary

Laboratory evaluation hypocalcemia

	PTH	Corrected serum calcium	Phos	Mag	25OHD	1,25 (OH) 2D	Creatinine
Hypoparathyroidism	Low	Low	Elevated	Normal	Normal	Normal or low	Normal
Activating mutation calcium sensing receptor	Normal or low	Low	Elevated	Normal	Normal	Normal	Normal
Hypomagnesemia	Normal or low	Low	Normal	Low	Normal	Normal	Normal
PTH resistance (pseudohypoparathyroidism)	Elevated	Low	Elevated	Normal	Normal	Normal	Normal
Vitamin D deficiency	Elevated	Low or normal	Low or normal	Normal	Low	Normal or high	Normal
Chronic kidney disease	Elevated	Low	Elevated	Elevated or normal	Normal or low*	Low	Elevated

* In individuals with concurrent nutritional deficiency.

UpToDate

TREATMENT OF HYPOPARATHYROIDISM

- Active vitamin D: 1,25(OH)2D3 = calcitriol (Rocaltrol): 0.5-1µg/d; can also use One-Alpha
- Combined with high oral Ca intake (>=1g/d)
- If not available: normal Vitamin D 40,000-120,000U/d
- Be careful: can develop kidney stones
- Thiazides can ↑ s-Ca, ↓ u-Ca, ↓ kidney stones
  - helpful in brittle hypoparathyroidism

PAGET'S DISEASE

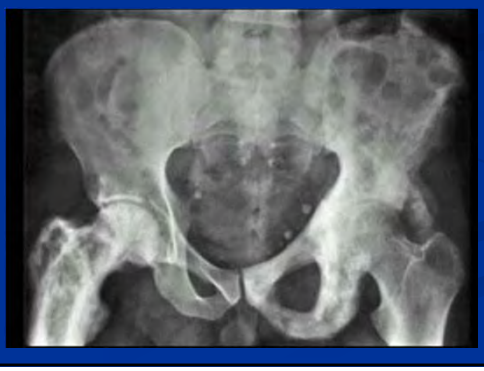
- Disorder of bone remodelling
- Excessive resorption with compensatory increase in bone formation
- New bone is structurally abnormal and therefore weak
- Increase in local blood flow
- Increase in fibrous tissue in adjacent marrow

Paget's (cont)

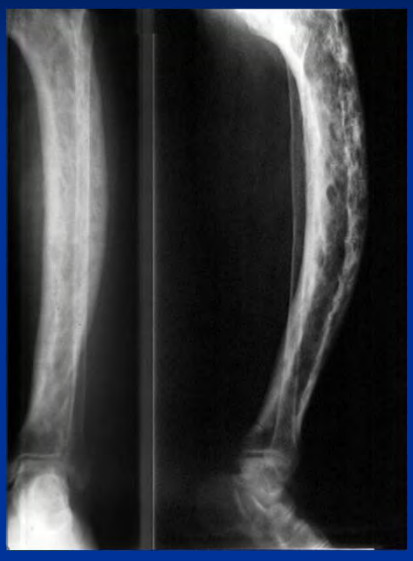
- Older patients > 60 years
- Often incidentally detected on X-rays
- Diagnosis:
  - high ALP
  - Ca often increases when immobilized
  - X-ray findings

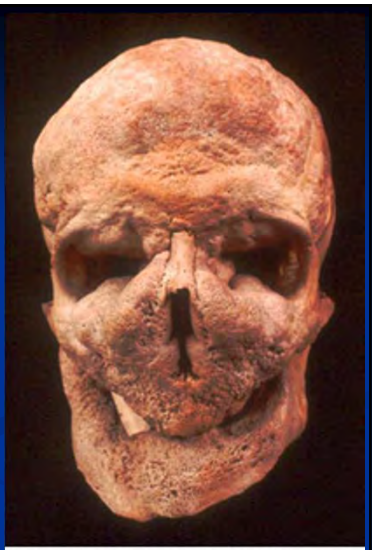
Clinical picture

- Bone pain: often of pelvis or spine
- Joint pain: if the area involved is close to a joint or causes deformity, it can lead to cartilage damage or osteoarthritis



Deformities: tibia or skull

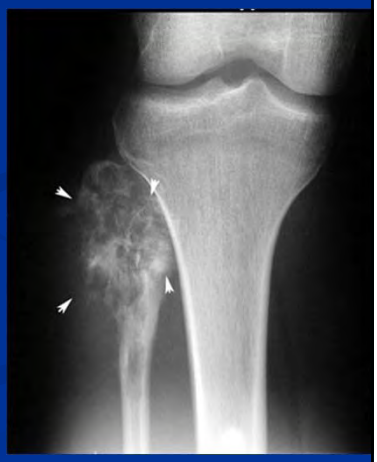




FACIAL BONE that is grossly thickened and symmetrically deformed may result from Paget's disease, a condition in which bone grows drastically out of control. The skull of the warrior Egil, a hero of the Icelandic sagas, may have looked similar to this one of a man who suffered from the disease several centuries ago.

Complications

- Increased blood flow: heart failure
- Nerve compression:
  - VIII: deafness; also II, V, VII
- Bone weakness:
  - pathological fractures
- Rarely osteogenic sarcoma
- Deformities
- Osteoarthritis



Treatment

- Asymptomatic: nil
- Osteoarthritis: symptomatically
- Bisphosphonates
- Surgery for deformities