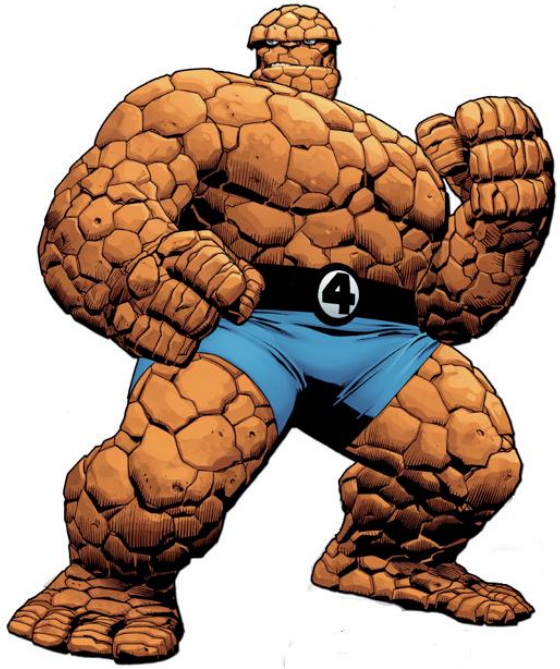


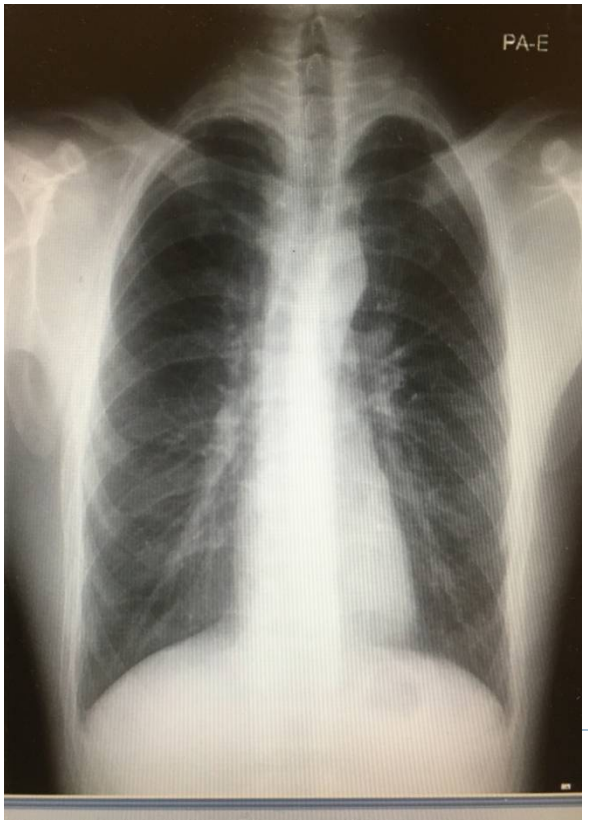
“The Thing”

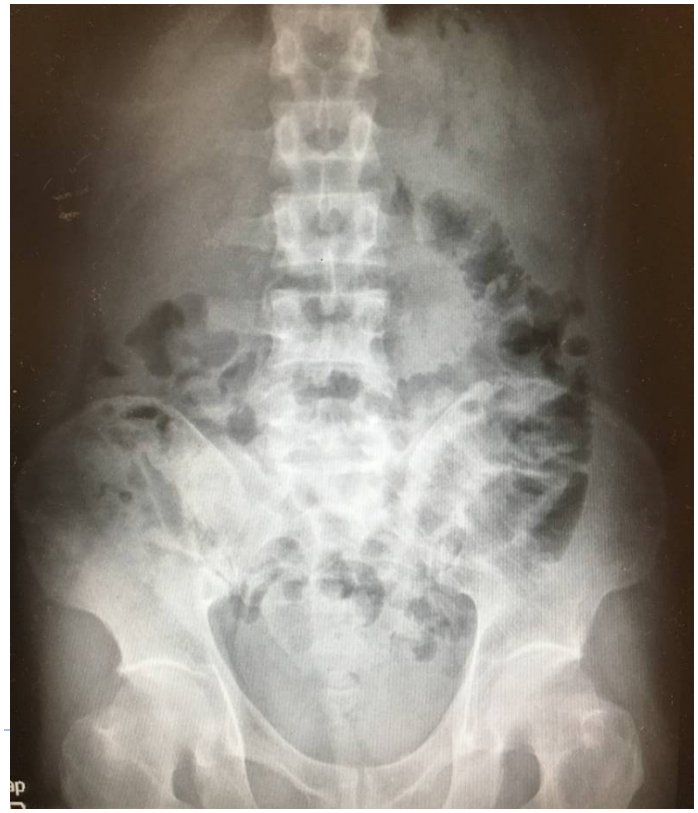
Speaker: Dr. Catherine Tam
Chairman: Dr. HP Shum

PYNEH ICU

Case

- 29yo/M
- Good past health
- 7/1/2016 Admitted to surgical ward x repeated vomitting, NBO x 4/7





Lab results

					C		
Collect Date :	07/01/16	08/01/16	08/01/16	09/01/16	10/01/16		
Collect Time :	22:18	07:26	09:18	03:51	04:39		
Arrive Date :	07/01/16	08/01/16	08/01/16	09/01/16	10/01/16		
Arrive Time :	23:55	09:11	10:26	04:35	06:41		
Request No. :	C5016450	C5016681	C5017006	C5019874	C5021304	Reference	
Urgency :	URGENT	URGENT	URGENT	URGENT	URGENT	Range	Units
Specimen Type: Blood							
Sodium	145	148 H	149 H	149 H	149 H	136 - 145	mmol/L
Potassium	3.9	4.2	3.8	3.6	3.5 L	3.6 - 5.2	mmol/L
Urea	7.9 H	8.9 H	9.2 H	10.1 H	12.1 H	2.7 - 7.2	mmol/L
Creatinine	176 H	189 H	189 H	216 H	248 H	69 - 110$	umol/L
Total Protein	68	68	68	69	73	64 - 83	g/L
Albumin	41	41	40	40	42	35 - 50	g/L
Globulin	28	27	27	29	31		g/L
Total Bilirubin	13	12	11	11	11	3 - 21$	umol/L
ALP	249 H	242 H	236 H	230 H	239 H	47 - 168$	IU/L
ALT	17	19	19	25	43	< 49	IU/L
Calcium					5.35 H	2.20 - 2.60$	mmol/L
Phosphate					1.24	0.76 - 1.40$	mmol/L
Amylase	99					25 - 125	IU/L
Heat Stable ALP		22					IU/L
Heat Stability		0.09				See Below	

- Hypercalcemia total calcium 5.35
- Ionized calcium 2.73
- Heat stability index 0.09 (bone origin)
- Impaired renal function

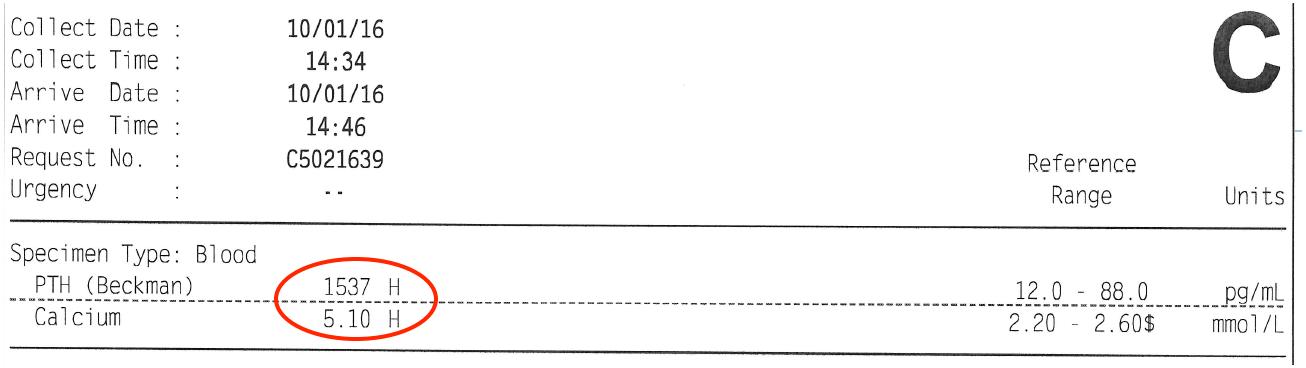
- 9/1/16 USG kidney showed bilateral renal parenchymal disease with **several bilateral renal stones** without hydronephrosis

- Therefore admitted to ICU for further management of severe hypercalcemia
- Meanwhile also consulted endocrine team

Treatment

- Vigourous hydration (4000-9000ml/day)
- Frusemide infusion
- Calcitonin and pamidronate
- Haemodialysis (management of severe hypercalcemia with limited response)

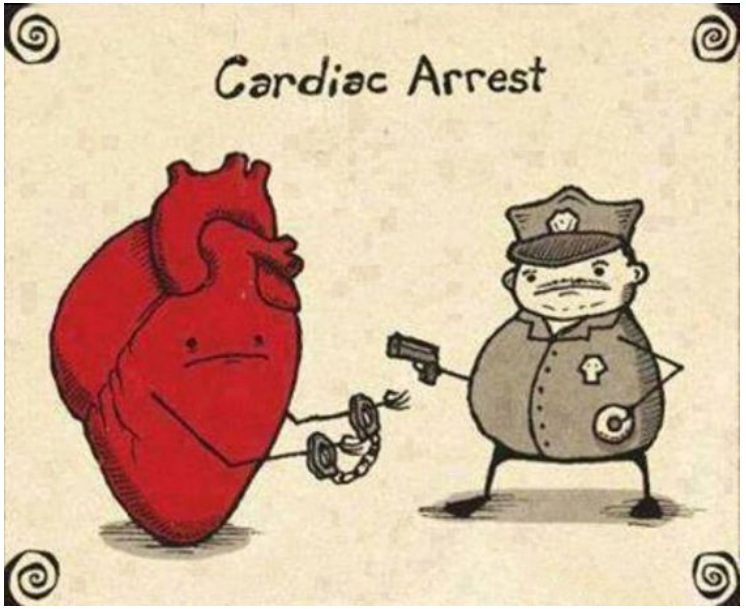
- Urine output achieve 400-1000ml/hr



Collect Date :	10/01/16		C
Collect Time :	14:34		
Arrive Date :	10/01/16		
Arrive Time :	14:46		
Request No. :	C5021639		
Urgency :	--	Reference Range	Units
Specimen Type: Blood			
PTH (Beckman)	1537 H	12.0 - 88.0	pg/mL
Calcium	5.10 H	2.20 - 2.60$	mmol/L

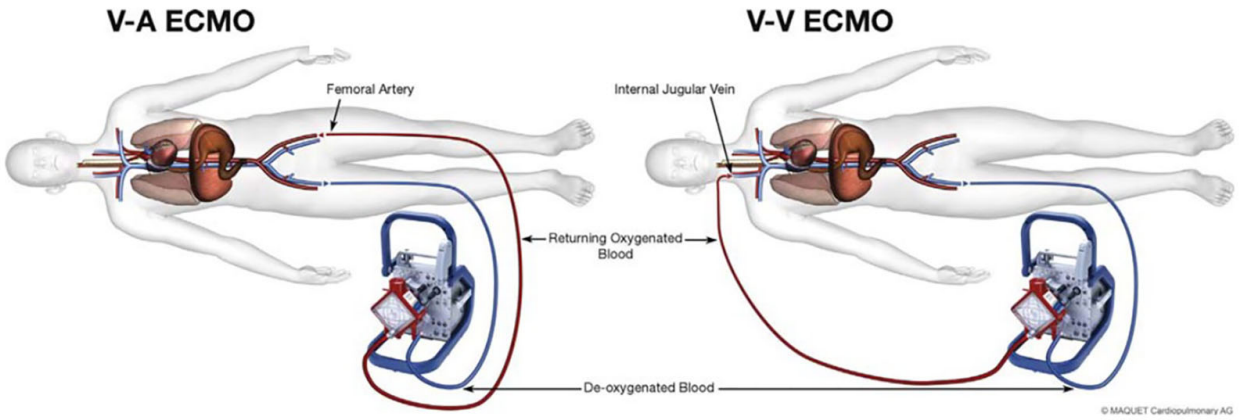
- PTH raised → diagnosed primary hyperparathyroidism
- 13/1/16 bedside ultrasound of thyroid by surgeon showed solitary nodule over right inferior parathyroid gland
- Operative intervention was offered
- However…

- Cardiac arrest on 13/1/16 ~17:00
- Emergency parathyroidectomy was performed
- Transferred back to ICU for further dialysis support
- Calcimimetic given



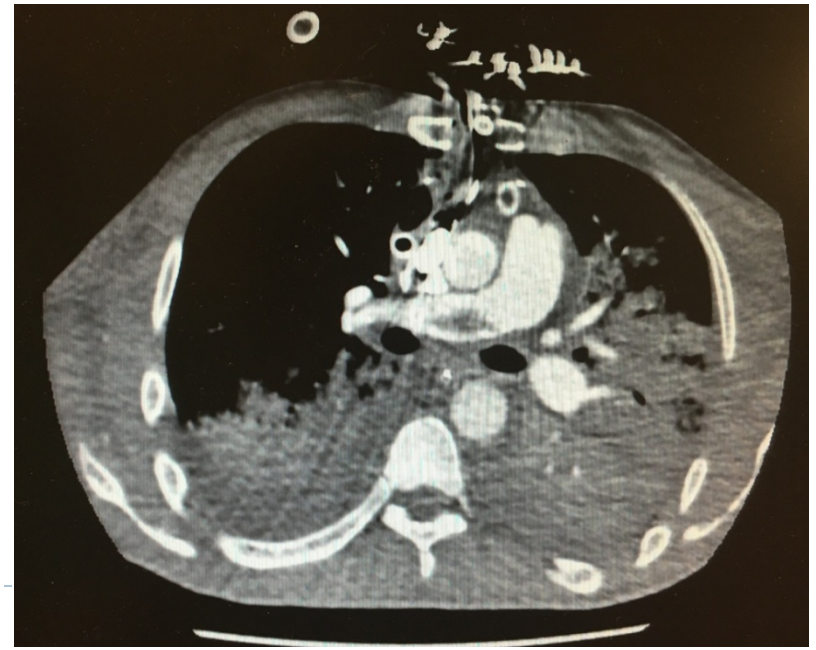
- Histology:
  - Right inferior parathyroid gland measures 3.9x3.2x2.1cm
  - there is no definite histological evidence to suggest malignancy

Progress



- Developed refractory respiratory failure which failed ventilatory support
- Required venovenous extra-corporeal membrane oxygenation (vv-ECMO) support 14/1/16
- Haemodynamic condition deteriorated rapidly
- Vv-ECMO changed to va-ECMO for cardiopulmonary support

- Difficult reperfusion catheter insertion and subsequently inserted by vascular surgeon
- Bilateral intra-ventricular thrombus → QMH CTS
- Right lower limb ischemia → QMH orthopedics for right above knee amputation and right hip disarticulation



- Weaned off ECMO on 21/1/16
- Clinical course in QMH complicated with pneumonia and wound infection
- Gradually weaned off ventilatory support in PYNEH ICU on 2/3/16 and later transferred back to QMH orthopedics for further management

C

Collect Date :	10/01/16	18/02/16	25/02/16	12/03/16	**19/09/16**		
Collect Time :	14:34	05:46	05:53	05:40	**13:26**		
Arrive Date :	10/01/16	18/02/16	25/02/16	12/03/16	**19/09/16**		
Arrive Time :	14:46	06:38	06:43	06:11	**14:43**		
Request No. :	C5021639	C5115595	C5134263	C5177592	**C5659820**	Reference Range	Units
Urgency :	--	--	--	--	--		
Specimen Type: Blood							
PTH (Beckman)	1537 H	126 H	368 H	174 H	127 H	12.0 - 88.0	pg/mL
Calcium	5.10 H	2.43	1.72 L	1.84 L		2.20 - 2.60$	mmol/L

Hypercalcemia

- >2.6mmol/L
- Hypercalcemia crisis marked elevation of serum calcium, usually more than 3.5mmol/L or 14mg/dL is associated with acute signs and symptoms of hypercalcemia
- Associated with the presence of multi organ dysfunction

Clinical presentation

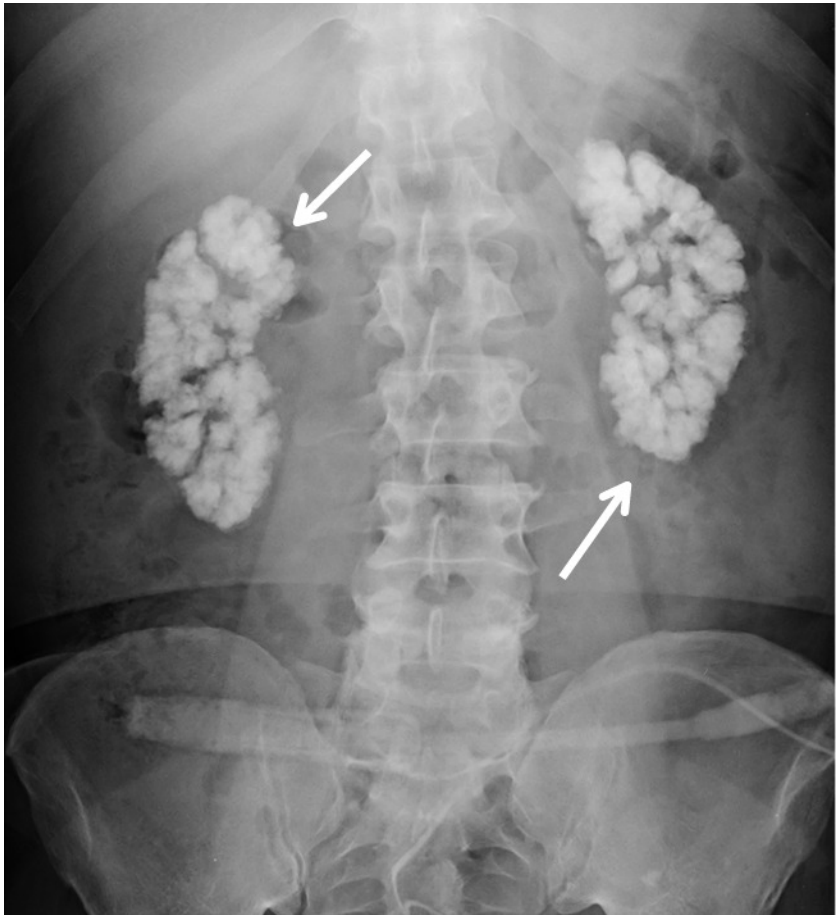
- Mild hypercalcemia (3mmol/L) may be asymptomatic or nonspecific symptoms (constipation, fatigue, depression)
- Calcium of 3-3.5.mmol/L may be well tolerated chronically, while acute rise may cause marked symptoms
- In severe hypercalcemia (>3.5mmol/L), there is progression of these symptoms
- "stones, bones, groans, moans"

Clinical presentation

- **Gastrointestinal**:
  - anorexia
  - dyspepsia
  - constipation
  - nausea
  - vomitting
  - abdominal pain
  - peptic ulcer disease
  - pancreatitis

Clinical presentation

- **Renal manifestations**:
  - dehydration
  - polydipsia
  - oliguria
  - acute kidney injury
  - nephrocalcinosis

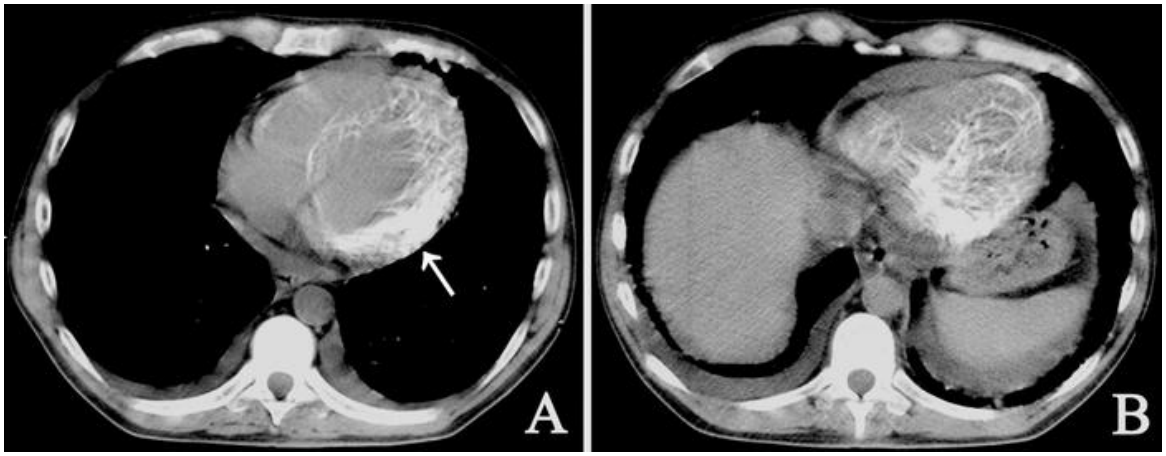


Clinical presentation

- **Neuromuscular**:
  - muscle weakness
  - confusion
  - poor concentration
  - personality changes
  - depression
  - lethargy
  - coma

Clinical presentation

- **Cardiovascular**:
  - hypertension
  - shortened QT interval with increased susceptibility to arrhythmias
  - accelerated vascular calcification

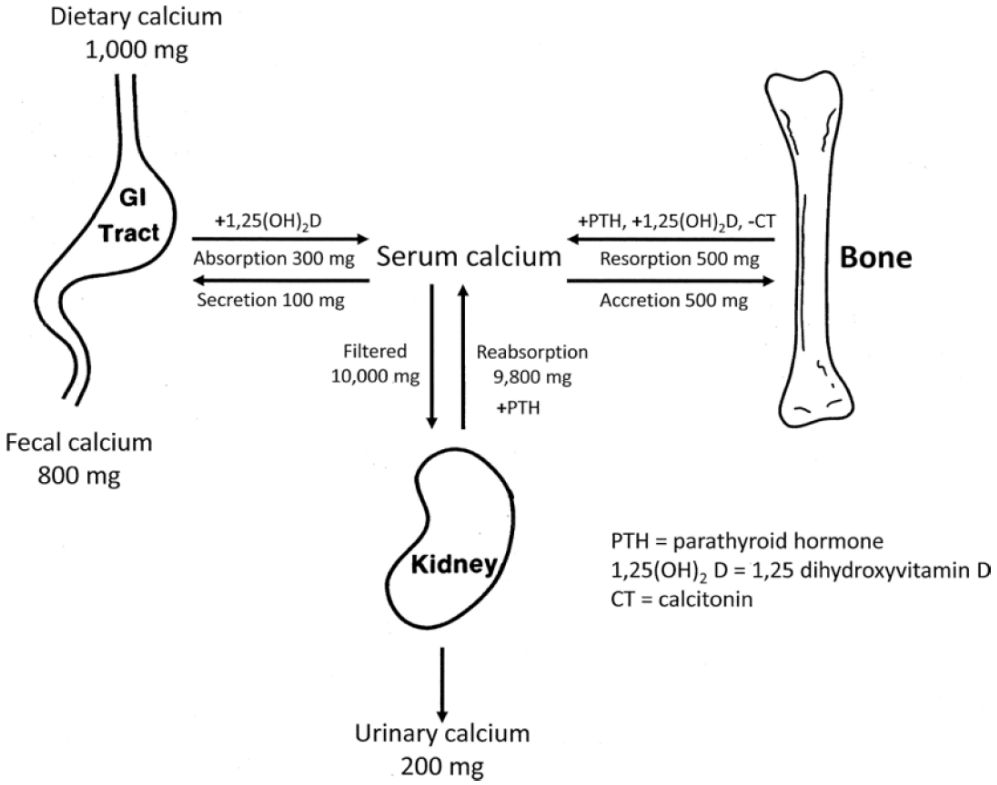


Calcium homeostasis

- 99% of total body calcium stores are present in skeletal tissue, only a small fraction exists in the ECF and ICF

  - normal propagation of action potentials
  - muscular contraction
  - exocytosis of neurotransmitters and hormones
  - regulation of cell growth
  - activation of coagulation factors
  - regulation of numerous calcium-dependent enzymes

Calcium homeostasis



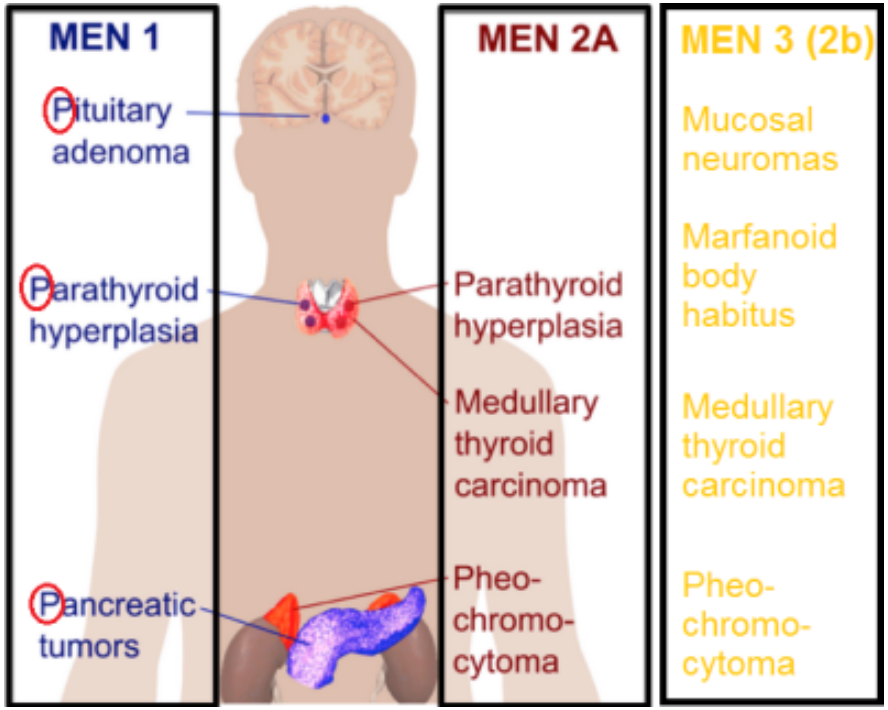
- 50% is protein bound (to albumin) and remaining 45-50% is ionized
- Corrected calcium = measured calcium + 0.8 x (4.0-albumin)

Causes of hypercalcemia

- Parathyroid disease
  - **primary hyperparathyroidism** (benign PTH adenoma, PTH carcinoma)
  - tertiary hyperparathyroidism
- **Malignancy**
  - Parathyroid hormone related protein
  - local osteolysis mediated by cytokine release
  - lytic bone metastasis
  - multiple myeloma
  - ectopic production of 1,25 dihydroxyvitamin D by tumour

Causes of hypercalcemia

- Endocrinopathies
  - Adrenal insufficiency
  - MEN 1, 2A
  - Thyrotoxicosis
- Granulomatous disease
  - Tuberculosis
  - Sarcoidosis
- Medications
  - Estrogens
  - Lithium
  - Thiazide diuretics
- Miscellaneous
  - Familial hypocalciuric hypercalcemia

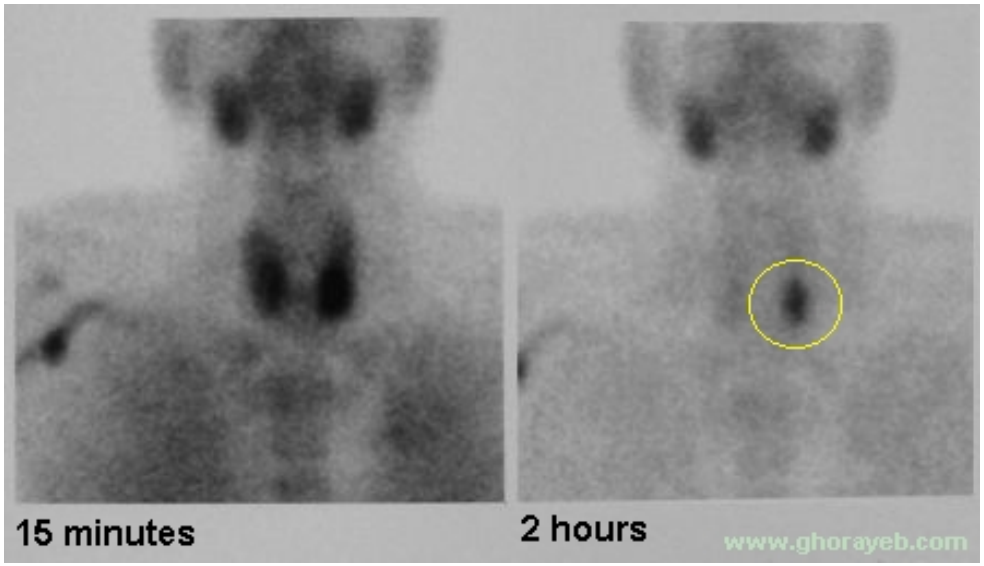


Diagnosis

- Persistently elevated serum calcium level
- Ionized calcium and PTH
- Serum phosphorus (will be low in patients with hyperparathyroidism)
- Urinary calcium
- Assay for PTHrP
- Individualized tests: urine protein electrophoresis, vitamin D levels, bone scans, thyroid tests

Imaging procedures for parathyroid

- Once diagnosis is biochemically confirmed, imaging can assist in identifying enlarged glands before surgery

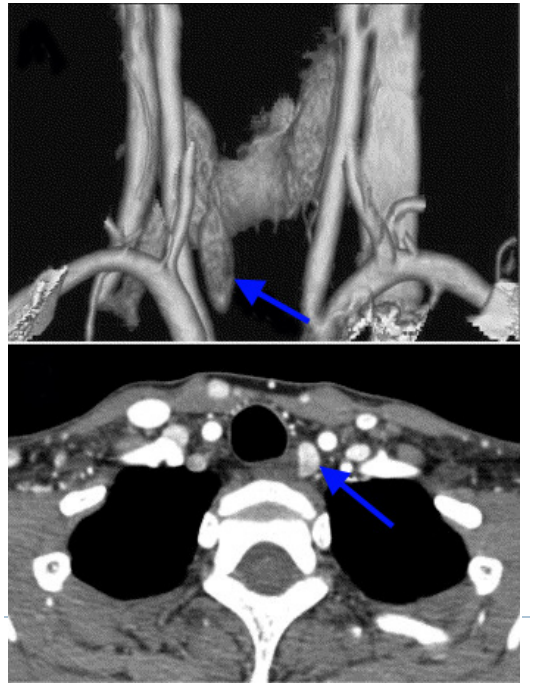


- Technetium sestimibi parathyroid scanning is most commonly utilized

- Neck ultrasound

Imaging procedures for parathyroid

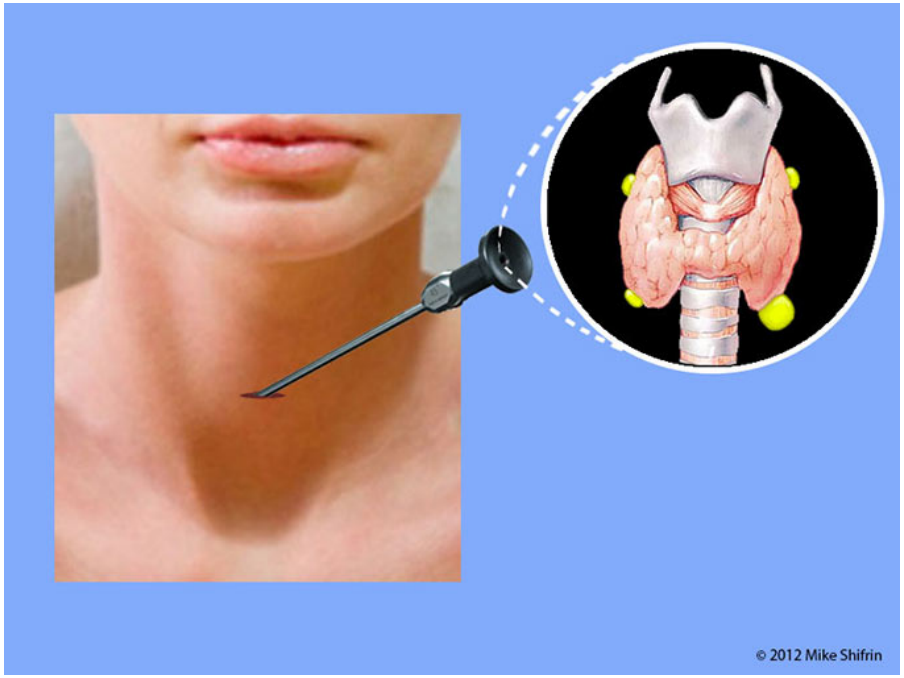
- Ultrasound-guided needle aspiration with analysis of the aspirate for PTH will confirm an adenoma in the neck
- CT or MRI
- 4-dimensional CT scans (greater sensitivity than parathyroid scans in localizing single adenomas as well as multigland disease)



Surgical management of hyperparathyroidism

- Generally an elective procedure

- Advances in preoperative localization of parathyroid adneomas and use of intraoperative PTH monitoring allows for minimally invasive parathyroid surgery



Medical treatment

- Depend upon the degree of hypercalcemia
- As calcium exceed 3mmol/L, patients are more likely to be symptomatic and even if asymptomatic, they are at higher risk of developing complications such as soft tissue calcification

- Goals of therapy:
  1) lowering calcium levels
  2) correcting dehydration, increasing renal calcium excretion
  3) decreasing osteoclast-mediated bone resorption

Intravenous fluids

- Polyuria, anorexia, nausea and vomiting lead to decreased fluid intake

- Initial treatment with intravenous isotonic saline solutions will often lower the serum calcium and induce diuresis

Intravenous fluids

- Infusing approximately 3-6L of intravenous fluid during the initial 24hour period is commonly recommended

- For patients at risk of fluid overload, some studies recommend rehydration with no more than 75-150ml/hr of 0.9% sodium chloride

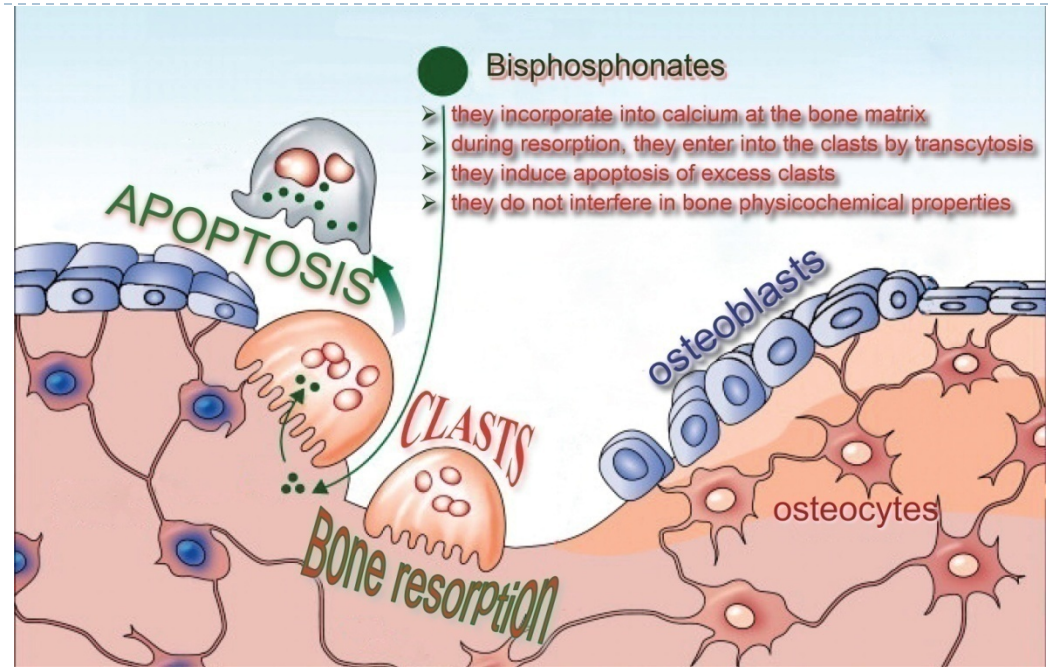
Legrand SB. Modern management of malignant hypercalcemia. Am J Hosp Palliat Care. 2011;28(7):515-517

Loop diuretics (frusemide)

- Often combined with isotonic saline infusion
- Block calcium re-absorption in the ascending limb of the loop of Henle, inducing calciuresis

- Thiazide diuretics are contraindicated in severe hypercalcemia. They enhance calcium re-absorption in the distal nephron and may exacerbate hypercalcemia

Bisphosphonate



- Block osteoclast-mediated bone resorption via promotion of osteoclast apoptosis

- Regarded as first-line therapy, in conjuction with intravenous volume expansion

Bisphosphonate

- Zoledronate has the advantage of rapid infusion over 5-15mins

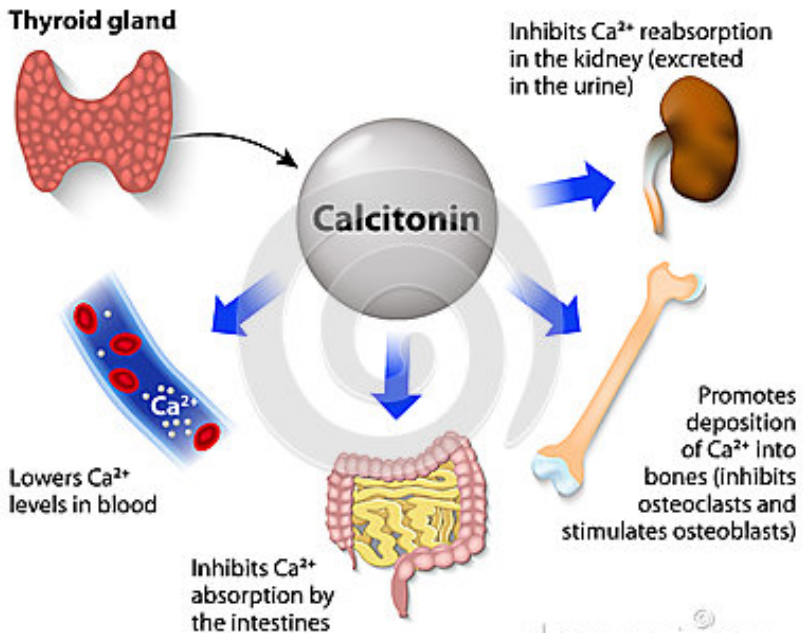
- Pamidronate is to be given over at least 2 hours
- Zoledronate is superior to pamidronate in restoring normocalcemia in hypercalcemia (88% for zoledronate vs 70% for pamidronate)

- In patients with creatinine clearance <30ml/min, zoledronate is not recommended

Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001;19(2):558-567

Calcitonin

- Most rapid onset of action of all available drugs and has been used successfully in combination with IV bisphosphonates
- Lowers calcium levels by reducing osteoclastic bone resorption and promoting calciuresis
- Monotherapy lacks potency and durability



Calcitonin

- Rapid calcium lowering is desirable, highly valuable as a temporizing agent to facilitate reductions while waiting for more potent, slower-acting bisphosphonates to become effective

- Combination calcitonin and bisphosphonates, in addition to forced diuresis, may therefore be most valuable in acutely ill patients

Calcimemetics

- In a dose-finding study of patients with primary hyperparathyroidism (calcium levels 3.5mmol/L), cinacalcet can reduce serum calcium reaching normal range 2 hours after the second dose

- Effective in reducing severe hypercalcemia in patients with parathyroid carcinoma

- Not been studied for the treatment of PTH-dependent hypercalcemic crisis, though rapid onset and success in patients with parathyroid carcinoma suggest a role

Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. J Clin Endocrinol Metab. 2003;88(12):5644-5649

Glucocorticoids

- Decreases intestinal absorption of calcium via decreased synthesis of 1,25-dihydroxy vitamin D and increasing urinary calcium excretion

- Useful in a limited subset of individuals:
  - multiple myeloma
  - lympoma-related hypercalcemia

- Doses of prednisolone 1-2mg/kg or hydrocortisone 200-300mg daily for 3 to 5 days may be considered

Dialysis

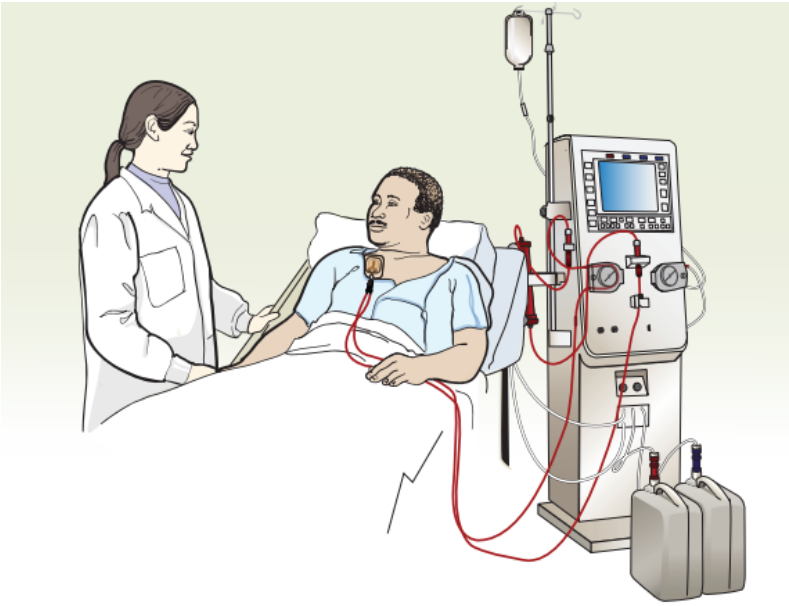
- Haemodialysis against a low- or zero-calcium dialysate may be necessary as a salvage therapy where other options have failed or are contraindicated

- No randomized trials comparing haemodialysis to other treatments of hypercalcemia though in several cases, renal replacement therapies were effective when IVF and bisphosphonates had failed

Dialysis

- Temporizing measure as they do not treat the source of hypercalcemia

- Dialysis with a low-calcium dialysate can induce transient hypotension in up to 35% of patients (through rapid decreases in calcium levels)



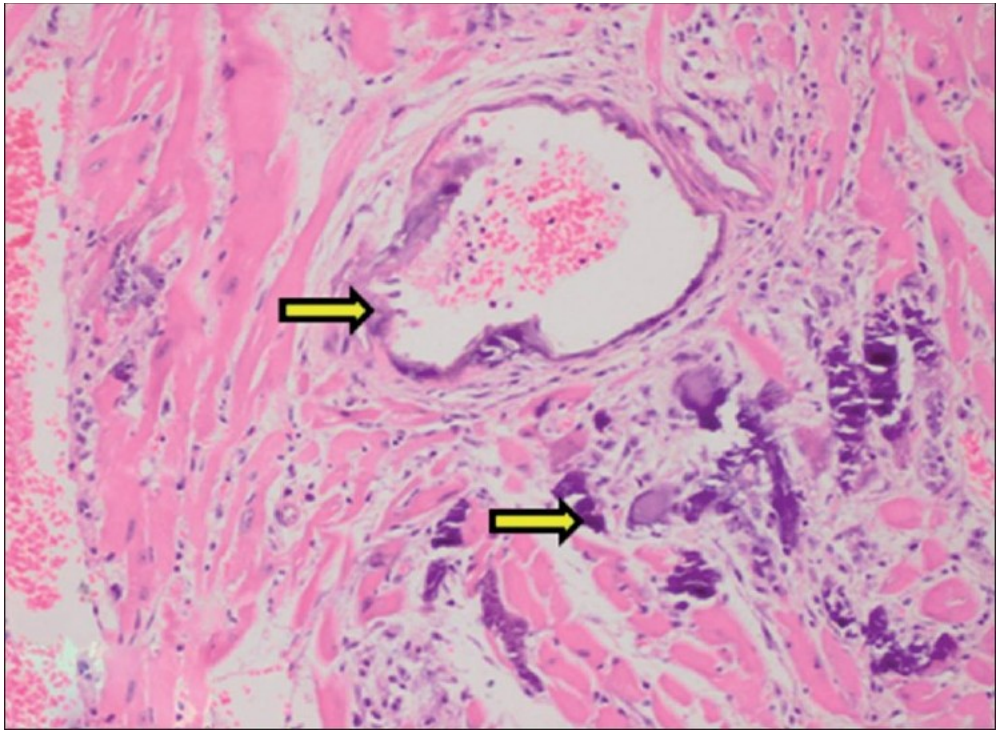
Camus C, Charasse C, Jouannic-Montier I, et al. Calcium free hemodialysis: experience in the treatment of 33 patients with severe hypercalcemia. Intensive Care Med. 1996;22(2):116-121

Recap of our case

- Hypercalcemia of 5.35mmol/L
- Treated with vigourous fluids, frusemide, pamidronate, calcimimetic, calcitonin, and eventually hemodialysis
- Cardiac arrest and had emergency parathyroidectomy

Recap of our case

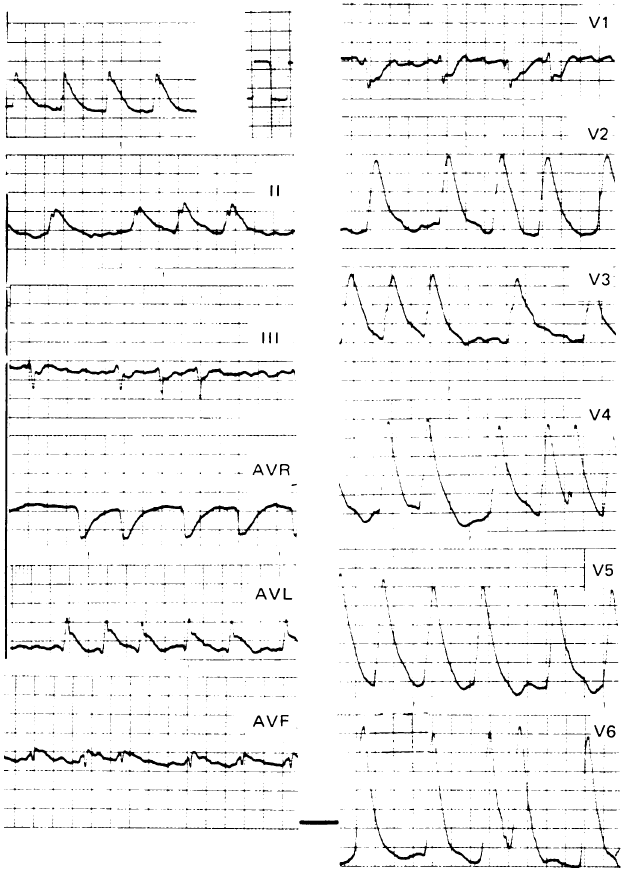
- Right ventricle and left ventricle biopsy showed: **microcalcification** present, compatible with changes of hypercalcemic crisis



Myocardial calcification

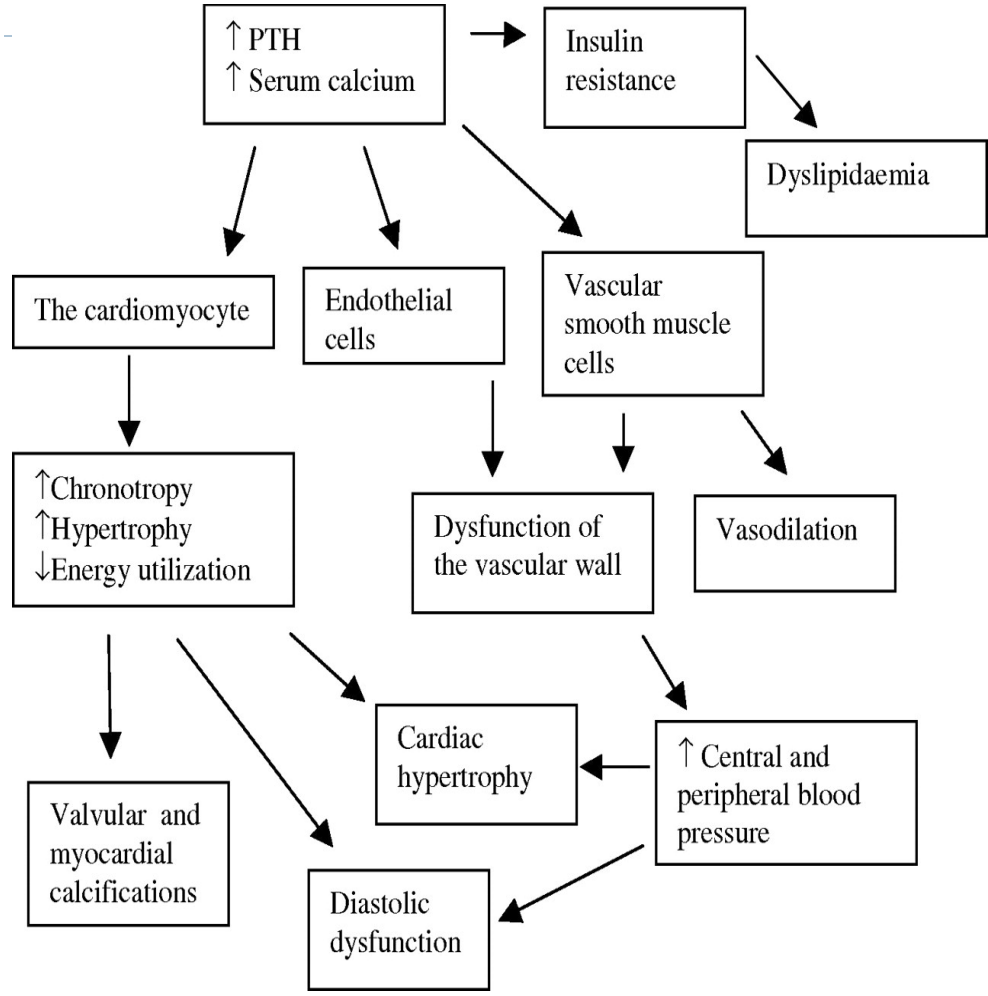
- Case report in 1986:

  - 61yo/F complained of pains, anorexia, indigestion, urinary frequency
  - serum calcium 5.8mmol/L
  - died of cardiac arrest 28 hours after admission



Rayner HC, Hasking DJ. Hyperparathyroidism associated with severe hypercalcaemia and myocardial calcification despite minimal bone disease. *British Medical Journal (Clinical research ed)*. 1986;293(6557):1277-1278

- - adenoma of left lower parathyroid gland measuring 4cm in diameter
- - lungs were oedematous and contained embolic thrombus
- - histological exam showed extensive myocardial calcification



Post-op issues

- Parathyroid hormone levels normalize rapidly following parathyroidectomy
- Patients may develop symptomatic hypocalcemia
- Our patient post-op ionized calcium levels gradually decreased from 2.31 →1.36
- However, patient had hemodynamic collapse after OT

Collect Date :	10/01/16	18/02/16	25/02/16	12/03/16	**19/09/16**		**C**
Collect Time :	14:34	05:46	05:53	05:40	**13:26**		
Arrive Date :	10/01/16	18/02/16	25/02/16	12/03/16	**19/09/16**		
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Request No. :	C5021639	C5115595	C5134263	C5177592	**C5659820**	Reference Range	Units
Urgency :	--	--	--	--	--		
Specimen Type: Blood							
PTH (Beckman)	1537 H	→ 126 H	368 H	174 H	127 H	12.0 - 88.0	pg/mL
Calcium	5.10 H	2.43	1.72 L	1.84 L		2.20 - 2.60$	mmol/L

PTH inotropic effects

- Studies show PTH caused a sharp, dose-dependent reduction in BP of several mamalian models
- Mediated by direct interaction of PTH with vascular smooth muscle of arteries and resistance vascular beds
- Direct positive inotropic and chronotropic effects have been observed in cardiac tissue after treatment with PTH

Ogino K. et al. The hemodynamic basis for the cardiac effects of parathyroid hormone (PTH) and PTH-related protein. Endocrinology. 1995 Jul;136(7):3024-30

PTH inotropic effects

- PTH and PTHrP are both vasodilators and directly increase heart rate independent of autonomic reflexes

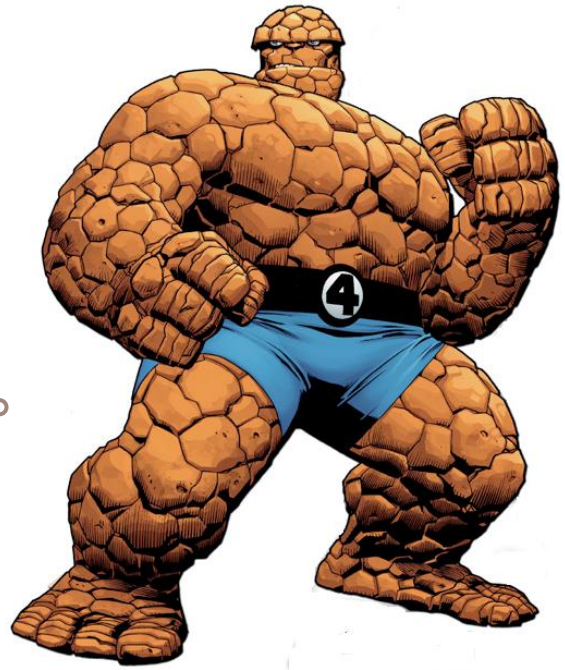
- It has been reported that PTH stimulates G protein action and increases intracellular calcium in cardiac myocytes

Summary

- Hypercalcemic crisis is a rare manifestation of decompensated calcium homeostasis, most often resulting from primary hyperparathyroidism
- Timely work-up and intensive medical therapy to optimize organ function should be prioritized, while urgent surgery is expedited
- Aggressive saline volume expansion and bisphosphonates are first line therapy
- Haemodialysis against a low- or zero-calcium dialysate may be necessary as a salvage therapy

Bones

Groans



Stones

Moans

Thank you