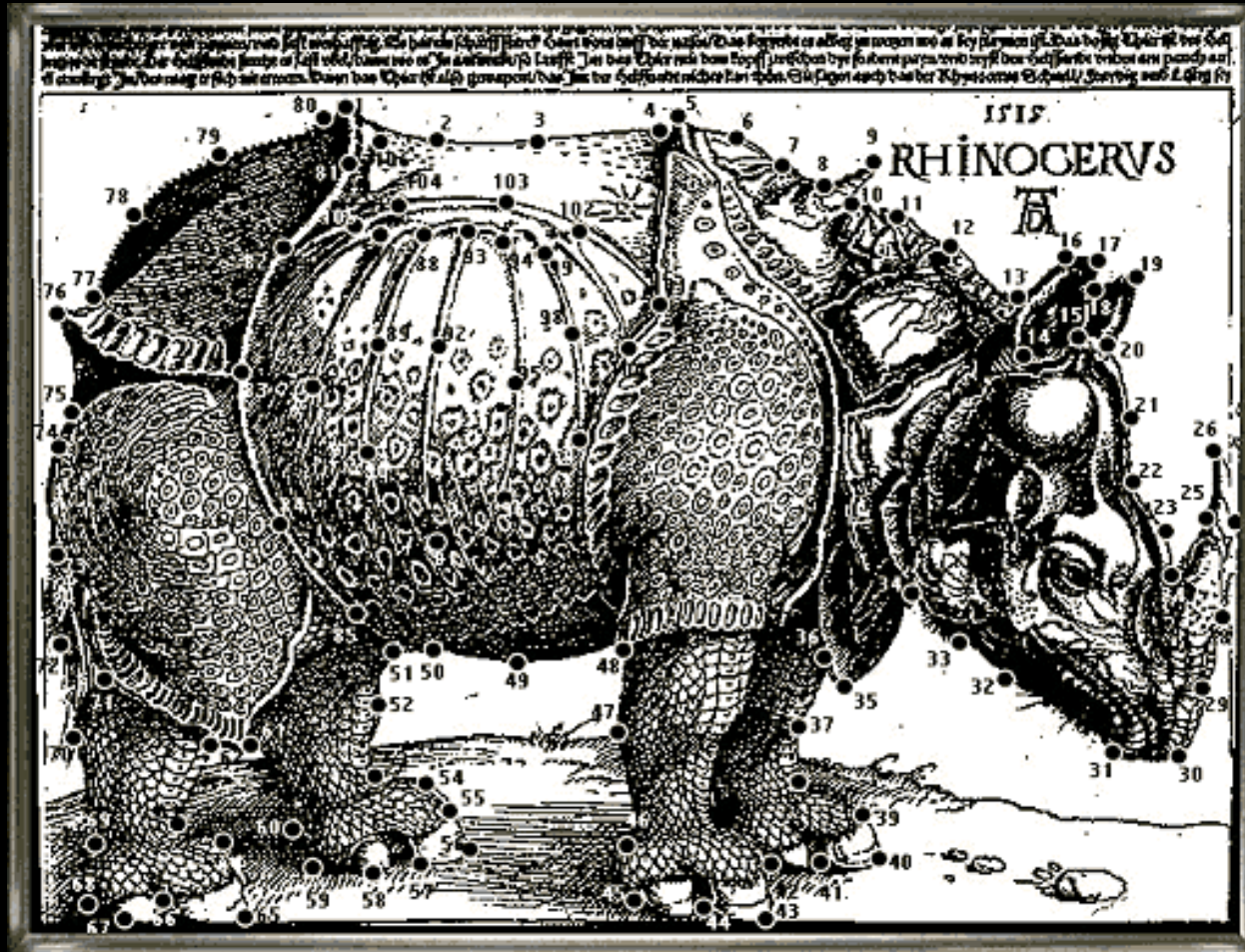


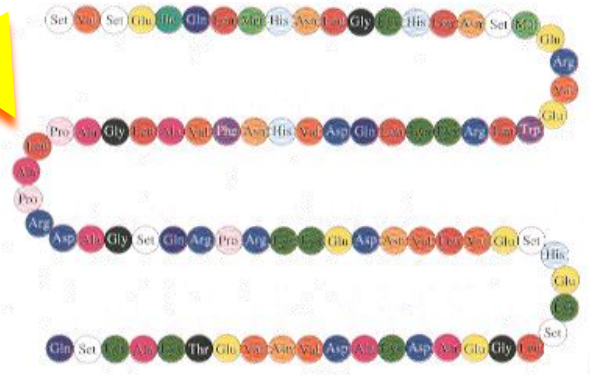
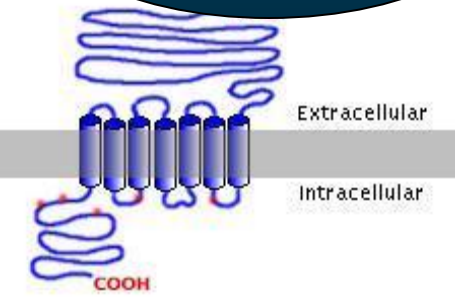
Hypercalcemia



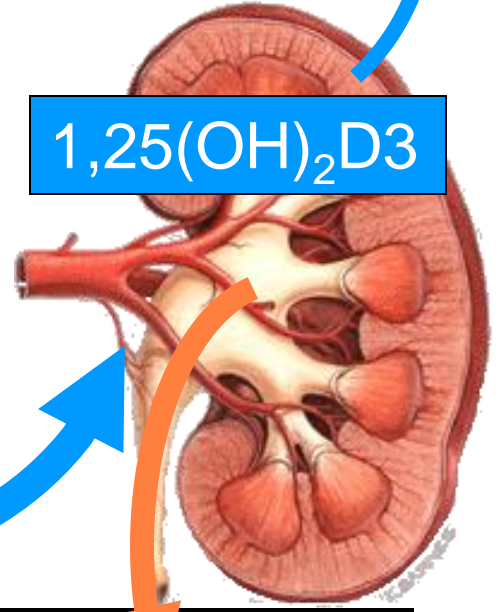
1. Calcium homeostasis: physiology and pathophysiology
2. Signs and symptoms of hypercalcemia
3. Primary hyperparathyroidism
 - 3.1 Epidemiology – symptomatic vs "asymptomatic" HPT?
 - 3.2 Diagnosis and treatment
 - 3.3 Cinacalcet – alternative to surgery?
4. Differential diagnosis of hypercalcemia
5. Summary

Calcium

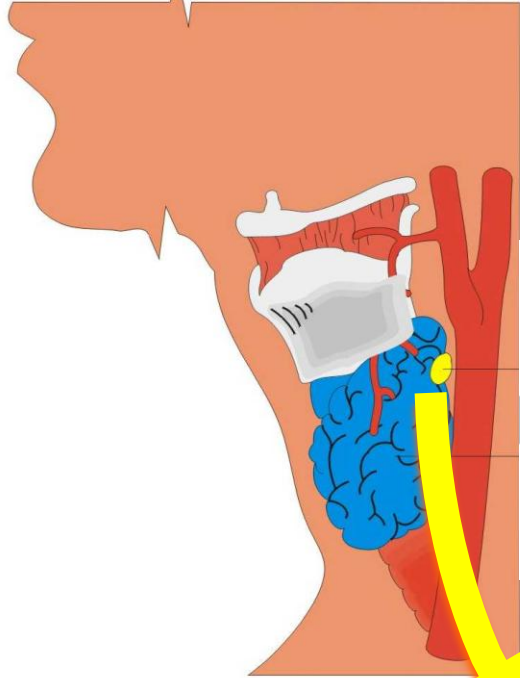
Relationship
vitamin D and PTH



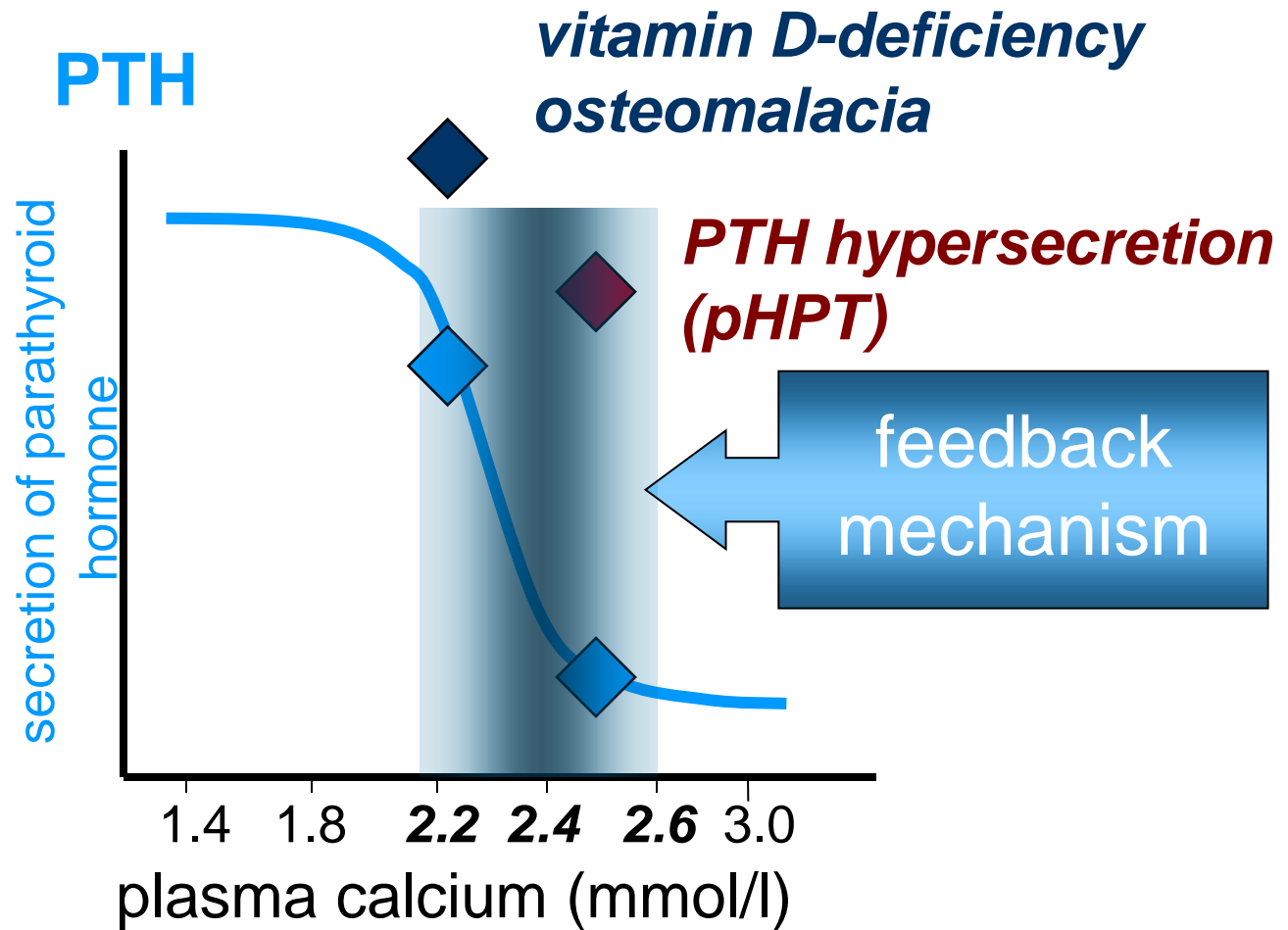
1,25(OH)₂D₃



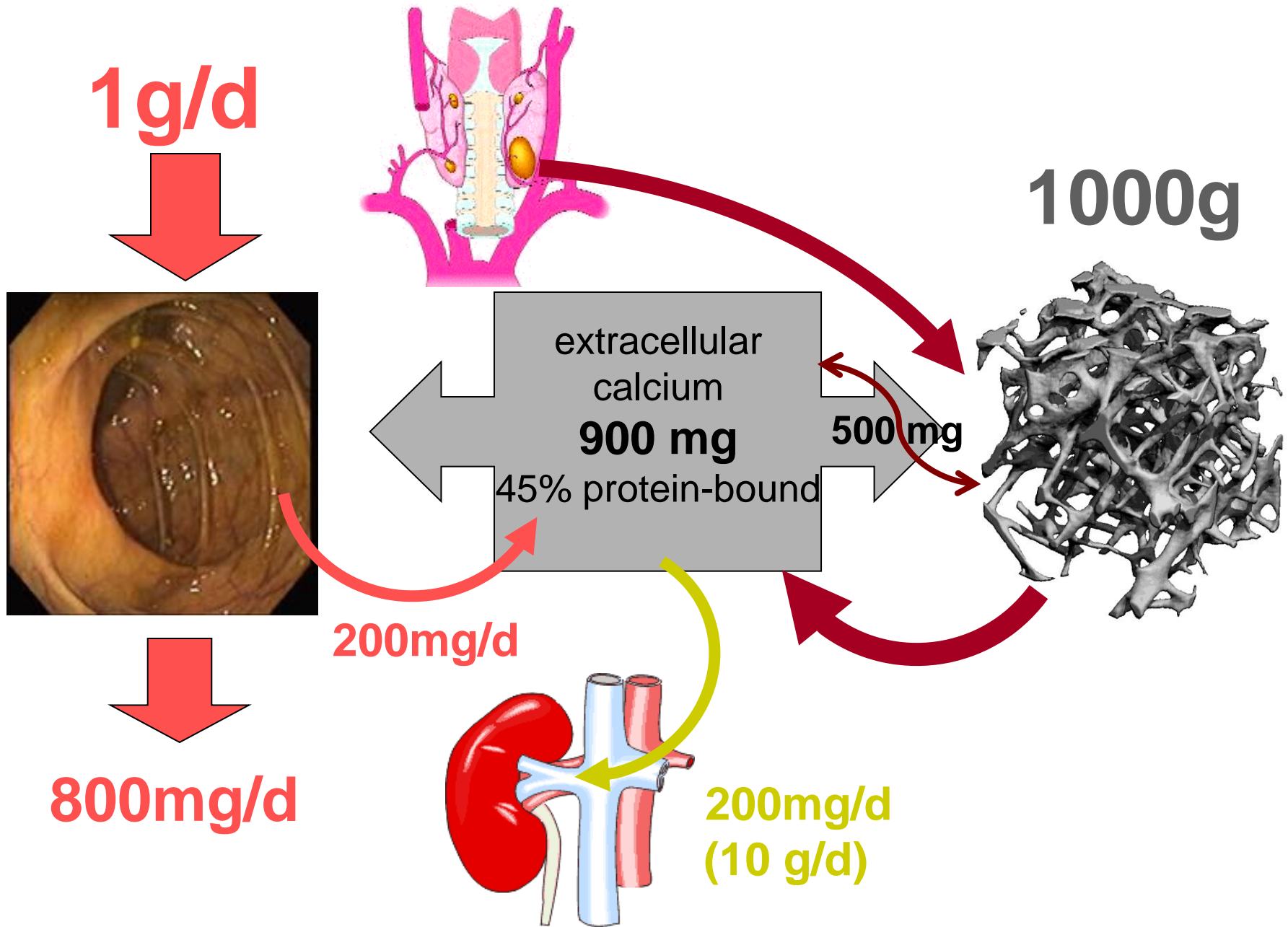
phosphate HCO₃⁻



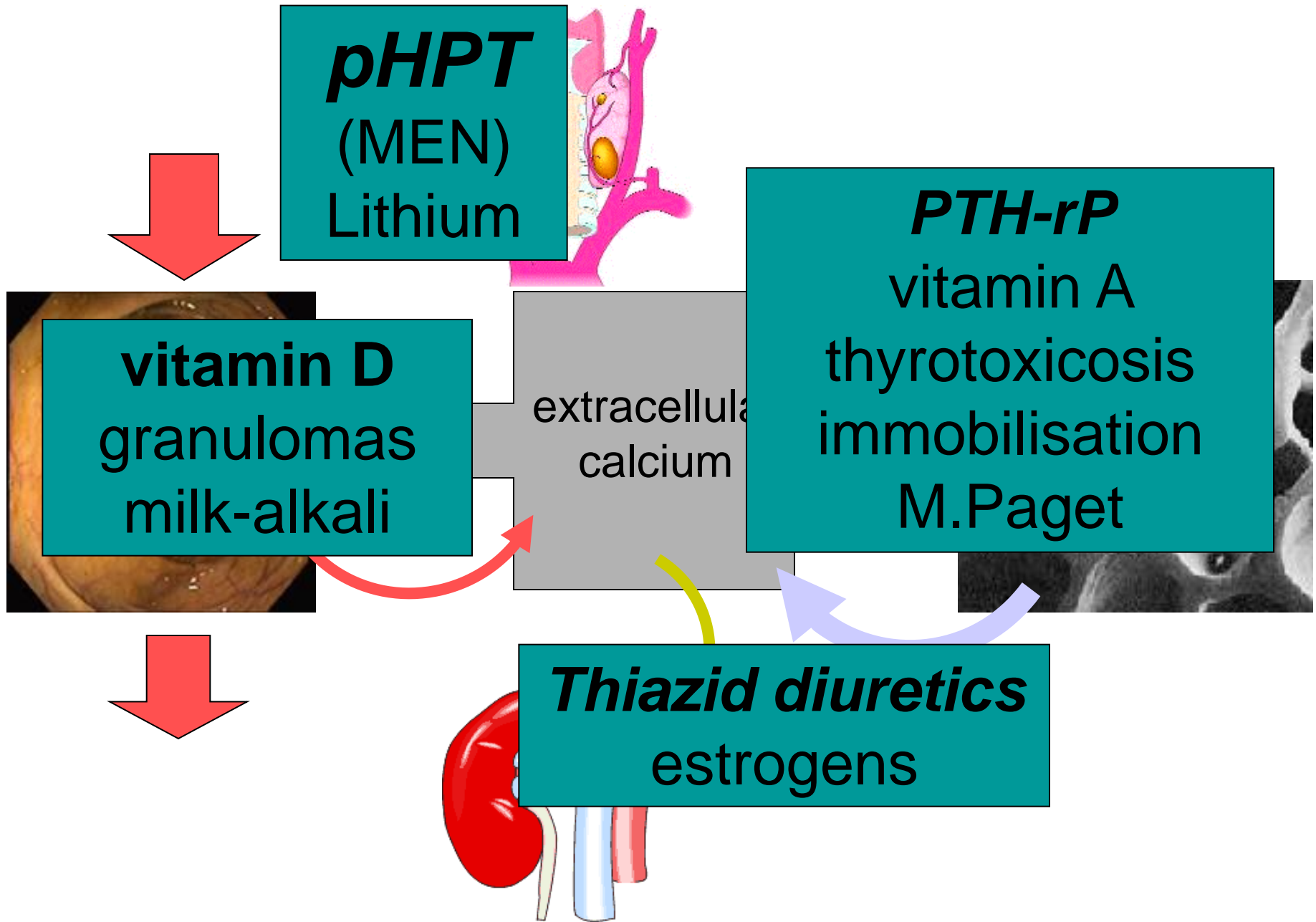
Calcium concentration and parathyroid hormone (PTH) secretion



Calcium flux in the adult



Causes of hypercalcemia



Friedrich von Recklinghausen



1833-1910

F. von Recklinghausen

Signs and symptoms of hypercalcemia

"Stein-, Bein- und Magenpein"

**"*Stones, bones*, abdominal
groans and psychiatric *moans*"**

Signs and symptoms of hypercalcemia

Metabolic CNS dysfunction

Depression, anxiety, fatigue, adynamia, cognitive impairment, arterial hypertension

Neuromuscular

Muscular weakness, constipation, short QT syndrome

Renal

Polyuria, reduced GFR, ECV deficit, metab. acidosis

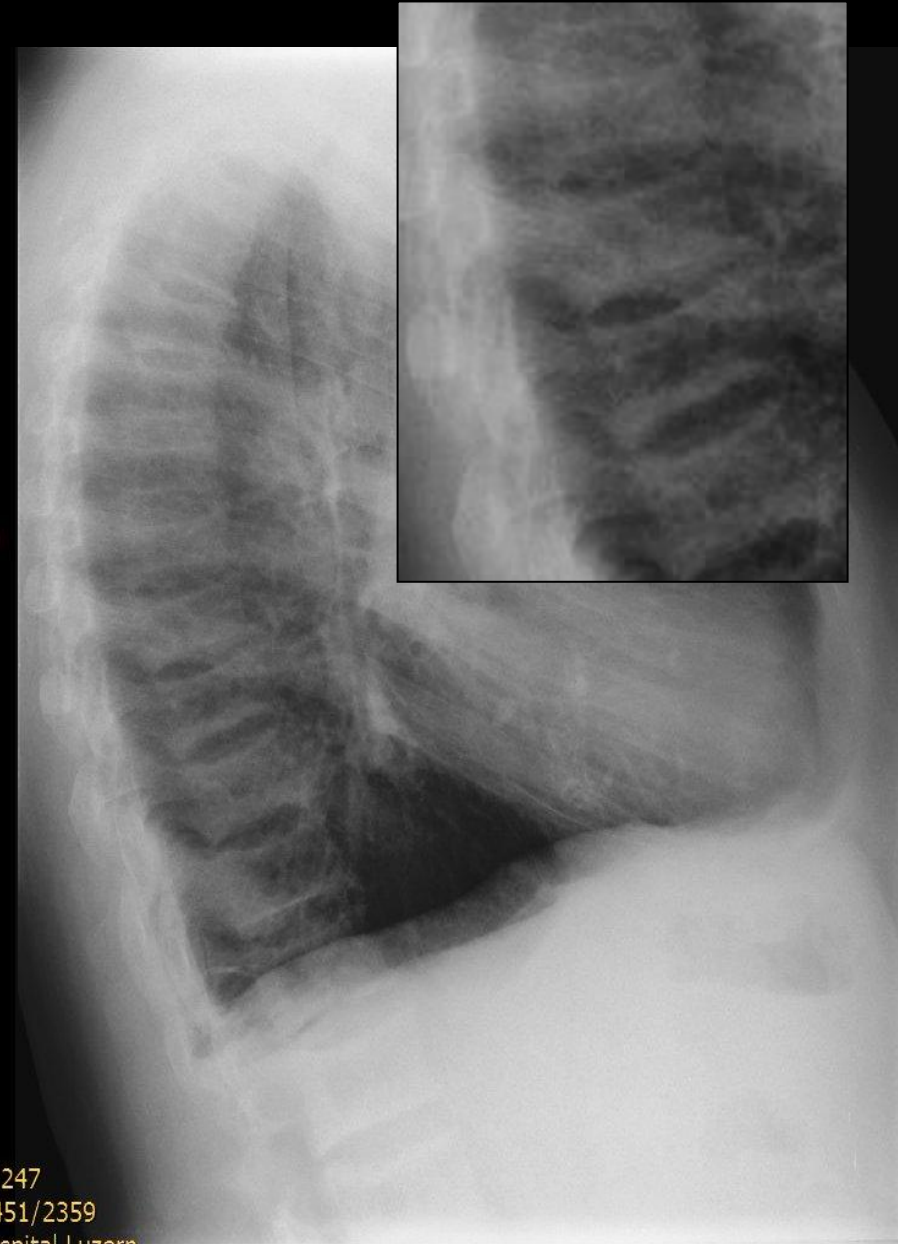
Gastrointestinal

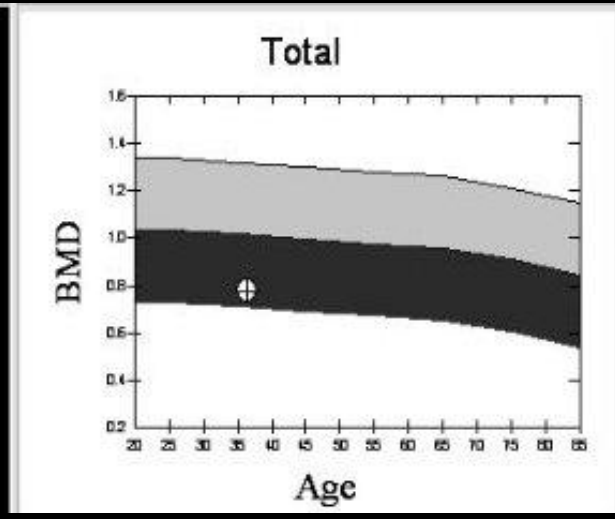
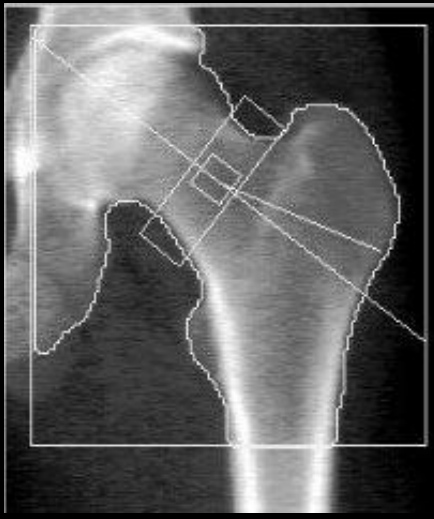
nausea, anorexia, pancreatitis, ulcer (?)

Ostitis fibrosa cystica
in about 2%

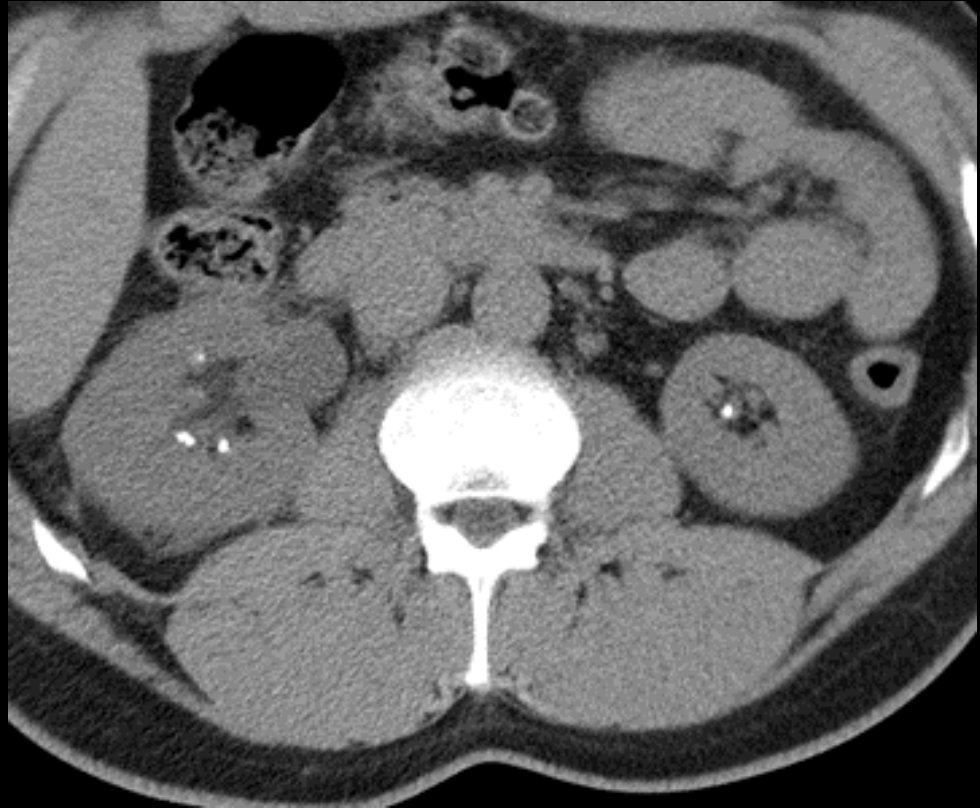


"Rugger jersey spine"





Osteoporosis of the cortical bone (femur or 1/3 radius)



Nephrolithiasis 15%

acute pankreatitis 5%



Primary Hyperparathyroidism (pHPT)?

Mrs M. S., 74y

Fatigue, diffuse arthralgias

Ca^{2+} 2.23 (N 2.1 - 2.6)

Phosph 1.2 (N 0.9 - 1.5)

PTH 84 (N 13 - 65)

Vitamin D deficiency
(osteomalacia)

Mr B. M., 38y

Fatigue, diffuse arthralgias

Ca^{2+} 2.79 (N 2.1 - 2.6)

Phosph 0.7 (N 0.9 - 1.5)

PTH 59 (N 13 - 65)

Primary
hyperparathyroidism

Primary hyperparathyroidism

Prevalence: 1:500 F/1:2000 M; >60y 0.4-2.6%

Incidence: 22/100.000

(Christensson, Acta Med Scan 1976, Heath, NEJM 1980, Marcocci, NEJM 2011)

Etiology: 85% solitary parathyroid adenoma

Localization: imaging vs. surgeon

Treatment: symptomatic pHPT →
parathyroidectomy (alternative: calcimimetics)
(„asymptomatic“ pHPT?)

Curative Tx in 90 – 98%, morbidity < 2%

CAVE experienced surgeon!

(Sosa, JCEM 1998; Strewler, Clin Endo 2000)

Mr K.A., 1927

→ *Hypercalcemia*

Osteoporosis (vertebral fractures),
Reflux oesophagitis/gastritis 8/05,
Urolithiasis 2/01 and 7/08.



Adynamia, intestinal discomfort, constipation,
polyuria, weight loss -3kg → **Ca⁺⁺ 3.2**

BP 186/92, P 96/min, BMI 31; Struma nodosa II;
3/6 systolic murmur, no focal neurological deficits.

Mr K.A., 1927

Ca⁺⁺ : 3.2 mmol/l (N 2.1 -2.6)

Phosph: 0.7 mmol/l (N 0.9-1.4)

Albumin: 40 g/l

Creatinine: 154 μ mol/l (N 48-100)

TSH : 2.8 mU/l (N 0.27-4.2)

PTH : 143 pg/ml (N 13-65)

Primary hyperparathyroidism

PTH : 12 pg/ml ?

Localization imaging sensitivity

Ultrasound → 36 – 70%

CT → 42 – 68%

MRI → 57 – 90%

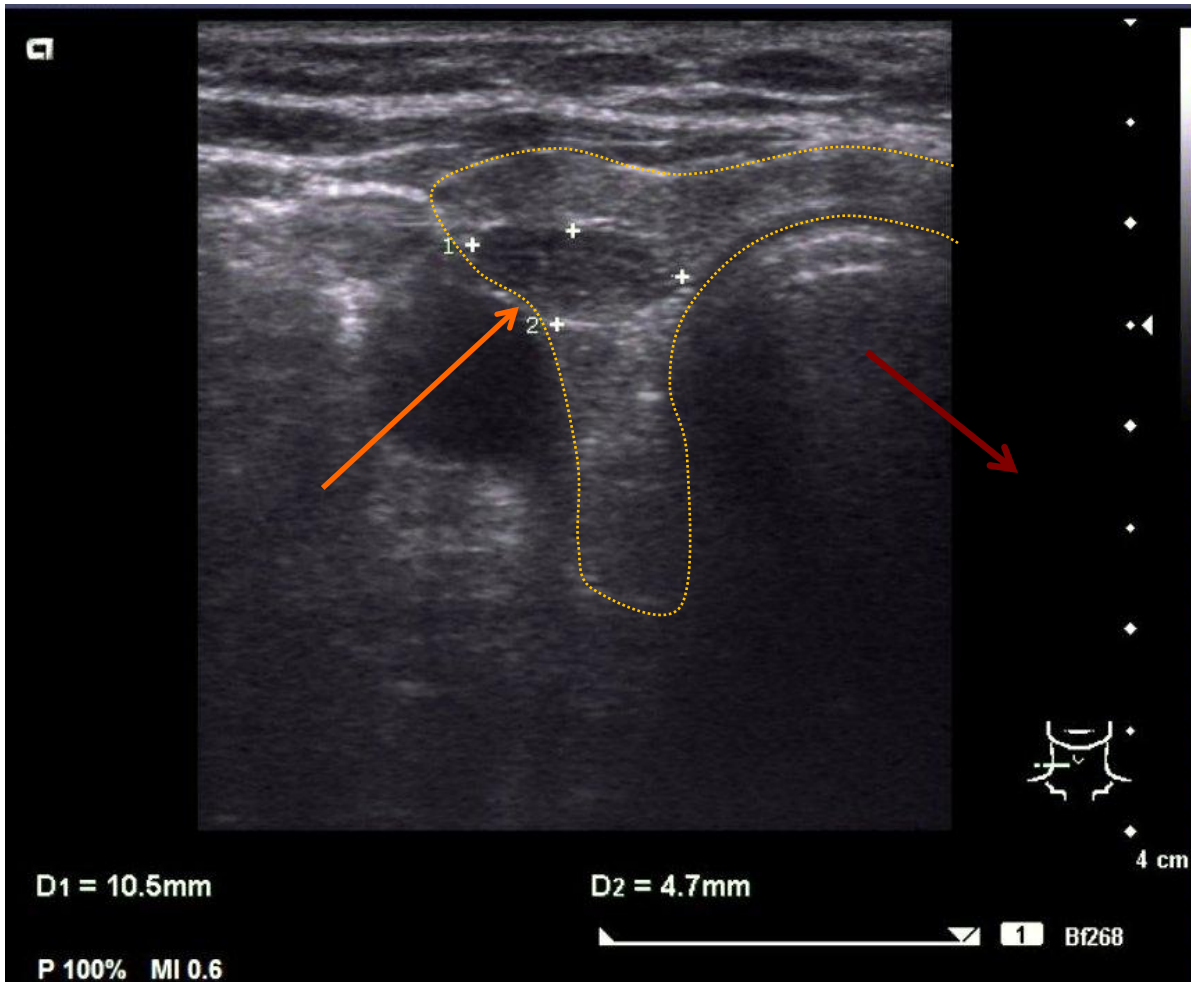
Scintigraphy → 70 – 91%

Surgeon → 95 – 98%

Marcocci 2011, Eigelberger 2000, Shen 1996, Numerow 1995, Rodriquez 1994

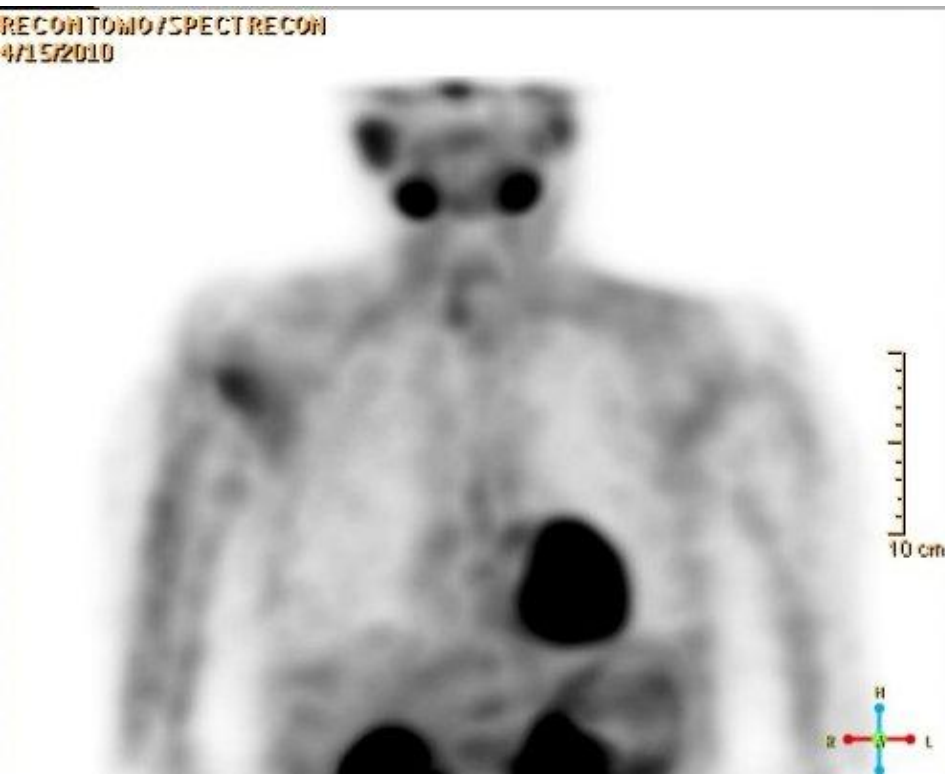
Mr K.A., 1927

Ultrasound



Herr K.A., 1927

Tc 99m-Sestamibi scan



SPECT-CT

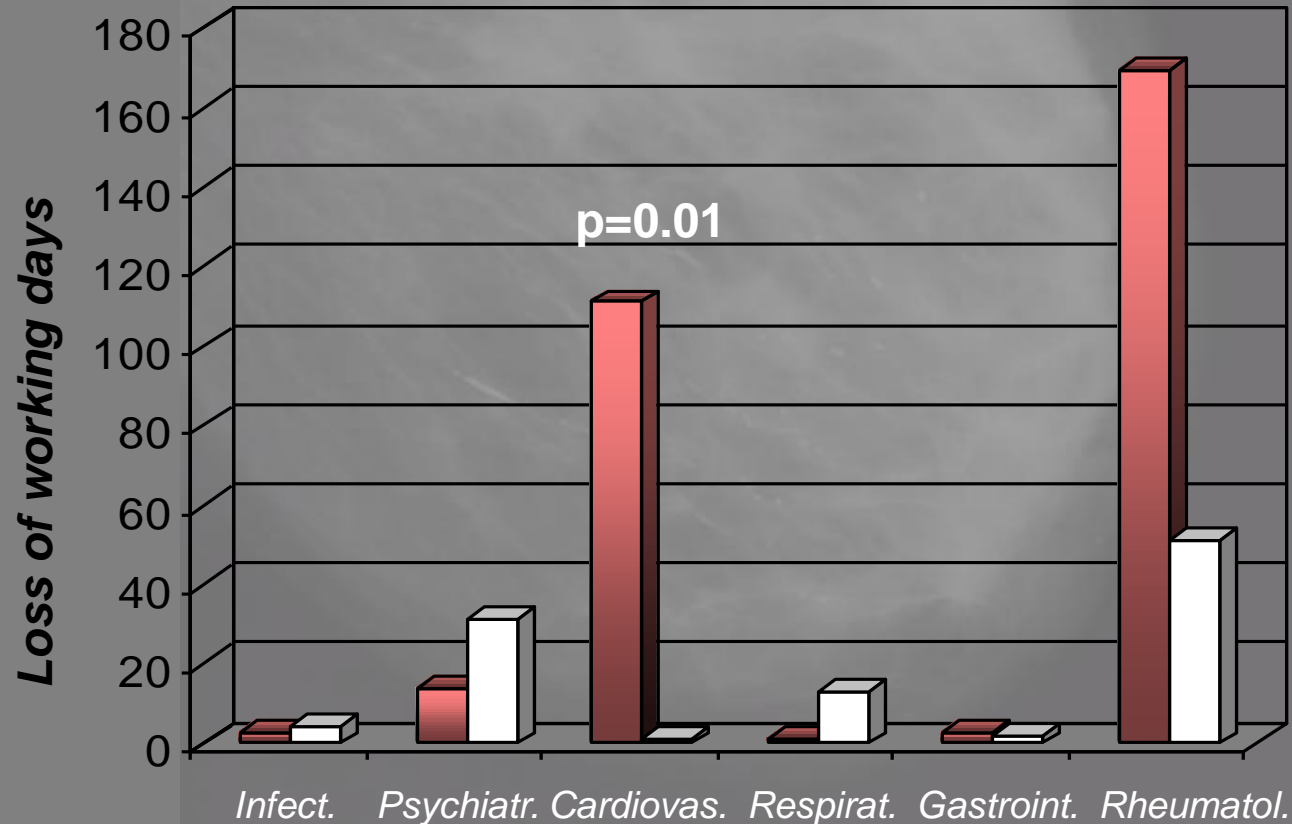


„asymptomatic“ hyperparathyroidism

5202 women 55-75y → **109 (2.1%) pHPT**

calcium: 2.6 mmol/l (N 2.2-2.6)

PTH : 69 ng/l (N 12-55)



Surgery for asymptomatic pHPT?

121 patients over 10 y
Serum-Ca⁺⁺ 2.65, PTH 121

Surgery: 61 patients
Serum-Ca⁺⁺ **2.35**
PTH **49**

BMD +12% LS
BMD +14% Femur

0/12 Nephrolithiasis

No surgery: 60 patients
Serum-Ca⁺⁺ **2.6**
PTH **106**

BMD ± 0%

6/8 Nephrolithiasis

Surveillance
Calcium 6 mts
BMD 2 y

...progression of disease in about ¼ of asymptomatic patients...

Guidelines for parathyroidectomy

serum-calcium >3 mmol/l (>0.25 UNL)

hypercalcaemic crisis

Creatinine (-clearance) -30% or <60 ml/min

hypercalciuria >10 mmol/24h

T-Score <-2.5 SD at any site or fragility fx

age <50y

*NIH Consensus 2002,
Intern Workshop, JCEM 2009;94:335-
NEJM 2011;365:2389-*

Pharmacological treatment of pHPT

Estrogens (progestogens)

Drinking > 1.5 L

Cinacalcet (Mimpara®)

Correction of vitamin D-deficiency

CAVE: Thiazids, lithium, vitamin A

Acute hypercalcemia:

NaCl 0.9% + loop diuretics

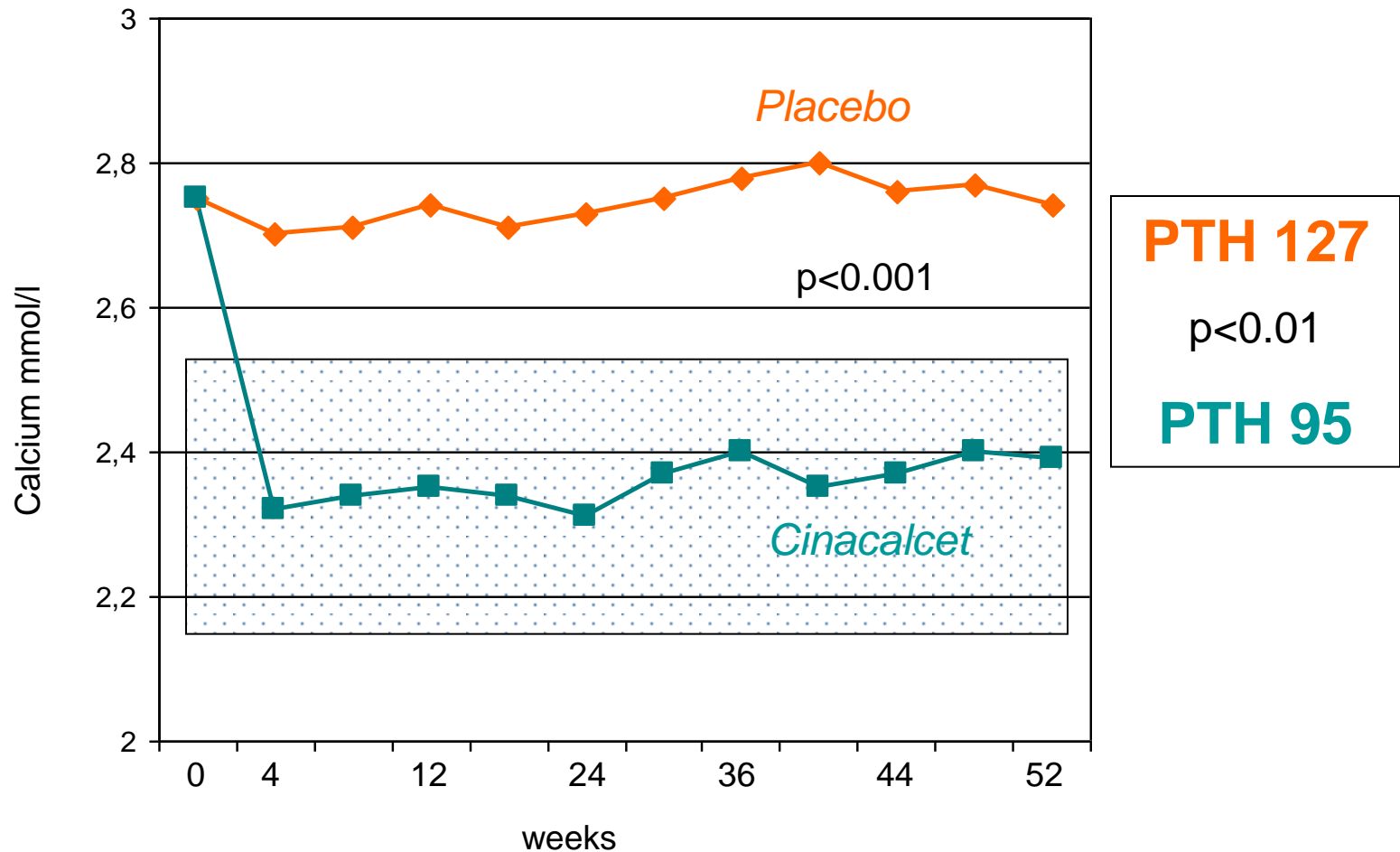
Bisphosphonates

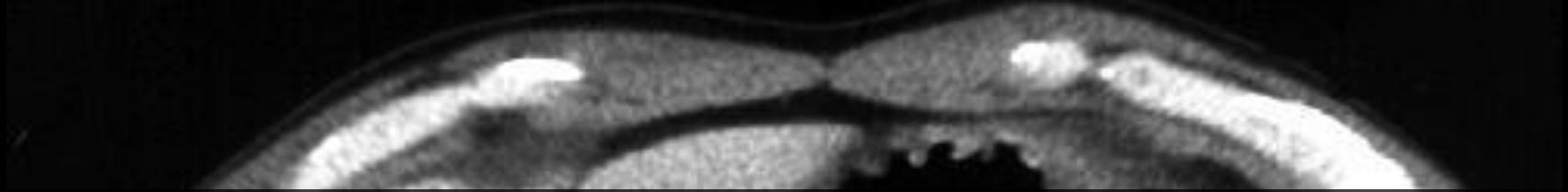
Calcitonin

Cinacalcet (Mimpara®) in patients with pHPT

Peacock et al, JCEM 2004;90;135-

78 patients (57 F/21 M, 27 – 83y) with pHPT RCT Cinacalcet 2x30 – 50mg/d vs Placebo → normocalcemia





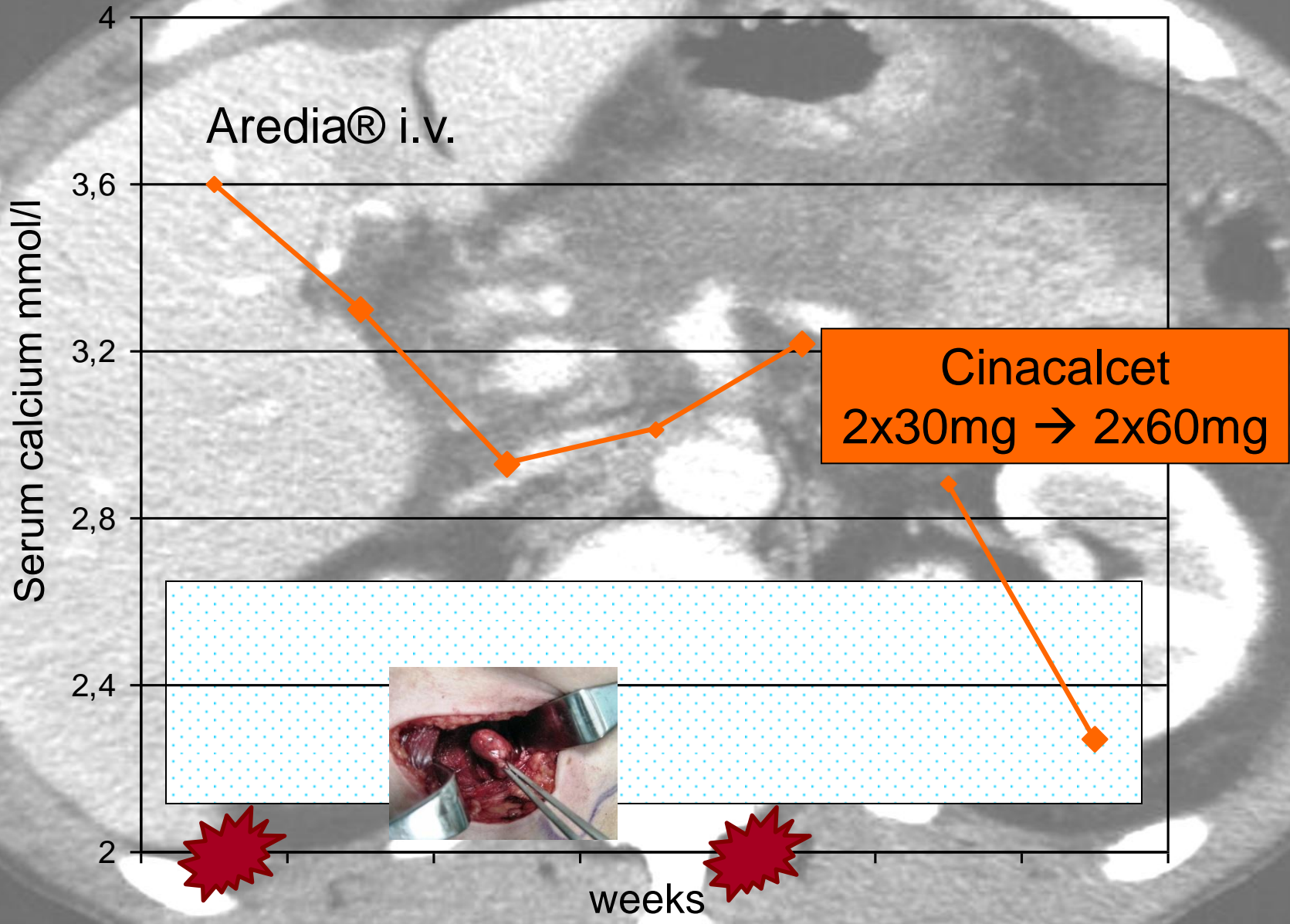
59y man with necrotizing pancreatitis with cyst/fistula and intraabdominal bleeding

Primary hyperparathyroidism → adenoma excision

Persistent hypercalcemia → MRI and scintigraphy negative

Recurrent pancreatitis → Treatment with cinacalcet





Aredia® i.v.

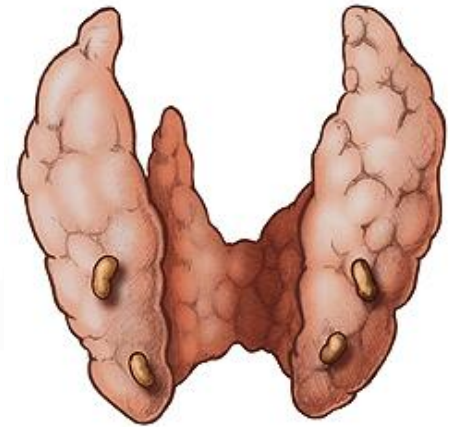
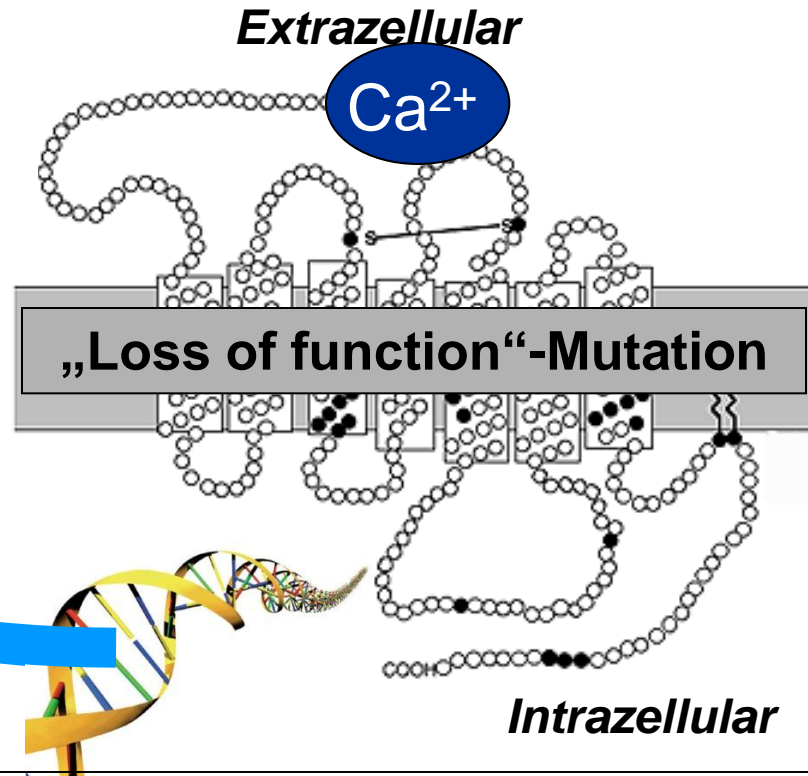
Cinacalcet
2x30mg → 2x60mg

weeks

DD:

Hypercalcemia

PTH



Familial hypocalciuric hypercalcemia (FHH)

$Ca^{++}/Kreatinin-Cl < 0.01$

(24h-urinary calcium < 2.5 mmol/l)

DD:

Tumor-induced hypercalcemia

**Parathyroid
hormone-related
peptide**

80% humoral hypercalcemia

20% local osteolysis

(exzessive secretion $1,25(\text{OH})_2\text{D}$ or PTH)

Lung cancer
breast cancer
esophagus ca
renal cell carcinoma
lymphoma
hepatoma
melanoma...

DD:

Multiple endocrine Neoplasia (MEN)

Multiple endocrine
Neoplasie 2

Multiple endocrine
Neoplasie 1

Medullary thyroid carcinoma
100%

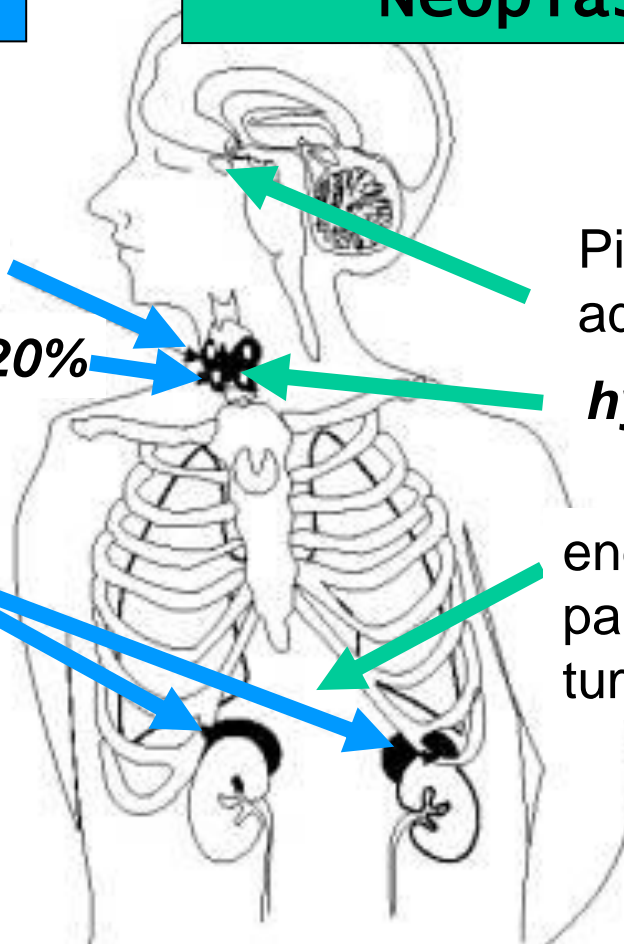
hyperparathyroidism 10-20%

pheochromocytoma 50%

Pituitary
adenoma 25%

hyperpara 95%

endocrine
pancreatic
tumors ~ 80%



DD:

68y man, flu-like infection →
immobilization → fatigue →
→ shoulder pain at left, radiating
in the arm

Prostatic hyperplasia; 34 PY;
Hypertension (amlodipine 5 mg)

→ Laboratory findings:

*Ca⁺⁺ 2.6 (n 2.1-2.5),
PTH 17 ng/ml (n 10-65),
alk phosph: 567 (n 30-120)
PSA: 6.8 (n < 4.0),
BSR 34,
CRP 11.*

**Paget's
disease**

Summary I

1. Hypercalcemia and pHPT are common, particularly in >60y (prevalence ~2%)
2. Signs and symptoms may be subtle: parathyroidectomy for symptomatic pHPT, guidelines for „asymptomatic“ pHPT (trial with cinacalcet?)
3. However, pHPT may be the cause of kidney stones, cortical osteoporosis, or pancreatitis
4. Beware of secondary elevated PTH levels in patients with vitamin D-deficit

Summary II

5. pHPT may be part of MEN 1, particularly in patients <40y, with familial history or other endocrine tumours
6. Hypercalcemia in sarcoidosis is caused by overproduction of calcitriol
7. Calcimimetics (Mimpara®) are a pharmacological alternative to surgery
8. In acute hypercalcemia treatment consists of fluid administration with NaCl 0.9% and loop diuretics, and bisphosphonates (e.g. zoledronate i.v.)