

METABOLIC BONE DISEASE

Introduction, Overview and Biochemistry

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What is metabolic bone disease?

A group of diseases that cause a DECREASE in

bone density
bone strength

by

1. INCREASING bone resorption
2. DECREASING bone formation

And may be associated with disturbances in
mineral metabolism

What are the main diseases?

Primary hyperparathyroidism

Rickets/ Osteomalacia

Osteoporosis

Paget's Disease

Renal osteodystrophy

Symptoms in these diseases

Metabolic

Hypocalcaemia

Hypercalcaemia

Hypo/Hyperphosphataemia

Bone

Pain

Deformity

Fractures

Bone Calcium

Hydroxyapatite $\text{Ca}^{2+}_{10-x}(\text{H}_3\text{O}^+)_{2x}(\text{PO}_4^{3-})_6(\text{OH}^-)_2$

Cancellous bone metabolically active

remodelling 5% anytime
total skeleton over 7 years

continuous exchange of ECF with bone fluid
reserve

Bone strength

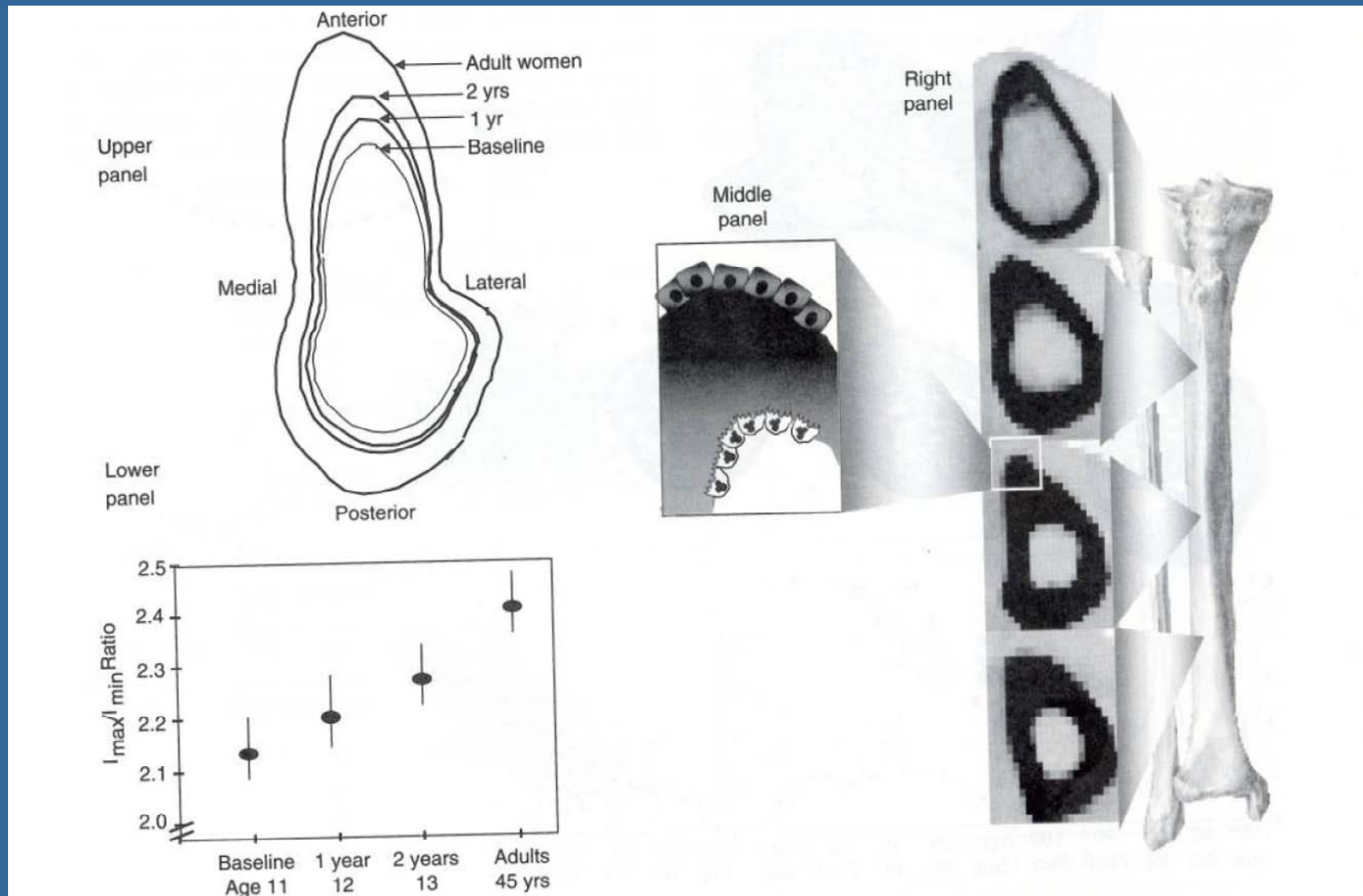
QUANTITY

- **Cortical thickness**
- **mineral density**
- **size**

QUALITY

- **Architecture**
- **Bone turnover**
- **Cortical porosity**
- **Trabecular connectivity**

Tibial bone modeling during growth



Bone structure and function may be assessed in different ways

- Bone histology
- Biochemical tests
- Bone mineral densitometry, e.g. osteoporosis
- Radiology e.g. osteomalacia, Paget's disease

**CLINICAL and BIOCHEMICAL
FEATURES OF METABOLIC BONE
DISEASE**

Biochemical Investigations in Metabolic Bone disease

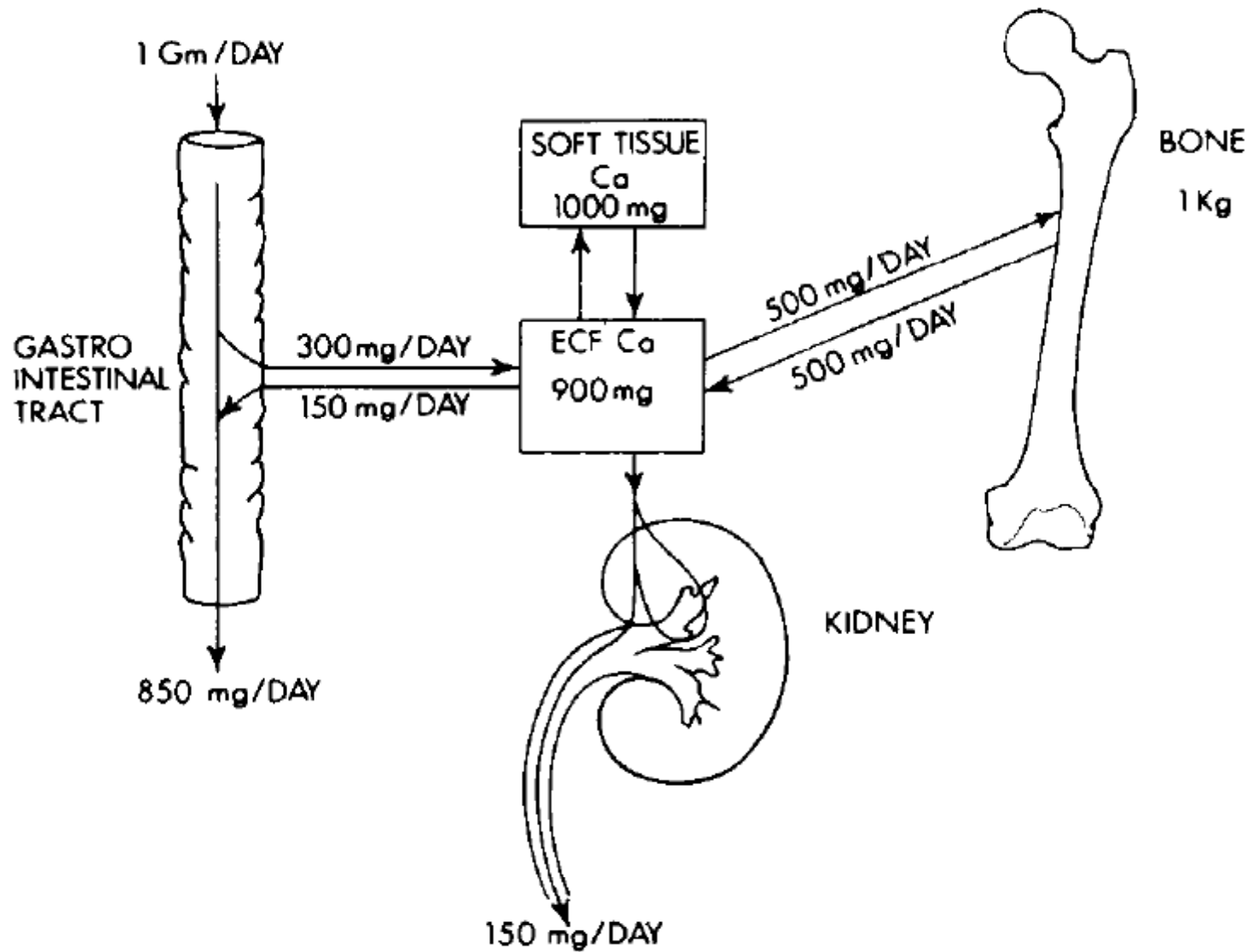
Serum calcium
 corrected calcium
 albumin
 phosphate
 parathyroid hormone
 25-hydroxy vitamin D

Urine NTX
 Calcium
 Phosphate

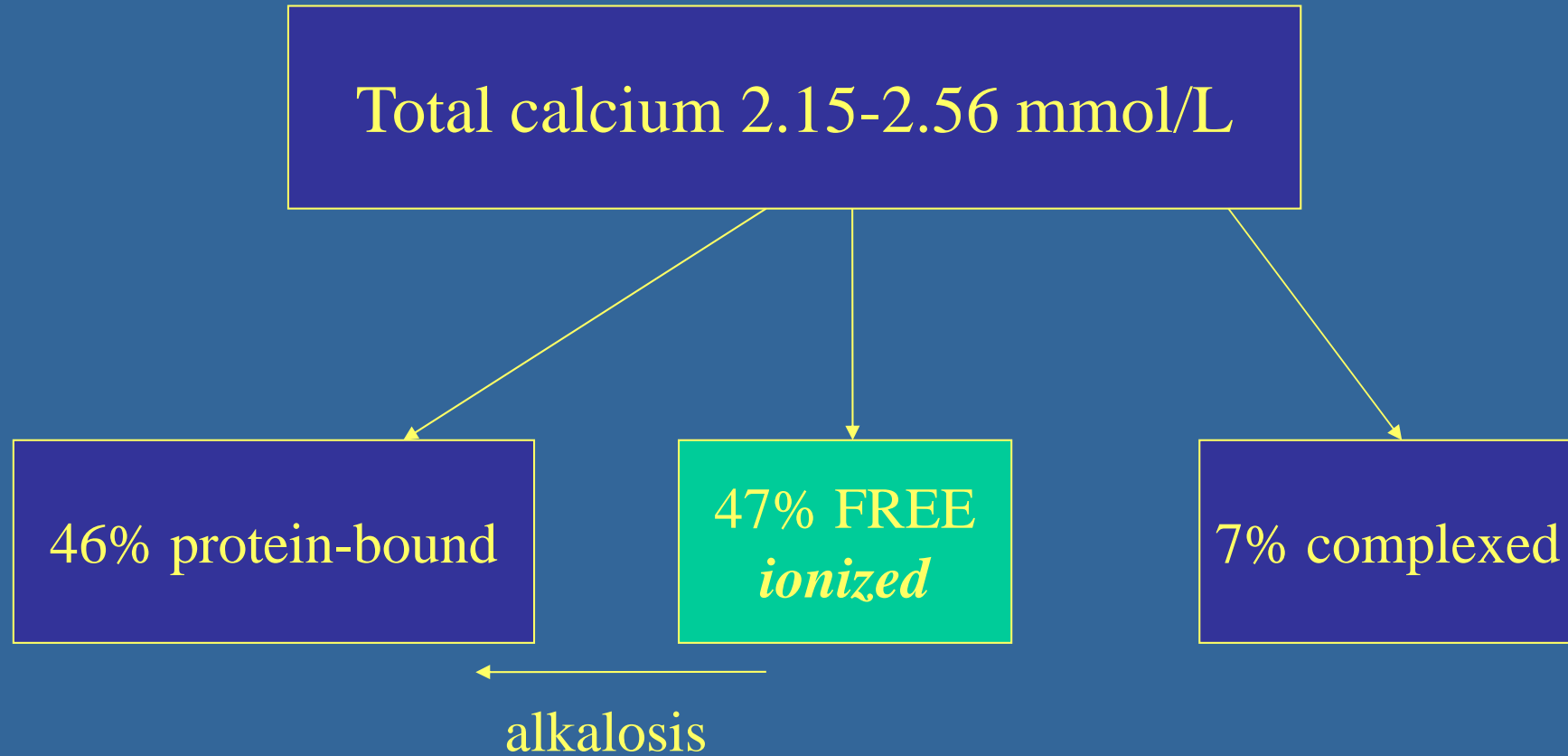
Summary of Biochemical changes in bone disease

Condition	Ca	P	Alk P	Bone form	Bone resorpt
osteoporosis	N	N	N	↑ →	↑↑
osteomalacia	N or ↓	↓	↑		
Pagets	N	N	↑↑↑	↑↑	
Primary HPT	↑	↓	N↑		↑↑
Renal osteodystrophy	↓ N	↑	↑		
metastases	↑	↑	↑		↑

NORMAL CALCIUM HOMEOSTASIS



Serum Calcium



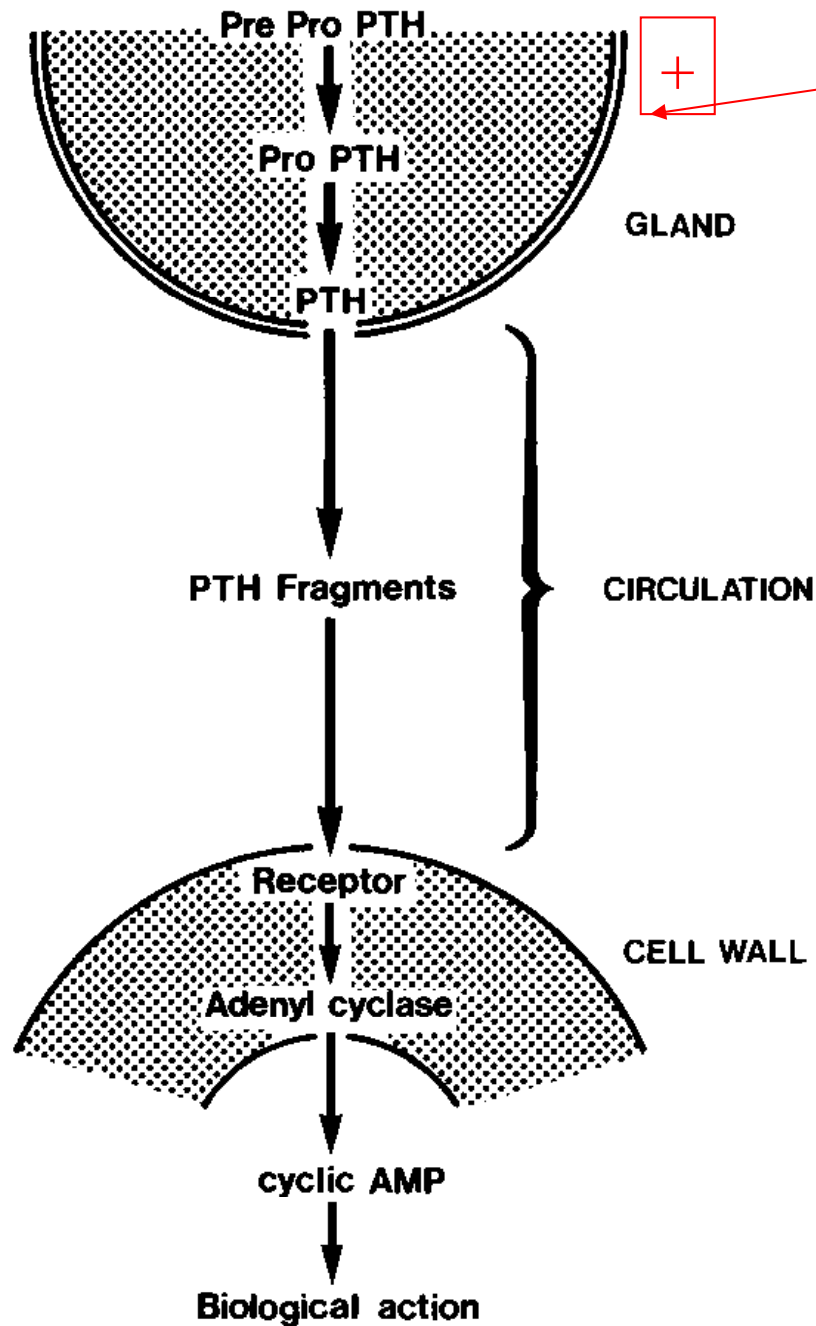
$$\text{Corrected calcium} = [\text{calcium}] + 0.02(45 - [\text{albumin}])$$

PTH

Extracellular Ca concentration is controlled with $< 2\%$ variation

PTH has the predominant role in minute by minute regulation

Afferent limb - sensing PTH response within seconds to low calcium
continued PTH secretion at high calcium levels

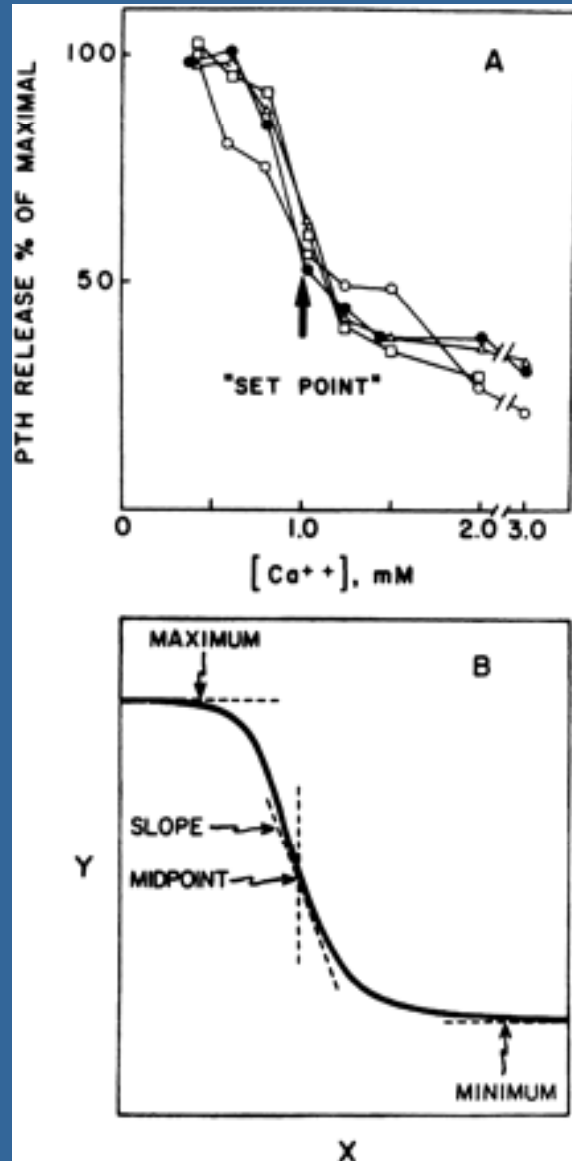


Hypocalcaemia

84 amino acid peptide
 $T_{1/2}$ 8 min
 N1-34 active
 Mg dependent

PTH 1/PTHrP receptor

The calcium-sensing receptor

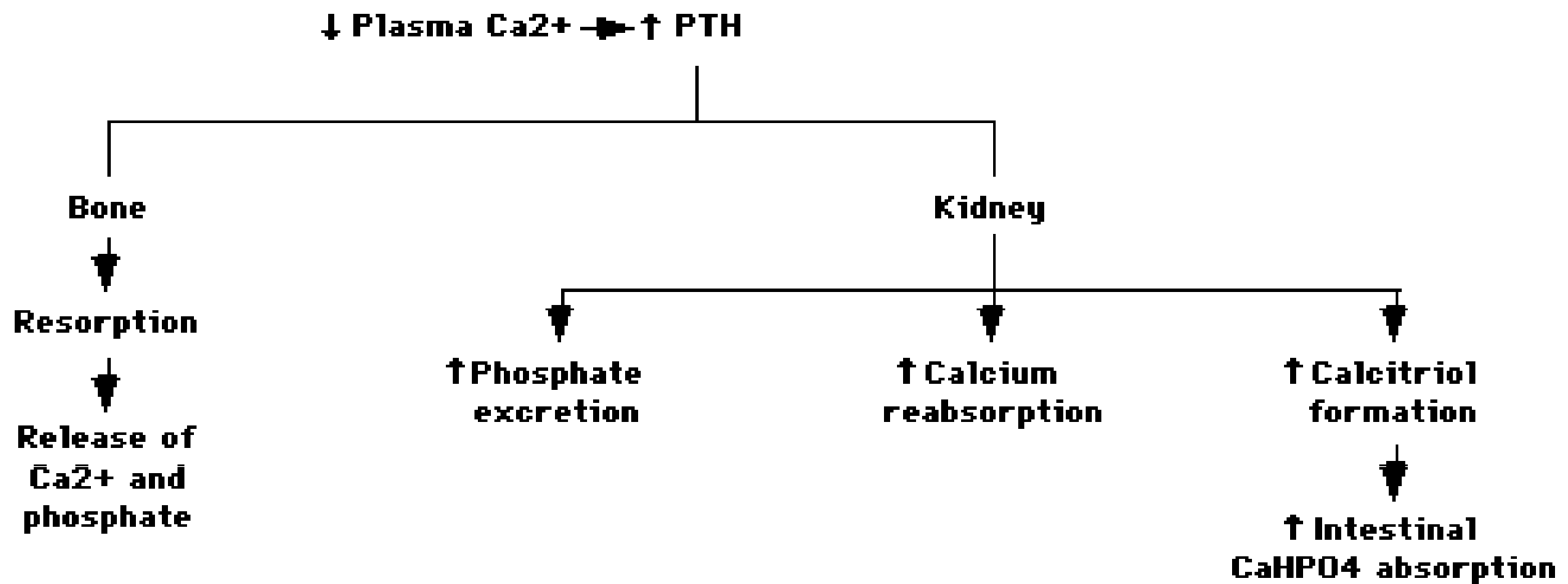


A steep inverse sigmoidal function relates PTH levels and Ca_o^{2+} in vivo.

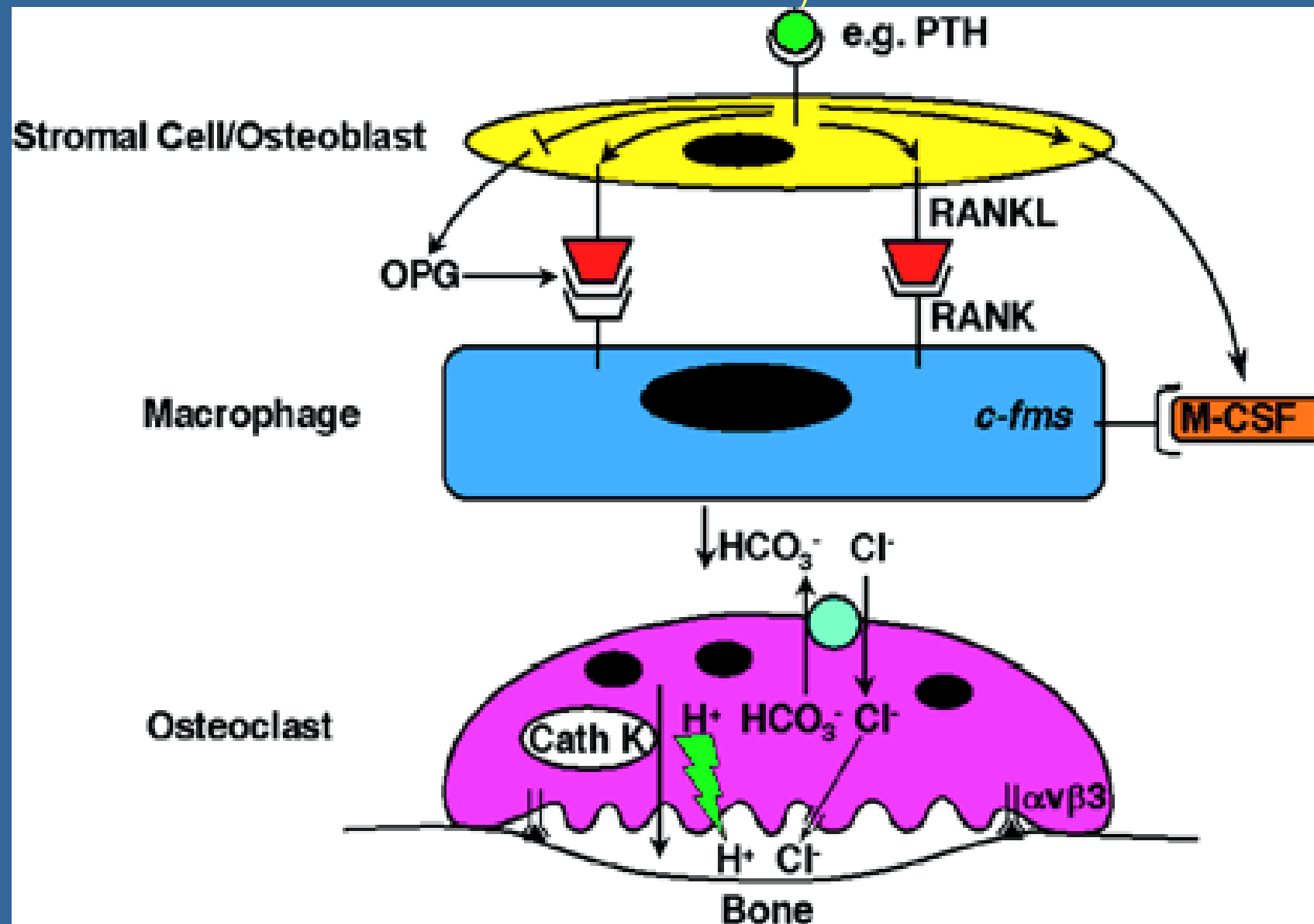
MINIMUM: even at high calcium levels there is base-line PTH secretion

SET-POINT: point of half maximal suppression of PTH; steep part of slope; Small perturbation causes large change PTH

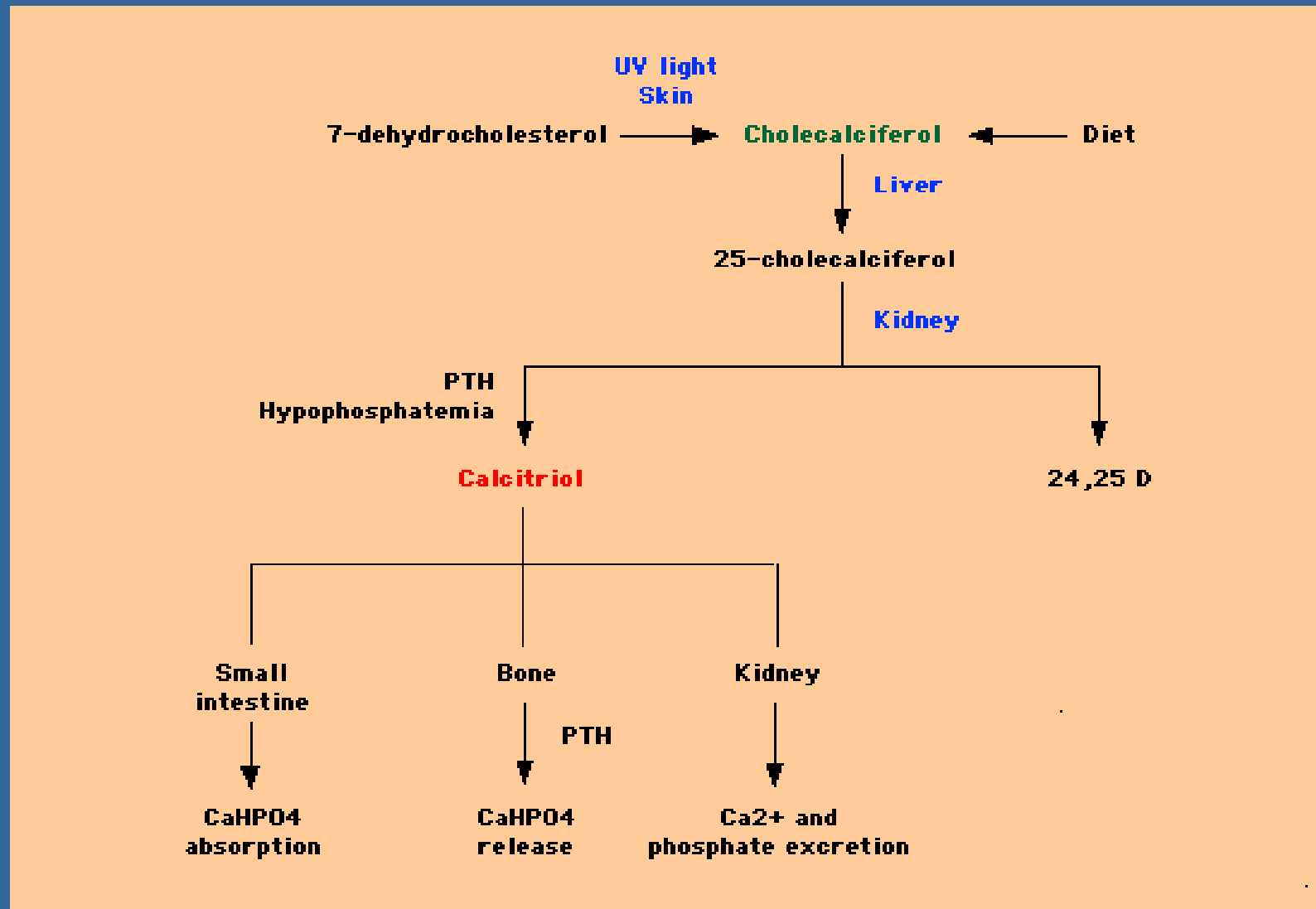
PTH effect



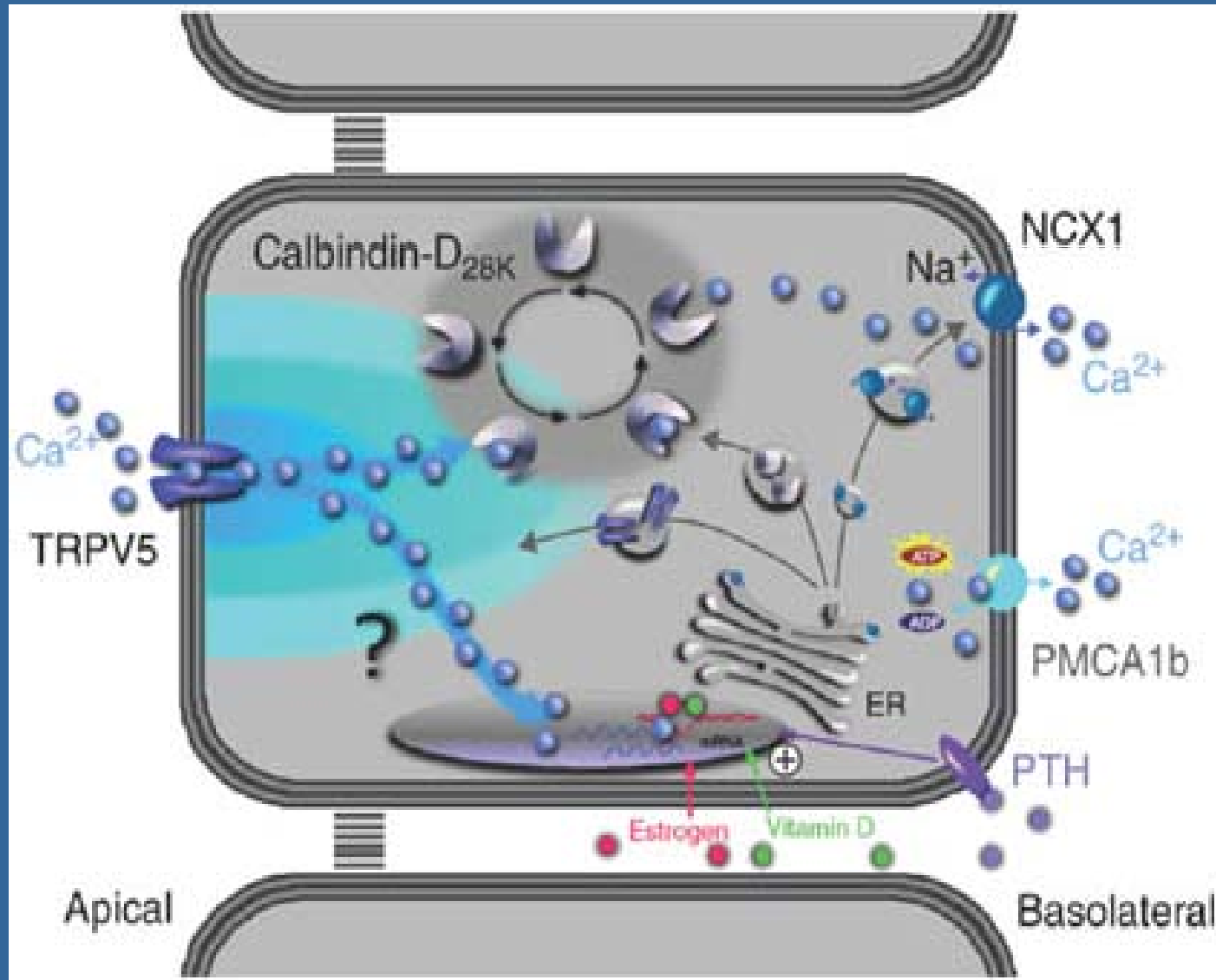
PTH releases calcium from bone by activating the RANK System



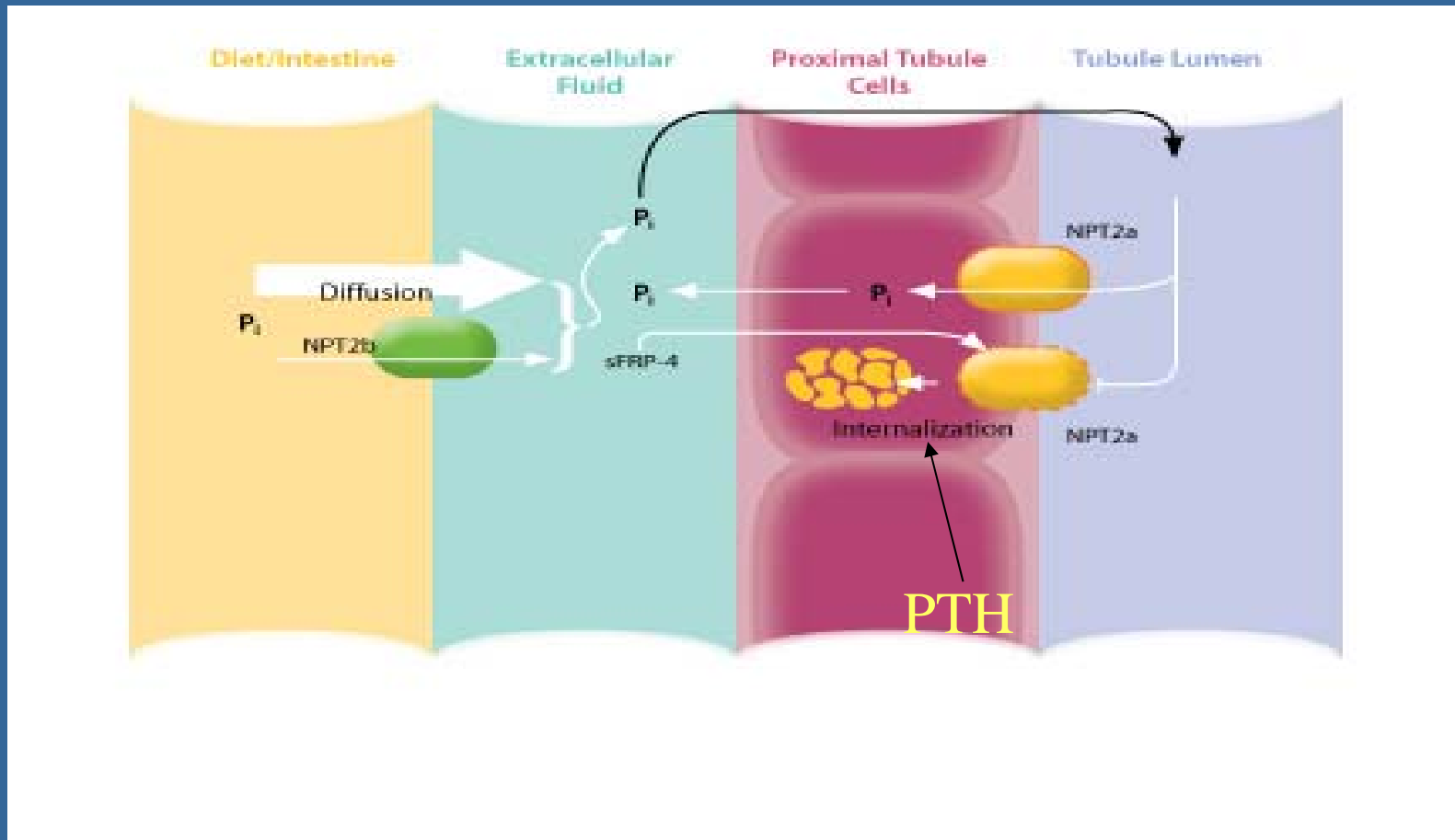
PTH activates vitamin D in the PT of the kidney



PTH increases calcium re-absorption in the DT of the kidney



PTH reduces phosphate re-absorption in the PT of the kidney



Primary hyperparathyroidism

A common disorder affecting 2% postmenopausal women

Causes

Parathyroid adenoma 80%

Parathyroid hyperplasia 20%

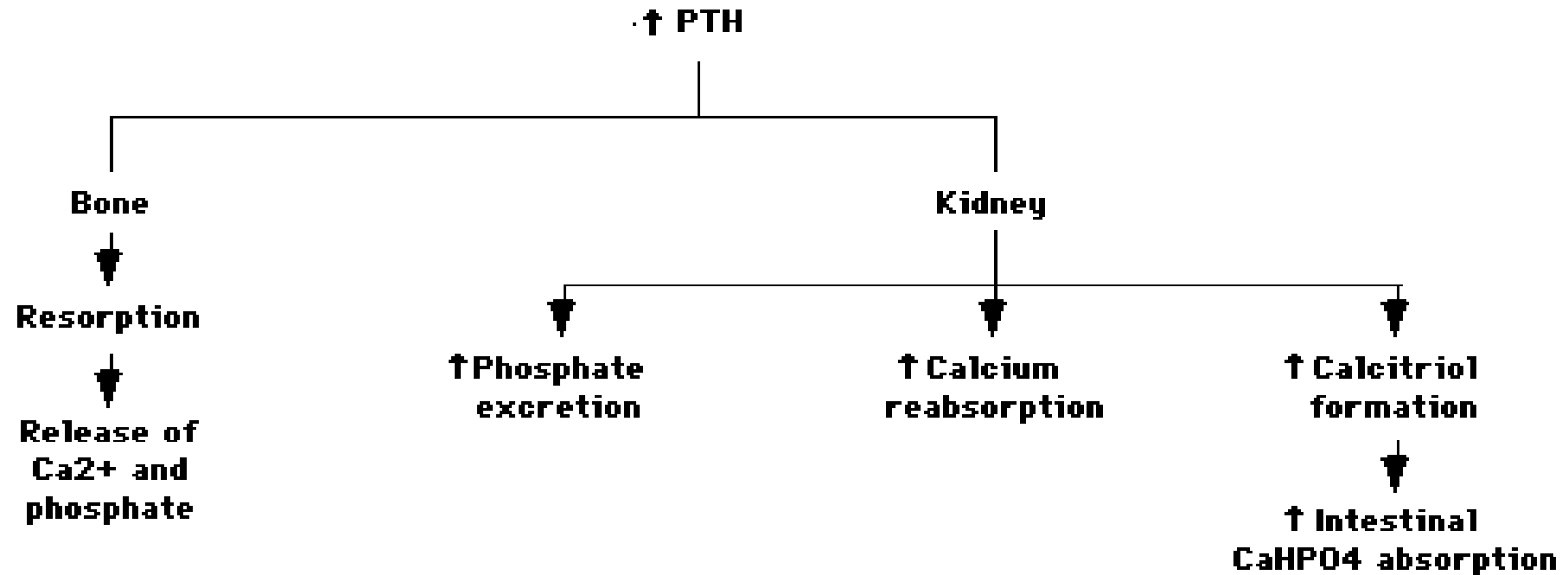
Parathyroid CA <1%

Familial Syndromes

MEN 1 2%

MEN 2A rare

Biochemistry of Primary Hyperparathyroidism



- . **Increase serum calcium**, by absorption from bone/gut/kidney
- . **Decrease serum PO₄**, as increased absorption is overcome by marked renal excretion
- . **Increase urine calcium excretion**, as increased renal resorption is overcome by the hugely increased filtered load
- . **Increase markers of bone resorption**

Primary hyperparathyroidism

Clinical Features are due mainly to high calcium

Thirst, polyuria

Tiredness, fatigue, muscle weakness

“Stones, abdominal moans and psychic groans”

Renal colic, nephrocalcinosis, CRF

Dyspepsia, pancreatitis

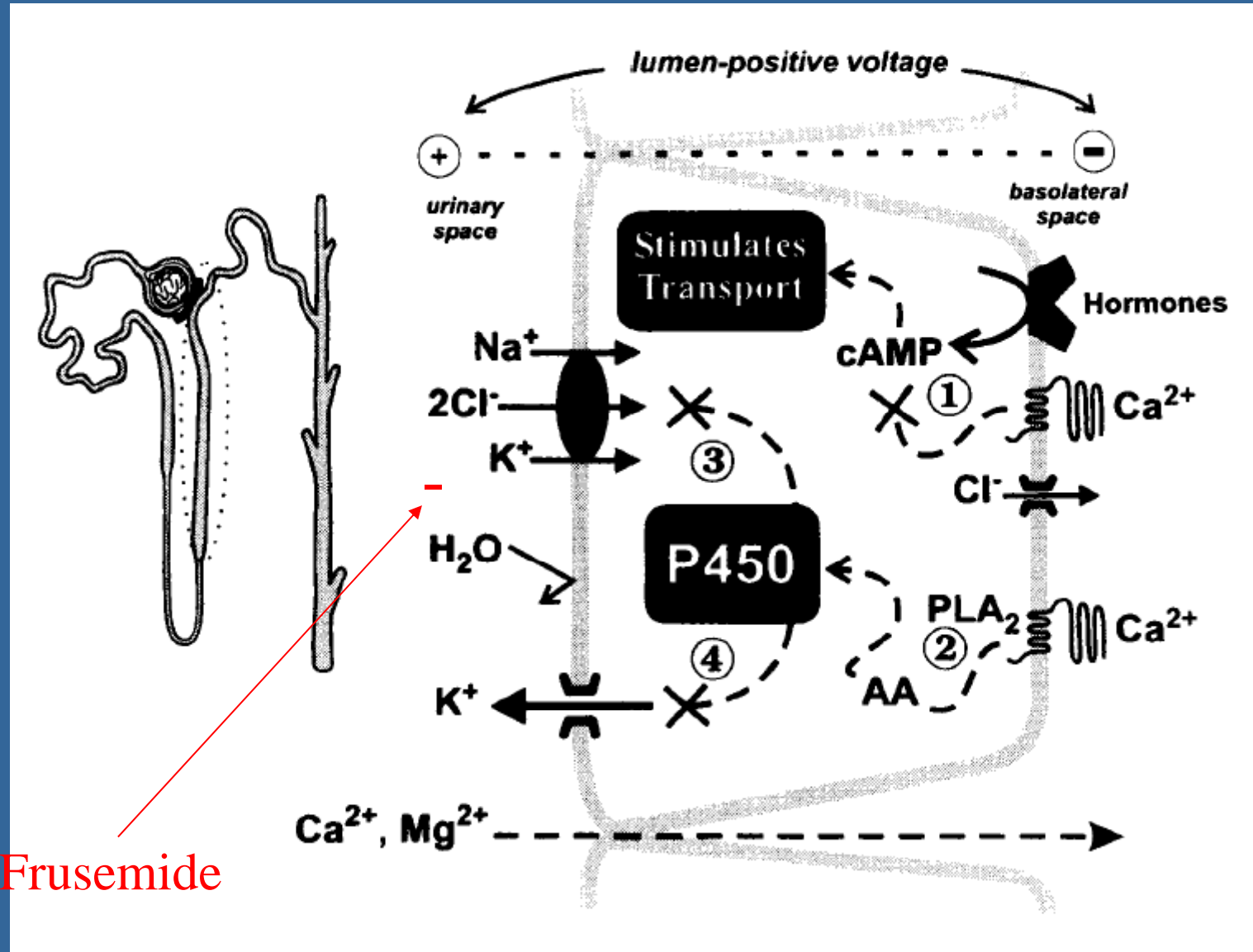
Constipation, nausea, anorexia

Depression, impaired concentration

Drowsy, coma

Patients may also suffer fractures secondary to bone resorption

Polyuria in Hypercalcaemia



Management of Primary hyperparathyroidism

If high calcium >2.8
young <50
complications

osteoporosis
renal stones
renal failure

localise

SURGERY

Investigations

BMD

Renal U/S

24hr CrCl

⁹⁹Tc-sestamibi scan

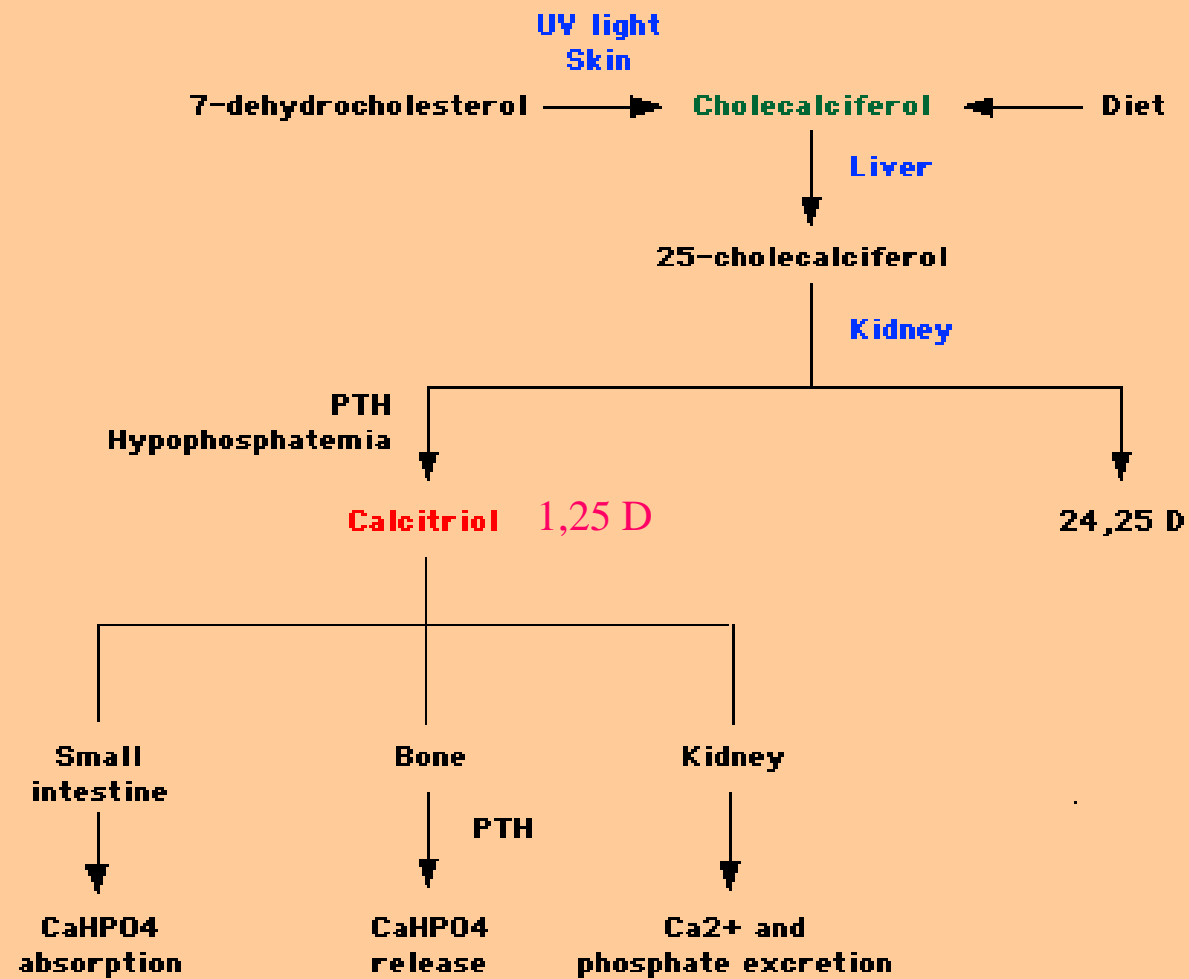
neck U/S

Conservative management

bisphosphonates

Calcimimetics- cinacalcet

VITAMIN D ACTION



Osteomalacia

“inadequate Vitamin D activity leads to defective mineralisation of the cartilagenous growth plate (before a low calcium)”

Symptoms

Bone pain and tenderness (axial)

Muscle weakness (proximal)

Lack of play

Signs

Age dependent deformity

Myopathy

Hypotonia

Short stature

Tenderness on percussion

Osteomalacia - causes

Vitamin D related

Dietary

Gastrointestinal Small bowel malabsorption/ bypass

Pancreatic insufficiency

Liver/biliary disturbance

Drugs- phenytoin, phenobarbitone

Renal Chronic renal failure

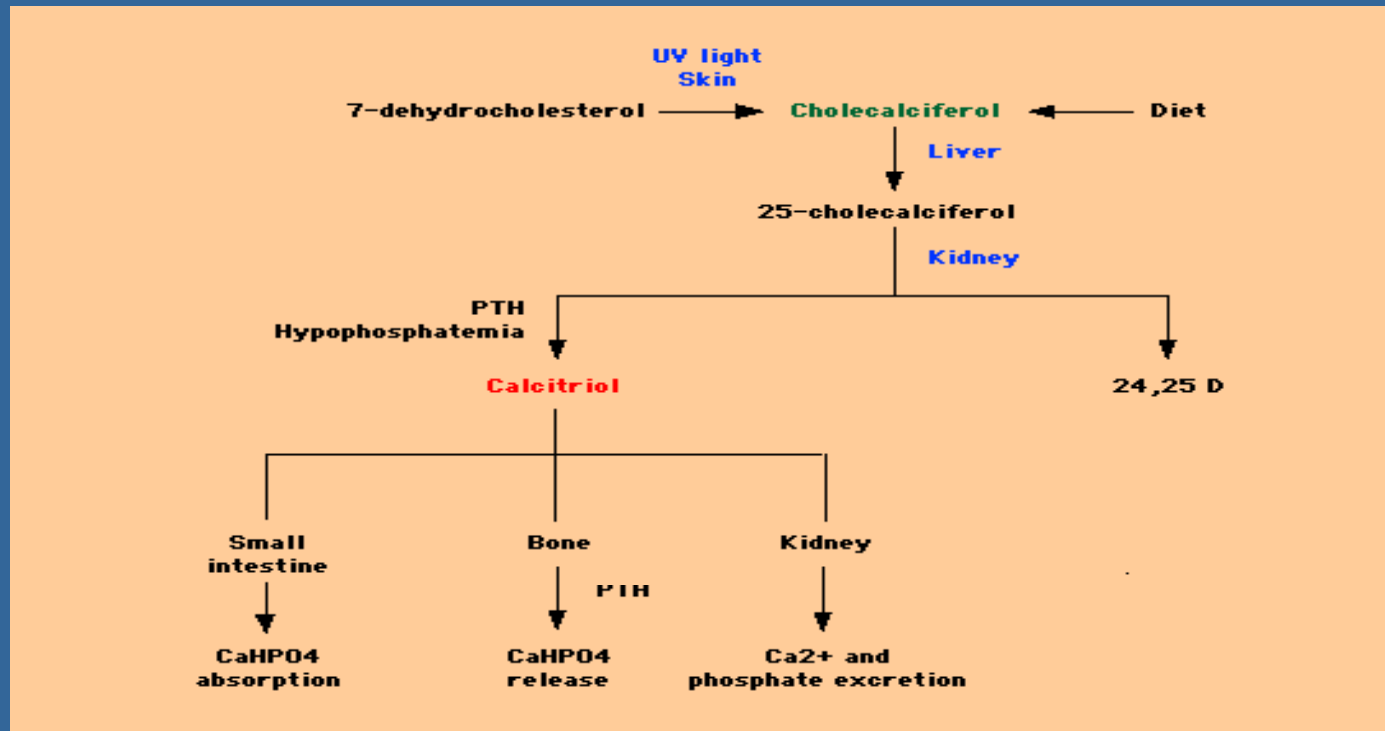
Vitamin D dependent rickets type I

autosomal recessive, no 1α -hydroxylation

Resistance Vitamin D dependent rickets type II

autosomal recessive, VDR defect

Biochemistry in Rickets and Osteomalacia



Calcium N/low

Phosphate N/low

Alk phos High

PTH High

- Urine Phosphate High

Glycosuria, aminoaciduria, high pH, proteinuria

Osteomalacia and phosphate

'can also get with renal phosphate loss, when calcium and Vitamin D levels are usually normal'

Renal

hypophosphataemia

X-linked hypophosphataemic Rickets

1;20,000

mutations in PHEX; do not destroy phosphaturic factor

toddlers with leg deformity

enthesopathy, dentin anomalies

oncogenic osteomalacia

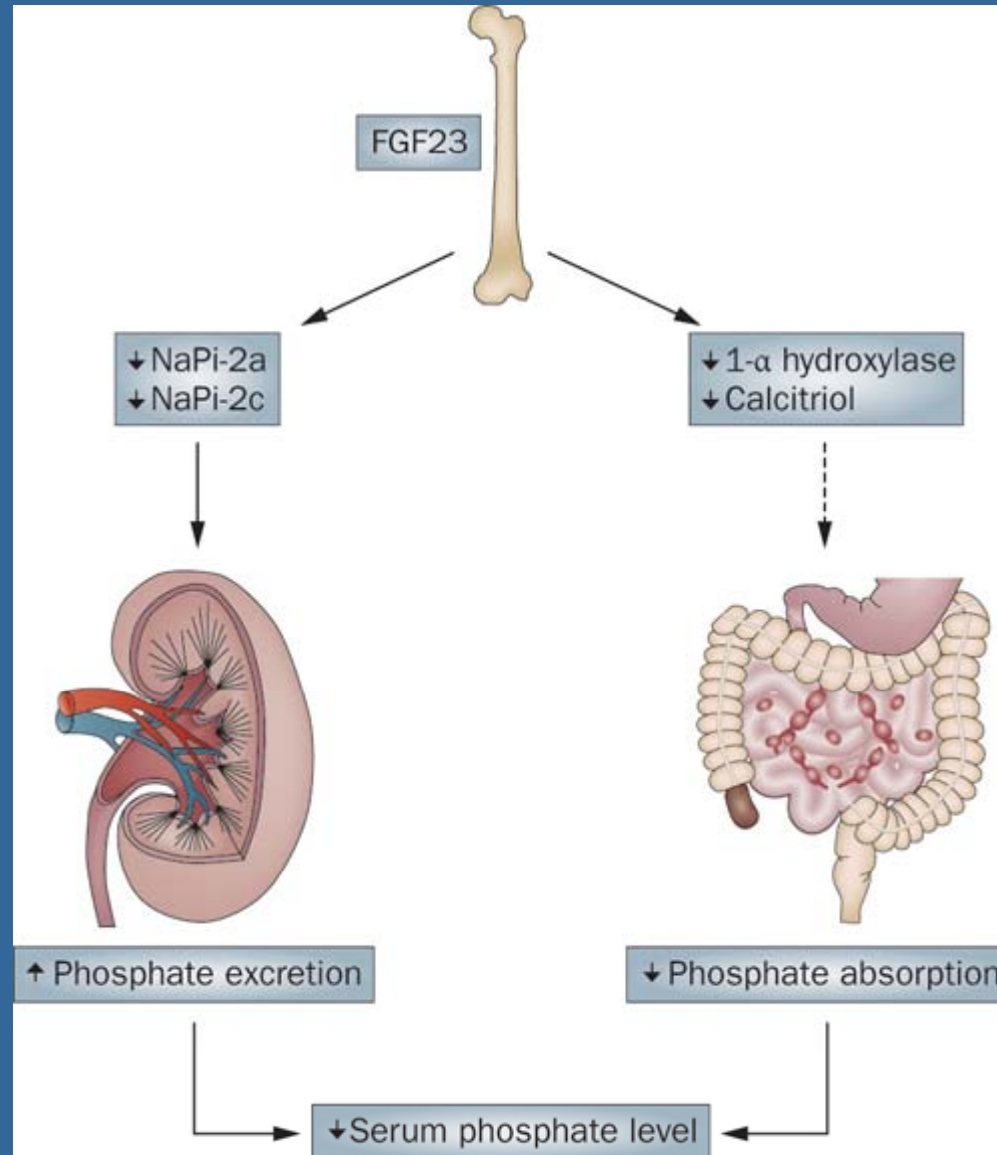
mesenchymal tumours

produce FGF-23, causes phosphaturia and stops 1α OHase

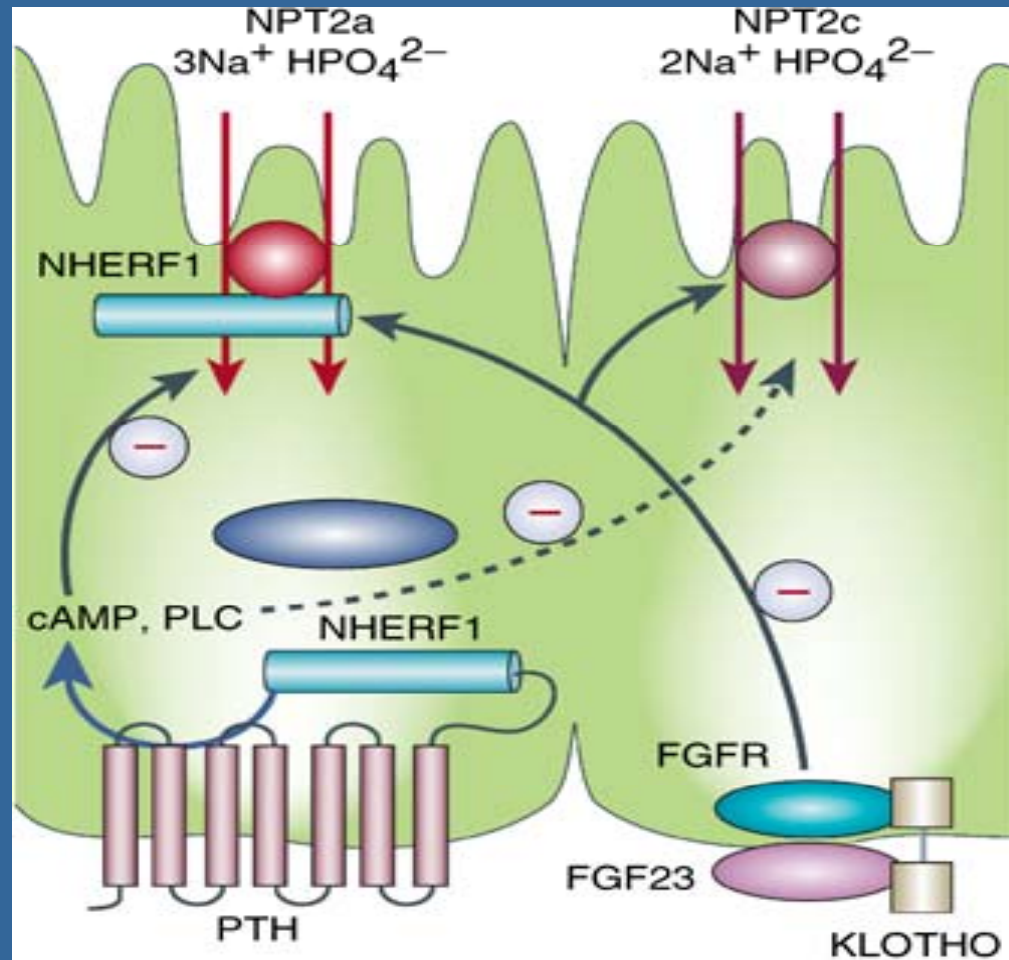
Fanconis syndrome

Proximal renal tubular acidosis

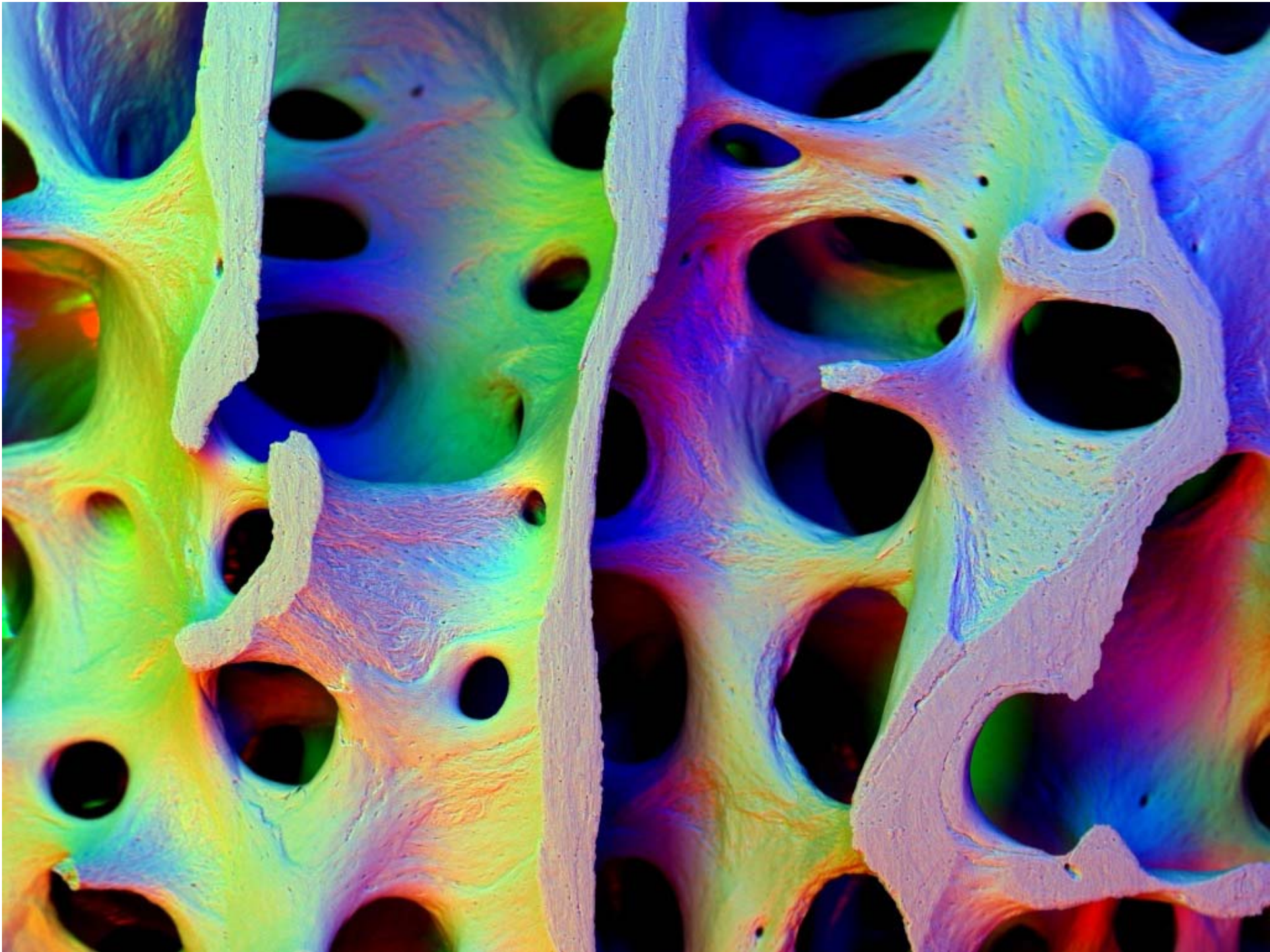
Osteomalalacia and FGF-23

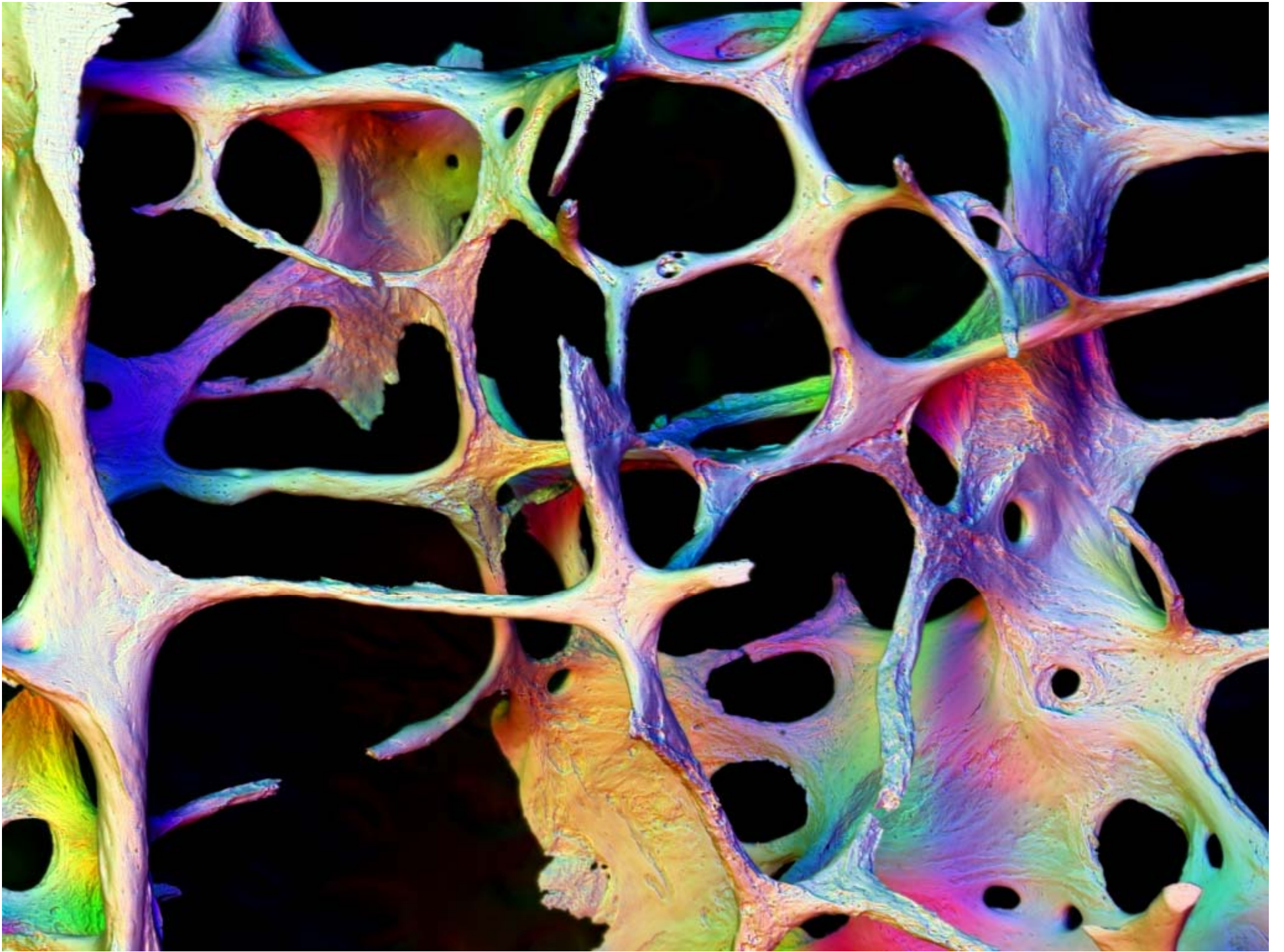


Osteomalacia and FGF-23

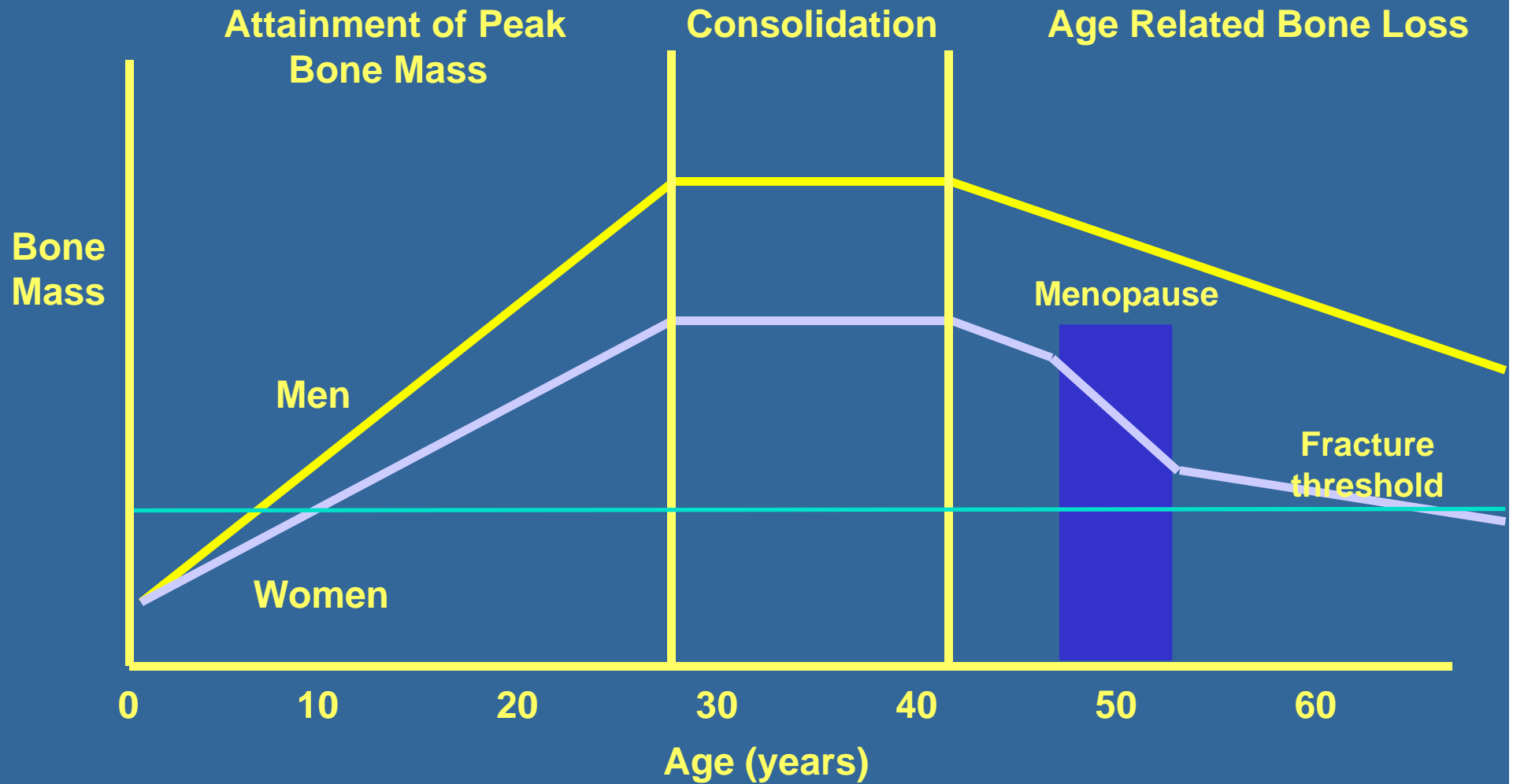


Osteoporosis

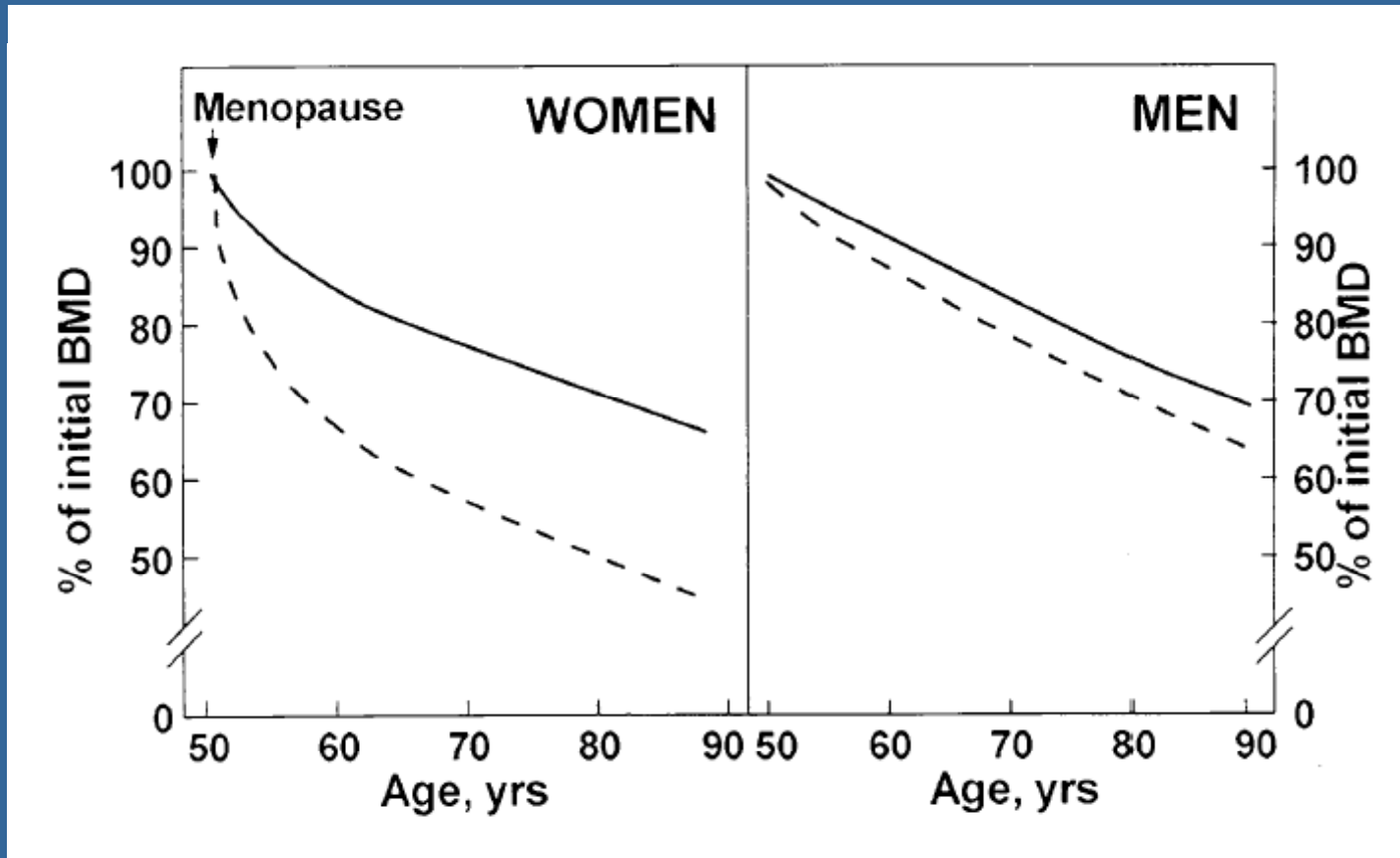




Age Related Changes in Bone Mass¹

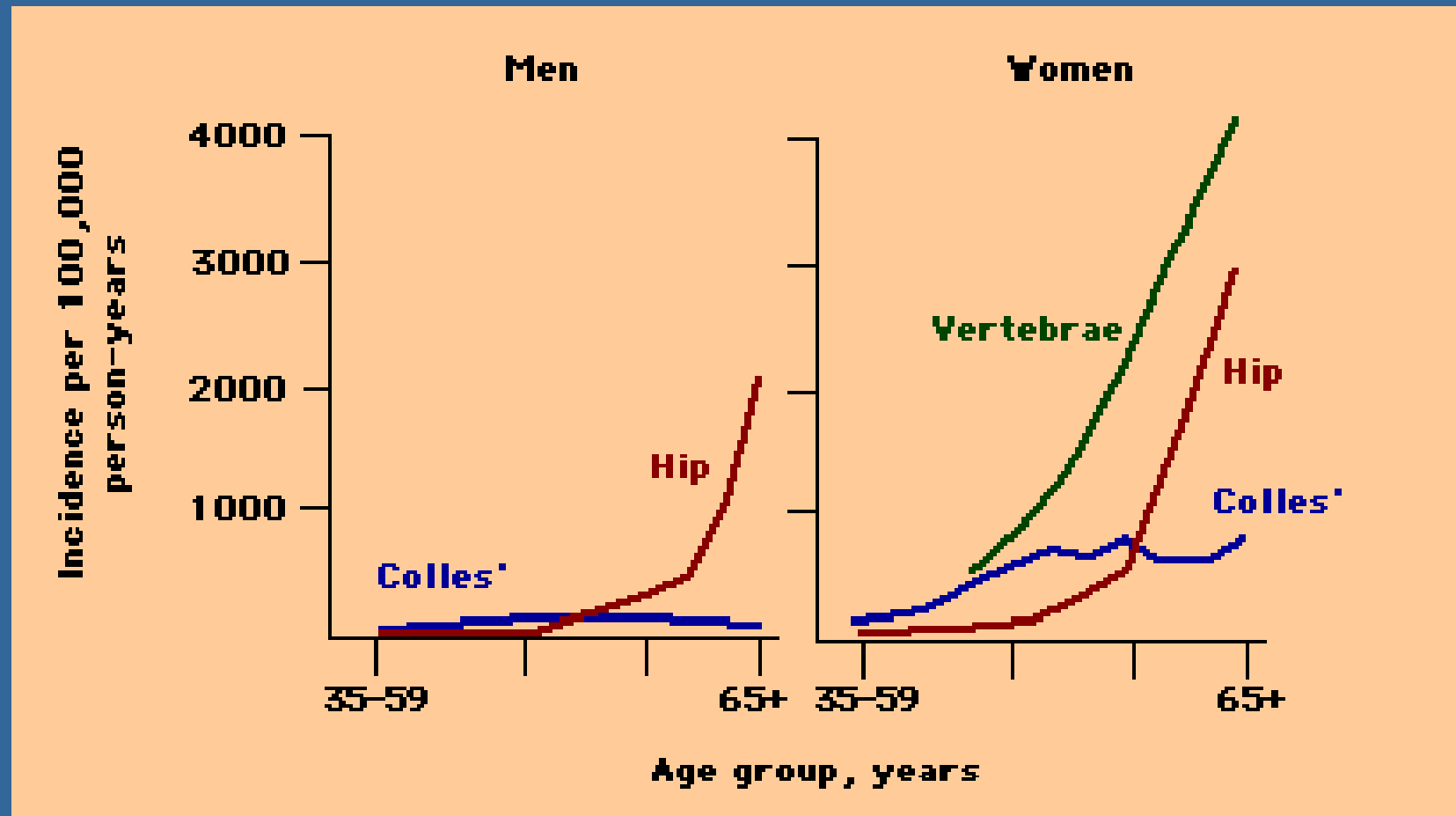


Age Related Changes in Bone Mass



Disproportionate loss of cancellous bone post-menopause

The osteoporosis problem



Oestrogen deficiency; bone changes

- Increases the activation frequency of remodelling units (ie number of both osteoclasts and blasts)
- Causes remodelling imbalance

Decreases osteoclast apoptosis, increases osteoblast apoptosis

Deeper and more resorption pits

Increased bone resorption (90%) compared to bone formation (45%)

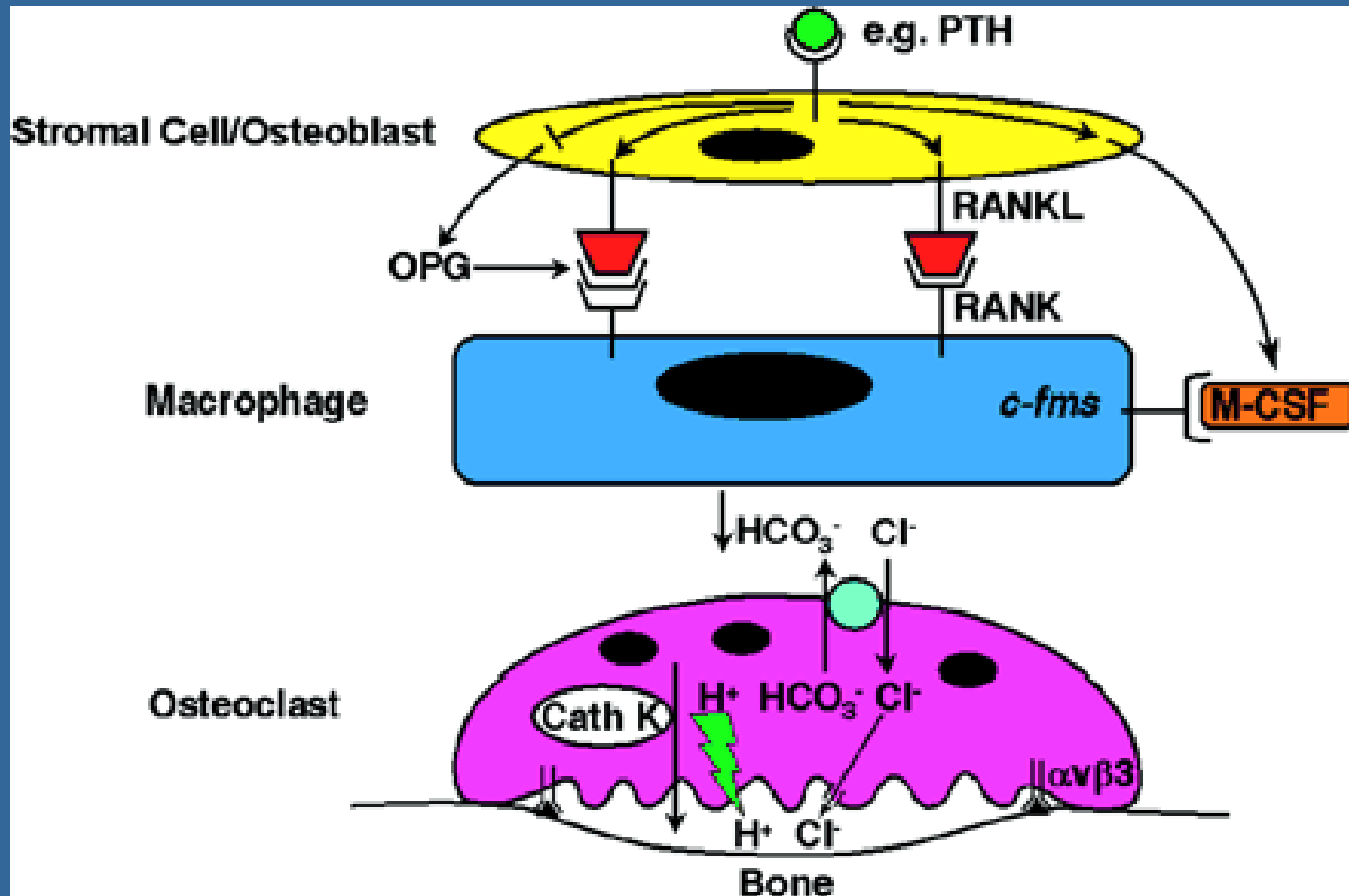
Remodelling errors

Trabecular perforation

Cortical excess Haversian excavation

- Decreased osteocyte sensing

Molecular Action



Causes of Osteoporosis According to Probable Mechanism

High turnover – increased bone resorption greater than increased bone formation

- Estrogen deficiency – primarily in postmenopausal women
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism in young women and in men
- Cyclosporine (?)
- Heparin

Low turnover – decreased bone formation more pronounced than decreased bone resorption

- Liver disease – primarily primary biliary cirrhosis
- Heparin
- Age above 50 years

Increased bone resorption and decreased bone formation

- Glucocorticoids

Biochemistry of osteoporosis

Serum biochemistry should all be normal

1. Check for Vit D deficiency
2. Check for secondary endocrine causes

Primary hyperparathyroidism PTH high

Primary hyperthyroidism free T3 high

TSH suppressed

Hypogonadism Testosterone low

3. Exclude multiple myeloma
4. May have high urine calcium

Bone Density

Why measure bone density?

We can!

Single best predictor of fracture risk
BMD represents 70% of total risk

DXA

Dual energy X-ray absorptiometry

Measures transmission through the body of
X-rays of two different photon energies

Enables densities of two different tissues to
be inferred, i.e. bone mineral, soft tissue

Radiation dose - 1-10 μSv

Background - 7 μSv

CXR - 100 μSv

Definition of Osteoporosis

World Health Organisation 1994

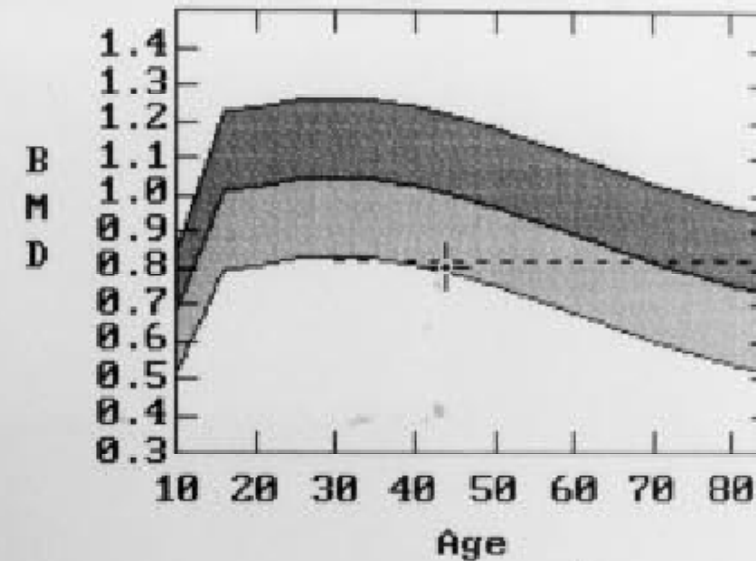
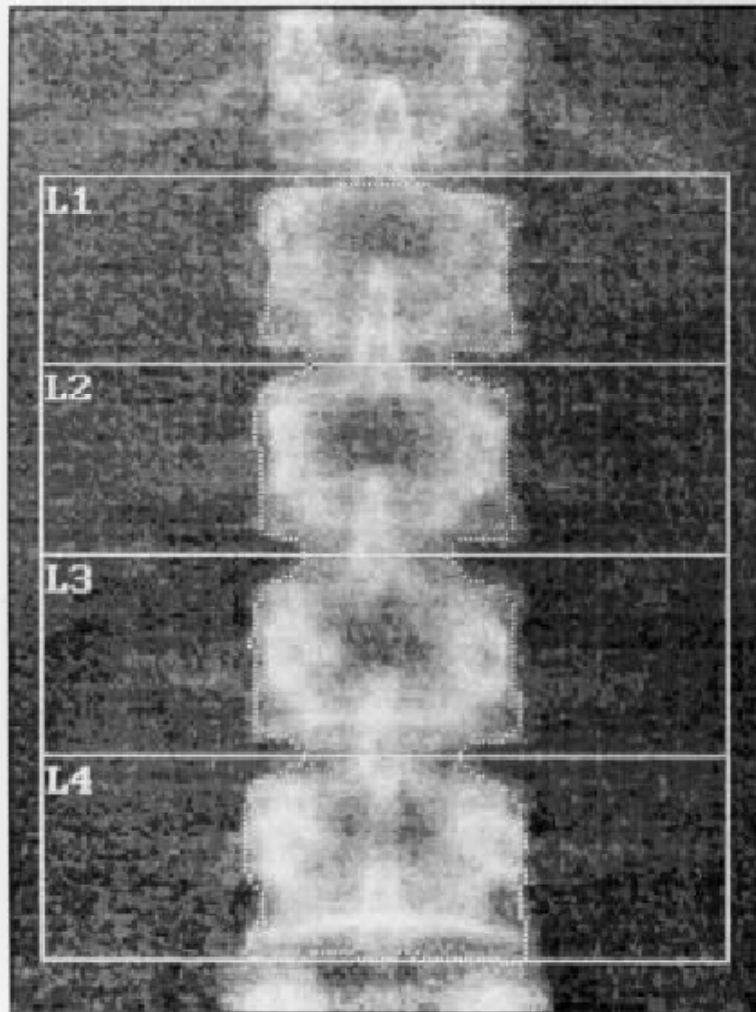
$$\text{T-score} = \frac{\text{measured BMD} - \text{young adult mean BMD}}{\text{young adult standard deviation}}$$

ie How many standard deviations are you off the average for a 25 year old ?

T-score = -2.5 OSTEOPOROSIS
 -1to -2.5 OSTEOPAENIA
 <-1 NORMAL

Printout

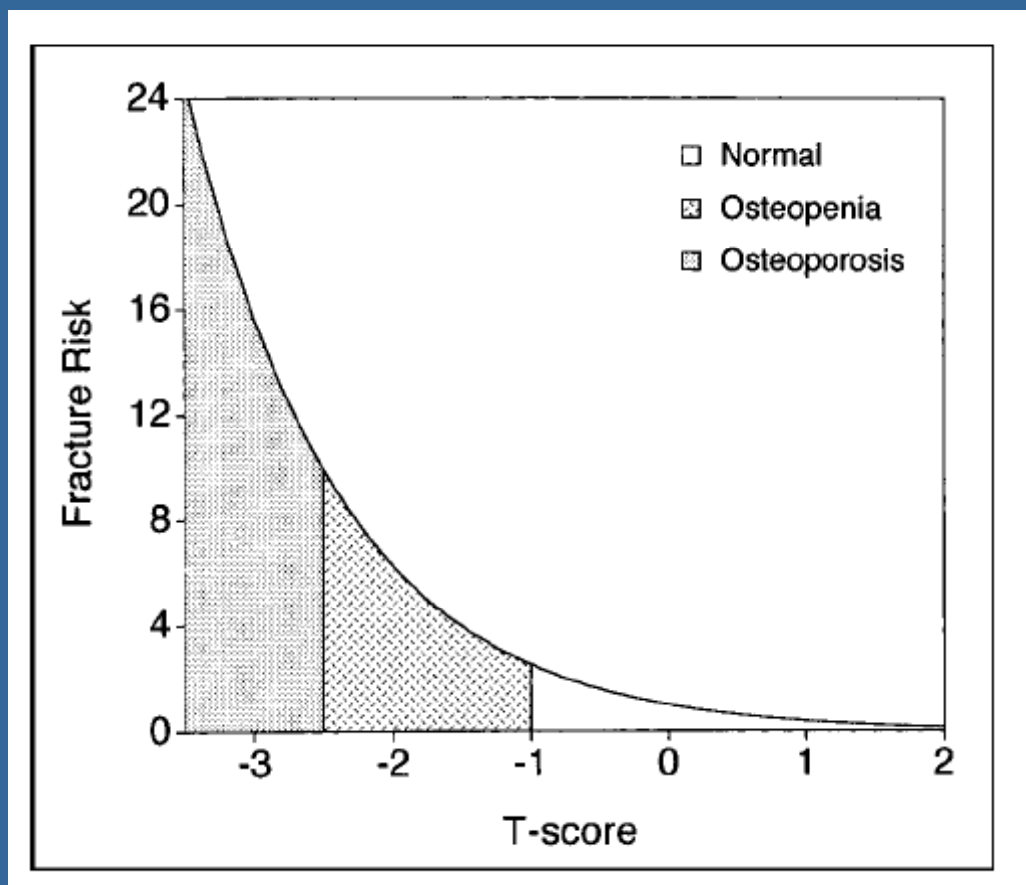
B



$$\text{BMD(L1-L4)} = 0.797 \text{ g/cm}^2$$

Region	BMD	T(30.0)	Z
L1	0.702	-2.02 76%	-1.68 79%
L2	0.764	-2.40 74%	-2.01 78%
L3	0.825	-2.35 76%	-1.95 79%
L4	0.873	-2.21 78%	-1.79 82%
L1-L4	0.797	-2.27 76%	-1.88 79%

How does risk of fracture correlate with this ?



1 SD reduction = 2.5 increase in risk of fracture

Certain situations interfere with interpretation

- Degenerative change, osteoarthritis
- Vertebral fractures
- Metal artefacts
- Osteomalacia
- Vascular calcification
- Scoliosis
- Paget's disease

Who should we measure?

Presence of risk factors

- oestrogen deficiency
- corticosteroid treatment
- maternal history of hip fracture
- low body mass index
- other endocrine diseases, e.g.
 hyperparathyroidism
 thyrotoxicosis
- Malabsorption

Radiographic evidence of osteopenia and vertebral deformity

Previous fragility fracture

Loss of height, marked kyphosis

Bone Markers

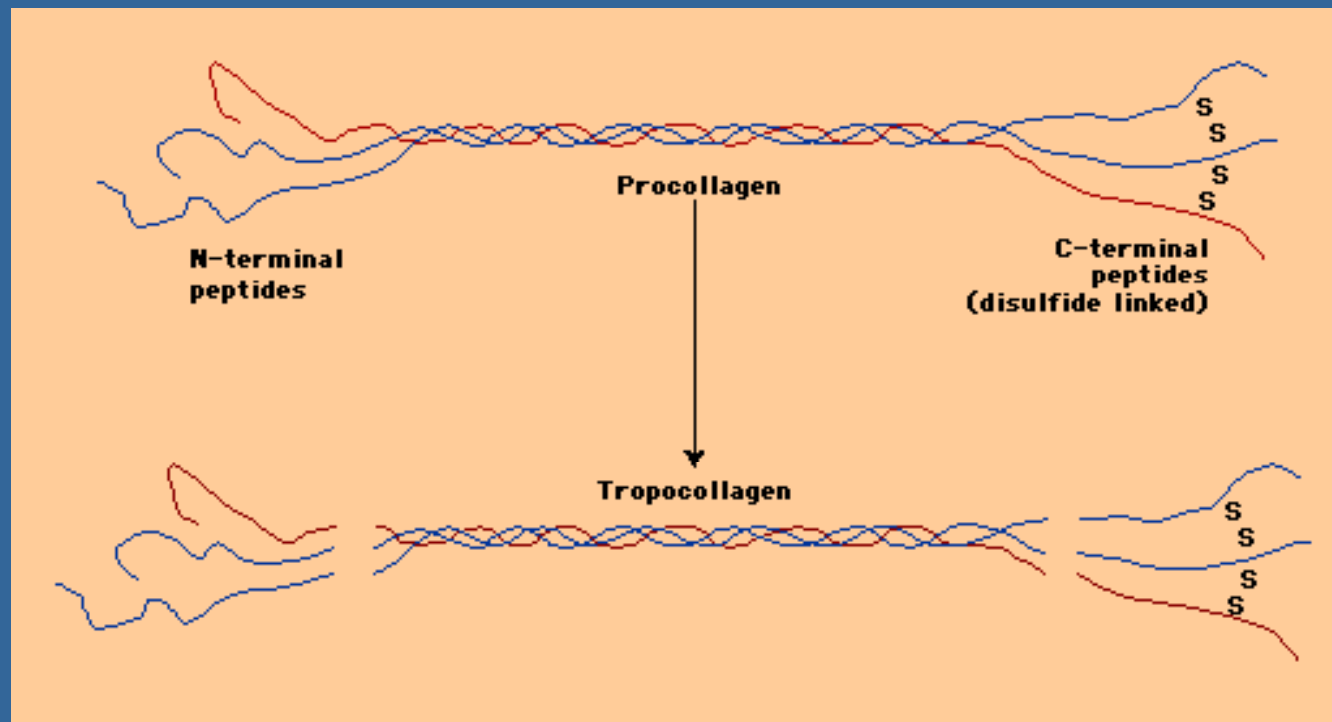
In most bone diseases the bone cycle is disrupted

Markers of bone formation and resorption give us insight into activity

Bone formation; collagen synthesis

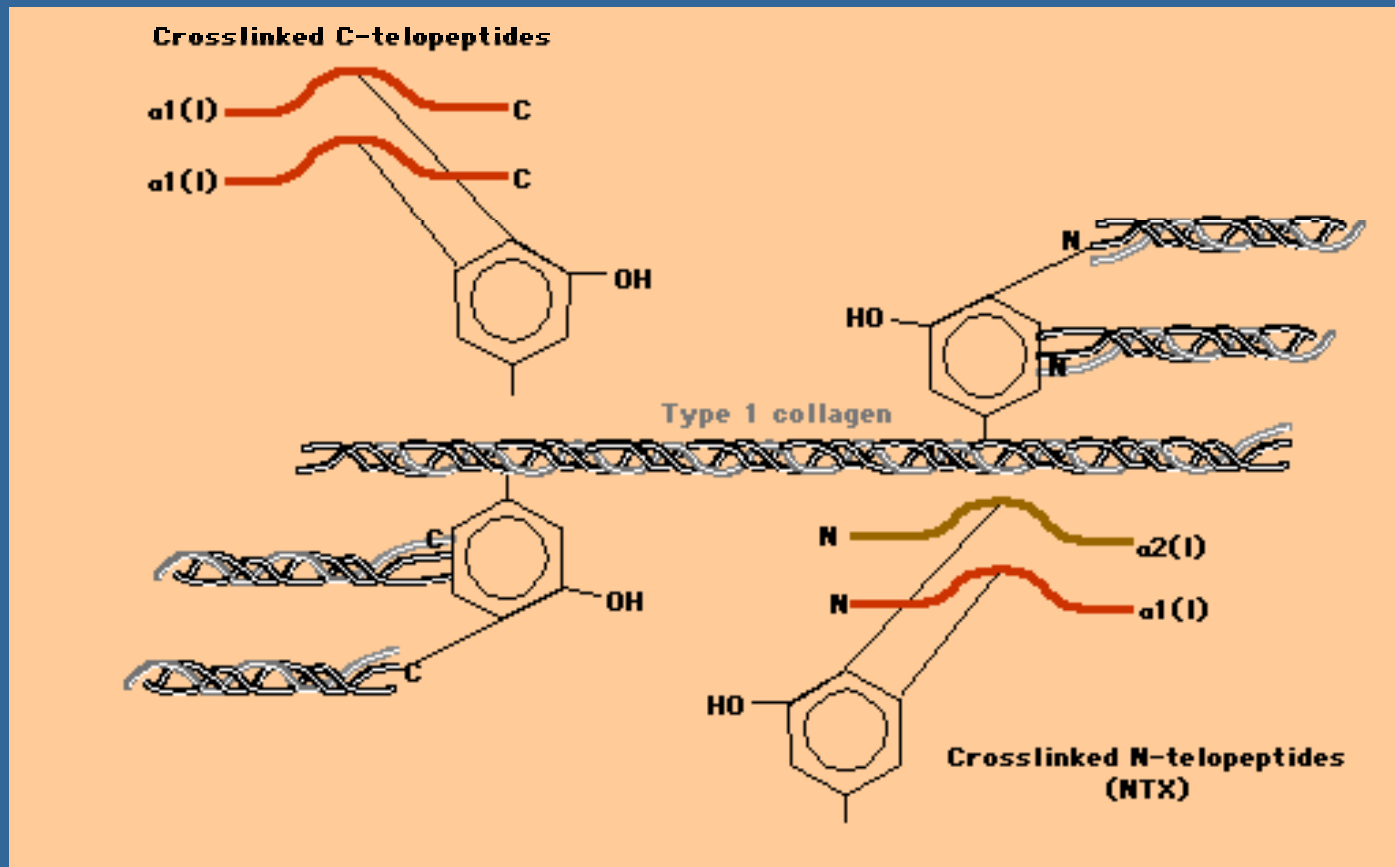
Alpha 1 and 2 chains of type I collagen produced by osteoblast

Proline and lysine residues hydroxylated



Bone formation; collagen synthesis

3 hydroxylysine molecules on adjacent tropocollagen fibrils condense to form a PYRIDINIUM ring linkage



Measurement of Osteoclast activity

Urine hydroxyproline

Urine Collagen crosslinks

Pyridinium (Pyd and Dpd)

N-terminal telopeptide (NTX)

C-terminal telopeptide (CTX)

Serum CTX and NTX

Tartrate resistant acid phosphatase

Uses of bone markers in osteoporosis?

1. Diagnosis of osteoporosis
2. Prediction of fracture risk.
3. Monitoring of treatment

Uses of bone markers in monitoring treatment

1. Monitoring of response to treatment with anti-resorptive drugs.

bone resorption markers fall in 4-6 weeks

bone formation markers fall in 2-3 months

expect a 50% drop of NTx by 3 months

not only osteoporosis

Pagets

primary hyperparathyroidism

Problems with cross-links

1. Reproducibility

TABLE 6. Within subject reproducibility of bone markers

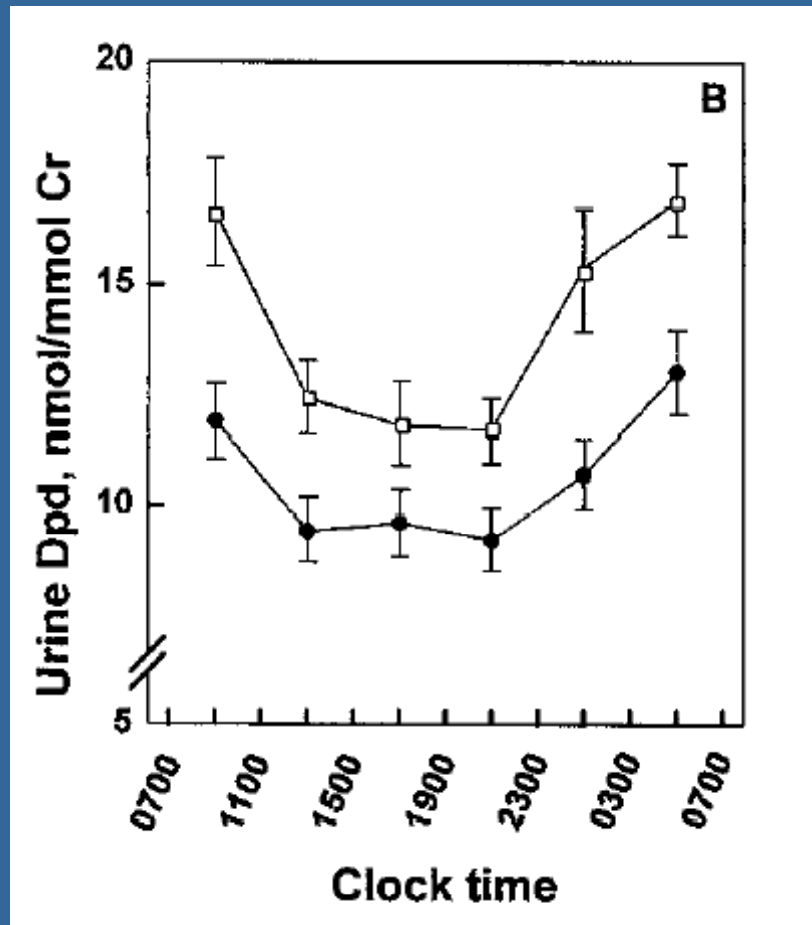
Marker	% CV
NTX	20.2
Dpy (HPLC)	62.9
Hyp	53.0
Osteocalcin	27.3
ALP	10.3

2. Positive association with age

3. Need to correct for Cr

Problems with cross-links

4. Diurnal variation in urine markers



Peak 4-8am

Measure 24 hr or
2nd urine

Measure osteoblast function/ bone formation

Serum

alkaline phosphatase

total

bone-specific

osteocalcin

propeptide of type 1 collagen

carboxyterminal PICP

aminoterminal PINP

BSAP

Types

tissue-specific form; liver vs bone
intestine, germ cell, placental forms

Role

essential for mineralisation
regulates concentrations of phosphocompounds

Uses

Consistent within an individual; $t_{1/2}$ 40 hours

Increased in Paget's disease

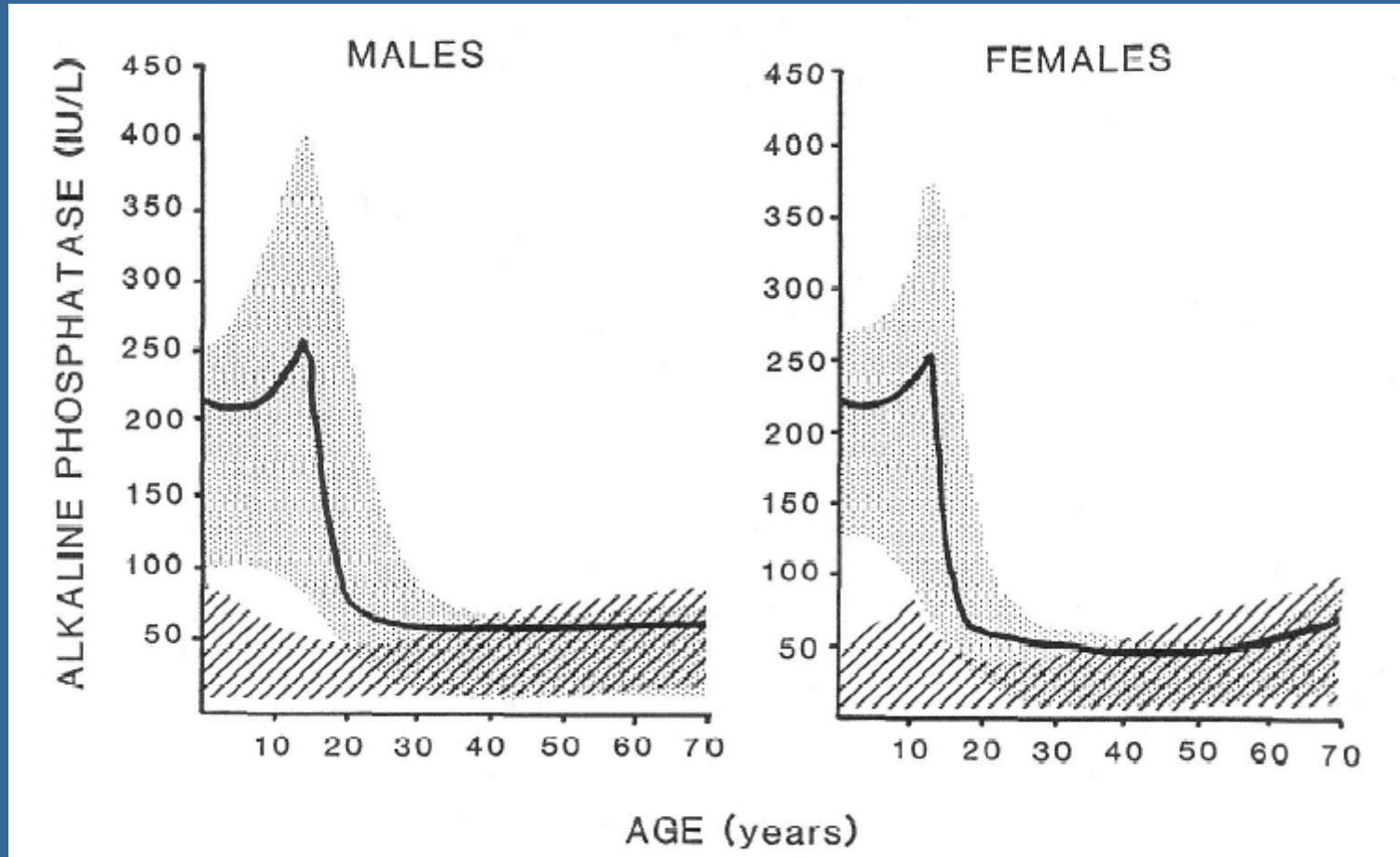
Osteomalacia

Bone metastases

Hyperparathyroidism

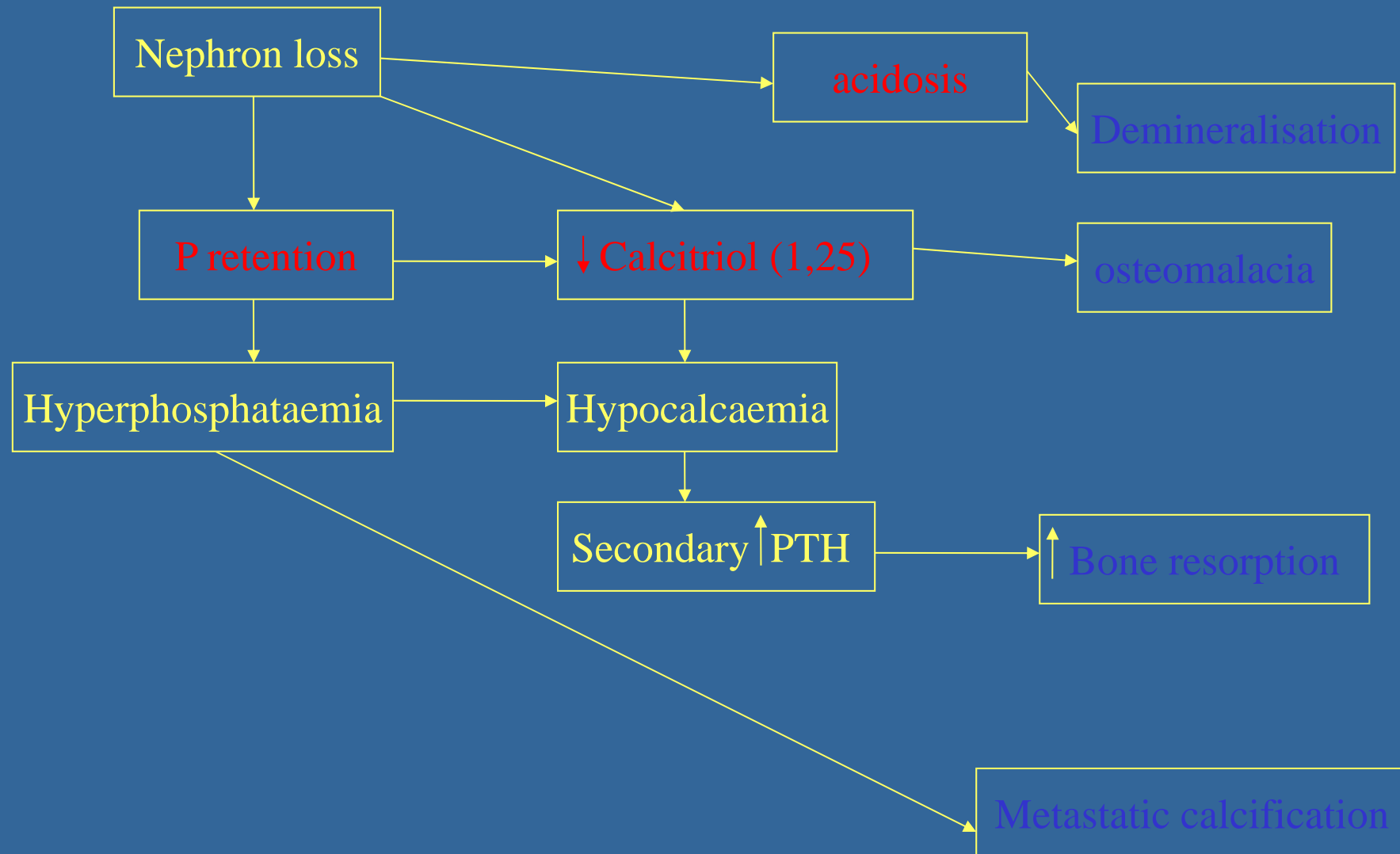
Hyperthyroidism

Alkaline phosphatase with age



Labs don't standardly give isoforms!

Tertiary hyperparathyroidism



Tertiary hyperparathyroidism

