METABOLIC BONE DISEASE

Introduction, Overview and Biochemistry

Dr Jeremy PD Cox

St Mary's Hospital, Imperial College

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

Hypocalacaemia

Hypercalcaemia

Hypo/Hyperphosphataemia

Bone
Pain

Deformity

Fractures

Bone Calcium

Hydroxyapatite $Ca^{2+}_{10-x}(H_30^+)_{2x}(PO_4{}^{3-})_6(OH^-)_2$

Cancellous bone metabolically active

remodelling 5% anytime
total skeleton over 7 years

continuous exchange of ECF with bone fluid
reserve

Bone strength

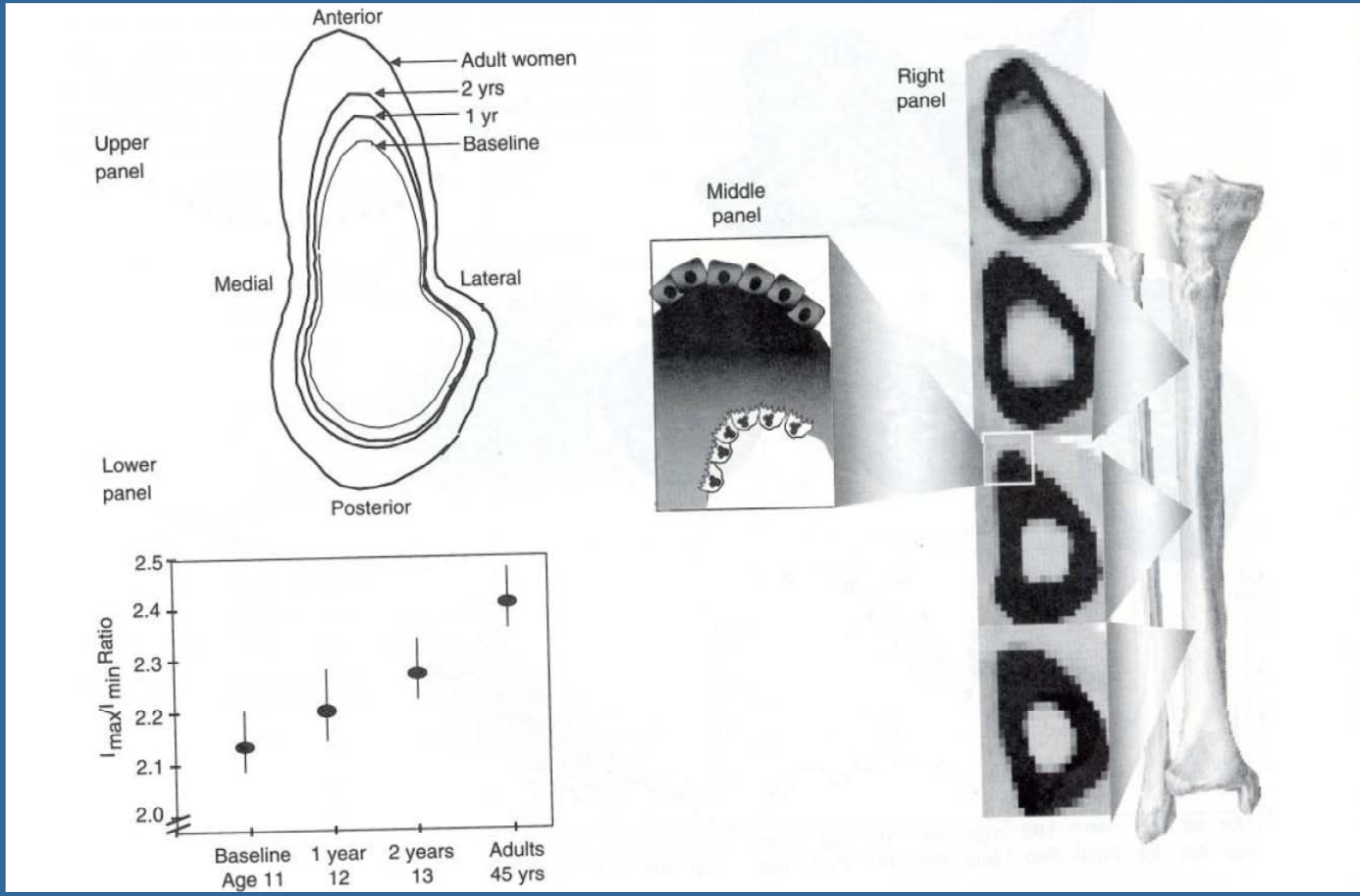
QUANTITY

- Cortical thickness
- mineral density
- size

QUALITY

- Architecture
- Bone turnover
- Cortical porosity
- Trabecular connectivity

Tibial bone modeling during growth



Wang Q, Seeman E.

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

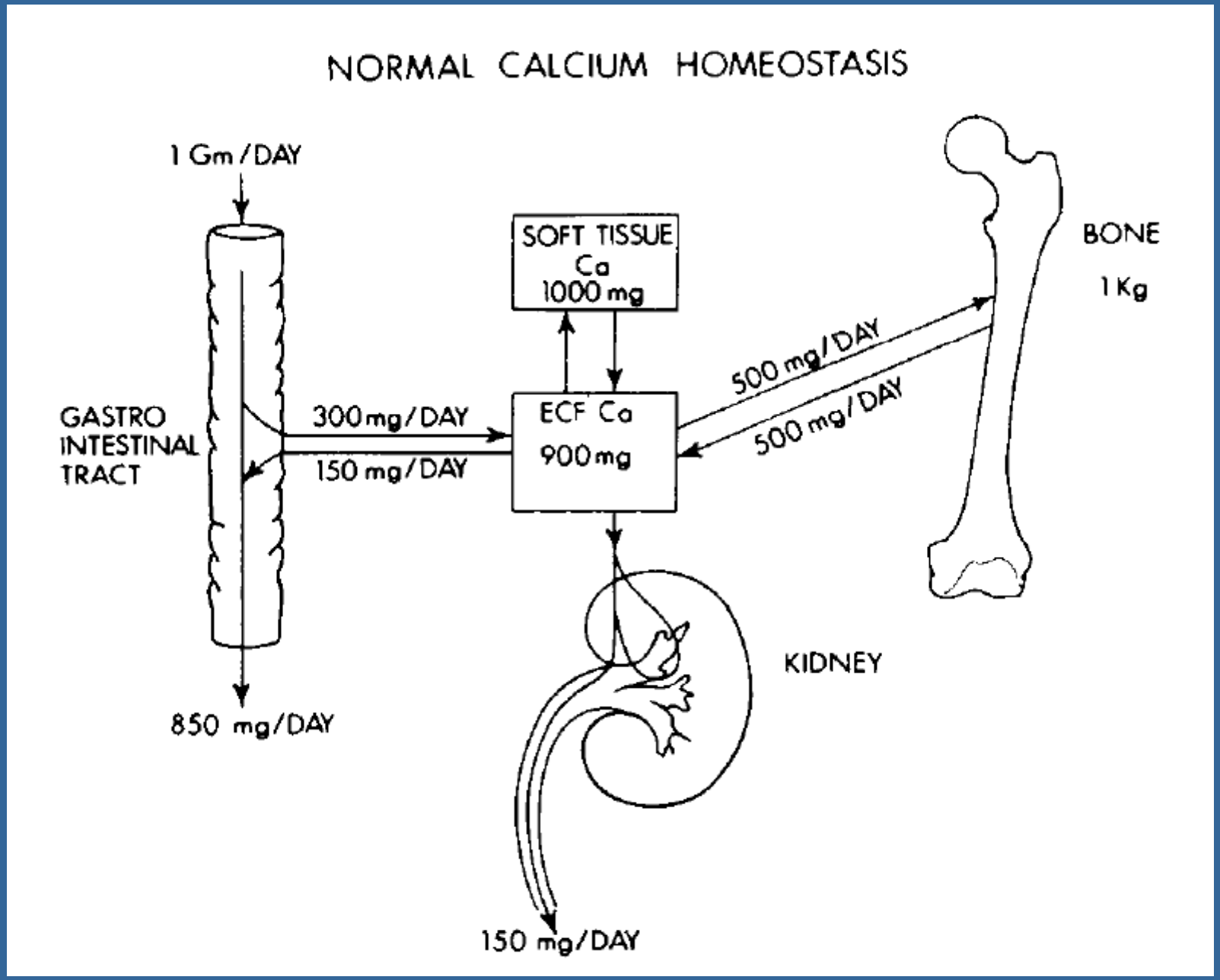
CLINICAL and BIOCHEMICAL FEATURES OF METABOLIC BONE DISEASE

Biochemical Investigations in Metabolic Bone disease

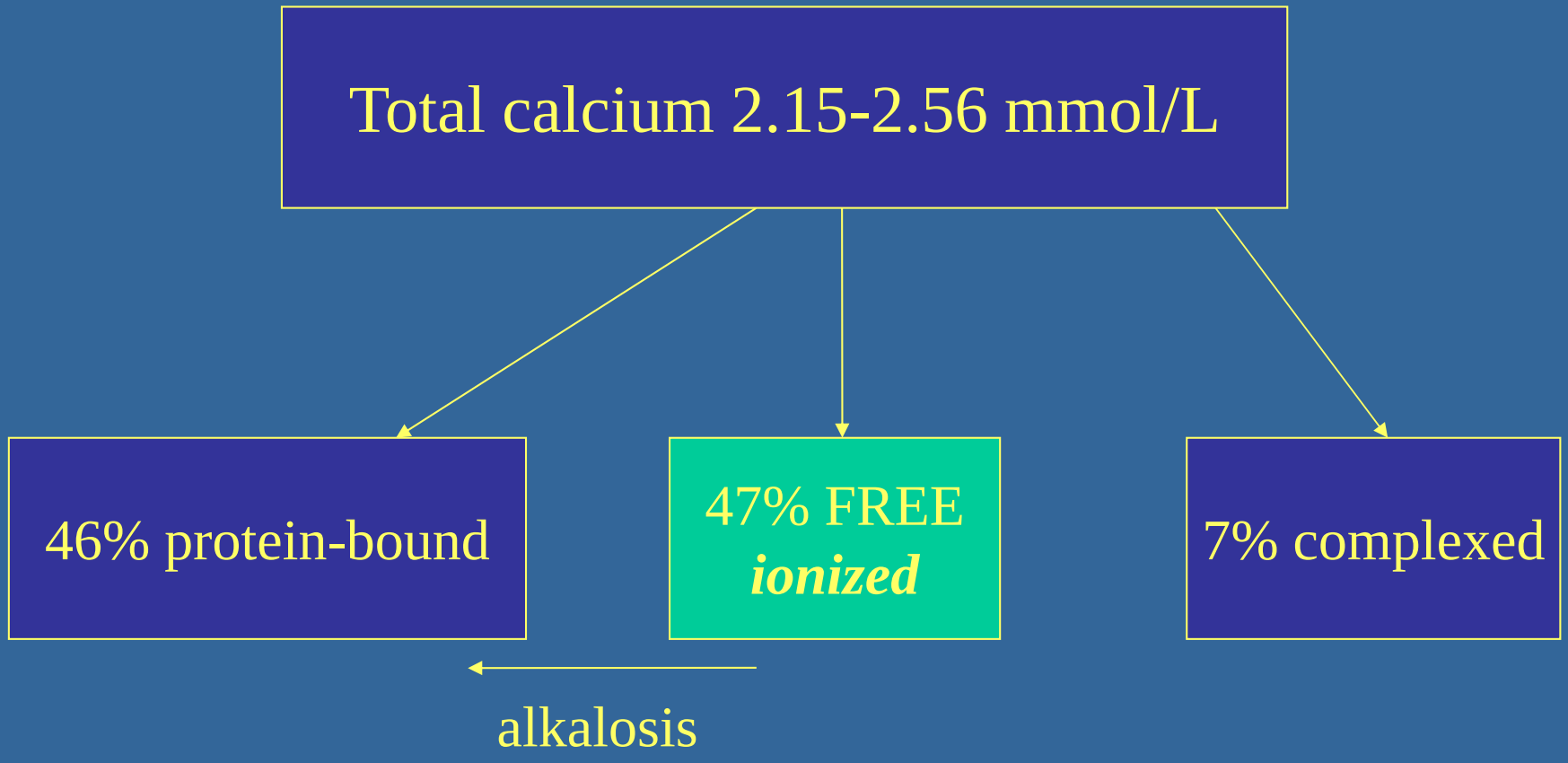
Serum	calcium
	corrected calcium
	albumin
	phosphate
	parathyroid hormone
	25-hydroxy vitamin D
Urine	NTX
	Calcium
	Phosphate

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
1 Gm / DAY
SOFT TISSUE
Ca
1000 mg
BONE
1 Kg
500 mg/DAY
500 mg/DAY
GASTRO
INTESTINAL
TRACT
300 mg/DAY
150 mg/DAY
ECF Ca
900 mg
KIDNEY
850 mg/DAY
150 mg/DAY

Serum Calcium



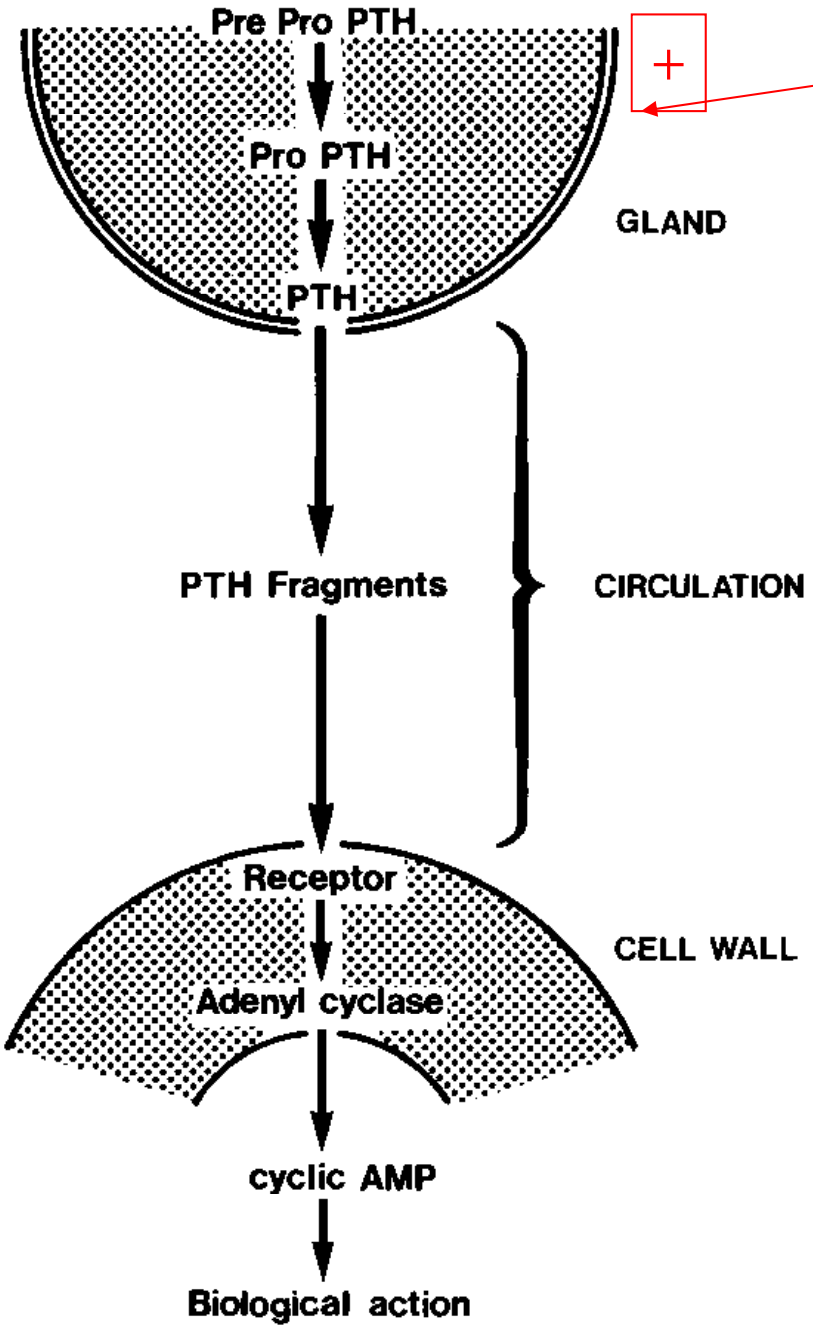
Corrected calcium = [calcium] + 0.02(45 – [albumin])

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

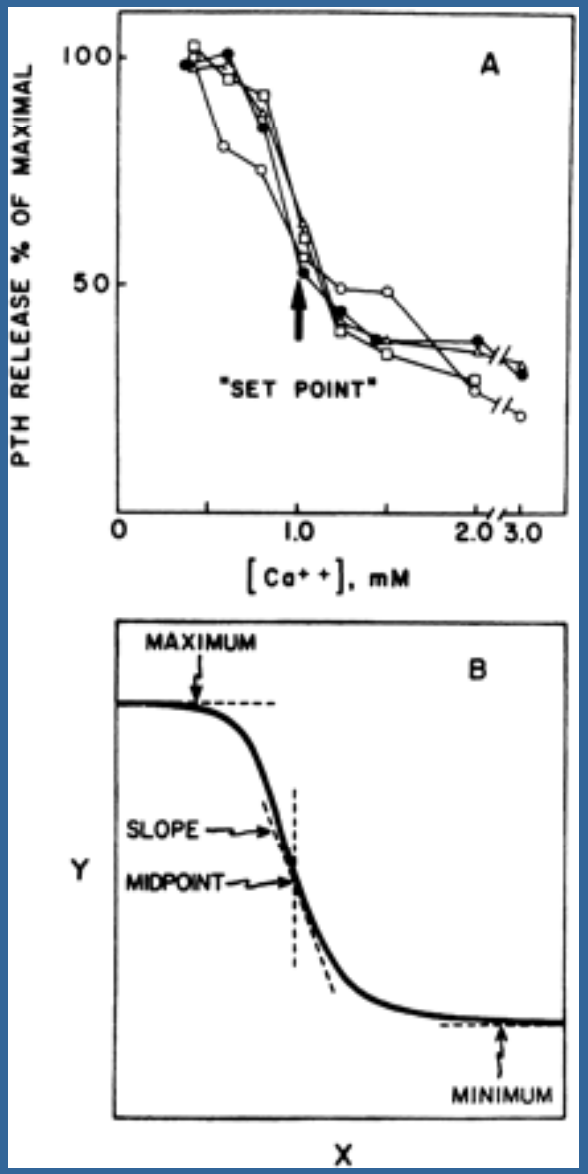
$T_{1/2}$ 8 min

N1-34 active

Mg dependent

PTH 1/PTHrP receptor

The calcium-**sensing** receptor

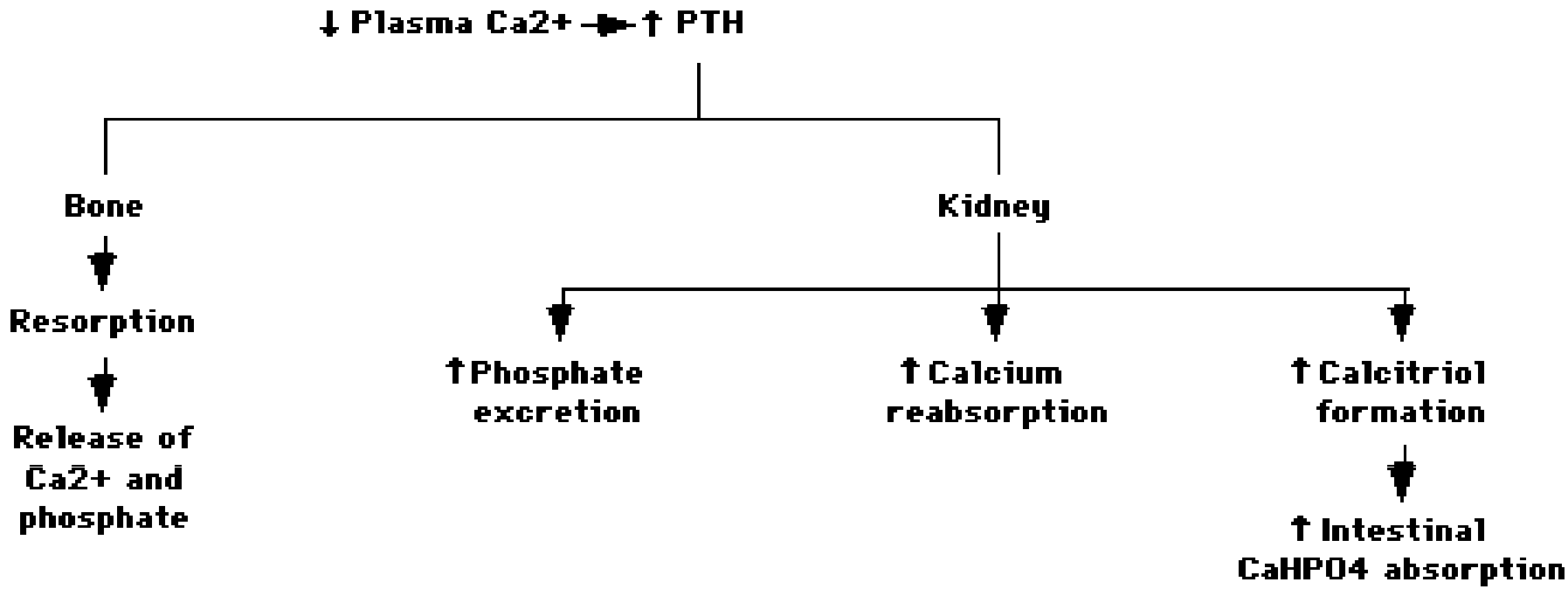


A steep inverse sigmoidal function relates PTH levels and Ca_o^{2+} in vivo.

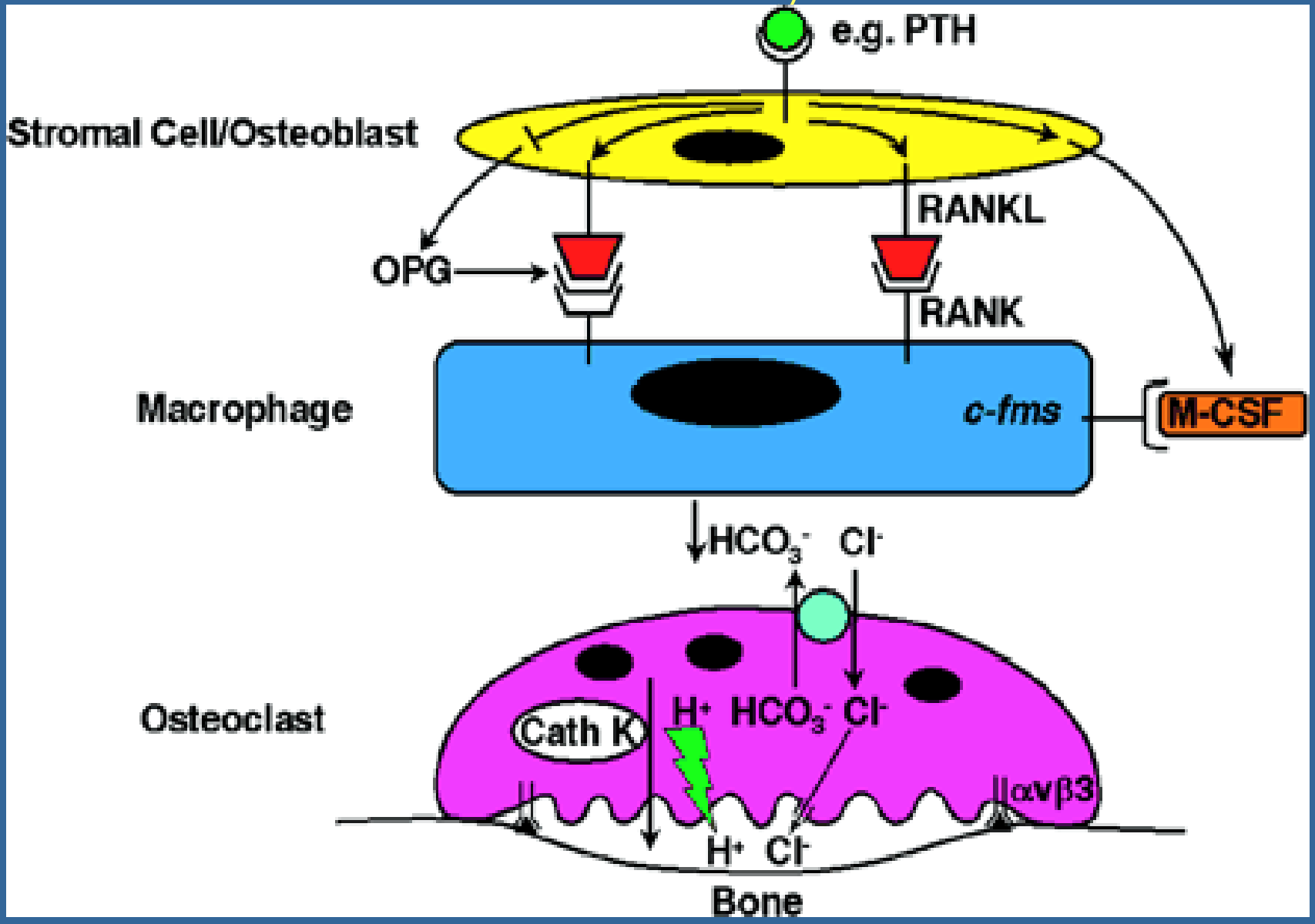
MINIMUM: even at high calcium levels there is base-line PTH secretion

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

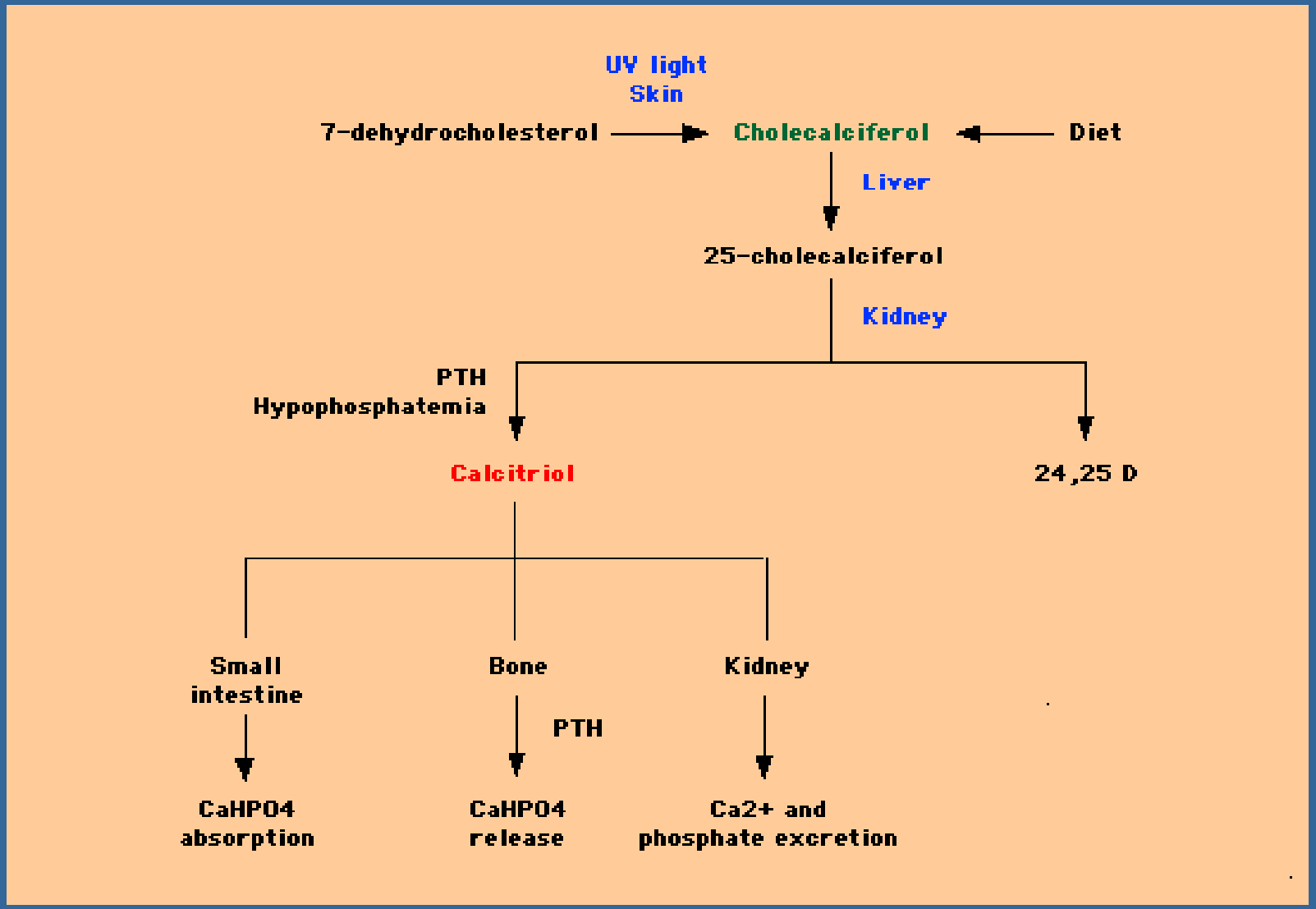
PTH effect


↓ Plasma Ca2+
↑ PTH
Bone
Resorption
Release of Ca2+ and phosphate
Kidney
↑ Phosphate excretion
↑ Calcium reabsorption
↑ Calcitriol formation
↑ Intestinal CaHPO4 absorption

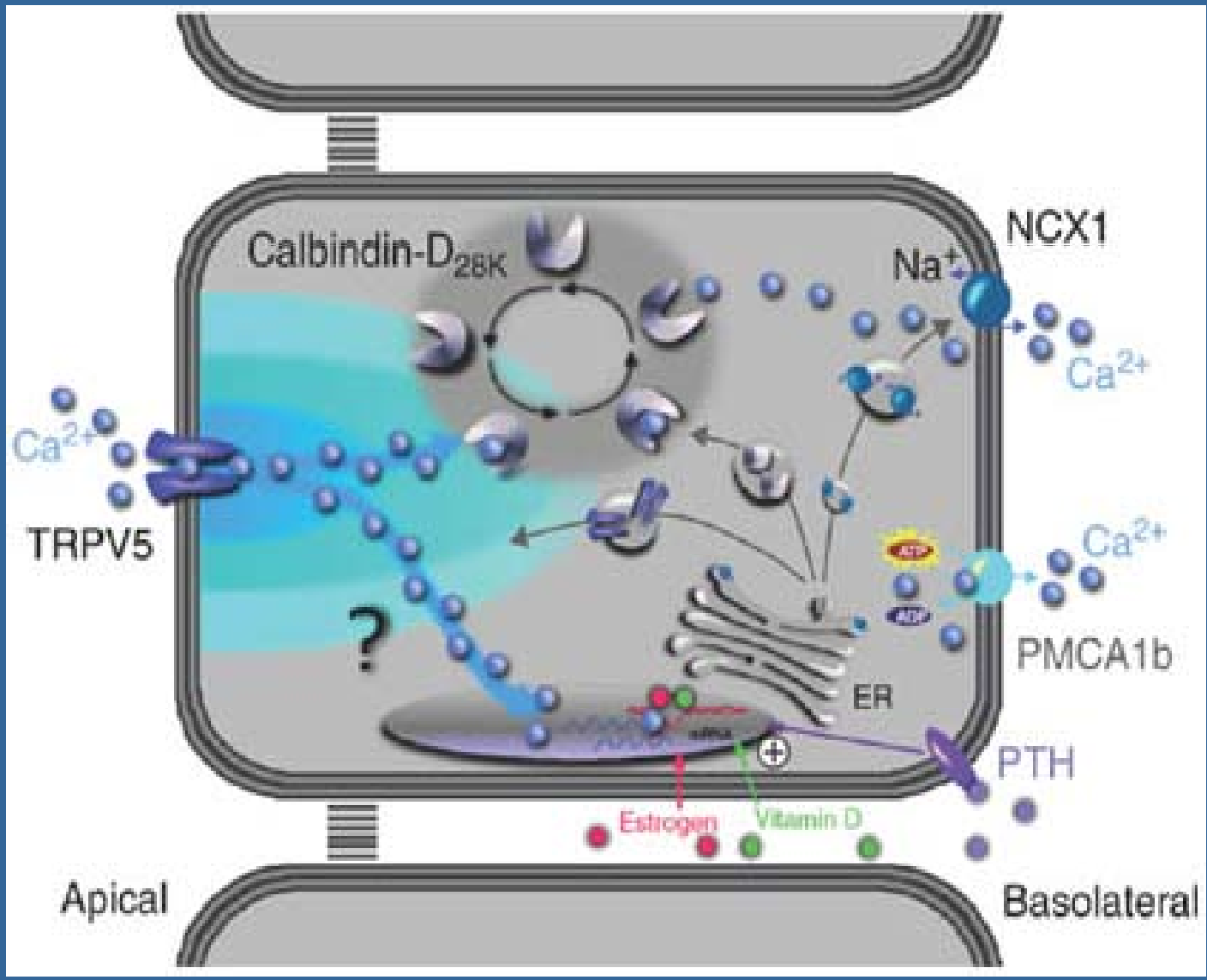
PTH releases calcium from bone by activating the RANK System



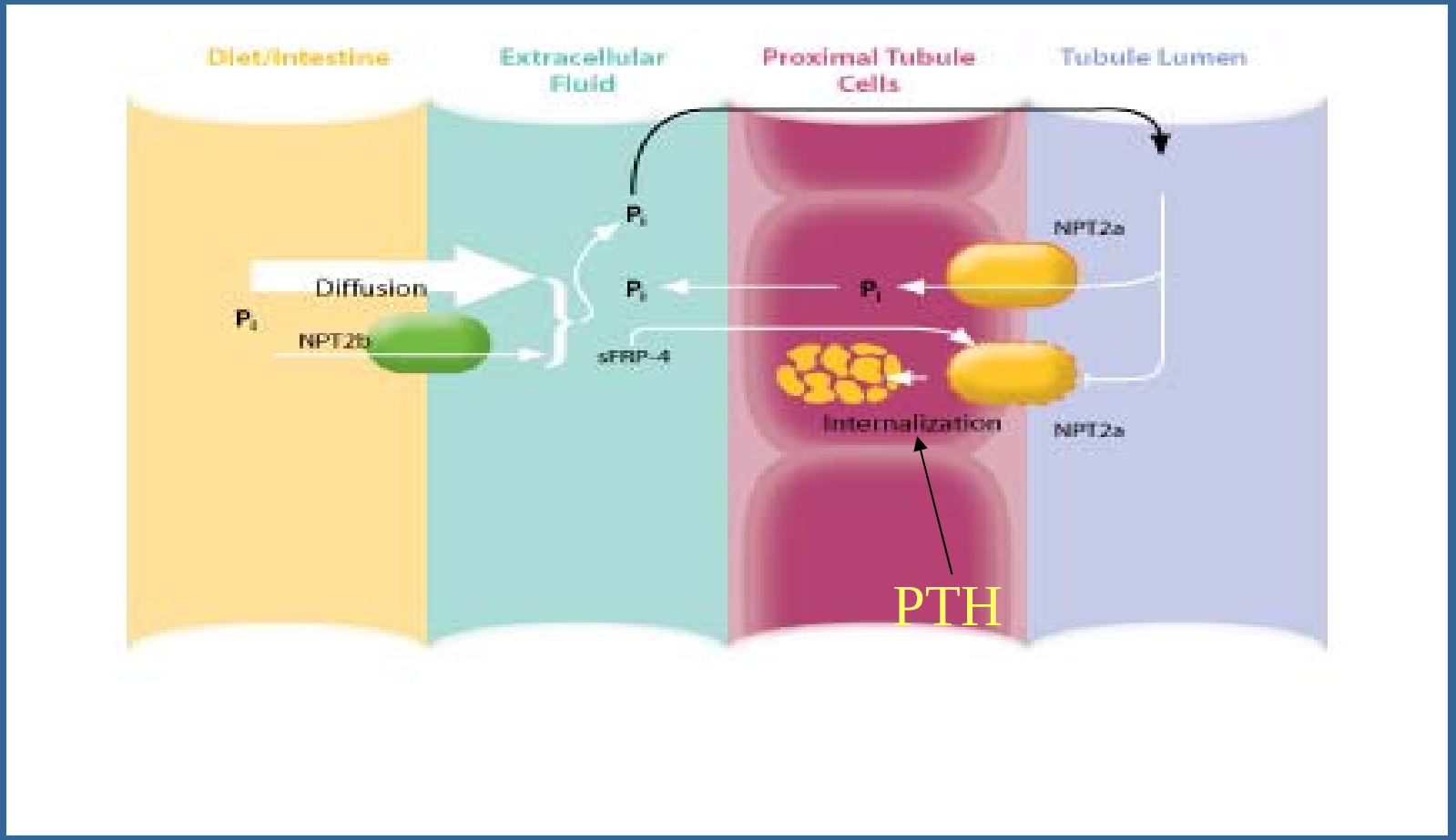
PTH activates vitamin D in the PT of the kidney



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



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



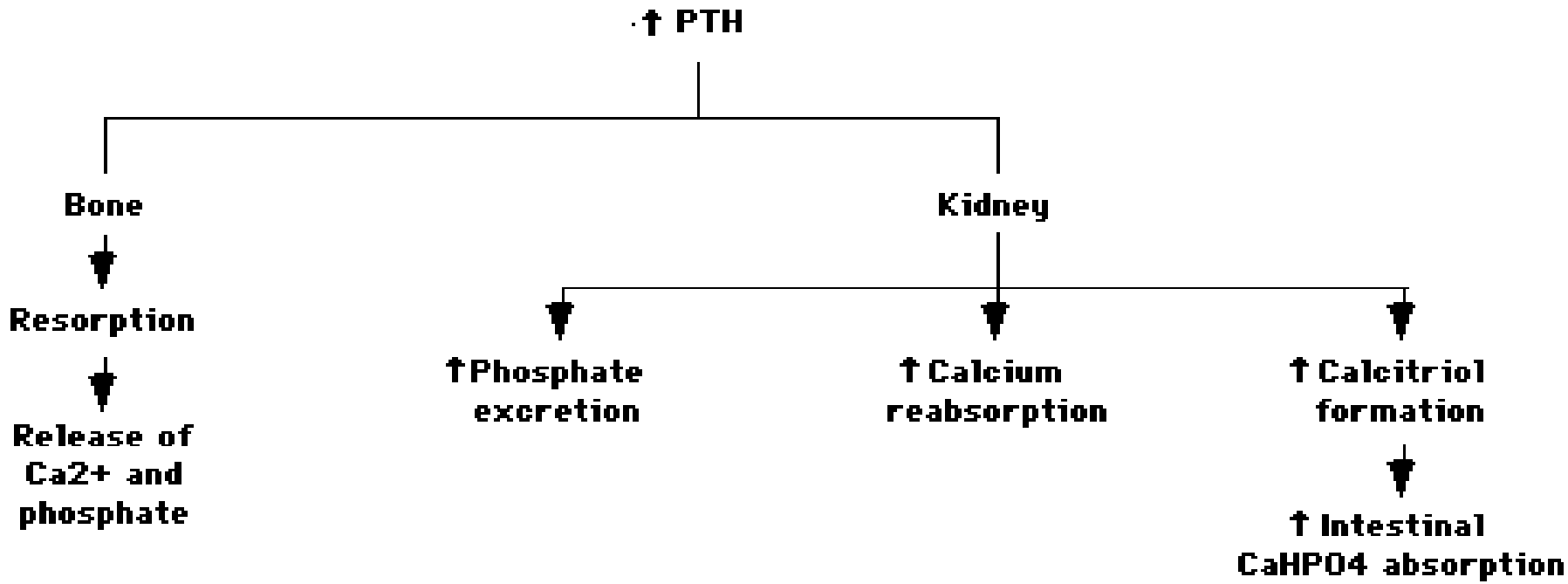
Primary hyperparathyroidism

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



1. ***Increase serum calcium***, by absorption from bone/gut/kidney
2. ***Decrease serum PO4***, as increased absorption is overcome by marked renal excretion
3. ***<u>Increase urine calcium excretion</u>***, as increased renal resorption is overcome by the hugely increased filtered load
4. ***Increase markers of bone resorption***

Primary hyperparathyoidism

Clincal Features are due mainly to high calcium

Thirst, polyuria
Tiredness, fatigue, muscle weakness

“Stones, abdominal moans and psychic groans”

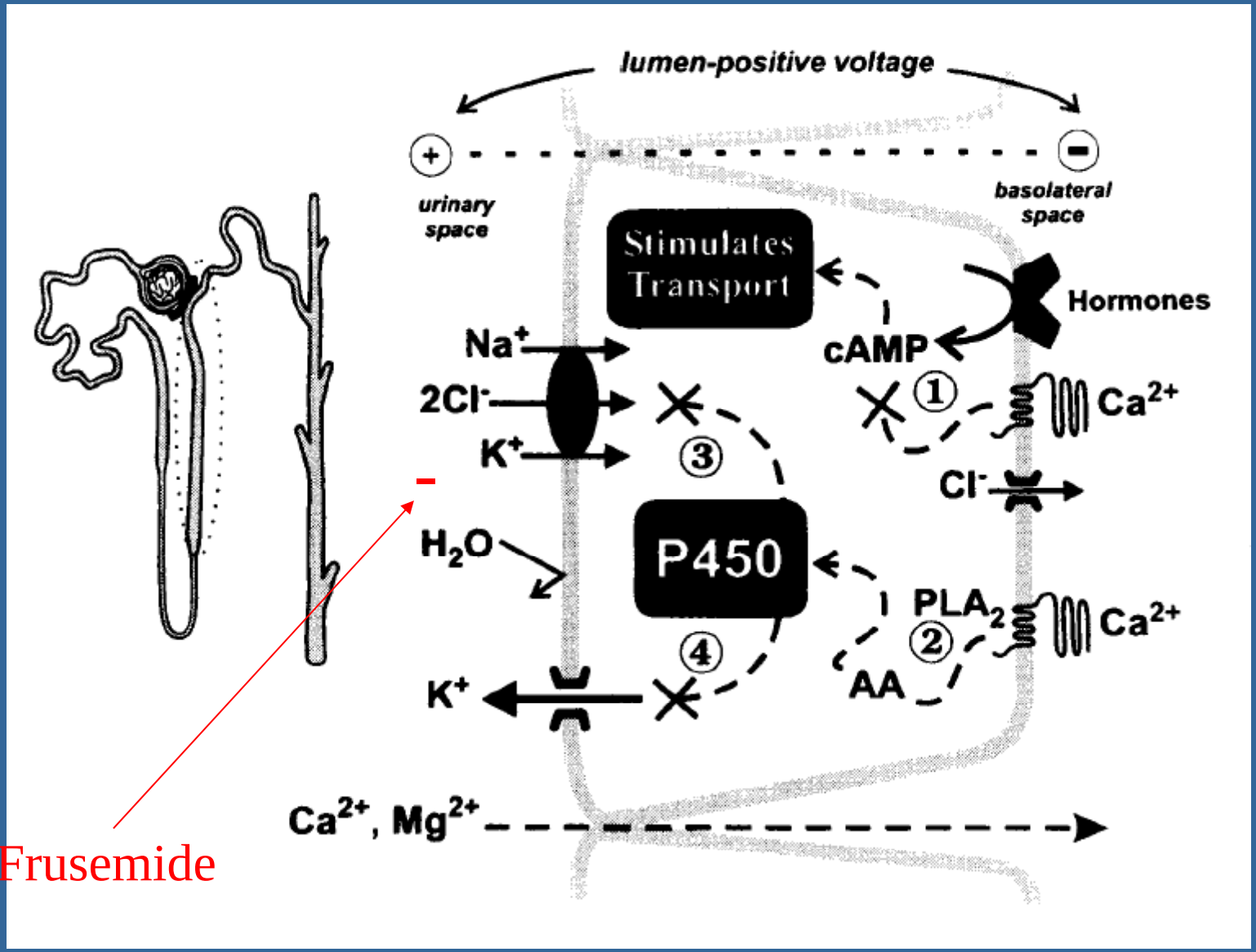
Renal colic, nephrocalcinosis, CRF

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	BMD
renal stones	Renal U/S
renal failure	24hr CrCl
localise	^{99}Tc-sestamibi scan neck U/S
SURGERY	

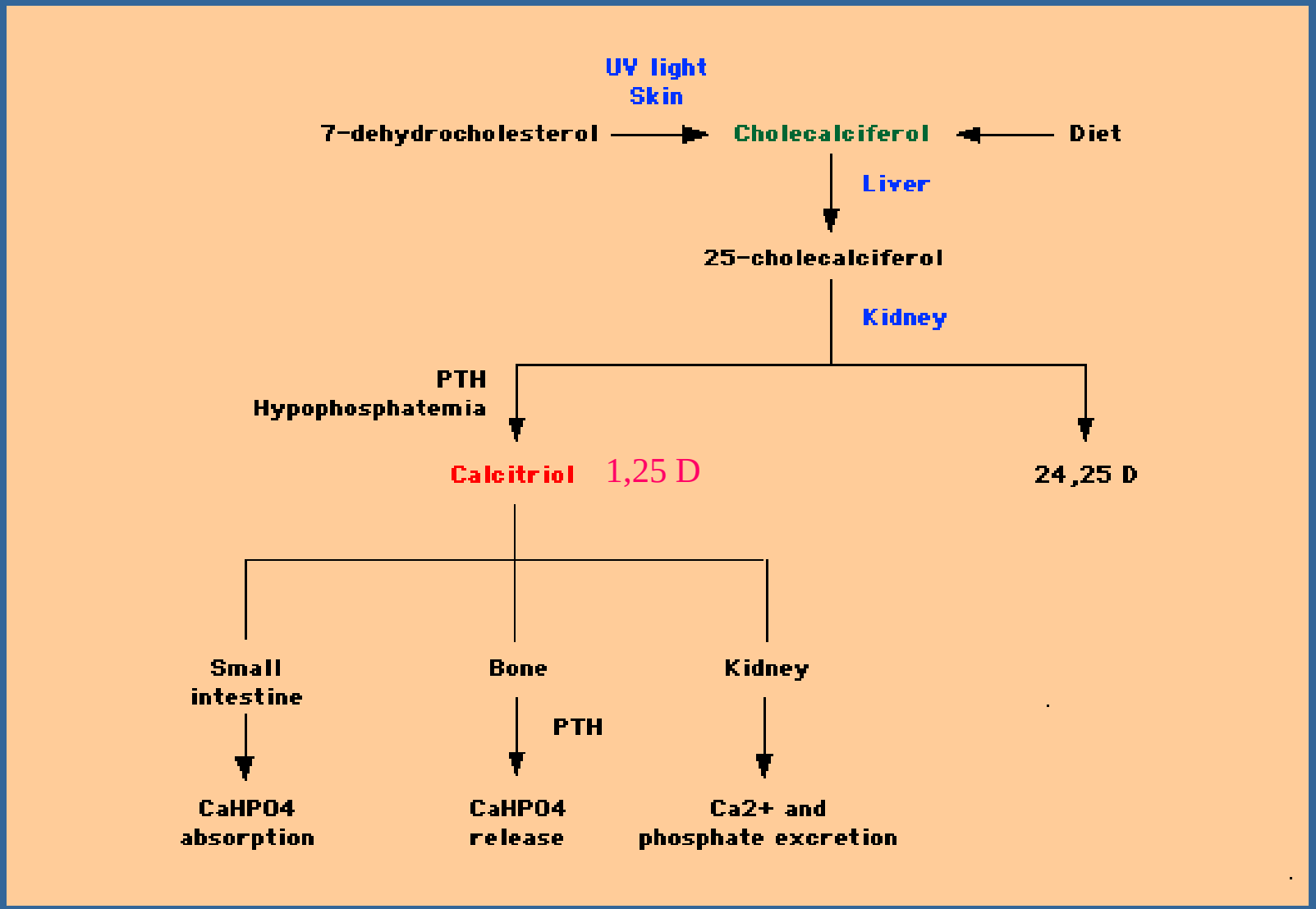
Investigations

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

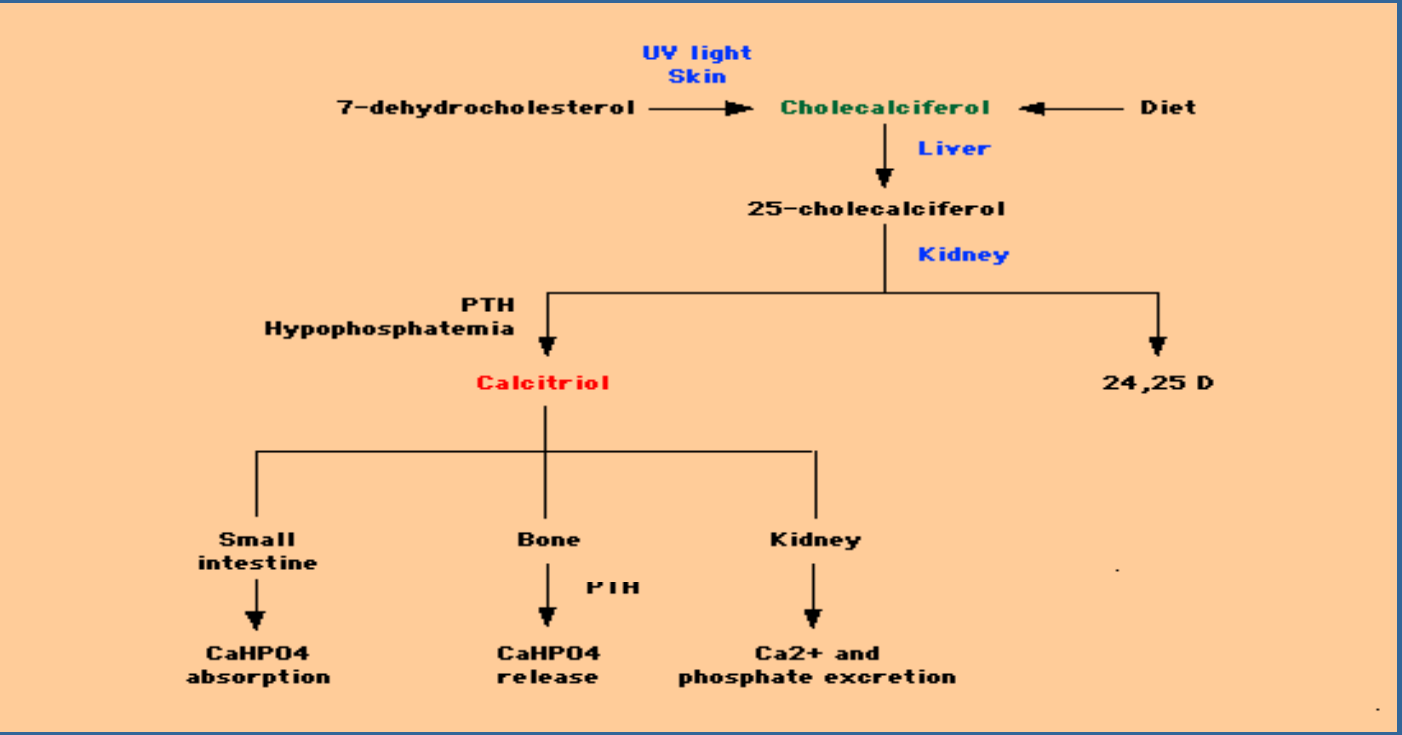
Vitamin D dependent rickets type I

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

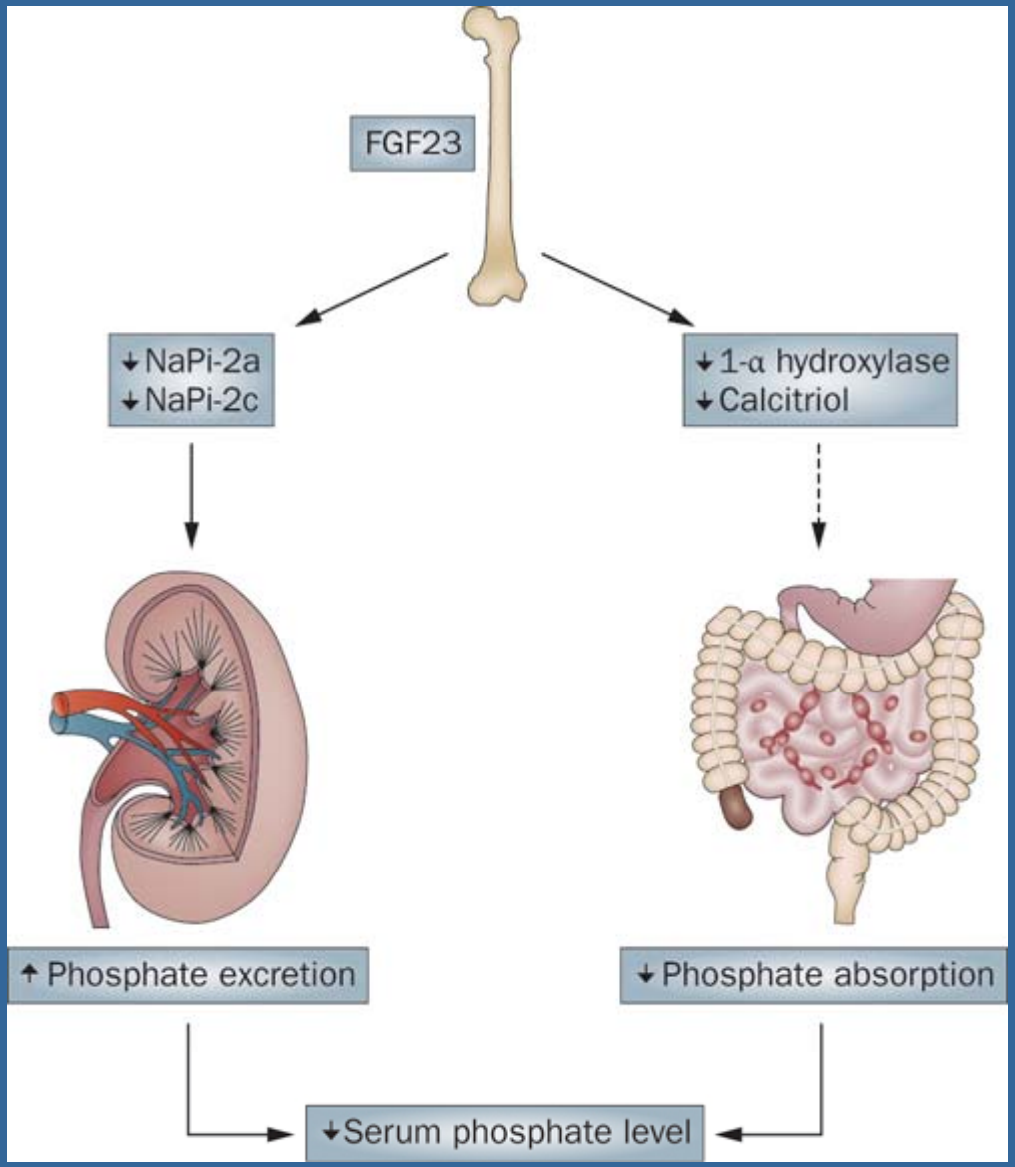
- X-linked hypophosphataemic Rickets
  - 1;20,000
  - mutations in PHEX; do not destroy phosphaturic factor
  - toddlers with leg deformity
  - enthesopathy, dentin anomalies

- oncogenic osteomalacia
  - mesenchymal tumours
  - produce FGF-23, causes phosphaturia and stops 1α OHase

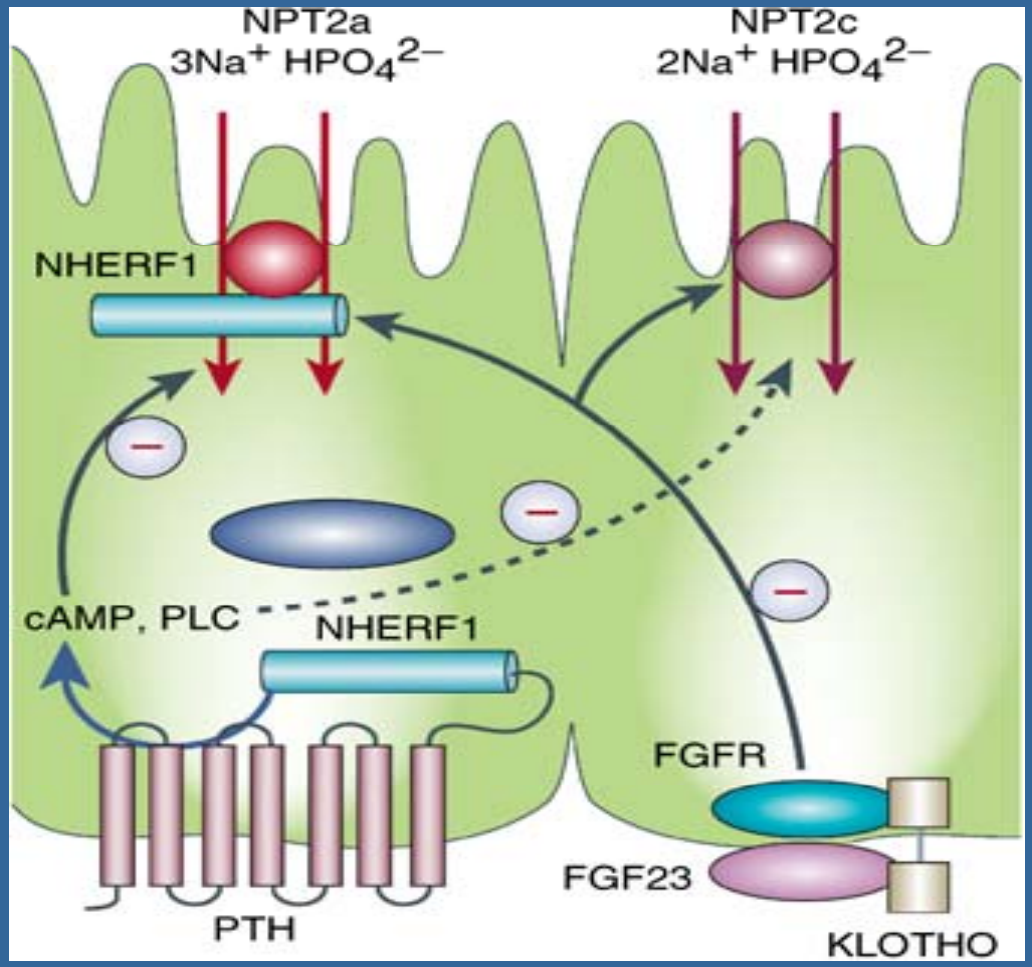
Fanconis syndrome

Proximal renal tubular acidosis

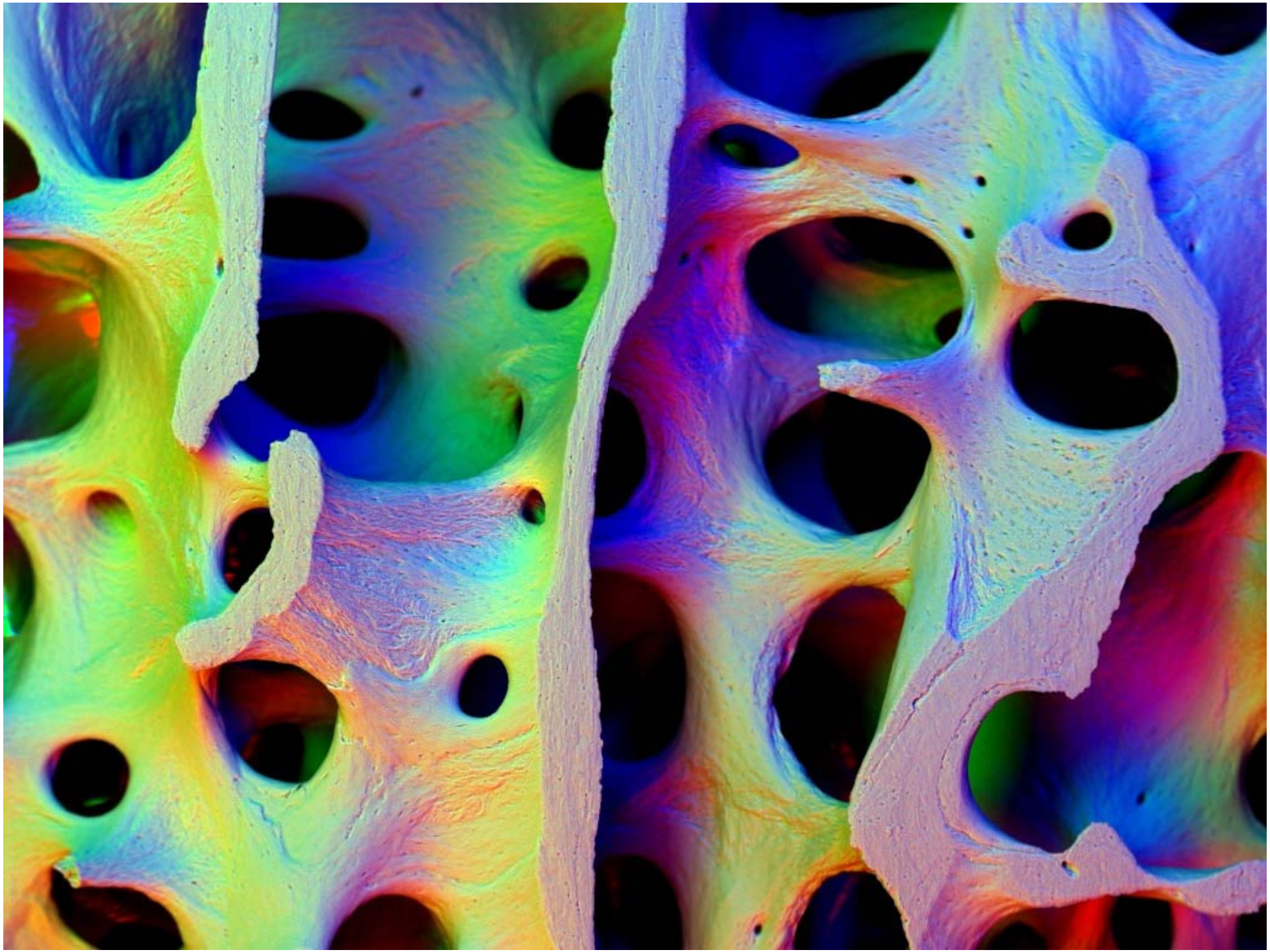
Osteomalacia and FGF-23

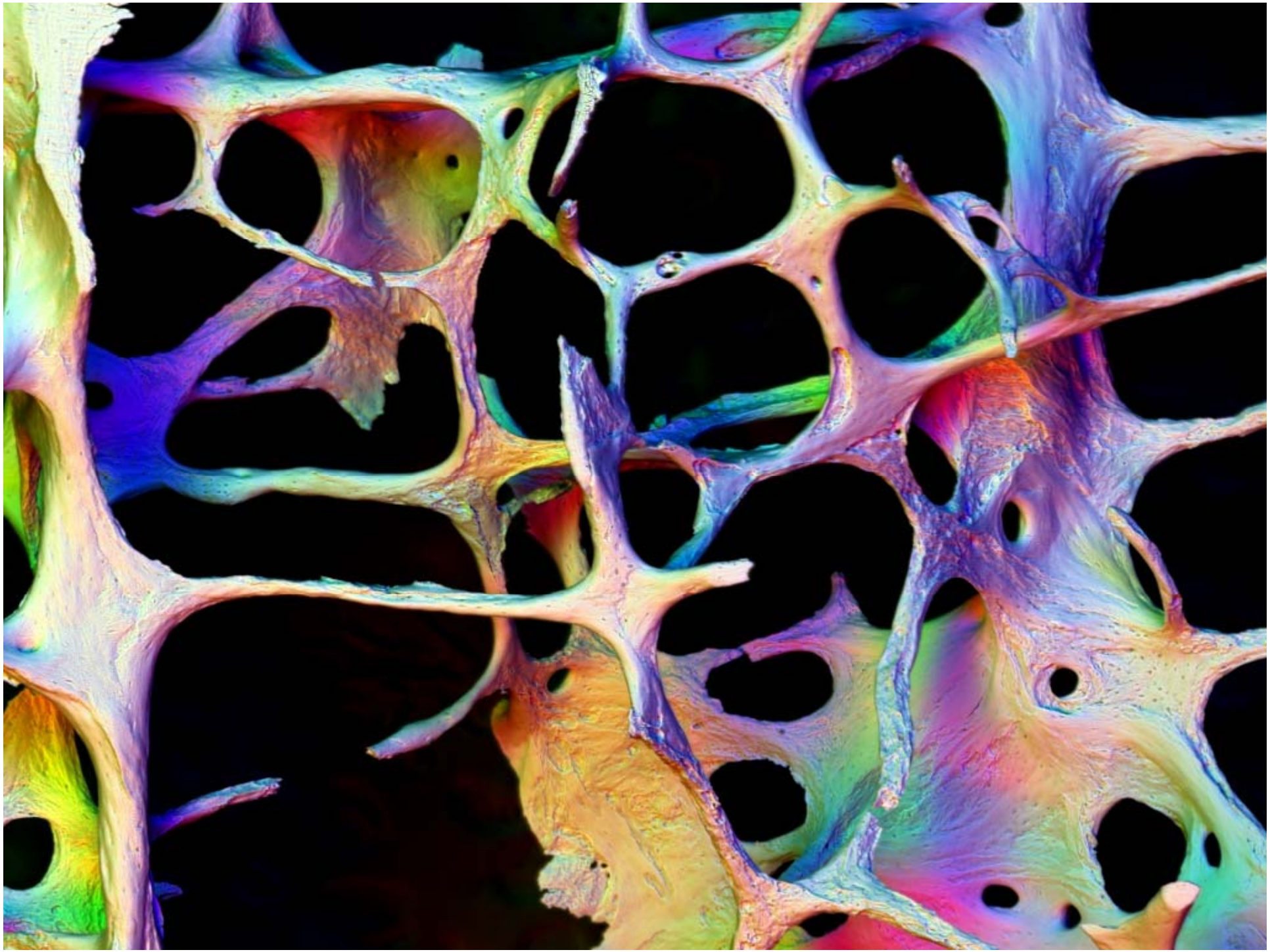


Osteomalacia and FGF-23

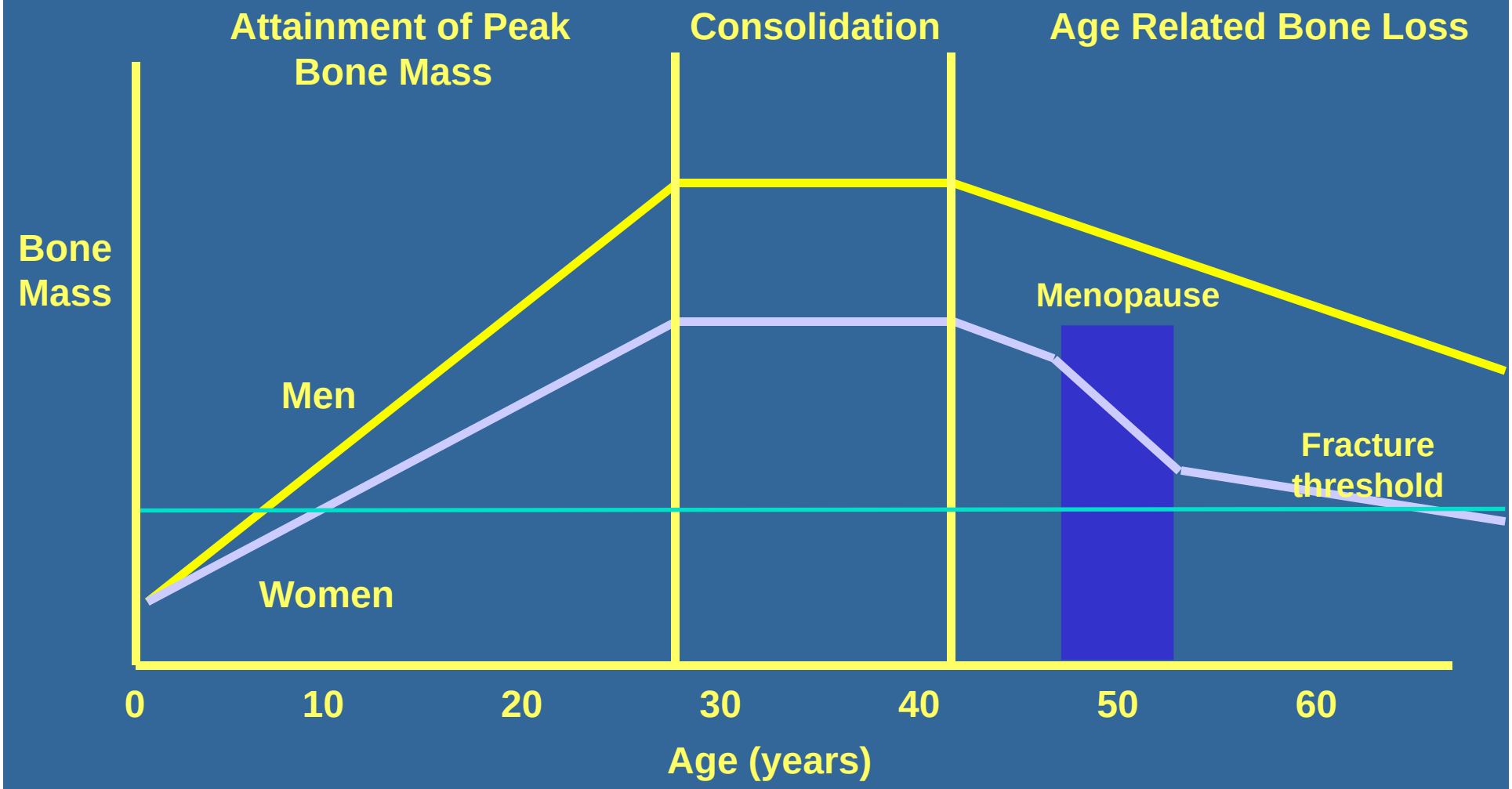


Osteoporosis

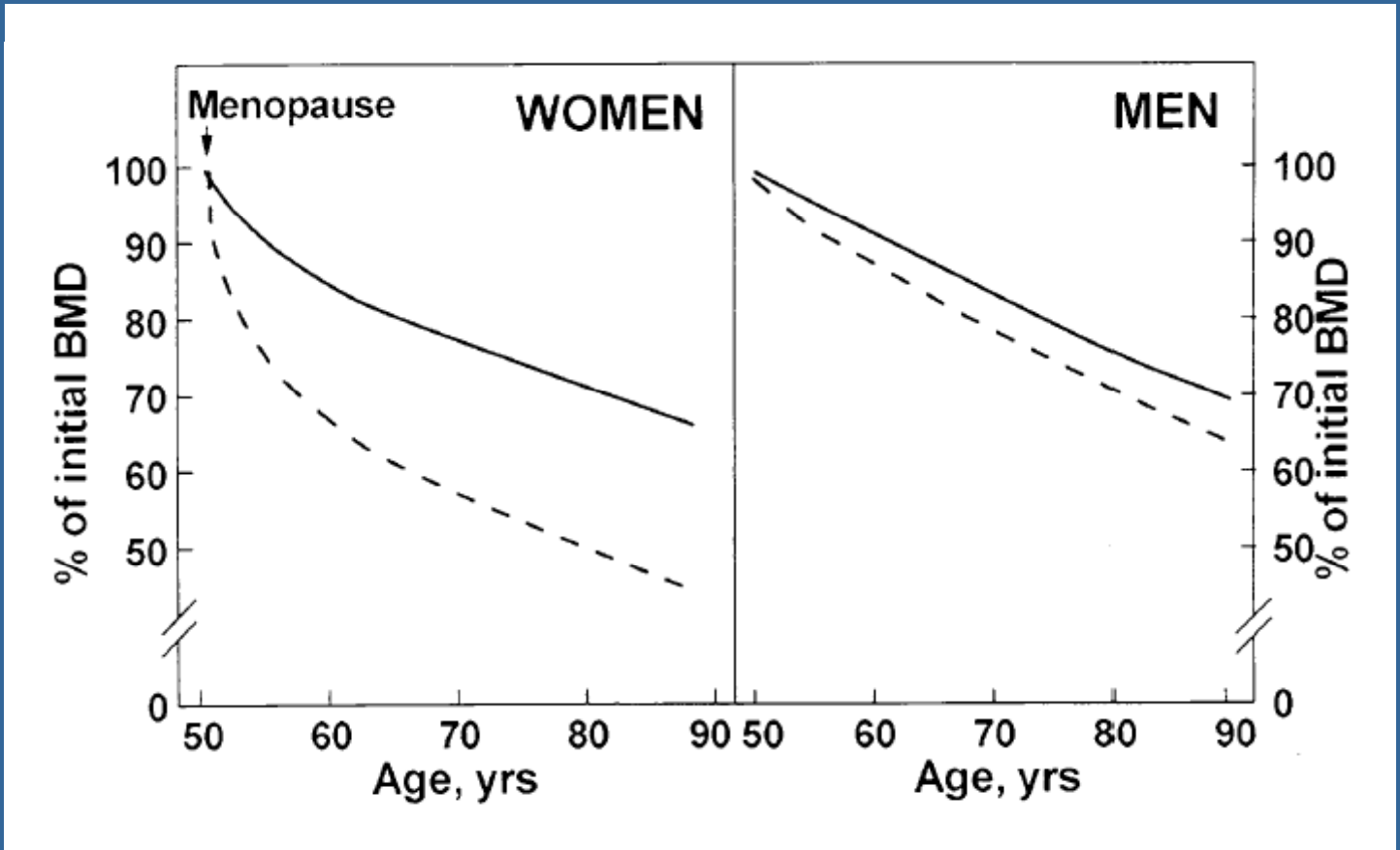




Age Related Changes in Bone Mass[1]

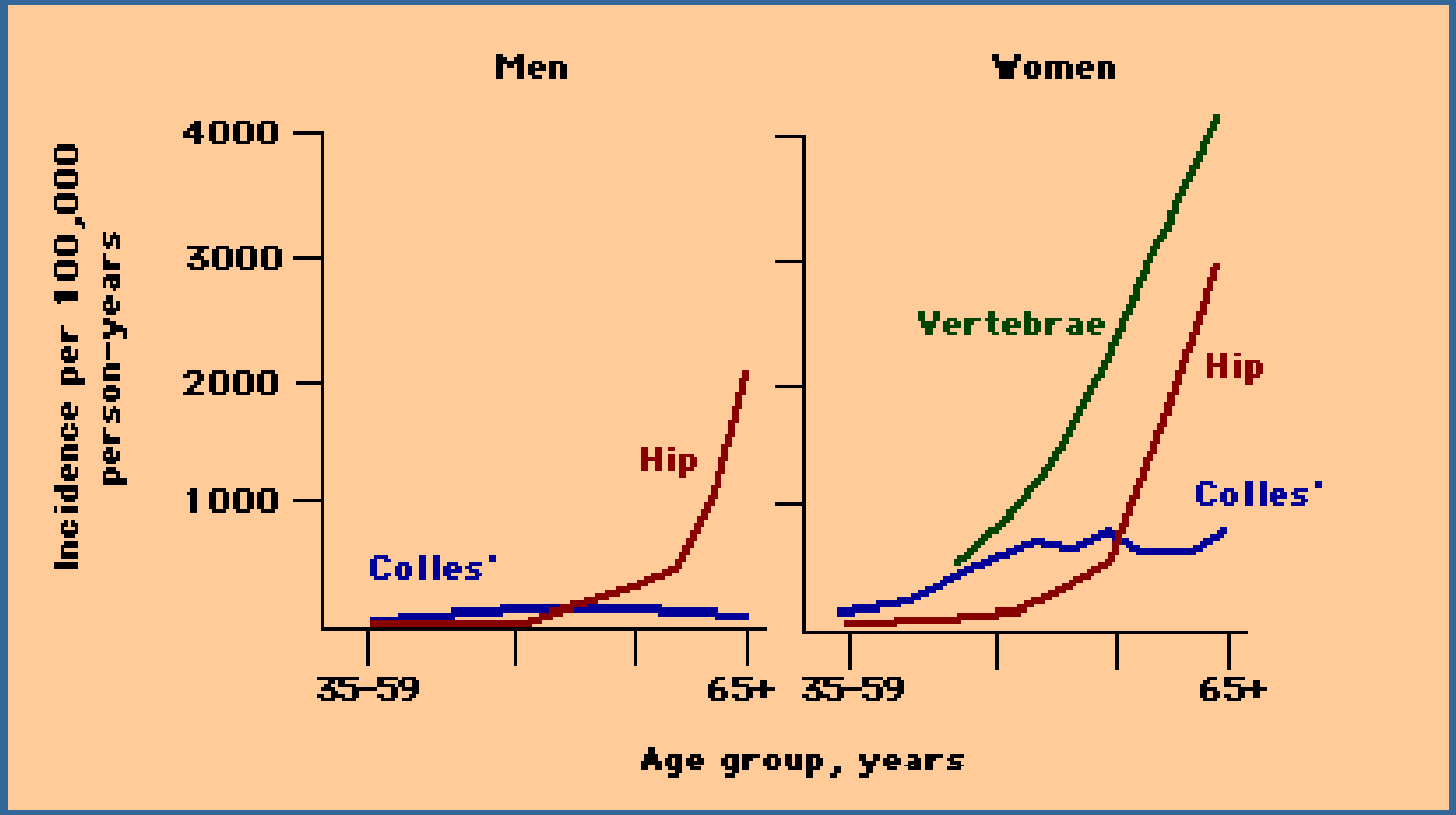


Age Related Changes in Bone Mass



Disproportionate loss of cancellous bone post-menopause

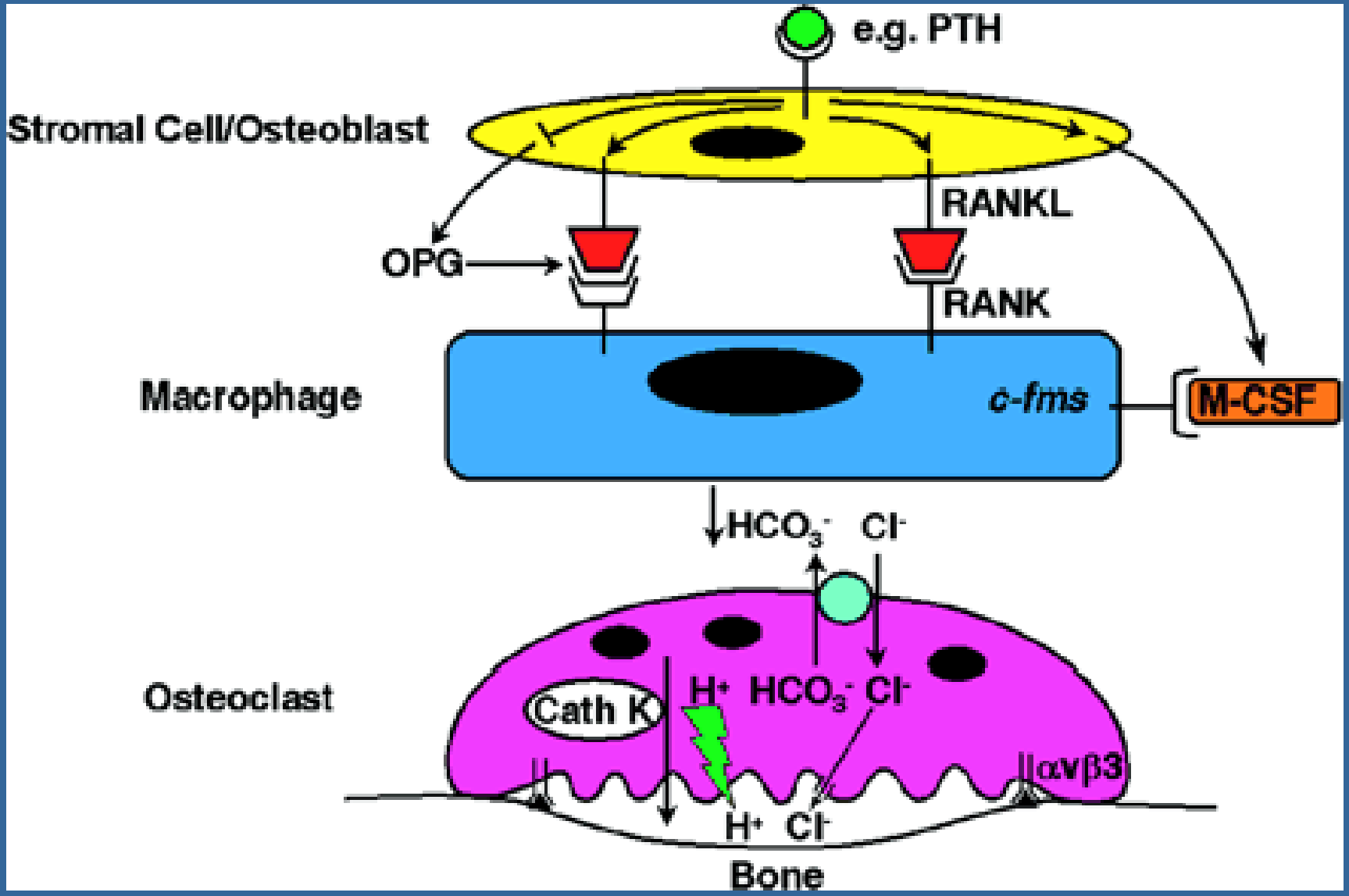
The osteoporosis problem



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

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

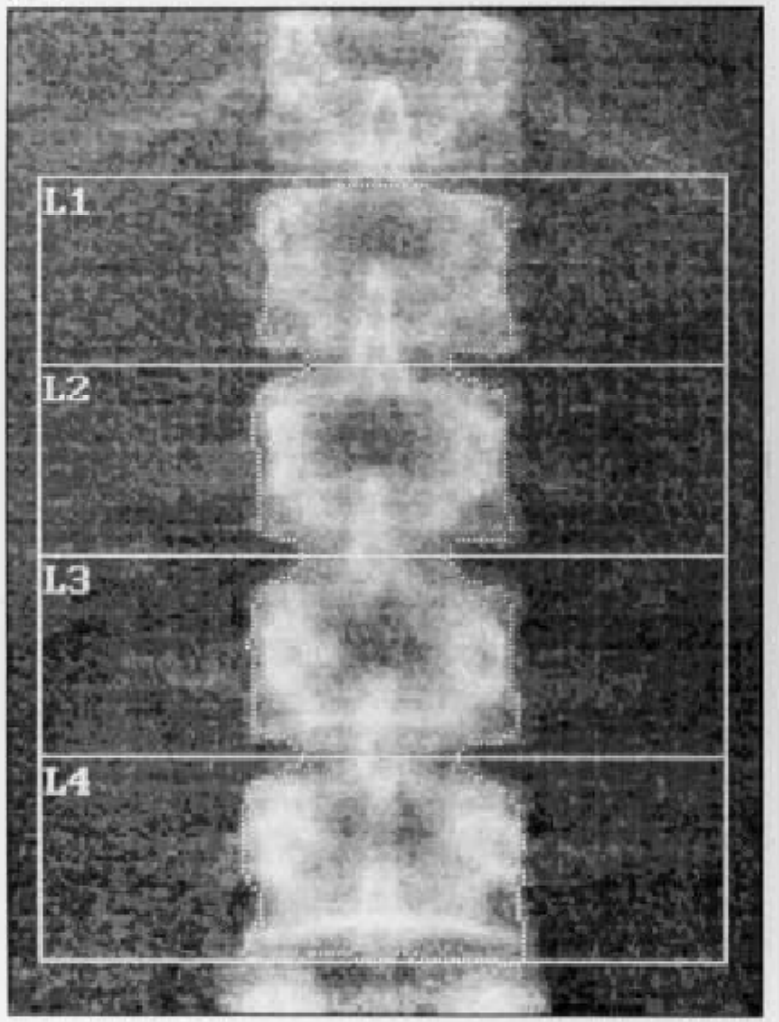
ie How many standard deviations are you off the average for a 25 year old ?

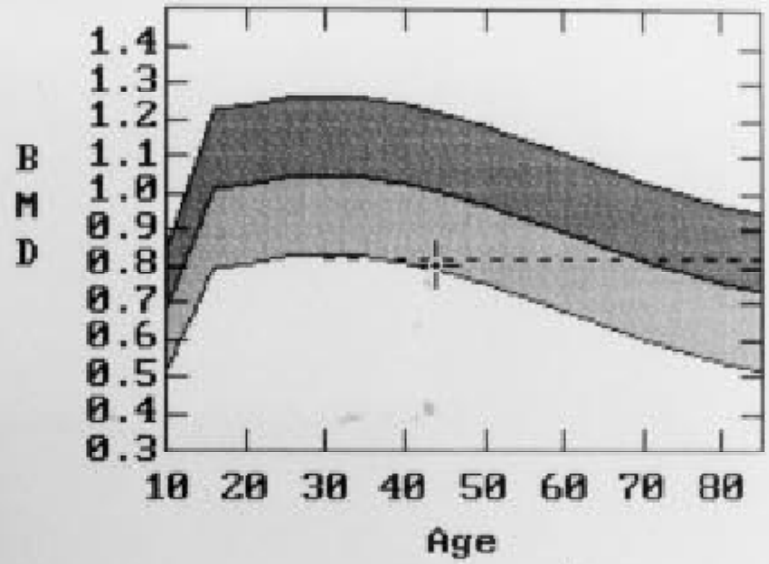
T-score = -2.5 OSTEOPOROSIS

-1to -2.5 OSTEOPAENIA

<-1 NORMAL

Printout

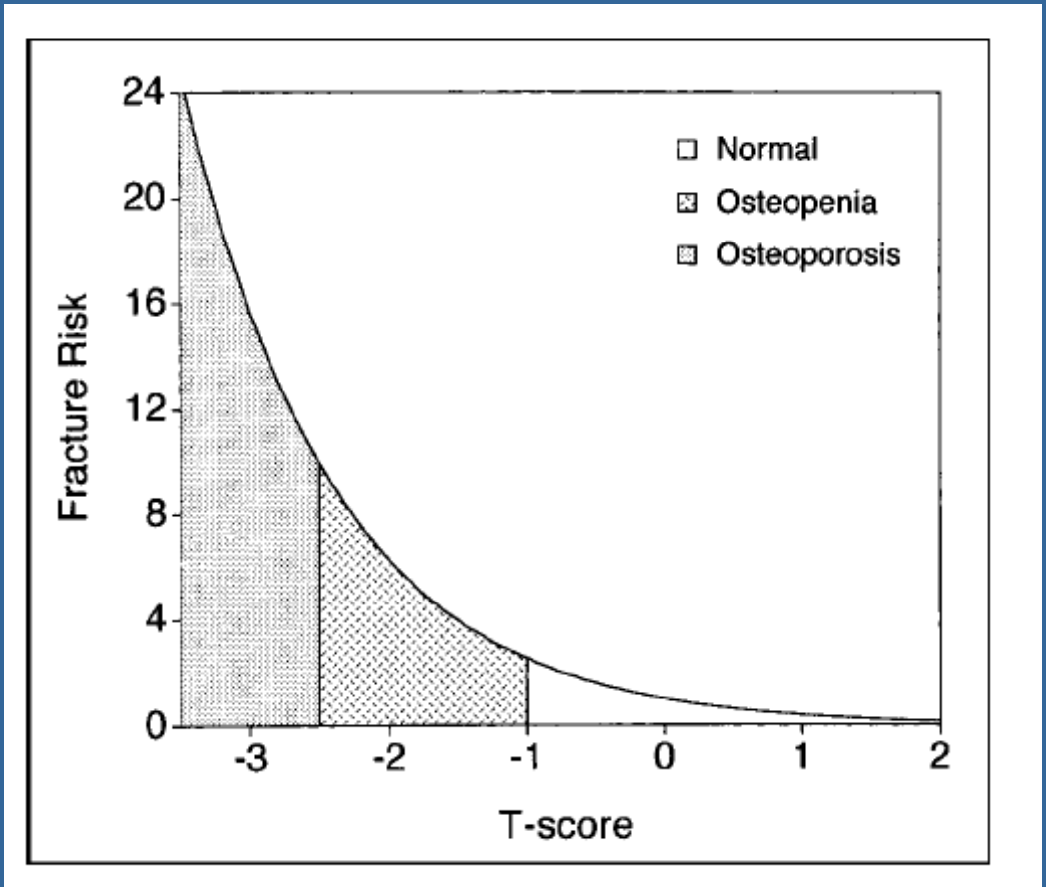




BMD(L1-L4) = 0.797 g/cm^2

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

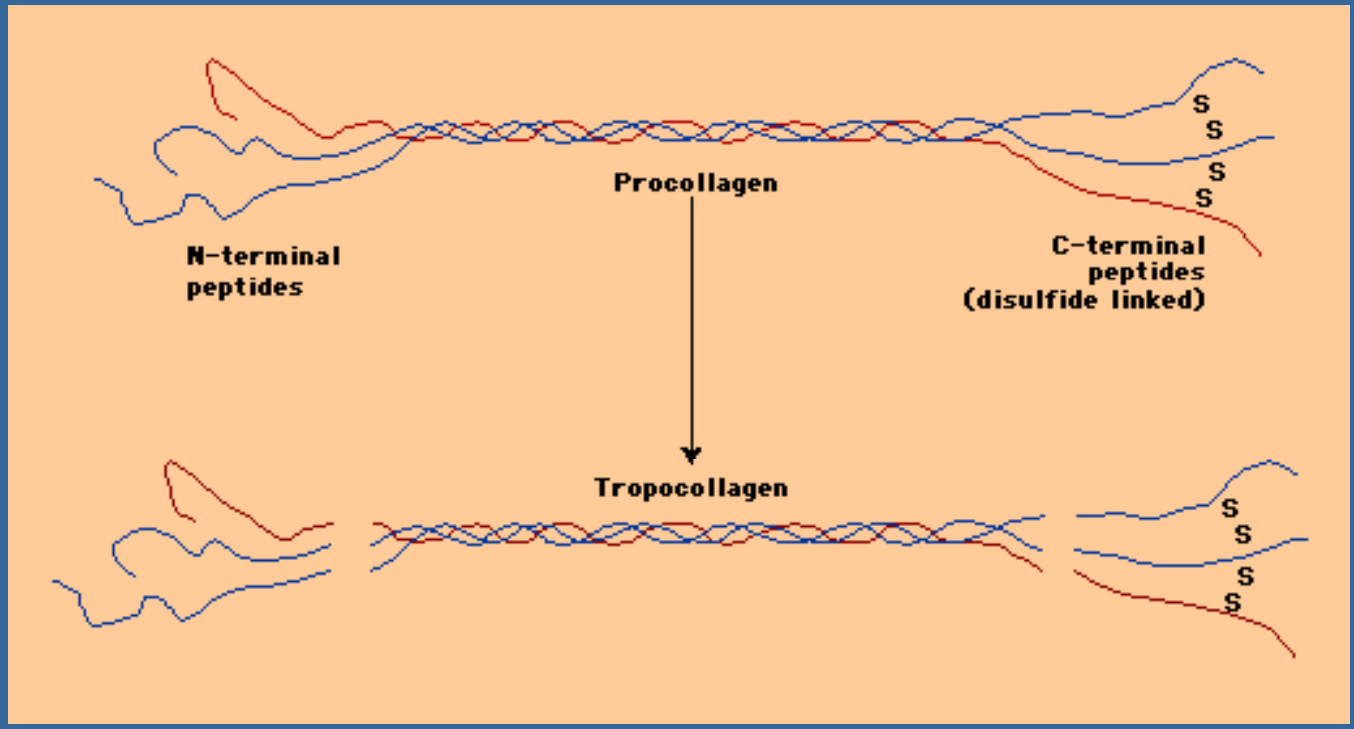
In most bone diseases the bone cycle is disrupted

Markers of bone formation and resorption give us insight into activity

Bone formation; collagen synthesis

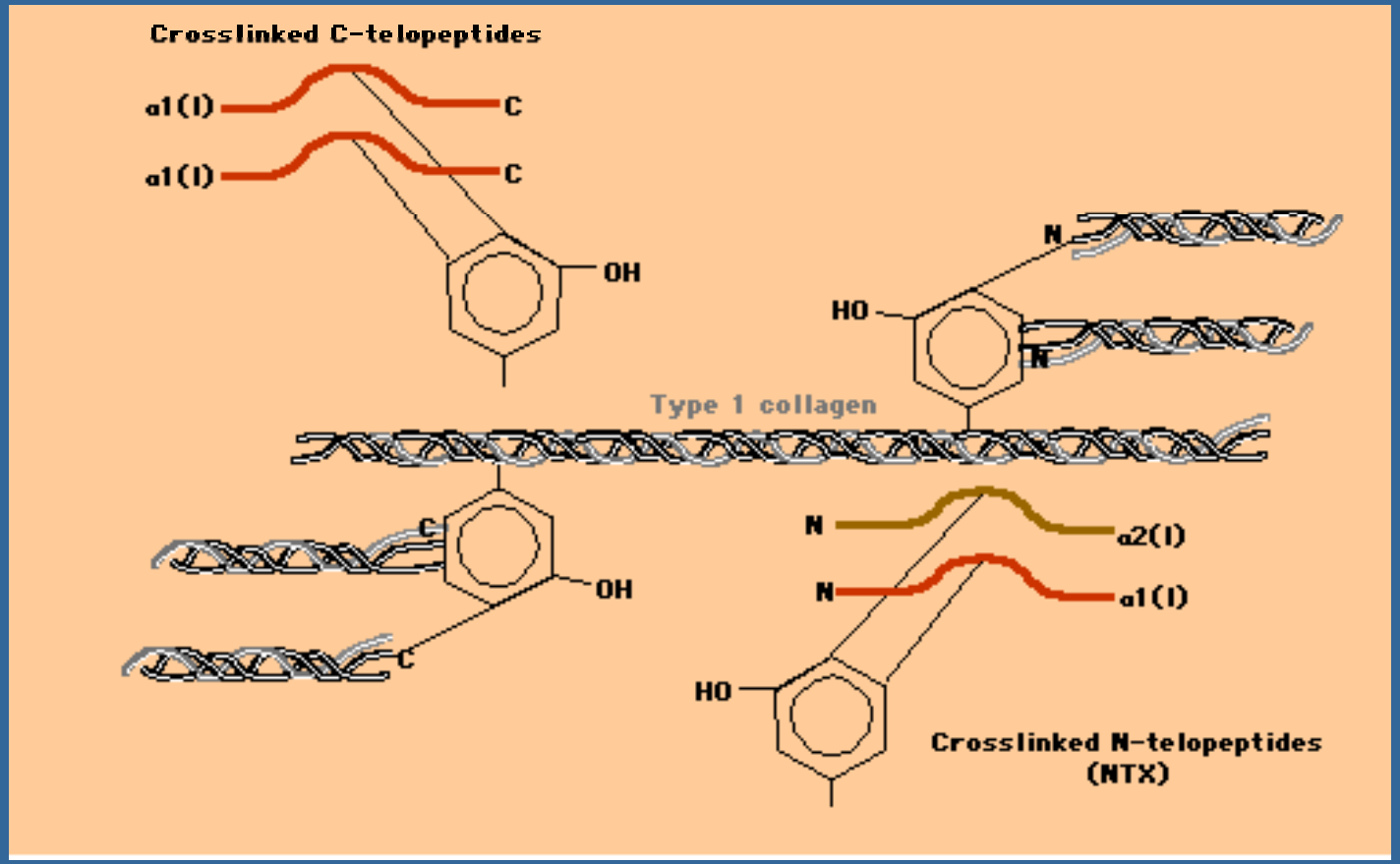
Alpha 1 and 2 chains of type I collagen produced by osteoblast

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

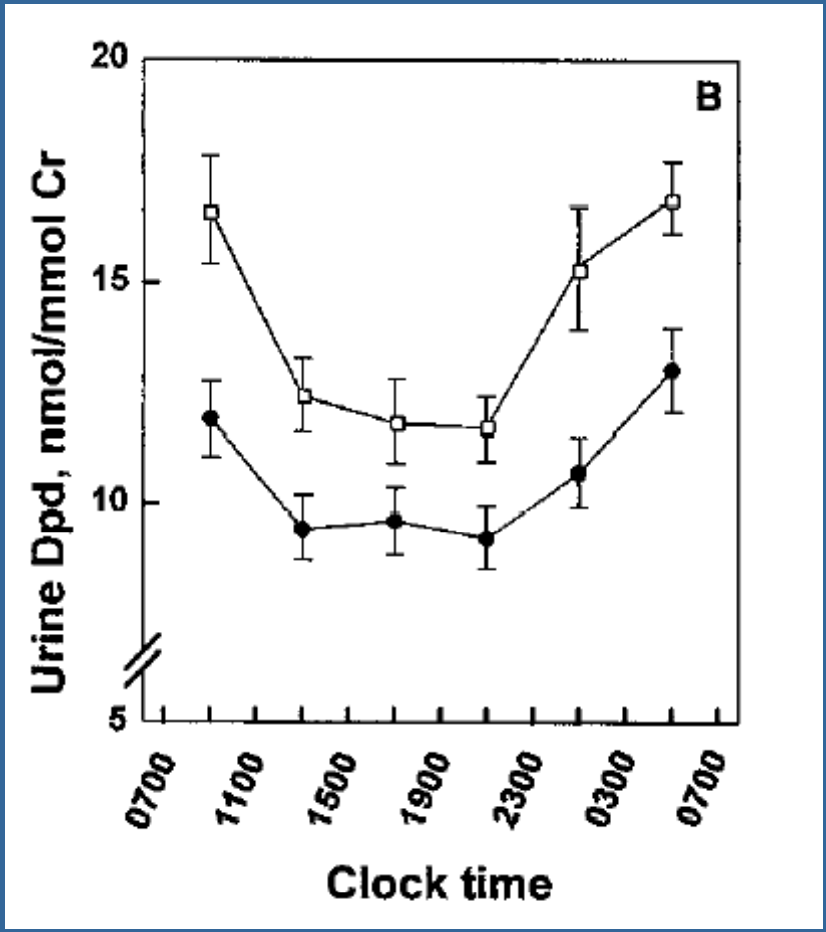
Marker	% CV
NTX	20.2
Dpy (HPLC)	62.9
Hyp	53.0
Osteocalcin	27.3
ALP	10.3

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

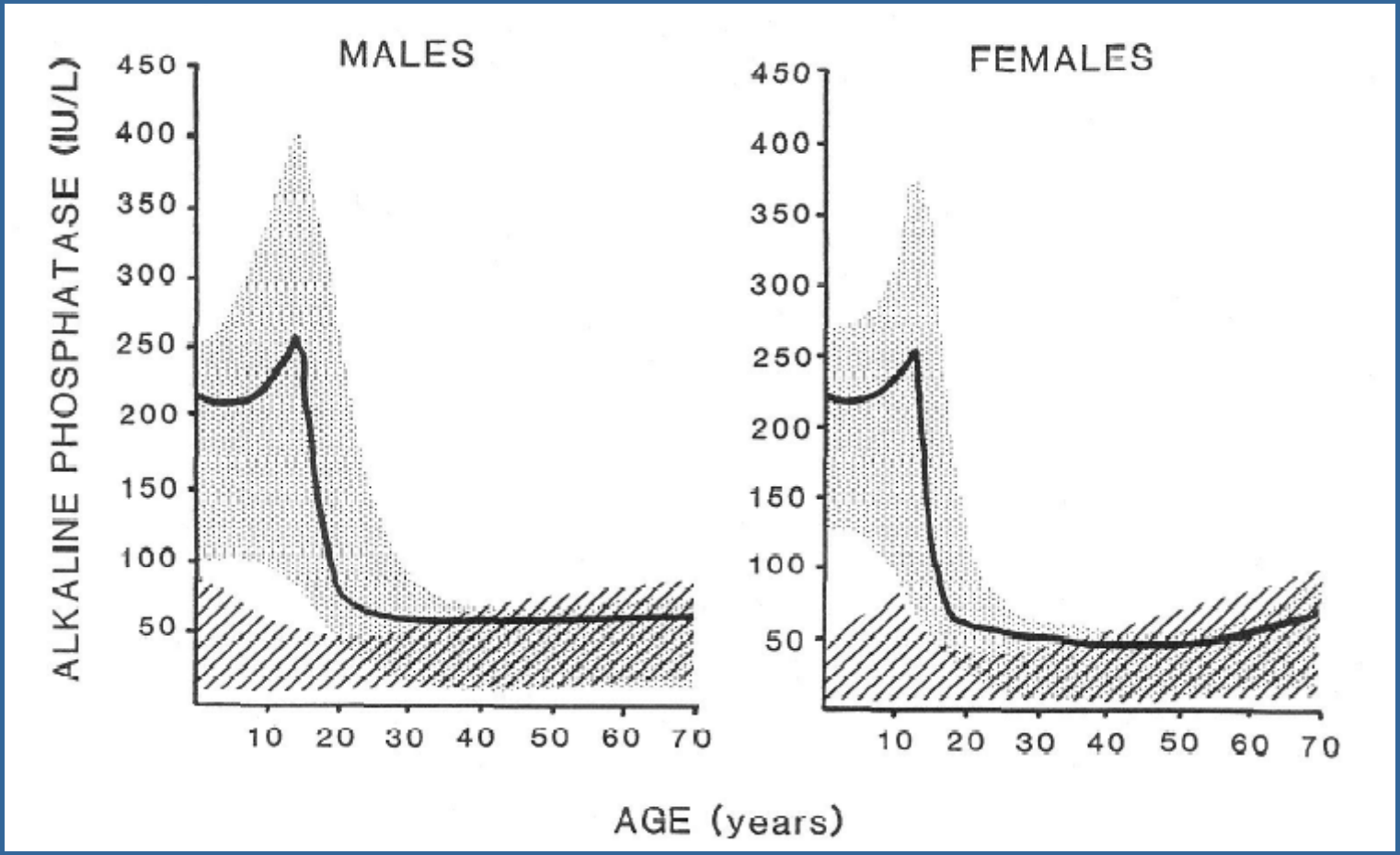
Uses

Consistent within an individual; t ½ 40 hours

Increased in Paget's disease

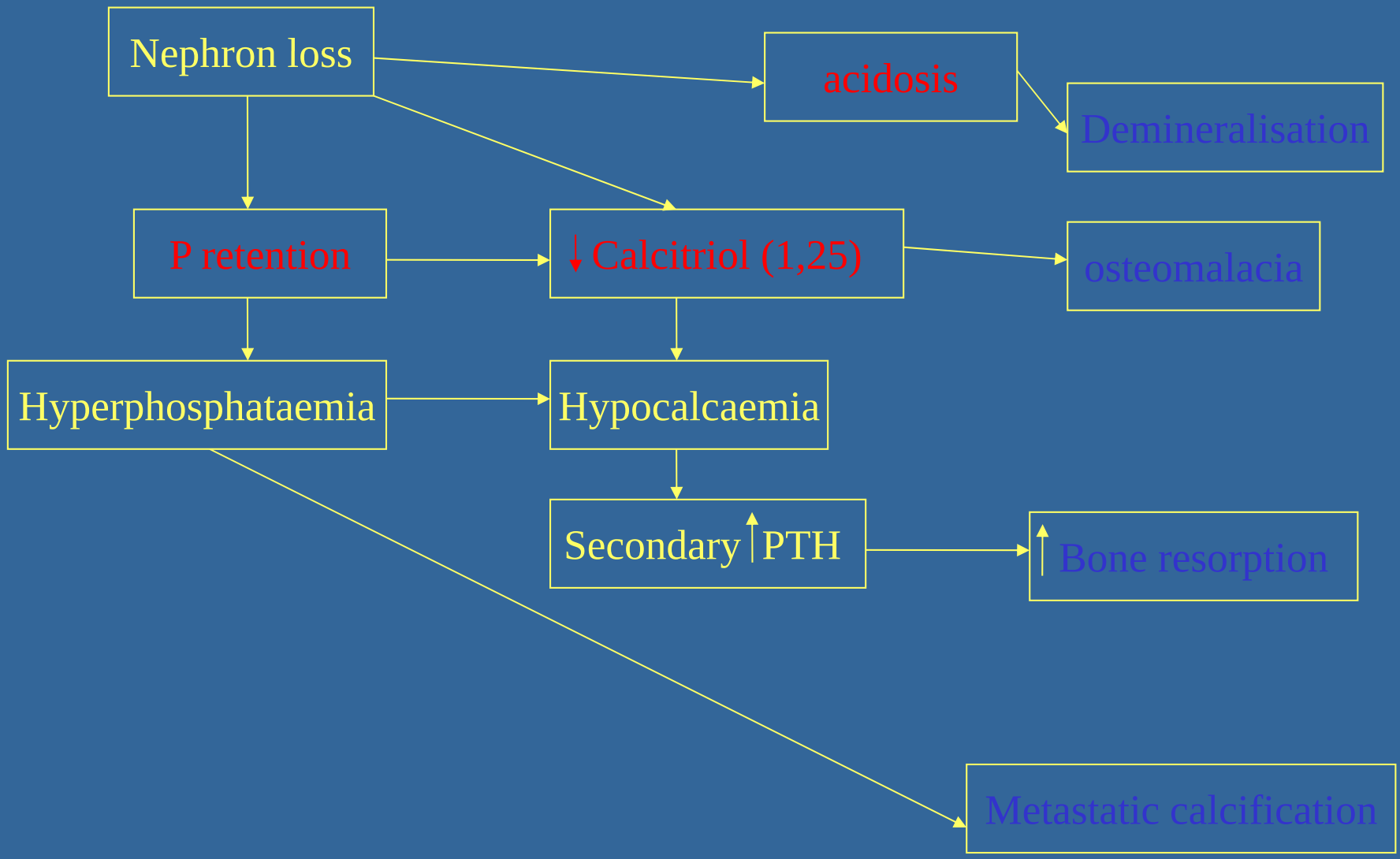
- Osteomalacia
- Bone metastases
- Hyperparathyroidism
- Hyperthyroidism

Alkaline phosphatase with age



Labs don’t standardly give isoforms!

Tertiary hyperparathyroidism



Tertiary hyperparathyroidism