Calcium metabolism
&
Parathyroid Glands
Physiological functions

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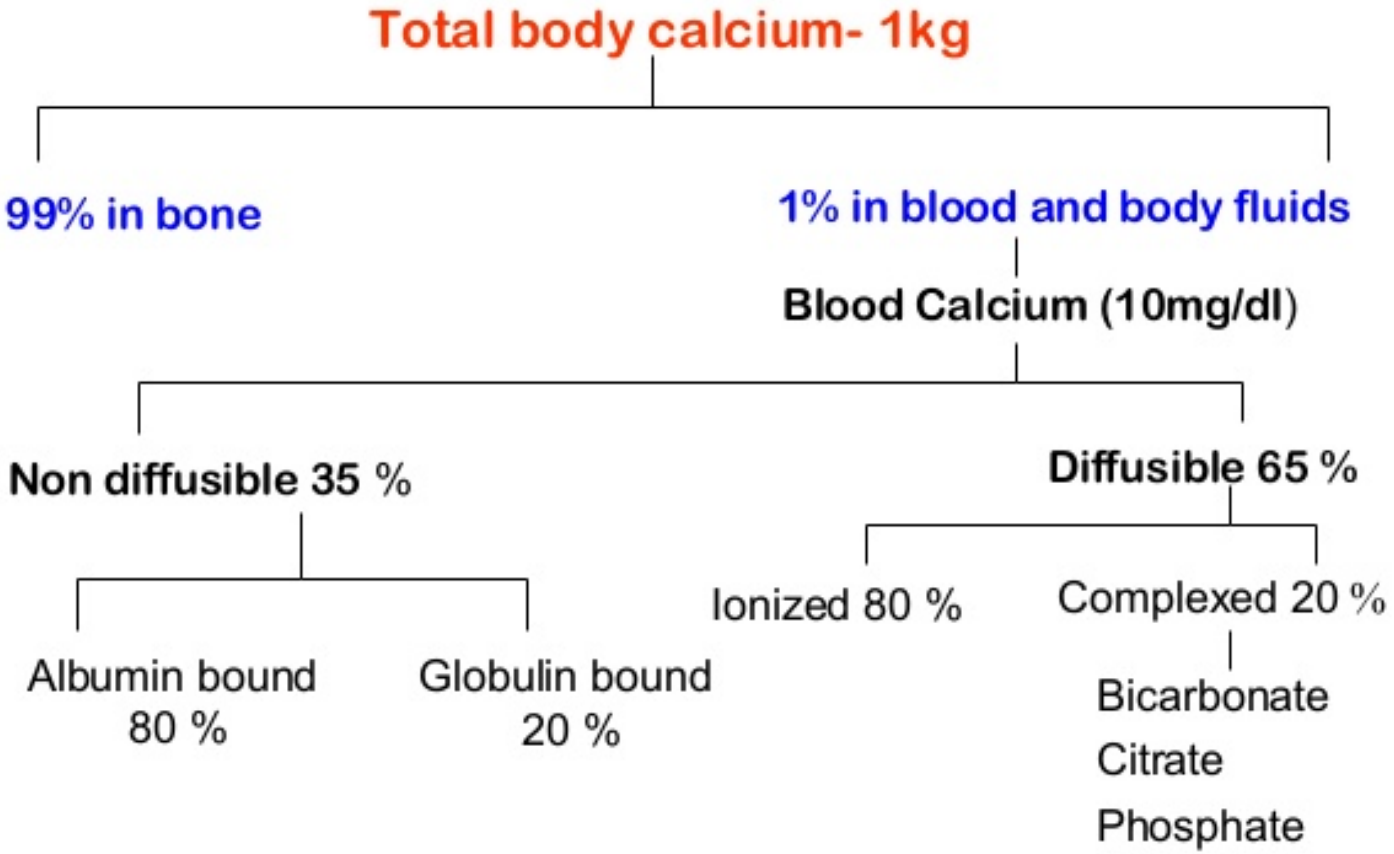
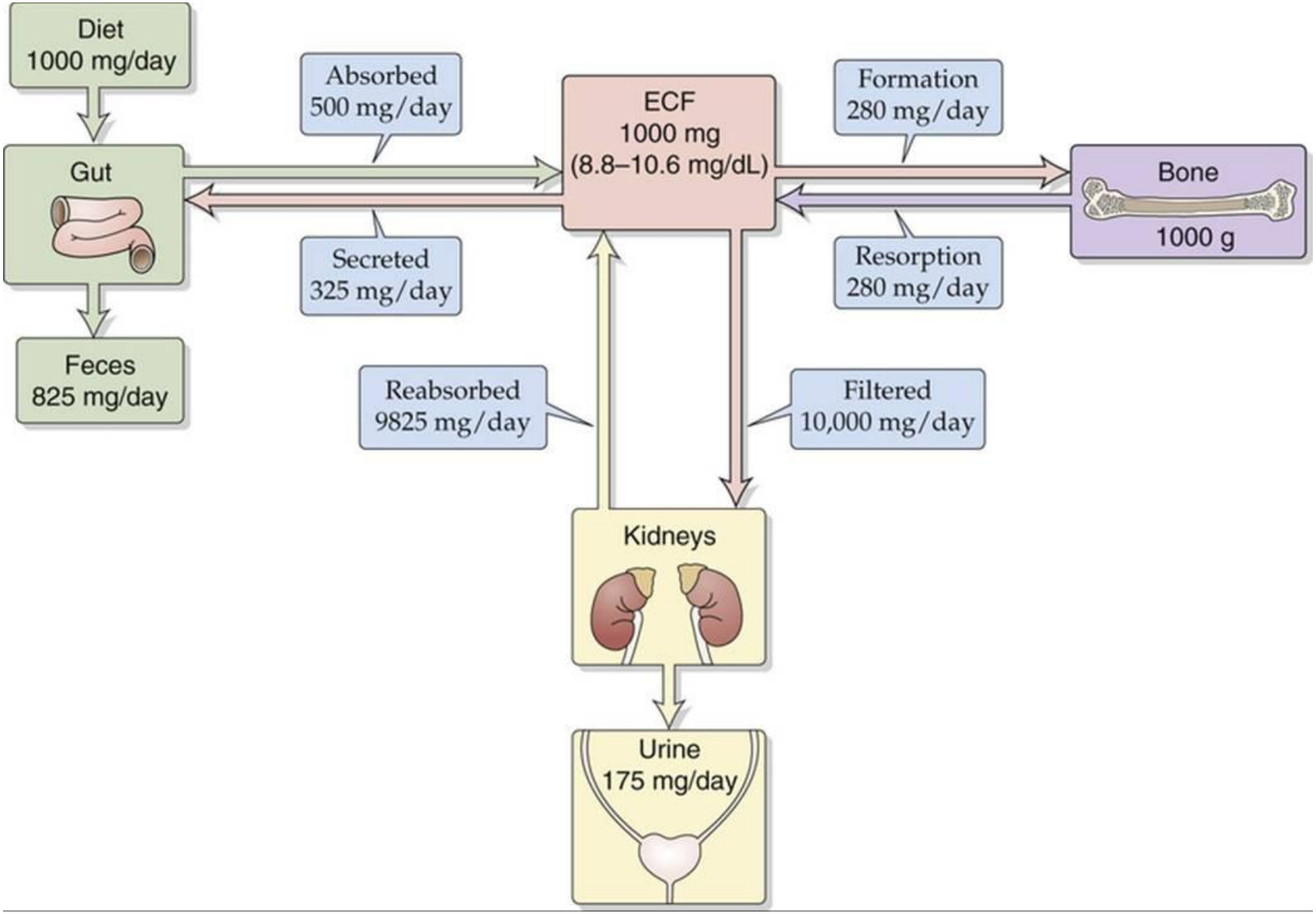
Learning outcomes

- Distribution of calcium and phophate in body
- Parathyroid gland -Introduction
- PTH synthesis,metabolism,regulation and actions
- Vitamin D
- Calcitonin
- Bone physiology

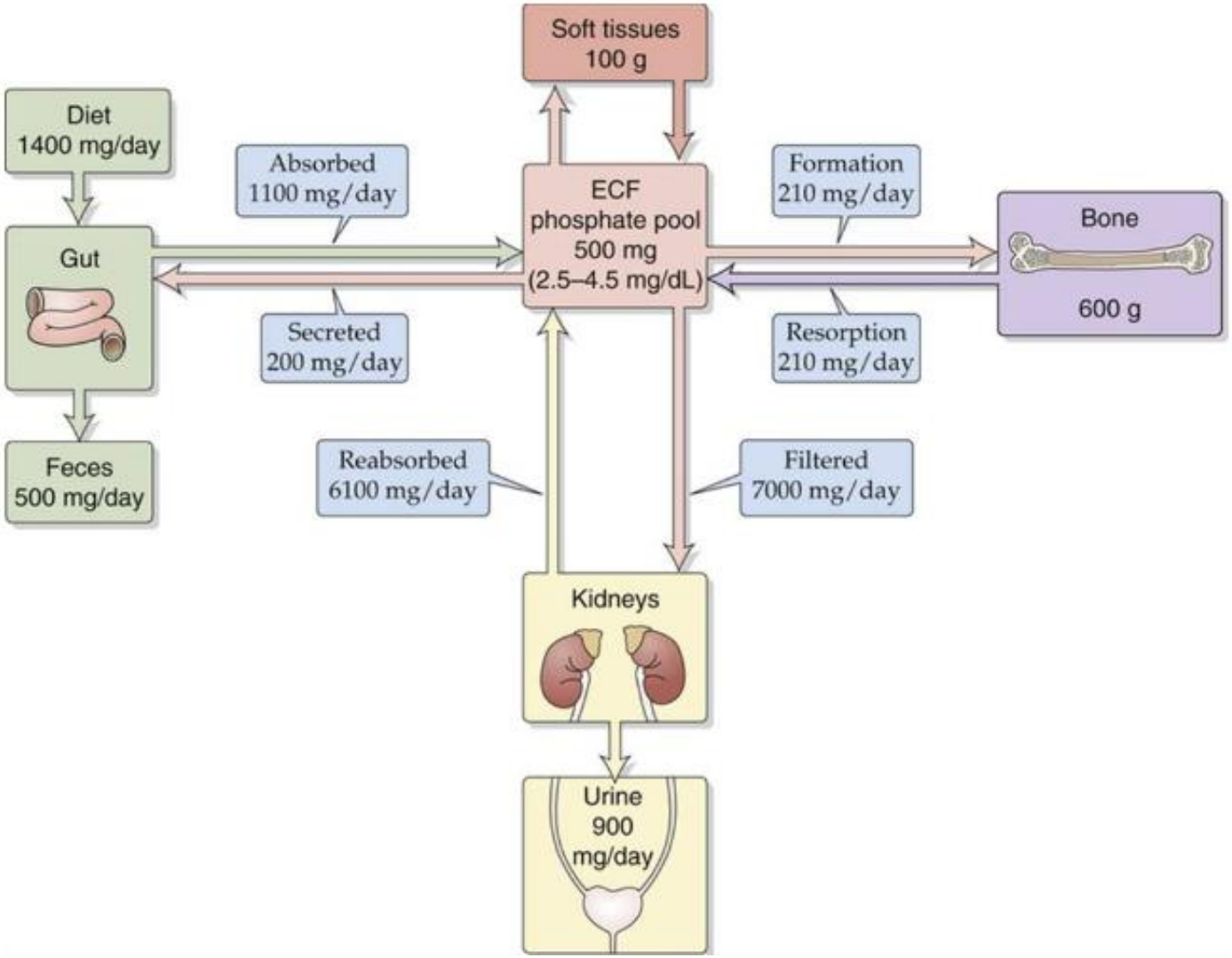
Distribution of Calcium in Body



Calcium distribution

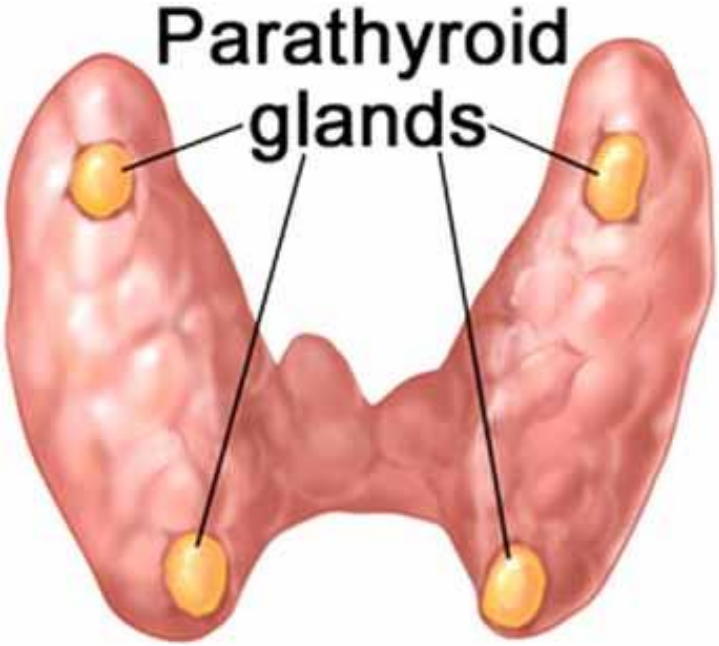


Phosphate distribution



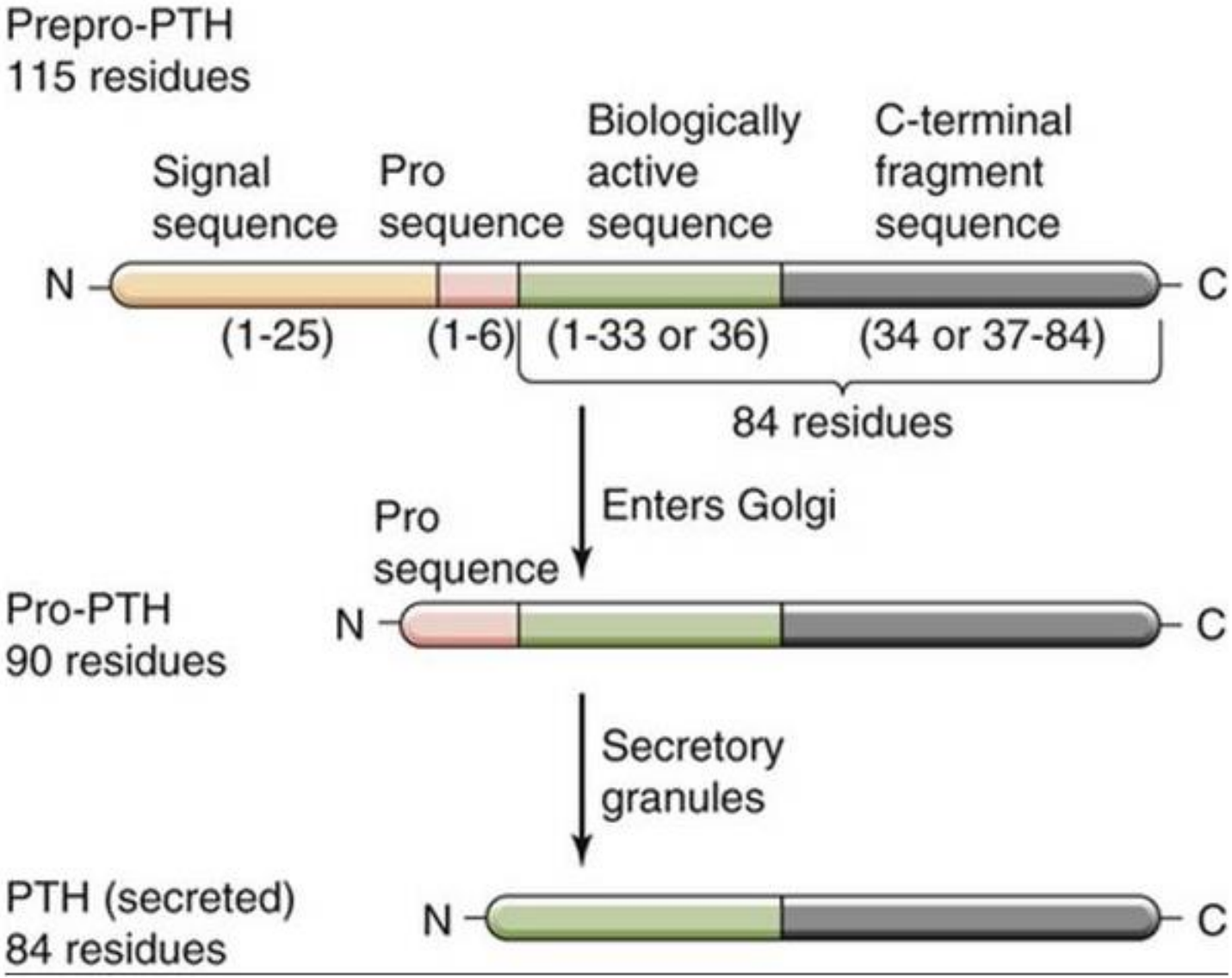
Parathyroid gland

- Four parathyroid glands
- Each is 3,6,2 cm
- 2 types of cells
- Chief cells and oxyphil cells



Synthesis of PTH

- Liniear polypeptide
- All 4 glands weigh less than 500g
- Synthesized as a part of larger molecules as Preprohormone
- Synthesized in roughER
- Active form is 84-amino acid PTH (Intact PTH)
- Major regulator of PTH secretion is ionized plasma calcium


Prepro-PTH
115 residues
Signal sequence
Pro sequence
Biologically active sequence
C-terminal fragment sequence
N
C
(1-25)
(1-6)
(1-33 or 36)
(34 or 37-84)
84 residues
Enters Golgi
Pro sequence
Pro-PTH
90 residues
N
C
Secretory granules
PTH (secreted)
84 residues
N
C

Metabolism of PTH

- Circulates free in plasma
- rapidly metabolized
- Half-life of 1-84 PTH is ~4 minutes

- PTH is cleaved into two principal fragments, a 33– or 36–amino-acid N-terminal peptide and a larger C-terminal peptide

- Virtually all the known biological activity of PTH resides in the N-terminal fragment

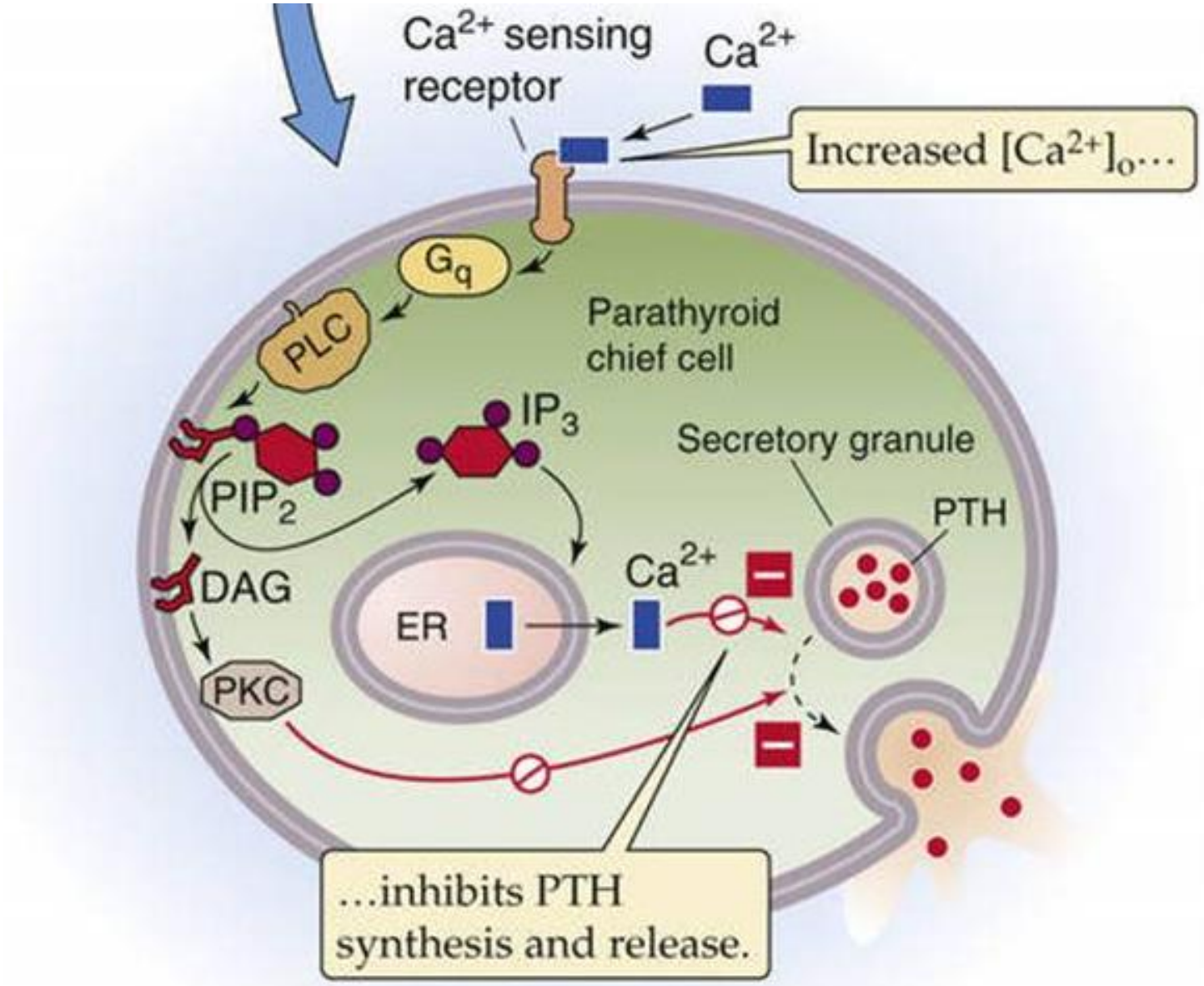
Regulation of secretion

- Major stimulus for PTH secretion is a decline in the concentration of Ca2+ in the blood (hypocalcemia) and ECF.

- Hypocalcemia also stimulates synthesis of new PTH.

- There is a Ca2+-sensing receptor (CaSR) that resides in the plasma membrane of the parathyroid cell

- CaSR is a member of the G protein–coupled receptor (GPCR) family

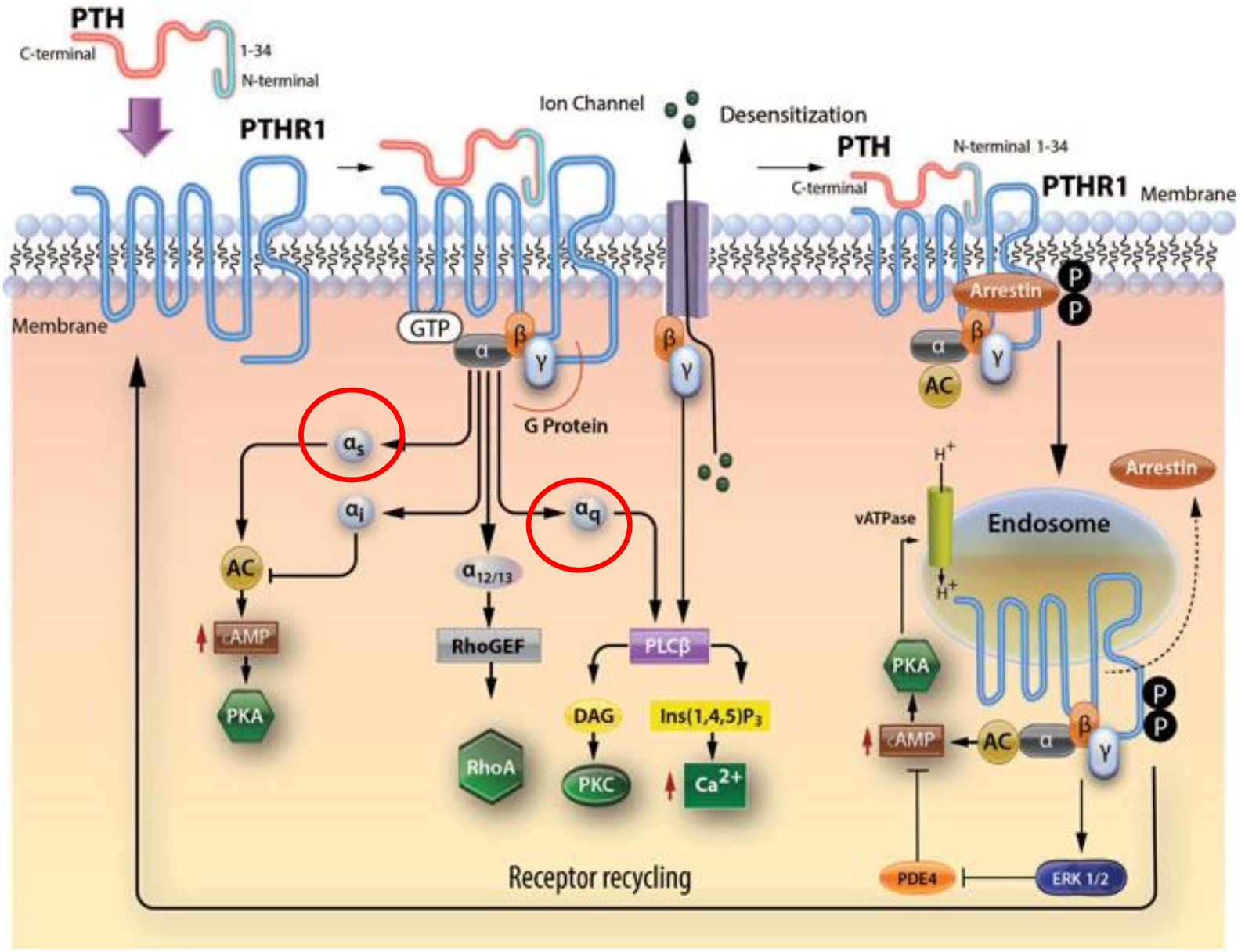

Ca2+ sensing receptor
Ca2+
Increased [Ca2+]o…
Gq
PLC
Parathyroid chief cell
IP3
PIP2
Secretory granule
PTH
DAG
ER
Ca2+
PKC
…inhibits PTH synthesis and release.

PTH Receptors

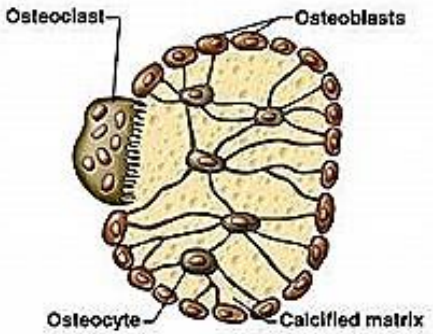
- PTH binds to the PTH 1R receptor (PTH1R).
- A second PTH receptor, PTH2R, has been identified.
- Kidney and bone have the greatest abundance of PTH1R.
- Within the kidney, PTH1R is most abundant in the proximal and distal convoluted tubules
- In bone, the preosteoblast and osteoblast appear to be the major target cells
- PTH1R is a GPCR that binds some N-terminal fragments of PTH, the biologically active 1-34 peptide, as well as the 1-84 intact PTH molecule

PTH Receptor activation

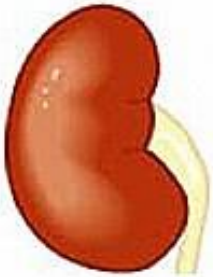
- PTH1R appears to be coupled to two heterotrimeric G proteins
- Binding of PTH to the receptor stimulates Gαs, which in turn activates adenylyl cyclase and thus releases cAMP and stimulates protein kinase A
- The activated PTH receptor also stimulates Gαq, which in turn stimulates phospholipase C to generate IP3 and DAG.
- The IP3 releases Ca2+ from internal stores, thus increasing [Ca2+]i and activating Ca2+-dependent kinases.


PTH
C-terminal
1-34
N-terminal
PTHR1
Membrane
Ion Channel
Desensitization
PTH
N-terminal 1-34
C-terminal
PTHR1
Membrane
GTP
α
β
γ
G Protein
Arrestin
P
P
AC
α_s
α_i
α_q
$\alpha_{12/13}$
cAMP
PKA
RhoGEF
RhoA
PLCβ
DAG
PKC
$Ins(1,4,5)P_3$
Ca^{2+}
H^+
vATPase
Endosome
Arrestin
PDE4
ERK 1/2
Receptor recycling

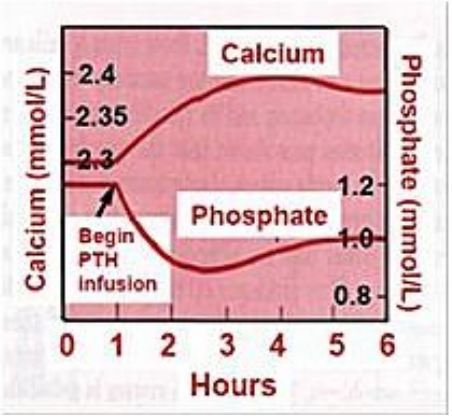
PTH Actions



- **Major target organs**
  - **bone**
    - ↑ Bone resorption by stimulating osteoclasts inhibiting osteoblasts
  - **kidney**
    - ↑Reabsorption of Ca^{++} and excretion of phosphate
  - **intestinal tract (indirect effect)**
    - ↑Absorption of calcium from the small intestine



- **Overall effect**
  - **increase plasma [Ca^{2+}]**
  - **decrease plasma [P_i]**



PTH action in the kidney

- PTH promotes

☐ Ca2+ reabsorption

☐ phosphate loss

☐ 1-hydroxylation of 25-hydroxyvitamin D

Stimulation of Ca2+ Reabsorption

- A key action of PTH is to promote the reabsorption of Ca2+ in the thick ascending limb (TAL) and distal convoluted tubule (DCT) of the kidney
- Most of the ~25 mmol of Ca2+ filtered each day is reabsorbed in the proximal tubule (~65%) and TAL (~25%).
- The distal nephron is responsible for reabsorbing an additional 5% to 10% of the filtered load of Ca2+, with ~0.5% of the filtered load left in the urine.
- When PTH stimulates distal Ca2+ reabsorption, it greatly decreases the amount of Ca2+ excreted in the urine (usually 4 to 5 mmol/day) and tends to raise plasma [Ca2+]

Inhibition of Phosphate Reabsorption

- PTH reduces phosphate reabsorption in the proximal tubule
- Produces a characteristic phosphaturia and decreasing plasma phosphate levels

PTH on 1,25 DHC

- PTH is to stimulate the 1-hydroxylation of 25-hydroxyvitamin D in the mitochondria of the proximal tubule

- 1,25-dihydroxyvitamin D is the most biologically active metabolite of dietary or endogenously produced vitamin D

Actions of 1,25-dihydroxyvitamin D

- (1) enhancement of renal Ca2+ reabsorption
- (2) enhancement of Ca2+absorption by the small intestine
- (3) modulation of the movement of Ca2+ and phosphate in and out of bone

PTH Effects on Kidney

1

- ↓the loss of Ca++ ions in the urine by **stimulating Ca++ reabsorption**
- **inhibits phosphate reabsorption**

↑Ca
↓ PO4

2

- **stimulate production of 1,25(OH)2D**

Bone and PTH

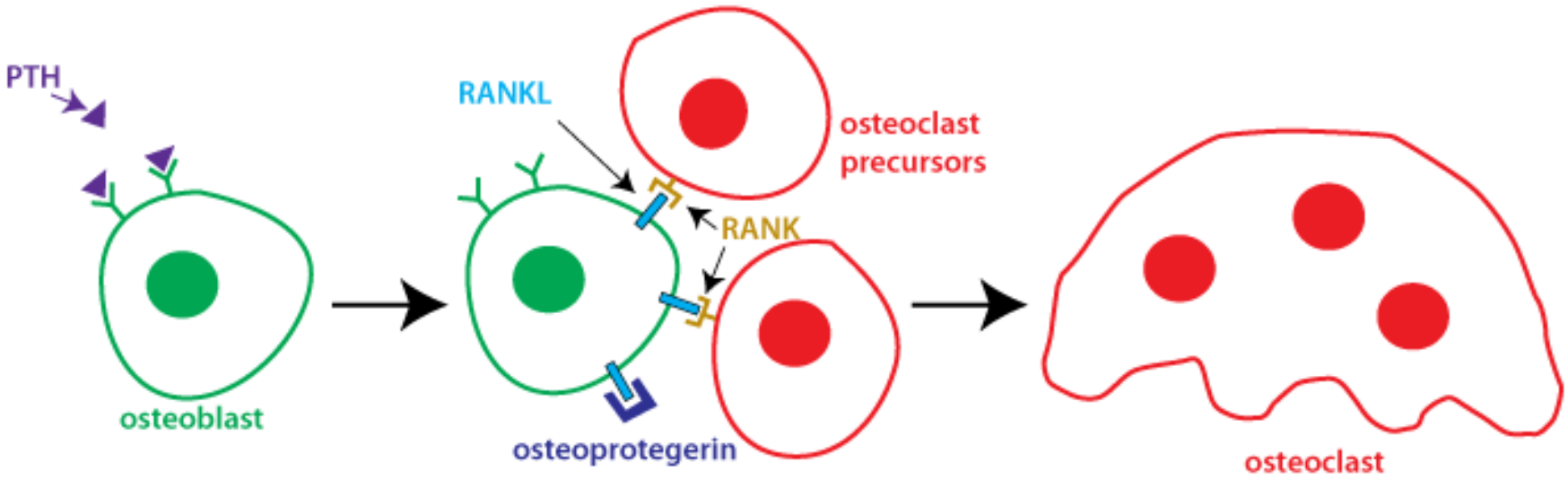
- PTH promotes both bone resorption and bone synthesis.
- The net effect of persistent increases of PTH on bone is to stimulate bone resorption, increasing plasma [Ca2+].

- Osteoblasts express abundant surface receptors for PTH; osteoclasts do not.
- Because osteoclasts lack PTH receptors, PTH by itself cannot regulate the coupling between osteoblasts and osteoclasts.

Bone and PTH

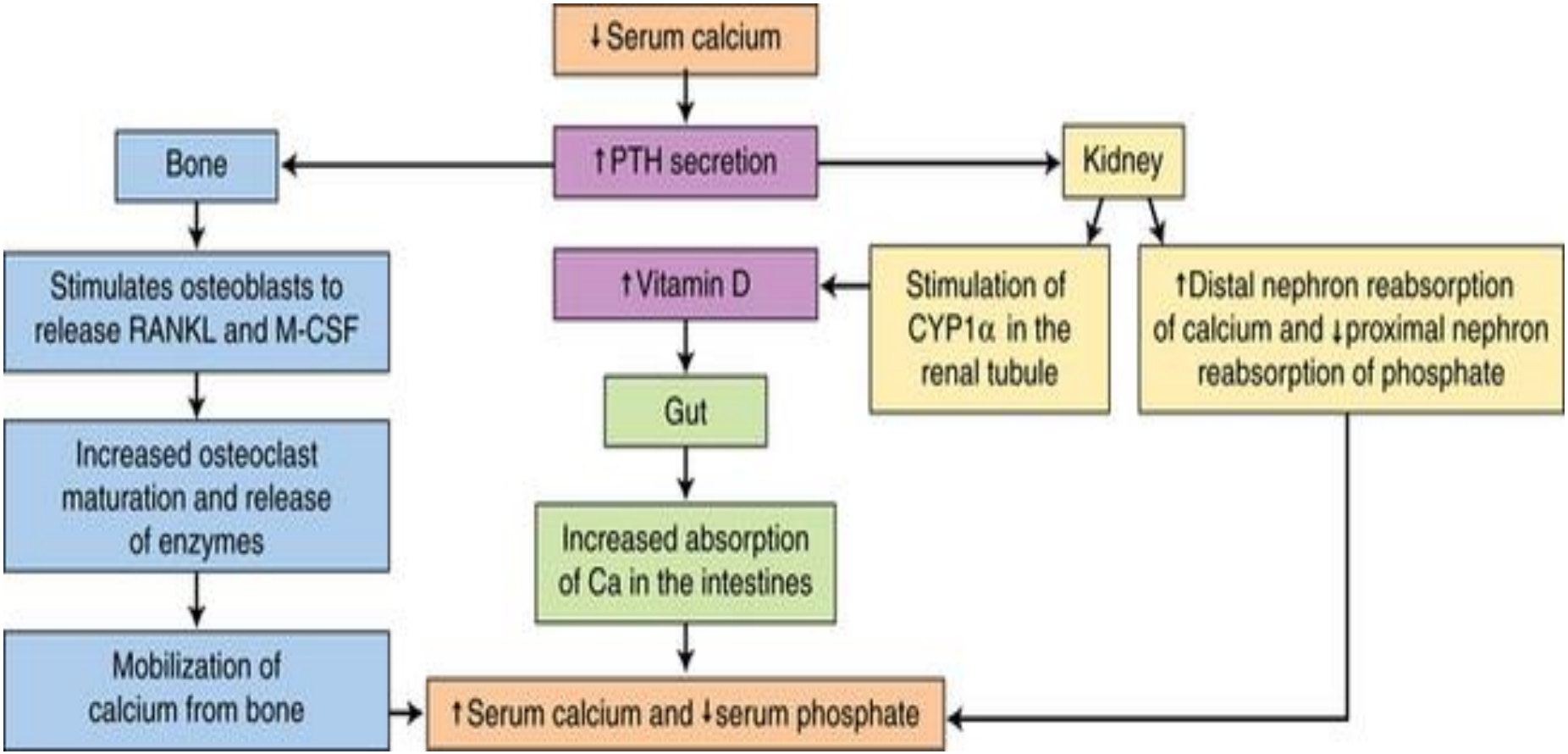
- PTH acts on osteoblasts and osteoclast precursors to induce the production of several cytokines that increase both the number and the activity of bone-resorbing osteoclasts.

- PTH causes osteoblasts to release agents such as M-CSF and stimulates the expression of RANKL, actions that promote the development of osteoclasts .


PTH
osteoblast
RANKL
osteoclast
precursors
RANK
osteoprotegerin
osteoclast

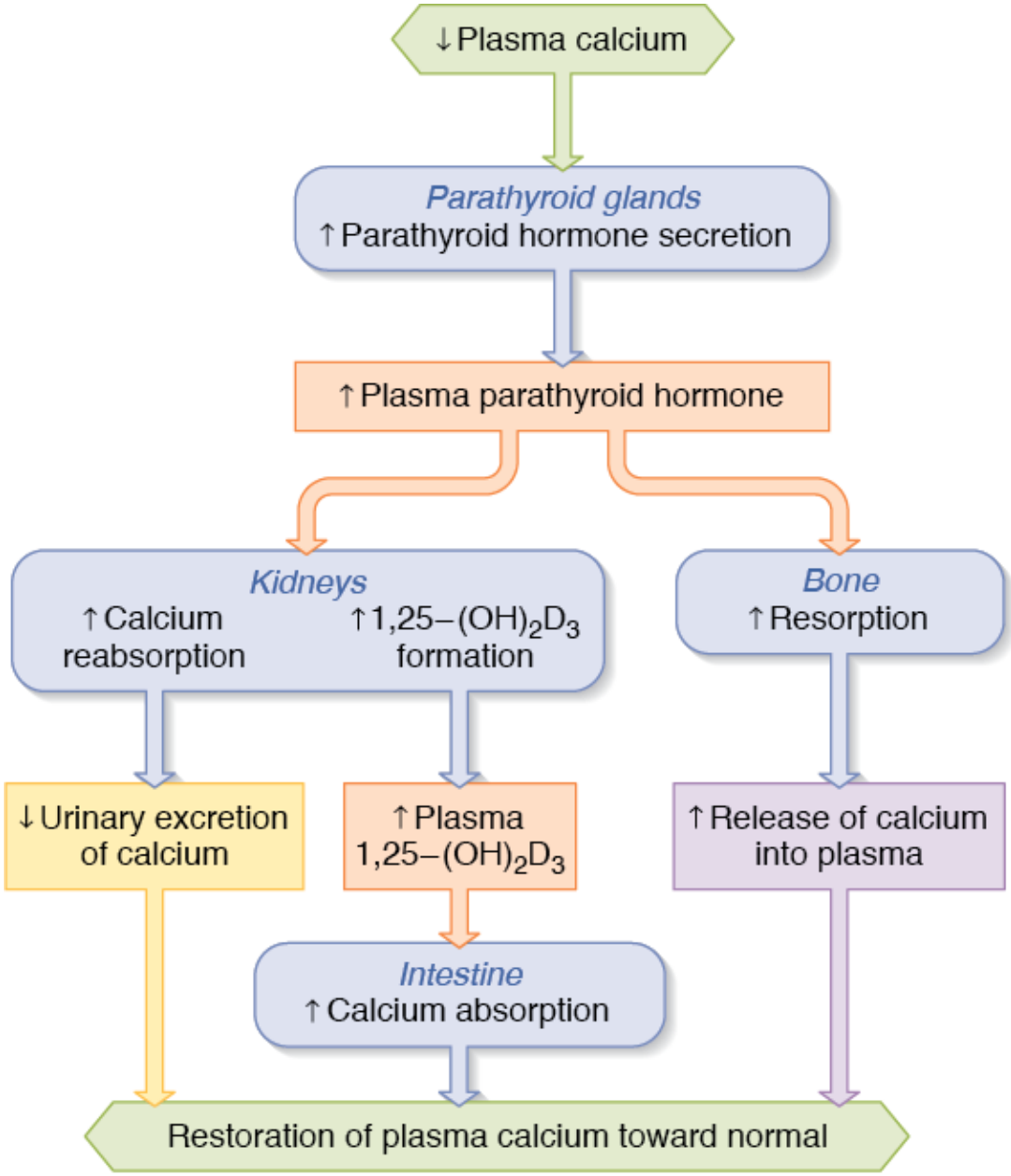
Bone Deposition by PTH

- Whereas persistent increases in PTH favor net resorption, intermittent increases in plasma [PTH] have predominately bone-synthetic effects, inducing higher rates of bone formation and mineral apposition.


↓Serum calcium
↑PTH secretion
Bone
Kidney
Stimulates osteoblasts to release RANKL and M-CSF
Increased osteoclast maturation and release of enzymes
Mobilization of calcium from bone
↑Vitamin D
Stimulation of CYP1α in the renal tubule
↑Distal nephron reabsorption of calcium and ↓proximal nephron reabsorption of phosphate
Gut
Increased absorption of Ca in the intestines
↑Serum calcium and ↓serum phosphate

PTH rP

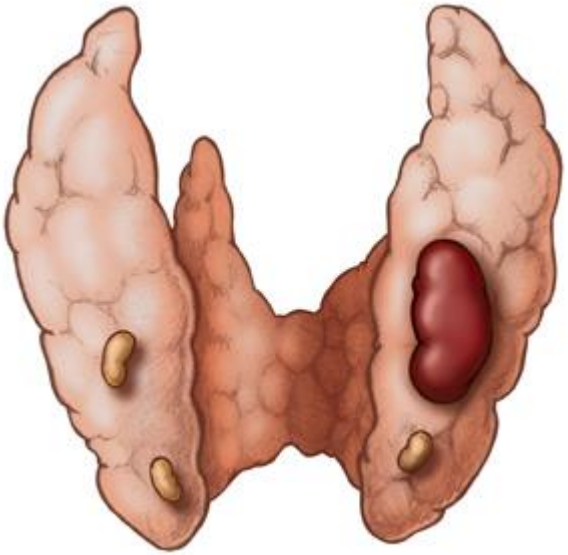
- Protein with PTH activity
- Produced by many differnt tissues in body
- Physiologic functional differnces to PTH
- Acts on the PTH receptors
- Marked effect on growth of cartilage in utero
- Found in placenta,brain,keatinocytes



Source: Barrett KE, Barman SM, Boitano S, Brooks HL:
Ganong's Review of Medical Physiology: www.accessmedicine.com

Hyperparathyroidism

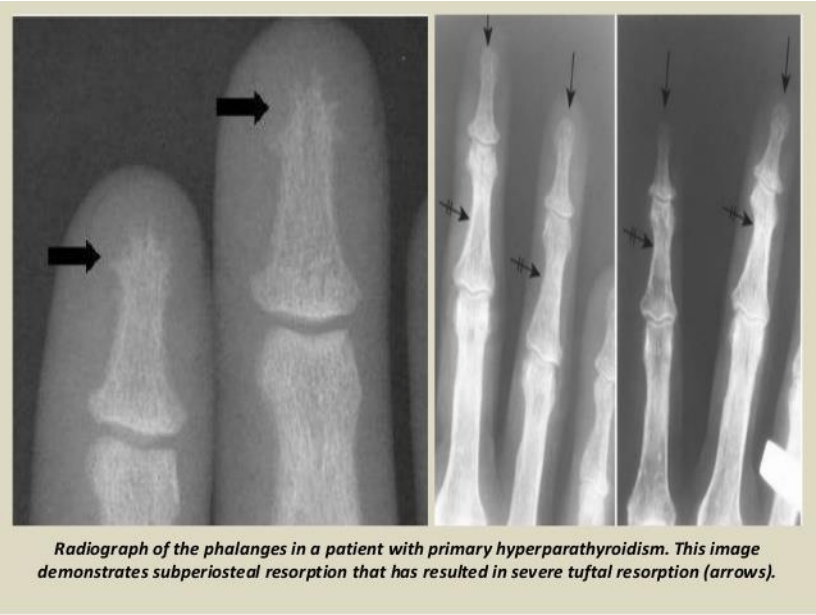
Symptoms
Stones
Bones
Abdominal groans



Primary hyperparathyroidism

- ***Parathyroid hyperplasia.***
- ***Parathyroid adenoma.***
- ***Parathyroid carcinoma.***
- It may be part of **MEN** (Multiple Endocrine Neoplasia) syndromes.

MEN type I 3P	MEN type II PTP
•**P**arathyroid adenoma, •**P**ituitary adenoma & •**P**ancreatic islet cell tumor	•**P**arathyroid adenoma, •**T**hyroid medullary carcinoma & •**P**heocrhomocytoma

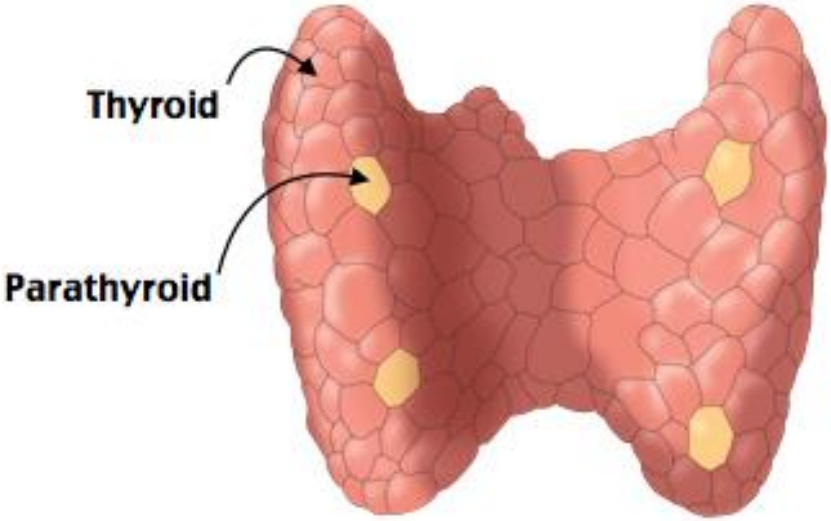


Radiograph of the phalanges in a patient with primary hyperparathyroidism. This image demonstrates subperiosteal resorption that has resulted in severe tuftal resorption (arrows).

Peper pot skull

Hypoparathyroidism

↓PTH = ↓Calcium



Causes

- Thyroid surgery
- Parathyroid surgery
- Autoimmune
- Infiltrative
- Familial
- Idiopathic

Hypocalcemia

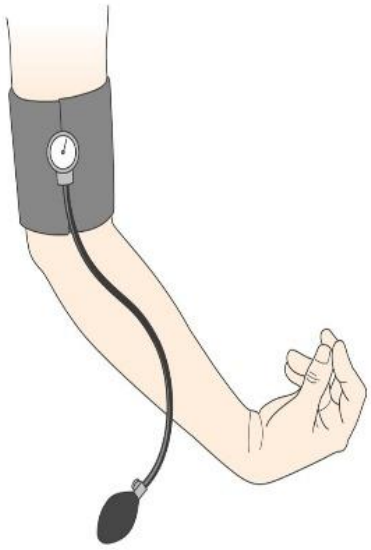
- Tetany
- Chvostek sign (Contraction of facial muscles after tapping facial nerve)
- Trousseau sign (Induction of carpal pedal spasm)
- Paresthesias (Fingertips/perioral)
- Prolonged QT interval

Signs of hypocalcemia

Trousseau sign:
(very uncomfortable and painful)

- A blood pressure cuff is inflated to 20mm Hg above systolic blood pressure level.
- arterial blood flow to the hand is occluded for 3 to 5 minutes.
- Carpopedal spasm:
  * flexion at the wrist
  * flexion at the MCP joints
  * extension of the IP joints
  * adduction thumbs/fingers

A. Positive Chvostek's Sign



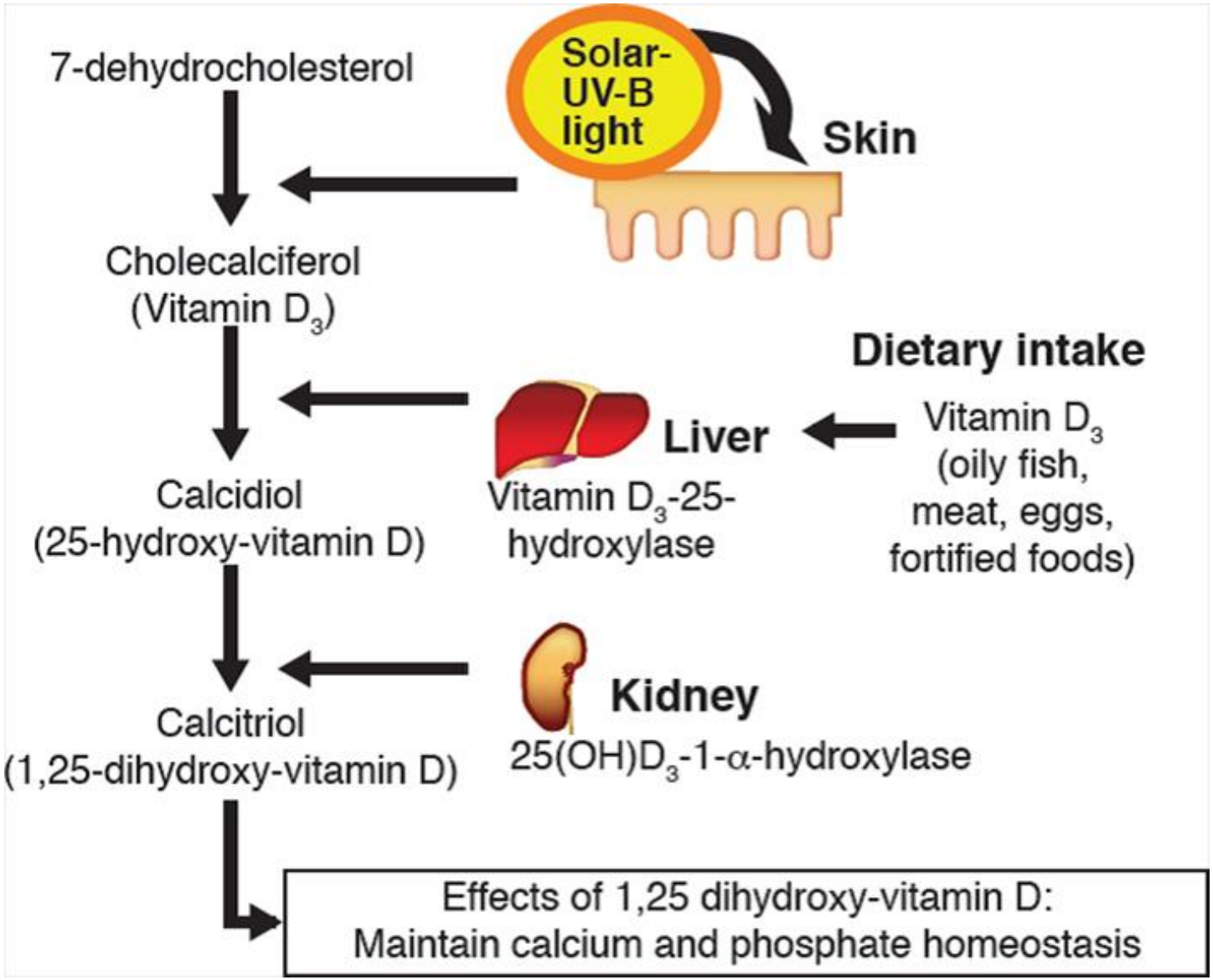
B. Positive Trousseau's Sign

Familial Hypocalciuric Hypercalcemia

- Caused by an inactivating MUTATION of calcium-sensing receptors.
- Sensitivity of receptors to calcium DECREASES, requiring higher calcium levels to suppress PTH secretion.
- Fractional excretion of calcium is lower than 1%, despite hypercalcemia.
- Hypercalcemia in FHH has a generally benign course and is resistant to medications, except for some cases successfully treated with the calcimimetic agent cinacalcet.

Vitamin D

- Vitamin D exists in the body in two forms, vitamin D3 and vitamin D2
- Group of sterols
- Vitamin D3 can be synthesized from the 7-dehydrocholesterol that is present in the skin
- Vitamin D2 is obtained only from the diet, largely from vegetables.
- Vitamin D3 and vitamin D2 differ only in the side chains of ring D.


7-dehydrocholesterol
Solar-UV-B light
Skin
Cholecalciferol (Vitamin D_3)
Dietary intake
Liver
Vitamin D_3 (oily fish, meat, eggs, fortified foods)
Calcidiol (25-hydroxy-vitamin D)
Vitamin D_3-25-hydroxylase
Kidney
Calcitriol (1,25-dihydroxy-vitamin D)
25(OH)D_3-1-α-hydroxylase
Effects of 1,25 dihydroxy-vitamin D:
Maintain calcium and phosphate homeostasis

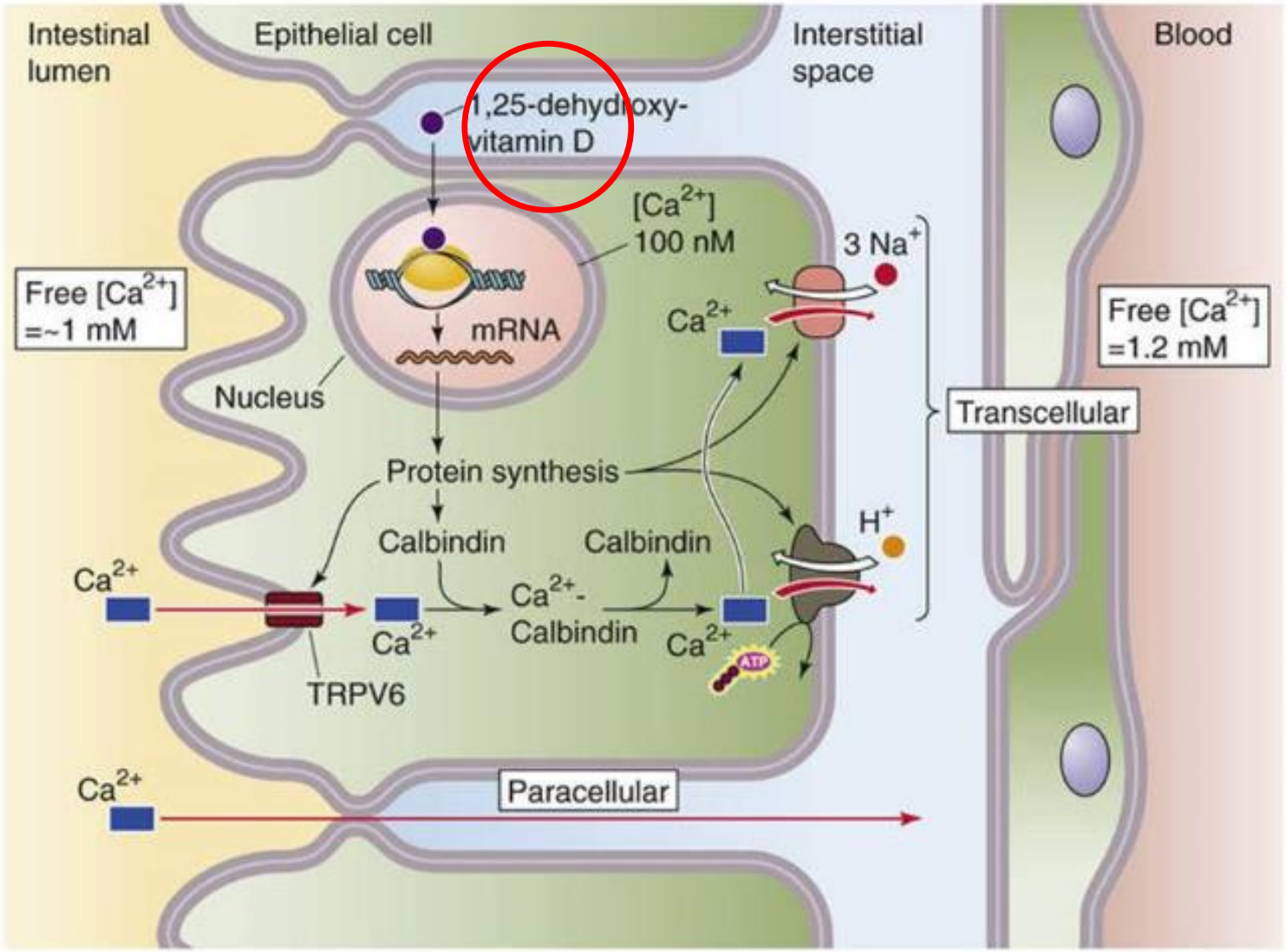
Vitamin D

- Vitamin D is fat soluble, but water insoluble.
- Its absorption from the intestine depends on its solubilization by bile salts .
- In the circulation, vitamin D is found either solubilized with chylomicrons or associated with a vitamin D–binding protein.
- Most of the body stores of vitamin D are located in body fat.
- The body's pools of vitamin D are large, and only 1% to 2% of the body's vitamin D is turned over each day.
- Several years of very low dietary intake are required before the endogenous pools are depleted and deficiency develops.
- The actions of vitamin D on the small intestine, bone, and kidney serve to prevent any abnormal decline or rise in plasma [Ca2+].

Small Intestine

- 1,25-dihydroxyvitamin D increases the production of several proteins that enhance Ca^{2+} absorption.
- Eg-Calmodulin

- Also stimulates phosphate absorption by the small intestine


A INTESTINAL Ca2+ ABSORPTION
Intestinal lumen
Epithelial cell
Interstitial space
Blood
1,25-dehydroxy-vitamin D
[Ca2+] 100 nM
Free [Ca2+] =~1 mM
mRNA
Nucleus
Protein synthesis
Calbindin
Calbindin
Ca2+-Calbindin
Ca2+
Ca2+
Ca2+
Ca2+
TRPV6
3 Na+
H+
ATP
Transcellular
Free [Ca2+] =1.2 mM
Paracellular

Kidney

- Act synergistically with PTH to enhance Ca2+ reabsorption in the DCT
- vitamin D promotes phosphate reabsorption in the kidney
- Directly inhibits the 1-hydroxylation of vitamin D, establishing a negative-feedback loop.

Bone

- Major effects of vitamin D on bone are indirect:
- the action of vitamin D on both the small intestine and the kidneys makes more Ca2+ available to mineralize previously unmineralized osteoid.

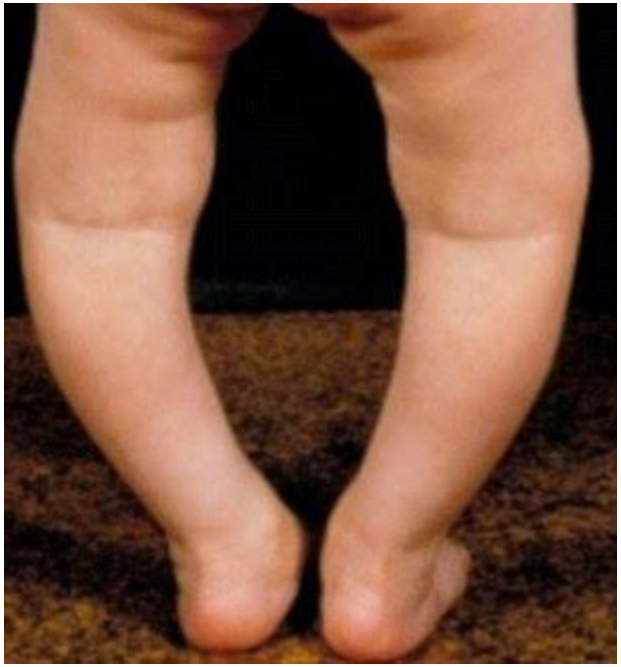
- The direct effect of vitamin D on bone -increases both osteoblastic and osteoclastic differentiation

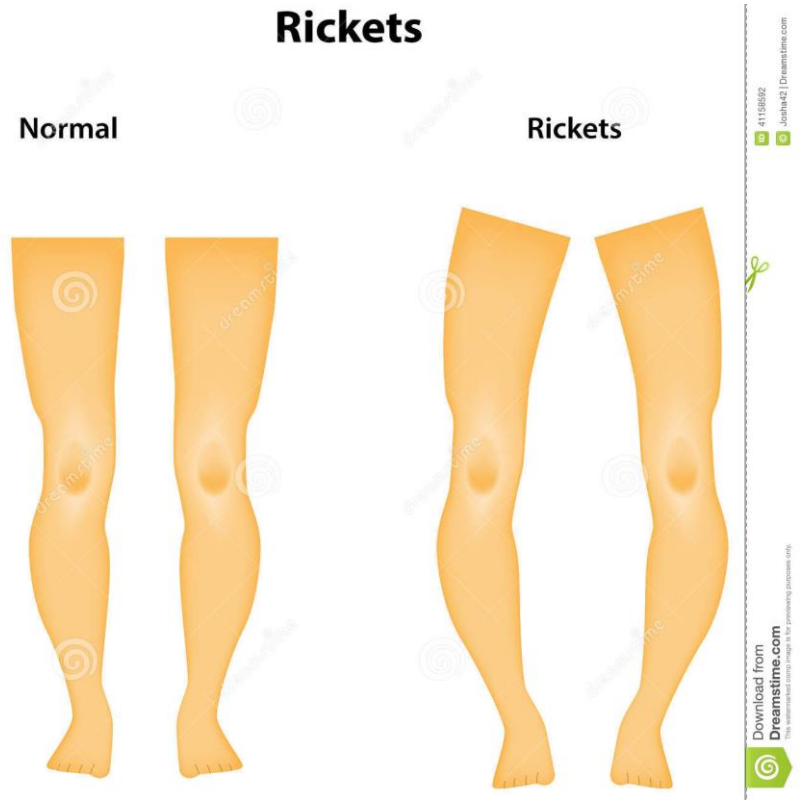
- Vitamin D simply increases bone turnover.

Rickets

- Deficiency of vitamin D in children produces the disease rickets, in which bone has abnormal amounts of unmineralized osteoid.
- Both cortical and trabecular bone are involved.
- The lack of mineralization diminishes bone rigidity and leads to a characteristic bowing of the long bones of the legs of affected children.

Rickets





Osteomalacia

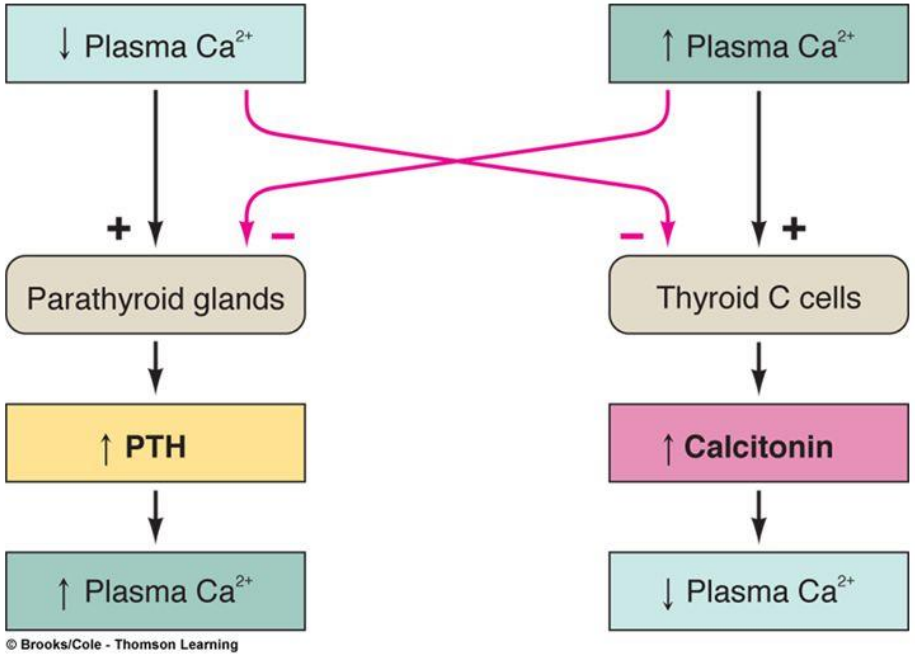
- In adults, vitamin D deficiency produces a disorder called osteomalacia.
- Because the longitudinal growth of the long bones has been completed in adults, bowing of weight-bearing bones does not occur.
- Instead, the increased unmineralized osteoid content of bone causes a decline in bone strength.
- Affected individuals are more prone to the development of bone fractures.


Osteomalacia
Normal Bone

Calcitonin

- Calcitonin is a 32–amino-acid peptide hormone made by the clear or C cells of the thyroid gland
- Stored in secretory vesicles within the C cells, and its release is triggered by a rise in the extracellular [Ca2+] above normal.
- Calcitonin inhibits the resorptive activity of the osteoclast, thus slowing the rate of bone turnover
- It reduces plasma calcium levels
- Medullary Thyroid carcinoma produces Calcitonin

Negative-feedback Loops Controlling Parathyroid Hormone (PTH) and Calcitonin Secretion



Physiology of Bone

- Dense cortical bone and the more reticulated trabecular bone are the two major bone types

- Bone consists largely of an extracellular matrix composed of proteins and hydroxyapatite crystals, in addition to a small population of cells.

- Bone has three types of bone cells

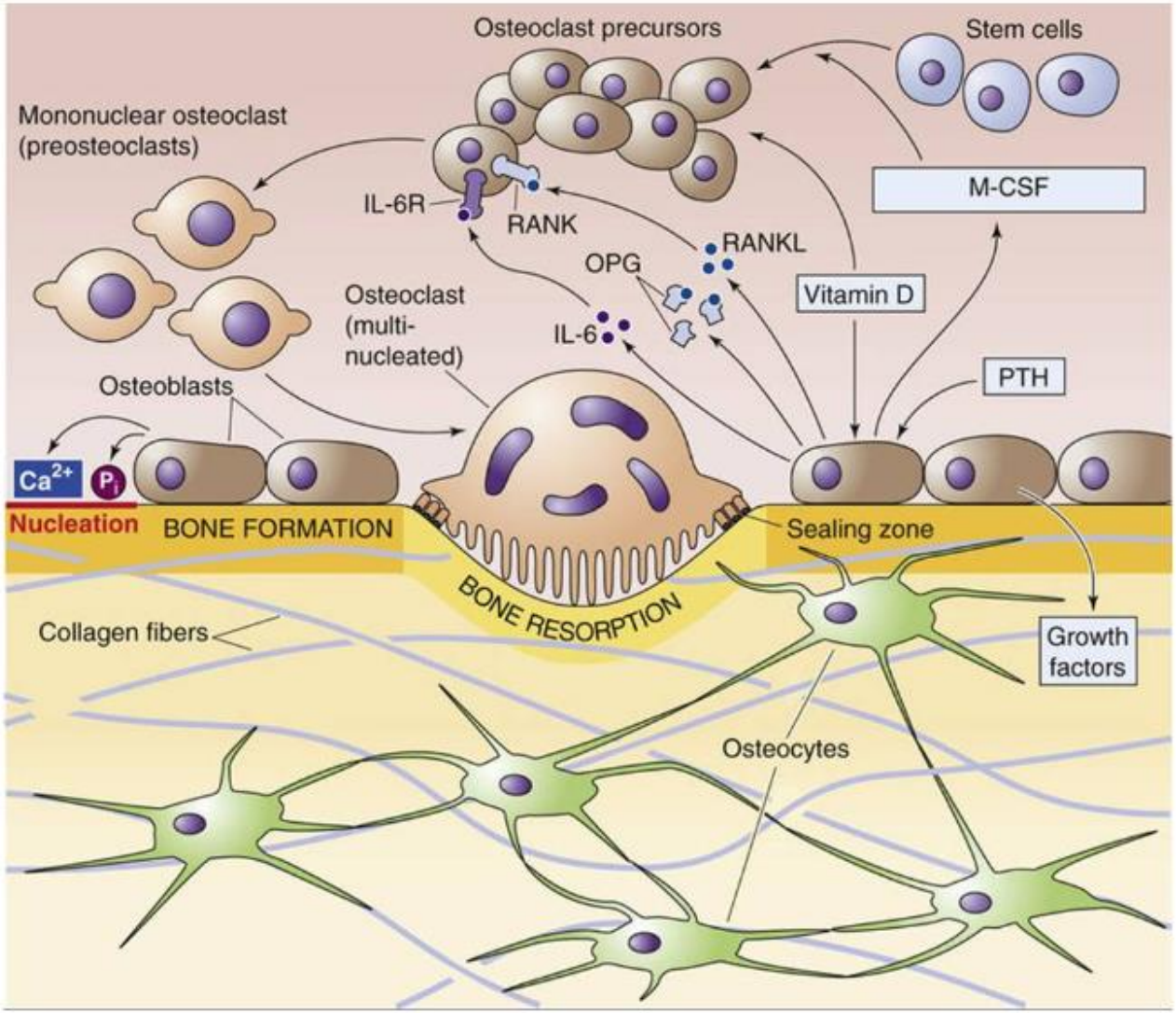
Bone cells

- Osteoblasts promote bone formation.
- Osteoblasts and preosteoblasts are the principal target cells for PTH's action to stimulate bone growth.
- Osteoclasts promote bone resorption and are found on the growth surfaces of bone. Their activity is increased by cytokines, with RANK ligand being particularly important.

- Osteocytes are found within the bony matrix and are derived from osteoblasts that have encased themselves within bone.

- Bone remodeling consists of a carefully coordinated interplay of osteoblastic, osteocytic, and osteoclastic activities.

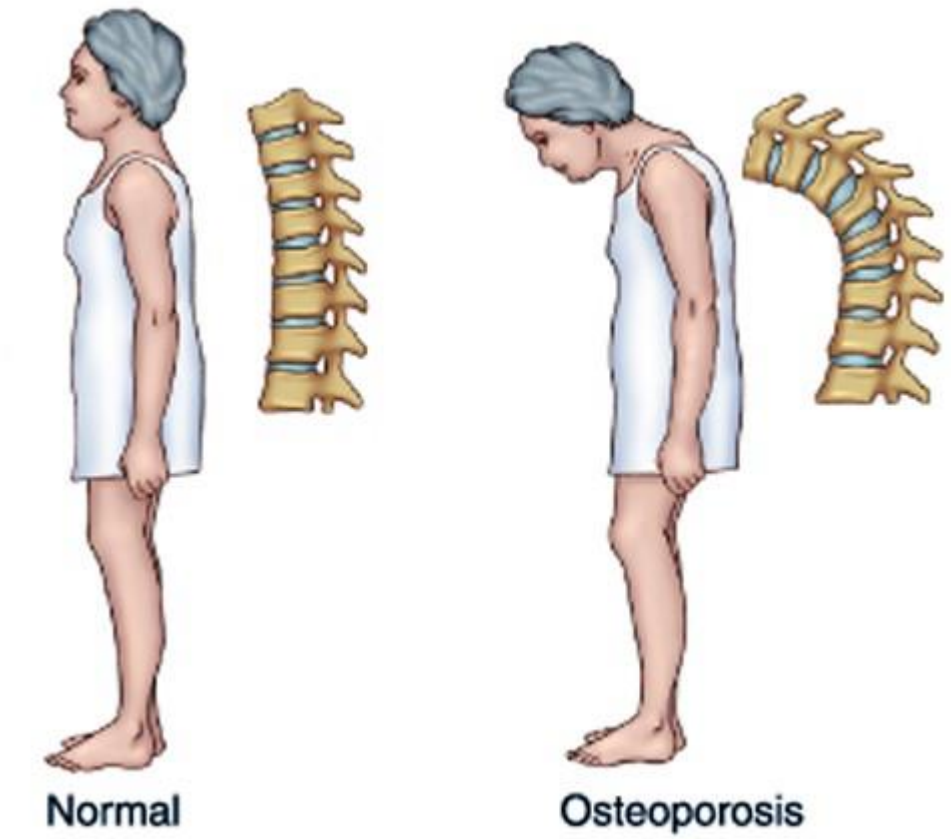
Bone formation and resorption



Osteoporosis

- Due to defecitive bone mineralization
- Relative excess of osteoclastic function
- Loss of bone matrix and increase in fracture incidence
- Fractures in spine,hip and forearm are common
- Most commonly in post menopausal age due to loss of estrogen

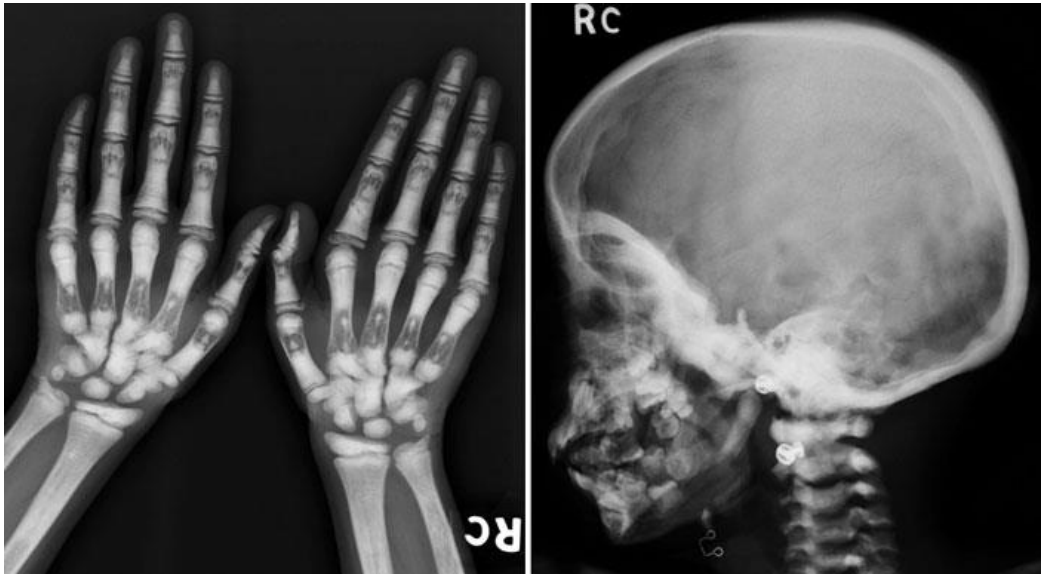
Widow's hump



Osteopetrosis

- Osteoclasts are defecticve, thereore Osteoblasts are unopposed

- Increase in bone density



Summary

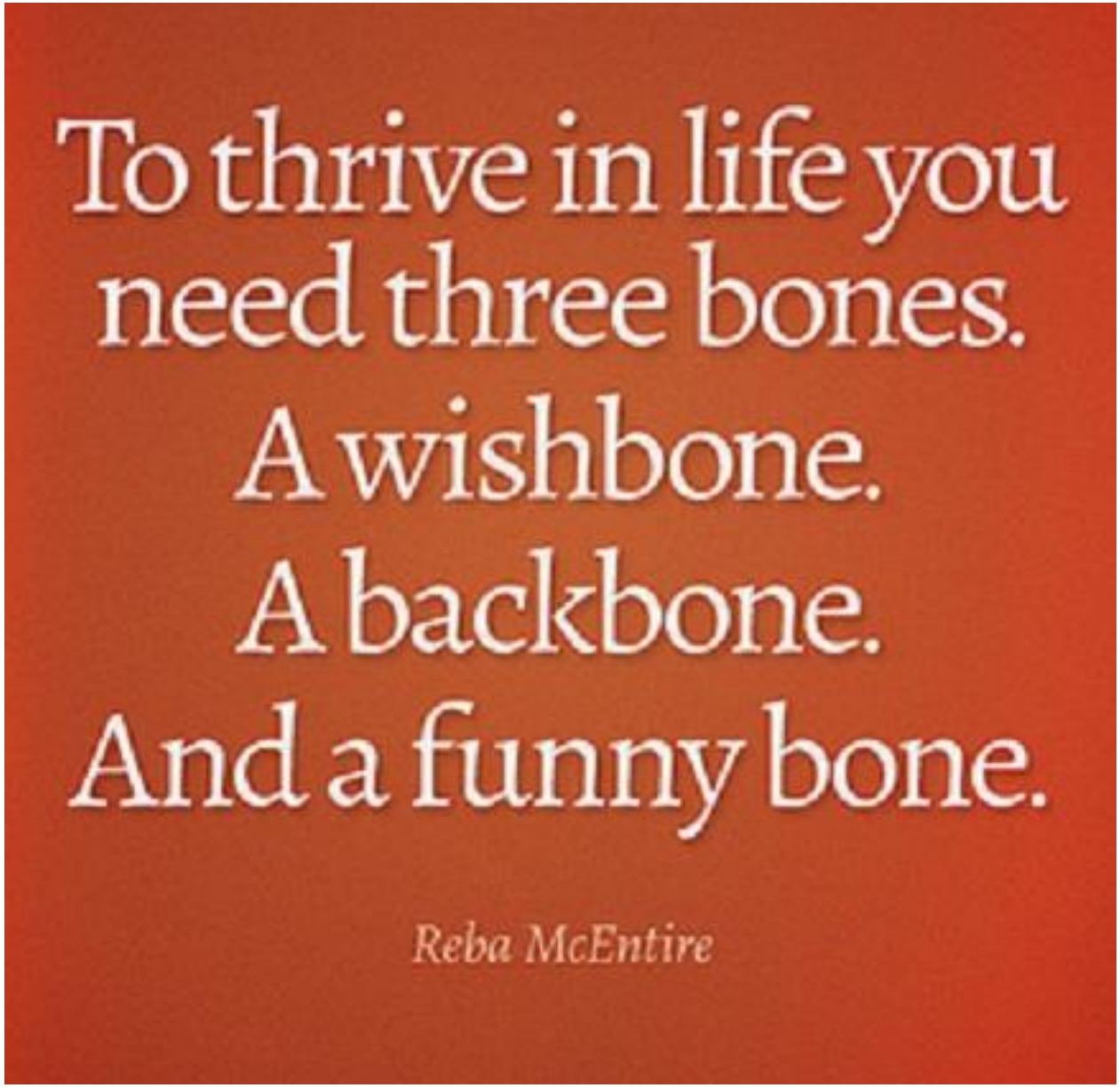
- Calcium metabolism in body is maintained by PTH,Vtamin D and calcitonin
- PTH and vitamin D have actions on bone,kidney and intestine
- Defects in meatabolism leads to various disease conditions

True /False regarding PTH

- PTH is synthesiszed in C cells
- Active unit of PTH is the N terminal
- Hypercalcemia will enhance PTH secretion
- CaSR are present in Chief cells in parathyroid glands.
- PTH causes phosphatiuria
- Hyperparathyroidism leads to forearm fractures

T/F regarding Vitamin D

- Vitamin D is a hormone
- Active form of Vitamin D is D3
- Increase the absorption of calcium and phophate from kidney
- Vitamin D deficeincy leads to osteomalacia in adults
- Increases bone formation


To thrive in life you need three bones.
A wishbone.
A backbone.
And a funny bone.
Reba McEntire