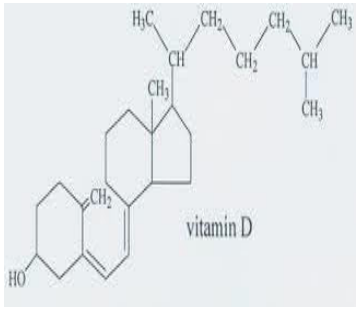
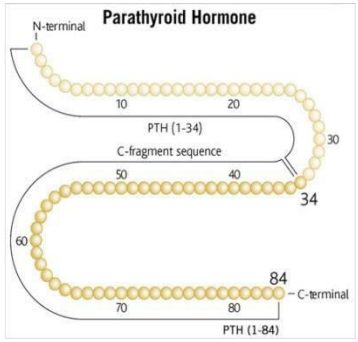
CALCIUM METABOLISM

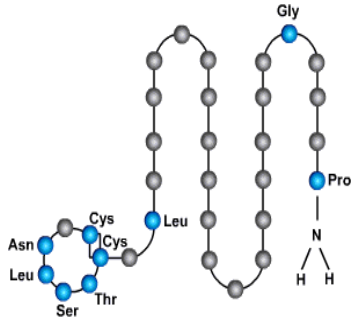
OBJECTIVES

- Calcium and phosphate metabolism
- Role of vitamin D, PTH and calcitonin in calcium homeostasis
- Causes and effects of hypo & hyper- parathyroidism

3HORMONES

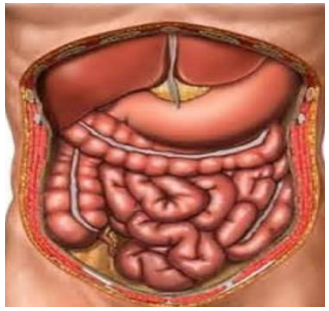




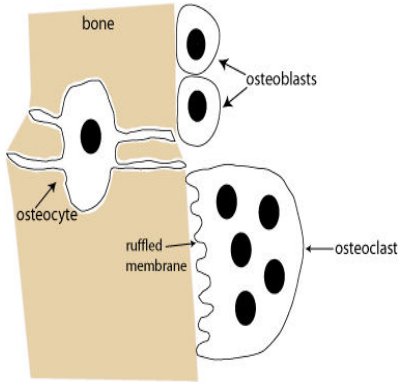


Calcitonin

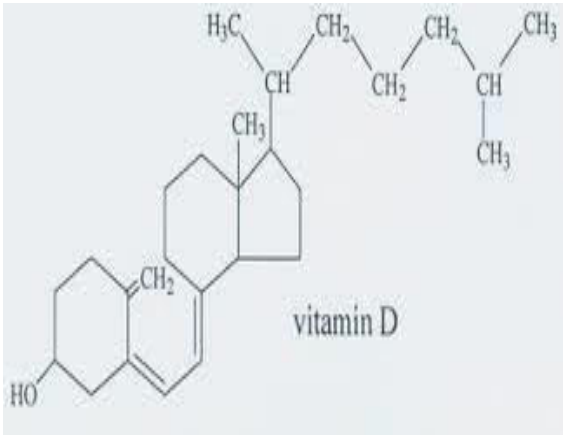
3 TISUUES

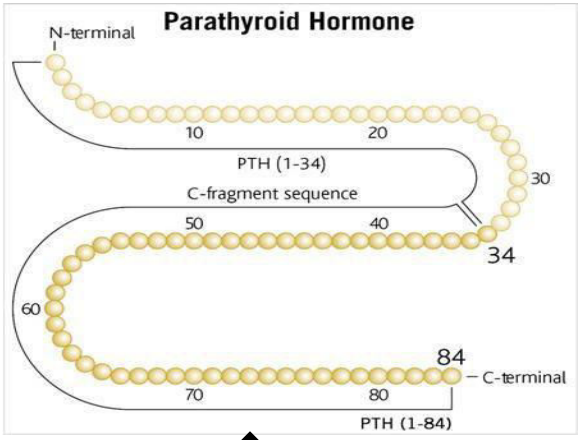


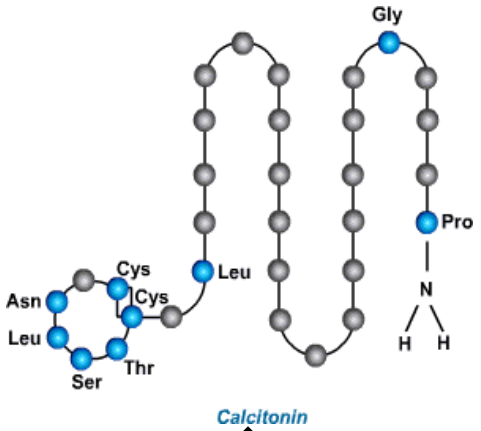
3 CELLS

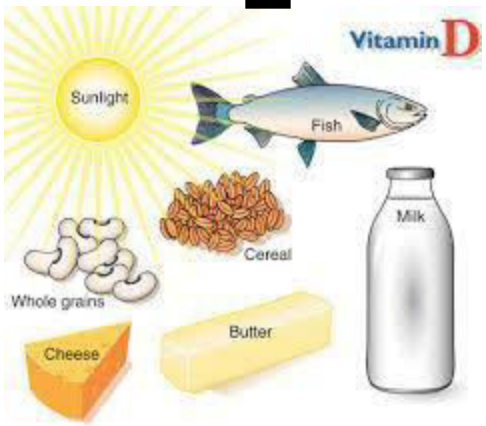


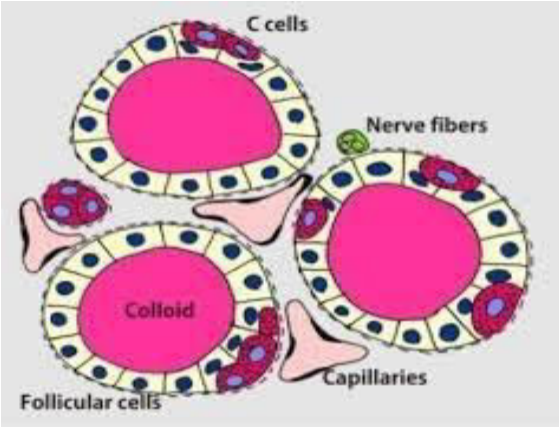
Vitamin D, PTH and calcitonin











Calcium

- Body contains 1000g of calcium
- 99% in bone and teeth
- Plasma level= 10mg/dl

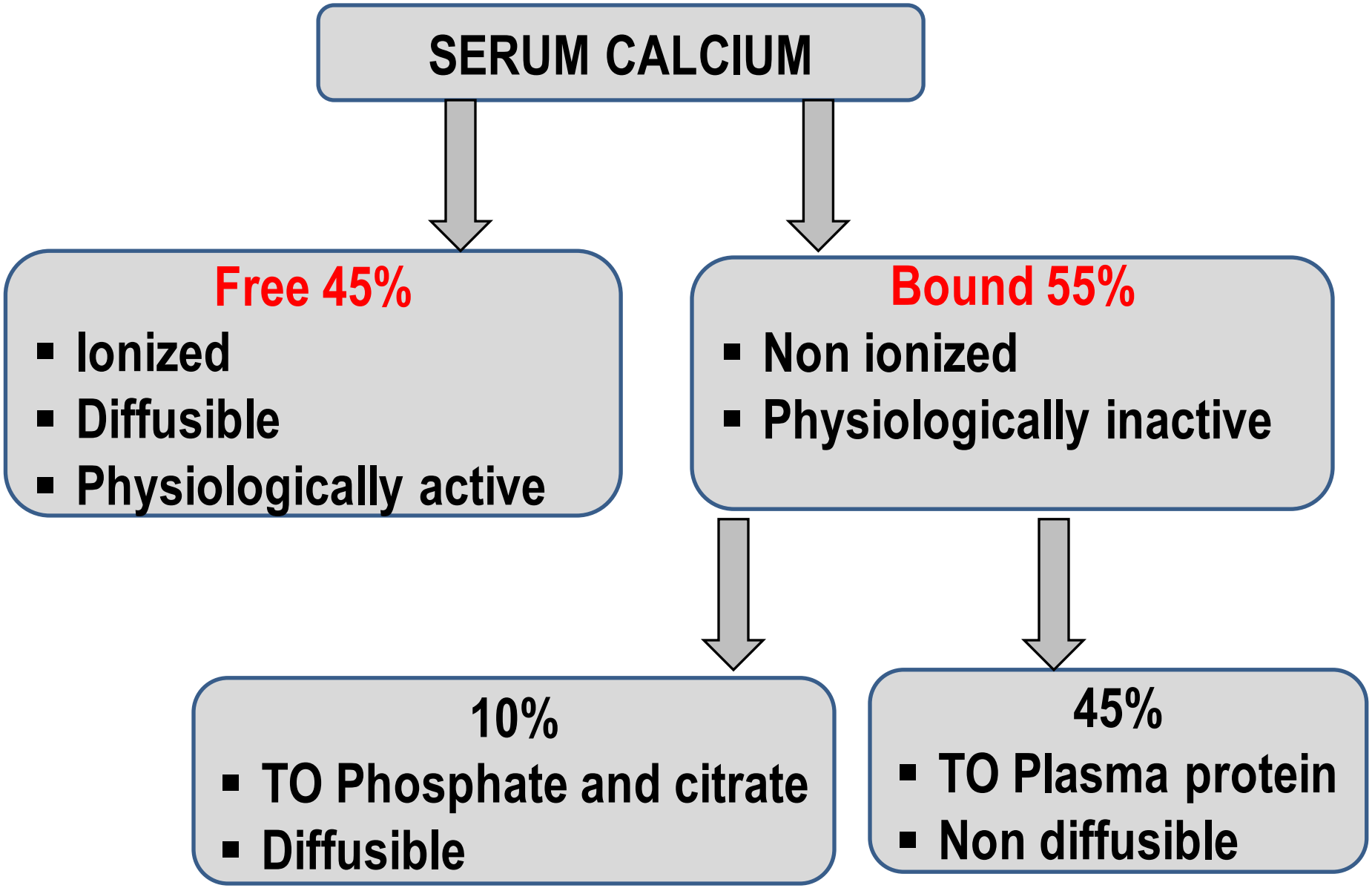
Function

A) Calcium salts

1. Hard tissue (bone, teeth)
2. Milk

B) Ionized Ca^{2+}

1. Blood coagulation
2. 2nd messenger
3. Exocytosis (protein hormones and chemical transmitters)
4. Nerve: excitability: Excitability α $\frac{1}{Ca^{2+}}$ ($\mathbf{Ca^{2+}}$ & mg^{2+})
5. Muscle: contraction
6. Cardiac muscle: rhythmicity

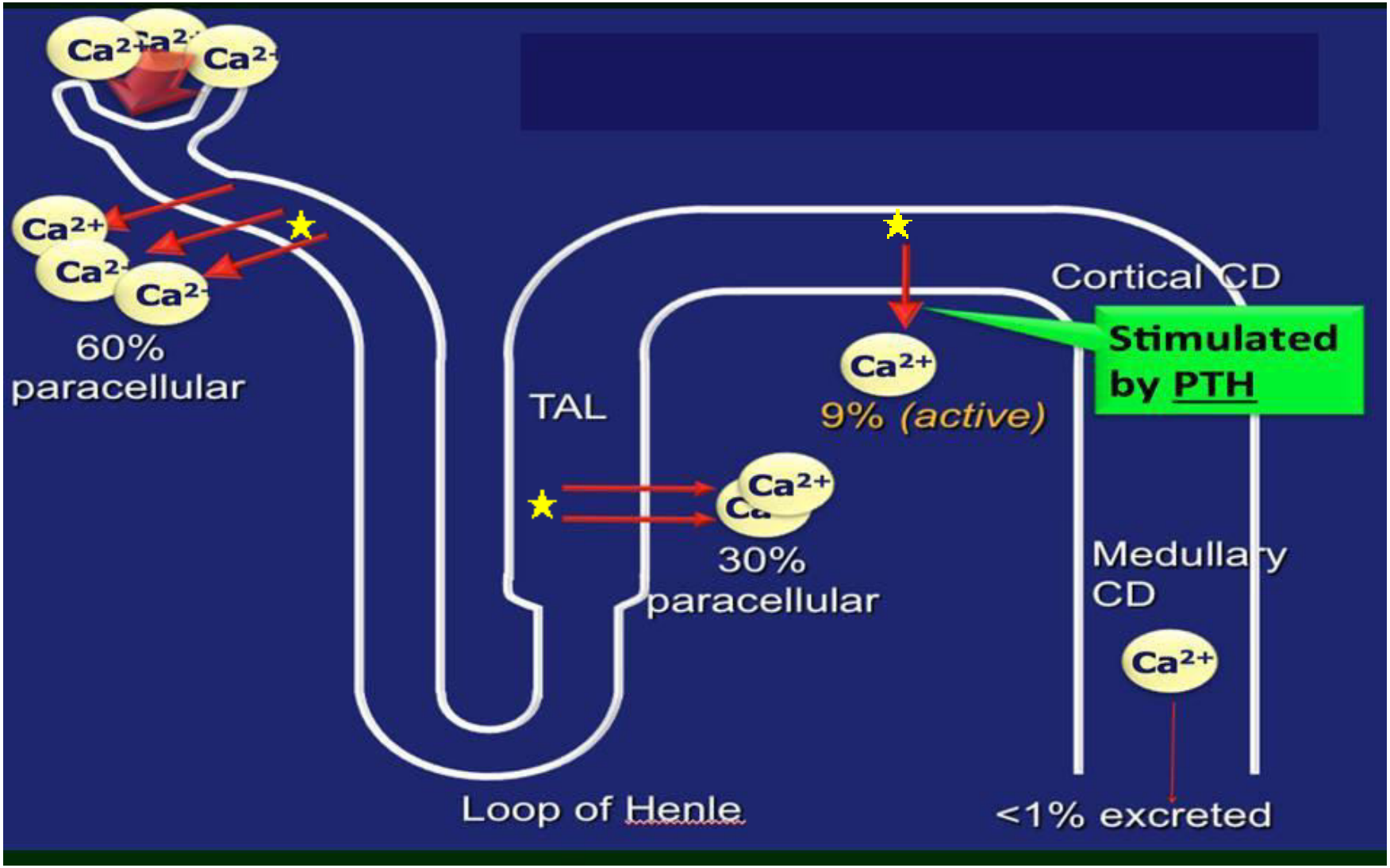

SERUM CALCIUM
Free 45%
Ionized
Diffusible
Physiologically active
Bound 55%
Non ionized
Physiologically inactive
10%
TO Phosphate and citrate
Diffusible
45%
TO Plasma protein
Non diffusible

Calcium absorption

- **In upper small intestine (duodenum)**
  - Ca^{2+} is soluble in acid
  - Divalent metallic transporter
  - Competition between Ca^{2+} and Fe^{2+}

↑**Absorption**	↓ **Absorption**
▪ Acidic food ▪ AA (protein) ▪ Acidic milk products (yogurt) ▪ Active form of vitamin D3	▪ Oxalate ▪ Phosphate ↓ Insoluble salts

Renal handling of calcium



Phosphorus

- Adult man 700g of P (1% of B.W.)
- 85% in bone
- Plasma level 2.5-4.5mg/dl

✺ **Function**

A) Bone

B) Every cell

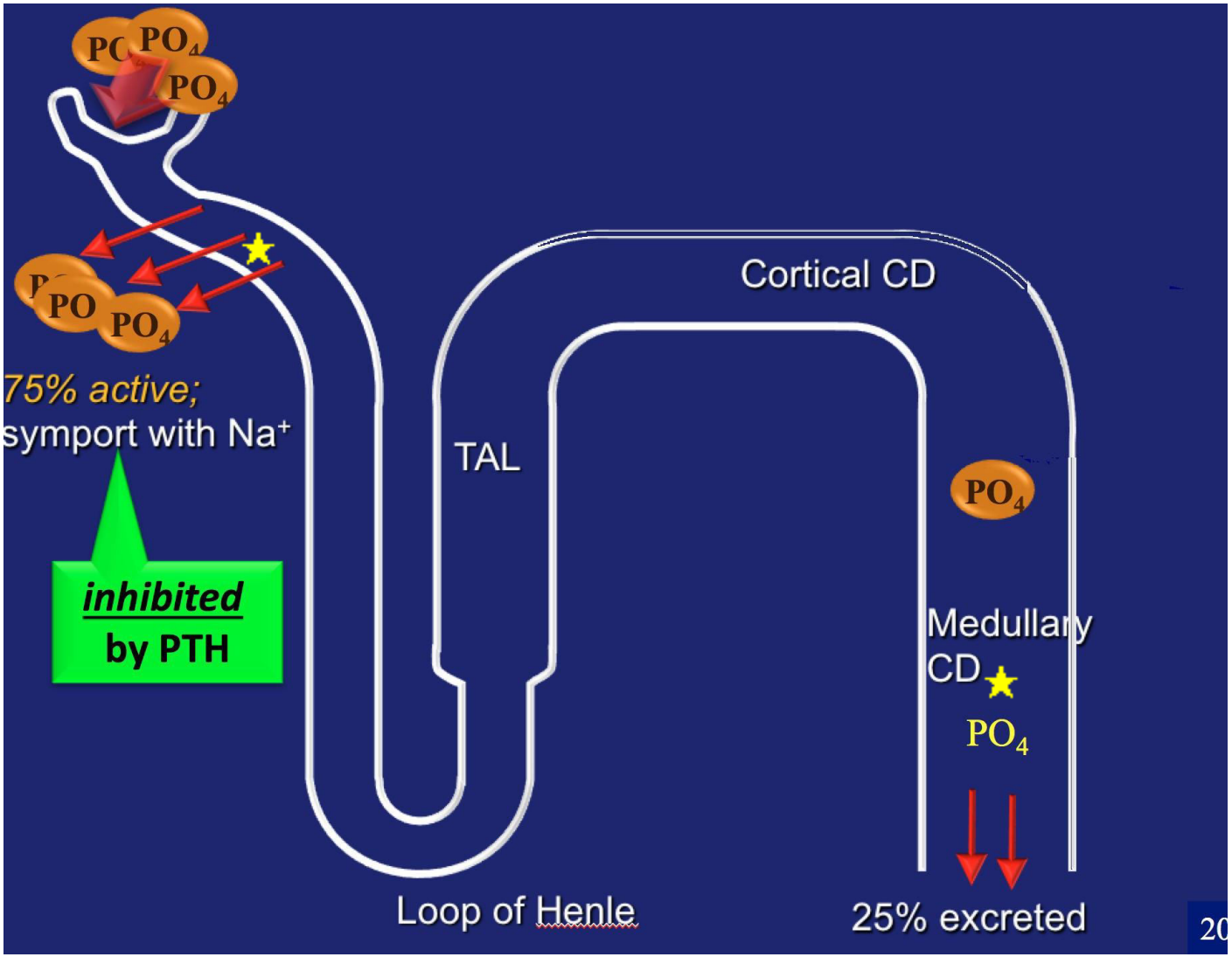
- Membrane
- Nucleic acids
- High energy phosphate compounds (ATP)
  - ☞ Phospholipids and AA containing phosphate are rich in phosphorus

✺ **Regulated mainly by kidney**

- ↑Serum PO_4^{3-} Kidney diseases
- ↓Serum PO_4^{3-} ↑PTH & ↓Vitamin D

✺ **Major changes in PO_4** (not accompanied by changes in serum calcium) **have minimal effect on body.**

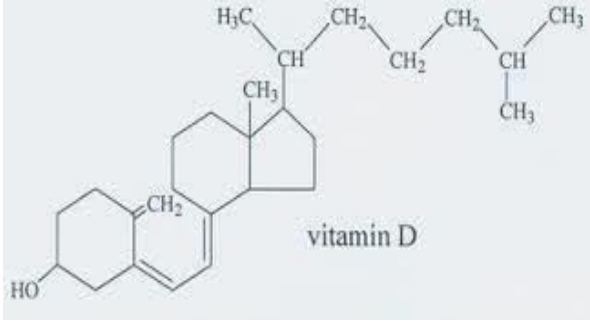
Renal handling of phosphate



Solubility products (SP)

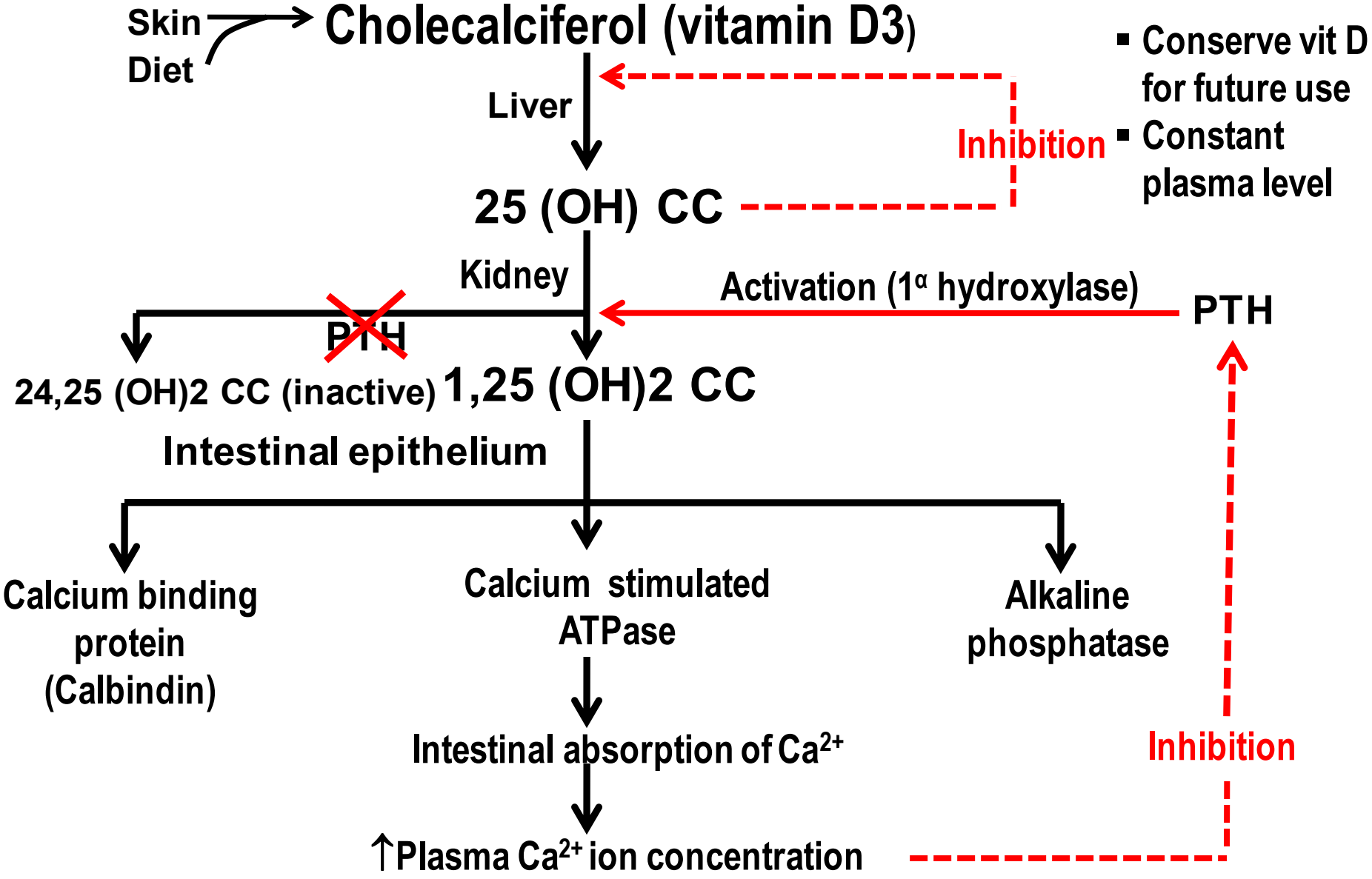
- $\uparrow Ca^{2+} \times \downarrow PO_4^{3-}$ = constant (SP)
- $\downarrow Ca^{2+} \times \uparrow PO_4^{3-}$ = constant (SP)
- $\downarrow Ca^{2+} \times \downarrow PO_4^{3-}$ = $\downarrow$ SP ($\uparrow$pH)
- Body fluids (blood) supersaturated with calcium phosphate
- Precipitation is prevented by pyrophosphate
- Pyrophosphate inhibitor $\longrightarrow$ precipitation of calcium phosphate in bone & dead tissue

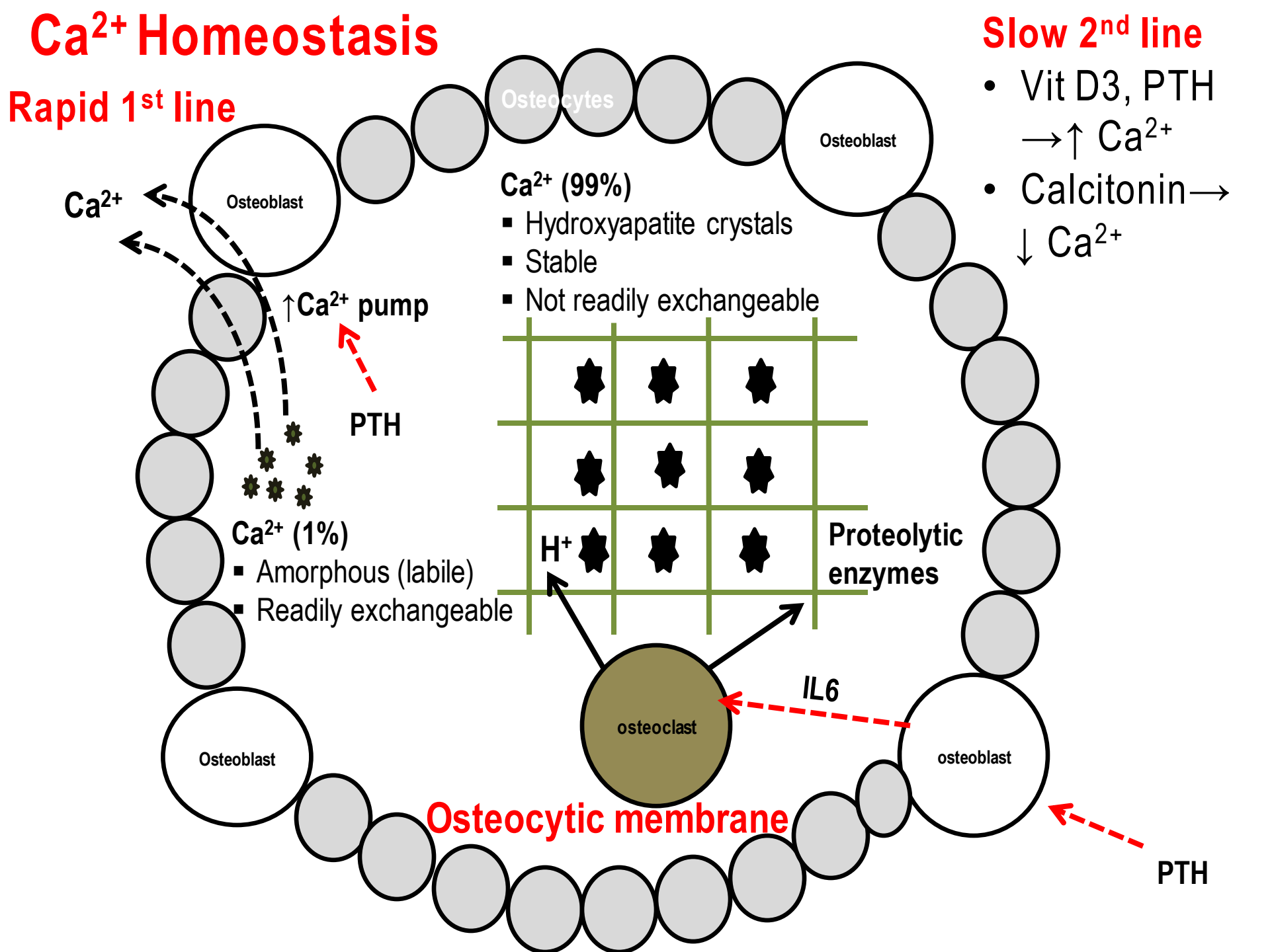
Active vitamin D



- Vitamin D3 is a hypercalcemic hormone
- Absorbed in the small intestine (required bile salts)
- Most of vitamin D3 is formed in the skin (irradiation of 7-dehydrocholesterol by UV rays from the sun
  - ☛ Vitamin D3 (cholecalciferol) → vitamin OR hormone?
- 25 hydroxycholecalciferol (calcidiol) is 2 to 5 times more potent than cholecalciferol.
- 1,25 dihydroxycholecalciferol(calcitriol) is 100 times more potent than calcidiol.

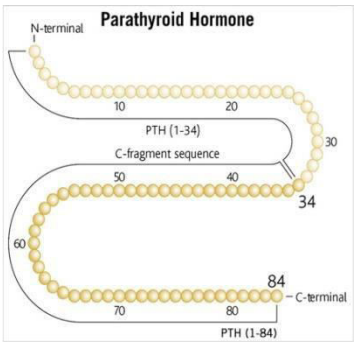
Synthesis and regulation of active vitamin D



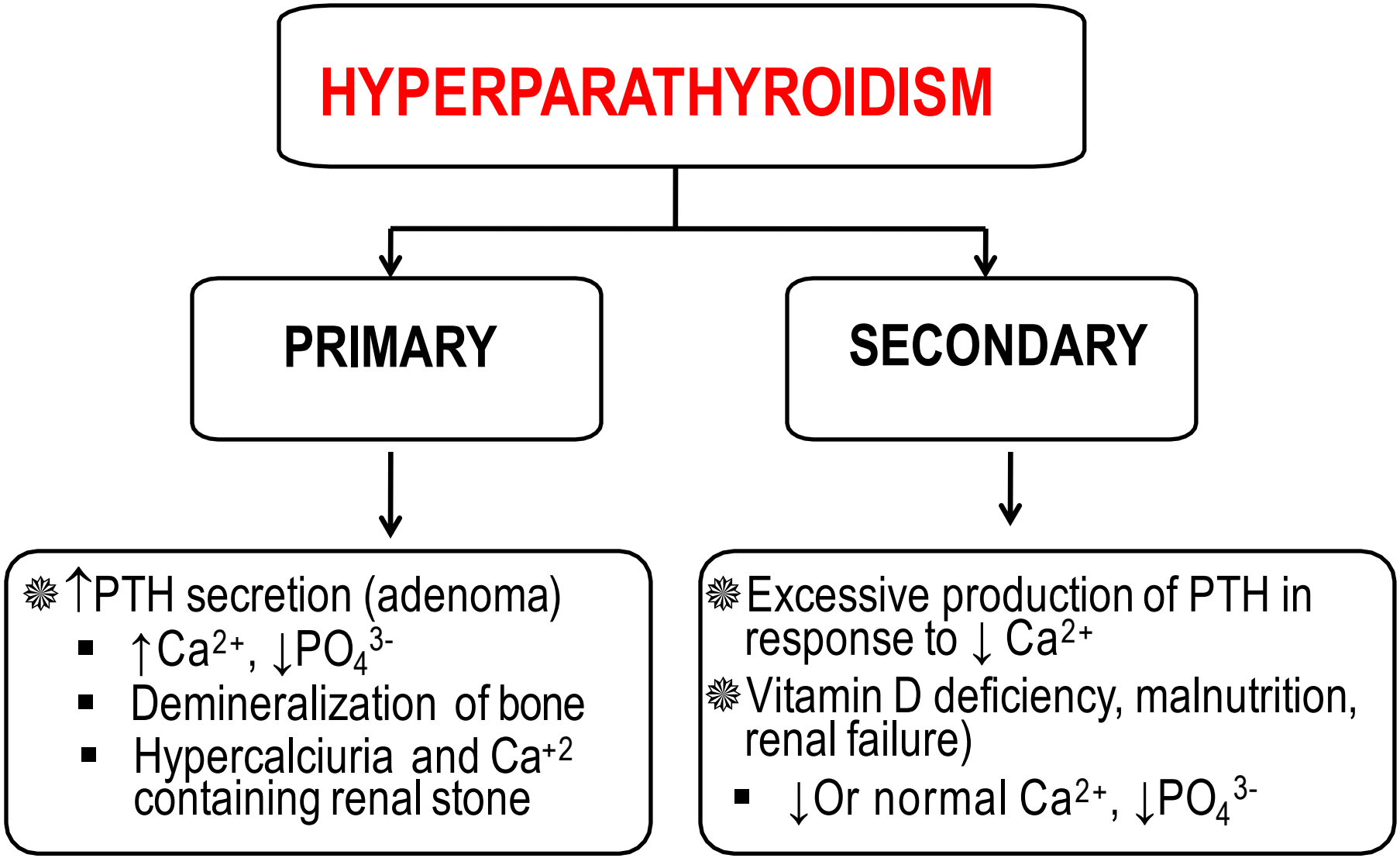

Ca2+ Homeostasis
Rapid 1st line
Slow 2nd line
• Vit D3, PTH →↑ Ca2+
• Calcitonin→ ↓ Ca2+
Osteocytes
Osteoblast
Osteoblast
Ca2+
↑Ca2+ pump
PTH
Ca2+ (99%)
▪ Hydroxyapatite crystals
▪ Stable
▪ Not readily exchangeable
Ca2+ (1%)
▪ Amorphous (labile)
▪ Readily exchangeable
H+
Proteolytic enzymes
osteoclast
IL6
Osteoblast
osteoblast
Osteocytic membrane
PTH

Osteocytes ← Most abundant (relatively inert)	**Osteoblasts**	**Osteoclasts**
▪ Control osteoblast and osteocytes ▪ Ca^{2+} pump	**Bone formation** via secretion of ▪ Pyrophosphate inhibitor ▪ Alkaline phosphate	**Bone resorption** via Secretion of ▪ H^{+} ▪ Proteolytic enzymes

PTH (from parathyroid glands)



Structure		Polypeptide (84AA)
Plasma Ca^{2+}		$\uparrow Ca^{2+}$
Action	Bone	**Resorption** ▪ Rapid ($\uparrow Ca^{2+}$ pump osteocytes & osteoblasts) ▪ Slow (activate osteoclasts)
	Kidney	▪ $\uparrow Ca^{2+}$ **reabsorption** (DCT) ▪ Inhibits PO_4^{3-} reabsorption (PCT) ▪ Formation of $1,25(OH)_2$ CC
	Intestine	▪ $\uparrow Ca^{2+}$ **absorption** (indirect via activation of $1,25(OH)_2$ CC
Control	Stimulation	▪ **$\downarrow$Plasma Ca^{2+}** (Direct effect) & $\downarrow Mg^{2+}$ ▪ $\uparrow PO_4^{3-}$ (lowers plasma Ca^{2+})
	Inhibition	▪ $\uparrow Ca^{2+}$ & Mg^{2+} ▪ 1,25(OH)2 CC


HYPERPARATHYROIDISM
PRIMARY
SECONDARY
↑PTH secretion (adenoma)
↑Ca^{2+}, ↓PO_4^{3-}
Demineralization of bone
Hypercalciuria and Ca^{+2} containing renal stone
Excessive production of PTH in response to ↓ Ca^{2+}
Vitamin D deficiency, malnutrition, renal failure)
↓Or normal Ca^{2+}, ↓PO_4^{3-}

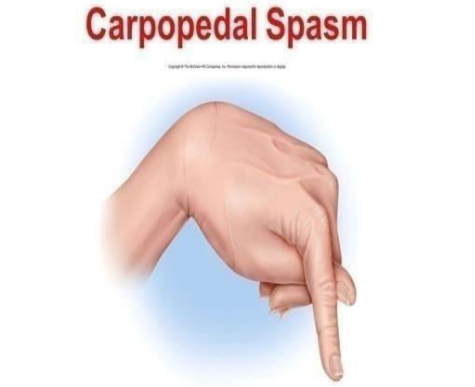
HYPOPARATHYROIDISM

Causes:

- PTH-deficient hypoparathyroidism
  - Reduced or absent synthesis of PTH (occurs after thyroidectomy)
- PTH-ineffective hypoparathyroidism
  - Synthesis of biologically inactive PTH
- PTH-resistant (pseudohypoparathyroidism)
  - Defect in PTH receptor

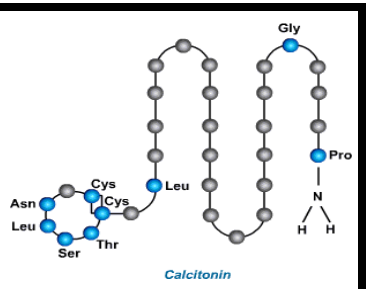
Features:

- Hpocalcemia →signs of neuromuscular hyperexcitability →hypocalcemic tetany



• Hypocalcemia demonstrated by muscle spasm of hands and feet.

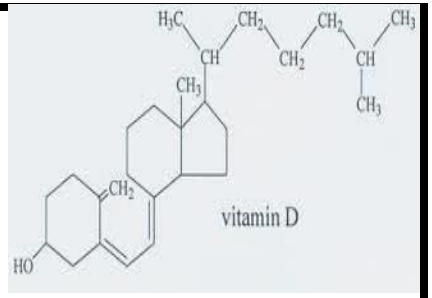
Calcitonin (from parafollicular cells of thyroid)

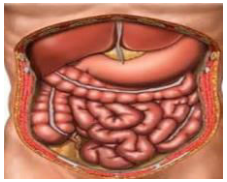


Structure	Polypeptide (32AA)
Plasma Ca^{2+}	↓Ca^{2+}

Action  	Bone	**Deposition (building)** ▪ ↑Osteoblasts activity ▪ ↓Osteoclast activity (major effect)
	Kidney	**Excretion** ▪ ↓Ca^{2+} reabsorption (DCT) ▪ ↓PO_4^{3-} reabsorption (PCT) (minor effect)
Control	Stimulation	▪ **↑Plasma Ca^{2+}** ▪ GI hormones (gastrin) to prevent hypercalcemia) ▪ Estrogen (pregnancy) & prolactin (lactation) to inhibits Ca^{2+} loss from bones.
	Inhibition	▪ ↓ Plasma Ca^{2+}

1,25 (OH)2 cholecalciferol



Structure		Steroid
Plasma Ca^{2+}		Ca^{2+} ↑
Action 	Bone	**Resorption and deposition** ▪ Bone remodeling depending on plasma Ca^{2+}
	Kidney	**Reabsorption** ▪ ↑Ca^{2+} reabsorption (DCT) ▪ ↑PO_4^{3-} reabsorption (PCT)
	Intestine	**Absorption** ▪ ↑ Absorption of Ca^{2+}, Mg^{2+} & PO_4 via calbindin
Control	Stimulation	▪ ↓ **Ca^{2+}** ▪ ↑ PTH ▪ ↓ 1,25 (OH)2 CC (negative feed back)
	Inhibition	▪ ↑ Plasma Ca^{2+}