بسم الله الرحمن الرحيم

ENDOCRINOLOGY

Calcium Homeostasis
Hypo and hyper–parathyroidism

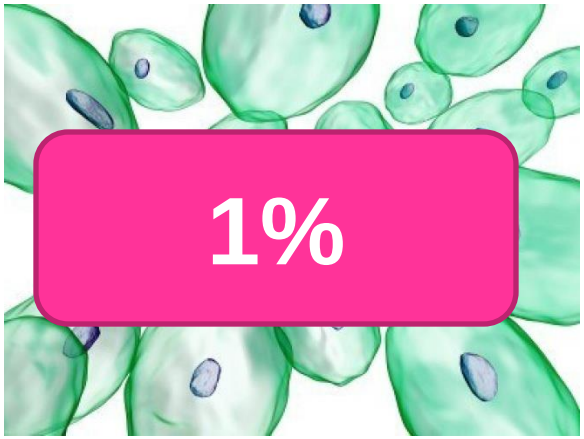
Dr. Abeer Al-Ghumlas
M.B.B.S., MSc. Physiology
Ph-D. Physiology

Objectives

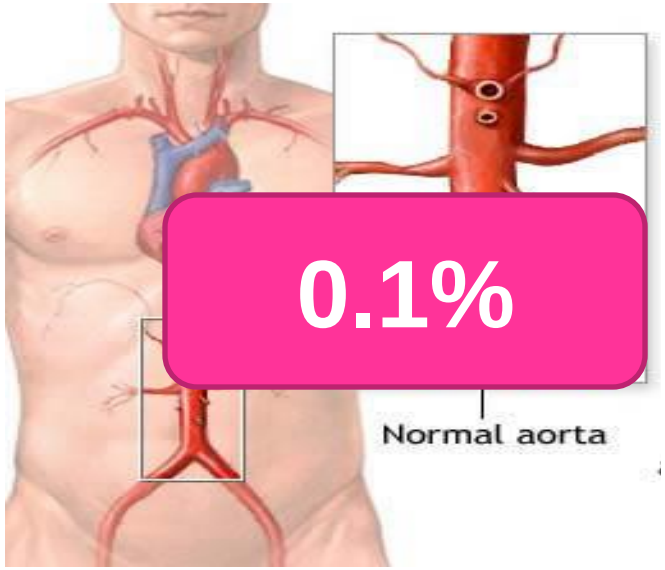
At the end of this lecture you should be able to:

- **List the functions of calcium**
- **Describe calcium metabolism**
- **Describe physiology of bone**
- **Understand and explain hormonal regulation of calcium metabolism**
  - **Parathyroid hormone**
  - **Calcitonin**
  - **Vitamine D_3**
- **Understand hypo and hyper-parathyroidism**

99%



1%



0.1%

Distribution of Ca^{++} in Body

- **Skeleton & Teeth**
- **ICF** (Endoplasmic Reticulum)
- **ECF**

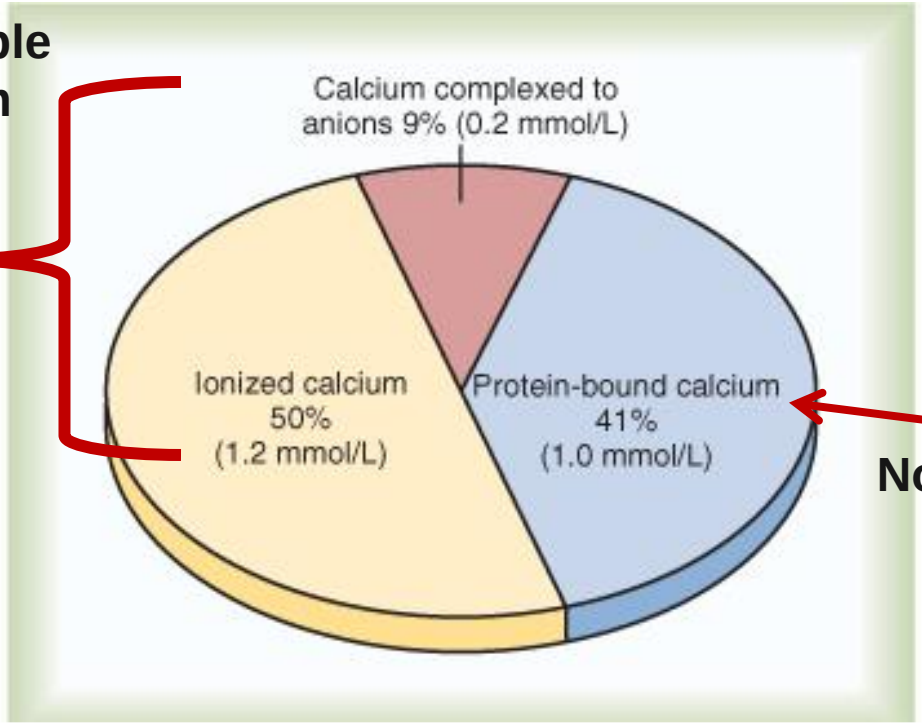
TABLE 36.1 Body Content and Tissue Distribution of Calcium and Phosphorus in a Healthy Adult

	Calcium	Phosphorus
Total Body Content	1,300 g	600 g
Relative Tissue Distribution (% of total body content)		
Bones and teeth	99%	86%
Extracellular fluid	0.1%	0.08%
Intracellular fluid	1.0%	14%

Distribution of Ca^{++} in ECF

- **Total plasma calcium= 9-10.5 mg/dl**

Diffusible calcium



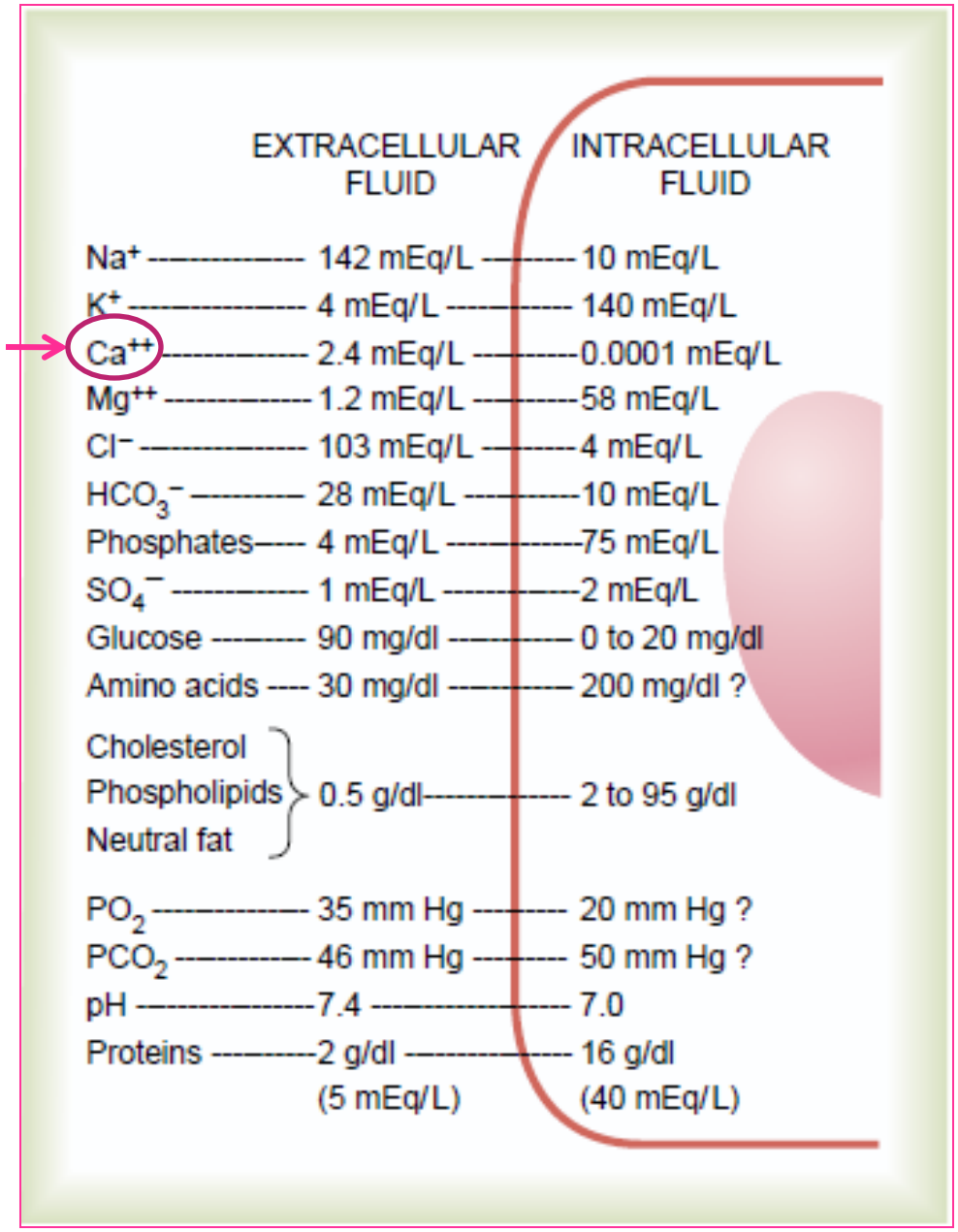
Non- diffusible calcium

Protein-bound calcium:

- Most of this calcium is bound to albumin & much smaller fraction is bound to globulin

- Binding of calcium to albumin is pH-dependent

- Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level


EXTRACELLULAR FLUID
INTRACELLULAR FLUID
Na^+ 142 mEq/L 10 mEq/L
K^+ 4 mEq/L 140 mEq/L
Ca^{++} 2.4 mEq/L 0.0001 mEq/L
Mg^{++} 1.2 mEq/L 58 mEq/L
Cl^- 103 mEq/L 4 mEq/L
HCO_3^- 28 mEq/L 10 mEq/L
Phosphates 4 mEq/L 75 mEq/L
SO_4^- 1 mEq/L 2 mEq/L
Glucose 90 mg/dl 0 to 20 mg/dl
Amino acids 30 mg/dl 200 mg/dl ?
Cholesterol
Phospholipids 0.5 g/dl 2 to 95 g/dl
Neutral fat
PO_2 35 mm Hg 20 mm Hg ?
PCO_2 46 mm Hg 50 mm Hg ?
pH 7.4 7.0
Proteins 2 g/dl 16 g/dl
(5 mEq/L) (40 mEq/L)

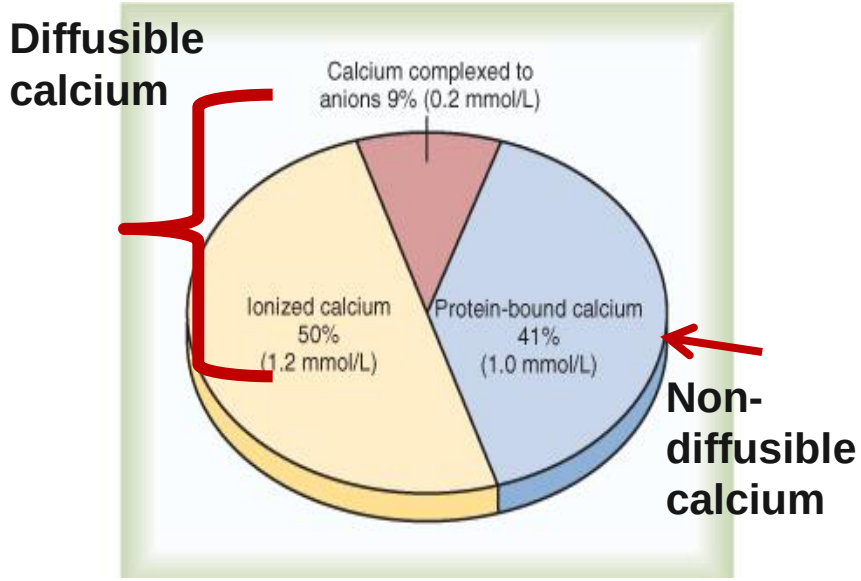
Plasma Calcium

9-10.5 mg/dl

Non Diffusible = 41%

Diffusible = 59%

- **Complexed 9 %**
- **Ionized 50%**



Physiological importance of Calcium

- Calcium salts in bone provide structural integrity of the skeleton

- Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes
  - Neuoromuscular excitability
  - Hormonal secretion
  - Enzymatic regulation
  - Blood coagulation
  - Second messenger.

Phosphate

- **Phosphorous is an essential mineral necessary:**
  for ATP and cAMP second messenger systems

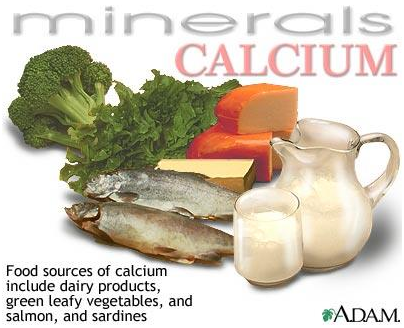
- **Phosphate plasma concentration is around 4 mg/dL.**

- **Forms:**
  - **Ionized (diffusible) → around 50% of total**
  - **un-ionized (non-diffusible) and protein- bound (50%)**

- **Calcium is tightly regulated with Phosphorous in the body.**

Calcuim metabolism cont…

Source



- **Milk**
- **dairy products**
- **Fish**

Daily requirements

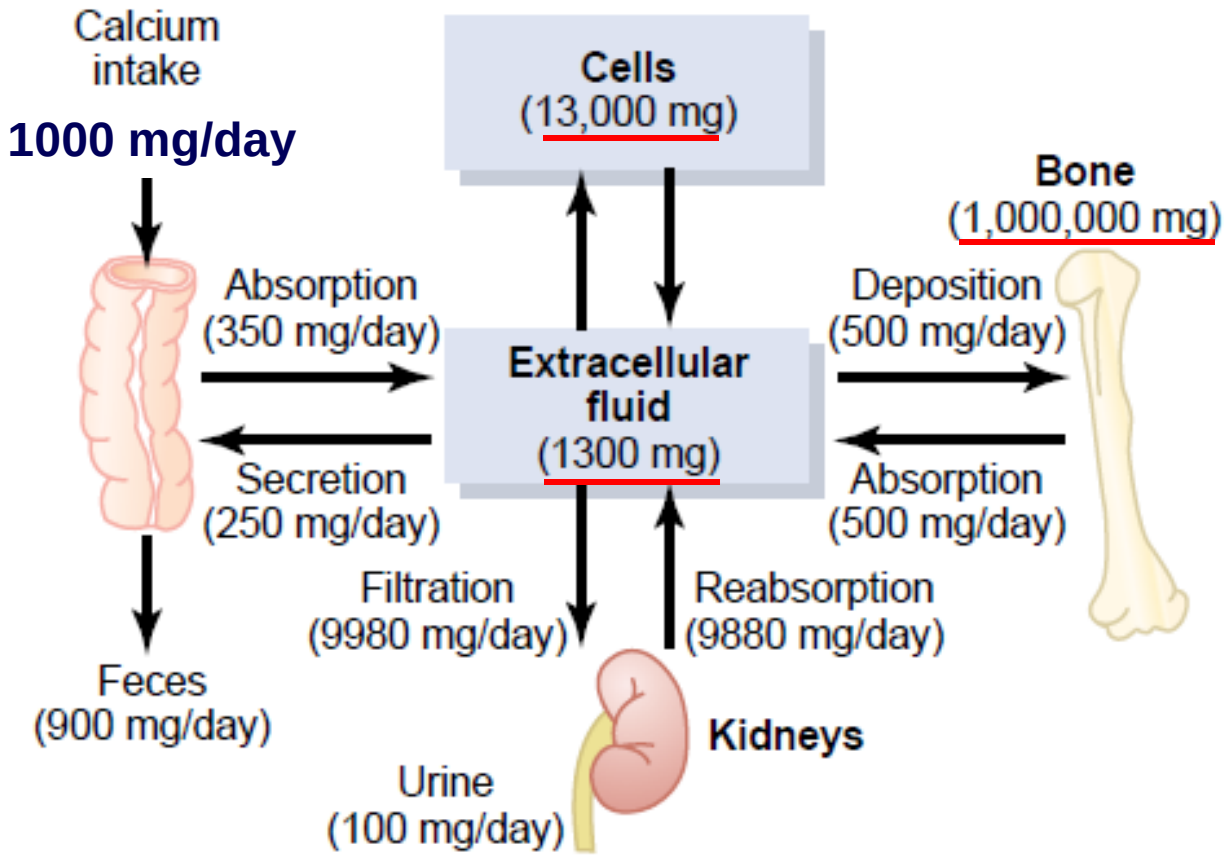
- **Infants & adults: 12.5 -25 mmol/day**
- **Pregnancy,**
- **lactation**
- **after menopause:**

25-35 mmol/day

Absorption

- **Duodenum: active transport**
- **small intestine: concentration gradient**

Calcium Metabolism in an adult human



Physiology Of Bone:

Bone composition

(1) Organic Matrix (30%)

- Collagen Fibers (95%)
- Ground Substance (5%)
  - ECF
  - Proteoglycans

(2) Bone Salts (70%)

Bone composition

(2) Bone Salts

- Hydroxyapatite crystals

[In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$]

- Mg, Na, K, Carbonate ions

Bone composition

- **Organic Matrix**
  - Collagen Fibers (95%)
  - Ground Substance (5%)
    - ECF
    - Proteoglycans
- **Bone Salts**
  - Salts of Ca^{++} & $PO4^{-}$
  - In the form of
    Hydroxyapatite crystals (99%)
    $Ca_{10}(PO_4)_6(OH)_2$
    Mg, Na, K, Carbonate ions

Tensile force

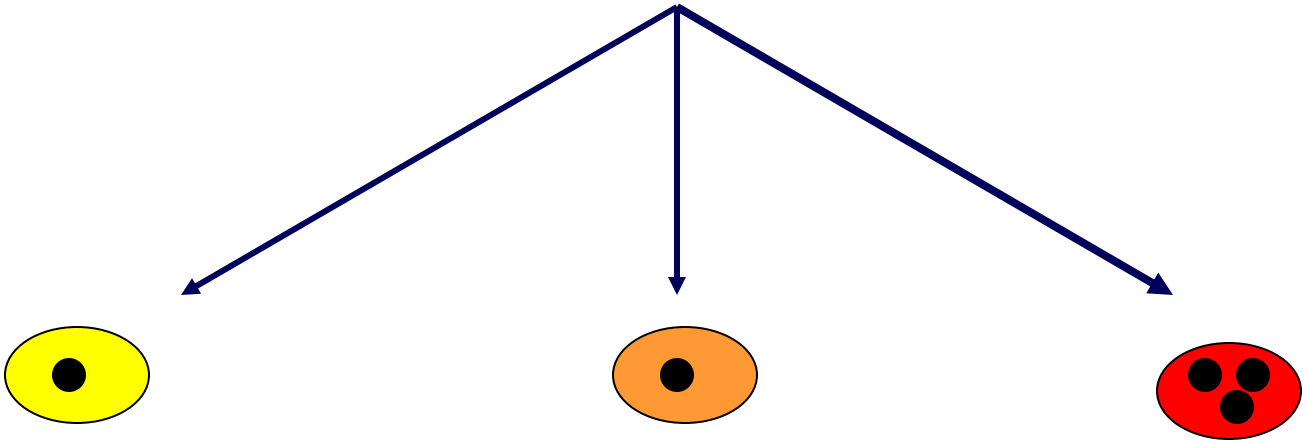
Compressional force

Composition of bones

Inorganic Constituents of Bone

Constituent	% of Total Body Content Present in Bone
Calcium	99
Phosphate	86
Carbonate	80
Magnesium	50
Sodium	35
Water	9

Bone Cells



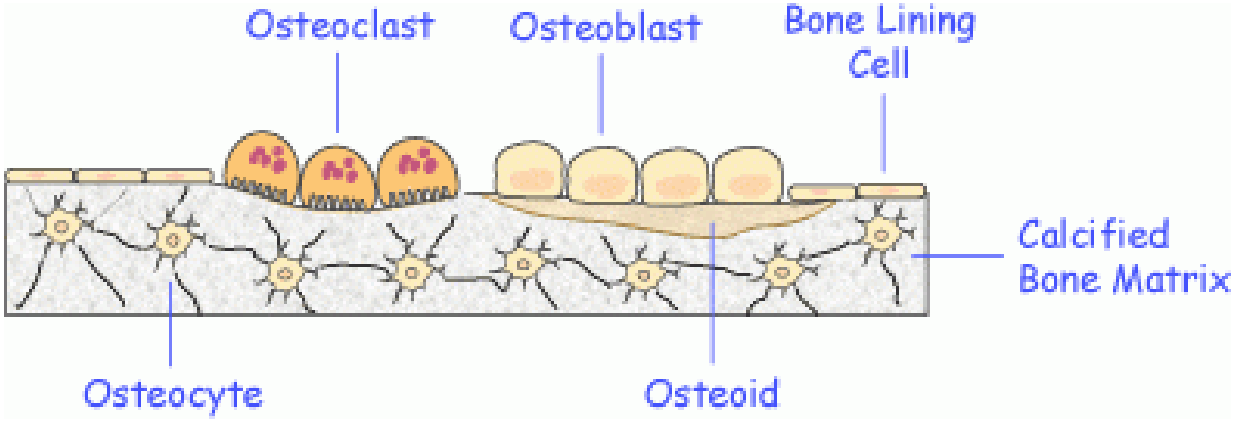
Osteoblasts

(bone forming cells)

Osteocytes

(osteoblasts surrounded by calcified matrix)

Osteoclasts bone eroding Cell (resorping)



Osteoblasts (matrix-forming cells)
Origin?

Osteocytes
Originate from osteoblasts

Osteoclasts
Originate from bone marrow - derived macrophage-monocyte line

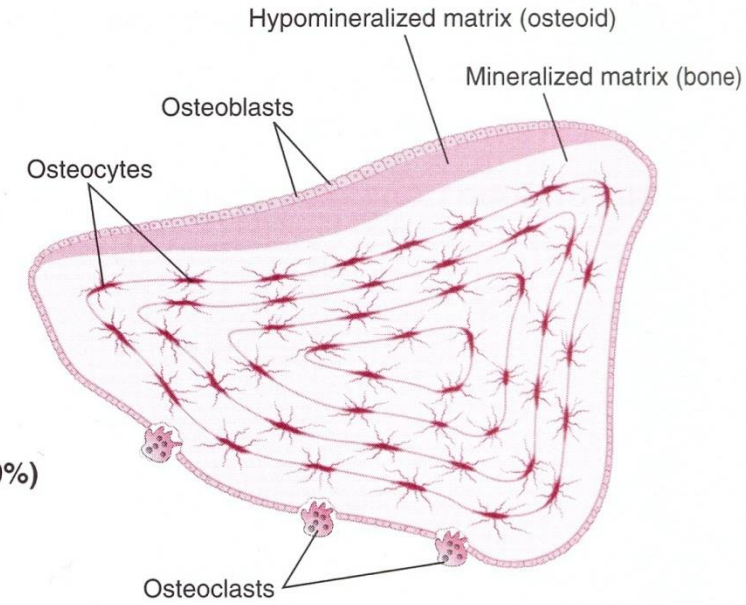
Cells (2%)

Collagen (95%)
Type I ($\alpha 1[I]_2 \alpha 2$)

Non-Collagen (5%)
Osteocalcin (bone Gla protein), vitamin K dependent
Osteonectin
Bone proteglycan
Bone sialoprotein
Bone morphogenic protein
Bone proteolipid
Bone phosphoprotein

Matrix (98%)

Organic (30%)



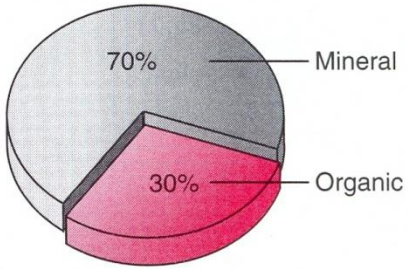


Figure 8.1 The composition of bone.

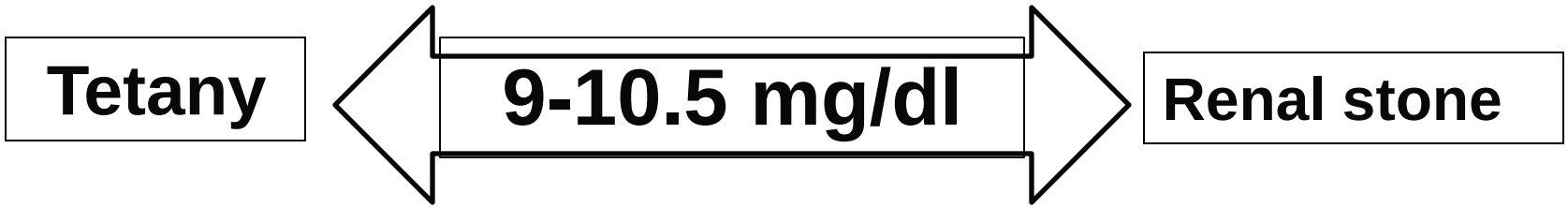

Hydrangea Garden, Clermont, Kentucky

Regulation of Calcium level

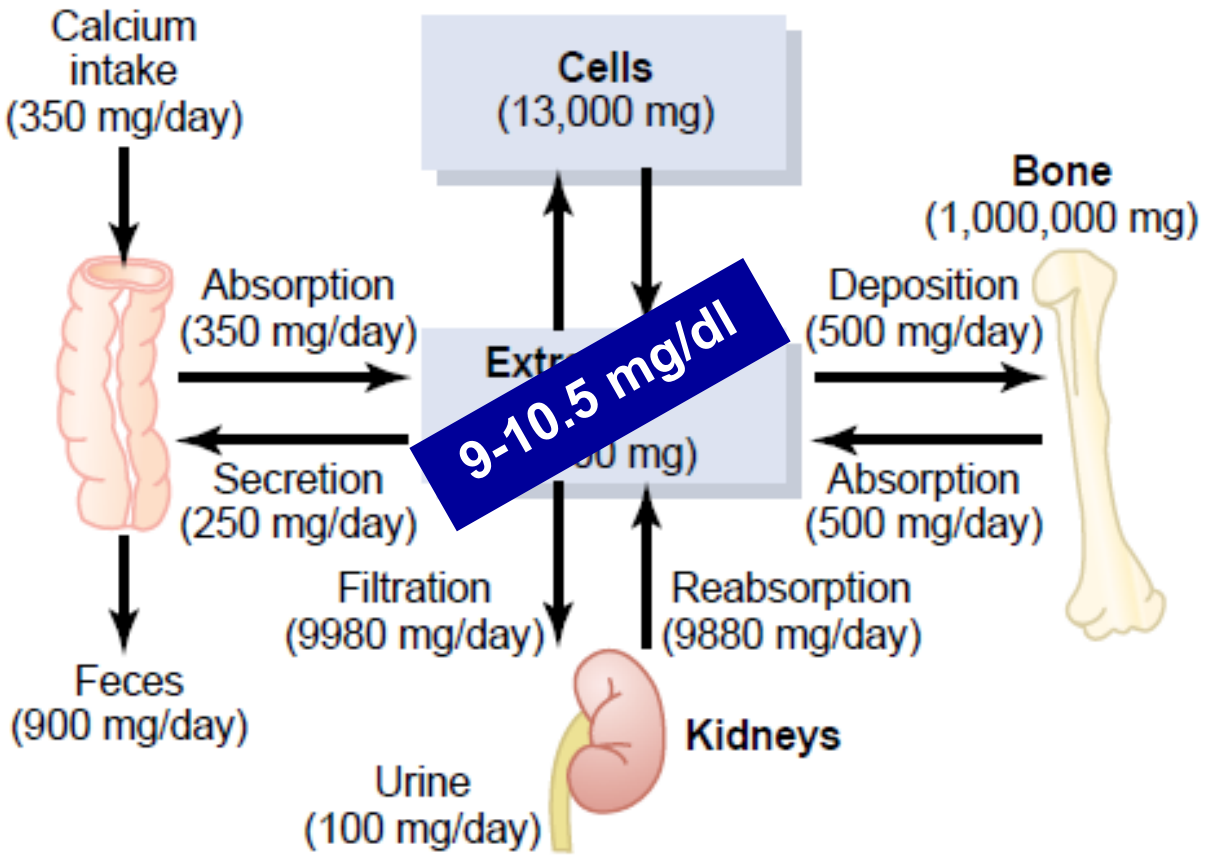
REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS

- Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium

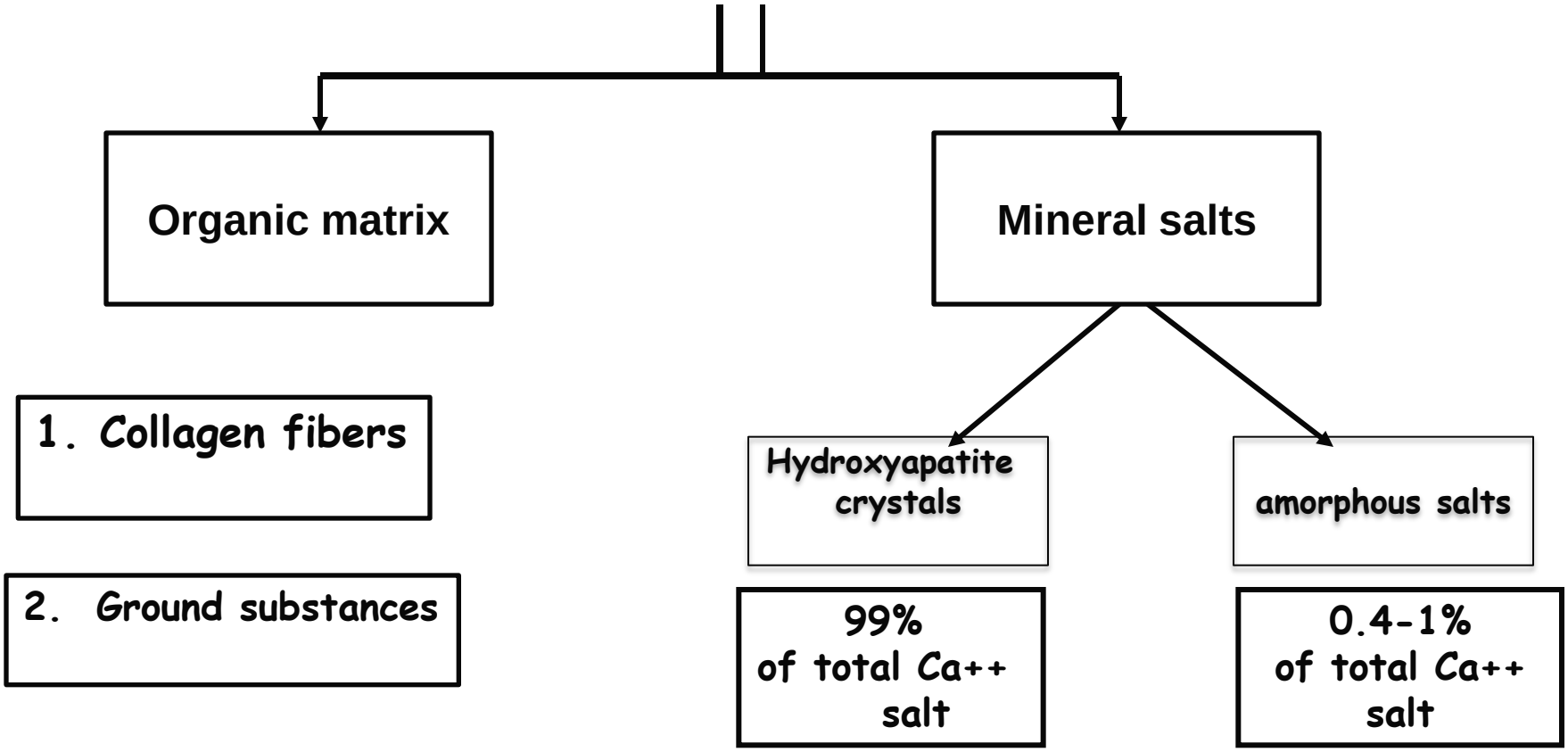
- Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations


Tetany
9-10.5 mg/dl
Renal stone

Calcium Metabolism in an adult human



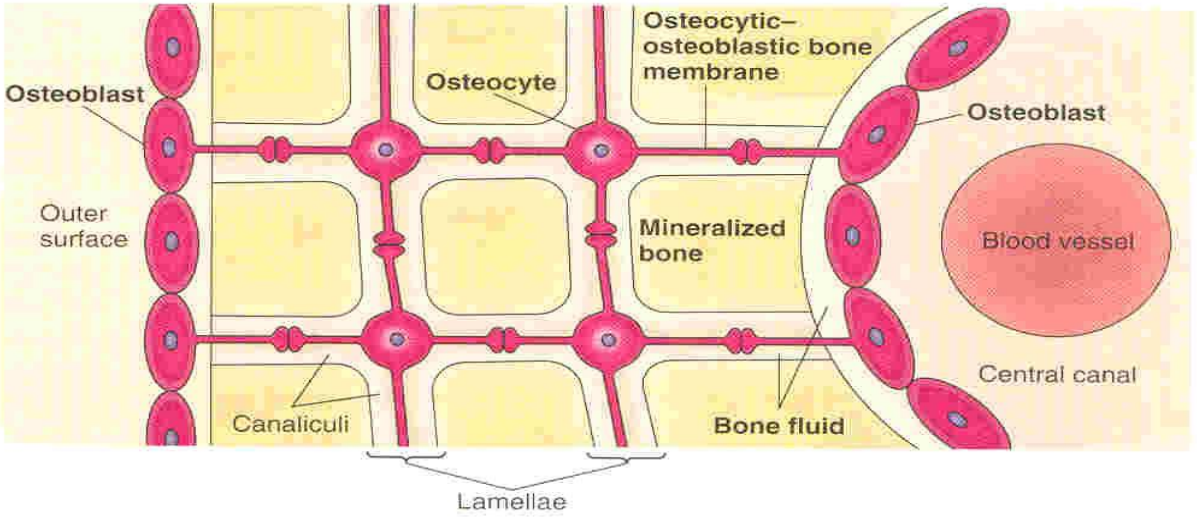
Composition of bones



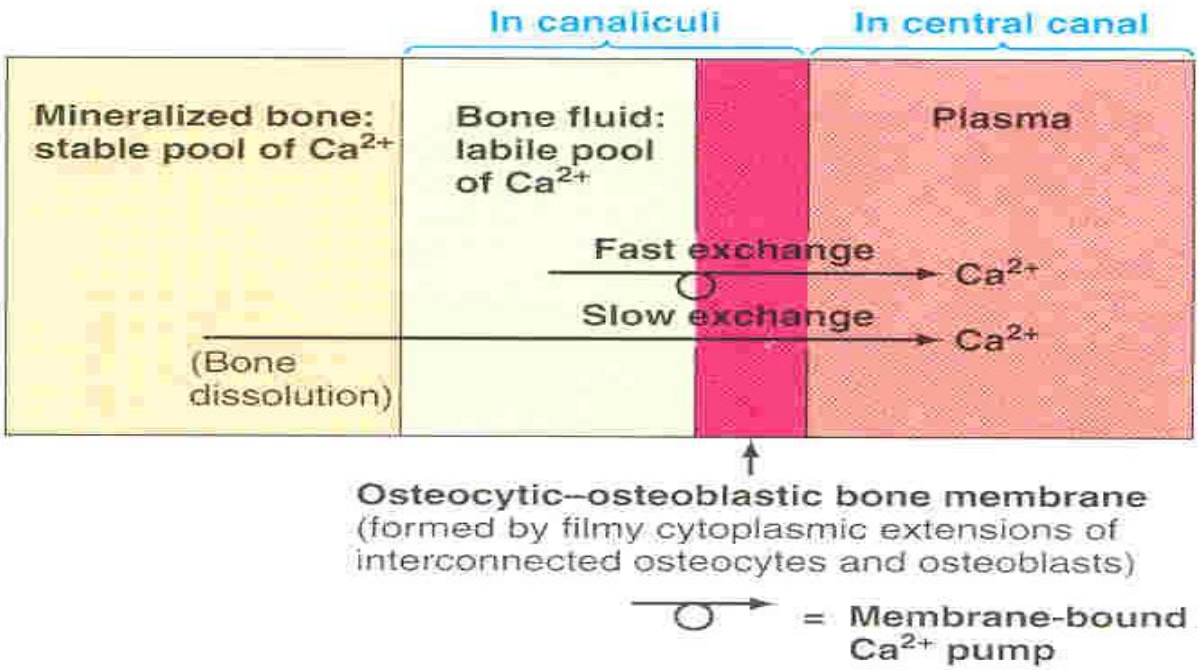
Bone composition

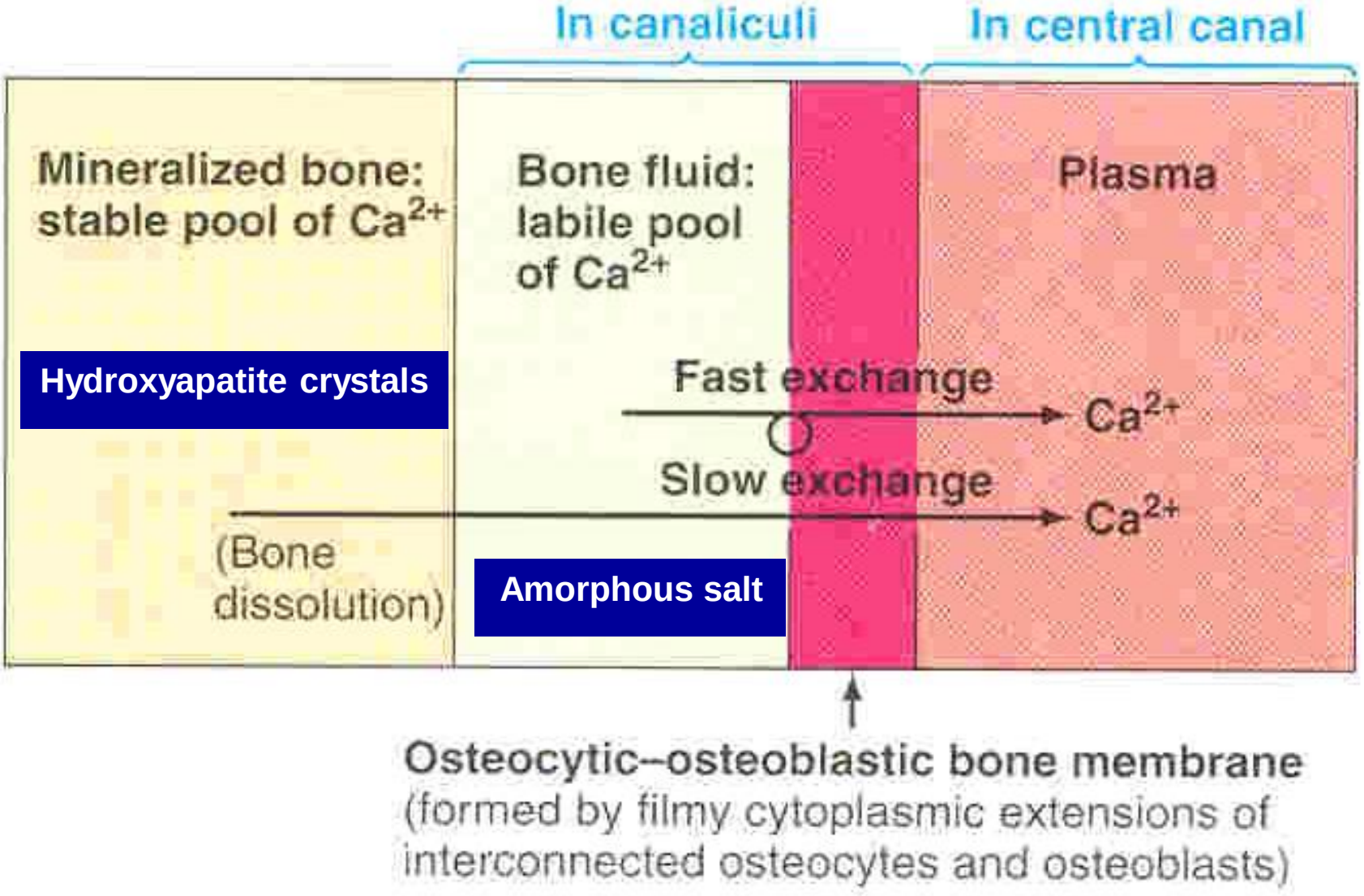
(2) Bone Salts

- Hydroxyapatite crystals
  [In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$]
- Mg, Na, K, Carbonate ions
- Amorphous salts:
  - A type of exchangeable calcium
  - Play role in rapid regulation of ionized Ca++ level in ECF
  - 0.4-1% of total bone Ca++
  - always in equilibrium with Ca^{2+} in ECF

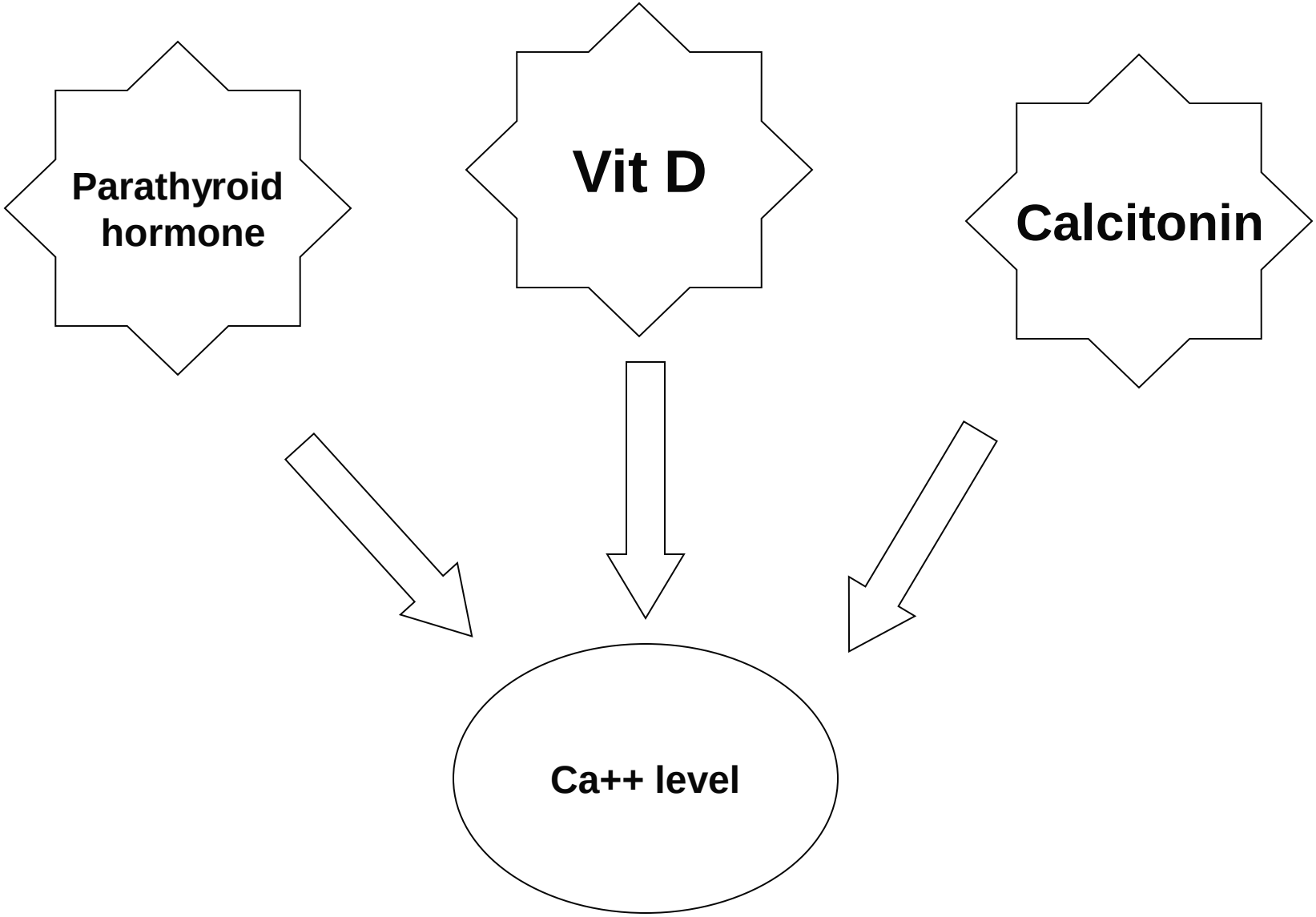

Osteoblast
Osteocyte
Osteocytic–
osteoblastic bone
membrane
Osteoblast
Outer
surface
Mineralized
bone
Blood vessel
Central canal
Canaliculi
Bone fluid
Lamellae

(a)


In canaliculi
In central canal
Mineralized bone:
stable pool of Ca^{2+}
Bone fluid:
labile pool
of Ca^{2+}
Plasma
Fast exchange
Ca^{2+}
Slow exchange
Ca^{2+}
(Bone
dissolution)
Osteocytic–osteoblastic bone membrane
(formed by filmy cytoplasmic extensions of
interconnected osteocytes and osteoblasts)
= Membrane-bound
Ca^{2+} pump

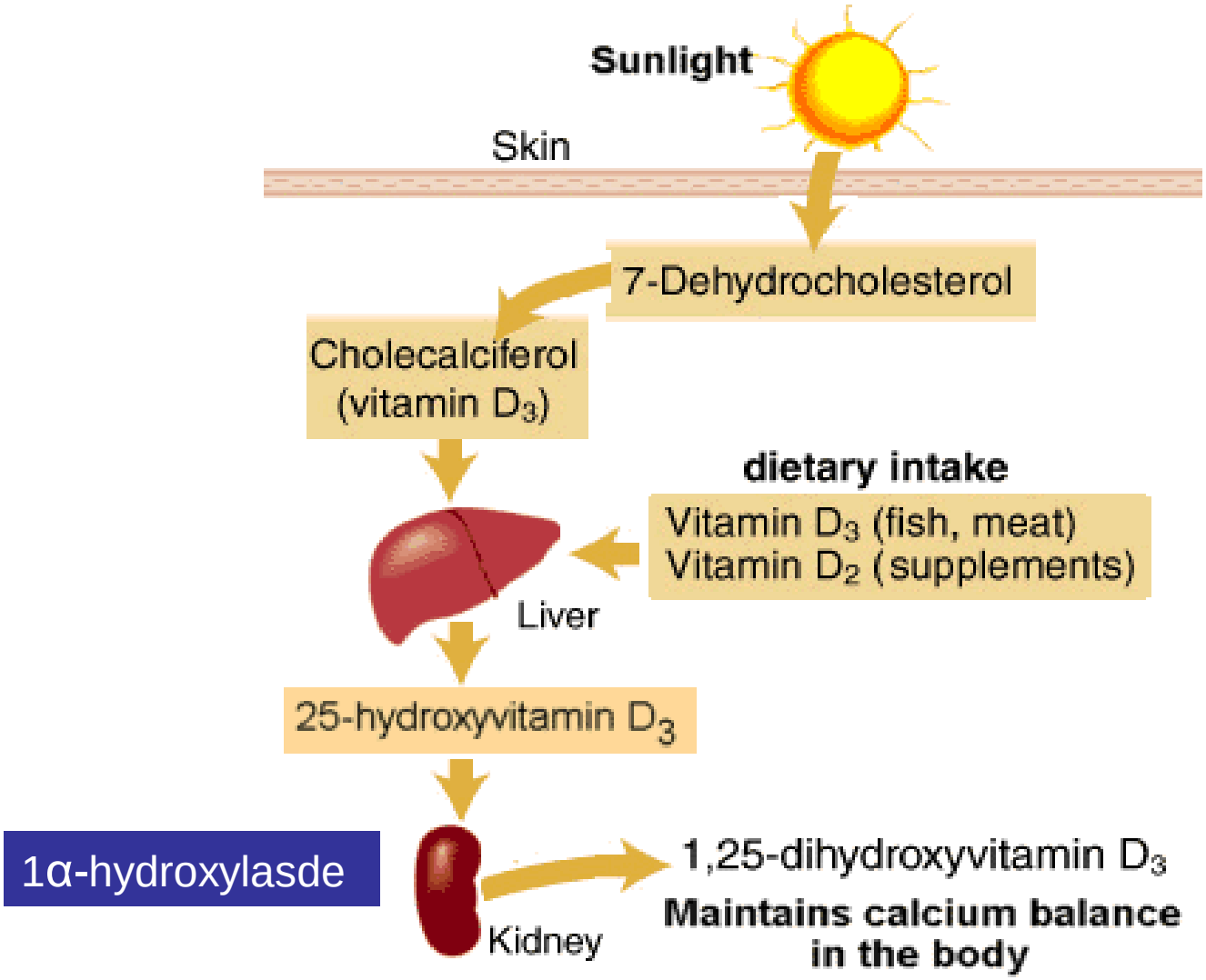

In canaliculi
In central canal
Mineralized bone: stable pool of Ca^{2+}
Bone fluid: labile pool of Ca^{2+}
Plasma
Hydroxyapatite crystals
Fast exchange
Ca^{2+}
Slow exchange
Ca^{2+}
(Bone dissolution)
Amorphous salt
Osteocytic–osteoblastic bone membrane
(formed by filmy cytoplasmic extensions of interconnected osteocytes and osteoblasts)

Three Hormones



Vitamin D

1,25 Dihydroxycholecalciferol (Vit D)

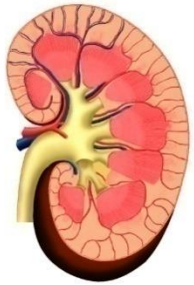


Vitamin D

1.Intestinal tract.

Has a potent effect to increase calcium & phosphate absorption

2.Renal

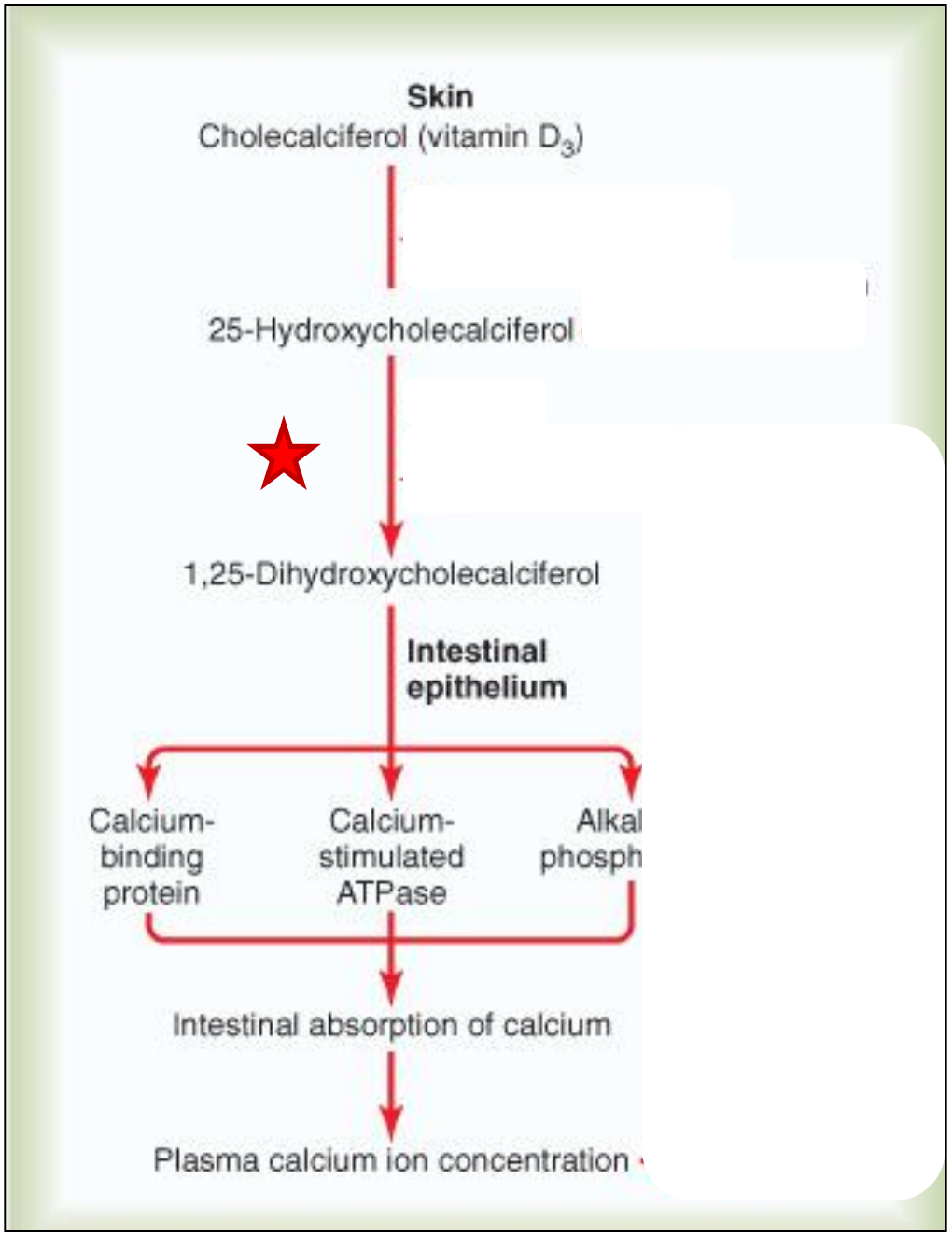


Increases Renal calcium and Phosphate absorption

3.Bone

Bone absorption

Increase calcium blood level


Skin
Cholecalciferol (vitamin D_3)
25-Hydroxycholecalciferol
1,25-Dihydroxycholecalciferol
Intestinal epithelium
Calcium-binding protein
Calcium-stimulated ATPase
Alkal phosph
Intestinal absorption of calcium
Plasma calcium ion concentration

Effects of Vitamin D on Bone & Its Relation to Parathyroid Hormone Activity.

-Vitamin D in *smaller quantities* :
- promotes *bone calcification* (by ↑ calcium and phosphate absorption from the intestine and enhances the mineralization of bone.

- The administration of extreme quantities of vitamin D causes *absorption of bone:*

** by facilitating PTH action on bones.*
** number & activity of esteoclasts.*

Vitamin D

4- stimulates differentiation of immune cells.

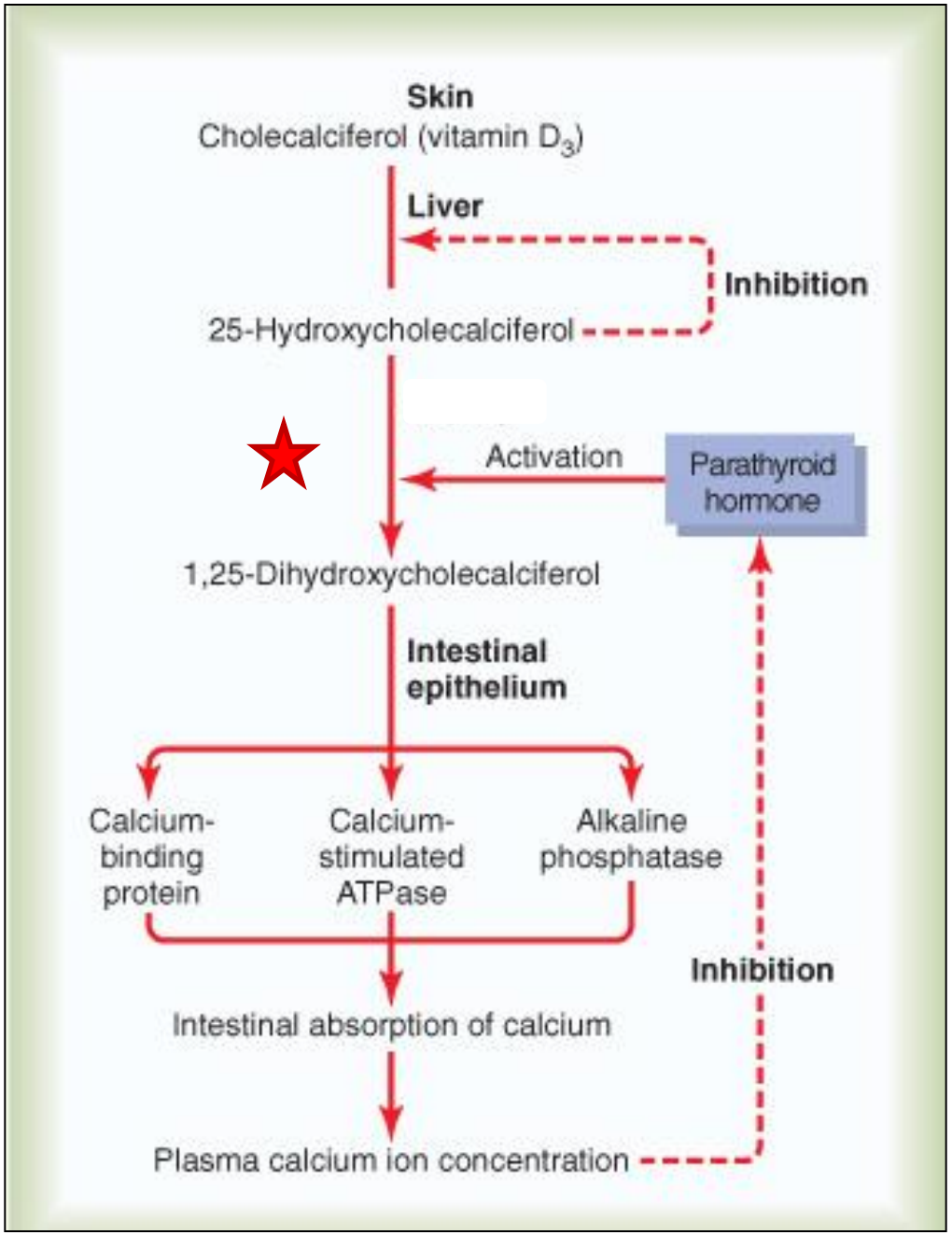
❑Control of Vit D:

1- low Ca++ ions

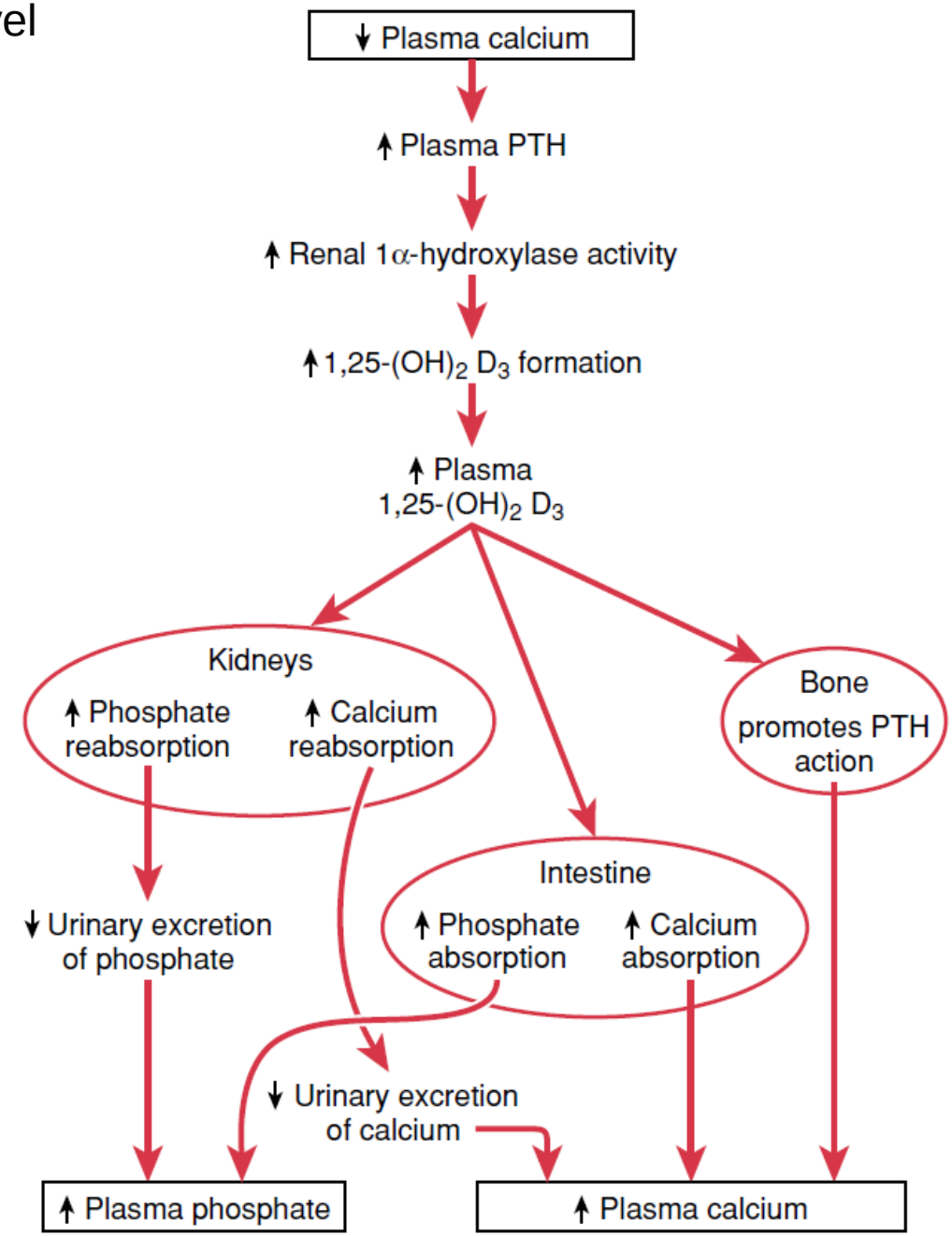
2- prolactin

3- PTH

All stimulate renal ★ 1,alpha hydroxylase.

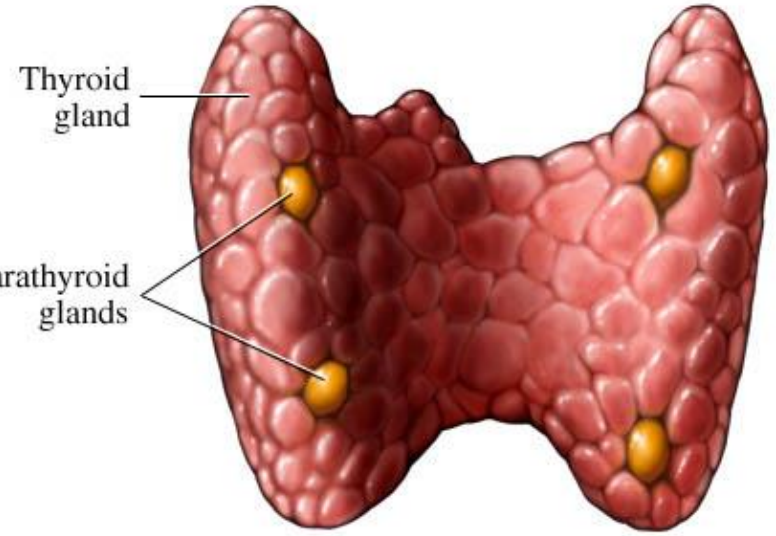


Regulation of Calcium level



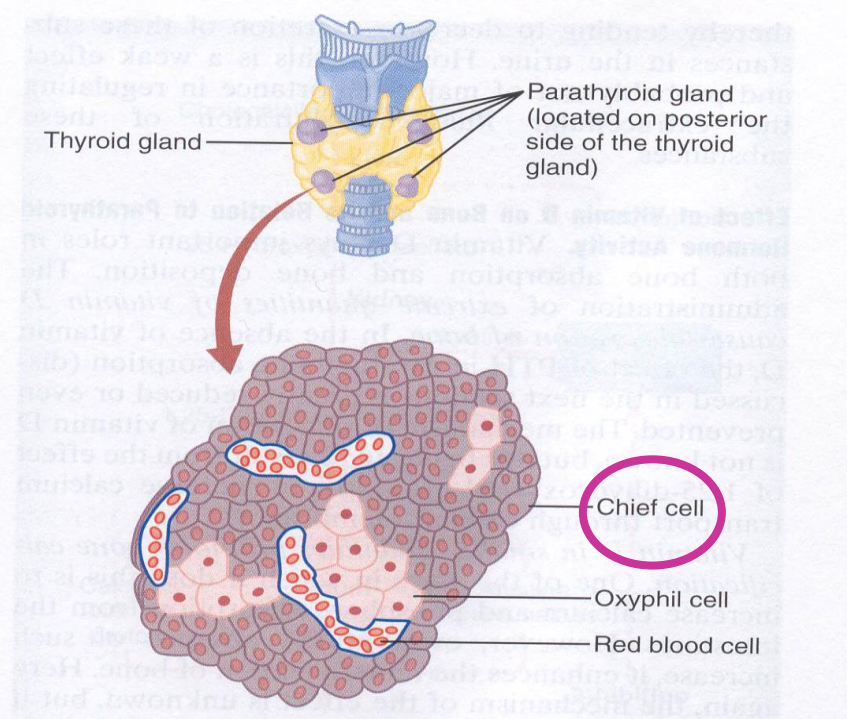
Parathyriod gland

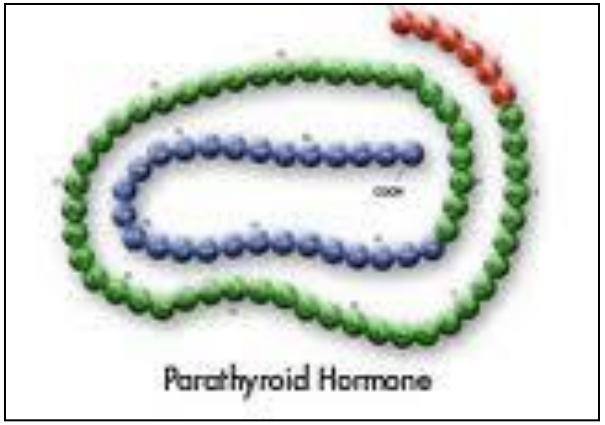
Parathyroid hormone (PTH)



Parathyroid hormone (PTH)

- **Source: Parathyroid gland**
- **Polypeptide hormone: (84 aa)**
- **Molecular Weight: 9500**
- **Half Life: 10 min**
- **Mechanism of action: acts via 2nd messenger mechanism utilizing cAMP**
- **Actions: Bone**
  Kidney
  Intestine





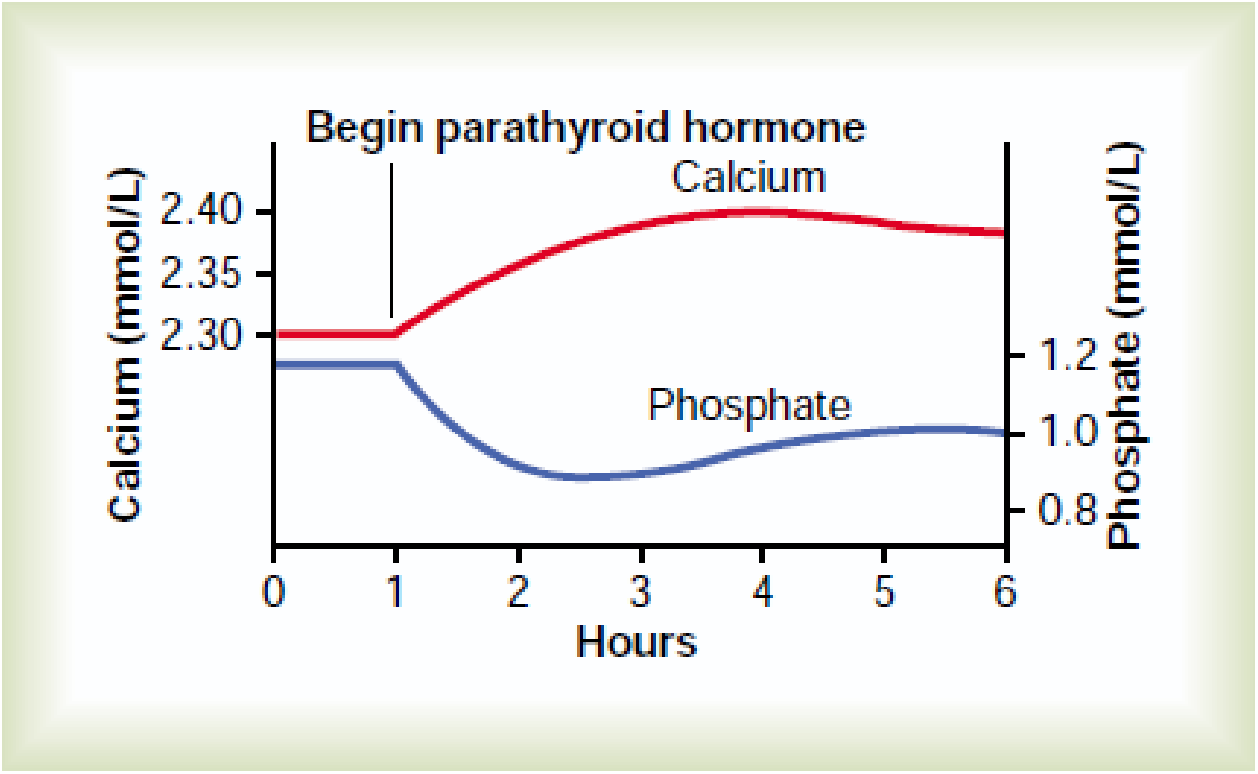


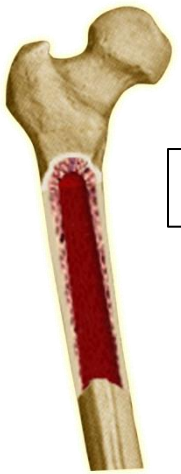
Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

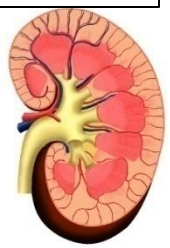
Parathyroid hormone (PTH)

Increase plasma Ca^{++} level

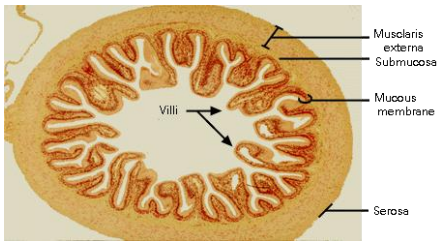
Bone



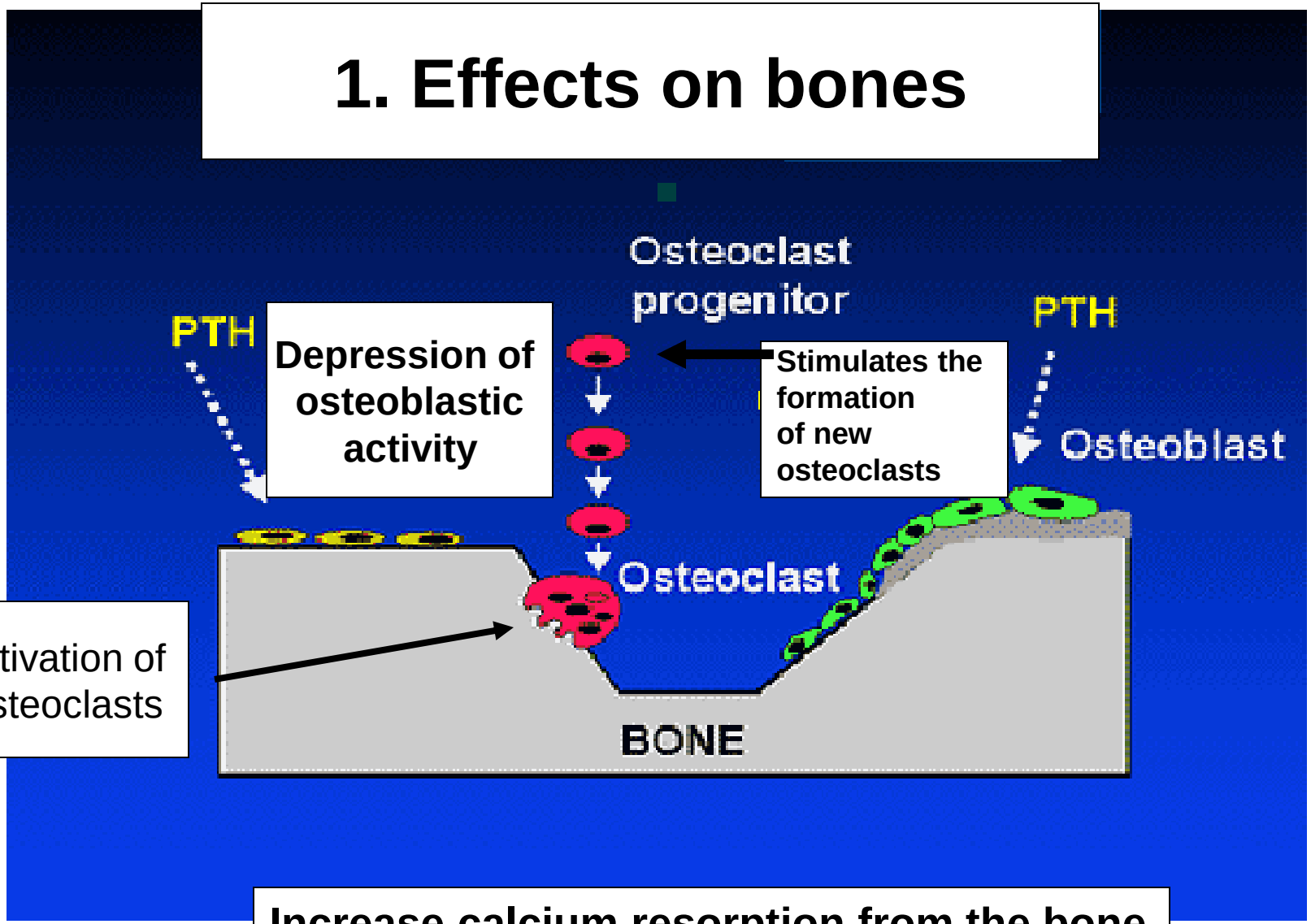
Kidney



Intestine



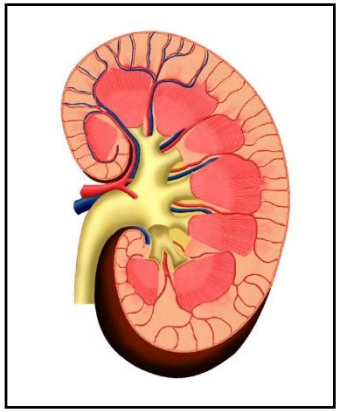
1. Effects on bones



Increase calcium resorption from the bone

2. Effects on Kidneys

(PTH) →



1. ↓ phosphate reabsorption from the proximal convoluted tubules (phosphaturic action).

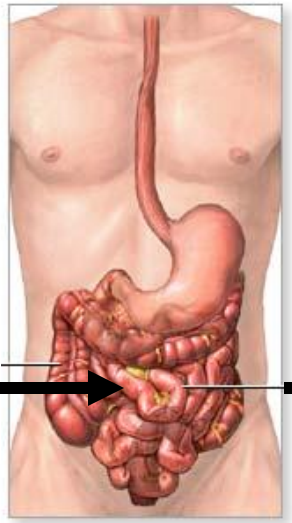
   ↑ Phosphate excretion in the urine

   ↓ plasma phosphate concentration

2. ↑ Ca++ & Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle.

3. ↑ Formation of 1,25 vit D3 in the kidney.

3. Effects on intestine

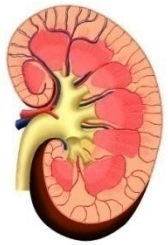
(PTH) →  → ↑ absorption of calcium and phosphate indirectly through stimulating formation of $1,25 – (OH)_2\text{-}D_3$ in kidney

Parathyroid hormone (PTH)

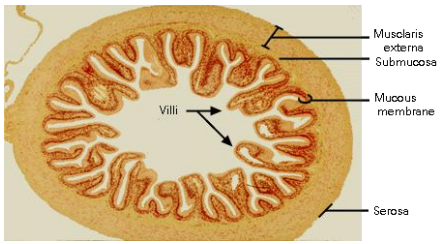
Increase plasma Ca++ level
Decrease phosphate level

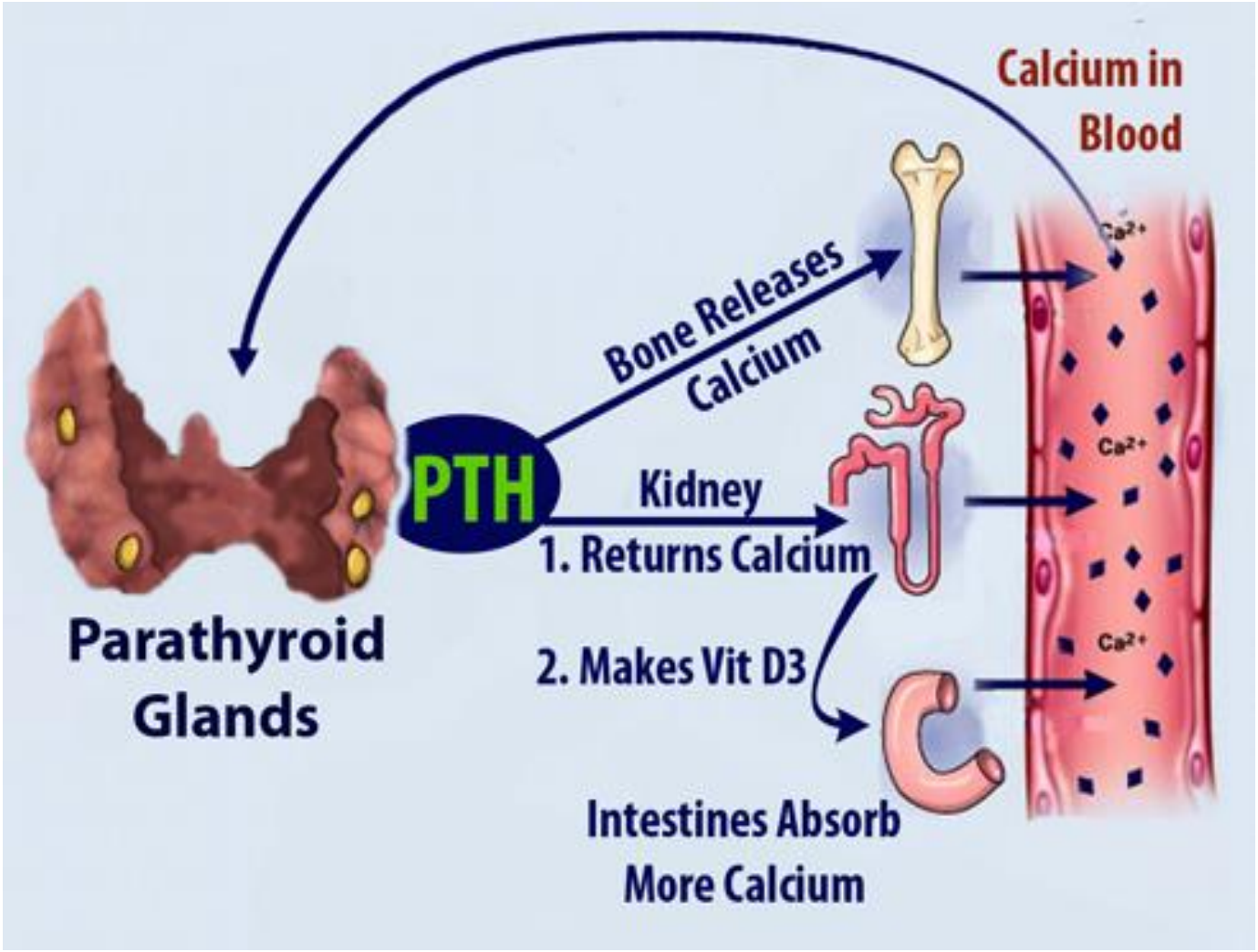
Bone

Kidney

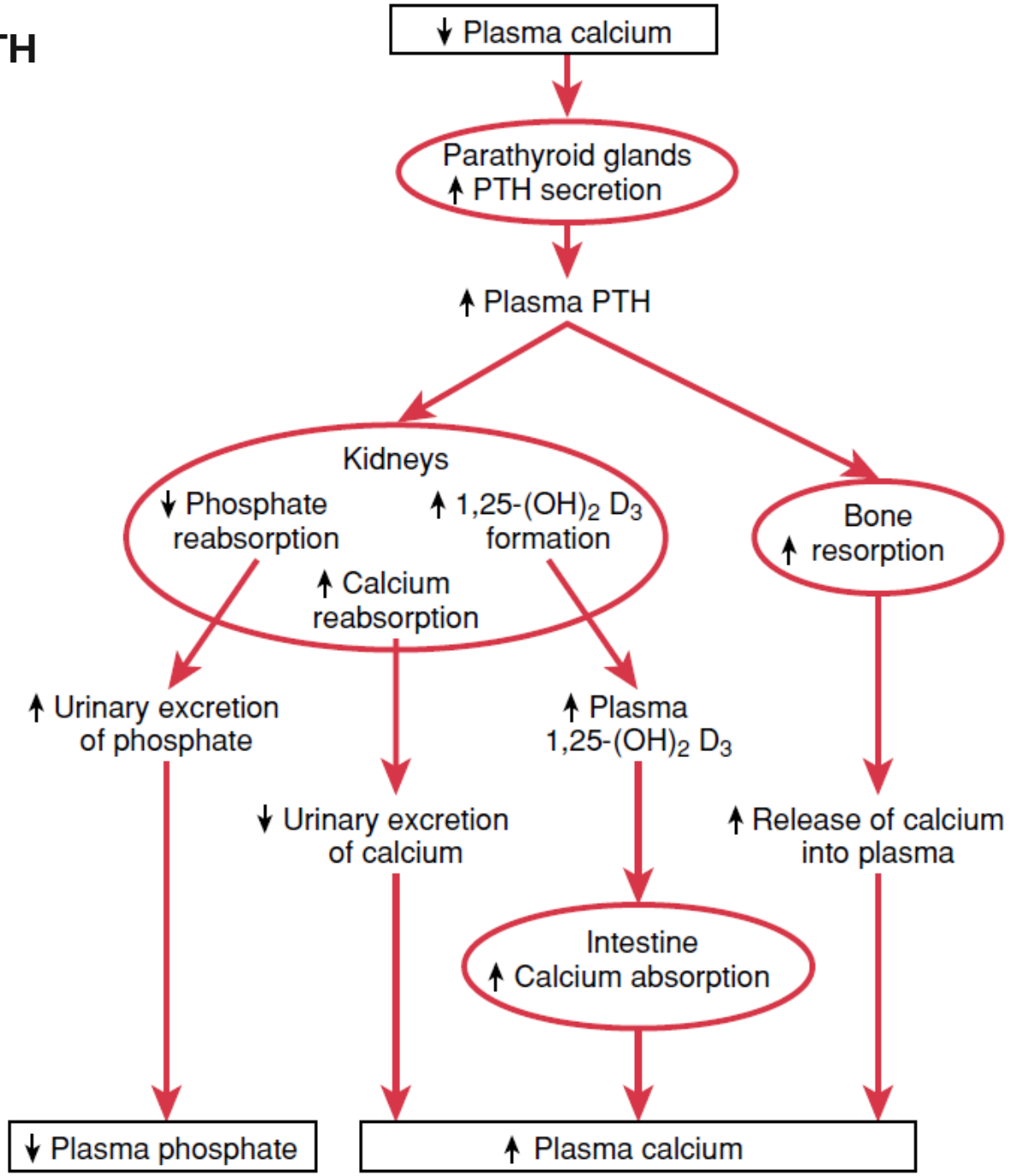


Intestine

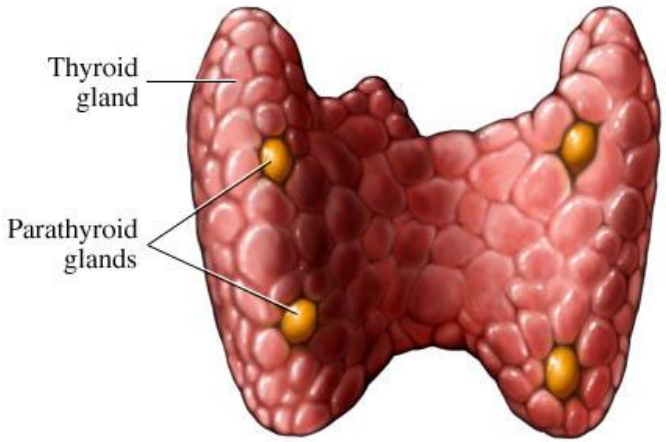



Calcium in Blood
Bone Releases Calcium
PTH
Kidney
1. Returns Calcium
2. Makes Vit D3
Parathyroid Glands
Intestines Absorb More Calcium
Ca2+
Ca2+
Ca2+

Effect of Calcium level on PTH



Parathyriod gland

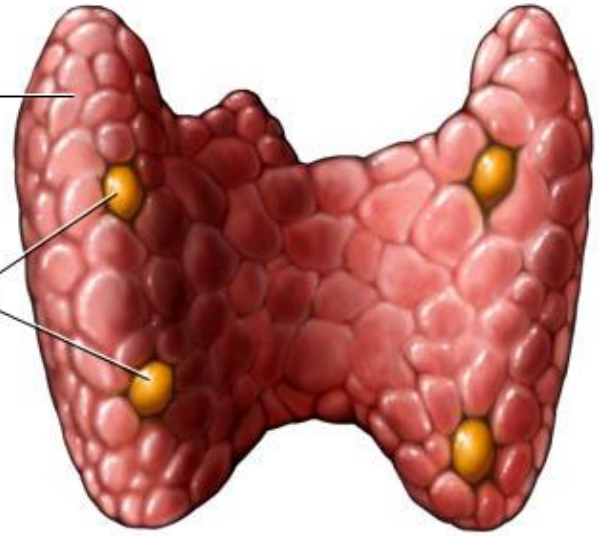


It is essential for life

Calcitonin

Calcitonin ←

Parathyroid hormone (PTH) ←



Calcitonin

- Source: **Secreted by the parafollicular cells (C cells) of the thyroid gland.**
- **Nature: 32 amino acid peptide.**
- **Function:**
  - **Decrease blood** Ca++ **level very rapidly within minutes.**
  - **Opposite effect to PTH**
- **Stimulus for secretion:**
  Increased plasma calcium concentration

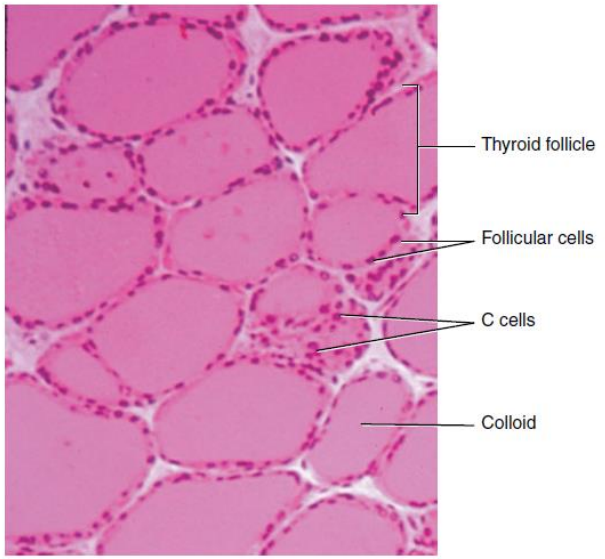
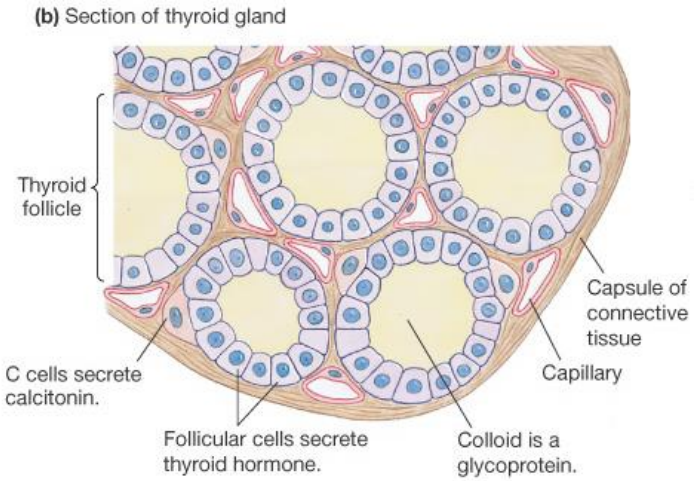


Figure 17.8 The Thyroid Gland. (*a*) Gross anatomy; (*b*) histology.



Actions:

Calcitonin

↓

Plasma calcium concentration

On bone

[1] ↑ Ca++ deposition of bone

[2] Inhibits Bone resorption:

inhibition of osteoclasts

↓ formation of osteoclasts

On kidney

↓↓ Ca++ reabsorption

↑↑ Ca++ excretion (in addition to phosphate)

Calcitonin secretion:

- **Other causes of ↑ calcitonin secretion**

1 –Estrogen

2- gastrin

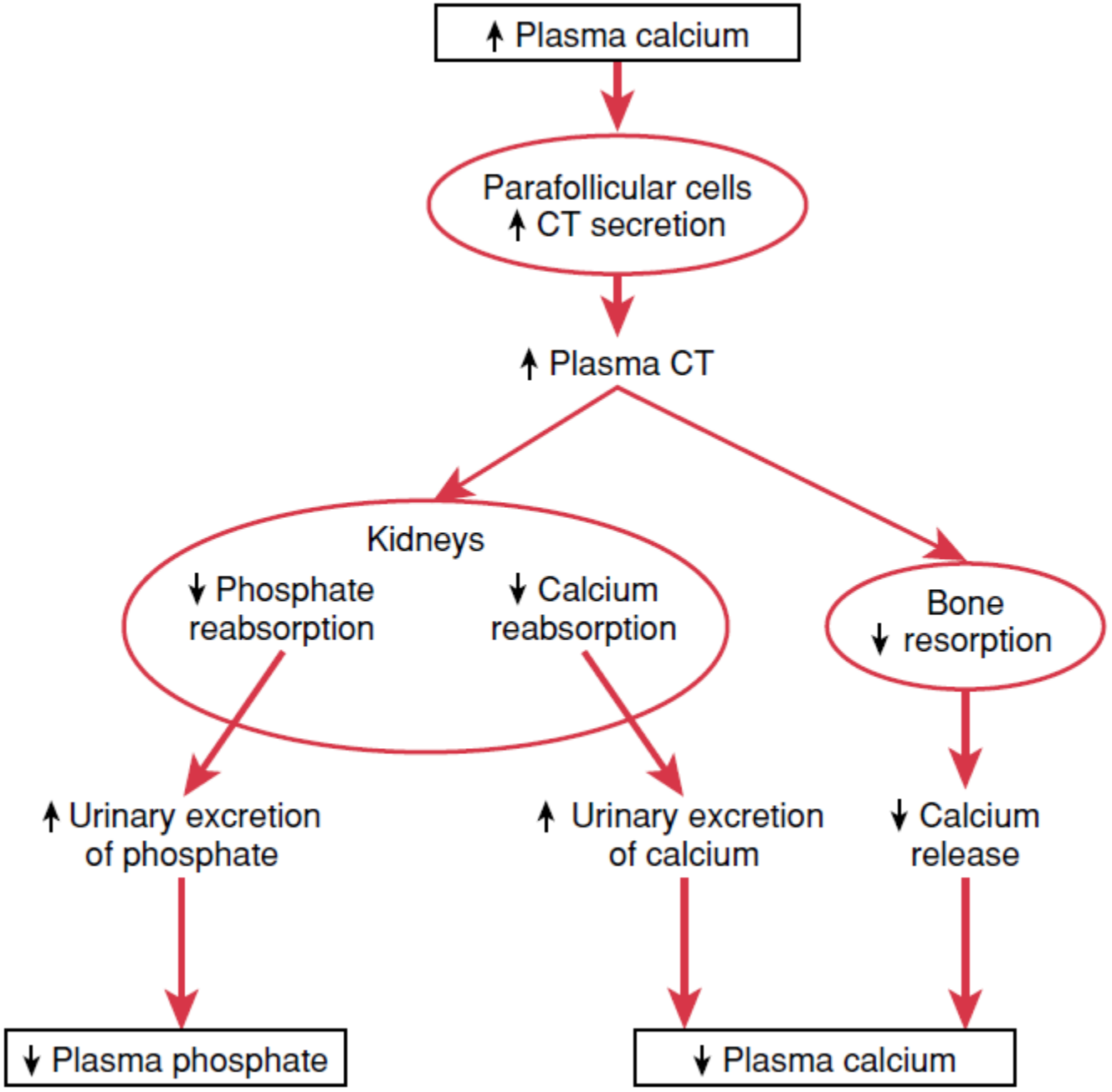
3- glucagon

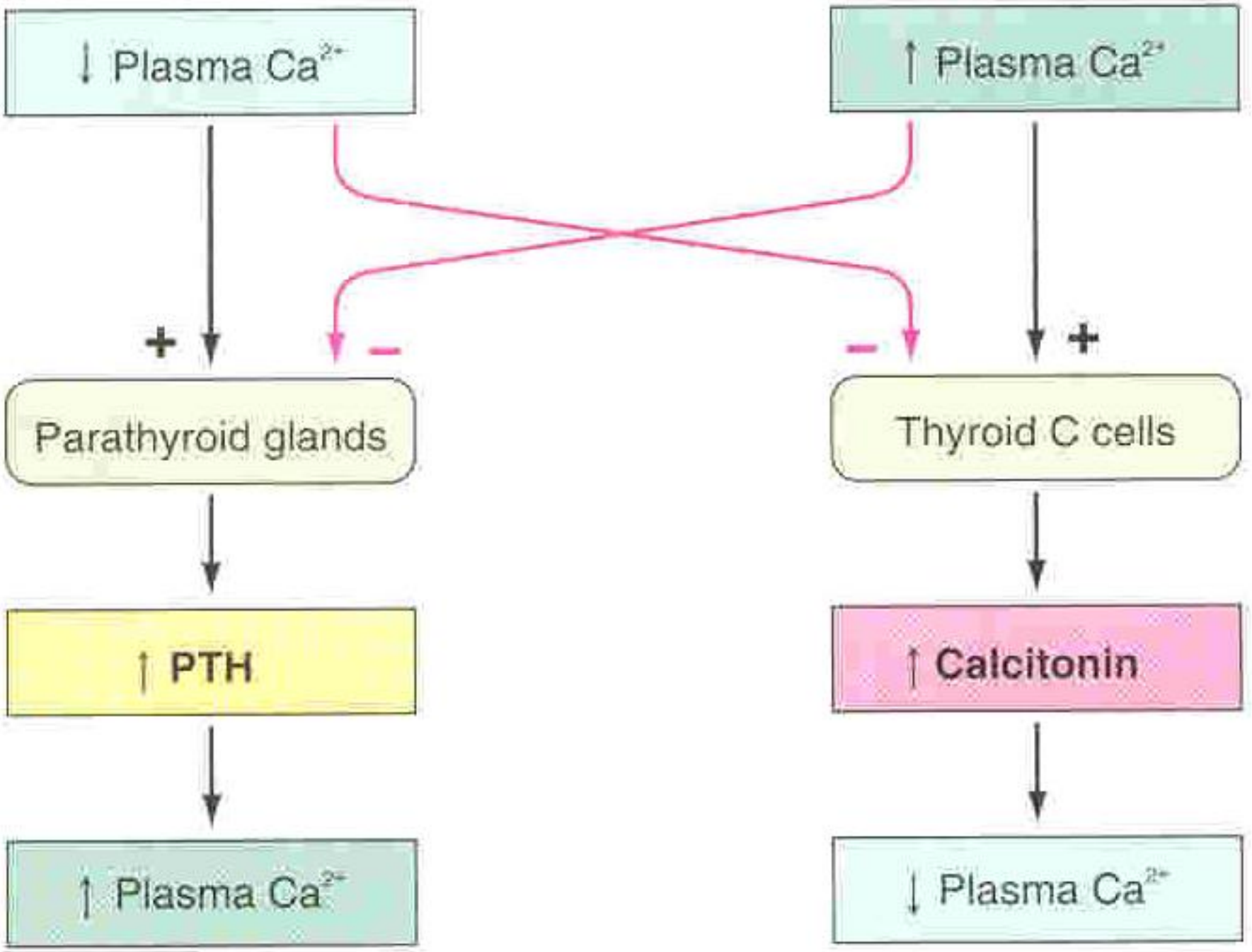
4-secretin

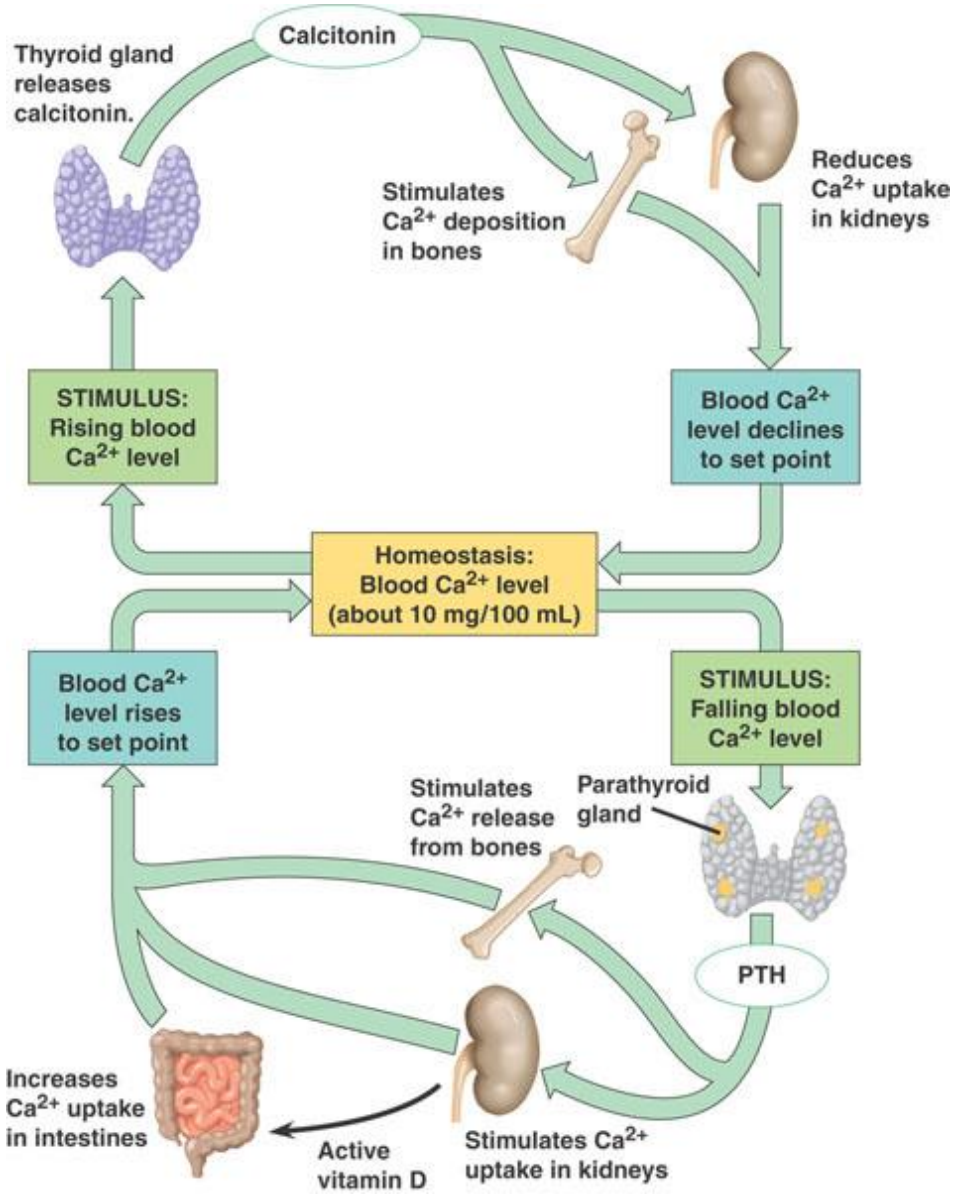
5- cck

6- beta-adrenergic stimulation

Effect of Calcium level on calcitonin




↓ Plasma Ca^{2+}
↑ Plasma Ca^{2+}
+
−
−
+
Parathyroid glands
Thyroid C cells
↑ PTH
↑ Calcitonin
↑ Plasma Ca^{2+}
↓ Plasma Ca^{2+}


Calcitonin
Thyroid gland releases calcitonin.
Stimulates Ca^{2+} deposition in bones
Reduces Ca^{2+} uptake in kidneys
STIMULUS: Rising blood Ca^{2+} level
Blood Ca^{2+} level declines to set point
Homeostasis: Blood Ca^{2+} level (about 10 mg/100 mL)
Blood Ca^{2+} level rises to set point
STIMULUS: Falling blood Ca^{2+} level
Stimulates Ca^{2+} release from bones
Parathyroid gland
PTH
Increases Ca^{2+} uptake in intestines
Active vitamin D
Stimulates Ca^{2+} uptake in kidneys

Abnormalities:

- **Rickets**
- **Osteomalacia**
- **Osteoporosis**
- **Hypo/hyperparathyroidism**

❑ Rickets (In children)

• **Cause:**
lack of vitamin D leading to calcium/phosphate deficiency in ECF

•Occur in the spring???

•Features:
- -Low plasma calcium and phosphate
- -Weak bones
- -Tetany

• Treatment of Rickets:
supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D.

Tetany in Rickets

early stages:

- no tetany
- (PTH stimulate osteoclastic absorption of bone)
- ECF Calcium level is normal

When the bones finally become exhausted of calcium

Calcium level falls rapidly.

blood level of calcium falls below 7 mg/dl

→ signs of tetany:
(positive Chvostek's sign)

→Death:
tetanic respiratory spasm

positive Chvostek's sign is facial nerve irritability/spasms elicited by tapping the nerve

❑ Osteomalacia-"Adult Rickets".

(rare).

• serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat).

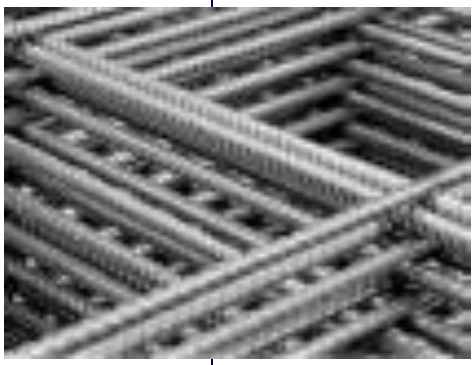
• almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

❑ Osteomalacia-“Renal Rickets".

- **Due to prolonged kidney disease**
- **Failure of the damaged kidney to form…..**

Bone composition

- **Organic Matrix**
  - **Collagen Fibers (95%)**
  - **Ground Substance (5%)**
    - **ECF**
    - **Proteoglycans**

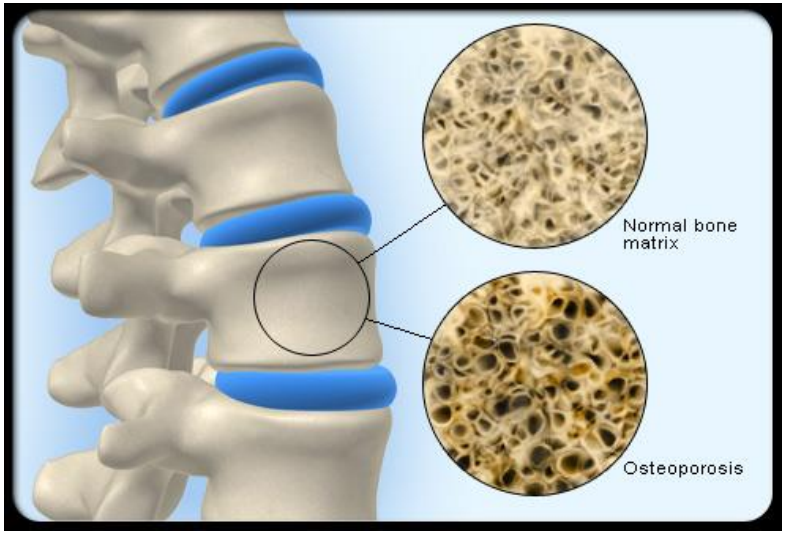


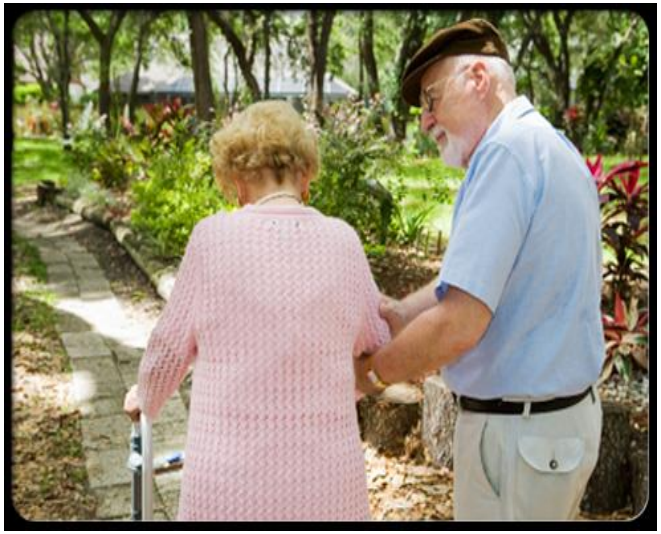
- **Bone Salts**
  - **Salts of Ca^{++} and PO$_4^{3-}$**
  - **In the form of**
    Hydroxyapatite crystals
    $Ca_{10}(PO_4)_6(OH)_2$
    Mg, Na, K, Carbonate ions

In adequate bone mineralization

- Rickets
- Osteomalacia


Osteoporosis


Normal bone matrix
Osteoporosis



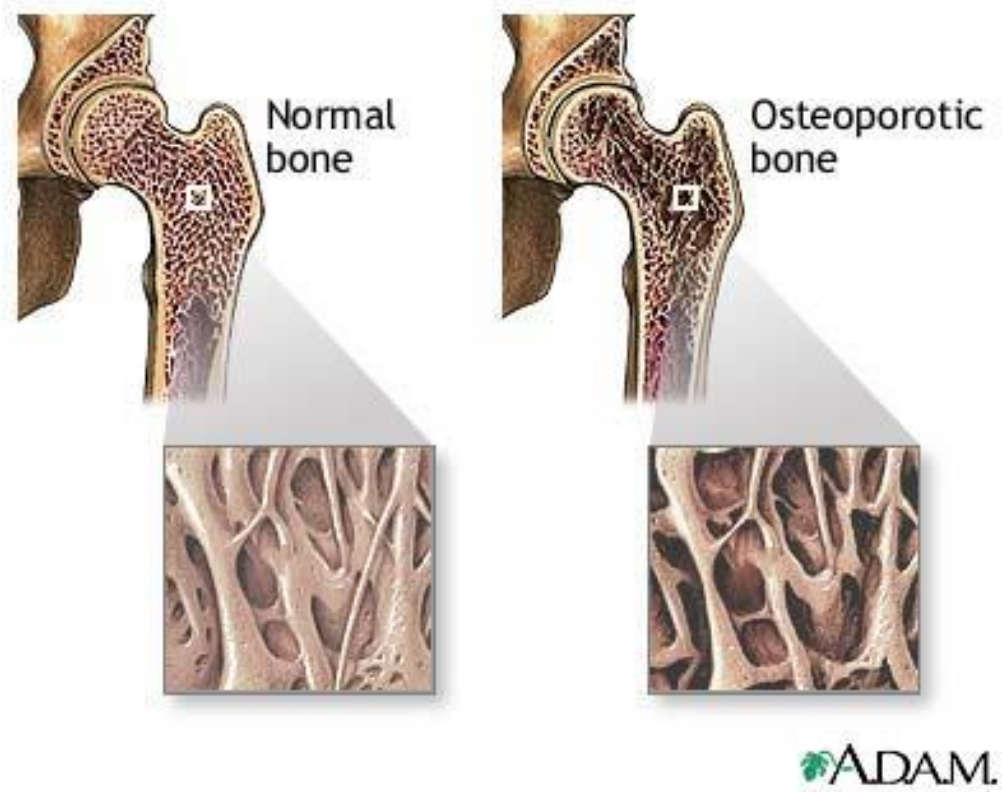
❑ Osteoporosis

- Osteoporosis is the most common of all bone diseases in adults, especially in old age.

- results from equal loss of both organic bone matrix and minerals resulting in loss of total bone mass and strength

- the cause of the diminished bone:
  - the osteoblastic activity in the bone is usually less than normal so the rate of bone osteoid deposition is depressed.
  - excess osteoclastic activity.

Osteoporosis

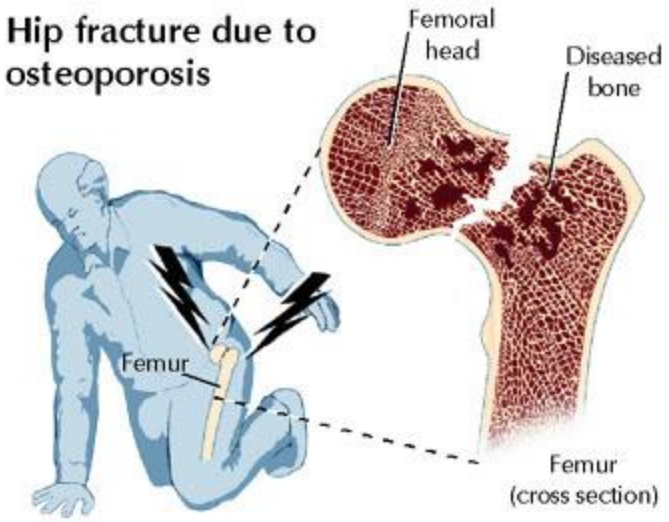


Osteoporosis

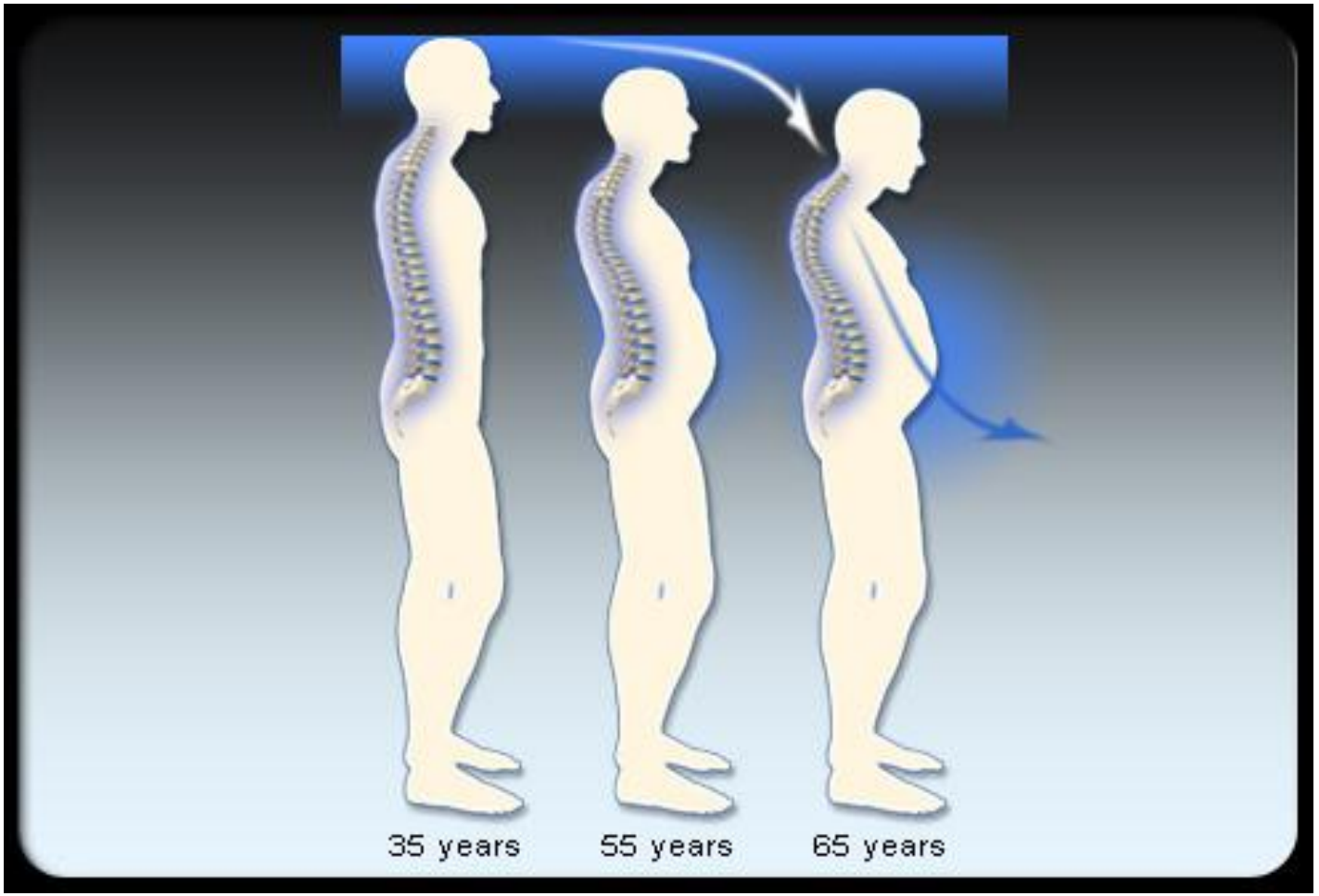
- causes of osteoporosis:

(1) lack of physical stress
(2) malnutrition
(3) lack of vitamin C
(4) postmenopausal lack of estrogen
(5) old age
(6) Cushing's syndrome

❑ symptoms of osteoporosis



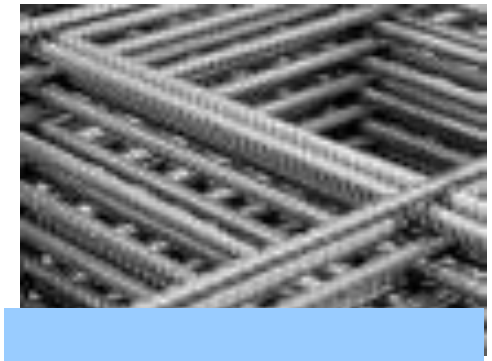
Osteoporosis



Bone composition

- **Organic Matrix**
  - **Collagen Fibers (95%)**
  - **Ground Substance (5%)**
    - **ECF**
    - **Proteoglycans**
- **Bone Salts**
  - **Salts of Ca++ & PO_4^-**
  - **In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$**
  - **Mg, Na, K, Carbonate ions**

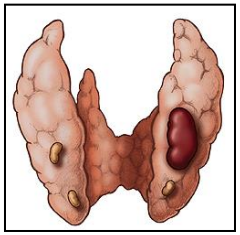
In adequate bone matrix and minerals



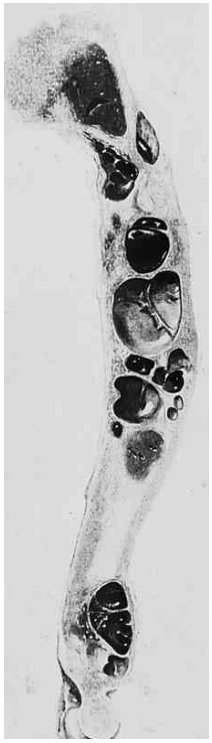
•Osteoporosis

Disorders of parathyroid hormone secretion

Hyperparathyroidism (PTH Excess)



Primary



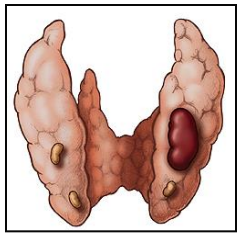
Manifestations:

- Hypercalcemia ↑ Ca^{2+}
- Hypophosphemia ↓PO^{-}_{4}
- Hypercalciuria
- Demineralisation of bone
  multiple bone cysts (osteitis fibrosa cystic)
- Broken bones
- ↑ Alkaline phosphatase

Manifestations:

- CNS depressed
- Peripheral nervous system depressed
- muscle weakness
- Constipation
- Abdominal pain
- Peptic ulcer
- Decrease appetite
- Depressed relaxation of the heart during systole.
- Calcium containing stones in kidney
- Parathyroid poisoning:
  Precipitation of calcium in soft tissues occur when Ca^{2+} > 17mg/dl → death

Hyperparathyroidism (PTH Excess)



Primary

Manifestations:

- Hypercalcemia ↑ Ca^{2+}
- Hypophosphemia ↓PO^{-}_{4}
- Hypercalciuria
- Demineralisation of bone
  multiple bone cysts (osteitis fibrosa cystic)
- Calcium containing stones in kidney
- Precipitation of calcium in soft tissues occur when Ca^{2+} > 17mg/dl.

Secondary (compensatory) Hyperparathyroidism

- **(due to ↓ Ca^{2+} in ECF)**
- **Causes:**

1) Low calcium diet
2) Pregnancy
3) Lactation
4) Rickets
5) Osteomalcia
6) Chronic renal failure
↓ 1,25(OH) – D3 synthesis

Hypoparathyroidism (rare)

causes

- Injury to the parathyroid glands (surgery).
-Autoimmune.

symptoms (due to hypocalcaemia)

Tingling in the lips, fingers, and toes
Dry hair, brittle nails, and dry, coarse skin
Muscle cramps and pain in the face, hands, legs, and feet
Cataracts on the eyes
Malformations of the teeth, including weakened tooth enamel.
Loss of memory
Headaches

Signs of Hypoparathyroidism

- Tetany can be overt or latent

- **Chvostek's sign:** Tapping the facial nerve as it emerge from the parotid gland in front of the ear → causes contraction of facial muscles.
- **Trousseau's sign :**
- Arresting (stopping) blood flow to the forearm for few minutes (e.g., by sphygmomanometer) → causes flexion at the wrist, thumb and metacarpophalangeal joints.

Signs of Hypoparathyroidism

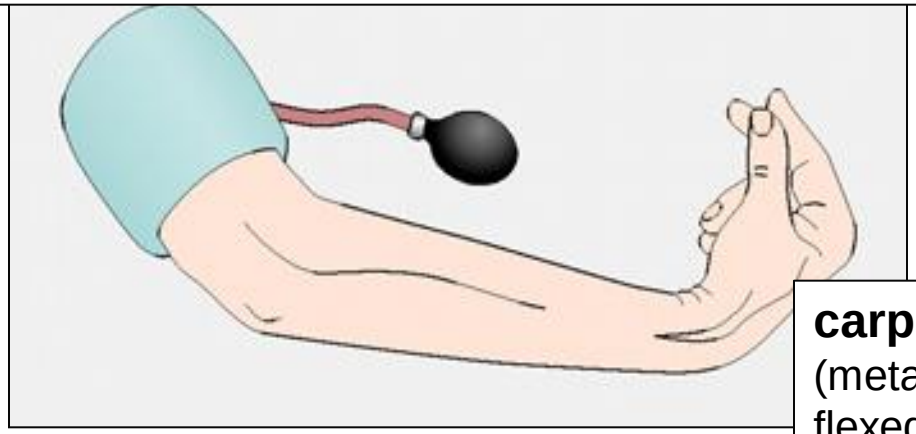
- Positive Chvostek's sign(facial muscle twitch)
- Positive Trousseau's sign(carpal spasm)
- Delayed cardiac repolarization with prolongation of the QT interval
- Paresthesia
- Tetany: can be overt or latent

- **Treatment:**

Calcium carbonate and vitamin D supplements

Trousseau Sign

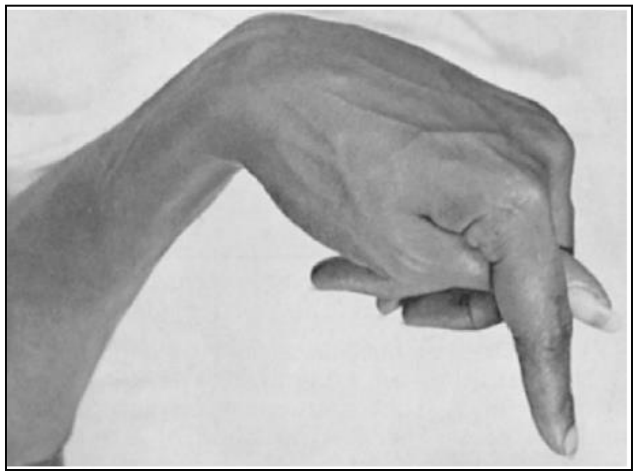
When an occlusion of brachial artery with a blood pressure cuff:



carpal spasms occur.
(metacarpophalangeal and wrist joints are flexed, fingers are adducted)

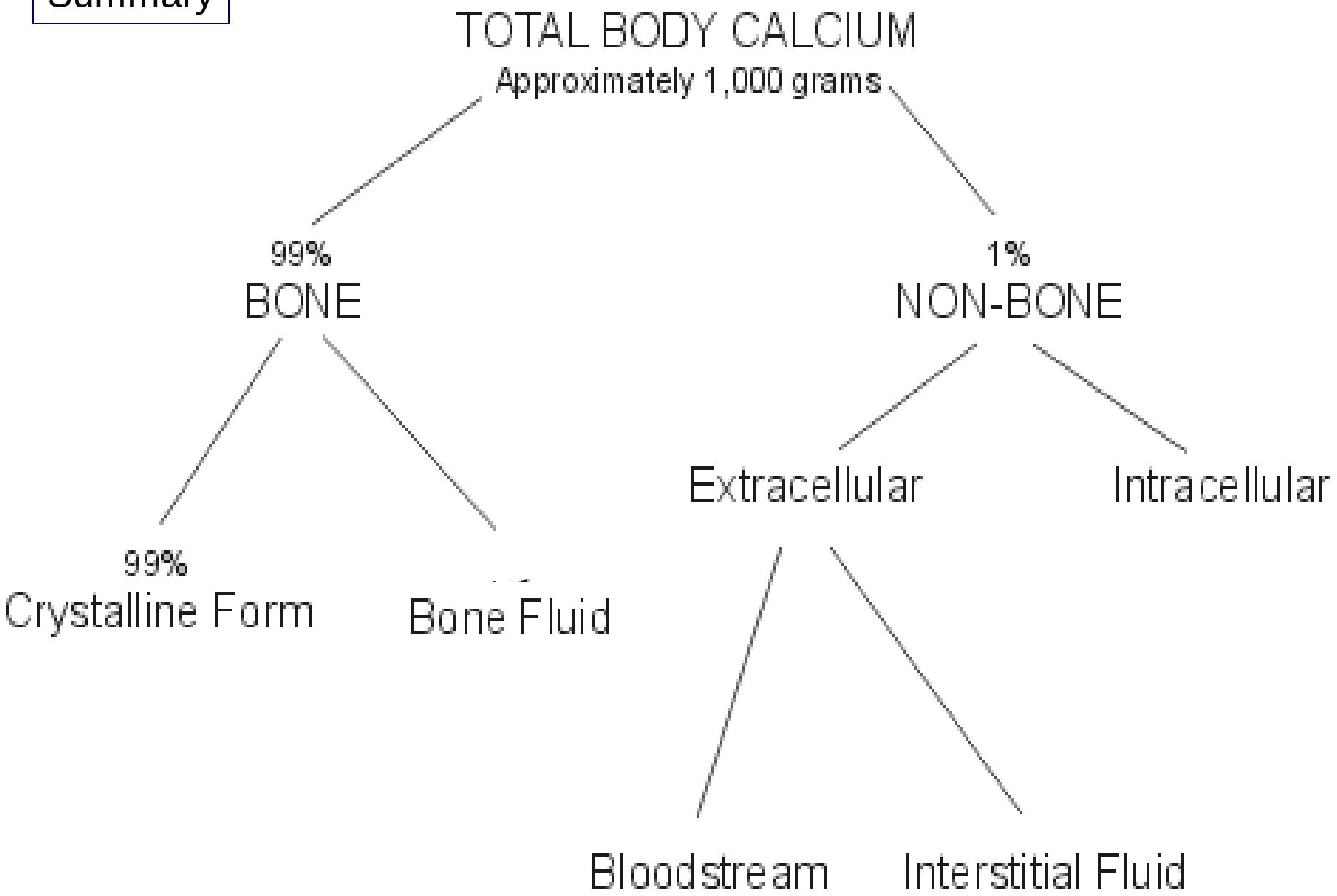
A

B



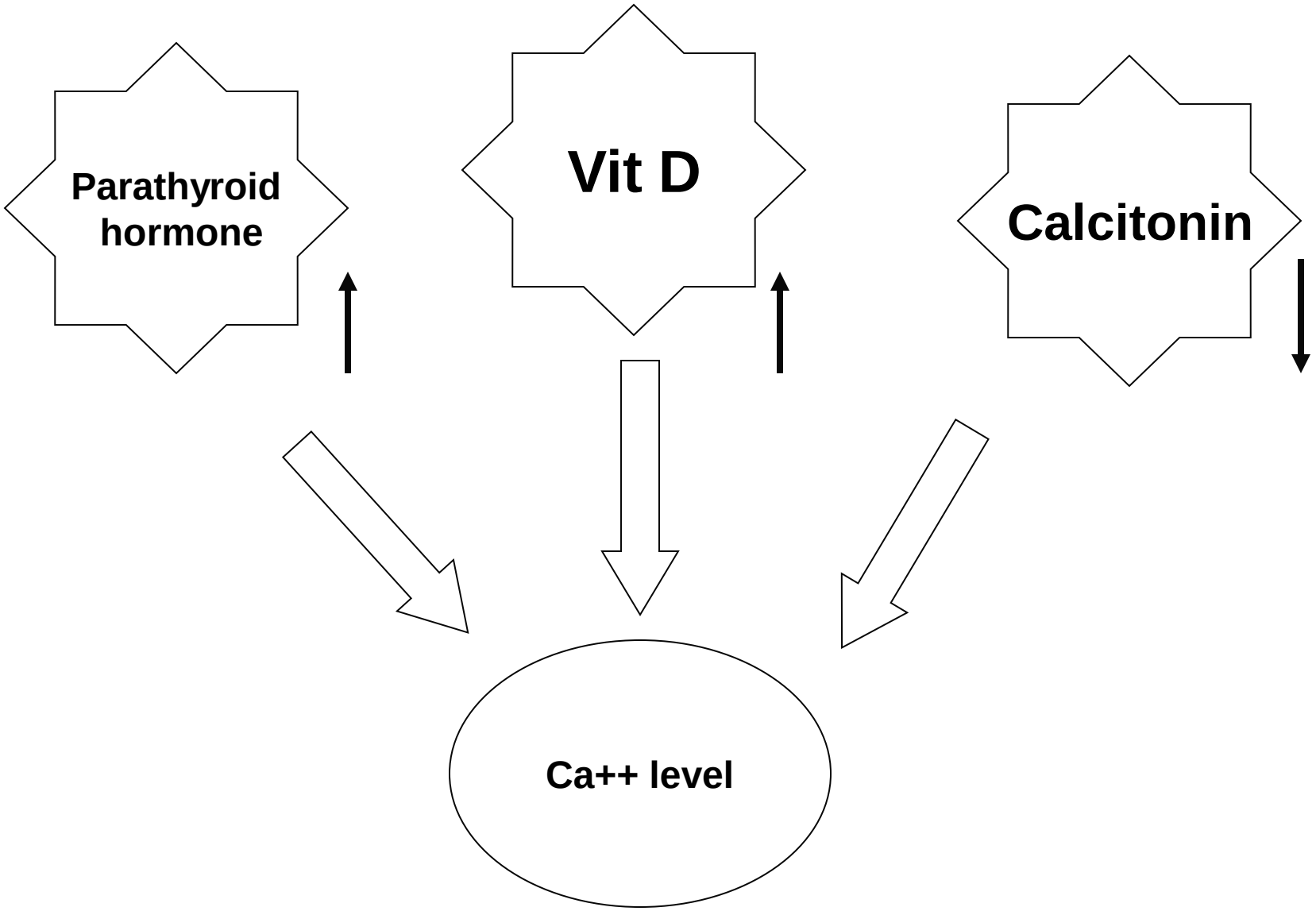
(This is due to enhanced neuromuscular excitability)

Summary


TOTAL BODY CALCIUM
Approximately 1,000 grams
99%
BONE
1%
NON-BONE
99%
Crystalline Form
Bone Fluid
Extracellular
Intracellular
Bloodstream
Interstitial Fluid

Summary

Three Hormones



VITAMIN D

Actions:

- Calcium
  - ↑Absorption from Bone
  - ↓Renal Excretion
  - ↑Absorption from GIT
- Phosphate
  - ↑Absorption from Bone
  - ↓Renal Excretion

PARATHORMONE

Targets are Bones & Kidneys

Actions:

- **Calcium**
  - **↑ Absorption from Bone**
  - **↓ Renal Excretion**
- **Phosphate**
  - **↑ Absorption from Bone**
  - **↑ Renal Excretion**

CALCITONIN

Actions

- **Immediate effect**
  - **Osteoclastic Activity ↓**
- **Prolonged Effect**
  - **Formation of new Osteoclasts ↓**
- **Calcium ↓**
- **Phosphate ↓**

Save your bones

THANK YOU

Dr. Abeer Al-Ghumlas