بسم الله الرحمن الرحيم

ENDOCRINOLOGY

Calcium Homeostasis
Hypo and hyper–parathyroidism

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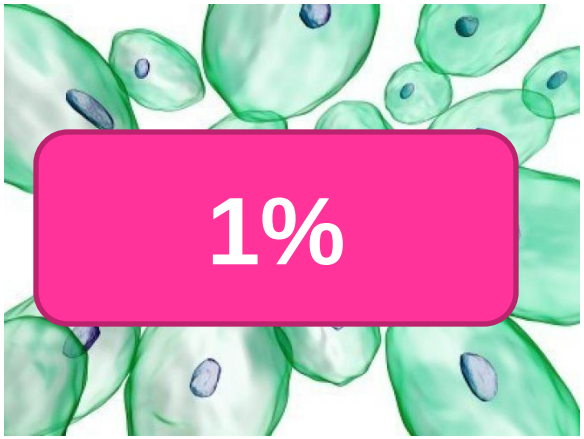
Objectives

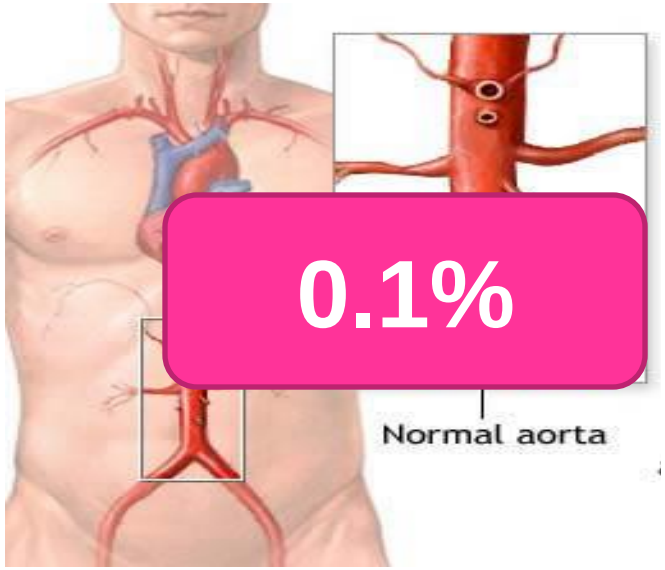
At the end of this lecture you should be able to:

- **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%

Protein-bound calcium:

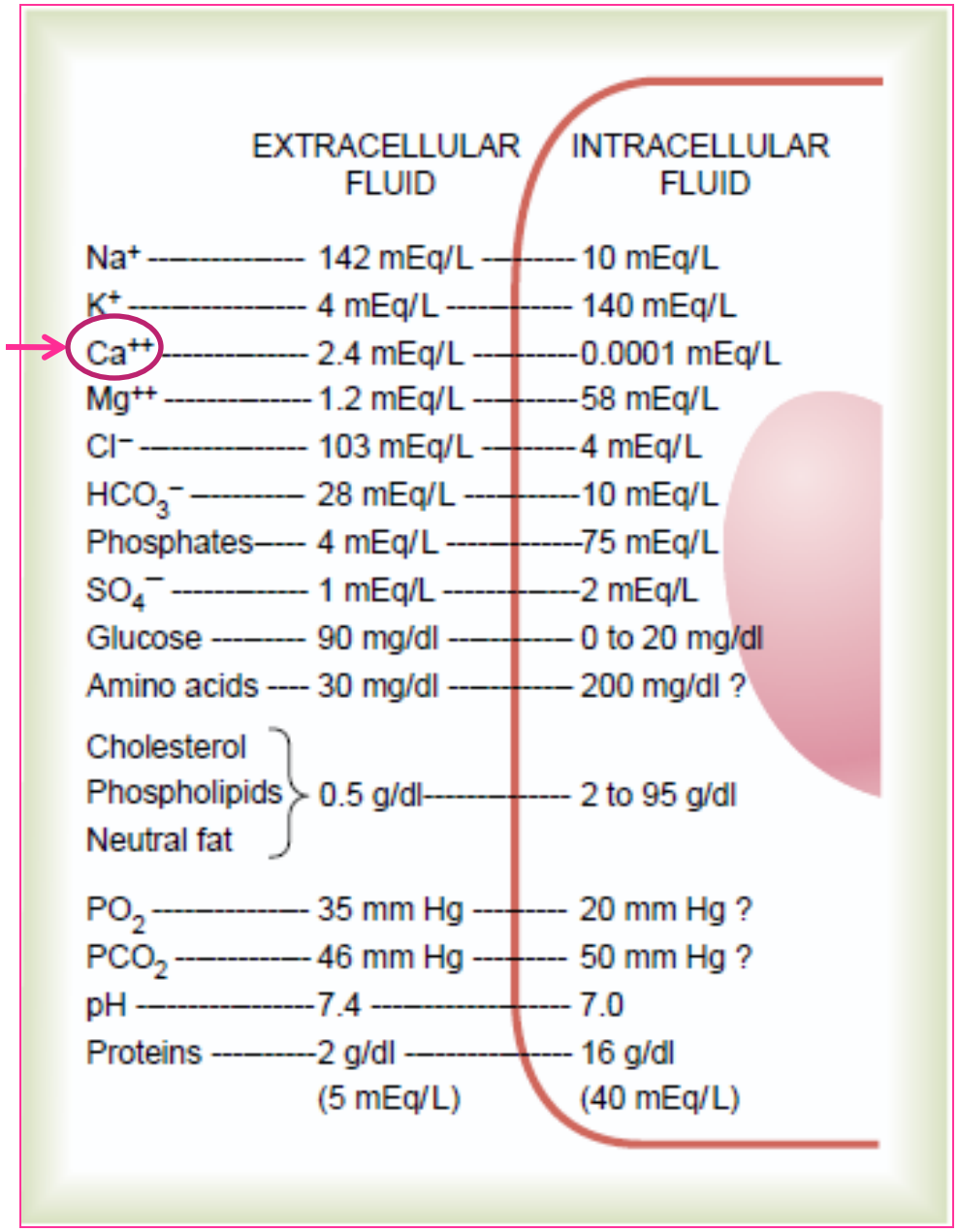
- Most of this calcium is bound to albumin & much smaller fraction is bound to globulin

- Binding of calcium to albumin is pH-dependent

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

- **Alkalosis** ↓ **Ionized Ca^{2+}**

- **Acidosis** ↑ **Ionized Ca^{2+}**


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)

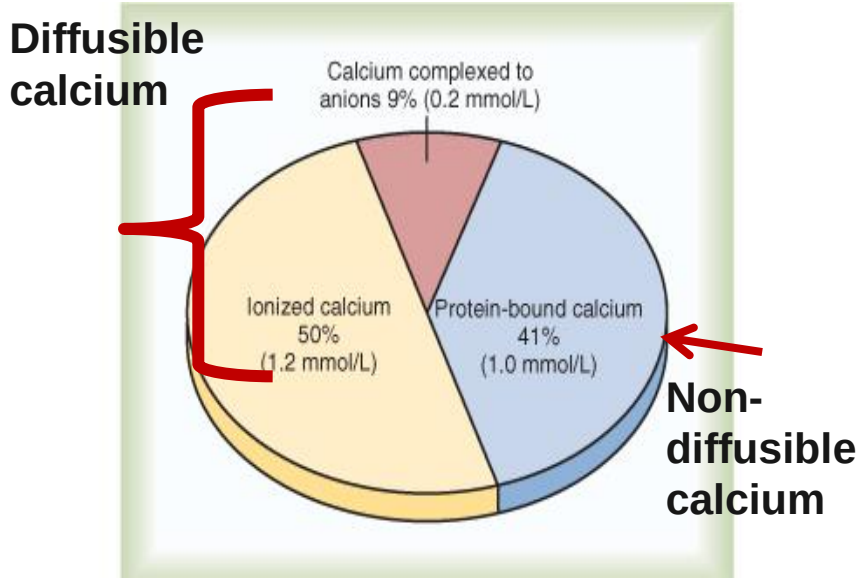
Plasma Calcium

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

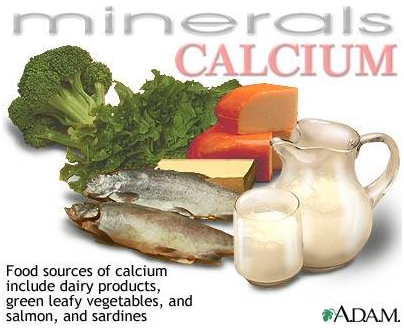
- **Phosphate plasma concentration is around 4 mg/dL.**

- **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

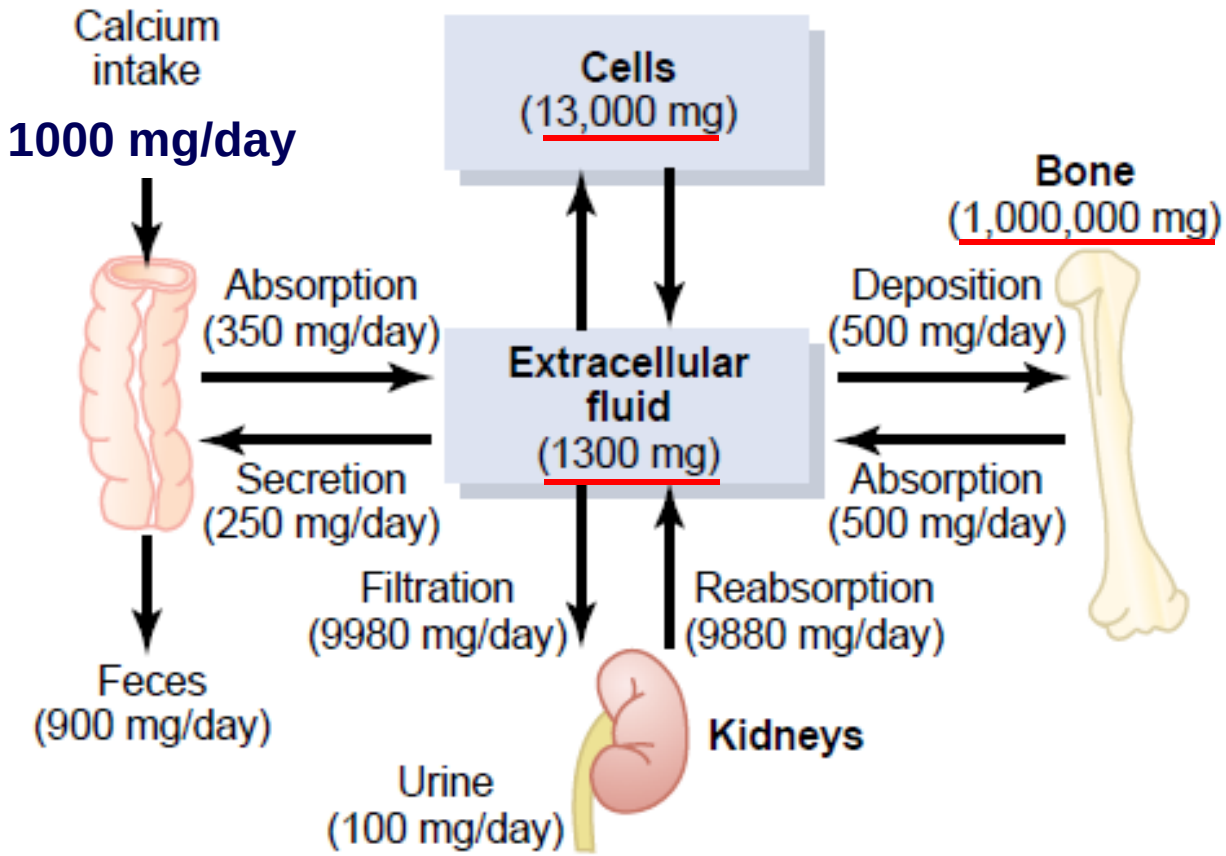
- **Infants & adults: 12.5 -25 mmol/day**
- **Pregnancy,**
- **lactation**
- **after menopause:**

25-35 mmol/day

Absorption

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

Calcium Metabolism in an adult human



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

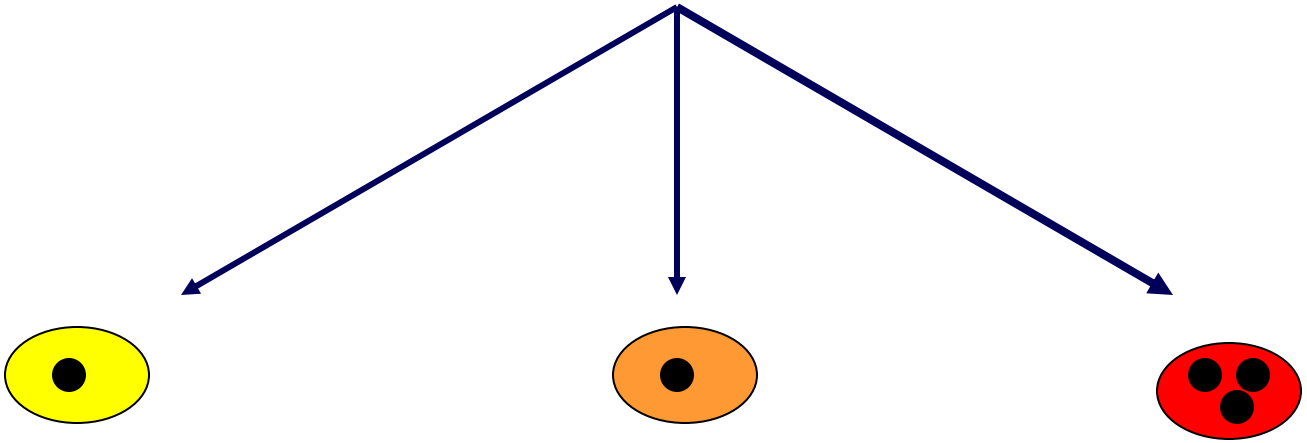
Compressional force

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



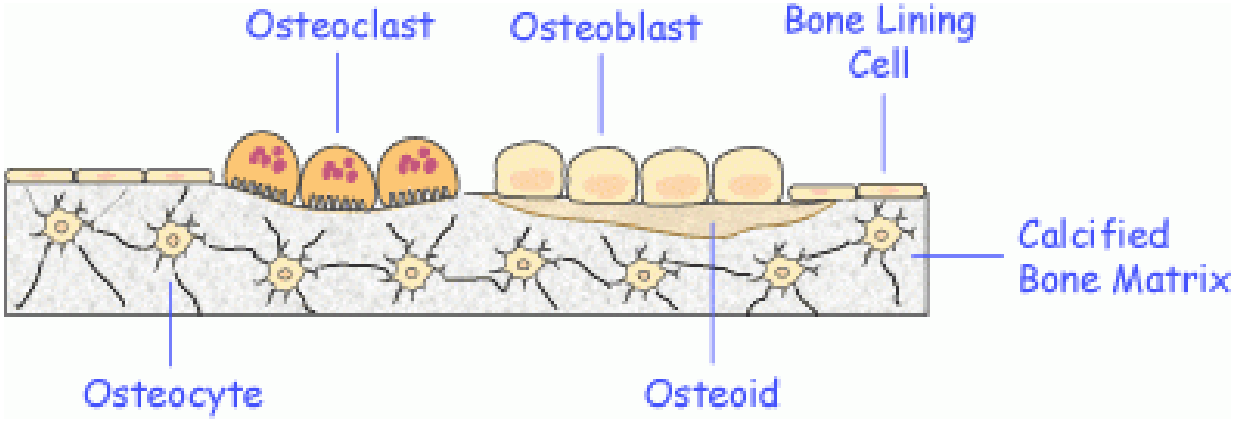
Osteoblasts

(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

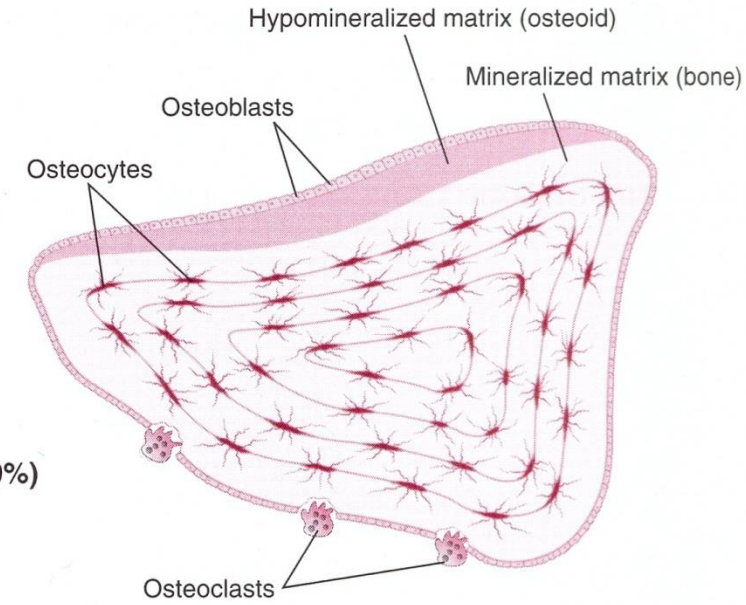
Cells (2%)

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%)



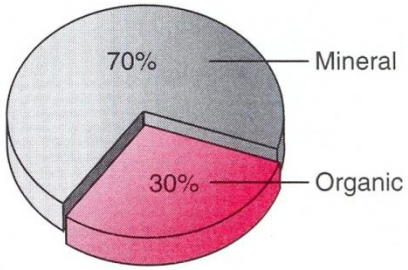


Figure 8.1 The composition of bone.


Hydrangea Garden, Clermont, Kentucky

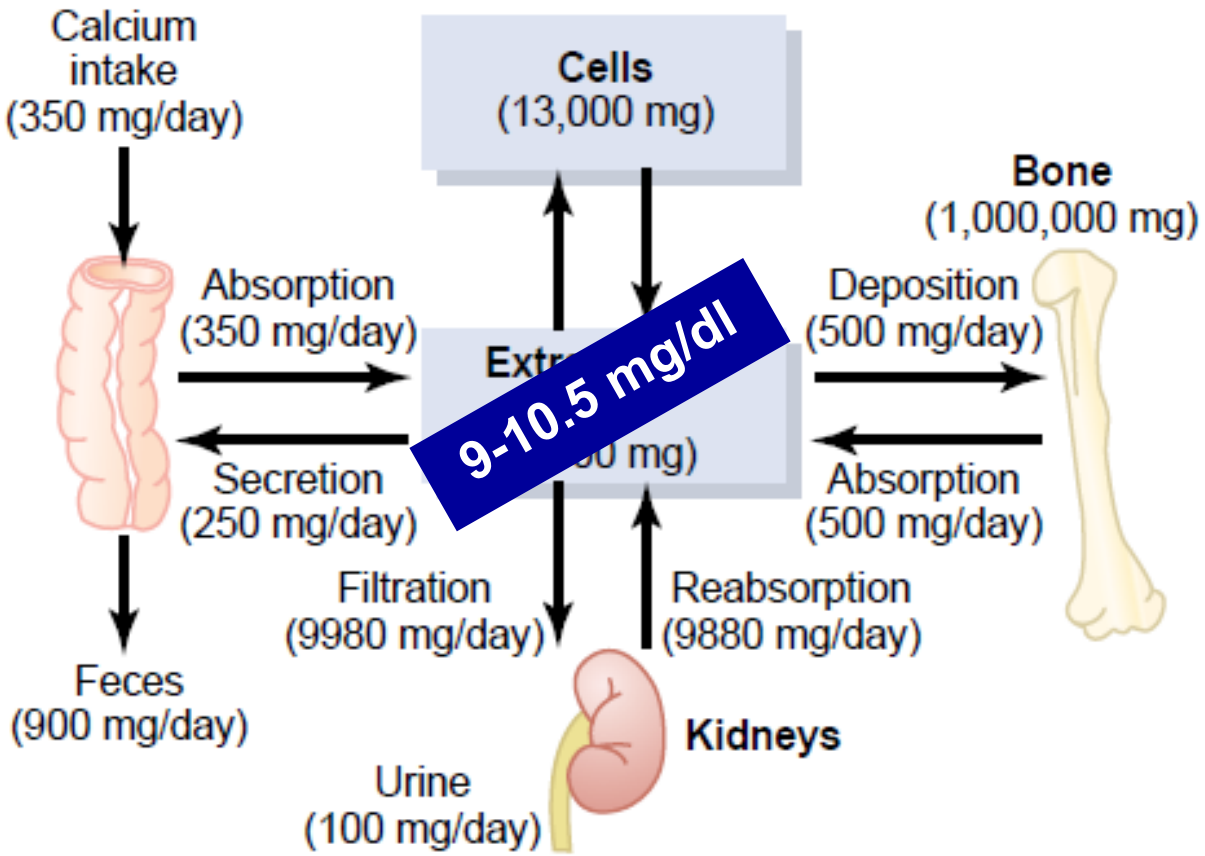
Regulation of Calcium level

REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS

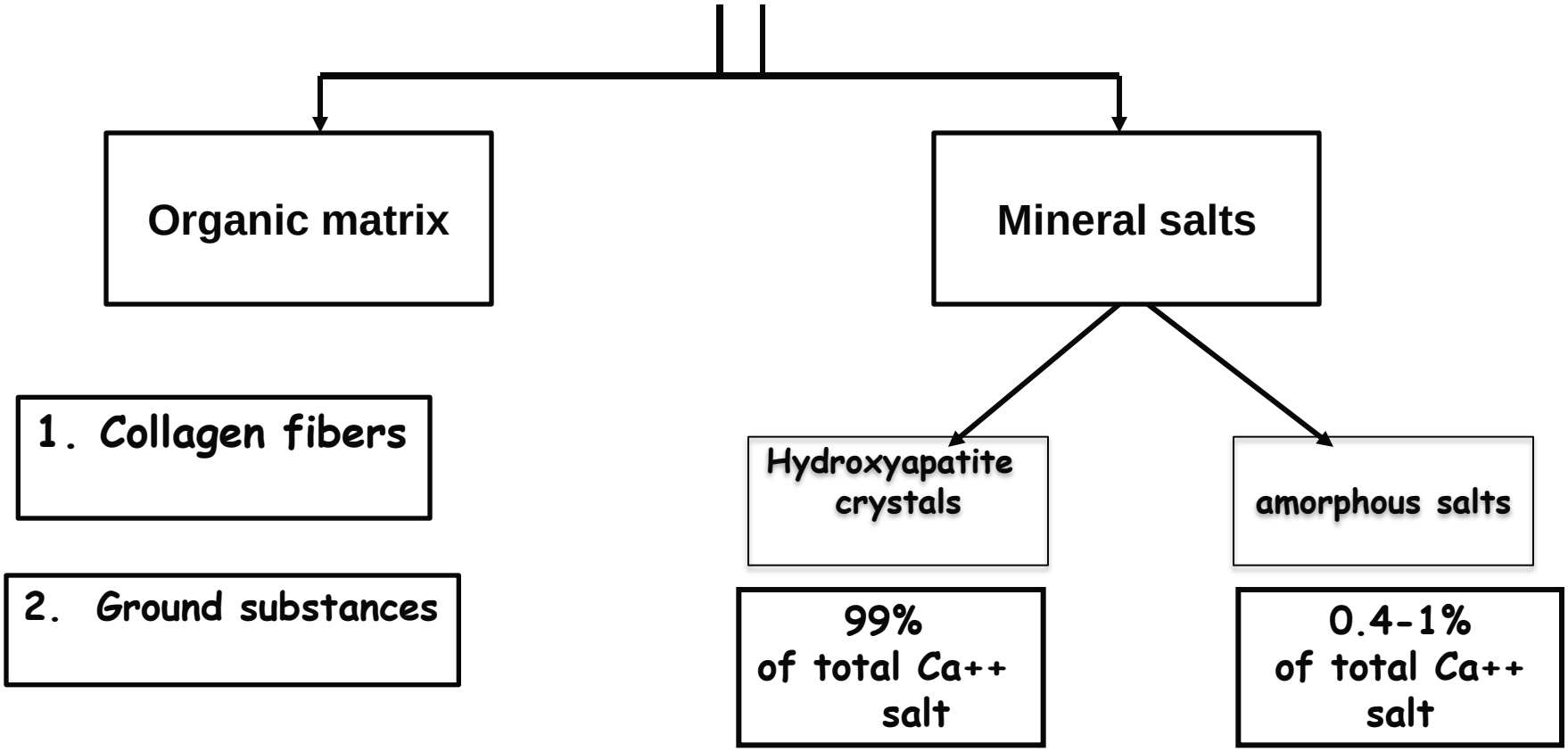
- Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium

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

Calcium Metabolism in an adult human



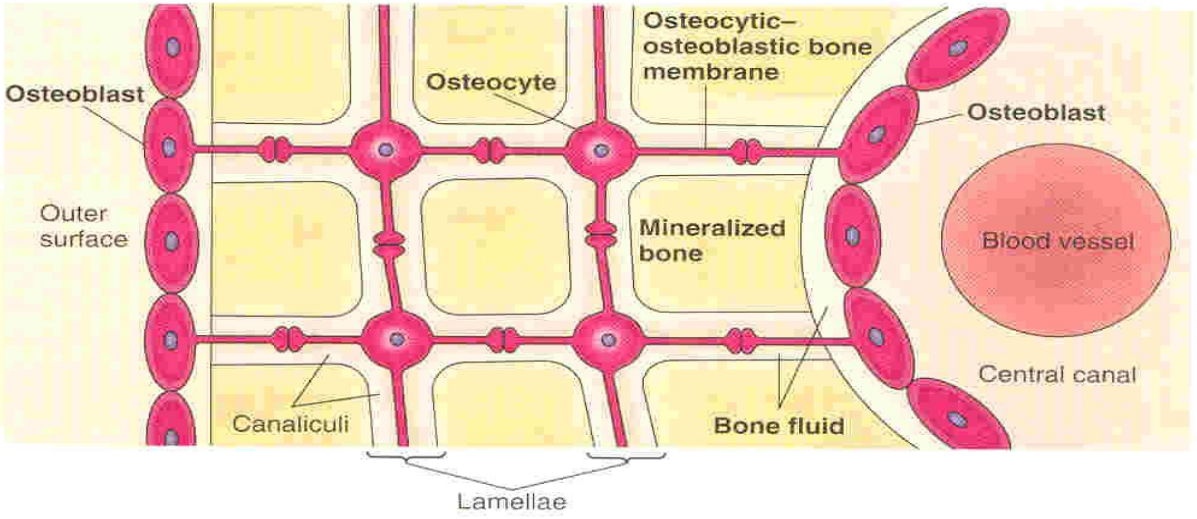
Composition of bones



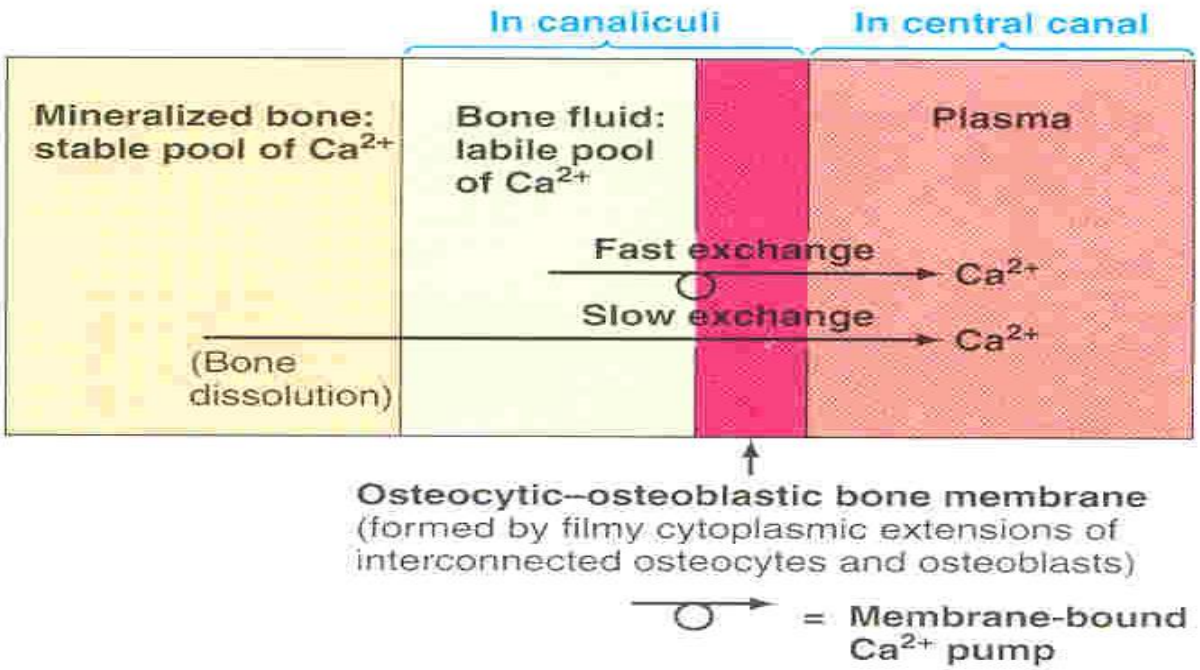
Bone composition

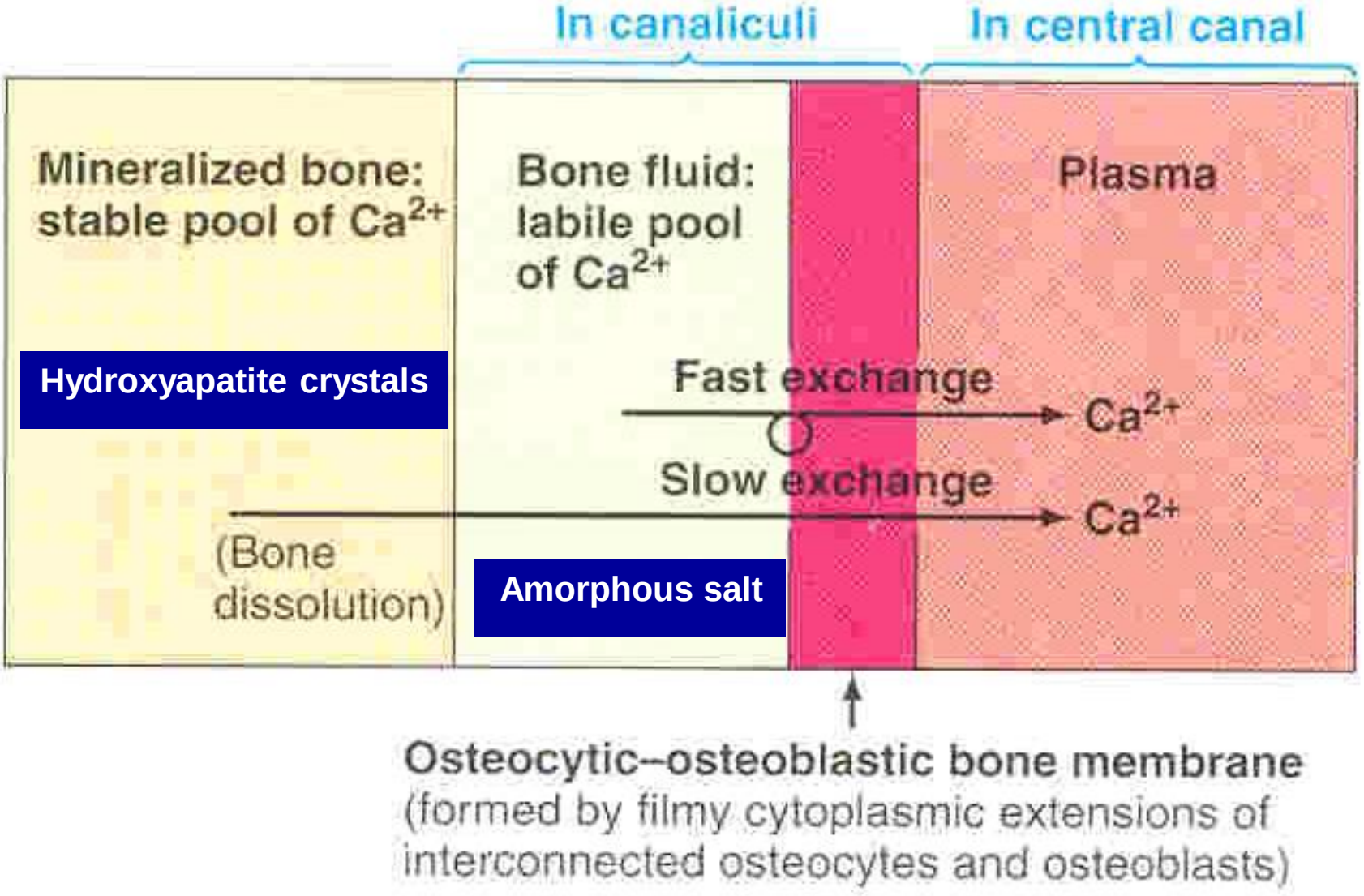
(2) Bone Salts

- 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

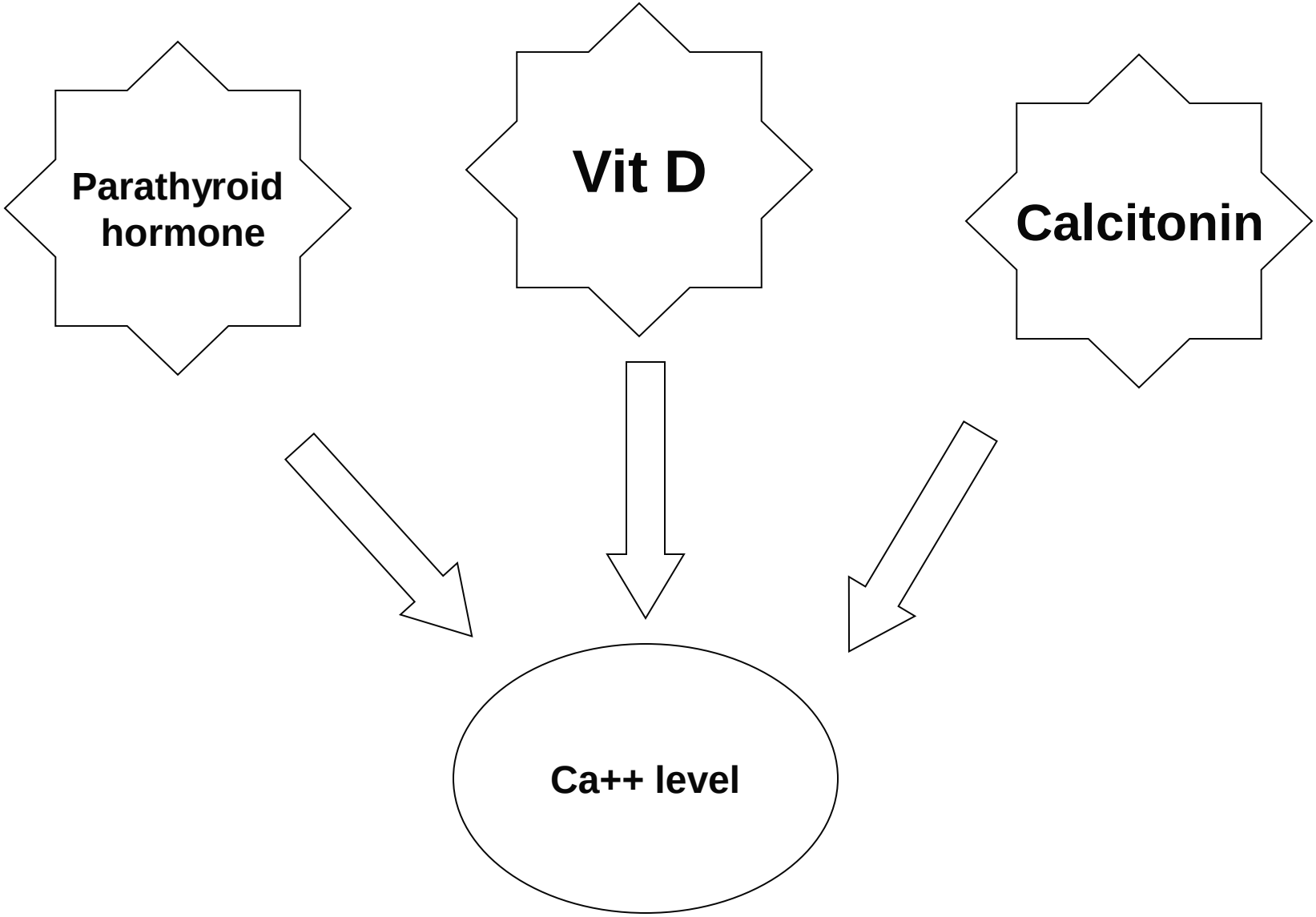

Osteoblast
Osteocyte
Osteocytic–
osteoblastic bone
membrane
Osteoblast
Outer
surface
Mineralized
bone
Blood vessel
Central canal
Canaliculi
Bone fluid
Lamellae

(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

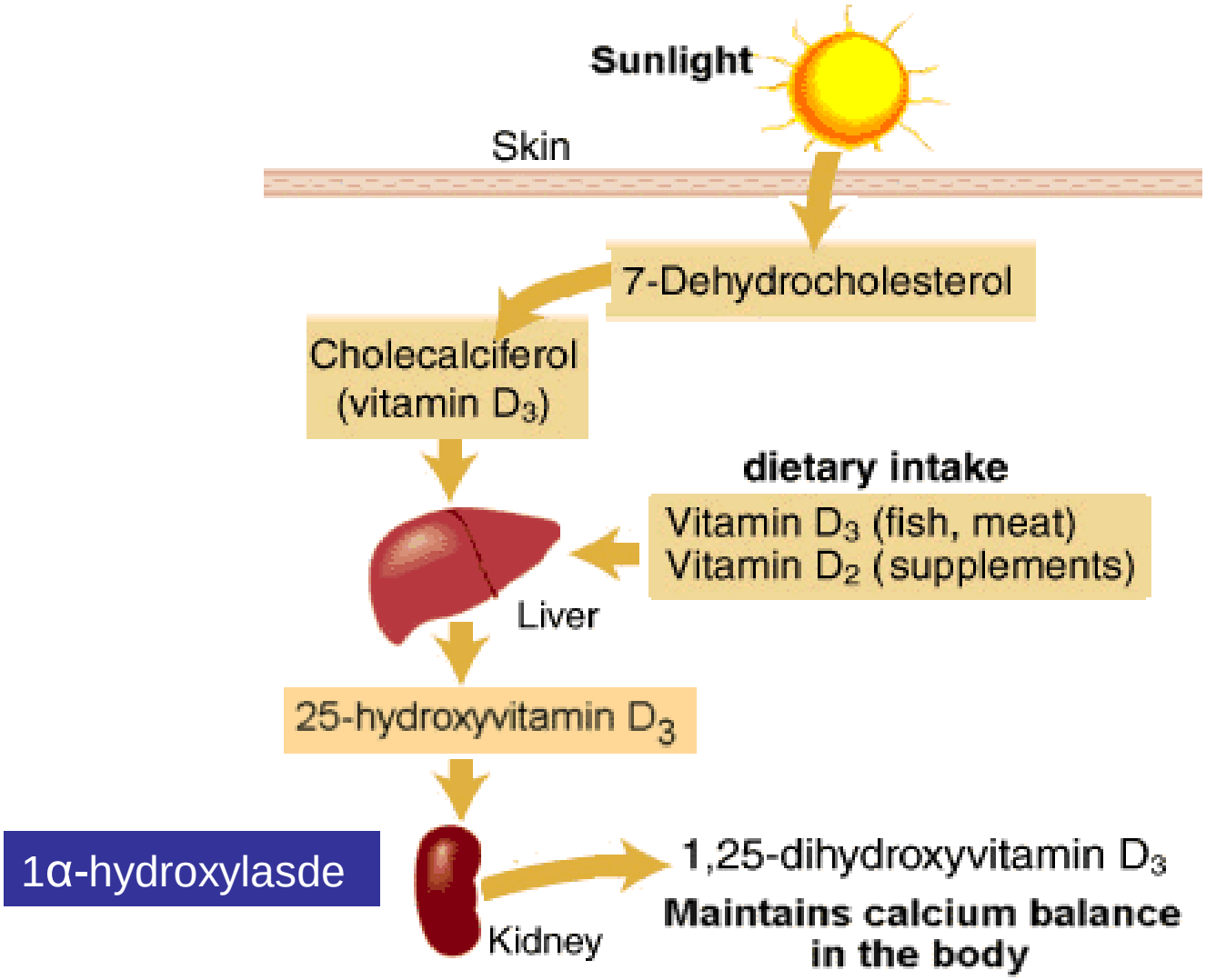

In canaliculi
In central canal
Mineralized bone: stable pool of Ca^{2+}
Bone fluid: labile pool of Ca^{2+}
Plasma
Hydroxyapatite crystals
Fast exchange
Ca^{2+}
Slow exchange
Ca^{2+}
(Bone dissolution)
Amorphous salt
Osteocytic–osteoblastic bone membrane
(formed by filmy cytoplasmic extensions of interconnected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

Three Hormones



Vitamin D

1,25 Dihydroxycholecalciferol (Vit D)

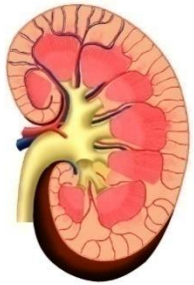


Vitamin D

1.Intestinal tract.

Has a potent effect to increase calcium & phosphate absorption

2.Renal

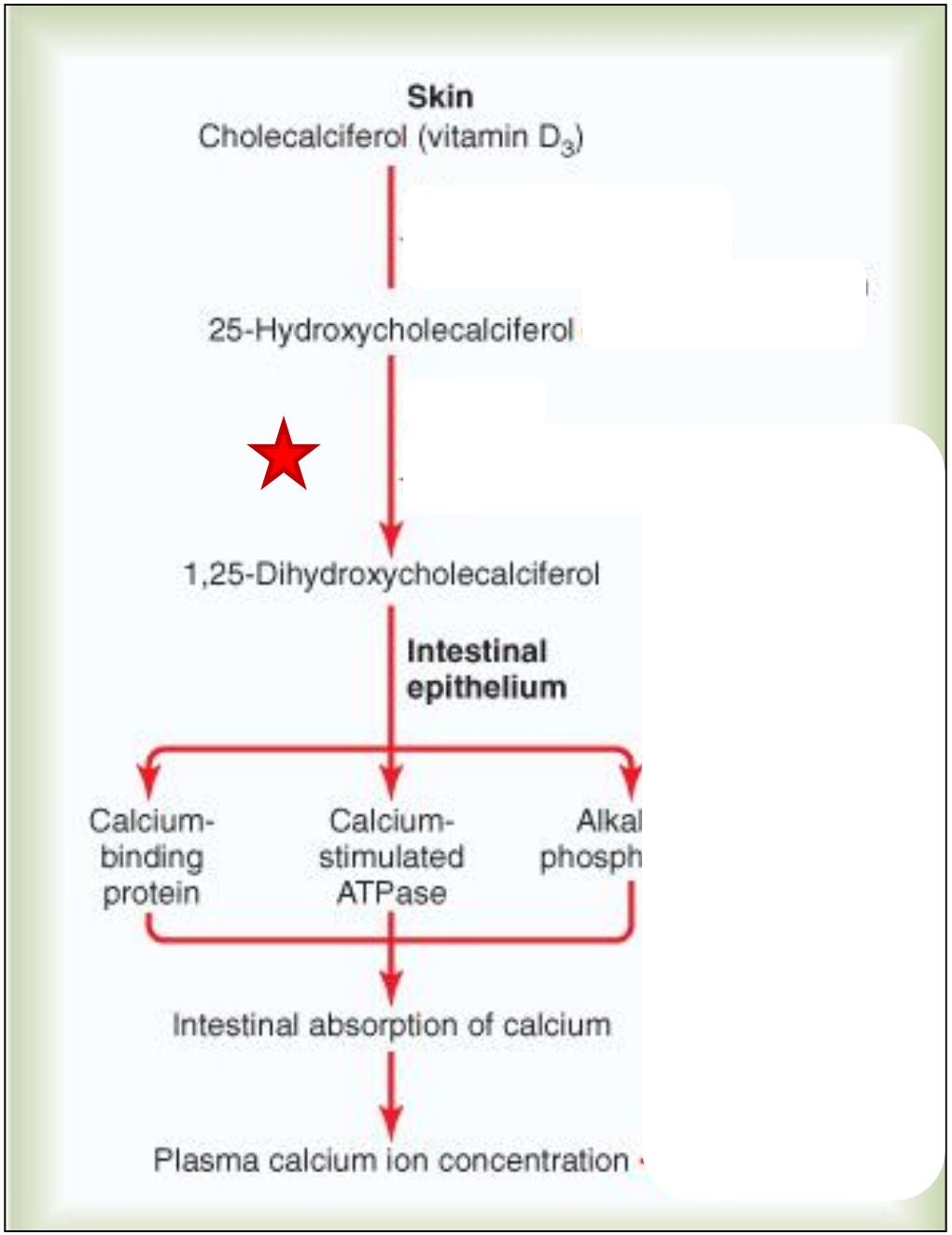


Increases Renal calcium and Phosphate absorption

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.

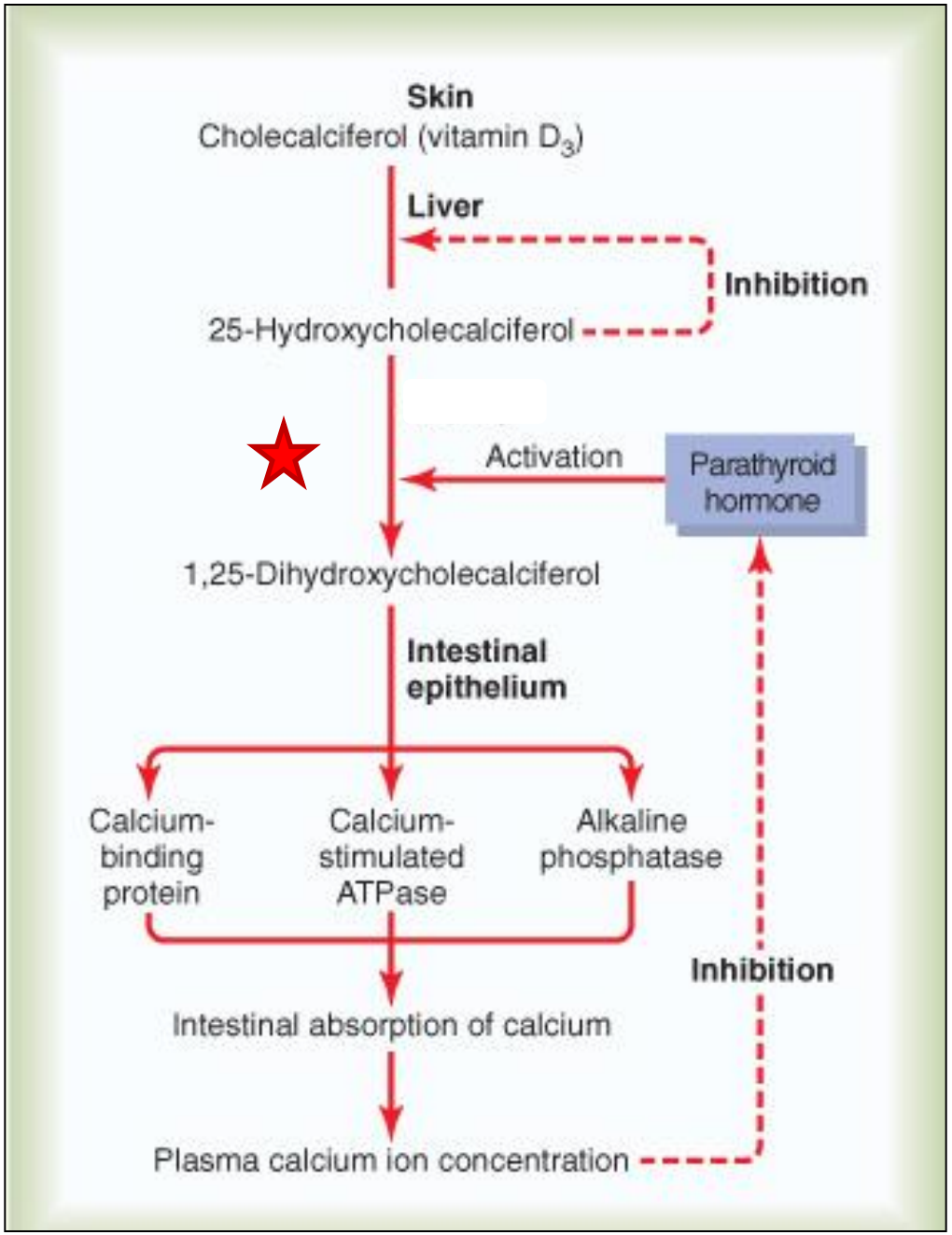
❑Control of Vit D:

1- low Ca++ ions

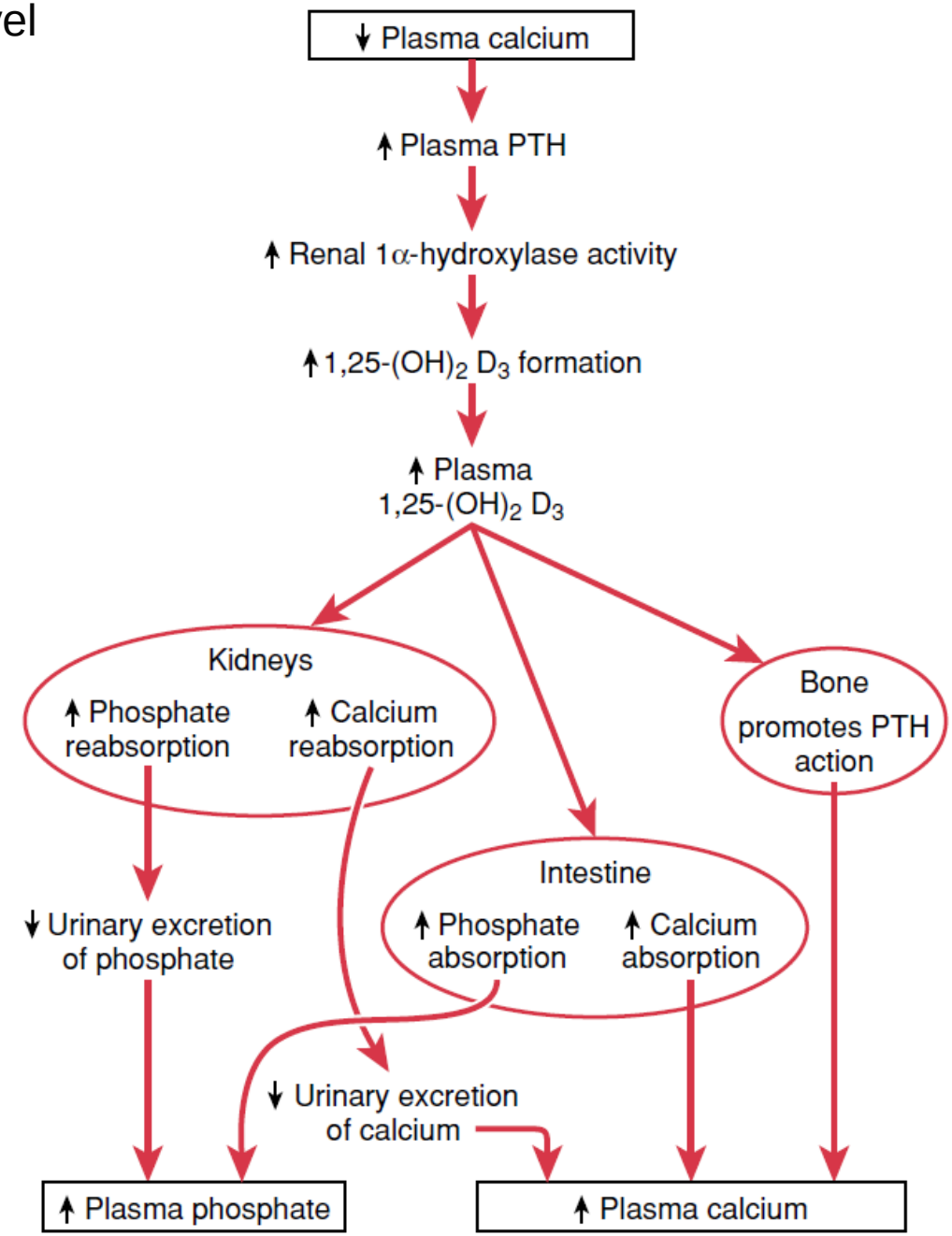
2- prolactin

3- PTH

All stimulate renal ★ 1,alpha hydroxylase.

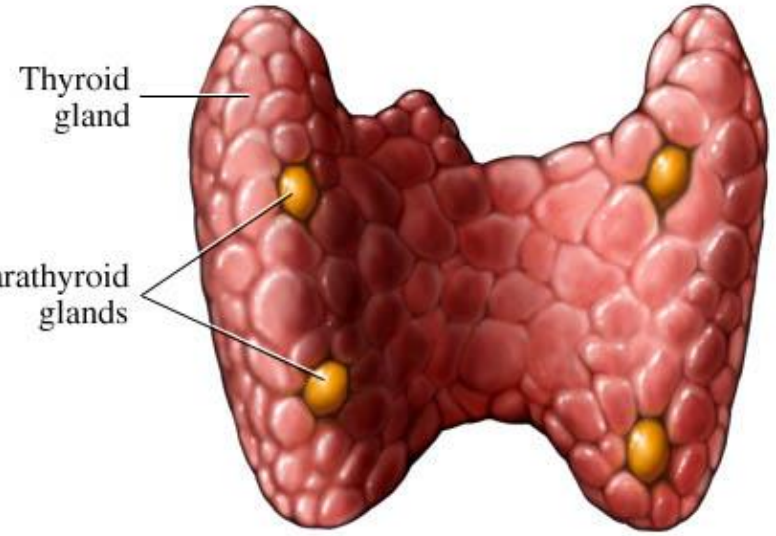


Regulation of Calcium level



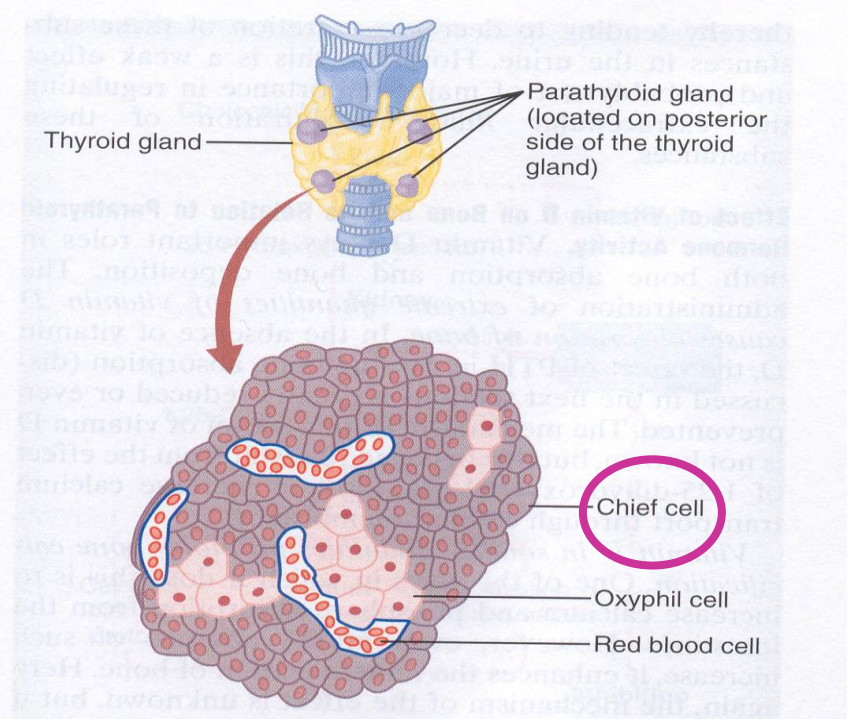
Parathyriod gland

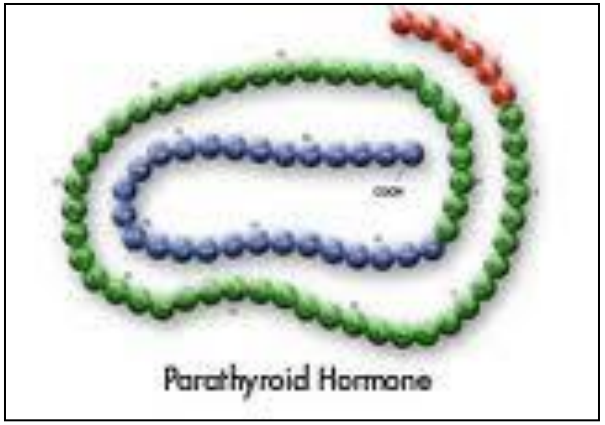
Parathyroid hormone (PTH)



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





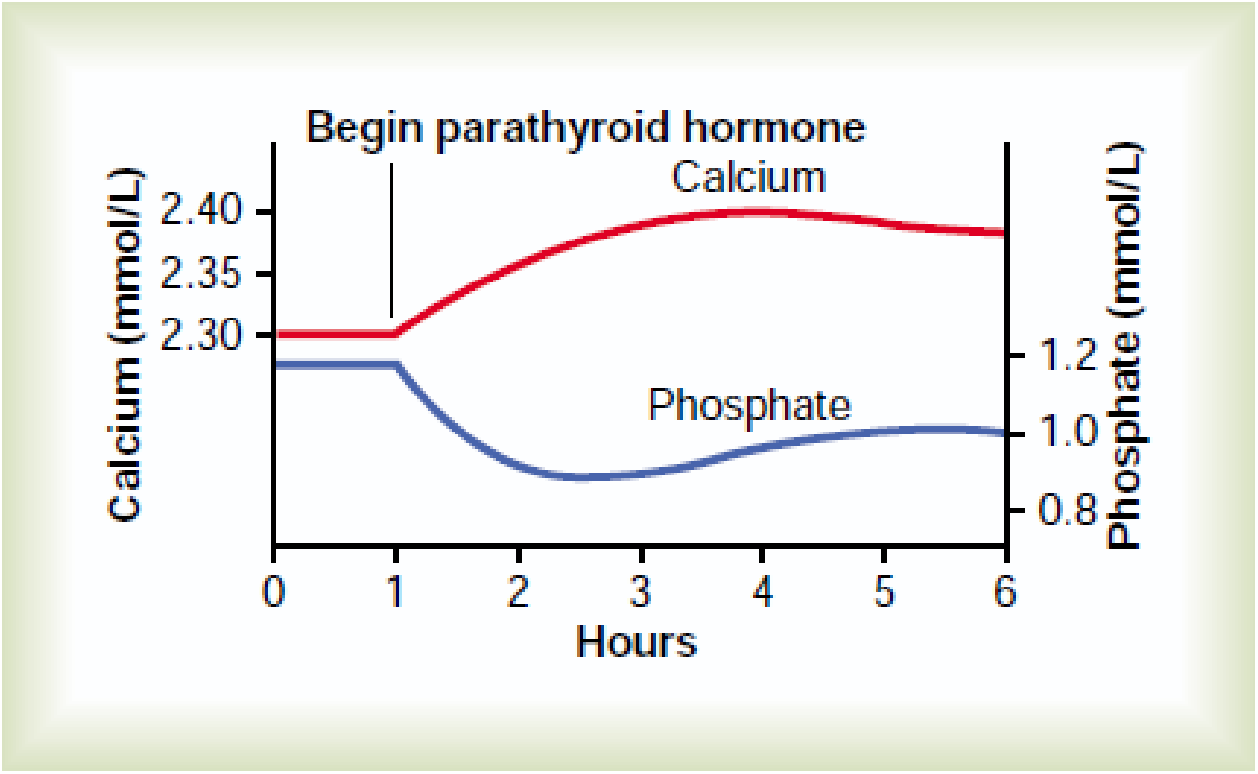


Figure 79–10

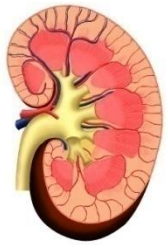
Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

Parathyroid hormone (PTH)

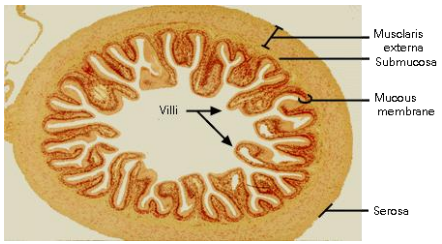
Increase plasma Ca++ level
Decrease phosphate level

Bone

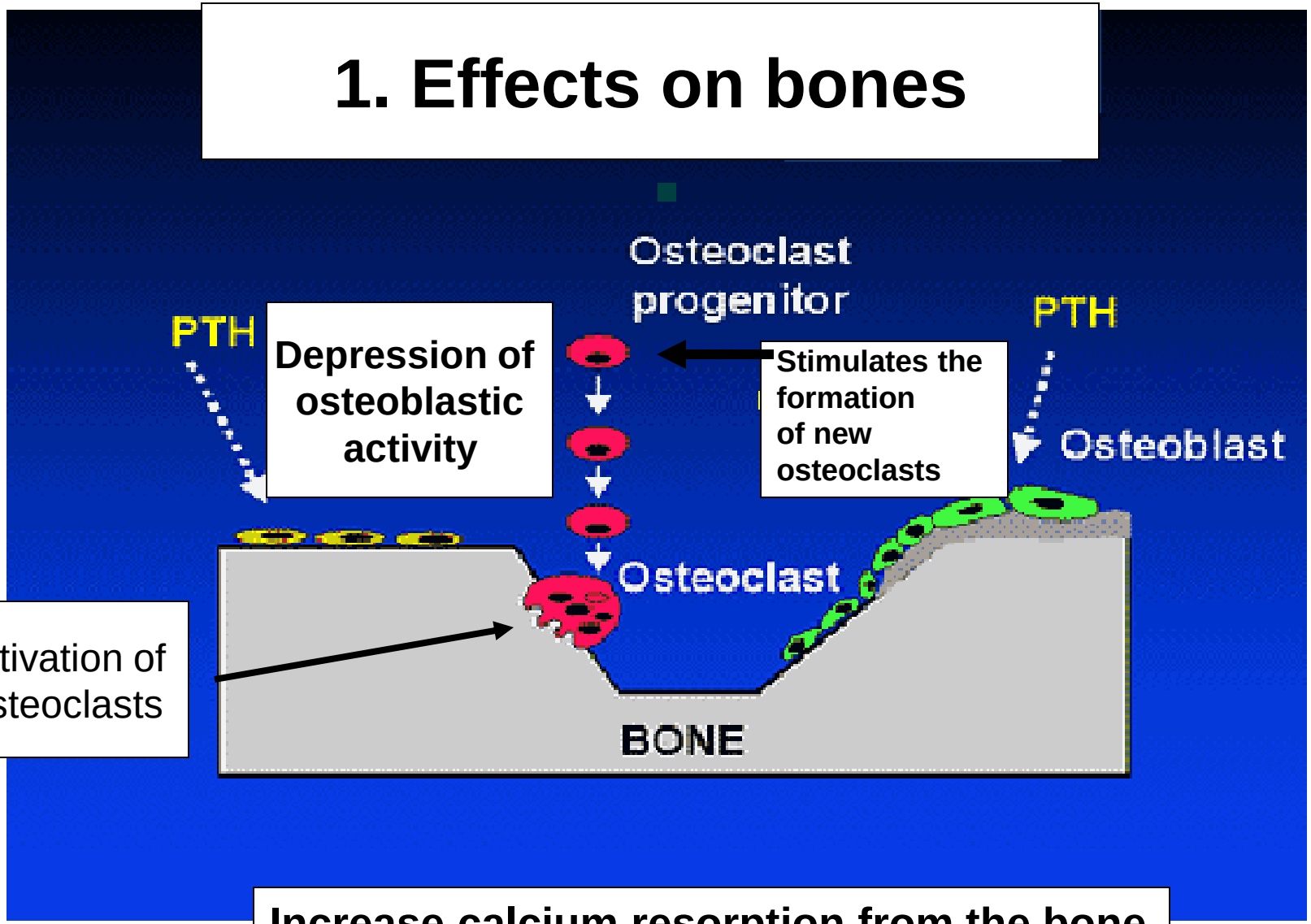
Kidney



Intestine



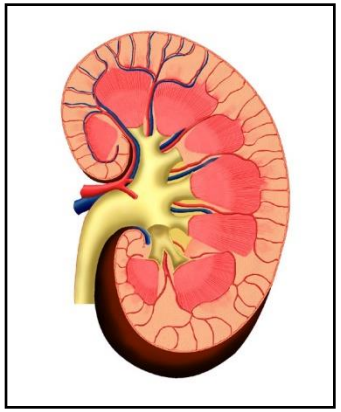
1. Effects on bones



Increase calcium resorption from the bone

2. Effects on Kidneys

(PTH) →



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

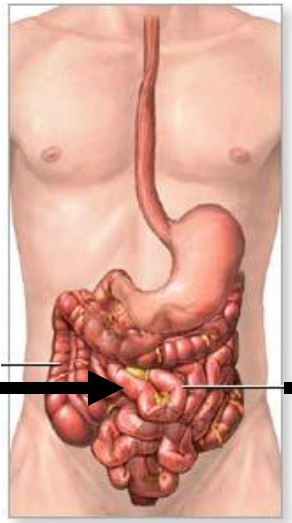
   ↑ Phosphate excretion in the urine

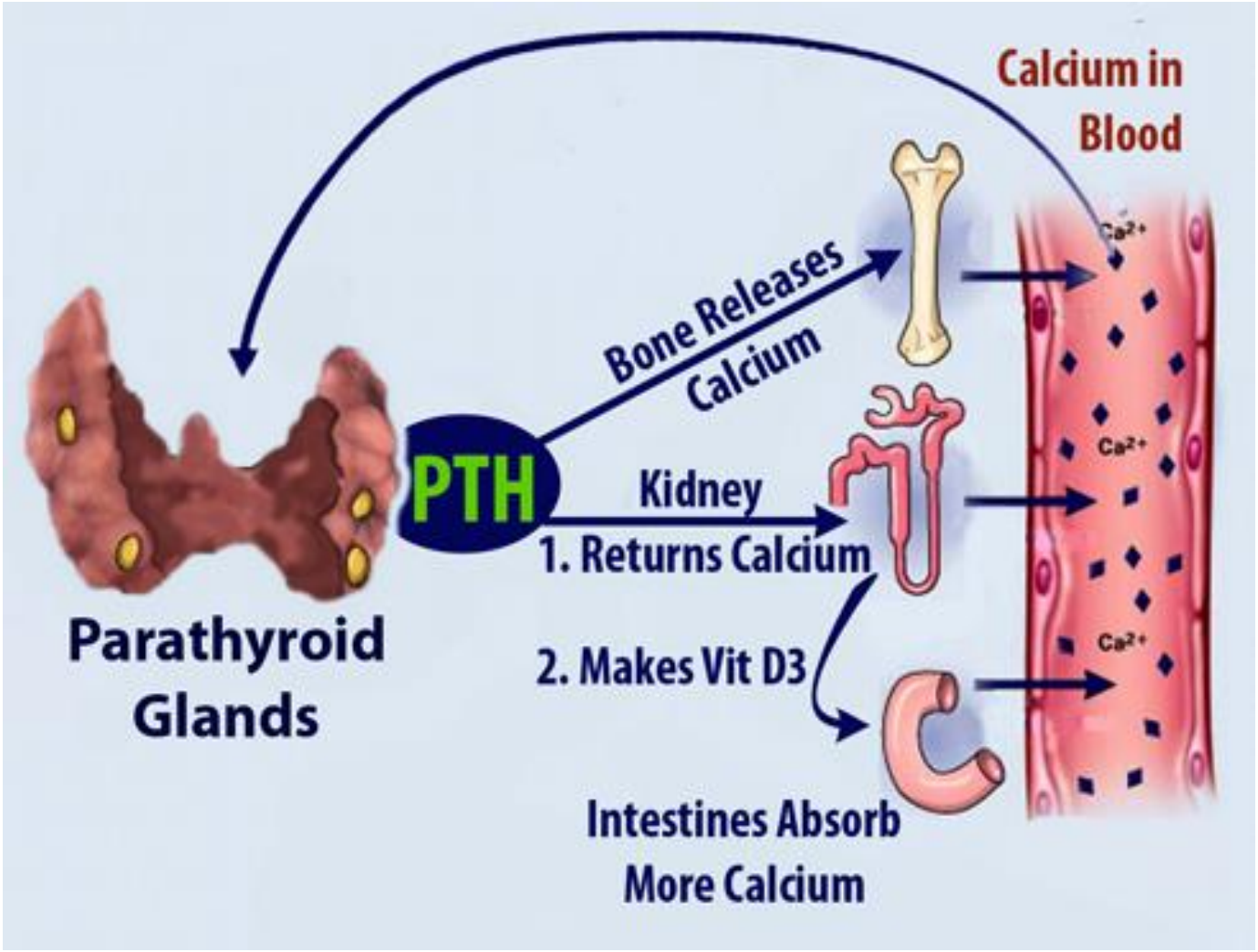
   ↓ plasma phosphate concentration

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

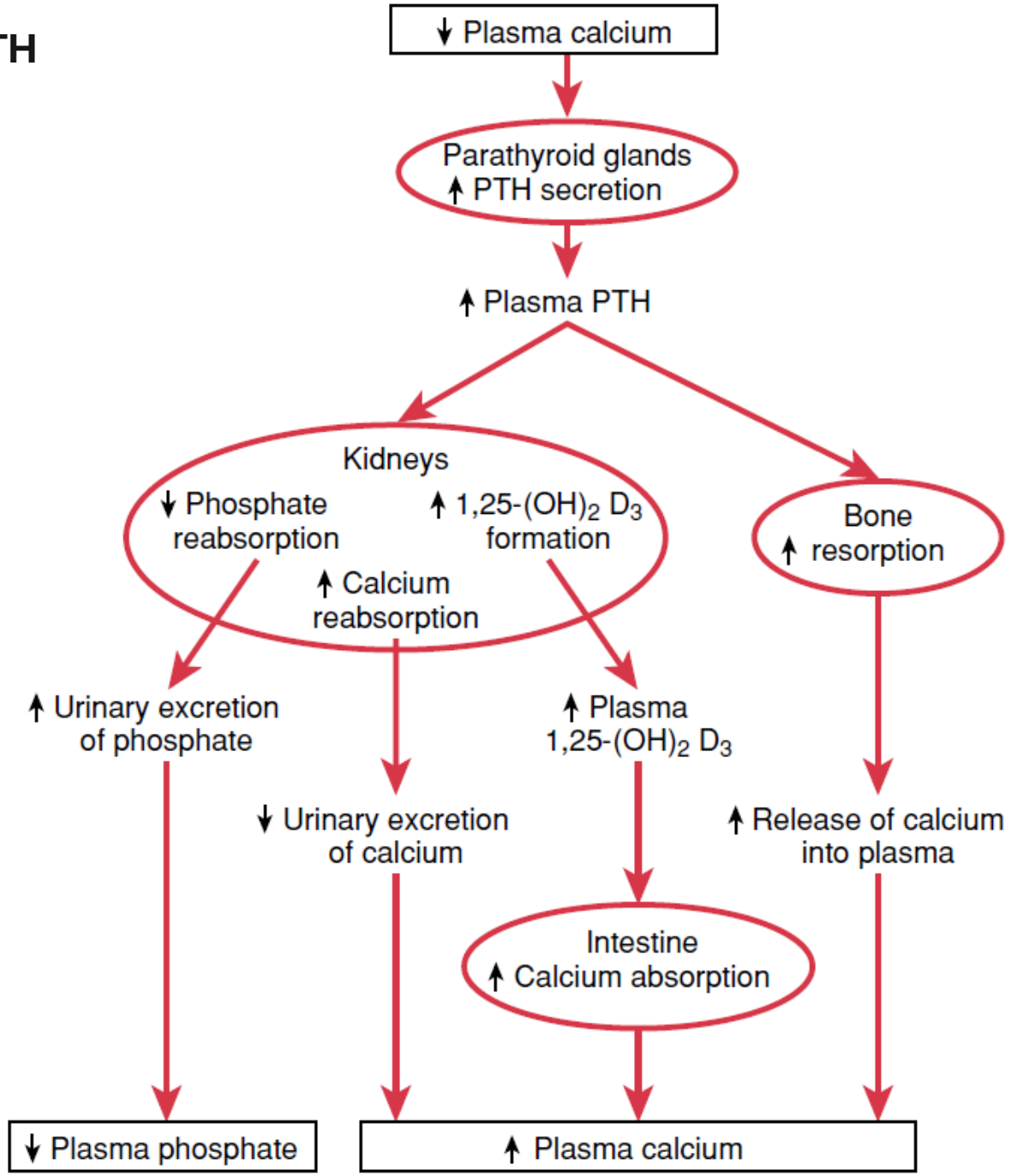
3. ↑ Formation of 1,25 vit D3 in the kidney.

3. Effects on intestine

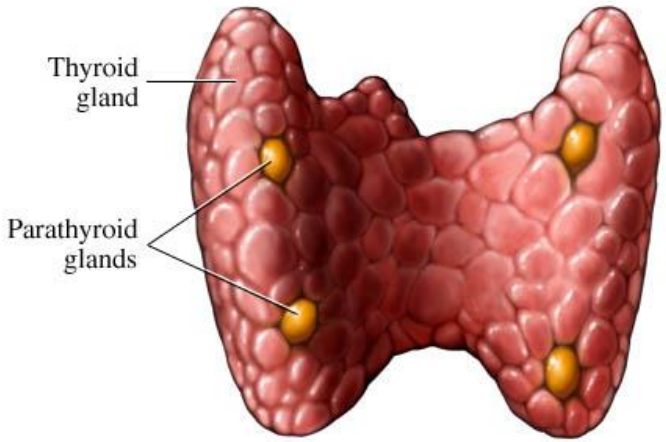
(PTH) →  → ↑ absorption of calcium and phosphate indirectly through stimulating formation of $1,25 – (OH)_2\text{-}D_3$ in kidney


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

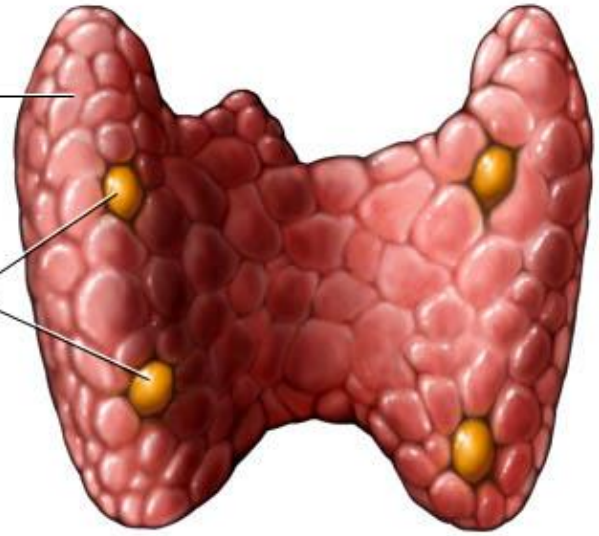


It is essential for life

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

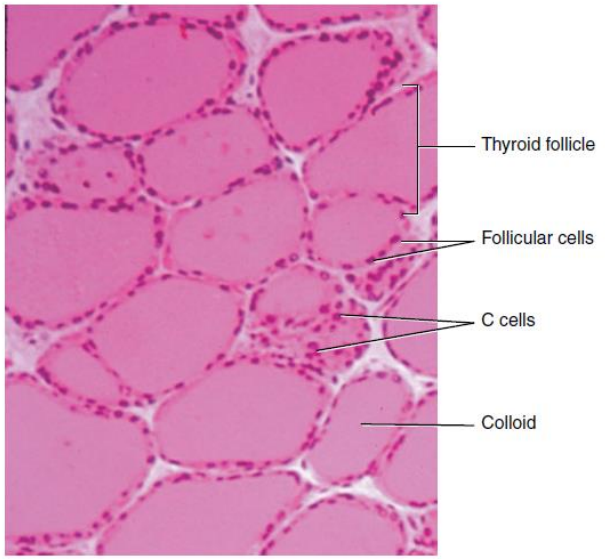
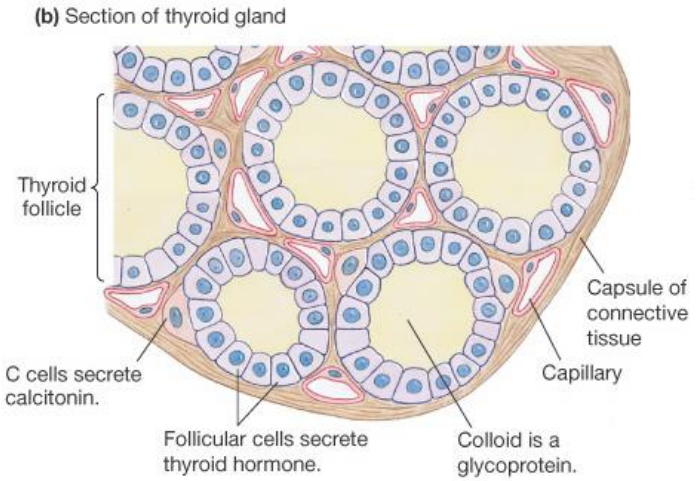


Figure 17.8 The Thyroid Gland. (*a*) Gross anatomy; (*b*) histology.



Actions:

Calcitonin

↓

Plasma calcium concentration

On bone

[1] ↑ Ca++ deposition of bone

[2] Inhibits Bone resorption:

inhibition of osteoclasts

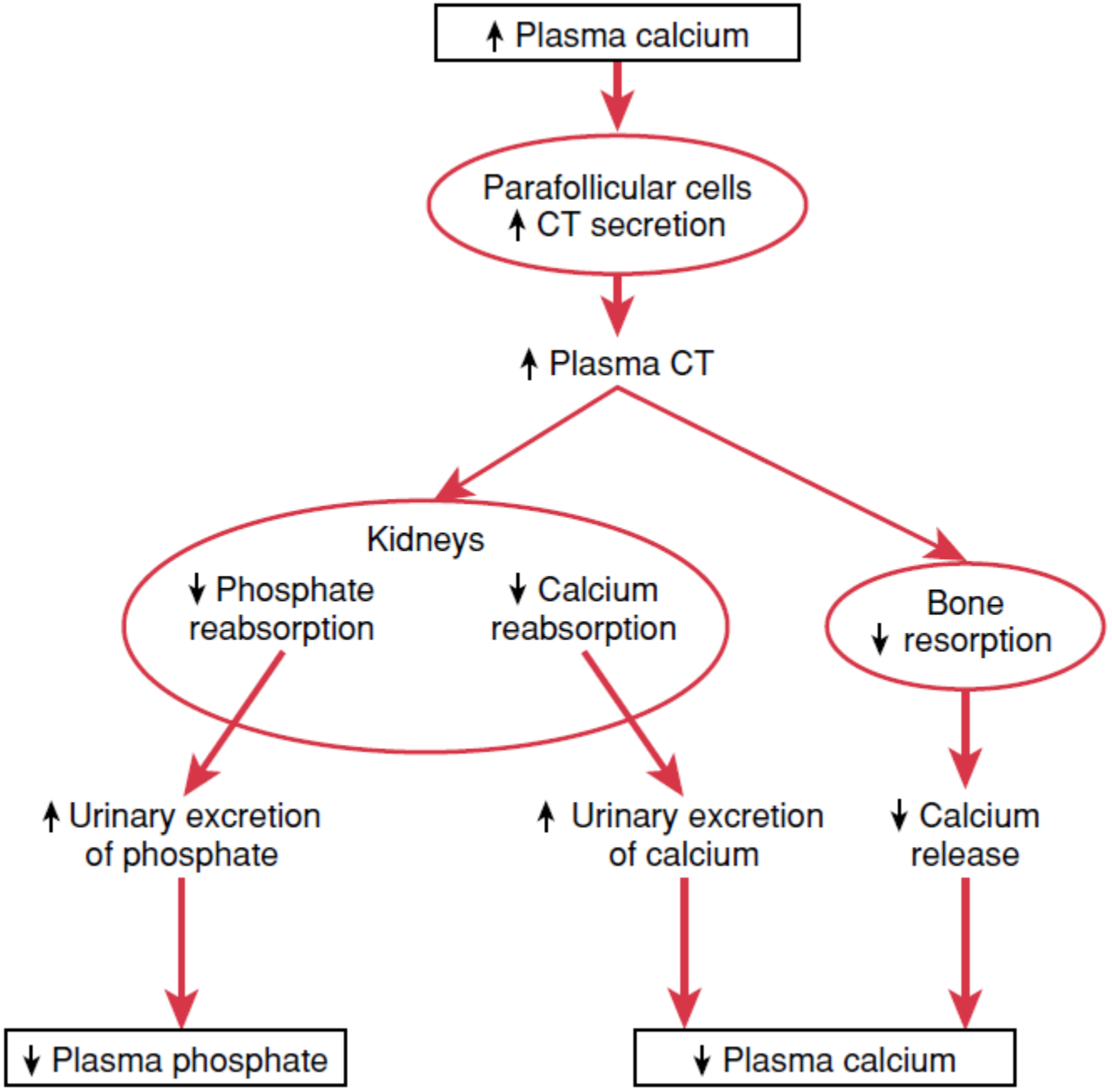
↓ formation of osteoclasts

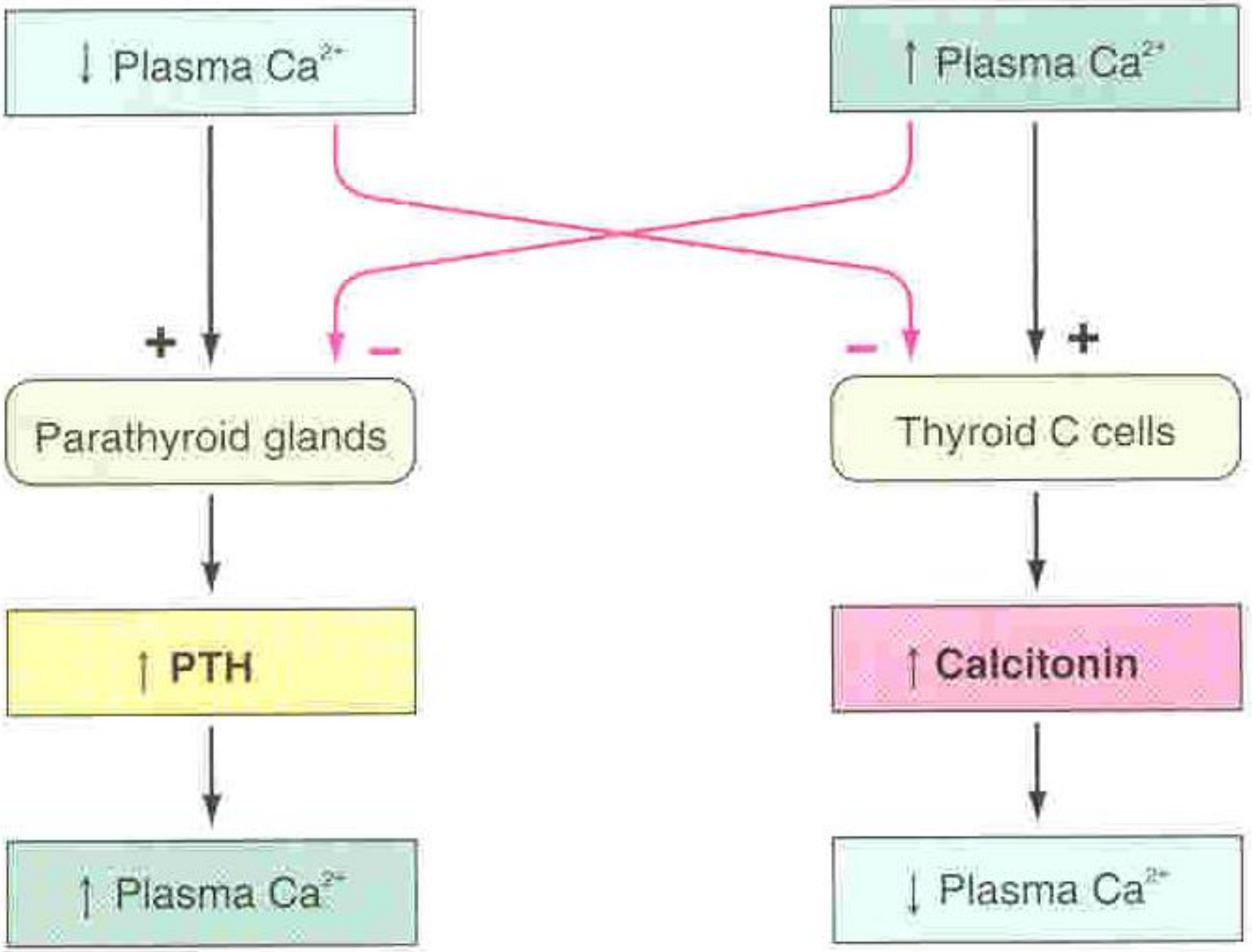
On kidney

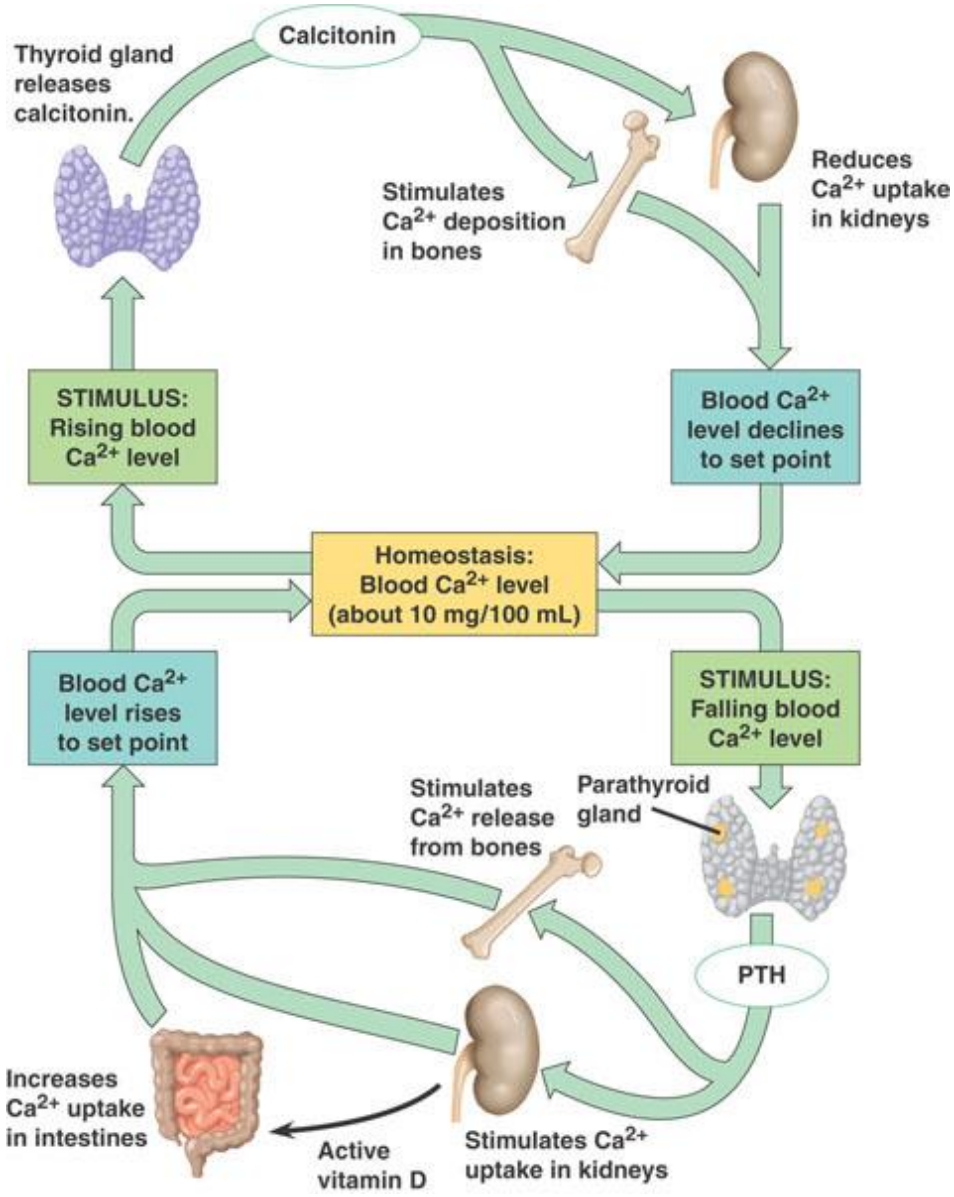
↓↓ Ca++ reabsorption

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

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)

Rickets is the softening and weakening of bones in children leading to defective calcification of the bone matrix.

- **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).

•Poor absorption of vitamin D and calcium

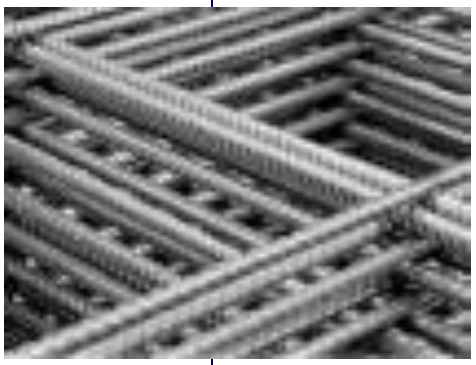
• almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

❑ Osteomalacia-"Renal Rickets".

- **It is a type of Osteomalacia due to prolonged kidney disease**
- **Failure of the damaged kidney to form…..**

Bone composition

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

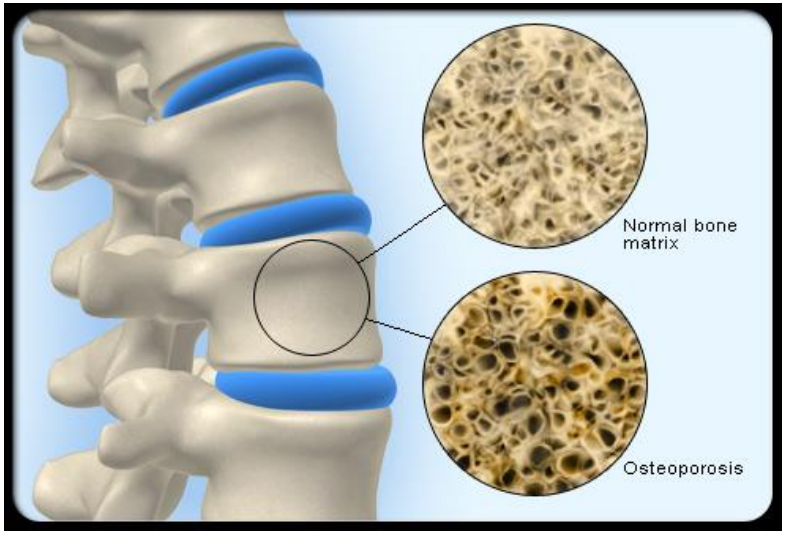


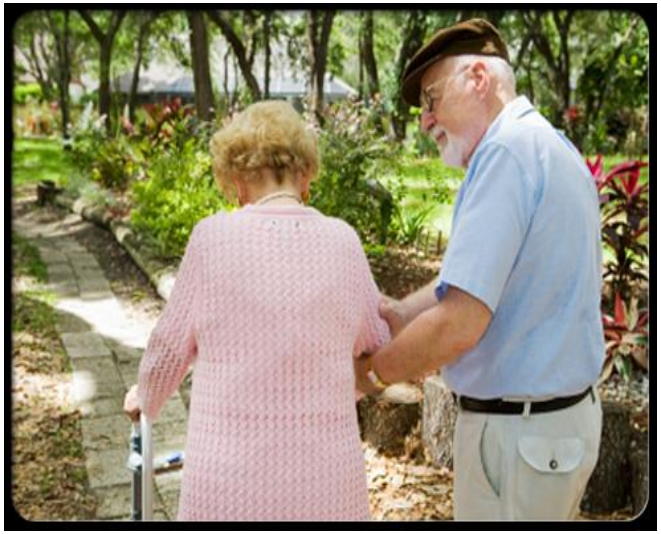
- **Bone Salts**
  - **Salts of Ca^{++} and PO$_4^{3-}$**
  - **In the form of**
    Hydroxyapatite crystals
    $Ca_{10}(PO_4)_6(OH)_2$
    Mg, Na, K, Carbonate ions

In adequate bone mineralization

- Rickets
- Osteomalacia


Osteoporosis


Normal bone matrix
Osteoporosis



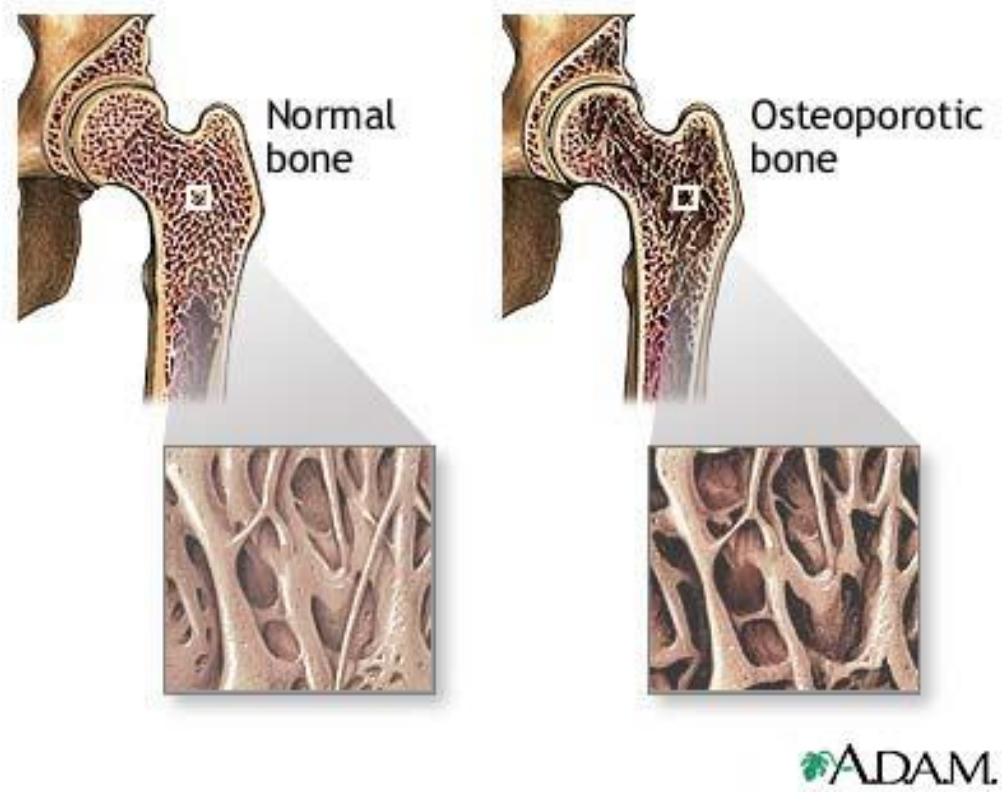
❑ Osteoporosis

- 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



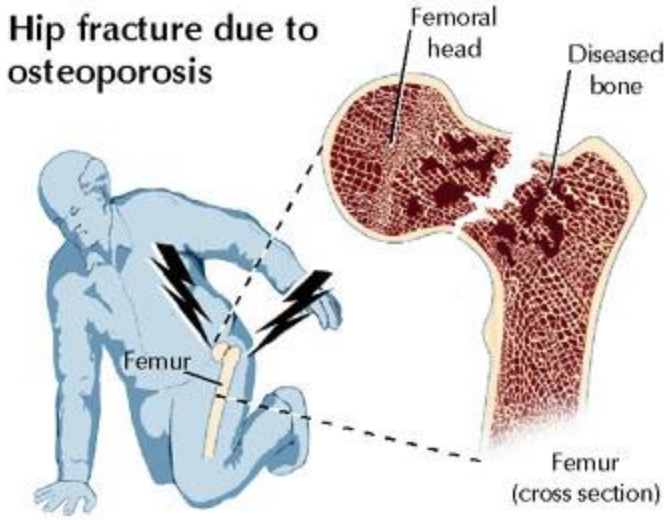
Osteoporosis

- causes of osteoporosis:

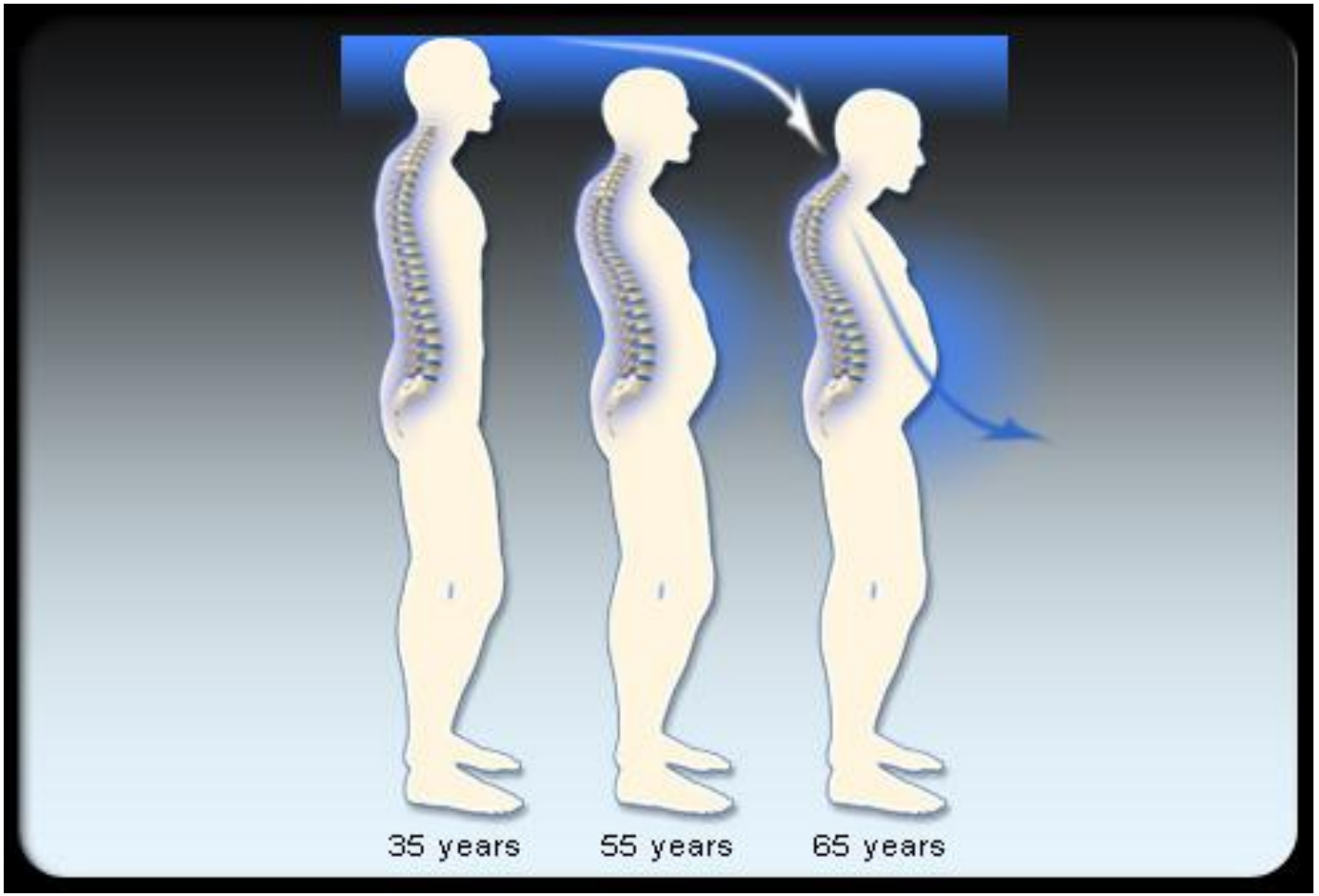
(1) lack of physical stress
(2) malnutrition
(3) lack of vitamin C
(4) postmenopausal lack of estrogen
(5) old age
(6) Cushing's syndrome

❑ symptoms of osteoporosis

- **Typically silent (without symptoms) until it leads to fracture at a minimal trauma.**
- **Most affected:**
  - **vertebral compression (may be asymptomatic)**
  - **hip fractures (requires surgery in most cases).**



Osteoporosis



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  - **Salts of Ca++ & PO_4^-**
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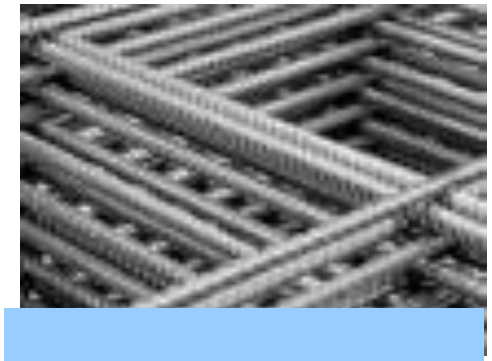
  - **Mg, Na, K, Carbonate ions**

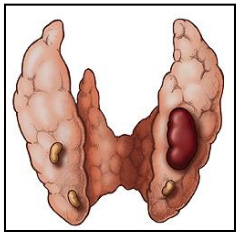
In adequate bone matrix and minerals



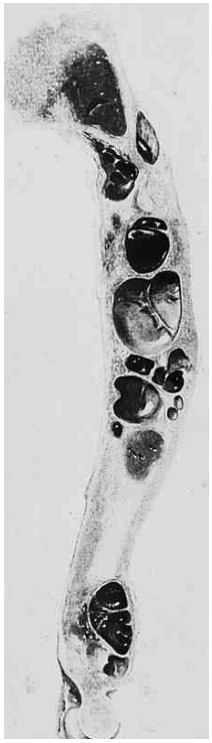
•Osteoporosis

Disorders of parathyroid hormone secretion

Hyperparathyroidism (PTH Excess)



Primary



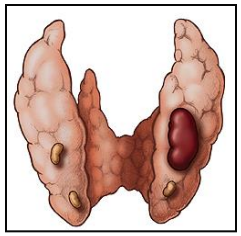
Manifestations:

- 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)



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- 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.

Signs & symptoms (due to hypocalcaemia)

- Muscle weakness, cramps and pain in the face, hands, legs, and feet.
- Tingling in the lips, fingers, and toes
- Dry hair, brittle nails, and dry, coarse skin
- 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

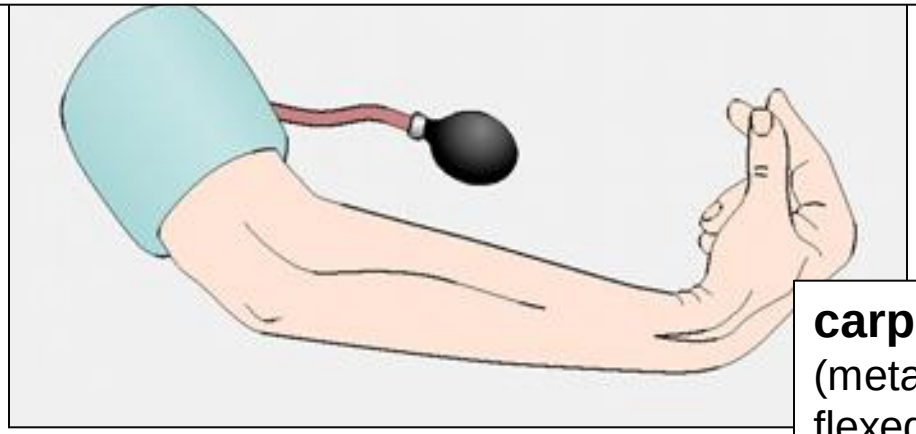
- Positive Chvostek's sign(facial muscle twitch)
- Positive Trousseau's sign(carpal spasm)
- Delayed cardiac repolarization with prolongation of the QT interval
- Paresthesia
- Tetany: can be overt or latent

- **Treatment:**

Calcium carbonate and vitamin D supplements

Trousseau Sign

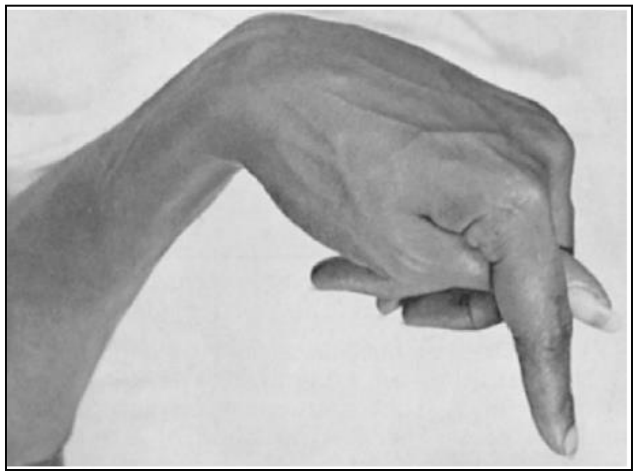
When an occlusion of brachial artery with a blood pressure cuff:



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

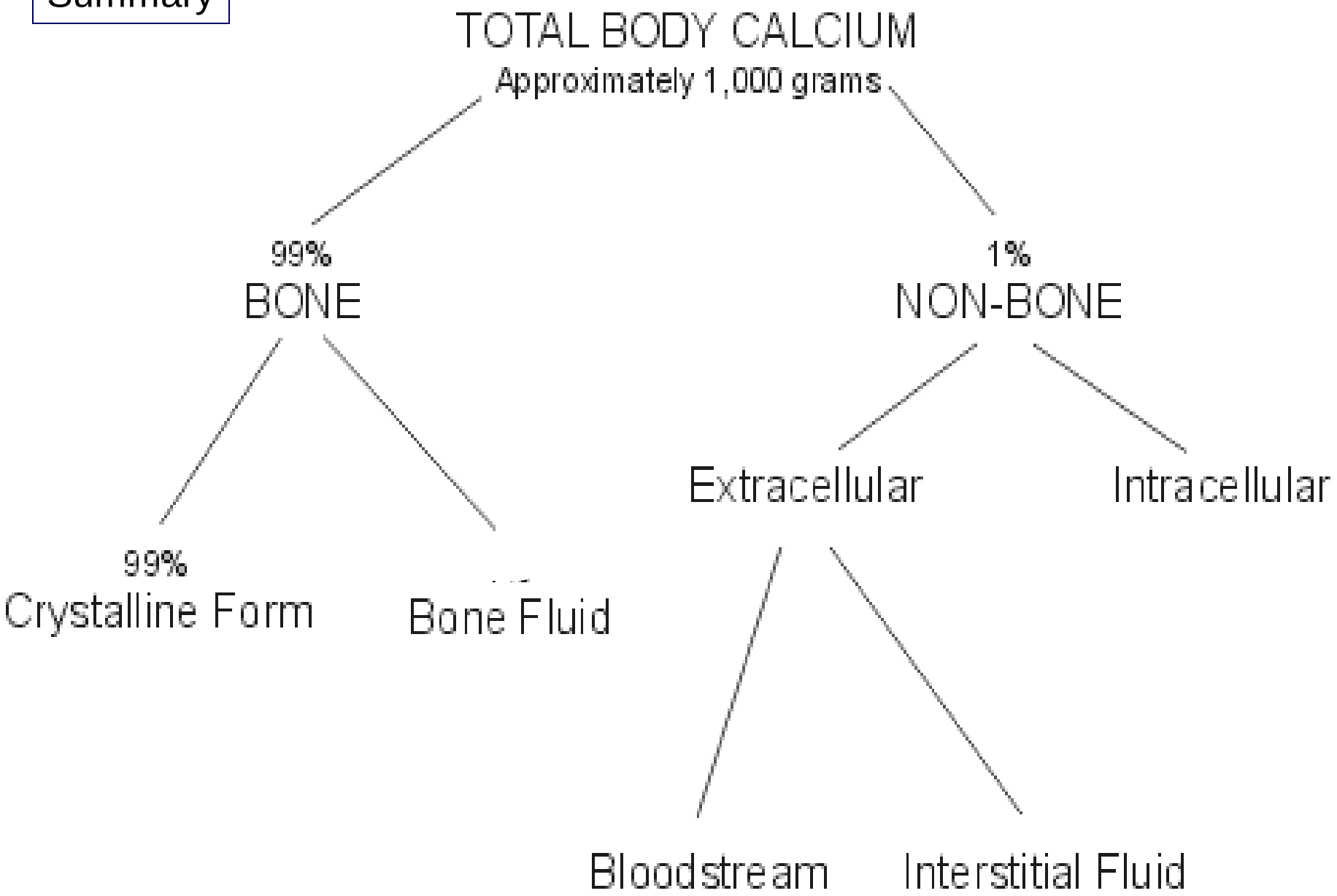
A

B



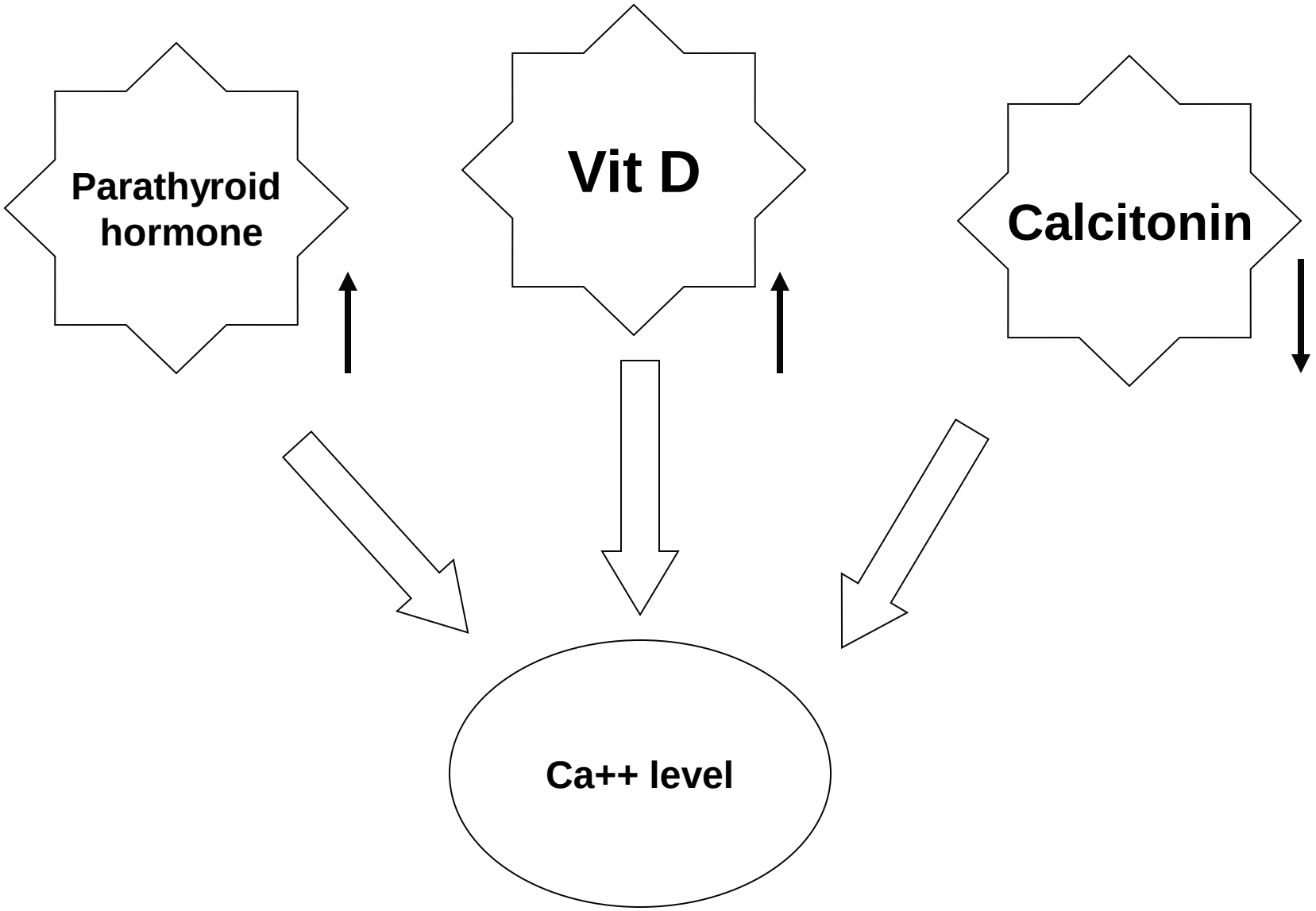
(This is due to enhanced neuromuscular excitability)

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