

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ





ENDOCRINOLOGY

Calcium Homeostasis Hypo and hyper-parathyroidism

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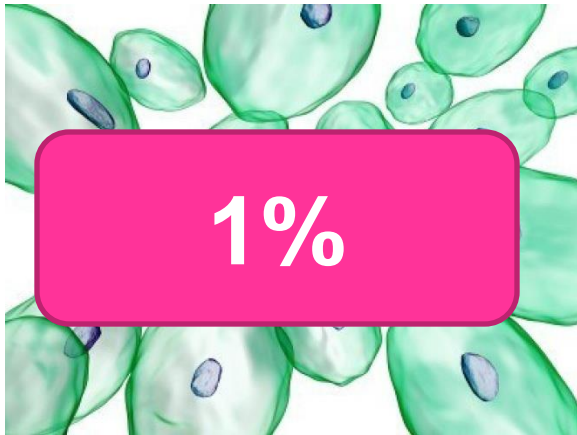
Objectives

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

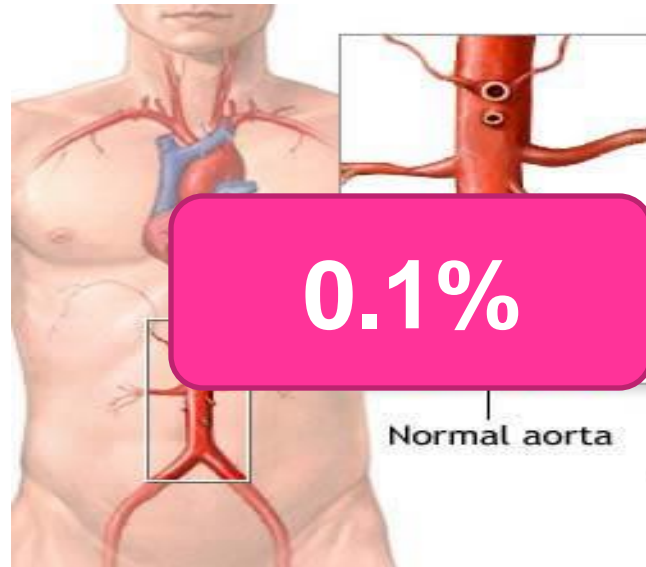
- List the functions of calcium
- Describe calcium metabolism
- Describe physiology of bone
- Understand and explain hormonal regulation of calcium metabolism
 - Parathyroid hormone
 - Calcitonin
 - Vitamine D₃
- Understand hypo and hyper-parathyroidism



99%



1%



0.1%

Distribution of Ca^{++} in Body

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

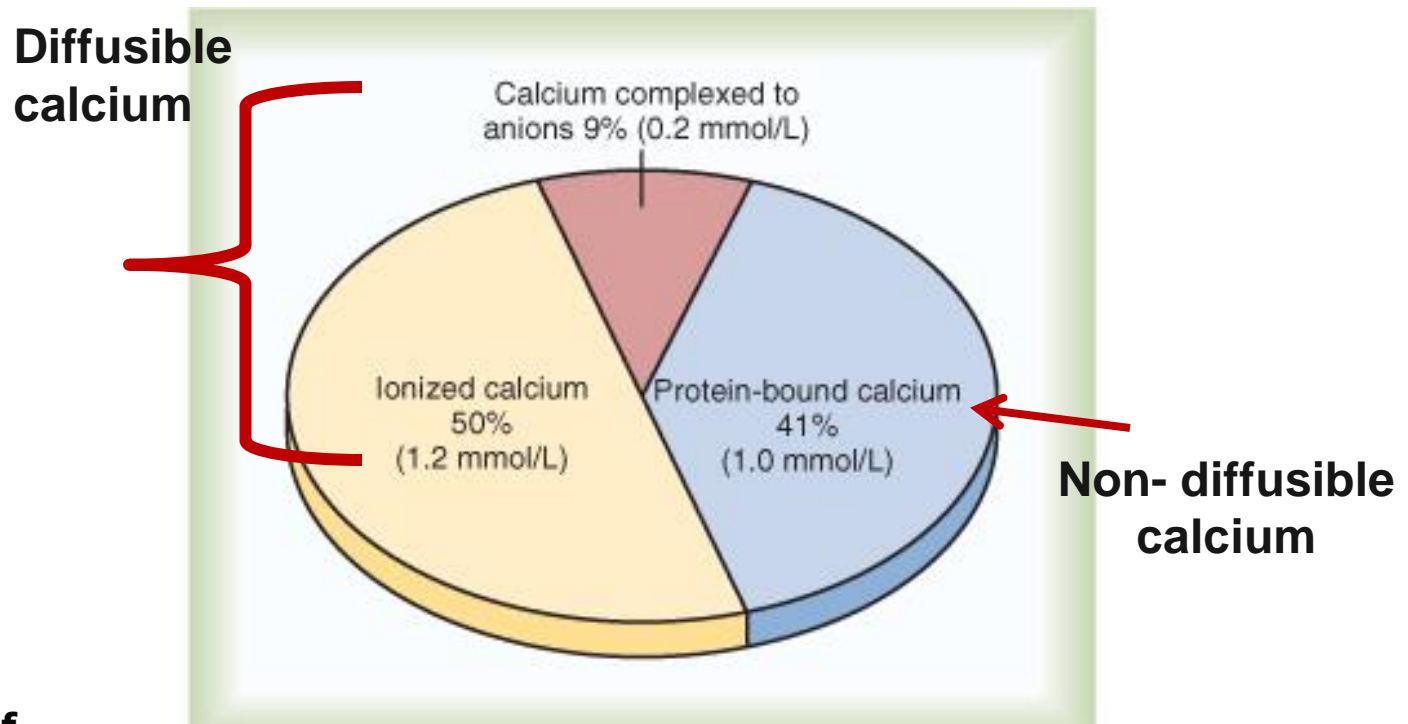
TABLE 36.1

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



■ Total conc of calcium in ECF =
10 mg/dl
5m mEq/L
2.5 mmol/L

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 Ca²⁺

• **Acidosis** ↑ Ionized Ca²⁺

	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	0.5 g/dl	2 to 95 g/dl
Phospholipids		
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 (5 mEq/L)	16 g/dl (40 mEq/L)

Plasma Calcium

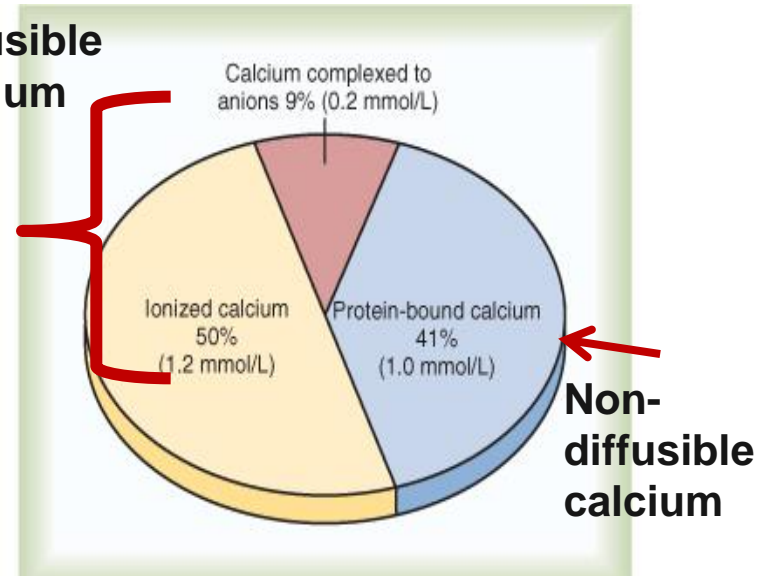
9-10.5 mg/dl

Non Diffusible = 41%

Diffusible = 59%

- Complexed 9 %
- Ionized 50%

Diffusible calcium



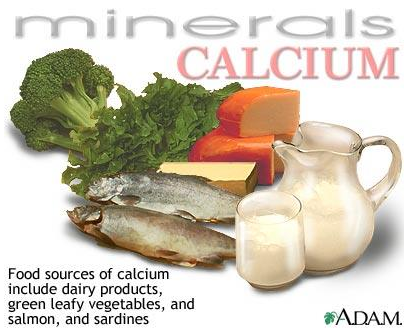
Physiological importance of Calcium

- 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
 - Neuromuscular 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.**

Source



- Milk
- dairy products
- Fish

Daily requirements

•Infants & adults:
12.5 -25 mmol/day

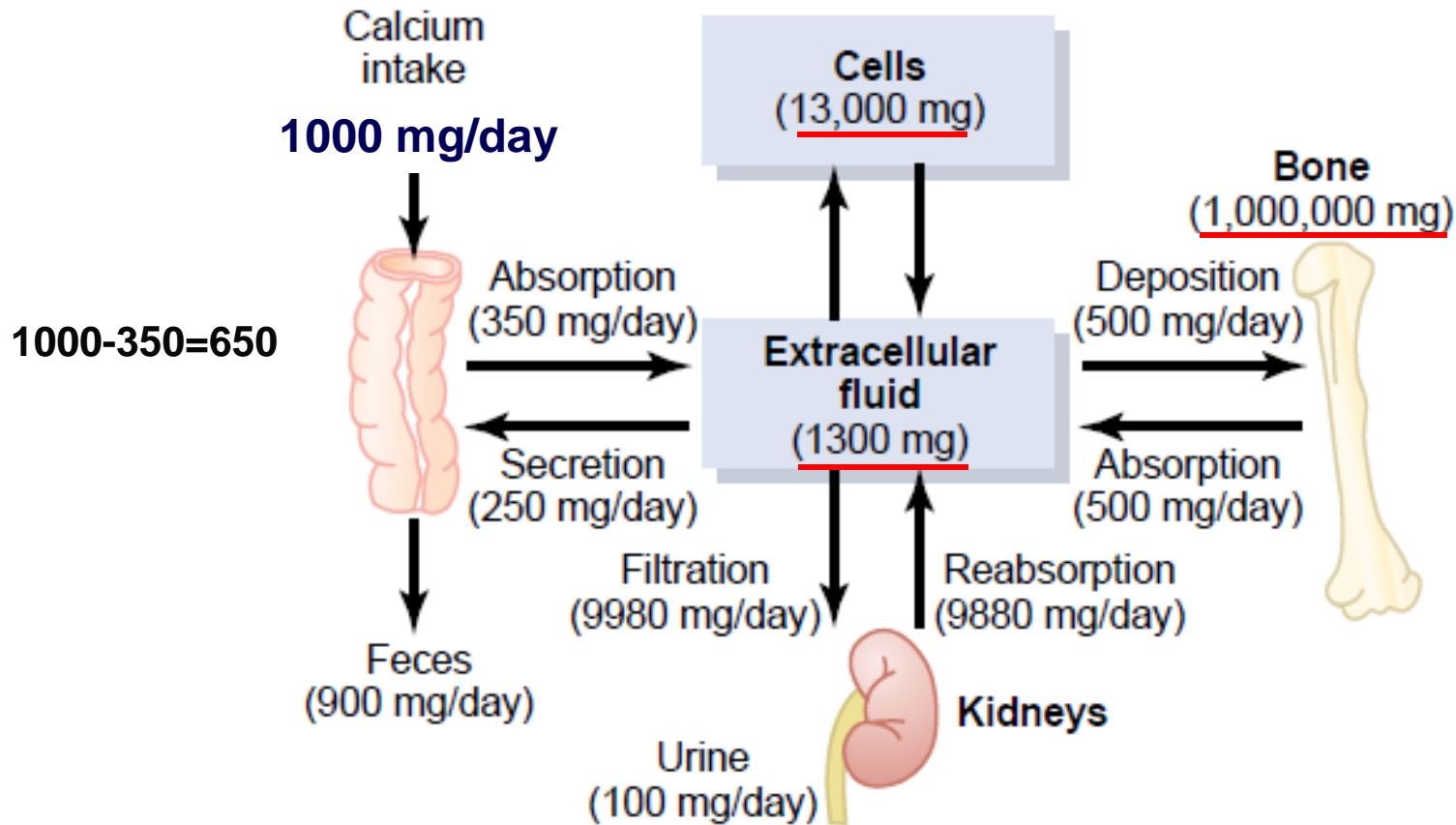
•Pregnancy,
•lactation
•after menopause:

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

Tensile force

- **Bone Salts**

- Salts of Ca^{++} & PO_4^-
- In the form of
Hydroxyapatite crystals (99%)
 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
Mg, Na, K, Carbonate ions

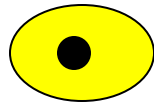
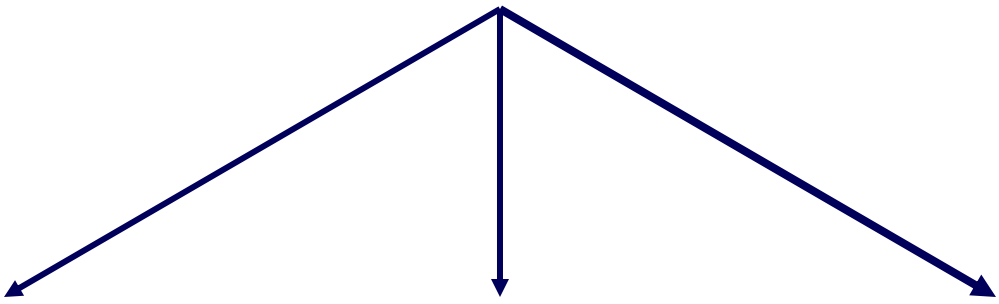
Compressional
force

Composition of bones

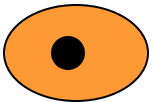
Inorganic Constituents of Bone

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

Bone Cells



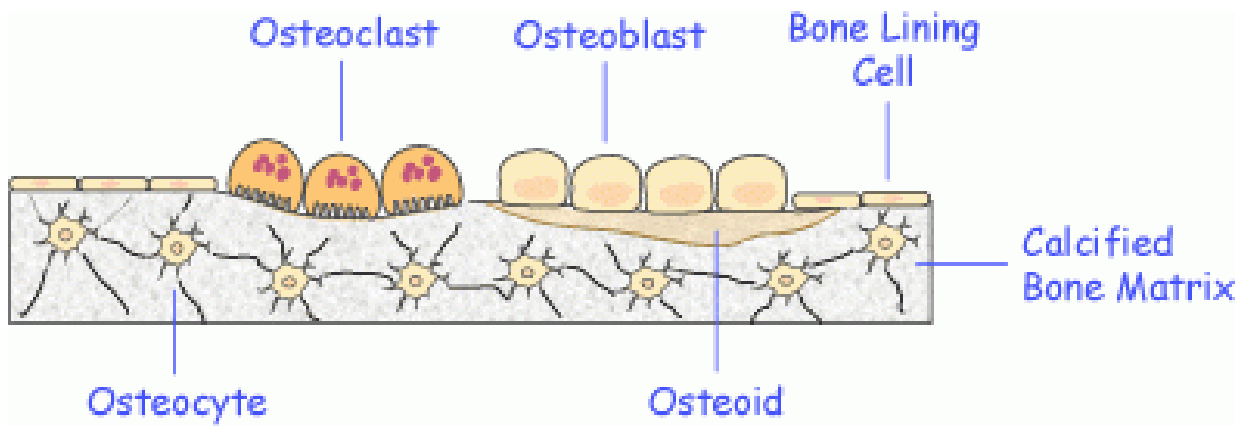
Osteoblasts
(bone forming cells)



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

Collagen (95%)

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

Non-Collagen (5%)

Osteocalcin (bone Gla protein),
vitamin K dependent
Osteonectin
Bone proteoglycan
Bone sialoprotein
Bone morphogenic protein
Bone proteolipid
Bone phosphoprotein

Cells (2%)

Matrix (98%)

Organic (30%)

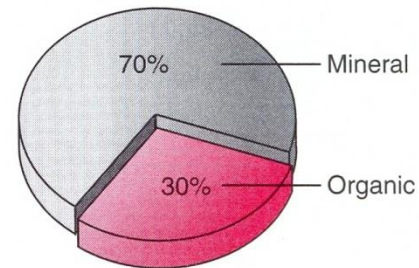
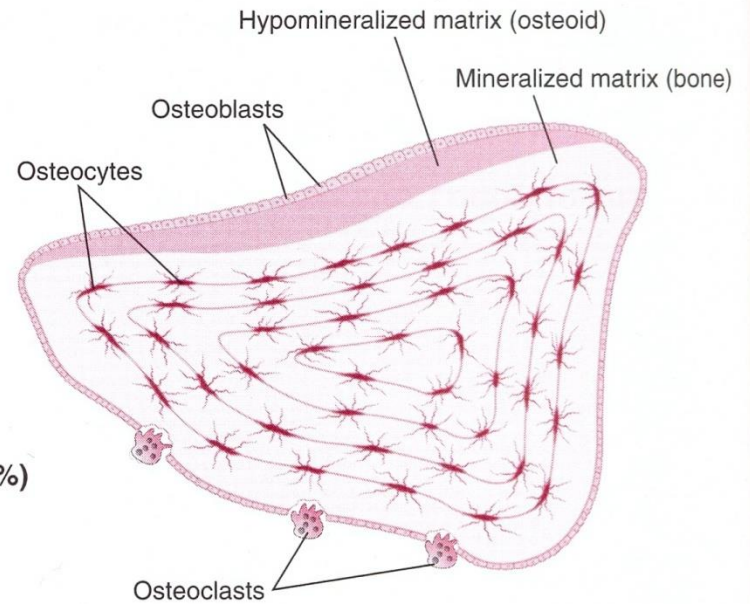


Figure 8.1 The composition of bone.

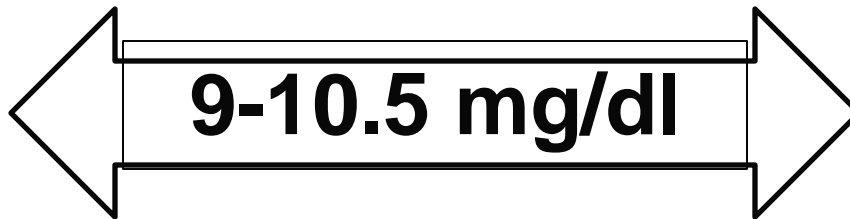


Regulation of Calcium level

REGULATION OF PLASMA CALCIUM AND PHOSPHATE CONCENTRATIONS

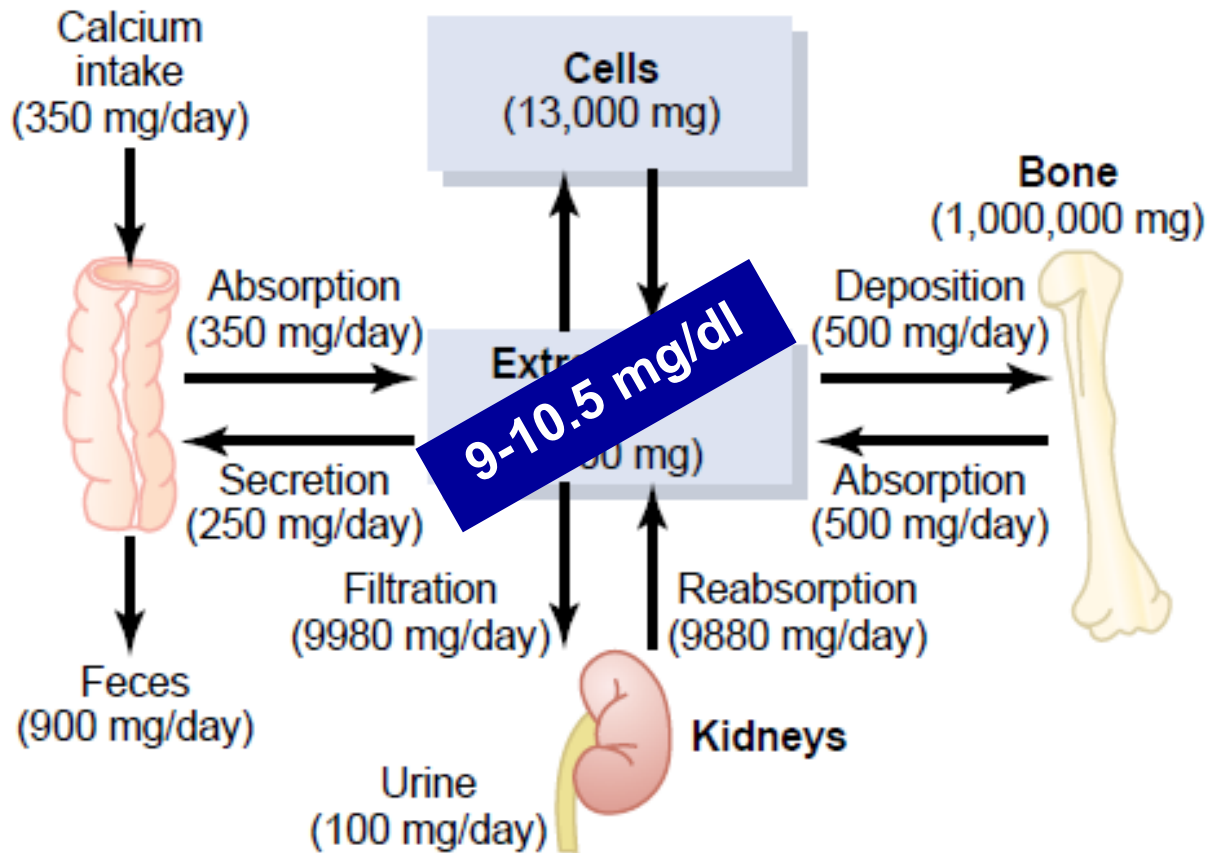
- ❑ Nonhormonal Mechanisms Can Rapidly Buffer Small Changes in Plasma Concentrations of Free Calcium
- ❑ Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations

Tetany

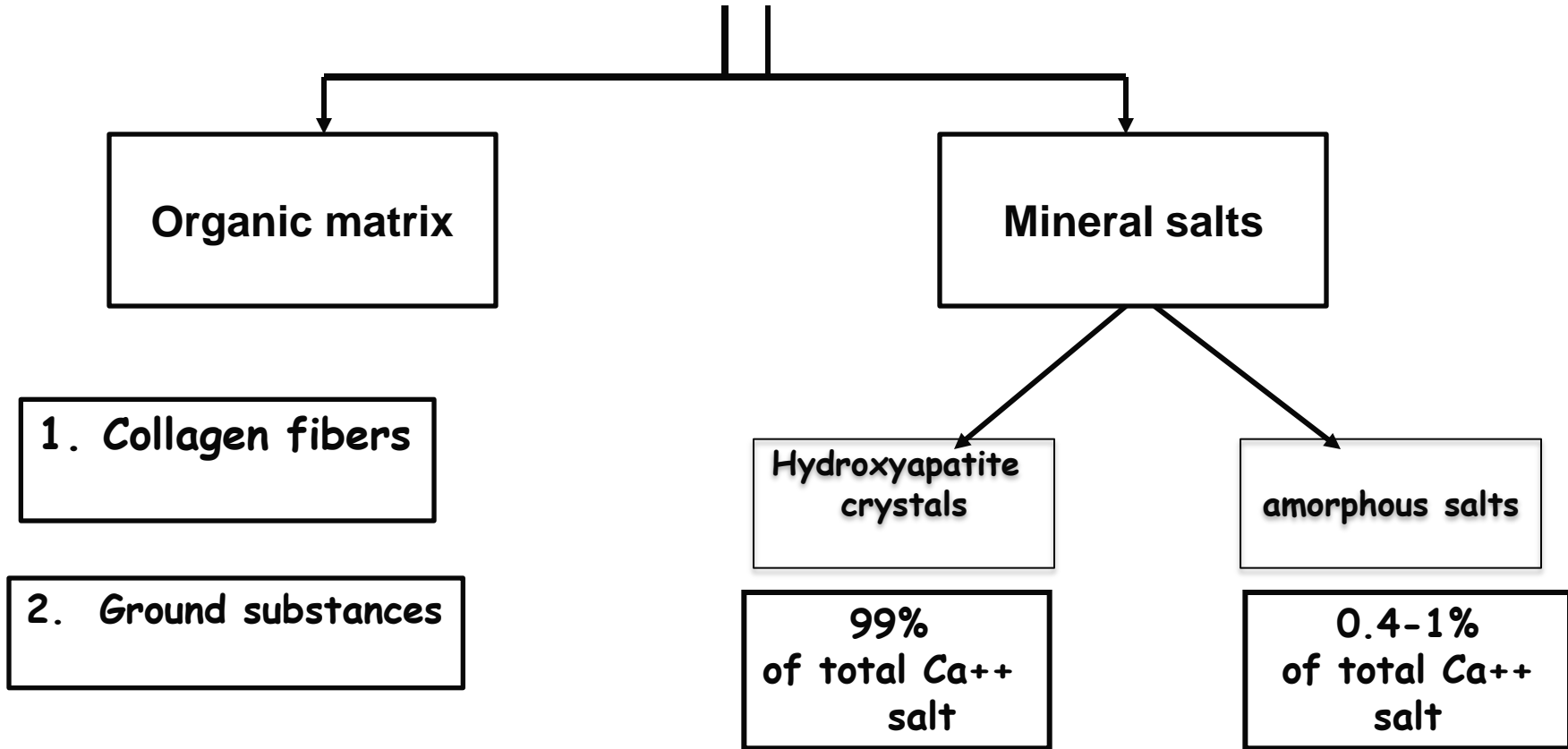


Renal stone

Calcium Metabolism in an adult human



Composition of bones



Bone composition

(2) Bone Salts

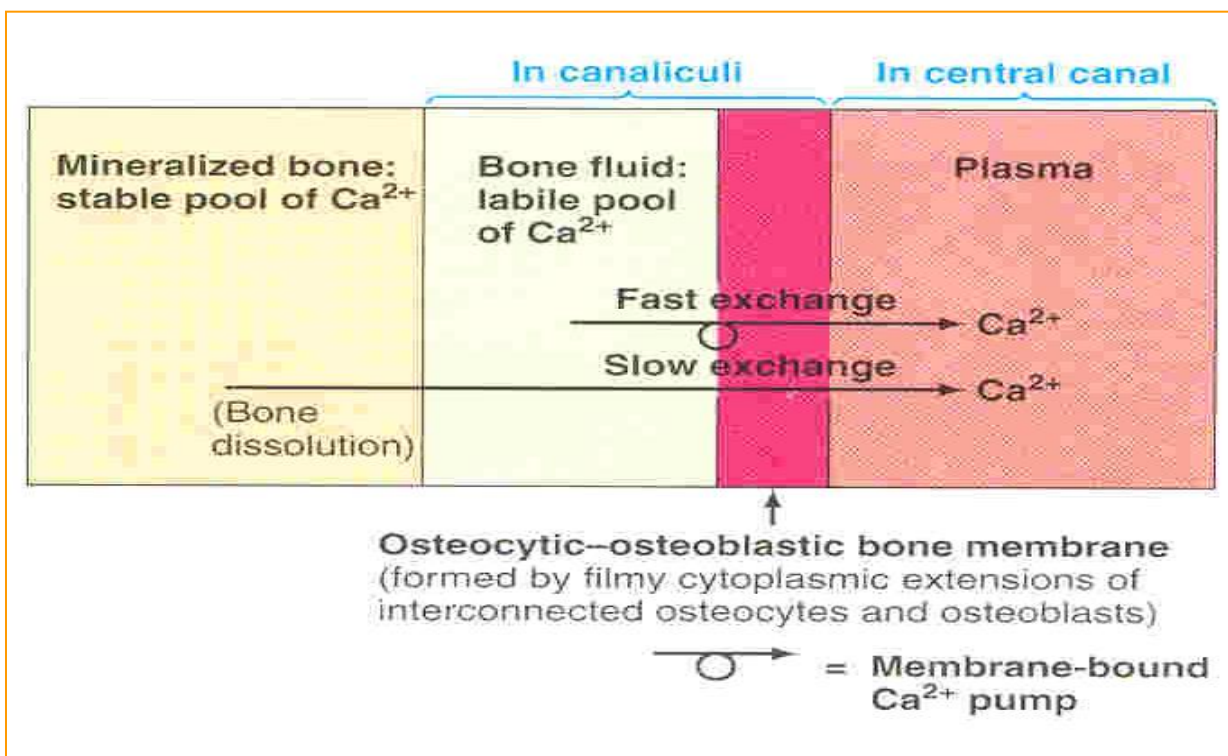
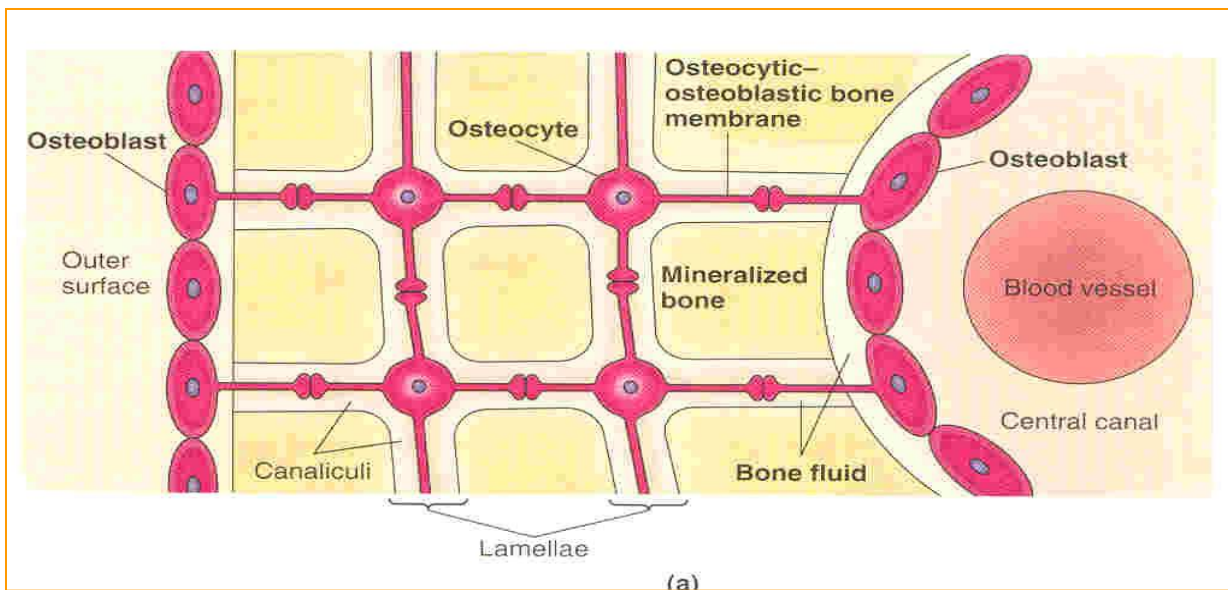
- ❑ Hydroxyapatite crystals

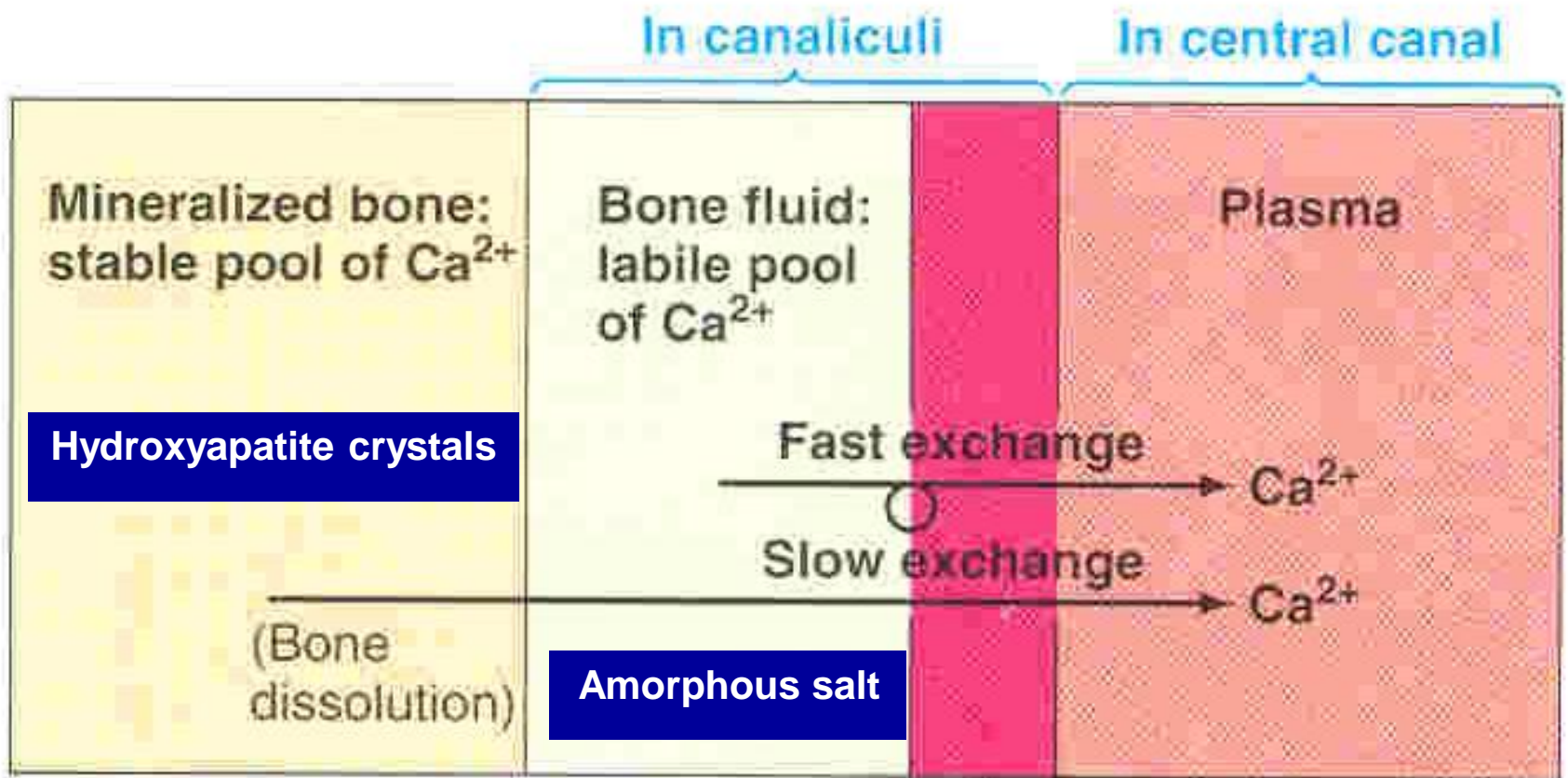
[In the form of Hydroxyapatite crystals $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$]

- ❑ 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





↑
Osteocytic–osteoblastic bone membrane
 (formed by filmy cytoplasmic extensions of interconnected osteocytes and osteoblasts)

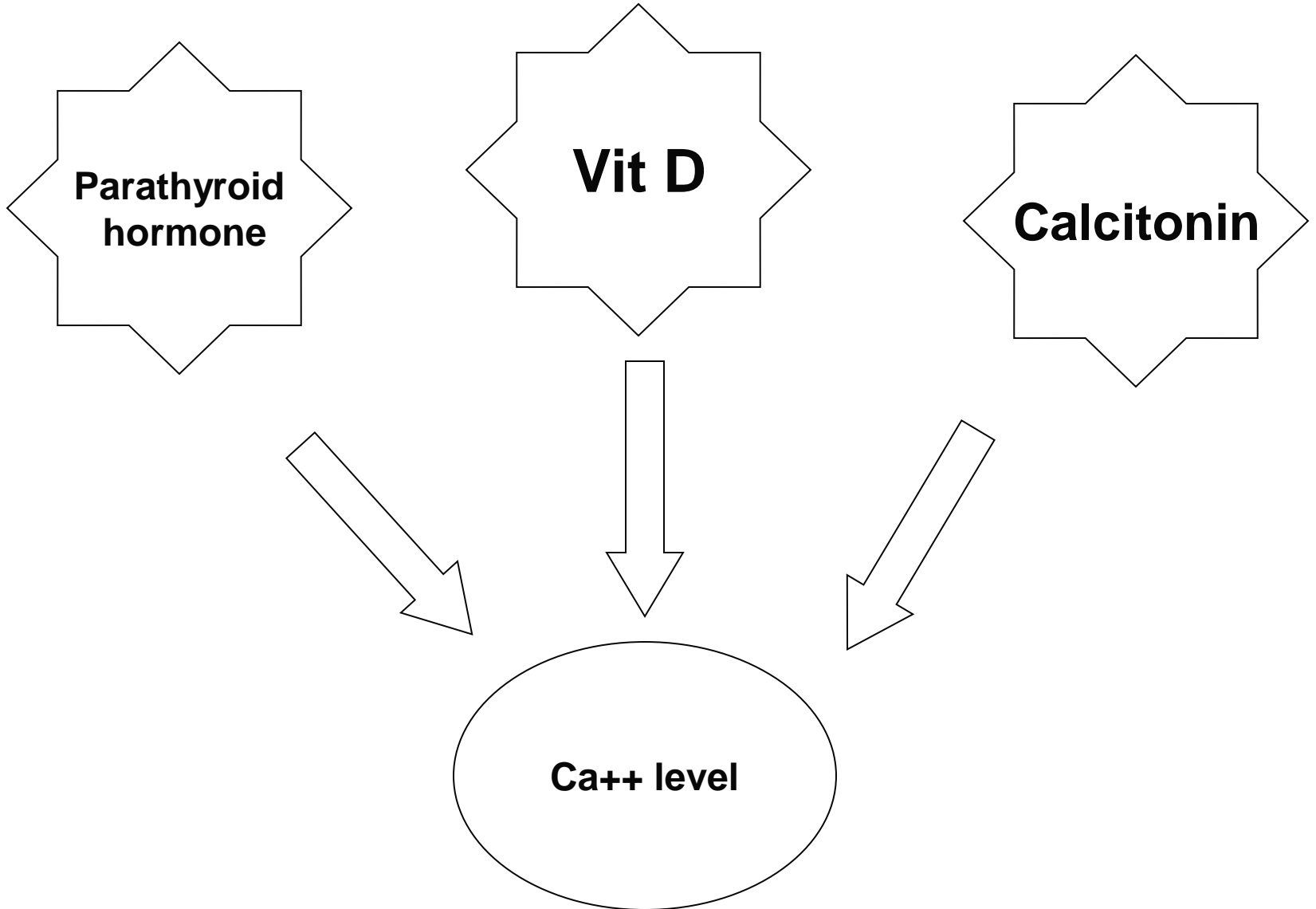
Three Hormones

**Parathyroid
hormone**

Vit D

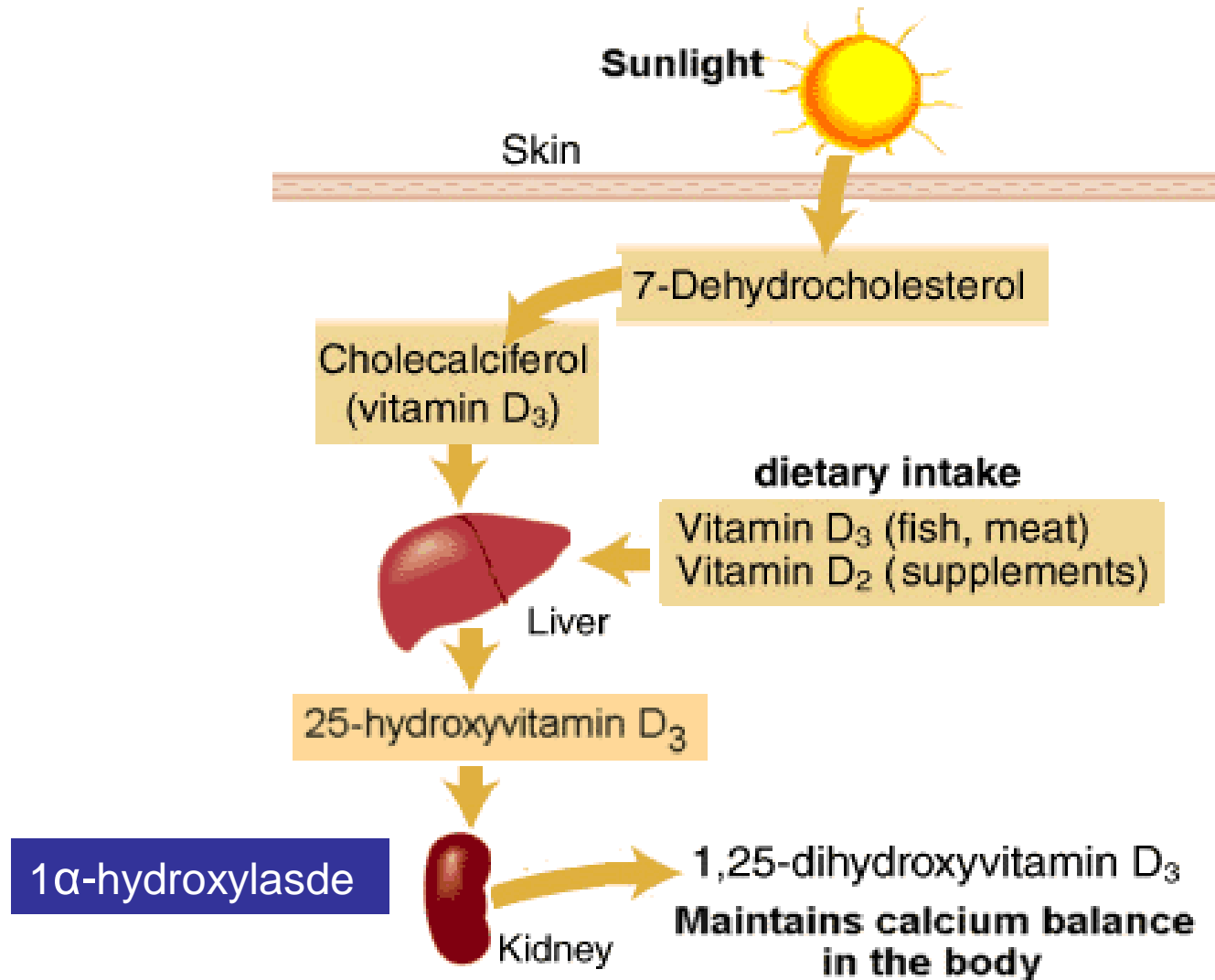
Calcitonin

Ca⁺⁺ level



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

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 osteoclasts.*

Vitamin D

4- stimulates differentiation of immune cells.

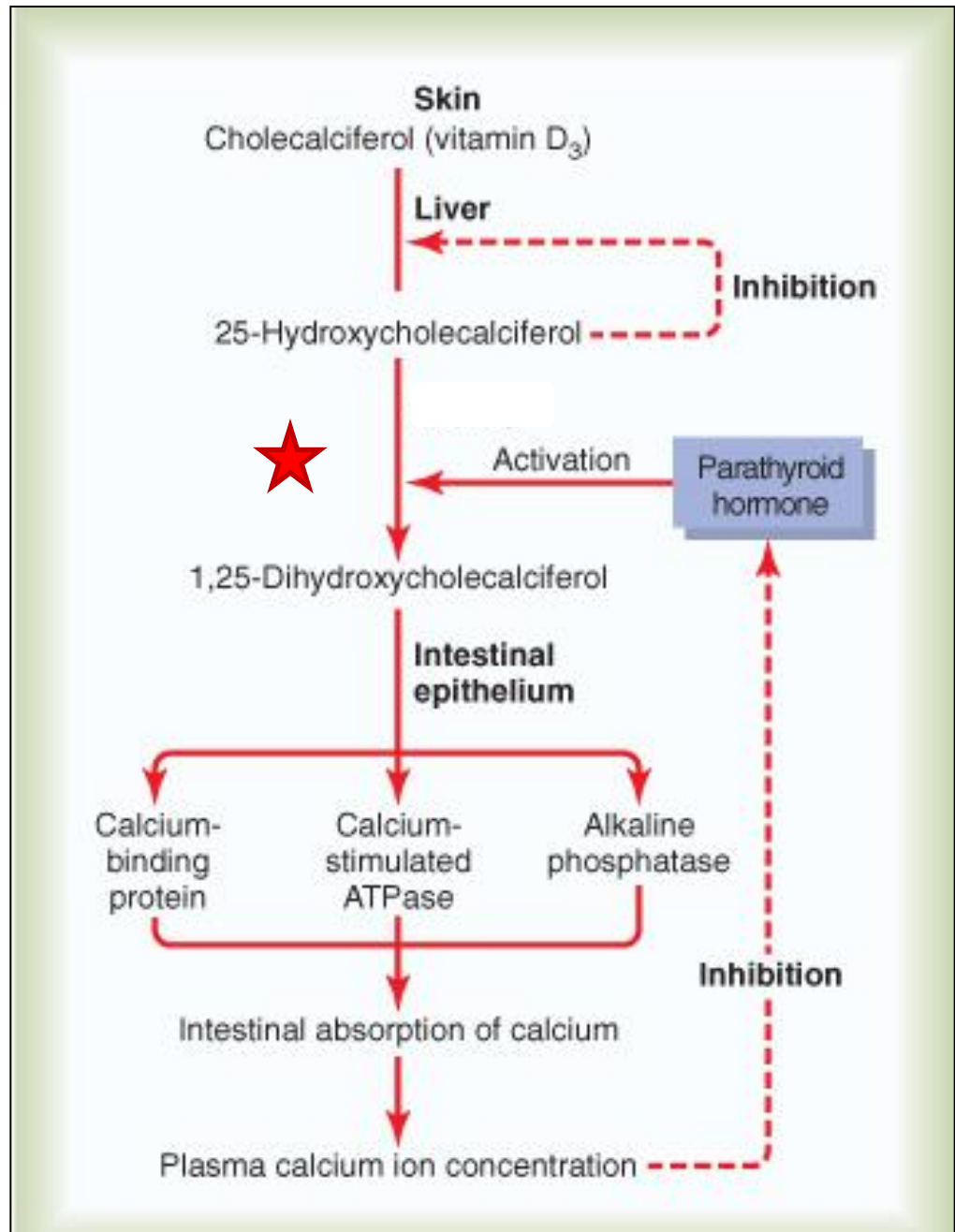
□ Control of Vit D:

1- low Ca^{++} ions

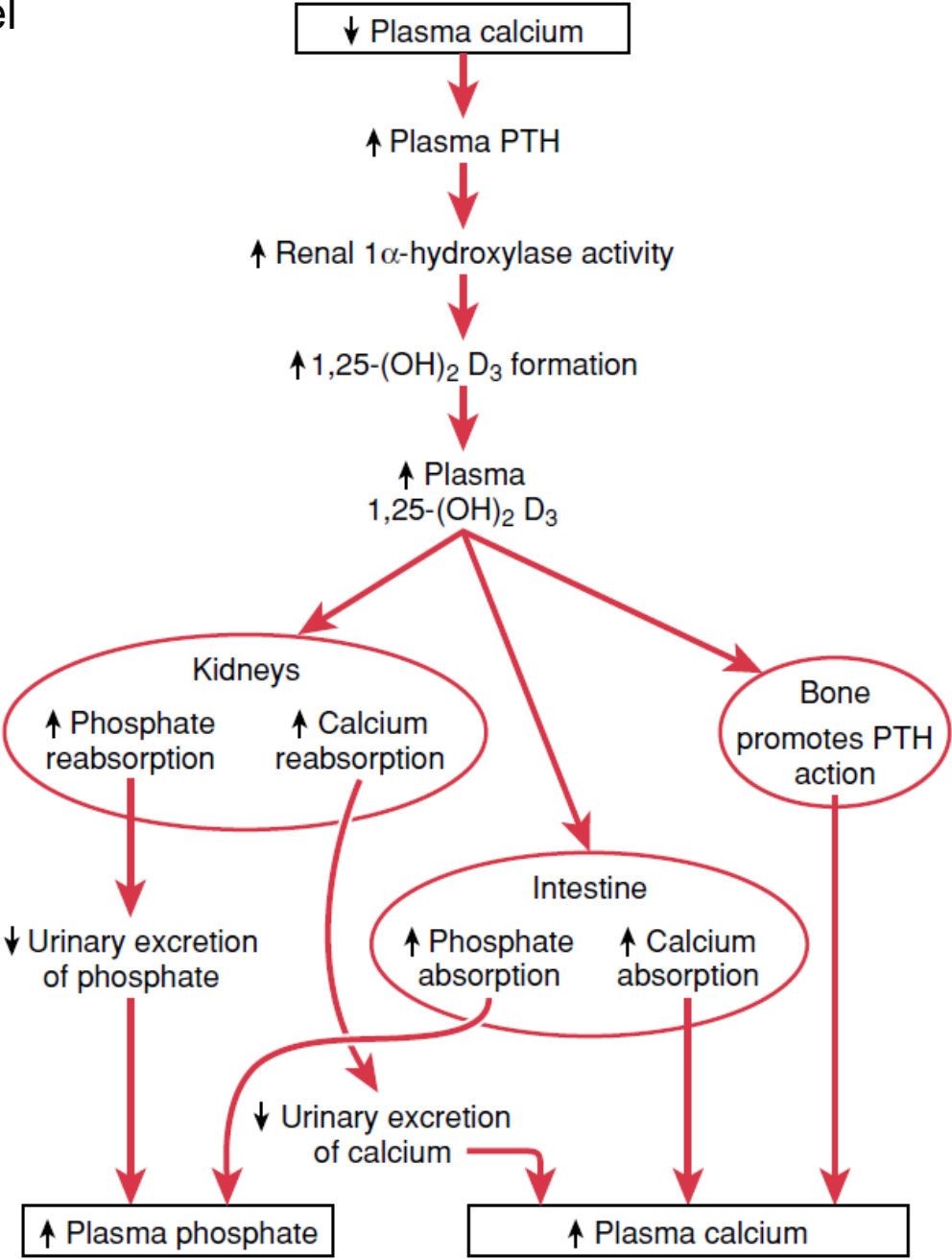
2- prolactin

3- PTH

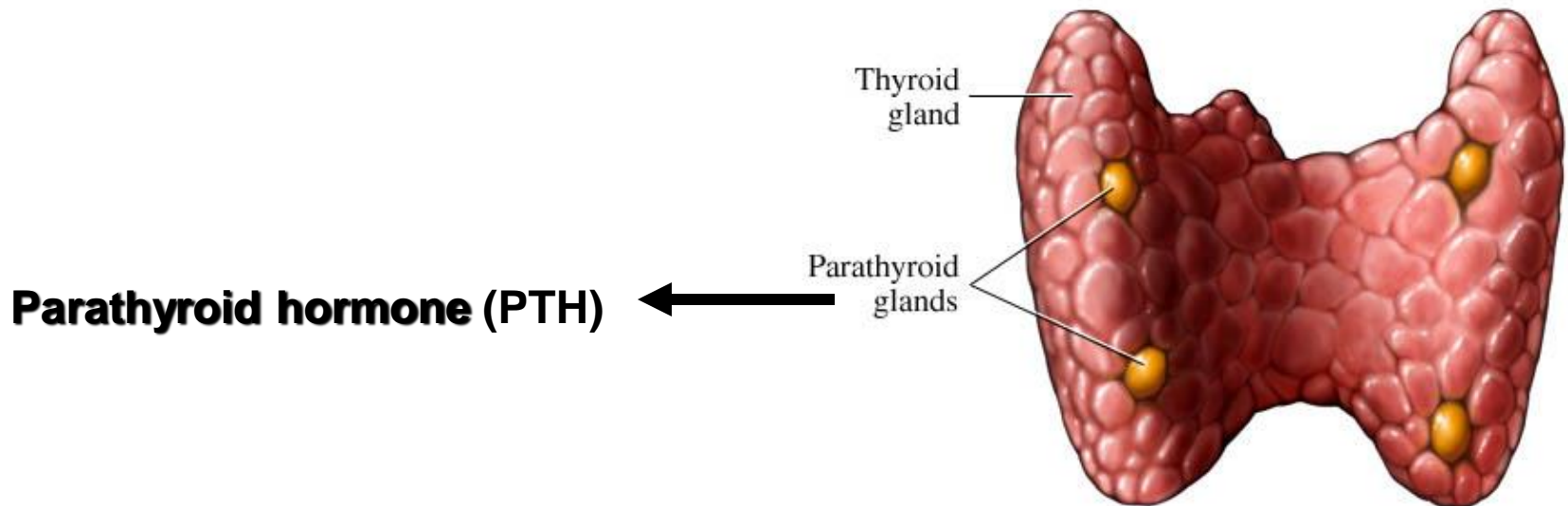
All stimulate renal $1, \alpha$ hydroxylase. ★



Regulation of Calcium level

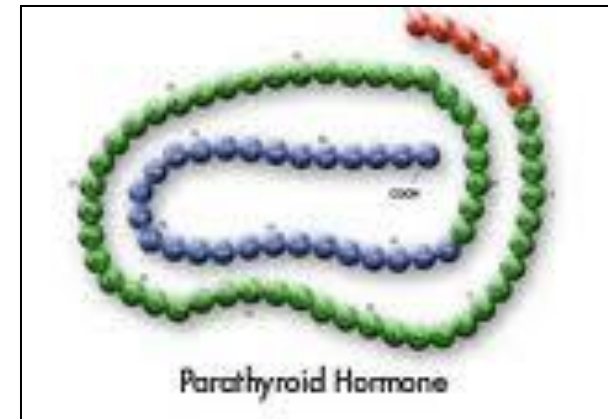
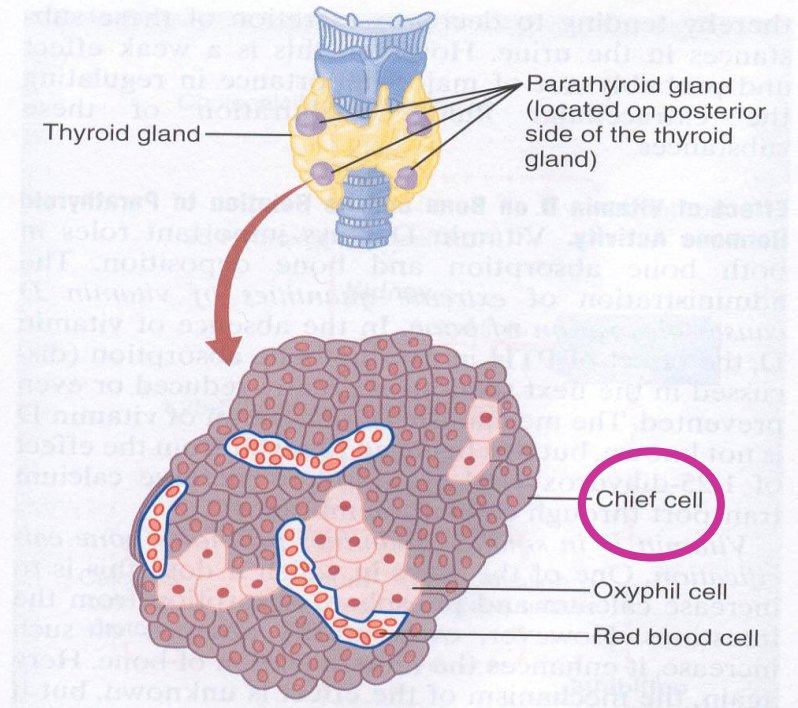


Parathyriod gland



Parathyroid hormone (PTH)

- **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**



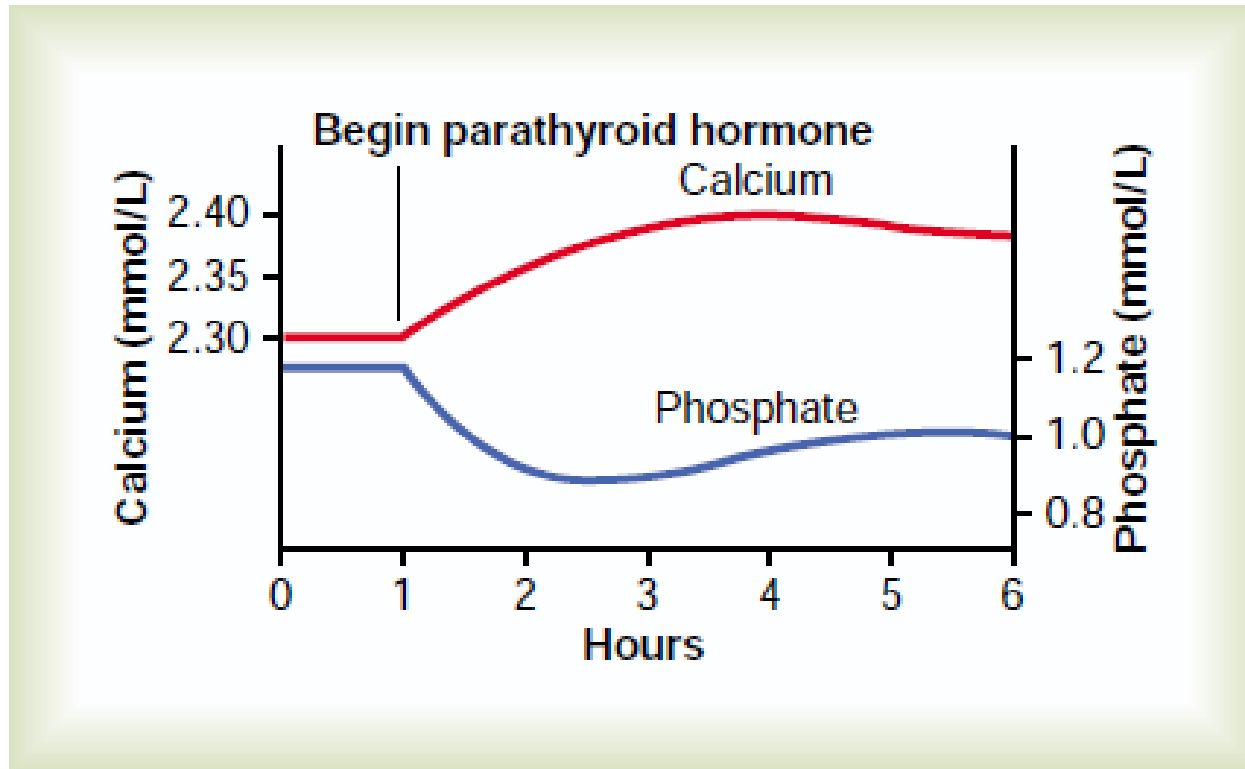
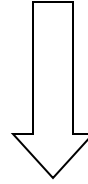


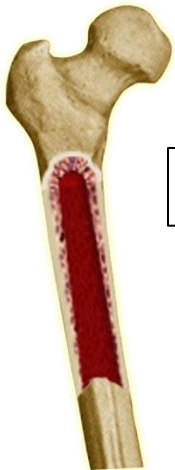
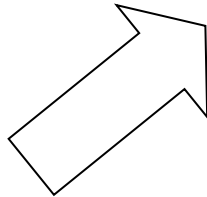
Figure 79–10

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

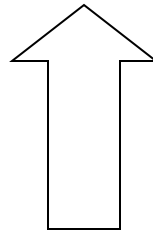
Parathyroid hormone (PTH)



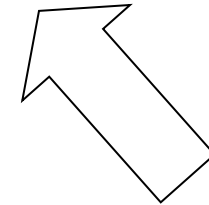
Increase plasma Ca⁺⁺ level



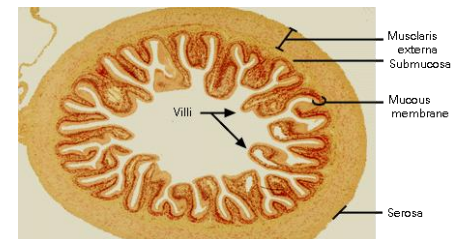
Bone



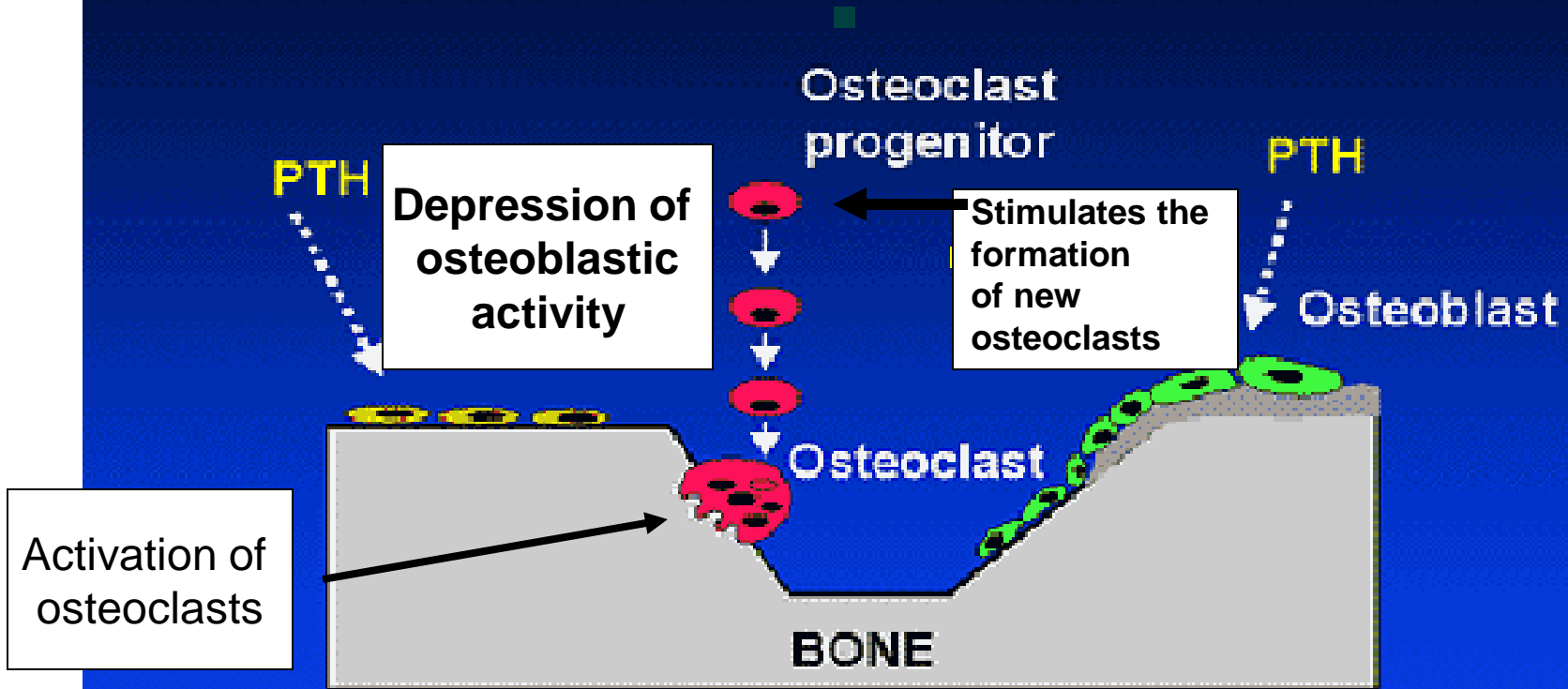
Kidney



Intestine



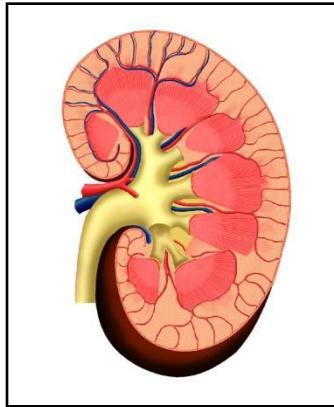
1. Effects on bones



Increase calcium resorption from the bone

2. Effects on Kidneys

(PTH)



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

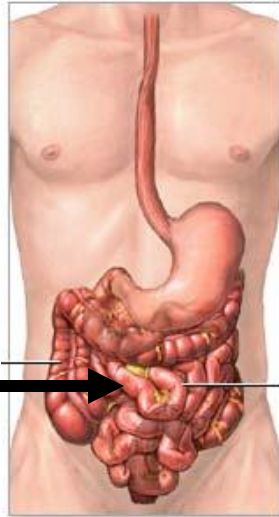
↑ Phosphate excretion in the urine

↓ 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

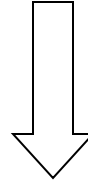


(PTH)

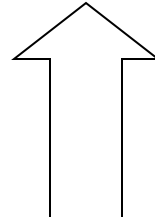


↑ absorption of calcium and phosphate indirectly through stimulating formation of $1,25 - (\text{OH})_2\text{-D}_3$ in kidney

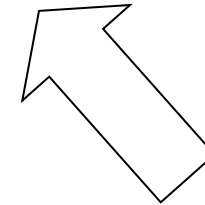
Parathyroid hormone (PTH)



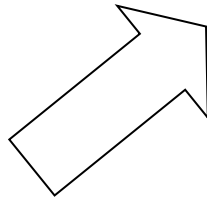
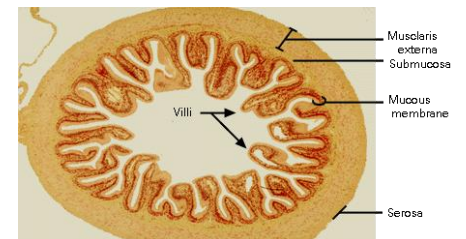
Increase plasma Ca^{++} level
Decrease phosphate level



Kidney

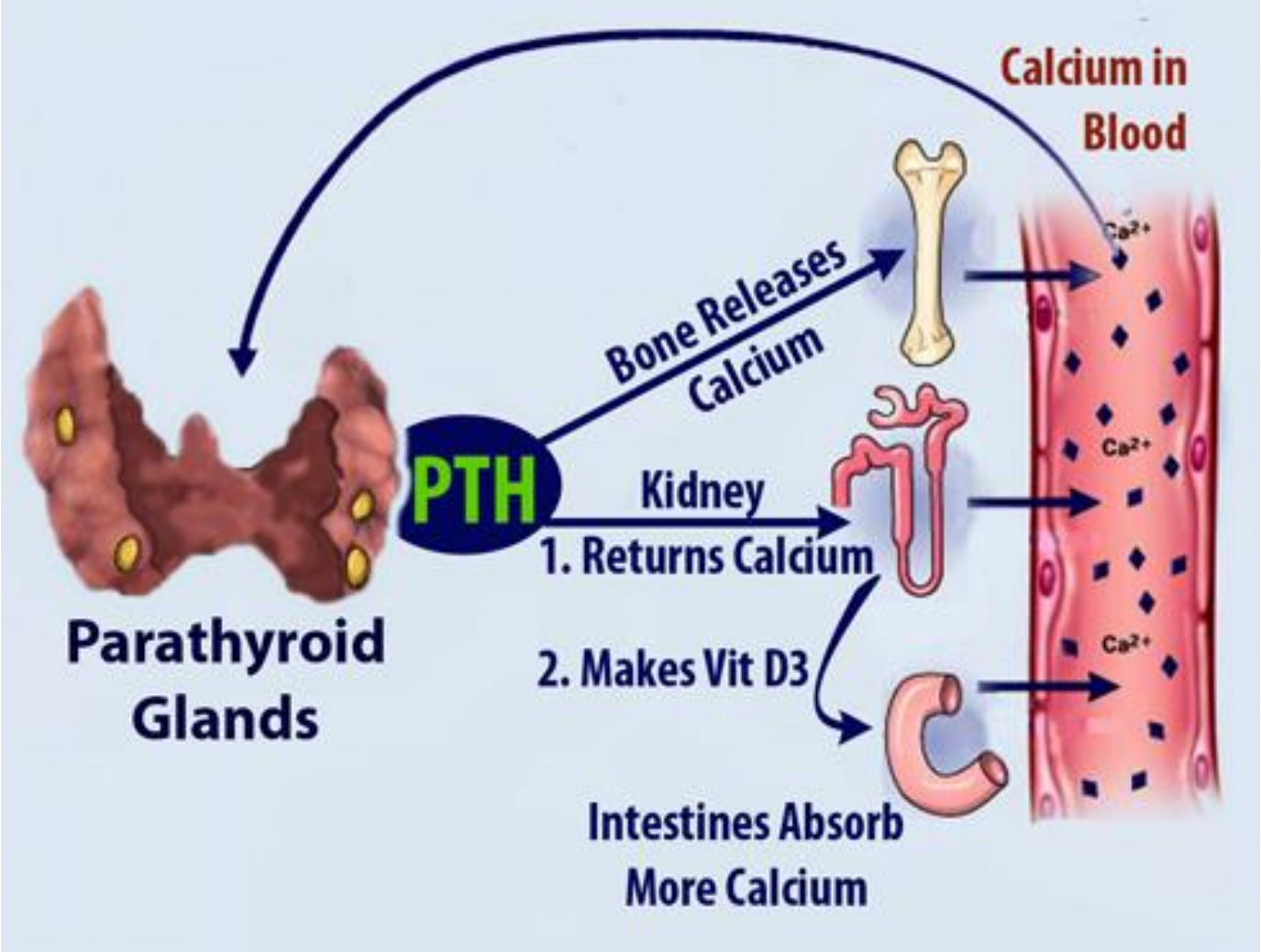


Intestine

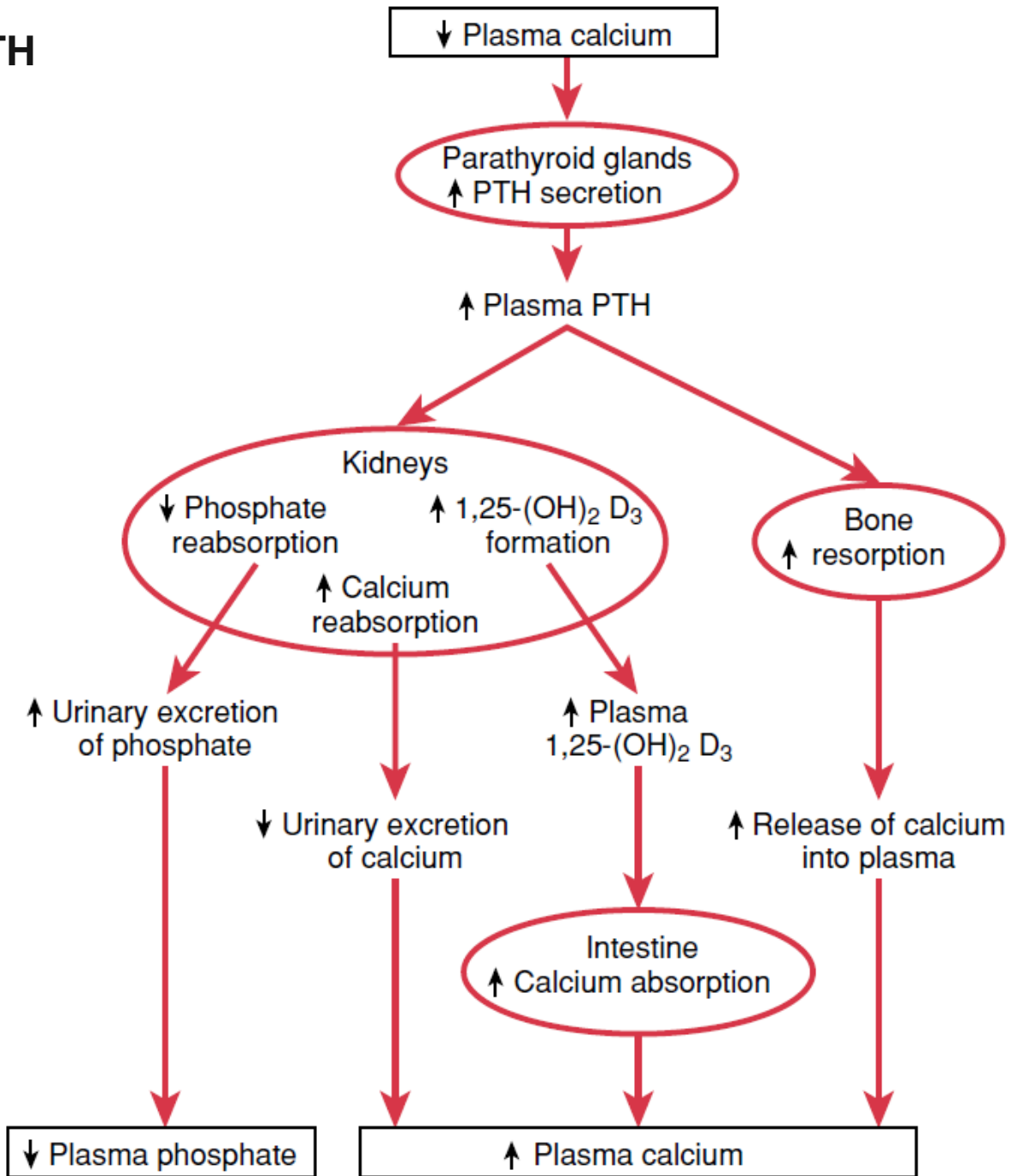


Bone

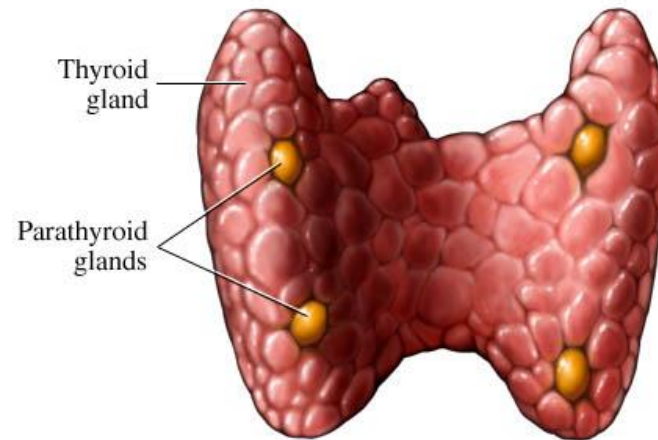




Effect of Calcium level on PTH

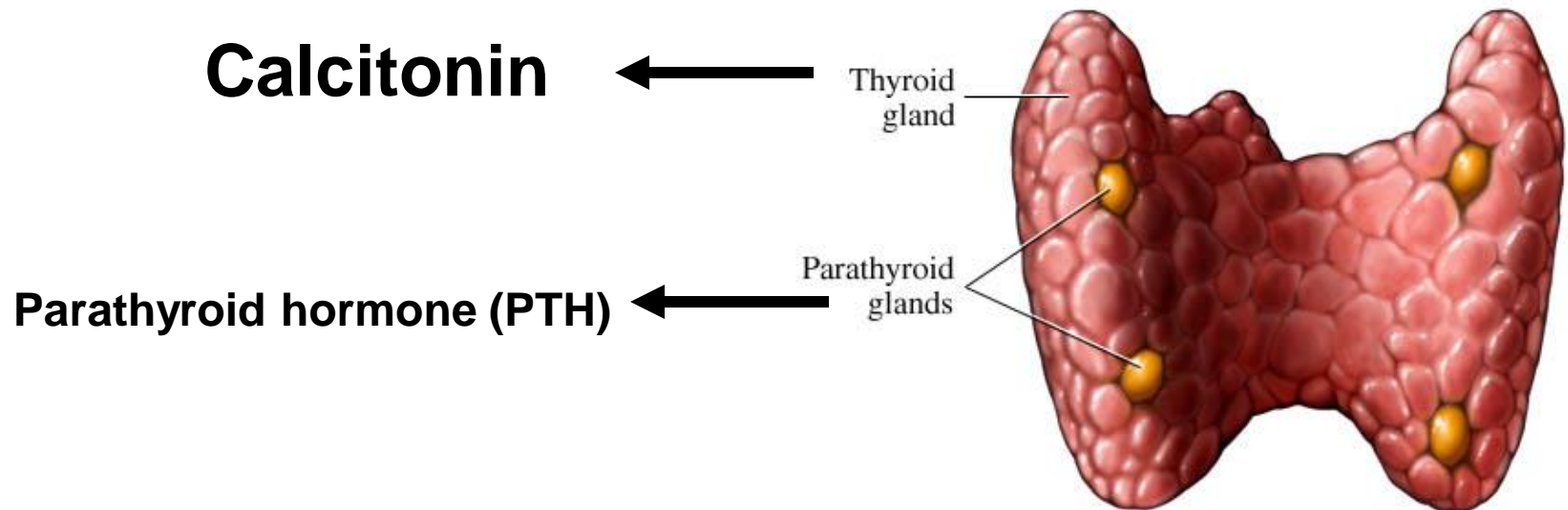


Parathyroid gland



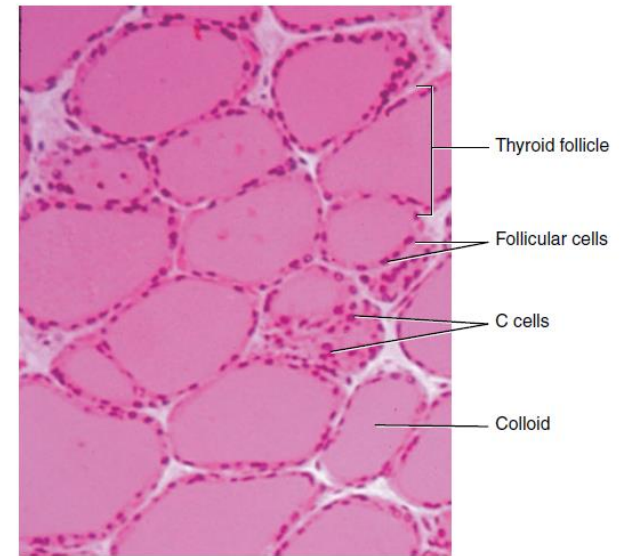
It is essential for life

Calcitonin



Calcitonin

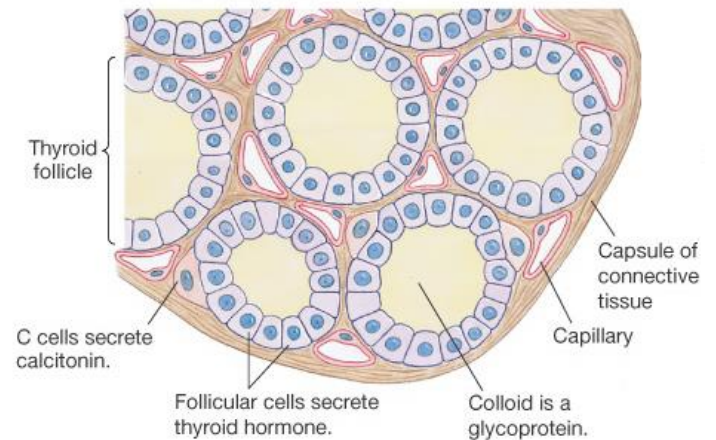
- ❑ Source: **Secreted by the parafollicular cells (C cells) of the thyroid gland.**
- ❑ Nature: **32 amino acid peptide.**
- ❑ Function:
 - **Decrease blood Ca^{++} level very rapidly within minutes.**
 - **Opposite effect to PTH**
- ❑ Stimulus for secretion:
Increased plasma calcium concentration



(b)

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

(b) Section of thyroid gland



Actions:

On bone

[1] ↑ Ca⁺⁺ deposition of bone

[2] Inhibits Bone resorption:

inhibition of osteoclasts

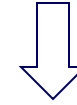
↓ formation of osteoclasts

On kidney

↓↓ Ca⁺⁺ reabsorption

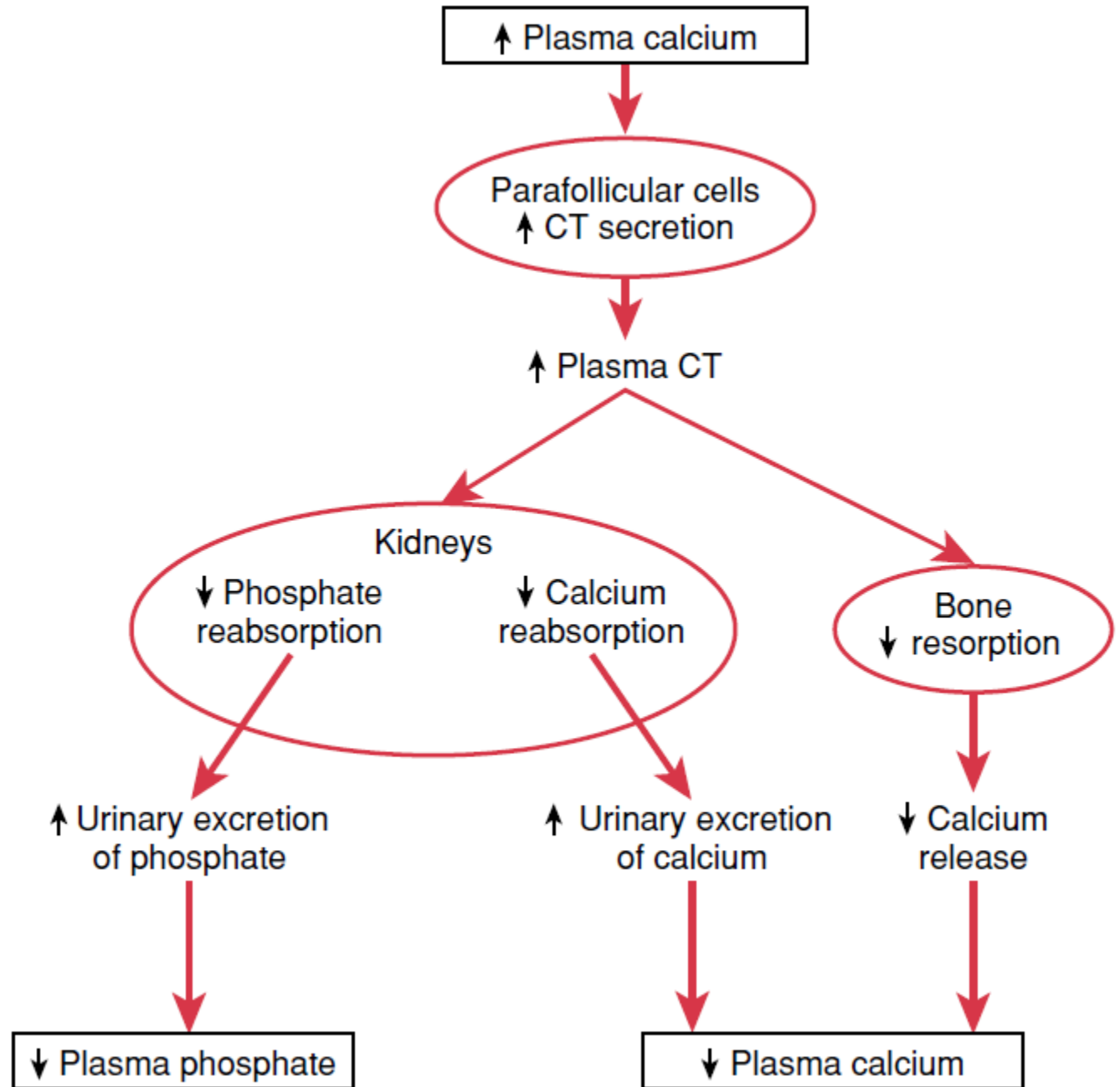
↑↑ Ca⁺⁺ excretion (in addition to phosphate)

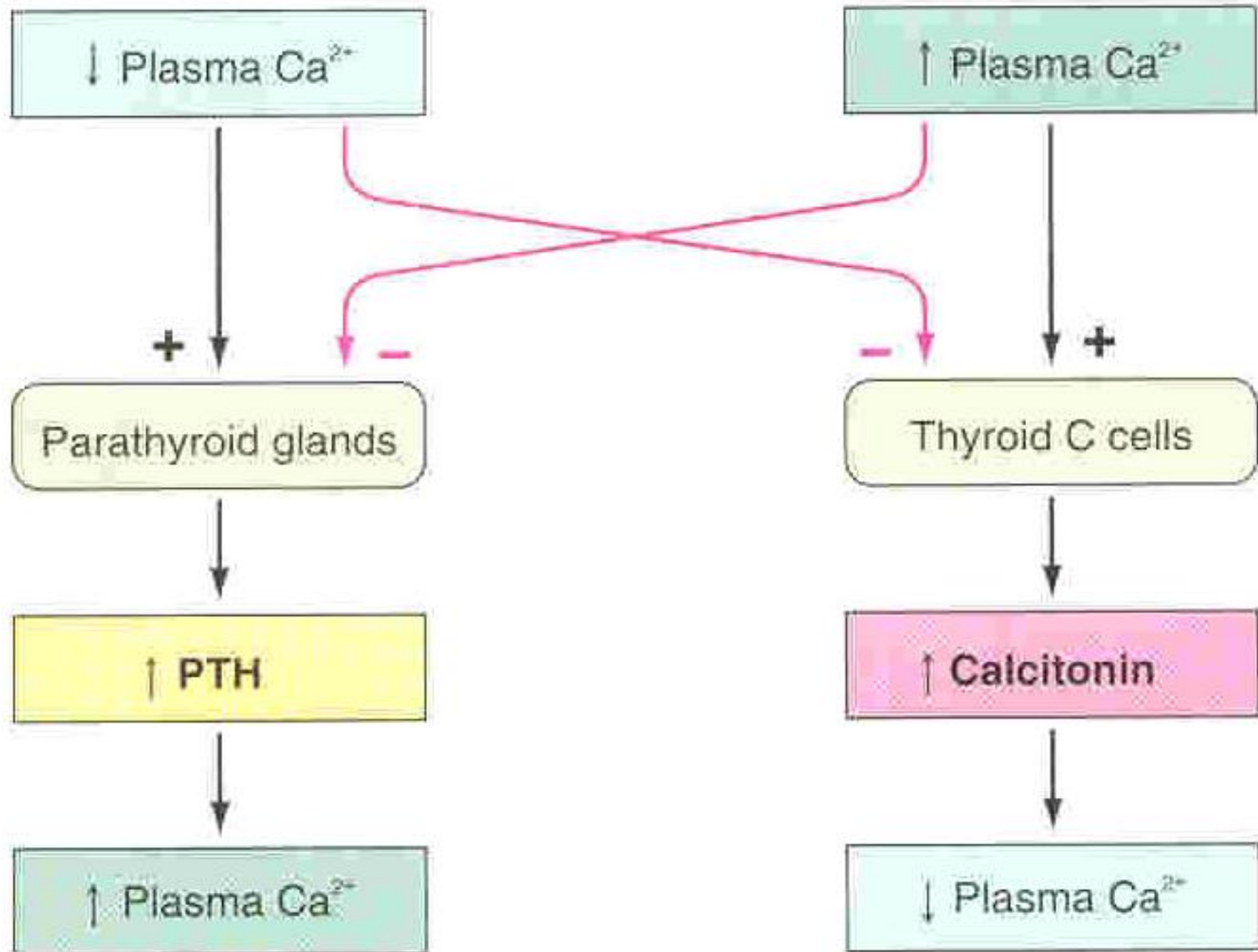
Calcitonin

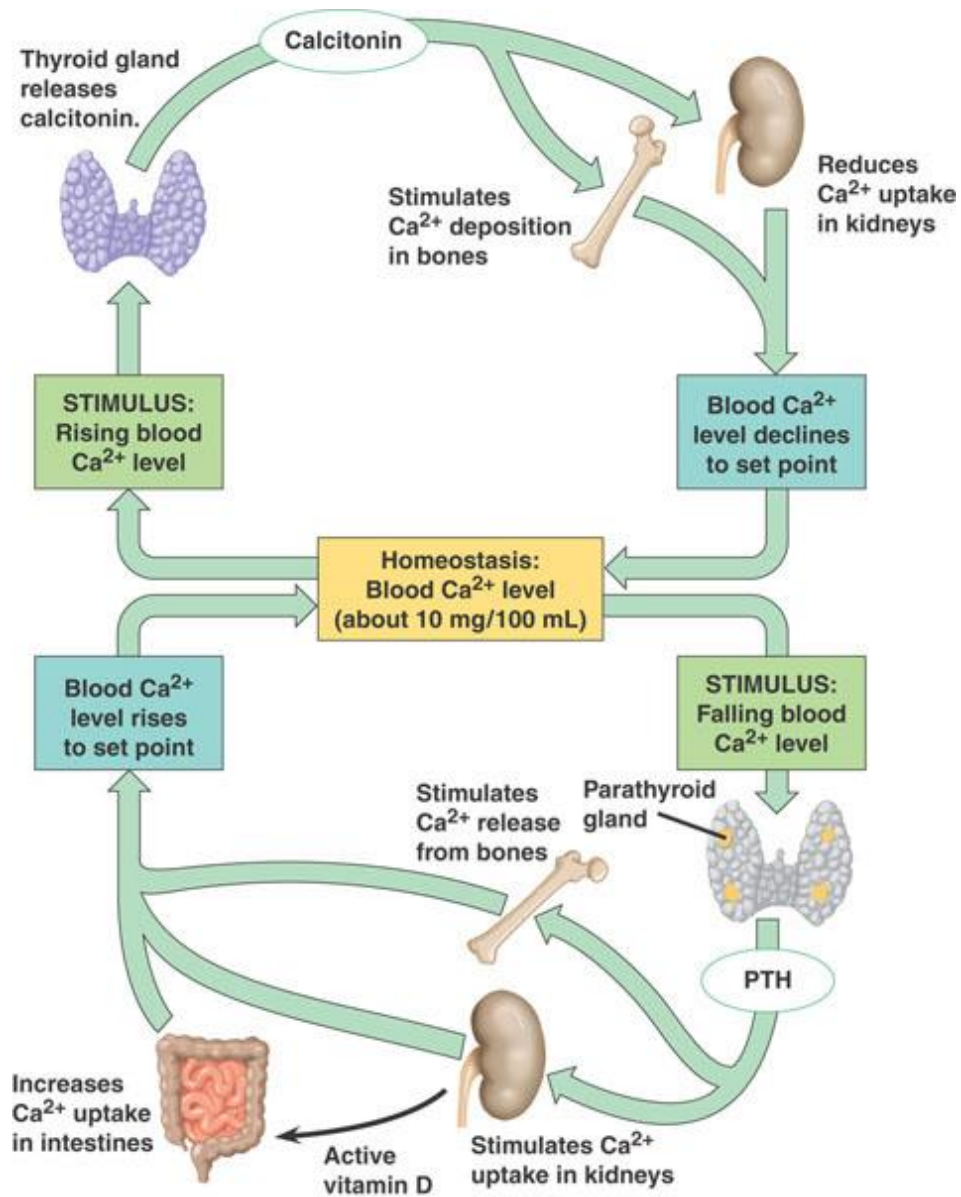


Plasma calcium concentration

Effect of Calcium level on calcitonin







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).

- Poor absorption of vitamin D and calcium

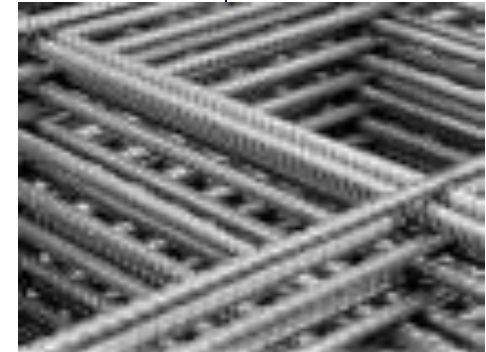
- almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

❑ 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

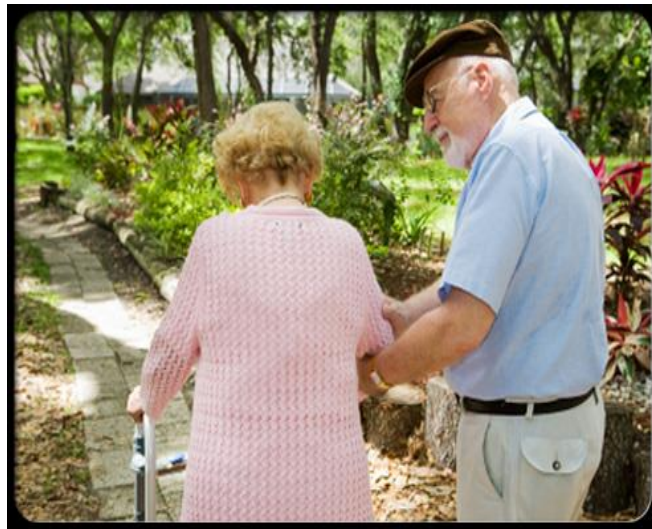
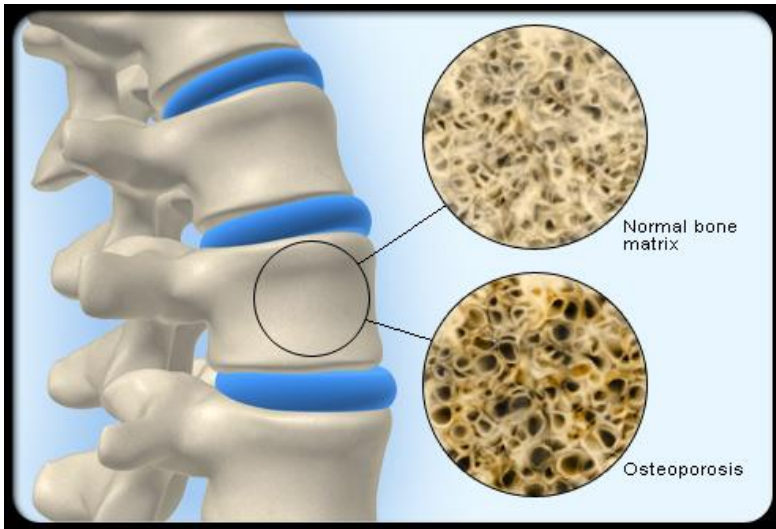


- **Bone Salts**
 - Salts of Ca^{2+}
 - In the form of hydroxyapatite crystals
 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
Mg, Na, K, Carbonate ions

In adequate bone mineralization

- Rickets
- Osteomalacia

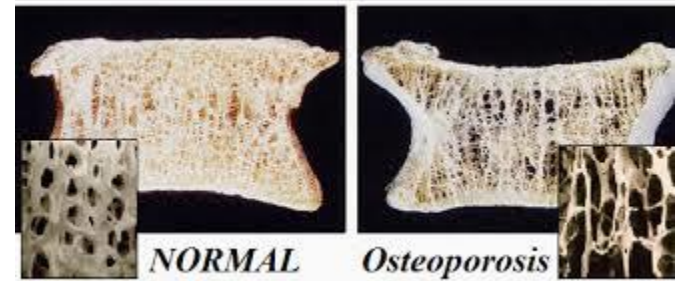




□ Osteoporosis

- 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

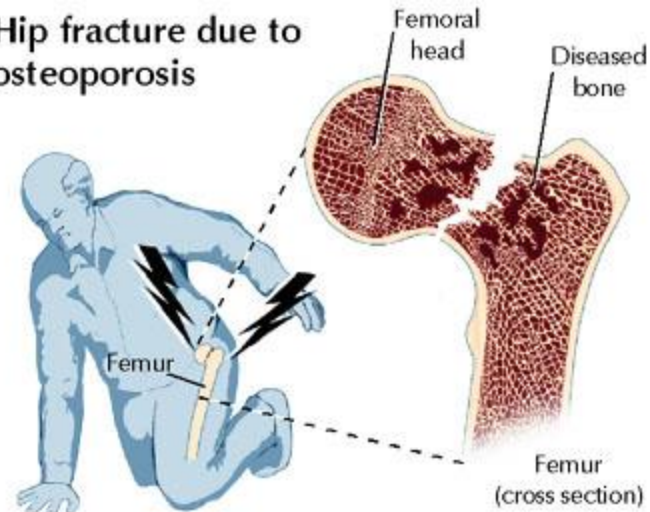
□ causes of osteoporosis:

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

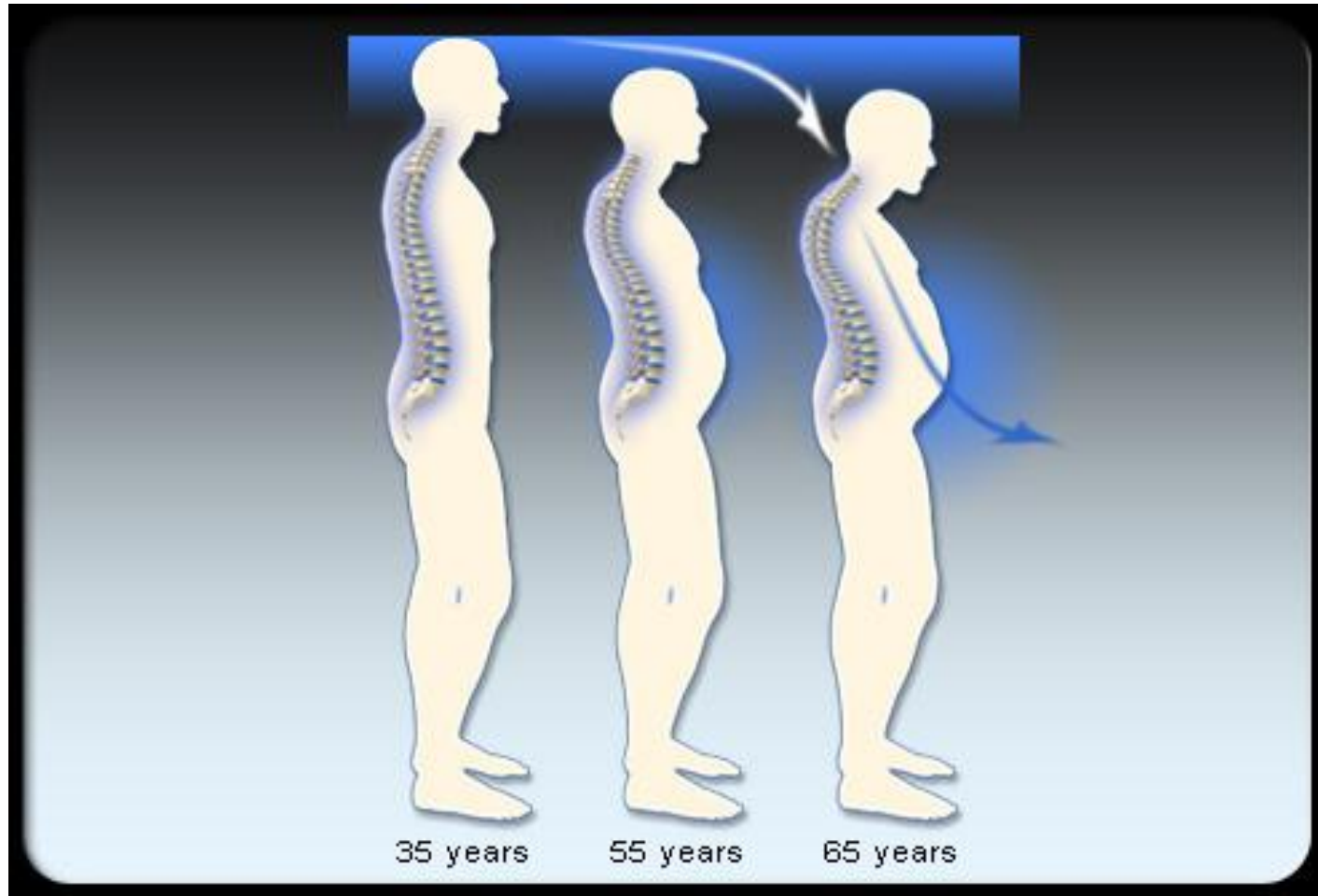
□ symptoms of osteoporosis



Hip fracture due to osteoporosis



Osteoporosis



Bone composition

- **Organic Matrix**

- Collagen Fibers (1%)
- Ground Substance (5%)
 - ECF
 - Proteoglycans

- **Bone Salts**

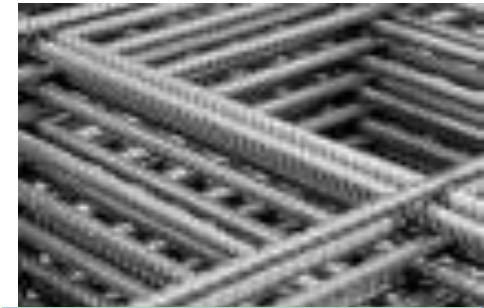
– Salts of Ca^{++} & PO_4^-

In the form of

Hydroxyapatite crystals



Mg, Na, K, Carbonate ions



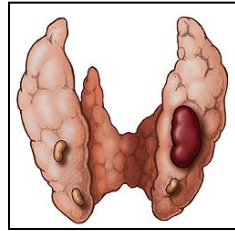
• Osteoporosis



In adequate bone matrix and minerals

**Disorders of
parathyroid hormone
secretion**

Hyperparathyroidism (PTH Excess)



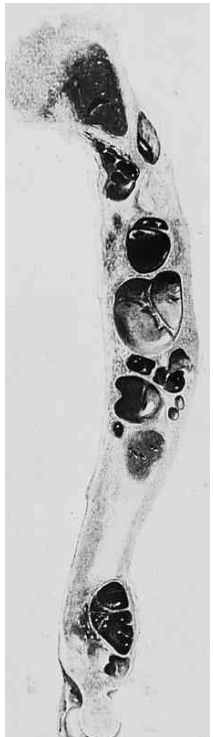
Primary

Manifestations:

- Hypercalcemia $\uparrow \text{Ca}^{2+}$
- Hypophosphemia $\downarrow \text{PO}_4^-$
- Hypercalciuria
- Demineralisation of bone
multiple bone cysts (osteitis fibrosa cystica)
- Broken bones
- \uparrow 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 $\text{Ca}^{2+} > 17\text{mg/dl} \rightarrow \text{death}$



Hyperparathyroidism (PTH Excess)

Primary

Secondary (compensatory) Hyperparathyroidism

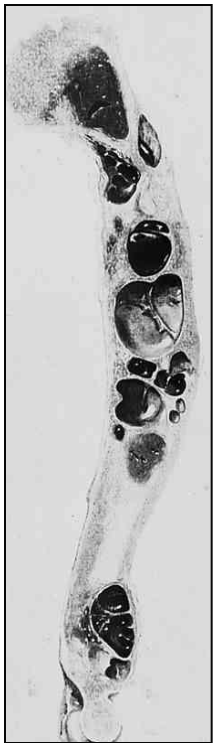
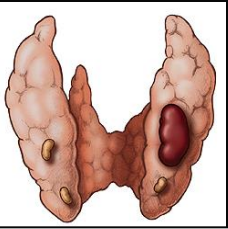
Manifestations:

- Hypercalcemia $\uparrow \text{Ca}^{2+}$
- Hypophosphemia $\downarrow \text{PO}_4^-$
- Hypercalciuria
- Demineralisation of bone
multiple bone cysts (osteitis fibrosa cystica)
- Calcium containing stones in kidney
- Precipitation of calcium in soft tissues occur when $\text{Ca}^{2+} > 17\text{mg/dl}$.

• (due to $\downarrow \text{Ca}^{2+}$ in ECF)

• Causes:

- 1) Low calcium diet
- 2) Pregnancy
- 3) Lactation
- 4) Rickets
- 5) Osteomalcia
- 6) Chronic renal failure
 \downarrow **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

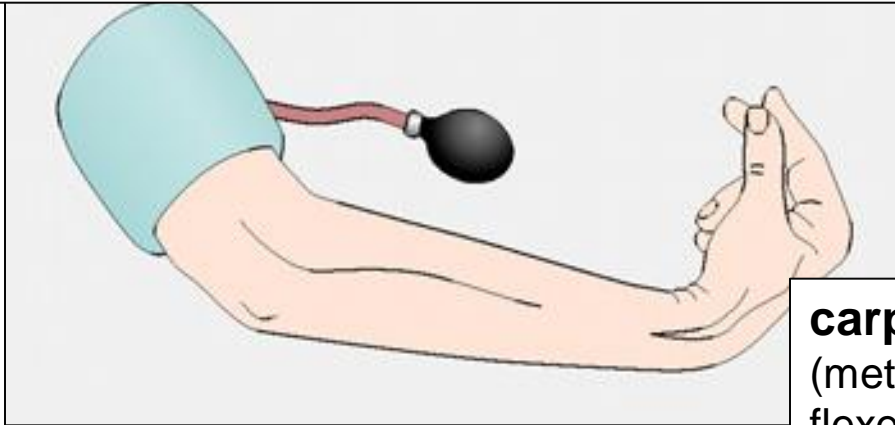
- Positive Chvostek's sign (facial muscle twitch)
- Positive Trousseau's sign (carpal spasm)
- Delayed cardiac repolarization with prolongation of the QT interval
- Paresthesia
- Tetany: can be overt or latent

• 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

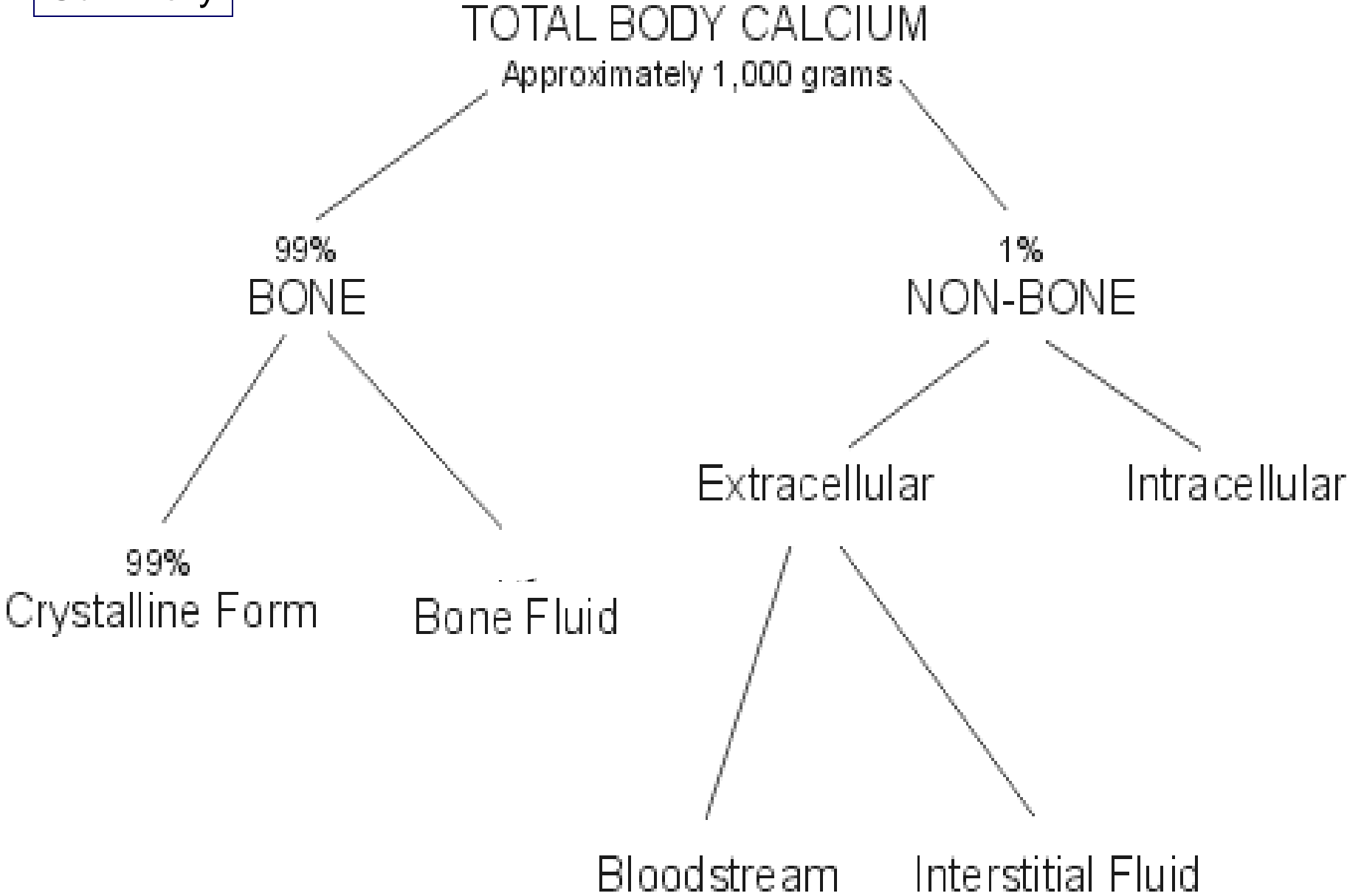


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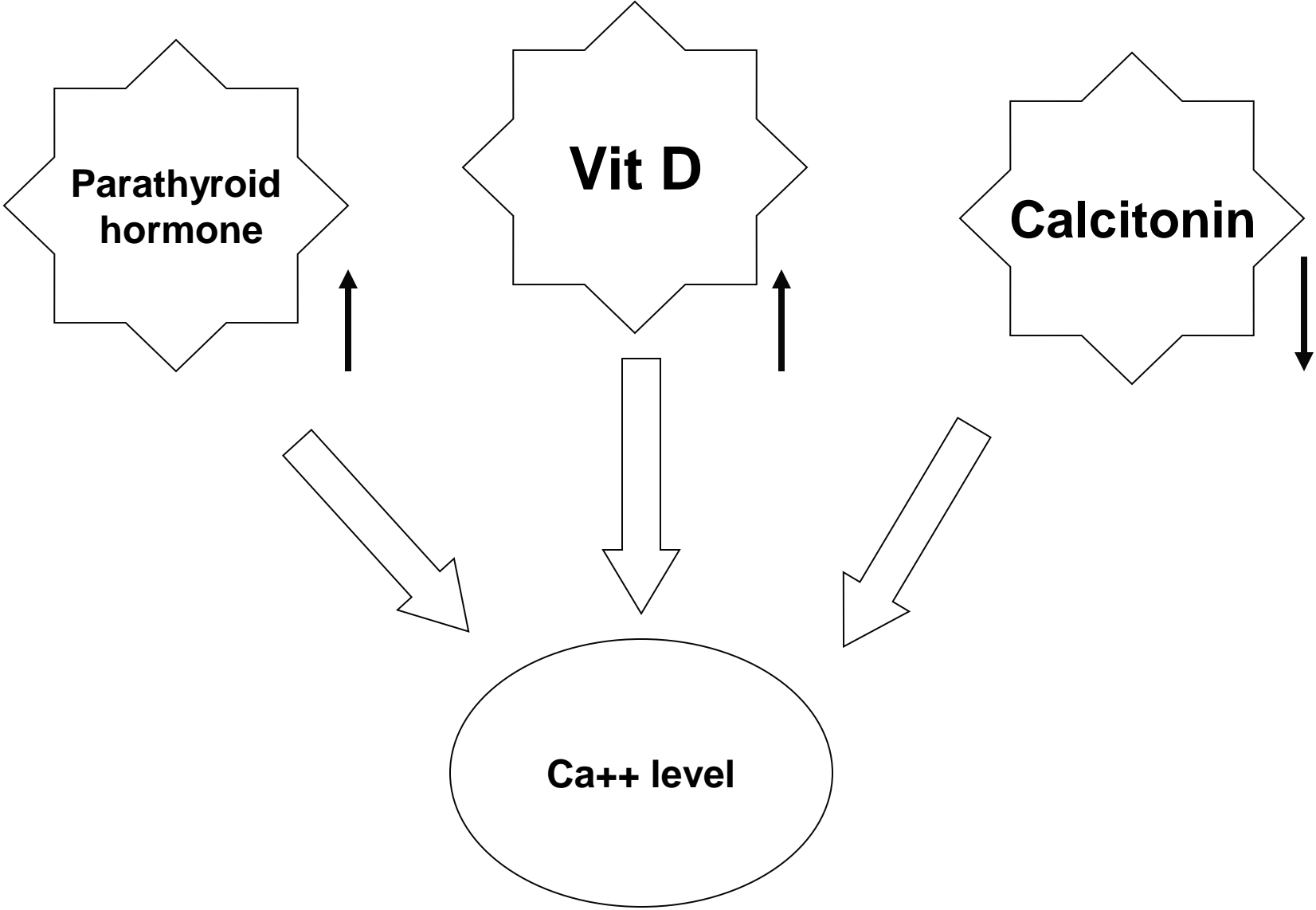


(This is due to enhanced neuromuscular excitability)

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