بسم الله الرحمن الرحيم

ENDOCRINOLOGY

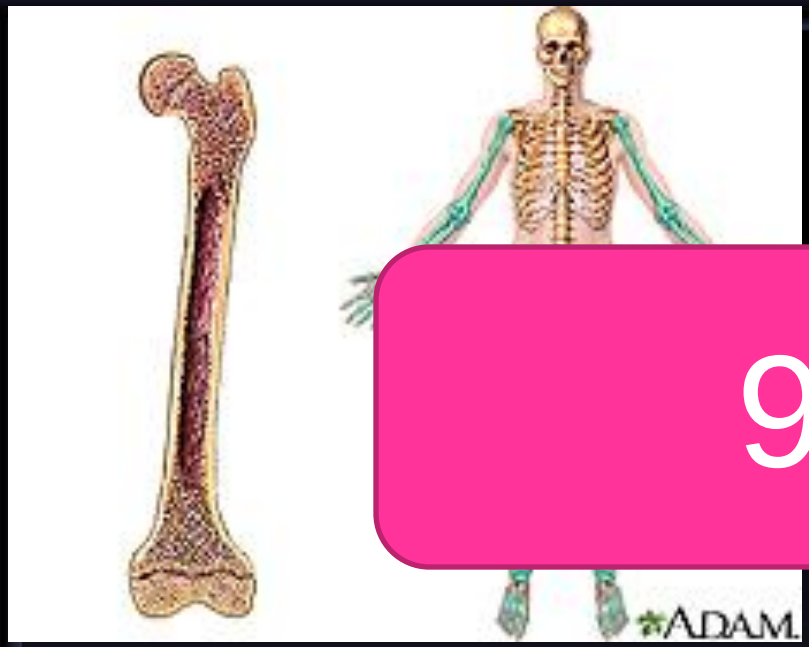
CALCIUM HOMEOSTASIS PARATHYROID GLAND

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

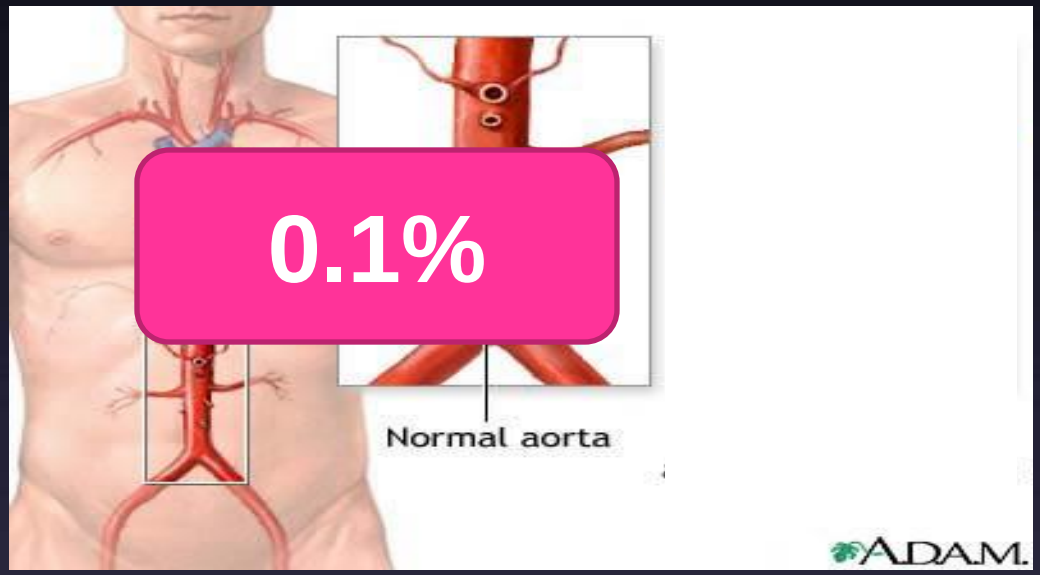
OBJECTIVES

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

- List 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%



0.1%

Distribution of Ca^{++} in Body

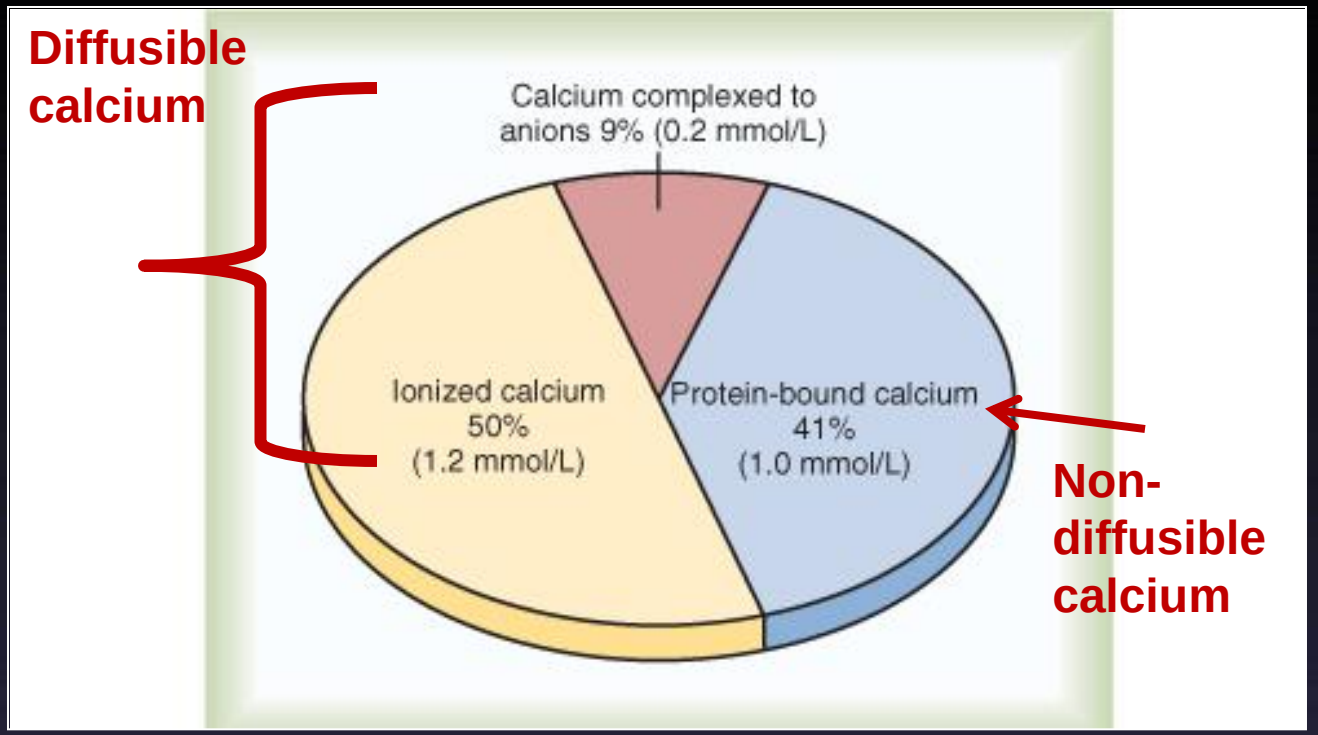
- **Skeleton & Teeth**
- **ICF (Endoplasmic Reticulum)**
- **ECF**

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%

Calcuim metabolism

- Total plasma calcium= 9-11 mg/dl



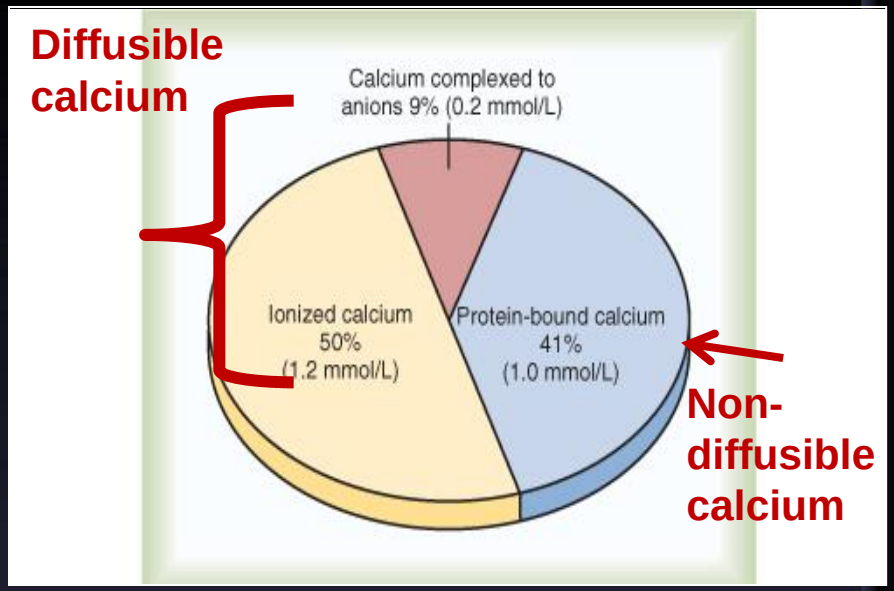
Plasma Calcium

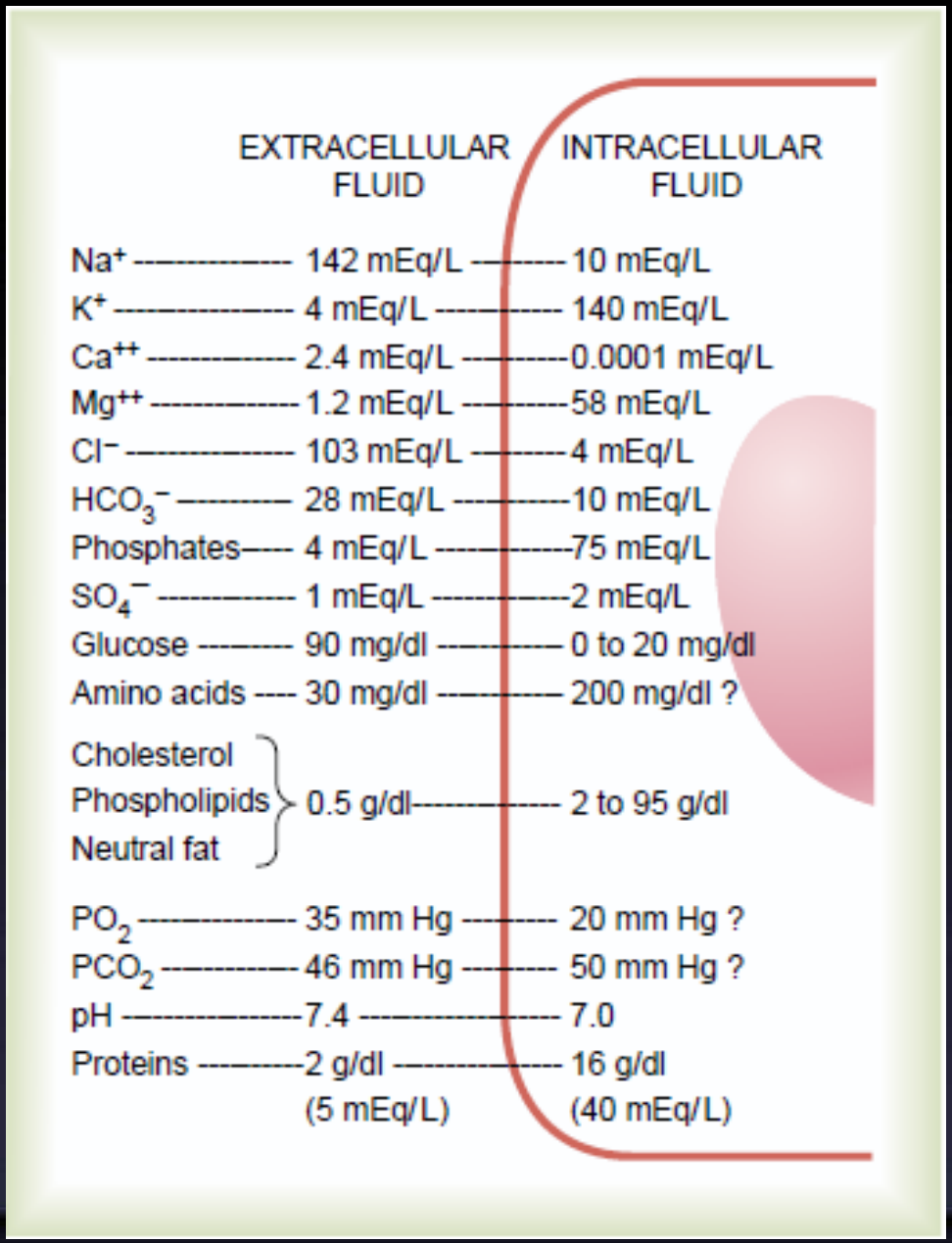
9-11 mg/dl

Non Diffusible = 41%

Diffusible = 59%

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

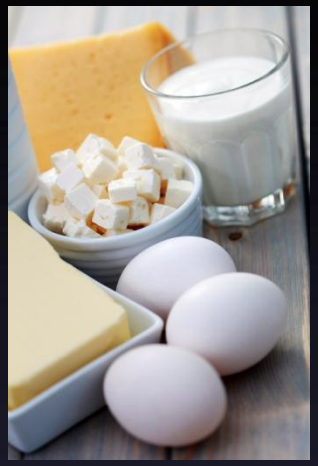



EXTRACELLULAR FLUID
INTRACELLULAR FLUID
Na+ 142 mEq/L 10 mEq/L
K+ 4 mEq/L 140 mEq/L
Ca++ 2.4 mEq/L 0.0001 mEq/L
Mg++ 1.2 mEq/L 58 mEq/L
Cl− 103 mEq/L 4 mEq/L
HCO3− 28 mEq/L 10 mEq/L
Phosphates 4 mEq/L 75 mEq/L
SO4− 1 mEq/L 2 mEq/L
Glucose 90 mg/dl 0 to 20 mg/dl
Amino acids 30 mg/dl 200 mg/dl ?
Cholesterol
Phospholipids 0.5 g/dl 2 to 95 g/dl
Neutral fat
PO2 35 mm Hg 20 mm Hg ?
PCO2 46 mm Hg 50 mm Hg ?
pH 7.4 7.0
Proteins 2 g/dl 16 g/dl
(5 mEq/L) (40 mEq/L)

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
  - Blood coagulation
  - Hormonal secretion
  - Enzymatic regulation
  - Second messenger.
  - Milk production.
  - Maintains normal permeability of cell membranes.

Source



- milk
- dairy products.

Daily requirements

- Infants & adults:
  12.5 -25 mmol/day

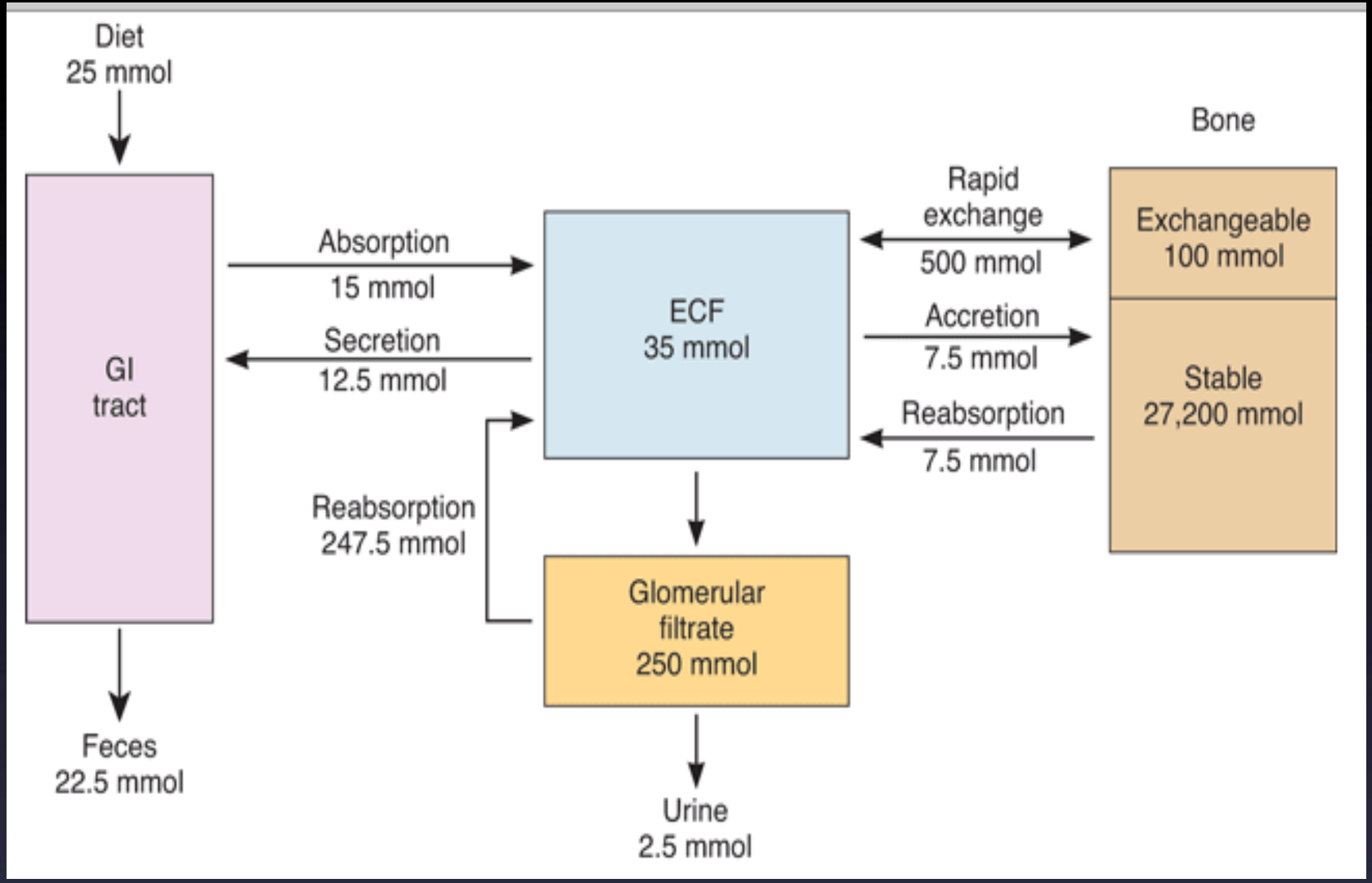
- Pregnancy,
- lactation
- after menopause:

  25-35 mmol/day

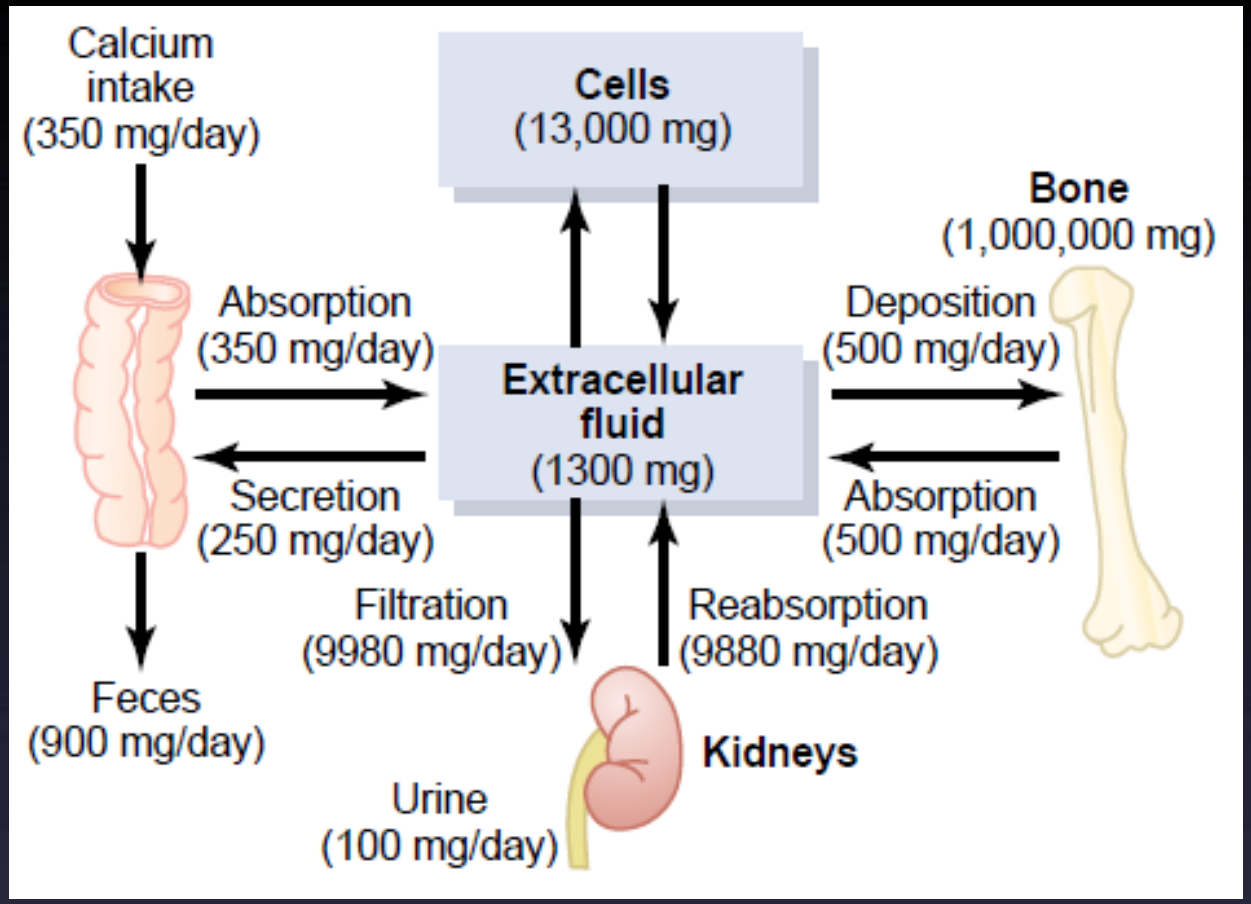
Absorption

- Duodenum:
  active transport
- small intestine:
  concentration gradient

Calcium Metabolism in an adult human



Calcium Metabolism in an adult human



Bone & Ca^{++}

- Organic Matrix
  - Collagen Fibers
  - Ground Substance
    - ECF
    - Proteoglycans
- Bone Salts
  - Salts of Ca & PO4
    - Amorphous form
    - Crystalline Form (Hydroxyapatite)
    - Mg, Na, K, Carbonate

Composition of bones

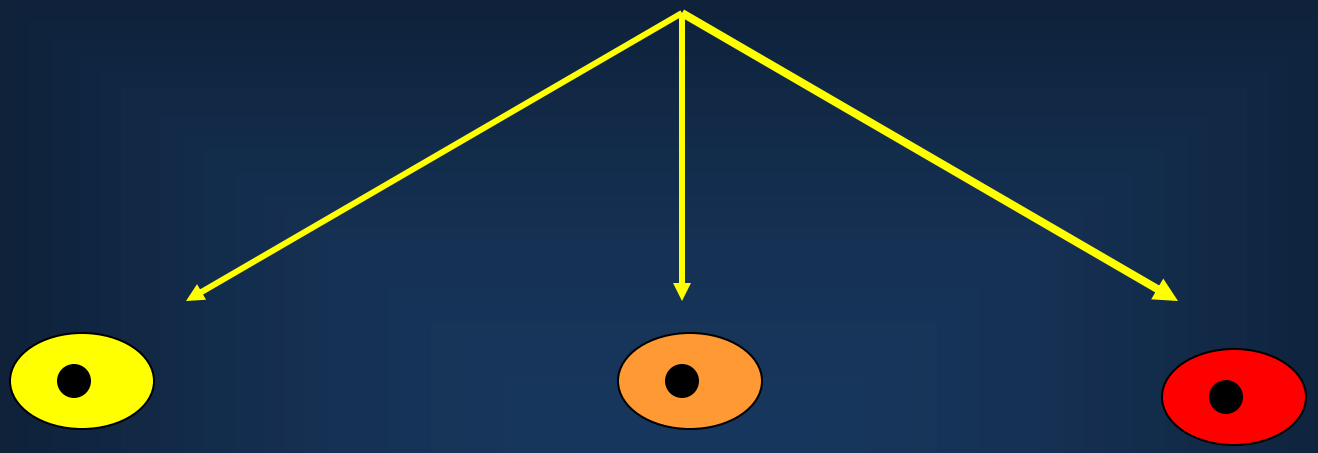
Inorganic Constituents of Bone

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

Bone & Ca^{++}

- Organic Matrix
  - Collagen Fibers
  - Ground Substance
    - ECF
    - Proteoglycans
- Bone Salts
  - Salts of Ca & PO4
    - Amorphous form
    - Crystalline Form (Hydroxyapatite)
    - Mg, Na, K, Carbonate

Bone Cells



Osteoblasts

(bone forming cells)

Osteocytes

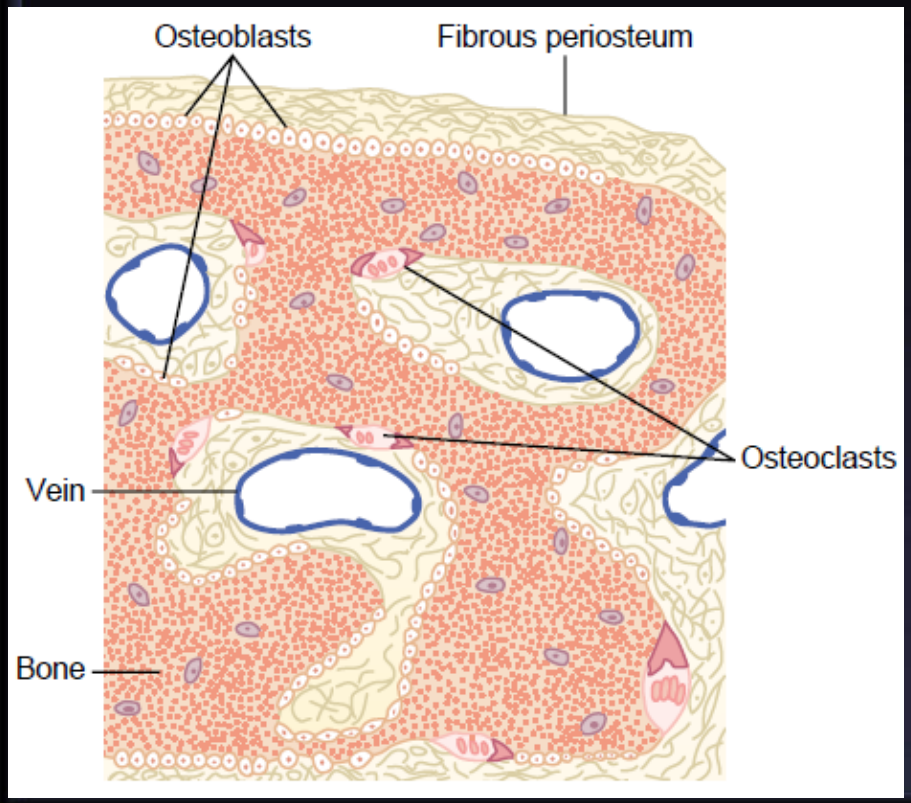
(osteoblasts surrounded by calcified matrix)

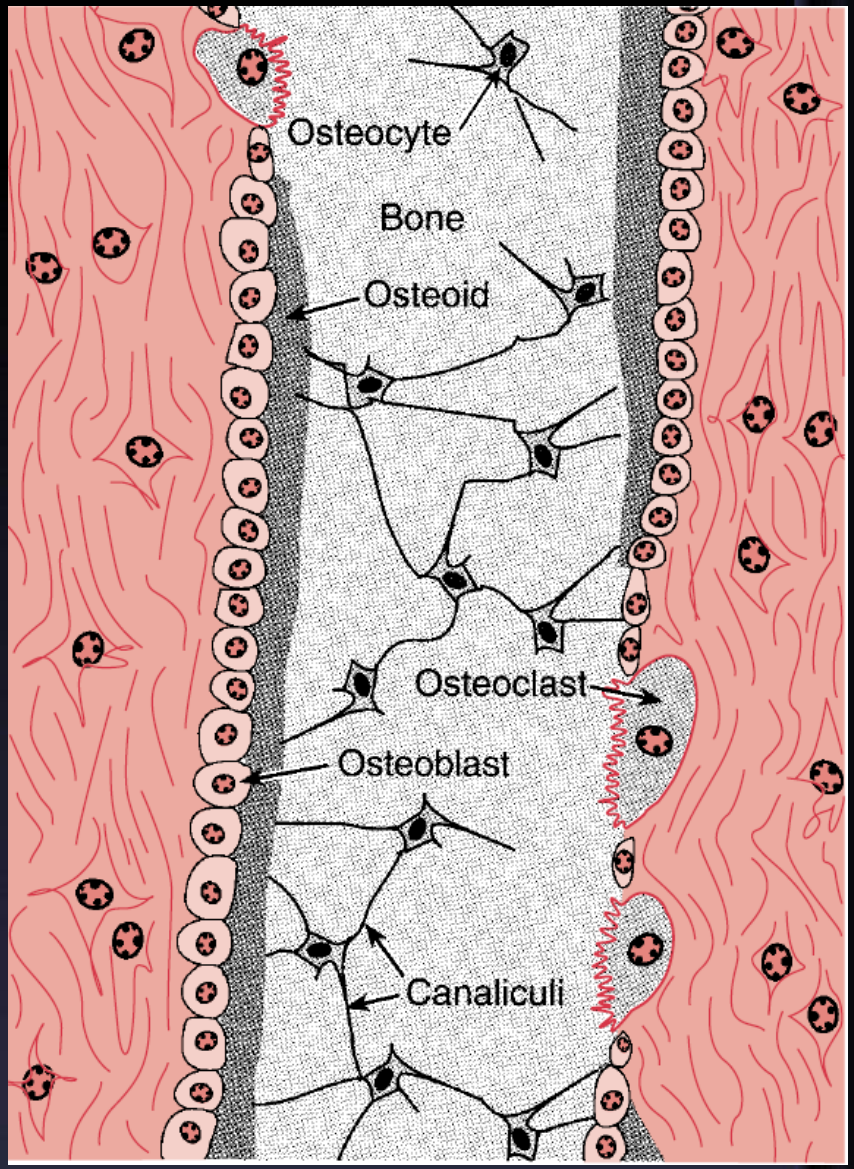
Osteoclasts

bone eroding Cell (resorping)

Bone & Ca^{++} Cont…

- **Types of Bone Cells**
  - **Osteoblasts**
  - **Osteoclasts**
  - **Osteocytes**





Osteoblasts (matrix-forming cells)
Origin?

Osteocytes
Originate from osteoblasts

Osteoclasts
Originate from bone marrow - derived macrophage-monocyte line

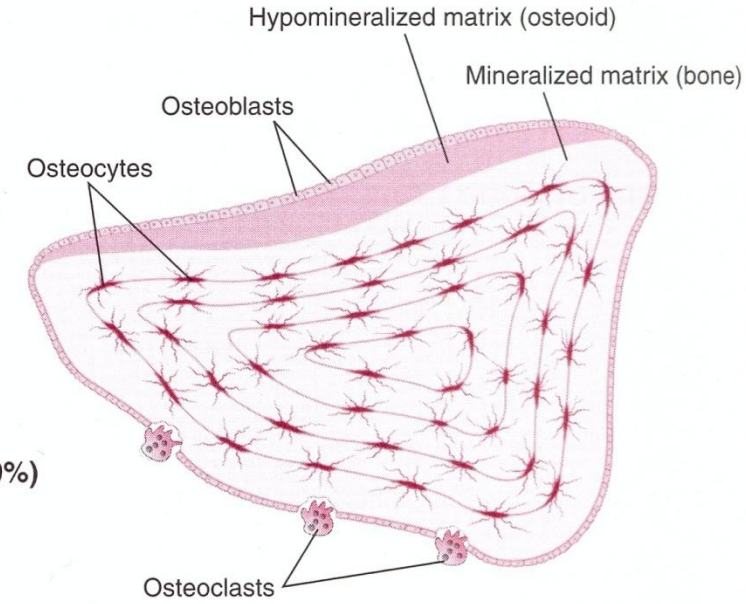
Cells (2%)

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%)



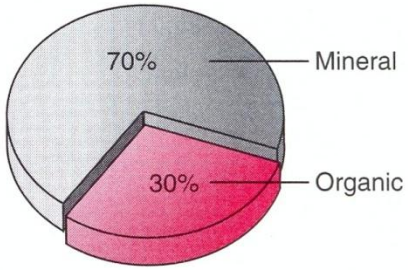
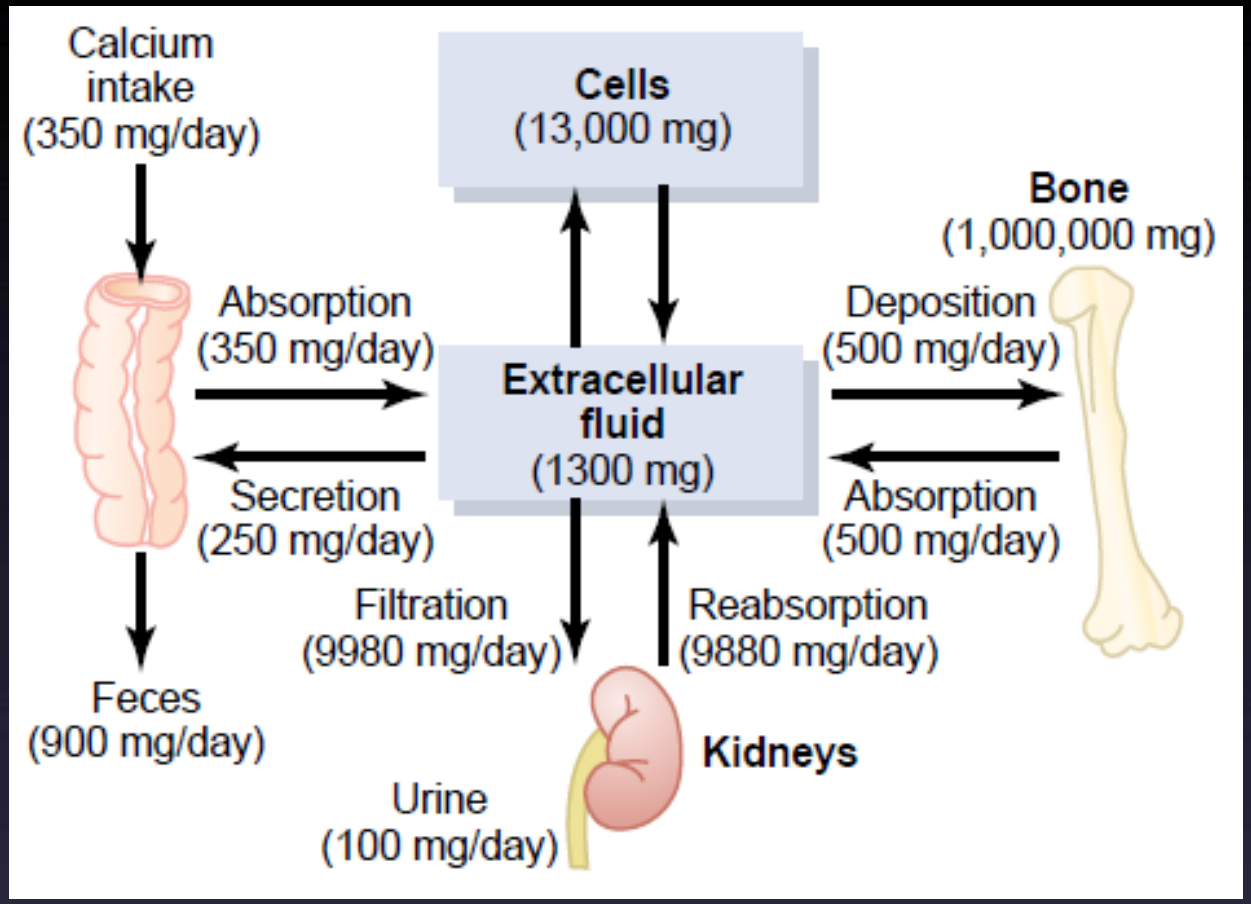


Figure 8.1 The composition of bone.

Calcium Metabolism in an adult human



Blood supply??

Bone & Ca^{++} Cont…

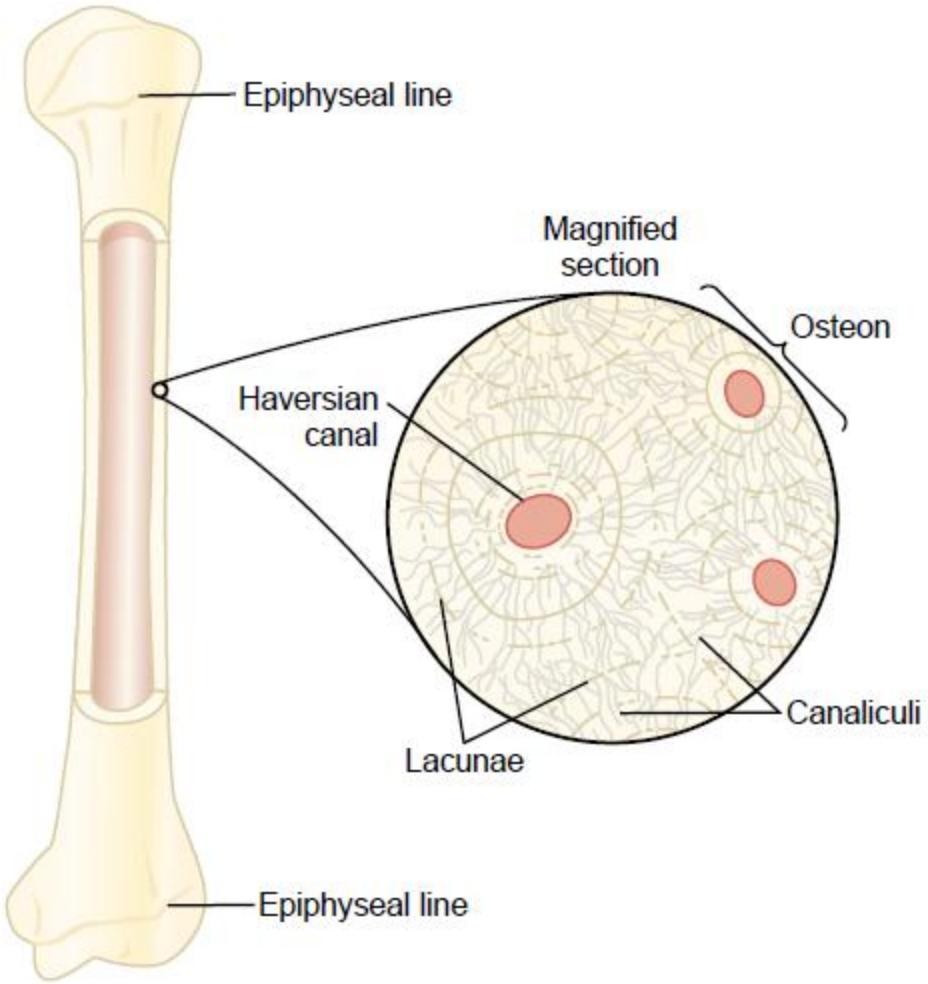
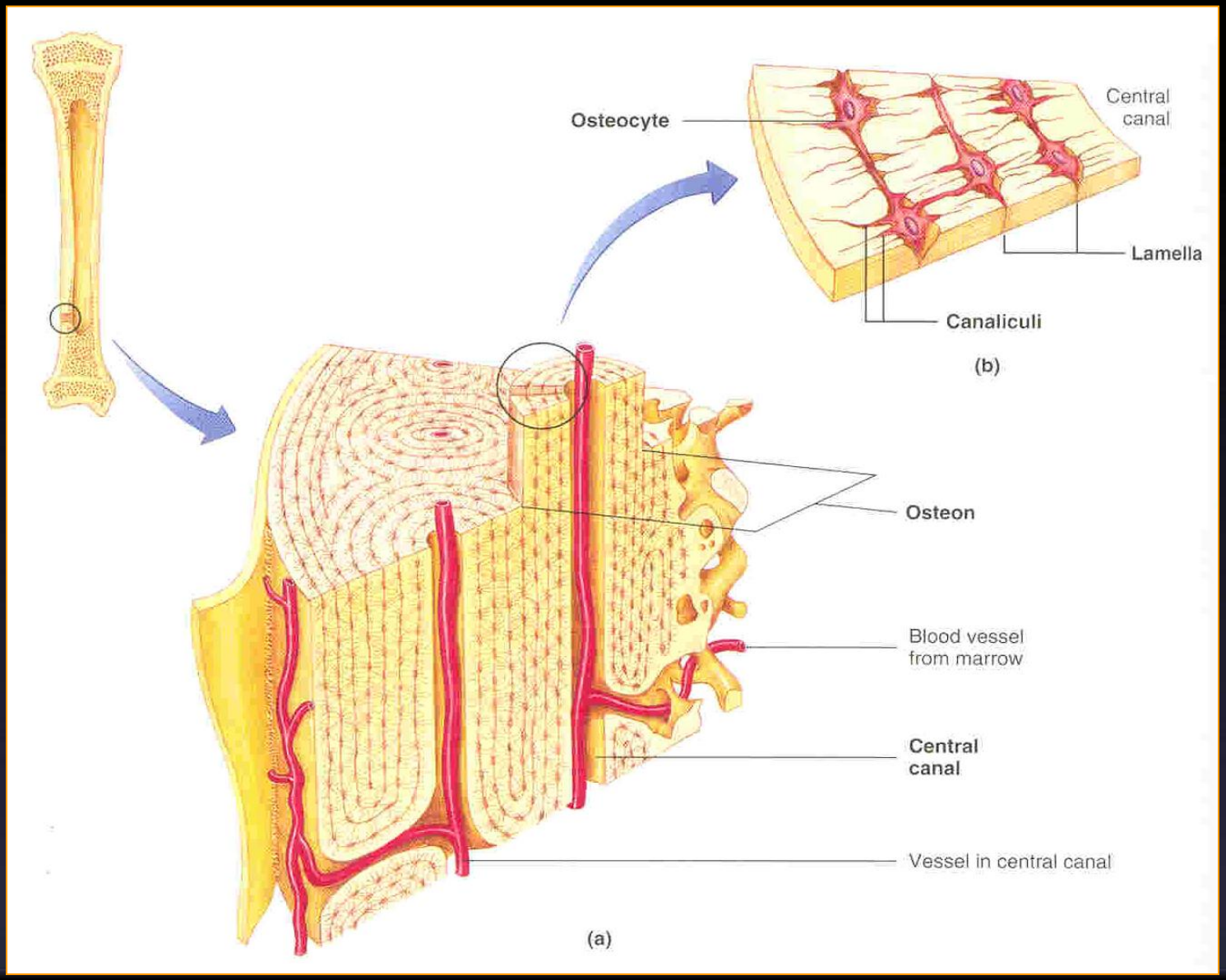


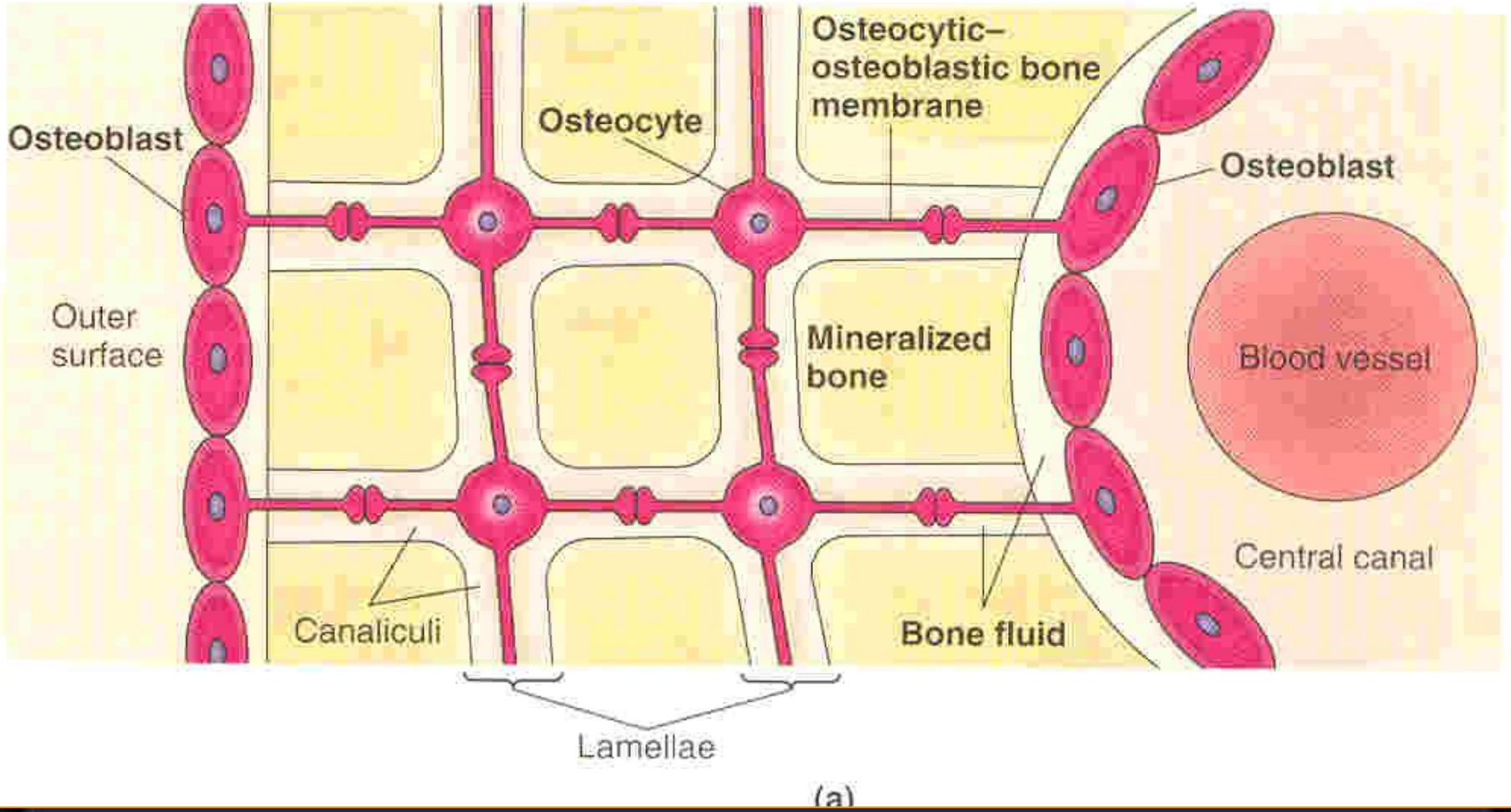
Figure 79–5

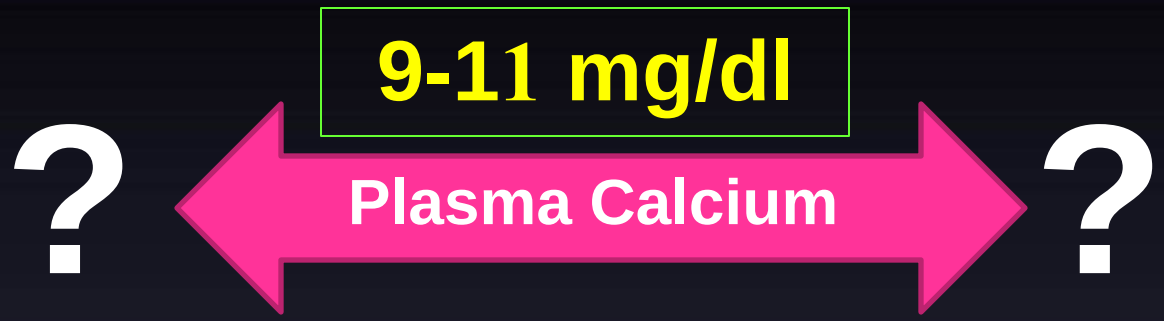
Structure of bone.

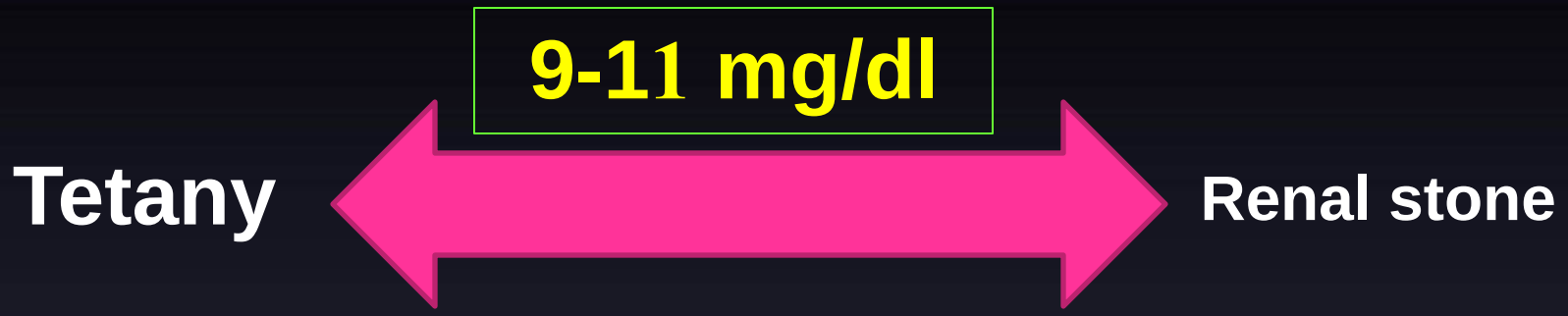
Bone & Ca^{++} Cont…


Osteocyte
Central canal
Lamella
Canaliculi
(b)
Osteon
Blood vessel from marrow
Central canal
Vessel in central canal
(a)

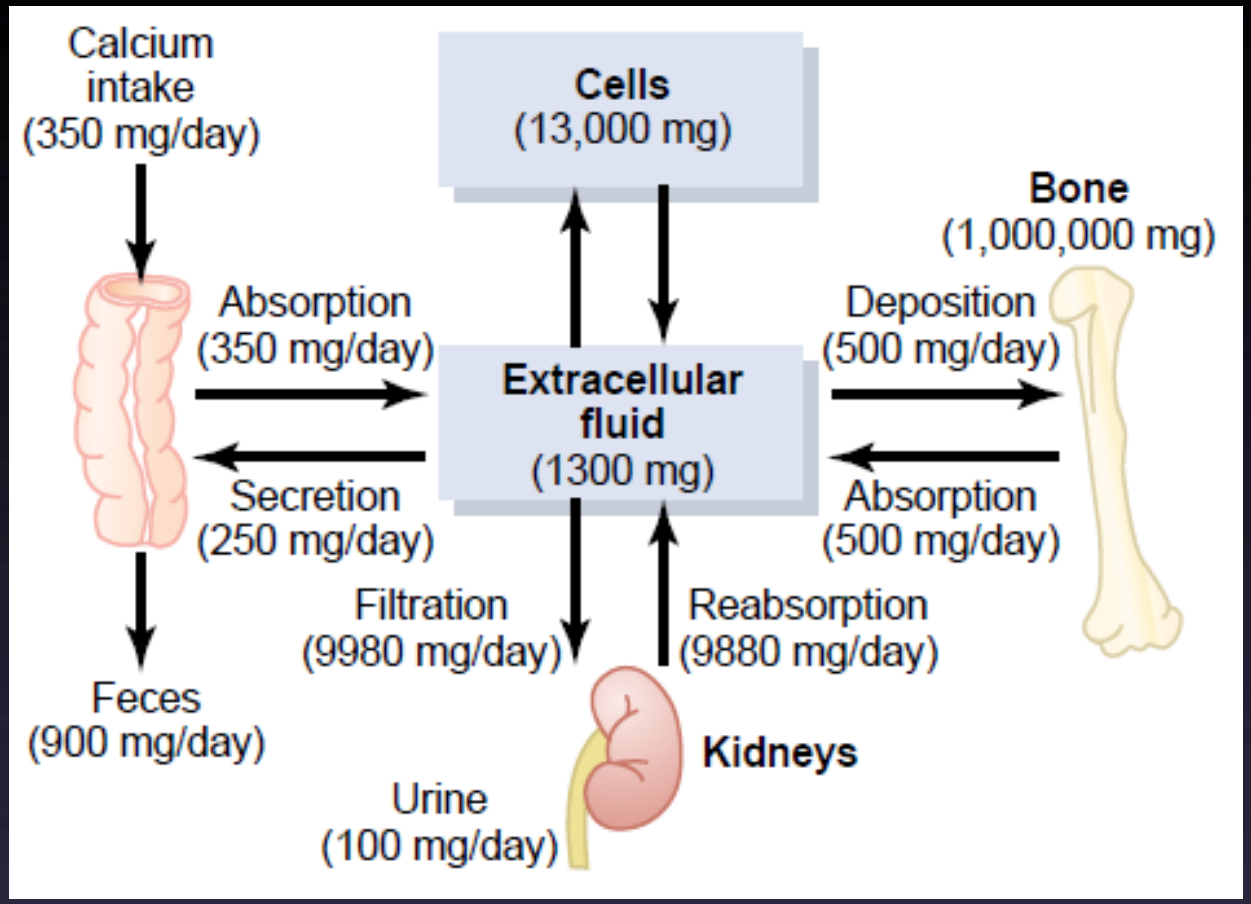
Bone & Ca^{++} Cont…

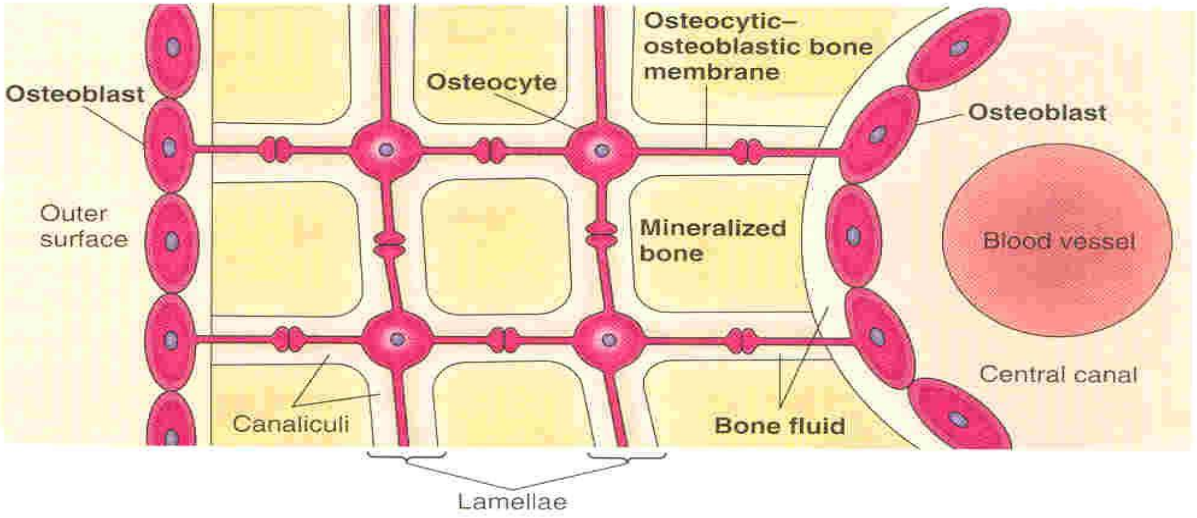

Osteocytic–
osteoblastic bone
membrane
Osteocyte
Osteoblast
Osteoblast
Outer
surface
Mineralized
bone
Blood vessel
Central canal
Canaliculi
Bone fluid
Lamellae
(a)


9-11 mg/dl
?
Plasma Calcium
?

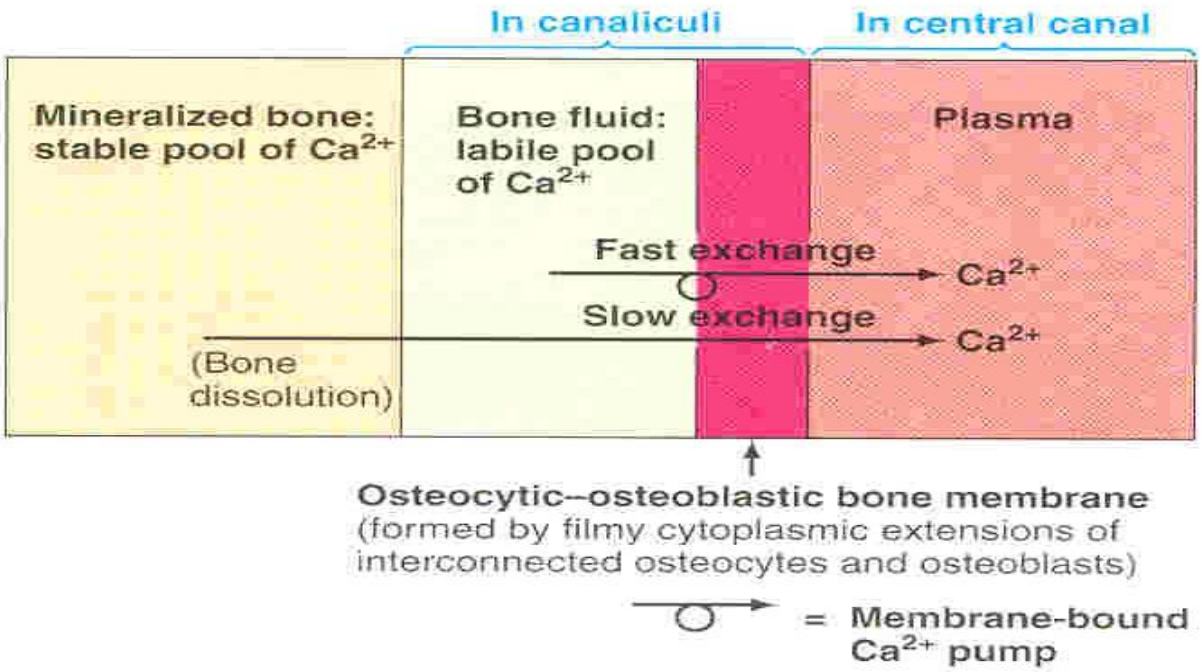

9-11 mg/dl
Tetany
Renal stone

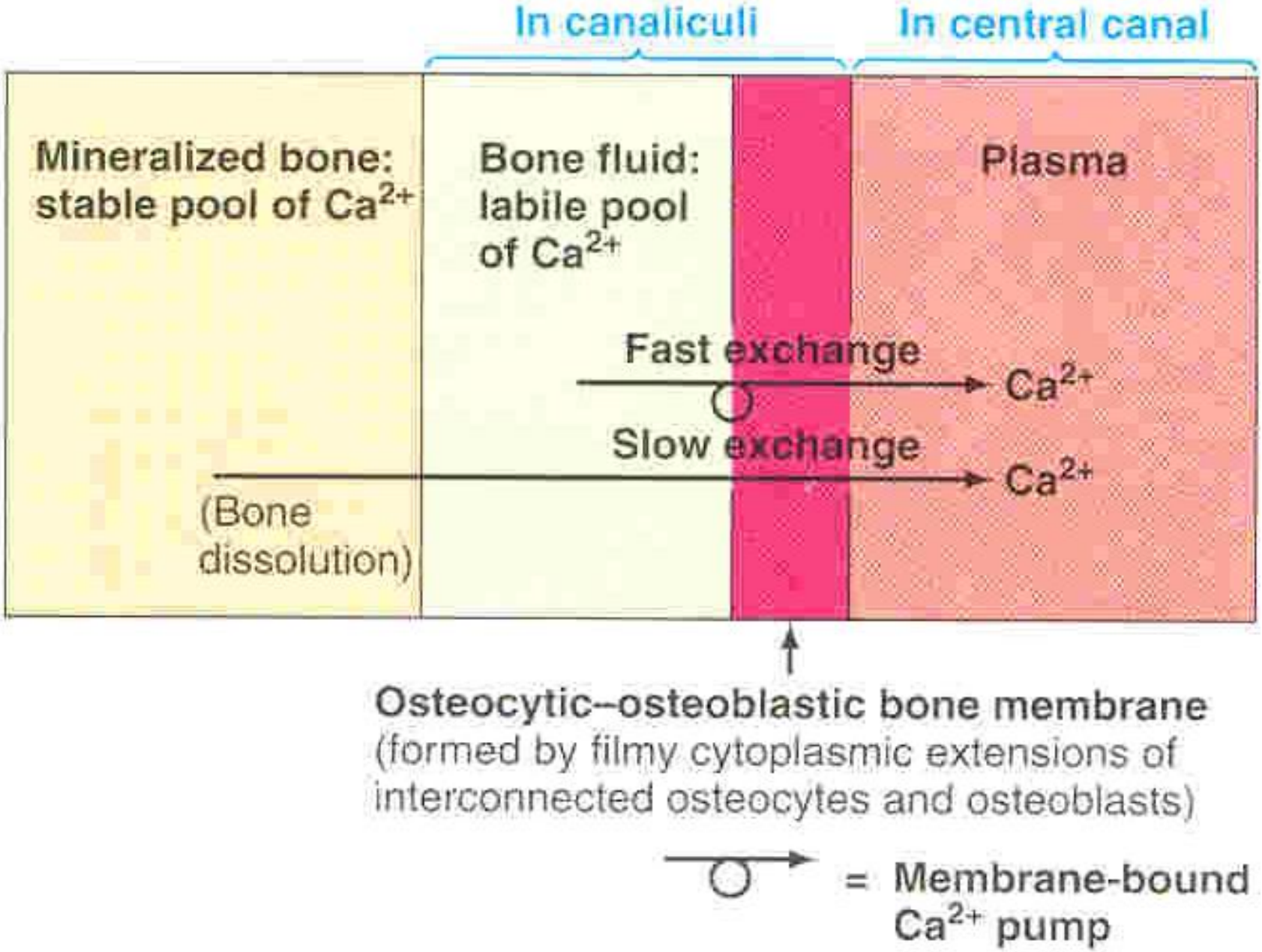
Calcium Metabolism in an adult human



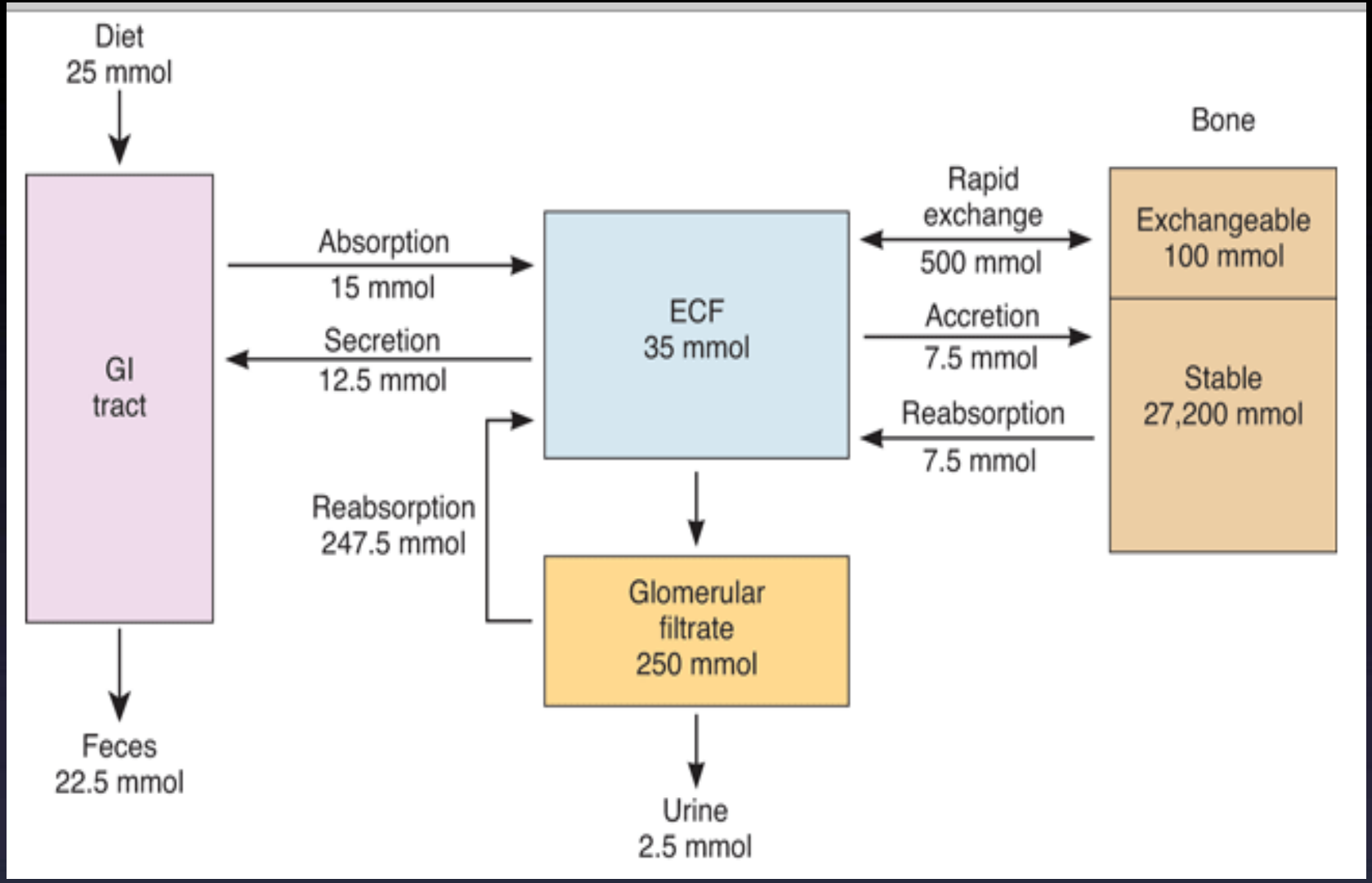

Osteoblast
Osteocyte
Osteocytic–
osteoblastic bone
membrane
Osteoblast
Outer
surface
Mineralized
bone
Blood vessel
Central canal
Canaliculi
Bone fluid
Lamellae

(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

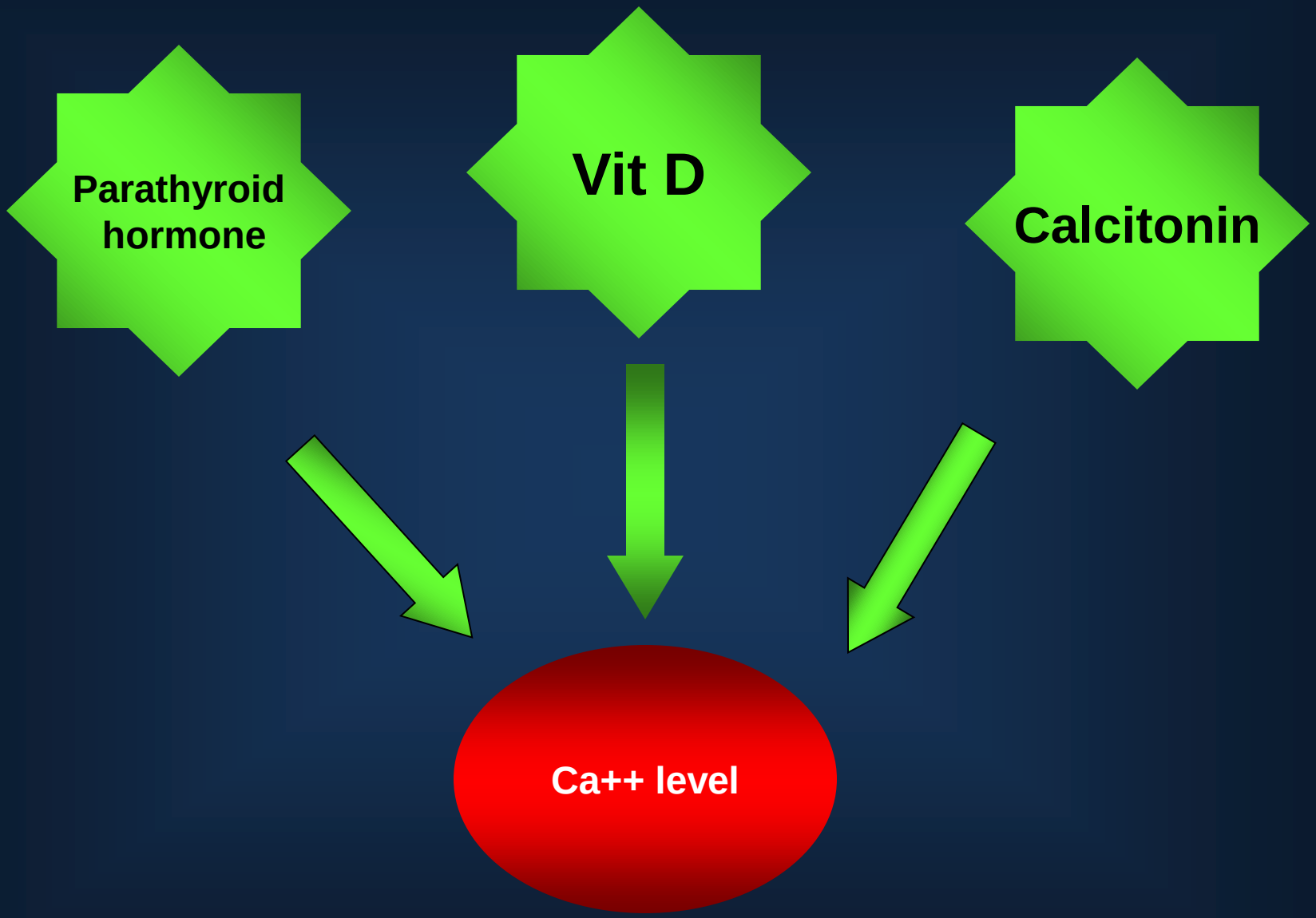

In canaliculi
In central canal
Mineralized bone: stable pool of Ca^{2+}
Bone fluid: labile pool of Ca^{2+}
Plasma
Fast exchange
Ca^{2+}
Slow exchange
Ca^{2+}
(Bone dissolution)
Osteocytic–osteoblastic bone membrane
(formed by filmy cytoplasmic extensions of interconnected osteocytes and osteoblasts)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

Calcium Metabolism in an adult human



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


Parathyroid hormone
Vit D
Calcitonin
Ca++ level

B. Brief overview of bone physiology (***Fig. 1***)

1. **Osteocyte: A major source of endogenous Ca^{2+} (via demineralization) and primary site of Ca^{2+} deposition (via mineralization)**

2. **Osteoblast: The mediator of bone mineralization**

   - **Synthesis of collagen by osteoblast with formation of extracellular matrix**

   - **Precipitation in this matrix of $Ca_{10}(PO_4)_6(OH)_2$ — hydroxyapatite**

3. **Osteoclast: Mediator of bone demineralization**

   - **Release of acid phosphatase and hyaluronic acid**

   - **Decrease in pH causes solubilization of hydroxyapatite with release of Ca^{2+} and PO_4^{3-}**

Hormones regulating Ca^{++}

Three Hormones

- Vitamin D
- Parathyroid Hormone
- Calcitonin

The Role of Vit D in Calcium Homeostasis

- Source
- Chemistry
- Molecular Weight
- Half Life
- Blood Levels
- Fate Skin, Liver & Kidneys

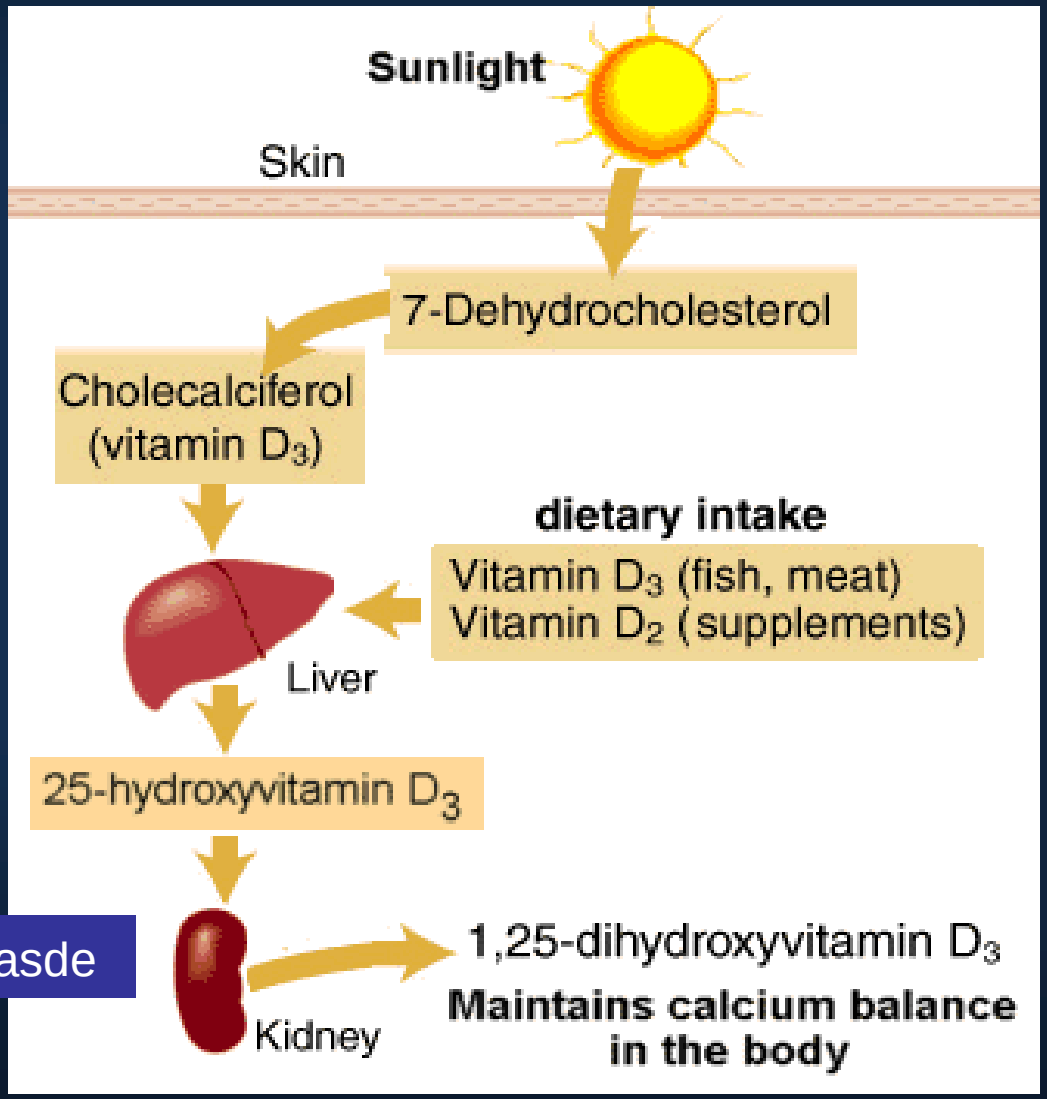
1,25 Dihydroxycholecalciferol (Vitamin D):

- **It is a *hormone*:**
  - **1- produced by the body.**
  - **2- transported in the blood stream to produce effects target cell.**

Vitamin D

1,25Dihydroxycholecalciferol (Vit D)

- Nature: it is steroid
- Source:
- Actions:



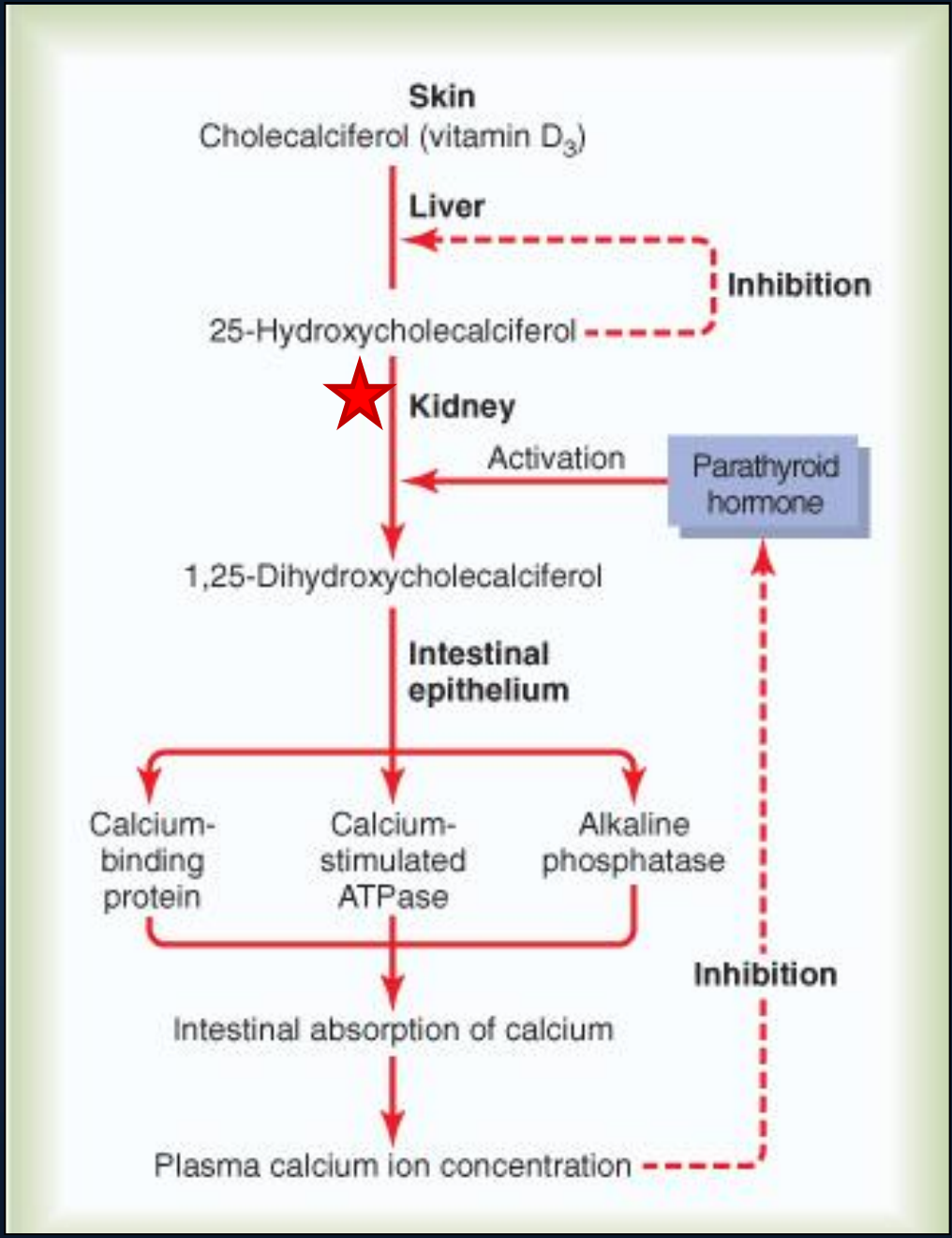
❑Control of Vit D3:

1- low Ca++ ions

2- prolactin

3- PTH

All stimulate renal 1,alpha hydroxylase.

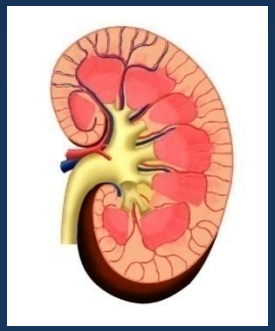


Vitamin D

1.Intestinal tract.

Has a potent effect to increase calcium & phosphate absorption

2.Renal



Increases Renal calcium and Phosphate absorption

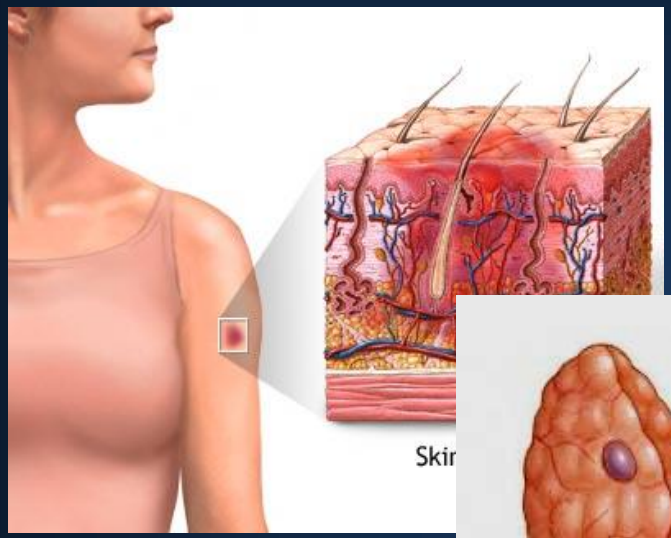
3.Bone

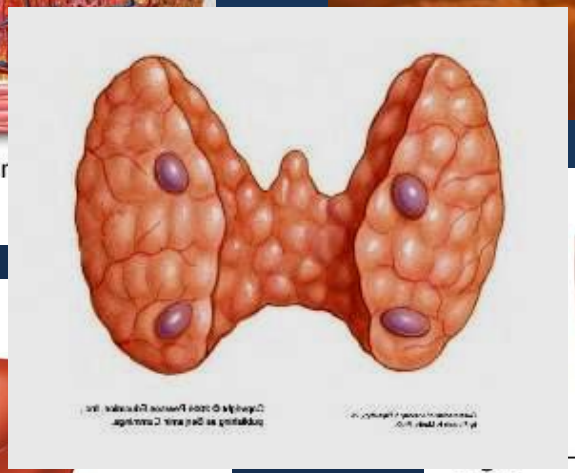
Bone absorption

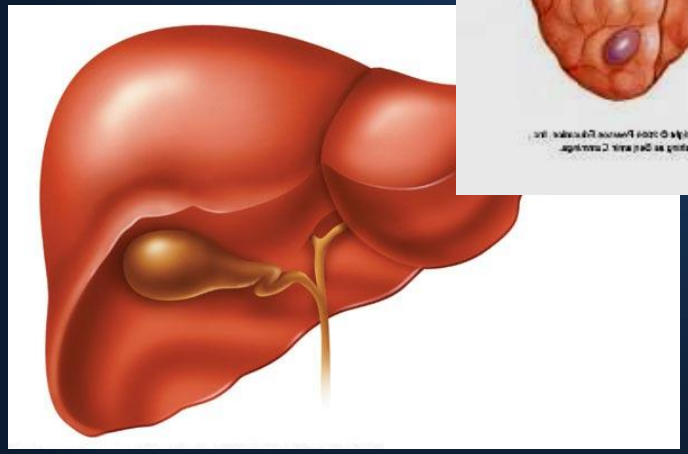
Vitamin D

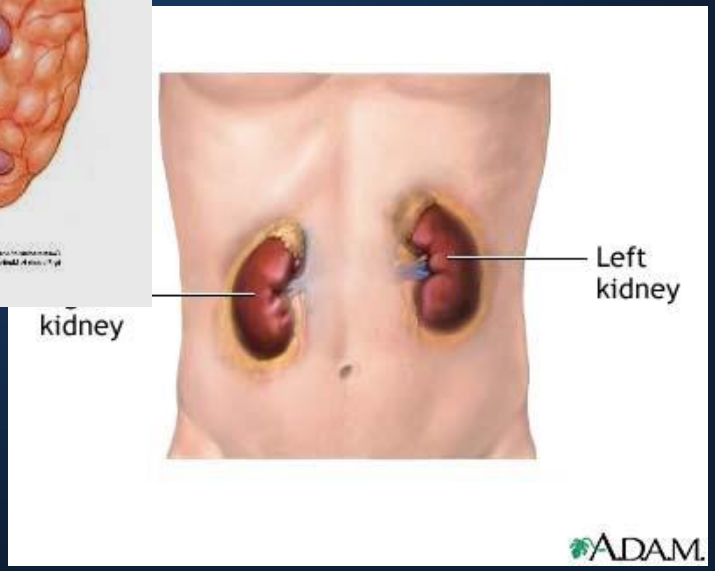
4- stimulates differentiation of immune cells.

Vitamin D







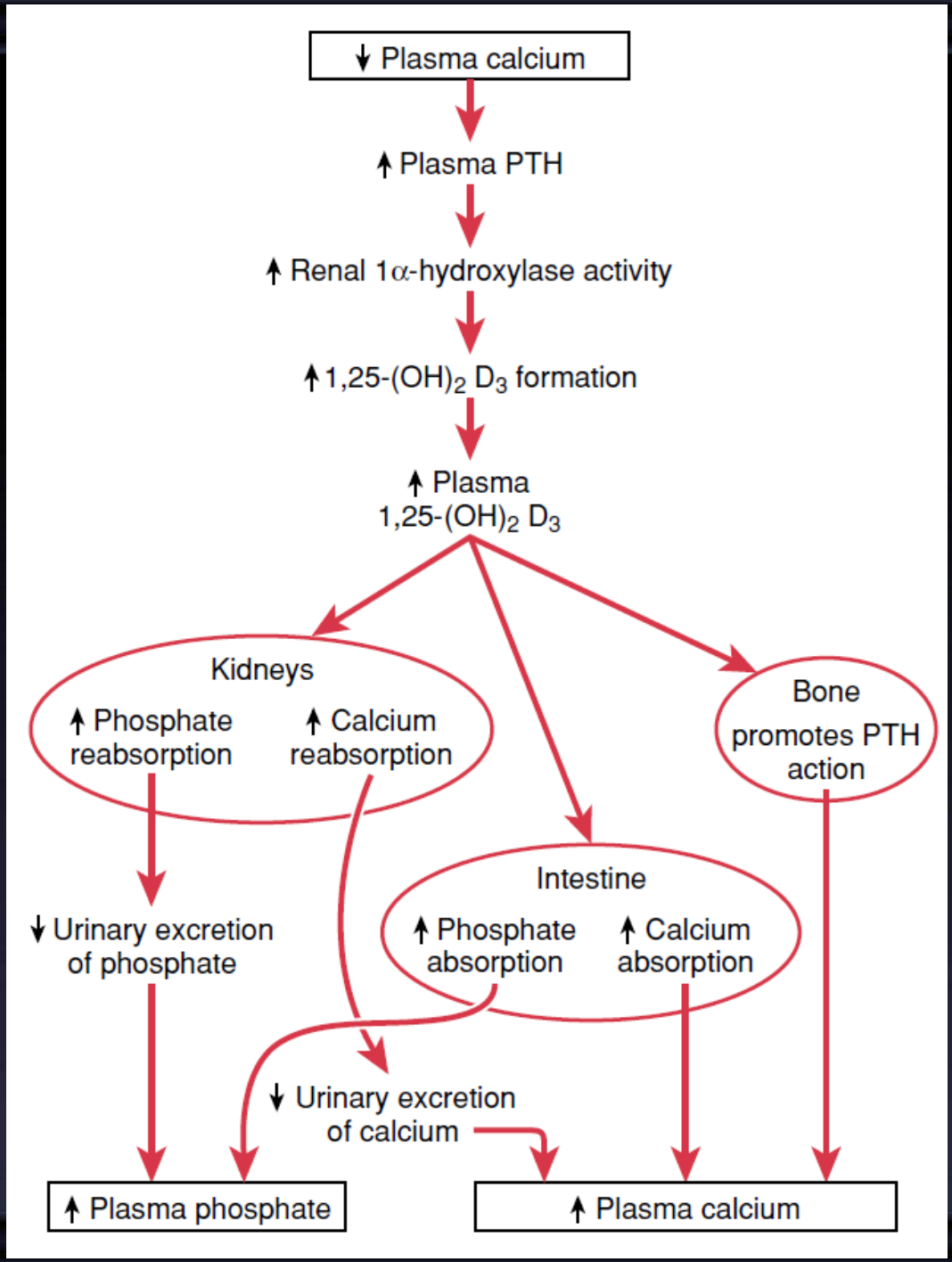


VITAMIN D_3

Actions

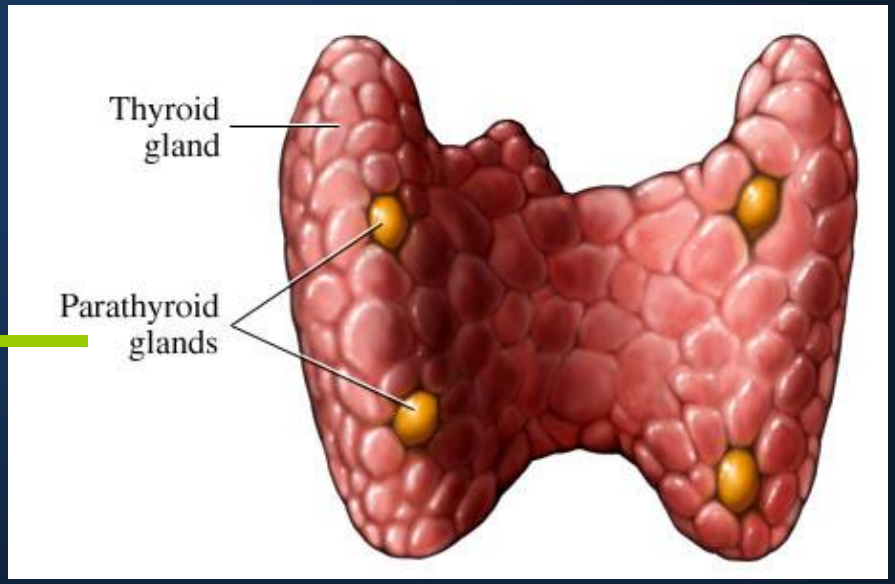
- Calcium
  - ↑Absorption from Bone
  - ↓Renal Excretion
  - ↑Absorption from GIT
- Phosphate
  - ↑Absorption from Bone
  - ↓Renal Excretion

Regulation of Calcium level



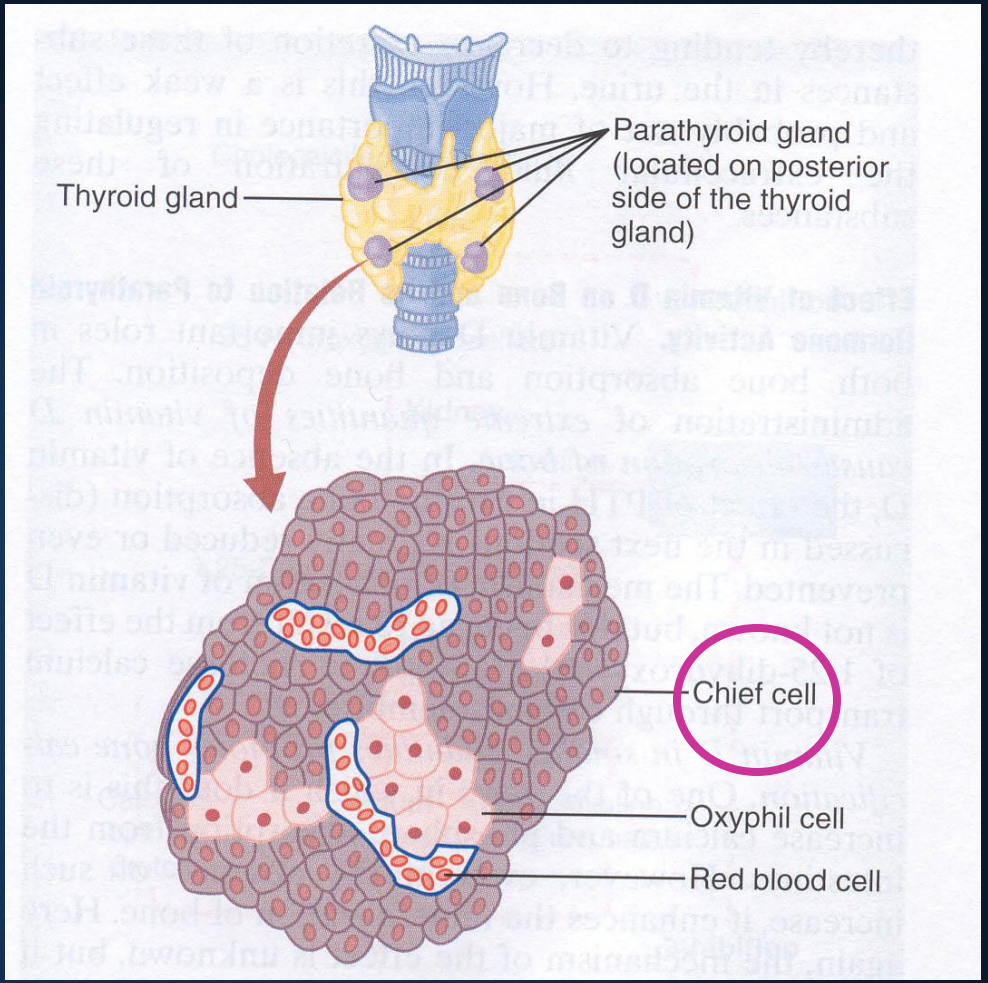
Parathyriod gland

Parathyroid hormone (PTH)



Parathyroid hormone (PTH)

- Source: Parathyroid gland
- Polypeptide hormone: (84 aa)
- Mechanism of action: acts via 2nd messenger mechanism utilizing cAMP
- Molecular Weight 5808
- Half Life 10 min
- Fate Liver & Kidneys
- Actions: Bone
  Kidney
  Intestine



It is essential for life

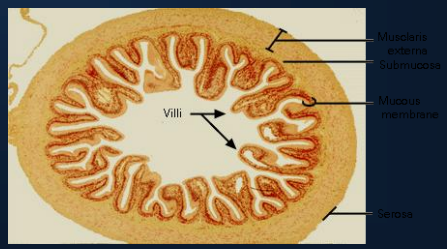
Parathyroid hormone (PTH)

Increase plasma Ca^{++} level

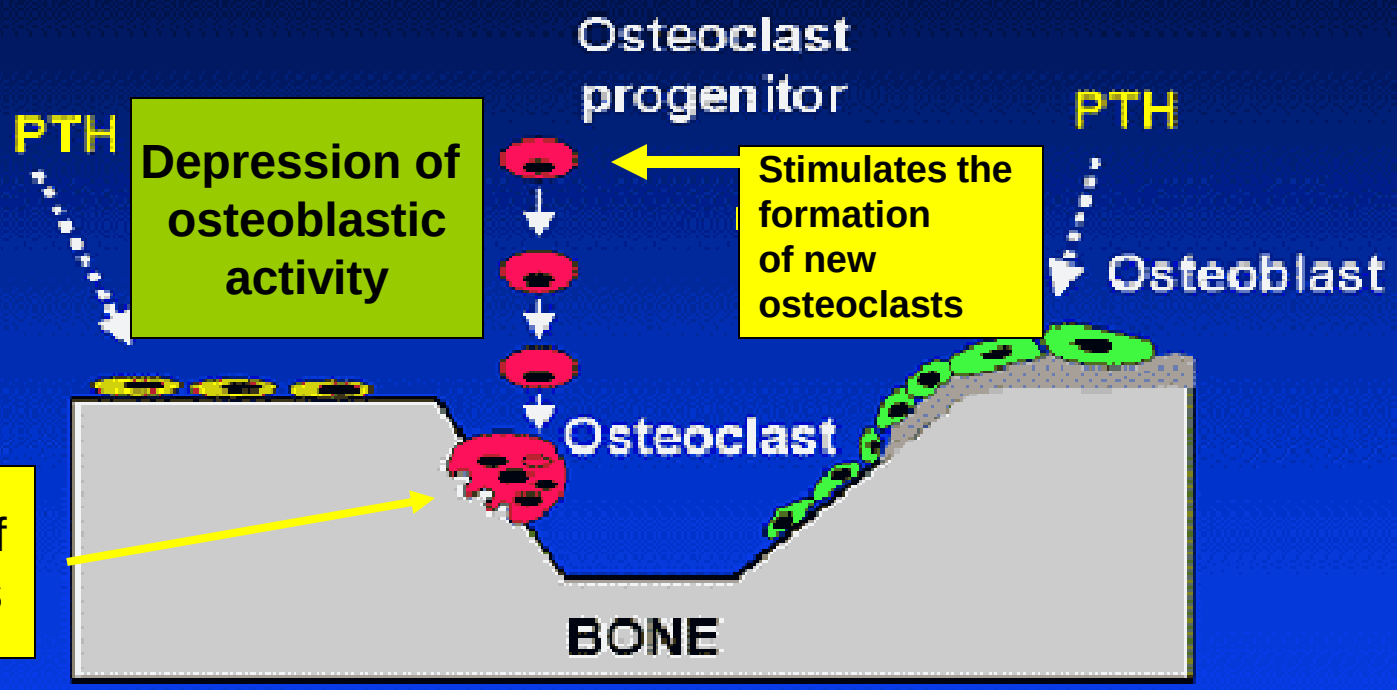
Bone

Kidney

Intestine



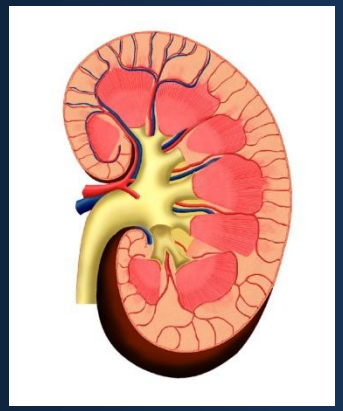
1. Effects on bones



Activation of osteoclasts

2. Effects on Kidneys

(PTH)



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

   ↑ Phosphate excretion in the urine

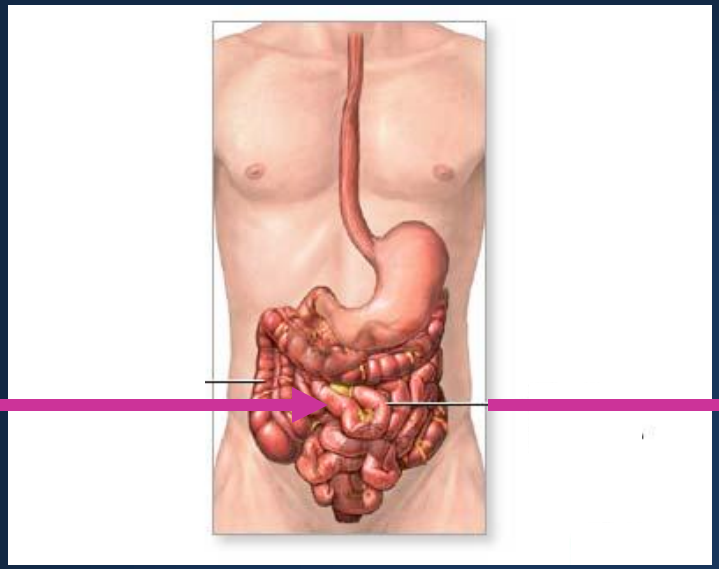
   ↓ plasma phosphate conc

2. ↑ Ca++ & Mg ions reabsorption from the distal convoluted tubules and collection ducts.

3. ↑ Formation of 1,25 vitD3 in the kidney.

3. Effects on intestine

(PTH)



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

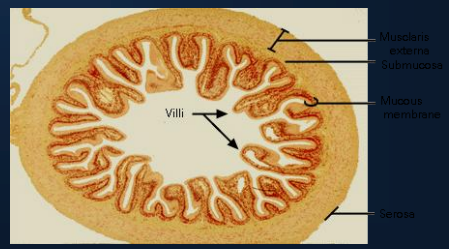
Parathyroid hormone (PTH)

Increase plasma Ca++ level
Decrease phosphate level

Bone

Kidney

Intestine



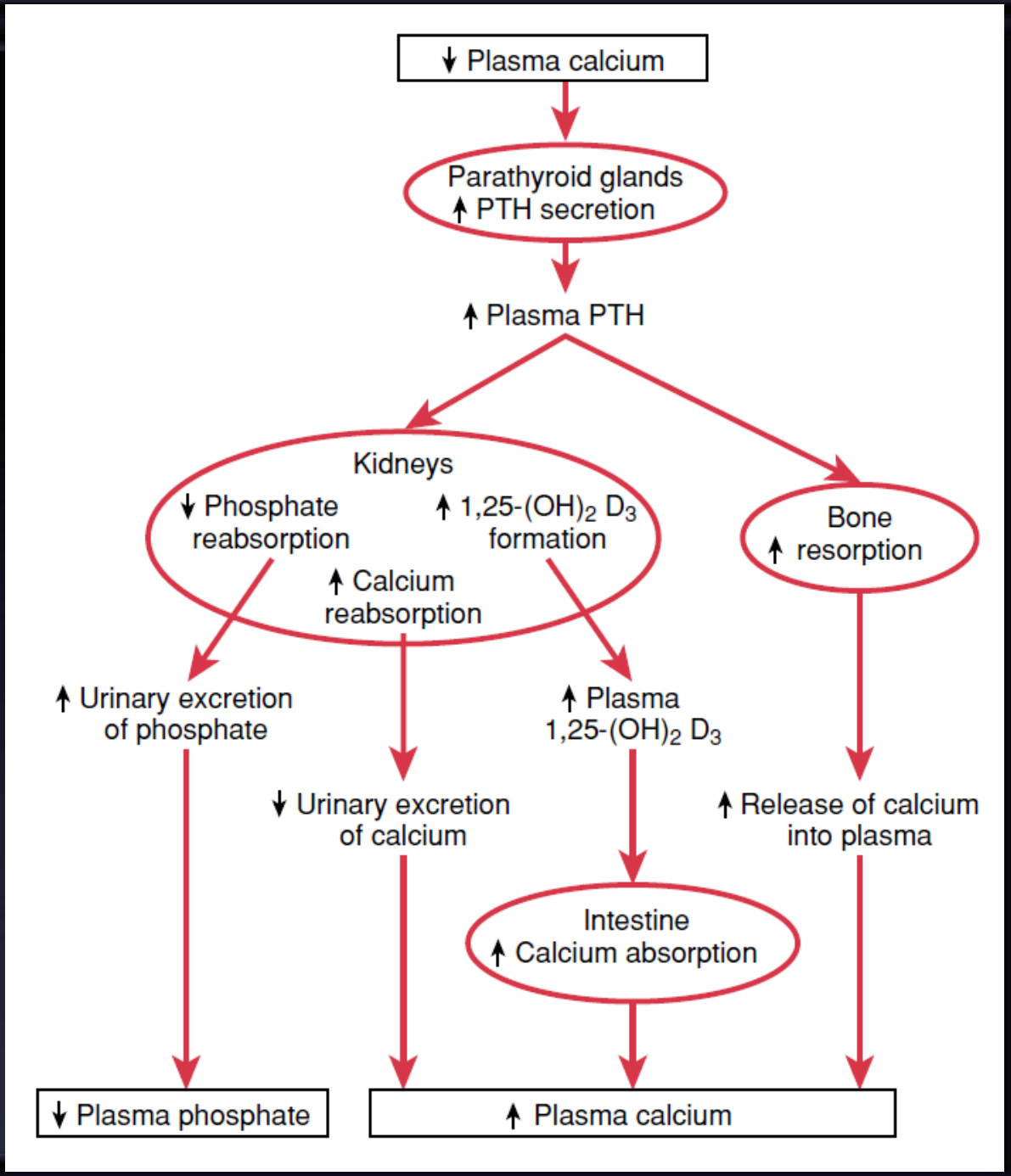
PARATHORMONE

Targets are Bones & Kidneys

Actions

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

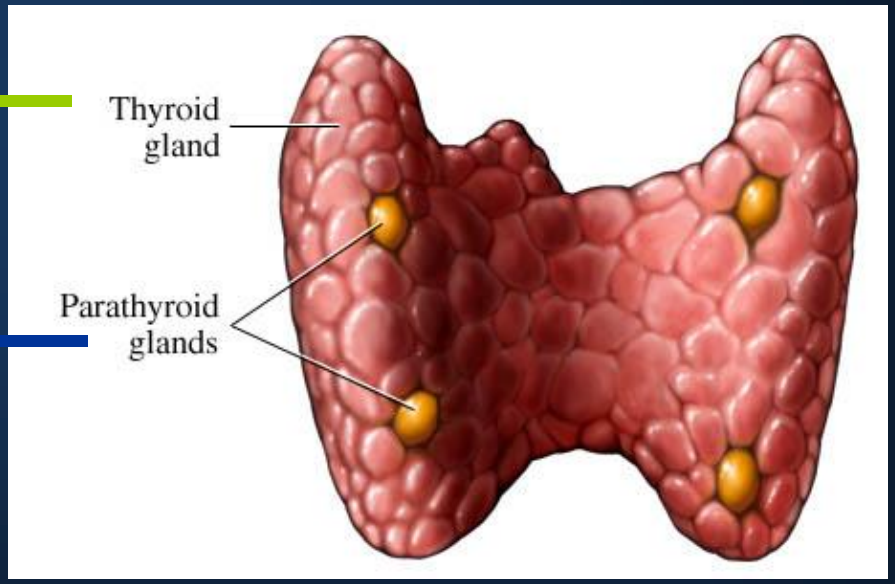
Effect of Calcium level on PTH



Calcitonin

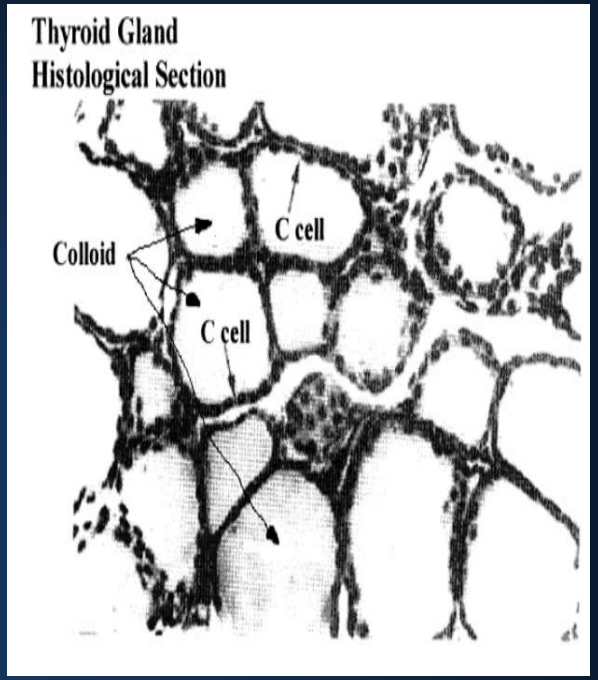
Calcitonin

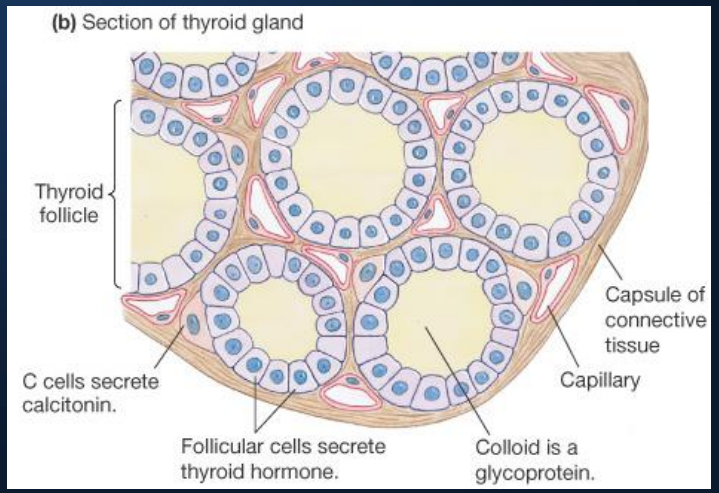
Parathyroid hormone (PTH)



Calcitonin

- Source: **Secreted by the C cells of the thyroid gland**
- **Nature: Polypeptide**
- **Function: Decrease blood** Ca++ **level very rapidly within minutes**





Actions:

On bone

[1] ↑ Ca deposition of bone by:

- ↓ osteolysis.
- ↑ osteoblastic activity

[2] ↓↓ Bone resorption:

inhibition of osteoclasts.

↓ formation of osteoclasts

On kidney

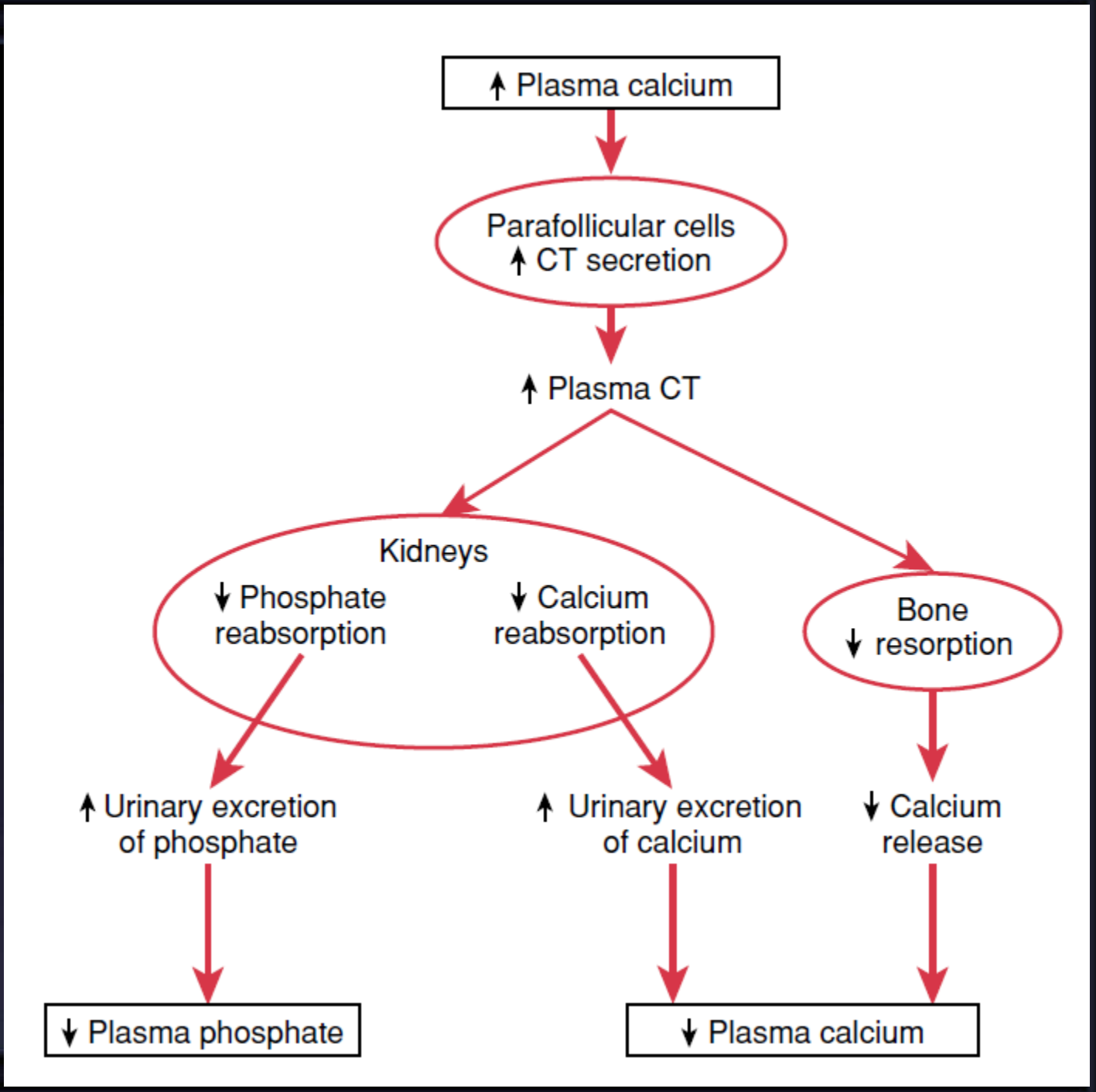
- ↓↓ Ca reabsorption
- ↑↑ Ca excretion (in addition to phosphate)

CALCITONIN

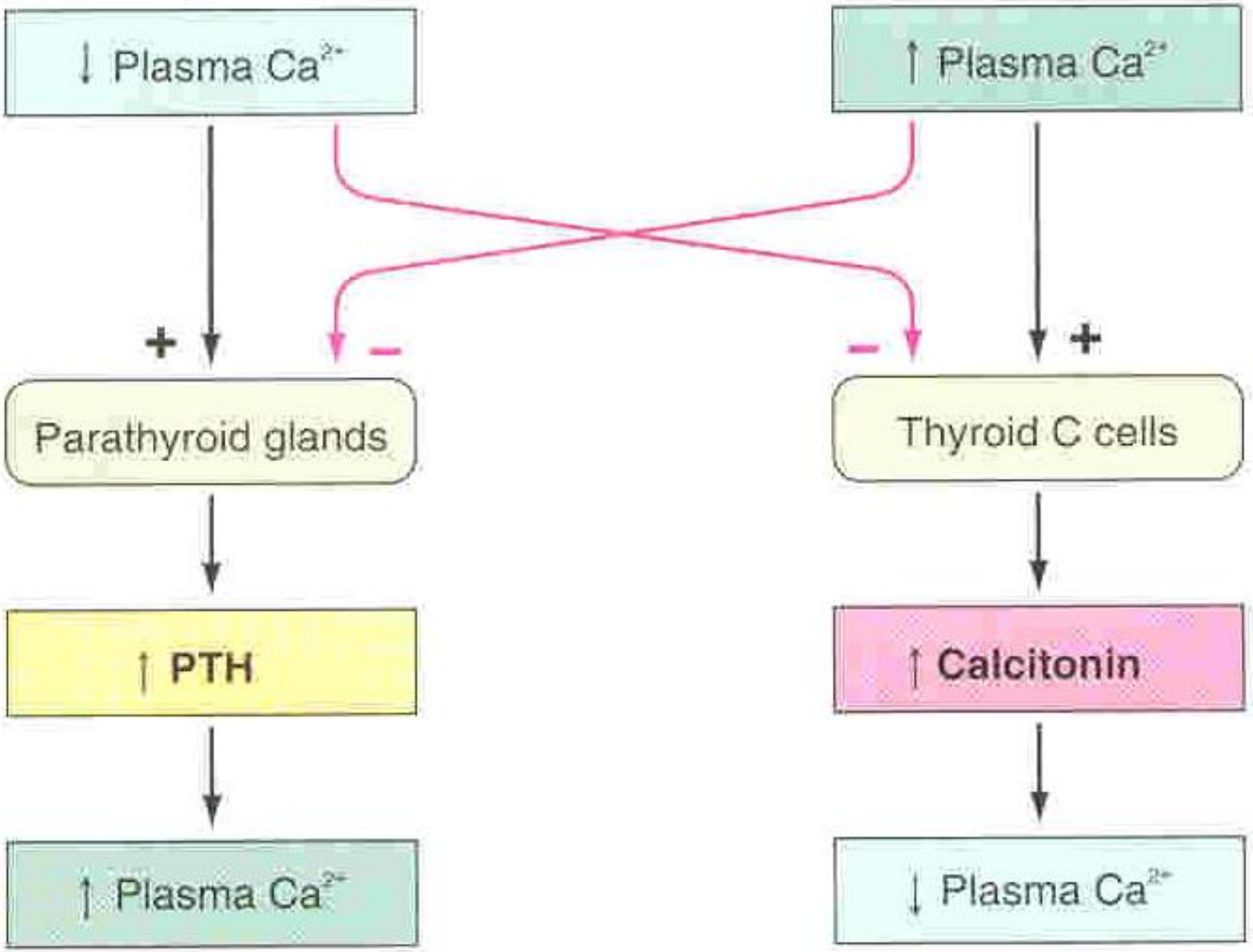
Actions

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

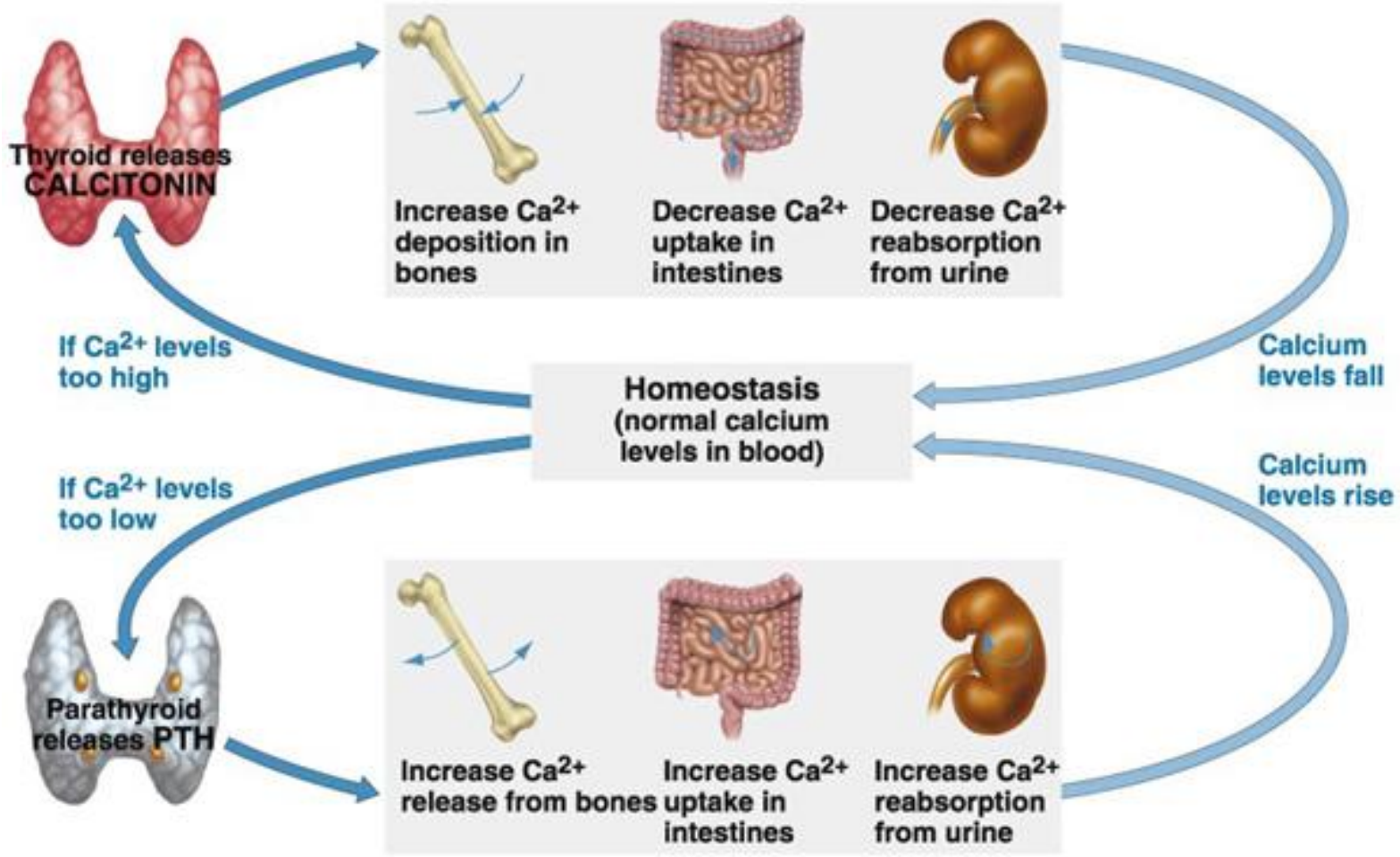
Effect of Calcium level on calcitonin



Regulation of blood calcium level

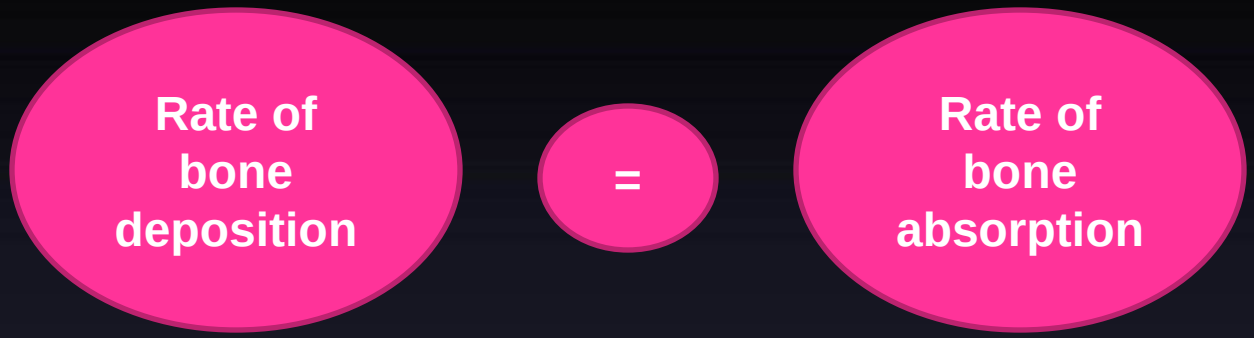

↓ Plasma Ca^{2+}
↑ Plasma Ca^{2+}
+
−
−
+
Parathyroid glands
Thyroid C cells
↑ PTH
↑ Calcitonin
↑ Plasma Ca^{2+}
↓ Plasma Ca^{2+}

Calcium Homeostasis



Copyrigł

Bone remodeling



Total mass of bone remains constant

Bone remodeling

- Bone is always being deposited by osteoblast.
- Bone is always being absorbed by osteoclast.
- Bone deposition and absorption are normally in equilibrium.
- Effect of stress on bone deposition:

  Athletes

  Prolonged immobilization

  Space astronounts

  Old age

Abnormalities

❑ Rickets (In children)

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

- Occur in the spring???

- 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).

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

Carbopedal spasm

❑ 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.

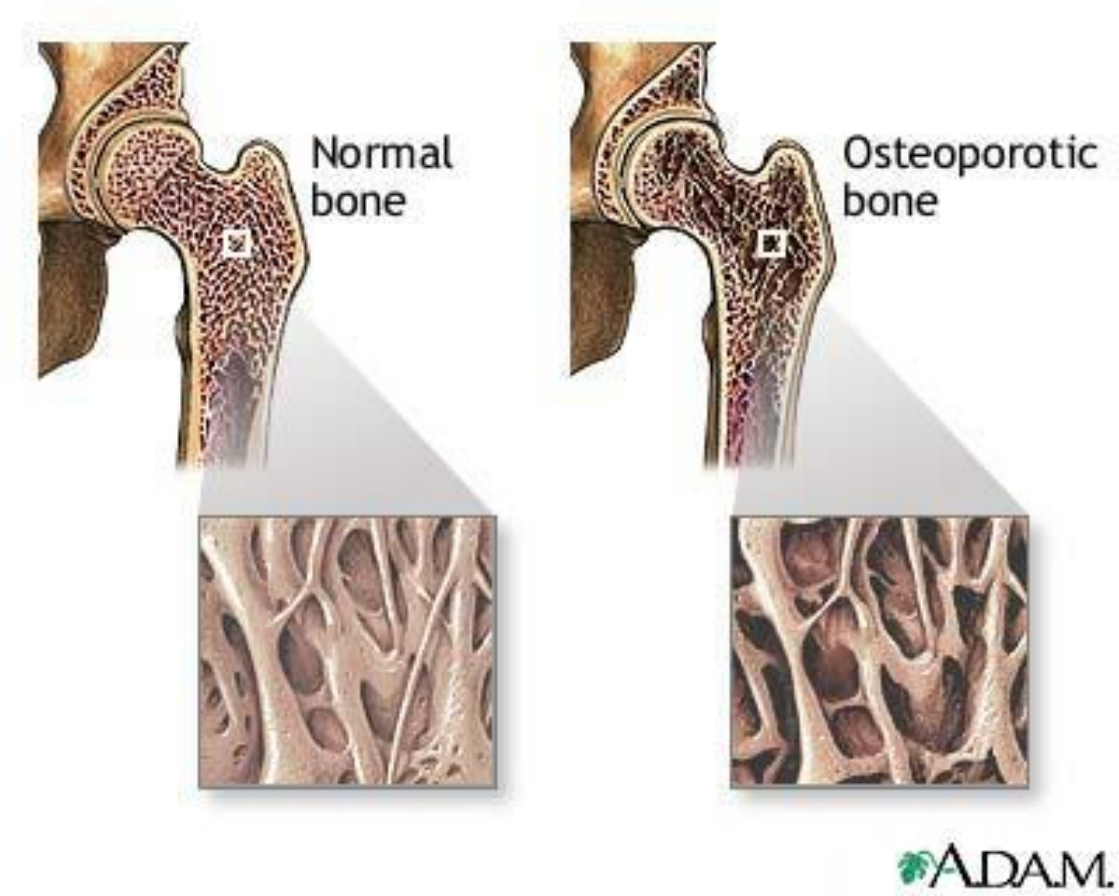
Osteoporosis—Decreased Bone Matrix

- Osteoporosis is the most common of all bone diseases in adults, especially in old age.
- It is different from osteomalacia
- results from diminished organic bone matrix rather than from poor bone calcification.

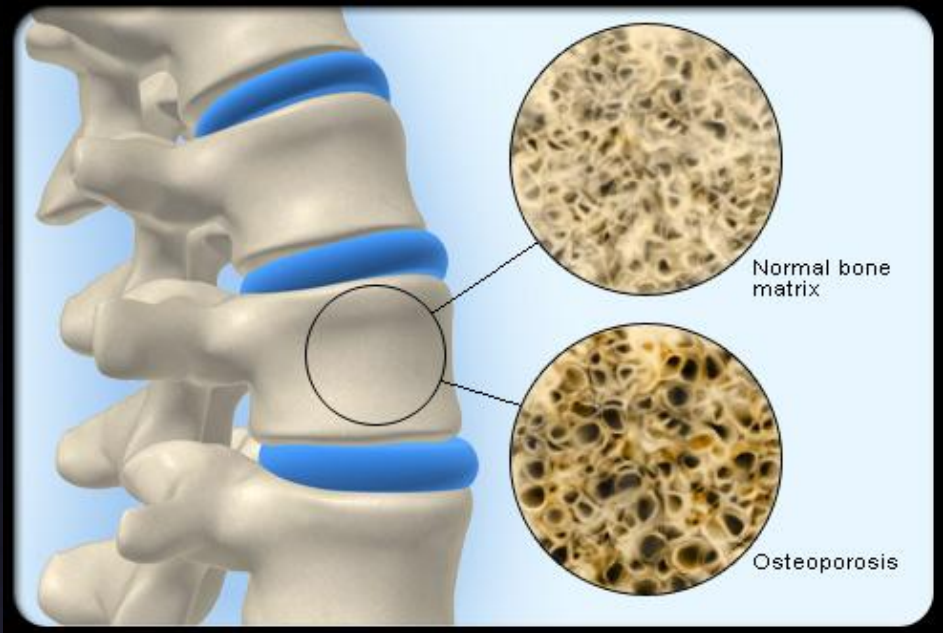
- The osteoblastic activity in the bone usually is less than normal, and consequently the rate of bone osteoid deposition is depressed.

(But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity).

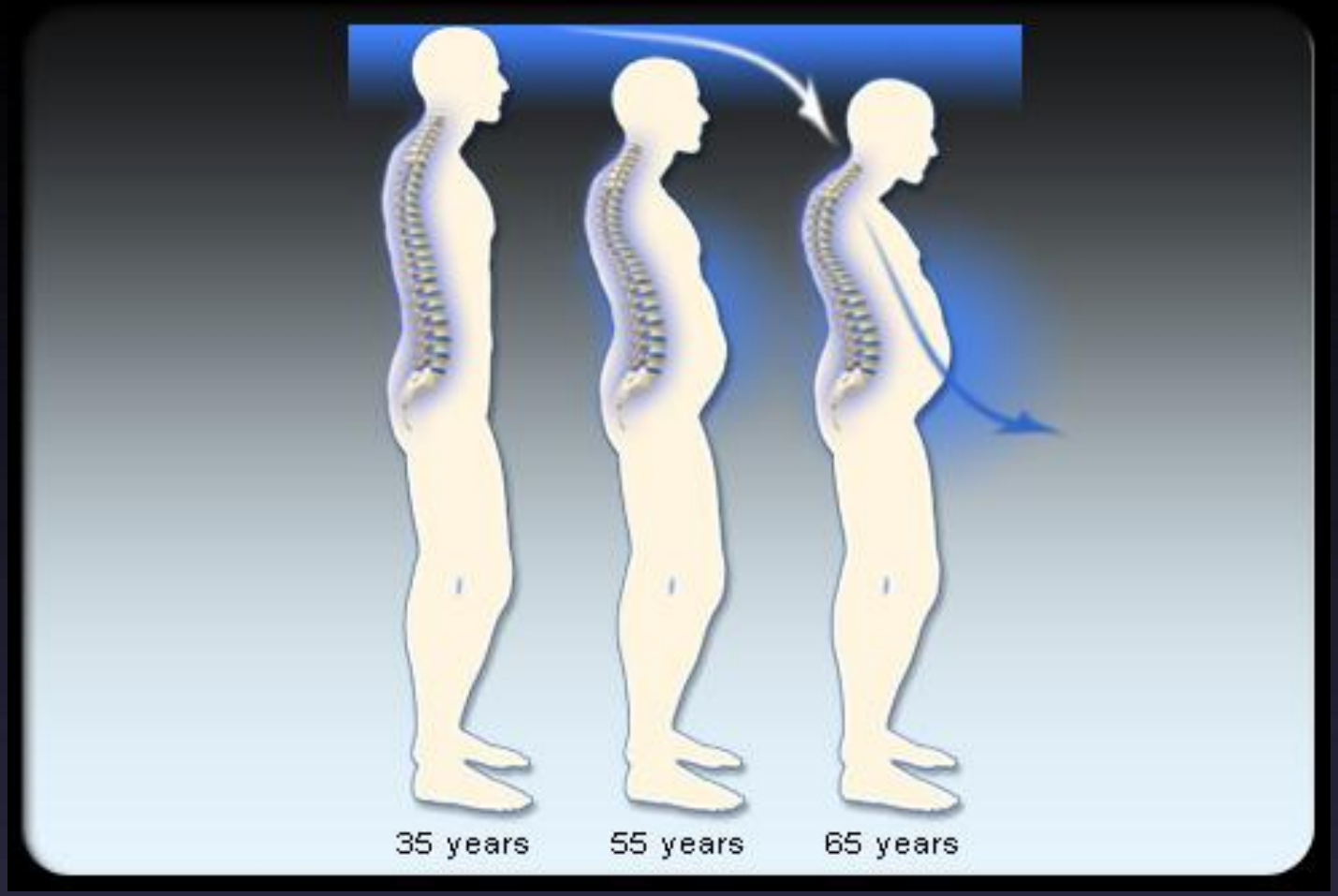
Osteoporosis—Decreased Bone Matrix



Osteoporosis—Decreased Bone Matrix



Osteoporosis—Decreased Bone Matrix

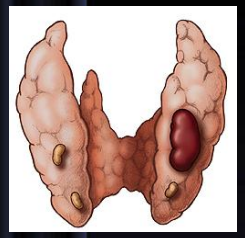


Osteoporosis—Decreased Bone Matrix

- 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

Disorders of parathyroid hormone secretion

Hyperparathyroidism (PTH Excess)



Primary

Secondary (compensatory) Hyperparathyroidism

Manifestations:

- Hypercalcemia ↑ Ca^{2+}
- Hypophosphemia ↓Po4
- Hypercalciuria
- Calcium containing stones in kidney
- Demineralisation of bone
  multiple bone cysts (osteitis fibrosa cystic)
- Precipitation of calcium in soft tissues occur when Ca > 17mg/dl.

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

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

Hypoparathyroidism (rare)

causes

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

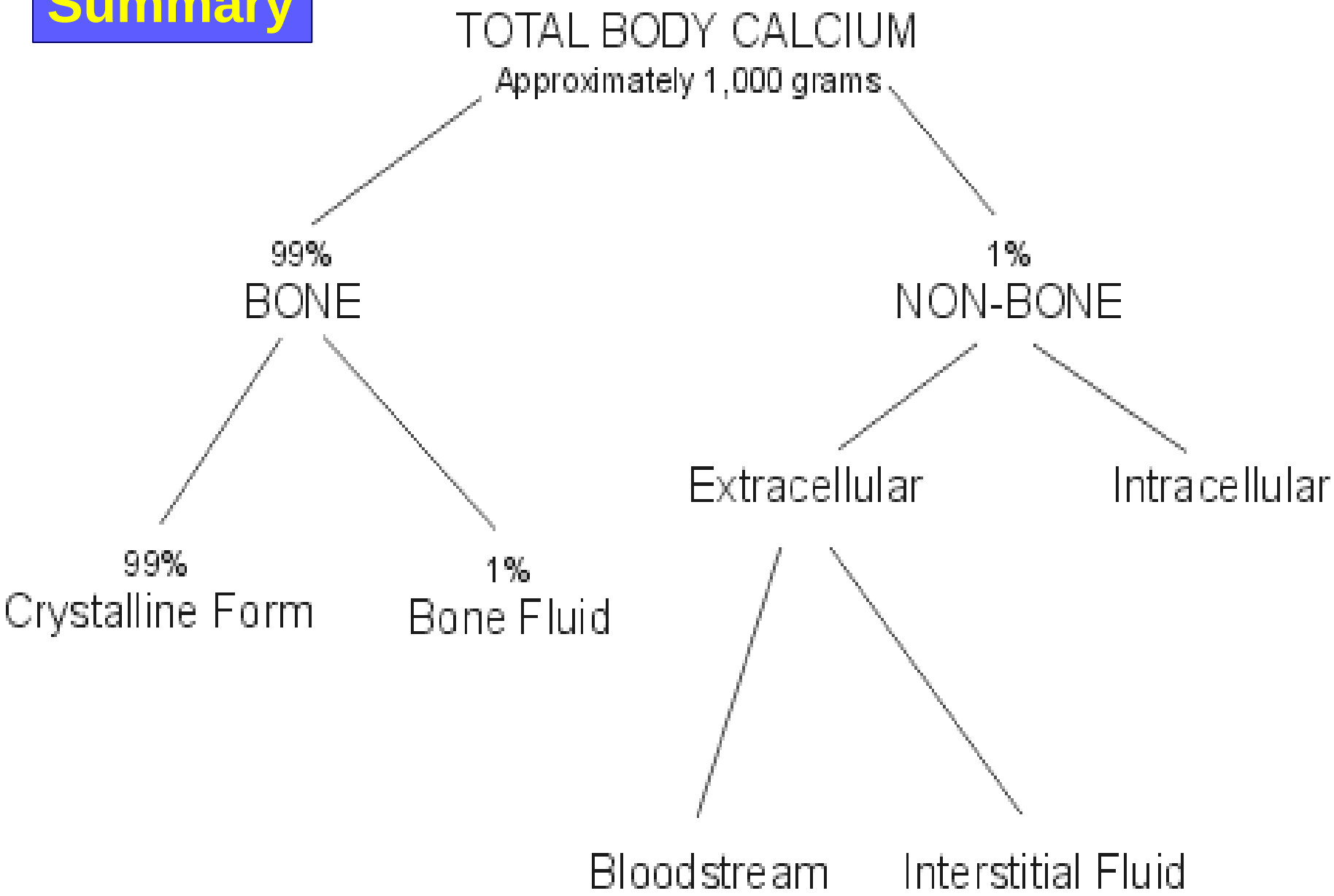
Signs & symptoms (due to hypocalcaemia)

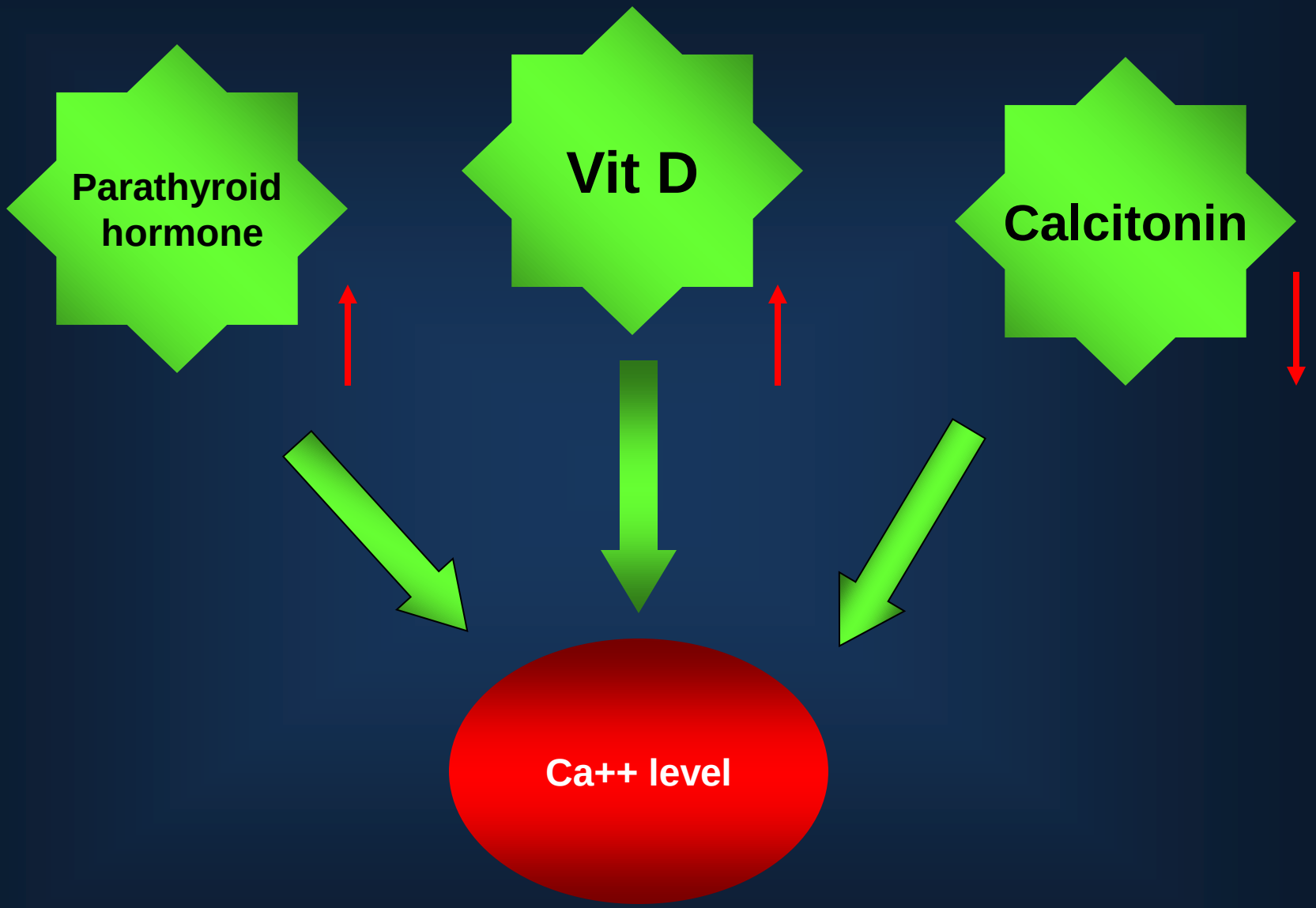
Tingling in the lips, fingers, and toes
Dry hair, brittle nails, and dry, coarse skin
Muscle cramps and pain in the face, hands, legs, and feet
Cataracts on the eyes
Malformations of the teeth, including weakened tooth enamel.
Loss of memory
Headaches
sever muscle spasms(tetany) and convulsions

Treatment

Calcium carbonate and vitamin D supplements

Summary


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


Parathyroid hormone
Vit D
Calcitonin
Ca++ level

THANK YOU