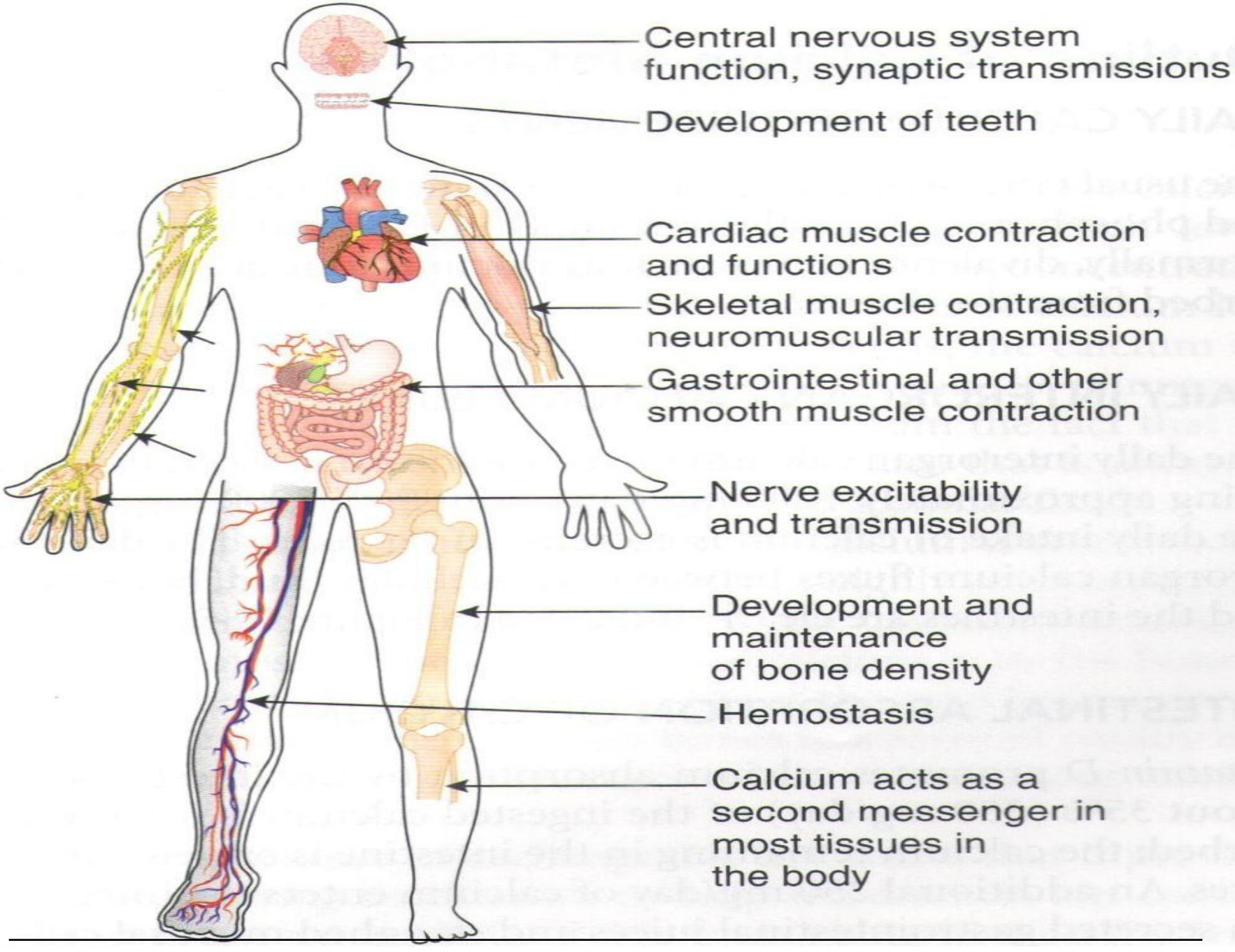
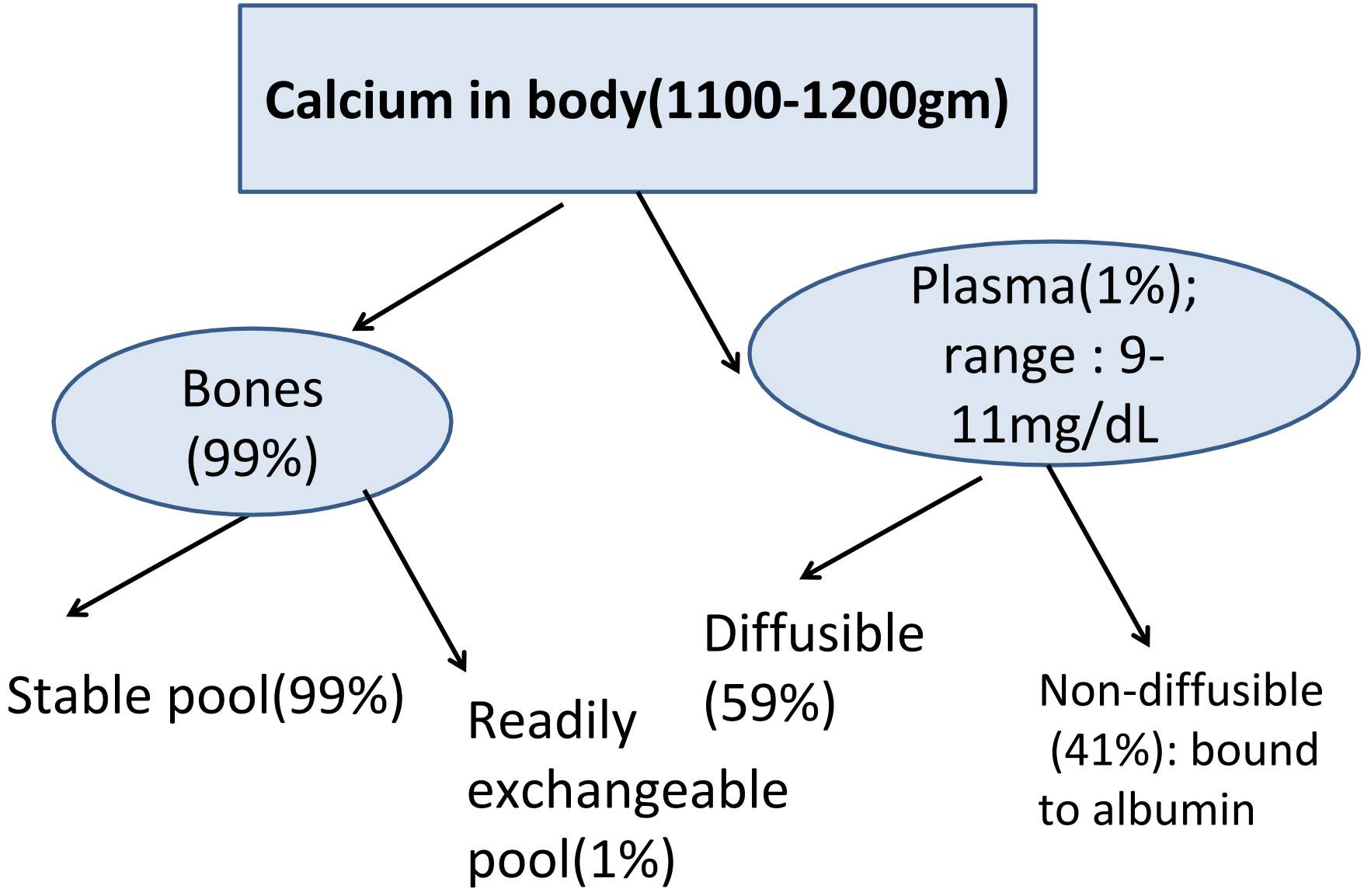
LEARNING OBJECTIVES

- List the physiological effects of calcium.
- Outline calcium metabolism with regard to:
  - Forms of total serum calcium.
  - Daily calcium requirements.
  - Daily interorgan calcium fluxes.
  - Intestinal absorption of calcium.
  - Role of the kidneys in excretion of calcium.
  - Sites of calcium storage.
- Describe in detail calcium metabolism in bone with regard to:
  - Pools of calcium storage.
  - Cells involved.
  - Functions of each cell type.
- List the mechanism of action of parathormone, calcitonin, and vitamin D_3 in the regulation of calcium homeostasis.
- List the clinical features of (a) hypo- and hypercalcemia, (b) hypo- and hyperparathyroidism, (c) osteoporosis, and (d) osteomalacia.





- **Facts to keep in mind:-normal plasma level of calcium is 9-10.5mg/dl(5mEq/L,2.5mmol/L)**
  - ***Free, ionized calcium (Ca^{2+})*** is important for blood coagulation, muscle contraction and neuronal function
  - Extent of calcium binding to plasma protein ≈ levels of plasma proteins
- **What is the effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood?**

Absorption of calcium in GIT

- **TRPV6 channels-**---> responsible for calcium absorption in intestine
- Absorbed calcium sequestered by **calbindin-D**
- Enters the blood stream via **sodium calcium exchanger/ calcium dependent ATPase TRPV6 channels-**---> responsible for calcium absorption in intestine
- Absorbed calcium sequestered by **calbindin-D**
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Plasma calcium –filtered by kidneys

98%-99% are reabsorbed (60% from PCT; remaining –ascending loop of Henle and distal tubule)

*PTH ---- regulates the re-absorption from distal tubule (regulates the expression of **TRPV5** channels)*

Phosphorous

Total : **500-800 gm** (plasma level = **2.5-4.5mg%**)

80-85% : skeletal

2/3rd :organic; 1/3rd inorganic (***total plasma level = 12mg/dL***)

kidney : 85%-90% of filtered P_i reabsorbed (PCT :active transport---***sodium dependent Pi cotransport***)

Na- Pi IIa and Na- Pi IIc

Na-Pi II a **----->** powerfully ***inhibited by PTH***

GIT : Pi absorbed in duodenum & other parts of small intestine (**Na-Pi IIb**)

Excretion : ↑ed : high phosphate diet, hyperparathyroidism

↓ed : low phosphate diet, hypoparathyroidism

Physiological effects of altered calcium levels:-

Hypocalcemia :-

- ↑ed neuronal excitability
- tetany (*calcium level about 6.4mg/dL*)
- seizures

- **Features of hypocalcemic tetany**
  - Chvostek's sign
  - Trousseau's sign
  - carpopedal spasm
  - laryngospasm

Hypercalcemia (>12mg/dL)

- Depresses nervous system
- Sluggish reflex
- Muscle activity depressed
- Lack of appetite
- Constipation

List various functions of calcium and phosphate

Physiology of Bone

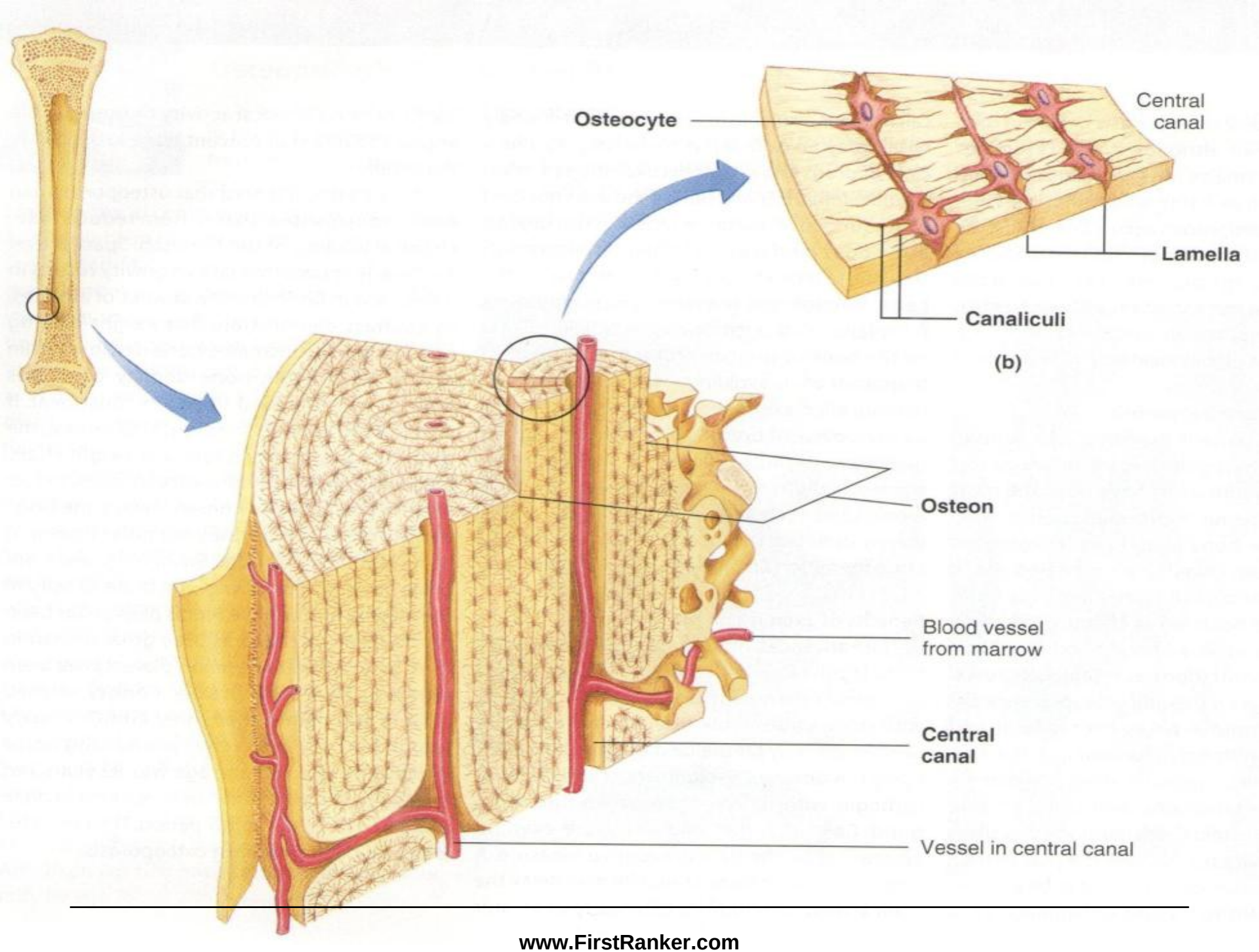
- Bone is a living tissue
- It is a specialized connective tissue
- Compact bone -30% matrix(framework)
  & 70% salts
- Organic matrix :90-95% **collagen fibers,mainly type1** &Groundsubstance (**ECF+Proteoglycans**).
- Bone salts:**Hydroxypatites**{$Ca_{10}(PO4)(OH)_2$}

Compact /cortical bone

- 80%
- Forms outer layer of bone.
- Surface to volume ratio low
- Nutrients provided by **Haversian canal.**

Trabecular/Spongy bone

- 20%
- **Inside** the cortical bone
- Surface to volume ratio high
- Nutrients diffuse from ECF

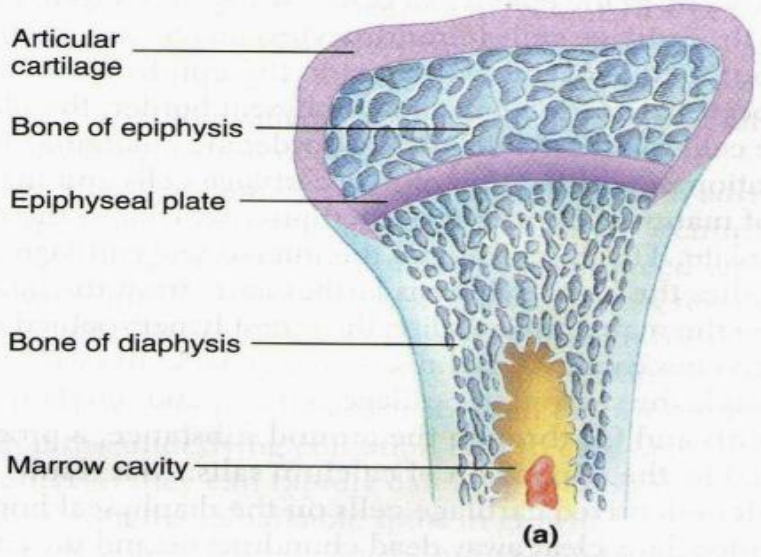


Bone formation

- During fetal development bone formation occurs by:

Enchondral bone formation(majority)

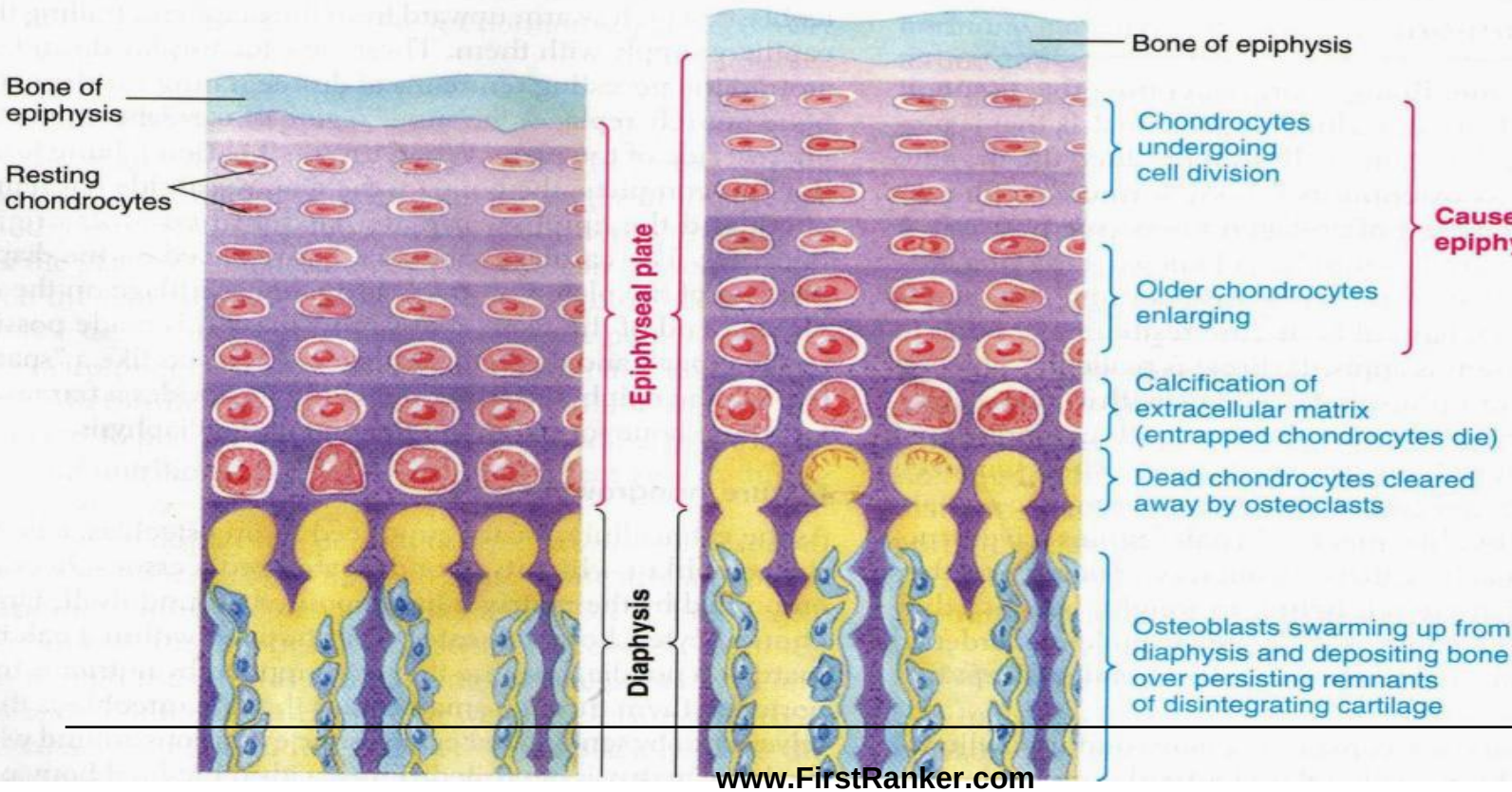
Intramembranous bone formation e.g.; clavicle, mandible, certain bones of skull.



● FIGURE 18-16

Anatomy and growth of long bones

(a) Anatomy of long bones. (b) Two sections of the same epiphyseal plate at different times, depicting the lengthening of long bones.



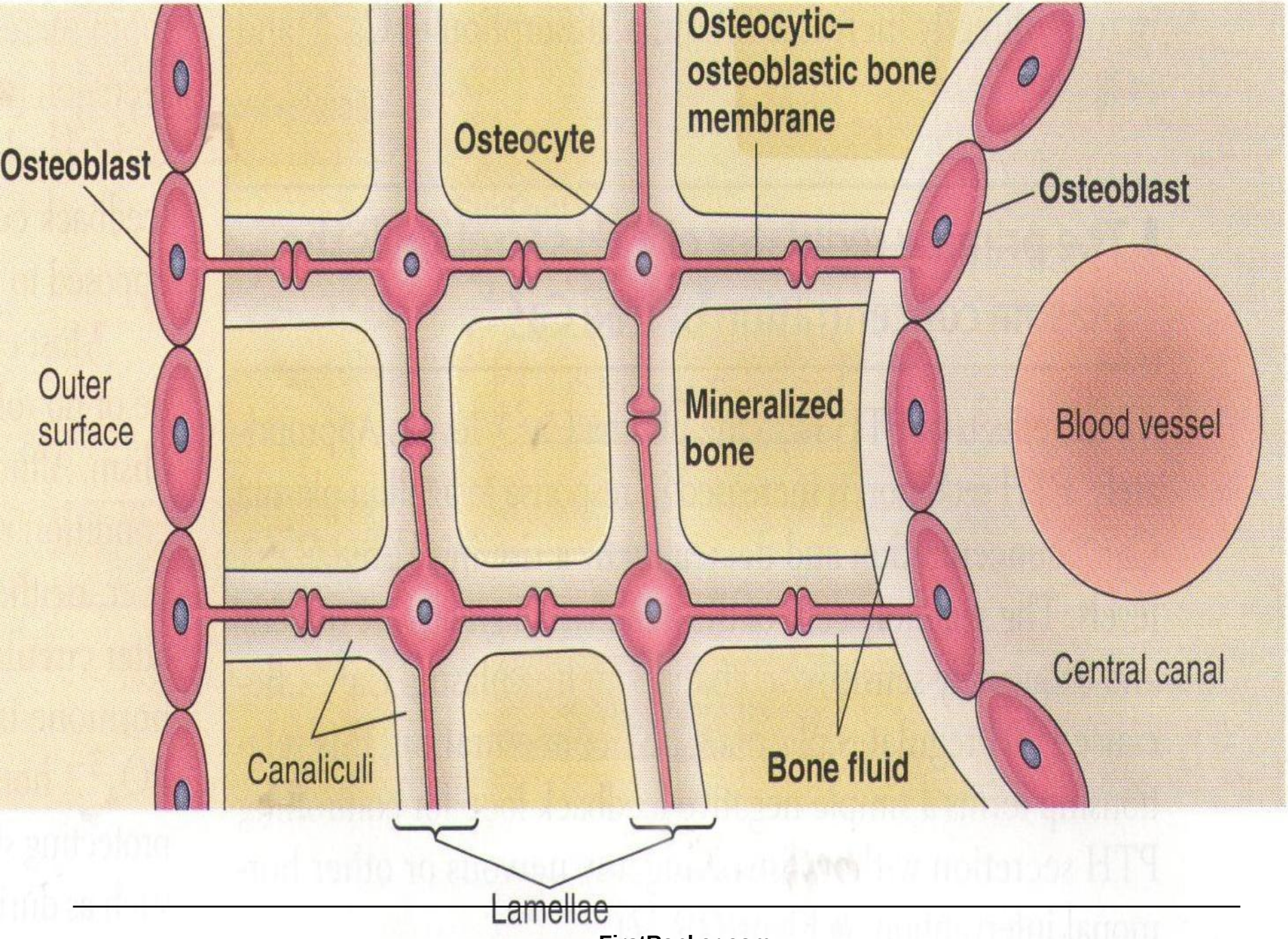
Bone formation by osteoblasts

- **Osteoid** formation (95% collagen+5% proteoglycan) by **osteoblasts.**
- **Osteoid is secreated towards the interior of bone.**
- **Precipitation of calcium and phosphate** on surface of collagen **(mineralization)**
- Formation of ***hydroxyapatite*** , $Ca_{10}(PO_4)_6(OH)_2$, crystals (Ca:P:: 1.3-2)

Magnesium, sodium, potassium, and carbonate ions are also present among the bone salts

- **Collagen :tensile strength**;
- **hydroxypatite : compressional strength**

- **Deposition and absorption of bone—remodeling of bone**
- **Bone deposition and absorption are normally in equilibrium.**
- Continual physical stress stimulates osteoblastic deposition and calcification of bone.



Bone Remodelling

Bone deposition & Bone resorption.

Requires 3 types of cells.

- **Osteoblasts**: secrete extracellular organic matrix within which calcium phosphate crystal precipitate.
- **Osteocyte**: Retired osteoblast imprisoned within bony wall around them.
- **Osteoclasts**: Resorb bone by secreting acids & enzymes.They are cells of mononuclear phygocytic system.

Mechanism of bone resorbtion

- Osteoclasts attaches to the part of bone to be reabsorbed by integrins .

↓

Forms “sealing zone”

↓

- **Proton pump**(H+ dependent ATPases)migrate From endosomes to the cell membrane.

↓

↓Ph to 4 in this zone

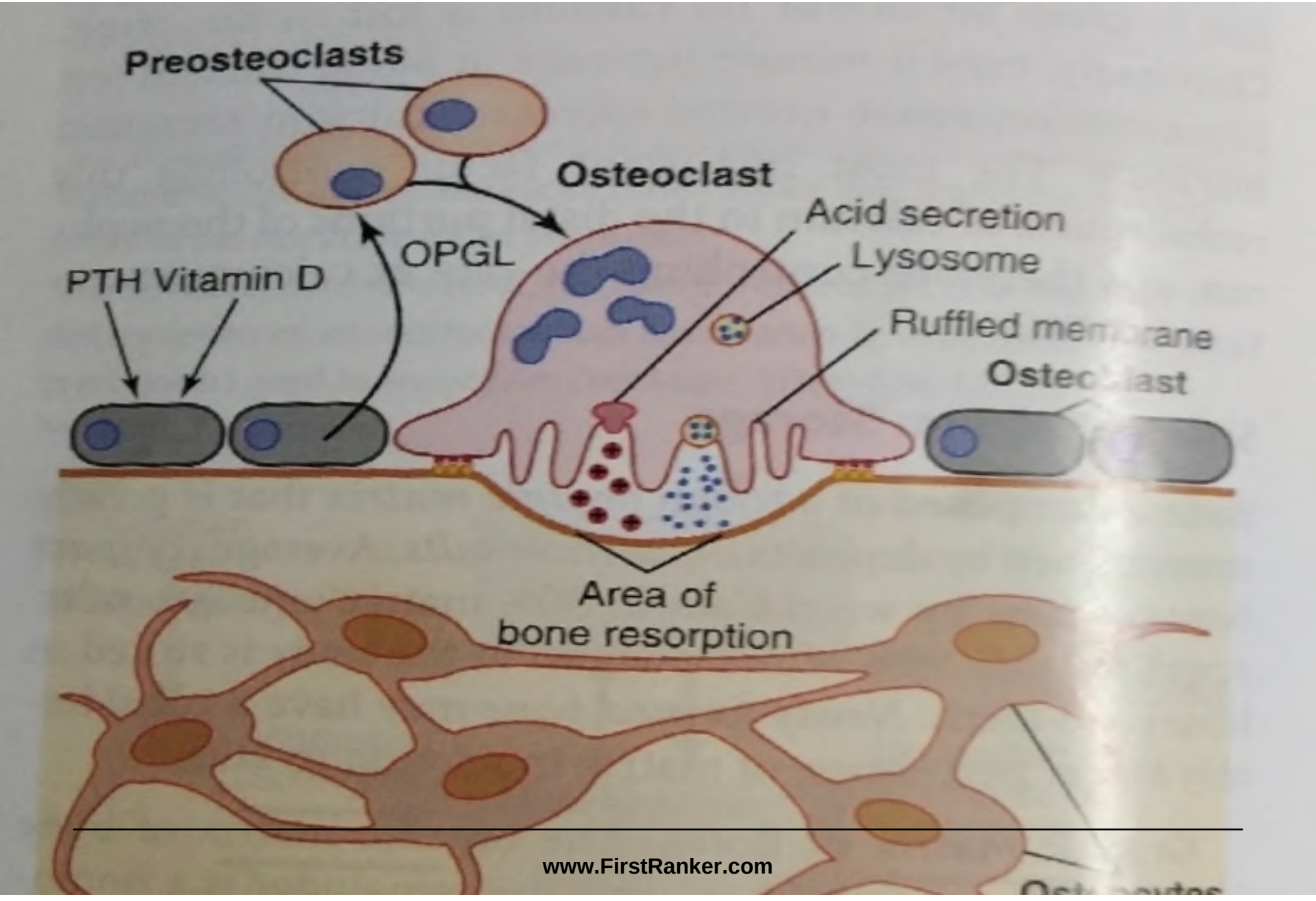
Contd.

- The acidic pH dissolves **hydroxypatite,**

  And **proteases** breakdown collagen.

Ca, P,and collagen breakdown products are released into the interstitial fluid.

➢ Hydroxyproline is an index of bone resorbtion.



Factors controlling bone formationand resorbtion

- GH, IGF, insulin, estrogen, testosterone, vit D , calcitonin, PDGF, → Stimulates bone formation.
- **Cortisol** inhibits bone formation.
- Parathormone, cortisol,thyroxine,PGs,IL-1&6, TNF, → Stimulates bone resorbtion.

- Despite supersaturation of calcium and phosphorus ions in ECF hydroxypatite crystals fail to precipitate in other tissues……. Why?
- Osteoid? Osteocytes?
- Mechanism of bone absorption by osteoclasts?
- The importance of exchangeble calcium ion in bone? Physiological importance of continued deposition and absorption of bone?
- Continual physical stress stimulates osteoblastic deposition and calcification of bone……. How?
- Factors that control bone formation and resorption?

Applied physiology

- Osteoporosis : decrease in bone mass and density.
  - ➢ Involutional osteoporosis
  - ➢ Postmenopausal osteoporosis
- Causes:Hyperparathyroidism,Hyperthyroidism, Cushing's syndrome ,vit c ↓,alcoholism,etc.
- Treatment: Administeration of vit D and calcium tablets.

Contd.

Osteopetrosis

- There is defective increase in bone formation.
- Rare & often severe disease.
- Osteoclasts are defective, unable to resorb bone in usual fashion so osteoblasts operate unopposed.
- Neurological and hematological abnormalities.