Calcium Metabolism

DR BELA GOYAL

Learning Objectives

- Forms of calcium and factors affecting its analysis
- Regulation of calcium with its molecular mechanisms and applications
- Functions of calcium, mechanism of action and clinical application
- Clinical Significance

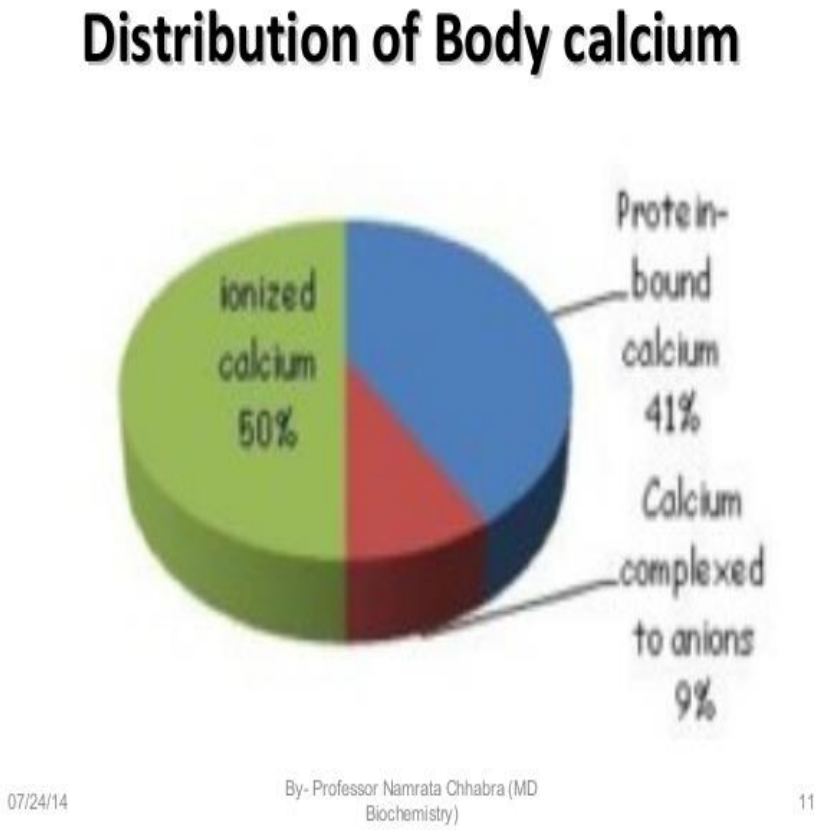
CALCIUM

Total Body Content : 1-1.5kg

Bones : 99%

ECF : 1%

Plasma : 9-11mg/dl



Tissue distribution and states of calcium

Tissue	Calcium
Skeleton	99%
Soft tissues	1%
Extracellular fluid	<0.2%
Total	1000 g (25 mol)

Free (ionized)	50
Protein-bound	40
Complexed	10
Total (mg/dL)	8.6-10.3
(mmol/L)	2.15-2.57

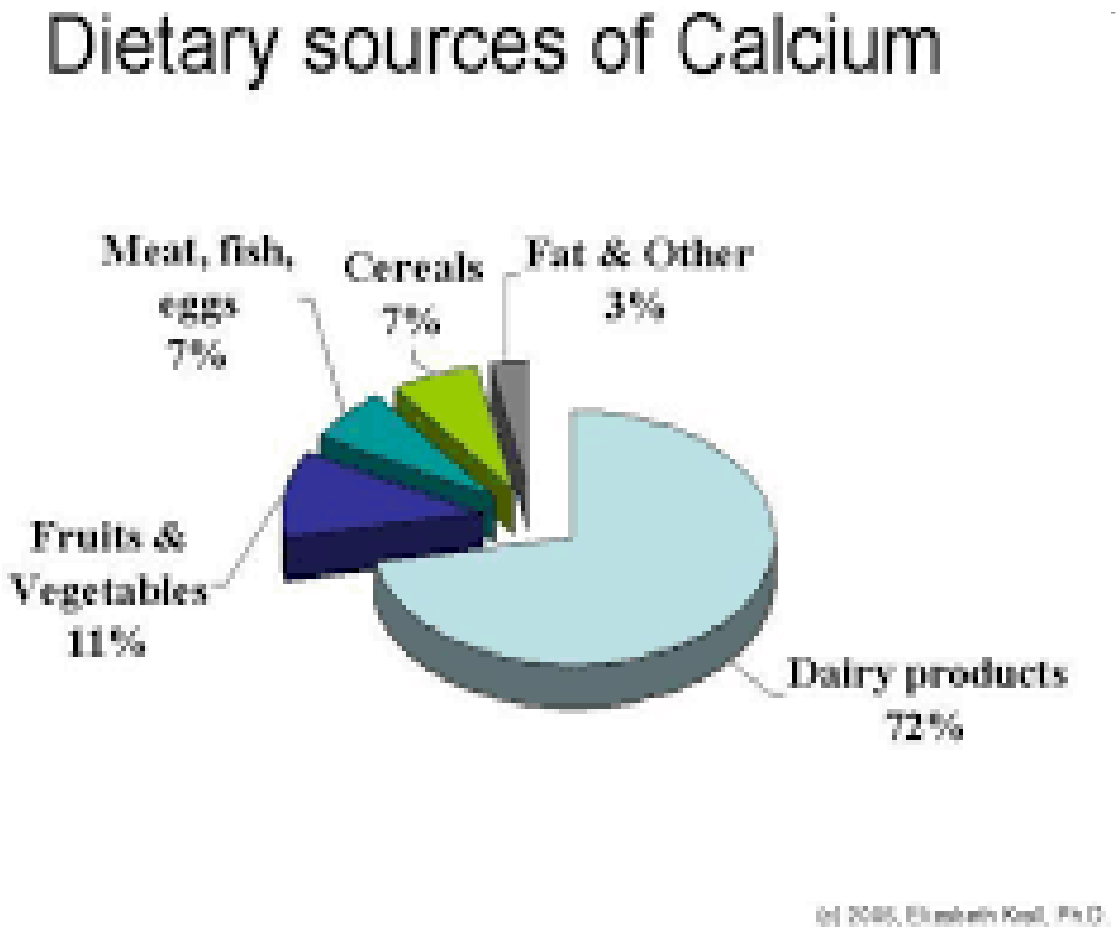
Daily Requirement and Dietary sources

Adults : 800mg

Children : 1200mg

Preg. & Lactation : 1500mg

Postmenopausal- 1500 mg



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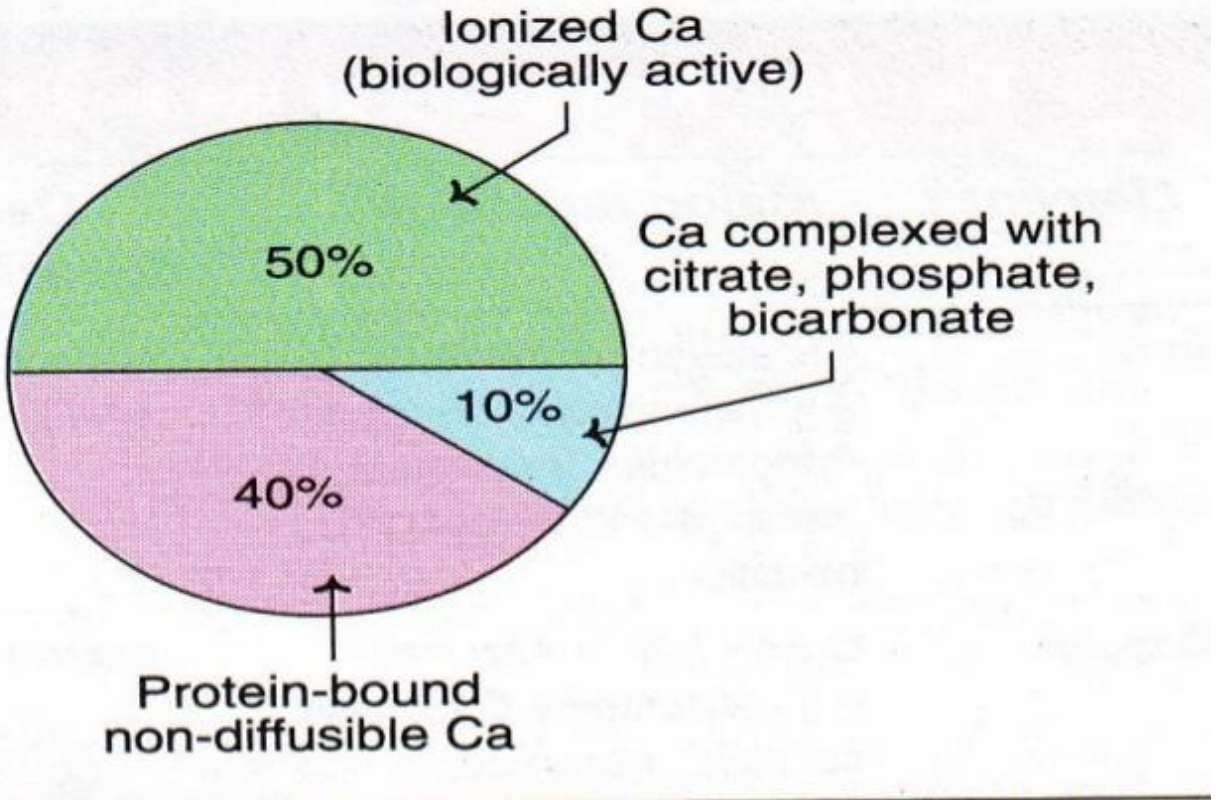
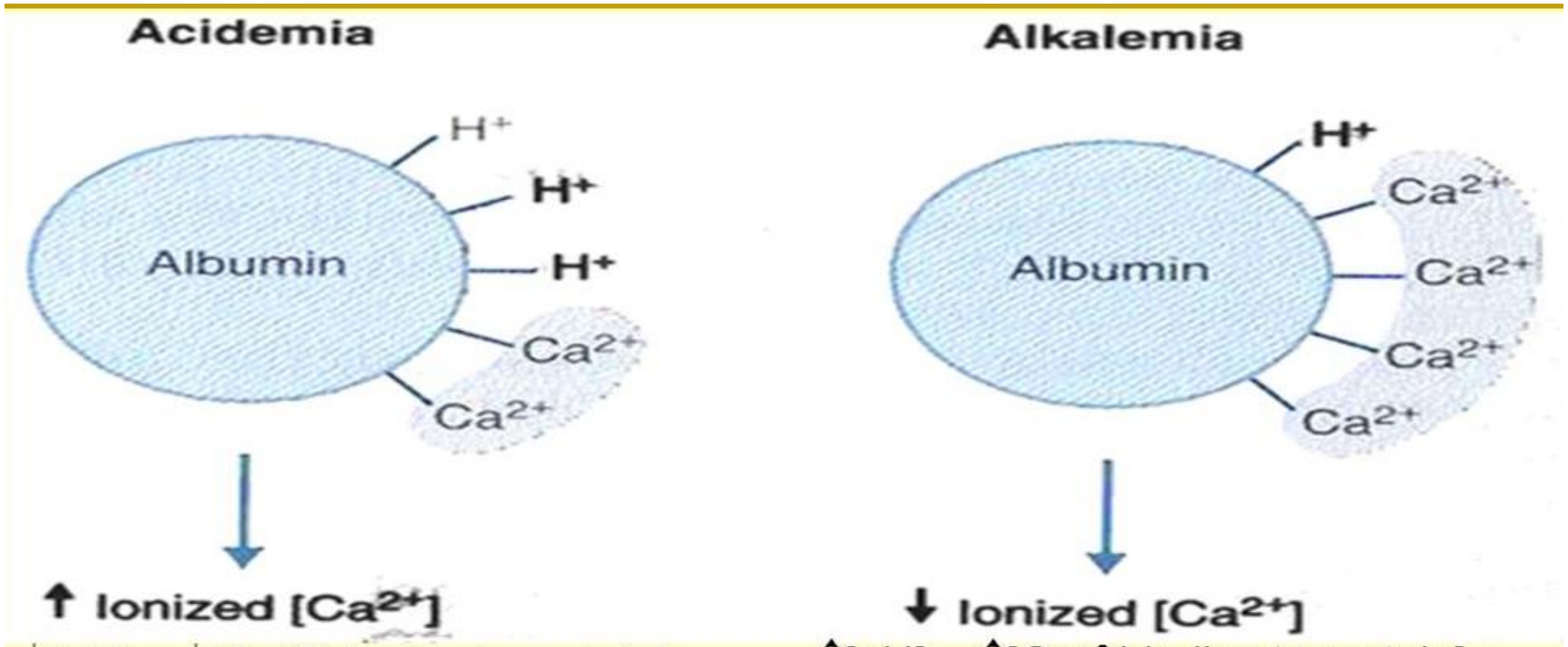
Forms of calcium



Different forms of circulating calcium.

Effect of albumin concentration and acid base balance on plasma concentration of ionised calcium



↓[pH]→ ↓[Ca^{+2} binding to protein]

Acidosis

↑[pH]→ ↑[Ca^{+2} binding to protein]

Alkalosis

Adjusted Calcium for Hypoalbuminemia

Total calcium (mg/dL) corrected for hypoalbuminemia =
Total calcium (measured) + [(Normal albumin − Patient's albumin) × 0.8]

Corrected Total Calcium (mg / dL) =
Total Calcium (mg / dL) + 0.8 (4 - Albumin [g / dL])

Free calcium: ISE
More useful

Pre analytical factors for measurement of calcium

Torniquet application: increased total not ionized Calcium

Fist Clinching/forearm exercises: increased free calcium.

Posture: standing increase total calcium

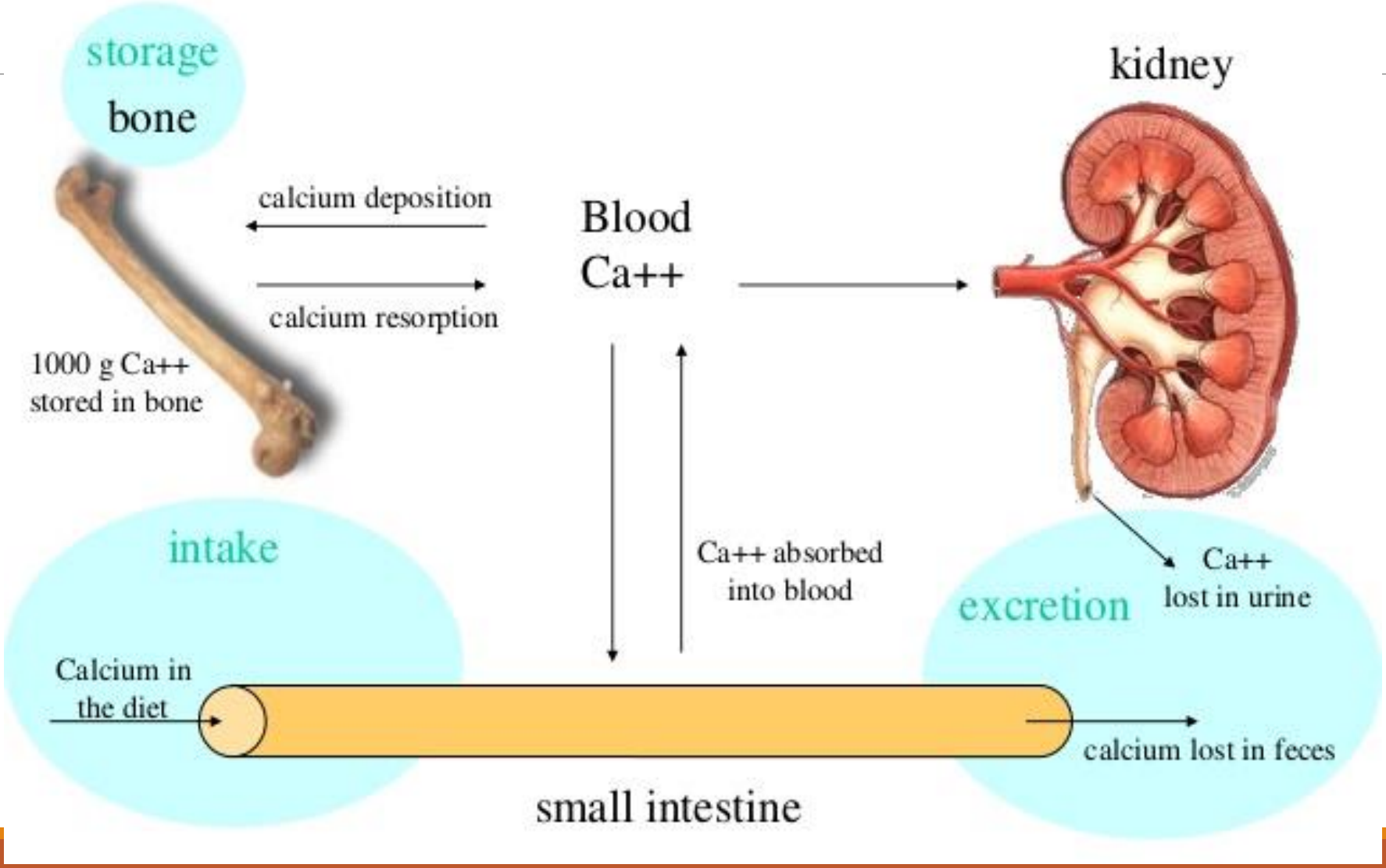
Prolonged immobilization and rest: decreased bone density and increased free calcium

Physiological Variation:

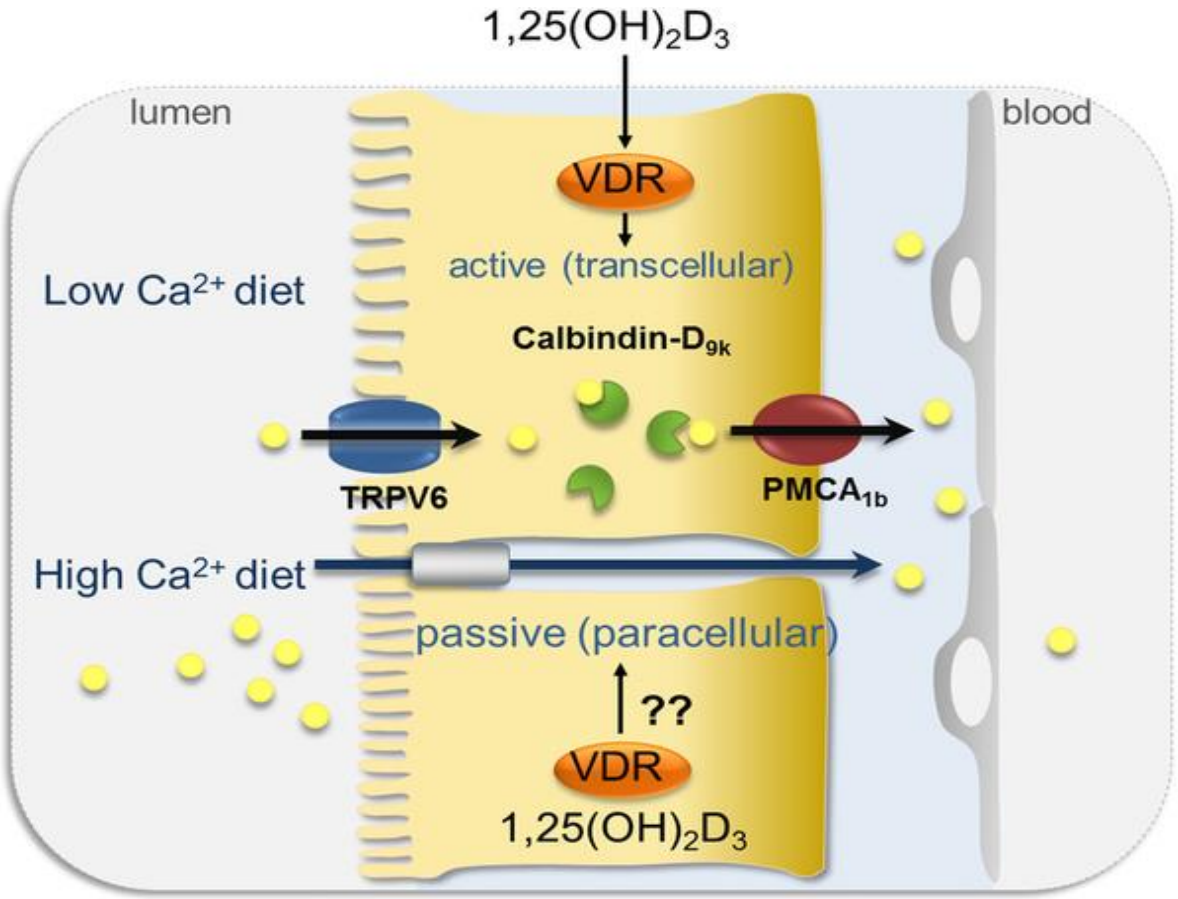
Age

Pregnancy: decreased total calcium

Calcium homeostasis



Calcium absorption in intestine



Factors Promoting Absorption

Vit.D: calcitriol induces synthesis of carrier protein (calbindin) in intestinal epithelial cells

PTH: increases synthesis of calcitriol

Acidic pH of intestinal milieu makes Ca salts soluble

Factors Decreasing Ca Absorption

Alkaline pH

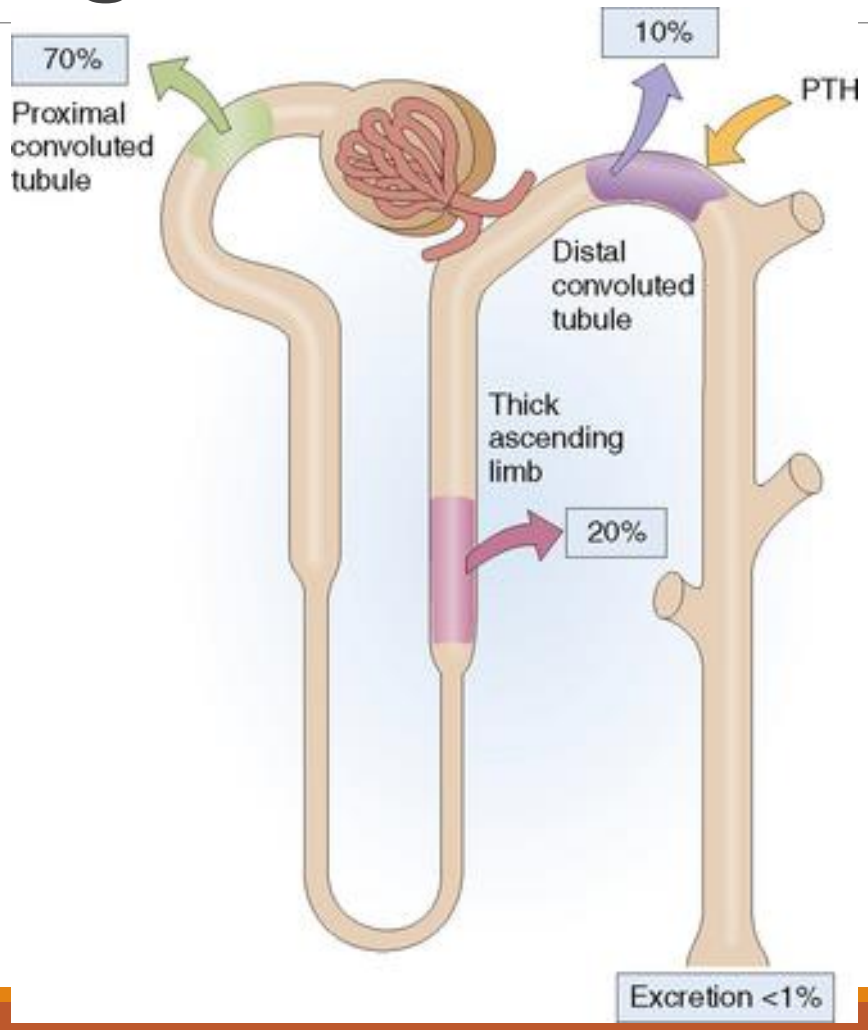
Phytates & oxalates

Malabsorption syndrome: fatty acids are not absorbed forming insoluble Ca soaps

Excess of dietary fibres

Excess of phosphates (1:2 to 2:1)

Renal handling of calcium



Control of Calcium Excretion By the Kidneys

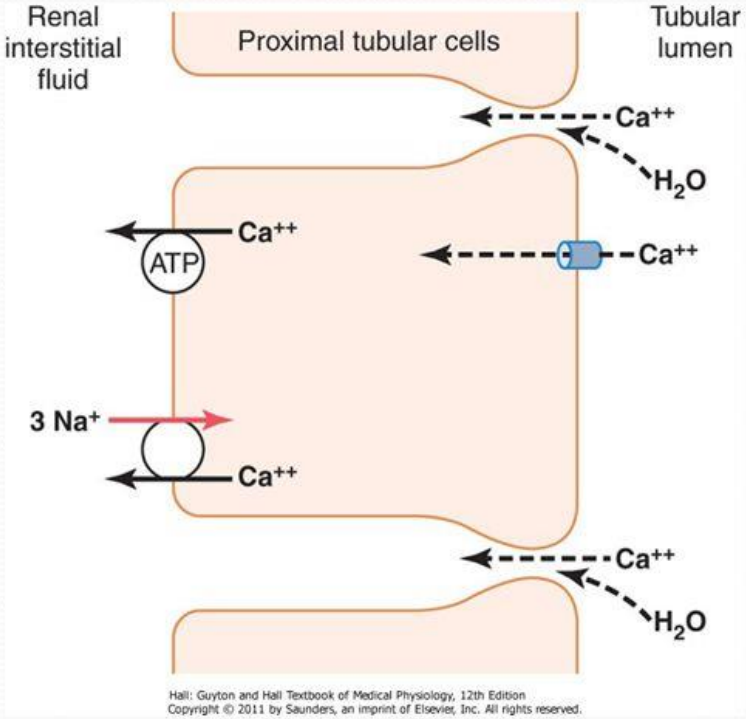
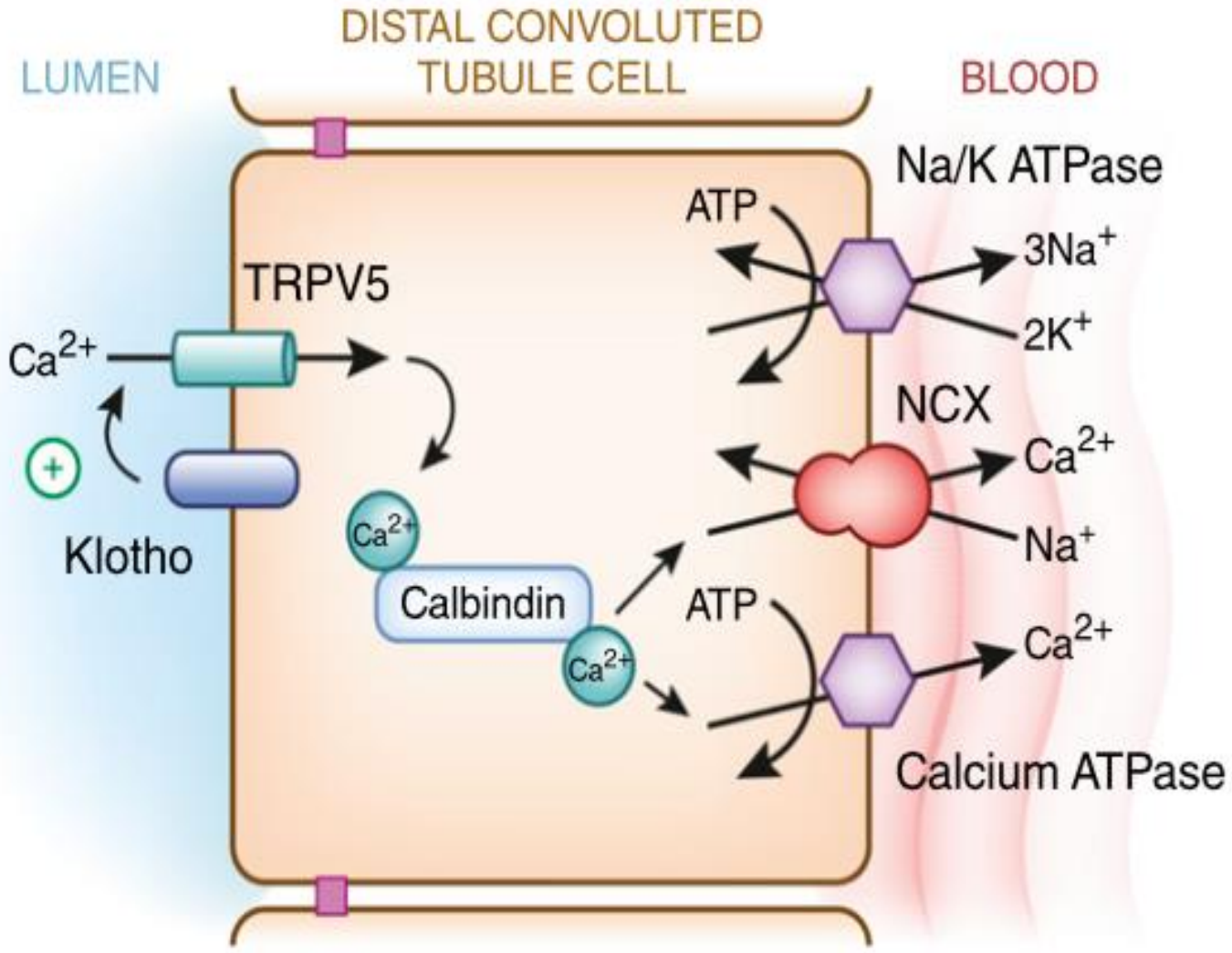
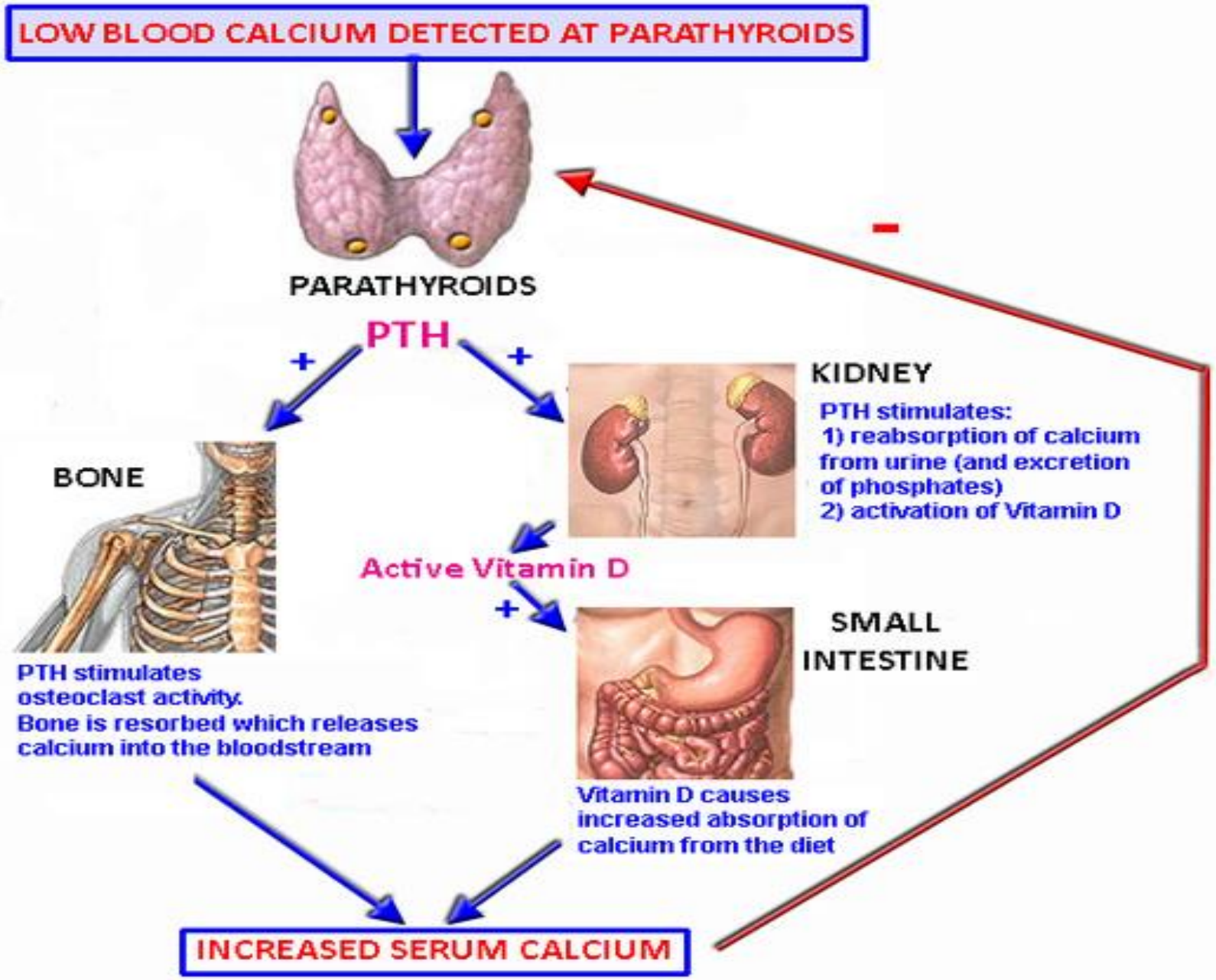
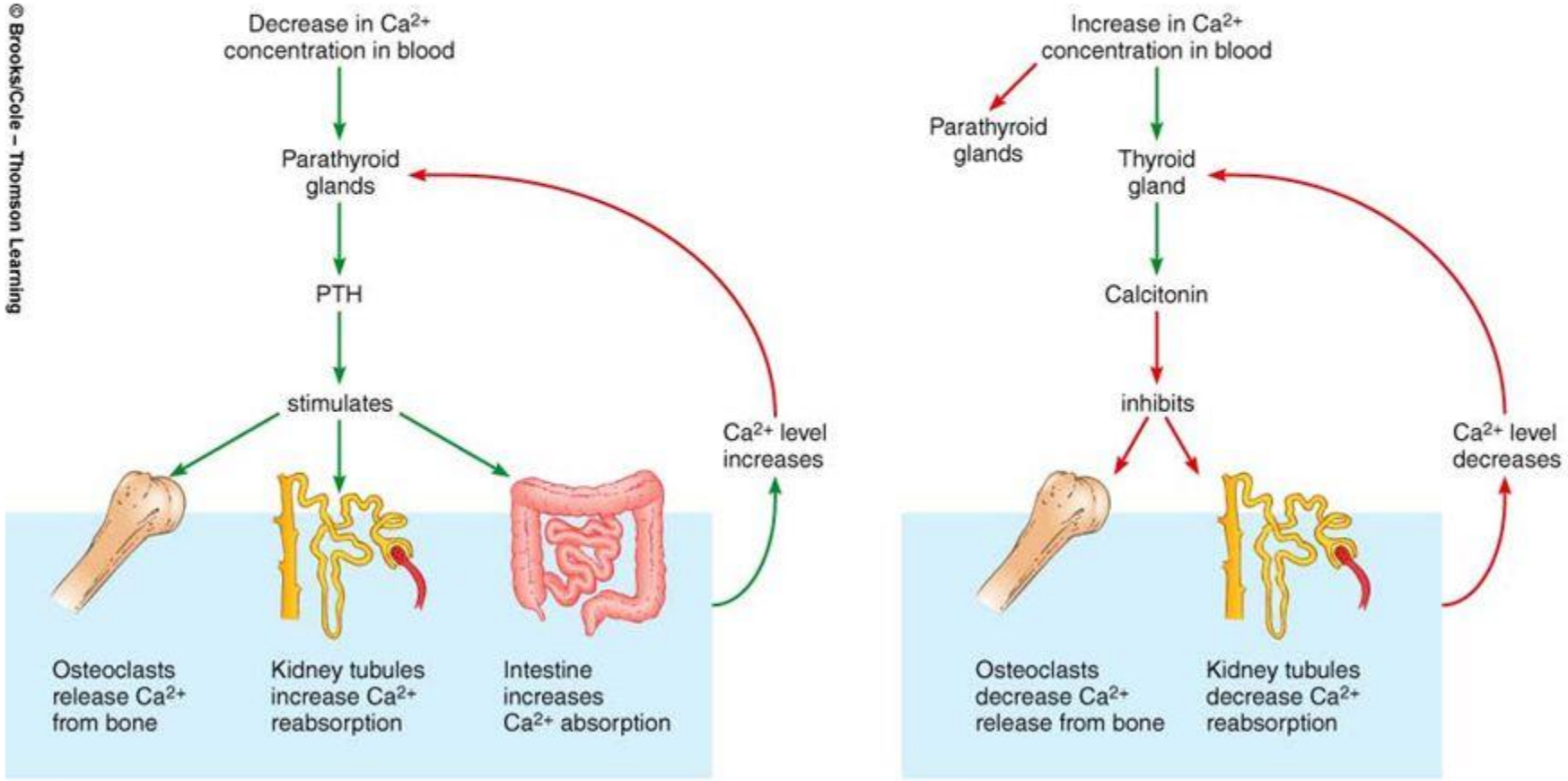


Fig. 29.12 Mechanisms of calcium reabsorption by paracellular and transcellular pathways in the proximal tubular cells


LUMEN
DISTAL CONVOLUTED TUBULE CELL
BLOOD
Na/K ATPase
ATP
3Na+
2K+
TRPV5
Ca2+
NCX
Ca2+
Na+
Klotho
Ca2+
Calbindin
Ca2+
ATP
Ca2+
Calcium ATPase


LOW BLOOD CALCIUM DETECTED AT PARATHYROIDS
PARATHYROIDS
PTH
+
+
-
BONE
PTH stimulates osteoclast activity. Bone is resorbed which releases calcium into the bloodstream
KIDNEY
PTH stimulates:
1) reabsorption of calcium from urine (and excretion of phosphates)
2) activation of Vitamin D
Active Vitamin D
+
SMALL INTESTINE
Vitamin D causes increased absorption of calcium from the diet
INCREASED SERUM CALCIUM

Regulation of calcium homeostasis by PTH and calcitonin



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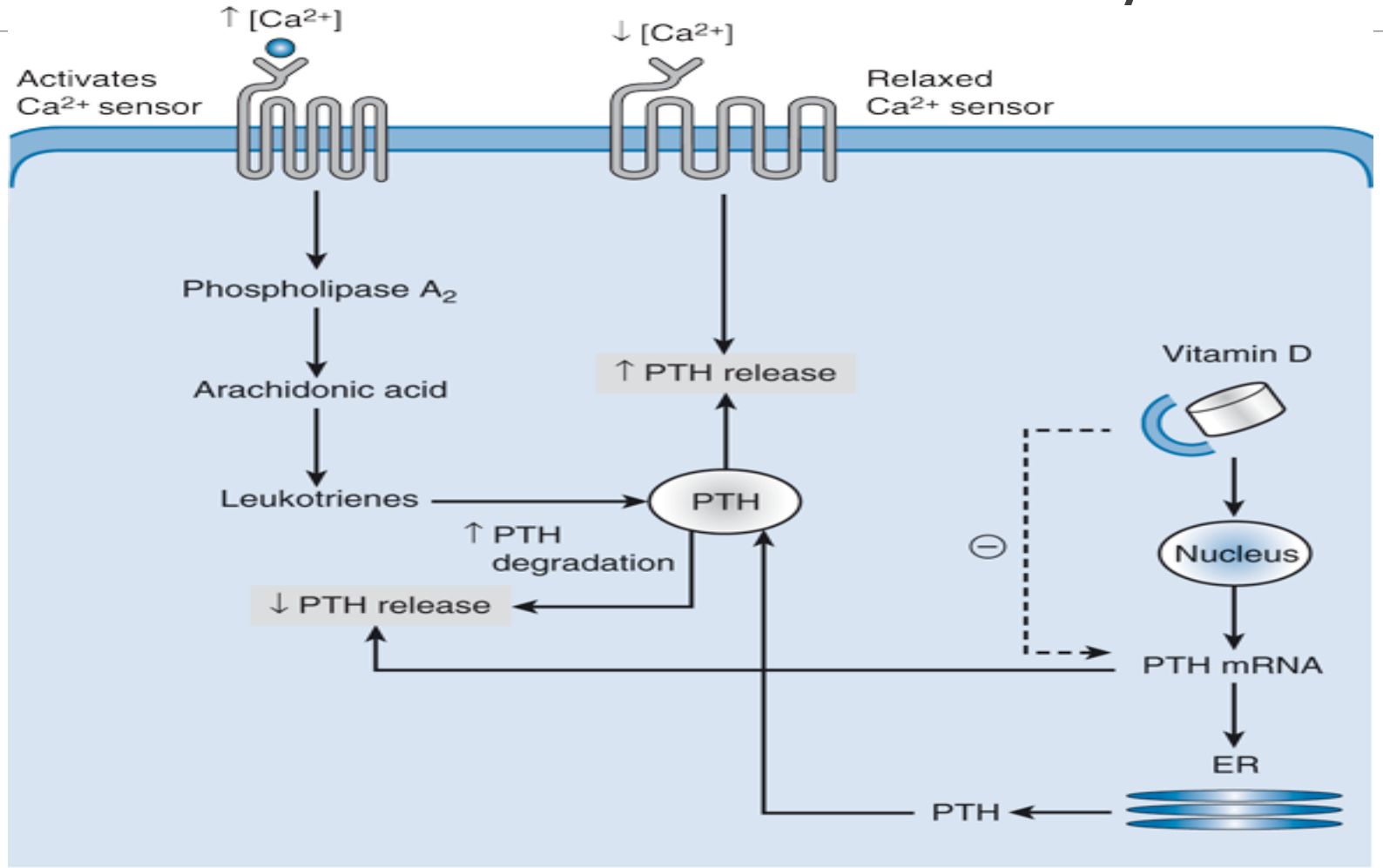
Regulation of PTH secretion by Ca



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com
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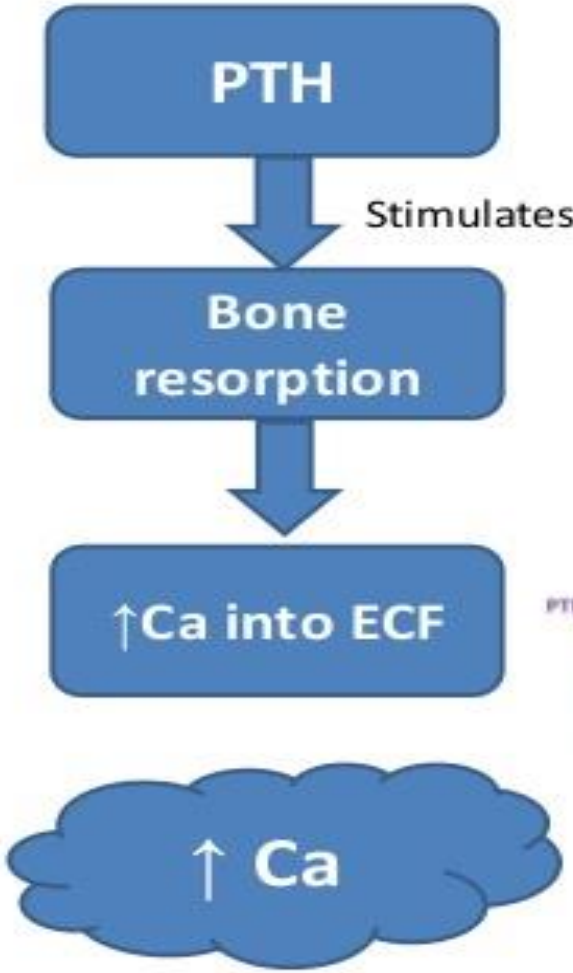
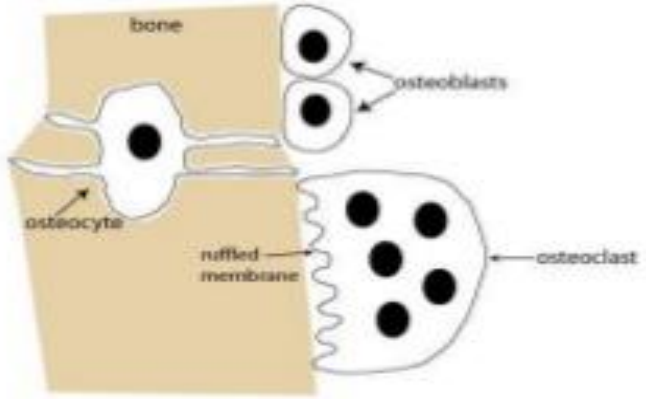
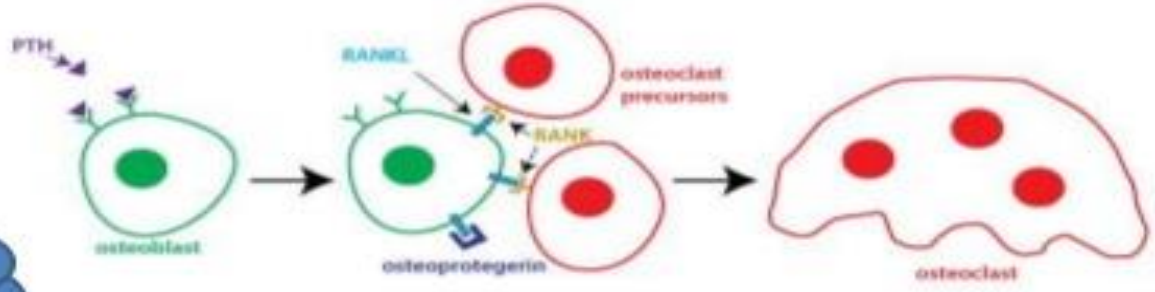
PTH Effects on Bone

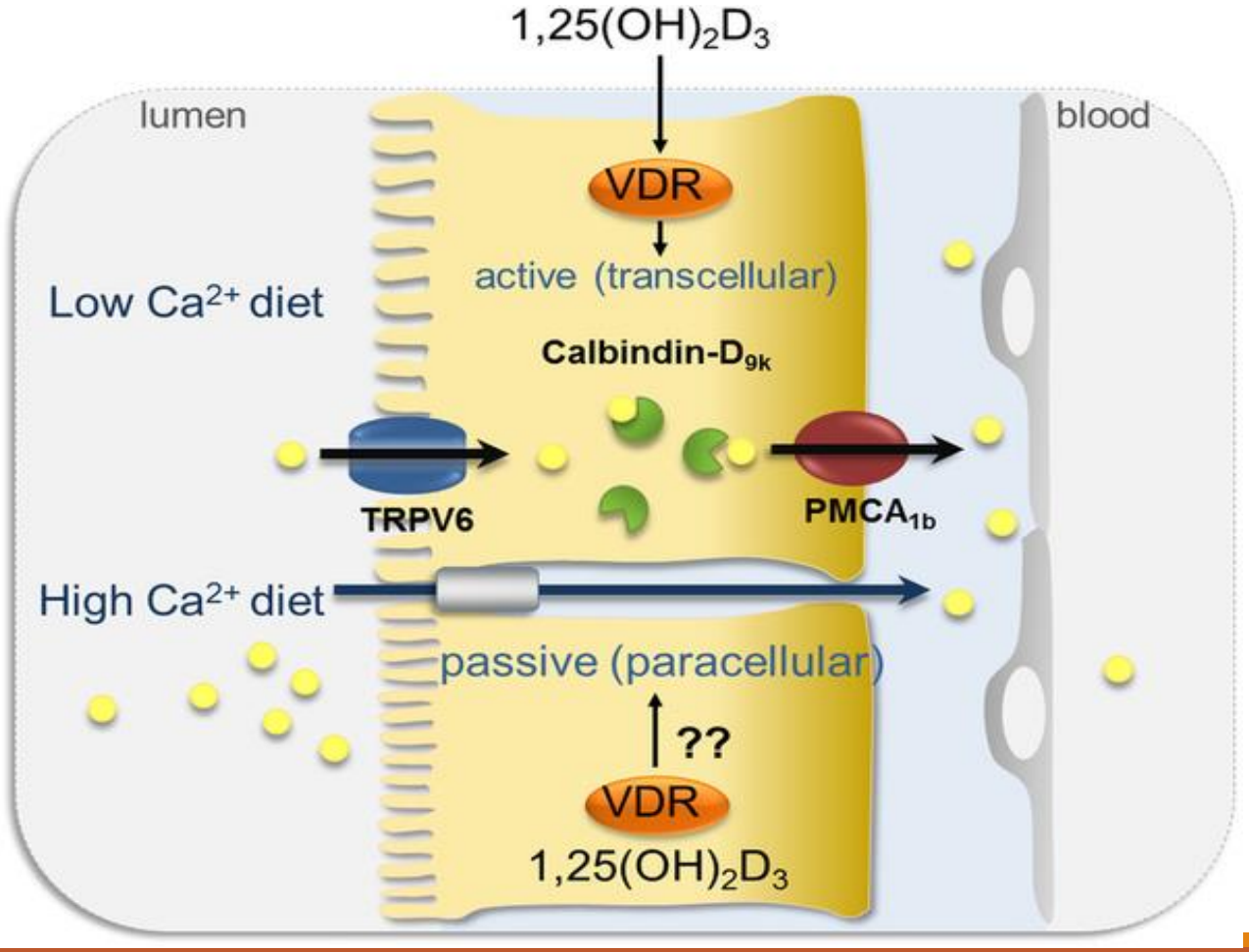




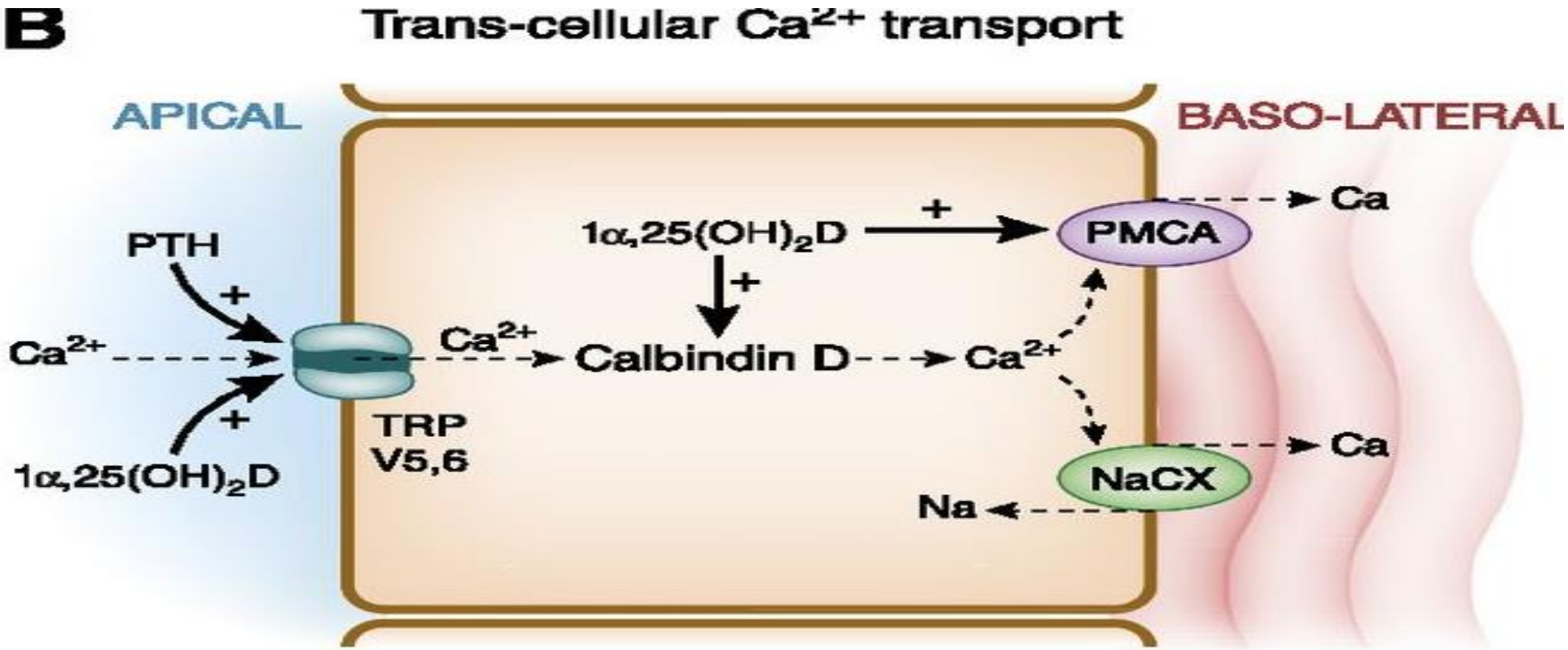


http://courses.washington.edu/conj/bess/bone/bone2.html

Calcium absorption



Calcium reabsorption from kidneys



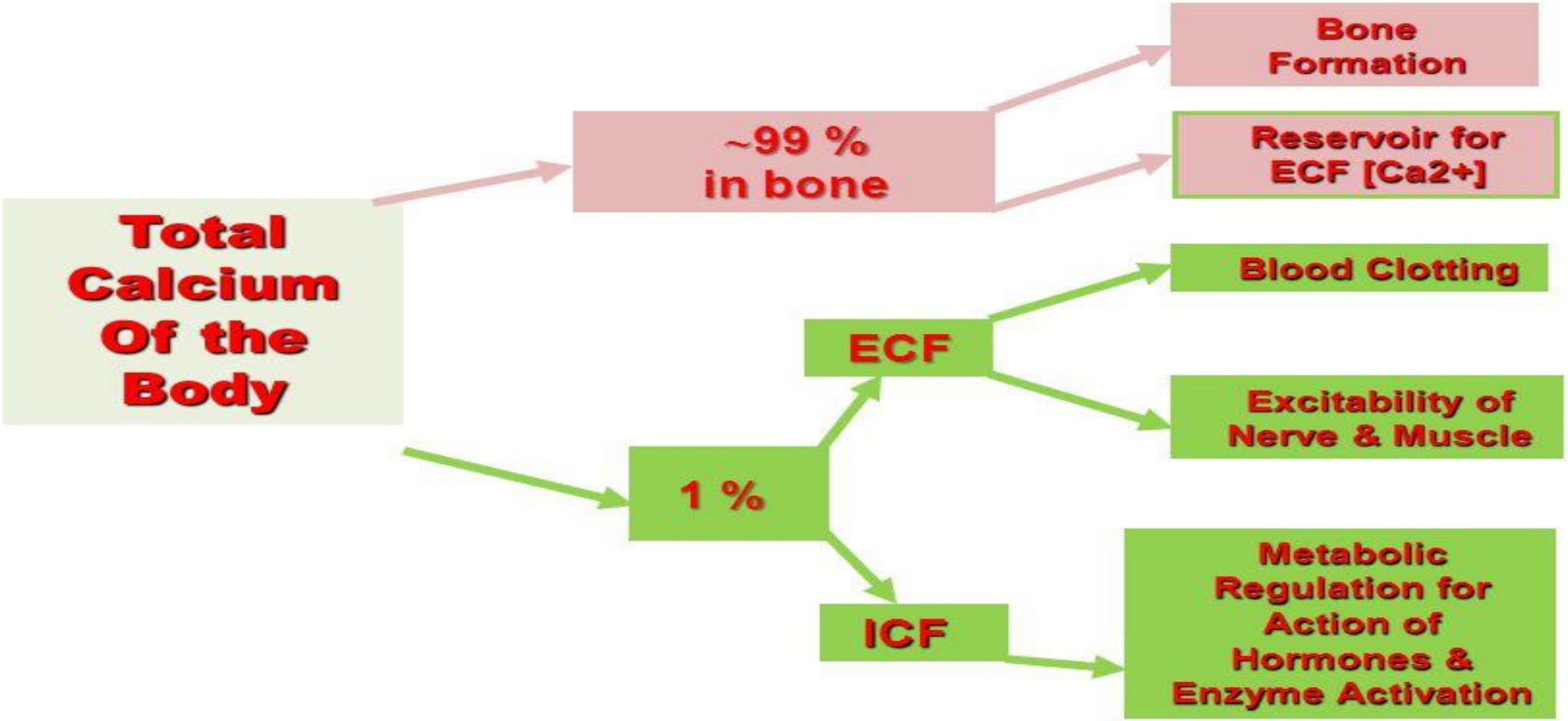
Hypercalcemia of malignancy?

PTHrP?

RANKL?

Denosumab is being clinically used for the treatment of osteoporosis and cancer-related bone disorders

Biological Functions of Calcium



Preserves bone density

Chemical Composition of Bone

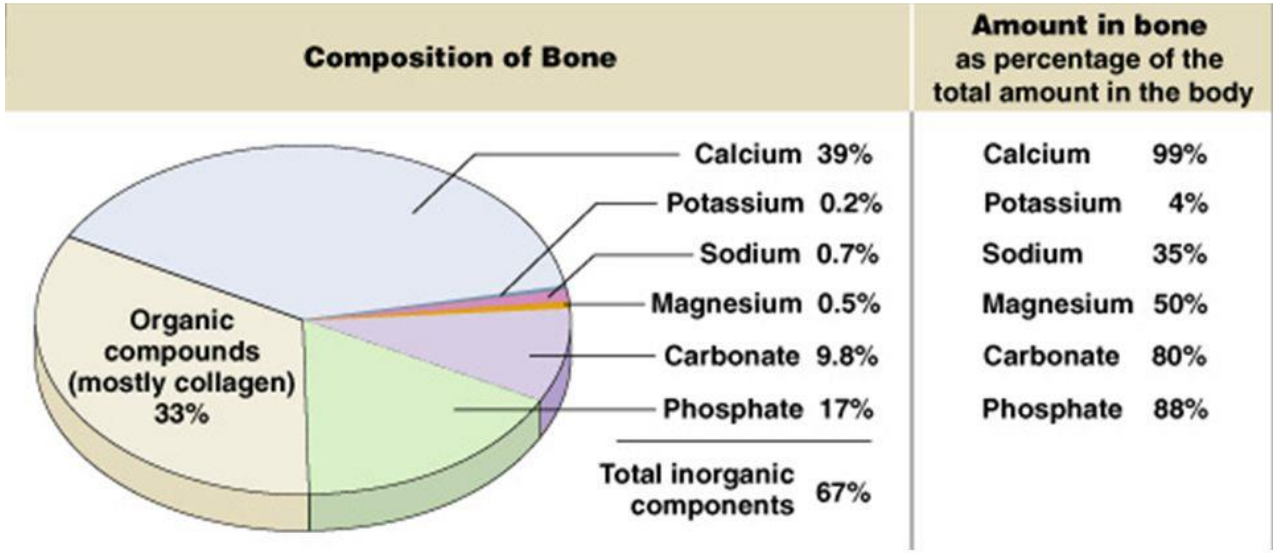
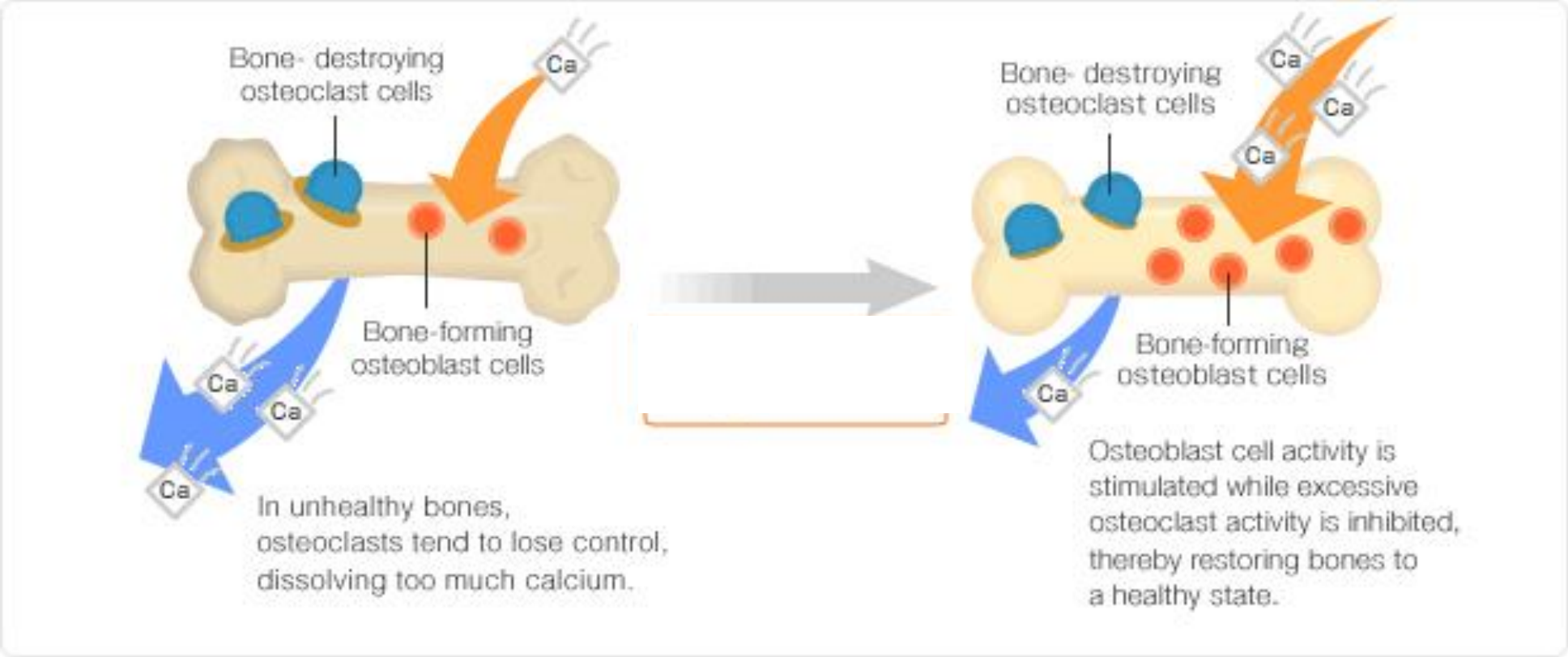
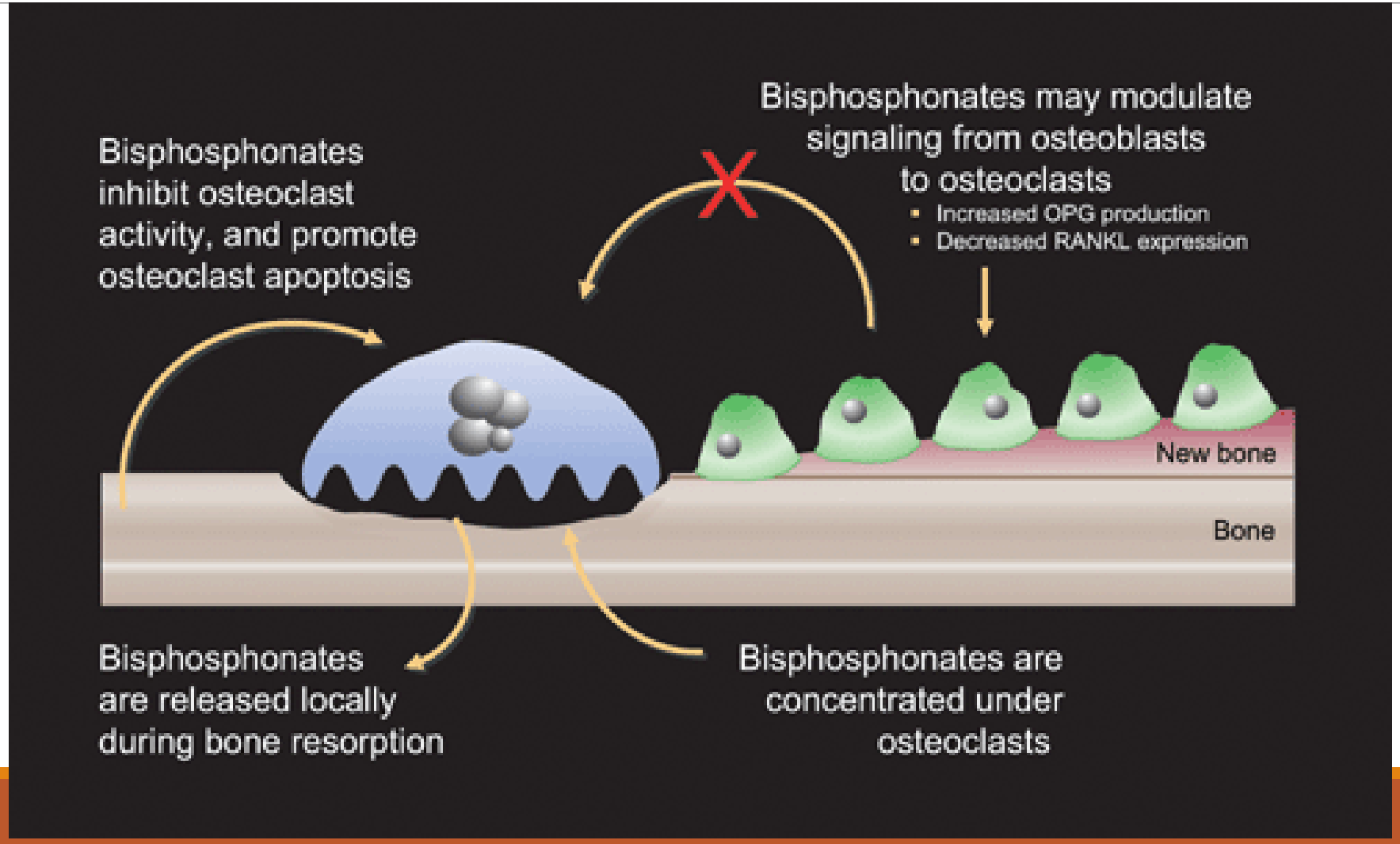


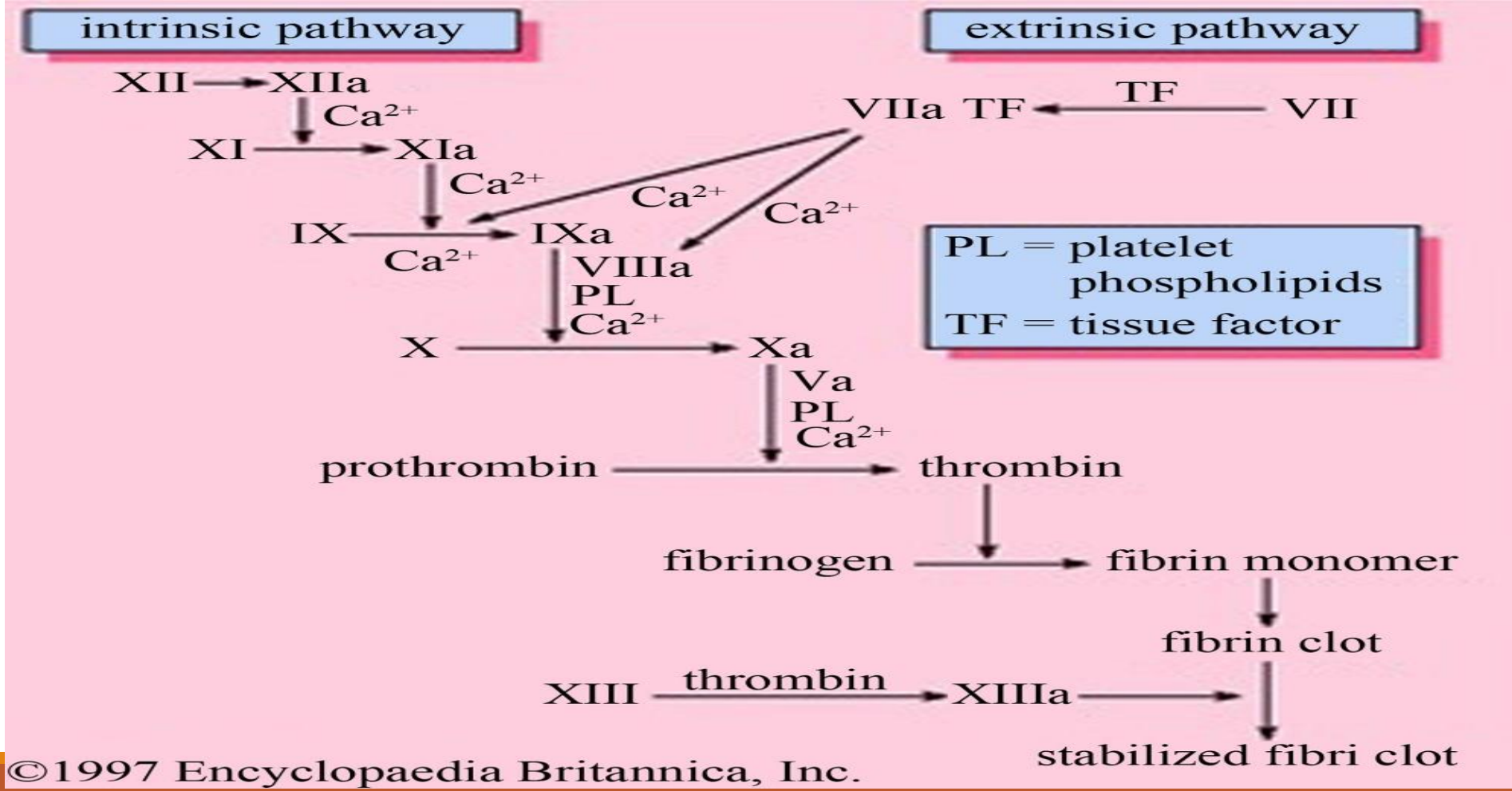
Figure 6-13

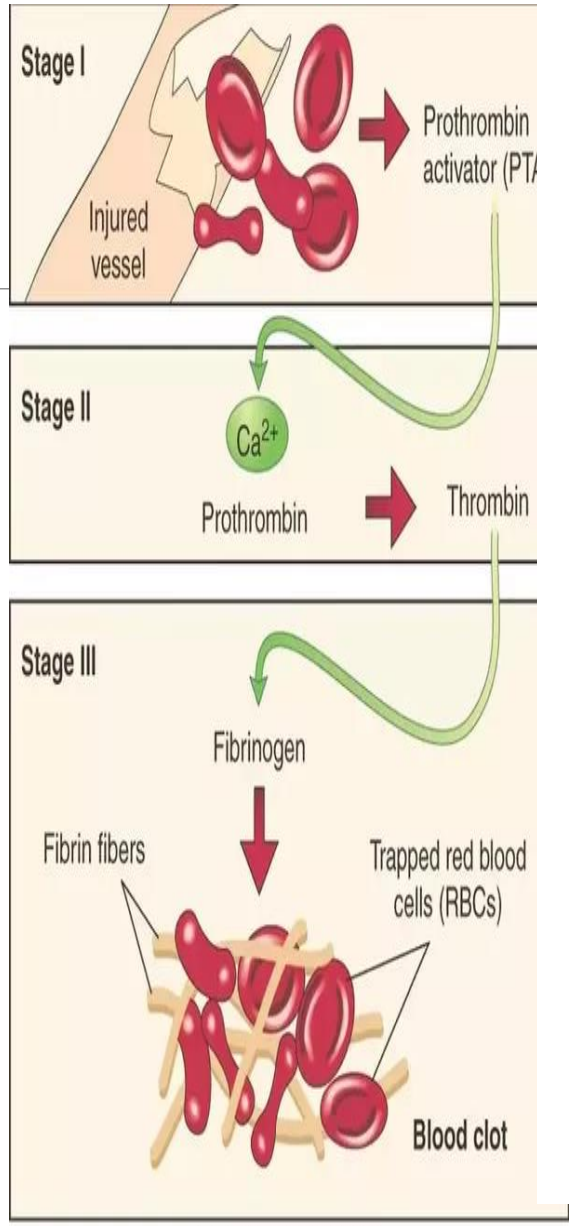

Bone- destroying osteoclast cells
Ca
Bone-forming osteoblast cells
Ca
Ca
Ca
In unhealthy bones, osteoclasts tend to lose control, dissolving too much calcium.
Bone- destroying osteoclast cells
Ca
Ca
Ca
Bone-forming osteoblast cells
Ca
Osteoblast cell activity is stimulated while excessive osteoclast activity is inhibited, thereby restoring bones to a healthy state.

Mechanism of action of Bisphosphonates



Role of Ca in blood clotting





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Role of Calcium in Blood Coagulation

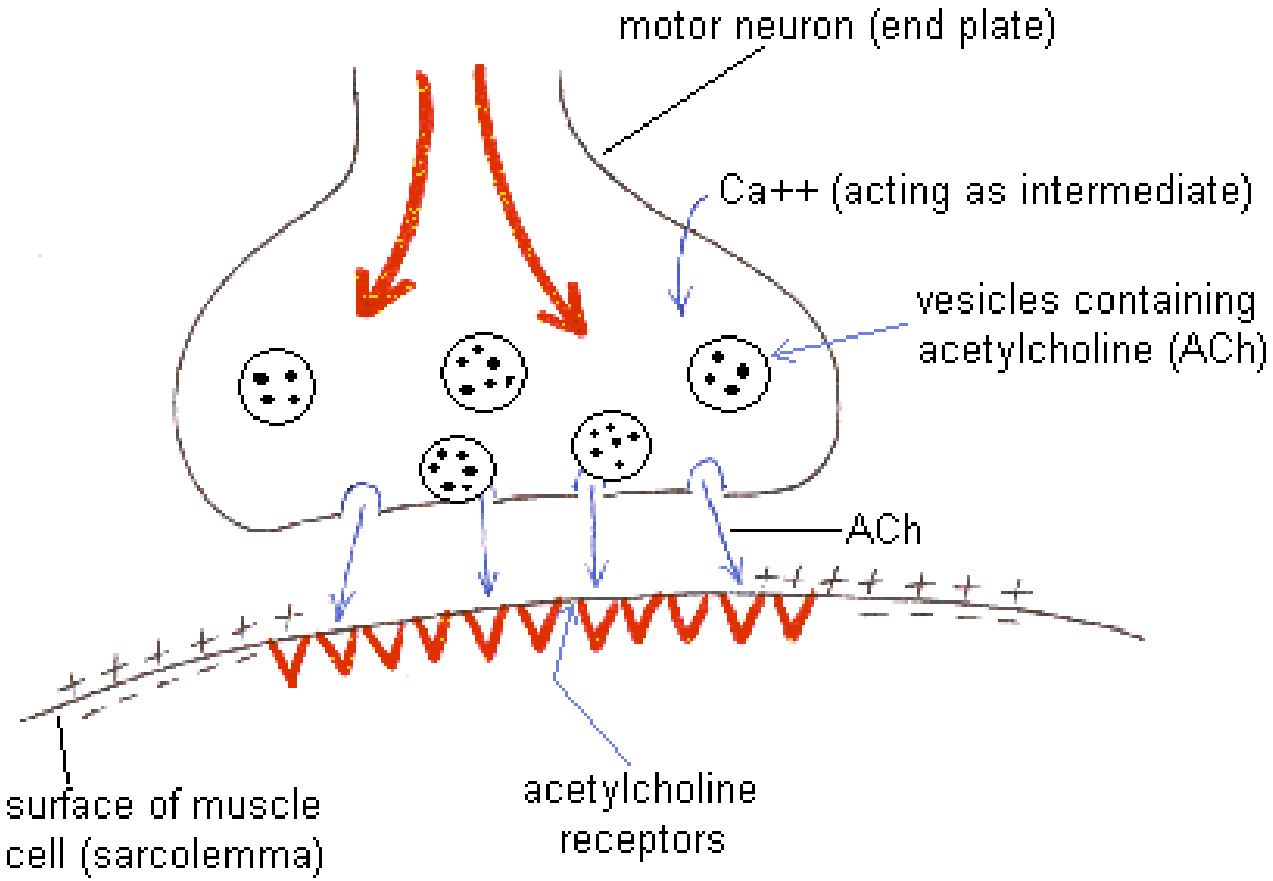
Clotting factors (thrombin, VII, IX and X) contain a unique modified glutamate residue, called carboxyglutamate (Gla).

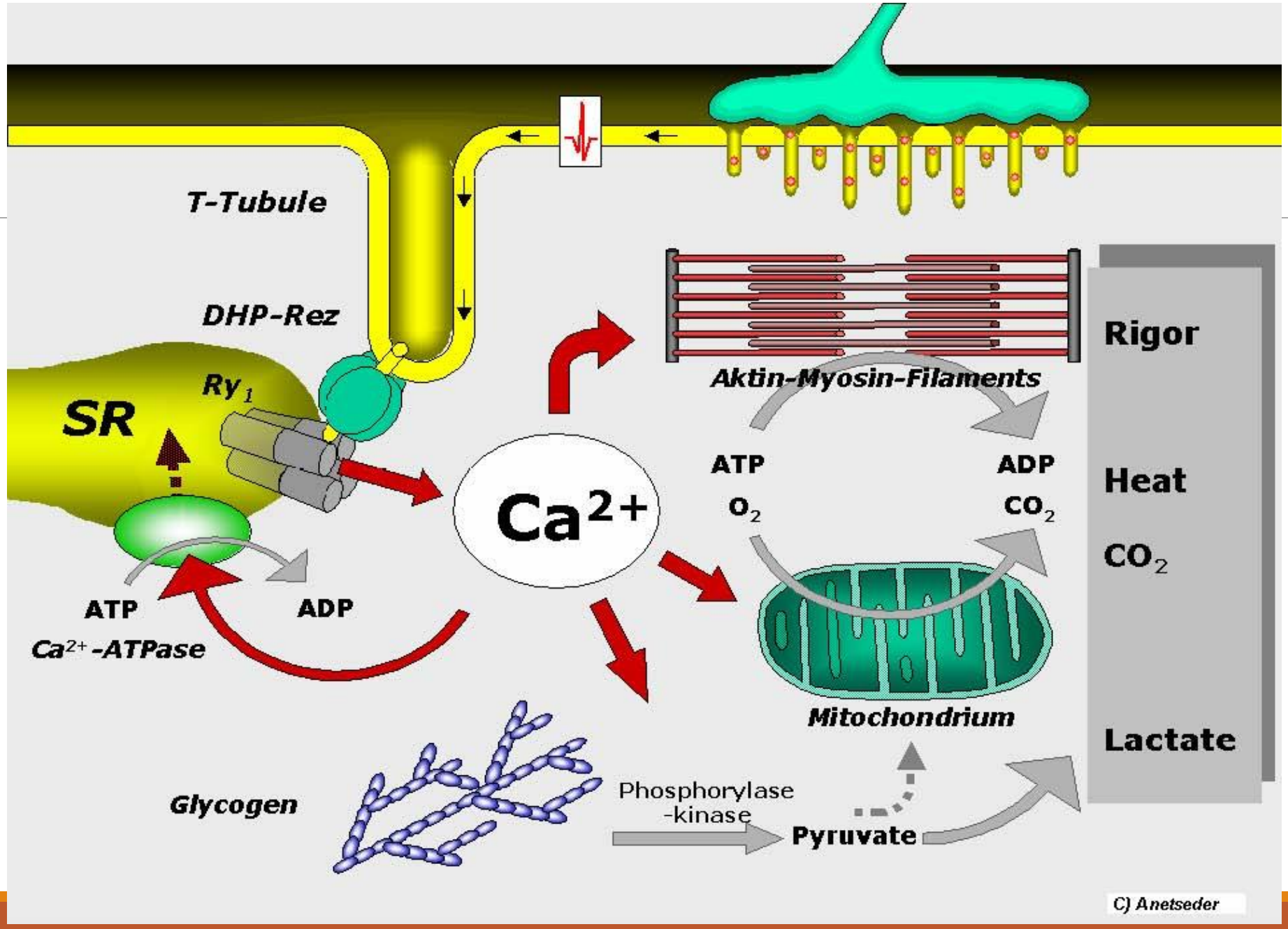
Synthesis of these Gla residues results from post-translational modifications of the newly synthesized factors in the liver endoplasmic reticulum by a vitamin K

This amino acid is a natural high affinity binder (or chelator) of calcium ions, hence the designation of calcium as a co-factor in the blood clotting cascade.

Calcium - Gla-factors complex allow specific interactions with acidic membrane lipids that ultimately lead to correct tertiary and quaternary protein structures recognized by other proteins in the pathway.

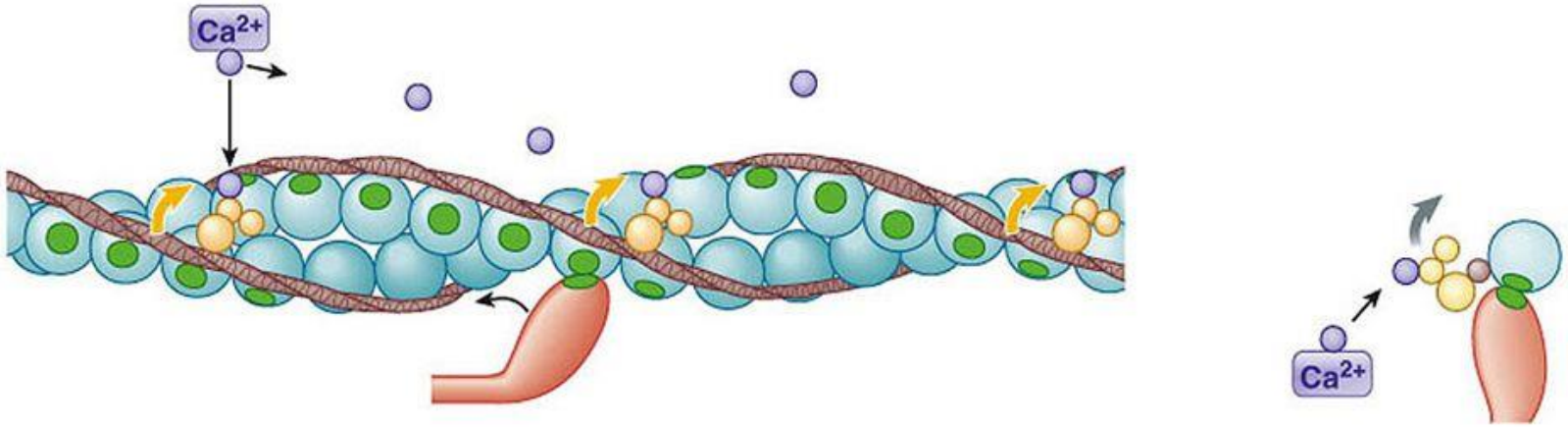
Neuromuscular transmission




T-Tubule
DHP-Rez
SR
Ry1
ATP
ADP
Ca2+-ATPase
Ca2+
Aktin-Myosin-Filaments
ATP
O2
ADP
CO2
Mitochondrium
Rigor
Heat
CO2
Lactate
Glycogen
Phosphorylase
-kinase
Pyruvate
C) Anetseder

Role of Calcium in Cross-Bridge Formation

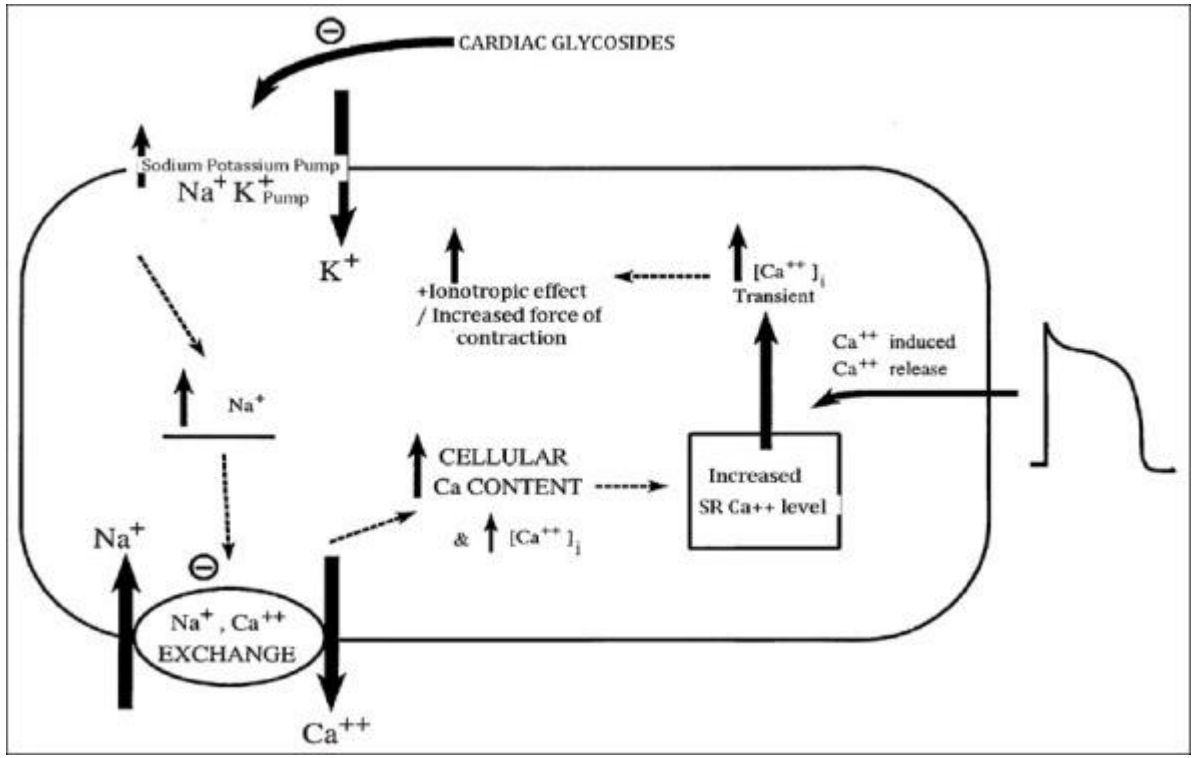
- Excited



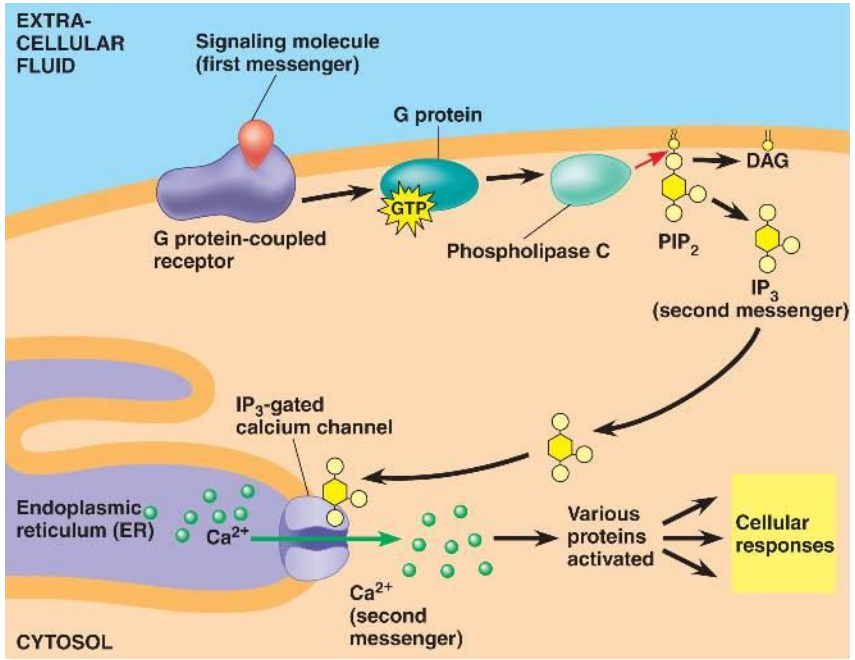
(b) Excited

1. Muscle fiber is excited and Ca^{2+} is released.
2. Released Ca^{2+} binds with troponin, pulling troponin-tropomyosin complex aside to expose cross-bridge binding site.
3. Cross-bridge binding occurs.
4. Binding of actin and myosin cross bridge triggers power stroke that pulls thin filament inward during contraction.

Mechanism of action of cardiac glycosides



Calcium as second messenger



The second messenger is calcium or phosphatidylinositols (or both)

Acetylcholine (muscarinic)

α_1-Adrenergic catecholamines

Angiotensin II

Antidiuretic hormone (vasopressin)

Cholecystokinin

Gastrin

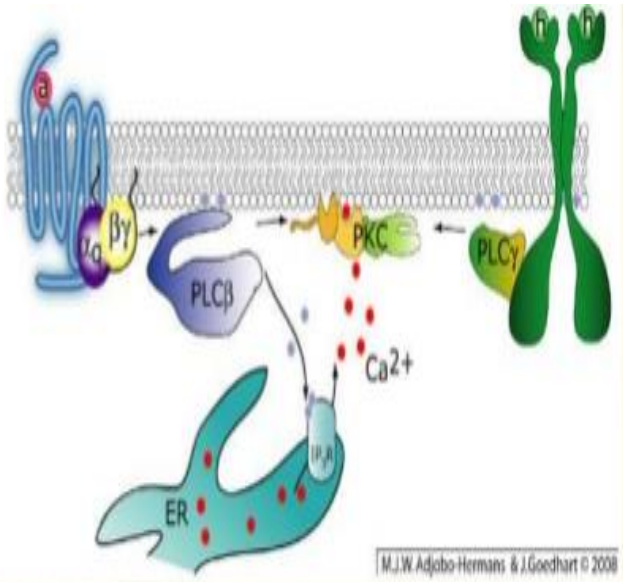
Gonadotropin-releasing hormone

Oxytocin

Platelet-derived growth factor (PDGF)

Substance P

Thyrotropin-releasing hormone (TRH)



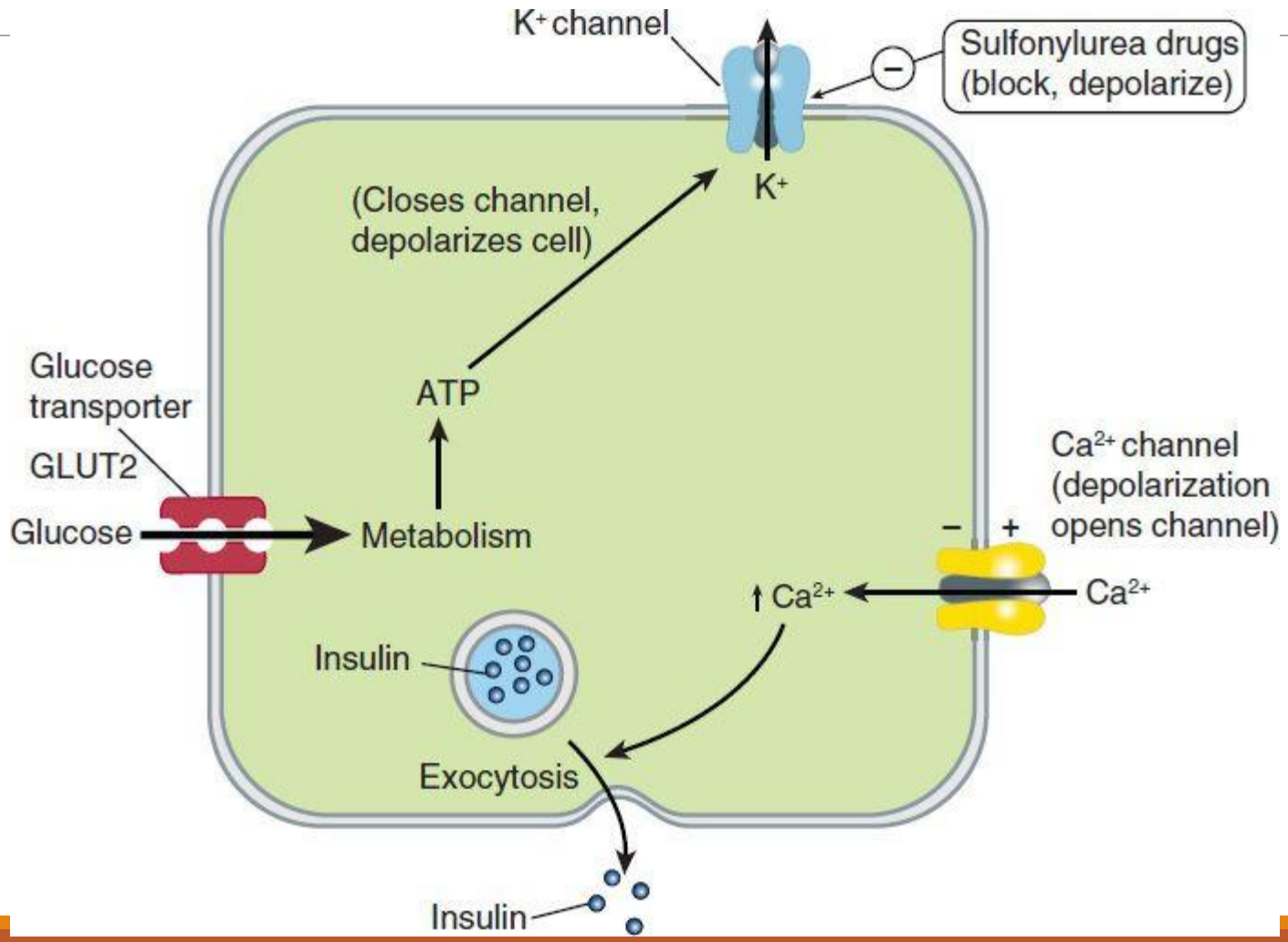
As 2nd messenger

Activation of enzymes- ATPase, Lipase, SDH

Release of Hormones- PTH, Calcitonin, Insulin, Vitamin D

Secretory process- Endocytosis, exocytosis, cell motility

Mechanism of action of Sulfonylurea drugs



Clinical Significance

Hypercalcemia

Hypocacemia

Hypercalcemia

TABLE 65-1 CAUSES OF HYPERCALCEMIA

- Excessive PTH production
  - Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
  - Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
  - Ectopic PTH secretion (very rare)
  - Inactivating mutations in the CaSR or in G proteins (FHH)
  - Alterations in CaSR function (lithium therapy)
- Hypercalcemia of malignancy
  - Overproduction of PTHrP (many solid tumors)
  - Lytic skeletal metastases (breast, myeloma)
- Excessive $1,25(OH)_2D$ production
  - Granulomatous diseases (sarcoidosis, tuberculosis, silicosis)
  - Lymphomas
  - Vitamin D intoxication
- Primary increase in bone resorption
  - Hyperthyroidism
  - Immobilization
- Excessive calcium intake
  - Milk-alkali syndrome
  - Total parenteral nutrition
- Other causes
  - Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
  - Medications (thiazides, vitamin A, antiestrogens)

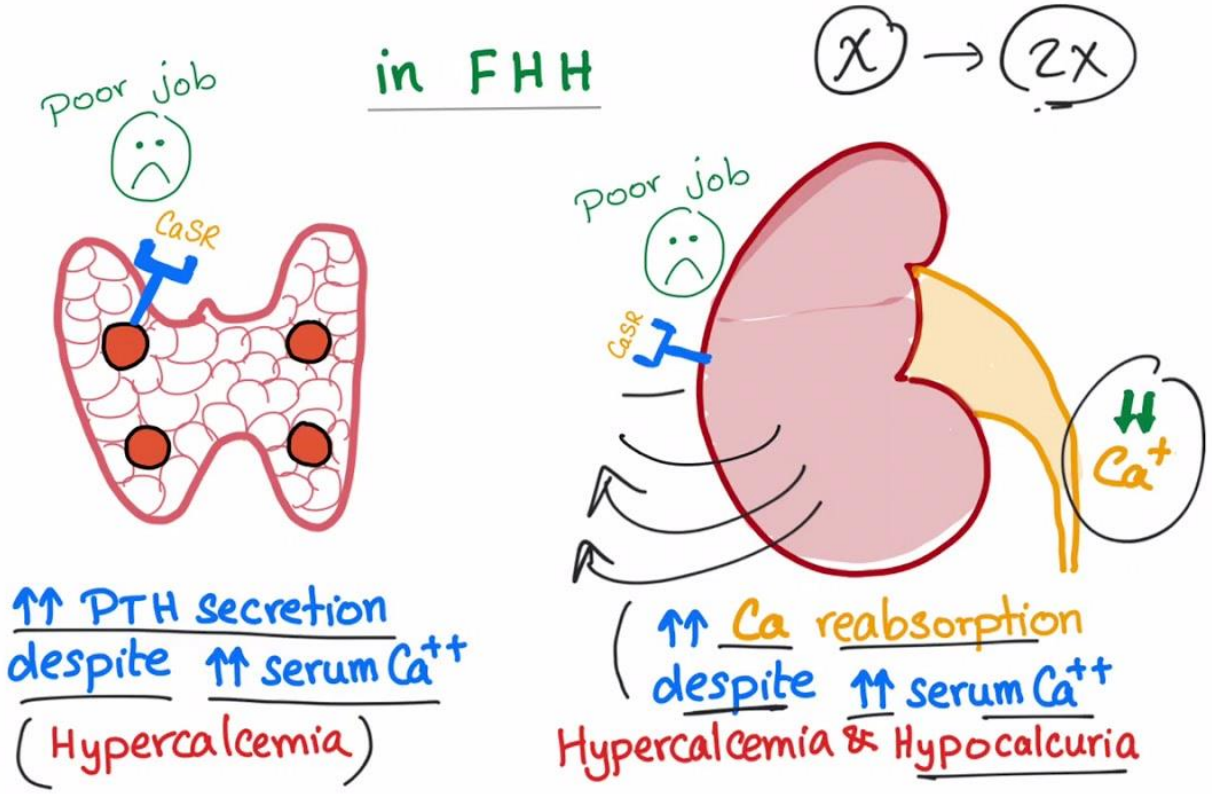
Hyperparathyroidism

Primary, Tertiary

Ectopic

Hypocalceuric hypercalcemia

? CaSR



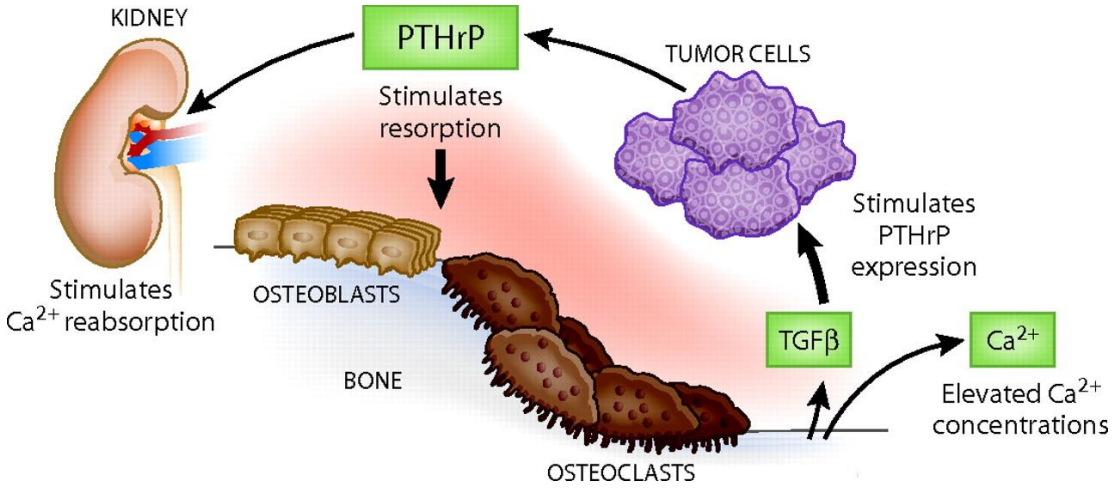
Hypercalcemia of malignancy

Types of Hypercalcemia of Malignancy

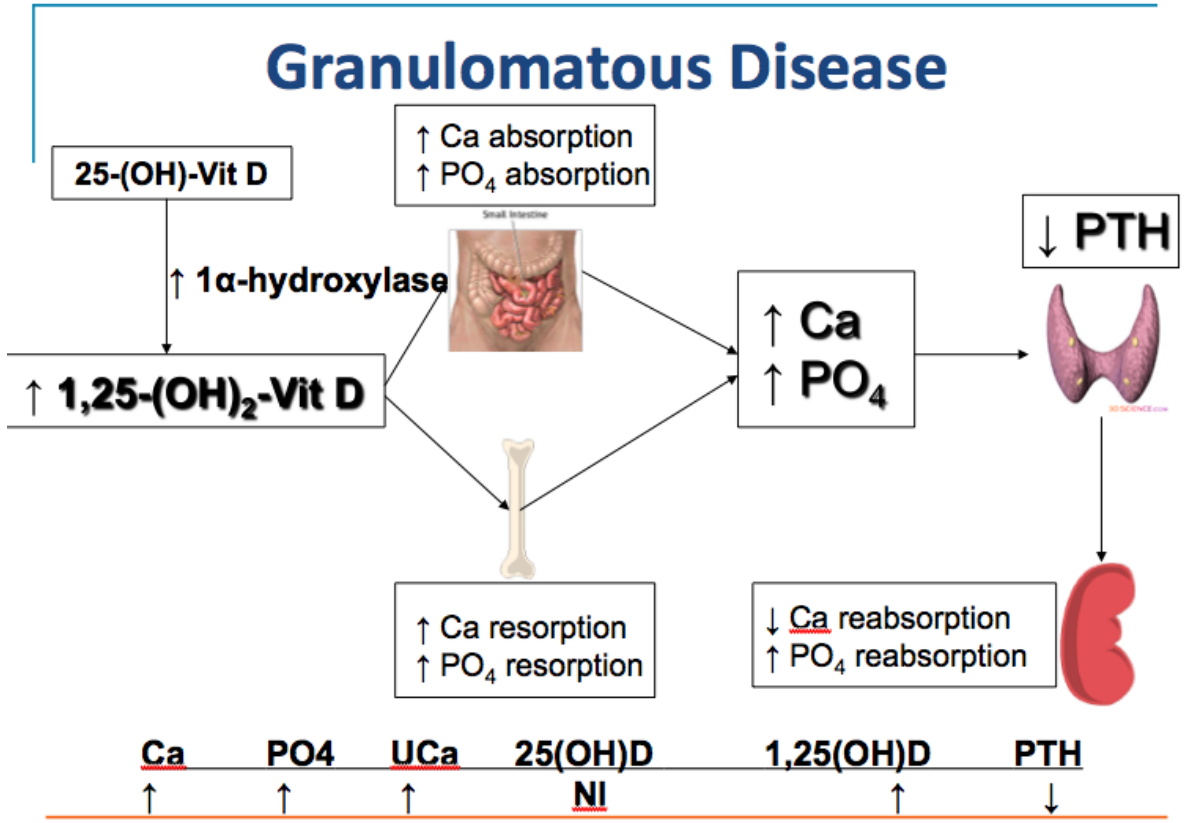
Table 1. Types of Hypercalcemia Associated with Cancer.*

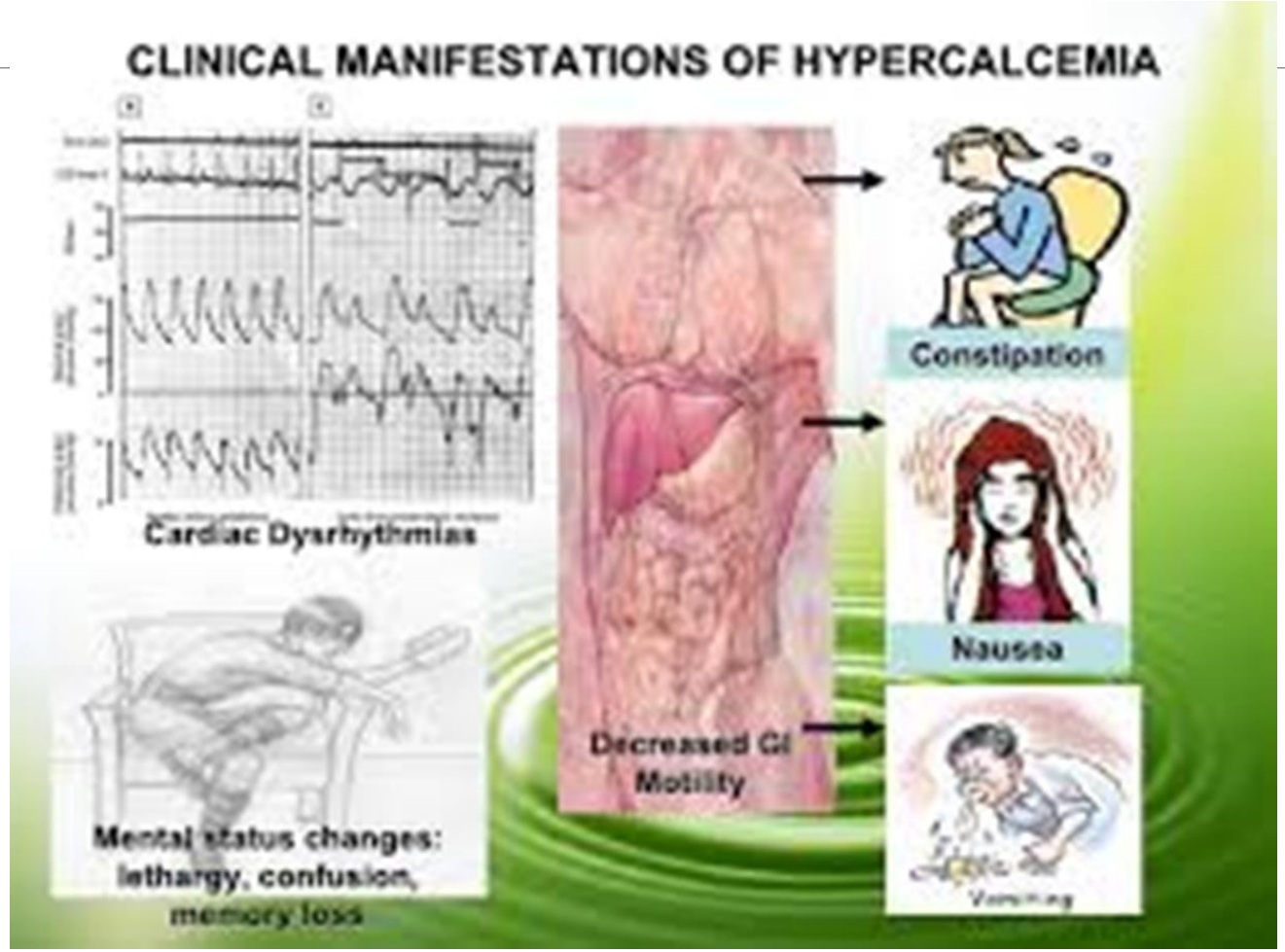
Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous cell cancer Renal cancer, Ovarian caner, Endometrial cancer, ATLL, Breast cancer
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemo-kines, PTHrP	Breast cancer, multiple myeloma, lymphoma

Stewart, A.F. (2005), *NEJM*, **352**, p.374.



Hypercalcemia of granulomatous disorders




CLINICAL MANIFESTATIONS OF HYPERCALCEMIA
Cardiac Dysrhythmias
Mental status changes:
lethargy, confusion,
memory loss
Decreased GI
Motility
Constipation
Nausea

Diagnostic approach to Hypercalcemia

Albumin concentrations

A detailed history

Serum PTH level and serum Phosphate

Serum creatinine and calcium/creatinine clearance ratio(<0.01 is suggestive of FHH)

sequence analysis of the CaSR gene

? A suppressed PTH level in the face of hypercalcemia

PTHrP

Serum 1 ,25(OH), vitD levels are increased in granulomatous disorders

Treatment

Volume expansion

Bisphosphonates

Hydrocortisone

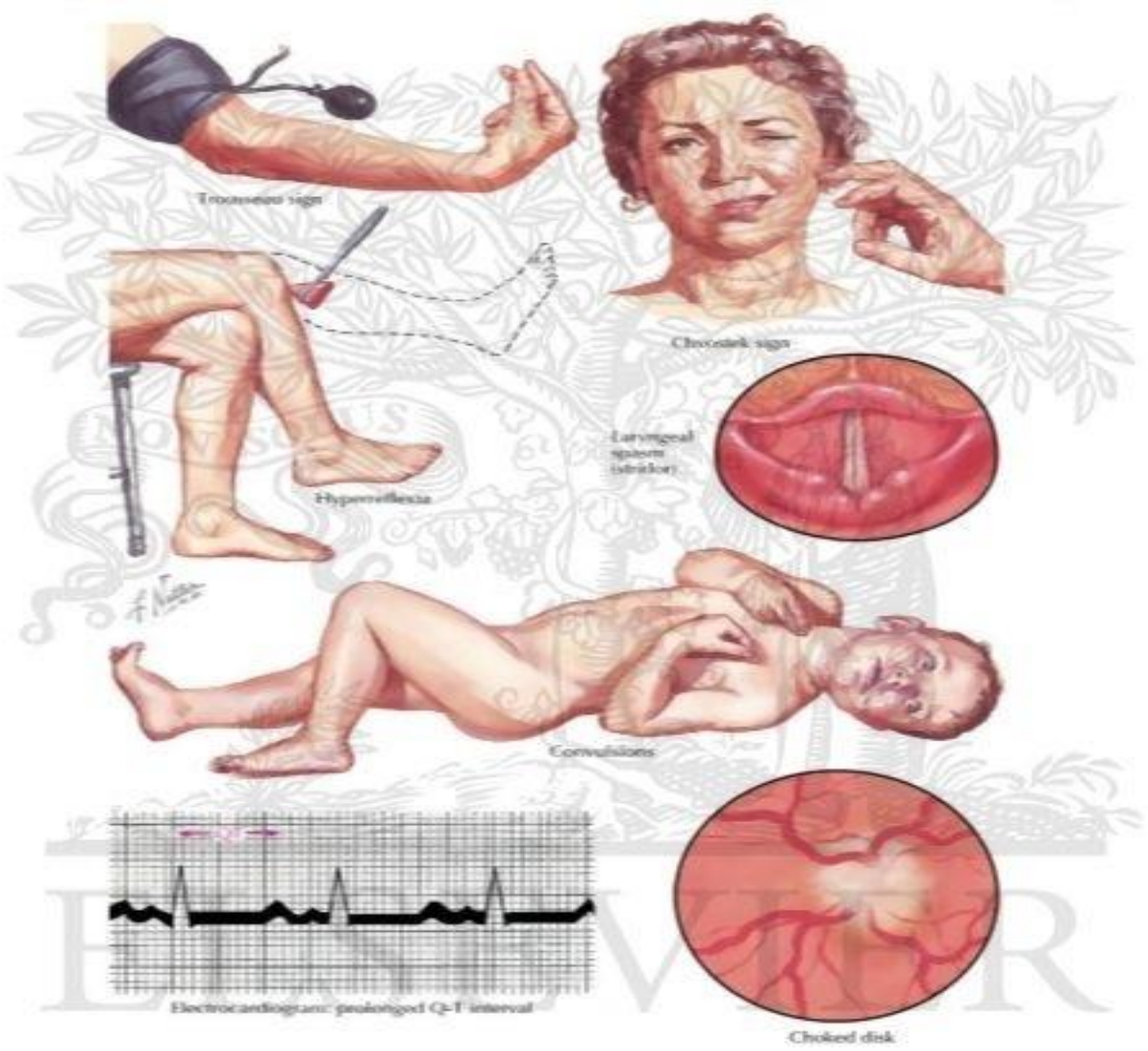
Hypocalcemia

TABLE 65-2 CAUSES OF HYPOCALCEMIA

Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated
DiGeorge's syndrome
Parathyroid destruction
Surgical
Radiation
Infiltration by metastases or systemic diseases
Autoimmune
Reduced parathyroid function
Hypomagnesemia
Activating CaSR or G protein mutations

High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)
Vitamin D deficiency or impaired $1,25(OH)_2D$ production/action
Nutritional vitamin D deficiency (poor intake or absorption)
Renal insufficiency with impaired $1,25(OH)_2D$ production
Vitamin D resistance, including receptor defects
Parathyroid hormone resistance syndromes
PTH receptor mutations
Pseudohypoparathyroidism (G protein mutations)
Drugs
Calcium chelators
Inhibitors of bone resorption (bisphosphonates, plicamycin)
Altered vitamin D metabolism (phenytoin, ketoconazole)

Tetany



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Diagnostic evaluation

Albumin, Phosphorus and Magnesium levels

PTH level

History

serum 25-hydroxyvitaminD levels

Treatment

Iv Ca gluconate

Oral Calcium and vitamin D supplements

Treatment

Acute

i.v. calcium gluconate

Magnesium supplementation

Chronic

Calcium supplements and either vitamin D, or D3


Thank you