Calcium Metabolism

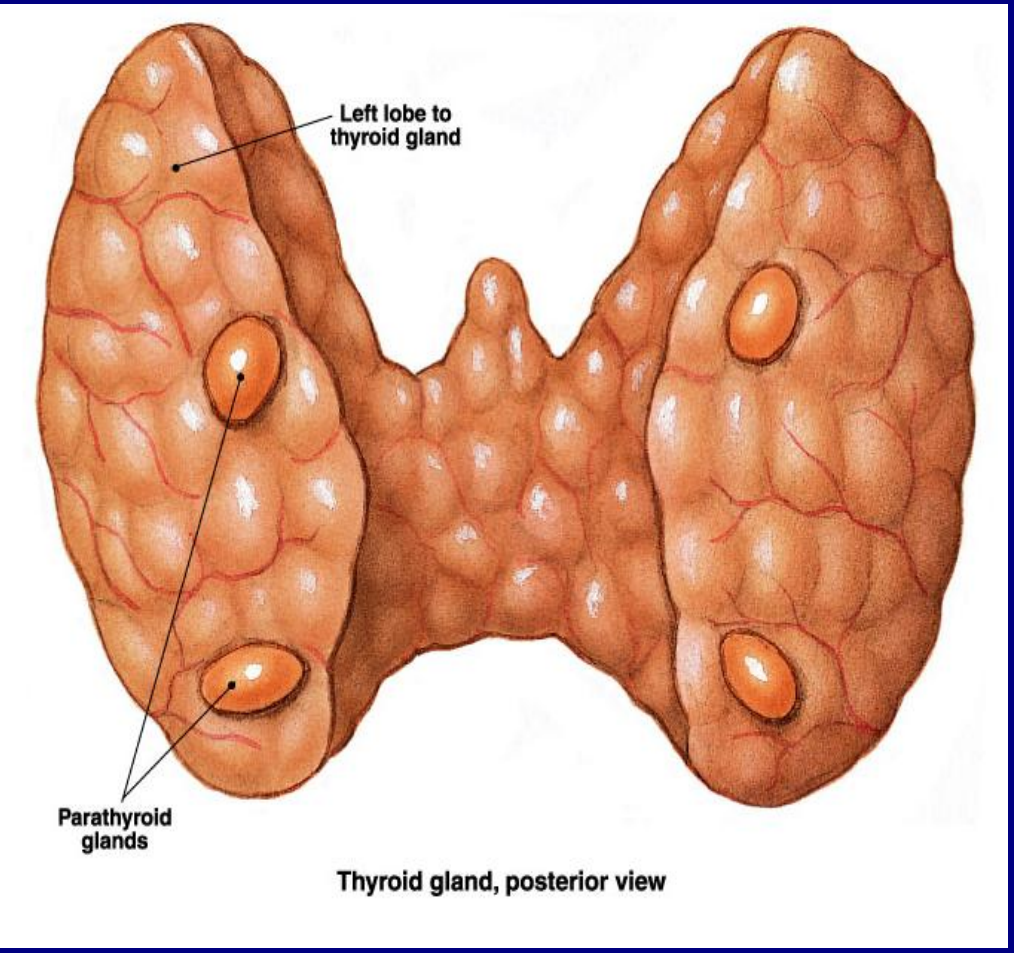
Extra cellular Ca

- 8.5-10.5 mg/100 ml
- Only ionized calcium [Ca^{++}] (50% of total) is regulated; 40% bound to albumin; 10% complexed to phosphate and citrate.
- Excitation – contraction of heart and other muscles, secretion, synaptic transmission, platelet aggregation, coagulation.

Intracellular Ca

- Second messenger, cell division, muscle contraction, cell motility, membrane trafficking and secretion.

Parathyroid Glands



- The parathyroid glands are small in size and are found on the posterior aspect of the thyroid gland.
- Typically, there are four of them but the actual number may vary.

Calcium Metabolism

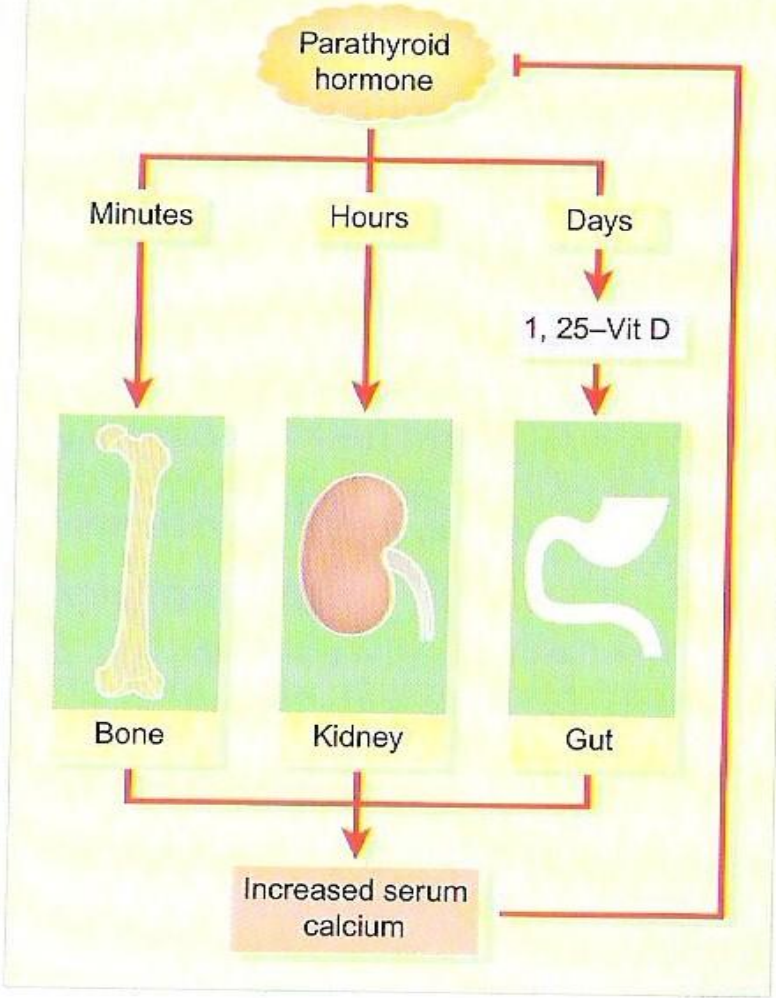
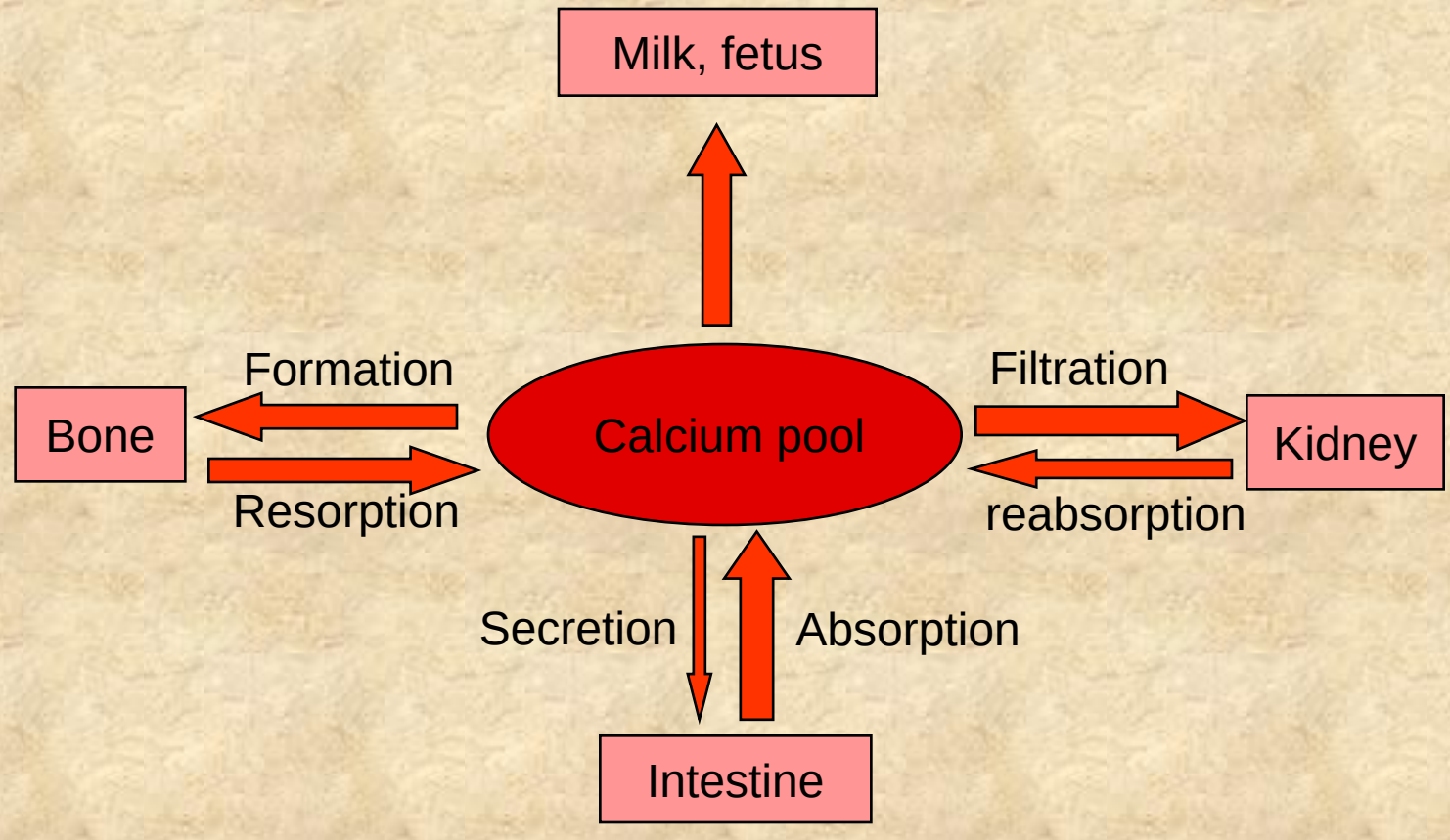


Fig. 1 **Calcium homeostasis and parathyroid hormone feedback.**

Calcium Homeostasis

- Maintain [Ca^{++}] ECF.
- Requires parathyroid hormone (PTH) and Vit. D.
- Regulate Ca exchange: the gut, bone, renal tubule.

Calcium Flow



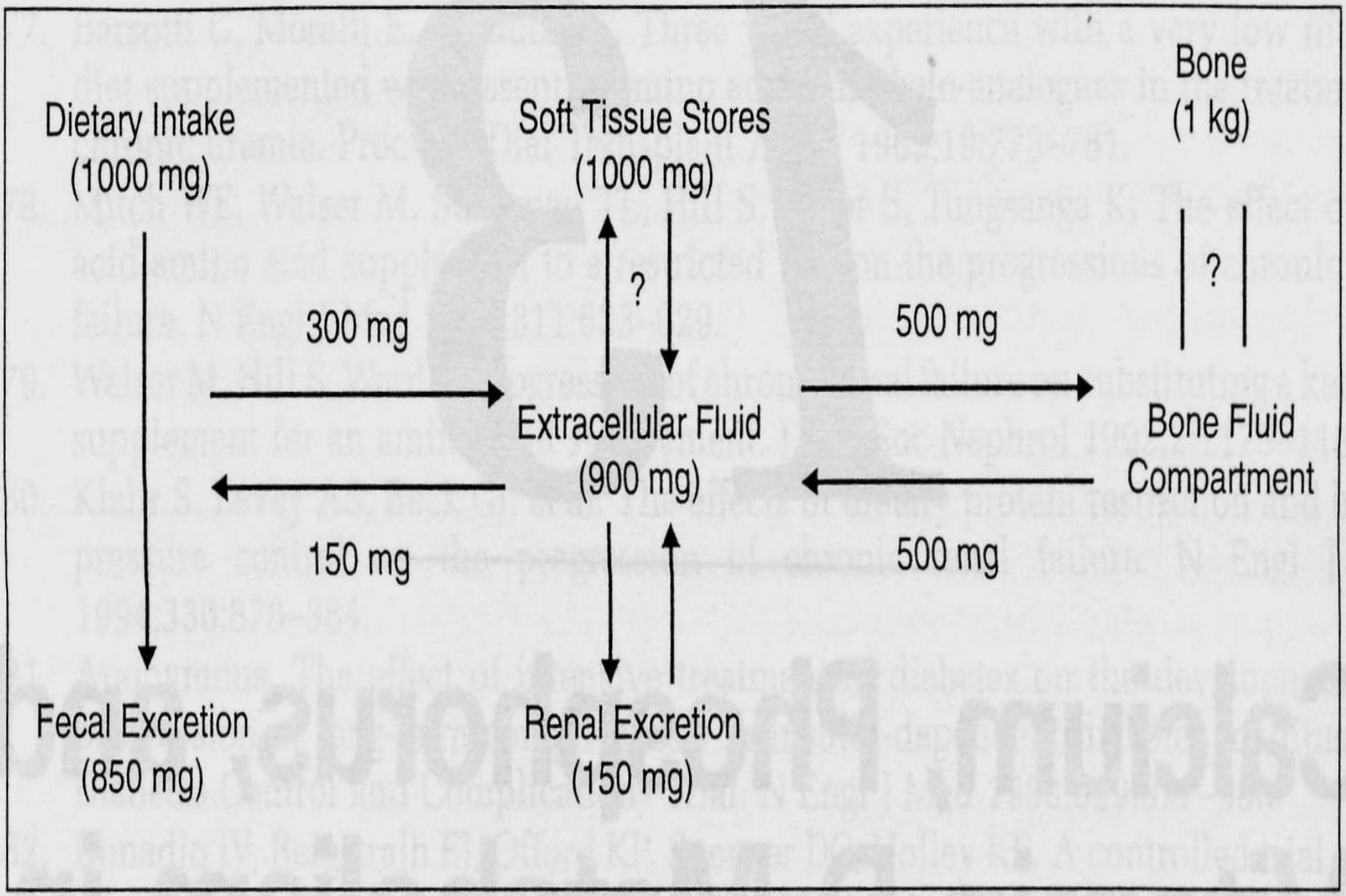


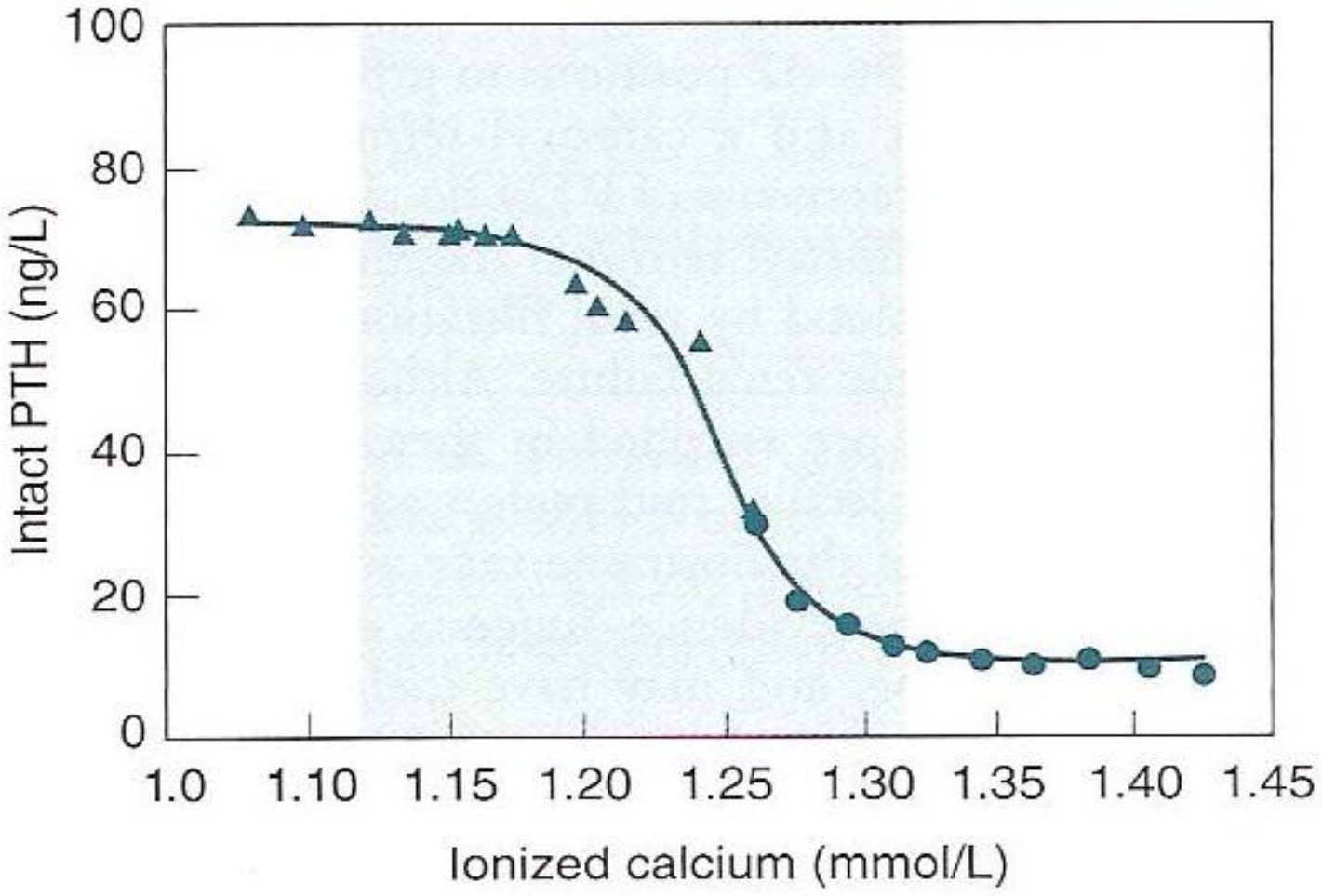
Figure 13.1. Diagrammatic representation of normal adult calcium balance.

Parathyroid Hormone [PTH]

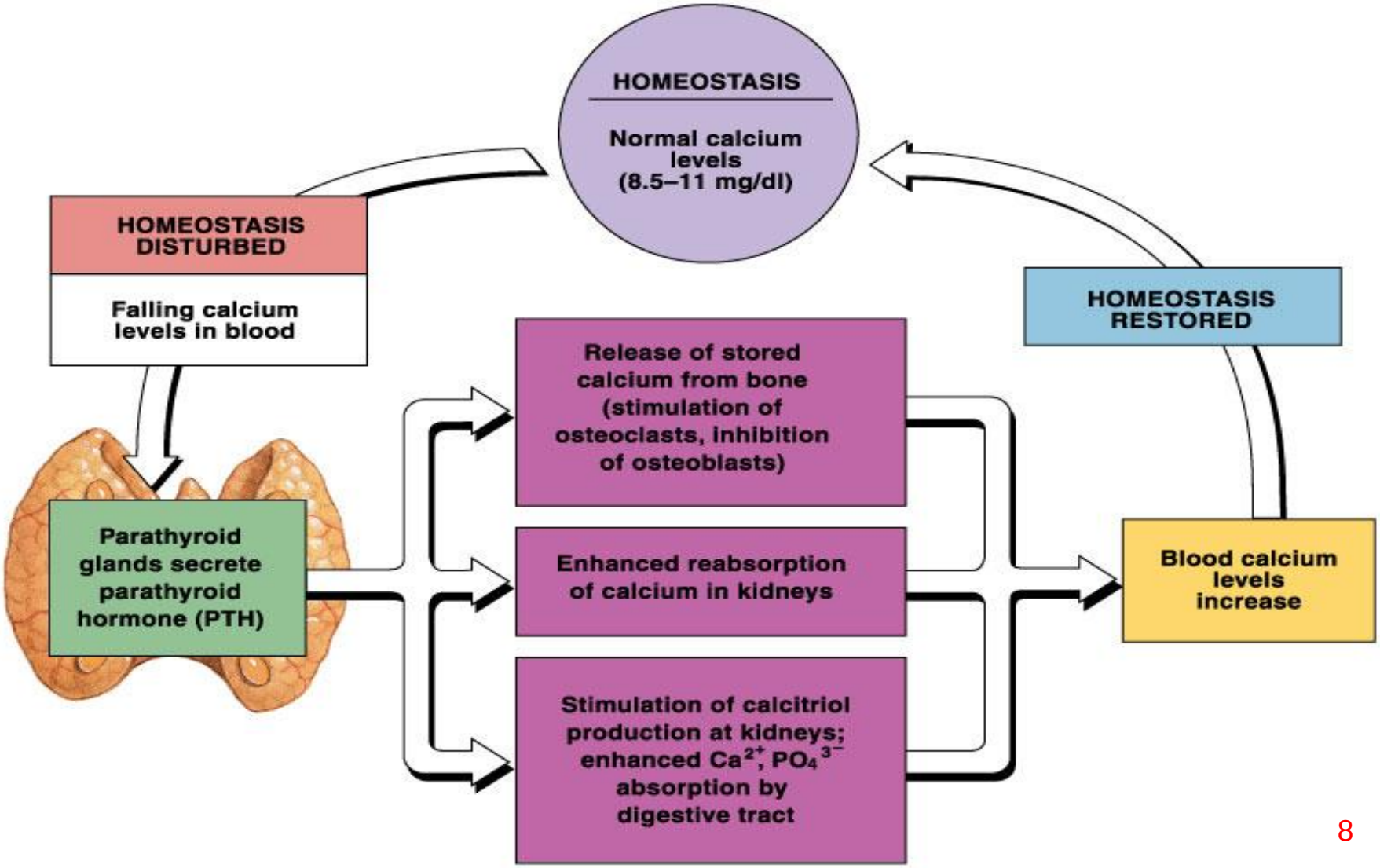
Secretion of PTH: Role of serum Ca^{++}

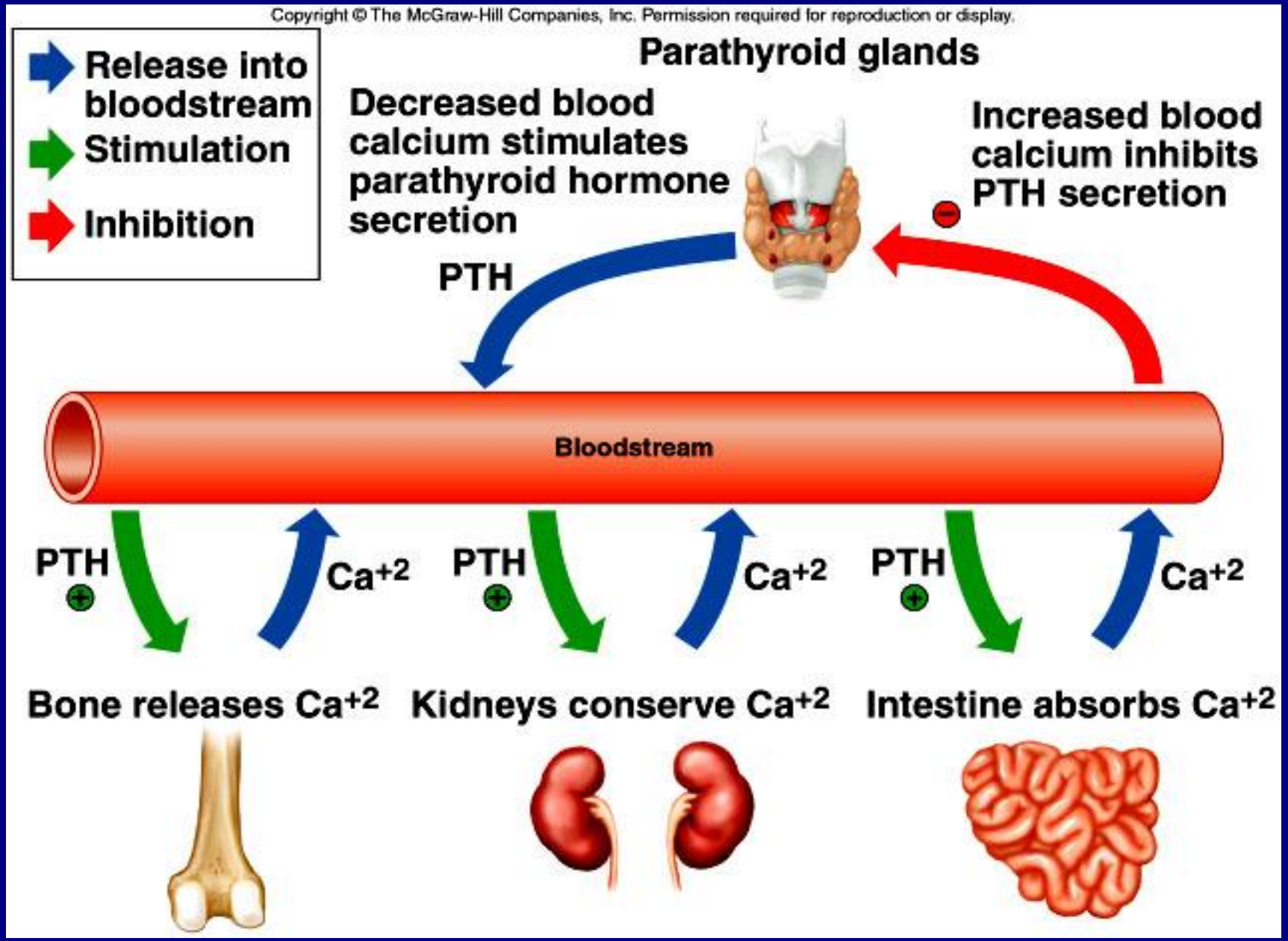
- Ca^{++} negatively feedback inhibits PTH (sigmoidal)
- Ca receptor: G protein coupled (Gq) $PIP_2 \rightarrow IP_3 \rightarrow$ ↑ Ca influx, ↑Ca release from stores → ↑ $[Ca^{++}]i \rightarrow$ ↓ PTH secretion [Mg++ - mediated process].
- Low $Ca^{++} \rightarrow$ ↑ prepro-PTH mRNA stabilization, ↑ Gene transcription
- Vit. D → ↓ PTH gene transcription

Serum Ca^{++} and PTH secretion



Calcium Homeostasis: Role of PTH





Parathyroid hormone (PTH) stimulates bone to release calcium (Ca+2) and the kidneys to conserve calcium. It indirectly stimulates the intestine to absorb calcium. The resulting increase in blood calcium concentration inhibits secretions of PTH

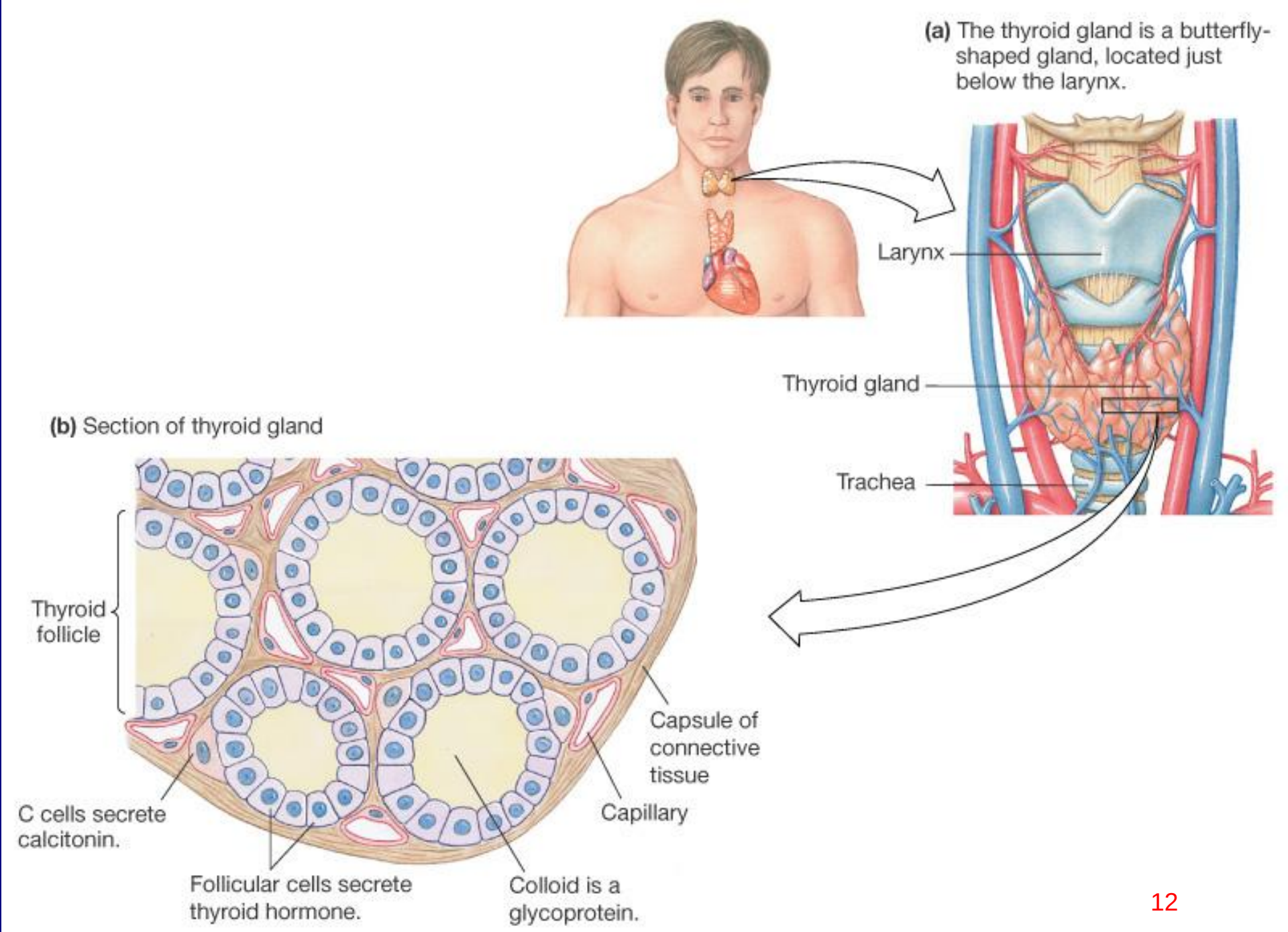
Mechanism of Action of PTH

- PTH receptor -1 (kidney and bone): recognizes PTH and PTH related Protein (PTH-rP).
- PTH receptor-2: PTH only.
- G_s: ↑ cAMP (Calcium homeostasis, phosphate excretion).
- G_q: ↑ PLC → ↑ [Ca^{++}] → ↑ protein kinas C.

Calcitonin

Structure

- Peptide: 32 amino acids.
- Secreted by: parafollicular C cells of the thyroid



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Calcitonin

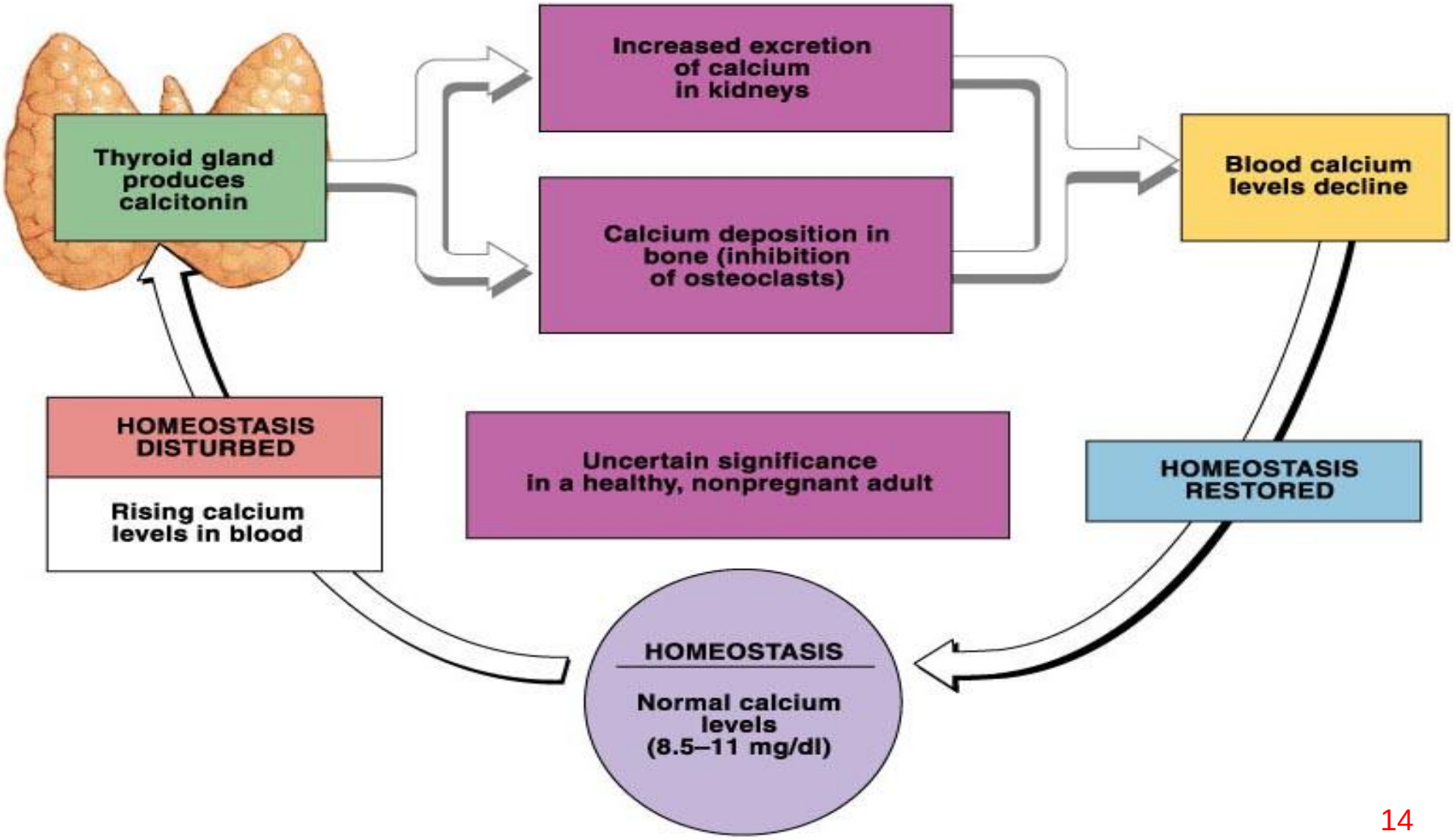
Function

- No physiologic role.
- Removal of thyroid: no impact on Calcium.
- ↑ Calcitonin by thyroid carcinoma: no effect on Calcium homeostasis.

Clinical

- Tumor marker in thyroid carcinoma.
- Therapeutic: inhibitor of osteoclastic bone resorption. Treatment of hypercalcemia and osteoporosis.

Calcium Homeostasis: Role of Calcitonin



Vitamin D

Chemistry

- Vitamin D (calciferol): D_2 (ergocalciferol) + D_3 (cholecalciferol).
- Vit. D_3 is produced from 7-delydrocholesterol (skin).

Dietary Source

- Dairy products supplemented with vit. D.
- Fish-oils, fish liver, eggs.
- RDA: 400 units (1U = 0.025 mg vit. D)

Vitamin D …

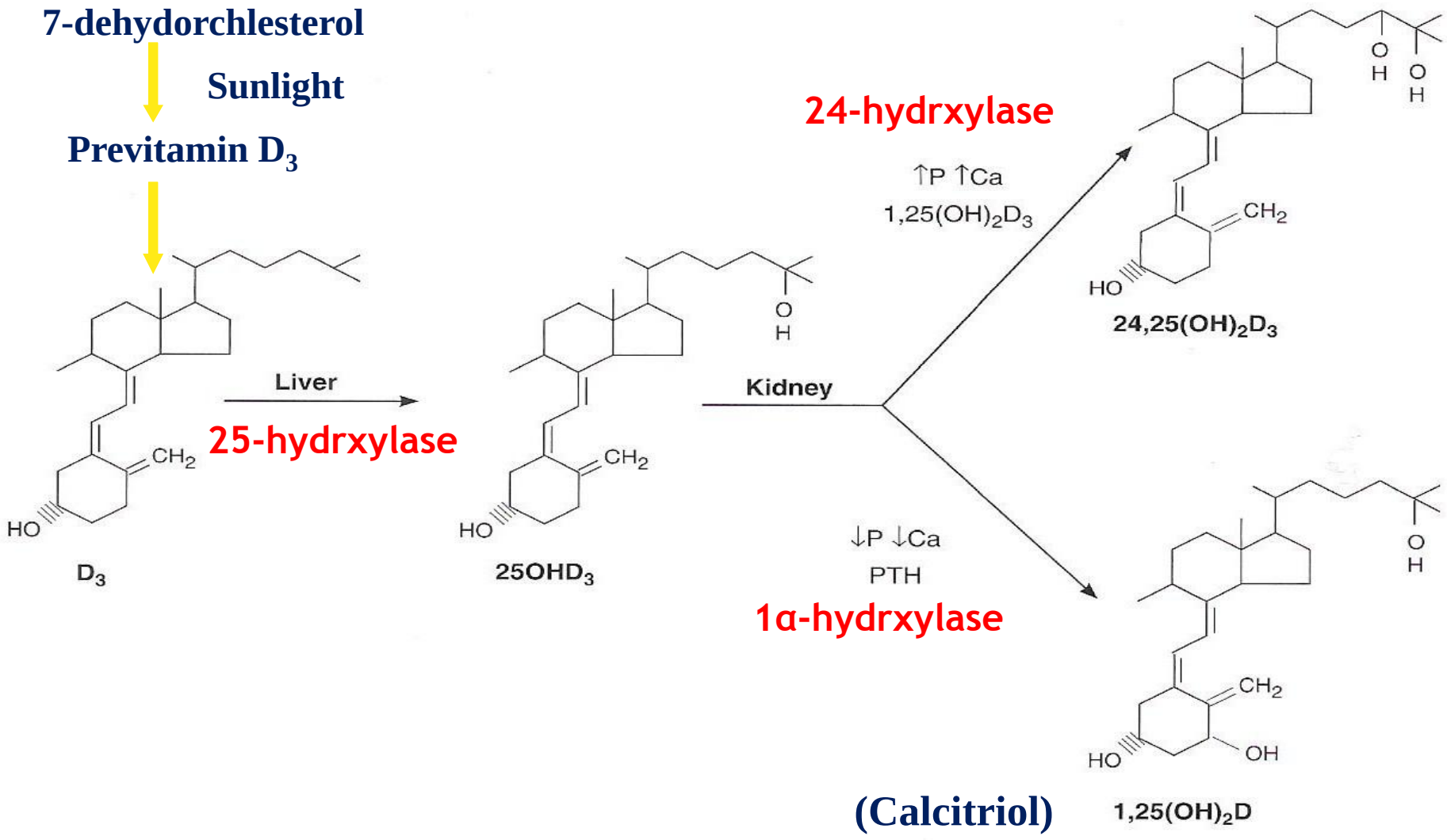


Figure 8–9. The metabolism of vitamin D. The liver converts vitamin D to 25(OH)D. The kidney converts 25(OH)D to $1,25(OH)_2D_3$ and $24,25(OH)_2D$. Control of metabolism is exerted primarily at the level of the kidney, where low serum phosphorus, low serum calcium, and high parathyroid hormone (PTH) levels favor production of $1,25(OH)_2D_3$.

Vitamin D …

Binding Proteins

- Vit. D Binding Protein (DBP) 85%, albumin 15%

Metabolism

- Vit. D → 25(OH) D in liver.
- Kidney: 25(OH) D_3 → 1,25$(OH)_2$ D_3 (stimulated by PTH) or 24,25 $(OH)_2$ D_3.

Vitamin D Effects

a. Intestinal Calcium Transport: 1,25 $(OH)_2D_3$

- Entrance of Ca across brush border membrane: ↑ calcium channel (CaT1) in brush border membrane.
- Passage Ca transport through cytosol: ↑ calbindin.
- Removal from cell across basolateral membrane: ↑ Ca^{++} ATPase (Ca pump).

Vitamin D Effects …

b. Action of Vitamin D on Bone

- 1,25 $(OH)_2$ D_3 regulates bone formation + resorption.
- Deficiency 1,25 $(OH)_2$ D_3: Rickets.
- Type 1 (Vit. D- dependent, pseudo vitamin D deficient). Treated with calcitriol.
- Type 2 (Vit. D-dependent, hereditary 1,25 $(OH)_2$ D_3 – resistant). Treated with Ca and phosphate.

In organ culture of bone:

- Bone resorption: best established action.
- ↑ Osteoclast, ↓ collagen synthesis.
- Osteoblast differentiation: less clear, depend on stage.
  - Early stage : ↑ collagen, alkaline phosphate.
  - Mature osteoblasts: ↓ collagen ↓ alkaline phosphate.

Vitamin D Effects …

c. Action of Vitamin D Kidney

- 1,25 $(OH)_2$ D_3 ↑ calbindin and Ca-ATPase in distal tubule.
- Role of 1,25 $(OH)_2$ D_3 in Ca and PO_4 transport (controversial) 25$(OH)D_3$ may be more important.

Vitamin D Effects …

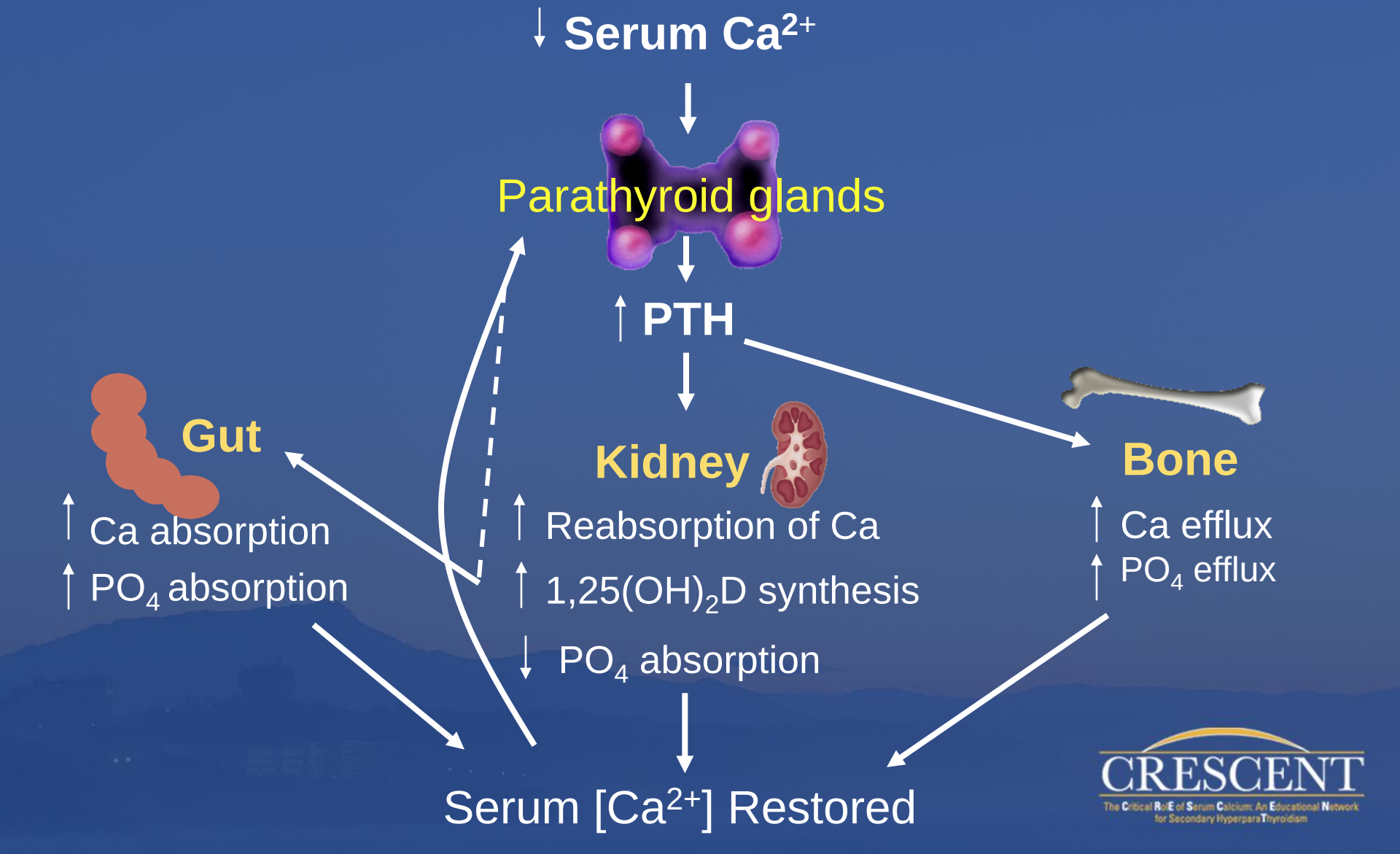
- Malignancies (anti proliferating actions of 1,25 $(OH)_2$ D_3
- Vitamin D analogs: treatment of hyperparathyroidism and osteoporosis.

Integrated Control of Mineral Homeostasis

↓ Ca level leads to

- **↑ PTH**
  - ↑ Ca, PO_4 release from bone.
  - Retention of Ca by the kidney, PO_4 excretion.
- **↑ 1,25 $(OH)_2$ D_3**
  - ↑ Ca absorption.
  - ↑ bone resorption.

PTH Primarily Regulates Calcium With Secondary Effects on Phosphorus



CRESCENT
The Critical RolE of Serum Calcium: An Educational Network for Secondary HyperparaThyroidism

Hypercalcemia

Clinical Features

CNS effects, neuromuscular effects, cardio-vascular effects, renal effects, G.I. effects, eye effects, calcification

Mechanisms

1. ↑ G.I absorption of Ca.
2. ↑ Bone resorption (Common)
3. ↓ Renal excretion of Ca

Hypercalcemia Disorders

Primary Hyperparathyroidism

Excessive secretion of PTH, 2-3x in women as in men

Etiology

- Parathyroid carcinoma
- Parathyroid hyperplasia

Primary Hyperparathyroidism …

Clinical Features

1. **Bone disease:**

   Osteitis fibrosa cystica: bone pain, fracture

   Osteoporosis: loss of cortical bone

2. **Kidney disease:**

   Kidney stones (15% of cases): Ca oxalate

   Compromise renal concentrating ability: polyuria

3. **Nonspecific features:**

   Coma, CNS mild impairment

Lab. Findings: ↑Ca, ↓PO_4,↑PTH

Hypocalcemia

Classification

1. PTH: Failure to secrete or respond to PTH.
2. Vitamin D: deficiency of vitamin D or failure to respond vitamin D.

Hypocalcemia …

Clinical Features

- ↑ Neuromuscular excitability: Tetany, paresthesias, seizures.
- Ca deposition in soft tissues: Cataract, calcification of basal ganglia.
- Cardiac effects: Prolonged QT interval,

  Impaired excitation–contraction coupling.
- Dermatologic effects: Dry and flaky skin, brittle nails.

Causes of Hypocalcemia

1. Hypoparathyroidism

Causes

- Surgical: Neck surgery (cancer surgery, total thyroidectomy or parathyroidectomy)
- Idiopathic: polyglandulor endocrinopathies.
- Familial Hypoparathyroidism
  - PTH gene mutations: affect PTH processing.
  - Parathyroid Ca - sensing receptor gene mutations: active receptor suppresses PTH at low or normal Ca levels.

Causes of Hypocalcemia …

1. Hypoparathyroidism …

Other causes of Hypoparathyroidism

- Thalassemia: Fe deposition in the glands.
- Cu deposition in Wilson's disease.
- Al deposition.
- Mg depletion: prevents PTH secretion and action (G.I. and renal disorders, alcoholism).

Causes of Hypocalcemia …

2. Pseudohypoparathyroidism

Causes

- PTH resistance of target tissues: hypocalcemia, hyperphosphatemia, elevated PTH

Causes of Hypocalcemia …

3. Vitamin D Deficiency

- **Pathogenesis**

  Inadequate sunlight exposure, inadequate nutrition, malabsorption.

- **Clinical Features**

  Osteomalacia and rickets, low serum Ca and PO_4.

  Low 25 (OH) D (diagnostic), normal 1,25 $(OH)_2$ D_3.

- **Treatment**

  Vitamin D supplemented with Ca.

Causes of Hypocalcemia …

4. Vitamin D-Dependent Rickets Type 1

- Low levels of 1,25 $(OH)_2$ D_3
- Mutation in 1-hydroxylase.
- Treatment : calcitriol

5. Vitamin D-Dependent Rickets Type II

- Hereditary 1,25 $(OH)_2$ D_3 – resistant rickets
- High 1,25 $(OH)_2$ D_3
- Mutations in VDR gene
- Treatment: large doses of calcitriol and dietary Ca

Causes of Hypocalcemia …

6. **Other Hypocalcemic Disorders:**
    1. **Hypoalbuminemia.**
    2. **Transfusion of Citrate Blood.**

Bone Anatomy and Remodeling

Functions of Bone

1. Support of extremities and body cavities.
2. Locomotion (levers, sites of attachment to muscles)
3. Reservoir of ions: Ca, PO_4, Mg, Na.

Bone Anatomy and Remodeling …

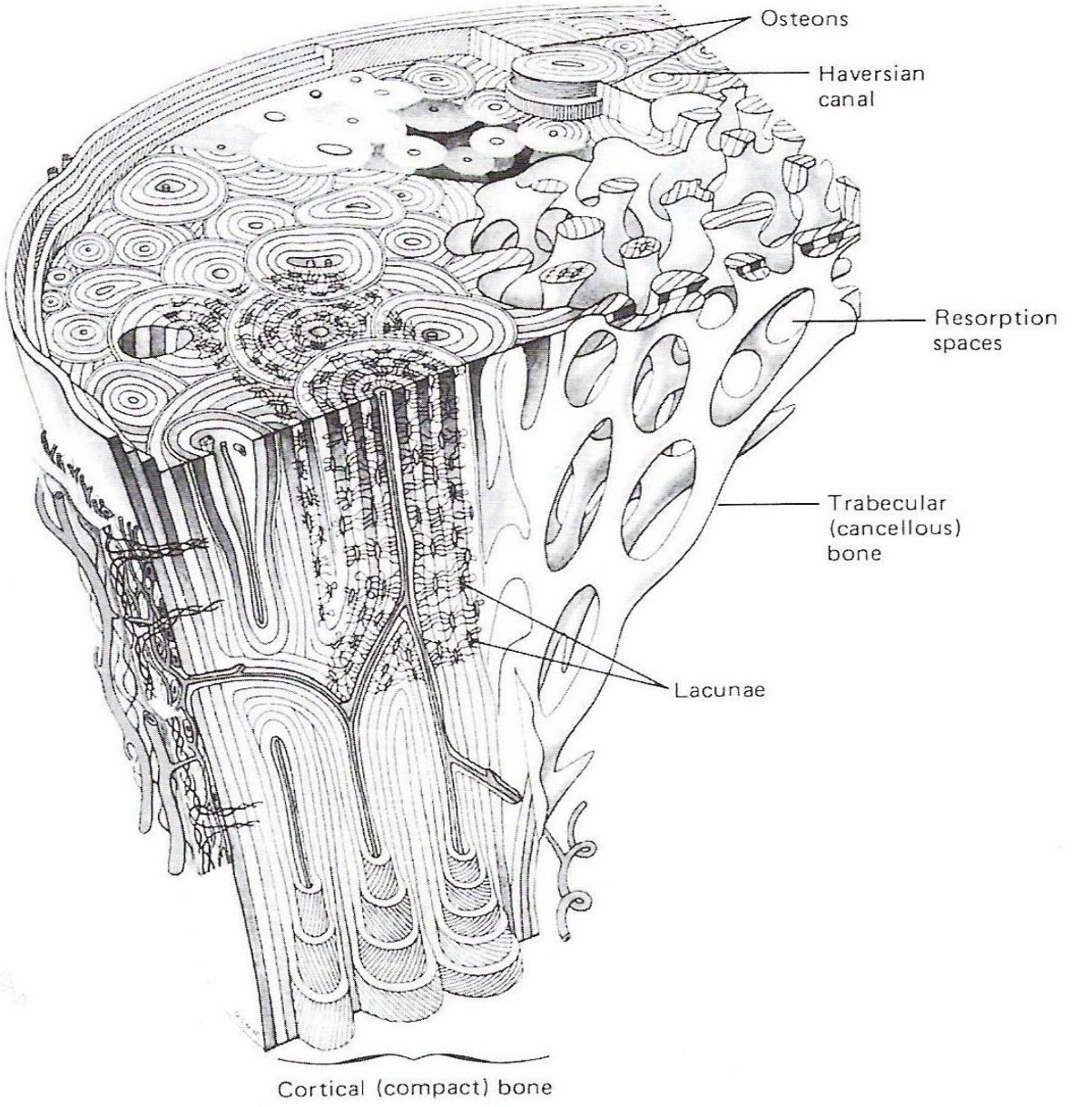
Structure of Bone

- Mineralized collagen: rigidity.
- Trabecular (cancellous): strength and elasticity.
- Bone weight: ⅔ Minerals, ⅓ (collagen + H_2O).

Bone minerals

- Hydroxyapatite
- Amorphous Ca, PO_4 (active bone formation, young bones)

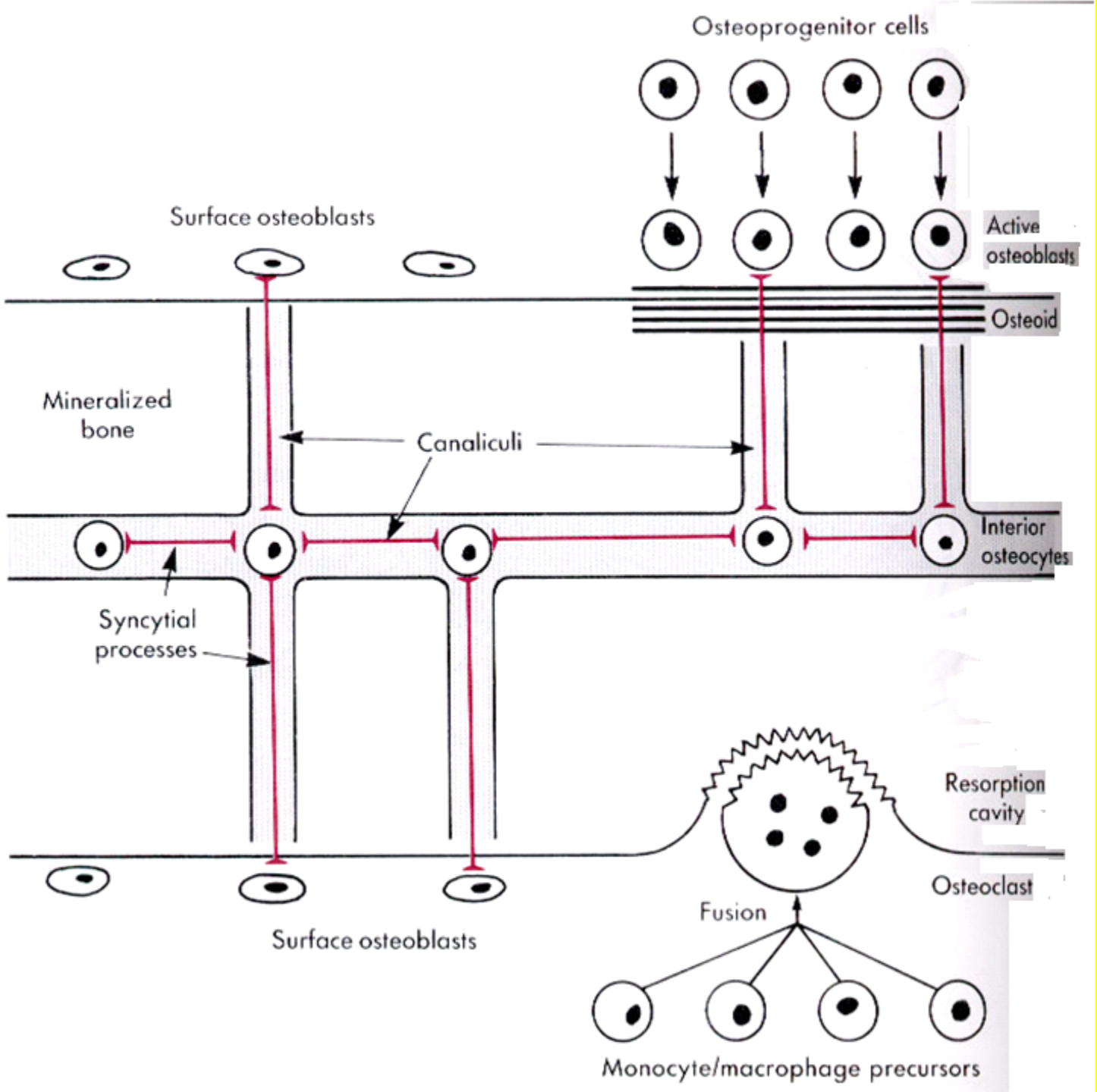
Bone Structure



Bone Cells

1. Osteoblast: Bone–forming cell

- PTH and vitamin D receptors. Alkaline phosphatase required.
- Bone matrix protein genes: type1 collagen, osteocalcin
- Mineralization: deposition of hydroxyapatite on collagen layers, Ca, PO_4, alkaline phosphatase


Osteoprogenitor cells
Surface osteoblasts
Active osteoblasts
Osteoid
Mineralized bone
Canaliculi
Interior osteocytes
Syncytial processes
Resorption cavity
Osteoclast
Fusion
Surface osteoblasts
Monocyte/macrophage precursors

Bones cells

Bone Cells …

2. Osteocyte:

- Trapped osteoblasts during remodeling.
- Translocation of mineral in and out of removed bone regions.

Bone Cells …

3. Osteoclast: bone resorption cell

- Secretes acid, proteases.
- Regulation of bone resorption: number and activity of osteoclasts.
- Receptors for calcitonin, not PTH or vitamin D.

Osteoclasts: Bone resorption

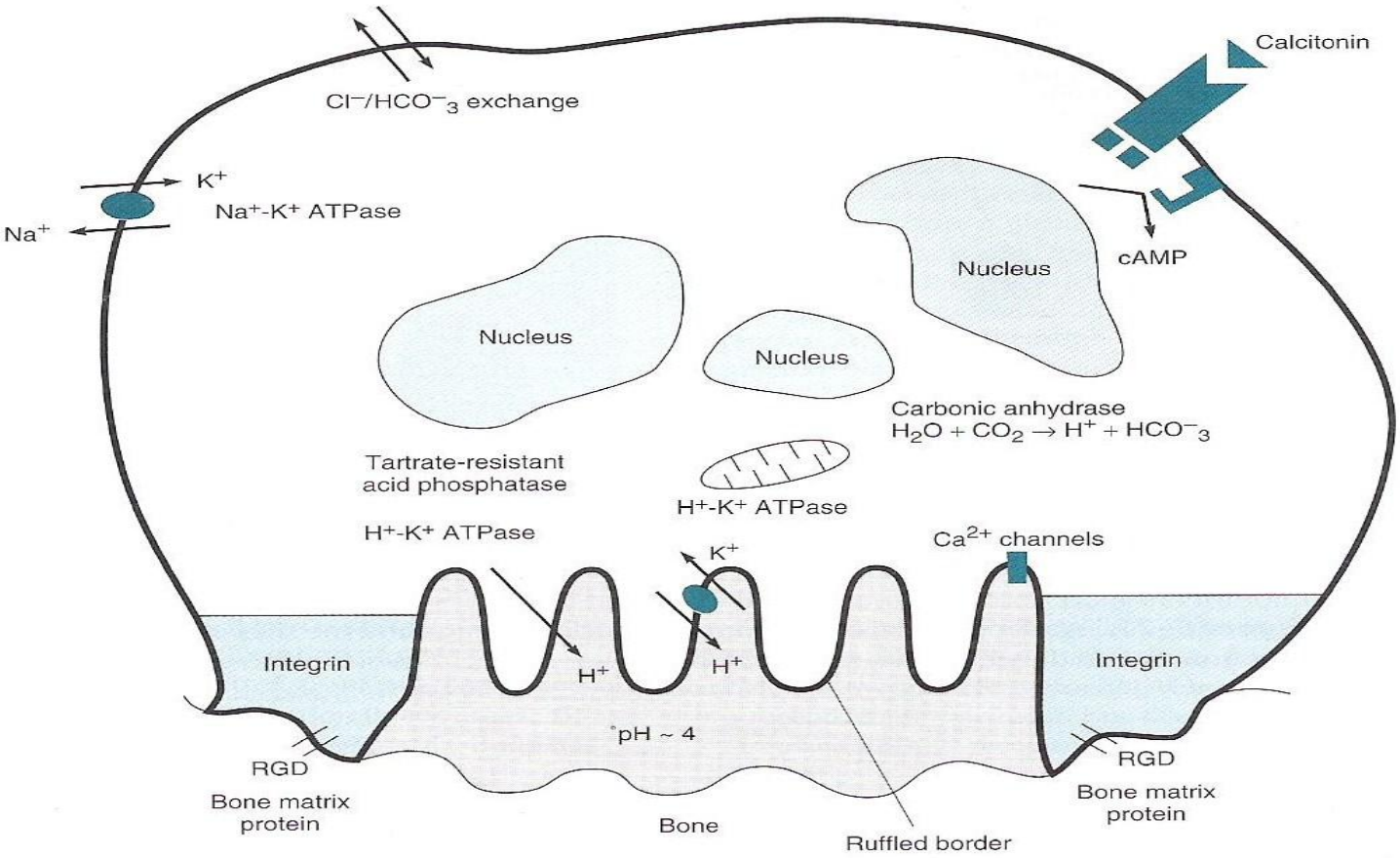


Figure 8–22. Osteoclast-mediated bone resorption. The osteoclast attaches to the bone surface via integrin-mediated binding to bone matrix bone proteins. When enough integrin binding has occurred, the osteoclast is anchored and a sealed space is formed. The repeatedly folded plasma membrane creates a "ruffled" border. Secreted into the sealed space are acid and enzymes forming an extracellular "lysosome." (Reproduced, with permission, from Felig P, Baxter JD, Frohman LA [editors]: *Endocrinology and Metabolism*, 3rd ed. McGraw-Hill, 1995.)

Bone Remodeling

- A continuous process of breakdown and renewal that occurs throughout life.

Bone remodeling units (BMUs)

- Appropriate signal: bone marrow cells migrate, fuse to form osteoclasts, dig a cavity into the bone.
- Resorption is completed (60 μm deep) by 2-3 months.
- Precursors of osteoblasts recruited to the base of resorption cavity.
- Expression of bone-specific proteins: alkaline phosphatase , osteopontin, osteocalcin (bone matrix) 20μm.
- Mineralization begins
- Remodeling cycle 6 months.

Bone Remodeling Unit

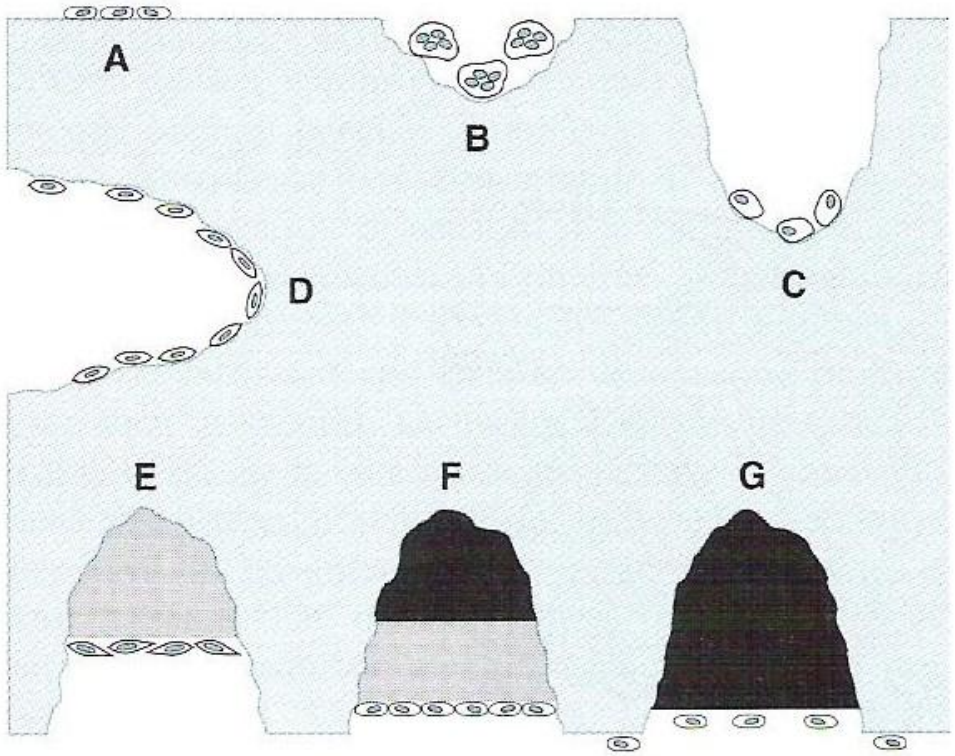


Figure 8–20. The remodeling cycle. ***A:*** Resting trabecular surface. ***B:*** Multinucleated osteoclasts dig a cavity of approximately 20 microns. ***C:*** Completion of resorption to 60 microns by mononuclear phagocytes. ***D:*** Recruitment of osteoblast precursors to the base of the resorption cavity. ***E:*** Secretion of new matrix (gray shading) by osteoblasts. ***F:*** Continued secretion of matrix, with initiation of calcification (black areas). ***G:*** Completion of mineralization of new matrix. Bone has returned to quiescent state, but a small deficit in bone mass persists.

Osteoporosis

Osteoporosis: low bone mass and microarchitectural disruption that results in fractures.

Primary osteoporosis: reduced bone mass and fractures in postmenopausal women (postmenopausal osteoporosis) or in older men and women ("senile" osteoporosis)

Secondary osteoporosis: bone loss resulting from specific clinical disorders, such as thyrotoxicosis, hyperadrenocortisolism.

Common sites of fragility: vertebral bodies, distal forearm, proximal femur.

Glucocorticoid–induced osteoporosis

Children: chronic exposure to glucocorticoids impairs skeletal growth.

Adults: glucocorticoids induced bone loss and muscle weakness:

a. renal Ca losses: ↓Ca reabsorption

b. intestinal Ca losses: ↓Ca absorption →↑ PTH action (independent of vitamin D)

c. Skeletal losses: ↓osteoblast maturation + activity; ↑osteoblast apoptosis

↓ gonadotropin → loss of gonadal function → bone.

Gain, Maintenance and Loss of Bone

Bone Acquisition

- Completed by 17 years in girls and 20 years in boys.
- Factors: Genes, gonadal steroids, physical activity, nutrition.
- Estradiol: initiation of adolescence growth and bone acquisition.
- "hygienic" factors: diet, physical activity, reproductive status.

Bone Loss

Bone Loss

- Estrogen deficiency: ↑osteoblast cytokines IL-6 → ↑osteoclast activity.
- ↑ Ca loss from 20 mg to 60 mg, fracture in women 2x as men.

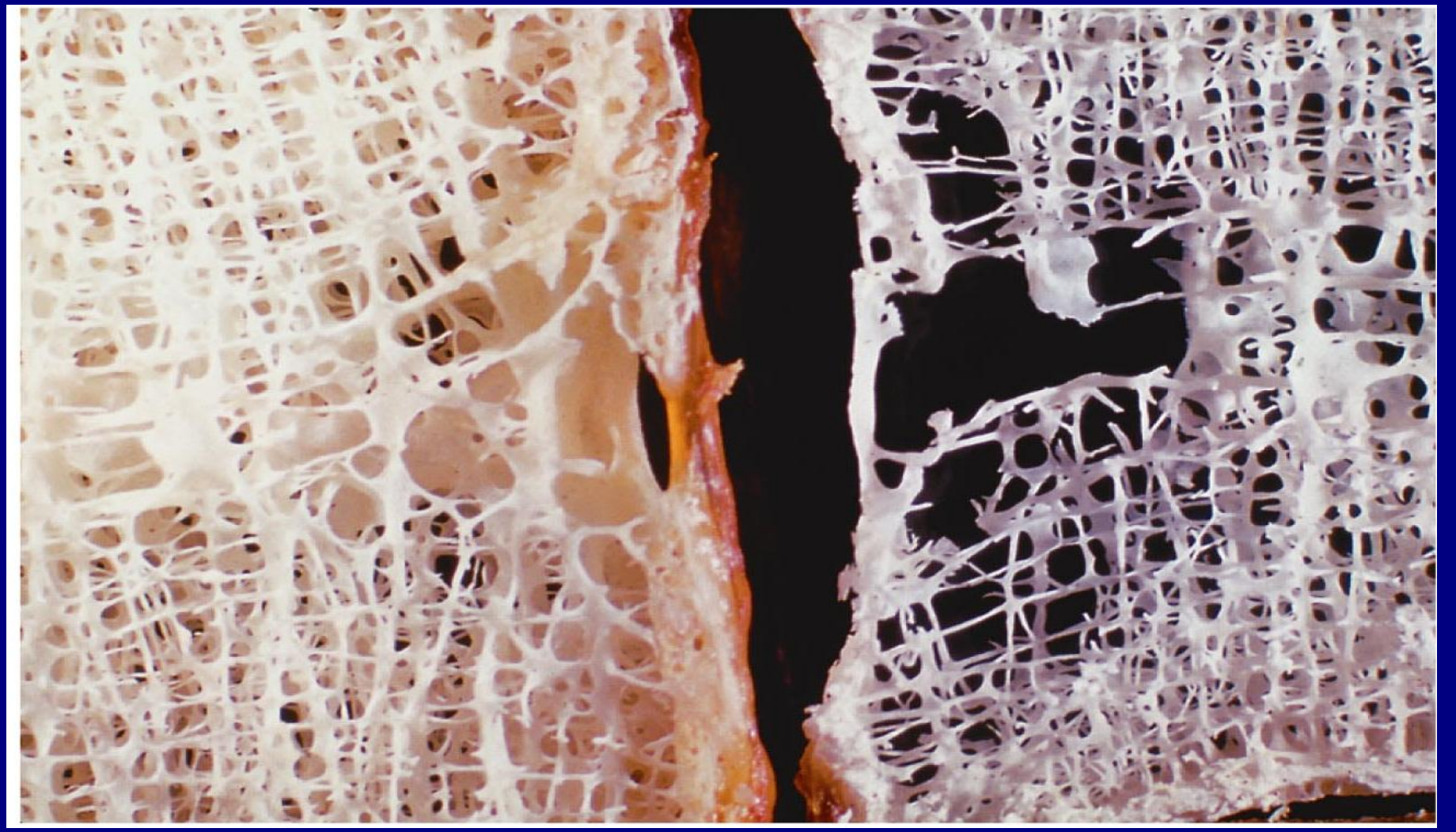
Bone loss in later life

- Progressive deficit in renal and intestinal function → ↓ 1,25 $(OH)_2$ D_3 → ↓intestinal Ca absorption → ↑PTH.

Diagnosis of Osteoporosis

- X-ray, BMD (Osteoporosis: ↑ -2.5 SD); (Osteopenia: -1 to -2.5 SD).

Osteoporosis



Normal bone (left) and bone loss in osteoporosis (right)

Treatment of Osteoporosis

Specific Antiresorptive Agents

a. Calcium

- Adequate Ca intake: prevention and treatment of osteoporosis in all patients.

b. Vitamin D and Calcitriol

- Vitamin D below 25-30 ng/ml ↑ PTH secretion → ↑ bone turnover
- Vitamin D analogs or metabolites (calcitriol)
- Vitamin D nutritional adequacy.

Treatment of Osteoporosis …

c. Estrogens

- Timely replacement of estrogen conserves bone mass
- (Early menopause) + Calcium supplementation.
- Side effects: hot flushes, cardiovascular disease, breast cancer.

Treatment of Osteoporosis …

d. Selective Estrogen Response Modulators

- Tamoxifen: estrogen agonist on bone, liver, uterus, antiestrogen at the breast and brain.
- Raloxifen: estrogen agonist at bone and liver (conservation of BMD, lowering LDL). Inert at the endomentrium, potent antiestrogen at the beast.

e. Calcitonin

Inhibitor of osteoclastic bone resorption, ↑ spine BMD

f. Bisphosphonates

Alendronate, potent antiresorptive drug.

Treatment of Osteoporosis …

Bone-Forming Agents

a. Fluoride

Although fluoride ↑BMD, Doubt to reduce fracture.

b. Androgen

Testosterone increases bone mass of hypogonadal men.

In women: virilizing side effects.

c. PTH

Recombinant human PTH (rh PTH 1-34) ↓vertebral factures by 50%.

Coadministration (PTH with estrogen or androgen) impressive gain in spine mineral density.

Osteomalacia and Rickets

Abnormal mineralization of bone and cartilage.

Pathogenesis

Osteomalacia

Bone defect, the epiphysis plates have closed (in adults).

Rickets

In growing bone (in children). Abnormal mineralization affects the transformation of cartilage into bone.

Causes:

- Vitamin D deficiency (main cause).
- Hypophosphatasia → alkaline phosphatase deficiency.
- Drugs: (Inhibitors of mineralization, Al, F, Etidronate)

Paget's Disease of Bone (Osteitis Deformans)

Etiology

- Accelerated rates of bone turnover.
- Gross deformities of bone might be due to virus infection of bone.

Pathology

- Highly vascular and cellular bone (high metabolic activity).
- Huge osteoclasts (100 nuclei/cell).
- Mosaic pattern of lamellar bone.

Renal Osteodystrophy

Pathogenesis

- Reduction in conversion of 25(OH)D $\rightarrow$1,25 $(OH)_2$ D3 or 24,25 $(OH)_2$ D_3
- $\downarrow$1,25 $(OH)_2$ $D_3 \rightarrow \downarrow$intestinal Ca absorption $\rightarrow$ hypocalcemia
- $\downarrow PO_4$ excretion in kidney $\rightarrow$ hyperphosphatemia.
- $\downarrow$Ca, $\downarrow$1,25 $(OH)_2$ $D_3 \rightarrow$ hyperparathyroidism $\rightarrow$ osteitis fibrosa, osteomalacia.

Renal Osteodystorphy …

Clinical Features

Osteitis fibrosa, osteomalacia

↓Ca, ↑ PO_4, alkaline phosphatase, ↑ PTH.

Treatment

Calcitriol, Ca carbonate

Phosphate restriction

Renal Osteodystorphy …

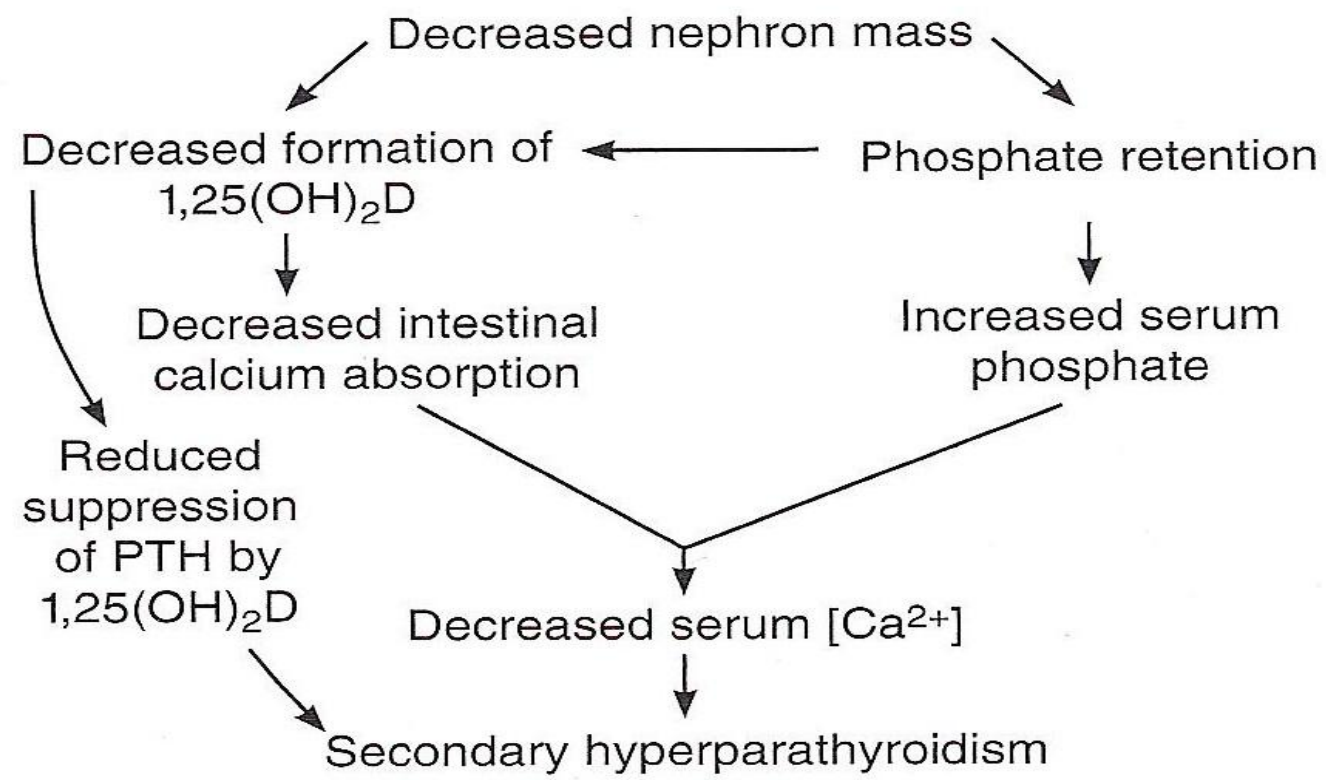


Figure 8–34. Schema for the pathogenesis of renal osteodystrophy.