The Endocrine Physiology

Calcium Homeostasis

1 and 2

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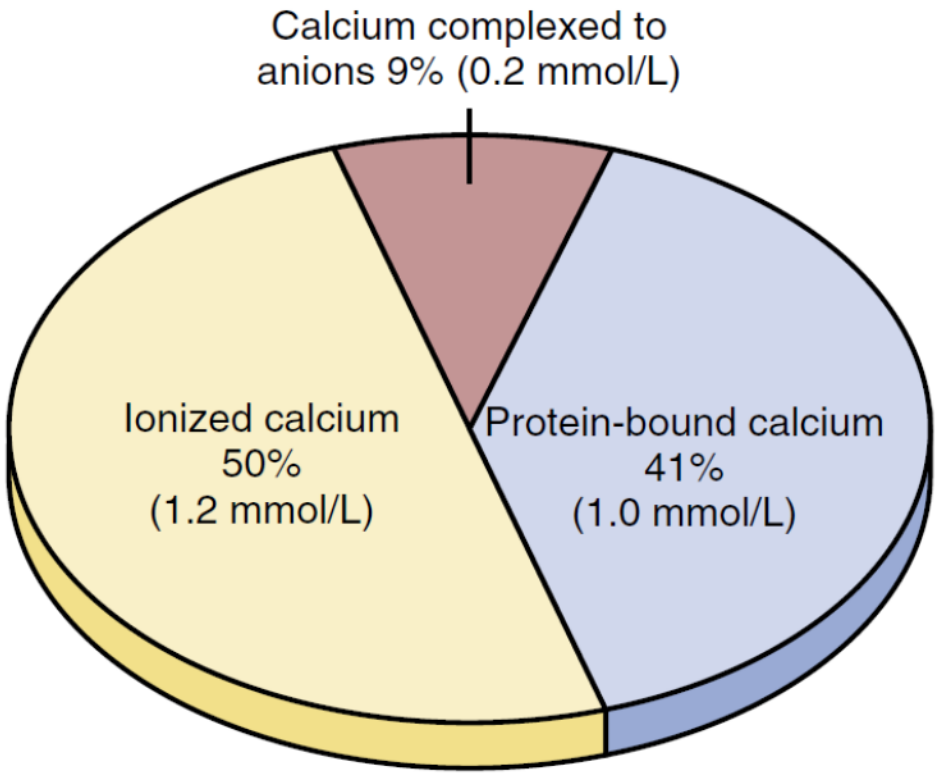
Objectives

1. Identify the normal range of dietary calcium and phosphate intake, distribution in the body, and routes of excretion.
2. Know the cells of origin for parathyroid hormone,
3. List the target organs and cell types for parathyroid hormone and describe its effects on each.
4. Describe the functions of the osteoblasts and the osteoclasts in bone remodeling.
5. Describe the regulation of parathyroid hormone secretion and the role of the calcium-sensing receptor.
6. Understand the causes and consequences of a) over-secretion, and b) under-secretion of parathyroid hormone, as well as its therapeutic use.
7. Identify the sources of vitamin D and the organs involved in modifying it to the biologically active 1,25(OH2)D3 (1-25 dihydroxycholecalciferol).
8. Identify the target organs and cellular mechanisms of action for vitamin D.
9. Describe the negative feedback relationship between parathyroid hormone and the biologically active form of vitamin D [1,25(OH2)D3].
10. Describe the consequences of vitamin D deficiency and vitamin D excess.
11. Name the stimuli that can promote secretion of calcitonin, and its actions.

Plasma Calcium

- Plasma calcium totals 2.4 mM (9.4 mg/dl)
  - Ionized calcium is 1.2 mM (50% of total calcium), it is the physiologically active form.
  - 41% protein-bound, 9% complexed to anions



Phosphate

- Approximately 85 % of the body's phosphate is stored in bones,
- 14-15 % is in the cells,
- Less than 1% is in the extracellular fluid.
- Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.

Forms of Ca and P_i in plasma

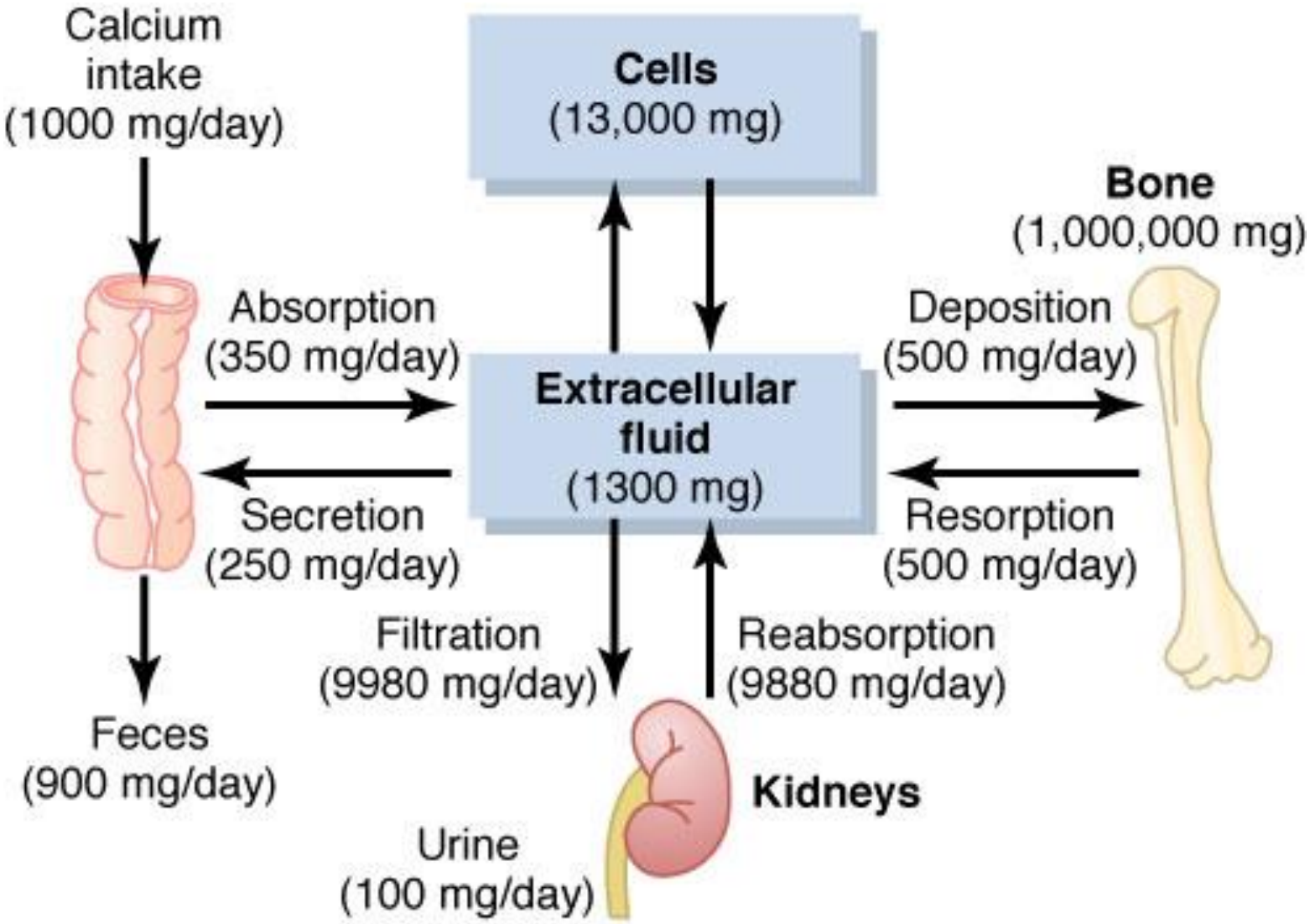
TABLE 40.1 Forms of Ca and P_i in Plasma

Ion	mg/dL	Ionized	Protein Bound	Complexed
Ca	8.5–10.2	50%	45%	5%
P_i	3–4.5	84%	10%	6%

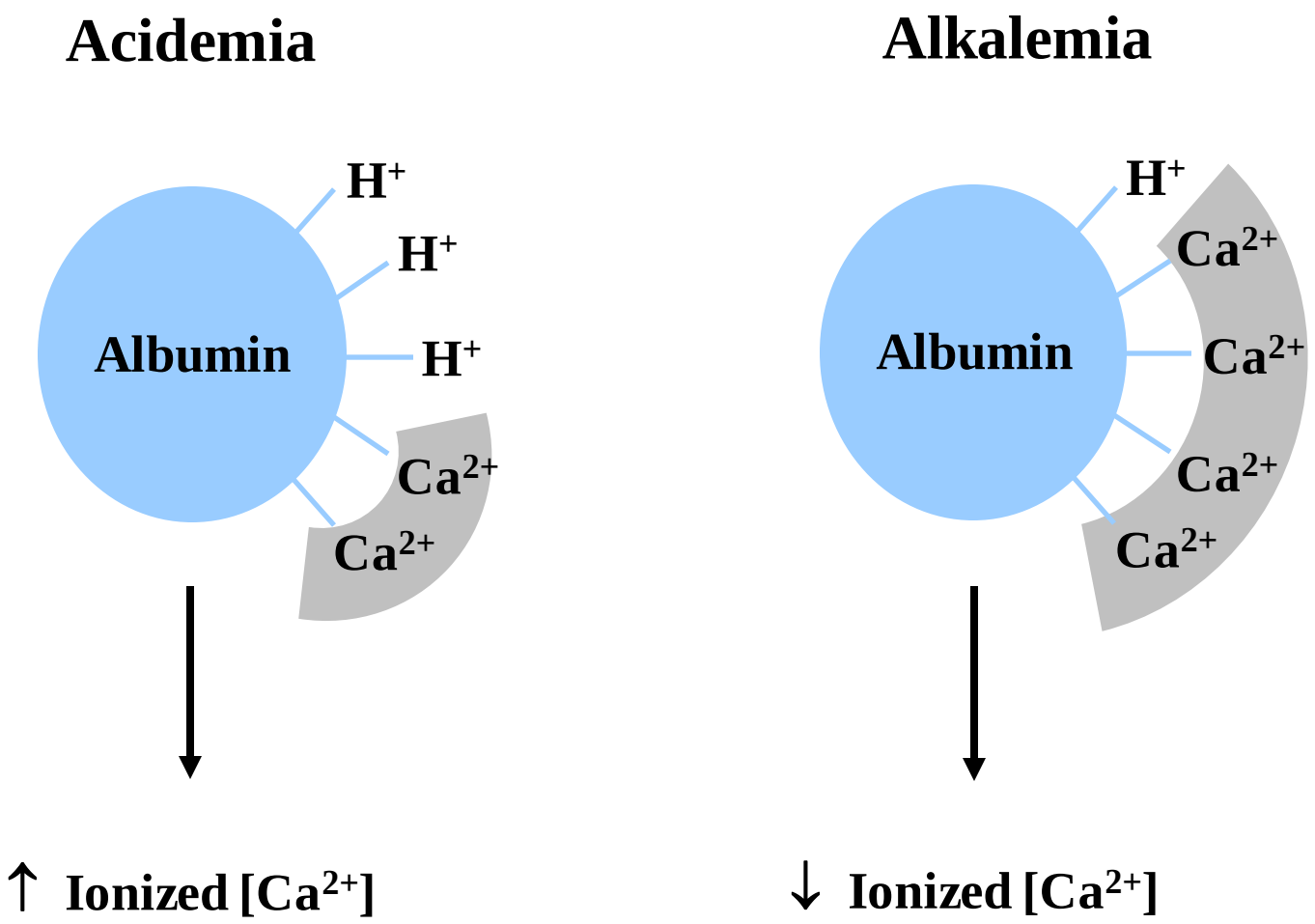
Ca^{++} is bound (i.e., complexed) to various anions in plasma, including HCO_3^-, citrate, and SO_4^{2-}. P_i is complexed to various cations, including Na^+ and K^+.

From Koeppen BM, Stanton BA. *Renal Physiology.* 4th ed. Philadelphia: Mosby; 2007.

Calcium Metabolism



Effects of Acid-Base Disturbances on Ionized Calcium

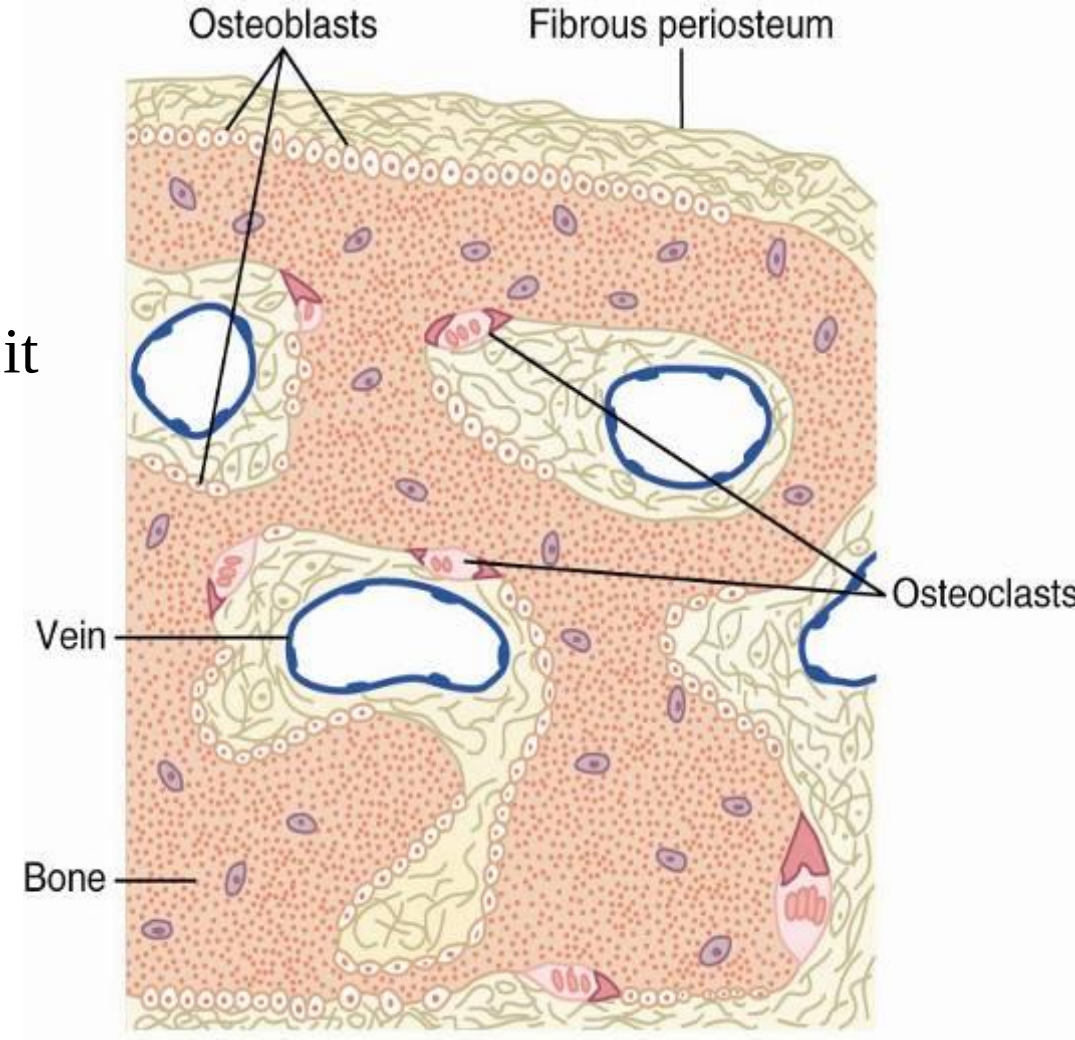


Hormonal Control of Calcium

- **Vitamin D3**
  - Diet and sun
- **Parathyroid hormone**
  - Parathyroid gland
- Calcitonin
  - Thyroid gland

Remodeling of Bone

Bone is continually being **deposited** by *osteoblasts*, and it is continually being **resorbed** where *osteoclasts* are active



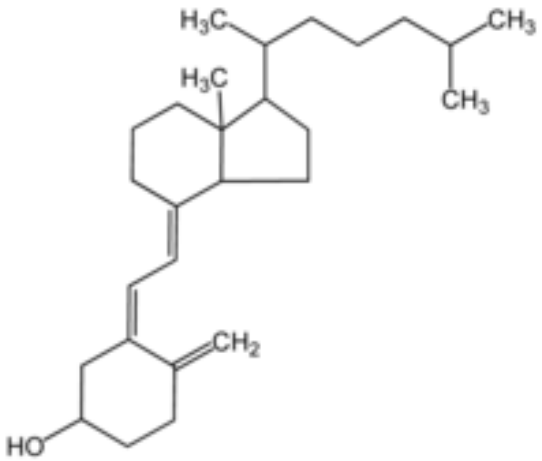
Mechanical Stress (Wolff's Law):

- States that bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading.
- For example, the bones of athletes become considerably heavier than those of nonathletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30% decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified.

Vitamin D3

- **Vitamin D3 (cholecalciferol)** is a prohormone that must undergo two successive hydroxylation reactions to become the active form known as **1,25-dihydroxyvitamin D** or **calcitriol**

1. It is formed in the skin from (7-dehydrocholesterol) by Ultraviolet B light.



Vitamin D3 (continued)

2. Then stored in the liver

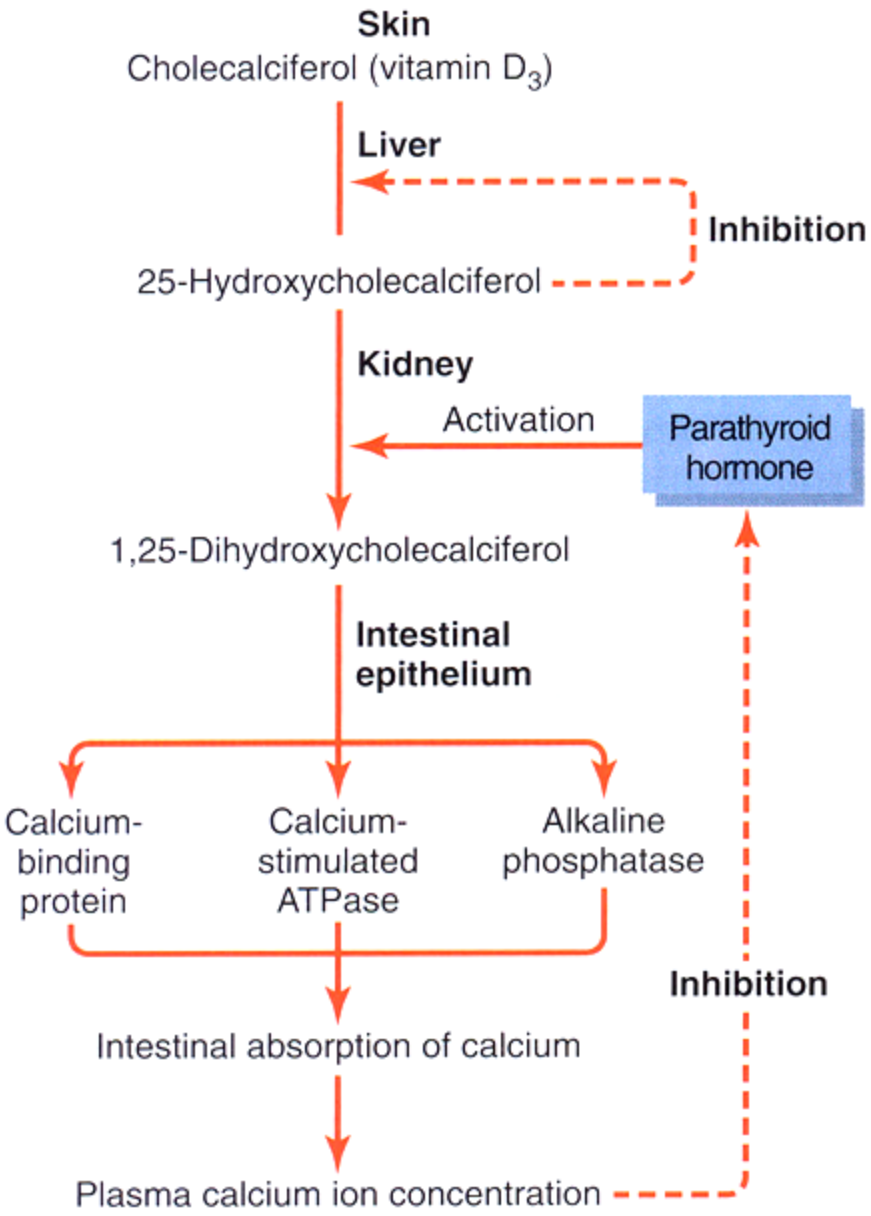
3. Converted in the liver to 25-Hydroxycholecalciferol

- Feedback control limits concentration

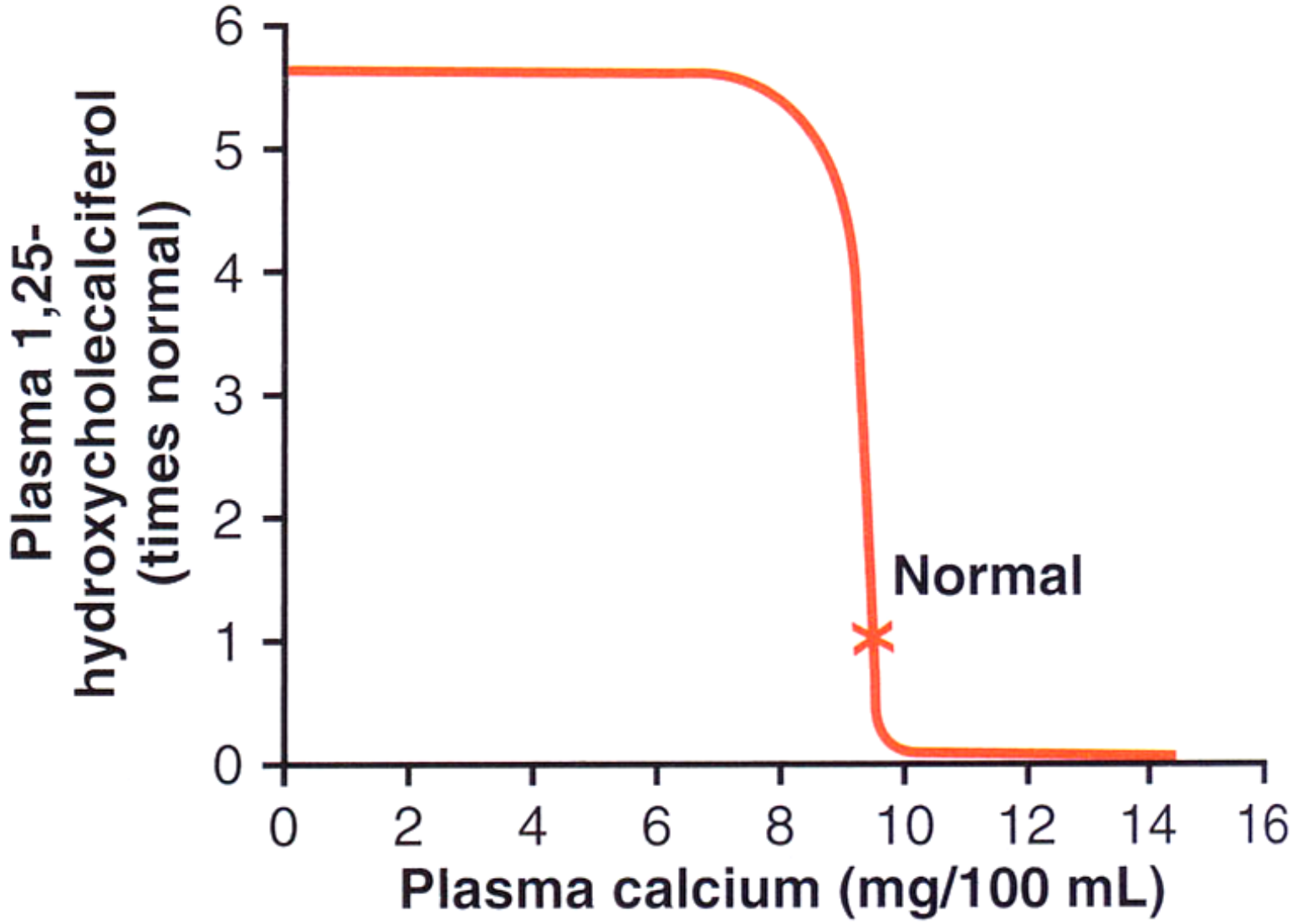
4. Converted to the active form in the kidney: (parathyroid hormone (PTH) stimulates 1α hydroxylase which makes 1,25-Dihydroxycholecalciferol (calcitriol)

- Under the feedback control of (PTH)

Activation of Vitamin D3



Calcium Ion Concentration Controls the Formation of 1,25-Dihydroxycholecalciferol



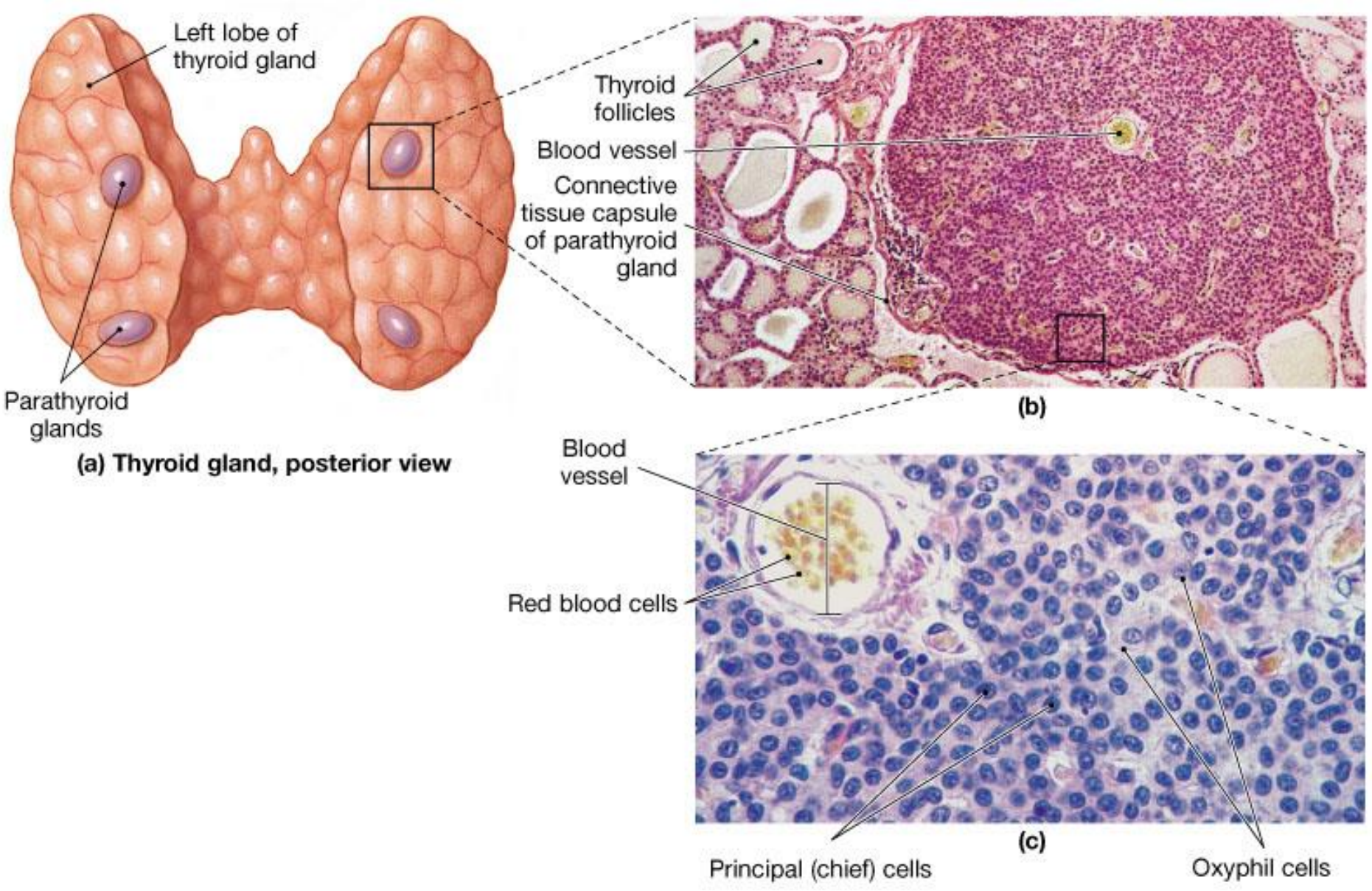
Effects of Active Form of Vitamin D3

- Promotes intestinal absorption of calcium and phosphates
- Causes synthesis of calcium-binding protein and related facilitated transport
- Takes a couple of days to fully develop response
- Has slight effect to increase calcium re-absorption in kidneys
- Works with PTH to cause calcium absorption from bone

Vitamin D Actions

- **Intestine**
  - ↑ Ca^{2+} absorption
  - ↑ phosphate absorption
- **Bone**
  - ↑ mineralization
  - ↑ bone resorption
- **Kidney**
  - ↑ Ca^{2+} reabsorption (weak effect)
  - ↑ phosphate reabsorption (weak effect)

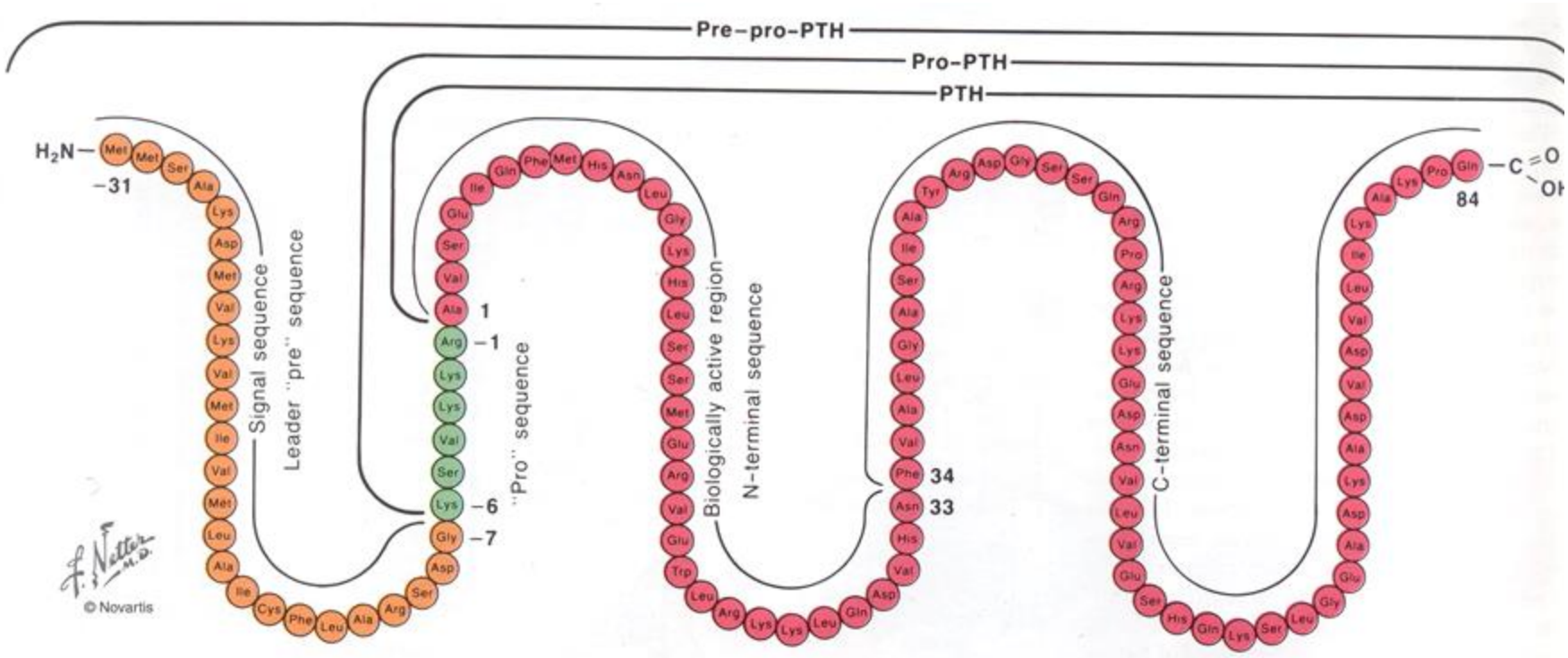
Parathyroid Gland



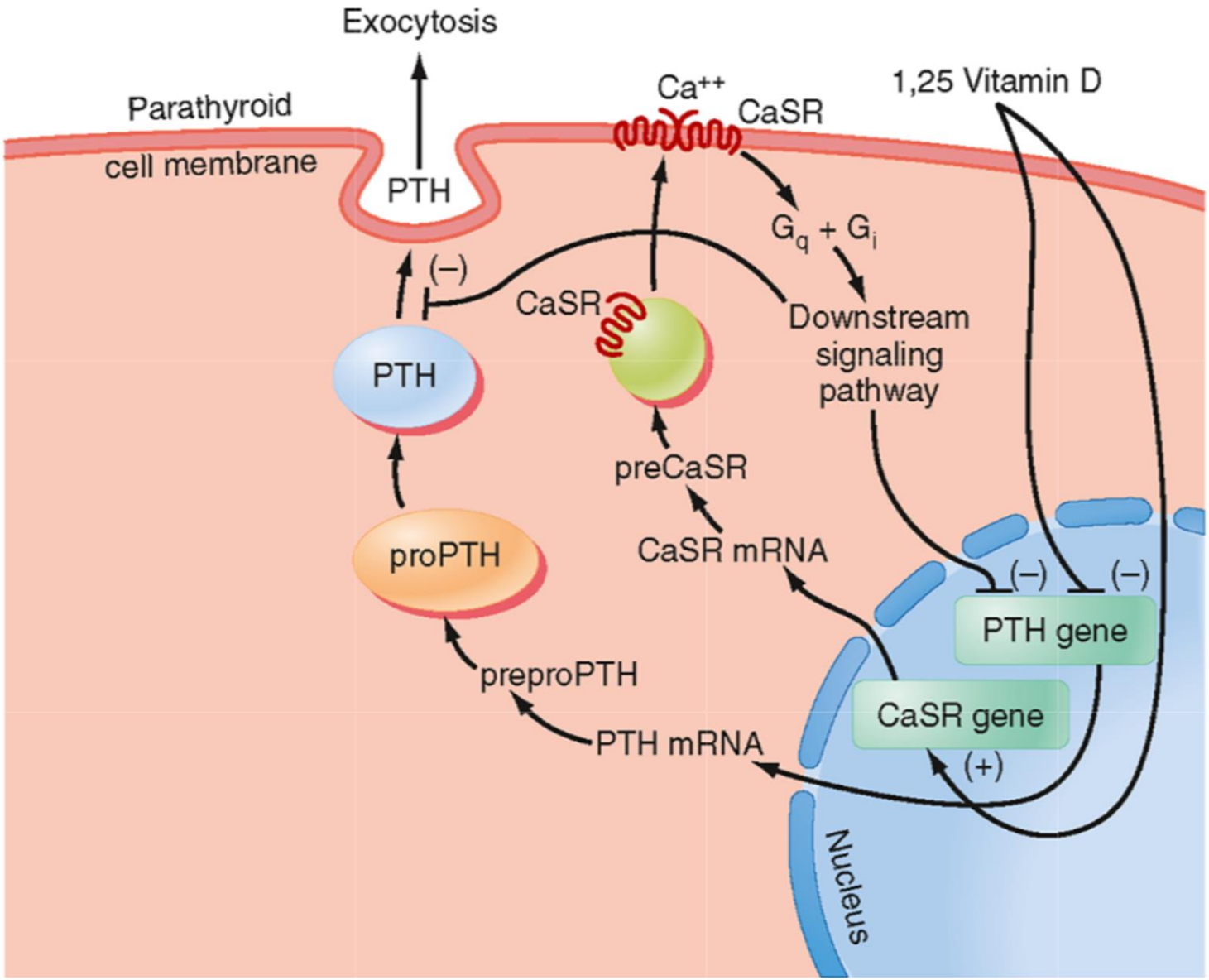
Parathyroid Hormone

- Secreted by Chief (principal) cells of the parathyroid glands
  - Rapid response to reduced calcium (minutes)
- Polypeptide
  - 84 amino acid
  - 9,500 daltons M.W.
- Operates in tissues via GPCRs, cAMP second messenger
- The primary targets of PTH are bone and the kidneys.

Parathyroid Hormone

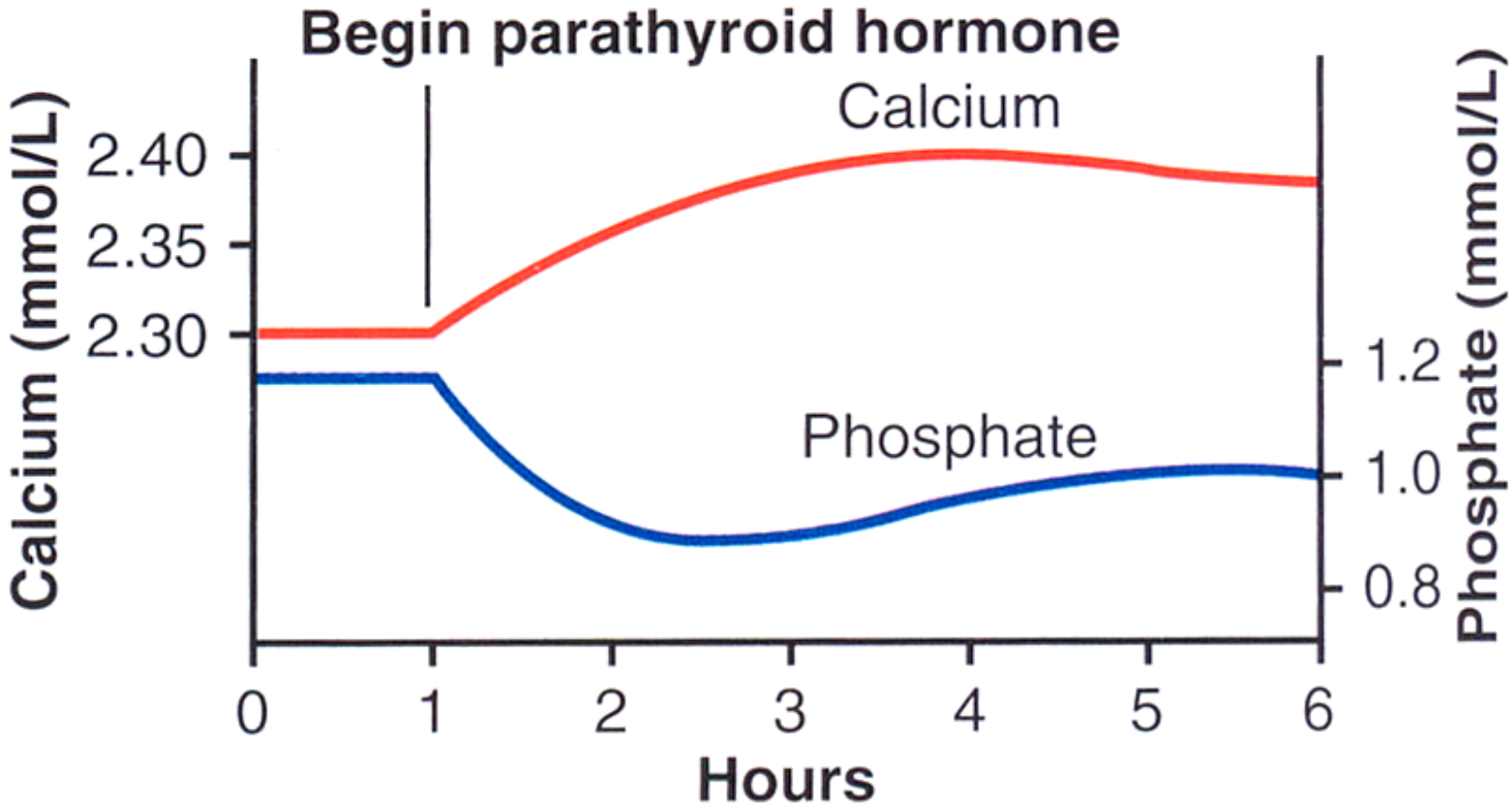


Reduced plasma Ca is the main trigger of PTH release



Effects of PTH

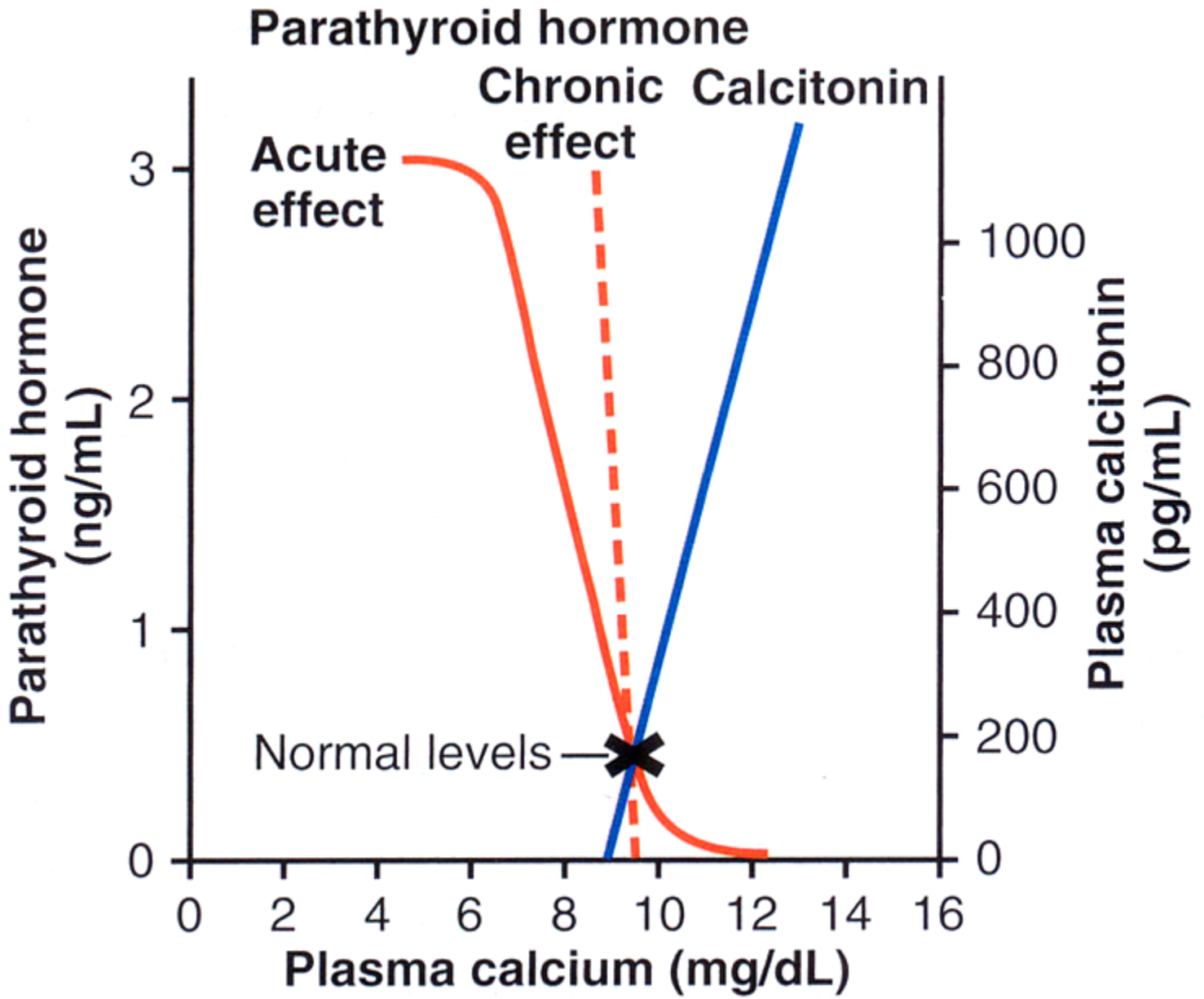
- Increases Calcium and Phosphate Absorption from the Bone
  - Existing osteocytes stimulated (minutes to hours) to transport calcium – calcium pumps
  - Existing osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium and phosphate.
    - Stimulated indirectly by osteoblasts: osteoblasts express RANKL which binds to RANK on osteoclasts leading to its activation.


Begin parathyroid hormone
Calcium
Phosphate
Calcium (mmol/L)
2.40
2.35
2.30
1.2
1.0
0.8
Phosphate (mmol/L)
0
1
2
3
4
5
6
Hours

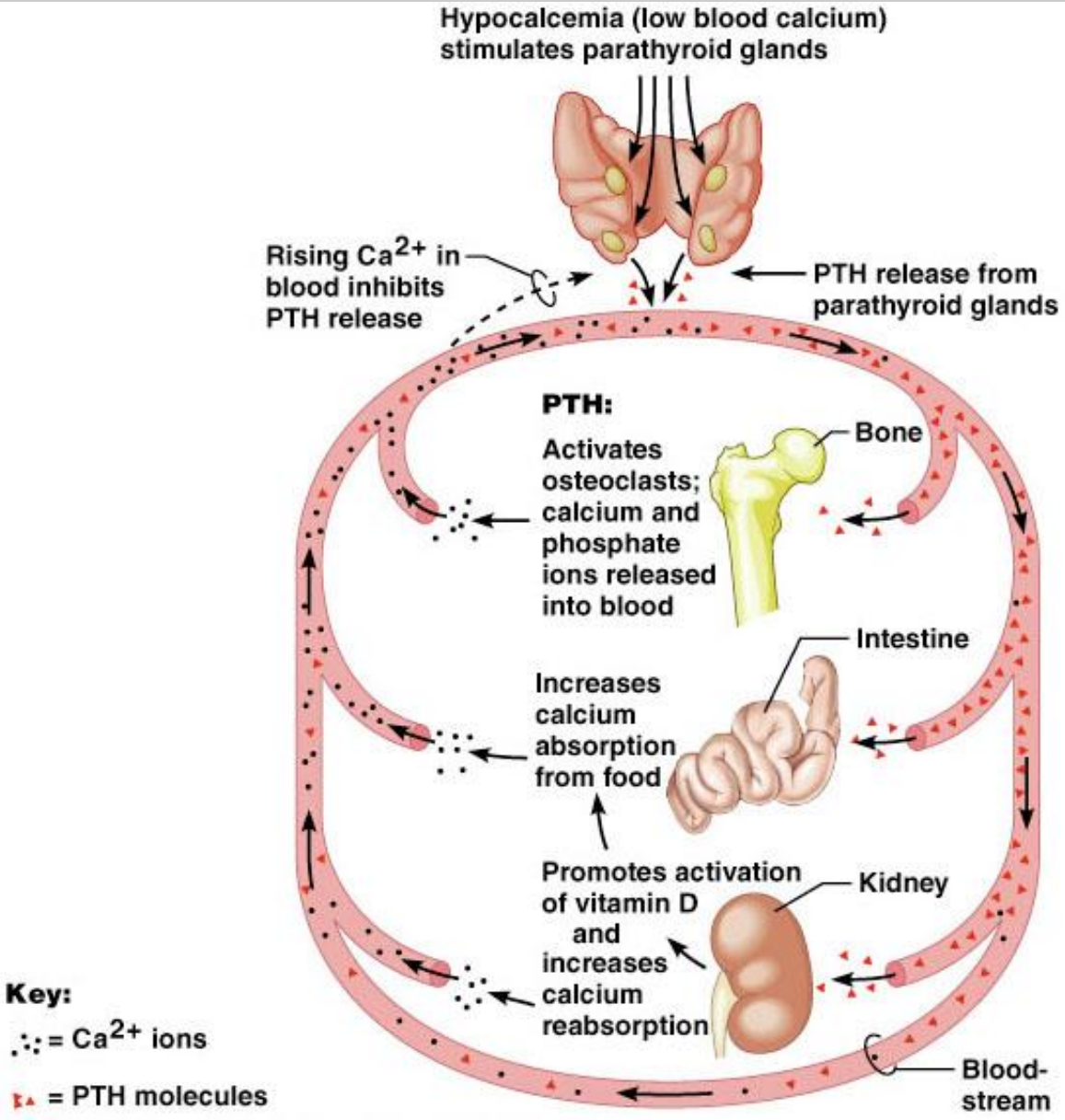
Effects of PTH (continued)

- Decreases excretion of calcium by kidneys
  - Important to prevent bone deterioration
- Increases phosphate excretion by the kidney
- Increases calcium absorption by the intestines
  - Effect manifested via Vitamin D3
    - Produces most active form of Vitamin D3 in the kidney (1,25-dihydroxy-cholecalciferol)
- It also increases phosphate absorption

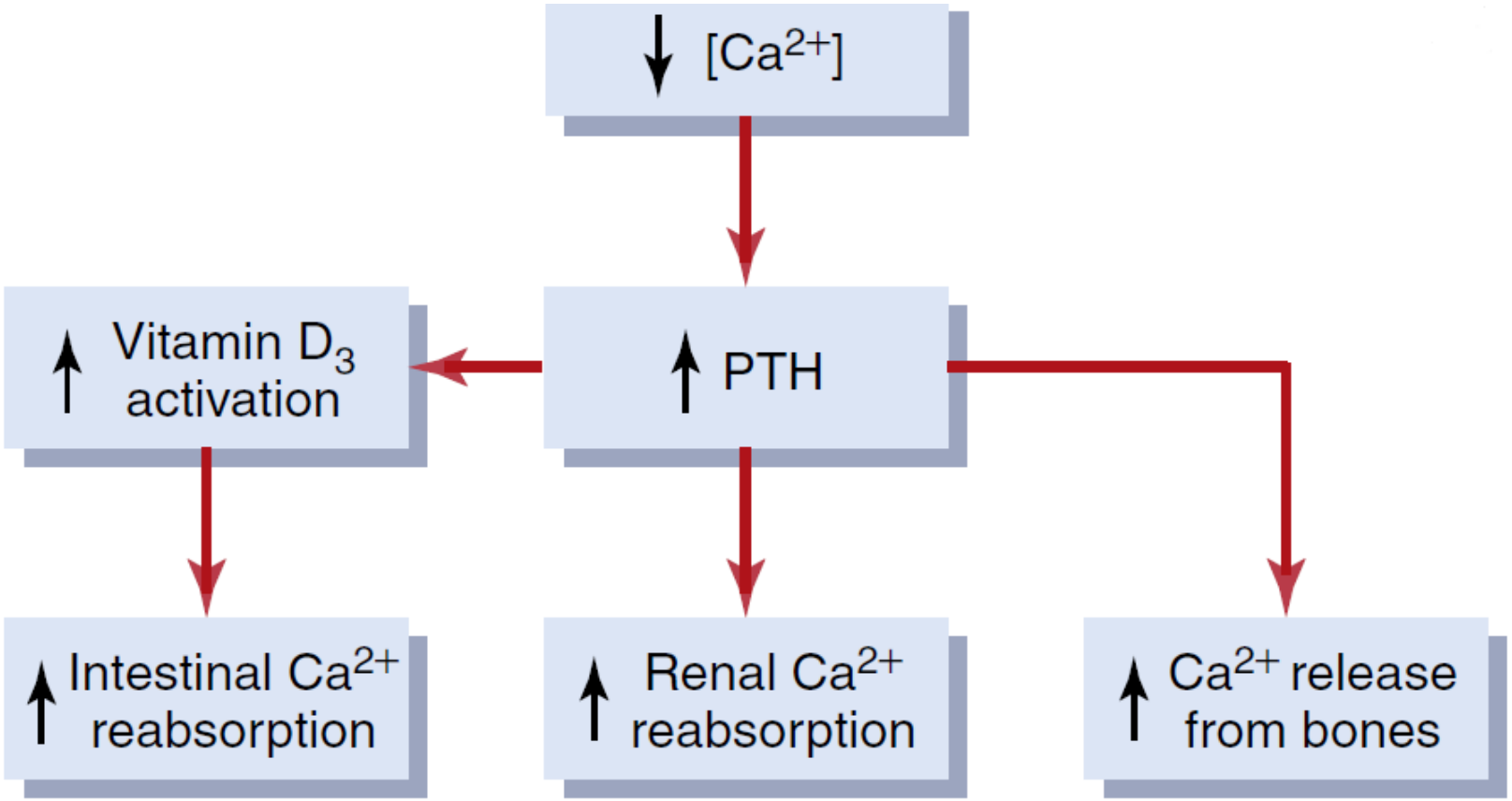
Effects of plasma calcium concentration on PTH & calcitonin



Effects of Parathyroid Hormone

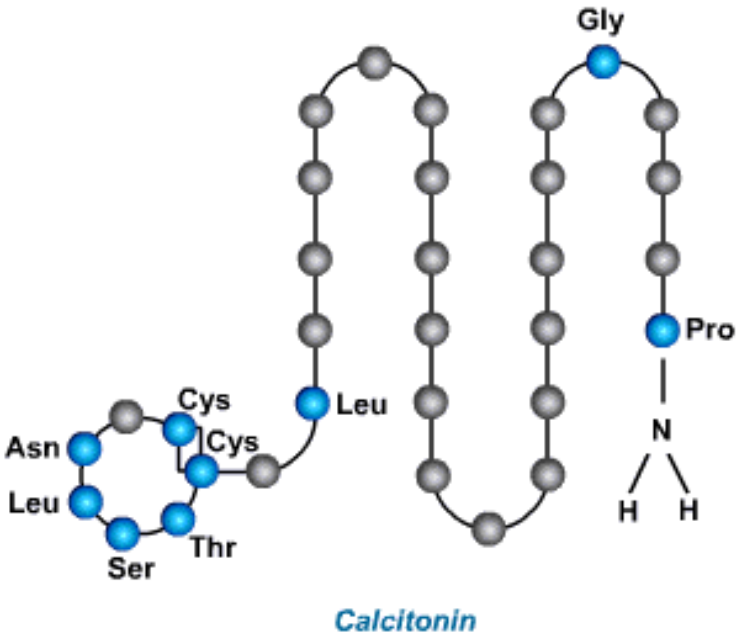


Summary

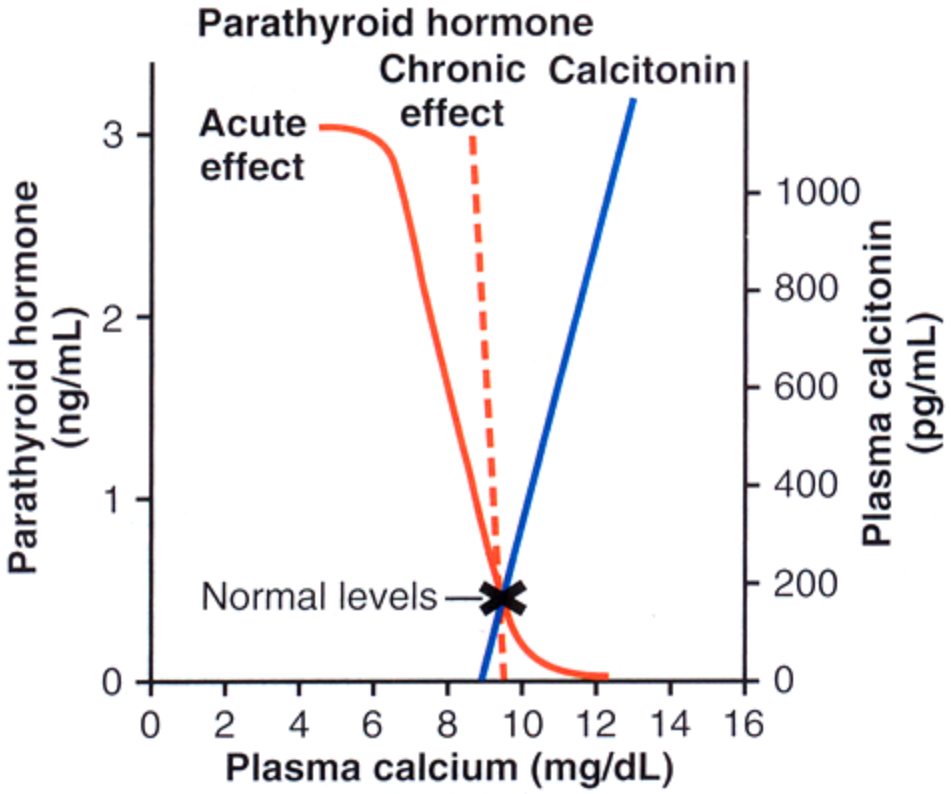

↓ [Ca2+]
↑ PTH
↑ Vitamin D3 activation
↑ Intestinal Ca2+ reabsorption
↑ Renal Ca2+ reabsorption
↑ Ca2+ release from bones

Calcitonin

- A peptide hormone , 32 amino acids
- produced by the parafollicular, or C cells of the thyroid gland



Calcitonin



Effects of Calcitonin

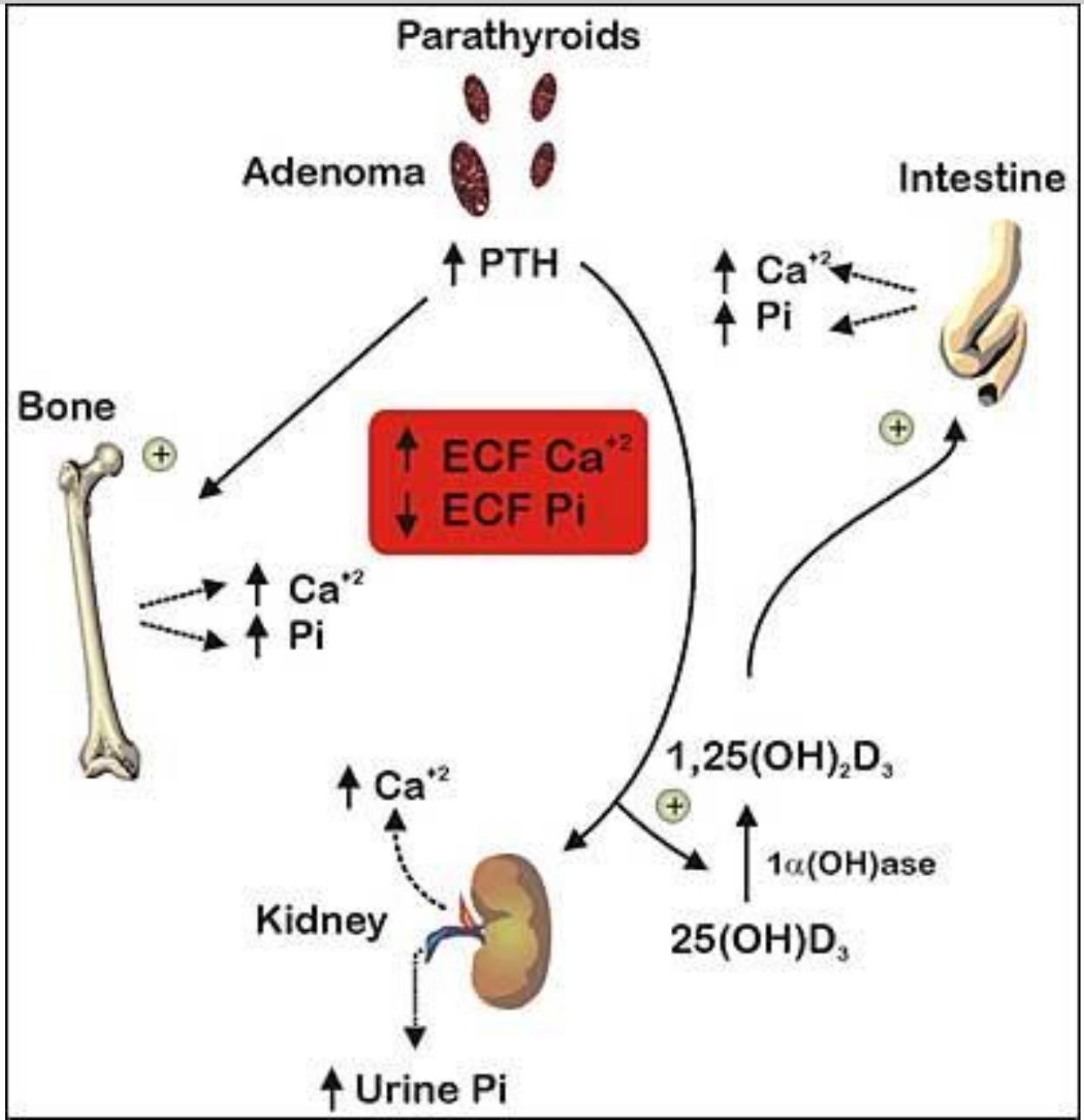
- Attenuates absorptive ability of osteoclasts
- Inhibits formation of new osteoclasts
  - Effect to decrease calcium is transitory
  - Causes reduced bone turnover
- Has weak effect in kidney and intestines

Hypercalcemia

Common causes of hypercalcemica

- PTH mediated
  - Primary hyperparathyroidism
- Non-PTH mediated
  - Parathyroid hormone–related peptide **(PTHrP):** certain tumors secrete high levels of PTHrP, which causes **hypercalcemia of malignancy**.
  - Vitamin D intoxication, granulomatous disorders, osteolytic bone metastases, malignancy
- Immobility
- Dehydration
- Medications
  - Lithium, thiazide diuretics

Hyperparathyroidism



Hyperparathyroidism

- The disorder is characterized by hypercalcemia, hypercalciuria, hypophosphatemia, and hyperphosphaturia
- Parathyroid hormone causes phosphaturia and a decrease in serum phosphate
- Plasma Calcium rises and it is also secreted in the urine
- Renal stones made of calcium phosphate can result.
- Most serious complication is the deposition of calcium in the kidney tubules resulting in impaired renal function

Hyperparathyroidism (Causes)

- Primary
  - Adenoma (90%)
  - Multiple gland enlargement (10%)
    - Familial hyperparathyroidism
  - Carcinoma (<1%)
  - Familial benign hypercalcemia (FBH)
- Secondary (normo- or hypocalcemic)
  - Renal failure
  - Vitamin D deficiency

Primary hyperparathyroidism

- Affects approximately 100,000 patients a year (in the US).
- Prevalence: 0.1 to 0.3% of the general population.
- More common in women (1:500) than in men (1:2000).
- Patients with single adenoma (~90%): minimally invasive surgery

Clinical Manifestations of Hypercalcemia

- **Nausea, vomiting**
- **Anorexia, weight loss**
- **constipation**
- **Lethargy and Fatigue**
- **Confusion, stupor, coma**
- **Impaired concentration and memory**
- **Depression & anxiety**
- **Reduced neuromuscular excitability and muscle weakness**
- **Easy fatigability and muscle weakness more common in hyperparathyroidism than other hypercalcemic conditions**
- **Cardiac arrhythmias**
- **Vascular calcification**
- shortening of the QT interval.

Hypercalcemia - Treatment

Severe hypercalcemia:

- Indications for therapy
  - Symptoms of hypercalcemia
  - Plasma [Ca] >14 mg/dl
- Principles of therapy
  - Expand ECF volume
  - Increase urinary calcium excretion
  - Decrease bone resorption

Hypercalcemia - Treatment

- NS bolus to restore volume; then 100 – 200 ml/hr
- Bisphosphonates (onset 24-48 hrs)
- Calcitonin 4 – 8 IU q6-8 hrs (onset immediate, resistance develops in 24-48 hrs)
- Surgery for adenoma

Hypocalcemia

Hypocalcemia: causes

- **Hypoparathyroidism**
  - **Surgical** (thyroid, parathyroid surgery)
  - Autoimmune
  - Magnesium deficiency
- PTH resistance (pseudohypoparathyroism)

Normal PTH levels but deficient receptors

- Vitamin D deficiency
- Vitamin D resistance

Lack of 1α hydroxylase, no vit D3 activation

- Other: renal failure, pancreatitis, tumor lysis

Hypoparathyroidism

Causes Hypocalcemia ,hyperphosphatemia neuromuscular irritability, numbness, cramps, anxiety , Tetany, carpopedal spasms. Severe Hypocalcemia is followed by convulsions, stridor, dystonia, and depression.

Two common signs of Hypocalcemia are:

- Chvostek's sign
- Trousseau's sign

A prolonged QT interval on the ECG can also be seen.

Two signs of Hypocalcemia are

- **Chvostek's sign**. It refers to an abnormal reaction to the stimulation of the facial nerve. When the facial nerve is tapped at the angle of the jaw (i.e. masseter muscle), the facial muscles on the same side of the face will contract momentarily (typically a twitch of the nose or lips) because of hypocalcemia.

- **Trousseau's sign**. To elicit the sign, a blood pressure cuff is placed around the arm and inflated to a pressure greater than the systolic blood pressure and held in place for 3 minutes. This will occlude the brachial artery. In the absence of blood flow, the patient's hypocalcemia and subsequent neuromuscular irritability will induce spasm of the muscles of the hand and forearm. The wrist and metacarpophalangeal joints flex.

Clinical Signs of Hypocalcemia:

- **Neuromuscular excitability**
- **Paraesthesia (tingling sensation) around mouth, fingers and toes**
- **Muscle cramps, carpopedal spasms**
- **Tetany**
- **Seizures – focal or generalised**
- **Laryngospasm, stridor and apneas (neonates)**
- **Cardiac rhythm disturbances (prolonged QT interval)**
- **Chvostek's and Trousseau's signs – latent hypocalcemia**

Vitamin D deficiency

RICKETS

Normal formation of the collagen matrix

BUT

Incomplete mineralization (poor calcification)

↓

Soft Bones

↓

CLINICALLY: Bone Deformity (Rickets)

Vitamin D deficiency

Osteomalacia:

Demineralization (poor calcification) of preexisting bones which leads to more susceptibility to Fracture