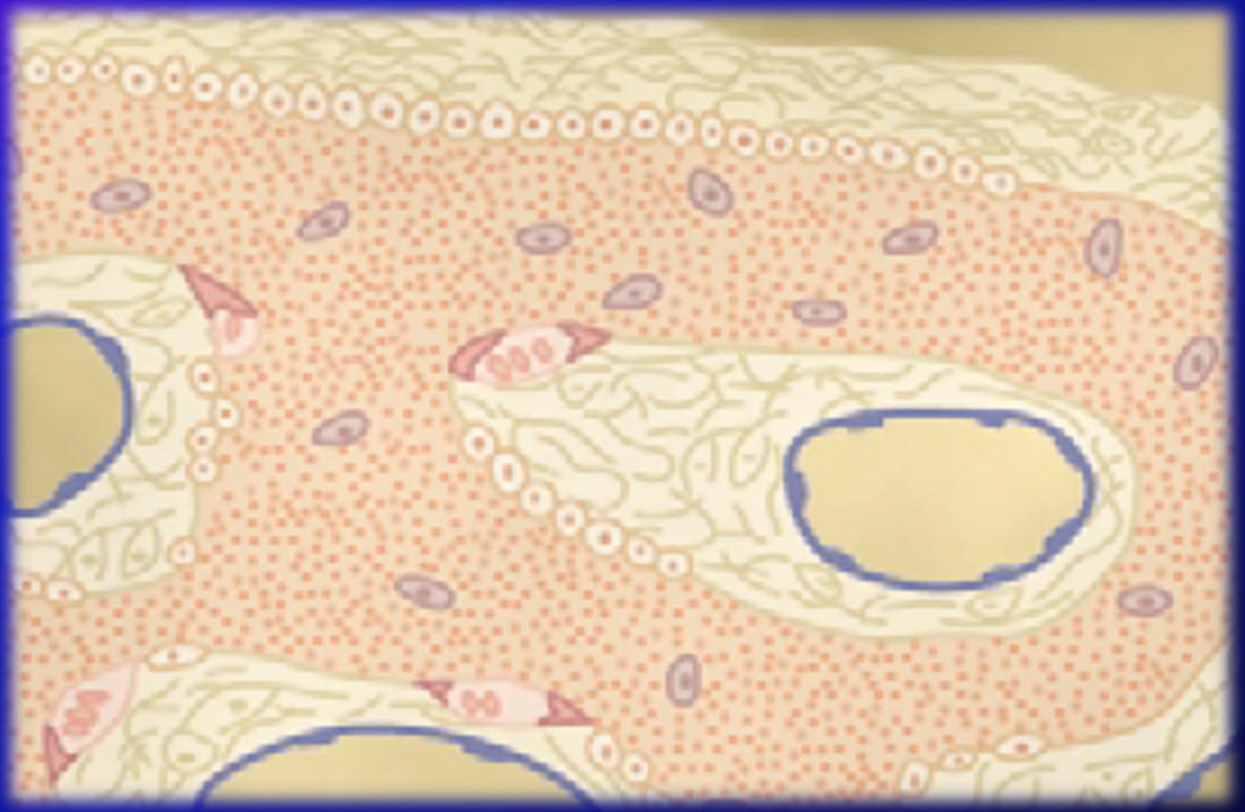
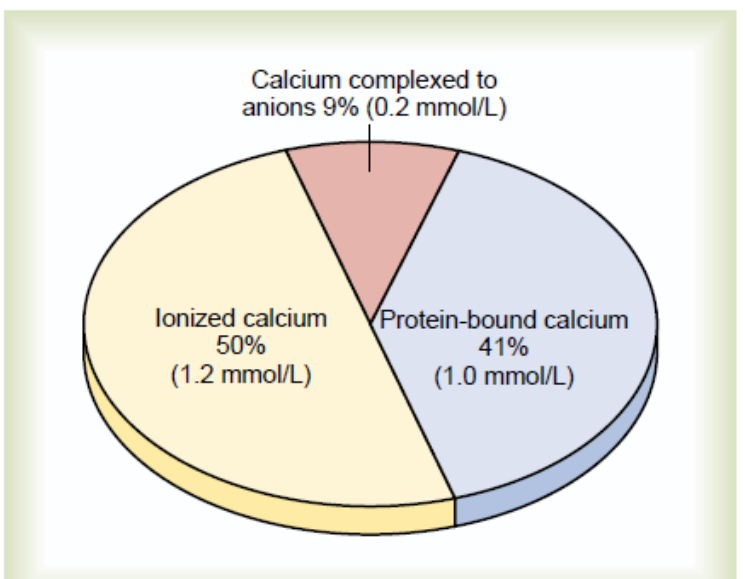
Regulation of Calcium Ion Level in the Blood



Calcium

The Total Body Calcium (1 100 g):

- MAJORITY - BONES (1 000 000 mg)
- 1 % - CELLS (13 000 mg)
- 0,1% - EXTRACELLULAR FLUID (1 300 mg):



Calcium level :

2,25 – 2,75 mmol/L

(9-11 mg/dL)

Phosphate

TOTAL - 500-800 g:

- 85% - BONES
- 14-15% - CELLS
- 1% - EXTRACELLULAR FLUID:

  - HPO_4^{2-}-1.05 mmol/L
  - $H_2PO_4^-$ -0.26 mmol/L

Expressed in terms of milligrams of phosphorus per deciliter of blood

- 3-4 mg/dL (adults)
- 4-5 mg/dL (children)

Extracellular calcium ion concentration is regulated by hormones:

- Parathyroid hormone (PTH)
- 1,25-Dihydroxycholecalciferol (active form of vitamin D_3)
- Calcitonin

Parathyroid glands

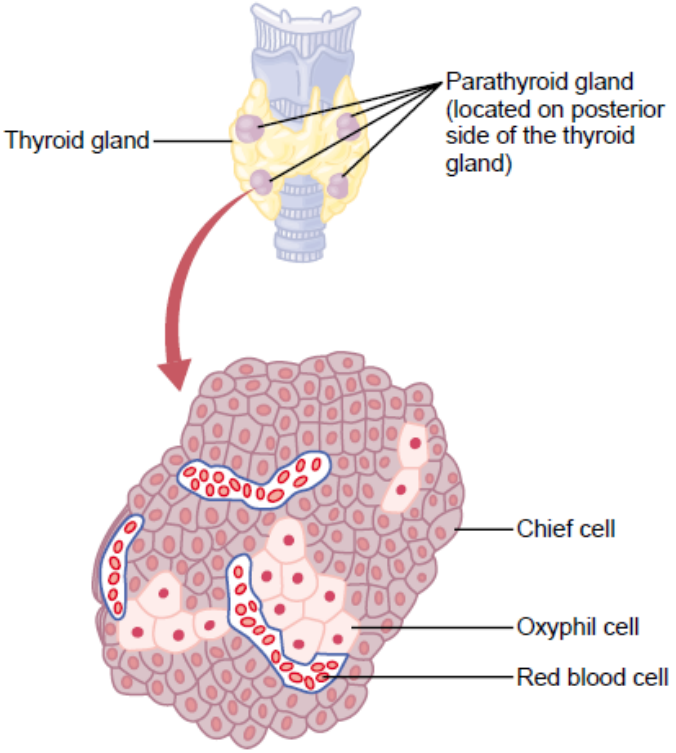


Figure 79–9

The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.

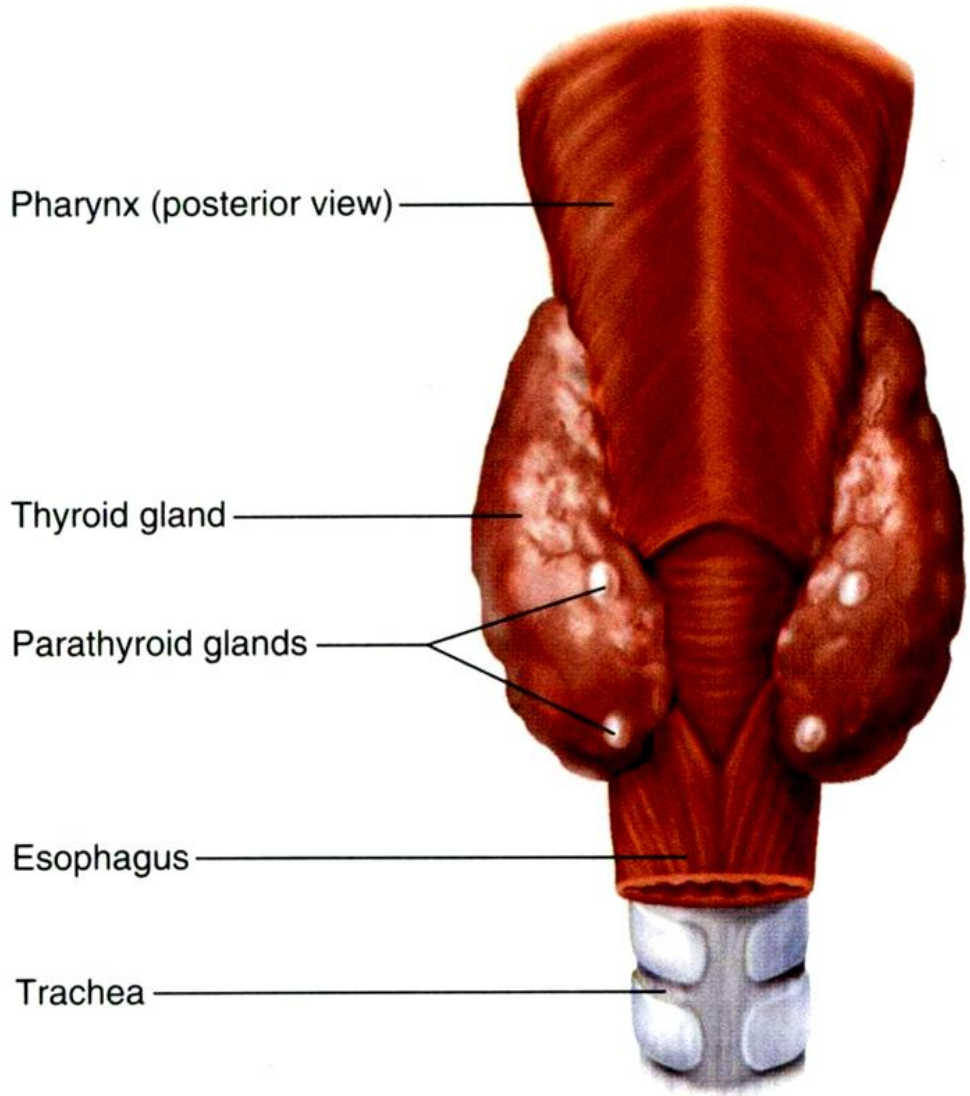
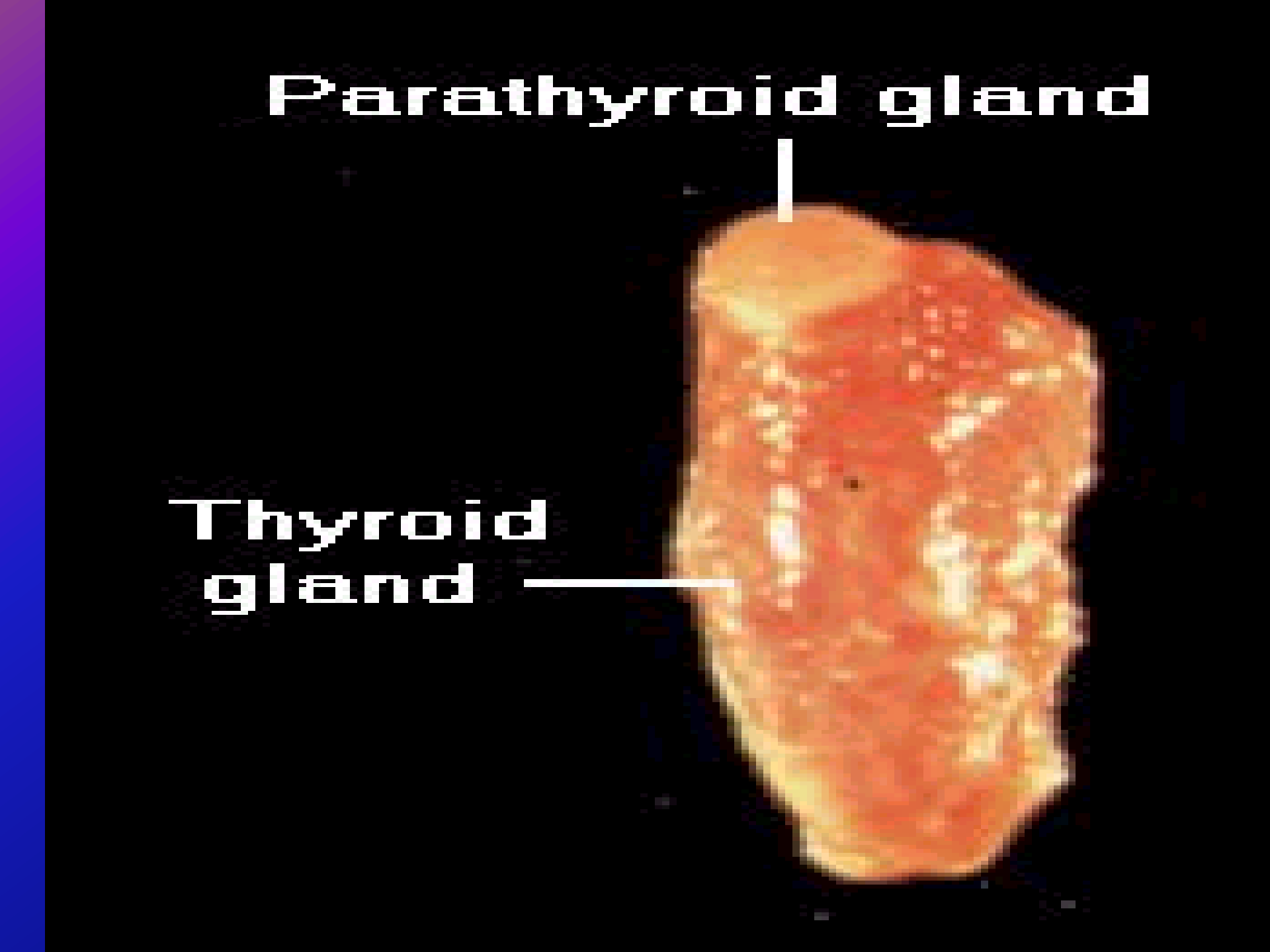


Figure 17.12 **The Parathyroid Glands.** There are usually four parathyroid glands embedded in the posterior surface of the thyroid gland.


Parathyroid gland
Thyroid gland

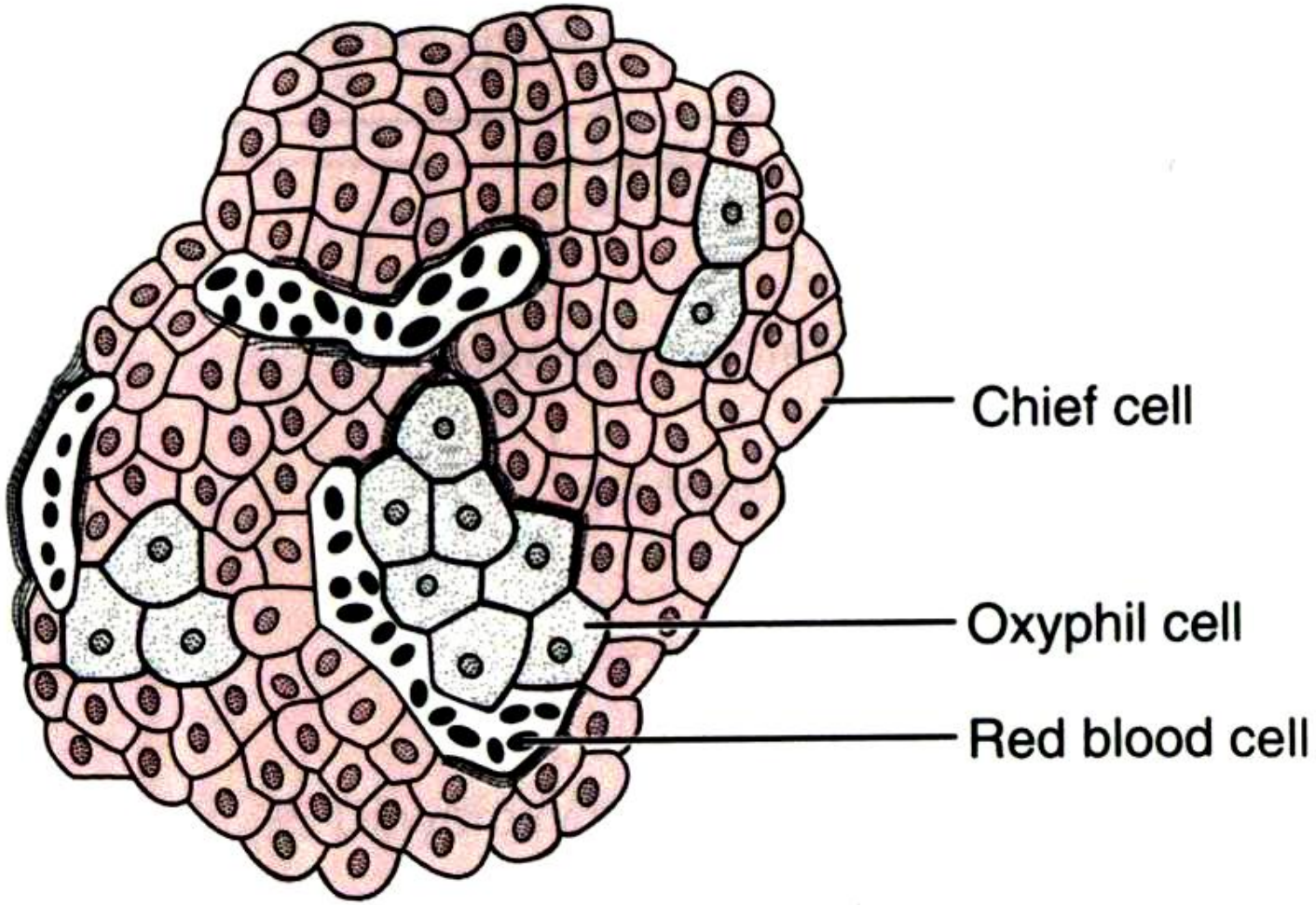
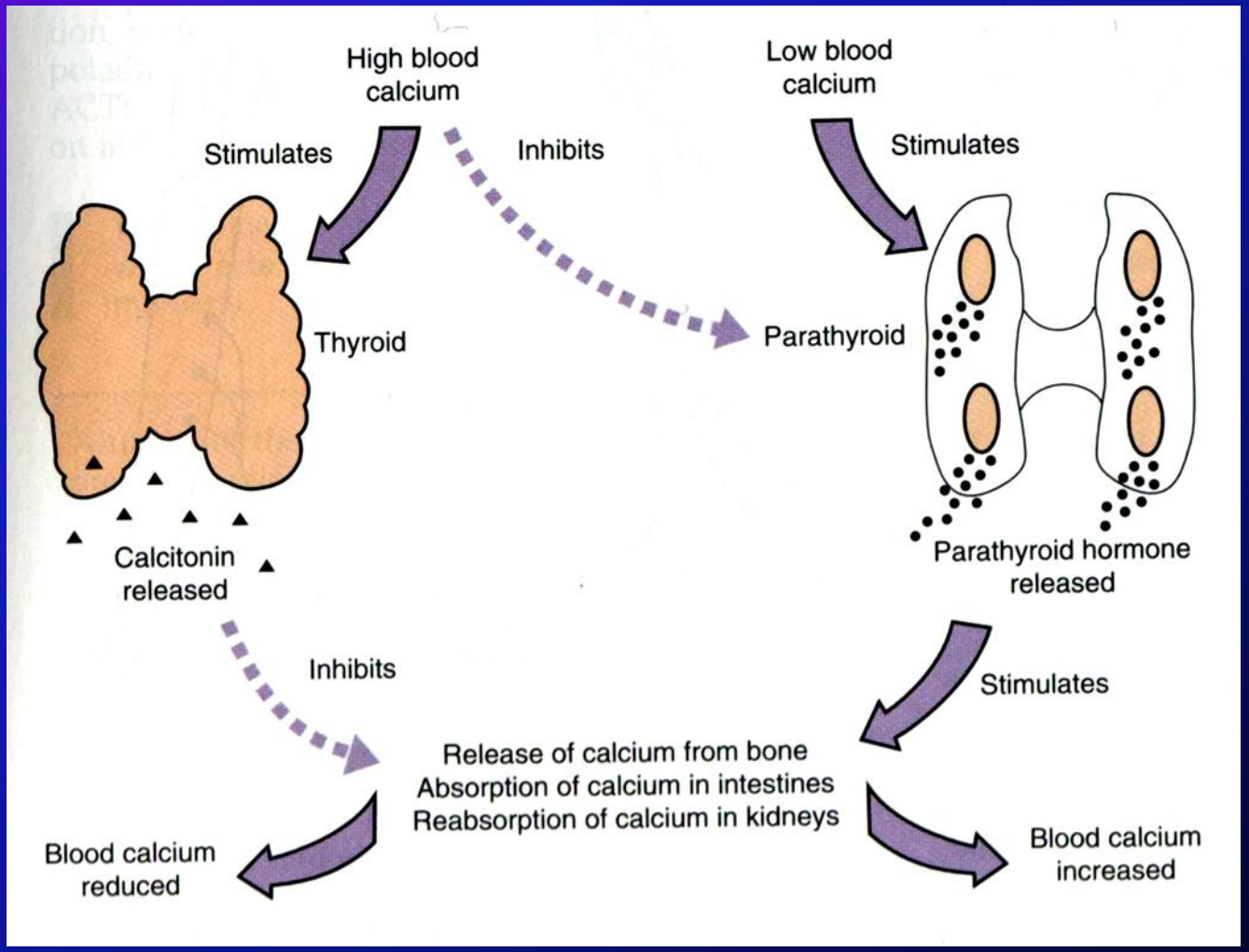


FIGURE 79-9

Histological structure of a parathyroid gland.

Effect of PTH and Calcitonin on Blood Calcium Level



Actions of PTH are coordinated to produce

- *an increase in serum [Ca^{2+}]*
- *a decrease in serum [phosphate]*

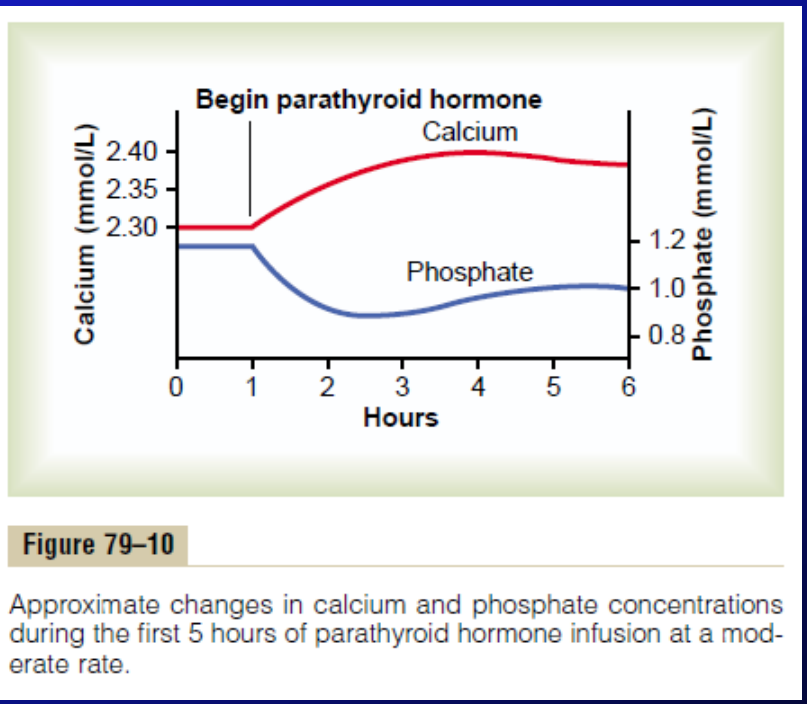


Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

Actions of PTH

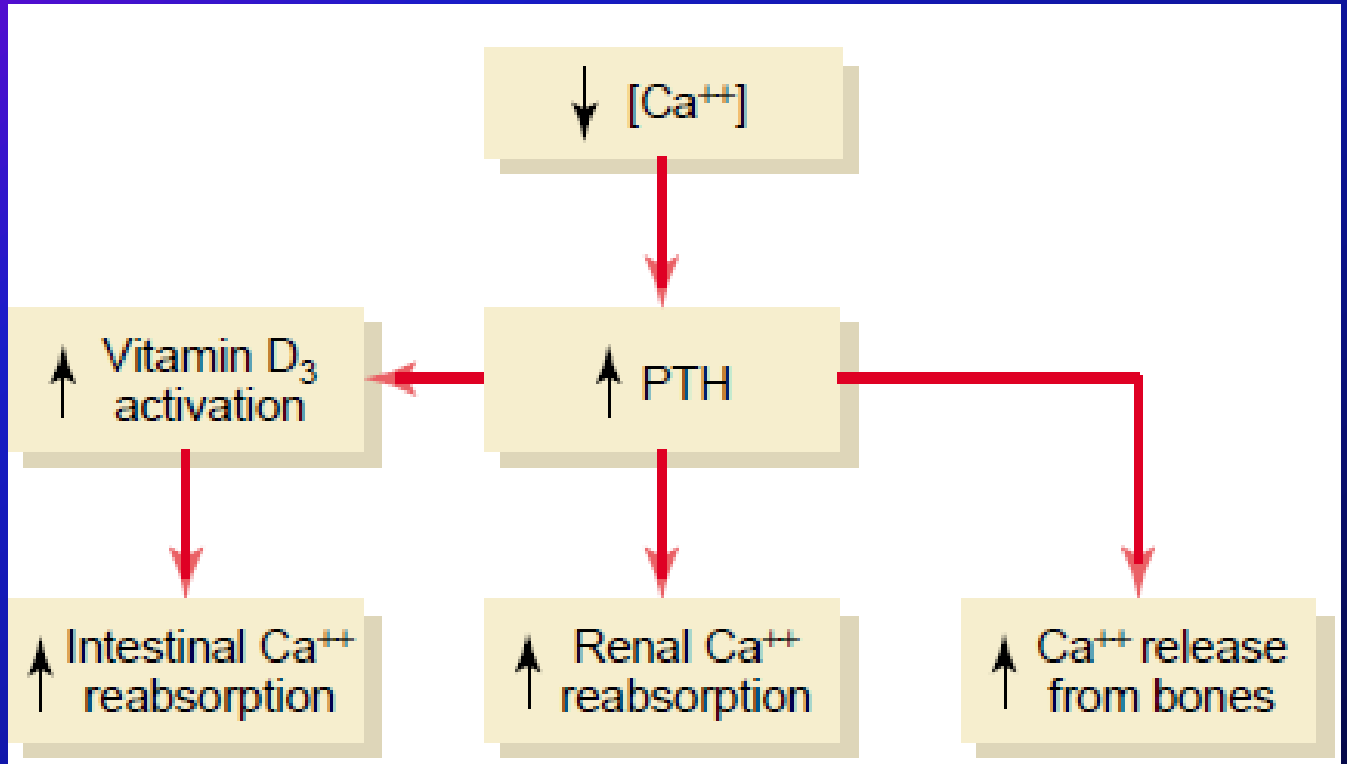
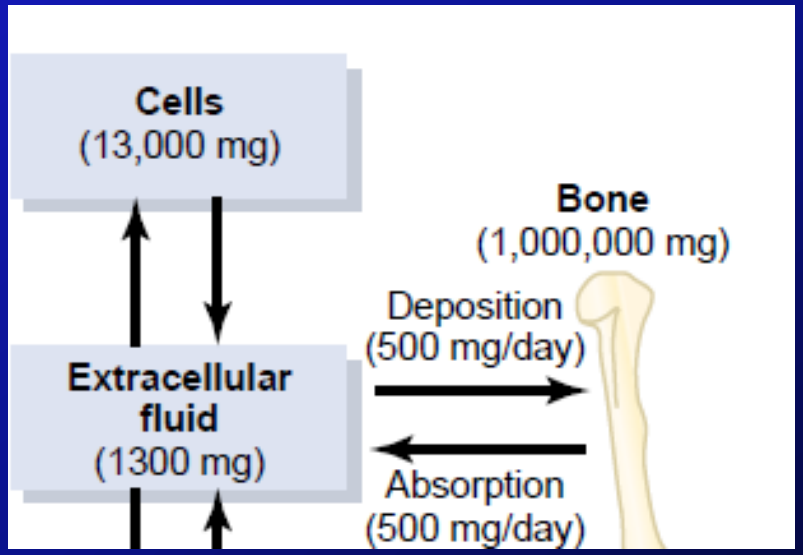


Figure 29–10

Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.

Overview of Calcium Distribution - Bone

The bones can serve
as large reservoirs, releasing calcium when extracellular fluid concentration decreases and storing excess calcium.



Bone – PTH Action

2. Slow Phase - Activation of Osteoclasts

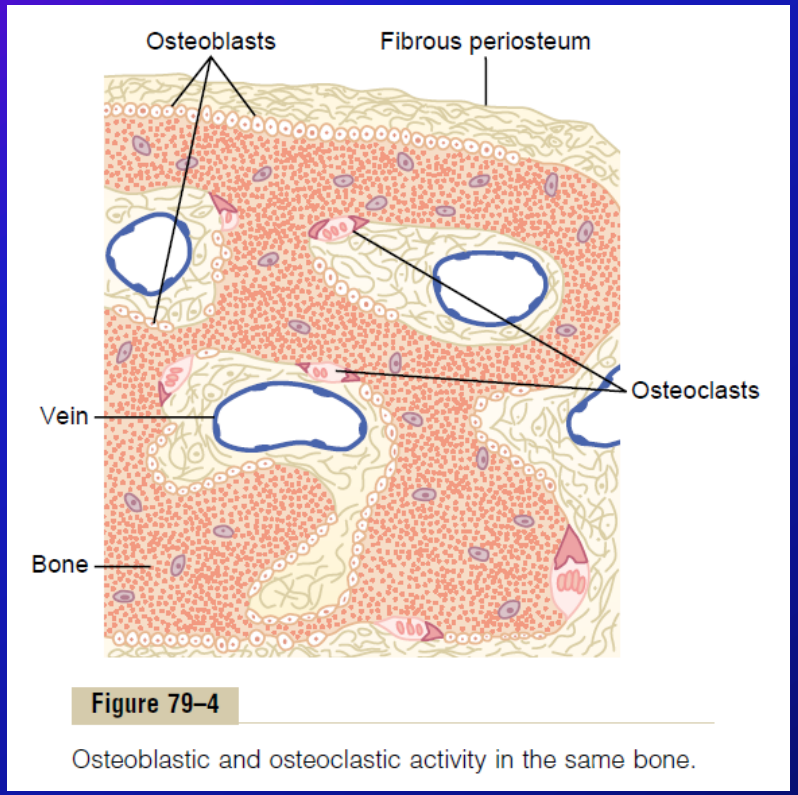


Figure 79–4

Osteoblastic and osteoclastic activity in the same bone.

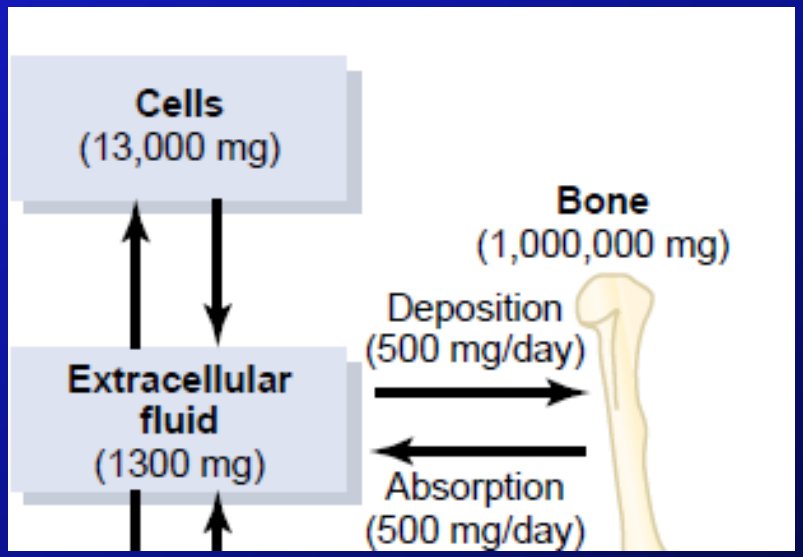
- Requires several days or weeks to become fully developed
- ***Osteoclastic reabsorption of the bone itself:***
- ***Removal of calcium phosphate from hydroxyapatite crystals - $Ca_{10}(PO_4)_6(OH)_2$***

(1) Proteolytic enzymes digest or dissolve the organic matrix
(2) Acids (citric, lactic) cause solution of the bone salts.

Overview of Calcium Distribution - Bone

Calcium salts in bone:

- Majority - hydroxyapatite crystals, bound tightly to collagen fibers
- 0.4 to 1 per cent – amorphous (noncrystalline) compounds



Exchangeable calcium

- A rapid *buffering mechanism*
- *In equilibrium* with the calcium ions in the extracellular fluids.

Bone – PTH Action

1. Rapid Phase - Activation of the Osteocytic Membrane System

A system of interconnected cells (osteoblasts and osteocytes) – a membrane that separates the bone itself from the extracellular fluid.

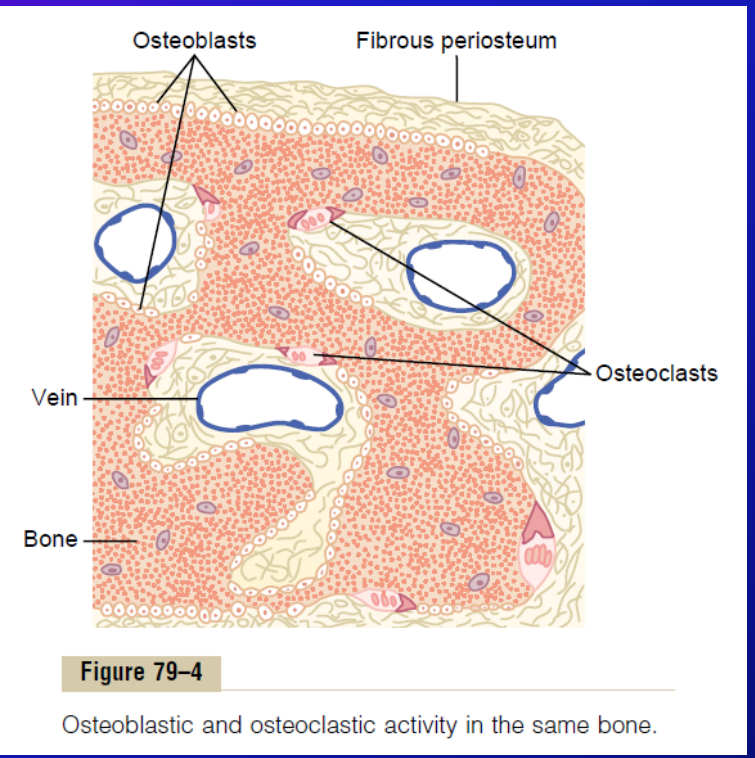


Figure 79–4

Osteoblastic and osteoclastic activity in the same bone.

- pumps calcium ions from the bone fluid into the extracellular fluid
- mobilizes exchanchable calcium

- PTH stimulates this pump
  - rapid phase begins in minutes, increases progressively for several hours.

Actions of PTH

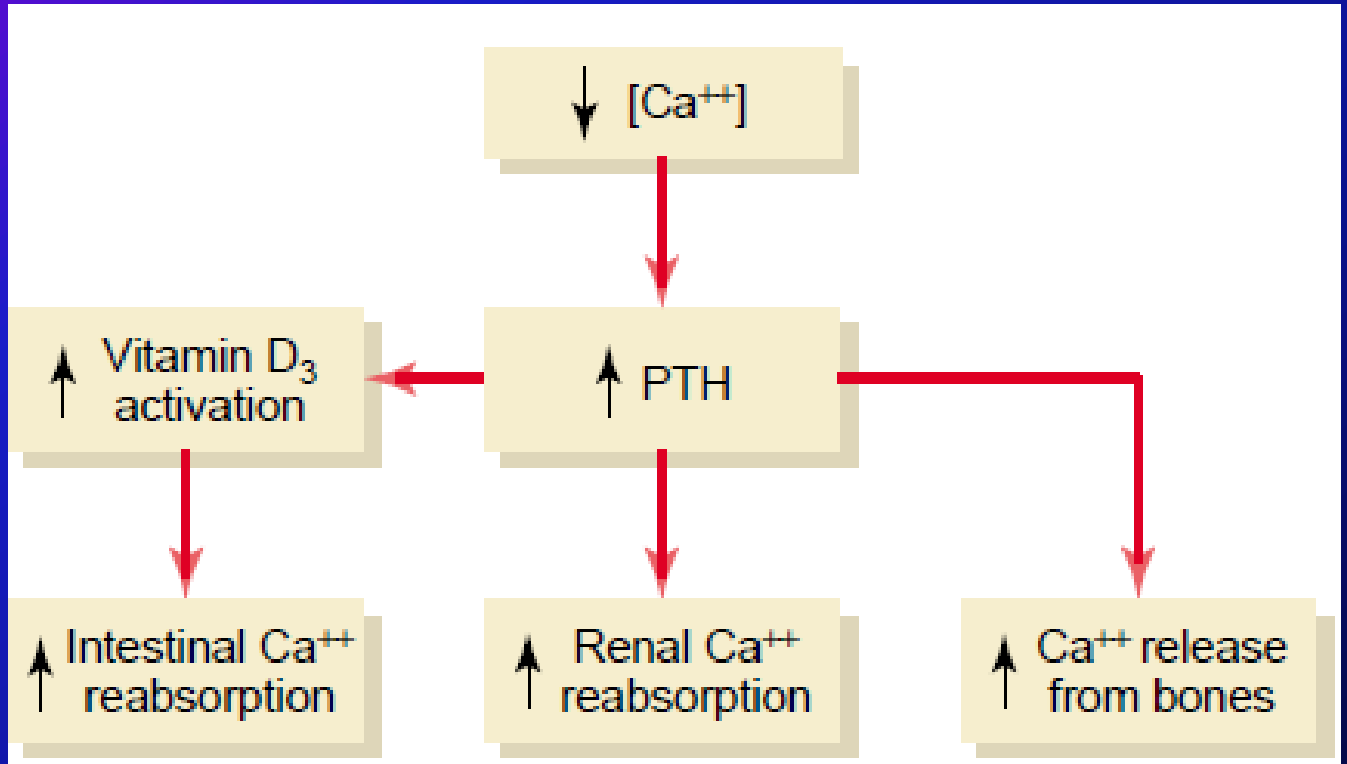


Figure 29–10

Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.

Overview of Calcium Distribution

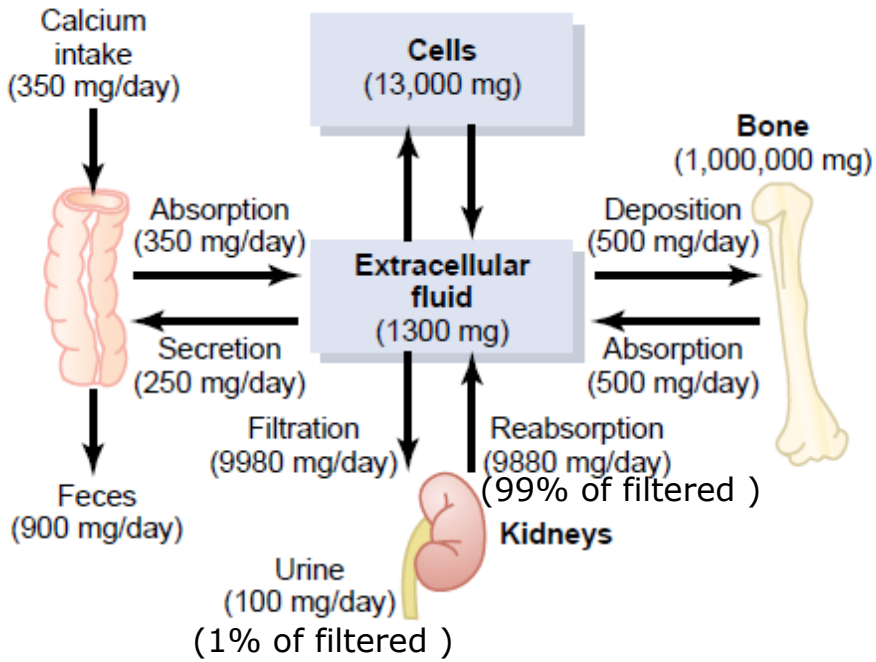


Figure 79–3

Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Kidney

Normally
- the renal tubules reabsorb 99 per cent of the filtered calcium
- about 1% -100 mg/day is excreted in the urine

-Normal calcium excretion –
- <4 mg/kg body weidht/day
- < 200 mg/d (5 mmol/d)

- > 4 mg/kg body mass /day – hypercalciuria

Kidney - Calcium Reabsorption in the Renal Tubules

1). Proximal tubule

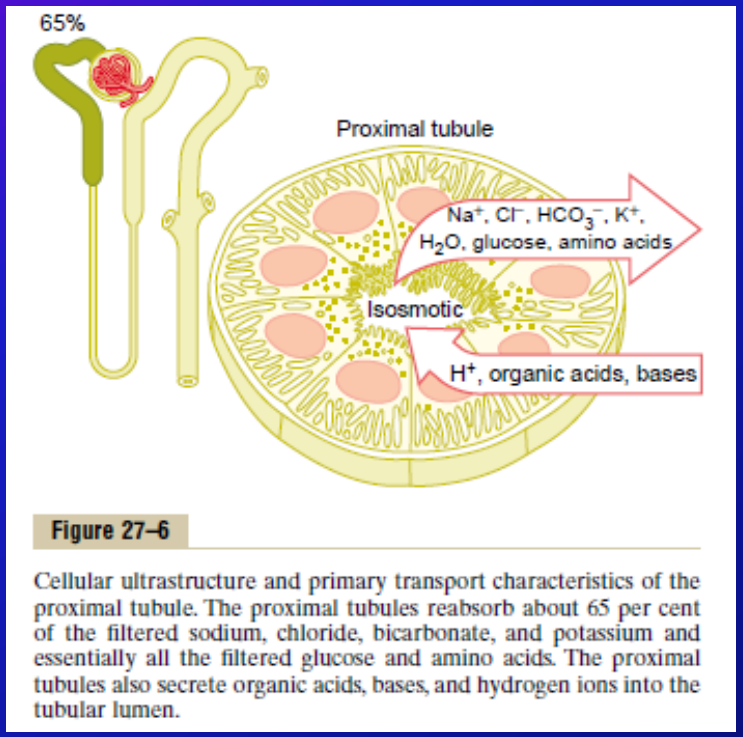


Figure 27–6

Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 per cent of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.

- Independent on PTH
- Usually parallels sodium and water reabsorption.

- Absorbed 65 per cent of the filtered calcium

Kidney - Calcium Reabsorption in the Renal Tubules

2). Thick ascending loops of Henle

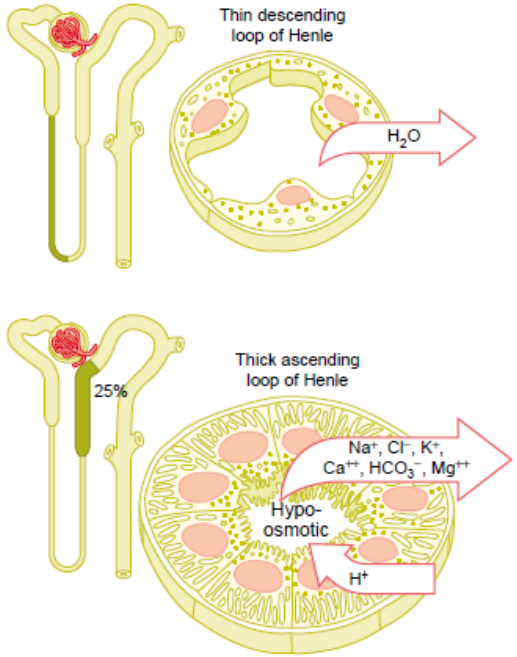


Figure 27–8

Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and the thick ascending segment of the loop of Henle (*bottom*). The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption. The thick ascending limb of the loop of Henle reabsorbs about 25 per cent of the filtered loads of sodium, chloride, and potassium, as well as large amounts of calcium, bicarbonate, and magnesium. This segment also secretes hydrogen ions into the tubular lumen.

- Dependent on PTH
- Absorbed 20-35 per cent of the filtered calcium

Calcium Reabsorption in the Renal Tubules

3). Distal and collecting tubules

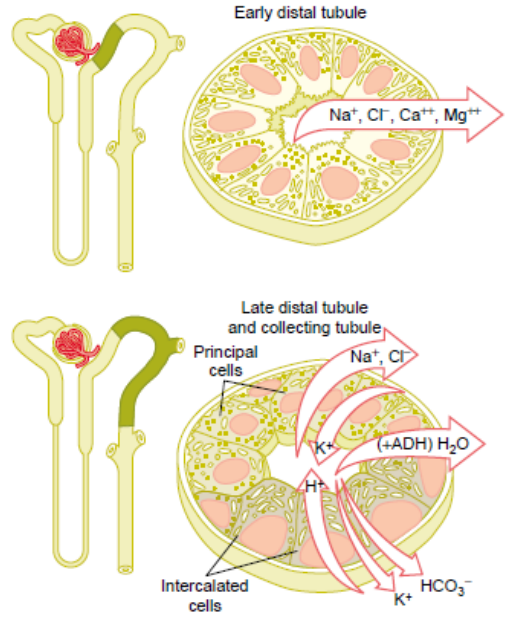


Figure 27–11

Cellular ultrastructure and transport characteristics of the early distal tubule and the late distal tubule and collecting tubule. The early distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium, chloride, calcium, and magnesium but is virtually impermeable to water and urea. The late distal tubules and cortical collecting tubules are composed of two distinct cell types, the *principal cells* and the *intercalated cells*. The principal cells reabsorb sodium from the lumen and secrete potassium ions into the lumen. The intercalated cells reabsorb potassium and bicarbonate ions from the lumen and secrete hydrogen ions into the lumen. The reabsorption of water from this tubular segment is controlled by the concentration of *antidiuretic hormone*.

- Dependent on PTH
- Absorbed 4-9 per cent of the filtered calcium

Kidney - Phosphate Reabsorption in the Renal Tubules

Proximal tubule

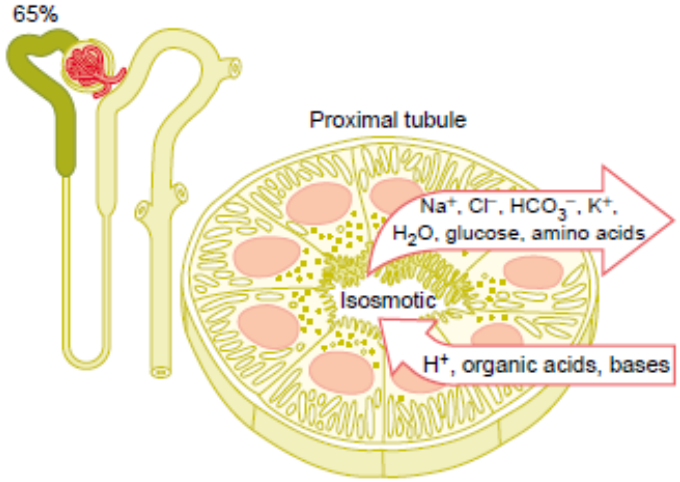


Figure 27–6

Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 per cent of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.

- *Usually -continual excretion of phosphate into the urine*
- *Phosphate threshold = 0.8 mM/L*
- *Tm = 0.1 mM/min*

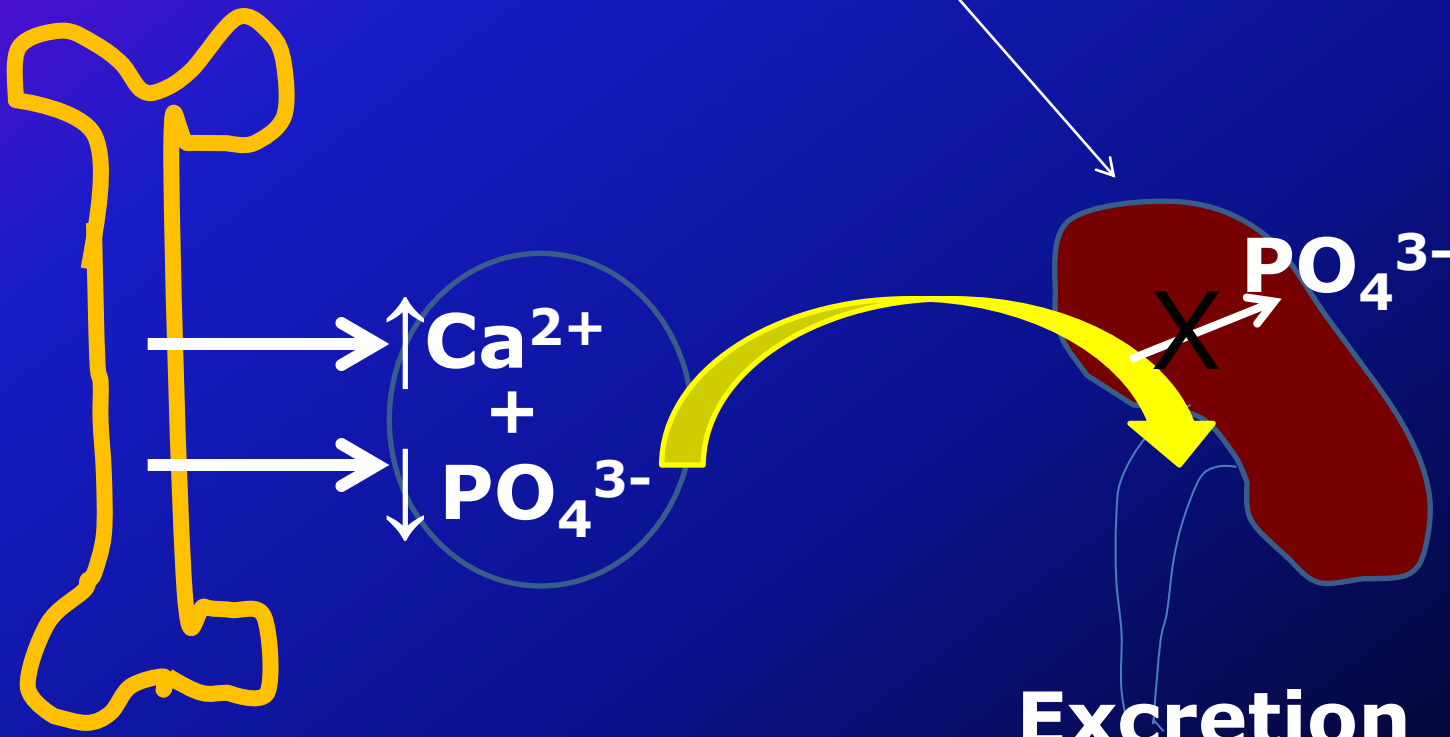
PTH

- inhibits phosphate reabsorption
- increases phosphate excretion **(phosphaturic effect)**
  - inhibits Na^+-phosphate cotransport
  - lowers Tm

PTH

+ $1,25(OH)_2D_3$

Bone resorption



Kidney – Reabsorption in the Renal Tubules

- ↑ reabsortion of magnesium ions, hydrogen ions
- ↓ reabsortion of sodium, potassium, and amino acids

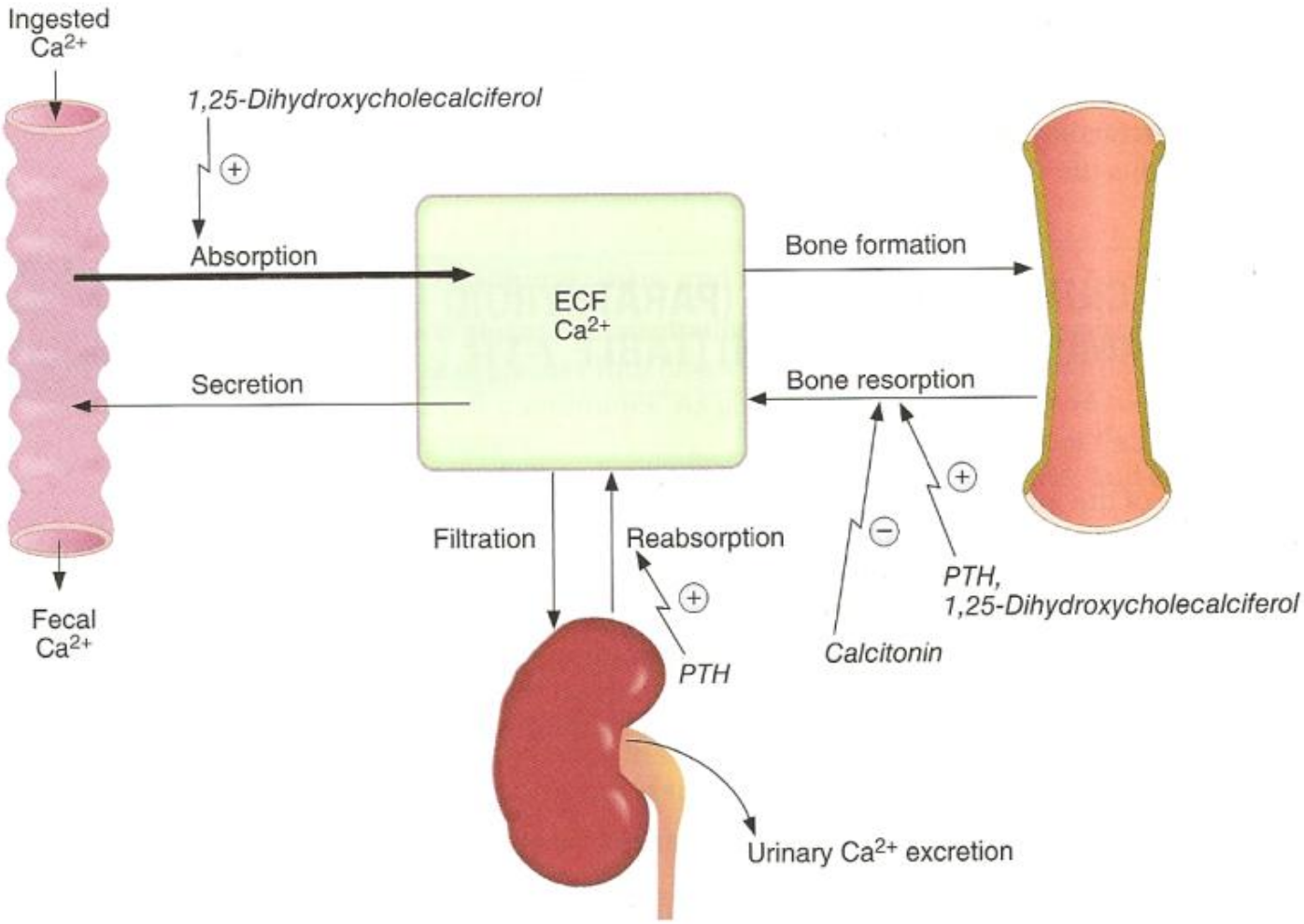


FIGURE 7-13 Hormonal regulation of Ca^{2+} metabolism. ECF = extracellular fluid; PTH = parathyroid hormone.

Actions of PTH

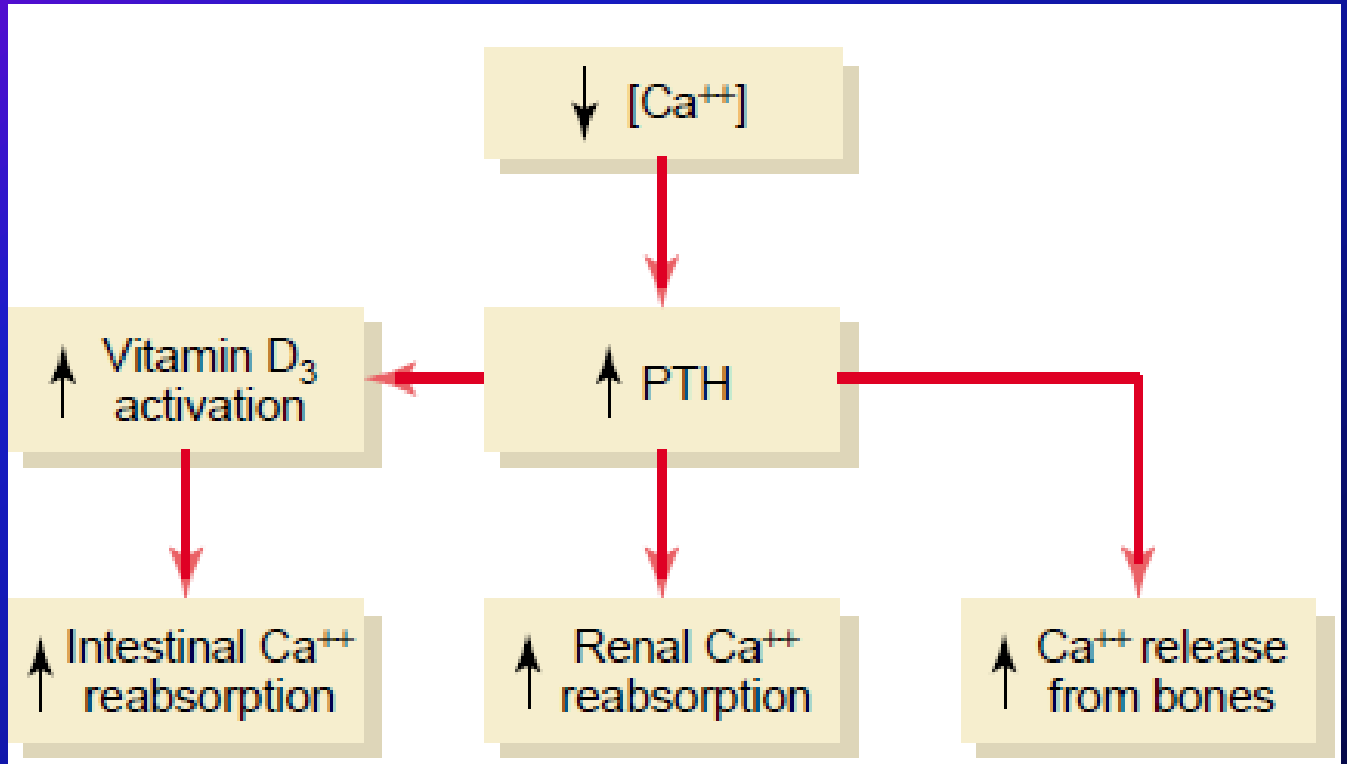
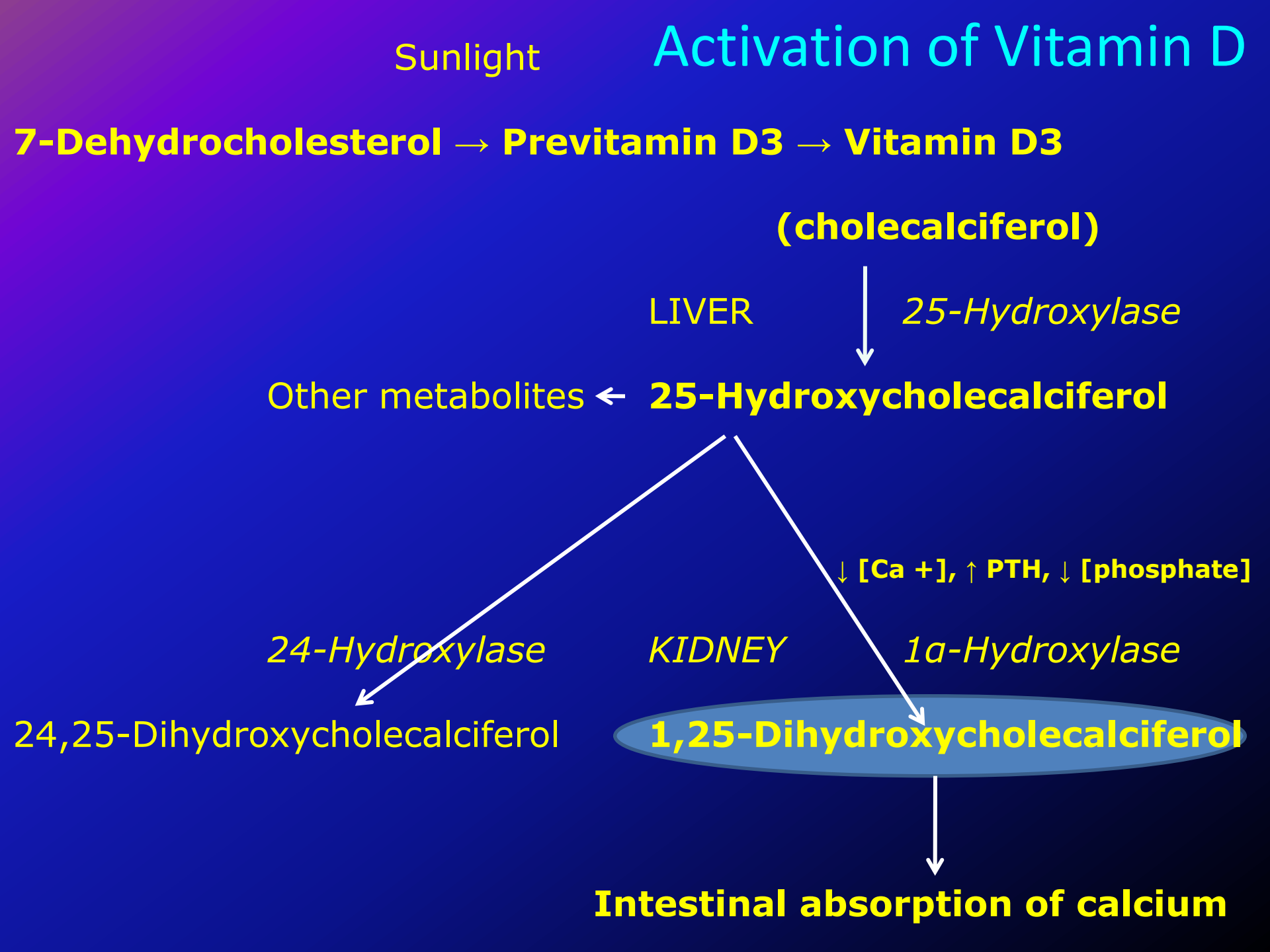


Figure 29–10

Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.

Activation of Vitamin D



Activation of Vitamin D

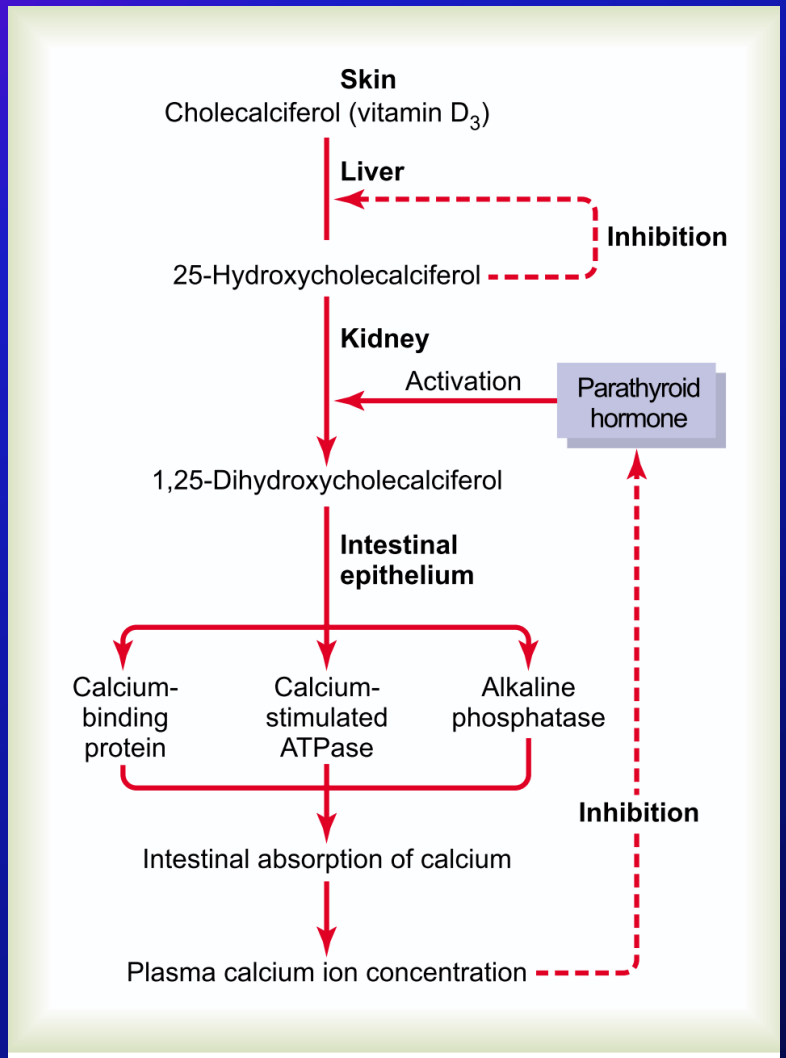


Figure 79–6

Activation of vitamin D_3 to form 1,25-dihydroxycholecalciferc and the role of vitamin D in controlling the plasma calciur concentration.

Activation of Vitamin D

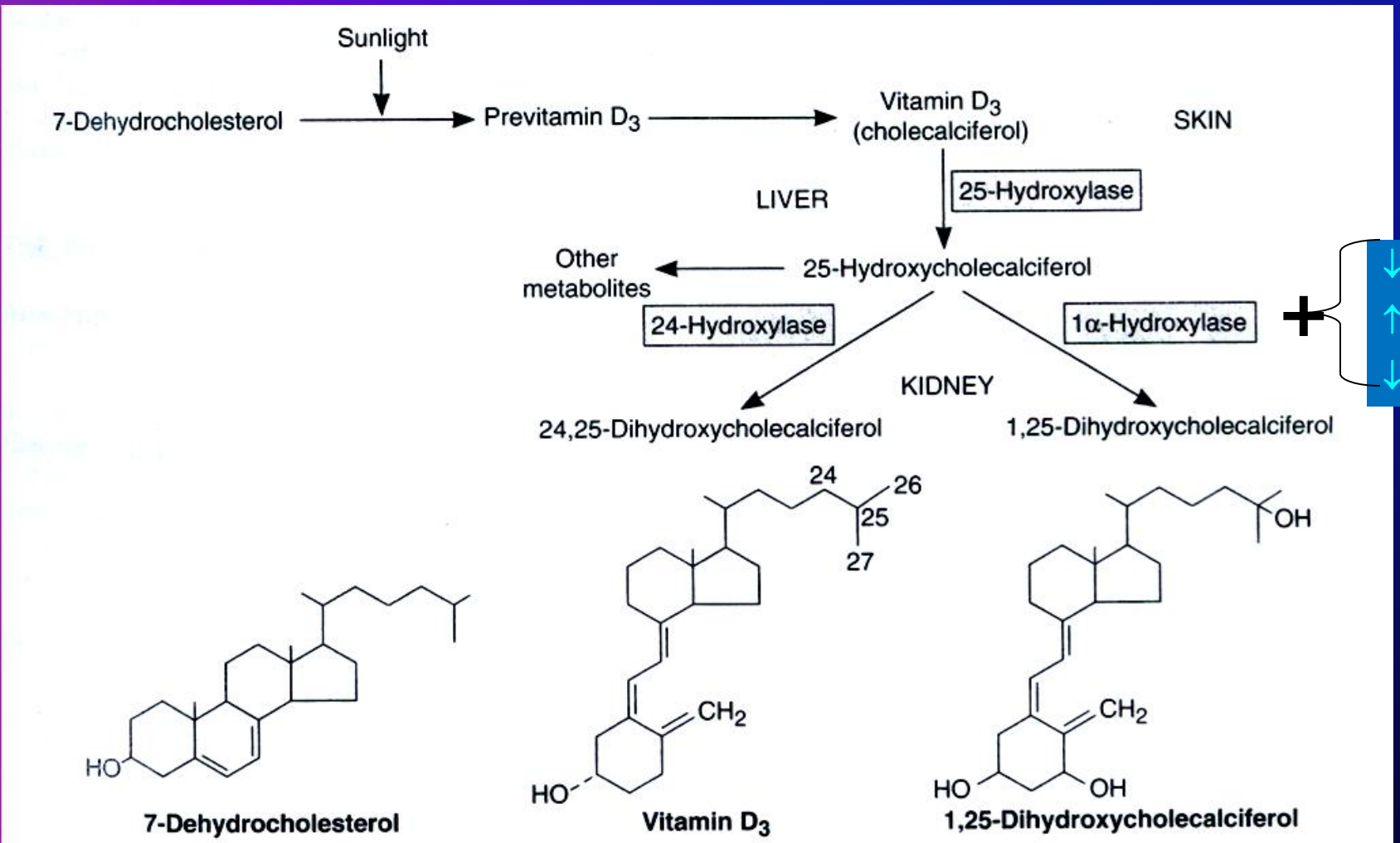


Figure 21–7. Formation and hydroxylation of vitamin D_3. 25-Hydroxylation takes place in the liver, and the other hydroxylations occur primarily in the kidneys. The formulas of 7-dehydrocholesterol, vitamin D_3, and 1,25-dihydroxycholecalciferol are also shown.

Effect of Plasma Calcium Level on Plasma 1,25-Dihydroxycholecalciferol Concentration

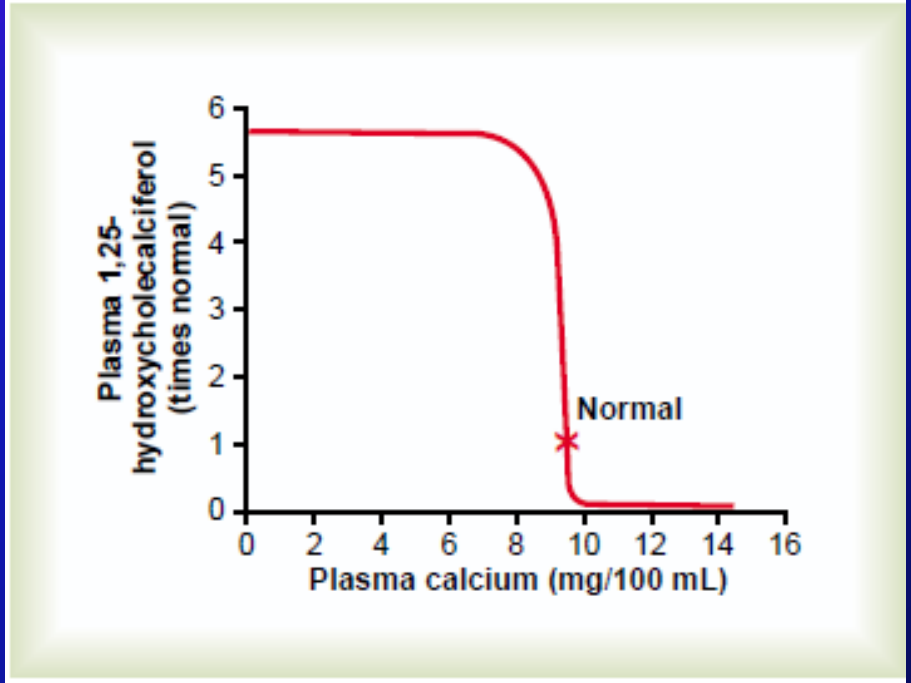


Figure 79–8

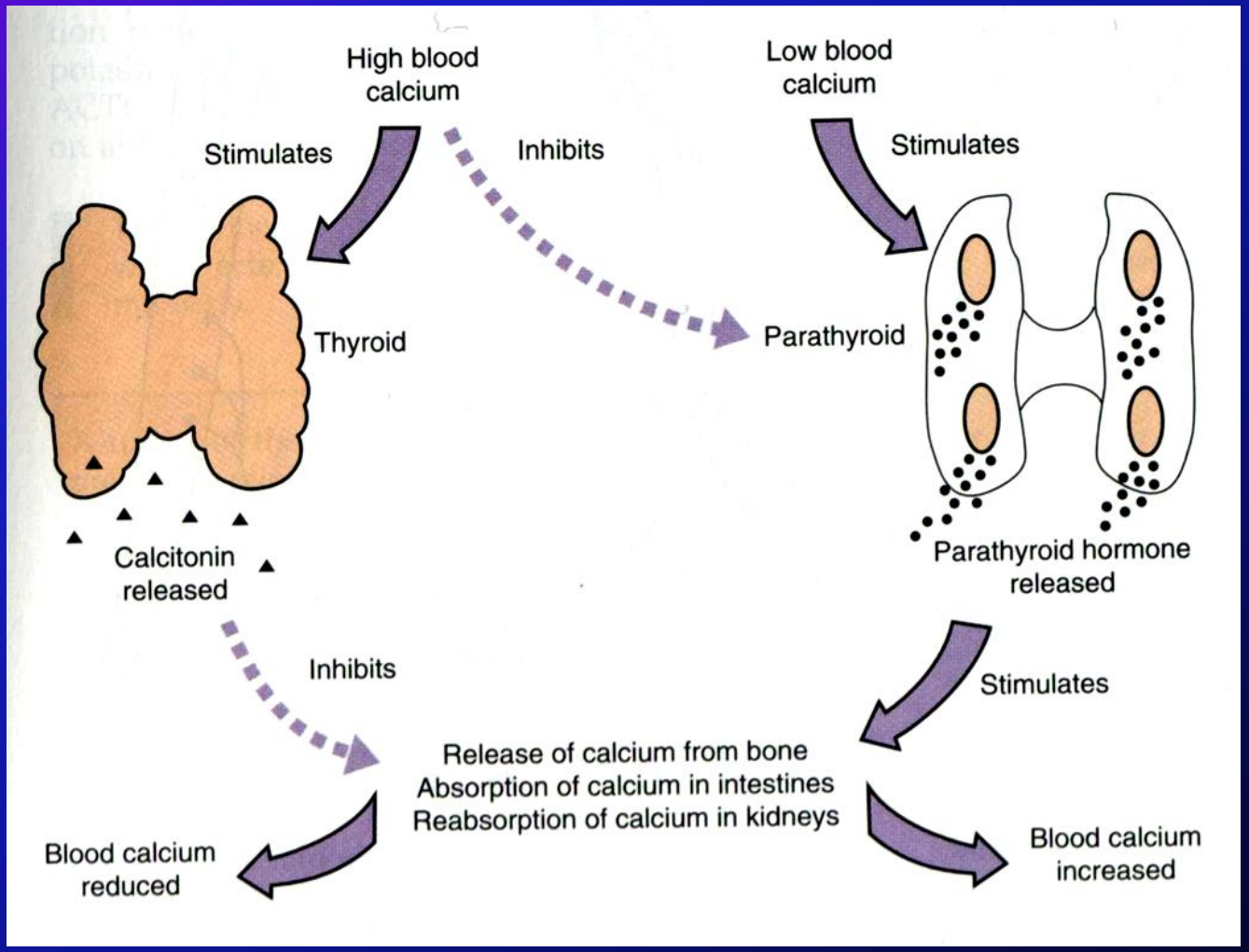
Effect of plasma calcium concentration on the plasma concentration of 1,25-dihydroxycholecalciferol. This figure shows that a slight decrease in calcium concentration below normal causes increased formation of activated vitamin D, which in turn leads to greatly increased absorption of calcium from the intestine.

table 7-11 Summary of Hormones that Regulate Ca^{2+}

	PTH	Vitamin D	Calcitonin
Stimulus for secretion	↓ Serum [Ca^{2+}]	↓ Serum [Ca^{2+}] ↑ PTH ↓ Serum [phosphate]	↑ Serum [Ca^{2+}]
Action on:			
Bone	↑ Resorption	↑ Resorption	↓ Resorption
Kidney	↓ P reabsorption (↑ urinary cAMP)	↑ P reabsorption	
	↑ Ca^{2+} reabsorption	↑ Ca^{2+} reabsorption	
Intestine	↑ Ca^{2+} absorption (via activation of vitamin D)	↑ Ca^{2+} absorption (calbindin D-28K) ↑ P absorption	
Overall effect on:			
Serum [Ca^{2+}]	↑	↑	↓
Serum [phosphate]	↓	↑	

cAMP = cyclic adenosine monophosphate. See Table 7-1 for other abbreviation.

Effect of PTH and Calcitonin on Blood Calcium Level



Case

Carl is a 53-year-old violinist with a local symphony orchestra. He has always been in excellent heath. However after two sets of tennis on a hot day, he suddenly experienced the worst pain in his life. The pain came in waves that started in his right flank and radiated into his groin. When he went to bathroom, he voided bright red urine.

His tennis partner drove him to the emergency room, where an utrasonography showed several small stones in the right kidney and an enlarged ureter.

Carl was sent home with a prescription of narcotics and instruction to drink lots of water and „wait it out”. This evening he voided red urine and two brown stones.

There was nothing unusual in this history, except for constipation and his wife`s new „health kick” (She had convinced Carl to take multivitamins and Ca2+ supplementation).

Carl` Laboratory Finding

➢ *Total serum Ca^{2+}*	*11.5 mg/dL*	*(normal , 9-11 mg/dL)*
➢ *Serum ionized Ca^{2+}*	*5,75 m/dL*	*(normal, 4-5,2 mg/d)*
➢ *Serum phosphate*	*2 mg/dL*	*(normal, 3-4 mg/dL)*
➢ *Serum PTH*	*125 pg/mL*	*(normal, 10-65 pg/mL)*
➢ *Alkaline phosphate*	*Elevated*	
➢ *Urinary Ca^{2+} excretion*	*Elevated*	

Diagnosis?

table 7-12 Pathophysiology of PTH

Disorder	PTH	1,25-Dihydroxy-cholecalciferol	Bone	Urine	Serum [Ca^{2+}]	Serum [P]
Primary hyperparathyroidism	↑	↑ (PTH stimulates 1α-hydroxylase)	↑ Resorption	↑ P excretion (phosphaturia) ↑ Ca^{2+} excretion (high filtered load of Ca^{2+}) ↑ urinary cAMP	↑	↓
Humoral hypercalcemia of malignancy	↓	—	↑ Resorption	↑ P excretion	↑	↓
Surgical hypoparathyroidism	↓	↓	↓ Resorption	↓ P excretion ↓ urinary cAMP	↓	↑
Pseudohypoparathyroidism	↑	↓	↓ Resorption (defective G_s)	↓ P excretion ↓ urinary cAMP (defective G_s)	↓	↑
Chronic renal failure	↑ (2°)	↓ (caused by renal failure)	Osteomalacia (caused by ↓ 1,25-dihydroxy-cholecalciferol) ↑ Resorption (caused by ↑ PTH)	↓ P excretion (caused by ↓ GFR)	↓ (caused by ↓ 1,25-dihydroxy-cholecalciferol)	↑ (caused by ↓ P excretion)

cAMP = cyclic adenosine monophosphate; GFR = glomerular filtration rate. See Table 7-1 for other abbreviation.

Primary Hyperparathyroidism („stones, bones, and groans”)

- Cause

- autonomous secretion of PTH (not inhibited by hypercalcemia)

- Single adenoma (85%)
- Parathyroid hyperplasia (15%)
- Parathyroid carcinoma (1%)

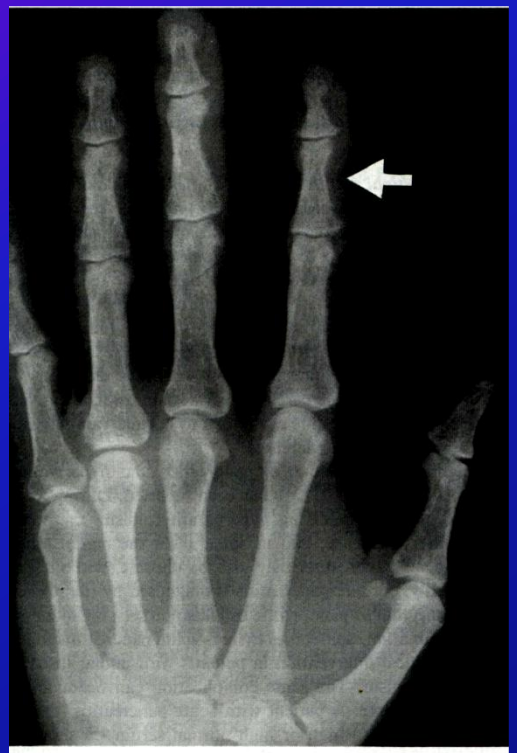
In 50-60% patients - only one manifestation !

Primary Hyperparathyroidism - ↑PTH
↑Bone resorption

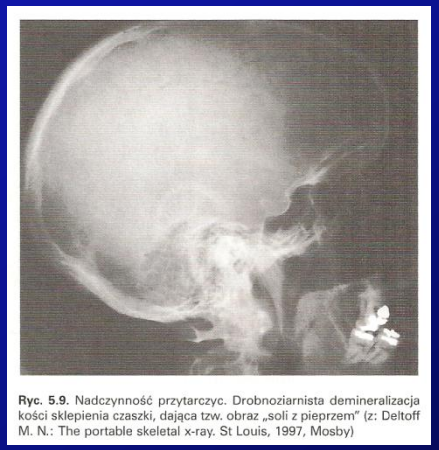
MILD - bone deposition can compensate for reabsorption

SEVERE- bone reabsorption outstrips deposition

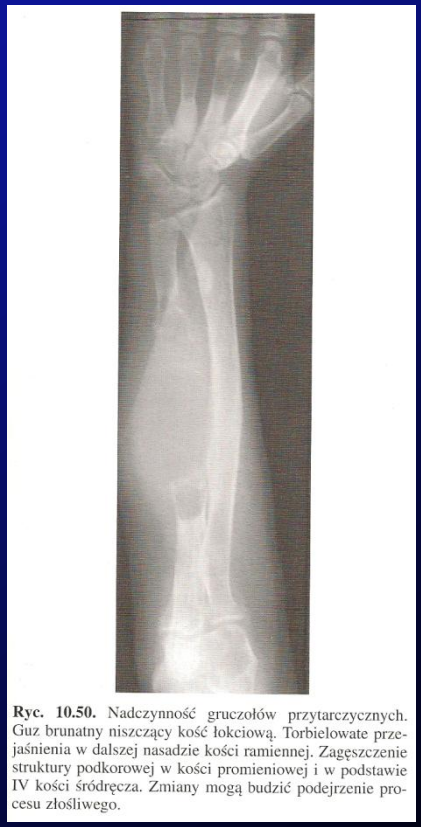
- *osteoporosis, osteolysis;*
- *subperiosteal resorption*
- *bone cysts, fractures*



igure 11-8 X-ray of hand showing marked evidence of yperparathyroidism in a patient with renal failure and secondary ypersecretion of PTH. Note resorption of tips of distal phalanges nd subperiosteal resorption on radial sides of phalanges from econd and third fingers.



Ryc. 5.9. Nadczynność przytarczyc. Drobnoziarnista demineralizacja kości sklepienia czaszki, dająca tzw. obraz „soli z pieprzem" (z: Deltoff M. N.: The portable skeletal x-ray. St Louis, 1997, Mosby)



Ryc. 10.50. Nadczynność gruczołów przytarczycznych. Guz brunatny niszczący kość łokciową. Torbielowate przejaśnienia w dalszej nasadzie kości ramiennej. Zagęszczenie struktury podkorowej w kości promieniowej i w podstawie IV kości śródręcza. Zmiany mogą budzić podejrzenie procesu złośliwego.

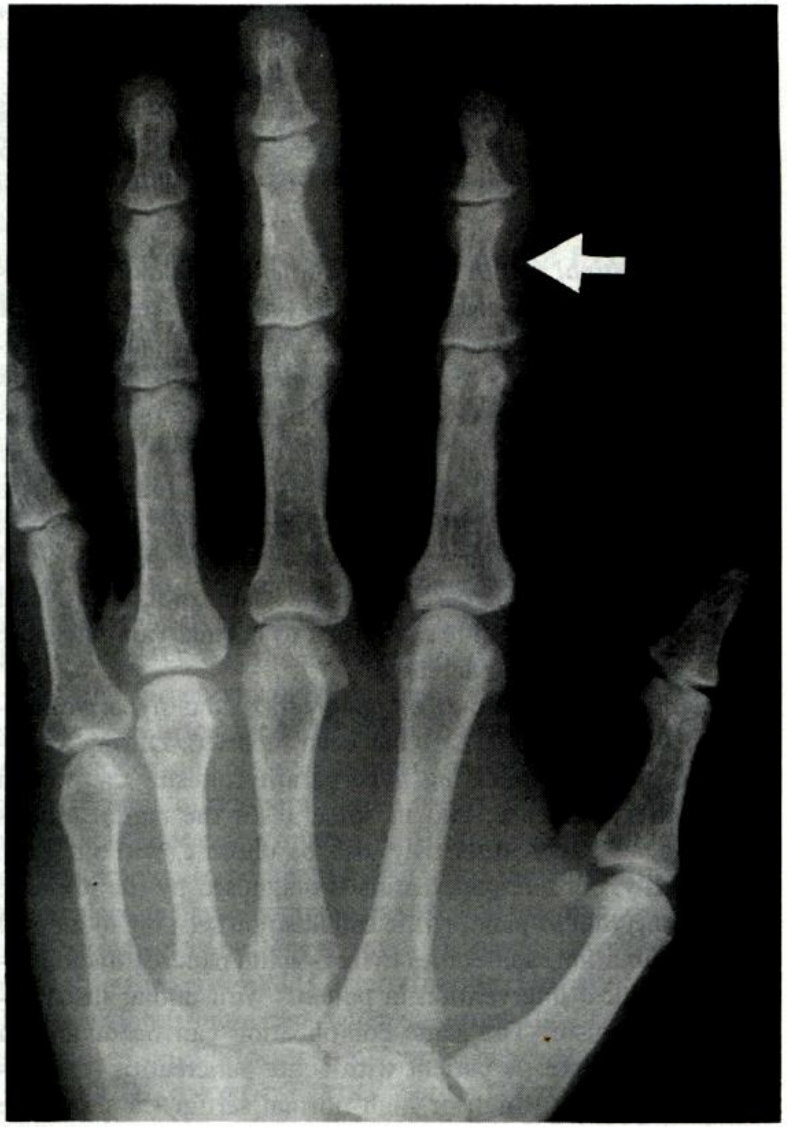
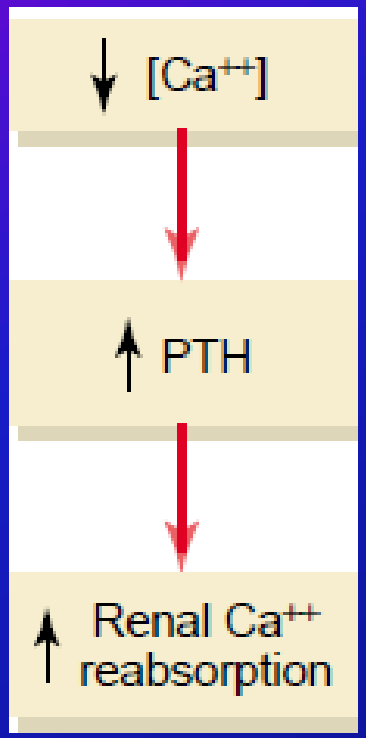


Figure 11-8 X-ray of hand showing marked evidence of hyperparathyroidism in a patient with renal failure and secondary hypersecretion of PTH. Note resorption of tips of distal phalanges and subperiosteal resorption on radial sides of phalanges from second and third fingers.

Kidney - Calcium Reabsorption in the Renal Tubules

Physiologic condition



↓ urine Ca^{2+} excretion
↑ serum Ca^{2+} conc.

Primary Hyperparathyroidism - Excess PTH

- Hypercalcemia
- ↑ filtered load of Ca^{2+}
- Despite increased Ca^{2+} reabsorption, the filtered load of Ca^{2+} eventually overwhelms the reabsorptive capacity of the kidney
- ↑ urinary Ca^{2+} excretion

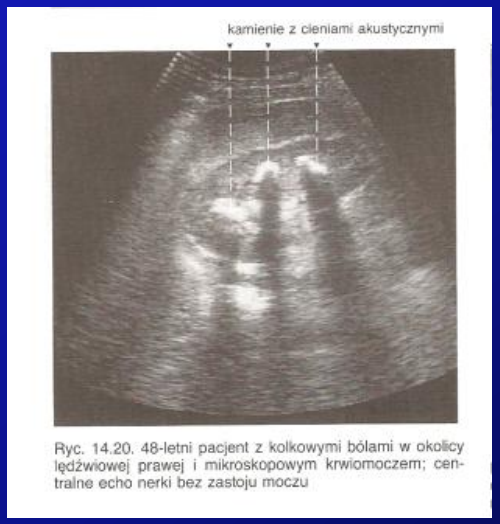
Extreme tendency to form kidney stones

- ↑urinary phosphate excretion

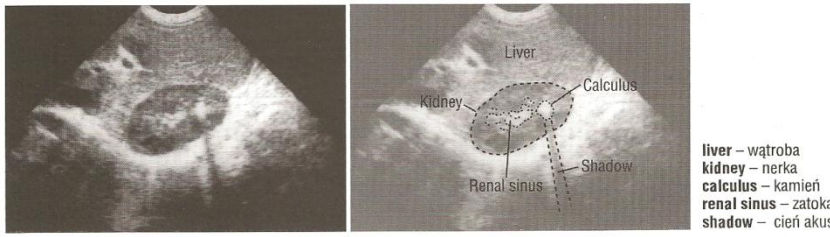
Primary Hyperparathyroidism - Excess PTH

Renal Manifestations

- Nephrocalcinosis
- Kidney stones

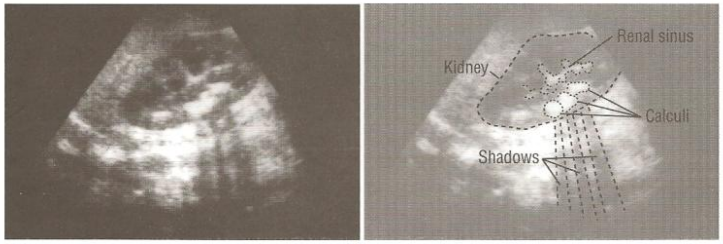


Ryc. 14.20. 48-letni pacjent z kolkowymi bólami w okolicy lędźwiowej prawej i mikroskopowym krwiomoczem; centralne echo nerki bez zastoju moczu



liver – wątroba
kidney – nerka
calculus – kamień
renal sinus – zatoka nerkowa
shadow – cień akustyczny

Ryc. 114a. Przekrój podłużny, kamień w prawej nerce.



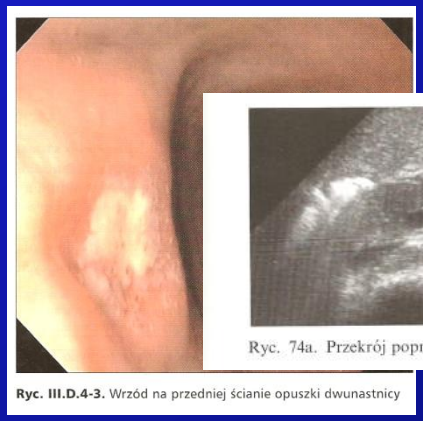
kidney – nerka
renal sinus – zatoka nerkowa
calculi – kamienie
shadows – cienie

Ryc. 114b. Przekrój podłużny: liczne kamienie w prawej nerce.

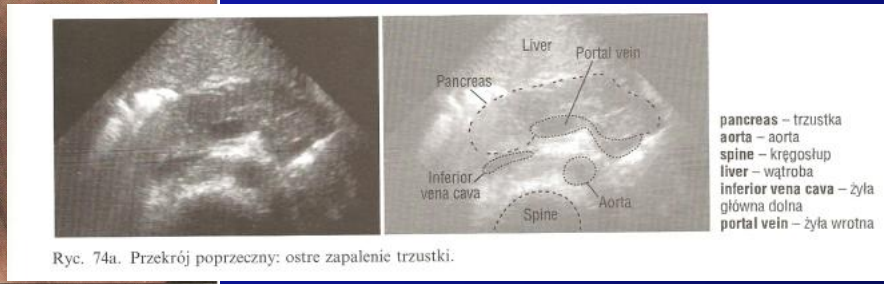
Primary Hyperparathyroidism - ↑PTH

GI Manifestations

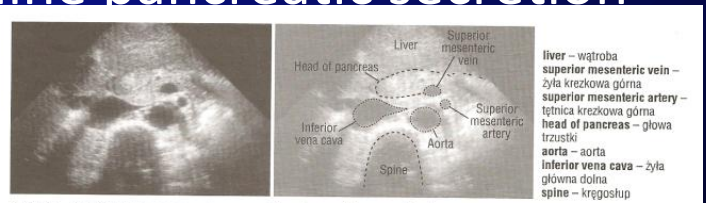
- Nausea, constipation
- Peptic ulcer
  - Calcium stimulates secretion od gastrin
- Pancreatitis – pathogenesis (?)
  - Ca^{2+} may activate pancreatic trypsynogen
  - Increased intravascular coagulation
  - Precipitation of calcium in alkaline pancreatic secretion



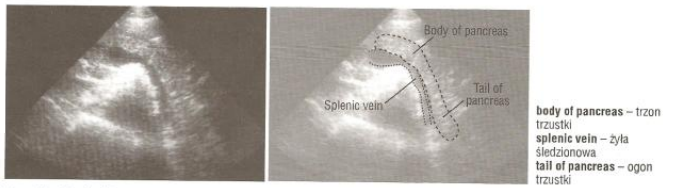
Ryc. III.D.4-3. Wrzód na przedniej ścianie opuszki dwunastnicy



Ryc. 74a. Przekrój poprzeczny: ostre zapalenie trzustki.



Ryc. 70b. Przekrój poprzeczny: głowa prawidłowej trzustki — projekcja przez lewy płat wątroby.



Ryc. 70c. Przekrój poprzeczny: ogon prawidłowej trzustki.

Primary Hyperparathyroidism - ↑PTH

Nervous and Muscular Systems

- First manifestation – calcium above about 12 mg/dL
- Marked manifestation – calcium level above 15 g/dL
- Calcium above 17 mg/dL - calcium phosphate crystals are likely to precipitate throughout the body

➢ **Depression of Nervous System and Muscle Activity**

- Sluggish reflex activities
- Muscle weakness, atrophy
- Drowsiness, lethargy
- A great spectrum of psychiatric disorders (depression, memory impairment)

table 7-12 Pathophysiology of PTH

Disorder	PTH	1,25-Dihydroxy-cholecalciferol	Bone	Urine	Serum [Ca^{2+}]	Serum [P]
Primary hyperparathyroidism	↑	↑ (PTH stimulates 1α-hydroxylase)	↑ Resorption	↑ P excretion (phosphaturia) ↑ Ca^{2+} excretion (high filtered load of Ca^{2+}) ↑ urinary cAMP	↑	↓
Humoral hypercalcemia of malignancy	↓	—	↑ Resorption	↑ P excretion	↑	↓
Surgical hypoparathyroidism	↓	↓	↓ Resorption	↓ P excretion ↓ urinary cAMP	↓	↑
Pseudohypoparathyroidism	↑	↓	↓ Resorption (defective G_s)	↓ P excretion ↓ urinary cAMP (defective G_s)	↓	↑
Chronic renal failure	↑ (2°)	↓ (caused by renal failure)	Osteomalacia (caused by ↓ 1,25-dihydroxy-cholecalciferol) ↑ Resorption (caused by ↑ PTH)	↓ P excretion (caused by ↓ GFR)	↓ (caused by ↓ 1,25-dihydroxy-cholecalciferol)	↑ (caused by ↓ P excretion)

cAMP = cyclic adenosine monophosphate; GFR = glomerular filtration rate. See Table 7-1 for other abbreviation.

HYPOPARATHYROIDISM

Causes - Idiopathic (parathyroid glands absent, hypoplastic),

- Surgical hypoparathyroidism (most common)

PTH level	↓
1,25 $(OH)_2$ D_3	↓
BONE	↓ resorption
URINE	↓ P excretion
Serum [P]	↑
Serum [Ca^{2+}]	↓ - ***HYPOCALCEMIA***

Nervous System ↑ permeability of neuronal membranes to Na^+ → ↑ excitability of nervous system → **TETANY**

Muscular system Muscle cramps, stiffness, contractions – "carpopedal spasm": "obstetrical hand", plantar flexion of toes

Latent tetany - positive results of provocative tests:

- Chvostek`s sign – a twitch of facial and upper lip muscles produced by a sharp tap given over the facial nerve
- Trousseau`s sign – "carpopedal spasm" induced by a sharp reduction of blood flow obtained with a blood pressure cuff

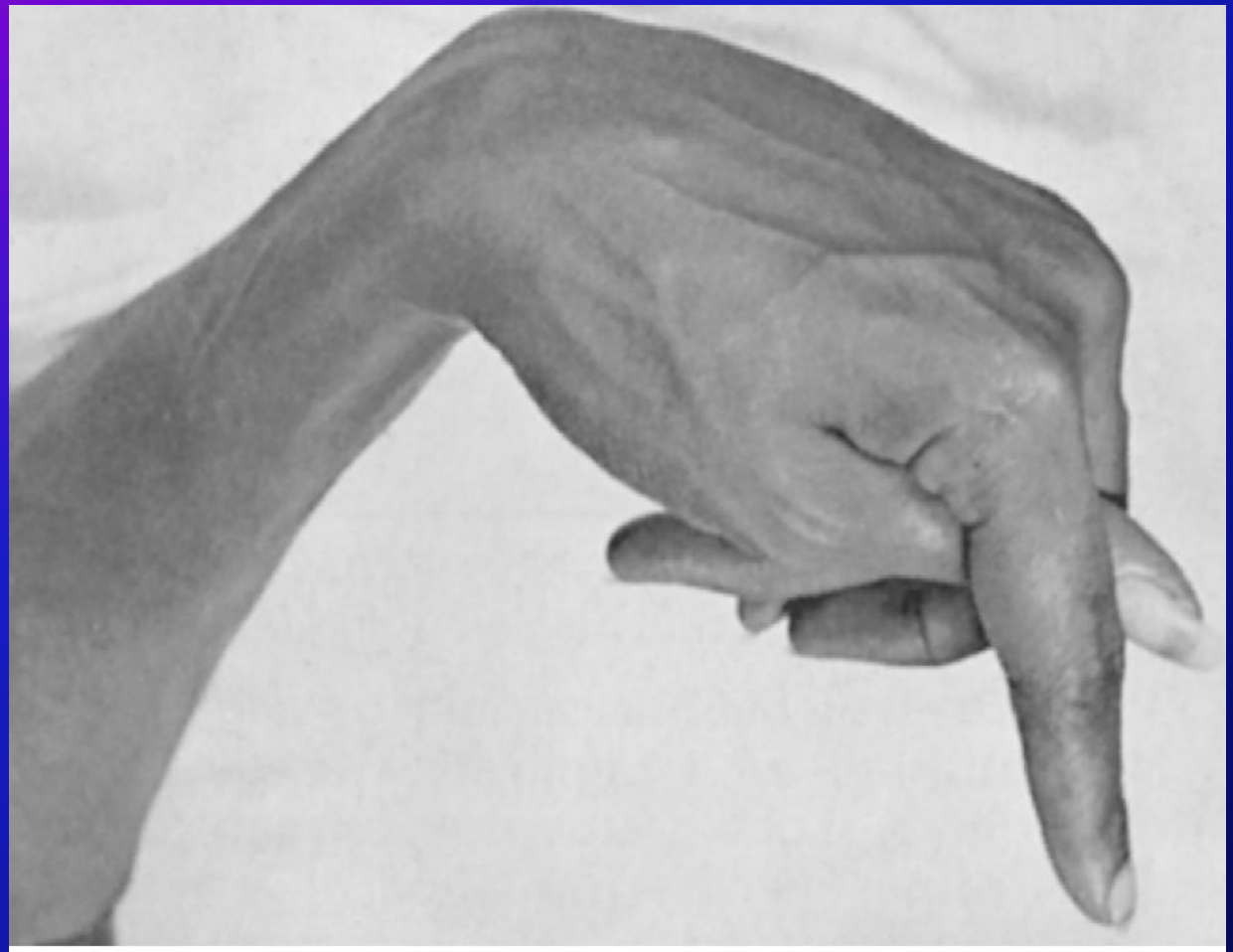


Figure 79–2

Hypocalcemic tetany in the hand, called carpopedal spasm.


Thank you