Calcium homeostasis and bone metabolism

Biological functions of Calcium

- Bone and teeth mineralization
- Regulate neuromuscular excitability
- Blood coagulation
- Relaxation and constriction of blood vessels
- Secretory processes
- Membrane integrity
- Plasma membrane transport
- Enzyme reactions
- Release of hormones and neurotransmitters
- Intracellular second messenger

Calcium dietary sources

Milk – 100 ml =120mg

Cheese – 15gm = 110mg

Yoghurt pot – 80gm = 160mg

Other sources

- **Fish**
- **Meat**
- **Bread**
- **Cereal**

Absorption of Calcium

- **Increased absorption by:**
  - **1,25 dihydroxycholecalciferol, (active form of Vit.D)**
  - **Parathyroid hormone (PTH)**
  - **Acidic PH**
  - **Lysine and Arginine**

- **Decreased absorption by:**
  - **Phytates**
  - **Oxalates**
  - **Phosphate**
  - **Mg**

Interactions

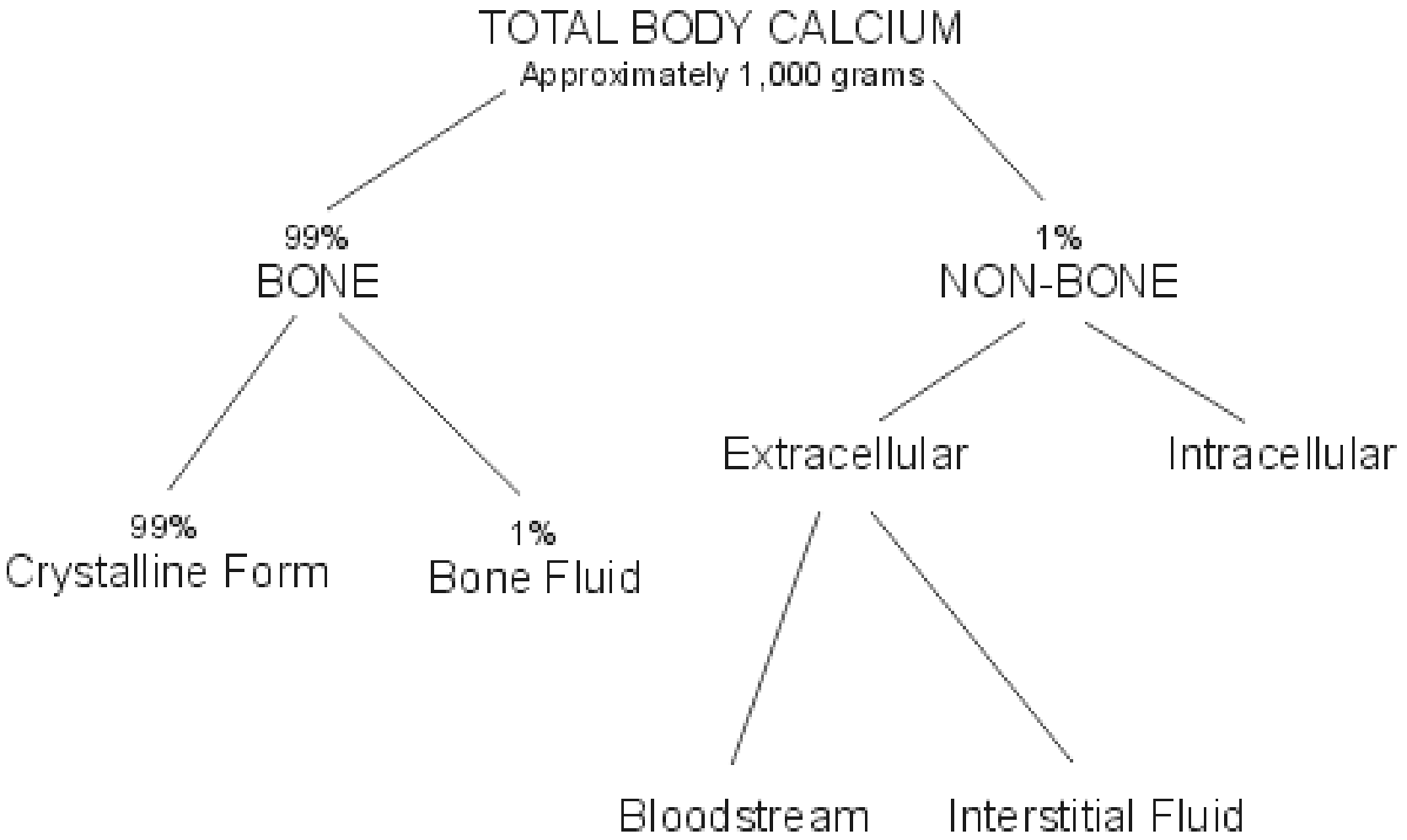
- **Phosphate: ↓ calcium excretion in the urine**
- **Caffeine: ↑ urinary and fecal excretion of calcium**
- **Sodium: ↑ sodium intake, ↑ loss of calcium in urine**
- **Dietary constituents: Phytic acid can reduce absorption of calcium by forming an insoluble salt (calcium phytate)**
- **Iron: calcium might have inhibitory effect on iron absorption**

Body requirements

Age (in years)	Calcium Requirement
1 – 3	500mg
4 - 8	800mg
9 - 18	1300mg
19 - 50	1000mg
51+	1500mg

Pregnant and lactating women are recommended a daily calcium intake of **1000mg**.

Distribution



Different Forms of Calcium

Most of the calcium in the body exists as the mineral hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$.

Calcium in the plasma:

- **50% in ionized form (the physiologically active form)**
- **40% bound to proteins (predominantly albumin)**
- **10% complexed with anions (citrate, sulfate, phosphate)**

Both total calcium and ionized calcium measurements are available in many laboratories

Circulating calcium fractions

total Ca^{2+}	=	ionized Ca^{2+}	+	protein bound Ca^{2+}	+	complexed Ca^{2+}
(2.2–2.6 mmol/L)		(1.1–1.3 mmol/L)		(0.9–1.0 mmol/L)		(0.2–0.3 mmol/L)

Relationship between hydrogen and calcium ions

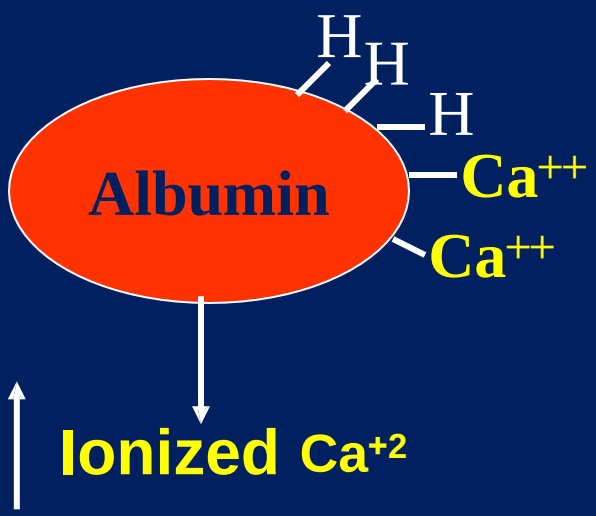
- **In acidosis :**

Hydrogen ion competes with calcium to bind protein, as well as the increase of the solubility of calcium substances in bone so the free fraction elevates (hypercalcemia) and may cause osteomalacia.

- **In alkalosis :**

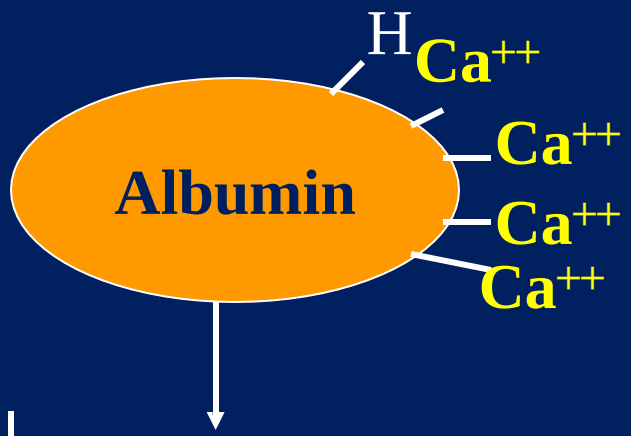
The protein bound fraction increases and the solubility of calcium substances is low, so the free fraction decreases (hypocalcemia) and may leads to tetany.

Acidosis



↑ **Ionized Ca^{+2}**

Alkalosis



↓ **Ionized Ca^{+2}**

Hyperventilation →Respiratory alkalosis → ↓ionized Ca^{+2} → Tetany.

- Increase in protein con. → ↑ in total Ca^{+2} conc.
- Decrease in protein con. → ↓ in total Ca^{+2} conc.
- The effects on ionized Ca^{+2} conc. are insignificant.
- Changes in anion con. alter the ionized Ca^{+2} con. e.g.
- ↑plasma phosphate con. → ↑ in the conc. of Ca^{2+} complexd to phosphate → ↓ ionized Ca^{+2} con.

Ca^{+2} affects the Na^{+} permeability of nerve membranes.

↓plasma Ca^{+2} →Generation of spontaneous action potentials in nerves → tetany

Regulation of Calcium Metabolism

- **Minerals; serum concentration**
  - –Calcium (Ca^{2+}) = 2.2-2.6 mmol/L (total)
  - –Phosphate (HPO_4^{2-}) = 0.7-1.4mmol/L

- **Organ systems that play an import role in Ca^{+2} metabolism**
  - Skeleton
  - GI tract
  - Kidney

- **Calcitropic Hormones**
  - Parathyroid hormone (PT)
  - Calcitonin (CT)
  - Vitamin D (1,25 dihydroxycholecalciferol)
  - Parathyroid hormone related peptide (PTHrP), is markedly elevated in humoral hypercalcemia of malignancy (sq. cell carcinoma of the lung).

Calcium homeostasis

storage
bone

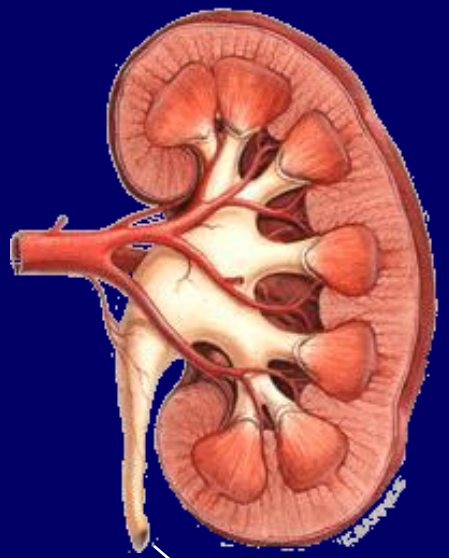
1000g Ca++ stored in bone

calcium deposition

calcium resorption

Blood
Ca++

kidney



intake

Calcium in the diet

Ca++ absorbed into blood

excretion

Ca++ lost in urine

calcium lost in feces

small intestine

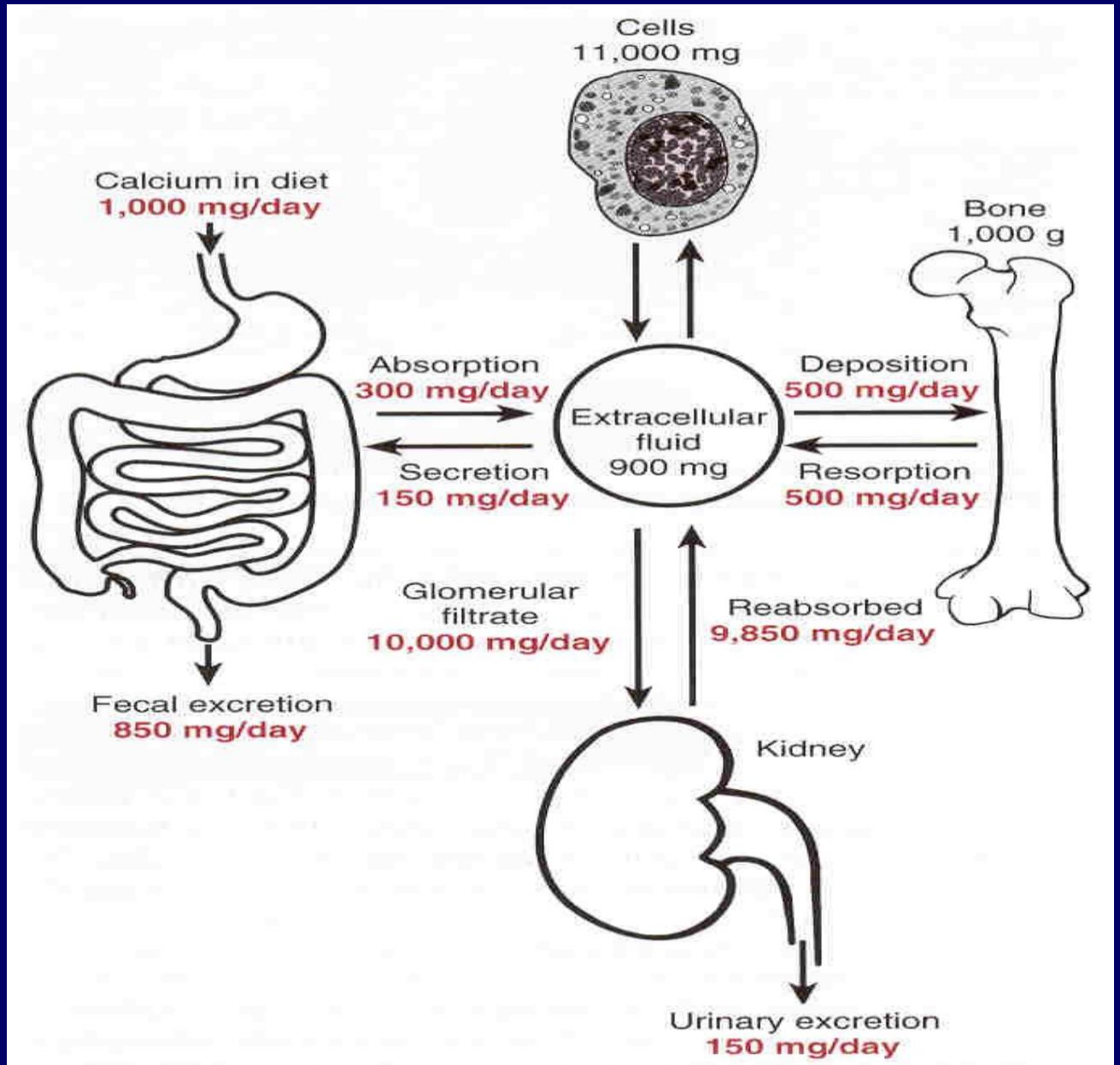


FIGURE 36.1 **Typical daily exchanges of calcium between different tissue compartments in a healthy adult.** Fluxes of calcium (mg/day) are shown in red. Total calcium content in each compartment is shown in black. Note that the

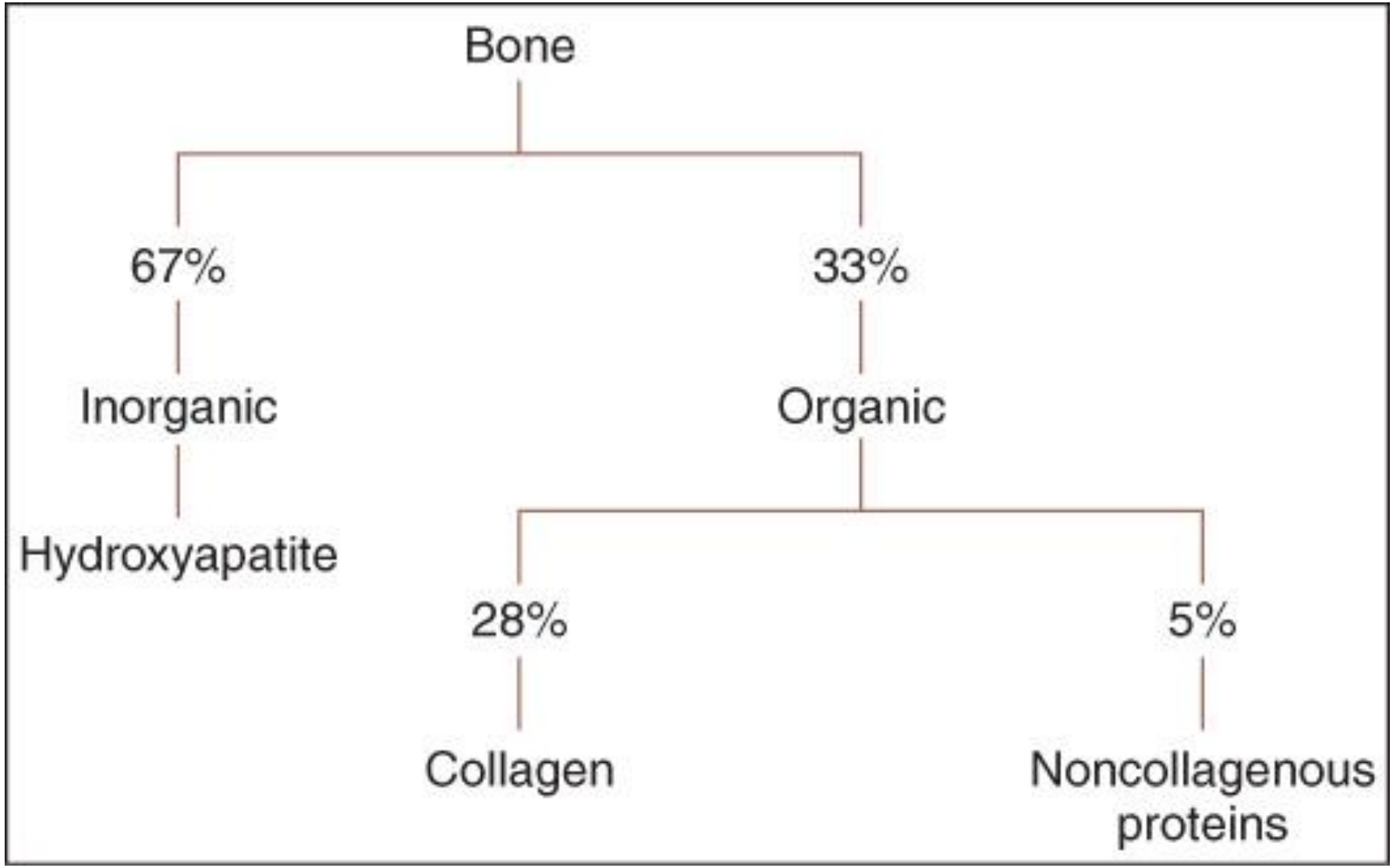
Bone

- **Inorganic (67%)**
  - –Hydroxyapatite 3 $Ca_{10}(PO_4)_6(OH)_2$
  - –There is some amorphous calcium phosphate

- **Organic (33%) component is called osteoid**
  - Type I collagen (28 %)
  - Non-collagen structural proteins (5%)
  - Growth factors and cytokines (Trace)

- **Bone undergoes continuous turnover or remodeling throughout life**
  - –About 20% of bone is undergoing remodeling at any one time.

Chemical Composition of Bone



Calcium cycling in bone tissue

Bone formation

Osteoblasts (bone builders)

Synthesize a collagen matrix that
holds **Calcium Phosphate** in crystallized form.
Once surrounded by bone, become **osteocyte.**

Bone resoption

Osteoclasts (bone breakers) Change local pH,
causing Ca++ and phosphate to dissolve
from crystals into extracellular fluids.

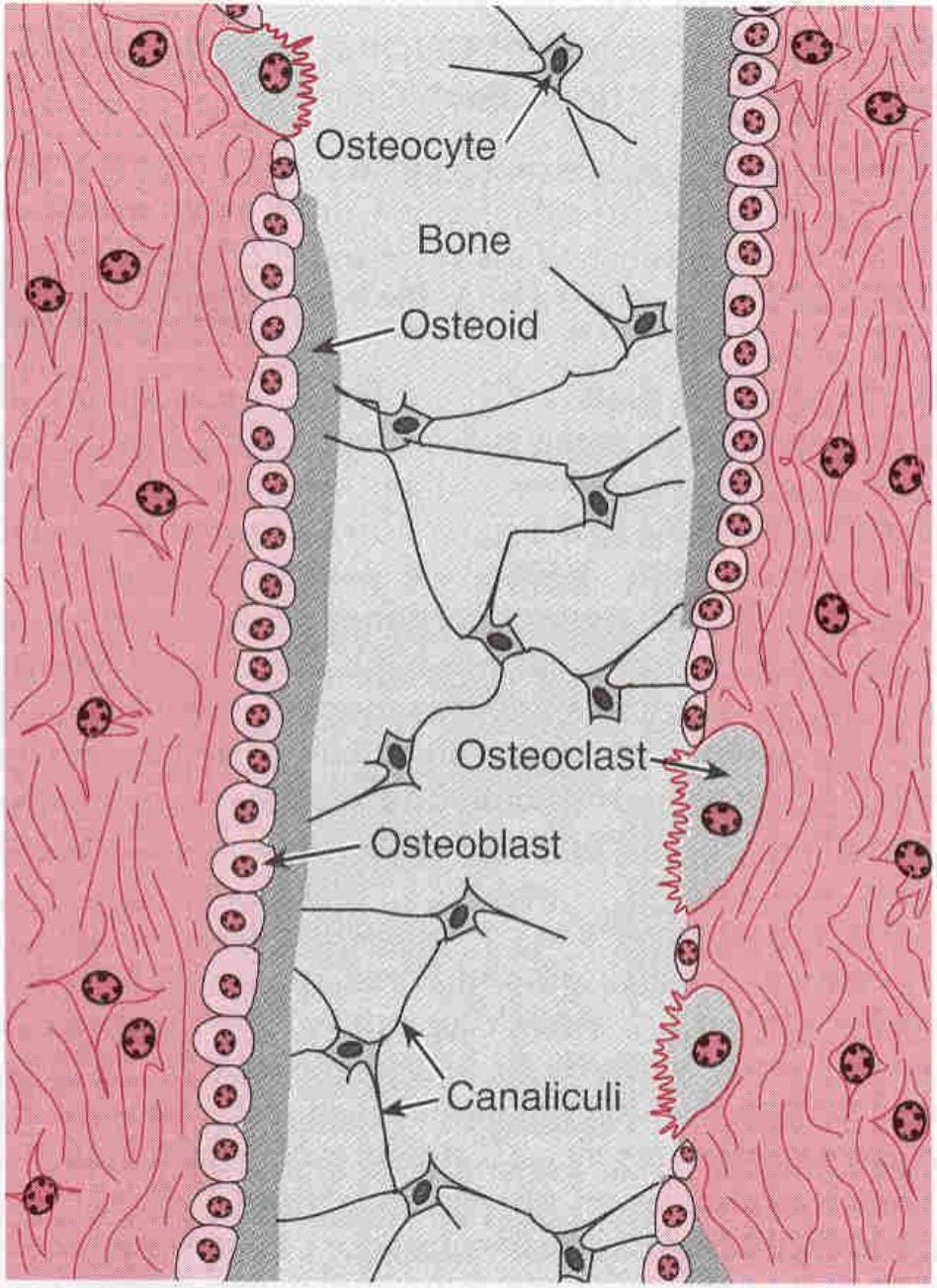


FIGURE 36.3 The location and relationship of the three primary cell types involved in bone me-

Phosphorus

- Important role in cellular metabolism
- Source of energy in cellular reactions
- Component of phospholipids in membranes

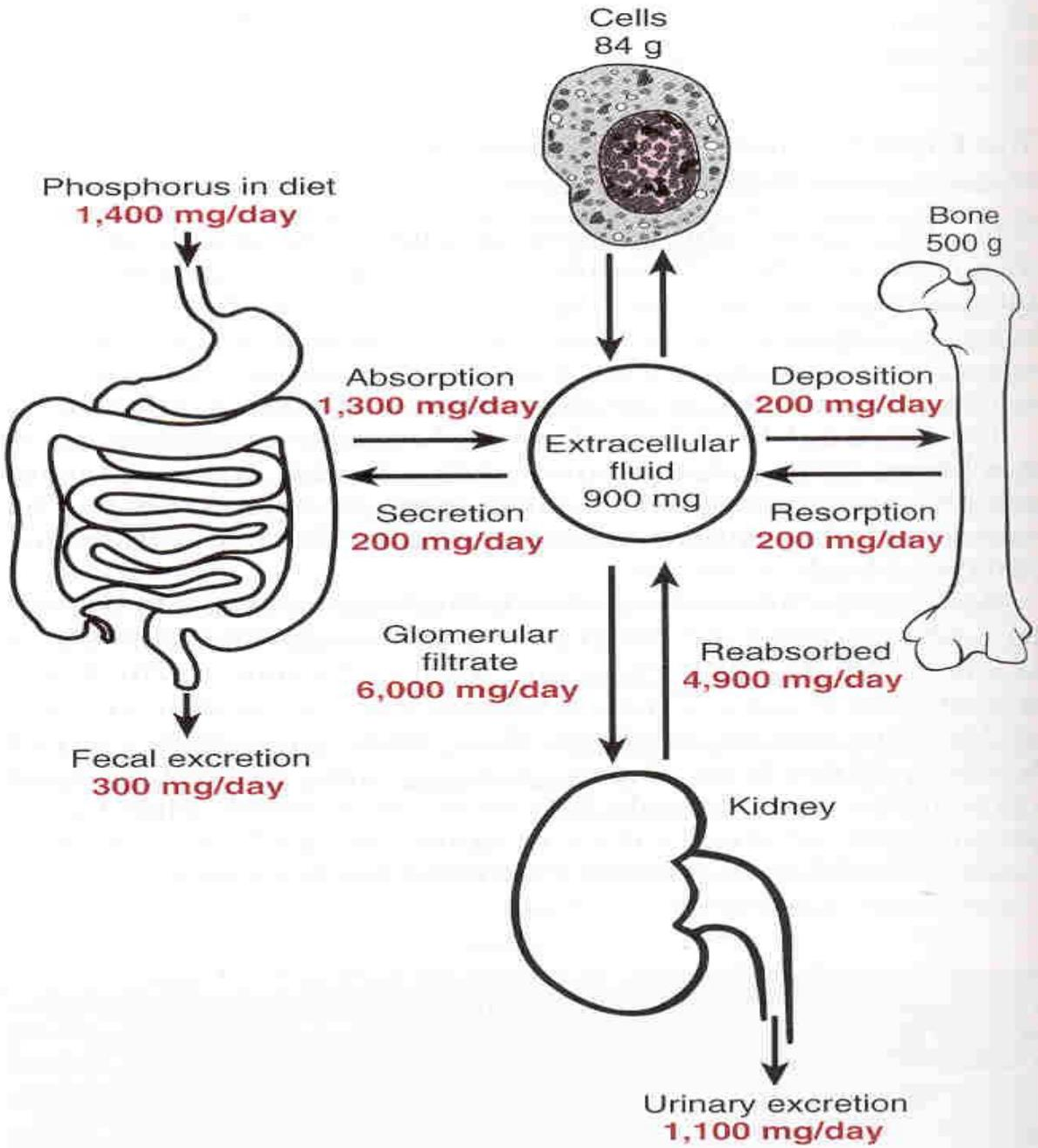


FIGURE 36.2 **Typical daily exchanges of phosphorus between different tissue compartments in a healthy adult.** Fluxes of phosphorus (mg/day) are shown in red.

Inorganic constituents of bone

%age of total body content

constituent	Present in bone
Calcium	99
Phosphate	86
Carbonate	80
Magnesium	50
Sodium	35
Water	9

Table 48-1 Major effects of various hormones on bone

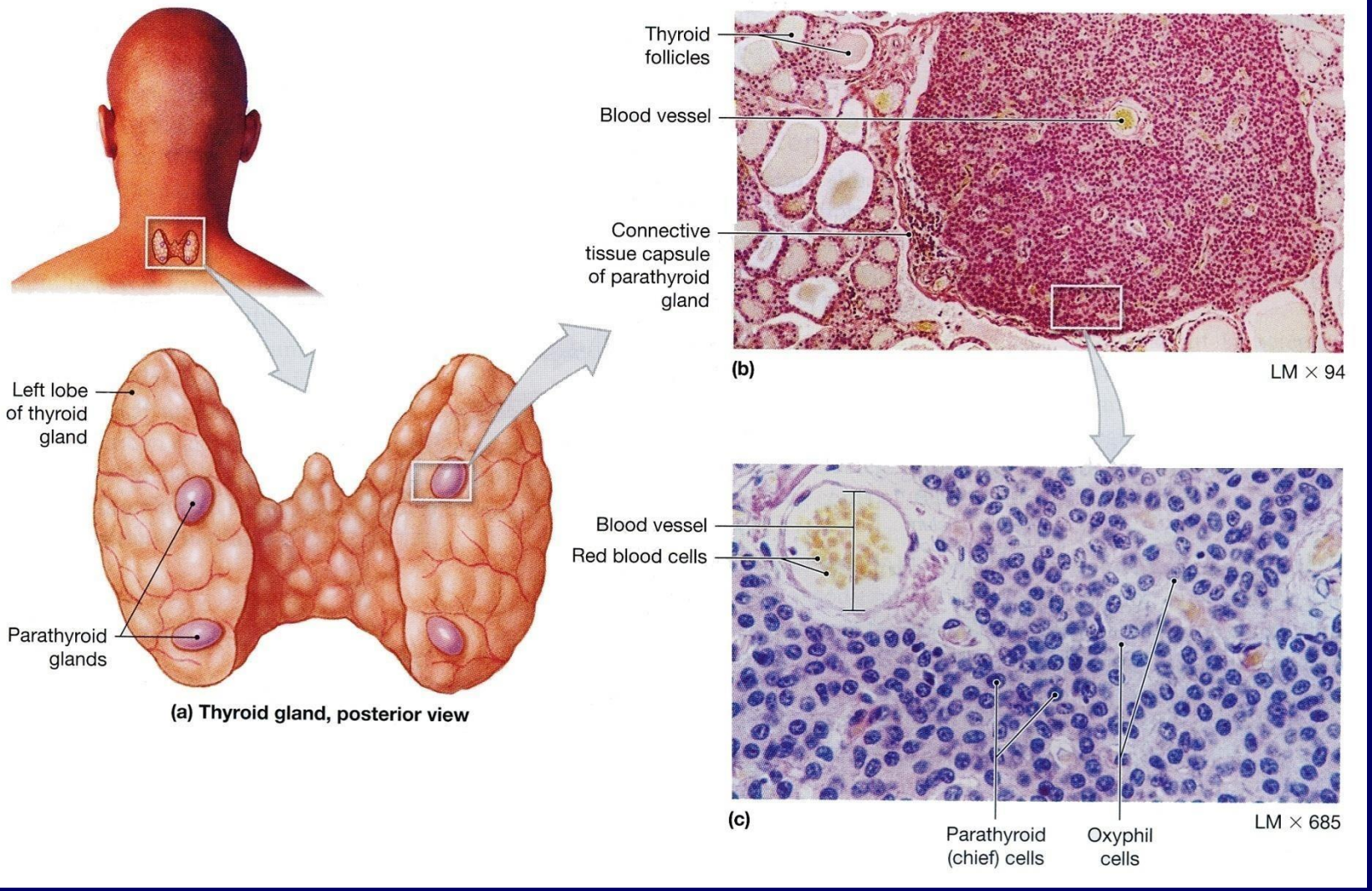
Bone formation	*Bone resorption*
Stimulated by	**Stimulated by**
Growth hormone (constant)	Parathyroid hormone (constant)
Insulin-like growth factors	Vitamin D
Insulin	Cortisol
Estrogen	Thyroid hormone
Androgen	Prostaglandins
Vitamin D (mineralization)	Interleukin-1
Transforming growth factor-β	Interleukin-6
Skeletal growth factor	Tumor necrosis factor α
Bone-derived growth factor	Tumor necrosis factor β
Platelet-derived growth factor	
Calcitonin	
Parathyroid hormone (intermittent)	
Inhibited by	**Inhibited by**
Cortisol	Estrogen
	Androgen
	Calcitonin
	Transforming growth factor-β
	γ-Interferon
	Nitric oxide

Hormonal Control of Bones

The Parathyroid Hormone

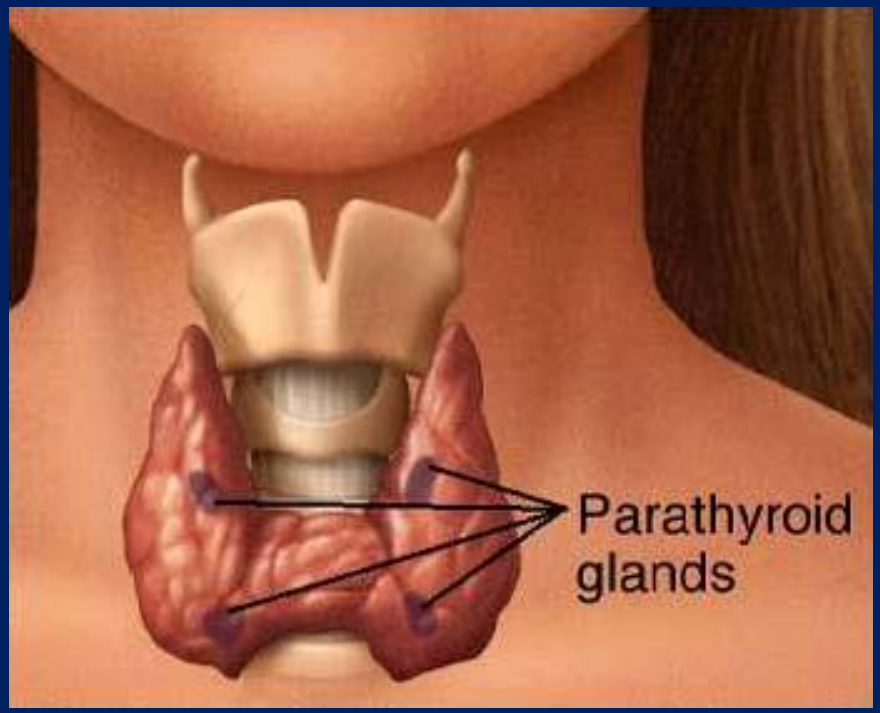
Secreted by the parathyroid glands.

Stimulated by hypocalcaemia.



The Parathyroid Glands. (a) The location of the parathyroid glands on the posterior surfaces of the thyroid lobes. (The thyroid lobes are located anterior to the trachea). (b) Both parathyroid and thyroid tissues. (c) Parathyroid cells.

Parathyroid Glands



Actions of Parathyroid Hormone

Necessary for fine control of ionized serum levels.

- **It increases Ca^{+2}**
- **It decreases P_i**

- **Parathyroid hormone acts directly on bone to stimulate resorption and release of Ca^{+2} into the extracellular space (slow)**

- **Two effects in kidney**
  - **Parathyroid hormone acts directly on kidney to increase calcium reabsorption and phosphate excretion (rapid)**
  - **Stimulates transcription of 1-alpha hydroxylase enzyme for Vitamin D activation in kidney**
    - **Vitamin D increases calcium and phosphate absorption from intestine.**

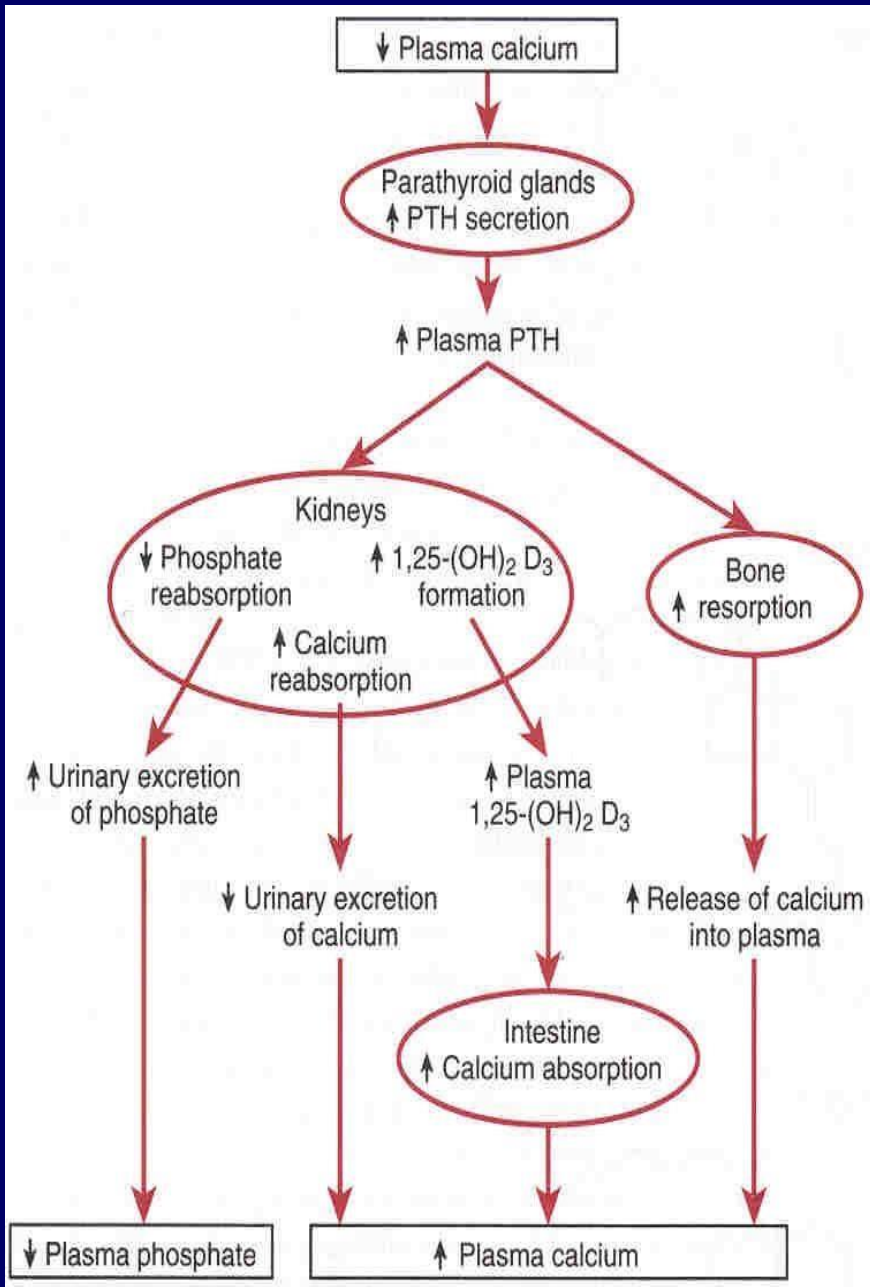
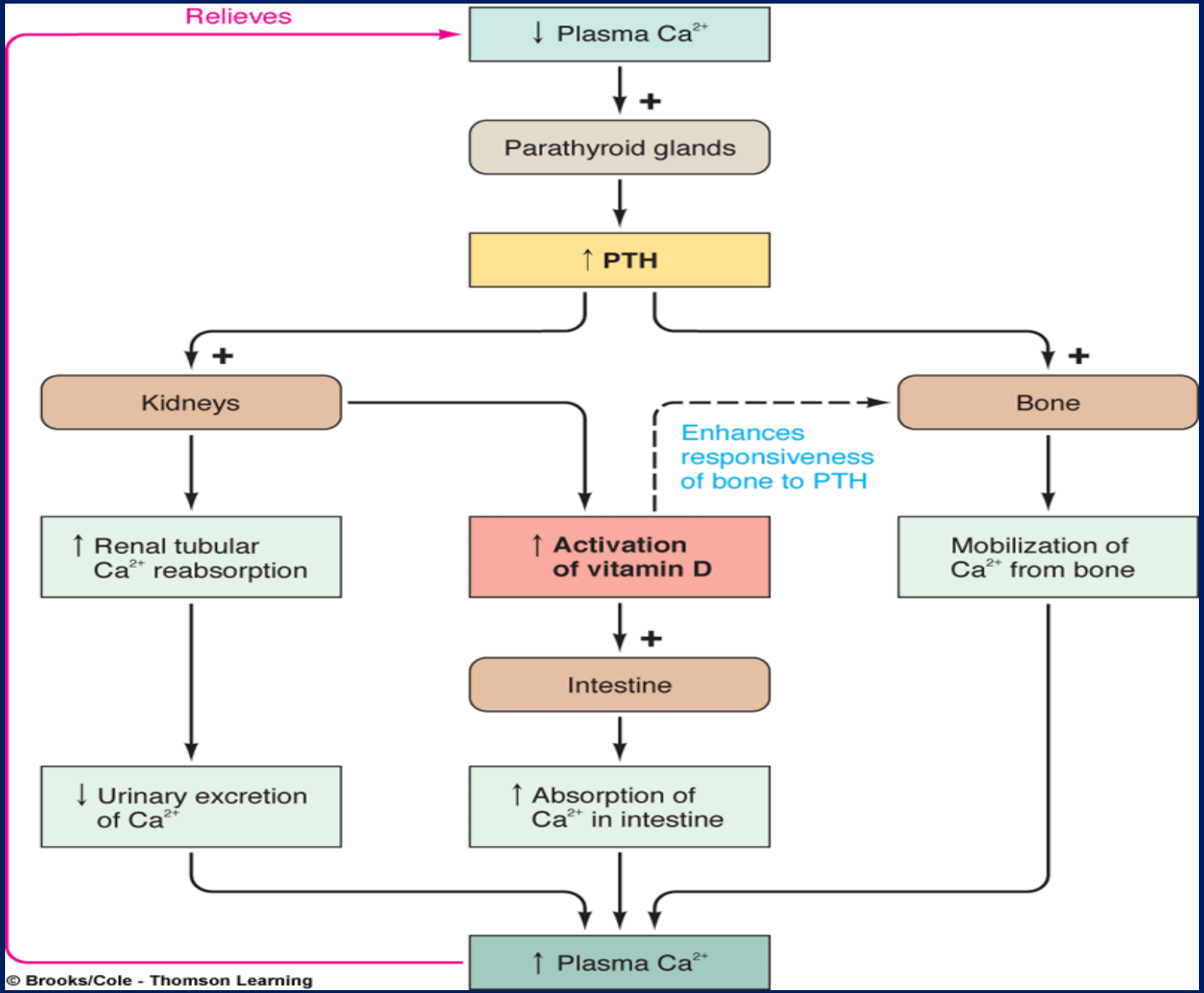


FIGURE 36.7 Effects of parathyroid hormone (PTH) on calcium and phosphate metabolism.


Relieves
↓ Plasma Ca^{2+}
+
Parathyroid glands
↑ PTH
+
Kidneys
+
Bone
Enhances responsiveness of bone to PTH
↑ Renal tubular Ca^{2+} reabsorption
↑ Activation of vitamin D
Mobilization of Ca^{2+} from bone
+
Intestine
↓ Urinary excretion of Ca^{2+}
↑ Absorption of Ca^{2+} in intestine
↑ Plasma Ca^{2+}
© Brooks/Cole - Thomson Learning

Calcitonin

Secreted by the parafollicular or C-cells of the thyroid gland.

Stimulated by hypercalcaemia.

Lowers Ca^{+2} in blood

Promotes deposition of Ca^{+2} into bone (inhibits osteoclasts)

Promotes renal excretion of Ca^{+2}

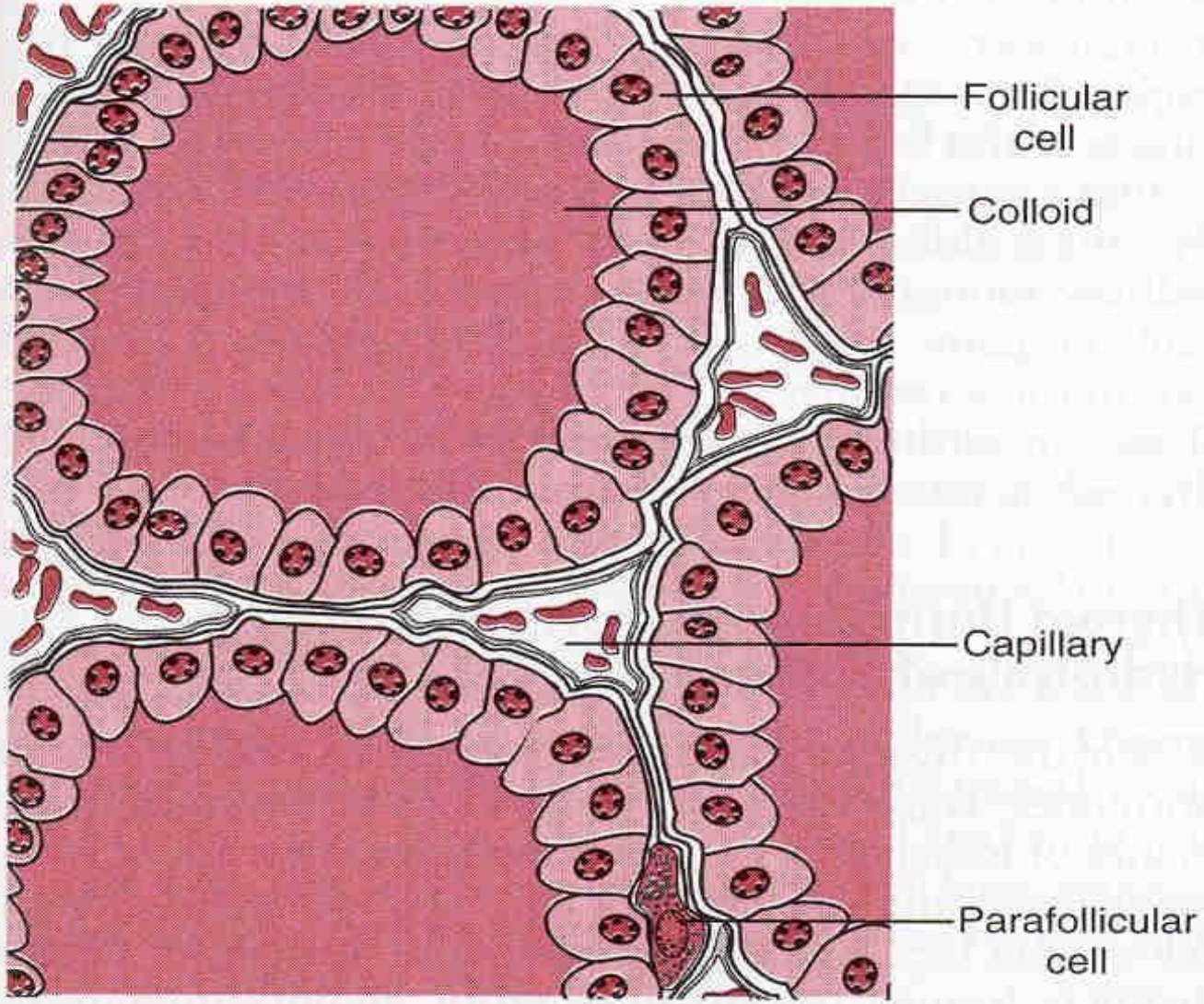


FIGURE 33.1 A cross-sectional view through a portion of the human thyroid gland.

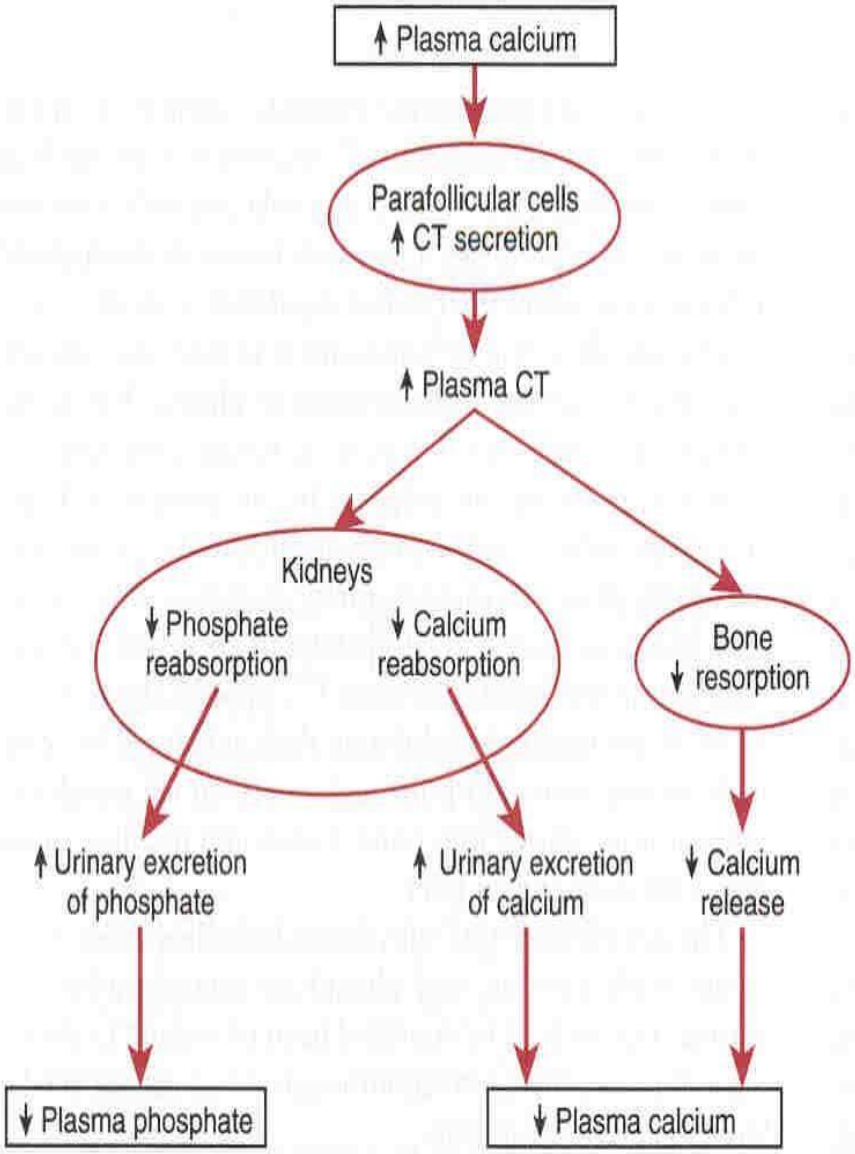
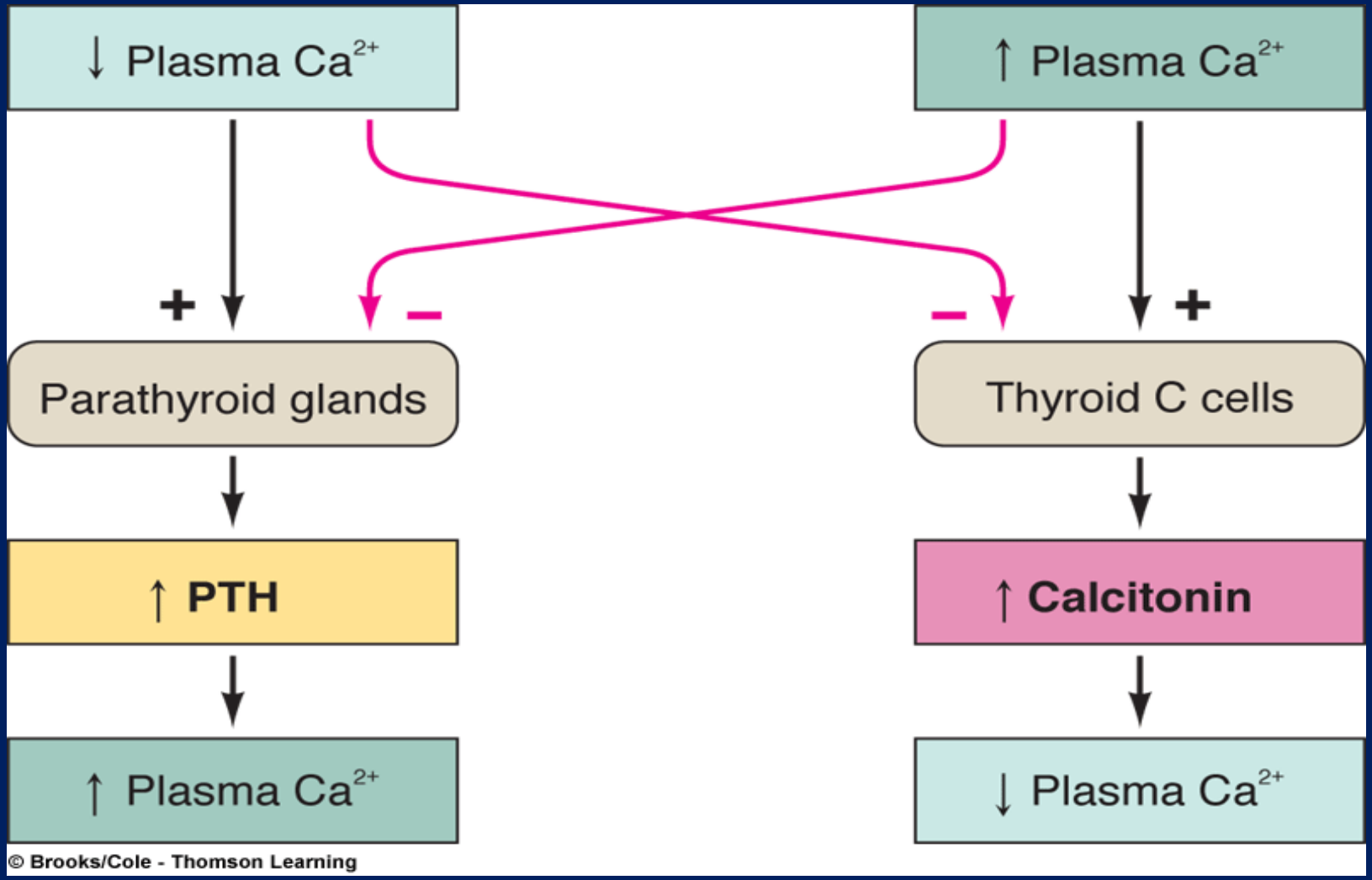


FIGURE 36.8 Effects of calcitonin (CT) on calcium and phosphate metabolism.

Negative feed back loops



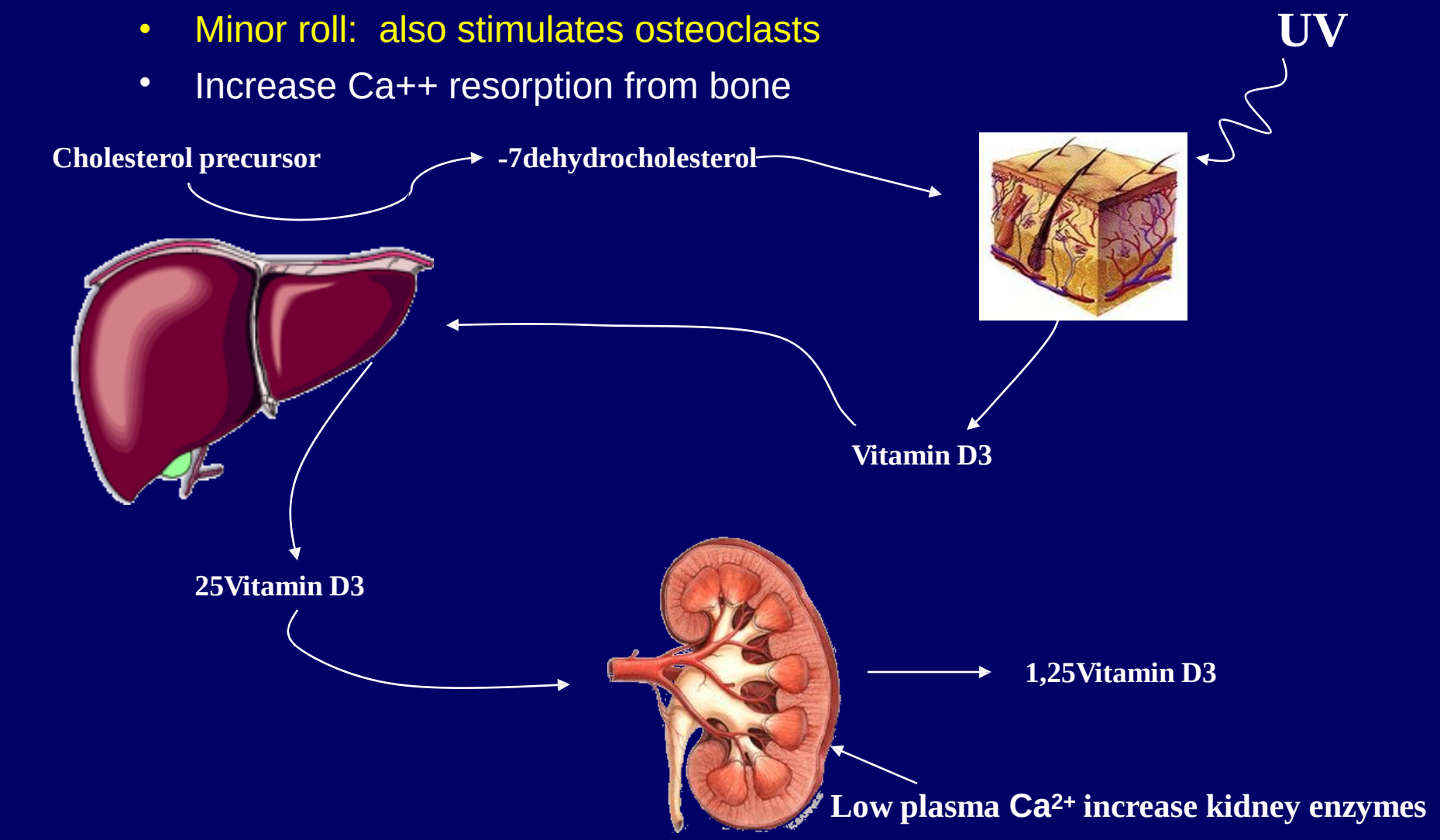
- Calcitonin plays a role in skeletal integrity in pregnancy or breast feeding
- proposed to protect the maternal skeleton against excessive resorption during times of increased calcium demand.

Vitamin D

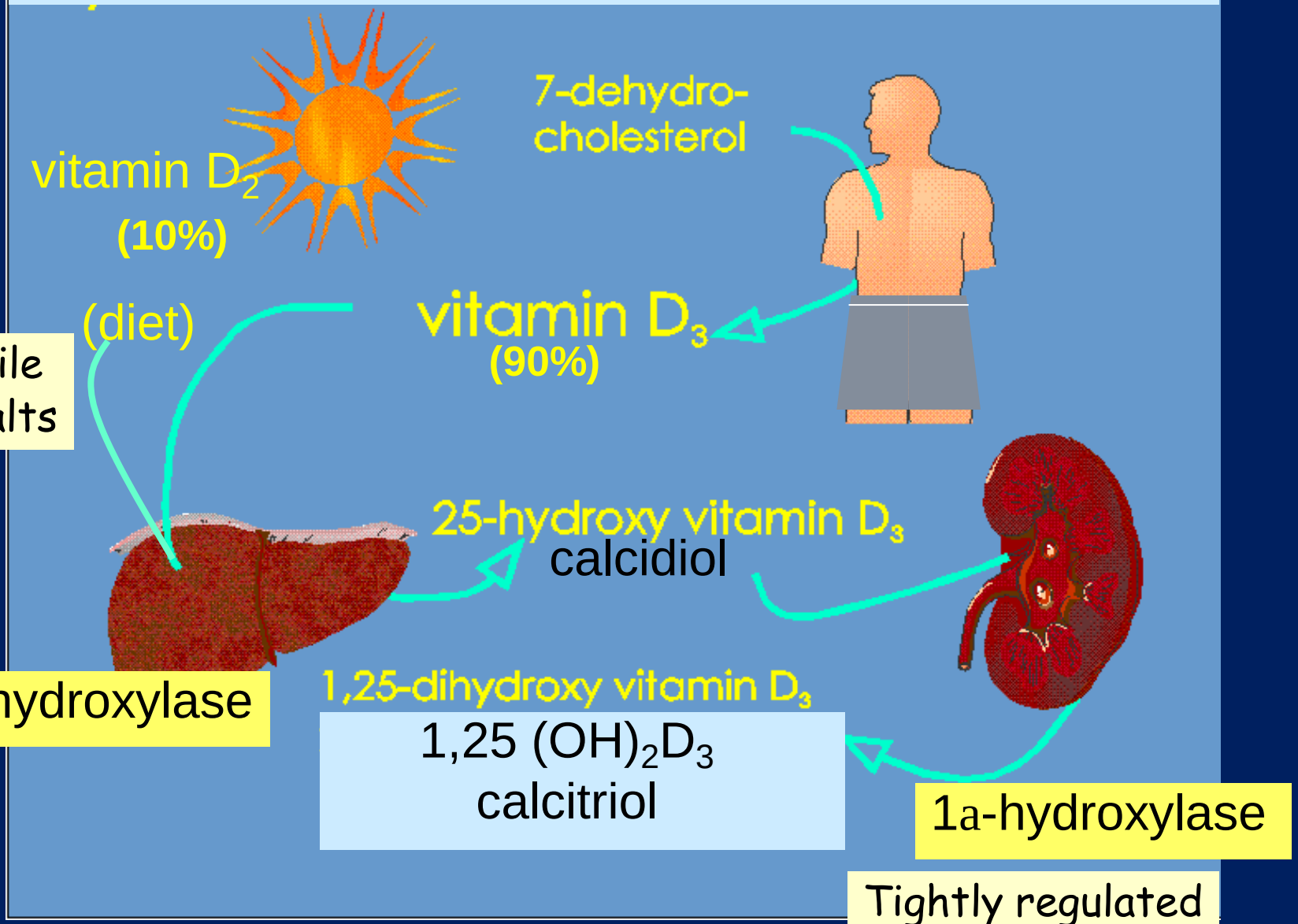
- Synthesized by the body or taken in food.
- 7,Dehydrocholestrol (in skin) + Ultraviolet light
  →Vit. D_3 (inactive form).
- Hydroxylation of Vit.D first in the liver to
  25,hydroxycholicalciferol (inactive form).
- Second hydroxylation of Vit.D in the kidneys to
  1,25 →dihydroxycholicalciferol (active form).

1,25Vitamin D3

- Increases Ca^{+2} uptake from the gut
- Increase transcription and translation of Ca^{+2} transport proteins in
- gut epithelium
- Minor roll: also stimulates osteoclasts
- Increase Ca++ resorption from bone



Synthesis of active vitamin D



Other regulator of Ca^{+2} homeostasis

Estrogens:

Stimulate osteoblast activity , **limits** osteoclast activity, and enhance PTH secretion.

Estrogens changes the **set point** of PTH cells in the parathyroid so a greater **reduction** of Ca^{+2} is needed to increase PTH secretion so:

Estrogen **decreases** Ca^{+2} **loss from bones.**

Ca^{+2} homeostasis in pregnancy and lactation

The daily required dose of Ca^{2+} is greatly increased during pregnancy.

30 grams of Ca^{2+} are transferred to the fetus and lost in urine during pregnancy.

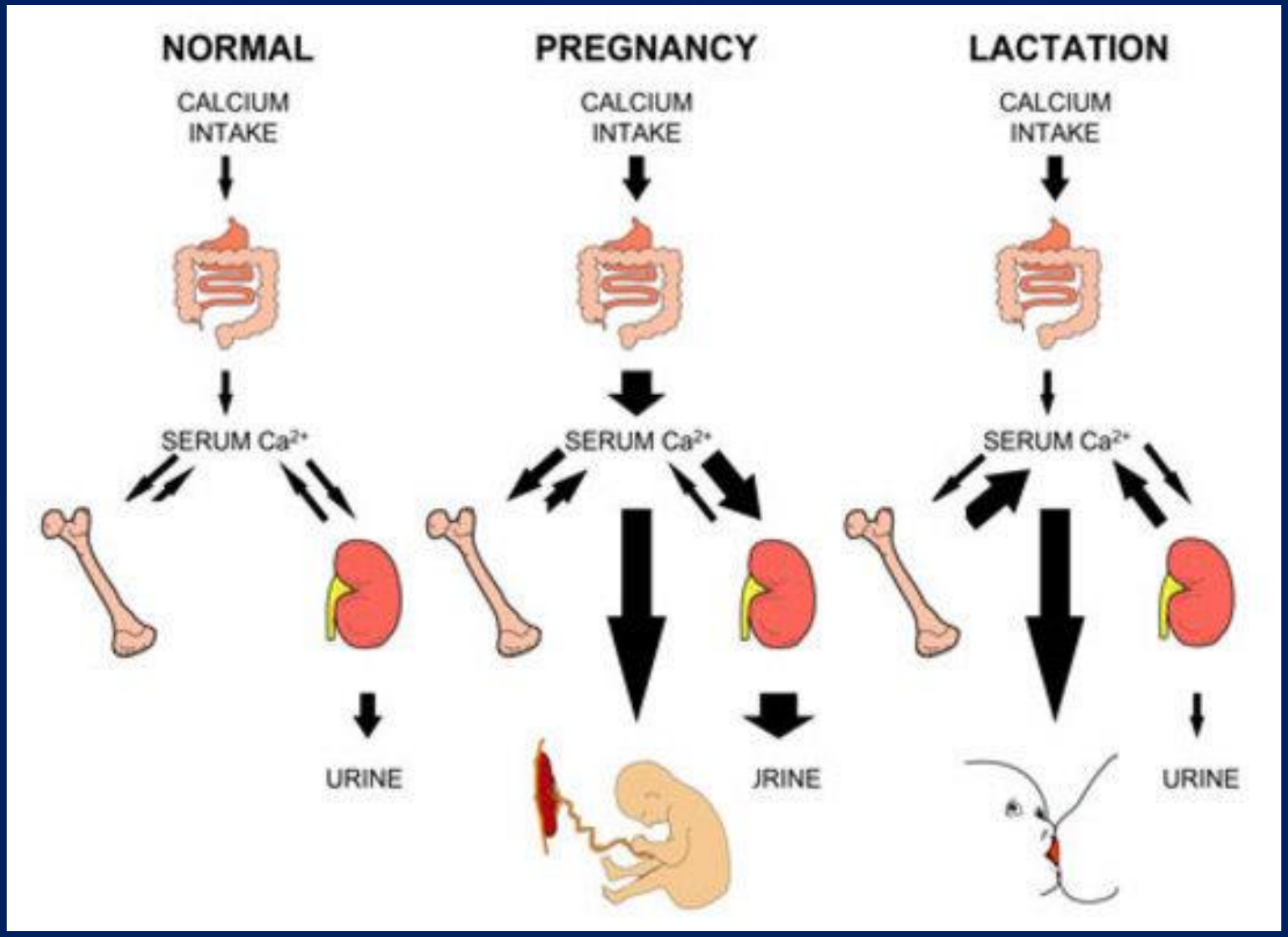
Bone turn over is increased during pregnancy → osteoporosis especially hip bone.

800 - 280mg of Ca^{+2} is lost in breast milk per day during lactation.

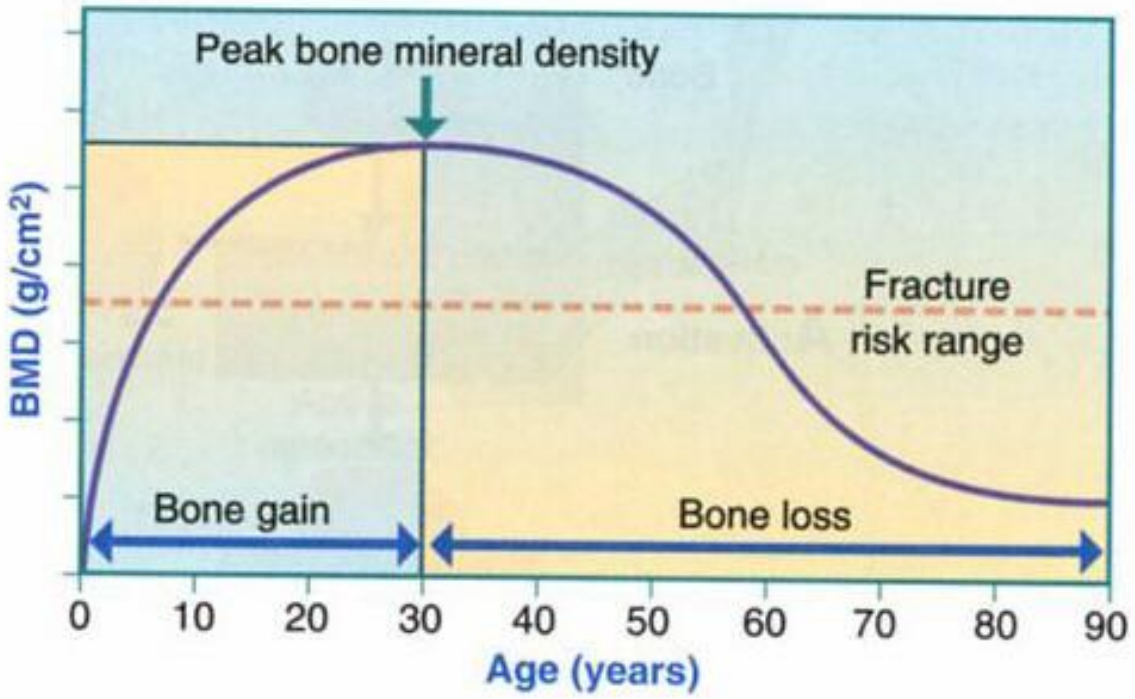
The mother compensate by:

1- ↑ intestinal absorption → main adaptation
2- ↓ renal excretion
3- ↑ bone resorption

Ca^2 homeostasis in pregnancy and lactation



Bone Density as a Function of Age



- Early gain and later loss of bone in females.

Peak bone mineral density (BMD) is typically achieved by age 30. Menopause occurs at approximately age 50 or within a few years thereafter. Postmenopausal women typically enter the fracture risk range after age 60. Men have a more gradual decline in BMD, which starts at 50 years of age. (Copyright of John J. B. Anderson and Sanford C. Garner.)

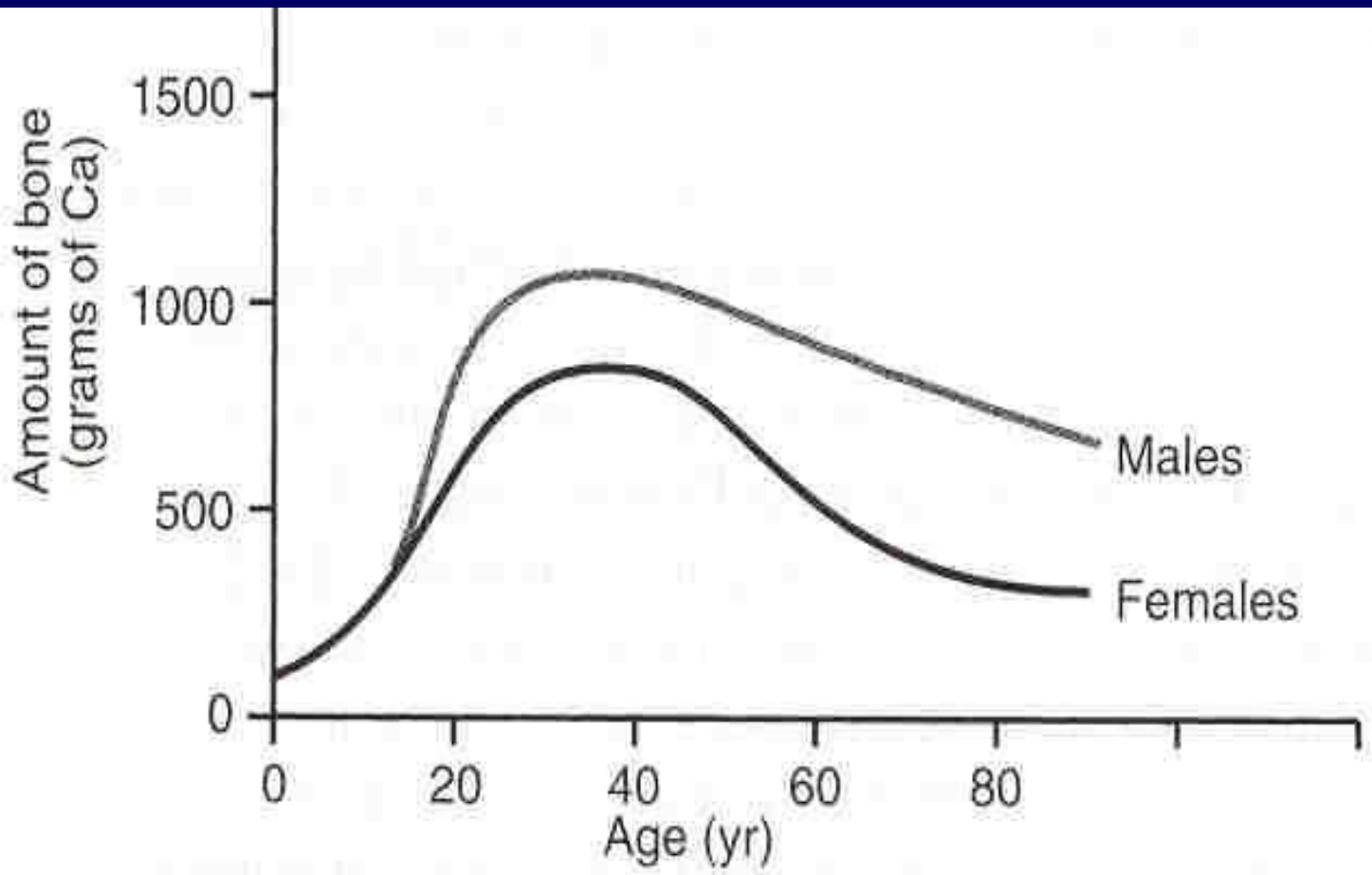


FIGURE 36.10 **Changes in bone calcium content as a function of age in males and females.** These changes can be roughly extrapolated into changes in bone mass and bone strength.

Nutrition and Calcium

- Caffeine is most popular drug consumed world-wide.
- 75% comes from coffee
- Deleterious effects associated with pregnancy and osteoporosis.
  - Low birth-rate and spontaneous abortion with excessive consumption
  - For every cup of coffee consumed there was a net loss of 4.6 mg of calcium
  - However, if you add milk to your coffee, you can replace the calcium that is lost.

Effects of soft drinks

- **Intake of carbonated beverages has been associated with increased excretion and loss of calcium**
- **Another significant consideration is obesity and increased risk for diabetes.**

Effects of Exercise

Bone cells respond to pressure gradients in laying down bone.

Lack of weight-bearing exercise decreases bone formation, while increased exercise helps form bone.

- **Increased bone resorption during immobilization may result in hypercalcemia**