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Faculty of Medicine

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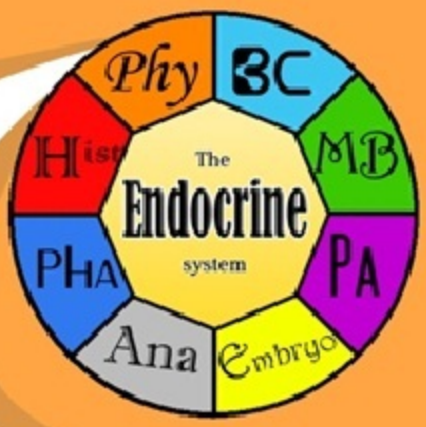

Physiology

■ Slides
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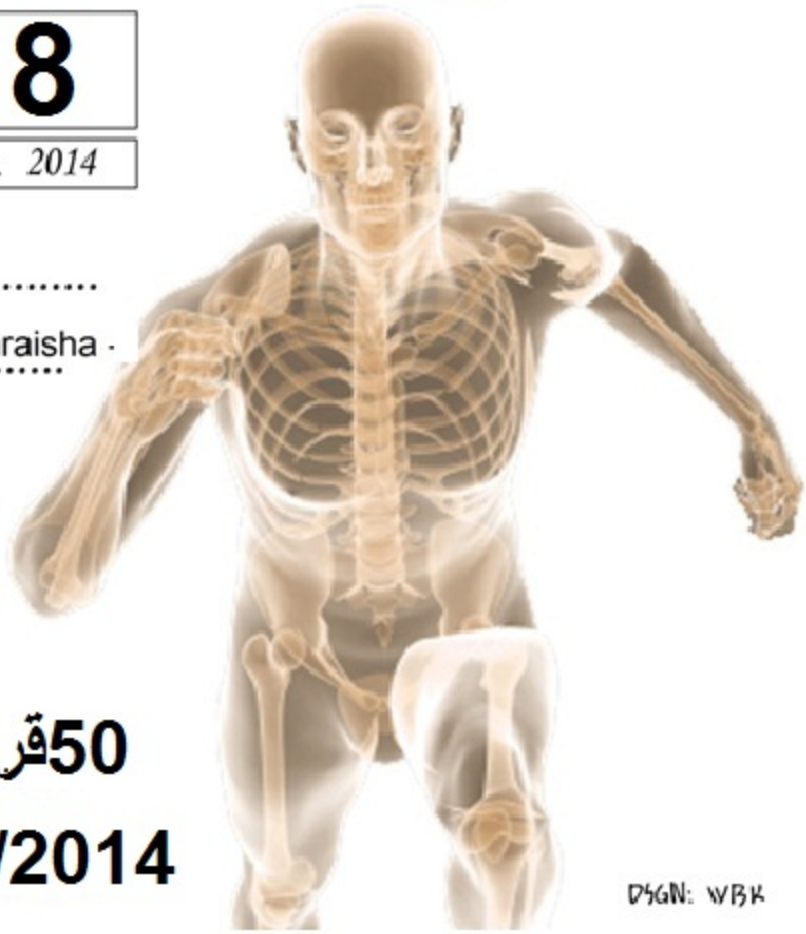
14th Apr. 2014



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In vivo, proinsulin has a biologic potency that is only about 10% of that of insulin.

It is of clinical significance that insulin and C-peptide are cosecreted in equal amounts.

50% to 60% of the insulin produced by the pancreas is extracted by the liver without ever reaching the systemic circulation. In contrast, the liver does not extract C-peptide.

Because C-peptide is secreted in equimolar concentrations with insulin and is not extracted by the liver, β-cell insulin secretion rates can be calculated.

another advantage of measuring C-peptide is that the standard insulin radioimmunoassay does not distinguish between endogenous and exogenous insulin, making it an ineffective measure of endogenous β-cell function in an insulin-treated diabetic patient

When glucose is infused intravenously at a constant rate, a biphasic secretory response is observed that consists of a rapid, early insulin peak followed by a second, more slowly rising peak (Fig. 34.3B). In contrast to the slow rise in plasma glucose concentration following an oral glucose challenge, glucose given intravenously promotes a rapid rise in plasma glucose concentration (compare Fig. 34.3A and B). Sensing a rapid rise in plasma glucose concentration, the β cells first secrete their stores of presynthesized insulin. Following this *acute phase*, the cells begin to secrete newly synthesized insulin in the *chronic phase*, which lasts as long as the glucose challenge. *In vitro* studies of isolated islet cells and the perfused pancreas have identified a *third phase* of insulin secretion, commencing 1.5 to 3.0 hours after exposure to glucose and characterized by a spontaneous decline in secretion to 15% to 25% of the amount released during peak secretion: a level maintained for more than 48 hours.

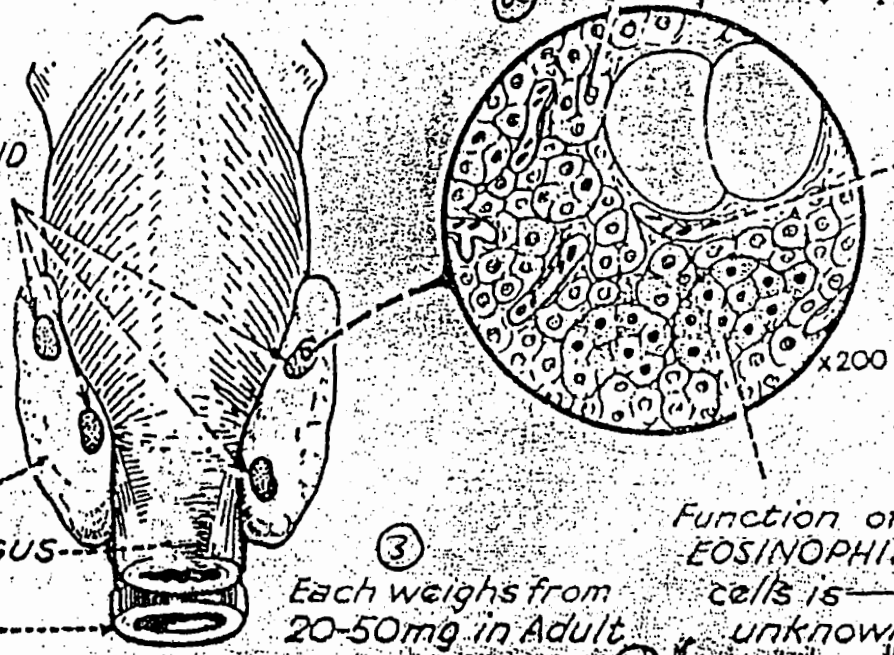
GLUCAGON

Glucagon is the other major pancreatic islet hormone that is involved in the regulation of body fuel metabolism. Ingestion of protein appears to be the major stimulus to secretion of glucagon. Glucagon's principal target tissue is the liver. Like insulin, glucagon is secreted first into the portal blood and is therefore anatomically well positioned to regulate hepatic metabolism.

Although the *amino acids* released by digestion of a protein meal appear to be the major glucagon secretagogue, glucagon's main actions on the liver appear to involve the regulation of *carbohydrate* and *lipid* metabolism. Glucagon is particularly important in stimulating glycogenolysis, gluconeogenesis, and ketogenesis. Glucagon does not act solely on the liver, but also has glycogenolytic action on cardiac and skeletal muscle and lipolytic action on adipose tissue, and it promotes the breakdown of protein by several tissues. However, these effects on protein tissue breakdown appear to be more prominent when tissues are exposed to pharmacological concentrations of glucagon. At more physiological concentration, the liver appears to be the major target tissue.

PARATHYROIDS

FOUR small glands composed of *cords of cells* which secrete Parathyroid Hormone – PARATHORMONE or PTH



(a) (Chief Cells)

(b) (Oxyphil cells)

Function of EOSINOPHIL cells is unknown

(3) Each weighs from 20-50mg in Adult

CAPILLARIES

GENERAL CIRCULATION

to ALL TISSUES of the body

But not all tissues are sensitive to it.

It plays an important rôle in CALCIUM and PHOSPHATE METABOLISM

(4) PARATHORMONE acts on KIDNEY TUBULES, BONE and on GUT to maintain ionized BLOOD CALCIUM level at 11mg/100ml PLASMA (*necessary for normal neuromuscular excitability*).

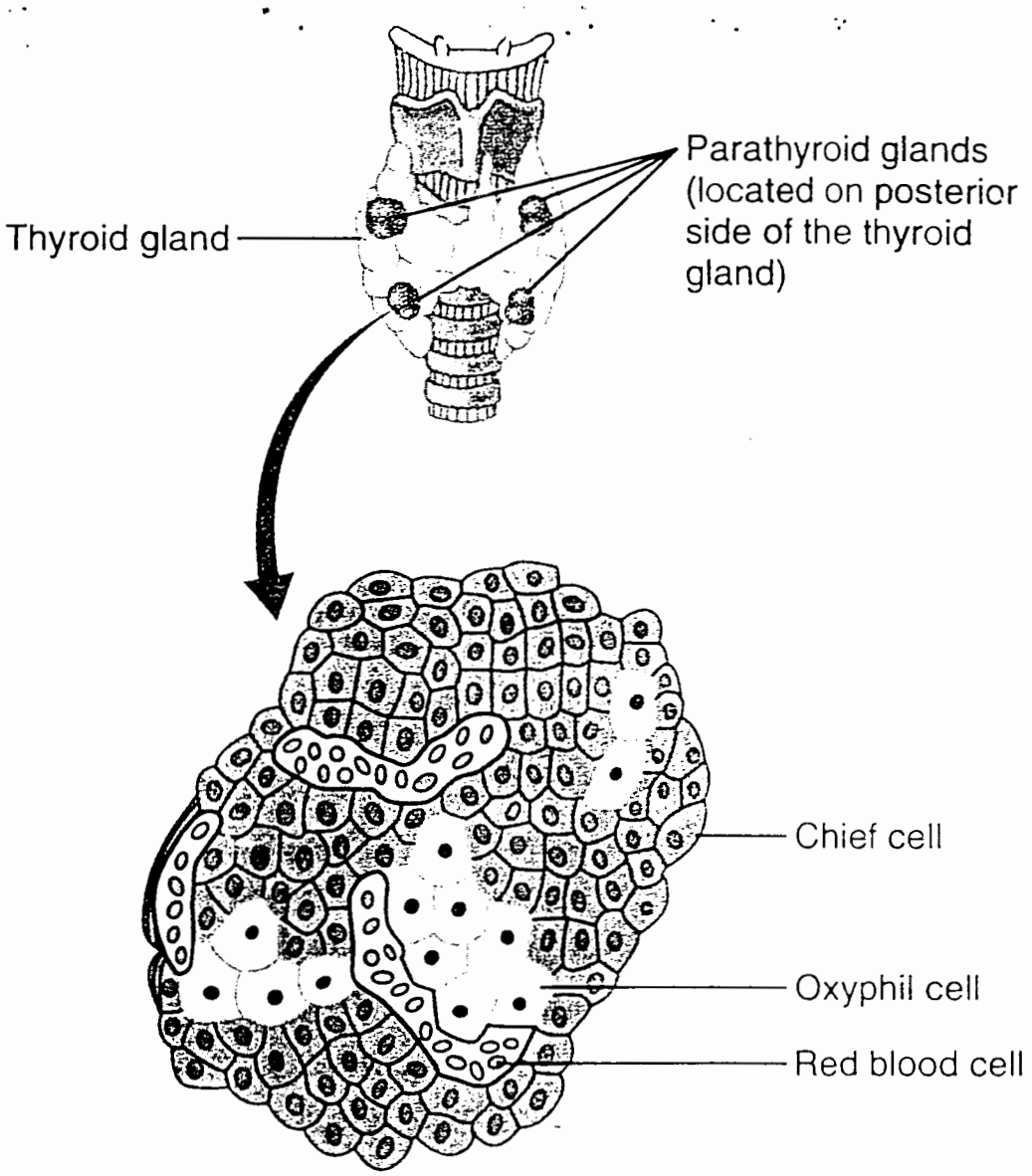


Figure 79-10 The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.

1-The parathyroid glands develop at 5-14 weeks of gestation.

2- PTH is a single chain protein (9600 molecular weight) that contains 84 amino acids.

The biologic activity of the hormone resides within a.a.1-34.

3- PTH interacts with receptors on the surface of the target cells increasing the formation of cAMP, IP & diacylglycerol.

4- PTH is free in plasma with half life 25 m.

5- PTH is essential for life, without it Ca++ falls in plasma neuromuscular excitability ↑, tetany & death occurs.

6- The dominant regulator of PTH secretion is the plasma Ca++ level.

7- Ca++ also regulates the size & the number of parathyroid cells.

8- Hypomagnesemia stimulates PTH secretion such as Ca++ but less potent.

9- Arise in plasma phosphate concentration indirectly causes a transient ↑ in PTH secretion.

10- 1,25 $(OH)_2$ -D directly redues PTH secretion.

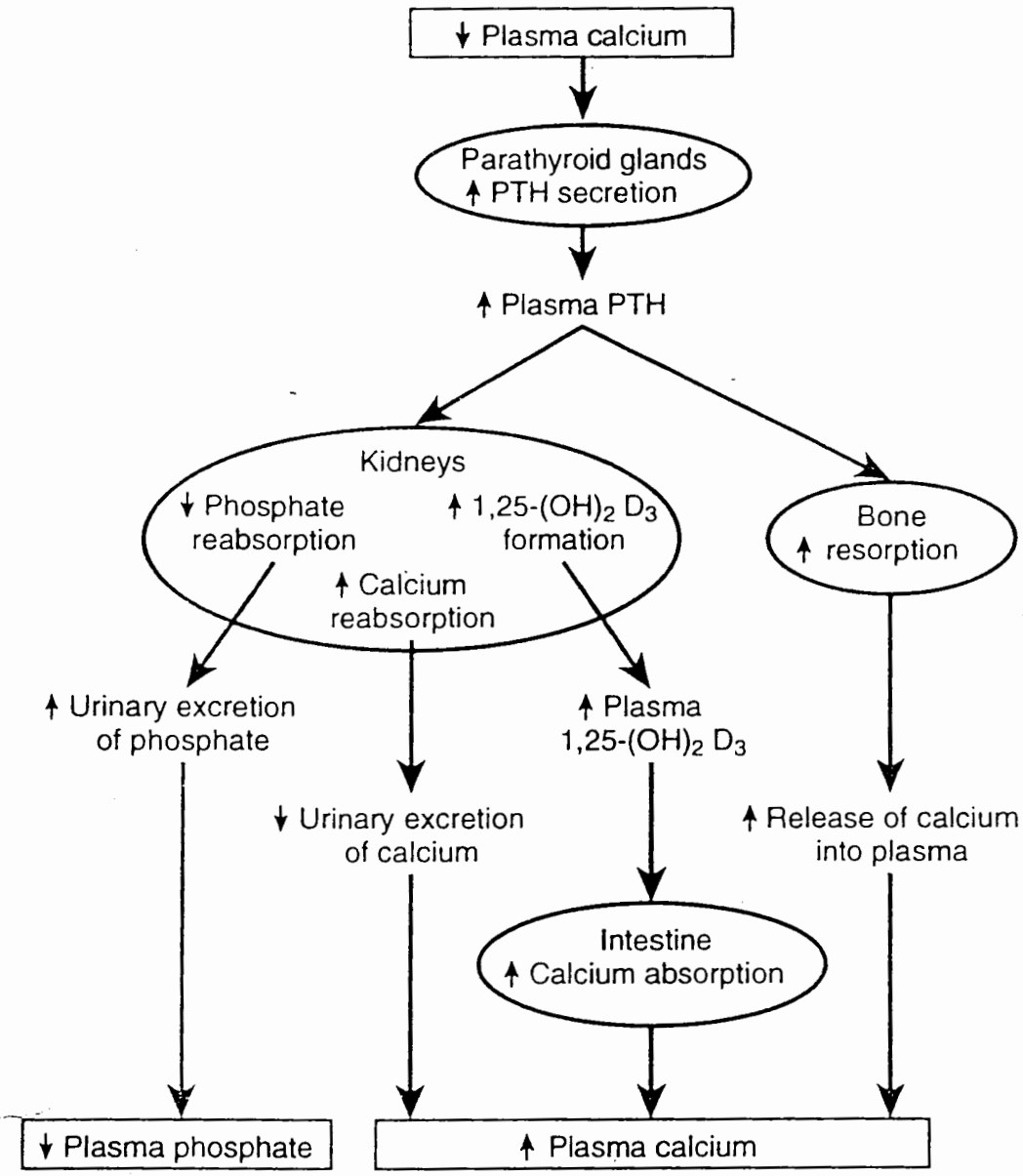


FIGURE 36.7 Effects of parathyroid hormone (PTH) on calcium and phosphate metabolism.

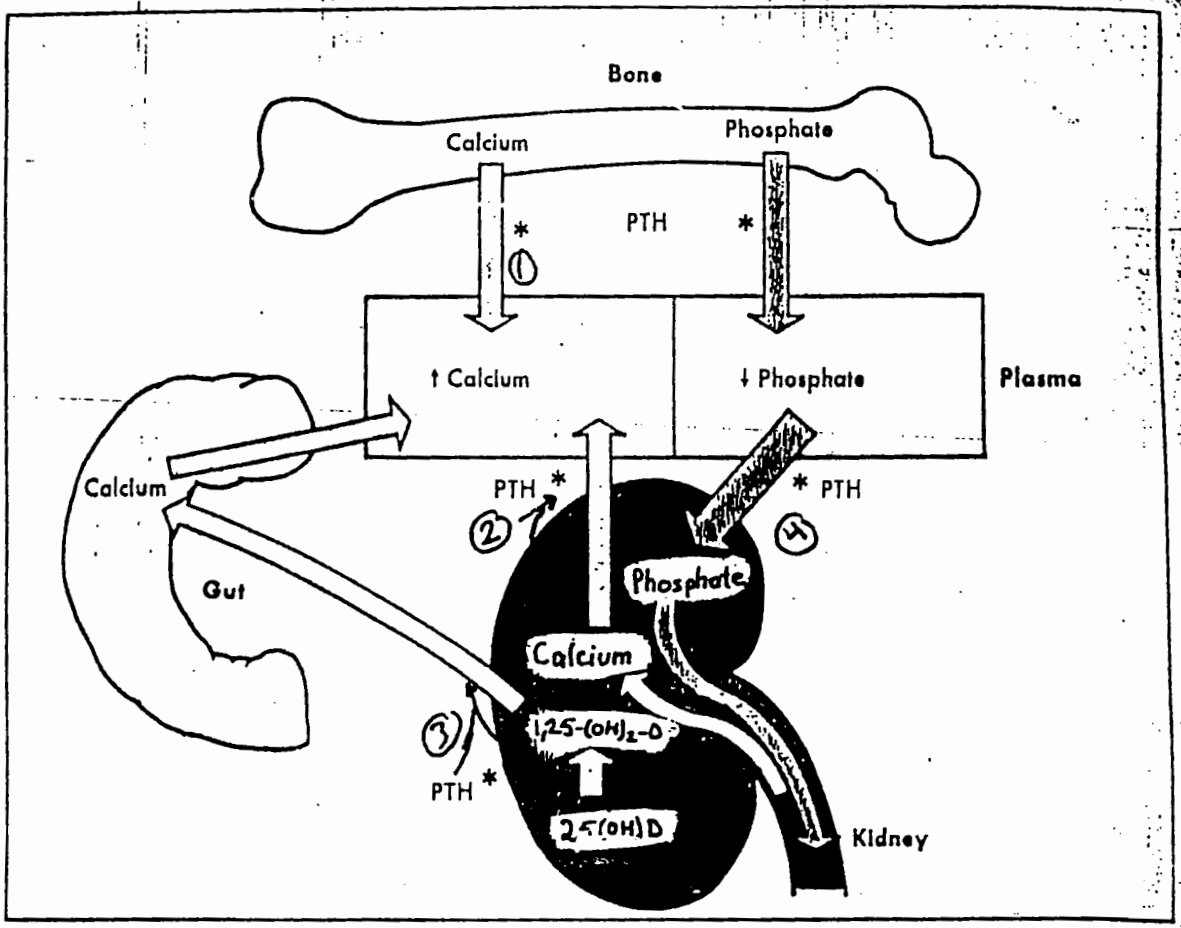
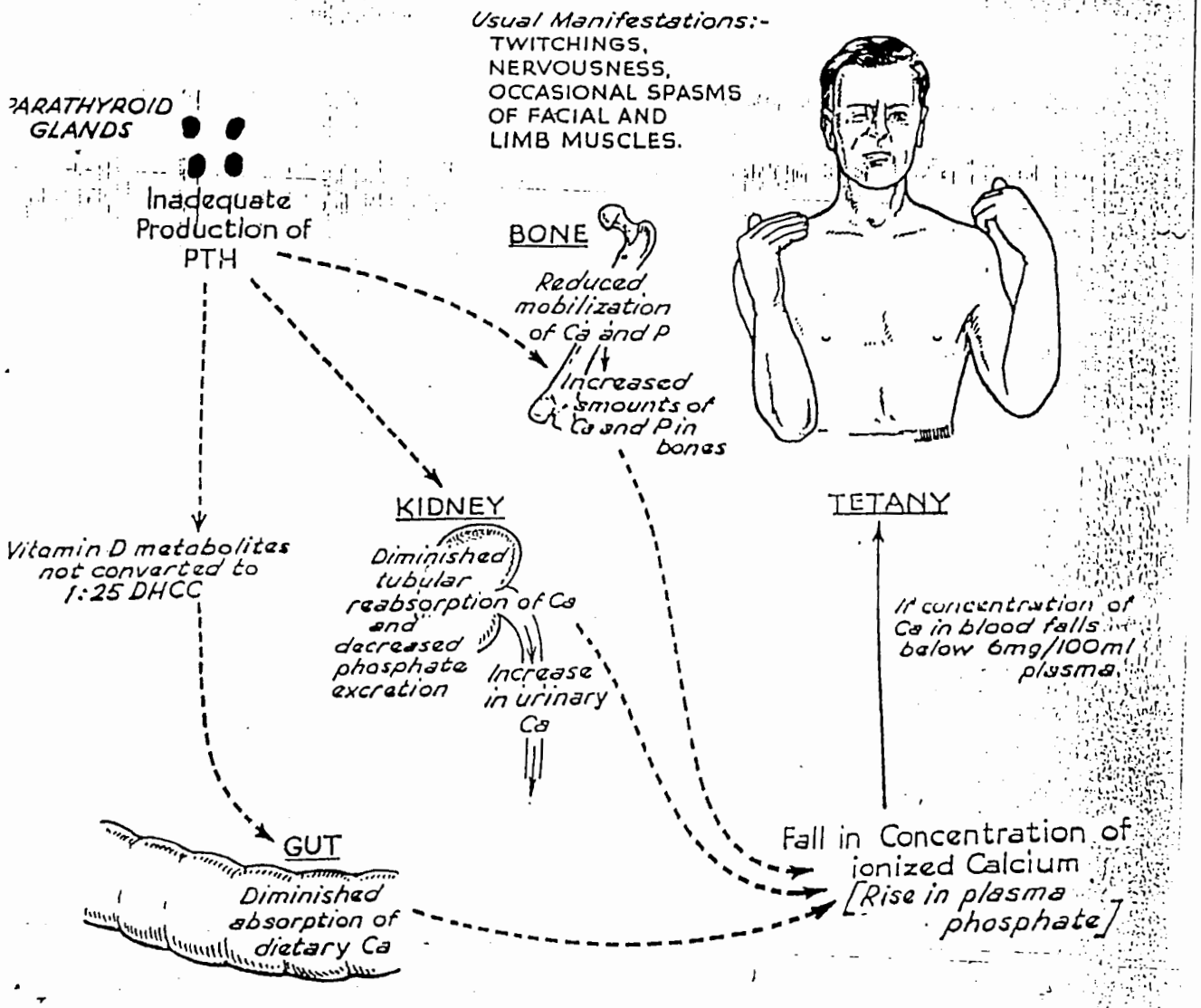


FIGURE 38-7 Overview of parathyroid hormone *(PTH)* actions. PTH acts directly on bone and kidney to increase calcium influx into plasma. By stimulating 1,25-$(OH)_2$-D synthesis, PTH indirectly also increases calcium absorption from the gut. Thus plasma calcium level increases. In contrast, PTH inhibits renal tubular resorption of phosphate, thereby increasing urinary phosphate excretion. This effect quantitatively offsets entry of phosphate from bone and gut. Therefore plasma phosphate level decreases.

(2)

UNDERACTIVITY of PARATHYROIDS

Atrophy or removal of Parathyroid tissue causes a fall in BLOOD CALCIUM level and increased excitability of Neuromuscular tissue. This leads to severe convulsive disorder – TETANY.



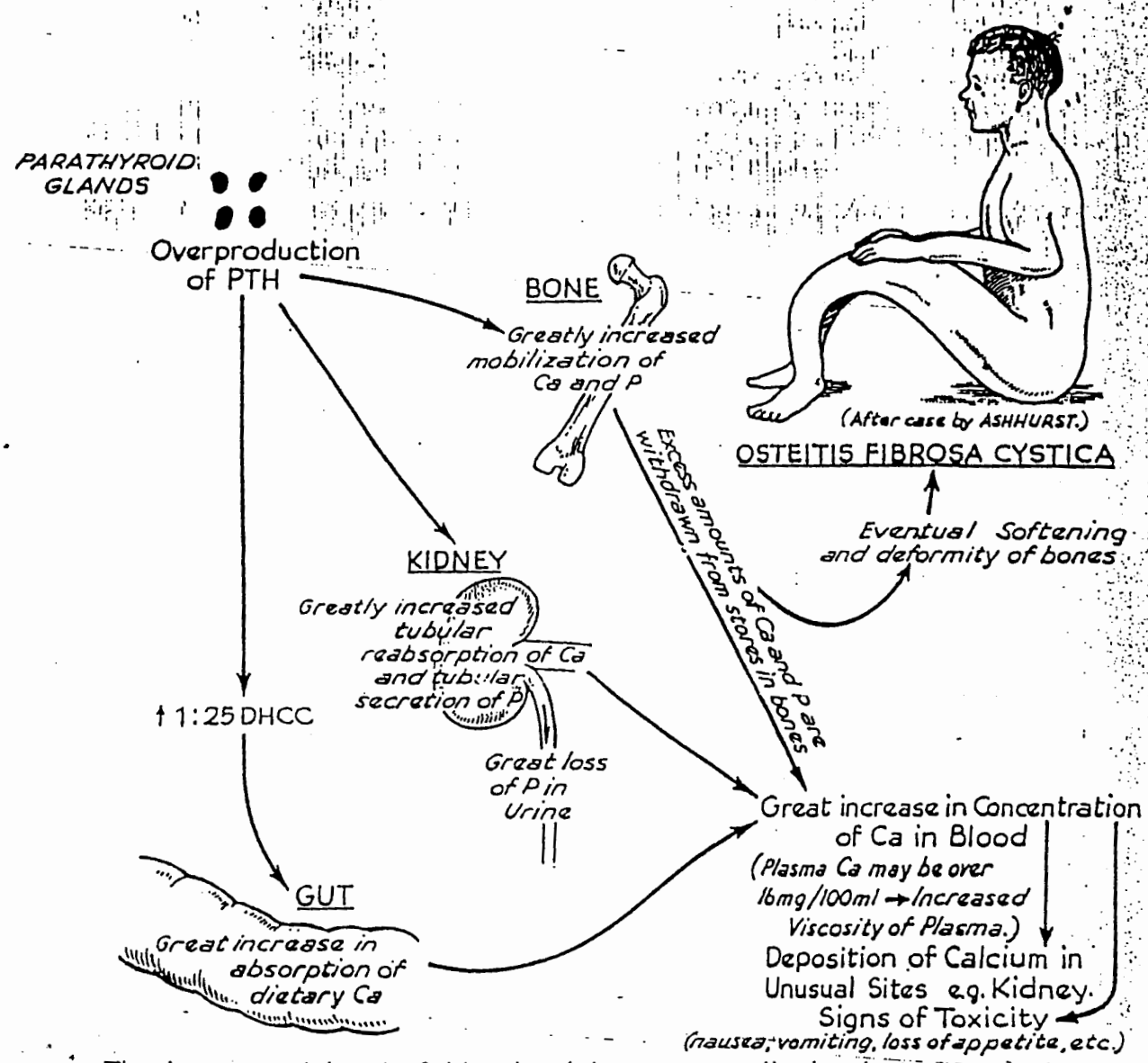
[Note the inverse relationship between plasma calcium and inorganic phosphate]

Symptoms are relieved by injection of Calcium, large doses of a Vit.D compound and Parathormone.

3

OVERACTIVITY of PARATHYROIDS

Overactivity of the Parathyroids *(due often to tumour)* leads to rise in BLOOD CALCIUM level and eventually to OSTEITIS FIBROSA CYSTICA.



The increased level of blood calcium eventually leads to excessive loss of CALCIUM in URINE (in spite of ↑ reabsorption) and also of WATER since the salts are excreted in solution. POLYURIA and THIRST result.

Excision of the overactive Parathyroid tissue abolishes syndrome.

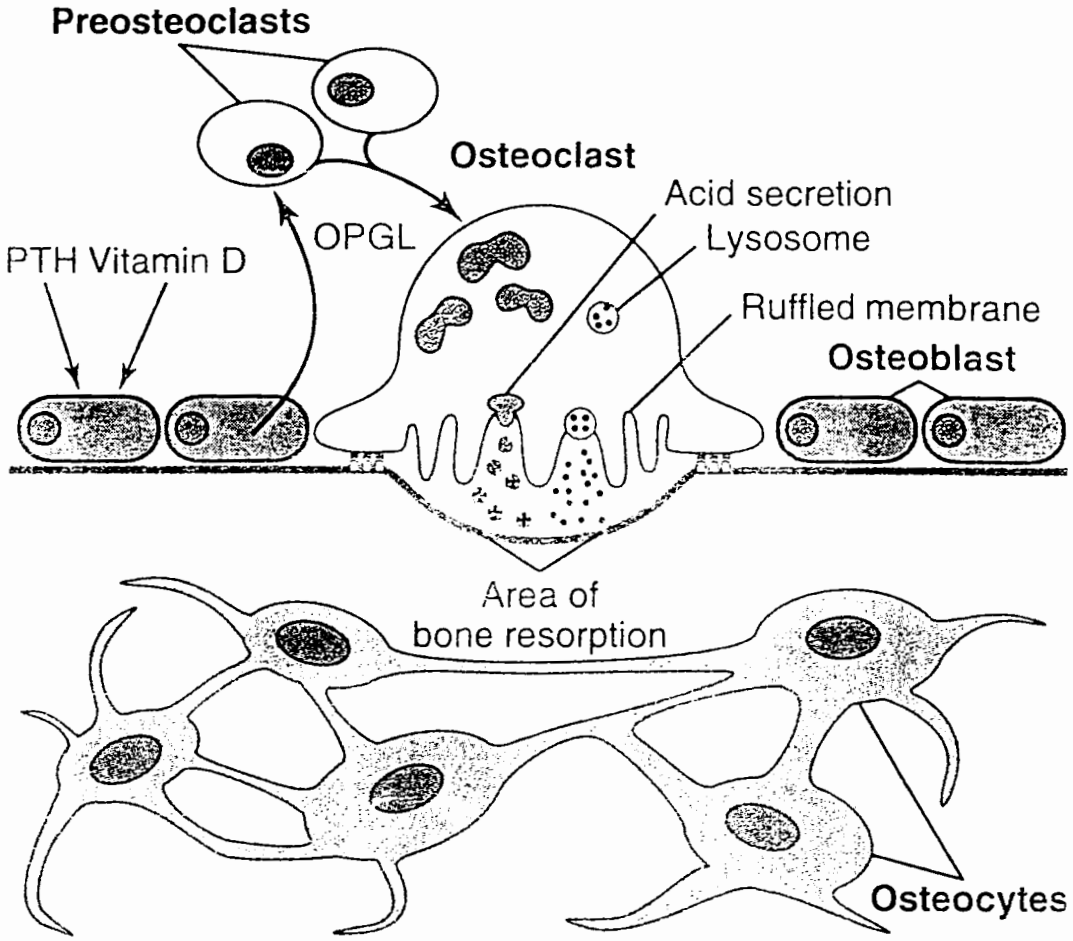


Figure 79-5 Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads all through the bone.

Vitamin D

Vitamin D, in conjunction with PTH, is the second major regulatory hormone for Ca^{2+} and phosphate metabolism. The roles of PTH and vitamin D can be distinguished as follows. The role of *PTH* is to maintain the plasma Ca^{2+} concentration, and its actions are coordinated to increase the ionized Ca^{2+} concentration toward normal. The role of *vitamin D* is to promote mineralization of new bone, and its actions are coordinated to increase *both* Ca^{2+} and phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

- **Bone.** In bone, 1,25-dihydroxycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical, since the overall action of 1,25-dihydroxycholecalciferol is to promote bone mineralization. However, mineralized "old" bone is resorbed to provide more Ca^{2+} and phosphate to ECF so that "new" bone can be mineralized (bone remodeling).

Vitamin D & its Metabolism

1. Vitamin D, is a major regulator of calcium & phosphate metabolism.

2. Vitamin D is a hormone in the sense that it is synthesized in the body, although not by an endocrine gland; after further processing, it is transported via the circulation to act on target cells.

3. It is a vitamin in the sense that when it cannot be synthesized in sufficient quantities, it must be ingested in minimal amounts for health to be maintained.

4. Deficiency of vitamin D causes failure of bone mineralization & results in the classic disease of rickets in children & softening of the bones (osteomalacia) in adults.

5. The sterol structure of the synthesized form of vitamin D (D_3) differs slightly from the form usually ingested (D_2).

6. Vitamins D_3 & D_2 are essentially prohormones that undergo identical processing that converts them to molecules with identical qualitative & quantitative actions.

7. Once vitamin D enters the circulation from the skin or the gut, it is concentrated in the liver. There it is hydroxylated to 25-OH-D. this molecule is transported to the kidney where it undergoes alternative fates.

8. 24,25-$(OH)_2$-D is only 1/20th as potent as 1,25-$(OH)_2$-D & mainly serves to dispose of excess vitamin D.

9. Vitamin D, 25-OH-D & 1,25-$(OH)_2$-D circulate bound to a protein carrier. 1,25-$(OH)_2$-D has by far the lowest concentration & the shortest half-life of the three.

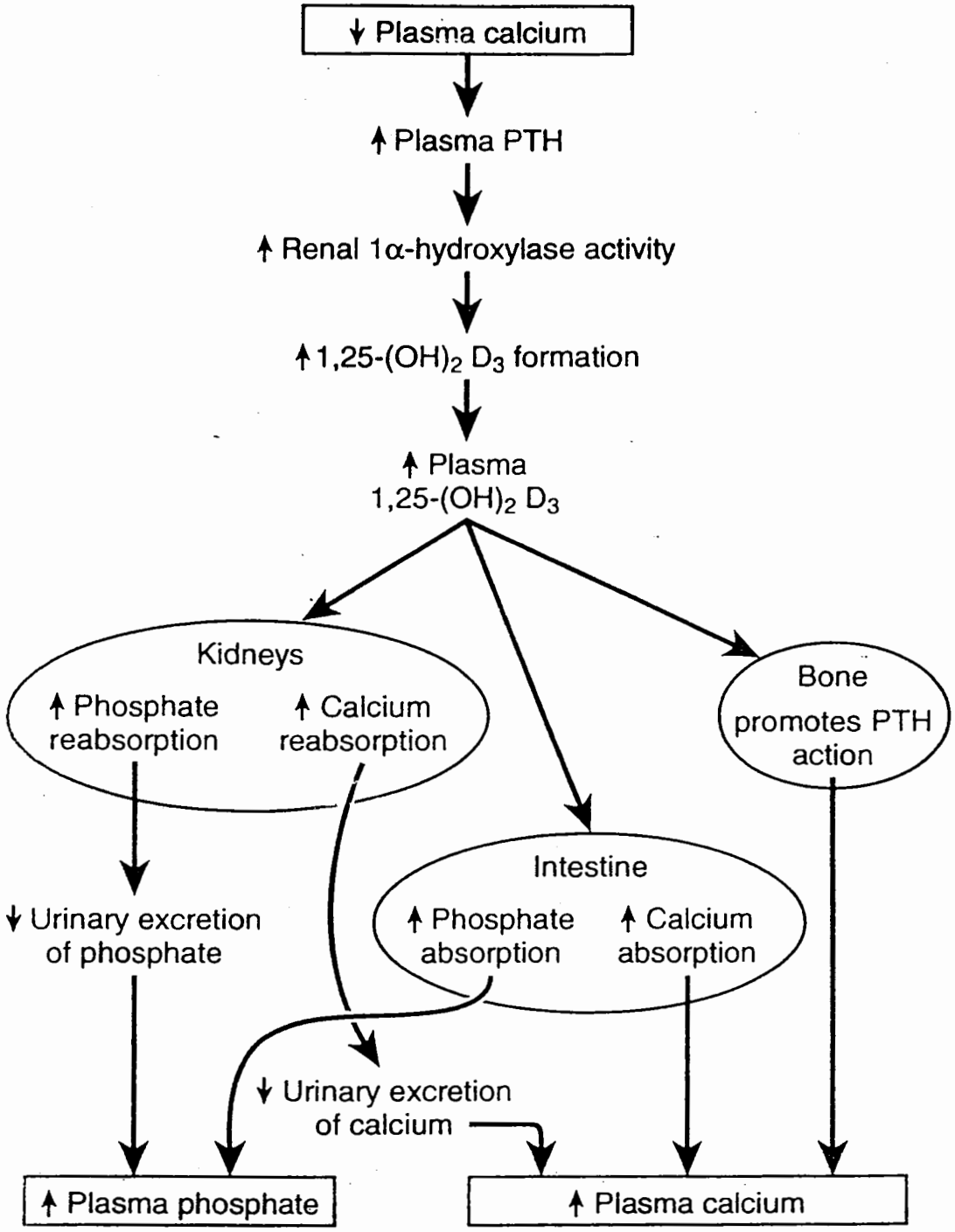


FIGURE 36.9 Effects of 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] on calcium and phosphate metabolism.

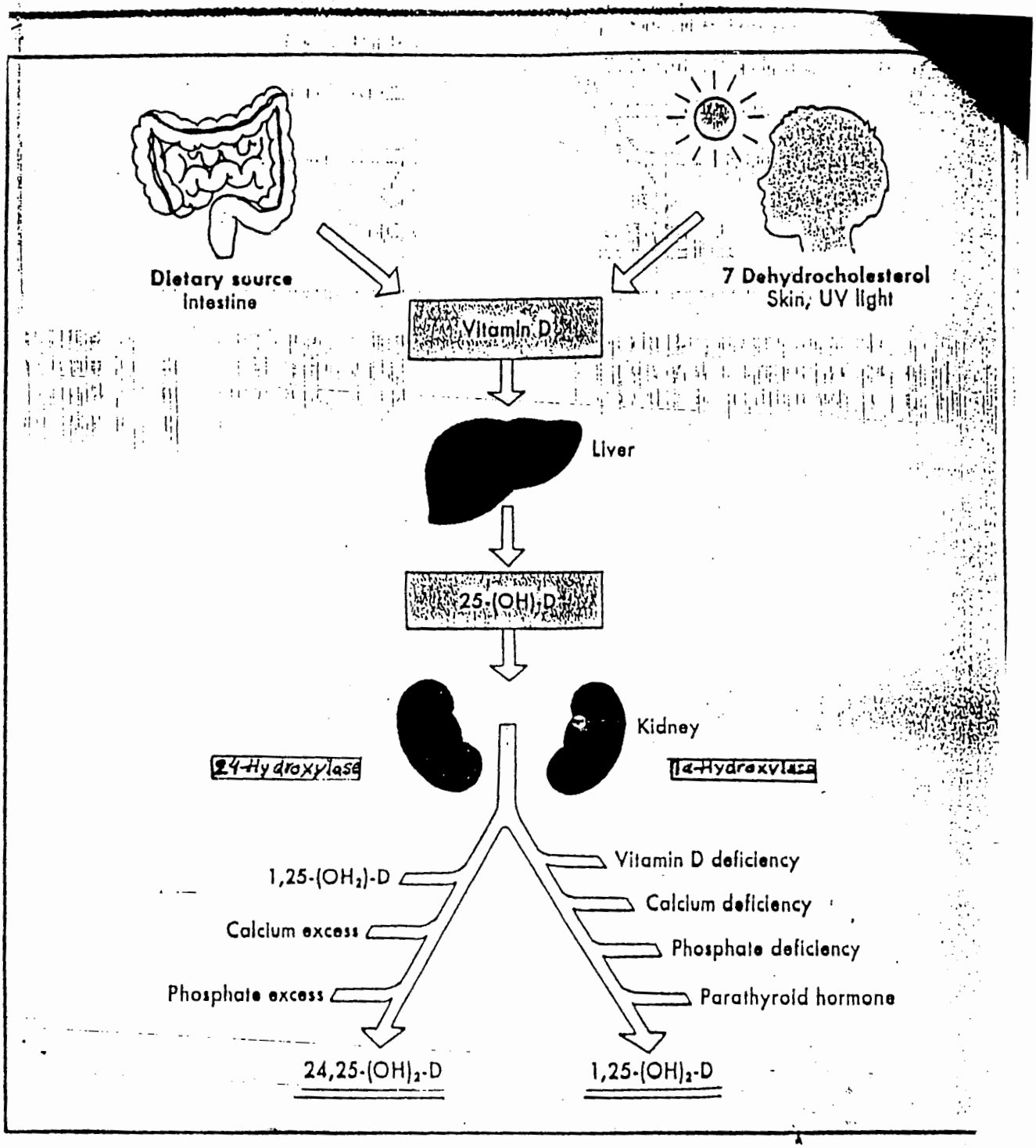


FIGURE 38-5 Vitamin D metabolism. Whether synthesized in the skin or absorbed from the d vitamin D undergoes 25 hydroxylation in the liver. In the kidney, it is further hydroxylated in 1 position when more biological activity is required or in the 24 position when less biol activity is required.

TABLE 51-2. Vitamin D metabolism in humans

	Plasma concentration (μg/L)	*Plasma half-life (days)*	*Estimated production rate (μg/day)*
1.25-$(OH)_2$-D_3	0.03	1 to 3	1
24,25-$(OH)_2$-D_3	2	15 to 40	1
25-OH-D_3	20	5 to 20	10

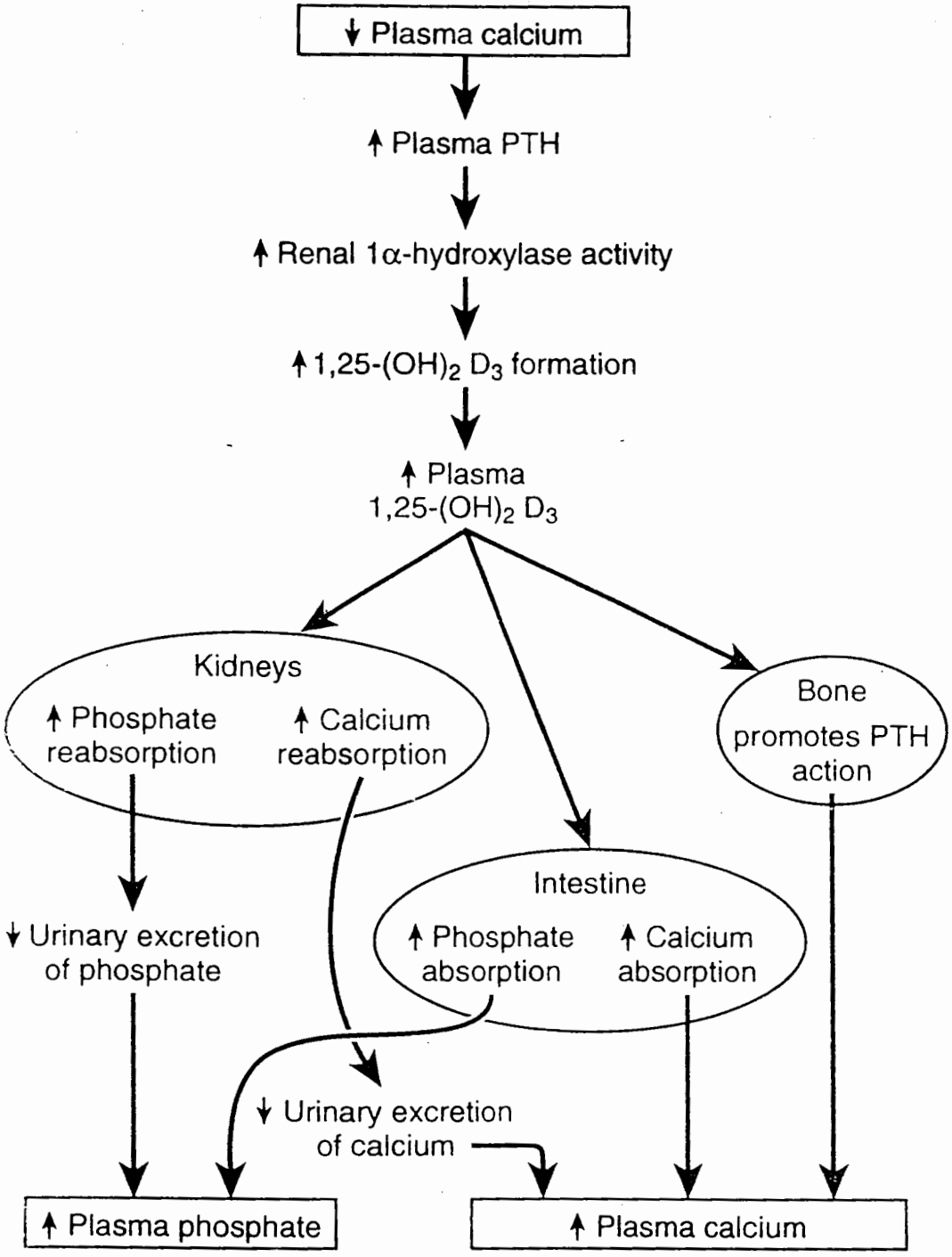


FIGURE 36.9 Effects of 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] on calcium and phosphate metabolism.

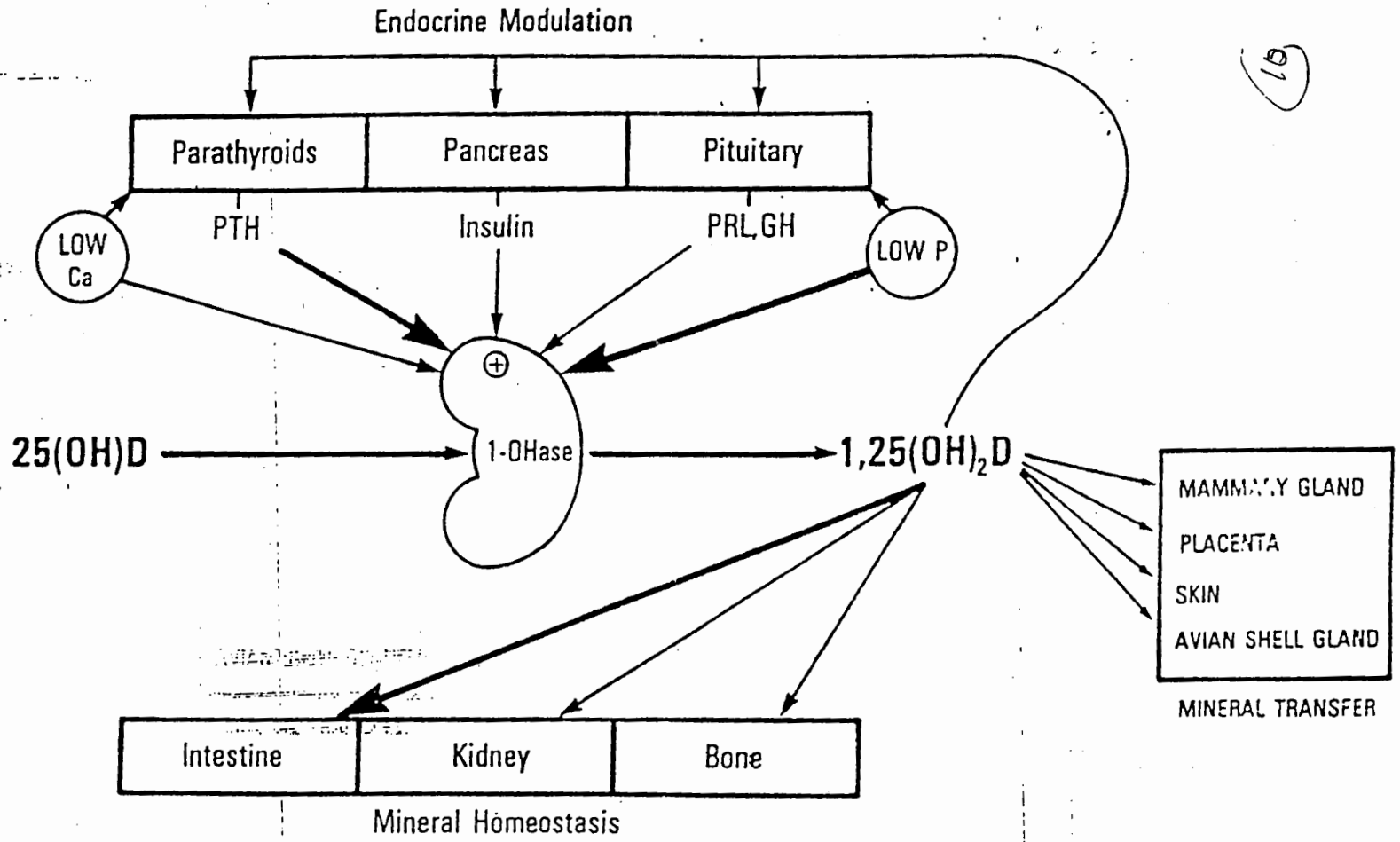


Figure 8.41. Function and regulation of 1,25-$(OH)_2D$. (From Haussler and McCain, 1977.)

Table 7.5 Causes of deficiency of 1:25-dihydroxycalciferol

Failure to synthesize cholecalciferol in the skin (this occurs in dark-skinned people in a temperature climate)
Dietary deficiency of cholecalciferol (relatively unimportant)
Failure to hydroxylate cholecalciferol in the 25 position (this occurs in chronic liver disease; hepatic osteodystrophy)
Rapid metabolism of cholecalciferol and its active metabolites (this occurs when hepatic enzymes are induced and is seen in patients taking anticonvulsants)
Failure to hydroxylate 25-cholecalciferol in the 1 position (this occurs in patients with chronic renal failure; renal osteodystrophy)

Table 27–1
Some of the Physiological Actions of Calcium

1. Required for the maintenance of normal sodium permeability in nerves
2. Involved in triggering the release of acetylcholine from nerve endings at the neuromuscular junction
3. Involved in excitation-contraction coupling in muscle cells
4. Serves as an intracellular signal for some hormones
5. Required by some enzymes for normal activity
6. Required for blood clotting to occur normally
7. Required for protein secretion
8. Constituent of bone

(14)

Table 21–1. Distribution (mmol/L) of calcium in normal human plasma.

Diffusible		1.34
Ionized (Ca^{2+})	1.18	
Complexed to HCO_3^-, citrate, etc	0.16	
Nondiffusible (protein-bound)		1.16
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		2.50

Ionized Ca^{++} concentration, depends on blood pH. Alkalosis increases the protein-bou and decreases the lonized Ca^{++} concentration, whereas acidosis has the opposite eff. ect.

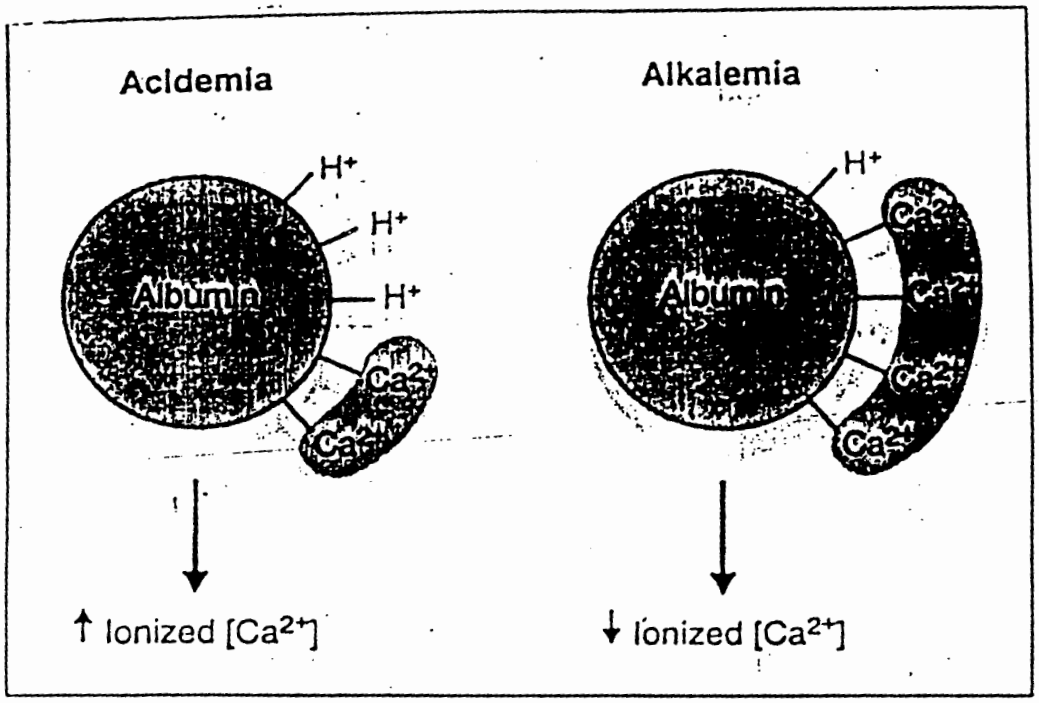


FIGURE 9–32. Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

(16)

Constituent	Total Body Content Present In Bone (%)
Calcium	99
Phosphate	85
Carbonate	80
Magnesium	50
Sodium	35
Water	9

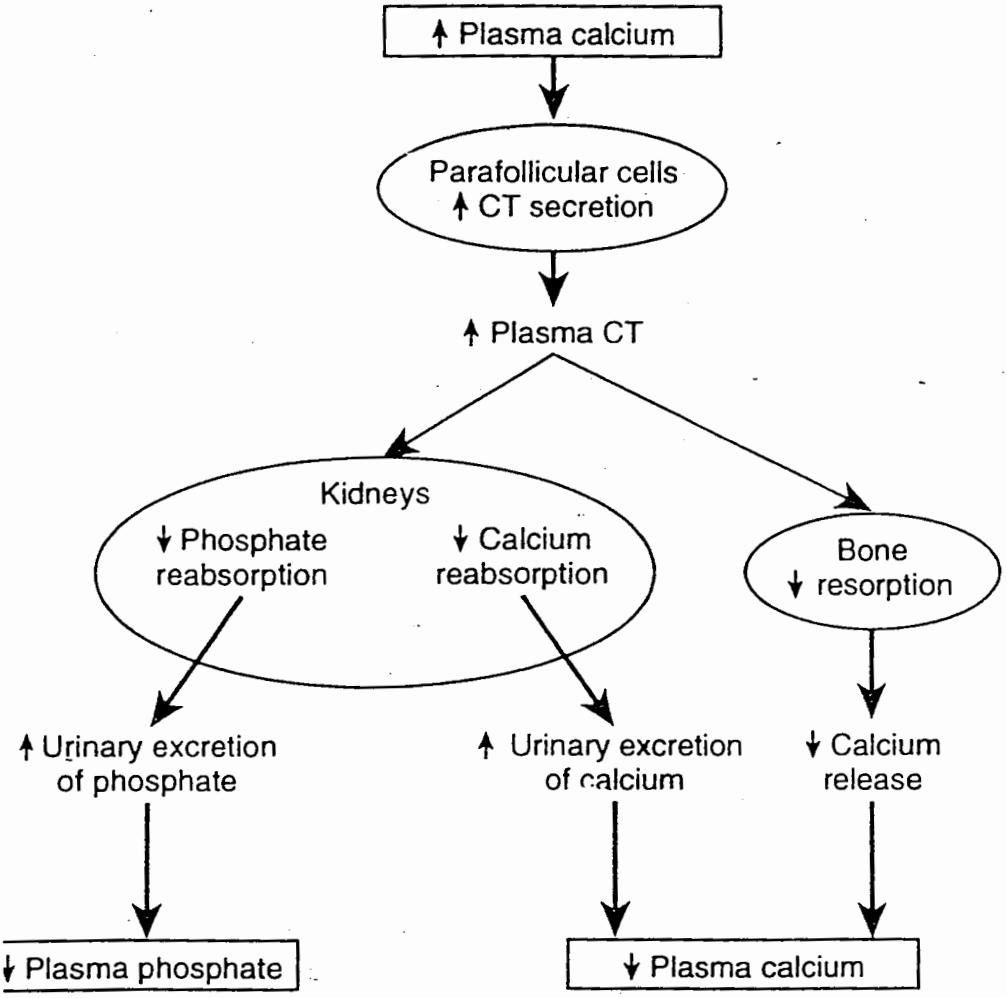


FIGURE 36.8 **Effects of calcitonin (CT) on calcium and phosphate metabolism.**

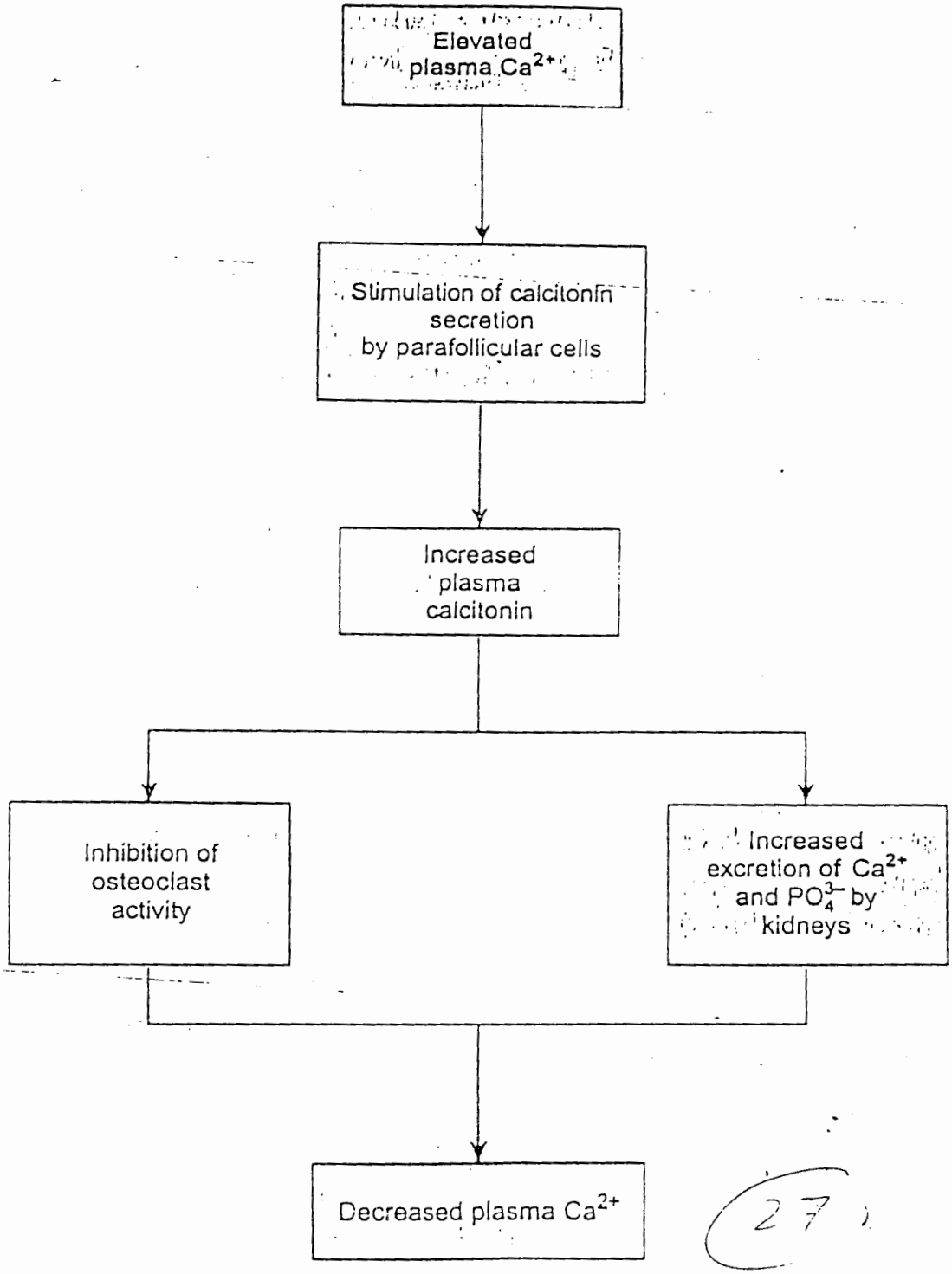


Fig. 12.26 The principal actions of calcitonin and the factors thought to regulate its secretion.

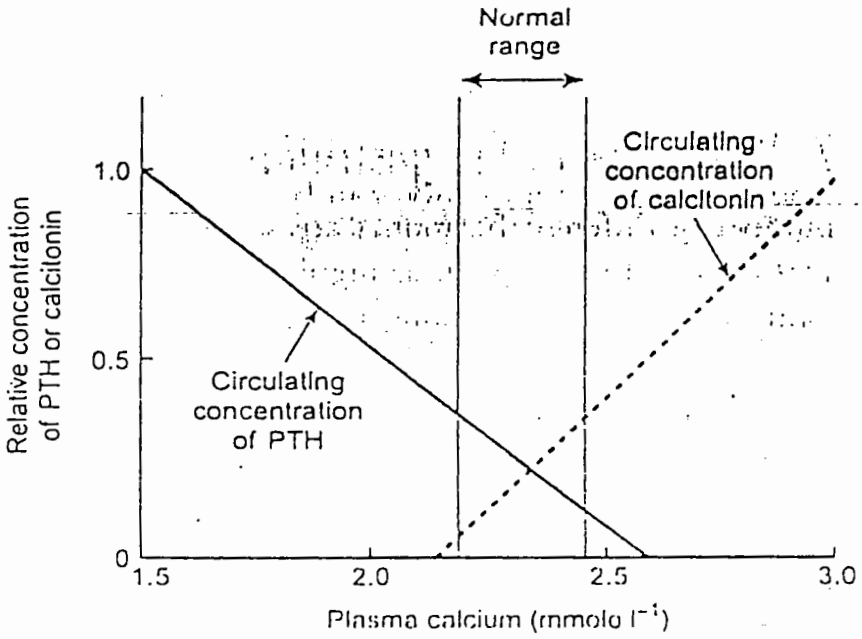


Fig. 12.25 The relationship between the plasma calcium concentration and the secretion of both parathyroid hormone and calcitonin. As calcium rises, the secretion of parathyroid hormone falls while that of calcitonin rises.

28

Calcitonin

1. Calcitonin, a straight-chain peptide of 32 amino acids, has a molecular weight of 3400.
2. The biologically active core of the molecule probably resides in its central region.
3. Calcitonin is secreted by thyroid parafollicular cells known as "C" cells.
4. Calcitonin, (CT), decreases plasma calcium levels by antagonizing the actions of PTH on bone.
5. Calcitonin is also present in nervous tissue, where it may function as a neuromodulator.
6. The major stimulus to CT secretion is a rise in plasma calcium concentration.
7. The hypocalcemic action is caused by inhibition both of osteocytic osteolysis & osteoclastic bone resorption particularly when these are stimulated by PTH.
8. However, with respect to phosphate, it has the same net effect as PTH; that is, CT decreases plasma phosphate concentration & increases urinary phosphate excretion slightly.
9. The importance of CT in humans is controversial CT deficiency does not lead to hypercalcemia & CT hypersecretion does not produce hypocalcemia. It may be that abnormal CT secretion is easily compensated for by adjustment in PTH & vitamin D levels.
10. Is degraded within the liver & kidney, after half-life of 30-60 minutes.

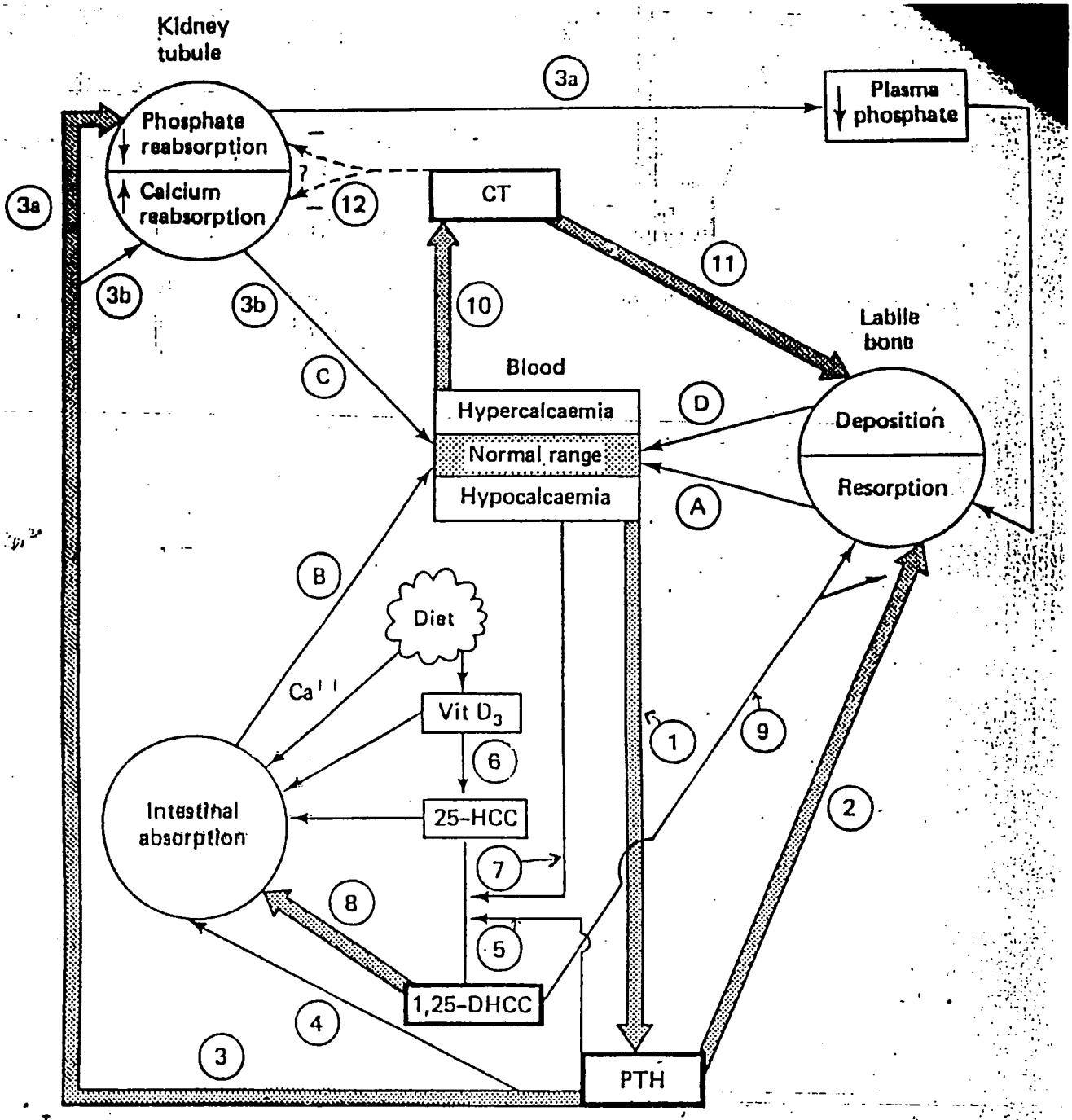


Fig. 12.7 A diagram to illustrate the interactions of parathormone, calcitonin and vitamin D_3 and its derivatives in calcium homeostasis.

(1) Ca^{+}, PO_4^{-} and Mg^{++} homeostasis are essential for health and life. A complex system acts to maintain normal body contents and ECF levels of these minerals in the face of environmental (e.g., diet) and internal (e.g., pregnancy) changes.

(2) The key elements in the system are:-
Ⓐ- vit. D. Ⓑ- PTH. Ⓒ- calcitonin. Ⓓ- other hormones.

(3) The G.I.T, the kidneys, the skeleton, the skin and the liver are involved in the homeostatic regulation.

Table 21–2. Factors that affect bone formation and calcium metabolism.

Parathyroid hormone
1,25-Dihydroxycholecalciferol
Calcitonin
Glucocorticoids
Growth hormone and somatomedins
Thyroid hormones
Estrogens
Insulin
IGF-I
Epidermal growth factor
Fibroblast growth factor
Platelet-derived growth factor
Prostaglandin E_2
Osteoclast activating factor

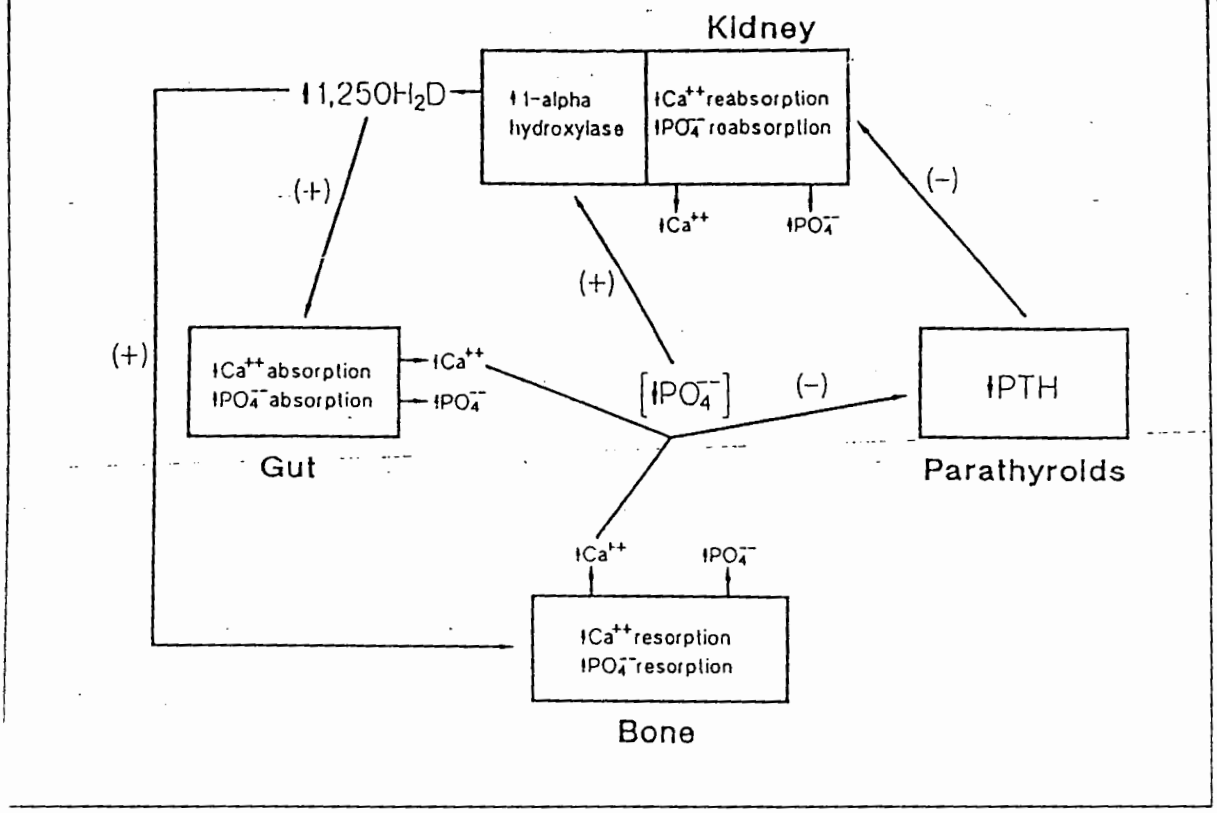


Fig. 51-3. Integrated phosphate homeostasis. The responses to marked decreases of serum phosphate concentrations are shown; opposite responses occur to marked increases. (+ = stimulation; − = inhibition; *PTH* = parathyroid hormone.)

(26)

Some Physiological Actions of Phosphate

1. Functions as part of the intracellular buffer system
2. Important constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins
3. Constituent of bone

VITAMIN D

The active form of vitamin D is its 1,25-dihydroxy metabolite

By the 1920s, investigators recognized that dietary deficiency of a fat-soluble vitamin was responsible for the childhood disease **rickets**. This disorder is characterized clinically by hypocalcemia and multiple skeletal abnormalities. Dietary replacement of vitamin D corrects this disorder and has led to the practice of adding vitamin D to milk, bread, and other products. This practice has greatly reduced the prevalence of this previously common disorder.

Our understanding of the involvement of vitamin D in the regulation of plasma [Ca^{2+}] and skeletal physiology has been clarified only over the past 2 decades. Vitamin D exists in the body in two forms, vitamin D_3 and vitamin D_2 (Fig. 52-9). **Vitamin D_3** can be synthesized from the 7-dehydrocholesterol that is present in the skin, provided sufficient ultraviolet light is absorbed. This observation explains why nutritional rickets had been a much more prevalent problem in northern countries, where clothing covers much of the skin and where individuals remain indoors much more of the year. Vitamin D_3 is also available from several natural sources, including cod and halibut liver, eggs, and fortified milk. **Vitamin D_2** is obtained only from the diet, largely from vegetables. Vitamins D_3 (Fig. 52-9A) and vitamin D_2 (Fig. 52-9B) differ only in the side chains of ring D. The side chain in vitamin D_3 (cholecalciferol) is characteristic of cholesterol, whereas that of vitamin D_2 (ergocalciferol) is characteristic of plant sterols.

Vitamin D (i.e., either D_2 or D_3) is fat soluble but water insoluble. Its absorption from the intestine depends on its solubilization by bile salts (see Chapter 45). In the circulation, vitamin D is found either solubilized with chylomicrons (see Chapter 46) or associated with a plasma binding protein. Most of the body stores of vitamin D are located in body fat. The body's pools of vitamin D are large, and only 1% to 2% of the body's vitamin D is turned over each day. Therefore, several years of very low dietary intake (as well as diminished endogenous synthesis) is required before the endogenous pools are depleted and deficiency develops.

In addition to vitamins D_2 and D_3 and their respective 25-hydroxy and 1,25-dihydroxy metabolites, more than 15 other metabolites of vitamin D have been identified in plasma. However, the specific physiological function of these metabolites, if any, is unclear.

نقص فيتامين «دي» يؤدي لمخاطر بالقلب لدى الشباب

اظهرت دراسة جديدة ان المراهقين الذين يعانون من نقص في الفيتامين دي يواجهون خطرا اكبر بالاصابة بمشاكل في القلب والسكري وارتفاع الضغط ونسبة السكر في الدم.

وتظهر الدراسة كذلك ان المراهقين البيض لديهم معدل من الفيتامين دي اكثر بمرتين تقريبا من الشباب السود واكثر بنسبة ٣٠٪ من المراهقين الاميركيين من اصل مكسيكي.

وقال روبرت اكيل الرئيس السابق لجمعية ''اميركان هارت'' ان هذه ''المعطيات حول الفيتامين دي عند الشباب تثير مخاوف حول الخيارات الغذائية وحول الوقت الذي يمضونه في الشمس''.

وينتج جسم الانسان الفيتامين دي من خلال التعرض لاشعة الشمس وهذا الفيتامين موجود ايضا في اغذية مثل الحليب والسمك والبيض. ويساعد الفيتامين دي في امتصاص الكالسيوم وابقاء مستوى مناسب من الفوسفور والكالسيوم في الدم.

والفيتامين دي يتحلل في الدهون لذا فان الاشخاص الذين يعانون من زيادة في الوزن او من البدانة عند مستوى البطن لديهم مستويات غير كافية من هذه الفيتامين. والمراهقون الذين لديهم مستويات متدنية جدا من الفيتامين دي يواجهون خطر الاصابة بمجموعة من المشاكل في القلب والسكري ومستوى منخفض من الكوليسترول اربع مرات اكثر من الاشخاص الاخرين.

اما خطر الاصابة بارتفاع ضغط الدم فيترفع ٢،٣٦ مرة ونسبة السكر في الدم ٢،٥٤ مرة.

وحللت الدراسة التي عرضت خلال المؤتمر السنوي ل ''اميركان هارت اسوسييشن'' معطيات عن ٣٥٧٧ مراهقا.

اف ب

Osteomalacia

Osteomalacia is rickets in adults and is frequently called "adult rickets."

Normal adults rarely have a serious *dietary* deficiency of vitamin D or calcium because large quantities of calcium are not needed for bone growth as in children. However, a serious deficiency of both vitamin D and calcium occasionally occurs as a result of steatorrhea (failure to absorb fat), for vitamin D is fat-soluble, and calcium tends to form insoluble soaps with fat; consequently, in steatorrhea both vitamin D and calcium tend to pass into the feces. Under these conditions an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, though this almost never proceeds to the stage of tetany — but very often is a cause of severe bone disability.

TABLE 36.3 Causes of Osteomalacia and Rickets

Inadequate availability of vitamin D	Dietary deficiency or lack of exposure to sunlight
	Fat-soluble vitamin malabsorption
Defects in metabolic activation of vitamin D	25-Hydroxylation (liver)
	Liver disease
	Certain anticonvulsants, such as phenobarbital
	1-Hydroxylation (kidney)
	Renal failure
	Hypoparathyroidism
	Certain anticonvulsants
Impaired action of 1,25-dihydroxycholecalciferol on target tissues	1,25-Dihydroxycholecalciferol receptor defects
	Uremia

RICKETS

Rickets occurs mainly in children as a result of calcium or phosphate deficiency in the extracellular fluid. Yet, ordinarily rickets is due to lack of vitamin D, rather than a dietary lack of calcium or phosphate. If the child is properly exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D_3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter.

Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementary therapy in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and is still available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

OSTEOPOROSIS

Osteoporosis, the most common of all bone diseases in adults and especially in old age, is a different disease from osteomalacia and rickets, for it results from diminished organic matrix rather than abnormal bone calcification. Usually, in osteoporosis the osteoblastic activity in the bone is less than normal, and consequently the rate of bone deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.