Fig. 11.1. Relationships of calcium kinetics and the production of PTH and 1,25-DHCC. (Note: Horse kidneys lack 1α-hydroxylase and thus do not form 1,25-DHCC.)

- PTH production in parathyroid glands is stimulated by ↓ [fCa^{2+}] and ↓ [1,25-DHCC] and inhibited by ↑ [fCa^{2+}] and ↑ [1,25-DHCC].
- Conversion of 25-HCC to 1,25-DHCC in kidneys is catalyzed by 1α-hydroxylase. The activity of 1α-hydroxylase is promoted by ↓ [fCa^{2+}] and ↑ PTH and inhibited by ↑ [fCa^{2+}] and ↑ [PO_4].
- Ca^{2+} mobilization from bone and Ca^{2+} absorption in intestine are promoted by ↑ [1,25-DHCC] and ↑ PTH. Less Ca^{2+} mobilization and absorption occur if there is ↓ [1,25-DHCC] or ↓ PTH.
- Urinary excretion of Ca^{2+} is enhanced by ↑ [fCa^{2+}], and excretion is reduced by ↓ [fCa^{2+}], ↑ PTH, and ↑ 1,25-DHCC. Increased excretion of anions may obligate Ca^{2+} excretion and thus decreases in [fCa^{2+}].
- During lactation, a large amount of Ca^{2+} is excreted via milk.
- Ca^{2+} is present in plasma in three forms: fCa^{2+}, Ca^{2+} bound to proteins, and Ca^{2+} bound to small anions such as citrate and PO_4.

+, positive effector or stimulates the process; −, negative effector or inhibits the process; Ca^{2+}/Pr^{-}, calcium bound to protein; and Ca^{2+}/A^{-}, calcium bound to nonprotein anions.

Fig. 11.2. Sequential events during the development of secondary renal hyperparathyroidism caused by chronic renal disease in dogs, cats, and cattle. Eventually, tCa^{2+}, Pi, and 1,25-DHCC concentrations may be abnormal (see Fig. 11.3).

- Renal disease causes a loss of nephrons and a decrease in GFR, which causes less PO_4 to be filtered from plasma and a mild hyperphosphatemia develops.
- Damaged tubular epithelial cells may result in less endocytic resorption of 25-HCC and vitamin D–binding protein.
- Either because of the damaged tubular cells or inhibition of 1α-hydroxylase by increased [PO_4], there is less conversion of 25-HCC to 1,25-DHCC, and thus less vitamin D is available for Ca^{2+} metabolism.
- Decreased [1,25-DHCC] leads to ↓ [fCa^{2+}] and perhaps ↓ [tCa^{2+}] because of ↓ intestinal Ca^{2+} absorption and ↓ Ca^{2+} resorption from bone.
- Decreased [1,25-DHCC] also reduces the 1,25-DHCC inhibition of PTH synthesis, and thus PTH synthesis increases.
- Decreased [fCa^{2+}] causes ↑ PTH production, ↓ calcitonin release, and ↑1α-hydroxylase activity.
- Increased PTH promotes vitamin D–dependent Ca^{2+} absorption in intestine, stimulates Ca^{2+} and PO_4 resorption from bone, stimulates 1α-hydroxylase activity in kidneys, and inhibits renal PO_4 resorption (promotes phosphaturia).
- Actions of increased PTH due to parathyroid hyperplasia tend to correct the hypocalcemia, hyperphosphatemia, and decreased [1,25-DHCC]. At this point, secondary renal hyperparathyroidism is present.

Fig. 11.3. Schematic pathogenesis of secondary renal hyperparathyroidism in dogs, cats, and cattle. *Shaded areas* represent reference intervals for GFR or each analyte concentration.

- Initial renal damage: The sequence of events described in Fig. 11.2 initially compensates for the decreased clearance of PO_4 and inadequate activation of vitamin D. A new homeostasis in Ca^{2+} and PO_4 balance is maintained by ↑ PTH secretion.
- Additional renal damage: As renal disease progresses and more nephrons are lost, pathophysiologic responses recur that stimulate more PTH synthesis in an attempt to maintain physiologic concentrations of fCa^{2+}, PO_4, and 1,25-DHCC.
- Progressed to renal failure: Eventually, renal disease reduces GFR sufficiently for serum [Pi] to remain increased, and insufficient 1,25-DHCC and PTH are made to maintain [fCa^{2+}]. The animal is presented with clinical signs of renal insufficiency or failure, azotemia, impaired ability to concentrate or dilute urine, mild hypocalcemia, and hyperphosphatemia. The [tCa^{2+}] may not reflect the abnormal regulation of the [fCa^{2+}] because of the Ca^{2+} that is bound to anions that are not excreted in renal failure.

Fig. 11.4. Conceptual illustration of the effects of plasma or serum pH on the [fCa^{2+}]. The drawing illustrates the effect of the [H^+] in plasma on the binding of Ca^{2+} to negatively charged proteins. A similar effect occurs with Mg^{2+}.

- At a pH of 7.4, there are Ca^{2+} and H^+ ions bound to plasma or serum proteins and Ca^{2+} and H^+ ions that are free in the plasma or serum water. The free ions create the [fCa^{2+}] and pH of the fluid. In this illustration, there are four protein-bound and four free Ca^{2+} ions.
- If sample handling, respiratory disorders, or metabolic disorders cause an ↑ [H^+], then more H^+ and less Ca^{2+} bind to the proteins. The release of Ca^{2+} from the proteins increases the [fCa^{2+}]. In this illustration with a pH of 7.3, the sample contains six free Ca^{2+} ions.
- If either sample handling, respiratory disorders, or metabolic disorders cause a ↓ [H^+], then less H^+ and more Ca^{2+} bind to the proteins. The binding of Ca^{2+} to the proteins decreases the [fCa^{2+}]. In this illustration with a pH of 7.5, the sample contains two free Ca^{2+} ions.

Fig. 11.5. Conceptual relationships of total, free, and bound Ca^{2+} fractions in serum or plasma.

A. Healthy animal: The [tCa^{2+}] and [fCa^{2+}] are within respective reference intervals.

B. Hypoproteinemia (hypoalbuminemia): The hypocalcemia is caused by a decreased concentration of protein-bound Ca^{2+}. The [fCa^{2+}] (the regulated concentration) is within its reference interval.

C. Primary hypoparathyroidism, hypovitaminosis D: The hypocalcemia is primarily caused by a decreased [fCa^{2+}] because of either inadequate PTH or vitamin D activity. In this schematic example, the bound Ca^{2+} concentration is unchanged.

D. Primary hyperparathyroidism, hypervitaminosis D, humoral hypercalcemia of malignancy, humoral hypercalcemia of benign disorders: The hypercalcemia is primarily caused by increased [fCa^{2+}] because of increased activity of PTH, PTHrp, or vitamin D activity. In this schematic example, the bound-Ca^{2+} concentration is unchanged.

E. HHM and concurrent hypoproteinemia: The [fCa^{2+}] is increased because of the increased PTHrp activity, but the protein-bound Ca^{2+} concentration is decreased because of concurrent hypoproteinemia. The net result is a [tCa^{2+}] within its reference interval.

F. Chronic renal failure: The [fCa^{2+}] is mildly decreased because of the inadequate formation of 1,25-DHCC. Concurrently, the concentration of Ca^{2+} bound to nonprotein anions (e.g., Ca^{2+} bound to citrate or PO_4) is increased. In this schematic example, the protein-bound Ca^{2+} concentration is unchanged and the net result is a mild hypocalcemia. The protein-bound Ca^{2+} concentration would be decreased with hypoalbuminemia caused by a protein-losing nephropathy.

G. Lactic acidosis: The acidemia promotes Ca^{2+} detaching from proteins (thus, a decreased protein-bound [Ca^{2+}]). Some of the released Ca^{2+} binds to lactate to increase the Ca^{2+} bound to nonprotein anions. In this schematic example, the [tCa^{2+}] is within its reference interval.

H. Excess heparin in plasma: Collection of blood with an inappropriate amount of heparin (an anion) results in some of the fCa^{2+} binding to heparin and thus a decreased [fCa^{2+}]. The [tCa^{2+}] does not change.

Fig. 11.6. Relationships of PO_4 kinetics and the production of PTH and 1,25-DHCC. (Note: Horse kidneys lack 1α-hydroxylase and thus do not form 1,25-DHCC.)

- PTH production in parathyroid glands is stimulated by ↓ [fCa^{2+}] and ↓ [1,25-DHCC] and inhibited by ↑ [fCa^{2+}] and ↑ [1,25-DHCC].
- Conversion of 25-HCC to 1,25-DHCC in kidneys is catalyzed by 1α-hydroxylase. The activity of 1α-hydroxylase is promoted by ↓ [fCa^{2+}] and ↑ PTH and inhibited by ↑ [fCa^{2+}] and ↑ [PO_4].

- PO_4 mobilization from bone is promoted by ↑ [1,25-DHCC] and ↑ PTH. Less PO_4 mobilization occurs with ↓ [1,25-DHCC] and ↓ PTH.
- PO_4 absorption in intestine is promoted by ↑ [1,25-DHCC] and ↑ dietary PO_4. Less PO_4 absorption occurs with ↓ [1,25-DHCC] and ↓ dietary PO_4.
- Urinary excretion of PO_4 is enhanced by ↑ PTH, and excretion is reduced by ↓ GFR, ↓ PTH, and ↑ GH activity.
- Insulin promotes the uptake of PO_4 by cells. However, cell damage will allow PO_4 to escape from the cells and enter plasma.
- During lactation, a large amount of PO_4 is excreted via milk.
- PO_4 present in plasma is mostly in two forms (HPO_4^{2-} and $H_2PO_4^-$), but the measured phosphorus is reported in terms of inorganic phosphorus (Pi).
- In vitro hemolysis or delayed removal of serum or plasma allows PO_4 in erythrocytes to enter serum or plasma and thus cause an erroneous [PO_4].

+, positive effector (stimulates the process); and −, negative effector (inhibits the process).